Noninvasive Measurement of the Rest and Exercise Peak Systolic Pressure/End-Systolic Volume Ratio: 
A Sensitive Two-Dimensional Echocardiographic Indicator of Left Ventricular Function

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Thirty-five patients with previous myocardial infarction and 25 normal subjects underwent subcostal view two-dimensional echocardiography at rest and at peak upright bicycle exercise. The purpose was to assess changes in left ventricular volume with maximal upright bicycle exercise and to compare the utility of the peak systolic pressure/end-systolic volume index ratio and ejection fraction as indicators of left ventricular function.

With exercise, normal subjects had a decrease in end-systolic volume index (22 ± 8 to 11 ± 3 ml/m²) (p < 0.001); the normal ejection fraction (59 ± 9 to 72 ± 8%, p < 0.001) and the pressure/volume ratio (6 ± 3 to 18 ± 6, p < 0.001) increased. In patients with prior myocardial infarction there was no change in end-systolic volume index, ejection fraction or pressure/volume ratio with exercise. Although at peak exercise significant differences between normal subjects and patients with prior infarction were demonstrated in end-systolic volume index (p < 0.001), ejection fraction (p < 0.001) and pressure/volume ratio (p < 0.001), the pressure/volume ratio provided sharper delineation between the two groups than did ejection fraction. The exponential relation of the pressure/volume ratio and ejection fraction at peak exercise demonstrates that the pressure/volume ratio is more sensitive as an indicator of normal or borderline left ventricular function and that ejection fraction is more sensitive in quantifying the degree of left ventricular dysfunction.

It is concluded that 1) the peak systolic pressure/end-systolic volume ratio at the peak of upright bicycle exercise is better than ejection fraction in distinguishing between normal subjects and patients with prior myocardial infarction and 2) the pressure/volume ratio and ejection fraction have complementary roles in identifying and quantifying abnormal left ventricular function.

Left ventricular ejection fraction during dynamic exercise has been shown to be a reliable indicator of left ventricular function in patients with a wide variety of cardiac diseases (1). However, the utility of ejection fraction as a measure of ventricular function has been questioned because it is partly dependent on preload and afterload (2). Left ventricular function has also been defined by the relation between the instantaneous left ventricular pressure and left ventricular volume at the end of systole in both canine (2) and human studies (3–6). This relation has the advantage of being relatively independent of preload and afterload in a wide range of left ventricular pressures and volumes.

Two-dimensional echocardiography at rest and during exercise has provided a unique opportunity for the direct noninvasive measurement of ventricular volume changes on a beat to beat basis in response to exercise. Two-dimensional echocardiography has been shown (7,8) to correlate significantly with cineangiographic and radionuclide measurements of left ventricular volume and ejection fraction. Subcostal view two-dimensional echocardiography during symptom-limited upright bicycle exercise reported by this laboratory enables noninvasive beat to beat measurement of regional (9) and global (10) left ventricular function at high levels of cardiac stress.

The purpose of this study was 1) to assess left ventricular volume changes in response to symptom-limited upright
bicycle exercise in normal subjects and patients with prior myocardial infarction, and 2) to compare the utility of the peak systolic pressure/end-systolic volume index ratio with ejection fraction as an indicator of left ventricular function in patients with prior myocardial infarction.

Methods

Study groups. Group 1 (normal control subjects) consisted of 25 healthy adults with no clinical or historical evidence of cardiovascular disease or hypertension. Their mean age was 28.7 years (range 18 to 45). All subjects had a normal rest 12 lead electrocardiogram and no ischemic changes on 12 lead electrocardiograms during symptom-limited upright bicycle exercise. The control group was significantly younger than the group with prior myocardial infarction. This age group was intentionally chosen so that their risk of having occult coronary artery disease (by Bayesian analysis) was less than 2% (11).

Group 2 consisted of 35 patients with coronary artery disease and documented prior myocardial infarction being followed up in a cardiac rehabilitation program. Their mean age was 53.4 years (range 33 to 73). The electrocardiographic localization of myocardial infarction was anterior in 9 patients, anterolateral in 7, inferior in 10, inferolateral in 2 and subendocardial in 7. All patients were clinically stable; their pattern of angina had not changed since their myocardial infarction or for at least 4 weeks. Nine patients were taking long-acting nitrates as their only antianginal therapy, 8 were taking a beta-adrenergic blocking drug, 10 were taking nitrates and a beta-blocking agent in combination, 4 were taking calcium channel blocking agent and 4 were not receiving antianginal therapy.

