PATHOPHYSIOLOGY AND NATURAL HISTORY

AORTIC REGURGITATION

Cardiovascular response to dynamic exercise in patients with chronic symptomatic mild-to-moderate and severe aortic regurgitation

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ABSTRACT Fifteen patients with symptomatic mild-to-moderate and severe chronic aortic regurgitation (AR) performed supine bicycle exercise while measurements of rest and exercise hemodynamics and left ventricular function were obtained. A continuous Doppler method was used to determine the change in distribution of total left ventricular stroke volume between forward stroke volume and regurgitant volume (RgV) with exercise. The pulmonary arterial wedge pressure (PAWP) was lower in the mild-to-moderate AR group than in the severe AR group at rest (8 ± 1.2 vs 19 ± 3.6 mm Hg, p = 0.01) and during exercise (15 ± 3.9 vs 30 ± 4.3 mm Hg, p = .02). In all patients there were increases in heart rate (78 ± 4 to 96 ± 5 beats/min, p < .001), forward stroke volume (41 ± 2 to 46 ± 2 ml/m²), and the cardiac index (3.1 ± 0.2 to 4.4 ± 0.3 liters/min-m², p < .001), despite a fall in total left ventricular stroke volume index from 84 ± 5 to 76 ± 5 ml/m² (p = .03). The systemic vascular resistance (SVR) decreased with exercise from 1277 ± 72 to 1031 ± 64 dynes-sec/cm⁵ (p < .001), and the RgV and regurgitant fraction (RgF) both decreased with exercise from 43 ± 5 ml/m² to 30 ± 4 ml/m² (p = .002) and 0.50 ± 0.03 to 0.37 ± 0.03 (p < .001), respectively. Left ventricular ejection fraction increased on exercise from 0.51 ± 0.03 to 0.55 ± 0.03 (p = .02) for the group, but it either decreased or failed to increase by at least 0.05 in seven of 13 patients. The change in ejection fraction on exercise was directly related to the change in SVR (r = .80, p < .001). We conclude that: (1) in patients with mild-to-moderate AR, the PAWP is generally normal at rest and exercise, (2) in most of those with severe AR, the PAWP is elevated at rest and increases significantly with exercise, which is the likely mechanism for dyspnea on exertion in these patients, (3) the cardiac index in both groups is normal at rest and increases on exercise, (4) the increase in cardiac output results from both an increased heart rate and forward stroke volume, (5) the increase in forward stroke volume results from reductions of RgV and RgF, (6) the RgV and RgF are decreased due to a decreased SVR, and (7) the ejection fraction response to exercise is variable and correlates best with changes in SVR with exercise. Circulation 73, No. 1, 62–72, 1986.

DETERMINATION OF the optimum time for surgical intervention in patients with chronic symptomatic aortic regurgitation (AR) is an area of much clinical concern.1–7 The responses of either left ventricular filling pressure and of left ventricular ejection fraction to dynamic exercise as well as exercise capacity have been suggested as three criteria that might be of value in making this determination.8–10 The effects of dynamic exercise in patients with AR are not fully understood, especially regarding the relative effects of changes in heart rate, preload, afterload, and left ventricular contractility.11–14 Reduction of systemic vascular resistance (SVR) with arteriolar dilators has been shown to favorably affect the redistribution of total left ventricular stroke volume such that forward stroke volume increases at the expense of regurgitant volume.15 We reasoned that a decrease of SVR with dynamic exercise may similarly increase forward stroke volume at the expense of regurgitant volume (RgV).

We therefore determined, in symptomatic patients...
with mild-to-moderate and severe AR, the effects of
dynamic exercise on (1) Intracardiac and intravascular
pressures and cardiac output, (2) the redistribution
of total left ventricular stroke volume into forward stroke
volume and RgV and its relationship to changes in the
systemic vascular resistance (SVR), and (3) changes in
left ventricular ejection fraction.

Methods

Twenty-one patients with chronic symptomatic mild-to-
moderate and severe AR who were scheduled for diagnostic cardiac
catheterization were initially considered for participation in the
study. All patients had cardiac catheterization that included left
ventricular, ascending aortic, and coronary angiography. The exercise protocol with Doppler studies was performed within 48
hr of the cardiac catheterization. Left ventricular ejection fac-

tion at rest and during supine bicycle exercise was obtained by
equilibrium-gated radionuclide angiography.

