TARGETING LEFT VENTRICULAR MECHANICS IN PATIENTS WITH PHEOCHROMOCYTOMA/PARAGANGLIOMA: AN UPDATED META-ANALYSIS.

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ABSTRACT

Background and Aim Numerous studies targeting left ventricular (LV) systolic function by measuring LV ejection fraction (LVEF) in patients with pheochromocytoma and paraganglioma (PPGL) either failed to reveal any impairment of this parameter or found a super-normal systolic function compared to essential hypertensives or normotensive controls. In order to provide an updated piece of information on LV systolic dysfunction in the PPGL setting, we performed a meta-analysis of speckle tracking echocardiography (STE) studies investigating LV mechanics via global longitudinal strain (GLS), a more sensitive index of LV systolic function than LVEF.

Methods A computerized search was performed using Pub-Med, OVID, EMBASE and Cochrane library databases from inception until September, 30st 2022. Full articles reporting data on LV GLS and LVEF in patients with PPGL and controls were considered suitable.

Results A total of 252 patients with PPGL and 187 controls were included in 6 studies.LV GLS was worse in the pooled PPGL group than in the control group (-17.3±1.2 vs -20.0±0.6) with a standard means difference (SMD) of 1.13±0.36 (CI: 0.43-1.84, p =0.002), whereas this was not the case for LVEF (67.3±1.9 and 66.4±1.6%, respectively), SMD: 0.12±0.03, CI: -0.41/0.65, p=0.66). A meta-regression analysis in PPGL patients showed an inverse relationship between adrenergic activity and GLS (p <0.0001).

Conclusions Our findings suggest that early changes in LV systolic function not detectable by conventional echocardiography in the PPGL setting can be revealed by STE; therefore, STE implementation in the work-up of patients with PPGL may improve the detection subclinical systolic dysfunction.

Key words: pheochromocytoma, paraganglioma, left ventricular ejection fraction, left ventricular global longitudinal strain.

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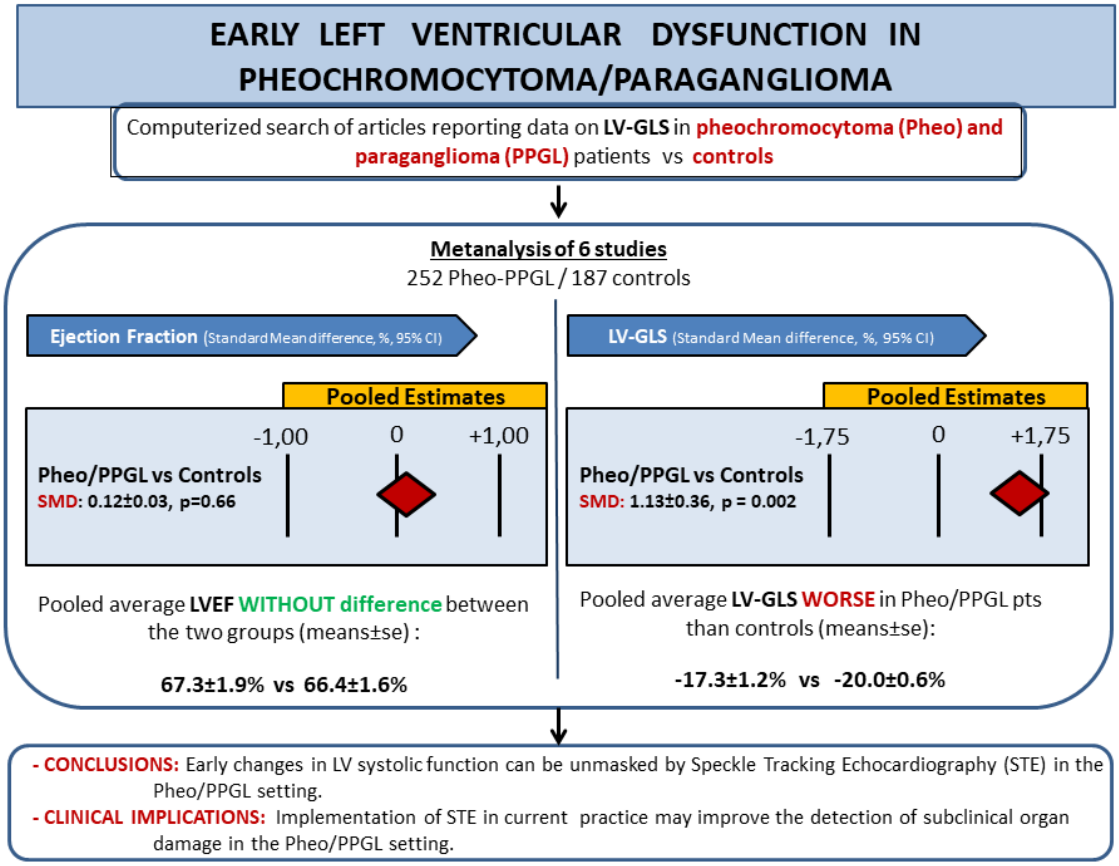

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INTRODUCTION

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumours originating from adrenal or extra-adrenal sites that secrete excess catecholamines (1). They represent a rare cause of secondary hypertension in young and middle age individuals, their estimated annual incidence being approximately 0.6-1.0/100.000 person-years (2). The catecholamine excess (i.e. epinephrine or norepinephrine) secreted by PPGL is responsible of a wide spectrum of cardiac manifestations ranging from early subclinical myocardial damage to severe cardiac complications, including heart failure, myocardial infarction, arrhythmias and stress-induced cardiomyopathy such as Takotsubo syndrome (3-5).

