Differential Impairment of Vasodilator Responsiveness of Peripheral Resistance and Conduit Vessels in Humans With Atherosclerosis

James K. Liao, Michael A. Bettmann, Tomas Sandor, Julia I. Tucker, Sharon M. Coleman, and Mark A. Creager

The purpose of this study was to assess the effect of atherosclerosis on the regulation of limb blood flow. To examine this issue, the reactivity of resistance and conduit vessels was evaluated in 11 patients with peripheral atherosclerotic disease and six control subjects. Responsiveness of resistance vessels was measured by venous occlusion plethysmography. Responsiveness of conduit vessels was determined by quantitative angiography to measure the diameter of the superficial femoral artery. To distinguish endothelium-dependent vasodilation from that caused by direct smooth muscle relaxation, each participant received intra-arterial infusions of methacholine and nitroprusside, respectively. Flow-mediated dilation of the superficial femoral artery was determined during reactive hyperemia. Vasoconstrictor function was determined by the infusion of phenylephrine. Methacholine reduced calf vascular resistance in the control subjects but not in the patients with atherosclerosis (−64±11% versus 6±18%, p<0.01). Nitroprusside decreased calf vascular resistance comparably in each group (−51±5% versus −42±4%, p=NS). The vasoconstrictor effect of phenylephrine was similar in each group (105±30% versus 108±22%, p=NS). In the superficial femoral artery, the vasodilator responses to both methacholine (20±4% versus 1±4%, p<0.05) and nitroprusside (19±4% versus 5±4%, p<0.05) were blunted in the atherosclerotic patients as was the vasoconstrictive response to phenylephrine (−15±1% versus −1±5%, p<0.05). Reactive hyperemia induced a fivefold increase in calf blood flow in both control subjects (1.6±0.2 to 11.1±2.9 ml/100 ml/min, p<0.05) and atherosclerotic patients (2.2±0.3 to 10.0±1.5 ml/100 ml/min, p<0.05). During this flow augmentation, the superficial femoral artery dilated in control subjects (7.5±0.8 to 8.2±0.3 mm, p<0.05) but not in atherosclerotic patients (6.0±0.5 to 6.1±0.5 mm, p=NS). Therefore, in humans with peripheral atherosclerosis, endothelium-dependent vasodilation in resistance vessels is impaired. Atherosclerotic conduit vessels are essentially unresponsive to vasodilator and vasoconstrictor stimuli, implicating functional abnormalities intrinsic to the vascular smooth muscle. These disturbances in vasomotor control may adversely affect blood flow regulation in humans with peripheral atherosclerosis and contribute to symptoms of claudication that occur in this disorder. (Circulation Research 1991;68:1027-1034)

Intermittent claudication and rest pain are symptoms resulting from peripheral atherosclerotic disease. Factors governing blood flow to the affected extremity that influence the symptoms include the number, severity, and location of stenotic lesions and the presence of collateral vessels.1 It is also possible that reduced vasodilator potential of resistance and conduit vessels adversely affects blood flow regulation, thereby contributing to symptoms of claudication. In normal conditions, resistance vessels regulate regional blood flow.2-5 During physical exertion, resistance vessels in an exercising extremity

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dilate and facilitate an augmentation of blood flow to working muscle. Flow-mediated dilation of conduit vessels has been described; this phenomenon may allow the larger vessels to accommodate the greater volume of blood entering the legs.

Whether the function of these vessels is impaired in patients with peripheral atherosclerosis is not known. Indeed, studies in animal models of atherosclerosis have demonstrated that conduit vessel function is abnormal; there are reports of reduced endothelium-dependent relaxation and increased vasoconstrictor sensitivity. In the human atherosclerotic coronary artery, there is also evidence of abnormal endothelial function because these vessels do not dilate appropriately when infused with acetylcholine or stimulated by increases in flow. Little information is available about resistance vessel function when the feeding conduit vessels are atherosclerotic. Unlike the walls of larger arteries, the walls of resistance vessels do not develop atheroma; thus, one cannot assume that their function is impaired. Several recent studies did show that endothelium-dependent relaxation is abnormal in the resistance vessels of cholesterol-fed atherosclerotic rabbits and monkeys.

