Heart failure (HF) with preserved left ventricular (LV) ejection fraction (EF; or HFrEF) is seen in approximately half of patients with HF and confers morbidity and mortality similar to that of HF with reduced left ventricular ejection fraction (HFrEF). HFrEF has been characterized by abnormal LV diastolic function, abnormal LV-central vascular coupling, impaired systolic reserve and chronotropic response during exercise, abnormal skeletal muscle function, and dysfunction of the right ventricle (RV)–pulmonary vascular (PV) unit. The pathophysiological heterogeneity underlying HFrEF likely explains, in part, why there are no HFrEF-specific therapies to date associated with improved survival in this population. Careful delineation of HFrEF subphenotypes on the basis of predominant pathophysiologic inputs may improve diagnostic classification, guide targeted therapy, and ultimately improve clinical outcome.

Historically, the RV has been considered to play a minor role in maintaining adequate blood flow, and as a result, the importance of RV function in various cardiopulmonary diseases has been underinvestigated and often overlooked. In the normal heart, the RV is closely coupled to a low-impedance pulmonary vascular system that is best considered as a RV-PV unit. In the setting of increased RV afterload, it is increasingly recognized that RV function is critical for augmentation of forward cardiac output and prevention of systemic venous congestion. Accordingly, RV dysfunction (RVD) has emerged as a potent predictor of poor prognosis in pulmonary arterial hypertension, intrinsic lung disease, and HFrEF. In HFrEF, integrated indexes of RV-PV dysfunction such as the combination of RVEF <0.35 and elevated pulmonary artery pressure confer a 7-fold increase in mortality. These findings have appropriately prompted efforts to therapeutically target the RV-PV unit with pulmonary vasodilators, with mixed results to date in HFrEF, likely owing to whether patients selected had a high burden of RV-PV dysfunction.

At present, the prevalence and prognostic significance of abnormal RV-PV structure and function in patients with HFrEF is not well established (Table). The study by Mohammed and colleagues in this issue of Circulation represents an important step forward in our understanding of the burden and significance of RV-PV dysfunction in HFrEF as defined by multiple easily derived echocardiographic measurements. Strengths of the study include the investigation of a HFrEF cohort at a center of excellence in HFrEF and echocardiography with complete follow-up data available on HF hospitalization rate, cardiovascular mortality, and all-cause mortality; the establishment of an independent relationship between RVD and prognosis in HFrEF using feasible and readily available echocardiographic measurements; and careful disentanglement of prognostic contributions of abnormal RV structure and function versus pulmonary vascular pressures. RVD in this study was defined by 1 of 2 echocardiographic metrics: reduced tricuspid annular plane systolic excursion (TAPSE), which captures the degree to which longitudinal contraction of the RV is preserved, and integration of qualitative visual RV function assessment and quantitative RV-LV size ratio. Patients in this study with RVD by either echocardiographic measurement demonstrated impaired LV performance (diastolic dysfunction), abnormal RV structure (increased RV dilation), and increased RV afterload (increased pulmonary artery systolic pressure [PASP]). Both metrics of RVD were associated with increased mortality (all-cause and cardiovascular) and an increased risk of HF hospitalizations. These prognostic associations persisted after adjustment for clinical covariates and PASP, although TAPSE no longer demonstrated significant association with all-cause mortality in multivariate models.

Characteristics of the Study Population and Their Implications
To understand the findings of the study, it is important to consider the inclusion criteria for HFrEF used, particularly because definitions of HFrEF vary across studies and the optimal criteria to define HFrEF remain under debate. First, HFrEF patients in this study were identified with the use of the Framingham criteria for HF diagnosis, a diagnostic system significantly reliant on clinical examination findings that largely reflect right heart dysfunction (eg, jugular venous pressure elevation, hepatomegaly, hepatojugular reflux, ankle edema) and therefore may have disproportionately identified HFrEF patients with RVD (HFrEF-RVD). In fact, the use of Framingham criteria without requisite echocardiographic features of LV diastolic dysfunction (eg, left atrial enlargement, E/E’ may have led to the inclusion of subjects with RV-PV dysfunction from other mechanisms of pulmonary hypertension beyond left heart dysfunction (eg, pulmonary embolism, chronic obstructive pulmonary disease). Alternative diagnostic systems that focus on LV-specific imaging criteria (eg, the European Study Group on Diastolic Heart Failure)
### Table. Prevalence and Prognostic Significance of RV-PV Structure and Function Measurements in HFpEF

