The right ventricle in heart failure with preserved ejection fraction
Gorter, Thomas Michiel

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General Discussion and Future Perspectives

Thomas M. Gorter
In the past few years, several research groups pointed our attention to the RV in patients with heart failure with preserved ejection fraction (HFpEF).\textsuperscript{1,2} It was time to look at heart failure with preserved ejection from the right side.\textsuperscript{3} The growing recognition to take notion of the RV in HFpEF is the result of a series of important observations. Firstly, HFpEF is a disease of growing epidemic proportion and is associated with significant morbidity and mortality.\textsuperscript{4} Secondly, most trials testing drugs and devices that are recommended for patients with heart failure with reduced ejection fraction have been neutral in patients with HFpEF. Furthermore, the heterogenous nature of the disease often leads to serious diagnostic dilemmas for clinicians.\textsuperscript{5} These observations, in combination with failed clinical trials have led to the hypothesis that HFpEF consists of different sub-phenotypes that may all require specific treatments.\textsuperscript{6,7} One important subtype that has now been recognized is right-heart-failure-predominant HFpEF.\textsuperscript{6} It is important to gain more pathophysiological insights into this sub-phenotype, in order to design specific therapies and to improve prognosis, because since so far, none of the drugs and devices tested for “general” HFpEF were successful. This thesis provides more insight into this right-heart-failure-predominant HFpEF phenotype, may improve diagnosing and prognostication of this HFpEF type, and may function as a starting point of developing novel treatment strategies of HFpEF.

**Diagnosis and consequences for the prevalence of right ventricular dysfunction in HFpEF**

Because of the difficulties in diagnosing RV dysfunction and HFpEF alone or in combination, the reported prevalence rates of RV dysfunction in HFpEF vary across individual studies. For instance, Melenovsky et al. reported a prevalence rate of 33% in their study,\textsuperscript{1} which is considerably higher than the 4% reported by Shah et al., using the exact same parameter and cutoff value.\textsuperscript{8} There are several explanation for this observation, which are discussed in detail in Chapter 2.

First, the study setting (e.g. population- or hospital-based) may influence the prevalence and severity of RV dysfunction among different studies. Our systematic review and meta-analysis included randomized controlled trials, community-based studies and cohort studies. In most randomized controlled trials, several comorbidities that are associated with more severe right-sided heart failure such as renal dysfunction, were often excluded. Furthermore, in several cohort studies with invasive hemodynamics, patients were often referred to a center with expertise in
right heart catheterization. Both examples may result in a selection bias with either under- or overrepresentation of RV dysfunction.

Furthermore, in Chapter 2 we also demonstrate that the identification of RV dysfunction in HFpEF depends on the used methods. Fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic velocity are most often used conventional echocardiographic parameters for RV systolic function. By using currently recommended cutoff values of each measure, we observed different prevalence rates of RV systolic dysfunction: 18%, 28%, 21%, respectively. In Chapter 7 we therefore proposed that, if possible, multiple conventional measures are simultaneously used to assess RV systolic function. This recommendation has been applied to Chapters 3, 5 and 6, although it needs further validation in other cohorts.

Finally, different studies often chose different criteria for HFpEF, which may influence the prevalence of RV dysfunction. In Chapter 2 we therefore explored RV dysfunction in studies with stringent HFpEF criteria – according the current guidelines – versus studies with more lenient criteria. Prevalence rate of RV systolic dysfunction seem to be more reliable when stringent criteria were used, because prevalence rates according to the different parameters were more comparable with each other.

To summarize – despite these limitations and considerations – based on the current data, RV dysfunction is present in at least one-fifth, and potentially up to one-third, of all patients with HFpEF.

**Prognosis of right ventricular dysfunction in HFpEF**

To assess the association between RV dysfunction and outcome in HFpEF, we conducted a systematic review and meta-analysis of individual studies with outcome data in patients with HFpEF. In Chapter 2, pooled data of RV function in relation to mortality and hospitalization for heart failure were analyzed. In Chapter 2 it was demonstrated that mortality risk increased with 20-30% with every 5-unit decrease in TAPSE and FAC, respectively. In a recent prospective study in 230 patients with HFpEF, more than half of the patients died with clinical and echocardiographic evidence of right heart failure. In Chapter 2 we were not able to perform multivariable analyses for outcome because of inter-study differences. Especially,
the relation between comorbidities and RV dysfunction, in relation to outcome in HFP EF, warrants further research.