To examine these issues in humans, we designed a study to assess the responsiveness of resistance vessels in patients with peripheral atherosclerotic disease. Furthermore, we sought to determine whether atherosclerosis affects vascular function in peripheral conduit vessels in a manner similar to that observed in the coronary vasculature. We not only examined the vascular responses to pharmacological stimuli but also measured changes in vessel diameter during reactive hyperemia, an intervention that causes flow augmentation similar to that occurring during exercise.

Subjects and Methods

Participants

All participants in this study were scheduled for diagnostic arteriography. There were 11 patients with atherosclerosis. This group consisted of eight men and three women whose ages ranged from 43 to 82, averaging 60±4 years (p=NS versus control subjects). Each patient had characteristic symptoms of leg claudication and a physical examination that revealed such abnormalities as bruits and decreased or absent peripheral pulses. They had diagnostic angiography before surgical revascularization. There were six control subjects, five men and one woman, whose ages ranged from 33 to 81 years, averaging 55±8 years. None of the individuals in the control group had clinical or angiographic evidence of atherosclerosis. Pertinent characteristics of each participant and the reasons for angiography are listed in Table 1.

No participant had taken aspirin for at least 5 days before this study. Other medications had been discontinued at least 12 hours before the research protocol was performed. All participants provided written, informed, voluntary consent for participa-

The study was approved by the Human Subjects Research Committee at the Brigham and Women's Hospital, Boston.

Experimental Protocol

All participants were studied in the angiography suite approximately 30 minutes after diagnostic arteriography. In each individual, the common femoral artery was cannulated with an 8F introducer by the standard Seldinger technique, and a 7F catheter was positioned retrograde in the contralateral iliac artery. This configuration avoided catheter injury to the vessel of interest. The leg was securely strapped to the catheterization table. Two phantom markers, which were spaced 25 cm apart, were placed on the anterior aspect of the thigh to serve as reference markers for subsequent calculation of vessel diameters. To examine conduit vessel diameter, serial angiography was performed with low osmolar contrast media (15 ml Hexabrix) that was injected for 2 seconds. Images of the superficial femoral artery were acquired with high-resolution film at a rate of 3 fps. To record calf blood flow to evaluate resistance vessels, venous occlusion plethysmography was used. In the atherosclerotic patients, the leg least affected by atherosclerosis was studied, which was always different from the leg considered for revascularization. In the one control subject who had previously had a systemic embolus, we examined the uninvolved leg.

During the baseline period, 5% dextrose was infused by way of the arterial catheter at a rate of 0.4 ml/min. Measurements of calf blood flow and blood pressure were repeated every 10 minutes until stable. Thereafter, angiography of the superficial femoral artery was performed. Basal conditions were reestablished and confirmed by measuring calf blood flow after each intervention. To assess flow-mediated vasodilation in conduit vessels, calf blood flow was measured during reactive hyperemia following 5 minutes of ischemia produced by inflation of a thigh cuff to suprasystolic pressure. Consequent to the vasodilation in resistance vessels, flow through the conduit vessels increases. Therefore, angiography was performed during a second induction of reactive hyperemia, approximately 10–20 seconds after release of the thigh cuff. To evaluate endothelium-dependent vasodilation in both resistance and conduit vessels, each individual received methacholine chloride (a congener of acetylcholine) by way of the arterial catheter at a dose of 30 μg/min. To distinguish abnormalities in endothelial function from those of vascular smooth muscle, each individual received an intra-arterial infusion of sodium nitroprusside at a dose of 10 μg/min. This agent directly relaxes vascular smooth muscle by stimulating soluble guanylate cyclase. To evaluate vasoconstrictor responsiveness in resistance and conduit vessels, each participant then received intra-arterial phenylephrine, an α₁-adrenergic agonist, at a dose of 10 μg/min. Preliminary dose–response studies of nor-
mascular subjects demonstrated that the doses of drugs used in this study caused maximum calf vasodilation without affecting systemic blood pressure or contralateral limb blood flow. All drug infusions were given for 5 minutes at a rate of 0.4 ml/min before measurements were made. Basal conditions were reestablished by plethysmography between interventions. In one individual, angiography was performed before intervention to determine whether vessel caliper returned to baseline status. This procedure was not done for other subjects because of the large amounts of contrast media already required in this study. The following time intervals were sufficient to establish basal conditions between interventions: 16±2 minutes between reactive hyperemia and the methacholine chloride infusion, 12±1 minutes between the methacholine chloride and sodium nitroprusside infusions, and 11±2 minutes between the sodium nitroprusside and phenylephrine infusions.

