



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

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BACKGROUND: Heart failure with preserved ejection fraction (HFpEF) is a prevalent disorder for which no effective treatment yet exists. Pulmonary hypertension (PH) and right atrial (RA) and ventricular (RV) dysfunction are frequently observed. The question remains whether the PH with the associated RV/RA dysfunction in HFpEF are markers of disease severity.

METHODS: To obtain insight in the relative importance of pressure-overload and left-to-right interaction, we compared RA and RV function in 3 groups: 1. HFpEF (n=13); 2. HFpEF-PH (n=33), and; 3. pulmonary arterial hypertension (PAH) matched to pulmonary artery pressures of HFpEF-PH (PH limited to mPAP ≥ 30 and ≤ 50 mmHg) (n=47). Patients underwent right heart catheterization and cardiac magnetic resonance imaging.

RESULTS: The right ventricle in HFpEF-PH was less dilated and hypertrophied than in PAH. In addition, RV ejection fraction was more preserved (HFpEF-PH: 52 ± 11 versus PAH: $36 \pm 12\%$). RV filling patterns differed: vena cava backflow during RA contraction was observed in PAH only. In HFpEF-PH, RA pressure was elevated throughout the cardiac cycle (HFpEF-PH: $10 [8-14]$ versus PAH: $7 [5-10]$ mm Hg), while RA volume was smaller, reflecting excessive RA stiffness (HFpEF-PH: $0.14 [0.10-0.17]$ versus PAH: $0.08 [0.06-0.11]$ mm Hg/mL). RA stiffness was associated with an increased eccentricity index (HFpEF-PH: 1.3 ± 0.2 versus PAH: 1.2 ± 0.1) and interatrial pressure gradient ($9 [5$ to $12]$ versus $2 [-2$ to $5]$ mm Hg).

CONCLUSIONS: RV/RA function was less compromised in HFpEF-PH than in PAH, despite similar pressure-overload. Increased RA pressure and stiffness in HFpEF-PH were explained by left atrial/RA-interaction. Therefore, our results indicate that increased RA pressure is not a sign of overt RV failure but rather a reflection of HFpEF-severity.

Key Words: heart failure ■ pulmonary arterial hypertension ■ right atrium ■ right ventricle ■ ventricular dysfunction

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WHAT IS NEW?

This is the first study to show that the response of the right heart to a similar amount of pressure-overload is different in patients with heart failure with preserved ejection fraction (HFpEF)-pulmonary hypertension (PH) and pulmonary arterial hypertension:

- Right ventricular (RV) function was preserved in HFpEF-PH with no signs of RV dilatation, whereas in pulmonary arterial hypertension the right ventricle was dilated and its function was depressed.
- Right atrial function was preserved with no signs of vena cava backflow during right atrial contraction in HFpEF-PH in contrast to pulmonary arterial hypertension.
- Elevated right atrial pressure and stiffness in HFpEF-PH were explained by changes in left atrial and right atrial interaction.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Our study shows that the response of the right heart to a similar amount of pressure-overload in HFpEF-PH and pulmonary arterial hypertension is different. The increase in right atrial pressure and stiffness in patients with HFpEF-PH is mainly explained by an enhanced left-to-right atrial interaction and an enhanced pericardial constraint. Rather than a sign of overt right heart failure, the increased right atrial pressure and stiffness is a reflection of HFpEF-severity. Whether the new treatment strategies in HFpEF including atrial septostomy have a beneficial effect on the right heart should be explored in future investigations.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
Cpc-PH	combined pre- and postcapillary pulmonary hypertension
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
LA	left atrial
LV	left ventricular
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
RA	right atrial
RAP	right atrial pressure
RV	right ventricular
RVEF	right ventricular ejection fraction
SV	stroke volume

Heat failure with preserved ejection fraction (HFpEF) is a highly prevalent condition for which no treatments yet exist.¹ HFpEF is characterized by stiffening

of the left ventricle, resulting in increased left-sided filling pressure. Passive backward transmission of left-sided filling pressure eventually results in increased pulmonary venous and arterial pressure.² Pulmonary hypertension (PH) is therefore a well-known complication in patients with HFpEF.^{2–4} Interestingly, the pulmonary vascular remodeling in advanced HFpEF shows striking resemblance to pulmonary arterial hypertension (PAH).⁵

Recent studies demonstrated that right atrial (RA) and right ventricular (RV) dysfunction are prevalent in HFpEF-PH and are associated with poor outcomes.^{6–12} Worsening PH and increased RV afterload induce RV hypertrophy, RV dysfunction, and increased RV filling pressures and subsequently increased RA afterload.¹³ RA reservoir function is depressed compared with controls, and RA pressure (RAP) is elevated in HFpEF-PH.^{12,14} Based on these observations, it is speculated that patients with HFpEF may benefit from PAH-specific medication. These agents partially reverse pulmonary vascular remodeling and will thereby lower RV pressure overload and restore right heart function.^{13,15,16} However, the cause of right heart dysfunction in HFpEF-PH may also be related by left-to-right interaction. Both sides of the heart share the same pericardium, and as a result, changes on the left side will directly affect the right side of the heart and vice versa.

It remains an open question whether the PH with the associated RV/RA dysfunction in HFpEF are markers of disease severity. Until now, most studies have evaluated RV and RA function relative to control subjects, making it difficult to interpret the pathophysiological relevance of the observed differences in RA and RV function. Therefore, we combined sophisticated imaging and hemodynamic analyses of the right atrium and ventricle in patients with HFpEF-PH and PAH, that were matched on pulmonary artery pressure (PAP).

MATERIALS AND METHODS

The data, methods used in the analysis, and materials used to conduct the research are available from the corresponding author to any researcher for purposes of reproducing the results or replicating the procedure upon request.

Study Design and Patients

This is a retrospective analysis of patients with HFpEF-PH (mean PAP or mPAP ≥ 25 mmHg, pulmonary capillary wedge pressure or PCWP ≥ 15 mmHg) and treatment-naïve PAH (mPAP ≥ 25 mmHg, PCWP < 15 mmHg), diagnosed according to guidelines^{17,18} at Amsterdam University Medical Centers between June 2000 and May 2020. Patients underwent right heart catheterization and cardiac magnetic resonance imaging within a maximum interval of a month. Only patients with PAH with a mPAP between 30 and 50 mmHg were included to correct for differences in pressure overload. As reference group, we included patients with HFpEF without PH (mPAP < 25 mmHg, PCWP ≥ 15 mmHg or an increase to ≥ 25 mmHg at

exercise). Medical charts of patients were reviewed for comorbidities including history of smoking, history of coronary artery disease, history of atrial fibrillation (AF), history of hypertension, history of chronic obstructive pulmonary disease, history of obstructive sleep apnoea syndrome, history of diabetes, history of chronic renal disease, and history of hypothyroidism. The Medical Ethics Review Committee of the Amsterdam University Medical Centre did not consider the current study to fall within the scope of Medical Research Involving Human Subjects act (WMO), and informed consent was not required (approval number VUMC 2012288).

