Left ventricular systolic and diastolic function in coronary artery disease: effects of revascularization on exercise-induced ischemia

JOHN D. CARROLL, M.D., OTTO M. HESS, M.D., HEINZ O. HIRZEL, M.D., MARKO TURINA, M.D., and HANS PETER KRAYENBUEHL, M.D.

ABSTRACT  Left ventricular systolic and diastolic function were studied before and after surgical revascularization in a group of 24 patients with stable angina who all had an excellent clinical response to surgery. With use of micromanometer left ventricular pressure measurements and ventricular volumes, calculated from biplane cineangiograms, left ventricular function at rest and during exercise before and after surgery was compared. Before surgery all patients had exercise-induced ischemia with new asynergy, a fall in ejection fraction from 57% to 49% (p < .001), and a rise in left ventricular end-diastolic pressure from 23 to 37 mm Hg (p < .001). Postoperative exercise resulted in no new asynergy and ejection fraction rose from 59% to 61% (p < .05). Left ventricular end-diastolic pressure still rose from 17 to 25 mm Hg (p < .01). Left ventricular pressure decay during exercise was greatly improved after revascularization and allowed maintenance of reduced early diastolic pressures. The early diastolic pressure nadir before surgery rose from 9 to 21 mm Hg (p < .001); the postoperative nadir was 5 mm Hg at rest and 6 mm Hg during exercise. All patients had an upward shift in the diastolic pressure-volume relationship during preoperative exercise. After revascularization there was no upward shift in some patients and a much smaller shift in others. The postoperative increase in left ventricular end-diastolic pressure was due to increased end-diastolic volume, not altered compliance. There was an increase in mean right atrial pressure during exercise either before (6 to 11 mm Hg) or after surgery (4 to 10 mm Hg). These increases were quite variable, suggesting no consistent role of pericardial restraint during exercise. Early diastolic peak filling rate during exercise was greater after surgery (1260 vs 950 ml/sec, p < .001). In fact, during postoperative exercise early diastolic filling rates were greater than normal, reflecting the persistence of abnormally high atrial pressures for filling. As at preoperative study, late diastolic filling during exercise was restricted after revascularization when compared with that in a control group. Postoperatively patients undergoing bypass procedures with a good clinical result showed significantly improved left ventricular diastolic and systolic function. Persistent elevation of end-diastolic and atrial pressures and other abnormalities of diastolic function may reflect chronic structural changes and need to be taken into account when evaluating patients after bypass surgery.


BYPASS SURGERY dramatically alters the symptomatic status of many patients and prolongs life in some. An increasing number of patients with prior surgery are undergoing clinical and hemodynamic evaluation. It has not been clear to what extent surgery alters the left ventricular dysfunction often associated with exercise, and misinterpretation of hemodynamic abnormalities may lead to incorrect clinical decisions. Therefore, this study was designed to investigate not only the degree to which “complete revascularization” alters hemodynamics, but also to contrast the postoperative results with those in a group of control patients without significant cardiac disease.

The pathophysiology of ischemic mechanical dysfunction, particularly of the left ventricle, has been extensively studied. Animal preparations have provided important insights into the nature of regional dysfunction.1–4 Yet, the human coronary circulation is clearly different from those of all other species because of the presence of collaterals and the diffuse and varied manifestations of atherosclerosis. Thus, human studies

From the Department of Internal Medicine, University of Chicago, and the Medical Polyclinic, Cardiology and Surgical Clinic A, University Hospital, Zurich.

Supported by a grant from the Swiss National Science Foundation.

Address for correspondence: Hans Peter Krayenbuehl, M.D., Med. Poliklinik, Kardiologie, Universitatsspital Zurich, 8091, Zurich, Switzerland.

Received Nov. 7, 1984; revision accepted March 15, 1985.
of the pathophysiology of ischemia have been of paramount importance. The induction of ischemia in man by pacing has provided the initial human model of left ventricular ischemic dysfunction. New asynergy, impaired pressure decay, elevated diastolic pressures, and the upward diastolic pressure-volume shift are some of the typical manifestations of ischemia.\textsuperscript{5–9} We have described the nature of left ventricular dysfunction in man during ischemia induced by exercise.\textsuperscript{10–15} These studies have emphasized the complex interplay of exercise-induced changes in function and ischemia-related abnormalities.

It has been well documented that after revascularization exercise tolerance improves even when antianginal medications are reduced.\textsuperscript{16–18} There have been other studies showing that global and regional systolic left ventricular function during exercise improve with successful bypass grafting of significantly stenosed, major epicardial coronary arteries.\textsuperscript{19–23} Much less has been published regarding the reversibility of ischemia-related alterations in left ventricular relaxation, diastolic filling dynamics, and diastolic pressure-volume relationships. Therefore, for this study we selected patients who had exercise-induced ischemia before surgery, subsequently had an uncomplicated bypass operation (with bypass of all major stenotic lesions), and were symptomatically improved after surgery. This approach provides unique data concerning left ventricular function after a clinically optimal surgical result in patients with definite preoperative functional abnormalities.

