The Effect of Exercise and Atrial Pacing on Left Ventricular Volume and Contractility in Patients with Innervated and Denervated Hearts

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SUMMARY The effect of maximum exercise on left ventricular function was assessed in 12 patients with normally innervated hearts (IH) and six patients with denervated hearts (DH) who had undergone cardiac transplantation. Left ventricular function was assessed by computer-assisted analysis of the motion of surgically implanted midwall myocardial tantalum markers, visualized fluoroscopically. Measurements were made at rest, and peak supine exercise in both groups of patients. The effect of atrial pacing to the heart rate achieved with peak exercise was also assessed in the patients with denervated hearts. The mean ejection fraction was increased at peak exercise in both groups of patients, although to a greater extent in patients with DH (14% vs 5%). With atrial pacing the mean ejection fraction decreased from the resting value by 4% in DH. The velocity of circumferential fiber shortening increased with peak exercise by 43% in IH and 38% in DH, but did not increase with atrial pacing in the DH group. Stroke volume index increased with peak exercise by 3% in IH and 14% in DH, but decreased by 6% with atrial pacing. There was no significant difference between end-diastolic volumes at rest, exercise or atrial pacing. Although these data may be important with milder exercise, they suggest that the preload effect was not predominant at peak exercise. By exclusion, adrenergic drive was the most important inotropic factor in the left ventricular response to peak exercise. The comparison between denervated and innervated patients' response to strenuous exercise suggests that comparably good exercise performance can be obtained by the denervated heart in the absence of normal autonomic control. Circulating catecholamines may therefore be contributing a very important inotropic action at peak exercise.

THE CIRCULATORY AND HEMODYNAMIC effects of muscular exercise have been extensively studied, but direct measurement of left ventricular contractility and volume during exercise has been more difficult to achieve. Although the adaptation of the left ventricle to dynamic exercise has been measured in both innervated and denervated dogs, few studies are available in man. These studies have used echocardiography, radarkymographic video tracking, left ventriculography and epicardial marker systems to assess the left ventricular response to both isometric and dynamic exercise. Through such studies, some data have become available on the left ventricular response to mild exercise; however, little data are available on the response to strenuous supine exercise.

In this study, the response of the left ventricle to strenuous supine exercise was assessed. In order to estimate the relative importance of autonomic as opposed to circulating adrenergic mechanisms in the left ventricular response to exercise, patients with either innervated and denervated hearts were compared. In addition, to assess the relative contribution of heart rate effect versus adrenergic mechanisms in determining ventricular performance, the effects of exercise, with its concomitant tachycardia, were compared to the effects of atrial pacing to the same heart rate without exercise.

Methods

Patients Eighteen male patients ranging in age from 35–58 years, with a mean age of 49 years, were included in the study. Informed consent was obtained from all patients and there were no complications of procedures. The innervated heart group consisted of 12 patients who had undergone coronary artery bypass graft surgery from 5–26 months (mean 16.3) before the study. These patients were completely asymptomatic with no history of angina pectoris following cardiac surgery. Four patients had a history of myocardial infarction before surgery and no patients had a history of congestive heart failure. Three patients were on maintenance digoxin, and none were receiving propranolol or diuretics. No patient had evidence of mitral regurgitation or other valvular disease. The denervated heart group consisted of six patients who had received human cardiac allografts six to 10 weeks before the study. There was no evidence of acute rejection in any of these six patients at the time of this study, as evidenced by electrocardiographic monitoring and myocardial biopsies.
These patients had all satisfactorily recovered from surgery and were engaged in a regular and rigorous daily exercise program. All patients were studied in the fasting state.

**Left Ventricular Function Analysis**

Left ventricular function was assessed by computer-assisted analysis of fluoroscopic motion of surgically implanted midwall markers outlining the left ventricular cavity, as described by Ingels et al.\(^4\) Tantalum myocardial markers were inserted at the time of surgery in the midwall myocardium to a depth of 5 mm from the epicardial surface (fig. 1A).

Seven markers were placed in the myocardium of each patient, one at the left ventricular apex, and six at three equidistant points from the apex to the base along both the anterolateral and inferior margins of the left ventricle so that the left ventricular chamber was outlined in the 30° right anterior oblique (RAO) projection. Two silver tantalum clips were also attached to the adventitia of the aorta 3 cm above the level of the aortic valve to delineate the anterior and posterior aspects of the valve, as seen in the RAO position.

