Heart Failure

Right Ventricular Function in Heart Failure With Preserved Ejection Fraction
A Community-Based Study

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Background—The prevalence and clinical significance of right ventricular (RV) systolic dysfunction (RVD) in patients with heart failure and preserved ejection fraction (HFpEF) are not well characterized.

Methods and Results—Consecutive, prospectively identified HFpEF (Framingham HF criteria, ejection fraction ≥50%) patients (n=562) from Olmsted County, Minnesota, underwent echocardiography at HF diagnosis and follow-up for cause-specific mortality and HF hospitalization. RV function was categorized by tertiles of tricuspid annular plane systolic excursion and by semiquantitative (normal, mild RVD, or moderate to severe RVD) 2-dimensional assessment. Whether RVD was defined by semiquantitative assessment or tricuspid annular plane systolic excursion ≤15 mm, HFpEF patients with RVD were more likely to have atrial fibrillation, pacemakers, and chronic diuretic therapy. At echocardiography, patients with RVD had slightly lower left ventricular ejection fraction, worse diastolic dysfunction, lower blood pressure and cardiac output, higher pulmonary artery systolic pressure, and more severe RV enlargement and tricuspid valve regurgitation. After adjustment for age, sex, pulmonary artery systolic pressure, and comorbidities, the presence of any RVD by semiquantitative assessment was associated with higher all-cause (hazard ratio=1.35; 95% confidence interval, 1.03–1.77; P=0.03) and cardiovascular (hazard ratio=1.85; 95% confidence interval, 1.20–2.80; P=0.006) mortality and higher first (hazard ratio=1.99; 95% confidence interval, 1.35–2.90; P=0.0006) and multiple (hazard ratio=1.81; 95% confidence interval, 1.18–2.78; P=0.007) HF hospitalization rates. RVD defined by tricuspid annular plane systolic excursion values showed similar but weaker associations with mortality and HF hospitalizations.

Conclusions—in the community, RVD is common in HFpEF patients, is associated with clinical and echocardiographic evidence of more advanced HF, and is predictive of poorer outcomes. (Circulation. 2014;130:2310-2320.)

Key Words: diastole ■ heart failure ■ hypertension, pulmonary ■ ventricular dysfunction, right

In heart failure (HF) with reduced ejection fraction (HFrEF), right ventricular (RV) systolic dysfunction (RVD) is common,1 is associated with impaired functional capacity, and portends a poor prognosis.2-7 In HFrEF, ischemic or myopathic processes may directly involve the RV and lead to RVD. Isolated insults to the left ventricle (LV) can lead to pulmonary hypertension (PH) and neurohormonal and cytokine activation. The resulting RV pressure overload, inflammation, and altered RV myocardial gene expression promote RVD in the absence of primary RV myocardial injury.8

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The prevalence and functional and prognostic implications of RVD in HF with preserved ejection fraction (HFpEF) are less clear. Whereas infarction or myopathic processes isolated to the RV are uncommon, PH is equally prevalent in HFrEF and HFpEF,9-11 neurohormonal activation occurs in HFrEF,12 and comorbidities, which are highly prevalent in HFpEF, may play a fundamental role in the pathogenesis of altered myocardial function in HFpEF.13 Thus, HFpEF patients may be at risk for RVD.

Understanding the prevalence and clinical implications of altered RV function in large HF cohorts is hindered by the challenges to quantitative assessment of RV structure and function.14,15 Although a growing number of RV functional indexes have been proposed, the feasibility, concordance, sensitivity and specificity for RVD, and clinical implications of these parameters are poorly described, particularly in HF.16 In the limited studies to date, estimates of RVD prevalence in

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2310
HFpEF vary widely with the cohort studied, RV functional measure used, and partition values used to define RVD.\(^{17-19}\)

Recognition of the prevalence and clinical implications of RVD and its relation to PH in HFpEF patients is important to better understand HFpEF pathophysiology, to facilitate accurate diagnosis and prognostication, and to identify potential therapeutic targets.\(^ {20,21}\) Accordingly, the objective of the present study was to characterize RV function using 2 highly feasible and widely available measures in a large, community-based cohort of HFpEF patients. Clinical and echocardiographic features and outcomes associated with differences in RV function (as assessed by tricuspid annular plane systolic excursion [TAPSE] and semiquantitative assessment of RV function) were studied.

**Methods**

The study was approved by the Mayo Clinic Institutional Review Board. All subjects provided written consent for inclusion in this study.

**Study Subjects**

This Olmsted County HFpEF cohort has been described previously.\(^ {22}\) Briefly, consecutive adult patients with HFpEF (Framingham criteria for HF diagnosis and LV ejection fraction [LVEF] \(\geq 50\%\)) were identified by real-time interrogation of electronic medical records using natural language processing techniques and were prospectively enrolled between September 2003 and August 2009. Exclusion criteria were significant left-sided valve disease, known cardiomyopathies, congenital heart disease, and pericardial disease. Clinical characteristics and comorbidities, including chronic obstructive pulmonary disease and obstructive sleep apnea, were defined as previously described.\(^ {22}\)

**Echocardiography**

Body size, blood pressure, and heart rate were measured at the time of echocardiography.

**Tricuspid Annular Plane Systolic Excursion**

Because M-mode TAPSE was not routinely measured in our echocardiography laboratory during the enrollment period, TAPSE was measured on previous studies using 2-dimensional (2D) images from the apical 4-chamber view. Measurement of 2D TAPSE was done by subtracting the distance between the tricuspid leaflet insertion to the lateral tricuspid annulus and sector apex in systole from the distance between the 2 in diastole. Three measurements in sinus rhythm (5 in atrial fibrillation) were averaged. Measurement of 2D TAPSE was feasible in 500 subjects (89%).

Correlation of off-line 2D and M-mode-derived TAPSE was examined in subjects undergoing echocardiography for other indications (n=15) who had M-mode TAPSE measured. We also measured 2D TAPSE in an age- and sex-matched normal cohort without HFpEF, coronary artery disease, diabetes mellitus, or hypertension (n=89).

