Pulmonary Vascular Response Patterns During Exercise in Left Ventricular Systolic Dysfunction Predict Exercise Capacity and Outcomes

Gregory D. Lewis, MD; Ryan M. Murphy, BA; Ravi V. Shah, MD; Paul P. Pappagianopoulos, MEd; Rajeev Malhotra, MD; Kenneth D. Bloch, MD; David M. Systrom, MD; Marc J. Semigran, MD

Background—Elevated resting pulmonary arterial pressure (PAP) in patients with left ventricular systolic dysfunction (LVSD) purports a poor prognosis. However, PAP response patterns to exercise in LVSD and their relationship to functional capacity and outcomes have not been characterized.

Methods and Results—Sixty consecutive patients with LVSD (age 60±12 years, left ventricular ejection fraction 0.31±0.07, mean±SD) and 19 controls underwent maximum incremental cardiopulmonary exercise testing with simultaneous hemodynamic monitoring. During low-level exercise (30 W), LVSD subjects, compared with controls, had greater augmentation in mean PAPs (15±1 versus 5±1 mm Hg), transpulmonary gradients (5±1 versus 1±1 mm Hg), and effective pulmonary artery elastance (0.05±0.02 versus −0.03±0.01 mm Hg/mL, P<0.0001 for all). A linear increment in PAP relative to work (0.28±0.12 mm Hg/W) was observed in 65% of LVSD patients, which exceeded that observed in controls (0.07±0.02 mm Hg/W, P<0.0001). Exercise capacity and survival was worse in patients with a PAP/watt slope above the median than in patients with a lower slope. In the remaining 35% of LVSD patients, exercise induced a steep initial increment in PAP (0.41±0.16 mm Hg/W) followed by a plateau. The plateau pattern, compared with a linear pattern, was associated with reduced peak VO₂ (10.6±2.6 versus 13.1±4.0 mL·kg⁻¹·min⁻¹, P=0.005), lower right ventricular stroke work index augmentation with exercise (5.7±3.8 versus 9.7±5.0 g/m², P=0.002), and increased mortality (hazard ratio 8.1, 95% CI 2.7 to 23.8, P<0.001).

Conclusions—A steep increment in PAP during exercise and failure to augment PAP throughout exercise are associated with decreased exercise capacity and survival in patients with LVSD, and may therefore represent therapeutic targets.


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Key Words: hypertension, pulmonary ▪ exercise ▪ heart failure

Resting pulmonary hypertension (PH), defined as mean pulmonary arterial pressure (PAP) >25 mm Hg, is present in the majority of patients with left ventricular systolic dysfunction (LVSD) and is associated with right ventricular dysfunction and poor prognosis.1-3 Despite the recognized importance of resting PH and right ventricular dysfunction in LVSD, little is known about how PAP changes during exercise in subjects with LVSD relate to exercise capacity and outcomes.

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The measurement of blood pressure in the systemic circulation during exercise provides incremental prognostic information to resting measurements of systemic blood pressure in healthy individuals4,5 and in patients with LVSD.6 Exercise-induced systemic hypertension also predicts future onset of resting hypertension.7,8 In healthy individuals, passive distention of a compliant pulmonary circulation and active flow-mediated vasodilation allows the pulmonary vasculature to accommodate increased cardiac output during exercise with only a modest increment in PAP9 and a fall in pulmonary vascular resistance.10,11 Flow-mediated vasodilation is impaired in the systemic vasculature of LVSD patients and contributes to reduced left ventricle (LV) performance and to inappropriate distribution of systemic blood flow away from vital organs.12-14 Less is known about how PAP responds to increased blood flow in LVSD. Characterization of pulmonary vascular responses to exercise in LVSD and the compensatory responses of the right ventricular-pulmonary vas-
cicular circuit may aid in earlier diagnosis of functionally significant PH complicating LVSD.

Invasive hemodynamic monitoring during incremental exercise testing is technically difficult to perform and not routinely incorporated into clinical exercise testing. Previous studies of LVSD, in which PAP was measured during exercise, have reported only peak-exercise measurements that have not been controlled for the major confounding factor of heterogeneity in workload achieved at peak exercise.15,16

In this study, we performed continuous hemodynamic monitoring throughout exercise in patients with LVSD and in age-matched controls to determine patterns of the pulmonary and systemic vascular responses to exercise. We sought to determine the relationship between PAP and workload (in watts) on the cycle ergometer during exercise, as well as the relative contributions of the LV filling pressure and the transpulmonary gradient to changes in the PAP during exercise. Based on the propensity of patients with left-sided heart disease (ie, LVSD and mitral stenosis) to develop PH out of proportion to left-sided filling pressures at rest,1–3 we hypothesized that exercise would elicit disproportionate precapillary pulmonary vasconstriction in LVSD subjects relative to matched controls. We further hypothesized that a steep increment in the PAP-workload relationship during exercise would be associated with reduced exercise capacity and worse outcomes. Serial exercise testing in a subset of the subjects that we studied permitted assessment of the reproducibility of the relationship between PAP and work rate during exercise. Finally, in a subset of the subjects we assessed whether or not the selective pulmonary arterial vasodilator, sildenafil, decreased the increment in PAP relative to work during exercise.