Subclinical manifestations of heart disease associated with PPGL extend beyond the mechanical effect of the increased blood pressure (BP) load, as catecholamines excess may determine heterogeneous BP phenotypes characterized by sudden hypertensive paroxysms of different severity and frequency on a background of sustained hypertension or normotension (6). The high prevalence of left ventricular hypertrophy (LVH), concentric geometry and subtle LV functional abnormalities supports the view that these changes in patients with PPGL are largely mediated by catecholamines via stimulation of myocardial alpha- and beta-adrenoceptors (7). The hypothesis that adrenergic stimulation leading to LVH can preserve systolic function has been suggested by numerous studies based on conventional echocardiography reporting that LV ejection fraction (LVEF) is normal or even increased in most patients with PPLG (8). However, in the last decade this view has been challenged by the growing evidence that LVEF is unable to fully reflect the complexity of the systolic function (9). New ultrasonographic techniques, indeed, such as speckle tracking echocardiography (STE), have provided consistent evidence that alterations in myocardial mechanics in different clinical settings are already detectable in patients with preserved LVEF (10). This topic in patients with PPGL has been scarcely investigated, so far, due to the rarity of catecholamine-secreting neuroendocrine tumours (11). Therefore, we performed an updated meta-analysis of STE studies reporting findings on LV mechanics in patients with

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PPGL and preserved LVEF in order to provide a new piece of information in this clinical and research area.

METHODS

We reported the systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (12). Pertinent literature was systematically scrutinized to identify all papers assessing the association between PPGL and LV systolic dysfunction by comparing LVEF and GLS in patients with PPGL versus essential hypertensive patients or healthy normotensive controls.

The PubMed, OVID-MEDLINE, and Cochrane library databases were systematically analysed to search English-language articles published from inception to September 30, 2022. Studies were identified by using Me-SH terms and crossing the following terms: “pheochromocytoma”; “paraganglioma”, “left ventricular ejection fraction”, “ventricular mechanics”,“systolic dysfunction”, “global longitudinal strain”, “echocardiography” and “STE echocardiography”.

Three authors assessed all titles and abstracts retrieved with the search. When there was no agreement on a specific record, the full text of the study was analyzed by all reviewers in order to establish its eligibility according to the inclusion criteria mentioned below. Data extraction was performed by two reviewer and independently checked by another reviewer.

Main inclusion criteria were: I) English articles published in peer-reviewed journals; II) comparative studies providing data on LVEF and LV mechanics (i.e. GLS) by 2D or 3D STE echocardiography in patients with PPGL and essential hypertensives or normotensive controls; III) minimum set of clinical/demographic data (i.e. sex, age, body mass index; office and/or ambulatory BP). Specific exclusion criteria were: I) studies with less than 10 patients with PPGL; II) studies conducted in children and adolescents (age <18 years); III) case reports, reviews, and editorials,

The Newcastle-Ottawa Scale (NOS) was used to measure study quality. (http://www, ohri ca/programs/clinical_epidemiologyoxford htm).

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Echocardiographic Methods

The conventional analysis of cardiac structure and function as well as the assessment of LV myocardial longitudinal strain had been performed in all studies according to recommendations of contemporary guidelines. In particular, GLS was measured off-line from 2D-3D echocardiographic images in all studies using a commercial dedicated software; R-R gating was used for LV strain assessment. In all studies, LV endocardium was manually traced and corrected, if necessary, and average longitudinal strain curve was automatically provided by the software.

Statistical analysis

A pooled analysis of cardiac parameters was performed using fixed or random effects meta-analysis by Comprehensive Meta-Analysis Version 2, Biostat, Englewood, NJ. Standard means difference (SMD) with 95% confidence interval (CI) was used to calculate the statistical difference of continuous echocardiographic variables between cases and controls. Demographic and clinical data provided by selected studies were expressed as absolute numbers, percentage, mean± SD, mean± SE or mean with CI. Meta-regression analysis was used to determine the impact of BP and adrenergic activity (i.e. plasma or urinary catecholamines) upon LV mechanics.

Heterogeneity was estimated using the I-squared test; random effect models were applied when heterogeneity across studies was high (I^2>75). Publication bias was assessed by using the funnel plot method (Trim and fill test). Observed and adjusted values, their lower and upper limits have been calculated. Statistical significance was set at P<0.05.

