Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management.

A Position Statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

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ABSTRACT

There is an unmet need for effective treatment strategies to reduce morbidity and mortality in patients with heart failure with preserved ejection fraction (HFpEF). Until recently, attention in patients with HFpEF was almost exclusively focused on the left side. However, it is now increasingly recognized that right heart dysfunction is common and contributes importantly to poor prognosis in HFpEF. More insights into the development of right heart dysfunction in HFpEF may aid to our knowledge about this complex disease and may eventually lead to better treatments to improve outcomes in these patients. In this recommendation paper from the Heart Failure Association of the European Society of Cardiology, the Committee on Heart Failure with Preserved Ejection Fraction reviews the prevalence, diagnosis and pathophysiology of right heart dysfunction and failure in patients with HFpEF. Finally, potential treatment strategies, important knowledge gaps and future directions regarding the right side in HFpEF are discussed.

INTRODUCTION

For many years, the right ventricle (RV) was largely neglected in the consideration of left-sided heart failure. In the last two decades however, several studies have clearly demonstrated that RV dysfunction (RVD) is not only common in left heart failure, its presence also strongly contributes to increased morbidity and mortality.(1,2) The mechanisms behind the development of RVD in patients with left heart failure have been well established, but these data were, until recently, almost exclusively obtained in patients suffering from heart failure with reduced ejection fraction (HFrEF).(3)

It is now evident that RVD is highly prevalent and contributes to poor prognosis in patients with left-sided heart failure with preserved ejection fraction (HFpEF).(4-7) However, the underlying pathways that lead to RVD in HFpEF are less clear. In addition, patients with idiopathic pulmonary arterial hypertension (PAH) or pulmonary fibrosis, and patients with chronic obstructive pulmonary disease (COPD) also present with signs and symptoms of heart failure with a preserved left ventricular (LV) ejection fraction. Better insight into the mechanisms causing the development of RVD and its clinical role in HFpEF may aid to 1) our understanding of this complex disease and 2) develop novel treatment strategies to improve outcomes. The present recommendation paper reviews the pathophysiology, potential treatment strategies, knowledge gaps and future directions regarding the right-side of the heart in HFpEF.

PREVALENCE

One of the first studies that investigated RV function in HFpEF was conducted by Puwanant *et al.* in 2009.(8) This prospective study included 51 patients with HFpEF and demonstrated a prevalence of 33%, 40% and 50% for RVD, as categorized by abnormalities in RV fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular

systolic velocity (RV S'), respectively.(8) Since then, several other studies have been published, examining RVD in HFpEF.(4,5,9-11) Determining exact prevalence data for RVD is challenging, because HFpEF severity across different studies has varied, as well as the echocardiographic methods, criteria and cut-off values employed for the assessment of RVD. Some of these cut-off values for RVD are less well established or have also changed over time.(12-14) Aschauer *et al.* used cardiac magnetic resonance (CMR) imaging for the detection of RVD in 171 patients with HFpEF, and RVD (defined as RV ejection fraction <45%) was present in 19% of the patients,(10) whereas Melenovsky *et al.* reported a prevalence of 33% for RVD (defined as RV FAC <35%) in 96 patients.(4)

It is important to keep in mind that the prevalence of RVD may also be influenced by inclusion criteria that are applied to define HFpEF. The classic signs of left- and right-sided heart failure are not mutually exclusive. For instance, the often used Framingham criteria for the diagnosis of HFpEF include signs consistent with right-sided decompensation, such as hepatomegaly and peripheral oedema. Furthermore, the inclusion of patients with (concomitant) pulmonary vascular disease (PVD) caused by other mechanisms other than left heart failure (e.g. severe chronic obstructive pulmonary disease and pulmonary arterial hypertension) may result in the overrepresentation of RVD unrelated to concomitant left-sided HF.(15,16) Furthermore, the application of different exclusion criteria among individual studies may also affect the prevalence rate of RVD. For instance, renal dysfunction is strongly associated with pulmonary hypertension (PH) and RVD.(17) The prevalence of RVD may therefore be relatively higher in community-based studies compared to clinical trials, because (severe) renal dysfunction is often an exclusion criterion in the latter. In addition, because signs suggestive of RVD are used to diagnose heart failure in community studies, there may be a relatively higher identification of HFpEF patients with RVD compared to HFpEF

patients without RVD in these studies compared to clinical trials in which more often stringent HFpEF criteria are used.

Finally, it is challenging to define the prevalence of RVD considering the small number of patients among individual studies. In a recent meta-analysis, in which pooled data of RV function in HFpEF was summarized from multiple studies that used HFpEF criteria according to the 2016 European Society of Cardiology Heart Failure Management Guidelines, the prevalence of RVD was 18%, 28% and 21% using RV FAC, TAPSE and RV S', respectively.(7) Thus despite variable reports, methods and criteria, the best available current data indicate that RVD is present in *at least* one-fifth and *potentially* up to 30-50% of patients with HFpEF.

Given the heterogeneity of previous studies investigating the right heart in HFpEF, we recommend for future studies that HFpEF should be stringently defined according to the current criteria for the diagnosis of HFpEF.(18)

PROGNOSIS

The annual mortality rate in HFpEF ranges from ~10% in clinical trials up to almost 30% in several population-based studies, of which cardiovascular deaths comprise 51-60% in epidemiological studies and ~70% in clinical trials.(19) Most cardiovascular deaths in HFpEF can be attributed to end-stage circulatory failure.(19) It is now increasingly evident that RVD is also a major predictor of the clinical course of HFpEF.(7) Melenovsky *et al.* reported a 2.2-fold increased risk for all-cause mortality per 7% decrease in FAC, after adjustment for pulmonary pressures.(4) In the study by Aschauer *et al*., the hazard ratio for the composite endpoint of cardiovascular death and HF hospitalisation was 4.9 for patients with RV ejection fraction <45% on CMR, after adjustment for e.g. diabetes mellitus and pulmonary pressures.(10) Pooled data from individual studies recently showed that the risk of mortality

increases with ~26% per 5 mm decrease in TAPSE and with ~16% per 5% decrease in FAC.(7)

In a recent prospective study in 230 patients with HFpEF, 38 (16.5%) patients died during a mean follow-up of 30 months. Of these, 55% died with the presence of end-stage RV failure, defined as 1) echocardiographic evidence of RVD and 2) clinical signs of right-sided decompensation such as ascites, liver enzyme elevation, peripheral oedema and jugular distension.(20)

DIAGNOSIS

Right heart dysfunction versus failure

The distinction between RVD and right heart failure may be likened to that between LV systolic dysfunction and left heart failure, in that the former is defined by abnormal values of functional parameters, whereas the latter is defined by haemodynamic decompensation with typical clinical signs and symptoms.

Right heart *dysfunction* is present when a measure of RV function falls outside the recommended range of normal (**Table 1**).(13) In the absence of clear normal values, the range that is published varies and hinges on agreement to what defines normal and abnormal. Right ventricular dysfunction may be asymptomatic, but there may be evidence of adaptive RV remodelling in response to increased afterload such as RV hypertrophy, which seems present in ~22% of patients with HFpEF and ~45% of patients with PH-HFpEF.(21) Preliminary evidence suggests that there may be increased reliance on a contraction pattern more suited for increased afterload to preserve global systolic function (e.g. reduced longitudinal shortening but enhanced transverse contraction), analogue to the LV.(22) Hence, multiple measurements that reflect RV systolic function are preferably used. We herein propose that RV systolic dysfunction is present in HFpEF if 1) at least two echocardiographic parameters

for RV systolic function are below their recommended cut-off value (**Table 1**), or 2) if RV ejection fraction measured with CMR is <45%. Still, it must be noted that the majority of data regarding RVD is obtained from patients with HFrEF instead of HFpEF.