Fifteen patients had technically adequate Doppler studies
both at rest and during supine bicycle exercise, and these constit-
tute the final study group. There were 11 men and four women
with a mean age of 49 (range 25 to 73) years. They were divided
into two groups based on the size of the left ventricle as deter-
mined at angiography. The six patients with a left ventricular
end-diastolic volume equal to or less than 112 ml/m² were
considered to have mild-to-moderate AR, while nine patients
with end-diastolic volumes greater than 112 ml/m² were con-
sidered to have severe AR. The upper limit of "normal" for left
ventricular end-diastolic volume is 112 ml/m² (mean + 2SD; 86
± 26 ml/m²) and we arbitrarily separated the patients into two
groups based on this value. There were four men and two
women, 54 ± 6 years old (mean ± SEM), in the mild-to-
moderate AR group and eight men and one woman, 45 ± 6 years old,
in the severe AR group. All patients continued on their precath-
eterization medications during the Doppler exercise and radio-
uclide studies. Five of the nine patients with severe AR were
taking a combination of digoxin and furosemide and a sixth was
taking digoxin alone. One patient in the severe AR group and
two in the mild-to-moderate AR group were taking α-methyl-
dopa for hypertension. The clinical, electrocardiographic, chest
x-ray, echocardiographic, and treadmill exercise characteristics
of the patients in each group are listed in table 1. All were in
New York Heart Association functional classes II or III. 1,3 The
cause of the AR was rheumatic in one patient with mild-to-
moderate AR who had previously undergone successful mitral
valve commissurotomy (postoperative mitral valve area = 1.4
cm²). Two patients with severe AR had prior endocarditis, and
one of these also had trace mitral regurgitation. The cause of the
AR was unknown in the remaining 12 patients. No patient had
aortic stenosis and only one had trace mitral regurgitation.

Exercise hemodynamics. The patients performed supine bi-
cycle exercise beginning at a load of 25 W/sec with increases of
25 W/sec every 3 min. Rest and exercise hemodynamics were
measured with a pulmonary artery balloon floatation right heart
catheter. Resting measurements were obtained twice, once 15
min before and again immediately before the exercise. The sec-
ond measurement was used as a control value. Right atrial,
pulmonary arterial and pulmonary arterial wedge (PAWP) pres-
ures were recorded with a strip-chart recorder. The brachial
arterial pressure was measured by sphygmomanometer. Pres-
sure measurements were made in patients at rest with their legs
in the exercise position and again at the onset of symptoms
during exercise or when the heart rate reached 130 beats/min; in
our experience Doppler determinations at heart rates greater

<table>
<thead>
<tr>
<th>TABLE 1 Patient characteristics</th>
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<tr>
<td></td>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Male/female</td>
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<tr>
<td>Age (years, mean ± SEM)</td>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
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<tr>
<td>Functional class</td>
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<tr>
<td>II</td>
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<tr>
<td>III</td>
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<tr>
<td>Pulse pressure (mm Hg)</td>
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<tr>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>(Romhilt-Estes ECG criteria)</td>
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<tr>
<td>Echocardiographic dimensions (mm)</td>
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<tr>
<td>Left ventricular diameter,</td>
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<tr>
<td>end-diastole</td>
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<tr>
<td>Left ventricular diameter,</td>
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<tr>
<td>end-systole</td>
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<tr>
<td>Angiographic grade of AR</td>
</tr>
<tr>
<td>2+</td>
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<tr>
<td>3+</td>
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<tr>
<td>4+</td>
</tr>
<tr>
<td>Angiographic left ventricular</td>
</tr>
<tr>
<td>end-diastolic volume index</td>
</tr>
<tr>
<td>(ml/m²)</td>
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<tr>
<td>treadmill exercise, Bruce</td>
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<tr>
<td>protocol (min)</td>
</tr>
</tbody>
</table>

ECG = electrocardiographic.

*p < .01 for comparisons between the two groups.

This would be an expected finding (please see Methods).

