Pulmonary vascular (PV) distensibility, defined as the percent increase in pulmonary vessel diameter per mmHg increase in pressure, permits the pulmonary vessels to increase in size to accommodate increased blood flow. We hypothesized that PV distensibility is abnormally low in patients with heart failure (HF) and serves as an important determinant of right ventricular performance and exercise capacity.

Methods and Results—Patients with HF with preserved ejection fraction (n=48), HF with reduced ejection fraction (n=55), pulmonary arterial hypertension without left heart failure (n=18), and control subjects (n=30) underwent cardiopulmonary exercise testing with invasive hemodynamic monitoring and first-pass radionuclide ventriculography. PV distensibility was derived from 1257 matched measurements (mean±SD, 8.3±2.8 per subject) of pulmonary arterial pressure, pulmonary arterial wedge pressure and cardiac output. PV distensibility was lowest in the pulmonary arterial hypertension group (0.40±0.24% per mmHg) and intermediate in the HF with preserved ejection fraction and HF with reduced ejection fraction groups (0.92±0.39 and 0.84±0.33% per mmHg, respectively) compared to the control group (1.39±0.32% per mmHg, P<0.0001 for all three). PV distensibility was associated with change in right ventricular ejection fraction (RVEF; r=0.39, P<0.0001) with exercise and was an independent predictor of peak VO₂. PV distensibility also predicted cardiovascular mortality independent of peak VO₂ in HF patients (n=103; Cox hazard ratio, 0.30; 95% confidence interval, 0.10–0.93; P=0.036). In a subset of patients with HF with reduced ejection fraction (n=26), 12 weeks of treatment with the pulmonary vasodilator sildenafil or placebo led to a 24.6% increase in PV distensibility (P=0.015) in the sildenafil group only.

Conclusions—PV distensibility is reduced in patients with HF and pulmonary arterial hypertension and is closely related to RV systolic function during exercise, maximal exercise capacity, and survival. Furthermore, PV distensibility is modifiable with selective pulmonary vasodilator therapy and may represent an important target for therapy in selected HF patients with pulmonary hypertension.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00309790.

Key Words: heart failure ■ mortality ■ physiology ■ pulmonary heart disease ■ pulmonary hypertension
closed vessels to accommodate increased blood flow, resulting in an attenuated increase in mPAP and a curvilinear relationship with CO.2,13,14 Thus, mPAP is also dependent on a fourth variable termed pulmonary vascular (PV) distensibility. The human pulmonary circulation has been shown to lose distensibility under chronic hypoxic conditions, which contributes to PH and increased workload for the right ventricle.3,4,15

Although PVR only represents the static component of or average right ventricular afterload, other parameters such as PV distensibility, capacitance, and impedance also take into account the dynamic, pulsatile components of afterload and, therefore, are considered to be potentially better measures of PV function than PVR.16 PV distensibility is a mechanical property of the pulmonary vessels defined as the relative change in pulmonary arterial diameter or area for a given change in pressure, whereas PV capacitance is the change in volume associated with a change in pressure (calculated as the ratio of stroke volume/pulmonary pulse pressure, SV/PP), and impedance is the ratio of the PAP waveform to the flow during the entire cardiac cycle.16,17 PV distensibility has been estimated with different imaging modalities, including magnetic resonance imaging.18–20 echocardiography,21 gated CT,22,23 and intravascular ultrasound.24 However, these techniques are limited in that they all estimate distensibility based on fractional change in diameter or area of the main pulmonary artery (PA) or large PA segments and do not account for the distensibility of the entire PV circuit including the medium-sized pulmonary arterioles where much of the abnormal vascular remodeling occurs in PH.25 Furthermore, these techniques only assess PV distensibility or capacitance at rest and not over a range of different flows, which limits the sensitivity of detecting abnormal PV function. To address these limitations, Linehan et al13 developed a distensible vessel model for the pulmonary circulation that predicts pressure–flow relationships taking into account the PV distensibility and incorporating the entire PV circuit. This model can be used to determine average PV distensibility with pressure information (mPAP and PAWP) at different COs. The model depends on the distensibility (α), in units of percent diameter change per unit mmHg increase in pressure. The equation relating distensibility with mPAP at constant hematocrit is:

$$\text{mPAP} = \frac{[(1+\alpha P_w)^3 + 5\alpha R_p Q]^{1/5} - 1}{\alpha}$$

where mPAP is in units of mmHg; Pw, is the pulmonary artery wedge pressure (PAWP, mm Hg); R, the total pulmonary resistance at rest calculated as mPAP/Q (in Wood units); and Q, the pulmonary blood flow (L/min).13 This distensibility model has been validated in both perfused canine lungs13 and in normal humans.14 A typical PV distensibility value consists of a 1.5% to 2% increase in pulmonary vessel diameter per mm Hg increase in pressure.14,26

PV distensibility in HF has not been previously defined. Because of the close relationship between PAP and outcomes in HF, it is important to understand relative contributions of the determinants of PAP in HF. The recent recognition that longitudinal PAP monitoring can lead to improved HF outcomes further highlights the importance of characterizing the distensibility component of PAP in HF.27 In this study, we define the clinical correlates and physiological and prognostic significance of PV distensibility in patients with either HF or with pulmonary arterial hypertension (PAH) in the absence of left heart disease compared with control patients.

