Reflex constriction of significant coronary stenosis as a mechanism contributing to ischemic left ventricular dysfunction during isometric exercise

B. Greg Brown, M.D., Ph.D., Arthur B. Lee, M.D., Edward L. Bolson, M.S., and Harold T. Dodge, M.D.

ABSTRACT To study the mechanisms of myocardial ischemia during isometric exercise, handgrip was sustained, for 4.5 min at 25% of maximum by 11 patients with at least one significant coronary stenosis each, during cardiac catheterization. After recovery, the handgrip that was repeated with simultaneous infusion of nitroglycerin (50 µg over 4 min) directly into the diseased vessel. The cardiovascular response was assessed by hemodynamic and by computer-assisted measurements of stenosis. During the first handgrip test pulmonary capillary wedge pressure rose 56% (15 to 23 mm Hg; p < .001), the heart rate–systolic pressure product rose 33% (p < .01), and the diseased epicardial arteries constricted. Luminal area in the stenotic segment was reduced by 35% (p < .01), resulting in a 243% increase in estimated stenotic flow resistance (30 to 103 mm Hg/ml/sec; p < .001). During handgrip with intracoronary nitroglycerin, the pressure-rate product again increased 33%, but relative to resting control, capillary wedge pressure fell 4 mm Hg in association with a 32% increase in luminal area of the stenosis and a 28% reduction in flow resistance (all significantly different from the response to handgrip alone: p < .001, .01, and .005, respectively). Thus, coronary vasoconstriction, not increased pressure-rate product, is the dominant mechanism for ischemic left ventricular dysfunction during isometric exercise in patients with significant coronary stenoses.


ISOMETRIC HANDGRIP is a potentially useful stress test for the noninvasive detection of coronary artery disease and other cardiac diseases associated with diminished left ventricular functional reserve. Although it would seem to be a modest cardiovascular stress, Mitamura et al. have shown that handgrip produces significant regional left ventricular dysfunction that is evident on the two-dimensional echocardiogram. Since the regional contraction abnormalities that were observed during handgrip were localized to myocardium perfused by diseased vessels, they represent an ischemic response. Ischemia during handgrip may be due to a modest increase in myocardial oxygen demand (systolic pressure, heart rate, and inotropic state) in the setting of markedly diminished coronary flow reserve, or it may be due to "inappropriate" coronary vasoconstriction that occurs under conditions associated with sympathetic nervous system activation. The latter has already been demonstrated for the coronary vascular bed in the distribution of diseased arteries, for the arteriolar bed distal to experimental stenosis, and for normal and atherosclerotic segments of the larger epicardial vessels. This report describes clinical studies designed to test the hypothesis that handgrip-induced constriction of diseased epicardial coronary arteries plays a major role in the regional ischemic response to this type of stress.

Methods

Hemodynamic measurements. Eleven men underwent cardiac catheterization for evaluation of chest pain syndromes. These patients were selected because they were found to have at least one high-grade stenosis each. Their clinical characteristics and angiographic findings are listed in table 1. All were fully informed about the proposed studies and signed an approved consent document. Premedication was avoided in the majority of patients; all cardiac medications except nitroglycerin (given as needed) were discontinued at least 16 hr before the procedure. Any patient who had taken nitroglycerin within 4 hr of catheterization was excluded from this study. The left heart and pulmonary artery were catheterized with standard No. 8F pig-
Clinical and angiographic characteristics and pulmonary capillary wedge pressure response to isometric handgrip with and without intracoronary nitroglycerin

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Angina</th>
<th>Previous myocardial infarction</th>
<th>Coronary disease</th>
<th>Visible collaterals</th>
<th>Ejection fraction</th>
<th>Pulmonary capillary wedge (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>O</td>
<td>II</td>
<td>LAT SEMI</td>
<td>LAD to LCX</td>
<td>0.64</td>
<td>16 + 10 - 4</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>N</td>
<td>III</td>
<td>—</td>
<td>—</td>
<td>0.66</td>
<td>8 0 - 1</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>O</td>
<td>IIIa</td>
<td>—</td>
<td>—</td>
<td>0.59</td>
<td>6 + 4 - 3</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>F</td>
<td>II–IIIb</td>
<td>LAT SEMI</td>
<td>LAD to LCX</td>
<td>0.70</td>
<td>10 + 8 - 6</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>N</td>
<td>III</td>
<td>LAT SEMI</td>
<td>LAD to LCX</td>
<td>0.62</td>
<td>10 + 1 - 5</td>
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<tr>
<td>6</td>
<td>42</td>
<td>O</td>
<td>II–III</td>
<td>INF TMI</td>
<td>LCX to RCA</td>
<td>0.67</td>
<td>7 + 13 + 6</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>F</td>
<td>I</td>
<td>INF TMI</td>
<td>LCA to RCA</td>
<td>0.64</td>
<td>7 + 2 - 2</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>N</td>
<td>III</td>
<td>A-S SEMI</td>
<td>RCA to RCA</td>
<td>0.22</td>
<td>27 + 14 + 4</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>O</td>
<td>III</td>
<td>INF TMI</td>
<td>RCA to RCA</td>
<td>0.23</td>
<td>28 + 9 - 14</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>F</td>
<td>III</td>
<td>ANT TMI</td>
<td>RCA to LAD</td>
<td>0.27</td>
<td>24 + 14 - 9</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>N</td>
<td>IIIa</td>
<td>INF SEMI</td>
<td>—</td>
<td>0.42</td>
<td>20 + 19 + 3</td>
</tr>
</tbody>
</table>

