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

Running Title: Lewis et al: Pulmonary Vascular Responses to Exercise in Heart Failure

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Abstract

**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, LV 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 Watts), LVSD subjects compared to controls, had greater augmentation in mean PAPs (15±1 vs. 5±1 mmHg), transpulmonary gradients (5±1 vs. 1±1 mmHg), and effective PA elastance (0.05±0.02 vs. -0.03±0.01 mmHg/ml, p<0.0001 for all). A linear increment in PAP relative to work (0.28±0.12 mmHg/watt) was observed in 65% of LVSD patients, which exceeded that observed in controls (0.07±0.02 mmHg/watt, 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 mmHg/watt) followed by a plateau. The plateau pattern, compared to a linear pattern, was associated with reduced peak VO₂ (10.6±2.6 vs. 13.1±4.0 ml/kg/min, P=0.005), lower right ventricular stroke work index augmentation with exercise (5.7±3.8 vs. 9.7±5.0 g/m², P=0.002), and increased mortality (HR 8.1, 95% CI 2.7-23.8, 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.

**Clinical Trial Information**—URL: [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov). Unique Identifier: NCT00309790

**Key Words:** hypertension, pulmonary; exercise; heart failure
Resting pulmonary hypertension (PH), defined as mean pulmonary arterial pressure (PAP) > 25 mmHg, is present in the majority of patients with LVSD and is associated with right ventricular dysfunction and poor prognosis.\textsuperscript{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 or the relationship of these PAP-exercise response patterns to exercise capacity and outcomes.

The measurement of blood pressure in the systemic circulation during exercise provides incremental prognostic information to resting measurements of systemic blood pressure in normal individuals\textsuperscript{4, 5} and in patients with LVSD.\textsuperscript{6} Exercise-induced systemic hypertension also predicts future onset of resting hypertension.\textsuperscript{7, 8} In normal 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 PAP\textsuperscript{9} and a fall in pulmonary vascular resistance (PVR).\textsuperscript{10, 11} Flow-mediated vasodilation is impaired in the systemic vasculature of LVSD patients and contributes to reduced LV performance and to inappropriate distribution of systemic blood flow away from vital organs.\textsuperscript{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 vascular 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.\textsuperscript{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 (i.e. LVSD and mitral stenosis) to develop PH out of proportion to left-sided filling pressures at rest, we hypothesized that exercise would elicit disproportionate pre-capillary pulmonary vasoconstriction in LVSD subjects relative to matched controls. We further hypothesized that a steep increment in the PAP-work load 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 (LVEF) < 0.40 and chronic NYHA 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 $V_e/(FEV_1 \times 35) > 0.717^{17,18}$ 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). 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 VO$_2$ greater than 80% of that predicted on the basis of age, gender, and height. Subjects meeting these inclusion criteria who were similar in age to the LVSD subjects composed the control cohort.

Cardiopulmonary exercise testing (CPET)

Subjects were instructed to take their prescribed medications according to their usual schedule prior to 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, 5-15 Watt/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.\textsuperscript{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 pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and radial arterial pressure (MAP) were measured in the upright position, at end-expiration, while patients were seated on the cycle, at rest and at one-minute intervals during exercise. Fick cardiac output (CO) was also determined at one minute intervals throughout exercise by simultaneously measuring radial and pulmonary arterial oxygen content to determine the difference in arterio-venous oxygen content (C(a-v)O\textsubscript{2}) and oxygen uptake (VO\textsubscript{2}). Peak VO\textsubscript{2} was defined as the highest oxygen uptake, averaged over 30 seconds, during the last minute of symptom-limited exercise, as previously described.\textsuperscript{21} Right ventricular stroke work index (RVSWI) 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 (t\textsubscript{d}), resulting in:

\[ Ea(WK) = (\text{mean PAP} - \text{PCWP}) \div \text{stroke volume}. \textsuperscript{22} \]

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 (i.e. freewheel or unloaded exercise at 0 Watts). Unloaded exercise results in energy expenditure and augmentation in oxygen uptake and cardiac output, 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).\textsuperscript{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 Watts \((500 \text{ ml/min} - 300 \text{ ml/min})/(10 \text{ ml/W})\) to their external work achieved during subsequent incremental exercise (see Figure 1). The derived watt increment during unloaded exercise was related to body weight \((R=0.55, \text{ P}<0.001)\), 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: \(R^2>0.9\) 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 non-linear increment in pressure \((R^2<0.9)\) 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 (StatCorp 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’s chi square, or Fisher’s exact test, as appropriate. For clinical characteristics, comparisons between groups for continuous variables were performed using unpaired two-sample t tests or the Wilcoxon signed rank test. Survival was determined starting from the day of the initial cardiopulmonary exercise test, until 11/30/2009. The Kaplan-Meier method was utilized 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 utilized 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 was 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 IRB approved. In addition, the study of subjects outside of the sildenafil trial was also IRB approved. The authors had full access to the data and take responsibility for its integrity and for the manuscript as written.
Results

Baseline clinical characteristics for the LVSD (n=60) and normal 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 DVT without chronic thromboembolic pulmonary hypertension (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 (TPG) at rest than did controls. All of these hemodynamic differences persisted at peak exercise (Table 2).

