Exercise Testing in Asymptomatic or Minimally Symptomatic Aortic Regurgitation: Relationship of Left Ventricular Ejection Fraction to Left Ventricular Filling Pressure During Exercise

CHARLES A. BOUCHER, M.D., RICHARD A. WILSON, M.D., DAVID J. KANAREK, M.D., ADOLPH M. HUTTER, JR., M.D., ROBERT D. OKADA, M.D., RICHARD R. LIBERTHSON, M.D., H. WILLIAM STRAUSS, M.D., AND GERALD M. POHOST, M.D.

SUMMARY  Exercise radionuclide angiography is being used to evaluate left ventricular function in patients with aortic regurgitation. Ejection fraction is the most common variable analyzed. To better understand the rest and exercise ejection fraction in this setting, 20 patients with asymptomatic or minimally symptomatic severe aortic regurgitation were studied. All underwent simultaneous supine exercise radionuclide angiography and pulmonary gas exchange measurement and underwent rest and exercise measurement of pulmonary artery wedge pressure (PAWP) during cardiac catheterization. Eight patients had a peak exercise PAWP < 15 mm Hg (group 1) and 12 had a peak exercise PAWP ≥ 15 mm Hg (group 2). Group 1 patients were younger and more were in New York Heart Association class I. Group 1 patients also had a higher mean rest ejection fraction (0.64 ± 0.08 vs 0.49 ± 0.13, p < 0.01), higher exercise ejection fraction (0.63 ± 0.10 vs 0.40 ± 0.18, p < 0.01), lower end-systolic volume (38 ± 13 vs 79 ± 36 mL/m², p < 0.01) and higher peak oxygen uptake (24.9 ± 5.1 vs 16.6 ± 4.9 ml/kg/min, p < 0.01) than group 2 patients. However, the two groups had similar cardiothoracic ratios, changes in ejection fractions with exercise, and rest and exercise regurgitant indexes. Using multiple regression analysis, the best correlate of the exercise PAWP was peak oxygen uptake (r = −0.78, p < 0.01). No other measurement added significantly to the regression. When peak oxygen uptake was excluded, rest and exercise ejection fraction also correlated significantly (r = −0.62 and r = −0.60, respectively, p < 0.01). Patients with asymptomatic or minimally symptomatic severe aortic regurgitation have a wide spectrum of cardiac performance in terms of the PAWP during exercise. The absolute rest and exercise ejection fraction and the level of exercise achieved are noninvasive variables that correlate with exercise PAWP in aortic regurgitation, but the change in ejection fraction with exercise by itself is not.

ASYMPTOMATIC PATIENTS with severe aortic regurgitation present a difficult management problem, because the left ventricular volume overload may be well tolerated clinically, yet significant myocardial degenerative changes such as fibrosis may occur in association with the physiologic adaptation to the volume overload.1-8 As a result, after valve replacement, left ventricular function may be abnormal, altering the clinical course.9-20 Therefore, noninvasive approaches to assessing left ventricular function are important in the evaluation of patients with aortic regurgitation.

Exercise radionuclide angiography is one means of noninvasively detecting left ventricular dysfunction in these patients.14, 21-25 Of the radionuclide measurements available to define left ventricular function, ejection fraction is the simplest and most widely used. However, ejection fraction alone may not completely reflect left ventricular performance in this setting. Exercise is a complex intervention of changing preload, afterload, heart rate and contractile state, and ejection fraction may be variably affected by these factors.26, 27 The degree of aortic regurgitation changes with exercise,28 which may also affect the ejection fraction during exercise. The level of exercise performed may vary considerably due to interpatient differences in fitness and motivation.29-31 Also, the “normal” ejection fraction response during exercise has been defined in patients with normal left ventricular stroke volumes and end-diastolic volumes.14, 21-24, 27, 32 Since patients with aortic regurgitation have elevated stroke volumes and end-diastolic volumes,33, 34 it may be inappropriate to compare their ejection fraction values to those from patients with normal left ventricles when defining the adequacy of left ventricular function in aortic regurgitation.

To better understand the ejection fraction response to exercise and to improve the use of radionuclide angiography in aortic regurgitation, we performed simultaneous exercise radionuclide angiography and pulmonary gas exchange measurements in 20 patients with severe aortic regurgitation and minimal or no symptoms. Clinical, respiratory gas exchange, hemodynamic and radionuclide data (including ejection fraction) were compared. Although previous studies have used symptoms or valve replacement to categorize aortic regurgitation patients,21, 22, 35, 36 we chose the pulmonary artery wedge pressure during exercise as an objective measurement to stratify the patients for data analysis.

From the Cardiac and Pulmonary Unit and the Division of Nuclear Medicine, Massachusetts General Hospital, Boston, Massachusetts. Supported in part by USPHS grants HL 21751 and 26215, NIH. Drs. Okada and Pohost are Established Investigators of the American Heart Association.