Methods

Patient Selection

Consecutive patients at the Massachusetts General Hospital who underwent cardiopulmonary exercise testing (CPET) with pulmonary arterial catheter measurements for the evaluation of dyspnea were prospectively enrolled after obtaining informed consent. Patients had chronic New York Heart Association class II–IV symptoms and were classified based on left ventricular ejection fraction (LVEF), resting and exercise PAWP, and resting mPAP. Patients were classified by the following criteria: (1) HFrEF: chronic LVEF <0.45 on guideline-based pharmacotherapy; (2) HFpEF: LVEF ≥0.50 and supine PAWP >15 mmHg at rest; and (3) PAH: supine mPAP ≥25 mmHg at rest (or 21–24 mm Hg with a PVR >3 WU), supine PAWP ≤15 mm Hg at rest and PAWP ≤25 mmHg with exercise. Patients who did not fall into any of the above groups were included as part of the control population. Controls were required to have a normal LVEF, a supine mPAP <25 mm Hg at rest, a supine PAWP ≤15 mm Hg at rest, exercise PAWP <25 mm Hg, and a normal exercise capacity as reflected by a peak VO2 >80% of that predicted on the basis of age, sex, and height.28 Although it is possible that these patients have subclinical cardiopulmonary disease, this should bias to the null when comparing HF and PAH groups to controls, so that the findings might be even stronger if a truly normal population were used. Patients were excluded from the study if they had any of the following: (1) known active flow limiting coronary artery disease, (2) severe valvular heart disease, (3) intracardiac shunting, (4) incomplete pulmonary arterial catheter pressure measurements, (5) submaximal exercise as evidenced by peak respiratory exchange ratio <1.0, or (6) the presence of a pulmonary mechanical limitation to exercise as defined by V̇/f(forced expiratory volume in 1 s [FEV1]×35)>0.7 at the ventilatory threshold.29–31 Twenty-six patients in the HFrEF group participated in a previously reported 12-week, double-blind, randomized controlled trial of treatment with either placebo (n=12) or sildenafil (n=14).31 This clinical trial was registered (ClinicalTrials.gov #NCT00309790). The study was approved by the institutional review board, and informed consent was obtained.

Protocol for CPET

Patients were instructed to take their prescribed medications as usual before exercise testing. Subjects underwent placement of a pulmonary arterial catheter via the internal jugular vein and a systemic arterial catheter via the radial artery. Measurements of resting right atrial pressure, PAP, and PAWP were obtained in the supine and upright positions. Resting first-pass radionuclide biventriculography was performed immediately before initiation of exercise (OnePass GVI Medical Devices, Twinsburg, OH) to obtain resting LVEF and RVEF, as previously described.31 Subjects then performed maximum incremental exercise with upright cycle ergometry after an initial 3-minute period of unloaded exercise (MedGraphics, St. Paul, MN). An individualized ramp protocol was used based on the subject’s estimated fitness level (5–25 Watts/min), to target at least 5 minutes of incremental exercise. Simultaneous hemodynamic measurements were obtained with exercise (Witt Biomedical Inc, Melbourne, FL), as previously described.11–13 Right atrial pressure, PAP, PAWP, and systemic arterial pressures were measured in the upright position, at end-expiration, while patients were seated on the cycle, both at rest and at 1-minute intervals during exercise. Fick CO34,35 was determined at 1-minute intervals throughout exercise by measuring oxygen uptake (VO2) and simultaneous radial arterial and mixed venous O2 saturation to calculate the C(a–v)/O2 during a linear ramp protocol. PVR was calculated as: [(mPAP–PAWP)/CO]. Peak VO2 was defined as the highest O2 uptake, averaged over 30 s, during the last minute of symptom-limited exercise, as previously described.31 First-pass radionuclide biventriculography was repeated at peak exercise.
### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (30)</th>
<th>HfPEF (48)</th>
<th>HfREF (55)</th>
<th>PAH (18)</th>
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<tr>
<td>Age, y*</td>
<td>58±15</td>
<td>63±12</td>
<td>59±12</td>
<td>61±13</td>
</tr>
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<td>Male sex, n (%)†</td>
<td>19 (63)</td>
<td>19 (40)</td>
<td>45 (82)§</td>
<td>9 (50)</td>
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<tr>
<td>White race, n (%)†</td>
<td>28 (93)</td>
<td>46 (96)</td>
<td>49 (89)</td>
<td>17 (94)</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>27.6±4.0</td>
<td>33.7±7.9∥</td>
<td>27.9±5.8$</td>
<td>27.7±4.9</td>
</tr>
</tbody>
</table>

**Comorbidities, n (%)**

| Hypertension†   | 11 (37)       | 29 (60)    | 34 (62)¶   | 9 (50)   |
| Diabetes mellitus†| 1 (3)       | 12 (25)∥  | 11 (20)    | 2 (11)   |
| Hyperlipidemia†  | 7 (23)        | 25 (52)∥  | 32 (58)¶   | 9 (50)   |

**Pharmacotherapy, n (%)**

| Diuretics†      | 2 (7)         | 24 (50)∥  | 48 (87)§¶  | 4 (22)   |
| ACE inhibitor or ARB†| 8 (27)   | 14 (29)    | 45 (82)§¶  | 3 (17)   |
| β-adrenergic blocker†| 5 (17)   | 24 (50)∥  | 52 (95)§¶  | 6 (33)   |
| Aldosterone antagonist†| 0         | 4 (8)      | 29 (53)§¶  | 0        |