SEMI = subendocardial myocardial infarction; TMI = transmural myocardial infarction; INF = inferior; ANT = anterior; OMB = obtuse marginal branch; LAD = left anterior descending artery; LCX = left circumflex artery; LAT = lateral; A-S = anteroseptal; RCA = right coronary artery; N = never; O = occasional; F = frequent; HGP = handgrip test; NTG = nitroglycerin.

aNew York Heart Association functional class.

bChest pain induced during handgrip test.

cLesion analyzed. In all patients but No. 11 nitroglycerin infusion was into the left coronary artery.

tail, Judkins coronary, and Swan-Ganz thermodilution catheters. Routine measurements included left ventricular, aortic, and right heart pressures, and left ventricular and coronary angiograms were also routinely recorded.

Patients who were selected because they had high-grade coronary stenoses underwent the following protocol: By review of a videotape, an arteriographic projection was selected in which the diseased segment of interest was best visualized. All hemodynamic and arteriographic measurements were repeated as a baseline control. Each patient then performed 4.5 min of sustained isometric handgrip exercise at 25% of a predetermined maximum grip strength using a commercially available device. All measurements described below were made at between 4 and 4.5 min. After this effort the patient rested and hemodynamic parameters were carefully monitored until they returned to control levels.

After recovery the handgrip test was repeated. During this second test 0.05 mg nitroglycerin was infused slowly by direct infusion through the catheter into the ostium of the coronary artery that contained the lesion of interest. The infusion was started at the onset of handgrip and continued at a uniform rate until the fourth minute; all measurements were repeated at between 4 and 4.5 min. This dose and rate of administration were selected because they approximated the concentration of nitroglycerin in coronary arterial blood (approximately 120 ng/ml after sublingual administration of 0.6 mg in a patient with 5 liters/min venous return), but was small enough in total dose that it would not effect systemic hemodynamics. After recovery from the second handgrip test, sublingual nitroglycerin (0.4 mg) was given in the absence of handgrip. Aortic, pulmonary arterial, and pulmonary capillary wedge pressures, heart rate, and coronary arteriograms were obtained from patients in the control state, at the peak of the first and second handgrip tests, and in the resting state 4.5 min after the sublingual nitroglycerin dose. There were no complications of the catheterization procedures.

Quantitative angiography. The isolated significant coronary stenoses were measured in 10 of our 11 patients at control and during each of the three subsequent stress/drug conditions. A computer-assisted method was used. To eliminate observer bias in the arteriographic analysis, those analyzing the lesions were blinded to which of the four study conditions (control, handgrip, handgrip plus intracoronary nitroglycerin, sublingual nitroglycerin) the arteriograms represented. The diseased arterial segment, including the 'normal' parts of the vessel at each end, was analyzed independently by two experienced observers using three cine frames each for each of the four study conditions. The application of this method for the measurement of pharmacologically induced changes in coronary arterial luminal caliber has been described, and further details on this method are available in these reports.

Statistical analysis. The hemodynamic and arterial caliber response to handgrip and to handgrip combined with intracoronary nitroglycerin, expressed as changes from control, were compared by paired t test. Significance was defined as a less than 5% probability of the null hypothesis.

Results

Clinical data. As shown in table 1, each of the 11 patients had at least one significant coronary stenosis.
In each case the lesion studied was one appearing to contribute substantially to the patient's ischemic syndrome, as determined by localized electrocardiographic changes during pain or by the fact that it was the only high-grade stenosis present. Three of 11 patients had chest pain during their first handgrip tests; pain did not occur in any instance during combined handgrip and intracoronary nitroglycerin. In five patients an additional totally occluded vessel was supplied distally by collaterals arising from the artery into which the nitroglycerin was infused.

