Radionuclide and Hemodynamic Assessment of Left Ventricular Functional Reserve in Patients with Left Ventricular Aneurysm and Congestive Cardiac Failure

Response to Exercise Stress and Isosorbide Dinitrate


SUMMARY  The hemodynamic response to exercise stress was assessed in 17 patients with left ventricular (LV) aneurysm, demonstrated by contrast left ventriculography, and congestive cardiac failure (CCF) before and after sublingual isosorbide dinitrate (ISDN). Radionuclide ventriculography was performed at rest and during exercise in 14 patients. ISDN increased mean exercise LV stroke work index (LVSWI) from 31 to 39 g-m/m² (p < 0.001) and reduced mean exercise LV filling pressure from 38 to 25 mm Hg (p < 0.001). Using the combined criteria of LVSWI and ejection fraction of the contractile section of the left ventricle (EFCS), no patient with rest EFCS < 40% achieved a good absolute response to exercise in LV performance with or without ISDN. Of the six patients with rest EFCS ≥ 40% only three achieved a good response. While rest EFCS < 40% indicates poor LV functional reserve, good LV functional reserve is not always indicated by rest EFCS ≥ 40%.

ISOSORBIDE DINITRATE (ISDN) is effective in reducing left ventricular filling pressure in patients with congestive cardiac failure at rest. A recent study demonstrated the effectiveness of acutely administered sublingual ISDN in improving exercise left ventricular function in patients with congestive cardiac failure secondary to generalized left ventricular dysfunction.

In patients with congestive cardiac failure secondary to left ventricular aneurysm, left ventricular aneurysmectomy is an important therapeutic possibility. This procedure, although successful in some patients, has a significant surgical mortality and does not always result in clinical improvement.

Recent studies have indicated that an important predictor of surgical survival in patients with left ventricular aneurysm is the function of the contractile section of the left ventricle. In this study we attempted to develop a more refined technique to assess residual left ventricular function in patients with left ventricular aneurysm.

Patients and Methods

Seventeen patients, ages 44-64 years, were studied at the time of diagnostic cardiac catheterization. There were 14 men and three women (table 1). Each patient gave informed consent for the procedure. Patients took only their current diuretic on the day of the study, at least 4 hours before, together with light premedication with diazepam. No patient took a digitalis glycoside for at least 7 days before the study.

The principal presenting symptom in all patients was exertional dyspnea (grade III, New York Heart Association classification); patients 2, 4, and 6 also had angina pectoris. All patients had a history and electrocardiographic evidence of at least one myocardial infarction. All patients were in sinus rhythm and had clinical and radiographic evidence of congestive cardiac failure. Some patients had a soft apical systolic murmur.

On the day before the study a supine, submaximal work rate was determined on a bicycle supine ergometer. Patients who could not for any reason perform leg exercise for 2-3 minutes were excluded from the study.

Hemodynamic Studies

After left ventriculography (right anterior oblique view using 40 ml Conray 420 contrast medium) and coronary arteriography, 30 minutes was allowed for hemodynamic recovery from the effects of contrast media. A flow-directed thermol dilution catheter was positioned in a pulmonary artery and a 20-gauge Medicut cannula was inserted into the brachial artery. In three patients a 7 NIH catheter was positioned in the left ventricle for pressure measurements. In these patients systemic arterial pressure was not recorded. Lead II of the ECG was recorded. Pressures were measured using Bell and Howell transducers and recorded on a Mingograf 82 recorder at various paper speeds. Mean pressures were obtained by electronic integration. Cardiac output was measured by the thermodilution technique using a Waters cardiac output computer. Each measurement was made in triplicate.

In three patients left ventricular filling pressure was measured directly by a catheter in the left ventricle, in the other patients it was measured by the mean pulmonary capillary wedge pressure.
Control measurements were made of heart rate, systemic arterial pressure, pulmonary arterial pressure, left ventricular filling pressure and cardiac output. Each patient then performed submaximal supine leg exercise on a bicycle ergometer at a previously determined work rate (table 1) for 2–3 minutes, when measurements were repeated. Ten minutes were allowed for recovery, when control measurements were repeated; then 5 mg of ISDN was administered sublingually. After 15 minutes measurements were made at rest and during exercise after the same period as before.

There were no complications. No patients complained of angina during either exercise period. No ST-T changes occurred in the ECG during exercise.

