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Exercise hemodynamics in heart failure patients with preserved and mid-range ejection fraction: key role of the right heart

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Abstract

Objective We sought to explore whether classification of patients with heart failure and mid-range (HFmrEF) or preserved ejection fraction (HFpEF) according to their left ventricular ejection fraction (LVEF) identifies differences in their exercise hemodynamic profile, and whether classification according to an index of right ventricular (RV) function improves differentiation.

Background Patients with HFmrEF and HFpEF have hemodynamic compromise on exertion. The classification according to LVEF implies a key role of the left ventricle. However, RV involvement in exercise limitation is increasingly recognized. The tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure (TAPSE/PASP) ratio is an index of RV and pulmonary vascular function. Whether exercise hemodynamics differ more between HFmrEF and HFpEF than between TAPSE/PASP tertiles is unknown.

Methods We analyzed 166 patients with HFpEF (LVEF ≥ 50%) or HFmrEF (LVEF 40–49%) who underwent basic diagnostics (laboratory testing, echocardiography at rest, and cardiopulmonary exercise testing [CPET]) and exercise with right heart catheterization. Hemodynamics were compared according to echocardiographic left ventricular or RV function.

Results Exercise hemodynamics (e.g. pulmonary arterial wedge pressure/cardiac output [CO] slope, CO increase during exercise, and maximum total pulmonary resistance) showed no difference between HFpEF and HFmrEF, but significantly

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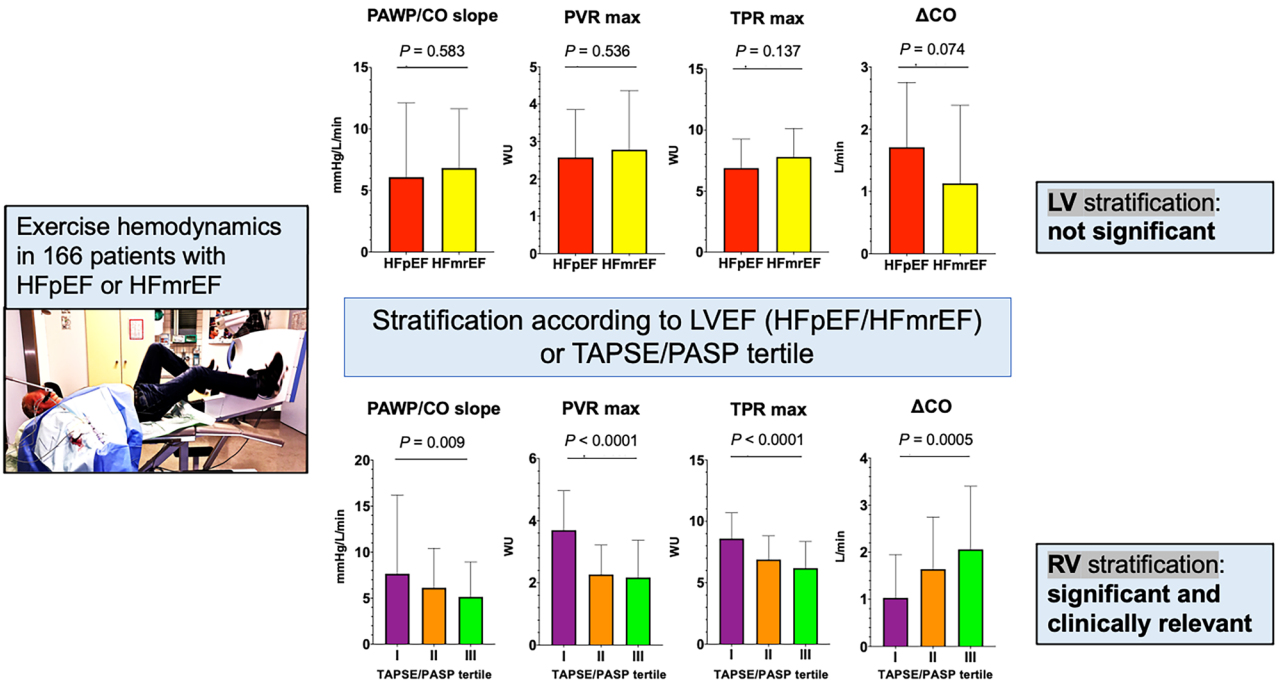
differed across TAPSE/PASP tertiles and were associated with CPET results. N-terminal pro-brain natriuretic peptide concentration also differed significantly across TAPSE/PASP tertiles but not between HFpEF and HFmrEF.

Conclusion In patients with HFpEF or HFmrEF, TAPSE/PASP emerged as a more appropriate stratification parameter than LVEF to predict clinically relevant impairment of exercise hemodynamics.

Graphic abstract



Stratification of exercise hemodynamics in patients with HFpEF or HFmrEF according to LVEF or TAPSE/PASP, showing significant distinctions only with the RV-based strategy. All data are shown as median [upper limit of interquartile range] and were calculated using the independent-samples Mann–Whitney *U* test or Kruskal–Wallis test. *PVR* pulmonary vascular resistance; *max* maximum level during exercise.

Keywords Exercise hemodynamics · Heart failure with preserved ejection fraction · Heart failure with mid-range ejection fraction · Right heart · TAPSE/PASP ratio

Introduction

Since its introduction in the "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" [1], the term "heart failure with mid-range ejection fraction" (HFmrEF, left ventricular ejection fraction (LVEF) 40–49%) has been the subject of broad discussion and controversy. There is still no general consensus as to whether HFmrEF truly represents a distinct entity or whether it should be grouped with "heart failure with preserved ejection fraction" (HFpEF; LVEF ≥ 50%) or "heart failure with reduced ejection fraction" (HFrEF; LVEF < 40%). Patients with HFmrEF show a high prevalence of coronary artery disease (similar to patients with HFrEF) and benefit from HFrEF drug therapies (in contrast to patients with HFpEF), leading some authors to propose categorizing HFmrEF together with HFrEF [2, 3]. However, HFmrEF shows greater similarity to HFpEF in other characteristics such as long-term prognosis [2]. Not least because of these inconsistencies, the concept of classifying patients with heart failure (HF) merely by their LVEF has been challenged fundamentally, and a more pathophysiological approach (e.g. based on hemodynamic characteristics) has been proposed [4–7].

