Enhanced Pulmonary Vasodilator Reserve and Abnormal Right Ventricular:  
Pulmonary Artery Coupling In Heart Failure With Preserved Ejection Fraction

Andersen et al: Right Ventricular-Pulmonary Artery Coupling in HFpEF

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Abstract

Background—Pulmonary hypertension (PH) and right ventricular (RV) dysfunction are common in patients with advanced HFpEF, yet their underlying mechanisms remain poorly understood. We sought to examine RV-pulmonary artery (PA) functional reserve responses and RV-PA coupling at rest and during β-adrenergic stimulation in subjects with earlier-stage HFpEF.

Methods and Results—In a prospective trial, subjects with HFpEF (n=39) and controls (n=18) underwent comprehensive invasive and non-invasive hemodynamic assessment using high fidelity micromanometer catheters, echocardiography and expired gas analysis at rest and during dobutamine infusion. HFpEF subjects displayed similar RV structure but significantly impaired RV systolic (lower RV dP/dt_max*IP-1 and s’) and diastolic function (higher RV τ) coupled with more severe pulmonary vascular disease, manifest by higher PA pressures, higher PA resistance and lower PA compliance compared to controls. Dobutamine infusion caused greater pulmonary vasodilation in HFpEF compared to controls, with enhanced reductions in PA resistance, greater increase in PA compliance and a more negative slope in the PA pressure-flow relationship as compared to controls (all p<0.001). Right ventricular-PA coupling analysis revealed that dobutamine improved RV ejection in HFpEF subjects through afterload reduction alone, rather than through enhanced contractility, indicating RV systolic reserve dysfunction.

Conclusions—Pulmonary hypertension in early stage HFpEF is related to partially reversible pulmonary vasoconstriction coupled with RV systolic and diastolic dysfunction, even in the absence of RV structural remodeling. Pulmonary vascular tone is more favorably responsive to β-adrenergic stimulation in HFpEF than controls, suggesting a potential role for β-agonists in the treatment of patients with HFpEF and PH.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01418248.

Key Words: heart failure, pulmonary hypertension, pulmonary circulation, right ventricular function, diastolic heart failure
Approximately half of patients with heart failure (HF) have a preserved left ventricular (LV) ejection fraction (HFpEF). Recent studies have identified pulmonary hypertension (PH) and right ventricular (RV) dysfunction as markers of adverse outcome in HFpEF, but the mechanisms underlying their development remain unclear. While RV dysfunction has been demonstrated noninvasively by echocardiography, direct, simultaneous invasive assessments of RV function and RV-pulmonary artery (PA) coupling at rest and with stress have not been performed in HFpEF.

Acute stress responses in the cardiovascular system are mediated predominantly through the autonomic nervous system. Previous studies have shown that left ventricular (LV) - systemic arterial responses to β-adrenergic stimulation are depressed in patients with HFpEF. The pulmonary vasculature is richly innervated by adrenergic and cholinergic fibers, the expression pattern of which may be altered in patients with HF. Excessive α-adrenergic vasoconstriction is clearly linked to the development of PA vascular remodeling and Group 1 PH, but the effects of β-adrenergic stimulation on pulmonary vascular function and RV-PA coupling in Group 2 PH due to HFpEF remain unclear.

Accordingly, we performed a prospective invasive hemodynamic study examining resting RV and pulmonary vascular function along with RV-PA coupling responses to acute β-adrenergic stimulation with dobutamine in patients with HFpEF and controls. We hypothesized that RV systolic and diastolic function and RV-PA coupling would be impaired in HFpEF at rest and with β-stimulation, and that dobutamine would differentially affect pulmonary vascular function in subjects with HFpEF as compared to controls.
Methods

Subjects referred to the Mayo Clinic catheterization laboratory for invasive hemodynamic testing were enrolled in this prospective study between August 2011 and July 2013. Written informed consent was provided by all patients prior to participation in study-related procedures. A convenience sample of subjects meeting the predefined criteria as HFpEF and controls (below) was taken from a larger group of subjects participating in this prospective trial. The study was approved by the Mayo Clinic Institutional Review Board and the study was registered (NCT01418248).

Subjects

HFpEF was defined by clinical symptoms of chronic HF (dyspnea, fatigue), preserved left ventricular ejection fraction (LVEF; >50%), and elevated pulmonary capillary wedge pressure (PCWP) at rest (>15mmHg) or with exercise (≥25mmHg). Subjects with significant valvular heart disease (>mild stenosis, >moderate regurgitation), severe pulmonary disease, congenital heart disease, high output heart failure, unstable ischemic heart disease (acute coronary syndrome or recent myocardial infarction <60 days), hypertrophic or infiltrative cardiomyopathy, primary renal or hepatic disease or pericardial disease were excluded. Control subjects had no demonstrable cardiac etiology for symptoms, with normal rest and exercise pulmonary artery (PA) pressures (rest<25mmHg, exercise<40mmHg) and normal rest-exercise PCWP as defined above.
Study Design

Subjects were studied on chronic medications in the fasted state after minimal sedation in the supine position. After providing consent, subjects underwent history, physical examination, and resting echocardiogram. Echocardiography was performed by trained research cardiac sonographers using a General Electric Vivid E9 (General Electric Healthcare) cardiac ultrasound system. Images were stored digitally for offline analysis with measurements made in EchoPac (General Electric Healthcare) by an investigator blinded to subject diagnosis. Atrial and ventricular chamber dimensions were determined according to standard recommendations.19 Cardiac catheterization, simultaneous echocardiography and expired gas analysis were performed at rest, during low dose dobutamine infusion (5 μg/kg/min for 5 minutes), and higher dose dobutamine infusion (10 μg/kg/min for 5 minutes).

