

# Central Cardiac Limit to Aerobic Capacity in Patients With Exertional Pulmonary Venous Hypertension

## Implications for Heart Failure With Preserved Ejection Fraction

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**Background**—The mechanism of functional limitation in heart failure with preserved ejection fraction remains controversial.

We examined the contributions of central cardiac and peripheral mechanisms and hypothesized that the pulmonary vascular response to exercise is an important determinant of aerobic capacity among patients with exertional pulmonary venous hypertension (ePVH).

**Methods and Results**—We compared 31 ePVH patients (peak  $\dot{V}_{O_2}$  <80% of predicted and peak pulmonary arterial wedge pressure  $\geq 20$  mmHg) with 31 age- and sex-matched controls (peak  $\dot{V}_{O_2}$  >80% predicted) who underwent invasive cardiopulmonary exercise testing for unexplained exertional intolerance. ePVH patients had lower peak cardiac output ( $73 \pm 14\%$  versus  $103 \pm 18\%$  predicted;  $P < 0.001$ ) compared with controls, related both to impaired chronotropic response (peak heart rate  $111 \pm 25$  beats per minute versus  $136 \pm 24$  beats per minute;  $P < 0.001$ ) and to reduced peak stroke volume index ( $47 \pm 10$  mL/min per  $m^2$  versus  $54 \pm 15$  mL/min per  $m^2$ ;  $P = 0.03$ ). Peak systemic  $O_2$  extraction was not different between groups (arterial-mixed venous oxygen content difference:  $13.0 \pm 2.1$  mL/dL versus  $13.4 \pm 2.4$  mL/dL;  $P = 0.46$ ). ePVH patients had higher resting ( $150 \pm 74$  versus  $106 \pm 50$  dyne/s per  $cm^{-5}$ ;  $P = 0.009$ ), peak ( $124 \pm 74$  dyne/s per  $cm^{-5}$  versus  $70 \pm 41$  dyne/s per  $cm^{-5}$ ;  $P < 0.001$ ), and isoflow pulmonary vascular resistance ( $124 \pm 74$  dyne/s per  $cm^{-5}$  versus  $91 \pm 33$  dyne/s per  $cm^{-5}$  at cardiac output  $\approx 10.6$  L/min;  $P = 0.04$ ). Pulmonary vascular resistance decreased with exercise in all control subjects but increased in 36% ( $n = 11$ ) of ePVH patients. Abnormal pulmonary vascular response was not associated with peak  $\dot{V}_{O_2}$ .

**Conclusions**—Reduced cardiac output response, rather than impaired peripheral  $O_2$  extraction, constrains oxygen delivery and aerobic capacity in ePVH. Pulmonary vascular dysfunction is common in patients with ePVH at rest and during exercise. (*Circ Heart Fail.* 2015;8:278-285. DOI: 10.1161/CIRCHEARTFAILURE.114.001551.)

**Key Words:** exercise ■ heart failure ■ hemodynamics ■ pulmonary vascular resistance

Heart failure is characterized by the inability to provide adequate cardiac output (CO) to satisfy peripheral metabolic needs at normal intracardiac filling pressures.<sup>1</sup> In approximately half of heart failure patients, left ventricular (LV) ejection fraction (EF) is preserved (HFpEF). These patients demonstrate similar symptoms, prognosis, and functional capacity to those with reduced ejection fraction heart failure.<sup>2-4</sup> Although exertional intolerance in reduced ejection fraction heart failure is predominantly attributed to the reduced CO augmentation, the primary mechanism of functional limitation in HFpEF remains controversial. Diastolic dysfunction, impaired cardiac contractility, abnormal peripheral vasodilation, chronotropic incompetence, and abnormal skeletal muscle may all limit maximal oxygen delivery and consumption.<sup>5-8</sup> Many studies ascribe exertional intolerance in

HFpEF to inadequate  $CO$ ,<sup>5,9-12</sup> with increasing attention toward the role of the right ventricle (RV) and pulmonary circulation in limiting  $CO$ .<sup>13</sup> In reduced ejection fraction heart failure, exercise performance inversely correlates with the slope of the flow-related increase in pulmonary arterial pressure and pulmonary vascular resistance (PVR).<sup>14,15</sup> The prevalence of pulmonary hypertension in HFpEF subjects is high and pulmonary hypertension is independently associated with poor prognosis in this population.<sup>16</sup> Nonetheless, the relative effect of abnormalities of the pulmonary circulation on functional capacity in HFpEF is poorly understood. The central limitation paradigm itself, however, has been challenged; others

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Received July 13, 2014; accepted December 24, 2014.

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*Circ Heart Fail* is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.114.001551

have suggested that abnormal peripheral  $O_2$  extraction may be the primary limiting factor to exercise performance.<sup>17–19</sup> A better understanding of the relative weight of central and peripheral mechanisms to the functional impairment in HFpEF will help to identify relevant pathophysiological subgroups in this heterogeneous disease and to target therapies.

We examined the physiological correlates of impaired aerobic capacity in patients with unexplained dyspnea, preserved LVEF and elevated LV filling pressure at peak exercise, exploring the specific contribution of central cardiac and peripheral mechanisms. Specifically, we hypothesized that the pulmonary vascular response limits CO and is, therefore, an important determinant of maximal aerobic capacity among these patients.

## Methods

### Study Population and Design

This exploratory study included patients with exertional intolerance of indeterminate cause referred to the Dyspnea Clinic at Brigham and Women's Hospital between March 2011 and September 2013 who underwent resting supine right heart catheterization followed by upright cycle invasive cardiopulmonary exercise testing.<sup>20</sup> We excluded those with submaximal exercise testing (respiratory exchange ratio < 1.0), moderate or severe mitral or aortic valve disease, LVEF < 50%, forced expiratory volume in 1 s/forced vital capacity ratio < 70% predicted, marked anemia (hemoglobin < 11 g/dL), or diagnostic testing suggestive of clinically relevant myocardial ischemia.