However, both HFpEF and HFrEF often share progressive right ventricular (RV) impairment at rest and during exercise [8]. In this regard, the ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary arterial pressure (PASP) has been validated as an echocardiographic surrogate of right ventricular to pulmonary artery (RV-PA) coupling in HFpEF [9] and pulmonary hypertension (PH) [10], and further explored as an important determinate of afterload, symptomatology, and

Table 1 Baseline characteristics of patients with HFpEF and patients with HFmrEF

	N	HFpEF	HFmrEF	*P* value*
Patients, *n* (%)	166	125 (75.3)	41 (24.7)	
Male/female, (*n*/*n*)	166	54/71	28/13	0.005[a]
Age, years	166	74 [71–77]	73 [65–78]	0.216[b]
BMI, (kg/m^2)	166	28 ± 5	29 ± 5	0.487[c]
NYHA functional class, *n* (%)	166			0.347[a]
II		32 (25.6)	6 (14.6)	
III		90 (72.0)	34 (82.9)	
IV		3 (2.4)	1 (2.4)	
Clinical characteristics				
Hypertension, *n* (%)	165	100 (80.0)	36 (90.0)	0.148[a]
Diabetes mellitus, *n* (%)	162	23 (18.7)	17 (43.6)	0.002[a]
Coronary artery disease, *n* (%)	164	41 (33.1)	19 (47.5)	0.099[a]
Atrial fibrillation/flutter, *n* (%)	166	95 (76.0)	31 (75.6)	0.960[a]
Pacemaker or ICD, *n* (%)	166	23 (18.4)	18 (43.9)	0.001[a]
ICD		3 (2.4)	9 (22.0)	
Pacemaker		20 (16.0)	9 (22.0)	
Permanent RV pacing, *n* (%)	164	11 (8.8)	6 (14.6)	0.301[a]
CRT, *n* (%)	155	4 (3.2)	7 (17.1)	0.005[d]
Duration of HF diagnosis, months	166	0 [0–8]	9 [0–57]	< 0.001[b]
History of HF hospitalization, *n* (%)	148	49 (39.2)	22 (61.1)	0.085[d]
Medications, *n* (%)				
ACEI/ARB	165	82 (66.1)	32 (78.0)	0.115[a]
≥ 50% of target dose			21 (65.6)	
Beta-blockers	164	102 (82.3)	34 (82.9)	0.697[a]
≥ 50% of target dose			25 (73.5)	
Mineralocorticoid receptor antagonists	141	38 (38.4)	29 (70.7)	< 0.001[d]
≥ 50% of target dose			23 (88.5)	
Diuretics	163	100 (80.6)	36 (92.3)	0.087[a]
Digitoxin	163	18 (14.5)	9 (23.1)	0.210[a]
Laboratory tests				
NT-proBNP, (pg/mL)	88	1187 [679–1990]	1742 [908–4124]	0.124[b]
BNP, (pg/mL)	78	174 [130–295]	196 [144–377]	0.459[b]
GFR, (L/min/m^2)	163	70 ± 25	61 ± 23	0.05[c]
Echocardiography				
LVEF, (%)	165	60 [55–65]	45 [40–45]	< 0.001[b]
LVMI, (g/m^2)	86	120 ± 33	139 ± 27	0.004[c]
E/e'	71	16 [13–19]	13 [11–18]	0.156[b]
TAPSE, (mm)	166	19 [17–23]	15 [13–19]	< 0.001[b]
PASP, (mmHg)	166	45 [37–54]	48 [39–61]	0.455[b]
TAPSE/PASP, (mm/mmHg)	166	0.44 [0.35–0.58]	0.30 [0.24–0.54]	< 0.001[b]
Mitral regurgitation grade (1–3)	166			0.324[a]
0 (no mitral regurgitation)		42 (33.6)	19 (46.3)	
1		42 (33.6)	12 (29.3)	
2		41 (32.8)	10 (24.4)	
Tricuspid regurgitation grade (1–3)	166			0.559[a]
0 (no tricuspid regurgitation)		8 (6.4)	1 (2.4)	
1		59 (47.2)	24 (58.5)	
2		40 (32.0)	11 (26.8)	
3		18 (14.4)	5 (12.2)	
CPET				
Workload, (W)	79	65 ± 38	58 ± 26	0.461[c]

Table 1 (continued)

	N	HFpEF	HFmrEF	*P* value*
Peak V´O_2, (mL/min/kg)	79	12.3 [10.6–15.4]	11.6 [10.2–14.0]	0.227[b]
V´E/V´CO_2 slope	53	35 [31–40]	41 [34–47]	0.111[b]

Values represent mean ± standard deviation or median [interquartile range] except where otherwise indicated. *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CPET* cardiopulmonary exercise testing, *CRT* cardiac resynchronization therapy, *E/e'* ratio of mitral inflow velocity to annular relaxation velocity, *GFR* glomerular filtration rate, *ICD* implantable cardiac defibrillator, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *NT-proBNP* N-terminal fragment of pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PASP* systolic pulmonary arterial pressure, *RV* right ventricular, *TAPSE* tricuspid annular plane systolic excursion, *V´E/V´CO_2* minute ventilation/carbon dioxide production, *V´O_2* oxygen uptake

*HFpEF vs HFmrEF

[a]Pearson Chi-square test

[b]Mann–Whitney *U* test

[c]Independent Student's *t* test

[d]Fisher´s exact test

Table 2 Resting and exercise pulmonary hemodynamics in patients with HFpEF compared with patients with HFmrEF