**Mechanisms of right ventricular dysfunction in HFP EF**

There were several mechanisms postulated how RV dysfunction develops in patients with HFP EF.

Firstly, RV dysfunction may evolve with HFP EF severity and is mainly a consequence of more advanced HFP EF. For instance, chronically increased left ventricular (LV) filling pressure leads to pulmonary congestion and RV pressure overload. Especially in the setting of acute decompensating heart failure this may lead to adverse RV remodeling and dysfunction due to oxygen-perfusion mismatch and myocardial ischemia, and aggravated RV overload due to tricuspid regurgitation. In Chapter 3 and 4 we observed that patients with HFP EF and concomitant pulmonary hypertension (PH) were indeed older, more often had atrial fibrillation, had higher LV filling pressures and lower exercise capacity, used more diuretics and had more symptomatic heart failure, compared to HFP EF patients without PH. This suggests that the right-heart-failure-predominant HFP EF phenotype represents a more progressive and severe HFP EF sub phenotype.

Secondly, the development of RV remodeling and dysfunction may also occur more or less simultaneously with and independently from left-sided myocardial remodeling due to circulating factors that negatively impact the myocardium. There is evidence that coronary endothelial inflammation induced by the presence of comorbidities leads to a reduction in nitric oxide bioavailability, cyclic guanosine monophosphate content and protein kinase G activity in adjacent cardiomyocytes. This sequence of mechanisms may then trigger myocardial hypertrophy, interstitial fibrosis and eventually the onset of HFP EF. This concept requires circulating factors that theoretically have similar impact on the myocardium of both ventricles. For instance, diabetes mellitus negatively impacts the myocardium – independently from systemic hypertension and coronary artery disease – via inflammation, oxidative stress and fibrosis. Diabetes mellitus is highly prevalent in patients with HFP EF and is suggested to play an important role into the development of LV diastolic dysfunction. In Chapter 6 we hypothesized that diabetes mellitus may also be associated with adverse myocardial remodeling of the RV. Indeed, we observed that HFP EF patients
with diabetes mellitus more often had RV systolic as well as diastolic dysfunction, compared to patients without diabetes mellitus. This association was independent from RV afterload and suggests that RV myocardial remodeling may occur simultaneous to LV myocardial remodeling in HFP EF, possibly due to circulating factors triggered by comorbidities such as diabetes mellitus. However, Chapter 6 was a small, cross-sectional study and further research is needed to explore cause-effect relations between diabetes mellitus and RV myocardial remodeling in HFP EF. This may be especially relevant to design targeted therapies to prevent the onset of HFP EF in patients with diabetes mellitus.\textsuperscript{15,16}

In Chapter 2 we also observed that obstructive epicardial coronary artery disease is associated with RV dysfunction in HFP EF, and this might occur independently from the severity of HFP EF. Recently, coronary microvascular dysfunction is also reported to be of relevance in HFP EF patients without obstructive coronary artery disease, and may independently result in adverse myocardial remodeling of both ventricles.\textsuperscript{17,18}

Lastly, pulmonary vascular disease and overt right heart failure may also be the predominant drivers of signs and symptoms of heart failure in patients with a normal LV ejection fraction. In this concept, right heart failure may even precede the clinical diagnosis of HFP EF. Older patients with profound pulmonary vascular disease may also have (subclinical) LV diastolic dysfunction, left atrial dilatation and/or LV hypertrophy. Thus, the current diagnostic criteria for HFP EF may also be fulfilled in these patients with “atypical” pulmonary arterial hypertension.\textsuperscript{19} In addition, RV overload may hemodynamically result in reduced LV filling, which is a key phenomenon for HFP EF. This phenomenon was explored in Chapter 4, in HFP EF patients with and without pulmonary vascular disease. We observed that severe pulmonary vascular disease, together with resulting RV pressure overload, leads to enhanced ventricular interdependence, with under-filling of the LV. This diastolic ventricular interdependence is especially enhanced with exercise as venous return to the right heart increases, leading to reduced LV distensibility and impaired Frank-Starling recruitment of the LV with limited ability to augment cardiac output.

