PATHOPHYSIOLOGY AND NATURAL HISTORY
LEFT VENTRICULAR PERFORMANCE

Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve

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ABSTRACT Thirty-three patients with chest pain despite angiographically normal coronary arteries underwent both coronary flow studies during pacing and resting and exercise gated blood pool scintigraphy. During atrial pacing after administration of ergonovine, those patients developing their typical chest pain demonstrated significantly lower great cardiac vein flow (97 ± 31 vs 150 ± 33 ml/min, p < .001), higher coronary resistance (1.27 ± 0.43 vs 0.77 ± 0.18 mm Hg/ml/min, p < .005), and less lactate consumption (30.5 ± 22.0 vs 69.7 ± 41.1 mM · ml/min, p < .005) and a higher left ventricular end-diastolic pressure after pacing (20 ± 4 vs 12 ± 1, p < .001) compared with those without pain and in the absence of significant luminal narrowing of the epicardial coronary arteries. The 26 patients with abnormal vasodilator reserve demonstrated reduced left ventricular ejection fraction during exercise (58 ± 8%) compared with the seven patients with appropriate vasodilator reserve (66 ± 4%, p < .05) and with a group of 52 control patients of similar age and sex distribution and free of known heart disease (66 ± 10%, p < .001). In addition, 12 of the 26 patients with abnormal vasodilator reserve demonstrated exercise-induced regional wall motion abnormalities. Many of these patients also manifested impaired left ventricular diastolic filling at rest compared with the control subjects (peak filling rate 2.6 ± 0.7 vs 3.2 ± 0.7 end-diastolic volume/sec, p < .005). Thus, patients with chest pain resulting from abnormal vasodilator reserve demonstrate abnormalities of left ventricular systolic and diastolic function suggestive of myocardial ischemia.


MUCH DEBATE has focused on whether or not patients with chest pain despite normal epicardial coronary arteries truly experience myocardial ischemia.1-6 Several investigators have found that many of these patients clearly have a noncardiac cause of their pain, including esophageal,7,8 chest wall,9 and psychosomatic causes.10 However, others have found many such patients to have abnormal exercise electrocardiograms,11-18,23 abnormal lactate metabolism during infusion of isoproterenol or atrial pacing,1,14,17,19-21,21 elevation of left ventricular end-diastolic pressure during exercise,12,14,22 and limited vasodilator reserve after infusion of dipyridamole.23 More recently, radionuclide studies have demonstrated abnormal myocardial perfusion18,24-26 and abnormal left ventricular function in patients with chest pain and angiographically normal coronary arteries.18,27,28 Results of such studies have been interpreted as "false positives" at one extreme and as indicative of myocardial ischemia of uncertain cause at the other. The most compelling argument against the presence of myocardial ischemia is that the prognosis of patients with chest pain and angiographically normal epicardial coronary arteries is believed to be benign,10,13-15,29-31 even if they continue to experience frequent and disabling chest pain.30,31

We recently found that many patients with chest pain who have angiographically normal coronary arteries and no evidence of large vessel spasm after ergonovine challenge demonstrate a limited capacity to decrease coronary resistance and increase coronary flow in response to atrial pacing.32 This apparent inappropriate vasodilator reserve was associated with the patient’s typical chest pain and diminished lactate consumption. Cold pressor testing and ergonovine infusion resulted in unmasking this abnormality in many
patients with apparently normal flow responses to pacing alone, and in exacerbating abnormal vasodilator reserve in others. No significant change in epicardial coronary artery luminal diameter was noted after cold pressor testing or ergonovine, suggesting that this abnormality was localized in vessels too small to be imaged angiographically: either small coronary arteries or arterioles. However, the question remains whether this abnormality of coronary vasodilator reserve truly results in myocardial ischemia. In the current study, we compared left ventricular function at rest and during exercise in patients with chest pain related to impaired coronary vasodilator reserve with that in subjects of similar age and sex distribution and free of known heart disease.