Catheterization Protocol

Right heart catheterization was performed through a 9-French sheath via the internal jugular vein as previously described.18 Transducers were zeroed at the phlebostatic axis using laser calipers. Right atrial (RA) pressure, PA pressure and PCWP were measured at end-expiration using 2-Fr high fidelity micromanometer-tipped catheters (Millar Instruments, Houston, TX) advanced through the lumen of a 7-Fr fluid-filled balloon-tipped catheter (Arrow, Research Triangle Park, NC, USA). Pressure tracings were continuously recorded throughout the study, digitized at 240 Hz and stored for offline analysis. High fidelity RV pressure tracings were evaluated offline using Mathematica (Wolfram, Champaign, IL, USA) from a minimum of 10 beats, with extrasystolic and post extrasystolic beats excluded.
Arterial blood pressure (BP) was measured continuously through a 4-6 Fr radial artery cannula. Oxygen consumption (VO₂) was measured by expired gas analysis (MedGraphics, St. Paul, MN). Systemic and mixed venous (PA) blood was sampled to measure oxygen content (=saturation*hemoglobin*1.34). Arterial-venous O₂ content difference (CₐO₂ - CᵥO₂) was calculated as the difference between systemic arterial and PA O₂ content. Cardiac output (CO) was determined by the direct Fick method (= VO₂/ [CₐO₂ - CᵥO₂]). Stroke volume (SV) was determined from the quotient of CO and heart rate (HR). The diastolic pressure gradient (DPG) was calculated as PA diastolic pressure minus mean PCWP. Pulmonary vascular resistance (PVR= [mean PA-PCWP]/CO) and PA compliance (PAC= SV/[PA pulse pressure]) were calculated using standard formulas.

Assessment of RV Systolic Function and RV-PA coupling

RV systolic function was assessed using both ejection phase and isovolumic indices. The peak systolic velocity of the lateral tricuspid annulus (s’) measured by tissue Doppler echocardiography was assessed as an ejection phase index of systolic function. RV-PA coupling was then evaluated by plotting s’ as a function of ejection load (mean PA pressure). RV systolic function was also assessed invasively by the maximal rate of pressure increase during isovolumic contraction indexed to instantaneous pressure (dP/dtₘₐₓ*IP⁻¹) in order to minimize preload-dependence.

Assessment of RV Diastolic Function

RV diastolic function was assessed during filling by the lateral tricuspid annular diastolic tissue velocity (e’) and the ratio of tricuspid early diastolic flow to annular velocity (E/e’). RV
diastolic function was also assessed invasively by the mono-exponential time constant of pressure decay during isovolumic relaxation (τ), fitted using the following equation
\[ P = P_0e^{-t/\tau} + P_B \]
where \( P \) is pressure, \( \tau \) is the pressure decay constant, and \( P_B \) is a baseline offset, and for which the first derivative with respect to time is the equation
\[ \frac{dP}{dt} = \left(-\frac{1}{\tau}\right)P + \frac{P_B}{\tau}. \]
Only diastolic pressure decay data with \( R^2 \geq 0.99 \) fit were included.\(^{24, 25}\)

**Statistical Analysis**

Results are reported as mean (SD), median (IQR) or number (%). Between group differences for individual time points were tested using Student's t-test, Fisher’s Exact test, or Wilcoxon rank sum test. To provide the highest power to detect group differences in ventricular-vascular function, data points from baseline, low dose dobutamine and high dose dobutamine were compared between HFpEF and controls using repeated measures ANOVA (RMANOVA). The significance of HFpEF vs control differences in each of the functional parameters are reported as the “Group effect p value”, the within-group effect of dobutamine is reported as the “Drug effect p value” and differences in dobutamine response between groups are reported by the “Group*drug p value” in the Tables and Figures. Right ventricular-PA coupling responses were analyzed using linear regression analysis. All tests were two-sided, with a P-value < 0.05 considered significant. Analyses were performed using JMP 10.0.0 SAS Institute, Cary, NC, USA.

**Results**

Compared to controls (n=18), subjects with HFpEF (n=39) were older, heavier, more likely to have a history of hypertension, be treated with diuretics, and have jugular venous distension
(Table 1). In keeping with an earlier stage of HFP EF, very few subjects displayed findings of marked volume overload such as rales, gallop sounds, or peripheral edema. As expected, subjects with HFP EF had higher NT-proBNP levels, more renal dysfunction and lower hemoglobin compared to control subjects. There were no statistically significant differences in sex, beta blocker use (62% vs 50%, p=0.6), or other medical comorbidities between the two groups.