**Methods**

**Patient population.** Characteristics of the patients studied are summarized in table 1. Twenty-four patients with coronary artery disease between the ages of 34 and 68 years old (mean = 56) had stable angina refractory to medical therapy. Six had two-vessel disease (greater than 50% diameter narrowing) and the remainder had three-vessel disease. At the time of preoperative catheterization all had exercise-induced ischemia defined as new asynergy (table 2). All patients underwent coronary artery bypass surgery at the Surgical Clinic A at the University Hospital, Zurich, between June 1981 and October 1983. A total of 83 distal anastomoses were placed: 81 were patent at postoperative catheterization. All patients improved symptomatically after surgery, with a reduction in mean New York Heart Association class of from 2.5 to 1.2 and with only five patients having any angina with strenuous exertion. This was despite a reduction in the number of antianginal medications being taken (nitrates, \( \beta \)-blockers, calcium antagonists) from an average of 2.3 to 0.4 per patient, with 14 patients taking no antianginal medications postoperatively. In 12 patients there was a preoperative history of hospitalization for myocardial infarction documented by cardiac enzyme levels and electrocardiography. In seven of these Q waves had developed on the electrocardiogram.

Five patients with no or minimal cardiovascular disease and a rise in ejection fraction with exercise served as a control group.

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients studied before and after surgery</td>
<td>24</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>56 (range 34–68)</td>
</tr>
<tr>
<td>Mean No. of major (3) epicardial vessels diseased</td>
<td>2.7 (range 2–3)</td>
</tr>
<tr>
<td>Clinical history of past infarction (n)</td>
<td>12</td>
</tr>
<tr>
<td>Mean No. of daily cardiac medications</td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>2.3 (range 0–3)</td>
</tr>
<tr>
<td>After surgery</td>
<td>0.4 (range 0–1)</td>
</tr>
<tr>
<td>Mean NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>2.5 (range 2–3)</td>
</tr>
<tr>
<td>After surgery</td>
<td>1.2 (range 1–2)</td>
</tr>
<tr>
<td>Mean maximum exercise level achieved at catheterization (W)</td>
<td>90 (range 50–140)</td>
</tr>
<tr>
<td>Mean total duration of exercise (min)</td>
<td>3.6 (range 1.5–7)</td>
</tr>
<tr>
<td>No. of patients with angina during exercise</td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>16</td>
</tr>
<tr>
<td>After surgery</td>
<td>0</td>
</tr>
<tr>
<td>No. of distal bypass anastomoses</td>
<td>83 (mean 3.5, range 1–7)</td>
</tr>
<tr>
<td>No. of patent anastomases at postoperative catheterization</td>
<td>81</td>
</tr>
</tbody>
</table>

All were undergoing catheterization because of atypical chest pain.

**Cardiac catheterization.** Informed consent was obtained from all patients. All 29 patients underwent right and left heart catheterization and biplane cineangiography at rest and during supine bicycle exercise. The 24 patients undergoing postoperative catheterization were studied an average of 7.7 months after surgery (range 3 to 18 months). Cardiovascular medications were withheld for 12 to 24 hr before catheterization. Premedication consisted of 10 mg of chlordiazepoxide given orally 1 hr before catheterization. Left ventricular pressure was measured with a Millar pigtail angiographic micromanometer catheter introduced from the femoral artery. Pressures were recorded at a paper speed of 250 mm/sec (Electronics for Medicine VR16), along with the first derivative of pressure (dP/dt), (dP/dt)/ instantaneous pressure, and an intracardiac electrocardiogram from the right-sided catheter (figure 1). Before resting and exercise recordings were obtained the pressure was calibrated against a fluid-filled system.

Biplane left ventricular cineangiograms were obtained in the right anterior oblique (30 degrees) and left anterior oblique (60 degrees) projections at a filming rate of 50 frames/sec. Volumes were calculated by the area-length method. Each angiographic frame had a digital time corresponding to time marks on the pressure recordings.

**Exercise protocol.** All patients underwent bicycle exercise testing before preoperative catheterization to determine achieved workload and exercise limitations. At catheterization, pressures were recorded before and after each patient’s feet were strapped to the bicycle device. All resting data presented here are from the first angiogram, which was obtained with the patient’s legs in this elevated position. As previously shown, this accounts, in the majority of the patients, for the elevation in end-diastolic pressures at rest.\textsuperscript{10} After the resting angiogram and subsequent 12 to 15 min pause, patients began to exercise to a low level. Preoperatively patients exercised at progressively higher workloads until either angina or other limiting symptoms occurred or until they achieved a submaximal heart rate predicted by sex, height, and age. After surgery patients followed the
### Table 2