Methods

**Patient selection.** Between January 1982 and June 1984, 33 patients referred to the Cardiology Branch, NHLBI, for evaluation of chest pain syndromes despite angiographically normal-appearing coronary arteries and normally contracting left ventricles during diagnostic cardiac catheterization underwent both a coronary flow study during pacing and gated blood pool scintigraphy. There were 15 men and 18 women ranging in age from 33 to 64 years (average 51 years). In all patients, physical examination and M mode and two-dimensional echocardiographic studies excluded the possibility of hypertrophic cardiomyopathy or mitral valve prolapse. No patient reported a history of hypertension and none had left ventricular hypertrophy by electrocardiography or echocardiography. Eight patients were current cigarette smokers, three were insulin-dependent diabetics, one described classic migraine headaches, and one reported a history of Raynaud’s phenomenon. Most of these patients described chest pain that was consistent with ischemic cardiac pain: substernal pressure often radiating to the neck and/or arms associated with dyspnea. Features of the pain that were atypical of an obstructive coronary artery cause included variable an- ginal threshold (including resting and nocturnal chest pain) and variable relief by nitrates, although most patients used nitroglycerin. If the chest pain occurred during activity, the majority were forced to rest. Pain usually lasted minutes, but a few episodes of pain lasting for half an hour were described.

All the patients were participating in this study so that the possibility that dynamic changes in coronary vascular resistance were contributing to the precipitation of their angina pectoris could be examined. The radionuclide results were compared with those from 52 consecutive subjects who were free of known heart disease and who were similar in age (mean age 44 years, range 26 to 64) and sex distribution (33 men, 19 women) to the above-described study population. These patients were undergoing prechemotherapy evaluation because of a variety of solid tumor malignancies. Radionuclide studies were performed in these control subjects over the same 2 year period as the study patients.

**Cardiac catheterization.** This study was approved by the Clinical Research Subpanel, NHLBI. Informed consent was obtained from all patients, and medications were stopped for at least 48 hr before the catheterization study. After sedation with 10 mg oral diazepam, patients were taken to the catheterization laboratory, usually at 8 A.M., while in the fasting state and while free of any other premedication. A thermodilution catheter (Elecath Corporation) was introduced into the right atrium of each percutaneously via the right internal jugular vein. The great cardiac vein (GCV), which drains the majority of blood flowing through the left anterior descending artery system, was cannulated.

Before the coronary flow study, all patients underwent diagnostic contrast ventriculography and coronary arteriography in multiple angulated views. Arteriograms of the coronary arteries for quantitative measurement were always obtained in two views 90 degrees apart, usually the 60 degree left anterior oblique and 30 degree right anterior oblique, using Siemens-Elema equipment with C arm so that the patient was not moved during the study. The developed films were projected on a Vanguard Cine projector at approximately threefold magnification. In 14 patients, 10 × 12 cut films were obtained at two films per second for 3 sec. For either angiographic technique, luminal diameter of the coronary artery was measured with calipers at multiple positions along the proximal, mid, and distal epicardial arteries. Measurements were made by two observers without knowledge of the catheterization results who used the known dimensions of the No. 8F Judkins left coronary catheter as a reference measurement. Care was taken to use frames in which the region of interest was centered on the screen or cut film to avoid magnification and other distortion artifacts. Measurements were made at identical points in the two views, with use of branch arteries as references, and were averaged.

Position of the thermodilution catheter in the GCV was veri- fied initially by small injections of contrast material and kept constant throughout the study by frequent inspection of the relation of the pacing electrodes to bony landmarks via fluoroscopy. The thermodilution technique for determining GCV and coronary sinus flow has been described previously. Flow measurements were recorded over a 20 sec period after tempera- ture equilibration. A 20-gauge catheter was placed in the left brachial artery for arterial pressure measurements. Coronary resistance in the anterior circulation was calculated as mean blood pressure divided by GCV flow. A No. 8F pigtail catheter was advanced into the left ventricle via the right femoral artery in 20 patients for measurement of left ventricular end-diastolic pressure (LVEDP). Arterial pressure and three electrocardio- graphic monitor leads (I, aVF, and V5) were recorded with each flow measurement and immediately after pacing. Lactate samples were obtained from the GCV through the distal port of the thermodilution catheter at the beginning of each study and during peak pacing. Specimens were collected in tubes containing sodium fluoride and potassium oxylate for inhibition of glycolysis and immediately centrifuged at 4 °C and 5000 rpm for 5 min. The decanted serum was then processed for lactate content on a Dupont automatic clinical analyzer by a modification of the technique of Marbach and Weil. Lactate consumption was calculated as GCV flow multiplied by the difference between the arterial and GCV lactate concentrations.