Methods

Study Design

Consecutive patients, who underwent cardiopulmonary exercise testing (CPET) with invasive hemodynamic monitoring at Massachusetts General Hospital and had a left ventricular ejection fraction of <0.40 and chronic New York Heart Association class II–IV symptoms despite standard therapy, were included in the study population. Patients were excluded if complete pulmonary arterial catheter pressure measurements were not available or if they had documented severe primary valvular heart disease, intracardiac shunting, or a pulmonary mechanical limitation to exercise, as defined by VE/(FEV1 × 35)>0.717–18 at the anaerobic threshold. Fifty percent of the LVSD subjects (n=30) participated in a previously reported 12-week randomized, double-blind clinical trial of treatment with sildenafil (n=15) or placebo (n=15).19 The control group consisted of individuals referred for CPET to evaluate dyspnea on exertion during the same period of time as the LVSD group. Controls were required to have normal left ventricular function and normal exercise capacity as reflected by a peak VO2>80% of that predicted on the basis of age, sex, and height. Subjects meeting these inclusion criteria who were similar in age to the LVSD subjects composed the control cohort.

Cardiopulmonary Exercise Testing

Subjects were instructed to take their prescribed medications according to their usual schedule before exercise testing. All patients underwent placement of a pulmonary arterial catheter via the internal jugular vein and placement of a systemic arterial catheter via the radial artery. Subjects then underwent maximum incremental upright cycle ergometry cardiopulmonary exercise testing (CPET, 5 to 15 W/min continuous ramp after an initial 2-minute period of unloaded exercise, MedGraphics, St. Paul, MN) with simultaneous hemodynamic monitoring (Witt Biomedical Inc, Melbourne, FL) as previously described.19,20 In subjects enrolled in the clinical trial of sildenafil treatment, CPET was performed at baseline and after 12 weeks of treatment with sildenafil or placebo. Right atrial pressure (RAP), phasic and mean PAP, pulmonary capillary wedge pressure (PCWP), and mean radial arterial pressure (MAP) were measured in the upright position, at end-expiration, while patients were seated on the cycle, at rest and at 1-minute intervals during exercise. Fick cardiac output (CO) was also determined at 1-minute intervals throughout exercise by simultaneously measuring radial and pulmonary arterial oxygen content to determine the difference in arterial venous oxygen content [C(a–v)O2] and oxygen uptake (VO2). Peak VO2 was defined as the highest oxygen uptake, averaged over 30 seconds, during the last minute of symptom-limited exercise, as previously described.21 Right ventricular stroke work index was calculated by taking the product of Fick stroke volume indexed to BSA multiplied by the difference between mean PAP and RAP. Effective arterial elastance (Ea) of the pulmonary vasculature was calculated according to Windkessel parameters (WK), assuming that the diastolic pressure decay time constant (τ) is significantly longer than the duration of diastole (tD), resulting in: 

$$Ea(WK) = \frac{\text{mean PAP} - \text{PCWP}}{\text{stroke volume}}$$

We assessed the relationship between PAP augmentation during exercise and work (in watts) performed on the cycle ergometer. The initial stage of the cycle ergometry exercise test protocol used in this study consisted of turning the cycle pedals against no resistance (ie, freewheel or unloaded exercise at 0 W). Unloaded exercise results in energy expenditure and augmentation in oxygen uptake and CO, with resultant increase in PAP. To account for this internal work performed by individuals, an “internal work correction factor” was applied for the unloaded exercise period in each subject based on the known relationship between the increment in VO2 and the increment in watts during incremental exercise (10 mL/W).18,23 For example, if a subject’s VO2 increased from 300 mL/min at rest to 500 mL/min during the unloaded exercise period, we added 20 W [500 mL/min − 300 mL/min]/(10 mL/W)] to their external work achieved during subsequent incremental exercise (see Figure 1). The derived watt increment during unloaded exercise was related to body weight (R=0.55, P<0.001), as one would expect based on the increased work required to move heavier legs. Criteria for determining whether hemodynamic responses to exercise were linear relative to workload throughout exercise included: R2>0.9 for the relationship between the hemodynamic variable and watts of work, and an increment in pressure during each minute of exercise without slope attenuation during the final 3 minutes of exercise. A plateau response was defined as a nonlinear increment in pressure (R2<0.9) coupled with a <10% increment in pressure over the course of the final 3 minutes of measurements.