Right heart *failure* is a clinical diagnosis with signs and symptoms of systemic congestion in combination with structural and/or functional abnormalities of the right heart.(23) Right heart failure may be caused by RVD itself, RV remodelling including annular dilation causing tricuspid insufficiency and right atrial dysfunction or occasionally by pulmonary valve disease. These changes ultimately cause symptoms of exertional dyspnoea and reduced exercise capacity, and/or signs of right-sided decompensation such as jugular venous distension, hepatomegaly, ascites and peripheral oedema (**Table 1**).(23) Ultimately after longstanding right-sided pressure and/or volume overload, the right heart is unable to provide adequate blood flow through the pulmonary circulation at a normal central venous pressure and cardiac output decreases which ultimately leads to death, if not treated adequately.(23)

It is important to acknowledge that staging phases of RVD and right heart failure vary of time and some patients may not have RVD at rest, but rather during exercise. In contrast to left-sided heart failure, there is currently no clear staging of right heart failure, although attempts have been made to develop a staging system.(3) For right heart failure in the setting of HFpEF, we herein propose a staging system of RVD and right heart failure (**Table 2**). Of note, although lower extremity oedema is a classic sign of chronic right-sided congestion, in the acute setting the causes of lower extremity oedema are more complex, seem not entirely associated with HF severity and central venous pressure, and can mislead clinicians, at least in patients hospitalized for acute heart failure.(24)

Echocardiography

Right ventricular function can be assessed using several methods. Echocardiography is generally the first-line tool for this purpose. TAPSE is most frequently used and has an independent prognostic value in HFpEF.(5,10,25-27) The currently recommended lower limit cut-off for TAPSE is <17mm,(14) although prior studies frequently used <16 mm. Fractional area change (with a lower limit of normal <35%(14)) is also commonly used, and is predictive of all-cause mortality and heart failure hospitalisations in HFpEF.(4,10,26,28). In a recent meta-analysis, both TAPSE (unadjusted hazard ratio [HR] 1.26/5 mm decrease [95% CI 1.16-1.38], p<0.0001) and FAC (HR 1.16/5% decrease [95% CI 1.08-1.24], p<0.0001) were shown to be associated with all-cause and cardiovascular mortality in HFpEF.(7)

Thus, for TAPSE and FAC there is the most available evidence in relation to prognosis in patients with HFpEF. Consequently, these two measures should preferably be assessed, if possible, in all patients with HFpEF. Other echocardiographic indices related to RVD used in HFpEF include RV S' (<9.5 cm/s(14))(4,8,9,29-31) and RV longitudinal strain (>-20%(14)).(9,31) The latter has advantages because it is angle-independent and has the potential ability to detect subtle, regional myocardial changes in HFpEF, when conventional echocardiographic parameters remain within the normal range.(31) In addition, TAPSE and RV S' are sometimes falsely elevated when the LV is hyper-dynamic, due to tethering effects of the LV secondary to both ventricles sharing myocardial muscle fibres.(32) RV strain may be lesser influenced by these tethering effects in this context. The association between RV strain and prognosis has been described in patients with HFpEF,(28) but further evidence from other prospective HFpEF cohorts, using dedicated RV-focused strain imaging, is still needed. Furthermore, the RV index of myocardial performance (RIMP) or RV Tei-index is an index of global RV function. Higher values of RIMP indicate impaired myocardial performance, with upper limit of normal >0.43 (when using pulsed Doppler) and >0.54 (when using tissue Doppler).(14)

Assessment of pulsed-wave Doppler for tricuspid inflow (i.e. tricuspid E/A ratio) or hepatic vein diastolic flow, tissue Doppler for lateral tricuspid annular diastolic velocity, and right atrial size, may all be useful to measure RV diastolic function.(33) However, these diastolic indices are influenced by age, respiration, heart rate, pulmonary pressures and other covariates.(33) Right ventricular diastolic function is not routinely assessed in clinical practice but dysfunction is present, at least during exercise, early in the course of HFpEF and in parallel with LV diastolic dysfunction, probably due to combined myocardial processes that affect both ventricles simultaneously.(34)

Echocardiography is also the first-line tool for the evaluation of increased right-sided pressures and its effect on the RV in the setting of PVD.(13,35) Given the high prevalence of PH in HFpEF, it is recommended to asses direct and indirect echocardiographic signs related to increased pulmonary pressures in all patients with HFpEF. This assessment includes several conventional measures, such as estimation of pulmonary artery systolic pressure (PASP in mmHg) using the tricuspid regurgitation (TR) jet velocity and estimated central venous pressure, RV basal end-diastolic diameter (>41 mm), RV hypertrophy (wall thickness >5 mm), right atrial dilatation (right atrial end-systolic area >18 cm^2) and inferior vena cava size and collapsibility for the estimation of right atrial pressure.(13,35) More specific measures that can be obtained for a non-invasive estimation of pulmonary vascular resistance (PVR) include RV outflow tract (RVOT) notching on the pulse-wave Doppler profiles, and the peak TR velocity/RVOT velocity-time integral.(35) For the latter, a value <0.18 suggests elevated PVR to be unlikely.(35) Echocardiography can also be used to differentiate between PAH and PVD-HFpEF, using left and right atrial size ratio and interatrial and interventricular septal bowing.(35) In patients with PH-HFpEF, interventricular septal bowing may be less pronounced than in PAH due to typically higher left-sided systolic pressures in HFpEF compared to patients with PAH.

Cardiac magnetic resonance imaging

The assessment of the right heart using echocardiography may be challenging, due to its complex geometry, limited echocardiographic windows and high prevalence of obesity and COPD in HFpEF that make imaging and interpretation challenging. Therefore, CMR is increasingly being used and is currently recommended in patients with suspected or established heart failure (Class IC recommendation) for the assessment of myocardial structure and function (including the right heart), in subjects with poor acoustic window (taken account for cautions/contra-indications to CMR).(18) Reduced RV ejection fraction on CMR is associated with worse prognosis in HFpEF,(10,36) and <45% is most commonly used as cut-off for RVD.(37) CMR is also reliable in measuring RV volume and hypertrophy, which may be useful in the setting of PVD-HFpEF. In addition, the pulmonary artery to aorta diameter ratio seems useful as non-invasive indicator of the presence of PH in HFpEF.(38)

Quantification of focal and diffuse myocardial fibrosis is also feasible by CMR, using late gadolinium enhancement, T1 time and extracellular matrix fraction.(38,39) Lower LV myocardial post contrast T1 time is associated with higher extracellular matrix and collagen content, and predicts poor prognosis in HFpEF.(39) Late gadolinium enhancement can typically be observed near the septal insertion points of the RV, and this finding is reported in patients with PH(40) and hypertrophic cardiomyopathy,(41) as well as in patients with various aetiologies of HFpEF.(10) As for the RV itself, the myocardial wall is often too thin for reliable quantitative assessment of T1 time using the standard modified look-locker sequences. However, high-resolution look-locker images have higher pixel density and may be reliable for the estimation of extracellular volume content in the thin-walled RV myocardium.(42)

Right ventricular-pulmonary artery coupling

The RV is exquisitely sensitive to changes in afterload,(43) and this heightened afterload-dependence is exaggerated in patients with HFpEF.(4) In view of the frequent presence of PVD and increased RV afterload in HFpEF, consideration of RV-pulmonary artery (RV-PA) coupling is important. This was recently demonstrated in a trial of dobutamine in HFpEF, where greater pulmonary vasodilator response in HFpEF (compared to non-heart failure controls) resulted in improved RV-PA coupling.(29)

The gold standard assessment of RV-PA coupling involves invasive pressure-volume loops, but this method is cumbersome and not without risk.(43) Recent studies have examined RV-PA coupling non-invasively in patients with pulmonary hypertension (PH).(44-46) Guazzi *et al*. proposed an echocardiographic estimate of RV-PA coupling in heart failure, using both TAPSE and PASP.(47) Reduced TAPSE/PASP ratio was associated with worse prognosis, both in HFrEF and in HFpEF,(11,47-49) and a prognostic cut-off of this ratio was identified: <0.36.(11,47,49) In a study with parallel invasive pulmonary haemodynamic assessment, the TAPSE/PASP ratio was gradually reduced across the PA resistance-compliance hyperbolic relationship, which suggests that this simple, non-invasive marker could reflect the 'operating load' the RV has to work against and this ratio may already been reduced when cardiac output is still preserved.(48) Reduced TAPSE/PASP ratio also seems to be a reliable non-invasive parameter to identify HFpEF patients with a high likelihood of having additional pre-capillary PH.(49)

Finally, RV stroke work index can be estimated non-invasively in patients with heart failure, by calculating the RV contraction pressure index as the product of TAPSE and the transtricuspid systolic pressure gradient.(50,51)