<table>
<thead>
<tr>
<th>Study</th>
<th>Heart Failure Population</th>
<th>Classification of RV-PV Function</th>
<th>Prevalence, %</th>
<th>Outcome (Median Follow Up)</th>
<th>HR/SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RV function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burke et al(^{15}) (n=419) NYHA I-IV (49% class III/IV)</td>
<td>TAPSE &lt;16 mm RVFAC &lt;35%</td>
<td>28</td>
<td>Death/HF hospitalization (18 mo)</td>
<td>Adjusted HR: 1.09/6 mm ↓ TAPSE (P=NS)*</td>
<td></td>
</tr>
<tr>
<td>Melenovsky et al(^{14}) (n=96) Mean NYHA, 3±0.6</td>
<td>RVFAC &lt;35%</td>
<td>33</td>
<td>Death (18 mo)</td>
<td>Adjusted HR: 2.2/10% ↓ RVFAC (P=0.001)†</td>
<td></td>
</tr>
<tr>
<td>Morris et al(^{11}) (n=201) NYHA II-IV (30% III/IV)</td>
<td>TAPSE &lt;15 mm RVFAC &lt;35%</td>
<td>28</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Mohammed et al(^{17}) (n=562) Not reported</td>
<td>TAPSE &lt;16 mm</td>
<td>35</td>
<td>CV death (55 mo)</td>
<td>Adjusted HR: 1.3/4 mm ↓ RVFAC (P=NS)</td>
<td></td>
</tr>
<tr>
<td>Puwanant et al(^{12}) (n=51) NYHA II-IV (74% class III/IV)</td>
<td>TAPSE &lt;15 mm RVFAC &lt;45%</td>
<td>33</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Shah and Solomon(^{14}) (n=935) NYHA I-IV (33% class III/IV)</td>
<td>RVFAC &lt;35%</td>
<td>4</td>
<td>CV death/SCD/HF hospitalization (35 mo)</td>
<td>Unadjusted HR: 0.99/5% ↑ RVFAC (P=NS)</td>
<td></td>
</tr>
<tr>
<td><strong>RV structure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burke et al(^{15}) See above</td>
<td>RWH RV dilation RV/LV ratio</td>
<td>34</td>
<td>Death/HF hospitalization (18 mo)</td>
<td>Adjusted HR: 1.37/0.9 mm ↑ RWWT (P&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Morris et al(^{11}) See above</td>
<td>RWH RV dilation</td>
<td>49</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Melenovsky et al(^{14}) See above</td>
<td>RVEDA</td>
<td>2</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Shah and Solomon(^{14}) See above</td>
<td>RVEDA</td>
<td>4</td>
<td>CV death/HF hospitalization (35 mo)</td>
<td>Adjusted HR: 1.01/1 cm² ↑ RVEDA (P=NS)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary arterial pressure</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Burke et al(^{15}) See above</td>
<td>PASP (continuous)</td>
<td>...</td>
<td>Death/HF hospitalization (18 mo)</td>
<td>Adjusted HR: 1.04/15 mm Hg ↑ PASP (P=NS)</td>
<td></td>
</tr>
<tr>
<td>Lam et al(^{19}) (n=244) Not reported</td>
<td>PASP &gt;35 mm Hg</td>
<td>83</td>
<td>Death</td>
<td>Adjusted HR: 1.2/10 mm Hg ↑ PASP (P=0.03)</td>
<td></td>
</tr>
<tr>
<td>Leung et al(^{19}) (n=455) Not reported</td>
<td>mPAP &gt;25 mm Hg</td>
<td>53</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Melenovsky et al(^{14}) See above</td>
<td>mPAP &gt;25 mm Hg</td>
<td>81</td>
<td>Death (18 mo)</td>
<td>Unadjusted HR: 1.6/18mmHg ↑ PASP (P=0.006)</td>
<td></td>
</tr>
<tr>
<td>Mohammed et al(^{17}) See above</td>
<td>PASP &gt;40 mm Hg</td>
<td>64</td>
<td>Death (55 mo)</td>
<td>Adjusted HR: 1.57/SDDEV (P=0.001)</td>
<td></td>
</tr>
<tr>
<td>Morris et al(^{11}) See above</td>
<td>PASP &gt;41 mm Hg</td>
<td>53</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Shah and Solomon(^{14}) See above</td>
<td>PASP &gt;40 mm Hg</td>
<td>36</td>
<td>CV death/HF hospitalization (35 mo)</td>
<td>Adjusted HR: 1.23/10 mm Hg ↑ PASP (P=0.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary vascular function</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Melenovsky et al(^{14}) See above</td>
<td>PVR &gt;2.6</td>
<td>=50</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Morris et al(^{11}) See above</td>
<td>PVR &gt;3‡</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Schwartzberg et al(^{11}) (n=83) Not reported</td>
<td>PVR &gt;3.3</td>
<td>=50</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Shah and Solomon(^{14}) See above</td>
<td>PVR &gt;2.5‡</td>
<td>11</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

