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Prognostic Importance of Pathophysiologic Markers in Patients With Heart Failure and Preserved Ejection Fraction

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Abstract

Background—Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome associated with multiple pathophysiologic abnormalities, including left ventricular (LV) diastolic dysfunction, longitudinal LV systolic dysfunction, abnormal ventricular-arterial coupling, pulmonary hypertension, and right ventricular (RV) remodeling/dysfunction. However, the relative prognostic significance of each of these pathophysiologic abnormalities in HFpEF is unknown.

Methods and Results—We prospectively studied 419 patients with HFpEF using echocardiography and sphygmomanometry to assess HFpEF pathophysiologic markers. Cox proportional hazards analyses were used to determine the associations between pathophysiologic markers and outcomes. Mean age was 65±12 years; 62% were women; 39% were black; comorbidities were common; and study participants met published criteria for HFpEF. RV abnormalities were frequent: 28% had abnormal tricuspid annular plane systolic excursion, 15% had reduced RV fractional area change, and 34% had RV hypertrophy. During a median follow-up time of 18 months, 102 (24%) were hospitalized for HF and 175 (42%) experienced the composite end point of cardiovascular hospitalization or death. Decreased LV compliance, measured as reduced LV end-diastolic volume at an idealized LV end-diastolic pressure of 20 mm Hg (EDV_{20}), and RV remodeling, as indicated by increased RV wall thickness, were the 2 pathophysiologic markers most predictive of worse outcomes: adjusted hazard ratio per 1 SD decrease in EDV_{20}=1.39 (95% confidence interval [CI], 1.10–1.75; P=0.006), and hazard ratio per 1 SD increase in RV wall thickness=1.37 (95% CI, 1.16–1.61; P<0.001). These associations persisted after additional adjustment for markers of HF severity. By contrast, markers of LV relaxation, longitudinal LV systolic dysfunction, and ventricular-arterial coupling were not significantly associated with adverse outcomes.

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Disclosures

None.

Conclusions—In patients with HFpEF, reduced LV compliance and RV remodeling are the strongest pathophysiologic predictors of adverse outcomes.

Keywords

heart failure, diastolic; heart ventricles; ventricular dysfunction, right

Heart failure with preserved ejection fraction (HFpEF) represents ≈50% of prevalent cases of HF and is associated with increased mortality independent of associated cardiac dysfunction and comorbidities.[1–3] No treatment has been demonstrated in clinical trials to improve outcomes in HFpEF,[4–9] a fact likely attributable to the etiologic and pathophysiologic heterogeneity associated with HFpEF.[10] Thus far, several pathophysiologic abnormalities have been reported in HFpEF, including (1) diastolic dysfunction, manifested both as impaired left ventricular (LV) relaxation and decreased LV compliance[11,12]; (2) longitudinal LV systolic dysfunction[13,14]; (3) abnormal ventricular-arterial (VA) coupling[15]; and (4) pulmonary hypertension with right ventricular (RV) remodeling and dysfunction.[16–18]

Impaired LV contractility[19] and variably diastolic dysfunction have been independently linked to worsened outcomes in HFpEF,[3,20,21] but no such association is known for other pathophysiologic abnormalities, and no previous studies have compared the relative prognostic use of pathophysiologic parameters in HFpEF. Abnormalities in RV structure and function are potent predictors of adverse outcomes in a wide variety of cardiac diseases. In patients with HF and reduced EF, RV dysfunction is a well-established and strong predictor of outcomes, including death.[22–25] More recent data indicate that RV hypertrophy predicts incident HF and reduced survival even in subjects free of baseline cardiovascular disease.[26] RV dysfunction is common in HFpEF, with a prevalence of ≈75% depending on the metric used; however, no previous study has linked RV dysfunction with outcomes in this population.[17,27]

Given the lack of proven effective treatments for HFpEF, a better understanding of the relative impact of known pathophysiologies on outcomes in at-risk HFpEF patients could help identify pathophysiologic states that would be most important to improve outcomes. We hypothesized that among the known pathophysiologic markers in HFpEF, RV abnormalities would be most predictive of adverse outcomes. Therefore, we prospectively studied the prognostic importance of a variety of pathophysiologic markers in a well-characterized HFpEF cohort.

Methods

Study Population

Between March 2008 and May 2011, consecutive patients were prospectively enrolled from the outpatient clinic of the Northwestern University HFpEF Program as part of a systematic observational study of HFpEF (ClinicalTrials.gov; NCT01030991). All patients were enrolled in the study in the outpatient setting after a hospitalization for HF. Patients were initially identified by an automated daily query of the inpatient electronic medical record at

Northwestern Memorial Hospital using the following search criteria: (1) diagnosis of HF or the term heart failure in hospital notes; or (2) B-type natriuretic peptide (BNP) >100 pg/mL; or (3) administration of ≥2 doses of intravenous diuretics. Patients were offered postdischarge follow-up in a specialized HFpEF outpatient program if they met the following 3 inclusion criteria: age ≥21 years, LVEF ≥50%, and presence of HF as defined by Framingham criteria.[28] Posthospitalization, HF diagnosis was confirmed in the outpatient HFpEF clinic. Consistent with previously published criteria,[29] all patients were found to have ≥1 of the following 3 diagnostic hallmarks of HFpEF: grade 2 or worse LV diastolic dysfunction on echocardiography; elevated pulmonary capillary wedge pressure or LV end-diastolic pressure on invasive hemodynamic testing; or elevated BNP (>100 pg/mL). Patients were excluded if they had more than moderate valvular disease, previous cardiac transplantation, previous history of reduced LVEF <40% (ie, recovered EF), LV end-diastolic volume (EDV) >97 mL/m^2, or constrictive pericarditis. All study participants gave written informed consent, and the institutional review board at Northwestern University approved the study.

Clinical Characteristics

We collected the following data in all study participants: demographics, race/ethnicity, New York Heart Association (NYHA) functional class, comorbidities, medications, vital signs, body mass index, and laboratory data, including serum sodium, blood urea nitrogen, creatinine, hemoglobin, and BNP. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation. Comorbidity definitions are included in the Data Supplement.

Echocardiography

All study participants underwent comprehensive 2-dimensional echocardiography with Doppler and tissue Doppler imaging using commercially available ultrasound systems with harmonic imaging (Philips iE33 or 7500; Philips Medical Systems, Andover, MA; or Vivid 7, GE Healthcare, General Electric Corp, Waukesha, WI). Blood pressure was recorded at the time of echocardiography using a digital blood pressure monitor (Omron HEM-907XL; Omron Healthcare Inc, Vernon Hills, IL). Cardiac structure and function were quantified as recommended by the American Society of Echocardiography,[30–32] including the use of the biplane method of discs (as opposed to M-mode–derived formulas) for the calculation of LV volumes. All measurements were performed by an experienced research sonographer (blinded to clinical data and outcomes) using ProSolv 4.0 echocardiographic analysis software (ProSolv CardioVascular; FujiFilm, Indianapolis, IN) and verified by an experienced investigator with expertise in echocardiography.