Statistical Methods

The STATA 10.0 software package (StataCorp LP, College Station, TX) was used for statistical analysis. The Wilk-Shapiro test was used to assess the normality of distribution of the data. All continuous, normally distributed measurements are presented as the mean ±SEM, unless otherwise noted. Group baseline characteristics were compared using either the Student t test, Pearson χ2, or Fisher exact test, as appropriate. For clinical characteristics, comparisons between groups for continuous variables were performed using unpaired 2-sample t tests or the Wilcoxon signed rank test. Survival was determined starting from the day of the initial cardiopulmonary exercise test, until November 30, 2009. The Kaplan–Meier method was used to estimate the proportion of patients surviving at a given time point, and survival curves were compared using the log rank test. Multivariate Cox proportional hazard ratio modeling was used to determine clinical and exercise hemodynamic predictors of survival. Univariate and multivariate linear regression was used to determine relationships between clinical and exercise variables and
exercise capacity. Pearson or Spearman correlation coefficients were calculated, as appropriate, based on whether or not the data were either normally or not normally distributed, respectively. Relationships between hemodynamic parameters and exercise capacity were assessed by linear regression analysis. One-way ANOVA was used to assess the effect of treatment on differences in the change in continuous variables measured at baseline and at 12 weeks of study drug treatment. Reproducibility of PAP measurements was assessed in a subset of patients by determining the intraclass correlation coefficient for repeated measurements at 0 and 12 weeks. The sildenafil trial was registered (ClinicalTrials.gov number NCT00309790), informed consent was obtained from participating subjects and the study was approved by the institutional review board. In addition, the study of subjects outside of participating subjects and the study was approved by the institutional review board.

Results

Baseline clinical characteristics for the LVSD (n=60) and control (n=19) subjects are reported in Table 1. Underlying medical conditions in the control subjects included hypertension (n=8), hyperlipidemia (n=5), non–flow-limiting coronary artery disease (n=1), previous deep vein thrombosis without chronic thromboembolic PH (n=2), fibromyalgia (n=2), and mild asthma (n=1). All patients surpassed their ventilatory anaerobic thresholds and lactate thresholds during exercise. Results of hemodynamic measurements and ventilatory gas exchange at rest and at peak exercise are displayed in Table 2. As expected, patients with LVSD had lower resting MAPs and stroke volumes and higher RAP, mean PAP, and PCWP than did controls. In addition, patients with LVSD had higher transpulmonary gradients (TPGs) at rest than did controls.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heart Failure (60)</th>
<th>Control (19)</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Age, years</td>
<td>60±12</td>
<td>60±12</td>
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<td>Male sex, %</td>
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<td>79</td>
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<td>Primary cause of heart failure, %</td>
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<tr>
<td>Nonischemic cardiomyopathy</td>
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<td>NA</td>
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<tr>
<td>NYHA class, %</td>
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<td></td>
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</tr>
<tr>
<td>II</td>
<td>53</td>
<td></td>
<td></td>
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<tr>
<td>III</td>
<td>41</td>
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<tr>
<td>IV</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>Body mass index</td>
<td>28.0±5.7</td>
<td>27.5±3.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Heart failure pharmacotherapy</td>
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<td></td>
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<tr>
<td>Diuretic</td>
<td>85</td>
<td>5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>80</td>
<td>37</td>
<td>0.002</td>
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<tr>
<td>β-Adrenergic receptor antagonist</td>
<td>90</td>
<td>21</td>
<td>&lt;0.0001</td>
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<td>Spironolactone–aldosterone antagonist</td>
<td>50</td>
<td>0</td>
<td>&lt;0.0001</td>
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<tr>
<td>Digoxin</td>
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<td>0</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cardiac resynchronization therapy, %</td>
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<td>0.0002</td>
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<td>RVF</td>
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<td>0.56±0.01</td>
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</tr>
<tr>
<td>LV EF</td>
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<td>0.68±0.01</td>
<td>&lt;0.0001</td>
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<tr>
<td>Workload achieved during exercise,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>watts</td>
<td>75±5</td>
<td>142±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak VO₂, mL · kg⁻¹ · min⁻¹</td>
<td>12.2±0.5</td>
<td>23.8±1.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Baseline clinical characteristics for the LVSD and control subjects. NYHA indicates New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; RVF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction.

All of these hemodynamic differences persisted at peak exercise (Table 2).

Pulmonary Vascular Responses to Standardized Submaximal and Peak Exercise

To isolate the influence of physical activity on pulmonary hemodynamics, we examined changes in hemodynamic variables elicited by exercise. We first assessed PAP changes induced by low level, standardized exercise exposure indicative of activities of daily living (30 W on the cycle ergometer). PAP increased to a markedly greater extent in patients with LVSD at 30 W than in controls (15±1 versus 5±1 mm Hg, respectively, P<0.0001; Figure 2), whereas the change in systemic MAP did not differ between LVSD and control subjects (8±2 versus 5±2 mm Hg, P=0.20; Figure 2B). The exaggerated increase in PAP in LVSD patients induced by exercise was because of both a 2.4-fold greater increase in left ventricular filling pressure (9±1 versus 4±1 mm Hg, P<0.0001) and a 4.5-fold greater increase in TPG (5±1 versus 1±1 mm Hg, P<0.0001).

At peak exercise, LVSD patients also demonstrated greater PAP increases than did controls (23±1 versus 13±1 mm Hg, P<0.0001; Figure 2, left), despite achieving significantly lower peak work rates (75±5 versus 141±11 W, respectively, P<0.0001). Differences in PAP augmentation be-
between groups at peak exercise were attributable to a greater TPG augmentation in LVSD patients (10 ± 1 versus 3 ± 1 mm Hg, \( P < 0.001 \); Figure 2, right), whereas PCWP increases at peak exercise were similar between groups (13 ± 1 versus 10 ± 1 mm Hg, \( P = 0.11 \), Figure 2, right panel). However, at a matched workload corresponding to the peak workload achieved by LVSD patients, controls did have less PCWP augmentation than LVSD patients (ie, 6 ± 1 mm Hg in controls at 75 W versus 13 ± 1 mm Hg in LVSD subjects at 75 W, \( P < 0.001 \)).