Cardiac Magnetic Resonance Imaging

Cardiac function and volumes were assessed using cardiac magnetic resonance imaging. Scans were made with a Siemens 1.5-T Sonata or Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). Acquisition and analyses of images were performed as previously described.¹⁹ Only scans with sufficient quality were included in the final analysis, and all patients were in sinus rhythm at time of cardiac magnetic resonance measurements (which does not exclude patients with episodes of AF in the past). We also determined RV volumes at diastasis (phase before atrial contraction) to make a distinction between RV passive filling (RV diastasis volume minus RV end-systolic volume) and RV active filling (RV end-diastolic volume minus RV diastasis volume). Volumes and mass were indexed to body surface area. Stroke volume (SV) was determined with left ventricular (LV) and RV volumes.²⁰ Tricuspid regurgitation volume was calculated by the difference between RV and LV SV.²¹ Tricuspid regurgitation severity was graded into mild (<30 mL), moderate (30–59 mL), and severe (>60 mL). RA and left atrial (LA) maximum, diastasis and minimal volumes were determined with the area-length method on the 4-chamber view using Circle CVI42 software (version 5.1.1.4). Next, we determined RA passive emptying by differences between RA maximal and RA diastasis volume. RA active emptying was determined by the difference between RA diastasis and RA minimal volume. Subsequently, total RA or LA emptying fraction, passive emptying fraction, and active emptying fraction were calculated.²² In addition, we determined vena cava backflow by differences in RA active emptying and RV active filling volume. To determine the LA/RA-interaction, we quantified the RA eccentricity index at end-systole on the 4-chamber view.²³ The eccentricity index D2/D1 was calculated as the ratio between the length of 2 perpendicular diameters, where D2 is defined as the diameter perpendicular to the tricuspid valve and D1 is defined as the atrial diameter from left to right perpendicular to D2.

Feature Tracking Analysis

Cardiac magnetic resonance Feature Tracking analysis was performed using Circle CVI42.^{24,25} LV, LA, RV, and RA longitudinal strain was assessed on the 4-chamber view, and LV and RV circumferential and radial strain was assessed using the short-axis stack. Epicardial and endocardial contours excluding trabeculations were drawn at end-diastole. RV analysis only included the free wall.²⁶ A distinction was made between LA and RA reservoir, passive strain and active strain.²⁷ The reservoir strain or function phase is characterized by the venous return during systole of the ventricles and isovolumetric contraction when the tricuspid valve is closed. Passive strain or function is characterized by passive emptying of the atria during

early diastole and active strain or function by active contraction of the atria.²⁸ The automated feature tracking performance was reviewed and manually adjusted if needed.

Right Heart Catheterization

Hemodynamic assessment was performed as reported with a balloon-tipped, flow-directed 7.5-F triple lumen Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, CA).²⁹ Measurements of PAP, RAP, PCWP, and cardiac output were taken. Pulmonary vascular resistance was determined with: pulmonary vascular resistance = (mPAP–PCWP)/cardiac output. RA and RV pressure curves were obtained and stored for analysis. The RAP curve was analyzed end-expiratory at the a-wave, v-wave, and minimal pressure during the x-descent for 5 heartbeats of which averages were taken. RA stiffness was quantified as slope between increase in RAP (minimal to maximal pressure) divided by the increase in RA volume (minimal to maximal volume).

Pressure-Volume Analysis

RV pressure-volume analyses were carried out using the single-beat method as previously described.²⁹ In short, the end-systolic pressure-volume relation (Ees) slope, as measure for RV contractility, was calculated by: $Ees = (P_{iso} - mPAP) / (RV \text{ end-diastolic volume} - RVESV)$. RV isovolumic pressure (P_{iso}) was derived with the single-beat method of Sunagawa et al.³⁰ The arterial elastance (Ea), as measure for RV afterload, was determined by dividing mPAP by SV. The RV-arterial coupling was defined as the ratio between Ees and Ea. Next, we assessed the end-diastolic elastance (Eed) as measure for RV diastolic stiffness, by calculating the slope of the diastolic pressure-volume relation at the end of diastole using α and β in the formula: $Eed = \alpha \cdot \beta \cdot e^{(\beta \cdot RV_{EDV})}$.^{31,32}

Statistical Analysis

Data are presented as mean \pm SD for normally distributed data or as median (interquartile range [IQR]) for non-normally distributed data. For non-normally distributed data, logarithmic transformation was performed before the analysis. Groups were compared using a 1-way ANOVA for normally distributed data, after which post hoc analysis with unpaired *t* test and Bonferroni correction was applied. If logarithmic transformation did not result in normal distribution, Kruskal-Wallis testing and post hoc testing was performed with pairwise Mann-Whitney *U* test. Group differences for categorical variables were assessed with Pearson's χ^2 or Fisher exact test. Relationships between 2 or more continuous variables were assessed with univariate and multivariate linear regression. To determine the relative contribution of history of AF and PH disease etiology (PAH versus HFpEF-PH) as predictors of RV dysfunction as indicated by RV ejection fraction (RVEF), we performed multivariate linear regression. A *P* of <0.05 was considered statistically significant. Statistical analyses were performed in R (version 3.5.2).

RESULTS

Baseline Characteristics

We screened 195 patients for inclusion, of which 39 patients were excluded due to initiation of PAH-specific

treatment before hemodynamic baseline measurements or a high H₂FPEF-score (score >5), to exclude patients with PAH with possible concealed LV diastolic dysfunction (Figure 1).³³ Next, we matched the PAH-cohort on mPAP (PH limited to mPAP ≥30 and ≤50 mmHg) to the HFpEF-PH cohort. In total, 93 patients were included, of which 47 PAH, 33 HFpEF-PH, and 13 patients with HFpEF (Figure 1). Baseline characteristics are presented in the Table. In general, patients with HFpEF-PH were older and had higher BMI values than PAH. Comorbidities including history of coronary artery disease and history of AF were more frequent in HFpEF-PH than PAH. Tricuspid regurgitation severity was similar for both groups (Table S1). Minor mitral valve regurgitation was visually observed in a small number of patients (≈15%) and was therefore considered neglectable. Diuretics use was more frequent in HFpEF-PH compared with patients with PAH (59% versus 33%). In addition, renal function

was significantly worse in patients with HFpEF-PH compared with PAH, shown by a lower eGFR (59 ± 18 versus 73 ± 14 mL/minute per 1.72 m^2). In 23 (70%) patients with HFpEF-PH, combined pre- and postcapillary PH (Cpc-PH) was observed, defined as mPAP >25 mmHg, PCWP >15 mmHg, and pulmonary vascular resistance >3 Wood units (WU; Table S2).

RV Dysfunction Most Prominent in Patients With PAH

To compare RV dysfunction in patients with HFpEF-PH and PAH, we analyzed imaging and hemodynamic data. In addition, we performed pressure-volume analyses to obtain information on RV systolic and diastolic function. Although PAP was similar between PAH and HFpEF-PH, patients with HFpEF-PH showed a more preserved RV phenotype with less RV dilatation as shown by RV