**Baseline Ventricular-Vascular Structure, Function and Hemodynamics**

Right atrial volume and RV dimensions were similar in HFP EF and controls, with the exception of RV basal diameter, which was greater in HFP EF (Table 2). Right-sided valvular disease was rare in both groups, with no between group differences in prevalence. Compared to controls, HFP EF subjects had more LV diastolic dysfunction (higher E/e’ and diastolic function grade) and larger left atrial volumes. There were no group differences in LV size, mass or EF. LV systolic and diastolic function, assessed by s’ and e’ velocities was significantly impaired in HFP EF subjects compared to controls (Table 2).

Compared to controls, HFP EF subjects had higher blood pressure at baseline, but similar HR, SV and CO (Table 3). By design, subjects with HFP EF displayed higher left heart filling pressures, and they also had higher RA and PA pressures. Pulmonary vascular dysfunction was evident at baseline in HFP EF subjects, manifest by higher TPG and PVR, and lower PA compliance compared to controls. In contrast, the DPG was similar in HFP EF and controls (2±2 vs 3±3 mmHg, p=0.4).

RV systolic function, assessed by s’ velocity and RV dP/dt max*IP-1 was or tended to be lower in HFP EF subjects compared to controls at baseline (9.9±3.0 vs 11.5±3.1 cm/sec, p=0.07
and 10.4±3.2 vs 15.6±5.2 sec⁻¹, p=0.001, respectively, Table 4). HFpEF subjects displayed RV
diastolic dysfunction with more prolonged isovolumic relaxation at baseline compared to
controls (τ 61±11 vs 50±17 msec, p=0.009), though tricuspid annular e’ and the E/e’ did not
differ between the groups. These differences in RV function remained significant after adjusting
for beta blocker use (p<0.01 for all).

Expired Gas and Ventilatory Analysis

In keeping with its known actions, dobutamine infusion modestly increased metabolism and
ventilation, with increases in VO₂ (225 to 275 ml/min, p<0.0001), tidal volume (520 to 650 ml,
p<0.0001), respiratory rate (15 to 17 min⁻¹, p=0.03), and minute ventilation (7.5 to 10.3 L/min,
p<0.0001) resulting in a decrease in end-tidal CO₂ (ETCO₂; 38 mmHg to 35 mmHg, p=0.004).
Ventilation relative to CO₂ production was increased with dobutamine (37 to 41 L/min/mmHg,
p=0.01). There were no differences between HFpEF subjects and controls in any of the
ventilatory or metabolic parameters at rest or with dobutamine infusion (all p>0.1).

Pulmonary Vascular Responses to β-Adrenergic Stimulation

Dobutamine similarly increased HR, BP, SV, and CO in HFpEF and control subjects, with no
between-group differences in the magnitude of change (Table 3). Dobutamine reduced RAP
more in HFpEF than controls but there was no differential effect on PCWP. Dobutamine
reduced PA pressure, PVR and TPG significantly more in subjects with HFpEF, with greater
improvement in PA compliance as compared to controls (Figure 1, Table 3). The differing
pulmonary vascular response to β-adrenergic stimulation in HFpEF and controls was further
evidenced by PA pressure-flow and TPG-flow relationships, which displayed negative slopes in
HFpEF subjects, in keeping with greater dynamic PA vasodilation with increasing doses of
dobutamine, in contrast to flat or positive PA-flow and TPG-flow relationships that were
observed in controls (Figure 2). Each of these differences remained significant after adjusting
for beta-blocker use (p<0.01 for all).

*Right Ventricular Responses to β-Adrenergic Stimulation*

Incorporating baseline and dobutamine data points, RV systolic function was significantly
impaired in HFpEF compared to controls, assessed by both tricuspid annular s’ velocity and
dP/dt\(_{\text{max}}\) * IP and (Table 4, Figure 3A, B). Notably, there was no significant correlation between
the ejection phase and isovolumic indices of RV systolic function (p=0.11). While the
dobutamine-mediated increase in RV systolic function (systolic reserve) tended to be lower in
HFpEF for tricuspid annular s’ (group*drug p=0.05), it was not different between HFpEF and
control for dP/dt\(_{\text{max}}\) * IP (p=0.5).

Similarly, RV diastolic function was impaired in HFpEF compared to controls, with
higher tau incorporating baseline and dobutamine data points (Table 4). RV diastolic reserve
assessed by tissue Doppler tended to be impai red in HFpEF (less increase in tricuspid annular e’,
p=0.05), but changes in tau with dobutamine were not different between groups. Similar to the
systolic indices, there was no correlation between isovolumic (τ) and filling phase indices (e’) of
RV diastolic function (p=0.98).

*Right Ventricular-Pulmonary Artery Coupling Reserve*

In control subjects, dobutamine infusion shifted the relationship between s’ and PA pressure
upward (p<0.0001, Figure 3C). This indicates an increase in RV contractility, since the velocity
of shortening was increased at any given afterload (PA pressure). In contrast, the relationship between s’ and PA pressure during dobutamine infusion in HFrEF subjects was not different from baseline (p=0.6, Figure 3D). This indicates that the increase in s’ velocity observed with dobutamine in HFrEF subjects was related to RV afterload reduction from pulmonary vasodilation, rather than an increase in RV contractility.