Informed consent was obtained from all patients according to a protocol approved by the Harbor-UCLA Medical Center Human Research Committee on December 14, 1981 and renewed July 27, 1982. (The first 10 normal subjects and 11 patients were studied as a pilot project using the identical protocol, but before formal approval of the protocol.)

Exercise protocol. The patients were exercised in the upright position on a bicycle ergometer with continuous electrocardiographic monitoring. Blood pressure was measured by a sphygmomanometer on the arm. Blood pressure, heart rate and a 12 lead electrocardiogram were measured at rest and every 3 minutes during exercise, at peak exercise and every 3 minutes during recovery. The work load was initially 0 kilopond-meters (kpm) and was increased by 75 kpm every minute to the maximal attainable stress. The end point was: 1) significant chest pain; 2) fatigue causing the patient to refuse further exercise; 3) flat or downsloping ST segment depression of at least 0.2 mV; or 4) complex ventricular arrhythmias. The patient remained sitting in the upright position on the bicycle during the recovery period and pedaling slowly without ergometer resistance for the first 1 to 2 minutes of recovery. No long-acting nitrates were taken for at least 3 hours before exercise.

Echocardiography. Two-dimensional echocardiograms were obtained using a wide angle rotating transducer mechanical scanner (Advanced Technology Laboratories Mark III) and recorded on videotape (Sanyo VTC 7100). Patients were examined at rest from the subcostal four chamber view in the upright position before the commencement of bicycle exercise and from approximately 30 seconds before the cessation of exercise until peak exercise. To validate subcostal view two-dimensional echocardiographic volume measurements, apical and subcostal four-chamber views in the supine position at rest were obtained in the first 10 normal subjects and in the first 11 patients with prior myocardial infarction.

The following protocol was established to obtain diagnostic quality and reproducible subcostal view two-dimensional echocardiograms. The hand-held transducer was placed in the subcostal position, just to the left of the xiphoid process, and gently pressed inward and upward so that the two-dimensional echographic beam passed just underneath the costal margin. During held partial inspiration, the subject was asked to sit 'at attention' with the back straight and shoulders back, to facilitate visualization of the heart. The four chamber view was obtained by visualizing the mitral leaflets and then rotating and angling the transducer during held partial inspiration to obtain the longest axis of the left ventricle while still imaging the mitral valve. This technique ensured that the region of the apex was adequately visualized. During the exercise study, the transducer was angled from side to side during held partial inspiration to further ensure that the longest axis of the left ventricle was visualized (Fig. 1 and 2).

Radionuclide angiography. To validate ejection fraction determinations at rest and during peak exercise, comparison was made with first pass radionuclide angiography in the first 10 normal subjects and 11 patients with prior myocardial infarction. All were exercised upright on a bicycle ergometer using the previously described exercise protocol to a maximal heart rate as close as possible to that obtained during the two-dimensional echocardiographic exercise study.

At peak exercise, an upright first pass radionuclide angiogram was obtained in the 30° right anterior oblique projection using a 15 mCi intravenous bolus injection of technetium-99m pertechnetate, as previously described by investigators from this institution (12). An upright first pass 30° right anterior oblique radionuclide angiogram was obtained at rest at least 1 hour later.

Two-dimensional echocardiographic measurements. The left ventricle was considered to be measurable if all or nearly all of the endocardial echoes could be identified on a single stop frame image. End-diastole was defined as the
Figure 1. Subcostal view end-systolic two-dimensional echocardiogram during peak exercise in a normal subject. The symmetric wall thickness and small left ventricular (LV) cavity size are apparent. Heart rate was 180 beats/min, peak systolic pressure was 180 torr, ejection fraction was 74% and the peak systolic pressure/end-systolic volume ratio was 20.0. The electrocardiogram was retraced for clarity. The arrow on the electrocardiogram indicates the end-systolic timing of the echocardiographic image. AO = aorta; IVS = interventricular septum; LA = left atrium; RA = right atrium.