Parameters	At rest				During exercise			
	n	HFpEF	HFmrEF	*P* value*	*n*	HFpEF	HFmrEF	*P* value*
mPAP, (mmHg)	166	24 [20–30]	23 [20–36]	0.680[a]	166	41 [35–50]	44 [36–53]	0.341[a]
PAWP, (mmHg)	166	15 [12–20]	16 [12–22]	0.503[a]	166	28 ± 6	27 ± 7	0.901[b]
TPG, (mmHg)	166	9 [7–12]	10 [7–14]	0.312[a]	166	15 [10–20]	16 [12–24]	0.208[a]
RAP, (mmHg)	165	7 [4–10]	7 [4–11]	0.794[a]	114	15 ± 7	17 ± 7	0.352[b]
CO, (L/min)	166	4.2 [3.5–4.8]	4.4 [3.4–5.3]	0.351[a]	166	6.1 [4.7–7.7]	6.1 [4.7–7.2]	0.535 [a]
PAC, (mL/mmHg)	165	2.4 [1.9–3.4]	2.4 [1.7–3.1]	0.862[a]	165	1.6 [1.3–2.1]	1.5 [1.2–2.0]	0.521 [a]
PAPi, (mmHg)	165	3.5 [2.7–6.9]	3.7 [2.8–6.1]	0.824[a]	114	2.8 [2.0–4.1]	2.5 [2.1–3.3]	0.381 [a]
RVSWI, (g/m^2/beat)	165	8.0 [6.3–9.9]	7.9 [5.7–11.0]	0.814[a]	116	13 ± 6	13 ± 6	0.932[b]
PVR, (WU)	166	2.0 [1.2–2.9]	2.1 [1.2–3.2]	0.644[a]	165	2.6 [1.8–3.9]	2.8 [1.8–4.4]	0.536 [a]
TPR, (WU)	166	6.0 [4.7–7.5]	5.6 [4.5–8.3]	0.983[a]	166	6.9 [5.5–9.3]	7.8 [6.1–10.1]	0.137 [a]
Heart rate, (beats/min)	165	65 [59–75]	66 [62–72]	0.673[a]	165	90 [76–105]	86 [75–96]	0.324 [a]
Systolic blood pressure, (mmHg)	165	129 ± 20	127 ± 19	0.483[b]	164	151 ± 26	145 ± 24	0.224[b]
Ea, (mmHg/mL)	165	0.50 [0.38–0.70]	0.52 [0.33–0.86]	0.836[a]	165	0.92 [0.68–1.3]	0.97 [0.72–1.3]	0.616 [a]
Total RV power, (watts)	166	0.29 [0.23–0.39]	0.31 [0.23–0.46]	0.301[a]	166	0.74 [0.56–0.95]	0.78 [0.59–0.91]	0.785[a]
mPAP/CO slope, (mmHg/L/min)	–	–	–	–	160	9.4 [5.9–16.5]	11.8 [7.2–21.7]	0.119[a]
PAWP/CO slope, (mmHg/L/min)	–	–	–	–	159	6.1 [3.5–12.1]	6.8 [3.9–11.6]	0.583[a]
ΔCO, (L/min)	–	–	–	–	166	1.7 [1.0–2.8]	1.1 [0.6–2.4]	0.074[a]
Workload, (W)	–	–	–	–	145	30 [25–50]	25 [25–50]	0.431[a]
Atrial fibrillation/flutter during RHC, *n* (%)	–	–	–	–	165	72 (57.6)	26 (63.4)	0.545[c]

Values represent mean ± standard deviation or median [interquartile range]

CO cardiac output, Δ*CO* change in cardiac output in response to exercise, *Ea* arterial elastance, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *mPAP* mean pulmonary arterial pressure, *PAC* pulmonary arterial capacitance, *PAPi* pulmonary artery pulsatility index, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RHC* right heart catheterization, *RV* right ventricular, *RVSWI* right ventricular stroke work index, *TPR* total pulmonary resistance, *WU* Wood Units

*HFpEF vs HFmrEF

[a]Mann–Whitney *U* test

[b]Independent Student's *t* test

[c]Pearson Chi-square test

outcome [11–13]. Our hypothesis was that classification of patients with HFpEF or HFmrEF according to LVEF is not suitable to predict exercise hemodynamic profile, and that classification using tertiles of the TAPSE/PASP ratio could be more appropriate for this purpose. Therefore, the primary objective of our study was to compare exercise hemodynamics during right heart catheterization (RHC) in a cohort of patients with HFpEF or HFmrEF stratified by LVEF or the TAPSE/PASP ratio. The secondary objective was to compare the exercise hemodynamic profile of patients with HFmrEF with that of patients with HFrEF.

Methods

Patients

We retrospectively analyzed data from the prospectively recruiting Kerckhoff-Klinik HF Registry and the Giessen PH Registry [14]. First, consecutive patients registered from 04/2009 to 03/2017 with available exercise RHC data were identified within the two databases (online resource 1). The main indication for RHC was suspected PH or evaluation of dyspnea (76%); other common indications were controls in patients already diagnosed with post-capillary PH (11%) and evaluation of valve defects of unknown significance (10%). We then excluded patients without a final diagnosis of HFpEF or HFmrEF according to current guidelines [1]. Patients without adequate medical treatment (i.e. patients with volume overload and [in patients with HFmrEF] lack of guideline-directed drug treatment), patients with severe valvular defects (left-sided stenosis and regurgitation more than moderate), ventricular assist devices, or acute untreated HF, and those without available measurements of TAPSE and/or PASP were also excluded.

Echocardiographic evaluation included standard acquisition of LVEF, baseline left ventricular mass index (LVMI), the ratio of mitral inflow velocity to annular relaxation velocity (E/e'), PASP derived from continuous wave Doppler assessment of the peak tricuspid regurgitant velocity, and TAPSE. In patients with atrial fibrillation, measurements of PASP and TAPSE were repeated until consistent measurements could be achieved. Baseline laboratory measurements, cardiopulmonary exercise testing (CPET) parameters, and New York Heart Association (NYHA) functional class were included in the analysis as available.

In addition, we analyzed patients with HFrEF (LVEF < 40%) from a previously published cohort [7]; patients with LVEF 40–45% ($n = 12$) and without available TAPSE and/or PASP measurements ($n = 47$) were excluded.

Exercise RHC

RHC was performed under local anesthesia with insertion of a Swan-Ganz catheter (7F Thermodilution Catheter, Biosensors International, Singapore) via the internal jugular vein or a cubital vein. The exercise protocol of the Kerckhoff-Klinik was published in detail previously [7]. Briefly, exercise was performed on a standard cycle ergometer in the supine position with an adjusted external workload, and workload was adapted stepwise until the patient was exhausted. The exercise protocol of the Giessen PH Division involved an incremental exercise test (step protocol with 3-min steps) in the semi-supine position with repeated hemodynamic measurements. The zero reference levels for the pressure transducer were placed as recommended for the supine position and the semi-supine position [15]. In both centers, workload was determined based on the workload achieved during CPET and/or adjusted on an individual, clinical basis to allow measurement of hemodynamic parameters for a total duration of < 10 min. In both centers, exercise was started 30 min after catheter insertion and all pulmonary pressures were averaged over several respiratory cycles [15].