**Coronary flow during pacing.** The study protocol was initi- ated at least 20 min after use of angiographic contrast material so that any effects of dye on coronary blood flow or metabolism would subside. GCV flow and lactate and arterial lactate mea- surements were determined in patients at rest, as were measure- ments of LVEDP. Pacing via the coronary sinus thermodilution catheter was initiated at a heart rate of 100 beats/min and in- creased by 10 beats/min increments at 1 min intervals up to a heart rate of 150 beats/min. In six patients, 0.5 to 1.0 mg atropine was administered intravenously to achieve a heart rate of 150 beats/min without atrioventricular block. In two patients, pacing was terminated at a heart rate of 130 beats/min. At the final heart rate, repeat GCV flow and lactate and arterial lactate measurements were made. After termination of pacing, the LVEDP was measured in 20 patients for 10 sec and averaged, eliminating the first 4 beats.
In 30 patients repeat baseline GCV flow, lactate, and LVEDP (in 20 patients) were obtained after a rest period of 10 min, followed by administration of 0.15 mg iv ergonovine. Because of pronounced limitation to GCV flow increase during pacing associated with severe chest pain, ergonovine was not administered to three patients. Although the patients were aware that ergonovine would be administered at some time during the study, the actual administration of the drug was performed without their knowledge. Repeat measurements of GCV flow were performed after 45 sec, and immediately thereafter pacing was begun at a heart rate of 130 beats/min. Pacing rate was then increased to 150 beats/min (less in three patients because of second-degree atrioventricular block) and repeat measurements were made as described for the control study. After pacing was discontinued LVEDP was measured for 10 sec. Arteriography was then performed (approximately 4 min after administration of ergonovine) in the same views as those used before the initial pacing study. The majority of patients received an additional 0.25 mg of ergonovine with subsequent repeat arteriograms.

Gated blood pool cardiac scintigraphy. Gated blood pool scintigraphy was performed within 1 month of the pacing study in 90% of patients. The radionuclide studies were performed at least 48 hr after discontinuation of propranolol, calcium-channel blockers, or long-acting nitrate preparations. Studies were performed in subjects in the supine position at rest and during maximum symptom-limited exercise with use of red blood cells labeled in vivo with 15 to 20 mCi of technetium-99m. Imaging was accomplished with a conventional Anger camera equipped with a high-sensitivity, parallel-hole collimator, oriented in a modified left anterior oblique position to isolate the left ventricle. The cardiac image sequence spanning the average cardiac cycle was constructed by computer-based electrocardiogram gating, and high temporal resolution (50 to 100 frames/sec) left ventricular time-activity curves were generated from the cardiac image sequence after background correction.36 Left ventricular ejection fraction was determined by computer analysis of the time-activity curve. Regional left ventricular function was assessed subjectively by visual inspection of the cardiac image sequence, displayed in movie format, and by inspection of the count-based stroke volume functional map, constructed by computer subtraction of the end-systolic image from the end-diastolic image.38

The radionuclide studies were performed and analyzed without knowledge of the results of the pacing study. Assignment of wall motion abnormality was made by the consensus of three experienced observers with no knowledge of the results of the pacing study. Two of these observers had no knowledge that the patients being studied were free of obstructive coronary artery disease.

Exercise studies were performed by subjects on a bicycle ergometer with a restraining harness to minimize motion under the camera. Exercise loads were increased in 25 W increments every 2 min until the development of angina, limiting fatigue, or dyspnea. In patients who developed angina, exercise continued until angina reached at least the severity typically causing the patient to stop exercise. Heart rate and blood pressure (by sphygmomanometry) were monitored during exercise. Imaging was begun shortly after the onset of exercise, but only that portion of the data series that occurred during maximal exercise, encompassing approximately the last 2 min of exercise, was selected for analysis.

Left ventricular diastolic filling was assessed for the resting studies by fitting a third-order polynomial function to the rapid diastolic filling phase of the time-activity curve by a least-squares technique.39 The peak filling rate was compared in left ventricular counts per second, normalized for the number of counts at end-diastole, and expressed as end-diastolic counts (volume) per second (EDV/sec). This does not imply knowledge of actual left ventricular end-diastolic volume. The time to peak filling rate was computed as the interval from end-systole (nadir of the time-activity curve) to occurrence of the peak filling rate.

Data analysis. All group data are reported as mean ± SD. Data from the pacing studies were analyzed by two-tailed Student’s t test for unpaired data. Hemodynamic and ejection fraction data from gated blood pool scintigraphic testing were analyzed by analysis of variance with Scheffe’s method of multiple comparisons. The p values for the 2 × 2 contingency tables for comparisons of responses to gated blood pool scintigraphic testing were estimated by Fisher’s exact test. A value of less than .05 was considered to indicate significance.

