Effect of isotonic exercise training on left ventricular volume during upright exercise

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ABSTRACT To determine the changes in left ventricular volume and their time course during exercise we studied 30 runners. Left ventricular end-diastolic and end-systolic volumes were measured from biapical two-dimensional echocardiograms recorded during graded upright bicycle exercise. The validity of this echocardiographic technique was assessed by comparing measurements at rest and exercise with results obtained by gated equilibrium radionuclide angiography in 10 patients with coronary artery disease. Although the absolute volume measurements were lower by echocardiography, ejection fraction was not significantly different and the directional changes in volume during exercise were comparable. In the runners, resting left ventricular end-diastolic volume measurements by echocardiography correlated with their maximum bicycle exercise endurance times (r = .80). Left ventricular end-diastolic volume, stroke volume, and ejection fraction increased during exercise with the most marked changes occurring in the first half of exercise. Systolic blood pressure/end-systolic volume (SBP/ESV) also increased during exercise, but the largest change occurred during the second half of exercise. Left ventricular volumes were larger in the 12 competitive marathon runners (maximum exercise duration ≥ 27 min) as compared with the 18 noncompetitive runners (exercise duration ≤ 23 min): resting end-diastolic volume 130 ± 29 (SD) ml vs 87 ± 20 ml (p < .001), respectively. During exercise the competitive runners exhibited a larger increase in end-diastolic volume and the noncompetitive athletes showed a greater increase in SBP/ESV. Therefore, highly trained competitive marathon runners make greater use of the less energy-consuming Frank-Starling mechanism to accomplish high levels of isotonic exercise performance as compared with less well-trained runners.


LONG-TERM isotonic exercise training results in a reduction in resting heart rate and an increase in left ventricular end-diastolic volume. Also, isotonically trained individuals are able to achieve higher values for stroke volume, cardiac output, and exercise workload as compared with untrained individuals, despite similar values for peak exercise heart rate, blood pressure, and ejection phase indexes of left ventricular performance. However, it is unclear whether the increased left ventricular output during exercise in athletes is related simply to the larger resting end-diastolic volume that persists during exercise, or whether further increases in left ventricular volume occur. If the latter is the case, what is the time course of volume changes during exercise? The relative contribution of increases in contractile state as estimated by the systolic pressure-volume relationship and the time course of these changes are poorly understood. Therefore we sought to determine whether the large ventricular end-diastolic volume of the trained individual can be increased further to take advantage of the less energy-consuming Frank-Starling effect and if so, to determine when it occurs during exercise. We also wished to evaluate changes in the systolic pressure-volume relationship during exercise and compare these with the changes in end-diastolic volume. Finally, the response of the left ventricle during exercise in highly trained competitive athletes was compared with that in less well-trained individuals to ascertain any differences during exercise that would explain the greater performance of the former. For this study, two-dimensional echocardiography was used during exercise to measure left ventricle.
tricular volumes after validation of the technique in comparison with gated equilibrium radionuclide angiography in a group of patients with coronary artery disease.

Methods

Subject selection. Two groups of subjects were selected for this study. The first group consisted of 10 patients with angina pectoris caused by fixed coronary artery disease who agreed to participate in a study of the validation of two-dimensional echocardiographically derived volumes during exercise, with gated radionuclide angiography used as the standard of reference. This validation could not be done in the second group (normal subjects) because of a reluctance by many of them to receive radioactive tracers and questions raised by our Institutional Review Board concerning the advisability of giving radionuclides to young normal individuals. The second group was chosen to evaluate the effect of isotonic conditioning on left ventricular performance during exercise and consisted of 30 members of a YMCA-sponsored running club.

Thirty men with chronic stable angina pectoris were evaluated for the validation part of the experiment; of these, 10 (77%) had suitable upright biplanar two-dimensional echocardiograms for participation in the study. All 10 patients had previously demonstrated exercise-induced ischemia on a Bruce protocol exercise treadmill test as manifested by 0.1 mV of electrocardiographic ST segment depression in an anterolateral precordial lead and typical angina pectoris. Nine of the 10 patients had previous well-documented myocardial infarctions and eight had prior selective coronary cineangiographic results demonstrating at least one vessel with greater than 70% diameter narrowing. All 10 patients had been off antianginal medications for 1 week before the study.

