The right ventricle in heart failure with preserved ejection fraction
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Exercise Unmasks Distinct Pathophysiologic Features in Heart Failure with Preserved Ejection Fraction and Pulmonary Vascular Disease

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Submitted
Abstract

Aims: Pulmonary hypertension (PH) and pulmonary vascular disease (PVD) are common and associated with adverse outcomes in heart failure with preserved ejection (HFpEF). Little is known about the impact of PVD on the pathophysiology of exercise intolerance.

Methods and Results: HFpEF patients (n=161) and controls without heart failure or PH (n=53) underwent invasive hemodynamic exercise testing. HFpEF patients were classified into 3 groups: non-PH-HFpEF (n=21); PH but no PVD (isolated post-capillary PH, IpcPH; n=95); and PH with PVD (combined post- and pre-capillary PH, CpcPH; n=45). At rest, CpcPH-HFpEF patients had more right ventricular dysfunction and lower pulmonary arterial (PA) compliance compared to all other groups. While right atrial pressure (RAP) and left ventricular transmural pressure (LVTMP) were similar in HFpEF with and without PH or PVD at rest, CpcPH-HFpEF patients demonstrated greater increase in RAP, enhanced ventricular interdependence, and paradoxical reduction in LVTMP during exercise, differing from all other groups (p<0.05). Lower PA compliance was correlated with greater increase in RAP with exercise. During exercise, CpcPHHFpEF patients displayed an inability to enhance cardiac output, reduction in forward stroke volume, and blunted augmentation in RV systolic performance, changes that were coupled with marked limitation in aerobic capacity.

Conclusion: HFpEF patients with pulmonary vascular disease demonstrate unique hemodynamic limitations during exercise that constrain aerobic capacity, including impaired recruitment of LV preload due to excessive right heart congestion and blunted right ventricular systolic reserve. Interventions targeted to this distinct pathophysiology require testing in patients with HFpEF and PVD.
Introduction

Heart failure with preserved ejection (HFpEF) accounts for approximately half of all heart failure patients, affecting millions worldwide.\textsuperscript{1} Although there are features common to all HFpEF patients, there may be substantial pathophysiologic heterogeneity as well.\textsuperscript{2} HFpEF is initially defined by an elevation in left-sided filling pressures, but many patients progress to develop pulmonary vascular disease (PVD) secondary to chronic left heart congestion.\textsuperscript{3-14} This cohort experiences worse outcomes when compared to HFpEF patients with isolated left heart disease, but the mechanisms explaining this observation remain poorly understood.\textsuperscript{3-14}

Patients with HFpEF universally complain of exertional intolerance, but the causes may differ between patients with different phenotypes. Exercise introduces an impressive stress to the right heart and lungs, where elevations in venous return increase pulmonary blood volume by 50\% while increasing lung blood flow 300\%.\textsuperscript{15} The healthy pulmonary vasculature is a high compliance, low resistance circuit that can readily accommodate these marked increases in blood volume and flow.\textsuperscript{4,16} However, this reserve may be compromised in patients with HFpEF and PVD, which may lead to important differences compared to HFpEF patients with left heart disease and no PVD.

We performed invasive hemodynamic exercise testing with expired gas analysis in a well-defined cohort of HFpEF patients with and without PVD, and then contrasted them to controls without heart failure or pulmonary hypertension. We hypothesized that the presence of PVD in HFpEF would compromise the ability of the right heart and lungs to accommodate increased blood flow during exercise, increasing ventricular interaction, limiting right ventricular (RV) reserve, and impairing aerobic capacity.