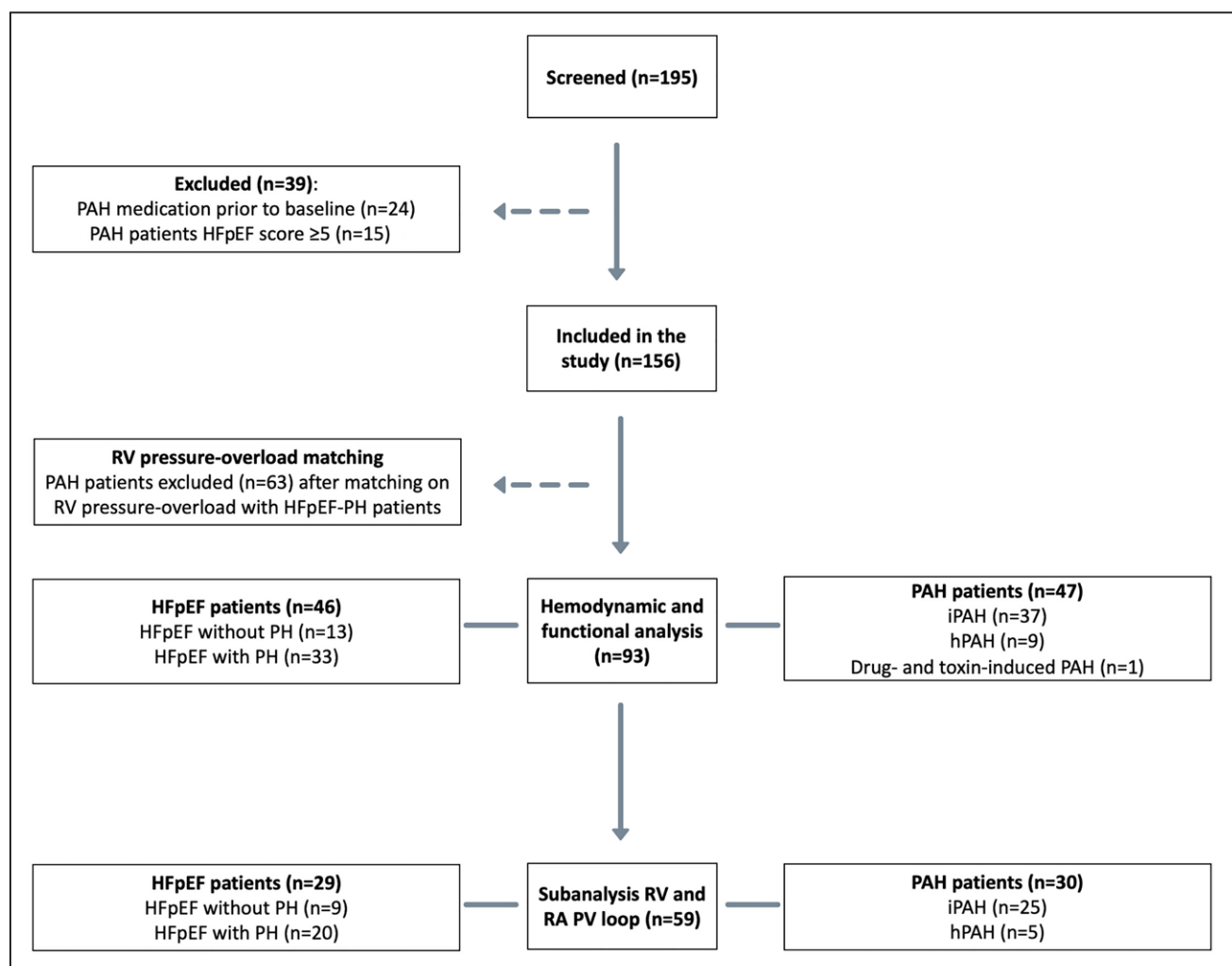


Figure 1. Flowchart.

Flowchart showing the number of patients included in the study. In total, 195 patients were screened for inclusion, after which 39 were excluded. After matching on pulmonary arterial pressures or right ventricular (RV) pressure-overload (pulmonary hypertension [PH] limited between mean pulmonary artery pressure ≥30 and ≤50 mmHg), we selected in total 93 patients for the final analysis, of which 47 pulmonary arterial hypertension (PAH; idiopathic pulmonary hypertension [iPAH] n=37; hereditary pulmonary arterial hypertension [hPAH] n=9), 33 heart failure with preserved ejection fraction (HFpEF)-PH, and 13 HFpEF without PH patients. PV indicates pressure volume; and RA, right atrial.

Table. Baseline Characteristics

Variable	HFpEF	HFpEF-PH	PAH	P value HFpEF-PH vs HFpEF	P value HFpEF-PH vs PAH
N	13	33	47		
Age, y	62 (11)	67 (9)	53 (18)	0.96	<0.001
Female sex, n (%)	7 (54)	23 (70)	27 (57)	0.50	0.38
BMI, m ² /kg	30 (4)	32 (7)	25 (4)	0.78	<0.001
NYHA functional class, n (%)					
Class I	0 (0)	2 (6)	2 (4)	0.51	0.93
Class II	7 (54)	11 (33)	17 (37)		
Class III	5 (40)	18 (55)	23 (50)		
Class IV	1 (8)	2 (6)	4 (9)		
6MWD, m	495 (363–636)	320 (243–403)	436 (328–497)	0.006	0.01
NTproBNP, ng/L	99 (64–282)	931 (288–1783)	837 (293–2345)	<0.001	0.99
Hb, mmol/L	8.7 (1.2)	8.5 (1.3)	9.3 (1.3)	0.99	0.02
eGFR, mL/min per 1.73 m ²	71 (19)	59 (18)	73 (14)	0.11	0.002
Diuretics use, n (%)	8 (62)	19 (59)	15 (33)	0.99	0.006
Comorbidities					
History of smoking, n (%)	7 (54)	22 (67)	26 (55)	0.64	0.43
History of coronary artery disease, n (%)	9 (69)	14 (42)	10 (21)	0.19	0.07
History of atrial fibrillation, n (%)	5 (39)	18 (55)	0 (0)	0.52	<0.001
History of hypertension, n (%)	8 (62)	24 (73)	13 (28)	0.70	<0.001
History of COPD, n (%)	2 (15)	8 (24)	6 (13)	0.80	0.30
History of OSAS, n (%)	4 (31)	10 (30)	4 (9)	0.99	0.03
History of diabetes, n (%)	4 (31)	9 (27)	8 (17)	0.99	0.41
History of chronic renal disease, n (%)	0 (0)	9 (27)	2 (4)	0.09	0.009
History of hypothyroidism, n (%)	1 (8)	8 (24)	2 (4)	0.39	0.02
RHC measurements					
mPAP, mmHg	19 (4)	41 (9)	44 (5)	<0.001	0.28
mRAP, mmHg	6 (5–6)	10 (8–14)	7 (5–10)	0.002	0.007
PCWP, mmHg	14 (4)	20 (3)	9 (3)	<0.001	<0.001
PVR, WU	0.6 (0.6–1.1)	3.5 (2.9–4.9)	7.9 (6.0–10.2)	<0.001	<0.001
CMR measurements					
LVEDV index, mL/m ²	61 (17)	58 (17)	52 (13)	0.99	0.25
LVEF, %	65 (9)	64 (10)	58 (10)	0.99	0.04
SV index, mL/m ²	39 (9)	37 (8)	30 (9)	0.99	0.006
RVEDV index, mL/m ²	62 (17)	68 (20)	87 (22)	0.99	<0.001
RVEF, %	58 (11)	52 (11)	36 (12)	0.29	<0.001

Data are presented as mean (SD), median (IQR), or n (%). 6MWD indicates 6-minute walking distance; BMI, body mass index; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HFpEF, heart failure with preserved ejection fraction; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NTproBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; OSAS, obstructive sleep apnoea syndrome; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; SV, stroke volume; and WU, Wood units.

end-diastolic volume (68 ± 20 versus 87 ± 22 mL/m²), and a moderate increase in RV mass (34 ± 15 versus 40 ± 14 g/m²) in comparison to PAH (Figure 2). RV function was also more preserved in patients with HFpEF-PH, shown by SV, RVEF, and strain values (Figure 2, Table S1). Although, RVEF was slightly lower in Cpc-PH than in isolated postcapillary PH patients (Cpc-PH: $51 \pm 10\%$, isolated precapillary pulmonary hypertension:

$56 \pm 12\%$), RVEF remained significantly higher than in patients with PAH ($36 \pm 12\%$; Table S2). Interestingly, like RVEF, LV ejection fraction was significantly lower in PAH compared with HFpEF-PH, albeit still within normal range ($58 \pm 10\%$ versus $64 \pm 10\%$; Table S1). Pressure-volume analyses demonstrated similar changes in RV-arterial coupling, and a stepwise increase in RV diastolic stiffness (Figure 2, Table S3).