**Semiquantitative RV Systolic Function and RV Size Assessment**

Per local echocardiography protocol, RV systolic function was assessed by integrating visual assessment of the contractility of the RV outflow tract, RV apex, and interventricular septum from different views and characterized on an ordinal scale. RV size was assessed semiquantitatively as normal size (two thirds or less of the LV size) or as mildly (RV similar to the LV size), moderately (RV larger than the LV), or severely (RV much larger than the LV) enlarged.

When semiquantitative RV enlargement (n=7, 1.2%) or dysfunction (n=8, 1.4%) was described without a quantifier, the severity was assumed to be mild. When RV function was not specifically commented on (n=21, 4%), the following methods were preferentially used to approximate RV function in the following order: linear interpolation (closest echocardiograms before and after; n=14), last observation carried forward (n=4), or next observation carried backward (n=3). For the carried observations, the median time from index echocardiograms was 2 years.

Throughout this article, the term RVD is used to denote RV systolic dysfunction.

**Pulmonary Artery Systolic Pressure**

Pulmonary artery systolic pressure (PASP) was measurable in 496 patients (88%) and was estimated as the RV systolic pressure because pulmonary valve stenosis was excluded in all patients. RV systolic pressure was calculated from the continuous-wave Doppler tricuspid valve regurgitant velocity using the simplified Bernoulli equation, and right atrial pressure was estimated in 5-mmHg increments between 5 and 20 mmHg on the basis of the size and collapsibility of the inferior vena cava.\(^ {23}\)

**LV Structure and Function**

LVEF assessment was based on the echocardiographer’s collation of multiple assessments as previously described.\(^ {24,25}\) Other standard LV structural and functional indexes were calculated from 2D, M-mode, and Doppler measurements according to American Society of Echocardiography guidelines as previously described.\(^ {22}\) Left atrial volume was measured with the area-length method.\(^ {22}\) Characterization of LV diastolic function was performed as previously described.\(^ {24}\) Briefly, the speed of LV relaxation was estimated by the early diastolic medial LV septal tissue velocity (‘e’). The early transmitial flow velocity (E) to ‘e’ (E/e’) ratio was used as an estimate of LV filling pressure. The early diastolic transmitial flow deceleration time was used to assess restriction to LV filling because it reflects rapid elevation of LV diastolic pressures with filling in the setting of impaired relaxation.\(^ {26}\)

**Tricuspid Valve Regurgitation**

Routine assessment of tricuspid valve regurgitation (TR) in our echocardiographic laboratory incorporates semiquantitative methods (color-flow imaging and hepatic vein flow pulsed-wave Doppler integration) and is graded on a 6-point (trivial to severe) ordinal scale as described previously.\(^ {22}\) For the present analysis, patients with moderate, moderate to severe, or severe TR were characterized as having moderate to severe TR; patients with mild or mild to moderate TR were characterized as having mild or mild to moderate TR; and patients with trivial or no TR were characterized as having no TR.

**Laboratory Data**

Glomerular filtration rate was estimated with the Modification of Diet in Renal Disease formula.

**Follow-Up and Outcomes**

Subjects were followed up for up to 10 years (through October or November 2013). HF hospitalization was defined as a primary dismissal diagnosis of HF (International Classification of Disease, Ninth Revision, Clinical Modification code 428.xx).\(^ {28}\) Death was ascertained from the Mayo electronic records and the Rochester epidemiology project as described previously.\(^ {29}\) Cause of death (immediate) was obtained from the death certificate or autopsy report as documented by a pathologist as described previously. Cardiovascular death was defined as death caused by HF, arrhythmia, ischemic heart disease, valvular heart disease, stroke, vascular disease, or pulmonary embolism.

**Statistical Analysis**

Data are presented as medians (25th–75th percentile) or percent frequency. Nonparametric rank tests and \( \chi ^2 \) test for independence/Fisher exact test were used for across-group comparison of continuous and
categorical variables, respectively. We did not adjust for multiple comparisons.

Kaplan–Meier analysis and log-rank statistics were used to compare survival and event-free survival between groups. Cox proportional hazards regression was used to adjust for pertinent covariates. Stepwise linear regression model with backward elimination was constructed by forcing age and sex into the model and entering all potential explanatory variables: comorbidities (atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, and obstructive sleep apnea), PASP, TR, and RV function. Variables with a value of P>0.10 were eliminated.

Andersen and Gill formulation of the Cox proportional-hazards regression was used to model time to multiple HF hospitalizations whereby subjects were allowed to experience multiple events with risk discontinuation during a hospitalization episode. The hazard ratio (95% confidence interval) associated with dichotomous variables or a 1-SD change in continuous variables was provided. All analyses were 2 tailed, and a value of P<0.05 was considered statistically significant. Analyses were performed with the JMP and SAS statistical software (SAS Corp).

Results

2D TAPSE

Values for TAPSE derived by 2D or M-mode methods showed good correlation and agreement (Figure IA and IB in the online-only Data Supplement). In an age- (78 years [72–85 years]) and sex- (56% women) matched normal community cohort without HFpEF or cardiovascular disease (n=89), the median 2D TAPSE was 19.0 mm (16.8–21.7 mm), and the mean 2D TAPSE was 19.5±3.8 mm, similar to values for M-mode TAPSE previously reported in healthy people >70 years of age (18.0±3.0 mm).30

RV Function in HFpEF

In HFpEF patients, the median TAPSE was 17 mm (14–21 mm), and 177 of 500 patients (35%) with measurable TAPSE had a value below the American Society of Echocardiography–specified lower limit of normal (16 mm; Figure IA).15 By semiquantitative assessment, 118 of 562 patients (21%) had some degree (mild or moderate to severe) of RVD, and TAPSE was lower in these patients (13 mm [10–16 mm]) than in patients with normal RV function (19 mm [15–22 mm]; P<0.0001) by semiquantitative assessment. TAPSE values declined with increasing severity of semiquantitative RVD (Figure 1B). The distribution of TAPSE differed from that observed in the age- and sex-matched control population (Figure 1C). Agreement (κ) between categorical designsations of RVD (TAPSE <16 mm or any RVD by semiquantitative) was not strong (κ=0.30; 95% confidence interval, 0.21–0.38; Table I in the online-only Data Supplement).

