PATHOPHYSIOLOGY AND NATURAL HISTORY
VALVULAR HEART DISEASE

Evaluation of relationship between myocardial contractile state and left ventricular function in patients with aortic regurgitation


ABSTRACT We studied the relationship between myocardial contractile state and left ventricular functional response to exercise in 14 asymptomatic patients with isolated moderate-to-severe aortic regurgitation and six control subjects. The slope of the systolic blood pressure—left ventricular end-systolic volume (pressure-volume) relationship determined by radionuclide ventriculography during angiotensin infusion was used as an indirect measure of myocardial contractility and was compared with left ventricular ejection fraction at rest and during both isometric handgrip and dynamic bicycle exercise. The slope of the pressure-volume relationship was significantly lower in patients with aortic regurgitation than in the control subjects (1.75 ± 0.57 vs 2.78 ± 0.42, p < 0.01). The slope correlated exponentially with resting ejection fraction and was linearly related to changes in left ventricular ejection fraction during both handgrip and bicycle exercise. In patients with aortic regurgitation, resting ejection fraction may overestimate myocardial function. The slope of the pressure-volume relationship measured during afterload stress and left ventricular ejection fraction response to exercise intervention more reliably reflect the degree of left ventricular dysfunction.


PATIENTS with aortic regurgitation may remain asymptomatic for many years even with significant left ventricular dysfunction³,⁴ and the optimal timing of aortic valve replacement is controversial. Left ventricular ejection fraction is often normal at rest,⁴ but may respond abnormally to exercise.⁵-⁹ The mechanism of the abnormal response is difficult to define because of markedly altered loading conditions in such patients.

The slope of end-systolic pressure-volume relationship has been shown to be a sensitive index of myocardial contractile state independent of preload.¹⁰-¹³ The utility of this measurement as an index of myocardial contractility in man has been enhanced since systolic blood pressure measured noninvasively can be substituted for left ventricular end-systolic pressure without significantly altering its validity.¹³-¹⁷ The purpose of this study was to determine the systolic blood pressure—left ventricular end-systolic volume (pressure-volume) relationship in patients with aortic regurgitation and to correlate this parameter with left ventricular performance during both isometric handgrip and dynamic bicycle exercise.

Methods

Study patients. Fourteen asymptomatic patients (13 men and one woman, mean age 36 years, range 24 to 44) with isolated moderate-to-severe aortic regurgitation were studied. Four patients had undergone cardiac catheterization and had aortic regurgitation of angiographic grade III out of IV, with no peak systolic pressure gradient, no mitral regurgitation, and normal coronary arteries. The remaining 10 patients had clinical signs of isolated moderately severe aortic regurgitation, with pulse pressure of more than 55 mm Hg and cardiomegaly on radiographs. In all 10 patients echocardiograms showed diastolic fluttering of the mitral valve, left ventricular end-diastolic dimension greater than 6.0 cm, aortic leaflet separation of more than 2.0 cm, and average diastolic wall thickness less than 1.1 cm. No patient had evidence of any other valve disease and none had angina or segmental wall motion abnormalities on radionuclide ventriculograms obtained at rest and during exercise. All patients were in sinus rhythm and none were on medication.

Six patients (five men and one woman, mean age 44 years, range 36 to 53) with angiographically normal left ventricular function and coronary arteries served as the control group. All had undergone previous testing because of atypical chest pain. None had evidence of valvular heart disease or were on medications and all were in sinus rhythm.

Written informed consent was obtained from all patients and

From the Hallstrom Institute of Cardiology, Department of Nuclear Medicine, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia.

Address for correspondence: Professor David T. Kelly, Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Camperdown N.S.W. 2050, Australia.

Received July 2, 1984; revision accepted Sept. 13, 1984.

Vol. 71, No. 1, January 1985
the procedure was approved by the Institutional Ethics Committee.

Exercise protocol

Handgrip exercise. All patients were studied while in a supine position. Baseline 12-lead electrocardiograms, cuff blood pressure, and gated radionuclide ventriculograms were obtained at rest. Each patient exerted 33% of maximal voluntary compressive force, as previously determined on a hand dynamometer (Martin, Vigometer), for 3 min. Patients were instructed to breathe normally and to avoid any Valsalva maneuver. Radionuclide counts were collected in the last 2 min of handgrip exercise. Serial 12-lead electrocardiograms were obtained every minute and duplicate readings of blood pressure determined from the opposite arm were recorded during the third minute of the handgrip exercise.

