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Large Coronary Arteries in Humans Are Responsive to Changing Blood Flow: An Endothelium-Dependent Mechanism That Fails in Patients With Atherosclerosis

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Changes in blood flow can alter vasomotion of conduit arteries. This study examined vasomotor responses to incremental blood flow induced by papaverine in the epicardial arteries of 10 patients with angiographically normal coronary arteries (group 1) and in 14 patients with arterial irregularities (group 2) using quantitative angiography and Doppler ultrasound flow velocity measurements. An increase in coronary blood flow of 384.3 ± 32.8% ($p < 0.001$) in group 1 patients was associated with dilation of the proximal coronary artery segment and a 23.2 ± 4.6% increase in cross-sectional area ($p < 0.001$). In contrast, in group 2 patients a similar increase in coronary blood flow of 339.3 ± 18.7% ($p < 0.001$) was associated with mixed responses and a modest net constriction in cross-sectional area of −7.4 ± 2.8% ($p < 0.05$). The dilation response to nitroglycerin was intact in group 1 (31.7 ± 4.2%, $p < 0.001$) and in group 2 (26.4 ± 3.2%, $p < 0.001$).

In five patients from group 1 acetylcholine, an endothelium-dependent dilator, produced an increase in cross-sectional area of 20.7 ± 4.6% ($p < 0.05$) that paralleled the response to an increase in flow in the same segment (a 24.3 ± 6.1% increase in cross-sectional area, $p < 0.05$). Five group 2 patients demonstrated a vasoconstrictor response to acetylcholine (a −22.8 ± 3.4% decrease in cross-sectional area, $p < 0.05$) together with an impaired dilation response to incremental flow (a −6.4 ± 3.2% decrease in cross-sectional area). Thus, the normal flow-mediated dilation of coronary arteries is lost in atherosclerosis and this impairment may be due to endothelial cell vasodilator dysfunction.

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The vasomotion of epicardial coronary arteries in humans is of interest in relation to the causes of transient myocardial ischemia. The pattern of dilation of normal coronary arteries and paradoxic constriction of atherosclerotic arteries has been observed during common stimuli for ischemia such as physical exercise (1,2) and cold pressor testing (3). Although these stimuli are important in the pathophysiology of ischemia during everyday life, their mechanisms are difficult to interpret in light of simultaneous changes in multiple variables, such as heart rate, blood pressure, coronary blood flow and the activation of the sympathetic nervous system.

The large epicardial arteries must accommodate changes in coronary blood flow. With the aim of investigating this important function, this study examined the vasomotion of epicardial coronary arteries under conditions of increasing blood flow. This condition was of particular interest because increasing blood flow results in endothelium-dependent relaxation of the conduit arteries in animals (4–6) and in angiographically smooth coronary arteries in humans (7). The present study describes the responses of angiographically normal and atherosclerotic coronary arteries to increases in blood flow produced by papaverine, a dilator of resistance vessels. To further define the mechanisms of this response, the same segments of the normal and atherosclerotic coronary arteries examined with increased flow were also studied with acetylcholine, an endothelium-dependent vasodilator, to test the hypothesis that flow-mediated dilation in humans is endothelium dependent and that the loss of

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this reaction in patients with atherosclerosis is due to dysfunction of the endothelium.

Methods

Patient classification. Twenty-four patients undergoing diagnostic cardiac catheterization were studied. Patient classification was based on the extent of atherosclerosis on the diagnostic angiogram before initiation of the experimental protocol.

Group 1. Normal control group. Ten patients had angiographically normal, smooth coronary arteries throughout the coronary system with no luminal irregularities in the study or nonstudy vessels. All of these patients had atypical chest pain and normal exercise tolerance test results. Seven patients were women and three were men with ages ranging from 39 to 63 years (mean 49.8).

Group 2. Patients with atherosclerosis. Fourteen patients were studied who had angiographic luminal irregularities consistent with coronary atherosclerosis. None of the patients had a focal stenosis ≥50% in the study vessel to avoid the confounding effect of a flow-limiting stenosis. Nine patients had a stenosis of >50% diameter narrowing in a nonstudy vessel. These patients had chest pain and abnormal exercise tolerance test results. Five patients had luminal irregularities and no stenosis >50% diameter narrowing in the nonstudy vessel. These five patients had nondiagnostic exercise test results. Four patients were women and 10 were men; their ages ranged from 39 to 72 years (mean 55.1) (p = NS compared with group 1). One patient carried a diagnosis of variant angina but had had normal results on a previous ergonovine study. Patients with unstable angina, myocardial infarction, valvular heart disease, left ventricular hypertrophy or heart failure were excluded.