Of note, resting PAP was not directly related to the increment in PAP relative to work (ie, PAP slope, \( R = -0.1 \)), or to the change in PAP between rest and 30W (\( R = -0.14 \)), indicating that resting hemodynamic values do not adequately predict pulmonary vasodilatory reserve during physical activity. The change in PAP between rest and peak exercise was inversely related to resting PAP (\( R = -0.35 \)), likely because low resting PAP permitted subjects to exercise for longer with a resultant greater excursion in PAP. There was no relationship between duration of HF (mean, 65 ± 7 months;
range, 5 to 184 months) and exercise-induced increment in PAP ($r = -0.01$, $P=0.93$).

Reproducibility of Exercise-Induced PAP Augmentation
Potential sources of variability in hemodynamic measurements at rest and with exercise include timing of diuretic exposure, diurnal patterns, and recent dietary intake. We sought to determine the reproducibility of PAP augmentation patterns and absolute PAP achieved during exercise in LVSD. In 15 subjects enrolled in the placebo arm of a 12-week randomized trial, repeated CPETs at baseline and 12 weeks demonstrated highly reproducible PAP augmentation patterns at both 30 W (intraclass $r=0.81$) and peak exercise (intraclass $r=0.92$, both $P<0.0005$).

Coefficients of reproducibility from Bland-Altman analysis to examine the reproducibility of rest and exercise hemodynamics are summarized in online-only Data Supplement Table 1.

Patterns of Pulmonary Vascular Responses to Exercise
Continuous hemodynamic monitoring permitted precise assessment of PAP response patterns throughout exercise. Control subjects demonstrated a linear, modest increase in PAP per watt throughout exercise (0.07±0.02 mm Hg/W, Figure 1A). The majority of patients with LVSD ($n=39$, 65%) also demonstrated a linear increase in PAP throughout exercise, with a greater slope (0.28±0.12 mm Hg/W) than that observed in controls ($P<0.0001$; Figure 1B). A minority of LVSD patients demonstrated a distinct PAP pattern in which there was an initial steep linear increment in PAP per watt (PAP increase = 0.41±0.16 mm Hg/W) followed by a plateau in which PAP did not increase despite increasing workload ($n=21$, Figure 1C). This pattern indicates an inability of the right ventricle to further augment pressure despite increasing workload.

Assessment of PAP Augmentation Relative to Cardiac Output
To specifically analyze PAP response patterns to increased blood flow into the pulmonary vasculature, we assessed the relationship between PAP and CO augmentation during exercise. LVSD subjects had a PAP/CO slope of 7.0 mm Hg/L during exercise compared to a slope of 0.12 mm Hg/W in controls (Figure 3; $P<0.0001$). The PAP/CO slope in controls was highly consistent with that previously reported (1.45 mm Hg/L) in healthy middle-aged subjects undergoing upright exercise. PAP/CO correlated with PAP/W among subjects with linear PAP/W during exercise ($R=0.75$, $P<0.0001$). Patients with PAP/W >0.25 (median value) had PAP/CO of 9.1±3.2 mm Hg·L$^{-1}$·min$^{-1}$ compared with patients with PAP/W <0.25 who had PAP/CO of 5.0±1.5 mm Hg·L$^{-1}$·min$^{-1}$. In the control group, subjects with below median PAP/W (which was 0.07 mm Hg/W) the PAP/CO slope was 1.08 mm Hg/L and in the above median group, the PAP/W ratio was 1.64 mm Hg/L ($P=0.015$). The similarity between PAP/W and PAP/CO relationships is not surprising based on the expected linear increment in $V_{O2}$ and CO relative to the work rate during exercise.

Pulmonary Effective Arterial Elastance
We examined the pulmonary effective Ea according to Windkessel parameters in LVSD patients compared with controls at rest and with exercise. At rest, LVSD subjects had higher Ea values than controls (0.27±0.03 mm Hg/mL versus 0.14±0.02 mm Hg/mL, respectively, $P<0.0001$). At submaximal exercise (30 W) Ea increased to 0.33±0.03 in LVSD patients ($P=0.04$) and decreased to 0.11±0.01 in controls ($P=0.03$), indicating discordant effects of exercise in the 2 groups. Peak exercise Ea values remained unchanged compared with 30 W values.
Relationship Between Exercise Hemodynamic Measurements, Exercise Capacity, and Outcomes

Whether PAP response patterns to exercise are related to exercise capacity is unknown. Among LVSD subjects with a linear PAP increase with exercise, PAP slope was inversely related to peak VO₂ (R = -0.6, P < 0.001), suggesting that impaired pulmonary vasodilation in response to exercise is associated with reduced exercise capacity. Patients with LVSD and a PAP plateau pattern, compared with a linear pattern, had lower exercise capacity (peak VO₂ = 10.6 ± 2.6 versus 13.1 ± 4.0 mL·kg⁻¹·min⁻¹, respectively, P = 0.005) and lesser augmentation of the right ventricular stroke work index with exercise (5.7 ± 3.8 versus 9.7 ± 5.0 g/m², respectively; P = 0.002). Univariate predictors of lower peak VO₂ included age, female sex, resting RAP, PAP, PCWP, PAP slope, and a PAP plateau pattern (Supplemental Table 2A). In a multivariate regression analysis age, female sex, resting RAP, PAP, PCWP, PAP slope, and a PAP plateau pattern emerged as independent predictors of lower peak VO₂ (online-only Data Supplement Table 2B).