**Hemodynamic data.** Figures 1 and 2 show the response of systemic and pulmonary capillary wedge pressures to the sequence of stress and drugs. Systemic and wedge pressures and heart rate did not change significantly during the mean 35 min interval between the initial hemodynamic measurements and the pre-handgrip control. At peak exertion during the first handgrip test mean blood pressure rose 23% (p < .01), pulmonary wedge pressure rose 56% (p < .001), and double product rose 33% (p < .01). Similarly, blood pressure and double product rose 21% and 33% during the second handgrip test when intracoronary nitroglycerin was given. However, despite this rise in two of the principal determinants of cardiac work and O₂ requirement, pulmonary wedge pressure fell to 21% below control, a response that differed significantly from that without intracoronary nitroglycerin (p < .001). Finally, after sublingual nitroglycerin in the absence of handgrip, systemic pressure and double product each fell to 12% below control and pulmonary wedge pressure to 62% below control. The wedge reduction at rest after sublingual nitroglycerin was significantly greater than that after intracoronary nitroglycerin during handgrip (p < .05).

**Angiographic data.** Figure 3 shows responses of two high-grade coronary lesions to handgrip with and without intracoronary nitroglycerin. The averaged changes in normal vessel and coronary stenotic dimensions and in flow resistance are given in table 2 and figure 2. Both the normal and the most diseased portions of the vessels constricted with handgrip, but during handgrip combined with intracoronary nitroglycerin they dilated. Little additional coronary dilation occurred after sublingual nitroglycerin. Thus, intracoronary nitroglycerin, at pharmacologically effective plasma con-
to 40% increases in blood pressure, heart rate, and cardiac output\textsuperscript{13-15} and with a 45% to 65% increase in coronary flow.\textsuperscript{14} The reports cited above indicate that well-compensated ventricles adapt to these increased circulatory demands by increasing the cardiac inotropic state and heart rate in order to maintain constant left ventricular volume\textsuperscript{16} and filling pressure.\textsuperscript{6-8} However, patients with cardiac diseases associated with left ventricular dysfunction typically demonstrate inadequate functional reserve during stress of this kind — pulmonary capillary wedge pressure rises, cardiac output does not, and global ejection fraction falls. In patients with coronary disease, this typically occurs when resting left ventricular function is abnormal, but it is also quite common in those with normal global and regional left ventricular performance at rest.\textsuperscript{5} Our 11 patients, each with at least one significant stenosis, demonstrated a typical ischemic response to handgrip in that wedge pressure rose an average of 56%. Traditionally, ischemic left ventricular dysfunction has been related to increased systolic pressure $\times$ heart rate (double product), an index of myocardial oxygen requirement, which increased only modestly (33%) during handgrip in these studies. Another potentially important, recently described\textsuperscript{16},\textsuperscript{19} contributing mechanism is handgrip-induced vasoconstriction of diseased as well as normal segments of the epicardial coronary arteries. In this study, estimated flow resistance in severe lesions increased about threefold.

Does this phenomenon contribute substantially to the handgrip-induced ischemic response? Our studies were designed to separate the direct coronary effects of handgrip on left ventricular function from the systemic hemodynamic effects. The significant worsening of left ventricular function that occurred with handgrip in this group of patients was prevented by a very small intracoronary infusion of nitroglycerin (50 $\mu$g into the affected artery slowly over 4 min). Pulmonary wedge actually fell below control during combined handgrip

### Discussion

Handgrip would seem to be a modest cardiovascular stress.\textsuperscript{9-12} In normal subjects it is associated with 15%

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Normal luminal area (mm$^2$)</th>
<th>Minimum luminal area (mm$^2$)</th>
<th>Stenotic flow resistance$^a$ (mm Hg/ml/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At control (±SD)</td>
<td>5.1 (± 2.2)</td>
<td>0.81 (± 0.46)</td>
<td>30.5 (± 49.7)</td>
</tr>
<tr>
<td>Percent change from control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric handgrip</td>
<td>− 14</td>
<td>− 35</td>
<td>+ 243</td>
</tr>
<tr>
<td>Handgrip plus nitroglycerin</td>
<td>+ 29$^b$</td>
<td>+ 32$^b$</td>
<td>− 28$^c$</td>
</tr>
<tr>
<td>Sublingual nitroglycerin</td>
<td>+ 18$^b$</td>
<td>+ 30$^b$</td>
<td>− 32$^c$</td>
</tr>
</tbody>
</table>

$^a$Estimated at assumed stenotic flow of 1 ml/sec.
Comparison of responses for handgrip vs (handgrip + nitroglycerin): $^b$p < .01; $^c$p < .005.
Comparison of responses for (handgrip + nitroglycerin) vs nitroglycerin: $^d$p = NS.
and intracoronary nitroglycerin despite increases in systemic pressure, heart rate, and double product that were virtually identical to those during the first handgrip test. This nitroglycerin dose has been previously shown to have no effect on systemic hemodynamics, including central venous pressure.20, 21 Thus, constriction of severe coronary stenoses, and not increased double product, appears to be the principal mechanism for ischemic left ventricular dysfunction during isometric exercise.

