Left Ventricular Response to Isometric Exercise in Patients with Denervated and Innervated Hearts

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with the assistance of Anne Schwarzkopf

SUMMARY Patients with cardiac denervation resulting from allograft transplantation have been observed to increase their diastolic and systolic blood pressure during isometric exercise without concomitant cardioacceleration. To determine the mechanism for the blood pressure increase, heart rate, blood pressure, and ventricular volumes (measured using fluoroscopy of tantalum midwall myocardial markers) were recorded before and after a 50% maximal voluntary contraction. Seven cardiac transplant recipients (denervated heart) and seven nontransplant patients (innervated heart) were studied. Innervated and denervated heart patients increased systolic blood pressure by 16% and 21% and total peripheral resistance by 20% and 12%, respectively. The percentage responses were not significantly different between groups, except for heart rate, which increased 17% in innervated heart patients and 2% in denervated heart patients ($p < 0.05$). Neither group had enhanced contractility or increases in cardiac output, suggesting that the blood pressure increases resulted in both groups from increased peripheral resistance.

ISOMETRIC EXERCISE is known to increase systemic arterial blood pressure in healthy adults and cardiac patients. This increase in pressure is independent of the size of the muscle mass involved and the absolute amount of work being performed, but is proportional to contraction intensity relative to the isometric strength of the muscle mass involved (percent of maximal voluntary contraction). Sustained isometric contractions above about 15% of maximal voluntary contraction result in an accumulation of metabolites in the contracting muscle, which stimulates reflex afferents causing general sympathetic activation and vagal withdrawal. This reflex stimulation (along with cortical irradiation) increases heart rate, causes arterial vasoinhibition in nonexercising skeletal muscle, and increases cardiac output with little change in stroke volume.

The increase in heart rate due to direct autonomic control has been considered important in the blood pressure response to isometric exercise. Preliminary observations in our laboratory have indicated that heart transplant patients (denervated hearts) have a normal increase in blood pressure with isometric exercise, though heart rate is not increased. This study was designed to determine whether denervated hearts increase blood pressure by elevating cardiac output through some non-neurally mediated enhancement of contractility or if peripheral mechanisms of blood pressure elevation are responsible.

Methods

Seven cardiac transplant patients with denervated hearts and seven patients with innervated hearts who had undergone surgery for coronary artery bypass grafting or valve replacement were selected for study. Each of the 14 subjects had tantalum wire coils implanted during surgery, allowing left ventricular wall motion to be observed using fluoroscopy. Heart rate, blood pressure and ventricular volumes were determined before and after 1 minute of a 50% maximal voluntary contraction. From the fluoroscopic data, cardiac output, ejection fraction, velocity of circumferential fiber shortening and total peripheral resistance were calculated.

The technique of implanting and analyzing results from intramyocardial markers has been described previously. Seven tantalum wire coils were implanted during surgery in the midwall of the left ventricle so that the chamber is outlined when viewed in the $30^\circ$ right anterior oblique projection. Two additional clips were attached to the aortic adventitia to serve as reference points for the aortic valve. Several cardiac cycles were recorded before and after isometric exercise, during suspended respiration. The fluoroscopic image was recorded on a videodisc recorder along with the ECG signal to allow precise detection of QRS onset. After each study, the video recordings were played back frame by frame and the $x$ and $y$ coordinates for each marker were digitized using a light pen and a minicomputer system. Data for each condition, preexercise control and isometric exercise, were obtained frame by frame over three heart beats. From the digitized data representing changes in marker coordinates, the velocity of circumferential fiber shortening, ventricular volumes, ejection fraction and cardiac output were calculated.

