Paradoxical Narrowing of Atherosclerotic Coronary Arteries Induced by Increases in Heart Rate

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Vasodilation in normal and vasoconstriction in atherosclerotic coronary arteries have been observed in response to complex stimuli such as exercise and the cold pressor test. To study a single parameter that changes during these activities, and to better understand the pathophysiology of ischemia associated with increases in heart rate, we studied coronary vasomotion and blood flow response to increasing heart rate alone, produced by atrial pacing, with quantitative angiographic and Doppler flow-velocity measurements in 15 patients. In five patients with angiographically smooth coronary arteries (group 1), tachycardia produced progressive dilation of the epicardial artery with increases in cross-sectional area (CSA) of +15.5 ± 3.4%, +22.4 ± 2.1%, +28.5 ± 3.3%, and +30.6 ± 2.2% at 90, 110, 130, and 150 beats/min, respectively. In contrast, in five patients with mild angiographic narrowings (group 2), coronary segments failed to dilate with progressive tachycardia (−6.3 ± 2.0%, −8.3 ± 2.0%, −12.5 ± 2.0%, and −11.4% at 90, 110, 130, and 150 beats/min, respectively), and progressive loss of luminal area was observed in five patients with severe angiographic narrowings (group 3) (−34.4 ± 3.4%, −49.6 ± 2.2%, −59.2%, and −72.8% at 90, 110, 130, and 150 beats/min, respectively). Coronary blood flow increased significantly with tachycardia in group 1 (+44.5 ± 10.2%, +86.0 ± 24.6%, +105.8 ± 29.3%, and +137.5 ± 46.0%), increased slightly in group 2 (+7.8 ± 3.2%, +9.4 ± 4.4%, +8.4 ± 3.9%, and +10.0%), and decreased significantly in group 3 (−31.8 ± 6%, −42.6 ± 10.7%, −61.0%, and −70.0%). We conclude that an isolated increase in heart rate in patients with normal coronary arteries results in a modest increase in flow and vasodilation. In early atherosclerosis, the flow increase is blunted and dilation is replaced with paradoxical loss in luminal size. In patients with stenoses, further loss in luminal size occurs accompanied by a decrease in coronary blood flow. Thus, increasing heart rate alone in the setting of coronary stenoses could produce myocardial ischemia by a reduction in coronary supply, as well as by an increase in oxygen demand. (Circulation 1990;81:850–859)

Coronary artery stenoses are dynamic and can alter coronary luminal area in response to vasoactive drugs and physiological stimuli.1–7 Our previous studies have demonstrated dynamic changes in coronary artery diameter with the cold pressor test and with exercise.8,9 We have shown that the normal response of coronary arteries to these provocations is vasodilation but that atherosclerosis alters the normal dilator response and produces vasoconstriction. Although of importance to the pathophysiology of ischemia, the responses to exercise and the cold pressor test are difficult to interpret because of simultaneous changes in multiple parameters such as heart rate, blood pressure, and the sympathetic nervous system activity. To investigate a single parameter that changes during these activities, the present study examined the effects of increases in heart rate on the vasomotion and blood flow responses of epicardial coronary arteries. Previous animal studies have demonstrated a reduction in coronary blood flow across coronary artery stenoses in response to an increase in heart rate, suggesting that heart rate in this model of arterial obstructions might be an important determinant of coronary artery luminal size and blood flow.1,10 Therefore, to define the effect of increasing

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heart rate on coronary vasomotion and blood flow in patients with normal and diseased vessels, we used quantitative coronary arteriography and Doppler flow-velocity measurements to assess the response to pacing-induced tachycardia.

Methods

Patient Classification

Fifteen patients undergoing diagnostic cardiac catheterization were studied. These patients were divided into three groups on the basis of their diagnostic angiograms. Classification decisions were made by the investigators on blinded review of the angiograms before initiation of the research protocol and analysis of vasomotion.