LV Diastolic Function

Comprehensive diastolic functional assessment was performed according to published guidelines.[31] LV relaxation was estimated using tissue Doppler e′ velocity. Given the contribution of RV to septal e′, we used e′ measured at the lateral mitral annulus as an estimate of LV diastolic relaxation. For the estimation of LV compliance, we calculated the end-diastolic pressure–volume relationship (EDPVR) using a single-beat method[33] with the equation: $LVEDP=\alpha(LVEDV)^{\beta}$, where LVEDP is the LV end-diastolic pressure. EDPVR

represents the nonlinear relationship between ventricular pressure and volume at end diastole and can be estimated noninvasively. The parameters α and β, which are constants that allow point measurements of nonlinear EDPVR as reviewed elsewhere,[34] were calculated for each individual based on their LVEDV and LVEDP (estimated by [1.9+1.24*(lateral E/e′ ratio)]).[35] These parameters were then used to calculate LVEDV at an idealized LVEDP of 20 mm Hg (EDV_{20}) for each patient as a basis for determining whether EDPVR was related to outcomes. For the purpose of sensitivity analyses, EDV_{20} was recalculated using the average of septal and lateral e′ velocities to derive E/e′.

LV Systolic Function

To evaluate LV contractility, we estimated the end-systolic PVR as represented by the slope of end-systolic elastance (E_{es}).[34] E_{es} is a load-independent measure of LV contractility and can be estimated using a single-beat method.[36,37] The relationship between end-systolic pressure (P_{es}) and end-systolic volume (ESV) was defined as: $P_{es}=E_{es}(ESV–V_0)$. Using 0.9*(systolic blood pressure) at the time of echocardiography as an estimate of P_{es}, we estimated V_0, the volume–axis intercept, for each patient. We generated the estimated ESV at an idealized P_{es} of 120 mm Hg (ESV_{120}) for each patient to determine whether end-systolic PVR was associated with adverse outcomes.

Longitudinal LV systolic function was estimated using tissue Doppler s′ velocity of the lateral mitral annulus. Tissue Doppler s′ velocity of the medial (septal) mitral annulus was also recorded for comparison purposes.

VA Coupling

For the purpose of VA coupling measurements, LV quantification and estimation of E_{es} were performed as described above. Effective arterial elastance (E_a), which is a measure of systemic arterial stiffness, was estimated using the equation: E_a=0.9*systolic blood pressure/stroke volume.[38] Stroke volume was estimated on echocardiography using the equation: stroke volume=(LV outflow tract diameter/2)^2×π×LV outflow tract velocity time integral. VA coupling was defined as E_a/E_{es}.[34]

RV Assessment

Echocardiographic markers of RV structure and function, including RV end-diastolic and end-systolic area (indexed to body size),[39] RV basal diameter, RV wall thickness, RV fractional area change (RVFAC), and tricuspid annular plane systolic excursion (TAPSE) were measured using 2-dimensional echocardiography and quantified as recommended by the American Society of Echocardiography.[32] RV hypertrophy was defined as RV end-diastolic free wall thickness >5.0 mm (measured in the subcostal view and measurable in 362/419 [86%] of patients); abnormal TAPSE was defined as <1.6 cm, and abnormal RVFAC was defined as <35%.[32] Pulmonary artery pressure (PASP) and right atrial pressure (RAP) were estimated using echocardiography as previously described.[16,40]

Outcomes

After enrollment, study participants were evaluated in the Northwestern HFpEF Program at least every 6 months or as clinically indicated. At each visit, intercurrent hospitalizations

were documented, reviewed, and categorized as due to cardiovascular or noncardiovascular causes. For cardiovascular hospitalizations, specific causes (eg, HF, acute coronary syndrome, arrhythmia) were identified. Every 6 months, participants (or their proxy) were contacted to determine vital status with verification of deaths through query of the Social Security Death Index. Enrollment date was defined as the first visit to the outpatient HFpEF clinic. Date of last follow-up was defined as date of death or last HFpEF clinic visit. Follow-up was complete in all patients. Our primary end point was a combined outcome of cardiovascular hospitalization and death, which included hospitalization for any cardiovascular cause (including HF) and death from any cause. We also assessed the secondary outcome of HF hospitalization.

Statistical Analysis

Clinical characteristics, laboratory data, and echocardiographic parameters were summarized for the full cohort. Categorical variables are displayed as count and percentage, and continuous data with a normal distribution are displayed as mean±SD. Right-skewed data are presented as median (first to third quartiles). Intra- and interobserver variability analyses of select pathophysiologic markers (EDV_{20} and RV wall thickness) were conducted in a randomly selected subset of 20 HFpEF patients (Table I in the Data Supplement). A comparison of study participants with versus without measurable RV wall thickness is displayed in Table II in the Data Supplement.

For survival analyses, all pathophysiologic measurements were standardized to display hazard ratios for a 1 SD worsening of each pathophysiologic marker. We used Cox proportional hazards regression to evaluate the unadjusted relationship between the markers of HFpEF pathophysiology and outcomes (model 1). Models were then adjusted for age, sex, and clinical comorbidities, including body mass index, coronary artery disease, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, estimated glomerular filtration rate, hemoglobin, degree of mitral regurgitation, LV mass index, and NYHA functional class (model 2). For pathophysiologic variables that were significant with $P<0.05$ after adjustment, we performed additional Cox regression analyses using models with further adjustment for common markers of HF severity, including estimated PASP, estimated RAP, BNP, E/e' ratio, and left atrial volume index. Because some of these variables had missing values, we adjusted for each marker of HF severity individually to avoid sample size depletion in our multivariable models.

Multiplicative interaction terms were created to test the interaction between all covariates and the primary predictor variable (ie, RV wall thickness or EDV_{20}) to test for interactions in the associations with outcome variables. $P<0.05$ for the interaction term was used as evidence of a significant interaction. Model comparison was performed using the likelihood ratio (LR) test. All analyses were performed using Stata 12 (StataCorp, College Station, TX).

Results

Baseline Characteristics

Clinical characteristics for the entire HFpEF cohort (N=419) are shown in Table 1. The average age was 65 years, 62% were women, and nearly half of the study participants were nonwhite. Comorbidities, including coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking, were common. Advanced HF (NYHA functional class III or IV) was present in 49%, and BNP was elevated in the majority of patients. As mentioned above, all study participants were required to meet ≥1 objective criterion (elevated BNP, grade 2 or 3 diastolic dysfunction, or elevated pulmonary capillary wedge pressure) for the confirmation of HF diagnosis. Of the 419 subjects, 293 (70%) had elevated BNP and 303 (72%) had grade 2 or 3 diastolic dysfunction. Study subjects who met neither of these criteria (N=38 [9%]) were all confirmed to have elevated pulmonary capillary wedge pressure (>15 mm Hg).

Echocardiographic Characteristics

Table 2 summarizes the echocardiographic characteristics of the study cohort. The majority of study participants had concentric LV remodeling, as demonstrated by increased LV mass/volume ratio and increased relative wall thickness. LV hypertrophy, as defined by elevated LV mass index, was present in 59% of the cohort. Hemodynamic estimates by echocardiography demonstrated increased PASP, RAP, and E/e′ ratio—evidence of pulmonary hypertension, fluid overload, and elevated LV filling pressures, respectively. LV diastolic function was abnormal based on reduced tissue Doppler e′ velocity and EDV_{20}, increased left atrial volume index, and a high frequency of grade 2 or worse diastolic function in the study participants. Although LVEF was preserved (mean 61%), longitudinal LV systolic function as measured by tissue Doppler s′ velocity was decreased.