**Radionuclide Studies**

In addition to the hemodynamic investigations, all but three patients (nos. 9, 10, and 12) underwent radionuclide left ventriculography at rest and during exercise. The radionuclide ventriculograms were obtained using a multicrystal gamma camera with high count rate capability (Baird Atomic System 77). A 10-mCi bolus of high-specific activity technetium-99m ($^{99m}$Tc) as pertechnetate was injected into the right atrium with a rapid saline flush. One thousand frames of data were collected at 50-msec framing intervals to monitor the first pass of the radionuclide through the central circulation.

The rest radionuclide ventriculogram was obtained the day before that obtained during exercise. The exercise studies were performed before (14 patients) and after (13 patients) ISDN administration. In five patients the exercise radionuclide studies were performed at the time of the hemodynamic studies and in nine they were performed separately. The radionuclide was injected immediately after exercise. The second radionuclide ventriculogram (after ISDN administration) was obtained at least 25 minutes after the first to allow for the clearance of the first bolus of $^{99m}$Tc from the intracardiac blood pool.

Before the second exercise study a static back- ground frame was counted to a maximum 9000 counts per cell and the second study was corrected for residual blood-pool activity, field nonuniformity and dead time. Because constant patient positioning was crucial, enabling accurate background blood-pool correction, the position of four light beams emitted by the detector head were marked on the patient’s chest and adjusted as necessary before the radionuclide bolus administered after ISDN.

**Calculations**

**Hemodynamic Data**

From the measured data the following derived data were calculated: cardiac index (l/min/m$^2$); stroke volume index (ml/m$^2$); total systemic vascular resistance (dyn-sec-cm$^{-5}$); and left ventricular stroke work index (LVSWI) (g-m/m$^2$). In the three patients in whom left ventricular pressure was measured, LVSWI was calculated from the formula:

$$LVSWI = (LVSP - LVEDP) \times SVI \times 0.0136$$

where LVSP = mean left ventricular systolic pressure (mm Hg) (obtained from the left ventricular pressure trace between the onset of the upstroke to the point on the downstroke where pressure fell below the end diastolic pressure), LVEDP = left ventricular end-diastolic pressure (mm Hg) and SVI = stroke volume index (ml/m$^2$). In the remaining patients LVSWI was calculated from the formula:

$$LVSWI = (AP - PCWP) \times SVI \times 0.0136$$

where $AP = \text{mean systemic arterial pressure (mm Hg)}$ and $PCWP = \text{mean pulmonary capillary wedge pressure (mm Hg)}$.

**Angiographic Data**

Total left ventricular ejection fraction was calculated from the contrast left ventricular angiogram using the method of Sandler and Dodge. Ejection fraction of the contractile section of the left ventricle (EFCS) was calculated by the method of Watson et al.
Radionuclide Data

Analysis of the radionuclide data was performed using manufacturer-supplied software. The parameters of the left ventricle at end-diastole and endsystole were generated by a computerized edge-enhancement technique after linear interpolation of the end-diastolic and end-systolic frames from a data matrix of 294 points (14 × 21) to one of 4704 points (56 × 84). From the parameters generated EFCS was calculated in the same way as for the contrast ventriculograms. The data were evaluated by analysis of variance and linear regression analysis.

Results

Contrast Angiographic Data (table 1)

In all patients the left ventricular cineangiogram revealed the presence of an aneurysm (defined as a dyskinetic or akinetic section of the left ventricle clearly demarcated from a contractile section). The aneurysm was anterolateral or apical in all cases. EFCS was 40% or more in six patients and less than 40% in 11.

Coronary arteriography was performed in 16 patients. In 14 patients the predominant lesion totally occluded the left anterior descending branch of the left coronary artery. This was the only lesion in nine. Two patients had two-vessel coronary disease and three had three-vessel disease.

Of the six patients with EFCS of 40% or more, four had one-vessel, one had two-vessel and one had three-vessel coronary disease. Of the nine patients with EFCS of less than 40% in whom coronary arteriography was performed, seven had one-vessel and two had three-vessel coronary disease. The left ventricular cineangiogram revealed minimal mitral regurgitation (grade I/IV) in patients 6, 8, 11, 15 and 17.

Radionuclide Data

The radionuclide ventriculograms confirmed the presence of ventricular aneurysm in all of the 14 patients studied. There was a good correlation between radionuclide EFCS and contrast EFCS (r = 0.92, p < 0.001; fig. 1). During exercise EFCS increased in nine patients and decreased in five. There was no change in the mean value. After ISDN, exercise EFCS increased in seven patients and decreased in six compared with rest values. The mean value increased from 34 (rest) to 37% (exercise after ISDN), but this change did not achieve statistical significance. Compared with exercise values before ISDN, exercise EFCS after ISDN increased in 10 patients, decreased in one and did not change in two. The increase in the mean value (34–37%) did not achieve statistical significance. Individual changes in radionuclide EFCS are illustrated in figure 2.