Bicycle exercise. Fifteen minutes after handgrip exercise each patient performed supine bicycle exercise on an exercise table (Atomic Products, NY) on which an electronically braked ergometer was mounted (Siemens Elema). Exercise was continuous, multistage, and symptom limited. The initial workload of 15 W was increased by 15 to 30 W every 3 min according to each patient’s exercise tolerance. The pedal speed was held at a constant rate of 60 rpm. Patients were verbally encouraged to exercise until peak tolerance. During exercise a 12-lead electrocardiogram was recorded every minute and duplicate cuff measurements of blood pressure and radionuclide count data were obtained during the last 2 min of each exercise level.

Pressure-volume relationships. After completion of the exercise study an 18-gauge cannula was inserted into right radial artery of each subject and blood pressure was monitored on a multichannel recorder (Electronics for Medicine, VR-12). After a resting period of 1 hr, 0.6 mg of atropine sulfate was injected intravenously over 3 min. This was done to minimize the baroreflex-mediated bradycardia that accompanied the infusion of the pressor agents. Ten to fifteen minutes later a baseline electrocardiogram, blood pressure, and a radionuclide ventriculogram were recorded.

Angiotensin (Hypertensin, Ciba) was administered in a 5 μg/ml solution. The infusion rate was started at 0.17 μg/min and adjusted so that the systolic blood pressure was increased stepwise by approximately 10 mm Hg. At each increase in monitored pressure, a constant infusion was maintained for 3 to 5 min followed by 2 min of radionuclide ventriculographic examination. A minimum of 2 million counts were accumulated during each data collection. In each patient an average of seven measurements (range five to 11) were obtained at various systolic blood pressure levels. If heart rate varied more than 10 beats/min, the data were discarded. The left ventricular end-systolic volume index was plotted against the corresponding systolic blood pressure and the slope of the pressure-volume relationship was determined (figure 1).

The rate of angiotensin infusion necessary for an initial satisfactory pressor response ranged from 0.17 to 0.42 μg/min and the average rate at the time of the final pressure increment (30 to 60 mm Hg) ranged from 1.0 to 2.5 μg/min. The duration of angiotensin infusion averaged 60 to 90 min. After termination of the infusion, the blood pressure declined to control levels in 10 to 15 min. Postinfusion hypotension was not observed, although this has been described by others. 18

Radionuclide ventriculography. Gated radionuclide ventriculography was performed by a standard procedure that has been previously described. 19 20 Red blood cells were labeled in vivo with 25 mCi of 99mTc. 21 22 A single crystal gamma camera (Technicare Ohio Sigma 420) fitted with a 30 degree slant-hole, high-sensitivity collimator was positioned over the chest wall of each patient in a 25 to 40 degree left anterior oblique projection; angulation of the camera head was adjusted so that the image of the left ventricle was clearly separated from that of right ventricle and the left atrium. Images were stored on-line in a commercial nuclear medicine computer system (PDP 11/34). The data were recorded with use of a 64 × 64 matrix and the average cardiac cycle was divided into 24 frames.

Radionuclide data were processed by means of a semiautomatic edge-detection program. 23 We have previously validated this radionuclide technique of measuring left ventricular ejection fraction against contrast angiography. 19 Left ventricular volumes were determined by a nongeometric technique. 24 25 To compensate for differences in the amount of radioactivity injected, a peripheral venous blood sample was drawn immediately after each imaging session, counted at a distance of 8.5 cm by the same collimator, and corrected for background in the field. With knowledge of the transpired time and half-life of 99mTc, the activity in blood at the midpoint of each imaging session was calculated. 26 Attenuated radionuclide left ventricular volumes were derived from a standard formula. 24 25 In our laboratory, the nongeometric radionuclide estimation of absolute left ventricular end-diastolic volume has been validated against the value obtained with contrast angiography in which angiographic end-diastolic volume = 3.77 × attenuated radionuclide end-diastolic volume + 9.1 (r = .88, SEE = 15 ml, n = 21). The reproducibility of the radionuclide of left ventricular volumes was high when studies were repeated on two occasions 24 hr apart (r = .98). 27 In patients without valvular regurgitation, the changes in radionuclide stroke volume during exercise paralleled the direction and magnitude of changes in simultaneously measured thermodilution stroke volume. 28 In the present study, stroke volume and end-systolic volume were derived from end-diastolic volume and ejection fraction. All volumes were reported as volume indexes (in ml/m²).

