Faculté de Médecine

The Role of Exercise Hemodynamics in Heart Failure with Preserved Ejection Fraction

Thesis submitted by Claudia BARATTO

in fulfilment of the requirements of the PhD Degree in Medical Sciences (ULB - "Doctorat en Sciences Médicales") and in Public Health (UNIMIB – "Dottore in Sanità Pubblica")

Academic year 2024-2025

Supervisors: Professor Céline DEWACHTER(Université libre de Bruxelles)

and Professor Gianfranco PARATI Università degli Studi di Milano-Bicocca

Co-Supervisor: Professor Jean-Luc VACHIÉRY (Université libre de Bruxelles)

Γένοιο οἷος εἰ – Pindaro

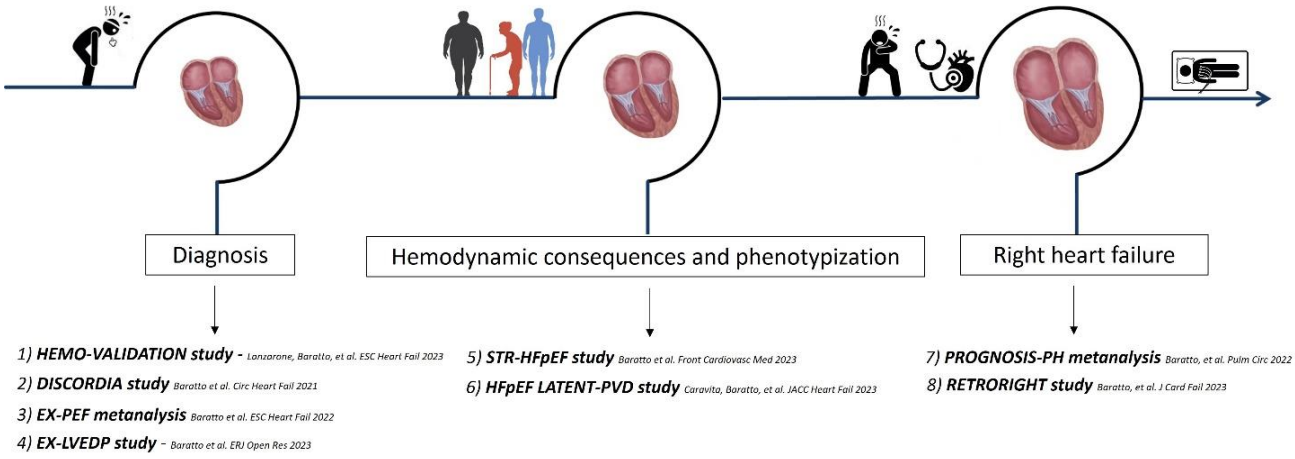
Ascolta il tuo cuore. Esso conosce tutte le cose – L'alchimista, Paulo Cohelo

My heartfelt thanks to all my Mentors for teaching me to discover the magic of the heart.

Never enough thanks to all my Family who helps my heart by spreading love.

INDEX

PREFACE



Central illustration. The role of exercise right heart catheterization in tracing the natural history of heart failure with preserved ejection fraction. Exercise right heart catheterization contributes to diagnosis, phenotypization and prognostic stratification of heart failure with preserved ejection fraction patients, as highlighted in the eight studies included in this PhD thesis.

The present PhD thesis with joint supervision of Université Libre de Bruxelles and University of Milano-Bicocca includes 6 original manuscripts (4 as first author, 2 as corresponding author) and 2 meta-analysis (first author):

I. **Study 1, HEMO-VALIDATION study** [55]
II. **Study 2, DISCORDIA study** [57]
III. **Study 3, EX-PEF meta-analysis** [59]
IV. **Study 4, EX-LVEDP study** [86]
V. **Study 5, STR-HFpEF study** [87]
VI. **Study 6, HFpEF LATENT-PVD study** [92]
VII. **Study 7, PROGNOSIS-PH meta-analysis** [96]
VIII. **Study 8, RETRORIGHT study** [115]

The Role of Exercise Hemodynamics

in Heart Failure with Preserved Ejection Fraction

ABSTRACT

BACKGROUND

Diagnosing heart failure with preserved ejection fraction (HFpEF) in early phase could be challenging using non-invasive tests. Exercise right heart catheterization (RHC) has been claimed as the gold standard diagnostic test, but exercise RHC methodology, interpretation and hemodynamic HFpEF definition are still poorly standardized. Moreover, HFpEF is a progressive disease. Severe tricuspid regurgitation (TR), the development of a pre-capillary component to pulmonary hypertension (PH), and/or right heart failure (RHF) could occur over time and drive prognosis. However, these hemodynamic consequences of HFpEF remain neither fully described nor completely understood.

AIM

Aim of this PhD thesis was to demonstrate how hemodynamics can contribute to early HFpEF diagnosis, to identify distinct disease phenotypes with worse profile, adding to clinical evaluation, and to providing prognostic information.

METHODS

We performed 6 retrospective data analysis on different cohorts of patients with unexplained dyspnea or PH, who underwent a thorough clinical evaluation and exercise RHC between 2006 and 2021. In particular, we focused on: i) the diagnosis of HFpEF based on left heart filling pressures behavior during exercise, i.e. absolute pulmonary artery wedge pressure (PAWP), PAWP indexed to cardiac output (CO), left ventricular end-diastolic pressure (LVEDP), also in relation to non-invasive scores and algorithms (H_2FPEF score or HFA-PEFF score); ii) the identification of early RHF and of the hemodynamic impact of TR in HFpEF patients, based

on right atrial pressure (RAP) trajectories (absolute RAP, RAP V wave and RAP indexed to cardiac output); iii) the clinical and prognostic relevance of a pre-capillary component to PH, both at rest and during exercise, based on the analysis of pulmonary vascular resistance (PVR) behavior, distinguishing between normal PVR behavior and latent pulmonary vascular disease (PVD), i.e. exercise PVR > 1.74 WU.

Furthermore, we performed 2 meta-analysis, on studies: i) conducted on HFpEF patients who underwent an exercise RHC, describing the methodology of exercise RHC, the clinical and hemodynamic profile of HFpEF cohorts and extrapolating the PAWP/CO slope from available data; ii) evaluating the association between prognosis and hemodynamic markers of a pre-capillary component in patients with PH associated with left heart disease (LHD).

RESULTS

HFpEF diagnosis

We validated the 2nd and 3rd step of the HFA-PEFF algorithm against exercise RHC in a cohort of 73 consecutive patients. Sensitivity of the 2nd step of the HFA-PEFF algorithm was poor (45%) despite good specificity (100%), and its diagnostic performance did not improve after adding the 3rd step, i.e. diastolic stress echocardiography (sensitivity 46%, specificity 88%). Sensitivity of the 2nd step might could be improved ($p = 0.08$) by lowering the rule-in threshold from >4 to >3.

Exercise hemodynamics resulted heavily dependent upon respiratory pressure swings: in 57 consecutive patients, end-expiratory pulmonary artery pressure (PAP) and PAWP were higher than values averaged across the respiratory cycle ($p < 0.05$), leading to a larger proportion of patients exceeded the pathologic threshold at end-expiration than when values were averaged through the respiratory cycle (70% vs 53%, $p < 0.01$). The diagnostic criteria proposed in literature to diagnose HFpEF based on exercise hemodynamic (PAWP ≥ 25 mmHg at peak, PAWP/CO slope > 2 mmHg/L/min, total pulmonary resistance at peak > 3 WU plus PAWP > 20 mmHg) were concordant in only 70% of patients. PAWP/CO slope resulted the most sensitive parameter, incorporating over 97% of abnormal hemodynamic responses.

In cohorts of 2180 HFpEF patients and 680 controls from 27 meta-analyzed studies, we found a huge heterogeneity in both exercise RHC methodology and interpretation, as well as in absolute PAWP values obtained at peak exercise (I^2 = 93%). PAWP/CO slope was steeper in HFpEF than in controls (3.75 [3.20–4.28] vs. 0.95 [0.30–1.59] mmHg/L/min, p-value < 0.0001), even after adjustment for covariates (p = 0.007).

The accuracy and precision of PAWP to estimate LVEDP during exercise was evaluated in a cohort of 46 consecutive patients who underwent simultaneous exercise left and RHC. PAWP estimated LVEDP with minimal bias but large limits of agreement (±11 mmHg). As a result, 11% of patient presented with discordant LVEDP and PAWP at peak exercise. In these discordant cases, PAWP/CO slope was always found > 2 mmHg/L/min.

Tracking HFpEF complications and prognosis

Thirteen (14%) of 96 HFpEF patients who underwent exercise RHC presented with severe secondary TR (STR), which was atrial-functional in 12. These 12 HFpEF-STR patients, as compared 12 with age- sex- and BMI-matched HFpEF controls, presented with higher RAP (23±2 vs 14±2 mmHg) and lower stroke volume (54±10 vs 93±10 mL) during exercise (p <0.05), associated to a relative pulmonary derecruitment with augmented PVR and LV underfilling.

Among 86 HFpEF patients, HFpEF latent-PVD were 21%. HFpEF latent-PVD had PVR >2 WU at rest in 78% of cases. Exercise PVR trajectories differed in HFpEF latent-PVD and HFpEF-controls, slightly increasing in the former and decreasing in the latter (p interaction = 0.008). HFpEF latent-PVD displayed more frequently exercise PH (94% vs 60%), hemodynamic signs consistent with STR during exercise (50% vs 16%, p < 0.01) and had more impaired CO and stroke volume reserve (p < 0.05). Finally, HFpEF latent-PVD had a lower event-free survival (at 3 years 72% vs 93%, log-rank test p = 0.004).

In a meta-analysis on 9600 patients from 16 studies, PVR confirmed to be strong prognostic marker in patients with PH associated with left heart disease (PVR: hazard ratio [HR], 1.07; 95% confidence interval [CI]: 1.05-1.08). Similar results were found when subdividing cohorts according to the underlying LHD, including HFpEF.

The upper limit of normal for RAP trajectories during exercise (RAP > 12 mmHg at peak, RAP/CO slope > 1.3 mmHg/L/min) were derived from 21 individuals with non-cardiac dyspnea and applied to a cohort of PH-HFpEF (n=30) and PAH (n=30). PH-HFpEF had higher peak RAP and RAP/CO slope than PAH (20 [16-24] vs 12 [9-19] mmHg and 3.47 [2.02-6.19] vs 1.90 [1.01-4.29] mmHg/L/min, $p < 0.05$). A higher proportion of PH-HFpEF had RAP/CO slope and peak RAP above normal ($p < 0.001$). In the whole cohort, preload-related factors (such as age, the rate of increase in estimated stressed blood volume during exercise, the presence of severe TR, and right atrial dilation) were found to be associated with the RAP/CO slope.

CONCLUSIONS

Non-invasive tests are specific, but not sensitive in identifying early HFpEF, highlighting the need of invasive evaluation. The methodological and interpretative heterogeneity in performing exercise RHC to identify HFpEF could be solved using as diagnostic criteria a PAWP/CO slope > 2 mmHg/L/min, which is sensitive, relatively independent from exercise body position and respiratory pressure swings, allowing to overcome limitations of an isolated PAWP value at peak exercise. Beyond PAWP, RHC captures complications related to HFpEF progression. The analysis of RAP trajectories and waveform during exercise allows to unmask early RHF, highlighted preload-related mechanisms of RHF in HFpEF, and revealed the hemodynamic consequences of STR in HFpEF. Moreover, not only resting PVR but also exercise PVR individuate a subgroup of patients with more advanced disease, worse hemodynamic adaptation to exercise, and higher risk of adverse events.

Le rôle de l’hémodynamique à l’effort

dans l’insuffisance cardiaque à fraction d’éjection préservée

RÉSUMÉ

INTRODUCTION

Le diagnostic de l'insuffisance cardiaque à fraction d'éjection préservée (HFpEF) au stade précoce est difficile en utilisant des tests non invasifs. Le cathétérisme cardiaque droit à l’effort (KTD) a été proposé comme le test diagnostic de référence pour l’identification de l’HFpEF. Cependant, la méthodologie du KTD à l’effort, ainsi que l'interprétation et la définition hémodynamique de l’HFpEF ne sont pas encore précisément standardisées. De plus, l’HFpEF est une maladie évolutive et progressive. Beaucoup de facteurs et de complications peuvent survenir avec le temps et déterminer le pronostic des patients souffrant d’HFpEF, comme l’apparition d’une régurgitation tricuspidienne sévère, le développement d'une composante pré-capillaire à l'hypertension pulmonaire (HTP) et/ou d’une défaillance du ventricule droit (VD). Cependant, les conséquences hémodynamiques de l'HFpEF ne sont ni entièrement décrites ni complètement comprises pour le moment.

OBJECTIFS

L'objectif de cette thèse de doctorat était de démontrer comment l'hémodynamique à l’effort peut contribuer au diagnostic précoce de l'HFpEF, à l’identification des différents phénotypes de la maladie avec un profil défavorable, et contribuer à l'évaluation clinique ainsi que de fournir des informations pronostiques.

MÉTHODES

Nous avons réalisé 6 analyses rétrospectives de données collectées sur des cohortes de patients, qui ont été soumis à une évaluation clinique approfondie et à un KTD à l’effort entre 2006 et 2021, dans le cadre d’un bilan pour dyspnée à l’effort d’origine inexpliquée ou pour suspicion d'HTP. En particulier, nous nous sommes intéressés à: i) le diagnostic précoce de l’HFpEF, sur la base du comportement à l'effort de la pression de remplissage du cœur gauche, c'est-à-dire de la pression artérielle pulmonaire d'occlusion (PAPO), la PAPO

indexée sur le débit cardiaque (DC), la pression télédiastolique du ventricule gauche (PTDVG), mis en relation avec des scores non invasifs, comme le score H_2FPEF ou l'algorithme HFA-PEFF; ii) la détection de la défaillance du VD en phase précoce, et la description de l'impact hémodynamique de la régurgitation tricuspidienne sévère chez les patients HFpEF, sur la base de l'évolution de la pression de l'oreillette droite (POD) pendant l'effort, en analysant la valeur absolue de la POD ainsi que l'onde V tricuspide et la POD indexée sur le DC; iii) la relevance clinique et pronostique du développement d'une composante pré-capillaire de l'HTP, au repos et à l'effort, basée sur l'analyse du comportement de la résistance vasculaire pulmonaire (RVP), en distinguant le comportement normal de la RVP et la « maladie vasculaire pulmonaire latente », définie sur base d'une RVP au pic d'effort > 1.74 WU.

En plus, nous avons réalisé 2 méta-analyses: i) une méta-analyse sur des études menées chez des patients HFpEF qui ont été soumis au KTD à l'effort, en décrivant la méthodologie du KTD à l'effort, le profil clinique et hémodynamique des cohortes HFpEF décrit dans la littérature et extrapolant la pente PAPO/DC; ii) une méta-analyse pour évaluer l'association entre les marqueurs hémodynamiques d'une composant pré-capillaire et le pronostic chez les patients atteints d'un HTP liée à une maladie cardiaque gauche.

RÉSULTATS

Diagnostic de l'HFpEF

Nous avons validé la 2ème et la 3ème étape de l'algorithme HFA-PEFF versus l'hémodynamique à l'effort dans une cohorte de 73 patients consécutifs. La sensibilité de la 2ème étape de l'algorithme HFA-PEFF était faible (45%) malgré une bonne spécificité (100%), et ses performances diagnostiques ne se sont pas améliorées après l'ajout de la 3ème étape, c'est-à-dire l'échocardiographie à l'effort (sensibilité 46%, spécificité 88%). La sensibilité de la 2ème étape pourrait être améliorée ($p = 0.08$) en abaissant le seuil pathologique de >4 à >3.

L'hémodynamique à l'effort était fortement dépendante des excursionnes respiratoires : chez 57 patients consécutifs, la pression artérielle pulmonaire et la PAPO mesurées en fin d'expiration étaient supérieures aux valeurs moyennées sur plusieurs cycles respiratoires ($p < 0.05$), ce qui a conduit à une plus grande proportion de patients dépassant le seuil pathologique en fin d'expiration (70 % vs 53 %, $p < 0.01$). Les critères

diagnostiques basés sur l'hémodynamique à l'effort qui ont été proposés pour identifier l'HFpEF (PAPO au pic d'effort ≥ 25 mmHg ; pente PAPO/DC > 2 mmHg/L/min ; RVP totale au pic d'effort > 3 WU avec une PAPO au pic d'effort > 20 mmHg) étaient concordants seulement chez le 70% des patients. La pente PAPO/DC était le paramètre le plus sensible, intégrant plus de 97% des réponses hémodynamiques anormales.

Nous avons constaté une hétérogénéité significative dans la méthodologie et l'interprétation du KTD à l'effort, ainsi que dans les valeurs absolues de PAPO mesurées au pic d'effort (I2 = 93 %), chez des cohortes de 2180 patients HFpEF et de 680 patients avec une dyspnée d'origine non-cardiaque étudiées sur base d'une revue de la littérature dans 27 études. La pente PAPO/DC était plus raide chez les patients du groupe HFpEF que chez les patients du groupe contrôle (3.75 [3.20–4.28] contre 0.95 [0.30–1.59] mmHg/L/min, $p < 0.0001$), même après ajustement pour les covariables ($p = 0.007$).

L'exactitude et la précision de la PAPO pour estimer la PTDVG pendant l'effort ont été évaluées dans une cohorte de 46 patients consécutifs qui ont été soumis à un cathétérisme cardiaque droit et gauche à l'effort. La PAPO estime la PTDVG avec un biais minimal mais de grands intervalles de confiance (± 11 mmHg). En conséquence, 11 % des patients présentaient une discordance entre la PTDVG et la PAPO au pic d'effort. Dans ces cas discordants, la pente PAPO/DC était toujours > 2 mmHg/L/min.

Suivi des complications et du pronostic de l'HFpEF

Treize patients (14%) parmi 96 HFpEF qui ont été soumis à un KTD à l'effort présentaient une régurgitation tricuspidienne secondaire sévère, qui était secondaire à la dilatation de l'oreillette droite chez 12 patients, définis STR-HFpEF. Ces 12 patients HFpEF-STR, par rapport à 12 patients HFpEF contrôles appariés selon l'âge, le sexe et l'indice de masse corporelle, et sans régurgitation tricuspidienne, présentaient une POD plus élevée (23 ± 2 vs 14 ± 2 mmHg) ainsi qu'un volume éjecté systolique plus faible pendant l'effort (54 ± 10 vs 93 ± 10 mL, $p < 0.05$). Ces caractéristiques étaient associées à un relatif dérecrutement vasculaire pulmonaire, avec augmentation artéfactuelle de la RVP, et à un relatif sous-remplissage du ventricule gauche.

Parmi 86 patients HFpEF, 21% de ceux-ci avaient une « maladie vasculaire pulmonaire latente » (HFpEF latent-PVD). Les HFpEF latent-PVD présentaient une RVP > 2 UW au repos dans 78 % des cas. L'évolution de la RVP

à l'effort différait entre les HFpEF latent-PVD et les HFpEF sans « maladie vasculaire pulmonaire latente » (HFpEF-contrôles), augmentant légèrement chez les premiers et se réduisant chez les seconds (interaction p = 0.008).

Les HFpEF latent-PVD présentaient plus fréquemment une HTP à l'effort (94 % contre 60 %), des signes hémodynamiques compatibles avec une régurgitation tricuspidienne sévère pendant l'effort (50 % vs 16 %, p < 0.01) et une plus faible réserve de DC et de volume d'éjection systolique à l'effort (p < 0.05). Enfin, le groupe des HFpEF latent-PVD avait une survie sans événement plus faible par rapport aux HFpEF-contrôles (72% contre 93% à 3 ans, test du log-rank p = 0.004).

Dans une métanalyse incluant 16 études et 9600 patients, la RVP a été identifiée comme un marqueur pronostique important chez les patients atteints d'HTP liée à une maladie du cœur gauche (RVP: risque relatif: 1.07; intervalle de confiance à 95 %: 1.05-1.08). Des résultats similaires ont été obtenus en subdivisant les cohortes en fonction de la maladie du cœur gauche sous-jacente, comprenant l'HFpEF.

Nous avons pu déterminer les limites supérieures de la normale pour le comportement de la POD pendant l'effort (POD > 12 mmHg au pic d'effort, pente POD/débit cardiaque > 1.3 mmHg/L/min) chez 21 patients souffrant de dyspnée d'origine non cardiaque, et nous les avons appliquées à une cohorte de 30 patients avec HTP liée à une HFpEF (PH-HFpEF) et de 30 patients avec de l'hypertension artérielle pulmonaire (HTAP). Les PH-HFpEF présentaient une POD au pic d'effort et une pente POD/DC plus élevés que les HTAP (20 [16-24] vs 12 [9-19] mmHg et 3.47 [2.02-6.19] vs 1.90 [1.01-4.29] mmHg/L/min, p < 0.05). Une proportion plus élevée des PH-HFpEF avait une pente POD/DC et une POD au pic d'effort supérieures à la limite supérieure de la normale (p < 0.001). Dans l'ensemble de la cohorte, des facteurs liés à la précharge du VD se sont avérés associés à la pente POD/DC, tels que l'âge, le taux d'augmentation du « stressed blood volume » estimé pendant l'effort, la présence d'une régurgitation tricuspidienne sévère et la dilatation de l'oreillette droite.

CONCLUSIONS

Les tests non invasifs se sont révélés spécifiques, mais peu sensibles pour identifier l'HFpEF précoce, soulignant la nécessité d'une évaluation invasive. L'hétérogénéité méthodologique et interprétative dans la

réalisation du KTD à l'effort pour le diagnostic de l'HFpEF pourrait être résolue en utilisant comme critère diagnostic une pente PAPO/DC > 2 mmHg/L/min, qui est sensible, relativement indépendante de la position du corps pendant l'effort, et des variations respiratoires, permettant de surmonter les limites liées à une valeur isolée de la PAPO au pic d'effort.

Au-delà de la PAPO, le KTD met en évidence les complications liées à la progression de l'HFpEF. L'analyse de l'évolution et de la forme d'onde de la POD pendant l'effort permet de démasquer la défaillance du VD précocement, de mettre en évidence les mécanismes physiopathologiques sous-jacents liés à la précharge du VD, et de révéler les conséquences hémodynamiques de la régurgitation tricuspidienne sévère chez les patients HFpEF.

En plus, non seulement la RVP au repos, mais également la RVP à l'effort permettent d'identifier un sous-groupe de patients HFpEF présentant une maladie plus avancée, ainsi qu'une moins bonne adaptation hémodynamique à l'effort et un pronostic plus défavorable.

Il ruolo dell'emodinamica da sforzo

nell'insufficienza cardiaca a frazione di eiezione preservata

ABSTRACT

INTRODUZIONE

La diagnosi di insufficienza cardiaca a frazione di eiezione preservata (HFpEF) può essere difficile utilizzando test non invasivi, specialmente in fase precoce di malattia. Il cateterismo cardiaco destro (RHC) da sforzo è stato proposto come il test diagnostico di riferimento per identificare l'HFpEF. Tuttavia, ad oggi né la metodologia del RHC né la sua l'interpretazione e la definizione dell'HFpEF sulla base dell'emodinamica da sforzo sono stati standardizzati. Inoltre, l'HFpEF è una malattia progressiva, con un rischio intrinseco di sviluppare nel tempo delle complicanze potenzialmente impattanti sulla prognosi, tra cui l'insufficienza tricuspidale (TR) severa, lo sviluppo di una componente pre-capillare all'ipertensione polmonare (PH), e la progressiva disfunzione del ventricolo destro (RV). Tuttavia, le conseguenze emodinamiche dell'HFpEF rimangono oggi non completamente descritte né comprese in modo esauriente.

OBIETTIVI

L'obiettivo di questa tesi di dottorato era dimostrare come l'emodinamica possa contribuire alla diagnosi precoce di HFpEF, all'identificazione di diversi fenotipi di malattia con un profilo sfavorevole ed alla stratificazione prognostica.

METODI

Abbiamo eseguito 6 analisi retrospettive di dati raccolti in coorti di pazienti che sono sottoposti a una valutazione approfondita, compreso RHC da sforzo, per dispnea da sforzo non spiegata o nel sospetto di PH, tra il 2006 e il 2021.

In particolare, ci siamo interessati a: i) la diagnosi precoce di HFpEF, basata sul comportamento delle pressioni di riempimento del cuore sinistro, ovvero pressione di incuneamento capillare polmonare (PAWP) durante l'esercizio, sia in termini assoluti sia normalizzata per gittata cardiaca (CO), della pressione telediastolica del

ventricolo sinistro (LVEDP), anche in relazione agli score diagnostici non invasivi, quali il H_2FPEF o l'HFA-PEFF score; ii) l'individuazione precoce della disfunzione ventricolare destra e la valutazione dell'impatto emodinamico della TR severa nei pazienti HFpEF, sulla base del comportamento della pressione atriale destra (RAP) durante esercizio, analizzandone sia il valore assoluto, sia le onde V, sia la pendenza della relazione RAP/CO; iii) la rilevanza clinica e prognostica dello sviluppo di una componente pre-capillare della PH, sulla base dell'analisi della resistenza vascolare polmonare (PVR) sia a riposo sia durante esercizio.

Inoltre, abbiamo eseguito 2 metanalisi: i) una su studi condotti in pazienti HFpEF sottoposti a RHC da sforzo, per descrivere metodologie procedurali, profilo clinico ed emodinamico dei pazienti HFpEF, ed estrapolare la pendenza della relazione PAWP/CO dai dati disponibili; ii) una per valutare l'associazione tra gli indici emodinamici di componente pre-capillare della PH e la prognosi in pazienti con PH legata a malattia del cuore sinistro.

RISULTATI

Diagnosticare l'HFpEF

Abbiamo validato il 2° e il 3° step del HFA-PEFF score contro il RHC da sforzo in una coorte di 73 pazienti consecutivi. La sensibilità del 2° step dello score era subottimale (45%) nonostante una buona specificità (100%), e la performance diagnostica dello score non migliorava dopo l'aggiunta del 3° step, ovvero l'ecocardiografia da sforzo (sensibilità 46%, specificità 88%). La sensibilità del 2° step potrebbe essere parzialmente migliorabile ($p = 0.08$) abbassando la soglia patologica da >4 a >3.

Abbiamo evidenziato quanto l'emodinamica da sforzo sia fortemente dipendente dalle escursioni respiratorie: in 57 pazienti consecutivi, la pressione arteriosa polmonare e la PAWP misurate a fine espirazione sono risultati superiori ai valori mediati su più cicli respiratori ($p < 0.05$). Conseguentemente, una maggiore proporzione di pazienti superava la soglia patologica considerando le misure a fine espirazione vs quelle mediate (70% vs 53%, $p <0.01$). I criteri diagnostici basati sull'emodinamica da sforzo proposti per identificare l'HFpEF (PAWP al picco ≥ 25 mmHg; PAWP/CO slope > 2 mmHg/L/min; resistenza polmonare totale al picco >

3 WU con PAWP al picco > 20 mmHg) erano concordanti solo nel 70% dei pazienti. La PAWP/CO slope risultava il parametro più sensibile, includendo oltre il 97% delle risposte emodinamiche anomale.

Abbiamo riscontrato una significativa eterogeneità nella metodologia e nell'interpretazione del RHC da sforzo in 2180 pazienti HFpEF e 680 pazienti con dispnea non cardiogena riportati in 27 studi, nonché nei valori assoluti di PAWP misurati al picco dell'esercizio (I2 = 93%). La PAWP/CO slope è risultata più ripida negli HFpEF rispetto ai controlli (3.75 [3.20–4.28] vs 0.95 [0.30–1.59] mmHg/L/min, p < 0.0001), anche dopo aggiustamento per le covariate (p = 0.007).

L'accuratezza e la precisione della PAWP nella stima della LVEDP durante sforzo sono state valutate in una coorte di 46 pazienti consecutivi sottoposti a cateterismo cardiaco destro e sinistro durante sforzo. La PAWP stimava la LVEDP con un minimo bias, ma con ampi intervalli di confidenza (±11 mmHg). Di conseguenza, vi era discordanza tra la PAWP e la LVEDP al picco dello sforzo nell'11% dei casi. In questi casi discordanti, la PAWP/CO slope era sempre > 2 mmHg/L/min.

Tracciare le complicanze e la prognosi dell'HFpEF

Tredici pazienti (14%) su 96 HFpEF che sono stati sottoposti a RHC durante sforzo presentavano una TR severa secondaria, in 12 casi di natura atriogenica, definiti HFpEF-STR. Questi 12 HFpEF-STR, rispetto a 12 "controlli" HFpEF senza TR ed abbinati per età, sesso e indice di massa corporea, presentavano durante esercizio una RAP più elevata (23 ± 2 vs 14 ± 2 mmHg) nonché una minore gittata sistolica (54 ± 10 vs 93 ± 10 mL, p < 0.05). Tutto ciò si associava ad un relativo dereclutamento vascolare polmonare, con un aumento "artefattuale" della PVR, e ad un riempimento ventricolare sinistro deficitario.

Tra 86 HFpEF, i pazienti con PVR > 1.74 durante esercizio ("malattia vascolare polmonare latente" o HFpEF latent-PVD) erano il 21%. Gli HFpEF latent-PVD presentavano nel 78% dei casi una PVR > 2 WU a riposo. Il comportamento della PVR differiva tra HFpEF latent-PVD e HFpEF controlli: nei primi PVR aumentava modestamente durante sforzo, mentre diminuiva nei secondi (p-value interazione=0.008).

Gli HFpEF latent-PVD presentavano più frequentemente PH durante l'esercizio (94% vs 60%), segni emodinamici di TR severa (50% vs 16%, p < 0,01) e minore riserva di gittata cardiaca e di gittata sistolica

durante l'esercizio ($p < 0.05$). Infine, il gruppo latent-PVD risultava avere una sopravvivenza libera da eventi inferiore rispetto ai controlli (72% vs 93% a 3 anni, log-rank test $p = 0.004$).

In una metanalisi di 16 studi su 9.600 pazienti con PH secondaria a malattia del cuore sinistro, la PVR si è confermata un consolidato indicatore prognostico (rischio relativo: 1.07; intervallo di confidenza al 95%: 1.05-1.08). Risultati simili sono stati ottenuti suddividendo le coorti in base alla patologia cardiaca sinistra sottostante, incluso l'HFpEF.

Da 21 pazienti con dispnea non cardiogena abbiamo derivato il limite superiore di norma di RAP durante sforzo (RAP > 12 mmHg al picco, RAP/FO slope > 1.3 mmHg/L/min), per poi applicarlo ad una coorte di 30 pazienti con PH-HFpEF e 30 con ipertensione arteriosa polmonare (PAH). I PH-HFpEF presentavano una RAP più elevata al picco e una RAP/CO slope più ripida rispetto ai PAH (20 [16-24] vs 12 [9-19] mmHg e 3.47 [2.02-6.19] vs 1.90 [1.01-4.29] mmHg/L/min, $p < 0.05$). Una percentuale maggiore di PH-HFpEF aveva una RAP/CO slope e un RAP al picco superiore alla norma ($p < 0.001$). Nell'intera coorte, la RAP/CO slope era associata all'età e ad una serie di fattori correlati al precarico ventricolare destro, come l'entità di incremento dello "stressed blood volume" durante l'esercizio, la presenza di una TR severa e la dilatazione atriale destra.

CONCLUSIONI

I test diagnostici non invasivi sono specifici ma poco sensibili nell'identificare l'HFpEF in fase precoce, evidenziando la necessità di una valutazione invasiva. L'eterogeneità metodologica ed interpretativa del RHC da sforzo finalizzato all' individuazione di HFpEF potrebbe essere risolta utilizzando come criterio diagnostico una PAWP/CO slope > 2 mmHg/L/min. Tale parametro è risultato molto sensibile, relativamente indipendente dalla posizione del corpo durante l'esercizio e dalle variazioni respiratorie, consentendo di superare i limiti legati ad un valore isolato di PAWP al picco.

Oltre alla PAWP, il RHC consente di captare le complicanze legate alla progressione dell'HFpEF. L'analisi del comportamento durante sforzo della RAP e della sua forma d'onda consente di smascherare precocemente la disfunzione ventricolare destra, di evidenziare i meccanismi fisiopatologici sottostanti precarico-relati, e di rivelare le conseguenze emodinamiche della TR severa nell'HFpEF.

Inoltre, le PVR non solo a riposo, ma anche da sforzo consentono di identificare un sottogruppo di pazienti HFpEF con malattia più avanzata, nonché un peggiore adattamento emodinamico all'esercizio fisico e una prognosi più sfavorevole.

ABBREVIATIONS

AF = atrial fibrillation

Avg = averaged over respiratory cycles

BMI = body mass index

BNP= brain natriuretic peptide

CAD = coronary artery disease

CI = cardiac index

CO = cardiac output

COPD = chronic obstructive pulmonary disease

CpcPH = combined post and pre-capillary pulmonary hypertension

DPG = diastolic pressure gradient

DSE = diastolic stress echocardiography

ERS = European Respiratory Society

ESC = European Society of Cardiology

Exp = end-expiratory

HF = heart failure

HFA = Heart Failure Association

HFA-PEFF = Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final etiology

HFpEF = heart failure with preserved ejection fraction

HR = heart rate

IpcPH = isolated post-capillary pulmonary hypertension

LA = left atrium

LAVI = left atrial volume index

LAP = left atrial pressure

LHD = left heart disease

LV = left ventricle

LVEDP = left ventricular end-diastolic pressure

LVEDVI = left ventricular end-diastolic volume index

LVEF = left ventricular ejection fraction

mPAP = mean pulmonary artery pressure

NCD = non-cardiac dyspnea

NT-proBNP = N-terminal pro-brain natriuretic peptide

NYHA FC = New York Heart Association functional class

O_2 = oxygen

PAC = pulmonary artery compliance

PAH = pulmonary arterial hypertension

PAP = pulmonary artery pressure

PAWP = pulmonary artery wedge pressure

PH = pulmonary hypertension

PH-HFpEF = pulmonary hypertension due to heart failure with preserved ejection fraction

PVD = pulmonary vascular disease

PVR = pulmonary vascular resistance

RA = right atrium

RAP = right atrial pressure

RHC = right heart catheterization

RV = right ventricle

RVD = right ventricular dysfunction

RVEF = right ventricular ejection fraction

RVF = right ventricular failure

SBV = stressed blood volume

SD = standard deviation

STR = secondary tricuspid regurgitation

SV = stroke volume

TA = tricuspid anulus

TPG = transpulmonary pressure gradient

TPR = total pulmonary resistance

TR = tricuspid regurgitation

TV = tricuspid valve

VHD = valvular heart disease.

VO_2 = oxygen consumption

BACKGROUND

HFpEF EPIDEMIOLOGY

Heart failure with preserved ejection fraction (HFpEF) is considered the actual public health burden of the Western World, associated with disabling symptoms and morbi-mortality [1]. By the year 2030, the prevalence of HFpEF in the US is projected to reach approximately 4 million cases, representing about 1.5% of people [1,2]. In Europe, 4.9% of people aged > 60 years were identified to have HFpEF, implying several millions of affected individuals [3].

HFpEF DEFINITION

2021 European Society of Cardiology (ESC) guidelines definition

Definition of HFpEF is based on a simplified pragmatic approach, widely available to clinicians, including clinical picture of heart failure (signs, symptoms) in presence of a preserved left ventricular (LV) systolic function (left ventricular ejection fraction, LVEF, ≥ 50%) and of LV diastolic dysfunction/raised LV filling pressure including raised natriuretic peptides (**figure 1**) [4].

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

Figure 1. Definition of heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) [4].

Existing HFpEF definitions correspond to successive stages along the HFpEF timeline

Despite this growing epidemic, the definition of HFpEF has remained problematic, with lack of consensus between societal organizations and large outcome trials [4]. The challenge of a satisfactory definition of HFpEF was highlighted by the existence of more than 7 definitions, including 3 societal definitions based on expert consensus (American College of Cardiology/American Heart Association, ACC/AHA, 2013, European Society of Cardiology, ESC 2016, Heart Failure Society of America, HFSA, 2010) and 4 sets of trial entry criteria (Irbesartan in HF and PRESERVed Ejection fraction, I-PRESERVE trial, Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction, RELAX trial, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist, TOPCAT trial, and Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction, PARAGON trial) [5]. Ho et al reported the mortality rates of the 7 HFpEF populations showing a progressive decline from TOPCAT to ACC/AHA, with the first having the highest (6.56 per 1000 person-years), and the latter the lowest (0.46 per 1000 person-years) death incidence rates (**figure 2**). It becomes evident that the 7 populations assess HFpEF at different time points along the HFpEF timeline, with ACC/AHA at the earliest and TOPCAT at the most advanced time (**figure 3**) [5,6].

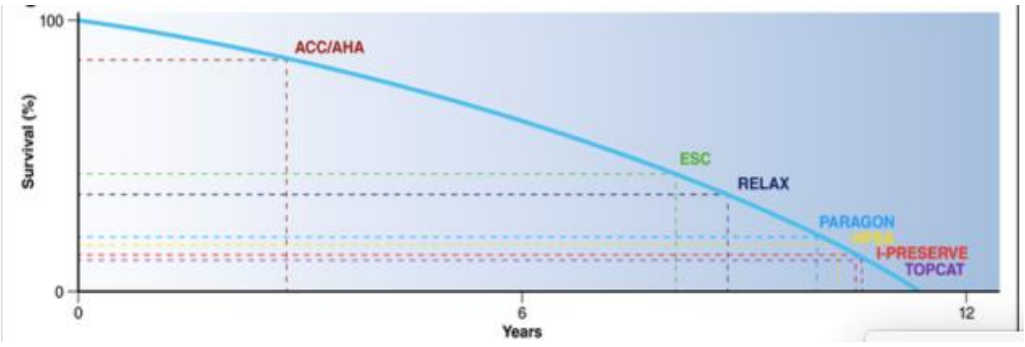


Figure 2: Schematic survival curve of HFpEF according to 7 existing definitions of the disease. Mortality rates equal the slope of the tangents to the survival curve and decline from TOPCAT to ACC/AHA [5]

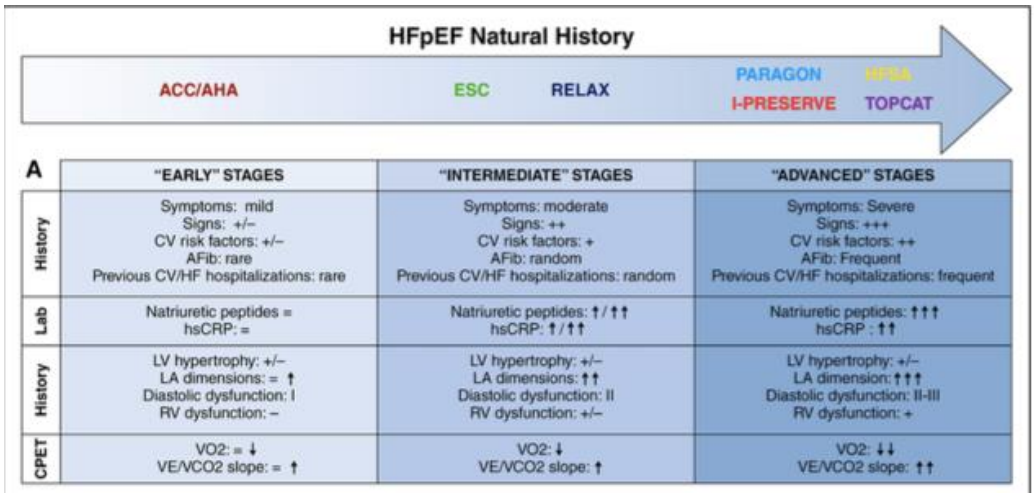


Figure 3: Successive stages of disease severity that can be described on clinical basis according to a noninvasive multiparametric assessment including clinical history, blood tests, echocardiography, and cardiopulmonary exercise test [5].

This interpretation would suggest that HFpEF has a natural history that ends with the overt stages of the disease, when traditional diagnostic criteria are largely fulfilled. The natural HFpEF history thus begins in the so-called “early stages”, in which neither clinical evaluation, echo, natriuretic peptides nor functional tests are yet pathognomonic, that typically represents the most underdiagnosed and unrecognized phase of the disease.

“Early” HFpEF

Identification of HFpEF relies on history of exertional symptoms coupled with evidence of congestion which may be absent among outpatients (**figure 4)** [7]. The absence of indicators of congestion is not useful for excluding HFpEF, especially in obese patients [8]. This is partly related to low sensitivity of these estimations, given that approximately one-third of HFpEF patients develop hemodynamic alterations only during exercise [9].

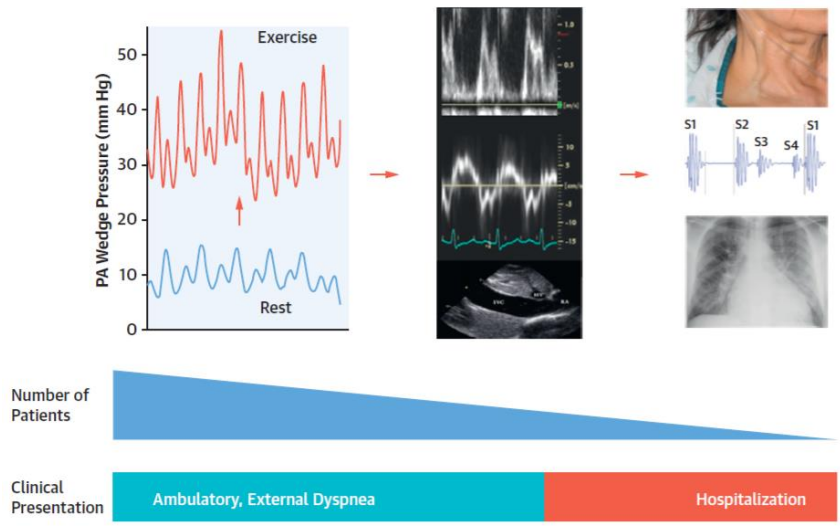


Figure 4. Clinical presentation of heart failure with preserved ejection fraction (HFpEF). Patients with earlier stage HFpEF display elevation in pulmonary artery wedge pressures (PAWP) only during exercise (red tracing), despite normal values at rest (blue tracing). With more dramatic elevation in cardiac filling pressure at rest, evidence of congestion becomes apparent at rest, with elevation in the E/e' ratio and dilation/loss of collapsibility of the inferior cava. Patients with the most overt congestion present with jugular distention, S3 gallops, and radiographic edema. These patients typically require hospitalization and represent only a small fraction of the broader HFpEF spectrum [7].

Thus, in patients with complaining effort symptoms, the invasive exercise test (i.e. the right heart catheterization, RHC) is considered the gold standard exam to diagnose or exclude HFpEF, providing objective evidence of congestion, even intermittent [7]. Recent evidence suggested that "early" HFpEF could be highly prevalent, however remaining yet an insidious disorder, diagnosed too late. An early HFpEF diagnosis would potentially allow personalized treatment of risk factors and comorbidities as well as defining follow-up, in order to limit disease progression and hospitalizations, and promptly treat complications. Nowadays the problem of HFpEF under-recognition is even greater, given the emergence of new therapies, pharmacological or not, as potentially highly effective treatments [7].

HFpEF PATHOPHYSIOLOGY

HFpEF was considered to be characterized by diastolic dysfunction caused by hypertensive LV remodeling in isolation ('diastolic heart failure'). Over the past 2 decades, the predominant clinical phenotype in HFpEF has shifted from older adults with isolated hypertensive heart disease to multimorbid patients with obesity, diabetes, and metabolic syndrome, focusing greater attention toward systemic inflammation, endothelial dysfunction, altered myocardial energetics, and muscular abnormalities [10].

HFpEF is suggested to be characterized by proinflammatory state with increased oxidative stress and depressed nitric oxide signaling, promoting the development of microvascular endothelial dysfunction [10,11]. Furthermore, extracardiac mechanisms contribute to the HFpEF pathophysiology, including abnormalities in conduit arterial vessels [12], the endothelium and microvasculature [13], skeletal muscle [14], lung [15], kidney [16], and adipose tissue, especially among patients with excess visceral fat [17]. The role of the obesity promoting a cardiometabolic syndrome was recently explored, highlighting that obese HFpEF patients display higher and an abnormal distribution of blood volume, contributing to elevated filling pressures, and partly related to an impaired venous capacitance [8, 18]. Moreover, autonomic dysfunction is common, promoting chronotropic incompetence, blunted arterial baroreflex sensitivity [19], and abnormalities in venous capacitance [18].

Thus, HFpEF is nowadays conceptualized as a concertation of pathophysiological phenotypes, where different alterations from a cellular, organ, and tissue basis, and multiple mechanisms, such as LV diastolic dysfunction, ventricular stiffening, endothelial dysfunction, obesity-related cardiometabolic stress, interact in a complex fashion to cause the typical hemodynamic abnormalities [7].

HFpEF DIAGNOSIS

Non-invasive assessment: ASE/EACVI criteria, H_2FPEEF score, HFA-PEFF algorithm

The American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) proposed in 2015 a comprehensive examination incorporating several echocardiographic data, given that no one single variable is sufficiently accurate to be used in isolation to make a diagnosis of diastolic dysfunction. As shown in **Figure 5**, features considered key structural alterations are: a left atrial volume index (LAVI) > 34 mL/m^2 or a left ventricular mass index (LVMI) ≥ 115 g/m^2 for males and ≥ 95 g/m^2 for females. Key functional alterations are an E/e' ≥ 13 and a mean e' septal and lateral wall < 7 and < 10 cm/s, respectively. Other derived measurements are LV longitudinal strain or tricuspid regurgitation velocity (TRV) [20].

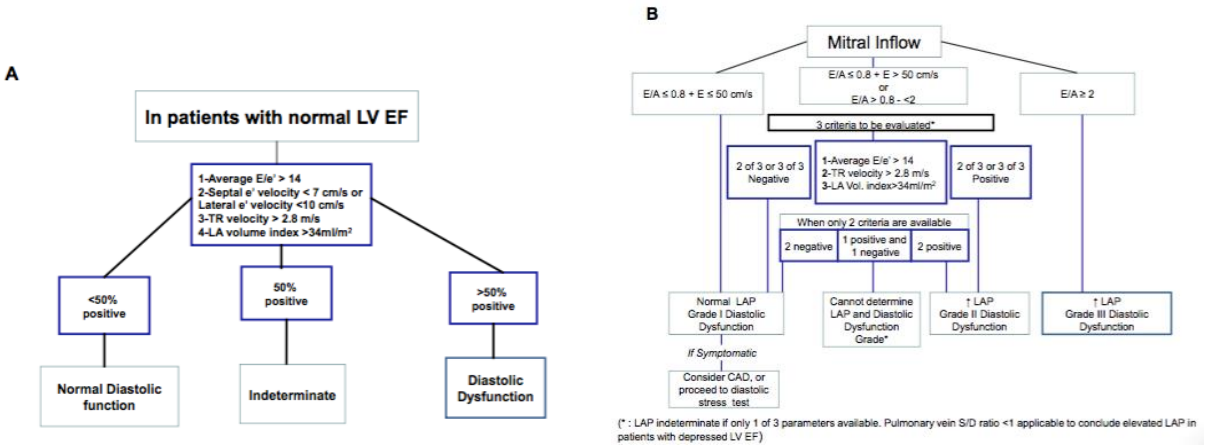


Figure 5: (A) Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF. (B) Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEF and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data [20].

However, these diagnostic criteria vary widely in their sensitivities and specificities for diagnosing HFpEF, making the diagnosis further challenging. More recently, two score-based algorithms have been proposed to aid the diagnosis and to improve the diagnostic power of non-invasive algorithm to identify HFpEF [21,22].

In 2018, Reddy et al derived a score using clinical and echocardiographic including obesity, arterial hypertension, atrial fibrillation, systolic PAP > 35 mmHg, E/e' > 9, age > 60 years, called H_2FPEF score (**figure 6**). The authors derived the score by analyzing data from consecutive patients in whom the diagnosis of HFpEF

was ascertained conclusively by invasive exercise testing, and then validated this new scoring system in a separate cohort. They showed that, using simple and available in daily practice characteristics, the probability that HFpEF is present can be accurately estimated in the patient presenting with exertional dyspnea [21].

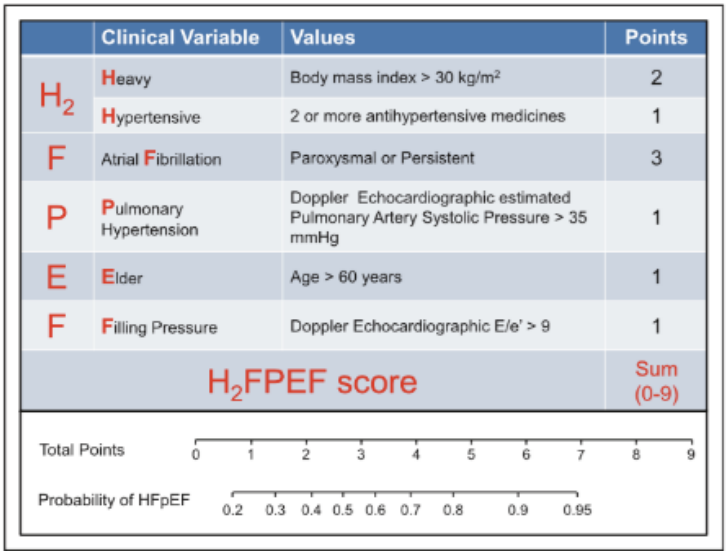


Figure 6. Description of the H_2FPEF score and point allocations for each clinical characteristic (top), with associated probability of having HFpEF based on the total score as estimated from the model (bottom) [21].

Additionally, a writing committee initiated by the Heart Failure Association (HFA) of the ESC has produced an updated consensus recommendation, the HFA–PEFF diagnostic algorithm, where the PEFF acronym stands for 'Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final etiology', **figure 7**) based on expert consensus [22]. The authors recommended a step-wise diagnostic approach based on a combination of parameters derived from clinical, laboratory, and imaging tests that together will give a probability for the diagnosis.

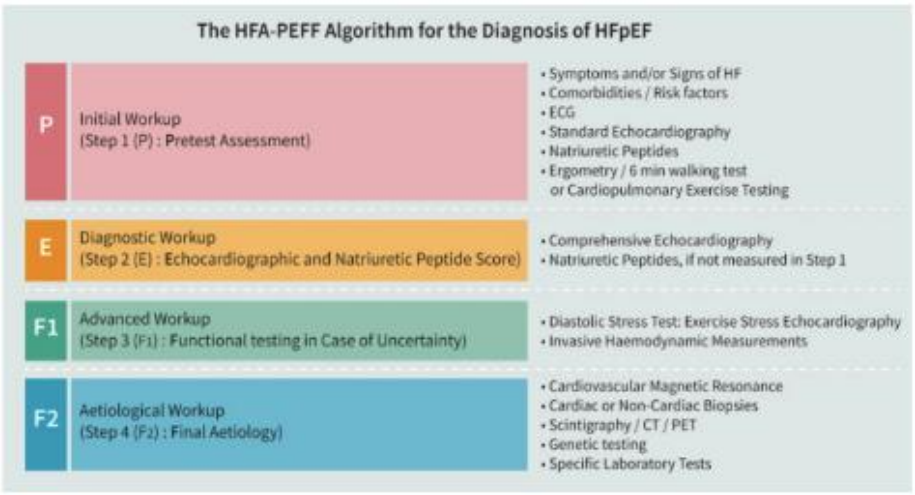


Figure 7: HFA-PEFF diagnostic algorithm. Overview of the diagnostic HFpEF steps 1–4 (P–F) [22].

In particular, the 2nd step of the HFA-PEFF algorithm includes HF symptoms and signs, clinical demographics, and several echocardiographic parameters (E/e', LAVI, LV mass index, LV relative wall thickness, TR velocity), attributing also a relevant complementary role to serum natriuretic peptides levels (**figure 8**).

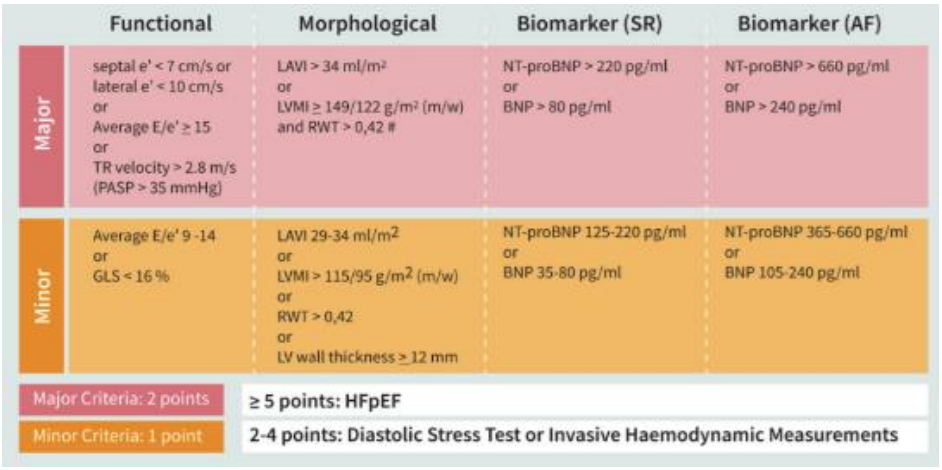


Figure 8: Step 2 of HFA-PEFF (E): Echocardiographic and natriuretic peptide heart failure with preserved ejection fraction workup and scoring system [22].

When individuals fall in the intermediate-risk category, it is required to move on with the 3rd step of the algorithm, that is the use of additional (functional) tests to confirm or exclude the diagnosis of HFpEF. In particular, a diastolic stress echocardiography (DSE) might be used as an additional non-invasive tool before considering rest/exercise RHC [6, 23].

When comparing the results from invasive exercise hemodynamics with the diagnostic power of these 2 non-invasive scores, it emerges that both the H_2FPEF and the HFA-PEFF algorithms had good accuracy and specificity to discriminate patients with HFpEF from non-cardiac dyspnea (NCD) (**figure 9**) [24,25]. False-positive rates were low for both algorithms in the rule-in range, in particular looking at the H_2FPEF score, which provides a good diagnostic accuracy despite the requirement of fewer input variables than the HFA-PEFF [24].

However, both scores are characterized by low sensitivity, witnessed by a non-negligible rate of false-negative results, up to 47% for the H_2FPEF and 61% for the HFA-PEFF score. Authors showed that, in daily practice, we can potentially have a high rate of false-negative results among patients deemed to be at low probability of HFpEF (up to 55% with the HFA-PEFF score and up to 25% with the H_2FPEF score).

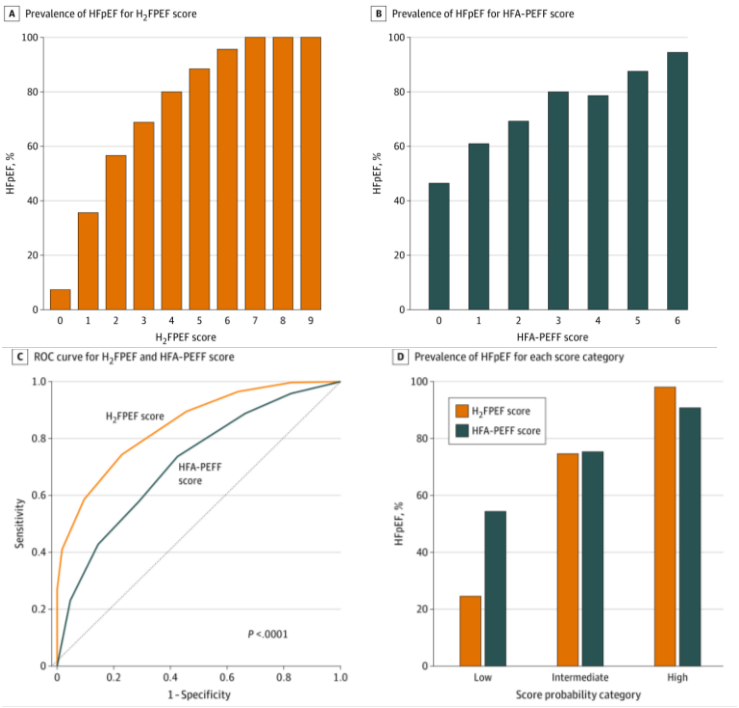


Figure 9. Comparison of H_2FPEF and HFA-PEFF scores for diagnosis of HFpEF. H_2FPEF and HFA-PEFF scores of 0 to 1 indicated a low probability of HFpEF; H_2FPEF scores of 6 to 9 and HFA-PEFF scores of 5 to 6 indicated a high probability of HFpEF. Intermediate probability of HFpEF required additional exercise testing for diagnosis. C, the p-value is for the difference in area under the curve between scores. ROC indicates receiver operating characteristic [24].

Ù

Limits of non-invasive diagnostic scores

Quite often, at the time of a decompensated HF, patients report a long history of unexplained exertional dyspnea, whose earlier phase of HFpEF remained poorly characterized. As anticipated above, non-invasive diagnostic criteria applied at rest may miss a large proportion of diagnosis, especially in early phase.

Long before manifest alterations, the left heart in HFpEF loses its ability to maintain low filling pressures while trying to meet the increased demands of exercise. In this field physical exercise represents the most physiological provocative test for the heart which, stressing the cardiovascular system to its limit, allows to unmask the typical hemodynamic maladaptation to exercise. Applying Braunwald's definition of heart failure, HFpEF could be configure as a syndrome where the heart may be able to meet the peripheral metabolic needs only at the expenses of high filling pressure [26].

Due to the poor sensitivity of clinical and non-invasive diagnostics, mandating the need for an invasive test in case of non-conclusive results, invasive hemodynamic testing plays a key role in obtaining a definite and definitive HFpEF diagnosis.

Exercise RHC as the gold standard test to diagnose HFpEF

More than 10 years ago, findings supporting the existence of an earlier or milder stage of HFpEF, characterized by normal resting but abnormal exercise hemodynamics, were shown by the Mayo Clinic group [23]. They demonstrated that in "early" stage HFpEF, hemodynamic evidence of volume overload and diastolic dysfunction is present only during the stress of exercise, as shown in **figure 10**.

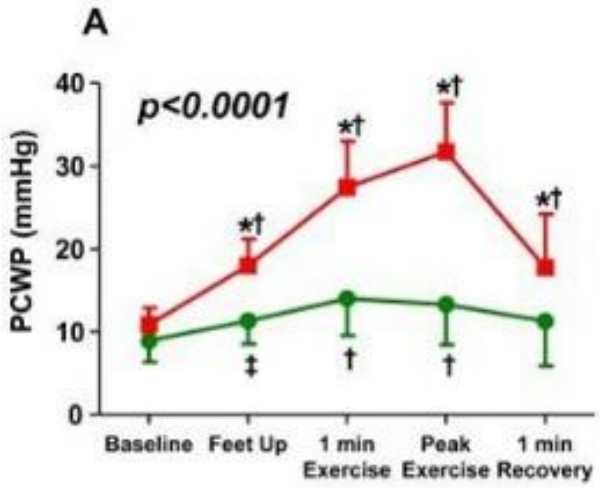


Figure 10: Pulmonary artery wedge pressure (PAWP) increased to a greater extent in HFpEF compared with non-cardiac dyspnea (NCD)with leg elevation and during exercise. PAWP returned to baseline almost immediately in recovery [23].

As such, the diagnosis of HFpEF may only be made by assessing hemodynamic responses during exercise, allowing to identify the actual hemodynamic signature of HFpEF, i.e. the marked increase in filling pressure during exercise, by a direct measure of pulmonary artery wedge pressure (PAWP), as a surrogate for LA pressure) in spite of normal hemodynamics at rest, as represented in **figure 11**. Indeed, the increase in PAWP with leg raise and submaximal exercise along with the increase in pulmonary artery pressure (PAP) with peak exercise, identified HFpEF with greater accuracy compared to conventional, non-invasive testing [23]. The findings reported by Borlaug et al. in 2010 opened a new era in the diagnostic algorithm of HFpEF: they indeed showed that the diagnosis may be missed if one relies exclusively on measures of ventricular function and filling pressures obtained at rest.

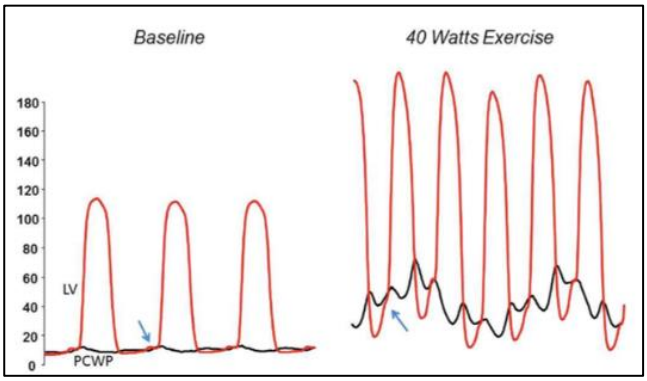


Figure 11: exercise-induced changes in LV filling pressures in patients with heart failure and normal LVEF. Patients with normal EF and exertional dyspnea displayed normal ventricular filling pressures (i.e., LV end-diastolic pressure, LVEDP, and PAWP) at rest (left) but marked elevation on exercise (right), making the positive diagnosis of HFpEF as the cause of dyspnea [23].

However, even if in recent years the dynamic measure of PAWP has been claimed as the key measurement to identify HFpEF, actually there is still insufficient evidence supporting specific threshold for abnormal PAWP during exercise. So far, indeed, there are three main approaches which have been proposed to diagnose HFpEF based on exercise hemodynamics.

Existing hemodynamic definitions of HFpEF: Borlaug, Eisman and Herve's proposals

Based on evidence coming from data obtained in healthy young subjects in the 1960s to 1980s, where PAWP did not trespass 20 to 23 mmHg, Borlaug et al in 2010 defined HFpEF by an end-expiratory PAWP ≥ 25 mmHg at peak exercise in the supine position in patients complaining exertional breathlessness, as represented in **figure 12**.

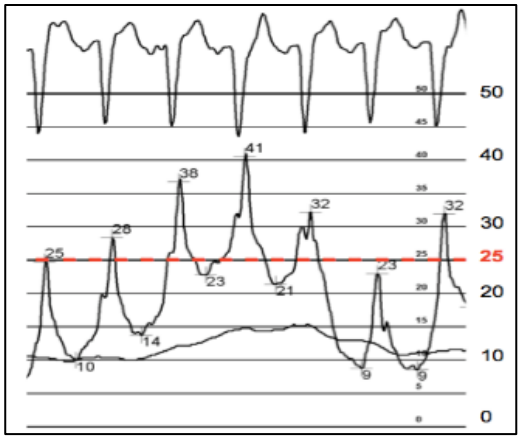


Figure 12: Original example of a PAWP pressure traces at peak of exercise with an end-expiratory PAWP ≥ 25 mmHg in one representative patient, suggestive per HFpEF according to Borlaug's definition.

However, PAWP can be time-variant and age-dependent, and it was shown that a not negligible proportion of apparently healthy elderly subjects can develop PAWP values above 25 mmHg during exercise [27,28].

Moreover, pulmonary pressures are flow dependent; the exercise-induced pulmonary hypertension (PH) might indeed be best defined according to the ratio between mean PAP and cardiac output (CO) during supine exercise [29]. Thus, a more physiologically sound approach might consider the kinetics of PAWP increase throughout exercise. Accordingly, in 2018 Eisman et al proposed to normalized PAWP increase for CO increase, defining an end-expiratory PAWP/CO slope > 2 mmHg/L/min as an abnormal hemodynamic response indicative of HFpEF, as represented in **figure 13**. Even though this definition was done "a priori" (i.e. 2 standard deviations above the mean among control subjects), they could prove its prognostic implications, conferring per se a significant albeit low risk of cardiovascular hospitalization and death, consistent with an insidious, early stage and slowly progressing disease [30,6].

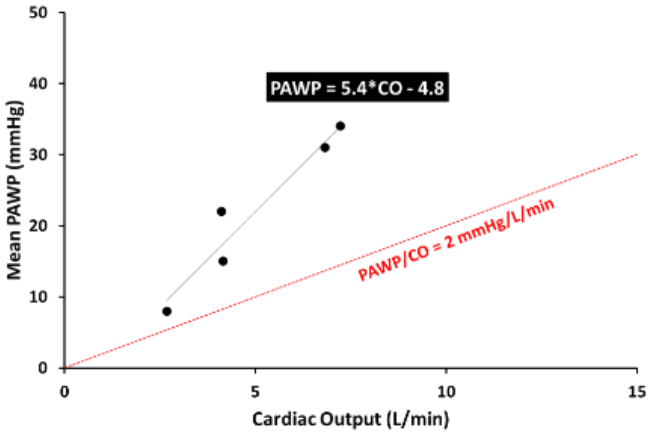


Figure 13: PAWP versus CO measurements through exercise in a representative patient (original data). The dotted line represents a PAWP/CO slope of 2.0 mmHg/L/min.

As already mentioned, another way to describe an abnormal hemodynamic response is by analyzing mean PAP (mPAP) behavior during exercise in relationship with CO variations [31]. Indeed, PH during exercise has been defined by Herve's et al as a mPAP > 30 mmHg (averaged over several respiratory cycles) with a ratio between mPAP and CO (total pulmonary resistance, TPR) at peak exercise > 3 WU. This hemodynamic diagnosis is not disease-specific, but can result either from abnormal PAWP increase in left heart disease (LHD) or from inability to reduce pulmonary vascular disease (PVR) in pulmonary vascular diseases [32]. Thus,

in order to define exercise-induced PH due to HFpEF, Herve et al combined this definition with an averaged PAWP at peak > 20 mmHg (**figure 14**).

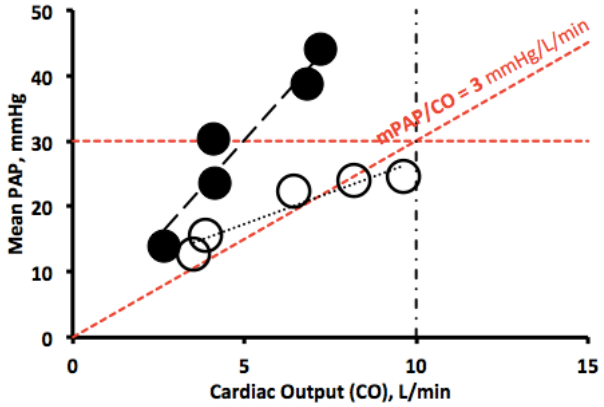


Figure 14: mPAP versus CO measurements through exercise of two exemplificative patients (original data). The dotted line represents a mPAP/CO slope of 3.0 mmHg/L/min. Two mPAP/CO slopes from two exemplificative patients are represented, in white the normal one, and in black the abnormal one (mPAP/CO slope > 3 mmHg/L/min).

Thus, so far, 3 different approaches have been proposed to diagnose HFpEF based on exercise hemodynamic measurements: end-expiratory PAWP ($PAWP_{exp}$) ≥25 mmHg at peak exercise [23]; $PAWP_{exp}$/CO slope > 2 mmHg/L per minute [6,30]; respiratory-averaged mPAP ($mPAP_{avg}$) > 30 mmHg at peak exercise with a $mPAP_{avg}$/CO ratio (TPR_{avg}) > 3 WU and $PAWP_{avg}$ ≥ 20 mmHg [32].

However, 2 of these criteria, based on peak exercise thresholds, might be highly dependent on the dose of exercise performed. Furthermore, 2 definitions adopt end-expiratory pressure measures while the latter use respiratory-averaged values, although the phase of the respiratory cycle in which measures are performed might lead to different results. Indeed, the extent of concordance of these 3 hemodynamic definitions for HFpEF in the individual patient has never been tested, and in case of discordance among them, there is no indication on how to interpret the test. Finally, the clinical usefulness of the invasive exercise hemodynamics is limited by several methodological issues in pulmonary pressure measurements. They include the effect of respiratory pressure swings (particularly relevant during exercise and in patients with obesity or respiratory diseases), and how to take into account systolic and diastolic PAWP components.

Potential methodological issues in measuring PAWP: pleural pressure respiratory swings systolic and PAWP systo-diastolic components

Regardless of the disease definition, the actual true marker of HFpEF is constituted by an anomalous increase in pulmonary and left filling pressures during exercise, and this is what the exercise RHC has the task of definitively excluding or confirming. However, when evaluating pulmonary and cardiac filling pressures especially during exercise, several potential methodological issues should be acknowledged.

Firstly, the heart and pulmonary vessels are intrathoracic and influenced by the pleural pressure swings (**figure 15**). It is debated whether pulmonary vascular and intracardiac pressure should be measured at end-expiration (when intrapleural pressure should be less negative) or averaged over several respiratory cycles. This issue is particularly relevant for patients with air trapping (e.g. obese, chronic obstructive pulmonary disease, COPD) or during exercise, where end-expiratory values are frequently deemed to overestimate "true" intravascular or intracardiac pressures. Indeed, when dynamic hyperinflation is suspected, e.g. in obese patients, in those with lung disease as well as in patients hyperventilating during exercise, averaging values throughout the respiratory cycle could be advisable to avoid filling pressure overestimation (**figure 16**) **[**33].

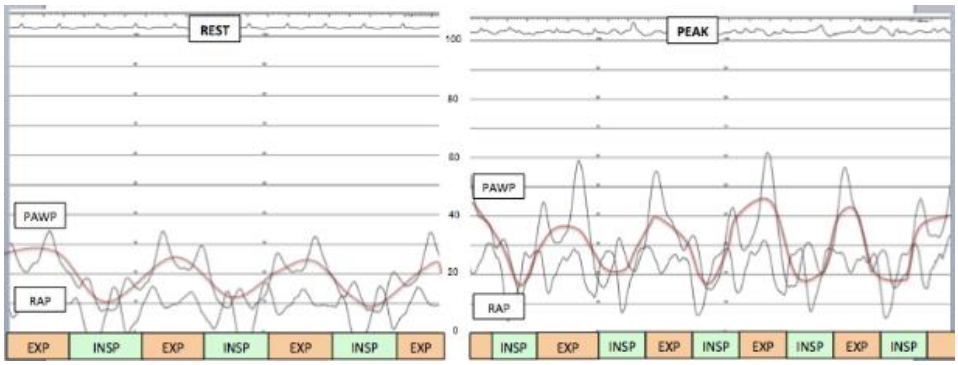


Figure 15: Original PAP and PAWP pressure tracing at rest (left) and with exercise (right), with pleural pressures (red lines) in one exemplificative patient (original data).

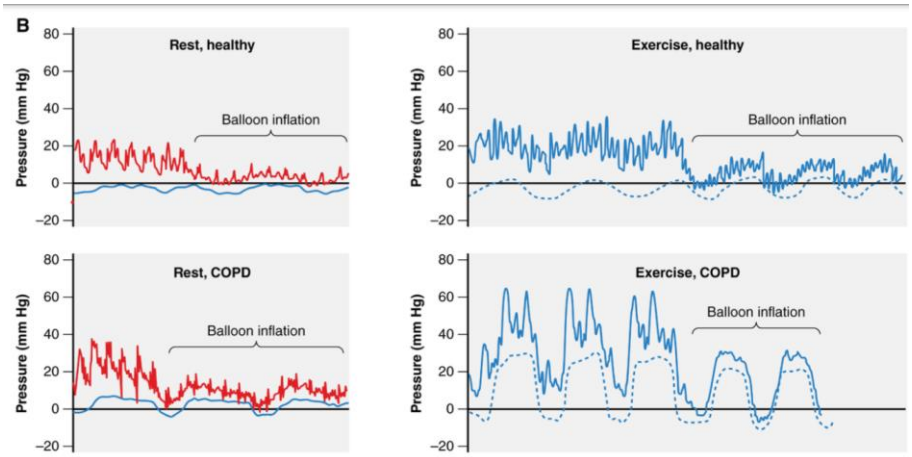


Figure 16: PAP and PAWP tracing at rest (red) and with exercise (blue), with pleural pressures shown below (dashed lines). Pulmonary vascular pressure changes follow pleural pressure changes, which are more pronounced in COPD [33].

CO is generally obtained through several respiratory cycles, and this is why the European Respiratory Society (ERS) suggests averaging pulmonary pressure values over several respiratory cycles during exercise [31]. However, both Borlaug's and Eisman's hemodynamic definition of HFpEF have been based on end-expiratory PAWP values (while Herve's definition of exercise PH has been based on averaged mPAP values) [23,30].

Secondly, PAWP is an atrial pressure waveform, composed by distinct, systolic and diastolic components (V and A wave), reflecting respectively LA compliance and LV diastolic function.

The PAWP A wave represents the increase in pressure in the left atrium during its systole and is an indirect index of left ventricular compliance. It is considered that the average A-wave or its mean value, approximating the pre-C wave at end-diastole, is the best approximation of left ventricular end-diastolic pressure (LVEDP). The PAWP V wave is a systolic event caused by increased pressure in the left atrium due to atrial filling 'against' a closed mitral valve. When it is prominent, it might reflect the presence of mitral regurgitation as well as of LA stiffness. Indeed, a stiff LA, either due to reduced intrinsic compliance (fibrosis) or overdistention (decompensated LV diastolic dysfunction), requires high pressure (hence the V-wave) to be effectively filled during ventricular systole.

Not considering A and V waves and expressing PAWP only as a mean value, could neglect the relative contribution of distinct mechanisms to PAWP increase. QRS gating may facilitate end-diastolic PAWP reading

(ie, the best surrogate for LVEDP), but the use of PAWP averaged over the full cardiac cycle is generally preferred, because V-wave pressure is transmitted upstream to PAP during systole (**figure 17**). Considering that assessment of PAWP only at the end of diastole (mid-A wave) will underestimate mean pulmonary venous pressure, as in the example represented in **figure 18.** Indeed, the presence of tall V waves is generally considered as a sign suggestive for LHD [33].

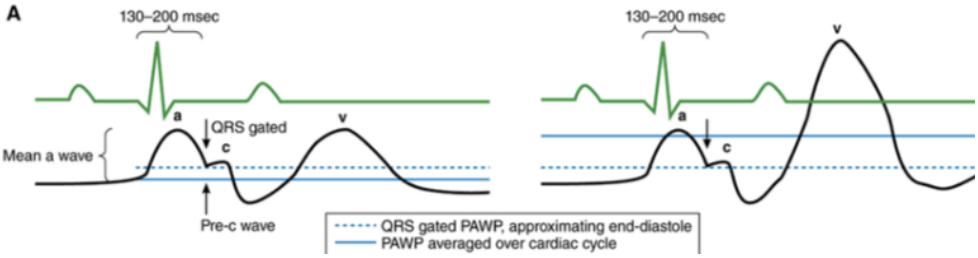


Figure 17. Measurements that approximate end diastole: mean a wave, pre-c wave, and QRS-gated (130–160 ms from the onset of QRS). This value is usually slightly lower than the PAWP averaged over the cardiac cycle (solid line) in the setting of a large V wave [33].

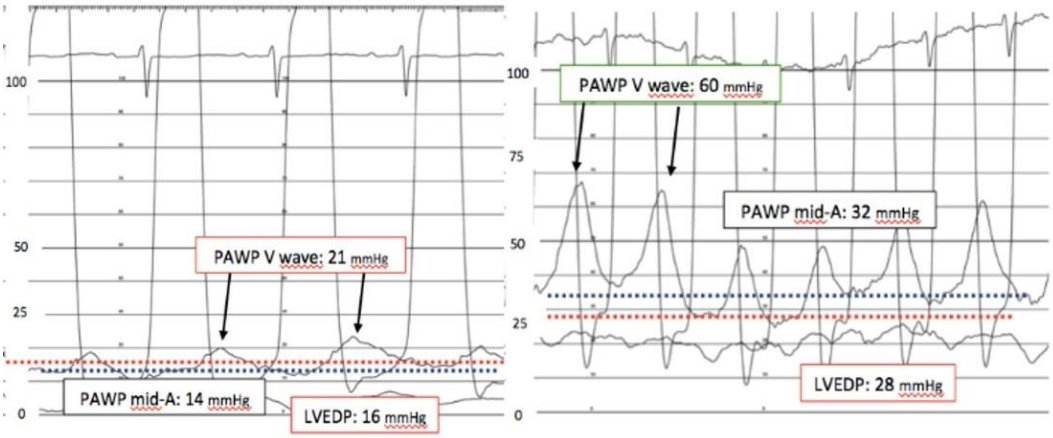


Figure 18. Original PAWP tracing at rest (left) and during exercise (right) in an exemplificative patient, representing an abnormal increase in PAWP with the development of tall V waves.

Thus, despite several recent efforts and research on exercise hemodynamics, the methodology to conduct exercise cardiac catheterization, the way to perform measures and the definition of abnormal responses seem to be far from being clear, straightforward and widely shared across the medical community.

PAWP as a surrogate of LVEDP

In clinical practice the terms 'PAWP' and 'LVEDP' are often used interchangeably to define LV filling pressures but reflect different hemodynamic loads. LVEDP is obtained by a direct measure in the LV by transaortic retrograde left cardiac catheterization. It represents the 'operational' pressure of the LV (**figure 19**), and is considered an index of chamber distensibility and a surrogate for left ventricular preload, simplifying for clinical reasons the concept of LV pressure-volume curve to a single time point (**figure 20**). The more the LVEDP is increased, the more functionally 'stiff' the left ventricular LV chamber will be.

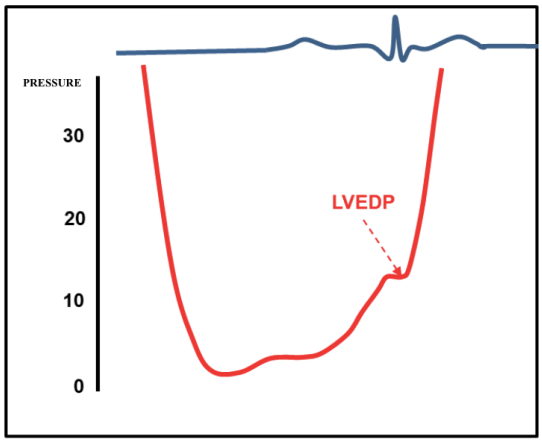


Figure 19. Exemplificative representation of left ventricular end-diastolic pressure (LVEDP). On the LV pressure curve, the end-diastole is the point that precedes the rapid pressure rise in systole.

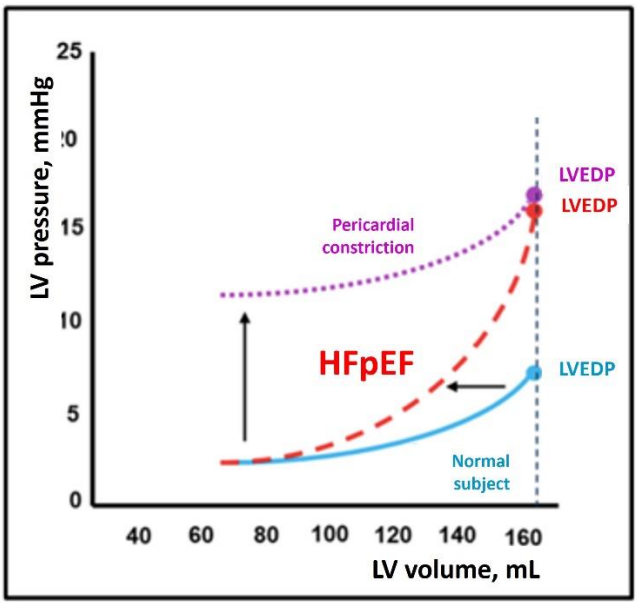


Figure 20: Representative illustration of pressure-volume loop of the LV in diastole. In blue, a normal subject; in red, a subject with HFpEF; in purple, a subject with pericardial constriction. As can be seen from the figure, the subject with HF has a steeper pressure-

volume curve in diastole, shifted to the left, due to lower chamber compliance. The reduced compliance of the LV therefore explains the high-pressure values at the end of diastole. Conversely, the subject with pericardial constriction has an upwardly shifted relation but normal chamber stiffness.

A high resting LVEDP (i.e. ≥ 16 mmHg) in the right clinical context is specific for LV diastolic dysfunction, but a normal LVEDP does not exclude diastolic dysfunction. In analogy to other intrathoracic pressures, also LVEDP is affected by respiratory swings.

Additionally, LVEDP is not routinely measured during exercise. On the other hand, PAWP allows to obtain information on left heart filling pressures by a (much easier) right sided venous access, and through the occlusion of the pulmonary artery with the balloon mounted at the tip of the Swan-Ganz catheter. Thus, downstream pressure, approximating the left atrial pressure, can be measured. Moreover, PAWP describes the cumulative hemodynamic load on the pulmonary circulation as a sum of the functional elements placed in between the LV and the PAWP position where especially the characteristics of the left atrium may contribute to explain occasional differences between PAWP and LVEDP. A stiff atrial chamber can greatly increase the pressures that are transmitted to the pulmonary circulation, and conversely, larger or elastic atrial chambers can store and redistribute pressures to the point of equalization. The result is that in the former example, mean PAWP can be higher than LVEDP, as shown in **figure 281**. This typically happens in patients where the high V-wave alters the PAWP profile.

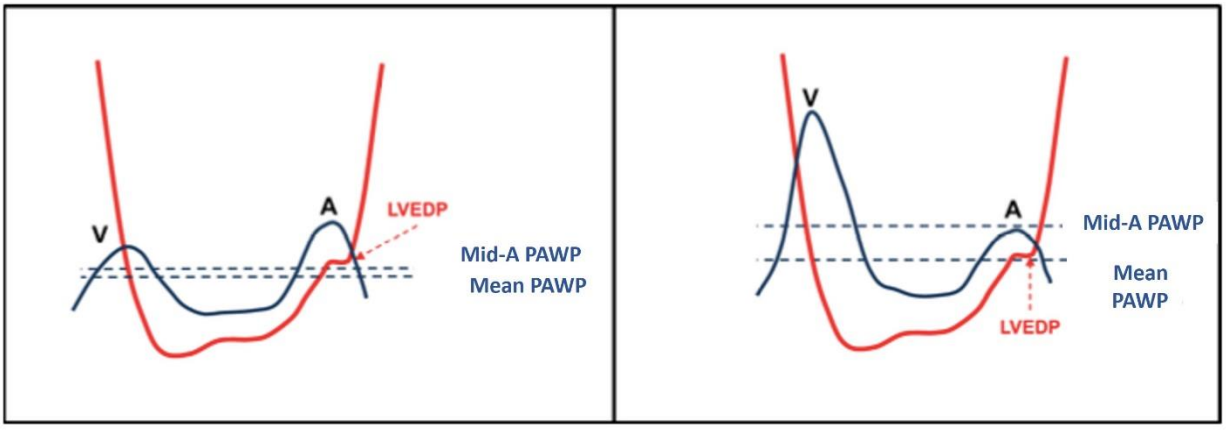


Figure 21. Exemplificative representation pf the difference between PAWP and LVEDP. In the left panel, coincidence of PAWP (taken

as A-wave mean or automated mean) and LVEDP. In the right panel, the automated average PAWP exceeds the LVEDP due to the presence of a high V-wave at the wedge position. However, there is a good match between the mean A-wave and LVEDP.

HFpEF HEMODYNAMIC CONSEQUENCES

Left atrial myopathy

The increase of intracardiac pressures is transmitted backward to the pulmonary veins, pulmonary capillaries and pulmonary arteries, as represented in **figure 22,** especially in presence of a predominant LA dysfunction.

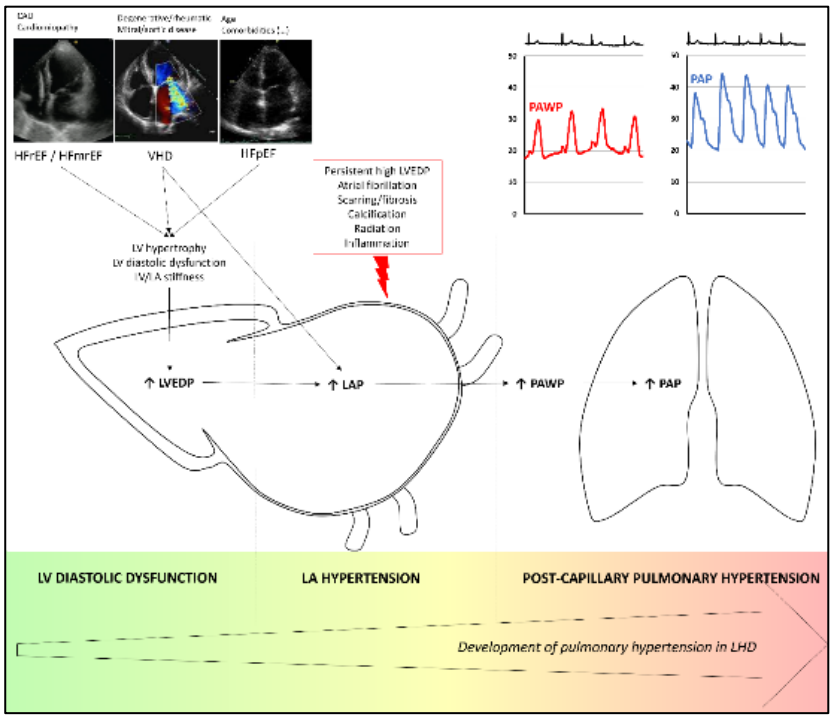


Figure 22. Pathophysiological cascade leading to post-capillary PH, starting from the left heart. Diseases affecting the LV or the left heart valves eventually lead to an increase of LAP, backward transmitting to the pulmonary circulation.

Over time and when atrial fibrillation (AF) and/or LA fibrosis occurs, the LA booster pump function may become compromised, causing high LA pressure (LAP), to maintain LV filling. The increase in LAP becomes evident during the ventricular systole, manifesting as tall V waves in the PAWP position, enhancing the pulsatile load of the pulmonary circulation. This may occur either when the LA becomes “overstretched” and

functionally stiffer due to chronically elevated LVEDP (decompensated LA), or when the LA compliance is intrinsically reduced due to scarring, calcification or fibrosis, which could be an age-related phenomenon, tightly linked to AF, and potentially favored by environmental triggers, such as radiation or inflammation. LA dysfunction is generated by and generates a high-pressure status leading to a vicious circle of further LA remodeling, with progressive dilation and dysfunction [34].

The vicious circle of left atrial myopathy and atrial fibrillation

A dysfunctional LA could promote a pro-arrhythmic substrate and the occurrence of AF, and it has been shown that LA volume and strain may refine the prediction of AF recurrences [35]. Moreover, a strict bidirectional link may be suggested between HFpEF and AF. It has been shown that HFpEF patients may experience over time a progressive increase in AF prevalence, and that AF and HFpEF may often coexist and precipitate each other [36]. In HFpEF patients, the occurrence of AF may be associated with volume expansion, cardiac remodeling with bi-atrial dilation, tricuspid regurgitation (TR), and development of right ventricular dysfunction (RVD) (**figure 23**) [37].

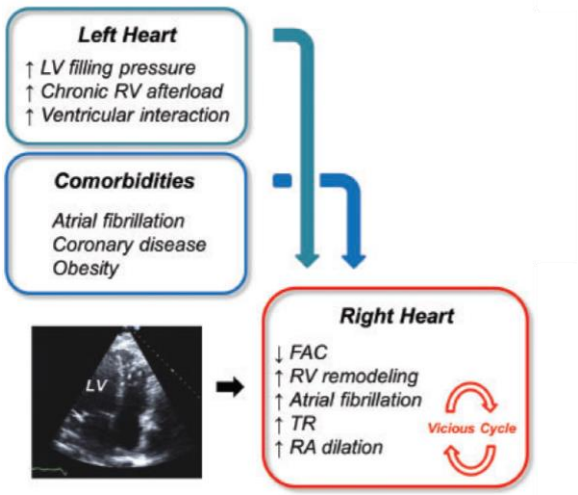


Figure 23. The strict link between high left heart filling pressures and common comorbidities in HFpEF including AF, coronary disease and obesity [37].

Atrial secondary tricuspid regurgitation

Recent findings suggest that AF could lead to several morpho-functional changes not only in the LA, but also in the right atrium (RA) [38-40]. In persistent AF, we could assist to a progressive dilation and the dysfunction of the RA, leading to a dilation as well as decrease (or loss) of the tricuspid annulus (TA) sphincter function. The TA has only a single right fibrous trigone, and is in contact with RA myocardium over the largest part of its circumference. These changes may determine an imbalance between the TA and leaflet areas, resulting in malcoaptation of the tricuspid valve (TV) leaflets, even in the presence of normal RV size and function, leading to an atrio-genic functional/secondary TR in AF patients (**figure 24**) [39].

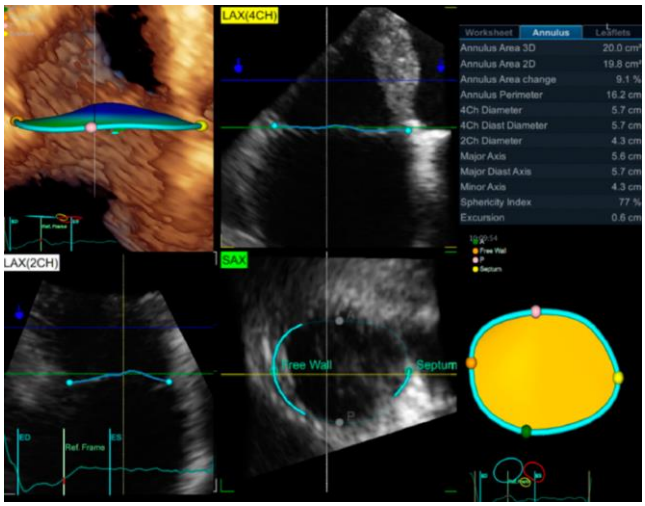


Figure 24. Evaluation of a dilated tricuspid annular size and shape by 3D echocardiography [39].

Moreover, it has been clarified that AF may cause by itself a distinct form of secondary TR (STR) through the prevalent dilation of TA and RA ("atrial STR") [41,42], and AF has been reported as a risk factor itself for STR worsening (**figure 25**) [43].

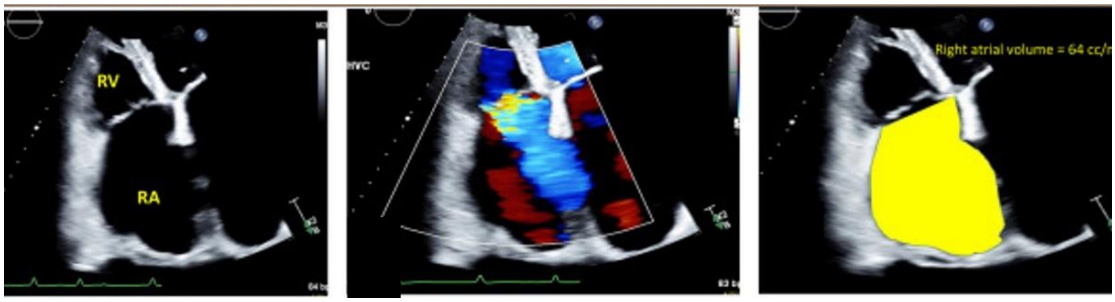


Figure 25. Atrial secondary tricuspid regurgitation in an exemplificative patient. The figure shows a dilated RA (left panel, right panel) in presence of a normal RV and leaflet valve (left panel) determining TA dilation and severe TR (central panel).

Given the strict link between AF and atrial STR as well as between HFpEF, LA myopathy and AF, a high prevalence of patients with HFpEF might be expected among patients with STR, sharing risk factors as well as pathophysiological mechanisms. The association between AF, HFpEF [37] and atrial-STR [39,41,42] has been already shown; moreover, the long-standing HFpEF may induce PH [29], which might predispose to and perpetuate ventricular STR [38,40]. Thus, the clinical manifestations of HFpEF and severe STR may overlap and "confound" each other.

Pulmonary hypertension: the progression from isolated post-capillary (IpC) to a combined post- and pre-capillary (CpC) PH in HFpEF

The passive backward transmission of high left heart filling pressures to the pulmonary circulation could lead to the development of an isolated postcapillary PH presentation, defined by a mPAP > 20mmHg and a PAWP > 15 mmHg according to the last PH guidelines in 2022 [29]. As a consequence of endothelial dysfunction with an imbalance between vasodilation/vasoconstriction and growth factor signaling, pulmonary vascular remodeling may eventually occur also in HFpEF, mainly and firstly on the pulmonary venous side. Repetitive and sustained elevation of pulmonary capillary pressure could promote several alterations to the alveolo-capillary membrane, from interstitial oedema up to a rupture (capillary stress failure). The series of injury-repair cycles of the membrane, leading to collagen deposition, alveolar septal thickening and cellular proliferation will impair capillaries' diffusion efficiency. The occurrence of both arteriolar and venular remodeling has been associated with increased PVR and pulmonary pressure gradients, as well as a (further) reduction of pulmonary artery compliance (PAC) [9,44,45]. It has already shown that the development of a phenotype of combined post and precapillary PH (CpcPH) may expose patients to a poorer [46]. A recent meta-analysis, indeed, highlights that hemodynamic indexes of the presence of a pre-capillary component of

PH, including the diastolic pressure gradient (DPG), PVR and PAC, appeared to be associated with mortality in more than 2500 PH due to LHD patients [46]. This linear association between higher PVR and adverse clinical outcomes [47] recently led the European Society of Cardiology to lower the threshold to identify the precapillary component of PH (PVR > 2 WU), reintroducing PVR alone to differentiate IpcPH to CpcPH.

HFpEF with a "latent" pulmonary vascular disease (PVD)

In 2022, a randomized sham-controlled trial evaluated the efficacy of the atrial shunting through the implant of an interatrial device (Corvia Medical device, Inc IASD System II) to reduce elevated LAP in HFpEF [48]. However, it emerged that atrial shunting did not provide clinical benefit, leading to an increase in pulmonary blood flow, even reducing LAP. Authors speculated that this latter effect may be poorly tolerated in patients presenting with a sort of "pre-capillary" component unmasked by exercise. Soon after, Borlaug and colleagues conducted a post-hoc analysis of the REDUCE LAP HF II trial, comparing outcomes and characteristics of patients with or without "latent PVD", defined by PVR ≥ or < 1.74 WU (highest tertile) at peak exercise [49].

The authors demonstrated that the "latent PVD" phenotype identify a worse clinical and hemodynamic profile of HFpEF patients, characterized by a poorer prognosis and a poorer response to the creation of an interatrial septal defect than HFpEF non latent-PVD [49]. Better understanding the pathophysiology of specific hemodynamic HFpEF profiles, such as the "latent-PVD", may potentially help the design of ad hoc treatment for subgroups of patients at higher risk of adverse events and without any available treatment strategy.

Right heart failure in HFpEF

Since 2010s, studies have shown that a significant number of HFpEF patients display RVD [37]. It is well known that right heart failure (RHF) represents the final step of different distinct diseases, and that is associated with a dismal prognosis also in HFpEF patients, which suffer from high morbidity and mortality after the occurrence

of RVD [37,50]. RVD could be considered to be a reflection of greater disease progression in the HFpEF syndrome.

Obokata et al. described the prevalence and the incidence of RVD and its impact on outcomes in 271 HFpEF patients, showing on average a significant decline in RV systolic function over a median of 4.0 (2.1–6.1) years, with a 2.5-fold increase in the prevalence of RVD. Moreover, the occurrence of RVD over time was associated with a nearly two-fold increased risk of death. Numerous features including AF, higher body weight, coronary artery disease (CAD), adverse hemodynamics, and RV dilation were independently associated with development of RVD, supporting the notion that more "severe" HFpEF patients are more likely to develop incident RVD over time (**figure 26**) [37].

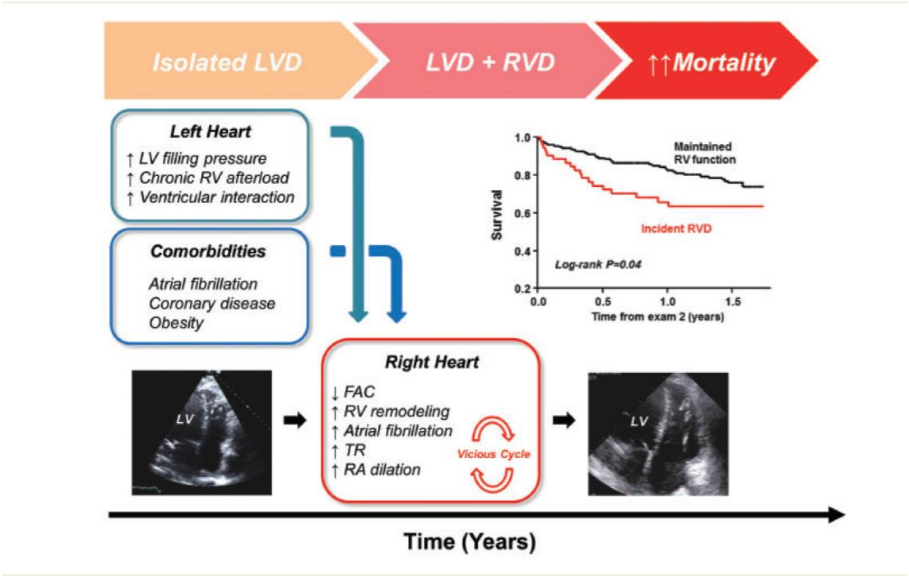


Figure 26. RVD develops over time in patients with HFpEF that initially present with isolated LV dysfunction, and changes in RV structure and function greatly exceed changes observed in the left side of the heart in these more advanced phases of disease. Development of RVD is related to elevated pulmonary artery and left heart filling pressures, as well as common comorbidities in HFpEF including AF, CAD, and obesity [37].

Pathophysiology of RVD in HFpEF: RV afterload-mediated mechanism

The RV is thought to adapt PH by an early increase in contractility (homeometric adaptation or Anrep effect), followed by remodeling (hypertrophy) and dilation (heterometric adaptation or Starling effect). However, the

complex shape of the RV is generally not thought to be well suited to cope with sustained increase in afterload, becoming dysfunctional over time. Mechanisms underlying RV failure could be depending on afterload-mismatch, as well as on preload-mediated mechanisms [51].

In HFpEF, the PAWP increase augments the pulsatile load of the pulmonary circulation, and shifts downward the PAC-PVR relationship, so that at any given resistive load, the PAC will be lower, and the pulsatile load will be higher [52]. This mechanism has been used to explain the prognostic role of PAC also in patients without PH at rest. Furthermore, the development of a pre-capillary PH component augments the pulmonary vascular resistive load, being associated with a larger prevalence of RV dilation and dysfunction [53] (**figure 27**). Thus, PH could be an important mediator of RVD. However, the development of RHF could be not simply explained by PH alone in HFpEF.