**Resting LVEF, %***

<table>
<thead>
<tr>
<th>Controls (30)</th>
<th>HfPEF (48)</th>
<th>HfREF (55)</th>
<th>PAH (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67±5</td>
<td>62±8∥</td>
<td>30±6%¶</td>
<td>63±7</td>
</tr>
<tr>
<td>53±7</td>
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<td>38±11%¶</td>
<td>46±7#</td>
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<td>14±4</td>
<td>30±5∥</td>
<td>35±13%¶</td>
<td>28±5#</td>
</tr>
<tr>
<td>8±3</td>
<td>20±3∥</td>
<td>22±3%¶</td>
<td>10±3</td>
</tr>
</tbody>
</table>

**CI, L/min per m²* | 13.3±1.3 | 13.2±1.5 | 13.0±2.0 | 14.0±1.8 |

**Upright rest hemodynamics**

| mPAP, mm Hg* | 14.5±1.9 | 20.9±5.5∥ | 27.2±9%¶ | 25.6±5.1# |
| PAWP, mm Hg* | 5.1±1.4  | 9.4±4.7∥  | 15.4±7.6%¶ | 7.4±2.8# |
| CI, L/min per m²* | 2.8±0.5 | 2.5±0.7∥ | 1.8±0.5%¶ | 2.6±0.7 |
| SV/PP, mL/mm Hg† | 6.0±2.8 | 3.0±1.2∥ | 1.8±0.93%¶ | 2.7±0.78# |

**Peak upright exercise**

| Maximum watts achieved* | 153±52 | 82±33∥ | 76±36%¶ | 83±39# |
| Minutes exercised*      | 8.5±1.6 | 7.1±2.2∥ | 5.5±1.7%¶ | 7.3±2.1# |
| Peak exercise RER*      | 1.16±0.08 | 1.15±0.11 | 1.16±0.15 | 1.09±0.10 |
| Peak exercise lactate, mmol/L* | 7.5±1.5 | 5.3±2.5∥ | 4.8±2.0%¶ | 5.4±2.5# |
| Peak VO₂, mL/kg per min* | 25.3±7.5 | 13.9±3.3∥ | 12.4±3.8%¶ | 15.4±4.0# |
| Exercise LVEF (%)*      | 71±6     | 64±8∥     | 33±8%¶   | 65±8#    |
| Exercise RVEF (%)*      | 56±7     | 49±8∥     | 38±10%¶  | 45±7#    |
| mPAP, mm Hg*            | 30.3±3.6 | 43.4±9.8∥ | 49.7±10.2%¶ | 50±11.7# |
| PAWP, mm Hg*            | 16.8±4.3 | 28.3±9.0∥ | 29.8±8.9%¶ | 15.3±4.8 |
| CI, L/min per m²*       | 7.5±1.6  | 5.1±1.3∥  | 3.7±1.2%¶ | 5.5±1.2# |

Mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CI, cardiac index; HfPEF, heart failure with preserved ejection fraction; HfREF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PP, pulmonary pulse pressure; RVEF, right ventricular ejection fraction; RER, respiratory exchange ratio; and SV, stroke volume.

*ANOVA with Bonferroni-adjusted post hoc test.
†Fisher exact test.
‡Kruskal–Wallis with Dunn post hoc pairwise test.
§P<0.05 between HfPEF & HfREF.
∥P<0.05 between HfPEF and controls.
¶P<0.05 between HfREF and controls.
#P<0.05 between PAH and controls.
Pulmonary vascular distensibility was determined using pulmonary arterial pressure, pulmonary arterial wedge pressure, and Fick cardiac output measurements at rest and during exercise, as previously described. In control (n=30), heart failure was a preserved ejection fraction (HFpEF; n=48), HF with reduced ejection fraction (HFrEF, n=55), and PAH (n=18) patients. Means±SD is depicted in the graph.

Figure 1. Characterization of pulmonary vascular distensibility in heart failure and pulmonary arterial hypertension (PAH) patients. Pulmonary vascular distensibility was determined using pulmonary arterial pressure, pulmonary arterial wedge pressure, and Fick cardiac output measurements at rest and during exercise, as previously described. In control (n=30), heart failure was a preserved ejection fraction (HFpEF; n=48), HF with reduced ejection fraction (HFrEF, n=55), and PAH (n=18) patients. Means±SD is depicted in the graph. HFpEF (/) and HFrEF (/) patients exhibit a reduced pulmonary vascular distensibility compared with control patients (P<0.001 for both comparisons). Patients with PAH have a reduced distensibility compared with all 3 other groups (P<0.001 for all 3 comparisons).

Arterial O$_2$ content (CaO$_2$) is the amount of O$_2$ carried by blood to the periphery and was calculated as (hemoglobin [g/dL]×1.39×SaO$_2$)+(0.003×PaO$_2$). Similarly mixed venous O$_2$ content (CvO$_2$) represents the O$_2$ content of blood returning from the peripheral tissues to the right heart, which was calculated as (hemoglobin×1.39×SvO$_2$)+(0.003×PvO$_2$).