Statistical analysis. Regression analysis of paired data was performed according to standard methods. Comparison between groups was made by unpaired t test and changes from rest to exercise or peak pressure loading during angiotensin infusion was tested by a paired t test. A p value < .05 was considered significant. 29 All results are given as mean ± SD.
TABLE 1
Hemodynamic and left ventricular response to exercise

<table>
<thead>
<tr>
<th>Control subjects (n = 6)</th>
<th>Aortic regurgitation (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120 ± 11</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>EF (%)</td>
<td>58 ± 4</td>
</tr>
</tbody>
</table>

CI = total left ventricular output; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; HR = heart rate; SBP = systolic blood pressure; SVI = stroke volume index.

\*p < .01; \*p < .05 compared with resting values.

Results

Exercise data

Handgrip exercise. Hemodynamic and left ventricular functional responses to both handgrip and bicycle exercise are summarized in Table 1. At rest, 13 of 14 patients with aortic regurgitation had ejection fractions of 50% or more and mean resting ejection fractions did not differ in the control subjects and patients with aortic regurgitation. During handgrip exercise heart rate and systolic blood pressure were increased similarly in the control subjects and patients with aortic regurgitation. Stroke volume was unchanged and cardiac index was increased in the control subjects, but both measurements were unchanged in patients with aortic regurgitation. In the control subjects left ventricular end-diastolic and end-systolic volumes and ejection fraction were not significantly altered. By contrast, in patients with aortic regurgitation left ventricular end-diastolic volume was slightly but significantly increased, while ejection fraction was decreased as a result of a disproportionate increase in end-systolic volume (figure 2).

Bicycle exercise. Heart rate and systolic blood pressure responded in a similar fashion in both groups. Stroke volume and cardiac index were increased in the control subjects, but stroke volume was unchanged in patients with aortic regurgitation. In the control subjects left ventricular end-diastolic volume increased, end-systolic volume was unchanged, and ejection fraction increased. However, in patients with aortic regurgitation left ventricular end-diastolic and end-systolic volumes and ejection fraction were unchanged (figure 3).

In no patient was the change in left ventricular ejection fraction from rest to handgrip and bicycle exercise related to resting ejection fraction (r = .15 and r = .15) or to the changes in left ventricular end-diastolic volume.

FIGURE 2. Left ventricular functional response to handgrip exercise in six control subjects and 14 patients with aortic regurgitation (AR).
volume (r = .45 and r = .13), but it did correlate with resting end-systolic volume (r = .58 and r = .62).

There was no significant difference in mean maximal workload achieved between patients with aortic regurgitation and control subjects (116 ± 23 vs 100 ± 50 W, p = NS).

**Pressure-volume relationship.** The mean values for heart rate, systolic blood pressure, left ventricular volumes, and ejection fraction at rest and peak pressure loading during angiotensin infusion are summarized in table 2.

Systolic blood pressure was linearly related to end-systolic volume in all 20 patients and the slope of the pressure-volume relationship was less steep in patients with aortic regurgitation than in control subjects, although there was some overlap (table 3). The slope of the pressure-volume relationship correlated exponentially with resting ejection fraction before angiotensin infusion. The position of the curve for the patients with aortic regurgitation shifted downward and to the right compared with that for the control subjects (figure 4). There was a close relationship between the slope of the pressure-volume relationship and the changes in left ventricular ejection fraction from rest to handgrip (figure 5) and bicycle (figure 6) exercise.