Results

Catheterization data

Angiographic studies. Diagnostic coronary arteriographic examinations of the 33 study patients revealed normal epicardial coronary arteries in all patients, as independently interpreted by two experienced observers. Contrast ventriculography revealed normal left ventricular size and contractility in all patients.

Control pacing study. The 33 patients participating in the study were grouped depending on whether or not they experienced their typical chest pain during pacing. There was no difference in heart rate, blood pressure, GCV flow, calculated coronary resistance, LVEDP, or lactate consumption at rest between the two groups (table 1). However, during pacing the group experiencing chest pain demonstrated lower GCV flow and higher coronary resistance and consumed less lactate at the final paced heart rate than those without chest pain. After pacing, the LVEDP

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Hemodynamic data from control study</th>
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<tbody>
<tr>
<td></td>
<td>No chest pain</td>
</tr>
<tr>
<td></td>
<td>(n = 15)</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>HR</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>BP</td>
<td>99 ± 12</td>
</tr>
<tr>
<td>GCV-F</td>
<td>69 ± 18</td>
</tr>
<tr>
<td>CR</td>
<td>1.54 ± 0.52</td>
</tr>
<tr>
<td>LVEDP</td>
<td>11 ± 4</td>
</tr>
</tbody>
</table>

Lactate consumption

21.8 ± 11.1 | 41.7 ± 22.1 | 23.4 ± 16.4 | 24.0 ± 16.1*

Measurements are mean ± SD.

HR = heart rate; BP = mean arterial blood pressure; GCV-F = great cardiac vein flow (ml/min); CR = coronary resistance in the anterior circulation (mm Hg/ml/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); lactate consumption = (arterial − GCV lactate) × GCV-F (mM · ml/min).

*p < .025; *p < .01 for patients developing chest pain vs those without pain.
coronary arteriography performed immediately after pacing (approximately 4 min after ergonovine administration) in those patients experiencing chest pain showed no focal spasm and only minimal luminal narrowing of the epicardial coronary artery (−5 ± 5% proximal, −6 ± 8% mid, −4 ± 5% distal LAD) compared with control arteriograms. In the majority of patients administration of additional doses of ergonovine up to a cumulative dose of 0.4 mg produced less than 20% epicardial artery narrowing and no focal spasm.

**Radionuclide angiographic data**

*Left ventricular function at rest*. On the basis of the coronary flow study during pacing, two groups were established for analysis of radionuclide cineangiographic data. Seven patients who experienced no chest pain during either the control or ergonovine pacing studies were considered to have appropriate vasodilator reserve. At rest, control subjects and patients with normal vasodilator reserve had similar heart rates and systolic blood pressure–heart rate products, an estimate of myocardial oxygen demand (table 3). Patients with abnormal vasodilator reserve had a slightly lower resting heart rate and pressure-rate product compared with control subjects. The resting ejection fraction was similar among the three groups (table 3, figure 1).

*Left ventricular function during exercise*. The peak exercise heart rate and pressure-rate product were similar in control subjects and patients with normal vasodilator reserve, and slightly lower in the abnormal vasodilator reserve group (table 3). None of the 52 control subjects experienced chest pain during exercise, but four demonstrated no change or a decrease in ejection fraction during exercise, and an additional four had less than a 5% increase (figure 1, table 4). One of these patients had a resting and exercise-induced wall motion abnormality. Hence, a total of eight of the 52 control subjects (15%) had one or more abnormalities of left ventricular systolic function during exercise.

### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>No chest pain (n = 8)</th>
<th>Developing chest pain (n = 22)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Pacing</td>
</tr>
<tr>
<td>HR</td>
<td>83 ± 12</td>
<td>150 ± 0</td>
</tr>
<tr>
<td>BP</td>
<td>103 ± 14</td>
<td>111 ± 12</td>
</tr>
<tr>
<td>GCV-F</td>
<td>76 ± 17</td>
<td>150 ± 33</td>
</tr>
<tr>
<td>CR</td>
<td>1.4 ± 0.35</td>
<td>0.77 ± 0.18</td>
</tr>
<tr>
<td>LVEDP</td>
<td>9 ± 2</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>(after pacing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate consumption</td>
<td>26.5 ± 13.5</td>
<td>69.7 ± 41.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD; abbreviations as in table 1.
a p < .005; b p < .001 for patients developing chest pain vs those without pain.

was higher in patients with pacing-induced chest pain. No significant electrocardiographic changes were noted in any patient immediately after pacing.