Group 1. Controls

Five patients with angiographically smooth coronary arteries in all three epicardial arteries served as control subjects. These patients had atypical chest pain and were referred for diagnostic angiography. Three patients had no risk factors for coronary artery disease, whereas two had a previous smoking history but did not smoke at the time of study. All five patients had negative exercise tolerance tests. Additionally, two patients had negative thallium stress tests, and two other patients had negative ergonovine studies. None of the patients carried the diagnosis of coronary X syndrome although invasive studies assessing possible microvascular angina had not been performed. Three subjects were women, and two were men. Their ages were in the range of 32–50 years (mean, 42 years). All had angiographically smooth coronary arteries without luminal irregularities.

Group 2. Patients With Mild Angiographic Narrowings

Five patients were studied who had luminal irregularities (<30% stenosis) in the study coronary artery and coronary atherosclerosis in the remaining coronary arteries. Two patients had less than 30% stenoses in all coronary arteries, whereas three patients had a severe stenosis (>70% narrowing) in one other coronary artery. They were considered to have early atherosclerosis in the study vessel because they had risk factors for coronary artery disease and definite luminal irregularities identified by the blinded reviewers on diagnostic angiography. Two patients had a positive exercise tolerance test, one patient had electrocardiographic changes suggestive of ischemia at rest, and two patients had equivocal exercise tolerance tests for ischemia. Four patients were hypertensive, one was diabetic, and one was a current smoker. All five patients were hyperlipidemic with an average serum cholesterol level of 226±5 mg/dl. The four women and one man were in the age range of 61–84 years (mean, 70 years).

Group 3. Patients With Severe Angiographic Narrowings

Five patients were studied who had symptomatic stable angina pectoris, exercise tolerance tests diagnostic of myocardial ischemia, and an angiographically documented stenosis of greater than 70% severity in at least one coronary artery. Four women and one man were studied; their ages were in the range of 34–65 years (mean, 59 years). Patients with unstable angina, recent myocardial infarction, conduction system disease, or 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 hours before catheterization except for the unrestricted use of sublingual nitroglycerin, which was held 1 hour before catheterization. Long-acting β-blockers were withheld 72 hours before study.

Diagnostic right and left heart catheterization and coronary arteriography were performed by a standard percutaneous femoral approach. At least 15 minutes after the catheterization was completed and on review of the diagnostic angiograms, patient classification and determination of study vessel was made by a consensus decision. An 8.0F guiding catheter was introduced into the left main coronary artery, and through it, the Doppler flow-velocity catheter was placed subselectively into the left anterior descending coronary artery (LAD) or left circumflex (LCx) artery. A 5F unipolar pacing wire was placed in the high lateral right atrial wall.

The pacing study was then performed. After control conditions were established, rapid atrial pacing was conducted at 90 beats/min for 2 minutes, followed by increments in the pacing rate of 20 beats/min (110, 130, and 150 beats/min) each for 2 minutes until a final pacing rate of 150 beats/min was reached, angina was produced, or atrioventricular Wenckebach block developed. After rapid atrial pacing, a 5-minute recovery period was allowed. A steady-state intracoronary infusion of nitroglycerin (50 µg total dose) was administered over 4 minutes. Atroventricular Wenckebach block was not treated with intravenous atropine in order to not influence coronary vasomotion and blood flow.

Measurements of heart rate and mean and phasic femoral artery pressure were made, and serial injections of the study vessel with nonionic contrast media were performed at control, at the end of a 2-minute period at each pacing rate, after the recontrol period, and after intracoronary nitroglycerin.

