Pulmonary Hypertension and Exercise Intolerance in Patients With Heart Failure

Javed Butler, MD, Don B. Chomsky, MD, John R. Wilson, MD, FACC
Nashville, Tennessee

OBJECTIVES
This study was undertaken to investigate the relationship between pulmonary hypertension and exercise performance in patients with heart failure.

BACKGROUND
The exercise capacity of patients with heart failure is frequently reduced. Pulmonary hypertension may contribute to this exercise intolerance by impaireing blood flow through the pulmonary circulation.

METHOD
Three hundred twenty patients with heart failure underwent upright treadmill exercise testing with hemodynamic monitoring. The incidence of pulmonary hypertension and the relationship between pulmonary vascular resistance (PVR) and exercise cardiac output and minute oxygen consumption (VO$_2$) were examined.

RESULTS
Pulmonary vascular resistance was normal (<1.5 Wood Units; Group 1) in 28% of the patients, mildly elevated (1.5 to 2.49 Wood Units; Group 2) in 36%, moderately elevated (2.5 to 3.49 Wood Units; Group 3) in 17% and severely elevated (>3.5 Wood Units; Group 4) in 19%. Increasing PVR was associated with significantly lower peak exercise VO$_2$ (Group 1: 13.9 ± 3.7; 2:13.7 ± 3.4; 3: 11.8 ± 2.4; 4: 11.5 ± 2.6 L/min, p < 0.01 Groups 3 and 4 vs. 1) and lower peak exercise cardiac output (Group 1: 10.0 ± 2.8, 2:9.0 ± 3.0; 3: 7.4 ± 2.1; 4: 6.3 ± 2.0 L/min, p < 0.05, Groups 2, 3 and 4 vs. 1). The pulmonary wedge pressure decreased during exercise, consistent with impaired left ventricular filling, in 36% of patients with severe pulmonary hypertension (Group 4) versus only 13% of patients with normal PVR (p < 0.01).

CONCLUSIONS
Pulmonary vascular resistance is frequently increased in heart failure and is associated with a reduced cardiac output response to exercise, suggesting that pulmonary hypertension impairs exercise performance in heart failure. (J Am Coll Cardiol 1999;34:1802–6) © 1999 by the American College of Cardiology

Exercise intolerance is a serious and almost universal problem in patients with chronic heart failure (1,2). In the past, this problem has been attributed primarily to left ventricular dysfunction, impaired skeletal muscle arteriolar vasodilation and changes in skeletal muscle characteristics, possibly due to muscle deconditioning (1–4). Relatively little attention has been focused on the pulmonary circulation and right ventricle, aside from reports of a correlation between right ventricular function, pulmonary artery pressures and maximal exercise performance (5).

Pulmonary hypertension is a well-established complication of chronic heart failure (6,7). During exercise, excessive pulmonary vascular resistance theoretically could impair the delivery of blood to the left ventricle and thereby attenuate the cardiac output response to exercise. Therefore, pulmonary hypertension may be an important contributor to exercise intolerance in heart failure.

This study was undertaken to investigate the relationship between pulmonary hypertension and exercise performance in heart failure. Specifically, we sought to define the incidence of pulmonary hypertension in ambulatory patients with heart failure. Second, we examined the relationship between pulmonary vascular resistance (PVR), peak exercise minute oxygen consumption (VO$_2$) and the cardiac output response to exercise.

METHODS

Patient population. The study population consisted of all ambulatory patients with heart failure who underwent right heart catheterization with exercise studies between December 1993 and March 1997. During that time period, right heart catheterization with exercise was used routinely to investigate exercise performance in patients referred to the Vanderbilt Heart Failure and Heart Transplantation Programs. Patients were excluded if their ejection fraction was more than 40%, if they were dependent on inotropic or

From the Division of Cardiology, Vanderbilt University Medical Center, Nashville, Tennessee. Supported in part by RO-1 HL53059 from the National Institutes of Health and by a Grant-in-Aid from the National American Heart Association.

Manuscript received October 14, 1998; revised manuscript received June 15, 1999, accepted August 6, 1999.
mechanical support, if they were limited by angina during exercise, or if they exhibited arterial oxygen desaturation during exercise. A total of 320 patients were studied. Average age of these patients was 52 ± 10 years (range: 21 to 75 years). Seventy-four percent of the patients were men. There were approximately equal proportions of patients with ischemic and dilated cardiomyopathy. Left ventricular ejection fraction was 23% ± 9% (range: 8% to 40%). Overall, mean peak VO\textsubscript{2} was 13.0 ± 3.4 ml/min/kg. All patients had exertional dyspnea, fatigue or both and were classified according to New York Heart Association classification between class II to IV.