Address for correspondence: Charles A. Boucher, M.D., Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114. Received October 18, 1982; revision accepted February 3, 1983. Circulation 67, No. 5, 1983.
Methods

Study Population

Thirty-one patients who underwent cardiac catheterization were studied: 20 patients with aortic regurgitation and 11 control patients. The 20 patients had severe chronic isolated aortic regurgitation with no aortic valve gradient during systole. None had severe dyspnea and all were graded as either New York Heart Association (NYHA) functional class I or II. None had angina or syncope. Fourteen were men and six were women, ages 25–68 years (mean 41 years). No patients were being treated with diuretics, vasodilators or β blockers. Eleven had been placed on digitalis preparations. Electrocardiograms were reviewed and the presence of left ventricular hypertrophy determined using Romhilt-Estes criteria. A cardiothoracic ratio was measured on the posteroanterior chest roentgenogram. The presence or absence of a third heart sound was noted by at least one senior staff cardiologist.

The control group consisted of 11 patients referred for evaluation of chest pain who had normal coronary angiograms, a normal left ventricular end-diastolic pressure and normal left ventriculography at cardiac catheterization. Seven were men and four were women, ages 20–56 years (mean 42 years). None had hypertension and none had evidence of mitral valve prolapse or hypertrophic cardiomyopathy by contrast left ventriculography in all or echocardiography in five.

Exercise Protocol

Aortic regurgitation patients underwent two supine exercise tests, one during catheterization and one during radionuclide angiography. The two tests were performed on separate days but within 1 month of each other, with no change in clinical status or medications. The same electronically braked bicycle ergometer (Warren Collins, Inc.) was used. The heart rate, blood pressure and ECG were recorded during each minute of exercise. The initial work load of 25 W was increased by 25 W every 3 minutes. A constant pedal speed of 60 rpm was maintained. Subjects were verbally encouraged to exercise until peak tolerance.

Cardiac Catheterization

All aortic regurgitation patients underwent right- and left-heart catheterization, left ventriculography, aortography and coronary angiography. The right-heart catheter was placed in the pulmonary artery from the right brachial vein, and each patient underwent maximal supine bicycle exercise with determination of rest and peak exercise pulmonary artery wedge pressures. All patients had aortic regurgitation graded as severe by supravalvular cineangiography. The control population did not undergo an exercise evaluation during the catheterization.

For the subsequent analysis, the patients with aortic regurgitation were separated into two groups according to their pulmonary artery wedge pressures during exercise. Group 1 consisted of eight patients with a pulmonary artery wedge pressure of less than 15 mm Hg at peak exercise. Group 2 consisted of 12 patients in whom the pulmonary artery wedge pressure rose to 15 mm Hg or more at peak exercise.

Radionuclide Data Acquisition

Exercise radionuclide angiography and pulmonary gas exchange measurements were obtained simultaneously. After in vivo labeling of red blood cells with 20 mCi of technetium-99m pertechnetate, blood pool images were acquired using a gamma scintillation camera (Ohio Nuclear Series 120, Technicare Corporation, or Picker Dynacamera) interfaced to an imaging computer (MUGA-CART, Medical Data Systems). Image collection was synchronized with the QRS complex of the ECG to obtain 14 images within the cardiac cycle using a 64 × 64 word mode matrix. Rest images were obtained in the anterior and the left anterior oblique projection that displayed the interventricular system most homogeneously. No caudal tilt of the collimator was used. Exercise left anterior oblique images were acquired during the second 2 minutes of each 3-minute bicycle exercise stage.

Radionuclide Data Analysis

The left anterior oblique images at rest and at each exercise level were analyzed to determine left ventricular ejection fraction and regurgitant index. Left ventricular ejection fraction was determined by a standard counts method using a semiautomatic algorithm for defining left ventricular edges. Ejection fraction was calculated as background-corrected end-diastolic minus end-systolic counts divided by end-diastolic counts. The interobserver variance (± 2 SD) of this method of determining ejection fraction (± 0.06) in our laboratory has been reported.

