



Right heart dysfunction in heart failure with preserved ejection fraction

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Aim

Right heart function is not well characterized in patients with heart failure and preserved ejection fraction (HFpEF). The goal of this study was to examine the haemodynamic, clinical, and prognostic correlates of right ventricular dysfunction (RVD) in HFpEF.

Methods and results

Heart failure and preserved ejection fraction patients ($n = 96$) and controls ($n = 46$) underwent right heart catheterization, echocardiographic assessment, and follow-up. Right and left heart filling pressures, pulmonary artery (PA) pressures, and right-sided chamber dimensions were higher in HFpEF compared with controls, while left ventricular size and EF were similar. Right ventricular dysfunction (defined by RV fractional area change, FAC < 35%) was present in 33% of HFpEF patients and was associated with more severe symptoms and greater comorbidity burden. Right ventricular function was impaired in HFpEF compared with controls using both load-dependent (FAC: 40 ± 10 vs. $53 \pm 7\%$, $P < 0.0001$) and load-independent indices (FAC adjusted to PA pressure, $P = 0.003$), with enhanced afterload-sensitivity compared with controls (steeper FAC vs. PA pressure relationship). In addition to haemodynamic load, RVD in HFpEF was associated with male sex, atrial fibrillation, coronary disease, and greater ventricular interdependence. Over a median follow-up of 529 days (IQR: 143–1066), 31% of HFpEF patients died. In Cox analysis, RVD was the strongest predictor of death (HR: 2.4, 95% CI: 1.6–2.6; $P < 0.0001$).

Conclusion

Right heart dysfunction is common in HFpEF and is caused by both RV contractile impairment and afterload mismatch from pulmonary hypertension. Right ventricular dysfunction in HFpEF develops with increasing PA pressures, atrial fibrillation, male sex, and left ventricular dysfunction, and may represent a novel therapeutic target.

Keywords

Heart failure • Ventricular function • Haemodynamics • Pulmonary hypertension • Atrial fibrillation • Gender

Introduction

With a normal pulmonary vasculature, the left ventricle is able to sustain the entire circulation, even in the absence of a functional right ventricle (RV).^{1,2} However, when left ventricular systolic or diastolic function becomes impaired, or if pulmonary vascular disease develops, RV function becomes essential to maintain forward cardiac output and prevent systemic venous congestion.³ The deleterious impact of RV dysfunction (RVD) on functional capacity⁴ and prognosis^{5–7} is well established in patients with heart failure (HF) and reduced ejection fraction.^{5–9} However, while half of patients with HF have preserved ejection fraction (HFpEF),¹⁰ the burden, mechanisms, and prognostic impact of right heart dysfunction

in this form of HF remain unclear. Improved understanding of RV-pulmonary artery (PA) coupling in HFpEF is essential given the absence of effective therapies and the emergence of novel medicines targeting the pulmonary vasculature and the right heart.

Prior studies have reported that RVD is present in HFpEF based upon non-invasive measures of RV shortening or systolic velocities.^{11–13} However, systolic RV shortening is highly sensitive to afterload^{1,14} which is typically elevated in HFpEF due to pulmonary hypertension,^{15–17} making it difficult to determine whether RVD in HFpEF is reflective of myocardial dysfunction, afterload-mismatch, or both. Indeed, there may be other load-independent factors that promote RVD, such as primary intrinsic myocardial disease, neurohormone activation and remodelling, ischaemia, dysrhythmias,

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ventricular interaction, and male sex.^{1,2,18} Accordingly, the current study sought to comprehensively assess and compare right heart function in HFpEF and controls, to analyse clinical and haemodynamic determinants of RVD, and to explore the impact of right heart dysfunction on outcome in HFpEF.

Methods

Study subjects

Consecutive patients who underwent right heart catheterization and echocardiography at the Mayo Clinic (Rochester, MN, USA) within a 48-h window between April 2005 and August 2012 with sufficient raw data stored (pressure waveforms and echocardiographic images) available were included in this retrospective study. Heart failure and preserved ejection fraction was defined by cardiologist-adjudicated HF diagnosis according to the Framingham criteria¹⁹ (Supplementary material online, Table S1) of >6 months duration, LVEF $\geq 50\%$ and elevated PA wedge pressure (≥ 15 mmHg at rest or ≥ 25 mmHg at exercise). Patients with congenital heart disease, endocarditis, carcinoid, amyloid, constrictive, restrictive or hypertrophic cardiomyopathy, intracardiac shunt [other than small patent foramen ovale (PFO)], high output HF, non-Group II PH, severe chronic obstructive or interstitial pulmonary disease, mitral valve replacement, organic valvular disease, acute coronary syndrome, or haemodynamic instability were excluded.

A convenience sample of patients referred for right heart catheterization for small PFO closure ($n = 28$) and for evaluation of exertional dyspnoea where no demonstrable cardiovascular pathology was identified ($n = 18$) served as the control group. Past medical history, medication use, and contemporaneous laboratory data (± 1 week) were abstracted from the medical records. Vital status was determined using outpatient records and the social security death index. The study was approved by Mayo Clinic institutional review board.

Assessment of haemodynamics and chamber morphology

Right heart catheterization was performed in the supine position via the jugular or femoral vein using a balloon-tipped catheter as previously described.²⁰ Right atrial (RA), RV, PA, and PA wedge pressures were determined at end-expiration. Transpulmonary gradient (TPG) was calculated as PA mean-PA wedge pressure, pulmonary vascular resistance (PVR) as TPG/cardiac output, and total pulmonary resistance (TPR) as mean-PA/cardiac output. Pulmonary artery compliance was determined from the quotient of stroke volume/PA pulse pressure.

Two-dimensional and Doppler echocardiography was performed according to ASE guidelines^{21,22} by experienced sonographers and cardiologists. Left ventricular ejection fraction (LVEF) was determined by the modified Quinones formula.²³ Apical four-chamber views were reviewed off-line by a cardiologist (V.M.) unaware of patient characteristics to measure RV and atrial dimensions. Maximal left atrial volume were measured by the area-length method and normalized to the body surface area.