Thirty-four normal individuals were screened and 30 (88%) had suitable upright two-dimensional echocardiograms for inclusion in the study. All 30 were active and asymptomatic and had normal physical examinations and two-dimensional echocardiograms at rest. They varied greatly in their degree of training, from those who were highly trained and regularly competed in marathons to those that had just joined the running club and were practically sedentary. Objective testing readily separated them into two groups: 12 completed 27 min or longer of graded bicycle exercise (range 27 to 33 min), claimed to run more than 50 miles/week, and were regularly competing in marathons. There were three women and nine men. The other 18 had an exercise time of 23 min or less (range 12 to 23), ran less than 30 miles/week, and were considered noncompetitive in the marathon. There were four women and 16 men.

Exercise protocol. All subjects were exercised on an upright mechanically braked bicycle ergometer. Exercise was begun at 150 kpm/min and was increased by the same amount every 3 min. The electrocardiogram was monitored continually and heart rate and cuff blood pressure were recorded at rest and after each minute of exercise. All 10 patients with ischemic heart disease exercised until the onset of both angina pectoris and ischemic ST segment depression in the lateral precordial leads. All the normal subjects exercised to the point of fatigue that they considered near maximal from their experience. The patients exercised twice, 4 to 24 hr apart, with the order of radionuclide angiography and two-dimensional echocardiography being randomized.

Despite the marked differences in exercise duration between the two groups of subjects as noted above, maximum exercise heart rates were not significantly different (177 ± 15 beats/min competitive vs 162 ± 25 beats/min noncompetitive). To compare values of left ventricular size and performance during exercise between the two groups, heart rate was used to identify four points during exercise for each group. Therefore, comparison between groups were made at rest, at 60%, 70%, and 85% of maximum heart rate, and at maximum heart rate. Also, there is a well-known relationship between heart rate and oxygen consumption during exercise.  

Exercise two-dimensional echocardiography. Exercise biplanar two-dimensional echocardiograms were recorded with a phased-array echocardiograph and an 84 degree wide-angle 2.25 MHz transducer. Two- and four-chamber views were recorded on video tape at rest and after each minute of exercise with the patient upright on the bicycle and leaning slightly forward as we have previously described. The length of time for data acquisition at each exercise point was 10 to 15 sec. Echocardiograms were analyzed from the video tape recordings with a light pen–equipped microprocessor programmed for Simpson’s rule. End-diastolic and end-systolic volumes as well as ejection fractions were calculated at rest and at peak exercise from beats at end-expiration. Analysis of the two-dimensional echocardiograms at peak exercise were done at the time corresponding to the midpoint of data acquisition for the radionuclide angiogram. This allowed comparison of the instantaneous single-beat data acquisition for two-dimensional echocardiography with the 2-min data acquisition period for gated equilibrium radionuclide angiography as we have described previously. For the purpose of this study, we did not apply normalizing regression equations to correct for the echocardiographic underestimation of left ventricular end-diastolic volume and end-systolic volume that we have previously demonstrated at rest in comparison with biplane left ventricular cineangiography. There were two reasons for this decision. First, this underestimation was shown to be consistent in the previous study, since ejection fraction was not significantly different by the two techniques. Second, the previous study involved patients, many of whom had wall motion abnormalities. Thus regression equations based on their data may not be applicable to normal individuals.

The ratio of systolic blood pressure (cuff) to end-systolic volume (SBP/ESV) was calculated in the normal subjects at rest and during exercise as an index of contractility. This index has been shown to be reliable even when peak systolic pressure is substituted for end-systolic pressure and has been used to differentiate changes in contractile state vs those induced by the Frank-Starling mechanism.  

Exercise radionuclide angiography. The patients were taken to the exercise laboratory after injection of 1.7 mg of stannous chloride as pyrophosphate. Twenty minutes later, 20 mCi of 99m-technetium pertechnetate were injected intravenously. The patient was positioned on the exercise ergometer and connected to the leads for an electrocardiographic physiologic gate. A portable 37-photo multiplier tube gamma camera (Ohio Nuclear VIP) was positioned to obtain 45 degree left anterior oblique views centered on the left ventricle. The gamma camera was equipped with a parallel-hole medium-sensitivity collimator. Gated equilibrium radionuclide angiography was performed over a 2 min data acquisition period, with the patient at rest seated on the bicycle. The patient’s heart rate and blood pressure and the duration (min) of data acquisition were recorded. During exercise, gated equilibrium radionuclide angiograms were recorded during the last 2 min of each exercise stage and at peak exercise. All data acquisition was performed with 40 msec time frames and a maximum of 16 frames per cardiac cycle.  