Pulmonary Vascular Responses to Standardized Submaximal and Peak Exercise

In order 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 vs. 5±1 mmHg, respectively, P<0.0001, Figure 2) whereas the change in systemic MAP did not differ between LVSD and control subjects (8±2 vs. 5±2 mmHg, P=0.20, Figure 2B). The exaggerated increase in PAP in LVSD patients induced by exercise was due to both a 2.4-fold greater increase in left ventricular filling pressure (9±1 vs. 4±1 mmHg, P<0.0001) and a 4.5-fold greater increase in transpulmonary gradient (5±1 vs. 1±1 mmHg, P<0.0001).

At peak exercise, LVSD patients also demonstrated greater PAP increases than did controls (23±1 vs. 13±1 mmHg, P<0.0001, Figure 2, left panel), despite achieving significantly lower peak
work rates (75±5 vs. 141±11 W, respectively, P<0.0001). Differences in PAP augmentation between groups at peak exercise were attributable to a greater transpulmonary gradient augmentation in LVSD patients (10±1 vs. 3±1 mmHg, P<0.001, Figure 2, right panel), whereas PCWP increases at peak exercise were similar between groups (13±1 vs. 10±1 mmHg, 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 (i.e. 6±1 mmHg in controls at 75 W vs. 13±1 mmHg 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 (i.e. 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 5-184 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 Supplemental 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 mmHg/watt, Figure 1, panel A). The majority of patients with LVSD (n=39, 65%) also demonstrated a linear increase in PAP throughout exercise, with a greater slope (0.28±0.12mmHg/watt) than that observed in controls (P<0.0001, Figure 1, panel B). 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 mmHg/W) followed by a plateau in which PAP did not increase despite increasing workload (n=21, Figure 1 panel C). 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 cardiac output (CO) augmentation during exercise. LVSD subjects had a PAP/CO slope of 7.0 mmHg/L during exercise compared to a slope of 1.4 mmHg/L in controls (Figure 3, P<0.0001). The PAP/CO slope in controls was highly consistent with that previously reported (1.45 mmHg/L) in normal middle-aged subjects undergoing upright exercise.25 PAP/CO correlated with PAP/W among subjects with linear PAP/W during exercise with R=0.75, P<0.00001). Patients with PAP/W > 0.25 (median value) had PAP/CO of 9.1 ± 3.2 mmHg/L/min compared to patients with PAP/W<0.25 who had PAP/CO
of 5.0 ± 1.5 mmHg/L/min. In the control group, subjects with below median PAP/W (which was 0.07 mmHg/W) the PAP/CO slope was 1.08 mmHg/L and in the above median group, the PAP/W ratio was 1.64 mmHg/L (P=0.015). The similarity between PAP/W and PAP/CO relationships is not surprising based on the expected linear increment in VO₂ and CO relative to work rate during exercise.¹⁸, ²³

**Pulmonary Effective Arterial Elastance**

We examined the pulmonary effective arterial elastance (Ea) according to Windkessel parameters²² in LVSD patients compared to controls at rest and with exercise. At rest, LVSD subjects had higher Ea than controls (0.27±0.03 mmHg/ml vs. 0.14±0.02 mmHg/ml, respectively, P<0.0001). At submaximal exercise (30 Watts) 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 two groups. Peak exercise Ea values remained unchanged compared to 30W 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 to a linear pattern, had lower exercise capacity (peak VO₂ =10.6±2.6 vs. 13.1±4.0 ml/kg/min, respectively, P=0.005) and lesser augmentation of the right ventricular stroke work index with exercise (5.7±3.8 vs. 9.7±5.0 g/m², respectively; P=0.002). Univariate predictors of lower peak VO₂ included age, female gender, resting RAP, PAP, PCWP, PAP slope, and a PAP
plateau pattern (Supplemental Table 2A). In a multivariate regression analysis age, right atrial pressure at rest, and PAP slope pattern emerged as independent predictors of lower peak VO₂ (Supplemental Table 2B).