On the basis of previous studies reporting peak upright exercise pulmonary artery wedge pressure (PAWP) of healthy subjects,<sup>21–23</sup> we defined our study sample as PAWP ≥ 20 mm Hg at peak exercise and peak  $Vo_2$  < 80% predicted.<sup>24</sup> Despite having symptoms compatible with heart failure, preserved LVEF and abnormal PAWP increase at peak exercise in the absence of reduced LVEF and significant valvular disease, we acknowledge a limited ability to apply our findings to community-based HFpEF patients because of the referral bias and the use of the exercise hemodynamics criterion; therefore, we will herein refer to them as exertional pulmonary venous hypertension (ePVH). Because our aim was to study the physiological correlates of impaired aerobic capacity, our age- and sex-matched control group comprised patients referred for invasive cardiopulmonary exercise testing who were found to have normal aerobic capacity (peak  $Vo_2$  ≥ 80% predicted) irrespective of central hemodynamics. LVEF was estimated by transthoracic echocardiography by board-certified staff echocardiographers at Brigham and Women's Hospital by visual estimation, Teichholtz, or biplane Simpson methods. Charts were reviewed for demographic, anthropometric, and clinical baseline characteristics. Data from right heart catheterization and hemodynamic, respiratory and metabolic data at peak exercise testing from invasive cardiopulmonary exercise testing were also collected. The Partners Human Research Committee approved this retrospective chart review and waived the requirement for informed consent.

### Right Heart Catheterization Placement

A flow-directed, balloon-tipped, 4-port pacing pulmonary artery catheter (Edwards Lifesciences, Irvine, CA) was placed into the pulmonary artery, with fluoroscopic guidance as necessary. An arterial line was inserted into the radial artery using a 20-gauge IV or 5-French sheath. End expiratory systemic arterial, right atrial pressure, right ventricular pressure, pulmonary artery pressure, and PAWP were measured using a hemodynamic monitoring system (Xper Cardio Physiointegration System, Philips, Andover, MA) calibrated before each study. The pressure transducer was leveled using as references the mid axillary line (supine) and 5 cm below the axillary fold (upright).<sup>25</sup>

### Exercise Protocol

All exercise tests were performed in the Brigham and Women's Hospital cardiopulmonary exercise laboratory using an upright cycle ergometer with the subject breathing room air. Two minutes of rest were followed by 2 minutes of unloaded cycling at 55 to 65 rpm. Work rate was continuously increased using at 5, 10, 15, or 20 W/min, chosen on the basis of exertional tolerance history, to a symptom-limited maximum. Minute ventilation ( $V_E$ ), pulmonary gas exchange, heart rate (HR), radial arterial blood pressure, right atrial pressure, right ventricular pressure, and pulmonary artery pressure were measured continuously, whereas PAWP and a 12-lead electrocardiogram were obtained at rest and during each minute of exercise. Blood samples were simultaneously drawn from the radial artery and pulmonary artery during the last minute of the rest period and during the last 15 s of each minute during exercise, during a 2-minute unloaded cycling recovery period immediately after peak exercise. Systemic arterial and PA samples were analyzed for  $PO_2$ ,  $Pco_2$ , pH and  $O_2$  saturation ( $SaO_2$ ), hemoglobin concentration, and  $O_2$  content ( $CaO_2$  and  $CvO_2$ , respectively) by co-oximetry. Breath-by-breath pulmonary gas exchange was measured using a commercially available metabolic cart (MGC Diagnostics, St. Paul, MN).

### Data Analysis

Resting ventilatory and gas exchange data were obtained from the averaged final 30-s interval of the 2-minute rest period. Exercise ventilatory and gas exchange data were averaged during contiguous 30-s intervals. Peak  $Vo_2$  was defined as the highest 30-s averaged  $Vo_2$  during the last minute of the symptom-limited exercise test. CO was calculated using the Fick principle ( $CO = Vo_2 / [CaO_2 - CvO_2]$ ), and stroke volume (SV) as  $CO/HR$ . Arterial-mixed venous oxygen content difference ( $CavO_2$  diff) was calculated as the difference between  $CaO_2$  and  $CvO_2$ . Predicted maximal CO was calculated from predicted peak  $Vo_2$  and an assumed maximal arterial-mixed venous  $O_2$  content difference equivalent to hemoglobin concentration for healthy subjects.<sup>26</sup> PVR, transpulmonary gradient, diastolic pressure gradient, systemic vascular resistance (SVR), percentage of predicted maximal HR, and heart rate reserve were calculated using standard formulas (Data Supplement). To assess exercise-induced hemodynamic changes, we used the upright resting data (using measured  $Vo_2$  to calculate Fick CO), instead of supine right heart catheterization data (which use thermodilution or estimated  $Vo_2$  to calculate Fick CO) to avoid the error of using different methods to measure CO and the error of the hemodynamic changes because of different body position.

### Statistical Analysis

Continuous variables are expressed as mean ± SD or median (25th and 75th percentiles) as appropriate for distribution. Categorical variables are expressed as number of subjects and proportion [n (%)]. Comparisons between groups were performed using 2-sided parametric or nonparametric tests (unpaired or paired *t* or Wilcoxon rank sums) for normally and non-normally distributed data, respectively. Fisher exact test was applied to compare proportions. One-way ANOVA with the Bonferroni correction was used to perform multiple group comparisons. Univariate linear regression analysis was performed to study associations between aerobic capacity and clinical and physiological variables. Correlations between hemodynamic and metabolic variables were determined using Pearson or Spearman correlation, as appropriate. A 2-sided  $P < 0.05$  was considered significant. Statistical analysis was performed using Stata software Version 12.1 (Stata Corp LP, College Station, TX).