PV Distensibility Model

As described in the introduction, a previously developed distensible vessel model (Equation 2) was used to calculate the PV pressure–flow relationship. In our population, we measured mPAP, PAWP, and Q both at rest and at multiple points during exercise. Using an iterative approach with least-squares methodology, as reported previously, we determined the $\alpha$-value that best predicted observed mPAP values.

Subject Follow-Up

Vital status of each patient was confirmed by medical record review as of May 2015. Deaths were considered as cardiovascular deaths if they were primarily attributed to heart failure, arrhythmia, or ischemic events.

Statistical Methods

STATA 11 (Statacorp, College Station, TX) was used for statistical analysis. Measurements are presented as mean±SD, unless otherwise indicated. The Shapiro–Wilk test was used to assess the normality of variables. Group baseline characteristics were compared using either 1-way ANOVA with Bonferroni-adjusted post hoc pairwise comparisons, Kruskal–Wallis test with Dunn post hoc pairwise comparisons, or Fisher exact test, as appropriate. Receiver operator characteristic analysis was performed to determine the ability of PV distensibility to distinguish HF and PAH populations from the control population. To identify predictors of PV distensibility, we used either Pearson correlation or Spearman rank correlation, based on whether the data were normally distributed. Multivariable stepwise linear regression using backward elimination was performed to determine independent predictors of peak VO$_2$ in patients with HF. Age and sex were required in the multivariable model. In addition to PV distensibility, a comprehensive set of covariates measured at rest were selected for an initial univariable analysis, including mPAP, PAWP, hemoglobin, CavO$_2$, cardiac index, LVEF, RVEF, systolic blood pressure, diastolic blood pressure, systemic pulse pressure, and heart rate. Some variables were eliminated because they did not serve as a univariable predictor of peak VO$_2$ (P>0.10). These variables included resting systolic blood pressure, systemic pulse pressure, and heart rate. The remaining variables were included for multivariable analysis using a backward elimination regression model until all remaining predictor variables had a P<0.05. Kaplan–Meier survival with Log-Rank testing and Cox regression analysis was used to determine if PV distensibility and other variables predict cardiovascular mortality in patients with HF. A paired t test was used to determine if placebo or sildenafil treatment altered PV distensibility, and an independent t test was used to compare differences between the placebo- and sildenafil-treated arms. A P value of <0.05 was considered significant unless otherwise noted.

This study was approved by the Partners Healthcare Institutional Review Board. The authors had full access to the data and take responsibility for its integrity and for the article as written.

Results

Population Characteristics

Baseline characteristics for the HFpEF (n=48), HFrEF (n=55), PAH (n=18), and control subjects (n=30) are reported in Table 1. Patients with HFrEF exhibited a greater male predominance relative to patients with HFpEF, whereas patients with HFrEF had a greater BMI relative to the other groups of patients, consistent with the known demographic characteristics of HFpEF and HFrEF populations. A greater percentage of patients with HFrEF were treated with diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, $\beta$-blockers, and mineralocorticoid receptor antagonists than patients with HFpEF. Patients with PAH consisted of either World Health Organization Group I PH patients (n=10, 7 with idiopathic PAH and 3 with scleroderma) or World Health Organization Group III PH patients (n=8). Only 1 of 18 patients with PAH was previously diagnosed with PAH and on PAH-specific pharmacotherapy (sildenafil and bosentan) at the time of CPET. Hemoglobin levels were similar in all 4 groups.

All subjects in the 4 groups exceeded their ventilatory threshold with peak respiratory exchange ratio >1.0, indicating a maximal effort during exercise (Table 1). Peak VO$_2$ was reduced in HFpEF (13.9±3.3 mL/kg per minute), HFrEF (12.4±3.8 mL/kg per minute), and PAH (15.4±4.0 mL/kg per minute) compared with controls (25.3±7.5 mL/kg per minute, P<0.001 for all 3 comparisons). Similarly, maximal watts achieved at peak exercise were reduced in all 3 groups of patients compared with control subjects.

PV Distensibility in Heart Failure and PAH Patients

Among the entire cohort studied (n=151), PV distensibility was determined from a total of 1257 matched invasive hemodynamic measurements obtained during exercise (where each measurement consists of mPAP, PAWP, and CO). This represents an average of 8.3±2.8 measurements per patient (with a minimum number of measurements of 4 per subject). Previous studies have established that normal humans have a PV distensibility of 1.5% to 2% per mmHg. Our control population
Malhotra et al  Pulmonary Vascular Distensibility in HF

(consisting of patients being evaluated for dyspnea who were older than previously reported normals) exhibited a similar, albeit lower, distensibility of 1.39±0.32% per mm Hg (with range of 0.98–2.12). The PV distensibility of patients with HFpEF (0.92±0.39% per mm Hg) and HFrEF (0.84±0.33% per mm Hg) were significantly lower than the control subjects (P<0.001 for both comparisons, Figure 1). Interestingly, patients with HFpEF and HFrEF exhibited similar PV distensibility. Patients with PAH had a PV distensibility of 0.40±0.24% per mm Hg, which was reduced when compared with both control subjects and patients with either HFpEF or HFrEF (P<0.001 for all 3 comparisons). Distensibility in the PAH cohort restricted to patients with resting mPAP ≥25 mm Hg (n=13) was 0.36±0.27% per mm Hg.