Doppler study. A computerized continuous-wave Doppler
system (Ultracom, Lawrence Medical Systems, Inc.) was used
to calculate the total left ventricular output at rest and during
exercise. These calculations were based on the cross-sectional
area of the aortic root and the velocity of blood flow at that
location. The aortic root cross-sectional area was calculated by
the computer from the diameter of the aortic root, which was
previously measured with the use of two-dimensionally directed
M mode echocardiogram (Advanced Technology Laboratories,
Inc.) at a level just above the sinuses of Valsalva. The velocity
of blood flow was measured with a continuous-wave Doppler
probe that was attached to the computer and positioned in the
suprasternal notch and directed caudal. Great care was taken to
obtain the highest possible velocity determination to ensure
alignment of the Doppler signal as parallel as possible with that
of blood flow. Each measurement was made immediately be-
fore each thermodilution measurement of cardiac output. The
mean of three to five measurements was used for subsequent
calculations.
Data from our and other laboratories have shown this technique to be reasonably accurate and reproducible with experience in selected patients. In a previous study from our laboratory, interobserver variability was examined by comparison of measurements made by two observers in 29 volunteer subjects; the correlation was very good, with a correlation coefficient of \( r = .98 \) (\( p < .001 \)). Similarly, in 18 volunteer subjects, intraobserver variability was very small, with a correlation coefficient of \( r = .97 \) between two measurements made by the same observer.

**Derived values.** The differences between the total left ventricular cardiac output (LVO, liters/min) determined by the Doppler technique and the forward cardiac output (CO, liters/min) measured by thermodilution is the RgV (liters/min):

\[
RgV = LVO - CO
\]

This value was calculated for both rest and exercise measurements. The values for left ventricular stroke volume (ml/min), forward stroke volume (ml/min), and \( RgV/\text{beat} \) (ml/min) were obtained by dividing the corresponding output value by the heart rate. Values were indexed by dividing by the patient’s body surface area. Mean systemic arterial pressure (MAP) was derived from the formula

\[
\text{MAP (mm Hg)} = D + \frac{(S-D)}{3}
\]

where \( S \) is the peak systolic and \( D \) the diastolic pressure (in mm Hg). SVR (dynes-sec/cm\(^5\)) was calculated as

\[
\text{SVR} = \frac{\text{MAP} - \text{RAP}}{\text{CO}} \times 80
\]

where RAP is mean right atrial pressure and 80 is the conversion factor. Regurgitant fraction (RgF) was calculated as

\[
RgF = \frac{RgV/\text{beat}}{\text{LVSV}}
\]

**Equilibrium-gated radionuclide angiography.** Red blood cells were labeled in vivo with 7.5 mg of stannous pyrophosphate followed by 20 to 25 mCi \(^{99m}\text{Tc} \) pertechnetate. A Searle Pho/Gamma V camera was positioned in the left anterior oblique projection. For each ventriculogram, data were acquired over a 2 min period at 16 frames/cycle. Data were processed with an Informatek computer system utilizing variable region of interest, semiautomated computer edge detection, and computer-determined background. The left ventricular ejection fraction was calculated as

\[
\text{EF} = \frac{\text{end-diastolic minus end-systolic counts}}{\text{end-diastolic counts}}
\]

after correction was made for background counts. Patients performed supine bicycle exercise at an initial load of 25 W with increments of 25 W every 3 min. Data were acquired during the last 2 min of each stage. Heart rate and brachial arterial pressure by sphygomanometer were also measured at the end of each stage. Thirteen of the 15 patients had technically adequate measurements of left ventricular ejection fraction at both rest and exercise. In the other two patients, measurement of ejection fraction during exercise was considered inaccurate due to a combination of either poor labeling of the red cell pool or to high background counts coupled with excessive motion of the patient during the exercise study.

**Statistics.** All group values are expressed as the mean ± SEM. The changes from rest to exercise were compared by the paired \( t \) test. Changes were considered significant at the \( p < .05 \) level. Correlations between parameters were tested by linear regression.