The following parameters were measured: mean pulmonary arterial pressure (mPAP); right atrial pressure (RAP); pulmonary arterial wedge pressure (PAWP); and cardiac output (CO) by the thermodilution technique. The single CO measurements were repeated at least three times, until three measurements with < 10% deviation could be obtained, which were then averaged. The slopes of hemodynamic parameters/CO were calculated as recommended [16]. The pulmonary artery pulsatility index (PAPi), pulmonary arterial capacitance (PAC), total pulmonary resistance (TPR), pulmonary vascular resistance (PVR), transpulmonary gradient (TPG), right ventricular stroke work index (RVSWI), arterial elastance ($Ea = 1.65 \times mPAP - 7.79$/stroke volume), and total RV power were calculated as described previously [17–23]. The presence/absence of atrial fibrillation or flutter (AF) during RHC was also noted.

Statistical analysis

Statistical analysis was performed using SPSS, version 22.0 (IBM, Armonk, NY). Data are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] for normally or non-normally distributed parameters, respectively. Adherence to a Gaussian distribution was determined using the Kolmogorov–Smirnov test. Missing values were not imputed. Numbers of patients with available data for each parameter are provided.

Patients were stratified by tertile of TAPSE/PASP ratio as previously proposed [11, 13] (tertile 1: < 0.35 mm/mmHg; tertile 2: 0.35–0.51 mm/mmHg; tertile 3: > 0.51 mm/mmHg).

For independent samples, comparison was made with the independent-samples Kruskal–Wallis test or Mann–Whitney *U* test for non-normally distributed parameters, the Student's *t* test or analysis of variance for normally distributed parameters, and the Pearson Chi-square test or Fisher's exact test for categorical parameters as appropriate, with $P < 0.05$ considered statistically significant. Associations between parameters were assessed using simple linear regression.

Results

Comparison of patients with HFpEF vs HFmrEF

The analysis included 125 patients with HFpEF and 41 patients with HFmrEF. In comparison with the HFmrEF group, the patients with HFpEF presented with significantly lower rates of diabetes mellitus, markedly higher LVEF and TAPSE, and lower left ventricular (LV) mass index. Diastolic LV dysfunction was present in both the HFpEF and HFmrEF groups. Of note, the ratio of TAPSE/PASP was significantly higher in the HFpEF group compared with the HFmrEF group, despite both groups having similar PASP. The majority of patients in both groups were in NYHA functional class III, and the two groups showed no significant difference in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Both groups achieved similar levels of workload and peak oxygen uptake ($V´O_2$) during CPET, with no significant difference observed in the minute ventilation/carbon dioxide production ($V´E/V´CO_2$) slope. High rates of AF and systemic hypertension were reported. Use of devices (pacemaker/implantable cardiac defibrillator) was more common in the group with HFmrEF than the group with HFpEF. The degree of mitral or tricuspid regurgitation did not differ between the two groups (Table 1).

There was no difference in resting or exercise hemodynamics between the HFpEF and HFmrEF groups (Table 2). Of note, the increase of CO during exercise (ΔCO) showed no significant difference between the two groups. Starting from median resting pulmonary pressures below the definition of PH (mPAP ≥ 25 mmHg) [24], patients with HFpEF and HFmrEF showed a comparable pattern of concomitant increases in mPAP, PAWP, and RAP during exercise. These increases were accompanied by only a moderate increase of CO, resulting in steep mPAP/CO and PAWP/CO slopes. PAC decreased and RVSWI increased during exercise to a similar extent in the HFpEF and HFmrEF groups. Resting TPG and PVR were low in both groups. Interestingly, PAPi substantially decreased (i.e. worsened) from rest to exercise in both the HFpEF and HFmrEF groups (for both groups: $P < 0.001$; related-samples Wilcoxon signed rank test).

Impact of RV function

Echocardiography at rest revealed significantly better longitudinal RV function in patients with HFpEF versus HFmrEF (TAPSE 19 [17–23] vs 15 [13–19] mm, $P < 0.001$). LVEF and TAPSE were moderately correlated (Spearman $r = 0.41$, $P < 0.001$). However, these findings did not translate into differences in symptoms or hemodynamics between the HFpEF and HFmrEF groups at rest and during exercise. By contrast, stratification of the patients by TAPSE/PASP tertile revealed that those in the lowest tertile had higher NT-proBNP levels, steeper $V´E/V´CO_2$ and mPAP/CO slopes, and a substantially higher degree of LV backward failure (higher PAWP/CO slope and PAWP during exercise), pulmonary vascular disease and thus RV afterload (higher PVR, TPR, and Ea, and lower PAC during exercise), and impairment of CO reserve (reduced maximum CO and ΔCO) than those in the intermediate and highest tertiles (Tables 3 and 4 and graphic abstract). However, hemodynamic indices of RV contractile function during exercise (RVSWI and PAPi) were not significantly different between the TAPSE/PASP tertiles. NYHA functional class showed a difference between TAPSE/PASP tertiles which was borderline significant ($P = 0.053$; Table 3), and TAPSE/PASP showed a significant decrease with increasing NYHA functional class ($P = 0.035$; Fig. 1).

PAWP/CO slope, maximum TPR and PVR, and ΔCO showed associations with exercise capacity (peak $V´O_2$) and ventilatory inefficiency ($V´E/V´CO_2$ slope) during CPET (Fig. 2).

In summary, key hemodynamic and CPET parameters as well as NT-proBNP concentration were markedly more different between TAPSE/PASP tertiles than between patients with HFpEF and those with HFmrEF.