Figure 2. Subcostal view end-systolic two-dimensional echocardiogram during peak exercise in a patient with prior myocardial infarction. The difference in end-systolic volume from the normal subject (Fig. 1) is apparent. Heart rate was 130 beats/min, peak systolic pressure was 160 torr, ejection fraction was 43% and the peak systolic pressure/end-systolic volume ratio was 3.1. The electrocardiogram was retraced for clarity, and the arrow at the end of the T wave indicates the end-systolic timing of the echocardiogram. Abbreviations as in Figure 1.

onset of the QRS complex of the electrocardiogram and end-systole was defined as the smallest left ventricular area just before mitral valve opening. All normal subjects and patients with prior myocardial infarction had subcostal view end-diastolic and end-systolic images identified at rest and during peak exercise. The first 10 normal subjects and 11 patients with prior myocardial infarction had apical four chamber end-diastolic and end-systolic rest images recorded also. Each frame was digitized into a minicomputer (Informatek Simis 3) using a 256 × 256 pixel matrix. A line identifying the endocardium was drawn by the operator at the interface of the endocardial echoes and the left ventricular cavity. Vertical and horizontal calibrations were obtained from a calibration phantom. The left ventricular volume was calculated using a single plane Simpson’s rule algorithm with the long axis of the ventricle automatically divided into 25 equal segments.

Statistical methods. Statistical significance was tested using the paired and unpaired Student’s t test. Correlation coefficients and regression equations were calculated according to standard formulas.

Results

To obtain two-dimensional echocardiographic images that met the criteria for volume measurements both at rest and during peak exercise, 31 normal subjects and 46 patients with prior myocardial infarction were screened. Thus, the overall success rate in obtaining images of satisfactory diagnostic quality was 78%.

In the 25 normal subjects (Group 1) in whom left ventricular volumes could be calculated, the heart rate increased from 73 ± 11 (mean ± SD) beats/min at rest to 180 ± 13 beats/min at peak exercise. Systolic blood pressure increased from 115 ± 13 to 174 ± 22 torr.

In the 35 patients with prior myocardial infarction (Group 2) whose left ventricular volumes could be measured, the heart rate increased from 75 ± 15 to 131 ± 20 beats/min with exercise. Systolic blood pressure was 126 ± 21 torr at rest and 175 ± 30 torr at peak exercise. Exercise was terminated because of angina in 8 patients and fatigue in the other 27. Electrocardiographic ST segment depression occurred in 21 of the 35 patients, but was not an indication for discontinuing exercise in any of the patients.
Changes in end-diastolic volume index with exercise.

In the normal subjects (Group 1), the end-diastolic volume index decreased modestly but significantly from $56 \pm 20$ ml/m² at rest to $40 \pm 13$ ml/m² at peak exercise ($p < 0.025$). The end-diastolic volume index for the patients with prior myocardial infarction (Group 2) was not significantly different from that in the normal subjects at rest ($71 \pm 23$ ml/m²) and did not change significantly at peak exercise ($73 \pm 25$ ml/m²).

Changes in end-systolic volume index with exercise.

At peak exercise, the normal subjects had a significant decrease in end-systolic volume index from $22 \pm 8$ to $11 \pm 3$ ml/m² ($p < 0.001$). In contrast, patients with prior myocardial infarction demonstrated no change in end-systolic volume index (from $40 \pm 19$ to $40 \pm 20$ ml/m²). The difference in end-systolic volume index between the two groups was significant both at rest ($p < 0.001$) and at peak exercise ($p < 0.001$).

Figure 3. Correlation of subcostal and apical four chamber two-dimensional echocardiographic left ventricular volumes at rest. The solid lines are the linear regression lines. MI = myocardial infarction; n = number of patients; p = probability; r = correlation coefficient.