There is a strong interaction between atrial fibrillation and onset and progression of HFP EF.\textsuperscript{20} In HFP EF, increased LV filling pressures and left atrial overload leads to remodeling changes in the left atrium that may trigger the onset and progression of
atrial fibrillation. Atrial fibrillation is generally considered to represent more advanced HFpEF.\textsuperscript{21} A direct relation between atrial fibrillation and RV dysfunction in HFpEF remains inaccurately defined, but both may an expression of more severe and progressive HFpEF. In Chapter 5 we explored the relation between atrial fibrillation and right heart dysfunction. In this study, it was demonstrated that HFpEF patients with atrial fibrillation more often had RV dysfunction than patients without. However, patients in sinus rhythm but with a history of atrial fibrillation also had more RV and right atrial dysfunction, coupled with higher right atrial pressures. Previously, it was observed in patients with pulmonary arterial hypertension and with chronic thromboembolic PH, two conditions that not characterized by left atrial hypertension, that there is an association between the presence of atrial fibrillation and higher right atrial pressure.\textsuperscript{22,23} We therefore speculate that in some patients with HFpEF and high pulmonary pressures, atrial fibrillation may be triggered by right atrial overload rather than left atrial overload. However, this needs to be proven in future longitudinal studies.

To summarize, different mechanisms are postulated to cause the development of RV dysfunction and failure in HFpEF. Pulmonary hypertension is present in approximately two-thirds of patients with HFpEF and is repeatedly linked to RV dysfunction in multiple studies. Based on the available data, we therefore believe that PH is the most important cause of RV dysfunction and failure. About one-third of HFpEF patients with PH had evidence of profound pulmonary vascular disease leading to more severely depressed RV function. In these patients, pulmonary vascular disease and right heart failure may be the main drivers of signs and symptoms of heart failure. Thus, potentially up to one-sixth of all patients with HFpEF may have a true right-heart-failure-predominant phenotype of HFpEF, that may even precede the clinical diagnosis of HFpEF. Finally, we performed two hypothesis-generating studies (\textit{Chapters 5 and 6}) and showed that also other factors than PH may lead to right heart dysfunction in HFpEF, independently from PH.

\textbf{Treatment strategies of the right heart in HFpEF}

The present thesis provides more insight into several (potential) treatment options targeting the right heart in HFpEF. These treatment options are mainly discussed in Chapter 7. We herein summarize the current key treatment strategies for the right heart in HFpEF.
First, the importance of adequate volume management by controlling excessive fluid and salt intake and optimizing diuretic therapy was stressed, especially in patients with recurrent hospitalizations for heart failure. Excessive volume overload is a major driver of acute decompensation and leads to systemic congestion and further risk of multi-organ dysfunction. Furthermore, acute central venous hypertension may also lead to coronary venous congestion and myocardial interstitial edema which may have a deleterious effect on the myocardium itself. Adequate volume management may be especially relevant in HFpEF patients with pulmonary vascular disease, since they demonstrate impaired ability to enhance blood flow through the lungs, as observed in Chapter 4. In addition, it may also be important in obese patients with HFpEF, because they have higher plasma volumes and venous return, coupled with more profound RV dysfunction, pericardial restraint and enhanced ventricular interdependence. In Chapter 8 we discussed the use of continuous monitoring of central pressures to control volume status and to prevent recurrent hospitalizations for heart failure. In patients with HFpEF, up-titration of diuretics was mainly responsible for the observed reduction in pulmonary artery pressures and the number of re-hospitalizations for heart failure. Wireless pulmonary artery pressure monitoring now has a class IIb-B recommendation to reduce recurrent hospitalizations for heart failure. Besides conventional loop diuretics, aldosterone receptor antagonists should also be considered in symptomatic and fluid overloaded patients (taking account of renal function and potassium concentration).

