Right Heart Adaptation to Exercise in Pulmonary Hypertension: An Invasive Hemodynamic Study

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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.

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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].

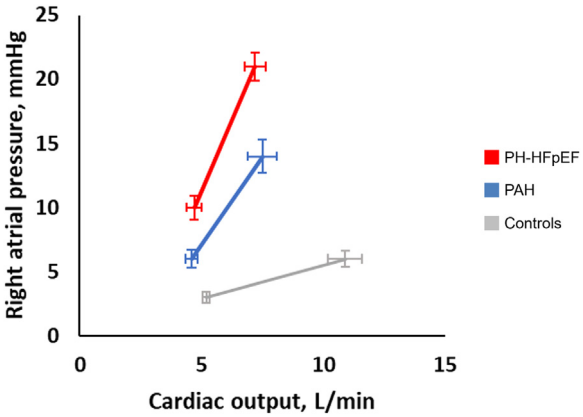

Fig. 1. Hemodynamics at rest and at peak exercise in patients with pulmonary hypertension owing to heart failure with preserved ejection fraction (PH-HFpEF, red) and in patients with pulmonary arterial hypertension (PAH, blue). Individuals with noncardiac dyspnea (gray) are displayed as normal reference. 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

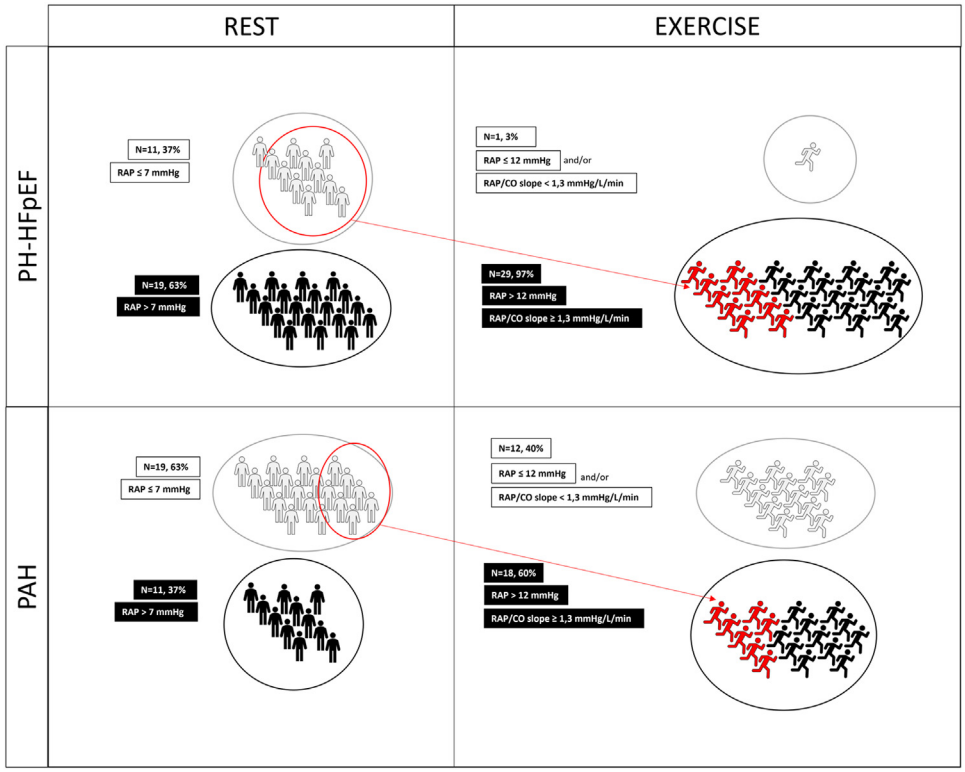

Fig. 2. Right atrial hypertension in PH-HFpEF (top) and in PAH (bottom), at rest (left) and during exercise (right). CO, cardiac output; RAP, right atrial pressure. Other abbreviations as in Fig. 1.

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

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.04.009.

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