Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test

ELIZABETH G. NABEL, M.D., PETER GANZ, M.D., JOHN B. GORDON, M.D., R. WAYNE ALEXANDER, M.D., PH.D., AND ANDREW P. SELWYN, M.D.

ABSTRACT Increased vascular constriction has been observed at the site of atherosclerotic lesions, suggesting an association between atherosclerosis and altered vascular tone. While atherosclerosis may increase sensitivity to exogenous vasoconstrictors, little is known about the response of normal and atherosclerotic coronary arteries to an exogenous stimulus that excites the sympathetic nervous system. Therefore, we studied the response to cold pressor test (CPT) using quantitative angiography and Doppler flow velocity measurements in eight patients with angiographically normal coronary arteries (group I), nine patients with mild coronary atherosclerosis (< 50% diameter narrowing) (group II), and 13 patients with advanced coronary stenoses (> 50% diameter narrowing) (group III). In 31 segments of angiographically smooth arteries in group I, the CPT produced vasodilation from a control mean diameter of 2.68 ± 0.09 (mean ± SE) to 2.99 ± 0.09 mm at peak CPT (p < 0.001), a 12 ± 1% increase in diameter. In group II, 27 irregular segments constricted to peak CPT from a mean control diameter of 1.82 ± 0.12 to 1.66 ± 0.12 mm (p < .001), a 9 ± 1% decrease, while 10 smooth segments dilated from a mean control diameter of 1.98 ± 0.11 mm to 2.34 ± 0.15 mm (p < .01), a 19 ± 2% increase in diameter. Likewise, in group III, the 17 stenotic segments constricted from 1.16 ± 0.09 to 0.89 ± 0.09 mm (p < .001), a 24 ± 6% decrease; the irregular segments also constricted from 2.44 ± 0.11 to 2.22 ± 0.12 mm (p = .002), a 10 ± 2% decrease. In contrast, two smooth segments dilated from 2.98 to 3.23 mm (mean), an 8% increase in diameter. Coronary blood flow increased 65 ± 4% (mean) during CPT in group I, it increased 15 ± 6% in group II, and it decreased 39 ± 8% in group III. The vasodilator response in four normal patients was partly inhibited by the administration of intracoronary propranolol (17 ± 3% increase during control, 10 ± 2% increase after propranolol, 41% less dilatation; p = .002). We conclude that the response of normal coronary arteries to the CPT test is dilation, in part related to β-adrenoreceptor stimulation and possibly flow-mediated endothelial dilation or α2-adrenergic activity. The paradoxical vasoconstrictor response induced by atherosclerosis may represent altered catecholamine sensitivity and/or a defect in endothelial vasodilator function. The presence of atherosclerosis impairs vasodilator responses and thus may contribute to the pathogenesis of myocardial ischemia.


DISTURBANCES of coronary vasomotion manifested as enhanced constriction may contribute to transient myocardial ischemia in patients with coronary artery disease (CAD).1-3 Although the causes of abnormal vasomotion are not well defined, the observation that enhanced vascular reactivity may occur at sites of atherosclerosis implies an association between this disease process and the alterations in local tone.4 Studies in vitro have indicated that atherosclerosis may increase sensitivity to vasoconstrictors.5 Also, in contrast to normal arteries, coronary vessels with angiographically evident atherosclerosis are susceptible to focal spasm induced by ergonovine.6, 7 There is little information, however, concerning the responses of either normal or diseased coronary arteries to sympathetic nerve stimulation, a major endogenous regulator of vascular tone. Although it appears to be widely assumed that the focal vasospasm induced by sympathetic stimulation is simply an exaggeration of the normal vasoconstrictor response, this may not necessarily be the case. Thus, sympathetic nerve stimulation

From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.
Supported in part by a research grant (HL-36028) from the National Institutes of Health. Dr. Ganz is a Clinical Investigator of the National Heart, Lung, and Blood Institute (HL-01045).
Address for correspondence: Andrew P. Selwyn, M.D., Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.
Received June 16, 1987; revision accepted Sept. 17, 1987.
of canine coronary arteries in vivo results in β-adrenergic–mediated vasodilation. To define the effects of sympathetic nervous system stimulation on vasomotion of coronary arteries in patients with normal and diseased vessels, we used quantitative coronary arteriography and Doppler flow velocity measurements to assess the response to the cold pressor test. In addition, the role of β-adrenergic receptors in mediating the response of normal arteries was determined.