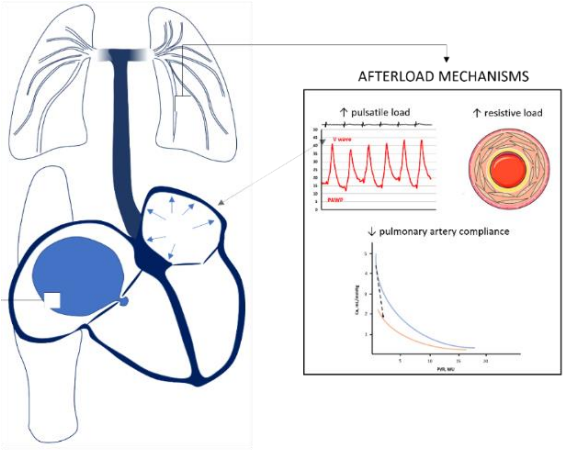


Figure 27. Representation of the RV afterload-dependent mechanisms of RHF.

The role of preload and HFpEF's relative hypervolemia

It has been described that HFpEF patients are subject to progressive RV adverse remodeling over time, with deleterious changes in wall stress and chamber geometry, TA dilation and consequent TR, leading to a vicious distortion of the TV apparatus, is extremely frequent in patients with HFpEF, and may contribute to a pre-load dependent mechanism of RV failure, with RV dilation and impaired RV stroke volume (SV). Atrial STR occurs mainly due to RA enlargement, favored by volume overload and bi-atrial dilation accompanying any forms of AF, with consequent TA dilation. Once developed, secondary TR could impair forward SV and promote RA and

venous hypertension, further volume overload and enhanced ventricular interdependence, impairing LV filling. Thus, mechanisms relatively independent from RV afterload may contribute to explain the pathophysiology underlying RVD in HFpEF, and the role of preload dependent RVD during exercise has been recently investigated in HFpEF.

Indeed, cardiac filling pressures increase as total blood volume (TBV) increases, but the distribution of blood in the circulation may be even more important. TBV is functionally divided into an unstressed blood volume (UBV) pool, which 'fills' the vascular space just to the point of developing wall tension and intravascular pressure, and the stressed blood volume (SBV) pool, which is the volume of blood that increases wall tension and contributes to pressure. The distribution between SBV and UBV is regulated by the autonomic nervous system: sympathetic outflow causes venoconstriction mobilizing blood from the hepato-splanchnic venous reservoir to the central circulation, reducing systemic venous capacitance to increase SBV. Central venous pressure (CVP) accordingly increases as SBV rises, but CVP is also influenced by the compliance properties of the central veins and the ability of the right heart to discharge blood and perfuse the lungs, measures that could be impaired in HFpEF [18].

Sorimachi et al. showed that HFpEF, particularly obesity-related, presented greater increases in estimated SBV (eSBV) at rest and especially during exercise [18]. During physical activity, venous return to the heart is enhanced through the combined pumping actions of skeletal muscle and the venoconstriction in the abdominal capacitance veins. In healthy subjects, venous capacitance is high, meaning that SBV is low also during exercise, when the increase in venous return is accompanied by a significant increase in CO and only mild increase in CVP (**figure 28**), thanks to enhanced inotropy, chronotropy, and vasodilatation. At variance, in HFpEF, venous capacitance is reduced shifting blood from the UBV to the SBV, increasing mean systemic filling pressure, reflected by a rightward shift in the venous return curve at rest. During exercise, a greater increase in SBV was observed in HFpEF patients than controls (**figure 28**), resulting in a greater rightward shift in the venous return curve [18, 54].

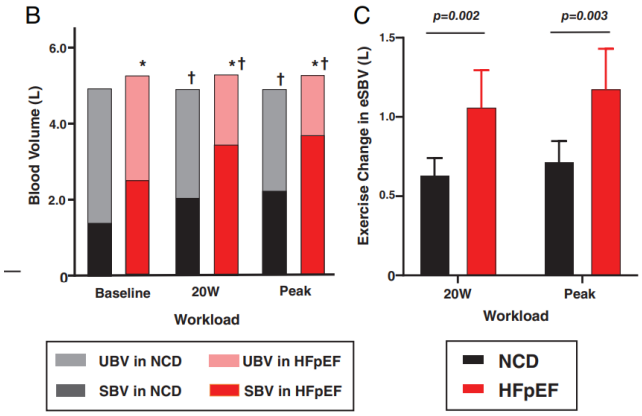


Figure 28. Panel B. Stressed blood volume (SBV) was greater in HFpEF patients compared with NCD at rest and during exercise. SBV increased significantly with exercise in both groups. Panel C. The absolute SBV change with exercise from baseline was greater in the HFpEF group compared with non-cardiac dyspnea (NCD). †p <0.05 vs. baseline in SBV. *p <0.05 vs. NCD in SBV [18].

CO increases minimally with respect to the increase in CVP, and relative to SBV, suggesting that the heart is operating on the plateau of the Starling curve, where further increases in CO are not achieved with venoconstriction. Authors shown that SBV was greater in HFpEF compared to NCD, and the ratio of eSBV to TBV was greater, implying an abnormality in systemic venous capacitance. Despite the greater augmentation in eSBV to facilitate venous return, the inability to augment CO suggests an impaired Frank-Starling adaptative mechanism in HFpEF patients during exercise. These recently described findings provide new evidence on the preload factors-related RVD in HFpEF including also extracardiac contributors, such as the venous dysfunction, mirroring the previously described increases in arterial stiffness in this syndrome [12] (**figure 29**).

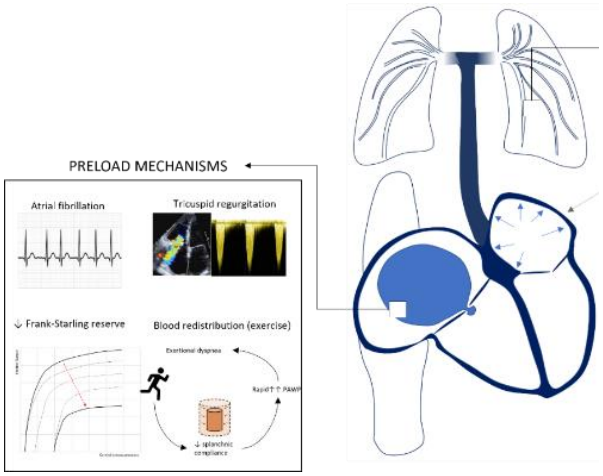


Figure 29. Representation of the RV preload-dependent mechanisms of RHF.

OBJECTIVES

GAPS IN EVIDENCE

I. The H_2FPEF score has been derived and validated against exercise RHC. The HFA-PEFF algorithm has not been derived from exercise RHC. The second step of the HFA-PEFF algorithm may have a lower sensitivity than the H_2FPEF score, with many individuals falling in the intermediate-risk category, requiring moving on with the third step using additional (functional) tests. However, the HFA-PEFF algorithm (and in particular the third step of the algorithm) has not been validated against RHC.

II. Exercise RHC has been proposed as the gold standard test to identify HFpEF. However, 3 different approaches have been proposed to diagnose HFpEF based on exercise hemodynamic measurements, whose concordance in the individual patient has never been tested, and in case of discordance among them, there is no indication on how to interpret the test.

III. The procedural approach of exercise RHC across laboratories all over the world, including patients' body position and exercise protocol as well as the hemodynamic measurements and their interpretation, has not been standardized and may vary widely. The HFpEF patients' populations in literature may thus present with different hemodynamic characteristics, depending on way of measurements and definitions adopted in each center.

IV. PAWP during exercise, as a surrogate for LVEDP, is used to diagnose HFpEF. All this reasoning is based upon the assumption that PAWP approximates LVEDP. However, LVEDP reflects LV diastolic stiffness more directly than PAWP, while PAWP reflects the hemodynamic load imposed by the left heart on the pulmonary vascular bed and on the right heart. Thus, it might be supposed that, during exercise, PAWP and LVEDP may disagree.

V. Among patients with STR, a high prevalence of patients with HFpEF might be expected because of common risk factors such as elderly age, AF, PH, leading to an overlap and "confusion" between each other. However, the net hemodynamic effect of developing STR in patients with an underlying hemodynamic abnormality, such as HFpEF, has not been clarified.

VI. Exercise PVR >1.74 WU may identify a worse clinical and hemodynamic phenotype of HFpEF patients, called HFpEF with latent PVD. In consequence, there is a need to better understand the pathophysiology of patients with HFpEF and an overt or latent precapillary component, which may help the design of ad hoc treatment for this subgroup of patients at higher risk of adverse events and without any available treatment strategy.

VII. Several hemodynamic parameters have been proposed to identify a more severe profile of PH due to LHD, although their association with outcome has led to contrasting results, where PVR and PAC seemed to be more strongly associated with outcome than DPG.

VIII. Development of RHF in HFpEF is associated with a dismal prognosis, highlighting the need for an early identification. Exercise RHC may unmask right heart maladaptation as a sign of early RHF, however, neither the cut-offs for RA pressure (RAP) rise during exercise, nor the patterns of right heart adaptation to exercise in HFpEF as well as their determinants, have been fully described

AIMS

To try to fill these gaps in evidence, aims of our studies were to:

I. provide a validation of the three-step HFA-PEFF score vs. invasive resting and exercise hemodynamics (study 1, HEMO-VALIDATION study);

II. evaluate the concordance of the 3 proposed definitions for an abnormal hemodynamic response to exercise consistent with HFpEF in patients with unexplained dyspnea, to lead to unequivocal confirmation or exclusion of HFpEF when performing exercise RHC (study 2, DISCORDIA study);

III. describe the exercise hemodynamics profile of HFpEF cohorts reported in literature, in order to compare exercise RHC results of patients evaluated in different centers, potentially adopting distinct procedural and interpretative protocols (study 3, EX-PEF meta-analysis);

IV. assess the validity of the PAWP as an estimate of the LVEDP during exercise (study 4, EX-LVEDP study);

V. explore the impact pf STR on hemodynamic and cardiopulmonary adaptation to exercise in patients with HFpEF (study 5, STR-HFpEF study);

VI. explore the clinical characteristics of HFpEF patients with latent PVD, as well as hemodynamic and cardiorespiratory adaptation to exercise of this peculiar phenotype (study 6, LATENT-PVD study);

VII. provide an updated analysis on the association of hemodynamic variables, such as PVR, PAC and DPG, with prognosis in PH-LHD (study 7, PROGNOSIS-PH meta-analysis);

VIII. define the normal limits of RAP increase during exercise, and describe the extent and the frequency of right heart maladaptation to exercise in HFpEF and in pulmonary vascular diseases, as well as the factors associated with right heart maladaptation (study 8, RETRO-RIGHT study).

METHODS AND RESULTS

METHODOLOGICAL OVERVIEW OF ORIGINAL STUDIES

Since some of the above-mentioned original studies (HEMO-VALIDATION, DISCORDIA, EX-LVEDP, STR-HFpEF, LATENT-PVD, RETRO-RIGHT) share similar study population, a methodological overview in inclusion and exclusion criteria among the different studies is reported in the following paragraphs.

STUDY POPULATION

Most of our original studies are based on retrospective data obtained from patients referred to our Dyspnea/Pulmonary Hypertension Centers for unexplained exertional dyspnea, i.e. exertional breathlessness not explained by a cardiac, respiratory or musculoskeletal origin, and/or in suspicion of PH. Patients underwent a diagnostic structured work-up including a comprehensive clinical, echocardiographic, ergospirometric and, in absence of diagnostic criteria and univocal conclusive results, an invasive hemodynamic evaluation at rest and during exercise.

Inclusion criteria. HFpEF was defined by signs and/or symptoms of chronic HF, normal LVEF (≥ 50%), and elevated left heart filling pressures at rest (PAWP at rest > 15 mmHg) and/or during exercise (end-expiratory PAWP at peak exercise equal or higher than 25 mmHg, and/or PAWP/CO slope higher than 2 mmHg/L/min). Specific HFpEF populations, such as STR and latent PVD, as well as control groups (NCD, PAH) were included in some studies (STR, LATENT-PVD, and RETRORIGHT respectively), and explained below in their respective sections.

Exclusion criteria. We excluded patients with reduced LVEF(< 50%); valvular heart disease (any valvular stenosis, > moderate left-sided valvular regurgitation); secondary forms of HFpEF (restrictive, hypertrophic, or infiltrative cardiomyopathy); myocardial ischemia, congenital heart disease, constrictive pericarditis; unstable patients (non-elective hospitalization, rapid worsening of symptoms, hemodynamic compromise); patients with severe comorbidities (chronic obstructive pulmonary disease with Global Initiative for Chronic

Obstructive Lung Disease, GOLD, classification ≥ 3, severe restrictive lung disease, severe obesity with body mass index >40 kg/ m^2, severe anemia with hemoglobin < 9 g/dL, end-stage chronic kidney disease).

Furthermore, in all but one study (RETRORIGHT study) we also excluded patients with pulmonary vascular diseases (pulmonary arterial hypertension, pulmonary veno-occlusive disease, chronic thromboembolic PH, chronic thromboembolic disease) and those with pre-capillary PH due to lung disease and/or hypoxia or with PH due to unclear/multifactorial mechanisms.

DATA COLLECTION

Methodological details pertinent to each original study as well as methods and statistics of meta-analysis are reported in the specific sections.

In the following section, methodological details and results pertinent to each study are reported in detail.

INCLUDED STUDIES:

I. **Study 1, HEMO-VALIDATION study [55]**

II. **Study 2, DISCORDIA study [57]**

III. **Study 3, EX-PEF meta-analysis [59]**

IV. **Study 4, EX-LVEDP study [86]**

V. **Study 5, STR-HFpEF study [87]**

VI. **Study 6, HFpEF LATENT-PVD study [92]**

VII. **Study 7, PROGNOSIS-PH meta-analysis [96]**

VIII. **Study 8, RETRORIGHT study [115]**

Study 1: HEMO-VALIDATION of the HFA-PEFF algorithm [55]

METHODS

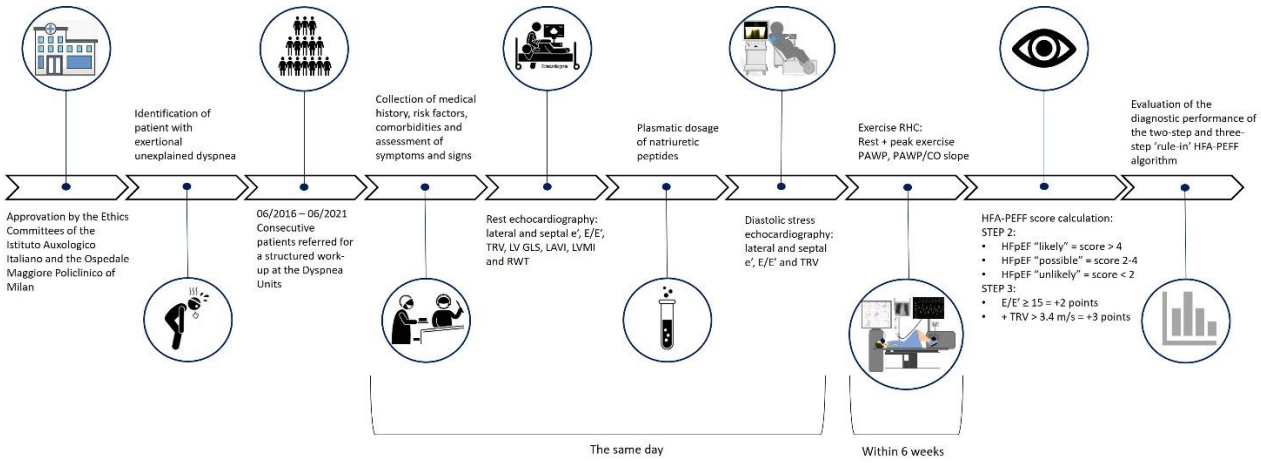


Figure 30. Representation of the HEMO-VALIDATION study design.

Study design

HEMO-VALIDATION study is a multi-centric, retrospective analysis on outpatients with exertional dyspnea underwent a comprehensive diagnostic assessment including exercise RHC. Whitin 6 weeks, patients underwent a non-invasive evaluation including clinical examination, rest echocardiography along with dosage of natriuretic peptides and, on the same day, a diastolic stress echocardiography (DSE). Data were then analyzed to calculate the HFA-PEFF score (both 2nd and 3rd step). The diagnostic performance of the two-step and three-step 'rule-in' HFA-PEFF algorithm was evaluated (**figure 30**).

EC approbation

This study was approved by the Ethics Committees of the Istituto Auxologico Italiano (Protocol No. 2020_04_21_03), Milan, Italy, and the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Ref ID 195/2017), Milan, Italy.

Inclusion criteria

Consecutive patients with exertional dyspnea referred for a structured work-up at the two dyspnea units of the above-mentioned hospitals, who underwent the exams suggested by the HFA-PEFF algorithm.

Clinical assessment and rest echocardiography

Clinical data were extracted from the clinical charts. Echocardiography was performed with a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway) in both recruiting Centers following current recommendations [56]. In particular, items required in the 2nd step of HFA-PEFF algorithm were collected, such as acquisition focused on pulsed wave Doppler of mitral inflow, medial and lateral tissue Doppler of the mitral annulus, TRV, and LV global longitudinal strain, as well as LAVI and LV geometry parameters (LVMI and LV relative wall thickness, LVRWT) [22].

Exercise echocardiography

Exercise echocardiography was performed with a step-incremental protocol on a semi-recumbent cycle ergometer up to exhaustion, with echocardiographic acquisition focused on pulsed wave Doppler of mitral inflow, medial and lateral tissue Doppler of the mitral annulus, and TRV, to collect the items required by the third step of the HFA-PEFF algorithm [22]. The presence of dynamic mitral regurgitation was checked in all patients. Images were stored in digital format for quantitative analysis, which were performed offline by trained personnel, blinded to clinical and hemodynamic data.

HFA-PEFF score calculation

The HFA-PEFF score (two-step) was calculated integrating morphological and functional data coming from echocardiography at rest with natriuretic peptides [22]. An HFA-PEFF score < 2 classifies a low probability of

HFpEF (HFpEF unlikely); score values between 2 and 4 classify an intermediate probability of HFpEF (HFpEF possible); and a score > 4 classifies a high probability of HFpEF (HFpEF likely). Diastolic stress echocardiography was considered positive when E/e' was ≥ 15, conferring 2 points to be added to the score obtained at the second step of the algorithm. When E/e' ≥ 15 is associated with a TR velocity > 3.4 m/s, 3 points can be added to the second-step HFA-PEFF score (**figure 31**) [22].

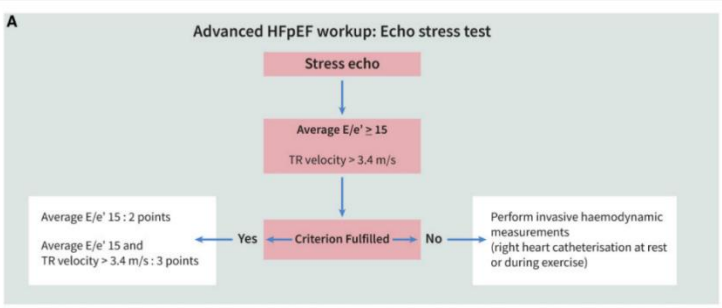


Figure 31. HFA-PEFF score, step 3 (F): Functional tests. It shows the diastolic stress test workup with exercise echocardiography is shown [22].

As measurement of E/e' might not be possible at high heart rate due to fusion of the waves of the mitral inflow pattern, we reported both the maximal workload reached during DSE and the workload at which echocardiographic measures were taken.

Exercise RHC

Exercise RHC was performed according to procedural methodology mentioned above. Briefly, patients were studied in supine position, wearing a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA), with a 7-F fluid-filled Swan-Ganz catheter [Edwards LifeScience] placed in the pulmonary artery and a 4 F catheter placed in the radial artery [Arrow]. Hemodynamic measurements as well as blood samples from pulmonary artery and radial artery were taken in order to calculate CO by the direct Fick method in each step of exercise RHC. Hemodynamic assessment was thus realized in resting conditions, after one minute of passive leg raise (feet on the pedals), and during

the last minute of each step of a symptom-limited exercise test, whose increment in workload was personalized in order to obtain at least three steps (about 10 minutes) of exercise before exhaustion [31].

Hemodynamic measurements

Pressures were measured at end-expiration, and hemodynamic data reflect the agreement of two expert independent readers blinded to patients' data, who visually reviewed all pressure traces offline. A hemodynamic diagnosis of HFpEF was defined by either an end-expiratory PAWP ≥ 15 mmHg at rest and/or ≥ 25 mmHg at peak exercise or a PAWP/CO slope > 2 mmHg/L/min.

Statistics

Continuous variables are reported as mean ± standard deviation normal when normally distributed (p-value of Shapiro's test > 0.05) and as median together with [25th and 75th percentiles] otherwise. Categorical data are showed as frequencies and proportions. Independency or dependency between variables was assessed creating contingency tables and performing the Fisher exact test with R, where p-values were computed through Monte Carlo simulation as required for tables larger than 2 × 2. A significant association between variables (rows and column of the table) was assessed by a p-value < 0.05.

RESULTS

Included population

Between June 2016 and June 2021, 73 consecutive patients with exertional dyspnea were evaluated at Istituto Auxologico Italiano and at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan and had all items required by the second and third steps of the HFA-PEFF algorithm, including echocardiography at rest, natriuretic peptides' values, DSE, and RHC at rest and during exercise.

Median age was 71 years, 67% were females, and mean body mass index (BMI) was 26 kg/m^2. Arterial hypertension was the most represented cardiovascular risk factors (67%), followed by dyslipidemia (44%) and obesity (16%). All individuals were in sinus rhythm, with 15% of patients who experienced paroxysmal AF. Twenty-two per cent of patients had mild COPD.

2nd step

Echocardiography at rest showed a normal median LA size (32 mL/m^2), with a mean E/e' of 9. The median TR velocity of 2.6 m/s and an estimated median systolic PAP of 31 mmHg. Median N-terminal pro-brain natriuretic peptide (NT-proBNP) was 193 ng/L. Eight per cent of individuals had a low probability of HFpEF (HFA-PEFF score < 2), 52% an intermediate probability (score 2–4), and 40% a high probability (score > 4).

3rd step

Eight patients had a positive DSE (E/e' ≥ 15), however 6 of these 8 patients already had an HFA-PEFF score > 4 at the 2nd step of the algorithm. Two patients at intermediate risk category at the 2nd step (4% of this latter cohort), shifted to the high-risk category after the DSE. Only 6 of the 29 individuals at high risk of HFpEF after the 2nd step (21%) had a positive DSE. No patient with a low risk of HFpEF had a positive DSE. The distribution of HFpEF risk based on the HFA-PEFF score marginally changed from the 2nd step to the 3rd step of the algorithm.

HFA-PEFF algorithm against hemodynamics

After rest and exercise RHC, 65 out of 73 individuals (89%) were diagnosed with HFpEF. The HFA-PEFF score (either two steps or three steps), resulted significantly associated with the hemodynamic diagnosis of HFpEF based on exercise RHC ($p < 0.001$).

Among the 65 individuals in whom HFpEF was confirmed by RHC, 2 belonged to the low-risk category, 34 to the intermediate-risk category, and 29 to the high-risk category of the two-step HFA-PEFF score (**figure 32).**

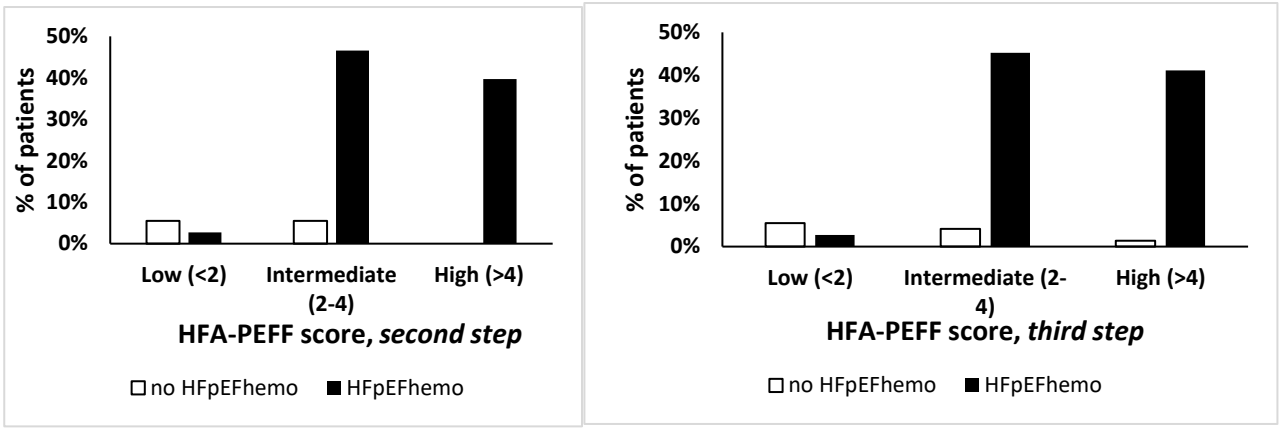


Figure 32. Proportion of patients classified as heart failure with preserved ejection fraction (HFpEF), or non-HFpEF, based on invasive hemodynamics (HFpEFhemo), stratified according to the pre-test probability provided by the 2-step and 3-step HFA-PEFF score.

The 'rule-in approach', which arbitrarily dichotomizes the score in >4 (HFpEF) and ≤4 (no HFpEF), correctly classified 37 (51%) patients as either HFpEF or non-HFpEF, both at the second step and at the third step, respectively. However, 36 (49%) and 35 (48%) patients resulted false negative both with two-step and with three-step HFA-PEFF algorithm.

Accordingly, specificity and positive predictive value of the HFA-PEFF were high, but sensitivity and negative predictive value were low (**table 1**). Neither age, sex, BMI, obesity, COPD, or paroxysmal AF influenced the performance of the HFA-PEFF algorithm. Lowering the threshold of the two-step HFA-PEFF score to >3 vs. >4 resulted in non-significantly higher sensitivity (60% vs. 45%, p = 0.08) and accuracy (64% vs. 51%, p = 0.09), without losing specificity (100% vs. 100%).

	Rule-in approach, HFA-PEFF score > 3				**Rule-in approach, HFA-PEFF score > 4**			
	Sens	**Spec**	**PPV**	**NPV**	**Sens**	**Spec**	**PPV**	**NPV**
HFA-PEFF, 2 steps	60%	100%	100%	24%	45%	100%	100%	18%
HFA-PEFF, 3 steps	62%	88%	98%	22%	46%	88%	97%	17%

Table 1. Performance of the 2-step and 3-step "rule-in" HFA-PEFF algorithm, both with the usual diagnostic threshold (> 4) and with a lower diagnostic threshold (> 3) to diagnose HFpEF, as compared with invasive hemodynamics. Abbreviations. NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Study 2: DISCORDIA: exercise hemodynamic definition of HFpEF [57]

METHODS.

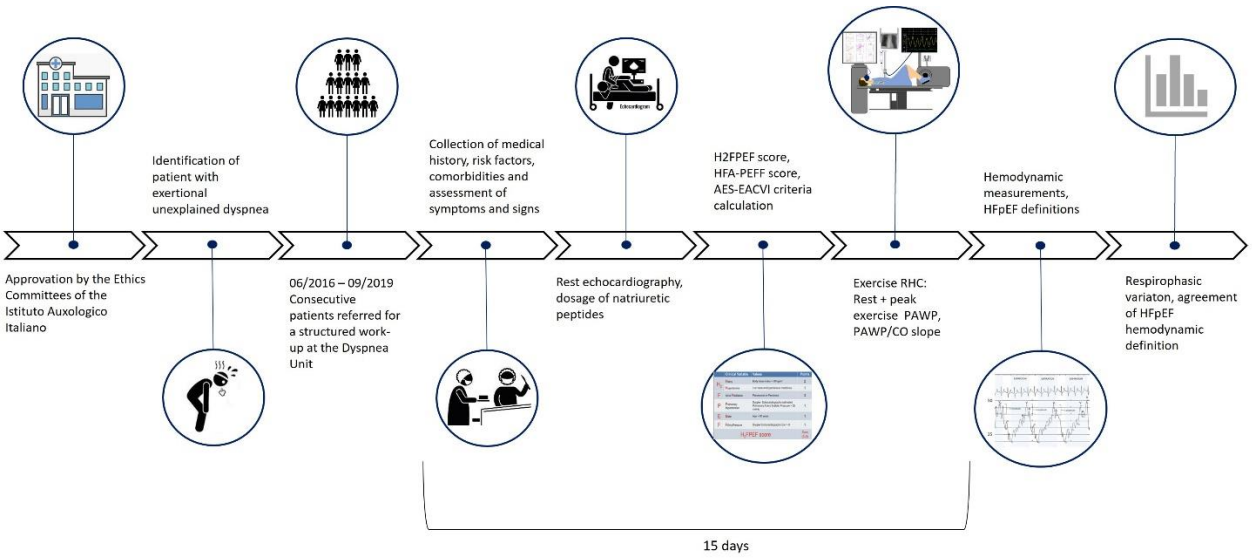


Figure 33. Representation of the DISCORDIA study design.

Study design

DISCORDIA study is a mono-centric, retrospective analysis on outpatients with exertional dyspnea underwent a comprehensive diagnostic assessment including exercise RHC. Whitin 15 days, patients underwent a non-invasive evaluation including clinical examination, rest echocardiography along with dosage of natriuretic peptides. Data were then analyzed to calculate the H_2FPEF probability score [21], the HFA-PEFF score [22], and according to echocardiographic features of diastolic function alone based on ASE/EACVI criteria [20]. Respirophasic variation of PAP and PAWP as well as the concordance between diagnostic criteria for HFpEF based in exercise hemodynamic were evaluated (**figure 33**).

EC approbation

The Ethics Committee of the Istituto Auxologico Italiano approved the study on April 21, 2020 (protocol n 2020_04_21_03). All patients signed a written informed consent to the use of their data for research purposes.

Inclusion criteria

Consecutive patients who underwent a cardiac catheterization at rest and during exercise for exertional dyspnea, i.e. not explained by a cardiac, respiratory or musculoskeletal origin, based on a thorough noninvasive assessment.

Clinical assessment

Echocardiography was performed with a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway) following current recommendations [56]. Clinical and echocardiographic data, obtained before the indication to cardiac catheterization, were analyzed to calculate both the H_2FPEF probability score [21] and the HFA-PEFF score [22]. In contrast to the H_2FPEF and HFA-PEFF scores which combine clinical and imaging data, we also examined the patients based on echocardiographic features of diastolic function alone according to ASE/EACVI criteria [20].

Exercise RHC

Patients were studied in supine position, wearing a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA), with a 7-F fluid-filled Swan-Ganz catheter [Edwards LifeScience] placed in the pulmonary artery and a 4 F catheter placed in the radial artery [Arrow]. Hemodynamic measurements as well as blood samples from pulmonary artery and radial artery

were taken in order to calculate CO by the direct Fick method in each step of exercise RHC. Hemodynamic assessment was thus realized in resting conditions, after one minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test, whose increment in workload was personalized in order to obtain at least three steps (about 10 minutes) of exercise before exhaustion [31].

Hemodynamic measurements

PAP and PAWP were measured both during inspiration, at end-expiration and as an average of at least 5 respiratory cycles in each step id exercise RHC. The phase of the respiratory cycle had been identified during the test using a respiratory belt and confirmed both by visual inspection of thoracic excursion and capnography waveforms from the metabolic cart. V waves were measured, and their amplitude was calculated as the difference between the zenith of the V wave and the mean PAWP value. When tall V waves appeared during exercise, if not previously done, patients underwent exercise stress echocardiography to exclude dynamic mitral regurgitation. Respirophasic variations of PAWP tracings were calculated as the difference between end-expiratory and inspiratory values. Two blinded experts independent averaged PAWP values so that both systolic and diastolic PAWP components allowing to compare the hemodynamics irrespectively of cardiac rhythm (sinus rhythm or atrial fibrillation). Visual measurement was preferred over automatic, software-based analysis. Indeed, during exercise, motion artifacts, catheter whip, and aberrant respiratory swings may lead to imprecise automatic readings of pressure traces dynamically recorded during relatively short time windows at each step of effort using fluid-filled catheters.

CO was calculated by direct Fick method. TPR was computed as mPAP/CO [32]. A linear regression was applied to multiple pairs of PAWP and CO points to calculate the PAWP/CO linear regression slope [6,30]. Three hemodynamic definitions of HFpEF were considered: i) $PAWP_{exp} \geq$ 25 mm Hg at peak exercise [23]; ii) $PAWP_{exp}$/CO slope > 2 mm Hg/L/min [6,30]; iii) $mPAP_{avg}$ > 30 mm Hg, TPR_{avg} > 3 WU, and $PAWP_{avg} \geq$ 20 mmHg [32].

Statistics

Continuous variables are reported as mean± standard deviation (SD) normal when normally distributed (visual inspection of distribution) and as median and interquartile range in case of non-normal data. Categorical data are shown as frequencies and proportions. To compare end-expiratory and respiratory-averaged pulmonary hemodynamic values, we used paired t test (or Wilcoxon signed rank-sum test in case of non-normal distribution) when the variables were continuous. Analogously, we applied the McNemar test for binary variables dichotomized according to proposed pathological cutoffs. Moreover, we used t-test for unpaired data (or Wilcoxon test) to detect the differences (end-expiratory − respiratory-averaged) between patients with obesity or respiratory comorbidities and patients without these clinical problems. We classified each patient in term of discrepancy at rest comparing end-expiratory and averaged values using the cutoff of 15 mm Hg. Analogously, we considered discrepancy at peak exercise using the cutoff of 25 mm Hg. To evaluate the relationship between respirophasic difference (either at rest or at peak exercise) and discrepancy at rest and at peak exercise, we implemented 2 logistic regression models. The predictive performance of respirophasic difference at rest and at peak exercise was estimated by the area under the curve. Moreover, the optimal threshold value of this covariate was assessed by the Youden method which assumes that sensitivity and specificity are diagnostically equally important. To evaluate the agreement of 3 hemodynamic definitions of HFpEF, we calculated the first-degree agreement coefficient (AC1) statistic (and its 95% confidence interval, CI) proposed by Gwet [58]. This AC1 can assume values from 0 (no concordance) to 1 (maximum concordance). The strength of agreement can be categorized according to benchmark scale of Altman20 as follows: poor: <0.2; fair: 0.21 to 0.4; moderate: 0.41 to 0.6; good: 0.61 to 0.8; and very good: 0.81 to 1.0. AC1 can be calculated across >2 raters and overcome some typical problems affecting Cohen κ.21 To evaluate the potential determinants of discordance among criteria, we dichotomized each patient in 2 levels (discordant when not all criteria identified the same status, concordant otherwise) and performed an exploratory univariate analysis implementing the Poisson model with robust error variances considering the discordant status as a dependent variable. We included in this analysis both clinical, gas-exchange, and hemodynamic variables. Association estimates were reported as relative risk (RR) and its 95% CI. To evaluate

anthropometric, demographic, and clinical differences among patients categorized according to the number of exercise hemodynamic criteria met for HFpEF, we applied ANOVA model (or Kruskal-Wallis test) for continuous variables and $\chi 2$ test (or Fisher test) for categorical ones. All analyses were performed using the Statistical Analysis System Software (version 9.2; SAS Institute, Cary, NC). Statistical significance was set at the 0.05 level. All p-values were 2-sided.

RESULTS

Fifty-seven patients with exertional dyspnea underwent RHC at rest and during exercise between June 2016 and September 2019 were included in this study.

Non-invasive assessment

Clinical characteristics, blood tests and echocardiography were reported in **table 2**, and reflected a quite typical population overall at intermediate-high risk for HFpEF.

Demographics and anthropometrics	
Age, years	70±9
Females, *N (%)*	40 (70%)
BMI, Kg/m^2	27±5
Vital signs	
Systolic blood pressure, mmHg	130 [120-140]
Diastolic blood pressure, mmHg	80 [70-80]
Heart rate, bpm	71 [63-74]
Rhythm	
Sinus rhythm *N (%)*	47 (82%)
AF *N (%)*	
No	38 (67%)
Persistent or permanent AF	10 (17%)
Paroxysmal AF	9 (16%)
Comorbidities and risk factors	
Obesity, *N (%)*	13 (23%)
Arterial hypertension, *N (%)*	45 (79%)
Glucose intolerance or diabetes mellitus, *N (%)*	10 (17%)
Coronary artery disease, *N (%)*	9 (16%)
Previous stroke or TIA, *N (%)*	6 (11%)
History of pulmonary embolism, *N (%)*	6 (11%)
Previous cardiac surgery, *N (%)*	7 (12%)
Mitral valve replacement,	6 (11%)
Aortic valve replacement,	1 (2%)
AF ablation *N (%)*	7 (12%)
Thoracic radiotherapy *N (%)*	8 (14%)

COPD *N (%)*	
No	39 (68%)
GOLD 1-2	16 (28%)
GOLD 3	2 (4%)
Obstructive sleep apnea, *N (%)*	14 (29%)
Systemic sclerosis, *N (%)*	7 (12%)
Blood tests	
Hemoglobin, g/dL	13.2±1.6
Creatinine, mg/dL	0.9 [0.8-1.1]
NT-proBNP, ng/L	195 [55-673]
Echocardiography	
IVS thickness, mm	10 [9-11]
PW thickness, mm	9 [9-10]
LVEDV, mL	80 [71-99]
LVMI, g/m^2	86±19
LVEF, %	63 [61-65]
LAVI, mL/m^2	31 [25-44]
Average E/e'	9 [8-12]
Systolic PAP, mmHg	34 [28-47]
Mitral regurgitation *N (%)*	
None/mild	54 (95%)
Moderate	3 (5%)
More than moderate	0 (0%)
Tricuspid regurgitation *N (%)*	
None/mild	36 (63%)
Moderate	12 (21%)
Moderate-severe	9 (16%)
Severe	0 (0%)

Table 2. General characteristics of the DISCORDIA study population.

Abbreviations. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IVS, interventricular septum; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAP, pulmonary artery pressure; PW, posterior wall; and TIA, transient ischemic attack.

According to the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) and HFA-PEFF algorithms, and the H_2FPEF score, HFpEF was the likely cause of their unexplained dyspnea in 33%, 40%, and 33% of patients, respectively. There was a relatively large gray zone of possible HFpEF according to the non-invasive scores, 47% and 54% respectively, according to the HFA-PEFF algorithm and H_2FPEF scores.

Hemodynamics and respiratory swings: end-expiratory vs averaged

End-expiratory pulmonary pressures were significantly higher than those obtained by averaging the values throughout the respiratory cycle, both as absolute values or flow-normalized, both at rest and at peak exercise (**table 3**).

Mean differences between $PAWP_{exp}$ and $PAWP_{avg}$ were 2 [2–4] mm Hg at rest and 5 [4–7] mmHg at peak exercise. Thus, a significantly larger number of patients presented with PAWP values above diagnostic thresholds for HFpEF if considering end-expiratory rather than respiratory-averaged values, both at rest and at peak exercise (**table 3**).

REST				**EXERCISE**			
	Averaged	**End-exp**	**p-value**		**Averaged**	**End-exp**	**p-value**
mPAP				**mPAP**			
Median, mmHg	17 [13-21]	19 [15-25]	**<0.001**	***Median, mmHg***	36 [29-42]	39 [32-47]	**<0.001**
≥25 mmHg, n (%)	11 (19)	19 (33)	**0.008**	***≥30 mmHg, n (%)***	39 (71)	43 (78)	0.125
>20 mmHg, n (%)	19 (33)	26 (46)	**0.039**				
				TPR			
				Median, WU	4.2 [2.6-5.6]	4.5 [3.0-6.1]	**<0.001**
				TPR > 3 WU, n (%)	37 (66)	42 (75)	0.063
PAWP				**PAWP**			
Median, mmHg	9 [6-14]	12 [9-18]	**<0.001**	***Median, mmHg***	25 [18-30]	30 [23-38]	**<0.001**
> 15 mmHg, n (%)	8 (14)	15 (26)	**0.016**	***≥ 25 mmHg, n (%)***	30 (52)	40 (70)	**0.002**
> 12 mmHg, n (%)	17 (30)	25 (44)	**0.008**	***≥ 20 mmHg, n (%)***	39 (67)	48 (83)	**<0.001**
				PAWP/CO slope			
				Median, WU	2.7 [1.8-4.0]	3.3 [2.1-4.4]	**<0.001**
				> 2 WU, n (%)	39 (70)	47 (84)	**0.008**

Table 3. Pulmonary hemodynamics at rest and at peak exercise.

Abbreviations. CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; and TPR, total pulmonary resistance.

Influence of obesity and COPD

In obesity/COPD patients, PAWP values exceeded the pathological PAWP cutoff at end-expiration but not when PAWP was respiratory-averaged in 14% at rest and in 18% at peak exercise. The optimal threshold of respirophasic difference associated with PAWP discrepantly exceeding the pathological cutoff at end-expiration, but not respiratory-averaging, was 7 mmHg at rest (AUC, 0.800 [0.677–0.923]; sensitivity, 0.88

[0.47–0.99]; and specificity, 0.67 [0.52–0.80]) and 12 mmHg at peak exercise (AUC, 0.676 [0.508–0.843]; sensitivity, 0.70 [0.35–0.93]; specificity, 0.62 [0.46–0.75]). Respirophasic PAWP changes were higher in patients with obesity or COPD than in nonobese and non-COPD patients, both at rest (7 [5–9] versus 3 [3–5] mm Hg, p < 0.001) and at peak exercise (13 [9–18] versus 9 [7–13] mm Hg, p = 0.004). Moreover, in obese and COPD patients, the difference between end-expiratory and respiratory-averaged values of PAP, PAWP, and TPR at peak exercise was larger than in nonobese, non-COPD patients, in opposite to $PAWP_{exp}$/CO slope and $PAWP_{avg}$/CO slope (**table 4**).

	Obese and/or COPD			**Non-obese and non-COPD**			
	AVG	**EXP**	**EXP-AVG**	**AVG**	**EXP**	**EXP-AVG**	**p-value**
Mean PAP, mmHg	36 [30-42]	41 [35-50]	4.2 [3.0-7.3]	36 [27-39.7]	39 [30-43]	2. 7 [2.2-4.0]	**0.001**
PAWP, mmHg	27 [24-33]	33 [29-38]	6 [4-8]	22 [17-30]	27 [21-34]	4 [3-6]	0.062
TPR, WU	4.0 [2.7-5.6]	4.3 [3.2-6.0]	0.4 [0.3-0.7]	4.2 [2.5-6.1]	4.7 [2.9-6.2]	0.4 [0.2-0.4]	**0.015**
PAWP/CO slope, WU	2.6 [1.8-3.9]	3.3 [2.2-4.4]	0.3 [0.2-0.9]	2.7 [1.8-4.1]	3.3 [2.1-4.5]	0.5 [0.3-0.8]	0.448

Table 4. Influence of obesity and chronic obstructive pulmonary disease on the difference between end-expiratory and respiratory-averaged pressure hemodynamic values.

Abbreviations. CO, cardiac output; COPD, chronic obstructive pulmonary disease; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; and TPR, total pulmonary resistance.

Concordance in between hemodynamic HFpEF definitions

Sixty-four percent of patients had TPR_{avg} > 3 WU, 69% of patients presented with a $PAWP_{exp}$ ≥ 25 mmHg, and 81% with a $PAWP_{exp}$/CO slope > 2 mmHg/L per minute, as represented in **figure 34**.

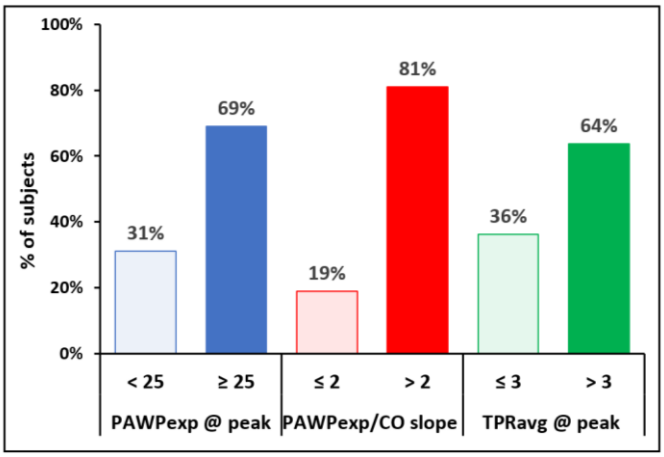


Figure 34. Performance of the 3 exercise hemodynamic definitions for HFpEF in DISCORDIA population.

Abbreviations. CO, cardiac output; PAWP, pulmonary artery wedge pressure; and TPR, total pulmonary resistance.

The 3 hemodynamic criteria for HFpEF were moderately concordant in 70% of patients (AC1, 0.67 [0.52–0.83]). In 56% of patients HFpEF was diagnosed based on the presence of 3/3 hemodynamic criteria, while in 14% of patients, no hemodynamic criteria suggested HFpEF, and were thus classified as NCD, with 0/3 positive diagnostic criteria. We found a discordance between definition of HFpEF in 30% of the population, represented in gray in **figure 35**, of which 9% with 1/3 and 21% with 2/3 positive diagnostic criteria for HFpEF.

In an exploratory univariate analysis, factors associated with discordance among exercise hemodynamic definitions of HFpEF were age (RR, 0.96), H_2FPEF score (RR, 0.82), $PAWP_{exp}$ and $PAWP_{avg}$ at rest (RR, 0.88 and 0.87, respectively), $PAWP_{exp}$ and $PAWP_{avg}$ at peak (0.95 and 0.94, respectively), and peak CO (RR, 1.21).

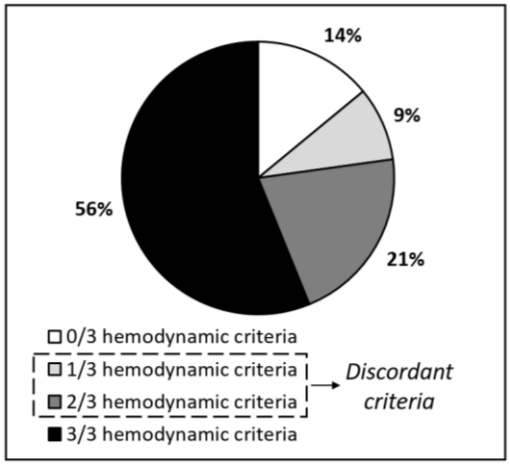


Figure 35. Discordance between exercise hemodynamic definitions for HFpEF.

This non-negligible discordance between results obtained by exercise RHC could potentially impact on patient's clinical diagnosis, unless more standardization is obtained across laboratories. In this perspective, $PAWP_{exp}$/CO slope appeared as the most inclusive and robust variable to diagnose HFpEF in cath lab: indeed, a $PAWP_{exp}$/CO slope > 2 mm Hg/L per minute incorporated 97% and 98% of both abnormal $PAWP_{exp}$ and TPR_{avg} at peak exercise, respectively, as shown in **figure 36**.

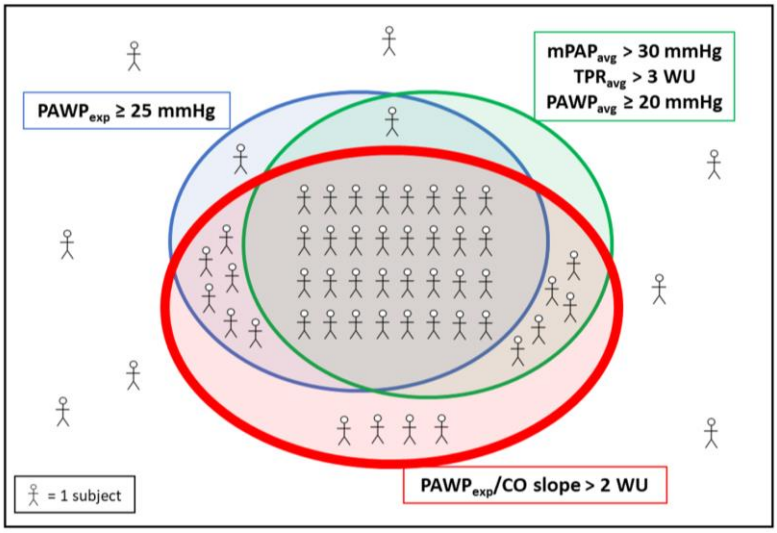


Figure 36. Performance of the 3 exercise hemodynamic definitions for HFpEF in our population: PAWP/CO slope > 2 mmHg/L/min includes most of the positive responses of the other criteria.

Abbreviations. CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; and TPR, total pulmonary resistance.

Moreover, $PAWP_{exp}$/CO slope was the only parameter always above the threshold for HFpEF when the pretest probability of HFpEF was high based on noninvasive algorithms or scores, given that in 2% to 5% of these patients we found peak $PAWP_{exp}$ < 25 mmHg or TPR_{avg} ≤ 3 WU.

HFpEF as a continuum of hemodynamic alterations

As shown in **table 5**, we found a crescendo of hemodynamic abnormalities with increasing number of exercise hemodynamic criteria met. Patients with 3/3 positive hemodynamic criteria presented with the worst clinical and hemodynamic profile: they were slightly older than the other groups, had larger left atrial volume and more prevalence of AF, higher NT-proBNP values, higher prevalence of overt echocardiographic left ventricular diastolic dysfunction, as well as higher HFA-PEFF and H_2FPEF scores. Moreover, they displayed a worse exercise profile, characterized by lower peak oxygen consumption and CO, higher PAWP at rest and at peak exercise, taller PAWP V waves, as well as higher $PAWP_{exp}$/CO slope and TPR_{avg} at peak exercise.

	0/3 hemodynamic criteria (n=8)	1/3 hemodynamic criteria (n=5)	2/3 hemodynamic criteria (n=12)	3/3 hemodynamic criteria (n=32)	p-value
Anthropometric, demographic and clinical parameters					
Age, years	63.0 [59.5-69.0]	58.0 [56.0-75.0]	67.5 [63.5-78.5]	73.0 [71.0-78.5]	**0.029**†
Male sex, n (%)	6 (75%)	3 (60%)	9 (75%)	22 (69%)	0.97‡
BMI, Kg/m2	24.0 [21.4-26.7]	26.6 [25.3-28.8]	27.1 [25.3-29.6]	27.3 [23.9-30.3]	0.49†
Atrial fibrillation, n (%)	0 (0%)	0 (0%)	1 (8%)	11 (34%)	0.40‡
COPD, n (%)	2 (25%)	2 (40%)	2 (17%)	12 (38%)	0.62‡
NT-proBNP, ng/L	101 [47-168]	45 [33-98]	96 [46-397]	408 [174-881]	**0.021**†
LVMI, g/m²	73 [62-88]	96 [96-96]	83 [72-102]	85 [72-96]	0.19†
E/e'	9.5 [8.2-12.9]	10.0 [9.0-11.8]	10.4 [8.4-12.4]	11.1 [9.4-12.8]	0.71†
LAVI, mL/m²	25.6 [22.8-30.7]	26.4 [23.5-27.6]	31.8 [26.0-45.0]	37.8 [27.7-50.4]	**0.020**†
ASE/EACVI ↑ filling pressure, n (%)	0 (0%)	0 (0%)	3 (25%)	16 (50%)	**0.011**‡
HFA-PEFF score	1.5 [1-3]	2 [2-2]	4 [2.5-5]	5 [4-6]	<**0.001**†
H_2FPEF score	2 [1-2.5]	2 [2-3]	3.5 [2-5]	4 [4-7]	<**0.001**†
Cardiopulmonary exercise test, peak exercise					
Workload, Watts	50 [35-77.5]	75 [65-75]	55 [47.5-80]	50 [40-60]	0.36†
VO_2, mL/Kg/min	15.4 [13.8-18.0]	17.0 [15.6-17.3]	14.8 [13.2-17.9]	12.9 [10.3-16.0]	0.16†
VO_2, % of predicted	73 [65-87]	86 [81-100]	79 [73-88]	76 [62-92]	0.79†
RQ	0.98 [0.83-1.08]	0.93 [0.84-1.11]	1.02 [0.9-1.2]	0.97 [0.88-1.07]	0.73†
Lactate, mmoL/L	3.6 [2.6-4.6]	3.0 [2.8-6.0]	3.7 [2.4-4.3]	4.3 [3.2-5.0]	0.67†
CO, L/min	10.2 [9.9-11.7]	11.1 [10.7-12. 7]	10.1 [8.0-12.1]	7.9 [5.9-9.9]	**0.002**†
CO increase, %	110 [91-166]	144 [116-150]	96 [64-157]	104 [60-152]	0.65†
SV, mL	89 [69-104]	105 [98-106]	96 [64-115]	78 [60-93]	0.11†
HR, bpm	118 [105-135]	120 [97-129]	114 [106-131]	104 [87-122]	0.32†
SaO_2, %	95.5 [94.7-97.6]	95.0 [94.7-95.7]	97.0 [94.9-97.6]	95.5 [93.6-97.0]	0.53†
$PetCO_2$, mmHg	33.3 [32.3-35.8]	32.4 [31.0-34.6]	33.3 [32.2-35.4]	32.2 [29.9-36. 5]	0.96†
$VECO_2$	35.3 [33.3-37.8]	35.1 [30.8-35.2]	32.6 [32.0-38.3]	36.7 [32.1-40.0]	0.45†
Invasive hemodynamics					
$PAWP_{exp}$ @ rest, mmHg	8 [6-9]	6 [3-9]	11 [7-13]	17 [12-20]	**<0.001**†
$PAWP_{avg}$ @ rest, mmHg	5 [3-6]	2 [2-7]	8 [5-11]	13 [9-17]	<**0.001**†
$PAWP_{exp}$ @ peak, mmHg	17 [13-20]	19 [18-19]	27 [23-30]	35 [31-40]	<**0.001**†
$PAWP_{avg}$ @ peak, mmHg	11 [9-15]	15 [14-15]	23 [19-25]	29 [26-34]	<**0.001**†
$PAWP_{exp}$ V wave amplitude @ peak, mmHg	3 [2-5]	6 [5-6]	7 [4-10]	7 [4-14]	**0.015**†
PAWP respiratory swings @ peak, mmHg	9.5 [7-12]	9 [9-12]	9 [7.5-13]	12.5 [8.5-15]	0.42†
$PAWP_{exp}$/CO slope	1.4 [1.0-1.5]	2.1 [2.0-2.5]	2.8 [2.1-3.3]	4.2 [3.6-5.1]	<**0.001**†
TPG_{avg} @ peak, mmHg	10 [9-13]	11 [9-11]	11 [7-17]	11 [7-17]	0.99†
TPR_{avg} @ peak, WU	2.4 [1.9-2.6]	2.1 [2.1-2.4]	3.4 [2.5-4.3]	5.5 [4.2-6.4]	<**0.001**†

Table 5. Patients' characteristics according to the number of HFpEF exercise hemodynamic criteria met.† Kruskal-Wallis test; Chi-square test.

Abbreviations. ASE, American Society of Echocardiography; Avg, respiratory-averaged; BMI, body mass index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; EACVI, European Association of Cardiovascular Imaging; exp, end-expiratory; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LAVI, left atrial volume index; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; $PetCO_2$, end-tidal partial pressure for carbon dioxide; RQ, respiratory quotient; SaO_2, arterial oxygen saturation; SV, stroke volume; TPG, transpulmonary pressure gradient; TPR, total pulmonary resistance; VCO_2, carbon dioxide production; VE, minute ventilation; and VO_2, oxygen consumption. *Kruskal-Wallis test. †χ2 test.

Study 3: META-EXPEF: a systematic review and meta-analysis on exercise hemodynamics in HFpEF [59]

METHODS

Research strategy

We performed a systematic literature review until December 2020 including studies reporting PAWP at rest and peak exercise, extracted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA) statement [60] for reporting systematic reviews and meta-analysis. A comprehensive literature research on PubMed included the following search terms included: ('right heart catheterization' OR 'hemodynamics' OR 'cardiac catheterization' OR 'hemodynamics') AND ('exercise' OR 'effort') AND ('heart failure with preserved ejection fraction' OR 'HFPEF' OR 'dyspnea' OR 'diastolic dysfunction' OR 'diastolic heart failure' OR 'left heart disease') AND ('PAWP' OR 'PCWP' OR 'wedge pressure' OR 'occlusion pressure').

Data collection and analysis

For each study, non-invasive data (clinical, echocardiography, and blood tests) as well as hemodynamics (e.g. PAWP and CO) at rest and at peak exercise were extracted. Additionally, for all studies reporting PAWP and CO at rest and at peak exercise, we calculated the slope of their relationship during effort. We compared the summary estimates of HFpEF and controls both at rest and during exercise by meta-regression analysis without and with adjustment for age, sex, BMI, and body position. Control subjects were mainly individuals who underwent an invasive cardiopulmonary evaluation for unexplained dyspnea and who did not satisfy the hemodynamic diagnostic criteria for HFpEF. Healthy volunteers served as control group only in one study [61].

Statistics

Clinical characteristics of HFpEF and control patients of each study were reported as mean and SD (for continuous variables) or proportions (for categorical variables). A summary estimate of each clinical characteristic, for HFpEF and control patients, was reported as median and interquartile range of study-specific values and jointly represented with a radar plot. When only median and interquartile range of hemodynamic variable were available in included studies, they were transformed in mean and SD value [62] before applying the meta-analytic procedure. Summary estimates of each hemodynamic variable were separately evaluated for HFpEF and control cohorts. Additionally, summary estimates of PAWP and delta CO were separately evaluated also for exercise body position. The random effect summary mean estimate and the corresponding 95% confidence intervals (95% CI) were calculated according to the DerSimonan and Laird's method [63]. Between-studies' heterogeneity was quantified using the I2 index. Values of this index more than 75% suggest high heterogeneity [64]. Homogeneity between summary mean estimates stratified for body position during exercise was performed by a $\chi 2$ statistic. In order to account for potential populations' heterogeneity, reflecting differences in inclusion criteria of individual studies, we performed a stratified analysis. In particular, we subdivided studies defining HFpEF based on hemodynamic criteria only, from studies defining HFpEF based on clinical criteria or including patients with LVEF < 50%. Finally, univariate and multivariate meta-regression models were implemented for each hemodynamic variable, including status (HFpEF or control) as independent variable, and age, sex, BMI, and body position as dependent variables. Meta-regression is a linear weighted mixed model including study as random effect and standard error of published mean as weight [65]. The estimated coefficient related to status variable gives information about the summary means difference. Results were considered statistically significant when two-tailed p-value was lower than 0.05. All analyses were performed with R Version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS.

Included studies

Out of 128 articles, 27 responded to the pre-specified inclusion criteria, reporting PAWP at rest and at peak exercise [6,8,12,23,27,30,61,66-85]. We excluded 90 studies because not pertinent or non-original studies (reviews, editorials, case reports), 18 with data replication, and 2 not reporting hemodynamic data (**figure 37**). The analyzed population consisted in 35 HFpEF cohorts and 21 control cohorts, including 2180 HFpEF patients and 682 subjects with NCD.

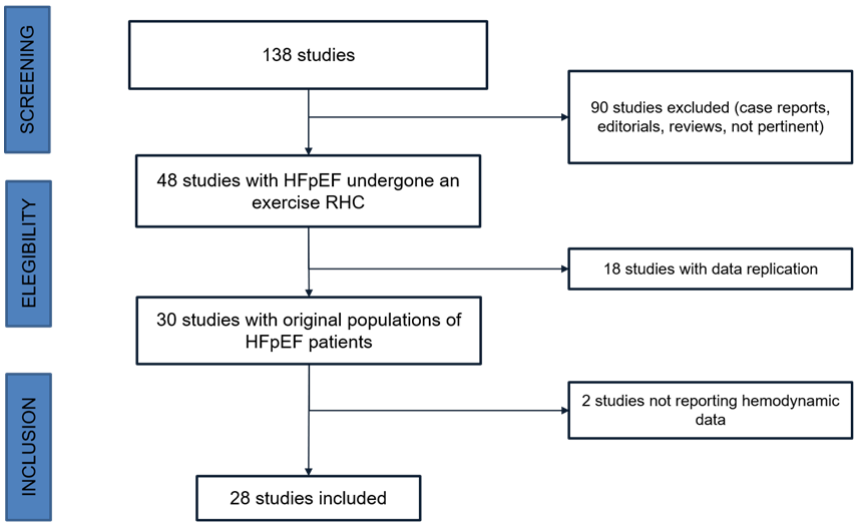


Figure 37. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Characteristics of included studies

Sixty-three percent of the selected studies were performed in 3 Centers of the United States (**table 6**). All patients performed a symptom-limited exercise testing, in supine position in 21 studies and in upright position in the other 6 studies (**table 6**). Exercise PAWP was measured at end-expiration in almost all studies, and CO was measured by direct Fick method in most studies (n = 16, 59%) (**table 6**). Contrarily, few studies reported information about how measurement were taken in the cardiac cycle (Mean/midA PAWP).

The diagnosis of HFpEF was confirmed based on rest or peak PAWP in all but 4 studies, which used non-invasive diagnostic criteria (**table 6**). The diagnostic cut-off of 25 mmHg for the PAWP at peak exercise was used in all but one of the studies performing the effort in supine position, while in 4 of the 6 studies evaluating patients in the upright position, a peak PAWP > 20 mmHg or a PAWP/CO slope > 2 mmHg/L/min was considered as a pathological threshold to define HFpEF (**table 6**).

Author	Center	HFpEF (N)	Controls (N)	Timing of enrollment	Exercise position	PAWP (end-exp/ avg)	HFpEF diagnosis	Other remarks
Tschope et al.[83]	Campus Benjamin Franklin (DE)	15	15	2003	Supine		Hemodynamic (rest and/or exercise), Echo	restPAWP>12, peakPAWP>20
Borlaug et al. [23]	Mayo clinic (USA)	32	23	2005-2009	Supine	End-exp	Hemodynamic (exercise)	
Maeder et al. [61]	Alfred hospital (AUS)	14	8	2008-2009	Supine	End-exp	↓ ex capacity	
Abudiab et al. [66]	Mayo clinic (USA)	109	73	2002-2011	Supine	End-exp	Clinical	
Andersen et al. [80]	Rigshospitalet& Copenhagen University (DK)	61		2010-2012	Supine	Avg	Echo	LVEF>45% and post-STEMI
Santos et al. [79]	Brigham and Women's Hospital (USA)	31	31	2011-2013	Upright	End-exp	Hemodynamic (exercise)	PAWP peak>20
Houstis et al. [67]	Massachusetts general hospital (USA)	79	55	2006-2016	Upright	End-exp	Hemodynamic (rest and/or exercise), ↓ ex capacity	
Obokata et al. [8]	Mayo clinic (USA)	195	71	2000-2014	Supine	End-exp	Hemodynamic (rest and/or exercise)	
Reddy et al. [12]	Mayo clinic (USA)	98	22		Supine	End-exp	Hemodynamic (rest and/or exercise)	
Nanayakkara et al. [76]	Alfred hospital (AUS)	21	19		Supine	End-exp	Hemodynamic (rest and/or exercise)	
Eisman et al. [30]	Massachusetts general hospital (USA)	77	98		Upright	End-exp	Hemodynamic (exercise)	
Gorter et al. [68]	Mayo clinic (USA)	161		2006-2013	Supine	End-exp	Hemodynamic (rest)	
McCabe et al. [75]	Brigham and Women's Hospital (USA)	8	14		Upright	Avg	Hemodynamic (rest and/or exercise)	PAWP rest>15, peak>20 mmHg
Platz et al. [77]	Brigham and Women's Hospital (USA)	13	12		Upright	End-exp	Hemodynamic (rest)	
Ho et al. [6]	Massachusetts general hospital (USA)	243		2006-2017	Upright	End-exp	Hemodynamic (exercise)	
Obokata et al. [69]	Mayo clinic (USA)	38	20		Supine	End-exp	Hemodynamic (rest and/or exercise)	
Reddy et al. [70]	Mayo clinic (USA)	238	125		Supine	End-exp	Hemodynamic (rest and/or exercise)	
Van Empel et al. [71]	Alfred hospital (AUS)	9	21		Supine	End-exp	Hemodynamic (exercise), Echo	LVEF>45%
Wolsk et al. [27]	Multicenter (USA, EU, AUS)	108	42	2013-2016	Supine	End-exp	Hemodynamic (rest and/or exercise), BNP, Echo	LVEF>40%; prior HF hosp, PAWP or LVEDP>RAP
Beale et al. [73]	Alfred Hospital (AUS)	161		2008-2018	Supine	End-exp	Hemodynamic (rest and/or exercise)	
Chen et al. [74]	Taiwan University Hospital (TW)	34		2018	Supine	End-exp	Clinical, BNP, Echo	
Telles et al. [78]	Alfred hospital (AUS)	49	22	2016-2018	Supine	End-exp	Hemodynamic (rest and/or exercise)	
Obokata et al. [81]	Multicenter (USA, EU, AUS)	79		2014-2016	Supine	End-exp	Hemodynamic (rest and/or exercise), BNP, Echo	LVEF>40%; prior HF hosp, PAWP or LVEDP>RAP
Fermoyle et al. [72]	Mayo clinic (USA)	30		2009-2012	Supine	End-exp	Hemodynamic (rest and/or exercise)	

Sorimachi et al. [82]	Mayo clinic (USA)	105	51	2007-2018	Supine	End-exp	Hemodynamic (rest and/or exercise)	
Ahmad et al. [83]	Mayo clinic (USA)	22	29	2010-2019	Supine	End-exp	Hemodynamic (rest and/or exercise)	non-obstructive CAD
Koepp et al. [85]	Mayo clinic (USA)	169		2000-2014	Supine	End-exp	Hemodynamic (rest and/or exercise)	BMI≥30

Table 6. Characteristics of included studies.

Abbreviations. BMI, body mass index; CAD, coronary artery disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Clinical characteristics of HFpEF and control patients

HFpEF were slightly older than controls, with more women and higher BMI, as reported in **figure 38**. They had a larger burden of comorbidities including AF, higher NT-proBNP, larger LAVI, and higher E/e'.

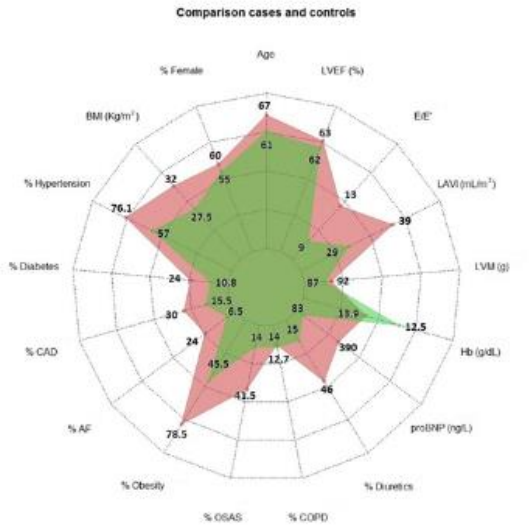


Figure 38. Radar plot with the clinical characteristics of HFpEF patients (pink) and control subjects (green).

Abbreviations. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; LAVI, left atrial volume indexed; LVM, left ventricular mass; NT-proBNP, N terminal pro brain natriuretic peptide; OSAS, obstructive sleep apnea syndrome.

Rest and exercise hemodynamics of HFpEF and control patients

As reported in **table 7**, mean rest PAWP was higher in HFpEF than in control cohorts, as well as RAP. HFpEF had normal CO and CI, slightly lower than those of controls, but not after adjustment for age, sex, BMI, and body position.

During exercise, HFpEF cohorts showed markedly higher filling pressures than controls: PAWP at peak was twice as high in HFpEF as compared with controls, as well as of delta PAWP, and of RAP (**table 7**), even after adjustment for age, sex, BMI, and body position. Similar to resting conditions, peak CO and CI were lower in HFpEF than in controls, but not after adjustment for the covariates.

	HFpEF		**Controls**		**Unadjusted meta-regression models**		**Adjusted meta-regression models**	
	Mean (95% CI)	**N estimate**	**Mean (95% CI)**	**N estimate**	**p-value**	**N estimate**	**p-value**	**N estimate**
REST								
PAWP, mmHg	15 (14-16)	36	9 (8-9)	23	<**0.0001**	59	<0.0001	56
CO, L/min	5.13 (4.69-5.29)	16	5.39 (5.19-5.60)	12	0.0566	28	0.091	28
CI, L/min/m^2	2.61 (2.54-2.68)	19	2.78 (2.69-2.87)	11	0.0065	30	0.545	27
RAP, mmHg	8 (7-9)	27	4 (3-5)	17	**<0.0001**	44	**0.008**	44
PEAK								
PAWP, mmHg	30 (29-31)	35	16 (15-17)	22	**<0.0001**	57	**<0.0001**	54
CO, L/min	9.49 (8.95-10.03)	19	13.21 (11.72-14.70)	14	**<0.0001**	33	0.116	31
CI, L/min/m^2	4.73 (4.31-5.14)	21	6.44 (5.55-7.33)	10	**<0.0001**	31	0.068	28
RAP, mmHg	18 (17-19)	26	8 (8-9)	16	**<0.0001**	42	**<0.0001**	42
DELTA PEAK-REST								
PAWP, mmHg	15 (14-16)	35	7 (6-8)	22	**<0.0001**	57	**<0.0001**	54
CO, L/min	4.29 (3.66-4.91)	16	8.02 (6.68-9.37)	12	**<0.0001**	28	0.0985	28

Table 7. Rest and exercise hemodynamics of heart failure with preserved ejection fraction and control subjects. Adjustment was performed using meta-regression models including age, sex, body mass index, and body position as covariates. Data are reported as mean (95% confidence interval). The p-value reflects the comparison between the 2 groups, both unadjusted, and after adjustment for age, sex, BMI and body position.

Abbreviations. 95% CI, 95% of the confidence interval; CI, cardiac index; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; N, number; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

Heterogeneity of rest and peak PAWP

Summary estimates of PAWP were highly heterogeneous, especially in HFpEF group, both at rest (I2 = 97% and I2 = 82% in HFpEF and control cohorts, respectively) and at peak exercise (**figure 39**). This heterogeneity did not show relevant differences analyzing studies adopting pure hemodynamic criteria for the HFpEF diagnosis as opposed to studies adopting non-invasive, clinical or atypical definitions of disease. This wide

dispersion of PAWP values among the cohorts led to a zone of partial overlap between HFpEF and controls at values between 20 and 25 mmHg.

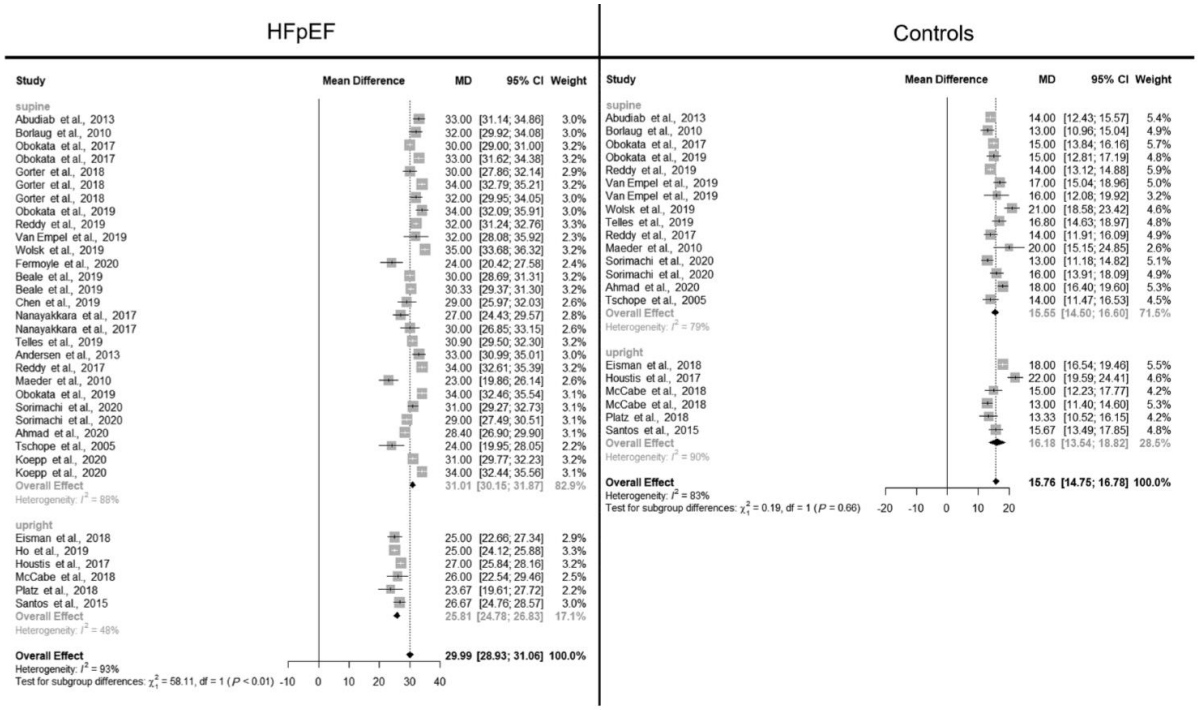


Figure 39. Forest plots with pooled standardized mean pulmonary artery wedge pressure values at peak exercise both in heart failure with preserved ejection fraction and in the controls.

Abbreviations. HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

PAWP/CO slope

We calculated the slope of the relationship between the increase of PAWP and CO during effort for each HFpEF and control cohort, with the aim to express the hemodynamic findings in a more homogeneous way, and to overcome the limits related to a certain methodological heterogeneity in the procedure and the measurement of a single absolute pressure value. Coherent with what shown above for rest and peak PAWP as well as for CO data, HFpEF cohorts had a significantly larger impairment in the hemodynamic response to exercise than controls (**figure 38**). Indeed, HFpEF presented with a steeper PAWP/CO slope than controls (3.75; 95% CI: 3.20–4.28 mmHg/L/min and 0.95; 95% CI: 0.30–1.59 mmHg/L/min, p < 0.0001) even after adjustment for age, sex, BMI, and body position (p = 0.007). All PAWP/CO slopes in HFpEF cohorts were found

above the proposed pathological threshold of > 2 mmHg/L/min while control cohorts showed slopes always < 2 mmHg/L/min.

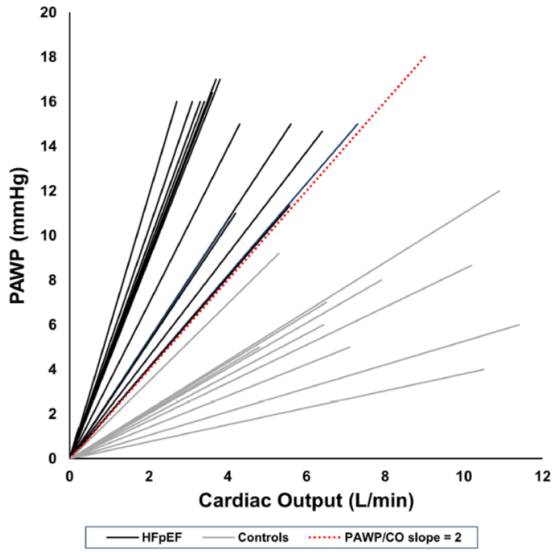


Figure 40. PAWP/ CO regression slopes in cohorts of patients with HFpEF and in control cohorts. The red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.

Abbreviations. CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

Body position: supine vs upright exercise

As previously pointed out, in 21 studies patients underwent exercise in supine position and in upright position in the remaining 6 (**table 6**). At peak exercise, HFpEF cohorts presented with a slightly higher summary estimates of PAWP in supine position than those obtained in upright position (supine position: 31; 95% CI:30–32 mmHg vs. upright position; 26; 95% CI: 25–27 mmHg, respectively, $p < 0.01$) as well as with a slightly lower delta CO in the supine than in the upright position (delta CO: 3.46 [3.18-3.73] vs 5.79 [5.44-6.15] L/min in supine and upright position, respectively, $p < 0.01$). As result, in HFpEF cohorts, summary estimate of PAWP/CO slope was higher in cohorts performing exercise in the supine position compared with those in upright position ($p < 0.0001$ and $p = 0.0002$ at non-adjusted and adjusted analysis, respectively), as represented in **figure 41**. Thus, absolute value of PAWP/CO slope might not provide comparable results in

patients performing supine or upright exercise, even if its cut-off of 2 mmHg/L/min might be valid to diagnose HFpEF irrespectively from body position during effort.

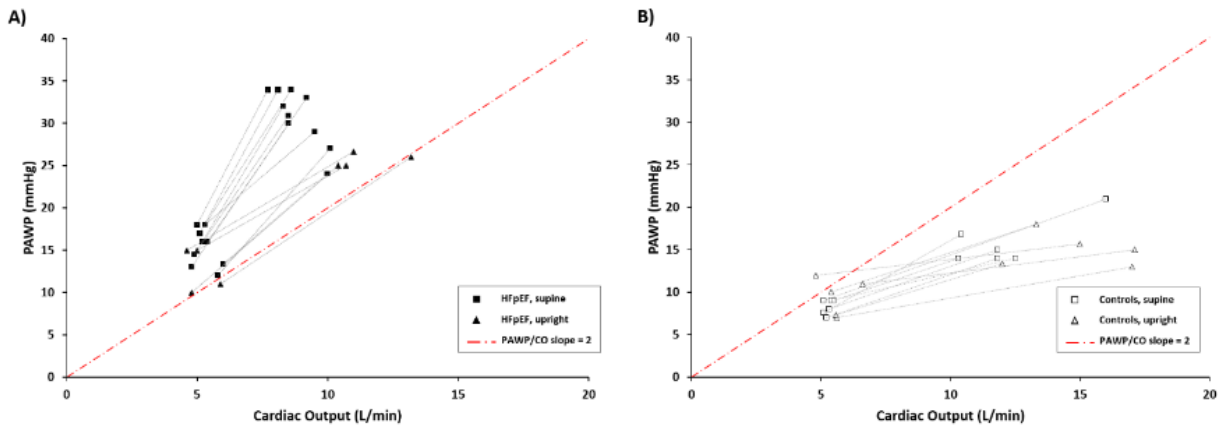


Figure 41. PAWP/CO regression slopes in patients with HFpEF and in the control groups, stratified by body position. Panel A represents the mean PAWP/CO slope of HFpEF patients and panel B represents the mean PAWP/CO slope of the control group. Squares represented cohorts performing exercise in supine position, while triangles represented whose who performed exercise in upright position. In both panels the red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.

Abbreviations. CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

Stratified analyses

Stratified analyses were performed according to inclusion criteria of individual studies to account for potential populations' heterogeneity, subdividing studies defining HFpEF based on hemodynamic criteria only, from those defining HFpEF based on non-invasive, clinical criteria or including patients with LVEF < 50%. The high heterogeneity of rest PAWP as well as the rest PAWP summary estimates did not show relevant differences at this stratified data analysis not at rest nor even at peak exercise. Moreover, because there were more cohort studies per center with overlapped recruitment period, we performed a sensitivity analysis including only one cohort per center [6,12,30,69,72,73,77,78,79,83], obtaining comparable results with those obtained on the entire dataset, confirming the robustness of results.

Study 4: EX-LVEDP: PAWP and LVEDP during exercise in HFpEF [86]

METHODS.

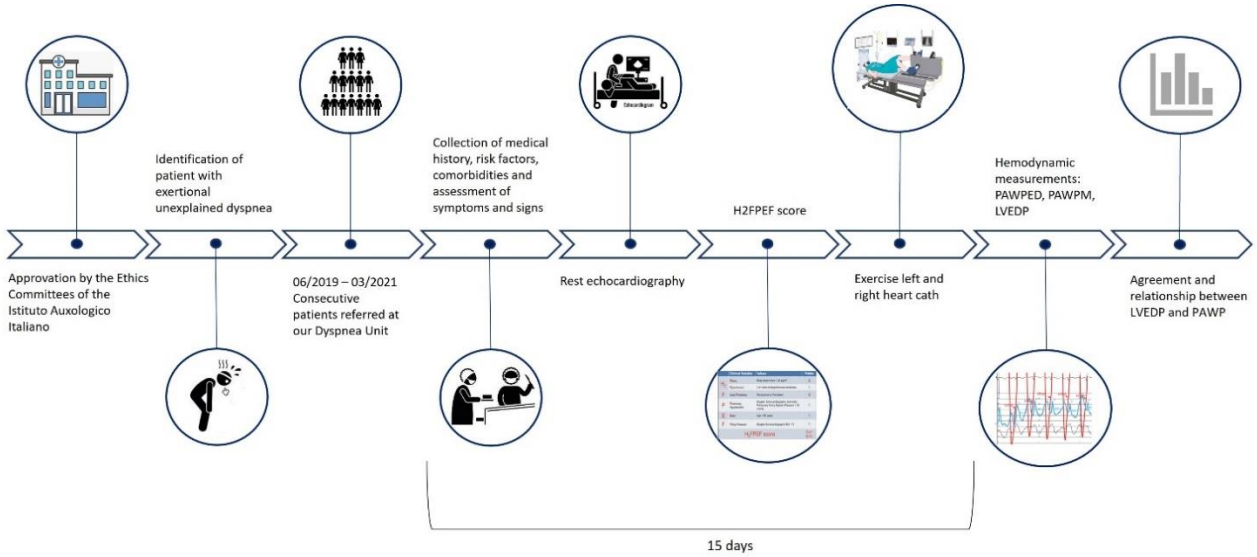


Figure 42. Representation of the EX-LVEDP study design.

Study design

EX-LVEDP study is a mono-centric, retrospective analysis on outpatients with exertional dyspnea underwent a comprehensive diagnostic assessment including exercise left and RHC. Whitin 15 days, patients underwent a non-invasive evaluation including clinical examination and rest echocardiography. Data were then analyzed to calculate the H_2FPEF probability score [21]. The agreement and the relationship between LVEDP and PAWP both at rest and during exercise were evaluated (**figure 42**).

EC approbation

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2020_04_21_03).

Inclusion criteria

Consecutive patients with exertional breathlessness referred for elective cardiac catheterization in suspicion of HFpEF or PH. Additionally, they needed to have been instrumented with both a Swan-Ganz catheter in the pulmonary artery and a pig-tail catheter in the left ventricle, and to have completed an exercise test in the supine position with a readable LVEDP at peak exercise.

Clinical assessment

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication to cardiac catheterization, were abstracted from clinical charts. Echocardiography was performed by experienced cardiologists following current recommendations [56]. The pre-test probability of HFpEF was assessed through the H_2FPEF score [21].

Exercise right and left heart catheterization

Patients were studied in supine position, wearing a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA), with a 7-F fluid-filled Swan-Ganz catheter [Edwards LifeScience] placed in the pulmonary artery. A 5-F pig-tail catheter was placed in the LV through a 6-F right radial artery sheath [Cordis]. Hemodynamic measurements as well as blood samples from pulmonary artery and radial artery were taken in order to calculate CO by the direct Fick method in each step of exercise RHC. Hemodynamic assessment was thus realized in resting conditions, after one minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test, whose increment in workload was personalized in order to obtain at least three steps (about 10 minutes) of exercise before exhaustion [31].

Hemodynamic measurements

Pressures were measured both at end-expiration, and averaged over several (at least 5) respiratory cycles. Additionally, PAWP was measured: i) at end-diastole (PAWPED): at mid-A for patients in sinus rhythm, at mid-C – when visible – or at pre-V for patients in atrial fibrillation; ii) averaging PAWP throughout the cardiac cycle (mean PAWP or PAWPM). V waves were measured on the PAWP waveform, and their amplitude was calculated as the difference between the zenith of the V wave and the mean PAWP value. A linear regression was applied to multiple pairs of PAWP and CO points, in order to calculate the PAWP/CO slope [6]. The speed sweep was adapted to better visualize LVEDP despite increasing heart rate during exercise. HFpEF was defined by either an end-expiratory PAWPM or LVEDP > 15 mmHg at rest and/or ≥ 25 mmHg at peak exercise. In case of disagreement between these two variables at peak exercise, an end-expiratory PAWP/CO slope > 2 mmHg/L/min was considered as an additional hemodynamic parameter indicative of HFpEF.

Statistics

Continuous variables are reported as mean ± SD when normally distributed and as median and [first, Q1, – third, Q3 quartile] otherwise. Categorical data are showed as absolute number [percentage]. The agreement and the relationship between LVEDP and PAWP at different conditions was tested by Bland-Altman analysis and linear regression analysis, respectively; whilst the reliability of agreement was assessed using the Cohen's kappa.

RESULTS.

Forty-six patients undergone a left and right cardiac catheterization at rest and during exercise between June 2019 and March 2021 were analyzed.

Clinical characteristics

Mean age of the included population was 71 years, 67% of individuals were females, mean body mass index was 27 Kg/m^2. Cardiovascular risk factors were well represented including arterial hypertension (79%), obesity (22%), diabetes mellitus (15%), paroxysmal AF (20%) and coronary artery disease (15%). Median brain natriuretic peptide was 106 ng/L and median LA volume index was 34 mL/m^2.

Hemodynamics

Pressures were measured both at end-expiration and averaged over at least 5 respiratory cycles. Additionally, PAWP was measured both at end-diastole (PAWPED) as well as averaging PAWP throughout the cardiac cycle (mean PAWP or PAWPM). Rest and exercise end-expiratory hemodynamic data of the whole cohort are reported in **Table 8**.

	Rest	Peak exercise
Workload, Watt		50 (40-75)
HR, bpm	69 (60-76)	110 (97-122)
HR, % of predicted		74 (66-82)
Systolic BP, mmHg	144 (136-155)	180 (160-195)
Diastolic BP, mmHg	73 (64-80)	87 (75-100)
Mean PAP, mmHg	20 (16-25)	40 (37-49)
LVEDP, mmHg	15 (10-20)	30 (25-36)
$PAWP_M$, mmHg	13 (9-18)	31 (26-39)
$PAWP_{ED}$, mmHg	13 (9-17)	30 (25-38)
$PAWP_M$ / CO slope, mmHg/L/min		2.4 (1.8-4.3)
PAWP, V wave, mmHg	15 (10-24)	38 (32-48)
Mean RAP, mmHg	6 (4-8)	16 (12-22)
CO, L/min	4.6±1.5	9.1 (7.1-11.1)
CI, L/min/m^2	2.6±0.7	5.1 (4.1-6.2)

Table 8. Rest and exercise hemodynamics of the study population. **End-expiratory pressure measurements are reported.**

Abbreviations. BP, blood pressure; CO, cardiac output; CI, cardiac index; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressure; $PAWP_{ED}$, end-diastolic pulmonary artery wedge pressure; $PAWP_M$, mean pulmonary artery wedge pressure; RAP, right atrial pressure.

Linear associations between end-expiratory rest and peak exercise LVEDP and PAWP (both PAWPED and PAWPM) were found, as represented in **figure 43**.

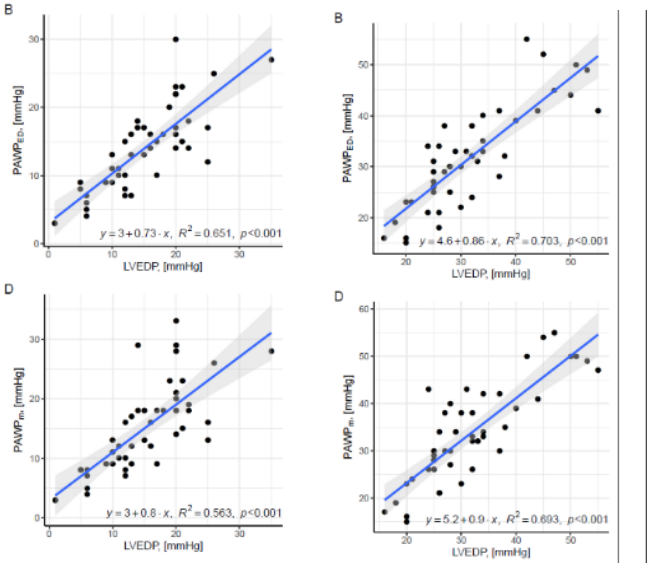


Figure 43. Linear regression analysis of end-expiratory LVEDP vs PAWP (both PAWPED and PAWPM) both at rest (left) and at peak exercise (right).

Abbreviations. LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary artery wedge pressure.

Concordance between LVEDP and PAWP

Mean bias for end-expiratory PAWPED vs LVEDP at peak exercise was minimal (+0.11 mmHg) but with large confidence intervals (±10.76 mmHg). At peak exercise, end-expiratory PAWPM overestimated LVEDP by 2 mmHg, again with large confidence intervals (±11.35 mmHg), as reported in **figure 44**.

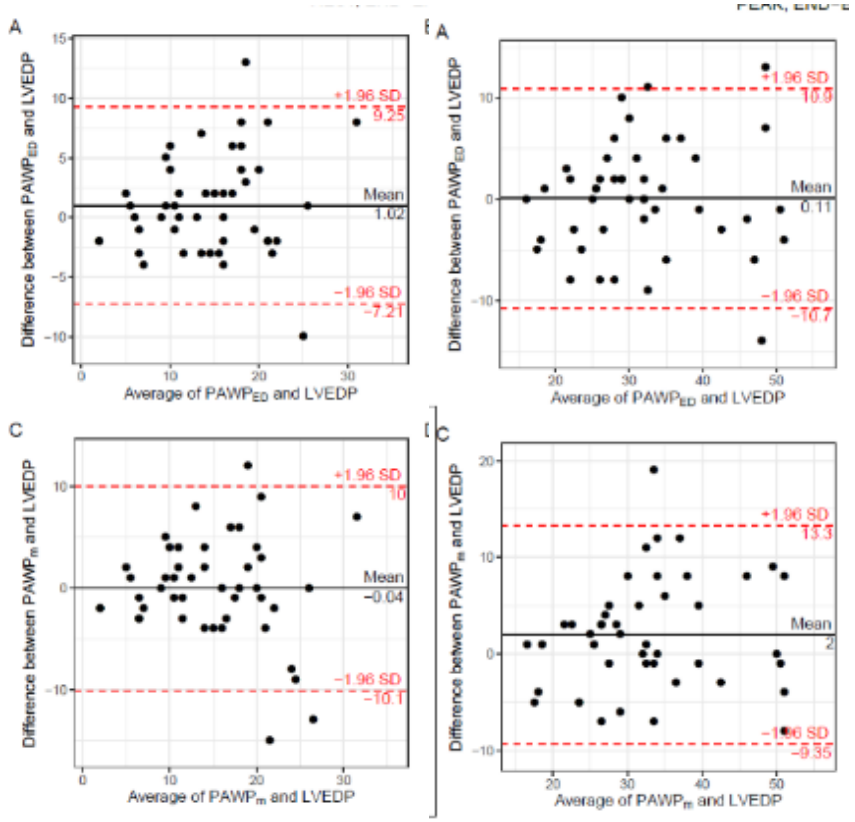


Figure 44. Bland-Altman plot of end-expiratory rest (left) and peak exercise (right) LVEDP vs PAWP (both PAWPED and PAWPM).

Abbreviations. LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary artery wedge pressure.

At rest, 46% of individuals had either an end-expiratory PAWPM or a LVEDP > 15 mmHg, and 57% had a PAWPM and/or a LVEDP > 15 mmHg at rest. The rate of concordance between both PAWPM and PAWPED and LVEDP, dichotomized according to a value of 15 mmHg, was 78%, with moderate agreement (Cohen's K = 0.56).

During exercise, 80% and 83% of individuals had either an end-expiratory PAWPM or LVEDP ≥ 25 mmHg. However, at peak exercise, 87% of patients had an end-expiratory PAWPM and/or LVEDP ≥ 25 mmHg. The two so-dichotomized measures were concordant in 89% of cases with substantial agreement (Cohen's K = 0.64).

In particular, 3 patients had a PAWPM ≥ 25 mmHg but a LVEDP < 25 mmHg, and 2 patients had a LVEDP ≥ 25 mmHg but a PAWPM < 25 mmHg. All these 5 patients, with discordant PAWPM and LVEDP, had a PAWPM/CO slope > 2 mmHg/L/min, as represented in **figure 45**.

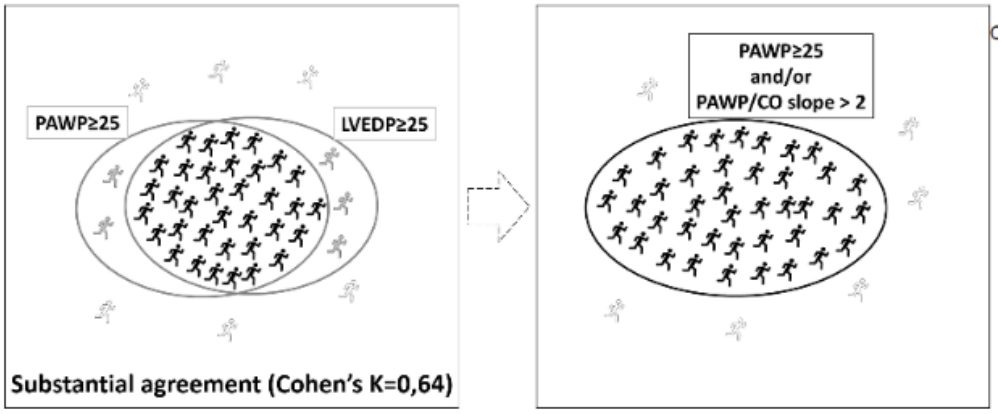


Figure 45. Venn diagrams show the agreement of dichotomized PAWP and LVEDP values above the diagnostic threshold to diagnose HFpEF at peak exercise. Despite substantial agreement at peak exercise, 5 individuals had either PAWP or LVEDP above the diagnostic threshold for HFpEF. All of them presented with a PAWP/CO slope > 2 mmHg/L/min, suggesting that incorporation of flow-corrected PAWP in the definition of HFpEF (PAWP ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min) may maximize the diagnostic yield of exercise RHC.

Abbreviations. CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary artery wedge pressure.

Study 5: HFPEF-STR: impact of severe secondary TR on HFpEF hemodynamics [87]

METHODS

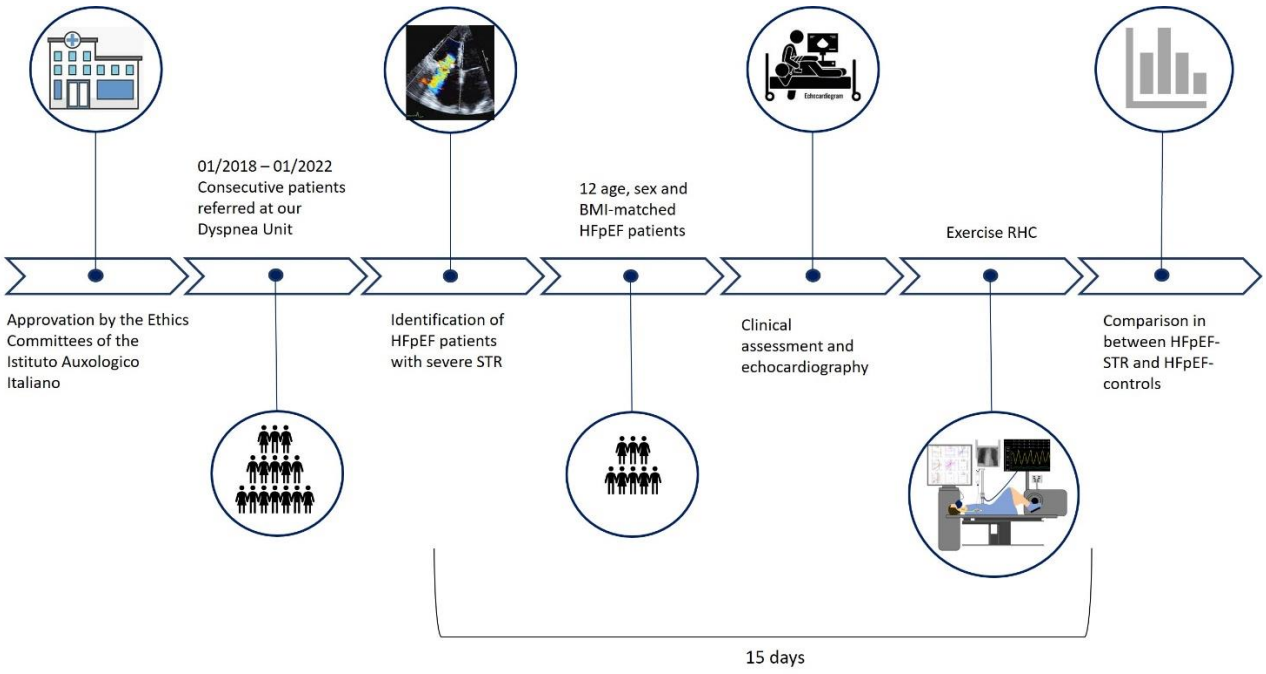


Figure 46. Representation of the STR-HFpEF study design.

Study design

STR-HFpEF study is a mono-centric, retrospective analysis on outpatients with exertional dyspnea underwent a comprehensive diagnostic assessment including exercise RHC. Whitin 15 days, patients underwent a non-invasive evaluation including clinical examination and rest echocardiography. Among patients diagnosed with HFpEF, we selected those with severe TR, and an equal number of matched HFpEF patients with no or mild TR. Then, we compared the clinical and hemodynamic profile of HFpEF patients with and without severe TR (**figure 46**).

EC approbation

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2020_04_21_03 approved on April 21st, 2020).

Inclusion criteria

Consecutive patients who underwent a cardiac catheterization at rest and during exercise for exertional dyspnea. Cases were the patients with HFpEF and severe STR (HFpEF-STR). From 74 patients with HFpEF without severe TR, an equal number of controls for an individual matching to cases (ratio 1:1) considering sex-, age- (±5 years), and body mass index- (±2 Kg/m2) was selected.

Clinical assessment and echocardiography

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication to cardiac catheterization, were abstracted from clinical charts. Echocardiography was performed according to current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography on the same day of the RHC [56], using a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway). Echocardiographic evaluation of STR severity was based on an integrative approach considering multiple qualitative and quantitative parameters [88,89]. Definition of "atrial" STR was based on the exclusion of other common secondary causes of TR and on an echocardiographic estimation of systolic PAP < 50 mmHg [90].

Exercise RHC

Patients were studied in supine position, wearing a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA), with a 7-F fluid-filled Swan-Ganz catheter [Edwards LifeScience] placed in the pulmonary artery and a 4 F catheter placed in the radial artery [Arrow]. Hemodynamic measurements as well as blood samples from pulmonary artery and radial artery were taken in order to calculate CO by the direct Fick method in each step of exercise RHC. Hemodynamic assessment was thus realized in resting conditions, after one minute of passive leg raise (feet on the pedals),

and during the last minute of each step of a symptom-limited exercise test, whose increment in workload was personalized in order to obtain at least three steps (about 10 minutes) of exercise before exhaustion [31].

