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RESEARCH ARTICLE

Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis

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Aims Right ventricular (RV) dysfunction and pulmonary hypertension (PH) are increasingly recognized in heart failure with preserved ejection fraction (HFpEF). The prevalence and prognostic value of RV dysfunction in HFpEF have been widely but variably reported. We therefore conducted a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Methods and results English literature until May 2016 was evaluated for prevalence of RV dysfunction [i.e. tricuspid annular plane systolic excursion (TAPSE) <16 mm, fractional area change (FAC) <35%, or tricuspid annular systolic velocity (RV S') <9.5 cm/s)] and PH [i.e. mean pulmonary artery pressure (MPAP) ≥25 mmHg or pulmonary artery systolic pressure (PASP) ≥35 mmHg]. Combined hazard ratios (HRs) for outcomes were calculated. A total of 38 studies was included. In studies with stringent HFpEF criteria, prevalence of RV dysfunction was 28% for TAPSE, 18% for FAC, and 21% for RV S'. Prevalence of PH was 68% for both increased MPAP and PASP. TAPSE (HR 1.26/5 mm decrease; $P < 0.0001$), FAC (HR 1.15/5% decrease; $P < 0.0001$), MPAP (HR 1.26/5 mmHg increase; $P < 0.0001$), and PASP (1.16/5 mmHg increase; $P < 0.0001$) were all univariably associated with mortality. HRs for RV S' were not reported.

Conclusion RV dysfunction and PH are highly prevalent and are both associated with poor outcome in patients with HFpEF.

Keywords Heart failure with preserved ejection fraction • Right ventricular dysfunction • Pulmonary hypertension • Meta-analysis

Introduction

Heart failure with preserved ejection fraction (HFpEF) is an increasingly large medical problem which is present in around half of all heart failure (HF) patients and which has a poor outcome.[1–3] In contrast to HF with reduced ejection fraction (HFrEF), the treatment options for patients with HFpEF are still very limited. Increasing knowledge of the pathophysiology of HFpEF and the exploration of its heterogeneous nature will aid in the development of future therapies.

One of the key defining features in HFpEF is LV diastolic dysfunction and contractile dysfunction, despite the preservation of global EF.[4] Right ventricular (RV) dysfunction is frequently found in HFpEF as well, although the reported prevalence of RV dysfunction varies widely from 4% to 48% in individual studies.[5,6] Although RV dysfunction in HFpEF has mainly been linked to the development of pulmonary hypertension (PH),[6,7] RV remodelling in HFpEF may also occur in other conditions, independent of pulmonary pressures, such as shared risk factors for combined RV and LV dysfunction.[8] It has been demonstrated that RV dysfunction is associated with

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poor prognosis,[9,10] yet other studies were not able to observe such an association.[11–13] Given the variability of prior reports, and the importance of understanding right-sided cardiovascular function in HFpEF as a potential therapeutic target,[14–16] we aimed to evaluate systematically the current literature and conducted a meta-analysis of studies investigating RV dysfunction and PH in HFpEF.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

Literature search strategy

We conducted a systematic search in the EMBASE and MEDLINE databases from inception to 18 May 2016. The search strategy composed the DDO method (Domain = patients with HFpEF, Determinant = RV function and/or pulmonary hypertension, Outcome = mortality and/or HF hospitalization). Indexing terms 'diastolic heart failure', 'heart failure with preserved/normal ejection fraction', 'right ventricular function', and 'pulmonary hypertension' were used to design the search strategy, detailed in the Supplementary material online.

Study selection

Studies were eligible if: (i) they were performed in a clearly defined (sub)group of patients with HFpEF and (ii) a measure of RV dysfunction and/or PH was reported. Our search was limited to studies conducted in humans, published in peer-reviewed journals, and written in English. After removal of duplicates, all items were independently reviewed by two observers (T.M.G. and J.P.M.), and studies were subsequently excluded at title, abstract, or full text level. Disagreement was resolved by consensus. Reference lists of included articles were reviewed for relevant publications, not identified by our initial search. If studies were performed in the same study population, the study with the most complete data on RV dysfunction and/or PH was included.

Data extraction

The following data were extracted: (i) study characteristics [i.e. publication year and number, sex, and age of study subjects, setting (e.g. acute or chronic HF), and design (e.g. clinical trial or prospective cohort study)]; (ii) HFpEF criteria as stated in the new 2016 ESC guidelines[18] (i.e. elevation of natriuretic peptides, evidence of structural heart disease and/or diastolic dysfunction, and/or increased LV filling pressures); and (iii) co-morbidities [i.e. hypertension, CAD, AF, diabetes mellitus, body mass index (BMI), and COPD]. When studies reported outcome, follow-up time in months, outcome measure, and adjustment variables were also documented. Unadjusted and adjusted hazard ratios (HRs) for the association between measures of RV dysfunction and/or PH with outcome were denoted.

If a study reported RV dysfunction and/or PH, but no absolute values of these indices were available, the corresponding author was contacted by Email to request additional data. Two reminder Emails were sent.

Quality assessment

Two reviewers (T.M.G. and J.P.M.) independently assessed the risk of bias according to the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data.[19] Agreement for the methodological quality assessment between both observers was tested, and disagreement was resolved by consensus.

Definitions

The HFpEF criteria used for study selection were any (sub)group of patients with signs and/or symptoms of HF or HF hospitalization <12 months; in combination with normal or mildly reduced LVEF, for which in the present study the LVEF cut-off of ≥45% was used. Sensitivity analyses were performed in the studies with stringent HFpEF criteria according to the 2012 ESC guidelines vs. studies with lenient HFpEF criteria.[20] Stringent criteria were present if at least one of the following criteria was used: (i) relevant structural heart disease; (ii) LV diastolic dysfunction; and (iii) increased LV filling pressures during haemodynamic testing. Studies with lenient HFpEF criteria were defined when no additional criteria, besides symptomatic HF, LVEF ≥45%, and elevated natriuretic peptides, were used for patient inclusion.

Right ventricular dysfunction was considered present when RV fractional area change (FAC) was <35% or tricuspid annular systolic velocity (RV S') was <9.5 cm/s.[21] According to the current recommendations, tricuspid annular plane systolic excursion (TAPSE) <17 mm is considered the cut-off for RV dysfunction.[21] However, the majority of studies was performed before the publication of the new recommendations and, consequently, they reported according to the previous recommended cut-off of <16 mm.[22] Therefore, in the present study, TAPSE <16 mm was used. Since no definite cut-offs for RV longitudinal strain are currently available, this measure was not included in the present study. Because only one included study reported RV function with cardiac magnetic resonance imaging (MRI),[13] RV function with MRI was also excluded from the meta-analysis.