Left ventricular volumes were calculated using...
Sandler and Dodge's single-plane method. Left ventricular volumes obtained by myocardial markers and simultaneous contrast angiograms have been linearly related \((r = 0.97)\). End-diastolic volume was determined from the maximum of the instantaneous volume curve, end-systolic volume from the minimum of the instantaneous volume curve, and stroke volume as the difference between the two volumes. In a report of six patients who underwent left ventricular volume determinations by markers and contrast ventriculography simultaneously, the mean error from contrast-derived values was \(-7.7\%\), +9.1\%, and \(-3.3\%\), respectively, for stroke volume, end-systolic volume and end-diastolic volume. Though biplane radiography of marker patients has demonstrated a wringing action of the left ventricle during systole, the plane of the markers retains its orientation in the right anterior oblique position during contraction. All volumes were corrected for chamber volume overestimation resulting from calculations using midwall markers with a previously validated regression line.

All subjects tested were healthy at the time of the study. The primary criteria for study inclusion were current good health and presence of markers. Transplant patients were in the hospital for a routine follow-up visit, innervated patients came to the laboratory as outpatients specifically for this study. Because of the disparate indications for transplantation and coronary artery bypass surgery, closer age matching of subjects was not practicable. Informed consent was obtained from each subject in accordance with our institutional Human Subjects Committee policy. Maximal grip strength of the dominant hand was assessed before the marker studies using a Jamar dynamometer (J.A. Preston, New York). Patients were studied in the supine position. In transplant patients, direct blood pressure was obtained in the descending aorta during the test using a catheter transducer. In four innervated patients, blood pressure was measured in the nondominant arm by sphygmomanometer, in another, direct pressures were measured via the radial artery, and in two, pressures were not obtained. During each study, marker motion was recorded for several seconds before and during the last few seconds of handgrip contraction.

Arterial blood was withdrawn and placed in tubes containing reduced glutathione immediately before and within 40 seconds after contraction for analysis of catecholamines in six of the denervated and in one of the innervated patients. These samples were cooled immediately upon withdrawal, spun in a refrigerated centrifuge, and the plasma was decanted off and frozen until analysis could be performed by the method of Passon and Peuler. Direct pressures and the ECG were recorded on a Hewlett Packard multichannel recorder before grip and throughout the contraction.

Preexercise values were compared between innervated and denervated hearts using unpaired \(t\) tests. Because the groups differed before exercise in several respects, the percentage change with exercise from control was compared within groups using the paired \(t\) test and between groups using the unpaired \(t\) test. The significance level was set at \(p < 0.05\).

### Results

Physical characteristics of the patients studied are shown in table 1. The mean age of innervated heart patients was 59 years and that of denervated patients was 44 years \((p < 0.02)\). The mean height of innervated and denervated heart groups was 169 cm and 179 cm \((p < 0.02)\), respectively, while mean body mass was 69.7 kg and 81.7 kg \((p < 0.05)\), respectively. Though the groups differed significantly in body mass and height, the ponderal index \((mass^{1/5} \times height^2)\) of each group was nearly identical \((2.43 \times 10^{-2} \text{kg cm}^{-1} \text{ vs } 2.41 \times 10^{-2} \text{kg}^{1/5} \text{cm}^{-1}, p < 0.60)\).

In both groups, blood pressures and total peripheral resistance increased substantially with isometric grip, while only innervated patients significantly increased heart rate (table 2).

Each patient increased diastolic pressure with grip and only one patient (innervated heart group) failed to increase systolic pressure (fig. 1). Figure 2 shows the responses of total peripheral resistance, cardiac output and heart rate to isometric exercise in both groups. Both baseline and isometric heart rates were significantly higher in denervated than in innervated patients \((p < 0.001\) baseline, \(p < 0.01\) isometric). Cardiac output did not increase significantly in either group. Total peripheral resistance increased significantly in both groups, increasing to some extent in every subject.