Parameters of left ventricular contractility and wall motion were determined by analysis of the motion of the myocardial markers, visualized radiographically. Cardiac fluoroscopy was performed with the patient in the 30° RAO position at end-inspiration using a cesium iodide 9 in image intensifier coupled to an Ampex DR 10A video disc recorder operating at 30 frames/sec. The analog ECG signal was also recorded to allow precise identification of QRS onset. The magnification factor was determined echocardiographically using a protractor-like device permitting calculation of the distance between the left ventricular center and the table top. Magnification constants were obtained from fluoroscopy of a lead grid containing 1 cm squares.

After each fluoroscopic study, video recordings were replayed in a frame-by-frame manner and XY coordinates of the marker images were identified using a computerized light pen system. After correction of the marker image coordinates by the computer, the coordinates were punched on paper tape for each marker in each frame. Three complete cardiac cycles were analyzed and the means of these three measurements were used for final analysis (fig. 1A). Instantaneous myocardial dynamics and left ventricular volumes were calculated in the CDC-6700 digital computer as previously described.\(^4\) The instantaneous length of the longitudinal axis was derived for each frame using the apical marker and the midpoint of the aortic valve as end points. The aortic plane was identified by computer translation of the aortic markers to a position which had been defined by superimposition of the preoperative ventriculogram on the initial postoperative fluoroscopic marker study. The instantaneous lengths of the six minor radii (R1-R6, Fig. 1B) were calculated as the perpendicular distances between the corresponding markers. The average

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**Figure 1.** A) Two frames of reconstructed noninvasive cineventriculogram of one beat and end-diastolic frame. □—□, end-systolic frame, ▽—▽. The unconnected symbols at the top represent the aortic clips. Solid symbols are computer-generated coordinates of the aortic valve. B) Schematic representation of noninvasive cineventriculogram. Points 2-8 are implanted markers, and aortic valve points (A1, A9) are obtained by translation of the coordinates of the aortic clips. R1-R6 are ventricular radii. L is the ventricular length. \(D_{26}, D_{37}, D_{48}\) are transverse ventricular diameters.

Minor diameter (D avg) was calculated for each frame as one-third the sum of the six minor radii. The D avg maximum time was defined as end-diastole and the D avg minimum time was defined as end-systole. Using the longitudinal and minor axis, ventricular volumes were calculated by the single plane area length method.
of Sandler and Dodge. Because the myocardial markers were not positioned at the endocardial surface, a portion of myocardium was included in the chamber volume computation. When volumes calculated from myocardial markers were compared with volumes calculated from simultaneous postoperative contrast left ventriculograms by Alderman et al., a linear relationship was observed \((r = 0.97)\). There was a constant overestimation by the marker method, which reflects the fact that on the average, for a relatively normal-sized ventricle, there was a volume of about 30 ml included between the shell defined by the markers and that defined by the ventricular (endocardial) border seen angiographically. This slight overestimation was corrected in all calculations. After determination of end-diastolic and end-systolic volumes, stroke volume was calculated. Cardiac output was determined from stroke volume and heart rate. The normalized mean circumferential shortening velocity \((V_{\text{cf}})\) during ejection was calculated as the mean shortening rate of the average normalized diameter from end-diastole to 167 msec after the occurrence of the maximum end-diastolic diameter. Variations in repeated measurements of the same beats, and variability in day-to-day measurements in the same patients, were not found to be significant.

### Patient Studies

All patients were studied in the resting state. These studies were carried out with the patient supine in the cradle, tilted at a 30° RAO position, and with the legs elevated in position on the bicycle ergometer pedals. Resting indirect blood pressure was measured by a mercury sphygmomanometer, and the resting heart rate was also recorded.