**Effect of revascularization on ventricular function**

<table>
<thead>
<tr>
<th></th>
<th>Before surgery (n = 24)</th>
<th>After surgery (n = 24)</th>
<th>Before vs after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67 ± 12</td>
<td>115 ± 11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75 ± 16</td>
</tr>
<tr>
<td>EF (%)</td>
<td>57 ± 9</td>
<td>49 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59 ± 11</td>
</tr>
<tr>
<td>ESVI (ml/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>49 ± 14</td>
<td>64 ± 19&lt;sup&gt;c&lt;/sup&gt;</td>
<td>44 ± 18</td>
</tr>
<tr>
<td>EDVI (ml/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>114 ± 24</td>
<td>125 ± 23&lt;sup&gt;b&lt;/sup&gt;</td>
<td>108 ± 25</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>23 ± 6</td>
<td>37 ± 8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>P&lt;sub&gt;L&lt;/sub&gt; (mm Hg)</td>
<td>9 ± 4</td>
<td>21 ± 8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>Peak LVP (mm Hg)</td>
<td>149 ± 23</td>
<td>156 ± 19</td>
<td>144 ± 21</td>
</tr>
<tr>
<td>Max + dP/dt (mm Hg/sec)</td>
<td>1530 ± 274</td>
<td>2210 ± 512&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1637 ± 370</td>
</tr>
<tr>
<td>Max - dP/dt (mm Hg/sec)</td>
<td>1546 ± 284</td>
<td>1873 ± 419&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1589 ± 297</td>
</tr>
<tr>
<td>T (msec)</td>
<td>54 ± 9</td>
<td>37 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>52 ± 11</td>
</tr>
<tr>
<td>P&lt;sub&gt;P&lt;/sub&gt; (mm Hg)</td>
<td>-9 ± 8</td>
<td>10 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-10 ± 10</td>
</tr>
</tbody>
</table>

HR = heart rate; EF = ejection fraction; ESVI = end-systolic volume index; EDVI = end-diastolic volume index; LVEDP = left ventricular end-diastolic pressure; Max + dP/dt = maximum rate of left ventricular pressure rise; Max - dP/dt = maximum rate of left ventricular pressure decline.

<sup>a</sup>p < .05, rest vs exercise; <sup>b</sup>p < .01, rest vs exercise; <sup>c</sup>p < .001, rest vs exercise.

---

**Data analysis.** Methods of analysis have previously been described in detail. In summary, resting and exercise data were derived from well-opacified sinus beats that were not immediately postextrasystolic. Pressure tracings were digitized. The characteristics of isovolumetric pressure decay were derived from a linear regression of pressure and dP/dt coordinates as shown in figure 2. Thus two variables, T, representing the negative reciprocal of the slope, and P<sub>P</sub>, representing the pressure axis intercept, were derived for each patient at rest and during exercise.

Ventricular volumes were calculated from frame-by-frame analysis of biplane angiograms. End-diastole was taken as the beginning of the rapid rise in left ventricular pressure after the onset of the QRS complex. End-systole was taken as the smallest volume at the end of ejection with the aid of the intracardiac phonocardiogram to identify aortic valve closure. To describe filling dynamics (figure 3) the time of mitral valve opening was noted as 20 msec before the time of the first frame showing the entry of unopacified blood into the left ventricle. The time from mitral valve opening to end-diastole is referred to as the filling time. This filling time was divided into halves, the midpoint being mid-diastole. The average filling times were calculated for the first and second halves of diastole. In addition, the peak early diastolic filling rate was derived from three-point smoothing of frame-by-frame volume calculations. The total filling volume was taken as the volume entering the ventricle from mitral valve opening to end-diastole.

Left atrial pressure is a major determinant of filling. Since left atrial pressure was not measured, we recorded the pressure at the time at which unopacified blood first entered the ventricle. This pressure is termed the opening pressure and is an index of the left atrial pressure responsible for mitral valve opening, i.e., the driving pressure for early diastolic filling.

Diastolic pressure-volume relationships for resting and exercise data were constructed as in figure 4. To permit comparability, the same exercise protocol they had followed before surgery to match external workloads. Exercise duration and maximal workload for each patient were therefore identical for both studies. At the point of peak exercise, pressures were again recorded and simultaneous cineangiography was completed. Coronary arteriograms by the Judkins technique were obtained after exercise.

**FIGURE 1.** Left ventricular pressure tracings at rest and during exercise-induced ischemia from one patient with severe triple-vessel disease. Before surgery, there was a dramatic rise in the early diastolic pressure nadir, P<sub>L</sub>, from 6 to 18 mm Hg during ischemia. Right atrial mean pressure (RA) also increased during ischemia. Simultaneous cineangiography showed the development of severe anterior wall ischemia with exercise. The same patient also underwent exercise testing 4 months after complete revascularization. P<sub>L</sub> did not rise with exercise but left ventricular end-diastolic pressure increased to 30 mm Hg. Simultaneous cineangiography revealed no new asynergy with exercise and there was no angina. Right atrial pressure increased with exercise in the absence of significant left ventricular ischemia.
sons of preoperative and postoperative data and that from control subjects we derived mean pressure-volume relationships for each group at rest and during exercise. Three diastolic pressure-volume coordinates were used, including the early diastolic pressure nadir, mid-diastole, and end-diastole (figure 5).