Regurgitant index (left ventricular stroke counts/right ventricular stroke counts) was determined by a modification of the method of Bough et al. The right and left ventricular end-systolic and end-diastolic frames were determined first by visual inspection of the 14 frames of the cardiac cycle. The end-systolic frame was subtracted from the end-diastolic frame to obtain a stroke volume image. From this image, right and left ventricular regions of interest were drawn using the light-pen facility on the computer. These regions of interest were then applied to the original 14 frames of the cardiac cycle and counts for right and left ventricular regions were determined. If the right or left ventricular end-diastolic or end-systolic frames originally chosen to create the stroke volume image were not the same as the frames with maximum and minimum counts from the regions of interest, then the new end-diastolic and end-systolic frames (defined by the maximum and minimum counts) were used to derive a new stroke volume image and new right and left ventricular regions were drawn. This process was repeated until the right and left ventricular end-diastolic and end-systolic frames corresponded to the maximum and minimum counts of the 14-frame sequence. Regurgitant index was the ratio of left ventricular to right ventricular stroke counts measured on the stroke volume image. Because the ventricular stroke counts are assumed to reflect stroke volume, this value should
normally be unity. In aortic regurgitation, the left ventricular stroke volume should be larger than the right ventricular stroke volume and the ratio should exceed unity. However, it is likely that this method does not precisely reflect stroke volume or even stroke counts because of factors such as overlap of atrial activity within the ventricular regions of interest and imprecise edge detection. Nevertheless, several studies have shown that this measurement approximates the severity of regurgitation and that when valve regurgitation is corrected, the value approaches unity.\textsuperscript{32, 34}

Left ventricular end-diastolic volume at rest was determined from the anterior and left anterior oblique images using a previously described geometric biplane area-length method.\textsuperscript{32, 34} The gamma camera was calibrated using a line phantom of known dimensions and a uniform technetium-99m source. Each picture element on the computer was determined to be equivalent to 0.40 cm using the Ohio-Nuclear camera and 0.37 cm using the Picker camera. The end-diastolic frame was manually outlined in both views using the light-pen region of interest facility of the computer. The areas of these outlines and the longest possible chord were determined by the computer. Minor axis (D) in each view was then calculated as $2 \times \frac{\text{area}_{\text{pi}}}{\text{longest chord (L)}}$. Since the area-length formula assumes two views 90° apart, the anterior (ANT) and 40–50° left anterior oblique (LAO) view axis measurements were adjusted to the orthogonal 30° right anterior oblique (RAO) and the 60° LAO projection, respectively, using trigonometry. From the corrected axis measurements, end-diastolic volume was then derived from the formula:

$$V = \frac{4}{3\pi} \frac{L_{\text{RAO}}}{2} \cdot D_{\text{ANT}} \cdot D_{\text{LAO}}.$$ 

Previous work from our laboratory has demonstrated a correlation of this method with contrast left ventriculography of $r = 0.80$ and interobserver and intraobserver variances ($\pm 2$ so) of 28 ml/m$^2$ and 8 ml/m$^2$, respectively.\textsuperscript{32, 34} Stroke volume was calculated as ejection fraction multiplied by end-diastolic volume and end-systolic volume as end-diastolic volume minus stroke volume, avoiding geometric assumptions about the shape of the left ventricle at end-systole. All ventricular volumes were corrected for body surface area.

Exercise to rest pulmonary blood volume ratios were derived using the method of Okada.\textsuperscript{39, 45} The activity in a computer-generated region of interest over the left lung on the left anterior oblique exercise image is compared to the activity in the same region on the rest image and expressed as a ratio. We previously reported that a normal pulmonary blood volume ratio is less than 1.06.

**Pulmonary Gas Exchange Analysis**

Throughout exercise, the patients inhaled room air and exhaled through a low-resistance, one-way valve, a 5-foot length of respiratory tubing, and a pneumotachometer (Digital Pneumotach 47303A, Hewlett-Packard) into a mixing chamber. Each 15 seconds, an aliquot of mixed expired gas from the chamber was sampled, dried and analyzed for the concentration of oxygen (Beckman OM 1, Beckman Instruments, Inc.) and carbon dioxide (Beckman LB 2). The data were analyzed on a computer (Hewlett-Packard No. 9825A) allowing derivation of oxygen consumption and minute ventilation.\textsuperscript{31}

**Statistical Analysis**

Rest vs exercise values in the same patients were compared using a paired $t$ test and values in different patients were compared using an unpaired $t$ test. Variables were compared by linear regression analysis. Differences between correlation coefficients were calculated using Fisher's Z transform. The variables that best predicted the pulmonary capillary wedge pressure response to exercise were determined by stepwise multiple linear regression analysis.\textsuperscript{46} Values were expressed as mean $\pm$ SD.

**Results**

The clinical and hemodynamic data in the 20 patients with aortic regurgitation and the mean values in the 11 control patients are shown in table 1. The patients are listed in order of increasing exercise pulmonary artery wedge pressure. The ages, sex distribution, rest and peak exercise heart rates, peak work load during exercise and peak oxygen uptake were similar in both groups. Systolic blood pressure at rest and at peak exercise was higher in aortic regurgitation patients than in control patients. Eight aortic regurgitation patients were NYHA class I and 12 were NYHA class II. Eleven patients have undergone aortic valve replacement. The cardiothoracic ratio exceeded 0.60 in four. At rest, the pulmonary artery wedge pressure was less than 15 mm Hg in 15 of 20 patients (75%); with exercise, it was less than 15 mm Hg in only eight (40%), $p < 0.05$.