Increased RV wall thickness, indicative of RV hypertrophy, was present in 34% of the study participants. RV chamber size was increased in approximately one third of the cohort (eg, RV basal diameter >4.2 cm in 30% of the study participants). Although the majority of study patients had TAPSE and RVFAC values within the normal range, 28% had reduced TAPSE (<1.6 cm) and 14% had reduced RVFAC (<35%).

Clinical Outcomes

The median follow-up time was 17.7 months (25th–75th percentile, 9.5–30.0 months). During the follow-up period, 138 patients (33%) were hospitalized for a cardiovascular reason, 102 (24%) were hospitalized for HF, 59 (14%) died, and 175 (42%) experienced the composite end point of cardiovascular hospitalization or death.

In unadjusted Cox proportional hazards models (model 1), conventional hemodynamic markers of HF severity (estimated PASP, estimated RAP, log BNP, and E/e′) were significantly associated with an increased risk for the combined outcome of cardiovascular hospitalization and death as well as HF hospitalization alone (Table 3). Furthermore, in unadjusted analyses, multiple parameters of RV structure/function and LV parameters (EDV_{20} and s′ velocity) were associated with the composite outcome. Of the conventional

markers of HF severity, estimated RAP and BNP remained predictive of outcomes after adjustment for clinical covariates (model 2).

Association of Reduced LV Compliance With Worse Outcomes

Lower EDV_{20} (reflecting a stiffer LV) was associated with both the combined outcome of cardiovascular hospitalization and death, as well as HF hospitalization, after adjustment for clinical covariates (Table 3; Figure I in the Data Supplement). Additional models adjusting for markers of HF severity (estimated PASP, estimated RAP, log BNP, and E/e′) did not attenuate the prognostic utility of EDV_{20} (Table 4). Recalculation of EDV_{20} using average e′ or septal e′ velocity (for the calculation of E/e′) did not change any of the results. Testing for interactions (Table III in the Data Supplement) demonstrated that there was a significant interaction between EDV_{20} and hemoglobin. EDV_{20} was associated with the composite outcome in patients who were not anemic (hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.13–2.40; P=0.001), but there was no association in those who were anemic (HR, 1.17; 95% CI, 0.95–1.46; P=0.13). The interaction between EDPVR and hemoglobin level is demonstrated in Figure 1.

Using an alternative equation proposed for estimating LVEDP in subjects with atrial fibrillation,[41] we recalculated EDV_{20} in 14% of the cohort who had atrial fibrillation at the time of echocardiography. Replacing the revised estimates of EDV_{20} for patients in atrial fibrillation did not affect the relationship between EDV_{20} and outcomes (adjusted HR for the combined outcome of cardiovascular hospitalization or death=1.37, 95% CI, 1.08–1.74; P=0.008).

To exclude the possibility that patients with HFpEF due to amyloidosis were driving the association between EDV_{20} and worse outcomes, we repeated our analyses after removing patients with cardiac amyloidosis (N=15) from the cohort. Baseline characteristics and echocardiographic parameters were not significantly different compared with the entire cohort. Cox proportional hazards modeling (Tables IV and V in the Data Supplement) showed that the removal of patients with cardiac amyloidosis did not eliminate the association between EDV_{20} and the primary outcome (HR per 1 SD decrease in EDV_{20}=1.32; 95% CI, 1.04–1.67; P=0.02), which was not significantly different than the entire cohort (HR, 1.39; 95% CI, 1.10–1.75; P=0.006). The adjustment for markers of HF severity did not blunt this association.

Association of RV Abnormalities With Worse Outcomes

Among measurements of RV structure and function, RV wall thickness was the strongest predictor of outcomes (Figure 2; Figure I in the Data Supplement). Additionally, RV end-diastolic area index, RV end-systolic area index, and RV basal diameter, all measures of RV dilatation, were associated with worse outcomes on unadjusted analyses and remained associated with worse outcomes after adjustment for clinical covariates (Table 3). Of the RV function parameters, TAPSE was predictive of HF hospitalization but not the primary (composite) outcome, whereas RVFAC did not remain significantly associated with outcomes after multivariable adjustment (Table 3). Excluding patients with chronic obstructive pulmonary disease did not eliminate the aforementioned associations between

RV parameters and outcomes (data not shown). Excluding patients with cardiac amyloidosis (N=15) also did not change the association between increased RV wall thickness and worse outcomes (Tables III and IV in the Data Supplement).

The prognostic utility of RV wall thickness for all outcomes, and TAPSE for HF hospitalization, were not significantly attenuated by adjustment for HF severity (Table 4). The associations between RV dilation and outcomes were somewhat attenuated after adjustment for markers of HF severity (Table 4). There was an interaction between RV wall thickness and LV mass index in predicting the composite outcome (Table III in the Data Supplement). When adjusted for all the covariates, including LV mass index, in model 2, RV wall thickness was more predictive of the composite outcome in patients without LV hypertrophy (adjusted HR, 1.56; 95% CI, 1.19–2.04; P=0.001) compared with those with LV hypertrophy (adjusted HR, 1.31; 95% CI, 1.06–1.62; P=0.014).

Additive Prognostic Importance of Reduced EDV_{20} and RV Abnormalities

Figure 3 shows the Kaplan–Meier curves for the composite end point, stratified by median EDV_{20} and median RV wall thickness. Because EDV_{20} and RV wall thickness were the 2 strongest predictors of outcomes, we evaluated whether these 2 parameters were correlated, but found no significant relationship between them (r=−0.02; P=0.67).

The addition of these predictors to the multivariable model (model 2) showed that RV wall thickness and EDV_{20} have predictive ability beyond the baseline model (LR test P=0.0003 and 0.005 for RV wall thickness and EDV_{20}, respectively). RV wall thickness was superior to EDV_{20} when both were included in the multivariable model (LR test P=0.002 when RV wall thickness added to model 2 plus EDV_{20}; LR test P=0.09 when EDV_{20} added to model 2 plus RV wall thickness). We also tested the additive value of RV wall thickness and EDV_{20} on top of conventional echocardiographic predictors of worse outcomes (LVEF, E/e′ ratio, LA volume index, TAPSE) and comorbidities. Both RV wall thickness (LR test P=0.002) and EDV_{20} (LR test P=0.039) demonstrated incremental prognostic value over conventional echocardiographic characteristics.

HFpEF patients with EDV_{20} below the median (<80.6 mL) and RV wall thickness above the median (>4.8 mm) had worse outcomes compared with either abnormality alone (Figure 4). Similarly, higher RV wall thickness and lower TAPSE were also additive for the outcome of HF hospitalization (Figure 5).