Resting and exercise data within groups and preoperative and postoperative results were tested for significant differences by use of the paired t test. Differences between the control group and the patients were tested with an unpaired t test. Data on figures are mean ± SEM while those in tables and text are mean ± SD.

**Results**

A summary of hemodynamic and angiographic data is presented in table 2. During exercise before surgery, when all patients developed new asynergy, ejection fraction fell from 57% to 49% as end-systolic and end-diastolic volumes increased. During exercise after surgery ejection fraction rose from 59% to 61% due to an increased end-diastolic volume, but there was no significant change in end-systolic volume. This was in contrast to the case in the control group, in which ejection fraction increased from 64 ± 3 to 73 ± 4 (p < .01) and end-systolic volume decreased (35 ± 5 to 28 ± 6, p < .05) and there was no significant increase in end-diastolic volume (96 ± 6 to 102 ± 11). Only six patients had a 5% or more increase in ejection fraction during exercise, and end-systolic volume decreased in only six as well.

Peak left ventricular systolic pressure did not rise significantly during preoperative exercise. Eight of 25 patients experienced an exercise-induced drop of 5 mm Hg or more. Postoperatively, there was a significant rise in peak pressure (from 144 to 177 mm Hg) and no patient experienced a fall in pressure during exercise. This appeared to be due, in part, to improved generation of left ventricular pressure. Preoperatively maximum positive dP/dt was 2210 mm Hg/sec during exercise; postoperatively it was 3314 mm Hg/sec (p < .001). In the control group maximum positive dP/dt with exercise increased from 1418 ± 374 to 2894 ± 558 (p < .01). The increase in heart rate in the control group was slightly smaller (70 to 119 beats/min) than that in the postoperative patients.

Diastolic pressures became greatly elevated during preoperative exercise. The early diastolic pressure nadir rose from 9 to 21 mm Hg and end-diastolic pressure rose from 23 to 37 mm Hg. During exercise after surgery the early diastolic pressure nadir remained low (6 mm Hg), but end-diastolic pressure still rose from 17 to 25 mm Hg. In 20 of 24 patients, after surgery end-diastolic pressure rose during exercise by 5 mm Hg or more. During exercise in the control group there was a fall in the early diastolic pressure nadir from 11 ± 6 to 4 ± 5 mm Hg and no significant rise in end-
FIGURE 3. Left ventricular filling dynamics for three groups of patients: a control group with normal exercise hemodynamics, a preoperative group (n = 13) of patients who developed exercise-induced ischemia, and a postoperative group (the patients in the preoperative group after successful revascularization). Left, Mean values for early diastolic peak filling rate are shown at rest and during exercise. Despite abnormal pressure decay, the patients in the preoperative group had peak filling rates during exercise similar to those in the control subjects. After revascularization, peak filling increased to a greater extent during exercise. Middle, Mean values for the left ventricular pressure at which mitral valve opening occurred. This index of the left atrial driving pressure for filling did not change with exercise in the control group but greatly increased during exercise-induced ischemia before surgery. After revascularization the driving pressure was not as great but still increased during exercise. The combination of accelerated pressure decay and high driving pressures probably produced the high peak filling rates seen during postoperative exercise. Mean filling rates for the second half of diastole are shown on the right. Mean filling rates for the second half of diastole were significantly lower than control during preoperative exercise, and did not statistically increase after revascularization. Chronic, passive chamber properties may have restricted late filling during postoperative exercise. See text for details. *p < .05; **p < .01.

FIGURE 4. The preoperative and postoperative diastolic pressure-volume relationships for six patients. During preoperative exercise there was an upward shift composed of an increased end-systolic volume, abnormal isovolumetric pressure decay, and an increased pressure at which mitral valve opening occurred. After revascularization there were no or minimal shifts during exercise. There was an increased left ventricular end-diastolic pressure during exercise, but it appeared on the same pressure-volume curve as at rest.
diastolic pressure (18 ± 8 to 20 ± 9 mm Hg). The high resting values reflect, in large part, leg elevation.

The characteristics of isovolumetric pressure decay were clearly altered by exercise-induced ischemia and, subsequently, by revascularization (figure 2). The time constant of isovolumetric relaxation, T, decreased during preoperative exercise from 54 to 37 msec, while in the control group it fell to a greater extent (49 ± 15 to 22 ± 2 msec, p < .01). Postoperatively, T fell from 52 to 30 msec, which was significantly different from before surgery, with nine of 24 patients having a value less than 25 msec during exercise. The second characteristic describing isovolumetric pressure decay, P<sub>b</sub>, increased during preoperative exercise from −9 to 10 mm Hg, but postoperatively it did not change during exercise. This postoperative response was similar to that in the control group, in which P<sub>b</sub> did not change during exercise (0 ± 1 to 3 ± 11 mm Hg).