Assessment of right heart structure and function

Right ventricular length and diastolic diameters were measured at the base- and mid-ventricle perpendicularly to the septum.²² Right ventricular function was assessed by systolic annular tissue velocity of the lateral tricuspid annulus²⁴ and by tracing the RV endocardium in the apical four-chamber view in systole and diastole to obtain fractional area change (RV FAC%).^{22,25} Right ventricular dysfunction was defined categorically as RV

FAC $< 35\%$ according to published guidelines.²² Right ventricular diastolic stiffness was calculated as (RV end-diastolic pressure – RV minimal-diastolic pressure) divided by (RV end-diastolic area – RV end-systolic area).²⁶

The right atrial endocardium was tracked in the frame prior to tricuspid valve opening and at the frame of minimal RA size in order to obtain maximal, minimal, and diastasis RA volume (prior tricuspid valve opening, only in patients with sinus rhythm) using the area-length method.²⁷ Right ventricular function was assessed by total RA ejection fraction (max – min volume/max volume), active RA ejection fraction (diastasis – min/diastasis volume, a measure of pump function), and passive RA ejection fraction (max – diastasis/max volume, a measure of reservoir function). Tricuspid and pulmonary regurgitation were measured using the ordinal grading scheme endorsed by the ASE.²⁸

Statistical methods

Data were analysed using JMP10 (SAS Institute, Inc., Cary, NC, USA). Distributions of continuous variables were visually assessed for normality and summary data are reported as mean (standard deviation) or median (25–75th inter-quartile range). Between-group differences were compared by the t-test, Wilcoxon rank-sum test, or χ^2 tests as appropriate. Group comparisons of haemodynamic and echocardiographic parameters (Table 1) were adjusted for age and body mass using a general linear model; the two-sided *P*-values reported in the text and tables are after this adjustment. Bivariate linear regression (Pearson) was performed to examine relationships between haemodynamic and functional parameters. Logistic regression or Cox proportional hazard models were used to examine correlates of RVD and relationships with outcome. Independent variables entered into the model include those hypothesized *a priori* to cause or contribute to RVD, including PA pressure load, age, sex, atrial fibrillation (AF), LV EF, systolic BP, and history of coronary disease. To separate the influence of haemodynamic load from non-haemodynamic factors, univariate predictors were also adjusted to PA systolic pressure (Tables 2 and 3). Continuous variables were z-standardized to allow comparisons of odds ratios based upon a one standard deviation change in each parameter.

Results

Comparisons of heart failure and preserved ejection fraction and controls

Patients with HFpEF ($n = 96$) had similar gender as controls ($n = 46$), but were older and heavier (Table 4). Nearly half of HFpEF subjects (45%) had been previously hospitalized for decompensated HF and 71% reported NYHA III or IV symptoms. As in prior studies, HFpEF was frequently associated with co-morbidities including diabetes, hypertension, AF, coronary artery disease, renal dysfunction, and anaemia.

Heart rate and cardiac index were similar in HFpEF and controls (Table 1). Left and right heart filling pressures were elevated in HFpEF, as were PA pressures, PVR and TPG, while PA compliance was lower in HFpEF compared with controls. Pulmonary hypertension (mean-PA > 25 mmHg) was present in 81% of HFpEF patients. Left ventricular diastolic dysfunction, LV mass, and LA volume were greater in HFpEF, while LV size and LVEF were similar in HFpEF and controls (Table 1). In contrast, RA volumes and RV dimensions were significantly increased in HFpEF (Table 1). The right ventricular diastolic area was correlated with PA wedge pressure in HFpEF ($r = 0.34$, $P = 0.001$) but not in controls ($r = -0.1$, $P = 0.5$).

Table 1 Haemodynamic and echocardiographic characteristics

	Controls (n = 46)	HFpEF (n = 96)	P-value ^a	HFpEF no RVD (n = 64)	HFpEF with RVD (n = 32)	P-value ^a
Haemodynamics						
Heart rate, min ⁻¹	69 ± 13	69 ± 13	0.6	69 ± 12	69 ± 15	0.9
Cardiac index, L min ⁻¹ m ⁻²	3.0 ± 0.5	3.0 ± 0.5	0.3	3.0 ± 0.5	3.0 ± 0.5	0.6
RA mean pressure, mmHg	5 ± 3	13 ± 6	<0.0001	12 ± 5.3	15 ± 5.6	0.004
PA systolic pressure, mmHg	27 ± 7	56 ± 18	<0.0001	51 ± 15	67 ± 21	0.0001
PA mean pressure, mmHg	16 ± 4.5	36 ± 11	<0.0001	33 ± 9	41 ± 12	0.0002
Pulm. vascular resistance, w.u.	1.5 ± 0.7	2.6 ± 0.2	0.01	2.3 ± 1.2	3.4 ± 2.2	0.003
Pulm. arterial compliance, mL mmHg ⁻¹	4.4 ± 1.4	3.0 ± 1.4	0.004	3.2 ± 1.3	2.8 ± 1.4	0.2
Transpulmonary gradient, mmHg	8 ± 1	15 ± 1	0.0001	13 ± 6.4	20 ± 9.6	<0.0001
PAWP mean, mmHg	8 ± 3	21 ± 6	<0.0001	20 ± 6.0	22 ± 5.8	0.3
RA mean/PAWP pressure ratio	0.6 ± 0.2	0.6 ± 0.2	0.8	0.6 ± 0.2	0.7 ± 0.2	0.005
Systemic systolic blood pressure, mmHg	121 ± 13	128 ± 19	0.2	131 ± 18	123 ± 19	0.04
Systemic mean blood pressure, mmHg	89 ± 7	88 ± 13	0.8	90 ± 13	84 ± 12	0.06
Echocardiography						
RA volume index, mL m ⁻²	19 ± 7	35 ± 18	0.0004	32 ± 17	41 ± 17	0.03
RA total ejection fraction (EF), %	60 ± 15	37 ± 20	<0.0001	42 ± 18	27 ± 19	0.0008
RA active EF, % ^b	44 ± 22	34 ± 14	0.02	36 ± 15	30 ± 9.4	0.2
RV base diameter, mm	32 ± 5	41 ± 8	<0.0001	39 ± 7	44 ± 8	0.002
RV midventricular diameter, mm	23 ± 5	31 ± 8	0.001	29 ± 7	35 ± 8	0.0005
RV length, mm	63 ± 9	70 ± 10	0.02	67 ± 9	76 ± 9	<0.0001
RV diastolic area, cm ²	15 ± 3	21 ± 6	0.0004	19 ± 5	25 ± 6	<0.0001
RV fractional area change (FAC), %	53 ± 6.6	40 ± 10	<0.0001	45 ± 6	29 ± 5	<0.0001
RV diastolic stiffness, mmHg cm ⁻²	0.7 ± 0.3	1.0 ± 0.6	0.005	0.9 ± 0.5	1.4 ± 0.7	0.0003
Tricuspid annular S' velocity, cm s ⁻¹	14 ± 0.8	11 ± 3.2	0.0008	12 ± 2.9	9.0 ± 3.1	0.0004
Tricuspid regurgitation grade, (0–4)	0.7 ± 0.8	2.2 ± 1.2	<0.0001	2.2 ± 1.1	2.3 ± 1.2	0.9
LA volume index, mL m ⁻²	23 ± 6	41 ± 12	<0.0001	41 ± 12	43 ± 13	0.5
LV internal diameter in diastole, mm	47 ± 4	49 ± 6	0.6	48 ± 5.5	51 ± 6.2	0.05
LV ejection fraction, %	63 ± 5	62 ± 6	0.4	63 ± 5.5	59 ± 5.6	0.0009
Mitral regurgitation grade, (0–4)	0.7 ± 0.7	1.8 ± 0.8	<0.0001	1.8 ± 0.8	1.7 ± 0.9	0.6
Transmitral E flow velocity, cm s ⁻¹	70 ± 22	105 ± 31	<0.0001	107 ± 31	106 ± 28	0.9
Mitral E' tissue velocity (aver.), cm s ⁻¹	8.7 ± 1.5	7.8 ± 2.0	0.2	7.8 ± 2.0	7.9 ± 2.2	0.8
E/E' ratio	9.2 ± 3.1	17 ± 8.3	<0.0001	16 ± 8.1	19 ± 8.6	0.2
LV diastolic dysfunction grade (% of intermediate/0°/1°/2°/3°)	6/53/18/ 24/0	35/10 /14/24 /18	0.01	24/12/18/26/18	53/6/6/18/18	0.4