To determine the diagnostic performance of PV distensibility for distinguishing patients with HF from controls, we performed receiver operator characteristic area under the curve (AUC±SE) analysis. The AUC for distinguishing patients with HF (HFpEF and HFrEF, n=103) from control patients (n=30) was 0.86±0.03. The AUC for distinguishing patients with PAH (n=18) from control patients (n=30) was 1.0.

We assessed the effect of PV distensibility on changes in PAP and TPG during exercise. The pulmonary pressure–flow relationship for a patient with representative HFpEF is depicted in Figure 2, along with an idealized pressure–flow relationship based on a normal distensibility of 2.0% per mm Hg, while maintaining PAWP and CO fixed (14). At peak exercise, the actual mPAP and TPG are 44 and 20 mm Hg, respectively, whereas the idealized values of mPAP and TPG are 31 and 7 mm Hg, respectively.

Clinical and Hemodynamic Variables Associated With PV Distensibility

PV distensibility decreased with age (r=0.18, P=0.031), but it was not associated with BMI (Table 2) or with sex in each of the 4 groups of our study. Because PV distensibility reflects a mechanical property of the pulmonary vessels to vasodilate in response to increased blood flow during exercise, we hypothesized that distensibility would exhibit its strongest associations with hemodynamic variables during exercise rather than at rest. Indeed, PV distensibility was associated with VO2, cardiac index, RVEF, and pulse pressure at peak exercise but not with these same parameters at rest (Table 2). The correlation coefficients for PV distensibility with peak VO2, peak cardiac index, peak RVEF, and peak pulse pressure were 0.40, 0.35, 0.36, and 0.42 (P<0.0001 for all). These results suggest that...
Table 2. Predictors of Pulmonary Vascular Distensibility in All Patients (n=151)

<table>
<thead>
<tr>
<th>Parameter</th>
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</tr>
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<td>Age, y</td>
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<tr>
<td>Cl, L/min per m²</td>
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<tr>
<td>RVEF</td>
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<tr>
<td>LVEF</td>
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<td>0.06</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
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Parameters at peak exercise

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>VO₂, mL/kg per min</td>
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<tr>
<td>O₂ pulse, mL/beat</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Lactate, mmol/L</td>
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<td>0.006</td>
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</tbody>
</table>

Unadjusted P values are presented. 16 variables were tested and thus, when adjusting for multiple comparisons the threshold for significance is P<0.003. BMI indicates body mass index; Cl, cardiac index; LVEF, left ventricular ejection fraction; and RVEF, right ventricular ejection fraction. Pearson correlation used except where * indicated for Spearman correlation.

PV distensibility is a potent indicator of cardiovascular functional reserve capacity during exercise. Changes in RV-PV hemodynamic measurements with exercise are important predictors of outcome in cardiopulmonary diseases. We, therefore, determined the association of PV distensibility with changes in RV-PV functional measurements during exercise. We observed that PV distensibility is associated with both percent change in PVR (Spearman ρ=−0.50, P<0.0001) and absolute change in RVEF (P=0.38, P<0.0001) from rest to peak exercise (Figure 3). These associations were also present when assessing individual groups of our cohort (Figure 3). In patients with HFpEF and HFrEF, PV distensibility was strongly associated with change in RVEF and PVR with exercise (ρ=0.38 and −0.34, respectively; P<0.001 for both), whereas resting PAWP was not (ρ=0.04, P=0.72 and ρ=0.13, P=0.20, respectively). These findings highlight a potentially important role for the distensibility of the pulmonary vasculature, rather than the hemodynamic severity of left-sided heart disease, in determining RV reserve capacity in patients with both HFpEF and HFrEF.

Relationship Between PV Distensibility, Exercise Capacity, and Survival

Peak VO₂ is a potent predictor of prognosis in patients with HF. We performed multivariable, stepwise linear regression with a backward elimination technique to identify if PV distensibility predicted peak VO₂ independently of demographic, functional, and resting hemodynamic parameters (Table 3). PV distensibility was an independent predictor of peak VO₂ (normalized β coefficient 0.25, P<0.001) in a model that also included age, sex, hemoglobin, resting cardiac index, resting PAWP, and resting mPAP. These results indicate an important role for PV distensibility in predicting exercise capacity.

We next sought to determine if PV distensibility predicts cardiovascular mortality in patients with HF. Of the 103 patients with HF (HFpEF and HFrEF), median follow-up time was 4.0 years, and there was a total of 33 cardiovascular deaths. Fourteen patients underwent cardiac transplant or placement of a left ventricular assist device. Distensibility was analyzed both as a continuous variable and when dichotomized (<0.70% and ≥0.70% per mm Hg), based on the range of normal distensibility values in our control population and that previously published. In both univariable (Cox hazard ratio [HR], 0.33 per 1% per mm Hg increase; P=0.039) and age- and sex-adjusted multivariable Cox regression analysis (Cox HR, 0.33; P=0.034), PV distensibility predicted cardiovascular survival. Similarly, PV distensibility predicted transplant-free and LVAD-free cardiovascular survival (Cox HR, 0.43 per 1% per mm Hg increase; P=0.049). Compared with those with a lower distensibility, HF patients with a distensibility ≥0.70% per mm Hg had a 55% reduced hazard of cardiovascular mortality (Figure 4; Cox HR, 0.45; P=0.028). Importantly, PV distensibility was a strong predictor of cardiovascular survival independent of peak VO₂ (Table 4; Cox HR, 0.30 per 1% per mm Hg increase; P=0.036). Dichotomized distensibility also predicted survival independent of peak VO₂ (Cox HR, 0.49 for PV distensibility ≥0.70% per mm Hg; P=0.05). Therefore, PV distensibility was an independent predictor of cardiovascular survival for patients with HF in our cohort.