Figure 4. Correlation of subcostal view echocardiographic (ECHO) and radionuclide angiographic ejection fraction at rest and during peak exercise. The solid line represents the linear regression line. The open arrows indicate the normal subjects and the solid arrows the patients with prior myocardial infarction (POST MI). The tail of the arrow represents the ejection fraction at rest and the head of the arrow represents the ejection fraction at peak exercise. 2D = two-dimensional; abbreviations as in Figure 3.
Changes in peak systolic pressure/end-systolic volume index ratio with exercise. At rest, the pressure/volume ratio of the normal subjects (5.9 ± 2.5) was slightly higher than that of the patients with prior myocardial infarction (4.0 ± 2.0) (p < 0.005). However, at peak exercise, the normal subjects increased the pressure/volume ratio threefold (18.0 ± 6.3), whereas the patients with prior myocardial infarction had no significant change (6.0 ± 3.0) from rest values (Fig. 5). The difference in pressure/volume ratio at peak exercise between the two groups was significant (p < 0.001).

The smallest increase in the pressure/volume ratio in the normal subjects was 1.36 times the baseline value, and only 2 of the 25 subjects had a less than twofold increase in pressure/volume ratio, whereas the largest increase in the patients with prior myocardial infarction was 1.66 times the control level. In contrast, in five normal subjects echocardiographic ejection fraction failed to increase by more than 5 percentage units while in 15 of the 35 patients with prior myocardial infarction ejection fraction increased by more than 5 percentage units, and 7 of the 15 had an exercise ejection greater than 60%. Thus, in this group, the pressure/volume ratio at peak exercise provided a sharper delineation of normal subjects from patients with prior myocardial infarction than did either the absolute exercise ejection fraction or ejection fraction change with exercise.

Discussion

Previous studies. The ejection fraction has been widely used as an indicator of left ventricular function. Unfortunately, the left ventricular ejection fraction is dependent on both preload and afterload (2). Maneuvers such as postural changes that alter preload without significantly changing the inotropic state may reduce the ejection fraction even in normal subjects (13). In contrast, the left ventricular pressure/volume relation at the end of systole has been demonstrated (2,6) to have the advantage of being only minimally influenced by preload and afterload over a wide range of preload and afterload conditions.

The original observations of Suga and Sagawa (14) have been confirmed by a number of invasive studies (3,4,6). Nivatpumin et al. (4) demonstrated that similar results can be obtained whether the peak ratio of left ventricular pressure and volume (Emax) or the end-systolic pressure/volume ratio is utilized. Noninvasive evaluation of the end-systolic pressure/volume ratio was first proposed by Sagawa and Suga (2). They demonstrated that ultrasonic left ventricular dimension could be substituted for left ventricular volume and proposed that peak carotid pressure could be substituted for end-systolic left ventricular pressure.

Dehmer et al. (5) used left ventricular volume derived from radionuclide electrocardiographic-gated equilibrium angiograms at rest and during exercise to demonstrate the utility of the peak systolic pressure/end-systolic volume ratio in identifying patients with multiple vessel coronary artery disease and exercise-induced left ventricular ischemic dysfunction. Unfortunately, the prolonged acquisition time necessary in gated radionuclide angiography necessitates the averaging of volume data over a 2 to 3 minute period. Therefore, this technique may not accurately reflect left ventricular function at peak exercise when there may be rapid changes in ventricular volumes, pressure and inotropic state (15).

Methodologic considerations. Two-dimensional echocardiography has proved to be an accurate method of measuring left ventricular volume and ejection fraction (7,8). In this study, we found a good correlation between left ventricular ejection fraction during rest and exercise compared with first pass radionuclide angiography, which measures ejection fraction averaged over only three to five cardiac cycles (as opposed to several hundred cycles in gated scans). In addition, subcostally determined left ventricular volumes correlated well with apical echocardiographic left ventricular volumes at both end-diastole and end-systole (Fig. 3), with a regression line slope very close to unity. The ventricular volumes reported in this study are slightly lower than those commonly reported in contrast cineangiographic studies. This is probably partly due to the echocardiographic equipment used, which has been reported to

Figure 5. Comparison of changes in ejection fraction and peak systolic pressure/end-systolic volume index (PSP/ESVI) ratio with exercise. Note the greater change in the ratio than in ejection fraction in normal subjects. M ± S.D. = mean ± standard deviation; MI = myocardial infarction.
underestimate ventricular cavity area in vitro (16). However, the underestimation has been found to be linear over a range of volumes with a significant correlation with actual cavity area (16). In addition, controversy exists regarding the most appropriate reference standard for determining left ventricular volumes (17,18). Since our purpose was to assess relative changes between rest and exercise, we chose to report our data unaltered.