Discussion

In a contemporary HFpEF population, we prospectively evaluated the relationship between markers of different pathophysiologies associated with HFpEF and adverse outcomes. We found that lower LV compliance (determined by reduced EDV_{20}) and increased RV remodeling (indicated by increased RV wall thickness) were both independently associated with the primary composite outcome of cardiovascular hospitalization or death, as well as HF hospitalization. Importantly, these parameters predicted outcomes after adjustment for age, sex, a wide range of comorbidities, and markers of HF severity. In addition, reduced EDV_{20} and increased RV wall thickness were uncorrelated and had an additive association

with outcomes, implying that these pathophysiologic changes are independent indicators of adverse prognosis in HFpEF. Conversely, impaired LV relaxation, longitudinal LV systolic function, and VA coupling did not predict outcomes, indicating that although these pathophysiologies may play a role in HFpEF development or exercise intolerance, they do not necessarily herald future morbidity and mortality. Collectively, these results offer insight into the most important pathophysiologies in HFpEF. Given that previously hospitalized HFpEF patients have poor prognosis, patients with increased RV wall thickness or reduced EDV_{20} represent those in the greatest need of intervention.

The role of the RV in HFpEF has been incompletely described. RV hypertrophy, defined electrocardiographically, has been linked to worse outcomes in pulmonary hypertension due to HFpEF.[42] Given the exquisite afterload dependence of RV, it is expected that RV dysfunction would occur in the setting of elevated pulmonary pressures,[43] and in pulmonary arterial hypertension, RV dysfunction has been associated with a worse prognosis, even in those patients with improvement in pulmonary vascular resistance on therapy.[44] RV systolic and diastolic dysfunction have both been shown to be prevalent in HFpEF,[17,27] but this has not been clearly associated with poor outcomes. In an echocardiographic study, reduced TAPSE, as a marker of RV systolic dysfunction, was linked to mortality in those with HF with reduced EF, but not in those with HFpEF.[45] In the present study, we showed an association between TAPSE and HF hospitalization, suggesting that RV dysfunction did drive some outcomes in HFpEF. However, RV wall thickness was a much stronger predictor of outcomes even after controlling for elevated pulmonary pressures, suggesting an independent association between RV wall thickness and outcomes in patients with HFpEF.

RV hypertrophy is thought to be an adaptive response to chronically elevated left-sided filling pressures and, consequently, would be expected to precede RV dysfunction. This in turn leads to RV decompensation, overt RV failure, and, predictably, worse outcomes. As such, metrics of frank RV dysfunction would be expected to be a stronger predictor of outcomes in HFpEF, contrary to our findings. Two possibilities exist for this phenomenon. First, longer follow-up (allowing for the progression of RV pathology) of this cohort could reveal a stronger association with echocardiographic measures of RV dysfunction and outcomes. Alternatively, better metrics of RV function, such as RV strain imaging,[46] or RV EF measured using 3-dimensional echocardiography or cardiac MRI, may more accurately reflect the degree of RV dysfunction in these individuals and consequently show a stronger association with outcomes. Regardless, as in patients with other cardiopulmonary disorders, we demonstrated for the first time that abnormalities of RV structure and function are associated with worse outcomes in patients with HFpEF.

Diastolic dysfunction is known to be an important pathophysiologic contributor to HFpEF,[11] and various markers of diastolic dysfunction have been linked to poor prognosis in HFpEF. The results from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Echocardiographic Substudy (CHARMES) indicated that diastolic dysfunction as measured by mitral inflow parameters using Doppler echocardiography predicted worse outcomes in HFpEF.[20] Other proxies for diastolic dysfunction, such as BNP, PASP, and E/e' ratio, have also been linked to worse prognosis, but these are all load-dependent measures.[21] Alternatively, Ohtani et al[21] proposed diastolic wall strain as a load-

independent, noninvasive measurement of diastolic stiffness and showed that this value predicted worse outcomes in HFpEF. However, it has been suggested that diastolic wall strain is likely to be a marker of systolic function because it is also an index of the degree of LV wall thickening.[10]

To our knowledge, ours is the first study to demonstrate echocardiographic estimation of LV diastolic chamber compliance (ie, EDV_{20}) as independently prognostic in HFpEF. These data illustrate the fact that although many pathophysiologic factors contribute to HFpEF, a stiff LV is important in dictating the natural history of HFpEF. Patients with cardiac amyloidosis are a subset of patients that can have particularly severe diastolic dysfunction (due to stiff ventricles) that drives outcomes.[47] However, we showed that even after excluding those with cardiac amyloidosis (N=15), EDV_{20} remained significantly associated with both composite outcome and HF hospitalization.

The reasons underlying the interaction between anemia and EDV_{20} in the prediction of outcomes in HFpEF (Figure 1) are unknown. Whereas reduced LV compliance was predictive of outcomes in nonanemic HFpEF patients, the association was eliminated in anemic HFpEF patients. As shown in Figure 1, LV volumes were larger in HFpEF patients with anemia, likely owing to increased cardiac output and increased circulating blood volume in anemic HFpEF patients. Although previous studies have shown an association between anemia and diastolic dysfunction,[48,49] these prior studies were based on mitral inflow, pulmonary vein flow, and E/e' characteristics, all of which can be altered by volume overload alone and not necessarily intrinsic diastolic dysfunction of the LV myocardium. Thus, in anemic HFpEF patients, LV compliance (as measured by EDV_{20}) may not be as important in predicting outcomes compared with other factors such as extracardiac causes of volume overload or anemia-related comorbidities.

The fact that tissue Doppler s' velocity and E_{es}, markers of longitudinal LV systolic function and chamber contractility, respectively, failed to emerge as predictors of adverse outcomes in our study further emphasizes the prognostic importance of diastolic pathophysiology, but it should be noted that, based on our findings, reduced LV diastolic compliance, and not impaired LV relaxation, seems to drive outcomes in HFpEF. Systolic function and VA coupling parameters have previously failed to predict outcomes. In a community-based cohort of HFpEF patients, E_{es}, E_a, and EF all failed to predict mortality, though stress-corrected midwall fractional shortening was predictive of adverse events.[19] Nonetheless, LV systolic dysfunction likely contributes to the development of HFpEF syndrome. Indeed, systolic dysfunction and diastolic dysfunction frequently coincide, implying shared risk factors and pathophysiology. However, our results suggest that although risk factors may be generally shared, underlying disease and pathways of disease progression are not necessarily uniform across all HFpEF patients. Those with increased RV wall thickness and significantly reduced LV compliance as indicated by a lower EDV_{20} are at greatest risk for poor outcomes and are in greatest need of targeted interventions.

Strengths and Limitations

The strengths of our study include the prospective and standardized recruitment of high-risk HFpEF patients and the use of detailed, quantitative echocardiographic phenotyping to

evaluate HFpEF pathophysiologies. Our study also included detailed adjudication of adverse events, and follow-up was complete on all patients. Thus, for the first time to our knowledge, we were able to determine the relative prognostic importance of several HFpEF pathophysiologies. Finally, the recruitment of patients posthospitalization provided a unique opportunity to study the pathophysiologic predictors of rehospitalization in a prospective fashion. Postdischarge, HF patients are at highest risk for adverse outcomes and have the most urgent need for effective therapies.[2]

Our study has some potential limitations. First and foremost, our study mainly provides pathophysiologic insights—the parameters we studied are not necessarily clinically useful markers for risk prediction. Although RV wall thickness and EDV_{20} provided incremental prognostic information, the increase in log LRs was modest; thus, there may be little clinical use in measuring markers such as EDV_{20}. Second, because we do not have data on the duration of HF, RV remodeling and dysfunction may represent a late pathophysiologic change that could explain its association with poor outcomes. However, the adjustment of HF severity did not nullify the association between RV remodeling and dysfunction and adverse outcomes. Third, although we performed detailed echocardiographic quantification, we did not measure the indices of RV diastolic function, which could have provided additional insight into the pathophysiology of RV dysfunction in HFpEF. RV wall thickness was also not measurable in 13.6% of the study participants because of lack of adequate subcostal views; however, the clinical characteristics among those with immeasurable RV wall thickness were similar to those with measurable RV wall thickness (Table II in the Data Supplement).