Coronary Blood Flow Velocity Studies

Coronary blood flow velocity was measured in all subjects during the pacing protocol using a 20 MHz
pulsed Doppler crystal mounted on a 2.5F Millar catheter (Millar Instruments, Inc., Houston, Texas). The Doppler catheter was positioned through the 8.0F guiding catheter and placed in the proximal LAD or LCx artery using a 0.014-in. guidewire. In group 1 subjects because both LAD and LCx arteries were angiographically smooth, the study vessel was selected based on ease of insertion of the Doppler flow-velocity catheter. The catheter was positioned in a proximal portion of the vessel, in an area free from side branches or vessel overlap. The arterial segment just distal to the tip of the Doppler catheter was analyzed. In group 2 patients, the study vessel (LAD or LCx) contained luminal irregularities defined as less than 30% narrowing, and the Doppler catheter was positioned in the proximal portion of the vessel, in an area void of side branches or vessel overlap. In group 3 patients, the Doppler flow-velocity catheter was positioned in the prestenotic segment of a stenosis of greater than 70% severity. The Doppler catheter was placed in the center of the vessel with the guide wire extending from the tip of the catheter to obtain a stable flow-velocity signal with minimal noise. The Doppler catheter was connected to a photographic multichannel oscillographic recorder (Electronics for Medicine VR16; Pleasantville, New York) to display mean and phasic velocity waveforms. Before placement in the guiding catheter, the Doppler catheter was zeroed and calibrated on a 1–4-MHz scale. Heparin (10,000 units total) was given before the Doppler catheter was positioned. Baseline recordings of mean and phasic flow velocity were made during control conditions. Continuous measurements of mean and phasic flow velocity were obtained during the pacing protocol, recontrol, and nitroglycerin conditions.

Quantitative Coronary Angiography

Quantitative coronary angiography was performed by a previously described and validated technique.12,13 Nonionic contrast medium was injected into the left coronary artery at a rate of 5 ml/sec to a total of 8 or 9 ml with a Medrad power injector to optimize the quality and reproducibility of the opacification.14 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 artery under study was placed in isocenter. The segment of the coronary artery interrogated by the Doppler flow velocity catheter was analyzed, and coronary artery diameter was determined.12 Calibration was achieved by measuring a magnification factor based on the known size of the angiographic catheter.

Estimates of Changes in 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), as follows: 

$$Q = V \times CSA.$$ 

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

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

where D1 is the coronary artery diameter in the anteroposterior projection and D2 is the coronary artery diameter in the lateral projection.15

Statistical Analysis

All data are expressed as the mean±SEM. Statistical comparisons of vessel cross-sectional area, coronary blood flow, and systemic blood pressure between control, each pacing rate, recontrol, and nitroglycerin conditions were made by two-tailed paired t test. Level of significance was determined by Bonferroni correction.16 The difference in directional response of blood flow to rapid atrial pacing in atherosclerotic and angiographically smooth coronary arteries was tested by unpaired t test. Statistical significance was assumed if the null hypothesis could be rejected at the 0.05 probability level.

Results

Systemic Blood Pressure

During rapid atrial pacing, an isolated increase in heart rate was achieved without a significant change in mean arterial blood pressure at 2 minutes after initiation of pacing (Table 1).

Reaction of Epicardial Arteries to Rapid Atrial Pacing

Group 1. Controls. The epicardial segments of patients with normal coronary arteries all dilated in response to rapid atrial pacing. A progressive increase in cross-sectional area was observed with each increment in pacing rate (Figure 1) from control area of 4.9±0.5 mm² to 5.7±0.4 mm² (90 beats/min), 6.0±0.6 mm² (110 beats/min) (p<0.01), 6.3±0.6 mm² (130 beats/min) (p<0.01), and 6.4±0.8 mm² (150 beats/min) (p<0.05), representing +15.5±3.4%, +22.4±2.1%, +28.5±3.3%, and +30.6±2.2% increase in cross-sectional area, respectively. All vessels dilated in response to nitroglycerin from a recon-
control area of 4.8±0.7 mm² to 6.9±0.5 mm² (p<0.01), a +41.6±5.5% increase in cross-sectional area.

**Group 2. Patients with mild angiographic narrowings.** The coronary artery segments of patients with minimal angiographic narrowings failed to dilate in response to rapid atrial pacing (Figure 2). From a control area of 4.8±0.5 mm², the segments decreased to 4.5±0.5 mm² (90 beats/min), 4.4±0.5 mm² (110 beats/min), 4.2±0.4 mm² (130 beats/min) (p=NS, all pacing rates), and 2.5 mm² (150 beats/min) (one patient, see Figure 2). This was a progressive percentage of decrease in cross-sectional area as compared with control of −6.3±2.0% (90 beats/min), −8.3±2.0% (110 beats/min), −12.5±2.0% (130 beats/min) (p=NS, all pacing rates), and −11.4% (150 beats/min). One patient experienced angina at a pacing rate of 150 beats/min. Three patients demonstrated AV Wenckebach conduction at 150 beats/min. All segments dilated in response to nitroglycerin from a recontrol area of 4.8±0.5 mm² to 5.7±0.7 mm², a +18.8±4.7% increase in cross-sectional area.