Clinical Characteristics of Subjects According to RV Function

The clinical characteristics of patients with TAPSE values in the highest and middle tertiles did not differ from each other (Table 1). Compared with patients in the highest/middle tertiles (combined), patients in the lowest TAPSE tertile were more likely to have coronary artery disease, atrial fibrillation, permanent pacing, and treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and diuretics.

Compared with patients with normal RV function, those with mild RVD by semiquantitative analysis were more likely to have atrial fibrillation and permanent pacing. Patients with moderate to severe RVD by semiquantitative assessment were slightly younger but otherwise similar to those with mild RVD (Table 2). Compared with patients with normal RV function, patients with any RVD (mild and moderate to severe combined) were more likely to have atrial fibrillation, permanent pacing, and treatment with diuretics.

Cardiovascular Structure and Function According to RV Function Assessed With TAPSE

Among HFpEF patients, LV structure, LV systolic and diastolic function, systemic arterial function, and right heart function did not differ in patients with TAPSE values in the highest versus middle tertiles, except for LV diastolic dimension, which was slightly larger in the middle versus the highest TAPSE tertile (Table 3).

Compared with patients in the highest and middle TAPSE tertiles (combined), patients in the lowest tertile had similar

Figure 1. Distribution of tricuspid annular plane systolic excursion (TAPSE) in patients with heart failure with preserved ejection fraction (HFpEF; A: red, lowest; gray, middle; and black, highest tertile). Inset (B) shows Tukey box-and-whisker plots of TAPSE values in patients with normal, mildly depressed, or moderate to severely depressed right ventricular (RV) systolic function by semiquantitative assessment. *P<0.05 vs normal RV function; †P<0.05 vs mildly depressed RV systolic function. Inset (C) shows the distribution of TAPSE in HFpEF and an age- and sex-matched healthy control population without cardiovascular disease. RVD indicates RV dysfunction.
LV structure (diastolic dimension, mass, and relative wall thickness) and similar LVEF but lower stroke volume and cardiac index despite higher heart rate (Table 3). Patients in the lowest TAPSE tertile also had worse LV diastolic function, as evidenced by larger left atrial volume and shorter deceleration time, although relaxation (e') and filling pressure (E/e') were not different from those in patients with higher TAPSE. Patients in the lowest TAPSE tertile had lower systemic systolic blood pressure and pulse pressure despite higher arterial elastance and similar systemic vascular resistance and arterial compliance. Patients in the lowest TAPSE tertile had a higher prevalence of RV enlargement, as evidenced by larger left atrial volume and shorter deceleration time, although relaxation (e') and filling pressure (E/e') were not different from those of patients with normal RV function. Patients with RVD had lower systolic blood pressure and pulse pressure, but their arterial elastance, systemic vascular resistance, and arterial compliance were similar to those observed in patients with normal RV function. Patients with RVD had a higher prevalence of RV enlargement and moderate to severe TR, lower TAPSE, and higher PASP.

Cardiovascular Structure and Function According to RV Function by Semiquantitative Assessment

By semiquantitative analysis, patients with moderate to severe RVD had similar LV dimensions, lower systolic blood pressure and pulse pressure, higher prevalence of RV enlargement, and lower TAPSE than patients with mild RVD (Table 4). However, in general, findings were similar when patients with mild RVD or any RVD (mild or moderate to severe combined) were compared with those with normal RV function.

Compared with patients with normal RV function by semiquantitative assessment, patients with any RVD (mild and moderate to severe combined) had similar LV dimension, LV mass, and relative wall thickness but lower LVEF, stroke volume, and cardiac index (Table 4). Patients with RVD also had worse LV diastolic function, as evidenced by larger left atrial volume and shorter deceleration time, although relaxation (e') and filling pressure (E/e') were not different from those with normal RV function. Patients with RVD had lower systolic blood pressure and pulse pressure, but their arterial elastance, systemic vascular resistance, and arterial compliance were similar to those observed in patients with normal RV function. Patients with RVD had a higher prevalence of RV enlargement and moderate to severe TR, lower TAPSE, and higher PASP.

PH and RV Function in HFpEF

In this HFpEF cohort, age increased across tertiles (≤39, 40–52, and ≥53 mm Hg) of PASP, but the prevalence of other comorbidities, including chronic obstructive pulmonary disease and obstructive sleep apnea, was not different across tertiles of PASP in all patients (Table II in the online-only Data Supplement) and in those with evidence of RV dysfunction by TAPSE or semiquantitative assessment (data not shown).

The distribution of PASP tertiles was not different across TAPSE tertiles (P=0.17), but more patients with RVD by semiquantitative analysis had PASP in the highest tertile (P<0.0001; Figure III in the online-only Data Supplement).

Table 1. Clinical Characteristics of Subjects According to TAPSE-Assessed RV Function

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Upper and Middle Combined</th>
<th>Upper Tertile, TAPSE ≥20 mm</th>
<th>Middle Tertile, TAPSE 16–19 mm</th>
<th>Lower Tertile, TAPSE ≤15 mm</th>
<th>Across-Group P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>323</td>
<td>178</td>
<td>145</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>78 (70–85)</td>
<td>77 (68–85)</td>
<td>79 (72–87)</td>
<td>80 (73–86)</td>
<td>0.10</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>186 (58)</td>
<td>102 (57)</td>
<td>84 (58)</td>
<td>100 (57)</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.9 (25.1–34.4)</td>
<td>29.7 (25.3–35.1)</td>
<td>27.7 (24.4–32.7)</td>
<td>27.8 (24.2–33.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>273 (85)</td>
<td>153 (86)</td>
<td>120 (83)</td>
<td>152 (86)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>113 (35)</td>
<td>69 (39)</td>
<td>44 (30)</td>
<td>63 (36)</td>
<td>0.29</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>169 (52)</td>
<td>94 (53)</td>
<td>75 (52)</td>
<td>101 (57)</td>
<td>0.59</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>161 (50)</td>
<td>87 (49)</td>
<td>74 (51)</td>
<td>116 (66)*</td>
<td>0.003</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>113 (35)</td>
<td>64 (36)</td>
<td>49 (34)</td>
<td>114 (64)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>91 (28)</td>
<td>50 (28)</td>
<td>41 (28)</td>
<td>65 (37)</td>
<td>0.14</td>
</tr>
<tr>
<td>GFR, mL·min⁻¹·1.73 m⁻² (n=333)</td>
<td>56 (42–69)</td>
<td>55 (42–69)</td>
<td>57 (43–70)</td>
<td>53 (41–63)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hemoglobin, g/dL (n=333)</td>
<td>12.0 (10.5–13.6)</td>
<td>12.2 (10.7–13.4)</td>
<td>11.8 (10.4–13.6)</td>
<td>12.2 (10.8–13.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>149 (46)</td>
<td>81 (46)</td>
<td>68 (47)</td>
<td>101 (57)*</td>
<td>0.06</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>203 (63)</td>
<td>112 (63)</td>
<td>91 (63)</td>
<td>117 (66)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diuretics</td>
<td>194 (60)</td>
<td>105 (59)</td>
<td>89 (61)</td>
<td>124 (70)*</td>
<td>0.08</td>
</tr>
<tr>
<td>Statins</td>
<td>142 (44)</td>
<td>73 (41)</td>
<td>69 (48)</td>
<td>89 (50)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Across-group P value is for the difference across the tertiles of TAPSE (lower, middle, and upper tertiles) by the Kruskal-Wallis test. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; OSA, obstructive sleep apnea; RV, right ventricular; and TAPSE, tricuspid annular plane systolic excursion.