Methods

Consecutive patients who underwent invasive hemodynamic exercise testing at the Mayo Clinic in Rochester, MN between 2000 and 2016 were identified. The Mayo Clinic Institutional Review Board approved the study and all subjects provided written informed consent. All authors had full access to the data and take full responsibility for its integrity.
HFpEF was defined by the presence of typical symptoms (exertional dyspnea and fatigue), left ventricular ejection fraction (LVEF) ≥50% and elevated left-sided filling pressures at rest (pulmonary capillary wedge pressure [PCWP] >15 mmHg). HFpEF patients with normal resting PCWP, but elevated PCWP on exercise were not included. To investigate exercise hemodynamics according to the presence of PVD, we divided HFpEF patients into pulmonary hypertension (PH) subgroups according to published recommendations: 1) non-PH (mean pulmonary artery pressure [PAP] <25 mmHg), 2) PH with no PVD (isolated post-capillary PH, IpcPH; mean PAP ≥25 mmHg with PVR ≤3.0 WU and diastolic pressure gradient [DPG] <7 mmHg), and 3) PH with PVD (combined post- and pre-capillary PH, CpcPH; mean PAP ≥25 mmHg with PVR >3.0 and/or DPG ≥7 mmHg).\(^{17}\)

Control subjects without HF or PH, with no evident cardiac cause of dyspnea, including normal left-sided filling pressures (PCWP ≤15 mmHg at rest and <25 mmHg with exercise), and normal PA pressures (mean PAP <25 mmHg at rest and PAP <40 mmHg with exercise) were included as a comparator. Patients with LVEF <50%, primary right-sided HF, valvular heart disease (>moderate left-sided regurgitation and/or >mild stenosis), unstable coronary artery disease or recent revascularization, constrictive pericarditis, high-output heart failure, and infiltrative, restrictive or hypertrophic cardiomyopathy were excluded.

**Echocardiography**

Echocardiography was performed at rest according to the guidelines of the American Society of Echocardiography.\(^{18}\) Using RV-focused views, RV basal and mid-cavity dimensions were measured at end-diastole, and RV end-diastolic and end-systolic areas were traced to calculate fractional area change (FAC = \(\frac{RV \text{ end-diastolic area} - \text{end-systolic area}}{\text{end-diastolic area} \times 100}\)). Pericardial restraint and ventricular interaction were assessed by the LV eccentricity index as recently described.\(^{19}\) An LV eccentricity index >1.0 indicates a leftward septal shift due to right-sided overload and enhanced ventricular interdependence.

**Cardiac catheterization protocol**

Patients were assessed on chronic medications, in fasted state, after minimal sedation and in supine position, as previously described.\(^{19-23}\) Right heart catheterization was performed through a 9F sheath via the right internal jugular vein at both rest and with
exercise, with simultaneous directly measured oxygen consumption (VO2) using expired gas analysis (MedGraphic, St. Paul, MN). Right atrial pressure (RAP), PAP and PCWP were recorded at end-expiration, using the mean of ≥3 beats. Pressure tracings were digitized (240 Hz) and stored for offline analysis. The net distending pressure that determines LV preload volume, LV transmural pressure (LVTMP), was calculated as PCWP minus RAP,\textsuperscript{19, 24-27} with RAP taken as an estimate of pericardial pressure.\textsuperscript{24}

Arteriovenous oxygen difference (A-VO2diff) was determined from directly measured arterial and mixed venous O2 contents from blood sampling (saturation*hemoglobin*1.34*10). Cardiac output (CO) was determined by the direct Fick method (CO = VO2/A-VO2diff) and indexed for body surface area to calculated cardiac index (CI). Pulmonary vascular resistance (PVR= [mean PAP – PCWP]/CO) and systemic vascular resistance (SVR= [mean arterial blood pressure – RAP]/CO), stroke volume (SV=CO/heart rate), systemic and pulmonary pulse pressure, and diastolic pressure gradient (DPG=PA diastolic - PCWP) were calculated. Pulmonary arterial compliance (PAC) and total arterial compliance (TAC) were calculated (PAC=SV/pulmonary pulse pressure; TAC=SV/systemic pulse pressure, respectively). End systolic pressure (ESP) was taken as 0.9*systolic blood pressure. Systemic and pulmonary arterial elastance (Ea-S, Ea-P) were calculated as ESP/SV and PA systolic pressure/SV, respectively.

Following rest measures, patients engaged in supine cycle ergometry starting at 20 Watt workload and increasing in 10 to 20 Watt increments (3 minutes per stage) until subject-reported exhaustion. Hemodynamic data were again acquired at peak exercise in all participants using the same methods.