Methods

Classification of patients. Thirty patients undergoing diagnostic cardiac catheterization were studied. These patients were divided into three groups based on the extent of their atherosclerosis on the diagnostic angiogram, and classification decisions were made by consensus of three investigators upon review of the coronary angiograms after the diagnostic catheterization and before the research study. Group I: controls. Eight patients with angiographically normal coronary arteries served as control subjects. Five patients had atypical chest pain with negative exercise tolerance tests; three patients had supraventricular tachycardia and were referred for diagnostic angiography and electrophysiologic study. Their ages ranged from 17 to 53 years (mean 37 years); five subjects were men, and three were women. All had angiographically normal, smooth coronary arteries without luminal irregularities. Group II: minimal disease. Nine patients were studied who had luminal irregularities in at least one coronary artery with no focal stenosis of more than 50% diameter narrowing. All nine subjects (six men; three women) had chest pain, but negative or equivocal exercise tolerance tests. None had documented small-vessel disease or spasm. Whether the chest pain syndromes were of cardiac origin in unknown. They were considered to have early atherosclerosis because they had risk factors for atherosclerosis and clear-cut intimal irregularities on diagnostic angiography. They ranged in age from 38 to 66 years, with a mean of 48 years. Group III: advanced stenoses. Thirteen patients were studied who had symptomatic stable angina pectoris, exercise tolerance tests diagnostic of myocardial ischemia, and an angiographically documented stenosis of greater than 50% narrowing in at least one coronary artery. Ten subjects were men and three were women. Their ages ranged from 36 to 71 years, with a mean of 59 years. Patients with unstable angina, recent myocardial infarction, conduction system disease, and clinical evidence of heart failure were excluded.

Written informed consent was obtained from all patients before the diagnostic catheterization, in accordance with guidelines established by the Committee for the Protection of Human Subjects at the Brigham and Women’s Hospital.

Study design. Antianginal therapy was discontinued at least 24 hr before cardiac catheterization, except for the unrestricted use of sublingual nitroglycerin, which was withheld 1 hr before catheterization. Long-acting β-adrenergic blockers were withheld 72 hr before study. Diagnostic right and left heart catheterization and coronary arteriography were performed by a standard percutaneous femoral approach. At least 15 min after completion of the diagnostic catheterization, patient classification was made and vessel(s) to be studied were determined by consensus decision. A No. 7F Judkins-type catheter or an 8.0F or 8.8F guiding catheter was introduced into the left main or right coronary artery. A No. 7F Swan-Ganz catheter was placed in the pulmonary capillary wedge position.

The cold pressor test was then performed. After control conditions were established, each patient’s hand and forearm was immersed in a slurry of ice water for 90 sec. After the hand and forearm were removed from the ice water, a 5 min recovery period was allowed. A steady-state intracoronary infusion of nitroglycerin (50 μg) was administered over 4 min.

Measurements of heart rate, mean and phasic femoral artery pressure, and mean and phasic pulmonary capillary wedge pressure (PCWP) were made, and serial injections of the study vessel with nonionic contrast medium were performed at control, at the peak of the cold pressor test (immediately before removal of the forearm from ice water), at recontrol (5 min after cold pressor test), and after intracoronary nitroglycerin.