RESULTS

After removing duplicates, the initial literature search identified 977 papers**.** After the initial screening of titles and abstracts, 868 studies were excluded as they were not related to the topic. Therefore, 109 studies were reviewed; of these, 89 did not report any data on myocardial mechanics, 14 were case reports, reviews, commentary, and editorial articles. Thus, a total of 6

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comparative studies reporting data on GLS and LVEF in patients with PPGL versus their hypertensive or normotensive controls and containing echocardiographic data of interest, were included in the final review (13-18) (Figure 1).

Characteristics of the studies

On the whole, 252 patients with PPGL and 187 controls were included in 6 studies (sample size ranging from 35 to 131 participants), performed in six countries (Bulgaria, China, Czechoslovakia, India, France and Poland). The NOS the quality of studies ranged from 7 to 9 (i.e. score of fair or good quality). Therefore, no study was excluded based on its limited quality.

Table 1 shows demographic and clinical characteristics of patients with PPGL and controls belonging to selected studies such as sample size, mean age, prevalence of men, body mass index (BMI), office and/or 24-hour systolic/diastolic BP. The mean age range of patients with PPGL was 38-51 years; 45% of participants were men; BMI and office systolic/diastolic BP values ranged from 24.1±4.8 to 29.0±5.0 kg/m^2, and from 122±16/72±9 to 190±32/110±18 mmHg, respectively. Corresponding average 24-hour BP values ranged from 124±14/77±10 to 140±15/87±12 mmHg.

In all selected studies mean age and sex distribution were completely superimposable between patients with PPGL and controls. Furthermore, differences in BMI were not statistically significant. Office BP values were significantly higher in PPGL than in controls only in two out of six studies. This was also the case for heart rate (HR) in three of the six studies

Echocardiographic findings

Table 2 shows structural and functional echocardiographic variables in patients with PPGL as compared to their control counterparts. As for LV structure, three out office studies providing this kind of information, showed that patients with PPGL exhibited a significantly greater LVM indexed to body surface area (BSA). Data on relative wall thickness (RWT), a prognostically

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validated marker of LV geometry, reported by four studies, showed mixed findings (a significantly increased RWT in patients with PPGL was documented in two studies).

As for LV systolic function, assessed by standard echocardiography, all studies except one found no significant differences in LVEF between patients with PPGL and controls.

The ratio of early (E) peak of mitral inflow velocity to early (e') peak mitral annular velocity (E/e') was found to be significantly greater (worse) in patients with PPGL in two out of five reports. The four studies targeting left atrial volume index (LAVI) provided inconsistent findings, LA enlargement in patients with PPGL being reported by only two studies.

Finally, as for LV mechanics, five of six studies showed an impaired (less negative) GLS in patients with PPGL than in their control counterparts.

Meta-analysis findings

Pooled average LVEF was not different between patients with PPGL and controls: 67.3±1.9 and 66.4±1.6%, respectively. As shown by the forest plot in Figure 2, the meta-analysis of 6 studies did not reveal a significant difference in LVEF between groups (SMD: 0.12±0.03, CI: -0.41/0.65, p=0.66). On the contrary, GLS was less negative in cases with PPGL (-17.3±1.2%) than in controls (-20.0±0.6%). Figure 3 shows the results of the meta-analysis where SMD suggested a worse LV systolic function in the pooled PPGL group (SMD: 1.13±0.36, CI: 0.43-1.84, p =0.002).

The early to late mitral flow velocity ratio (E/A ratio) was lower (worse) in patients with PPGL (1.12±0.05) than in controls (1.26±0.08) with a statistically significant SMD (-0.32±0.01, CI -0.51/-0.13, $p < 0.001$). The average value of E/e' ratio was higher (worse) in patients with PPGL (8.3±0.48) than in controls (7.6±0.50). The meta-analysis of five studies providing data regarding this index showed a SMD of 0.28±0.10, CI:0.08/048, p= 0.006 (Figure 4). Pooled LAVI (data from 4 studies) tended to be greater in patients with PPGL (32.5±4.5 ml/m^2) than in controls (23.6±2.1 ml/m^2), but this difference failed to reach the statistical significance (p=0.106).

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LVM index (LVMI) was higher in the pooled PPGL group (101.4±8.5 g/m^2) than in control group (83.6±5.8 g/m^2). Figure 5 depicts the results of the meta-analysis of 4 studies where SMD revealed an increased LVMI in the pooled PPGL group (SMD: 0.67±0.12, CI: 0.43-0.90, p < 0.0001).

Relative wall thickness (RWT) was significantly higher in patients with PPGL than in controls (0.39±0.02 versus 0.37±00.2) and SMD was positive in the PPGL group (0.33±0.11, 95% CI: 0.12/0.55p=0.003, data from 4 studies)

Meta-regression analyses

The meta-regression analysis between SBP and LV GLS did not reveal any relationship between these two variables in the pooled PPGL group (p=0.09). On the contrary the meta-regression of GLS on catecholamines (expressed as time-fold increase of catecholamine metabolites in plasma/urine compared to controls) in patients with PPGL showed a significant inverse relationship (data from 5 studies, intercept 0.06, p<0.0001) (Figure 6).