*P<0.05, lowest tertile vs highest and middle TAPSE tertiles combined.
Prognostic Significance of RV Function and PH in HFpEF

All-Cause Mortality

At 8 years, of the 562 subjects, 367 had died and 195 were censored (median follow-up, 4.6 years). Survival varied by TAPSE tertiles, but mortality risk appeared to be confined to the lowest tertile, and survival curves did not diverge until \( \approx 3 \) years after assessment (Figure 2A and Table 5). Survival varied by semiquantitative characterization of RVD in which mild RVD and moderate to severe RVD were associated with a similar reduction in survival with early and progressive divergence of survival curves (Figure 2B and Table 5).

Survival varied across PASP tertiles among patients in the highest, middle, or lowest TAPSE tertiles (Figure 3A–3C). Survival varied across PASP tertiles in patients with normal RV function and in patients with any RVD by semiquantitative assessment (Figure 4A and 4B).

After adjustment for pertinent covariates, higher PASP and lower TAPSE were independently associated with higher cardiovascular mortality (Table 5). Similarly, PASP and semiquantitative evidence of RVD (any RVD) were independently associated with higher cardiovascular mortality (Table 5).

**HF Hospitalizations**

Among HFpEF patients with assessment of both PASP and TAPSE (n=451), during follow-up, there were 340 HF hospitalizations among 164 unique subjects (range, 1–10 hospitalizations). In univariate analysis, TAPSE, semiquantitative RVD, and PASP were associated with time to first or multiple HF hospitalizations (Table 5). After adjustment for pertinent covariates, higher PASP and lower TAPSE were independently associated with time to first or multiple HF hospitalizations (Table 5).

**TR in HFpEF**

TR was quantified in 519 (92%) of the HFpEF patients and was moderate to severe in 142 (27%), mild or mild to moderate in 241 (47%), and absent in 136 (26%). Moderate to severe TR was more common in patients with RVD (Tables 3 and 4). In univariate analysis, the severity of TR was associated with higher all-cause (Figure 2C) and cardiovascular mortality.

### Table 2. Clinical Characteristics of Subjects According to Semiquantitatively Assessed RV Function

<table>
<thead>
<tr>
<th></th>
<th>Normal RV Function</th>
<th>Mild RVD</th>
<th>Moderate to Severe RVD</th>
<th>Across-Group P Value</th>
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<tr>
<td>n</td>
<td>444</td>
<td>65</td>
<td>53</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>79 (62–86)</td>
<td>82 (74–85)</td>
<td>74 (66–82)†</td>
<td>0.01</td>
<td>79 (69–84)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>258 (58)</td>
<td>32 (49)</td>
<td>30 (57)</td>
<td>0.40</td>
<td>62 (53)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.94 (1.71–2.15)</td>
<td>1.94 (1.79–2.18)</td>
<td>1.86 (1.73–2.19)</td>
<td>0.73</td>
<td>1.90 (1.74–2.20)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.86 (24.7–34.5)</td>
<td>28.4 (25.6–34.2)</td>
<td>26.2 (23.5–36.7)</td>
<td>0.59</td>
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Across-group P value is for the difference across the 3 groups of RV function (normal, mild, and moderate to severe RVD) by the Kruskal-Wallis test. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease, GFR, glomerular filtration rate; OSA, obstructive sleep apnea; RV, right ventricular; and RVD, right ventricular dysfunction.

*Mild RVD vs normal RV function.
†P<0.05, moderate to severe vs mild RVD.
‡P<0.05, any RVD vs normal RV function.

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</tbody>
</table>

Across-group P value is for the difference across the 3 groups of RV function (normal, mild, and moderate to severe RVD) by the Kruskal-Wallis test. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease, GFR, glomerular filtration rate; OSA, obstructive sleep apnea; RV, right ventricular; and RVD, right ventricular dysfunction.

*Mild RVD vs normal RV function.
†P<0.05, moderate to severe vs mild RVD.
‡P<0.05, any RVD vs normal RV function.
mortality (Table 5), as well as with time to first or multiple HF hospitalizations (Table 5). However, in models including TAPSE or semiquantitative RVD, severity of TR was no longer significantly associated with any of the outcomes and was eliminated from the models.

Discussion
In the community, whether assessed by TAPSE (35%) or semiquantitative methods (21%), RVD was present in a significant subset of HFrEF patients. HFrEF patients with RVD were more likely to have atrial fibrillation, pacemakers, and diuretic therapy. At echocardiography, patients with RVD had slightly lower LVEF, worse diastolic dysfunction, and lower blood pressure and cardiac output, as well as more significant PH, RV enlargement, and TR. Although those categorized as having RVD by either method shared similar clinical and echocardiographic characteristics on average, concordance for RVD designation by the 2 methods was not strong. The prognostic implications of semiquantitative RVD were more striking with patients with any severity of RVD by semiquantitative assessment having worse all-cause and cardiovascular mortality and risk of first and all HF hospitalizations after adjustment for level of PH and pertinent comorbidities. The prognostic implications of a low TAPSE were less striking. Patients with higher PASP and RVD had the worst outcomes. These data may assist in the recognition of HFrEF in that it should be realized that RVD is common in HFrEF and is associated with clinical and echocardiographic evidence of more advanced HF and with poorer outcomes.