**Protocol.** On the day of the study, patients arrived in the morning at Vanderbilt University Heart Failure and Heart Transplantation Program’s catheterization procedure laboratory having fasted overnight. A 7F Swan Ganz thermodilution catheter was inserted percutaneously through an internal jugular vein (brachial vein if internal jugular cannulation unsuccessful) and positioned in the pulmonary artery.

Supine central hemodynamic measurements were obtained that included pulmonary artery pressure, right atrial pressure and pulmonary capillary wedge pressure. Blood pressure was measured by a sphygmomanometer. Supine cardiac output was also determined by thermodilution, in triplicate. Blood samples were drawn from the pulmonary artery for measurement of hemoglobin oxygen (O\textsubscript{2}) saturation.

Patients then stood up on the treadmill and were connected to a Medgraphics Cardio O\textsubscript{2} Metabolic Cart. The patient’s left index finger was attached to a pulse oximeter to continuously monitor arterial hemoglobin O\textsubscript{2} saturation.

The patient then began exercising on the treadmill, using a modified Naughton protocol. Each exercise stage lasted 3 min. Speed and grade for each stage was as follows: 1 (1 mph, 0), 2 (2 mph, 0), 3 (2 mph, 3.5), 4 (2 mph, 7), 5 (2 mph, 10.5), 6 (2 mph, 14), 7 (2 mph, 17.5), 8 (2 mph, 21), 9 (2.5 mph, 21), 10 (3 mph, 21). All patients continued exercising until symptoms of dyspnea or fatigue, or both, forced them to stop. Central hemodynamic measurements and respiratory gas exchange analysis were recorded continuously throughout exercise. Blood sampling from the pulmonary artery was performed during the last 45 s of each stage.

**Measured variables.** Arterial hemoglobin concentration was measured by Coulter Counter; hemoglobin O\textsubscript{2} saturation was measured with a Instrumentation Laboratories 282 Co-oximeter precalibrated with human blood. Blood O\textsubscript{2} content was calculated as the product of hemoglobin, 1.34 ml O\textsubscript{2}/g hemoglobin and percent O\textsubscript{2} saturation. Oxygen extraction was calculated as the ratio of the arteriovenous O\textsubscript{2} difference and arterial O\textsubscript{2} content.

**Derived variables.** The following hemodynamic variables were calculated using standard formulas: mean arterial pressure, arteriovenous O\textsubscript{2} difference and systemic vascular resistance. Mean arterial pressure was calculated as diastolic pressure + one-third of the pulse pressure. Total pulmonary resistance was calculated as the mean pulmonary artery pressure divided by the cardiac output. Pulmonary vascular resistance was calculated as (mean pulmonary artery pressure–pulmonary wedge pressure)/cardiac output. Thermodilution cardiac output values were obtained with the patient in the resting supine position whereas Fick cardiac output values were calculated during upright exercise.

**Statistical analysis.** Initially descriptive analyses were performed on all the patients. The patients were then divided into four groups. Group 1 consisted of patients with normal resting PVR (<1.5 Wood Units). Group 2 had PVR between 1.5 and 2.49 Wood Units, Group 3 had pulmonary vascular resistance between 2.5 and 3.49 Wood Units and Group 4 had >3.5 Wood Units. These groups were compared for various clinical, hemodynamic and ventilatory parameters. Categorical variables were compared using chi-square test and continuous variables using analysis of variance (ANOVA). A two-tailed p value of <0.05 was used for statistical significance. When continuous variables were found to be significantly different using ANOVA and a p value <0.05, post hoc analyzes were performed with unpaired t testing using Bonferonni correction to detect differences between individual classes. Continuous variables are presented as mean ± SD and categorical variables as percentages. SPSS for Windows Release 7 (SPSS Inc., Chicago, Illinois) was used for statistical calculations.

**RESULTS**

Supine resting and peak exercise hemodynamic responses for the entire population are summarized in Tables 1 and 2. Resting pulmonary artery pressure averaged 28 ± 11 mm Hg, pulmonary wedge pressure 18 ± 9 mm Hg, total pulmonary resistance 7.06 ± 4.28 Wood Units and PVR 2.45 ± 1.57 Wood Units. With exercise, patients achieved peak VO\textsubscript{2} levels of 13.0 ± 3.4 ml/min/kg. At peak exercise, PVR was unchanged from resting levels (2.41 ± 1.52 Wood Units).

**Pulmonary vascular resistance.** Resting PVR was normal (<1.5 Wood Units; Group 1) in 28% of the patients, mildly elevated (1.5–2.49 Wood Units; Group 2) in 36%, moderately elevated (2.5–3.49 Wood Units; Group 3) in 17%, and severely elevated (>3.5 Wood Units; Group 4) in 19%. There were no significant differences in these group in their
age, etiology of heart failure and baseline ejection fractions (Table 1).