Publication bias

The presence of single study effect was excluded at sensitivity analysis; furthermore, a publication bias of LV GLS between patients with PPGL and controls was excluded, as no study was imputed by the trim and fill test in addition to the observed studies (Supplementary figure 1).

Sensitivity analyses

A sensitivity analysis restricted to 5 studies comparing PPGL patients and essential hypertensives confirmed that GLS (SMD: 1.57±0.35, CI :0.87 / 2.26, p<0.001), but not LVEF (SMD:0.19±0.13, CI: -0.06 / 0.45, p=0.13), was lower in the pooled PPGL group than in their essential hypertensive counterparts.

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Additional analyses

In addition to GLS, global circumferential strain (GCS) was calculated in three out the six studies included in the meta-analysis. The average GCS value was higher in PPGL patients than in controls (-23.4±2.1vs -20.8±1.9). Supplementary Figure 3 reports the findings of the meta-analysis regarding the GCS where SMD suggested a higher myocardial circumferential deformation in patients with PPGL (-0.65±0.14, CI: -0.91/-0.38, $p < 0.0001$).

DISCUSSION

The intriguing relationship between adrenergic tumors and LV remodeling has been investigated for decades (19-21). The role of sympathetic nervous system (SNS) in development of LVH in hypertensive patients has been widely accepted, although this role can be hardly distinguished from the effect of the renin-angiotensin-aldosterone system (RAAS) or comorbidities. Patients with PPGL provide a suitable model to study the effects of SNS on LV structure and function. In a previous study about three decades ago, the authors failed to observe significant differences in BP as well as LVM values between patients with PPGL and essential hypertensive patients, despite the remarkable differences in plasma epinephrine and norepinephrine levels between the two groups (22). More recent studies reported inconsistent results about LV functional and structural changes in patients with adrenergic tumors. Evaluation of LV mechanics by GLS has improved the study of LV function and its predictive value in a wide range of cardiovascular conditions (23). Therefore, GLS can be seen as a reliable parameter for detecting subclinical myocardial damage in patients with adrenergic tumors. Unfortunately, limited data are available on this topic, as existing studies enrolled a small, heterogeneous groups of patients (13-18). Thus, our meta-analysis offers a new piece of information in this area of research by highlighting the fact that GLS was significantly impaired in PPGL patients with normal LVEF. This suggests that GLS is a sensitive marker of LV subtle dysfunction also in patients with adrenergic tumors. In our previous meta-analyses including a smaller number of patients, we documented that GLS was worse in patients with PPGL (11) and this parameter

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improved after surgery (24). As the impaired LV longitudinal function was associated with higher LVMI levels, concentric geometry, and diastolic dysfunction, these associated echocardiographic alterations do not allow to conclude that the reduced GLS is the earliest indicator of subclinical cardiac damage in patients with PPGL.

A novelty of this meta-analysis, that included also GCS parameter, is that GCS, at difference from GLS, was significantly higher in patients with PPGL than in the controls. In spite of the limited number of patients, as only 3 studies investigated GCS, this finding provides the first consistent evidence that the increased GCS may be regarded as a compensatory mechanism to preserve normal LVEF in the setting of adrenergic tumors. A possible explanation is that the subendocardial layer, which primarily contributes to the longitudinal LV mechanics, is more exposed than the mid and epicardium layers to the combined effects of BP overload and excess secretion of catecholamines.

Our findings show no association between SBP and GLS in patients with PPGL, in accordance with previous reports that failed to show a significant correlation between SBP and LVMI in these patients (22). These data may support the hypothesis that the increased BP in patients with adrenergic tumors is not the main responsible of LV structural and functional changes (25). This notion is strengthened by the results of our meta-regression between the indexes of adrenergic activity in patients with PPGL and GLS which showed that a higher concentration of plasma and urinary catecholamines is associated with a greater impairment of LV longitudinal function.

A further aspect of the present meta-analysis is the larger amount of information regarding LV diastolic function in patients with PPGL. Our results showed that E/A ratio was lower, E/e' ratio was higher, and there was a trend of enlarged LA, although not statistically significant, in patients with adrenergic tumors. These findings speak in favor of LV diastolic dysfunction development in patients with PPGL.

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Limitations

There are several limitations of the current meta-analysis that should be listed. This type of investigation does not provide any conclusion regarding the causal relationship between catecholamines-secreting tumors, cardiac remodeling and LV dysfunction. Furthermore, the impact on LV strain of comorbidities. such as obesity and diabetes, was not addressed in the individual studies and therefore precluded such line of assessment by our meta-analysis. It should be noted, however, that in all selected studies, although cases and controls were carefully matched for age and sex there were some differences in BMI, office and 24-h BP values as well as in heart rate which in some circumstances were statistically significant. As most patients were taking antihypertensive BP lowering drugs, the potential confounding impact of these agents on LV function cannot be excluded. The meta-regression between indexes of adrenergic activity and GLS combined plasma and urinary data, in relation to the heterogeneity of the information provided by the various studies. Finally, results regarding GCS were provided in only 3 studies, and do not allow to draw definite conclusions.