End-diastolic volume was significantly lower in transplants than in innervated patients before and after isometric exercise \((p < 0.01)\) (table 2). Both diastolic and systolic volumes increased in denervated patients. Stroke volume was lower in transplants than in innervated patients before exercise \((p < 0.05)\), but neither group increased stroke volume significantly with grip. Ejection fraction and velocity of cir-

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Body mass (kg)</th>
<th>Sex</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>170</td>
<td>84</td>
<td>F</td>
<td>21 mo pCABG</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>163</td>
<td>66</td>
<td>M</td>
<td>33 mo pCABG</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>165</td>
<td>58</td>
<td>M</td>
<td>37 mo pAO replace</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>165</td>
<td>60</td>
<td>F</td>
<td>52 mo pCABG</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>175</td>
<td>69</td>
<td>M</td>
<td>24 mo pCABG</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>165</td>
<td>72</td>
<td>F</td>
<td>28 mo pCABG</td>
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<tr>
<td>7</td>
<td>59</td>
<td>178</td>
<td>79</td>
<td>M</td>
<td>52 mo pCABG</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>170</td>
<td>85</td>
<td>M</td>
<td>31 mo pTx</td>
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<tr>
<td>9</td>
<td>51</td>
<td>177</td>
<td>78</td>
<td>M</td>
<td>35 mo pTx</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>188</td>
<td>90</td>
<td>M</td>
<td>23 mo pTx</td>
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<tr>
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<td>53</td>
<td>170</td>
<td>67</td>
<td>M</td>
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<td>M</td>
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<td>49</td>
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<td>89</td>
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<td>49 mo pTx</td>
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<tr>
<td>14</td>
<td>49</td>
<td>192</td>
<td>95</td>
<td>M</td>
<td>12 mo pTx</td>
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</tbody>
</table>

Abbreviations: mo pCABG = months after coronary bypass graft surgery; mo pAO replace = months after aortic valve replacement; mo pTx = months after cardiac transplantation.
LV RESPONSE TO ISOMETRICS/Savin et al.

TABLE 2. Comparison of Responses to Isometric Contraction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Innervated hearts (n = 7)</th>
<th>Denervated hearts (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Isometric</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>139.4 ± 14.9</td>
<td>162.0 ± 22.7</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>76.4 ± 6.2</td>
<td>98.0 ± 16.2</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>65.0 ± 11.6</td>
<td>75.9 ± 9.7</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>167.4 ± 38.3</td>
<td>176.6 ± 38.0</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>90.6 ± 25.4</td>
<td>105.2 ± 32.8</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>76.8 ± 15.9</td>
<td>71.4 ± 17.2</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.00 ± 1.31</td>
<td>5.36 ± 1.17</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>1343 ± 524</td>
<td>1612 ± 665</td>
</tr>
<tr>
<td>(dyn-sec-cm⁻²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>46.2 ± 5.0</td>
<td>41.1 ± 9.3</td>
</tr>
<tr>
<td>Velocity of circumferential fiber shortening (circ/sec)</td>
<td>0.63 ± 0.14</td>
<td>0.56 ± 0.18</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

* p < 0.05.
† p < 0.02.
‡ p < 0.01.
§ p < 0.001.

n = 5 for means of systolic and diastolic blood pressure as well as total peripheral resistance in the innervated group.

cumferential fiber shortening did not change significantly in either group with exercise. There were no significant group differences in percentage change during isometric exercise for any of the variables measured other than heart rate (p < 0.05).

Catecholamine responses of the denervated and innervated heart patients were directionally similar. In the denervated heart group, norepinephrine rose from 231 ± 94 pg/ml of plasma (mean ± sd) to 304 ± 123 pg/ml with isometric exercise. Epinephrine and dopamine concentrations were measured at 23 ± 16 pg/ml and 34 ± 36 pg/ml before exertion and 27 ± 13 pg/ml and 18 ± 19 pg/ml after exertion. Corresponding values for the single innervated subject (patient 7) in whom measurements were available

Figure 1. Systolic and diastolic blood pressures before (C) and after 1 minute of a 50% isometric contraction (I) are plotted in patients with innervated and denervated hearts. Means and standard deviations are shown.