**Statistical analysis**
Data are reported as mean _ standard deviation (SD), median (25th, 75th percentile) or numbers (percentages). Between-group differences were calculated using one-way ANOVA, Kruskal-Wallis test, or χ2 test, as appropriate. The Tukey honestly-significant-difference test or Steel-Dwass test were applied to adjust for multiple testing for the paired analyses. Correlations were calculated using Spearman’s or Pearson’s correlation, when appropriate. An interaction term was applied to calculate correlation differences between two groups.
Chapter 4

Results

Of patients with HFrEF (n=161), the vast majority (n=140, 87%) displayed PH (i.e. mean PA pressure≥25 mmHg) at rest. Of this group, 68% (n=95) displayed lpcpH and 32% (n=45) had CpcPH-HFrEF. All CpcPH patients displayed elevated PVR (>240 dynes/sec*cm5) but only 11 (24%) displayed elevated DPG.

As compared to controls (n=53), patients with lpcpH-HFrEF were more obese and diabetic, and both PH-HFrEF groups were more likely to have atrial fibrillation (AF) and sleep apnea (Table 1). The prevalence of AF was higher in CpcPH-HFrEF than any other group (61%). HFrEF patients were more likely to be treated with HF medicines and had lower hemoglobin levels. Patients with HFrEF and any PH, in particular CpcPH, displayed higher NT-proBNP levels (Table 1).

Cardiac structure, Function and Hemodynamics at rest

Left ventricular dimensions, mass and EF were similar in controls and HFrEF groups (Table 1). HFrEF patients with PH displayed increased left atrial volume and higher E/e’. Patients with CpcPH displayed more RV systolic dysfunction compared to all other groups, reflected by lower tricuspid annular s’ velocities and FAC (Figure 1A). RV dimensions tended to be increased in CpcPH. The LV eccentricity index was increased in HFrEF patients with PH, indicating greater flattening of the interventricular septum towards the left ventricle at rest and thus greater ventricular interdependence (Table 1).

There were no differences in heart rate or blood pressures between the groups (Table 2). RAP was higher in HFrEF than in controls, but similar among HFrEF patients with and without PH at rest. The RAP/PCWP ratio and LV transmural pressure were also similar in all HFrEF groups at rest.