The second key target for therapy in HFpEF relates to obesity and functional status. Obesity is highly prevalent in HFpEF and promotes hypertension, insulin resistance, inflammation and dyslipidemia. Obesity is associated with RV dysfunction in the community. Recently, Obokata et al. demonstrated that also patients with obesity-related HFpEF had more RV dysfunction and dilatation and demonstrate unique hemodynamic derangements during the stress of exercise that further impair their functional capacity. Besides these hemodynamic features, visceral and epicardial adipose tissue are also related to obesity and the metabolic syndrome. In obese patients, epicardial fat yields several pro-inflammatory chemokines and cytokines. The close anatomical relation of epicardial fat with the myocardium provides a possible local inflammatory and mechanical effect on the myocardium and the coronary arteries. Via these local inflammatory mechanisms, obesity may therefore
be a driver of adverse myocardial remodeling of both ventricles in HFpEF. The current heart failure guidelines recommend that aerobic exercise training and caloric restriction should be encouraged in obese patients with HFpEF, to improve their functional capacity and reduce symptoms, especially in older patients.\textsuperscript{10,34,35} Future trials may be designed to investigate whether HFpEF patients with severe obesity who are refractory to conventional weight reduction may benefit from gastric bypass surgery.\textsuperscript{36}

Another important strategy that is under investigation in patients with HFpEF and RV dysfunction is the reduction of pulmonary pressures using PH-specific drugs.\textsuperscript{37} Currently, drugs approved for pulmonary arterial hypertension are not recommended for patients with PH secondary to left-sided heart failure (group 2 PH).\textsuperscript{29} Some of these drugs may even have detrimental effects due to rapid increases in left-sided filling pressures and acute pulmonary edema.\textsuperscript{38} Sildenafil is a phosphodiesterase type 5 inhibitor and is tested in HFpEF, although with mixed results. Sildenafil is not beneficial in “general” HFpEF and in HFpEF patients with isolated post-capillary PH.\textsuperscript{39,40} Sildenafil may have potential in specific HFpEF patients with high pulmonary vascular resistance.\textsuperscript{19,41} Clearly, further evidence is needed for the use of sildenafil in HFpEF patients with combined pre- and post-capillary PH. Also, other potential therapies such as riociguat and vericiguat, both soluble guanylate-cyclase stimulators that are beneficial in patients with pulmonary arterial hypertension, need further testing in specific patients with HFpEF and combined pre- and post-capillary PH in order to reduce pulmonary vascular resistance and unload the RV. In Chapter 7 we recommended to identify HFpEF patients with a suspicion of PH, and to refer them to a center of expertise for comprehensive invasive hemodynamic characterizing and to further select individual treatment options or participation in clinical trials. In Chapter 3 we demonstrate that impaired right ventricular-vascular coupling assessed with echocardiography may reliably identify these HFpEF patients with additional pulmonary vascular disease and may therefore be a useful, non-invasive screening tool in this regard.

**Future perspectives**

In Chapter 7 we also discussed further knowledge gaps and future directions regarding the right-side in HFpEF. We herein further discuss several future perspectives related to diagnosis, mechanistic insights and future clinical trials to be
evaluated.

**Diagnosis**

Since plasma NT-proBNP is not specifically enough to differentiate between left- and right-sided heart failure, it may be of relevance to explore a sensitive biomarker-signal profile unique to the right heart, to better identify the right-heart-failure-predominant HFpEF phenotype. Elevated liver enzymes may be useful to detect systemic congestion, yet they are often elevated in more severe staged right heart failure, with peripheral organ dysfunction already being present. Fibroblast growth factor 23 (FGF23) is key regulator of phosphate metabolism by inhibiting reabsorption of phosphate in the proximal renal tubule. Recently, it was shown that higher levels of FGF23 were independently associated with volume overload and with increased risk for recurrent hospitalization in patients with new-onset or worsening heart failure.\textsuperscript{42} In this study, higher FGF23 was also strongly associated with signs of right heart congestion, such as peripheral edema, jugular vein distension, hepatomegaly and third heart tone.\textsuperscript{42} Whether FGF23 may be a sensitive marker to monitor volume status and to guide medical therapy in order to prevent recurrent hospitalization for heart failure in HFpEF patients with RV dysfunction requires further study.