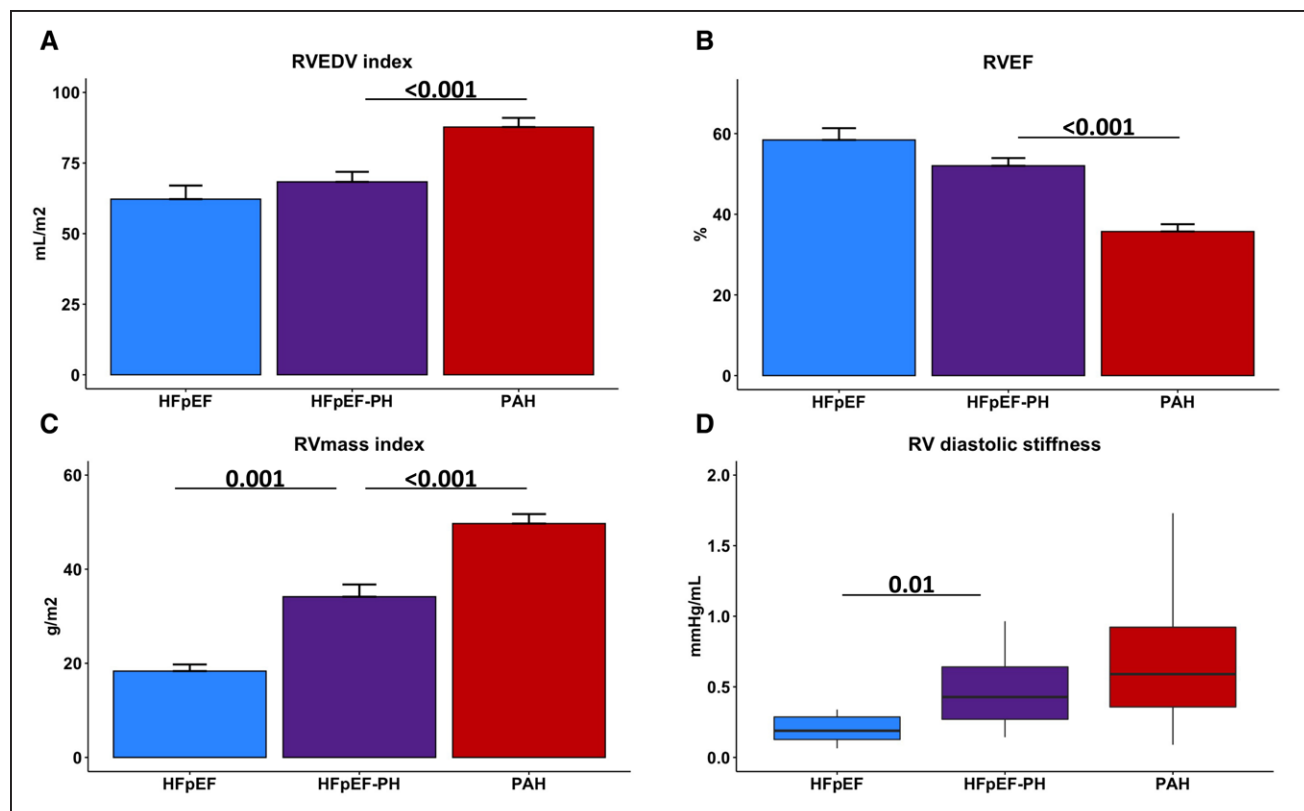


Figure 2. Right ventricular (RV) phenotype and RV diastolic stiffness.

Measurements of RV end-diastolic volume (RVEDV) index in **A**, right ventricular ejection fraction (RVEF) in **B**, RV mass index in **C**, and RV diastolic stiffness as indicated by end-diastolic elastance in **D** in 13 patients with heart failure with preserved ejection fraction (HFpEF) without pulmonary hypertension (PH), 33 with HFpEF-PH, and 47 with pulmonary arterial hypertension (PAH). Only significant differences between HFpEF-PH vs HFpEF and HFpEF-PH vs PAH are depicted.

Preserved RA/RV Interaction in HFpEF-PH

To further explore consequences of increased RV diastolic stiffness in patients with HFpEF-PH and PAH on RV filling, we calculated passive and active emptying volumes of the right atrium and passive and active filling volumes of the right ventricle. Among the groups, there was no difference in RA passive emptying or RV passive filling (Figure 3). In PAH, RA active emptying was the highest, whereas RV active filling was the lowest. This RA inefficiency in PAH was explained by vena cava back-flow during RA contraction (Figure 3), vena cava back-flow was not observed in HFpEF-PH.

The Right Atrium Was Most Affected in PAH, Whereas the Left Atrium Was Most Affected in HFpEF-PH

Next, we assessed the effect of pressure-overload on LA and RA volume and function. LA volume was significantly increased in patients with HFpEF-PH, together with a severely impaired reservoir, conduit and active LA function in comparison to PAH (Figure 4).

RA volume was significantly increased in patients with PAH (Figure 4). No differences in reservoir, conduit, and

active RA function could be observed between groups (Table S1). Only a small reduction in total RA emptying fraction was seen in patients with HFpEF-PH relative to HFpEF. This difference might be explained by the higher prevalence of AF history in patients with HFpEF-PH. In general, patients with HFpEF-PH with a history of AF were older, had more LA dilatation and ancillary atrial dysfunction (Figure S1, Table S3). In addition, total and active RA emptying fraction was significantly lower in patients with HFpEF-PH with or without a history of AF. However, no differences could be observed in LV or RV dimensions, nor function between patients with or without history of AF. Furthermore, we showed that RV dysfunction is explained by etiology of PH, rather than history of AF (Table S4).

RAP Is Elevated Throughout the Cardiac Cycle in HFpEF-PH

All hemodynamic measurements are presented in Table S5. Despite a similar RV pressure-overload, HFpEF-PH showed a significantly elevated mean RAP compared with patients with PAH (Figure 5). In addition, RAP was consistently elevated throughout the cardiac cycle in HFpEF-PH. In contrast to the increased RAP, no excessive RA dilatation in HFpEF-PH was observed.

