It’s Time to Look at Heart Failure with Preserved Ejection Fraction

From the Right Side

Running title: Chatterjee et al.; Right ventricle in heart failure preserved ejection fraction

Neal Chatterjee, MD¹; Johannes Steiner, MD¹; Gregory D. Lewis, MD¹,²

¹Cardiology Division; ²Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Address for Correspondence:
Gregory D. Lewis MD
Heart Failure and Cardiac Transplantation Unit
Massachusetts General Hospital, Bigelow 800
Fruit Street
Boston, MA 02114
Tel: 617-726-9554
Fax: 617-726-4105
E-mail: glewis@partners.org

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Heart failure with preserved left ventricular (LV) ejection fraction (HFpEF) represents approximately half of patients with heart failure and confers similar morbidity and mortality as HF with reduced left ventricular ejection fraction (HFrEF).\(^1\) HFpEF has been characterized by abnormal LV diastolic function, abnormal LV-central vascular coupling, impaired systolic reserve and chronotropic response during exercise, abnormal skeletal muscle function, and dysfunction of the right ventricular-pulmonary vascular (RV-PV) unit. The pathophysiological heterogeneity underlying HFpEF likely explains, in part, why there are no HFpEF-specific therapies to date associated with improved survival in this population. Careful delineation of HFpEF subphenotypes on the basis of predominant pathophysiologic inputs may improve diagnostic classification, guide targeted therapy, and ultimately improve clinical outcome.

Historically, the RV has been considered to play a minor role in maintaining adequate blood flow and as a result the importance of RV function in various cardiopulmonary diseases has been under-investigated and often overlooked.\(^2\) In the normal heart, the right ventricle (RV) is closely coupled to a low impedance pulmonary vascular system that is best considered as a RV-pulmonary vascular (RV-PV) unit.\(^3\) In the setting of increased RV afterload it is increasingly recognized that RV function is critical for augmentation of forward cardiac output and prevention of systemic venous congestion. Accordingly, RV dysfunction has emerged as a potent predictor of poor prognosis in pulmonary arterial hypertension (PAH), intrinsic lung disease, and HFrEF.\(^4,5\) In HFrEF, integrated indices of RV-PV dysfunction such as the combination of RVEF<0.35 and elevated PAP confer a 7-fold increase in mortality.\(^6\) These findings have appropriately prompted efforts to therapeutically target the RV-PV unit with pulmonary vasodilators, with mixed results to date in HFrEF,\(^7,8\) likely owing to whether patients selected had a high burden of RV-PV dysfunction.
At present, the prevalence and prognostic significance of abnormal RV-PV structure and function in patients with HFP EF remains an open question (Table 1).\textsuperscript{9-14} The study by Dr. Mohammed and colleagues in this issue of Circulation\textsuperscript{15} represents an important step forward in our understanding of the burden and significance of RV-PV dysfunction in HFP EF as defined by multiple easily-derived echocardiographic measurements. Strengths of the study include (1) investigation of a HFP EF cohort at a center of excellence in HFP EF and echocardiography with complete follow up data available on HF hospitalization rate, cardiovascular (CV) mortality, and all-cause mortality; (2) the establishment of an independent relationship between RVD and prognosis in HFP EF using feasible and readily available echocardiographic measurements; and (3) careful disentanglement of prognostic contributions of abnormal RV structure and function versus pulmonary vascular pressures. RVD in this study was defined by one of two echocardiographic metrics: (1) reduced tricuspid annular plane systolic excursion (TAPSE), which captures the degree to which longitudinal contraction of the RV is preserved; and (2) integration of qualitative visual RV function assessment and quantitative RV:LV size ratio.

Patients in this study with RVD by either echocardiographic measurement demonstrated impaired LV performance (diastolic dysfunction), abnormal RV structure (increased RV dilation), and increased RV afterload (increased PA systolic pressure (PASP)). Both metrics of RVD were associated with increased mortality (all-cause and cardiovascular) as well as an increased risk of HF hospitalizations. These prognostic associations persisted following adjustment for clinical covariates and pulmonary pressure (PASP), although TAPSE no longer demonstrated significant association with all-cause mortality in multivariate models.