We sought to determine the ability of PV distensibility to predict outcomes after adjusting for PV capacitance (calculated as the ratio of resting SV/PP), determined under resting conditions. SV/PP was lower in the HFpEF, HFrEF, and PAH populations compared with the control group (Table 1). There was a trend toward correlation between SV/PP and α in patients with HF (ρ=0.22, P=0.07). We found that SV/PP
In this study, we used the distensible vessel model to characterize PV distensibility for the first time in patients with HF. Average PV distensibility was significantly lower in HFpEF and HFrEF (34% and 40% lower, respectively) compared with control subjects of similar age. On average, abnormal distensibility in patients with HF, compared with controls, led to a >70% increased level of peak exercise transpulmonary gradients. PV distensibility was closely associated with change in RVEF in response to exercise as well as peak VO2 and other indices of cardiac function during exercise. PV distensibility was also an independent predictor of cardiovascular survival in patients with HF. Moreover, treatment of HFrEF patients with a selective pulmonary vasodilator increased PV distensibility by ≈25%, and this improvement was associated with improved RV function with exercise.

The presence of PH in HFpEF and HFrEF predicts functional capacity and long-term outcomes. The strategy of regularly measuring PAP and adjusting therapies accordingly in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial reduced HF-related hospitalizations by 37% and led to recent Food and Drug Administration approval of an implantable device to continuously monitor PAP in HF. Moreover, PAP responses to volume challenge and exercise have recently been recognized to provide additive diagnostic and prognostic value in evaluating patients with HF. Therefore, understanding the determinants of PAP during exercise or other states of increased blood flow in patients with HF is critically important. Although the standard ohmic-Starling model of the pulmonary circulation describes PAP as dependent on 3 variables (PVR, CO, and PAWP), this model does not account for the curvilinear relationship observed between PAP and flow at higher levels of CO due to the distensible nature and increased recruitment of the pulmonary vessels. Here, we describe the impact that this fourth variable, PV distensibility, has on PAP responses during exercise. In our study, abnormal PV distensibility in patients with HF accounted for >30% of the rise in PAP with exercise. PV distensibility was also a sensitive and specific measure to distinguish either HF (AUC, 0.86) or PAH (AUC, 1.0) from controls based on receiver operator characteristic analysis. Future studies will need to explore the ability of noninvasive exercise measures of PV distensibility, such as with exercise echocardiography, to act as surrogates of PV distensibility derived from invasive measurements, in an effort to broaden its clinical use.

**Modulation of PV Distensibility by Chronic Phosphodiesterase Type 5 Inhibitor Therapy**

We assessed whether abnormal PV distensibility in HF could be improved with 12 weeks of treatment with the pulmonary vasodilator sildenafil. Of 26 patients with HFrEF, 14 patients were treated with sildenafil (25–75 mg orally three times per day) and 12 patients were treated with placebo in a double-blinded fashion. These patients underwent comprehensive CPET before and after treatment. Both the sildenafil-treated group (0.99±0.34% per mm Hg) and the placebo-treated group (0.88±0.29% per mm Hg) had similar baseline PV distensibilities (P=0.38). The average post-treatment distensibility in the sildenafil-treated group was 1.17±0.31% per mm Hg and that in the placebo-treated group was 0.88±0.34% per mm Hg. The sildenafil-treated group demonstrated a 24.6% increase in distensibility (Figure 5, P=0.015), whereas the placebo-treated arm had no significant change (P=0.05 compared with the sildenafil group). In the sildenafil-treated group, the change in distensibility with treatment was associated with an improved augmentation in RVEF with exercise (Spearman ρ=0.80, P=0.01). Taken together, these findings indicate that the selective pulmonary vasodilator sildenafil is able to improve PV distensibility in HFrEF and that improvements in PV distensibility are associated with improvements in RV function.

**Discussion**

In this study, we used the distensible vessel model to characterize PV distensibility for the first time in patients with HF. Average PV distensibility was significantly lower in HFpEF and HFrEF (34% and 40% lower, respectively) compared with control subjects of similar age. On average, abnormal distensibility in patients with HF, compared with controls, led to a

**Table 3. Multivariable Model for Predicting Peak VO2 in All Patients With HF (n=103)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normalized β-Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.16</td>
<td>0.008</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Resting cardiac index, L/min per m²</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting PAP, mm Hg</td>
<td>−0.22</td>
<td>0.003</td>
</tr>
<tr>
<td>Resting mPAP, mm Hg</td>
<td>−0.19</td>
<td>0.018</td>
</tr>
<tr>
<td>Distensibility, % per mm Hg</td>
<td>0.25</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hb indicates hemoglobin; HF, heart failure; mPAP, mean pulmonary arterial pressure; and PAP, pulmonary arterial wedge pressure.