Rest and peak exercise radionuclide angiograms were analyzed with a semiautomated computer program. After nine-point spatial smoothing, an operator-identified periventricular region of interest was used for background subtraction. An automated left ventricular edge-detection algorithm was used providing for variable regions of interest and definition of the
left ventricular time-activity curve. Care was taken to ensure that the left ventricular silhouette excluded left atrial activity and did not overlap the right ventricle. From the left ventricular time-activity curve, left ventricular end-diastolic and end-systolic counts were recorded and ejection fraction was determined by the ratio of stroke counts to end-diastolic counts. Left ventricular end-diastolic and end-systolic counts were converted to left ventricular end-diastolic and end-systolic volumes by a photon attenuation correction method based on a geometric method of attenuation distance quantitation that we have previously described. This method accurately estimates cardiac output determined by the Fick technique (r = .91). It overestimates left ventricular volumes by approximately 20% as compared with contrast cineangiography; but the values are correlated at r = .80. Left ventricular volume estimates were not corrected by regression equations because the error has been shown to be systematic and the echocardiographic volumes were not corrected.

Data analysis. The two-dimensional echocardiographic and radionuclide angiographic measurements made at rest and peak exercise in the patients were compared by linear regression analysis and paired Student's t tests. The serial two-dimensional echocardiographic data recorded at rest and during exercise in the two groups of normal subjects were analyzed by a one-way analysis of variance for repeated measures to ascertain differences across time in each group and by a two-way analysis of variance for repeated measures to compare the values across time between the two groups. Individual mean differences were determined by the Newman-Kuels mean comparison test based on the range and a significant difference was defined as p < .05.

Results

Validation experiment (table 1). End-diastolic and end-systolic volumes were smaller by two-dimensional echocardiography as compared with radionuclide angiography both at rest and during exercise, but there was a correlation between the values by each technique considering that the former was measured from 1 beat in the midpoint of the 2 min collection for the latter. Ejection fraction values were not significantly different between the two techniques, which supports the concept that the differences in volumes were consistent. Also, the average directional change in volumes during exercise was the same by both techniques, although the change was somewhat greater by radionuclide angiography. End-diastolic volume increased by an average of 8% by echocardiography and 22% by radionuclide angiography; end-systolic volume increased 22% by echocardiography and 38% by radionuclide angiography. The average change in ejection fraction with exercise was almost identical by the two techniques (14% two-dimensional echocardiography vs 15% radionuclide angiography). Thus, in these patients left ventricular volume and ejection fraction measurements by both techniques correlated and their directional changes during exercise were the same.

Effects of conditioning on resting left ventricular performance. Resting left ventricular end-diastolic volume estimates varied considerably between subjects (range 60 to 190 ml). They were related to maximum exercise duration (r = .80) (figure 1) but not to resting heart rate (r = .23) or body surface area (r = .38). Also, the relationship of end-diastolic volume to maximum exercise duration persisted when the former was corrected for body surface area (r = .70). Therefore, the major determinant of resting left ventricular size seemed to be the isotonic exercise capability of the individual, which is a reflection of the degree of training.

Maximum isotonic exercise duration readily separated the normal subjects into two groups as described above; a highly trained competitive group and a less well-trained noncompetitive group. The resting left ventricular end-diastolic volume estimate of 130 ± 29 (SD) ml in the 12 competitive marathon runners was significantly larger than the estimate of 87 ± 20 in the 18 noncompetitive subjects (p < .001), despite no significant difference in resting heart rate (70 ± 15 vs 68 ± 12 beats/min). The difference persisted when end-diastolic volume was divided by body surface area (p < .001). Resting left ventricular ejection fraction was similar in the two groups (55 ± 9% vs 54 ± 11%), but because of the marked difference in end-diastolic volume, resting left ventricular stroke volume

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<th>TABLE 1</th>
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<td><strong>Comparison of rest and peak exercise left ventricular volume and performance measured by two-dimensional echocardiography and radionuclide angiography in the patients with coronary artery disease</strong></td>
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<td><strong>EDV (ml)</strong></td>
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EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; Ex. = exercise; 2DE = two-dimensional echocardiography; RNA = radionuclide angiography.
was much greater in the competitive athletes at 72 ± 22 ml vs 48 ± 16 ml in the noncompetitive subjects (p < .001). SBP/ESV was significantly greater in the noncompetitive group as compared with the competitive group (3.3 ± 1.0 vs 2.0 ± 0.5 mm Hg/ml; p < .001), largely because end-systolic volume was larger in the competitive group.