HFpEF, heart failure with preserved ejection fraction; RA, right atrial; PA, pulmonary artery; PAWP: PA wedge pressure; w.u.: Wood's units; LV, left ventricle; RV, right ventricle.

^aComparison P-value is adjusted for age and body mass index.

^bOnly in the subjects with sinus rhythm.

Tricuspid and pulmonary regurgitation were more prevalent in HFpEF compared with controls.

Right ventricular systolic function was depressed in HFpEF: both RV FAC and tricuspid annular systolic velocities were ~20–25% lower in HFpEF than controls (Table 1, Figure 1A). Even after accounting for the higher PA pressures and greater TPR in HFpEF, RV FAC remained significantly depressed compared with controls (Figure 1B and Supplementary material online, Figure S1A), indicating primary impairment in RV contractility rather than simple afterload-mismatch. In addition, the slope of the relationship between RV FAC and PA pressures was steeper in HFpEF ($P = 0.003$), indicating enhanced afterload-sensitivity. Within the HFpEF group, RV FAC correlated positively with LV EF ($r = 0.42$, $P < 0.001$) and systolic

blood pressure (Figure 1C), and was strongly related to both RV systolic longitudinal function (tricuspid annular tissue velocity) and LV septal annular systolic velocities, but not LV lateral velocities (Figure 2). These data collectively suggest that higher LV load and better LV function (particularly regional septal function) enhance RV function via systolic interventricular interaction.

Correlates of right ventricular dysfunction in heart failure and preserved ejection fraction

One-third (33%) of HFpEF patients displayed RVD (RV FAC < 35%). Compared with HFpEF patients without RVD, those with RVD were

Table 2 Predictors of right ventricle dysfunction in heart failure and preserved ejection fraction by logistic regression

Univariate predictors	χ^2	OR (95% CI)	P-value	RV afterload-adjusted ^a		
				χ^2	OR (95% CI)	P-value
PA systolic pressure (per 1 SD)	15	2.5 (1.5–4.2)	<0.0001	–	–	–
Male gender (y/n)	16	6.1 (2.5–16)	<0.0001	14	8.0 (2.9–26)	<0.0001
Transpulmonary pressure gradient (per 1 SD)	15	2.5 (1.5–4.3)	0.0004	–	–	–
LV ejection fraction,% (per 1 SD)	11	0.5 (0.3–0.7)	0.001	6.5	2.0 (1.2–3.5)	0.01
Atrial fibrillation (y/n)	10	4.2 (1.7–11)	0.0001	8.1	4.0 (1.5–11)	0.004
Coronary artery disease (y/n)	10	4.0 (1.7–10)	0.002	5.2	3.1 (1.2–8.1)	0.03
Right atrial pressure (per 1 SD)	8.0	2.0 (1.2–3.3)	0.005	1.3	1.3 (0.8–2.5)	0.3
Systemic systolic BP (per 1 SD)	4.4	0.6 (0.4–0.97)	0.04	4.0	0.6 (0.4–0.9)	0.04
PA wedge pressure (per 1 SD)	1.2	1.3 (0.8–2.0)	0.3	–	–	–

Odds ratios (OR) are standardized to distribution in HFpEF population.
 Transpulmonary pressure gradient was not adjusted to because of colinearity.
 PA, pulmonary artery pressure; LV, left ventricle; CI, confidence intervals; SD, standard deviation.
^aRV afterload: PA systolic pressure.

Table 3 Predictors of mortality in heart failure and preserved ejection fraction group by Cox proportional hazard model