**Characteristics of the Study Population and Their Implications**

To understand the findings of the study it is important to consider the inclusion criteria for
HFpEF utilized, particularly since definitions of HFpEF vary across studies and the optimal
criteria to define HFpEF remain under debate.16 First, HFpEF patients in this study were
identified using the Framingham criteria for HF diagnosis, a diagnostic system significantly
reliant on clinical exam findings that largely reflect right heart dysfunction (eg. jugular venous
pressure elevation, hepatomegaly, hepatojugular reflux, ankle edema) and therefore may have
disproportionately identified HFpEF patients with RV dysfunction (HFpEF-RVD). In fact, the
use of Framingham criteria without requisite echocardiographic features of LV diastolic
dysfunction (eg. left atrial enlargement, E/e’) may have led to inclusion of subjects with RV-PV
dysfunction from other mechanisms of pulmonary hypertension (PH) beyond left heart
dysfunction (eg. pulmonary embolism, chronic obstructive pulmonary disease). Alternative
diagnostic systems which focus on LV-specific imaging criteria (eg. European Study Group on
Diastolic Heart Failure)17 or hemodynamic response to provocation (i.e. increment in PCWP
with exercise testing or saline loading) may identify a more LV-specific HF population with
lower prevalence and severity of RVD than that reported in the study by Mohammed et al. To the
credit of the authors, however, COPD and OSA were adjusted for in multivariable analyses and
RVD remained a significant prognostic indicator (Table 1).

Second, patients in this study were relatively older when compared to contemporary
randomized and observational HFpEF populations studied.16 Advanced age (>82 years, on
average, over the median 4.6 years of follow-up) likely contributed to the high mortality rate
during the study period (65%) and has also been associated with factors that impact RV afterload
such as reduced pulmonary vascular distensibility and increased pulmonary vascular resistance
during activity.18 In this study, the prevalence of cardiometabolic conditions was consistent with
other HFpEF cohorts (eg. hypertension in ~80%, atrial fibrillation and diabetes in ~1/3rd of
patients, mean GFR 53-57 ml/min/1.73m²). By either echocardiographic metric, patients with RVD were more likely to have atrial fibrillation and a permanent pacemaker and those with TAPSE-defined RVD were more likely to have coronary disease. Somewhat surprisingly, despite the association between right heart dysfunction and impaired renal function (owing to elevated central venous pressure and impaired cardiac output) in patients with HFrEF, pulmonary hypertension, and another HFpEF cohort, renal function was not significantly different between those with and without echocardiographically-defined RVD in this study.

Right ventricular dysfunction in HFpEF: Definition and Prevalence

In response to elevated afterload and PV dysfunction, the RV faces increased wall stress, subendocardial ischemia, and depletion of myocardial oxygen extraction reserve. Adaptive RV responses to elevated afterload include RV hypertrophy (concentric remodeling) and preservation of RV function at the macroscopic level (Figure 1). In contrast, maladaptive RV responses to increased afterload are characterized by RV dilation and hypokinesis, reflected at the ultrastructural level by increased fibrosis and at the subcellular level by increased apoptosis, contractile apparatus dysfunction, dysregulation of β-receptor signaling, impaired angiogenesis, and a metabolic switch to aerobic glycolysis. The temporal progression as well as molecular and metabolic adaptation of RVD in HFpEF is yet to be characterized.

Imaging of RV structure and function (Figure 1) is challenging because of its unique geometry, limited definition of the RV endocardial surface, the unique contraction pattern of the RV, as well as the load-dependence of RV function measurements. As highlighted recently in a model of RV pressure overload, established indices of RV function (RV fractional area change [RVFAC], RV myocardial performance index [RVMPI] and TAPSE) appear more closely related to ventricular-arterial coupling as opposed to intrinsic RV contractility, the latter of
which may better approximate the likelihood of improved RV contractility in response to pharmacotherapy intervention.\textsuperscript{25} While comprehensive comparison of available imaging metrics of RV structure and function would have been desirable (Figure 1), the study by Mohammed focused on only two: TAPSE and semi-quantitative RV function. TAPSE reflects longitudinal shortening of the RV and is a known determinant of RV stroke volume. In heterogeneous populations with variable prevalence of cardiovascular disease, TAPSE has shown modest correlation with gold-standard assessment of RVEF by MRI or nuclear ventriculography.\textsuperscript{23, 26} In addition, TAPSE has been proposed as an integrative marker of RV-PV performance in PAH based on significant associations with RV structural remodeling (right atrial enlargement, RV dilation) and inverse association with PVR.\textsuperscript{4} However, in PAH TAPSE demonstrated weaker correlations with RVEF compared to indices of transverse contraction (septum to RV free wall),\textsuperscript{27} suggesting important additional contribution of this bellows-like action in states of elevated RV afterload where ultrastructural alterations in septal fiber orientation and function may significantly impact RV cardiac output.

Mohammed and colleagues’ finding of a 33\% incidence of abnormal TAPSE is consistent with previous reports in HFrEF populations (Table 1). Lower TAPSE did not predict all-cause mortality in fully adjusted models but was independently associated with CV mortality and HF hospitalizations, consistent with the findings of Burke et al.\textsuperscript{28} Given the noted structural and mechanical adaptation of the RV in response to increased afterload and LV diastolic dysfunction, isolated metrics of longitudinal RV shortening (i.e. TAPSE) may not fully capture the complexity of RV adaptation in HFrEF.