Increasing PVR was associated with significantly lower resting cardiac output (Group 1: 5.2 ± 1.3; 2: 4.6 ± 1.0; 3: 4.2 ± 1.2; 4: 3.3 ± 0.7 L/min, p < 0.01 Groups 2, 3 and 4 vs. Group 1), lower peak exercise VO2 (Group 1: 13.9 ± 3.7; 2: 13.7 ± 3.4; 3: 11.8 ± 2.4; 4: 11.5 ± 2.6 ml/min/kg, p < 0.01 Groups 3 and 4 vs. Group 1), and lower peak exercise cardiac output (Group 1: 10.0 ± 2.8; 2: 9.0 ± 3.0; 3: 7.4 ± 2.1; 4: 6.3 ± 2.0 L/min, p < 0.05 Groups 2, 3 and 4 vs. Group 1) (Table 3; Fig. 1). However, pulmonary hypertension was observed in patients with preserved exercise capacity as well as in patients with severe exercise intolerance. For example, 18% of the patients in this study had peak exercise VO2 levels >16 ml/min/kg. In these patients, 41% had PVR of 1.5–2.49 Wood Units, 5% had pulmonary resistances of 2.5–3.49 Wood Units and 7% had pulmonary resistance >3.5 Wood Units.

Pulmonary vascular resistance decreased significantly with exercise in patients with severe pulmonary hypertension (Group 4) but increased significantly in patients with normal PVR (Group 1) (Fig. 2).

Pulmonary wedge pressures decreased during exercise in 28% of the entire population (mean decrease = 5 ± 3 mm Hg), possibly reflecting impaired delivery of blood to the left ventricle. Thirteen percent of the patients in Group 1 decreased their pulmonary wedge pressure with exercise as compared with 22%, 29% and 36% in Groups 2, 3 and 4, respectively (p = 0.005). When compared with patients who increased their pulmonary wedge pressure with exercise, patients who exhibited a decrease in pulmonary wedge pressure during exercise had significantly higher resting PVR (3.65 ± 2.14 vs. 2.25 ± 1.36 Wood Units) and higher right atrial pressures at peak exercise (13 ± 7 vs. 9 ± 7 mm Hg) (both p < 0.0001).

DISCUSSION

Pulmonary vascular resistance in normal individuals is <1.5 Wood Units (8). During exercise, pulmonary pressures increase as a function of increased blood flow. Cardiac output, however, increases out of proportion to pulmonary pressures, resulting in a drop in PVR.

In patients with longstanding heart failure and high pulmonary wedge pressures, several histologic changes occur that lead to initially reversible and then irreversible pulmonary hypertension. These changes include medial hypertrophy, intimal and adventitial fibrosis and focal hemosiderosis (6). Theoretically, these changes can impair flow through the lungs and contribute to exercise intolerance in heart failure.

To investigate the impact of PVR on exercise performance in heart failure, we examined hemodynamic parameters at rest and during exercise in a large group of patients referred to the Vanderbilt Heart Failure and Transplant Programs. The patients in general had relatively severe exercise intolerance, as evidenced by an average peak exercise VO2 of 13.4 ml/min/kg. However, 16% of the patients had peak VO2 levels >16 ml/min/kg, consistent with Functional Class II exercise limitation.

Incidence of pulmonary hypertension. Seventy-two percent of the patients studied had pulmonary hypertension (>1.5 Wood Units), including 19% with severe pulmonary hypertension (PVR >3.5 Wood Units). This frequency of pulmonary hypertension is similar to that observed by Costard-Jackle et al. (9) in 288 patients evaluated at Stanford University Medical Center for heart transplanta-

Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PVR (WU)</th>
<th>PVR (WU)</th>
<th>PVR (WU)</th>
<th>PVR (WU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.5</td>
<td>1.5–2.49</td>
<td>2.5–3.49</td>
<td>&gt;3.5</td>
<td>p</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52 ± 10</td>
<td>49 ± 12</td>
<td>53 ± 09</td>
<td>52 ± 10</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23 ± 9</td>
<td>24 ± 07</td>
<td>23 ± 08</td>
<td>24 ± 13</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>NYHA %</td>
<td>2</td>
<td>34</td>
<td>36</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>45</td>
<td>41</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>19</td>
<td>28</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>IHD (%)</td>
<td>51</td>
<td>49</td>
<td>55</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>DCM (%)</td>
<td>49</td>
<td>51</td>
<td>45</td>
<td>50</td>
<td>48</td>
</tr>
</tbody>
</table>

DCM = dilated cardiomyopathy; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NS = nonsignificant; NYHA = New York Heart Association Classification; PVR = pulmonary vascular resistance; WU = Wood Units.