Five of 14 patients with aortic regurgitation (group A) had normal slopes of the pressure-volume relationship, defined as those lying within 2 SDs of the mean value in the control subjects, and nine patients (group B) had a slope below the normal range. There was no significant difference in age, resting hemodynamics, left ventricular ejection fraction, or mean maximal workload achieved in the two groups, but patients in group A had larger left ventricular end-diastolic and end-systolic volumes at rest than those in group B. During handgrip exercise ejection fraction was maintained in group A, whereas in seven of nine patients (78%) in group B there was an abnormal response of ejection fraction (decrease of > 5%). During bicycle exercise left ventricular ejection fraction was increased by 5% in all group A patients, while it was unchanged or decreased in all group B patients.

**Discussion**

In this study we assessed the myocardial contractile state by analyzing the pressure-volume relationship over a wide range of afterload conditions rather than extrapolating conclusions from a single measurement. The results suggest that the determination of the myocardial contractile state with use of the slope of the pressure-volume relationship may be useful in assessing left ventricular performance in such patients.

**Resting left ventricular ejection fraction in patients with aortic regurgitation.** Ejection fraction is commonly used in clinical practice as a measure of the left ventricular function.
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TABLE 3
Measurement of the pressure-volume relationship and ejection fraction

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age (yr) and sex</th>
<th>BSA</th>
<th>P-V slope</th>
<th>r value</th>
<th>Resting EF</th>
<th>ΔEF with handgrip EX</th>
<th>ΔEF with bicycle EX</th>
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<tbody>
<tr>
<td>Control subjects</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>1</td>
<td>50 M</td>
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<td>+9</td>
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<tr>
<td>2</td>
<td>49 F</td>
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<td>2.36</td>
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<tr>
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<tr>
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<td>.96</td>
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<td>1.22</td>
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<td>13</td>
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<td>0.12</td>
<td>0.57</td>
<td>.05</td>
<td>9</td>
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<td>7</td>
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</table>

EF = ejection fraction; ΔEF = change in ejection fraction; EX = exercise; P-V = pressure-volume; BSA = body surface area.

* p < .05, ** p < .01 compared with control subjects.

Functional state, but it is influenced by changes in heart rate, preload, and afterload.1,2 When preload is increased or afterload is decreased, the ejection fraction is maintained even if myocardial contractility is depressed. These extrinsic factors are especially relevant in patients with aortic regurgitation because of chronic compensatory mechanisms, such as left ventricular dilatation, hypertrophy, and alteration in aortic impedance.33,34 The slope of the pressure-volume relationship is independent of preload and incorporated with afterload, and may more accurately reflect the inotropic state of the left ventricle.10-13 In this study the slope of the pressure-volume relationship correlated exponentially with resting ejection fraction, indicating that at a given normal ejection fraction myocardial contractile state may vary considerably. This confirms previous findings.14,35 In addition, the relationship between the slope and resting ejection fraction showed that at any given ejection fraction, the corresponding slope of the pressure-volume relationship is lower in patients with aortic regurgitation than in control subjects. This suggests that resting ejection fraction overestimates myocardial function in patients with aortic regurgitation and the slope of the pressure-volume relationship more accurately identifies myocardial dysfunction in such patients.36

Left ventricular response to handgrip exercise in patients with aortic regurgitation. Handgrip exercise is useful in the clinical evaluation of left ventricular function.37,38 In our control subjects, despite high pressure loading during handgrip exercise, neither left ventricular end-diastolic nor end-systolic volumes significantly increased. Stroke volume and ejection fraction remained unchanged, which suggests an increase in myocardial contractility and which is in agreement with previous reports in normal subjects.37,39

In contrast, patients with aortic regurgitation responded to the increase in systolic blood pressure with an increase in left ventricular end-diastolic volume, suggesting that the Frank-Starling mechanism was used to maintain cardiac output during handgrip exercise. Seven of 14 patients with aortic regurgitation...
developed abnormal left ventricular functional responses characterized by an increase in end-systolic volume and a decrease in ejection fraction of 5% or more. This is consistent with previous findings.\(^8\,9\)

The present study shows that left ventricular performance during handgrip exercise is closely related to myocardial contractile state determined by the slope of the pressure-volume relationship. Seven of nine patients with aortic regurgitation and a slope below the normal range had abnormal left ventricular response to handgrip exercise (ejection fraction decrease of \(\geq 5\%\)), whereas all five patients with aortic regurgitation and a normal slope had normal left ventricular functional response. This suggests that handgrip exercise–induced left ventricular dysfunction in these patients was mainly due to a decreased myocardial contractile state. The possibility that an "afterload mismatch" occurred that resulted in a decrease in ejection fraction in our patients is unlikely since left ventricular stroke volume was maintained despite increases in pressure loading.\(^{40}\)