Univariate predictors	χ^2	HR (95% CI)	P-value	RV afterload adjusted ^a		
				χ^2	HR (95% CI)	P-value
RV fractional area change, % (per 1 SD)	18	2.4 (1.6–2.6)	<0.0001	11	2.2 (1.4–3.5)	0.001
RV diastolic area (per 1 SD)	18	2.3 (1.6–3.4)	<0.0001	11	2.1 (1.4–3.4)	0.001
RA volume index (per 1 SD)	15	2.1 (1.5–3.1)	<0.0001	11	2.0 (1.4–2.9)	0.0007
RA pressure (per 1 SD)	14	2.1 (1.4–3.1)	0.0002	7.4	1.8 (1.2–2.8)	0.007
LV ejection fraction (per 1 SD)	13	2.1 (1.4–3.1)	0.0003	7.4	1.8 (1.2–2.8)	0.007
Male gender (y/n)	12	3.7 (1.8–8.1)	0.0005	12	3.8 (1.8–8.3)	0.0005
NYHA functional class (per 1 grade)	11	2.5 (1.4–4.4)	0.001	8.9	2.4 (1.3–4.4)	0.003
Left atrial volume index (per 1 SD)	8.8	1.8 (1.2–2.5)	0.003	11	1.9 (1.3–2.7)	0.001
RA/PA wedge pressure ratio (per 1 SD)	8.3	1.6 (1.2–2.3)	0.004	6.6	1.6 (1.1–2.2)	0.01
PA systolic pressure (per 1 SD)	7.6	1.6 (1.1–2.2)	0.006	–	–	–
Glomerular filtration rate (per 1 SD)	6.9	2.0 (1.2–3.8)	0.009	4.3	1.9 (1.04–3.8)	0.04
Coronary artery disease (y/n)	5.3	2.3 (1.1–4.9)	0.02	1.2	1.6 (0.7–3.7)	0.3
PA wedge pressure (per 1 SD)	5.0	1.5 (1.1–2.2)	0.03	1.0	1.3 (0.8–2.0)	0.3
RA ejection fraction (per 1 SD)	4.8	0.6 (0.4–0.96)	0.03	2.4	0.7 (0.5–1.1)	0.1
Atrial fibrillation (y/n)	3.9	2.1 (1.01–4.4)	0.05	2.9	1.9 (0.9–4.1)	0.09
Age (per 1 SD)	3.3	1.5 (0.97–2.2)	0.07	–	–	–
Tricuspid regurgitation (per 1 grade)	1.2	1.2 (0.8–1.6)	0.4	–	–	–

Hazard ratios (HR) are standardized to distribution in HFpEF population.
 LV, left ventricular; RV, right ventricular; RA, right atrial; CI, confidence intervals; SD, standard deviation.
^aRV afterload: PA systolic pressure.

more likely to be males and had worse functional class, more renal dysfunction, higher natriuretic peptide levels, more AF and more prevalent coronary disease (Table 4). Patients with RVD had higher right heart filling pressures, more severe pulmonary vascular disease (higher PA pressures, PVR, and TPG), and lower LV EF (Table 1). While systemic arterial pressures, cardiac index, and PA wedge pressures were similar in HFpEF patients with and without RVD, the ratio of RA to PA wedge pressure was higher in RVD.

Right ventricular dysfunction in HFpEF was coupled with higher RA volumes, more severely reduced total and active RA ejection fraction, greater RV dilatation, increased RV diastolic stiffness, and more severely reduced RV longitudinal function compared with HFpEF patients without RVD (Table 1, Figure 2B and Supplementary material online, Figure S2). Right- and left-sided valvular regurgitation and LV diastolic dysfunction were similar in HFpEF patients with or without RVD.

Table 4 Clinical and laboratory characteristics

	Controls (n = 46)	HFpEF (n = 96)	P-value	HFpEF no RVD (n = 64)	HFpEF with RVD (n = 32)	P-value
Age, years	60 ± 8	71 ± 10	<0.0001	71 ± 10	72 ± 9	0.4
Female gender, %	54	59	0.6	73	31	<0.0001
Body mass index, kg m ⁻²	29 ± 5.2	34 ± 8.6	<0.0001	34 ± 8.6	34 ± 9.3	0.9
NYHA class	1.2 ± 0.6	3.0 ± 0.6	<0.0001	2.9 ± 0.6	3.3 ± 0.6	0.01
Coronary artery disease ^a , %	0	37	0.0004	26	59	0.002
Atrial fibrillation, %	0	43	<0.0001	31	66	0.001
Diabetes mellitus/hypertension, %	2/52	48/94	<0.0001/ <0.0001	47/95	59/91	0.2/0.4
Loop diuretics daily dose, mg	0	46 ± 47	<0.0001	43 ± 52	53 ± 32	0.3
Betablocker/ACEI or ARB/ARA, %	11/37/6	67/59/16	0.0001/0.02/0.1	72/61/14	56/53/19	0.1/0.5/0.6
NT-pro-BNP, pg mL ⁻¹	30 (15–98)	1142 (408–2914)	<0.0001	1116 (375–2883)	1735 (998–3442)	0.1
Glomerular filtration rate, mL min ⁻¹ 1.73 m ⁻²	73 ± 35	47 ± 21	0.006	53 ± 22	38 ± 14	0.004
Haemoglobin, g L ⁻¹	14 ± 1.2	12 ± 1.6	<0.0001	12 ± 1.7	12 ± 1.4	0.6

NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARA, aldosterone receptor antagonist; NT-pro-BNP, N-terminal B-type natriuretic peptide.

^aSignificant coronary artery disease (CAD): ≥1≥70% epicardial artery stenosis or previous revascularization; angiography available in 82% of HFpEF.