Hemodynamic and ergospirometric measurements

PAP, PAWP and RAP were reported as an average of several respiratory cycles. CO was calculated by the direct Fick method, solving the VO_2 equation as follows: CO = VO_2/arteriovenous O_2 difference ($C(a\text{-}v)O_2$). To evaluate the relative contribution of the elements of the Fick equation to exercise capacity, we plotted CO as a function of $C(a\text{-}v)O_2$ on which we represented VO_2-isophlets. LV trans-mural pressure (LVTMP), as a measure of LV preload, independent of right heart filling and pericardial restraint, was calculated as PAWP–RAP [91]. We plotted the relationship between PVR and SV to explore whether low anterograde SV may be linked to pulmonary vascular derecruitment and higher than normal PVR [44]. Key ergospirometric measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters. Peak VO_2 was measured as the highest 30-s value obtained at the end of the effort. The slope of the relationship between minute ventilation and carbon dioxide production ($VECO_2$ slope) was calculated over the linear component of VE vs. VCO_2 [53].

Statistics

Continuous variables are reported as mean and SD or median and interquartile range if the data did not follow a normal distribution. The categorical variables are shown as absolute frequencies and proportions. For data at rest, unpaired T-test (or Wilcoxon signed rank sum test in case of non-normal distribution) was applied to compare the continuous variables between HFpEF-STR and HFpEF-controls, while Chi-square test (or Fisher test) was used to compare the categorical variables. For each hemodynamic variable measured during exercise, an ANOVA model for repeated measures was fitted, considering an unstructured variance-covariance matrix to take into account the correlation among measurements on the same subjects. The included covariates in each model were group (HFpEF-STR or HFpEF-controls), time (Rest, Leg Raise and Peak)

and their interaction. The statistical significance of interaction term suggested a different trend of the hemodynamic variables between groups. Moreover, we tested the least square means (LS-means) differences among groups at each time by means of unpaired t-test applying the False Discovery Rate (FDR) approach to control the inflation of the type I error. The relationship between continuous hemodynamic variables at specific time-point was investigated by means quadratic B-spline with 1 knot. The goodness of fit of the model was estimated by means of R2. This value, ranging from 0 to 1, represents the proportion of total variance of an independent variable explained by a dependent variable. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

RESULTS

Twelve HFpEF-STR patients were 1:1 matched by sex-, age- (±5 years), and BMI-(±2 Kg/m^2) with 12 HFpEF without STR (HFpEF-controls), selected from the cohort of patients undergone an exercise RHC between January 2018 and January 2022, as represented in **figure 47.** HFpEF-STR represented 14% of the entire HFpEF population underwent a RHC during the study period.

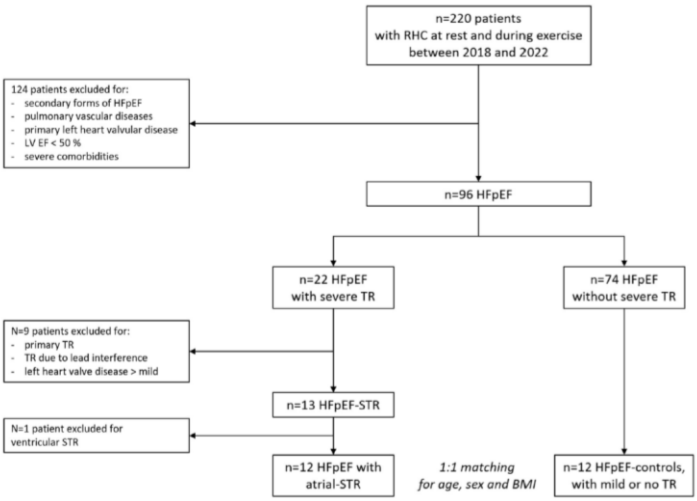


Figure 47. Patients' selection flow-chart.

Abbreviations. BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; LV EF, left ventricular ejection fraction; RHC, right heart catheterization; STR, secondary tricuspid regurgitation; TR, tricuspid regurgitation.

Clinical characteristics

Included patients represented quite typical elderly, overweight and predominantly female HFpEF population, with a quite wide burden of cardiovascular comorbidities. Of note, 83% of patients with HFpEF-STR had permanent atrial fibrillation, as compared with only 8% of HFpEF-controls ($p < 0.01$). Representation of HF signs and symptoms as well as BNP values did not significantly differ between groups. Data reflecting secondary organ damage (renal, hepatic) showed similar values. HFpEF-STR patients presented more frequently with a dilated RV than HFpEF-controls (58 vs. 11%, $p = 0.067$), and with larger LA and RA volumes that were (43 and 84% larger than in HFpEF-STR than in HFpEF-controls, respectively, $p < 0.01$).

Hemodynamics

At rest, patients with HFpEF-STR had higher mean PAP and PAWP than HFpEF-controls, as shown in **Table 9.** PH (i.e. mPAP > 20 mmHg) was present in 83% of HFpEF-STR and in 25% of HFpEF-controls. SV was lower in HFpEF-STR than in HFpEF-controls, compensated by higher heart rate to maintain a similar and preserved cardiac index. PVR was slightly increased in HFpEF-STR patients (2.1±0.3 WU) but not significantly higher to that of HFpEF-controls. RAP was twice as high in HFpEF-STR than in HFpEF-controls, with tall V waves and a high RAP/PAWP ratio.

	Rest		Leg raise		Peak	
	HFpEF-controls	HFpEF-STR	HFpEF-controls	HFpEF-STR	HFpEF-controls	HFpEF-STR
HR, bpm	66 ± 4	81 ± 4*	68 ± 4	81 ± 4*	99 ± 6	120 ± 6*
SVI, mL/min/m^2	43 ± 4	28 ± 4*	45 ± 4	32 ± 4*	52 ± 2	32 ± 5*
CI, mL/min/m^2	2.8 ± 0.2	2.2 ± 0.2	2.9 ± 0.2	2.5 ± 0.2	4.9 ± 0.3	3.7 ± 0.3*
C(a-v)O_2, mL/dL	4.2 ± 0.3	5.3 ± 0.3**	4.3 ± 0.3	6.0 ± 0.3**	11.2 ± 0.7	13.3 ± 0.7*
PVR, WU	1.5 ± 0.3	2.1 ± 0.3	1.3 ± 0.3	1.6 ± 0.3	1.1 ± 0.3	1.7 ± 0.3
mPAP, mmHg	18 ± 1	24 ± 1*	23 ± 2	27 ± 2	36 ± 2	39 ± 2
PAWP, mmHg	11 ± 2	17 ± 2*	16 ± 2	21 ± 2	28 ± 2	29 ± 2
LVMTP, mmHg	6 ± 1	7 ± 1	8 ± 1	8 ± 2	13 ± 2	7 ± 2*
RAP, mmHg	5 ± 1	10 ± 1**	8 ± 1	14 ± 1**	14 ± 2	23 ± 2**
RAP V wave, mmHg	6 ± 1	13 ± 1***	9 ± 2	18 ± 2***	17 ± 2	28 ± 2***
RAP/PAWP	0.45 ± 0.08	0.64 ± 0.08	0.52 ± 0.05	0.67 ± 0.05*	0.50 ± 0.06	0.79 ± 0.06**

Table 9. Hemodynamics at rest, with feet on the pedals and at peak exercise in the study cohort. ∗p < 0.05; ∗∗p < 0.01; ∗∗∗p < 0.001.

Abbreviations. CI, cardiac index; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LVMTP, left ventricular transmural pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; STR, secondary tricuspid regurgitation; SVI, stroke volume index.

During exercise PAWP increased less in HFpEF-STR patients than in HFpEF-controls (**figure 48)**: despite higher PAWP in HFpEF-STR than in HFpEF-controls at rest, at peak exercise PAWP was not different in the two groups (**table 9**). Mean RAP and RAP V waves displayed an opposite behavior, increasing more in HFpEF-STR patients than in HFpEF-controls (interaction p-value = 0.06, **figure 48**), with persistently higher RAP and RAP/PAWP ratio in HFpEF-STR patients than in HFpEF-controls (group p-value < 0.01, **table 9**). Accordingly, LVTMP increased only in HFpEF-controls during exercise (interaction p-value = 0.006, **figure 48**), coherent with LV underfilling in HFpEF-STR patients.

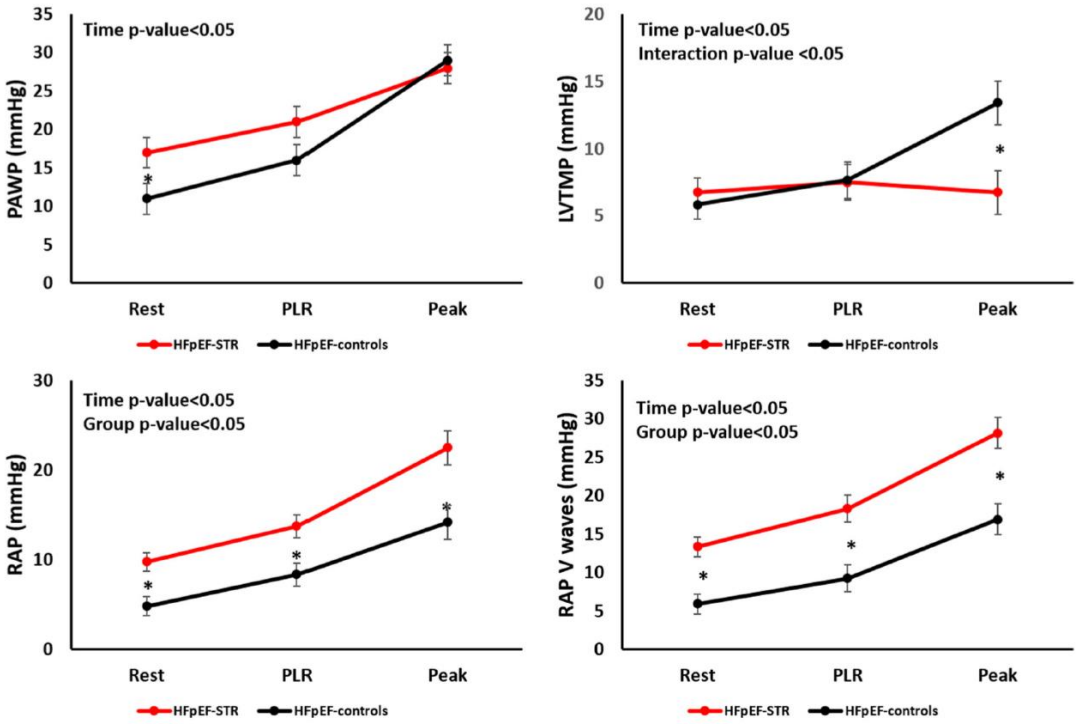


Figure 48. Evolution of left and right heart hemodynamics during exercise in our patients' population. *p < 0.05

Abbreviations. HFpEF, heart failure with preserved ejection fraction; LVTMP, left ventricular transmural pressure; PAWP, pulmonary artery wedge pressure; PLR, passive leg raising; RAP, right atrial pressure; STR, secondary tricuspid regurgitation

Functional capacity

Peak VO_2 was not different between HFpEF-STR and HFpEF-controls (12±4 and 13±3 mL/kg/min, respectively, p = 0.690). However, the determinants of VO_2 (**Figure 45**) behaved differently in the two groups, with a lower increase in CO (group p-value < 0.05) and a higher $C(a\text{-}v)O_2$ in HFpEF-STR patients as compared with HFpEF-controls (13.3±0.7 vs 11.2±0.7 respectively, group p-value < 0.05). In particular, HFpEF-STR and HFpEF-controls roughly lay on the same VO_2 isophlets at each step of exercise, with HFpEF-STR rightward and downward shifted (**Figure 49**). Accordingly, the CO/VO_2 slope, as a measure of CO reserve, was lower in HFpEF-STR patients than in HFpEF-controls (3.9 vs. 5.5, p = 0.024) as well as the SV at peak exercise, which resulted 40 mL lower in HFpEF-STR (group p-value = 0.018). Despite that, the rate of increase of SV did not significantly differ in the two groups (p = 0.174), as well as PVR which, similarly between the 2 groups, physiologically decreased (by 0.4–0.5 WU) during exercise.

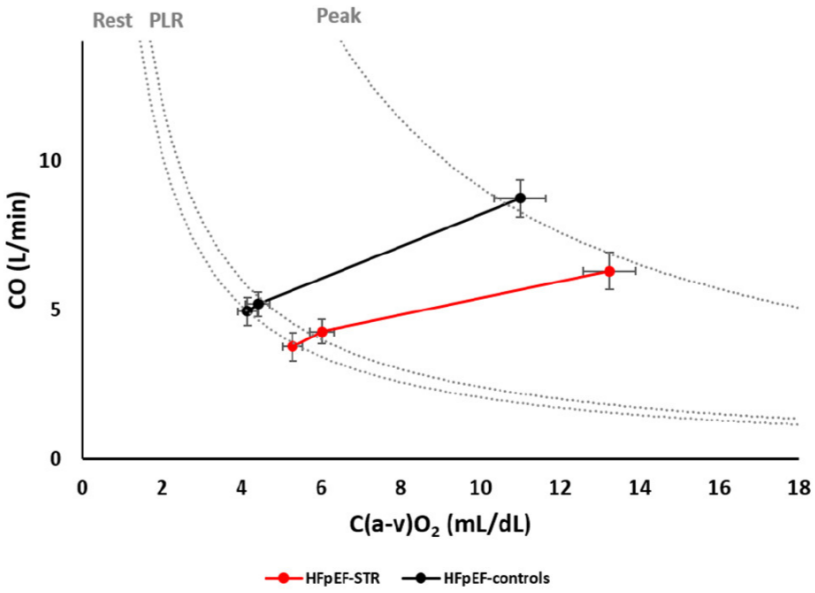


Figure 49. Relative weight of cardiac output and arteriovenous oxygen difference in determining oxygen consumption at rest, during passive leg raising and at peak exercise. **Dotted lines represent oxygen consumption isophlets, i.e., cardiac output and arteriovenous oxygen difference coordinates whose product is a given oxygen consumption, at rest, during passive leg raising, and at peak exercise.**

Abbreviations. $C(a\text{-}v)O_2$, arteriovenous oxygen difference; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PLR, passive leg raising; STR, secondary tricuspid regurgitation.

Study 6: LATENT-PVD HFpEF phenotype [92]

METHODS

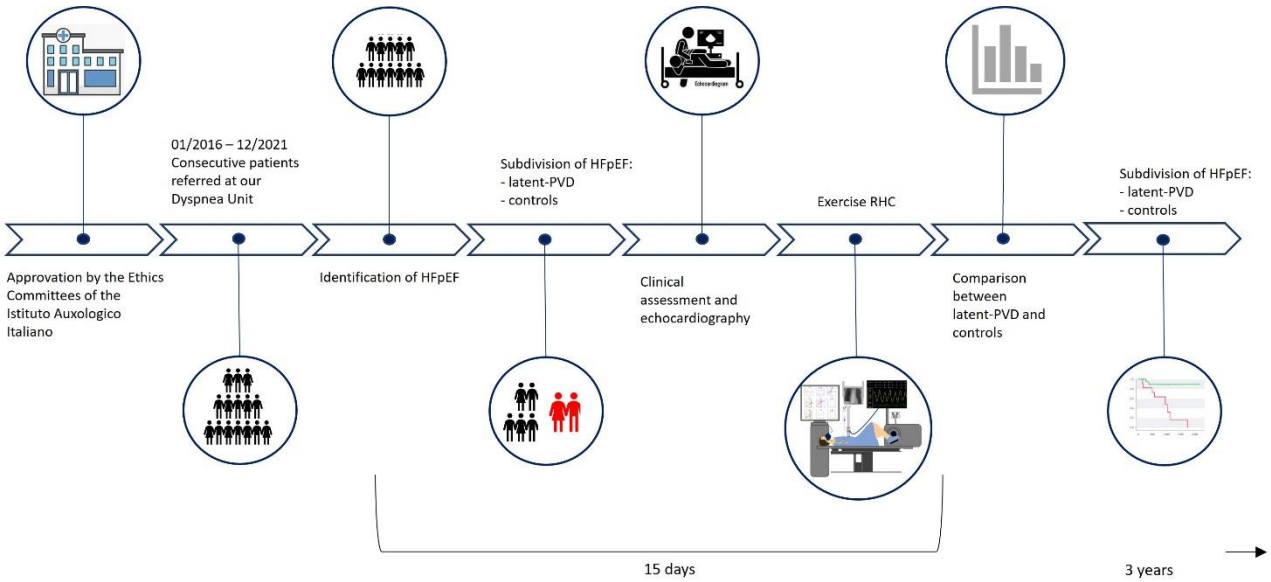


Figure 50. Representation of the HFpEF LATENT-PVD study design.

Study design

HFpEF LATENT-PVD study is a mono-centric, retrospective analysis on outpatients with exertional dyspnea underwent a comprehensive diagnostic assessment including exercise RHC. Whitin 15 days, patients underwent a non-invasive evaluation including clinical examination and rest echocardiography. Among patients diagnosed with HFpEF, we identified those diagnosed with HFpEF, and we subdivided this cohort based on PVR at peak exercise: > 1.74 WU (HFpEF latent-PVD) or ≤ 1.74 WU (HFpEF control patients) [49]. Then, we compared the clinical and hemodynamic profile of HFpEF latent-PVD patients with HFpEF patients non latent-PVD (**figure 50**).

EC approbation

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2022_09_27_01 approved on September 27, 2022).

Inclusion criteria

Consecutive patients who underwent a cardiac catheterization at rest and during exercise for exertional dyspnea. We included only hemodynamically-proven HFpEF patients (i.e. PAWP at rest > 15 mm Hg, or a peak PAWP ≥ 25 mm Hg, or a PAWP/ CO slope > 2 mm Hg/L/min [6]), subdivided this cohort of patients based on PVR at peak exercise: > 1.74 WU (HFpEF latent-PVD) or ≤ 1.74 WU (HFpEF control patients) [49].

Clinical assessment and echocardiography

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication to cardiac catheterization, were abstracted from clinical charts. Echocardiography was performed according to current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography on the same day of the RHC [56], using a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway). Clinical and echocardiographic data were analyzed to calculate both the H_2FPEF probability score [21] and the HFA-PEFF score [22].

Exercise RHC

Patients were studied in supine position, wearing a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA), with a 7-F fluid-filled Swan-Ganz catheter [Edwards LifeScience] placed in the pulmonary artery and a 4 F catheter placed in the radial artery [Arrow]. Hemodynamic measurements as well as blood samples from pulmonary artery and radial artery were taken in order to calculate CO by the direct Fick method in each step of exercise RHC. Hemodynamic assessment was thus realized in resting conditions, after one minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test, whose increment in workload was personalized in order to obtain at least three steps (about 10 minutes) of exercise before exhaustion [31].

Key ergospirometric measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters. Peak VO_2 was measured as the highest 30-second value obtained at the end of the effort. Minute ventilation was normalized for CO_2 production. Dead space ventilation was calculated based on standard formula [93].

Hemodynamic and ergospirometric measurements

PAP, PAWP and RAP were measured at end-expiration over several cardiac and respiratory cycles. In addition to end-expiratory mean PAWP and RAP, the diastolic and systolic components of each atrial pressure were evaluated, including the following: i) End-diastolic PAWP and RAP: mid-A for in patients in sinus rhythm and mid-C (when visible) or pre-V For patients in atrial fibrillation; ii) PAWP V amplitude: the difference between V wave and mean PAWP; iii) Systolic increase in RAP: the difference between right atrium V wave and RAP nadir, reflecting the severity of tricuspid regurgitation [94]. CO was calculated by the direct Fick method, solving the VO_2 equation as follows: $CO = VO_2/C(a\text{-}v)O_2$. Furthermore, to evaluate the relative contribution of the elements of the Fick equation to exercise capacity, we plotted CO as a function of peripheral O_2 extraction, i.e., $C(a\text{-}v)O_2$/arterial O_2 content, i.e. $C(a\text{-}v)O_2/CaO_2$. Pivotal hemodynamic variables were also dichotomized (normal vs pathologic) both at rest and during exercise, based on previously described cutoff values. This served to define, during each stage of the test (rest and exercise), the following predefined hemodynamic phenotypes: pulmonary hypertension [29], left atrial hypertension, left atrial dysfunction as determined by the presence of tall PAWP V waves (V wave amplitude > 5 mmHg) in the absence of significant mitral regurgitation, precapillary pulmonary vascular component [29,49], severe tricuspid regurgitation [94], and low CO or low CO increase [95] (**table 12**).

Follow up

Relevant clinical events occurring during the follow-up (hospitalization for HF, access to the emergency department > 12 hours and/or need of intravenous diuretics, death) were captured through a review of electronic medical records by an investigator blinded to the hemodynamic data.

Statistics

Continuous variables are reported as mean ± SD or median (interquartile range, IQR) if the data did not follow a normal distribution. The categorical variables are shown as absolute frequencies and proportions. For baseline characteristics, comparisons between HFpEF latent-PVD patients and HFpEF control patients were performed by unpaired Student's t-test (or Wilcoxon rank sum test in case of nonnormal distribution) for continuous variables and by chi-square test (or Fisher test) for categorical variables. For each hemodynamic variable measured during exercise, a linear mixed-effect model for repeated measures was fitted, considering an unstructured variance-covariance matrix to take into account the correlation among measurements on the same subjects. The included covariates in each model were group (HFpEF latent-PVD patients and HFpEF control patients), step (rest and peak exercise), and their interaction. The statistical significance of interaction term suggested a different trend of the hemodynamic variables between groups. Moreover, we tested the least square means differences among groups at each step by means of unpaired Student's t-test. Kaplan-Meier curves were used to estimate the event-free survival rates in HFpEF latent-PVD patients and HFpEF control patients, and, in an exploratory analysis, the differences between groups were evaluated through the log-rank test. All analyses were performed with SAS version 9.4 software (SAS Institute). Statistical significance was set at the 0.05 level. All p-values were 2-sided.

RESULTS.

Eighty-six patients with an exercise RHC between January 2016 and December 2021 and diagnosed with HFpEF were included in this study. Patients were stratified according to PVR at peak exercise: n=18 (21%)

HFpEF latent-PVD patients (peak PVR > 1.74 WU) and n=68 (79%) HFpEF control patients (peak PVR ≤ 1.74 WU) [49].

Clinical characteristics

In general, the included population represented typical elderly, overweight, and predominantly female HFpEF population. HFpEF latent-PVD patients were older, more frequently had atrial fibrillation, had higher probability of HFpEF based both on the HFA-PEFF and the H_2FPEF scores as well as higher NT-proBNP (**table 10**). Interestingly, HFpEF latent-PVD patients more frequently had at least moderate TR (61% vs 28%; p = 0.009).

	HFpEF-controls n=68	**HFpEF latent-PVD n=18**	**p-value**
Demographic and anthropometrics			
Age, years	72 [67-78]	77 [71-81]	**0.025**
Female sex, n (%)	46 (68)	13 (72)	0.710
BMI, Kg/m^2	27.0±5.6	26.3±4.6	0.607
Vital signs			
SBP, mmHg	132±16	130±17	0.602
DBP, mmHg	75±11	74±12	0.761
HR, mmHg	70±11	69±10	0.807
Rhythm			**0.004**
Sinus rhythm	48 (71)	8 (44)	
Paroxysmal AF	12 (18)	1 (6)	
Persistent AF	6 (9)	6 (33)	
Permanent AF	2 (3)	3 (17)	
Comorbidities			
Obesity, n (%)	20 (29)	2 (11)	0.139
Arterial hypertension, n (%)	50 (74)	16 (89)	0.221
Diabetes mellitus / impaired glucose tolerance, n (%)	7 (10)	7 (39)	**0.003**
Coronary artery disease, n (%)	9 (13)	5 (28)	0.158
History of pulmonary embolism, n (%)	5 (7)	2 (11)	0.633
Smoking history, n (%)	27 (40)	5 (28)	0.420
COPD (only GOLD I-II), n (%)	18 (26)	4 (22)	1.000
Obstructive sleep apnea, n (%)	15 (22)	4 (22)	1.000
Implanted pace-maker, n (%)	8 (12)	4 (22)	0.266
AF ablation, n (%)	6 (9)	3 (17)	0.388
Thoracic radiotherapy, n (%)	9 (13)	2 (11)	1.000
Blood tests			
Hemoglobin, g/dL	13.3±1.6	12.6±1.7	0.103
Creatinine, mg/dL	0.93 [0.81-1.02]	1.07 [0.71-1.29]	0.512

BNP, ng/L	99 [55-210] N=49/68	88 [42-414] N=12/18	0.684
proBNP, ng/L	193 [55-408] N=41/68	673 [304-881] N=13/18	**0.013**
Echocardiography			
LVEF, %	64 [62-66]	61 [54-65]	**0.007**
LVEDVI, mL/m^2	47 [41-64]	46 [42-59]	0.691
IVS thickness, mm	10.3±1.4	10.8±1.0	0.167
PW thickness, mm	9.3±1.2	9.8±1.1	0.176
LAVI, mL/m^2	34 [26-49]	43 [30-51]	0.166
E/e'	9.2 [8.1-12.0]	11.5 [7.7-14.9]	0.236
Estimated SPAP, mmHg	33 [28-45]	40 [35-53]	**0.003**
Moderate or > moderate TR, n (%)	19 (28)	11 (61)	**0.009**
Moderate MR, n (%)	5 (7)	4 (22)	0.087
Probability of HFpEF			
H_2FPEF score	3.9±2.0	5.1±2.0	**0.022**
H_2FPEF score > 4, n (%)	36 (53)	13 (72)	0.142
HFA-PEFF score	3.3±2.0	4.8±1.3	**0.004**
HFA-PEFF score > 4, n (%)	22 (32)	10 (56)	0.070

Table 10. Clinical Characteristics of the Study Groups. Values are median (IQR), mean±SD, or n (%).

Abbreviations. AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; GOLD, global initiative for obstructive lung disease; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; IVS, interventricular septum; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PW, posterior wall; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

Rest hemodynamics

Resting hemodynamics differed between the 2 groups only for mean pulmonary artery pressure and PVR (**table 11)**, both of which were higher in HFpEF latent-PVD patients than in HFpEF control patients ($p < 0.05$), at similar PAWP, RAP, CO, and stroke volume values.

	REST		**EXERCISE**		**Group p-value**	**Step p-value**	**Interaction p-value**
	HFpEF-controls	**HFpEF latent-PVD**	**HFpEF-controls**	**HFpEF latent-PVD**			
Hemodynamics							
Mean PAP, mmHg	20±1	26±2*	41±1	47±2*	**0.005**	**<0.001**	0.738
End-diastolic PAWP, mmHg	8±1	8±1	20±1	23±2	0.532	**<0.001**	0.087
Mean PAWP, mmHg	14±1	16±2	34±1	30±2	0.678	**<0.001**	**0.009**
PAWP V amplitude, mmHg	4±1	5±1	9±1	9±2	0.472	**<0.001**	0.268
Mean RAP, mmHg	7±1	6±1	17±1	18±2	0.989	**<0.001**	0.432
End-diastolic RAP, mmHg	7±1	6±1	17±1	16±2	0.679	**<0.001**	0.849

RAP systolic increase, mmHg	2±1	3±1	6±1	10±2*	**0.033**	**<0.001**	**0.003**
PVR, WU	1.3±0.1	2.4±0.2*	0.8±0.1	2.6±0.1*	**<0.001**	0.199	**0.008**
HR, bpm	69±2	71±3	111±3	105±5	0.652	**<0.001**	0.182
CO, L/min	4.7±0.2	4.3±0.4	9.7±0.3	6.9±0.6*	**<0.001**	**<0.001**	**<0.001**
SV, mL	69±3	62±5	88±3	68±5*	**0.010**	**<0.001**	**0.006**
Ventilation & gas exchange							
VO_2, mL	195±15	209±8	1097±42	828±80*	**0.006**	**<0.001**	**0.004**
PvO_2, mmHg	40±1	40±1	25±1	22±1*	0.184	**<0.001**	**0.003**
SvO_2, %	72±1	69±1	38±1	30±2*	**<0.001**	**<0.001**	**0.009**
C(a-v)O_2, mL/dL	4.5±0.1	4.6±0.2	11.4±0.3	12.1±0.5	0.294	**<0.001**	0.228
C(a-v)O_2/CaO_2	0.25±0.01	0.28±0.01*	0.60±0.01	0.68±0.02*	**<0.001**	**<0.001**	**0.010**
Hb, g/dL	13.4±0.2	12.4±0.4*	14.2±0.2	13.3±0.4	**0.039**	**<0.001**	0.253
VE, L/min	8.2±0.4	8.2±0.7	38.3±1.6	30.8±3.0*	**0.043**	**<0.001**	**0.029**
$VECO_2$	55.0±1.9	55.7±3.6	35.7±0.7	36.2±1.3	0.811	**<0.001**	0.951
V_D/V_T	0.50±0.06	0.63±0.11	0.35±0.01	0.40±0.02*	0.174	**0.005**	0.571
$PaCO_2$, mmHg	39±1	43±1*	39±1	41±1*	**0.002**	**0.014**	0.183

Table 11. Resting and exercise hemodynamics in the 2 study groups.

Abbreviations. Hb, hemoglobin; $PaCO_2$, arterial partial pressure for carbon dioxide; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PvO_2, mixed venous oxygen pressure; PVR, pulmonary vascular resistance; SV, stroke volume; SvO_2, mixed venous oxygen saturation; VD/VT, dead space ventilation; VE, minute ventilation; $VECO_2$, minute ventilation over CO_2 production.

After dichotomization of resting hemodynamic patterns based on preestablished cutoff values (**table 12**), the 2 groups presented with similar distributions of left atrial hypertension, tall PAWP V waves, higher systolic increase of RAP and low CO. Pulmonary hypertension was non-significantly more represented in latent PVD. More HFpEF latent-PVD patients than HFpEF control patients presented with resting PVR > 2 WU (**table 13)**.

	Rest		Peak	
	No	**Yes**	**No**	**Yes**
Pulmonary hypertension	mPAP ≤20 mm Hg	mPAP >20 mm Hg	mPAP/CO slope ≤3	mPAP/CO slope >3
LA hypertension	PAWP ≤15 mm Hg	PAWP >15 mm Hg	PAWP <25 mm Hg and/or PAWP/CO slope ≤2	PAWP ≥25 mm Hg and/or PAWP/CO slope >2
LA dysfunction	PAWP V wave amplitude ≤5 mm Hg	PAWP V wave amplitude >5 mm Hg	PAWP V wave amplitude ≤5 mm Hg	PAWP V wave amplitude >5 mm Hg
Precapillary component	PVR <2 WU	PVR >2 WU	PVR ≤1.74 WU	PVR >1.74 WU
Tricuspid regurgitation	RAP V wave − RAP nadir ≤8 mm Hg	RAP V wave − RAP nadir >8 mm Hg	RAP V wave − RAP nadir ≤8 mm Hg	RAP V wave − RAP nadir >8 mm Hg
Low CO	CI ≥2.2 L/min/m^2	CI <2.2 L/min/m^2	CO ≥80% of predicted	CO <80% of predicted
Low CO increase			CO/VO_2 slope ≥4.7	CO/VO_2 slope <4.7

Table 12. Dichotomization of hemodynamic profiles at rest and during exercise: resting and exercise threshold definitions.

Abbreviations. CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; VO_2, oxygen consumption.

	Rest			Exercise		
	HFpEF Control Patients	HFpEF-latentPVD Patients	*P* Value	HFpEF Control Patients	HFpEF-latentPVD Patients	*P* Value
Pulmonary hypertension	32 (47)	13 (72)	0.068	41 (60)	17 (94)	0.005
LA hypertension	27 (40)	9 (50)	0.431	68 (100)	18 (100)	1.000
LA dysfunction	15 (22)	7 (39)	0.146	38 (56)	15 (83)	0.054
Pre-capillary component	7 (10)	13 (72)	<0.001	0 (0)	18 (100)	<0.001
Tricuspid regurgitation	4 (6)	2 (11)	0.601	11 (16)	9 (50)	0.002
Low CO	20 (29)	8 (44)	0.226	8 (12)	6 (33)	0.028
Low CO increase				20 (29)	10 (56)	0.039

Table 13. Dichotomization of hemodynamic profiles at rest and during exercise.
Abbreviations. CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; VO_2, oxygen consumption.

Exercise hemodynamics

During exercise, mean pulmonary artery pressure remained higher in HFpEF latent-PVD patients, despite lower PAWP (**table 11**). Moreover, HFpEF latent-PVD patients presented with a smaller increase in CO during exercise as well as in stroke volume, which irrelevantly increased from 62 mL at rest to 68 mL at peak (**table 11**). All this was mirrored by a lack of decrease of PVR in HFpEF latent-PVD patients as compared with HFpEF control patients, in whom PVR physiologically reduced with exercise (**figure 51**). The association between rest and exercise PVR witnessed that the HFpEF latent-PVD phenotype it could have been anticipated by PVR >2 WU at rest in 72% of cases (**figure 51**).

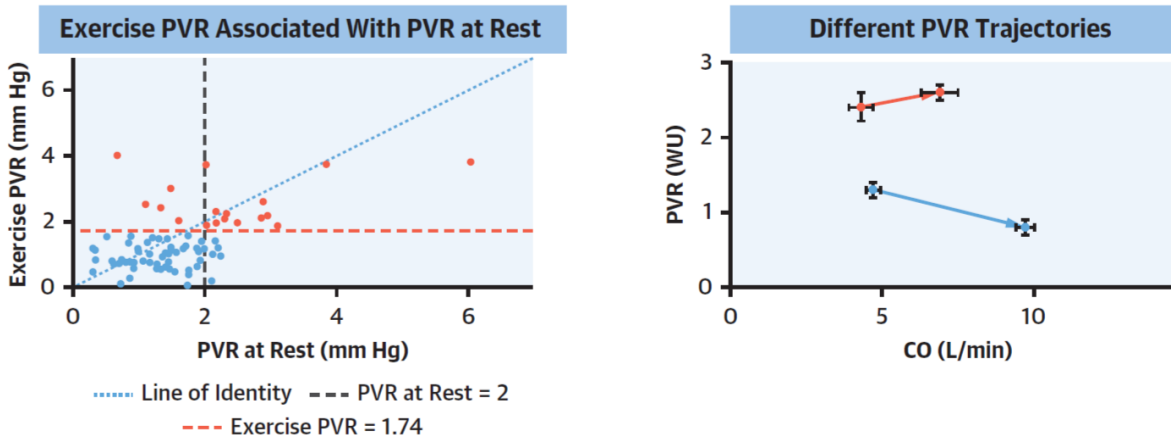


figure 51. PVR Behavior during exercise in HFpEF latent-PVD (red) and HFpEF controls (blue).

Abbreviations. CO, cardiac output; PVR, pulmonary vascular resistance.

Mean RAP increased to similar values in the 2 groups, while at variance the RAP systolic component rose more steeply and to higher values in HFpEF latent-PVD patients (**table 11)**. We found a higher proportion of PH (i.e. mPAP/CO slope > 3 mmHg/L/min), tall PAWP V waves, systolic RAP increase, and low CO (i.e. peak CO < 80% of predicted and/or CO/VO_2 slope < 4.7) in HFpEF latent-PVD group as compared with HFpEF-controls (**table 13**).

Functional capacity

VO_2 increased less in HFpEF latent-PVD patients up to lower values at peak exercise, driven by impaired CO response (**table 11)**. At variance, peripheral O_2 extraction increased more and to higher values in HFpEF latent-PVD patients. The HFpEF latent-PVD patients had had higher dead space ventilation during exercise and higher arterial partial pressure for carbon dioxide ($PaCO_2$) ($p < 0.05$) even if the extent of hyperventilation, as reflected by the ratio between minute ventilation and CO_2 production, was similar in the 2 groups (**table 11)**. PVR at rest was directly associated with $PaCO_2$ in HFpEF latent-PVD patients only (**figure 52**).

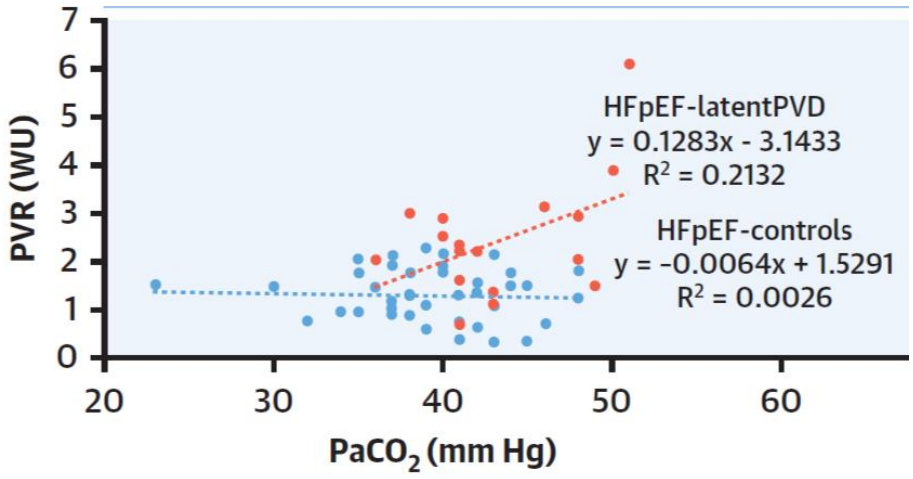


Figure 52. Rest PVR correlates with $PaCO_2$ in HFpEF latent-PVD patients (R^2=0.2132). Abbreviations. $PaCO_2$, arterial partial pressure for carbon dioxide; HFpEF, heart failure with preserved ejection fraction; PVR, pulmonary vascular resistance.

At peak exercise, PVR was inversely associated with stroke volume and stroke volume index, as shown in **figure 53**.

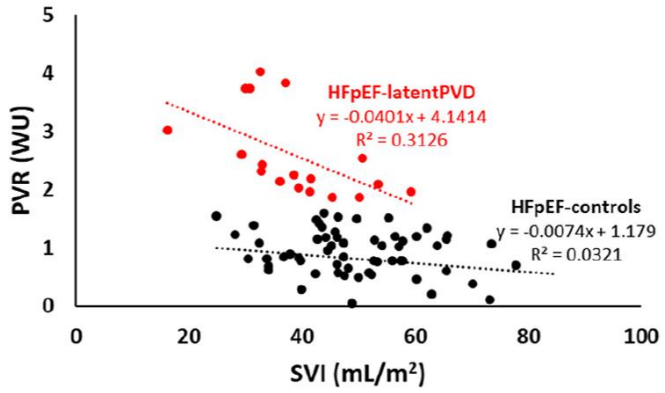


figure 53. PVR as a function of SVi at peak exercise in HFpEF latent-PVD patients (R^2=0.3126). Abbreviations. PVR, pulmonary vascular resistance; SVI, stroke volume indexed.

During a median follow-up of 1,186 (825-1586) days, the 3-year event-free survival was 72% in HFpEF latent-PVD patients and 93% in HFpEF control patients, as represented in **figure 54** (log-rank test p = 0.004).

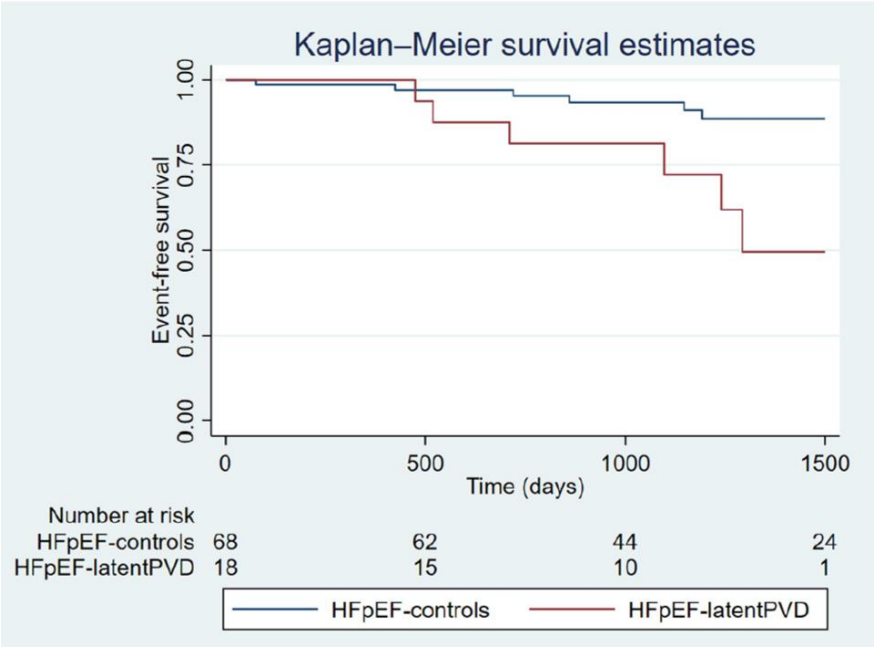


Figure 54. Kaplan-Meier curves for event-free survival in the study groups.

Study 7: Meta-analysis PROGNOSIS-PH: hemodynamic prognosticators in PH due to left heart disease [96]

METHODS

Research strategy

We followed the PRISMA statement [60] for reporting systematic reviews and meta-analysis. A comprehensive literature research in Pubmed bibliographic database was updated to December 2020, and the search terms included: ("left heart disease" OR "LHD" OR "heart failure with preserved ejection fraction" OR "HFpEF" OR "heart failure" OR "HF" OR "diastolic dysfunction" OR "diastolic heart failure" OR "HFrEF" OR "heart failure with reduced ejection fraction" OR "VHD" OR "valvular heart disease") AND ("PH" OR "pulmonary hypertension" OR "PH-LHD" OR "PHLHD" or "pulmonary hypertension due to left heart disease" OR "postcapillary pulmonary hypertension" OR "IpcPH" OR "CpcPH" OR "isolated post-capillary pulmonary hypertension" OR "combined post- and pre-capillary pulmonary hypertension") AND ("hemodynamics" OR "wedge pressure" OR "PAWP" OR "PCWP" OR "pulmonary capillary wedge pressure" OR "occlusion pressure" OR "right heart catheterization" OR "RHC" OR "cardiac catheterization") AND ("mortality" OR "death"). Each term was considered as both free text and Mesh terms. We only included English-language publications. We only included cohort studies reporting association measurements (and corresponding 95% confidence intervals [CI] or data allowing the estimation of their standard error) between DPG and/or PVR and/or PAC and death (or heart failure hospitalization) in PH-LHD patients. Relative risk, odds ratio and hazard ratio (HR) were considered adequate association measurements. In case of duplicated data, only the most recent publication was selected. Studies focusing on the effects of specific treatments (including drugs approved for pulmonary arterial hypertension), investigating the outcome after left ventricular assistance device implantation or heart transplantation, or those evaluating short-term follow-up (i.e., less or equal to 1 year) were excluded.

Extraction data

For each included study, we recorded the following variables: country, length of follow-up, sample size, etiology of LHD, age, sex, BMI, NYHA functional class, prevalence of comorbidities (arterial hypertension, AF, diabetes, CAD, and obesity), background treatments (diuretics, betablockers, or angiotensin-converting enzyme inhibitors), NT-proBNP, glomerular filtration rate, LVEF, hemodynamic data (HR, PAP, PAWP, RAP, CO, CI, DPG, TPG, SV, PVR, and PAC), thus including hemodynamic variables tested for association with outcomes, as well as covariates included in multivariate analysis.

Statistics

Sociodemographic and clinical continuous characteristics of each cohort were reported as mean and SD. If the original paper showed median [IQR] we transformed them in mean and SD value following Wan et al. [62]. Categorical variables were reported as proportion. Summary of clinical and hemodynamic characteristics of included studies was performed by order statistics (minimum, maximum, median, and IQR). For each hemodynamic variable of interest, we estimated the pooled HR of death and its 95% CI from a fixed model. This was done both for continuous variables and for dichotomized variables according to more frequently used thresholds (PVR > 3 WU, DPG ≥ 7 mmHg, PAC < 2.3 mL/mmHg). A random effect model [63] was applied when the Q-statistic was statistically significant. Moreover, between-studies' heterogeneity was quantified by means of I2 index [64]. A subgroup analysis was performed based on the presence of adjustment covariates to estimate the original HR. The homogeneity between subgroup pooled HRs was tested. Cumulative meta-analysis was performed to investigate temporal trends in the effects reported in the literature as well as the impact of sample size. An influence analysis was conducted to verify the impact of each estimate on the pooled HR, omitting one study at time. Publication bias presence was evaluated by both funnel plot and Egger test [97]. Moreover, when Egger test resulted statistically significant, a trim and fill approach was applied to correct the funnel plot asymmetry [98]. An exploratory analysis on the association between hemodynamics and outcomes stratifying patients according to the underlying LHD was performed only for the studies that

reported the HR for a given hemodynamic variable in a homogeneous patients' cohort. Results were considered statistically significant when two-tailed p-value was lower than 0.05. All analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

Out of 394 screened studies, 16 fulfilled the pre-specified inclusion criteria [53,99-114], in which DPG, PVR and/or Ca were analyzed for their capability to predict survival in PH-LHD (**figure 55**).

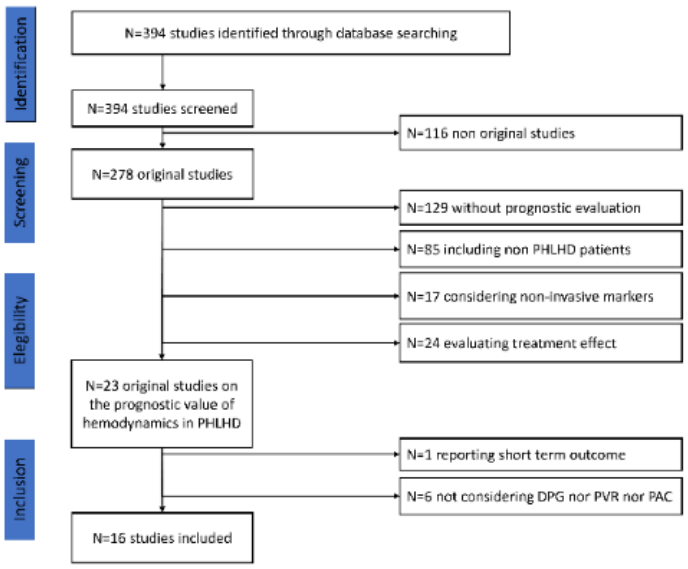


Figure 55. PRISMA flow diagram of study selection.

Abbreviations. DPG, diastolic pressure gradient; LVAD, left ventricular assistance device; MRI, Magnetic Resonance Imaging; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PHLHD, pulmonary hypertension due to left heart disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PVR, pulmonary vascular resistance.

The final analysis was conducted on 16 articles, including 9600 LHD patients, whose characteristics were reported in **table 14**.

Author (year)	Country	Sample size, N	Age, years	Female gender, %	BMI, kg/m²	HFpEF	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis
Gerges (2013) [110]	Austria	1094	63±13		26.3±4.5	≈55%	DPG continuous	Sex, age, GFR <60, CAD
Miller	USA	337	59±14	25	29.1±6.4	0%	PVR dichotomized (>/≤ 3 WU)	Risk factors that were significantly different among

(2013) [102]							PAC continuous and dichotomized (>/≤ 2.3 ml/mmHg)	the groups at baseline and clinically important factors
Dragu (2014) [108]	Israel	264	66±12	55		45%	PVR continuous PAC continuous	age, gender, estimated GFR, LV and RV function, RAP, PAWP, and type of PH
Al-Naamani (2015) [99]	USA	73	69±12	74	33±10	100%	DPG continuous and dichotomized (≥/<7mmHg) PVR continuous PAC continuous	Age, sex, ethnicity, BMI, haemodynamic parameters
O'Sullivan (2015) [105]	Switz	269	83±5	58	26.3±5		DPG dichotomized (≥/<7mmHg)	Age, sex, BMI, DM, previous CABG, PVD, previous MI, CAD, LVEF ≤30%, COPD
Gerges (2015) [114]	Austria	668				67%	DPG dichotomized (≥/<7mmHg)	Sex, age, GFR <60, CAD
Assad (2016) [109]	USA	1820	61±14	44	31.2±8.2		DPG continuous and dichotomized (≥/<7mmHg)	Age, sex, BMI, COPD, ILD, OSA, CAD, AF, VHD, lupus, scleroderma
Palazzini (2017) [113]	Italy	276	69 (60-75)	75		41%	DPG continuous and dichotomized (≥/<7mmHg) PVR continuous and dichotomized (>/≤ 3 WU) PAC continuous and dichotomized (>/≤ 2 mL/mmHg)	
Brunner (2017) [106]	Canada	133	80±8	47	28±7		DPG dichotomized (≥/<7mmHg) PVR dichotomized (>/≤ 3 WU)	Age, sex, BMI, SPAP
Vanderpool (2018) [100]	USA	2587	65±38	45	31±9	100%	DPG continuous and dichotomized (≥/<7; >/<4.7 mmHg) PVR continuous and dichotomized (>/≤ 3; >/<2.3 WU) PAC continuous	
Tampakakis (2018) [107]	USA	1036	57 (45-67)	39	27.7(23.9-33.3)		DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous PAC continuous	Model 1: age Model 2: age, BMI, HR, sex, and cohort
Caravita (2018) [53]	Belgium	93	64±13	55	29±5	51+45+63	DPG continuous and dichotomized (≥/<7; >/<2.5 mmHg) PVR continuous and dichotomized (>/≤ 3 WU) PAC Continuous	
Dragu (2019) [111]	Israel	393	66±12	56			DPG dichotomized (≥/<7 mmHg) PVR dichotomized (≥/< 3 WU)	Age, gender, GFR, Hb, LV and RV function, RAP, PAWP, type of PH
Quan (2019) [101]	China	92	47±13	17	24±4.7	0%	PVR continuous or dichotomized (>/≤ 3 WU) DPG continuous or dichotomized (≥/<7 mmHg) PAC continuous	
Sugimoto (2020) [112]	Japan	243	64±15	44			PVR continuous or dichotomized (>/≤ 3 WU) DPG continuous and dichotomized (≥/<7 mmHg) PAC continuous	
Bermejo (2021) [103]	Multicentric	222	72 (66-77)	76		0%	PVR continuous or dichotomized (>/≤ 3 WU) DPG continuous and dichotomized (≥/<7 mmHg) PAC continuous	

Table 14. Characteristics of included studies. Continuous data are reported as mean±SD or median (interquartile range); proportions are reported as percentage.

Abbreviations. AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CABG, Coronary artery bypass graft; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease; DM, diabetes mellitus; DPG, diastolic pressure gradient; GFR, glomerular filtration rate; Hb, hemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ILD, interstitial lung disease; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction;

MI, myocardial infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA FC, New York Heart Association functional class; OSA, obstructive sleep apnea; PAC, pulmonary artery compliance; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; SPAP, systolic pulmonary artery pressure, USA, United States of America; VHD, valvular heart disease.

Clinical and hemodynamic characteristics

Most of studies included PH-LHD patients independently from the underlying cardiac disease while six studies focused on one specific etiological subgroup, of which 2 on HFpEF [99,100]. The overall included population was in median 64 years old (47-83 years old), with a prevalence of female sex varying from 17% to 76%, and was characterized by a significant burden of comorbidities, including AF, whose prevalence varied from 15% to 71%, and was largely treated with diuretic, betablocker and antihypertensive therapies. LVEF was reported in most studies, with a median value of 44.2% (IQR 39%−51%), as well as BNP, with a median value of 802.7 pg/mL (IQR 464.7−970.0 pg/mL). Mean PAP was on average 38 (36−42) mmHg, mean PAWP 24 [22−24] mmHg, mean PVR 3.9 [2.7−5.1] WU. Mean DPG was on average was 1.8 [−0.4 to 6.9] mmHg (derived from 12 studies) and median PAC was 2.1 [1.8−2.4] mL/mmHg (derived from 11 studies).

Almost all studies defined PH according to 2015 PH Guidelines, except for one [103] in which the definition proposed during the 6th Symposium of PH was adopted. A major part of authors stratified the patients on the base of the presence of a precapillary component, mostly considering a DPG ≥ 7 mmHg [99,105,109, 110,114], PVR > 3 WU [103] or a combination of both [53,106,111-113], while 2 authors considered also a TPG > 12 mmHg [108,110]. Following this heterogeneous classifications of the pre-capillary component, IpcPH cohort was composed of 5234 patients and CpcPH one by 2374 patients.

Association between hemodynamic variables and outcomes

Forest plots analysis for survival according to DPG, PVR and Ca are depicted in **figure 56**. Unitary increase in PVR was significantly associated with outcome in PH-LHD (HR, 1.07; 95% CI: 1.05−1.08), either with or without adjustment for relevant covariates. These findings were consistently achieved when 1263 patients were

analysed, or in the year 2015, as suggested by cumulative meta-analysis (**figures 57**). DPG was associated with mortality in PH-LHD (HR, 1.02; 95% CI: 1.01−1.02), but this association was no more significant when considering only the 2 studies performing an adjustment for covariates (**figure 56**). Cumulating evidence by publication year noted that the initial statistically significant strong effect of 2013 was not confirmed until 2018 and with weaker pooled HR (**figure 57**). Moreover, at the cumulative meta-analysis based on the sample size, the studies demonstrated a high degree of heterogeneity and the overall effect gained stability only after having included 480 patients (**figure 57**). PAC was significantly associated with mortality in PH-LHD (HR, 0.76; 95% CI: 0.69−0.84) (**figure 56**). Despite a non-negligible heterogeneity between included studies (I2 = 60%), results were consistent when only 73 patients were analysed or in the year 2015 (**figure 57**).

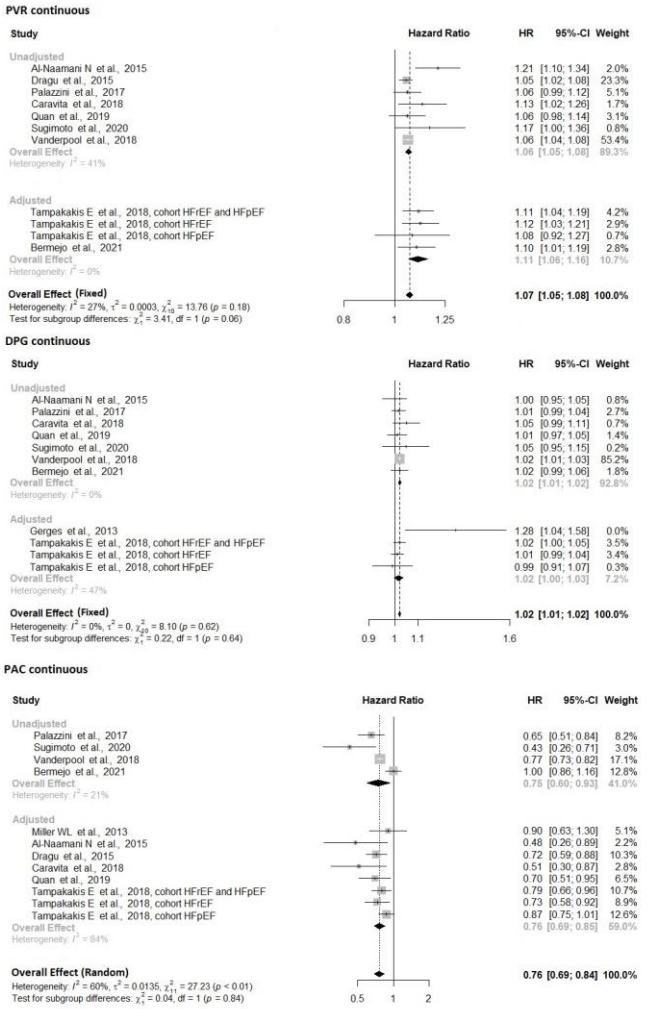


Figure 56. Forest plots with pooled standardized hazard ratio for hemodynamic variables reported in a continuous way. For each variable, unadjusted and adjusted analysis are reported.

Abbreviations. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

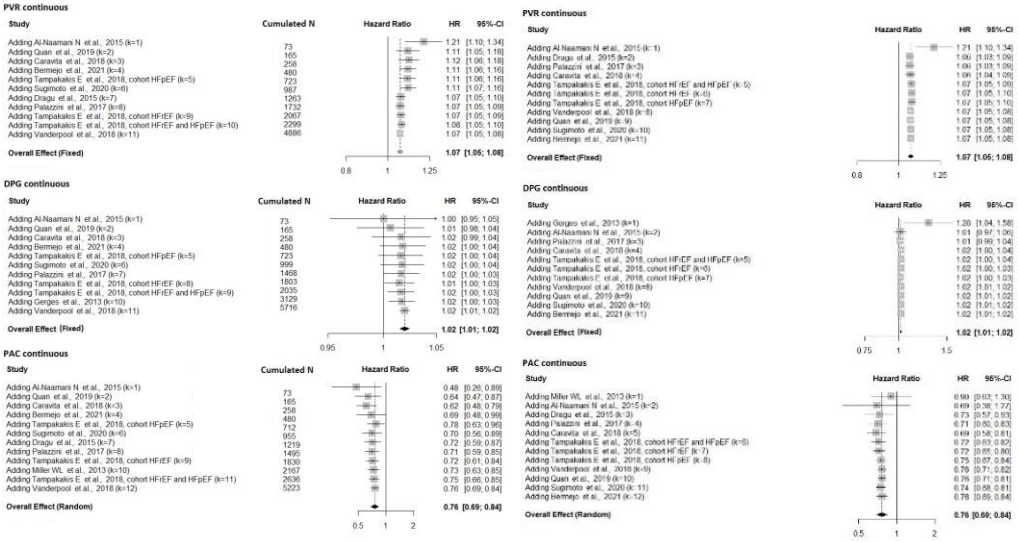


Figure 57. Cumulative meta-analysis according to sample size (panel on the left) and to year of publication (panel on the right) for each hemodynamic variable.

Abbreviations. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

We also performed the analysis considering DPG, PVR, and PAC as dichotomous variables using the "traditional" following cut-off values (PVR > 3 WU; DPG ≥ 7 mmHg; PAC < 2.3 mL/mmHg). DPG > 7 mmHg as well as PVR > 3 WU were both associated to a higher risk for mortality, with HR of 1.36 (95% CI: 1.24−1.49) and 1.53 (95% CI: 1.40−1.67), respectively. PAC < 2.3 mL/mmHg carried the highest risk of mortality (HR 2.14, 95% CI: 1.62−2.84).

Furthermore, in an exploratory analysis, stratifying patients according to the underlying LHD (HFpEF, heart failure with reduced ejection fraction, HFrEF, and valvular heart disease, VHD), PVR was the only hemodynamic parameter significantly associated with outcomes (**figure 58**).

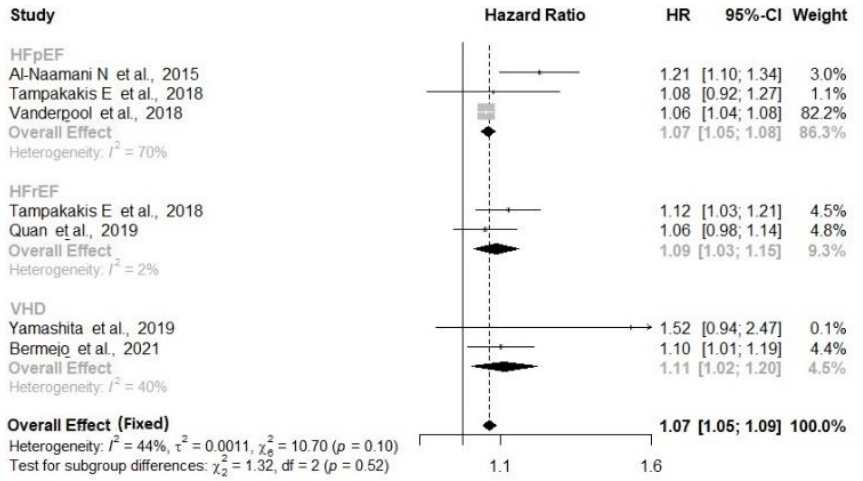


Figure 58. Association between hemodynamic and outcome, stratifying cohorts according to the underlying left heart disease. **Abbreviations**. CI, confidence interval; DPG, diastolic pressure gradient; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular; VHD, valvular heart disease.

Influence and publication bias analysis

An influence analysis was conducted to verify the impact of each estimate on the pooled HR. No study influenced the summary estimates of PVR, DPG and PAC evaluated by both funnel plot and Egger test [97]. Moreover, Egger test suggested publication bias for both PVR and PAC although in an opposite direction, that is, with an underestimation for PAC and an overestimation for PVR. However, trim and fil approach confirmed findings of the main analysis after controlling for this source of bias.

Study 8: RETRORIGHT: right heart adaptation to exercise in pulmonary hypertension

[115]

METHODS

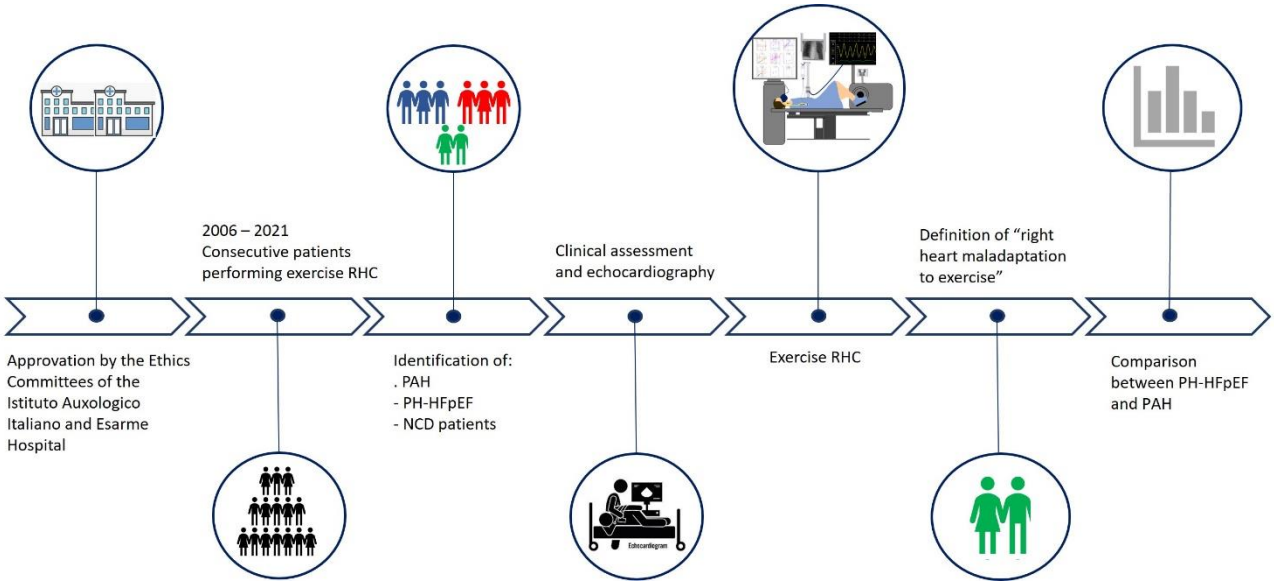


Figure 59. Representation of the RETRORIGHT study design.

Study design

RETRORIGHT study is a multi-centric, retrospective analysis on outpatients with exertional dyspnea underwent a comprehensive diagnostic assessment including exercise RHC. Whitin 15 days, patients underwent a non-invasive evaluation including clinical examination and rest echocardiography. We identified patients with PH due to HFpEF, PAH and NCD. Patients with NCD served as reference to used define "right heart maladaptation to exercise". Then, we compared the clinical and hemodynamic profile of PH-HFpEF and PAH patients (**figure 59**).

EC approbation

The Ethics Committee of Erasme Hospital (P2021/452) and Istituto Auxologico Italiano (protocol n 2022_09_27_01 approved on September 27th, 2022) approved the study.

Inclusion criteria

Consecutive patients who underwent a cardiac catheterization at rest and during exercise with PH-HFpEF, PAH, or NCD.

PH-HFpEF was defined by signs and or symptoms of chronic heart failure, normal left ventricular ejection fraction (LVEF) (≥ 50%), and elevated left heart filling pressures (pulmonary artery wedge pressure, PAWP, at rest > 15 mmHg) associated with PH at rest, i.e. mean pulmonary artery pressure (PAP) ≥ 25 mmHg.

Patients with PAH met the traditional hemodynamic definition of precapillary PH (mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR, ≥ 3 WU) [116] provided that of other forms of precapillary PH, such as chronic thromboembolic PH, PH due to lung disease, or multifactorial PH have been excluded.

Individuals with NCD, who had normal hemodynamics at rest and during exercise, served to define abnormal increase in RAP, i.e. values of RAP and of RAP/CO slope > 97.5° percentile. They were individuals referred for invasive exercise assessment because of exercise intolerance, but who did not display any demonstrable cardiac or respiratory etiology for symptoms, with normal rest and exercise PA hemodynamics, i.e. mean PAP at rest < 25 mmHg with PVR < 3 WU, mean PAP during exercise <30 mmHg with total pulmonary resistance, TPR, < 3 WU; PAWP at rest < 15 mmHg, PAWP during exercise < 25 mmHg, together with a PAWP/CO slope < 2 mmHg/L/min).

Clinical assessment

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication to cardiac catheterization, were abstracted from clinical charts. Echocardiography was performed with a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway) at Istituto Auxologico Italiano and with a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway) at Erasme Hospital, following current recommendations [56].

Exercise RHC

Exercise RHC was performed according to procedural methodology mentioned above. Patients were studied in supine position, with a 7-F fluid-filled Swan-Ganz catheter [Edwards LifeScience] placed in the pulmonary artery. In patients performing exercise RHC at Istituto Auxologico Italiano, a 4 F catheter was placed in the radial artery [Arrow]. Hemodynamic measurements as well as blood samples from pulmonary artery (and radial artery for patients studied at Istituto Auxologico Italiano) were performed in each step of exercise RHC. Hemodynamic assessment was thus realized in resting conditions, after one minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test, whose increment in workload was personalized in order to obtain at least three steps (about 10 minutes) of exercise before exhaustion [31].

Hemodynamic variables

Pressure values were averaged over several heartbeats and at least 3 respiratory cycles. CO was calculated by direct Fick method (Auxologico) or by thermodilution (Erasme Hospital). CO measured via thermodilution was based on 3–5 cold water injections at rest, while during exercise, CO was measured using a mean of 3 cold water injections, verifying the visualized temperature curve, as the mean of all available thermodilution measurements recorded at the end of each exercise step [117]. In order to calculate CO via the direct Fick method, patients were connected with a non-rebreathing Hans-Rudolph mask to a metabolic cart (Vmax

SensorMedics 2200, Yorba Linda, CA, USA) in order to obtain, at the end of each step of the test, in steady-state conditions, a 30-second average of VO_2. At the same time, blood was sampled both from the pulmonary artery and from the radial artery for gas analysis and hemoglobin determination. Direct Fick CO was thus calculated from VO_2, hemoglobin, radial and pulmonary artery oxygen saturation and oxygen partial pressure, using standard formula. TPR was computed as mean PAP/CO at peak exercise [32]. A linear regression was applied to multiple pairs of PAWP and CO points, to calculate the PAWP/CO linear regression slope [6]. The same methodology was applied to multiple pairs of RAP and CO points. Right heart adaptation to exercise was described either using absolute or CO-normalized RAP increase during exercise (RAP/CO slope). LVTMP, which reflects LV preload independent of right heart filling and pericardial restraint, was calculated as PAWP−RAP [91]. eSBV, a measure of functional preload, was computed using a commercially available hemodynamic simulator (retrieved online from URL: http://harvi.online access date 4 May 2022) that has been used in prior studies [18,118]. For estimation of SBV, the measured values of HR, CO, RAP, PAWP, systolic and diastolic systemic pressure and PAP, as well as cardiac chamber dimensions, are provided to the software.

Statistics

Results are expressed as mean±SD or absolute number (N and %) or median [1st- 3rd quartile] if the data did not follow a normal distribution. Hemodynamic data of individuals with NCD that, by definition, were characterized by normal pulmonary pressures at rest and normal exercise hemodynamic responses, are reported as 2.5 - 97.5 CI as “reference” normal values, without formal comparison with the other group of patients defined by abnormal hemodynamics at rest, to avoid underpowered multiple comparisons. Demographic, clinical and hemodynamic data between different patients’ groups (PH-HFpEF and PAH) were compared using Wilcoxon rank sum test with continuity correction for the continuous variables and Pearson's Chi-squared test or Fisher's Exact Test (when the expected counts were less than 5) for the categorical data. Additionally, we performed a sensitivity analysis excluding patients with severe TR in order to control for potential confounders. Kendall's rank correlation tau was used to verify correlations between RAP/CO slope

and continuous variables (age, BMI, TAPSE, TAPSE/SPAP, NT-proBNP, creatinine, $VECO_2$ slope, SBV, deltaSBV, PAWP, PVR, TPR and PAC). Wilcoxon rank sum test was used to perform a comparison of dichotomized variables (NYHA I-II vs III-IV, TR severe vs non-severe; RA dilated vs non-dilated; AF vs SR; presence of diuretic therapy) between patients with RAP/CO slope above or below the pathological threshold, in order to determine those variables associated with high RAP/CO slope. All these association were tested both in the whole PH cohort as well as stratifying patients according to the underlying diagnosis (PH-HFpEF and PAH) All tests were two-tailed at $p < 0.05$. Statistical analysis was performed with "R: A language and environment for statistical computing. R Foundation for Statistical Computing", R Core Team (2021).

RESULTS

We retrospectively analysed data from 60 PH patients who underwent an exercise RHC at Istituto Auxologico Italiano or at Erasme Hospital from 2006 to 2021, of which 30 PH due to HFpEF and 30 PAH. 21 individuals with NCD, who had normal hemodynamic at rest and during exercise, served to define abnormal increase in RAP, i.e. values of RAP and of RAP/CO slope > 97.5° percentile.

Clinical characteristics

General characteristics and comorbidities as well as blood tests and echocardiography of PH-HFpEF and PAH are reported in **table 15** and **table 16**, respectively.

	PH-HFpEF (N=30)	**PAH (N=30)**	**p-value**
Characteristics			
Age, years	74.4 [71.7-80.9]	62.0 [49.3-68.4]	**<0.001**
Female sex, N (%)	21 (70)	21 (70)	<0.99
BMI, kg/m^2	27.5 [24.2-30.3]	25.1 [22.9-28.4]	0.097
NYHA FC II, % III, %	 13 (43) 17 (57)	 8 (27) 22 (73)	0.105
Comorbidities			
Systemic hypertension, N (%)	26 (87)	10 (35)	**<0.001**
Diabetes mellitus, N (%)	8 (27)	2 (7)	0.038
Dyslipidemia, N (%)	8 (27)	9 (30)	0.774

Atrial fibrillation, N (%)	21 (70)	3 (10)	**<0.001**
Obesity, N (%)	7 (23)	2 (7)	0.145
Coronary artery disease, N (%)	5 (17)	5 (17)	>0.99
OSAS, N (%)	7 (23)	1 (3)	0.052
Connective tissue disease, N (%)	3 (10)	6 (20)	0.472
COPD, N (%)	5 (17)	1 (3)	0.195
Interstitial lung disease, N (%)	6 (20)	1 (3)	0.103
Treatment			
Loop diuretics, N (%)	28 (93)	16 (55)	**<0.001**
MRAs, N (%)	10 (33)	3 (10)	**<0.001**
PAH specific therapy			
Endothelin receptor antagonist, N (%)	0 (0)	23 (77)	
PDE5i, N (%)	0 (0)	21 (70)	
sGC stimulator, N (%)	0 (0)	4 (13)	
Parenteral prostacyclin, N (%)	0 (0)	2 (7)	
Monotherapy, N (%)		12 (40)	
Dual therapy, N (%)		16 (53)	
Triple therapy, N (%)		2 (7)	
PAH etiology			
Idiopathic PAH, N (%)		13 (43)	
Heritable PAH, N (%)		1 (3)	
Drug-induced PAH, N (%)		3 (10)	
CTD-PAH, N (%)		9 (30)	
CHD-PAH, N (%)		2 (7)	
POPH, N (%)		2 (7)	

Table 15. General characteristics and comorbidities of PH-HFpEF and PAH.

Abbreviations. AF, atrial fibrillation; BMI, body mass index; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HFpEF, heart failure with preserved ejection fraction; MRAs, Mineralocorticoid receptor antagonists; NYHA FC, New York Heart Association functional class; OSAS, obstructive sleep apnea syndrome; PCI, percutaneous coronary intervention; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; POPH, porto-pulmonary hypertension; sGC, soluble guanylate cyclase.

	PH-HFpEF (N=30)	**PAH (N=30)**	**p-value**
Blood tests			
NT-proBNP, pg/mL	682 (279-1029]	401 [238-1584]	0.300
Creatinine, mg/dL	1.0 [0.9-1.2]	0.9 [0.7-0.9]	**0.026**
Hemoglobin, g/dL	12.7 [11.2-13.8]	14.3 [13.7-14.9]	**0.001**
Echocardiography			
LVEF, N (%)	63.8 [58.1-66.0]	60.0 [60.0-67.0]	0.7
RV dilation, N (%)			**0.038**
Non/mild, N (%)	20 (67)	12 (40)	
Moderate/severe, N (%)	10 (33)	18 (60)	
LA dilation			**<0.001**
Non/mild, N (%)	8 (27)	23 (77)	
Moderate/severe, N (%)	22 (73)	7 (23)	
RA dilation			0.787
Non/mild, N (%)	19 (63)	20 (67)	
Moderate/severe, N (%)	11 (37)	10 (33)	
E/e' avg	12 [10-14]	9 [8-10]	**0.006**

TAPSE, mm	22 [19-25]	17 [15-19]	**0.001**
SPAP, mmHg	50 [43-58]	65 [55-75]	**<0.001**
TAPSE/SPAP	0.42 [0.38-0.51]	0.27 [0.20-0.32]	**<0.001**
TR			**0.032**
Non/mild, N (%)	7 (23)	15 (50)	
Moderate/severe, N (%)	23 (77)	15 (50)	

Table 16. Blood tests and echocardiography of PH-HFpEF and PAH patients.

Abbreviations. EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension; RA, right atrium; RV, right ventricle; PAH, pulmonary arterial hypertension; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Reference values for resting and exercise hemodynamics from NCD individuals

NCD individuals showed on average a resting RAP, a peak RAP and a RAP/CO slope of 4 [1-5] mmHg, 5 [4-7] mmHg, and 0.32 [0.11-0.73] mmHg/L/min respectively. Abnormal resting RAP, peak RAP and RAP/CO slope, defined by values above 97.5° percentile obtained in this cohort of control subjects, were > 7 mmHg, > 12 mmHg and ≥ 1.30 mmHg/L/min respectively.

Hemodynamics

At rest, as shown in **table 17**, PAH had typically higher PAP, higher PVR and lower PAWP than PH-HFpEF ($p < 0.01$). CI, as well as CO, was preserved and similar between the 2 groups ($p < 0.99$ and $p = 0.800$, respectively). PH-HFpEF patients had higher RAP than PAH patients ($p = 0.003$). Eleven PH-HFpEF (37%) and 19 PAH (63%) had a normal RAP (< 8 mmHg) at rest ($p < 0.001$). Estimated SBV did not differ between 2 groups ($p = 0.700$).

	PH-HFpEF (N=30)	**PAH (N=30)**	**p-value**
eSBV, mL	1708 [1541-2138]	1808 [1489-2235]	0.700
HR, bpm	72 [60-80]	77 [72-83]	0.070
Systolic BP, mmHg	149 [141-163]	115 [107-137]	**<0.001**
Diastolic BP, mmHg	74 [62-92]	73 [63-80]	0.70
Systolic PAP, mmHg	44 [38-47]	66 [54-82]	**<0.001**
Diastolic PAP, mmHg	21 [18-22]	30 [23-35]	**<0.001**
Mean PAP, mmHg	28 [26-30]	43 [32-51]	**<0.001**
PAWP, mmHg	18 [18-25]	8 [5-12]	
RAP, mmHg	10 [7-13]	6 [3-10]	0.003
RAP/PAWP	0.53 [0.38-0.67]	0.68 [0.40-0.92]	0.098
LVTMP, mmHg	10 [5-12]	3 [1-4]	**<0.001**
CO, L/min	4.62 [3.87-5.56]	4.59 [3.73-5.14]	0.8

CI, L/min/m²	2.50 [2.14-3.07]	2.59 [2.16-2.91]	>0.99
PVR, WU	1.92 [1.51-2.16]	6.98 [5.39-8.96]	**<0.001**
TPR, WU	6.02 [4.78-7.69]	8.71 [6.56-11.28]	**<0.001**
SaO_2, %	95.8 [95.0-96.9]	95.2[89.5-69.7]	0.4
SvO_2, %	69.9 [65.6-73.1]	67.5 [60.7-74.9]	0.8
SV, mL	66 [51-85]	56 [49-71]	0.2
PAC, mL/mmHg	3.01 [2.32-4.01]	1.65 [1.005-2.33]	**<0.001**
TPG, mmHg	8 [5-11]	35 [26-40]	**<0.001**
DPG, mmHg	1 [-2-3]	21 [18-25]	**<0.001**

Table 17. Rest hemodynamics in PH-HFpEF and PAH patients.

Abbreviations. BP, blood pressure; CI, cardiac index; CO, cardiac output; DPG, diastolic pulmonary gradient; eSBV, estimated stressed blood volume; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LVTMP, left ventricular transmural pressure; NCD, non-cardiac dyspnea; PAP, pulmonary artery pressure; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SV, stroke volume; SO_2, central venous oxygen saturation; TPG, transpulmonary gradient; TPR, total pulmonary resistance.

At peak exercise, PAH patients presented with higher PAP and higher indexes of RV afterload than PH-HFpEF patients ($p < 0.001$), as shown in **table 18**, while these latter presented, per definition, with a higher peak PAWP and higher PAWP/CO slope than PAH ($p < 0.001$, **table 18**). CO as well as CI at peak did not differ between PH-HFpEF and PAH patients, who also presented at the same step of exercise with non-different values of heart rate and stroke volume (**table 18**).

	PH-HFpEF (N=30)	**PAH (N=30)**	**p-value**
SBV, mL	3158 [2834-3429]	2710 [2349-3347]	**0.049**
HR, bpm	91 [78-121]	111 [100-119]	0.9
Systolic BP, mmHg	181 [149-190]	149 [127-170]	0.06
Diastolic BP, mmHg	80 [66-88]	83 [75-92]	0.5
Systolic PAP, mmHg	64 [55-74]	97 [79-116]	**<0.001**
Diastolic PAP, mmHg	33 [28-41]	43 [38-55]	**<0.001**
Mean PAP, mmHg	45 [36-49]	62 [52-74]	**<0.001**
PAWP, mmHg	33 [26-39]	15 [11-17]	**<0.001**
RAP, mmHg	20 [16-24]	12 [9-19]	**<0.001**
RAP/PAWP	0.64 [0.57-0.79]	0.82 [0.67-1.18]	**0.005**
LVTMP, mmHg	12 [6-16]	3 [-2-5]	**<0.01**
TPG, mmHg	10 [7-17]	48 [38-55]	**<0.001**
DPG, mmHg	1 [-4-6]	28 [24-38]	**<0.001**
CO, L/min	6.80 [5.56-9.03]	7.21 [3.35-8.92]	0.9
CI, L/min/m²	4.06 [3.14-4.49]	3.63 [3.24-5.30]	0.7
SV, mL	79 [58-94]	65 [48-81]	0.2
PVR, WU	1.37 [1.01-2.62]	6.68 [4.63-8.59]	**<0.001**
TPR, WU	6.14 [5.09-7.49]	9.05 [6.45-10.52]	**0.001**
PAC, mL/mmHg	2.48 [2.02-3.26]	1.29 [0.82-2.06]	**<0.001**

SaO_2, %	95.9 [93.4-96.6]	90.2 [82.5-94.2]	**0.002**
SvO_2, %	31.8 [24.0-38.9]	42.4 [36.6-46.8]	**0.010**
RAP/CO slope	3.47 [2.02-6.19]	1.90 [1.01-4.29]	**0.025**
PAWP/CO slope	3.75 [2.43-4.97]	1.82 [0.68-3.06]	**<0.001**
Mean PAP/CO slope	4.99 [4.21-6.34]	6.44 [4.39-8.64]	0.1
Workload, Watts	45 [30-60]	30 [20-40]	**0.004**

Table 18. Hemodynamics at peak exercise in PH-HFpEF and PAH patients.

Abbreviations. BP, blood pressure; CI, cardiac index; CO, cardiac output; DPG, diastolic pulmonary gradient; eSBV, estimated stressed blood volume; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LVTMP, left ventricular transmural pressure; PAP, pulmonary artery pressure; NCD, non-cardiac dyspnea; PAP, pulmonary artery pressure; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SV, stroke volume; SvO_2, venous mixed oxygen saturation; TPG, transpulmonary gradient; TPR, total pulmonary resistance.

Right heart maladaptation to exercise

Even if both PH-HFpEF and PAH patients presented with a mean peak RAP and RAP/CO slope higher than the references values (**figure 23** and **table 18**), PH-HFpEF had higher peak RAP than PAH ($p < 0.001$) as well as higher RAP/CO slope ($p = 0.025$). A higher proportion of PH-HFpEF had a RAP/CO slope and a peak RAP above normal, compared with PAH (90% and 91% vs 69% and 44%, respectively, $p < 0.001$). Ninety-one percent of PH-HFpEF with normal resting RAP had a pathological RAP increase (both when considered in absolute values and when it was flow-normalized). Thirty-two percent and 71% of PAH with normal resting RAP had an abnormally high RAP or a steep RAP/CO slope during exercise, respectively (**figure 60**). ESBV, as a measure of RV functional preload, computed at peak exercise, was found to be higher in PH-HFpEF than PAH group as well as its rate of increase from resting to peak values ($p < 0.01$).

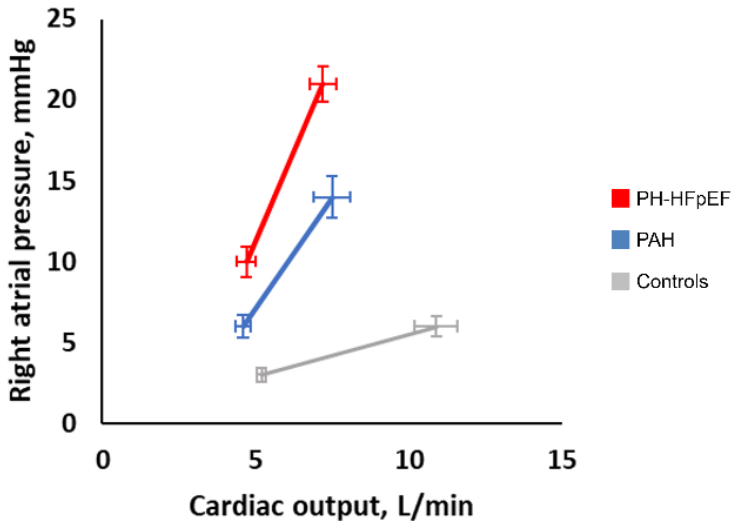


Figure 60. Hemodynamics at rest and at peak exercise in patients with pulmonary hypertension due to heart failure with preserved ejection fraction (PH-HFpEF, red) and in patients with pulmonary arterial hypertension (PAH, blue). Individuals with non-cardiac dyspnea (grey) are displayed as normal reference. Mean right atrial pressure and cardiac output coordinates (±standard error of the mean) at rest and at peak exercise are plotted for the three groups. p = 0.025.

RAP/CO slope was associated with age ($\tau = 0.237$, $p = 0.012$), with the rate of increase in eSBV during exercise ($\tau = 0.274$, $p = 0.003$), as well as with the presence of severe TR ($p = 0.005$), and RA dilation ($p = 0.027$) in the whole cohort. Considering only PH-HFpEF, RAP/CO slope was associated with BMI ($\tau = 0.264$, $p = 0.045$). In the PAH group, RAP/CO slope was associated with PVR ($\tau = 0.289$ $p = 0.038$), TPR ($\tau = 0.302$, $p = 0.031$), severe TR ($p = 0.026$) and the rate of increase in eSBV during exercise ($p = 0.032$).

A sensitivity analysis on rest and exercise hemodynamics of PH-HFpEF and PAH patients excluding the subgroup with severe TR (n=13) is made, whose results are in line with those reported without excluding PH patients with severe TR.

DISCUSSION

KEY MESSAGES

Exercise hemodynamic highlights several aspects of HFpEF, from the diagnostic field up to phenotypization and characterization of the disease progression.

Studies 1,2,3 and 4 [55,57,59,86] show that in the diagnostic phase, the CO-normalized PAWP increase during exercise (i.e. PAWP/CO slope) retains an excellent diagnostic value:

- allowing to overcome limitations of an isolated, absolute PAWP value at peak exercise;

- maximizing the diagnostic performance of RHC;

- resulting independent from the body position and respiratory swings.

Studies 5,6,7 and 8 [87,92,96,115] show that exercise hemodynamics, beyond the PAWP, allows to highlight distinct HFpEF phenotypes:

- RAP analysis (as a waveform, and CO-normalized during exercise) provided insights on STR and early RHF;

- PVR have prognostic value not only at rest but also during exercise (**figure 61**).

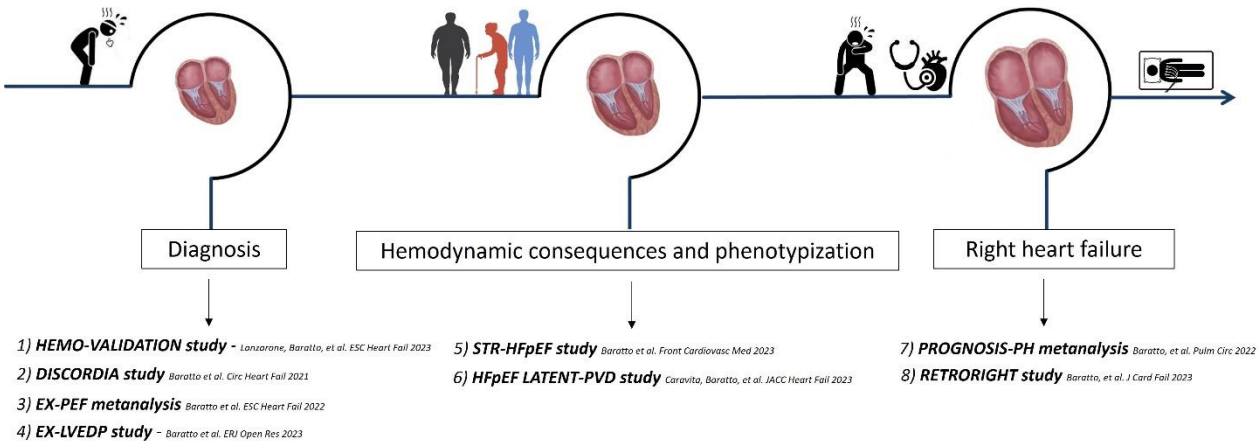


Figure 61. The role of exercise hemodynamics in the natural history of HFpEF and the 8 studies included in this PhD thesis.

The relevance of the invasive ("hemo") exercise ("dynamic") evaluation to better understand the HFpEF

A "hemo-" (invasive) "-dynamic" (during exercise) evaluation provides thorough information for a holistic understanding of patients suffering from HFpEF. Exercise RHC provides the possibility of identifying HFpEF in an early phase, in the absence of overt non-invasive alterations. Additionally, RHC could highlight distinct disease phenotypes, allowing the identification of a more severe HFpEF profile, with prognostic implications. This was the case, for example, of CpcPH, HFpEF patients presenting with all positive exercise hemodynamic criteria, those with STR, as well as of HFpEF patients with a latent PVD phenotype. Finally, exercise RHC has proved to be useful also in identifying as well as in better understanding the underlying pathophysiological mechanisms of RHF in HFpEF. The hemo-dynamic evaluation could indeed unmask features suggestive right heart maladaptation, allowing an early identification of RHF, and suggest that RHF in HFpEF might be favored by preload-dependent mechanisms, and related to the inability of the right heart to accommodate large increase in preload, with a flatter CO increase, suggesting an impaired Frank-Starling reserve.

HFpEF DIAGNOSIS

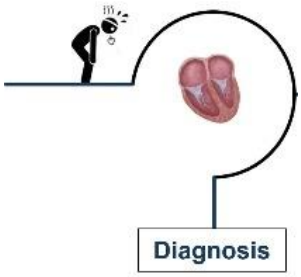


Figure 61. The begin of the natural HFpEF history: the "early phase" of disease as a diagnostic challenge,

HFpEF diagnosis: the earlier the HFpEF phase, the lower the sensitivity of non-invasive diagnostic tests

The diagnosis of HFpEF poses a unique challenge, especially in those patients with lifestyle-limiting symptoms but no evidence of hypervolemia (**figure 61**). A combination of several items, such as those included in the

H_2FPEF score and in the HFA-PEFF algorithm [21,22] has been suggested to help in this complex diagnostic process. The H_2FPEF score has been originally derived and validated in a single-center study against invasive exercise hemodynamics. The performance of such scoring model has been subsequently confirmed in multicenter studies. The HFA-PEFF algorithm comes from an experts' consensus. It has been subsequently validated using the reference standards of diagnosis established by clinical impression, trial eligibility, and previous HF hospitalization [24]. Some studies compared the HFA-PEFF performance (2 steps) against invasive exercise hemodynamics [24, 57], reporting good specificity but suboptimal sensitivity.

In such a perspective, our work confirms and expands the evidence coming from previous reports [24], incorporating also the third step of the algorithm, i.e. the additional role of diastolic stress echocardiography. In particular, our results highlight the relationship between the HFA-PEFF score and RHC results, and demonstrating the good specificity of the 'rule-in' approach based on a score > 4 at the second step of the algorithm, using exercise hemodynamics as reference and, in particular, a combination of PAWP at rest > 15 mmHg and/or PAWP at peak ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/ min.

However, our results show that, despite good specificity, the HFA-PEFF score is characterized by suboptimal sensitivity, and that the implementation of the DSE did not seem to add significantly to the diagnostic performance of the score.

DSE has been advocated to increase the diagnostic yield of resting examination [119]. However, the diagnostic value of the DSE as a third step in the HFA-PEFF algorithm appears questionable based on our results, being moreover time and resource consuming. This is at variance from a previous report where DSE enhanced the diagnosis of HFpEF if added to the ESC criteria rather than to the comprehensive multiparametric evaluation proposed by the second step of the HFA-PEFF algorithm [119].

Stratification according to both the 2nd and 3rd step of HFA-PEFF score of patients who were finally (hemodynamically) diagnosed with HFpEF led to a large "gray zone", i.e. at intermediate risk of HFpEF, mirroring the low sensitivity of the HFA-PEFF algorithm. Indeed, it did not allow to diagnose HFpEF in roughly 50% of cases, thus requiring additional diagnostic tests. This is reflected by the HFpEF population enrolled in

the HEMO-VALIDATION study, of which 52% (almost all hemodynamic HFpEF) at intermediate risk, as well as that included in the DISCORDIA study, characterized by a relatively large gray zone of possible HFpEF (47% of the whole population). In this context, results from HEMO-VALIDATION study may suggest that the second step of the HFA-PEFF score might be lowered to > 3 [59]. This could slightly improve sensitivity and accuracy, without impacting on specificity of the score.

Early HFpEF: who are these patients?

Clinical profile. The earlier the phase of disease, the most challenging could be the diagnosis. As already suggested, patients with early HFpEF not only exist, but may even represent the largest part of affected patients (the bottom of the iceberg). They are generally characterized by absence of clear clinical diagnostic indicators, where neither natriuretic peptides nor echocardiography help enough to correctly identify, among individuals with exertional breathlessness, those with HFpEF. Most of the studies presented herein have thus focused on this specific patients' population, i.e. that with suspicion of HFpEF but non-conclusive findings at non-invasive tests, either at rest or during exercise, that might be candidate to RHC at rest and (if indicated) during exercise. Patients included in our studies had on average a quite typical clinical profile, mostly elderly women, with a high burden of comorbidities associated with accelerated cardiovascular ageing [120]. Coherent with data coming from our center, also the meta-analysis EXPEF showed that on average patients referred for exertional dyspnea tend to have overall a quite typical HFpEF profile. Despite that, the non-invasive assessment was not deemed to be sufficient to allow per se for a definite diagnosis of HFpEF in the individual patient before the exercise invasive hemodynamic study. This might reflect the complexity of HFpEF, where comorbidities may act as confounders in explaining patients' complaints (i.e. exertional breathlessness) in the absence of sensitive non-invasive markers for early stages of disease [23,25,57].

Hemodynamic profile. As emerged by the meta-analysis EXPEF, the hemodynamic phenotype of pooled HFpEF patients is characterized by higher resting left filling pressures when compared with control patients,

but with PAWP just at the upper limit of normal. Similar to HFpEF cohorts reported in literature, also patients include di our studies showed similar hemodynamic picture, with PAP and PAWP on average within or at the upper limit of normal in resting conditions, requiring provocative tests to confirm or exclude the HFpEF diagnosis.

Exercise-induced steep increase in PAWP as the hallmark of HFpEF

In this field, exercise RHC has been traditionally considered the gold standard diagnostic test allowing to identify the actual hemodynamic signature of HFpEF i.e. the steep, increase in PAWP in spite of normal hemodynamics at rest [23]. However, there is limited evidence to support specific thresholds for abnormal PAWP during exercise. Additionally, there is no clear consensus on the phase of the respiratory cycle in which pulmonary pressures should be measured, especially during exercise. Moreover, there were 3 main approaches proposed to diagnose HFpEF based on exercise hemodynamic measurements (including i) end-expiratory pulmonary artery wedge pressure ($PAWP_{exp}$) ≥ 25 mmHg at peak exercise [23]; ii) $PAWP_{exp}$/CO slope > 2 mmHg/L/min [6,30]; iii) respiratory-averaged mPAP > 30mmHg at peak exercise with a $mPAP_{avg}$/CO ratio (TPR_{avg}) > 3 WU and $PAWP_{avg}$ ≥ 20 mmHg [32].

In our DISCORDIA study, we performed an in deep analysis of the exercise hemodynamics in patients complaining exertional dyspnea to clarify the above mentioned methodological and diagnostic aspects. Firstly, we could show that the phase of the respiratory cycle in which pulmonary pressure measurements are performed (end-expiratory or respiratory- averaged) can dramatically change the interpretation of data, both at rest, as previously demonstrated, and to an even proportionally greater extent during exercise. End-expiratory pulmonary pressures were significantly higher than those obtained by averaging the values throughout the respiratory cycle, considering pressures both as absolute values or flow-normalized. Moreover, PAWP was significantly different if measured at end-expiration or averaged among respiratory cycles both at rest and at peak exercise: at rest, mean differences between $PAWP_{exp}$ and $PAWP_{avg}$ were 2 [2–4] mmHg, and at peak $PAWP_{exp}$ and $PAWP_{avg}$ differed of 5 [4–7] mmHg. Our data showed how, consequently,

in a significantly larger number of patients it was possible to diagnose HFpEF according to end-expiratory than respiratory-averaged PAWP values. Considering end-expiratory PAWP, 33% of population might have HFpEF at rest, versus a 19% pf HFpEF prevalence at rest considering respiratory-averaged resting PAWP; similarly, at peak exercise 70% of patients might have HFpEF according to end-expiratory peak PAWP, against only 53% who would have HFpEF based on the respiratory-averaged peak PAWP.

Our data highlighted the relevance of taking into account respiratory-related pulmonary pressure swings in the hemodynamic analysis to differentiate between HFpEF and NCD in patients with exertional dyspnea, and showed that pulmonary pressure values, absolute or flow-normalized, differ whether measured at end-expiration or averaged over several respiratory cycles and cannot thus be used interchangeably. Furthermore, we showed that the threshold of respirophasic difference associated with PAWP values discrepantly exceeding the pathological cutoff (i.e. exceeding the cutoff at end-expiration, but not when pressures were respiratory-averaged) was 7 mmHg at rest and 12 mmHg at peak exercise.

Discordance in between the 3 exercise hemodynamic definitions of HFpEF

The main finding from DISCORDIA study was that the 3 proposed approaches to define HFpEF based on exercise hemodynamics are only moderately concordant with each other: we found a 30% of discordant results, a non-negligible percentage that could relevantly impact on patient's clinical diagnosis.

The previous mentioned relevance of considering respiratory-related PAWP swings in the analysis might have implications also when adopting the different PAWP cutoffs to diagnose HFpEF [33]. In particular, the ERS [31], while acknowledging the relative lack of evidence on abnormal PAWP cutoffs during exercise, suggests averaging pulmonary pressure values over several respiratory cycles. At variance, the definitions of HFpEF proposed by Borlaug et al and by Eisman et al, and Ho et al. have been based on $PAWP_{exp}$ values, potentially leading to different results [6,23,30]. Moreover, 2 of these criteria, based on peak exercise thresholds, might be highly dependent on the dose of exercise performed. All these factors led to a discordance in between the 3 exercise hemodynamic definitions of HFpEF: from our data, indeed, the 3 hemodynamic definitions of

HFpEF proved to be consistent only in 70% of cases, with concordant hemodynamic criteria (0/3 or 3/3 positive criteria). Somehow unexpectedly for an invasive test which should hopefully dispel any diagnostic doubt, 30% of patients presented with 1/3 or 2/3 hemodynamic criteria, and therefore, might have not received an unequivocal HFpEF diagnosis.

DISCORDIA study may also suggest respiratory swings might be more relevant when PAWP is dichotomized at 25 mmHg and measured either averaged or at end-expiration, as discussed above, rather than when a different cutoff is applied to $PAWP_{exp}$ and to $PAWP_{avg}$. Indeed, the median difference between $PAWP_{exp}$ and $PAWP_{avg}$ at peak exercise in our population was 5 mmHg, which roughly correspond to the difference between the cutoffs of $PAWP_{avg}$ included in Herve's definition (≥ 20 mmHg) [32] and of $PAWP_{exp}$ considered in Borlaug's definition (≥ 25 mmHg) [23].

Multipoint PAWP/CO slope as the parameter "of choice" to diagnose HFpEF in real-world population

Data from DISCORDIA study showed that, in case of discordance in between the 3 exercise hemodynamic definitions of HFpEF, $PAWP_{exp}$/CO slope was the variable that could identify HFpEF more frequently than the other 2 hemodynamic definitions in a real-world population at intermediate-high risk for this condition. A $PAWP_{exp}$/CO slope > 2 mmHg/L/min, indeed, included most of the positive responses to other criteria. A multipoint PAWP/CO regression retained reliability also in presence of large respiratory pressure swings, being less influenced by the respiratory phase in which pressures were measured. Additionally, no patient at high probability of HFpEF based on the H_2FPEF and HFA-PEFF score had a $PAWP_{exp}$/CO slope < 2 mmHg/L/min, making the PAWP/CO slope a quite highly sensitive diagnostic parameter in comparison with non-invasive algorithm, also highlighting the importance of exercise hemodynamics in order not to miss the diagnosis of HFpEF.

Findings from our population suggest thus that $PAWP_{exp}$/CO slope may be viewed as the most stable, sensitive and inclusive hemodynamic parameter to diagnose HFpEF, and might thus be preferred over the other definitions when seeking to substantiate or exclude HFpEF in patients with nonconclusive data.