Right ventricular dilatation was considered present when basal RV end-diastolic diameter (RVEDD) was >41 mm or when RV end-diastolic area index (RVEDAi) was >12.1 cm^2/m^2 (i.e. mean in the upper normal value between males and females).[21]

Pulmonary hypertension is present when invasively measured mean pulmonary artery pressure (MPAP) was ≥25 mmHg.[23] In the absence of invasive haemodynamic measurements, PH was considered present when pulmonary artery systolic pressure (PASP) was ≥35 mmHg on echocardiography.[22]

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) and categorical data as number or percentage. Reported medians and interquartile ranges [i.e. first quartile (q1) and third quartile (q3)] were translated to means and SDs using the following formulae, according to previous recommendation:[24]

$$\text{Mean} = \left(q_1 + \text{median} + q_3\right)/3$$

$$\text{SD} = \left(q_3 - q_1\right)/1.35$$

If prevalence rates of RV dysfunction and PH were reported by the authors, the reported values were obtained. When only means and SDs were denoted by the authors, prevalence rates of values below or above the cut-offs for RV dysfunction and PH were estimated by

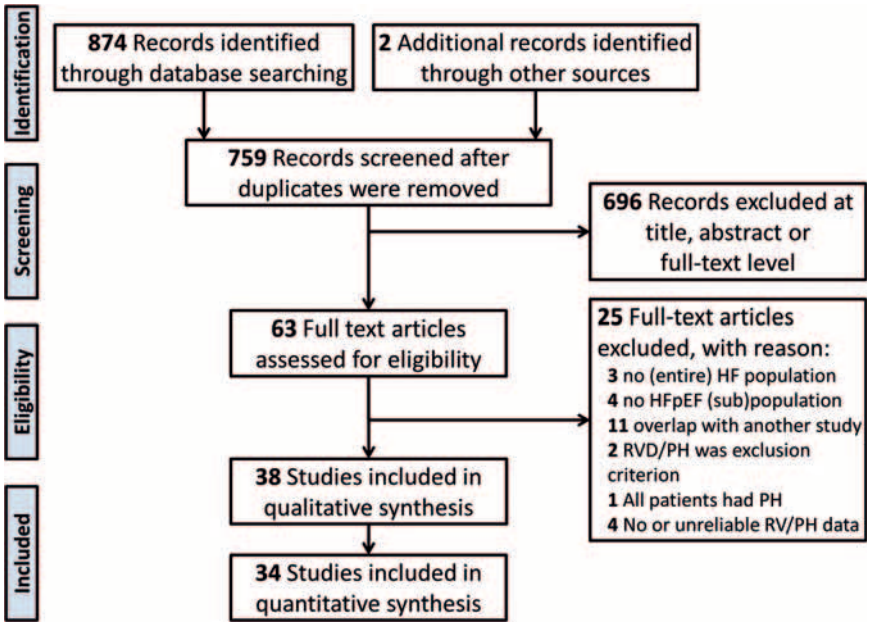

Figure 1 Flow chart of study selection. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; PH, pulmonary hypertension; RVD, right ventricular dysfunction.

calculating the *Z*-value and subsequently by calculating the area under the standard normal distribution curve up to *Z* for RV dysfunction and from *Z* onwards for PH. Sensitivity analysis was performed by correlating the self-reported prevalence rates with the estimated prevalence rates. The reliability of estimated prevalence rates of RV dysfunction and PH was calculated using the two-way mixed intraclass correlation coefficient.

The summary and pooled analyses of RV dysfunction and PH among the included studies were depicted in forest plots. Pooled values were calculated by the weighted average according to number of patients.

Pooled HRs for the relationship between RV dysfunction and PH with outcome were calculated by inverse variance weighted averaging. HRs of each study were converted to reflect a five unit change.

Inter-rater agreement for the quality assessment was tested using Cohen's kappa coefficient. Statistical analyses were performed using SPSS (Version 20, 2011).

Results

Search results and eligible studies

The search strategy retrieved 759 individual titles. After study selection, a total of 38 studies were included in the qualitative analysis (*Figure 1*).[17] Characteristics of these studies are detailed in *Table 1*. Mean percentage females was 54.3%, mean age 71.7 years, and mean BMI was 30.7 kg/m^2. The prevalence of hypertension was on average 82%, AF 36%, CAD 47%, diabetes 36%, and the prevalence of COPD was 24%. The corresponding authors of eight studies were contacted to request additional data on PASP, and four of them responded and delivered the requested data. These studies could therefore be added to the quantitative analysis, which comprised 4835 patients in 34 studies.

Quality assessment

The summary of the quality assessment is illustrated in the Supplementary material online, *Figure S1*. Risk of bias was highest in the items sample size and confounding factors. The inter-rater agreement on the methodological quality assessment was substantial: overall agreement 83% (316/380); Cohen's kappa 0.65.

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

Pooled mean TAPSE was 18.5 mm and the mean prevalence of RV dysfunction, as determined by TAPSE, was 31% in 2797 patients (*Figure 2A*). Mean FAC was 45.6% and the prevalence of RV dysfunction according to FAC was 13% in 2467 patients (*Figure 2B*). In *Figure 2C*, RV S' measurements are illustrated, and 26% of the 1065 patients had reduced RV S' with mean RV S' of 11.3 cm/s.

The prevalence of RV dysfunction reported by authors varied widely (*Table 1*). The prevalence of TAPSE <16 mm ranged from 26% to 49%,[10,12,28,36,39,49] and the prevalence of FAC <35% from 4% to 33%.[9,28,49,50,56] Several studies used >1 echocardiographic method for the assessment of RV dysfunction, and a summary is given in Supplementary material online, *Table S1*.

Pooled mean RVEDD was 36.8 mm, and 29% of 1212 patients had RVEDD >41 mm.[9,26–28,33,41,49–51] Pooled mean RVEDAi was 12.4 cm^2/m^2, and 44% of 832 patients had RV dilatation according to RVEDAi >12.1 cm^2/m^2.[12,28,40]

Table 1 Characteristics of included studies

Study/publication year	No. of HFpEF patients	Study design	Study setting	LVEF cut-off %	Structural heart disease	Diastolic dysfunction	Elevated natriuretic peptides	Elevated LV filling pressures	Comment on HFpEF criteria[a]	RV dysfunction and dilatation measure	RV dysfunction and dilatation prevalence and definition reported by author	PH measure	PH prevalence and definition reported by author
Adamson-2014[25]	66	RCT	CHF	50					Lenient	–	–	MPAP	…
Andersen-2015[26]	39	RCT/substudy	CHF	50				•	Stringent	RV S'	–	–	…
										RVEDD	–		
Aschauer-2016[27]	171	Prospective cohort	CHF	50		•	•	•	Stringent (all three items)	TAPSE	–	MPAP	…
										FAC	–		
										RVEF	–		
										RVEDD	–		
Burke-2014[28]	419	Prospective cohort	CHF	50		•	•	•	Stringent (Paulus-2007)[29]	TAPSE	28% (<16 mm)	PASP	…
										FAC	14% (<35%)		
										RVEDD/RVEDAi	–		
Dabbah-2006[30]	49	Prospective cohort	ADHF	45					Lenient	–	–	PASP	…
Damy-2012[12]	309	Prospective cohort	ADHF	45					Lenient	TAPSE	27% (<16 mm)	–	…
										FAC	–		
										RVEDAi	–		
Donal-2015[31]	413	Prospective cohort	ADHF	45			•		Lenient	TAPSE	–	–	…
										RV S'	–	–	…
Ennezat-2013[32]	37	Prospective cohort	ADHF	45					Lenient	–	–	PASP	…
Farrero-2014[33]	28	Prospective cohort	CHF	50	•	•			Stringent (ESC-2012)[20]	TAPSE	–	PASP	78% (≥35 mmHg)
Freed-2016[34,b]	117	Prospective cohort	CHF	50	•	•	•	•	Stringent (Paulus-2007)[29]	–	–	MPAP	…
Fujimoto-2013[35]	11	Prospective cohort	ADHF	50			•	•	Stringent (≥1 item)	–	–	MPAP	…
Guazzi-2013[36]	46	Prospective cohort	CHF	…			•		Lenient	TAPSE	35% (<16 mm)	PASP	…
Gupta-2008[37]	10	Prospective cohort	CHF	50					Lenient	TAPSE	–	–	…
										FAC	–		
Hasselberg-2015[38]	37	Prospective cohort	CHF	50		•			Stringent	TAPSE	–	PASP	…
										FAC	–		
										RV S'	–		
										GLS	–		
Hussain-2016[39]	137	RCT/substudy	CHF	50			•	•	Stringent (≥1 item)	TAPSE	44.4% (<16 mm)	PASP	69.3% (≥35 mmHg)
Kalogeropoulos-2014[40]	104	Retrospective cohort	CHF	45		•	•		Stringent (all items)	RVEDAi	–	PASP	42.3% (≥35 mmHg)
Kasner-2012[41]	10	Prospective cohort	CHF	50		•			Stringent	–	–	MPAP	…
Kjaergaard-2007[42]	96	RCT/substudy	CHF	50					Lenient	–	–	PASP	…
Kurt-2009[43]	20	Prospective cohort	CHF	50				•	Stringent	–	–	MPAP	…
Maeder-2012[44]	10	Prospective cohort	CHF	50					Lenient	TAPSE	–	MPAP	…
										FAC	–		
										RV S'	–		
Marechaux-2011[45]	70	Prospective cohort	CHF	50					Lenient	–	–	PASP	35% (≥35 mmHg)