RV dilation is defined as RV end-diastolic dimension at the base >42 mm. RVH is defined as RV free wall thickness >5 mm. Ellipses indicate that the end point or value of interest was not assessed. Unless otherwise, the specified adjustment is for clinical covariates. *P=0.05 is insignificant. CV indicates cardiovascular; HF, heart failure; HR, hazard ratio; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association class; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RVD, right ventricular dysfunction; RVEDA, right ventricular end-diastolic area; RVFAC, right ventricular fractional area change; RVH, right ventricular hypertrophy; RV-PV, right ventricular–pulmonary vascular; SCD, aborted sudden cardiac death; TAPSE, tricuspid annular plane excursion; and TR, tricuspid regurgitation.

*Unless otherwise specified, the HRs are reported as per 1-SD increase in the predictor variable.
†Adjustment includes PASP.
‡Echocardiography-derived pulmonary vascular resistance.
or hemodynamic response to provocation (ie, an increase in pulmonary capillary wedge pressure with exercise testing or saline loading) may identify a more LV-specific HF population with lower prevalence and severity of RVD than that reported in the study by Mohammed et al. To the credit of the authors, however, chronic obstructive pulmonary disease and obstructive sleep apnea were adjusted for in multivariable analyses, and RVD remained a significant prognostic indicator (Table).

Second, patients in this study were relatively older compared with contemporary randomized and observational HFpEF populations studied. Advanced age (>82 years, on average, over the median 4.6 years of follow-up) likely contributed to the high mortality rate during the study period (65%) and has been associated with factors that affect RV afterload such as reduced pulmonary vascular distensibility and increased pulmonary vascular resistance (PVR) during activity. In this study, the prevalence of cardiometabolic conditions was consistent with other HFpEF cohorts (eg, hypertension in >80%, atrial fibrillation and diabetes mellitus in about one third of patients, mean glomerular filtration rate of 53–57 mL·min⁻¹·1.73 m⁻²). By either echocardiographic metric, patients with RVD were more likely to have atrial fibrillation and a permanent pacemaker, and those with TAPSE-defined RVD were more likely to have coronary disease. Somewhat surprisingly, despite the association between right heart dysfunction and impaired renal function (owing to elevated central venous pressure and impaired cardiac output) in patients with HFpEF, pulmonary hypertension, and another HFpEF cohort renal function was not significantly different between those with and without echocardiographically defined RVD in this study.