Atrial pacing was carried out on the transplant patients using a Medtronic temporary pacemaker coupled to atrial electrode wires implanted at the time of transplant surgery and brought transthoracically to the skin surface. Several pacing rates were selected in order to include the peak heart rate obtained with subsequent exercise. Fluoroscopic measurements, which were made at the pacing rate equal to the heart rate at peak exercise, were used in the final data analysis. Fluoroscopic recordings and measurements of blood pressure were made after 2 minutes of steady state pacing with the patient in the 30° RAO position and legs elevated. Following completion of the pacing studies, a 10-minute rest period was completed with the patient remaining in the supine position. The patient then began supine leg exercise in the same position using a Collins bicycle ergometer. The exercise protocol was designed to permit each patient to exercise for a total duration of 6–12 minutes. Patients started with a workload of 150 kpm and increased by 150–300 kpm every 3 minutes continuously to the maximum workload. The maximum workload for all patients ranged from 450–750, with a mean of 600 kpm. All exercise studies were carried out to an end point of fatigue and no patient experienced angina pectoris. Nine lead monitoring, including the limb leads and leads V4, V5, V6, during exercise demonstrated no ST segment depression suggestive of ischemia. When the patient approached test-limiting fatigue, the cradle was turned to the 30° RAO position with the patient continuing to cycle. Fluoroscopic measurements were then made at held end-inspiration.

Rest, atrial pacing and exercise studies were completed for each patient in sequence. On completion of these studies, the parameters of left ventricular contractility and volume were calculated for the rest, paced and exercise conditions in each transplant patient. Patients with innervated hearts underwent the same study protocol with the exception that atrial pacing was not performed.

Statistical analysis was carried out by the paired \(t\) test in comparing exercise and paced values to resting

### Table 1. Changes from Rest to Atrial Pacing and Exercise

<table>
<thead>
<tr>
<th></th>
<th>Denervated Hearts</th>
<th>Percent change</th>
<th>Exercise</th>
<th>Percent change</th>
<th>Innervated Hearts</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (\text{beats/min})</td>
<td>80 ± 4</td>
<td>102 ± 7†</td>
<td>28%</td>
<td>103 ± 7†</td>
<td>69 ± 5</td>
<td>112 ± 6†</td>
</tr>
<tr>
<td>Cardiac index (\text{L/mm}^2\text{m}^2)</td>
<td>3.9 ± 0.2</td>
<td>4.6 ± 0.3</td>
<td>18%</td>
<td>5.8 ± 0.3†</td>
<td>2.3 ± 0.1</td>
<td>4.2 ± 0.3†</td>
</tr>
<tr>
<td>Systolic blood pressure (\text{mm Hg})</td>
<td>111 ± 3</td>
<td>113 ± 3</td>
<td>2%</td>
<td>125 ± 3</td>
<td>13%</td>
<td>127 ± 6</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.56 ± 0.01</td>
<td>0.54 ± 0.01*</td>
<td>4%</td>
<td>0.64 ± 0.03‡</td>
<td>14%</td>
<td>0.55 ± 0.03</td>
</tr>
<tr>
<td>Vcf (\text{circumferences/sec})</td>
<td>1.02 ± 0.03</td>
<td>1.04 ± 0.05</td>
<td>2%</td>
<td>1.41 ± 0.05‡</td>
<td>38%</td>
<td>0.80 ± 0.04</td>
</tr>
<tr>
<td>End-diastolic volume index (\text{ml/m}^2)</td>
<td>90 ± 8</td>
<td>87 ± 8</td>
<td>3%</td>
<td>90 ± 8</td>
<td>0%</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>Stroke volume index (\text{ml/kg})</td>
<td>50 ± 4</td>
<td>47 ± 4†</td>
<td>6%</td>
<td>57 ± 5*</td>
<td>14%</td>
<td>36 ± 3</td>
</tr>
</tbody>
</table>

Measurements are in mean and SEM values.

\(\*P < 0.05)\)

\(\dagger P < 0.01)\)

\(\ddagger P < 0.001)\)

Abbreviation: \(V_{\text{cf}}\) = velocity of circumferential fiber shortening.
values and by the unpaired t test in comparing the innervated to denervated groups.

Results

Hemodynamic data for the patients with innervated and denervated hearts are summarized in table 1. Individual patient data are plotted in figures 2–4. Patients with normally innervated hearts responded at peak exercise with an 82% increase in cardiac index (fig. 2B). This increase in cardiac index reflected primarily a 62% increase in heart rate (fig. 2A) and a small 3% increase in stroke volume index (fig. 4B). The significant increase in contractility, reflected by a 43% increase in velocity of circumferential fiber shortening (fig. 3B) and a 5% increase in ejection fraction (fig. 3A), was accomplished at a constant end-diastolic volume index (fig. 4A). Systolic blood pressure rose 39% (fig. 2C).