**Ergonovine pacing study**. During pacing after ergonovine administration, 22 of 30 patients experienced their typical chest pain, including eight patients who experienced no chest pain during the control pacing study. One patient who experienced chest pain during the control study did not develop chest pain during the ergonovine study. There was no difference with respect to resting hemodynamic and metabolic parameters between the two groups (table 2). However, during pacing patients developing chest pain manifested both a lower GCV flow and a higher coronary resistance than those without pain at the final paced heart rate. Patients with chest pain during pacing after ergonovine also demonstrated less lactate consumption and a higher LVEDP after pacing than those in the group not experiencing chest pain during pacing. Two patients with chest pain with ergonovine plus pacing developed greater than 1 mm horizontal ST depression immediately after pacing.

**Quantitative angiography after ergonovine**. Selective

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>DP</td>
</tr>
<tr>
<td>Control subjects (n = 32)</td>
<td>77 ± 12</td>
<td>9.8 ± 2.1</td>
</tr>
<tr>
<td>NVR (n = 7)</td>
<td>77 ± 11</td>
<td>9.4 ± 1.1</td>
</tr>
<tr>
<td>AVR (n = 26)</td>
<td>69 ± 10a</td>
<td>8.5 ± 1.8a</td>
</tr>
</tbody>
</table>

NVR = normal vasodilator reserve; AVR = abnormal vasodilator reserve (see text); HR = heart rate; DP = double product (systolic blood pressure × heart rate); EF = ejection fraction.
a p < .05; b p < .001 vs controls; c p < .05 vs NVR.
FIGURE 1. Resting and exercise left ventricular ejection fractions in control subjects free of known heart disease and patients who underwent the coronary flow study during pacing. NVR = normal vasodilator reserve; AVR = abnormal vasodilator reserve; R = rest; Ex = exercise; large circles with bars indicate mean value; open circles identify patients with regional wall motion abnormalities.

Two of the seven patients with normal vasodilator reserve and 16 of the 26 patients considered to have abnormal vasodilator reserve described chest pain during exercise. The ejection fraction during exercise in the control subjects and the patients with normal vasodilator reserve was identical (66 ± 10% and 66 ± 4%, respectively; table 3, figure 1). All patients with normal vasodilator reserve demonstrated a greater than 5% increase in ejection fraction with exercise, and none had regional wall motion abnormalities at rest or during exercise (table 4).

In contrast, the ejection fraction during exercise in the patients with abnormal vasodilator reserve (58 ± 8%) was significantly lower than that in either the control subjects (p < .001) or the patients with normal vasodilator reserve (p < .05; table 3). Likewise, the change in ejection fraction from rest to exercise in the abnormal vasodilator group (4 ± 6%) was significantly lower than that in either the control subjects (9 ± 6%, p < .001) or patients with normal vasodilator reserve (14 ± 3%, p < .001). Six patients with abnormal vasodilator reserve demonstrated no change or a decrease in ejection fraction with exercise, and an additional nine had a less than 5% increase with exercise. Although no patient had a wall motion abnormality at rest, 12 developed wall motion abnormalities with exercise. Thus, 18 of 26 patients (69%) with abnormal vasodilator reserve had one or more abnormalities of left ventricular systolic function during exercise (figure 1, table 4).

Left ventricular functional reserve in women. In our study, an increase in ejection fraction of 5% or greater during exercise was considered normal. However, since the exercise ejection fraction response of normal women has been reported lower than that of men, this might result in misclassification of a normal woman as abnormal. Hence, we analyzed the data from women separately (table 5). Of the 17 women classified as having abnormal vasodilator reserve, ejection fraction decreased or remained unchanged during exercise in six, increased by less than 5% in five (three of whom had regional wall motion abnormalities during exercise), and increased 5% or more in six (two of whom demonstrated wall motion abnormalities). Overall, 13 of the 17 women (77%) with abnormal vasodilator reserve had an abnormal ejection fraction response and/or a wall motion abnormality during exercise. In contrast, 19 of the 52 control subjects were women in whom the average increase in ejection fraction with exercise was 8%; only three women demonstrated an increase of less than 5%.