Right ventricular function during exercise

Evaluation of right-sided filling pressures, RV-PA coupling and RV systolic and diastolic function during exercise has the potential to enhance haemodynamic assessment at different stages of HFpEF.(34) Patients with advanced HFpEF and concomitant PVD may have normal RV functions at rest, but RVD may be present during exercise, if the ability of the pulmonary vasculature to dilate in response to increased cardiac output is lost. RV free wall strain may be a sensitive indicator for this phenomenon. On the contrary, impaired RV function at rest may not necessarily also imply a worse adaptive contractile response during exercise in patients with heart failure.(52) An additive role for cardiopulmonary exercise testing in patients with PAH is recently highlighted in the 2016 European Society Guidelines on the Diagnosis and Management of PH,(53) and may also be useful to explore the various phenotypes and different levels of risk in patients with heart failure.(52,54)

Remarkably, studies by Borlaug *et al.* have shown that RV-PA uncoupling occurs during exercise, even in the earlier stages of HFpEF.(34) Elevation in left atrial pressure and impaired left atria strain response during exercise (despite preserved LV ejection fraction) is pathognomonic for HFpEF,(55,56) and this acutely shifts the PA resistance-compliance relationship leftward, causing an increase in pulsatile RV load.(56,57) Assessment of PA pressure-flow relationships with exercise has been proposed as a useful and prognostically relevant metric to evaluate vascular reserve in HFpEF,(58) and some HFpEF phenotypes, such as those with obesity-related HFpEF, may display greater abnormalities in RV-PA coupling during exercise that potentially move forward towards therapeutic implications.(59)

AETIOLOGY

Pulmonary hypertension

The most important mechanism of RVD in HFpEF is contractile impairment and afterload mismatch in the setting of PH-HFpEF (**Figure 1**).(4,5) Pulmonary hypertension, which

includes both isolated post-capillary and combined post- and pre-capillary PH, is a common finding in patients with HFpEF and is associated with worse symptoms, reduced exercise capacity, higher natriuretic peptide levels and increased hospitalisation rates and mortality.(49,60,61) In response to increased vascular load, the RV adapts by increased myocardial contractility and wall thickness ("coupling").(43) In the next stage, the RV dilates and heart rate increases to maintain sufficient cardiac output, which will lead to increased wall stress and oxygen demand.(43) Ultimately after longstanding high metabolic demand, the RV is unable to maintain cardiac output ("uncoupling"), which is accompanied by signs and symptoms of severe right heart failure.(43)

In a population-based study from Lam *et al.*, up to 83% of all-comers with HFpEF had non-invasive evidence of PH (as defined by echocardiography-derived PASP >35 mmHg).(62) In a later invasive study by Melenovsky *et al.* in 96 patients with HFpEF (on the basis of Framingham criteria, LV ejection fraction ≥50% and increased LV filling pressures), 81% of the patients had PH (defined as mean pulmonary artery pressure ≥25 mmHg).(4) On the contrary, Leung *et al.* previously reported PH to be present in 53% in their invasive study, although they only included patients with high LV end-diastolic pressure, and ~22% of patients were diagnosed with left heart failure.(63) Data from the large TOPCAT clinical trial revealed a much lower PH prevalence rate of 36%, based on tricuspid jet velocity >2.9 m/s.(64) The presence of PH may thus vary considerably among different HFpEF populations and may be influenced by the different stages of HFpEF severity enrolled in the different studies (e.g. clinical trials versus community-based studies), as well as the frequent exclusion of comorbidities in most clinical trials that are strongly associated with PH, such as severe renal dysfunction and significant pulmonary disease.(7,65) If pulmonary haemodynamics are not invasively assessed, it remains unclear which amount of included patients with heart

failure and a preserved LV ejection fraction have PH due to (concomitant) pulmonary arterial hypertension/fibrosis, COPD or other systemic diseases.

Ventricular interdependence

One of the key features in HFpEF is LV diastolic dysfunction. Although, global LV ejection fraction is by definition preserved in HFpEF, there is evidence of LV contractile dysfunction.(66) Because both ventricles share myocardial muscle fibres and the interventricular septum, approximately 20 to 40% of RV systolic performance can be attributed to LV contraction.(32) This concept of systolic ventricular interdependence might be the mechanism behind the previously reported associations between subtly reduced LV systolic function and the higher prevalence of RVD in HFpEF.(4,5,10) In the setting of regional LV contractile dysfunction despite preserved global LV ejection fraction in HFpEF, the direct contribution of LV contraction to RV systolic function is also reduced. This left-to-right ventricular contribution is also lost in the setting of RV-pacing in HFpEF.

Diastolic ventricular interdependence (DVI) is also important in HFpEF. Approximately 30 to 40% of LV diastolic pressures is related to extrinsic forces including right heart pressure and pericardial restraint.(67) Even slight increase in pulmonary pressure already leads to a leftward septal shift and impaired LV diastolic compliance induced by DVI in the absence of prior intrinsic LV disease.(68) This effect is already present in patients with even mild to moderate PH, and may aggravate clinical manifestation of (exertional) dyspnoea.(68) Diastolic ventricular interdependence with inhomogeneous septal movement can be assessed using 2-D speckle tracking echocardiographic strain (**Figure 2**). Diastolic ventricular interdependence might also belong to the mechanisms that contribute to septal mechanical delay and asynchronicity, which can be found in ~20% of the patients with HFpEF.(69) Haemodynamic changes induced by DVI are also accompanied by neurohormonal

activation.(68) Recent data have shown that DVI is increased in HFpEF patients with obesity, coupled with increases in right heart remodelling and dysfunction.(59) Intriguingly, the degree of DVI is synergistically enhanced as PA pressure increased in these patients. An important repercussion of this phenomenon is that higher pulmonary venous pressure is required to achieve a given LV transmural distending pressure, which is then transmitted back to further increase of RV afterload.(59)

Finally, aortic stiffness, reduced systemic compliance and ventricular-arterial coupling, especially in the hypertensive patient, contribute importantly to the diagnosis and clinical syndrome of HFpEF.(70,71) Both the main pulmonary artery and the aortic root are situated close to each other (**Figure 3C**). In children with PAH, severe dilation of the pulmonary artery was recently reported to be associated with limited aortic expansion during systole, which may have impact on LV performance and left-sided haemodynamics.(72) Whether there is existence of such "vascular interdependence" in patients with PVD-HFpEF and severe PA dilatation, needs further study.

Atrial fibrillation

Atrial fibrillation (AF) is also common in HFpEF, with a prevalence that ranges between 21 to 54% in individual registries and trials,(73,74) and approaches 67% when considering the entire lifetime of a patient.(75) Atrial fibrillation is independently associated with exercise intolerance and poor prognosis, and is in part a reflection of worsening HFpEF.(76) Several studies have indicated a link between AF and the presence of RVD in HFpEF.(4,5,11,76) Both may relate to HFpEF, in which increased LV filling pressures leads to left atrial stretch and remodelling on the one hand;(74) and furthermore to increased pulmonary pressures and RV afterload. Indeed, HFpEF patients with AF have higher pulmonary capillary wedge

pressure (PCWP) and mean pulmonary artery pressure (PAP), compared to HFpEF patients in sinus rhythm.(76)

Left atrial function and adverse remodelling is important in the context of heart failure.(77) As left atrial function deteriorates, particularly with development of AF, there is more profound pulmonary vascular dysfunction and consequent impairment in RV function in patients with HFpEF.(78) However, it is not just afterload mismatch, as RV shortening is worse in HFpEF patients with AF for any given PA pressure load.(4) Possible mechanisms might be related to decreased RV longitudinal contraction and rhythm irregularity with negative inotropic effects in the setting of AF,(79,80) although we lack prospective studies that addressed such hypotheses in HFpEF. Conversely, RVD is also a strong predictor of the occurrence of AF after acute decompensated heart failure.(81)

Atrial fibrillation is also prevalent patients with PH without left heart failure (~20 to 23%),(82,83) and its presence is also associated with more right atrial dilation and higher right atrial pressures, compared to PH patients without AF.(83) Reduced TAPSE and right atrial dilatation was previously linked to both history and development of AF in patients with hypertrophic cardiomyopathy.(84) To what extent *right atrial* overload beyond *left atrial* overload may facilitate the onset or progression of AF, in patients with PVD-HFpEF, needs to be evaluated.