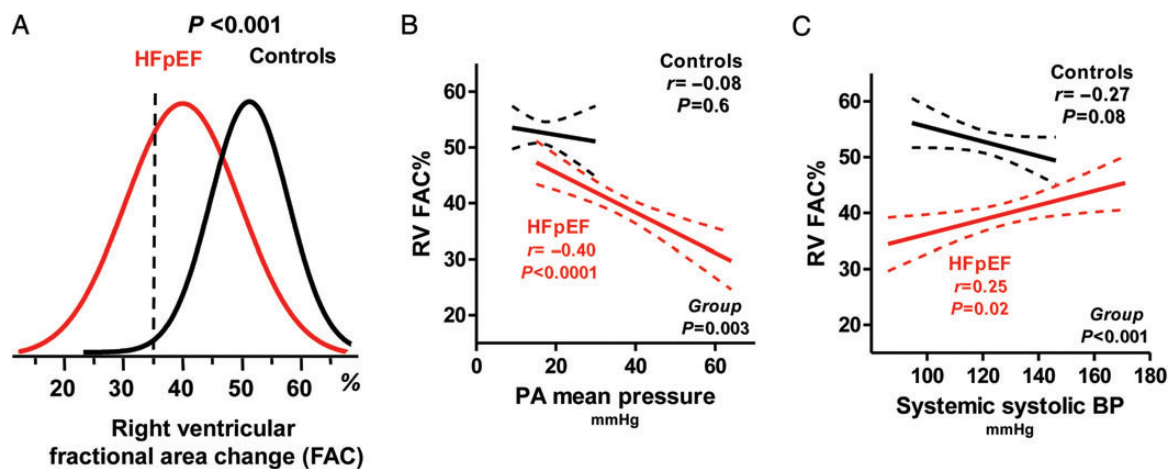


Figure 1 (A) Distribution of right ventricular function (fractional area change fractional area change %) in controls and heart failure and preserved ejection fraction. (B) Stress-shortening relation of right ventricular fractional area change % to pulmonary artery pressure in controls and heart failure and preserved ejection fraction. If right ventricular dysfunction in heart failure and preserved ejection fraction were purely due to afterload-mismatch all fractional area change pulmonary artery pressure coordinates in heart failure and preserved ejection fraction and controls would fall along a single regression slope. The lower and steeper slope in heart failure and preserved ejection fraction indicates impaired contractility and heightened afterload-sensitivity in addition to more severe pulmonary hypertension. (C) Differential relation of right ventricular fractional area change % to systemic arterial blood pressure (SBP, left ventricular afterload) and pulmonary artery pressure (right ventricular afterload, B) in heart failure and preserved ejection fraction and controls. See text for details. Solid lines: linear regression, Interrupted lines: 95% CI bands; *r*, Pearson's correlation coefficient.

In logistic regression analysis, the strongest predictors of RVD were male sex, higher PA pressures, AF, lower LV EF, coronary disease and lower systemic blood pressures (Table 2). Adjusting for PA pressures did not eliminate these factors as predictors of RVD, and male sex remained predictive of RVD after adjusting for history

of coronary disease (OR: 5.2, 95%CI: 2.0–14, $P = 0.006$). Coronary disease did not completely explain RV dysfunction in HFpEF, as patients with HFpEF and no coronary disease displayed worse RV function than controls ($P < 0.0001$, Supplementary material online, Figures S1 and S3). In contrast, age, right-sided valve regurgitation,

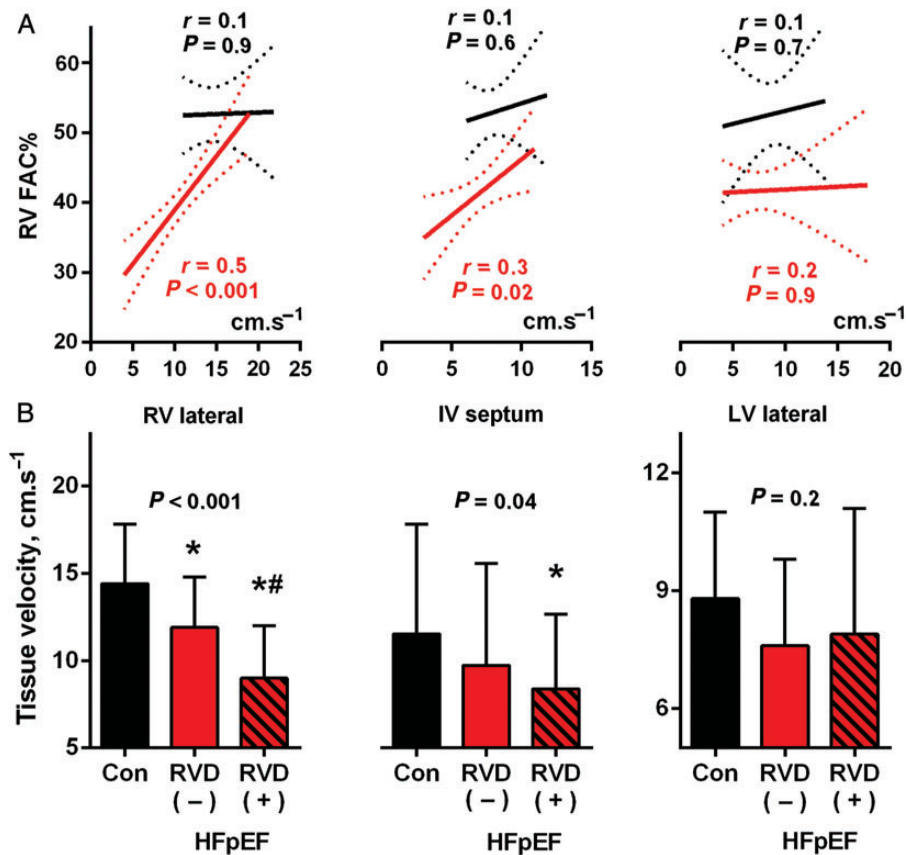


Figure 2 (A) Correlations (with regression line and 95% confidence intervals) between right ventricular function (right ventricular fractional area change %) and myocardial systolic tissue velocities at left ventricular lateral mitral annulus (left), interventricular septum (middle) or right ventricular lateral tricuspid annulus in controls (black) and heart failure patients (red). (2) Comparison of tissue velocities between controls, heart failure and preserved ejection fraction with (+) or without (-) right ventricular dysfunction by ANOVA and Tukey's *post hoc* test (* $P < 0.05$ vs. controls, # $P < 0.05$ vs. RVD (-)).

PA wedge pressure, and the presence of RV pacing leads ($n = 11$) were not predictive of RVD.

Right ventricular dysfunction was more severe in men than women with HFpEF despite similar severity of pulmonary hypertension or TPR (Figure 3, Supplementary material online, Figure S1). Compared with patients in sinus rhythm, HFpEF patients with AF displayed more right-sided chamber dilatation, more severely depressed RA and RV function, and higher PA pressures (Figure 4A). On tissue Doppler, patients in AF displayed lower septal mitral annular systolic velocities compared with patients in sinus rhythm, while lateral mitral annular velocities were similar (Figure 4B). Right ventricular FAC in HFpEF patients with AF was unrelated to PA pressure or TPR, in striking contrast to patients in sinus rhythm (Figure 4C, Supplementary material online, Figure S1), suggesting that RV contractile impairment in patients with AF may be more related to load-independent factors.

Right ventricular dysfunction and prognosis

Over a median follow-up duration of 529 (IQR; 143–1066) days, 31% ($n = 30$) of HFpEF patients died. Heart failure and preserved ejection

fraction patients with RVD had higher mortality compared with patients without RVD, with median 2-year survival of 56 vs. 93% (Figure 5). In a univariate Cox proportional model, RVD was the strongest single predictor of mortality (HR: 2.4, 95%CI: 1.6–2.6; $P < 0.0001$), exceeding RV dilatation, PH severity, comorbidities, and measures of left heart structure and function (Table 3). Right ventricular dysfunction remained significantly predictive of survival after adjusting for PA pressure (HR: 2.2, 95% CI: 1.4–3.5; $P = 0.001$).