The use of EDV_{20} as a measure of LV compliance is also a limitation, because it is based on a single-beat, noninvasive methodology that requires the estimation of both LVEDV by the biplane method of discs and LVEDP by the E/e' ratio, which may be unreliable at values of 8 to 15. In addition, 14% of the cohort was in atrial fibrillation at the time of echocardiography; in these patients, E/e' ratio was still used to calculate EDV_{20}, although the calculation of EDV_{20} has not been validated in the setting of atrial fibrillation. However, we showed good reproducibility of EDV_{20} measurement, and any error in the single-beat estimation of EDPVR (EDV_{20}) would have most likely reduced our ability to show an association between reduced LV compliance and worse outcomes.

Finally, all the study participants were recruited from a single academic medical center. However, Northwestern Memorial Hospital serves a large, diverse urban environment. Although the participants in our cohort were younger than those described in epidemiological and registry HFpEF studies, the frequencies of comorbidities were similar, and our cohort was more racially diverse. Therefore, our cohort may represent the broader population of HFpEF patients.

Conclusions

Among the pathophysiologic abnormalities that contribute to the heterogeneous syndrome of HFpEF, reduced LV compliance and RV abnormalities are the strongest predictors of adverse outcomes. These specific pathophysiologies may represent targets for novel management strategies and therapies aimed at reducing morbidity and mortality in HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL PERSPECTIVE

Heart failure with preserved ejection fraction (HFpEF) represents ≈50% of prevalent cases of HF, but no treatment has improved outcomes in clinical trials. This fact is likely because of the pathophysiologic heterogeneity of HFpEF. Abnormalities in left ventricular (LV) diastolic function, longitudinal LV systolic function, ventricular-arterial (VA) coupling, and right ventricular (RV) structure and function have all been reported in HFpEF and likely contribute to the pathogenesis of the HFpEF syndrome. However, the relative contribution of these pathophysiologic abnormalities to adverse outcomes is not well understood. We aimed to study the prognostic importance prospectively of each of these pathophysiologies in a well-characterized HFpEF cohort. We determined that lower LV compliance (as estimated by a reduced LV end-diastolic volume at an idealized pressure of 20 mm Hg [EDV_{20}]) and increased RV remodeling (as indicated by increased RV wall thickness) are associated with both HF hospitalization and the composite outcome of cardiovascular hospitalization or death. Moreover, these associations were independent of age, sex, comorbidities, and markers of HF severity. Furthermore, these 2 pathophysiologic markers were uncorrelated and were additive in their association with adverse outcomes. Conversely, impaired LV relaxation, longitudinal LV systolic dysfunction, and abnormal VA coupling were not independently associated with adverse outcomes. These results suggest that both reduced LV compliance and worse RV remodeling are the most important pathophysiologies driving outcomes in HFpEF. Thus, targeting these 2 pathophysiologic domains may be the key to improving the track record of HFpEF clinical trials.

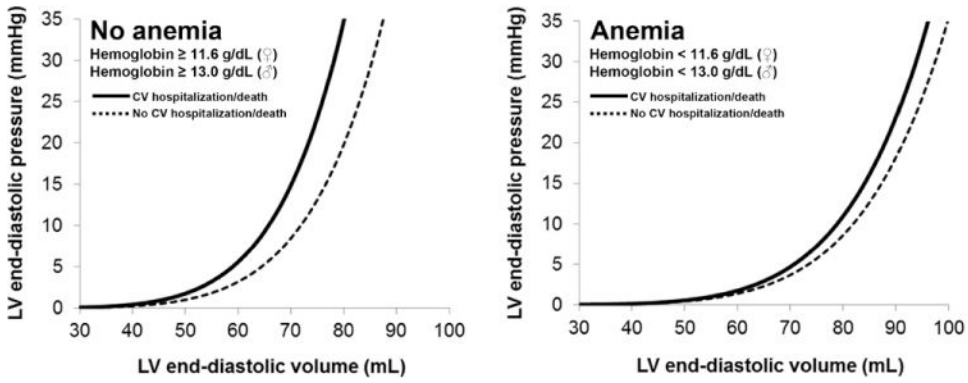

Figure 1.

LV end-diastolic pressure–volume relationships stratified by the combined outcome of cardiovascular hospitalization or death. In the group of heart failure with preserved ejection fraction (HFpEF) patients who were not anemic (N=224, 53% of the cohort), lower EDV_{20} was significantly associated with adverse events, as shown by the end-diastolic pressure–volume relationship (EDPVR) curves. The EDPVR curve was shifted up and to the left, reflecting a stiffer LV, in nonanemic patients who had an adverse event during follow-up. The association between LV stiffness (EDV_{20}) and outcomes was not present in HFpEF patients who were anemic at baseline (N=195, 47% of the cohort). CV indicates cardiovascular; and EDV_{20}, left ventricular (LV) end-diastolic volume at an idealized LV end-diastolic pressure of 20 mm Hg.

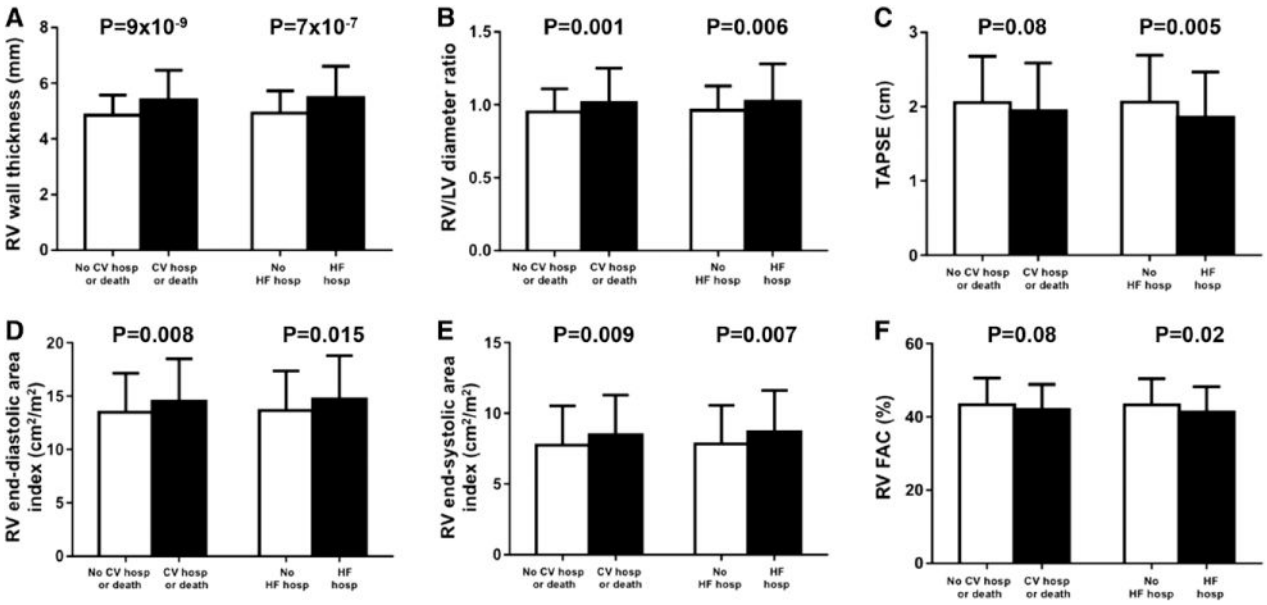

Figure 2.