Exercise left ventricular performance. The difference in end-diastolic volume between the competitive and noncompetitive athletes persisted during exercise (figure 2). However, the changes during exercise were not parallel because the difference between the two groups was significantly greater as exercise progressed (p < .01). Also, in each group end-diastolic volume at each point during exercise was significantly different from the resting values (p < .001), but the change from time to time during exercise was not significant after 70% of maximum heart rate was achieved. Thus end-diastolic volume in both groups increased significantly only during the first half of exercise.

The difference in stroke volume between the two groups also persisted during exercise (figure 3). Again, the changes during exercise were not parallel, because the difference between the two groups was significantly greater at higher exercise levels (p < .01). In both groups each value during exercise was significantly different from the resting value (p < .001). However, the change as exercise progressed was no longer significant after 70% of maximum heart rate was achieved. Therefore, as with end-diastolic volume, stroke volume in both groups did not increase significantly after the first half of exercise.

The difference in SBP/ESV between the two groups observed at rest was not consistent during exercise, because SBP/ESV increased more during exercise in the noncompetitive group (p < .03). However, in both groups the changes were most marked during the latter part of exercise (figure 4). Significant increases as compared with the resting value and over time during exercise were observed after 70% of maximum heart rate in the competitive group and after 85% in the noncompetitive group. Therefore, SBP/ESV in both groups increased significantly only during the second half of maximal bicycle exercise.

Throughout exercise there was no significant difference between the ejection fraction values of the two groups and the values paralleled each other (figure 5). In each group ejection fraction was significantly different from control at each point during exercise (p < .001); however, after 70% of maximum heart rate there was no significant change in ejection fraction as exercise progressed. Therefore, in each group significant changes in ejection fraction only occurred during the first half of exercise.

Discussion

A potential concern regarding our study is the reliability of two-dimensional echocardiographic left ventricular volume and performance measures during exercise. It has been shown that two-dimensional
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FIGURE 3. Left ventricular stroke volume at rest and during exercise. Abbreviations as in figure 2.

Echocardiographically derived resting left ventricular volumes correlate well with those derived by cineangiography but are underestimations. Ejection fraction calculations, on the other hand, are nearly equivalent by two-dimensional echocardiography, cineangiography, and radionuclide angiography at rest. Recent studies have shown the feasibility of recording high-quality two-dimensional echocardiograms during exercise. We recently demonstrated that ejection fraction determinations during upright bicycle exercise by two-dimensional echocardiography are equivalent to those by gated equilibrium radionuclide angiography if the former are measured during the midpoint of data collection for the latter.

Although these data would suggest that the volume estimates from which the ejection fractions were derived were accurate, we decided to further establish their validity as compared with a new radionuclide technique for estimating volume with correction for photon attenuation. We have shown that the latter technique accurately measures cardiac output as compared with the Fick technique but consistently overestimates left ventricular volumes measured by cineangiography with a good correlation. As expected, the two-dimensional echocardiography values measured at rest and during exercise were lower than the radionuclide measures. However, the differences were consistent, since ejection fraction values by the two techniques were similar and the directional changes in volume during exercise were the same by both techniques. Because normal individuals are easier to image by echocardiography than patients, we would expect the results in our athletic subjects would be more accurate than those in previous studies with patients. Also, we have previously demonstrated that the reproducibility of exercise two-dimensional echocardiographic estimates of left ventricular size and performance is not adversely affected by exercise. Similar results have been reported by others.