**Discussion**

This prospective study invasively characterized RV function and dynamic RV-PA coupling at rest and during β-adrenergic stimulation in subjects with HFrEF and controls without HF. Similar to prior studies, HFrEF subjects displayed LV dysfunction, elevated biventricular filling pressures, and impaired pulmonary vascular function compared to controls. With acute β-adrenergic stimulation, there was a much greater degree of pulmonary vasodilation in HFrEF subjects compared to controls, an effect that was consistently observed across all indices examined. This indicates that the pulmonary vascular disease present in patients with relatively early stage HFrEF is largely reversible. Right ventricular systolic and diastolic function were impaired in HFrEF subjects compared to controls using both invasive and noninvasive indices. Dynamic RV-PA coupling analysis revealed that RV systolic ejection was enhanced with β-adrenergic stimulation in HFrEF subjects through PA vasodilation, rather than increased RV contractility, as in controls. This identifies a limitation in RV systolic reserve and points to the potential benefits of RV afterload reduction in HFrEF. These data confirm and extend upon a growing body of literature illustrating the importance of pulmonary vascular and RV dysfunction in HFrEF, while also identifying a new, previously unrecognized role of autonomic signaling in the pathophysiology of pulmonary hypertension in HFrEF. The more favorable pulmonary
vascular response to dobutamine in HFP EF suggests a potential role for novel therapies such as inhaled β-agonists to improve outcomes in the growing cohort of patients with HFP EF and PH.

**Pulmonary Vascular Disease in HFP EF**

Pulmonary hypertension is common in HFP EF, and its presence predicts increased mortality.\(^2,5,7\) The traditional thinking has been that PH develops in the early stages of HFP EF simply from passive transmission of downstream left atrial hypertension.\(^7,18\) Here, we show that a partially reversible element of pulmonary vasoconstriction is observed even in patients with early stage HFP EF, where gross volume overload is absent. Notably, this degree of pulmonary vascular disease was not detectable by the DPG, raising questions with the utility of this index in patients with less advanced disease. Patients with HFrEF and coexisting pulmonary vascular disease display higher mortality compared to those with ‘passive’ PH alone, though this is less well-characterized in HFP EF.\(^26-28\) Because of the association between pulmonary vascular disease and adverse outcome, and the enhanced afterload-sensitivity of the failing RV in HFP EF,\(^5\) recent phase 2 trials have begun testing whether pulmonary vasodilators may improve hemodynamics, exercise capacity and clinical status in this cohort of patients.\(^29-32\) The absence of RV inotropic reserve in HFP EF demonstrated by RV-PA coupling analysis in the current study (Figure 3D) reinforces the importance of RV unloading as a viable approach to improve RV function in this population.

The primary novel finding in the current study is the greater degree of pulmonary vasodilation achieved with acute β-adrenergic stimulation in HFP EF subjects compared to controls. This augmented vasodilation was observed in each measure used to assess PA function (Figure 1). Pulmonary pressure-flow relationships have recently been proposed to provide the
most sensitive and robust way to assess pulmonary vascular function. The fact that increases in blood flow with dobutamine were associated with progressively decreasing PA pressure in HFP EF subjects, but not controls (Figure 2A) provides clear evidence of greater pulmonary vasodilation in the HF group. PA pressure is directly related to PCWP, which tended to drop more in HFP EF than controls, but this cannot explain the differential response in PA pressures, because plotting TPG vs flow also reveals a greater pulmonary dilatory response in HFP EF subjects with dobutamine (Figure 2B).

What might explain this differential PA vasodilatory response in HFP EF and controls? Pulmonary vascular tone is most often conceptualized as being dictated by the relative balance of nitric oxide, prostacyclin and endothelin signaling pathways, but sympathetic tone also plays an important role. Alpha-adrenergic stimulation constricts the pulmonary vasculature, an effect that is speculated to contribute to hypoxic vasoconstriction in pulmonary parenchymal disease, in addition to the well-characterized entity of PH associated with anorectic drug use. While vasodilating β2-adrenergic receptors are also known to be expressed in pulmonary vascular smooth muscle, previous studies have revealed minimal vasodilator response with agonists such as isoproterenol. This absence of vasodilation is believed to be related to the fact that the sympathetic contribution to pulmonary vascular tone at steady state tonically favors dilation, at least in normal adults. The current data suggest that this may not be the case in HFP EF. Many factors dictate the balance of vasoconstriction and dilation in the lung, and the current data suggest that further study is warranted to determine whether changes in α or β1/β2 receptor expression might exist in HFP EF and contribute to the differential response to β-stimulation.

These findings may have important implications for treatment. For example, perhaps novel interventions such as inhaled β-agonists such as those used in obstructive lung diseases
could be effective to treat pulmonary hypertension in patients with HFpEF, potentially with less risk for untoward systemic effects given the targeted inhaled delivery to the pulmonary vasculature. In addition, devices targeting sympathetic/parasympathetic balance are being developed and tested to treat HF, and reduction in pulmonary arterial impedance could be a novel target of such devices that had not been previously considered. These questions merit further study.