**Group 3. Patients with severe angiographic narrowings.** The five patients with advanced atherosclerosis all demonstrated progressive luminal narrowing with rapid atrial pacing (Figure 3). There was a progressive decrease in the cross-sectional area of the prestenotic region with each increment in pacing rate from a control area of 3.4±0.2 mm², to 2.5±0.2 mm² (90 beats/min) (p<0.05), 2.1±0.3 mm² (110 beats/min) (p<0.05), 1.8 mm² (130 beats/min) (two patients), and 1.6 mm² (150 beats/min) (one patient).
(Figure 3, top panel). This was a $-26.4\pm3.1\%$ (90 beats/min), $-38.2\pm3.5\%$ (110 beats/min), $-47.0\%$ (130 beats/min), and $-52.9\%$ (150 beats/min) change in cross-sectional area, respectively. In the stenotic region, decreases in cross-sectional area were observed from a control area of $1.25\pm0.08$ cm$^2$ to $0.82\pm0.07$ cm$^2$ ($-34.4\pm3.4\%$, 90 beats/min), $0.63\pm0.04$ cm$^2$ ($-49.6\pm2.2\%$, 110 beats/min) ($p<0.01$), $0.51$ cm$^2$ ($-59.2\%$, 130 beats/min), and $0.34$ cm$^2$ ($-72.8\%$, 150 beats/min) (Figure 3, bottom panel). All patients experienced angina with incremental pacing (three at 110, one at 130, and one at 150 beats/min). The arteries dilated in response to nitroglycerin in the prestenotic region from a control area of $3.3\pm0.3$ mm$^2$ to $4.3\pm0.2$ mm$^2$ ($p<0.05$), a $30.3\%$ increase in cross-sectional area.

Coronary Blood Flow Studies

Individual examples from groups 1, 2, and 3 of the change in coronary blood flow velocity with incremental rapid atrial pacing and angiographic displays are demonstrated in Figure 4. The patients with smooth and mild angiographic narrowings increased flow velocity, whereas the patient with advanced angiographic disease decreased flow velocity with progressive increases in pacing rates.

Group 1. Controls. Coronary blood flow increased with incremental rapid atrial pacing in normal arteries, as follows: $+44.5\pm10.2\%$ at 90 beats/min ($p<0.05$), $+86.0\pm24.6\%$ at 110 beats/min ($p<0.05$), $+105.8\pm29.3\%$ at 130 beats/min ($p<0.05$), and $+137.5\pm46.0\%$ at 150 beats/min ($p<0.05$) (Figure 5).
**Figure 4.** Photomicrographs and recording of changes in coronary blood flow velocity during incremental rapid atrial pacing in three patients, that is, patient from group 1 with angiographically smooth coronary arteries (normal artery) (top), patient from group 2 with mild angiographic narrowings (irregular artery) (middle), and patient from group 3 with severe angiographic narrowings (stenotic artery) (bottom). Bpm, beats per minute; NTG, 50 μg intracoronary nitroglycerin.

**Group 2. Patients with mild angiographic narrowings.** In contrast, there was a nonsignificant increase in blood flow in vessels with minimal atherosclerosis in response to rapid atrial pacing, as follows: +7.8±3.2% at 90 beats/min, +9.4±4.4% at 110 beats/min, +8.4±3.9% at 130 beats/min (p=NS, all pacing rates), and +10.0% at 150 beats/min (one patient) (Figure 6).

**Group 3. Patients with severe angiographic narrowings.** In contrast, significant decreases in coronary blood flow were observed in the prestenotic regions of vessels with advanced atherosclerosis. From control conditions, a -31.8±7.6% decrease occurred with rapid atrial pacing at 90 beats/min (p<0.05), -42.6±10.7% at 110 beats/min (p<0.05), -61.0% at 130 beats/min, and -70% at 150 beats/min.