Discussion

This is the first study to comprehensively assess right heart structure and function in a large, well-characterized group of patients with HFpEF using both echocardiography and invasively measured pressures to account for RV loading. We show that compared with controls, patients with HFpEF displayed right-sided chamber enlargement, RV diastolic dysfunction, and RV contractile dysfunction, with evidence for heightened afterload-sensitivity given the steeper reduction in RV function for a given PA pressure. Right ventricular function in HFpEF was related to haemodynamic factors including

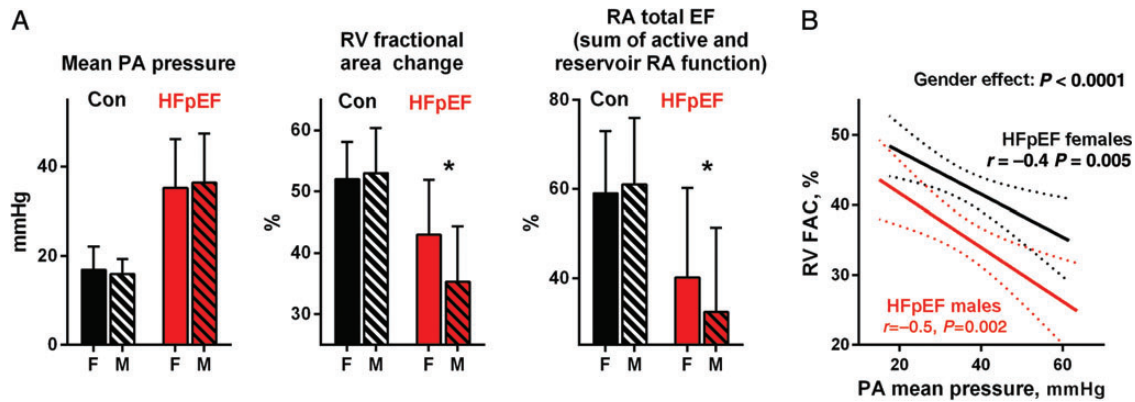


Figure 3 (A) Impact of gender on right ventricular and Right atrial function and right ventricular haemodynamic load in heart failure and preserved ejection fraction patients (red) and controls. * $P < 0.05$ vs. females. (B) Distinct relations between right ventricular function and afterload in male and female heart failure and preserved ejection fraction patients.

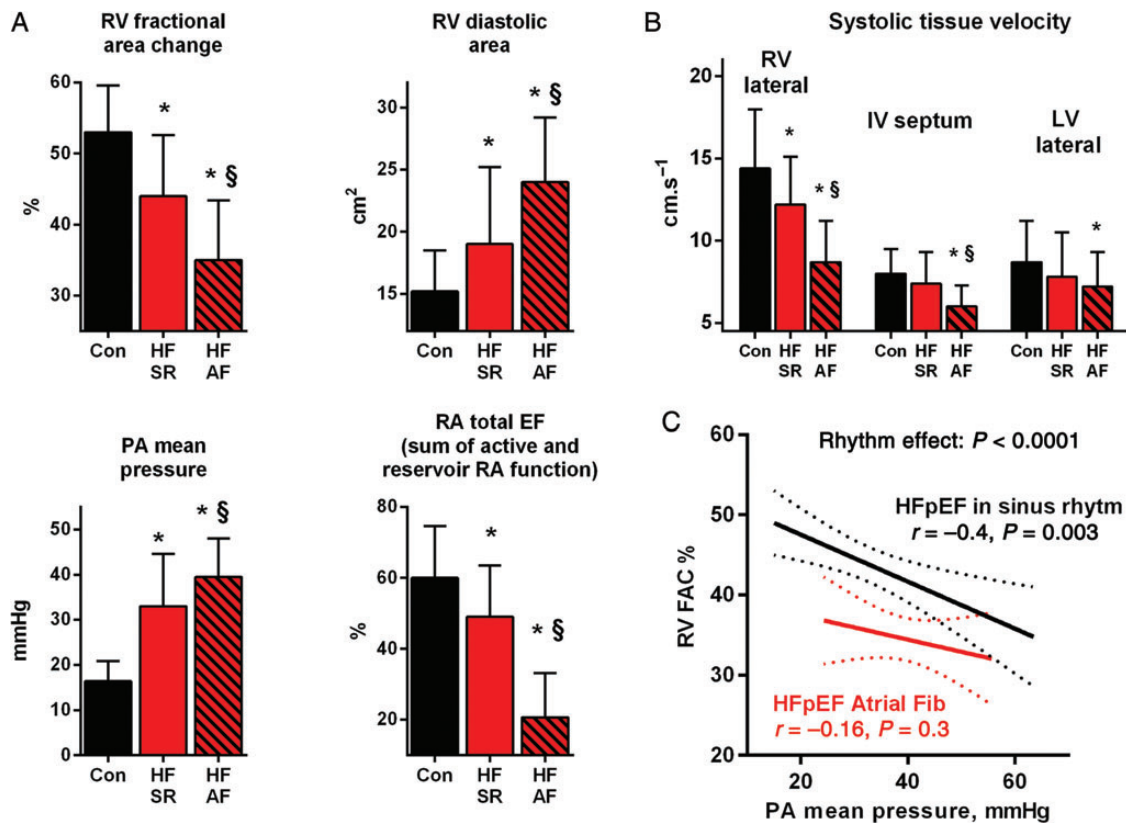


Figure 4 (A) Impact of atrial fibrillation on haemodynamic parameters and right ventricular function in heart failure and preserved ejection fraction and controls (RA, right atrial, PA, pulmonary artery, SR, sinus rhythm). Differences tested with ANOVA and Tukey's *post hoc* test, * $P < 0.05$ vs. Con, $^{\S}P < 0.05$ vs. heart failure and preserved ejection fraction in sinus rhythm. (B) The impact of atrial fibrillation on maximal systolic tissue velocities of mitral and tricuspid annulus by tissue Doppler imaging. (C) Distinct relations between right ventricular function and afterload in heart failure and preserved ejection fraction in sinus rhythm and in atrial fibrillation.

the severity of pulmonary hypertension and ventricular interaction as well as non-haemodynamic factors including male sex, coronary disease, and AF, allowing for greater pathophysiological insight.