Written informed consent was obtained from all patients before the diagnostic angiogram in accordance with guidelines established by the Committee for the Protection of Human Subjects at the Brigham and Women's Hospital and the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan Medical Center.

Study design. Antianginal therapy was discontinued 24 to 72 h before the study began except for the unrestricted use of sublingual nitroglycerin for up to 1 h before catheterization.

Diagnostic left heart catheterization and coronary arteriography were performed using a standard percutaneous femoral approach. After the diagnostic catheterization was completed the coronary angiograms were reviewed and patient classification and study vessel were determined. An 8F guide catheter was introduced into the left main coronary artery. Heparin (10,000 U) was administered intravenously. A 2.5F Doppler flow velocity catheter (20 MHz pulsed Doppler catheter, Millar Instruments) was connected to a velocimeter (model DC-101, Millar Instruments) and then to a photographic multichannel oscillographic recorder (Electronics for Medicine VR16 and MEICOR, Siemens) to display mean and phasic velocity signals. Before placement in the guide catheter, the Doppler catheter was zeroed and calibrated on a 0 to 40 cm/s scale. The Doppler flow velocity catheter was positioned through the guide catheter over an 0.035 cm (0.014 in.) guide wire into the midportion of the left anterior descending or left circumflex artery. The Doppler flow velocity catheter was placed in the center of the vessel, the guide wire was removed and a stable flow velocity signal with minimal noise was obtained. Before beginning the experimental protocol the position of the Doppler flow velocity catheter and the range gate control were adjusted to optimize the audio flow velocity signal and the phasic flow velocity waveform. The Doppler catheter position and the range gate control were not changed after this. The position of the Doppler flow velocity catheter was checked frequently through the protocol.

The experimental protocol was then performed. After control conditions were established, papaverine (12 mg) was infused as a bolus through the Doppler flow velocity catheter (8). Angiography was performed at the peak increase in coronary blood flow velocity between 90 and 120 s after the bolus injection. A 5 min recovery period was allowed. A steady state intracoronary infusion of nitroglycerin (50 μg) was administered through the Doppler flow velocity catheter over 4 min to test smooth muscle dilator function (9).

Heart rate and mean and phasic arterial pressure were measured continuously. Serial angiograms in orthogonal views of the study vessel with nonionic contrast medium were performed in the control period, after the papaverine dose, after the recontrol period and after intracoronary nitroglycerin infusion. Continuous measurements of coronary blood flow velocity were recorded from the Doppler flow velocity catheter.

The coronary artery segment proximal to this catheter was analyzed to study the effects of increasing blood flow alone on coronary artery diameter in contrast to the combined effects of blood flow and papaverine (Fig. 1). The last five consecutive patients in each group underwent combined papaverine and acetylcholine study. In these patients, after the serial papaverine infusion and reestablishment of recontrol conditions, the Doppler flow velocity catheter was pulled back to the same proximal segment that was analyzed for the effects of increasing blood flow (Fig. 1). Serial infusions of intracoronary acetylcholine were delivered through the Doppler catheter to this proximal segment so that the same segment could be analyzed for the response to increasing blood flow and to acetylcholine. Two-minute infusions (0.8 ml/min) were used to deliver increasing doses of acetylcholine to achieve estimated final intracoronary blood concentrations in the proximal segment of 10^{-7} and 10^{-6} mol/liter (10). Coronary angiograms were obtained and coronary flow velocity, electrocardiogram, heart rate and

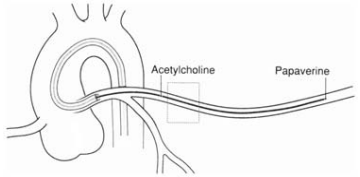


Figure 1. Schematic drawing of placement of the Doppler flow velocity catheter (**solid black line**) within the left anterior descending coronary artery. Papaverine was infused through the distal port of the Doppler flow velocity catheter. A segment proximal to the papaverine infusion was analyzed for coronary vasomotion. For the subsequent acetylcholine studies, the Doppler flow velocity catheter was withdrawn proximal to the previously analyzed coronary artery segment and acetylcholine was infused through the Doppler catheter. The vasomotor response to acetylcholine was analyzed in the same segment as previously analyzed for papaverine.

blood pressure were measured at the end of each 2 min infusion. The final coronary blood concentrations of acetylcholine were estimated with the assumption that blood flow in the left anterior and left circumflex arteries was 80 ml/min (11). A second recontrol period was established and followed by intracoronary infusion of nitroglycerin, as described previously.