## Results

### Demographic and Clinical Characteristics

Demographic data, comorbidities, and medications among controls (n=31) and ePVH patients (n=31) are presented in Table 1. Controls were well matched for age and sex. Patients with ePVH had higher body mass index and a higher prevalence

**Table 1. Baseline Characteristics of Studied Subjects**

Characteristic	Controls (n=31)	ePVH (n=31)	P Value
Age, y	65±12	65±12	0.97
Female sex, n (%)	8 (26)	8 (26)	1.00
BMI, kg/m <sup>2</sup>	28.8±6.2	32.5±5.5	0.02
BSA, m <sup>2</sup>	2.0±0.2	2.1±0.2	0.70
Comorbidities			
Hypertension, n (%)	18 (56)	24 (77)	0.10
Diabetes mellitus, n (%)	4 (13)	9 (29)	0.12
Coronary artery disease, n (%)	6 (19)	14 (45)	0.03
Atrial fibrillation, n (%)	6 (19)	7 (23)	0.76
Medication			
CCB, n (%)	6 (19)	10 (32)	0.25
β-blockers, n (%)	8 (26)	19 (61)	0.005
ACEi/ARBs, n (%)	6 (19)	17 (55)	0.004
Diuretics, n (%)	10 (33)	20 (65)	0.02
Blood analysis			
Hemoglobin, g/dL	14.4±1.8	14.4±1.7	0.94
Creatinine, g/dL	1.1±0.2	1.1±0.3	0.82
Estimated GFR, mL/min per 1.73 m <sup>2</sup>	74±9	73±10	0.81
NT-proBNP, pg/mL	109 (53–194)	191 (52–588)	0.20
LVEF, %	60 (60–65)	65 (60–65)	0.68
LVEDD, mm	47±6	44±8	0.24
LVESD, mm	32±6	29±6	0.23
SWT, cm	1.1±0.2	1.2±0.4	0.25
PWT, cm	1.0±0.1	1.0±0.2	0.84
LV mass index, g/m <sup>2</sup>	87±19	90±33	0.69
RWT	0.44±0.09	0.48±0.14	0.28
LA AP diameter, mm	38±5	40±8	0.34
Resting supine hemodynamics			
mPAP, mm Hg	19±5	24±8	0.003
PAWP, mm Hg	12±5	15±5	0.02
TPG, mm Hg	8±3	10±5	0.03
Diastolic pressure gradient, mm Hg	0.7±3.2	−0.5±4.6	0.25
PVR, dyne/s per cm <sup>−5</sup>	106±50	150±74	0.009
RAP, mm Hg	6±3	8±4	0.006
CO, L/min	5.8±1.3	5.4±1.2	0.24
CI, L/min per m <sup>2</sup>	2.8±0.5	2.7±0.6	0.40
SV, mL/min	89±24	84±20	0.43
SVi, mL/min per m <sup>2</sup>	43±10	41±10	0.44
HR, beats per minute	72±14	72±13	0.97

Data are presented as mean±SD, median (25th and 75th interquartile range) or number of subjects (n) and % of cohort. ACEi indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; BMI, body mass index; BSA, body surface area; CCB, calcium channel blocker; CI, cardiac index; CO, cardiac output; ePVH, exertional pulmonary venous hypertension; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GFR, glomerular filtration rate (estimated using the Modified Diet in Renal Disease equation); HR, heart rate; LA AP, left atrium antero-posterior; LVEDD, left ventricular end-diastole diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal probrain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; PWT, posterior wall thickness; RAP, right atrial pressure; RWT, relative wall thickness; SV, stroke volume; SVi, indexed stroke volume; SWT, septum wall thickness; and TPG, transpulmonary pressure gradient.

of coronary artery disease. They were also more likely to be prescribed β-blockers, angiotensin-converting enzyme inhibitors, and diuretics. There were no significant differences in hemoglobin concentration, estimated glomerular filtration rate, or N-terminal probrain natriuretic peptide levels.

### Baseline Supine Resting Hemodynamics

Resting supine hemodynamic data are presented in Table 1. ePVH patients had higher PAWP than controls (15±5 mmHg versus 12±5 mmHg;  $P=0.02$ ), with a PAWP>15 mmHg in 13 (42%) ePVH patients versus 5 (16%) controls ( $P=0.03$ ). ePVH patients also had higher mean pulmonary artery pressure, right atrial pressure, and PVR compared with control group. Eleven (36%) ePVH patients presented a hemodynamic profile compatible with group 2 pulmonary hypertension defined by an mean pulmonary artery pressure≥25 mmHg and PAWP>15 mmHg, compared with 3 (10%) of control group. Among ePVH patients, 4 (13%) had a PVR>240 dyne/s per cm<sup>−5</sup>, 16 (52%) had a transpulmonary gradient>12 mmHg, and 2 (7%) had a diastolic pressure gradient (diastolic pulmonary artery pressure—PAWP)>7 mmHg. Resting PVR did not correlate with resting PAWP ( $r=0.25$ ;  $P=0.18$ ). Resting cardiac index and HR were similar between groups (Table 1). None of the supine resting hemodynamic variables was associated with % of predicted peak V<sub>O<sub>2</sub></sub>. The hemodynamic and metabolic data of resting upright are displayed in Table 2. Differences in right and left heart filling pressures persisted with the transition to upright posture, except that PVR increased modestly in the control group.