Right ventricular dysfunction predicted increased mortality in HFpEF, even after accounting for the magnitude of PA pressure elevation. Collectively, these results emphasize the importance of

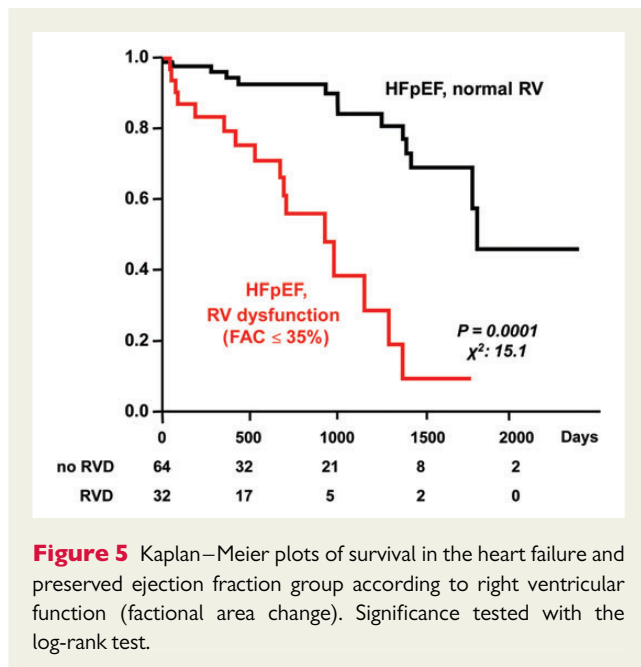


Figure 5 Kaplan–Meier plots of survival in the heart failure and preserved ejection fraction group according to right ventricular function (factual area change). Significance tested with the log-rank test.

right heart dysfunction in the pathophysiology of HFpEF and suggest that efforts to reduce pulmonary pressure, maintain LV septal function, and restore or maintain sinus rhythm may be useful to improve RV function and thus outcomes in this form of HF for which there is currently no effective treatment.

Prevalence of right ventricular dysfunction in heart failure and preserved ejection fraction

In contrast to the left heart, few studies have examined the RV in HFpEF.^{11–13,29} In one echocardiographic study, RVD (defined as RV FAC < 45%) was less frequent in HFpEF than in HFrEF, and the prevalence of RVD was similar to the current study (33%) despite the higher cut-off, perhaps reflecting a less sick HF cohort.¹¹ In another echo-based study, HFpEF was associated with reduced RV systolic and diastolic strain.¹² Damy *et al.*¹³ reported reduced tricuspid annular plane systolic excursion (TAPSE) in 20% of HFpEF and 47% of HFrEF patients, and Guazzi *et al.*²⁹ have recently shown that the quotient of TAPSE and echo-estimated PA systolic pressure provides optimal predictive value for adverse outcome in HF. None of these studies evaluated RV systolic function in the context of invasive pressure data to account for RV afterload. This is critically important, because the RV is ill-suited to pump against high pressures^{1,14} and because PH is highly prevalent in people with HFpEF.^{16,30}

Afterload and right ventricular dysfunction in heart failure and preserved ejection fraction

The current data show that impaired RV systolic function in HFpEF is related to both impaired myocardial contractility and elevated RV afterload. Intriguingly, the drop in RV shortening with increasing pressure load was steeper in HFpEF than in controls (*Figure 1B*), suggesting heightened RV afterload-sensitivity, similar to what is seen in the left

ventricle in HFrEF.³⁰ Diastolic RV stiffness in HFpEF was also increased, similar to pulmonary arterial hypertension (PAH).²⁶ Prior studies have shown that RV end-systolic elastance, an alternative measure of RV contractility, is enhanced in patients with primary pulmonary vascular disease due to PAH or Eisenmenger's syndrome, and that impaired RV function in these patients is simply related to afterload-mismatch.^{26,31} However, in contrast to HFpEF, where there is primary or secondary myocardial disease, PAH patients are characterized by robust adaptive RV response to increased afterload. Indeed, it has recently been shown that despite similar degrees of pulmonary vascular disease, patients with scleroderma (who have both myocardial and vascular disease) display much lower RV Ees than patients with idiopathic PAH.³²

Heart failure and preserved ejection fraction patients displayed elevated TPG, coupled with increases in PA resistance and reductions in PA compliance, confirming the presence of significant pulmonary vasculopathy in HFpEF.^{14,16,33} The mean-PA pressure is equal to the sum of TPG and PA wedge pressure, and it is interesting that RVD was associated with the former but not the latter (*Table 2*, Supplementary material online, *Figure S4*), suggesting that targeting the component of PA pressure elevation related to pulmonary vascular disease (TPG) may be more effective to improve RV function when compared with decongestion (PA wedge pressure reduction) alone. The clear abnormalities in RV afterload observed in the current study, coupled with the striking inverse relationships between RV function and PA pressure loading lend strong support for the notion that novel therapies targeting the pulmonary vasculature may be effective in people with HFpEF. Pulmonary vascular resistance was only modestly elevated, but treatments directed at the pulmonary vasculature may still be helpful to reduce load-dependent RVD.

While there is currently no therapy to specifically target intrinsic load-independent RV dysfunction, if this is due in part to the HF syndrome, then standard neurohormonal antagonists or other novel therapies may possibly be of benefit. The presence of intrinsic RV dysfunction in HFpEF is not dissimilar to HFrEF,^{7,8,13} but the mechanisms are unclear. Neurohormonal activation in HFrEF causes structural and molecular remodelling that may affect both ventricles, but further study is required to determine how this might affect the RV in HFpEF, via load-dependent and load-independent pathways.

Sex and right heart function in heart failure and preserved ejection fraction

Male sex predicted the presence of RV dysfunction in HFpEF, independent of the severity of PH or presence of CAD. Prior studies in HFrEF have reported relationships between male sex and RV dysfunction^{13,34,35} and dilatation.³⁶ In non-HF populations, men tend to have greater RV mass and volumes, but lower EF than women—differences that have been linked to sex hormone levels.¹⁸ Experimental studies have demonstrated a more deleterious impact of pressure overload on RV function in male than female mice, which can be corrected by testosterone depletion.³⁷ In patients with PAH, men have decreased survival and greater decline in RV function despite similar haemodynamic benefits from pulmonary vasodilators.³⁸ Prior studies in HFpEF have shown that survival is lower in men compared with women,³⁹ and the current data suggest that this

sex-difference might be mediated in part by differences in RV structure and function.