Exercise in the denervated patients yielded directionally similar hemodynamic findings. However, comparison of the percentage increments using unpaired t test statistics showed a significantly larger increase in ejection fraction (P < 0.05), and smaller increase in heart rate (P < 0.05) and cardiac index (P < 0.05) in the denervated group. There were no significant differences in stroke volume index and velocity of circumferential fiber shortening between the two groups. There was a smaller increase of 13% in systolic blood pressure in the denervated group (fig. 2C).

Atrial pacing in denervated patients to a heart rate equivalent to that achieved during peak exercise yielded distinctly different hemodynamic measurements. The cardiac index increase was 18% with atrial pacing, compared to 49% with exercise (fig. 2B). Thus, although heart rate increased by atrial pacing to the same extent as exercise, stroke volume index fell by 6% (fig. 4B). The fall in stroke volume index reflected a 3% decline in end-diastolic volume index during atrial pacing (fig. 4A) along with a 4% decline in ejection fraction (fig. 3A) and unchanged velocity of circumferential fiber shortening (fig. 3B). Systolic blood pressure, similarly, did not rise comparably to the exercise response (fig. 2C).

Discussion

In this study, we assessed the effect of strenuous supine exercise on left ventricular function in patients. Although the circulatory effects of exercise have been extensively investigated, there has been some difficulty in assessing left ventricular function. Ultrasound and lead titanate zirconate crystal transducers attached to the left ventricular endocardial surface have been used to measure internal ventricular diameters during exercise in dogs. O'Rourke et al. used radarkymographic video tracking to measure left ventricular dimensions during hand grip exercise in patients. Other workers have used echocardiography to assess left ventricular size and performance during isometric hand grip exercise. However, left ventricular function in patients performing dynamic exercise is more difficult to assess using echo techniques because of exaggerated cardiac and thoracic motion which impairs the stability of transducer aim. Nevertheless, Stein et al. have used echocardiography to obtain left ventricular dimensions during, and immediately following, leg exercise.

Left ventriculography before and during supine submaximal exercise has been reported by Sharma et al., Braunwald and coworkers studied patients with silver tantalum markers implanted on the epicardial surface at the time of surgery. Using this technique, Sonnenblick evaluated the effects of mild supine dynamic exercise, atrial pacing and beta-adrenergic blockade. Recently, Borer et al. have reported the use of radionuclide angiography to assess left ventricular function during exercise. In this study, we used radiopaque markers to evaluate the effects of dynamic exercise on left ventricular volumes and contractility. The placement of seven midwall markers allows a more complete delineation of the left ventricular silhouette in the 30° RAO position than is possible with the more limited epicardial marking system used in previous studies. The midwall location also has better dynamic excursion than epicardial markers and more directly reflects endocardial motion. The use of multiple markers, each of which contributes to the calculation of the velocity of shortening, tends to reduce noise and improve the accuracy of these measurements. The use of fluoroscopic measurements does not require the use of premedication nor contrast medium which may have depressant effects on autonomic or left ventricular function.

This study differs significantly from previous studies assessing left ventricular function in that symptomlimited exercise to fatigue was employed instead of milder exercise. The exercise was performed supine with the legs elevated, and thus may not mimic more physiological measurements made in conscious, walking animals or bicycle exercise in man. The supine exercise position may be particularly relevant in understanding the smaller than expected increases in peak heart rate and cardiac index observed in these patients. Supine exercise in the cradle requires the patient to hold his body stiff and rigid with continued hand grip to prevent slipping from the bicycle. This contributes a considerable isometric component to the isotonic work as reflected by the high systolic pressures in the innervated group, and contributes to the fatigue which terminated exercise in all patients. This isometric component would tend to limit the increase in heart rate and cardiac output before fatigue.

The question arises as to the degree of innervation and denervation of the two patient groups studied. Previous work has shown that cardiac transplant recipients are indeed denervated. Furthermore, the relatively short interval between the time of surgery and study would leave little time for sympathetic regeneration. Finally, the absence of autonomic augmentation is also apparent in the attenuated heart rate response at peak exercise in the transplant group, as has previously been reported by Clark. In contrast, the post-bypass patients are highly likely to be normally innervated. The 16.3-month interval be-
Figure 2. The heart rate (A), cardiac indices (B), and systolic blood pressure (C) at rest, maximum exercise and atrial pacing are plotted for each of the patients with denervated and innervated hearts, with the mean values for each condition on the left side of the graphs.
between surgery and study was sufficiently long enough to reasonably expect restoration of normal innervation which may have been disrupted during surgery. Finally, although previous work has demonstrated abnormal cardiac parasympathetic control in some patients with congestive failure, patients in this study had no history of failure, and for the most part, good ventricular function as reflected by their ejection fractions.