### Exercise Performance

#### Exercise Capacity Determinants: CO and Systemic Oxygen Extraction

Exercise hemodynamic and metabolic data are displayed in Table 2. By study design, ePVH patients had lower peak V<sub>O<sub>2</sub></sub> than controls. Peak PAWP in ePVH correlated modestly with % of predicted peak V<sub>O<sub>2</sub></sub> ( $r=-0.33$ ;  $P=0.07$ ). Among ePVH patients, β-blocker treatment was the only baseline feature associated with % of predicted peak V<sub>O<sub>2</sub></sub> ( $P=0.02$ ).

Compared with controls, peak CO was decreased in ePVH patients (Figure 1), and this difference persisted after adjusting individually for age, sex, and body size. For each liter of O<sub>2</sub> consumed, patients from both the groups had the same increase in CO because there was no significant difference in ΔCO/ΔV<sub>O<sub>2</sub></sub> slope ( $P=0.38$ ). At peak exercise, we observed similar absolute peak CavO<sub>2</sub>diff values between groups (13.4±2.4 mL/dL versus 13.0±2.1 mL/dL;  $P=0.46$ ).

#### HR and SV

ePVH patients demonstrated impaired chronotropic response, with lower absolute peak HR, % of predicted peak HR and heart rate reserve (Table 2). Heart rate reserve was significantly, although modestly, correlated with peak V<sub>O<sub>2</sub></sub> ( $r=0.37$ ;  $P=0.04$ ). Likewise, ePVH patients had a lower peak indexed stroke volume (SVi; Table 2) and decreased SVi augmentation (ΔSVi: 14±12 mL/m<sup>2</sup> versus 21±12 mL/m<sup>2</sup>;  $P=0.05$ ) compared with controls.

Excluding those on β-blockade, ePVH patients and controls (12 and 23, respectively) had similar HR response to exercise

(peak HR:  $84 \pm 10\%$  versus  $88 \pm 14\%$  predicted;  $P=0.29$ ). CO remained significantly lower among ePVH patients in this subset of patients ( $78 \pm 9\%$  versus  $103 \pm 18\%$  predicted;  $P<0.001$ ), primarily related to lower peak SVi ( $46 \pm 10$  mL/m<sup>2</sup> versus  $56 \pm 16$  mL/m<sup>2</sup>;  $P=0.06$ ). Peak CavO<sub>2</sub>diff was similar between ePVH and controls in this subset of patients ( $13.0 \pm 1.7$  mL/dL versus  $13.6 \pm 2.7$  mL/dL;  $P=0.48$ ), consistent with no peripheral limitation.

#### Vascular Response to Exercise: Systemic and Pulmonary Circulations

SVR was similar at rest between ePVH and controls, and decreased in both the groups. With exercise, a less pronounced fall in SVR was noted in ePVH ( $-862 \pm 617$  dyne/s per cm<sup>-5</sup> versus  $-1263 \pm 471$  dyne/s per cm<sup>-5</sup>;  $P=0.008$ ), resulting in a higher peak exercise SVR ( $782 \pm 222$  dyne/s per cm<sup>-5</sup> versus  $589 \pm 208$  dyne/s per cm<sup>-5</sup>;  $P=0.001$ ). In ePVH group, peak SVR modestly correlated with % of predicted peak V<sub>O<sub>2</sub></sub> ( $r=-0.39$ ;  $P=0.04$ ).

In addition to the higher resting PVR, ePVH patients had higher peak PVR ( $124 \pm 74$  dyne/s per cm<sup>-5</sup> versus  $70 \pm 41$  dyne/s per cm<sup>-5</sup>;  $P<0.001$ ). Thirteen (43%) ePVH patients had a peak PVR  $>120$  dyne/s per cm<sup>-5</sup> compared with 3 (10%) controls; 11 (36%) ePVH patients had an increase in PVR during exercise compared with none of the control subjects (Figure 2). Using as reference the peak CO of ePVH group, we compared an isoflow ( $10.6 \pm 1.1$  L/min versus  $10.6 \pm 3.5$  L/min;  $P=0.98$ ) PVR between control and ePVH groups. ePVH patients had an increased isoflow PVR ( $124 \pm 74$  dyne/s per cm<sup>-5</sup> versus  $91 \pm 33$  dyne/s per cm<sup>-5</sup>;  $P=0.04$ ) when compared with controls. The control group had a greater decrease in PVR during exercise ( $\Delta$ PVR:  $-70 \pm 51$  dyne/s per cm<sup>-5</sup> versus  $-24 \pm 66$  dyne/s per cm<sup>-5</sup>;  $P=0.004$ ). The V<sub>E</sub>/V<sub>CO<sub>2</sub></sub> slope modestly correlated with peak PVR ( $r=0.39$ ;  $P=0.03$ ) in ePVH group.

Among ePVH patients, peak PVR was not associated with % of predicted peak V<sub>O<sub>2</sub></sub> ( $r=-0.20$ ;  $P=0.29$ ). There were no significant differences in peak V<sub>O<sub>2</sub></sub> of ePVH patients divided by peak PVR tertiles ( $68 \pm 8\%$  versus  $69 \pm 10\%$  versus  $63 \pm 10\%$  predicted;  $P=0.34$ ). Likewise, the presence of resting group 2 pulmonary hypertension ( $P=0.74$ ), a transpulmonary gradient  $>12$  mmHg ( $P=0.12$ ), and an abnormal increase in PVR ( $P=0.28$ ) during exercise were not associated with the degree of aerobic impairment (% of predicted peak V<sub>O<sub>2</sub></sub>). Also notable, peak PVR was not correlated with peak PAWP in ePVH group ( $r=0.10$ ;  $P=0.43$ ).