Bar graphs comparing RV structural and functional parameters by the presence or absence of the primary (CV hospitalization or death) and secondary outcomes (HF hospitalization). RV wall thickness (**A**), RV/LV maximal diameter ratio (**B**), TAPSE (**C**), RV end-diastolic area index (**D**), RV end-systolic area index (**E**), and RVFAC (**F**). CV indicates cardiovascular; FAC, fractional area change; HF, heart failure; hosp, hospitalization; LV, left ventricular; RV, right ventricular; and TAPSE, tricuspid annular plane systolic excursion.

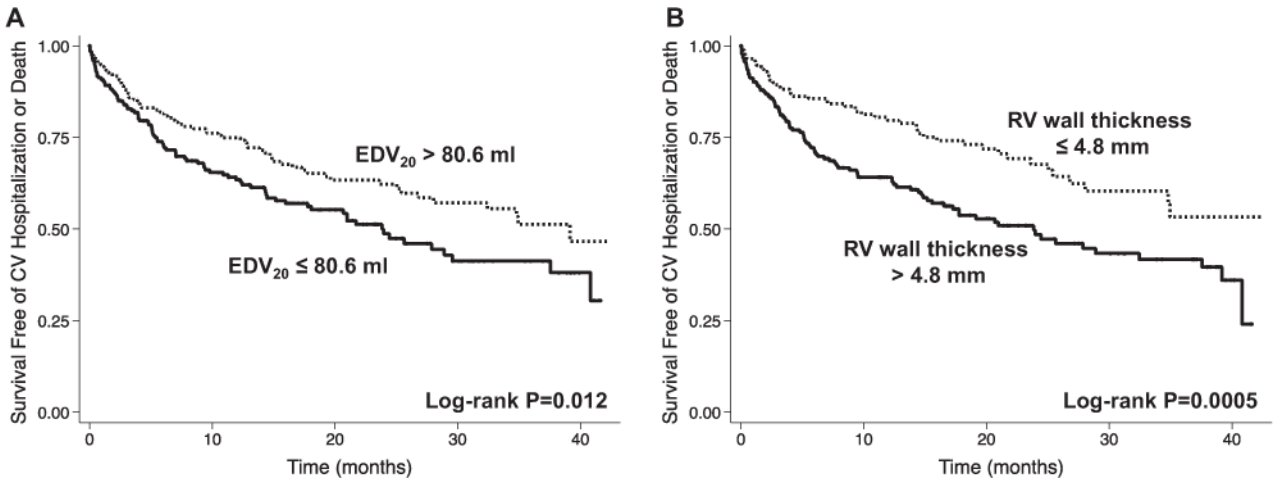

Figure 3.

Kaplan–Meier survival curves for cardiovascular hospitalization or death, stratified by the median values of EDV_{20} and RV wall thickness. **A**, Patients with reduced LV compliance (ie, stiffer LV). **B**, Patients with increased RV wall thickness were more likely to have an adverse outcome (cardiovascular hospitalization or death) during follow-up. EDV_{20} indicates left ventricular (LV) end-diastolic volume at an idealized LV end-diastolic pressure of 20 mm Hg; and RV, right ventricular.

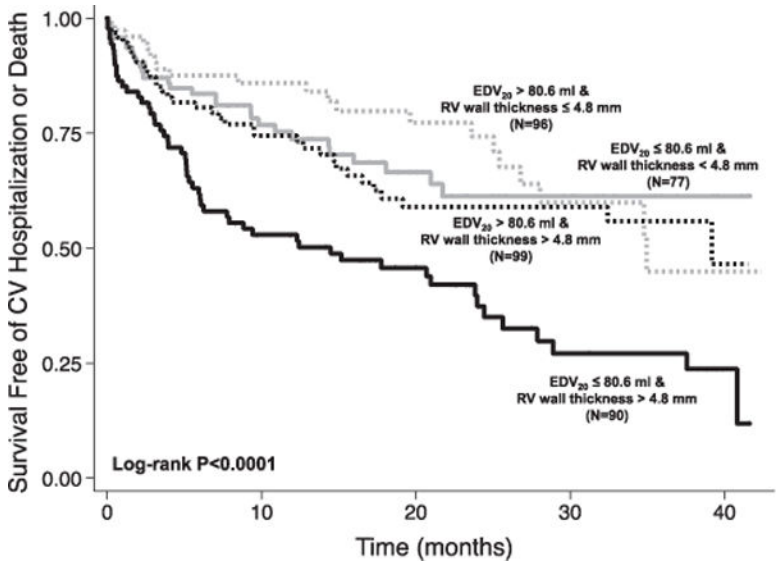

Figure 4.

Kaplan–Meier survival curves for cardiovascular hospitalization or death according to the presence or absence of reduced LV compliance and increased RV wall thickness. Patients with both reduced LV compliance and increased LV wall thickness had worse outcomes, indicating an additive effect of both abnormalities on prognosis. EDV_{20} indicates left ventricular (LV) end-diastolic volume at an idealized LV end-diastolic pressure of 20 mm Hg; and RV, right ventricular.

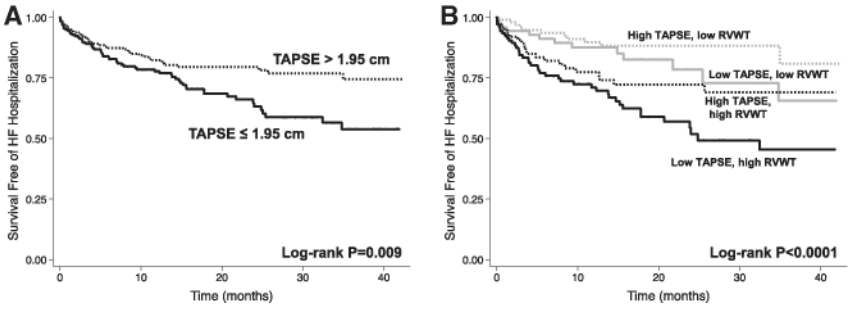

Figure 5.

