Association of pulmonary hypertension and right ventricular function with exercise capacity in heart failure

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Abstract

Aim Relationships of pulmonary artery systolic pressure (PASP) and right ventricular (RV) dysfunction with exercise capacity are understudied. To assess the relationship of PASP and RV function with functional capacity and ventilatory efficiency in heart failure (HF) with a wide range of left ventricular ejection fraction (LVEF).

Methods and results Five hundred thirty-two consecutive HF patients referred for cardiopulmonary exercise testing [percent predicted peak VO2 (ppVO2), V̇E/V̇CO2 slope] and echocardiography [LVEF, PASP, and RV fractional area change (RVFAC)] were studied. Associations of PASP and RVFAC with ppVO2 and V̇E/V̇CO2 slope were assessed by multivariable linear regression and restricted cubic splines. Associations with composite of death, heart transplant, and LV assist device (median 3.9 year follow-up) was assessed using multivariable Cox proportional hazard models.

Mean age was 56 ± 14 years and mean LVEF was 35 ± 15%. Mean PASP was 34 ± 12 mmHg, RVFAC was 41 ± 13%, ppVO2 was 60 ± 21%, and V̇E/V̇CO2 slope was 35 ± 12. After adjusting for demographics, co-morbidities, LVEF, mitral regurgitation severity, and left atrial volume index, higher PASP was associated with worse ppVO2 (P = 0.004) and was more robust in patients with LVEF ≥45% vs. <45% (Pinteraction = 0.006). Lower RVFAC was associated with both worse ppVO2 (P = 0.002) and higher V̇E/V̇CO2 slope (P = 0.002). Higher PASP and lower RVFAC were both associated with heightened risk of composite endpoint (HR 1.07 per 5 mmHg increase, P = 0.03; HR 1.17 per 5% decrease, P < 0.001, respectively).

Conclusions In HF across wide range of LVEF, greater PASP and worse RV function predict worse functional capacity and greater respiratory inefficiency, independent of LV structure and function.

Keywords Heart failure; Pulmonary hypertension; Right ventricular dysfunction; Functional capacity; Respiratory efficiency

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Introduction

Both pulmonary hypertension (PH) and right ventricular (RV) dysfunction predict worse functional capacity and ventilatory efficiency and worse clinical outcomes in heart failure (HF) patients.1 PH is observed in 40–75%2, 3 of patients with HF with reduced ejection fraction (HFrEF) and 30–80%4,5 of those with HF with preserved ejection fraction (HFrEF), while RV dysfunction has been reported in 60% of HFrEF and up to 50% of HFrEF patients.6 PH in HF primarily occurs secondary to left atrial hypertension. RV dysfunction in this context is thought to be secondary to elevated RV afterload, although existing studies also suggest a primary contractile abnormality of the RV itself.7 Limited data are available regarding the association of PH and RV dysfunction with functional capacity and ventilatory efficiency independent of the degree of left heart dysfunction and left atrial hypertension and the extent to which these associations vary by left ventricular ejection fraction [LVEF]–based HF phenotype.
We studied the association of pulmonary artery systolic pressure (PASP), RV function [RV fractional area change (FAC)], and the RVFAC/PASP ratio with functional capacity (percent predicted peak oxygen consumption [VO\textsubscript{2}]) and respiratory efficiency [minute ventilation to carbon dioxide production ratio (V\textsubscript{E}/V\textsubscript{CO2} slope)] in 532 HF patients with a broad range of LVEF referred for cardiopulmonary exercise testing (CPET) and echocardiography. We hypothesized that higher pulmonary pressure and worse RV function at rest would predict worse functional capacity and ventilatory efficiency independent of LV systolic and diastolic function and that these associations will be similar among HF patients with preserved and impaired LVEF.