Right Ventricular Dysfunction and RV-PA Coupling in HFpEF

Right heart remodeling and dysfunction have recently been shown to be associated with increased risk of death in HFpEF. We observed that for the most part right heart structure was similar in subjects with HFpEF and controls in the current study. This contrasts with Melenovsky et al., who observed that RV and right atrial volumes were markedly increased in HFpEF. The discrepancy likely relates to different stages of HFpEF enrolled in the two studies. The HFpEF patients in the latter study had advanced disease, with much higher NT-proBNP, PCWP, and more severe PH. The current study enrolled subjects with an earlier stage of HFpEF, where filling pressures were closer to normal at rest and physical examination evidence of congestion was largely absent. Despite the absence of right-sided structural remodeling, RV systolic and diastolic function were significantly impaired in the HFpEF group, differences that became more evident in the setting of β-stimulation, similar to prior studies evaluating left ventricular-systemic arterial reserve with adrenergic stimulation or exercise stress.

In HFpEF subjects, tricuspid annular s’ increased with dobutamine in relation to afterload reduction from dobutamine, rather than an increase in contractility, which would manifest by an upward shift in the s’ vs PA pressure relationship. This indicates an abnormality in RV systolic
reserve and abnormal RV-PA coupling that is present even in the earliest stages of HFpEF. It is possible that interventions to target RV function or afterload may be of greater benefit in patients at this stage of disease progression. Subjects were studied on chronic medications including beta blockers. The group differences in hemodynamic response persisted after adjusting for beta blocker usage, arguing against background therapy as an explanation for the primary findings. The favorable response to beta stimulation in HFpEF observed in the current study provides further evidence that beta blockers might have unfavorable effects on RV reserve and RV-PA coupling in HFpEF.

This is the first study to invasively characterize RV systolic and diastolic function using high fidelity micromanometer catheters. We show that similar to the LV, there is prolonged diastolic relaxation in the RV in patients with HFpEF, manifest by prolonged tau. Similarly, RV systolic function, assessed by dP/dtmax*IP⁻¹, was also impaired in HFpEF, confirming previous noninvasive echocardiographic studies. Intriguingly, there was no significant correlation between the isovolumic (dP/dtmax*IP⁻¹, τ) and ejection or filling phase (s’, e’) indices of RV function examined. This suggests that there is uncoupling in the right ventricle between the rate of pressure change during the isovolumic periods and the velocity of tissue motion during contraction and relaxation. Despite the lack of correlation, the finding that RV systolic and diastolic function was impaired consistently across all indices increases confidence in the conclusion that RV function is significantly impaired in HFpEF patients, even in the early stages of disease, prior to the onset of RV remodeling.
Limitations

There were baseline differences in age, body mass, prevalence of hypertension, renal function, and hemoglobin, and we cannot exclude the possibility that some of these baseline differences might contribute to the group differences observed. However, these characteristics are very typical of HFrEF and are believed to play a major role in the pathophysiology, such that statistical adjustment for them could mask important physiologic observations that might be targeted therapeutically in future trials. Assessing RV contractility using dP/dt is limited because of its dependence on loading conditions. This load dependence was attenuated by indexing to instantaneous developed pressure, but this index of RV function has potential pitfalls. This study is also subject to bias in that participants had all been referred for invasive hemodynamic assessment, though this has become standard practice at our institution in the evaluation of exertional dyspnea.

Conclusions

Patients with early stage HFrEF display pulmonary vascular dysfunction that is partly reversible and more favorably responsive to \( \beta \)-adrenergic stimulation than what is observed in controls. This suggests that the pulmonary vasculature in HFrEF is not maximally vasodilated at rest, and that interventions to enhance \( \beta \)-receptor activation in the pulmonary vasculature may hold promise to treat HFrEF patients with PH. RV systolic and diastolic function are impaired in tandem with altered RV-PA coupling in patients with early stage HFrEF, even when structural remodeling is absent, providing further support for therapies targeting RV and pulmonary vascular function as novel approaches to improve outcomes in HFrEF.
Sources of Funding

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Disclosures

None.

References

12. Charoenpanichkit C, Little WC, Mandapaka S, Dall’Armellina E, Morgan TM, Hamilton CA, Hundley WG. Impaired left ventricular stroke volume reserve during clinical


### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=18)</th>
<th>HFP EF (n=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>61±13</td>
<td>71±11</td>
<td>0.009</td>
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<tr>
<td><strong>Male sex (n, %)</strong></td>
<td>10 (56%)</td>
<td>16 (41%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>26.2±4.3</td>
<td>35.0±7.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>10 (56%)</td>
<td>36 (92%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>3 (17%)</td>
<td>14 (36%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Coronary artery disease (n, %)</td>
<td>5 (28%)</td>
<td>15 (38%)</td>
<td>0.6</td>
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<tr>
<td><strong>Physical examination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular venous distention (n, %)</td>
<td>0 (0%)</td>
<td>20 (50%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Rales (n, %)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>0.99</td>
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<tr>
<td>S3 gallop (n, %)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0.99</td>
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<td>Peripheral edema (n, %)</td>
<td>0 (0%)</td>
<td>6 (15%)</td>
<td>0.16</td>
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<tr>
<td><strong>Medications</strong></td>
<td></td>
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<tr>
<td>ACE inhibitor or ARB (n, %)</td>
<td>10 (42%)</td>
<td>33 (66%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Beta blocker (n, %)</td>
<td>9 (50%)</td>
<td>24 (62%)</td>
<td>0.6</td>
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<tr>
<td>Calcium channel blocker (n, %)</td>
<td>4 (22%)</td>
<td>8 (21%)</td>
<td>0.99</td>
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<tr>
<td>Diuretic (n, %)</td>
<td>4 (22%)</td>
<td>25 (64%)</td>
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<td><strong>Laboratories</strong></td>
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<td>Hemoglobin (g/dl)</td>
<td>13.8±1.2</td>
<td>12.5±1.4</td>
<td>0.001</td>
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<tr>
<td>eGFR mL/min/1.73 m²</td>
<td>88±18</td>
<td>67±22</td>
<td>0.0006</td>
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<tr>
<td>NT-proBNP (pg/ml)</td>
<td>76 (38-228)</td>
<td>457 (161-2302)</td>
<td>0.002</td>
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</table>

HFP EF, heart failure with preserved ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate
### Table 2. Baseline Right and Left Ventricular Structure and Function

<table>
<thead>
<tr>
<th></th>
<th>Control (n=18)</th>
<th>HFpEF (n=39)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Right heart parameters</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RA volume index, ml.m⁻²</td>
<td>33 ± 27</td>
<td>33 ± 16</td>
<td>0.9</td>
</tr>
<tr>
<td>RV base diameter, mm</td>
<td>33 ± 8</td>
<td>39 ± 6</td>
<td>0.01</td>
</tr>
<tr>
<td>RV midventricular diameter, mm</td>
<td>29 ± 7</td>
<td>32 ± 6</td>
<td>0.14</td>
</tr>
<tr>
<td>RV length, mm</td>
<td>70 ± 8</td>
<td>68 ± 10</td>
<td>0.4</td>
</tr>
<tr>
<td>RV diastolic area, cm²</td>
<td>20 ± 5</td>
<td>20 ± 6</td>
<td>0.9</td>
</tr>
<tr>
<td>RV systolic area, cm²</td>
<td>11 ± 3</td>
<td>11 ± 4</td>
<td>0.5</td>
</tr>
<tr>
<td>Transtricuspid E flow velocity, cm.s⁻¹</td>
<td>52 ± 12</td>
<td>57 ± 19</td>
<td>0.3</td>
</tr>
<tr>
<td>Transtricuspid A flow velocity, cm.s⁻¹</td>
<td>34 ± 11</td>
<td>49 ± 25</td>
<td>0.04</td>
</tr>
<tr>
<td>Tricuspid regurgitation grade &gt;II, (%)</td>
<td>1 (6)</td>
<td>3 (8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary regurgitation grade &gt;II, (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Left heart parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA volume index, ml.m⁻²</td>
<td>30 ± 13</td>
<td>41 ± 17</td>
<td>0.03</td>
</tr>
<tr>
<td>LV internal diameter in diastole, mm</td>
<td>48 ± 6</td>
<td>48 ± 6</td>
<td>0.8</td>
</tr>
<tr>
<td>LV internal diameter in systole, mm</td>
<td>33 ± 6</td>
<td>31 ± 6</td>
<td>0.3</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>59 ± 9</td>
<td>62 ± 8</td>
<td>0.2</td>
</tr>
<tr>
<td>LV mass index, g.m⁻²</td>
<td>90 ± 20</td>
<td>85 ± 24</td>
<td>0.4</td>
</tr>
<tr>
<td>LV e' (cm/s)</td>
<td>9.0 ± 2.6</td>
<td>7.2 ± 1.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Medial E/e’ ratio</td>
<td>9.3 ± 2.5</td>
<td>15.4 ± 6.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Lateral E/e’ ratio</td>
<td>6.7 ± 2.2</td>
<td>12.8 ± 5.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic dysfunction grade, (0-3)</td>
<td>0.3 ± 0.6</td>
<td>2.1 ± 0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV s’ (cm/s)</td>
<td>8.5 ± 2.3</td>
<td>6.9 ± 1.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

HFpEF, heart failure with preserved ejection fraction; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle
Table 3. Hemodynamics at Baseline with Dobutamine