Coronary blood flow velocity studies. Measurements of coronary blood flow velocity were made during the cold pressor test in four normal subjects (group I), three patients with irregular arteries (group II), and four patients with advanced stenoses (group III). These patients had anatomy suitable for placement of a Doppler flow velocity catheter. An additional 5000 units of heparin was given after the diagnostic catheterization. A 20 MHz pulsed Doppler crystal mounted on a No. 2.5F Millar catheter (Millar Instruments Inc., Houston) was positioned through an 8.0F or 8.8F guiding catheter and placed in the proximal left anterior descending artery (LAD) or left circumflex artery (LCx) within the region of the coronary artery under study. In stenotic coronary arteries (group III), the Doppler flow velocity catheter was placed in the prestenotic segment. The Doppler flow velocity catheter was positioned in the center of the vessel with the guidewire extending from the tip of the catheter in order to obtain a stable flow velocity signal with minimal noise. The Doppler catheter was connected to a photographic multichannel oscillographic recorder (Electronics for Medicine VR 16, Pleasantville, NY) to display phasic and mean velocity waveforms. Before placement in the guiding catheter, the Doppler flow velocity recordings were zeroed and calibrated on a 1 to 4 MHz scale. The Doppler flow velocity catheter position was optimized in the coronary artery and baseline recordings of mean and phasic velocity were made. Continuous phasic and mean coronary flow velocity measurements were obtained during control, peak cold pressor test, recontrol, and after nitroglycerin with the other measurements listed above.

β-Blockade studies. To study the role of β-adrenergic receptors in mediating the response of normal coronary arteries, four patients with angiographically normal coronary arteries (group I) were randomly selected to undergo two serial cold pressor studies before and after the intracoronary administration of propranolol. Atrial pacing was performed throughout both cold pressor tests at a paced rate 10 beats/min above the intrinsic heart rate. An initial cold pressor test was performed according to the protocol described above with control, peak cold pressor test, and recontrol angiograms. A steady-state infusion of intracoronary propranolol (1 mg) was administered over 3 min into the left main coronary artery (LMCA). This dosing was calculated to deliver a drug concentration to the left coronary artery in excess of that known to produce β-blockade in the myocardium. A second cold pressor test was then performed with angiograms obtained under control, peak cold pressor test, and recontrol conditions. A steady-state infusion of nitroglycerin (50 μg) was delivered into the LMCA over 4 min followed by repeat angiography. Responses of the LAD and the LCx were analyzed.

Quantitative coronary arteriography. Quantitative coronary arteriography was performed by a previously described and validated technique. Nonionic contrast medium was injected into the left or right coronary artery at a rate of 5 ml/sec to a total of 8 to 9 ml with use of a Medrad power injector to optimize the
quality and reproducibility of the opacification. A Phillips Polydiagnost-C biplane system was used to allow two image intensifiers to be positioned so that the center of each field of view was in line with a single position in space (isocenter). The coronary arteries under study were positioned in isocenter. After the diagnostic catheterization and before the cold pressor study, patients were classified into one of three groups (group I, II, or III). The study angiograms were examined by three investigators and all of the proximal, mid, and distal segments of the left or right coronary artery under study that were free of vessel overlap and side branches in both orthogonal views were chosen for analysis. Segments were then classified as smooth, irregular, or stenotic before analysis by a consensus decision. The epicardial coronary artery segment under study was centered, and the cine image was digitized with use of a Microvax 11 and RC1 image processing. Five cine frames were scanned and averaged with two anatomic references in each to ensure accurate repositioning of each frame. Calibrated grids, filmed at isocenter, were used to scale the data from pixels to millimeters. A series of measurements of diameter were recorded for each fixed line for the length of the arterial segment. The data were then displayed in graph form, showing diameter versus segment length. Four to six millimeter segments from angiographically normal vessels and vessels with luminal irregularities were selected and measured. The narrowest portion of the stenosis, as well as 1 mm segments with minimal taper proximal and distal to the stenosis, were measured in group III patients. Fixed coordinates were used to reproduce these regions of interest spatially in repeated measurements to assess serial changes. Data on the reproducibility of the measurements has been previously published.