Comparison of patients with HFmrEF vs HFrEF

Patients with HFrEF ($n = 108$) showed no differences in NYHA functional class and age, lower rates of AF and hypertension, higher rates of implantable cardiac defibrillator and ß-blocker use, and markedly higher NT-proBNP levels compared with patients with HFmrEF (online resource 2). Interestingly, TAPSE, PASP, and the TAPSE/PASP ratio did not show significant differences between the two groups. Exercise hemodynamics showed important differences: patients with HFrEF had lower CO at rest and during exercise, lower ΔCO, and higher TPR, Ea, and total RV power than patients with HFmrEF (online resources 3 and 4).

Table 3 Baseline characteristics in patients with HFpEF and HFmrEF stratified by TAPSE/PASP tertile

	TAPSE/PASP tertile			
	I	II	III	*P* value*
Patients, *n* (%)	55	56	55	
Male/female, (*n*/*n*)	34/21	26/30	22/33	0.063[a]
Age, years	75 [71–79]	74 [69–77]	74 [65–77]	0.167[d]
BMI, (kg/m^2)	28 ± 7	27 ± 5	29 ± 6	0.501[b]
NYHA class, *n* (%)				0.053[a]
II	6 (10.9)	18 (32.1)	14 (25.5)	
III	47 (85.5)	36 (64.3)	41 (74.5)	
IV	2 (3.6)	2 (3.6)	0	
Clinical characteristics				
Hypertension, *n* (%)	44 (80.0)	45 (80.4)	47 (85.5)	0.761[a]
Diabetes mellitus, *n* (%)	24 (43.6)	10 (17.9)	6 (10.9)	< 0.001[a]
Coronary artery disease, *n* (%)	29 (52.7)	17 (30.4)	14 (25.5)	0.003[a]
Atrial fibrillation/flutter, *n* (%)	48 (87.3)	44 (78.6)	34 (61.8)	0.007[a]
Pacemaker or ICD, *n* (%)	14 (25.5)	14 (25.0)	12 (23.6)	0.974[a]
Permanent RV pacing, *n* (%)	6 (10.9)	7 (12.5)	4 (7.3)	0.665[a]
CRT, *n* (%)	5 (9.1)	1 (1.8)	5 (9.1)	0.508[c]
Duration of HF diagnosis, months	1 [0–16]	1.5 [0–18.5]	0 [0–10]	0.672[d]
History of HF hospitalization, *n* (%)	24 (43.6)	24 (42.9)	23 (41.8)	0.874[a]
Medications, *n* (%)				
ACEI/ARB	40 (72.7)	40 (71.4)	35 (63.6)	0.466[a]
Beta-blockers	44 (80.0)	45 (80.4)	47 (85.5)	0.761[a]
Mineralocorticoid receptor antagonists	27 (49.1)	17 (30.4)	23 (41.8)	0.327[a]
Diuretics	47 (85.5)	47 (83.9)	42 (76.4)	0.148[a]
Digitoxin	7 (12.7)	12 (21.4)	8 (14.5)	0.476[a]
Laboratory tests				
NT-proBNP, (pg/mL)	1849 [1152–3739]	1132 [668–1768]	1000 [521–1748]	0.005[d]
BNP, (pg/mL)	216 [174–377]	187 [110–282]	154 [121–282]	0.060[d]
GFR, (L/min/m^2)	62 ± 24	73 ± 25	70 ± 25	0.062[b]
Echocardiography				
LVEF, (%)	50 [45–60]	55 [55–60]	60 [50–65]	< 0.001[d]
LVMI, (g/m^2	135 ± 28	114 ± 25	124 ± 39	0.012[b]
E/e'	18 [13–22]	16 [13–18]	14 [12–17]	0.107[d]
TAPSE, (mm)	14 [13–17]	19 [17–22]	22 [19–26]	< 0.001[d]
PASP, (mmHg)	58 [50–69]	48 [40–52]	35 [31–40]	< 0.001[d]
TAPSE/PASP, (mm/mmHg)	0.26 [0.21–0.30]	0.42 [0.38–0.46]	0.62 [0.57–0.72]	< 0.001[d]
Mitral regurgitation grade (1–3)				0.642[a]
0 (no mitral regurgitation)	20 (36.4)	20 (35.7)	21 (38.2)	
1	15 (27.3)	22 (39.3)	17 (30.9)	
2	20 (36.4)	14 (25.0)	17 (30.9)	
Tricuspid regurgitation grade (1–3)				0.380[a]
0 (no tricuspid regurgitation)	2 (3.6)	2 (3.6)	5 (9.1)	
1	26 (47.3)	25 (44.6)	32 (58.2)	
2	20 (36.4)	19 (33.9)	12 (21.8)	
3	7 (12.7)	10 (17.9)	6 (10.9)	
CPET				
Workload, (W)	50 [40–58]	50 [40–90]	60 [46–90]	0.075[d]
Peak V´O_2, (mL/min/kg)	11.5 [9.8–13.6]	11.6 [10.3–16.3]	13 [11.4–15.3]	0.163[d]

Table 3 (continued)

	TAPSE/PASP tertile			
	I	II	III	*P* value*
V´E/V´CO_2 slope	42 [35–53]	32 [30–47]	37 [32–40]	0.015[d]

Values represent mean ± standard deviation or median [interquartile range] except where otherwise indicated

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BMI* body mass index, *BNP* brain natriuretic peptide, *CPET* cardiopulmonary exercise testing, *CRT* cardiac resynchronization therapy, *E/e'* ratio of mitral inflow velocity to annular relaxation velocity, *GFR* glomerular filtration rate, *ICD* implantable cardiac defibrillator, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *NT-proBNP* N-terminal fragment of pro-brain natriuretic peptide, *NYHA* New York Heart Association, *PASP* systolic pulmonary arterial pressure, *RV* right ventricular, *TAPSE* tricuspid annular plane systolic excursion, *V´E/V´*CO_2 minute ventilation/carbon dioxide production, *V´*O_2 oxygen uptake

*Comparison across all TAPSE/PASP tertiles

[a]Pearson Chi-square test

[b]Analysis of variance

[c]Fisher´s exact test, tertile I + II vs III

[d]Independent-samples Kruskal–Wallis test

Discussion

We here present an analysis of invasive hemodynamics at rest and during exercise in patients with HFpEF, HFmrEF, and HFrEF. Our cohort of patients had manifest HF, as indicated by their NYHA functional class and NT-proBNP levels. The relevant findings of our study are as follows: (1) patients with HF classified based on LVEF (mid-range vs preserved) do not show relevant differences in their exercise hemodynamic and clinical profile; (2) patients with HF stratified according to the TAPSE/PASP ratio as an echocardiographic surrogate of RV-PA coupling show several important differences in their hemodynamic, CPET, and clinical profile, supporting a key role of the right ventricle in determining the severity of both HFpEF and HFmrEF; and (3) in terms of exercise hemodynamic phenotype, HFmrEF shares greater similarity with HFpEF than with HFrEF.