Methods

Study population

Details of the study population have been previously described.\textsuperscript{5} Of 975 consecutive patients referred for clinically indicated CPET for an indication of HF or cardiomyopathy between July 2007 and December 2014 at the Brigham and Women’s Hospital, 137 did not undergo echocardiography and were excluded, another 290 patients were excluded because of inadequate tricuspid regurgitation (TR) and/or RV assessments, and an additional 16 patients were excluded because of missing data on clinical outcomes. This analysis therefore included 532 patients. This study was approved by the Partners Human Research Committee, who waived requirement for informed consent.

Definition of clinical variables and data collection

Clinical covariates including demographics, co-morbidities, and medication usage were identified at the time of exercise testing. New York Heart Association (NYHA) functional class and values for serum haemoglobin and creatinine closest in time to the CPET date were extracted from chart review.

Cardiopulmonary exercise testing

All CPET studies were performed at the Brigham and Women’s Hospital exercise testing laboratory as previously described.\textsuperscript{9} All patients underwent symptom-limited CPET breathing room-air with minute ventilation (V\textsubscript{E}), oxygen consumption (VO\textsubscript{2}), and carbon dioxide production (V\textsubscript{CO2}) measurements averaged over a 10 second-interval. Peak VO\textsubscript{2} was defined as the highest 10 second averaged VO\textsubscript{2} during the last stage of the exercise test. Percent predicted peak VO\textsubscript{2} was calculated using the Wasserman formula.\textsuperscript{10} Minute ventilation to carbon dioxide production ratio (V\textsubscript{E}/V\textsubscript{CO2}) was recorded from rest to peak exercise. Age-predicted maximal heart rate was estimated by Astrand’s formula.\textsuperscript{11}

Conventional echocardiography

All quantitative measurements were performed by a single trained analyst in accordance with American Society of Echocardiography guidelines\textsuperscript{12} and blinded to clinical information. Pulmonary arterial systolic pressure was calculated as PASP = 4 * (peak TR velocity)\textsuperscript{2}. RV end-diastolic area (RVEDA) and end-systolic area (RVESA) were measured in the apical four-chamber view focused on RV, and RVFAC was calculated as ((RVEDA − RVESA)/RVEDA) * 100. Mitral regurgitation (MR) severity was assessed as the MR jet area-to-left atrial area ratio.

Ascertainment of clinical outcomes

All-cause mortality was ascertained through the National Death Index. Left ventricular assist device (LVAD) implantation and heart transplantation were ascertained through chart review. Occurrence of death, LVAD implantation, and heart transplantation were assessed through 31 December 2014 (median follow-up 3.8 years). HF hospitalization was ascertained through 2 years after the CPET date by chart review and adjudication as previously described.\textsuperscript{5}

Statistical analysis

Clinical characteristics, cardiac structure and function, and exercise capacity were described by quartiles of PASP and of RVFAC. Unadjusted tests for trend across quartiles were performed, in addition to trend tests with the following adjustments: (1) demographics (age, sex, and race); (2) demographics and relevant co-morbidities (coronary artery disease [CAD], hypertension, diabetes, atrial fibrillation, and chronic kidney disease [CKD]); and (3) demographics, co-morbidities, and LVEF. Adjusting covariates were selected based on a priori knowledge.

The continuous associations of PASP, RVFAC, and RVFAC/PASP ratio with percent predicted peak VO\textsubscript{2} and V\textsubscript{E}/V\textsubscript{CO2} slope were assessed using multivariable linear regression. Possible non-linear associations were assessed using restricted cubic splines modelled. For analyses with PASP as primary predictor variable, linear regression and cubic spline models were adjusted for demographics and co-morbidities, LVEF, presence of moderate or greater MR, and left atrial volume index (LAVI). Analyses with RVFAC as the primary predictor employed the same adjustment covariates, except that PASP was included while LAVI and moderate or greater MR were not included as.
### Table 1  Baseline Characteristics for PASP quartiles