Table 1 Continued

Study/publication year	No. of HFpEF patients	Study design	Study setting	LVEF cut-off %	Structural heart disease	Diastolic dysfunction	Elevated natriuretic peptides	Elevated LV filling pressures	Comment on HFpEF criteria[a]	RV dysfunction and dilatation measure	RV dysfunction and dilatation prevalence and definition reported by author	PH measure	PH prevalence and definition reported by author
Martinez Santos-2016[46]	123	Prospective cohort	ADHF	50		•	•	•	Stringent (≥1 item)	TAPSE	–		
Melenovsky-2014[9]	96	Retrospective cohort	CHF	50				•	Stringent	FAC	33% (<35%)	MPAP	81% (≥25 mmHg)
										RV S'	–		
										RVEDD	–		
Meluzin-2011[47]	30	Prospective cohort	CHF	50					Lenient	–	–	PASP	13.3% (≥35 mmHg)
Merlos-2013[48]	232	Prospective cohort	ADHF	50					Lenient	–	–	PASP	84% (≥35 mmHg)
Mohammed-2014[10]	500	Population-based study	CHF	50					Lenient	TAPSE	35% (<16 mm)	PASP	35.5% (≥39 mmHg)
Morris-2011[49]	201	Prospective cohort	CHF	50		•	•	•	Stringent (ESC-2012)[20]	TAPSE	48.7% (<16 mm)	PASP	52.7% (≥41 mmHg)
										FAC	28.3% (<35%)		
										RV S'	…		
										GLS	75.1% (>16%)		
										RVEDD	1.9% (>42 mm)		
Morris-2016[50]	218	Prospective cohort	CHF	50	•	•		•	Stringent (≥1 item)	TAPSE	6.0% (<17 mm)	PASP	17.9% (≥35 mmHg)
										FAC	5.0% (<35%)		
										RV S'	5.5% (<9.5 cm/s)		
										GLS	11.5% (>17%)		
										RVEDD	–		
Orozco-2010[51]	30	RCT	CHF	45	•	•			Stringent (both items)	RVEDD	–	PASP	77% (≥35 mmHg)
Pellicori-2014[52]	237	Prospective cohort	CHF	50	•		•		Stringent (≥1 item)	TAPSE	–	PASP	…
Puwanant-2009[53]	51	Prospective cohort	ADHF	50					Lenient	TAPSE	40% (<15 mm)	PASP	…
										FAC	33% (<45%)		
										RV S'	50% (<11.5 cm/s)		
Rifaie-2010[54]	100	Prospective cohort	CHF	50		•			Stringent	–	–	PASP	20% (≥37 mmHg)
Schwartzenberg-2012[55]	83	Retrospective cohort	CHF	50					Lenient	–	–	MPAP	…
Shah-2014[56]	935	RCT/substudy	CHF	45			•		Lenient	FAC	4% (<35%)	PASP	36% (≥39 mmHg)
Stein-2012[57]	5534	Retrospective cohort	CHF	45					Lenient	–	–	PASP	27.5% (≥40 mmHg)
Van Empel-2014[58]	9	Prospective cohort	CHF	50		•		•	Stringent (≥1 item)	–	–	MPAP	…
Vanhercke-2015[59]	193	Prospective cohort	ADHF	50					Lenient	–	–	PASP	73% (≥30 mmHg)
Weeks-2008[60]	10	Prospective cohort	CHF	50					Lenient	TAPSE	–	PASP	…
										FAC	–		

ADHF, acute decompensated heart failure; CHF, chronic heart failure; FAC, fractional area change; GLS, global longitudinal strain; HF, heart failure; LA, left atrial; MPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; RCT, randomized controlled trial; RVD, right ventricular dysfunction; RVEDAi, right ventricular end-diastolic area index; RVEDD, right ventricular end-diastolic diameter; RV S', velocity of the tricuspid annular systolic motion; TAPSE, tricuspid annular plane systolic excursion.

[a] 0 bullet points, patients did not fulfil any additional inclusion criterion; 1 bullet point, all patients fulfilled this inclusion criterion; ≥1 bullet point, patients fulfilled either all inclusion criteria or at least one criterion (see comment in separate column). Stringent HFpEF criteria: patients fulfilled ≥1 item: (1) LV diastolic dysfunction; (2) relevant structural heart disease; or (3) elevated LV filling pressures. Lenient HFpEF criteria: patients did not fulfil any additional criterion besides elevated natriuretic peptides.

[b] Overlap with Burke-2014[28] for TAPSE, FAC, and PASP.

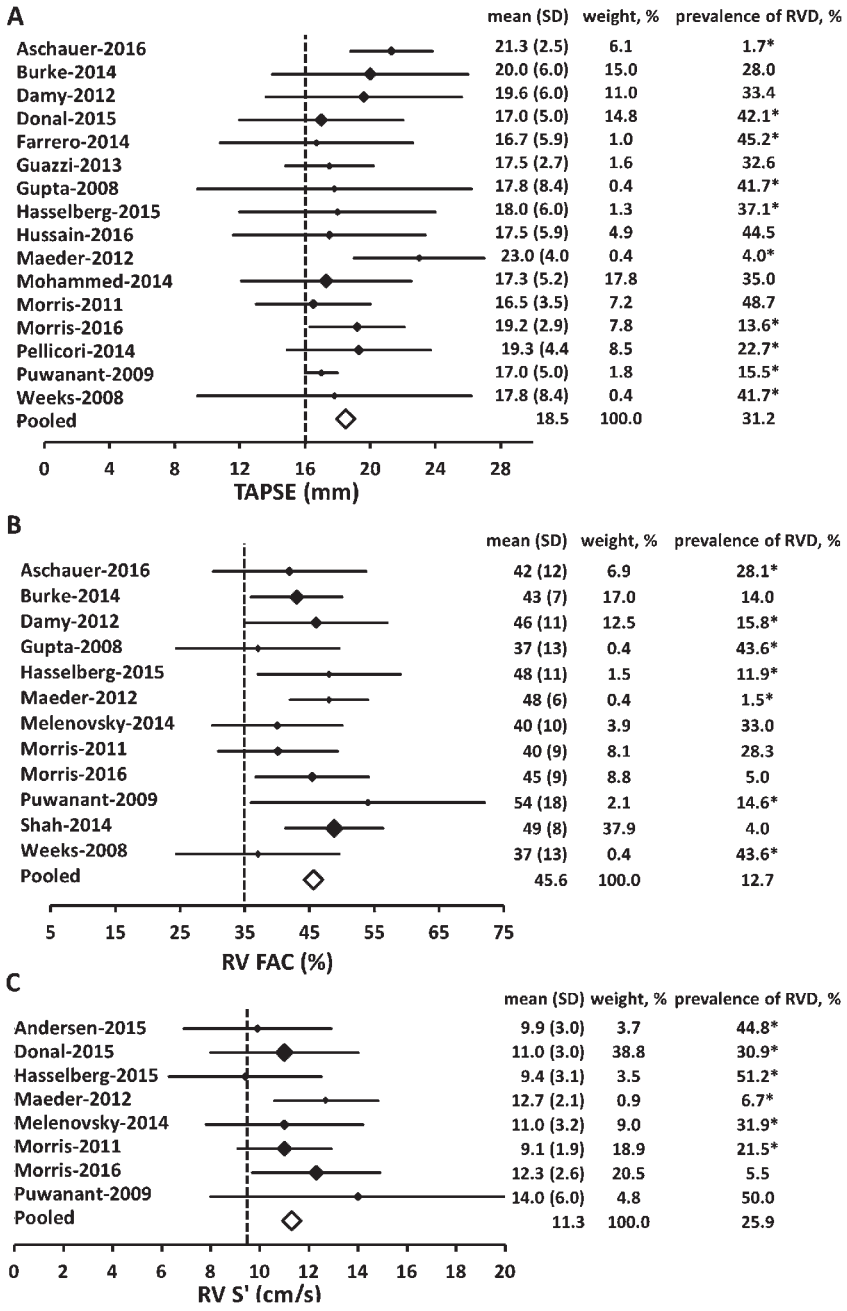

Figure 2 Prevalence of right ventricular dysfunction (RVD) in heart failure with preserved ejection fraction. Dotted lines represent the cut-offs for RVD. *Estimated prevalence rates. FAC, fractional area change; RV S', tricuspid annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