Prevalence of RV Dysfunction in HFrEF
In HFrEF, the frequency of RVD has been assessed using a number of different RV function parameters in variable study populations. In HFrEF patients with ischemic or nonischemic
LV systolic dysfunction referred for transplantation or with moderate or severe symptoms, reduced RV ejection fraction (<35%–40%) measured by a thermodilution technique or radionuclide ventriculography was present in 50% to 75% of patients.4,31–33 A study of unselected HFrEF patients found evidence of RVD assessed by tricuspid annular S′ in 68% of patients.34 A meta-analysis including 4732 patients with HF or LV systolic dysfunction reported an overall prevalence of RVD of 47% but emphasized the high variability in prevalence, RV assessment techniques, and study population characteristics.1

Because the RV may be involved by an ischemic or myopathic process in patients with HFrEF, the prevalence of RVD may be lower in HFpEF, in which underlying origins for HFpEF are thought to affect primarily the LV. Indeed, in the present study, using either TAPSE or semiquantitative assessment of RV function, we found a lower prevalence of RVD than in HFrEF studies that used RV ejection fraction to assess RV function. The community-based nature of the present study may also contribute to the lower prevalence because most studies in HFrEF were confined to referral cohorts with advanced HF.

Few studies have assessed the prevalence or prognostic implications of RVD in HFpEF. In a small cohort study, Puwanant et al17 reported that ≈30% of HFpEF patients had a reduced (<45%) RV fractional area change. This quantitative measure is most analogous to the semiquantitative estimation of RVD used here, and the prevalence of RVD based on this measure is similar to that observed in our study. Consistent with our results, in the same cohort, the prevalence of RVD based on reduced (<15 mm) TAPSE or on reduced (<11.5 cm/s) tricuspid annulus peak systolic tissue velocity (S′) was higher (≈40%–50%).17 These data suggest that TAPSE is either a more sensitive or less specific measure of RVD. In a much larger study, Morris et al18 reported that a variety of RV assessment parameters (RV longitudinal systolic strain, TAPSE, S′, RV fractional area change) were lower in patients

Table 4. Cardiovascular Structure and Function of Subjects According to Semiquantitatively Assessed RV Function

<table>
<thead>
<tr>
<th></th>
<th>Normal RV function</th>
<th>Mild RVD</th>
<th>Moderate to Severe RVD</th>
<th>Across-Group P Value</th>
<th>Any RVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>444</td>
<td>65</td>
<td>53</td>
<td></td>
<td>118</td>
</tr>
<tr>
<td>LV structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDd/BSA, mm/m²</td>
<td>25.4 (23.2–27.9)</td>
<td>25.6 (23.7–27.7)</td>
<td>23.9 (21.6–26.9) †</td>
<td>0.06</td>
<td>25.1 (22.3–27.3)</td>
</tr>
<tr>
<td>LV mass/BSA</td>
<td>98 (84–122)</td>
<td>100 (87–127)</td>
<td>87 (74–107)</td>
<td>0.008</td>
<td>94 (78–118)</td>
</tr>
<tr>
<td>LV mass/height 1.4</td>
<td>94 (79–113)</td>
<td>96 (81–126)</td>
<td>85 (67–112)</td>
<td>0.06</td>
<td>91 (72–117)</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.44 (0.40–0.51)</td>
<td>0.47 (0.42–0.54)*</td>
<td>0.44 (0.40–0.52)</td>
<td>0.13</td>
<td>0.45 (0.40–0.53)</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>61 (56–66)</td>
<td>58 (54–64)*</td>
<td>61 (56–66)</td>
<td>0.007</td>
<td>59 (54–65)‡</td>
</tr>
<tr>
<td>Stroke volume/BSA, mL/m²</td>
<td>44 (38–51)</td>
<td>39 (34–48)*</td>
<td>40 (32–45)</td>
<td>0.0004</td>
<td>39 (33–45)‡</td>
</tr>
<tr>
<td>Cardiac index, L/min−1·m−2</td>
<td>3.0 (2.6–3.7)</td>
<td>3.0 (2.4–3.3)</td>
<td>2.8 (2.3–3.4)</td>
<td>0.11</td>
<td>2.9 (2.4–3.4)‡</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69 (60–80)</td>
<td>72 (61–82)</td>
<td>71 (60–83)</td>
<td>0.47</td>
<td>71 (61–82)</td>
</tr>
<tr>
<td>LV diastolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial volume/BSA, mL/m²</td>
<td>44 (35–54)</td>
<td>49 (42–58)*</td>
<td>47 (4–57)</td>
<td>0.05</td>
<td>48 (40–57)‡</td>
</tr>
<tr>
<td>Medial e′, m/s</td>
<td>0.06 (0.04–0.07)</td>
<td>0.05 (0.05–0.08)</td>
<td>0.06 (0.05–0.07)</td>
<td>0.56</td>
<td>0.06 (0.05–0.07)</td>
</tr>
<tr>
<td>E/e′ (medial e′)</td>
<td>16 (11–23)</td>
<td>18 (13–25)</td>
<td>16 (10–21)</td>
<td>0.28</td>
<td>17 (12–22)</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>198 (169–235)</td>
<td>176 (157–205)*</td>
<td>183 (156–213)</td>
<td>0.0025</td>
<td>182 (157–210)‡</td>
</tr>
<tr>
<td>Systemic arterial function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>132 (118–148)</td>
<td>131 (110–142)</td>
<td>118 (108–130)‡</td>
<td>0.001</td>
<td>128 (110–142)‡</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>64 (50–80)</td>
<td>60 (48–78)</td>
<td>55 (42–66)†</td>
<td>0.002</td>
<td>58 (47–72)‡</td>
</tr>
<tr>
<td>Ea, mmHg/mL</td>
<td>1.45 (1.18–1.72)</td>
<td>1.42 (1.19–1.95)</td>
<td>1.53 (1.12–1.88)</td>
<td>0.84</td>
<td>1.48 (1.18–1.89)</td>
</tr>
<tr>
<td>SVR, dynes·cm−3 †</td>
<td>1237 (1013–1501)</td>
<td>1212 (985–1653)</td>
<td>1277 (991–1658)</td>
<td>0.96</td>
<td>1231 (994–1605)</td>
</tr>
<tr>
<td>SAC, mL/mmHg</td>
<td>1.31 (0.99–1.65)</td>
<td>1.30 (0.89–1.66)</td>
<td>1.30 (1.00–1.89)</td>
<td>0.58</td>
<td>1.30 (0.97–1.74)</td>
</tr>
<tr>
<td>Right heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV enlargement, n (%)</td>
<td>85 (20)</td>
<td>54 (84)*</td>
<td>52 (98)†</td>
<td>&lt;0.0001</td>
<td>106 (91)‡</td>
</tr>
<tr>
<td>Moderate–severe TR, n (%)</td>
<td>78 (18)</td>
<td>33 (51)*</td>
<td>31 (58)</td>
<td>&lt;0.0001</td>
<td>64 (54)‡</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>44 (34–54)</td>
<td>55 (48–64)*</td>
<td>58 (49–75)</td>
<td>&lt;0.0001</td>
<td>56 (48–69)‡</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>19 (15–22)</td>
<td>15 (12–17)*</td>
<td>12 (9–15)‡</td>
<td>&lt;0.0001</td>
<td>13 (10–16)‡</td>
</tr>
</tbody>
</table>