Patients with CpcPH-HFrEF displayed more deranged RV-PA coupling, with greater reduction in RV FAC and more RV dilatation as resting PVR increased (Figures 1B-C). Patients with CpcPH-HFrEF also displayed increased Ea-P, lower PA compliance, and reduced stroke volume and cardiac index at rest, with a higher AVO2 difference (Table 2). Patients with HFrEF and PH (regardless of PVD) displayed increased RV stroke work index, reflecting the greater pressure-volume work needed to eject blood through the pulmonary vasculature in the setting of PH. CpcPH-HFrEF patients also
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Figure 1: Right ventricular function and size at rest. (A) At rest, heart failure with preserved ejection fraction (HFpEF) patients with combined post- and pre-capillary pulmonary hypertension (CpcPH) displayed the lowest right ventricular fractional area change (RV FAC) compared to other groups. (B-C) Higher pulmonary vascular resistance (PVR) was associated with decreased FAC and with increased RV size in CpcPH-HFpEF, while these associations were absent in HFpEF patients with isolated post-capillary PH (IpcPH). Error bars reflect SEM. *p<0.05 vs controls; †p<0.05 vs Non PH-HFpEF; and #p<0.05 vs IpcPH-HFpEF.
Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=53)</th>
<th>Non-PHF (n=21)</th>
<th>IpcPH (n=95)</th>
<th>CpcPH (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±9</td>
<td>65±13</td>
<td>68±11</td>
<td>70±11</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>33(62%)</td>
<td>13 (62%)</td>
<td>60 (63%)</td>
<td>29 (64%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30±5</td>
<td>34±10</td>
<td>35±8 *</td>
<td>32±6</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.94±0.26</td>
<td>2.02±0.32</td>
<td>2.05±0.29</td>
<td>1.99±0.22</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (96%)</td>
<td>17 (89%)</td>
<td>82 (92%)</td>
<td>36 (93%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17 (32%)</td>
<td>6 (29%)</td>
<td>32 (34%)</td>
<td>13 (31%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (11%)</td>
<td>2 (10%)</td>
<td>30 (32%) *†</td>
<td>27 (61%) *†#</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (17%)</td>
<td>2 (10%)</td>
<td>31 (33%) *†</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>6 (20%)</td>
<td>6 (32%)</td>
<td>37 (51%) *</td>
<td>20 (59%) *</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>17 (32%)</td>
<td>10 (48%)</td>
<td>42 (44%)</td>
<td>20 (45%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>14 (26%)</td>
<td>11 (52%) *</td>
<td>59 (62%) *</td>
<td>25 (57%) *</td>
</tr>
<tr>
<td>Diuretics</td>
<td>14 (26%)</td>
<td>11 (52%) *</td>
<td>56 (59%) *</td>
<td>30 (68%) *</td>
</tr>
<tr>
<td>Laboratories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>13.0±1.2</td>
<td>12.3±1.5</td>
<td>12.1±1.6 *</td>
<td>12.1±1.7 *</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>103 (49, 213)</td>
<td>203 (60, 713)</td>
<td>809 (225, 1407) *</td>
<td>1056 (502, 2223) *†</td>
</tr>
<tr>
<td>Fractional area change (%)</td>
<td>10.0 (7.5, 12.0)</td>
<td>10.0 (8.8, 11.5)</td>
<td>13.9 (10.0, 20.0) *</td>
<td>16.0 (13.0, 20.9) *†</td>
</tr>
<tr>
<td>E/e'</td>
<td>10.0 (7.5, 12.0)</td>
<td>10.0 (8.8, 11.5)</td>
<td>13.9 (10.0, 20.0) *</td>
<td>16.0 (13.0, 20.9) *†</td>
</tr>
<tr>
<td>TV s' (cm/s)</td>
<td>14±2</td>
<td>12±2</td>
<td>12±2 *</td>
<td>12±3 *</td>
</tr>
<tr>
<td>Fractional area change (%)</td>
<td>10.0 (7.5, 12.0)</td>
<td>10.0 (8.8, 11.5)</td>
<td>13.9 (10.0, 20.0) *</td>
<td>16.0 (13.0, 20.9) *†</td>
</tr>
<tr>
<td>RV end-diastolic area (cm²)</td>
<td>7.3±2.1</td>
<td>6.8±1.3</td>
<td>7.3±2.1</td>
<td>8.3±3.1</td>
</tr>
<tr>
<td>RV basal diameter (mm)</td>
<td>33±8</td>
<td>33±5</td>
<td>34±8</td>
<td>37±8 *</td>
</tr>
<tr>
<td>RV mid diameter (mm)</td>
<td>25±6</td>
<td>25±3</td>
<td>26±7</td>
<td>29±9</td>
</tr>
<tr>
<td>LV eccentricity index</td>
<td>0.97±0.11</td>
<td>1.05±0.13</td>
<td>1.05±0.18 *</td>
<td>1.08±0.16 *</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation, median (25th, 75th percentile), or n (%). Final column reflects overall group differences.

*p<0.05 vs controls; †p<0.05 vs non-PHF; and #p<0.05 vs IpcPH.

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CpcPH combined post- and pre-capillary pulmonary hypertension; IpcPH isolated post-capillary pulmonary hypertension; PH, pulmonary hypertension; RV, right ventricular; TV, tricuspid valve.
Exercise Unmasks Distinct Pathophysiologic Features in Heart Failure with Preserved Ejection Fraction and Pulmonary Vascular Disease

displayed increased systemic vascular stiffening, with higher SVR and Ea-S, and lower total arterial compliance (Table 2).

**Exercise hemodynamics**
Exercise capacity was reduced in HFrEF patients with PH, evidenced by lower work load achieved and decreased peak VO2 (Table 3). Cardiac output, which by definition is equal to venous return to the right heart at steady state, increased similarly with exercise in Non-PH and IpcPH-HFrEF, but was lower for any exercise workload in CpcPH-HFrEF (Figure 2A). The 3 HFrEF groups displayed similar absolute increases in PCWP with exercise, though PCWP elevation occurred at lesser cardiac output or venous return in CpcPH-HFrEF (Table 3, Figure 2B).