The capability to image repeatedly the same portion of the left ventricle at rest and exercise is critical to the comparison of rest and exercise left ventricular function by this technique. We have found that strict adherence to the previously described protocol does indeed provide long-axis images of similar regions of the left ventricle at rest and exercise. This conclusion is supported by the high correlation between echocardiographic ejection fraction at rest and during exercise and ejection fraction determined by first pass radionuclide angiography, a technique that is not dependent on left ventricular geometry. In addition, we previously reported (9) a significant correlation between regional wall motion assessment at rest and during exercise by subcostal view two-dimensional echocardiography and radionuclide angiography.

The ability to determine noninvasively the left ventricular pressure/volume relation is dependent on three factors: an accurate estimate of peak systolic pressure, an accurate measure of left ventricular end-systolic volume and assurance that these values are obtained as simultaneously as possible. Reichek et al. (19) demonstrated a close correlation between sphygmomanometric peak systolic pressure and both left ventricular peak systolic and end-systolic pressures. As we have demonstrated, the subcostal view two-dimensional echocardiogram produces left ventricular volume data that avoid the potential variation resulting from averaging many cardiac cycles. In contrast with gated radionuclide angiography, two-dimensional echocardiographic analysis of ventricular volumes allows both systolic pressure and left ventricular end-systolic volume to be determined simultaneously. This capability is especially critical at peak exercise, at which time the left ventricular systolic volumes and pressures are changing rapidly. Therefore, it is evident that subcostal view two-dimensional echocardiography permits the accurate measurement of the left ventricular peak systolic pressure/end-systolic volume ratio.

Critique of study groups. There were two differences between the control and patient groups that could theoretically influence the results observed. First, the normal subjects were younger than the patients with prior myocardial infarction. As stated previously, the control group was specifically chosen to be young adults to minimize the chance of their having occult ischemic heart disease, since they did not undergo coronary arteriography. However, although the difference in mean age of the two groups was significant, there was an overlap in ages between the groups. Of importance, when the entire study group was classified by subsets by age, the older normal subjects had responses similar to those of the younger normal subjects with regard to exercise-induced changes in left ventricular volume, ejection fraction and the pressure/volume ratio. Similarly, the younger patients with prior myocardial infarction responded in a fashion similar to that of the older patients with ischemic heart disease with respect to these variables. Thus, it seems unlikely that different ages of the study groups alone could explain the left ventricular functional changes observed.

The other difference between the study groups was the medications taken by the postinfarction patients. Thirty-one of the 35 postinfarction patients were receiving some form of therapy, most commonly a beta-adrenergic blocking agent alone or in combination with a long-acting nitrate (see Methods). The patients with prior myocardial infarction had a lower maximal heart rate than the normal control subjects. In addition, the postinfarction patients taking a beta-adrenergic blocking drug had a lower peak heart rate than the postinfarction group as a whole. It is possible that the differences in left ventricular volumes observed during exercise represent differences in maximal heart rate achieved, rather than the presence or absence of left ventricular dysfunction. However, there were no significant differences in left ventricular end-systolic volume, ejection fraction or pressure/volume ratio at peak exercise in the patients with prior myocardial infarction whether or not they were taking a beta-adrenergic blocking agent. Furthermore, in normal subjects left ventricular end-systolic volume progressively decreases as dynamic exercise intensity increases (20,21). This suggests that the pressure/volume ratio should not fail to increase with moderate stress in normal subjects. Therefore, it seems unlikely that peak heart rate differences between the study groups can account for all the observed differences in left ventricular function.

Rest and exercise pressure/volume relations. The linear extrapolation of the left ventricular end-systolic pressure/volume ratio to zero load ($V_{es}$) has been considered to be a method for obtaining the intrinsic inotropic state of the heart muscle (2,3). However, the slope of the end-systolic pressure/volume relation is linear only if the inotropic state of the left ventricle remains unchanged. Upright dynamic exercise clearly changed the inotropic state of the left ventricle in both the normal and postmyocardial infarction groups to an unpredictable degree. Thus, a linear relation cannot be assumed in the pressure/volume ratio between rest and exercise. Rather, these must be considered two separate tests of left ventricular function. Therefore, no conclusions may be drawn regarding the slope of the pressure/volume relation or $V_{es}$ with this experimental design.