The alternative metric of RVD utilized by Mohammed et al. was an integrative assessment of visually estimated RV function that relied on estimates of contractility and RV...
relative to LV size. This approach has not been validated in the heart failure population, and has
been shown to have significant inter-reader variability with limited accuracy compared to gold-
standard MRI assessment.29 Despite these limitations, and limited concordance of the two RV
measures as categorical variables, this approach identified 21% of the HFP EF population
characterized by higher PASP, more TR, and larger RV size. Mortality, CV mortality, and
hospitalization were significantly increased in patients with semi-quantitative RVD. Of note,
given the heterogeneous patterns of LV adaptation in HFP EF with possibly distinct prognostic
implications of eccentric versus concentric LV hypertrophy,30 descriptive and prognostic
markers of RV:LV ratio may need to additionally account for patterns of LV remodeling.

HFP EF-RVD: A Unique Clinical, Structural, and Hemodynamic Phenotype?

A critically important question raised by this study is whether HFP EF-RVD represents a distinct
subphenotype or simply a manifestation of worsening LV function and congestion that imposes
heightened afterload on the RV. While some indices of diastolic function (shorter deceleration
time, modestly higher LA size) were worse in HFP EF-RVD, LV relaxation (e’), LV mass and
LV filling pressure (E/e’) were the same in the most advanced RVD group vs. the normal RV
function group, and in the lowest TAPSE tertile compared to the highest. The identical E/e’
values are important to consider in light of the fact that the average PASP was 32% higher in the
moderate-to-severe RVD group compared to the normal RV group. This combination of findings
points to the presence of increased pre-capillary PAP (i.e. increased trans-pulmonary gradient) in
HFP EF-RVD. Studies using invasive hemodynamic measurements and echocardiography have
shown a wide range of PVR values in HFP EF (Table 1) and to date the prognostic and
functional significance of elevated PVR in HFP EF remains underinvestigated and unknown
(Table 1). The presence of a distinct subset of HFP EF patients with RV dilation relative to LV
size, RV hypokinesis, and high PVR should prompt consideration of the role of pulmonary vasodilator therapy in carefully selected HFpEF-RVD patients. Indeed, Guazzi et al showed marked hemodynamic improvements when phosphodiesterase 5 inhibition was administered to a HFpEF population with RVD (average TAPSE 11mm, PVR>3 WU, RAP>PCWP), yet no benefit in exercise capacity accrued in a broad HFpEF population treated with phosphodiesterase 5 inhibition in the RELAX Trial.

The authors frame additional mechanistic considerations based on their findings that atrial fibrillation and permanent pacing were associated with RVD. With reduced oxygen extraction reserve arising with high RV afterload in HFpEF, the authors appropriately postulate that HFpEF patients can ill-afford the negative inotropic effects of atrial fibrillation and RV pacing-induced dyssynchrony (Figure 1). While the sequence of RV structural adaptation to elevated RV afterload is uncharacterized in HFpEF, the prevalence of RV dilation and hypertrophy was nearly 30% in one recent HFpEF cohort and both demonstrated significant association with clinical outcome (Table 1). The more potent prognostication associated with semi-quantitative RVD compared to TAPSE-defined RVD may reflect more advanced RV structural remodeling, inclusive of abnormalities in transverse shortening, present in the former group. The authors do demonstrate that the prognostic significance of their RVD metrics persists even after adjustment for PASP – and by corollary, PASP maintains its prognostic significance at each strata of RVD. Similar prognostic association with elevated PAP has been identified in HFrEF, though the most potent prognosticator was the combination of abnormal RV function and elevated PAP.

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

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

Conclusion

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

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Conflict of Interest Disclosures: None.

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35. Gillis AM. Optimal pacing for right ventricular and biventricular devices: minimizing, maximizing, and right ventricular/left ventricular site considerations. *Circ Arrhythm Electrophysiol.* 2014;7:968-977.
Table 1. Prevalence and Prognostic Significance of RV-PV Structure and Function Measurements in HFrEF