CONCLUSION

The present meta-analysis reported important, novel findings in a large pooled population of patients with PPGL. In addition to extending our previous findings in a smaller cohort of patients by showing that GLS is deteriorated in patients with adrenergic tumors, our results indicate that this was not the case for GCS. It is reasonable to hypothesize that GLS is a more sensitive marker of humoral and hemodynamic changes induced by adrenergic tumors than GCS and the outdated LVEF.

The conundrum of a normal LVEF in PPGL patients with LV structural and functional alterations shown by our meta-analysis underlines the limit of this index in properly assessing LV systolic

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function and the need to systematically implement conventional echocardiography with assessment of myocardial mechanics.

Further cross-sectional and longitudinal studies on LV mechanics in patients with adrenergic tumors are needed in order to clarify whether the impaired LV strain is limited to the longitudinal function, whether it is reversible after tumor removal and whether it plays a role in predicting CV outcomes.

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REFERENCES

1) Pacak K. New biology of pheochromocytoma and paraganglioma. *Endocr Pract.* 2022 Sep 21:S1530-891X(22)00621-8. doi: 10.1016.

2) Al Subhi AR, Boyle V, Elston MS. Systematic review: incidence of pheochromocytoma and paraganglioma over 70 years. *J Endocr Soc.* 2022 Jul 3;6(9):bvac105. doi: 10.121.

3) Y-Hassan S, Falhammar H. Cardiovascular manifestations and complications of pheochromocytomas and paragangliomas. *J Clin Med.* 2020;30;9(8):2435.

4) Yu Y, Chen C, Han W, Zhang Y Zhang ,Yang Y. Metanephrine and normetanephrine associated with subclinical myocardial injuries in pheochromocytoma and paraganglioma**.** *Front. Oncol.* 12:1024342. doi: 10.3389.

5) Cornu E, Motiejunaite J, Belmihoub I, Vidal-Petiot E, Mirabel M, Amar L. Acute stress cardiomyopathy: heart of pheochromocytoma. *Ann Endocrinol (Paris)*. 2021; **82**:201-205.

6) Canu L, Parenti G, De Filpo G, Mannelli M. Pheochromocytomas and paragangliomas as causes of endocrine hypertension. *Front Endocrinol (Lausanne).* 2019 Jun 4;10:333. doi: 10.3389.

7) Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NAB, Francis JM, Robson MD, Arnold JR, Mihai R, Thomas JDJ, Herincs M, Hassan-Smith ZK, Greiser A, Arlt W, Korbonits M, Karavitaki N, Grossman AB, Wass JAH, Neubauer S. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction. *J Am Coll Cardiol.* 2016;**67**:2364-2374.

8) Shub C, Cueto-Garcia L, Sheps SG, Ilstrup DM, Tajik A. Echocardiographic findings in pheochromocytoma. *J Am J Cardiol.* 1986 ;**57** :971-5.

Accepted Manuscript

Downloaded from https://academic.oup.com/ajh/advance-article/doi/10.1093/ajh/hpad006/6976011 by Universita di Milano Bicocca user on 28 January 2023

9) Marwick TH, Shah SJ, Thomas JD. Myocardial strain in the assessment of patients with heart failure: a review. *JAMA Cardiol*. 2019;**4**:287-294.

10) Haji K, Marwick TH. Clinical utility of echocardiographic strain and strain rate measurements. *Curr Cardiol Rep.* 2021 ;23(3):18.

11) Tadic M, Sala C, Carugo S, Mancia G, Grassi G, Cuspidi C. Left ventricular global longitudinal strain in secondary hypertension: A meta-analysis of echocardiographic studies. *Eur J Intern Med.* 2022;**96**:81-89.

12) Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (Clinical Research ed). 2009;339:b2535.

13) Ding L, Zhu WL, Zeng ZP, Li HZ, Ji J, Fang LG, Sun JP. Subclinical left ventricular systolic dysfunction detected by two dimensional speckle tracking echocardiography in patients with pheochromocytoma and paraganglioma and preserved ejection fraction. *Echocardiography.* 2018; **35**:184-189.

14) Kvasnicka J, Zelinka T, Petrák O, Rosa J, Štrauch B, Krátká Z, Indra T, Markvartová A, Widimský J Jr, Holaj R. Catecholamines induce left ventricular subclinical systolic dysfunction: a speckle-tracking echocardiography study. *Cancers* 2019;11,318; doi:10.3390/cancers11030318.

15) Boulestreau R, Jambon F, Cremer A, Doublet J, Nunes ML, Ferrière A, Tabarin A, Haissaguerre M, Gosse P. Chronic pheochromocytoma-induced myocardial injuries: What should we expect from modern and classical echocardiographic tools? *Annales de Cardiologie et d'Angéiologie.* 2020;**69**:241–246.

16) Dobrowolski P, Januszewicz A, Klisiewicz A, Gosk-Przybyłek M, Peczkowska M, Kabat M, Kwapiszewska A, Warchoł-Celinska E, Ambroziak U, Doroszko A, Toutounchi S, Gałazka Z, Bednarczuk T, Górnicka B, Januszewicz M, Hoffman P, Lenders JWM, Eisenhofer G, Prejbisz A.