### Discussion

These data demonstrate that reduced aerobic capacity in ePVH patients is constrained by a central cardiac limit rather than a peripheral one, and that impaired CO reserve is determined by reduced SV augmentation and inadequate chronotropic response during exercise, with the latter related to  $\beta$ -blocker treatment. Systemic O<sub>2</sub> extraction in ePVH was the same as for controls and did not contribute to decreased peak V<sub>O<sub>2</sub></sub>. Also, pulmonary vascular dysfunction is present in a sizable subset of ePVH patients, as evidenced by the increased resting, peak and isoflow PVR, and also by the abnormal increase in PVR during exercise observed in a significant subset of patients.

#### Exercise Capacity Impairment: Central versus Peripheral Limit

Low peak V<sub>O<sub>2</sub></sub> may be the result of inadequate CO augmentation or abnormal CavO<sub>2</sub>diff, which is a function of pulmonary blood oxygenation, hemoglobin O<sub>2</sub> transport capacity (which together comprise arterial O<sub>2</sub> content), and systemic O<sub>2</sub> extraction by working muscles from systemic capillaries. In this study, peak CO (whether considered as absolute value, body surface area normalized, or adjusted to age, sex, and body size) was reduced in ePVH patients compared with age- and sex-matched controls. In contrast, peak CavO<sub>2</sub>diff was normal for both the groups. Therefore, consistent with several previous reports<sup>5,6,9,12</sup> but contrary to others,<sup>17,18</sup> these data do not support an important role for abnormal peripheral O<sub>2</sub> extraction in aerobic limitation in HFpEF. This may be explained by both methodological differences and how the population of interest was sampled in various studies. Direct Fick is the reference standard for measurement of CO. Non-invasive methods to estimate CO reported in some studies are imprecise and introduce variability<sup>27</sup> when used to indirectly estimate peripheral O<sub>2</sub> extraction. In addition, HFpEF is a heterogeneous disease that may present subgroups of patients whose central and peripheral mechanisms have different weights in constraining exercise capacity.<sup>28</sup> Our sample may represent a mild phenotype of HFpEF whose peak systemic oxygen extraction is still intact; it is possible that patients with longstanding HFpEF develop secondary changes in O<sub>2</sub> extraction and that this contributes importantly to the pathophysiology of chronic disease.

#### Determinants of Low CO Augmentation

Chronotropic incompetence is an important correlate of peak V<sub>O<sub>2</sub></sub> in HFpEF.<sup>5,6,29-31</sup> In this study, the severity of chronotropic impairment was similar to recent HFpEF trials,<sup>30,32</sup> and it was associated with lower exercise capacity. The ELANDD trial observed a lowered exercise capacity because of reduced HR response related to nebivolol treatment in HFpEF patients.<sup>33</sup> The current comprehensive physiological assessment during exercise draws attention to the potentially adverse effect of  $\beta$ -blockers on exercise capacity in patients with HFpEF. The effect of withdrawal negative chronotropic drugs requires further study.

Importantly, there was no difference in chronotropic response between controls and the subset of HFpEF patients without  $\beta$ -blockade; these HFpEF patients, although, still had reduced peak V<sub>O<sub>2</sub></sub> because of lower peak CO and peak SVi. This predominant role of SV in exercise capacity was previously described in patients with LV diastolic dysfunction.<sup>10,34</sup> Load-dependent and load-independent mechanisms had been put forward to explain constrained SV augmentation in HFpEF, such as higher LV elastance, impaired contractile reserve, and afterload mismatch because of abnormal systemic vasodilation.<sup>6,7</sup> Abnormalities in systemic vascular function influence SV by increasing LV afterload.<sup>35</sup> Consistent with previous studies,<sup>5,9,12</sup> we observed reduced decline in SVR and higher peak SVR in HFpEF patients. This has been ascribed to systemic endothelial and autonomic dysfunction.<sup>6,36</sup>