To further investigate whether a steeper increment in PAP with work was associated with worse outcomes in patients with LVSD, we stratified patients by the median slope of the PAP versus work (P < 0.001). Kaplan–Meier analysis shows that the PAP increment pattern during exercise was linear, middle line, as well as by plateau pattern (bottom line).

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Modulation of Exercise PAP and Pulmonary Ea by Chronic Phosphodiesterase Type 5 (PDE5) Inhibitor Therapy

We assessed whether PAP augmentation patterns during exercise were modifiable by 12-week administration of a pulmonary vasodilator, sildenafil. In patients with a linear PAP versus work pattern (n = 7) 12 weeks of sildenafil treatment reduced the PAP versus work slope from 0.22 ± 0.03 to 0.18 ± 0.04 mm Hg/W (P = 0.04). Consistent with this finding, in the entire cohort of subjects treated with sildenafil, PAP augmentation at peak exercise was unchanged versus presildenafil despite significantly greater exercise capacity (peak VO₂ + 18%). At a standardized 30 W exercise-induced mean PAP augmentation was 12 ± 1 mm Hg presildenafil versus 10 ± 1 mm Hg postsildenafil, P = 0.13 (Figure 5). Assessment of the components of PAP augmentation at 30 W indicated that sildenafil did not affect the increment in PCWP (7 ± 2 mm Hg before sildenafil treatment versus 8 ± 1 mm Hg following sildenafil treatment), but did lower transpulmonary-gradient augmentation (5 ± 2 mm Hg to 2 ± 1 mm Hg, P = 0.029; Figure 5) relative to presildenafil measurements. Furthermore, sildenafil treatment was associated with a reduction in pulmonary Ea at 30 W from 0.35 ± 0.05 mm Hg/mL to 0.28 ± 0.05 mm Hg/mL (P = 0.01). Taken together, these findings indicate that the selective pulmonary vasodilator sildenafil is able to blunt the exaggerated precapillary contribution to PAP augmentation during exercise and improve pulmonary effective arterial elastance.

Discussion

By characterizing the pulmonary vascular response patterns during exercise, we found that LVSD is associated with disproportionate increases in both PCWP and TPGs throughout exercise. The PAP increment during exercise was linear in the majority of LVSD patients, highly reproducible, and inversely related to exercise capacity and survival. Failure to augment PAP throughout exercise, resulting in a PAP plateau pattern, was associated with failure to augment right ventricular stroke work index and portended a particularly poor prognosis.

Characterization of PAP responses to exercise in LVSD patients relative to healthy individuals has been limited by the invasive nature of measurements, technical challenges associated with hemodynamic measurements during exercise, and limited normative data on exercise PAP values. The strengths of our study include the use of age-matched LVSD and control cohorts, uniform use of upright exercise repre-
sentative of most physical activity in humans, and analysis of multiple hemodynamic measurements throughout exercise in each individual that permitted comparisons of PAP responses at matched workloads.

In response to standardized exercise exposure of 30 W, the 2.4-fold greater increase in PCWP (9 ± 1 versus 4 ± 1 mm Hg, \( P < 0.0001 \)) that we observed was expected in the setting of LV dysfunction. However, the observed 4.5-fold greater increase in TPG at 30 W in LVSD subjects, compared with controls, indicates that the precapillary pulmonary arterial response to exercise is also abnormal. The exercise increment in TPG per liter of CO augmentation during exercise in LVSD compared with controls is similarly striking. Furthermore, we found that exercise increased pulmonary vascular reserve in LVSD patients and decreased it in controls.

Several potential explanations exist for exaggerated TPG and abnormal Ea responses to exercise in LVSD patients. First, in controls, upright exercise recruits the pulmonary vasculature through opening of blood vessels in West Zones 1 and 2 that are underperfused at rest. In contrast in LVSD patients at rest, pulmonary arterial and venous pressures exceed alveolar pressures throughout the lungs (ie, West Zone 3 only). As a result, LVSD patients, unlike healthy subjects, are less able to recruit additional pulmonary vasculature during exercise. Reduced pulmonary vascular recruitment may therefore contribute to the lack of pulmonary vascular reserve in LVSD.

PAP responses to exercise in LVSD may also reflect an inability to reduce pulmonary vascular tone in response to increased blood flow. An imbalance between endothelium-derived vasoactive and vasoconstrictive mediators, including nitric oxide, endothelin, and natriuretic peptides has been postulated to contribute to secondary PH in LVSD. Several studies have shown that nitric oxide production by endothelial nitric oxide synthase is markedly diminished in LVSD. Because endothelial nitric oxide synthase is normally unregulated by shear stress and increased pulmonary blood flow, exercise may accentuate the relative deficiency in vasodilator substances present at rest in LVSD and may, thereby, contribute to the exaggerated increases in TPG with exercise that we observed in LVSD patients. Further investigation is required to correlate exercise hemodynamics with circulating vasoactive molecules in LVSD patients.