Estimates of changes coronary blood flow. Estimates of coronary blood flow (Q) were made from measurements of mean coronary flow velocity (V) and vessel cross-sectional area (CSA):

\[ Q = V \times CSA \]

Cross-sectional area was determined from measurements of coronary artery diameter in the region studied from orthogonal views, assuming an elliptical model:

\[ CSA = \frac{(D_1 \times D_2)}{4} \pi \]

where D1 = coronary artery diameter in the anteroposterior projection; D2 = coronary artery diameter in the lateral projection and both projections were obtained in the orthogonal position.

Statistical analysis. All data are expressed as the mean ± SE. Statistical comparisons of vessel diameters under control and peak cold pressor test conditions and between recontrol and postnitroglycerine conditions were made by use of a paired Student’s t test. The difference in directional response to peak cold pressor test and postnitroglycerin conditions in atherosclerotic and angiographically normal coronary arteries was tested by unpaired t test. Changes in systemic hemodynamics and coronary blood flow, and comparisons of vessel diameters at peak cold pressor test before and after propranolol were made by Student’s paired t test. Statistical significance was assumed if a null hypothesis could be rejected at the .05 probability level.

Results

Systemic hemodynamics. During cold pressor stimulation, heart rate and systolic blood pressure increased in all patients from groups I, II, and III. In group I, the heart rate and systolic blood pressure rose from 79.4 ± 6.2 to 90.6 ± 4.2 beats/min and from 128.0 ± 8.7 to 149.5 ± 9.5 mm Hg, respectively (p < .001 for both). Likewise, in group II, the heart rate and systolic blood pressure increased from 68.9 ± 4.3 to 83.8 ± 4.3 beats/min and from 141.0 ± 7.9 to 169.1 ± 8.2 mm Hg, respectively (p < .001 for both). Heart rate and systolic blood pressure also rose in group III patients, from 71.8 ± 3.2 to 85.1 ± 3.2 beats/min and from 140.8 ± 6.9 to 183.1 ± 9.4 mm Hg (p < .001 for both).

The mean PCWP increased from 8.9 ± 1.1 to 16.5 ± 1.9 mm Hg (p < .001) in group II patients during cold pressor stimulation and from 10.8 ± 1.3 to 17.7 ± 1.8 mm Hg (p < .001) in group III patients. It did not significantly change in group I patients (8.4 ± 1.3 to 8.8 ± 1.2 mm Hg).

Reactions of epicardial coronary arteries to cold pressor stimulation

Group I: controls. Thirty-one segments of angiographically smooth coronary arteries were analyzed in the eight group I patients. All 31 segments dilated in response to cold pressor test, with a mean control vessel diameter of 2.68 ± 0.09 mm, which increased to 2.99 ± 0.09 mm at peak cold pressor test (p < .001), representing a 12.0 ± 1.0% increase in vessel diameter (figure 1). The 31 segments also dilated in response to nitroglycerin, with a mean recontrol vessel diameter of 2.67 ± 0.09 mm, which increased to 3.51 ± 0.14 mm (p < .001), reflecting an increase in vessel diameter of 32.0 ± 2.0%.

Group II: minimal disease. Thirty-seven segments were
analyzed in the nine patients in group II. Twenty-seven of the segments were analyzed in regions of intimal irregularities and 10 segments were examined in smooth regions of the arteries. A heterogenous response was found in the group II patients (figure 2). The 27 irregular segments constricted from a mean control diameter of 1.82 ± 0.12 to 1.66 ± 0.12 mm at peak cold pressor test (p < .001), a decrease in diameter of 9.0 ± 1.0%. In contrast, the smooth segments dilated in response to cold pressor test from a mean control diameter of 1.98 ± 0.11 to 2.34 ± 0.15 mm (p < .01), a 19.0 ± 2.0% increase in vessel diameter. All segments, including the 27 irregular and the 10 smooth coronary artery segments, dilated in response to intracoronary nitroglycerin. Irregular segments dilated 20 ± 2% from mean recontrol diameters of 1.77 ± 0.14 to 2.12 ± 0.17 mm (p < .001). Smooth segments dilated 39 ± 7%, from a recontrol diameter of 2.00 ± 0.11 to 2.76 ± 0.16 mm (p < .001).