**RVD in HFpEF: Definition and Prevalence**

In response to elevated afterload and PV dysfunction, the RV faces increased wall stress, subendocardial ischemia, and depletion of myocardial oxygen extraction reserve. Adaptive RV responses to elevated afterload include RV hypertrophy (concentric remodeling) and preservation of RV function at the macroscopic level (Figure). In contrast, maladaptive RV responses to increased afterload are characterized by RV dilation and hypokinesis, reflected at the ultrastructural level by increased fibrosis and at the subcellular level by increased apoptosis, contractile apparatus dysfunction, dysregulation of β-receptor signaling, impaired angiogenesis, and a metabolic switch to aerobic glycolysis. The temporal progression and molecular and metabolic adaptation of RVD in HFpEF are yet to be characterized.

Imaging of RV structure and function (Figure) is challenging because of its unique geometry, the limited definition of the RV endocardial surface, the unique contraction pattern of the RV, and the load dependence of RV function measurements. As highlighted recently in a model of RV pressure overload, established indexes of RV function (RV fractional area change, RV myocardial performance index, and TAPSE) appear to be more closely related to ventricular-arterial coupling than intrinsic RV contractility, the latter of which may better approximate the likelihood of improved RV contractility in response to pharmacotherapy intervention. Although a comprehensive comparison of available imaging metrics of RV structure and function would have been desirable (Figure), the study by Mohammed focused on only 2: TAPSE and semi-quantitative RV function. TAPSE reflects longitudinal shortening of the RV and is a known determinant of RV stroke volume. In heterogeneous populations with variable prevalence of cardiovascular disease, TAPSE has shown modest correlation with gold-standard assessment of RVEF by magnetic resonance imaging or nuclear ventriculography. In addition, TAPSE has been proposed as an integrative marker of RV-PV performance in pulmonary arterial hypertension on the basis of significant associations with RV structural remodeling (right atrial enlargement, RV dilation) and inverse association with PVR. However, in pulmonary arterial hypertension, TAPSE demonstrated weaker correlations with RVEF compared with indexes of transverse contraction (septum to RV free wall), suggesting an important additional contribution of this bellows-like action in states of elevated RV afterload in which ultrastructural alterations in septal fiber orientation and function may significantly affect RV cardiac output.

Mohammed and colleagues’ finding of a 33% incidence of abnormal TAPSE is consistent with previous reports in HFpEF populations (Table). Lower TAPSE did not predict all-cause mortality in fully adjusted models but was independently associated with cardiovascular mortality and HF hospitalizations, consistent with the findings of Burke et al. Given the noted structural and mechanical adaptation of the RV in response to increased afterload and LV diastolic dysfunction, isolated metrics of longitudinal RV shortening (ie, TAPSE) may not fully capture the complexity of RV adaptation in HFpEF.

The alternative metric of RVD used by Mohammed et al was an integrative assessment of visually estimated RV function that relied on estimates of contractility and RV relative to LV size. This approach has not been validated in the HF population and has been shown to have significant interreader variability with limited accuracy compared with gold-standard magnetic resonance imaging assessment. Despite these limitations and the limited concordance of the 2 RV measures as categorical variables, this approach identified 21% of the HFpEF population characterized by higher PASP, more tricuspid regurgitation, and larger RV size. Mortality, cardiovascular mortality, and hospitalization were significantly increased in patients with semi-quantitative RVD. Of note, given the heterogeneous patterns of LV adaptation in HFpEF with possibly distinct prognostic implications of eccentric versus concentric LV hypertrophy, descriptive and prognostic markers of RV:LV ratio may need to additionally account for patterns of LV remodeling.