**Table 2. Hemodynamic and Metabolic Data of Upright Resting and Peak Exercise**

Characteristic	Control (n=31)	ePVH (n=31)	P Value
<b>Upright resting data</b>			
mPAP, mm Hg	15±4	19±6	<0.001
PAWP, mm Hg	7±4	12±4	<0.001
TPG, mm Hg	8±3	8±4	0.54
RAP, mm Hg	3±3	7±4	<0.001
CO, L/min	4.8±1.4	4.6±1.7	0.71
Rest CI, L/min/m <sup>2</sup>	2.3±0.6	2.2±0.7	0.59
PVR, dyne/s per cm <sup>-5</sup>	141±58	148±77	0.68
SV, mL/min	67±20	67±30	0.98
SVi, mL/min/m <sup>2</sup>	33±9	32±12	0.76
HR, beats per minute	73±14	72±13	0.89
Systolic BP, mm Hg	153±21	142±33	0.11
Diastolic BP, mm Hg	80±11	76±20	0.42
MAP, mm Hg	104±13	98±23	0.20
SVR, dyne/s per cm <sup>-5</sup>	1834±595	1712±628	0.44
Vo <sub>2</sub> , mL/min	314±81	324±84	0.62
SaO <sub>2</sub> , %	98±1	97±1	0.004
SvO <sub>2</sub> , %	65±5	63±6	0.11
<b>Exercise data</b>			
Peak mPAP, mm Hg	30±8	41±9	<0.001
Peak PAWP, mm Hg	15 (12–20)	27 (23–30)	<0.001
Peak TPG, mm Hg	13±8	15±8	0.25
Peak RAP, mm Hg	8±7	13±6	0.003
Peak CO, L/min	15±4	11±4	<0.001
Peak CO, %predicted	107±22	72±21	0.001
ΔCO/ΔVo <sub>2</sub>	6.1±1.2	5.8±1.7	0.38
Peak CI, L/min per m <sup>2</sup>	7.2±1.8	5.1±1.4	<0.001
Peak PVR, dyne/s per cm <sup>-5</sup>	70±41	124±74	<0.001
Δ PVR, dyne/s per cm <sup>-5</sup>	-70±51	-24±66	0.004
Δ PVR, %	-48±25	-5±55	<0.001
Peak SV, mL	111±35	97±25	0.07
Peak SVi, mL/m <sup>2</sup>	54±15	47±10	0.03
ΔSV, mL	43±27	30±25	0.05
ΔSVi, mL/m <sup>2</sup>	21±12	14±12	0.05
Peak HR, beats per minute	136±24	111±25	<0.001
Peak HR, % predicted	87±14	71±13	<0.001
HRR, %	45±12	33±13	<0.001
Peak systolic BP, mm Hg	175±39	167±49	0.52
Peak diastolic BP, mm Hg	74±16	78±19	0.40
Peak MAP, mm Hg	108±21	110±24	0.72
Peak SVR, dyne/s per cm <sup>-5</sup>	589±208	782±222	0.001
ΔSVR, dyne/s per cm <sup>-5</sup>	-1263±471	-862±617	0.008
Peak workload, W	147±61	91±37	<0.001
Peak RER	1.21 (1.08–1.26)	1.09 (1.05–1.20)	0.004
Peak Vo <sub>2</sub> , mL/min	2042 (1323–2326)	1245 (1044–1850)	<0.001
Peak Vo <sub>2</sub> , % predicted	94 (83–112)	68 (61–75)	<0.001
ΔVo <sub>2</sub> /Peak workload, mL/min per W	12±3	12±3	0.76

(Continued)

**Table 2. Continued**

Characteristic	Control (n=31)	ePVH (n=31)	P Value
V <sub>E</sub> /co <sub>2</sub> slope	31.3 (27.8–33.3)	32.9 (26.4–41.7)	0.20
Peak CaO <sub>2</sub> , mL/dL	19.4±2.5	19.4±2.6	0.93
Peak CavO <sub>2</sub> diff, mL/dL	13.4±2.4	13.0±2.1	0.46
Peak SvO <sub>2</sub> , %	33±10	35±10	0.43
Peak SaO <sub>2</sub> , %	97±1	96±3	0.06

Data are presented as mean±SD. Δ, delta (difference between peak exercise and upright resting values); BP indicates blood pressure; CAVO<sub>2</sub>diff, arterial-mixed venous oxygen content difference; CI, cardiac index; CO, cardiac output; ePVH, exertional pulmonary venous hypertension; HR, heart rate; HRR, heart rate reserve; MAP, mean systemic arterial pressure; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular disease; RAP, right atrial pressure; RER, respiratory exchange ratio; SaO<sub>2</sub>, arterial oxygen hemoglobin saturation; SV, stroke volume; SVi, indexed stroke volume; SvO<sub>2</sub>, venous oxygen hemoglobin saturation; SVR, systemic vascular resistance; and TPG, transpulmonary pressure gradient.

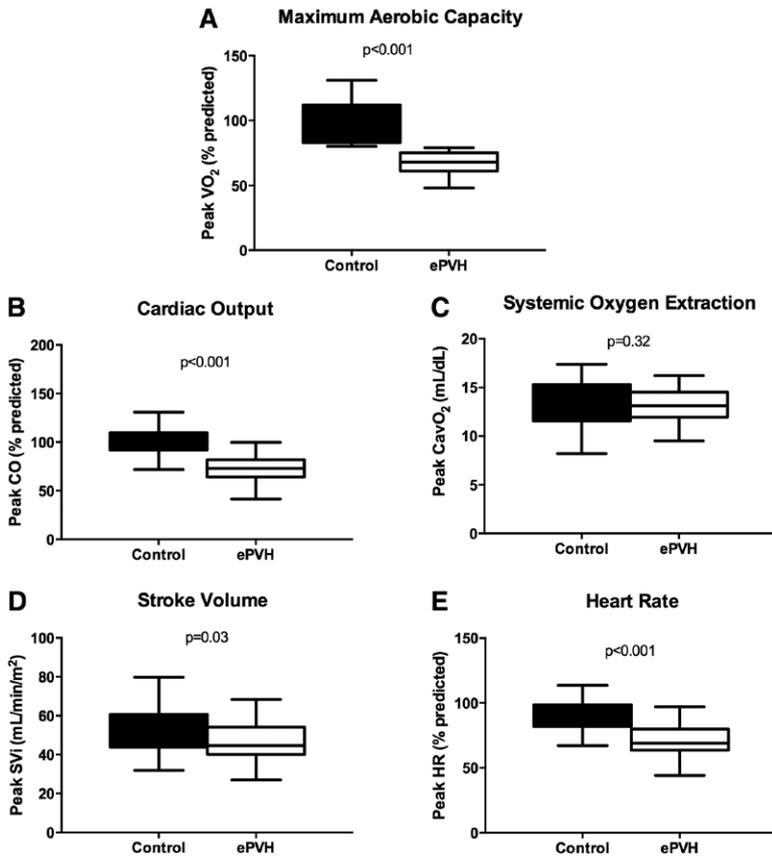
### Pulmonary Vascular Response to Exercise