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Left ventricular structural and functional alterations in patients with pheochromocytoma/paraganglioma before and after surgery. *JACC Cardiovascular Imaging.* 2020; **13**:2499-2507.

17) Elenkova A, Shabani R, Kinova E, Vasilev V, Assen Goudev A, Zacharieva S. Global longitudinal strain as a marker for systolic function in patients with pheochromocytomas. *Endocrine-Related Cancer.* 2020; **27**:561–570.

18) Vishvak-Chanthar KMM, Khanna R, Agarwal G, Rout SR, Kapoor A, Sabaretnam M, Chand G, Mishra A, Agarwal A, Mishra SK. Cardiac Changes and Their Reversal Following Curative Surgery in Pheochromocytoma: PheoCard Prospective Cohort Study.*World J Surg.* 2022 Oct 10. doi: 10.1007/s00268-022-06731-6.

19) Scheuer J. Catecholamines in cardiac hypertrophy. *Am J Cardiol.* 1999; **83**:70-74.

20) Mobine HR, Baker AB, Wang L, Wakimoto H, Jacobsen KC, Seidman CE, Seidman JG, Edelman ER Pheochromocytoma-induced cardiomyopathy is modulated by the synergistic effects of cell-secreted factors. *Circ Heart Fail.* 2009 ;**2**:121-8.

21) Fitzgibbons TP, Aurigemma GP. How do adrenergic tumors affect left ventricular remodeling and function? A "Loaded" Question. *JACC Cardiovasc Imaging*. 2020 ;**13** :2510-2512.

22) Fouad-Tarazi FM, Imamura M, Bravo EL, Rossi G, Nagi HK, Lin WW, Cressman M, Wicker P. Differences in left ventricular structural and functional changes between pheochromocytoma and essential hypertension. Role of elevated circulating catecholamines. *Am J Hypertens*. 1992; **5**:134-40.

23) Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging*. 2018;**11**(2 Pt 1):260-274.

Accepted Manuscript

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24) Tadic M, Sala C, Carugo S, Cuspidi C. Effect of surgical treatment on myocardial strain in patients with pheochromocytoma and paraganglioma: a mini-review and meta-analysis. *J Endocrinol Invest.* 2021;**44**: 2327-2332.

25) Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NAB, Francis JM, Robson MD, Arnold JR, Mihai R,. Thomas JDJ, Herincs M, MD, Hassan-Smith ZK, Greiser A, Arlt W, Korbonits M, Karavitaki N, Grossman AB, Wass JAH, Neubauer S. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction *J Am Coll Cardiol*, 2016; **67**: 2364-2374.

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Figure Legend

Figure 1. Schematic flow-chart for the selection of studies.

Figure 2. Forest plot for standard means difference (SMD) of left ventricular ejection fraction (LVEF) in patients with PPGL and controls (random model). Relative weight of each study is reported on the right side. CI= confidence intervals.

Figure 3. Forest plot for standard means difference (SMD) of left ventricular global longitudinal strain (LV GLS) in patients with PPGL and controls (random model). Relative weight of each study is reported on the right side. CI= confidence intervals.

Figure 4. Forest plot for standard means difference (SMD) of the ratio of early (E) peak of mitral inflow velocity to mitral annular velocity (E/e' ratio) patients with PPGL and controls (fixed model). Relative weight of each study is reported on the right side. CI, confidence intervals.

Figure 5. Forest plot for standard means difference (SMD) of left ventricular mass index (LVMI) in patients with PPGL and controls (fixed model). Relative weight of each study is reported on the right side. CI, confidence intervals.

Figure 6. Meta-regression of GLS on catecholamines (expressed as time-fold increase of catecholamine metabolites in plasma/urine compared to controls) in patients with PPGL.

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Table 1. Summary of 6 studies targeting left ventricular strain, as assessed by speckle tracking echocardiography, in patients with pheochromocytoma /paraganglioma and respective controls.

Author Publication year	Sample size (n)		Age (years)		Sex (% male)		BMI (kg/m^2)		Office BP (mmHg)		24-hour BP (mmHg)		Office HR (b/min)		24-hour HR (b/min)	
	PHEO/PPGL	Controls	PHEO/PPGL	Controls	PHEO/PPGL	Controls	PHEO/PPGL	Controls	PHEO/PPGL	Controls	PHEO/PPGL	Controls	PHEO/PPGL	Controls	PHEO/PPGL	Controls
Ding 2018	38 NTN	48	43±10	42±14	58	52	n.a.	n.a.	114±9/ 70±7	141±25/ 91±18	n.a.	n.a.	69±11	82±13	n.a	n.a
Kvasnicka 2019	18 EH	17	49±6	50±11	50	42	30.0±4.0	29.0±5.0	140±8/ 89±5	141±13/ 88±6	132±8/ 80±5	127±9/ 76±7	74±8	81±9	71±6	77±10
Boulestreau 2020	47 EH	47	51±15	51±17	45	45	22.5±3.0	24.1±4.8	119±11/ 75±5	122±16/ 72±9	n.a.	n.a.	64±12	72±17	n.a.	n.a.
Dobrowolski 2020	50 EH	81	45±13	47±14	42	47	26.2±4.8	25.3±4.3	129±14/ 80±11	130±17/ 81±11	123±11/ 76±11	124±14/ 77±10	80±11	78±10	68±11	75±12
Elenkova 2020	24 EH	24	49±16	49±16	58	58	26.4±5.0	26.8±5.3	n.a.	n.a.	140±15/ 87±12*	140±15/ 87±12*	n.a.	n.a.	78±8*	84±13*
Vishvak Chanthar 2022	10 EH	35	38±15	38±13	40	46	25.2±3.8	26.3±3.4	160±6/ 96±3	190±32/ 110±18	n. a.	n. a.	n.a.	n.a.	n.a.	n.a.