**Results**

**Ejection fraction response to exercise.** The ejection fraction at rest for the patients with mild-to-moderate AR (0.64 ± 0.05, range 0.54 to 0.74) was higher than in patients with severe AR (0.45 ± 0.03, range 0.30 to 0.55; \( p = .02 \)). For the entire group, the ejection fraction was 0.51 ± 0.03 at rest and increased to 0.55 ± 0.03 with exercise (\( p = .02 \); figure 1); the ejection fraction failed to increase by at least 0.05 in six pa-

![FIGURE 1](http://circ.ahajournals.org/issue/1/1/CIRCULATION.1.1.DC1.png)
tients and decreased by 0.10 in another. The failure to increase the ejection fraction by at least 0.05 during supine exercise was considered an “abnormal” response; the rationale and derivation of this value has previously been reported by others. Of six patients who had a “normal” increase in ejection fraction of at least 0.05 with exercise, three had a resting ejection fraction of less than 0.50, and five of seven with an “abnormal” ejection fraction response to exercise had a resting ejection fraction greater than 0.50. Thus, 10 of the 13 patients had either a reduced ejection fraction at rest, an “abnormal” response to exercise, or both.

**Hemodynamic measurements at rest.** There was no significant difference between the two resting measurements of heart rate, intracardiac or intravascular pressure, and cardiac output or systemic vascular resistance. Although as previously noted, studies in our laboratory suggest that intraobserver variability for the measurement of cardiac output using this continuous Doppler technique in subjects without AR is very small, there have been no published observations concerning the reproducibility of measurements in patients with AR. Therefore, in the 10 patients in whom duplicate resting Doppler measurements were made, calculated regurgitant volume and fraction could be compared and these measurements were found to be highly reproducible (figure 2, A and B).

**Hemodynamic response to exercise (table 2).** The changes in heart rate, mean systemic arterial pressure, cardiac index, and systemic vascular resistance were similar between the mild-to-moderate and severe AR groups. The patient in the severe AR group who had the lowest SVR at rest (870 dynes-sec/cm²) had an increase of SVR to 926 dynes-sec/cm² during exercise (figure 3).

Mean PAWP increased with exercise in both groups; however, the PAWP was significantly higher in the severe AR group both at rest (19 ± 3.6 vs 8 ± 1.2 mm Hg, p = .01) and during exercise (30 ± 4.3 vs 15 ± 3.9 mm Hg, p = .02; table 2 and figure 4). The mean PAWP at rest was less than 15 mm Hg in all five patients with mild-to-moderate AR in whom it was measured, while it was greater than 15 mm Hg in five of nine patients in the severe AR group. During exercise, the PAWP exceeded 15 mm Hg in two of the five patients with mild-to-moderate AR and eight of nine patients with severe AR. The higher PAWP during exercise in the patients with severe AR correlated with the frequency of exertional dyspnea in this group (table 1). Despite the large increases in PAWP with exercise in two of the patients with mild-to-moderate AR, the response for the group varied over a wide range and the change failed to reach statistical significance (p = .07; figure 4). The mean pulmonary arterial pressures reflected the levels and changes in PAWP.

With exercise, there was a decrease in the total left
TABLE 2
Hemodynamic changes with exercise (mean ± SE; n = 15 except where indicated)

<table>
<thead>
<tr>
<th></th>
<th>All AR (n = 15)</th>
<th>Mild-to-moderate AR (n = 6)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78 ± 4</td>
<td>96 ± 5</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>87 ± 3</td>
<td>102 ± 4</td>
</tr>
<tr>
<td>Mean PAWP (mm Hg)</td>
<td>15 ± 2.7</td>
<td>24 ± 3.6</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>25 ± 3.3</td>
<td>36 ± 4.4</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>4 ± 0.7</td>
<td>8 ± 1.8</td>
</tr>
<tr>
<td>Cardiac index (l/min-m²)</td>
<td>3.1 ± 0.2</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes-sec/cm²)</td>
<td>1277 ± 72</td>
<td>1031 ± 64</td>
</tr>
<tr>
<td>Cardiac index (1/min-m²)</td>
<td>3.1 ± 0.2</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>Total left ventricular output (l/min-m²)</td>
<td>6.4 ± 0.5</td>
<td>7.4 ± 0.7</td>
</tr>
<tr>
<td>RgV index/minute (1/min-m²)</td>
<td>3.3 ± 0.4</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>Total left ventricular stroke volume index (ml/m²)</td>
<td>84 ± 5</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>Forward stroke volume index (ml/m²)</td>
<td>41 ± 2</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>RgV index/beat (ml/m²)</td>
<td>43 ± 5</td>
<td>30 ± 4</td>
</tr>
<tr>
<td>RgF</td>
<td>0.50 ± 0.03</td>
<td>0.37 ± 0.03</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.51 ± 0.03</td>
<td>0.55 ± 0.03</td>
</tr>
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</table>

n = 14; n = 13.