Reduced exercise capacity is a hallmark symptom in HFpEF. In Chapter 4 we stressed the importance of exercise testing in these patients. However, invasive exercise testing is rather cumbersome and not without risk. Therefore, it seems worthwhile to develop standardized protocols for non-invasive stress testing in patients with HFpEF. These protocols may aid to the diagnosis of HFpEF,\textsuperscript{43} and may reveal right-heart impairment under stress, that may not be visible at rest.\textsuperscript{44} These protocols may involve tools such as supine cycle ergometry, or preload augmentation with a fluid challenge, passive leg raise or leg positive pressure.\textsuperscript{44}

For the diagnosis of PH, invasive right heart catheterization is still the golden standard and current consensus states that PH is present when mean pulmonary arterial pressure is $\geq 25$ mmHg.\textsuperscript{29} However, the differentiation between PH secondary to left-heart failure versus pulmonary arterial hypertension, and isolated post-capillary PH versus combined post- and pre-capillary PH, is much more difficult. Although current consensus classifies these different entities based on conventional invasive measurements, the corresponding cut-off values are rather arbitrary and do not truly
reflect pulmonary vascular disease. Currently, combined post- and pre-capillary PH is differentiated from isolated post-capillary PH based on either the diastolic pressure gradient or pulmonary vascular resistance.\textsuperscript{29}

In Chapter 4 we observed that all of the patients with combined post- and pre-capillary PH displayed elevated pulmonary vascular resistance, yet only a minority demonstrated an elevated diastolic pressure gradient. Prior studies have shown that the diastolic pressure gradient does not predict prognosis in heart failure and our data also show that the diastolic pressure gradient is not superior to pulmonary vascular resistance to identify patients with pulmonary vascular disease leading to profound hemodynamic derangements during exercise. In left-sided heart failure, morphological changes of the pulmonary vasculature that can be observed include pulmonary vein muscularization, haemangiomatosis-like endothelial cell proliferation in pulmonary capillaries and intimal hypertrophy of small pulmonary arteries.\textsuperscript{45} Pulmonary vascular remodeling in left-sided heart failure is different than in pulmonary arterial hypertension, in which there are more irreversible neointimal lesions such as concentric laminar intimal fibrosis and plexiform lesions.\textsuperscript{46} We need specific hemodynamic parameters and cut-off values that are truly associated with these specific pulmonary vascular remodeling patterns observed in left-sided heart failure, to better discriminate pulmonary vascular disease from “passive” pulmonary venous hypertension in HFpEF. HFpEF patients with true pulmonary vascular disease may perhaps benefit from PH-specific therapies via reduction in pulmonary vascular resistance and further unloading of the RV. Further research is needed to investigate whether other hemodynamic parameters such as pulmonary arterial compliance may provide added value in this regard.

Lastly, in Chapter 7 we also discussed the importance of an accurate assessment of pulmonary capillary wedge pressure. In patients with HFpEF, wedge pressure might be <15 mmHg at rest, in fasting state and with optimal diuretic therapy. Pulmonary capillary wedge pressure may typically rise with exercise or after a fluid challenge, which enhances the diagnosis of HFpEF.\textsuperscript{47} Consequently, pulmonary capillary wedge pressure <15 mmHg at rest in combination with increased pulmonary artery pressure does not necessarily implies that the patient has isolated pulmonary arterial hypertension. Standardized diagnostic protocols should be designed specifically for these occurrences.
Mechanistic insights
There is an increasing amount of data available that consequently shows that RV dysfunction is of great importance in patients with HFpEF. However, there is still much unknown about the underlying pathways that lead to RV dysfunction in HFpEF, because most data is obtained from relatively small, cross-sectional studies. Therefore, direct cause-effect relations have not been extensively studied so far, and we need further time-course studies to gain more mechanistic insights.