The results of our study demonstrate that the increase in resting end-diastolic volume observed in isotonically trained athletes was related to their ability to perform exercise. These data are consistent with the results of Zeldis et al., who found that the resting left ventricular internal dimension by M mode echocardiography was correlated with maximum oxygen consumption during exercise in athletes. It is also consistent with the findings of Cohen et al., who found that left ventricular end-diastolic volume index estimated by M mode echocardiography was related to the number of hours of dancing per year in ballet dancers. Thus

FIGURE 4. SBP/ESV at rest and during exercise. Abbreviations as in figure 2.
it appears that the well-recognized phenomenon of increased left ventricular end-diastolic volume in endurance-trained athletes is proportional to their level of training and represents a major adaptive mechanism to isotonic exercise training.

Our data also demonstrated that during upright exercise, left ventricular end-diastolic volume increases in the competitive and noncompetitive athletes and the patients with coronary artery disease. Previous studies have not consistently demonstrated increases in left ventricular size during exercise. The conflicting data concerning whether or not left ventricular end-diastolic volume increases during exercise seems to be explainable if the exercise position and amount of exercise are considered. Almost all studies employing maximum upright isotonic exercise have shown an increase in left ventricular size at peak exercise as compared with rest.\textsuperscript{20-24} However, studies using supine exercise often have failed to show an increase in left ventricular size, especially during submaximal exercise.\textsuperscript{3, 25} Of interest is that studies employing previously instrumented conscious dogs subjected to severe exercise by swimming or running also showed increases in left ventricular end-diastolic dimensions during maximal exercise.\textsuperscript{26, 27}

In our athletes the increase in end-diastolic volume was greatest during the first half of exercise and plateaued during the second half of exercise. These findings are consistent with those of Steingart et al.,\textsuperscript{24} who used gated equilibrium radionuclide angiographic changes in end-diastolic counts to estimate left ventricular volume in 17 normal subjects undergoing maximum upright bicycle exercise. However, they are at variance with the results of Weiss et al.,\textsuperscript{28} who studied normal subjects during maximal semisupine exercise by M mode echocardiography. They found increases in end-diastolic left ventricular size only at higher levels of exercise. Perhaps this difference is due to the semisupine position, which may augment venous return.

The increases in ejection fraction and stroke volume during exercise in both groups paralleled the changes in end-diastolic volume and thus were significant only during the first half of exercise. By contrast, increases in SBP/ESV were significant only during the second half of exercise. The latter results are consistent with those in the normal subjects studied by Steingart et al.\textsuperscript{24} They examined SBP/ESV derived from radionuclide angiography at 150, 300, and 600 kpm of supine bicycle exercise and found significant differences from the resting values only at 600 kpm. Thus it appears that the increase in cardiac performance during upright exercise is more dependent on the Frank-Starling mechanism in early exercise and on increases in contractile state toward the end of exercise. However, the Frank-Starling mechanism is probably still operant at peak exercise, since Sonnenblick et al.\textsuperscript{29} have shown that end-diastolic dimensions are larger during exercise than would be anticipated if the heart rate attained was duplicated by atrial pacing at rest.

Another concern regarding our study is the finding that the noncompetitive athletes had higher values for SBP/ESV than the competitive marathon runners. Does this mean that the former group has a higher contractile state than the latter? This index of contractility must be interpreted with caution, since it is an estimate of the slope of the end-systolic pressure-volume relationship based on a single point.\textsuperscript{30} To compare such slope estimates, a volume intercept of zero must be assumed. However, we know this is probably not the case, since the competitive athletes have larger hearts. Thus comparing the two groups may be inaccu-
rate, but the measure probably can be used to assess changes during exercise in the same group.

In comparing the response of the left ventricle to exercise in the highly trained competitive athletes vs the less well-trained noncompetitive runners, it is apparent that there are significant differences in the end-diastolic volume, stroke volume, and SBP/ESV at rest and during exercise, despite similar ejection fractions. Also, the differences in these variables between the two groups are always greatest at the end of exercise. More specifically, the left ventricle of the highly trained athlete is not only enlarged but also can increase in size during exercise proportionately more as compared with the left ventricle of less well-trained individuals. In addition, the SBP/ESV of the competitively trained athlete steadily increases during exercise, whereas in noncompetitive runners this measure increases markedly near maximum exercise. Thus it appears that the highly trained competitive athlete makes greater use of the less energy-consuming Frank-Starling mechanism to accomplish high levels of isotonic exercise performance as compared with the less well-trained noncompetitive runner.

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