| PASP Quartile | ANOVA p-values |
|---------------|----------------|
|               | Overall N | Overall (%) | Quartile 1 n = 134 | Quartile 2 n = 133 | Quartile 3 n = 132 | Quartile 4 n = 133 | Trend P-value | Demo* adjusted | Demo + Co-morbid + LVEF + LAVI adjusted |
|               |           | [5.9–22.9]  | [23.0–29.3]  | [29.4–37.8]  | [37.9–97.0]  |               |               |               |                                      |
| Clinical background |          |            |            |            |            |               |               |               |                                      |
| Demographic    | 532       | 55.9 ± 14.0 | 51.3 ± 13.7 | 55.3 ± 14.3 | 58.2 ± 14.3 | 58.9 ± 12.6 | < 0.001       | -              | -                                      |
| Male, (%)      | 532       | 350 (66%)   | 80 (60%)    | 87 (66%)    | 82 (60%)    | 101 (77%)   | 0.013         | -              | -                                      |
| White, (%)     | 532       | 444 (84%)   | 113 (84%)   | 109 (83%)   | 116 (85%)   | 106 (81%)   | 0.580         | -              | -                                      |
| BMI, kg/m²     | 532       | 27.7 ± 0.2  | 27.4 ± 0.4  | 27.1 ± 0.9  | 27.6 ± 0.6  | 27.7 ± 0.5  | 0.020         | 0.67          | -                                      |
| NYHA III & IV, (%) | 532 | 296 (39%) | 36 (27%) | 40 (31%) | 60 (44%) | 70 (53%) | < 0.001       | < 0.001       | 0.001        |
| Ischemic cardiomyopathy, (%) | 532 | 132 (25%) | 21 (16%) | 27 (20%) | 35 (27%) | 49 (37%) | < 0.001       | 0.047         | -                                      |
| Co-morbidities | 532       | 313 (59%)   | 62 (46%)    | 71 (54%)    | 88 (65%)    | 92 (70%)    | < 0.001       | 0.07          | -                                      |
| Hypertension, (%) | 532 | 138 (26%) | 28 (21%) | 50 (38%) | 53 (40%) | 55 (42%) | 0.002         | 0.001         | -                                      |
| Diabetes, (%)  | 532       | 138 (26%)   | 17 (13%)    | 28 (21%)    | 43 (32%)    | 50 (38%)    | < 0.001       | < 0.001       | 0.004        |
| CAD, (%)       | 532       | 196 (37%)   | 30 (22%)    | 42 (32%)    | 54 (40%)    | 70 (53%)    | < 0.001       | 0.004         | -                                      |
| Afib, (%)      | 532       | 191 (36%)   | 35 (26%)    | 43 (33%)    | 58 (43%)    | 55 (42%)    | 0.002         | 0.29          | -                                      |
| CKD, (%)       | 532       | 170 (32%)   | 24 (18%)    | 36 (28%)    | 52 (38%)    | 58 (44%)    | < 0.001       | 0.01          | -                                      |
| COPD, (%)      | 532       | 52 (10%)    | 4 (3%)      | 9 (7%)      | 21 (15%)    | 18 (14%)    | < 0.001       | 0.026         | -                                      |
| Anaemia, (%)   | 532       | 150 (28%)   | 24 (18%)    | 33 (25%)    | 42 (31%)    | 51 (39%)    | < 0.001       | 0.014         | -                                      |
| Demographic; age, sex, and race |
| Cardiovascular disease; hypertension, diabetes, chronic kidney disease, atrial fibrillation |
| PASP, pulmonary arterial systolic pressure; ANOVA, Analysis of variance; BMI, body mass index; NYHA, New York Heart Association classification; CAD, coronary artery disease; Afib, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MWT, mean wall thickness; LVEDVI, left ventricular end-diastolic volume index; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; MR, mitral regurgitation; RVFAC, right ventricular fractional area change; TR, tricuspid regurgitation; PVR, pulmonary vascular resistance; RER, respiratory exchange ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure
adjustment variables as elevations in left atrial pressure are expected to impact RV function primarily through associated elevations in pulmonary artery pressure. The association of PASP and RVFAC with incident events was assessed using multivariable Cox proportional hazard models with the same adjustment variables. The proportional hazards assumption was tested based on the Schoenfeld residuals, and no violation was detected. All analyses were also performed stratified by LVEF (≥45% vs. <45%), with tests for interaction performed using multiplicative interaction terms.