The seven patients who had Q wave infarction had a fall in ejection fraction with exercise of from 49 ± 8% to 45 ± 10%. Postoperatively ejection fraction was 49 ± 9 at rest and 49 ± 9 with exercise. Left ventricular end-diastolic pressure rose from 24 ± 7 to 38 ± 9 mm Hg (p < .01) during preoperative exercise and from 13 ± 4 to 27 ± 4 mm Hg (p < .01) postoperatively. End-diastolic volume increased during preoperative (115 ± 24 to 127 ± 26 ml/m<sup>2</sup>, p < .05) and postoperative exercise (116 ± 28 to 127 ± 31 ml/m<sup>2</sup>, p < .01). Left ventricular pressure generation improved with revascularization. Preoperatively left ventricular systolic pressure did not rise significantly (143 ± 13 to 155 ± 14 mm Hg), while during postoperative exercise it did (137 ± 19 to 169 ± 15 mm Hg, p < .01). Maximum +dP/dt also increased from 1365 ± 159 to 2033 ± 394 mm Hg/sec (p < .001) during preoperative exercise and from 1586 ± 264 to 3102 ± 800 mm Hg/sec (p < .001) during postoperative exercise. As in the whole group of 24 patients, the seven with prior Q wave infarctions had a greater exercise heart rate after surgery despite a similar workload. Preoperative heart rate increased from 66 ± 9 to 115 ± 14 beats/min (p < .001) and after surgery it increased from 77 ± 15 to 135 ± 15 (p < .001).

The seven patients with Q wave infarction had more impressive improvement in early diastolic pressures during exercise after revascularization. The early diastolic pressure nadir, P<sub>e</sub>, increased from 11 ± 4 to 24 ± 11 mm Hg (p < .01) during preoperative exercise, but did not change significantly during postoperative exercise (5 ± 3 to 8 ± 1 mm Hg, NS). Pressure decay improved with revascularization: T had fallen from 60 ± 12 to 40 ± 12 msec (p < .05) before surgery, but fell to 31 ± 9 msec during postoperative exercise from a resting value of 55 ± 10 msec (p < .01). Before surgery P<sub>b</sub> rose from −8 ± 7 to +11 ± 16 mm Hg (p < .05), but was unchanged during postoperative exercise (−9 ± 5 to −4 ± 9 mm Hg, NS).

In a subgroup of 13 patients in whom all four ventriculograms were of the highest quality frame-by-frame analysis was completed for diastole. These 13 patients were representative of all the patients in terms of the previously presented angiographic and pressure data at rest and during exercise. For example, ejection fraction fell during preoperative exercise from 58 ± 10% to 47 ± 9% (p < .001) and after surgery it rose from 57 ± 12% to 59 ± 12% (p < .05). Diastolic filling data are presented for these patients in table 3. Before surgery, the filling time fell during exercise from 486 to 185 msec and the total filling volume decreased from 110 to 89 ml. In contrast, during postoperative exercise filling volume increased from 102 to 112 ml despite a greater abbreviation of diastolic filling time. The greater decrease in filling time was probably due to the higher heart rate during postoperative exercise. Filling rates were also altered by revascularization, particularly in early diastole (figure 3). The peak filling rate increased before surgery from 585 to 950 ml/sec during exercise and after surgery it increased from 604 to 1260 ml/sec. The mean filling rate for the first half of diastole showed a similar trend. Neither filling rate at rest was significantly increased by revascularization, but during exercise both rates
TABLE 3
Effect of revascularization on left ventricular filling dynamics

<table>
<thead>
<tr>
<th></th>
<th>Before surgery (n = 13)</th>
<th>After surgery (n = 13)</th>
<th>Before vs after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Diastolic filling time  (msec)</td>
<td>486±81</td>
<td>185±47c</td>
<td>391±121</td>
</tr>
<tr>
<td>Filling volume (ml)</td>
<td>110±24</td>
<td>89±20c</td>
<td>102±29</td>
</tr>
<tr>
<td>Peak filling rate (ml/sec)</td>
<td>585±210</td>
<td>950±185c</td>
<td>604±235</td>
</tr>
<tr>
<td>Mean filling rate 1 (ml/sec)</td>
<td>296±93</td>
<td>693±174c</td>
<td>336±134</td>
</tr>
<tr>
<td>Mean filling rate 2 (ml/sec)</td>
<td>171±72</td>
<td>296±188a</td>
<td>258±164</td>
</tr>
<tr>
<td>LVP at MVO (mm Hg)</td>
<td>17±6</td>
<td>44±10c</td>
<td>11±4</td>
</tr>
<tr>
<td>T (msec)</td>
<td>55±11</td>
<td>38±11b</td>
<td>52±11</td>
</tr>
<tr>
<td>P&lt; (mm Hg)</td>
<td>−7±6</td>
<td>10±11c</td>
<td>−9±10</td>
</tr>
</tbody>
</table>

LVP at MVO = left ventricular pressure at mitral valve opening.