Group III: advanced stenoses. A total of 32 segments from Group III patients were analyzed: 17 stenotic segments, 13 irregular segments, and two smooth segments. A heterogenous response, similar to that in group II patients, was observed (figure 3). The 17 stenotic segments constricted from 1.16 ± 0.09 mm at control to 0.89 ± 0.09 mm at peak cold pressor test (p < .001), a 24.0 ± 6.0% decrease in vessel diameter. All 13 irregular segments also constricted from 2.44 ± 0.11 to 2.22 ± 0.12 mm at peak cold pressor test (p = .002), a 10.0 ± 2% decrease. In contrast, the two smooth segments that were found both dilated at peak cold pressor test from a control diameter of 2.99 to 3.23 mm (mean), an 8% increase in vessel diameter. All segments dilated in response to nitroglycerin. The stenotic segments increased in mean diameter from 1.18 ± 0.09 mm at recontrol to 1.44 ± 0.14 mm after nitroglycerin (a 23.0 ± 6.0% increase, p = .01). The irregular segments dilated 12.0 ± 6.0% from 2.41 ± 0.12 at recontrol to 2.66 ± 0.12 mm after nitroglycerin (p < .001). The two smooth segments also dilated from 3.12 to 3.89 after nitroglycerin, a 25% increase in diameter.

An example of the heterogenous response of epicardial arteries to cold pressor stimulation in an individual patient is demonstrated in figure 4. This 50-year-old man had a severe stenosis of the mid LCx, an irregular proximal LAD, and angiographically smooth distal LCx. During cold pressor testing, the stenotic mid LCx segment constricted, as did the irregular proximal LAD segment; however, the smooth distal LCx segment dilated. All three segments dilated in response to nitroglycerin.

The coronary segments from the three groups were combined so that all stenotic, irregular, and smooth segments were analyzed together. Figure 5 demonstrates the constrictor behavior of atherosclerotic arter-

**FIGURE 2.** Responses to cold pressor stimulation in 27 irregular segments (A) and 10 smooth segments (B) of group II patients. C1 denotes control; CPT peak is peak of the cold pressor test. *p < .01; **p < .001 for the comparison with C1.
ies, both irregular and stenotic segments, in response to cold pressor test. The values for the 17 stenotic segments are reported above. The 40 irregular segments in groups II and III patients constricted from 2.02 ± 0.13 to 1.83 ± 0.12 mm (p < .001), a 9.0 ± 1.0% decrease in diameter, and dilated from 1.99 ± 0.13 mm at recontrol to 2.30 ± 0.14 mm after nitroglycerin (a 17 ± 2% increase, p < .001). In contrast, the 43 smooth segments dilated from 2.51 ± 0.09 to 2.84 ± 0.09 mm (p < .001) at peak cold pressor test (14.0 ± 1.0% increase), returned to a recontrol diameter of 2.52 ± 0.09 mm, and dilated again in response to nitroglycerin to 3.34 ± 0.12 mm (p < .001), a 34.0 ± 2.0% increase in vessel diameter.

**Coronary blood flow studies.** Directional changes in coronary blood flow were studied in four patients with stenotic arteries, three patients with irregular arteries, and four patients with smooth arteries. In all 11 patients, the heart rate—systolic blood pressure product increased during cold pressor stimulation: normal arteries 7476.0 ± 589.0 to 11,344.0 ± 1353.0 (n = 4), irregular arteries 10,272 to 16,558 (n = 3), and stenotic arteries 10,878.0 ± 2221.0 to 15,215.0 ± 2631.0 (n = 4) (mean ± SE). In normal arteries, coronary blood flow increased 65.0 ± 4.0% during cold pressor stimulation (figure 6). Coronary blood flow in irregular arteries showed a variable response, but the mean change also showed a small increase of 15% (n = 3). In contrast, coronary blood flow in the prestenotic regions of stenosed arteries decreased 39 ± 8% during cold exposure. The percent change in coronary blood flow between control and peak cold pressor test was significantly different in normal and irregular arteries (p = .001), in normal and stenosed arteries (p < .001), and in irregular and stenosed arteries (p = .003).