Kaplan–Meier survival curves for heart failure hospitalization according to the presence or absence of RV dysfunction and increased RVWT. **A**, Heart failure hospitalization stratified by median TAPSE showing that patients with heart failure with preserved ejection fraction with lower TAPSE were more likely to be hospitalized for heart failure. **B**, Patients with low TAPSE and increased RVWT were most likely to be hospitalized for heart failure, showing the additive effect of both RV hypertrophy and dysfunction. RVWT indicates right ventricular wall thickness; and TAPSE, tricuspid annular plane systolic excursion. High/low TAPSE defined by median value (1.95 cm); and high/low RVWT defined by median value (4.8 mm).

Table 1

Clinical Characteristics of the Study Cohort

Clinical Characteristics	Total Cohort (N=419)
Age, y	65±13
Women	260 (62)
Race	
White	216 (52)
Black	162 (39)
Other	41 (10)
NYHA functional class	
I	50 (12)
II	164 (39)
III	192 (46)
IV	11 (3)
Comorbidities	
Coronary artery disease	200 (48)
Hypertension	323 (77)
Hyperlipidemia	228 (54)
Diabetes mellitus	137 (33)
Chronic kidney disease	139 (33)
Smoker	168 (40)
Atrial fibrillation	110 (26)
Obesity	222 (53)
Chronic obstructive pulmonary disease	154 (37)
Obstructive sleep apnea	152 (36)
Vital signs and laboratory data	
Heart rate, bpm	71±14
Systolic blood pressure, mm Hg	125±20
Diastolic blood pressure, mm Hg	70±12
Pulse pressure, mm Hg	55±17
Body mass index, kg/m^2	32.5±9.3
Serum sodium, mEq/L	138.4±2.9
Blood urea nitrogen, mg/dL	24.5±16.2
Serum creatinine, mg/dL	1.6±1.5
Estimated glomerular filtration rate, mL/min per 1.73 m^2	58±27
Fasting glucose, mg/dL	119±54
Hemoglobin, g/dL	11.9±1.9
B-type natriuretic peptide, pg/mL	230 (77–520)
Medications	
ACE inhibitor or angiotensin II receptor blocker	229 (55)
β-Blocker	280 (67)
Calcium channel blocker	134 (32)

Clinical Characteristics	Total Cohort (N=419)
Nitrate	53 (13)
Loop diuretic	61 (15)
Thiazide diuretic	246 (59)
Statin	96 (23)
Aspirin	209 (50)

Categorical variables are presented as counts and percentages; continuous variables are presented as mean±SD, and right-skewed variables are presented as median (first–third quartiles). ACE indicates angiotensin-converting enzyme; and NYHA, New York Heart Association.

Table 2

Echocardiographic Characteristics and Pathophysiologic Markers of the Study Cohort

Parameters	Total Cohort (N=419)	Normal Range
Left heart parameters		
LV end-systolic volume index, mL/m^2	16.3±6.5	<31
LV end-diastolic volume index, mL/m^2	40.9±11.5	<76
Relative wall thickness	0.51±0.15	≤0.42
LV mass/volume ratio	2.6±1.1	…
LV mass, g	210±79	<163 in women, <225 in men
LV mass index, g/m^2	104±38	<96 in women, <116 in men
LV hypertrophy	246 (59)	…
Left atrial volume index, mL/m^2	34.2±14.3	<28
Mitral regurgitation		…
None	246 (59)	
Mild	114 (27)	
Moderate	59 (14)	
LV ejection fraction, %	61±7	>55
Stroke volume, mL	50±15	>60
Cardiac index, L/min per m^2	2.9±1.1	>2.0
Hemodynamics		
Pulmonary artery systolic pressure, mm Hg	43.8±15.3	<30
Right atrial pressure, mm Hg	7.7±4.1	<5
E/e′ lateral annulus	13.3±7.9	<10
LV diastolic function parameters		
e′ lateral annulus, cm/s	9.3±3.9	Varies by age
End-diastolic volume$_{20}$, mL	85.8±28.5	…
LV systolic function parameters		
s′ lateral annulus, cm/s	8.5±2.7	Varies by age
End-systolic elastance, mm Hg/mL	2.3±0.7	…
End-systolic volume$_{120}$, mL	37.7±17.2	…
Ventricular-arterial coupling		
E_a/E_{es}	1.6±0.2	…
RV structural and functional parameters		
RV basal diameter, cm	3.9±0.7	≤4.2
RV length, cm	8.0±1.1	<8.0 in women, <8.8 in men
RV outflow tract diameter, PLAX, cm	3.4±0.6	≤3.3
RV end-systolic area index, cm^2/m^2	8.0±2.8	<6.5 in women, <6.9 in men
RV end-diastolic area index, cm^2/m^2	13.9±3.8	<12.6
RV wall thickness, mm	5.1±0.9	≤5.0
RV/LV maximum diameter ratio	0.98±0.20	<0.67
RV fractional area change, %	43±7	≥35

Parameters	Total Cohort (N=419)	Normal Range
Tricuspid annular plane systolic excursion, cm	2.0±0.6	≥1.6

Continuous variables are presented as mean±SD. LV indicates left ventricular; PLAX, parasternal long axis; and RV, right ventricular.

Table 3

Association of Pathophysiologic Markers with Outcomes in Heart Failure with Preserved Ejection Fraction