To further investigate whether a steeper increment in PAP per watt was associated with worse outcomes in patients with LVSD, we stratified patients by the median slope of the PAP to work rate relationship. Survival curves were then compared between the two linear PAP subgroups and the PAP plateau pattern group. Kaplan Meier analysis shows that the plateau pattern was associated with significantly worse survival than a linear response pattern (unadjusted Cox HR for mortality 8.1, 95% CI 2.7-23.8, P<0.001, Figure 4). A steep, linear PAP-work rate slope was associated with intermediate outcomes, and a shallow PAP-work rate slope, similar to that seen in controls, was associated with the most favorable outcomes (Figure 4). The only two significant independent predictors of mortality in multivariate analysis were peak VO₂ (P=0.007) and PAP slope pattern (P=0.002, Supplemental Table 3).

Modulation of Exercise PAP and pulmonary Ea by chronic 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 vs. work pattern (n=7) 12 weeks of sildenafil treatment reduced the PAP vs. work slope from 0.22±0.03 to 0.18±0.04 mmHg/watt (P=0.04). Consistent with this finding, in the entire cohort of subjects treated with sildenafil, PAP augmentation at peak exercise was unchanged vs. pre-sildenafil despite significantly greater exercise capacity (peak VO₂ +18%). At a standardized 30 Watt exercise-induced mPAP augmentation was 12±1 mmHg pre-sildenafil vs. 10±1 mmHg post-sildenafil, P=0.13 (Figure 5). Assessment of the components of PAP-augmentation at 30W indicated that sildenafil did not effect the increment in PCWP (7±2 mmHg prior to sildenafil
treatment vs. 8±1 mmHg following sildenafil treatment), but did lower transpulmonary-gradient augmentation (5±2 mmHg to 2±1 mmHg, P=0.029, Figure 5) relative to pre-sildenafil measurements. Furthermore, sildenafil treatment was associated with a reduction in pulmonary Ea at 30W from 0.35±0.05 mmHg/ml to 0.28±0.05 mmHg/ml (P=0.01). Taken together, these findings indicate that the selective pulmonary vasodilator sildenafil is able to blunt the exaggerated pre-capillary contribution to PAP augmentation during exercise and improve pulmonary effective arterial elastance.
Discussion

By characterizing the pulmonary vascular response patterns during exertion, 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 RVSWI and portended a particularly poor prognosis.

Characterization of PAP responses to exercise in LVSD patients relative to normal 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 normal control cohorts, uniform use of upright exercise representative 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 Watts, the 2.4-fold greater increase in PCWP (9±1 vs. 4±1 mmHg, 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 30W in LVSD subjects, compared to controls, indicates that the pre-capillary pulmonary arterial response to exercise is also abnormal. The exercise increment in TPG per liter of cardiac output augmentation during exercise in LVSD compared to controls is similarly striking. Furthermore, we found that exercise increased pulmonary Ea in LVSD patients and decreased it in normal controls.

Several potential explanations exist for exaggerated TPG and abnormal Ea responses to exercise in LVSD patients. First, in normal controls, upright exercise recruits the pulmonary vasculature through opening of blood vessels in West Zones 1 and 2 that are underperfused at
rest.\textsuperscript{28} In contrast in LVSD patients at rest, pulmonary arterial and venous pressures exceed alveolar pressures throughout the lungs (i.e. West Zone 3 only). As a result, LVSD patients, unlike normal subjects, are less able to recruit additional pulmonary vasculature during exercise.\textsuperscript{27} Reduced pulmonary vascular recruitment may therefore contribute to 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 naturetic peptides has been postulated to contribute to secondary PH in LVSD.\textsuperscript{29} Several studies have shown that nitric oxide production by endothelial nitric oxide synthase (eNOS) is markedly diminished in LVSD.\textsuperscript{30-32} Because eNOS is normally upregulated by shear stress and increased pulmonary blood flow,\textsuperscript{33} 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 (HPV) 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.\textsuperscript{34,35} These findings suggest that alveolar oxygen tension, the major determinant of HPV,\textsuperscript{36,37} 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 occurs 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.\textsuperscript{38}
Finally, dynamic mitral regurgitation has been implicated in contributing to exercise PAP, estimated non-invasively, in LVSD.\textsuperscript{39} If dynamic MR 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 MR alone does not account for heightened exercise-induced increase in PAP in LVSD. It is possible that chronic MR, 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 non-invasive imaging modalities, such as echocardiography, to estimate PAPs during exercise. For example, echocardiography can be used to estimate both mean PAP and to assess RV structure and function.\textsuperscript{40} In LVSD patients with linear PAP response patterns, acquisition of non-invasive 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 BP measurements observed within individuals during submaximal exercise compared to at rest.\textsuperscript{41} 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.\textsuperscript{1, 2}
Relationship between PAP responses to exercise and exercise performance and outcomes