**β-Blockade studies in normal arteries.** During the first (control) cold pressor test, all LAD and LCx segments dilated from a control diameter of 2.36 ± 0.19 to 2.72 ± 0.18 mm (p < .001) at peak cold pressor test, a 17.0 ± 3.0% increase in diameter (figure 7). The smooth segments returned to a recontrol diameter of 2.38 ± 0.19 mm. After the administration of intracoronary propranolol, there was no change in systemic hemodynamics, even with the transient termination of atrial pacing. A similar pressor response to the second cold pressor test (after propranolol) was observed. All arteries again dilated from a postpropranolol control diameter of 2.35 ± 0.19 to 2.56 ± 0.17 mm (p < .001) at peak cold pressor test (after propranolol), but with a smaller percentage dilation (mean increase in diameter of 10.0 ± 2.0%). This represents 41% less dilation after propranolol compared with that at the control cold pressor test (p = .002). There were no significant

![FIGURE 3. Responses to cold pressor stimulation in 17 stenotic segments (A), 13 irregular segments (B), and two smooth segments (C) of group III patients. C1 denotes control; CPT peak is peak of the cold pressor test. *p < .01; **p < .001 for the comparison with C1.](http://circ.ahajournals.org/)

Vol. 77, No. 1, January 1988
changes in the resting diameters of the arteries from the recontrol condition in the first cold pressor test (before propranolol) to the control condition in the second cold pressor test (after propranolol). All arteries dilated in response to nitroglycerin, with a 37.0 ± 4.0% increase in diameter (2.30 ± 0.18 to 3.20 ± 0.17 mm, p < .001).

**Discussion**

This study has demonstrated that the cold pressor test dilates normal and constricts atherosclerotic coronary arteries. Normal vasodilation is impaired in the presence of early and late atherosclerosis and is replaced by paradoxical vasoconstriction.

**Vasodilator response.** The finding that angiographically normal coronary arteries consistently dilated in response to cold pressor stimulation was somewhat surprising. Previous studies have reported vasoconstriction as the predominant normal response to sympathetic nerve stimulation produced by the cold pressor test. However, these studies were limited by the failure to carefully select patients with a low pretest likelihood of coronary disease and with completely smooth coronary arteries on angiography. The strict requirement in this study was that a vessel be completely smooth angiographically to be classified as a normal segment. Since angiography underestimates the extent of atherosclerosis, the pathologic presence of some atherosclerosis cannot be completely excluded even in these smooth segments. Nonetheless, the lack of strict anatomic classification requirements in previous studies may account for reported vasoconstric-
PATHOPHYSIOLOGY AND NATURAL HISTORY—CORONARY VASOSPASM

FIGURE 6. Directional changes in coronary blood flow during cold pressor stimulation in four normal coronary arteries (left), three irregular coronary arteries (middle), and four stenotic coronary arteries (right). C1 denotes control, CPT peak the peak of the cold pressor test, and Q coronary blood flow.

tion in "normal" vessels. In addition, earlier studies failed to withhold adrenergic agonists and antagonists in normal subjects and these drugs may have interfered with the dilator response. Differences in findings may also have been due to earlier, less precise quantitative angiographic methods.

The cold pressor test produces sympathetic release of norepinephrine and epinephrine and an elevation in

FIGURE 7. Responses of normal coronary arteries to cold pressor stimulation before and after intracoronary propranolol (arrow). C1 denotes control, CPT peak 1 peak of the cold pressor test, C2 recontrol, C3 control after propranolol, CPT peak 2 peak of the cold pressor test after propranolol, C4 recontrol after propranolol, and NTG nitroglycerin. IC = intracoronary. **p < .001 for the comparison of CPT peak 1 with C1 and CPT peak 2 with C3. p = .002 for the comparison of CPT peak 1 with CPT peak 2.
NABEL et al.

mean arterial pressure.\textsuperscript{17} Sympathetic nerve activation may dilate normal coronary arteries by several mechanisms, including \( \beta \)-adrenergic receptors in the coronary vasculature, increases in coronary blood flow, and \( \alpha_2 \)-adrenergic activity.