Figure 4. Pulmonary vascular (PV) distensibility predicts cardiovascular mortality in patients with heart failure (HF). Kaplan–Meier survival curves of patients with HF (n=103, both HF with preserved ejection fraction [HFpEF] and HF with reduced ejection fraction [HFrEF]) are depicted, dichotomized by PV distensibility value. Compared with those with lower PV distensibility, HF patients with a distensibility ≥0.70% per mm Hg exhibit reduced cardiovascular mortality (P=0.03).
The average PV distensibility in control subjects was 1.39±0.32% per mm
Hg. This value is lower than that previously observed in a normal healthy
population (2.0±0.2% per mm Hg)\(^4\); however, our control subjects were older
than that of the previous study and were undergoing evaluation for
dyspnea on exertion. We did not observe a difference in
distensibility between genders, in contrast to previous stud-
ies that found young females have greater distensibility than
males, potentially owing to the older age and postmenopausal
status of females in our study.\(^4\) PV distensibility is known
to decrease with age (Table 2), as shown in our study and
others.\(^14,43\) It is also possible that the lower PV distensibility
observed in our control population with dyspnea compared
with the normal population in the previous study may reflect
signs of early PV disease.\(^4,40\) A recent study by Lau et al\(^40\)
found PV distensibility to be abnormally low in patients with
PV disease (eg, confirmed by the presence of thromboem-
bo
disease of the pulmonary circulation or an abnormal
lung biopsy) but with mPAP <25 mm Hg at rest, indicating
that PV distensibility may be a useful index for early disease
detection.\(^40\) The study by Lau et al\(^40\) and our study highlight
the ability of exercise-based hemodynamic measurements to add incremental information to resting hemodynamic
measurements to carefully define PV function in patients
with suspected PH. The striking differences in distensibility
between patients with mild PAH in our study versus controls
indicates that pathological reduction in distensibility may
represent a relatively early finding in PAH in light of the fact
that the resting mPAP was only 28 mm Hg in our population
with PAH.

Although PV distensibility did not correlate with resting
cardiac indices, it was a strong predictor of cardiac indices at
peak exercise (Table 2). Peak VO\(_2\) serves as the gold standard
measure of exercise capacity and also a significant prognostic
indicator in patients with HF.\(^39\) Our finding that PV disten-
sibility predicts peak VO\(_2\) independent of other demographic
and CPET variables indicates the important contribution PV
distensibility has as a marker of maximal exercise capacity
in HF and PAH patients. Similar to our findings, in a study of
24 healthy subjects, those with the greatest PV distensibility
exhibited the highest peak VO\(_2\), further supporting its role in
determining exercise capacity.\(^26\)

Increased stiffness of the pulmonary artery measured by
combining right heart catheterization and cardiac magnetic
resonance measurements is associated with worse RV per-
formance, dilation, and hypertrophy with chronic PH.\(^44\) We
observed a strong correlation between impaired PV dis-
sten
sibility, measured with exercise hemodynamic parameters,
and abnormal RVEF augmentation during exercise, measured
using the independent technique of ventriculography (Figure
3). The association between low PV distensibility and reduced
RVEF augmentation with exercise was observed not only in
HF and PAH patients but also in control patients. These results
suggest that PV distensibility is an important determinant of
RV function that complements imaging-based assessments of
RV function. We found that PV distensibility predicted cardio-
vascular survival independently of peak VO\(_2\) in patients with
HF. RVEF at rest and with exercise are important predictors
of outcomes and exercise capacity in patients with HF.\(^6,46\) PV
distensibility is likely a critical property of the pulmonary ves-
sels that helps to limit the afterload that the right ventricle con-
fronts. Therefore, therapeutically targeting RV function and
PV distensibility may improve outcomes in HF.

Multiple mechanisms may contribute to abnormal PV
function and distensibility in HF including both functional
and structural alterations.\(^1\) Studies in both experimental mod-
els and patients have suggested a maladaptive imbalance
between pulmonary vasodilators and vasconstrictors in HF.
Dysregulated arginine metabolism and nitric oxide signal-
ing may contribute to the pathophysiology of PH in HF.\(^46\)
Decreased production of prostacyclin and increased pulmo-

dary vascular distensibility.


**Figure 5.** Twelve weeks of treatment with sildenafil improves pulmonary vascular dis-
tensibility in patients with heart failure with reduced ejection fraction. Sildenafil treat-
ment was associated with a 24.6% increase in distensibility (n=14, P=0.015), whereas
no appreciable change in distensibility was observed in the placebo-treated group
(n=12). Treatment with a selective pulmonary vasodilator can, therefore, improve pulmo-
nary vascular distensibility.
including intimal fibrosis and medial vessel hypertrophy.\(^4^9\) In our study, patients with HFrEF treated with 12 weeks of phosphodiesterase type 5 (PDE5) inhibitor therapy demonstrated a 24.6% increase in PV distensibility (Figure 5). Improvement in PV distensibility with short-term PDE5 inhibitor therapy suggests that a strong contributor to reduced distensibility in HF occurs via abnormal vasodilator (nitric oxide dependent) signaling. More studies are needed to determine the long-term benefits of treatments directed at the pulmonary vasculature, such as PDE5 therapy, in patients with HF and reduced PV distensibility.