Several studies have indicated that RV dysfunction and elevated PAP in LVSD are more closely related to exercise intolerance than LVEF in LVSD.\textsuperscript{1,2,42} 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 right ventricle is a thin-walled conduit that has been shown to be exquisitely sensitive to changes in afterload in animal models subjected to vasoconstrictor challenge.\textsuperscript{43} Hence, our findings that the average exercise-induced increase in PAP in patients with LVSD was >80%, compared to a 16% average increase in systemic MAP, indicates the marked relative burden imposed on the RV compared to 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 utilized to detect dynamic right ventricular and pulmonary vascular dysfunction. Here, we demonstrate that exaggerated PAP augmentation (i.e. PAP/W slope $>0.25$ mmHg), increased effective PA elastance (versus decreased effective PA elastance in normal 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 counteracting 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 cardiac output.

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 normal controls. However, our LVSD subjects demonstrated resting hemodynamics, medication exposures, and peak VO2 that were highly consistent with community-based NYHA 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 VO$_2$ > 80% predicted, and their average PAP increased from 15±3 to 28±7 mmHg. This increment in PAP with exercise in control subjects is consistent with findings from a recent meta analysis of PAP responses to exercise in normal individuals in which subjects over the age of 50 demonstrated an increase in PAP from 14.7±4.0 to 29.4±8.4 mmHg with upright exercise.$^9$ 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 physiologic 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 increment 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. PDE 5 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.
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Disclosures

None.
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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>
<tbody>
<tr>
<td>Age — years</td>
<td>60±12</td>
<td>60±12</td>
<td>0.93</td>
</tr>
<tr>
<td>Male sex — %</td>
<td>78</td>
<td>79</td>
<td>0.96</td>
</tr>
<tr>
<td>Primary Cause of Heart Failure — %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>50</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-ischemic cardiomyopathy</td>
<td>50</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NYHA class — %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>53</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>III</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>β-adrenergic receptor antagonist</td>
<td>90</td>
<td>21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone – aldosterone antagonist</td>
<td>50</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>50</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy — %</td>
<td>22</td>
<td>0</td>
<td>0.0002</td>
</tr>
<tr>
<td>RVEF has affected</td>
<td>0.38±0.01</td>
<td>0.56±0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.31±0.01</td>
<td>0.68±0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Workload achieved during exercise — Watts</td>
<td>75±5</td>
<td>142±11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak VO₂ — ml/kg/min</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 normal control subjects. RVEF indicates right ventricular ejection fraction, LVEF indicates left ventricular ejection fraction.
Table 2. Hemodynamic and Arterial Blood Gas values measured at rest and at peak exercise

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LVSD Rest</th>
<th>LVSD Exercise</th>
<th>Control Rest</th>
<th>Control Exercise</th>
<th>P Value Rest</th>
<th>P Value Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate, beats/min</td>
<td>75±2</td>
<td>114±3</td>
<td>72±3</td>
<td>137±4</td>
<td>0.29</td>
<td>0.0001</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>86±2</td>
<td>100±3</td>
<td>103±2</td>
<td>123±3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>6±1</td>
<td>16±1</td>
<td>3±0</td>
<td>9±1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>28±1</td>
<td>50±1</td>
<td>15±1</td>
<td>29±1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>15±1</td>
<td>30±1</td>
<td>6±1</td>
<td>17±1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TPG, mm Hg</td>
<td>12±1</td>
<td>21±1</td>
<td>9±1</td>
<td>11±1</td>
<td>0.002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke Volume, mL</td>
<td>50±2</td>
<td>67±3</td>
<td>70±4</td>
<td>114±5</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac Output, L/min</td>
<td>3.7±0.1</td>
<td>7.6±0.3</td>
<td>5.0±0.3</td>
<td>15.5±0.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR, dyne-s/cm5</td>
<td>299±26</td>
<td>229±19</td>
<td>161±15</td>
<td>64±6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SVR, dyne-s/cm5</td>
<td>1959±98</td>
<td>1015±47</td>
<td>1902±168</td>
<td>641±36</td>
<td>0.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulm Ea, ml/mmHg</td>
<td>0.27±0.02</td>
<td>0.35±0.02</td>
<td>0.14±0.02</td>
<td>0.11±0.01</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVSWI</td>
<td>7.3±0.4</td>
<td>15.6±0.7</td>
<td>5.7±0.5</td>
<td>14.1±0.9</td>
<td>0.01</td>
<td>0.20</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>89±2</td>
<td>97±2</td>
<td>98±2</td>
<td>99±2</td>
<td>0.02</td>
<td>0.34</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>37±1</td>
<td>34±1</td>
<td>35±1</td>
<td>36±1</td>
<td>0.13</td>
<td>0.68</td>
</tr>
<tr>
<td>C(a–v)O₂, mL O₂/dL</td>
<td>7.9±0.2</td>
<td>13.6±0.3</td>
<td>6.5±0.4</td>
<td>12.8±0.3</td>
<td>0.002</td>
<td>0.097</td>
</tr>
</tbody>
</table>