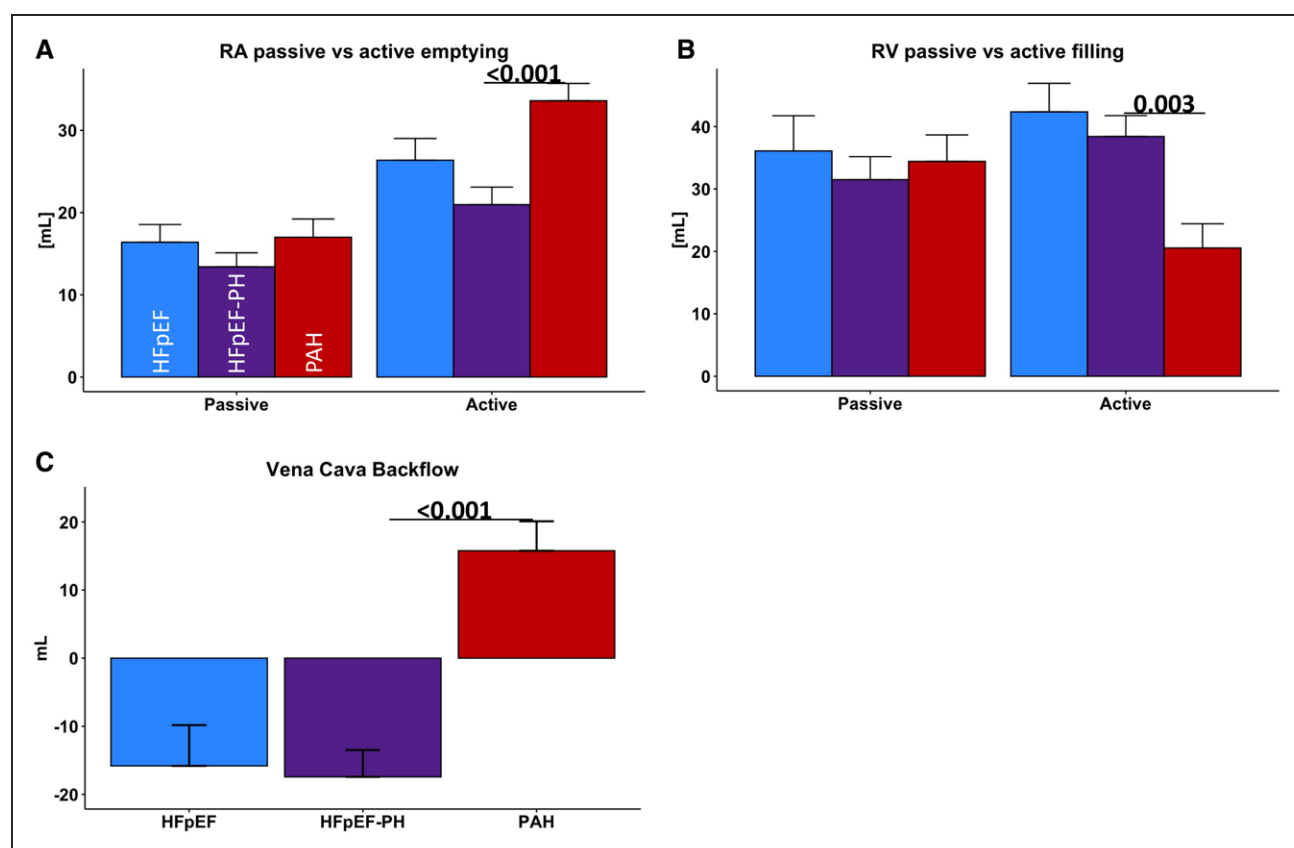


Figure 3. Right atrial (RA) and right ventricular (RV) interaction.

Measurements of RA passive and active emptying volumes in **A**, RV passive and active filling volumes in **B**, and vena cava backflow determined with the differences between RA active emptying and RV active filling volume in **C**, in 13 patients with heart failure with preserved ejection fraction (HFpEF) without pulmonary hypertension (PH), 33 with HFpEF-PH, and 47 with pulmonary arterial hypertension (PAH). Only significant differences between HFpEF-PH vs HFpEF and HFpEF-PH vs PAH are depicted.

In Figure 6, we plotted RA volume and RAP measurements and calculated $\Delta P/\Delta V$ during the reservoir phase to determine RA stiffness. HFpEF-PH had significantly greater RA stiffness than patients with PAH.

A potential factor contributing to the increased RAP and RA stiffness might be an enhanced LA/RA-interaction. To quantify LA/RA-interaction, we calculated the LA-to-RA pressure gradient and analyzed the RA eccentricity index (interatrial septum bulging; Figure 6). The LA-to-RA pressure gradient was significantly larger in HFpEF-PH than in PAH, but no difference was observed between HFpEF with or without PH. Also, the RA eccentricity index was significantly higher in HFpEF-PH compared with PAH (Figure 7, central figure).

DISCUSSION

This is the first study to directly compare the response of the right heart to a similar amount of pressure-overload in patients with HFpEF-PH and PAH. Interestingly, the RV response differed:

1. Despite similar RV pressure-overload, RV function was relatively preserved in HFpEF-PH with no signs of RV dilatation, whereas in PAH the right

ventricle was dilated and its function was severely depressed.

2. RAP was elevated throughout the cardiac cycle in patients with HFpEF-PH in comparison to PAH, whereas RA volumes were smaller. In HFpEF-PH, RA function was preserved with no signs of vena cava backflow during RA contraction in contrast to PAH. Elevated RAP and RA stiffness in HFpEF-PH were mainly explained by changes in LA/RA-interaction.

Whether the excessive increase in RAP is a beneficial adaptation to prevent the right heart from failing or a detrimental sign, needs to be investigated in future research. At least, we can conclude from this study that the increased RAP is not a sign of overt RV failure, but rather a reflection of HFpEF-severity.

PH-Specific Treatments for HFpEF-PH

PH is an important complication in patients with HFpEF. Passive backward transmission of increased left-sided filling pressure in HFpEF results in increased PAP and subsequently RV pressure-overload.^{24,34} As a consequence, changes in RV and RA function are observed in patients

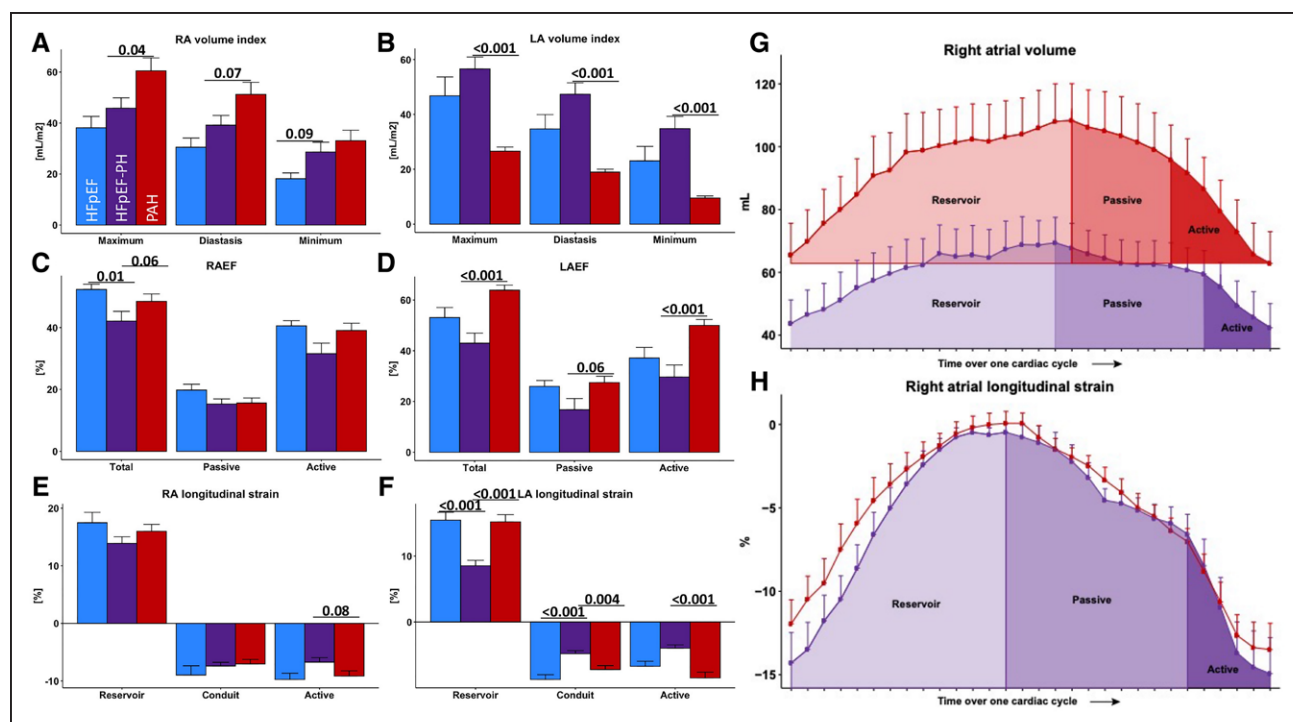


Figure 4. Left atrial (LA) and right atrial (RA) volumes and function.