Diagnostic value of PAWP/CO slope overcomes methodological and hemodynamic heterogeneity across HFpEF cohorts

In a perspective of wider standardization of this technique, we explored the capacity of PAWP/CO slope to diagnose HFpEF also in population of patients with exertional dyspnea described in literature, as reported in the meta-analysis EX-PEF.

Published data on exercise RHC come mainly from small cohorts of patients investigated in very few highly experienced centers in the world. Despite the small number of centers where RHC is performed, we found a relevant heterogeneity in the procedural methodology: exercise was performed in the supine position in most studies (78%), CO was measured by direct Fick method in 59%, and PAWP using fluid-filled catheters in 74%. In more than 90% of studies, PAWP was measured at end-expiration. This methodological heterogeneity underscores the need to ideally standardize exercise RHC in order to obtain comparable results across laboratories, and might at least in part explain the hemodynamic heterogeneity across HFpEF cohorts analyzed.

Nonetheless, findings from meta-analysis EX-PEF confirmed that the hemodynamic profile of HFpEF patients is consistent across studies and characterized by higher left filling pressure compared with controls, enhanced by physical exercise, and normal exercise CO response. However, PAWP resulted highly heterogeneous across the studies, with a partial overlap in PAWP estimates at peak exercise in some studies between HFpEF and controls. Methodological heterogeneity in performing exercise RHC across Centers might have partially affected the comparability and the reproducibility of obtained results: a single pressure measurement taken at peak exercise might be influenced by several factors, including exercise duration and intensity, the phase of the respiratory, or cardiac cycle in which measurements are taken, and the body position in which exercise is performed. Furthermore, the above-mentioned procedural factors, some of which were not systematically reported, as well as some non-invasive or atypical definitions of HFpEF in the included studies may, at least in part, account for the partial overlap in peak PAWP between HFpEF and controls.

The PAWP/CO slopes we could extrapolate from available studies retained a good diagnostic power and resulted valid across cohorts described in literature. The PAWP/CO slopes were always > 2 mmHg/L/min for HFpEF cohorts and < 2 mmHg/L/min for control cohorts, with non-overlapping confidence intervals, thus somehow confirming and extending the validity of such cut-off value.

PAWP/CO slope diagnosed HFpEF independently from body position.

Stratification for body position confirmed that PAWP values in HFpEF were 5 mmHg higher in the supine compared with the upright position, somehow indirectly reinforcing the validity of previously proposed distinct PAWP cut-off for the two body positions (25 and 20 mmHg, respectively). However, according to our data the PAWP/CO slope cutoff > 2 mmHg/L/min seems to retain validity also for studies conducted in the supine position, potentially overcoming the need of different supine and upright absolute PAWP thresholds. Anyway, we found that the steepness of the PAWP/CO slope was higher in the supine than in the upright position in HFpEF but not in control cohorts. Thus, at variance from healthy subjects [121], we might speculate that the flow-normalized behavior of the pulmonary circulation may not be completely independent from the body position, at least in patients with (occult) fluid overload, where dysfunctional preload could be magnified when laying down. Accordingly, even if the PAWP/CO slope cut-off of 2 mmHg/L/ min might be valid to diagnose HFpEF irrespectively from body position, its absolute value might not provide comparable results in patients performing supine or upright exercise.

Obese and COPD versus non-obese and non-COPD patients: how to deal with respiratory swings and hemodynamic HFpEF definitions.

Obese and COPD patients, well represented in a typical HFpEF population, are more exposed to larger pulmonary pressure swings during exercise than non-obese and non-COPD ones in consequence of the air trapping phenomenon, even more accentuated during exercise, where end-expiratory values are frequently deemed to overestimate “true” intravascular or intracardiac pressures. Our data showed that respirophasic

PAWP changes were higher in patients with obesity or COPD than in nonobese and non-COPD patients. At rest, $PAWP_{exp}$ and $PAWP_{avg}$ differed of 7 [5–9] mmHg in obese and COPD patients, more than the 3 [3–5] mmHg difference in non-obese and non-COPD patients. At peak exercise, the difference was even higher, where $PAWP_{exp}$ was in median 13 [9–18] mmHg higher than $PAWP_{avg}$ in obese and COPD patients, compared with a difference of 9 [7–13] mmHg difference between obese/COPD and non-obese and non-COPD patients. As hypothesized, the influence of respiratory swings in pressure measurements in patients with obesity or COPD resulted relevant and non-negligible. Thus, in the presence of these comorbidities, a single pressure value of PAWP taken at peak of exercise might be relevantly influenced by the respiratory phase during which it is measured. At variance, multipoint PAWP/CO regression resulted less influenced by the respiratory phase. Our results thus suggested that this variable may not lose its diagnostic power even in presence of obesity, COPD, or conditions leading to air-trapping.

PAWP estimates LVEDP with good accuracy but a relevant imprecision

As previously said, 'PAWP' and 'LVEDP' are often considered interchangeably in clinical practice to define LV filling pressures, even if representing different hemodynamic loads. Indeed, all the reasoning that a steep exercise-induced increase in PAWP is considered the signature of HFpEF (=diastolic heart failure) is based upon the assumption that PAWP approximates LVEDP.

In our EX-LVEDP study, we looked at the comparison between LVEDP and PAWP during exercise in order to assess the validity of the latter as an estimate of the former. Our findings suggest a good accuracy (minimal average bias) but a relevant imprecision (large confidence intervals) of PAWP estimates for LVEDP. This result was consistent both at rest and at peak exercise, both when these variables were measured at end-expiration (as it is commonly done in many US centers) and when they were averaged over the respiratory cycle (as it is recommended by the ERS when large respiratory swings are present, including during physical exercise [31]).

The advantage of the LVEDP is that it might more accurately represent LV diastolic stiffness. However, this measure is generally felt to be more “invasive” and riskier than PAWP. LVEDP has been rarely employed during

exercise for the diagnosis of HFpEF, with lower evidence on pathological LVEDP thresholds to diagnose this disease. Moreover, a left heart catheterization alone may carry less information than RHC: this latter incorporates pressures and flows of the pulmonary circulation; PAWPED (mid-A or mid-C) is believed to be an acceptable surrogate of LVEDP; and PAWPM provides additional information over LVEDP on left heart filling pressures [122]. The LA seems to play a crucial role in the pathophysiology of HFpEF: LA "myopathy", either due to intrinsically reduced LA compliance or to an upward shift of the LA compliance curve, might frequently manifest with tall (systolic) V waves in the PAWP position, increasing PAWPM well beyond PAWPED and LVEDP [70,123]. Accordingly, V wave amplitude > 5 mmHg at peak exercise was present in one quarter of our patients' population, likely contributing to elevate PAWPM in median slightly above PAWPED and LVEDP, irrespectively of the respiratory phase. Thus, it seems thus reasonable to prefer end-expiratory PAWPM over PAWPED (and LVEDP) for diagnostic purposes, in order to take into account the role of the left atrium in the clinical manifestations of HFpEF.

In analogy to our results obtained during supine exercise, clinical studies comparing PAWP and LVEDP in resting conditions have overall shown a moderate to good accuracy (minimal bias) but a large imprecision (wide limits of agreement) of PAWP estimates for LVEDP. Indeed, results coming from literature are quite heterogeneous, both in terms of sample size, patients' population being investigated, methodology and timing of pressure measurement over the respiratory and cardiac cycle, as well as results obtained. Some investigators found a small but potentially relevant underestimation (by 2-4 mmHg) either of respiratory averaged PAWPM or end-expiratory PAWPM, one study highlighted an overestimation of LVEDP by PAWP in patients with AF (as a marker of LA dysfunction/myopathy), while others showed the absence of a relevant bias of PAWP (especially PAWPED) estimates for LVEDP. However, all the studies are homogeneous in pointing to a relevant imprecision (large confidence intervals) of PAWP estimates for LVEDP in resting condition, indicating that these two measures may not coincide in an individual patient [124-128]. Even though PAWP and LVEDP are supposed to have a similar meaning (and accordingly they are quite fairly correlated with minimal albeit potentially relevant bias), intra-individual differences might be expected, either due to intrinsic limitation of pressure measurements with fluid-filled catheters, measurement errors (as for any physiological

measurement), or to the fact that PAWP and LVEDP are measured in different sites of the cardiovascular system or in different time frames of the cardiac cycle.

PAWP/CO slope discriminates HFpEF when PAWP and LVEDP disagree

A minimal bias in PAWP estimating LVEDP, together with the large limits of agreement, may be clinically relevant in those individuals with left heart filling pressure values close to the thresholds adopted to discriminate pre-capillary from post-capillary PH, as well as to diagnose or exclude HFpEF during exercise. This is why provocative testing in the cath lab are increasingly integrated in order to obtain a consistent and definitive diagnosis when resting hemodynamics lay in a “grey zone” [129,130].

In line with this reasoning, the rate of concordance between end-expiratory PAWPM and LVEDP was slightly higher during exercise than at rest, indirectly highlighting the importance of provocative maneuvers to unmask HFpEF. Despite this, 5 individuals (11%) reached either the end-expiratory LVEDP or the PAWPM threshold ≥ 25 mmHg at peak exercise. Interestingly, all of them presented also with a PAWPM/CO slope > 2 mmHg/L/min as an additional criterion supporting the diagnosis of HFpEF. Even though this is a marginal and exploratory result on a limited sample size, we may suggest that incorporation of the PAWP/CO slope in the definition of HFpEF (e.g. end-expiratory PAWP ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min) might help supporting the hemodynamic diagnosis of this condition, possibly overcoming the limitations of a solitary PAWP measurement at peak exercise. Additionally, the multipoint evaluation during exercise may indeed minimize and overcome the impact of aleatory fluctuations in hemodynamics at rest as well as error measurements.

HFpEF HEMODYNAMIC CONSEQUENCES

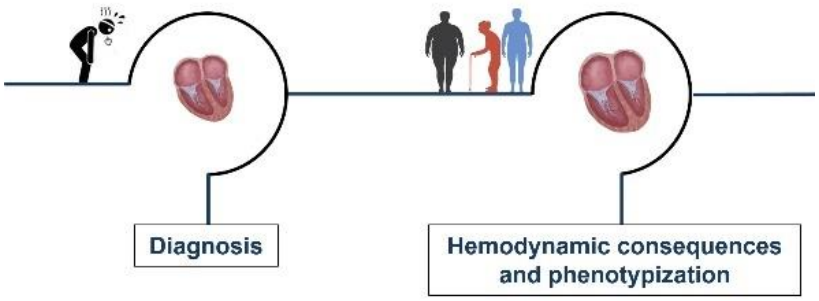


Figure 62. The progression of the natural HFpEF history: a crescendo of hemodynamic consequences leading to different hemodynamic phenotypes.

HFpEF as a continuum

Over time, several definitions of HFpEF have been proposed [6], which seem trace the natural history of the disease, assessing HFpEF at different time points along the disease timeline [5], suggesting a continuum of alterations in the pathophysiology of HFpEF (**figure 62**).

To highlight that HFpEF represents a continuous spectrum of alterations, we subdivided the population of patients included in the DISCORDIA study based on the number of exercise hemodynamic criteria met for HFpEF, and compared their clinical and hemodynamic characteristics. Patients meeting the highest number of diagnostic criteria were found to be older than the other groups with a higher prevalence of AF. Moreover, they presented with a more typical echocardiographic profile, including had larger LA volume, higher prevalence of overt LV diastolic dysfunction, as well as higher NT-proBNP values, and thus in general higher HFA-PEFF and H_2FPEF scores. This was paralleled by a crescendo of hemodynamic abnormalities with increasing number of exercise hemodynamic criteria met, with the worst profile in those patients presenting with 3/3 positive criteria. In particular, HFpEF patients meeting 3/3 diagnostic criteria displayed higher PAWP at rest and at peak exercise, taller PAWP V waves, as well as higher $PAWP_{exp}$/CO slope and TPR_{avg} at peak exercise. Finally, also their exercise profile was worse, characterized by lower peak oxygen consumption and CO.

Atrial-STR is a HFpEF complication, and is associated with a worse phenotype

As discussed in the background section, it might be expected that a non-negligible proportion of HFpEF patients may develop severe secondary TR, either due to PH with RV remodeling, or LA myopathy with AF and RA dilation. We thus explored the prevalence of severe STR in our population of hemodynamically-proven HFpEF patients, as well as the clinical and hemodynamic characteristics associated with severe STR [87].

Firstly, we found that STR prevalence was not irrelevant in our early HFpEF cohort, involving up to 14% of the entire population. The etiology of severe STR was atrial-functional in the great majority of these patients and no one presented with leaflet tenting. However, the definition of atrial-STR available at the time of this work [38-41,88,90] mainly relied on exclusion of other common secondary causes of TR and on an echocardiographic estimation of PAP (systolic PAP < 50 mmHg) to exclude severe PH [90].

The close link between HFpEF and atrial STR may be supported by several common denominators and underlying pathophysiological mechanisms shared by these two conditions. First, the prevalence of STR increases with age [131]. Similarly, HFpEF is a disease of cardiovascular aging, which promotes diastolic stiffening of the LV and LA myopathy [132]. Second, atrial fibrillation is associated with RA enlargement, negative remodeling of the tricuspid annular-valvular complex, and development of atrial-functional STR [38-42]. On the other hand, it has been proven that HFpEF diagnosis is a risk factor for the development, or the progression of AF [132] and that AF is a strong clue for HFpEF diagnosis [21]. Additionally, as already mentioned, AF plays a role in HFpEF progression promoting adverse bi-atrial remodeling, volume expansion, development of STR and RVD over time [37,133].

The STR-HFpEF study highlighted that the occurrence of severe STR had a relevant hemodynamic impact on cardiorespiratory adaptation to exercise of HFpEF patients. HFpEF-STR presented with a marked RA dilation and had RA hypertension, both at rest and during exercise. RAP, although often within normal limits in early-stage HFpEF, is generally 2-fold higher in this population than in healthy controls [59]. STR causes an additional

impact on the right heart of HFpEF patients, elevating RAP by another factor 2 in our HFpEF-STR as compared with HFpEF-controls.

Moreover, HFpEF-STR patients presented with reduced SV and CO reserve during exercise. We showed that HFpEF-STR had to rely more on heart rate and peripheral O_2 extraction to maintain an exercise performance similar to HFpEF-controls. This highlights the importance of avoid strict rate-control strategies in HFpEF with STR [134]. Additionally, our results suggest that VO_2 at peak exercise might not be an optimal surrogate for STR severity, since HFpEF-STR patients showed an ability to compensate for low CO by increasing peripheral extraction and, consequently, that interventions aimed at reducing STR severity might not necessarily improve peak VO_2, nonetheless potentially reducing muscular fatigue, in analogy to what shown after transcatheter mitral valve interventions [135].

Furthermore, STR seemed to be associated with low SV and pulmonary vascular de-recruitment, leading to spuriously increased PVR [44] (**figure 63**). In these cases, a slight increase in PVR might not necessarily reflect pulmonary vascular remodeling, as suggested by observing that the rate of decrease in PVR during exercise was similar in the two groups, with HFpEF-STR set at higher PVR values because of low SV. Thus, slightly increased PVR at rest should not necessarily contraindicate transcatheter interventions for the correction of STR [136], albeit potentially indicating a worse patients' profile [46,53].

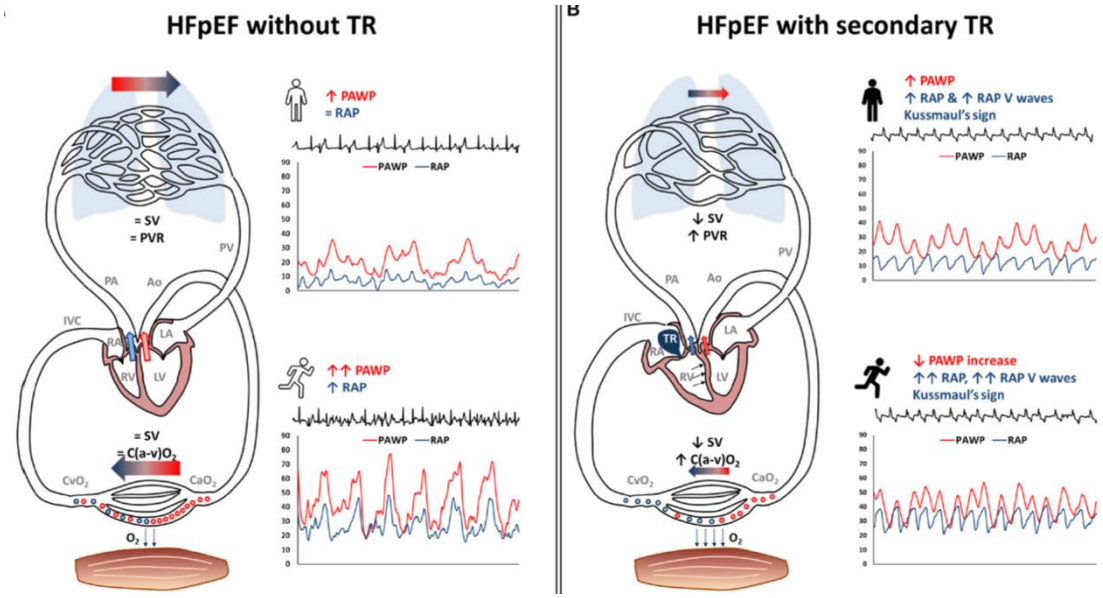


Figure 63. Exercise pathophysiology of STR in HFpEF. The typical HFpEF patient without STR (panel on the left) may present with (A) high pulmonary artery wedge pressure, either at rest or during exercise, with a steep pulmonary artery wedge pressure rise, and mildly increased right atrial pressure. (B) substantially normal stroke volume, pulmonary vascular resistance and peripheral oxygen extraction. This HFpEF pathophysiology is altered in the presence of STR (panel on the right), being characterized by: (i) high right atrial pressure that lacks inspiratory decrease or may present with overt Kussmaul's sign, tall V waves in the right atrium, right atrial enlargement and venous congestion; (ii) reduced forward stroke volume with pulmonary vascular derecruitment (increasing pulmonary vascular resistance), left ventricular underfilling, flatter pulmonary artery wedge pressure rise during exercise, and high ratio between right atrial pressure and pulmonary artery wedge pressure; (iii) higher reliance upon peripheral oxygen extraction to exercise despite low stroke volume [87].

Finally, low SV together with the marked increase in RAP probably contributed to LV underfilling in HFpEF-STR patients by reducing LVTMP [91]. This apparently counterintuitive finding, that volume-expanded HFpEF-STR patients had actually lower than expected rise in PAWP during exercise, might have clinical implications. Indeed, one might guess that STR may "protect" HFpEF-STR patients from pulmonary congestion, at the expense of reduced forward flow, even though pulmonary congestion might be favored by impaired lymphatic drainage associated with RAP hypertension. After STR correction, unimpeded LV filling as a result of increased SV, may be associated with a sharp rise in left heart filling pressure, potentially fading the net clinical benefit of tricuspid valve repair.

HFpEF latent-PVD phenotype: a marker of a more sever HFpEF profile

In a post-hoc analysis of the REDUCE LAP HF II trial, Borlaug and colleagues investigated the characteristics of subgroup of patients displaying higher PVR during exercise (the highest tertile, PVR > 1.74 WU), i.e. those presenting with worse outcome and response to creation of an interatrial shunt, called "latent-PVD" [49]. The latent-PVD HFpEF population, as compared with the rest of the HFpEF cohort, was characterized by older age, high prevalence of atrial fibrillation, large RA and right heart dysfunction, elevated PAWP, RAP, mean PA pressure, and PVR, as well as worse outcomes than patients without latent PVD.

In our HFPEF LATENT-PVD study, we provided an in-depth analysis of the HFpEF latent-PVD phenotype, in a real-world, single-center population.

As compared with the REDUCE LAP-HF II trial, in our cohort, the HFpEF latent-PVD phenotype was slightly less frequent (33 vs 21%). Additionally, very few patients with the HFpEF latent-PVD phenotype (6% of our HFpEF cohort) had isolated latent PVD (normal PVR at rest becoming abnormal during exercise), given that mostly presented with PVR > 2 WU at rest. Potential reasons for these discrepant results, among many similarities between our analysis and the analysis provided by Borlaug and colleagues [49], may be sought in: 1) the selection of the population under analysis; and 2) the methodology of exercise RHC. First, as compared with the REDUCE LAP-HF II trial, our patients with HFpEF were more frequently studied as a part of a routine evaluation for dyspnea, with very few of them having experienced worsening HF during the previous year (as compared with 43% of patients enrolled in the REDUCE LAP-HF II), showing lower median natriuretic peptide levels and presenting in about half of cases with PAWP <15 mm Hg (as compared with 29% in the REDUCE LAP-HF II). Thus, the more advanced phenotype of patients enrolled in the REDUCE LAP-HF II trial may justify a slightly higher proportion of patients classified as having HFpEF latent-PVD. Second, in the REDUCE LAP-HF II trial [48], CO was measured by a single-shot thermodilution injection at peak exercise, rather than through 3 sets of measurement with <10% variation, which is the standard during RHC at rest but may be too time consuming in a dynamic scenario such as at peak effort. It has been already demonstrated that thermodilution may underestimate CO during exercise [137], thus potentially leading to higher-than-expected PVR, even though the CO findings in our study and in the REDUCE LAP-HF II trial were comparable. However, by measuring CO by the direct Fick method, we could show a relative stability or decrease of PVR in the great majority of our HFpEF latent-PVD patients as compared with resting values, whereas PVR physiologically decreased in our HFpEF control patients.

As a novelty of our study, which expands the previous evidence generated by the post hoc analysis of the REDUCE LAP-HF II trial, we found that the HFpEF latent-PVD phenotype was associated with TR. Indeed, TR equal or more than moderate, as evaluated through echocardiography, was present in about one third of our patients whereas it was an exclusion criterion for the REDUCE LAP-HF II. TR may frequently complicate HFpEF: Obokata and colleagues [37] previously showed how AF, which is frequent in HFpEF [131], is associated with biatrial remodeling and TR, characteristics that we found especially in latent-PVD patients among our HFpEF

cohort. However, there is scarce information on the behavior of TR during exercise in HFpEF and on its hemodynamic impact. HFpEF patients, albeit not presenting with overt signs of fluid overload, may harbor increased stressed blood volume (functional preload), magnified by physical exercise [54,138]. On the basis of hemodynamic data (systolic RAP increase) [88], we found that the impact of even moderate or severe TR might have been missed at rest but became overtly evident during exercise, when stressed blood volume is shifted from the splanchnic reservoir to the chest [54,138], affecting first the right heart and the tricuspid annulus. Thus, hemodynamically relevant TR during exercise, mirrored by a higher systolic RAP increase in HFpEF latent-PVD patients [94], could help explain an afterload-independent, exercise-induced right ventricular failure. Indeed, the increase in regurgitant volume during exercise would potentially lead to lower forward stroke volume and reduced stroke volume reserve. We may speculate that in the presence of low forward stroke volume, associated with tricuspid regurgitation, CO limitation, and nearly exhausted peripheral O_2 extraction, the low blood O_2 content coming to the pulmonary vessels may favor a certain degree of pulmonary vasoconstriction in HFpEF latent-PVD [45]. This reasoning may partially explain the correlation we found between PVR on one side and stroke volume index as well as mixed venous O_2 pressure on the other side.

As an alternative hypothesis, increased PVR may have contributed to reduced stroke volume and CO in HFpEF latent-PVD patients (as well as to afterload related tricuspid regurgitation). However, it is important to note that the extent of PVR elevation was mild and relatively stable during exercise in the majority of HFpEF latent-PVD patients and thus was pretty unlikely to cause, per se, right ventricular failure and low CO. It is important to point out that other factors may contribute to higher PVR in our HFpEF latent-PVD population. First, we found a higher proportion of patients with PH during exercise, with a (non-significantly) higher proportion of tall V waves in the PAWP position in the HFpEF latent-PVD group. We speculate that a stiffer left atrium in HFpEF latent-PVD patients, which is expected based on the higher proportion of AF [37], may indeed promote pulmonary vasoconstriction and/or vascular remodeling (including venular congestive remodeling [45]) and high PVR. Second, $PaCO_2$ values were higher in HFpEF latent-PVD patients than in HFpEF control patients both at rest and during exercise, and resting $PaCO_2$ correlated with PVR in HFpEF latent-PVD patients. A relationship

of a modest age-related pulmonary comorbidity in HFpEF patients and/or an alteration of ventilatory control (reduced chemosensitivity) with the HFpEF latent-PVD phenotype we may speculate that our older HFpEF latent-PVD patients may present with a slightly blunted chemoreflex response to CO_2 and a higher $PaCO_2$ setpoint. Despite this, their exercise hyperventilation was similar to that of their counterparts without latent PVD, likely as a consequence of increased exercise dead space ventilation in latent PVD. Thus, our results may suggest an increased responsivity of the pulmonary vessels to chemical stimuli (O_2 and CO_2) in patients with HFpEF latent-PVD, who presented with signs of altered ventilatory control, that may further contribute to slightly increased PVR.

Lastly, we found that the mid-term (3-year) event-free survival significantly lower in HFpEF latent-PVD than in HFpEF control patients (72% vs 93%, log-rank test, p = 0.004). Thus, even with the limitation related to the retrospective nature of a study conducted on a limited number of HFpEF patients, our data suggest that the clinical, hemodynamic, and cardiorespiratory alterations associated with the HFpEF latent-PVD phenotype may lead to worse event-free survival in this population.

Hemodynamic prognosticators in pulmonary hypertension due to HFpEF

Development of PH is part of the natural history of HFpEF, exposing patients to a poorer outcome especially when developing a CpcPH phenotype [44,46]. However, how to hemodynamically define the presence of a pre-capillary component has been largely debated in recent years [44].

Thus, we updated a previous meta-analysis on the prognostic role of hemodynamic markers of pre-capillary PH [46], in the light of new evidence in an almost quadruple patients' population available in literature. Our meta-analysis confirms and reinforces the established association of PVR and PAC with prognosis: PVR and PAC appear to be stronger predictor of outcome, both when dichotomized or when used as continuous variables. Moreover, PVR proved capable to predict outcome independently of the underlying LHD, thus including either HFpEF, HFrEF, and VHD.

The heterogeneity of the populations included (9600 pts) in the analysis mirrors the broad spectrum of LHD [129], composed of HFrEF, HFpEF, and VHD. However, independently from the underlying LHD, the pooled cohort was an elderly one, characterized by a quite large burden of comorbidities including a high rate of atrial fibrillation. The average hemodynamic profile was quite typical, combining an elevated PAWP (> 20 mmHg), a mildly elevated mPAP (25–40 mmHg), and PVR ranging from 3 to 4.9 WU [129].

The unitary increase in PVR resulted associated with a 7% of increase in risk of adverse outcome. Our analysis could confirm available data on its robust prognostic discriminative potential in PH-LHD [46], even when the cohorts were subdivided based on the underlying etiology of PH. Thus, the prognostic role of PVR is undisputed. It is still uncertain whether it might represent a therapeutic target in PH-LHD. Indeed, the great majority of studies testing drugs targeting the pulmonary circulation in PHLHD have provided neutral or even negative results [129,139-141], so that these compounds should not be used in patients with PH-LHD [129]. This evidence is further corroborated by the results of our LATENT-PVD study, as discussed above. Indeed, a mild elevation of PVR in HFpEF, at rest or during exercise, seemed to be associated with a more advanced HFpEF clinical phenotype, potentially factitiously increased by TR, and associated with altered respiratory control / respiratory comorbidities. All this suggest that targeting the pulmonary circulation may not be a good option in CpcPH, at least when PVR is only mildly elevated. More favorable results have been obtained with the inodilator levosimendan in patients with HFrEF [142-144] and in patients with VHD [145] while its effects in HFpEF are less studied, but it might at least decrease PAWP in a subgroup of such patients [146]. Finally, PVR might be useful for the selection of HFpEF patients candidate to the placement of an interatrial septal device: in the REDUCE LAP-HF II trial [48], patients with high PVR during exercise (> 1.74 WU) had an increased incidence of HF events as compared with those with low PVR, who seemed to have more benefit from this device.

DPG was similarly found to be associated to outcome, but with a small increase in risk for a unitary increase. Moreover, the meta-analysis results were not extremely solid when separately analyzing studies in which the association of DPG with mortality was either adjusted or unadjusted. As it has been repeatedly remarked, the DPG is a small number and exposed to measurement error, potentially explained also by the relative

inaccuracy of the used catheters (“fluid filled” rather than “high fidelity”), the lack of standardization in the measure of PAWP across laboratories (mean PAWP vs. mid-A PAWP; end-expiratory vs. respiratory-averaged values), and the fact that the two terms of the subtraction, that is, the diastolic PAP and PAWP are not simultaneously measured in the same heartbeats and over the same breaths. Accordingly, a relevant proportion of negative DPGs was found in the studies under analysis. PAC has been proposed as predictor of outcome in LHD given its presumed pathophysiological meaning, even if the estimated PAC could overestimate its real value by 60%−80% [44,147]. Given the inverse relationship between PAC and PVR, the former has been advanced to be a better fit as prognostic marker when PVR are still “in the normal range” or when mean PAP is below 25 mmHg. However, the recent evidence linearly linking PVR with outcome since a lower cut-off than 3 WU might change current threshold to define diseases, potentially overcoming this previous limit of PVR.

Finally, the strong association of PAC with mortality reflects its dimension: it is an even smaller number than DPG, and similarly subject to measurement errors. Additionally, we still do not know which changes should be considered clinically meaningful, and thus it is probably impractical to assess fine changes in pulmonary vascular properties and right ventricular afterload. Thus, even though these three variables carry prognostic significance, we could propose a pragmatic approach, aiming at simplifying and rendering clinical practices and communication more homogeneous across laboratories, where PVR alone may suffice as a hemodynamic marker for risk stratification.

“Early” right heart failure in HFPEF: the right heart maladaptation to exercise

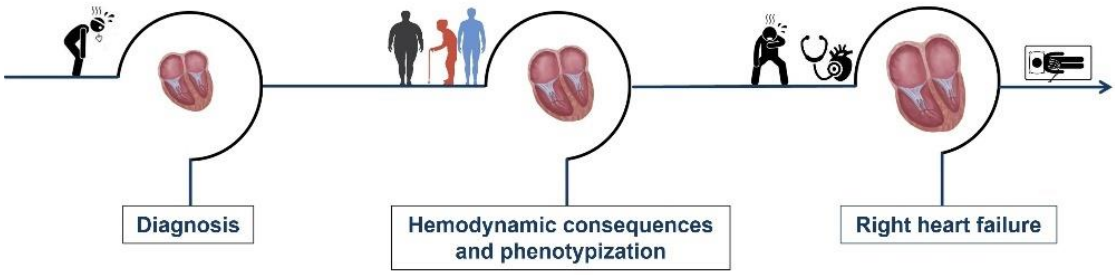


Figure 64. Advanced phase of the natural HFpEF history: the deterioration of the RV function over time drives the prognosis.

All the hemodynamic markers of a pre-capillary component are believed to be associated with prognosis because of their tight link with RV function (**figure 64**), either for the exquisite load sensitivity of the RV, or because they incorporate a measure of CO or stroke volume. However, RHF is generally a late diagnosis.

Given that RHF is associated with a dismal prognosis and worse outcomes, it would be desirable to early identify its occurrence [148-149]. In keeping with what was observed in left heart failure, RHF may be defined by the inability of the heart to maintain a normal CO or to do so at the expense of high RAP, at rest or during exercise [26]. Thus, we hypothesized that exercise RHC may unmask right heart maladaptation as a sign of early RHF [31]. In our RETRORIGHT study, we thus focused on the description of the patterns of right heart adaptation to exercise in distinct diseases, differently involving the pulmonary circulation, such as PH due to HFpEF and PAH.

Moreover, we provided an analysis on the “normal” cut-offs for RAP rise during exercise, taking as reference the data obtained from patients with NCD. Indeed, invasive data from 21 individuals without discernible cardiac or respiratory causes of exertional dyspnea allowed us to define the “right heart maladaptation to exercise”, i.e. when peak RAP was > 12 mmHg or RAP/CO slope was ≥ 1.30 mmHg/L/min.

Based on these, we expectedly found that both PH-HFpEF and PAH patients showed on average an abnormal increase in right heart filling pressure during exercise, both in absolute and flow-normalized values. This aspect might be particularly relevant for the proportion of PH patients with normal RAP at rest, presenting

features of RHF unmasked during physical exercise (**figure 65**), emphasizing the fundamental role of provocative tests in the cath lab.

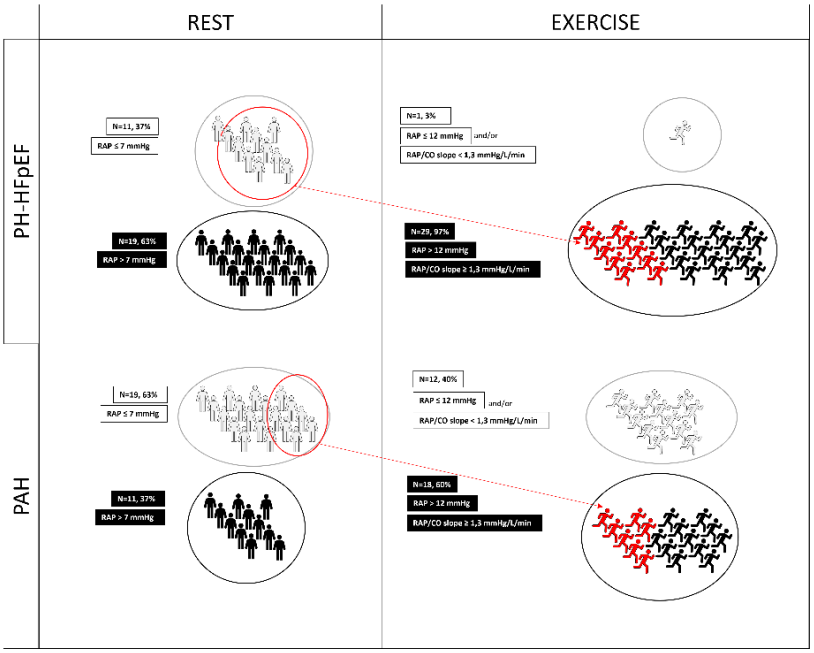


Figure 65. Right atrial hypertension in PH-HFpEF (top) and in PAH (bottom), at rest (left) and during exercise (right).

However, occurrence of RHF seemed to have a different prevalence, expression and physiopathology in the two groups, being more frequent and significantly worse in PH-HFpEF than PAH patients. Indeed, among patients with normal RAP at rest, 91% and 90% of the PH-HFpEF cohort presented with exercise-induced RHF (i.e. either high RAP or high RAP/CO slope), as compared with 32% or 71% of patients with PAH with higher-than-normal absolute peak RAP or flow-corrected RAP increase during exercise, respectively. Additionally, patients with PH-HFpEF, as compared with PAH, presented both with an upward shift and steepening of the RAP/CO relationship, despite a lower pulmonary hemodynamic load.

RV preload-related factors and their role in RHF

We found that preload-related parameters resulted associated with the development of exercise-induced RHF in PH-HFpEF, namely TR, RA dilation, and eSBV. It is true that even mild increase in PVR have been associated with outcome [47], and that, especially in HFpEF, high PAWP contributes to augment right

ventricular pulsatile (over resistive) load [52,150]. However, the mild alteration in PVR and PAC with which our PH-HFpEF patients presented both at rest and during exercise, were by far lower than those displayed by PAH patients, thus suggesting that other, non-afterload related factors may intervene in right heart maladaptation during exercise.

Preload- rather than afterload-mediated mechanisms may effectively account for the development of RHF in patients with HFpEF. Key elements driving hemodynamic disturbances and disease progression in HFpEF may include atrial fibrillation-induced cardiac remodeling [132], reduced capacitance and compliance of the venous system [54], expansion and redistribution of plasma volume with increased eSBV [54,132,138], as well as occurrence of functional TR [39,151]. In particular, increased eSBV, RA dilation and functional TR might be tightly linked in a vicious circle perpetuating a condition of relative hypervolemia [152]. This aspect, along with both the reduced capacitance and compliance of the venous system and the increased chamber stiffness which characterizes HFpEF, may explain higher RAP both at rest and during exercise in PH-HFpEF than in PAH patients.

Additionally, right heart maladaptation in PH-HFpEF was associated with BMI. This finding may be in line with higher ventricular interdependence in the obese HFpEF phenotype, favored by functional extrinsic constriction and greater volume overload [129] as well as with an enhanced LA/RA-interaction, recently suggested as a potential factor contributing to the increased RAP in HFpEF [153]. Indeed, our PH-HFpEF population presented with a less than expected rise in LVTMP from rest to peak exercise (+2 mmHg on average), which was not qualitatively different from the LVTMP increase in NCD (+3 mmHg), and half than values reported in literature in the HFpEF population (+7 mmHg) [8], suggesting functional pericardial constraint, potentially driven by obesity and/or TR. Therefore, our findings highlight the crucial role of preload-related mechanisms in the genesis of RHF in PH (and reinforce the importance of afterload-related mechanisms in the development of RHF in PAH patients: among other factors, PVR and TPR resulted associated to right heart maladaptation only in PAH). Although the right heart is able to accommodate large increase in preload [148], its reserve might be stretched up to its limits, favoring RHF. The relationship between RAP and CO could also be viewed as the right heart ability to increase CO as RAP rises during physical

effort, representing an “inverse” Frank-Starling relationship. Thus, the steeper RAP/CO slope in PH-HFpEF may indeed imply a flatter CO increase over RAP, and a rightward-shifted response in stroke volume, suggesting an impaired Frank-Starling reserve in this cohort, which is expected to be mainly favored by preload-dependent mechanisms (**figure 66**). This further reinforces the idea that drugs acting on the pulmonary circulation should not favorably impact on exercise hemodynamics in PH-HFpEF, while novel techniques modulating preload (e.g. splanchnic denervation) might be of benefit [138].

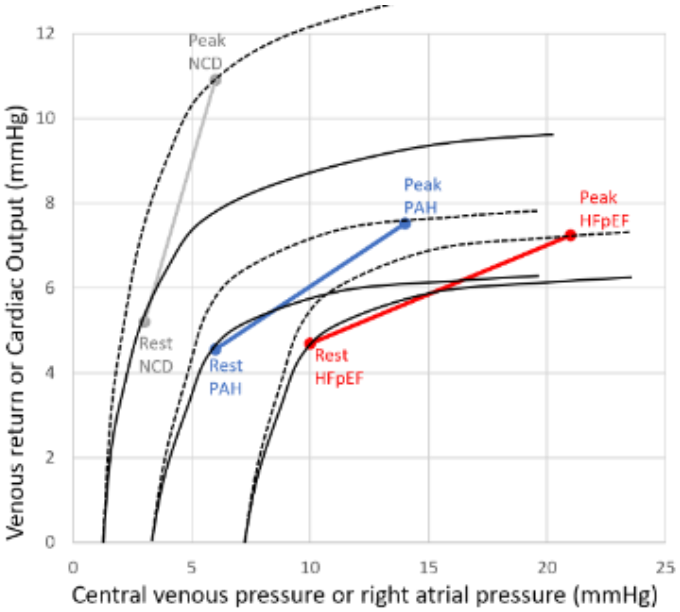


Figure 66. Venous return and Frank–Starling curves at rest and during exercise in HFpF (red), PAH (blue) and NCD (grey) patients. Group mean values for central venous pressure (RAP) and venous return (CO). The diagonal straight lines represent venous return curves, which intersect with the Frank–Starling curves at the coordinates of CVP and CO. The X intercept of the venous return curve represents mean RAP. In NCD, venous capacitance is high, meaning that most of blood volume resides in the UBV compartment and SBV is low. During exercise (dashed lines), the venous return curve shifts rightward as venous capacitance decreases, leading to an increase in SBV and mean systemic filling pressure. This increases venous return and is associated with increase in CO with only mild increase in CVP in controls, because the Starling curve also shifts up to the left due to enhanced inotropy, chronotropy, and vasodilatation. In HFpEF, venous capacitance is reduced shifting blood from the UBV to the SBV, increasing mean RAP, reflected by a rightward shift in the venous return curve at rest. During exercise, there is a greater increase in SBV in HFpEF patients, resulting in a greater rightward shift in the venous return curve. The fact that CO increases minimally with respect to the increase in CVP suggests that the heart is operating on the plateau of the Starling curve, where further increases in CO are not achieved with venoconstriction [115].

CONCLUSIONS

Our studies, taken together, show that the exercise hemodynamic evaluation could highlight several aspects of HFpEF, from the diagnostic field, including early diagnosis, up to the phenotypization of patients and the characterization of the disease progression.

In **HEMO-VALIDATION** study we confirmed the suboptimality of the lastly proposed, composite, non-invasive diagnostic tools, in particular of the HFA-PEFF score, which demonstrated low sensitivity and low negative predictive value in identify HFpEF in comparison with hemodynamic.

However, even if claimed as the gold-standard test to diagnose HFpEF, exercise RHC it is still limited by a series of methodological issues, as highlighted in our **meta-analysis EX-PEF.** We found, indeed, large methodological heterogeneity across highly experienced centers, partly mirrored in the high heterogeneity of hemodynamic responses to exercise across the different HFpEF cohorts analyzed.

We tried to solve some of these methodological heterogeneity in our study **DISCORDIA.** We showed that the phase of the respiratory cycle in which pulmonary pressure measurements are performed can dramatically change the interpretation of data, especially during exercise. Moreover, we showed that the 3 proposed hemodynamic HFpEF definitions based on exercise hemodynamic are only moderately concordant with each other, potentially leading to misdiagnosis of the disease.

Among the 3 definitions, we found that PAWP/CO slope > 2 mmHg/L/min might be considered the most consistent parameter to define HFpEF, since it appears to be more sensitive and inclusive parameter, independent from respiratory swings. Moreover, this parameter has demonstrated to have also a relevant diagnostic power when applied in the HFpEF population described in literature. In the **meta-analysis EX-PEF**, a PAWP/CO slope cutoff > 2 mmHg/L/min well discriminates HFpEF from controls, retaining validity also for studies conducted in the supine position.

Further, we tried to clarify another methodological aspect concerning HFpEF diagnosis, i.e. the potential disagreement between PAWP and LVEDP, especially during exercise. In the **EX-LVEDP** study, we could

demonstrate that PAWP and LVEDP are fairly correlated both at rest and during exercise, but this adequate accuracy of exercise PAWP vs LVEDP is counterbalanced by relevant imprecision. Assuming absolute pre-established cut-off value to diagnose HFpEF for PAWP and LVEDP, these two measures might disagree; in these cases, a PAWP/CO slope > 2 mmHg/L/min could optimize the diagnostic power of exercise cardiac catheterization.

Additionally, we tried to clarify the clinical factors associated with distinct exercise hemodynamic phenotypes, and their clinical implications. Fourteen percent of our hemodynamic cohort of HFpEF had severe STR. In the **STR-HFpEF study**, HFpEF with STR presented with RA hypertension, increased ventricular interdependence and a relative LV underfilling, with reduced CO reserve and pulmonary vascular derecruitment.

In line with this, in the **LATENT-PVD** study, we found that patients with PVR at peak exercise > 1.74 WU (HFpE latent-PVD) were characterized by a more advanced HFpEF phenotype (older, high burden of AF), had more frequently TR, had a more impaired hemodynamic adaptation to exercise (higher rate of tall V waves in the LA and in the RA) with overt cardiac limitation. The presence of TR, becoming more relevant during exercise, together with an altered respiratory control, seemed to mainly drive the mild increase in PVR observed in this group. Thus, high PVR, both at rest (meta-analysis PROGNOSIS-PH) and even during exercise (LATENT-PVD study) is confirmed as an undisputed prognostic marker in HFpEF.

Despite the expected association of PVR with right ventricular function, in the RETRO-RIGHT study we found that right heart maladaptation to exercise, as an early sign of RHF, was mainly associated with pre-load rather than afterload factors in PH-HFpEF. Indeed, a steep or relevant increase of RAP during exercise resulted associated, among other factors, with TR, eSBV and RA dilation. RHF in our population of PH-HFpEF seemed to be mainly related to the inability of the right heart to accommodate large increase in preload during physical effort, determining a flatter CO increase with a rightward-shifted response in stroke volume, suggesting an impaired Frank-Starling reserve.

REFERENCES

1. Redfield MM, Borlaug BA. Heart Failure With Preserved Ejection Fraction: A Review. JAMA. 2023 Mar 14;329(10):827-838. doi: 10.1001/jama.2023.2020. PMID: 36917048.
2. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032. doi:10.1161/CIR. 0000000000001063
3. Van Riet EE, Hoes AW , Wagenaar KP , Limburg A , Landman MA , Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016;18:242–252.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368. Erratum in: Eur Heart J. 2021 Oct 14;: PMID: 34447992.
5. Senni M, Caravita S, Paulus WJ. Do Existing Definitions Identify Subgroup Phenotypes or Reflect the Natural History of Heart Failure With Preserved Ejection Fraction? Circulation. 2019 Jul 30;140(5):366-369. doi: 10.1161/CIRCULATIONAHA.119.041657. Epub 2019 Jul 29. PMID: 31356132.
6. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Naylor M, Lewis GD. Differential clinical profiles, exercise responses and outcomes associated with existing HFpEF definitions. Circulation. 2019;140:353–365. doi: 10.1161/CIRCULATIONAHA.118.039136

7. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol. 2023 May 9;81(18):1810-1834. doi: 10.1016/j.jacc.2023.01.049. Epub 2023 Apr 19. PMID: 37137592.
8. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation. 2017; 136: 6–19. Epub 2017 Apr 5. PMID: 28381470; PMCID: PMC5501170.
9. Omote K, Verbrugge FH, Sorimachi H, et al. Central hemodynamic abnormalities and outcome in patients with unexplained dyspnea. Eur J Heart Fail. 2023;25:185–196.
10. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62:263–271.
11. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis: the heart failure with preserved ejection fraction paradigm revisited. Circ Res. 2021;128:1451–1467.
12. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, Olson TP, Borlaug BA. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2017; 70: 136–148. PMID: 28683960; PMCID: PMC5520668.
13. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J. 2018;39:3439–3450
14. Kitzman DW, Nicklas B, Kraus WE, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Physiol Heart Circ Physiol. 2014;306:H1364–1370.
15. Olson TP, Johnson BD, Borlaug BA. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. J Am Coll Cardiol HF. 2016;4: 490–498.
16. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and kidney. Circulation. 2020;142:998–1012.

17. Sorimachi H, Omote K, Omar M, et al. Sex and central obesity in heart failure with preserved ejection fraction. Eur J Heart Fail. 2022;24:1359– 1370.
18. Sorimachi H, Burkhoff D, Verbrugge FH, Omote K, Obokata M, Reddy YNV, Takahashi N, Sunagawa K, Borlaug BA. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. Eur J Heart Fail. 2021 Oct;23(10):1648-1658. doi: 10.1002/ejhf.2254. Epub 2021 Jun 17. PMID: 34053158.
19. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation.2006;114:2138–2147.
20. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016 Apr;29(4):277-314
21. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018 Aug 28;138(9):861-870. doi: 10.1161/CIRCULATIONAHA.118.034646. PMID: 29792299; PMCID: PMC6202181.
22. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019 Oct 21;40(40):3297-3317. doi: 10.1093/eurheartj/ehz641. Erratum in: Eur Heart J. 2021 Mar 31;42(13):1274. PMID: 31504452.

23. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010; 3: 588–595. Epub 2010 Jun 11. PMID: 20543134; PMCID: PMC3048586.
24. Reddy YNV, Kaye DM, Handoko ML, van de Bovenkamp AA, Tedford RJ, Keck C, Andersen MJ, Sharma K, Trivedi RK, Carter RE, Obokata M, Verbrugge FH, Redfield MM, Borlaug BA. Diagnosis of Heart Failure With Preserved Ejection Fraction Among Patients With Unexplained Dyspnea. JAMA Cardiol. 2022 Sep 1;7(9):891-899. doi: 10.1001/jamacardio.2022.1916. PMID: 35830183; PMCID: PMC9280610.
25. Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, Farrell R, Shoenike MW, Sbarbaro J, Malhotra R, Nayor M, Tschöpe C, de Boer RA, Lewis GD, Ho JE. Evaluation of 2 Existing Diagnostic Scores for Heart Failure With Preserved Ejection Fraction Against a Comprehensively Phenotyped Cohort. Circulation. 2021 Jan 19;143(3):289-291. doi: 10.1161/CIRCULATIONAHA.120.050757. Epub 2021 Jan 19. PMID: 33464963; PMCID: PMC8059354.
26. Braunwald E, Grossman W. Clinical aspects of heart failure. In: Braunwald E (ed). Heart Disease: A Textbook of Cardiovascular Medicine. 4th Ed. Philadelphia: Sunders; 1992. 444–463.
27. Wolsk E, Kaye D, Komtebedde J, Shah SJ, Borlaug BA, Burkhoff D, Kitzman DW, Lam CSP, van Veldhuisen DJ, Ponikowski P, Petrie MC, Hassager C, Møller JE, Gustafsson F. Central and peripheral determinants of exercise capacity in heart failure patients with preserved ejection fraction. JACC Heart Fail. 2019; 7: 321–332. Epub 2019 Mar 6. PMID: 30852235.
28. Wright SP, Esfandiari S, Gray T, Fuchs FC, Chelvanathan A, Chan W, Sasson Z, Granton JT, Goodman JM, Mak S. The pulmonary artery wedge pressure response to sustained exercise is time-variant in healthy adults. Heart. 2016 Mar;102(6):438-43
29. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. ESC/ERS scientific document group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. (2022) 5:ehac237. doi: 10.1183/13993003.00879-2022

30. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R, Lewis GD. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. Circ Heart Fail. 2018; 11: e004750. PMID 29695381; PMCID: PMC5937988
31. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grünig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J. 2017 Nov 22;50(5). pii: 1700578
32. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jaïs X, Parent F, Günther S, Humbert M, Simonneau G, Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J. 2015 Sep;46(3):728-37
33. Naeije R, Chin K. Differentiating precapillary from postcapillary pulmonary hypertension. Circulation. 2019;140:712–714. doi: 10.1161/CIRCULATIONAHA. 119.040295
34. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015 Mar;8(2):295-303. doi: 10.1161/CIRCHEARTFAILURE.114.001667. Epub 2015 Jan 15. PMID: 25593126.
35. Moreno-Ruiz LA, Madrid-Miller A, Martinez-Flores JE, et al. Left atrial longitudinal strain by speckle tracking as independent predictor of recurrence after electrical cardioversion in persistent and long standing persistent non-valvular atrial fibrillation. Int J Cardiovasc Imaging. 2019;35:1587-1596q
36. Ziff OJ, Carter PR, McGowan J, Uppal H, Chandran S, Russell S, Bainey KR, Potluri R. The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: insights from the United Kingdom ACALM registry. Int J Cardiol 2018;252:117121
37. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction.

Eur Heart J. 2019 Feb 21;40(8):689-697. doi: 10.1093/eurheartj/ehy809. PMID: 30544228; PMCID: PMC7963126.

38. Hahn RT, Badano LP, Bartko PE, Muraru D, Maisano F, Zamorano JL, et al. Tricuspid regurgitation: recent advances in understanding pathophysiology, severity grading and outcome. Eur Heart J Cardiovasc Imaging. (2022) 23:913– 29. doi: 10.1093/ehjci/jeac009
39. Florescu DR, Muraru D, Volpato V, Gavazzoni M, Caravita S, Tomaselli M, Ciampi P, Florescu C, Bălșeanu TA, Parati G, Badano LP. Atrial Functional Tricuspid Regurgitation as a Distinct Pathophysiological and Clinical Entity: No Idiopathic Tricuspid Regurgitation Anymore. J Clin Med. 2022 Jan 13;11(2):382. doi: 10.3390/jcm11020382. PMID: 35054074; PMCID: PMC8781398.;
40. Florescu DR, Muraru D, Florescu C, Volpato V, Caravita S, Perger E, Bălșeanu TA, Parati G, Badano LP. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. Eur Heart J Cardiovasc Imaging. 2022 Jun 21;23(7):930-940. doi: 10.1093/ehjci/jeab211. PMID: 34747460
41. Muraru D, Guta AC, Ochoa-Jimenez RC, Bartos D, Aruta P, Mihaila S, et al. Functional Regurgitation of Atrioventricular Valves and Atrial Fibrillation: An Elusive Pathophysiological Link Deserving Further Attention. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2020;33(1):42-53.
42. Guta AC, Badano LP, Tomaselli M, Mihalcea D, Bartos D, Parati G, et al. The Pathophysiological Link between Right Atrial Remodeling and Functional Tricuspid Regurgitation in Patients with Atrial Fibrillation: A Three-Dimensional Echocardiography Study. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2021;34(6):585-94 e1.
43. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. Eur Heart J. 2018.

44. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic phenotyping of pulmonary hypertension in left heart failure. Circ Heart Fail. (2017) 10:e004082. doi: 10.1161/CIRCHEARTFAILURE.117.004082
45. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. Circulation. 2018;137(17):1796–1810.
46. Caravita S, Dewachter C, Soranna D, D'Araujo SC, Khaldi A, Zambon A, Parati G, Bondue A, Vachiéry JL. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. Eur Respir J. 2018;51(4):1702427
47. Maron BA, Brittain EL, Hess E, Waldo SW, Barón AE, Huang S, Goldstein RH, Assad T, Wertheim BM, Alba GA, Leopold JA, Olschewski H, Galiè N, Simonneau G, Kovacs G, Tedford RJ, Humbert M, Choudhary G. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. Lancet Respir Med. 2020 Sep;8(9):873-884. doi: 10.1016/S2213-2600(20)30317-9. Epub 2020 Jul 27. Erratum in: Lancet Respir Med. 2021 Mar;9(3):e29. PMID: 32730752; PMCID: PMC8219057
48. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, Gao Q, Hasenfuß G, Kahwash R, Kaye DM, Litwin SE, Lurz P, Massaro JM, Mohan RC, Ricciardi MJ, Solomon SD, Sverdlov AL, Swarup V, van Veldhuisen DJ, Winkler S, Leon MB; REDUCE LAP-HF II investigators. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. Lancet. 2022 Mar 19;399(10330):1130-1140. doi: 10.1016/S0140-6736(22)00016-2. Epub 2022 Feb 1. PMID: 35120593.
49. Borlaug BA, Blair J, Bergmann MW, Bugger H, Burkhoff D, Bruch L, Celermajer DS, Claggett B, Cleland JGF, Cutlip DE, Dauber I, Eicher JC, Gao Q, Gorter TM, Gustafsson F, Hayward C, van der Heyden J, Hasenfuß G, Hummel SL, Kaye DM, Komtebedde J, Massaro JM, Mazurek JA, McKenzie S, Mehta SR, Petrie MC, Post MC, Nair A, Rieth A, Silvestry FE, Solomon SD, Trochu JN, Van Veldhuisen DJ, Westenfeld R, Leon MB, Shah SJ; REDUCE LAP-HF-II Investigators. Latent

Pulmonary Vascular Disease May Alter the Response to Therapeutic Atrial Shunt Device in Heart Failure. Circulation. 2022 May 24;145(21):1592-1604. doi: 10.1161/CIRCULATIONAHA.122.059486. Epub 2022 Mar 31. Erratum in: Circulation. 2022 Jul 26;146(4):e12. PMID: 35354306; PMCID: PMC9133195.

50. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, Crespo-Leiro MG, Guazzi M, Harjola V-P, Heymans S, Hill L, Lainscak M, Lam CSP, Lund LH, Lyon AR, Mebazaa A, Mueller C, Paulus WJ, Pieske B, Piepoli MF, Ruschitzka F, Rutten FH, Seferovic PM, Solomon SD, Shah SJ, Triposkiadis F, Wachter R, Tscho¨pe C, de Boer RA. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20:16–37.
51. Houston BA, Brittain EL, Tedford RJ. Right Ventricular Failure. N Engl J Med. 2023 Mar 23;388(12):1111-1125. doi: 10.1056/NEJMra2207410. PMID: 36947468.
52. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, Cingolani OH, Mudd JO, Borlaug BA, Redfield MM, Lederer DJ, Kass DA. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation. 2012 Jan 17;125(2):289- 97. doi: 10.1161/CIRCULATIONAHA.111.051540. Epub 2011 Nov 30. PMID: 22131357; PMCID: PMC3264431.
53. Caravita S, Faini A, Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, Naeije R, Parati G, Vachiéry JL. Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component. PLoS One. 2018;13:e0199164. doi: 10.1371/journal.pone.0199164
54. Fudim M, Hernandez AF, Felker GM. Role of Volume Redistribution in the Congestion of Heart Failure. J Am Heart Assoc. 2017 Aug 17;6(8):e006817. doi: 10.1161/JAHA.117.006817. PMID: 28862947; PMCID: PMC5586477.

55. Lanzarone E, Baratto C*, Vicenzi M, Villella F, Rota I, Dewachter C, Muraru D, Tomaselli M, Gavazzoni M, Badano LP, Senni M, Vachiéry JL, Parati G, Caravita S. Haemodynamic validation of the three-step HFA-PEFF algorithm to diagnose heart failure with preserved ejection fraction. ESC Heart Fail. 2023 Aug;10(4):2588-2595. doi: 10.1002/ehf2.14436. Epub 2023 Jun 15. PMID: 37321596; PMCID: PMC10375124. *equally first and corresponding author
56. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging. (2015) 16:233– 70. doi: 10.1093/ehjci/jev014
57. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati G, Vachiéry JL. Current Limitations of Invasive Exercise Hemodynamics for the Diagnosis of Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2021 May;14(5):e007555. doi: 10.1161/CIRCHEARTFAILURE.120.007555. Epub 2021 May 6. PMID: 33951935.
58. Gwet K. Handbook of Inter-Rater Reliability: How to Measure the Level of Agreement Between Two or Multiple Raters. Stataxis Publishing Company; 2001.
59. : Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, Badano LP, Parati G, Vachiéry JL. Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Fail. 2022 Oct;9(5):3079-3091. doi: 10.1002/ehf2.13979. Epub 2022 Jun 24. Erratum in: ESC Heart Fail. 2023 Jun;10(3):2144. PMID: 35748109; PMCID: PMC9715813.
60. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62: e1–e34

61. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol. 2010; 56: 855–863. PMID: 20813283.
62. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14: 135.
63. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177–188.
64. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539–1558.
65. Stanley TD, Doucouliagos H. Neither fixed nor random: weighted least squares meta-analysis. Stat Med. 2015; 34: 2116–2127
66. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. Eur J Heart Fail. 2013; 15: 776–785. Epub 2013 Feb 20. PMID: 23426022; PMCID: PMC3857919.
67. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. Circulation. 2018; 137: 148–161. Epub 2017 Oct 9. PMID: 28993402; PMCID: PMC5760316.
68. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. Eur Heart J. 2018; 39: 2825–2835. PMID: 29947750; PMCID: PMC6093469.
69. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, Borlaug BA. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. Eur Heart J. 2019; 40: 3707–3717. PMID: 31513270; PMCID: PMC7963136.

70. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail. 2019; 21: 891–900. Epub 2019 Mar 28. PMID: 30919562.

71. Van Empel VP, Mariani J, Borlaug BA, Kaye DM. Impaired myocardial oxygen availability contributes to abnormal exercise hemodynamics in heart failure with preserved ejection fraction. J Am Heart Assoc. 2014; 3: e001293. PMID: 25468660; PMCID: PMC4338724.

72. Fermoyle CC, Stewart GM, Borlaug BA, Johnson BD. Pulmonary vascular pressures and gas exchange response to exercise in heart failure with preserved ejection fraction. J Card Fail. 2020; 26: 1011–1015. Epub 2020 Aug 1. PMID: 32750488; PMCID: PMC7704759.

73. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CSP, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. JACC Heart Fail. 2019; 7: 239–249. PMID: 30819380.

74. Chen ZW, Huang CY, Cheng JF, Chen SY, Lin LY, Wu CK. Stress echocardiography-derived E/e' predicts abnormal exercise hemodynamics in heart failure with preserved ejection fraction. Front Physiol. 2019; 10: 1470. PMID: 31849715; PMCID: PMC6901703.

75. McCabe C, Oliveira RKF, Rahaghi F, Faria-Urbina M, Howard L, Axell RG, Priest AN, Waxman AB, Systrom DM. Right ventriculo-arterial uncoupling and impaired contractile reserve in obese patients with unexplained exercise intolerance. Eur J Appl Physiol. 2018; 118: 1415–1426. Epub 2018 Apr 30. PMID: 29713818; PMCID: PMC6028899.

76. Nanayakkara S, Haykowsky M, Mariani J, Van Empel V, Maeder MT, Vizi D, Kaye DM. Hemodynamic profile of patients with heart failure and preserved ejection fraction vary by age. J Am Heart Assoc. 2017; 6: e005434. PMID: 28939710; PMCID: PMC5634249.

77. Platz E, Merz A, Silverman M, Lewis E, Groarke JD, Waxman A, Systrom D. Association between lung ultrasound findings and invasive exercise haemodynamics in patients with undifferentiated

dyspnoea. ESC Heart Fail. 2019; 6:202–207. Epub 2018 Nov 26. PMID: 30474936; PMCID: PMC6352886.

78. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, William J, Marwick TH, Kaye DM. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. Eur J Heart Fail. 2019; 21: 495–505. Epub 2019 Jan 16. PMID: 30652393.
79. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. Circ Heart Fail. 2015; 8: 278–285. Epub 2014 Dec 30. PMID: 25550438; PMCID: PMC4936392.
80. Andersen MJ, Ersbøll M, Gustafsson F, Axelsson A, Hassager C, Køber L, Boesgaard S, Pellikka PA, Møller JE. Exercise-induced changes in left ventricular filling pressure after myocardial infarction assessed with simultaneous right heart catheterization and Doppler echocardiography. Int J Cardiol. 2013; 168: 2803–2810. Epub 2013 Apr 28. PMID: 23628301.
81. Obokata M, Reddy YNV, Shah SJ, Kaye DM, Gustafsson F, Hasenfuβ G Hoendermis E, Litwin SE, Komtebedde J, Lam C, Burkhoff D, Borlaug BA. Effects of interatrial shunt on pulmonary vascular function in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2019; 74: 2539–2550. PMID: 31753198.
82. Sorimachi H, Obokata M, Takahashi N, Reddy YNV, Jain CC, Verbrugge FH, Koepp KE, Khosla S, Jensen MD, Borlaug BA. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. Eur Heart J. 2021; 42: 1595–1605. Epub ahead of print. PMID: 33227126.
83. Ahmad A, Corban MT, Toya T, Verbrugge FH, Sara JD, Lerman LO, Borlaug BA, Lerman A. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. Eur J Heart Fail. 2020; 23: 765–772. Epub ahead of print. PMID: 32949186.

84. Tschöpe C, Kasner M, Westermann D, Walther T, Gaub R, Poller WC, Schultheiss HP. Elevated NT-ProBNP levels in patients with increased left ventricular filling pressure during exercise despite preserved systolic function. J Card Fail. 2005; 11: S28–S33. PMID: 15948097.

85. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. JACC Heart Fail. 2020; 8: 657–666. Epub 2020 Jul 8. PMID: 32653449; PMCID: PMC7395878.

86. Baratto C, Faini A, Gallone GP, Dewachter C, Perego GB, Bondue A, Muraru D, Senni M, Badano LP, Parati G, Vachiéry JL, Caravita S. Pulmonary artery wedge pressure and left ventricular end-diastolic pressure during exercise in patients with dyspnoea. ERJ Open Res. 2023 Sep 4;9(4):00750-2022. doi: 10.1183/23120541.00750-2022. PMID: 37670852; PMCID: PMC10475984.

87. Baratto C, Caravita S, Corbetta G, Soranna D, Zambon A, Dewachter C, Gavazzoni M, Heilbron F, Tomaselli M, Radu N, Perelli FP, Perego GB, Vachiéry JL, Parati G, Badano LP, Muraru D. Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction. Front Cardiovasc Med. 2023 Mar 1;10:1061118. doi: 10.3389/fcvm.2023.1061118. PMID: 36937944; PMCID: PMC10014840.

88. Caravita S, Figliozzi S, Florescu DR, Volpato V, Oliverio G, Tomaselli M, et al. Recent advances in multimodality imaging of the tricuspid valve. Expert Rev Med Devices. (2021) 18:1069–81. doi: 10.1080/17434440.2021.1990753

89. Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, Dweck M, Delgado V, Garbi M, Vannan MA, Montaigne D, Badano L, Maurovich-Horvat P, Pontone G, Vahanian A, Donal E, Cosyns B; Scientific Document Committee of the European Association of Cardiovascular Imaging. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. Eur Heart J Cardiovasc Imaging. 2022 Apr 18;23(5):e171-e232. doi: 10.1093/ehjci/jeab253. PMID: 35292799.

90. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation. (2021) 143:e72– 227. doi: 10.1161/CIR.0000000000000923

91. Andersen MJ, Nishimura RA, Borlaug BA. The hemodynamic basis of exercise intolerance in tricuspid regurgitation. Circ Heart Fail 2014;7:911–917.

92. Caravita S, Baratto C*, Filippo A, Soranna D, Dewachter C, Zambon A, Perego GB, Muraru D, Senni M, Badano LP, Parati G, Vachiéry JL, Fudim M. Shedding Light on Latent Pulmonary Vascular Disease in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2023 Oct;11(10):1427-1438. doi: 10.1016/j.jchf.2023.03.003. Epub 2023 Apr 26. PMID: 37115127.* equally first and corresponding author

93. Weatherald J, Sattler C, Garcia G, Laveneziana P. Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. Eur Respir J. 2018 Feb 7;51(2):1700860. doi: 10.1183/13993003.00860-2017. PMID: 29437936.

94. Mahowald MK, Nishimura RA, Pislaru SV, et al. Reduction in right atrial pressures is associated with hemodynamic improvements after transcatheter edge-to-edge repair of the tricuspid valve. Circ Cardiovasc Interv. 2021;14(12):e010557.

95. Sorajja P, Borlaug BA, Dimas VV, Fang JC, Forfia PR, Givertz MM, Kapur NK, Kern MJ, Naidu SS. SCAI/HFSA clinical expert consensus document on the use of invasive hemodynamics for the diagnosis and management of cardiovascular disease. Catheter Cardiovasc Interv. 2017 Jun 1;89(7):E233-E247. doi: 10.1002/ccd.26888. Epub 2017 May 10. PMID: 28489331

96. Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, Badano LP, Parati G, Vachiéry JL. An updated meta-analysis of hemodynamics markers of prognosis in patients with pulmonary hypertension due to left heart disease. Pulm Circ. 2022 Oct 1;12(4):e12145. doi: 10.1002/pul2.12145. PMID: 36568693; PMCID: PMC9768568.

97. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.

98. Duval S, Tweedie R. A nonparametric «trim and fill» method of accounting for publication bias in Meta-Analysis. J Am Stat Assoc. 2000;95(449):89.

99. Al-Naamani N, Preston IR, Paulus JK, et al. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail. 2015 Jun;3(6):467-474. doi: 10.1016/j.jchf.2015.01.013. PMID: 26046840; PMCID: PMC4536851.

100. Vanderpool RR, Saul M, Nouraie M, et al. Association Between Hemodynamic Markers of Pulmonary Hypertension and Outcomes in Heart Failure With Preserved Ejection Fraction. JAMA Cardiol. 2018 Apr 1;3(4):298-306. doi: 10.1001/jamacardio.2018.0128. Erratum in: JAMA Cardiol. 2018 Jul 1;3(7):665. PMID: 29541759; PMCID: PMC5875307.

101. Quan R, Huang L, Yang T, et al. Prognostic value of hemodynamics and comorbidities in pulmonary hypertension due to advanced heart failure. Heart Lung. 2020 Mar-Apr;49(2):158-164. doi: 10.1016/j.hrtlng.2019.10.003. Epub 2019 Oct 23. PMID: 31668361.

102. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Heart Fail. 2013 Aug;1(4):290-299. doi: 10.1016/j.jchf.2013.05.001. Epub 2013 Aug 5. PMID: 24621932.

103. Bermejo J, González-Mansilla A, Mombiela T, et al. Persistent Pulmonary Hypertension in Corrected Valvular Heart Disease: Hemodynamic Insights and Long-Term Survival. J Am Heart Assoc. 2021 Jan 19;10(2):e019949. doi: 10.1161/JAHA.120.019949. Epub 2021 Jan 5. PMID: 33399006; PMCID: PMC7955299.

104. Yamashita K, Abe T, Hayata Y, et al. Prognostic Value of Preoperative Pulmonary Arterial Capacitance for Patients Undergoing Aortic Valve Replacement for Severe Aortic Valve Stenosis. Circ J. 2019 Oct 25;83(11):2222-2228. doi: 10.1253/circj.CJ-19-0316. Epub 2019 Sep 5. PMID: 31484840.

105. O'Sullivan CJ, Wenaweser P, Ceylan O, et al. Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation: Insights From the New Proposed Pulmonary Hypertension Classification. Circ Cardiovasc Interv. 2015 Jul;8(7):e002358. doi: 10.1161/CIRCINTERVENTIONS.114.002358. PMID: 26156149.

106. Brunner NW, Yue SF, Stub D, et al. The prognostic importance of the diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance in patients undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2017 Dec 1;90(7):1185-1191. doi: 10.1002/ccd.27107. Epub 2017 May 4. PMID: 28471090.

107. Tampakakis E, Shah SJ, Borlaug BA, et al. Pulmonary Effective Arterial Elastance as a Measure of Right Ventricular Afterload and Its Prognostic Value in Pulmonary Hypertension Due to Left Heart Disease. Circ Heart Fail. 2018 Apr;11(4):e004436. doi: 10.1161/CIRCHEARTFAILURE.117.004436. PMID: 29643065; PMCID: PMC5901761.

108. Dragu R, Rispler S, Habib M, et al. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. Eur J Heart Fail. 2015 Jan;17(1):74-80. doi: 10.1002/ejhf.192. Epub 2014 Nov 11. PMID: 25388783.

109. Assad TR, Hemnes AR, Larkin EK, et al. Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension. J Am Coll Cardiol. 2016 Dec 13;68(23):2525-2536. doi: 10.1016/j.jacc.2016.09.942. PMID: 27931609; PMCID: PMC5157701.

110. Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013 Mar;143(3):758-766. doi: 10.1378/chest.12-1653. PMID: 23580984.

111. Dragu R, Hardak E, Ohanyan A, et al. Prognostic value and diagnostic properties of the diastolic pulmonary pressure gradient in patients with pulmonary hypertension and left heart disease. Int J Cardiol. 2019 Sep 1;290:138-143. doi: 10.1016/j.ijcard.2019.05.016. Epub 2019 May 13. PMID: 31126737.

112. Sugimoto K, Yoshihisa A, Nakazato K, et al. Significance of Pulmonary Vascular Resistance and Diastolic Pressure Gradient on the New Definition of Combined Post-Capillary Pulmonary Hypertension. Int Heart J. 2020;61(2):301-307. doi: 10.1536/ihj.19-476. PMID: 32224602.

113. Palazzini M, Dardi F, Manes A, et al. Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes. Eur J Heart Fail. 2018 Feb;20(2):248-255. doi: 10.1002/ejhf.860. Epub 2017 May 2. PMID: 28464427.

114. Gerges M, Gerges C, Pistritto AM, et al. Pulmonary Hypertension in Heart Failure. Epidemiology, Right Ventricular Function, and Survival. Am J Respir Crit Care Med. 2015 Nov 15;192(10):1234-46. doi: 10.1164/rccm.201503-0529OC. PMID: 26181215

115. Baratto C, Caravita S, Dewachter C, Faini A, Perego GB, Bondue A, Senni M, Muraru D, Badano LP, Parati G, Vachiéry JL. Right Heart Adaptation to Exercise in Pulmonary Hypertension: An Invasive Hemodynamic Study. J Card Fail. 2023 Sep;29(9):1261-1272. doi: 10.1016/j.cardfail.2023.04.009. Epub 2023 May 5. PMID: 37150503.

116. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. doi: 10.1093/eurheartj/ehv317. Epub 2015 Aug 29. PMID: 26320113.

117. Desole S, Obst A, Habedank D, Opitz CF, Knaack C, Hortien F, Heine A, Stubbe B, Ewert R. Comparison between thermodilution and Fick methods for resting and exercise-induced cardiac

output measurement in patients with chronic dyspnea. Pulm Circ. 2022 Jul 1;12(3):e12128. doi: 10.1002/pul2.12128. PMID: 36051350; PMCID: PMC9425001.

118. Fudim M, Patel MR, Boortz-Marx R, Borlaug BA, DeVore AD, Ganesh A, Green CL, Lopes RD, Mentz RJ, Patel CB, Rogers JG, Felker GM, Hernandez AF, Sunagawa K, Burkhoff D. Splanchnic Nerve Block Mediated Changes in Stressed Blood Volume in Heart Failure. JACC Heart Fail. 2021 Apr;9(4):293-300. doi: 10.1016/j.jchf.2020.12.006. Epub 2021 Mar 10. PMID: 33714749; PMCID: PMC9990498.

119. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive echocardiographic study. Circulation. 2017; 135: 825–838.

120. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological versus chronological aging: JACC Focus Seminar. J Am Coll Cardiol. 2020;75:919– 930. doi: 10.1016/j.jacc.2019.11.062

121. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. J Appl Physiol (1985). 2016 Nov 1;121(5):1145-1150. doi: 10.1152/japplphysiol.00372.2016. Epub 2016 Oct 7. PMID: 27763874.

122. Houston BA, Tedford RJ. What We Talk About When We Talk About the Wedge Pressure. Circ Heart Fail. 2017 Sep;10(9). pii: e004450

123. Reddy YNV, El-Sabbagh A, Nishimura RA. Comparing Pulmonary Arterial Wedge Pressure and Left Ventricular End Diastolic Pressure for Assessment of Left-Sided Filling Pressures. JAMA Cardiol. 2018 Jun 1;3(6):453-454

124. Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest. 2009 Jul;136(1):37-43. doi: 10.1378/chest.08-2784. Epub 2009 Mar 2. PMID: 19255293.

125. Bitar A, Selej M, Bolad I, Lahm T. Poor agreement between pulmonary capillary wedge pressure and left ventricular end-diastolic pressure in a veteran population. PLoS One. 2014 Jan 31;9(1):e87304. doi: 10.1371/journal.pone.0087304. PMID: 24498069; PMCID: PMC3909072.

126. Oliveira RK, Ferreira EV, Ramos RP, et al. Usefulness of pulmonary capillary wedge pressure as a correlate of left ventricular filling pressures in pulmonary arterial hypertension. J Heart Lung Transplant. 2014 Feb;33(2):157-62. doi: 10.1016/j.healun.2013.10.008. Epub 2013 Oct 11. Erratum in: J Heart Lung Transplant. 2014 Apr;33(4):459. de Oliveira, Rudolf K F [corrrected to Oliveira, Rudolf K F]. PMID: 24268673.

127. Ryan JJ, Rich JD, Thiruvoipati T, Swamy R, Kim GH, Rich S. Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension. Am Heart J. 2012 Apr;163(4):589- 94. doi: 10.1016/j.ahj.2012.01.024. PMID: 22520524.

128. Dickinson MG, Lam CS, Rienstra M, et al. Atrial fibrillation modifies the association between pulmonary artery wedge pressure and left ventricular end-diastolic pressure. Eur J Heart Fail. 2017 Nov;19(11):1483-1490. doi: 10.1002/ejhf.959. Epub 2017 Sep 25. PMID:28948687.

129. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, De Marco T. Pulmonary hypertension due to left heart disease. Eur Respir J. 2019;53(1):1801897.

130. Hsu S, Fang JC, Borlaug BA. Hemodynamics for the Heart Failure Clinician: A State-of-the-Art Review. J Card Fail. 2022 Jan;28(1):133-148. doi: 10.1016/j.cardfail.2021.07.012. Epub 2021 Aug 10. PMID: 34389460; PMCID: PMC8748277.

131. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. JACC Cardiovasc Imaging. (2019) 12:433–42. doi: 10.1016/j.jcmg.2018.06.014

132. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. J Am Coll Cardiol. (2020) 76:1051–64. doi: 10.1016/j.jacc.2020.07.009

133. Utsunomiya H, Itabashi Y, Mihara H, Berdejo J, Kobayashi S, Siegel RJ, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional

transesophageal echocardiography study. Circ Cardiovasc Imaging. (2017) 10:e004897. doi: 10.1161/CIRCIMAGING.116.004897

134. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM, de La Espriella R, Santas E, Miñana G, Bodí V, Sanchis J, Valle A, Chorro FJ, Llácer P, Bayés-Genís A, Núñez J. Effect of β-Blocker Withdrawal on Functional Capacity in Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2021 Nov 23;78(21):2042-2056. doi: 10.1016/j.jacc.2021.08.073. Erratum in: J Am Coll Cardiol. 2022 Mar 1;79(8):848. PMID: 34794685.

135. Vignati C, De Martino F, Muratori M, Salvioni E, Tamborini G, Bartorelli A, Pepi M, Alamanni F, Farina S, Cattadori G, Mantegazza V, Agostoni P. Rest and exercise oxygen uptake and cardiac output changes 6 months after successful transcatheter mitral valve repair. ESC Heart Fail. 2021 Dec;8(6):4915-4924. doi: 10.1002/ehf2.13518. Epub 2021 Sep 22. PMID: 34551212; PMCID: PMC8712840.

136. Lurz P, Orban M, Besler C, Braun D, Schlotter F, Noack T, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. Eur Heart J. (2020) 41:2785–95. doi: 10.1093/eurheartj/ehaa138

137. Hsu S, Brusca SB, Rhodes PS, Kolb TM, Mathai SC, Tedford RJ. Use of thermodilution cardiac output overestimates diagnoses of exercise-induced pulmonary hypertension. Pulm Circ. 2017 Jan 1;7(1):253-255. doi: 10.1086/690629. PMID: 28680584; PMCID: PMC5448537.

138. Fudim M, Kaye DM, Borlaug BA, et al. Venous tone and stressed blood volume in heart failure: JACC review topic of the week. J Am Coll Cardiol. 2022;79(18):1858–1869.

139. Al-Omary MS, Sugito S, Boyle AJ, Sverdlov AL, Collins NJ. Pulmonary hypertension due to left heart disease: diagnosis pathophysiology, and therapy. Hypertension. 2020;75(6):1397–408.

140. Bermejo J, Yotti R, García-Orta R, Sánchez-Fernández PL, Castaño M, Segovia-Cubero J, Escribano-Subías P, San Román JA, Borrás X, Alonso-Gómez A, Botas J, Crespo- Leiro MG, Velasco S, Bayés-Genís A, López A, Muñoz- Aguilera R, de Teresa E, González-Juanatey JR, Evangelista A,

Mombiela T, González-Mansilla A, Elízaga J, Martín-Moreiras J, González-Santos JM, Moreno-Escobar E, Fernández-Avilés F, Sildenafil for Improving Outcomes after VAlvular Correction (SIOVAC) i. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. Eur Heart J. 2018;39(15):1255–64.

141. Vachiéry JL, Delcroix M, Al-Hiti H, Efficace M, Hutyra M, Lack G, Papadakis K, Rubin LJ. Macitentan in pulmonary hypertension due to left ventricular dysfunction. Eur Respir J. 2018;51(2):1701886

142. Parissis JT, Paraskevaidis I, Bistola V, Farmakis D, Panou F, Kourea K, Nikolaou M, Filippatos G, Kremastinos D. Effects of levosimendan on right ventricular function in patients with advanced heart failure. Am J Cardiol. 2006;98(11):1489–92.

143. Hansen MS, Andersen A, Nielsen-Kudsk JE. Levosimendan in pulmonary hypertension and right heart failure. Pulm Circ. 2018;8(3):1–7.

144. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, Hutchins S, Leier CV, LeJemtel TH, Loh E, Nicklas J, Ogilby D, Singh BN, Smith W. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation. 2000;102(18):2222–7.

145. Mishra A, Kumar B, Dutta V, Arya VK, Mishra AK. Comparative effect of levosimendan and milrinone in cardiac surgery patients with pulmonary hypertension and left ventricular dysfunction. J Cardiothorac Vasc Anesth. 2016; 30(3):639–46.

146. Burkhoff D, Borlaug BA, Shah SJ, Zolty R, Tedford RJ, Thenappan T, Zamanian RT, Mazurek JA, Rich JD, Simon MA, Chung ES, Raza F, Majure DT, Lewis GD, Preston IR, Rich S. Levosimendan improves hemodynamics and exercise tolerance in PH-HFpEF. JACC Heart Fail. 2021;9(5):360–70

147. Gerges C, Gerges M, Fesler P, Pistritto AM, Konowitz NP, Jakowitsch J, Celermajer DS, Lang IM. In-depth haemodynamic phenotyping of pulmonary hypertension due to left heart disease. Eur Respir J. 2018;51(5):1800067.

148. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J. 2019;53(1):1801900. Published 2019 Jan 24. doi:10.1183/13993003.01900-2018

149. Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB; International Right Heart Failure Foundation Scientific Working Group. Right heart failure: toward a common language. J Heart Lung Transplant. 2014;33(2):123-126. doi:10.1016/j.healun.2013.10.015

150. Singh I, Rahaghi FN, Naeije R, Oliveira RKF, Systrom DM, Waxman AB. Right Ventricular-Arterial Uncoupling During Exercise in Heart Failure With Preserved Ejection Fraction: Role of Pulmonary Vascular Dysfunction. Chest. 2019 Nov;156(5):933-943. doi: 10.1016/j.chest.2019.04.109. Epub 2019 May 16. PMID: 31103695

151. Harada T, Obokata M, Omote K, Iwano H, Ikoma T, Okada K, Yoshida K, Kato T, Kurosawa K, Nagai T, Anzai T, Borlaug BA, Kurabayashi M. Functional Tricuspid Regurgitation and Right Atrial Remodeling in Heart Failure With Preserved Ejection Fraction. Am J Cardiol. 2022 Jan 1;162:129-135. doi: 10.1016/j.amjcard.2021.09.021. Epub 2021 Oct 24. PMID: 34702555.

152. Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence.Cardiovasc Res. 2017;113(12):1474-1485. doi:10.1093/cvr/cvx160

153. Van Wezenbeek J, Kianzad A, van de Bovenkamp A, Wessels J, Mouratoglou SA, Braams NJ, Jansen SMA, Meulblok E, Meijboom LJ, Marcus JT, Vonk Noordegraaf A, José Goumans M, Jan Bogaard H, Handoko ML, de Man FS. Right Ventricular and Right Atrial Function Are Less Compromised in Pulmonary Hypertension Secondary to Heart Failure With Preserved Ejection Fraction: A Comparison With Pulmonary Arterial Hypertension With Similar Pressure Overload. Circ Heart Fail. 2022 Feb;15(2):e008726. doi: 10.1161/CIRCHEARTFAILURE.121.008726. Epub 2021 Dec 23. PMID: 34937392; PMCID:PMC8843396.

INCLUDED MANUSCRIPTS

Eight original manuscripts published on peer-reviewed journals were included in this PhD thesis.

They are reported in the following pages in this order:

1. **Study 1, HEMO-VALIDATION study [55]**: Lanzarone E, Baratto C*, Vicenzi M, Villella F, Rota I, Dewachter C, Muraru D, Tomaselli M, Gavazzoni M, Badano LP, Senni M, Vachiéry JL, Parati G, Caravita S. Haemodynamic validation of the three-step HFA-PEFF algorithm to diagnose heart failure with preserved ejection fraction. ESC Heart Fail. 2023 Aug;10(4):2588-2595. doi: 10.1002/ehf2.14436. Epub 2023 Jun 15. PMID: 37321596; PMCID: PMC10375124. *equally first and corresponding author
2. **Study 2, DISCORDIA study [57]**: Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati G, Vachiéry JL. Current Limitations of Invasive Exercise Hemodynamics for the Diagnosis of Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2021 May;14(5):e007555. doi: 10.1161/CIRCHEARTFAILURE.120.007555. Epub 2021 May 6. PMID: 33951935.
3. **Study 3, EX-PEF meta-analysis [59]**: Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, Badano LP, Parati G, Vachiéry JL. Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Fail. 2022 Oct;9(5):3079-3091. doi: 10.1002/ehf2.13979. Epub 2022 Jun 24. Erratum in: ESC Heart Fail. 2023 Jun;10(3):2144. PMID: 35748109; PMCID: PMC9715813.
4. **Study 4, EX-LVEDP study [86]**: Baratto C, Faini A, Gallone GP, Dewachter C, Perego GB, Bondue A, Muraru D, Senni M, Badano LP, Parati G, Vachiéry JL, Caravita S. Pulmonary artery wedge pressure and left ventricular end-diastolic pressure during exercise in patients with dyspnoea. ERJ Open Res. 2023 Sep 4;9(4):00750-2022. doi: 10.1183/23120541.00750-2022. PMID: 37670852; PMCID: PMC10475984.
5. **Study 5, STR-HFpEF study [87]**: Baratto C, Caravita S, Corbetta G, Soranna D, Zambon A, Dewachter C, Gavazzoni M, Heilbron F, Tomaselli M, Radu N, Perelli FP, Perego GB, Vachiéry JL, Parati G, Badano

LP, Muraru D. Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction. Front Cardiovasc Med. 2023 Mar 1;10:1061118. Doi: 10.3389/fcvm.2023.1061118. PMID: 36937944; PMCID: PMC10014840.

6. **Study 6, HFpEF LATENT-PVD study** [92]: Caravita S, Baratto C*, Filippo A, Soranna D, Dewachter C, Zambon A, Perego GB, Muraru D, Senni M, Badano LP, Parati G, Vachiéry JL, Fudim M. Shedding Light on Latent Pulmonary Vascular Disease in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2023 Oct;11(10):1427-1438. doi: 10.1016/j.jchf.2023.03.003. Epub 2023 Apr 26. PMID: 37115127.* equally first and corresponding author
7. **Study 7, PH-PROGNOSIS meta-analysis [96]**: Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, Badano LP, Parati G, Vachiéry JL. An updated meta-analysis of hemodynamics markers of prognosis in patients with pulmonary hypertension due to left heart disease. Pulm Circ. 2022 Oct 1;12(4):e12145. Doi: 10.1002/pul2.12145. PMID: 36568693; PMCID: PMC9768568.
8. **Study 8, RETRORIGHT study [115]**: Baratto C, Caravita S, Dewachter C, Faini A, Perego GB, Bondue A, Senni M, Muraru D, Badano LP, Parati G, Vachiéry JL. Right Heart Adaptation to Exercise in Pulmonary Hypertension: An Invasive Hemodynamic Study. J Card Fail. 2023 Sep;29(9):1261-1272. doi: 10.1016/j.cardfail.2023.04.009. Epub 2023 May 5. PMID: 37150503.

ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 2588–2595
Published online 15 June 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14436

ORIGINAL ARTICLE

Haemodynamic validation of the three-step HFA-PEFF algorithm to diagnose heart failure with preserved ejection fraction

Ettore Lanzarone[1], Claudia Baratto[2]*, Marco Vicenzi[3,4], Francesco Villella[2,5], Irene Rota[6], Céline Dewachter[7], Denisa Muraru[2,5], Michele Tomaselli[2,5], Mara Gavazzoni[2,5], Luigi P. Badano[2,5], Michele Senni[5,8], Jean-Luc Vachiéry[7], Gianfranco Parati[2,5] and Sergio Caravita[1,2]

[1]*Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy;* [2]*Department of Cardiology, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Piazzale Brescia 20, Milan, 20149, Italy;* [3]*Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy;* [4]*Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy;* [5]*Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy;* [6]*UOC Cardiologia, Ospedale Civile di Legnano, ASST Ovest Milanese, Milan, Italy;* [7]*Department of Cardiology, Cliniques Universitaires de Bruxelles, Hôpital Académique Erasme, Bruxelles, Belgium; and* [8]*Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy*

Abstract

Aims The HFA-PEFF algorithm (Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology) is a three-step algorithm to diagnose heart failure with preserved ejection fraction (HFpEF). It provides a three-level likelihood of HFpEF: low (score < 2), intermediate (score 2–4), or high (score > 4). HFpEF may be confirmed in individuals with a score > 4 (rule-in approach). The second step of the algorithm is based on echocardiographic features and natriuretic peptide levels. The third step implements diastolic stress echocardiography (DSE) for controversial diagnostic cases. We sought to validate the three-step HFA-PEFF algorithm against a haemodynamic diagnosis of HFpEF based on rest and exercise right heart catheterization (RHC).

Methods and results Seventy-three individuals with exertional dyspnoea underwent a full diagnostic work-up following the HFA-PEFF algorithm, including DSE and rest/exercise RHC. The association between the HFA-PEFF score and a haemodynamic diagnosis of HFpEF, as well as the diagnostic performance of the HFA-PEFF algorithm vs. RHC, was assessed. The diagnostic performance of left atrial (LA) strain $< 24.5\%$ and LA strain/E/E' $< 3\%$ was also assessed. The probability of HFpEF was low/intermediate/high in 8%/52%/40% of individuals at the second step of the HFA-PEFF algorithm and 8%/49%/43% at the third step. After RHC, 89% of patients were diagnosed as HFpEF and 11% as non-cardiac dyspnoea. The HFA-PEFF score resulted associated with the invasive haemodynamic diagnosis of HFpEF ($P < 0.001$). Sensitivity and specificity of the HFA-PEFF score for the invasive haemodynamic diagnosis of HFpEF were 45% and 100% for the second step of the algorithm and 46% and 88% for the third step of the algorithm. Neither age, sex, body mass index, obesity, chronic obstructive pulmonary disease, or paroxysmal atrial fibrillation influenced the performance of the HFA-PEFF algorithm, as these characteristics were similarly distributed over the true positive, true negative, false positive, and false negative cases. Sensitivity of the second step of the HFA-PEFF score was non-significantly improved to 60% ($P = 0.08$) by lowering the rule-in threshold to >3. LA strain alone had a sensitivity and specificity of 39% and 14% for haemodynamic HFpEF, increasing to 55% and 22% when corrected for E/E'.

Conclusions As compared with rest/exercise RHC, the HFA-PEFF score lacks sensitivity: Half of the patients were wrongly classified as non-cardiac dyspnoea after non-invasive tests, with a minimal impact of DSE in modifying HFpEF likelihood.

Keywords HFpEF; Haemodynamics; Echocardiography; Exercise; HFA-PEFF algorithm

Received: 27 December 2022; Revised: 9 March 2023; Accepted: 23 May 2023
**Correspondence to: Claudia Baratto, MD, Dyspnea and Pulmonary Hypertension Center, Department of Cardiology, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Piazzale Brescia 20, 20149 Milan, Italy. Tel: +39 02 619112930. Email: c.baratto@auxologico.it*
Ettore Lanzarone, Claudia Baratto, and Marco Vicenzi contributed equally as the first authors.

Background

Diagnosing non-secondary heart failure (HF) with preserved ejection fraction (HFpEF) can be a challenge, especially in normovolaemic patients without a prior hospitalization for HF.[1–4] Accordingly, algorithms and scores have been proposed in recent years, to help clinicians evaluating patients with exertional dyspnoea.[5,6] In particular, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) proposed the HFA-PEFF algorithm (where the PEFF acronym stands for 'Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology') based on expert consensus.[5] Key echocardiographic parameters and natriuretic peptides' dosage compose the second step of the algorithm, whose performance has been validated against the advice of experienced HF physicians and/or previous hospitalization for HF,[7] as well as against invasive haemodynamics.[8] However, the second step of the HFA-PEFF algorithm may have a lower sensitivity than the simpler H_2FPEF score.[8] Indeed, many individuals may fall in the intermediate-risk category, requiring to move on with the third step of the algorithm, that is, the use of additional (functional) tests to confirm or exclude the diagnosis of HFpEF. In particular, a diastolic stress echocardiography might be used as an additional non-invasive tool before considering rest/exercise right heart catheterization (RHC).[2,3] However, the third (non-invasive) step of the HFA-PEFF score has not been validated against RHC. Thus, the aim of this study was to provide a validation of the three-step HFA-PEFF score vs. invasive resting and exercise haemodynamics, in a consecutive cohort of individuals referred for exertional dyspnoea who underwent a structured assessment comprehensive of all the items required by the HFA-PEFF algorithm.

Methods

This study was approved by the Ethics Committees of the Istituto Auxologico Italiano (Protocol No. 2020_04_21_03), Milan, Italy, and the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Ref ID 195/2017), Milan, Italy. We included consecutive patients with exertional dyspnoea referred for a structured work-up at the two dyspnoea units of the above-mentioned hospitals, which have adopted a similar methodology, in agreement with the HFA-PEFF algorithm. After an initial clinical assessment, outpatients complaining exertional breathlessness underwent rest and diastolic stress echocardiography on the same day, along with dosage of natriuretic peptides. After an outpatient re-evaluation, indication to proceed with RHC was considered and shared with the patient.

We included in the present analysis all the consecutive patients who, after a pre-test assessment, underwent the exams suggested by the HFA-PEFF algorithm, with a time lag in between the initial evaluation and echocardiography, as well as in between echocardiography and RHC, of no more than 6 weeks. Additionally, no changes in patients' conditions or background treatment had to intervene in between the first clinical assessment and RHC.

We excluded patients with left ventricular (LV) ejection fraction $< 50\%$, secondary forms of HFpEF (restrictive, hypertrophic, or infiltrative cardiomyopathy), congenital heart disease, constrictive pericarditis, inducible myocardial ischaemia, pre-capillary pulmonary hypertension at rest [defined by a mean pulmonary artery pressure (PAP) > 20 mmHg with pulmonary vascular resistance > 3 WU and pulmonary artery wedge pressure (PAWP) < 15 mmHg[9]], more than mild primary valvular regurgitation, any valvular stenosis, more than moderate respiratory disorders, and clinically unstable patients.

A final diagnosis of HFpEF was eventually established when, at the time of RHC, end-expiratory PAWP was $\geq$15 mmHg at rest and/or $\geq$25 mmHg at peak exercise and/or if the slope of the relationship between PAWP and cardiac output (CO) from rest to peak exercise was $>$2 mmHg/L/min.[2,3,10,11]

Non-invasive assessment

Clinical data were extracted from the clinical charts. Echocardiography was performed with a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway) in both recruiting centres by experienced cardiologists following current recommendations.[12] LV and left atrial (LA) strain analyses[13] were performed using vendor-licensed software (EchoPAC 204, GE Vingmed). Exercise echocardiography was performed with a step-incremental protocol on a semi-recumbent cycle ergometer up to exhaustion, with echocardiographic acquisition focused on pulsed wave Doppler of mitral inflow, medial and lateral tissue Doppler of the mitral annulus, and tricuspid regurgitation (TR) velocity, to collect the items required by the third step of the HFA-PEFF algorithm.[5] The presence of dynamic mitral regurgitation was checked in all patients. Images were stored in digital format for quantitative analysis, which were performed offline by trained personnel, blinded to clinical and haemodynamic data.

HFA-PEFF score calculation

The HFA-PEFF score (two-step) was calculated integrating morphological and functional data coming from echocardiography at rest with natriuretic peptides, as recommended.[5] An HFA-PEFF score < 2 classifies a low probability of HFpEF (HFpEF unlikely); score values between 2 and 4 classify an intermediate probability of HFpEF (HFpEF possible); and a score > 4 classifies a high probability of HFpEF (HFpEF likely).

Diastolic stress echocardiography was considered positive when E/E' was ≥15, conferring 2 points to be added to the score obtained at the second step of the algorithm. When E/E' ≥ 15 is associated with a TR velocity > 3.4 m/s, 3 points can be added to the second-step HFA-PEFF score.[5] As measurement of E/E' might not be possible at high heart rate due to fusion of the waves of the mitral inflow pattern, we reported both the maximal workload reached during diastolic stress echocardiography and the workload at which echocardiographic measures were taken.

Finally, among echocardiographic parameters measured at rest but not included in the HFA-PEFF algorithm, we also evaluated LA reservoir strain and the ratio between LA strain and E/E', given their diagnostic potential in patients with exertional breathlessness.[14,15] They were considered abnormal and, thus, potentially indicative of HFpEF when <24.5% and at <3%, respectively.[15]

Right heart catheterization

Patients were studied on chronic medications, in the non-fasting state, without sedation, in supine position. A 7 F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein or an antecubital vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace and by an oxygen saturation > 94% sampled at the tip of the catheter. A 4 F catheter was placed in the radial artery under local anaesthesia using the Seldinger technique. The transducers were zeroed at the midthoracic line using a laser calliper. Haemodynamic measurements were performed at rest, after 1 min of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test, as previously described.[10] The increment in workload was personalized in order to obtain at least three steps of exercise before exhaustion.[10] Two millilitres of blood was sampled at the same time from the tip of the Swan-Ganz catheter and from the radial artery, in order to calculate CO by the direct Fick method. Pressures were measured at end-expiration, and haemodynamic data reflect the agreement of two expert independent readers blinded to patients' data, who visually reviewed all pressure traces offline. As described above, a haemodynamic diagnosis of HFpEF was defined by either an end-expiratory PAWP ≥ 15 mmHg at rest and/or ≥25 mmHg at peak exercise or a PAWP/CO slope > 2 mmHg/L/min.[2,3,10,11]

Statistical analysis

Continuous variables are reported as mean ± standard deviation normal when normally distributed (*P*-value of Shapiro's test > 0.05) and as median together with [25th and 75th percentiles] otherwise. Categorical data are showed as frequencies and proportions.

Independency or dependency between variables was assessed creating contingency tables and performing the Fisher exact test with R, where *P*-values were computed through Monte Carlo simulation as required for tables larger than 2 × 2. A significant association between variables (rows and column of the table) was assessed by a *P*-value < 0.05.

Results

Between June 2016 and June 2021, 73 consecutive patients with dyspnoea and suspicion of HFpEF were evaluated (58 at Istituto Auxologico Italiano and 15 at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan). All of them had all items required by the second and third steps of the HFA-PEFF algorithm, including echocardiography at rest, natriuretic peptides' values, diastolic stress echocardiography, and RHC at rest and during exercise.

General characteristics

General characteristics of our cohort are summarized in *Table 1*. Median age was 71 years, 67% were females, and mean body mass index was 26 kg/m^2. The majority of patients had exertional dyspnoea (New York Heart Association II). Arterial hypertension was the most represented cardiovascular risk factors (67%), followed by dyslipidaemia (44%) and obesity (16%). All individuals were in sinus rhythm, with 15% of patients who experienced paroxysmal atrial fibrillation. Twenty-two per cent of patients had mild chronic obstructive pulmonary disease.