Prevalence of pulmonary hypertension in heart failure with preserved ejection fraction

Pooled MPAP was 32.0 mmHg, and 70% of 623 patients had MPAP ≥25 mmHg (*Figure 3A*). The prevalence of PASP ≥35 mmHg was 53%, with mean PASP of 38.2 mmHg in 3542 patients (*Figure 3B*).

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

A summary of clinical correlates of RV dysfunction is depicted in the Supplementary material online, *Table S2*. RV dysfunction in HFpEF is primarily associated with increased pulmonary pressures, reduced LVEF, and AF; and is also reported to be more prevalent in males

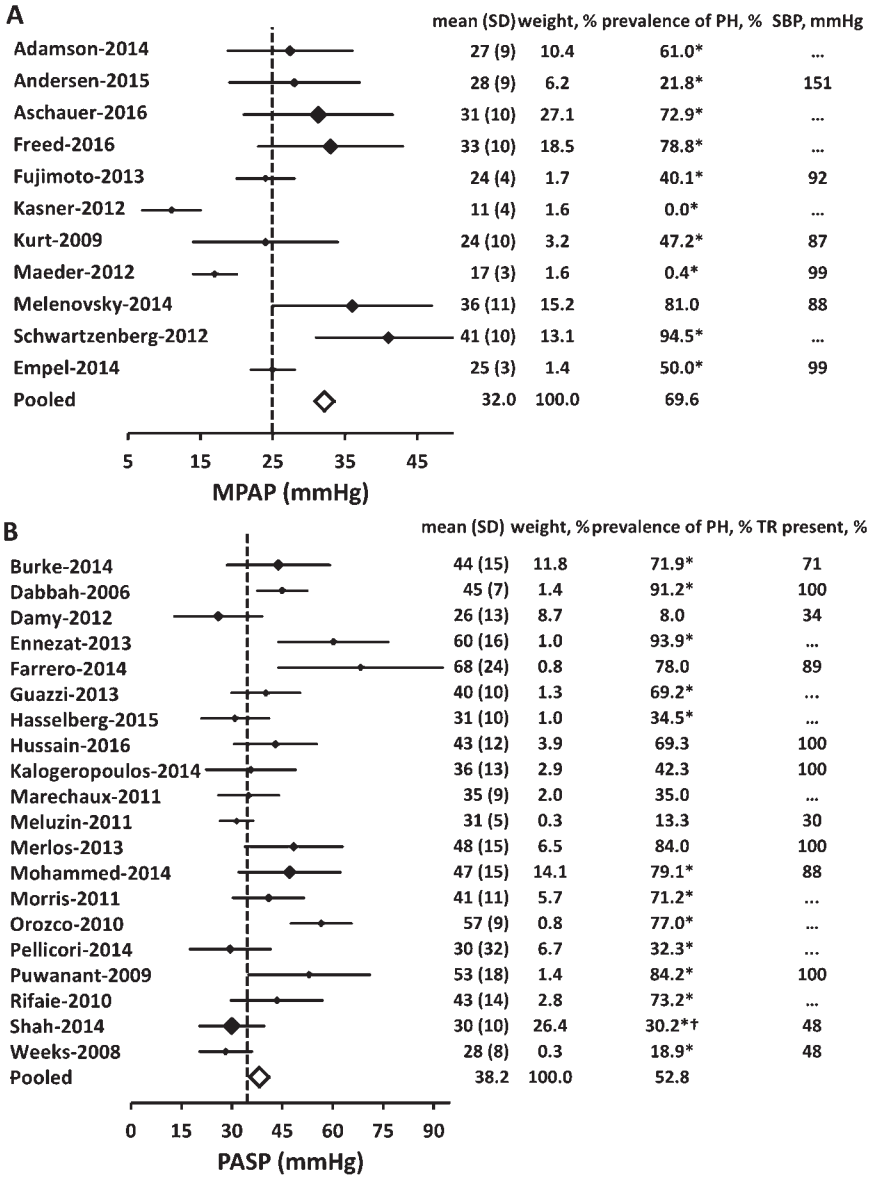

Figure 3 Prevalence of pulmonary hypertension (PH) in heart failure with preserved ejection fraction. The dotted line represents the cut-off for increased pulmonary pressures. *Estimated prevalence; †pulmonary artery systolic pressure (PASP) measured without estimate of right atrial pressure. Mean systemic blood pressure (SBP) was denoted if simultaneously measured with pulmonary pressures. If reported, the percentage of included patients in whom tricuspid regurgitation (TR) was present for measuring PASP was obtained for each study. MPAP, mean pulmonary artery pressure.

and in those with more severe LV diastolic dysfunction, CAD, and higher BMI.

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

The prognostic value of TAPSE was reported in six studies, FAC in five studies, and RV dilatation in three studies (*Table 2*). The prognostic value of RV S' was not reported.

Pooled unadjusted HR for the relationship between TAPSE and mortality was 1.26 per 5 mm decrease [95% confidence interval (CI) 1.16–1.38, $P < 0.0001$, $n = 1156$] (*Figure 4A*). The pooled HR per 5 mm decrease in TAPSE, in relation to HF hospitalization, was 1.38 (95% CI 1.21–1.58, $P < 0.0001$, $n = 919$).[10,28]

The pooled unadjusted HR of FAC in relation to mortality was 1.16 per 5% decrease in FAC (95% CI 1.08–1.24, $P < 0.0001$, $n = 965$) (*Figure 4B*). The pooled unadjusted HR per 5% decrease in FAC in relation to HF hospitalization was 1.09 (95% CI 1.00–1.19, $P = 0.07$, $n = 869$).[11,28]

Table 2 Right ventricular function and pulmonary hypertension in relation to outcome