Clinical implications. The subjects included in this study represent a broad spectrum of left ventricular function from normal to severe dysfunction. The peak exercise pressure/volume ratio separated these divergent groups. It re-
mains to be demonstrated whether mild degrees of left ventricular dysfunction in patients without myocardial infarction or other causes of ventricular depression can also be identified prospectively (these studies are presently underway). However, the results of Dehmer et al. (5) indicate that the pressure/volume ratio during exercise is helpful in identifying patients with single versus multiple vessel coronary artery disease. This suggests that milder forms of left ventricular dysfunction may be identified by the pressure/volume ratio during exercise. Indeed, the nonlinear relation between the pressure/volume ratio and ejection fraction previously reported (2,4,6) suggests that the pressure/volume ratio should be more sensitive an indicator of mild than severe left ventricular depression.

In the present study, both left ventricular ejection fraction and the end-systolic pressure/volume ratio at peak exercise separated the normal group from the postmyocardial infarction group. However, the degree of separation was much greater with the pressure/volume ratio (Fig. 5 and 6). In 43% (15 of the 35) of the patients with prior myocardial infarction ejection fraction increased by more than 5 percentage units above baseline values; seven patients had an exercise ejection fraction above 60%. On the other hand, in 20% (5 of the 25) of the normal subjects ejection fraction increased by less than 5 percentage units and two had a peak exercise ejection fraction less than 60%. Conversely, the change in peak exercise pressure/volume ratio completely separated the normal subjects from the patients with prior infarction. Thus, the pressure/volume ratio at the peak of symptom-limited upright exercise appears to be preferable to ejection fraction in distinguishing normal from abnormal left ventricular function.

Nivatpumin et al. (4) and others (2,5,6) reported an exponential relation between the end-systolic pressure/volume ratio and ejection fraction at rest when left ventricular volumes were measured by contrast cineangiography. In the present study, the exponential correlation between the pressure/volume ratio and ejection fraction at rest was only fair (r = 0.72) and the separation between normal subjects and patients with prior myocardial infarction was not good (Fig. 6, top). In contrast, the exponential correlation between the pressure/volume ratio and ejection fraction at peak exercise was 0.83, with a clear separation of the two groups (Fig. 6, bottom). One possible explanation for the discrepancy between the present study and previous studies might relate to the increased blood catecholamine levels that are frequently noted during the stress of cardiac catheterization (22). This could result in a somewhat enhanced inotropic state during cardiac catheterization. Although the enhanced inotropism might not be enough to cause significant changes in ejection fraction, there could be significant changes in the pressure/volume relation, especially in patients with normal left ventricular function.

Because of the exponential relation between the end-systolic pressure/volume ratio and ejection fraction at peak exercise (Fig. 6, bottom), this ratio has been shown to be a more sensitive indicator of left ventricular function than ejection fraction in the normal and mildly depressed ventricle. Conversely, it appears to be less sensitive than ejection fraction in assessing left ventricular function in a severely depressed ventricle (6).

Conclusion. This study has demonstrated that subcostal view two-dimensional echocardiography at rest and during symptom-limited upright bicycle exercise is a feasible method...
of evaluating left ventricular function in normal subjects and patients with prior myocardial infarction. Subcostal view left ventricular volume measurements correlated well with precordial left ventricular volume measurements, and ejection fraction correlated well with first pass radionuclide angiography. Two-dimensional echocardiography has the advantage in that it is entirely noninvasive without the concerns of cumulative radiation exposure, and it may be analyzed on a beat by beat basis.

The peak systolic pressure/end-systolic volume index ratio at the peak of exercise is better than ejection fraction in discriminating between the normal and postmyocardial infarction groups. Failure to increase this ratio with exercise is highly predictive of the presence of abnormal left ventricular function, but it is not as sensitive as ejection fraction in quantifying the severity of ventricular dysfunction. In comparison with ejection fraction, the end-systolic pressure/volume ratio is a better determinant of the presence of diminished left ventricular function, while ejection fraction is a better descriptor of the severity of left ventricular dysfunciton. Therefore, these two indexes have complementary roles in identifying and quantifying abnormal left ventricular function.

References