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Low dose dobutamine</th>
<th>High dose dobutamine</th>
<th>Drug effect p-value</th>
<th>Group effect p-value</th>
<th>Group*drug p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial systolic pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>132±15</td>
<td>140±22</td>
<td>139±28</td>
<td>0.03</td>
<td>0.0001</td>
<td>0.7</td>
</tr>
<tr>
<td>HFpEF</td>
<td>151±20*</td>
<td>167±27</td>
<td>166±26</td>
<td>0.0004</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate, beat/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>79±14</td>
<td>84±15</td>
<td>101±22</td>
<td>0.001</td>
<td>0.06</td>
<td>0.8</td>
</tr>
<tr>
<td>HFpEF</td>
<td>72±9</td>
<td>77±13</td>
<td>92±17</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke volume, ml</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>64±17</td>
<td>79±25</td>
<td>79±28</td>
<td>0.002</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>HFpEF</td>
<td>73±19</td>
<td>79±24</td>
<td>78±26</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac output, l/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.0±1.6</td>
<td>6.6±2.2</td>
<td>7.8±2.6</td>
<td>&lt;0.0001</td>
<td>0.3</td>
<td>0.16</td>
</tr>
<tr>
<td>HFpEF</td>
<td>5.2±1.3</td>
<td>6.1±1.8</td>
<td>6.9±2.2</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Filling pressures**

|                               |          |                     |                      |                     |                      |                     |
| RA pressure, mmHg             |          |                     |                      |                     |                      |                     |
| Control                       | 3±2      | 3±2                 | 3±2                  | 0.7                 | <0.0001              | 0.007               |
| HFpEF                         | 10±4*    | 9±4                 | 8±4                  | 0.003               |                      |                     |
| **Mean PCWP, mmHg**           |          |                     |                      |                     |                      |                     |
| Control                       | 5±4      | 5±4                 | 5±3                  | 0.18                | <0.0001              | 0.4                 |
| HFpEF                         | 16±6*    | 15±4                | 14±7                 | 0.02                |                      |                     |

**Pulmonary vascular function**

| Systolic PA pressure, mmHg    |          |                     |                      |                     |                      |                     |
| Control                       | 22±6     | 23±5                | 25±5                 | 0.004               | <0.0001              | 0.0002              |
| HFpEF                         | 41±13*   | 40±12               | 38±12                | 0.006               |                      |                     |
| **Mean PA pressure, mmHg**    |          |                     |                      |                     |                      |                     |
| Control                       | 13±4     | 13±3                | 14±3                 | 0.5                 | <0.0001              | 0.002               |
| HFpEF                         | 28±9*    | 26±8                | 24±8                 | 0.0003              |                      |                     |
| **PA pulse pressure, mmHg**   |          |                     |                      |                     |                      |                     |
| Control                       | 14±4     | 15±4                | 18±5                 | <0.0001             | 0.002                | 0.004               |
| HFpEF                         | 23±8*    | 21±9                | 22±8                 | 0.3                 |                      |                     |
| **Transpulmonary gradient, mmHg** |  |                     |                      |                     |                      |                     |
| Control                       | 8±2      | 8±3                 | 9±3                  | 0.04                | 0.002                | 0.002               |
| HFpEF                         | 12±5*    | 11±4                | 11±4                 | 0.02                |                      |                     |
| **Pulmonary vascular resistance, WU** |  |                     |                      |                     |                      |                     |
| Control                       | 1.7±0.7  | 1.4±0.6             | 1.3±0.5              | 0.007               | 0.01                 | 0.01                |
| HFpEF                         | 2.5±1.3* | 2.0±1.0             | 1.7±0.7              | <0.0001             |                      |                     |
| **PA compliance, ml/mmHg**    |          |                     |                      |                     |                      |                     |
| Control                       | 5.0±2.3  | 5.6±2.2             | 4.9±2.3              | 0.006               | 0.02                 | 0.0004              |
| HFpEF                         | 3.5±1.3* | 4.1±1.8             | 3.9±1.7              | 0.0007              |                      |                     |

*p<0.01 for between-group difference at baseline (unpaired t-test); RA, right atrial; PCWP, pulmonary capillary wedge pressure; PA, pulmonary arterial pressure.
Table 4. Right Ventricular Function at rest and with dobutamine

<table>
<thead>
<tr>
<th>Function</th>
<th>Baseline</th>
<th>Low dose dobutamine</th>
<th>High dose dobutamine</th>
<th>Drug effect p-value</th>
<th>Group effect p-value</th>
<th>Group*drug p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dP/dtmaxIP, sec⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15.6±5.2</td>
<td>16.2±5.8</td>
<td>21.4±6.7</td>
<td>0.0002</td>
<td>0.004</td>
<td>0.5</td>
</tr>
<tr>
<td>HFpEF</td>
<td>10.4±3.2*</td>
<td>11.8±3.4</td>
<td>16.4±5.1</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid annular s’, cm/sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11.5±3.1</td>
<td>15.0±4.7</td>
<td>18.1±4.4</td>
<td>0.001</td>
<td>0.0008</td>
<td>0.05</td>
</tr>
<tr>
<td>HFpEF</td>
<td>9.9±3.0</td>
<td>11.1±3.4</td>
<td>14.0±4.9</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau, msec</td>
<td>50±17</td>
<td>43±14</td>
<td>47±13</td>
<td>0.4</td>
<td>0.002</td>
<td>0.9</td>
</tr>
<tr>
<td>Control</td>
<td>61±11*</td>
<td>57±16</td>
<td>56±16</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td>9.3±3.0</td>
<td>10.1±3.2</td>
<td>14.1±8.4</td>
<td>0.12</td>
<td>0.16</td>
<td>0.05</td>
</tr>
<tr>
<td>Tricuspid annular e’, cm/sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.5±4.4</td>
<td>9.1±3.3</td>
<td>11.3±4.3</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td>5.9±1.8</td>
<td>4.7±2.0</td>
<td>4.5±2.5</td>
<td>0.3</td>
<td>0.13</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>E/e’</strong></td>
<td>6.9±4.9</td>
<td>6.9±4.7</td>
<td>6.5±2.8</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01 for between-group difference at baseline (unpaired t-test)
Figure Legends