Coronary artery disease

Coronary artery disease is associated with more advanced impairment of RV function in both HFpEF and HFrEF.(4,5,11) Although patients with large myocardial infarctions do not typically present as HFpEF, coronary artery disease is also common in HFpEF, up to 50-66%.(85) Although, the RV has the ability to recover from an acute ischaemic insult and isolated RV infarction is rare,(86,87) single occlusion of proximal right coronary artery or of

dominant circumflex coronary artery may result in RV systolic dysfunction while global LV systolic function is preserved. Furthermore, approximately one-third of HFpEF patients with coronary artery disease had previously undergone coronary artery bypass grafting.(85) In patients undergoing such major cardiac surgery and/or valve replacement, TAPSE may be considerably reduced, even up to one year after surgery.(88-90) Reduction in RV filling and contraction after cardiac surgery seems independent of cardiopulmonary bypass and is not seen in patients receiving percutaneous interventions.(91) The significant reduction in TAPSE may therefore be mediated by pericardial adhesions following pericardiectomy.(91) Potential other mechanisms have also been described, such as cytokine release, RV infarction due to ischemia or air emboli, and inflammation or effusion post-surgery.(91)

Besides the contribution of obstructive epicardial coronary artery disease, coronary microvascular dysfunction is also reported in patients with HFpEF without history of obstructive coronary artery disease.(92) Microvascular dysfunction might be an early but important stage in the pathogenesis in HFpEF, and may be equally important for both ventricles. Further research regarding the importance of myocardial flow reserve and microvascular dysfunction is clearly warranted.(93)

Non-cardiac comorbidities

Several non-cardiac comorbidities such as obesity, diabetes mellitus, renal dysfunction, COPD and hypertension are known to adversely impact myocardial function and remodelling via systemic pathways, including inflammation and endothelial dysfunction. The adverse impact of these processes in HFpEF has traditionally been focused on the LV.(94) However, given that these involve systemically circulating factors, there may plausibly be simultaneous involvement of the RV, resulting in RV remodelling and dysfunction. Co-existence of LV and RV remodelling in HFpEF has been described by Borlaug *et al.* Patients with HFpEF had

impaired RV reserve and high filling pressures with exercise, even in the early stages of the disease, and similar to changes observed in the LV.(34)

In subjects without cardiovascular disease, obesity may also be related to changes in RV structure and function.(95,96) Among the different comorbidities, obesity has recently been shown to be associated with more profound abnormalities in RV-PA coupling.(59) As compared to HFpEF patients without obesity, patients with obesity display more RV remodelling, greater plasma volume expansion, more ventricular interdependence and pericardial restraint, higher filling pressures, and greater pulmonary vascular dysfunction during exercise. Right ventricular dilatation and dysfunction in obesity may be related in part to excessive volume loading, which is typical of obesity-related HFpEF.(59) This hypothesis is supported by recent data revealing the development of RV dilatation and dysfunction following creation of arteriovenous fistula for dialysis access.(97)

Several HFpEF-associated comorbidities such as COPD may contribute to increased RV afterload via direct pulmonary vascular effects (**Figure 3**),(98) or impact RV remodelling by load-independent pathways.(99) Long standing systemic hypertension leads to LV hypertrophy and stiffening, but may also result in RV remodelling, independent of pulmonary pressures.(100,101) This phenomenon has been explained by circulating or paracrine vasoactive and trophic factors, targeting both ventricles,(102) and pressure-driven septal remodelling which in turn influences RV performance.(101,103)

Furthermore, systemic hypertension often interacts with obesity and diabetes mellitus in the development of RV remodelling and dysfunction in patients with the metabolic syndrome.(104-106) In the diabetic heart, early signs of RV diastolic dysfunction may be observed, even prior to development of RV systolic dysfunction.(107)

Renal dysfunction and HFpEF often co-exist, and each condition may contribute to progression of the other in a vicious cycle via inflammation and endothelial dysfunction.(108)

In left-sided heart failure, RVD is also strongly associated with renal dysfunction, mainly due to venous congestion resulting from chronic backward failure.(109) In a large cohort of 299 patients with HFpEF, renal dysfunction was also reported to be independently associated with higher PA pressures and lower RV free wall strain.(17) In addition, renal dysfunction strongly facilitates hypervolemia, which is a major factor of right-sided decompensation, even in mild stages of right heart dysfunction.(110)

In some patients, wild-type transthyretin amyloidosis (ATTRwt) is an unrecognized cause of HFpEF.(111) The RV may also be involved in advanced ATTRwt (**Figure 4**), although its clinical relevance is currently unknown.

PATHOPHYSIOLOGY

In left-sided heart failure, the RV myocardium may be subject to several stressors, where pressure overload in the setting of pulmonary vascular disease is most prominent. Chronic pulmonary congestion in left-sided heart failure leads to morphological changes of the pulmonary vasculature, including muscularization of pulmonary venules, haemangiomatosis-like endothelial cell proliferation in pulmonary capillaries and pulmonary arterial remodelling with intimal hypertrophy.(60) Pulmonary vascular remodelling in left-sided heart failure is different and seems more reversible than the remodelling patterns seen in patients with idiopathic PAH, in which there are more irreversible neointimal lesions such as concentric laminar intimal fibrosis and plexiform lesions.(112) The reversibility of severe PVD in patients with left-sided heart failure was previously demonstrated in a small group of patients with end-stage left-sided heart failure and presumably fixed high PVR. After implantation of LV assist device support, a progressive decrease of PVR and normalization of pulmonary pressures was observed.(113)

When the RV myocardium is exposed to increased afterload, several neurohormonal and molecular pathways are activated, such as cytokine release, activation of the endothelin system, the renin-angiotensin-aldosterone system (RAAS), the autonomic nervous system, and release of natriuretic peptides (**Figure 5**).(3) The myocardial wall of the normally unstressed RV thickens in order to maintain cardiac output. This remodelling pattern eventually leads to an increased mismatch between myocardial blood supply and oxygen demand, resulting in myocardial ischemia and downstream effects such as collagen formation and fibrosis.(114) Oxidative stress triggers the production of reactive oxygen species, limits the availability of nitric oxide (NO) and significantly contributes to cell necrosis and apoptosis through release of inflammatory cytokines, such as tumour necrosis factor-alpha, interleukin-1 and interleukin-6. Oxidative stress and cytokine release degrade the extracellular matrix and myofibrils, and enhance collage formation, resulting in RV dilatation and myocardial fibrosis. The activation of the endothelin system is important in the setting of PVD and resultant RV failure.(3) Endothelin-1 is a potent vasoconstrictor and has pro-inflammatory and proliferative properties. Enhanced expression of endothelin-1 and endothelin receptors is seen in experimental pulmonary artery banding models.(115) Elevated levels of catecholamines and overstimulation of the β-adrenergic receptors in the setting of RV failure, further stimulates maladaptive myocardial remodelling. For instance, in the presence of RV failure due to pulmonary artery banding, decreased expression of β-adrenergic receptors in the RV was observed.(116)

Apelin is an endogenous ligand for the APJ receptor that is present on endothelial cells, vascular smooth muscle cells and cardiomyocytes.(117,118) The apelin-APJ signalling pathway is a modulator of smooth muscle tone and myocardial contractility and can be regarded as a cardio-protective neurohormonal system.(119,120) Disruption of apelin-APJ signalling seems to play an important role in vascular remodelling and hyperproliferation of

pulmonary artery endothelial and smooth muscle cells in PVD.(121) The apelin-APJ system is also down-regulated in patients with systolic left-sided heart failure and may therefore be a potential therapeutic target in this context.(122,123)

Besides these cellular and molecular pathways involved in response to increased afterload, the changes in the pulmonary vasculature itself also leads to impaired pulmonary function and gas exchange.(60) Reduced diffusion capacity of the lung in patients with PVD-HFpEF is strongly associated with exercise intolerance and increased mortality.(124,125)

Finally, several of these pathways may also be activated in HFpEF – independent of PVD – and may be due to direct effects of comorbidities such as obesity, hypertension and diabetes mellitus, which activate the release of reactive oxygen species via inflammatory cytokines and induce endothelial dysfunction and adverse remodelling of cardiomyocytes.(94) However, in patients with HFpEF, the LV displays more concentric myocardial remodelling, stiffening and diastolic dysfunction, while the RV shows more eccentric remodelling with hypertrophy, dilatation and systolic failure as a result of predominant increased afterload (**Figure 5**).