Study/publication year	Follow-up (months)	Outcome	Measure	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Aschauer-2016[27]	19 ± 13	CV death/HF hospitalization	TAPSE <16 mm	2.75 (1.27–5.96), $P = 0.01$	…
			FAC <35%	2.26 (1.21–4.20), $P = 0.01$	…
			RVEF <45%	4.64 (2.50–8.59), $P < 0.001$	4.90 (2.46–9.75), $P < 0.001$[a]
			RVEDD/mm	1.05 (1.01–1.09), $P = 0.01$	…
			MPAP/mmHg	1.07 (1.04–1.10), $P < 0.001$	….
Burke-2014[28]	18 (10–30)	All-cause mortality/ CV hospitalization	TAPSE/6 mm↓	1.19 (1.02–1.39), $P = 0.03$	1.09 (0.91–1.30), NS[b]
			FAC/7%↓	1.18 (1.02–1.37), $P = 0.02$	1.05 (0.88–1.25), NS[b]
			RVEDD/cm	1.27 (1.10–1.47), $P = 0.001$	1.26 (1.04–1.52), $P = 0.017$[b]
			RVEDAi/cm^2/m^2	1.26 (1.10–1.44), $P = 0.001$	1.28 (1.05–1.56), $P = 0.02$[b]
			PASP/15 mmHg	1.31 (1.10–1.55), $P = 0.002$	1.04 (0.85–1.26), NS[b]
		HF hospitalization	TAPSE/6 mm↓	1.37 (1.11–1.68), $P = 0.003$	1.30 (1.02–1.67), $P = 0.04$[b]
			FAC/7%↓	1.27 (1.06–1.53), $P = 0.01$	1.08 (0.86–1.35), NS[b]
			RVEDD/cm	1.33 (1.11–1.59), $P = 0.002$	1.21 (0.95–1.55), $P =$ NS[b]
			RVEDAi/cm^2/m^2	1.30 (1.10–1.53), $P = 0.002$	1.41 (1.09–1.82), $P = 0.009$[b]
			PASP/15 mmHg	1.34 (1.07–1.67), $P = 0.01$	1.04 (0.81–1.32), NS[b]
Damy-2012[12]	63 (41–75)	All-cause mortality	TAPSE/quartile	9, 4, 6, and 5% mortality per TAPSE quartile, χ^2 for log-rank test: 5.8, $P = 0.12$	
Freed-2016[34]	14 (5–24)	All-cause mortality/ CV hospitalization	TAPSE/6 mm↓	1.19 (0.99–1.43), $P = 0.06$	–
			FAC/7%↓	1.20 (1.01–1.42), $P = 0.04$	–
			MPAP/10 mmHg	1.37 (1.08–1.72), $P = 0.008$	–
			PASP/15.5 mmHg	1.21 (0.98–1.49), $P = 0.08$	–
Kalogeropoulos-2014[40]	31 (20–47)	All-cause mortality/LVAD/HTX	PASP/10 mmHg	1.88 (1.42–2.50), $P < 0.007$	–
		All-cause mortality/ LVAD/HTX/HF hospitalization	PASP/10 mmHg	1.50 (1.20–1.88), $P < 0.001$	–
Kjaergaard-2007[42]	34	All-cause mortality	PASP ≥39 mmHg	Log-rank test: $P = 0.006$	
Melenovsky-2014[9]	17 (5–35)	All-cause mortality	FAC/7%↓	2.4 (1.6–2.6), $P < 0.0001$	2.2 (1.4–3.5), $P = 0.001$[c]
			RVEDA/6 cm^2	2.3 (1.6–3.4), $P < 0.0001$	2.1 (1.4–3.4), $P = 0.001$[c]
			PASP/18 mmHg	1.6 (1.1–2.2), $P = 0.006$	PASP adjusted
Merlos-2013[48]	N/A	1-year all-cause mortality	PASP/category	Log-rank test: $P = 0.001$	
Mohammed-2014[10]	55	All-cause mortality	TAPSE/4 mm	0.82 (0.73–0.91), $P = 0.0003$	0.99 (0.79–1.01), NS[d]
			PASP/15 mmHg	1.53 (1.37–1.69), $P < 0.0001$	1.50 (1.33–1.68), $P < 0.0001$[d]
		CV death	TAPSE/4 mm	0.73 (0.60–0.87), $P = 0.0005$	0.77 (0.64–0.94), $P = 0.01$[d]
			PASP/15 mmHg	1.67 (1.40–1.96), $P < 0.0001$	1.57 (1.29–1.90), $P < 0.0001$[d]
		HF hospitalization	TAPSE/4 mm	0.72 (0.61–0.85), $P < 0.0001$	0.82 (0.68–0.99), $P = 0.03$[d]
			PASP/15 mmHg	1.47 (1.25–1.71), $P < 0.0001$	1.44 (1.21–1.71), $P < 0.0001$[d]
Pellicori-2014[52]	19 (15–24)	CV death/ HF hospitalization	TAPSE/mm	0.87 (0.82–0.93), $P < 0.001$	…
			PASP/mmHg	1.04 (1.03–1.06), $P < 0.001$	1.00 (0.98–1.02), NS[e]
Shah-2014[11]	35 (18–54)	CV death/ HF hospitalization/ aborted SCD	FAC/5%	0.99 (0.89–1.09), NS	…
			PASP/11 mmHg	1.28 (1.07–1.52), $P = 0.006$	1.23 (1.02–1.49), $P = 0.029$[f]
		HF hospitalization	FAC/5%	0.99 (0.87–1.11), $P =$ NS	…
			PASP/11 mmHg	1.33 (1.09–1.62), $P = 0.004$	1.29 (1.04–1.60), $P = 0.02$[f]

Values are presented as median (interquartile range), mean ± standard deviation or hazard ratio (HR) and 95% confidence interval (CI).
CV, cardiovascular; FAC, fractional area change; HF, heart failure; HTX, heart transplantation; LVAD, left ventricular assist device; MPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; SCD, sudden cardiac death; TAPSE, tricuspid annular plane systolic excursion.
[a] Adjusted for diabetes mellitus, NYHA functional class, 6-min walk distance, FAC, TAPSE, invasive haemodynamic measurements (e.g. MPAP, pulmonary vascular resistance), left and right atrial size, and RV end-diastolic diameter.
[b] Adjusted for age, sex, and co-morbidities (i.e. body mass index, CAD, diabetes mellitus, AF, COPD, obstructive sleep apnoea, hypertension, glomerular filtration rate, haemoglobin concentration, degree of mitral regurgitation, LV mass index, and NYHA functional class).
[c] Adjusted for PASP.
[d] Adjusted for PASP, TAPSE, age, sex, and co-morbidities (i.e. AF, diabetes mellitus, COPD, and obstructive sleep apnoea).
[e] Adjusted for age, diagnostic category of HF with preserved ejection fraction; NYHA functional class, systolic blood pressure, urea, AF, NT-proBNP, global longitudinal strain, and congestion score.
[f] Adjusted for age, sex, race, LV ejection fraction, AF, heart rate, NYHA functional class, history of stroke, creatinine, hematocrit, trial randomization strata (prior HF hospitalization or biomarker criteria), region of enrolment (America vs. Russia or Georgia), and randomized treatment assignment.