Table 1 General characteristics of the study cohort

Anthropometrics and demographics	
Age, years	71 [65, 75]
Female sex, *n* (%)	49 (67%)
Body mass index, kg/m^2	26 ± 5
Symptoms	
NYHA class II, *n* (%)	50 (69%)
NYHA class III, *n* (%)	23 (31%)
Comorbidities	
Obesity, *n* (%)	12 (16%)
Arterial hypertension, *n* (%)	49 (67%)
Diabetes mellitus, *n* (%)	4 (5%)
Dyslipidaemia, *n* (%)	32 (44%)
Coronary artery disease, *n* (%)	11 (15%)
Paroxysmal atrial fibrillation, *n* (%)	11 (15%)
Chronic obstructive pulmonary disease, *n* (%)	16 (22%)
Blood tests	
Creatinine, mg/dL	0.9 [0.76, 1.01]
eGFR, mL/min/1.73 m^2	71 [50, 86]

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

HFA-PEFF score, second step: echocardiography at rest and natriuretic peptides

Echocardiographic and natriuretic peptide data are reported in *Table 2*. Echocardiography at rest showed a normal median LA size (32 mL/m^2), with a mean LA reservoir strain of 27%, and a mean E/E' of 9. TR was present and measurable in 93% of the cohort, with a median TR velocity of 2.6 m/s and an estimated median systolic PAP of 31 mmHg. Median N-terminal pro-brain natriuretic peptide was 193 ng/L.

Median HFA-PEFF score (second step) was 4. Eight per cent of individuals had a low probability of HFpEF (HFA-PEFF score $<$ 2), 52% an intermediate probability (score 2–4), and 40% a high probability (score $>$ 4).

HFA-PEFF score, third step: diastolic stress echocardiography

Diastolic stress echocardiography results are reported in *Table 3*. During exercise, median E/E' increased to 9.3. TR was present and measurable in 80% of the cohort, with a mean exercise TR velocity of 3.4 m/s. Eight patients displayed a positive diastolic stress echocardiography (E/E' $\geq$ 15), five of whom had also a TR velocity $>$ 3.4 m/s. Six out of these eight patients with a positive diastolic stress echocardiography already had an HFA-PEFF score $>$ 4 at the second step of the algorithm. Thus, only 6 of the 29 individuals at high risk of HFpEF after the second step of the HFA-PEFF algorithm (21%) had a positive diastolic stress echocardiography. Two patients with an HFA-PEFF score = 3, belonging to the intermediate HFpEF risk category (4% of this latter cohort), shifted to the high-risk category after the diastolic stress echocardiography. No patient with a low risk of HFpEF based on the second step of the HFA-PEFF score had a positive diastolic stress echocardiography.

Accordingly, the distribution of HFpEF risk based on the HFA-PEFF score marginally changed from the second step to the third step of the algorithm (two intermediate-risk individuals shifted to the high-risk category).

Table 2 Second step of the HFA-PEFF algorithm

Natriuretic peptides	
NT-proBNP, ng/L	193 [101; 311]
Echocardiography	
Interventricular septum thickness, mm	10 [9; 11]
Posterior wall thickness, mm	9 [8; 10]
Relative wall thickness	0.41 [0.37; 0.45]
Left ventricular end-diastolic diameter, mm	44 ± 6
Left ventricular mass index, g/m^2	80 ± 20
Left ventricular end-diastolic volume, mL	80 [67; 103]
Left ventricular ejection fraction, %	62 ± 5
Left ventricular global longitudinal strain, %	−18.7 ± 2.2
Left atrial volume index, mL/m^2	32 [26; 38]
Left atrial reservoir longitudinal strain, %	27 ± 9
E/E'	9.0 [7.3; 10.8]
Tricuspid regurgitation velocity, m/s (n = 68)	2.55 [2.40; 2.90]
Pulmonary artery systolic pressure, mmHg	31 [29; 40]
HFA-PEFF score, 2 steps	
Median value	4 [3; 5]
Low probability, n (%)	6 (8)
Intermediate probability, n (%)	38 (52)
High probability, n (%)	29 (40)

HFA-PEFF, Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 Third step of the HFA-PEFF algorithm and invasive haemodynamics

Diastolic stress echocardiography	
Workload, W	65 [50; 95]
Workload @ echocardiographic measurements, W	55 [35; 70]
Averaged E/E'	9.3 [7.5; 12.0]
Tricuspid regurgitation velocity, m/s (n = 58)	3.40 ± 0.56
HFA-PEFF score, 3 steps	
Median value	4 [3; 5]
Low probability, n (%)	6 (8)
Intermediate probability, n (%)	36 (49)
High probability, n (%)	31 (43)
Invasive haemodynamics	
Workload, W	50 [40; 75]
PAWP at rest, mmHg	11 [9; 13]
PAWP at peak, mmHg	29 ± 10
PAWP/CO slope, mmHg/L/min	3.50 [2.08; 4.45]
PAWP peak ≥ 25 mmHg and/or PAWP/CO slope $>$ 2 mmHg/L/min, n (%)	65 (89)

CO, cardiac output; HFA-PEFF, Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; PAWP, pulmonary artery wedge pressure.

Performance of the HFA-PEFF algorithm against invasive haemodynamics

At RHC, 65 out of 73 individuals (89%) presented a PAWP at peak exercise $\geq$ 25 mmHg and/or a PAWP/CO slope $>$ 2 mmHg/L/min. Invasive haemodynamic data of our cohort are reported in *Table 3*.

The HFA-PEFF score (either two steps or three steps), subdivided in low, intermediate, and high probability of HFpEF, resulted significantly associated with the haemodynamic diagnosis of HFpEF based on exercise RHC ($P < 0.001$).

Among the eight individuals in whom HFpEF was not confirmed by RHC, four were in the low-risk and four in the intermediate-risk two-step HFA-PEFF strata. Among the 65 individuals in whom HFpEF was confirmed by RHC, 2 belonged to the low-risk category, 34 to the intermediate-risk category, and 29 to the high-risk category of the two-step HFA-PEFF score. *Figure 1* represents the proportion of patients classified as HFpEF or non-HFpEF after RHC, stratified according to the pre-RHC probability, based on both the two-step and three-step HFA-PEFF scores.

Figure 1 Proportion of patients classified as heart failure with preserved ejection fraction (HFpEF), or non-HFpEF, based on invasive haemodynamics ($HFpEF_{haemo}$), stratified according to the pre-test probability provided by the two-step and three-step HFA-PEFF (Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology) scores.

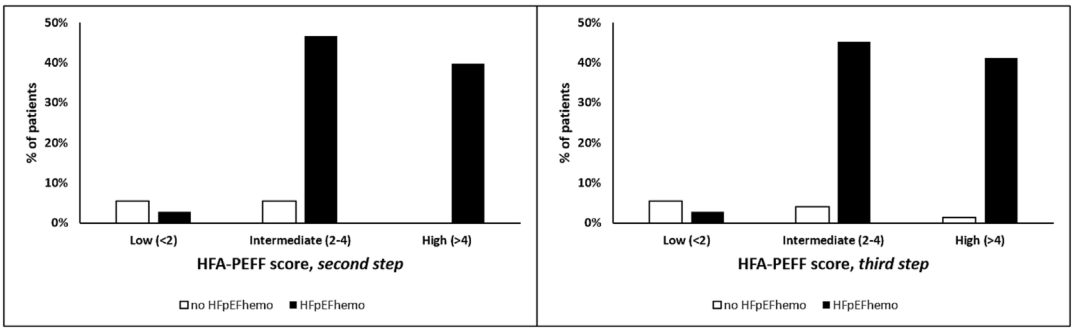


Figure 2 Proportion of correctly [true positive (TP) and true negative (TN)] and incorrectly [false negative (FN) and false positive (FP)] diagnosed patients, based on the two-step and three-step HFA-PEFF (Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology) scores, using invasive haemodynamics as gold-standard diagnostic reference.

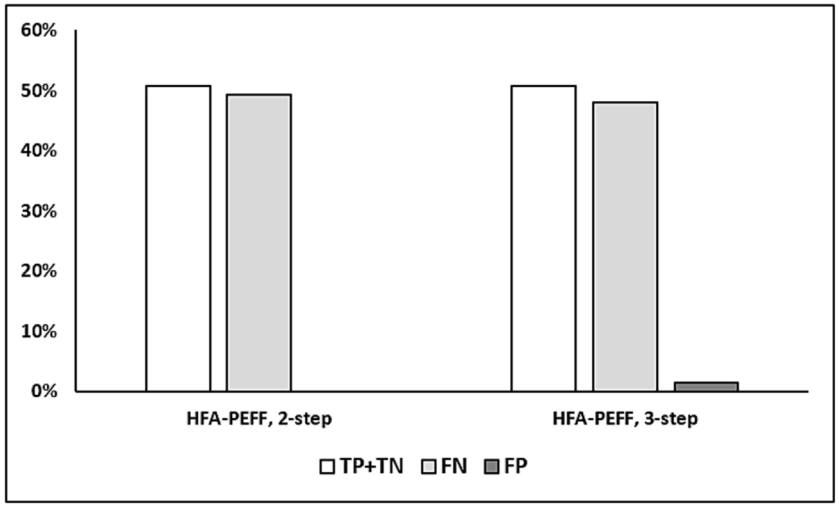


Table 4 Performance of the two-step and three-step 'rule-in' HFA-PEFF algorithm, both with the usual diagnostic threshold (>4) and with a lower diagnostic threshold (>3) to diagnose HFpEF, as compared with invasive haemodynamics

	Rule-in approach, HFA-PEFF score > 3				Rule-in approach, HFA-PEFF score > 4			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
HFA-PEFF, 2 steps	60%	100%	100%	24%	45%	100%	100%	18%
HFA-PEFF, 3 steps	62%	88%	98%	22%	46%	88%	97%	17%

HFA-PEFF, Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

The 'rule-in approach', which arbitrarily dichotomizes the score in >4 (HFpEF) and ≤4 (no HFpEF), correctly classified 37 (51%) patients as either HFpEF or non-HFpEF, both at the second step and at the third step, respectively (*Figure 2*). However, 36 (49%) and 35 (48%) patients resulted false negative both with two-step and with three-step HFA-PEFF algorithm. Only the three-step algorithm provided one false positive case. Accordingly, specificity and positive predictive value of the HFA-PEFF were high, but sensitivity and negative predictive value were low (*Table 4*). Neither age, sex, body mass index, obesity, chronic obstructive pulmonary disease, or paroxysmal atrial

fibrillation influenced the performance of the HFA-PEFF algorithm, as these characteristics were similarly distributed over the true positive, true negative, false positive, and false negative cases. Lowering the threshold of the two-step HFA-PEFF score to >3 vs. >4 resulted in non-significantly higher sensitivity (60% vs. 45%, P = 0.08) and accuracy (64% vs. 51%, P = 0.09), without losing specificity (100% vs. 100%).

Performance of other echocardiographic parameters proposed to diagnose heart failure with preserved ejection fraction

LA reservoir strain, with a cut-off < 24.5% to diagnose HFpEF, was significantly interrelated both with the three-step HFA-PEFF score (P = 0.024) and with the haemodynamic diagnosis of HFpEF (P = 0.023). Sensitivity, specificity, and accuracy of this parameter were 39%, 14%, and 50%, respectively.

The ratio between LA reservoir strain and E/E', with a cut-off < 3% to diagnose HFpEF, was significantly associated both with the two-step and three-step HFA-PEFF scores (P < 0.001) and with the haemodynamic diagnosis of HFpEF (P = 0.037). Sensitivity, specificity, and accuracy of this parameter were 52%, 22%, and 36%, respectively.

Discussion

This is the first study reporting the performance of the three-step HFA-PEFF score against rest and exercise RHC in consecutive patients with unexplained dyspnoea. Our results show that, compared with invasive rest and exercise haemodynamics, the HFA-PEFF score is characterized by good specificity but suboptimal sensitivity. Moreover, the implementation of the diastolic stress echocardiography did not seem to add significantly to the diagnostic performance of the score. Conversely, lowering the diagnostic threshold of the second step of the HFA-PEFF score to >3 vs. >4 slightly improved its diagnostic performance. Other echocardiographic parameters suggested to help in the diagnosis of HFpEF (such as LA reservoir strain and the ratio between LA strain and E/E') taken in isolation did not perform better than the HFA-PEFF algorithm.

As already mentioned, the diagnosis of HFpEF poses a unique challenge, especially in those patients with lifestyle-limiting symptoms but no evidence of hypervolaemia. A combination of several items, as those included in the HFA-PEFF score,[5] has been suggested to help in this complex diagnostic process. In such a perspective, our work confirms and expands the evidences coming from previous reports,[8,14] highlighting the relationship between the score and RHC results, and demonstrating the good specificity of the 'rule-in' approach, based on a score > 4 at the second step of the algorithm, compared with rest and exercise RHC. Similar results concerning the validation of the HFA-PEFF algorithm have been shown in a larger two-centre study where, however, diagnosis of HFpEF was not confirmed by invasive haemodynamics but codified either based on the judgement of an expert HF specialist or based on a history of previous HF hospitalization.[7] Using exercise haemodynamics as reference and, in particular, a combination of PAWP at rest > 15 mmHg and/or PAWP at peak ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min,[2,3,10,11] our results may suggest that the second step of the HFA-PEFF score might be lowered to >3, slightly improving sensitivity and accuracy, without impacting on specificity (i.e. without collecting false positive diagnosis). Additionally, our data are unique in providing evidence also on the third, non-invasive step of the algorithm. Diastolic stress echocardiography has been advocated to increase the diagnostic yield of resting examination.[5,16,17] However, our data do not seem to confirm such a strong additional value of diastolic stress echocardiography. Indeed, only two patients falling in the intermediate HFpEF risk profile based on the second step of the HFA-PEFF score were reclassified at high likelihood of HFpEF after diastolic stress echocardiography. Unfortunately, one of these two patients had the diagnosis of HFpEF not confirmed by rest and exercise RHC. Accordingly, the diagnostic value of the diastolic stress echocardiography as a third step in the HFA-PEFF algorithm appears questionable based on our results. It is time and resource consuming and does not seem to significantly improve the diagnostic accuracy of the second step of the algorithm. This is at variance from a previous report where diastolic stress echocardiography enhanced the diagnosis of HFpEF if added to the ESC criteria rather than to the comprehensive multiparametric evaluation proposed by the second step of the HFA-PEFF algorithm.[17] This might suggest that diastolic stress echocardiography may hold a place in the differential diagnosis of patients with exertional dyspnoea, when not all the items of the second step of the HFA-PEFF algorithm are available or, as more recently suggested, by lowering the E/E' decisional threshold.[18] Finally, incorporation of other tests/parameters in a non-invasive algorithm (e.g. cardiopulmonary exercise test data) might provide additional clues on the aetiology of patients presenting with exertional dyspnoea.[19]

Clinical implications

Despite its high specificity, the sensitivity of the HFA-PEFF algorithm is suboptimal, not allowing to diagnose HFpEF in roughly 50% of cases, even when time-consuming and resource-consuming tests such as diastolic stress echocardiography are implemented. Thus, a simpler and more cost-effective approach, for example, based on the H_2FPEF score,[8] might be advisable as a first-line diagnostic

DOI: 10.1002/ehf2.14436

evaluation, especially in low-resource settings and/or in primary/secondary health care facilities. A more personalized approach to unexplained dyspnoea, including cardiopulmonary exercise test, potentially combined with advanced rest and exercise stress echocardiography, could be advisable in tertiary referral centres, eventually recurring to exercise RHC in well-selected cases.[19]

Limitations

Several limitations of our work should be acknowledged: first, the relatively small sample size, which might limit generalizability of our results. Additionally, the great majority of our patients were eventually diagnosed with HFpEF after exercise RHC, limiting the information on the negative predictive value of the HFA-PEFF algorithm. However, our cohort was a real-world consecutive population of patients with exertional dyspnoea to whom a standard diagnostic approach was applied and who eventually accepted to undergo RHC, with clinical and haemodynamic characteristics in line with other reports in literature, and that should not be relevantly different to a general outpatient population screened for unexplained dyspnoea.

Conclusions

The HFA-PEFF score is associated with invasive haemodynamics at rest and during exercise, albeit its diagnostic performance is poor, due to low sensitivity (in spite of high specificity). Additionally, diastolic stress echocardiography did not improve the diagnostic yield of the second step of the HFA-PEFF algorithm in our cohort. Conversely, lowering the threshold of the second step of the HFA-PEFF score to >3 might marginally improve sensitivity and accuracy, maintaining high specificity. HFpEF remains a diagnostic challenge, in search for a widely available gold-standard test.

Acknowledgements

The authors are grateful to Laboratori Guidotti S.p.A. for providing free-of-charge software for echocardiographic analysis.

Open access funding provided by BIBLIOSAN.

Conflict of interest

None declared.

Funding

This study was funded by the Italian Ministry of Health (Conto Capitale) (Ministero della Salute). S.C. received the grant 'Vera Srebot' from the Fondazione CNR/Regione Toscana per la Ricerca Medica e di Sanità Pubblica. C.B. is the recipient of a research grant from the European Society of Cardiology. J.-L.V. is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department.

References

1. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011; **32**: 670–679.
2. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010; **3**: 588–595.
3. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation*. 2019; **140**: 353–365.
4. Senni M, Caravita S, Paulus WJ. Do existing definitions identify subgroup phenotypes or reflect the natural history of heart failure with preserved ejection fraction? *Circulation*. 2019; **140**: 366–369.
5. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019; **40**: 3297–3317.
6. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018; **138**: 861–870.
7. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VPM. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020; **22**: 413–421.
8. Reddy YNV, Kaye DM, Handoko ML, van de Bovenkamp AA, Tedford RJ, Keck C, Andersen MJ, Sharma K, Trivedi RK, Carter RE, Obokata M, Verbrugge FH, Redfield MM, Borlaug BA. Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. *JAMA Cardiol*. 2022; **7**: 891–899.
9. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019; **53**: 1801913.
10. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati

G, Vachiéry JL. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021 May; **14**: e007555.
11. Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, Badano LP, Parati G, Vachiéry JL. Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail*. 2022 Oct; **9**: 3079–3091.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015; **16**: 233–270.
13. Voigt JU, Mălăescu GG, Haugaa K, Badano L. How to do LA strain. *Eur Heart J Cardiovasc Imaging*. 2020; **21**: 715–717.
14. Thomas L, Muraru D, Popescu BA, Sitges M, Rosca M, Pedrizzetti G, Henein MY, Donal E, Badano LP. Evaluation of left atrial size and function: relevance for clinical practice. *J Am Soc Echocardiogr*. 2020 Aug; **33**: 934–952.
15. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019 Jul; **21**: 891–900.
16. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016; **17**: 1321–1360.
17. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation*. 2017; **135**: 825–838.
18. Harada T, Obokata M, Kagami K, Sorimachi H, Kato T, Takama N, Wada N, Ishii H. Utility of E/e' ratio during low-level exercise to diagnose heart failure with preserved ejection fraction. *JACC Cardiovasc Imaging*. 2022: S1936-878X(22)00666–0.
19. Verwerft J, Bertrand PB, Claessen G, Herbots L, Verbrugge FH. Cardiopulmonary exercise testing with simultaneous echocardiography: blueprints of a dyspnea clinic for suspected HFpEF. *JACC Heart Fail*. 2023 Feb; **11**: 243–249.

ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 3079–3091
Published online 24 June 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13979

ORIGINAL ARTICLE

Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Claudia Baratto[1,2], Sergio Caravita[1,3], Davide Soranna[4], Céline Dewachter[2], Antoine Bondue[2], Antonella Zambon[4,5], Luigi P. Badano[1,6], Gianfranco Parati[1,6] and Jean-Luc Vachiéry[2]*

[1]*Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milan, Italy;* [2]*Department of Cardiology, Hopital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070, Bruxelles, Belgium;* [3]*Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy;* [4]*Biostatistics Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy;* [5]*Department of Statistic and Quantitative Methods, University of Milano-Bicocca, Milan, Italyl and* [6]*Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*

Abstract

Aims Exercise right heart catheterization (RHC) is considered the gold-standard test to diagnose heart failure with preserved ejection fraction (HFpEF). However, exercise RHC is an insufficiently standardized technique, and current haemodynamic thresholds to define HFpEF are not universally accepted. We sought to describe the exercise haemodynamics profile of HFpEF cohorts reported in literature, as compared with control subjects.

Methods and results We performed a systematic literature review until December 2020. Studies reporting pulmonary artery wedge pressure (PAWP) at rest and peak exercise were extracted. Summary estimates of all haemodynamic variables were evaluated, stratified according to body position (supine/upright exercise). The PAWP/cardiac output (CO) slope during exercise was extrapolated. Twenty-seven studies were identified, providing data for 2180 HFpEF patients and 682 controls. At peak exercise, patients with HFpEF achieved higher PAWP (30 [29–31] vs. 16 [15–17] mmHg, $P < 0.001$) and mean right atrial pressure ($P < 0.001$) than controls. These differences persisted after adjustment for age, sex, body mass index, and body position. However, peak PAWP values were highly heterogeneous among the cohorts (I^2 = 93%), with a relative overlap with controls. PAWP/CO slope was steeper in HFpEF than in controls (3.75 [3.20–4.28] vs. 0.95 [0.30–1.59] mmHg/L/min, P value < 0.0001), even after adjustment for covariates ($P = 0.007$).

Conclusions Despite methodological heterogeneity, as well as heterogeneity of pooled haemodynamic estimates, the exercise haemodynamic profile of HFpEF patients is consistent across studies and characterized by a steep PAWP rise during exercise. More standardization of exercise haemodynamics may be advisable for a wider application in clinical practice.

Keywords Heart failure; Cardiac catheterization; Haemodynamics; Exercise testing; Meta-analysis

Received: 8 December 2021; Revised: 8 April 2022; Accepted: 8 May 2022
**Correspondence to: Jean-Luc Vachiéry, Department of Cardiology, Hopital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070 Brussels, Belgium. Tel: +32 (0) 2 555 5602; +32 (0) 2 555 4866. Email: jeanluc.vachiery@erasme.ulb.ac.be*

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent condition. Additionally, patients may present with lifestyle-limiting effort symptoms but no clinical evidence of hypervolemia.[1] Therefore, in case of non-conclusive exams and normal haemodynamics at rest, exercise right heart catheterization (RHC) has been claimed as the gold-standard diagnostic test for HFpEF, potentially overcoming several limitations of non-invasive examinations and algorithms.[2–4]

However, exercise RHC is a costly and time-consuming test with a limited availability. Moreover, the procedural approach, including patients' body position and exercise protocol as well as the haemodynamic measurements and their interpretation, has not been widely standardized. This non-negligible limitation could impact on the reproducibility and generalizability of the results.[5,6]

To address these issues, we conducted a systematic review and meta-analysis of studies on exercise haemodynamics in patients with HFpEF, taking into account potential heterogeneity of these populations and exercise RHC methodology. Our aim was to describe the exercise haemodynamic profile of a large population of patients diagnosed as HFpEF and to compare it with control subjects. It is important to mention that pulmonary artery wedge pressure (PAWP) is influenced by several factors, including the patient's body position and the timing of measurement during the respiratory and cardiac cycle. Therefore, the reading of pressure traces may differ across investigators, especially during exercise, and lead to heterogeneity of interpretations when a standardized procedure is not universally adopted by all laboratories. However, the impact of body position and of respiratory swings might be minimized when normalizing the exercise-induced changes of pulmonary pressures for cardiac output (CO) increase.[5,7] Additionally, and recent evidence suggests that flow-corrected PAWP during exercise might be a more sensitive marker of HFpEF than absolute PAWP values at peak effort,[5] with proven prognostic value.[4] Thus, we also sought to build and compare the PAWP/CO slope of HFpEF and controls for all studies, to test the validity of this composite variable in a large HFpEF cohort.

Methods

We followed the PRISMA statement[8] for reporting systematic reviews and meta-analysis. A comprehensive literature research on PubMed was updated to December 2020, and the search terms included: ('right heart catheterization' OR 'hemodynamics' OR 'cardiac catheterization' OR 'haemodynamics') AND ('exercise' OR 'effort') AND ('heart failure with preserved ejection fraction' OR 'HFPEF' OR 'dyspnea' OR 'diastolic dysfunction' OR 'diastolic heart failure' OR 'left heart disease') AND ('PAWP' OR 'PCWP' OR 'wedge pressure' OR 'occlusion pressure').

We included papers that met the following criteria: (i) published in peer-reviewed journal, (ii) designed to evaluate the exercise haemodynamics in the HFpEF population, and (iii) reporting PAWP at rest and at peak exercise (main endpoint measure).

We excluded case reports, editorials, reviews, not pertinent studies (e.g. not including HFpEF or not reporting exercise invasive haemodynamics data), and studies reporting follow-up data of HFpEF patients who had undergone implant of an interatrial septal device within a clinical trial. When the same patients were included in more than one study, the larger one was considered.

Two investigators independently reviewed the search results to select the studies based on the inclusion criteria. Additionally, we performed a manual search of secondary sources including references of initially identified articles, reviews, and commentaries to minimize missing relevant studies. Any discrepancy in the process of study selection and data extraction was resolved by discussion between the investigators, and all disagreements were solved by consulting with a third investigator. Study design was reported according to Participant, Intervention, Comparison, Outcome Study. Risk of bias was assessed by two reviewers, using a scale adapted from the Newcastle-Ottawa Quality Assessment Scale for cross-sectional studies.

For each study, non-invasive data (clinical, echocardiography, & blood tests) as well as haemodynamics (e.g. PAWP & CO) at rest and at peak exercise were extracted. Additionally, for all studies reporting PAWP and CO at rest and at peak exercise, we calculated the slope of their relationship during effort.

Statistical analysis

Clinical characteristics of HFpEF and control patients of each study were reported as mean and standard deviation (for continuous variables) or proportions (for categorical variables). A summary estimate of each clinical characteristic, for HFpEF and control patients, was reported as median and interquartile range of study-specific values and jointly represented with a radar plot.

When only median and interquartile range of haemodynamic variable were available in included studies, they were transformed in mean and standard deviation value[9] before applying the meta-analytic procedure. Summary estimates of each haemodynamic variable were separately evaluated for HFpEF and control cohorts. Additionally, summary estimates of PAWP and delta CO were separately evaluated also for exercise body position. The random effect summary mean estimate and the corresponding 95% confidence intervals (95% CI) were calculated according to the DerSimonan and Laird's method.[10] Between-studies' heterogeneity was quantified using the I^2 index. Values of this index more than 75% suggest high heterogeneity.[11] Homogeneity between summary mean estimates stratified for body position during exercise was performed by a χ^2 statistic. In order to account for potential populations' heterogeneity, reflecting differences in inclusion criteria of individual studies, we performed a stratified analysis. In particular, we subdivided studies defining HFpEF based on haemodynamic criteria only, from studies defining HFpEF based on clinical criteria or including patients with LVEF $< 50\%$.

Finally, univariate and multivariate meta-regression models were implemented for each haemodynamic variable, including status (HFpEF or control) as independent variable, and age, sex, body mass index (BMI), and body position as dependent variables. Meta-regression is a linear weighted mixed model including study as random effect and standard error of published mean as weight.[12] The estimated

coefficient related to status variable gives information about the summary means difference.

Results were considered statistically significant when two-tailed *P* value was lower than 0.05. All analyses were performed with R Version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection

One hundred and thirty-eight studies were identified. After preliminary screening based on the title and the abstract, 48 studies were selected for full-text review. Other studies were excluded because either reporting duplicate patients' data with other larger studies (19 studies) or not reporting the exercise haemodynamic variables (*Figure 1*). Study design of included manuscripts and the Newcastle-Ottawa Quality Assessment Scale are reported in Supporting Information, *Tables S1* and *S2*.

Characteristics of included studies

The 27 selected studies[2–4,13–36] included 2180 HFpEF patients and 682 controls. Characteristics of individual studies are reported in *Table 1*. Thirteen studies (48%) had a prospective design,[3,4,17,19,23,25–27,29–31,34] 13 (48%) were retrospective,[2,13–15,18,20–22,24,28,33,35,36] and 1 study (4%) was a randomized controlled trial.[32]

Of the 27 selected studies, 17 were performed in three centres of the United States,[2–4,13–18,21,24,26,28,30,33,34,36] 5 in one Australian centre,[19,22,25,27,31] and 2 in Europe.[29,35] Three studies were multicentric, with patients coming from American, Australian, and European centres.[20,23,32]

Overall, the selected studies included 35 cohorts of HFpEF patients and 21 cohorts of control subjects, whose clinical characteristics are reported in *Tables S3* and *S4*, respectively. Control subjects were mainly individuals who underwent a clinically indicated invasive cardiopulmonary evaluation for unexplained dyspnoea and who did not satisfy the haemodynamic diagnostic criteria for HFpEF. Healthy volunteers (n = 8) served as control group only in one study.[31]

A symptom-limited exercise testing protocol was used in all studies. Patients underwent supine exercise in 21 studies[2,13,15–23,25,27,29–34] and upright exercise in 6 studies.[3,4,14,24,26,28] Exercise PAWP was measured at end-expiration in almost all studies (25 of 27). Only in seven studies (26%) high-fidelity catheters were employed.[2,17,23,30,33,34,36] CO was measured by direct Fick method in most studies (n = 16, 59%).[2–4,13–18,21,23,24,26,28,30,36]

Only four studies used non-invasive diagnostic criteria to define HFpEF, including either clinical parameters, echocardiographic data, or reduced peak oxygen consumption at cardiopulmonary exercise test.[13,23,29,31] In all the other studies, the diagnosis of HFpEF was confirmed based on rest or peak PAWP. A peak PAWP cut-off of ≥25 mmHg was used in all but one of the studies performing the effort in supine position.[35] In four of the six studies evaluating patients exercising in the upright position, a peak PAWP > 20 mmHg or a PAWP/CO slope > 2 mmHg/L/min was considered as a pathological threshold to define HFpEF.[3,4,24,28]

Notably, six studies focused on specific HFpEF subpopulations, such as those with obesity, recent myocardial infarction, non-obstructive coronary artery disease, or patients included in an interventional trial.[20,24,29,32,34,36] Only in four studies the left ventricular ejection fraction to define

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. HFpEF, heart failure with preserved ejection fraction; RHC, right heart catheterization.

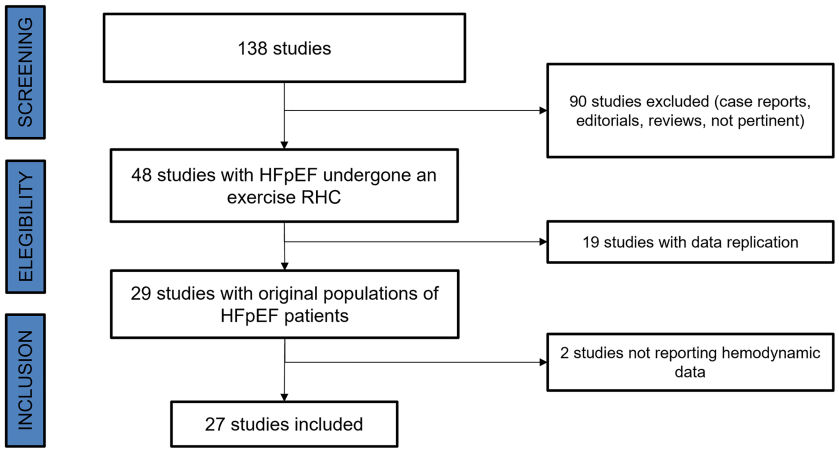


Table 1 Characteristics of the included studies

Author	Country	Centre	*n* HFpEF	*n* controls	Timing of enrolment
Tschöpe *et al.*[35]	Germany	Campus Benjamin Franklin	15	15	2003
Borlaug *et al.*[2]	USA	Mayo Clinic	32	23	2005–2009
Maeder *et al.*[31]	Australia	Alfred Hospital	14	8	2008–2009
Abudiab *et al.*[13]	USA	Mayo Clinic	109	73	2002–2011
Andersen *et al.*[29]	Denmark	Rigshospitalet & Copenhagen University	61		2010–2012
Santos *et al.*[28]	USA	Brigham and Women's Hospital	31	31	2011–2013
Houstis *et al.*[14]	USA	Massachusetts General Hospital	79	55	2006–2016
Obokata *et al.*[15]	USA	Mayo Clinic	195	71	2000–2014
Reddy *et al.*[30]	USA	Mayo Clinic	98	22	
Nanayakkara *et al.*[25]	Australia	Alfred Hospital	21	19	
Eisman *et al.*[3]	USA	Massachusetts General Hospital	77	98	
Gorter *et al.*[14]	USA	Mayo Clinic	161		2006–2013
McCabe *et al.*[24]	USA	Brigham and Women's Hospital	8	14	
Platz *et al.*[26]	USA	Brigham and Women's Hospital	13	12	
Ho *et al.*[4]	USA	Massachusetts General Hospital	243		2006–2017
Obokata *et al.*[17]	USA	Mayo Clinic	38	20	
Reddy *et al.*[18]	USA	Mayo Clinic	238	125	
Van Empel *et al.*[19]	Australia	Alfred Hospital	9	21	
Wolsk *et al.*[20]	USA, Europa, Australia	Multicentre	108	42	2013–2016
Beale *et al.*[22]	Australia	Alfred Hospital	161		2008–2018
Chen *et al.*[23]	Taiwan	Taiwan University Hospital	34		2018
Telles *et al.*[27]	Australia	Alfred Hospital	49	22	2016–2018
Obokata *et al.*[32]	USA, Europe, Australia	Multicentre	79		2014–2016
Fermoyle *et al.*[21]	USA	Mayo Clinic	30		2009–2012
Sorimachi *et al.*[33]	USA	Mayo Clinic	105	51	2007–2018
Ahmad *et al.*[34]	USA	Mayo Clinic	22	29	2010–2019
Houston and Tedford[37]	USA	Mayo Clinic	169		2000–2014

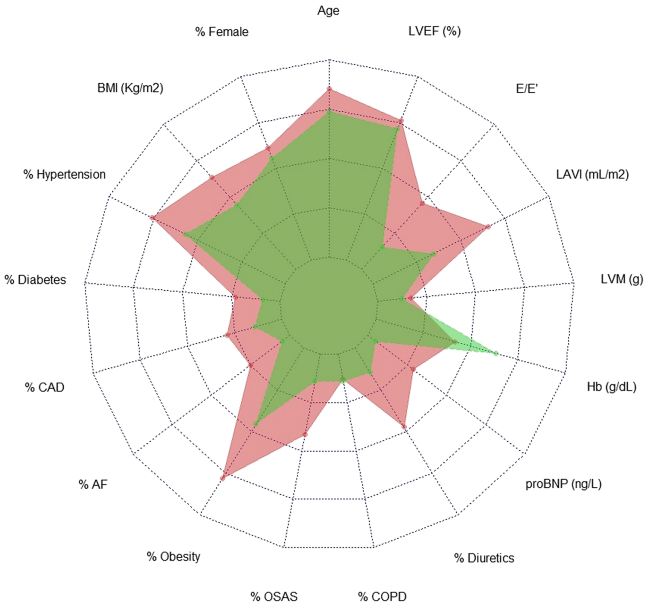
BMI, body mass index; CAD, coronary artery disease; CPCPH, combined post-capillary pulmonary hypertension; EAT, epicardial adipose tissue; END-EXP, end-expiratory phase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFpEFphys, physiological definition of heart failure with preserved ejection fraction; IPCPH, isolated post-capillary pulmonary hypertension; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Table 1 (continued)

Author	Exercise position	PAWP (end-exp/avg)	PAWP (mean/mid-A)	HFpEF diagnosis	Other remarks
Tschöpe *et al.*[35]	Supine			Haemodynamic (rest and/or exercise), echo	restPAWP > 12, peakPAWP > 20
Borlaug *et al.*[2]	Supine	End-exp		Haemodynamic (exercise)	
Maeder *et al.*[31]	Supine	End-exp	Mean	↓ ex capacity	
Abudiab *et al.*[13]	Supine	End-exp		Clinical	
Andersen *et al.*[29]	Supine	Avg		Echo	LVEF > 45% and post-STEMI
Santos *et al.*[28]	Upright	End-exp		Haemodynamic (exercise)	PAWP peak > 20
Houstis *et al.*[14]	Upright	End-exp		Haemodynamic (rest and/or exercise), ↓ ex capacity	
Obokata *et al.*[15]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Reddy *et al.*[30]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Nanayakkara *et al.*[25]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Eisman *et al.*[3]	Upright	End-exp		Haemodynamic (exercise)	
Gorter *et al.*[14]	Supine	End-exp		Haemodynamic (rest)	
McCabe *et al.*[24]	Upright	Avg		Haemodynamic (rest and/or exercise)	PAWP rest > 15, peak > 20 mmHg
Platz *et al.*[26]	Upright	End-exp		Haemodynamic (rest)	
Ho *et al.*[4]	Upright	End-exp		Haemodynamic (exercise)	
Obokata *et al.*[17]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Reddy *et al.*[18]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Van Empel *et al.*[19]	Supine	End-exp	Mean	Haemodynamic (exercise), echo	LVEF > 45%
Wolsk *et al.*[20]	Supine	End-exp	Mean	Haemodynamic (rest and/or exercise), BNP, echo	LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP
Beale *et al.*[22]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Chen *et al.*[23]	Supine	End-exp	Mid-A	Clinical, BNP, echo	
Telles *et al.*[27]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Obokata *et al.*[32]	Supine			Haemodynamic (rest and/or exercise), BNP, echo	LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP
Fermoyle *et al.*[21]	Supine	End-exp	Mid-A	Haemodynamic (rest and/or exercise)	
Sorimachi *et al.*[33]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Ahmad *et al.*[34]	Supine	End-exp	Mid-A	Haemodynamic (rest and/or exercise)	Non-obstructive CAD
Houston and Tedford[37]	Supine	End-exp		Haemodynamic (rest and/or exercise)	BMI ≥ 30

BMI, body mass index; CAD, coronary artery disease; CPCPH, combined post-capillary pulmonary hypertension; EAT, epicardial adipose tissue; END-EXP, end-expiratory phase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFpEFphys, physiological definition of heart failure with preserved ejection fraction; IPCPH, isolated post-capillary pulmonary hypertension; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Figure 2 Radar plot with the clinical characteristics of HFpEF patients (pink) and control subjects (green). AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin; LAVI, left atrial volume indexed; LVM, left ventricular mass; NT-proBNP, N terminal pro brain natriuretic peptide; OSAS, obstructive sleep apnoea syndrome.



HFpEF was >40% or >45%, rather than the currently adopted cut-off of ≥50%.[19,20,29,32]

Clinical characteristics of heart failure with preserved ejection fraction patients and controls

A graphical joint comparison of clinical characteristics of HFpEF patients and controls is reported in *Figure 2* and in *Table S5*. The HFpEF group was slightly older than the control group (median age 67 vs. 60 years), with more women (61% vs. 56%), and higher BMI (32.0 vs. 27.9 kg/m^2). Moreover, the HFpEF group had a larger burden of comorbidities (prevalence of arterial hypertension was 76% vs. 56%, and prevalence of diabetes was 23% vs. 9%), higher N terminal pro brain natriuretic peptide (NT-proBNP) (340 vs. 83 pg/mL), larger left atrial volume index (39 vs. 29 mL/m^2), and higher E/E' (13 vs. 9). The prevalence of atrial fibrillation was 25% in HFpEF vs. 5% in controls, but this information was reported only in about half of the cohorts.

Haemodynamics at rest

The summary estimates of PAWP at rest in HFpEF and controls are reported in *Figure S1*. The summary mean of PAWP was 15 (95% CI: 14–16) mmHg in HFpEF cohorts and 9 (95% CI: 8–9) mmHg in control cohorts. High heterogeneity, especially in HFpEF cohorts, was observed (I^2 = 97% and I^2 = 82%, respectively). This heterogeneity as well as the PAWP summary estimates did not show relevant differences at a stratified data analysis subdividing studies adopting pure haemodynamic definitions for HFpEF, as opposed to those adopting only non-invasive, clinical definitions of HFpEF, or including patients with LVEF < 50% (*Figure S2*). Notably, in all the studies adopting non-invasive or atypical HFpEF definitions, exercise was performed in the supine position. Similar to PAWP, also right atrial pressure at rest was higher in HFpEF than in control subjects (8, 95% CI: 7–10 mmHg vs. 4, 95% CI: 3–5 mmHg, respectively, *P* value < 0.0001).

In HFpEF, both CO and cardiac index (5.13; 95% CI: 4.95–5.31 L/min and 2.61; 95% CI: 2.53–2.68 L/min/m^2, respectively), even if within normal limits, were slightly lower than those of controls (5.41; 95% CI: 5.19–5.63 L/min and 2.76; 95% CI 2.61–2.91 L/min/m^2).

We compared the summary estimates of HFpEF and controls cohorts by meta-regression analysis without and with adjustment for age, sex, BMI, and body position (*Table 2*). In the meta-regression analysis without adjustment, we observed a statistically significant difference for all haemodynamic variables, except CO, between HFpEF and control cohorts. After adjustment, CO and cardiac index were no more different between the two groups.

Exercise haemodynamics

Complete rest and exercise haemodynamics of HFpEF patients and control subjects from each included study are reported in *Tables S6–S9*.

Table 2 Rest and exercise haemodynamics of heart failure with preserved ejection fraction and control subjects

Outcome	HFpEF		Controls		Unadjusted meta-regression models		Adjusted meta-regression models	
	Mean (95% CI)	*N* of cohorts	Mean (95% CI)	*N* of cohorts	*P* value	*N* of cohorts	*P* value	*N* of cohorts
REST								
PAWP (mmHg)	14.98 (13.84–16.13)	35	8.70 (8.16–9.24)	22	<0.0001	57	<0.0001	54
CO (L/min)	5.13 (4.95–5.31)	15	5.41 (5.19–5.63)	11	0.068	26	0.103	26
CI (L/min/m^2)	2.61 (2.53–2.68)	18	2.76 (2.61–2.91)	10	0.083	28	0.413	25
RAP (mmHg)	8.35 (7.25–9.82)	26	4.05 (3.23–4.87)	16	<0.0001	42	0.012	42
PEAK								
PAWP (mmHg)	29.99 (28.93–31.06)	34	15.76 (14.75–16.78)	21	<0.0001	55	<0.0001	54
CO (L/min)	9.50 (8.97–10.03)	18	12.95 (10.00–15.90)	13	<0.0001	31	0.128	31
CI (L/min/m^2)	4.60 (4.22–5.01)	20	6.75 (5.93–7.56)	9	<0.0001	29	0.047	26
RAP (mmHg)	17.73 (16.32–19.14)	25	8.18 (7.53–8.84)	15	<0.0001	40	<0.0001	40
DELTA PEAK-REST								
PAWP (mmHg)	15.00 (14.16–15.84)	34	7.15 (6.27–8.02)	21	<0.0001	55	<0.0001	52
CO (L/min)	4.38 (3.73–5.03)	15	8.15 (6.71–9.59)	11	<0.0001	26	0.096	26

95% CI, 95% of the confidence interval; CI, cardiac index; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; *N*, number; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.
Adjustment was performed using meta-regression models including age, sex, body mass index, and body position as covariates. Data are reported as mean (95% confidence interval).
The *P* value reflects the comparison between the two groups, both unadjusted, and after adjustment for age, sex, BMI, and body position.

During exercise, HFpEF cohorts showed markedly higher filling pressures than controls (*Table 2* and *Figure 3*). Similarly to resting data, these results were characterized by high heterogeneity (I^2 = 93% and 83%, respectively). This heterogeneity, as well as the PAWP summary estimates, did not show relevant differences at a stratified data analysis subdividing studies adopting pure haemodynamic definitions for HFpEF as opposed to studies adopting only non-invasive, clinical definitions of HFpEF, or including patients with LVEF < 50% (*Figure S3*). This wide dispersion of PAWP values among the cohorts led to a zone of partial overlap between HFpEF and controls at values between 20 and 25 mmHg. Nonetheless, HFpEF cohorts showed a summary estimate of PAWP at peak which was twice as high as compared with control cohorts (30; 95% CI: 29–31 mmHg and 16; 95% CI: 15–17 mmHg, respectively), as well as of delta PAWP (15; 95% CI: 14–16 mmHg and 7; 95% CI: 6–8 mmHg, respectively), and of right atrial pressure (18; 95% CI: 16–19 mmHg and 8; 95% CI: 8–9 mmHg, respectively). All these differences remained statistically significant after adjustment for the covariates (*P* value < 0.0001).

Additionally, summary estimates of PAWP at peak performed during supine exercise was slightly higher than those obtained in upright position only for HFpEF cohorts (supine position: 31; 95% CI:30–32 mmHg vs. upright position; 26; 95% CI: 25–27 mmHg, respectively, *P* value < 0.01; *Figure 3*).

Another relevant difference in the haemodynamic response to exercise between HFpEF and controls concerned the exercise-induced increase in CO (*Table 2*). Both CO and cardiac index at peak resulted significantly lower in HFpEF than in controls (*P* < 0.001). Moreover, the increase in CO during exercise was significantly lower in HFpEF than in controls (4.38; 95% CI: 3.73–5.02 L/min and 8.15; 95% CI: 6.71–9.59 L/min respectively, *P* value < 0.0001) although high heterogeneity was present (I^2 = 94% and I^2 = 96%), as shown in *Table 2* and *Figure 4*. However, this difference was no longer statistically significant after adjustment for the covariates. Finally, summary estimate of delta CO in the supine position resulted lower than in upright position only for HFpEF cohorts (*P* value < 0.01, *Figure 4*).

Because there were more cohort studies per centre with overlapped recruitment period, we performed a sensitivity analysis including only one cohort per centre[3,4,17,21,22,26–28,30,34] to verify the robustness of results. As shown in *Table S10*, summary point and interval estimates of each exercise haemodynamic variable in this subset of studies were comparable with those obtained on the entire dataset.

Pulmonary artery wedge pressure/circuit output slope

Figure 5 represents PAWP/CO slopes for cohorts reporting rest and at peak values for both haemodynamic variables.

Figure 3 Forest plots with pooled standardized mean pulmonary artery wedge pressure values at peak exercise both in heart failure with preserved ejection fraction and in controls. HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

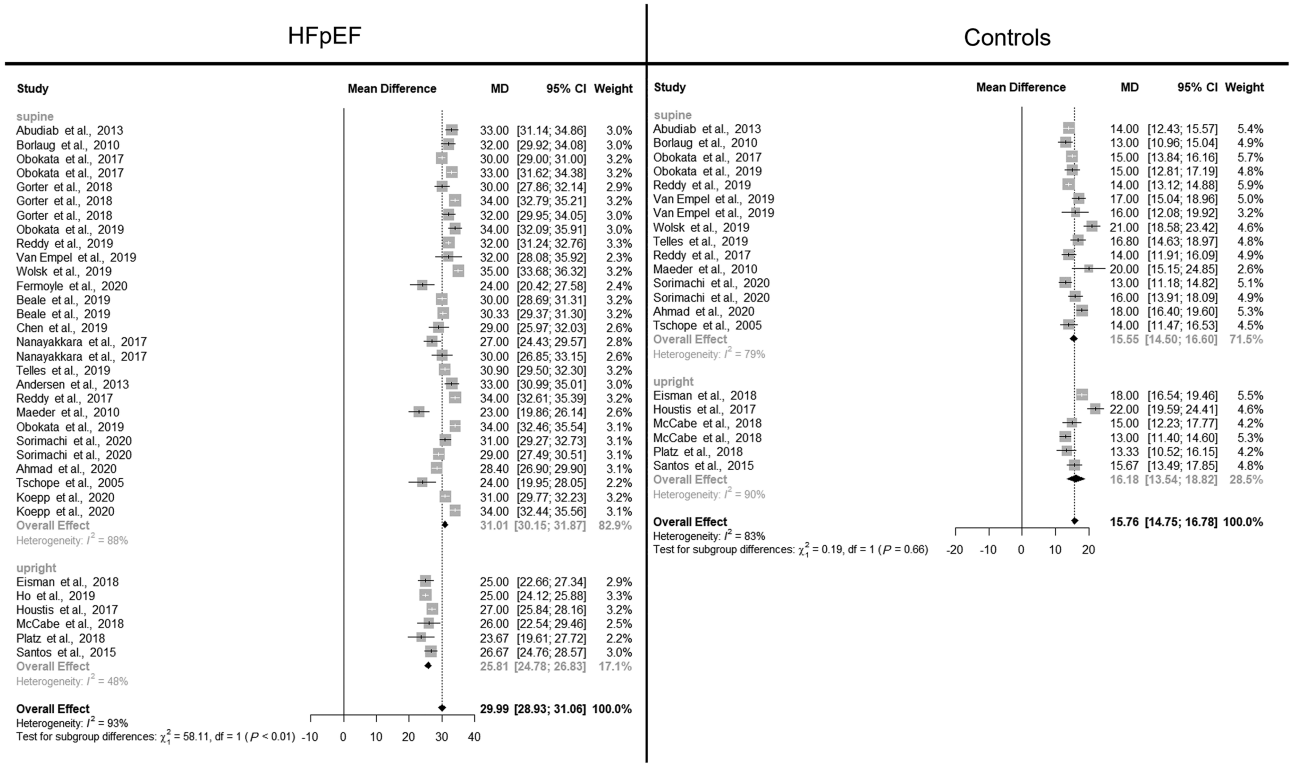
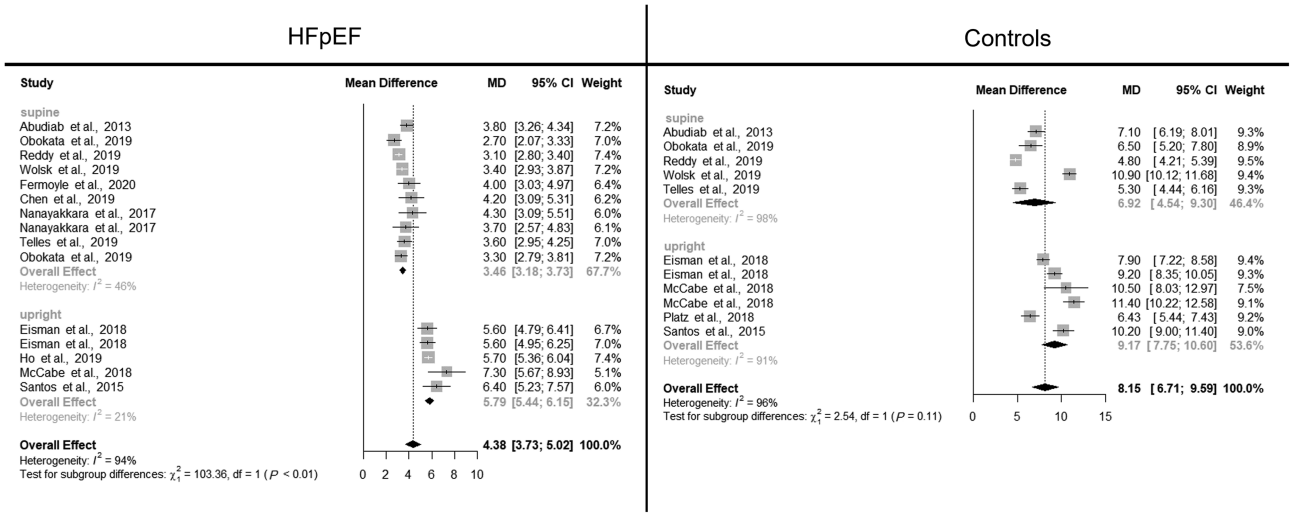
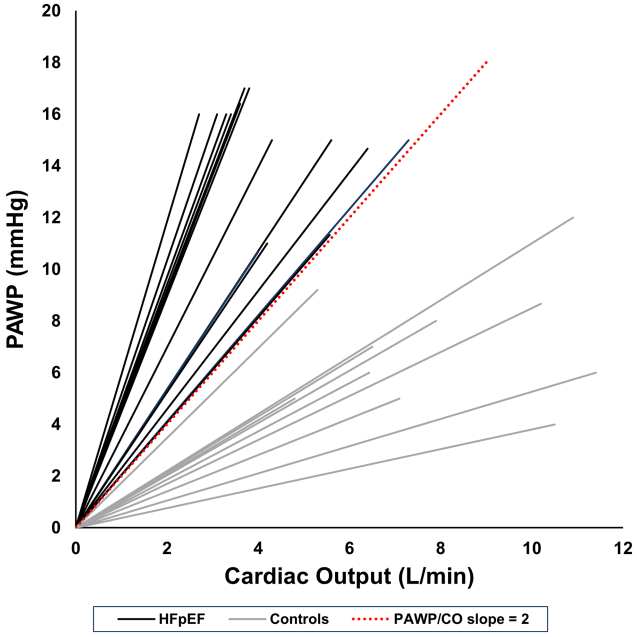


Figure 4 Forest plots with pooled standardized cardiac output increase during exercise both in heart failure with preserved ejection fraction and in the controls. CO, cardiac output; HFpEF, heart failure with preserved ejection fraction.



For all the studies, the Y-intercept of such relationship was fixed at 0, in order to focus on inter-studies differences in slopes, independent from baseline values. Coherent with what shown above for rest and peak PAWP as well as for CO data, HFpEF cohorts had a significantly larger impairment in the haemodynamic response to exercise compared with controls, witnessed by a steeper PAWP/CO slope. Indeed, in HFpEF cohorts, the summary PAWP/CO slope was higher

Figure 5 Pulmonary artery wedge pressure (PAWP)/cardiac output (CO) regression slopes in cohorts of patients with heart failure and preserved ejection fraction (HFpEF) and in control subjects cohorts. The red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.



than in control cohorts (3.75; 95% CI: 3.20–4.28 mmHg/L/min and 0.95; 95% CI: 0.30–1.59 mmHg/L/min, *P* value < 0.0001). This difference persisted even after adjustment for age, sex, BMI, and body position (*P* value = 0.007). All PAWP/CO slopes in HFpEF cohorts were found above the proposed pathological threshold of >2 mmHg/L/min while control cohorts showed slopes always <2 mmHg/L/min.

Finally, summary estimates of PAWP/CO slope were higher in HFpEF cohorts performing exercise in the supine position compared with those in upright position ($P < 0.0001$ and $P = 0.0002$ at non-adjusted and adjusted analysis, respectively), but not in control cohorts ($P = 0.135$ and $P = 0.966$ at non-adjusted and adjusted analysis, respectively). In *Figure S4*, the PAWP/CO slope in supine and upright position for HFpEF and control cohorts is presented.

Discussion

Our meta-analysis provides a thorough characterization of a large population of HFpEF and controls who underwent exercise RHC, highlighting (i) methodological heterogeneity in exercise haemodynamic protocols across centres; (ii) a quite typical clinical profile of HFpEF patients assessed through exercise haemodynamics, which differ from that of control subjects (even though clinical characterization was frequently incomplete as compared with what would be desired in order to apply current non-invasive HFpEF definitions); (iii) a high heterogeneity of haemodynamic responses to exercise across the different HFpEF cohorts; and (iv) the potential validity of a PAWP/CO slope cut-off value $>$ 2 mmHg/L/min to define HFpEF across laboratories independently from body position, as an alternative or as a complementary measure to absolute exercise PAWP supine or upright thresholds.

Published data on exercise RHC come mainly from retrospective analysis of relatively small contemporary cohorts of patients investigated in very few highly experienced centres in the world, albeit with methodological heterogeneity. In most studies, exercise was performed in the supine position (78%), CO was measured by direct Fick method (59%), and PAWP using fluid-filled catheters (74%). However, at variance from the suggestion from the European Respiratory Society to average pressure values over several respiratory cycles, in order to avoid PAWP overestimation during exercise,[6] in more than 90% of studies, PAWP was measured at end-expiration. Additionally, and despite the notion that PAWP values differ according to the phase of the cardiac cycle,[37] only 22% of studies reported such information, with mean PAWP value reported in half of them, and end-diastolic measurement (mid-A wave) in the other half. This underscores the need for more uniform standardization of the RHC procedure to obtain reproducible results across laboratories.

Heart failure with preserved ejection fraction patients were mostly elderly obese women, with a high burden of comorbidities associated with accelerated cardiovascular ageing,[38] an enlarged left atrium, and high NT-proBNP values. Only four studies included also patients with LVEF lower than 50% (LVEF $\geq$ 40–45%). However, many characteristics were not uniformly reported across the studies, precluding to determine whether these patients would fulfil the currently adopted diagnostic criteria for HFpEF in clinical practice (e.g. HFA-PEFF score and H2FPEF score).[39,40] Additionally, despite the non-invasive assessment might have overall suggested a quite typical HFpEF profile,[39] it was not deemed to be sufficient to allow per se for a definite diagnosis of HFpEF in the individual patient before the exercise invasive haemodynamic study. This might reflect the complexity of HFpEF, where comorbidities may act as confounders in explaining patients' complaints (i.e. exertional breathlessness) in the absence of sensitive non-invasive markers for early stages of disease.[2,5,41]

The haemodynamic phenotype of pooled HFpEF patients showed an increase of both left and right filling pressure as compared with control subjects, likely as a consequence of cardiovascular ageing with cardiac fibrosis and diastolic dysfunction[42] combined with dysfunctional preload (high stressed blood volume).[43] This observation was also made in a previous meta-analysis on 20 studies.[44] Filling pressures at rest in HFpEF were on average just at the upper limit of normal, but the difference between HFpEF and controls,

albeit being already present at rest, was greatly magnified by the physical stress, even after correction for age, sex, BMI, and body position. At a first glance, patients with HFpEF also seemed to have a reduced CO reserve, as compared with controls. However, the lower absolute CO response to exercise displayed by HFpEF lost statistical significance after adjustment for some relevant baseline differences in HFpEF and controls (age, sex, and BMI). This is at variance from the meta-analysis by Pandey *et al*.,[44] where both stroke volume and heart rate response to exercise were lower in HFpEF than in controls after adjustment for age or BMI, overall suggesting a reduced cardiac reserve during exercise. However, (i) cardiovascular responses may change as a function of ageing (in particular with lower chronotropic response),[45] potentially resulting in lower CO in older HFpEF patients than in controls—a difference that might reasonably disappear after correction for age; (ii) there is conflicting evidence on the role of cardiac reserve in exercise limitation of HFpEF patients, with arguments favouring a peripheral limitation[14]; (iii) our study, which was more focused on PAWP and PAWP/CO slope than on central vs. peripheral limit to exercise in HFpEF and conducted 3 years later, could include more than twice the patients studied by Pandey *et al*.,[44] potentially overcoming some limitations in the analysis related to the sample size. Thus, the above-mentioned haemodynamic characteristics (high filling pressures and normal age-corrected CO) are consistent with the definition of HFpEF as a clinical syndrome mainly characterized by the ability of the heart to accommodate blood flow for the increased metabolic needs at the expense of high filling pressures.[46]

However, the absolute thresholds of peak exercise PAWP to define HFpEF are not universally accepted and might be influenced by several factors, including exercise duration and intensity, the phase of the respiratory, or cardiac cycle in which measurements are taken,[5,6] and the body position in which exercise is performed. Indeed, as it would have been expected, stratification for body position confirmed that PAWP values in HFpEF were 5 mmHg higher in the supine compared with the upright position, somehow indirectly reinforcing the validity of previously proposed distinct PAWP cut-off for the two body positions (25 and 20 mmHg, respectively). Furthermore, the above-mentioned procedural factors, some of which were not systematically reported, as well as some non-invasive or atypical definitions of HfpEF in the included studies may, at least in part, account for both the heterogeneity of PAWP estimates across the studies, and for a partial overlap in PAWP estimates at peak exercise in some studies between HFpEF and controls.

As it could have been expected based on different peak PAWP and CO values, also PAWP/CO slope differed between HFpEF and controls. Notably, the slopes we could extrapolate from available studies were always >2 mmHg/L/min for HFpEF and <2 mmHg/L/min for controls, with non-overlapping confidence intervals, thus somehow confirming and extending the validity of such cut-off value, that has been generally reported only in upright studies. However, the steepness of the PAWP/CO slope was higher in the supine than in the upright position in HFpEF but not in control subjects cohorts. Thus, at variance from healthy subjects,[7] we might speculate that the flow-normalized behaviour of the pulmonary circulation is not independent from the body position, at least in patients with (occult) fluid overload, where dysfunctional preload could be magnified when laying down. Accordingly, even if the PAWP/CO slope cut-off of 2 mmHg/L/min might be valid to diagnose HFpEF irrespectively from body position (and from the phase of the respiratory cycle in which PAWP is measured),[5] its absolute value might not provide comparable results in patients performing supine or upright exercise.

Limitations

Most of the data used for this meta-analysis come from two US centres, potentially limiting the representativity of our results. However, as outlined above, clinical characteristics were overall in line with those of a typical HFpEF population. Furthermore, most studies selected patients based on rest and/or exercise haemodynamics rather than on clinical/non-invasive data. It is therefore possible that invasive haemodynamic criteria select a particular type or subgroup of HFpEF patients, and that these results might not be applicable to other cohorts.

Individual patients' data were not available, so that we drove conclusions based on pooled average of different populations. Accordingly, the results of our meta-analysis should be considered more hypothesis-generating than definitive, requiring further confirmation. Additionally, we plotted PAWP/CO slope based just on two PAWP/CO pairs (rest and peak) rather than building a multipoint PAWP/CO relationship throughout the whole exercise, as originally suggested.[3,4] However, in an ad hoc analysis, we performed on previously published exercise haemodynamic data from 57 patients from our laboratory,[5] the mean bias derived from such a methodological simplification was clinically negligible, that is, 3%. Indeed, the mean multipoint PAWP/CO slope in this cohort was 3.66 mmHg/L/min, while the PAWP/CO slope built based on rest and peak values only was 3.54 mmHg/L/min. Finally, in order to avoid further methodological confounders, control subjects were taken from the same studies of HFpEF patients. As declared, they were not healthy subjects but patients not qualifying as HFpEF based on exercise haemodynamics (non-cardiac dyspnoea), in most cases due to the retrospective nature of invasive, clinically indicated studies. Nonetheless, they sorted out to have different (and normal) haemodynamics as compared with HFpEF patients.

Conclusions

Despite methodological heterogeneity across highly experienced centres, the haemodynamic profile of HFpEF patients is consistent across studies and characterized by a higher left and right filling pressure at rest compared with controls, enhanced by physical exercise. A PAWP/CO slope cut-off $>$ 2 mmHg/L/min seems to retain validity also for studies conducted in the supine position, potentially overcoming the need of different supine and upright PAWP cut-offs. Rigorous methodological and interpretative requirements are advisable for a larger application of exercise haemodynamics in clinical practice, to provide consistent results across laboratories.

Acknowledgements

Dr Baratto is the recipient of a Research Grant from the European Society of Cardiology. Dr Caravita received the grant Vera Srebot from the Fondazione CNR/Regione Toscana per la Ricerca Medica e di Sanità Pubblica. Dr Bondue received support from the Belgian Fonds de la Recherche Scientifique (FRS-FNRS—grant J.0011.19), from the Erasme Foundation (ULB), and from the Belgian Cardiac Surgery Foundation. Dr Vachiéry is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department.

Conflict of interest

The authors have no conflict of interest to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. New-Castle Ottawa scale for quality assessment of cross-sectional studies.

Table S2. Participant, Intervention, Comparison, Outcome Study (PICOs).

Table S3. Clinical characteristics of heart failure with preserved ejection fraction cohorts as reported in individual studies.

Table S4. Clinical characteristics of control cohorts as reported in individual studies.

Table S5. Clinical characteristics of patients with heart failure with preserved ejection fraction and control subjects across included studies. Data are reported as median (interquartile range).

Table S6. Rest and exercise hemodynamics of heart failure with preserved ejection fraction cohorts in supine position as reported in individual studies.

Table S7. Rest and exercise hemodynamics of control cohorts in supine position as reported in individual studies.

Table S8. Rest and exercise hemodynamics of heart failure with preserved ejection fraction cohorts in upright position as reported in individual studies.

Table S9. Rest and exercise hemodynamics of control cohorts in upright position as reported in individual studies.

Table S10. Supporting Information.

Figure S1. Forest plots with pooled standardized mean pulmonary artery wedge pressure values at rest both in heart failure with preserved ejection fraction and in controls.

Figure S2. Forest plots with pooled standardized mean PAWP values at rest in patients with HFpEF, stratified by HFpEF definitions and body position.

Figure S3. Forest plots with pooled standardized mean PAWP values at peak exercise in patients with HFpEF, stratified by HFpEF definitions and body position.

Figure S4. Pulmonary artery wedge pressure (PAWP) /cardiac output (CO) regression slopes in cohorts of patients with heart failure and preserved ejection fraction (HFpEF) and in control subjects cohorts, stratified by body position. The panel on the top represents the mean PAWP/CO slope of cohorts (both HFpEF and control subjects) studied in the supine position. The panel on the bottom represents the mean PAWP/CO slope of cohorts (both HFpEF and control subjects) studied in the upright position. In both panels the red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.

References

1. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019; **124**: 1598–1617. PMID: 31120821; PMCID: PMC6534165.
2. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010; **3**: 588–595. Epub 2010 Jun 11. PMID: 20543134; PMCID: PMC3048586.
3. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R, Lewis GD. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail*. 2018; **11**: e004750. PMID: 29695381; PMCID: PMC5937988.

4. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation*. 2019; **140**: 353–365. Epub 2019 May 28. PMID: 31132875; PMCID: PMC6684250.
5. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati G, Vachiéry JL. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021; **14**: e007555. Epub ahead of print. PMID: 33951935.
6. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grünig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J*. 2017; **50**: 1700578.
7. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. *J Appl Physiol (1985)*. 2016; **121**: 1145–1150. Epub 2016 Oct 7. PMID: 27763874.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009; **62**: e1–e34.
9. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014; **14**: 135.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7**: 177–188.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; **21**: 1539–1558.
12. Stanley TD, Doucouliagos H. Neither fixed nor random: weighted least squares meta-analysis. *Stat Med*. 2015; **34**: 2116–2127.
13. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013; **15**: 776–785. Epub 2013 Feb 20. PMID: 23426022; PMCID: PMC3857919.
14. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O_2 pathway analysis. *Circulation*. 2018; **137**: 148–161. Epub 2017 Oct 9. PMID: 28993402; PMCID: PMC5760316.
15. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017; **136**: 6–19. Epub 2017 Apr 5. PMID: 28381470; PMCID: PMC5501170.
16. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J*. 2018; **39**: 2825–2835. PMID: 29947750; PMCID: PMC6093469.
17. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, Borlaug BA. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J*. 2019; **40**: 3707–3717. PMID: 31513270; PMCID: PMC7963136.
18. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; **21**: 891–900. Epub 2019 Mar 28. PMID: 30919562.
19. van Empel VP, Mariani J, Borlaug BA, Kaye DM. Impaired myocardial oxygen availability contributes to abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2014; **3**: e001293. PMID: 25468660; PMCID: PMC4338724.
20. Wolsk E, Kaye D, Komtebedde J, Shah SJ, Borlaug BA, Burkhoff D, Kitzman DW, Lam CSP, van Veldhuisen DJ, Ponikowski P, Petrie MC, Hassager C, Møller JE, Gustafsson F. Central and peripheral determinants of exercise capacity in heart failure patients with preserved ejection fraction. *JACC Heart Fail.* 2019; **7**: 321–332. Epub 2019 Mar 6. PMID: 30852235.
21. Fermoyle CC, Stewart GM, Borlaug BA, Johnson BD. Pulmonary vascular pressures and gas exchange response to exercise in heart failure with preserved ejection fraction. *J Card Fail*. 2020; **26**: 1011–1015. Epub 2020 Aug 1. PMID: 32750488; PMCID: PMC7704759.
22. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CSP, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail.* 2019; **7**: 239–249. PMID: 30819380.
23. Chen ZW, Huang CY, Cheng JF, Chen SY, Lin LY, Wu CK. Stress echocardiography-derived E/e' predicts abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *Front Physiol*. 2019; **10**: 1470. PMID: 31849715; PMCID: PMC6901703.
24. McCabe C, Oliveira RKF, Rahaghi F, Faria-Urbina M, Howard L, Axell RG, Priest AN, Waxman AB, Systrom DM. Right ventriculo-arterial uncoupling and impaired contractile reserve in obese patients with unexplained exercise intolerance. *Eur J Appl Physiol*. 2018; **118**: 1415–1426. Epub 2018 Apr 30. PMID: 29713818; PMCID: PMC6028899.
25. Nanayakkara S, Haykowsky M, Mariani J, Van Empel V, Maeder MT, Vizi D, Kaye DM. Hemodynamic profile of patients with heart failure and preserved ejection fraction vary by age. *J Am Heart Assoc*. 2017; **6**: e005434. PMID: 28939710; PMCID: PMC5634249.
26. Platz E, Merz A, Silverman M, Lewis E, Groarke JD, Waxman A, Systrom D. Association between lung ultrasound findings and invasive exercise haemodynamics in patients with undifferentiated dyspnoea. *ESC Heart Fail*. 2019; **6**: 202–207. Epub 2018 Nov 26. PMID: 30474936; PMCID: PMC6352886.
27. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, William J, Marwick TH, Kaye DM. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; **21**: 495–505. Epub 2019 Jan 16. PMID: 30652393.
28. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. *Circ Heart Fail*. 2015; **8**: 278–285. Epub 2014 Dec 30. PMID: 25550438; PMCID: PMC4936392.
29. Andersen MJ, Ersbøll M, Gustafsson F, Axelsson A, Hassager C, Køber L, Boesgaard S, Pellikka PA, Møller JE. Exercise-induced changes in left ventricular filling pressure after myocardial infarction assessed with simultaneous right heart catheterization and Doppler echocardiography. *Int J Cardiol*. 2013; **168**: 2803–2810. Epub 2013 Apr 28. PMID: 23628301.
30. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, Olson TP, Borlaug BA. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017; **70**: 136–148. PMID: 28683960; PMCID: PMC5520668.
31. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol*. 2010; **56**: 855–863. PMID: 20813283.
32. Obokata M, Reddy YNV, Shah SJ, Kaye DM, Gustafsson F, Hasenfuβ G,

Hoendermis E, Litwin SE, Komtebedde J, Lam C, Burkhoff D, Borlaug BA. Effects of interatrial shunt on pulmonary vascular function in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2019; **74**: 2539–2550. PMID: 31753198.
33. Sorimachi H, Obokata M, Takahashi N, Reddy YNV, Jain CC, Verbrugge FH, Koepp KE, Khosla S, Jensen MD, Borlaug BA. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur Heart J*. 2021; **42**: 1595–1605. Epub ahead of print. PMID: 33227126.
34. Ahmad A, Corban MT, Toya T, Verbrugge FH, Sara JD, Lerman LO, Borlaug BA, Lerman A. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020; **23**: 765–772. Epub ahead of print. PMID: 32949186.
35. Tschöpe C, Kasner M, Westermann D, Walther T, Gaub R, Poller WC, Schultheiss HP. Elevated NT-ProBNP levels in patients with increased left ventricular filling pressure during exercise despite preserved systolic function. *J Card Fail*. 2005; **11**: S28–S33. PMID: 15948097.
36. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020; **8**: 657–666. Epub 2020 Jul 8. PMID: 32653449; PMCID: PMC7395878.
37. Houston BA, Tedford RJ. What we talk about when we talk about the wedge pressure. *Circ Heart Fail*. 2017; **10**: e004450. PMID: 28912264.
38. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol*. 2020; **75**: 919–930.
39. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019; **40**: 3297–3317.
40. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018; **138**: 861–870.
41. Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, Farrell R, Shoenike MW, Sbarbaro J, Malhotra R, Nayor M, Tschöpe C, de Boer RA, Lewis GD, Ho JE. Evaluation of 2 existing diagnostic scores for heart failure with preserved ejection fraction against a comprehensively phenotyped cohort. *Circulation*. 2021; **143**: 289–291. Epub 2021 Jan 19. PMID: 33464963; PMCID: PMC8059354.
42. Senni M, Caravita S, Paulus WJ. Do existing definitions identify subgroup phenotypes or reflect the natural history of heart failure with preserved ejection fraction? *Circulation*. 2019; **140**: 366–369. Epub 2019 Jul 29. PMID: 31356132.
43. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc*. 2017; **6**: e006817. PMID: 28862947; PMCID: PMC5586477.
44. Pandey A, Khera R, Park B, Haykowsky M, Borlaug BA, Lewis GD, Kitzman DW, Butler J, Berry JD. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail*. 2018; **6**: 117–126. PMID: 29413366; PMCID: PMC8135913.
45. Wolsk E, Bakkestrøm R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, Hassager C, Møller JE, Gustafsson F. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. *JACC Heart Fail*. 2017; **5**: 337–346.
46. Braunwald E, Grossman W. Clinical aspects of heart failure. In Braunwald E., ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 4th ed. Philadelphia: Sunders; 1992. p 444–463.

ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 3079–3091
Published online 24 June 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13979

ORIGINAL ARTICLE

Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Claudia Baratto[1,2], Sergio Caravita[1,3], Davide Soranna[4], Céline Dewachter[2], Antoine Bondue[2], Antonella Zambon[4,5], Luigi P. Badano[1,6], Gianfranco Parati[1,6] and Jean-Luc Vachiéry[2]*

[1]*Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milan, Italy;* [2]*Department of Cardiology, Hopital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070, Bruxelles, Belgium;* [3]*Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy;* [4]*Biostatistics Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy;* [5]*Department of Statistic and Quantitative Methods, University of Milano-Bicocca, Milan, Italyl and* [6]*Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*

Abstract

Aims Exercise right heart catheterization (RHC) is considered the gold-standard test to diagnose heart failure with preserved ejection fraction (HFpEF). However, exercise RHC is an insufficiently standardized technique, and current haemodynamic thresholds to define HFpEF are not universally accepted. We sought to describe the exercise haemodynamics profile of HFpEF cohorts reported in literature, as compared with control subjects.

Methods and results We performed a systematic literature review until December 2020. Studies reporting pulmonary artery wedge pressure (PAWP) at rest and peak exercise were extracted. Summary estimates of all haemodynamic variables were evaluated, stratified according to body position (supine/upright exercise). The PAWP/cardiac output (CO) slope during exercise was extrapolated. Twenty-seven studies were identified, providing data for 2180 HFpEF patients and 682 controls. At peak exercise, patients with HFpEF achieved higher PAWP (30 [29–31] vs. 16 [15–17] mmHg, $P < 0.001$) and mean right atrial pressure ($P < 0.001$) than controls. These differences persisted after adjustment for age, sex, body mass index, and body position. However, peak PAWP values were highly heterogeneous among the cohorts (I^2 = 93%), with a relative overlap with controls. PAWP/CO slope was steeper in HFpEF than in controls (3.75 [3.20–4.28] vs. 0.95 [0.30–1.59] mmHg/L/min, P value < 0.0001), even after adjustment for covariates ($P = 0.007$).

Conclusions Despite methodological heterogeneity, as well as heterogeneity of pooled haemodynamic estimates, the exercise haemodynamic profile of HFpEF patients is consistent across studies and characterized by a steep PAWP rise during exercise. More standardization of exercise haemodynamics may be advisable for a wider application in clinical practice.

Keywords Heart failure; Cardiac catheterization; Haemodynamics; Exercise testing; Meta-analysis

Received: 8 December 2021; Revised: 8 April 2022; Accepted: 8 May 2022
**Correspondence to: Jean-Luc Vachiéry, Department of Cardiology, Hopital Universitaire de Bruxelles, Hôpital Académique Erasme, 808 Route de Lennik, 1070 Brussels, Belgium. Tel: +32 (0) 2 555 5602; +32 (0) 2 555 4866. Email: jeanluc.vachiery@erasme.ulb.ac.be*

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent condition. Additionally, patients may present with lifestyle-limiting effort symptoms but no clinical evidence of hypervolemia.[1] Therefore, in case of non-conclusive exams and normal haemodynamics at rest, exercise right heart catheterization (RHC) has been claimed as the gold-standard diagnostic test for HFpEF, potentially overcoming several limitations of non-invasive examinations and algorithms.[2–4]

However, exercise RHC is a costly and time-consuming test with a limited availability. Moreover, the procedural approach, including patients' body position and exercise protocol as well as the haemodynamic measurements and their interpretation, has not been widely standardized. This non-negligible limitation could impact on the reproducibility and generalizability of the results.[5,6]

To address these issues, we conducted a systematic review and meta-analysis of studies on exercise haemodynamics in patients with HFpEF, taking into account potential heterogeneity of these populations and exercise RHC methodology. Our aim was to describe the exercise haemodynamic profile of a large population of patients diagnosed as HFpEF and to compare it with control subjects. It is important to mention that pulmonary artery wedge pressure (PAWP) is influenced by several factors, including the patient's body position and the timing of measurement during the respiratory and cardiac cycle. Therefore, the reading of pressure traces may differ across investigators, especially during exercise, and lead to heterogeneity of interpretations when a standardized procedure is not universally adopted by all laboratories. However, the impact of body position and of respiratory swings might be minimized when normalizing the exercise-induced changes of pulmonary pressures for cardiac output (CO) increase.[5,7] Additionally, and recent evidence suggests that flow-corrected PAWP during exercise might be a more sensitive marker of HFpEF than absolute PAWP values at peak effort,[5] with proven prognostic value.[4] Thus, we also sought to build and compare the PAWP/CO slope of HFpEF and controls for all studies, to test the validity of this composite variable in a large HFpEF cohort.

Methods

We followed the PRISMA statement[8] for reporting systematic reviews and meta-analysis. A comprehensive literature research on PubMed was updated to December 2020, and the search terms included: ('right heart catheterization' OR 'hemodynamics' OR 'cardiac catheterization' OR 'haemodynamics') AND ('exercise' OR 'effort') AND ('heart failure with preserved ejection fraction' OR 'HFPEF' OR 'dyspnea' OR 'diastolic dysfunction' OR 'diastolic heart failure' OR 'left heart disease') AND ('PAWP' OR 'PCWP' OR 'wedge pressure' OR 'occlusion pressure').

We included papers that met the following criteria: (i) published in peer-reviewed journal, (ii) designed to evaluate the exercise haemodynamics in the HFpEF population, and (iii) reporting PAWP at rest and at peak exercise (main endpoint measure).

We excluded case reports, editorials, reviews, not pertinent studies (e.g. not including HFpEF or not reporting exercise invasive haemodynamics data), and studies reporting follow-up data of HFpEF patients who had undergone implant of an interatrial septal device within a clinical trial. When the same patients were included in more than one study, the larger one was considered.

Two investigators independently reviewed the search results to select the studies based on the inclusion criteria. Additionally, we performed a manual search of secondary sources including references of initially identified articles, reviews, and commentaries to minimize missing relevant studies. Any discrepancy in the process of study selection and data extraction was resolved by discussion between the investigators, and all disagreements were solved by consulting with a third investigator. Study design was reported according to Participant, Intervention, Comparison, Outcome Study. Risk of bias was assessed by two reviewers, using a scale adapted from the Newcastle-Ottawa Quality Assessment Scale for cross-sectional studies.

For each study, non-invasive data (clinical, echocardiography, & blood tests) as well as haemodynamics (e.g. PAWP & CO) at rest and at peak exercise were extracted. Additionally, for all studies reporting PAWP and CO at rest and at peak exercise, we calculated the slope of their relationship during effort.

Statistical analysis

Clinical characteristics of HFpEF and control patients of each study were reported as mean and standard deviation (for continuous variables) or proportions (for categorical variables). A summary estimate of each clinical characteristic, for HFpEF and control patients, was reported as median and interquartile range of study-specific values and jointly represented with a radar plot.

When only median and interquartile range of haemodynamic variable were available in included studies, they were transformed in mean and standard deviation value[9] before applying the meta-analytic procedure. Summary estimates of each haemodynamic variable were separately evaluated for HFpEF and control cohorts. Additionally, summary estimates of PAWP and delta CO were separately evaluated also for exercise body position. The random effect summary mean estimate and the corresponding 95% confidence intervals (95% CI) were calculated according to the DerSimonan and Laird's method.[10] Between-studies' heterogeneity was quantified using the I^2 index. Values of this index more than 75% suggest high heterogeneity.[11] Homogeneity between summary mean estimates stratified for body position during exercise was performed by a χ^2 statistic. In order to account for potential populations' heterogeneity, reflecting differences in inclusion criteria of individual studies, we performed a stratified analysis. In particular, we subdivided studies defining HFpEF based on haemodynamic criteria only, from studies defining HFpEF based on clinical criteria or including patients with LVEF $< 50\%$.

Finally, univariate and multivariate meta-regression models were implemented for each haemodynamic variable, including status (HFpEF or control) as independent variable, and age, sex, body mass index (BMI), and body position as dependent variables. Meta-regression is a linear weighted mixed model including study as random effect and standard error of published mean as weight.[12] The estimated

coefficient related to status variable gives information about the summary means difference.

Results were considered statistically significant when two-tailed *P* value was lower than 0.05. All analyses were performed with R Version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection

One hundred and thirty-eight studies were identified. After preliminary screening based on the title and the abstract, 48 studies were selected for full-text review. Other studies were excluded because either reporting duplicate patients' data with other larger studies (19 studies) or not reporting the exercise haemodynamic variables (*Figure 1*). Study design of included manuscripts and the Newcastle-Ottawa Quality Assessment Scale are reported in Supporting Information, *Tables S1* and *S2*.

Characteristics of included studies

The 27 selected studies[2–4,13–36] included 2180 HFpEF patients and 682 controls. Characteristics of individual studies are reported in *Table 1*. Thirteen studies (48%) had a prospective design,[3,4,17,19,23,25–27,29–31,34] 13 (48%) were retrospective,[2,13–15,18,20–22,24,28,33,35,36] and 1 study (4%) was a randomized controlled trial.[32]

Of the 27 selected studies, 17 were performed in three centres of the United States,[2–4,13–18,21,24,26,28,30,33,34,36] 5 in one Australian centre,[19,22,25,27,31] and 2 in Europe.[29,35] Three studies were multicentric, with patients coming from American, Australian, and European centres.[20,23,32]

Overall, the selected studies included 35 cohorts of HFpEF patients and 21 cohorts of control subjects, whose clinical characteristics are reported in *Tables S3* and *S4*, respectively. Control subjects were mainly individuals who underwent a clinically indicated invasive cardiopulmonary evaluation for unexplained dyspnoea and who did not satisfy the haemodynamic diagnostic criteria for HFpEF. Healthy volunteers (n = 8) served as control group only in one study.[31]

A symptom-limited exercise testing protocol was used in all studies. Patients underwent supine exercise in 21 studies[2,13,15–23,25,27,29–34] and upright exercise in 6 studies.[3,4,14,24,26,28] Exercise PAWP was measured at end-expiration in almost all studies (25 of 27). Only in seven studies (26%) high-fidelity catheters were employed.[2,17,23,30,33,34,36] CO was measured by direct Fick method in most studies (n = 16, 59%).[2–4,13–18,21,23,24,26,28,30,36]

Only four studies used non-invasive diagnostic criteria to define HFpEF, including either clinical parameters, echocardiographic data, or reduced peak oxygen consumption at cardiopulmonary exercise test.[13,23,29,31] In all the other studies, the diagnosis of HFpEF was confirmed based on rest or peak PAWP. A peak PAWP cut-off of ≥25 mmHg was used in all but one of the studies performing the effort in supine position.[35] In four of the six studies evaluating patients exercising in the upright position, a peak PAWP > 20 mmHg or a PAWP/CO slope > 2 mmHg/L/min was considered as a pathological threshold to define HFpEF.[3,4,24,28]

Notably, six studies focused on specific HFpEF subpopulations, such as those with obesity, recent myocardial infarction, non-obstructive coronary artery disease, or patients included in an interventional trial.[20,24,29,32,34,36] Only in four studies the left ventricular ejection fraction to define

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. HFpEF, heart failure with preserved ejection fraction; RHC, right heart catheterization.

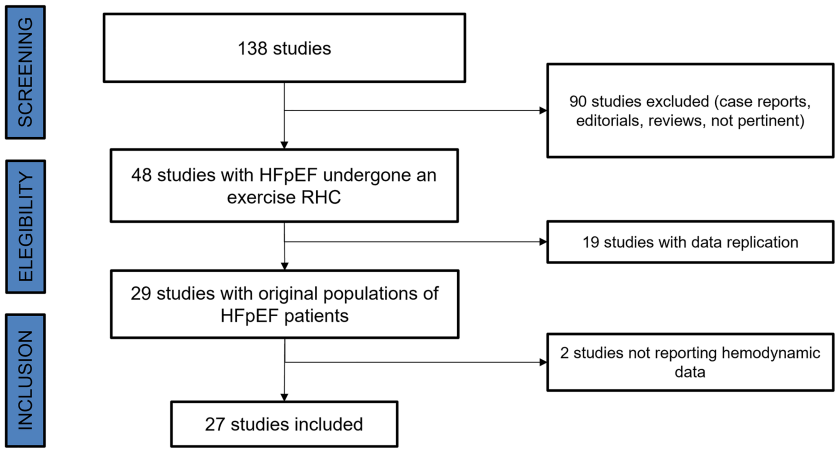


Table 1 Characteristics of the included studies

Author	Country	Centre	*n* HFpEF	*n* controls	Timing of enrolment
Tschöpe *et al.*[35]	Germany	Campus Benjamin Franklin	15	15	2003
Borlaug *et al.*[2]	USA	Mayo Clinic	32	23	2005–2009
Maeder *et al.*[31]	Australia	Alfred Hospital	14	8	2008–2009
Abudiab *et al.*[13]	USA	Mayo Clinic	109	73	2002–2011
Andersen *et al.*[29]	Denmark	Rigshospitalet & Copenhagen University	61		2010–2012
Santos *et al.*[28]	USA	Brigham and Women's Hospital	31	31	2011–2013
Houstis *et al.*[14]	USA	Massachusetts General Hospital	79	55	2006–2016
Obokata *et al.*[15]	USA	Mayo Clinic	195	71	2000–2014
Reddy *et al.*[30]	USA	Mayo Clinic	98	22	
Nanayakkara *et al.*[25]	Australia	Alfred Hospital	21	19	
Eisman *et al.*[3]	USA	Massachusetts General Hospital	77	98	
Gorter *et al.*[14]	USA	Mayo Clinic	161		2006–2013
McCabe *et al.*[24]	USA	Brigham and Women's Hospital	8	14	
Platz *et al.*[26]	USA	Brigham and Women's Hospital	13	12	
Ho *et al.*[4]	USA	Massachusetts General Hospital	243		2006–2017
Obokata *et al.*[17]	USA	Mayo Clinic	38	20	
Reddy *et al.*[18]	USA	Mayo Clinic	238	125	
Van Empel *et al.*[19]	Australia	Alfred Hospital	9	21	
Wolsk *et al.*[20]	USA, Europa, Australia	Multicentre	108	42	2013–2016
Beale *et al.*[22]	Australia	Alfred Hospital	161		2008–2018
Chen *et al.*[23]	Taiwan	Taiwan University Hospital	34		2018
Telles *et al.*[27]	Australia	Alfred Hospital	49	22	2016–2018
Obokata *et al.*[32]	USA, Europe, Australia	Multicentre	79		2014–2016
Fermoyle *et al.*[21]	USA	Mayo Clinic	30		2009–2012
Sorimachi *et al.*[33]	USA	Mayo Clinic	105	51	2007–2018
Ahmad *et al.*[34]	USA	Mayo Clinic	22	29	2010–2019
Houston and Tedford[37]	USA	Mayo Clinic	169		2000–2014

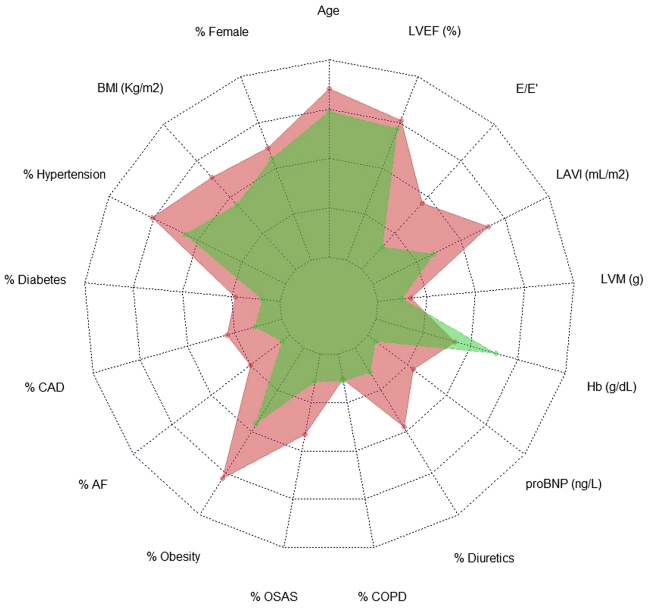
BMI, body mass index; CAD, coronary artery disease; CPCPH, combined post-capillary pulmonary hypertension; EAT, epicardial adipose tissue; END-EXP, end-expiratory phase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFpEFphys, physiological definition of heart failure with preserved ejection fraction; IPCPH, isolated post-capillary pulmonary hypertension; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Table 1 (continued)

Author	Exercise position	PAWP (end-exp/avg)	PAWP (mean/mid-A)	HFpEF diagnosis	Other remarks
Tschöpe *et al.*[35]	Supine			Haemodynamic (rest and/or exercise), echo	restPAWP > 12, peakPAWP > 20
Borlaug *et al.*[2]	Supine	End-exp		Haemodynamic (exercise)	
Maeder *et al.*[31]	Supine	End-exp	Mean	↓ ex capacity	
Abudiab *et al.*[13]	Supine	End-exp		Clinical	
Andersen *et al.*[29]	Supine	Avg		Echo	LVEF > 45% and post-STEMI
Santos *et al.*[28]	Upright	End-exp		Haemodynamic (exercise)	PAWP peak > 20
Houstis *et al.*[14]	Upright	End-exp		Haemodynamic (rest and/or exercise), ↓ ex capacity	
Obokata *et al.*[15]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Reddy *et al.*[30]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Nanayakkara *et al.*[25]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Eisman *et al.*[3]	Upright	End-exp		Haemodynamic (exercise)	
Gorter *et al.*[14]	Supine	End-exp		Haemodynamic (rest)	
McCabe *et al.*[24]	Upright	Avg		Haemodynamic (rest and/or exercise)	PAWP rest > 15, peak > 20 mmHg
Platz *et al.*[26]	Upright	End-exp		Haemodynamic (rest)	
Ho *et al.*[4]	Upright	End-exp		Haemodynamic (exercise)	
Obokata *et al.*[17]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Reddy *et al.*[18]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Van Empel *et al.*[19]	Supine	End-exp	Mean	Haemodynamic (exercise), echo	LVEF > 45%
Wolsk *et al.*[20]	Supine	End-exp	Mean	Haemodynamic (rest and/or exercise), BNP, echo	LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP
Beale *et al.*[22]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Chen *et al.*[23]	Supine	End-exp	Mid-A	Clinical, BNP, echo	
Telles *et al.*[27]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Obokata *et al.*[32]	Supine			Haemodynamic (rest and/or exercise), BNP, echo	LVEF > 40%; prior HF hospitalization, PAWP, or LVEDP > RAP
Fermoyle *et al.*[21]	Supine	End-exp	Mid-A	Haemodynamic (rest and/or exercise)	
Sorimachi *et al.*[33]	Supine	End-exp		Haemodynamic (rest and/or exercise)	
Ahmad *et al.*[34]	Supine	End-exp	Mid-A	Haemodynamic (rest and/or exercise)	Non-obstructive CAD
Houston and Tedford[37]	Supine	End-exp		Haemodynamic (rest and/or exercise)	BMI ≥ 30

BMI, body mass index; CAD, coronary artery disease; CPCPH, combined post-capillary pulmonary hypertension; EAT, epicardial adipose tissue; END-EXP, end-expiratory phase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFpEFphys, physiological definition of heart failure with preserved ejection fraction; IPCPH, isolated post-capillary pulmonary hypertension; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; STEMI, myocardial infarction with persistent ST elevation.

Figure 2 Radar plot with the clinical characteristics of HFpEF patients (pink) and control subjects (green). AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin; LAVI, left atrial volume indexed; LVM, left ventricular mass; NT-proBNP, N terminal pro brain natriuretic peptide; OSAS, obstructive sleep apnoea syndrome.



HFpEF was >40% or >45%, rather than the currently adopted cut-off of ≥50%.[19,20,29,32]

Clinical characteristics of heart failure with preserved ejection fraction patients and controls

A graphical joint comparison of clinical characteristics of HFpEF patients and controls is reported in *Figure 2* and in *Table S5*. The HFpEF group was slightly older than the control group (median age 67 vs. 60 years), with more women (61% vs. 56%), and higher BMI (32.0 vs. 27.9 kg/m^2). Moreover, the HFpEF group had a larger burden of comorbidities (prevalence of arterial hypertension was 76% vs. 56%, and prevalence of diabetes was 23% vs. 9%), higher N terminal pro brain natriuretic peptide (NT-proBNP) (340 vs. 83 pg/mL), larger left atrial volume index (39 vs. 29 mL/m^2), and higher E/E' (13 vs. 9). The prevalence of atrial fibrillation was 25% in HFpEF vs. 5% in controls, but this information was reported only in about half of the cohorts.

Haemodynamics at rest

The summary estimates of PAWP at rest in HFpEF and controls are reported in *Figure S1*. The summary mean of PAWP was 15 (95% CI: 14–16) mmHg in HFpEF cohorts and 9 (95% CI: 8–9) mmHg in control cohorts. High heterogeneity, especially in HFpEF cohorts, was observed (I^2 = 97% and I^2 = 82%, respectively). This heterogeneity as well as the PAWP summary estimates did not show relevant differences at a stratified data analysis subdividing studies adopting pure haemodynamic definitions for HFpEF, as opposed to those adopting only non-invasive, clinical definitions of HFpEF, or including patients with LVEF < 50% (*Figure S2*). Notably, in all the studies adopting non-invasive or atypical HFpEF definitions, exercise was performed in the supine position. Similar to PAWP, also right atrial pressure at rest was higher in HFpEF than in control subjects (8, 95% CI: 7–10 mmHg vs. 4, 95% CI: 3–5 mmHg, respectively, *P* value < 0.0001).

In HFpEF, both CO and cardiac index (5.13; 95% CI: 4.95–5.31 L/min and 2.61; 95% CI: 2.53–2.68 L/min/m^2, respectively), even if within normal limits, were slightly lower than those of controls (5.41; 95% CI: 5.19–5.63 L/min and 2.76; 95% CI 2.61–2.91 L/min/m^2).

We compared the summary estimates of HFpEF and controls cohorts by meta-regression analysis without and with adjustment for age, sex, BMI, and body position (*Table 2*). In the meta-regression analysis without adjustment, we observed a statistically significant difference for all haemodynamic variables, except CO, between HFpEF and control cohorts. After adjustment, CO and cardiac index were no more different between the two groups.

Exercise haemodynamics

Complete rest and exercise haemodynamics of HFpEF patients and control subjects from each included study are reported in *Tables S6–S9*.

Table 2 Rest and exercise haemodynamics of heart failure with preserved ejection fraction and control subjects

Outcome	HFpEF		Controls		Unadjusted meta-regression models		Adjusted meta-regression models	
	Mean (95% CI)	*N* of cohorts	Mean (95% CI)	*N* of cohorts	*P* value	*N* of cohorts	*P* value	*N* of cohorts
REST								
PAWP (mmHg)	14.98 (13.84–16.13)	35	8.70 (8.16–9.24)	22	<0.0001	57	<0.0001	54
CO (L/min)	5.13 (4.95–5.31)	15	5.41 (5.19–5.63)	11	0.068	26	0.103	26
CI (L/min/m^2)	2.61 (2.53–2.68)	18	2.76 (2.61–2.91)	10	0.083	28	0.413	25
RAP (mmHg)	8.35 (7.25–9.82)	26	4.05 (3.23–4.87)	16	<0.0001	42	0.012	42
PEAK								
PAWP (mmHg)	29.99 (28.93–31.06)	34	15.76 (14.75–16.78)	21	<0.0001	55	<0.0001	54
CO (L/min)	9.50 (8.97–10.03)	18	12.95 (10.00–15.90)	13	<0.0001	31	0.128	31
CI (L/min/m^2)	4.60 (4.22–5.01)	20	6.75 (5.93–7.56)	9	<0.0001	29	0.047	26
RAP (mmHg)	17.73 (16.32–19.14)	25	8.18 (7.53–8.84)	15	<0.0001	40	<0.0001	40
DELTA PEAK-REST								
PAWP (mmHg)	15.00 (14.16–15.84)	34	7.15 (6.27–8.02)	21	<0.0001	55	<0.0001	52
CO (L/min)	4.38 (3.73–5.03)	15	8.15 (6.71–9.59)	11	<0.0001	26	0.096	26

95% CI, 95% of the confidence interval; CI, cardiac index; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; *N*, number; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.
Adjustment was performed using meta-regression models including age, sex, body mass index, and body position as covariates. Data are reported as mean (95% confidence interval).
The *P* value reflects the comparison between the two groups, both unadjusted, and after adjustment for age, sex, BMI, and body position.

During exercise, HFpEF cohorts showed markedly higher filling pressures than controls (*Table 2* and *Figure 3*). Similarly to resting data, these results were characterized by high heterogeneity (I^2 = 93% and 83%, respectively). This heterogeneity, as well as the PAWP summary estimates, did not show relevant differences at a stratified data analysis subdividing studies adopting pure haemodynamic definitions for HFpEF as opposed to studies adopting only non-invasive, clinical definitions of HFpEF, or including patients with LVEF < 50% (*Figure S3*). This wide dispersion of PAWP values among the cohorts led to a zone of partial overlap between HFpEF and controls at values between 20 and 25 mmHg. Nonetheless, HFpEF cohorts showed a summary estimate of PAWP at peak which was twice as high as compared with control cohorts (30; 95% CI: 29–31 mmHg and 16; 95% CI: 15–17 mmHg, respectively), as well as of delta PAWP (15; 95% CI: 14–16 mmHg and 7; 95% CI: 6–8 mmHg, respectively), and of right atrial pressure (18; 95% CI: 16–19 mmHg and 8; 95% CI: 8–9 mmHg, respectively). All these differences remained statistically significant after adjustment for the covariates (*P* value < 0.0001).

Additionally, summary estimates of PAWP at peak performed during supine exercise was slightly higher than those obtained in upright position only for HFpEF cohorts (supine position: 31; 95% CI:30–32 mmHg vs. upright position; 26; 95% CI: 25–27 mmHg, respectively, *P* value < 0.01; *Figure 3*).

Another relevant difference in the haemodynamic response to exercise between HFpEF and controls concerned the exercise-induced increase in CO (*Table 2*). Both CO and cardiac index at peak resulted significantly lower in HFpEF than in controls (*P* < 0.001). Moreover, the increase in CO during exercise was significantly lower in HFpEF than in controls (4.38; 95% CI: 3.73–5.02 L/min and 8.15; 95% CI: 6.71–9.59 L/min respectively, *P* value < 0.0001) although high heterogeneity was present (I^2 = 94% and I^2 = 96%), as shown in *Table 2* and *Figure 4*. However, this difference was no longer statistically significant after adjustment for the covariates. Finally, summary estimate of delta CO in the supine position resulted lower than in upright position only for HFpEF cohorts (*P* value < 0.01, *Figure 4*).