The radionuclide data in the 20 aortic regurgitation patients and the mean values in the control patients are shown in table 2. At rest, left ventricular ejection fraction was lower, left ventricular end-diastolic volume, end-systolic volume and stroke volume were larger, and the regurgitant index was higher in aortic regurgitation patients compared to control patients. Among aortic regurgitation patients, ejection fraction increased during exercise by 0.05 or more in 5 (25%) and decreased by .05 or more in 11 (55%). Mean ejection fraction and mean regurgitant index decreased with exercise ($p < 0.05$). All but four aortic regurgitation patients had an elevated pulmonary blood volume ratio. These four were the only patients to have an exercise pulmonary artery wedge pressure below 10 mm Hg and an absolute decrease in pulmonary artery wedge pressure during exercise.

**Comparison Among Aortic Regurgitation Patients Stratified by Hemodynamic Response to Exercise**

The aortic regurgitation patients with exercise pulmonary artery wedge pressures below and above 15
TABLE 1. Clinical Data in Aortic Regurgitation and Normal Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>NYHA class</th>
<th>AVR</th>
<th>CT ratio</th>
<th>S₁</th>
<th>Heart rate</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
<td>Ex</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>0.59</td>
<td>0</td>
<td>60</td>
<td>156</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>0.48</td>
<td>0</td>
<td>62</td>
<td>118</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>0.57</td>
<td>0</td>
<td>70</td>
<td>181</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.62</td>
<td>0</td>
<td>74</td>
<td>170</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>0.48</td>
<td>+</td>
<td>100</td>
<td>177</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>M</td>
<td>2</td>
<td>0</td>
<td>0.51</td>
<td>0</td>
<td>72</td>
<td>154</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>M</td>
<td>2</td>
<td>0</td>
<td>0.45</td>
<td>0</td>
<td>70</td>
<td>133</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>0.43</td>
<td>0</td>
<td>68</td>
<td>128</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>M</td>
<td>1</td>
<td>+</td>
<td>0.56</td>
<td>0</td>
<td>81</td>
<td>145</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>M</td>
<td>1</td>
<td>+</td>
<td>0.52</td>
<td>0</td>
<td>93</td>
<td>155</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.49</td>
<td>0</td>
<td>85</td>
<td>175</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.63</td>
<td>0</td>
<td>108</td>
<td>146</td>
</tr>
<tr>
<td>13</td>
<td>55</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>0.42</td>
<td>0</td>
<td>72</td>
<td>160</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.65</td>
<td>0</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>15</td>
<td>51</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.51</td>
<td>0</td>
<td>91</td>
<td>156</td>
</tr>
<tr>
<td>16</td>
<td>32</td>
<td>M</td>
<td>2</td>
<td>0</td>
<td>0.67</td>
<td>0</td>
<td>82</td>
<td>130</td>
</tr>
<tr>
<td>17</td>
<td>42</td>
<td>F</td>
<td>2</td>
<td>+</td>
<td>0.55</td>
<td>0</td>
<td>119</td>
<td>153</td>
</tr>
<tr>
<td>18</td>
<td>44</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.51</td>
<td>+</td>
<td>82</td>
<td>144</td>
</tr>
<tr>
<td>19</td>
<td>57</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.56</td>
<td>+</td>
<td>71</td>
<td>141</td>
</tr>
<tr>
<td>20</td>
<td>54</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>0.57</td>
<td>0</td>
<td>84</td>
<td>162</td>
</tr>
</tbody>
</table>

Mean ± SD 41 ± 13 0.54 ± 0.07 81 ± 15 152 ± 17 159 ± 25 240 ± 88
Control * * * *

Mean ± SD 42 ± 12 71 ± 16 146 ± 17 125 ± 12 183 ± 22

*p < 0.01.

Abbreviations: NYHA = New York Heart Association; AVR = aortic valve replacement; BP = systolic blood pressure; Ex = exercise; PAWP = pulmonary artery wedge pressure; CT = cardiothoracic.

mm Hg (groups 1 and 2, respectively) are compared in table 3. Patients in group 1 were younger and more were in NYHA class I than patients in group 2. In six of the 20 patients (30%), there was a discordance between symptom class and exercise pulmonary artery wedge pressure: Three patients in group 1 were NYHA II and three in group 2 were NYHA I.

At rest, group 1 patients had a lower resting heart rate, higher ejection fraction and lower end-diastolic and end-systolic volumes. The systolic blood pressure, stroke volume and regurgitant index were not significantly different. With exercise, group 1 patients had a higher peak work load, oxygen uptake and ejection fraction. The pulmonary blood volume ratio was lower. The heart rate, blood pressure and regurgitant index were similar in group 1 and 2 patients. Mean ejection fraction decreased more with exercise in group 2 than in group 1, but the difference did not reach statistical significance.