Pulmonary artery pressures increased in all groups with exercise, but the greatest increases were observed in the CpcPH group, with higher pressures relative to blood flow (Table 3, Figure 2C). Patients in the CpcPH-HFrEF group experienced greater
Table 2: Resting hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=53)</th>
<th>Non-PH HFpEF (n=21)</th>
<th>IpPH PH HFpEF (n=95)</th>
<th>CpcPH HFpEF (n=45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67±13</td>
<td>65±12</td>
<td>63±11</td>
<td>62±14</td>
<td>0.2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>155±22</td>
<td>155±25</td>
<td>153±33</td>
<td>159±29</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>99±14</td>
<td>103±13</td>
<td>103±18</td>
<td>105±18</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Central pressures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA pressure (mmHg)</td>
<td>5±3</td>
<td>10±4</td>
<td>12±4</td>
<td>13±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PA systolic pressure (mmHg)</td>
<td>29±6</td>
<td>36±11</td>
<td>46±11</td>
<td>60±12</td>
<td>0.05</td>
</tr>
<tr>
<td>PA mean pressure (mmHg)</td>
<td>17±3</td>
<td>21±4</td>
<td>31±6</td>
<td>39±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9±3</td>
<td>18±4</td>
<td>21±5</td>
<td>20±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RAP/PCWP ratio</td>
<td>0.60±0.22</td>
<td>0.56±0.19</td>
<td>0.59±0.17</td>
<td>0.63±0.18</td>
<td>0.5</td>
</tr>
<tr>
<td>LVTMP (mmHg)</td>
<td>3.6±2.5</td>
<td>8.2±4.2 *</td>
<td>8.9±4.5</td>
<td>7.6±3.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Vascular and ventricular function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR (dyne/sec*cm^5)</td>
<td>1419±424</td>
<td>1441±446</td>
<td>1418±519</td>
<td>1809±713 #</td>
<td>0.01</td>
</tr>
<tr>
<td>TAC (ml/mmHg)</td>
<td>1.1±0.4</td>
<td>1.1±0.3</td>
<td>1.2±1.0</td>
<td>0.9±0.3 #</td>
<td>0.01</td>
</tr>
<tr>
<td>Ea-S (mmHg/ml)</td>
<td>1.7±0.5</td>
<td>1.8±0.4</td>
<td>1.7±0.7</td>
<td>2.3±0.9 #</td>
<td>0.003</td>
</tr>
<tr>
<td>PVR (dyne/sec*cm^5)</td>
<td>128±51</td>
<td>67±50</td>
<td>154±53</td>
<td>356±103 #</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PAC (ml/mmHg)</td>
<td>4.6±1.9</td>
<td>3.9±1.1</td>
<td>4.0±3.0</td>
<td>2.2±0.8 #</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ea-P (mmHg/ml)</td>
<td>0.34±0.11</td>
<td>0.40±0.09</td>
<td>0.50±0.19</td>
<td>0.81±0.25 #</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVSW index (g/m^2*beat)</td>
<td>7.1±2.8</td>
<td>5.7±3.8</td>
<td>11.3±4.5</td>
<td>12.8±5.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Flow measures and metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume index (ml/m^2)</td>
<td>43±12</td>
<td>40±11</td>
<td>44±13</td>
<td>36±11 #</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiac index (l/min/m^2)</td>
<td>2.9±0.8</td>
<td>2.6±0.7</td>
<td>2.7±0.6</td>
<td>2.2±0.6 #</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>O_2 consumption (ml/min/kg)</td>
<td>2.7±0.6</td>
<td>2.6±0.8</td>
<td>2.5±0.6</td>
<td>2.4±0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>A-V O_2 difference (ml/dl)</td>
<td>4.2±0.7</td>
<td>4.7±0.9</td>
<td>4.5±1.2</td>
<td>5.2±1.2 #</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. Final column reflects overall group differences.
*p<0.05 vs controls; †p<0.05 vs non-PH; and #p<0.05 vs IpPH.
BP, blood pressure; Ea, effective arterial elastance; LVTMP, left ventricular transmural pressure; PA, pulmonary artery; PAC, pulmonary arterial compliance; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RVSW, right ventricular stroke work; SVR, systemic vascular resistance; and TAC, total arterial compliance.