Hypoxic pulmonary vasoconstriction is a third putative mechanism to explain greater exercise-induced TPG increase in LVSD patients. Despite increases in PCWP, systemic arterial hypoxemia was not observed in our LVSD patients during exercise (Table 2), consistent with previous studies. These findings suggest that alveolar oxygen tension, the major determinant of hypoxic pulmonary vasoconstriction, remained normal in our patients.

A fourth explanation for greater exercise-induced TPG increase in LVSD is related to structural changes in large and small pulmonary arteries that occur in the setting of chronic left heart disease. This pulmonary vascular structural remodeling has been described in the setting of increased PCWP related to mitral stenosis.

Finally, dynamic mitral regurgitation has been implicated in contributing to exercise PAP, estimated noninvasively, in LVSD. If dynamic mitral regurgitation were the major cause of the exaggerated exercise-induced augmentation of TPG, it would be expected that the degree of TPG augmentation would correlate with the increase in PCWP induced by exercise. However, the magnitude of TPG augmentation did not correlate with rest or exercise PCWP, suggesting that dynamic mitral regurgitation alone does not account for heightened exercise-induced increase in PAP in LVSD. It is possible that chronic mitral regurgitation, however, may contribute to pulmonary vascular remodeling and reduced ability to accommodate increased blood flow during exercise. Additional studies combining quantification of mitral regurgitation and hemodynamic measurements during exercise may help to further clarify this relationship.

**Implications of High Reproducibility and Linearity of PAP Responses to Exercise in LVSD**

The reproducibility of PAP responses to exercise, as evidenced by the high intraclass correlation coefficients for repeated studies, coupled with the linearity of PAP augmentation in the majority of patients, has potential implications for applying noninvasive imaging modalities, such as echocardiography, to estimate PAPs during exercise. For example, echocardiography can be used to estimate both mean PAP and to assess right ventricle (RV) structure and function. In LVSD patients with linear PAP response patterns, acquisition of noninvasive PAP measurements during the first several minutes of a submaximum exercise test would suffice to assess exaggerated PAP responses to exercise. The observed reproducibility of the increase in PAP with exercise in our study is analogous to more reproducible systemic blood pressure measurements observed within individuals during submaximal exercise compared with at rest. Tracking patients over longer periods of time will permit determination of whether exaggerated PAP responses to exercise predict future development of overt resting WHO Group 2 PH, which purports a poor prognosis.1,2

**Relationship Between PAP Responses to Exercise and Exercise Performance and Outcomes**

Several studies have indicated that resting RV dysfunction and elevated PAP in LVSD are more closely related to exercise intolerance than left ventricular ejection fraction in LVSD. However, these studies did not incorporate invasive hemodynamic monitoring during exercise to measure PAP and the relative contributions of TPG and PCWP to PAP in patients with LVSD and matched controls. The RV is a thin-walled conduit that has been shown to be exquisitely sensitive to changes in afterload in animal models subjected to vasoconstrictor challenge. Hence, our findings that the average exercise-induced increase in PAP in patients with LVSD was >80%, compared with a 16% average increase in systemic MAP, indicates the marked relative burden imposed on the RV compared with the LV during exercise. LVSD subjects demonstrated greater exercise-induced increases in PAP than did controls but similar increases in systemic MAP.
augmentation, which further supports the notion that the compensatory capacity of the right ventricular-pulmonary vascular circuit may be more important than that of the LV-systemic vascular circuit in mediating exercise tolerance. By directly linking the exercise-induced increase in PAP to reduced exercise capacity, our findings also provide mechanistic support for previous studies that implicate the pulmonary vasculature in modulating functional capacity in LVSD.

To date, exercise has not been widely used to detect dynamic right ventricular and pulmonary vascular dysfunction. Here, we demonstrate that exaggerated PAP augmentation (ie, PAP/W slope >0.25 mm Hg), increased effective PA elastance (versus decreased effective PA elastance in controls), and inability to augment PAP throughout exercise are potential markers of abnormal pulmonary vascular tone and right ventricular dysfunction. The inverse relationship between the presence of these findings and exercise capacity, as well as survival, in our study, suggests a potentially important role of the right ventricular-pulmonary vascular circuit compensatory capacity in mediating LVSD disease progression. In light of current LVSD treatment guidelines, which focus on countering neurohormonal activation to treat LV dysfunction and on resynchronizing the left ventricle, our findings identify the right ventricular-pulmonary vascular circuit as a potentially important target for new therapeutic approaches to LVSD.