Table 2. Resting and Peak Exercise Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± SD)</th>
<th>Peak Exercise (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP (mm Hg)</td>
<td>86 ± 11</td>
<td>95 ± 16</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>8 ± 5</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>PA (mm Hg)</td>
<td>28 ± 11</td>
<td>40 ± 13</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>18 ± 09</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.5 ± 1.3</td>
<td>8.5 ± 3.0</td>
</tr>
<tr>
<td>TPR (wood units)</td>
<td>7.06 ± 4.28</td>
<td>5.54 ± 3.06</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>2.45 ± 1.57</td>
<td>2.41 ± 1.52</td>
</tr>
<tr>
<td>VO2 (ml/min/kg)</td>
<td>13.0 ± 3.4</td>
<td></td>
</tr>
</tbody>
</table>

MBP = mean blood pressure; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; TPE = total pulmonary resistance; VO2 = peak oxygen consumption.
tion. These investigators noted that approximately 79% of their patients had pulmonary hypertension, with close to 35% having PVR \[3.5\] Wood Units.

This high incidence of pulmonary hypertension may reflect a referral bias because patients with mild heart failure are rarely referred to specialty heart failure and heart transplantation programs. Nevertheless, these findings indicate that pulmonary hypertension is an extremely common problem in patients with moderate to severe heart failure. We also noted that some patients with relatively mild exercise symptoms had pulmonary hypertension. For example, 58 of the patients in our study had a peak exercise VO\(_2\) \[16\] ml/min/kg, a level of exercise ability usually associated with only mild exertional symptoms. In these patients, 41% had PVRFs of \[1.5\] to \[2.49\] Wood Units, 5% had pulmonary resistances of \[2.5\] to \[3.49\] Wood Units and 7% had pulmonary resistance \[3.5\] Wood Units. Therefore, the absence of major exertional symptoms does not exclude the possibility of severe pulmonary hypertension.

Effect of exercise on pulmonary resistance. During exercise, PVR changed relatively little, despite an increase in cardiac output. One might expect that an increase in cardiac output and pulmonary flow during exercise would produce pulmonary vasodilation, due to recruitment and distention of the pulmonary vascular bed. Instead, we observed a decrease in resistance in patients with high resting pulmonary vascular resistance but an increase in patients with normal resistance.

A similar response was noted by Janicki et al. (10). These investigators observed that pulmonary resistance increased by \[0.22\] Wood Units in patients with initial PVR \[1.5\] Wood Units whereas pulmonary resistance decreased by \[1.2\] Wood Unit in patients with initial PVR \[3.5\] Wood Units. The reason for this response is unclear, although the degree of change in either direction is small and unlikely to be physiologically important.

Effect of pulmonary hypertension on exercise performance. Does the presence of pulmonary hypertension impair exercise performance? In this study, pulmonary hypertension was associated with a reduced peak exercise VO\(_2\) and reduced cardiac output response to exercise, with the degree of exercise abnormalities paralleling the degree of

![Figure 1](image_url)  
**Figure 1.** Resting and peak exercise cardiac output in the patient population (n = 320).

![Figure 2](image_url)  
**Figure 2.** Effect of exercise on pulmonary vascular resistance.
pulmonary hypertension. These findings are consistent with an adverse effect of pulmonary hypertension on exercise performance. In addition, we frequently observed a decrease in the pulmonary wedge pressure during exercise in patients with moderate to severe pulmonary hypertension, suggesting impaired delivery of blood to the left ventricle. This pattern was observed in 36% of patients with severe pulmonary hypertension but only in 13% of patients with normal PVR. Patients who exhibited a decrease in pulmonary wedge pressure during exercise also had higher right atrial pressures at peak exercise than other patients, consistent with right ventricular failure.

It should be reiterated, however, that the presence of pulmonary hypertension was not invariably associated with major exercise intolerance, since over 50% of the patients with peak exercise VO₂ > 16 ml/min/kg had pulmonary hypertension. Other factors, such as right ventricular function, likely modulate the impact of pulmonary hypertension on cardiac output responses to exercise.

In summary, these observations suggest that pulmonary hypertension is a very common problem in patients with heart failure. These findings also provide suggestive evidence that pulmonary hypertension contributes to exercise intolerance in heart failure by impairing the cardiac output response to exercise. However, it should be emphasized that the presence of a relationship does not establish causality. Additional studies are needed to determine the impact of reducing PVR on exercise performance in heart failure.

REFERENCES