Figure 1. Bar graph of absolute changes with dobutamine infusion (10 μg/kg/min) for controls (black bars) and HFpEF (red bars) for [A] mean pulmonary arterial (PA) pressure, [B] Transpulmonary gradient (TPG), [C] Pulmonary vascular resistance (PVR), and [D] Pulmonary arterial compliance (PAC). Error bars indicate SEM.

Figure 2. Compared to controls subjects (Black circles), HFpEF subjects (Red squares) experienced [A] an improvement in their pulmonary pressure flow relationship with dobutamine infusion, manifest by a negative PA pressure-flow slope. [B] This was not related to lowering of left heart pressures, because the transpulmonary gradient (TPG) also decreased with increasing flow in HFpEF subjects, in contrast to the increase in TPG in controls. Base= Baseline, Low= 5μg/kg/min of Dobutamine, High= 10μg/kg/min of Dobutamine. Error bars indicates SEM.

Figure 3. Plot of absolute values with dobutamine infusion for controls (black bars) and HFpEF (red bars) for [A] dP/dt\_max*IP and [B] tricuspid annular systolic tissue Doppler velocity (s’). Base= Baseline, Low= 5μg/kg/min of Dobutamine, High= 10μg/kg/min of Dobutamine. Error bars indicates SEM. Linear regression analysis was used to analyze RV-PA coupling at rest (straight line) and with dobutamine (dotted line) in controls [C] and in HFpEF subjects [D]. See text for details. *p<0.01 between groups, unpaired t-test.
Figure 1

A

\[ \Delta PA \] (mmHg)

\begin{align*}
\text{Controls} & \quad \text{HFpEF} \\
-6 & \quad 0 \\
-4 & \quad 2 \\
-2 & \quad p < 0.0001 \\
0 & \quad 0 \\
2 & \quad 0 \\
4 & \quad 0 \\
6 & \quad 0 \\
\end{align*}

B

\[ \Delta TPG \] (mmHg)

\begin{align*}
\text{Controls} & \quad \text{HFpEF} \\
-3 & \quad 0 \\
-2 & \quad 0 \\
-1 & \quad 0 \\
0 & \quad 0 \\
1 & \quad 0 \\
2 & \quad 0 \\
3 & \quad 0 \\
\end{align*}

C

\[ \Delta PVR \] (WU)

\begin{align*}
\text{Controls} & \quad \text{HFpEF} \\
-1.5 & \quad 0.0 \\
-1.0 & \quad 0.0 \\
-0.5 & \quad 0.0 \\
0.0 & \quad 0.0 \\
0.5 & \quad 0.0 \\
1.0 & \quad 0.0 \\
1.5 & \quad 0.0 \\
\end{align*}

D

\[ \Delta PAC \] (ml/mmHg)

\begin{align*}
\text{Controls} & \quad \text{HFpEF} \\
-0.5 & \quad 0.0 \\
0.0 & \quad 0.0 \\
0.5 & \quad 0.0 \\
1.0 & \quad 0.0 \\
\end{align*}

\[ p = 0.002 \]

\[ p = 0.008 \]
Figure 2

A

Cardiac Output (L/min)

PA mean (mmHg)

Base Low High

p=0.0007

B

Cardiac Output (L/min)

TPG (mmHg)

Base Low High

p=0.008

● Control  ■ HFpEF
**Figure 3**

**A**

- dP/dt_max/IP (s⁻¹)
- Control
- HFpEF
- Group p=0.0004
- Group *drug p=0.5
- Baseline, Low dose Dobutamine, High dose Dobutamine

**B**

- Tricuspid s' (cm/s)
- Control
- HFpEF
- Group p=0.0008
- Group *drug p=0.5
- Baseline, Low dose Dobutamine, High dose Dobutamine

**C**

- dP/dt_max/IP (s⁻¹)
- Controls p<0.0001
- Baseline, Dobutamine

**D**

- Tricuspid s' (cm/s)
- HFpEF p=0.6
- Baseline, Dobutamine
- Mean PA pressure (mmHg)
Enhanced Pulmonary Vasodilator Reserve and Abnormal Right Ventricular: Pulmonary Artery Coupling In Heart Failure With Preserved Ejection Fraction

Mads J. Andersen, Seok-Jae Hwang, Garvan C. Kane, Vojtech Melenovsky, Thomas P. Olson, Kenneth Fetterly and Barry A. Borlaug

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