Because there were more cohort studies per centre with overlapped recruitment period, we performed a sensitivity analysis including only one cohort per centre[3,4,17,21,22,26–28,30,34] to verify the robustness of results. As shown in *Table S10*, summary point and interval estimates of each exercise haemodynamic variable in this subset of studies were comparable with those obtained on the entire dataset.

Pulmonary artery wedge pressure/circuit output slope

Figure 5 represents PAWP/CO slopes for cohorts reporting rest and at peak values for both haemodynamic variables.

Figure 3 Forest plots with pooled standardized mean pulmonary artery wedge pressure values at peak exercise both in heart failure with preserved ejection fraction and in controls. HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

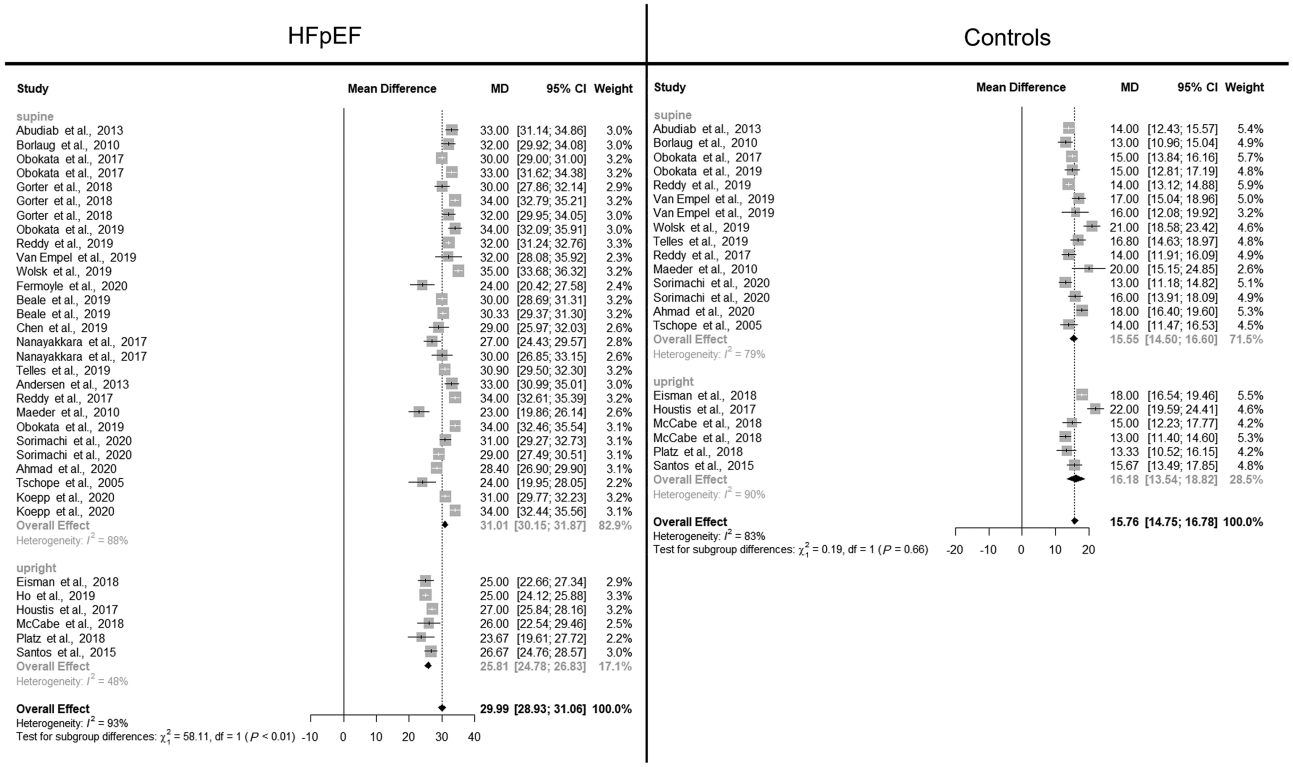
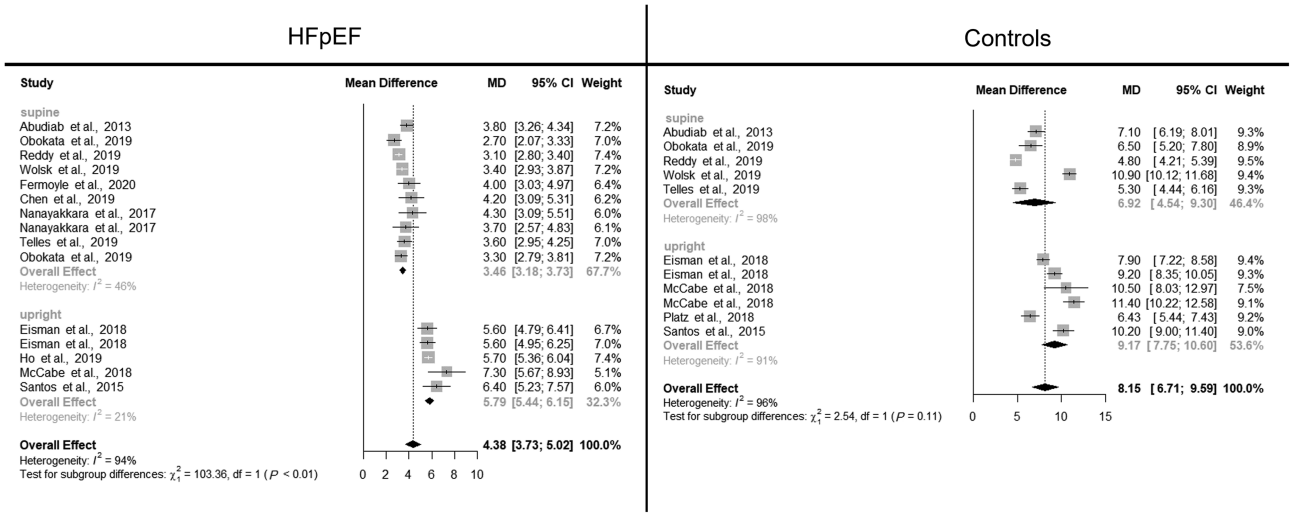
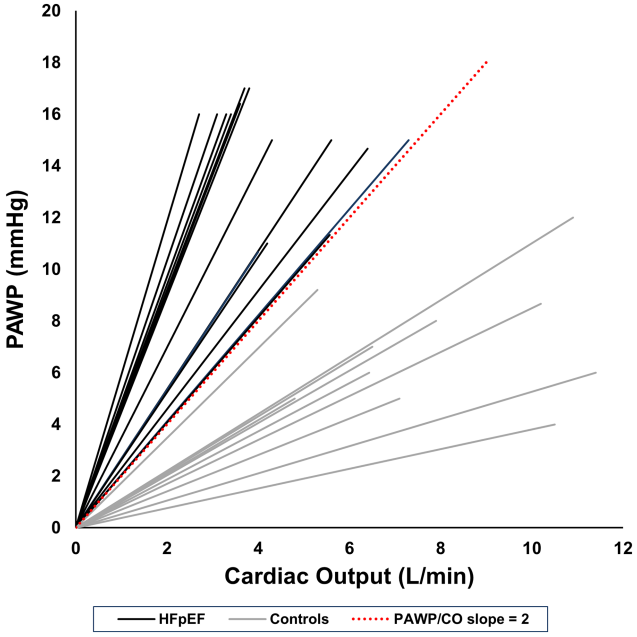


Figure 4 Forest plots with pooled standardized cardiac output increase during exercise both in heart failure with preserved ejection fraction and in the controls. CO, cardiac output; HFpEF, heart failure with preserved ejection fraction.



For all the studies, the Y-intercept of such relationship was fixed at 0, in order to focus on inter-studies differences in slopes, independent from baseline values. Coherent with what shown above for rest and peak PAWP as well as for CO data, HFpEF cohorts had a significantly larger impairment in the haemodynamic response to exercise compared with controls, witnessed by a steeper PAWP/CO slope. Indeed, in HFpEF cohorts, the summary PAWP/CO slope was higher

Figure 5 Pulmonary artery wedge pressure (PAWP)/cardiac output (CO) regression slopes in cohorts of patients with heart failure and preserved ejection fraction (HFpEF) and in control subjects cohorts. The red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.



than in control cohorts (3.75; 95% CI: 3.20–4.28 mmHg/L/min and 0.95; 95% CI: 0.30–1.59 mmHg/L/min, *P* value < 0.0001). This difference persisted even after adjustment for age, sex, BMI, and body position (*P* value = 0.007). All PAWP/CO slopes in HFpEF cohorts were found above the proposed pathological threshold of >2 mmHg/L/min while control cohorts showed slopes always <2 mmHg/L/min.

Finally, summary estimates of PAWP/CO slope were higher in HFpEF cohorts performing exercise in the supine position compared with those in upright position ($P < 0.0001$ and $P = 0.0002$ at non-adjusted and adjusted analysis, respectively), but not in control cohorts ($P = 0.135$ and $P = 0.966$ at non-adjusted and adjusted analysis, respectively). In *Figure S4*, the PAWP/CO slope in supine and upright position for HFpEF and control cohorts is presented.

Discussion

Our meta-analysis provides a thorough characterization of a large population of HFpEF and controls who underwent exercise RHC, highlighting (i) methodological heterogeneity in exercise haemodynamic protocols across centres; (ii) a quite typical clinical profile of HFpEF patients assessed through exercise haemodynamics, which differ from that of control subjects (even though clinical characterization was frequently incomplete as compared with what would be desired in order to apply current non-invasive HFpEF definitions); (iii) a high heterogeneity of haemodynamic responses to exercise across the different HFpEF cohorts; and (iv) the potential validity of a PAWP/CO slope cut-off value $>$ 2 mmHg/L/min to define HFpEF across laboratories independently from body position, as an alternative or as a complementary measure to absolute exercise PAWP supine or upright thresholds.

Published data on exercise RHC come mainly from retrospective analysis of relatively small contemporary cohorts of patients investigated in very few highly experienced centres in the world, albeit with methodological heterogeneity. In most studies, exercise was performed in the supine position (78%), CO was measured by direct Fick method (59%), and PAWP using fluid-filled catheters (74%). However, at variance from the suggestion from the European Respiratory Society to average pressure values over several respiratory cycles, in order to avoid PAWP overestimation during exercise,[6] in more than 90% of studies, PAWP was measured at end-expiration. Additionally, and despite the notion that PAWP values differ according to the phase of the cardiac cycle,[37] only 22% of studies reported such information, with mean PAWP value reported in half of them, and end-diastolic measurement (mid-A wave) in the other half. This underscores the need for more uniform standardization of the RHC procedure to obtain reproducible results across laboratories.

Heart failure with preserved ejection fraction patients were mostly elderly obese women, with a high burden of comorbidities associated with accelerated cardiovascular ageing,[38] an enlarged left atrium, and high NT-proBNP values. Only four studies included also patients with LVEF lower than 50% (LVEF $\geq$ 40–45%). However, many characteristics were not uniformly reported across the studies, precluding to determine whether these patients would fulfil the currently adopted diagnostic criteria for HFpEF in clinical practice (e.g. HFA-PEFF score and H2FPEF score).[39,40] Additionally, despite the non-invasive assessment might have overall suggested a quite typical HFpEF profile,[39] it was not deemed to be sufficient to allow per se for a definite diagnosis of HFpEF in the individual patient before the exercise invasive haemodynamic study. This might reflect the complexity of HFpEF, where comorbidities may act as confounders in explaining patients' complaints (i.e. exertional breathlessness) in the absence of sensitive non-invasive markers for early stages of disease.[2,5,41]

The haemodynamic phenotype of pooled HFpEF patients showed an increase of both left and right filling pressure as compared with control subjects, likely as a consequence of cardiovascular ageing with cardiac fibrosis and diastolic dysfunction[42] combined with dysfunctional preload (high stressed blood volume).[43] This observation was also made in a previous meta-analysis on 20 studies.[44] Filling pressures at rest in HFpEF were on average just at the upper limit of normal, but the difference between HFpEF and controls,

albeit being already present at rest, was greatly magnified by the physical stress, even after correction for age, sex, BMI, and body position. At a first glance, patients with HFpEF also seemed to have a reduced CO reserve, as compared with controls. However, the lower absolute CO response to exercise displayed by HFpEF lost statistical significance after adjustment for some relevant baseline differences in HFpEF and controls (age, sex, and BMI). This is at variance from the meta-analysis by Pandey *et al*.,[44] where both stroke volume and heart rate response to exercise were lower in HFpEF than in controls after adjustment for age or BMI, overall suggesting a reduced cardiac reserve during exercise. However, (i) cardiovascular responses may change as a function of ageing (in particular with lower chronotropic response),[45] potentially resulting in lower CO in older HFpEF patients than in controls—a difference that might reasonably disappear after correction for age; (ii) there is conflicting evidence on the role of cardiac reserve in exercise limitation of HFpEF patients, with arguments favouring a peripheral limitation[14]; (iii) our study, which was more focused on PAWP and PAWP/CO slope than on central vs. peripheral limit to exercise in HFpEF and conducted 3 years later, could include more than twice the patients studied by Pandey *et al*.,[44] potentially overcoming some limitations in the analysis related to the sample size. Thus, the above-mentioned haemodynamic characteristics (high filling pressures and normal age-corrected CO) are consistent with the definition of HFpEF as a clinical syndrome mainly characterized by the ability of the heart to accommodate blood flow for the increased metabolic needs at the expense of high filling pressures.[46]

However, the absolute thresholds of peak exercise PAWP to define HFpEF are not universally accepted and might be influenced by several factors, including exercise duration and intensity, the phase of the respiratory, or cardiac cycle in which measurements are taken,[5,6] and the body position in which exercise is performed. Indeed, as it would have been expected, stratification for body position confirmed that PAWP values in HFpEF were 5 mmHg higher in the supine compared with the upright position, somehow indirectly reinforcing the validity of previously proposed distinct PAWP cut-off for the two body positions (25 and 20 mmHg, respectively). Furthermore, the above-mentioned procedural factors, some of which were not systematically reported, as well as some non-invasive or atypical definitions of HfpEF in the included studies may, at least in part, account for both the heterogeneity of PAWP estimates across the studies, and for a partial overlap in PAWP estimates at peak exercise in some studies between HFpEF and controls.

As it could have been expected based on different peak PAWP and CO values, also PAWP/CO slope differed between HFpEF and controls. Notably, the slopes we could extrapolate from available studies were always >2 mmHg/L/min for HFpEF and <2 mmHg/L/min for controls, with non-overlapping confidence intervals, thus somehow confirming and extending the validity of such cut-off value, that has been generally reported only in upright studies. However, the steepness of the PAWP/CO slope was higher in the supine than in the upright position in HFpEF but not in control subjects cohorts. Thus, at variance from healthy subjects,[7] we might speculate that the flow-normalized behaviour of the pulmonary circulation is not independent from the body position, at least in patients with (occult) fluid overload, where dysfunctional preload could be magnified when laying down. Accordingly, even if the PAWP/CO slope cut-off of 2 mmHg/L/min might be valid to diagnose HFpEF irrespectively from body position (and from the phase of the respiratory cycle in which PAWP is measured),[5] its absolute value might not provide comparable results in patients performing supine or upright exercise.

Limitations

Most of the data used for this meta-analysis come from two US centres, potentially limiting the representativity of our results. However, as outlined above, clinical characteristics were overall in line with those of a typical HFpEF population. Furthermore, most studies selected patients based on rest and/or exercise haemodynamics rather than on clinical/non-invasive data. It is therefore possible that invasive haemodynamic criteria select a particular type or subgroup of HFpEF patients, and that these results might not be applicable to other cohorts.

Individual patients' data were not available, so that we drove conclusions based on pooled average of different populations. Accordingly, the results of our meta-analysis should be considered more hypothesis-generating than definitive, requiring further confirmation. Additionally, we plotted PAWP/CO slope based just on two PAWP/CO pairs (rest and peak) rather than building a multipoint PAWP/CO relationship throughout the whole exercise, as originally suggested.[3,4] However, in an ad hoc analysis, we performed on previously published exercise haemodynamic data from 57 patients from our laboratory,[5] the mean bias derived from such a methodological simplification was clinically negligible, that is, 3%. Indeed, the mean multipoint PAWP/CO slope in this cohort was 3.66 mmHg/L/min, while the PAWP/CO slope built based on rest and peak values only was 3.54 mmHg/L/min. Finally, in order to avoid further methodological confounders, control subjects were taken from the same studies of HFpEF patients. As declared, they were not healthy subjects but patients not qualifying as HFpEF based on exercise haemodynamics (non-cardiac dyspnoea), in most cases due to the retrospective nature of invasive, clinically indicated studies. Nonetheless, they sorted out to have different (and normal) haemodynamics as compared with HFpEF patients.

Conclusions

Despite methodological heterogeneity across highly experienced centres, the haemodynamic profile of HFpEF patients is consistent across studies and characterized by a higher left and right filling pressure at rest compared with controls, enhanced by physical exercise. A PAWP/CO slope cut-off $>$ 2 mmHg/L/min seems to retain validity also for studies conducted in the supine position, potentially overcoming the need of different supine and upright PAWP cut-offs. Rigorous methodological and interpretative requirements are advisable for a larger application of exercise haemodynamics in clinical practice, to provide consistent results across laboratories.

Acknowledgements

Dr Baratto is the recipient of a Research Grant from the European Society of Cardiology. Dr Caravita received the grant Vera Srebot from the Fondazione CNR/Regione Toscana per la Ricerca Medica e di Sanità Pubblica. Dr Bondue received support from the Belgian Fonds de la Recherche Scientifique (FRS-FNRS—grant J.0011.19), from the Erasme Foundation (ULB), and from the Belgian Cardiac Surgery Foundation. Dr Vachiéry is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department.

Conflict of interest

The authors have no conflict of interest to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. New-Castle Ottawa scale for quality assessment of cross-sectional studies.

Table S2. Participant, Intervention, Comparison, Outcome Study (PICOs).

Table S3. Clinical characteristics of heart failure with preserved ejection fraction cohorts as reported in individual studies.

Table S4. Clinical characteristics of control cohorts as reported in individual studies.

Table S5. Clinical characteristics of patients with heart failure with preserved ejection fraction and control subjects across included studies. Data are reported as median (interquartile range).

Table S6. Rest and exercise hemodynamics of heart failure with preserved ejection fraction cohorts in supine position as reported in individual studies.

Table S7. Rest and exercise hemodynamics of control cohorts in supine position as reported in individual studies.

Table S8. Rest and exercise hemodynamics of heart failure with preserved ejection fraction cohorts in upright position as reported in individual studies.

Table S9. Rest and exercise hemodynamics of control cohorts in upright position as reported in individual studies.

Table S10. Supporting Information.

Figure S1. Forest plots with pooled standardized mean pulmonary artery wedge pressure values at rest both in heart failure with preserved ejection fraction and in controls.

Figure S2. Forest plots with pooled standardized mean PAWP values at rest in patients with HFpEF, stratified by HFpEF definitions and body position.

Figure S3. Forest plots with pooled standardized mean PAWP values at peak exercise in patients with HFpEF, stratified by HFpEF definitions and body position.

Figure S4. Pulmonary artery wedge pressure (PAWP) /cardiac output (CO) regression slopes in cohorts of patients with heart failure and preserved ejection fraction (HFpEF) and in control subjects cohorts, stratified by body position. The panel on the top represents the mean PAWP/CO slope of cohorts (both HFpEF and control subjects) studied in the supine position. The panel on the bottom represents the mean PAWP/CO slope of cohorts (both HFpEF and control subjects) studied in the upright position. In both panels the red line represents the proposed normative PAWP/CO slope value of 2 mmHg/L/min.

References

1. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019; **124**: 1598–1617. PMID: 31120821; PMCID: PMC6534165.
2. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010; **3**: 588–595. Epub 2010 Jun 11. PMID: 20543134; PMCID: PMC3048586.
3. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R, Lewis GD. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail*. 2018; **11**: e004750. PMID: 29695381; PMCID: PMC5937988.

4. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation*. 2019; **140**: 353–365. Epub 2019 May 28. PMID: 31132875; PMCID: PMC6684250.
5. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, Perego GB, Bondue A, Senni M, Badano LP, Parati G, Vachiéry JL. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021; **14**: e007555. Epub ahead of print. PMID: 33951935.
6. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grünig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J*. 2017; **50**: 1700578.
7. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. *J Appl Physiol (1985)*. 2016; **121**: 1145–1150. Epub 2016 Oct 7. PMID: 27763874.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009; **62**: e1–e34.
9. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014; **14**: 135.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7**: 177–188.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; **21**: 1539–1558.
12. Stanley TD, Doucouliagos H. Neither fixed nor random: weighted least squares meta-analysis. *Stat Med*. 2015; **34**: 2116–2127.
13. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013; **15**: 776–785. Epub 2013 Feb 20. PMID: 23426022; PMCID: PMC3857919.
14. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O_2 pathway analysis. *Circulation*. 2018; **137**: 148–161. Epub 2017 Oct 9. PMID: 28993402; PMCID: PMC5760316.
15. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017; **136**: 6–19. Epub 2017 Apr 5. PMID: 28381470; PMCID: PMC5501170.
16. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J*. 2018; **39**: 2825–2835. PMID: 29947750; PMCID: PMC6093469.
17. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, Borlaug BA. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J*. 2019; **40**: 3707–3717. PMID: 31513270; PMCID: PMC7963136.
18. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; **21**: 891–900. Epub 2019 Mar 28. PMID: 30919562.
19. van Empel VP, Mariani J, Borlaug BA, Kaye DM. Impaired myocardial oxygen availability contributes to abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2014; **3**: e001293. PMID: 25468660; PMCID: PMC4338724.
20. Wolsk E, Kaye D, Komtebedde J, Shah SJ, Borlaug BA, Burkhoff D, Kitzman DW, Lam CSP, van Veldhuisen DJ, Ponikowski P, Petrie MC, Hassager C, Møller JE, Gustafsson F. Central and peripheral determinants of exercise capacity in heart failure patients with preserved ejection fraction. *JACC Heart Fail.* 2019; **7**: 321–332. Epub 2019 Mar 6. PMID: 30852235.
21. Fermoyle CC, Stewart GM, Borlaug BA, Johnson BD. Pulmonary vascular pressures and gas exchange response to exercise in heart failure with preserved ejection fraction. *J Card Fail*. 2020; **26**: 1011–1015. Epub 2020 Aug 1. PMID: 32750488; PMCID: PMC7704759.
22. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CSP, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail.* 2019; **7**: 239–249. PMID: 30819380.
23. Chen ZW, Huang CY, Cheng JF, Chen SY, Lin LY, Wu CK. Stress echocardiography-derived E/e' predicts abnormal exercise hemodynamics in heart failure with preserved ejection fraction. *Front Physiol*. 2019; **10**: 1470. PMID: 31849715; PMCID: PMC6901703.
24. McCabe C, Oliveira RKF, Rahaghi F, Faria-Urbina M, Howard L, Axell RG, Priest AN, Waxman AB, Systrom DM. Right ventriculo-arterial uncoupling and impaired contractile reserve in obese patients with unexplained exercise intolerance. *Eur J Appl Physiol*. 2018; **118**: 1415–1426. Epub 2018 Apr 30. PMID: 29713818; PMCID: PMC6028899.
25. Nanayakkara S, Haykowsky M, Mariani J, Van Empel V, Maeder MT, Vizi D, Kaye DM. Hemodynamic profile of patients with heart failure and preserved ejection fraction vary by age. *J Am Heart Assoc*. 2017; **6**: e005434. PMID: 28939710; PMCID: PMC5634249.
26. Platz E, Merz A, Silverman M, Lewis E, Groarke JD, Waxman A, Systrom D. Association between lung ultrasound findings and invasive exercise haemodynamics in patients with undifferentiated dyspnoea. *ESC Heart Fail*. 2019; **6**: 202–207. Epub 2018 Nov 26. PMID: 30474936; PMCID: PMC6352886.
27. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, William J, Marwick TH, Kaye DM. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; **21**: 495–505. Epub 2019 Jan 16. PMID: 30652393.
28. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. *Circ Heart Fail*. 2015; **8**: 278–285. Epub 2014 Dec 30. PMID: 25550438; PMCID: PMC4936392.
29. Andersen MJ, Ersbøll M, Gustafsson F, Axelsson A, Hassager C, Køber L, Boesgaard S, Pellikka PA, Møller JE. Exercise-induced changes in left ventricular filling pressure after myocardial infarction assessed with simultaneous right heart catheterization and Doppler echocardiography. *Int J Cardiol*. 2013; **168**: 2803–2810. Epub 2013 Apr 28. PMID: 23628301.
30. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, Olson TP, Borlaug BA. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017; **70**: 136–148. PMID: 28683960; PMCID: PMC5520668.
31. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol*. 2010; **56**: 855–863. PMID: 20813283.
32. Obokata M, Reddy YNV, Shah SJ, Kaye DM, Gustafsson F, Hasenfuβ G,

Hoendermis E, Litwin SE, Komtebedde J, Lam C, Burkhoff D, Borlaug BA. Effects of interatrial shunt on pulmonary vascular function in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2019; **74**: 2539–2550. PMID: 31753198.
33. Sorimachi H, Obokata M, Takahashi N, Reddy YNV, Jain CC, Verbrugge FH, Koepp KE, Khosla S, Jensen MD, Borlaug BA. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur Heart J*. 2021; **42**: 1595–1605. Epub ahead of print. PMID: 33227126.
34. Ahmad A, Corban MT, Toya T, Verbrugge FH, Sara JD, Lerman LO, Borlaug BA, Lerman A. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020; **23**: 765–772. Epub ahead of print. PMID: 32949186.
35. Tschöpe C, Kasner M, Westermann D, Walther T, Gaub R, Poller WC, Schultheiss HP. Elevated NT-ProBNP levels in patients with increased left ventricular filling pressure during exercise despite preserved systolic function. *J Card Fail*. 2005; **11**: S28–S33. PMID: 15948097.
36. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2020; **8**: 657–666. Epub 2020 Jul 8. PMID: 32653449; PMCID: PMC7395878.
37. Houston BA, Tedford RJ. What we talk about when we talk about the wedge pressure. *Circ Heart Fail*. 2017; **10**: e004450. PMID: 28912264.
38. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol*. 2020; **75**: 919–930.
39. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019; **40**: 3297–3317.
40. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018; **138**: 861–870.
41. Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, Farrell R, Shoenike MW, Sbarbaro J, Malhotra R, Nayor M, Tschöpe C, de Boer RA, Lewis GD, Ho JE. Evaluation of 2 existing diagnostic scores for heart failure with preserved ejection fraction against a comprehensively phenotyped cohort. *Circulation*. 2021; **143**: 289–291. Epub 2021 Jan 19. PMID: 33464963; PMCID: PMC8059354.
42. Senni M, Caravita S, Paulus WJ. Do existing definitions identify subgroup phenotypes or reflect the natural history of heart failure with preserved ejection fraction? *Circulation*. 2019; **140**: 366–369. Epub 2019 Jul 29. PMID: 31356132.
43. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc*. 2017; **6**: e006817. PMID: 28862947; PMCID: PMC5586477.
44. Pandey A, Khera R, Park B, Haykowsky M, Borlaug BA, Lewis GD, Kitzman DW, Butler J, Berry JD. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail*. 2018; **6**: 117–126. PMID: 29413366; PMCID: PMC8135913.
45. Wolsk E, Bakkestrøm R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, Hassager C, Møller JE, Gustafsson F. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. *JACC Heart Fail*. 2017; **5**: 337–346.
46. Braunwald E, Grossman W. Clinical aspects of heart failure. In Braunwald E., ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 4th ed. Philadelphia: Sunders; 1992. p 444–463.

Pulmonary artery wedge pressure and left ventricular end-diastolic pressure during exercise in patients with dyspnoea

Claudia Baratto[1], Andrea Faini[1,2], Gianluca P. Gallone[1], Céline Dewachter[3], Giovanni B. Perego[1], Antoine Bondue[3], Denisa Muraru[1,4], Michele Senni[4,5], Luigi P. Badano[1,4], Gianfranco Parati[1,4], Jean-Luc Vachiéry[3] and Sergio Caravita[1,6]

[1]Department of Cardiology, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milan, Italy. [2]Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy. [3]Department of Cardiology, Cliniques Universitaires de Bruxelles, Hôpital Académique Erasme, Brussels, Belgium. [4]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy. [5]Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy. [6]Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy.

Corresponding author: Sergio Caravita (s.caravita@auxologico.it and sergio.caravita@unibg.it)

Shareable abstract (@ERSpublications)
PAWP provides accurate but imprecise estimates for LVEDP during exercise. A combination of PAWP ⩾25 mmHg at peak and/or PAWP/CO slope >2 mmHg·L^{-1}·min^{-1} correctly identify HFpEF patients among those individuals with either PAWP or LVEDP ⩾25 mmHg at peak. https://bit.ly/3wTCSsX

Cite this article as: Baratto C, Faini A, Gallone GP, *et al*. Pulmonary artery wedge pressure and left ventricular end-diastolic pressure during exercise in patients with dyspnoea. *ERJ Open Res* 2023; 9: 00750-2022 [DOI: 10.1183/23120541.00750-2022].

Received: 27 Dec 2022
Accepted: 29 Jan 2023

Abstract

Background Pulmonary artery wedge pressure (PAWP) during exercise, as a surrogate for left ventricular (LV) end-diastolic pressure (EDP), is used to diagnose heart failure with preserved ejection fraction (HFpEF). However, LVEDP is the gold standard to assess LV filling, end-diastolic PAWP ($PAWP_{ED}$) is supposed to coincide with LVEDP and mean PAWP throughout the cardiac cycle ($PAWP_M$) better reflects the haemodynamic load imposed on the pulmonary circulation. The objective of the present study was to determine precision and accuracy of PAWP estimates for LVEDP during exercise, as well as the rate of agreement between these measures.

Methods 46 individuals underwent simultaneous right and left heart catheterisation, at rest and during exercise, to confirm/exclude HFpEF. We evaluated: linear regression between LVEDP and PAWP, Bland–Altman graphs, and the rate of concordance of dichotomised LVEDP and PAWP ⩾ or < diagnostic thresholds for HFpEF.

Results At peak exercise, $PAWP_M$ and LVEDP, as well as $PAWP_{ED}$ and LVEDP, were fairly correlated (R^2>0.69, p<0.01), with minimal bias (+2 and 0 mmHg respectively) but large limits of agreement (±11 mmHg). 89% of individuals had concordant PAWP and LVEDP ⩾ or <25 mmHg (Cohen's κ=0.64). Individuals with either LVEDP or $PAWP_M$ ⩾25 mmHg showed a $PAWP_M$ increase relative to cardiac output (CO) changes ($PAWP_M$/CO slope) >2 mmHg·L^{-1}·min^{-1}.

Conclusions During exercise, PAWP is accurate but not precise for the estimation of LVEDP. Despite a good rate of concordance, these two measures might occasionally disagree.

Introduction

Heart failure with preserved ejection fraction (HFpEF) can be considered a clinical syndrome of cardiovascular ageing, ensuing from a combination of increased left ventricular diastolic stiffness and increased stressed blood volume (or dysfunctional preload) [1–3]. Symptoms may occur despite euvolaemia at physical examination and normal natriuretic peptides, as well as with normal filling pressures at rest, either estimated through echocardiography or directly measured by cardiac catheterisation [4–6]. To overcome this diagnostic challenge, invasive exercise haemodynamic testing has been suggested to unmask HFpEF, allowing to detect a steep increase in pulmonary artery wedge pressure (PAWP), with peak PAWP values ⩾25 mmHg as the hallmark of the disease [5–7]. All this reasoning is based upon the assumption that PAWP approximates left ventricular (LV) end-diastolic pressure (EDP). However, LVEDP reflects LV diastolic stiffness more directly than PAWP, without the interposition of the left atrium (LA) and of the

pulmonary circulation, while PAWP reflects the haemodynamic load imposed by the left heart on the pulmonary vascular bed and on the right heart [8]. Thus, it might be supposed that, during exercise, PAWP and LVEDP may disagree, potentially questioning the diagnosis of HFpEF in a number of individuals, especially when absolute cut-off values are employed, taking into account the methodological heterogeneity in PAWP measurement during exercise haemodynamics across centres, as well as the absence of an undisputed gold-standard reference [9]. Additionally, the accuracy and precision of PAWP as a surrogate of LVEDP has been reported in resting condition only, both for end-diastolic PAWP ($PAWP_{ED}$) and for PAWP averaged over the cardiac cycle, *i.e.* mean PAWP ($PAWP_M$) [10–14]. Thus, the primary aim of our study was to compare LVEDP and PAWP during exercise in a cohort of consecutive patients referred for exercise cardiac catheterisation, in order to assess the validity of the latter as an estimate of the former. Anticipating that PAWP and LVEDP may occasionally disagree, we also exploratively aimed to verify whether additional haemodynamic parameters (*i.e.* flow-normalised PAWP trajectories) may reinforce the diagnosis of HFpEF in patients with either PAWP or LVEDP equal or above the arbitrary pathological threshold of 25 mmHg.

Methods

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2020_04_21_03). We included consecutive patients with exertional breathlessness referred for elective cardiac catheterisation in stable clinical conditions to confirm or exclude the diagnosis of HFpEF, who signed an informed consent for the use of their data for research purposes. Additionally, they needed to have been instrumented with both a Swan–Ganz catheter in the pulmonary artery and a pig-tail catheter in the left ventricle, and to have completed a symptom-limited step-incremental exercise test in the supine position. Finally, they needed to have readable LVEDP at peak exercise. We excluded patients who had not performed a left heart catheterisation, those with reduced LV ejection fraction (<50%), restrictive or hypertrophic or infiltrative cardiomyopathy, congenital heart disease, constrictive pericarditis and myocardial ischaemia, as well as those with a clinical and haemodynamic diagnosis of pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension (PH) [15], more than moderate respiratory disorders, more than mild primary valvular regurgitation and any valvular stenosis. We also excluded unstable patients (non-elective hospitalisation, rapid worsening of symptoms, haemodynamic compromise) and individuals not able to perform a physical exercise on a supine cycle ergometer.

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication to cardiac catheterisation, were abstracted from clinical charts. Echocardiography was performed by experienced cardiologists following current recommendations [16]. Images were stored in digital format for quantitative analysis, which was performed by trained personnel, blinded to clinical and haemodynamic data. The pre-test probability of HFpEF was assessed through the H_2FPEF score [17]. The H_2FPEF score is a continuous score with higher values associated with higher probability of HFpEF. For practical reasons, we considered HFpEF "likely" in those patients with an H_2FPEF score >4 (probability >70%), HFpEF "possible" in those with a H_2FPEF score 2–4 (probability 40–70%) and HFpEF "unlikely" in those with a H_2FPEF score <2 (probability <40%) [4].

Right heart catheterisation

Patients were studied on chronic medications, in the fasting state, without sedation, in supine position. They wore a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA) to measure oxygen consumption directly. A 7-F fluid-filled Swan–Ganz catheter was placed in the pulmonary artery through the right internal jugular vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace as well as by an oxygen saturation >94% sampled at the tip of the catheter. A 5-F pig-tail catheter was placed in the LV through a 6-F right radial artery sheath. The transducers were zeroed at the midthoracic line, halfway between the anterior sternum and the bed surface using a laser caliper. Haemodynamic measurements were performed at rest, after 1 min of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test. The increment in workload was personalised in order to obtain at least three steps of exercise before exhaustion [4]. 2 mL of blood was sampled at the same time from the tip of the Swan-Ganz catheter and from the radial artery, in order to calculate cardiac output (CO) by the direct Fick method.

Pressures were measured at end-expiration and averaged over several (at least five) respiratory cycles. Additionally, PAWP was measured:

- at end-diastole ($PAWP_{ED}$): at mid-A for patients in sinus rhythm, at mid-C – when visible – or at pre-V for patients in atrial fibrillation;
- averaging PAWP throughout the cardiac cycle (mean PAWP or $PAWP_M$).

V waves were measured on the PAWP waveform, and their amplitude was calculated as the difference between the zenith of the V wave and the mean PAWP value. A linear regression was applied to multiple pairs of PAWP and CO points, in order to calculate the PAWP/CO slope [4, 6]. The speed sweep was adapted to visualise LVEDP better despite increasing heart rate during exercise.

Haemodynamic data reflect the agreement of two expert independent readers blinded to patients' data, who visually reviewed all pressure traces offline.

HFpEF was defined by either an end-expiratory $PAWP_M$ or LVEDP >15 mmHg at rest and/or ⩾25 mmHg at peak exercise. In case of disagreement between these two variables at peak exercise, an end-expiratory PAWP/CO slope >2 $mmHg \cdot L^{-1} \cdot min^{-1}$ was considered as an additional haemodynamic parameter indicative of HFpEF [4, 9, 14].

Statistical analysis

Continuous variables are reported as mean±SD when normally distributed and as median (IQR) otherwise. Categorical data are showed as absolute number (%). The agreement and the relationship between LVEDP and PAWP at different conditions was tested by Bland–Altman analysis and linear regression analysis, respectively, while the reliability of agreement was assessed using Cohen's κ.

Results

General characteristics

Out of 96 exercise cardiac catheterisations performed between June 2019 and March 2021, 50 patients presented with exclusion criteria (secondary forms of HFpEF, pulmonary vascular diseases, more than mild primary valvular regurgitation, congenital heart disease). 46 patients fulfilled the inclusion criteria and were analysed.

General clinical characteristics of the study cohort are reported in table 1. Mean age was 71 years, 67% of individuals were females and mean body mass index was 27 $kg \cdot m^{-2}$. Cardiovascular risk factors were well represented (79% with arterial hypertension, 22% obese, 15% with diabetes mellitus or impaired glucose tolerance, 15% with stable coronary artery disease). The majority of patients were in sinus rhythm at the time of cardiac catheterisation. Median brain natriuretic peptide was 106 $ng \cdot L^{-1}$, median LA volume index was 34 $mL \cdot m^{-2}$, mean E/E' was 10 and systolic pulmonary arterial pressure was estimated at 36 mmHg. The pre-test probability of HFpEF, calculated based on the H_2FPEF score, was low in 13%, intermediate in 48% and high in 39% of individuals (figure 1).

Rest and exercise haemodynamics

Rest and exercise end-expiratory haemodynamic data for the whole cohort are reported in table 2.

From rest to peak exercise, end-expiratory $PAWP_M$ increased in median from 14 (9–18) to 33 (26–41) mmHg, $PAWP_{ED}$ from 14 (9–17) to 31 (25–38) mmHg, LVEDP from 15 (10–20) to 30 (25–36) mmHg. Respiratory-averaged $PAWP_M$ increased in median from 10 (6–15) to 26 (22–34) mmHg, $PAWP_{ED}$ from 10 (7–14) to 25 (20–30) mmHg, LVEDP from 13 (8–17) to 26 (21–30) mmHg. CO increased from 4.6 (3.6–5.9) $L \cdot min^{-1}$ at rest to 8.8 (7.1–11.2) $L \cdot min^{-1}$ at peak. 26% of patients had a PAWP V wave amplitude at peak exercise >5 mmHg.

Linear regression analysis and Bland–Altman plot of end-expiratory rest and peak exercise LVEDP *versus* PAWP (both $PAWP_{ED}$ and $PAWP_M$) are reported in the figure 1. Mean bias for end-expiratory $PAWP_{ED}$ *versus* LVEDP at peak exercise was minimal (+0.11 mmHg) but with large confidence intervals (±10.76 mmHg). At peak exercise, end-expiratory $PAWP_M$ overestimated LVEDP by 2 mmHg, again with large confidence intervals (±11.35 mmHg). Linear regression analysis and Bland–Altman plot of respiratory-averaged LVEDP *versus* PAWP are reported in figure 2 (at rest) and figure 3 (peak exercise).

Concordance between LVEDP and PAWP

At rest, 46% of individuals had either an end-expiratory $PAWP_M$ or a LVEDP >15 mmHg, and 57% had a respiratory-averaged $PAWP_M$ and/or a LVEDP >15 mmHg (figure 1). The rate of concordance of these two so-dichotomised measures at rest was 78%, with moderate agreement (Cohen's κ=0.56).

During exercise, 80% and 83% of individuals had either an end-expiratory $PAWP_M$ or LVEDP ⩾25 mmHg. 87% of cases had an end-expiratory $PAWP_M$ and/or LVEDP ⩾25 mmHg (figure 1). The two so-dichotomised measures were concordant in 89% of cases with substantial agreement (Cohen's κ=0.64). In particular, three patients had an end-expiratory $PAWP_M$ ⩾25 mmHg but a LVEDP <25 mmHg, and two

TABLE 1 General characteristics of the study population

Demographics and anthropometrics	
Age years	71±9
Female sex	31 (67)
BMI kg·m^{-2}	27±6
Comorbidities and cardiovascular risk factors	
Obesity	10 (22)
Arterial hypertension	36 (79)
Diabetes mellitus or impaired glucose tolerance	7 (15)
Coronary artery disease	7 (15)
Sinus rhythm	42 (91)
Paroxysmal or persistent atrial fibrillation	9 (20)
Permanent atrial fibrillation	4 (9)
COPD	10 (22)
Blood tests	
Creatinine mg·dL^{-1}	0.9±0.2
Haemoglobin g·dL^{-1}	13.1±1.6
BNP ng·L^{-1}	106 (51–240)
Echocardiography	
Interventricular septum thickness mm	10.4±1.3
Posterior wall thickness mm	9.4±1.3
LV mass index g·m^{-2}	85 (73–103)
LV EDV mL	85 (77–103)
LV ejection fraction %	64±6
LA volume index mL·m^{-2}	34 (26–49)
E/E' avg	10±4
Estimated sPAP mmHg	36±8
HFpEF probability	
H_2FPEF score	4±2
Low	6 (13)
Intermediate	22 (48)
High	18 (39)

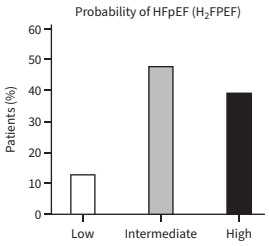
Data are expressed as mean±SD, median (Q_1–Q_3) or n (%). BMI: body mass index; BNP: brain natriuretic peptide; COPD: chronic obstructive pulmonary disease; EDV: end-diastolic volume; HFpEF: heart failure with preserved ejection fraction; LA: left atrium; LV: left ventricle; sPAP: systolic pulmonary arterial pressure.

patients had a LVEDP ⩾25 mmHg but a $PAWP_M$ <25 mmHg. All of these five patients, with discordant $PAWP_M$ and LVEDP, had a $PAWP_M$/CO slope >2 mmHg·L^{-1}·min^{-1}.

Discussion

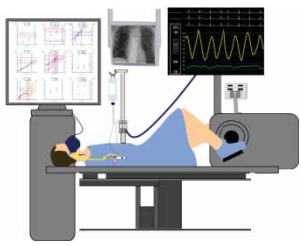
To the best of our knowledge, this is the first study comparing PAWP and LVEDP measurements obtained during exercise. Thus, obtaining LVEDP during supine exercise is feasible in patients with exertional breathlessness and/or suspicion of HFpEF. We could show a good accuracy (minimal mean bias) but a relevant imprecision (large confidence intervals) of PAWP estimates for LVEDP. This result was consistent in several scenarios: 1) both at rest and at peak exercise; and 2) both when these variables were measured at end-expiration (as is commonly done in many US centres [5, 6]) and when they were averaged over the respiratory cycle (as recommended by the European Respiratory Society when large respiratory swings are present, including during physical exercise [18]). The imprecision of PAWP estimates for LVEDP could have contributed to a small but not negligible discordance of these two variables (in 11% of patients) when both were arbitrarily dichotomised at ⩾25 mmHg at end-expiration at peak exercise to diagnose HFpEF. However, our preliminary results suggest that the incorporation of additional measures (*i.e.*, PAWP/CO slope) could overcome such modest discordance: all patients with either PAWP or LVEDP above diagnostic cut-off for LVEDP also had a PAWP/CO slope >2 mmHg·L^{-1}·min^{-1}.

LVEDP represents the operational pressure of the LV at end-diastole. Accordingly, it is generally viewed as a suitable marker of diastolic stiffness, albeit simplifying the gold-standard pressure–volume LV curve to one pressure point [19]. However, this measure is generally felt to be more "invasive" and riskier than PAWP. LVEDP has been rarely employed during exercise for the diagnosis of HFpEF, with lower evidence on pathological LVEDP thresholds to diagnose this disease [5]. Nonetheless, LVEDP measurement might be attractive, since obtaining a reliable PAWP tracing might not always be possible in all patients [14].

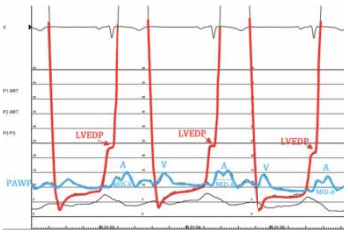


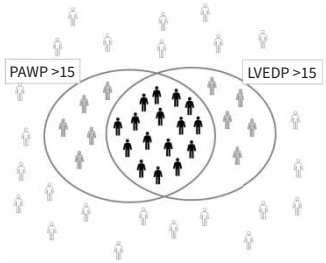
n=46 patients with dyspnoea and preserved LV ejection fraction

Simultaneous RHC and LHC at rest and during exercise



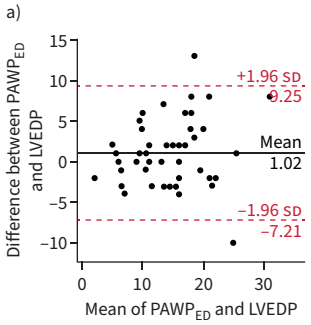
Rest

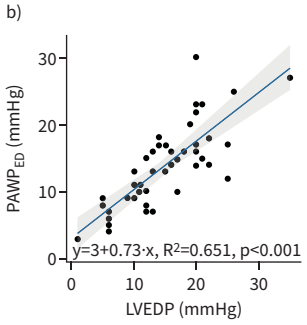


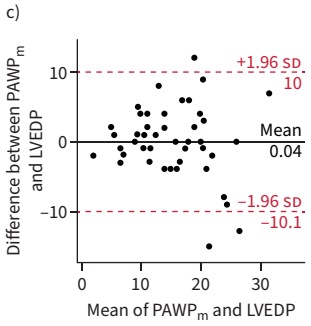


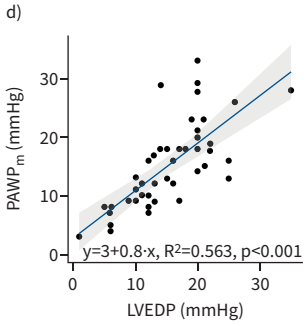
Moderate agreement (Cohen's κ=0.56)

Rest, end-expiratory

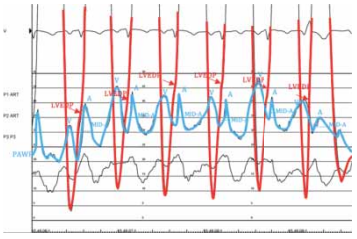


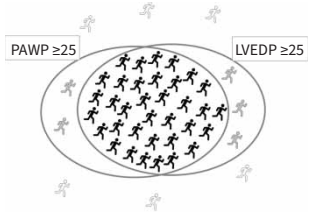


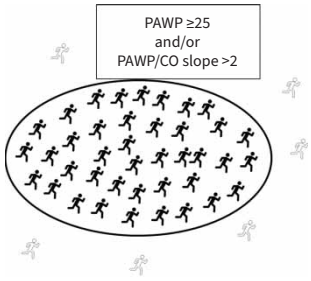




Peak exercise

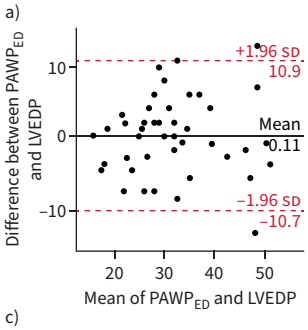


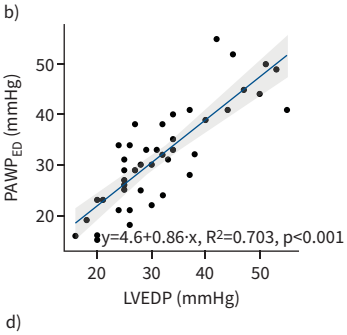


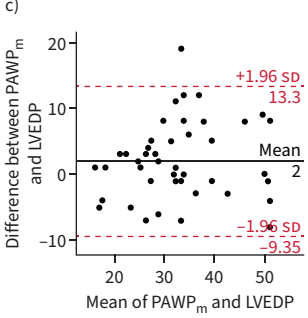


Substantial agreement (Cohen's κ=0.64)

Rest, end-expiratory







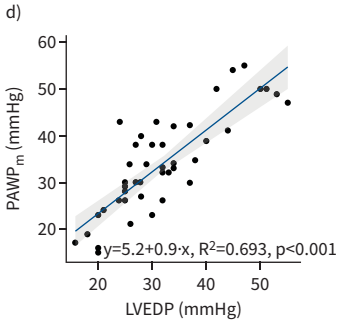


FIGURE 1 Accuracy and precision of end-expiratory $PAWP_{ED}$ and $PAWP_M$ estimates for LVEDP, as well as the rate of agreement of PAWP and LVEDP for the diagnosis of HFpEF at rest and during exercise in our population. The pre-test probability of HFpEF in our cohort was intermediate–high based on the H_2FPEF score. Exemplificative pressure trace recordings (LV pressure, red; PAWP, blue) are shown both at rest and during exercise. Linear regression analysis and Bland–Altman plot of end-expiratory LVEDP *versus* PAWP values are shown both at rest and at peak exercise. Both for rest and peak exercise, a and b) PAWP values are reported both at end-diastole (*i.e.* mid-A wave for patients in sinus rhythm; mid-C or pre-V wave for patients in atrial fibrillation) and c and d) averaged over the cardiac cycle (mean PAWP). Venn diagrams show the agreement of dichotomised PAWP and LVEDP values above the diagnostic threshold to diagnose HFpEF, both at rest and at peak exercise. Agreement between PAWP and LVEDP was higher during exercise than at rest. Despite substantial agreement at peak exercise, five individuals had either PAWP or LVEDP above the diagnostic threshold for HFpEF. All of them presented with a PAWP/CO slope >2 $mmHg \cdot L^{-1} \cdot min^{-1}$, suggesting that incorporation of flow-corrected PAWP in the definition of HFpEF (PAWP ⩾25 mmHg and/or PAWP/CO slope >2 $mmHg \cdot L^{-1} \cdot min^{-1}$) may maximise the diagnostic yield of exercise right heart catheterisation. CO: cardiac output; ED: end-diastolic; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; LVEDP: left ventricular end-diastolic pressure; M: mean; PAWP: pulmonary artery wedge pressure.

Despite this, a left heart catheterisation alone may carry less information than a right heart catheterisation: the latter incorporates pressures and flows of the pulmonary circulation; $PAWP_{ED}$ (mid-A or mid-C) is believed to be a good surrogate of LVEDP; and $PAWP_M$ provides additional information over LVEDP on left heart filling pressures [8]. Indeed, the LA may not be a passive bystander in HFpEF: LA "myopathy", either due to intrinsically reduced LA compliance or to an upward shift of the LA compliance curve, might frequently manifest with tall (systolic) V waves in the PAWP position, increasing $PAWP_M$ well beyond $PAWP_{ED}$ and LVEDP [20, 21]. Accordingly, V wave amplitude >5 mmHg at peak exercise was present in one quarter of our patient population, likely contributing to elevate median $PAWP_M$ slightly above $PAWP_{ED}$ and LVEDP, irrespectively of the respiratory phase. To take into account the role of the LA in the clinical manifestations of HFpEF [20, 21], it seems thus reasonable to prefer end-expiratory $PAWP_M$ over $PAWP_{ED}$ (and LVEDP) for diagnostic purposes.

In analogy to our results obtained during supine exercise, clinical studies comparing PAWP and LVEDP in resting conditions have overall shown a moderate to good accuracy (minimal bias) but a large imprecision (wide limits of agreement) of PAWP estimates for LVEDP [10–14].

Halpern *et al.* [10] reported data from 3926 patients (85% with a PAWP >15 mmHg) with an indication to LV ventriculography or coronary angiography, who were studied over 10 years by 10 physicians, without pressure trace re-reading. PAWP was recorded at rest as a mean pressure ($PAWP_M$), while LVEDP was taken following the A wave "in some patients". They found that, at end-expiration, $PAWP_M$ slightly underestimated LVEDP by 2.9 mmHg.

TABLE 2 Rest and exercise haemodynamics of the study population; end-expiratory pressure measurements are reported

	Rest	Peak exercise
Workload W		50 (40–75)
HR bpm	69 (60–76)	110 (97–122)
HR % of predicted		74 (66–82)
Systolic BP mmHg	144 (136–155)	180 (160–195)
Diastolic BP mmHg	73 (64–80)	87 (75–100)
Mean PAP mmHg	20 (16–25)	40 (37–49)
LVEDP mmHg	15 (10–20)	30 (25–36)
$PAWP_M$ mmHg	14 (9–18)	33 (26–41)
$PAWP_{ED}$ mmHg	14 (9–17)	31 (25–38)
$PAWP_M$/CO slope $mmHg \cdot L^{-1} \cdot min^{-1}$		2.4 (1.8–4.3)
PAWP, V wave mmHg	15 (10–24)	38 (32–48)
Mean RAP mmHg	6 (4–8)	16 (12–22)
CO $L^{-1} \cdot min^{-1}$	4.6±1.5	8.8 (7.1–11.2)
CI $L^{-1} \cdot min^{-1} \cdot m^{-2}$	2.6±0.7	5.1 (4.1–6.2)

Data are expressed as mean±SD or median (Q_1–Q_3). HR: heart rate; BP: blood pressure; PAP: pulmonary arterial pressure; LVEDP: left ventricular end-diastolic pressure; $PAWP_{ED}$: end-diastolic pulmonary artery wedge pressure; $PAWP_M$: mean pulmonary artery wedge pressure; CO: cardiac output; RAP: right atrial pressure; CI: cardiac index.

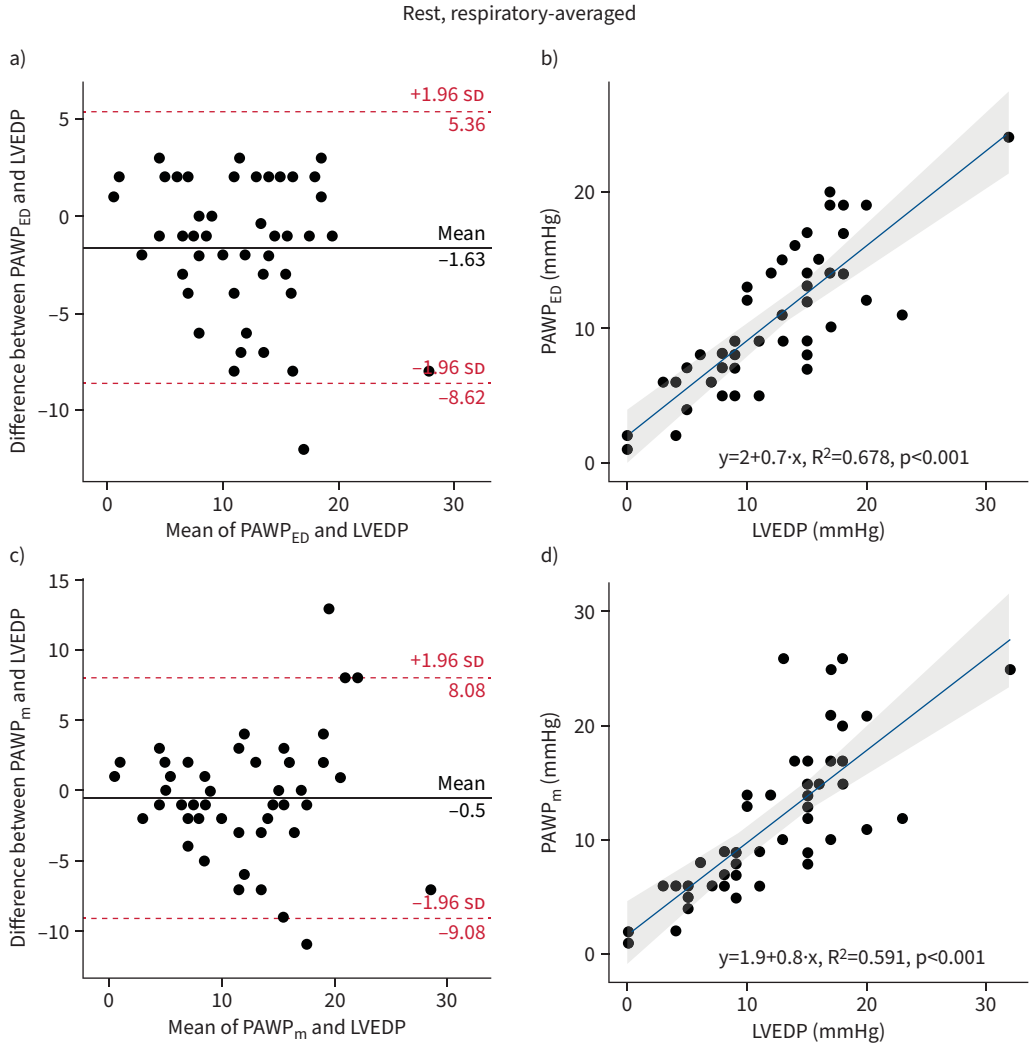


FIGURE 2 Linear regression analysis and Bland–Altman plot of respiratory-averaged LVEDP *versus* PAWP values at rest. Bland-Altman plot and linear regression analysis between end-diastolic PAWP (measured at mid-A in sinus rhythm, at mid-C or pre-V in atrial fibrillation) and LVEDP are shown in panels a) and b). Bland–Altman plot and linear regression analysis between mean PAWP (PAWP averaged over the cardiac cycle) and LVEDP are shown in panels c) and d). LVEDP: left ventricular end-diastolic pressure; $PAWP_{ED}$: end-diastolic pulmonary artery wedge pressure; $PAWP_M$: mean pulmonary artery wedge pressure.

Ryan *et al.* [11] studied 61 patients at rest (59% with PAH), and compared $PAWP_M$ (both end-expiratory and respiratory-averaged) and LVEDP measured at the C-point or at the point of upslope of the R wave at ECG. They found a slight overestimation (by 0.9 mmHg) of $PAWP_M$ *versus* LVEDP when these variables were both measured at end-expiration, and an underestimation (by 4.4 mmHg) when the variables were averaged over several respiratory cycles.

Bitar *et al.* [12] reported computer-generated values of haemodynamics measurements of 101 patients (58% with PH, three-quarters of whom were post-capillary). They found that digitalised, respiratory-averaged $PAWP_M$ underestimated LVEDP by 2.9 mmHg.

Oliveira *et al.* [13] studied 105 patients (79% with PAWP <15 mmHg) and found that, at end-expiration, $PAWP_{ED}$ had a good accuracy (mean bias +0.3 mmHg) to estimate LVEDP, the latter measured at the C-point.

Dickinson *et al.* [14] studied a quite heterogeneous cohort of patients, 57% of whom presented with post-capillary PH. Automated, respiratory-averaged $PAWP_M$ slightly underestimated LVEDP measured at

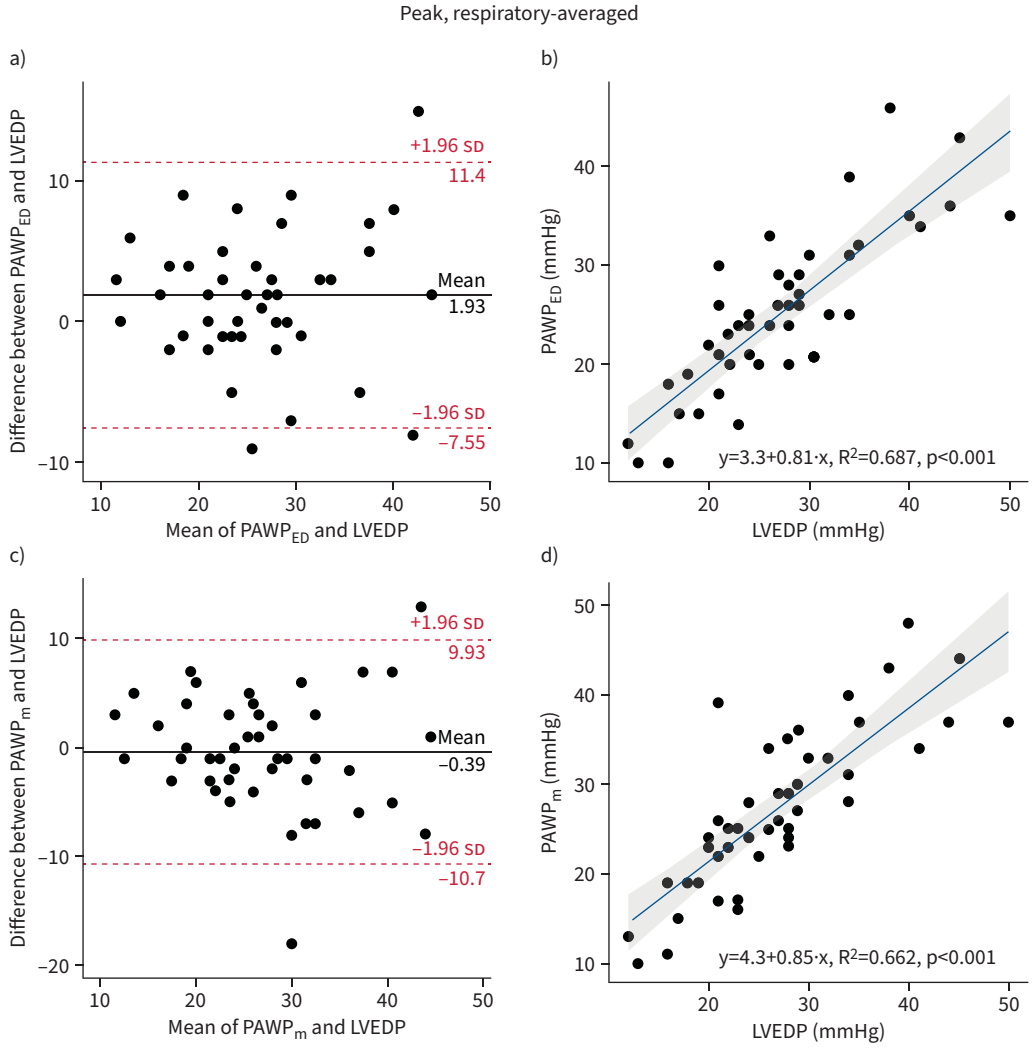


FIGURE 3 Linear regression analysis and Bland–Altman plot of respiratory-averaged LVEDP versus PAWP values at peak exercise. Bland–Altman plot and linear regression analysis between end-diastolic PAWP (measured at mid-A in sinus rhythm, at mid-C or pre-V in atrial fibrillation) and LVEDP are shown in panels a) and b). Bland–Altman plot and linear regression analysis between mean PAWP (PAWP averaged over the cardiac cycle) and LVEDP are shown in panels c) and d). LVEDP: left ventricular end-diastolic pressure; $PAWP_{ED}$: end-diastolic pulmonary artery wedge pressure; $PAWP_M$: mean pulmonary artery wedge pressure.

the Z point by 0.8 mmHg. However, when separating the population based on the presence of sinus rhythm or of atrial fibrillation (the latter as a marker of left atrial dysfunction), they found that respiratory-averaged $PAWP_M$ overestimated LVEDP in atrial fibrillation (by 5 mmHg) and underestimated LVEDP in sinus rhythm (by 3 mmHg).

Thus, results coming from the literature are quite heterogeneous, both in terms of sample size, patients' population being investigated, methodology and timing of pressure measurement over the respiratory and cardiac cycle, as well as results obtained. Indeed, some investigators found a small but potentially relevant underestimation (by 2–4 mmHg) either of respiratory-averaged $PAWP_M$ or end-expiratory $PAWP_M$, one study highlighted an overestimation of LVEDP by PAWP in patients with atrial fibrillation (as a marker of left atrial dysfunction/myopathy), while others showed the absence of a relevant bias of PAWP (especially $PAWP_{ED}$) estimates for LVEDP. However, all the studies are homogeneous in pointing to a relevant imprecision (large confidence intervals) of PAWP estimates for LVEDP in resting condition, indicating that these two measures may not coincide in an individual patient [10–14]. Even though PAWP and LVEDP are supposed to have a similar meaning (and accordingly they are fairly correlated with minimal albeit

potentially relevant bias), intra-individual differences might be expected, either due to intrinsic limitation of pressure measurements with fluid-filled catheters, measurement errors (as for any physiological measurement), or to the fact that PAWP and LVEDP are measured in different sites of the cardiovascular system or in different time frames of the cardiac cycle. Our results, obtained during physical exercise in a quite homogeneous patients' cohort investigated with exertional dyspnoea and/or suspicion of HFpEF, are overall in agreement with these previous reports obtained in resting conditions, by showing large imprecision (wide limits of agreement) and a minimal bias of PAWP (especially of $PAWP_M$), anyhow measured, in comparison with LVEDP.

Notably, a minimal bias, together with the large limits of agreement, may be clinically relevant in those individuals with left heart filling pressure values close to the thresholds adopted to discriminate pre-capillary from post-capillary PH, as well as to diagnose or exclude HFpEF during exercise. This is why provocative testing in the catheterisation laboratory is increasingly integrated with a pre-test probability assessment of HFpEF, in order to obtain a consistent and definitive diagnosis when resting haemodynamics lay in a "grey zone" [22, 23]: the dynamic, multipoint evaluation during provocative manoeuvres may minimise and overcome the impact of aleatory fluctuations in haemodynamics at rest as well as error measurements. In line with this reasoning, the rate of concordance between end-expiratory $PAWP_M$ and LVEDP was slightly higher during exercise than at rest, indirectly highlighting the importance of provocative manoeuvres to unmask HFpEF. Despite this, five individuals (11%) reached either the end-expiratory LVEDP or the $PAWP_M$ threshold $\geqslant$25 mmHg at peak exercise. Interestingly, all of them presented also with a $PAWP_M$/CO slope >2 mmHg as an additional criterion supporting the diagnosis of HFpEF. Even though this is a marginal and exploratory result on a limited sample size, we suggest that incorporation of the PAWP/CO slope in the definition of HFpEF (*e.g.* end-expiratory PAWP $\geqslant$25 mmHg and/or PAWP/CO slope >2 $mmHg \cdot L^{-1} \cdot min^{-1}$) might help support the haemodynamic diagnosis of this condition, possibly overcoming the limitations of a solitary PAWP measurement at peak exercise [4, 16, 24].

Limitations

This study was conducted on a relatively small number of highly selected patients, mainly at intermediate or high pre-test probability of HFpEF based on the H_2FPEF score (48% and 39% of our cohort, respectively), and the majority of them were eventually found to have HFpEF based on exercise haemodynamic results. From a clinical perspective, it represents the cohort of patients in whom LVEDP measurement might be expected to be most informative for diagnostic purposes. However, these results may deserve validation in cohorts of patients without HFpEF, or with additional confounding factors (pre-capillary PH, severe respiratory disorders or severe obesity). Nonetheless, we expect that obtaining LVEDP measures during exercise in patients with a small LV (such as patients with pulmonary vascular diseases) could be more challenging because of a higher likelihood of the pig-tail catheter to mechanically trigger ventricular ectopic beats.

Additionally, we arbitrarily defined as "pathological" an end-expiratory LVEDP at peak $\geqslant$25 mmHg, in the absence of validated reference values for this variable. However, PAWP, whose diagnostic and prognostic role in HFpEF is nowadays undisputed [25], was found to be fairly correlated with LVEDP. Thus, the adoption of an end-expiratory cut-off value at peak $\geqslant$25 mmHg might be reasonable for both variables.

Conclusions

PAWP and LVEDP are fairly correlated both at rest and during exercise in a population with exertional breathlessness and suspicion of HFpEF. While $PAWP_{ED}$ had no relevant bias as compared with LVEDP, $PAWP_M$ slightly overestimated LVEDP, likely due to concomitant left atrial dysfunction, increasing $PAWP_M$ values over end-diastolic values. This adequate accuracy of exercise PAWP *versus* LVEDP (minimal or no bias) is counterbalanced by relevant imprecision. However, the rate of agreement of these variables, dichotomised based on currently adopted PAWP cut-offs to diagnose HFpEF, increases from rest to exercise. In particular, when arbitrarily assuming an end-expiratory cut-off value to diagnose HFpEF of $\geqslant$25 mmHg for both end-expiratory $PAWP_M$ and end-expiratory LVEDP, these two measures might only occasionally disagree, questioning or preventing the diagnosis of HFpEF in a minority of patients. Incorporation of flow-corrected PAWP measures in the definition of HFpEF ($PAWP_M$ $\geqslant$25 mmHg and/or $PAWP_M$/CO slope >2 $mmHg \cdot L \cdot min^{-1}$) might maximise the diagnostic yield of exercise right heart catheterisation especially in those patients with peak PAWP just below 25 mmHg, without the need to resort to a simultaneous left heart catheterisation.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors are indebted with the nurses of the catheterisation laboratory for their support in data acquisition. The authors are grateful to Laboratori Guidotti S.p.A. for providing software free of charge for echocardiographic analysis.

Support statement: This study was supported by the Italian Ministry of Health (5×1000). C. Baratto is the recipient of a research grant from the European Society of Cardiology. A. Bondue received support from the Belgian Fonds de la Recherche Scientifique (grant J.0011.19), from the Erasme Foundation (ULB) and from the Belgian Cardiac Surgery Foundation. J-L. Vachiéry is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: None declared.

References

1 Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011; 32: 670–679.
2 Caravita S, Iacovoni A, Senni M. The right side of the circulation in not secondary heart failure with preserved ejection fraction: an elephant in the room? *Eur J Heart Fail* 2021; 23: 1659–1661.
3 Sorimachi H, Burkhoff D, Verbrugge FH, *et al.* Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2021; 23: 1648–1658.
4 Baratto C, Caravita S, Soranna D, *et al.* Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail* 2021; 14: e007555.
5 Borlaug BA, Nishimura RA, Sorajja P, *et al.* Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010; 3: 588–595.
6 Ho JE, Zern EK, Wooster L, *et al.* Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation* 2019; 140: 353–365.
7 Pieske B, Tschöpe C, de Boer RA, *et al.* How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; 40: 3297–3317.
8 Houston BA, Tedford RJ. What we talk about when we talk about the wedge pressure. *Circ Heart Fail* 2017; 10: e004450.
9 Baratto C, Caravita S, Soranna D, *et al.* Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail* 2022; 9: 3079–3091.
10 Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest* 2009; 136: 37–43.
11 Ryan JJ, Rich JD, Thiruvoipati T, *et al.* Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension. *Am Heart J* 2012; 163: 589–594.
12 Bitar A, Selej M, Bolad I, *et al.* Poor agreement between pulmonary capillary wedge pressure and left ventricular end-diastolic pressure in a veteran population. *PLoS One* 2014; 9: e87304.
13 Oliveira RK, Ferreira EV, Ramos RP, *et al.* Usefulness of pulmonary capillary wedge pressure as a correlate of left ventricular filling pressures in pulmonary arterial hypertension. *J Heart Lung Transplant* 2014; 33: 157–162.
14 Dickinson MG, Lam CS, Rienstra M, *et al.* Atrial fibrillation modifies the association between pulmonary artery wedge pressure and left ventricular end-diastolic pressure. *Eur J Heart Fail* 2017; 19: 1483–1490.
15 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2022; 43: 3618–3731.
16 Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16: 233–270.
17 Reddy YNV, Carter RE, Obokata M, *et al.* A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; 138: 861–870.
18 Kovacs G, Herve P, Barbera JA, *et al.* An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017; 50: 1700578.
19 Bastos MB, Burkhoff D, Maly J, *et al.* Invasive left ventricle pressure-volume analysis: overview and practical clinical implications. *Eur Heart J* 2020; 41: 1286–1297.
20 Reddy YNV, El-Sabbagh A, Nishimura RA. Comparing pulmonary arterial wedge pressure and left ventricular end diastolic pressure for assessment of left-sided filling pressures. *JAMA Cardiol* 2018; 3: 453–454.
21 Baratto C, Caravita S, Perego GB, *et al.* Stiff left atrial syndrome after low-dose radiotherapy for right breast cancer: the need for invasive hemodynamics at exercise. *Catheter Cardiovasc Interv* 2020; 95: 1059–1061.
22 Vachiéry JL, Tedford RJ, Rosenkranz S, *et al.* Pulmonary hypertension due to left heart disease. *Eur Respir J* 2019; 53: 1801897.

23 Hsu S, Fang JC, Borlaug BA. Hemodynamics for the heart failure clinician: a state-of-the-art review. *J Card Fail* 2022; 28: 133–148.
24 Caravita S, Baratto C. Understanding mechanisms of fontan failure: exercise hemodynamics to unmask diastolic dysfunction, Again! *Eur J Heart Fail* 2023: 25: 26–29.
25 Verbrugge FH, Omote K, Reddy YNV, *et al.* Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J* 2022; 43: 1941–1951.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 01 March 2023
DOI 10.3389/fcvm.2023.1061118

OPEN ACCESS

EDITED BY
Sylvestre Marechaux,
Lille Catholic University, France

REVIEWED BY
Nicola Riccardo Pugliese,
University of Pisa, Italy
Giacomo Ingallina,
San Raffaele Scientific Institute (IRCCS), Italy

*CORRESPONDENCE
Sergio Caravita
✉ sergio.caravita@unibg.it

SPECIALTY SECTION
This article was submitted to Structural Interventional Cardiology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 04 October 2022
ACCEPTED 06 February 2023
PUBLISHED 01 March 2023

CITATION
Baratto C, Caravita S, Corbetta G, Soranna D, Zambon A, Dewachter C, Gavazzoni M, Heilbron F, Tomaselli M, Radu N, Perelli FP, Perego GB, Vachiéry J-L, Parati G, Badano LP and Muraru D (2023) Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction. *Front. Cardiovasc. Med.* 10:1061118. doi: 10.3389/fcvm.2023.1061118

Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction

Claudia Baratto[1], Sergio Caravita[1,2]*, Giorgia Corbetta[1,3], Davide Soranna[4], Antonella Zambon[4,5], Céline Dewachter[6], Mara Gavazzoni[1], Francesca Heilbron[1], Michele Tomaselli[1], Noela Radu[1], Francesco Paolo Perelli[1,3], Giovanni Battista Perego[1], Jean-Luc Vachiéry[6], Gianfranco Parati[1,3], Luigi P. Badano[1,3] and Denisa Muraru[1,3]

[1]Department of Cardiology, Ospedale San Luca, Istituto Auxologico Italiano IRCCS, Milan, Italy, [2]Department of Management, Information and Production Engineering, University of Bergamo, Bergamo, Italy, [3]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy, [4]Biostatistic Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy, [5]Department of Statistics and Quantitative Methods, Università di Milano-Bicocca, Milan, Italy, [6]Department of Cardiology, Hôpital Académique Erasme, Cliniques Universitaires de Bruxelles, Brussels, Belgium

Background: Both secondary tricuspid regurgitation (STR) and heart failure with preserved ejection fraction (HFpEF) are relevant public health problems in the elderly population, presenting with potential overlaps and sharing similar risk factors. However, the impact of severe STR on hemodynamics and cardiorespiratory adaptation to exercise in HFpEF remains to be clarified.

Aim: To explore the impact of STR on exercise hemodynamics and cardiorespiratory adaptation in HFpEF.

Methods: We analyzed invasive hemodynamics and gas-exchange data obtained at rest and during exercise from HFpEF patients with severe STR (HFpEF-STR), compared with 1:1 age-, sex-, and body mass index (BMI)- matched HFpEF patients with mild or no STR (HFpEF-controls).

Results: Twelve HFpEF with atrial-STR (mean age 72 years, 92% females, BMI 28 Kg/m^2) and 12 HFpEF-controls patients were analyzed. HFpEF-STR had higher ($p < 0.01$) right atrial pressure than HFpEF-controls both at rest (10 ± 1 vs. 5 ± 1 mmHg) and during exercise (23 ± 2 vs. 14 ± 2 mmHg). Despite higher pulmonary artery wedge pressure (PAWP) at rest in HFpEF-STR than in HFpEF-controls (17 ± 2 vs. 11 ± 2, $p = 0.04$), PAWP at peak exercise was no more different (28 ± 2 vs. 29 ± 2). Left ventricular transmural pressure and cardiac output (CO) increased less in HFpEF-STR than in HFpEF-controls (interaction p-value < 0.05). This latter was due to lower stroke volume (SV) values both at rest (48 ± 9 vs. 77 ± 9 mL, $p < 0.05$) and at peak exercise (54 ± 10 vs. 93 ± 10 mL, $p < 0.05$). Despite these differences, the two groups of patients laid on the same oxygen consumption isophlets because of the increased peripheral oxygen extraction in HFpEF-STR ($p < 0.01$). We found an inverse relationship between pulmonary vascular resistance and SV, both at rest and at peak exercise ($R^2 = 0.12$ and 0.19, respectively).

Conclusions: Severe STR complicating HFpEF impairs SV and CO reserve, leading to pulmonary vascular de-recruitment and relative left heart underfilling, undermining the typical HFpEF pathophysiology.

KEYWORDS

right heart catheterization, tricuspid regurgitation, heart failure with preserved ejection faction, exercise, oxygen consumption, hemodynamics

Background

The development of transcatheter interventions might enlarge the number of candidates to tricuspid regurgitation (TR) repair, including elderly patients with several comorbities and secondary TR (STR) (1–4). Among patients with STR, a high prevalence of patients with heart failure with preserved ejection fraction (HFpEF) might be expected: (i) aging represents a strong risk factor both HFpEF (5) and STR (2, 6); (ii) atrial fibrillation is inextricably linked to HFpEF (7) and to atrial-STR (6, 8–13); (iii) long-standing HFpEF may induce pulmonary hypertension (14), which might predispose to ventricular-STR (12, 13, 15). Thus, the clinical manifestations of HFpEF and severe STR may overlap and "confound" each other. Additionally, the net hemodynamic effect of developing STR in patients with an underlying hemodynamic abnormality, such as HFpEF, has not been clarified. Nonetheless, such information might be useful to figure out symptoms' pathophysiology of HFpEF-STR more clearly. In turn, this may allow to better tailor specific interventions in this population that it is expected to grow exponentially in the future, due to the progressive aging of the general population. Thus, the aim of this study was to explore the hemodynamic alterations related to STR in patients with hemodynamically-proven HFpEF by combining right heart catheterization with cardiopulmonary exercise test.

Methods

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2020_04_21_03 approved on April 21st, 2020). All patients signed a written informed consent to allow the use of their clinical data for research purposes.

We analyzed the cohort of patients who underwent an elective, clinically indicated cardiac catheterization at rest and during exercise at Istituto Auxologico Italiano between January 2018 and January 2022.

Cases were the patients with HFpEF and severe STR (HFpEF-STR). HFpEF was defined based on the presence of signs and/or symptoms of heart failure, a left ventricular (LV) ejection fraction (EF) >50%, associated with invasive hemodynamic demonstration of HFpEF. Invasive diagnosis of HFpEF was established in patients with an end-expiratory pulmonary artery wedge pressure (PAWP) at peak exercise equal or higher than 25 mmHg, and/or PAWP/cardiac output (CO) slope higher than 2 mmHg/L/min) (16–18). From 74 patients with HFpEF without severe TR, we selected an equal number of controls for an individual matching to cases (ratio 1:1) considering sex-, age- (±5 years), and body mass index- (±2 Kg/m^2).

We excluded patients with LV EF <50%, secondary forms of HFpEF (cardiomyopathy, infiltrative diseases, pericardial constriction), more than mild left-sided valvular heart disease, congenital heart disease, pulmonary vascular diseases (pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension), pulmonary hypertension due to lung disease and/or hypoxia, severe comorbidities. Additionally, we excluded patients with congenital or acquired primary TR, cardiac implanted electronic device-related TR, and previous tricuspid surgery. Among the cases, we distinguished between atrial- and ventricular-STR, based on the detection of invasive pulmonary artery systolic pressure lower or higher than 50 mmHg (15).

Echocardiography

Echocardiography was performed according to current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography by experienced cardiologists on the same day of the right heart catheterization (19), using a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway). LV and left atrial (LA) volumes were measured using biplane disk summation algorithm on dedicated 4-chamber and 2-chamber apical views, taking care to avoid chamber foreshortening. Right atrial (RA) volume was measured in a right ventricle (RV) -focused 4-chamber view. Echocardiographic evaluation of STR severity was based on an integrative approach considering multiple qualitative and quantitative parameters (6, 20, 21). Due to the retrospective nature of the study, RV dimensions were qualitatively estimated in all patients.

Right heart catheterization and cardiopulmonary exercise test

Patients were studied on optimized medical therapy and in euvolemic state, in non-fasting state, without sedation, and in

Abbreviations: C(a-v)O_2, arteriovenous oxygen difference; CO, cardiac output; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; LVTMP, left ventricular transmural pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; STR, secondary tricuspid regurgitation; TR, tricuspid regurgitation; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption.

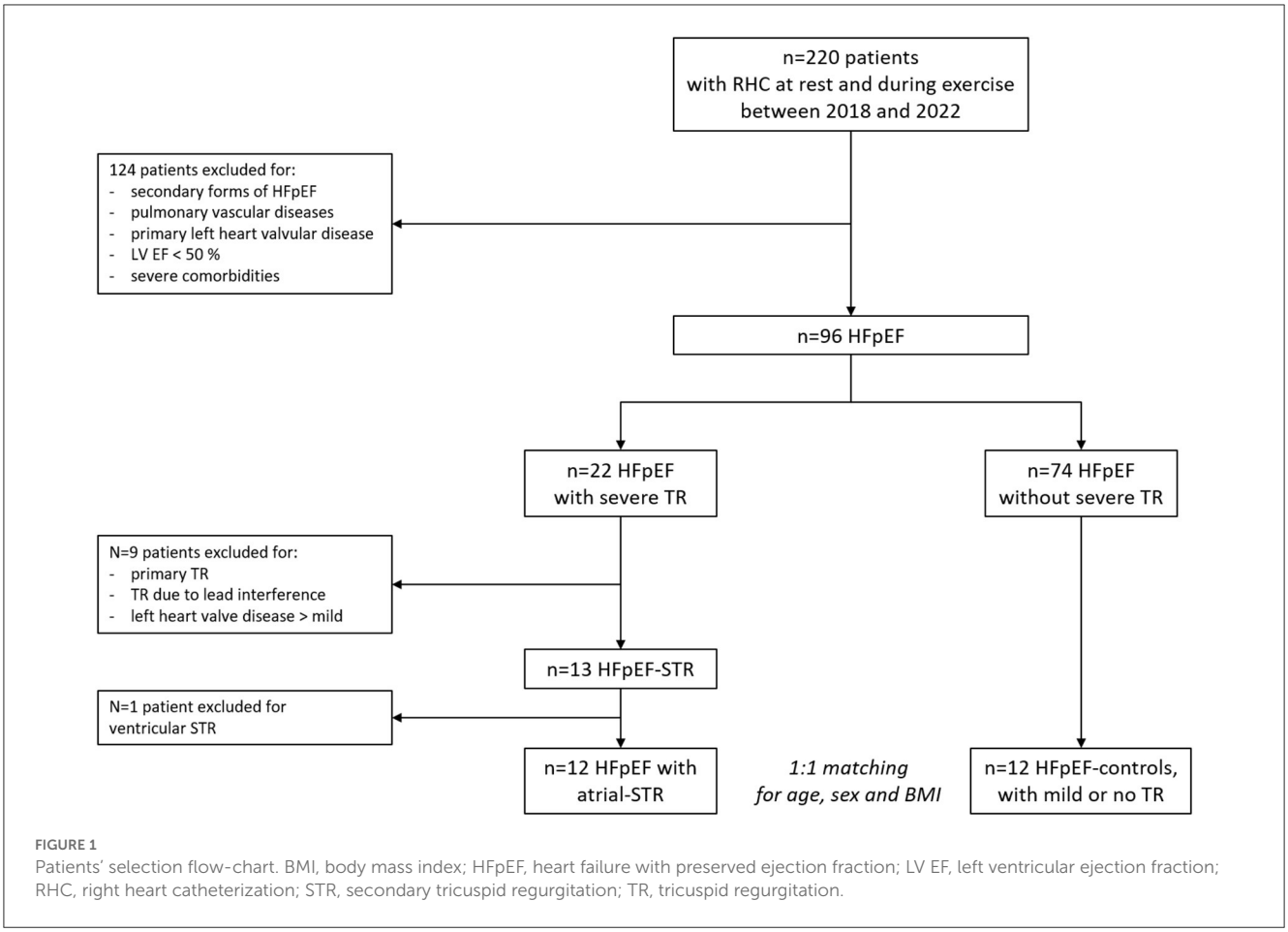


FIGURE 1
Patients' selection flow-chart. BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; LV EF, left ventricular ejection fraction; RHC, right heart catheterization; STR, secondary tricuspid regurgitation; TR, tricuspid regurgitation.

supine position. They wore a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA) to directly measure gas-exchange data and ventilation (17). A 7-F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace as well as by an oxygen saturation >94% sampled at the tip of the catheter. The right radial artery was cannulated with the Seldinger technique. The transducer was zeroed at the midthoracic line, halfway between the anterior sternum and the bed surface. Hemodynamic measurements were performed at rest, after 1 min of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited, maximal exercise test (18). Two milliliters of blood were sampled at the same time from the tip of the Swan-Ganz catheter and from the radial artery for blood gases analysis. The increment in workload was personalized in order to obtain at least three steps of exercise before exhaustion. Subjects were encouraged to exercise up to their maximal volitional effort. Pulmonary artery pressure, PAWP and RA pressure (RAP) were reported as an average of several respiratory cycles (18). Hemodynamic data reflect the agreement of two readers who visually reviewed all pressure traces. CO was calculated by direct Fick method, solving the oxygen consumption (VO_2) equation as follows: $CO = VO_2/C(a\text{-}v)O_2$, where $C(a\text{-}v)O_2$ is the oxygen arteriovenous difference. Furthermore, to evaluate the relative contribution of the elements of the Fick equation to exercise capacity, we plotted CO as a function of $C(a\text{-}v)O_2$ on which we represented VO_2-isophlets (22).

LV trans-mural pressure (LVTMP), as a measure of LV preload, independent of right heart filling and pericardial restraint, was calculated as PAWP–RAP (23). We plotted the relationship between pulmonary vascular resistance (PVR) and stroke volume (SV) to explore whether low anterograde SV may be linked to pulmonary vascular derecruitment and higher than normal PVR (24).

Key ergospirometric measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters. Peak VO_2 was measured as the highest 30-s value obtained at the end of the effort. The slope of the relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) was calculated over the linear component of VE vs. VCO_2 (25).

Statistics

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range if the data did not follow a normal distribution. The categorical variables are shown as absolute frequencies and proportions. For data at rest, unpaired *T*-test (or Wilcoxon signed rank sum test in

TABLE 1 Clinical characteristics of the study cohort.

	Whole cohort ($n = 24$)	HFpEF-controls ($n = 12$)	HFpEF-STR ($n = 12$)	*P*-value
Anthropometrics and demographics				
Age, years	72 ± 5	72 ± 5	72 ± 5	0.867†
Female sex, *n* (%)	22 (92%)	11 (92%)	11 (92%)	1.000¥
BMI, Kg/m^2	28 ± 5	27 ± 4	28 ± 5	0.768†
Comorbidities				
Arterial hypertension, *n* (%)	19 (79%)	9 (75%)	10 (83%)	1.000¥
Diabetes mellitus, *n* (%)	1 (4%)	0 (0%)	1 (8%)	1.000¥
Coronary artery disease, *n* (%)	3 (13%)	2 (17%)	1 (8%)	1.000¥
Paroxysmal/permanent AFib, *n* (%)	12 (50%)	2 (17%)	10 (83%)	0.001‖
Pace-maker, *n* (%)	2 (8)	1 (8)	1 (8)	1.000¥
Previous cardiac surgery, *n* (%)	2 (8)	1 (8)	1 (8)	1.000¥
Treatment				
Furosemide, *n* (%)	16 (68%)	7 (58%)	9 (75%)	0.667¥
Spironolactone, *n* (%)	8 (33%)	4 (33%)	4 (33%)	1.000¥
Hydrochlorothiazide, *n* (%)	3 (13%)	2 (17%)	1 (8%)	1.000¥
ACE-I/ARB, *n* (%)	14 (58%)	7 (58%)	7 (58%)	1.000‖
Beta-blocker, *n* (%)	17 (71%)	6 (50%)	11 (92%)	0.069¥
Oral anticoagulant, *n* (%)	12 (50%)	2 (17%)	10 (83%)	0.001‖
Symptoms				
NYHA class III-IV, *n* (%)	15 (63%)	9 (75%)	6 (50%)	0.400‖
Peripheral edema, *n* (%)	10 (42%)	4 (33%)	6 (50%)	0.408‖
JVD, *n* (%)	3 (13%)	0 (0%)	3 (25%)	0.217¥
Blood tests				
Hemoglobin, g /dL	12.7 ± 1.4	12.7 ± 1.4	12.7 ± 1.5	0.933†
BNP	251 ± 185	220 ± 202	289 ± 168	0.451†
eGFR, mL/min/1.73 m^2	57 ± 20	61 ± 23	54 ± 17	0.457†
AST, mg/dL	23 [21–30]	22.5 [19-25.5]	24 [21–30]	0.204‡
ALT, mg/dL	17.5 [14–26]	17 [13–19]	24.5 [18–40]	0.013‡
Echocardiography				
LVEF, %	63 ± 5	63 ± 5	63 ± 5	0.980†
LVEDVI, mL	47 ± 9	50 ± 8	44 ± 9	0.166†
RV dilation, *n* (%)	8 (38%)	1 (11%)	7 (58%)	0.067¥
LAVI, mL/m^2	44 ± 13	36 ± 10	50 ± 12	0.007†
RAVI, mL/m^2	37 ± 18	25 ± 10	46 ± 18	0.003†
Cardiopulmonary exercise test				
VO_2, % of predicted	74 ± 18	77 ± 21	71 ± 15	0.446†
VO_2, mL/Kg/min	13 ± 4	13 ± 3	12 ± 4	0.690†
CO/VO_2 slope	4.7 ± 1.8	5.5 ± 1.7	3.9 ± 1.5	0.024†
VE/VCO_2 slope	33 ± 5	35 ± 6	32 ± 5	0.327†

Continuous data are shown as mean ± standard deviation or median [interquartile range]. Categorical data are shown as number (percentage).

AFib, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; CO, cardiac output; eGFR, estimated glomerular filtration rate; JVD, jugular vein distension; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; RAVI, right atrial volume index; RV, right ventricle; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption.

† *T*-test; ‡ Wilcoxon test; ‖ Chi-square test; ¥ Fisher test.

10.3389/fcvm.2023.1061118

TABLE 2 Hemodynamics at rest, with feet on the pedals and at peak exercise in the study cohort.

	Rest		Leg raise		Peak	
	HFpEF-controls	HFpEF-STR	HFpEF-controls	HFpEF-STR	HFpEF-controls	HFpEF-STR
HR, bpm	66 ± 4	81 ± 4*	68 ± 4	81 ± 4*	99 ± 6	120 ± 6*
SVI, mL/min/m^2	43 ± 4	28 ± 4*	45 ± 4	32 ± 4*	52 ± 2	32 ± 5*
CI, mL/min/m^2	2.8 ± 0.2	2.2 ± 0.2	2.9 ± 0.2	2.5 ± 0.2	4.9 ± 0.3	3.7 ± 0.3*
C(a-v)O_2, mL/dL	4.2 ± 0.3	5.3 ± 0.3**	4.3 ± 0.3	6.0 ± 0.3**	11.2 ± 0.7	13.3 ± 0.7*
PVR, WU	1.5 ± 0.3	2.1 ± 0.3	1.3 ± 0.3	1.6 ± 0.3	1.1 ± 0.3	1.7 ± 0.3
mPAP, mmHg	18 ± 1	24 ± 1*	23 ± 2	27 ± 2	36 ± 2	39 ± 2
PAWP, mmHg	11 ± 2	17 ± 2*	16 ± 2	21 ± 2	28 ± 2	29 ± 2
LVMTP, mmHg	6 ± 1	7 ± 1	8 ± 1	8 ± 2	13 ± 2	7 ± 2*
RAP, mmHg	5 ± 1	10 ± 1**	8 ± 1	14 ± 1**	14 ± 2	23 ± 2**
RAP V wave, mmHg	6 ± 1	13 ± 1***	9 ± 2	18 ± 2***	17 ± 2	28 ± 2***
RAP/PAWP	0.45 ± 0.08	0.64 ± 0.08	0.52 ± 0.05	0.67 ± 0.05*	0.50 ± 0.06	0.79 ± 0.06**

CI, cardiac index; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LVMTP, left ventricular transmural pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; STR, secondary tricuspid regurgitation; SVI, stroke volume index. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 3 Changes in hemodynamics between rest and feet on the pedals, and between rest and at peak exercise in the study cohort.

	Delta feet on pedals—Rest			Delta peak exercise—Rest		
	HFpEF-controls	HFpEF-STR	*P*-value	HFpEF-controls	HFpEF-STR	*P*-value
HR, bpm	2 ± 4	−0.3 ± 4	0.713	33 ± 4	39 ± 5	0.296
SVI, mL/min/m^2	2 ± 2	4 ± 2	0.519	9 ± 2	4 ± 2	0.174
CI, mL/min/m^2	0.2 ± 0.2	0.3 ± 0.2	0.669	2.2 ± 0.2	1.5 ± 0.2	0.036
C(a-v)O2, mL/dL	0.26 ± 0.47	0.72 ± 0.47	0.492	6.84 ± 0.47	7.69 ± 0.47	0.099
PVR, WU	−0.2 ± 0.2	−0.6 ± 0.2	0.286	−0.5 ± 0.2	−0.4 ± 0.2	0.924
mPAP, mmHg	5 ± 1	4 ± 1	0.562	18 ± 1	15 ± 1	0.167
PAWP, mmHg	5 ± 1	5 ± 1	0.731	17 ± 1	13 ± 1	0.017
LVMTP, mmHg	2 ± 1	1 ± 1	0.548	8 ± 1	0 ± 1	0.0001
RAP, mmHg	4 ± 1	4 ± 1	0.724	9 ± 1	13 ± 1	0.019
RAP V wave, mmHg	3 ± 1	5 ± 1	0.294	11 ± 1	15 ± 1	0.019

CI, cardiac index; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LVMTP, left ventricular transmural pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; STR, secondary tricuspid regurgitation; SVI, stroke volume index.

case of non-normal distribution) was applied to compare the continuous variables between HFpEF-STR and HFpEF-controls, while Chi-square test (or Fisher test) was used to compare the categorical variables. For each hemodynamic variable measured during exercise, an ANOVA model for repeated measures was fitted, considering an unstructured variance-covariance matrix to take into account the correlation among measurements on the same subjects. The included covariates in each model were group (HFpEF-STR or HFpEF-controls), time (Rest, Leg Raise and Peak) and their interaction. The statistical significance of interaction term suggested a different trend of the hemodynamic variables between groups. Moreover, we tested the least square means (LS-means) differences among groups at each time by means of unpaired *t*-test applying the False Discovery Rate (FDR) approach to control the inflation of the type I error.

The relationship between continuous hemodynamic variables at specific time-point was investigated by means quadratic B-spline with 1 knot. The goodness of fit of the model was estimated by means of R2. This value, ranging from 0 to 1, represents the proportion of total variance of an independent variable explained by a dependent variable.

All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All *P*-values were two-sided.

Results

Clinical characteristics

Patients' selection flowchart is depicted in Figure 1. HFpEF-STR represented 14% of our HFpEF population who had

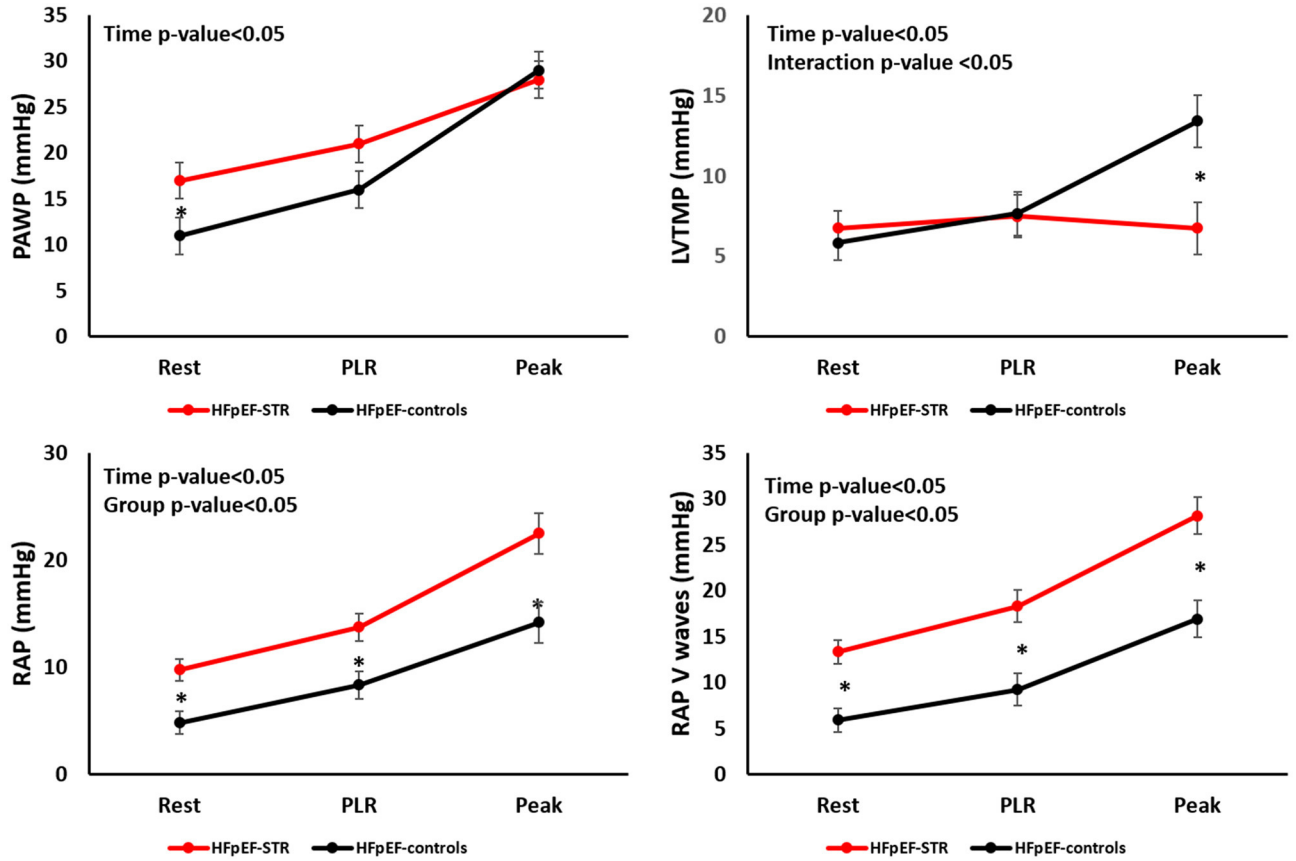


FIGURE 2
Evolution of left and right heart hemodynamics during exercise in our patients' population. HFpEF, heart failure with preserved ejection fraction; LVTMP, left ventricular transmural pressure; PAWP, pulmonary artery wedge pressure; PLR, passive leg raising; RAP, right atrial pressure; STR, secondary tricuspid regurgitation. *$P < 0.05$.

undergone exercise right heart catheterization during the study period. All HFpEF-STR patients but one (who had a typical HFpEF profile, but presented with a systolic PAP >50 mmHg) fulfilled the criteria for atrial-STR. In order to provide results on a more homogeneous patients' phenotype, we excluded from the analysis the patient that presented with a ventricular-STR. Indeed, the analyses focused on HFpEF with atrial-STR as compared with HFpEF-controls.