LVEF is universally accepted as an index of contractility, but it is known to have low specificity [25], and a more detailed phenotyping is desirable [26]. Recent analyses of outcomes and the effect of specific medications in HF indicate that LVEF may be more useful as a continuum than as a categorical variable with rigid cutoffs [4, 27]. Moreover, an index derived using a pathophysiological approach is expected to correlate better with HF symptoms and exercise capacity than LVEF, although the use of such an approach to guide HF therapy has not yet been validated [5]. Our results support these findings, since hemodynamic profiles at rest and during an exercise challenge showed very little association with LVEF classified as mid-range (40–49%) or preserved (≥ 50%) in our cohort [15, 25, 28]. However, comparison between patients with HFmrEF and patients with HFrEF showed more severe failure to increase CO during exercise and more advanced pulmonary vasculopathy with RV afterload elevation in the latter group, while maximum PAWP and PAWP/CO slope were not different. A cautious interpretation could suggest the right ventricle as a key factor for disease severity also in patients with HFrEF. Paradoxically, echocardiographic RV parameters were not different between HFrEF and HFmrEF; one possible explanation is that those were measured only at rest. All in all, HFmrEF shares more exercise hemodynamic characteristics with HFpEF than with HFrEF.

We used the TAPSE/PASP ratio as the key criterion to stratify our cohort of patients with preserved and mid-range ejection fraction. This stratification led to a clinically relevant differentiation of our cohort, as those with greater impairment of RV function according to the TAPSE/PASP ratio showed a depressed ability to increase CO and a higher degree of RV afterload during exercise. By contrast, indices of RV contractility during exercise showed no difference across TAPSE/PASP tertiles, possibly indicating a predominant role of afterload. Although TAPSE is known to reflect RV longitudinal contractility and to give prognostic information [29, 30], its value for a more comprehensive description of RV function is limited [31, 32]. Measuring contractility without respect to the related afterload may be insufficient to describe circulatory function. We interpret the marked differences in RV load in the absence of differences in hemodynamic indices of RV contractility across TAPSE/PASP tertiles in this context. Patients with a more favorable relationship of RV load to contractility have an increased CO reserve, which is ultimately the most important factor and has a positive impact on prognosis [7].

Surprisingly at first sight, those patients with a reduced TAPSE/PASP ratio also showed more pronounced LV dysfunction expressed by a steeper PAWP/CO slope and higher maximum PAWP. However, this is consistent with the left ventricle being the origin and driver of the dysfunctional RV-pulmonary circulation unit [33, 34].

Table 4 Resting and exercise pulmonary hemodynamics in patients with HFpEF and HFmrEF stratified by TAPSE/PASP tertile

Parameters	At rest				During exercise			
	I	II	III	*P* value*	I	II	III	*P* value*
mPAP, (mmHg)	30 [22–37]	24 [20–30]	22 [19–24]	< 0.001	47 [39–55]	42 [35–48]	39 [34–47]	< 0.001
PAWP, (mmHg)	18 [15–22]	15 [12–22]	13 [11–17]	0.001	29 [25–33]	28 [24–32]	25 [22–30]	0.036
RAP, (mmHg)	8 [6–10]	6 [3–10]	6 [4–9]	0.128	17 [12–22]	15 [10–20]	15 [10–19]	0.328
CO, (L/min)	4.3 [3.4–5.0]	4.2 [3.5–5.0]	4.1 [3.4–5.0]	0.905	5.5 [4.3–6.9]	6.3 [4.8–7.6]	6.3 [4.8–8.3]	0.041
PAC, (mL/mmHg)	2.0 [1.5–2.7]	2.4 [2.0–3.5]	2.7 [2.0–3.5]	< 0.001	1.4 [1.1–1.7]	1.7 [1.4–3.5]	1.8 [1.4–2.8]	< 0.001
PAPi, (mmHg)	3.5 [2.9–6.0]	3.7 [2.2–8.0]	3.8 [2.8–5.3]	0.866	2.8 [2.2–3.6]	2.8 [1.9–4.5]	2.8 [2.0–3.6]	0.820
RVSWI (g/m^2/beat)	9.5[6.8-12.0]	10.0 ± 4.1	8.0 ± 3.1	0.012	13.0 ± 6.1	15.0 ± 6.6	13.0 ± 6.0	0.392[b]
PVR, (WU)	2.9 [2.0–3.7]	1.7 [1.2–2.4]	1.7 [1.1–2.5]	< 0.001	3.7 [2.4–5.0]	2.3 [1.6–3.2]	2.2 [1.6–3.4]	< 0.001
TPR, (WU)	6.7 [5.2–9.3]	5.8 [4.3–7.3]	5.2 [4.2–7.2]	0.002	8.6 [6.7–10.7]	6.7 [5.4–8.8]	6.2 [4.9–8.4]	< 0.001
Ea, (mmHg/mL)	0.65 [0.45–0.96]	0.49 [0.34–0.70]	0.47 [0.33–0.61]	< 0.001	1.1 [0.85–1.5]	0.90 [0.63–1.3]	0.85 [0.59–1.0]	< 0.001
Total RV power, (watts)	0.35 [0.25–0.53]	0.28 [0.20–0.40]	0.27 [0.22–0.34]	0.007	0.79[0.59–0.94]	0.75 [0.57–0.98]	0.71 [0.53–0.85]	0.711
Heart rate (beats/min)	66 [60–75]	65 [59–75]	65 [57–71]	0.292	89 [75–102]	89 [78–101]	90 [71–102]	0.901
mPAP/CO slope, (mmHg/L/min)	–	–	–	–	14.1 [8.9–26.9]	8.7 [5.7–13.6]	7.5 [4.9–13.8]	< 0.001
PAWP/CO slope, (mmHg/L/min)	–	–	–	–	7.6 [4.5–16.2]	6.1 [3.6–10.4]	5.1 [2.8–8.9]	0.009
ΔCO, (L/min)	–	–	–	–	1.0 [0.5–2.0]	1.6 [1.0–2.7]	2.1 [1.1–3.4]	< 0.001
Workload, (W)	–	–	–	–	25 [25–40]	35 [25–50]	43 [25–50]	0.086
Atrial fibrillation/flutter during exercise RHC, *n* (%)	–	–	–	–	42 (76.4)	34 (60.7)	22 (40.0)	< 0.001[a]