All statistical analyses were performed using Stata software version 15.0 (Stata Corp LP, College Station, TX, USA). Two-sided P value of <0.05 was considered statistically significant.

Results

Among the 532 patients included in this analysis, mean age was 55.9 ± 14.0 years, 66% were male patients, 84% were white, and the mean LVEF was 35 ± 15% (Table 1). The median PASP was 29 mmHg (25th to 75th percentile range 23 to 38 mmHg), and the median RVFAC was 42% (31% to 52%). When compared with patients not included in this analysis, those included were older, less likely to be obese, had higher prevalence of atrial fibrillation and CKD, and higher NYHA class, but had similar peak VO2 (Table S1).

Higher PASP was associated with older age, male sex, and a higher prevalence of cardiovascular risk factors (hypertension, diabetes, and CKD) and CAD (Table 1). Similarly, lower RVFAC was associated with male sex, CAD, CKD, and was also robustly associated with atrial fibrillation (Table S2). In contrast to PASP, RVFAC was not associated with age or hypertension. Both higher PASP and lower RVFAC were associated with worse NYHA functional class.

Association of PASP and RVFAC with left heart structure and function

In models adjusted for patient demographics, higher PASP was associated with lower LVEF, larger LV volume, higher LV mass index, worse diastolic indices (lower TDI e’, higher E/e’), larger LAVI), worse MR, and worse RVFAC. After further adjustment for LVEF, only associations with higher LV filling pressure (E/e’, LA volume index) and worse RVFAC persisted.

Similar to PASP, worse RVFAC was associated with lower LVEF, larger LV volume, and higher LV mass index, worse diastolic indices (lower TDI e’, higher E/e’, and larger LA volume index), worse MR, and higher PASP in analyses adjusted for patient demographics (Table S2). After further adjusting for LVEF, only associations with measures of higher LV filling pressure (E/e’, LA volume index) and worse RVFAC persisted.
pressure \((E/e', \text{ LAVi})\) and higher PASP persisted. When additionally accounting for PASP, worse RVFAC remained related to higher \(E/e'\).

**Association of PASP and RVFAC with functional capacity and ventilatory efficiency**

Exercise effort, as reflected in the peak exercise respiratory exchange ratio, did not vary across PASP or RVFAC quartiles (Table 1 and Table S2). After accounting for demographics and LVEF, higher resting PASP was associated with lower peak exercise systolic blood pressure and lower systolic blood pressure reserve. Worse resting state RVFAC correlated with a higher resting heart rate in addition to lower peak exercise systolic blood pressure and lower systolic blood pressure reserve.

Higher PASP was linearly associated with lower percent predicted peak VO\(_2\) (Figure 1, Table 2). In models adjusted for age, sex, race, hypertension, diabetes, CAD, CKD, LVEF, the presence of moderate or greater MR, and LAVi, each 5 mmHg increase in PASP was associated with 1% point decrease in ppVO\(_2\). In adjusted analysis, higher PASP was not significantly associated with \(V_e/V_{CO2}\) slope. Lower RVFAC was also linearly associated with lower percent predicted peak VO\(_2\) in adjusted analysis, with each 5% decrease in RVFAC was associated with 1% point decrease in ppVO\(_2\) (Figure 2, Table 2). Worse RVFAC also predicted worse exercise ventilatory inefficiency, with each 5% decrease in RVFAC associated with a 0.67-point increase in \(V_e/V_{CO2}\) slope in adjusted analysis (Figure 2, Table 2). Lower RVFAC/PASP ratio, a measure of RV-to-PA coupling, demonstrated significant non-linear associations with both worse ppVO\(_2\) and higher \(V_e/V_{CO2}\) slope (Figure 3). Importantly, the relationships between RVFAC/PASP ratio and each measure were most robust within the range of values observed in the majority of study subjects (Figure 3, histogram).