Atrial fibrillation and right heart function heart failure and preserved ejection fraction

In addition to male sex, we observed that the presence of AF was an additional independent predictor of RVD in HFpEF. This is consistent with data from Ghio *et al.*⁷ in HFrEF patients, where the prevalence of AF was much greater in patients with RV dysfunction and normal PA pressure. The weaker inverse correlation between RV shortening and PA pressures observed in the AF subgroup provides further evidence that AF may contribute to RVD in a partially load-independent fashion. Indeed, cardioversion from AF to sinus rhythm may acutely improve RV function, likely due to enhancement of longitudinal septal function.⁴⁰ This observation is congruent with the lower systolic tissue velocities at the septum when compared with the lateral annulus noted in the current study in HFpEF patients with AF (Figure 4). Atrial fibrillation is common in HFpEF—as much as 66% of newly diagnosed HFpEF patients in a population-based cohort had prior, concurrent or subsequent diagnosis of AF.⁴¹ Given recent studies showing greater neurohumoral activation,^{42,43} functional disability,⁴² and worse outcomes^{41,43,44} in patients with AF and HFpEF, the current data provide further rationale to restore and maintain sinus rhythm in people with HFpEF.

Left-right ventricular interactions in heart failure and preserved ejection fraction

The right and left ventricles are connected in series but also may influence one-another in parallel, via forces transmitted from one ventricle to the other across the septum and mediated by pericardial restraint. These interactions can considerably modulate RV function both in systole or diastole. Left ventricular EF was associated with RVD in this study, similar to earlier reports in HFrEF,⁴⁵ healthy volunteers,⁴⁶ and HFpEF using strain-based analysis.¹² This enhanced coupling of LV and RV function may reflect common myopathic insults (e.g. ischaemia) or simply direct ventricular interdependence.⁴⁷ Owing to the helical arrangement of myofibres around both ventricles, LV contraction enhances RV emptying through the interventricular septum, contributing up to a 33% of RV stroke work.⁴⁸ This effect is enhanced in the setting of left-sided pressure overload,⁴⁹ as is common in HFpEF. This systolic ventricular interaction likely explains the positive correlation between RV FAC and systemic blood pressure as well as septal LV systolic velocities noted in the current study (Figures 1C and 2). These latter results underscore the importance of maintaining regional LV systolic function at the septum to preserve RV ejection in HFpEF.

In addition to systolic interaction, diastolic ventricular interaction is enhanced in patients with HF and right-sided enlargement^{47,50,51} due to elevated pericardial constraint.¹⁴ Patients with RVD and HFpEF in the current study also displayed an increased ratio of RA pressure to PA wedge pressure and positive correlation between RV diastolic area and PA wedge pressure, which may suggest a possibility of elevated diastolic interaction.⁵¹

Right ventricular dysfunction and prognosis in heart failure and preserved ejection fraction

Intriguingly, measures of right heart function were much more strongly correlated with prognosis in this study than left heart function. Similar to previous studies,^{15,16} pulmonary hypertension was predictive of increased mortality in HFpEF in the current sample. An important finding in this study is that the presence of RVD in HFpEF was more predictive of outcome than the magnitude of PH in Cox analysis, similar to what has been observed in patients with PAH.⁵² The important implication is that RVD is the most direct consequence and mediator of PH in HFpEF, and that therapies targeting RVD, whether they reduce RV load, maintain sinus rhythm, and/or improve RV contractility, would be expected to hold promise to improve outcomes.

Limitations

This was a retrospective study conducted on consecutive patients meeting eligibility criteria. Because of the requirement for adequate echocardiographic image, obese patients with limited windows might have been underrepresented. Haemodynamic and echocardiography data were not acquired simultaneously, but both occurred within a 48 h time frame. The measure of RV systolic function used (RV FAC) is supported by validation studies against MRI²⁵ and is related to outcomes,⁵³ but it may not completely describe RV function owing to the complex RV geometry. The sample size and the event rates were modest, such that multivariable modeling was not feasible. There is referral bias driven by clinical necessity of an invasive assessment, such that this sample is generally limited to patients with more advanced HFpEF. Therefore, our findings may not be applicable to the entire HFpEF population. The retrospective analysis limits our ability to determine which patients were referred for worsening HF symptoms, though presumably this was the case in many patients. While most patients complained of NYHA III-IV symptoms, less than half had been hospitalized for HF, and it is likely that this was an underestimate given the reliance on retrospective chart review to assess for hospitalizations. The control group was drawn from a convenience sample of consecutive patients referred for invasive assessment demonstrating no haemodynamic or structural evidence of HF. We cannot exclude the possibility that some eligible normal patients were not detected in our chart review. By virtue of being referred for cardiac catheterization, this is likely not representative of a truly normal comparator group. However, this invasive study would not have been feasible in healthy volunteers, and the fact that our controls had some cardiovascular risk factors such as hypertension would only bias our results towards the null. The control group was younger and less obese compared with HFpEF, and while we adjusted for age and body mass in all comparisons, this baseline difference could also influence our findings. Our analysis of mechanical properties and haemodynamics in the right heart was based upon fundamental tenets of ventricular-arterial interaction in the left heart-systemic circuit, and there are important differences between the RV and LV that must be considered.⁵⁴ For example, RV pressure-volume loops are more triangular in shape and the RV displays much shorter isovolumic periods. Right ventricular strain data were not available in our sample and would likely provide additional

insight into the nature of RV contractile dysfunction in HFpEF. The extent and localization of CAD was not quantified and predominant right coronary artery disease might have had a larger impact on RV function than categorically defined CAD.

In conclusion, right heart remodelling and dysfunction are common in HFpEF and are associated with increased morbidity and mortality. Right ventricular dysfunction in HFpEF is coupled with elevated afterload, but is not simply due to afterload-mismatch. Right ventricular dysfunction was independently correlated with male sex and AF, factors that may influence RV function in a potentially load-independent manner. Finally, RVD is a predictor of mortality in HFpEF, even accounting for the magnitude of PH, consistent with the notion that the RV serves as a final common transducer of pulmonary vascular pathologies to impair forward output and worsen venous congestion. Future trials are needed to test interventions to improve RV function through effects on cardiac rhythm, the pulmonary vasculature, and the right heart itself.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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