Values represent mean ± standard deviation or median [interquartile range] except where otherwise indicated

CO cardiac output, *ΔCO* change in cardiac output in response to exercise, *Ea* arterial elastance, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *mPAP* mean pulmonary arterial pressure, *PAC* pulmonary arterial capacitance, *PAPi* pulmonary artery pulsatility index, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RC time* constant of the pulmonary circulation, *RV* right ventricular, *RVSWI* right ventricular stroke work index, *TPG* transpulmonary gradient, *WU* Wood units

*Independent-samples Kruskal–Wallis test for comparison across all TAPSE/PASP tertiles, unless otherwise specified

[a]Pearson Chi-square test

[b]Analysis of variance

The clinical relevance of the hemodynamic key parameters we found related to TAPSE/PASP is underlined by their correlation to CPET parameters with proven prognostic impact [6].

Therefore, we see these hemodynamic differences across TAPSE/PASP tertiles as a strong hint for a key role of RV failure—as a consequence of LV dysfunction causing increased RV afterload—in depressed CO response and the heart failure syndrome, independent from the resting LVEF category (mid-range or preserved). Our findings are consistent with numerous previous reports indicating the dominance of RV dysfunction for the prediction of symptoms and risk stratification in patients with HFpEF [35] and HFrEF [36, 37]. Although the noninvasively measured index of TAPSE/PASP has been shown to indicate risk in all patients with HF [37], concerns have been raised about the use of echocardiography values alone because of broad confidence intervals [38]. Hemodynamic characteristics measured by RHC could complement echocardiographic measurements and provide the basis for clinical management and entry criteria for clinical trials [39]. How to improve RV loading conditions in patients with HF is an unsolved clinical issue and should be investigated in future studies. The TAPSE/PASP ratio and ΔCO could be used as selection criteria among others to test therapeutic strategies.

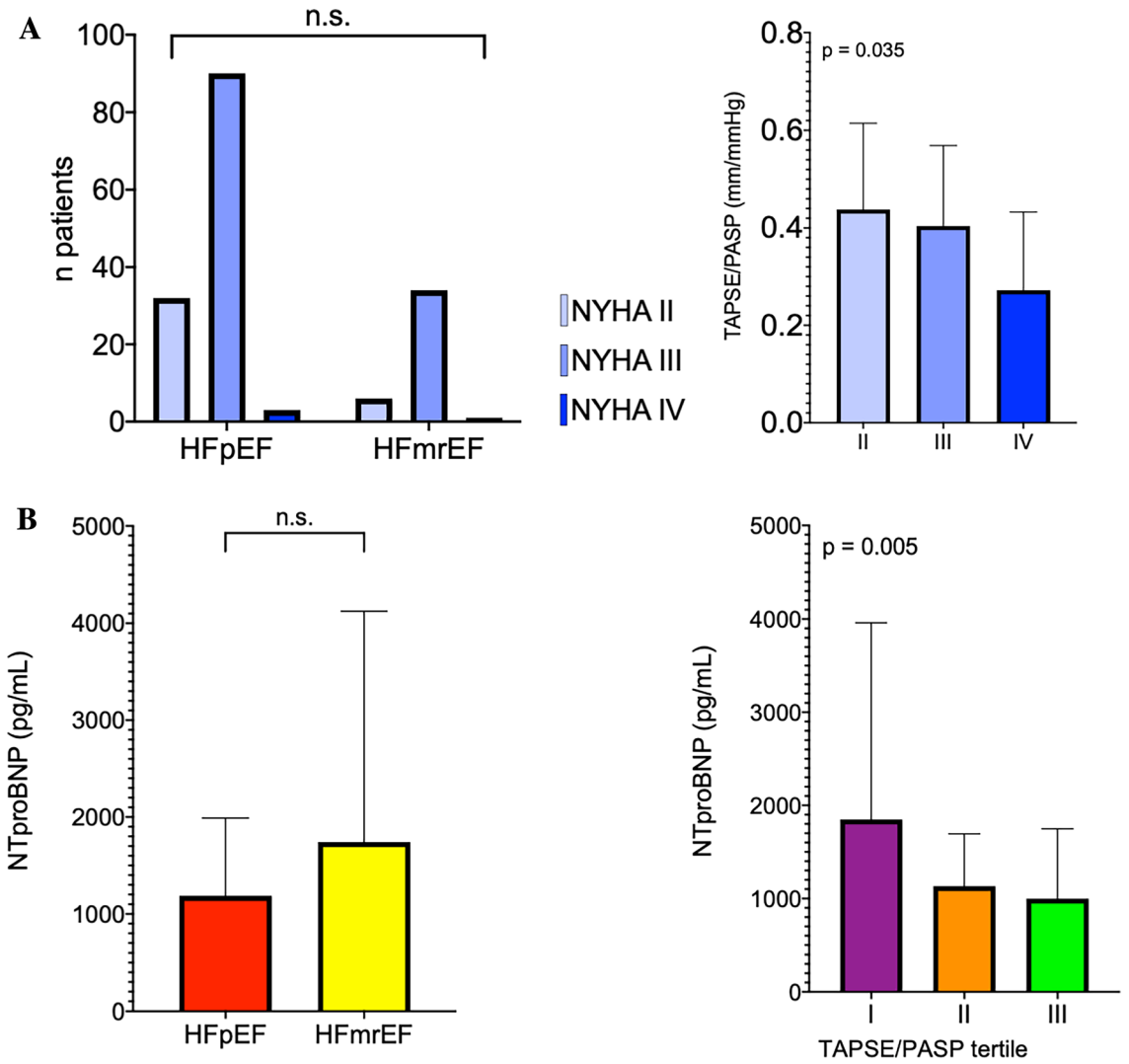


Fig. 1 **a** Stratification of New York Heart Association functional class according to heart failure with preserved or mid-range ejection fraction and TAPSE/PASP stratified by NYHA class. **b** Stratificaton of NT-proBNP levels according to HFpEF/HFmrEF or TAPSE/PASP. The first display shows numbers of patients, otherwise median values are shown, with error bars indicating the upper limit of the interquartile range. Statistical significance was assessed using the Chi-square test, the Kruskal–Wallis and the Mann–Whitney U test. *HFpEF* heart failure with preserved ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *NYHA* New York Heart Association, *PASP* systolic pulmonary arterial pressure, *TAPSE* tricuspid annular plane systolic excursion, *NT-proBNP* N-terminal pro-brain natriuretic peptide