	Combined Outcome				Heart Failure Hospitalization			
	HR (95% CI)	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Predictor Variables	**Unadjusted (Model 1)**		**Adjusted (Model 2)***		**Unadjusted (Model 1)**		**Adjusted (Model 2)***	
Hemodynamic markers								
Estimated PASP, mm Hg (N=299)	1.31 (1.10–1.55)	0.002	1.04 (0.85–1.26)	0.71	1.34 (1.07–1.67)	0.01	1.04 (0.81–1.32)	0.78
Estimated RAP, mm Hg (N=373)	1.35 (1.16–1.58)	<0.001	1.22 (1.02–1.45)	0.03	1.48 (1.22–1.79)	<0.001	1.25 (1.00–1.56)	0.05
Log BNP, pg/mL	1.71 (1.45–2.02)	<0.001	1.45 (1.13–1.85)	0.003	1.79 (1.45–2.21)	<0.001	1.56 (1.14–2.13)	0.006
E/e′ ratio	1.29 (1.14–1.46)	<0.001	1.10 (0.95–1.28)	0.21	1.36 (1.18–1.57)	<0.001	1.17 (0.98–1.39)	0.08
LA volume index, mL/m^2	1.16 (1.02–1.34)	0.025	1.02 (0.85–1.21)	0.86	1.20 (1.02–1.42)	0.029	1.06 (0.85–1.31)	0.62
LV diastolic function								
Lateral e′ velocity, cm/s†	1.14 (0.96–1.36)	0.14	0.94 (0.76–1.15)	0.54	1.12 (0.9–1.39)	0.31	0.93 (0.71–1.22)	0.60
EDV_{20}, mL†	1.29 (1.08–1.54)	0.005	1.39 (1.10–1.75)	0.006	1.29 (1.03–1.62)	0.03	1.67 (1.22–2.30)	0.001
LV systolic function								
Lateral s′ velocity, cm/s†	1.26 (1.06–1.51)	0.01	1.07 (0.88–1.31)	0.49	1.17 (0.94–1.45)	0.16	0.96 (0.75–1.22)	0.72
E_{es}, mm Hg/mL	1.08 (0.93–1.26)	0.33	1.07 (0.91–1.27)	0.40	1.10 (0.91–1.34)	0.33	1.20 (0.96–1.49)	0.11
ESV_{120}, mL	1.21 (0.97–1.50)	0.09	0.84 (0.70–1.02)	0.08	0.83 (0.67–1.03)	0.09	0.79 (0.62–1.02)	0.07
Ventricular-arterial coupling								
E_a/E_{es}	1.04 (0.89–1.22)	0.58	1.02 (0.86–1.21)	0.78	1.07 (0.88–1.31)	0.48	1.03 (0.83–1.27)	0.82
RV structure and function								
RV wall thickness, mm (N=362)	1.50 (1.32–1.71)	<0.001	1.37 (1.16–1.61)	<0.001	1.55 (1.32–1.81)	<0.001	1.43 (1.17–1.75)	0.001
RV basal diameter, cm	1.27 (1.10–1.47)	0.001	1.26 (1.04–1.52)	0.017	1.33 (1.11–1.59)	0.002	1.21 (0.95–1.55)	0.12
RV/LV diameter ratio	1.32 (1.12–1.55)	0.001	1.18 (0.98–1.41)	0.08	1.34 (1.09–1.65)	0.005	1.27 (1.00–1.61)	0.047
RVEDAI, cm^2/m^2	1.26 (1.10–1.44)	0.001	1.28 (1.05–1.56)	0.02	1.30 (1.10–1.53)	0.002	1.41 (1.09–1.82)	0.009
RVESAI, cm^2/m^2	1.25 (1.10–1.42)	0.001	1.23 (1.01–1.49)	0.04	1.30 (1.11–1.53)	0.001	1.33 (1.04–1.69)	0.02
RVFAC, %†	1.18 (1.02–1.37)	0.02	1.05 (0.88–1.25)	0.60	1.27 (1.06–1.53)	0.01	1.08 (0.86–1.35)	0.52
TAPSE, cm†	1.19 (1.02–1.39)	0.03	1.09 (0.91–1.3)	0.33	1.37 (1.11–1.68)	0.003	1.30 (1.02–1.67)	0.04

BNP indicates B-type natriuretic peptide; CI, confidence interval; E_a, effective arterial elastance; E_{es}, end-systolic elastance; EDV, end-diastolic volume; ESV, end-systolic volume; HR, hazards ratio; LA, left atrial; LV, left ventricular; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; RV, right ventricular; RVEDAI, RV end-diastolic area index; RVESAI, RV end-systolic area index; RVFAC, RV fractional area change; and TAPSE, tricuspid annular plane systolic excursion.

*Adjusted for age, sex, and clinical comorbidities, which include body mass index, coronary artery disease, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disorder, obstructive sleep apnea, hypertension, glomerular filtration rate, hemoglobin concentration, degree of mitral regurgitation, LV mass index, and New York Heart Association functional class.

†HRs are reported as per SD increase in predictor variable except when noted by † in which case HRs are reported as per SD decrease in predictor variable. Outcome tallies for variables with missing data for the combined outcome and heart failure hospitalization are as follows: PASP (N=123, N=73); RAP (N=148, N=90); RV wall thickness (N=141, N=87).

Table 4

Association of Pathophysiologic Markers with Outcomes After Adjustment for Hemodynamic Markers of Heart Failure Severity

	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Predictor Variables	**Model 2* Plus PASP**		**Model 2 Plus RAP**		**Model 2 Plus Log BNP**		**Model 2 Plus E/e′**		**Model 2 Plus LAVI**	
Combined outcome										
EDV_{20}, mL†	1.64 (1.21–2.22)	0.002	1.35 (1.05–1.71)	0.018	1.36 (1.08–1.71)	0.008	1.36 (1.07–1.74)	0.012	1.39 (1.10–1.75)	0.006
RV wall thickness, mm	1.56 (1.26–1.92)	<0.001	1.34 (1.12–1.61)	0.001	1.37 (1.17–1.61)	<0.001	1.40 (1.14–1.72)	0.001	1.37 (1.17–1.61)	<0.001
RV basal diameter, cm	1.21 (0.91–1.53)	0.12	1.25 (1.01–1.56)	0.04	1.15 (0.94–1.40)	0.18	1.25 (1.03–1.51)	0.02	1.24 (1.03–1.50)	0.02
RVEDAI, cm^2/m^2	1.27 (1.00–1.61)	0.05	1.25 (1.00–1.57)	0.05	1.18 (0.96–1.44)	0.12	1.37 (1.06–1.78)	0.02	1.24 (1.03–1.50)	0.03
RVESAI, cm^2/m^2	1.28 (1.01–1.61)	0.04	1.18 (0.95–1.48)	0.14	1.13 (0.92–1.38)	0.24	1.21 (0.99–1.48)	0.06	1.19 (0.99–1.43)	0.06
Heart failure hospitalization										
EDV_{20}, mL†	1.67 (1.13–2.49)	0.011	1.62 (1.16–2.27)	0.005	1.70 (1.24–2.33)	0.001	1.62 (1.17–2.26)	0.004	1.69 (1.24–2.33)	0.001
RV wall thickness, mm	1.56 (1.20–2.04)	0.001	1.40 (1.12–1.74)	0.003	1.38 (1.13–1.69)	0.002	1.40 (1.14–1.72)	0.001	1.42 (1.16–1.74)	0.001
RV/LV diameter ratio	1.28 (0.97–1.69)	0.08	1.36 (1.07–1.73)	0.01	1.29 (1.05–1.60)	0.02	1.36 (1.10–1.69)	0.005	1.37 (1.11–1.70)	0.003
RVEDAI, cm^2/m^2	1.39 (1.02–1.90)	0.04	1.34 (1.00–1.79)	0.05	1.28 (0.98–1.66)	0.07	1.37 (1.06–1.78)	0.02	1.38 (1.07–1.79)	0.01
RVESAI, cm^2/m^2	1.34 (0.99–1.81)	0.06	1.27 (0.96–1.69)	0.10	1.22 (0.95–1.56)	0.13	1.30 (1.01–1.67)	0.04	1.31 (1.02–1.17)	0.03
TAPSE, cm†	1.47 (1.09–2.00)	0.01	1.33 (1.02–1.74)	0.03	1.26 (0.98–1.62)	0.07	1.30 (1.02–1.66)	0.04	1.30 (1.02–1.67)	0.04

BNP indicates B-type natriuretic peptide; CI, confidence interval; EDV, end-diastolic volume; ESV, end-systolic volume; HR, hazards ratio; LV, left ventricular; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; RV, right ventricular; RVEDAI, RV end-diastolic area index; RVESAI, RV end-systolic area index; and TAPSE, tricuspid annular plane systolic excursion.

*Adjusted for age, sex, and clinical comorbidities, which include body mass index, coronary artery disease, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disorder, obstructive sleep apnea, hypertension, glomerular filtration rate, hemoglobin concentration, degree of mitral regurgitation, LV mass index, and New York Heart Association functional class.

†HRs are reported as per SD increase in predictor variable except when noted by † in which case HRs are reported as per SD decrease in predictor variable.