ventricular stroke volume index from 84 ± 5 to 76 ± 5 ml/m² (p = .03) and an increase in the forward stroke volume from 41 ± 2 to 46 ± 2 ml/m² (p < .001; table 2, figure 5). The calculated RgV/beat decreased from 43 ± 5 ml/m² to 30 ± 4 ml/m² with exercise (p = .002), and RgF decreased from 0.50 ± 0.03 to 0.37 ± 0.03 (p < .001). A small decrease in RgV index per minute from 3.3 ± 0.4 to 2.9 ± 0.5 liters/min-m² was not significant (p = .17); however, forward cardiac index increased from 3.1 ± 0.2 to 4.4 ± 0.3 liters/min-m² (p = .02).

**FIGURE 3.** Changes in heart rate, cardiac index, and SVR with exercise. Symbols are as in figure 1. Heart rate and cardiac index increased significantly, while SVR decreased significantly.

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TABLE 2 (Continued)

<table>
<thead>
<tr>
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<th>Severe AR (n = 9)</th>
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<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>p value</td>
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<tr>
<td>80 ± 6</td>
<td>98 ± 7</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>86 ± 4</td>
<td>100 ± 4</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>19 ± 3.6</td>
<td>30 ± 4.3</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>28 ± 4.2</td>
<td>39 ± 6.0</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>4 ± 1.1</td>
<td>10 ± 2.8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>3.1 ± 0.3</td>
<td>4.3 ± .5</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>1238 ± 96</td>
<td>1007 ± 103</td>
<td>.004</td>
<td></td>
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<tr>
<td>3.1 ± 0.3</td>
<td>4.3 ± 0.5</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>6.8 ± 0.8</td>
<td>7.5 ± 1.1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>3.7 ± 0.6</td>
<td>3.2 ± 0.7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>87 ± 7</td>
<td>76 ± 7</td>
<td>.02</td>
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</tr>
<tr>
<td>40 ± 3</td>
<td>44 ± 3</td>
<td>.002</td>
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<tr>
<td>47 ± 5</td>
<td>32 ± 5</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>0.53 ± 0.02</td>
<td>0.40 ± 0.04</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>0.45 ± 0.03</td>
<td>0.51 ± 0.04</td>
<td>.005</td>
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min-m² (p < .001) and total left ventricular cardiac index increased from 6.4 ± 0.5 to 7.4 ± 0.7 liters/min-m² (p = .005).

The change in left ventricular ejection fraction from rest to exercise was compared with the change in other hemodynamic parameters. No correlation was found between change in ejection fraction and the change in heart rate, mean arterial pressure, mean PAWP, or RgV (r = −.02, −.02, −.04, and .16, respectively). A trend toward a direct relationship with change in RgF was not significant (r = .48, p = .10). Despite the lack of correlation between change in heart rate and ejection fraction, there was a trend toward an inverse relationship between percent change in cardiac index and ejection fraction (r = −.51, p = .07).

There was a significant correlation between the percent change in stroke volume index and the change in ejection fraction (r = −.86, p < .001; figure 6). The negative slope of the relationship suggests that greater increases in forward stroke volume were associated with smaller increases in ejection fraction. Among the measured parameters that might have affected the stroke volume, such as heart rate, mean arterial pressure, and RgF (r = −.11, −.04, and .46, respectively), only the change in SVR correlated significantly with the change in ejection fraction (r = .80, p < .001, SEE = 119 dynes-sec/cm²; figure 7); the smaller increases in ejection fraction with exercise occurred in those patients who had a greater fall in SVR.

Discussion

The distinction between patients with symptomatic severe chronic AR from those with mild-to-moderate disease is of clinical importance in that surgery for
FIGURE 5. Changes in left ventricular stroke volume index (LVSV), forward stroke volume index (SV), regurgitant volume index per beat (RgV), and RgF with exercise. Symbols are as in figure 1. A small decrease in LVSV occurred, along with an increase in SV and a decrease in both RgV and in RgF.