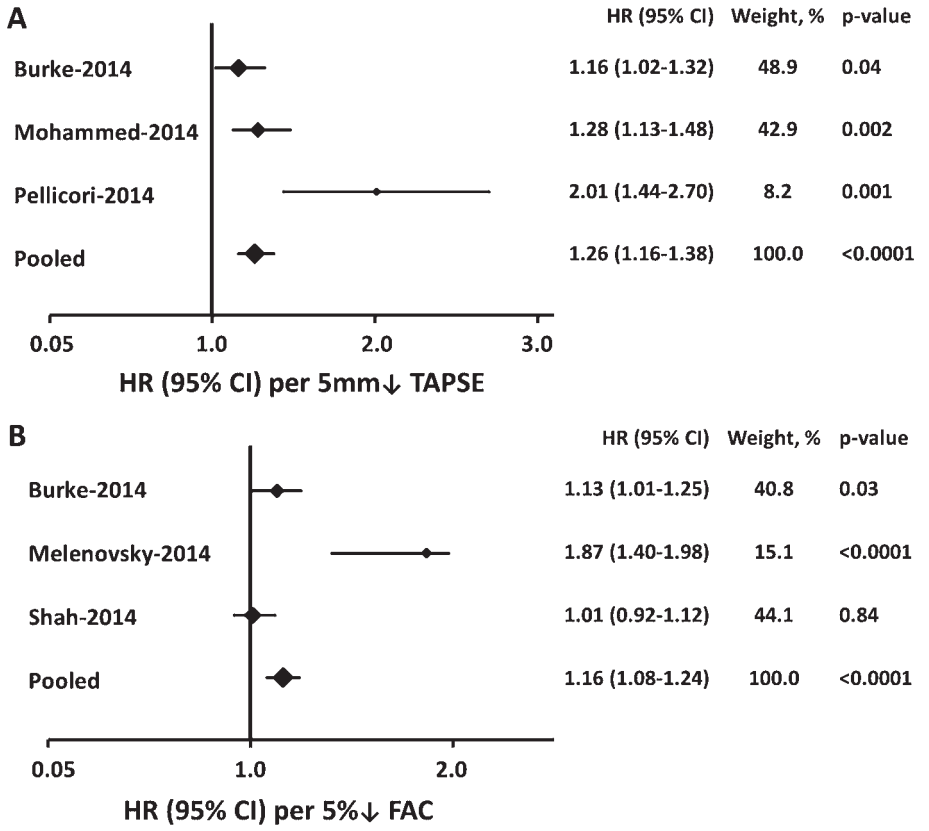

Figure 4 Predictive value of right ventricular dysfunction for mortality in heart failure with preserved ejection fraction. CI, confidence interval; FAC, fractional area change; HR, hazard ratio; TAPSE, tricuspid annular plane systolic excursion.

Pooled unadjusted HR for RVEDD in relation to mortality was 1.14 per 5 mm increase in RVEDD (95% CI 1.07–1.23, $P = 0.0002$, $n = 590$).[27,28]

Several studies also reported adjusted HRs for the relationship between RV function and dilatation with outcome (*Table 2*). However, adjustment variables varied widely among these studies and thus it was not possible to perform pooled analyses.

Pulmonary hypertension and prognosis in heart failure with preserved ejection fraction

Two studies reported the prognostic value of MPAP and 10 studies reported for PASP (*Table 2*). The pooled unadjusted HR for mortality was 1.26 per 5 mmHg increase in MPAP (95% CI 1.15–1.38, $P < 0.0001$, $n = 288$) (*Figure 5A*). The pooled unadjusted HR for the association between PASP and mortality was 1.15 (95% CI 1.12–1.18, $P < 0.0001$, $n = 1368$) per 5 mmHg increase in PASP (*Figure 5B*). The pooled unadjusted HR for the relationship between PASP and HF hospitalization was 1.13 per 5 mmHg increase in PASP (95% CI 1.09–1.17, $P < 0.0001$, $n = 1369$).[10,11,28]

Adjustment variables for MPAP and PASP in relation to outcome also varied widely among reporting studies, thus performing pooled analyses using adjusted HRs was not possible.

Sensitivity analysis

The results of the sensitivity analyses in studies with stringent HFpEF criteria vs. studies with lenient criteria are summarized in the Supplementary material online, *Tables S3–S7*. Overall, the prevalence rates of RV dysfunction according to TAPSE, FAC, and RV S' are more comparable in the studies with stringent criteria (i.e. 28% for TAPSE <16 mm, 18% for FAC <35%, and 21% for RV S' <9.5 cm/s). The same is demonstrated for the prevalence of PH in the studies with stringent criteria (i.e. both a prevalence of 68% for increased MPAP and increased PASP). Only one study included in the analysis on RV dilatation used less stringent HFpEF criteria; thus these values did not change importantly.

In the sensitivity analysis, TAPSE (HR 1.16, 95% CI 1.02–1.32, $P = 0.04$), FAC (HR 1.29, 95% CI 1.18–1.41, $P < 0.0001$), and RVEDD (HR 1.45, 95% CI 1.07–1.23, $P = 0.0002$) remained predictive of mortality in the studies with stringent criteria.

For PH in relation to outcome, both MPAP (HR 1.26, 95% CI 1.15–1.38, $P < 0.0001$) and PASP (HR 1.13, 95% CI 1.08–1.19, $P < 0.0001$) remained predictive of mortality in the sensitivity analysis.

The intraclass correlation between the reported and estimated prevalence rates of RV dysfunction and PH was 0.96 (95% CI 0.91–0.99, $P < 0.001$).

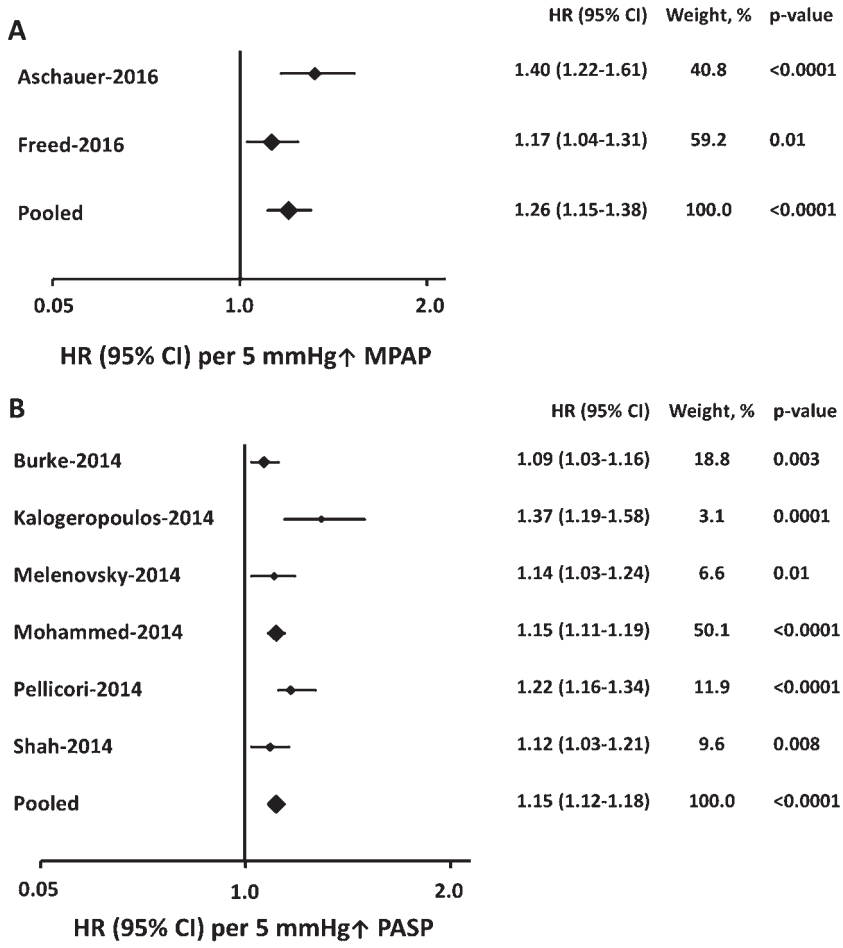

Figure 5 Predictive value of pulmonary hypertension for mortality in heart failure with preserved ejection fraction. CI, confidence interval; HR, hazard ratio; MPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure.

Discussion

To our knowledge, this is the first systematic evaluation of RV dysfunction and PH in HFpEF. In the studies with stringent HFpEF criteria, the prevalence of RV dysfunction is 28% for TAPSE, 18% for FAC, and 21% for RV S'. The prevalence of PH in HFpEF is 68% for both increased MPAP and PASP. The prevalence of RV dysfunction depends on the method used for its assessment. Finally, both RV dysfunction and PH are strongly predictive of outcome in HFpEF.

Definition of heart failure with preserved ejection fraction

The definition of HFpEF is crucial for patient selection, yet diagnosing HFpEF is challenging and definite criteria remain debated.[61] The majority of studies included in the present meta-analysis were published after the publication of the ESC 2012 guidelines and, very recently, a new diagnostic algorithm for HFpEF was proposed in the 2016 update of the guidelines.[18] Unfortunately, approximately half of the studies included in the present analysis reported according to previously recommended criteria for patient selection, with either structural heart disease and/or diastolic dysfunction, or the presence of elevated LV filling pressures. In the sensitivity analyses, performed in only those studies that used stringent HFpEF criteria, results regarding the prevalence of RV dysfunction and PH seemed more robust. Both RV dysfunction and PH also remained associated with outcome in this subset of studies.