\( \beta \)-Adrenergic receptor stimulation dilates large coronary arteries in the conscious dog and calf,\textsuperscript{8, 18} and this dilation can be attenuated by the administration of propranolol.\textsuperscript{19} The results of the present investigation are consistent with these animal studies and extend to humans the observation that the predominant effect of sympathetic nerve stimulation normally is coronary dilation.

Increases in coronary blood flow can also independently dilate large coronary arteries, possibly resulting from flow-mediated endothelium-dependent vasodilation.\textsuperscript{20–23} In the presence of intact endothelium, increases in flow produce vasodilation, presumably via the release of endothelium-dependent relaxation factor(s) (EDRF). Conversely, endothelium dysfunction or damage may result in a loss of this flow-dependent dilation.\textsuperscript{23} In this study, cold pressor stimulation produced a 64\% increase in epicardial coronary blood flow in the patients with normal coronary arteries and this increase in flow was associated with coronary vasodilation. It is possible that this effect may in part be mediated via the local effects of flow on the endothelium, although other metabolic and neural factors cannot be excluded.

\( \alpha_2 \)-Adrenergic activity produces dilation in normal coronary arteries indirectly through the release of EDRF.\textsuperscript{24, 25} Recent investigations have demonstrated the presence of \( \alpha_2 \)-receptors on endothelial cells and suggest that activation of these receptors may promote the release of EDRF, which counteracts the contraction of smooth muscle cells.\textsuperscript{26} Removal of endothelium or injury of the endothelium by atherogenesis has been shown to abolish the release of EDRF which then may permit adrenergic agonists to activate smooth muscle cell receptors to cause vasoconstriction.\textsuperscript{26, 27} Therefore, in the normal coronary artery, the integrated response to sympathetic stimulation during the cold pressor test may depend on coronary blood flow and at least four populations of receptors: \( \alpha_2 \)-adrenoceptors on the endothelial cell, and \( \alpha_1^+ \), \( \alpha_2^- \), and \( \beta \)-adrenoceptors on the smooth muscle cell.

**Vasoconstrictor response.** The failure of dilation in atherosclerotic coronary arteries may be due to altered catecholamine sensitivity and/or endothelial dysfunction. Hypersensitivity of vascular smooth muscle in the region of an atherosclerotic plaque may produce enhanced vasoconstriction.\textsuperscript{28, 29} Heistad et al.\textsuperscript{5} have shown that atherosclerotic coronary arteries in monkeys demonstrate an augmented constriction in response to vasoconstrictors such as norepinephrine and serotonin. Additional evidence suggests that responses to vasoconstrictor stimuli may be augmented by atherosclerosis in vivo: reflex coronary vasoconstriction has been reported to be greater in patients with atherosclerotic coronary disease than in patients with normal coronary anatomy.\textsuperscript{30} The intravenous or intracoronary administration of histamine has been reported to produce coronary artery spasm in atherosclerotic swine,\textsuperscript{31} and coronary artery spasm is more common in patients with coronary atherosclerosis.\textsuperscript{7} Our findings are consistent with these observations and suggest that atherosclerosis promotes a vasoconstrictor response in human epicardial arteries both early and late in the disease process.