The clinical characteristics of our study groups are summarized in Table 1. They represented a quite typical elderly, overweight and predominantly female HFpEF population. Of note, 83% of patients with HFpEF-STR had permanent atrial fibrillation, as compared with only 8% of permanent atrial fibrillation in HFpEF-controls ($p < 0.01$). The rhythm at the time of right heart catheterization was atrial fibrillation in 83% of HFpEF-STR and 8% of HFpEF-controls. Among the other cardiovascular comorbidities, arterial hypertension was the most common affecting 75% of HFpEF-controls and 83% of HFpEF-STR patients ($p = 1.000$).

Representation of HF signs and symptoms did not significantly differ between HFpEF-STR and HFpEF-controls (Table 1). Brain natriuretic peptide values were slightly elevated but similar between the groups. Most of the blood test data reflecting secondary organ damage (renal, hepatic) showed similar values in HFpEF-STR as compared with HFpEF-controls. Only alanine aminotransferease values resulted significantly higher in HFpEF-STR patients than in HFpEF-controls. Estimated glomerular filtration rate was lower than expected, especially in HFpEF-STR, but did not significantly differ between the two groups (Table 1).

LV geometry and function were similar between the two groups, while RV dilation was non-significantly more frequent in HFpEF-STR than in HFpEF-controls (58 vs. 11%, $p = 0.067$). As expected, because of the incidence of atrial fibrillation, patients with HFpEF-STR presented larger LA and RA volumes that were, respectively, 43 and 84% larger than in HFpEF-controls (respectively, $p < 0.01$). No patient with HFpEF-STR presented with leaflet tenting.

Right heart catheterization and exercise capacity

Complete hemodynamic data are shown in Table 2 and Supplementary Table 1, while relative changes in hemodynamics from rest to feet on the pedals and between rest and peak are shown in Table 3.

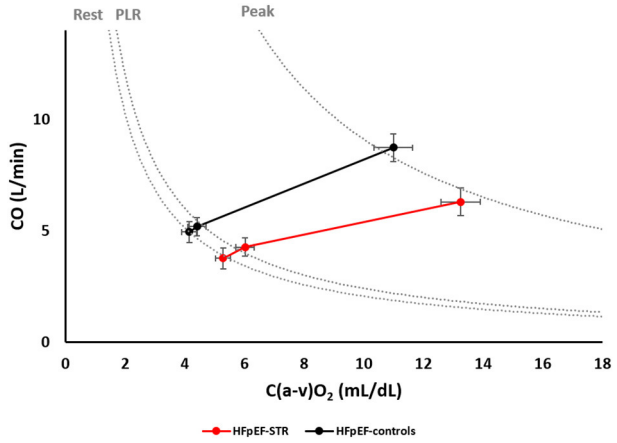


FIGURE 3
Relative weight of cardiac output and arteriovenous oxygen difference in determining oxygen consumption at rest, during passive leg raising and at peak exercise. Dotted lines represent oxygen consumption isophlets, i.e., cardiac output and arteriovenous oxygen difference coordinates whose product is a given oxygen consumption, at rest, during passive leg raising, and at peak exercise. C(a-v)O_2, arteriovenous oxygen difference; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PLR, passive leg raising; STR, secondary tricuspid regurgitation.

At rest, patients with HFpEF-STR had higher mean pulmonary artery pressure (24 ± 1 mmHg vs. 18 ± 1 mmHg, $p = 0.006$) and PAWP (17 ± 2 mmHg vs. 11 ± 2 mmHg, $p = 0.006$) than HFpEF-controls, consistent with mild post-capillary pulmonary hypertension (PH). PH, defined by a mean pulmonary artery pressure >20 mmHg, was present in 83% of HFpEF-STR and in 25% of HFpEF-controls. SV was lower in HFpEF-STR than in HFpEF-controls (28 ± 4 mL vs. 43 ± 4 mL/m^2, $p = 0.03$), which was compensated by higher heart rate (81 ± 4 bpm vs. 66 ± 4 bpm, $p = 0.022$) to maintain cardiac index, which resulted on average at the lower limit of normal in HFpEF-STR (2.2 ± 0.2 L/min/m^2 vs. 2.8 ± 0.2 L/min/m^2, $p = 0.147$). PVR was slightly increased in HFpEF-STR patients but not significantly higher to that of HFpEF-controls (2.1 ± 0.3 WU vs. 1.5 ± 0.3 WU, $p = 0.196$). RAP was twice as high in HFpEF-STR than in HFpEF-controls (10 ± 1 mmHg vs. 5 ± 1 mmHg, $p = 0.007$), with tall V waves (13 ± 1 mmHg vs. 6 ± 1 mmHg, $p < 0.001$) and a high RAP/PAWP ratio (0.64 ± 0.08 vs. 0.45 ± 0.08, $p = 0.079$).

During exercise (Figure 2, Table 3, and Supplementary Table 1), PAWP increased less in HFpEF-STR patients than in HFpEF-controls. Indeed, despite higher PAWP in HFpEF-STR than in HFpEF-controls at rest, at peak exercise PAWP was not different in the two groups (28 ± 2 vs. 29 ± 2, $p = 0.584$). RAP V waves displayed an opposite behavior, increasing more in HFpEF-STR patients than in HFpEF-controls (interaction p-value = 0.06), with persistently higher RAP and RAP/PAWP ratio in HFpEF-STR patients than in HFpEF-controls (group p-value < 0.01). Accordingly, LVTMP increased only in HFpEF-controls during exercise (interaction p-value = 0.006), coherent with LV underfilling in HFpEF-STR patients.

Exercise capacity, as evaluated through peak VO_2, was not different at peak exercise between HFpEF-STR and HFpEF-controls, who reached the 71 and 77% of predicted values, respectively ($p = 0.446$), as shown in Table 1. However, the determinants of VO_2 (Table 2, Supplementary Table 1, and Figure 3) behaved differently in the two groups, with a lower increase in CO and a higher C(a-v)O_2 in HFpEF-STR patients as compared with HFpEF-controls (group p-value < 0.05 for both variables). In particular, HFpEF-STR and HFpEF-controls roughly lay roughly on the same VO_2 isophlets at each step of exercise, with HFpEF-STR rightward and downward shifted (Figure 3). Accordingly, the CO/VO_2 slope, as a measure of CO reserve, was lower in HFpEF-STR patients than in HFpEF-controls (3.9 vs. 5.5, $p = 0.024$). Exercise hyperventilation (VE/VCO2 slope) did not differ between HFpEF-STR and HFpEF-controls.

The SV was lower in HFpEF-STR than in HFpEF-controls (group p-value = 0.018). In particular, at peak exercise, it resulted 40 mL lower in HFpEF-STR ($p = 0.03$). The rate of increase of SV in the two groups however did not significantly differ (Table 3). Similarly, PVR similarly decreased by 0.4–0.5 WU in both groups during exercise. SV and PVR were inversely correlated both at rest and peak, with higher PVR at lower SV (Supplementary Figure 1). However, the low R^2 values (0.12 and 0.19 for rest and peak timepoint, respectively) suggested high heterogenity in the relationship.

Discussion

Our study highlights the hemodynamic impact of developing STR in a cohort of patients with HFpEF. Indeed, in patients with HFpEF, STR was associated with (i) marked RA dilation and RA hypertension, both at rest and during exercise; (ii) reduced SV and CO reserve, with patients relying on heart rate and on peripheral compensation (O_2 extraction) to maintain exercise performance; (iii) pulmonary vascular derecruitment and LV underfilling, leading to lower than expected increase in left heart filling pressure during exercise (Figure 4).

In our relatively small cohort of highly-selected and hemodynamically-proven HFpEF patients who underwent a clinically-indicated right heart catheterization at rest and during exercise, STR prevalence was not irrelevant (14%). The etiology of severe STR was atrial-functional in the great majority of these patients, on whom we decided to focus our analyses. Of note, 83% of patients with atrial-STR had a hemodynamic diagnosis of PH at rest according to the new definition (14), even though the degree of mean pulmonary artery pressure elevation was only mild, and no patient presented with leaflet tenting. Indeed, the definition of atrial-STR (previously known as isolated TR) (6, 8–15) relies on exclusion of other more commonly known secondary causes of TR and on an imprecise echocardiographic surrogate to exclude severe PH, i.e., a systolic pulmonary artery pressure <50 mmHg (15). This distinction between ventricular-STR and atrial-STR may be better refined in the future, taking advantage of 3D reconstruction of the RV, the RA and of the tricuspid annulus, and considering the relative contribution of each of these elements in the pathogenesis of TR, as well as more precise measures of RV afterload.

10.3389/fcvm.2023.1061118

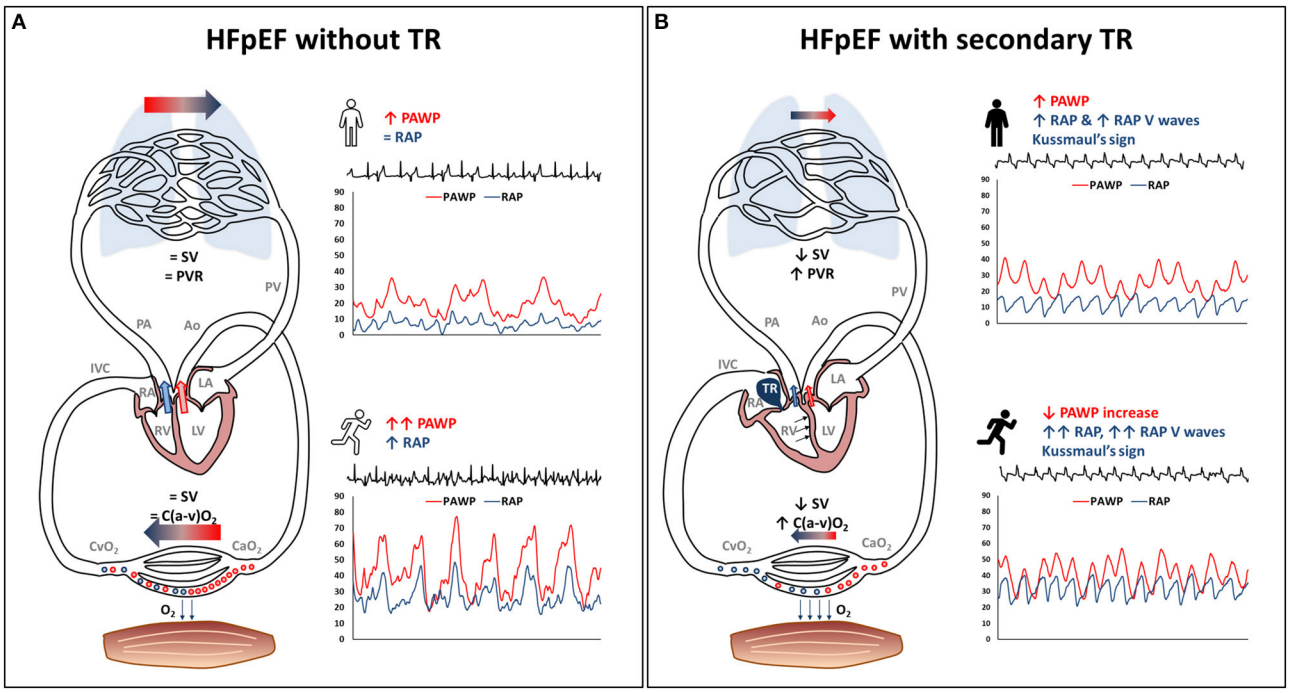


FIGURE 4
Exercise pathophysiology of secondary tricuspid regurgitation (STR) in heart failure with preserved ejection fraction (HFpEF). The typical HFpEF patient without STR (panel on the left) may present with **(A)** high pulmonary artery wedge pressure, either at rest or during exercise, with a steep pulmonary artery wedge pressure rise, and mildly increased right atrial pressure. **(B)** substantially normal stroke volume, pulmonary vascular resistance and peripheral oxygen extraction. This HFpEF pathophysiology is altered in the presence of STR (panel on the right), being characterized by: (i) high right atrial pressure that lacks inspiratory decrease or may present with overt Kussmaul's sign, tall V waves in the right atrium, right atrial enlargement and venous congestion; (ii) reduced forward stroke volume with pulmonary vascular derecruitment (increasing pulmonary vascular resistance), left ventricular underfilling, flatter pulmonary artery wedge pressure rise during exercise, and high ratio between right atrial pressure and pulmonary artery wedge pressure; (iii) higher reliance upon peripheral oxygen extraction to exercise despite low stroke volumeAo, aorta; C(a-v)O2, arteriovenous oxygen difference; CaO2, arterial oxygen content; CvO2, venous oxygen content; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; O_2, oxygen; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PV, pulmonary vein; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SV, stroke volume; TR, tricuspid regurgitation.

Coherent with the non-negligible prevalence of atrial-STR in our hemodynamically-proven HFpEF population, both atrial-STR and HFpEF share common denominators, such as aging and atrial fibrillation. First, the prevalence of STR increases with age (26). Similarly, HFpEF is a disease of cardiovascular aging (27), which promotes diastolic stiffening of the LV and LA myopathy (28). Second, atrial fibrillation is associated with RA enlargement, negative remodeling of the tricuspid annular-valvular complex, and development of atrial-functional STR (8, 9, 11–13, 29–32). On the other hand, it has been proven that HFpEF diagnosis is a risk factor for the development or the progression of atrial fibrillation (28) and that atrial fibrillation is a strong clue for HFpEF diagnosis (33). Additionally, atrial fibrillation plays a role in HFpEF progression: its persistence may be associated over time with adverse bi-atrial remodeling, volume expansion, development of STR and right ventricular dysfunction (5, 10, 34, 35).

RAP, although often within normal limits in early-stage HFpEF, is generally 2-fold higher in this population than in healthy controls (16). STR causes an additional impact on the right heart of HFpEF patients, elevating RAP by another factor 2 in our HFpEF-STR. Despite this marked RAP elevation both at rest and during exercise, symptoms and peak VO_2 did not relevantly differ between HFpEF-STR patients and HFpEF controls. Nonetheless, HFpEF-STR systematically presented with lower SV, and had to rely more on heart rate and peripheral O_2 extraction [despite this latter being slightly lower than normal (36), pointing to the additional component of peripheral limitation in HFpEF] to maintain an exercise performance similar to HFpEF-controls. This highlights the importance of avoid strict rate-control strategies in HFpEF patients with atrial-STR (37). Additionally, our results suggest that VO_2 at peak exercise might not be an optimal surrogate for STR severity, since HFpEF patients showed an ability to compensate for low CO by increasing peripheral extraction and, consequently, that interventions aimed at reducing STR severity might not necessarily improve peak VO_2 despite improving symptoms, nonetheless reducing muscular fatigue. Furthermore, low SV was associated with pulmonary vascular de-recruitment, that can lead to spuriously increased PVR (24), not necessarily reflecting pulmonary vascular remodeling. Indeed, the rate of decrease in PVR during exercise was similar in the two groups, with HFpEF-STR set at higher PVR values because of low SV. Thus, slightly increased PVR at rest should not necessarily contraindicate transcatheter interventions for the correction of STR (38), albeit potentially indicating a worse patients' profile (39, 40). Finally, low SV together with the marked increase in RAP probably contributed to LV underfilling in HFpEF-STR patients by

reducing LVTMP (23). This apparently counterintuitive finding, that volume-expanded HFpEF-STR patients had actually lower than expected rise in PAWP during exercise, might have clinical implications. Indeed, one might guess that STR may "protect" HFpEF-STR patients from pulmonary congestion, at the expense of reduced forward flow, even though pulmonary congestion might be favored by impaired lymphatic drainage associated with RA hypertension (41). After STR correction, unimpeded LV filling as a result of increased SV, may be associated with a sharp rise in left heart filling pressure with more overt pulmonary congestion, potentially fading the net clinical benefit of tricuspid valve repair.

Study limitations

This is a small, single-center retrospective study, conducted on a highly selected patients' population. To investigate the effect of STR on HFpEF pathophysiology, we sought to limit potential confounders by applying a 1:1 matching for age, sex, and body mass index, as well as rigorously identifying patients with HFpEF using exercise invasive hemodynamics. The careful and precise hemodynamic evaluation we performed, which could provide significant and physiologically-meaningful results, might at least partially compensate for the small sample size, albeit we cannot exclude the possibility of a type II error. However, we could not control for atrial fibrillation, which was expectedly more frequent in HFpEF-STR than in HFpEF-controls, and that might have contributed to some of the above-mentioned hemodynamic differences between these two population, which may eventually represent two extremes of the HFpEF progression (41). Additionally, the limited sample size of our well-characterized population might have hindered to highlight significant differences in some clinical variables between HFpEF-STR and HFpEF-controls. Due to the retrospective nature of the study, patients had only qualitative assessment of RV geometry and function, while three-dimensional evaluation would have been desirable for a better understanding of this complex chamber. Moreover, the use of exercise-stress echocardiography would have improved our understanding of hemodynamic behaviors, especially in terms of ventricular interdependence (42).

Conclusion

Occurrence of atrial-STR in patients with HFpEF is associated with atrial fibrillation. The hemodynamic characteristics at rest and during exercise of HFpEF-STR patients are consistent with afterload-independent right heart failure. Due to low SV, HFpEF-STR have to rely more on heart rate and peripheral O_2 extraction to maintain exercise capacity. Pulmonary vascular resistance in HFpEF-STR may be slightly increased due to pulmonary vascular derecruitment. LV underfilling may lead to lower than expected PAWP. Understanding this peculiar pathophysiology may be relevant in the perspective of transcatheter correction of STR in HFpEF patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2020_04_21_03 approved on April 21st, 2020). All patients signed a written informed consent to allow the use of their clinical data for research purposes.

Author contributions

CB contributed for conceptualization, data curation, investigation, methodology, visualization, and writing the original draft. SC contributed for conceptualization, data curation, investigation, methodology, supervision, and visualization and writing the original draft. GC contributed to data curation, investigation, methodology, and writing—review and editing. DS contributed for data analysis and writing—review and editing. AZ contributed for data analysis and writing—review and editing. CD contributed for supervision and writing—review and editing. MG, FH, MT, NR, and FP contributed to writing—review and editing. GPe contributed to supervision and writing—review and editing. J-LV contributed to conceptualization, supervision, and writing—review and editing. GPa contributed to supervision and writing—review and editing. LB and DM contributed to conceptualization, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was partially supported by the Italian Ministry of Health.

Acknowledgments

The authors are indebted with the nurses of the cath lab for their invaluable support in data acquisition. The authors are grateful to Laboratori Guidotti S.p.A., for providing free-of-charge software for echocardiographic analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GI declared a shared parent affiliation with the authors CB, SC, GC, DS, AZ, MG, FH, MT, NR, FP, GPe, GPa, LB, and DM to the handling editor at the time of the review.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1061118/full#supplementary-material

References

1. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. ESC/EACTS scientific document group. ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J.* (2022) 43:561–632. doi: 10.1093/ejcts/ezac209

2. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V, et al. Transcatheter treatment for tricuspid valve disease. *EuroIntervention.* (2021) 17:791–808. doi: 10.4244/EIJ-D-21-00695

3. Russo G, Taramasso M, Pedicino D, Gennari M, Gavazzoni M, Pozzoli A, et al. Challenges and future perspectives of transcatheter tricuspid valve interventions: adopt old strategies or adapt to new opportunities? *Eur J Heart Fail.* (2022) 24:442–54. doi: 10.1002/ejhf.2398

4. Ricci F, Bufano G, Galusko V, Sekar B, Benedetto U, Awad WI, et al. Tricuspid regurgitation management: a systematic review of clinical practice guidelines and recommendations. *Eur Heart J Qual Care Clin Outcomes.* (2022) 8:238–48. doi: 10.1093/ehjqcco/qcab081

5. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* (2020) 17:559–73. doi: 10.1038/s41569-020-0363-2

6. Caravita S, Figliozzi S, Florescu DR, Volpato V, Oliverio G, Tomaselli M, et al. Recent advances in multimodality imaging of the tricuspid valve. *Expert Rev Med Devices.* (2021) 18:1069–81. doi: 10.1080/17434440.2021.1990753

7. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J.* (2019) 40:689–97. doi: 10.1093/eurheartj/ehy809

8. Florescu DR, Muraru D, Volpato V, Gavazzoni M, Caravita S, Tomaselli M, et al. Atrial functional tricuspid regurgitation as a distinct pathophysiological and clinical entity: no idiopathic tricuspid regurgitation anymore. *J Clin Med.* (2022) 11:382. doi: 10.3390/jcm11020382

9. Guta AC, Badano LP, Tomaselli M, Mihalcea D, Bartos D, Parati G, Muraru D. The pathophysiological link between right atrial remodeling and functional tricuspid regurgitation in patients with atrial fibrillation: a three-dimensional echocardiography study. *J Am Soc Echocardiogr.* (2021) 34:585–94. doi: 10.1016/j.echo.2021.01.004

10. Muraru D, Caravita S, Guta AC, Mihalcea D, Branzi G, Parati G, et al. Functional tricuspid regurgitation and atrial fibrillation: which comes first, the chicken or the egg? *CASE.* (2020) 4:458–63. doi: 10.1016/j.case.2020.04.011

11. Muraru D, Guta AC, Ochoa-Jimenez RC, Bartos D, Aruta P, Mihaila S, et al. Functional regurgitation of atrioventricular valves and atrial fibrillation: an elusive pathophysiological link deserving further attention. *J Am Soc Echocardiogr.* (2020) 33:42–53. doi: 10.1016/j.echo.2019.08.016

12. Hahn RT, Badano LP, Bartko PE, Muraru D, Maisano F, Zamorano JL, et al. Tricuspid regurgitation: recent advances in understanding pathophysiology, severity grading and outcome. *Eur Heart J Cardiovasc Imaging.* (2022) 23:913–29. doi: 10.1093/ehjci/jeac009

13. Florescu DR, Muraru D, Florescu C, Volpato V, Caravita S, Perger E, et al. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging.* (2022) 23:930–40. doi: 10.1093/ehjci/jeab211

14. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. ESC/ERS scientific document group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* (2022) 5:ehac237. doi: 10.1183/13993003.00879-2022

15. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation.* (2021) 143:e72–227. doi: 10.1161/CIR.0000000000000923

16. Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, et al. Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail.* (2022). doi: 10.1093/eurheartj/ehac544.810

17. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, et al. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail.* (2021) 14:e007555. doi: 10.1161/CIRCHEARTFAILURE.120.007555

18. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, et al. An official European respiratory society statement: pulmonary haemodynamics during exercise. *Eur Respir J.* (2017) 50:1700578. doi: 10.1183/13993003.00578-2017

19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging.* (2015) 16:233–70. doi: 10.1093/ehjci/jev014

20. Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, et al. Scientific document committee of the European association of cardiovascular imaging. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging.* (2022) 23:e171–232. doi: 10.1093/ehjci/jeab253

21. Zaidi A, Oxborough D, Augustine DX, Bedair R, Harkness A, Rana B, et al. Echocardiographic assessment of the tricuspid and pulmonary valves: a practical guideline from the British Society of Echocardiography. *Echo Res Pract.* (2020) 7:G95–G122. doi: 10.1530/ERP-20-0033

22. Baratto C, Caravita S, Faini A, Perego GB, Senni M, Badano LP, Parati G. Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study. *J Appl Physiol.* (1985). 130:1470–8. doi: 10.1152/japplphysiol.00710.2020

23. Andersen MJ, Nishimura RA, Borlaug BA. The hemodynamic basis of exercise intolerance in tricuspid regurgitation. *Circ Heart Fail.* (2014 N) 7:911–7. doi: 10.1161/CIRCHEARTFAILURE.114.001575

24. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic phenotyping of pulmonary hypertension in left heart failure. *Circ Heart Fail.* (2017) 10:e004082. doi: 10.1161/CIRCHEARTFAILURE.117.004082

25. Caravita S, Faini A, Deboeck G, Bondue A, Naeije R, Parati G, et al. Pulmonary hypertension and ventilation during exercise: role of the pre-capillary component. *J Heart Lung Transplant.* (2017) 36:754–62. doi: 10.1016/j.healun.2016.12.011

26. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging.* (2019) 12:433–42. doi: 10.1016/j.jcmg.2018.06.014

27. Caravita S, Iacovoni A, Senni M. The right side of the circulation in not secondary heart failure with preserved ejection fraction: an elephant in the room? *Eur J Heart Fail.* (2021) 23:1659–61. doi: 10.1002/ejhf.2294

28. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol.* (2020) 76:1051–64. doi: 10.1016/j.jacc.2020.07.009

29. Volpato V, Badano LP, Figliozzi S, Florescu DR, Parati G, Muraru D. Multimodality cardiac imaging and new display options to broaden our understanding of the tricuspid valve. *Curr Opin Cardiol.* (2021) 36:513–24. doi: 10.1097/HCO.0000000000000890

30. Muraru D, Addetia K, Guta AC, Ochoa-Jimenez RC, Genovese D, Veronesi F, et al. Right atrial volume is a major determinant of tricuspid annulus area in functional tricuspid regurgitation: a three-dimensional echocardiographic study. *Eur Heart J Cardiovasc Imaging.* (2021) 22:660–9. doi: 10.1093/ehjci/jeaa286

31. Badano LP, Caravita S, Rella V, Guida V, Parati G, Muraru D. The added value of 3-dimensional echocardiography to understand the pathophysiology

of functional tricuspid regurgitation. *JACC Cardiovasc Imaging.* (2021) 14:683–9. doi: 10.1016/j.jcmg.2020.04.029

32. Muraru D, Parati G, Badano LP. The tale of functional tricuspid regurgitation: when atrial fibrillation is the villain. *Eur Heart J Cardiovasc Imaging.* (2020) 21:1079–81. doi: 10.1093/ehjci/jeaa223

33. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation.* (2018) 138:861–70. doi: 10.1161/CIRCULATIONAHA.118.034646

34. Utsunomiya H, Itabashi Y, Mihara H, Berdejo J, Kobayashi S, Siegel RJ, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. *Circ Cardiovasc Imaging.* (2017) 10:e004897. doi: 10.1161/CIRCIMAGING.116.004897

35. Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, Ivey-Miranda JB, Pereira J, Crandall I, et al. Understanding tricuspid valve remodeling in atrial fibrillation using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging.* (2020) 21:747–55. doi: 10.1093/ehjci/jeaa058

36. Pugliese NR, Mazzola M, Fabiani I, Gargani L, De Biase N, Pedrinelli R, et al. Haemodynamic and metabolic phenotyping of hypertensive patients with and without heart failure by combining cardiopulmonary and echocardiographic stress test. *Eur J Heart Fail.* (2020) 22:458–68. doi: 10.1002/ejhf.1739

37. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM, de La Espriella R, et al. Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. *J Am Coll Cardiol.* (2021) 78:2042–56. doi: 10.1016/j.jacc.2021.08.073

38. Lurz P, Orban M, Besler C, Braun D, Schlotter F, Noack T, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J.* (2020) 41:2785–95. doi: 10.1093/eurheartj/ehaa138

39. Caravita S, Dewachter C, Soranna D, D'Araujo SC, Khaldi A, Zambon A, et al. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. *Eur Respir J.* (2018) 51:1702427. doi: 10.1183/13993003.02427-2017

40. Caravita S, Faini A. Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, et al. Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component. *PLoS ONE.* (2018) 13:e0199164. doi: 10.1371/journal.pone.0199164

41. Omote K, Sorimachi H, Obokata M, Reddy YNV, Verbrugge FH, Omar M, et al. Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiologic implications. *Eur Heart J.* (2022) 3:ehac184. doi: 10.1093/eurheartj/ehac184

42. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation.* (2017) 136:6–19. doi: 10.1161/CIRCULATIONAHA.116.026807

JACC: HEART FAILURE VOL. ■, NO. ■, 2023

ORIGINAL RESEARCH PAPER

Shedding Light on Latent Pulmonary Vascular Disease in Heart Failure With Preserved Ejection Fraction

Sergio Caravita, MD, PhD,[a,b,*] Claudia Baratto, MD,[b,*] Aurora Filippo, MD,[c] Davide Soranna, MSc, PhD,[d] Céline Dewachter, MD, PhD,[e] Antonella Zambon, MSc, PhD,[d,f] Giovanni Battista Perego, MD,[b] Denisa Muraru, MD, PhD,[b,c] Michele Senni, MD,[c,g] Luigi P. Badano, MD, PhD,[b,c] Gianfranco Parati, MD,[b,c] Jean-Luc Vachiéry, MD,[e] Marat Fudim, MD, PhD[h,i]

ABSTRACT

BACKGROUND Among patients with heart failure with preserved ejection fraction (HFpEF), a distinct hemodynamic phenotype has been recently described, ie, latent pulmonary vascular disease (HFpEF-latentPVD), defined by exercise pulmonary vascular resistance (PVR) >1.74 WU.

OBJECTIVES This study aims to explore the pathophysiological significance of HFpEF-latentPVD.

METHODS The authors analyzed a cohort of patients who had undergone supine exercise right heart catheterization with cardiac output (CO) measured by direct Fick method, between 2016 and 2021. HFpEF-latentPVD patients were compared with HFpEF control patients.

RESULTS Out of 86 HFpEF patients, 21% qualified as having HFpEF-latentPVD, 78% of whom had PVR >2 WU at rest. Patients with HFpEF-latentPVD were older, with a higher pretest probability of HFpEF, and more frequently experienced atrial fibrillation and at least moderate tricuspid regurgitation ($P < 0.05$). PVR trajectories differed between HFpEF-latentPVD patients and HFpEF control patients ($P_{interaction} = 0.008$), slightly increasing in the former and reducing in the latter. HFpEF-latentPVD patients displayed more frequent hemodynamically significant tricuspid regurgitation during exercise ($P = 0.002$) and had more impaired CO and stroke volume reserve ($P < 0.05$). Exercise PVR was correlated with mixed venous O_2 tension ($R^2 = 0.33$) and stroke volume ($R^2 = 0.31$) in HFpEF-latentPVD patients. The HFpEF-latentPVD patients had had higher dead space ventilation during exercise and higher $PaCO_2$ ($P < 0.05$), which correlated with resting PVR ($R^2 = 0.21$). Event-free survival was reduced in HFpEF-latentPVD patients ($P < 0.05$).

CONCLUSIONS The results suggest that when CO is measured by direct Fick, few HFpEF patients have isolated latent PVD (ie, normal PVR at rest, becoming abnormal during exercise). HFpEF-latentPVD patients present with CO limitation to exercise, associated with dynamic tricuspid regurgitation, altered ventilatory control, and pulmonary vascular hyperreactivity, portending a poor prognosis. (J Am Coll Cardiol HF 2023;■:■–■) © 2023 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Management, Information and Production Engineering, University of Bergamo, Dalmine, Italy; [b]Department of Cardiology, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milano, Italy; [c]Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy; [d]Biostatistic Unit, IRCCS Istituto Auxologico Italiano, Milano, Italy; [e]Department of Cardiology, Cliniques Universitaires de Bruxelles, Hôpital Académique Erasme, Bruxelles, Belgium; [f]Department of Statistics and Quantitative Methods, Università di Milano-Bicocca, Milano, Italy; [g]Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy; [h]Duke Clinical Research Institute, Durham, North Carolina, USA; and the [i]Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA. *Drs Caravita and Baratto contributed equally to this work.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2023.03.003

ABBREVIATIONS AND ACRONYMS

CO = cardiac output

HFpEF = heart failure with preserved ejection fraction

$PaCO_2$ = arterial partial pressure for carbon dioxide

PAWP = pulmonary artery wedge pressure

PVD = pulmonary vascular disease

PVR = pulmonary vascular resistance

RAP = right atrial pressure

VO_2 = oxygen consumption

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent condition, associated with high left-sided cardiac filling pressure at rest and/or during exercise.[1] Backward transmission of high left cardiac filling pressure to the pulmonary circulation, leading to postcapillary pulmonary hypertension,[2] may promote pulmonary vascular remodeling over time, with increased pulmonary vascular resistance (PVR) and combined postcapillary and precapillary pulmonary hypertension in predisposed individuals.[3,4] The linear association between higher PVR and adverse clinical outcomes[5] recently led the European Society of Cardiology to lower the threshold to identify the precapillary component of pulmonary hypertension (PVR >2 WU).[2] Additionally, a post hoc analysis of the REDUCE LAP-HF II trial (A Study to Evaluate the Corvia Medical, Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients With Heart Failure)[6] highlighted that exercise PVR >1.74 WU may identify a worse clinical and hemodynamic phenotype of HFpEF patients, called HFpEF with latent pulmonary vascular disease (PVD).[7] Individuals with HFpEF-latentPVD may respond poorly to the creation of an interatrial septal defect, and they may not be correctly identified when undergoing only a resting hemodynamic evaluation.[7]

In consequence, there is a need to better understand the pathophysiology of patients with HFpEF and an overt or latent precapillary component, which may help the design of ad hoc treatment for this subgroup of patients at higher risk of adverse events and without any available treatment strategy.[2]

The aim of our study was to explore the clinical characteristics of HFpEF patients with latent PVD, as well as hemodynamic and cardiorespiratory adaptation to exercise of this peculiar phenotype. To do so, we performed a single-center, retrospective data analysis of serial patients with known or newly diagnosed HFpEF in our catheterization laboratory.

METHODS

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2022_09_27_01 approved on September 27, 2022). Signature of informed consent for this data analysis was waived because of the retrospective nature of the study, but at the time of right heart catheterization all patients had signed written informed consent to allow the use of their clinical data for research purposes.

We analyzed the consecutive cohort of patients who underwent an elective, clinically indicated cardiac catheterization at rest and during exercise at Istituto Auxologico Italiano between January 2016 and December 2021.

First, we identified patients who responded to the hemodynamic diagnosis of HFpEF, ie, those with compatible signs and symptoms as well as a pulmonary artery wedge pressure (PAWP) at rest >15 mm Hg, or a PAWP at peak exercise ≥25 mm Hg, or a PAWP/cardiac output (CO) slope >2 mm Hg/L/min.[8,9] Then, we subdivided this cohort of patients based on PVR at peak exercise: >1.74 WU (HFpEF-latentPVD) or ≤1.74 WU (HFpEF control patients).[7]

We excluded patients with left ventricular ejection fraction <50%, secondary forms of HFpEF (cardiomyopathy, infiltrative diseases, pericardial constriction), more than mild left-sided valvular heart disease, congenital heart disease; clinical and hemodynamic diagnosis of pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or chronic thromboembolic pulmonary disease, pulmonary hypertension caused by lung disease and/or hypoxia; severe comorbidities (chronic obstructive pulmonary disease with GOLD classification ≥3, severe restrictive lung disease, severe obesity with body mass index >40 kg/m^2, severe anemia with hemoglobin ≤9 g/dL, end-stage chronic kidney disease), and normal hemodynamics at rest and during exercise.

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication for cardiac catheterization, were analyzed to calculate both the pretest probability of HFpEF based on the H_2FPEF (heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure) score[10] and the HFA-PEFF (Heart Failure Association-Pretest assessment, Echocardiography and Natriuretic Peptide) score.[11] These data were generally collected during the 15 days before cardiac catheterization, provided that no change in clinical status, symptoms, or treatment had occurred

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 31, 2022; revised manuscript received February 27, 2023, accepted March 3, 2023.

TABLE 1 Dichotomization of Hemodynamic Profiles at Rest and During Exercise

	Rest		Peak	
	No	Yes	No	Yes
Pulmonary hypertension	mPAP ≤20 mm Hg	mPAP >20 mm Hg	mPAP/CO slope ≤3	mPAP/CO slope >3
LA hypertension	PAWP ≤15 mm Hg	PAWP >15 mm Hg	PAWP <25 mm Hg and/or PAWP/CO slope ≤2	PAWP ≥25 mm Hg and/or PAWP/CO slope >2
LA dysfunction	PAWP V wave amplitude ≤5 mm Hg	PAWP V wave amplitude >5 mm Hg	PAWP V wave amplitude ≤5 mm Hg	PAWP V wave amplitude >5 mm Hg
Precapillary component	PVR <2 WU	PVR >2 WU	PVR ≤1.74 WU	PVR >1.74 WU
Tricuspid regurgitation	RAP V wave − RAP nadir ≤8 mm Hg	RAP V wave − RAP nadir >8 mm Hg	RAP V wave − RAP nadir ≤8 mm Hg	RAP V wave − RAP nadir >8 mm Hg
Low CO	CI ≥2.2 L/min/m^2	CI <2.2 L/min/m^2	CO ≥80% of predicted	CO <80% of predicted
Low CO increase			CO/VO_2 slope ≥4.7	CO/VO_2 slope <4.7

CI = cardiac index; CO = cardiac output; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; VO_2 = oxygen consumption.

between the noninvasive assessment and cardiac catheterization. The H_2FPEF score[10] is a continuous score with higher values associated with higher probability of HFpEF. For practical reasons, we considered HFpEF "likely" in those patients with a H_2FPEF score >4 (probability >70%), HFpEF "possible" in those with a H_2FPEF score 2 to 4 (probability 40%-70%), and HFpEF "unlikely" in those with a H_2FPEF score <2 (probability <40%). The HFA-PEFF score[11] categorizes patients as HFpEF "likely" (score >4), HFpEF "possible" (score 2-4), and HFpEF "unlikely" (score <2).

ECHOCARDIOGRAPHY. Echocardiography was performed according to current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography by experienced cardiologists,[12] using a Vivid E9/E95 scanners (GE Vingmed). Left ventricular and left atrial volumes were measured by biplane disk summation algorithm on dedicated 4-chamber and 2-chamber apical views, care being taken to avoid chamber foreshortening. Echocardiographic evaluation of valvular regurgitation was based on an integrative approach considering multiple qualitative and quantitative parameters.[13]

RIGHT HEART CATHETERIZATION AND CARDIOPULMONARY EXERCISE TEST. Patients were studied while receiving optimized medical therapy and in a euvolemic nonfasting state, without sedation, and in a supine position. They wore a nonrebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200) to directly measure gas exchange data and ventilation.[8] A 7-F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace and by an O_2 saturation >94% sampled at the tip of the catheter. The right radial artery was cannulated with the Seldinger technique. Hemodynamic measurements were performed at rest, after 1 minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited, maximal exercise test.[8] Blood was sampled from the tip of the Swan-Ganz catheter and from the radial artery for blood gas analysis. The subjects were encouraged to exercise up to their maximal volitional effort.

Key ergospirometric measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters. Peak O_2 consumption (VO_2) was measured as the highest 30-second value obtained at the end of the effort. Minute ventilation was normalized for CO_2 production. Dead space ventilation was calculated based on standard formula.[14]

Pulmonary artery pressure, PAWP, and right atrial pressure (RAP) were measured at end-expiration over several cardiac and respiratory cycles.[8] In addition to end-expiratory mean PAWP and RAP, the diastolic and systolic components of each atrial pressure were evaluated, including the following:

- End-diastolic PAWP and RAP: mid-A for in patients in sinus rhythm and mid-C (when visible) or pre-V for patients in atrial fibrillation
- PAWP V amplitude: the difference between V wave and mean PAWP[8]
- Systolic increase in RAP: the difference between right atrium V wave and RAP nadir, reflecting the severity of tricuspid regurgitation[15]

Hemodynamic data reflect the agreement of 2 readers who visually reviewed all pressure traces. CO was calculated by the direct Fick method, solving the

TABLE 2 Clinical Characteristics of the Study Groups

	HFpEF Control Patients (n = 68)	HFpEF-latentPVD Patients (n = 18)	*P* Value
Demographic and anthropometrics			
Age, y	72 (67-78)	77 (71-81)	0.025
Female	46 (68)	13 (72)	0.710
BMI, kg/m^2	27.0 ± 5.6	26.3 ± 4.6	0.607
Vital signs			
SBP, mm Hg	132 ± 16	130 ± 17	0.602
DBP, mm Hg	75 ± 11	74 ± 12	0.761
HR, mm Hg	70 ± 11	69 ± 10	0.807
Rhythm			0.004
Sinus rhythm	48 (71)	8 (44)	
Paroxysmal AF	12 (18)	1 (6)	
Persistent AF	6 (9)	6 (33)	
Permanent AF	2 (3)	3 (17)	
Comorbidities			
Obesity	20 (29)	2 (11)	0.139
Arterial hypertension	50 (74)	16 (89)	0.221
Diabetes mellitus/impaired glucose tolerance	7 (10)	7 (39)	0.003
Coronary artery disease	9 (13)	5 (28)	0.158
History of pulmonary embolism	5 (7)	2 (11)	0.633
Smoking history	27 (40)	5 (28)	0.420
COPD (only GOLD I-II)	18 (26)	4 (22)	1.000
Obstructive sleep apnea	15 (22)	4 (22)	1.000
Implanted pace-maker	8 (12)	4 (22)	0.266
AF ablation	6 (9)	3 (17)	0.388
Thoracic radiotherapy	9 (13)	2 (11)	1.000
Blood test results			
Hemoglobin, g/dL	13.3 ± 1.6	12.6 ± 1.7	0.103
Creatinine, mg/dL	0.93 (0.81-1.02)	1.07 (0.71-1.29)	0.512
BNP, ng/L	99 (55-210), n = 49/68	88 (42-414), n = 12/18	0.684
proBNP, ng/L	193 (55-408), n= 41/68	673 (304-881), n = 13/18	0.013
Echocardiography			
LVEF, %	64 (62-66)	61 (54-65)	0.007
LVEDVI, mL/m^2	47 (41-64)	46 (42-59)	0.691
IVS thickness, mm	10.3 ± 1.4	10.8 ± 1.0	0.167
PW thickness, mm	9.3 ± 1.2	9.8 ± 1.1	0.176
LAVI, mL/m^2	34 (26-49)	43 (30-51)	0.166
E/E′	9.2 (8.1-12.0)	11.5 (7.7-14.9)	0.236
Estimated PASP, mm Hg	33 (28-45)	40 (35-53)	0.003
Moderate or > moderate TR	19 (28)	11 (61)	0.009
Moderate MR	5 (7)	4 (22)	0.087
Probability of HFpEF			
H_2FPEF score	3.9 ± 2.0	5.1 ± 2.0	0.022
H_2FPEF score >4	36 (53)	13 (72)	0.142
HFA-PEFF score	3.3 ± 2.0	4.8 ± 1.3	0.004
HFA-PEFF score >4	22 (32)	10 (56)	0.070

Values are median (IQR), mean ± SD, or n (%).

AF = atrial fibrillation; BMI = body mass index; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; GOLD = global initiative for obstructive lung disease; HFpEF = heart failure with preserved ejection fraction; HR = heart rate; IVS = interventricular septum; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PW = posterior wall; PASP = pulmonary artery systolic pressure; SBP = systolic blood pressure; TR = tricuspid regurgitation.

O_2 consumption (VO_2) equation as follows: CO = VO_2/arteriovenous O_2 difference. Furthermore, to evaluate the relative contribution of the elements of the Fick equation to exercise capacity, we plotted CO as a function of peripheral O_2 extraction, ie, arteriovenous O_2 difference/arterial O_2 content.[16]

Pivotal hemodynamic variables were also dichotomized (normal vs pathologic) both at rest and during exercise, based on previously described cutoff values, as shown in Table 1. This served to define, during each stage of the test (rest and exercise), the following predefined hemodynamic phenotypes: pulmonary hypertension,[2] left atrial hypertension,[8] left atrial dysfunction as determined by the presence of tall PAWP V waves (V wave amplitude >5 mm Hg) in the absence of significant mitral regurgitation,[8] precapillary pulmonary vascular component,[2,7] severe tricuspid regurgitation,[15] and low CO or low CO increase.[17]

FOLLOW-UP. Relevant clinical events occurring during the follow-up (hospitalization for heart failure, access to the emergency department >12 hours and/or need of intravenous diuretics, death) were captured through a review of electronic medical records by an investigator blinded to the hemodynamic data.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (IQR) if the data did not follow a normal distribution. The categorical variables are shown as absolute frequencies and proportions. For baseline characteristics, comparisons between HFpEF-latentPVD patients and HFpEF control patients were performed by unpaired Student's *t*-test (or Wilcoxon rank sum test in case of nonnormal distribution) for continuous variables and by chi-square test (or Fisher test) for categorical variables. For each hemodynamic variable measured during exercise, a linear mixed-effect model for repeated measures was fitted, considering an unstructured variance-covariance matrix to take into account the correlation among measurements on the same subjects. The included covariates in each model were group (HFpEF-latentPVD patients and HFpEF control patients), step (rest and peak exercise), and their interaction. The statistical significance of interaction term suggested a different trend of the hemodynamic variables between groups. Moreover, we tested the least square means differences among groups at each step by means of unpaired Student's *t*-test.

Kaplan-Meier curves were used to estimate the event-free survival rates in HFpEF-latentPVD

TABLE 3 Resting and Exercise Hemodynamics in the 2 Study Groups

	Rest			Exercise		
	HFpEF Control Patients	HFpEF-latentPVD Patients	*P* Value	HFpEF Control Patients	HFpEF-latentPVD Patients	*P* Value
Hemodynamics						
Mean PAP, mm Hg	20 ± 1	26 ± 2	0.006	41 ± 1	47 ± 2	0.021
End-diastolic PAWP, mm Hg	8 ± 1	8 ± 1	0.797	20 ± 1	23 ± 2	0.292
Mean PAWP, mm Hg	14 ± 1	16 ± 2	0.308	34 ± 1	30 ± 2	0.145
PAWP V amplitude, mm Hg	4 ± 1	5 ± 1	0.171	9 ± 1	9 ± 2	0.933
Mean RAP, mm Hg	7 ± 1	6 ± 1	0.603	17 ± 1	18 ± 2	0.788
End-diastolic RAP, mm Hg	7 ± 1	6 ± 1	0.521	17 ± 1	16 ± 2	0.818
RAP systolic increase, mm Hg	2 ± 1	3 ± 1	0.487	6 ± 1	10 ± 2	0.009
PVR, WU	1.3 ± 0.1	2.4 ± 0.2	<0.001	0.8 ± 0.1	2.6 ± 0.1	<0.001
HR, beats/min	69 ± 2	71 ± 3	0.520	111 ± 3	105 ± 5	0.347
CO, L/min	4.7 ± 0.2	4.3 ± 0.4	0.246	9.7 ± 0.3	6.9 ± 0.6	<0.001
SV, mL	69 ± 3	62 ± 5	0.258	88 ± 3	68 ± 5	0.001
Ventilation and gas exchange						
VO_2, mL	195 ± 15	209 ± 8	0.424	1,097 ± 42	828 ± 80	0.004
PvO_2, mm Hg	40 ± 1	40 ± 1	0.831	25 ± 1	22 ± 1	0.010
SvO_2, %	72 ± 1	69 ± 1	0.073	38 ± 1	30 ± 2	<0.001
$CavO_2$, mL/dL	4.5 ± 0.1	4.6 ± 0.2	0.694	11.4 ± 0.3	12.1 ± 0.5	0.244
$CavO_2/CaO_2$	0.25 ± 0.01	0.28 ± 0.01	0.036	0.60 ± 0.01	0.68 ± 0.02	<0.001
Hb, g/dL	13.4 ± 0.2	12.4 ± 0.4	0.021	14.2 ± 0.2	13.3 ± 0.4	0.076
VE, L/min	8.2 ± 0.4	8.2 ± 0.7	0.971	38.3 ± 1.6	30.8 ± 3.0	0.031
$VECO_2$	55.0 ± 1.9	55.7 ± 3.6	0.866	35.7 ± 0.7	36.2 ± 1.3	0.758
V_D/V_T	0.50 ± 0.06	0.63 ± 0.11	0.328	0.35 ± 0.01	0.40 ± 0.02	0.030
$PaCO_2$, mm Hg	39 ± 1	43 ± 1	0.002	39 ± 1	41 ± 1	0.026

Hb = hemoglobin; $PaCO_2$ = arterial partial pressure for carbon dioxide; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PvO_2 = mixed venous oxygen pressure; PVR = pulmonary vascular resistance; SV = stroke volume; SvO_2 = mixed venous oxygen saturation; V_D/V_T = dead space ventilation; VE = minute ventilation; $VECO_2$ = minute ventilation over CO_2 production; other abbreviations as in Tables 1 and 2.

patients and HFpEF control patients, and, in an exploratory analysis, the differences between groups were evaluated through the log-rank test.

All analyses were performed with SAS version 9.4 software (SAS Institute). Statistical significance was set at the 0.05 level. All *P* values were 2-sided.

RESULTS

CLINICAL CHARACTERISTICS. The patients' selection flowchart is depicted in Supplemental Figure 1. All patients were studied in stable clinical conditions and treatment >30 days. In 91% of cases, right heart catheterization was prescribed as part of a routine evaluation of dyspnea. Only 9% of patients were studied for either worsening symptoms or after a HF hospitalization/need of intravenous diuretic agents in the previous 12 months. HFpEF-latentPVD patients represented 21% of our HFpEF cohort who had undergone exercise right heart catheterization.

The clinical characteristics of our study groups are summarized in Table 2. They represented a typical elderly, overweight, and predominantly female HFpEF population. HFpEF-latentPVD patients were older (77 years [IQR: 71-81 years] vs 72 years [IQR: 67-78 years]; $P = 0.025$), more frequently had atrial fibrillation (56% vs 29%; $P = 0.004$), and had higher probability of HFpEF based both on the HFA-PEFF and the H_2FPEF scores (4.8 ± 1.3 vs 3.3 ± 2.0 and 5.1 ± 2.0 vs 3.9 ± 2.0, respectively; $P < 0.05$).

Albeit within normal limits, left ventricular ejection fraction was lower in HFpEF-latentPVD patients than in HFpEF control patients (61% [IQR: 54%-65%] vs 64% [IQR: 62%-66%]; $P = 0.007$). Additionally, HFpEF-latentPVD patients more frequently had at least moderate tricuspid regurgitation (61% vs 28%; $P = 0.009$) and slightly higher estimated systolic pulmonary artery pressure on echocardiography (40 mm Hg [IQR: 35-53 mm Hg] vs 33 mm Hg [IQR: 28-45 mm Hg]; $P = 0.003$).

Natriuretic peptides were not systematically collected, resulting in some missing data for this variable. ProBNP, but not BNP, was higher in HFpEF-latentPVD patients than in HFpEF control patients.

HEMODYNAMICS AND CARDIORESPIRATORY PROFILE. Complete hemodynamic and cardiorespiratory data at rest and during exercise are shown in Table 3. In 57%

TABLE 4 Dichotomization of Hemodynamic Profiles at Rest and During Exercise

	Rest			Exercise		
	HFpEF Control Patients	HFpEF-latentPVD Patients	*P* Value	HFpEF Control Patients	HFpEF-latentPVD Patients	*P* Value
Pulmonary hypertension	32 (47)	13 (72)	0.068	41 (60)	17 (94)	0.005
LA hypertension	27 (40)	9 (50)	0.431	68 (100)	18 (100)	1.000
LA dysfunction	15 (22)	7 (39)	0.146	38 (56)	15 (83)	0.054
Pre-capillary component	7 (10)	13 (72)	<0.001	0 (0)	18 (100)	<0.001
Tricuspid regurgitation	4 (6)	2 (11)	0.601	11 (16)	9 (50)	0.002
Low CO	20 (29)	8 (44)	0.226	8 (12)	6 (33)	0.028
Low CO increase				20 (29)	10 (56)	0.039

Values are n (%). See Table 1 for resting and exercise threshold definitions.
Abbreviations as in Tables 1 and 2.

of patients the mean PAWP at rest was <15 mm Hg, including 50% of HFpEF-latentPVD patients and 59% of HFpEF control patients ($P = 0.501$). When complete hemodynamic data (rest and exercise data together) were reviewed, all hemodynamic variables increased with exercise ($P < 0.01$) with the exception of PVR.

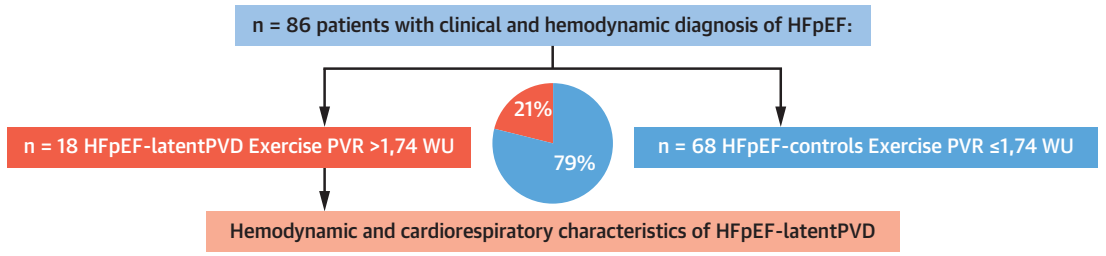
Resting hemodynamics differed between the 2 groups only for mean pulmonary artery pressure and PVR, both of which were higher in HFpEF-latentPVD patients than in HFpEF control patients ($P < 0.05$), at similar PAWP, RAP, CO, and stroke volume values. Even after dichotomization of resting hemodynamic patterns based on preestablished cutoff values (Table 1), the 2 groups presented with similar distributions of left atrial hypertension, tall PAWP V waves, higher systolic increase of RAP, and low CO (Table 4). Pulmonary hypertension was nonsignificantly more represented in latent PVD (72% vs 47%; $P = 0.068$). Interestingly, more HFpEF-latentPVD patients than HFpEF control patients (72% vs 10%; $P < 0.001$) presented with a precapillary component (PVR >2 WU) at rest. Among the 5 patients with HFpEF-latentPVD and normal PVR at rest (6% of the whole cohort), mean PVR at rest was 1.2 ± 0.4 WU.

The results of exercise hemodynamics were strikingly different between the 2 groups, as shown in Tables 3 and 4, Supplemental Table 1, and the Central Illustration, at similar levels of heart rate (73 ± 15% of predicted vs 74 ± 13% of predicted in HFpEF-latentPVD patients vs HFpEF control patients; $P = 0.621$) and lactates (4.3 mmoL/L [IQR: 3.5-4.6 mmoL/L] vs 3.7 mmoL/L [IQR: 2.5-5.0 mmoL/L] in HFpEF-latentPVD patients vs HFpEF control patients; $P = 0.648$).

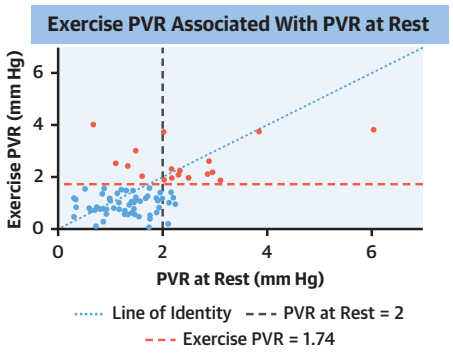
In particular, mean pulmonary artery pressure remained higher in HFpEF-latentPVD patients, despite lower PAWP (Figure 1) and a smaller increase in CO and stroke volume (Figure 2). In HFpEF-latentPVD patients, stroke volume irrelevantly increased with exercise, from 62 mL to 68 mL. All this was mirrored by a lack of decrease of PVR in HFpEF-latentPVD patients as compared with HFpEF control patients, in whom PVR physiologically reduced with exercise (Central Illustration). Mean RAP and end-diastolic RAP increased to similar values in the 2 groups; however, the RAP systolic component rose more steeply and to higher values in HFpEF-latentPVD patients. Dichotomization of exercise hemodynamic patterns based on preestablished cutoff values (Table 1) revealed a higher proportion of pulmonary hypertension, tall PAWP V waves, systolic RAP increase, and low CO in HFpEF-latentPVD patients as compared with HFpEF control patients (Table 4).

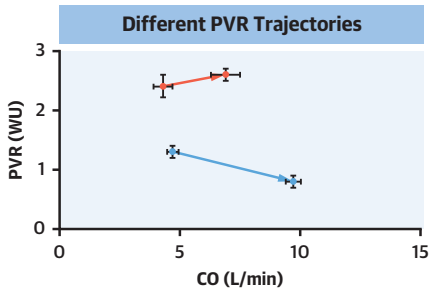
In regard to cardiorespiratory variables, differences related to the underlying group (HFpEF-latentPVD patients vs HFpEF control patients), to the stage of the test (rest vs exercise), and to their interaction were evident, as shown in Table 3 and Supplemental Table 1. As expected, all cardiorespiratory variables changed during exercise ($P < 0.05$). VO_2 increased less in HFpEF-latentPVD patients up to lower values at peak exercise, driven by impaired CO response. Peripheral O_2 extraction showed an opposite behavior, increasing more and to higher values in HFpEF-latentPVD patients, mirrored by opposite mixed venous O_2 saturation and mixed venous partial pressure O_2 pressure trajectories. Arterial partial pressure for carbon dioxide ($PaCO_2$) was higher both at rest and at peak exercise in HFpEF-latentPVD patients. Although minute ventilation increased less in HFpEF-latentPVD patients than in HFpEF control patients, the extent of hyperventilation, as reflected by the ratio between minute ventilation and CO_2 production, was similar in the 2 groups. However, this similar extent of hyperventilation at peak exercise

CENTRAL ILLUSTRATION Hemodynamic and Cardiorespiratory Characteristics of HFpEF-latentPVD Patients

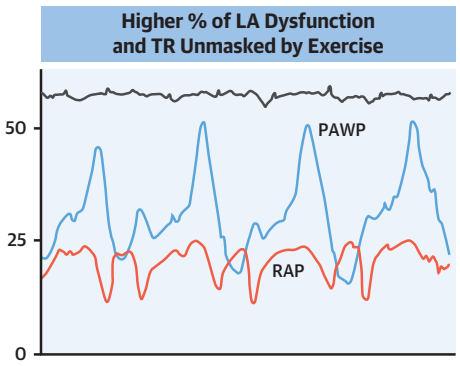


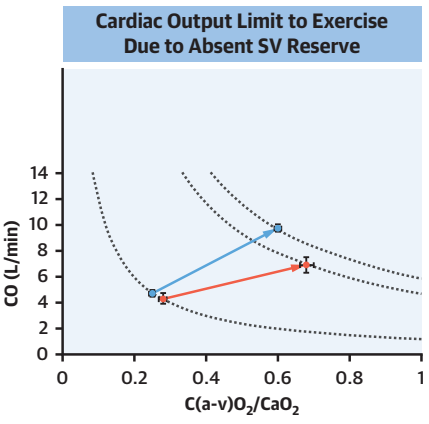
PVR Behavior



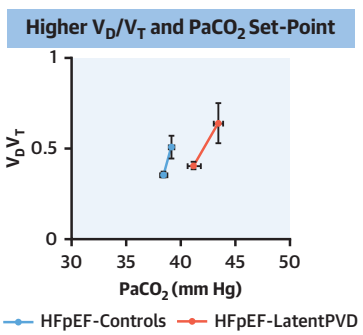


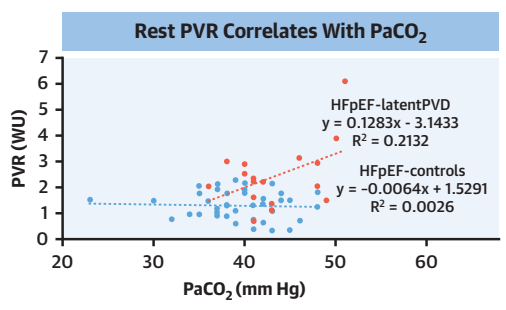
Central Hemodynamics





Ventilation Abnormalities

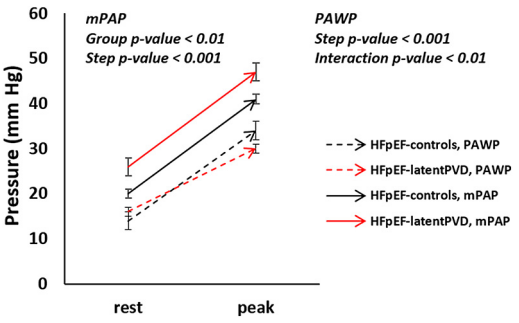




Caravita S, et al. J Am Coll Cardiol HF. 2023;■(■):■-■.

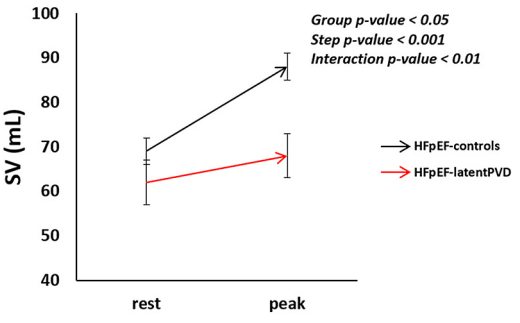
$C(a\text{-}v)O_2/CaO_2$ = peripheral oxygen extraction; CO = cardiac output; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; $PaCO_2$ = arterial partial pressure for carbon dioxide; PAWP = pulmonary artery wedge pressure; PVD = pulmonary vascular disease; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SV = stroke volume; TR = tricuspid regurgitation; V_D/V_T = dead space ventilation.

FIGURE 1 Evolution of Pulmonary Pressures From Rest to Peak Exercise in the 2 Study Groups



HFpEF = heart failure with preserved ejection fraction; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVD pulmonary vascular disease.

FIGURE 2 Evolution of SV From Rest to Peak Exercise in the 2 Study Groups



SV = stroke volume; other abbreviations as in Figure 1.

occurred at higher dead space ventilation and higher $PaCO_2$ in HFpEF-latentPVD patients.

PVR at rest was directly associated with $PaCO_2$ in HFpEF-latentPVD patients only (**Central Illustration**). At peak exercise, PVR was inversely associated with stroke volume and stroke volume index (**Figure 3**) and also with mixed venous O_2 pressure in HFpEF-latentPVD patients only (Supplemental Figure 2).

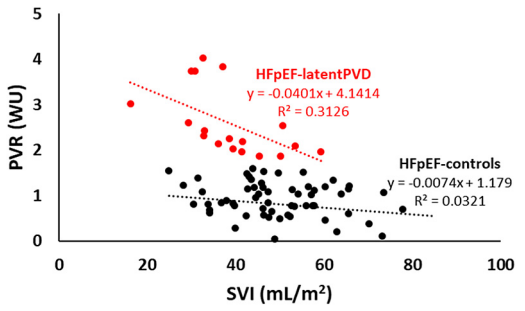
EVENT-FREE SURVIVAL. During a median follow-up of 1,186 (825-1586) days, 12 patients (6 HFpEF-latentPVD patients and 6 HFpEF control patients) experienced an event. The 3-year event-free survival was 72% in HFpEF-latentPVD patients and 93% in HFpEF control patients (**Figure 4**) (log-rank test $P = 0.004$).

DISCUSSION

Our work provides an in-depth analysis of the HFpEF-latentPVD phenotype and expands on a prior description provided by the REDUCE LAP-HF II study[7] in a real-world, single-center population. First, the HFpEF-latentPVD phenotype was present in 21% of our cohort, but in the great majority of cases (ie, 72%), it could have been anticipated by PVR >2 WU at rest. Thus, PVR did not increase during exercise in most of our HFpEF-latentPVD patients. Additionally, the HFpEF-latentPVD hemodynamic phenotype seems to be associated not only with the severity of the HFpEF profile but also with a steep systolic RAP increase during exercise. This feature suggests the presence of tricuspid regurgitation,[15] whose hemodynamic impact may be missed at rest, becoming overtly evident only during exercise and potentially leading to CO limitation and pulmonary vascular derecruitment with high PVR. Moreover, our results may suggest an increased responsivity of the pulmonary vessels to chemical stimuli (O_2 and CO_2) in patients with HFpEF-latentPVD, who presented with signs of altered ventilatory control, that may further contribute to slightly increased PVR. Finally, and irrespective of the pathophysiology behind the HFpEF-latentPVD profile, an exploratory analysis found this hemodynamic phenotype to be associated with worse prognosis.

In our cohort, the HFpEF-latentPVD phenotype was slightly less frequent than in the REDUCE LAP-HF II trial (21% vs 33%). Additionally, as compared with the REDUCE LAP-HF II trial, very few patients with the HFpEF-latentPVD phenotype (6% of our HFpEF cohort) had isolated latent PVD, ie, normal PVR at rest (<2 WU) that became abnormal (>1.74 WU) during exercise. Potential reasons for these discrepant results, among many similarities between our analysis and the analysis provided by Borlaug et al,[7] may be sought in: 1) the selection of the population under analysis; and 2) the methodology of exercise right heart catheterization. First, as compared with the REDUCE LAP-HF II trial, our patients with HFpEF were more frequently studied as a part of a routine evaluation for dyspnea, with very few of them having experienced worsening HF during the previous year (as compared with 43% of patients enrolled in the REDUCE LAP-HF II), showing lower median natriuretic peptide levels and presenting in about half of cases with PAWP <15 mm Hg (as compared with 29% in the REDUCE LAP-HF II). Thus, the more advanced phenotype of patients enrolled in the REDUCE LAP-HF II trial may justify a slightly higher proportion of patients classified as having

FIGURE 3 PVR as a Function of SVI at Peak Exercise



HFpEF-latentPVD patients are depicted in red. HFpEF control patients are depicted in black. PVR = pulmonary vascular resistance; SVI = stroke volume index; other abbreviations as in Figure 1.

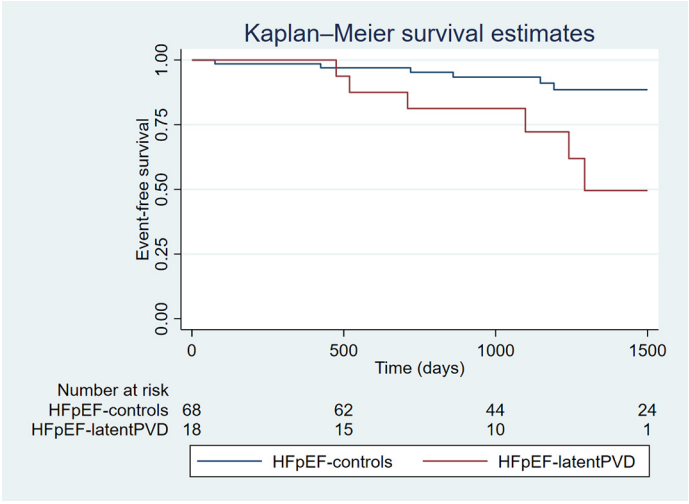
HFpEF-latentPVD. Second, in the REDUCE LAP-HF II trial,[6] CO was measured by a single-shot thermodilution injection at peak exercise, rather than through 3 sets of measurement with <10% variation, which is the standard during right heart catheterization at rest but may be too time consuming in a dynamic scenario such as at peak effort. It has been already demonstrated that thermodilution may underestimate CO during exercise,[18] thus potentially leading to higher than expected PVR, even though the CO findings in our study and in the REDUCE LAP-HF II trial were comparable. However, by measuring CO by the direct Fick method, we could show a relative stability or decrease of PVR in the great majority of our HFpEF-latentPVD patients as compared with resting values, whereas PVR physiologically decreased in our HFpEF control patients.

As a novelty of our study, which expands the previous evidence generated by the post hoc analysis of the REDUCE LAP-HF II trial,[7] we found that the HFpEF-latentPVD phenotype was associated with tricuspid regurgitation. Indeed, tricuspid regurgitation equal or more than moderate, as evaluated through echocardiography, was present in about one-third of our patients, whereas it was an exclusion criterion for the REDUCE LAP-HF II. Tricuspid regurgitation may frequently complicate HFpEF: Obokata et al[19] previously showed how atrial fibrillation, which is frequent in HFpEF,[20] is associated with biatrial remodeling and tricuspid regurgitation in the population with HFpEF. However, there is scarce information on the behavior of tricuspid regurgitation during exercise in HFpEF and on its hemodynamic impact.[21] Indeed, HFpEF patients, albeit not presenting with overt signs of fluid overload, may harbor increased stressed blood volume (functional preload), magnified by physical exercise.[22,23] On the basis of hemodynamic data (systolic RAP increase),[15] we found that the impact of even moderate or severe tricuspid regurgitation might have been missed at rest (no difference between HFpEF-latentPVD patients and HFpEF control patients in terms of systolic RAP increase in resting conditions) but became overtly evident during exercise, when stressed blood volume is shifted from the splanchnic reservoir to the chest,[22,23] affecting first the right heart and the tricuspid annulus. The tricuspid annulus is a virtual structure, largely composed of adipose tissue, with a smaller amount of fibrotic tissue,[24] potentially predisposing it to pathologic dilation when the right ventricle and/or the right atrium dilate.[25-28] Thus, hemodynamically relevant tricuspid regurgitation during exercise, mirrored by a higher systolic RAP increase in HFpEF-latentPVD patients,[15] could help explain an afterload-independent, exercise-induced right ventricular failure. Indeed, the increase in regurgitant volume during exercise would potentially lead to lower forward stroke volume and reduced stroke volume reserve. We may speculate that in the presence of low forward stroke volume, associated with tricuspid regurgitation, CO limitation, and nearly exhausted peripheral O_2 extraction, the low blood O_2 content coming to the pulmonary vessels may favor a certain degree of pulmonary vasoconstriction in HFpEF-latentPVD.[29] This reasoning may partially explain the correlation we found between PVR on one side and stroke volume index as well as mixed venous O_2 pressure on the other side.

As an alternative hypothesis, increased PVR may have contributed to reduced stroke volume and CO in HFpEF-latentPVD patients (as well as to afterload-related tricuspid regurgitation). However, it is important to note that the extent of PVR elevation was mild and relatively stable during exercise in the majority of HFpEF-latentPVD patients and thus was pretty unlikely to cause, per se, right ventricular failure and low CO. HFpEF-latentPVD patients had no stroke volume reserve during exercise and had to rely heavily on peripheral O_2 extraction, whose increase was, however, not enough to compensate for low CO, leading to reduced exercise capacity. In this regard, lower hemoglobin content, once again pointing to a more advanced (and potentially more hemodiluted) HFpEF phenotype, played a role in contributing to a reduction in peak VO_2 in this population.

It is important to point out that other factors may contribute to higher PVR in our HFpEF-latentPVD population. First, we found a higher proportion of patients with pulmonary hypertension during

FIGURE 4 Kaplan-Meier Curves for Event-Free Survival in the Study Groups



Abbreviations as in Figure 1.

exercise, with a (nonsignificantly) higher proportion of tall V waves in the PAWP position in the HFpEF-latentPVD group. We speculate that a stiffer left atrium in HFpEF-latentPVD patients, which is expected based on the higher proportion of atrial fibrillation,[19] may indeed promote pulmonary vasoconstriction and/or vascular remodeling (including venular congestive remodeling[30]) and high PVR. Second, $PaCO_2$ values were higher in HFpEF-latentPVD patients than in HFpEF control patients both at rest and during exercise, and resting $PaCO_2$ correlated with PVR in HFpEF-latentPVD patients. A relationship of a modest age-related pulmonary comorbidity in HFpEF patients and/or an alteration of ventilatory control (reduced chemosensitivity) with the HFpEF-latentPVD phenotype did not emerge from the analysis of the REDUCE LAP-HF II. Despite the known responsiveness of the pulmonary vessels to CO_2, which has been used to explain precapillary pulmonary hypertension in obesity-hypoventilation syndrome,[31] this finding may appear counterintuitive at first glance, inasmuch as previous evidence pointed to augmented exercise hyperventilation in combined postcapillary and precapillary pulmonary hypertension as opposed to isolated postcapillary pulmonary hypertension.[32-35] However, in previous studies, combined postcapillary and precapillary pulmonary hypertension was defined on the basis of older definitions, the studies included younger patients, with heterogeneous left heart disease and more severe hemodynamics (higher mean pulmonary artery pressure and PVR), and $PaCO_2$ was rarely collected at rest and/or during exercise, rather relying on its end-expiratory values. Thus, we may speculate that our older HFpEF-latentPVD patients may present with a slightly blunted chemoreflex response to CO_2 and a higher $PaCO_2$ setpoint. Despite this, their exercise hyperventilation was similar to that of their counterparts without latent PVD, likely as a consequence of increased exercise dead space ventilation in latent PVD. This may imply that the simple evaluation of the relationship of minute ventilation over CO_2 production during a noninvasive cardiopulmonary exercise test may not be able to correctly identify HFpEF-latentPVD patients bearing only a minor increase in PVR.

STUDY LIMITATIONS. This was a retrospective study conducted on a limited number of HFpEF patients, and that may limit the generalizability of our results. Additionally, we reported data from a relatively stable outpatient population of HFpEF patients, with relevant differences from those included in the REDUCE LAP-HF II trial; that may in part explain some divergent results, which nonetheless expand the understanding of this peculiar hemodynamic condition. Moreover, it is important to highlight that most of our results were consistent with those reported in the REDUCE LAP-HF II trial[7] (latent PVD being older, with a higher pretest probability of HFpEF based on validated scores, and more atrial fibrillation). Additionally, all tests were conducted and interpreted by the same cardiologists with a specific training in exercise hemodynamics, adopting gold-standard methodology.

Given that patients with isolated latent PVD (PVR <2 WU at rest and >1.74 WU at peak) were only 6% of our cohort, this analysis was unable to determine the clinical and hemodynamic characteristics of this subgroup; rather, we focused on all patients with exercise PVR >1.74 WU.

Again, due to the retrospective nature of our study, echocardiographic characterization of the right heart, which would benefit from a 3-dimensional analysis,[12] was not systematically available, even though it would have added additional insights into the HFpEF-latentPVD phenotype.

We relied on hemodynamic signs of tricuspid regurgitation during exercise rather than on its direct echocardiographic visualization. The cutoff of the systolic component of RAP we chose to identify severe tricuspid regurgitation comes from recent evidence that patients undergoing percutaneous tricuspid valve repair and displaying a systolic increase in RAP >8 mm Hg experience poorer

outcomes, suggesting procedure failure.[15] Thus, even though this cutoff has still not been validated, it seems to be quite specific for the presence of severe tricuspid regurgitation. Additionally, echocardiographic evaluation of the severity of tricuspid regurgitation requires a multiparametric approach,[13] which might not be easily applicable to exercise studies.

CONCLUSIONS

When CO is measured with the direct Fick method, isolated latent PVD that unmasked only with exercise (PVR <2 WU at rest and >1.74 WU at peak) was uncommon in our HFpEF cohort, whereas the majority of patients with PVR >1.74 WU during exercise already had high PVR (>2 WU) at rest. HFpEF-latentPVD patients presented with reduced right ventricular CO reserve, potentially favored by mildly increased PVR and by dynamic tricuspid regurgitation, whose hemodynamic impact was enhanced by physical exercise. Additional factors, including a more advanced HFpEF phenotype and mild CO_2 retention, this latter suggesting an underlying pulmonary comorbidity and/or an alteration of the ventilatory control, may play a role in pulmonary remodeling and/or vasoconstriction in this population. The clinical, hemodynamic, and cardiorespiratory alterations associated with the HFpEF-latentPVD phenotype may lead to worse event-free survival in this population.

ACKNOWLEDGMENTS The authors thank the nurses of the catheterization laboratory for their support in data acquisition; Laboratori Guidotti S.p.A. for providing free-of-charge software for echocardiographic analysis; and Giordano Maria Pugliesi, MD, for his help in data acquisition.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by the Italian Ministry of Health 5 x 1000. Dr Baratto is the recipient of a research grant from the European Society of Cardiology. Dr Vachiéry is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department. Dr Fudim was supported by the National Heart, Lung, and Blood Institute (K23HL151744), the American Heart Association (20IPA35310955), Doris Duke, Bayer, Bodyport, and Verily; and has been the recipient of consulting fees from Abbott, Alio Health, Alleviant, Audicor, Axon-Therapies, Bayer, Bodyguide, Bodyport, Boston Scientific, Cadence, Coridea, CVRx, Daxor, Deerfield Catalyst, Edwards LifeSciences, EKO, Feldschuh Foundation, Fire1, Gradient, Impulse Dynamics, Intershunt, Medtronic, NIMedical, NXT Biomedical, Pharmacosmos, PreHealth, ReCor, Shifamed, Splendo, Sumacor, SyMap, Verily, Vironix, Viscardia, and Zoll. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Claudia Baratto, Dyspnea and Pulmonary Hypertension Center, Department of Cardiology, Istituto Auxologico Italiano IRCCS Ospedale San Luca, Piazzale Brescia 20, Milano 20149, Italy. E-mail: c.baratto@auxologico.it. Twitter: @cla_baratto.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: When cardiac output is measured with the direct Fick method, HFpEF with latent PVD (exercise PVR >1.74 WU) may be anticipated in the majority of cases based on PVR >2 WU at rest; isolated latent PVD (rest PVR <2 WU and exercise PVR >1.74 WU) was uncommon. Older HFpEF patients with atrial fibrillation, higher H_2FPEF score, higher estimated systolic pulmonary artery pressure, and at least moderate tricuspid regurgitation are at risk for having latent PVD. The latent PVD profile identifies a small but not negligible proportion of HFpEF patients with more impaired cardiac reserve and exercise limitation, portending a poor prognosis.

TRANSLATIONAL OUTLOOK: Tricuspid regurgitation may dynamically occur or become aggravated during exercise in patients with HFpEF, impairing anterograde stroke volume and thus potentially contributing to the latent PVD profile (ie, contributing to a factitious PVR increase caused by pulmonary vascular derecruitment). Studies combining advanced hemodynamics and advanced echocardiography are warranted to better understand the dynamicity of tricuspid regurgitation and right heart adaptation to exercise in HFpEF patients. The precapillary component of right ventricular afterload appears to be more a consequence of the underlying disease and comorbidities, suggesting that the use of treatments targeting the pulmonary circulation may not be effective in this setting.

REFERENCES

1. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32(6):670–679.

2. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618–3731. https://doi.org/10.1093/eurheartj/ehac237

3. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic phenotyping of pulmonary hypertension in left heart failure. *Circ Heart Fail*. 2017;10(9):e004082.

4. Assad TR, Hemnes AR, Larkin EK, et al. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. *J Am Coll Cardiol*. 2016;68(23):2525–2536.

5. Maron BA, Brittain EL, Hess E, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med*. 2020;8:873–884.

6. Shah SJ, Borlaug BA, Chung ES, et al. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF

II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022;399(10330):1130–1140.

7. Borlaug BA, Blair J, Bergmann MW, et al. Latent pulmonary vascular disease may alter the response to therapeutic atrial shunt device in heart failure. *Circulation*. 2022;145:1592–1604.

8. Baratto C, Caravita S, Soranna D, et al. Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail*. 2022;9(5):3079–3091. https://doi.org/10.1002/ehf2.13979

9. Baratto C, Caravita S, Soranna D, et al. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021;14(5):e007555.

10. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):861–870.

11. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40(40):3297–3317.

12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015 Mar;16(3):233-270.

13. Lancellotti P, Pibarot P, Chambers J, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging*. 2022;23(5):e171–e232.

14. Weatherald J, Sattler C, Garcia G, Laveneziana P. Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. *Eur Respir J*. 2018 Feb 7;51(2):1700860.

15. Mahowald MK, Nishimura RA, Pislaru SV, et al. Reduction in right atrial pressures is associated with hemodynamic improvements after transcatheter edge-to-edge repair of the tricuspid valve. *Circ Cardiovasc Interv*. 2021;14(12):e010557.

16. Baratto C, Caravita S, Faini A, et al. Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study. *J Appl Physiol (1985)*. 2021;130(5):1470–1478.

17. Sorajja P, Borlaug BA, Dimas VV, et al. SCAI/HFSA clinical expert consensus document on the use of invasive hemodynamics for the diagnosis and management of cardiovascular disease. *Catheter Cardiovasc Interv*. 2017;89(7):E233–E247.

18. Hsu S, Brusca SB, Rhodes PS, Kolb TM, Mathai SC, Tedford RJ. Use of thermodilution cardiac output overestimates diagnoses of exercise-induced pulmonary hypertension. *Pulm Circ*. 2017;7(1):253–255.

19. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2019;40(8):689–697.

20. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol*. 2020;76(9):1051–1064.

21. Baratto C, Caravita S, Corbetta G, et al. Impact of severe tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular ejection fraction. *Front Cardiovasc Med*. Published online March 1, 2023. https://doi.org/10.3389/fcvm.2023.1061118

22. Fudim M, Kaye DM, Borlaug BA, et al. Venous tone and stressed blood volume in heart failure: JACC review topic of the week. *J Am Coll Cardiol*. 2022;79(18):1858–1869.

23. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc*. 2017;6(8):e006817.

24. Muraru D, Guta AC, Ochoa-Jimenez RC, et al. Functional regurgitation of atrioventricular valves and atrial fibrillation: an elusive pathophysiological link deserving further attention. *J Am Soc Echocardiogr*. 2020;33(1):42–53.

25. Caravita S, Figliozzi S, Florescu DR, et al. Recent advances in multimodality imaging of the tricuspid valve. *Expert Rev Med Devices*. 2021;18(11):1069–1081.

26. Guta AC, Badano LP, Tomaselli M, et al. The pathophysiological link between right atrial remodeling and functional tricuspid regurgitation in patients with atrial fibrillation: a three-dimensional echocardiography study. *J Am Soc Echocardiogr*. 2021;34(6):585–594.e1.

27. Muraru D, Caravita S, Guta AC, et al. Functional tricuspid regurgitation and atrial fibrillation: which comes first, the chicken or the egg? *CASE (Phila)*. 2020;4(5):458–463.

28. Florescu DR, Muraru D, Florescu C, et al. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging*. 2022;23(7):930–940.

29. Harvey RM, Enson Y, Ferrer MI. A reconsideration of the origins of pulmonary hypertension. *Chest*. 1971;59(1):82–94.

30. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation*. 2018;137(17):1796–1810.

31. Naeije R. Pulmonary hypertension in hypoventilation syndromes. *Eur Respir J*. 2014;43(1):12–15. https://doi.org/10.1183/09031936.00185213

32. Caravita S, Faini A, Deboeck G, et al. Pulmonary hypertension and ventilation during exercise: role of the pre-capillary component. *J Heart Lung Transplant*. 2017;36(7):754–762.

33. Lim HS, Theodosiou M. Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure. *J Card Fail*. 2014;20(9):650–657.

34. Taylor BJ, Smetana MR, Frantz RP, Johnson BD. Submaximal exercise pulmonary gas exchange in left heart disease patients with different forms of pulmonary hypertension. *J Card Fail*. 2015;21(8):647–655. https://doi.org/10.1016/j.cardfail.2015.04.003

35. Omote K, Sorimachi H, Obokata M, et al. Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiologic implications. *Eur Heart J*. 2022;43(36):3417–3431. https://doi.org/10.1093/eurheartj/ehac184

KEY WORDS exercise, heart failure, pulmonary hypertension, right heart catheterization, tricuspid regurgitation

APPENDIX For supplemental figures and a table, please see the online version of this paper.

DOI: 10.1002/pul2.12145

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

An updated meta-analysis of hemodynamics markers of prognosis in patients with pulmonary hypertension due to left heart disease

Claudia Baratto[1] | **Sergio Caravita**[1,2] | **Davide Soranna**[3] | **Céline Dewachter**[4] | **Antoine Bondue**[4] | **Antonella Zambon**[3,5] | **Luigi P. Badano**[1,6] | **Gianfranco Parati**[1,6] | **Jean-Luc Vachiéry**[4]

[1]Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milano, Italy

[2]Department of Management, Information and Production Engineering, University of Bergamo, Dalmine (BG), Italy

[3]IRCCS Istituto Auxologico Italiano, Biostatistics Unit, Milan, Italy

[4]Department of Cardiology, Cliniques Universitaires de Bruxelles, Hôpital Académique Erasme, Bruxelles, Belgium

[5]Department of Statistic and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

[6]Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy

Correspondence
Jean-Luc Vachiéry, Department of Cardiology, Pulmonary vascular diseases and heart failure Clinic, CUB - Hôpital Erasme, 808 Rte de Lennik, 1070 Brussels, Belgium.
Email: jeanluc.vachiery@erasme.ulb.ac.be

Funding information
Italian Ministry of Health

Abstract

Pulmonary hypertension (PH) is associated with a poor prognosis in left heart disease (LHD). We sought to provide an updated analysis on the association of hemodynamic variables, such as pulmonary vascular resistance (PVR), pulmonary artery compliance (PAC), and diastolic pressure gradient (DPG), with prognosis in PH-LHD, through a systematic literature review. Sixteen articles were identified, including 9600 patients with LHD, heterogeneous in terms of age, sex, and etiology of cardiac disease. In this large population, PVR (hazard ratio [HR], 1.07; 95% confidence interval [CI]: 1.05−1.0), DPG (HR, 1.02; 95% CI: 1.01−1.02) and PAC (HR, 0.76; 95% CI: 0.69−0.84) were associated with an increased risk of adverse outcome, albeit with a less solid performance of DPG. Similar results were found when hemodynamic variables were analyzed according to the thresholds commonly applied in clinical practice, or subdividing cohorts according to the underlying LHD. Furthermore, cumulative metanalysis indicated that these results are consistently stable since 2018. Thus, PVR, DPG and PAC have an established prognostic value in PH-LHD. These results are consistent through the years and unlikely to change with further studies.

KEYWORDS
hemodynamics, pulmonary hypertension, left heart disease, prognosis

BACKGROUND

Pulmonary hypertension (PH) is a common complication and a consequence of left heart disease (LHD). It is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg and a pulmonary arterial wedge pressure (PAWP) > 15 mmHg which corresponds to the postcapillary hemodynamic presentation.[1] As such, it can be interpreted as an abnormal biomarker of the underlying cardiac disorder, where the increase in pulmonary artery pressure (PAP) is explained by passive backward transmission of high filling pressure from the left atrium to the pulmonary circulation, defining isolated postcapillary PH (IpcPH).[1]

However, in a minority of patients, a precapillary component of PH may develop[1,2] through several mechanisms that may eventually lead to pulmonary vascular remodeling affecting the structure and function of the pulmonary circulation.[3,4] When present, the hemodynamic phenotype of combined post and precapillary PH (CpCPH) may potentially expose patients to a poorer outcome.[2,4]

Over the past years, several hemodynamic parameters have been proposed to identify this more severe profile, although their association with outcome has led to contrasting results. In a previous meta-analysis on the hemodynamic predictors of outcome ($n = 2513$ patients with PH-LHD), both the diastolic pressure gradient (DPG), pulmonary vascular resistance (PVR) and pulmonary artery compliance (PAC) appeared to be associated with mortality. However, PVR and PAC seemed to be more strongly associated with outcome than DPG.[5]

Accordingly, the new hemodynamic definition proposed at the 6th World Symposium on PH held in 2018, reintroduced PVR alone to differentiate IpcPH to CpcPH. This was thought to better reflect the impact of the right ventricle on outcome,[1] at variance from the previous guidelines' definition, where the PH-LHD profile was defined as "isolated" if DPG < 7 mmHg and/or PVR ≤ 3 WU; and "combined" if DPG ≥ 7 mmHg and/or PVR > 3 WU. Moreover, additional studies were performed to better characterize the severity of PH-LHD since 2018. We therefore sought to assess whether recent data were consistent with previous findings.

METHODS

We followed the PRISMA statement[6] for reporting systematic reviews and meta-analysis. A comprehensive literature research in Pubmed bibliographic database was updated to December 2020, and the search terms included: ("left heart disease" OR "LHD" OR "heart failure with preserved ejection fraction" OR "HFpEF" OR "heart failure" OR "HF" OR "diastolic dysfunction" OR "diastolic heart failure" OR "HFrEF" OR "heart failure with reduced ejection fraction" OR "VHD" OR "valvular heart disease") AND ("PH" OR "pulmonary hypertension" OR "PH-LHD" OR "PHLHD" or "pulmonary hypertension due to left heart disease" OR "post-capillary pulmonary hypertension" OR "IpCPH" OR "CpCPH" OR "isolated post-capillary pulmonary hypertension" OR "combined post- and pre-capillary pulmonary hypertension") AND ("hemodynamics" OR "wedge pressure" OR "PAWP" OR "PCWP" OR "pulmonary capillary wedge pressure" OR "occlusion pressure" OR "right heart catheterization" OR "RHC" OR "cardiac catheterization") AND ("mortality" OR "death"). Each term was considered as both free text and Mesh terms. We only included English-language publications.

We only included cohort studies reporting association measurements (and corresponding 95% confidence intervals [CI] or data allowing the estimation of their standard error) between DPG and/or PVR and/or PAC and death (or heart failure hospitalization) in PH-LHD patients. Relative risk, odds ratio and hazard ratio (HR) were considered adequate association measurements. In case of duplicated data, only the most recent publication was selected. Studies focusing on the effects of specific treatments (including drugs approved for pulmonary arterial hypertension), investigating the outcome after left ventricular assistance device implantation or heart transplantation, or those evaluating short-term follow-up (i.e., less or equal to 1 year) were excluded.

Two authors independently assessed paper's eligibility; disagreements between readers were solved by consensus.

Extraction data

For each included study, we recorded the following variables: country, length of follow-up, sample size, etiology of LHD, age, sex, body mass index (BMI), New York Heart Association functional class, prevalence of comorbidities (arterial hypertension, atrial fibrillation, diabetes, coronary artery disease, and obesity), background treatments (diuretics, betablockers, or angiotensin-converting enzyme inhibitors), N-terminal pro brain natriuretic peptide, glomerular filtration rate, left ventricular ejection fraction, hemodynamic data (heart rate, pulmonary artery pressures, pulmonary artery wedge pressure, right atrial pressure, cardiac output, cardiac index, DPG, transpulmonary pressure gradient, stroke volume, PVR, and PAC), thus including hemodynamic variables tested for association with outcomes, as well as covariates included in multivariate analysis.

Statistics

Sociodemographic and clinical continuous characteristics of each cohort were reported as mean and standard deviation (SD). If the original paper showed median and interquartile range [IQR] we transformed them in mean and SD value following Wan et al.[7] Categorical variables were reported as proportion. Summary of clinical and hemodynamic characteristics of included studies was performed by order statistics (minimum, maximum, median, and IQR). For each hemodynamic variable of interest, we estimated the pooled HR of death and its 95% CI from a fixed model. This was done both for continuous variables and for dichotomized variables according to more frequently used thresholds (PVR > 3 WU, DPG ≥ 7 mmHg, PAC < 2.3 ml/mmHg). A random effect model[8] was applied when the Q-statistic was statistically significant. Moreover, between-studies' heterogeneity was quantified by means of I^2 index.[9] A subgroup analysis was performed based on the presence of adjustment covariates to estimate the original HR. The homogeneity between subgroup pooled HRs was tested. Cumulative meta-analysis was performed to investigate temporal trends in the effects reported in the literature as well as the impact of sample size. An influence analysis was conducted to verify the impact of each estimate on the pooled HR, omitting one study at time. Publication bias presence was evaluated by both funnel plot and Egger test.[10] Moreover, when Egger test resulted statistically significant, a trim and fill approach was applied to correct the funnel plot asymmetry.[11] An exploratory analysis on the association between hemodynamics and outcomes stratifying patients according to the underlying LHD was performed only for the studies that reported the HR for a given hemodynamic variable in a homogeneous patients' cohort. Results were considered statistically significant when two-tailed *p* value was lower than 0.05. All analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

Out of 551 manuscripts identified by bibliographic search, 535 did not fulfilled inclusion criteria. Details about exclusion reasons as reported in Figure 1.

The final analysis was conducted on 16 articles, including a total of 9600 patients with LHD in whom

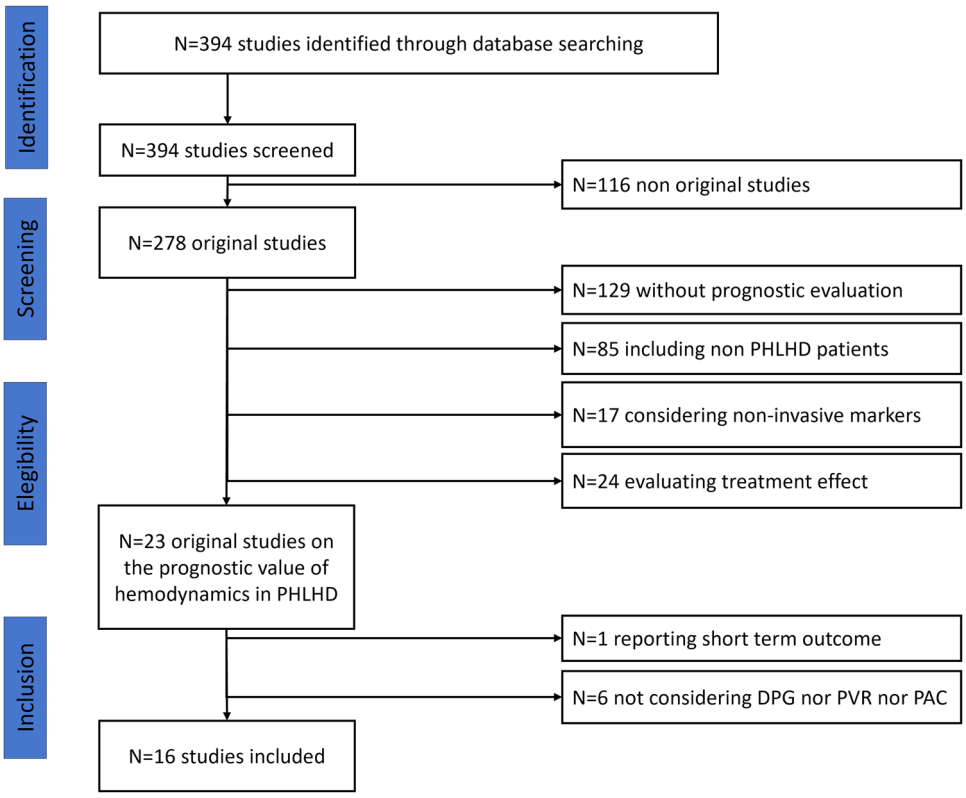


FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection. DPG, diastolic pressure gradient; LVAD, left ventricular assistance device; MRI, Magnetic Resonance Imaging; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PHLHD, pulmonary hypertension due to left heart disease; PVR, pulmonary vascular resistance.

invasive hemodynamics were performed. Characteristics of individual studies are reported in Table 1.

Most of studies included PH-LHD patients independently from the underlying cardiac disease (either heart failure with preserved or reduced left ventricular ejection fraction, or VHD), while six studies focused on one specific etiological subgroup, such as HFpEF,[12,13] HFrEF[14,15] and VHD.[16–18]

The association between hemodynamics (PVR, DPG, and PAC) and outcome was reported on continuous scale in 13 studies,[12–16,19–26] while 13 studies dichotomized PVR, DPG, and PAC according to prespecified cut-offs.[12–17,19,21,23–27]

In most of the studies, a multivariate analysis was performed to adjust the effect on PVR, DPG, and PAC of covariates such as age and sex,[12,15,17–23,27] BMI,[12,17–19,21] comorbidities[15,17,20–23,27] and hemodynamic parameters.[12,18,20,23]

Clinical and hemodynamic characteristics

Analysis of the different populations revealed heterogeneity in terms of age, sex, and etiology of PH-LHD (Table 1). As reported in Table 2, median age was 64 years old, with values varying from 47 to 83 years old. Female sex prevalence varied from 17% to 76% and median BMI was 28 kg/m^2 (from 26 to 30 kg/m^2).

The populations were characterized by a significant burden of comorbidities, including atrial fibrillation, whose prevalence varied from 15% to 71%, and were largely treated with diuretic, betablocker and antihypertensive therapies. However, a complete non-invasive assessment by echocardiography and biological tests was not reported in all studies, while left ventricular ejection fraction was reported in most studies, with a median value of 44.2% (IQR 39%−51%), as well as brain natriuretic peptide, with a median value of 802.7 pg/ml (IQR 464.7−970.0 pg/ml).

Mean PAP had a median value of 38 mmHg (36−42 mmHg). Almost all studies[12–19,21–26] reported PAWP and PVR, whose median values were, respectively, 24 [22−24] mmHg, and 3.9 [2.7−5.1] WU, which corresponds to the CpcPH presentation.

Twelve studies reported DPG[12–14,17–19,21,22,24–27] whose median value was 1.8 [−0.4 to 6.9] mmHg and 11 studies[12,14–17,21,23–27] reported PAC, with a median value of 2.1 [1.8−2.4] ml/mmHg. Thorough hemodynamic characteristics of included patients across studies are reported in Table 3.

Almost all studies defined PH according to 2015 PH Guidelines, except for one[16] in which the definition proposed during the 6th Symposium of PH was adopted.

A major part of authors[12,15,17,18,21–27] stratified the patients on the base of the presence of a precapillary component, mostly considering a DPG ≥ 7 mmHg,[12,17,18,21,22,27] PVR > 3 WU [15,18] or a combination of both,[23–26] while 2 authors considered also a TPG > 12 mmHg.[20,22] Following this heterogeneous classifications of the pre-capillary component, IpCPH cohort was composed of 5234 patients and CpCPH one by 2374 patients.

Association between hemodynamic variables and outcomes

Overall, unitary increase in PVR was significantly associated with outcome in PH-LHD (HR, 1.07; 95% CI: 1.05−1.08) (Figure 2). This held true also when separately analyzing studies where the association between PVR and mortality was either unadjusted or adjusted for relevant covariates. These findings were consistently achieved when 1263 patients were analyzed, or in the year 2015, as suggested by cumulative meta-analysis (Figures 3 and 4).

DPG was associated with mortality in PH-LHD (HR, 1.02; 95% CI: 1.01−1.02). However, such an association was no more significant when considering only the 2 studies performing an adjustment for covariates (Figure 2). Cumulating evidence by publication year noted that the initial statistically significant strong effect of 2013 was not confirmed until 2018 and with weaker pooled HR (Figure 4). Moreover, at the cumulative meta-analysis based on the sample size, the studies demonstrated a high degree of heterogeneity and the overall effect gained stability only after having included 480 patients (Figure 3).