Despite similar RAP at rest among the HFpEF subgroups, both PH-HFpEF groups developed greater increases in RAP during exercise, with CpcPH-HFpEF patients reaching the highest right heart filling pressures (Table 3). The intolerance of the right heart and pulmonary circulation to elevation in venous return during exercise was most dramatic in CpcPH-HFpEF (Figure 3A).

Increases in right heart congestion may compromise left heart filling in the setting of ventricular interdependence. Patients with Non-PH HFpEF and IpPH-HFpEF displayed an increase in LV transmural filling pressures, with stable RAP/PCWP ratio.
null
Figure 3: Ventricular interdependence with exercise in CpcPH-HFpEF. (A) Increase in venous return during exercise was associated with more dramatic increase in right atrial pressure (RAP) in CpcPH-HFpEF compared to the other HFpEF groups. (B) While patients with Non PH-HFpEF and lpcPH-HFpEF displayed an increase in left ventricular transmural pressure (LVTMP), CpcPH-HFpEF developed a paradoxical decrease in LVTMP as venous return to the right heart increased during exercise. (C-D) The reduction in LVTMP was increased as exercise PVR and transpulmonary gradient (TPG) increased, indicating that left heart underfilling was directly related to the severity of pulmonary vascular disease. Error bars reflect SEM. †p<0.05 vs Non PH-HFpEF; and #p<0.05 vs lpcPH-HFpEF. Other abbreviations as in Figure 1.

Thus, even as hydrostatic pressures in the pulmonary capillaries increased with exercise in CpcPH-HFpEF patients, there was effective under-distention of the LV. This reduction in LV transmural pressure was coupled with the impairment in cardiac output in CpcPH-HFpEF (Figure 2A), explained by a reduction in stroke volume, which actually decreased with exercise in CpcPH-HFpEF, even as PA pulse pressure increased, emphasizing the marked limitation in PA compliance (Figure 4C). Right ventricular systolic reserve was impaired in both of the PH-HFpEF groups, manifest by a blunted ability to augment RV stroke work index during exercise (Figure 4D).
Figure 4: Stroke volume reserve and right ventricular stroke work in HFpEF. (A) Compared with IpcPH-HFpEF, RAP was increased to greater extent as PA compliance decreased in CpcPH-HFpEF. (B) Patients with CpcPH developed a significant increase in RAP/PCWP ratio. (C) In CpcPH-HFpEF, stroke volume was decreased during exercise, coupled with an increase in PA pulse pressure. (D) RV systolic reserve was impaired in both of the PH-HFpEF groups, manifest by a blunted ability to augment RV stroke work index (RVSWI) during exercise. Error bars reflect SEM. †p<0.05 vs Non PH-HFpEF; and #p<0.05 vs IpcPH-HFpEF. Other abbreviations as in Figures 1, 2, and 3.

Discussion

This is the first comprehensive evaluation of exercise hemodynamics in a well-defined cohort of patients with invasively-verified HFpEF with and without pulmonary vascular disease (PVD). We demonstrate that HFpEF patients with CpcPH displayed multiple features consistent with more advanced HF, including greater RV dysfunction, higher natriuretic peptide levels, and greater burden of atrial fibrillation. CpcPH-HFpEF patients displayed more abnormal RV-PA arterial interaction at rest, with greater chamber dilation and dysfunction as pulmonary vascular resistance increased. Despite similar biventricular filling pressures at rest, patients with CpcPH-HFpEF developed more dramatic increases in right heart filling pressures as venous return increased during exercise, resulting in enhanced ventricular interdependence, which
compromised the transmural distending pressures that drive LV chamber filling. Together with reduced RV contractile reserve, this led to decreases in stroke volume and blunted ability to augment cardiac output with exercise in patients with CpcPH-HFpEF, which was associated with profound impairment in aerobic capacity. These data show that HFpEF patients with PVD demonstrate unique pathophysiologic features brought about by the stress of exercise that distinguish them from HFpEF patients without PVD, including impaired ability to enhance blood flow through the lungs, greater right heart congestion, failure to optimally utilize Frank-Starling reserve in the LV due to ventricular interaction, and limited capacity to augment RV systolic performance (Summary Figure). These pathophysiologic insights have important implications for clinical care and for the design of novel therapies targeted to HFpEF patients with and without pulmonary vascular disease.