Measurements of RA maximum, diastasis, and minimum volume index in **A**, LA maximum, diastasis, and minimum volume index in **B**, total, passive, and active right atrial ejection fraction (RAEF) in **C**, total, passive, and active left atrial ejection fraction (LAEF) in **D**, RA total, conduit and active longitudinal strain in **E**, LA total, conduit, and active longitudinal strain in **F**, in 13 patients with heart failure with preserved ejection fraction (HFpEF) without pulmonary hypertension (PH), 33 with HFpEF-PH, and 47 with pulmonary arterial hypertension (PAH). Representative measurements of RA volumes over 1 cardiac cycle in 30 phases in **G**, and of RA longitudinal strain over 1 cardiac cycle in 30 phases in **H**, in a subset of 10 HFpEF-PH and 10 PAH patients (**H**). Only significant differences between HFpEF-PH vs HFpEF and HFpEF-PH vs PAH are depicted.

with HFpEF in comparison to controls and are closely associated with mortality or heart failure hospitalization.⁸ It has been suggested that PH-specific medication may be beneficial in patients with HFpEF by reducing RV pressure-overload and thereby restoring right heart function. There is especially a large interest in testing PDE5-inhibition in patients with HFpEF, because it targets both pulmonary vascular remodeling as well as LV diastolic stiffness. PDE5-inhibition would alter expression of protein kinase G, an important regulator of titin phosphorylation and stiffness of LV cardiomyocytes. Nevertheless, in several clinical studies including the multicentre RELAX trial (Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure; REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT00763867), no beneficial effect of PDE5-inhibition on clinical end-points was observed.^{2,35–38} In contrast to most negative trials in HFpEF, a recent double-blinded trial showed that empagliflozin reduces risk of cardiovascular death or hospitalization for heart failure in patients with HFpEF.³⁹ In our study, we included patients with HFpEF without PH, patients with HFpEF with isolated post-capillary PH, patients with HFpEF with Cpc-PH and PAH. Surprisingly, patients with HFpEF-PH showed preserved RV and RA function in comparison to patients with PAH with similar RV pressure-overload. Only

in PAH, but not in patients with HFpEF-PH, we observed vena cava backflow with RA contraction, which reflects impaired filling of the right ventricle. The vena cava backflow in PAH may be explained by worse right heart function and increased diastolic stiffness.⁴⁰

RVEF was on average slightly lower in Cpc-PH patients than in isolated postcapillary PH patients but far better than RVEF in patients with PAH. Albeit right heart function in patients with HFpEF may differ in comparison to controls,⁹ it is relatively preserved in comparison to patients with PAH with similar pressure-overload. This raises the question whether PH-specific medication would give more benefit than harm. Especially, as a recent small study of our group has demonstrated that in patients with Cpc-PH, RV afterload and SV could improve with PDE5-inhibition, but at the expense of elevated LV filling pressures.³⁷

Nevertheless, this does not exclude the possibility that there might be a group of HFpEF patient with Cpc-PH that could indeed benefit from therapies targeting RV pressure-overload. Those patients would probably show a more severely compromised RV function (RV phenotype).² Inclusion of RV functional measurements, such as RVEF, may be valuable to identify these patients.

Interestingly, in our PAH cohort, LV function was slightly more depressed compared to patients with HFpEF-PH. The enlarged right ventricle, septal bowing, and

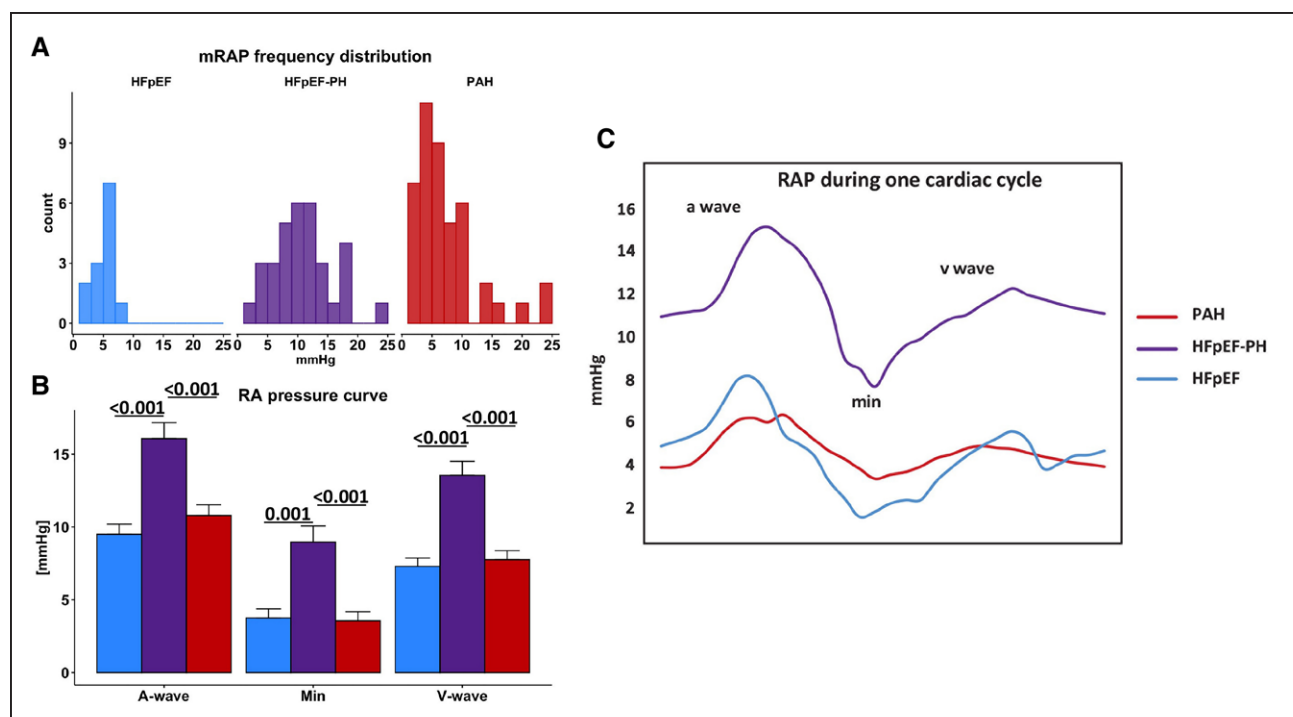


Figure 5. Right atrial (RA) pressures during cardiac cycle.