The results of our study permit a comparison of the ventricular response to exercise in denervated versus innervated patients. The resting heart rate in the denervated patients was slightly higher than in the innervated group, reflecting the absence of resting vagal tone. Similarly, the percentage increment in exercise heart in the denervated group was significantly lower than the increase in innervated patients, although the absolute increases in cardiac output were similar. This reflects the absence of intrinsic sympathetic drive and is similar to results obtained in denervated dogs. This is consistent with the responses obtained in man, exercising under autonomic blockade which similarly blocks the heart rate increase. Ejection fraction, a measure of ventricular performance, increased more prominently in denervated patients than innervated patients. There was only a 5% increase with peak exercise in innervated patients as compared to a 14% increase in denervated patients. There was also a comparably good ventricular response to peak exercise in the denervated group as assessed by the Vcf. The Vcf in the denervated group increased with maximum exercise by 38% as compared to 43% in the innervated group. There is considerable scatter in end-diastolic volume measurements from patient to patient, with overall similarity between the innervated and denervated groups. Some patients showed a slight increase...
The end-diastolic volume indices (A) and stroke volume indices (B) at rest, maximum exercise and atrial pacing are plotted for each of the patients with denervated and innervated hearts, with the mean values for each condition on the left side of the graph.

in end-diastolic volume index with fatigue-limited exercise, while other patients showed a slight decrease. The results in innervated patients concur with studies on similar patients using contrast ventriculography in supine submaximal exercise.\textsuperscript{11}

Studies using atrial pacing to the same heart rate level as attained during exercise permit the assessment of the relative contributions of heart rate and adrenergic mechanisms to the left ventricular response to peak exercise. Atrial pacing to the same heart rate attained with maximum exercise increased cardiac output by only 36\% of the increment which maximum exercise produced in denervated patients. In addition, atrial pacing had no effect on the velocity of circumferential fiber shortening and, in fact, caused a decrease in ejection fraction in contrast with the increase observed during peak exercise. These observations confirm that tachycardia in and of itself cannot account for the exercise performance of denervated patients.

Atrial pacing caused a small decline in end-diastolic volume in five of six patients. The fact that it did not decline significantly as compared to the more marked changes, observed by Sonnenblick and other workers in studies using atrial pacing in innervated patients, probably reflects the larger heart rate increments in those studies.\textsuperscript{13, 23, 24} The observation that exercise end-diastolic volumes in denervated patients were similar to the paced volumes confirms that augmented cardiac performance in strenuously exercising denervated patients is largely due to adrenergic mechanisms rather than increased preload. The denervated patients had a 13\% increase in systolic pressure at maximum exercise as compared to no change with atrial pacing. Yet an increase in afterload, as reflected by systolic blood pressure, caused a decline in ejection...
phase indices of ventricular function. This suggests that the extent of increase in Vcf and ejection fraction in denervated patients, and thus adrenergic contribution, may have been underestimated at peak exercise when systolic pressure was increased.

An important observation in this study, comparing denervated and innervated patients’ responses to supine exercise, suggests that comparably good exercise performance can be obtained by a denervated heart in the absence of normal autonomic control. It is apparent that circulating catecholamines must be contributing an important inotropic action in the denervated heart. The increases in heart rate, Vcf, and ejection fraction are all considerable and probably reflect high concentrations of circulating catecholamines at the time of maximum exercise. In addition, previous work has shown that denervated hearts have increased sensitivity to circulating catecholamines. It would, in these studies, be helpful to assess the effects of beta blockade in these two patient groups. However, previous studies in dogs suggest that maximum exercise in such a study would be hazardous for denervated patients. Similarly, measurements of circulating catecholamines would be useful, but were not available at the time of this study.

In conclusion, we believe that our studies show the prominent extent to which adrenergic mechanisms can be brought into play in the left ventricular response to fatigue-limited exercise. The contributions of increased preload are almost completely obscured at this exercise level. Furthermore, the comparably good ventricular response of the denervated heart suggests that circulating catecholamines may have a very important inotropic influence at peak exercise.

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