Hemodynamic Data (table 2)

Effects of Exercise

Left ventricular filling pressure at rest was ≥ 15 mm Hg in all patients. This increased in 15 patients on exercise (fig. 3). The mean value increased from 26 to 38 mm Hg (46%; p < 0.001). Mean heart rate increased from 87 to 112 beats/min (29%; p < 0.001). Mean systemic arterial pressure increased from 92 to 104 mm Hg (13%; p < 0.02) and mean pulmonary arterial pressure from 35 to 48 mm Hg (37%; p < 0.001). Mean cardiac index increased from 2.9 to 3.9 l/min/m² (34%; p < 0.001), but this was primarily caused by tachycardia because mean stroke volume index did not change significantly. There were variable changes in LVSWI (fig. 3), but no significant change in the mean. Mean systemic vascular resistance did not change significantly.

Effects of ISDN at Rest

Left ventricular filling pressure fell substantially in all patients. The mean value fell from 25 to 15 mm Hg (40%; p < 0.001). Mean systemic arterial pressure fell from 93 to 86 mm Hg (7%; p < 0.05).

Effects of ISDN During Exercise

Rest before ISDN vs exercise after ISDN. In contrast to the first exercise period, mean left ventricular filling pressure and mean values for mean systemic arterial pressure and mean pulmonary arterial pressure did not change significantly. Mean heart rate increased from 87 to 112 beats/min (29%; p < 0.001). Mean cardiac index increased from 2.9 to 4.5 l/min/m² (55%; p < 0.001), and mean stroke volume index increased from 34 to 41 ml/m² (21%; p < 0.01). Mean LVSWI increased from 30 to 39 g-m/m² (30%; p < 0.001) but there was considerable individual variation (fig. 3). Mean systemic vascular resistance fell from 1602 to 1107 dyn-sec-cm⁻¹ (31%; p < 0.001). Exercise before ISDN vs exercise after ISDN.
ISDN markedly improved exercise hemodynamics. Left ventricular filling pressure fell from 38 mm Hg to 25 mm Hg (34%; p < 0.001) and mean pulmonary arterial pressure fell from 48 to 33 mm Hg (31%; p < 0.001). Mean cardiac index increased from 3.9 to 4.5 l/min/m² (15%; p < 0.001) and mean stroke volume index increased from 35 to 41 ml/m² (17%; p < 0.001). Mean LVSWI increased from 31 to 39 g-m/m² (26%; p < 0.001). Mean systemic arterial pressure fell from 104 to 98 mm Hg (6%; p < 0.02) and mean systemic vascular resistance fell from 1359 to 1107 dyn-sec-cm⁻² (18%; p < 0.001). Mean heart rate did not change.

Relation of LVSWI and EFCS

Changes occurring from rest to exercise (fig. 4). Of the 14 patients in whom data for both LVSWI and EFCS were obtained, five patients had increases in both variables on exercise and five showed decreases in both. In the other four small increases in EFCS were associated with no change (one patient) or small decreases in LVSWI. Linear correlation statistics between hemodynamic and radionuclide data were not attempted because in nine of the patients the data were not obtained simultaneously.

### Table 2. Effects of Isosorbide Dinitrate on Rest and Exercise Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>n</th>
<th>Rest after ISDN</th>
<th>n</th>
<th>Exercise after ISDN</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>87 ± 14.0</td>
<td>112 ± 16.0$§$</td>
<td>17</td>
<td>87 ± 13.6</td>
<td>17</td>
<td>112 ± 17.6§</td>
<td>17</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>92 ± 11.9</td>
<td>104 ± 11.5†</td>
<td>14</td>
<td>93 ± 10.1</td>
<td>14</td>
<td>98 ± 10.8</td>
<td>14</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>35 ± 11.2</td>
<td>48 ± 11.6§</td>
<td>17</td>
<td>33 ± 9.6</td>
<td>17</td>
<td>33 ± 11.6</td>
<td>17</td>
</tr>
<tr>
<td>Left ventricular filling pressure (mm Hg)</td>
<td>26 ± 7.2</td>
<td>38 ± 8.8§</td>
<td>17</td>
<td>25 ± 7.6</td>
<td>17</td>
<td>25 ± 9.2</td>
<td>17</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.9 ± 0.8</td>
<td>3.9 ± 1.2§</td>
<td>17</td>
<td>2.8 ± 0.4</td>
<td>16</td>
<td>4.5 ± 1.2§</td>
<td>17</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>34 ± 11.2</td>
<td>35 ± 10.0</td>
<td>17</td>
<td>33 ± 9.3</td>
<td>16</td>
<td>41 ± 11.2‡</td>
<td>17</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g-m/m²)</td>
<td>30 ± 12.4</td>
<td>31 ± 13.2</td>
<td>17</td>
<td>30 ± 12.4</td>
<td>16</td>
<td>39 ± 14.4§</td>
<td>17</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn-sec-cm⁻²)</td>
<td>1602 ± 465</td>
<td>1359 ± 304</td>
<td>14</td>
<td>1635 ± 412</td>
<td>15</td>
<td>1558 ± 391</td>
<td>13</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Abbreviations: ISDN = isosorbide dinitrate; n = number of patients.