Across-group P value is for the difference across the 3 groups of RV function (normal, mild, and moderate to severe RVD) by the Kruskal-Wallis test or χ² test for independence. BP indicates blood pressure; BSA, body surface area; LV, left ventricular; LVEDd, LV end-diastolic dimension; Ea, arterial elastance; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVD, RV dysfunction; SAC, systemic arterial compliance; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid valve regurgitation.

*Mild RVD vs normal.
†P<0.05, moderate to severe vs mild RVD.
‡P<0.05, any RVD vs normal RV function.
with HFpEF than in patients with Doppler evidence of diastolic dysfunction but no HF. However, the concordance and prognostic implications of these multiple parameters were not assessed, and the majority of HFpEF patients (75%) had reduced RV \( S' \), calling into question the discriminatory value of RVD thus defined. In a large observational cohort of somewhat younger patients (mean age, 65 years) with well-defined HFpEF, 28% had a TAPSE <16 mm, and 14% had a RV fractional area change <35%. In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) echocardiographic substudy, TR velocity was measureable in 450 subjects (48% of substudy patients) and was abnormal (>2.9 m/s) in 162 (36%). RV fractional area change was abnormal (<35%) in only 4% of patients. Whether this represents a difference in the technique or the type of patients enrolled in this particular clinical trial is unclear.

The different measures of RV function (TAPSE and semiquantitative assessment) correlated only modestly with abnormal values for the 2 measures, identifying slightly different groups of patients. Our findings suggest that semiquantitative RVD carries more potent prognostic implications than TAPSE-defined RVD.

Although the prevalence of RVD in a community-based cohort of HFrEF patients was not addressed in this study, interpreted in the context of available studies in HFrEF, our findings suggest that the prevalence of RVD in HFpEF is significant but lower than in HFrEF.

### Table 5. Association of RV Function, PASP, and TR With Adverse Outcomes in HFpEF

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>CV Mortality</th>
<th>First HF Hospitalization</th>
<th>All HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (CI)</td>
<td>P Value</td>
<td>HR (CI)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (per SD)</td>
<td>1.53 (1.37–1.69)</td>
<td>&lt;0.0001</td>
<td>1.67 (1.40–1.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TAPSE (per SD)</td>
<td>0.82 (0.73–0.91)</td>
<td>0.0003</td>
<td>0.73 (0.60–0.87)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Semiquantitative RVD (any)</td>
<td>1.68 (1.32–2.12)</td>
<td>&lt;0.0001</td>
<td>2.12 (1.45–3.05)</td>
<td>0.0002</td>
</tr>
<tr>
<td>TR</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild–moderate</td>
<td>1.41 (1.07–1.87)</td>
<td>0.01</td>
<td>1.41 (0.88–2.32)</td>
<td>0.16</td>
</tr>
<tr>
<td>Moderate–severe</td>
<td>2.45 (1.83–3.30)</td>
<td>&lt;0.0001</td>
<td>2.77 (1.70–4.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Multivariable analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: PASP, TAPSE, and comorbidities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (per SD)</td>
<td>1.50 (1.33–1.68)</td>
<td>&lt;0.0001</td>
<td>1.57 (1.29–1.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TAPSE (per SD)</td>
<td>0.99 (0.79–1.01)</td>
<td>0.08</td>
<td>0.77 (0.64–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2: PASP, semiquantitative assessment of RV function, and comorbidities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP (per SD)</td>
<td>1.42 (1.26–1.60)</td>
<td>&lt;0.0001</td>
<td>1.48 (1.21–1.78)</td>
<td>0.0001</td>
</tr>
<tr>
<td>RVD (any)</td>
<td>1.35 (1.03–1.77)</td>
<td>0.03</td>
<td>1.85 (1.20–2.80)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Reference group for TR is no TR. CI indicates confidence interval; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; PASP, pulmonary artery systolic pressure; RV, right ventricular; RVD, RV dysfunction; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid valve regurgitation.

*HRs adjusted for age, sex, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, and obstructive sleep apnea.
Cause of RV Dysfunction in HFpEF

Although cause and effect cannot be established from this study, the higher prevalence of atrial fibrillation and permanent pacing in those with RVD suggests a potential role for these factors in contributing to impaired RV function in which the RV may display enhanced sensitivity to the negative inotropic effects of rhythm irregularity or pacing-induced dys synchrony. Both PH and diastolic dysfunction were more severe in HFpEF patients with RVD, suggesting a role for chronic pressure overload in contributing to RVD. Other potential contributing comorbidities such as coronary disease and lung disease were not consistently associated with RVD, but we cannot rule out a contribution of these factors in some patients.