Quantitative coronary angiography. Quantitative coronary angiography was performed by a previously described and validated technique (12). Nonionic contrast medium was injected into the left coronary artery at a rate of 5 ml/s to a total of 8 or 9 ml with a Medrad power injector to optimize the quality and reproducibility of the opacification (13). Angiograms were obtained while the patients held their breath to avoid the possible effects of respiration. A 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 artery under study was placed in isocenter. A segment of the coronary artery 2 to 3 cm proximal to the Doppler flow velocity catheter that was free of side branches or vessel overlap was analyzed at end-diastole (12). The same segment was analyzed after each control condition and drug infusion. The length of the segment analyzed was 6.4 ± 0.2 mm. The inter- and intraobserver variability of coronary artery diameter measurements using this validated system is low (r = 0.95 and r = 0.92, respectively) (14,15).

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

$$\dot{Q} = V \times CSA$$

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

$$CSA = \frac{(D1 \times D2) \times \pi}{4},$$

where D1 = coronary artery diameter in the anteroposterior projection and D2 = coronary artery diameter in the lateral projection.

Statistical analysis. All data are expressed as mean values ± SE. Statistical comparisons were made by two-tailed analysis of variance and level of significance was determined by Fisher's exact *t* test. The difference in directional response of cross-sectional area and blood flow between groups 1 and 2 was tested by unpaired *t* test. Statistical significance was assumed if the null hypothesis could be rejected at the 0.05 probability (p) level.

Results

Hemodynamics (Table 1). There were no significant changes in heart rate and systolic or diastolic blood pressure after the infusion of papaverine or acetylcholine compared with control conditions in either group 1 (normal artery) or group 2 (atherosclerotic artery). A minor decrease in systolic blood pressure ($p < 0.05$) was observed after the intracoronary administration of nitroglycerin in both groups.

Coronary blood flow. In patients with normal coronary arteries (group 1), papaverine produced an increase in cor-

Table 1. Hemodynamic Responses to Infusions of Papaverine, Acetylcholine and Nitroglycerin

	C_1	Papaverine (12 mg)	C_2	ACh (10^{-6} mol/liter)	C_3	NTG (50 μg)
Normal arteries (group 1)						
Blood pressure (S/D) (mm Hg)	118 ± 7/78 ± 3	115 ± 6/75 ± 3	115 ± 6/77 ± 3	117 ± 6/77 ± 3	116 ± 5/77 ± 3	113 ± 6*/75 ± 3
Heart rate (beats/min)	74 ± 3	75 ± 2	75 ± 3	75 ± 2	73 ± 3	75 ± 3
Atherosclerotic arteries (group 2)						
Blood pressure (S/D) (mm Hg)	110 ± 3/76 ± 3	110 ± 3/77 ± 3	111 ± 3/77 ± 3	110 ± 3/77 ± 3	110 ± 3/77 ± 3	106 ± 2*/75 ± 3
Heart rate (beats/min)	76 ± 4	76 ± 4	76 ± 4	76 ± 4	76 ± 4	80 ± 4

*$p < 0.05$. ACh = acetylcholine; C = control; D = diastolic; NTG = nitroglycerin; S = systolic.

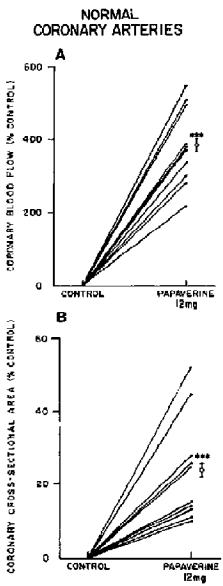


Figure 2. Increase in coronary blood flow (A) produced by papaverine infusion and the associated increase in coronary cross-sectional area (B) in the 10 patients with normal coronary arteries (group 1). The increment in blood flow produced by papaverine was associated with a dilation of the coronary artery segment proximal to the infusion site. ***$p < 0.001$.