The individual rest and exercise ejection fraction values in groups 1 and 2 are shown in figure 1. All group 1 patients had a rest ejection fraction above 0.50 and all five patients with rest ejection fraction below 0.50 were in group 2. Of the eight group 1 patients, three had a 0.05 or more increase in ejection fraction with exercise and three had a 0.05 or more decrease with exercise. Of the 12 group 2 patients, two had a 0.05 or more increase in ejection fraction with exercise and eight had a 0.05 or more decrease with exercise.

Prediction of Exercise Pulmonary Artery Wedge Pressure

Using stepwise multiple regression analysis, the best predictor of the exercise pulmonary artery wedge pressure was the oxygen uptake at peak exercise. The exercise pulmonary artery wedge pressure (PAW) in mm Hg was inversely proportional to peak oxygen uptake (VO₂) in ml/kg/min:

\[ PAW = 48.6 - 1.42 (VO₂) \ (r = -0.78, p < 0.01). \]

This relationship is illustrated in figure 2. Nine of 11 patients with a peak oxygen uptake below 20 ml/kg/min had an exercise pulmonary artery wedge pressure above 15 mm Hg, whereas seven of nine patients with a peak oxygen uptake above 20 ml/kg/min had an exercise pulmonary artery wedge pressure of 15 mm Hg or less. No other variable added significantly to this regression equation. However, when peak oxygen uptake was excluded, other variables also correlated with the exercise pulmonary artery wedge pressure (table 4). Ejection fraction, end-systolic volume, age, pulmonary blood volume ratio and peak exercise workload all correlated with the exercise pulmonary artery
wedge pressure. The peak oxygen uptake correlation was significantly better than that of any other variable \((p < 0.05)\). The cardiothoracic ratio, the presence of a third heart sound and the change in ejection fraction with exercise did not correlate significantly with the exercise pulmonary artery wedge pressure \((r = 0.22, 0.22 \text{ and } 0.29, \text{ respectively})\).

### Discussion

Previous studies have described the ejection fraction, regurgitant index, and end-diastolic and end-systolic volumes during exercise radionuclide angiography in both asymptomatic and symptomatic patients with aortic regurgitation. In this study, however, the population was limited only to those with minimal or no symptoms. Patients with severe and obvious symptoms, in whom the decision for valve replacement is usually straightforward, were not included. Nevertheless, this study population may also not represent all asymptomatic patients, because only patients who underwent catheterization were included. Although the patients were not severely symptomatic, it was sometimes difficult to decide whether they were asymptomatic or mildly symptomatic (NYHA class I or II). In some cases, the cardiologist managing the patient was not convinced that vague symptoms due to left-heart decompensation or to noncardiac factors, such as anxiety or poor fitness, could be distinguished.

This may explain the lack of precise correlation of symptom classification with the pulmonary artery wedge pressure with exercise. This is consistent with previous studies suggesting that symptoms are subjective and may be difficult to assess.

### Findings in Asymptomatic or Mildly Symptomatic Aortic Regurgitation

This group of aortic regurgitation patients had several interesting characteristics. Only three had third heart sounds. All had left ventricular hypertrophy by ECG. Cardiothoracic ratios ranged from 0.4 to 0.67. The majority of patients had normal or near-normal pulmonary artery wedge pressures at rest and the majority had elevated pulmonary artery wedge pressures at peak exercise. In 11 of the 20 patients, the ejection fraction fell by 0.05 or more during exercise, even though they were minimally symptomatic or asymptomatic, which is similar to previous observations. As a group, they exercised as well as a group of control patients of similar age in terms of work load achieved and peak oxygen uptake.

### Correlates of the Exercise Pulmonary Artery Wedge Pressure

Aortic regurgitation patients were stratified based on an objective measure of cardiac performance, the level to which the pulmonary artery wedge pressure rose during exercise. Previous studies have suggested that the normal response is no change or a decrease in left ventricular filling pressures with exercise. Using this criterion, only three patients had a normal pulmonary artery wedge pressure response to exercise. However, in another study, a normal left atrial pressure at rest was 9.8 ± 2.3 mm Hg (mean ± SD), with a 2-SD upper limit of 14.4 mm Hg. Therefore, a peak exercise pulmonary artery wedge pressure less than 15 mm Hg may be consistent with reasonable cardiac performance during exercise in group 1, and a pulmonary artery wedge during exercise of 15 mm Hg or more is consistent with abnormal left ventricular function in group 2. Although this criterion may define a subset of patients with left ventricular dysfunction, we have no data to suggest that this criteria has prognostic value in aortic regurgitation in terms of the development of severe symptoms, irreversible left ventricular dysfunction or death.