The observations presented here are in conflict with the report that intracoronary administration of nitroglycerin fails to alleviate pacing-induced angina.25 This discrepancy is due to differences in method of administration of intracoronary nitroglycerin, as discussed previously.21 The 75 μg bolus used in the study cited above20 predictably resulted in transient coronary drug concentrations approximating 200 times the pharmacologically effective levels. With such high concentrations, the coronary arterioles and the large epicardial vessels dilate, resulting in a 50% increase in regional blood flow.25 By contrast, pharmacologically effective systemic levels of nitroglycerin dilate the epicardial vessels but not the arterioles; regional flow actually decreases in response to reduced myocardial metabolic demand,26 and blood flow is distributed more uniformly across the left ventricular wall.27 Thus, in the setting of subendocardial ischemia, bolus intracoronary nitroglycerin produces an unnecessary pharmacologic dilation of the subepicardial arterioles but has little effect on the maximally dilated subendocardial microvasculature. Because stenotic flow increases somewhat with this drug-induced hyperemia, perfusion pressure may fall distal to the stenosis, as may the pressure-dependent subendocardial perfusion. The result is a "steal" of blood from the subendocardium to the subepicardium and failure to relieve ischemia. The slow infusion of a small dose (50 μg in 4 min) we used approximated pharmacologically effective coronary drug concentrations and it prevented handgrip-induced chest pain and ischemic myocardial dysfunction.

In each of five patients an additional totally occluded artery received collateral flow from the vessel into which nitroglycerin was infused. In these patients nitroglycerin-mediated vasodilation of these well-developed collateral vessels28, 29 may have contributed to the improvement in left ventricular functional reserve during the second handgrip test. The mechanisms of inappropriate coronary constriction during handgrip have been partially established. A sympathetic nervous reflex has been demonstrated.30 The afferent limb of this reflex appears to originate in skeletal muscle stretch receptors and to travel centrally via c-type unmyelinated nerve fibers to impinge on the sympathetic vasomotor center.31–33 The efferent limb is mediated by sympathetic nerve fibers impinging directly on the coronary arteries34–36 and by circulating epinephrine and norepinephrine, levels of which increase during isometric stress.37, 38 Constriction of normal and diseased coronary segments thus appears to be a response to α-adrenergic stimulation.39, 40 although the role of the sympathetic nervous system has not been completely confirmed in man. The relative importance of the neural and the humoral components of the efferent limb of this reflex remains to be determined. An additional dynamic mechanism that possibly contributes to handgrip-induced stenotic constriction is the observed partial collapse of significant coronary lesions in situations in which coronary flow is increased.4, 41, 42 However, this does not appear to be a dominant mechanism, since in our patients stenoses dilated after nitroglycerin during the second handgrip test despite a comparable increase in double product and, presumably, in coronary flow.4, 19

Competition between metabolic coronary vasodilation and superimposed α-adrenergic vasoconstriction has been demonstrated in the experimental setting of fixed coronary stenosis18 and in patients with coronary artery disease.17, 43 This competition appears to be an inappropriate physiologic response that may contribute to myocardial ischemia under certain circumstances. It appears to be of little consequence except in a state of near-maximal metabolic vasodilation, which most commonly occurs with near-maximal exercise or distal to a significant coronary stenosis. Under these conditions, α-adrenergic activity may limit the potential for maximal metabolic dilation and regional perfusion. In the studies of Mudge et al.17, 43 cold pressor–induced coronary vasoconstriction was presumed to be localized to the microvascular bed, although the possibility of constriction of the epicardial stenosis was not excluded. Our studies suggest that constriction of significant coronary stenoses plays an important and potentially dominant role in the ischemic left ventricular dysfunction that results from isometric stress. Intracoronary nitroglycerin, in concentrations that dilate the stenosis without dilating the coronary microvasculature, prevented the left ventricular dysfunction observed during handgrip alone.

Thus, the prevention of handgrip-induced ischemic left ventricular dysfunction by nitrates and certain other vasoactive drugs appears to be in large part due to their capacity to directly block the reflex constriction of significant coronary artery stenoses.44, 45
If stenotic constriction occurs during isometric exercise, it is reasonable to hypothesize that this phenomenon occurs as a general response to exertion, since both forms of muscular effort, isometric or dynamic, are associated with a substantial rise in serum catecholamines and with enhanced sympathetic neurogenic activation. The fact that coronary spasm can be induced by treadmill exercise is now well recognized. If this hypothesis is correct, the effectiveness of nitrates and calcium slow channel–blocking drugs in relieving ischemia associated with dynamic exercise may be explained in part by the demonstrated capacity of these drugs to block stenotic vasoconstriction in cardiovascular states associated with sympathetic activation.

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Vol. 70, No. 1, July 1984 23
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