PAC was significantly associated with mortality in PH-LHD (HR, 0.76; 95% CI: 0.69−0.84) (Figure 2). Despite a non-negligible heterogeneity between included studies ($I^2 = 60\%$), results were consistent when only 73 patients were analyzed (Figure 3) or in the year 2015 (Figure 4).

Only 9 out of 16 studies reported the association between PAWP and outcome. Only in 3 of these 9 studies such association was statistically significant.

Influence and publication bias analysis

No study influenced the summary estimates of PVR, DPG and PAC (e-Figure 1). Moreover, Egger test suggested publication bias for both PVR and PAC although in an opposite direction, that is, with an underestimation for PAC and an overestimation for PVR. However, trim and

TABLE 1 Characteristics of included studies

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
Gerges et al.[22]	Austria	1094	63 ± 13		26.3 ± 4.5	≈55%	≈45%	Significant VHD ≥ 1/3 of patients (comorbidity)	DPG continuous	Sex, age, GFR < 60, CAD	Death
Miller et al.[15]	USA	337	59 ± 14	25	29.1 ± 6.4	0%	100%	Significant VHD ≥ 1/3 of patients (comorbidity)	PVR dichotomized (>/≤3 WU) PAC continuous and dichotomized (>/≤ 2.3 ml/mmHg)	Risk factors that were significantly different among the groups at baseline and clinically important factors	Death
Dragu et al.[20]	Israel	264	66 ± 12	55		45%	76%	24%	PVR continuous PAC continuous	age, gender, estimated GFR, LV and RV function, RAP, PCWP, and type of PH	Death
Al-Naamani et al.[12]	USA	73	69 ± 12	74	33 ± 10	100%	0%	0%	DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous PAC continuous	Age, sex, ethnicity, BMI, haemodynamic parameters	Death
O'Sullivan et al.[17]	Switz	269	83 ± 5	58	26.3 ± 5			100%	DPG dichotomized (≥/<7 mmHg)	Age, sex, BMI, DM, previous CABG, PVD, previous MI, CAD, LVEF ≤ 30%, COPD	Death after transcatheter aortic valve implantation
Gerges et al.[27]	Austria	668				67%	38%	62%	DPG dichotomized (≥/<7 mmHg)	Sex, age, GFR < 60, CAD	Death

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
Assad et al.[21]	USA	1820	61 ± 14	44	31.2 ± 8.2			Significant VHD ≥ 8% of patients (comorbidity)	DPG continuous and dichotomized (≥/<7 mmHg)	Age, sex, BMI, COPD, ILD, OSA, CAD, AF, VHD, lupus, scleroderma	Death
Palazzini et al.[26]	Italy	276	69 (60–75)	75		41%	9%	50%	DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous and dichotomized (>/≤3 WU) PAC continuous and dichotomized (>/≤2 ml/mmHg)		Death
Brunner et al.[18]	Canada	133	80 ± 8	47	28 ± 7			100%	DPG dichotomized (≥/<7 mmHg) PVR dichotomized (>/≤3 WU)	Age, sex, BMI, PASP	Death after transcatheter aortic valve replacement
Vanderpool et al.[13]	USA	2587	65 ± 38	45	31 ± 9	100%	0%	0%	DPG continuous and dichotomized (≥/<7; >/<4.7 mmHg) PVR continuous and dichotomized (>/≤3; >/<2.3 WU) PAC continuous		Death

TABLE 1 (Continued)

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
Tampakakis et al.[19]	USA	1036	57 (45–67)	39	27.7 (23.9–3-3.3)				DPG continuous and dichotomized (≥/<7 mmHg) PVR continuous PAC continuous	Model 1: age Model 2: age, BMI, HR, sex, and cohort	Death
Caravita et al.[24]	Belgium	93	64 ± 13	55	29 ± 5	51 + 45 + 63	49 + 45 + 30	0 + 10 + 7	DPG continuous and dichotomized (≥/<7; >/<2.5 mmHg) PVR continuous and dichotomized (>/≤3 WU) PAC Continuous		Death
Dragu et al.[23]	Israel	393	66 ± 12	56					DPG dichotomized (≥/<7 mmHg) PVR dichotomized (≥/<3 WU)	Age, gender, GFR, Hb, LV and RV function, RAP, PAWP, type of PH	Death or HF admission
Quan et al.[14]	China	92	47 ± 13	17	24 ± 4.7	0%	100%	0%	PVR continuous or dichotomized (>/≤ 3 WU) DPG continuous or dichotomized (≥/<7 mmHg) PAC continuous		Death or transplanta-tion pr hospital-ization
Sugimoto et al.[25]	Japan	243	64 ± 15	44					PVR continuous or dichotomized (>/≤3 WU) DPG continuous and		Cardiac death

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Sample size, *N*	Age, years	Female gender, %	BMI, kg/m^2	HFpEF	HFrEF	VHD	Hemodynamic variables tested for association with outcomes	Covariates in multivariate analysis	Outcome
									dichotomized (≥/<7 mmHg) PAC continuous		
Bermejo et al.[16]	Multicentric	222	72 (66−77)	76		0%	0%	100%	PVR continuous or dichotomized (>/≤3 WU) DPG continuous and dichotomized (≥/<7 mmHg) PAC continuous		Death

Note: Continuous data are reported as mean ± SD or median (interquartile range); proportions are reported as percentage.

Abbreviations. AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CABG, Coronary artery bypass graft; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease; DM, diabetes mellitus; DPG, diastolic pressure gradient; GFR, glomerular filtration rate; Hb, hemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ILD, interstitial lung disease; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NTproBNP, N-terminal pro brain natriuretic peptide; NYHA FC, New York Heart Association functional class; OSA, obstructive sleep apnea; PAC, pulmonary artery compliance; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; USA, United States of America; VHD, valvular heart disease.

TABLE 2 Summary of clinical and hemodynamic characteristics of included studies

Variable	*N* papers	*N* estimates	Minimum	25° pctl	Median	75° pctl	Maximum	% missing data
Age, years	16	27	46.8	60.0	64.3	67.9	82.6	0%
Female sex, %	15	26	17.0	39.0	50.7	56.0	76.0	4%
BMI, Kg/cm^2	11	17	24.0	26.3	28.0	29.9	33.0	37%
NYHA FC III–IV,%	5	6	49.0	61.0	72.3	83.0	100.0	78%
Atrial fibrillation, %	9	17	15.3	32.0	44.0	46.0	71.0	37%
Arterial hypertension, %	8	14	22.0	38.3	64.0	80.0	86.0	48%
Diabetes, %	7	10	23.0	29.0	34.0	41.0	49.0	63%
CAD, %	7	13	19.0	36.7	50.0	57.0	81.0	52%
Diuretics, %	7	13	54.0	67.0	72.0	79.0	97.0	52%
Bblockers, %	8	16	43.0	56.5	71.5	79.0	92.0	41%
ACEi/ARBs, %	8	16	25.0	41.0	57.5	83.0	88.0	41%
BNP, pg/ml	4	7	313.0	464.7	802.7	970.0	1078.0	74%
GFR, ml/min	6	13	50.0	53.0	54.0	64.0	70.0	52%
LVEF, %	8	13	23.0	38.6	44.2	51.2	64.3	52%
HR, bpm	12	20	71.0	74.0	78.0	82.0	90.0	26%
SPAP, mmHg	13	21	30.4	53.7	57.0	62.0	74.0	22%
DPAP, mmHg	12	19	12.6	23.0	25.0	32.0	38.4	30%
MPAP, mmHg	16	27	18.9	36.4	38.0	42.0	50.1	0%
PAWP, mmHg	15	25	11.2	22.0	23.5	24.0	26.7	7%
CI, L/min/m^2	11	18	1.9	2.2	2.5	2.8	2.9	33%
RAP, mmHg	15	24	5.8	10.7	12.0	13.7	15.0	11%
DPG, mmHg	13	20	−3.7	−0.4	1.8	6.9	12.7	26%
PVR, WU	15	24	1.7	2.7	3.9	5.1	9.3	11%
PAC, ml/mmHg	11	20	0.6	1.8	2.1	2.4	3.1	26%

Note: Data are reported as median, 25° and 75° percentile, minimum/maximum value.

Abbreviations: ACEi, Angiotensin-converting-enzyme inhibitors; ARBs, Angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CI, cardiac index; DPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; GFR, glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; NYHA FC, New York Heart Association functional class; PAC, pulmonary artery compliance; PAWP, pulmonary artery wedge pressure; PCTL, percentile; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SPAP, systolic pulmonary artery pressure; WU, Wood Unit.

fil approach confirmed findings of the main analysis after controlling for this source of bias (e-Figure 1).

Stratification according to the underlying LHD

We performed an exploratory analysis on the association between hemodynamics and outcomes stratifying patients according to the underlying LHD (HFpEF, HFrEF, and VHD). The results of this exploratory analysis were in line with those obtained in the whole cohort, even though they resulted significant in all the three conditions only for PVR (e-Figure 2).

DPG, PVR, and PAC considered as dichotomous variables

For this analysis, we considered only papers reporting the association measurements when DPG, PVR and PAC were dichotomized using the following cut-off values: PVR > 3 WU; DPG ≥ 7 mmHg; PAC < 2.3 ml/mmHg. DPG > 7 mmHg as well as PVR > 3 WU were both

TABLE 3 Hemodynamics of patients with left heart disease as reported in individual studies

Author	SPAP	DPAP	MPAP	PAWP	RAP	TPG	DPG	HR	SV	CO	CI	PVR	PAC
Gerges et al.[22]	56 ± 16	25 ± 8	37 ± 10	24 ± 8	10 ± 5	13 ± 8	1 ± 7	78 ± 16		4.8 ± 1.4	2.6 ± 0.7	3.0 ± 2.1	
Miller et al.[15]	56 ± 12		38 ± 7		15 ± 7	14 ± 5		77 ± 17	56 ± 19		4.2 ± 1.1	3.7 ± 1.5	2.1 ± 0.8
Dragu et al.[20]	59 ± 14	26 ± 7	39 ± 8	24 ± 6	24 ± 6	15 ± 6			63 ± 25				
Al-Naamani et al.[12]			41 ± 11	21 ± 4	13 ± 5	19 ± 10	5 ± 7	71 ± 14	69 ± 29	4.7 ± 1.5		4.9 ± 3.7	2.1 ± 1.2
O'Sullivan et al.[17]	59 ± 12	24 ± 6	39 ± 8		9 ± 4	14 ± 8	−1 ± 6	80 ± 15	49 ± 15	3.7 ± 1.3	2.1 ± 0.5	4.2 ± 2.8	0.8 ± 0.4
Gerges et al.[27]			38 ± 9	24 ± 7	10 ± 5	14 ± 6	2 ± 5	78 ± 16		4.8 ± 3.4	2.5 ± 0.7	3.2 ± 1.7	2.3 ± 1.2
Assad et al.[21]	56 ± 15	25 ± 6	38 ± 9	24 ± 6	12 ± 6	18 ± 6	2 ± 5	74 ± 16		2.7 ± 0.9		3.2 ± 2.0	2.6 ± 1.7
Palazzini et al.[26]	60 (48–76)	22 (18–29)	37 (31–46)	20 (18–23)	12 (8–16)	16 (12–24)	1 (−2 to 7)	75 (65–85)			2.6 (2.2–3.1)	3.6 (2.3–5.6)	1.8 (1.2-2.2)
Brunner et al.[18]	59 ± 15	24 ± 6	38 ± 8	24 ± 7	11 ± 5	14 ± 8	0 ± 7	4.0 ± 3.1		3.9 ± 1.1			
Vanderpool et al.[13]	58 ± 18	23 ± 8	38 ± 10	24 ± 15	14 ± 7	12 (9-18)	−1 (−4-3)	77 ± 18	79 ± 36	5.7 ± 2.1	2.9 ± 0.9	2.3(1.5–3.6)	
Tampakakis et al.[19]	53(45–63)	27(22–31)	35(30–42)	25(20–35)	13(9–18)	11 (7–14)	1(−1 to 5)	81 (69–97)			2.3 (1.7–2.7)	2.3(1.4–3.5)	
Caravita et al.[24]	68 ± 18	28 ± 8	39 ± 10	23 ± 5	13 ± 6	16 ± 8	5 ± 5	71 ± 13	59 ± 19		2.2 ± 0.6	4 ± 3	2.1 ± 1.1
Dragu et al.[23]	60 ± 16	27 ± 6	40 ± 9	24 ± 6	13 ± 6	15 ± 6			62 ± 25	4.5 ± 1.4		3.45 ± 1.9	2.3 ± 1.2
Quan et al.[14]	55 ± 13		38 ± 9	25 ± 6	10 ± 6		4 ± 6	82 ± 15			1.9 ± 0.7	4.3 ± 2.8	1.93 ± 1.1
Sugimoto et al.25	47 ± 10	23 ± 5	32 ± 6	23 ± 6		10 ± 5	0 ± 3		73 ± 17		2.6 ± 0.7	2.5 ± 1.1	2.8 ± 1.3
Bermejo et al.[16]			37 (32–44)	22 (18–26)	12 (9–16)	15 (11–21)	2 (0–7)				2.8 (2.4–3.3)	3.2 (2.1–4.8)	2.0 (1.4–2.7)

Note: Data are reported as mean ± SD or median (interquartile range).

Abbreviations: CI, cardiac index; CO, cardiac output; DPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; HR, heart rate; MPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SPAP, systolic pulmonary artery pressure; SV, stroke volume; TPG, transpulmonary pressure gradient; WU, Wood Unit.

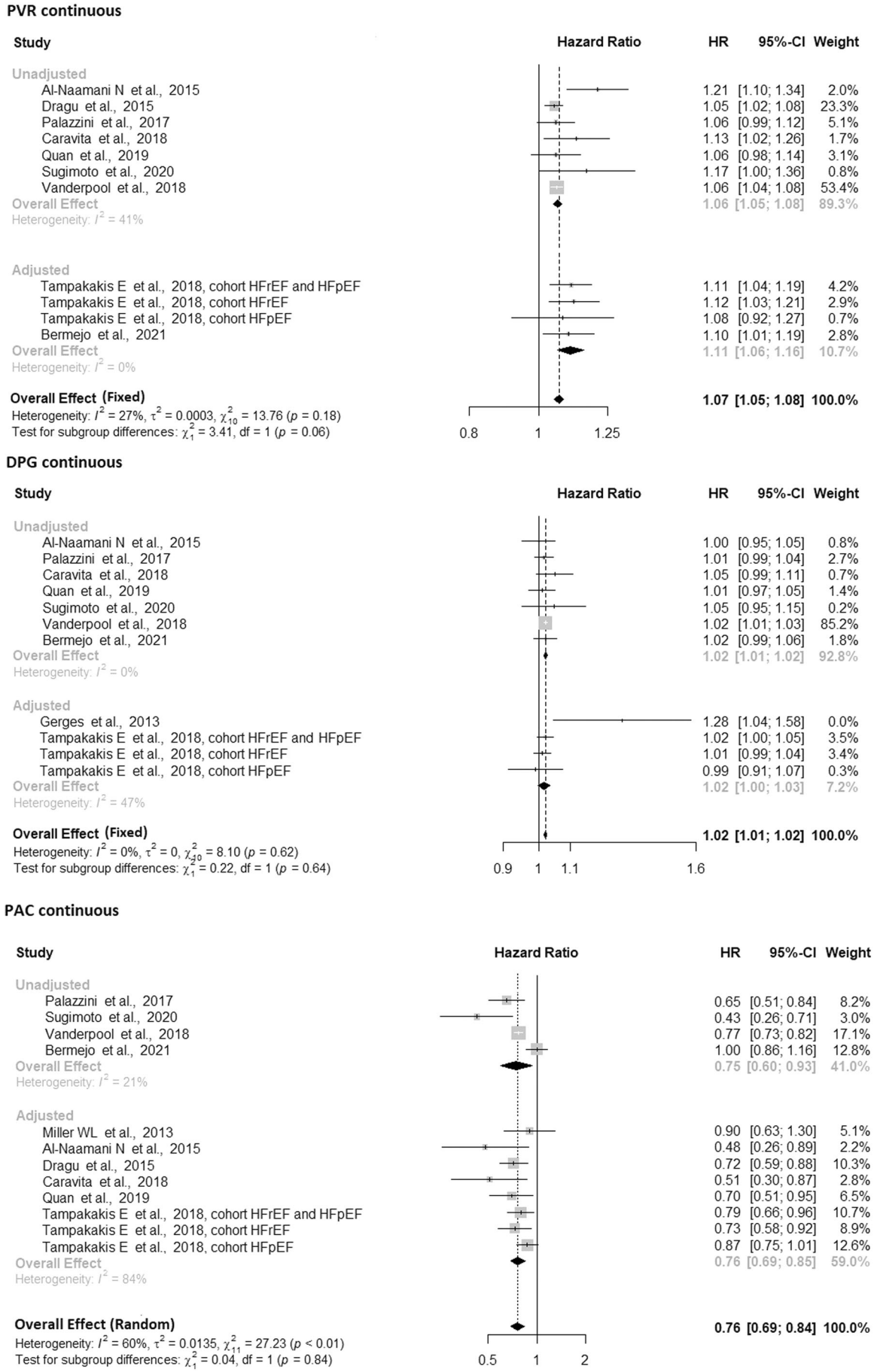


FIGURE 2 (See caption on next page)

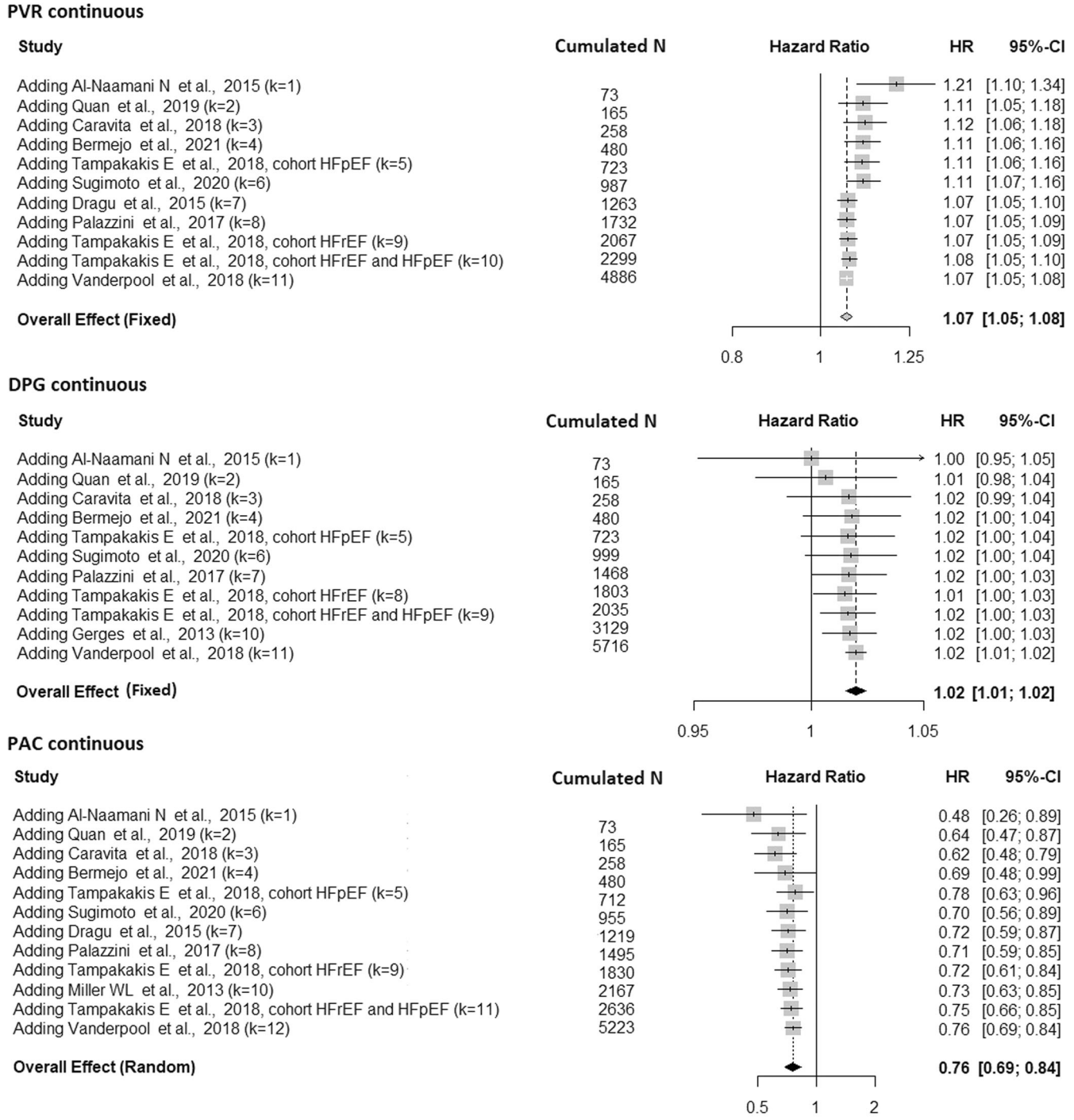


FIGURE 3 Cumulative metanalysis according to sample size for each hemodynamic variable. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

FIGURE 2 Forest plots with pooled standardized hazard ratio for hemodynamic variables reported in a continuous way. For each variable, unadjusted and adjusted analysis are reported. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

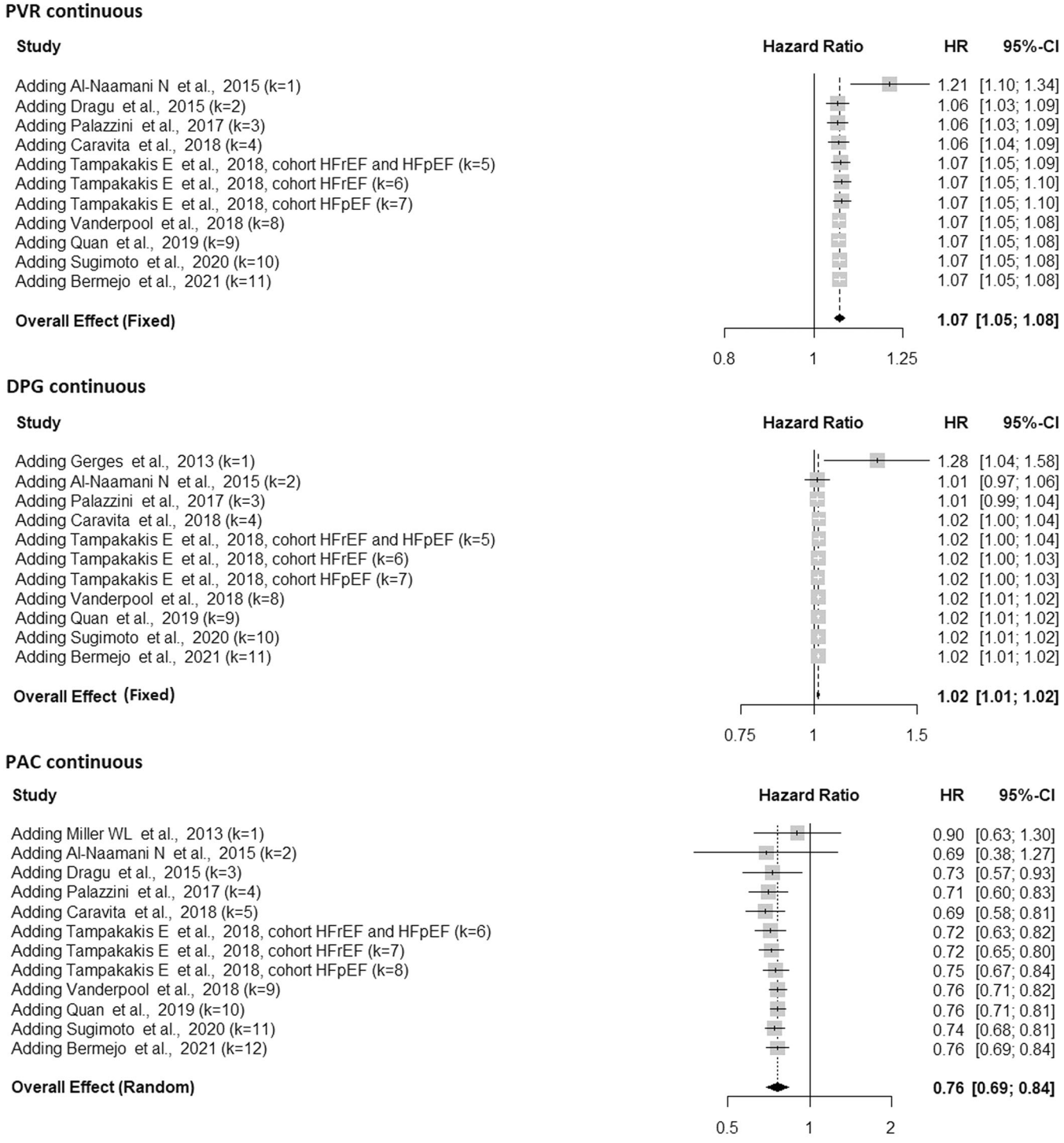


FIGURE 4 Cumulative metanalysis according to year of publication for each hemodynamic variable. CI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

associated to a higher risk for mortality, with HR of 1.36 (95% CI: 1.24–1.49) and 1.53 (95% CI: 1.40–1.67), respectively. Furthermore, a PAC < 2.3 ml/mmHg carried the highest risk of mortality (HR 2.14, 95% CI: 1.62–2.84) (Figure 5).

DISCUSSION

From pooling data from more than 9000 LHD patients with PH from various etiologies, our meta-analysis confirms and reinforces the established association of

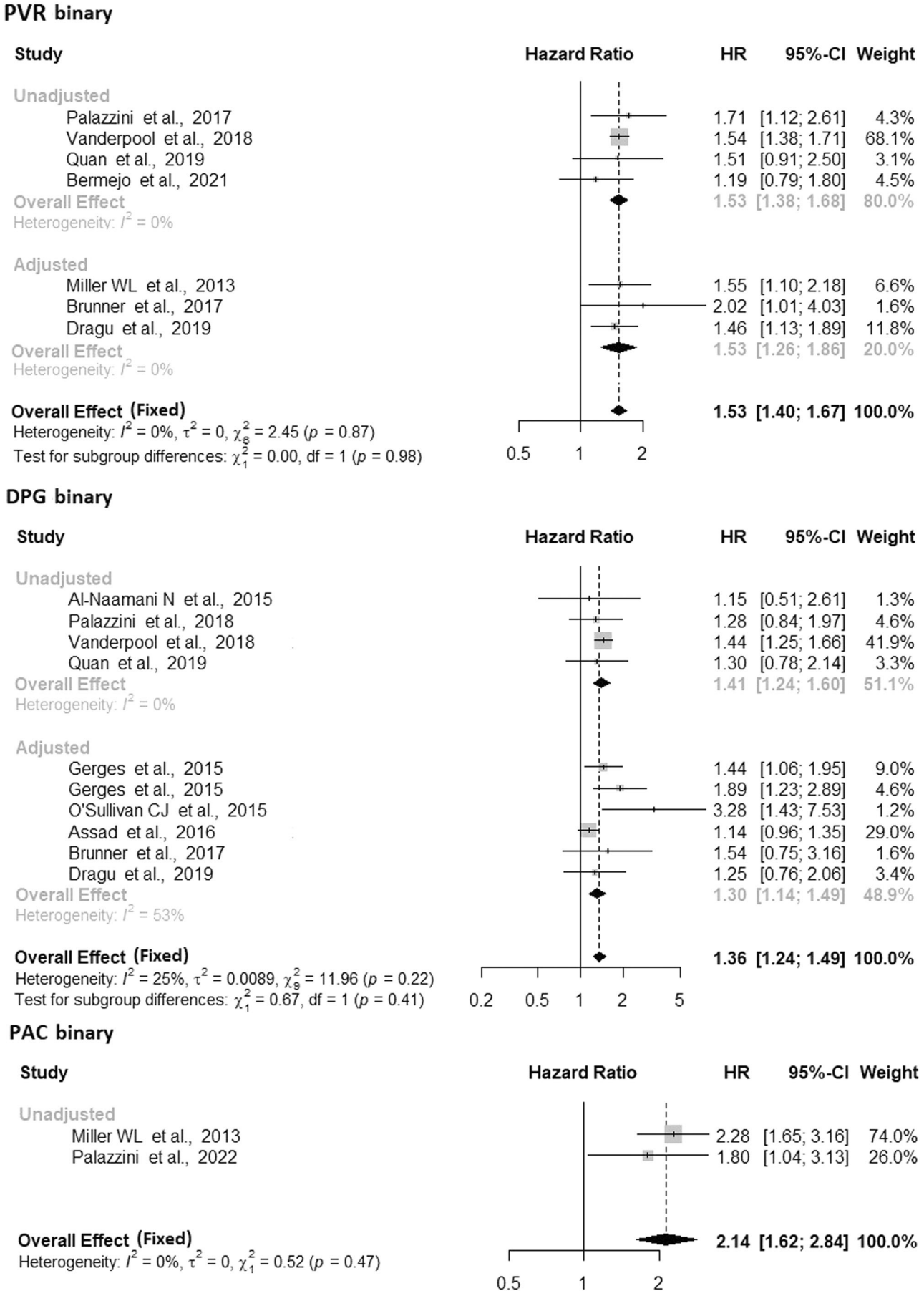


FIGURE 5 (See caption on next page)

PVR and PAC with prognosis, providing a synthesis of the evidence collected in the last 8 years also in term of cumulative meta-analysis. While the results for DPG appeared somehow less solid, at least when DPG was intended in a continuous way, PVR and PAC appear to be stronger predictor of outcome, both when dichotomized or when used as continuous variables. PVR proved capable to predict outcome independently of the underlying LHD (HFpEF, HFrEF, or VHD).

The heterogeneity of the populations included in the analysis mirrors the broad spectrum of LHD,[1] composed of HFrEF, HFpEF, and VHD. However, independently from the underlying LHD, the pooled cohort was an elderly one, characterized by a quite large burden of comorbidities including a high rate of atrial fibrillation. The average hemodynamic profile was quite typical, combining an elevated PAWP (>20 mmHg), a mildly elevated mPAP (25–40 mmHg), a normal DPG (<3 mmHg) and PVR ranging from 3 to 4.9 WU.[1]

In this large population, the unitary increase in PVR resulted associated with a 7% of increase in risk of adverse outcome, while a unitary increase in DPG carried a smaller increase in risk (+2%). At variance, a unitary increase in PAC was associated with a 24% mortality risk reduction.

Accordingly, evidence have not changed substantially since 2018.[5] Additional studies reinforced the consistency of results, which should be considered sufficiently stabilized and unlikely to change in the future. Furthermore, when variables were expressed in a binary way using high and commonly applied thresholds in clinical practice, the results were even more stable and consistent across hemodynamic variables, with similar HR between PVR and DPG.

Traditionally, PVR is a practical and widely accepted and used variable in clinical practice. On a physiological perspective, it normalizes the characteristics of the pulmonary circulation (mPAP−PAWP) for a marker of cardiac performance (CO). Accordingly, our analysis could confirm available data on its robust prognostic discriminative potential in PH-LHD,[5] even when the cohorts were subdivided based on the underlying etiology of PH.

DPG was similarly found to be associated to outcome, but with a small increase in risk for a unitary increase. Moreover, the meta-analysis results were not extremely solid when separately analyzing studies in which the association of DPG with mortality was either adjusted or unadjusted. As it has been repeatedly remarked, the DPG is a small number and exposed to measurement error, potentially explained also by the relative inaccuracy of the used catheters ("fluid filled" rather than "high fidelity"), the lack of standardization in the measure of PAWP across laboratories (mean PAWP vs. mid-A PAWP; end-expiratory vs. respiratory-averaged values), and the fact that the two terms of the subtraction, that is, the diastolic PAP and PAWP are not simultaneously measured in the same heartbeats and over the same breaths. Accordingly, a relevant proportion of negative DPGs was found in the studies under analysis.

PAC has been proposed as predictor of outcome in LHD [12–16,19,20,24,25] given its presumed pathophysiological meaning, even if the estimated PAC could overestimate its real value by 60%−80%.[2,28] Given the inverse relationship between PAC and PVR, the former has been advanced to be a better fit as prognostic marker when PVR are still "in the normal range" or when mean PAP is below 25 mmHg. However, the recent evidence linearly linking PVR with outcome since a lower cut-off than 3 WU might change current threshold to define diseases, potentially overcoming this previous limit of PVR. Finally, the strong association of PAC with mortality reflects its dimension: it is an even smaller number than DPG, and similarly subject to measurement errors. Additionally, we still do not know which changes should be considered clinically meaningful, and thus it is probably impractical to assess fine changes in pulmonary vascular properties and right ventricular afterload.

Thus, even though these three variables carry prognostic significance, a pragmatic approach aiming at simplifying and rendering clinical practices and communication more homogeneous across laboratories,[1,4,29,30] PVR alone may suffice as a hemodynamic marker for risk stratification. Finally, PAC might be used to strengthen the prognostic assessment.

Thus, the prognostic role of PVR is undisputed. It is still uncertain whether it might represent a therapeutic target in PH-LHD. Indeed, the great majority of studies testing drugs targeting the pulmonary circulation in PH-LHD have provided neutral or even negative results,[1,4,29,30] so that these compounds should not be used in patients with PH-LHD.[1] More favorable results have been obtained with the inodilator levosimendan in patients with HFrEF[31–34] and in patients with VHD[35] in

FIGURE 5 Forest plots with pooled standardized hazard ratio for hemodynamic variables reported in a dichotomous way. For each variable, unadjusted and adjusted analysis are reported. ACI, confidence interval; DPG, diastolic pressure gradient; HR, hazard ratio; PAC, pulmonary artery compliance; PVR, pulmonary vascular resistance.

whom this compound was demonstrated to improve PVR and RV function. Its effects in HFpEF are less studied, but it might at least decrease PAWP in a subgroup of such patients.[36] Finally, PVR might be useful for the selection of HFpEF patients candidate to the placement of an interatrial septal device: in the REDUCE LAP-HF II trial,[37] patients with high PVR during exercise (>1.74 WU) had an increased incidence of HF events as compared with those with low PVR, who seemed to have more benefit from this device.

LIMITATIONS

The literature search was done using only the Pubmed database, however screening nearly 400 studies. Hemodynamic predictors of prognosis in LHD may be influenced by the study characteristics (single center vs. multicentric; RHC methodology), timing of data collection (elective RHC vs. acute decompensation, changes under therapy), the characteristics of the referral center as well as of the population (HFrEF, HFpEF, and VHD). However, the large sample size may at least in part overcome such limitation.

There was an overlap of studies between our previously published meta-analysis[5] and this study. However, since studies on this topic doubled since the publication of our previous work, we thought appropriate to re-run an updated analysis, including additional information, such as a cumulative meta-analysis based on the sample size of the individual studies and the year of publication, expressing variables not only in continuous but also in a binary way (dichotomized according to currently used thresholds) and performing a sub-analysis stratifying the populations according to the underlying etiology of LHD (HFrEF, HFpEF, and VHD).

We only included studies published since 2013, with the aim to maintain a homogeneity in the definition of PH, to focus on contemporary patients' populations, and to better focus on more attractive hemodynamic variables with supposed prognostic value in this context. Indeed, in 2013 DPG was revived,[38] and suggested as diagnostic criterion to define a precapillary component to postcapillary PH,[39] then combined with PVR in the guidelines on PH.[40] Always in 2013, the prognostic value of PAC was similarly suggested for the first time.[15]

We did not explore the association between PAWP and outcomes in these studies. However, only in 3 of the studies reporting it, the association between PAWP and outcome resulted statistically significant. Indeed, all cohorts included in the analysis had, by definition, a high PAWP. Thus, we preferred to focus our study on hemodynamic markers more likely reflecting the presence of a precapillary component to postcapillary PH.

We could not explore the association of a lower threshold of PVR (e.g., 2 WU) with outcome since we did not perform an individual patients' data meta-analysis. However, since a unitary increase in PVR was associated with a 7% of risk, our data may indirectly suggest that the link of PVR with outcome may start from a lower threshold.

CONCLUSIONS

Despite the heterogeneity of PH-LHD group and the intrinsic limitations of each variable, PVR, DPG, and PAC are all associated with outcome. The strongest correlation with PVR and PAC supports their use in defining disease severity and identifying a subgroup of patients at higher risk of adverse outcome. We believe this evidence is robust enough for sufficient time to make it unlikely to change with the addition of similar studies. Nevertheless, further studies are needed to assess how these hemodynamic markers perform in predicting outcome in more homogeneous PH-LHD phenotypes, and how time- or treatment-induced changes may influence outcome.

AUTHOR CONTRIBUTIONS

Claudia Baratto: Conceptualization, data curation, investigation, methodology, writing–original draft. **Sergio Caravita**: Conceptualization, methodology, supervision, writing–review and editing. **Davide Soranna**: Methodology, formal analysis, writing–review and editing. **Céline Dewachter**: Conceptualization, data curation, methodology, supervision, writing–review and editing. **Antoine Bondue**: Supervision, writing–review and editing; **Antonella Zambon**: Methodology, formal analysis, writing–review and editing; **Luigi P. Badano**: Supervision, writing–review and editing. **Gianfranco Parati**: Supervision, writing–review and editing. **Jean-Luc Vachiéry**: Conceptualization, methodology, supervision, writing–review and editing.

ACKNOWLEDGMENTS

Dr Baratto is the recipient of a Research Grant from the European Society of Cardiology. Dr Caravita received the grant Vera Srebot from the Fondazione CNR/Regione Toscana per la Ricerca Medica e di Sanità Pubblica. Dr Bondue received support from the Belgian Fonds de la Recherche Scientifique (FRS-FNRS—grant J.0011.19), from the Erasme Foundation (ULB) and from the Belgian Cardiac Surgery Foundation. Dr Vachiéry is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department. Guarantor Jean-Luc Vachiéry. The study was partially supported by the Italian Ministry of Health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Claudia Baratto http://orcid.org/0000-0003-3472-4851

REFERENCES

1. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, De Marco T. Pulmonary hypertension due to left heart disease. Eur Respir J. 2019;53(1):1801897.
2. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic phenotyping of pulmonary hypertension in left heart failure. Circ Heart Fail. 2017;10(9): e004082.
3. Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, Frantz RP, Jenkins SM, Redfield MM. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. Circulation. 2018;137(17):1796–810.
4. Al-Omary MS, Sugito S, Boyle AJ, Sverdlov AL, Collins NJ. Pulmonary hypertension due to left heart disease: diagnosis pathophysiology, and therapy. Hypertension. 2020;75(6): 1397–408.
5. Caravita S, Dewachter C, Soranna D, D'Araujo SC, Khaldi A, Zambon A, Parati G, Bondue A, Vachiéry JL. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. Eur Respir J. 2018;51(4): 1702427.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7): e1000100.
7. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14(1):135.
8. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
9. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
10. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
11. Duval S, Tweedie R. A nonparametric «trim and fill» method of accounting for publication bias in Meta-Analysis. J Am Stat Assoc. 2000;95(449):89.
12. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. JACC Heart Fail. 2015;3(6):467–74.
13. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. JAMA Cardiol. 2018;3(4):298–306.
14. Quan R, Huang L, Yang T, Li W, Gu Q, Xiong C, He J. Prognostic value of hemodynamics and comorbidities in pulmonary hypertension due to advanced heart failure. Heart Lung. 2020;49(2):158–64.
15. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction. JACC Heart Fail. 2013;1(4):290–9.
16. Bermejo J, González-Mansilla A, Mombiela T, Fernández AI, Martínez-Legazpi P, Yotti R, García-Orta R, Sánchez-Fernández PL, Castaño M, Segovia-Cubero J, Escribano-Subias P, Alberto San Román J, Borrás X, Alonso-Gómez A, Botas J, Crespo-Leiro MG, Velasco S, Bayés-Genís A, López A, Muñoz-Aguilera R, Jiménez-Navarro M, González-Juanatey JR, Evangelista A, Elízaga J, Martín-Moreiras J, González-Santos JM, Moreno-Escobar E, Fernández-Avilés F, SIOVAC ("Sildenafil for Improving Outcomes after VAlvular Correction") Investigators. Persistent pulmonary hypertension in corrected valvular heart disease: hemodynamic insights and Long-Term survival. J Am Heart Assoc. 2021;10(2):e019949.
17. O'sullivan CJ, Wenaweser P, Ceylan O, Rat-Wirtzler J, Stortecky S, Heg D, Spitzer E, Zanchin T, Praz F, Tüller D, Huber C, Pilgrim T, Nietlispach F, Khattab AA, Carrel T, Meier B, Windecker S, Buellesfeld L. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation: insights from the new proposed pulmonary hypertension classification. Circ Cardiovasc Interv. 2015;8(7):e002358.
18. Brunner NW, Yue SF, Stub D, Ye J, Cheung A, Leipsic J, Lauck S, Dvir D, Perlman G, Htun N, Fahmy P, Prakash R, Eng L, Ong K, Tsang M, Cairns JA, Webb JG, Wood DA. The prognostic importance of the diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance in patients undergoing transcatheter aortic valve replacement: prognostic importance of the DPG, TPG, and PVR in patients. Catheter Cardiovasc Interv. 2017;90(7):1185–91.
19. Tampakakis E, Shah SJ, Borlaug BA, Leary PJ, Patel HH, Miller WL, Kelemen BW, Houston BA, Kolb TM, Damico R, Mathai SC, Kasper EK, Hassoun PM, Kass DA, Tedford RJ. Pulmonary effective arterial elastance as a measure of right ventricular afterload and its prognostic value in pulmonary hypertension due to left heart disease. Circ Heart Fail. 2018;11(4):e004436.
20. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galie N, Aronson D. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension: pulmonary arterial capacitance in patients with HF and reactive PH. Eur J Heart Fail. 2015;17(1):74–80.
21. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. Clinical and biological insights into combined post- and Pre-Capillary pulmonary hypertension. J Am Coll Cardiol. 2016;68(23):2525–36.
22. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient. Chest. 2013;143(3):758–66.
23. Dragu R, Hardak E, Ohanyan A, Adir Y, Aronson D. Prognostic value and diagnostic properties of the diastolic pulmonary pressure gradient in patients with pulmonary hypertension and left heart disease. Int J Cardiol. 2019;290:138–43.
24. Caravita S, Faini A, Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, Naeije R, Parati G, Vachiéry JL. Clinical phenotypes and outcomes of pulmonary hypertension

due to left heart disease: role of the pre-capillary component. PLOS ONE. 2018;13(6):e0199164.
25. Sugimoto K, Yoshihisa A, Nakazato K, Yokokawa T, Misaka T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Ishida T, Takeishi Y. Significance of pulmonary vascular resistance and diastolic pressure gradient on the new definition of combined Post-Capillary pulmonary hypertension. Int Heart J. 2020;61(2):301–7.
26. Palazzini M, Dardi F, Manes A, Reggiani MLB, Gotti E, Rinaldi A, Albini A, Monti E, Galiè N. Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes: pulmonary hypertension due to left heart disease. Eur J Heart Fail. 2018; 20(2):248–55.
27. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T, Lang IM. Pulmonary hypertension in heart failure. epidemiology, right ventricular function, and survival. Am J Respir Crit Care Med. 2015;192(10):1234–46.
28. Gerges C, Gerges M, Fesler P, Pistritto AM, Konowitz NP, Jakowitsch J, Celermajer DS, Lang IM. In-depth haemodynamic phenotyping of pulmonary hypertension due to left heart disease. Eur Respir J. 2018;51(5):1800067.
29. Bermejo J, Yotti R, García-Orta R, Sánchez-Fernández PL, Castaño M, Segovia-Cubero J, Escribano-Subías P, San Román JA, Borrás X, Alonso-Gómez A, Botas J, Crespo-Leiro MG, Velasco S, Bayés-Genís A, López A, Muñoz-Aguilera R, de Teresa E, González-Juanatey JR, Evangelista A, Mombiela T, González-Mansilla A, Elízaga J, Martín-Moreiras J, González-Santos JM, Moreno-Escobar E, Fernández-Avilés F, Sildenafil for Improving Outcomes after VAlvular Correction (SIOVAC) i. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. Eur Heart J. 2018;39(15):1255–64.
30. Vachiéry JL, Delcroix M, Al-Hiti H, Efficace M, Hutyra M, Lack G, Papadakis K, Rubin LJ. Macitentan in pulmonary hypertension due to left ventricular dysfunction. Eur Respir J. 2018;51(2):1701886.
31. Parissis JT, Paraskevaidis I, Bistola V, Farmakis D, Panou F, Kourea K, Nikolaou M, Filippatos G, Kremastinos D. Effects of levosimendan on right ventricular function in patients with advanced heart failure. Am J Cardiol. 2006;98(11):1489–92.
32. Russ MA, Prondzinsky R, Carter JM, Schlitt A, Ebelt H, Schmidt H, Lemm H, Heinroth K, Soeffker G, Winkler M, Werdan K, Buerke M. Right ventricular function in myocardial infarction complicated by cardiogenic shock: improvement with levosimendan. Crit Care Med. dicembre. 2009; 37(12):3017–23.
33. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, Hutchins S, Leier CV, LeJemtel TH, Loh E, Nicklas J, Ogilby D, Singh BN, Smith W. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation. 2000;102(18):2222–7.
34. Hansen MS, Andersen A, Nielsen-Kudsk JE. Levosimendan in pulmonary hypertension and right heart failure. Pulm Circ. 2018;8(3):1–7.
35. Mishra A, Kumar B, Dutta V, Arya VK, Mishra AK. Comparative effect of levosimendan and milrinone in cardiac surgery patients with pulmonary hypertension and left ventricular dysfunction. J Cardiothorac Vasc Anesth. 2016; 30(3):639–46.
36. Burkhoff D, Borlaug BA, Shah SJ, Zolty R, Tedford RJ, Thenappan T, Zamanian RT, Mazurek JA, Rich JD, Simon MA, Chung ES, Raza F, Majure DT, Lewis GD, Preston IR, Rich S. Levosimendan improves hemodynamics and exercise tolerance in PH-HFpEF. JACC Heart Fail. 2021;9(5):360–70.
37. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, Gao Q, Hasenfuß G, Kahwash R, Kaye DM, Litwin SE, Lurz P, Massaro JM, Mohan RC, Ricciardi MJ, Solomon SD, Sverdlov AL, Swarup V, van Veldhuisen DJ, Winkler S, Leon MB, REDUCE LAP-HF II i. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. The Lancet. 2022;399(10330):1130–40.
38. Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J. 2013;41(1):217–23.
39. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs JS, Martinez F, Semigran M, Simonneau G, Wells A, Seeger W. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013;62(25):D100–8.
40. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, ESC Scientific Document Group. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS) Endorsed by: association for european paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J. 2015;37(1):67–119.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, Badano LP, Parati G, Vachiéry J-L. An updated meta-analysis of hemodynamics markers of prognosis in patients with pulmonary hypertension due to left heart disease. Pulmonary Circulation. 2022;12:e12145. https://doi.org/10.1002/pul2.12145

Right Heart Adaptation to Exercise in Pulmonary Hypertension: An Invasive Hemodynamic Study

CLAUDIA BARATTO, MD,[1,#] SERGIO CARAVITA, MD, PhD,[1,2,#] CÉLINE DEWACHTER, MD, PhD,[3] ANDREA FAINI, MSc, PhD,[1,6] GIOVANNI BATTISTA PEREGO, MD,[1] ANTOINE BONDUE, MD,[3] MICHELE SENNI, MD,[4] DENISA MURARU, MD, PhD,[1,5] LUIGI P. BADANO, MD, PhD,[1,5] GIANFRANCO PARATI, MD,[1,5] AND JEAN-LUC VACHIÉRY, MD[2]

Milano, Dalmine (BG), and Bergamo, Italy; and Bruxelles, Belgium

ABSTRACT

Background: Right heart failure (RHF) is associated with a dismal prognosis in patients with pulmonary hypertension (PH). Exercise right heart catheterization may unmask right heart maladaptation as a sign of RHF. We sought to (1) define the normal limits of right atrial pressure (RAP) increase during exercise; (2) describe the right heart adaptation to exercise in PH owing to heart failure with preserved ejection fraction (PH-HFpEF) and in pulmonary arterial hypertension (PAH); and (3) identify the factors associated with right heart maladaptation during exercise.

Methods and Results: We analyzed rest and exercise right heart catheterization from patients with PH-HFpEF and PAH. Right heart adaptation was described by absolute or cardiac output (CO)-normalized changes of RAP during exercise. Individuals with noncardiac dyspnea (NCD) served to define abnormal RAP responses (>97.5th percentile). Thirty patients with PH-HFpEF, 30 patients with PAH, and 21 patients with NCD were included. PH-HFpEF were older than PAH, with more cardiovascular comorbidities, and a higher prevalence of severe tricuspid regurgitation ($P < .05$). The upper limit of normal for peak RAP and RAP/CO slope in NCD were >12 mm Hg and ≥1.30 mm Hg/L/min, respectively. PH-HFpEF had higher peak RAP and RAP/CO slope than PAH (20 mm Hg [16−24 mm Hg] vs 12 mm Hg [9−19 mm Hg] and 3.47 mm Hg/L/min [2.02−6.19 mm Hg/L/min] vs 1.90 mm Hg/L/min [1.01−4.29 mm Hg/L/min], $P < .05$). A higher proportion of PH-HFpEF had RAP/CO slope and peak RAP above normal ($P < .001$). Estimated stressed blood volume at peak exercise was higher in PH-HFpEF than PAH ($P < .05$). In the whole PH cohort, the RAP/CO slope was associated with age, the rate of increase in estimated stressed blood volume during exercise, severe tricuspid regurgitation, and right atrial dilation.

Conclusions: Patients with PH-HFpEF display a steeper increase of RAP during exercise than those with PAH. Preload-mediated mechanisms may play a role in the development of exercise-induced RHF. (*J Cardiac Fail 2023;29:1261−1272*)

Key Words: Pulmonary hypertension, right heart catheterization, exercise, heart failure, right atrial pressure.

From the [1]Department of Cardiology, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milano, Italy; [2]Department of Management, Information and Production Engineering, University of Bergamo, Dalmine (BG), Italy; [3]Department of Cardiology, Cliniques Universitaires de Bruxelles, Hôpital Académique Erasme, Bruxelles, Belgium; [4]Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy; [5]Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy and [6]Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano, Italy.

Manuscript received November 21, 2022; revised manuscript received April 12, 2023; revised manuscript accepted April 12, 2023.

Reprint requests: Sergio Caravita, MD, PhD, Department of Management, Information and Production Engineering, Dyspnea and Pulmonary Hypertension Center, Department of Cardiology, University of Bergamo, Istituto Auxologico Italiano IRCCS Ospedale San Luca, Piazzale Brescia 20, 20149 Milano, Italy. Tel: +39 02 619112930. E-mail: sergio.caravita@unibg.it

Funding: The study was funded by the Italian Ministry of Health. CB is the recipient of a Research Grant from the European Society of Cardiology. AB received support from the Belgian Fonds de la Recherche Scientifique (FRS-FNRS − grant J.0011.19), from the Erasme Foundation (ULB) and from the Belgian Cardiac Surgery Foundation. JLV is the holder of the Actelion Research Chair on Pulmonary Hypertension in his department.

[#]Contributed equally as first author.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2023.04.009

Right heart failure (RHF) represents the final step of distinct diseases, differently involving the pulmonary circulation, such as pulmonary hypertension (PH) owing to heart failure with preserved ejection fraction (HFpEF) and pulmonary arterial hypertension (PAH).[1] Irrespective from its etiology, RHF is associated with a dismal prognosis, highlighting the need for an early identification.[1,2] In keeping with what was observed in left heart failure,[3] RHF may be defined by the inability of the heart to maintain a normal cardiac output (CO) or to do so at the expense of high right atrial pressure (RAP), at rest or during exercise.[4] Thus, exercise right heart catheterization (RHC) may unmask right heart maladaptation as a sign of early RHF.[5] However, neither the cutoffs for RAP increases during exercise nor the patterns of right heart adaptation to exercise in PH-HFpEF and PAH, or their determinants, have been described fully. Thus, we sought to (1) define the normal limits of RAP increase during exercise; (2) describe the extent and the frequency of right heart maladaptation to exercise in PH-HFpEF and in PAH; and (3) identify the factors associated with exercise-induced RHF in PH-HFpEF and PAH.

Methods

The Ethics Committee of Erasme Hospital (P2021/452) and Istituto Auxologico Italiano (protocol n 2022_09_27_01 approved on September 27, 2022) approved the study. We retrospectively analyzed data from consecutive patients referred at Istituto Auxologico Italiano and at Erasme Hospital from 2006 to 2021 who underwent a clinically indicated RHC at rest and during exercise for exertional dyspnea and/or suspicion of PH.

Study Population

We included consecutive patients with PH-HFpEF, PAH, or noncardiac dyspnea (NCD). PH-HFpEF was defined by signs and or symptoms of chronic heart failure, normal left ventricular ejection fraction ($\geq$50%), and elevated left heart filling pressures (pulmonary artery wedge pressure [PAWP] at rest $>$15 mm Hg) associated with PH at rest, that is, a mean pulmonary artery pressure (PAP) of $\geq$25 mm Hg.[6]

Patients with HFpEF but with normal pulmonary hemodynamics at rest, as well as those with significant primary left valvular heart disease (more than mild stenosis, more than moderate regurgitation), reduced left ventricular ejection fraction, significant lung disease, congenital heart disease, left-to-right shunt, unstable coronary artery disease or myocardial infarction, hypertrophic or infiltrative cardiomyopathy, primary renal or hepatic disease, high-output HF, and constrictive pericarditis were excluded.

Patients with PAH met the traditional hemodynamic definition of precapillary PH (mPAP $\geq$ 25 mm Hg, PAWP $\leq$ 15 mm Hg, pulmonary vascular resistance [PVR] $\geq$ 3 WU)[6] provided that of other forms of precapillary PH, such as chronic thromboembolic PH, PH owing to lung disease, or multifactorial PH have been excluded.

Individuals with NCD, who had normal hemodynamics at rest and during exercise, served to define abnormal increase in RAP, that is, values of RAP and of RAP/CO slope of $>$97.5th percentile. They were individuals referred for invasive exercise assessment because of exercise intolerance, but who did not display any demonstrable cardiac or respiratory etiology for symptoms, with normal rest and exercise PA hemodynamics, that is, a mean PAP at rest of $<$25 mm Hg with a PVR of $<$3 WU, a mean PAP during exercise of $<$30 mm Hg with a total pulmonary resistance [TPR] of $<$3 WU, PAWP at rest of $<$15 mm Hg, and PAWP during exercise of $<$25 mm Hg, together with a PAWP/CO slope of $<$2 mm Hg/L/min.[7]

Patient history and physical examinations were obtained from the medical charts. Two-dimensional and Doppler echocardiography was performed according to American Society of Echocardiography guidelines by experienced ultrasound technicians and cardiologists.[8]

RHC at Rest and During Exercise

Patients were studied on chronic medications, in the nonfasting state, without sedation, in supine position. A 7F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace as well as by an oxygen saturation of $>$94% sampled at the tip of the catheter. The transducer was zeroed at the midthoracic line, halfway between the anterior sternum and the bed surface.[7] Hemodynamic measurements were performed at rest and during the last minute of each step of a symptom-limited, step-incremental, maximal exercise test in the supine position.[5] The increment in workload was personalized to obtain $\geq$3 steps of exercise before exhaustion. Each exercise step lasted approximately 2$-$3 minutes, to obtain a steady state for oxygen uptake on any given exercise level, aiming for a duration of the exercise time of approximately 10 minutes[5].

Hemodynamic Variables

Pressure values were averaged over several heartbeats and $\geq$3 respiratory cycles, and reflect the agreement of 2 readers who visually reviewed all pressure traces.[5] CO was calculated by the direct Fick

method (Auxologico) or by thermodilution (Erasme Hospital).

CO measured via thermodilution was based on 3−5 cold water injections at rest, whereas during exercise, CO was measured using a mean of 3 cold water injections, verifying the visualized temperature curve, as the mean of all available thermodilution measurements recorded at the end of each exercise step.[9] To calculate CO via the direct Fick method, patients were connected with a nonrebreathing Hans−Rudolph mask to a metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA) to obtain, at the end of each step of the test, in steady-state conditions, a 30-second average of oxygen consumption. At the same time, blood was sampled both from the pulmonary artery and from the radial artery for gas analysis and hemoglobin determination. The direct Fick CO was thus calculated from oxygen consumption, hemoglobin, radial and pulmonary artery oxygen saturation, and oxygen partial pressure, using the standard formula.[7]

TPR was computed as the mean PAP/CO at peak exercise.[10] A linear regression was applied to multiple pairs of PAWP and CO points, to calculate the PAWP/CO linear regression slope.[3,11,12] The same methodology was applied to multiple pairs of RAP and CO points. Right heart adaptation to exercise was described either using absolute or CO-normalized RAP increase during exercise (RAP/CO slope). The left ventricular transmural pressure (LVTMP), which reflects the LV preload independent of right heart filling and pericardial restraint, was calculated as PAWP − RAP.[13]

Estimated stressed blood volume (eSBV), a measure of functional preload, was computed using a commercially available hemodynamic simulator (retrieved online from URL: http://harvi.online; access date 4 May 2022) that has been used in prior studies.[14,15] For estimation of SBV, the measured values of heart rate, CO, RAP, PAWP, systolic and diastolic arterial pressures, and PAPs, as well as cardiac chamber dimensions are provided to the software.

Statistical Analysis

Results are expressed as mean ± standard deviation or absolute number (*n* and %) or median [first to third quartile] if the data did not follow a normal distribution. Hemodynamic data from individuals with NCD that, by definition, were characterized by normal pulmonary pressures at rest and normal exercise hemodynamic responses, are reported as 2.5−97.5 confidence interval as "reference" normal values, without formal comparison with the other group of patients defined by abnormal hemodynamics at rest, to avoid underpowered multiple comparisons. Demographic, clinical and hemodynamic data between different patients' groups (PH-HFpEF and PAH) were compared using the Wilcoxon rank-sum test with continuity correction for the continuous variables and Pearson's χ^2 test or Fisher's exact rest (when the expected counts were <5) for the categorical data. Additionally, we performed a sensitivity analysis excluding patients with severe tricuspid regurgitation (TR) to control for potential confounders.

Kendall's rank correlation tau was used to verify correlations between RAP/CO slope and continuous variables (age, body mass index [BMI], tricuspid annular plane systolic excursion, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure, N-terminal pro-brain natriuretic peptide, creatinine, ratio of minute ventilation to carbon dioxide production slope, SBV, change in SBV, PAWP, PVR, TPR, and pulmonary artery compliance). The Wilcoxon rank-sum test was used to perform a comparison of dichotomized variables (New York Heart Association functional classes I−II vs III−IV; TR severe vs nonsevere; RA dilated vs nondilated; AF vs SR; presence of diuretic therapy) between patients with RAP/CO slope above or below the pathological threshold, to determine those variables associated with high RAP/CO slope. All these association were tested both in the whole PH cohort as well as stratifying patients according to the underlying diagnosis (PH-HFpEF and PAH).

All tests were 2-tailed at *P* value of <.05. Statistical analyses were performed with "R: A language and environment for statistical computing. R Foundation for Statistical Computing," R Core Team (2021).

Results

Clinical Characteristics

Sixty patients (30 PH-HFpEF, 30 PAH) were included in the analysis, together with 21 individuals with NCD.

Patients with PH-HFpEF were older than patients with PAH and with a higher burden of cardiovascular comorbidities, such as systemic hypertension, diabetes mellitus, and atrial fibrillation. They were more frequently treated with diuretics, including both loop diuretics and mineralocorticoid receptor antagonists ($P < .01$); all patients with PAH received a specific therapy, including various combination of endothelin receptor antagonist, phosphodiesterase5 inhibitors, soluble guanylate cyclase stimulator and prostacyclin (Table 1). As shown in Table 2, blood tests in patients with PH-HFpEF were consistent for worse kidney function and lower hemoglobin values than patients with PAH. At variance, N-terminal pro-brain natriuretic peptide values did not show significant differences between groups.

Table 1. General Characteristics and Comorbidities of PH-HFpEF and PAH

	PH-HFpEF ($n = 30$)	PAH ($n = 30$)	P Value
Characteristics			
Age, y	74.4 [71.7−80.9]	62.0 [49.3−68.4]	<0.001
Female sex, *n* (%)	21 (70)	21 (70)	<0.99
BMI, kg/m^2	27.5 [24.2−30.3]	25.1 [22.9−28.4]	0.097
NYHA FC			
II, %	13 (43)	8 (27)	0.105
III, %	17 (57)	22 (73)	
Comorbidities			
Systemic hypertension, *n* (%)	26 (87)	10 (35)	<0.001
Diabetes mellitus, *n* (%)	8 (27)	2 (7)	0.038
Dyslipidemia, *n* (%)	8 (27)	9 (30)	0.774
Atrial fibrillation, *n* (%)	21 (70)	3 (10)	<0.001
Smoking, *n* (%)	1 (3)	0 (0)	0.731
Obesity, *n* (%)	7 (23)	2 (7)	0.145
Coronary artery disease, *n* (%)	5 (17)	5 (17)	>0.99
Cardiac surgery, *n* (%)	8 (27)	2 (7)	0.079
PCI, *n* (%)	0 (0)	4 (13)	0.112
OSAS, *n* (%)	7 (23)	1 (3)	0.052
Connective tissue disease, *n* (%)	3 (10)	6 (20)	0.472
Pulmonary embolism, *n* (%)	2 (7)	0 (0)	0.492
Cerebrovascular disease, *n* (%)	3 (10)	2 (7)	>0.99
Thoracic radiotherapy, *n* (%)	2 (7)	1 (3)	>0.99
AF ablation, *n* (%)	8 (27)	0 (0)	0.005
COPD, *n* (%)	5 (17)	1 (3)	0.195
Interstitial lung disease, *n* (%)	6 (20)	1 (3)	0.103
Treatment			
Loop diuretics, *n* (%)	28 (93)	16 (55)	<0.001
MRAs, *n* (%)	10 (33)	3 (10)	<0.001
PAH-specific therapy			
Endothelin receptor antagonist, *n* (%)	0 (0)	23 (77)	
PDE5i, *n* (%)	0 (0)	21 (70)	
sGC stimulator, *n* (%)	0 (0)	4 (13)	
Parenteral prostacyclin, *n* (%)	0 (0)	2 (7)	
Monotherapy, *n* (%)	0 (0)	12 (40)	
Dual therapy, *n* (%)	0 (0)	16 (53)	
Triple therapy, *n* (%)	0 (0)	2 (7)	
PAH etiology			
Idiopathic PAH, *n* (%)		13 (43)	
Heritable PAH, *n* (%)		1 (3)	
Drug-induced PAH, *n* (%)		3 (10)	
CTD-PAH, *n* (%)		9 (30)	
CHD-PAH, *n* (%)		2 (7)	
POPH, *n* (%)		2 (7)	

AF, atrial fibrillation; BMI, body mass index; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HFPEF, heart failure with preserved ejection fraction; MRAs, Mineralocorticoid receptor antagonists; NYHA FC, New York Heart Association functional class; OSAS, obstructive sleep apnea syndrome; PCI, percutaneous coronary intervention; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; POPH, porto-pulmonary hypertension; sGC, soluble guanylate cyclase.

Clinical characteristics of the 21 individuals with NCD are shown in Supplementary Table 1. It was on average a middle-aged, prevalently female, normal-weight population with few comorbidities.

Echocardiography

Echocardiography showed the typical left atrial dilation and a higher E/E' in patients with PH-HFpEF. Patients with PAH presented with more relevant right chamber remodeling and right ventricular (RV) dysfunction, higher estimated systolic PAP, and lower ratio between tricuspid annular plane systolic excursion and systolic PAP. Severe TR was frequent in both groups but more prevalent in PH-HFpEF (70% in PH-HFPEF and 50% in PAH, $P = .032$) (Table 2).

Reference Values for Resting and Exercise Hemodynamics From NCD Individuals

The 2.5%−97.5% confidence intervals for hemodynamics of NCD patients, individuating normal values, are shown in Supplementary Table 2. Among individuals with NCD, CO was calculated with the Fick direct method in 12 (57%) and with thermodilution in 9 (43%). NCD individuals showed on average a resting RAP, a peak RAP and a RAP/CO slope of 4 mmHg [1-5 mmHg], 5 mmHg [4-7 mmHg], and 0.32 mmHg/L/min [0.11 -0.73 mmHg/L/min], respectively.

Table 2. Blood Tests and Echocardiography of Patients with PH-HFpEF and Patients with PAH

	PH-HFpEF ($n = 30$)	PAH ($n = 30$)	*P* Value
Blood tests			
NTproBNP, pg/mL	682 (279–1029]	401 [238–1584]	.3
Creatinine, mg/dL	1.0 [0.9–1.2]	0.9 [0.7–0.9]	.026
Hemoglobin, g/dL	12.7 [11.2–13.8]	14.3 [13.7–14.9]	.001
Echocardiography			
Left ventricular ejection fraction, *n* (%)	63.8 [58.1–66.0]	60.0 [60.0–67.0]	.7
RV dilation, *n* (%)			.038
Non/mild, *n* (%)	20 (67)	12 (40)	
Moderate/severe, *n* (%)	10 (33)	18 (60)	
LA dilation			<.001
Non/mild, *n* (%)	8 (27)	23 (77)	
Moderate/severe, *n* (%)	22 (73)	7 (23)	
RA dilation			.787
Non/mild, *n* (%)	19 (63)	20 (67)	
Moderate/severe, *n* (%)	11 (37)	10 (33)	
E/E' avg	12 [10–14]	9 [8–10]	.006
TAPSE, mm	22 [19–25]	17 [15–19]	.001
SPAP, mm Hg	50 [43–58]	65 [55–75]	<.001
TAPSE/SPAP	0.42 [0.38–0.51]	0.27 [0.20–0.32]	<.001
TR			.032
Non/mild, *n* (%)	7 (23)	15 (50)	
Moderate/severe, *n* (%)	23 (77)	15 (50)	

EF, ejection fraction; LA, left atrium; LV, left ventricle; NTproBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RV, right ventricle; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation. Other abbreviations as in Table 1.

Data are median [first to third quartile] unless otherwise noted.

Abnormal resting RAP, peak RAP, and RAP/CO slope, defined by values of >97.5th percentile obtained in this cohort of control subjects, were >7 mm Hg, >12 mm Hg, and ≥1.30 mm Hg/L/min, respectively.

Resting Hemodynamics of Patients with PH

CO was calculated with the Fick direct method in 27 (90%) patients with PH-HFpEF and in 9 (30%) patients with PAH. At rest, patients with PAH had typically a higher systolic, diastolic, and mean PAP; higher PVR; and expectedly lower PAWP as well as LVTMP than PH-HFpEF ($P < .001$) (Table 3). Cardiac index, as well as CO, was similar between the 2 groups (2.50 L/min/m^2 [2.14–3.07 L/min/m^2] vs 2.59 L/min/m^2 [2.16–2.91 L/min/m^2], $P > .99$, and 4.62 L/min [3.87–5.56 L/min] vs 4.59 L/min [3.73–5.14 L/min], respectively, $P = .8$), along with similar heart rate and stroke volume. Patients with PH-HFpEF had higher RAP than patients with PAH (10 mm Hg [7–13 mm Hg] vs 6 mm Hg [3–10 mm Hg], $P = .003$). Eleven patients with PH-HFpEF (37%) and 19 patients with PAH (63%) had a normal RAP (<8 mm Hg) at rest ($P < .001$). The estimated SBV did not differ between the 2 groups ($P = .7$).

Exercise Hemodynamics of Patients with PH

All patients performed a maximal volitional effort to exhaustion. On average, patients performed 3 ± 1 steps of exercise. As shown in Table 4, patients with PAH presented higher systolic, diastolic and mean PAP at peak exercise than patients with PH-HFpEF ($P < .001$), together with a greater exercise-induced increase in mPAP (20 ± 8 mm Hg [15–24 mm Hg] vs 16 ± 7 mm Hg [11–20 mm Hg], $P = .01$), as reported in Supplementary Table 3. At peak exercise, patients with PAH presented higher indexes of RV afterload, including both PVR (6.68 WU [4.63–8.59 WU] vs 1.37 WU [1.01–2.62 WU], $P < .001$) and TPR (9.05 WU [6.45–10.52 WU] vs 6.14 WU [5.09–7.49 WU], $P < .001$) than patients with PH-HFpEF.

Per definition, patients with PH-HFpEF presented with an abnormal increase in left heart filling pressure (Table 4), with a mean PAWP at peak exercise of 33 mm Hg [26–39 mm Hg] and a higher PAWP/CO slope than PAH (3.75 mm Hg/L/min [2.43–4.97 mm Hg/L/min] vs 1.82 mm Hg/L/min [0.68–3.06 mm Hg/L/min], $P < .001$). Moreover, patients with PH-HFpEF showed a greater increase in PAWP during exercise than PAH (13 mmHg [7-17 mmHg] vs 5 mmHg [3-9 mmHg], respectively, $P < .01$), as shown in Supplementary Table 3. Patients with PH-HFpEF had a higher LVTMP than patients with PAH at peak exercise (12 mm Hg [6 to 16 mm Hg] vs 3 mm Hg [−2 to 5 mm Hg], $P < .01$), as well as a higher rate of increase in LVTMP (2 [−3 to 6] vs −1 [−4 to 1], $P = .033$). Only 3 patients with PAH had a peak PAWP of≥25 mm Hg, suggesting the presence of a latent LV diastolic disfunction.

CO as well as cardiac index at peak did not differ between PH-HFpEF and patients with PAH

Table 3. Rest Hemodynamics of Patients with PH-HFpEF and Patients with PAH

	PH-HFpEF ($n = 30$)	PAH ($n = 30$)	*P* Value
eSBV, mL	1708 [1541 to 2138]	1808 [1489 to 2235]	.7
HR, bpm	72 [60 to 80]	77 [72 to 83]	.07
Systolic BP, mm Hg	149 [141 to 163]	115 [107 to 137]	<.001
Diastolic BP, mm Hg	74 [62 to 92]	73 [63 to 80]	.7
Systolic PAP, mm Hg	44 [38 to 47]	66 [54 to 82]	<.001
Diastolic PAP, mm Hg	21 [18 to 22]	30 [23 to 35]	<.001
Mean PAP, mm Hg	28 [26 to 30]	43 [32 to 51]	<.001
PAWP, mm Hg	18 [18 to 25]	8 [5 to 12]	
RAP, mm Hg	10 [7 to 13]	6 [3 to 10]	.003
RAP/PAWP	0.53 [0.38 to 0.67]	0.68 [0.40 to 0.92]	.098
LVTMP, mm Hg	10 [5 to 12]	3 [1 to 4]	<.01
CO, L/min	4.62 [3.87 to 5.56]	4.59 [3.73 to 5.14]	.8
CI, L/min/m^2	2.50 [2.14 to 3.07]	2.59 [2.16 to 2.91]	>.99
PVR, WU	1.92 [1.51 to 2.16]	6.98 [5.39 to 8.96]	<.001
TPR, WU	6.02 [4.78 to 7.69]	8.71 [6.56 to 11.28]	<.001
SAO_2, %	95.8 [95.0 to 96.9]	95.2[89.5 to 69.7]	.4
SVO_2, %	69.9 [65.6 to 73.1]	67.5 [60.7 to 74.9]	.8
SV, mL	66 [51 to 85]	56 [49 to 71]	.2
PAC, mL/ mm Hg	3.01 [2.32 to 4.01]	1.65 [1.005 to 2.33]	<.001
TPG, mm Hg	8 [5 to 11]	35 [26 to 40]	<.001
DPG, mm Hg	1 [−2 to 3]	21 [18 to 25]	<.001

BP, blood pressure; CI, cardiac index; CO, cardiac output; DPG, diastolic pulmonary gradient; eSBV, estimated stressed blood volume; HR, heart rate; LVTMP, left ventricular transmural pressure; NCD, noncardiac dyspnea; PAP, pulmonary artery pressure; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SAO_2, arterial oxygen saturation; SV, stroke volume; SVO_2, central venous oxygen saturation; TPG, transpulmonary gradient; TPR, total pulmonary resistance. Other abbreviations as in Table 1.

Data are median [first to third quartile].

(6.80 L/min [5.56−9.03 L/min] vs 7.21 L/min [3.35−8.92 L/min], $P = .9$, and 4.06 L/min/m^2 [3.14−4.49 L/min/m^2] vs 3.63 L/min/m^2 [3.24−5.30 L/min/m^2], $P = .7$, respectively), who also presented at the same step of exercise with nondifferent values of heart rate and stroke volume, as well as similar increase in SV from rest to peak, as reported in Supplementary Table 3.

Right heart maladaptation to exercise was observed both in PH-HFpEF and patients with PAH,

Table 4. Hemodynamics at Peak Exercise in Patients With PH-HFpEF and Patients With PAH

	PH-HFpEF ($n = 30$)	PAH ($n = 30$)	*P* Value
SBV, mL	3158 [2834−3429]	2710 [2349−3347]	.049
HR, bpm	91 [78−121]	111 [100−119]	.9
Systolic BP, mm Hg	181 [149−190]	149 [127−170]	.06
Diastolic BP, mm Hg	80 [66−88]	83 [75−92]	.5
Systolic PAP, mm Hg	64 [55−74]	97 [79−116]	<.001
Diastolic PAP, mm Hg	33 [28−41]	43 [38−55]	<.001
Mean PAP, mm Hg	45 [36−49]	62 [52−74]	<.001
PAWP, mm Hg	33 [26−39]	15 [11−17]	<.001
RAP, mm Hg	20 [16−24]	12 [9−19]	<.001
RAP/PAWP	0.64 [0.57−0.79]	0.82 [0.67−1.18]	.005
LVTMP, mm Hg	12 [6−16]	3 [−2−5]	<.01
TPG, mm Hg	10 [7−17]	48 [38−55]	<.001
DPG, mm Hg	1 [−4−6]	28 [24−38]	<.001
CO, L/min	6.80 [5.56−9.03]	7.21 [3.35−8.92]	.9
CI, L/min/m^2	4.06 [3.14−4.49]	3.63 [3.24−5.30]	.7
SV, mL	79 [58−94]	65 [48−81]	.2
PVR, WU	1.37 [1.01−2.62]	6.68 [4.63−8.59]	<.001
TPR, WU	6.14 [5.09−7.49]	9.05 [6.45−10.52]	.001
PAC, mL/ mm Hg	2.48 [2.02−3.26]	1.29 [0.82−2.06]	<.001
SAO_2, %	95.9 [93.4−96.6]	90.2 [82.5−94.2]	.002
SVO_2, %	31.8 [24.0−38.9]	42.4 [36.6−46.8]	.010
RAP/CO slope	3.47 [2.02−6.19]	1.90 [1.01−4.29]	.025
PAWP/CO slope	3.75 [2.43−4.97]	1.82 [0.68−3.06]	<.001
Mean PAP/CO slope	4.99 [4.21−6.34]	6.44 [4.39−8.64]	.1
Workload, Watts	45 [30−60]	30 [20−40]	.004

Abbreviations as in Table 1 and 3.

Data are median [first to third quartile].

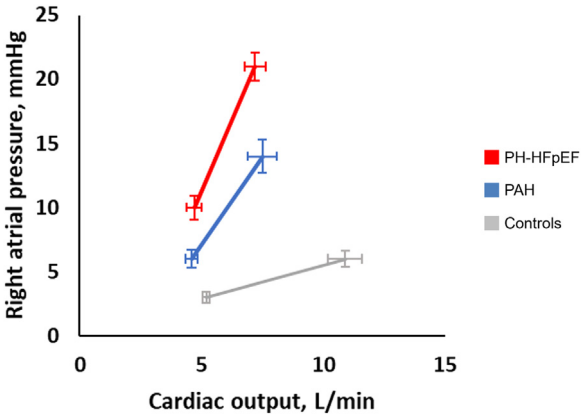


Fig. 1. Hemodynamics at rest and at peak exercise in patients with pulmonary hypertension owing to heart failure with preserved ejection fraction (PH-HFpEF, red) and in patients with pulmonary arterial hypertension (PAH, blue). Individuals with noncardiac dyspnea (gray) are displayed as normal reference. Mean right atrial pressure and cardiac output coordinates (± standard error of the mean) at rest and at peak exercise are plotted for the 3 groups. PAH, pulmonary arterial hypertension.

witnessed by mean peak RAP and RAP/CO slope higher than the references values (Fig. 1 and Table 4).

On average, patients with PH-HFpEF had higher peak RAP than PAH (20 mm Hg [16−24 mm Hg] vs 12 mm Hg [9−19 mm Hg], $P < .001$) as well as higher RAP/CO slope (3.47 mm Hg/L/min [2.02−6.19 mm Hg/L/min] vs 1.90 mm Hg/L/min [1.01−4.29 mm Hg/L/min], $P = .025$). Additionally, a greater proportion of patients with PH-HFpEF had a RAP/CO slope and a peak RAP above normal, compared with patients with PAH (90% and 91% of PH-HFpEF and 69% and 44% of PAH, respectively, $P < .001$). Ninety-one percent of patients with PH-HFpEF with a normal RAP at rest had a pathological increase in RAP, both when RAP was considered in absolute values and when it was flow normalized. Thirty-two percent and 71% of patients with PAH with a normal RAP at rest had either an abnormally high RAP or a steep RAP/CO slope during exercise, respectively. Moreover, both eSBV at peak exercise, as well as its rate of increase from resting values, were found to be higher in PH-HFpEF than PAH group ($P < .01$), as shown in Supplementary Table 3.

Finally, we found that the RAP/CO slope in the whole cohort was associated with age ($\tau = 0.237$, $P = .012$), with the rate of increase in eSBV during exercise ($\tau = 0.274$, $P = .003$), as well as with the presence of severe TR ($P = .005$), and right atrial dilation ($P = .027$), as shown in Supplementary Table 4. Considering only the PH-HFpEF group, we found that RAP/CO slope was associated with BMI ($\tau = 0.264$, $P = .045$). In the PAH group, RAP/CO slope was associated with PVR ($\tau = 0.289$ $P = .038$), TPR ($\tau = 0.302$, $P = .031$), severe TR ($P = .026$), and the rate of increase in eSBV during exercise ($P = .032$).

Sensitivity Analysis Excluding Patients With Severe TR

A sensitivity analysis on rest and exercise hemodynamics of patients with PH-HFpEF and patients with PAH excluding the subgroup with severe TR ($n = 13$) is reported in Supplementary Tables 5 and 6. These hemodynamic results are in line with those reported without excluding patients with PH with severe TR.

Discussion

Our data show that (1) both PH-HFpEF and PAH present an abnormal increase in RAP during exercise compared with control subjects; (2) the right heart maladaptation to exercise was both more frequent and severe in PH-HFpEF than in patients with PAH; and (3) both preload- and afterload-mediated mechanisms seem to account for the development of right atrial dysfunction during exercise in PH.

Invasive data collected during exercise from individuals without discernible cardiac or respiratory causes of exertional dyspnea allowed us to identify the normal limits of RAP increase, thus defining right heart maladaptation to exercise when the peak RAP was >12 mm Hg or the RAP/CO slope was ≥1.30 mm Hg/L/min. Based on these values, we expectedly found that both patients with PH-HFpEF and patients with PAH showed on average an abnormal increase in right heart filling pressure during exercise, both in absolute and flow-normalized values. This finding might be particularly relevant for the proportion of patients with PH with normal RAP at rest, presenting features of RHF unmasked during physical exercise (Fig. 2), emphasizing the fundamental role of provocative tests in the catheterization laboratory. However, the occurrence of RHF seems to have a different prevalence, expression and physiopathology in the 2 groups, being more frequent and significantly worse in patients with PH-HFpEF than in patients with PAH.

Indeed, among patients with a normal RAP at rest, 91% and 90% of the PH-HFpEF cohort presented with exercise-induced RHF (ie, either high RAP or high RAP/CO slope), as compared with 32% or 71% of patients with PAH with higher than normal absolute peak RAP or flow-corrected RAP increase during exercise, respectively. Additionally, patients with PH-HFpEF, as compared with PAH, presented both with an upward shift and steepening of the RAP/CO relationship, despite a lower pulmonary hemodynamic load (Fig. 1). Furthermore, preload-related parameters resulted associated with the development of exercise-induced RHF. At a first glance, these findings may appear counterintuitive, because we are

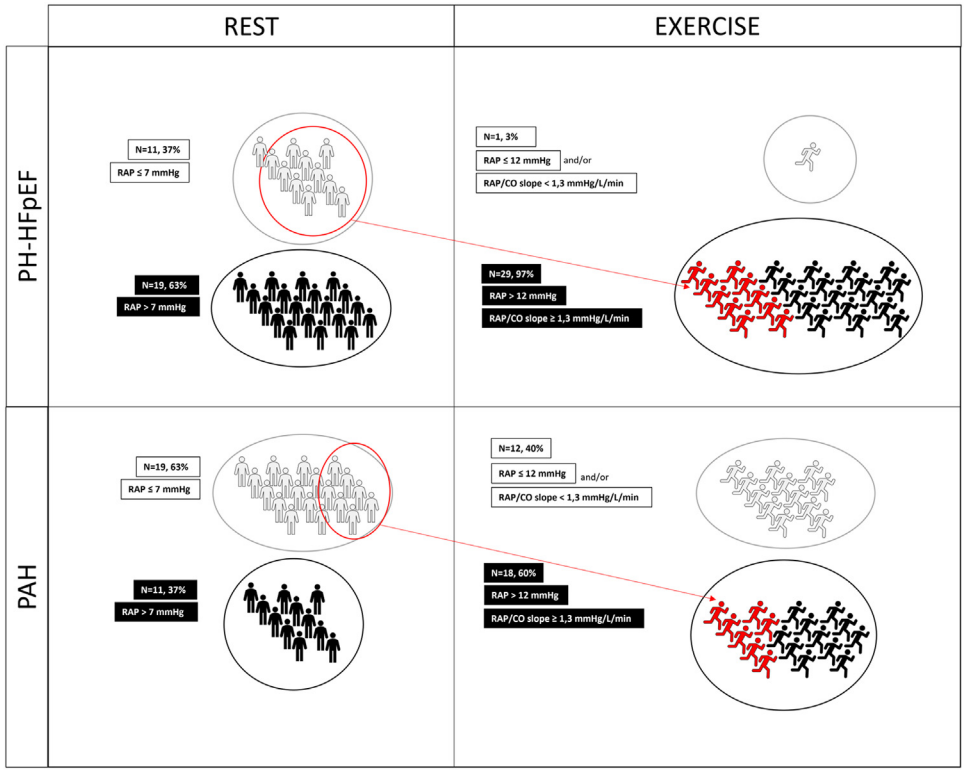


Fig. 2. Right atrial hypertension in PH-HFpEF (top) and in PAH (bottom), at rest (left) and during exercise (right). CO, cardiac output; RAP, right atrial pressure. Other abbreviations as in Fig. 1.

much more used to focus on afterload-dependent mechanisms of RHF.

It is true that even mild increases in PVR have been associated with outcomes,[16] and that, especially in HFpEF, high PAWP contributes to augment RV pulsatile (over resistive) load.[17,18] However, the mild alteration in PVR and pulmonary artery compliance with which our patients with PH-HFpEF presented both at rest and during exercise were by far lower than those displayed by patients with PAH, thus suggesting that other, non–afterload-related factors may intervene in right heart maladaptation during exercise. Indeed, it has been proposed recently that preload- rather than afterload-mediated mechanisms may account for the development of RHF in patients with HFpEF.[19] Key elements driving hemodynamic disturbances and disease progression in HFpEF may include atrial fibrillation-induced cardiac remodeling,[20] decreased capacitance and compliance of the venous system,[21] expansion and redistribution of plasma volume with increased eSBV,[20–22] as well as occurrence of functional TR.[23,24] In particular, increased eSBV, right atrial dilation, and functional TR might be tightly linked in a vicious circle perpetuating a condition of relative hypervolemia.[25] This finding, along with both the reduced capacitance and compliance of the venous system and the increased chamber stiffness that characterizes HFpEF, may explain the higher RAP both at rest and during exercise in PH-HFpEF than in patients with PAH. Additionally, right heart maladaptation in PH-HFpEF was associated with BMI. This finding may be in line with higher ventricular interdependence in the obese HFpEF phenotype, favored by functional extrinsic constriction and greater volume overload,[12] as well as with an enhanced LA/RA interaction, recently suggested as a potential factor contributing to the increased RAP in HFpEF.[26] Indeed, our PH-HFpEF population presented with a less than expected increase in LVTMP from rest to peak exercise (+2 mm Hg on average), which was not qualitatively different from the LVTMP increase in NCD (+3 mm Hg), and one-half the values reported in the literature in the HFpEF population (+7 mm Hg),[13] suggesting functional pericardial constraint, potentially driven by obesity and/or TR.

When looking only at the PAH cohort, whose more represented etiology was idiopathic, hereditary, or drug induced, with all patients receiving specific PAH treatment, we found that right heart maladaptation was less represented than in PH-HFpEF, and the results associated both with preload- and RV afterload-mediated factors. Patients with PAH presented a decrease in LVTMP during exercise, suggesting reduced LV preload, and a high ratio of RAP to PAWP, pointing to increased ventricular interaction in PAH,[27] together with a potential additional role of eSBV and TR, whose severity was,

however, less frequently represented in patients with PAH than in patients with PH-HFpEF. Additionally, despite the higher pulmonary hemodynamic load (PVR, TPR) and the more impaired ventriculoarterial coupling in patients with PAH than in patients with PH-HFpEF, we may hypothesize that the presence of sinus rhythm with preserved right atrial contraction in the former might allow to maintain more frequently a normal mean RAP, even in the presence of high afterload burden and RV diastolic dysfunction. Moreover, the relatively better right heart adaptation to exercise our PAH than patients with PH-HFpEF could be explained both by the fact that patients with PAH were all optimally titrated with PAH specific therapy, and that idiopathic, hereditary, or drug-induced PAH, rather than PAH associated with systemic sclerosis, was the most frequent etiology. Indeed, it has been shown that RV dysfunction is worse in PAH associated with systemic sclerosis than in idiopathic PAH.[28]

Therefore, our findings highlight the crucial role of preload-related mechanisms in the genesis of RHF in PH and reinforce the importance of afterload-related mechanisms in the development of RHF in patients with PAH. Although the right heart is able to accommodate large increase in preload,[1] its reserve might be stretched up to its limits, favoring RHF. The relationship between RAP and CO could also be viewed as the right heart ability to increase CO as RAP rises during physical effort, representing an inverse Frank−Starling relationship. Thus, the steeper RAP/CO slope in PH-HFpEF may indeed imply a flatter CO increase over RAP, and a rightward-shifted response in stroke volume, suggesting an impaired Frank−Starling reserve in this cohort, which is expected to be mainly favored by preload-dependent mechanisms (Visual Take Home Graphic). This finding reinforces the idea that drugs acting on the pulmonary circulation should not favorably impact on exercise hemodynamics in PH-HFpEF, whereas novel techniques modulating preload (eg, splanchnic denervation) might be of benefit.[15] Additionally, we cannot exclude that patients with PAH, in addition to specific drug treatment for this disease, may benefit from preload modulation.[15]

Limitations

This study was performed on a relatively small number of patients from 2 centers that used the same methodology for pulmonary and filling pressure measurements, but different tools for CO estimation. The use of thermodilution method in 41% of cohort, in particular in 90% of patients with PH-HFpEF and in 30% of patients with PAH, was one of the major limitations of this work, leading to a potential underestimation of CO and a potential overdiagnosis of exercise-induced RA hypertension.[29] However, thermodilution is generally viewed as a reliable alternative method to the gold standard direct Fick method.[5] Moreover, in a recent retrospective analysis on 300 patients evaluated with RHC at rest and during exercise, the mean bias of thermodilution as compared with the direct Fick method was small (difference between thermodilution and direct Fick method at rest = −0.33 ± 1.53 L/min, during 25 W exercise = −0.06 ± 2.29 L/min), even in presence of significant TR.[9] Despite this finding, if we assume that thermodilution might have underestimated CO as compared with direct Fick, especially during exercise, and, accordingly the RAP/CO slope might have been underestimated as well, our results showing higher RAP/CO slope in PH-HFpEF vs PAH would have been even more robust, because CO was measured by thermodilution in the majority of patients with PAH.

Our population included patients referred for RHC and was not selected randomly; thus, a referral bias may limit the generalizability of our findings. In particular, control patients were not truly normal in that they were referred for invasive hemodynamic stress testing because of exertional dyspnea and/or suspicion of PH. Additionally, the 3 groups considered were not matched for age, sex, and BMI, and 10% of our patients with PAH were characterized by a LV diastolic dysfunction unmasked by exercise. HFpEF was defined as comorbidity of PAH in these cases, given that they were characterized by a hemodynamic diagnosis of precapillary PH at rest, together with a clinical diagnosis of PAH.

Because of the retrospective nature of this study and given that data were collected over a long period of time, some echocardiographic variables are reported only as qualitative parameters, and simultaneous exercise echocardiographic data were not available. However, the left ventricular ejection fraction is not critical to the determination of eSBV. The strategy for estimating SBV by the software is to adjust model parameter values of all the capacitive elements in the model, including those of heart chambers, so that chamber volumes contribute a very small percentage to the total eSBV.[30]

The association of RAP/CO slope with eSBV and TR, evident when analyzing the whole cohort of patients with PH, was unfortunately missed when restricting the analysis to PH-HFpEF, who nonetheless presented with higher eSBV and more frequently with severe TR than PAH. However, our relatively small PH-HFpEF population quite homogeneously presented with these 2 alterations (high eSBV and severe TR), limiting the exploration of association between RAP/CO slope and these 2 variables in this population.

Finally, we did not explore the prognostic impact of right heart maladaptation to exercise in our population: patients with PH-HFpEF were found to homogeneously present with exercise-induced RHF, and patients with PAH were enrolled through a 15-year period, during which treatment algorithms have dramatically changed, with prognostic implications. However, owing to the relatively small sample size, we could not have controlled a prognostic analysis for these confounders. The main objective of our study was to individuate for the first time the normal patterns of right heart adaptation to exercise, and to describe the pathophysiological mechanisms underlying exercise-induced RHF in PH-HFpEF and in PAH. From this perspective, our results should be viewed as hypothesis generating, and the prognostic impact of right heart maladaptation should be explored in future prospective studies.

Conclusions

Patients with PH-HFpEF display more frequently a steeper increase of RAP during exercise than patients with PAH, despite similar CO, suggesting a more exhausted Frank–Starling reserve in the former group. A dysfunctional preload with functional pericardial constraint may play a role in determining steep RAP increase during exercise in PH.

Three brief bullet points about how our work applies to patients

- RAP during exercise should not exceed 12 mm Hg (absolute values) or 1.3 mm Hg/L/min (CO-normalized values).
- Patients with PH frequently display an abnormal increase in RAP during exercise, which may be more frequent and severe in PH owing to heart failure with preserved ejection fraction than in pulmonary arterial hypertension, implying an exhausted Frank–Starling reserve in the former group.
- Preload-related factors (including stressed blood volume and TR) may underlie right heart maladaptation to exercise in patients with PH.

Lay Summary

Right heart failure is the final step of any form of pulmonary hypertension, portending a poor prognosis. Early identification of right heart failure is desirable, and exercise right heart catheterization could unmask features suggestive of right heart maladaptation. Our study identified for the first time the limits of normal response of right heart filling pressure to exercise, and shows that right heart maladaptation to exercise may be more frequent and severe in patients with pulmonary hypertension owing to left heart disease than in patients with pulmonary arterial hypertension. Additionally, we could identify factors associated with the development of exercise right heart maladaptation in our population that may help to improve our understanding of right heart failure in pulmonary hypertension.

Declaration of Competing Interest

None

Acknowledgments

The authors are grateful to Laboratori Guidotti S. p.A. for providing free-of charge software for echocardiographic analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.04.009.

References

1. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53:1801900. https://doi.org/10.1183/13993003.01900-2018. Published 2019 Jan 24.
2. Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB, International Right Heart Failure Foundation Scientific Working Group. Right heart failure: toward a common language. J Heart Lung Transplant 2014;33:123–6. https://doi.org/10.1016/j.healun.2013.10.015.
3. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, et al. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. Circulation 2019;140:353–65. https://doi.org/10.1161/CIRCULATIONAHA.118.039136. Epub 2019 May 28. PMID: 31132875; PMCID: PMC6684250.
4. Braunwald E, Grossman W. Clinical aspects of heart failure. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine, 4th ed, Philadelphia: Saunders; 1992:444–63.
5. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, et al. An official European Respiratory

Society statement: pulmonary haemodynamics during exercise. Eur Respir J 2017;50:1700578.
6. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al., ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119. https://doi.org/10.1093/eurheartj/ehv317. Epub 2015 Aug 29. PMID: 26320113.
7. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, et al. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. Circ Heart Fail 2021;14:e007555. https://doi.org/10.1161/CIRCHEARTFAILURE.120.007555. Epub 2021 May 6. PMID: 33951935.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39. https://doi.org/10.1016/j.echo.2014.10.003. . e14PMID: 25559473.
9. Desole S, Obst A, Habedank D, Opitz CF, Knaack C, Hortien F, et al. Comparison between thermodilution and Fick methods for resting and exercise-induced cardiac output measurement in patients with chronic dyspnea. Pulm Circ 2022;12:e12128.. https://doi.org/10.1002/pul2.12128. PMID: 36051350; PMCID: PMC9425001.
10. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, et al. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J 2015;46:728–37. https://doi.org/10.1183/09031936.00021915.
11. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, et al. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. Circ Heart Fail 2018;11:e004750. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004750. PMID: 29695381; PMCID: PMC5937988.
12. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2019;53:1801897. https://doi.org/10.1183/13993003.01897-2018. PMID: 30545974; PMCID: PMC6351334.
13. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6–19. https://doi.org/10.1161/CIRCULATIONAHA.116.026807.
14. Sorimachi H, Burkhoff D, Verbrugge FH, Omote K, Obokata M, Reddy YNV, et al. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. Eur J Heart Fail 2021;23:1648–58. https://doi.org/10.1002/ejhf.2254. Epub 2021 Jun 17. PMID: 34053158.
15. Fudim M, Patel MR, Boortz-Marx R, Borlaug BA, DeVore AD, Ganesh A, et al. Splanchnic nerve block mediated changes in stressed blood volume in heart failure. JACC Heart Fail 2021;9:293–300. https://doi.org/10.1016/j.jchf.2020.12.006. Epub 2021 Mar 10. PMID: 33714749.
16. Maron BA, Brittain EL, Hess E, Waldo SW, Barón AE, Huang S, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. Lancet Respir Med 2020;8:873–84. https://doi.org/10.1016/S2213-2600(20)30317-9. Epub 2020 Jul 27. Erratum in: Lancet Respir Med. 2021 Mar;9:e29. PMID: 32730752; PMCID: PMC8219057.
17. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation 2012;125:289–97. https://doi.org/10.1161/CIRCULATIONAHA.111.051540. Epub 2011 Nov 30. PMID: 22131357; PMCID: PMC3264431.
18. Singh I, Rahaghi FN, Naeije R, Oliveira RKF, Systrom DM, Waxman AB. Right ventricular-arterial uncoupling during exercise in heart failure with preserved ejection fraction: role of pulmonary vascular dysfunction. Chest 2019;156:933–43. https://doi.org/10.1016/j.chest.2019.04.109. Epub 2019 May 16. PMID: 31103695.
19. Caravita S, Iacovoni A, Senni M. The right side of the circulation in not secondary heart failure with preserved ejection fraction: an elephant in the room? Eur J Heart Fail 2021;23:1659–61. https://doi.org/10.1002/ejhf.2294. Epub 2021 Jul 16. PMID: 34231304.
20. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. J Am Coll Cardiol 2020;76:1051–64. https://doi.org/10.1016/j.jacc.2020.07.009. PMID: 32854840; PMCID: PMC7455760.
21. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. J Am Heart Assoc 2017;6:e006817. https://doi.org/10.1161/JAHA.117.006817. PMID: 28862947; PMCID: PMC5586477.
22. Fudim M, Sobotka PA, Dunlap ME. Extracardiac abnormalities of preload reserve: mechanisms underlying exercise limitation in heart failure with preserved ejection fraction, autonomic dysfunction, and liver disease. Circ Heart Fail 2021;14:e007308. https://doi.org/10.1161/CIRCHEARTFAILURE.120.007308. Epub 2021 Jan 19. PMID: 33464948.
23. Harada T, Obokata M, Omote K, Iwano H, Ikoma T, Okada K, et al. Functional tricuspid regurgitation and right atrial remodeling in heart failure with preserved ejection fraction. Am J Cardiol 2022;162:129–35. https://doi.org/10.1016/j.amjcard.2021.09.021. Epub 2021 Oct 24. PMID: 34702555.
24. Florescu DR, Muraru D, Florescu C, Volpato V, Caravita S, Perger E, et al. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. Eur Heart J Cardiovasc Imaging 2021;22:jeab211.. https://doi.org/10.1093/ehjci/jeab211. Epub ahead of print. PMID: 34747460.
25. Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence. Cardiovasc Res 2017;113:1474–85. https://doi.org/10.1093/cvr/cvx160.
26. Van Wezenbeek J, Kianzad A, van de Bovenkamp A, Wessels J, Mouratoglou SA, Braams NJ, et al. Right ventricular and right atrial function are less compromised in pulmonary hypertension secondary to heart failure with preserved ejection fraction: a comparison with pulmonary arterial hypertension with similar

pressure overload. Circ Heart Fail 2022;15:e008726. https://doi.org/10.1161/CIRCHEARTFAILURE.121.008726. Epub 2021 Dec 23. PMID: 34937392; PMCID: PMC8843396.
27. Janicki JS. Influence of the pericardium and ventricular interdependence on left ventricular diastolic and systolic function in patients with heart failure. Circulation 1990;81(2):III15–20. SupplPMID: 2297880.
28. Tedford RJ, Mudd JO, Girgis RE, Mathai SC, Zaiman AL, Housten-Harris T, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. Circ Heart Fail 2013;6:953–63. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000008. PMID: 23797369; PMCID: PMC3815697.
29. Hsu S, Brusca SB, Rhodes PS, Kolb TM, Mathai SC, Tedford RJ. Use of thermodilution cardiac output overestimates diagnoses of exercise-induced pulmonary hypertension. Pulm Circ 2017;7:253–5. https://doi.org/10.1086/690629. PMID: 28680584; PMCID: PMC5448537.
30. Doshi D, Burkhoff D. Cardiovascular simulation of heart failure pathophysiology and therapeutics. J Card Fail 2016;22:303–11.