*p < .05, rest vs exercise; "p < .01, rest vs exercise; "p < .001, rest vs exercise.

were significantly increased after surgery. A major determinant of early filling rates, the left atrial pressure, was estimated by the left ventricular pressure at mitral valve opening. Left ventricular pressure at mitral opening increased during preoperative exercise from 17 to 44 mm Hg (figure 3). At postoperative exercise it increased from 11 to 31 mm Hg, which was significantly (p < .01) less than the preoperative exercise value. All postoperative patients, including those with apparently normal systolic function, had a 9 mm Hg or greater increase in left ventricular pressure at mitral opening during exercise. In the control group left ventricular pressure at mitral opening was 12 ± 7 at rest and 14 ± 10 with exercise and peak filling rate increased from 615 ± 163 to 1050 ± 318 ml/sec during exercise (p < .05). Mean filling rate for the first half of diastole increased from 358 ± 104 to 649 ± 244 ml/sec during exercise (p < .05). The early diastolic filling rates in the control group were actually less than those in the postoperative patients during exercise, but these differences did not achieve statistical significance.

Mean filling rates during the second half of diastole were likewise altered by revascularization, yet remained clearly different from those in the control group (figure 3). Before surgery the mean rate increased from 171 to 296 ml/sec during exercise and the postoperative mean rate was 258 ml/sec at rest and 414 ml/sec during exercise. The increased rates at rest and during exercise after surgery were not significantly different from preoperative values. The control group had a mean rate of filling for the second half of diastole of 199 ± 111 ml/sec at rest and 649 ± 244 ml/sec during exercise. The control group's exercise value was significantly greater than the preoperative value (p < .05), but not the postoperative one.

Mean diastolic pressure-volume relationship data are presented in figure 5. There was an upward shift in the relationship in all patients during preoperative exercise and no clear shifts during postoperative exercise. Results in six typical patients are presented in figure 4 and show not only the improvement after revascularization, but the heterogeneity of the preoperative upward shifts.

There was a great inconsistency in changes in mean right atrial pressure during exercise both before and after surgery. In nine patients right atrial pressure recordings were available for both periods. There was a preoperative increase in right atrial pressure from 6 ± 2 to 11 ± 4 mm Hg (p < .001) and a similar postoperative change (4 ± 2 to 10 ± 4 mm Hg, p < .001). The degree of right atrial pressure elevation was not a major, consistent determinant of the left ventricular diastolic pressure-volume relationship.

Discussion

The results of this study support the hypothesis that revascularization significantly improves both left ventricular systolic and diastolic function during exercise. Several key issues require discussion. First, to what extent does left ventricular function, both systolic and diastolic, return to normal after revascularization? What is the nature of the persistent abnormalities and their possible causes? What are the implications of these findings for patient care?

Systolic dynamics. The development of a transient regional wall motion abnormality is a classic manifestation of systolic dysfunction due to ischemia. By study design, all patients had exercise-induced asynchrony at the preoperative study, and none had it after revascularization. There was a postoperative improvement in both the shortening characteristics and pressure generation capability of the left ventricle. There was also a small increase in ejection fraction during
postoperative exercise, which is in agreement with results of other studies. The mechanism of this augmentation of ejection fraction was the significant increase in end-diastolic volume and preload, not a reduction in end-systolic volume as occurs in normal individuals. Thus, an increase in stroke volume during exercise does occur and combines with the tachycardia to allow a clear increase in exercise cardiac output, which is blunted before surgery. The inability of most of the patients to reduce end-systolic volume with exercise may not only limit the rise in ejection fraction, but has potential implications for subsequent pressure decay and diastolic events (see below).

The increase in pressure generation during exercise after revascularization is shown by maximum positive dP/dt. Achievement of an increased exercise heart rate and the greater degree of synchrony are two factors that influence the maximum value of dP/dt. In addition, muscle that before surgery had greatly reduced contractile strength because of ischemia was capable after surgery of contributing to pressure generation. This resulted in a significant rise in peak left ventricular pressure during exercise. The reversal of preoperative exercise-induced fall in systolic pressure has also been described by other investigators.

Left ventricular pressure decay and early diastolic pressures. The abnormal systolic dynamics of ischemia, including asynchrony and increased end-systolic volume, are probably major factors that combine with direct disruption of muscle relaxation by ischemia to produce abnormal pressure decay. In man both pacing and exercise induction of ischemia have been shown to alter pressure decay in the left ventricle. We have previously stressed the importance of the abnormalities in pressure decay that contribute to increased early diastolic pressures. These data show that abnormal pressure decay in the left ventricle can be greatly improved by revascularization. Subsequently, early diastolic pressures maintain a low level. The enhancement in relaxation is probably due to the correction of multiple biochemical and mechanical abnormalities that occur during preoperative ischemia. Blockers could have blunted the preoperative heart rate response to exercise and, thus, the catecholamine-mediated enhancement of relaxation. In addition, a heightened sympathetic state occurs postoperatively, although none of our patients were restudied before 3 months after surgery. The role of preoperative β-blocker therapy was probably an unimportant one in the pressure decay abnormalities during exercise. First, all cardiac medications were held for 12 to 24 hr before catheterization. Second, the gross abnormalities produced by exercise-induced ischemia probably greatly overshad-
own any effects of medication. And finally, the medications that were taken before surgery would be expected to lessen hemodynamic abnormalities because of their anti-ischemic effects.