Frequency distribution of mean right atrial pressure (mRAP) in **A**, right atrial pressure (RAP) at the v-wave, minimal or x-descent, and A-wave in **B**, in 13 patients with heart failure with preserved ejection fraction (HFpEF) without pulmonary hypertension (PH), 33 with HFpEF-PH, and 47 with pulmonary arterial hypertension (PAH). Representative RAP curves are shown in each patient group in **C**. Only significant differences between HFpEF-PH vs HFpEF and HFpEF-PH vs PAH are depicted.

interventricular mechanical desynchrony that are known to play a role in PAH may directly limit filling of the left ventricle,²⁶ also evident in our cohort by the reduced stroke volume in PAH. As a consequence, underfilling of the left ventricle may lead to LV atrophy and reduced LV function.²⁶

Enhanced LA/RA Interaction

We demonstrate for the first time that RAP is consistently elevated throughout the entire cardiac cycle in HFpEF-PH, compared with PAH despite similar pressure-overload. In combination with smaller RA volume, this implies increased RA stiffness.

Due to the shared pericardium, dilatation and increased pressure in the left atrium can directly affect the right atrium. Therefore, increased RA stiffness in HFpEF-PH may be the result of altered characteristics of the LV/RV and LA rather than a mere consequence of intrinsic RA wall characteristics. RAP can be used as surrogate for pericardial pressures and provides an estimation of pericardial constraint.^{41–43} The pericardium applies an external force on the ventricles and limits filling.⁴² Any increase in volumes or pressures or epicardial fat can lead to an increase in pericardial constraint.^{42,44}

Our results indicate that patients with HFpEF-PH have enhanced pericardial constraint and LA/RA-interaction, which may contribute to the increased RAP and RA stiffness. First, LA-to-RA pressure gradient was

higher in HFpEF (with or without PH) than PAH. As a result, RA eccentricity index in HFpEF was increased (bulging toward the right). Although the direction of LA/RA interaction was similar in HFpEF and HFpEF-PH, the final effect on RAP is larger in HFpEF-PH, as the driving force (LAP) was also higher in HFpEF-PH. Second, RV diastolic stiffness and RVEDP are similar between patients with HFpEF-PH and PAH. We therefore conclude that the observed increase in RAP over the complete cardiac cycle is a consequence of LA/RA-interaction, rather than a sign of overt RV failure.

Atrial fibrillation was previously associated with reduced RA function and reduced RA compliance.^{6,7,13} A significant proportion of patients with HFpEF-PH in our cohort had an history of AF (of note: all were in sinus rhythm at time of cardiac magnetic resonance), which was associated with LA and RA dysfunction. RAP was similarly increased in patients with or without AF history. In addition, an history of AF was not associated with increased vena cava backflow. Finally, by multivariate analyses, we could demonstrate that the differences in RVEF between PAH and HFpEF-PH continue to exist after correction of the history of AF. An important clinical consequence of the elevated RAP in patients with HFpEF-PH may be a higher prevalence of kidney dysfunction, eGFR levels were significantly reduced in patients with HFpEF-PH. Whether lowering RAP results in (partial) restoration of kidney function in this patient group is unknown, but of interest.

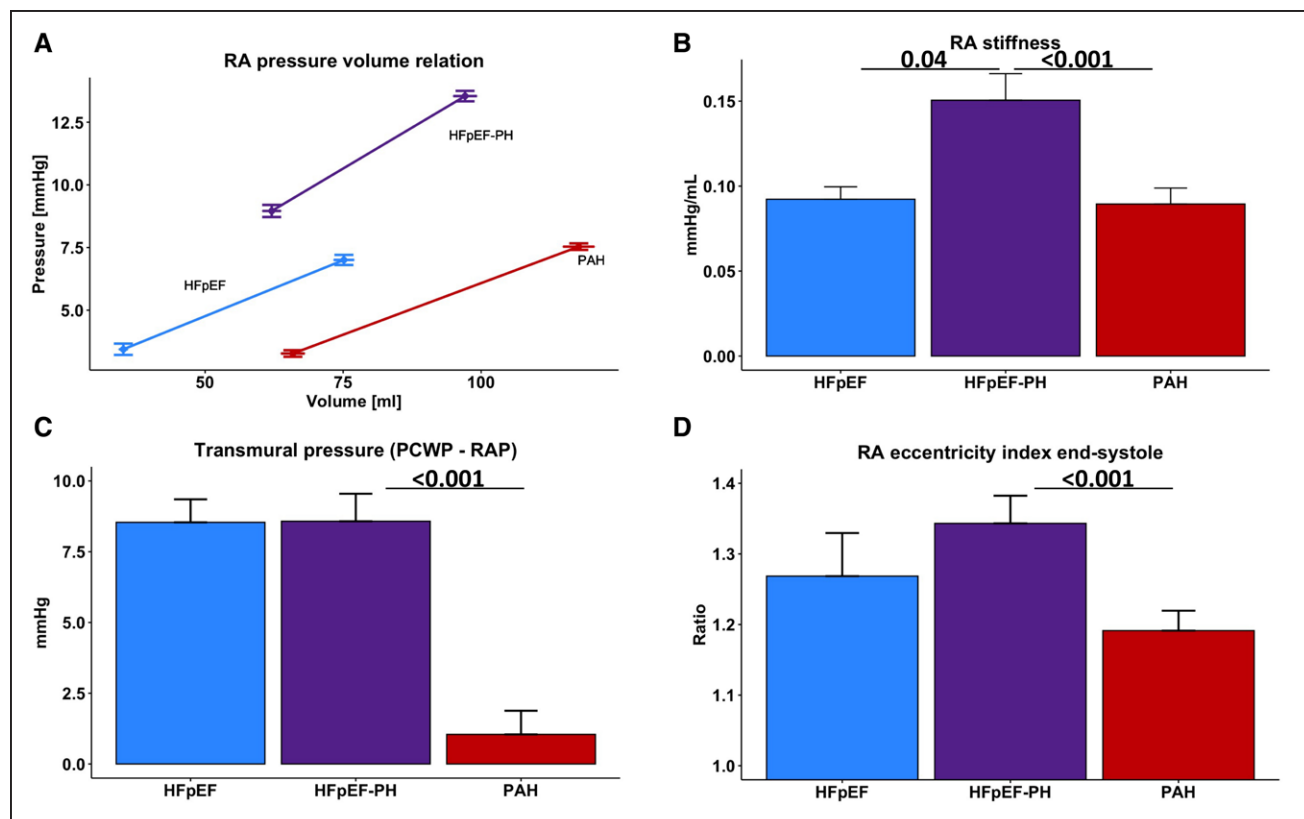


Figure 6. Left atrial and right atrial (RA) interaction.

The relationship between the increase in RA volume and pressure in **A**, the $\Delta P/\Delta V$ during the reservoir phase to determine RA stiffness in **B**, the interatrial septum pressure gradient indicated by the difference in pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) in **C**, and RA eccentricity index at end-systole in **D**, in 13 patients with heart failure with preserved ejection fraction (HFpEF) without pulmonary hypertension (PH), 33 with HFpEF-PH, and 47 with pulmonary arterial hypertension (PAH). Only significant differences between HFpEF-PH vs HFpEF and HFpEF-PH vs PAH are depicted. ES indicates end-systole.