The percentage of change in coronary blood flow between control and rapid atrial pacing was significantly different between smooth and minimally diseased arteries at 90 beats/min (p<0.01), 110 beats/min (p<0.05), and 130 beats/min (p<0.05); and between smooth and severely diseased arteries at 90 beats/min (p<0.01), 110 beats/min (p<0.01), and 130 beats/min (p<0.05).

**Coronary Blood Flow Velocity**

**Group 1. Controls.** An increase in coronary blood flow velocity was observed with incremental rapid atrial pacing in smooth arteries, as follows: +31.0±14.5% at 90 beats/min (p<0.05), +49.6±23.4% at 110 beats/min (p<0.05), +53.0±20.0% at 130 beats/min (p<0.05), and +70.7±30.5% at 150 beats/min (p<0.05). This was associated with an increase in cross-sectional area in group 1 subjects as previously presented.

**Group 2. Patients with mild angiographic narrowings.** Incremental atrial pacing produced an increase in blood flow velocity in group 2 patients (although the increase was smaller than that observed in group 1 patients), as follows: +12.6±1.7% at 90 beats/min, +16.6±1.2% at 110 beats/min, +20.0±2.8% at 130 beats/min, and +25% at 150 beats/min (one patient). The increase in flow velocity was associated with a progressive decrease in cross-sectional area.

**Group 3. Patients with severe angiographic narrowings.** Coronary blood flow velocity measured upstream from the stenosis did not increase in group 3 patients, as follows: -4.6±13% at 90 beats/min (p<0.05), -6.2±11.2% at 110 beats/min (p<0.05), -27.5 at 130 beats/min, and -38.0% at 150 beats/min. The decrease in blood flow velocity was associated with a progressive decrease in cross-sectional area.

**Discussion**

This study demonstrated that isolated increases in heart rate induced by rapid atrial pacing produced
dilation and an increase in coronary blood flow in angiographically normal arteries. In contrast, arteries with early atherosclerosis failed to dilate in response to rapid atrial pacing and increased their blood flow slightly. Arteries with advanced obstructive atherosclerosis paradoxically narrowed to the rapid atrial pacing stimulus and underwent a large decrease in flow.

**Coronary Blood Flow With Rapid Pacing**

An increase in myocardial oxygen demand as induced by rapid atrial pacing would be expected to increase coronary flow by dilating the distal arteriolar bed and lessening resistance to flow.\[^{17,18}\] In patients with normal coronary arteries, a progressive increase in coronary flow occurred with incremental rapid atrial pacing. These findings corroborate earlier studies that reported augmentation of coronary flow during pacing-induced tachycardia in normal coronary beds.\[^{19-21}\]

In contrast, coronary arteries with early and advanced atherosclerosis exhibited limitations to increases in coronary flow with pacing-induced tachy-
cardia. This flow limitation can be viewed as a spectrum with failure to augment flow and to vasodilate in vessels with mild disease and severe decreases in flow accompanied by a constriction in epicardial arteries with advanced stenoses. The results of the present study are in agreement with experimental studies that have demonstrated a decrease in flow through a stenosed artery in response to tachycardia,1,10 and extend the findings to human epicardial arteries. Thus, absolute coronary blood flow decreased in the epicardial regions of the myocardium in response to rapid atrial pacing in humans with severe luminal coronary narrowings, and could have been a precipitant for myocardial ischemia because all patients with severe coronary stenoses experienced angina with incremental tachycardia.

Possible Mechanisms of the Dilation of Normal Epicardial Coronary Arteries

The dilation of angiographically normal coronary arteries during rapid atrial pacing can be attributed to flow-mediated dilation.22–25 Dilation of conduit arteries induced by increasing blood flow has been demonstrated in experimental studies in animals, as well as in humans, and requires the presence of normal endothelium.25,26 Increased blood flow velocity and shear stress are thought to promote the release of endothelium-derived relaxing factor(s), possibly by activation of pressure sensitive Ca2+ channels in endothelial cells.27

Possible Mechanisms of the Constriction of Atherosclerotic Epicardial Coronary Arteries