**Effect measure modification by baseline left ventricular ejection fraction**

We observe significant effect modification of LVEF category on the relationship of PASP with percent predicted peak VO\(_2\) achieved (Figure 1; interaction \(P = 0.006\)). For any given increase in PASP, the associated decline in percent predicted VO\(_2\) was greater among patients with LVEF \(\geq 45\%\) compared with those with LVEF <45\%. Baseline LVEF (\(\geq 45\%\) or <45\%) did not significantly modify the relationship of PASP or RVFAC with \(V_e/V_{CO2}\) slope or the relationship of RVFAC with percent predicted peak VO\(_2\) (Figures 1 and 2). Similar results were observed in sensitivity analyses comparing patients

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**Table 2 Continuous association of pulmonary pressure and RV function vs. exercise capacity**

| Measure                             | Adjusted for demographics | Coefficient [CI] | p-value | Coefficient [CI] | p-value | p-value |
|-------------------------------------|---------------------------|-----------------|---------|-----------------|---------|---------|
| PASP (per 5 mmHg increase)           | Non-linear                | \(< 0.001^*\)   |         | \(0.98 [-1.63, -0.32]\) | \(< 0.001\)     |         |
| RVFAC (per 5% decrease)             | Non-linear                | \(< 0.001^*\)   |         | \(-1.02 [-1.69, -0.36]\) | \(< 0.001\)     |         |

| Measure                             | Adjusted for demographics | Coefficient [CI] | p-value | Coefficient [CI] | p-value | p-value |
|-------------------------------------|---------------------------|-----------------|---------|-----------------|---------|---------|
| PASP (per 5 mmHg increase)           | Non-linear                | \(< 0.001^*\)   |         | \(0.98 [-1.63, -0.32]\) | \(< 0.001\)     |         |
| RVFAC (per 5% decrease)             | Non-linear                | \(< 0.001^*\)   |         | \(-1.02 [-1.69, -0.36]\) | \(< 0.001\)     |         |

*Demographics; age, sex, and race
†Additional measures
‡Overall p-value from cubic spline regression

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with LVEF ≥50% with those with LVEF <50% (Figures S1 and S2).

**Association of PASP and RVFAC with clinical outcomes**

At a median follow-up of 3.9 years (25th to 75th percentile range 0.05 to 7.38), 167 patients experienced the composite of death, LVAD implantation, or transplantation [event rate 8.1 (95% CI 7.0–9.5) per 100 person years]. Each 5 mmHg increase in PASP was associated with a 7% increase in the risk of this composite in models adjusted for age, sex, race, LVEF, moderate or greater MR, and LAVi (P = 0.03; Table 3). Similarly, each 5% decrease in RVFAC was associated with a 17% increased risk for composite event (P < 0.001), and a 0.1 unit (%/mmHg) decrease in the RVFAC/PASP ratio was associated with a 4% increase in risk. These associations were not significantly non-linear (online Figure S3).

At 2 year follow-up, the composite of death, LVAD implantation, transplantation or HF hospitalization occurred in 165 patients [event rate 25.8 (95% CI 22.1–30.0) per 100 person years]. The association of PASP with this composite endpoint was of borderline statistical significance (Table 3). As opposed to PASP, each 5% decrease in RVFAC was associated with and 14% increase in risk, and each 0.1 unit (%/mmHg) decrease in RVFAC/PASP ratio was associated with a 4% increase in risk.