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

In the current study, RV dysfunction was primarily based on echocardiographic data. TAPSE and FAC are commonly used for this purpose and usually they strongly correlate with each other.[21] However, we observed different prevalence rates of RV dysfunction between TAPSE and FAC. There are several potential explanations for this discrepancy. First, RV systolic function is the sum of multiple contraction mechanisms of which the most important is longitudinal contraction due to the predominant longitudinal

arrangement of RV muscle fibres.[62] In response to increased afterload, however, the right ventricle increases its transverse contraction relative to decreased longitudinal shortening.[63,64] Transverse RV wall motion may be a better reflection of RV systolic function in PH, compared with TAPSE.[65] Consequently, as a result of increased afterload in HFpEF, TAPSE may be reduced while at the same time FAC is enhanced. RV function in HFpEF may therefore be overestimated with TAPSE or underestimated with FAC. However, as previously mentioned, the recommended cut-offs for RV dysfunction are also frequently subject to change. Perhaps the cut-off for RV dysfunction is more stringent for FAC compared with TAPSE.

Another reasonable interpretation is that reliable assessment of FAC, more than TAPSE, requires a sufficient acoustic window, which is rather challenging in such a population with a high prevalence of COPD and obesity. Although the RV S'-wave velocity may potentially be a more reliable measure of RV function,[21] its prognostic value in HFpEF is still unknown. Unfortunately, data on RV dysfunction in HFpEF using MRI are scarce. Very recently, Aschauer *et al.* demonstrated that RV dysfunction assessed with MRI was present in 19% of HFpEF patients and was also predictive of mortality, even after adjustment for pulmonary pressures.[27] We believe that RV dysfunction is present in ~20–25% of patients with HFpEF.

Right ventricular dysfunction in HFpEF is primarily determined in resting conditions. However, it has recently been demonstrated that although RV systolic and diastolic function may be preserved at rest, patients with HFpEF display impaired RV reserve with exercise, similar to LV mechanics during exercise.[66] These observations support the notion that RV dysfunction in HFpEF may occur in parallel to left-sided perturbations and also in the earliest stages of HFpEF, and is not only the result of worsening HF.[66] RV function is also highly sensitive to alterations in afterload.[66] Very recently, Hussain *et al.* demonstrated the importance of RV–pulmonary arterial (PA) coupling in HFpEF using the TAPSE/PASP ratio with echocardiography.[39] Previously, Guazzi and co-workers observed that this ratio is predictive of outcome in HF.[36] For the present meta-analysis, we did not have access to individual patient data, and published data on this topic in HFpEF is scarce. Further research is needed to investigate the importance of RV functional reserve and RV–PA coupling for our understanding of the pathophysiology and potential treatment strategies in HFpEF.

Prevalence of pulmonary hypertension in heart failure with preserved ejection fraction

Elevated LV end-diastolic pressure and increased PCWP are major determinants of PH in HFpEF. The diagnostic definition of PH is MPAP ≥25 mmHg measured with right heart catheterization.[23] However, for screening purposes for increased pulmonary pressures, echocardiography is widely used. Although echocardiography is inferior to right heart catheterization in measuring pulmonary pressures, we demonstrated similar rates of PH using both methods.

There are some important aspects in the interpretation of PH in relation to HFpEF that merit emphasis. The first regards the applied inclusion criteria. For instance, Melenovsky *et al.* reported a PH prevalence of 81%.[9] This rate is considerably higher than the 40% previously reported by the often cited study by Leung *et al.*[67] However, the latter study was performed in a different patient population, i.e. increased LV end-diastolic pressure, yet only 22% of patients were diagnosed with HF. Consequently, this study was not included in the present analysis. Other studies included in the present meta-analysis also reported lower prevalence rates of PH. However, criteria for HFpEF were sometimes less stringent and for instance LV filling pressures were often not tested invasively. It therefore remains questionable whether these studies included all true HFpEF patients. The PH prevalence rates between right heart catheterization and echocardiography were especially similar in the studies with stringent criteria, possibly reflected by the inclusion of more true HFpEF patients. Therefore, we believe that PH is present in around two-thirds of HFpEF patients.

Furthermore, PASP can only be derived in patients with sufficient tricuspid regurgitation (TR), and patients with TR are more likely to have higher pulmonary pressures than patients without TR.[23] The prevalence of PH might be overestimated since patients with HFpEF and no TR were consequently not included in the analysis of PASP.

Finally, the prevalence of 24% COPD in the current meta-analysis is an important contributor to increased pulmonary pressures,[23] and both patients with HFpEF and COPD might display signs and symptoms of HF and a 'preserved' LVEF.[68] For studying the right side in HFpEF, one should therefore take into account the possibility of an overlap in both diseases.

Co-morbidities and right ventricular dysfunction in heart failure with preserved ejection fraction

Right ventricular dysfunction in HF may occur secondarily to PH or independently of pulmonary pressures, for instance due to intrinsic myocardial disease, myocardial ischaemia and infarction, or neurohormonal activation.[69] Co-morbidities frequently present in HFpEF are known to alter myocardial structure and function independently.[70,71] Therefore, it may be questioned whether RV dysfunction in HFpEF is primarily the result of worsening HF and increased afterload in PH, or is also related to shared underlying pathophysiological mechanisms in HFpEF.[72,73] In the current meta-analysis, we observed that RV dysfunction is indeed strongly related to increased pulmonary pressures, yet other factors, such as male sex, AF, CAD, and obesity, also correlated with reduced RV function in several studies.

The role of AF in the development of RV dysfunction in HFpEF deserves further consideration. Chronic elevation of LV diastolic filling pressures in HFpEF results in structural and functional remodelling of the left atrium and thereby contributes to the development of AF.[74] Melenovsky *et al.* observed that RV dysfunction was more strongly related to AF than to pulmonary pressures.[9] AF seemed to contribute to RV dysfunction, yet in a partially pressure

load-independent manner. Interestingly, the same phenomenon was observed by Mohammed *et al.*, both in patients with AF and in those with permanent pacing.[10] Load-independent factors such as rhythm irregularity and contractile dyssynchrony by pacing might contribute to RV dysfunction in HFpEF. It is possible that AF directly affects RV systolic function via impaired longitudinal performance, since cardioversion for AF improves RV longitudinal contraction.[75]

Coronary artery disease is another common finding in HFpEF, with 47% prevalence in the current analysis. Isolated RV infarctions are rare,[76] and large myocardial infarctions more often lead to HFrEF instead of HFpEF. Although the amount of RV myocardial damage after myocardial infarction is currently very limited,[77] CAD seems independently associated with reduced RV function in HFpEF.[9,10] It is probable that the right ventricle is more vulnerable to CAD in HFpEF, since there is less myocardial mass as compared with the left ventricle.