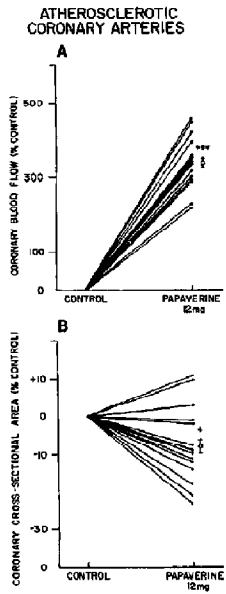


Figure 3. Increasing coronary blood flow (A) produced by papaverine infusion and the associated vasomotor response (B) in the 14 patients with atherosclerotic coronary arteries (group 2). The increment in coronary blood flow in atherosclerotic coronary arteries was associated with a modest net constriction of cross-sectional area, with constriction observed in 11 patients and dilation observed in 3 patients. *$p < 0.05$; ***$p < 0.001$.

onary blood flow of 384.3 ± 32.8% ($p < 0.001$). This increment in coronary blood flow was associated with dilation of the coronary artery segment proximal to the infusion site in all 10 patients; there was a mean increase of 23.2 ± 4.6% in cross-sectional area from 8.2 ± 0.8 mm^2 ($p < 0.001$) (Fig. 2). In all patients the coronary artery segments dilated in response to intracoronary nitroglycerin (50 μg), with a 31.7 ± 4.2% increase in cross-sectional area ($p < 0.001$).

In the patients with atherosclerosis (group 2), papaverine at an equivalent dose produced a similar increase in coronary blood flow of 339.3 ± 18.7% ($p < 0.001$). In contrast to the patients with normal coronary arteries, this increment in blood flow was associated with a modest net constriction of −7.4 ± 2.8% in cross-sectional area from 7.2 ± 0.9 mm^2 in the proximal segment exposed to an increase in blood flow ($p < 0.05$). Examination of the data revealed that 11 patients exhibited constriction and 3 patients exhibited dilation (Fig. 3). The dilator response to intracoronary nitroglycerin was intact in group 2 patients with a 26.4 ± 3.2% increase in cross-sectional area ($p < 0.001$). The spectrum of epicardial coronary artery response to incremental blood flow is demonstrated in Figure 4, which depicts the dilator response of normal arteries and the mixed but mostly constrictor response of atherosclerotic arteries.

Systemic recirculation of papaverine was excluded as a cause of dilation in group 1 patients and mixed responses in group 2 patients by examining the vasomotor response to papaverine in the proximal portion of the contralateral left

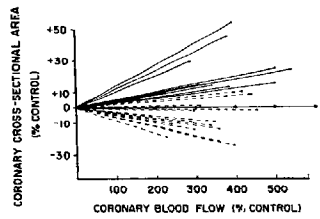


Figure 4. The range of epicardial coronary artery vasomotor response to incremental blood flow in normal coronary arteries (**solid line**) and atherosclerotic coronary arteries (**broken line**). Normal arteries exhibited a dilator response and atherosclerotic arteries had a mixed but mostly constrictor response to incremental blood flow.

coronary artery. There were no significant changes in cross-sectional area between control and papaverine infusions in group 1 (5.4 ± 0.2 to 5.3 ± 0.2 mm^2) and in group 2 (7.3 ± 0.5 to 7.2 ± 0.6 mm^2).

Paired responses to papaverine and acetylcholine. To study endothelium-dependent vasorelaxation as a mechanism for flow-mediated dilation, five consecutive patients in each group underwent sequential papaverine and acetylcholine study. In group 1 (normal control) papaverine produced an increase in coronary blood flow (395.2 ± 27.6%, $p < 0.01$) and associated vasodilation of 24.3 ± 6.1% from 9.2 ± 0.8 mm^2 ($p < 0.05$) in the proximal coronary artery segment in all five patients (Fig. 5). Acetylcholine infusion upstream of the proximal coronary artery segment also produced a significant dilation of the same segment of 20.7 ± 4.6% from 9.2 ± 0.8 mm^2 ($p < 0.05$). All proximal artery segments dilated with intracoronary nitroglycerin by 29.3 ± 6.9% from 9.2 ± 0.8 mm^2 ($p < 0.05$) and blood flow increased by 26.2 ± 7.4% ($p =< 0.05$).

In group 2 an increase in coronary blood flow was observed after papaverine infusion (322.6 ± 22.5%, $p < 0.01$), which was associated with a mean decrease in coronary cross-sectional area in the proximal coronary artery segment of −6.4 ± 3.2% from 8.4 ± 0.8 mm^2 (p = NS) compared with control measurements (Fig. 6). After infusion of acetylcholine to a concentration of 10^{-6} mol/liter, significant vasoconstriction was observed in the same segment, −22.8 ± 3.4%, from 8.4 ± 0.8 mm^2 ($p < 0.05$). Intracoronary nitroglycerin produced significant dilation in all proximal coronary segments (20.8 ± 6.7% from 8.4 ± 0.8 mm^2, $p < 0.05$) and blood flow increased by 63.8 ± 21.5% ($p < 0.05$).