Traditional strategies to reduce LV filling pressures in HFpEF consists of drugs such as diuretics. Although a beneficial effect of diuretics was suggested in the CHAMPION trial (CardioMEMS HF Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III Heart Failure Patients), clinical effectivity has not been proven in other randomized controlled trials.^{45,46} Therefore, new and nonpharmacological strategies to reduce disease severity and LA pressure in HFpEF are currently under investigation.^{15,45,47} Recently, an interatrial shunt device has been suggested in HFpEF.^{45,48–50} A left-to-right atrial shunt decreases the interatrial pressure gradient. As a result, left-sided pressures decrease at rest but particularly during exercise. The shunt device has shown to ameliorate symptoms and improve functional capacity in HFpEF.^{48–50} However, considering our findings, the question is how the interatrial shunt will impact the right atrium. On the one hand, by reducing left-sided pressure, atrial septostomy may reduce the interatrial pressure and thus the pericardial constraint and thereby also relieve the right atrium. On the other hand, a further increase in RAP may lead to increased central venous pressure, which may have detrimental effects on renal function. Nevertheless, the first results did not indicate further increase in

RAP. The results of 2 larger clinical on effectivity of atrial septostomy in HFpEF are expected soon (REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifiers: NCT03499236, NCT03088033).

Limitations

One of the limitations of our study is the retrospective nature and single-center setting, which could have led to a potential bias in the patient population. Because of the retrospective nature of the study, we could not match patients with PAH and patients with HFpEF-PH individually on mPAP value but group-matched the patients with PAH to pulmonary artery pressures of HFpEF-PH (only including patients with PAH with mPAP ≥ 30 and ≤ 50 mmHg). In addition, as a national PH referral center, the prevalence of Cpc-PH was larger in our cohort (70%) than is described in literature ($\approx 10\%$). Second, our analyses were limited to baseline measurements. We consider this the most relevant comparison, as patients with PAH are still treatment naive, and no approved treatment is currently available for HFpEF. Finally, PV loop data were only available in a subset of patients. However, our observations were sufficiently consistent to draw relevant conclusions. Importantly, we combined sophisticated

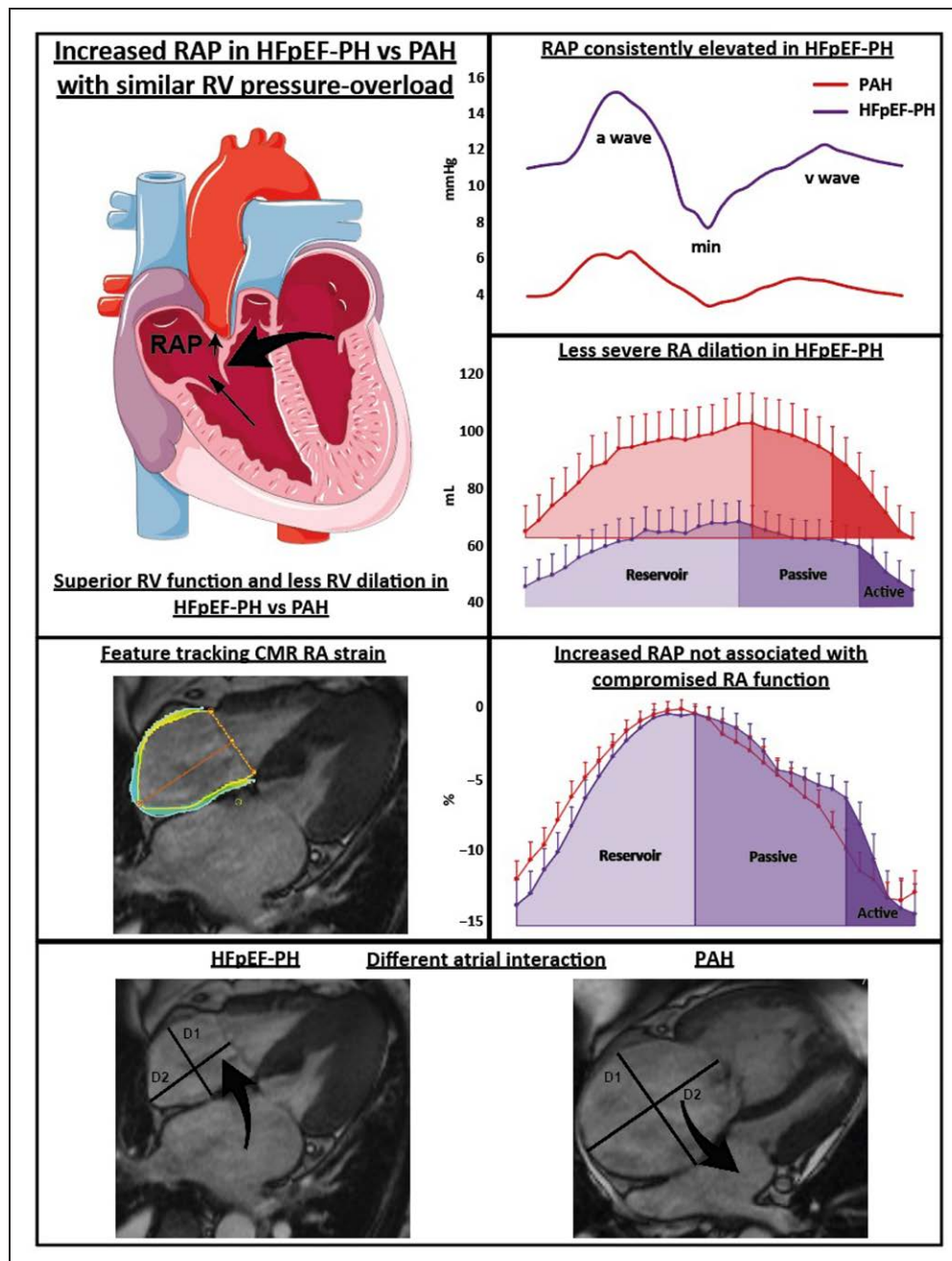


Figure 7. Overview of the main findings in this study.

We combined sophisticated imaging and hemodynamic analysis of the right atrium and ventricle in patients with heart failure with preserved ejection fraction (HFpEF)-pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) with similar pressure overload. We showed that right ventricular (RV) function in HFpEF-PH patients is preserved with no signs of RV dilatation in comparison to PAH. Right atrial (RA) pressure was highly elevated in HFpEF-PH patients, but RA function was preserved with no signs of vena cava backflow during RA contraction, in contrast to PAH patients. Elevated right atrium pressure (RAP) and RA stiffness in HFpEF-PH could be explained by an enhanced LA/RA interaction, rather than RV dysfunction. CMR indicates cardiac magnetic resonance.

imaging and hemodynamic analyses of the right atrium and ventricle in patients with HFpEF-PH and PAH, matched on PAP to have the most reliable comparison.

Conclusions

By comparing HFpEF-PH with PAH, we were able to demonstrate that RV function in patients with HFpEF-PH

is relatively preserved with no signs of RV dilatation in comparison to patients with PAH with similar RV pressure-overload. Although RAP was highly elevated in patients with HFpEF-PH, RA function was preserved with no signs of vena cava backflow during RA contraction, in contrast to patients with PAH. Elevated RAP and RA stiffness in HFpEF-PH could be explained by an enhanced LA/RA-interaction. Therefore, our results

indicate that increased RAP is not a sign of overt RV failure, but rather a reflection of HFpEF-severity.

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Disclosures

Dr Handoko serves on advisory boards for Novartis, Boehringer Ingelheim, Vifor Pharma, AstraZeneca, Bayer, MSD, and Quin. He has also received education and research grants from Novartis, Boehringer Ingelheim, and Vifor Pharma, which were paid to his employer.

Supplemental Material

Figure S1
Tables S1–S5

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