FIGURE 6. Comparison of changes in the forward stroke volume index (SV), expressed as a percentage of the resting SV, and change in left ventricular ejection fraction with exercise. Symbols for individual patients are as in figure 1. The regression line is shown. Change in forward SV and ejection fraction have a strong inverse relationship. Individuals with the greater increase in SV had less of an increase or even a decrease in ejection fraction with exercise.
volume overload in patients with AR and reduction of left ventricular systolic function and in combination with clinical findings, may have predictive value for postoperative survival. No uniformly agreed upon criterion exists for separating mild-to-moderate from severe AR. We chose a value of 112 ml/m² for left ventricular end-diastolic volume to separate patients with severe AR from those with less severe disease; this value represents the mean plus 2 standard deviations for left ventricular end-diastolic volume in "normal" individuals. Chronic and more severe regurgitation tends to be associated with greater dilatation of the left ventricular chamber, provided that systolic left ventricular pump function is maintained. However, it has to be recognized that in an individual patient it is difficult to know to what extent the ventricle is enlarged without knowledge of ventricular size before the onset of the AR. Therefore, the group of patients with left ventricular end-diastolic volumes of less than 112 ml/m² likely includes some individuals with mild and some with moderate AR, whereas the group with ventricles that are clearly larger than normal more likely have severe AR. In fact, when we used this single parameter to try to separate the two groups, it became apparent that other clinical findings and noninvasive parameters tended to corroborate the impression that the larger ventricular size was associated with more severe AR (table 1).

The change in RgV and RgF with exercise is of interest. The development of a noninvasive technique for direct measurement of left ventricular output has made it possible to observe such changes. It has been demonstrated in our laboratory and others that use of the continuous-wave Doppler system to measure cardiac output in patients without AR is reasonably accurate at rest, during exercise, and after various interventions such as pacing or administration of vasodilating agents, with correlation coefficients of .86 or greater when compared with cardiac output measured by the thermodilution technique. The continuous-wave Doppler technique requires considerable skill and attention to careful measurement of the cross-sectional diameter of the aortic root. In addition, care is required in positioning the transducer in the suprasternal notch such that a strong, steady, and reproducible signal is obtained. This is especially important in patients with

\[ \Delta \text{SYSTEMIC VASCULAR RESISTANCE} \]

\[ \Delta \text{EJECTION FRACTION} \]

\[ r = 0.8 \]
\[ p < 0.001 \]
\[ \text{SEE} = 120 \]
\[ y = -370 + 2734x \]

**FIGURE 7.** Comparison of changes in SVR and those in ejection fraction. Symbols are as in figure 1. The regression line is shown. A correlation between change in SVR and that in ejection fraction is seen. Individuals with the greatest fall in SVR had lesser increases in ejection fraction with exercise.
AR in whom the high velocity of flow may result in considerable turbulence, although correct transducer placement should still result in an accurate measure of left ventricular output. Only data from those patients whose continuous-wave Doppler signal levels were reproducibly high on multiple determinations at both rest and exercise were included in this study. A decrease of signal level, which would result in underestimation of left ventricular output and left ventricular stroke volume, would also result in erroneous underestimation of RgV. Detectable loss of signal resulted in the exclusion of six of the 21 potentially eligible patients (29%). For this reason also, measurements were made at less than maximal exercise since very high flows resulted in a loss of signal level in some patients at higher levels of exercise. Measurement of left ventricular output allows calculation of RgV and RgF; comparison of such measurements between the two baseline determinations showed a high degree of reproducibility (figure 2).

When these symptomatic patients performed supine bicycle exercise to moderate levels of exertion, SVR decreased. At the same time, the RgF and RgV/beat decreased. The forward stroke volume increased while the total left ventricular stroke volume decreased. The RgV per minute showed no significant change. These findings are in concert with previous deceptions of the beneficial effects of reduction of SVR with hydralazine in patients with severe AR. Those data suggested that afterload reduction contributed to increases in cardiac index, stroke volume index, and a reduction of PAWP both at rest and during exercise. Other prior exercise studies have also been suggestive. However, each had one or more of the following problems: (1) they did not measure RgF; (2) patients studied had associated valvular diseases; or (3) they used inadequate techniques of measuring the regurgitation. We have demonstrated that patients with AR have a mechanism for increasing forward stroke volume during exercise without increasing total left ventricular stroke volume; they do so at the expense of the RgV.