Intracoronary administration of acetylcholine also produced an increase in coronary blood flow of 284.0 ± 38.0% ($p < 0.01$) in group 1 and 191.2 ± 31.2% ($p < 0.01$) in group 2 patients.

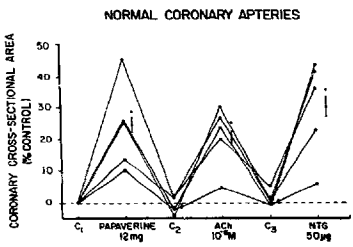
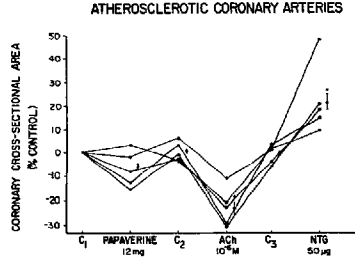


Figure 5. Sequential coronary vasomotor response to incremental blood flow (papaverine 12 mg) and intracoronary acetylcholine (10^{-6} mol/liter) in five patients with normal coronary arteries (group 1). Papaverine produced an increase in blood flow and associated vasodilation in the proximal coronary artery segment. A parallel vasodilator response was observed with acetylcholine (ACh) infusion. There was no significant difference in coronary cross-sectional area among C_1, C_2 and C_3 conditions. C_1 = baseline control; C_2 = repeat control; C_3 = second repeat control; NTG = nitroglycerin. *$p < 0.05$.

Discussion

The major findings of this study are that angiographically smooth human coronary arteries dilated in response to an increase in coronary blood flow and to the local administration of the endothelium-dependent vasodilator acetylcholine. This normal mechanism was lost in atherosclerotic

Figure 6. Sequential papaverine and acetylcholine (ACh) study in five patients with atherosclerotic coronary arteries (group 2). An increase in coronary blood flow after papaverine infusion was associated with a mean decrease in coronary cross-sectional area in the proximal coronary artery segment; after infusion of acetylcholine (10^{-6} mol/liter), vasoconstriction was also observed. There was no significant difference in coronary cross-sectional area among C_1, C_2 and C_3 conditions. Abbreviations as in Figure 5. *$p < 0.05$.



arteries, which failed to dilate in response to both increases in blood flow and acetylcholine. All coronary segments dilated in response to the smooth muscle cell relaxing agent nitroglycerin.

Endothelial regulation of local blood flow. Experimental evidence suggests that the endothelium regulates local vessel tone in response to changes in blood flow (5,6,16,17). The mechanism for the flow-induced vasodilation was initially proposed to be the spreading of a relaxing signal along the vascular wall, emerging from arterioles in the microcirculation (18,19), but later experiments failed to show inhibition of this response with transection of the artery distal to the site of measurements (20,21). The mechanism remained unknown until recently when Holtz et al. (4) demonstrated that endothelial cells act as mediators of flow-dependent dilation. Mechanical removal of endothelial cells from the canine femoral artery abolished dilation in response to both increased blood flow and acetylcholine but not in response to nitroglycerin, a direct smooth muscle relaxant (16,22). Use of the bioassay technique developed for the detection of the endothelium-derived relaxing factor demonstrated that acetylcholine and blood flow release a relaxing substance with the same characteristics (23,24).

The mechanisms by which endothelial cells sense and respond to mechanical forces generated by blood flow are not completely known. Recordings of calcium ion channel activity from endothelial cells have revealed that the opening frequency of these channels increases when the cell membrane is stretched (25). More recently a potassium-selective, shear stress-activated channel was identified that is activated by increasing levels of shear stress and that recovers fully on cessation of flow (26). These ionic currents may represent the first step in the transduction of a mechanical force (blood flow, shear stress) to a vascular response (flow-mediated dilation).

Mechanisms of vasodilation. This study provides evidence that incremental blood flow is associated with dilation in angiographically smooth coronary arteries and, as such, is a property of normal human arteries. In addition, the demonstration of vasodilation in response to increments in blood flow and acetylcholine suggests that the release of endothelium-dependent relaxing factor or factors (EDRF) by intact endothelium may promote vasodilation in human arteries. These data support previous findings in animal models that increases in blood flow trigger the release of a substance that has many characteristics of EDRF (24). Although it is unlikely that endothelial cells sense changes in volume flow in an artery, local changes in *shear stress* on the endothelium may stimulate the release of endothelium-dependent relaxing factors. We have recently demonstrated (27) vasodilation of angiographically smooth human coronary arteries in response to increased shear stress and loss of this response in atherosclerotic arteries. Alterations in shear stress result in disruption of endothelial cell morphology in animal models that are associated with abnormal responses to injury and platelet activation (28,29). Likewise, variations in the direction and magnitude of shear stress may promote atherogenesis (30,31). Recent data (32) also suggest that increases in shear stress may stimulate endothelin production by endothelial cells.