The mechanisms that underlie the paradoxical constriction of irregular or severely narrowed atherosclerotic arteries during rapid atrial pacing are less well defined; however, experimental studies have suggested that a passive collapse of arterial narrowings might be involved.28–30 Distal vasodilation can effectively increase the severity of a proximal stenosis by reducing poststenotic intraluminal pressure to the level of surrounding intramyocardial pressure, thus producing a passive collapse.31,32 Additionally, the development of myocardial ischemia at faster heart rates can stimulate circulating catecholamines and in this way contribute to coronary constriction.33

Endothelial cell dysfunction can also contribute to the altered vasomotion in these arteries because atherosclerosis has been shown to impair endothelium-dependent relaxation in human coronary arteries, which is normally triggered by increases in blood flow velocity.26 Hence, increases in luminal flow velocity generated as arterial constriction develops might not result in the secondary activation of compensatory dilator mechanisms in atherosclerotic vessels. In patients with severe stenoses, however, increases in blood flow velocity after 2 minutes of atrial pacing were not observed. Failure of flow-mediated dilation might not explain the arterial narrowing observed in group 3 patients, although it might be present in group 2 patients.

Potential Limitations of the Study

In the present study, we measured coronary blood flow velocity by means of an intracoronary Doppler catheter positioned in proximal coronary segments. This particular system has been validated in animal experiments34 and has been used extensively in

Figure 7. Plotting of directional changes in group 3, stenotic arteries. Directional changes in coronary blood flow in epicardial arteries with severe angiographic narrowings in response to rapid atrial pacing. Q, coronary blood flow; C, control; RC, repeat control; NTG, 50 μg intracoronary nitroglycerin; bpm, beats per minute. *p<0.05 for comparison with control. Solid lines are individual patient responses, whereas dashed line is mean response.
humans. Other studies have shown that the catheter can be inserted in proximal or middle segments of coronary arteries without significantly restricting maximal blood flow in normal or atherosclerotic vessel segments with luminal calibers of a size comparable with those encountered in the present study.

Clinical Implications

Stable angina pectoris was believed to reflect the inability of a “fixed” coronary stenosis to supply adequate flow during increases in myocardial oxygen demand. Studies of coronary vasomotion and coronary blood flow during ischemic episodes, however, have shown a range of mechanisms that start with the traditional view of fixed supply and varying demand but include intermittent impairment of blood supply associated with abnormal vasomotion in coronary lesions. The response to pacing-induced tachycardia observed in angiographically normal and diseased coronary arteries lends additional support to the concept that epicardial arteries are dynamic and exhibit active and passive changes.

Increases in heart rate accompany most daily activities including exercise. Interestingly, during exercise, coronary artery vasomotion demonstrates the same pattern as rapid atrial pacing, that is, normal coronary arteries dilate and those with luminal irregularities or stenoses constrict. It is likely that increases in heart rate and metabolic demand are at least, in part, responsible for these dynamic changes in coronary vasomotion during exercise because the paradoxical coronary constriction observed during exercise can be blunted by the administration of propranolol, presumably because of a local reduction in myocardial oxygen demand.

The findings of this study can also provide additional insights into the effects on the coronary circulation of pharmacological agents that prevent tachycardia. β-Adrenergic receptor antagonists have been highly effective in the treatment of angina pectoris in clinical practice despite the finding that they induced coronary vasoconstriction under laboratory conditions when administered at a constant, paced heart rate. The present study suggests that the effect of β-blockers on the coronary vasomotion during daily activities is likely to be more complex and that the control of heart rate by these agents might favorably alter the vascular tone of diseased coronary arteries by preventing the vasoconstriction of stenoses that accompanies tachycardia.

Increases in heart rate alone are associated with a paradoxical narrowing of atherosclerotic coronary arteries and a decrease in coronary blood flow. These findings suggest that a reduction in coronary supply, as well as an increase in myocardial oxygen demand, are likely to be common events in patients with coronary artery disease and can contribute to the pathogenesis of myocardial ischemia in atherosclerotic coronary arteries during rapid heart rates.

References


KEY WORDS • coronary vasomotion • coronary blood flow • tachycardia
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