In HFpEF, the RV faces elevated pulmonary artery impedance driven by increased pulmonary venous pressure. A subset of patients develop pulmonary vascular disease (arteriolar remodeling) with a further increase in impedance to RV ejection.<sup>37</sup> During exercise, RV afterload increases more steeply as the remodeled pulmonary vessels have limited capacity to accommodate increased CO<sup>38</sup>. Several findings support the presence of pulmonary vascular disease in ePVH patients. Resting PVR was higher in ePVH compared with controls, despite similar CO, and more than a third had PVR>240 dyne/s per cm<sup>-5</sup>. The increased peak and isoflow PVR and the subgroup of ePVH patients with a PVR augmentation during exercise, rather than the normal decrease, further support the presence of an abnormal pulmonary circulation. We did not find an association between the extent of pulmonary vascular dysfunction and the degree of exercise capacity impairment. It is possible that this is because we are detecting earlier disease in a younger patient population and that a relationship between depressed peak Vo<sub>2</sub> and blunted PVR fall during exercise would have been more apparent in an older population with established disease. The extent of pulmonary vascular disease of the studied patients might not be severe enough to affect RV-pulmonary artery coupling; the RV may be able to adapt to the increased PVR and maintain an adequate SV augmentation during exercise.

### Study Strengths

By directly measuring left heart filling pressures during upright exercise, our approach overcomes the limited sensitivity of the echocardiographic and circulating surrogate markers for detecting clinically relevant left heart diastolic dysfunction in patients with exertional intolerance.<sup>39,40</sup>

Another methodological strength of our study lies on the simultaneous measurement of Vo<sub>2</sub> and CavO<sub>2</sub>diff. The former is, particularly, important because several noncardiovascular factors (motivation, subjective dyspnea, fitness level, and obesity) may determine different load intensity and confound the comparison of hemodynamics between controls and heart failure patients. The determination of the CavO<sub>2</sub>diff avoids the



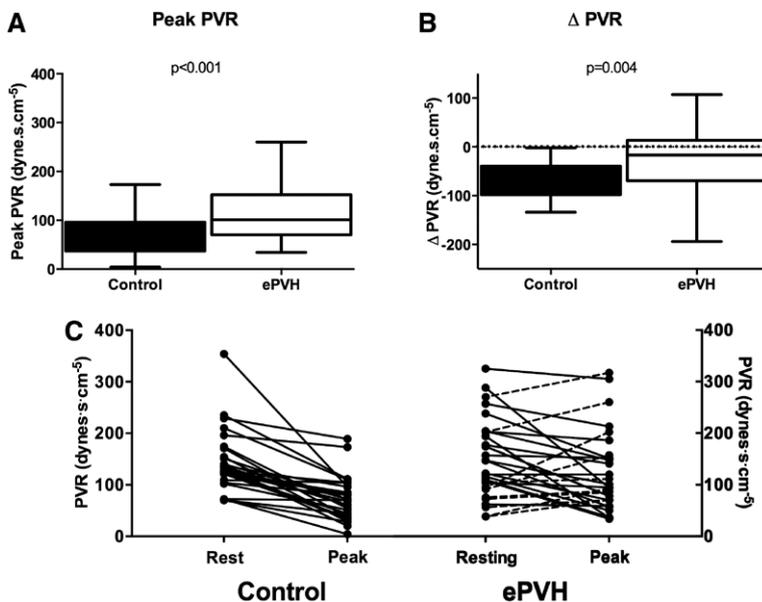
**Figure 1.** Differences of  $\text{V}_{\text{O}_2}$ , cardiac output (CO), heart rate (HR), indexed stroke volume (SV), and arterial-mixed venous  $\text{O}_2$  content difference ( $\text{CavO}_2$ -diff) between exertional pulmonary venous hypertension (ePVH) and control subjects (Tukey plots are shown).

measurement errors of its indirect estimation from  $\text{V}_{\text{O}_2}$  and noninvasive CO assessment.

### Study Limitations

This sample may represent an earlier and more mild phenotype of HFpEF, given that resting standard data yielded inconclusive diagnostic information leading to referral for invasive cardiopulmonary exercise testing. Therefore, the generalization to community-based HFpEF patients should be cautious.

The cross-sectional design of our study precludes insight into time-varying pathophysiology in different stages of HFpEF. In addition, we can only speculate about the causal nature of the observed association between  $\beta$ -blockade and chronotropic incompetence. The use of multiple statistical hypothesis testing increases the chance of type 1 error. We did not measure inotropic reserve with exercise, and cannot comment of the role of this to limited peak SVI. Nevertheless, this does not affect the conclusion that in this group of patients there is a



**Figure 2.** Pulmonary vascular resistance (PVR) changes during exercise of control and exertional pulmonary venous hypertension (ePVH) patients (Tukey plots are shown). Dashed lines depict ePVH patients whose PVR increased during exercise.

central limit to exercise and a markedly abnormal pulmonary vascular response to exercise, whereas peripheral oxygen extraction is preserved.

### Conclusions

Reduced CO because of chronotropic incompetence and decreased SV augmentation, rather than impaired peripheral O<sub>2</sub> extraction, constrain aerobic capacity in ePVH patients. The association between chronotropic incompetence and  $\beta$ -blockers stresses the need of further research about the management of HR in HFpEF. There is a significant burden of pulmonary vascular disease in ePVH patients apparent both at rest and during exercise. Together, this study findings uphold the multifactorial nature of exercise intolerance in HFpEF and emphasize the value of detailed exercise evaluation to discriminate between these distinct pathophysiological mechanisms in patients with unexplained exertional intolerance.

### Acknowledgments

We thank David Yang for his technical expertise and Manyoo Agarwal for his helpful assistance.

### Sources of Funding

Dr Santos receives funds from HMSP-ICJ/0013/2012 grant from the Portuguese Foundation for Science and Technology. Dr Shah receives funds from grant 1K08HL116792-01A1 from the National Institutes of Health. Dr Opatowsky receives support from the Dunlevie Family Fund.