MAP indicates mean systemic arterial pressure; RAP, mean right atrial pressure; PAP, mean pulmonary arterial pressure; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; Ea, effective arterial elastance; RVSWI, right ventricular stroke work index; C(a–v)O₂, arterio-venous difference in oxygen content (i.e. oxygen extraction). P values represent comparisons of the two groups (LVSD vs. control) at rest and with exercise.
Figure Legends

**Figure 1.** Representative patterns of pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) responses to exercise in normal controls (top), patients with LVSD with a linear PAP increment with exercise (middle), and patients with LVSD with a PAP plateau pattern during exercise (bottom).

**Figure 2.** *(Panel A):* Mean changes in pulmonary arterial pressure (Δ PAP) at 30 Watts and at peak exercise, compared to resting values, in patients with LVSD and controls. The relative contributions of pulmonary capillary wedge pressure (Δ PCWP) and transpulmonary gradient (Δ TPG) to Δ PAP are displayed on the right side of the panel. *(Panel B):* Mean changes in systemic arterial blood pressure (Δ MAP) in response to exercise in patients with LVSD and controls. * Indicates P<0.005 for the comparison of pressure changes in patients with LVSD with pressure changes in controls.

**Figure 3.** *(Left panel)* Mean pulmonary arterial pressures (PAP) relative to cardiac outputs during incremental exercise in patients with LVSD. *(Right panels)* Transpulmonary gradient (TPG) and pulmonary capillary wedge pressure (PCWP) responses to exercise relative to cardiac output augmentation in patients with LVSD. * Indicates P<0.005 for the comparison of pressure changes in patients with LVSD with pressure changes in controls.
**Figure 4.** Kaplan-Meier survival estimates for LVSD patients with linear pulmonary arterial pressure (PAP) responses to exercise stratified by median PAP slope (<0.25 mmHg/W, top line, and ≥ 0.25 mmHg/W, middle line), as well as by plateau pattern (bottom line).

**Figure 5.** Effect of sildenafil on pulmonary vascular responses to exercise. Exercise-induced increases in pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), and transpulmonary gradient (TPG) at 30 Watts. Sildenafil blunted the TPG augmentation with exercise. *P=0.02.
Slope = 0.1 mmHg/W, R=0.99
Slope = 0.08 mmHg/W, R=0.89
Slope = 0.3 mmHg/W, R=0.98
Slope = 0.1 mmHg/W, R=0.62
Initial Slope = 0.4 mmHg/W, R=0.98
**Cardiac Output (L/min)**

**PCWP (mmHg)**
- Slope = 3.9 mmHg/L
- R = 0.95

**Slope = 1.1 mmHg/L**
- R = 0.98

**Slope = 0.4 mmHg/L**
- R = 0.84

**Slope = 2.8 mmHg/L**
- R = 0.97

**Control**

**Heart Failure**

**PAP (mmHg)**
- Slope = 7.0 mmHg/L
- R = 0.98

- Slope = 1.5 mmHg/L
- R = 0.97

- Slope = 3.9 mmHg/L
- R = 0.95

- Slope = 1.1 mmHg/L
- R = 0.98
PAP increment <0.25 mmHg/W

PAP increment ≥0.25 mmHg/W

P<0.01 vs. top two groups

P=0.02
The bar chart compares the pressures of PAP, PCWP, and TPG before and after Sildenafil treatment. The bars indicate a statistically significant decrease (*) in TPG post-Sildenafil.
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 Δ (rest)</th>
<th>BL (ex)</th>
<th>12 wk (ex)</th>
<th>Average Δ (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>-1</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 VO₂ (ml/kg/min)</td>
<td>0.70</td>
<td>0.001</td>
</tr>
<tr>
<td>C(a-v)O₂ (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 VO₂</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.