Significance of RVD in HFpEF

In HFrEF, the presence of RVD is associated with worse clinical status, exercise capacity, and prognosis. Here, we found that RVD is also associated with higher all-cause and cardiovascular mortality and HF hospitalization rates in HFpEF, even after adjustment for age, comorbidities, and PH severity. Although functional status was not assessed in this study, patients with RVD had lower resting cardiac output, suggesting the potential for more impaired exercise capacity.

In this observational study, RVD predicted outcomes independently of PASP. This is in contradistinction to a study in advanced HFrEF in which RVD (thermodilution-derived RV ejection fraction) conferred poor prognosis only when (invasively measured) mean pulmonary artery pressure was >20 mm Hg. However, in the previous HFrEF study, numbers in some subgroups were small, patients were young (age, 51 years), and patients predominantly had nonischemic dilated cardiomyopathy.

Although not shown to be effective in unselected HFpEF patients enrolled in the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial, the phosphodiesterase type 5 inhibitor sildenafil had favorable effects in a small study of HFpEF patients who had significant RVD and PH. Our findings suggest that this HFpEF subgroup is significant and at high risk.

TR in HFpEF

Moderate to severe TR, atrial fibrillation, PH, and RV pacing were all more common in patients with HFpEF and RVD. Annular dilatation resulting from atrial enlargement in atrial fibrillation, RV failure, and dilatation caused by group II PH or pacemaker lead impingement on the tricuspid valve leaflets could cause or exacerbate TR in HFpEF. Once established, TR itself could contribute to progressive RV remodeling and RVD. Although TR was associated with worse outcomes in HFpEF, these associations were no longer significant after adjustment for the severity of RVD.

Limitations

We cannot distinguish between isolated precapillary and combined precapillary and postcapillary PH. The prognostic

Figure 3. Kaplan–Meier survival curves for patients with heart failure with preserved ejection fraction (HFpEF) according to tertiles of pulmonary artery systolic pressure (PASP) among patients in the highest (tricuspid annular plane systolic excursion [TAPSE] ≥20 mm; A), middle (TAPSE 16–19 mm; B), and lowest (TAPSE ≤15 mm; C) TAPSE tertile.

Figure 4. Kaplan–Meier survival curves for patients with heart failure with preserved ejection fraction (HFpEF) according to tertiles of pulmonary artery systolic pressure (PASP) among patients with normal right ventricular (RV) function by semiquantitative (SQ) assessment (A) or RV dysfunction (mild or moderate to severe) by semiquantitative assessment (B).
significance of PH and its association with RVD may be different according to the duration and type of PH.39,40 RV diastolic function was not assessed in this population and is likely more prevalent than systolic dysfunction. Data on New York Heart Association functional class were not available. Assessment of TR severity was semiquantitative. However, methods for quantitative assessment of TR are not as well established as for mitral regurgitation and are less often performed in routine clinical practice.

Conclusions

In this community-based HFpEF cohort, evidence of RVD was present in a significant subset of patients and was associated with more advanced clinical and echocardiographic characteristics and poorer outcomes. However, the prevalence of RVD depends on the method used to assess RV function, with different methods identifying slightly different patient groups. The optimal technique to assess RVD remains to be defined. These data may assist in the recognition of HFpEF in that it should be realized that RV systolic dysfunction may accompany HFpEF and portends a poorer prognosis, regardless of the severity of PH or comorbid conditions.

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Disclosures

None.

References


Among patients with heart failure (HF) with preserved ejection fraction (HFpEF), pulmonary hypertension is common and may ultimately contribute to perturbations in right ventricular (RV) structure and function. Understanding the prevalence and clinical implications of RV systolic dysfunction (RVD) in HFpEF is hindered by the challenges to assessment of RV structure and function. In this community-based HFpEF cohort, we assessed patient characteristics and outcomes according to the severity of RVD as assessed by semiquantitative visual assessment or tricuspid annular plane systolic excursion. The prevalence of RVD varied according to the method used to assess RV function, with RVD present in 20% of patients by semiquantitative assessment and 35% of patients by tricuspid annular plane systolic excursion criteria. The clinical and echocardiographic characteristics of patients with RVD were suggestive of more advanced HF, and those with RVD had worse all-cause and cardiovascular mortality and risk of first and all HF hospitalizations after adjustment for level of pulmonary hypertension and pertinent comorbidities. The different measures of RV function (tricuspid annular plane systolic excursion and semiquantitative assessment) correlated only modestly with abnormal values for the 2 measures, identifying somewhat different groups of patients. Semiquantitative RVD had more potent prognostic implications than tricuspid annular plane systolic excursion–defined RVD, but the optimal technique to assess RVD remains to be defined. These data may assist in the recognition of HFpEF in that it should be realized that RV systolic dysfunction may accompany HFpEF and portends a poorer prognosis, regardless of the severity of PH or comorbid conditions.

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Right Ventricular Function in Heart Failure With Preserved Ejection Fraction: A Community-Based Study
Selma F. Mohammed, Imad Hussain, Omar F. AbouEzzeddine, Hiroyuki Takahama, Susan H. Kwon, Paul Forfia, Véronique L. Roger and Margaret M. Redfield

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/content/131/17/e424.full.pdf

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In the article by Mohammed et al, “Right Ventricular Function in Heart Failure With Preserved Ejection Fraction: A Community-Based Study,” which was published in the December 23, 2014 issue of the journal (Circulation. 2014;130:2310–2320. DOI: 10.1161/CIRCULATIONAHA.113.008461), a correction is needed. The name and degree of one of the authors appeared incorrectly. Abou Ezzeddine should have appeared as AbouEzzeddine. Dr AbouEzzeddine’s degree should have been listed as MDCM, rather than MD.

These corrections have been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/130/25/2310.full. The authors regret the errors.
Supplemental Table 1: Agreement between TAPSE and semiquantitatively defined RV dysfunction.