BMI=body mass index; BP=blood pressure; EH=essential hypertensives; HR=heart rate. NTN=normotensive controls; Data are presented as absolute numbers, percentage, mean±SD. * mean day-time

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Table 2. Summary of echocardiographic variables in 6 studies targeting left ventricular mechanics in pheochromocytoma/paraganglioma as compared to essential hypertensive or normotensive individuals

Author (reference) Publication year		LVMI g/m² (§ g/h2.7)		RWT		LVEF %		GLS %		E/e' %		LAVI ml/m²	
		PHEO	Controls	PHEO	Controls	PHEO	Controls	PHEO	Controls	PHEO	Controls	PHEO	Controls
Ding[13]	**2018**	84±30 *	69±16	0.41±0.12 **	0.34±0.06	70±6	69±4	-20.0±4.0 **	-22.0±2.0	8.2±3.3 *	6.8±2.2	25±7 *	19±5
Kvasnicka [14]	**2019**	91±23	86±16	0.39±0.05	0.40±0.05	69±4	71±5	-14.8±1.5 **	-17.3±2.3	8.5±1.9	8.9±1.6	n.a.	n.a.
Boulestreau[15]	**2020**	31±12 §	36±9 §	0.35±0.07	0.33±0.08	68±6 **	61±7	-20.7±2.4	-20.2±2.7	7.7±2.8	7.2±3.0	21±8	23
Dobrowolski[16]	**2020**	103 ** (88-132)	94 (74-106)	0.42 ** (0.39-0.48)	0.41 (0.36-0.45)	71 (68-95)	69 (65-73)	-17.2 ** (-15.6/-18.9)	-19.3 (-17.7/-20.6)	6.8 (5.7-8.7)	6.4 (5.4-7.9)	29 (21-39)	28 (22-37)
Elenkova [17]	**2020**	122±23 **	88±21	n. a.	n. a.	67±7	64±6	-16.5±1.8 **	-19.4±2.2	11.1±4.5 *	8.8±2.2	58±17 **	24±8
Vishvak Chanthar[18] **2022**		n.a.	n.a.	n. a.	n. a.	58±6	60±4 ns	-14.4±3.0 **	-21.2±2.0	n. a.	n. a.	n .a.	n. a

E/e'= the ratio of early (E) peak of mitral inflow velocity to early (e') peak mitral annular velocity; FHEO=pheochromocytoma; GLS=global longitudinal strain; LAVI=left atrial volume indexed to body surface area; LVEF=left ventricular ejection fraction; LVMI=left ventricular mass index; RWT=relative wall thickness.

Data are presented as absolute numbers, percentage, mean±SD, and confidence intervals. * < 0.05; ** < 0.01