TREATMENT

The high prevalence of RVD and its potent prognostic consequences in HFpEF support the development of treatment strategies targeting the right side in HFpEF. The primary strategies of interest are 1) the reduction of pulmonary pressures in patients with PH-HFpEF using diuretics for congestion, and potentially novel vasoactive drugs targeting the cyclic guanosine monophosphate and endothelin pathways, and 2) to directly target RV myocardial tissue. Until now, many previous attempts have demonstrated neutral results.(60) There is even concern that several PH-targeted therapies could rather have detrimental effects in HFpEF, due to rapid increases of LV filling pressures and resulting acute pulmonary oedema.(126) As a consequence, there are currently no established strategies to treat PVD and RVD in HFpEF,

and the current European Society of Cardiology Guidelines for the Management of Pulmonary Hypertension therefore provides a class III recommendation for PAH-approved treatment for patients with PH due to left heart disease (group 2 PH).(53) Potential treatment strategies are summarized in **Table 3**. The majority of these therapies target the different pathways described above.

There is currently an unmet need for further study into the development of PVD in patients with HFpEF. It is important to acknowledge that the presence of PVD in patients with a preserved LV ejection fraction is a wide spectrum.(16,127) On the one side of this spectrum patients may present with "pure PVD" with high PVR and normal pulmonary capillary wedge pressure (both at rest and with exercise), and on the opposite side of this spectrum patients may have "pure HFpEF" with increased pulmonary wedge pressure and normal PVR.(127) The former group of patients responses well to PAH-targeted therapies while this response to these specific therapies gradually decreases along this spectrum towards patients with pure HFpEF.(16) It may therefore be recommended to invasively measure pulmonary haemodynamics in HFpEF patients with suspected PH and to evaluate the position of each patient on this spectrum and select for specific treatment options. Furthermore, a multidisciplinary strategy with cooperation of a pulmonologist may be recommended. Of note, drugs approved for PAH are also not recommended in patients with PH due to lung diseases (class IIIC recommendation).(53)

In clinical practice, in many patients with RVD in HFpEF, diuretics are not given in sufficiently high dosages to ensure decongestion/euvolemia. Hypervolemia is a major driver of decompensation in left-heart failure and early identification of patients who are at risk for diuretic resistance is important.(51,128) In addition, patients should be counselled to avoid excessive fluid and salt intake, and especially obese older patients with stable HFpEF benefit from caloric restriction and aerobic exercise training.(129) It is now recommended to

encourage regular aerobic exercise training in all patients with heart failure, to improve their functional capacity and symptoms (class IA recommendation).(18)

Cyclic guanosine monophosphate and nitric oxide pathway

Cyclic guanosine monophosphate (cGMP) and its target protein kinase G (PKG) are regulators of ion channel conductance and cellular apoptosis, and have an effect on vascular smooth muscle relaxation, vasodilatation and increased blood flow.(130) Phosphodiesterase (PDE) inhibitors prevent the breakdown of cGMP and thereby enhance the vasodilator effects of cGMP.(130)

The PDE type 5 inhibitor sildenafil is an established drug for patients with World Health Organization Group 1 PAH.(53) Sildenafil has also been tested in HFpEF, yet with mixed results.(131-133) In a recent post-hoc analysis from a Dutch trial, conducted in 52 HFpEF patients mean PAP ≥25 mmHg and PCWP ≥15 mmHg, sildenafil did not improve TAPSE and RV S' compared with placebo.(134) In a sub analysis from the RELAX trial in HFpEF patients with and without PH, sildenafil also did not improve TAPSE. An earlier Italian trial, in patients with HFpEF and predominant combined post- and pre-capillary PH, did show improvement in TAPSE and invasively assessed RV contractile state in the sildenafil treatment group.(131) The findings of a partial functional recovery in advanced RV failure associated with HFpEF by sildenafil were paralleled by a study providing mechanistic insights (i.e. restoration of cGMP pulmonary vascular concentration) on reported benefits. Although sildenafil will not be beneficial in all patients with HFpEF, it remains to be evaluated whether selected HFpEF patients with high PVR will benefit from PDE type 5 inhibition. Very recently, the PDE type 5A inhibitor vardenafil was tested in an animal model with Zucker diabetic fatty rats. It was reported that the development of HFpEF (defined as myocardial stiffness and diastolic dysfunction) was prevented and the activity of the cGMP-

PKG axis was restored in this experimental diabetes mellitus-associated HFpEF model.(135) Whether early treatment with PDE type 5 inhibition may prevent worsening heart failure in humans with diabetes mellitus-associated HFpEF is unknown.(136)

PDE type 9A regulates natriuretic peptide-stimulated rather than NO-stimulated cGMP. PDE type 9A is expressed in human myocytes, is upregulated in the setting of myocardial hypertrophy and heart failure, and has been suggested as a potential therapeutic target in stress-induced heart disease.(137) Its potential as a target in patients with HFpEF and predominant RV failure is currently unknown.

Riociguat is a soluble guanylate-cyclase stimulator, that induces vasodilatation, has antifibrotic, antiproliferative, anti-inflammatory properties, and is effective in patients with PVR.(53) In the small DILATE-1 trial, riociguat did not improve mean PAP in patients with PH-HFpEF, but did increase stroke volume and cardiac index.(138) In addition, riociguat significantly decreased systolic blood pressure, systemic vascular resistance and RV end-diastolic area, without changing PCWP or PVR.(138) Riociguat is currently being tested in another phase 2 trial for its effect on pulmonary haemodynamics as well as RV size and function on cardiac MRI, in patients with PH-HFpEF (NCT02744339).

Another phase 2 with the soluble guanylate-cyclase stimulator vericiguat in HFpEF (SOCRATES-PRESERVED, NCT01951638) has recently been completed. Vericiguat was well tolerated, did not change NT-proBNP and left atrial volume at 12 weeks compared with placebo, but was associated with improvement in quality of life.(139) RV-related endpoints were not included in the initial study protocol.(140)

Recent data from the Swedish Heart Failure Registry in an unselected HFpEF population demonstrated that the use of conventional nitrates was not associated with improvements in all-cause mortality or heart failure hospitalizations.(141) In the NEAT-HFpEF randomized controlled trial, the patients with HFpEF who received isosorbide mononitrate were less

active, and did not have better quality of life or submaximal exercise capacity compared to patients who received placebo.(142)

Inorganic nitrite administration represents a promising new therapy being tested in HFpEF. Nitrate and nitrite were formerly considered as inert by-products of NO metabolism, but it is now clear that these anions function as an important in vivo reservoir to generate NO under hypoxic circumstances in a NO synthase-independent fashion. Nitrite is reduced to NO by a variety of proteins including haemoglobin and myoglobin. This reaction is enhanced in the setting of hypoxia and acidosis, as develops in the tissues and veins during exercise. Intravenous nitrite was shown to reduce PA pressure and biventricular filling pressures in patients with HFpEF, with greater effect during exercise.(143) Cardiac output reserve was also enhanced. Inhaled, nebulized sodium nitrite has also been shown to reduce PA pressures and lower filling pressures at rest and during exercise, with improvements in PA compliance.(144,145) While acute administration of nitrite did not reduce PVR in the entire group of patients with HFpEF, it did lower PVR in those patients with higher PVR.(144) Nitrite is currently being tested in a National Institute of Health sponsored trial: Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF (INDIE-HFpEF, NCT02742129).

In conclusion, impairment of the NO-cGMP signalling pathway contributes to increased pulmonary pressures in patients with HFpEF. Currently, no therapies that specifically act on the NO-cGMP pathway have clearly proven to be beneficial in patients with HFpEF. However, there is minor evidence that some patients with HFpEF, especially those with advanced PVD and additional pre-capillary PH, might benefit from such therapies and several clinical trials are currently underway (**Table 3**).