**PDE5 Inhibition Reduces the Exercise-Induced Increase in TPG and Pulmonary Ea**

PDE5 inhibition has been shown to reduce pulmonary vascular tone in HF at rest. We observed that 12 weeks of treatment with the PDE5 inhibitor, sildenafil, was associated with reductions in exercise PAP/W, TPG, and pulmonary Ea. Based on the observed relationship between pulmonary vascular response patterns to exercise and exercise tolerance in this study, it is likely that the consistent improvement in peak VO₂ observed in HF trials with sildenafil is mediated by improvements in the ability of the RV-pulmonary vascular circuit to accommodate the exercise-induced increase in CO.

**Limitations**

There are several limitations to our study. First, the patient population consisted of a combination of a trial-based LVSD cohort and patients referred to a tertiary care center for further evaluation of exercise intolerance. The patients that we studied may not be representative of community-based LVSD patients or controls. However, our LVSD subjects demonstrated resting hemodynamics, medication exposures, and peak VO₂ that were highly consistent with community-based New York Heart Association class III LVSD populations. Our control population was limited in size (N=19) based on the infrequency with which subjects without significant cardiopulmonary disease undergo CPET with invasive hemodynamic monitoring. However, our controls demonstrated normal exercise capacity, based on their peak VO₂ > 80% predicted, and their average PAP increased from 15±3 to 28±7 mm Hg. This increment in PAP with exercise in control subjects is consistent with findings from a recent meta-analysis of PAP responses to exercise in healthy individuals in which subjects over the age of 50 demonstrated an increase in PAP from 14.7±4.0 to 29.4±8.4 mm Hg with upright exercise. Our sample size of LVSD subjects was also relatively small, which may have limited our ability to detect weaker associations between some hemodynamic variables, such as PCWP, and exercise capacity. We did not adjust for multiple exploratory analyses investigating the relationship between individual hemodynamic variables and exercise capacity. However, our findings related to abnormalities in pulmonary hemodynamic measurements were highly concordant from a physiological perspective. Finally, the lack of simultaneous echocardiographic assessment of mitral regurgitation at rest and during exercise precluded definitive assessment of the contribution of mitral regurgitation to the increase in exercise PAP.

**Conclusion**

This study establishes that patients with LVSD have exaggerated pulmonary arterial and pulmonary venous blood pressure augmentation in response to exercise. A steep increment in PAP in response to exercise is associated with reduced exercise capacity and reduced survival in patients with LVSD. Failure to augment PAP throughout exercise was indicative of dynamic RV dysfunction and portended a particularly poor prognosis. PDE5 inhibition attenuated abnormal pulmonary vascular responses to exercise in HF and represents a potentially promising strategy to treat LVSD. A greater knowledge of compensatory responses of the right ventricular-pulmonary vascular circuit during exercise in patients with LVSD may improve our understanding of its functional role in determining exercise capacity, aid in earlier diagnosis of PH complicating LVSD, and further inform targeted therapeutic interventions.

**Acknowledgments**

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**Disclosures**

None.

**References**


44. Lepore JJ, Maroo A, Biggelato LM, Dec GW, Zapol WM, Bloch KD, Semigran MJ. Hemodynamic effects of sildenafil in patients with con-
gestive heart failure and pulmonary hypertension: combined adminis-
of sildenafil in the therapeutic management of heart failure. *J Am Coll
47. Behling A, Rohde LE, Colombo FC, Goldraich LA, Stein R, Clausell N.
Effects of 5’-phosphodiesterase four-week long inhibition with sildenafil
in patients with chronic heart failure: a double-blind, placebo-controlled
48. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5-inhibition with
sildenafil improves left ventricular diastolic function, cardiac geometry
and clinical status in patients with stable systolic heart failure: results of
a 1-year prospective, randomized, placebo-controlled study. *Circ Heart
Fail*. 2011;4:8–17.
49. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E,
Kocovic DZ, Packer M, Clavell AL, Hayes DL, Eliestad M, Trupp RJ,
Underwood J, Pickering F, Traux C, McAtee P, Messenger J. Cardiac
1845–1853.
50. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B,
cardiac resynchronization and implantable cardioversion defibrillation in
advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA.*

**CLINICAL PERSPECTIVE**

Elevated resting pulmonary arterial pressure (PAP) in patients with left ventricular systolic dysfunction (LVSD) is common
and purports a poor prognosis. In this study, we performed continuous invasive hemodynamic monitoring during maximum
incremental cardiopulmonary exercise testing to characterize PAP response patterns to exercise in LVSD. The PAP
increment during exercise was linear in the majority of LVSD patients, highly reproducible, and inversely related to
exercise capacity and survival. PAP increased 81% in LVSD patients, compared with a 16% average increase in systemic
mean arterial pressure, indicative of the marked relative burden imposed on the right ventricle compared with the left
ventricle during exercise. Compared with controls, LVSD subjects had a 4.5-fold greater increase in transpulmonary
gradient and a 2.4-fold greater increase in left ventricular filling pressure during exercise. In 35% of LVSD subjects, there
was a steep rise in PAP during exercise followed by a distinct PAP plateau pattern that reflected the inability of the right
ventricle to increase stroke work and portended a particularly poor prognosis. Inhibition of phosphodiesterase type 5
attenuated the pulmonary vascular responses to exercise in LVSD and represents a potentially promising strategy to treat
LVSD. A greater knowledge of compensatory responses of the right ventricular-pulmonary vascular circuit during exercise
in patients with LVSD may improve our understanding of its functional role in determining exercise capacity, aid in earlier
diagnosis of pulmonary hypertension complicating LVSD, and further inform targeted therapeutic interventions.
Pulmonary Vascular Response Patterns During Exercise in Left Ventricular Systolic Dysfunction Predict Exercise Capacity and Outcomes