**Limitations**

This study was derived from a single-center cohort of patients referred to a tertiary care center, which may not be representative of the general HF or PAH populations. Multiple hypotheses were tested about the association of PV distensibility with exercise physiology parameters (Table 2), increasing the chance of a type I error. However, exact \(P\) values are included and the Bonferroni-adjusted \(P\) value of significance is provided, to limit the type I error. Our control population was limited in size (n=30) because of the low frequency with which subjects without significant cardiopulmonary disease undergo CPET with invasive hemodynamic monitoring. Moreover, our control population cannot be considered as normal individuals given that they were undergoing CPET for the evaluation of dyspnea. The use of clinically referred patients who had normal hemodynamic measurements as controls may underestimate the differences between patients with HF and true controls.

The distensible vessel model used in our study makes the assumption of a constant hematocrit.\(^1^3,^1^4\) However, hemoconcentration does occur to some degree during exercise. Because we perform individualized exercise protocols designed to achieve similar exercise durations, based on our previous experience with CPET, the degree of hemoconcentration is similar across patients. However, we do not have serial hemoglobin measurements to report in this study. Furthermore, it is important to note that the recruitment of pulmonary vessels during exercise can be differentially affected in HF versus control patients by variability in body position, direct control of dyspnea. The use of clinically referred patients who had normal hemodynamic measurements as controls may underestimate the differences between patients with HF and true controls.

The distensible vessel model does not differentiate between the distension that occurs of perfused pulmonary vessels during exercise and the recruitment of previously closed vessels.\(^1^4\)

**Clinical Implications**

Despite advances in HF therapy, morbidity and mortality remain high, particularly when PH is present. Chronic elevations in PAP exert negative hemodynamic effects on RV function, which range from RV hypertrophy to RV failure. The pulmonary vessels distend to protect the afterload-sensitive RV from excessive increases in pressure. Historically, elevated left-sided hydrostatic pressure has been thought to primarily govern the increased load on the RV at rest and in response to physiological stressors in patients with HF. Our findings that PV distensibility was closely related to change in RVEF during exercise, whereas PAWP was not, suggest that intrinsic properties of the pulmonary circulation play an important role in determining RV reserve capacity in HF. Further study is warranted to determine if PV distensibility can be used to inform candidate selection for heart transplantation or left ventricular assist device therapy, as clinical outcomes after these interventions are dependent on RV-PV function.

The RV-PV unit is increasingly recognized as a major determinant of exercise capacity and outcomes in patients with HF. However, the pulmonary circulation has not been effectively targeted for therapeutic interventions. Multicenter clinical trials, to date, that have evaluated the efficacy of pulmonary vasodilator therapy (ie, prostacyclins, PDE5 inhibitors, and endothelin antagonists) in patients with heart failure have not shown clinical benefit.\(^1^5,^1^6\) However, these studies of pulmonary vasodilators in HF have enrolled patients independently of their burden of precapillary PH or other indices that specifically reflect PV function. Integrating measurement of PV distensibility into the characterization of PH in HF may help to appropriately identify patients for targeted interventions directed at the pulmonary circulation.

**Conclusions**

Abnormally low PV distensibility in HF is a previously unrecognized important determinant of PAP elevation that is related to impaired cardiac performance during exercise and poor outcomes. Treatment with a PDE5 inhibitor seems to improve PV distensibility. These findings support the pursuit of further studies aimed at understanding and therapeutically targeting right ventricular and PV dysfunction in heart failure.

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**Disclosures**

Dr Malhotra serves as a consultant for Mallinckrodt Pharmaceuticals, formerly Ikaria, Inc. The other authors report no conflicts.

**References**


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Tibetans and from rare diseases of oxygen sensing.

Duhamel A, Remy J. Pulmonary hypertension: ECG-gated

1083. doi:10.1378/chest.103.4.1080.

Chest. 1993;103:1080–


Pasiertski TJ, Starling RC, Binkley PF, Pearson AC. Echocardiographic


1883. doi:10.1378/chest.103.4.1080.


**CLINICAL PERSPECTIVE**

Morbidity and mortality in heart failure (HF) remain high, particularly when pulmonary hypertension and right ventricular dysfunction are present. Pulmonary vascular (PV) distensibility, defined as the percent increase in pulmonary vessel diameter per mm Hg increase in pressure, permits the pulmonary arteries to increase in size to accommodate increased blood flow, thereby reducing the afterload of the right ventricle. This study combined exercise testing and invasive hemodynamic measurements to derive PV distensibility values and to determine that PV distensibility is reduced in HF patients with either reduced ejection fraction or preserved ejection fraction. We show that impaired PV distensibility in HF is associated with worse right ventricular function during exercise and reduced peak VO₂, and also predicts poor cardiovascular survival. In a randomized, placebo-controlled study of 26 HF patients with reduced ejection fraction, we demonstrated that treatment with sildenafil can improve PV distensibility. This study highlights an important role for pulmonary vascular responses to exercise in determining prognosis for patients with HF and potentially identifies a subset of patients with HF who would benefit from therapy selectively targeting impaired pulmonary vascular function.
Pulmonary Vascular Distensibility Predicts Pulmonary Hypertension Severity, Exercise Capacity, and Survival in Heart Failure
Rajeev Malhotra, Bishnu P. Dhakal, Aaron S. Eisman, Paul P. Pappagianopoulos, Ashley Dress, Rory B. Weiner, Aaron L. Baggish, Marc J. Semigran and Gregory D. Lewis

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