Figure 2. Responses of total peripheral resistance (TPR), cardiac output (CO), and heart rate (HR) to isometric contraction are shown as in figure 1.
were 368, 156 and 27 pg/ml before contraction and 401, 180 and less than 1 pg/ml after contraction. The changes in catecholamines in the transplant group were not statistically significant at the 0.05 level, though the increase in norepinephrine had a p value of 0.08.

Discussion

In this study we found that subjects with and without denervated hearts had similar blood pressure responses to isometric exercise. Blood pressure elevations were attributable to total peripheral resistance in both groups rather than any increase in cardiac output. Similarly, myocardial contractility did not change in either group as measured by velocity of circumferential fiber shortening and ejection fraction. The changes observed in plasma catecholamines are in the same direction as those previously seen with isometric exercise in normal patients and with dynamic exercise in heart patients.

The hemodynamic responses in both denervated and innervated groups were different from those previously observed in young normal subjects, though similar to results reported for coronary artery disease patients and some older subjects. Normal subjects elevated arterial pressure by increasing heart rate or contractility, which increases cardiac output without changing total peripheral resistance at low levels of contraction. Above 50% of maximal voluntary contraction, increased total peripheral resistance makes a significant contribution to the elevation of blood pressure. Coronary artery disease patients rely more on increases in total peripheral resistance and less on cardiac output elevation to increase arterial pressure than normal subjects do. This could be the result of an inordinate increase in total peripheral resistance suppressing the usual rise in cardiac output, as reported in the response of coronary artery disease patients to dynamic exercise. A possible explanation for this response is a high degree of α-adrenergic tone causing increased peripheral resistance combined with a compromised left ventricle that has difficulty increasing its output, particularly when faced with increased afterload.

Figure 3 summarizes the mechanisms available for increasing arterial pressure (for a detailed review see Longhurst and Mitchell) and helps explain the responses in denervated patients. When the isometric reflex is initiated by a metabolite activation of receptors, reflex efferents have no direct path to the denervated heart. Any increases in heart rate and contractility are mediated by circulating catecholamines, while α-receptor-mediated increases in peripheral resistance still respond to the neural reflex. In our subjects, total peripheral resistance was more important in elevating arterial pressure than humoraly mediated increases in cardiac output. This is in contrast to the importance of catecholamine-induced inotropy reported during peak dynamic exercise in denervated patients. The rapidity of neural vs humoral mechanisms may explain why neural rather than humoral mechanisms are favored in the isometric response of denervated patients.

Data on normal patients show an immediate increase in heart rate and diastolic and systolic aortic pressures with isometric onset. These immediate changes quickly attenuate the perturbation of perfusion pressure, blood flow and local metabolite accumulation (fig. 3), thus the stimulus for reflex activation (increased metabolite concentration) would be somewhat attenuated. If, as with the denervated patients, no immediate increases in heart rate or contractility can be elicited, one can imagine the reflex efferent activity to the α-receptors increasing until total peripheral resistance increases arterial pressure enough to offset the initial decrease in local blood flow. This preserves a heterogeneous vasoconstriction of the regional circulations, an idea that requires further experimental investigation. Arterial blood pressure is an important regulated variable in maintaining appropriate blood flow to isometrically exer-

**Figure 3.** The principle mechanisms available for arterial pressure elevation as a result of isometric contraction are summarized in a diagrammatic form. X is the symbol used for addition and subtraction, for example: ARTERIAL PRESSURE + PERFUSION PRESSURE shows that perfusion pressure is enhanced by increasing arterial pressure and diminished by increasing tissue pressure. ▶ represents multiplication, for example: STROKE VOLUME ▶ CARDIAC OUTPUT indicates that cardiac output equals heart rate times stroke volume. For further review of control systems nomenclature see Guyton.
cising muscle (fig. 3). We have shown that in the absence of an increase in cardiac output, increased total peripheral resistance fully accounts for blood pressure elevation.

Acknowledgments

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