Endothelin pathway

Endothelin receptor antagonists such as Bosentan are effective in World Health Organization Group 1 PAH.(53) On the contrary, Bosentan exerts rather detrimental effects in patients with PH-HFpEF due to acute pulmonary oedema.(126) Sitaxsentan, a selective endothelin type A (ETA) receptor antagonist, was shown to improve treadmill exercise time in patients with HFpEF treated for 24 weeks.(146)

Recently, it was demonstrated that endothelin-1 levels were elevated in humans with chronic stable HFpEF and these patients had increased myocardial hypertrophy.(147) In the same translational study, the endothelin-1 receptor antagonist macitentan reduced myocardial hypertrophy and stiffening via antihypertrophic mechanisms in a murine HFpEF model.(147) Endotelin-1 levels were also reported to be higher in HFpEF patients with diabetes mellitus, compared to patients without diabetes mellitus.(148) Whether there is a link between endothelin-1 levels, diabetes mellitus and RV hypertrophy and dysfunction in HFpEF, remains unknown. The effects of macitentan on RV performance in HFpEF also require further study. Macitentan was recently under study in patients with combined post- and pre-capillary PH due to LV systolic and diastolic dysfunction (MELODY-1, NCT02070991) and the primary results were presented at the 2017 Congress of the American College of Cardiology.(149) The macitentan group showed no change in PVR during 12 weeks. Moreover, this group was more likely to experience the primary composite endpoint of significant fluid retention or worsening functional class.(149)

Prostacyclin pathway

Prostacyclin is produced by endothelial cells and induce vasodilatation, inhibits platelet aggregation and has anti-proliferative effects.(53) Prostacycline analogues such as epoprostenol and iloprost are established treatments for patients with PAH.(53) Chronic intravenous epoprostenol is associated with increased risk of mortality in patients with

HFrEF, although the exact mechanisms are unclear.(150) In a small pilot study in patients with PH-HFpEF, acute inhalation of iloprost resulted in a significant reduction in PAP and PVR after 15 minutes.(151) No data regarding any effect of iloprost on RV performance in HFpEF are currently available. Treprostinil is another prostacyclin analogue that is indicated for the treatment of PAH,(53) and will be tested in patients with PH-HFpEF for its effect on 6-minute walk distance, functional class and NT-proBNP levels (NCT03037580).

Neurohormonal inhibition

Chronic increased afterload of the RV activates the autonomic nervous system and the RAAS system. However, there is insufficient evidence whether neurohormonal inhibition is beneficial in the setting of RV failure.

Nebivolol is a β-adrenergic receptor antagonist with vasodilator properties. Nebivolol is reported to be favourable in patients with PAH.(152) The role of beta-blockade in HFpEF is uncertain. Data from the SENIORS trial suggest that nebivolol might be as useful in patients with HFpEF as it was for patients with HFrEF,(153) and observational data from the Swedish Heart Failure Registry also suggests that beta-blockers may be beneficial in HFpEF.(154) However, the ELANDD trial did not show improvement by nebivolol in 6-minute walking distance in 116 patients with HFpEF, but no subgroup analyses for patients with RVD are available.(155) Hence, there is clearly insufficient evidence for the use of nebivolol in HFpEF to give it a place in the current guidelines, and more adequately powered studies are needed. Nebivolol is currently being tested in a phase 4 trial for its potential effect on PVR and 6-minute walk distance in patients with PH-HFpEF (NCT02053246).

Carvedilol is a β1/β2/α1-blocker, has anti-inflammatory and antioxidant properties, and might prevent pulmonary vascular remodelling.(156) Previously, carvedilol resulted in significant improvement in E/A ratio in patients with HFpEF from the SWEDIC trial.(157) Carvedilol

has also been demonstrated to improve RV systolic function in patients with HFrEF,(158) yet any effect on the RV in HFpEF is currently unknown.

Several randomized controlled trials that investigated RAAS inhibition in HFpEF have not demonstrated improvement in outcome, and thus RAAS inhibition has no recommendation in the guidelines for the treatment of HFpEF.(18,159-161) However, observational data suggests that RAAS inhibition may be beneficial in heart failure with LV ejection fraction ≥40%.(162) RAAS inhibition was beneficial in several animal models with PVR, since it was reported to prevent RV hypertrophy, dysfunction and fibrosis, but published results are conflicting.(156,163,164) In an earlier trial, captopril was tested in 14 male patients with HFrEF in combination with reduced RV ejection fraction, and captopril was demonstrated to improve RV function and filling pressures.(165) Furthermore, it was also reported in another small study in 40 patients with systemic hypertension, that RAAS inhibition resulted in improvement in RV global function, independent of changes in systemic blood pressure.(166)

The TOPCAT trial investigated the aldosterone antagonist spironolactone in patients with HFpEF and demonstrated no reduction in the composite primary outcome of cardiovascular death, aborted cardiac arrest or hospitalization for heart failure.(167) However, spironolactone slightly reduced the risk of heart failure hospitalizations compared with placebo. In addition, subgroup analysis demonstrated that the primary outcome was met in the patients with elevated natriuretic peptides at baseline.(167) In the mechanistic Aldo-DHF trial in patients with HFpEF, spironolactone reduced E/e', an estimate of LV filling pressures and leaded to improvements in cardiac structure (i.e. reduction in LV mass index) and reduction in NT-proBNP levels, but failed to improve symptoms or exercise capacity.(168) Aldosterone antagonists should be considered in the setting of fluid overload in patients with PAH.(53) It was reported in an animal model of PAH that spironolactone and eplerenone improved pulmonary haemodynamics.(169) In a sub study from the TOPCAT trial in 239 patients with

serial echocardiographic assessment, randomization to spironolactone was not associated with significant changes in RV function and pulmonary pressures.(170)

Based upon the observation that beta-adrenergic stimulation improves pulmonary vascular function in HFpEF patients more than controls,(29) the Inhaled Beta-adrenergic Agonists to Treat Pulmonary Vascular Disease in Heart Failure With Preserved EF (BEAT-HFpEF, NCT0288563) is a randomized controlled trial designed to investigate the inhalation of the β2-adrenergic agonist albuterol on changes in PVR in patients with HFpEF, with resting PCWP >15 mmHg or PCWP ≥25 mmHg with exercise.

Other drugs and experimental treatments

Ranolazine is an inhibitor of the late sodium channel current and is approved for the treatment of chronic stable angina. In a small open-label pilot study in 11 patients with symptomatic PAH, ranolazine (1,000 mg twice daily) was administered for three months and was demonstrated to be safe and associated with improvement in functional class, reduction in RV size and improvement in RV strain during exercise.(171) In another non-randomized pilot study in 10 patients with HFpEF and isolated post-capillary PH, mean PAP and PCWP significantly decreased, PVR remained unchanged, and 6-minute walking distance increased, during six months treatment with ranolazine (1,000 mg daily).(172) Clearly, further evidence in adequately powered, prospective studies is needed to investigate the effects of ranolazine on prognostic endpoints in PH-HFpEF.

Milrinone is a PDE type 3 inhibitor that has been studied for reduction of RV afterload in patients undergoing LV assist device implantation,(173) in an experimental dog model with pulmonary artery banding and RV failure,(174) and in infants with PH.(175) Recently in a small study, Kaye *et al.* investigated the use of intravenous milrinone in 20 patients with HFpEF and demonstrated improvement in pulmonary haemodynamics during exercise.(176)

Recent recommendation suggests that levosimendan may be preferentially indicated over dobutamine in patients with pulmonary hypertension caused by left heart disease.(110) Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor that has been proven to improve outcomes in patients with HFrEF.(177) Sacubitril/valsartan has previously also been tested in a phase II trial in 301 patients with HFpEF, but did not result in a reduction of TR velocity during 36 weeks treatment, compared with placebo.(178)

Although the evidence is limited, calcium channel blockers may be effective for the treatment of systemic hypertension in HFpEF. Verapamil might have a beneficial effect on symptoms and diastolic dysfunction in patients with congestive heart failure and normal LV systolic function.(179) Calcium channel blockers are recommended in specific patients with PAH who demonstrate a favourable response to acute vasodilator testing, but close follow-up is warranted.(53)

Digoxin has no recommendation in the guidelines for the treatment of HFpEF.(18,180) There is also no convincing data available for the use of digoxin in the setting of PH.(53) In a small, non-randomized prospective study in 17 patients with PAH in combination with RV failure and normal LV function, treatment with digoxin modestly increased cardiac output.(181)

It was previously reported from a small randomized trial in 20 patients with PAH that systemic infusion of apelin (10-100 nmol/min) resulted in increased cardiac output and stroke volume and in a reduction of PVR.(182) In two other small trials with respectively eight and twelve subjects, administration of apelin infusion was also demonstrated to have a positive effect on cardiac output, systemic blood pressure and peripheral vascular resistance in patients with chronic left-sided heart failure.(118,183) Apelin agonism is currently not under investigation in patients with HFpEF.