* p < 0.05.
† p < 0.02.
‡ p < 0.01.
§ p < 0.001.
FIGURE 3. Effects of exercise on relation between left ventricular filling pressure (LVFP) and left ventricular stroke work index (LVSWI). Closed circles represent rest values, open circles (left) exercise, (right) exercise after isosorbide dinitrate. Arrows indicate direction of change. Numerals indicate individual patients (table 1). Solid lines represent an EFCS ≥ 40%; dotted lines represent an EFCS < 40%. For explanation of values indicated by horizontal and vertical dotted lines, see text.

Discussion

High levels of circulating norepinephrine have been found in patients with congestive cardiac failure at rest and, more strikingly, during exercise compared with normals.16 Furthermore, although myocardial norepinephrine stores are depleted in congestive cardiac failure,17 there is evidence that the failing heart is supersensitive to circulating norepinephrine.18 This sympathetich activity supports the failing circulation by maintaining systemic arterial pressure through an increase in peripheral vascular tone and by an inotropic action on the heart. The beneficial effects of these actions may, however, be attenuated by the increase in left ventricular afterload that occurs as a result of systemic arteriolar vasoconstriction and reduced arterial compliance, which occurs in chronic congestive cardiac failure.19 If these untoward effects were prevented, for example by vasodilators, the response in left ventricular performance to exercise stress would represent more closely the left ventricular functional reserve; in the case of patients with left ventricular aneurysm, the functional reserve of the contractile section of the left ventricle.

In this study ISDN improved exercise left ventricular performance. This may be explained by reduced afterload (manifest by a fall in systemic vascular resistance) and preload because nitrates have been shown to reduce arteriolar and venous tone.20 Nitrate-induced improvement in exercise left ventricular performance may have been enhanced by the inotropic effect of circulating catecholamines; an additive effect of vasodilators and inotropic agents has been reported in patients with congestive heart failure.21, 22

Watson et al.18 described a method for assessing the function of the contractile section of the left ventricle in patients with left ventricular aneurysm whereby the EFCS was calculated from the left ventricular cineangiogram. The authors found that in nine patients who underwent left ventricular aneurysmectomy an EFCS of less than 44% predicted a poor result in terms of surgical mortality and functional improvement. Arthur et al.,2 in a study of 15 patients who underwent left ventricular aneurysmectomy, reported that an EFCS of less than 38% predicted a poor surgical result.

It may be inferred from these studies that an EFCS of approximately 40% or less indicates critical impairment of residual left ventricular function. If so, the ability of such a ventricle to respond to exercise stress would be limited. Of the 12 patients with compromised left ventricular function in the study of Ross et al.,23 who underwent supine leg exercise, five achieved a normal exercise factor (increase in cardiac output per 100 ml/min increase in total body oxygen consumption). The mean exercise LVSWI for this group was 70 ± 13 g-m/m².

Therefore, in analyzing the quantitative response in left ventricular performance to exercise of each patient in this study it is possible to suggest critical values of exercise EFCS and LVSWI that would categorize left ventricular function reserve. Such values would be 40% for EFCS and 57 g-m/m² for LVSWI. (The EFCS may be underestimated because...
it is derived from considerations of rest EFCS; however, no data on normal exercise EFCS are available.