The changes in RgV and RgF that we observed cannot be entirely accounted for by the effect of increased heart rate alone. Although there is a decrease in the duration of diastole with increased heart rate and a decrease in RgV/beat, the forward stroke volume also decreases with atrial pacing, and no change or fall in mean arterial or PAWP is seen. During incremental atrial pacing in dogs, Laniado et al. have shown that even though a decremental reduction in RgV/beat occurs, there is a decremental reduction of the forward stroke volume and of transmitial flow. Thus, increased cardiac output is due only to the increased number of beats per minute. Similar changes were observed by Judge et al. and Firth et al. during incremental atrial pacing in patients with AR in whom decreases in RgV/beat did not result in increases of forward stroke volume. These results contrast with our findings. Dynamic exercise in our patients with AR also resulted in a decrease in RgV/beat, but this was accompanied by an increase in forward stroke volume. This difference demonstrates that the observed effect is not due solely to the increase in heart rate.

The PAWP increased with exercise in our patients. However, the pressure at rest was greater than 15 mm Hg in five of nine patients with severe AR and in none of five patients with mild-to-moderate AR. The normal PAWP at rest is 9.8 ± 4.6 mm Hg (mean ± 2 SD); we therefore considered a PAWP less than 15 mm Hg normal. Dynamic exercise resulted in a pressure greater than 15 mm Hg in eight of the nine patients with severe AR (>20 in six) and in two of five patients with mild-to-moderate AR. The differences between the groups was significant both at rest and during exercise, a finding consistent with that of Boucher et al., who studied asymptomatic patients with AR. In our symptomatic patients, the greater incidence of exertional dyspnea in those with severe AR may be related to the greater frequency and degree of pressure elevation that was demonstrated during exercise. Similar to Boucher et al., we also did not find a correlation between the ejection fraction response to exercise and the change in PAWP.

At rest, the ejection fraction for the patients with mild-to-moderate AR was normal, while it was decreased below 0.50 in five of the nine patients with severe AR. With exercise, although a significant increase occurred for the group, the individual responses were variable and the direction and magnitude of change was not related to the resting ejection fraction or the severity of the AR.

The change in left ventricular ejection fraction with exercise has been used to detect left ventricular systolic dysfunction that is not apparent in the resting state. In the presence of coronary artery disease, the expected increase in ejection fraction may fail to occur, and a decrease in ejection fraction may even be seen if ischemia on exercise is significant. However, such a direct conclusion of myocardial dysfunction might not be warranted in the case of the patient with AR. Our study has shown that the body is able to redistribute the total left ventricular stroke volume through a reduction of SVR and increase forward stroke volume at the ex-
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pense of the RgF. In fact, in these patients, at a moderate level of exercise, the change in ejection fraction was directly related to the change in SVR; the patients with a fall or only a small increase in ejection fraction had the greatest gain in forward stroke volume by means of reduction of RgF. However, Shen et al. have recently presented evidence that exercise-induced changes in ejection fraction in patients with chronic AR are also correlated with the state of resting left ventricular function. Thus, ejection fraction on exercise appears to be dependent on at least two factors: changes in SVR and state of left ventricular function. Our findings suggest that (1) data about changes in ejection fraction in patients with AR cannot be interpreted for assessment of left ventricular function without knowledge about changes in SVR, and (2) great care must be used in drawing conclusions about left ventricular dysfunction from the ejection fraction response to exercise, especially if such conclusions are used in making the decision with regard to aortic valve replacement.

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References

32. Greenberg BJ, DeMots H, Murphy E, Rahimtoola S: Beneficial effects of hydralazine on rest and exercise hemodynamics in pa-
Erratum

In a recent article by McKay et al. (Circulation 72: 865, 1985), the bottom of figure 2 was inadvertently omitted. The figure should have appeared as below.

FIGURE 2. Change in CO over 12 hr after 50 mg oral hydralazine in patients with aortic regurgitation. Top. Individual baseline and peak effect CO. Middle. Mean changes over time. Bottom. Analyses of changes over time by $t$ test, ANOVA compared with a single baseline value (B), and ANOVA compared with spontaneous changes (SC).
Cardiovascular response to dynamic exercise in patients with chronic symptomatic mild-to-moderate and severe aortic regurgitation.

D T Kawanishi, C R McKay, P A Chandraratna, M Nanna, C L Reid, U Elkayam, M Siegel and S H Rahimtoola

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