### Disclosures

Dr Shah receives research support from Novartis. Dr Opatowsky has received research support from Actelion and Merck. The other authors report no conflicts.

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### CLINICAL PERSPECTIVE

Although exertional intolerance in heart failure with reduced ejection fraction is often predominantly attributed to limited cardiac output augmentation, the primary mechanism of functional limitation in heart failure with preserved ejection fraction remains controversial. We examined the relative contribution of central (cardiac output) and peripheral (systemic oxygen extraction) limitation to aerobic capacity impairment of patients with characteristics reflective of heart failure with preserved ejection fraction: unexplained dyspnea, preserved left ventricle ejection fraction, and an exaggerated pulmonary artery wedge pressure at peak exercise. The influence of pulmonary vascular response to aerobic capacity was also studied. These patients demonstrated a central limit to exercise. There was reduced cardiac output to exercise because of chronotropic incompetence and decreased stroke volume augmentation; peripheral O<sub>2</sub> extraction was the same as an age- and sex-matched comparison group. We investigated the cause of impaired stroke volume augmentation and found a significant burden of pulmonary vascular disease, both at rest and during exercise. Together, these findings argue that exercise intolerance in heart failure with preserved ejection fraction is primarily because of impaired cardiac output response, which itself has multiple mechanisms.

### Central Cardiac Limit to Aerobic Capacity in Patients With Exertional Pulmonary Venous Hypertension: Implications for Heart Failure With Preserved Ejection Fraction

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*Circ Heart Fail.* 2015;8:278-285; originally published online December 30, 2014;  
doi: 10.1161/CIRCHEARTFAILURE.114.001551

*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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## **Supplemental Material**

### **Supplement 1**

$PVR = (\text{mean PAP} - \text{PAWP}) / \text{CO} * 80; \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}.$

Transpulmonary gradient (TPG) = mean PAP - PAWP

Diastolic pressure gradient = diastolic PAP - PAWP

Systemic vascular resistance (SVR) =  $[\text{mean arterial pressure (MAP)} - \text{RAP}] / \text{CO} *$

$80; \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}.$

Percentage of the predicted maximal HR =  $[(220 - \text{age}) / \text{peak HR}] * 100$

Heart Rate Reserve (HRR) =  $[(\text{peak HR} - \text{resting HR}) / \text{peak HR}] * 100$

# 구혈률보존 심부전 환자에서 운동 시 호흡곤란(폐정맥 상승)은 심장 반응에 기인한다

김민석 교수 · 서울아산병원 심장내과

## 초록

### 배경

구혈률보존 심부전(heart failure with preserved ejection fraction)에서의 운동능력 저하 기전은 잘 알려져 있지 않다. 이에, 연구진은 심인성(central cardiac) 기전과 말초성(peripheral) 기전에 대해 살펴보고, 운동성 폐정맥 고혈압(exertional pulmonary venous hypertension, ePVH) 환자에서 운동에 대한 폐혈관 반응이 유산소능력을 결정하는 중요한 인자일 것이라 가정하였다.

### 방법 및 결과

연구진은 31명의 ePVH 환자[최대산소섭취량(peak  $\text{Vo}_2$ ) < 예측치의 80%, 폐동맥쇄기압  $\geq 24$  mmHg]와 설명할 수 없는 운동 불내성(exertional intolerance)으로 침습적 심폐운동 검사를 받은 연령, 성별이 매칭된 31명의 대조군(최대산소섭취량 > 예측치의 80%)을 비교하였다. ePVH 환자에서 최대심박출량이 감소되었고( $73 \pm 14\%$  vs.  $103 \pm 18\%$ ;  $P < 0.001$ ), 이는 변시성(chronotropic) 반응의 저하(최대맥박수  $111 \pm 25$  회/min vs.  $136 \pm 24$  회/min;  $P < 0.001$ )와 최대박출량지수(peak stroke volume index)의 감소( $47 \pm 10$  mL/min/m<sup>2</sup> vs.  $54 \pm 15$  mL/min/m<sup>2</sup>;  $P = 0.03$ )와 관련이 있었다. 최대 전신산소 추출(peak systemic O<sub>2</sub> extraction)은 양 군 간에

차이가 없었다[동맥-혼합정맥 산소 분율차(arterial-mixed venous oxygen content difference):  $13.0 \pm 2.1$  mL/dL vs.  $13.4 \pm 2.4$  mL/dL;  $P = 0.46$ ]. ePVH 환자에서 안정 시 폐혈관저항이 더 높았고( $150 \pm 74$  vs.  $106 \pm 50$  dyne/s/cm<sup>-5</sup>;  $P = 0.009$ ), 최대 폐혈관저항( $124 \pm 74$  dyne/s/cm<sup>-5</sup> vs.  $70 \pm 41$  dyne/s/cm<sup>-5</sup>;  $P < 0.001$ )과 등기류(isoflow) 폐혈관저항도 더 높았다(심박출량  $\approx 10.6$  L/min에서  $124 \pm 74$  dyne/s/cm<sup>-5</sup> vs.  $91 \pm 33$  dyne/s/cm<sup>-5</sup>;  $P = 0.04$ ). 폐혈관저항은 운동 시 대조군에서는 모두 감소하였으나, ePVH 환자군에서는 36% (11명)에서 증가하였다. 비정상적인 폐혈관 반응은 최대산소섭취량과 관련이 없었다.

### 결론

ePVH 환자에서 산소 전달과 유산소능력의 감소는 말초산소 추출의 감소보다는 심박출 반응의 저하에 기인한다. 폐혈관 기능 저하는 ePVH 환자에서 안정 시와 운동 시 모두 흔히 관찰된다.