Device therapies

The REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study was an open-label, single-arm, phase 1 study to assess the performance and safety of a transcatheter interatrial shunt device in HFpEF patients >40 years who remain symptomatic despite maximum pharmacological therapy. The use of this device was safe and reduced left atrial pressures during exercise and thus demonstrated its potential efficacy in patients with HFpEF.(184) The REDUCE LAP-HF study excluded patients with more than mild RVD as estimated by echocardiography, or TAPSE <14 mm, or RV size ≥ LV size, or RV FAC <35%, and with resting central venous pressure >14 mmHg and with evidence of PH with PVR >4 Woods units. During six months following the procedure, right atrial pressure and dimension, as well as RV end-diastolic volume, increased significantly. Whether the observed haemodynamic effects, and the sudden change from pressure to volume overload of the right heart, will be beneficial during longer follow-up in patients with HFpEF remains to be evaluated. The intraatrial shunt device is currently being studied in a randomized controlled, patient-blinded setting, with a non-implant control group (NCT01913613).(185)

In 2011, the results of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) Trial were published. Daily monitoring of pulmonary pressures in patients with heart failure using a wireless PA pressure monitor – and by acting on elevation of pulmonary pressures with up titration of diuretics, RAAS inhibitors or vasodilator drugs – significantly reduced pulmonary artery pressures and hospitalisations for heart failure, both in trial setting and in real-world patients.(186-189) Wireless monitoring of PA now has a class IIb-B recommendation in the 2016 European Society of Cardiology Heart Failure Management Guidelines in order to reduce the risk of recurrent hospitalizations for heart failure.(18) In a sub study from the CHAMPION trial in 119 patients with HFpEF, it was also shown that the number of hospitalizations for heart failure were reduced in the treatment group with active monitoring

of pulmonary pressures, compared with controls and this reduction seemed to be primarily achieved by adequate titration of loop and thiazide diuretics.(188,190) Wireless monitoring of PA pressures may therefore be especially beneficial in patients with RVD and renal dysfunction, in whom it is difficult to control volume overload.

In another small study, pulmonary arterial denervation using a radiofrequency ablation catheter was reported to improve pulmonary haemodynamics in patients with PAH,(191,192) as well as in one patient with PH in combination with left-sided heart failure.(193) Pulmonary arterial denervation is currently being tested in patients with PH associated with left heart failure (NCT02220335).

CONCLUSION

It is now well-established that RVD is highly prevalent and contributes to poor prognosis in HFpEF. We summarized available evidence regarding the prevalence, diagnosis, risk factors, pathophysiology and potential therapeutic targets for the right heart in HFpEF. The present recommendation paper also highlighted important remaining knowledge gaps and future directions (**Table 4**). Prospective studies are urgently needed to clarify the mechanisms underlying right heart remodelling and dysfunction, and to provide effective treatments that improve morbidity and mortality in HFpEF. We therefore advocate greater focus on the often neglected right side of the heart, and for the introduction of standardized endpoints of right heart dysfunction and failure in future clinical trials in HFpEF.

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FIGURE LEGENDS

Figure 1: Pathways leading to right ventricular dysfunction in heart failure with preserved ejection fraction.

The predominant mechanism for the development of right ventricular dysfunction (RVD) is the load-dependent pathway, caused by 1) post-capillary pulmonary hypertension (PH) due to increased left-sided filling pressures and 2) aggravated pulmonary vascular disease (PVD) with chronic pulmonary congestion and concomitant factors such as ageing, male sex, chronic obstructive pulmonary disease (COPD) and chronic thromboembolic pulmonary hypertension (CTEPH). Chronically increased afterload in PVD-HFpEF will lead to RV hypertrophy, dilatation and dysfunction (**B**). Increased right-sided pressure will also lead to leftward septal bowing and this 'diastolic ventricular interaction' further impairs left-sided filling. In isolated post-capillary PH, left atrial size typically increases before or together with increase in pulmonary artery pressure (PAP) while in the setting of additional pre-capillary PH, right atrial size may surpass left atrial size. There are also several load-independent factors associated with development of RVD. These include 1) mechanistic factors, such as atrial fibrillation (AF), right-sided pacing and 'systolic ventricular interaction' and 2) intrinsic myocardial processes that involve systemic inflammation and endothelial dysfunction caused by non-cardiac comorbidities and for instance right-sided involvement in wild-type transthyretin amyloidosis (ATTRwt) (**A**). CAD coronary artery disease; DM-II diabetes mellitus type 2; OSAS obstructive sleep apnoea syndrome; PCWP pulmonary capillary wedge pressure; PVD pulmonary vascular disease; RV right ventricle; RVP right ventricular pressure.

Figure 2: Inhomogeneous septal movement in a patient with mildly increased pulmonary pressures.

Example of 2-D echocardiographic speckle tracking on the apical four-chamber view in a patient with mildly increased pulmonary pressures. The endocardial borders of the left ventricle were traced (left image) and the left ventricle was divided into three septal (yellow/turquoise/green) and three lateral wall segments (red/blue/pink). Tracing of these segments during the cardiac cycle illustrate a leftward shift in the peak systolic strain of the basal and mid septal segments compared with the lateral wall segments (right image). This shift is caused by increased right-sided pressure and resulting leftward interventricular septal bowing, septal mechanical delay and asynchronicity.

Figure 3: Example of a patient with combined heart failure with preserved ejection fraction and chronic obstructive pulmonary disease. Figure 1A: Short-axis view showing both left ventricular (LV) and right ventricular (RV) hypertrophy, as well as RV dilatation on the long-axis four chamber view (**Figure 1B**). **Figure 1C**: Both dilatation of the main pulmonary artery (PA), with PA diameter almost equivalent to the aorta (Ao), and dilation of the left pulmonary artery (LPA) are demonstrated.

Figure 4: Right ventricular involvement (black arrow) in wild-type transthyretin amyloidosis.

Figure 5: Pathophysiology of myocardial and pulmonary vascular remodelling in heart failure with preserved ejection fraction

Comorbidities induce a systemic proinflammatory state with elevation of plasma cytokines, such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α. Microvascular endothelial

cells of the coronary vessels produce reactive oxygen species (ROS) which reduces the bioavailability of nitric oxide (NO) and this lowers the activity of soluble guanylate cyclase (sGC) in the cardiomyocytes. The resulting cascade of lower cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) ultimately results in myocardial remodelling and release of transforming growth factor beta (TGF-β) with deposition of collagen in the extracellular space. In theory, both ventricles are equally prone to these systemic mechanisms. However, the left ventricle (LV) displays more concentric remodelling, myocardial stiffening and diastolic dysfunction due to collagen deposition and fibrosis. On the contrary, the right ventricle (RV) exhibits more eccentric remodelling with hypertrophy, dilatation and systolic failure, mainly due to concomitant pulmonary vascular disease and resulting increased RV afterload. Chronic pulmonary congestion in the setting of increased LV filling pressures in HFpEF leads to remodelling changes of the pulmonary vasculature. The resulting increase in pulmonary artery pressures and RV overload triggers neurohormonal activation and cytokine release, which further activates the cyclic guanosine monophosphate pathway in RV cardiomyocytes, leading to myocyte apoptosis and necrosis and ultimately RV failure. COPD chronic obstructive pulmonary disease; PCWP pulmonary capillary wedge pressure; HFpEF heart failure with preserved ejection fraction; MPAP mean pulmonary artery pressure.

TABLES

Table 1: Right heart dysfunction and failure.