Left ventricular response to bicycle exercise in patients with aortic regurgitation. The normal left ventricle increases ejection fraction with exercise because of an ability to increase myocardial contractility to eject an increased stroke volume at a similar or lower end-systolic volume (contractile reserve).\(^{41}\) In contrast, almost two-thirds of patients with aortic regurgitation in this study had an abnormal ejection fraction response to exercise (decreased or increased \(<5\%)\), consistent with previous findings that exercise–induced left ventricular dysfunction is common in patients with chronic aortic regurgitation.\(^{42}\)

The abnormal ejection fraction response to exercise in patients with aortic regurgitation was reported to be the result of a decrease in left ventricular preload (end-
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diastolic volume) caused by the shortened diastolic filling period and reduced regurgitant volume secondary to the increase in heart rate. In recent studies, however, variable changes in left ventricular end-diastolic volume during exercise have been found in patients with aortic regurgitation. In our study the mean left ventricular end-diastolic volume in patients with aortic regurgitation was unchanged during bicycle exercise. The change in ejection fraction with exercise did not correlate with that in left ventricular end-diastolic volume, but did correlate with resting left ventricular end-systolic volume and was better related to the slope of the pressure-volume relationship. The slope identifies the patients with and without a normal left ventricular functional response to exercise. This suggests that myocardial contractile state may be one of the major factors determining left ventricular performance during dynamic exercise. Our patients exercised in the supine rather than the upright position, which may have altered peripheral vascular response in patients with aortic regurgitation.

Methodologic considerations. Determination of the pressure-volume relationship depends on the accurate measurement of small changes in left ventricular end-systolic volume. The count-based method for measuring left ventricular end-systolic volume, independent of ventricular geometric assumption, is probably more accurate than the geometric method. The validity of this technique has recently been shown by Kronenberg et al., who found that the slopes of the pressure-volume relationship determined by radionuclide and contrast angiographic methods were not significantly different.

Although accurate measurement of absolute left ventricular volumes in individual patients with a radionuclide count-based method requires precise knowledge of the attenuation factor in each patient, in this study 90% of patients were adult men, and the body surface areas of the control subjects and patients with aortic regurgitation were similar. The variation in attenuation among our patients may therefore be small. A large left ventricle may theoretically cause high self-attenuation within the blood pool that could underestimate left ventricular volumes when a single attenuation factor is used for calculation of left ventricular volumes. However, this would result in an overestimation of the slope of the pressure-volume relationship in patients with aortic regurgitation and it is therefore unlikely that it would affect the validity of our conclusions.

Since the direct effects of angiotensin on left ventricular contractility are minimal, the myocardial response during infusion should primarily be related to increased afterload. The heart rate remained relatively constant as afterload was altered, so that the possibility of reflex changes in the left ventricular inotropic state mediated by withdrawal of sympathetic tone is an unlikely one. In addition, it has been shown that sympathetically mediated reflexes make little, if any, contribution to the resting left ventricular contractility during acute pressure loading. Although it has been shown that angiotensin increases coronary vascular resistance, this effect is minor and is not unlikely to effect left ventricular function.

We conclude from this study that in patients with aortic regurgitation resting left ventricular ejection fraction is not a reliable index of myocardial function. The myocardial contractile state measured by the slope of the pressure-volume relationship is a major determinant of left ventricular functional response to handgrip and bicycle exercise. This study may provide the basis for further prospective evaluations to assess the effect of pharmacologic interventions on left ventricular function and may contribute to the difficult clinical decision on the timing of aortic valve replacement in asymptomatic patients with aortic regurgitation.

We gratefully acknowledge the excellent technical assistance of Anne Russell, Barbara Winch, Sue Stewart, and Heather Paterson.

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CIRCULATION
Evaluation of relationship between myocardial contractile state and left ventricular function in patients with aortic regurgitation.

W F Shen, G S Roubin, C Y Choong, B F Hutton, P J Harris, P J Fletcher and D T Kelly

doi: 10.1161/01.CIR.71.1.31

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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