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Figure 1

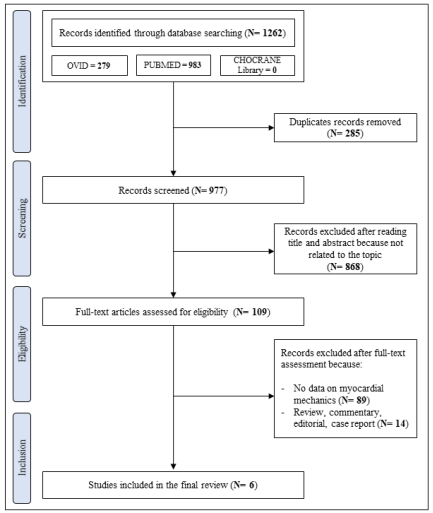

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Figure 2

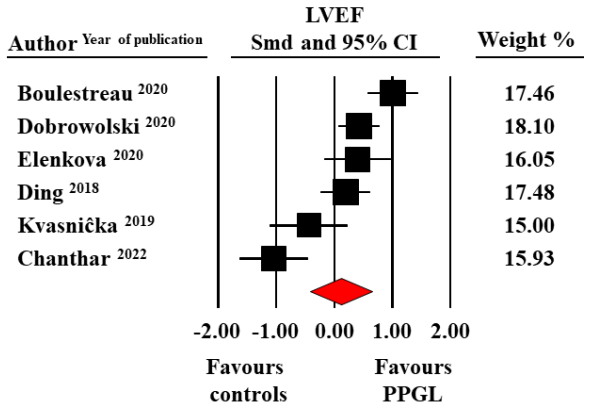

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Figure 3

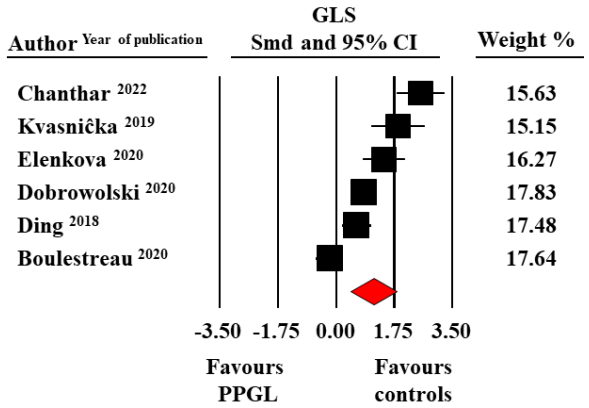

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Figure 4

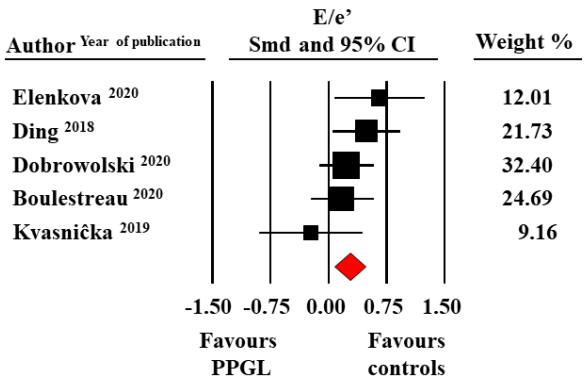

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Figure 5

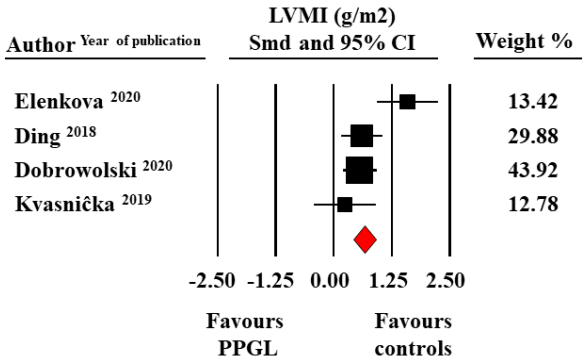

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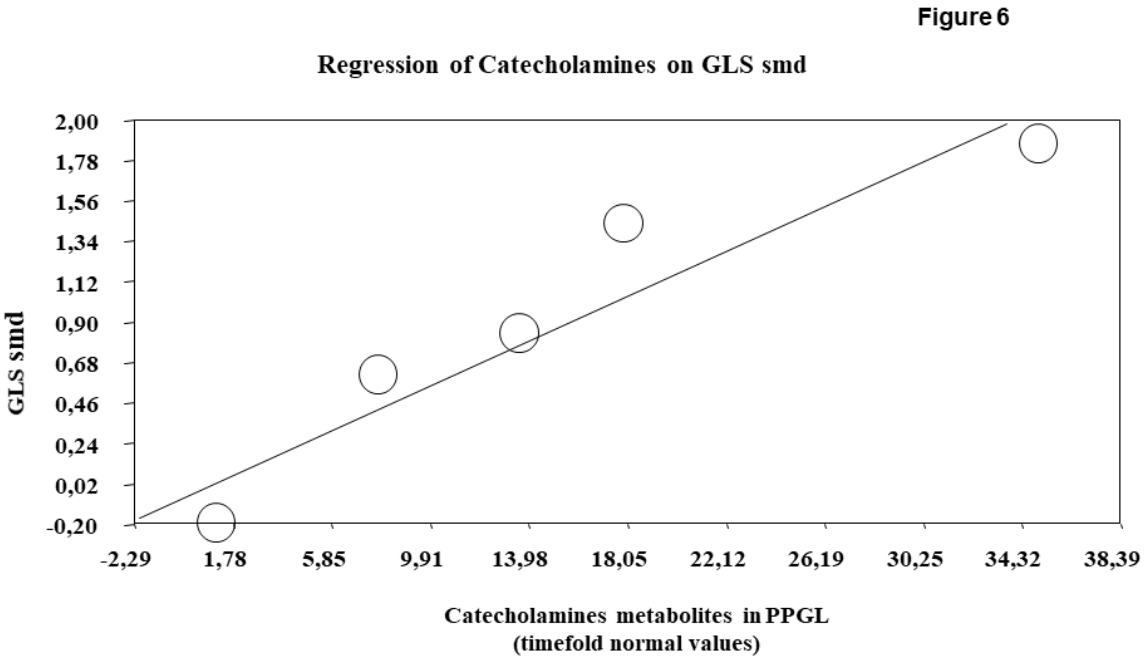
Figure 6



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