Indexes of left ventricular diastolic filling. The peak left ventricular filling rate at rest (figure 2) was higher in

<table>
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<tr>
<th>Parameters of left ventricular systolic function</th>
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<tbody>
<tr>
<td>Exercise EF</td>
</tr>
<tr>
<td>ΔEF ≤0%</td>
</tr>
<tr>
<td>Control (n = 52)</td>
</tr>
<tr>
<td>NVR (n = 7)</td>
</tr>
<tr>
<td>AVR (n = 26)</td>
</tr>
<tr>
<td>p values</td>
</tr>
<tr>
<td>AVR vs control</td>
</tr>
<tr>
<td>AVR vs NVR</td>
</tr>
</tbody>
</table>

NVR = normal vasodilator reserve; AVR = abnormal vasodilator reserve; EF = ejection fraction; ΔEF = change in ejection fraction from rest to exercise; WMA = wall motion abnormality.

TABLE 5
Radionuclide results in the 17 women with abnormal vasodilator reserve

<table>
<thead>
<tr>
<th>Radionuclide abnormality</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction response to exercise</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Increase between 1% and 5%</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Regional wall motion abnormality during exercise</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Patients with abnormal ejection fraction response to exercise and/or wall motion abnormality during exercise</td>
<td>13 (77)</td>
</tr>
</tbody>
</table>
control subjects (3.2 ± 0.7 EDV/sec) than in patients with normal (2.4 ± 0.6 EDV/sec, p < .01) or with abnormal vasodilator reserve (2.6 ± 0.7 EDV/sec, p < .005). Six of 52 control subjects had peak filling rates below the normal range (≥2.5 EDV/sec), and one of these had a reduced ejection fraction at rest and three manifested an abnormal ejection fraction response to exercise. In contrast, of 26 patients with abnormal vasodilator reserve, 11 (53%) had subnormal peak filling rates at rest. The time to peak left ventricular filling rate (figure 2) was similar in all three groups. Overall, of the 26 patients with abnormal vasodilator reserve, 15 (58%) had an abnormality of one or both indexes of diastolic filling. According to combined analysis of left ventricular diastolic filling at rest and systolic function during exercise, 21 of 26 patients (81%) with abnormal vasodilator reserve had evidence of left ventricular dysfunction.

**Discussion**

In this series of patients with chest pain despite angiographically normal-appearing coronary arteries and no evidence of large vessel spasm after ergonovine, three-quarters had an abnormally low coronary blood flow response to pacing after ergonovine administration. This abnormal flow response was associated with a failure of coronary resistance to decrease appropriately in patients developing chest pain during pacing, suggesting that the abnormality is caused by a limitation of coronary vasodilator reserve. This abnormality appears to be dynamic, since ergonovine exacerbated or unmasked coronary flow limitation in many patients who, during pacing alone, experienced no chest pain.

Pacing-induced changes in myocardial oxygen demand would be expected to produce vasodilation of the coronary microcirculation by autoregulatory control, so that the increase in demand is met by an appropriate increase in coronary blood flow. Since the epicardial coronary arteries in these patients had neither fixed obstructive lesions nor overt spasm and hence offered little resistance to flow, the abnormality appears to arise in vessels too small to be imaged reliably by current angiographic techniques. This implies an abnormality of autoregulation if the abnormality occurs at the arteriolar level. If the abnormality is at the small artery level, mechanisms other than autoregulation would have to be involved.

Regardless of the mechanism, these patients experienced chest pain in association with a limited coronary blood flow response to pacing, suggesting that their pain was ischemic in origin. Studies of myocardial ischemia secondary to atherosclerotic obstructive coronary artery disease have identified myocardial lactate production as a marker of ischemia. The abnormal lactate metabolism demonstrated by our patients
experiencing chest pain and abnormal vasodilator reserve may similarly reflect ischemia, although frank lactate production was rarely seen. Instead, most of these patients had decreased lactate consumption, an inappropriate response to increases in myocardial demand, since lactate is used as a metabolic substrate. Hence, although decreased lactate consumption probably represents a point on the spectrum toward the lactate production observed during severe ischemia, we sought to detect other abnormalities compatible with myocardial ischemia to more unequivocally demonstrate that these patients with chest pain and abnormal vasodilator reserve were experiencing true ischemia.

Abnormalities in left ventricular function often precede such metabolic markers of ischemia, at least in patients with obstructive coronary artery disease in whom ischemia is induced during pacing. Thus, the present study was performed to assess whether or not suspected myocardial ischemia related to impaired vasodilator reserve was associated with left ventricular dysfunction at rest or during exercise.