Limitations

Limitations of our study include its two-center design and the lack of additional echocardiographic parameters, such as deformation imaging of the left and right ventricle and RV fractional area change. The different exercise protocols in the Kerckhoff-Klinik and the Giessen PH Division (supine vs semi-supine exercise) may be a source of bias. In addition, the high rate of atrial fibrillation in our cohort carries a risk of error for CO measurement; however, repetitive measurements as described in our methods section have the potential to minimize this risk. Echocardiographic parameters during exercise would also have been of interest but were not available. In addition, CPET data were not available in all patients. Outcome data were not registered systematically; analyses of the available data on hospitalization for HF did not show associations with the TAPSE/PASP ratio, which is in contrast to previously published data [11]. Concerning mortality, the number of registered events was too low for meaningful analysis of prognostic relevance.

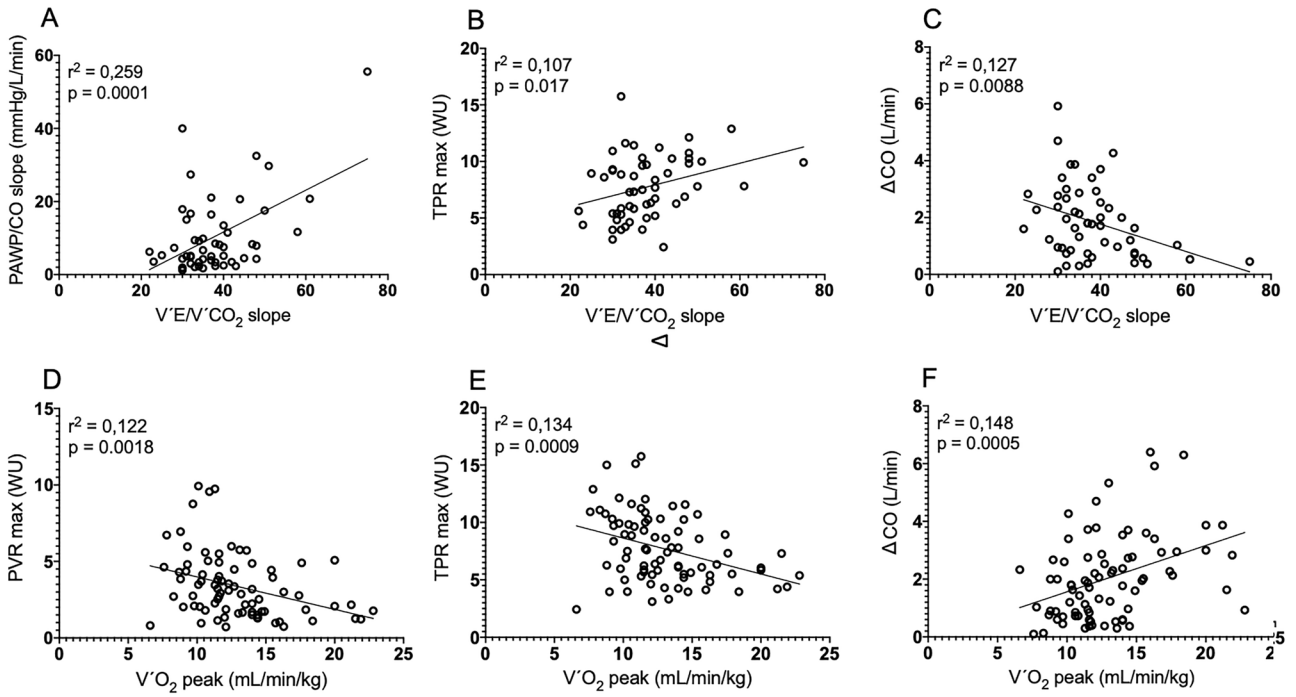


Fig. 2 Association of exercise hemodynamics with cardiopulmonary exercise test parameters. The association of ventilatory inefficiency ($V´E/V´CO_2$ slope) with **A** PAWP/CO slope, **B** TPR max, and **C** ΔCO, and the association of exercise capacity ($V´O_2$ peak) with **D** PVR max, **E** TPR max, and **F** ΔCO are shown. Data were calculated using simple linear regression. *CO* cardiac output, *ΔCO* change in cardiac output in response to exercise, *Max* maximum level during exercise, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *TPR* total pulmonary resistance, *$V´E/V´CO_2$* minute ventilation/carbon dioxide production, *$V´O_2$ peak* peak oxygen uptake, *WU* Wood Units

Conclusion

In conclusion, the categorization of HF as HFpEF and HFmrEF did not correspond to exercise hemodynamic profiles or exercise limitation in our cohort. Stratification based on an echocardiographic surrogate of RV-PA coupling demonstrated important differences within the exercise hemodynamic, CPET, and clinical profile of patients with HFpEF and HFmrEF. Our study underlines the right side of the heart as a key determinant of the heart failure syndrome in both HF entities and challenges the current HF classification based solely on the left side of the heart.

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Declarations

Conflict of interest All authors report that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Ethical approval The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients enrolled into the registries gave written informed consent, and data collection and analyses were approved by the ethics committee of the Faculty of Medicine at the University of Giessen (Approval No. 186/16, 266/11, 117/16).

Consent to participate All patients enrolled into the registries gave written informed consent.

Consent for publication All patients enrolled into the registries gave written informed consent.

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