Right-sided structural and functional abnormalities on echocardiography	
Presence of right ventricular systolic dysfunction	
▪ TAPSE	<17 mm
▪ RV FAC	<35 %
▪ RV S'	<9.5 cm/s
▪ RV FWLS	> -20% (<20 in magnitude with the negative sign)
▪ RIMP (pulsed Doppler)	>0.43 (pulsed Doppler) or >0.54 (tissue Doppler)
▪ 3D RV ejection fraction	<45%
Signs of right-sided pressure/volume overload	
▪ Tricuspid regurgitation	
▪ RV basal end-diastolic diameter	>41 mm
▪ RVEDD/LVEDD	>1.0
▪ Septal shift or D-shaped LV in systole and/or diastole	
▪ RV wall thickness	>5 mm
▪ Inferior vena cava diameter	>21 mm
▪ Inferior vena cava collapsibility	<50%
▪ Tricuspid regurgitation peak systolic velocity	>2.8 m/s
▪ Right atrial end-systolic area	>18 cm^2

Clinical evidence of right heart failure
▪ Evidence of right-sided structural and/or functional abnormalities (see above), in combination with: *Symptoms, e.g.:* ▪ Exertional dyspnoea ▪ Fatigue ▪ Dizziness ▪ Ankle swelling ▪ Epigastric fullness ▪ Right upper abdominal discomfort *Signs, e.g.:* ▪ Jugular venous distension ▪ Peripheral oedema ▪ Hepatomegaly ▪ Ascites ▪ Third heart sound

FAC fractional area change; FWLS free wall longitudinal strain; LV left ventricular; LVEDD left ventricular end-diastolic diameter; RIMP right ventricular index of myocardial performance; RV right ventricular; RVEDD right ventricular end-diastolic diameter; RV S' systolic velocity of the lateral tricuspid valve annulus; TAPSE tricuspid valve annular plane systolic excursion. Echocardiographic cut-off values adapted from the ESC/AHA guidelines.(13,14,110)

Table 2: Staging of right heart dysfunction and failure in HFpEF.

Stage 1	At risk for right heart failure without RV dysfunction and without signs/symptoms of right heart failure.
Stage 2	RV dysfunction without signs/symptoms of right heart failure.
Stage 3	RV dysfunction with prior or current signs/symptoms of right heart failure.
Stage 4	RV dysfunction with refractory signs/symptoms of right heart failure at rest (requiring specialized interventions).

RV right ventricular. Adapted from Haddad et al.(3)

Table 3: Treatment targets for the right heart in heart failure with preserved ejection fraction.

Established treatments					
▪ None					
Potential treatments	**PAH**	**HFpEF**	**Treatment effects in HFpEF**	**Under study**	**Rationale**
cGMP pathway					
▪ PDE5 (sildenafil)	++	+/-	No effect in isolated post-capillary PH, has some potential in selected patients with high PVR(131-133)	No	
▪ PDE9A	+/-	?	None	Pre-clinical	
▪ Riociguat	++	+	↑Stroke volume and ↑cardiac index and ↓RV end-diastolic area, but no change in PAP or PVR(138)	NCT02744339	PA vasodilation, anti-proliferative, anti-fibrotic and anti-inflammatory properties
▪ Vericiguat	?	?	None	NCT01951638	PA vasodilation
Nitric oxide pathway					
Inhaled NO	+	+	↓PAP, ↑CO, ↓PVR in patients with high	NCT02742129	Acute PA vasodilation

			PVR(143-145)		
Endothelin pathway					
▪ Bosentan	++	-	Acute pulmonary oedema(126)	No	
▪ Sitaxsentan	++	+/-	Improved treadmill exercise time(146)	No	
▪ Macitentan	++	-	Data from MELODY-1 suggests more fluid retention with macitentan	NCT02070991	Reduction hypertrophy and stiffening in animal model
Prostacyclin pathway					
▪ Epoprostenol	++	-	↑Mortality in HFrEF(150)	No	
▪ Iloprost	++	+/-	↓PAP and ↓PVR(151)	No	
▪ Treprostinil	++	?	None	NCT03037580	PA vasodilation
Beta blockade					
▪ Nebivolol	+	?	↑6MWD in HFpEF(155)	NCT02053246	β-adrenergic antagonist with vasodilator properties

▪ Carvedilol	+/-	?	None	No	
RAAS inhibitors					
▪ ACEi/ARBs	+/-	+/-	None	No	
▪ Spironolactone	+/-	+/-	No changes in RV function and pulmonary pressures(170)	No	
Other strategies					
▪ Ranolazine	+	+	↓PAP, no change in PVR, ↑6MWD(171,172)	No	
▪ PDE3 (milrinone)	+/-	?	None	No	
▪ ARNI	?	+/-	No reduction in TR velocity(178)	No	
▪ CCBs	+	-/+	None	No	
▪ Digoxine	+/-	+/-	None	No	
▪ Apelin	+	?	None	No	
▪ Albuterol	+	+	Improved pulmonary vascular function(29)	NCT02885636	PA vasodilation
▪ IASD	?	?	↓LA pressure, ↑RA pressure/volume	NCT01913613	Reduction in LA pressures

▪ PA denervation	?	?	None	NCT02220335	Destruction of pulmonary baroreceptors and sympathic nervous fibres
▪ Wireless PAP monitoring	?	+	↓HF hospitalizations(189,190). Class IIb-B recommendation in HF to reduce the risk of recurrent HF hospitalization(18)	No	
▪ Aerobic exercise training	++	++	Class IA recommendation to improve functional capacity and symptoms in HF(18)	NCT02435667 NCT02636439	Aerobic training improves exercise capacity and symptoms.

(++) established beneficial effect; (+) non-established beneficial effect; (+/-) neutral effect; (-) harmful effect; (?) any effect unknown.

ACEi angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; ARNI angiotensin receptor-neprilysin inhibitor; CCB calcium channel blocker; cGMP cyclic guanosine monophosphate; CO cardiac output; HF heart failure; HFpEF heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction; IASD intraatrial shunt device; LA left atrial; LVAD left ventricular assist device; NO nitric oxide; PA pulmonary artery; PAH pulmonary arterial hypertension; PAP pulmonary artery pressure; PDE phosphodiesterase; PH pulmonary hypertension; PVR pulmonary vascular resistance; RA right atrial, RV right ventricular; TR tricuspid regurgitation; 6MWD 6-minute walking distance.

Table 4: Knowledge gaps and future directions regarding the right side in HFpEF.

1. It is recommended to identify HFpEF patients with (additional) pulmonary vascular disease. More insight into the development of pulmonary vascular disease in HFpEF and adequate patient selection for future clinical trials is needed to develop and test more specific therapies that target the pulmonary vasculature in HFpEF.
2. There are several load-independent pathways for the development of RV dysfunction reported in cross-sectional studies, such as coronary artery disease and atrial fibrillation. However, clear cause-effect relations remain uncertain. Especially the hypothesis that the right heart is simultaneously affected in HFpEF, even in the early course of the disease may suggest an intrinsic myocardial process and warrants further research.
3. There remains insufficient knowledge regarding right heart performance, and RV-pulmonary artery coupling and uncoupling, during exercise in HFpEF. More insight into these measures is warranted to address the previous research question as to what extent RV remodelling in HFpEF occurs more or less simultaneously to left ventricular remodelling and independent of pulmonary pressures.
4. Obesity is highly prevalent in HFpEF and is associated with RV remodelling and dysfunction in the general community. More insight into the role of obesity and its effects on RV function and RV-pulmonary artery coupling is needed to investigate whether weight loss will be beneficial for right heart performance in HFpEF.
5. Endothelin-1 levels are associated with myocardial hypertrophy and stiffening in HFpEF. It has also been described that endothelin-1 levels are higher in HFpEF patients with diabetes mellitus than in patients without. It is recommended to investigate any link between endothelin, diabetes mellitus and RV hypertrophy and stiffening. Furthermore, whether PDE type 5 inhibition may be used as a preventive approach in patients with diabetes mellitus-associated HFpEF needs further study.

6. BNP is elevated in both left and right-sided overload and seems significantly more elevated in patients with HFpEF with additional pre-capillary pulmonary hypertension compared to HFpEF patients without pulmonary hypertension. There is an unmet need for a biomarker-signal profile unique to the right heart in patients with left-sided heart failure.
7. Many trials conducted in patients with HFpEF have not met with the primary endpoints and thus these drugs have no place in the guidelines for the treatment of HFpEF. Some of these drugs have shown to be beneficial for the RV, both in experimental models or in the setting of pulmonary arterial hypertension. For the future, it might be recommended to investigate whether some of these drugs may have a positive effect in selected patients with HFpEF, when the endpoints of such trials are more focused on right-sided parameters.