Our study demonstrated that the absolute rest and exercise ejection fraction correlated with the exercise pulmonary artery wedge pressure, whereas the change in ejection fraction with exercise did not. This is consistent with the work of Borer et al., who suggested that absolute lower limits rather than the change of ejection fraction from rest to exercise be used to define a normal ejection fraction in aortic regurgitation. In fact, since the mean change in ejection fraction with exercise in groups 1 and 2 was similar, the correlation of the exercise ejection fraction with the pulmonary artery wedge pressure was in part due to differences in the resting value. Therefore, the rest ejection fraction...
alone was a better correlate of left ventricular filling pressures than the change with exercise. The change in ejection fraction with exercise may not correlate with exercise pulmonary artery wedge pressure in aortic regurgitation for several reasons. First, exercise is a complex intervention with varying preload, afterload and contractile stimulation, and different patients may exercise in different ways in terms of the degree of change in these variables. Second, aortic regurgitation is characterized by a reduction in the amount of regurgitation during exercise. This has been shown in previous catheterization studies" and is consistent with our finding of a falling regurgitant index during exercise. Because aortic regurgitation represents an increased preload and afterload, when the degree of regurgitation diminishes, the loading conditions of the left ventricle are changed, and this may also affect ejection fraction. Third, the pulmonary artery wedge pressure may increase for reasons other than those related to reduced left ventricular systolic function. It may increase because of a relatively noncompliant, hypertrophied left ventricle or clinically unsuspected mitral regurgitation during exercise. Recently, Eichorn et al. showed that left ventricular relaxation in aortic valve disease may be diminished and that the extent of the diminution is not related to systolic function of the left ventricle. Abnormal diastolic properties of the left ventricle can elevate pulmonary artery wedge pressure. These factors may explain the findings in patients 13, 15 and 17 in group 2, who had normal or nearly normal rest and exercise ejection fractions and high exercise pulmonary artery wedge pressures.

The rest end-systolic volume was also a good predictor of exercise pulmonary artery wedge pressure in aortic regurgitation. This is consistent with previous studies that have suggested that the end-systolic size is useful in identifying left ventricular dysfunction in these patients. However, the method for radionuclide end-systolic volume, whether derived using a geometric or counts approach, is complex and normal values appear to vary from institution to institution. Therefore, the particular values generated in this study may not be comparable to those from other institutions that use different methods. This limits the widespread application of this variable to assess left ventricular function in aortic regurgitation.

Another correlate of the exercise pulmonary artery wedge pressure was the exercise to rest pulmonary blood volume ratio. This is consistent with previous work from our laboratory suggesting that the pulmonary blood volume ratio is a reflection of exercise-
TABLE 3. Comparison of Aortic Regurgitation Patients in Relation to the Exercise Pulmonary Artery Wedge Pressure

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Ex PAWP &lt; 15 mm Hg (n = 8)</th>
<th>Group 2 Ex PAWP ≥ 15 mm Hg (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32±10</td>
<td>47±11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sex (no. of males)</td>
<td>5(63%)</td>
<td>9(75%)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>5(63%)</td>
<td>3(25%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>AVR</td>
<td>1(13%)</td>
<td>10(83%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CT ratio</td>
<td>0.52±0.05</td>
<td>0.55±0.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

Rest data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Ex PAWP &lt; 15 mm Hg (n = 8)</th>
<th>Group 2 Ex PAWP ≥ 15 mm Hg (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>72±12</td>
<td>87±14</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>150±28</td>
<td>164±23</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen uptake (ml/kg/min)</td>
<td>4.0±1.0</td>
<td>3.5±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>EF</td>
<td>0.64±0.08</td>
<td>0.49±0.13</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>EDV (ml/m²)</td>
<td>105±27</td>
<td>146±46</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ESV (ml/m²)</td>
<td>38±13</td>
<td>79±36</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SV (ml/m²)</td>
<td>67±19</td>
<td>68±19</td>
<td>NS</td>
</tr>
<tr>
<td>RI</td>
<td>4.0±2.4</td>
<td>3.2±1.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Exercise data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Ex PAWP &lt; 15 mm Hg (n = 8)</th>
<th>Group 2 Ex PAWP ≥ 15 mm Hg (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>152±24</td>
<td>151±12</td>
<td>NS</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>217±42</td>
<td>225±36</td>
<td>NS</td>
</tr>
<tr>
<td>Peak work load (W)</td>
<td>113±30</td>
<td>85±23</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Oxygen uptake (ml/kg/min)</td>
<td>24.9±5.1</td>
<td>16.6±4.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>EF</td>
<td>0.63±0.10</td>
<td>0.40±0.18</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Change in EF with exercise</td>
<td>-0.01±0.10</td>
<td>-0.08±0.09</td>
<td>NS</td>
</tr>
<tr>
<td>RI</td>
<td>2.7±1.0</td>
<td>2.5±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>PBV ratio</td>
<td>1.11±0.13</td>
<td>1.24±0.08</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Abbreviations: AVR = aortic valve replacement; BP = systolic blood pressure; CT ratio = cardiothoracic ratio; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HR = heart rate; NYHA = New York Heart Association class; PBV = pulmonary blood volume; RI = regurgitant index; SV = stroke volume.