Our results indicate that the majority of patients with chest pain and normal epicardial coronary arteries who were classified by our pacing study as having abnormal vasodilator reserve had abnormal left ventricular systolic function during exercise. Two-thirds of the patients had an abnormal ejection fraction response to exercise, regional wall motion abnormalities during exercise, or both. This exercise response differed from that in both the asymptomatic control subjects and the patients with chest pain but normal coronary flow reserve (table 4).

The patients with abnormal vasodilator reserve also manifested impaired left ventricular diastolic filling at rest, which is frequently observed in patients with coronary artery disease and normal left ventricular function. This may represent the effects of low-grade ischemia or reduced coronary flow. In fact, 21 of these 26 patients (81%) had evidence of abnormal left ventricular systolic and/or diastolic function. Although neither left ventricular systolic dysfunction during exercise nor reduced left ventricular filling at rest is specific for ischemia, none of the patients had evidence of other cardiac conditions that might have limited left ventricular systolic function during exercise or diastolic function at rest. Hence, these data provide further evidence that chest pain in association with abnormal vasodilator reserve is indeed ischemic in origin.

Although eight of the 26 patients with abnormal vasodilator reserve manifested normal ventricular function during exercise, three factors may explain these apparent false-negative responses. First, these patients may have developed myocardial ischemia, but the severity of ischemia may not have been sufficient to result in measurable alterations in left ventricular function. In this regard, the 31% false-negative rate is similar to that reported for patients with single-vessel coronary artery disease. Second, exercise stress may not be the appropriate provocation to elicit an abnormal coronary vasodilator response in some patients. It is possible that coadministration of a vasoconstrictor stimulus during exercise (analogous to the administration of ergonovine during pacing) might have induced left ventricular dysfunction by unmasking or exacerbating small-vessel vasoconstriction or inappropriate vasodilation. Finally, it is also possible that these patients were misclassified by our catheterization study and as such represent “false positives” for abnormal vasodilator reserve.

Although no patient classified as having normal vasodilator reserve on the basis of the pacing study demonstrated abnormalities of systolic ventricular function during exercise, five demonstrated impaired diastolic filling (peak rate <2.5 EDV/sec). Although these patients were believed to have an appropriate vasodilator reserve, they did present with chest pain syndromes. Hence, they may have some cardiac abnormality unrelated to small-vessel dysfunction. Alternatively, they may have been misclassified by the pacing study and thus represent false-negative results of tests for abnormal vasodilator reserve.

Fundamental to our argument is the issue of whether radionuclide cineangiography can accurately detect left ventricular dysfunction induced by reversible myocardial ischemia. Patients with obstructive epicardial coronary artery disease usually demonstrate abnormalities of left ventricular function during exercise, and the frequency of such responses generally correlates with the number of diseased vessels and thus the mass of ischemic myocardium. However, patients with chest pain who are free of angiographically apparent coronary artery stenoses also have been found to demonstrate similar abnormalities during exercise. These apparent false-positive responses lower the specificity of radionuclide angiography for detecting coronary artery disease, and thus the usefulness of this test has been questioned. However, the majority of ‘‘control’’ subjects in studies assessing the specificity of radionuclide angiography have chest pain syndromes that are sufficiently severe to warrant cardiac catheterization and coronary arteriography. On the basis of our results we believe that many of the patients with false-positive evidence of obstructive
epicardial coronary artery disease may have truly positive responses for ischemia, but that the underlying coronary artery disease is to be found in abnormalities of the coronary microcirculation.

Although one-fourth of the patients prospectively entered into the Coronary Artery Surgery Study registry were subsequently found to have angiographically normal coronary arteries or "insignificant" coronary artery disease, the prevalence of abnormal vasodilator reserve is unknown. The pacing coronary flow study described by us is obviously an impractical test for identifying these patients. However, radionuclide angiography appears to offer an excellent noninvasive approach in that the majority of patients with abnormal vasodilator reserve in our study had abnormal diastolic function at rest and systolic function during exercise. We feel that these patients merit treatment with nitrates and calcium-channel blockers. In patients with normal resting and exercise radionuclide studies, a search for a noncardiac cause (e.g., esophageal motility disorder or reflux) of pain may be of diagnostic usefulness, although an empiric trial of drug therapy may be of symptomatic benefit.

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