Longitudinal studies may involve exploring whether pulmonary vascular disease in HFpEF is a reflection of more severe HFpEF and is a consequence of chronically increased left-sided filling pressure, or that it is rather a unique phenotype not directly related to the severity of HFpEF in some patients, as recently suggested. Furthermore, prospective studies may also elucidate whether atrial fibrillation in HFpEF is either a cause or a consequence of right heart failure. This may be of importance to further explore if the treatment of RV dysfunction in combination with atrial fibrillation in HFpEF should be focused on either reducing pulmonary pressures or restoring normal sinus rhythm. Although rhythm control therapy may be challenging in most patients with HFpEF given that they are older and often have multiple underlying comorbidities that maintain atrial fibrillation. For mechanistic insights, the implantable pulmonary artery pressure monitoring device discussed in Chapter 8 may be a useful tool to monitor if a rise in pulmonary artery pressure precedes the onset of atrial fibrillation, or vice versa, in patients with HFpEF.

Furthermore, the notion that obesity itself is linked to reduced RV function and more epicardial fat in HFpEF is interesting. More insights into the association between RV dysfunction and epicardial fat from dedicated imaging techniques in needed to explore whether epicardial fat is harmful to the myocardium or that it is a compensatory mechanism that rather protects the heart from harmful energy overload.

Future clinical trials
Most clinical trials performed in patients with HFpEF have not met with the primary endpoints and thus most drugs and devices tested in these trials have no recommendation in the guidelines for the treatment of HFpEF. Most trials were performed in “general” HFpEF, but given the highly heterogeneous nature of the
disease, treatment strategies are now increasingly focused on phenotype-specific treatments.\textsuperscript{6} We herein propose potential future trials for patients with right-heart-failure-predominant HFpEF.

In the large Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, the mineralocorticoid receptor antagonist spironolactone was tested in patients with HFpEF. Although the trial was negative for the primary endpoint, pre-specified analyses revealed that the number of re-hospitalizations for heart failure was lower in the treatment group, compared with placebo.\textsuperscript{49} In addition, the primary outcome was met in the patients with elevated natriuretic peptides at baseline.\textsuperscript{49} Spironolactone both has diuretic and anti-fibrotic properties and it may have potential in HFpEF patients with the right-heart-failure-predominant phenotype characterized by RV dysfunction and dilatation, tricuspid regurgitation and systemic congestion. A future randomized placebo-controlled trial might be designed to test spironolactone in this specific subgroup of patients.

Our notion that diabetes mellitus and elevated glucose levels were associated with more RV dysfunction in HFpEF suggests that this may be an attractive target for therapy. Sodium–glucose cotransporter-2 (SGLT2) inhibitors such as empagliflozin are known to prevent glucose reabsorption and thereby inducing a diuretic effect via glycosuria. Empagliflozin should be considered in patients with type II diabetes mellitus to prevent or delay the onset of heart failure.\textsuperscript{10} SGLT2 inhibition is currently tested in non-diabetic heart failure patients with reduced ejection fraction (EMPEROR-HFrEF-Trial) and with preserved ejection fraction (EMPEROR-HFpEF-Trial). A future clinical trial may be designed to investigate whether SGLT2-inhibition may be especially beneficial in diabetic HFpEF patients with RV dysfunction.

Furthermore, preliminary evidence suggests that the PDE5 inhibitor vardenafil may be used to prevent the onset of HFpEF in diabetic patients.\textsuperscript{15} Further research is needed to test whether vardenafil may also prevent the development of RV dysfunction in diabetic patients with HFpEF.

Furthermore, future trials should be performed to test if the phosphodiesterase type 5 inhibitor sildenafil and the soluble guanylate-cyclase stimulators riociguat and vericiguat are beneficial in HFpEF patients with combined post- and pre-capillary PH.
Although these drugs have partly demonstrated some potentially interesting results in smaller studies, they have not demonstrated any favorable effect on outcome and are therefore not recommended in the guidelines for HFpEF.

Finally, several drugs tested in HFpEF that demonstrated neutral results have shown to be beneficial for the RV, both in experimental models and in the setting of pulmonary arterial hypertension. For the design of future clinical trials in HFpEF, we highly recommend the additional use of right-heart-related endpoints.

References

3. Chatterjee NA, Steiner J, Lewis GD. It is time to look at heart failure with preserved ejection fraction from the right side. Circulation 2014;130:2272-2277.


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34. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA 2016;315:36-46.


46. van der Feen DE, Bartelds B, de Boer RA, Berger RM. Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease. Eur Heart J 2017;