Pulmonary vascular disease in HFpEF
Accumulating evidence supports the idea that there may be pathophysiologically unique phenotypes within the broader population of patients with HFpEF. The presence of PH and PVD appears to identify one such phenotype of importance. Prior studies have begun to characterize PVD in HFpEF clinically and

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Pathophysiology of HFpEF with Pulmonary Vascular Disease

- **Left Atrial Hypertension**
  - ↑ LV filling pressure
  - ↓ LV preload volume
  - ↓ LV Stroke volume

- **Right Heart Remodeling & Dysfunction**
  - ↑ Right heart congestion
  - ↓ RV systolic reserve
  - ↓ RV Stroke volume

- **Exertional Intolerance**
  - ↓ Peak O₂ consumption

- **Summary Figure**
  - Chronic Backward Transmission of ↓ hydrostatic pressure
  - Exercise:
    - ↑ Venous Return, ↑ Lung Blood Flow & Volume
  - Chronic ↑ Right Ventricular Afterload
  - ↑ Pulmonary Vascular Reserve
  - ↑ Pulmonary hypertension
  - ↑ Pulmonary vascular remodeling
  - ↑ Pulmonary vasoconstriction
  - ↓ Pulmonary artery compliance
  - ↑ ventricular interdependence
Exercise Unmasks Distinct Pathophysiologic Features in Heart Failure with Preserved Ejection Fraction and Pulmonary Vascular Disease

hemodynamically based upon resting data. Similar to the current data, these studies demonstrated that the presence of PVD in patients with HFpEF is associated with reduced exercise capacity, more severe RV dysfunction, and worse outcomes, but the mechanisms have remained unclear.

We observed that PVD in HFpEF is associated with more severe systemic arterial disease, reflected by higher mean vascular resistance and arterial elastance and lower total arterial compliance in patients with CpcPH. This might be related in part to interdependence between the great vessels. Alternatively, combined systemic and PA stiffening may be related to widespread loss of NO bioavailability in both the lungs and systemic vasculature. Systemic vascular stiffening in HFpEF is correlated with abnormal more severe exercise-induced pulmonary hypertension, and this is partially reversible with acute administration of NO providing therapies. These data support the hypothesis that endothelial dysfunction and NO deficiency plays an important role in both the pulmonary and systemic vasculature in patients with HFpEF, and that therapies targeting NO metabolism may hold great promise for patients with HFpEF and PVD. Recent data also indicate that there may be substantial pulmonary vascular remodeling in patients with HFpEF, which may require additional anti-proliferative therapies to restore pulmonary vascular reserve.

Exercise Unmasks a Unique Pathophysiology in HFpEF with PVD

We observed distinct hemodynamic responses to exercise in HFpEF patients that varied according to the presence or absence of PVD, many of which were related to the phenomenon of ventricular interdependence. We speculate that this was related to 2 key factors: an inability of the lung vasculature to accommodate increased blood volume and flow due to vasoconstriction and vascular remodeling, and impairments in right ventricular function that limited the ability to eject blood through the higher impedance pulmonary circulation as metabolic demand for systemic perfusion increases.

The RV and LV are connected in series, so RV output affects LV filling in this direct way. However, the two ventricles also occupy the same space in the cardiac fossa and may also interact in parallel. Ventricular interdependence refers to the phenomenon whereby changes in pressure, filling and volume in one chamber influences these characteristics in the other chamber. Diastolic ventricular interaction
may be observed in patients with right heart failure due to acute pulmonary embolism, or severe isolated tricuspid regurgitation, where the dilated right ventricle out-competes the left ventricle for space, and the interventricular septum bows from right to left, leading to "underloading" of the LV. A similar relationship is also observed in patients with the obese phenotype of HFpEF, where abnormal RV-PA interaction synergizes with volume overload and increased epicardial fat to amplify ventricular interaction.