Mechanisms of vasoconstriction. In the present study, the presence of atherosclerosis in human coronary arteries impaired flow-mediated dilation. One possible mechanism for the vasoconstrictor response in atherosclerosis may be endothelial cell dysfunction and a blunting of EDRF release (33,34). This conclusion is supported by the findings of paradoxic vasoconstriction to acetylcholine in the same atherosclerotic arteries with abnormal responses to increased blood flow. Interestingly, this study suggests that the precise mechanism of the action of acetylcholine may also be complex, involving a direct receptor-mediated (20,34) and an indirect flow-mediated effect (4,5). Indeed, intracoronary acetylcholine produced an increase in coronary blood flow in patients with atherosclerotic and normal coronary arteries, although of smaller magnitude than that observed with papaverine. Despite the possible multiple mechanisms of acetylcholine action, this agent has been shown to induce endothelium-dependent dilation in the normal artery and loss of dilation with constriction if the endothelium is dysfunctional (10). Further evidence of endothelial cell dysfunction in the atherosclerotic segments is the preserved dilation in response to the nonendothelium-dependent dilator nitroglycerin.

The failure of dilation in atherosclerotic coronary arteries may be the result of altered catecholamine sensitivity. Hypersensitivity of vascular smooth muscle in the region of an atherosclerotic plaque may also produce enhanced vasoconstriction (33). Several investigators (35–37) have reported impairment of endothelium-dependent relaxation in animal vessels with diet-induced atherosclerosis. Many substances that elicit the release of EDRF, such as serotonin, norepinephrine, vasopressin and others, also exert a direct vasoconstrictor effect on vascular smooth muscle (35,38). Although the release of EDRF normally modulates the constrictor action of these compounds, in the setting of atherosclerosis these neurohumoral agents could produce exaggerated vascular constriction because of an unopposed effect on the smooth muscle. It is unlikely that increased catecholamines produced the vasoconstrictor response observed in atherosclerotic vessels in this study because neither papaverine nor acetylcholine produced a change in heart rate or blood pressure.

Limitations. Although a variety of pharmacologic and physiologic stimuli are capable of promoting an increase in coronary blood flow, papaverine was chosen for this study because it is a relatively selective dilator of resistance vessels and has minimal effects on the large epicardial coronary arteries (8). Examination of the distal coronary

artery segment exposed to both incremental blood flow and papaverine failed to reveal a difference in the change in coronary luminal area compared with the change induced by the flow alone in the proximal segment (data not shown). In addition, the dilation observed in the proximal segment with papaverine is probably not due to systemic recirculation of this agent because similar dilation was not observed in the contralateral left coronary artery.

The time sequence of dilation after the onset of incremental flow in human coronary arteries is not known. Previous studies (5) in closed chest conscious dogs have suggested that peak dilation occurs approximately 60 s after the induction of reactive hyperemia in this model. In the current study coronary reactions were measured soon after the increase in coronary blood flow velocity peaked, approximately 90 to 120 s after papaverine injection.

Clinical implications. Flow-induced vasodilation of epicardial human coronary arteries may contribute to the normal physiologic response during exercise or other stresses. The response of normal coronary arteries to exercise or to the cold pressor test is dilation and this response is replaced by constriction in atherosclerotic arteries (2,3). These physiologic stimuli may exert their effect, in part, by increasing blood flow and promoting dilation in normal coronary arteries. Loss of this response in atherosclerotic and narrowed coronary arteries may have a role in the genesis of myocardial ischemia. In addition, vasodilation produced by incremental blood flow may protect the endothelium from injury by keeping shear stress and turbulence low; this may possibly reduce the progression of coronary atherosclerosis (31).

Conclusions. This study provides direct evidence of the failure of an adaptive mechanism, such as endothelium-dependent dilation in response to increases in blood flow, in patients with coronary atherosclerosis. This pathogenic mechanism clarifies at least one functional component of atherosclerotic stenoses that act intermittently to disturb coronary blood flow and cause myocardial ischemia.

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