Gregory D. Lewis, Ryan M. Murphy, Ravi V. Shah, Paul P. Pappagianopoulos, Rajeev Malhotra, Kenneth D. Bloch, David M. Systrom and Marc J. Semigran

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL RESULTS

Supplemental Table 1. Reproducibility of hemodynamic variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>BL (rest)</th>
<th>12wk (rest)</th>
<th>Average (rest)</th>
<th>BL (ex)</th>
<th>12 wk (ex)</th>
<th>Average (ex)</th>
<th>Coeff Rep (rest)</th>
<th>Coeff Rep (ex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (L/min/m²)</td>
<td>1.81</td>
<td>1.72</td>
<td>-0.08</td>
<td>3.02</td>
<td>3.00</td>
<td>-0.01</td>
<td>0.75</td>
<td>0.82</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>50</td>
<td>48</td>
<td>-3</td>
<td>59</td>
<td>59</td>
<td>0</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>70</td>
<td>73</td>
<td>3</td>
<td>104</td>
<td>105</td>
<td>1</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>8</td>
<td>7</td>
<td>-1</td>
<td>16</td>
<td>15</td>
<td>0</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>32</td>
<td>31</td>
<td>0</td>
<td>49</td>
<td>51</td>
<td>1</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>19</td>
<td>19</td>
<td>0</td>
<td>29</td>
<td>30</td>
<td>1</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>84</td>
<td>82</td>
<td>-2</td>
<td>97</td>
<td>94</td>
<td>-3</td>
<td>22</td>
<td>21</td>
</tr>
</tbody>
</table>

Average Δ indicates the average change between week 12 measurements and baseline measurements. CI indicates cardiac index; SV, stroke volume; HR, heart rate; RAP, right atrial pressure; PAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure; BL, baseline; wk, week; ex, exercise; Coeff Rep indicates the coefficient of reproducibility for Bland Altman analyses.

Supplemental Table 2A. Univariate Predictors of peak VO₂

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>R value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.08</td>
<td>0.261</td>
<td>0.044</td>
</tr>
<tr>
<td>Gender</td>
<td>-2.51</td>
<td>0.280</td>
<td>0.030</td>
</tr>
<tr>
<td>Race</td>
<td>0.243</td>
<td>0.057</td>
<td>0.666</td>
</tr>
<tr>
<td>Ischemic Etiology of CM</td>
<td>0.067</td>
<td>0.01</td>
<td>0.945</td>
</tr>
<tr>
<td>CRT</td>
<td>1.45</td>
<td>0.162</td>
<td>0.216</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.023</td>
<td>0.045</td>
<td>0.743</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>-0.339</td>
<td>0.363</td>
<td>0.004</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>-0.126</td>
<td>0.313</td>
<td>0.015</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>-0.137</td>
<td>0.278</td>
<td>0.032</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.010</td>
<td>0.036</td>
<td>0.785</td>
</tr>
<tr>
<td>PAP slope</td>
<td>-11.04</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAP slope group</td>
<td>-2.26</td>
<td>0.501</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure.

Supplemental Table 2B. Multivariate predictors of peak VO₂

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.077</td>
<td>0.021</td>
</tr>
<tr>
<td>RAP rest</td>
<td>-0.219</td>
<td>0.035</td>
</tr>
<tr>
<td>PAP_slope</td>
<td>-2.10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RAP indicates right atrial pressure; PAP, pulmonary arterial pressure.
**Supplemental Table 3A.** Univariate Predictors of Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>0.066</td>
</tr>
<tr>
<td>Gender</td>
<td>0.89</td>
<td>0.858</td>
</tr>
<tr>
<td>Race</td>
<td>0.85</td>
<td>0.549</td>
</tr>
<tr>
<td>Ischemic Etiology of CM</td>
<td>1.57</td>
<td>0.371</td>
</tr>
<tr>
<td>CRT</td>
<td>1.09</td>
<td>0.897</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.98</td>
<td>0.622</td>
</tr>
<tr>
<td>Peak VO$_2$ (ml/kg/min)</td>
<td>0.70</td>
<td>0.001</td>
</tr>
<tr>
<td>C(a-v)O$_2$ (ml/dl)</td>
<td>0.81</td>
<td>0.04</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>1.09</td>
<td>0.087</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>1.01</td>
<td>0.551</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>1.00</td>
<td>0.940</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>1.00</td>
<td>0.812</td>
</tr>
<tr>
<td>PAP slope pattern</td>
<td>2.84</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure.

**Supplemental Table 3B.** Multivariate Predictors of Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$</td>
<td>0.750</td>
<td>0.018</td>
</tr>
<tr>
<td>PAP slope pattern</td>
<td>4.96</td>
<td>0.002</td>
</tr>
</tbody>
</table>

PAP indicates mean pulmonary arterial pressure.