**HFpEF-RVD: A Unique Clinical, Structural, and Hemodynamic Phenotype?**

A critically important question raised by this study is whether HFpEF-RVD represents a distinct subphenotype or is simply a manifestation of worsening LV function and congestion that imposes heightened afterload on the RV. Although some indexes of diastolic function (shorter deceleration time, modestly higher left atrial size) were worse in HFpEF-RVD, LV relaxation (′e), LV mass, and LV filling pressure (E/e′) were the same in the most advanced RVD group compared with the normal RV function group and in the lowest TAPSE tertile compared with the highest. The identical E/e′ values are important to consider in light of the fact that the average PASP was 32% higher in the
moderate to severe RVD group compared with the normal RV group. This combination of findings points to the presence of increased precapillary pulmonary artery pressure (ie, increased transpulmonary gradient) in HFpEF-RVD. Studies using invasive hemodynamic measurements and echocardiography have shown a wide range of PVR values in HFpEF (Table), and to date, the prognostic and functional significance of elevated PVR in HFpEF remains underinvestigated and unknown (Table). The presence of a distinct subset of HFpEF patients with RV dilation relative to LV size, RV hypokinesis, and high PVR should prompt consideration of the role of pulmonary vasodilator therapy in carefully selected HFpEF-RVD patients. Indeed, Guazzi et al" showed marked hemodynamic improvements when phosphodiesterase-5 inhibition was administered to a HFpEF population with RVD (average TAPSE, 11 mm; PVR >3 Wood units; right atrial pressure greater than pulmonary capillary wedge pressure), yet no benefit in exercise capacity accrued in a broad HFpEF population treated with phosphodiesterase-5 inhibition in the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) Trial.12

The authors frame additional mechanistic considerations based on their findings that atrial fibrillation and permanent pacing were associated with RVD. With reduced oxygen extraction reserve arising with high RV afterload in HFpEF, the authors appropriately postulate that HFpEF patients can ill afford the negative inotropic effects of atrial fibrillation and RV pacing-induced dyssynchrony (Figure). Although the sequence of RV structural adaptation to elevated RV afterload is uncharacterized in HFpEF, the prevalence of RV dilation and hypertrophy was nearly 30% in a recent HFpEF cohort, and both demonstrated significant association with clinical outcome (Table).15 The more potent prognostication associated with elevated pulmonary artery pressure has been identified in HFrEF,33 although
the most potent prognosticator was the combination of abnormal RV function and elevated pulmonary artery pressure.6

**HFpEF Phenotypes: Physiological, Functional, and Structural Paradigm for Classification**

Going forward, characterization of HFpEF should ideally integrate metrics of RV function (regional, global, metabolic), RV structure (ventricular enlargement, hypertrophy), and pulmonary vascular function. There is an unmet need for repeated and longitudinal assessment of RV structure and function in HFpEF to provide insight into the mechanisms of adaptation, stages of pathological progression, and potential reversibility of RVD. At least 1 study of HFpEF-RVD suggested continued augmentation of PVR despite stable elevation of left atrial pressure over time.23 Confrontational testing with volume challenge, pulmonary vasodilators, and exercise may help to further refine HFpEF-RVD characterization. Exercise in HFpEF has been shown to unmask abnormal chronotropic reserve34 and steep augmentation in left-sided filling pressures and may be particularly well suited to defining RV reserve capacity in advance of developing overt RVD at rest, as we and others have shown in HFrEF.20 On the basis of the results from Mohammed et al, further assessment of the hemodynamic, metabolic, and subcellular influences of atrial arrhythmia and RV apical pacing in this population is also warranted. It is intriguing to consider potential therapeutic intervention targets such as rhythm versus rate control, invasive ablative strategies of arrhythmias, and biventricular or multisite pacing,35 specifically in HFpEF-RVD, on the basis of limited RV metabolic and contractile reserve.

**Conclusions**

Mohammed and colleagues demonstrate the prognostic value of assessing easily derived echocardiographic indexes of RV-PV function in HFpEF while also highlighting that isolated RVD measurements only partially reflect the complex hemodynamic, mechanical, and subcellular changes in the RV in HFpEF. The findings of Mohammed et al are an important addition to the expanding characterization and classification of HFpEF phenotypes. This study highlights the critical need for standardization of RV assessment in HFpEF and reinforces the integrative and complementary function of the RV and pulmonary vasculature in the pathophysiology and outcome of HF. Improved classification of HFpEF will require continued longitudinal assessment of RV-PV structure and function and integration of provocative testing. These efforts will continue to refine our understanding of HFpEF pathophysiology and, we hope, provide a roadmap to effective therapies in this expanding population.

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**Disclosures**

None.

**References**


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It Is Time to Look at Heart Failure With Preserved Ejection Fraction From the Right Side
Neal A. Chatterjee, Johannes Steiner and Gregory D. Lewis

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