<table>
<thead>
<tr>
<th>Study</th>
<th>Heart Failure Population</th>
<th>Classification of RV-PV Function</th>
<th>Prevalence</th>
<th>Outcome (Median F/U)</th>
<th>Hazard Ratio / Standard Deviation</th>
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<td>Death/HF hosp (18 mo)</td>
<td>Adj HR: 1.09 / 6mm ↓ TAPSE (p=NS)*</td>
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<td>Adj HR: 1.05 / 7% ↓ RVFAC (p=NS)</td>
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<td>28%</td>
<td>Death (18 mo)</td>
<td>Adj HR: 2.2 / 10% ↓ RVFAC (p=0.001)†</td>
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<td>14%</td>
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<td>Adj HR: 1.26 / 0.7 cm ↑ RVWT (p&lt;0.001)</td>
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<td>Adj HR: 1.26 / 0.7 cm ↑ RV base (p=0.02)</td>
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<td>Adj HR: 1.18 / 0.2 ↑ RV:LV ratio (p=NS)</td>
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<td>Death (18 mo)</td>
<td>Adj HR: 1.01 / 1 cm ↑ in RVEnDA (p=NS)</td>
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<td>Death</td>
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<td>Death (18 mo)</td>
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<td>Death (55 mo)</td>
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<td>Death/HF hosp (35 mo)</td>
<td>Adj HR: 1.23 / 10 mmHg ↑ PASP (p=0.03)</td>
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<td>CV death/SCD/HF hosp (35 mo)</td>
<td>Adj HR: 0.99 / 5% ↑ RVFAC (p=NS)</td>
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HF, heart failure; NYHA, New York Heart Association class; RV-PV, right ventricular-pulmonary vascular; F/U, follow-up; mo, months; RVH, right ventricular hypertrophy; vel; velocity; m/s, meter/second; TAPSE, tricuspid annular plane excursion; RVFAC, right ventricular fractional area change; Semi-quant RVD, semi-quantitative RV dysfunction; RVEDA, right ventricular end-diastolic area; PVR, pulmonary vascular resistance; TR, tricuspid regurgitation; HR, hazard ratio; Unadj, unadjusted; Adj, adjustment (unless otherwise specified adjustment is for clinical covariates); NS, not significant (p-value >0.05); CV, cardiovascular; SCD, sudden cardiac death; hosp, hospitalization; mPAP, mean pulmonary arterial pressure; TPG, trans-pulmonary gradient; IQR, inter-quartile range. Units for TAPSE are mm, for RVFAC is %, for PASP, mPAP, and TPG is mmHg, for RVEDA is cm². RV dilation is defined as RV end-diastolic dimension at the base > 42mm. RVH is defined as RV free wall thickness >5mm. *Unless otherwise specified, hazard ratio are reported as per standard deviation increase in predictor variable. – indicates that the endpoint or value of interest was not assessed. †Adjustment includes PASP. ²Echocardiography-derived pulmonary vascular resistance.
Figure Legend:

Figure 1. (A) Schematic representation of progression of heart failure with preserved ejection fraction (HFrEF) as reflected by development of elevated left atrial pressures (LAP), development and progression of pulmonary hypertension (PH) subtypes, stages of right ventricular remodeling, and impact of co-morbidities. RV, right ventricular; TPG, transpulmonary gradient; PAP, pulmonary artery pressure; OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; LV, left ventricle; LA, left atrium; MR, mitral regurgitation; HTN, hypertension; RVH, right ventricular hypertrophy; HK, hypokinesis; Afib, atrial fibrillation. (B) Imaging indices of abnormal right ventricular-pulmonary vascular (RV-PV) structure and function in HFrEF including echocardiography, MRI, PET, and invasive hemodynamics. PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; PVR, pulmonary vascular resistance; Eccentr, eccentricity; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; MPI, myocardial performance index; IVA, isovolumic acceleration; TR, tricuspid regurgitation; LGE, late gadolinium enhancement; FDG, fluorodeoxyglucose; RVEF, right ventricular ejection fraction; mPAP, mean pulmonary artery pressures; PCWP, pulmonary capillary wedge pressure; DPG, diastolic pulmonary gradient; PAC, pulmonary artery compliance (RV stroke volume/PA pulse pressure); RVSWI, right ventricular stroke work index; RVEDVI, right ventricular end-diastolic volume index; RAP, right atrial pressure; CO, cardiac output; Ex PAP, exercise pulmonary arterial pressure.
Atrial Fibrillation, RV pacing, Coronary disease, Neurohormonal activation

Morbidity & Mortality

Pulmonary Vasoconstriction
- Reactive to LAP↑
- ↓NO/cGMP, ↑ET
- Hypoxia
PA Structural Remodeling

LV + LA stiffness, MR,
LV-Vasc uncoupling, obesity,
renal dysfunction, HTN

↑Glycolytic metabolism
↑Subendocardial Ischemia
↓O₂ extraction reserve
↓β-receptor signaling
↑Fibrosis + apoptosis

Figure 1A
<table>
<thead>
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<th>Pulm Vasc</th>
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<th>Invasive</th>
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<td><strong>Resistance</strong></td>
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<td>RV:LV ratio</td>
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<td>RV hypertrophy</td>
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<tr>
<td><strong>RV Function</strong></td>
<td>TAPSE</td>
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**Figure 1B**
It's Time to Look at Heart Failure with Preserved Ejection Fraction from the Right Side
Neal Chatterjee, Johannes Steiner and Gregory D. Lewis