**Discussion**

Higher pulmonary pressure and reduced RV function both predict incident HF and mortality in the community and are associated with adverse prognosis in prevalent HF regardless of LVEF. Pulmonary vascular dysfunction is of particular interest in the heterogeneous syndrome of HfPEF, as older patients with PH and RV dysfunction appear to represent a disease sub-phenotype with particularly high risk of death and HF hospitalization. This study assessed the contributions of PH and RV dysfunction to functional capacity and respiratory efficiency in HF, independent of LV structure and function. We report three main findings. First, higher pulmonary pressure at rest significantly predicted worse functional capacity (i.e. reduced ppVO₂), and this relationship was stronger among HF patients with an LVEF ≥45% compared with those with LVEF <45% (Pinteraction = 0.006). Second, worse RV function at rest—even when within the normal range—was associated with both worse functional capacity and worse respiratory efficiency (i.e. increased V/E/VCO₂ slope) and apparently more so among subjects with reduced LVEF. Furthermore, worse RV-PA coupling (i.e. RVFAC/PASP ratio) at rest also predicted worse functional capacity and respiratory efficiency, supporting a primary role for RV dysfunction in limiting cardiopulmonary reserve in HF. Third, PASP, RVFAC, and RVFAC/PASP ratio were each associated with a higher risk of death, transplant, LVAD, and with the...
Table 3  Hazard ratio for composite event by PASP, RVFAC, and RVFAC/PASP

| Composite event | Composite event + HF Admission |
|-----------------|-------------------------------|
| Adjusted for demographics | Adjusted for additional measures |
| Adjusted for demographics | Adjusted for demographics |

| Event rate | [95% CI] | HR [95% CI] | p-value | HR [95% CI] | p-value |
|------------|---------|-------------|---------|-------------|---------|
| PASP (per 5 mmHg increase) | 167 | 8.1 (7.0-9.5) | 1.15 (1.09-1.21) | <0.001 | 1.07 (1.00-1.14) | 0.029 |
| RVFAC (per 5% decrease) | 165 | 2.58 (2.1-3.0) | 1.29 (1.22-1.38) | <0.001 | 1.17 (1.09-1.25) | <0.001 |
| RVFAC/PASP (per 0.1%/mmHg decrease) | 165 | 2.58 (2.1-3.0) | 1.25 (1.17-1.33) | <0.001 | 1.14 (1.07-1.22) | <0.001 |

Composite event includes all-cause death, heart transplant, and left ventricular assist device implantation.

PH is common in HFrEF in particular, with a prevalence of 50% in referral population and rising to up to 80% in some community-based HFrEF samples. Concordant with prior reports, we observed a heightened risk of cardiovascular morbidity and mortality associated with higher PASP irrespective of LVEF. Higher resting PASP also predicted lower ppVO2 and higher V5/VCO2 slope. Higher rest pulmonary pressures may simply be a marker of more advanced LV dysfunction (systolic and diastolic). However, our finding of significant associations of rest PH with functional capacity, ventilatory efficiency, and clinical events after adjusting for measures of LV systolic function and diastolic function argues against PH as just a risk marker in HF. The association of higher resting PASP with worse functional capacity was stronger among those with LVEF ≥45% compared with those with LVEF <45%. The reasons for this differential association are not clear but may provide support for an important role of PH in HFrEF morbidity and mortality. Multiple ongoing Phase II trials of interventions targeting PH in HFrEF will provide insights into the impact of treating PH on functional capacity or hemodynamics in HFrEF.