Exercise poses a profound stress on the heart and lungs: blood is rapidly redistributed from the abdomen and extremities to the thorax, leading in a 50% increase in lung blood volume and 300% increase in pulmonary blood flow in the healthy adult. Because patients with CpcPH-HFpEF display pulmonary vascular disease that may limit this reserve, we hypothesized that the increase in systemic venous return accompanying exercise might overwhelm the right heart and lungs, leading to more severe pulmonary hypertension, greater RV-PA uncoupling, and heightened right sided congestion, setting the stage for conditions that promote enhanced interdependence.

Consistent with this hypothesis, we found that lower PA compliance was associated with more exuberant increases in RA pressures in CpcPH-HFpEF patients during exercise (Figure 4), while greater elevations in PVR and transpulmonary gradient were correlated with greater reduction in LV transmural pressure (Figure 3), which more accurately reflects the true LV distending pressure or preload. The combination of a reduction in LV transmural distending pressure and blunted RV contractile reserve observed in the CpcPH-HFpEF group led to a striking reduction in stroke volume during exercise and impairment in cardiac output heightened venous return (Figure 4).

Clinical implications
The common existence of PVD in HFpEF and its association with adverse prognosis has stimulated new interest in novel therapies targeting the pulmonary vasculature in this disorder. The present data identifying unique features to the pathophysiology of PVD provide further support for conducting trials targeting pulmonary vascular structure and function in HFpEF. Multiple such trials targeting pulmonary vasoconstriction and remodeling are currently underway (NCT 03153111, 02742129, 03043651, 02885636, 03015402, and 02744339).
The current data suggest that there may be other therapeutic targets in HFpEF-PVD that merit study. The enhanced ventricular interdependence that occurs during exercise in HFpEF-PVD provides a theoretical basis for reducing pericardial restraint in order to preserve stroke volume reserve and improve cardiac output, similar to what is observed with pulmonary embolism.\textsuperscript{25, 33} In this regard, we have recently shown in animals without PVD that limited anterior pericardial resection abrogates the increase in cardiac filling pressures with volume loading, improving Frank-Starling reserve.\textsuperscript{34} However, because pericardial resection can promote eccentric remodeling,\textsuperscript{35} and because we observed greater RV dilation with increasing PVR, it might be important to treat pulmonary vascular disease in tandem with interventions targeted to the pericardial restraint in patients with HFpEF and PVD. Right ventricular contractile reserve was also impaired with exercise in this study, in agreement with previous studies performed in HFpEF patients without substantial PVD,\textsuperscript{22, 36} and this also supports testing new therapies that can improve RV function and functional reserve to improve clinical status in CpcPH HFpEF.

There is controversy on the best method to define the entity of CpcPH. Current guidelines recommend the use of either PVR or DPG criteria.\textsuperscript{17} We observed that all of the CpcPH patients displayed elevated PVR, yet only a minority demonstrated an elevated DPG. Prior studies have shown that DPG does not predict survival in HF,\textsuperscript{6} and the current data show that DPG is not superior to PVR to identify patients with this characteristic pathophysiology on exercise. Further research is needed to investigate whether other hemodynamic parameters such as PAC may provide added value in this regard.

\textbf{Limitations}

This study was single center and all patients were referred for right heart catheterization, introducing selection bias. Echocardiography was not performed during exercise. Although the control group was well-matched for age and sex, these subjects were also referred for invasive assessment and had similar comorbidities (e.g. hypertension, coronary artery disease, diabetes mellitus and obesity), so they cannot be considered to be truly normal. However, this would only bias our results toward the null as compared to rigorously-screened healthy volunteers.
Conclusions

Pulmonary vascular disease in HFpEF leads to unique pathophysiologic consequences during the stress of exercise, including inadequate PA vasodilation, greater right heart congestion, left heart underfilling, heightened ventricular interdependence, and impaired right ventricular reserve. These limitations markedly sabotage the ability of the heart to increase stroke volume and cardiac output during exercise, leading to profound limitations in aerobic capacity. Interventions targeted to this distinct pathophysiology require testing in patients with HFpEF with PVD.

References

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