As with other parameters, the mean values for pressure decay parameters clearly showed improvement during postoperative exercise. These mean values were obtained from data in the majority of patients who had some persistent abnormalities and the few who were indistinguishable from the control group. The exercise-induced abnormalities in a group of patients with prior infarction but no ischemia with exercise, a scar group, have been previously reported. Many of the postoperative patients with similar pressure decay abnormalities during exercise had prior infarctions, although only six had resting ejection fractions of 50% or less and only seven had Q waves on their electrocardiograms. It appears that revascularization converts the exercise hemodynamics of many patients from those typical of ischemia to those typical of chronic infarction without acute ischemia. Yet even patients without clinical histories or signs of transmural infarction have increased fibrotic content of the myocardium served by stenotic arteries. Recurrent bouts of ischemia may produce permanent structural changes with long-term hemodynamic sequelae similar to those abnormalities in patients with classic infarctions.

Diastolic pressure-volume relations. In individual patients (figure 4) and for groups (figure 5), the data show the reversibility of one of the classic manifestations of ischemia, the upward shift in diastolic pressure-volume relationship in the left ventricle. Few postoperative patients have totally normal diastolic pressure-volume relationships during exercise. As illustrated in figure 5, the control subjects had a reduction in the early diastolic pressure nadir, P(L), with a downward shift in the early diastolic pressure-volume relationship. It has been suggested that during exercise in individuals without heart disease, intense catecholamine stimulation produces a significant reduction in end-systolic chamber size, which may lead to a physiologically significant degree of internal restoring forces within the left ventricle. This could create diastolic suction. Whether this mechanism is present in our control subjects or postoperative patients cannot be determined from these data. As discussed above, very few of our patients experienced a reduction in end-systolic volume during postoperative exercise. This, combined with data showing that pressure decay normalization is infrequently achieved, may explain why
the diastolic pressure-volume relationship during exercise rarely normalizes despite clinically successful revascularization.

The complexity of the diastolic pressure-volume relationship has been discussed in several reviews. Previous experimental studies have shown that severe ischemia directly alters myocardial stress-strain characteristics. It has also been suggested that a component of the upward shift seen during ischemia is related to acute pericardial restraint. Janicki and Weber have shown that the pericardium can enhance ventricular interaction and mediate upward shifts in the left ventricle’s diastolic pressure-volume relationship. This problem was addressed in pacing-induced angina by Mann et al., who measured right ventricular end-diastolic pressure during ischemia, a time when there was a left ventricular diastolic pressure-volume shift. They found no significant increase in right ventricular end-diastolic pressure. Likewise, Momomura et al. recently presented data from a dog preparation that also showed that right ventricular compression of the left ventricle is not likely to be responsible for the upward shift during ischemia. We did see increases in right atrial mean pressure in many of our patients during exercise-induced ischemia and when upward shifts in the left ventricular diastolic pressure-volume relationship occurred, but there was no consistency in the degree of increase in right atrial pressure or the degree or type of upward shift. In some patients right atrial pressure rose by only several millimeters of mercury when large left ventricular upward shifts were seen. On the other hand, in many postoperative patients there were persistent gross elevations in right atrial pressures during exercise, but no upward shift was present in the left ventricle. We conclude that in exercise-induced ischemia there is no consistent effect of pericardial restriction. Other factors may elevate right atrial pressures during exercise. In some patients the pericardium may play a role in determining left ventricular diastolic properties during exercise, but this remains to be proven. Although the pericardium was left open postoperatively, some constricting effect cannot categorically be excluded. Alterations in intrapericardial pressures may also play a role in altered diastolic function.

An unexpected finding of this study was the degree to which left ventricular end-diastolic pressure increased during postoperative exercise. The increase in pressure was less than that before surgery and was not associated with clear signs of ischemia, i.e., new asynergy. The postoperative increase in end-diastolic pressure was related to a parallel increase in end-diastolic volume. This suggests that there was no significant acute change in compliance. During postoperative exercise heart rate increased more than before surgery. This increase should have tended to lower, not increase, end-diastolic pressure. The difference in the early diastolic pressure, P D, is striking, since it failed to rise during postoperative exercise. This can be seen in the example of figure 1. The increase in end-diastolic pressure may reflect the abnormally stiff ventricle frequently seen in coronary artery disease. Even in the absence of clinical infarction intraoperative transmural biopsies have shown the frequent occurrence of increased interstitial fibrosis and myocardial hypertrophy in these patients.