induced left ventricular dysfunction in terms of increases in pulmonary artery wedge pressure.39 The four patients who had a normal pulmonary blood volume ratio (less than 1.06) were the only patients who had a pulmonary artery wedge pressure at peak exercise of less than 10 mm Hg. In the other 16 patients, the pulmonary blood volume ratio did not correlate with the exercise pulmonary artery wedge pressure. In aortic regurgitation, therefore, it appears to be a sensitive measurement, but the degree of elevation of the pulmonary blood volume ratio does not predict the degree

FIGURE 1. Individual rest and exercise (EX) ejection fraction values for patients in group 1 (left) and group 2 (right). All five patients with a rest ejection fraction below 0.50 were in group 2 (exercise pulmonary artery wedge pressure [PAWP] of 15 mm Hg or more). Excluding these five patients, the remaining patients were evenly distributed between the two groups.

FIGURE 2. Correlation of exercise pulmonary artery wedge pressure (PAWP) with peak oxygen consumption for all 20 patients with severe aortic regurgitation (r = -0.78, p < 0.01).
of elevation of the pulmonary artery wedge pressure during exercise.

Age was the only clinical variable that correlated with the exercise pulmonary artery wedge pressure by multiple regression analysis. This is similar to previous observations that age may be a factor in the ability to tolerate aortic regurgitation. Associated coronary artery disease, which was not present in our patients, does not appear to explain this observation. Perhaps this is a reflection of the chronicity of the disease slowly producing fibrotic changes in the myocardium. Age-related abnormalities in cardiac contraction, ventricular relaxation and peripheral resistance occur in some patients, which would impair the ability of older patients to tolerate severe aortic regurgitation. Our finding is similar to the association of age and the development of congestive heart failure in another left-sided volume overload lesion, coronary arteriovenous fistula.

**Relationship of Oxygen Uptake to Exercise Pulmonary Artery Wedge Pressure**

Of all the variables studied, the best correlate of the exercise pulmonary artery wedge pressure in aortic regurgitation was peak oxygen uptake. No other measurement added significantly to the predictive value of this measurement using multiple regression analysis. Peak oxygen uptake reflects the integrity of the cardiovascular system in terms of its ability to adequately deliver oxygen to the working muscles. The three prime determinants of peak oxygen uptake are central cardiac output, the ability to shift regional cardiac output to the working muscles, and peripheral oxygen extraction. Patients with heart failure (increased pulmonary artery wedge pressure) have a lower capacity to deliver oxygen peripherally than patients who have less severe heart disease. The precise mechanism for the lower systemic oxygen uptake in these patients is complex. It may, in part, be due to a relatively reduced forward cardiac output response to exercise in these patients. This is consistent with the lower ejection values in patients with a lower peak oxygen uptake. In addition, the peak oxygen uptake may be reduced by reflex vasoconstriction or inability to adequately vasodilate, which may occur in patients with poor cardiac compensation (those in whom pulmonary artery wedge rises with exercise). The resulting reduced diversion of cardiac output to the working muscles and lower peak oxygen uptake may occur independent of reductions in central cardiac output, which may explain why peak oxygen uptake was a better correlate of exercise pulmonary artery wedge pressure than ejection fraction.

The exercise level achieved also correlated with the exercise pulmonary artery wedge pressure. Although peak oxygen uptake is relatively simple to measure, the equipment may not be available at all institutions. Therefore, the use of the level of exercise on a standard exercise protocol may be an alternative method of approximating peak oxygen uptake in aortic regurgitation patients.

Although a peak oxygen uptake value of 20 ml/min/kg appeared to separate the groups in this study, we caution against establishing a specific oxygen uptake criterion for decision making in aortic regurgitation. This is because peak oxygen uptake is not only determined by the status of the heart, but is also affected by fitness, age, sex, and other factors. However, in the same patient, maximal oxygen uptake is reproducible and changes minimally from year to year. Therefore, that this measurement may be used serially to follow patients and the presence of a higher peak oxygen uptake is reassuring in terms of establishing the adequacy of left ventricular function in an individual patient with aortic regurgitation.