In this study the individual responses to exercise in EFCS were variable and were not related to rest EFCS (fig. 2). Hence, of the six patients whose rest EFCS was 40% or more, four increased EFCS in response to exercise and two decreased EFCS. Conversely, of the eight whose EFCS was less than 40%, five had increases, although in none did EFCS reach or exceed 40%, and three had decreases. In general, ISDN improved exercise EFCS. However, if exercise EFCS after ISDN is analyzed with respect to rest EFCS, a wide spectrum of change is seen (fig. 2). The number of patients who achieved an EFCS on exercise of 40% would increase from four to six. Of the two additional patients in this group, rest EFCS exceeded 40% in one and in the other it was less than 40%. Eight patients did not achieve this level on exercise even after ISDN, one of whom had a rest EFCS greater than 40%. Thus, rest EFCS does not accurately predict the individual response in this variable to exercise with or without ISDN.

The individual response in LVSWI to exercise was poor in all but one patient (fig. 3). Reduced left ventricular filling pressure by ISDN in this patient resulted in a decrease in exercise LVSWI, possibly due to an excessive reduction in the former. The other patients had a spectrum of responses in LVSWI to exercise after ISDN was seen (fig. 3), unrelated to rest EFCS. Thus, in addition to the patient who achieved a good response in exercise LVSWI, three more achieved such a response after ISDN, two fewer than the good responders using the criterion of EFCS.

If the criteria of LVSWI and EFCS are combined to describe the maximum response in left ventricular performance to exercise, that the number of patients is further reduced to three (fig. 4).

The results of this study indicate that there may be severe impairment of left ventricular functional reserve in patients with left ventricular aneurysm and congestive cardiac failure. The rest EFCS does not reliably predict the degree of impairment, although an EFCS of less than 40% at rest invariably predicts severe impairment, judged by the combined criteria of EFCS and LVSWI (fig. 4). The reason for this degree of functional impairment is not clear. Exercise may have produced myocardial ischemia, causing deterioration in left ventricular function that was alleviated24 but not prevented by ISDN, and that left ventricular functional reserve was therefore underestimated. This is unlikely, however, because exercise was submaximal and did not produce angina or ischemic changes on the ECG. Furthermore, the response to exercise with or without ISDN was not related to the degree of coronary artery disease. Thus, of the three good responders by combined criteria of EFCS and LVSWI (patients 1, 8 and 13), two had one-vessel disease and one had two-vessel disease. Of the 13 patients who underwent coronary arteriography nine had one-vessel disease, one had two-vessel disease and three had three-vessel disease (table 1). Thus, compromised performance of the contractile section of the left ventricle occurred frequently in patients with single-vessel occlusions and otherwise normal coronary arteries.

Of the five patients in whom EFCS deteriorated on exercise (patients 4, 6, 7, 11 and 17), four had single-

**Figure 4.** Effects of exercise on relation between ejection fraction of contractile section of left ventricle (EFCS) and left ventricular stroke work index (LVSWI). Closed circles represent rest values; open circles (left) exercise, (right) exercise after ISDN. Arrows indicate direction of change. For explanation of values indicated by dotted lines, see text.
vessel occlusion and one also had a significant stenosis of one other major vessel (fig. 2 and table 1). If this deterioration were caused by ischemia, a regional deterioration in contractile section wall motion would be expected. This was not observed in these or any other patients in whom radionuclide ventriculography was performed.

Mitral regurgitation may have influenced the exercise response in left ventricular performance. This is unlikely, however, because only five patients had mitral regurgitation by contrast left ventriculography, and it was judged to be insignificant in all.

When considering the poor correlation between rest EFCS and the maximum hemodynamic response to exercise, it is possible to speculate that the measurement of EFCS from a single-plane, left ventricular angiogram did not accurately estimate true EFCS derived from biplane angiograms. However, there is evidence that the right oblique view is adequate to measure ejection fraction in the presence of aneurysms involving the anterolateral wall of the left ventricle.

If the functional reserve of the contractile section of the left ventricle is a critical factor in predicting the outcome of left ventricular aneurysmectomy, the results of this study suggest that exercise stress testing in the manner described should be performed. This appears to be particularly important in patients with a rest EFCS of 40% or more because such patients, although potentially suitable for left ventricular aneurysmectomy, may have significant impairment of left ventricular functional reserve (fig. 4). The relation between the observations of this study and the results of left ventricular aneurysmectomy requires further evaluation.

The improved exercise left ventricular performance by ISDN in this study suggests that ISDN may improve exercise tolerance and provide a useful alternative to left ventricular aneurysmectomy when the latter is considered inadvisable.

References

Radionuclide and hemodynamic assessment of left ventricular functional reserve in patients with left ventricular aneurysm and congestive cardiac failure. Response to exercise stress and isosorbide dinitrate.
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