The steep pressure-volume relationship with the increased end-diastolic pressure during postoperative exercise is probably a major reason mitral valve opening pressures were still elevated postoperatively in our patients, but other factors can contribute to the determination of left atrial pressure, e.g., the chamber’s own pressure-volume relationship and systolic performance. This could not be evaluated by our data. Significant mitral regurgitation was not present in any of our patients.

Filling dynamics. As seen in figure 3, filling dynamics are altered after revascularization, allowing an increased amount of blood to enter the left ventricle despite an even greater reduction in filling time during postoperative exercise. Left ventricular filling is a dynamic process involving the interaction of active and passive properties of the atria and ventricles. The rate of left ventricular pressure decay and the subsequent atrial-ventricular gradient are major factors determining early diastolic filling. The operative stiffness of the left ventricle becomes increasingly important as filling progresses. The strength and timing of atrial systole determines the end-diastolic “kick” to ventricular filling. We have previously shown that during exercise-induced ischemia filling dynamics are altered in a characteristic fashion. Despite the abnormalities in pressure decay, early filling rates are maintained during exercise by the gross elevation of the atrial driving force. Recent experimental data have also shown how changes in atrial pressure may increase filling rates despite alterations in relaxation that would tend to decrease filling. Unlike in the normal ventricle, filling in the later portion of diastole during exercise is restricted both before and after surgery. During ischemia with the acute increase in end-systolic volume, the ventricle begins to fill on a rightward, and thus steeper, portion of the diastolic pressure-volume curve. This is in addition to an acute stiffening of the
ventricle due to the ischemia itself. Despite the lack of significant upward diastolic pressure-volume shifts during postoperative exercise, late filling still shows some restriction compared with that in normal subjects. A useful analogy is provided by the filling profiles of patients with constrictive pericarditis in the study of Tyberg et al. Those with constriction had very rapid filling during the first half of diastole compared with normal and, subsequently, filling during the second half of diastole virtually stopped. The gross elevations in atrial driving pressures, small end-systolic volumes, probably near-normal pressure decay, and a stiff left ventricle (in this case due to the pericardium) produce a similar combination of filling parameters, as in our postoperative patients during exercise. Their study, like ours, also highlights the observation that rapid filling rates cannot be given qualitative labels such as “good” or “normal.” The elevation in atrial pressures required to produce these rates is clearly not normal.

Influence of chronic structural changes. The abnormalities in diastolic function that are observed during post-revascularization exercise may reflect increased amounts of interstitial fibrosis and myocardial hypertrophy. The structural changes may be gross (post-infarction scars) or more subtle (patchy fibrosis). Revascularization may prevent or minimize acute, exercise-induced ischemia with the acute stiffening of the left ventricular chamber. However, the chronic changes in chamber compliance would not be expected to be altered by revascularization. In figure 6 a summary of our functional data and the effect of revascularization is outlined.

Hess et al. studied the effect of myocardial structure on ventricular function in a group of postoperative patients with aortic valve disease. Residual abnormalities in diastolic stiffness were shown to be accompanied by a relative increase in interstitial fibrosis and regression of myocardial hypertrophy. In patients with coronary artery disease repetitive bouts of ischemia may induce hypertrophy and increase interstitial fibrosis and there is some evidence of a reduction in left ventricular mass after revascularization. Further clarification of the interrelationship of myocardial structure and function in this group of patients is needed.

We thank Brenda Cochran and Joyce Bolden in Chicago for typing the manuscript and Petrit Alibali for the graphics. Mafalda Hegetschweiler and Rosy Hug in Zurich are thanked for their technical assistance.

References
15. Carroll JD, Hess OM, Hirzel HO, Krayenbuehl HP: Determinants of left ventricular diastolic function during ischemia. Eur Heart J 5: 352, 1984 (abst)
31. Sonnenblick EH: The structural basis and importance of restoring forces and elastic recoil for the filling of the heart. Eur Heart J 1 (suppl A): 107, 1980
32. Sabbath HN, Stein PD: Pressure-diameter relations during early diastole in dogs. Incompatibility with the concept of passive left ventricular filling. Circ Res 45: 357, 1982
43. Ishida Y, Meisner JS, Tsujikka K, Galle J, Yuran C, Frater R, Yellin E: Peak rapid filling rate may not reflect left ventricular relaxation properties when left atrial pressure compensates for changes in loading conditions. Circulation 70 (suppl II): II-349, 1984 (abst)
47. Meester GT, Brower RW, Hugenholz PG: Regression of left ventricular wall mass index after coronary artery bypass surgery in a group of patients with stable angina pectoris. Eur Heart J 3 (suppl A): 155, 1982
Left ventricular systolic and diastolic function in coronary artery disease: effects of revascularization on exercise-induced ischemia.
J D Carroll, O M Hess, H O Hirzel, M Turina and H P Krayenbuehl

Circulation. 1985;72:119-129
doi: 10.1161/01.CIR.72.1.119

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/72/1/119

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/