**Clinical Implications**

Asymptomatic or minimally symptomatic patients with severe aortic regurgitation may have nearly normal or severely abnormal left ventricular performance in terms of the exercise pulmonary artery wedge pressure. The absolute ejection fraction value at rest correlates with left ventricular performance, as does the peak exercise value; however, the change in ejection fraction during exercise itself does not. Cardiotoracic ratio, ECG left ventricular hypertrophy and the presence of a third heart sound are unrelated to the exercise pulmonary artery wedge pressure. Also, exercise capacity as measured by peak oxygen uptake correlates well with the exercise pulmonary artery wedge pressure, and therefore is a noninvasive indicator of left ventricular function in patients with aortic regurgitation. If subsequent natural history studies suggest that a lower peak oxygen uptake predicts an adverse clinical course, then it may be valuable for following aortic regurgitation patients serially.

**Acknowledgment**

The authors thank Barry Callahan, William Shea and Maureen McCarthy for their technical assistance and Janice Cahill for her secretarial assistance in the preparation of this manuscript.

**References**

patients with aortic regurgitation and patients with aortic stenosis. Circulation 59: 1190, 1974


38. Romhilt DW, Estes EH Jr: A point score for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 75: 752, 1968


52. Boucher CA: Radionuclide assessment of ventricular function. In Noninvasive Cardiac Imaging, edited by Morganroth J, Parisi AF,
Significance of Left Ventricular Outflow Tract Cross-sectional Area in Hypertrophic Cardiomyopathy: A Two-dimensional Echocardiographic Assessment

PAOLO SPIRITO, M.D., AND BARRY J. MARON, M.D.

SUMMARY The morphologic determinants of subaortic obstruction in patients with hypertrophic cardiomyopathy are not completely understood. To define the relation between left ventricular outflow tract orifice size and presence or absence of subaortic obstruction, we studied 65 patients with hypertrophic cardiomyopathy and 16 normal controls by quantitative two-dimensional echocardiography. Left ventricular outflow tract area was measured at the onset of systole in the short-axis view in the stop-frame mode. Left ventricular outflow tract area was significantly smaller in patients with hypertrophic cardiomyopathy and subaortic obstruction (2.6 ± 0.7 cm²) than in patients without obstruction (5.9 ± 1.6 cm², p < 0.001). Twenty of 21 patients with obstruction had a left ventricular outflow tract area smaller than 4.0 cm², whereas 28 of 30 patients without obstruction had a left ventricular outflow tract area of 4.0 cm² or greater. The outflow tract area in patients with provokable obstruction (4.6 ± 1.6 cm²) was intermediate between the areas of patients with and without obstruction. Left ventricular outflow tract area was significantly smaller in patients with hypertrophic cardiomyopathy (4.6 ± 2.0 cm²) than in normal subjects (10.4 ± 1.2 cm², p < 0.001).

We conclude that the cross-sectional outflow tract area is closely related to the presence or absence of subaortic obstruction in patients with hypertrophic cardiomyopathy. Hence, the size of the outflow tract at the level of the mitral valve appears to be of major pathophysiologic significance in producing obstruction in these patients.

HYPERTROPHIC CARDIOMYOPATHY (HCM) has varied clinical and morphologic expressions. Obstruction to left ventricular outflow may be present under basal conditions or with provocative interventions, or may be absent.1-4 The mechanism by which subaortic obstruction occurs in HCM is not definitively known, but substantial data support the view that obstruction is produced by systolic anterior motion of the mitral valve.5-13 The factors responsible for this particular mitral valvular motion are not entirely understood. Some investigators have suggested that hydrodynamic forces generated by a high-velocity blood flow during ejection into a narrowed left ventricular outflow tract cause the mitral valve leaflets to move anteriorly and touch the ventricular septum.14, 15

Wide-angle, two-dimensional echocardiography permits accurate visualization of the anatomic configuration of the left ventricular outflow tract. Therefore, using two-dimensional echocardiography to measure the cross-sectional area of the outflow tract, we investigated the significance of left ventricular outflow tract size in determining the presence or absence of subaortic obstruction in patients with HCM.

Materials and Methods

Patient Selection

The case records of the Echocardiography Laboratory between February 1979 and April 1982 were reviewed. Sixty-five patients with HCM met the following criteria and were selected for this study: a technically satisfactory two-dimensional echocardiogram, i.e., clear recognition of the endocardial borders of the left ventricular wall in the short-axis view at the level of the mitral valve and clear delineation of the endocardial borders of ventricular septum in the long-axis view; and a cardiac catheterization that showed a peak systolic subaortic gradient that allowed classification of the patient into one of three groups: obstructive — basal subaortic gradient greater than 50 mm Hg (21 patients); provokable — gradient of 0 or less than 30 mm Hg under basal conditions and greater than 50...
Exercise testing in asymptomatic or minimally symptomatic aortic regurgitation: relationship of left ventricular ejection fraction to left ventricular filling pressure during exercise.

C A Boucher, R A Wilson, D J Kanarek, A M Hutter, Jr, R D Okada, R R Liberthson, H W Strauss and G M Pohost

_Circulation_. 1983;67:1091-1100
doi: 10.1161/01.CIR.67.5.1091

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/67/5/1091