Right ventricular dysfunction has been reported in up to 65% of patients with HFrEF and anywhere from 4–49% of patients with HFrEF. While some studies suggest an equivalent frequency in HFrEF and HFrEF, others have observed a 1.5 to two-fold higher prevalence in HFrEF. Using an RVFAC <35% to define RV dysfunction, as recommended by the American Society of Echocardiography, we observed RV dysfunction in 15% of HF patients with LVEF ≥45% and 39% of those with LVEF <45%. RV dysfunction is strongly associated with adverse outcomes in HF, including both mortality and recurrent HF hospitalization. Among patients with HFrEF, RV dysfunction is associated with reduced exercise capacity. Chronic RV dysfunction may primarily limit stroke volume and may exaggerate reductions in stroke volume and cardiac output related to LV dysfunction through ventricular interdependence. Resting state RV dysfunction may thereby also limit SV and CO augmentation in response to excise, contributing to blunted functional capacity in HF. Indeed, our findings show that resting-state RV dysfunction predicts worse functional capacity independent of LV structure and function and in both HF with LVEF ≥45% and <45%.
afterload. While PH is common in HFpEF, a steeper PA pressure-flow relationship has been described in HFpEF compared with HF-free controls, consistent with lower RV-PA coupling and worse intrinsic RV contractility.\textsuperscript{27} We observed that worse RV-PA coupling was also associated with lower functional capacity and greater respiratory inefficiency. Interestingly, this association was non-linear, with the most robust associations noted at RVFAC/PASP $<2\%$/mmHg, values observed in majority of our cohort. This is consistent with a prior study in which worse RV-PA coupling—assessed as the tricuspid annular plane systolic excursion/PASP ratio—was associated with worse functional capacity and respiratory efficiency.\textsuperscript{3} These relationships were not differential based on LVEF in our study.

This study has several limitations. This study was a single centre, observational study of clinically referred patients for CPET and echocardiography, which may limit the generalizability of our findings to HF patients more broadly. PASP was estimated by echocardiography. Although previous studies have demonstrated good correlation between non-invasively (Doppler echocardiography) obtained and invasively obtained pulmonary pressure,\textsuperscript{28} this remains an estimate and may result in misclassification. RV function was assessed using RVFAC. Although a well-validated and prognostic measure in HF, we did not have data on tricuspid annular plane systolic excursion, a commonly employed RV functional measure. We stratified LVEF at 45\% based on contemporary therapeutic HFpEF trial,\textsuperscript{29} although guideline recommendations for defining HFpEF specify an LVEF $\geq50\%$.\textsuperscript{30}

Among HF patients with a broad range of LVEF, greater resting-state pulmonary pressure and worse RV function both independently predict worse functional capacity and greater respiratory inefficiency, independent of LV structure and function. The magnitude of association of pulmonary pressure with functional capacity was greater in HFpEF compared with HFrEF, while no statistically significant differences in the association of RV dysfunction with functional capacity were noted by LVEF. These findings support a role for pulmonary vascular and RV dysfunction in contributing to impaired exercise tolerance in HF regardless of LV function.

**Conflict of interest**

Dr Shah reports consulting fees from Philips Ultrasound and Bellerophon Therapeutics and research support through Brigham and Women’s Hospital from Novartis.

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**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** - Baseline characteristics of those included versus excluded patients

**Table S2.** Baseline characteristics for RVFAC quartiles

**Figure S1.** - Association between PASP and (A) percent predicted peak VO$_2$, (B) Vf/V$_{CO2}$ slope stratified by LVEF.
References

1. Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ, Shah SJ. RV Contractile Function and its Coupling to Pulmonary Circulation in Heart Failure With Preserved Ejection Fraction: Stratification of Clinical Phenotypes and Outcomes. *Am Coll Cardiol Cardiovasc Imaging* 2017; 10: 1211–1221.

2. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *Am Coll Cardiol* 2013; 1: 290–299.

3. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Rosmini F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *Am J Cardiol* 2001; 37: 183–188.

4. Leung CC, Moonstra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. *Am J Cardiol* 2010; 106: 284–286.

5. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *Am Coll Cardiol* 2009; 53: 1119–1126.

6. Bosch L, Lam CSP, Gong L, Chan SP, Sim D, Yeo D, Jaufeerally F, Leong KTG, Ong HY, Ng TP, Richards AM, Arslan F, Ling LH. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. *Eur J Heart Fail* 2017; 19: 1664–1671.

7. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014; 35: 3452–3462.

8. Nadruz W Jr, West E, Santos M, Skali H, Groarke JD, Forman DE, Slager B, Skali H, Shah AM. Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction. *J Am Heart Assoc* 2017; 6: e006000.

9. Hanse JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129: S49–S55.

10. Astrand I. Aerobic work capacity in men and women with special reference to age. Acta Physiol Scand Suppl 1960; 49: 1–92.

11. Lang RM, Badano LP, Mor-Avi V, Ritter-Aue J, Ristic A, Schwitter J, Gobbi F, Vlahos I, Moulin H, Aurigemma GP, Franke-Lyon ML, Pellikka PA, Tajik AJ. Recommendations for chamber quantification by echocardiography in adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39.

12. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation* 2009; 119: 2663–2670.

13. Bursi F, McNally SM, Redfield MM, Nkomo VT, Lam CS, Weston SA, Jiang R, Roger VL. Pulmonary pressures and death in heart failure: a community study. *J Am Coll Cardiol* 2012; 59: 222–231.

14. de Groote P, Millaire A, Foucher-Hossein C, Nugue O, Marchandise X, Ducloix G, Lablanche JM. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol* 1998; 32: 948–954.

15. Mohammed SF, Hussain I, AbouElzadidline OF, Takahama H, Kwon SH, Forfia P, Roger VL, Redfield MM. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation* 2014; 130: 2310–2320.

16. Shah SJ, Kaiz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiu M, Monow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* 2015; 131: 269–279.

17. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O’Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD, Investigators TOPCAT. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail* 2014; 7: 104–115.

18. Parikh KS, Sharma K, Fiuza M, Surks HK, George JT, Honarpour N, Depre C, Desveigne-Nickens P, Nkliikinya R, Lewis GD, Gomberg-Maitland M, O’Connor CM, Stockbridge N, Califf RM, Fonstam MA, Januzzi JI Jr, Solomon SD, Borlaug BA, Shah SJ, Redfield MM, Felker GM. Heart Failure With Preserved Ejection Fraction Expert Panel Report: Current Controversies and Implications for Clinical Trials. *Am Coll Cardiol* 2018; 6: 619–632.

19. La Vecchia L, Zanolla L, Varotto L, Bonanno C, Spadaro GL, Ometto R, Fontanelli A. Reduced right ventricular ejection fraction as a marker for idiopathic dilated cardiomyopathy compared with ischemic left ventricular dysfunction. *Am Heart J* 2001; 142: 181–189.

20. Damy T, Kallivikabacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, Nikitin NP, Dubois-Randé JL, Hittinger L, Clark AL, Cleland JG. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. *J Card Fail* 2012; 18: 216–225.

21. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, Temporelli PL, Arena R. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol* 2013; 305: H1373–H1381.

22. Puwanant S, Pieterse TC, Mookadam F, Bruce GI, Redfield MM, Chandrasekaran K. Right ventricular function in patients with preserved and
reduced ejection fraction heart failure. Eur J Echocardiogr 2009; 10: 733–737.

24. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685–713 quiz 786-8.

25. Meluzín J, Spinarová L, Hude P, Krejcí J, Kincl V, Panovský R, Dusek L. Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure. J Am Soc Echocardiogr 2005; 18: 435–444.

26. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. Eur Heart J 2018; 39: 2825–2835.

27. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J 2016; 37: 3294–3302.

28. Nagueh SF, Bhatt R, Vivo RP, Krim SR, Sarvari SI, Russell K, Edvardsen T, Smiseth OA, Estep JD. Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. Circ Cardiovasc Imaging 2011; 4: 220–227.

29. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray Jv. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Random and Design of the PARAGON-HF Trial. J Am Coll Cardiol HF 2017; 5: 471–482.

30. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.