<table>
<thead>
<tr>
<th>Normal RV function</th>
<th>Normal TAPSE</th>
<th>Low TAPSE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal RV function</td>
<td>285 (57.0%)</td>
<td>108 (21.6%)</td>
<td>393 (78.6%)</td>
</tr>
<tr>
<td>RVD</td>
<td>38 (7.6%)</td>
<td>69 (13.8%)</td>
<td>107 (21.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>323 (64.6%)</td>
<td>177 (35.4%)</td>
<td>500</td>
</tr>
</tbody>
</table>

**Abbreviations: **RVD, right ventricular dysfunction. TAPSE, tricuspid annular plane systolic excursion
**Supplemental Table 2:**

**Clinical characteristics in subjects according to PASP tertiles**

<table>
<thead>
<tr>
<th>Tertile 1 PACP≤39 mmHg</th>
<th>Tertile 2 PACP 40-52 mmHg</th>
<th>Tertile 3 PACP≥53 mmHg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>176</td>
<td>151</td>
<td>169</td>
</tr>
<tr>
<td>Age, years</td>
<td>78 (70-84)</td>
<td>80 (73-88)</td>
<td>82 (75-87)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>95 (54)</td>
<td>100 (66)</td>
<td>103 (61)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.96 (1.71-2.17)</td>
<td>1.90 (1.70-2.10)</td>
<td>1.88 (1.70-2.10)</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>29.4 (25.3-34.6)</td>
<td>27.4 (24.1-32.6)</td>
<td>28.3 (24.1-32.7)</td>
</tr>
</tbody>
</table>

**Comorbidities**

- Hypertension, n (%) 150 (85) 124 (82) 150 (89) 0.24
- Diabetes, n (%) 55 (31) 45 (29) 56 (33) 0.81
- Ever smoker, n (%) 95 (54) 80 (53) 82 (49) 0.56
- CAD, n (%) 101 (57) 77 (51) 94 (56) 0.50
- Atrial fibrillation, n (%) 75 (43) 77 (51) 89 (53) 0.14
- COPD, n (%) 52 (30) 46 (30) 54 (32) 0.89
- OSA, n (%) 44 (25) 30 (20) 44 (26) 0.39
- Pacemaker, n (%) 49 (28) 42 (28) 52 (31) 0.79
- GFR, ml/min/1.73m² 57 (50-70) 55 (41-66) 51 (36-67) 0.005
- Hemoglobin, g/dl 12.5 (10.9-13.6) 12.0 (10.8-13.6) 11.7 (10.4-12.9) 0.06

**Medications**

- ACE/ARB, n (%) 91 (52) 70 (46) 83 (49) 0.63
- Beta blocker, n (%) 116 (66) 93 (62) 107 (63) 0.71
- Diuretics, n (%) 105 (60) 95 (63) 120 (71) 0.08
- Statins, n (%) 91 (52) 72 (48) 70 (41) 0.16

**Abbreviations:** PACP, pulmonary artery systolic pressure; BSA, body surface area; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive lung disease; GFR, glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker
Supplemental Figure 1: Correlation (A) and Agreement (B) between M mode and 2D TAPSE in 15 subjects from an independent cohort

**Abbreviations:** TAPSE, tricuspid annular plane systolic excursion
Supplemental Figure 2: Distribution of TAPSE in HFrEF patients according to right ventricular size (normal (n=317), mild enlargement (n=90), mild to moderate enlargement (n=58) and moderate to severe or severe RV enlargement (n=26)) by semi-quantitative assessment. Data are Tukey Box and Whiskers plots. Statistical comparison is by Kruskal-Wallis test for differences across groups.

**Abbreviations:** TAPSE, tricuspid annular plane systolic excursion; Mod, moderate; Mod-Sev/Sev, moderate to severe or severe
Supplemental Figure 3: Distribution of PASP in HFpEF patients according to right ventricular dysfunction as defined by tertiles of TAPSE (left) or semi-quantitative assessment (right).

**Abbreviations:** As in supplemental figure 1. PASP, pulmonary artery systolic pressure.

TAPSE tertiles: Upper tertile: TAPSE ≥ 20 mm, middle tertile: TAPSE 16-19 mm and lower tertile: TAPSE ≤ 15 mm

PASP tertiles: Tertile 1: PASP≤39 mmHg, Tertile 2: PASP 40-52 mmHg and Tertile 3: PASP≥53 mmHg

P value = 0.17 for TAPSE tertiles, p <0.0001 for semiquantitative RVD.
좌심실 수축기능이 보존된 심부전 환자에서 우심실 기능이상이 동반된 경우에는 예후가 나쁘다

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Summary

배경
좌심실 수축기능이 보존된 심부전(heart failure with preserved ejection fraction, HFpEF)환자에서 우심실 기능이상(right ventricular systolic dysfunction, RVD)의 유병률과 임상적 중요성에 대해서는 명확히 정립되어 있지 않다.

방법 및 결과
Olmsted County에서 연속적으로 Framingham 심부전 진단 기준에 합당하고 심초음파를 50% 이상인 562명의 HFpEF 환자 를 등록하여. 심부전 진단 당시에 심초음파를 시행하였고, 전향적으로 원인별 사망률과 심부전으로 인한 입원율을 추적 관찰하였다. 우심실 기능은 TAPSE(tricuspid annular plane systolic excursion)에 따라 3분위로 분류하거나, 반정상 이차원적 평가로 정상, 경중, 중등도 혹은 중증 이상으로 구분하였다. RVD를 반정상 이차원적 평가나 TAPSE ≤15mm로 정의한 경우, RVD를 동반한 HFpEF 환자는 심방세동, 인공심박동기, 만성적인 이뇨제 치료의 가능성이 높았다. 심초음파 상에서 RVD를 동반한 HFpEF 환자는 낮은 좌심실 구형률, 이완기능장애 악화, 낮은 혈압과 심박출량, 높은 수축기 폐동맥압, 심한 우심실 확장 및 심화 판 폐쇄부전의 소견을 보였다. 연령과 성별, 수축기 폐동맥압과 동반질환을 보정하면, RVD가 동반된 경우에 전체 사망률(HR, 1.35; 95% CI, 1.03-1.77; P=0.03), 심혈관계 사망률(HR, 1.85; 95% CI, 1.20-2.80; P=0.006) 및 심부전에 의한 입원율(HR, 1.81; 95% CI, 1.18-2.78; P=0.007)이 높았다.

결론
HFpEF 환자에서 RVD는 비교적 흔하게 동반되며, 임상적으로 나 심초음파 상에서 더욱 진행된 심부전의 증거를 보이고, 나쁜 예후를 보이는 예측인자이다.