Other co-morbidities in HFpEF that may affect RV structure and function, independent of pulmonary pressures, include hypertension,[78,79] diabetes,[80,81] COPD,[82] and obesity.[83,84] The remodelling effects on the right ventricle are rather complex and also differ between the sexes.[85] These observations suggest that RV dysfunction in HFpEF may be part of systematic inflammation and endothelial dysfunction, affecting both ventricles simultaneously (*Figure 6*).[8]

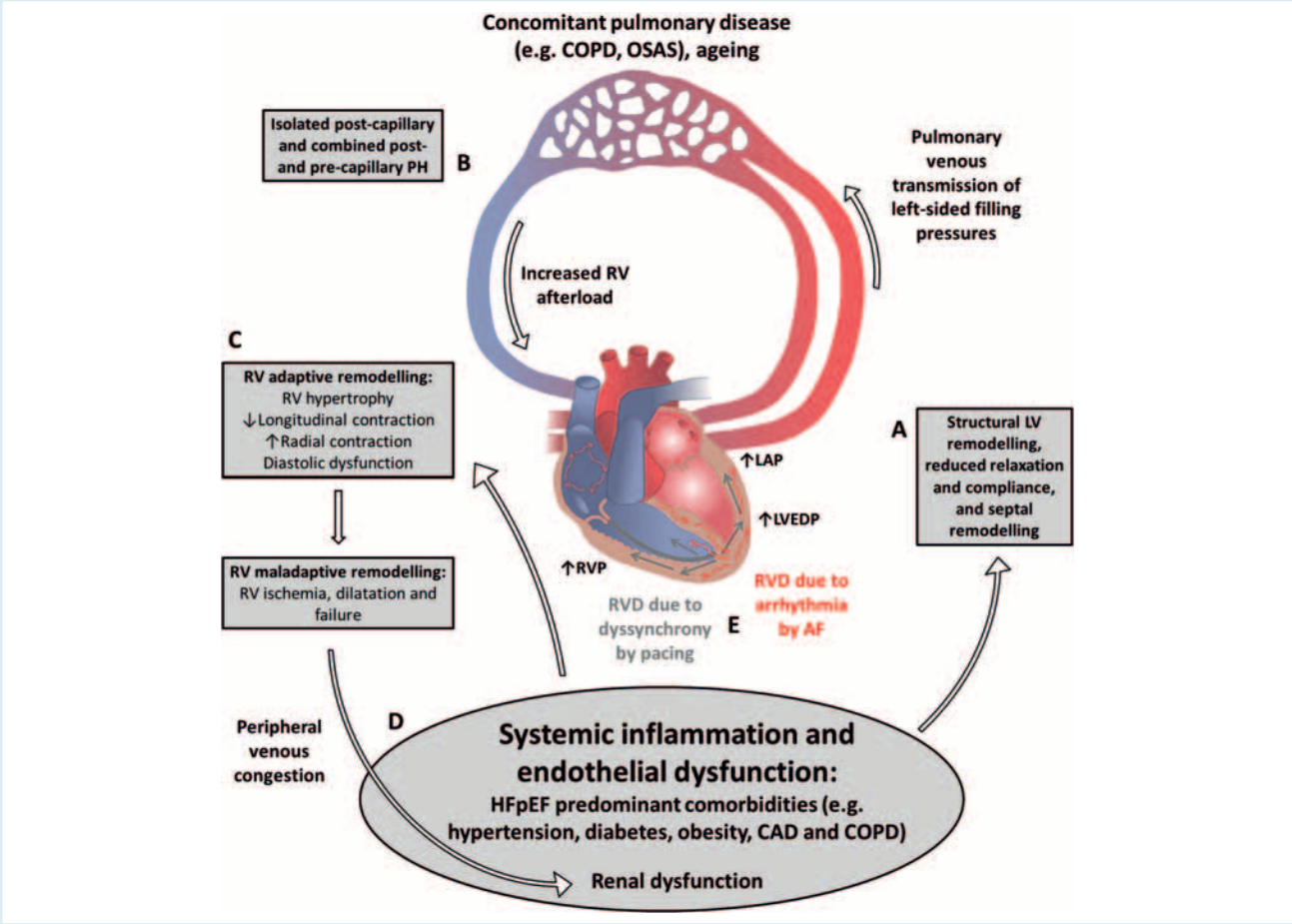

Figure 6 Proposed framework of right ventricular dysfunction (RVD) in heart failure with preserved ejection fraction (HFpEF). (*A*) One of the key observations in HFpEF is structural remodelling in terms of LV hypertrophy and left atrial (LA) dilatation, and reduced relaxation and compliance of the left ventricle. LV end-diastolic pressure (LVEDP), and LA pressure (LAP) increase. LV filling pressures are transmitted to the pulmonary venous circulation. (*B*) These pressures are the most important determinants of post-capillary pulmonary hypertension (PH) in HFpEF. A smaller subset of patients may develop combined post-capillary and pre-capillary PH. Concomitant pulmonary disease [e.g. COPD and obstructive sleep apnoea syndrome (OSAS)] in HFpEF may contribute to increased pulmonary pressures and often mimic symptoms of heart failure. (*C*) The right ventricle adapts to this afterload with increased contractility and right ventricular (RV) hypertrophy. When RV afterload progresses, RV remodelling may become maladaptive and RV dilatation and failure occur. RV failure is an important determinant of peripheral venous congestion, and backward failure may cause renal dysfunction. (*D*) Renal dysfunction and other HFpEF predominant co-morbidities are important load-independent factors that may cause the onset or progression of structural and functional remodelling of both ventricles simultaneously. (*E*) Both AF and permanent pacing in HFpEF may also directly result in RVD due to rhythm irregularity and contractile dyssynchrony.

Outcomes in heart failure with preserved ejection fraction

Right ventricular dysfunction and PH are strong predictors of adverse outcome in numerous cardiovascular diseases, including left-sided HF,[86,87] and their presence may have deleterious consequences.[88] The present review demonstrated that also in HFpEF, impaired right-sided cardiovascular function is a major determinant of poor prognosis. However, as previously reported, age and several non-cardiac co-morbidities also drive prognosis in HFpEF, independent of worsening HF.[89] These co-morbidities may directly provoke progressive decompensation via inflammation, microvascular obstruction, and subendocardial ischaemia.[89] Unfortunately, we were not able to investigate adjusted associations between RV dysfunction and outcome. However, adjusted results remain variable in individual studies, as seen in *Table 2*.[9–11,27,28,52] The aforementioned considerations may possibly influence prognosis in HFpEF, independently of RV function. However, the relationship between these co-morbidities and RV dysfunction, in relation to outcome in HFpEF, warrants further research.

Limitations

An important limitation is the variation in HFpEF criteria used among included studies. In addition, only half of these studies included patients according to previous recommendations. Since definite criteria of HFpEF remain debated and have changed over time, it is rather challenging to include HFpEF studies with similar inclusion criteria in such a meta-analysis. Sensitivity analyses in more true HFpEF patients also demonstrated more robust findings, indicating more true HFpEF populations. Differences in the design and setting of included studies are also important for the interpretation of the present results. Unfortunately, we did not have access to individual patient data and thus we were not able to substratify according to study characteristics. Secondly, the methods used for the evaluation of RV dysfunction varied across studies, and cut-off values for RV dysfunction may not be interchangeable. For the assessment of RV dysfunction with echocardiography, multiple indices are often used simultaneously. However, we were not able to use individual patient data to investigate the influence of multiple function indices. Combined measurements of RV dysfunction would certainly enhance the reliability of detection of RV dysfunction. Studies that reported RV dysfunction and/or PH in relation to outcome also used different outcome measures and adjustment variables. Thus, we were only able to report unadjusted relationships.

Conclusion

Both RV dysfunction and PH are highly prevalent in HFpEF. The prevalence of RV dysfunction, more than PH, is dependent on the method and cut-offs used for its assessment. RV dysfunction in HFpEF is strongly associated with PH and with co-morbidities such as AF, and predicts poor outcome. More studies on interventions that aim to reduce RV afterload and to restore normal heart rhythm are needed to improve prognosis in patients with HFpEF.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Search strategy.

Figure S2. Summary of the qualitative assessment for the risk of bias.

Table S1. Prevalence of RV dysfunction in studies that used >1 echocardiographic method for this purpose.

Table S2. Clinical correlates of right ventricular dysfunction in HFpEF.

Table S3. Sensitivity analyses for TAPSE.

Table S4. Sensitivity analyses for FAC.

Table S5. Sensitivity analyses for RV S'.

Table S6. Sensitivity analyses for MPAP.

Table S7. Sensitivity analyses for PASP.

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