Endothelial dysfunction may play a central role in precipitating altered vasomotion in the coronary artery. Atherosclerosis may impair release of EDRF or other

### TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>CPT peak</th>
<th>Recontrol</th>
<th>NTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double product (HR×SBP, ( \times 10^9 ))</td>
<td>10.3±1.3</td>
<td>13.7±1.2\textsuperscript{c}</td>
<td>10.6±1.3</td>
<td>9.4±1.1\textsuperscript{a}</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>8.4±1.3</td>
<td>8.8±1.2</td>
<td>8.3±1.2</td>
<td>6.4±0.5\textsuperscript{a}</td>
</tr>
<tr>
<td>II: minimal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double product (HR×SBP, ( \times 10^9 ))</td>
<td>9.6±0.5</td>
<td>14.1±0.9\textsuperscript{c}</td>
<td>10.0±0.5</td>
<td>8.7±0.5\textsuperscript{a}</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>8.9±1.1</td>
<td>16.5±1.9\textsuperscript{c}</td>
<td>11.5±1.6</td>
<td>6.9±1.1\textsuperscript{a}</td>
</tr>
<tr>
<td>III: advanced stenoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double product (HR×SBP, ( \times 10^9 ))</td>
<td>10.2±0.8</td>
<td>15.6±1.1\textsuperscript{c}</td>
<td>11.1±0.6</td>
<td>9.8±0.7</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>10.8±1.3</td>
<td>17.7±1.8\textsuperscript{c}</td>
<td>11.8±1.4</td>
<td>6.2±0.9\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± SE.

CPT = cold pressor test; HR = heart rate (beats/min); NTG = intracoronary nitroglycerin; SBP = systolic blood pressure.

Significance of difference when compared with control measurements: \( ^{a} \)p \(<\ .05; ^{b} \)p \(<\ .01; ^{c} \)p \(<\ .001. \)
vasodilator substances as part of a generalized dysfunction of the endothelium and thereby permit vasoconstrictor responses. The constrictor response of atherosclerotic arteries to cold exposure mimics the reactions of diseased epicardial arteries to the endothelium-dependent vasodilator and direct smooth muscle constrictor acetylcholine. Therefore, the endothelial dysfunction that is present in atherosclerosis may result in a loss of dilator function and permit constrictor responses to a variety of stimuli.

**Limitations of the study.** The cold pressor test produces a modest vasopressor stimulus, but all 30 patients demonstrated the typical sympathetic pressor response. The quantitative angiographic method used in this study has been previously developed and validated. Each scan is an average of four to six digitized frames, and therefore, a mean and standard deviation is calculated for each measurement of segmental diameter. This provides a determination of errors within each measurement and permits a statistical comparison of the differences between measurements made in different phases of each experiment. Measurements of flow velocity with the Doppler catheter are subject to errors caused by the shape of the velocity profile and the position of the sample volume within the profile. However, published experiments have shown that the measured velocity relates linearly to volume flow if the catheter position is stable, and therefore, the catheter can be used to determine flow response under controlled conditions. In animals, paired measurements of coronary blood flow velocity obtained with an intracoronary Doppler catheter and an epicardial Doppler probe have correlated highly. Since flow velocity measurements were made only after careful positioning of the Doppler catheter in the vessel lumen (with guidewire extended beyond the catheter to secure its position), and since the Doppler catheter position was not changed during the research protocol, it is unlikely that significant error was introduced into the flow velocity measurements. In addition, the major objective of this study was to assess directional changes and not absolute volume flow with each intervention.

**Clinical correlation.** The predominant effect of sympathetic nerve stimulation normally is coronary dilation. The loss of dilation in atherosclerosis and resulting paradoxical constriction could increase coronary vascular resistance in the presence of advanced stenoses and contribute to the development of transient myocardial ischemia. These findings suggest that coronary vasomotion is intimately related to the biology of atherosclerosis. Abnormal vasomotion may be a functional indicator of coronary atherosclerosis and may provide useful information in addition to the structural anatomy defined at angiography.

We are indebted to Ms. Yolanda Gooden for assistance in preparation of this manuscript.

**References**


22. Bessange E: The role of the endothelium and the local control of vascular tone. Basic Res Cardiol 85: 475, 1985
Dilation of normal and constriction of atherosclerotic coronary arteries caused by the
cold pressor test.
E G Nabel, P Ganz, J B Gordon, R W Alexander and A P Selwyn

Circulation. 1988;77:43-52
doi: 10.1161/01.CIR.77.1.43

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 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/77/1/43