Hemodynamic Measurements

The functional status of resistance vessels was assessed by measuring changes in calf vascular resistance. To accomplish this goal, calf blood flow was determined by venous occlusion strain-gauge plethysmography using a calibrated mercury-in-Silastic strain gauge (D.E. Hokanson, Inc., Issaquah, Wash.) and expressed as milliliters per 100 ml of tissue per minute. The leg was supported 15 cm above heart level. Venous occlusion was produced by inflation of a sphygmomanometric cuff located on the thigh just proximal to the patella. Venous occlusion pressure averaged 35 mm Hg. Circulation to the foot was arrested by inflating an ankle cuff to suprasystolic pressure before each calf blood flow determination. Each sequence included at least five separate measurements performed at 10–15-second intervals. Calf vascular resistance was calculated as the ratio of mean arterial pressure to calf blood flow and was expressed as units reflecting millimeter of mercury per milliliter per 100 ml of tissue per minute.

Blood pressure was measured by way of the arterial catheter using a Statham P23 pressure transducer (Gould Electronics, Cleveland, Ohio) coupled to an amplifier on an Electronics for Medicine physiological recorder (PPG Biomedical Systems, Lenexa, Kan.). Heart rate was assessed by measuring the RR interval obtained by electrocardiography.

Quantitative Angiography

Quantitative angiography was performed using a previously described boundary-detection algorithm to trace vessel edges. The angiograms that provided the most optimal visualization of the superficial femoral artery during each condition were selected for analysis. A magnified portion of the angiogram was

<table>
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<th>Sex</th>
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<th>MAP</th>
<th>FTC</th>
<th>Other</th>
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Characteristics of control subjects and atherosclerotic patients are summarized. MAP, mean arterial pressure; FTC, fasting total cholesterol; Other, cigarette smoking or diabetes; DM, diabetes mellitus; condition of SFA (superficial femoral artery) by quantitative angiography; normal, no evidence of atherosclerosis; mild, less than 30% stenosis; moderate, between 30% and 70% stenosis; severe, greater than 70% stenosis; occluded, no visible SFA.
processed by an image analyzing system consisting of a Cohu video camera (Cohu Electronics Division, San Diego, Calif.), an ITEX A/D-D/A converter (Imaging Technologies, Woburn, Mass.), and a Microvax-2 host computer (Digital Equipment Corp., Marlboro, Mass.). A window over the vessel segment of interest was first created on a video display. This image was then digitized onto a 512×512×8-bit pixel array. Transverse camera scans were obtained with an initial resolution of 10 μm/pixel in the image space. Each pixel was assigned a gray-scale value represented on an 8-bit logarithmic scale (2^n, or 256 levels). Vessel boundaries were automatically found by analyzing gray-scale values corresponding to vessel edges. Measurements of the image boundaries were converted from pixels to millimeters using a grid-derived magnification factor based on the size and distance of the aforementioned extrinsically placed calibrated phantom markers. To reduce fluctuations in diameter measurements as a result of radiographic noise, edges were tracked in both directions. A 20-cm segment of the superficial femoral artery was digitized and traced three times. Vessel diameters were determined by calculating the distance between parallel lines tangential to the vessel boundary at any given point along the segment of interest. About 200 diameters representing the 20-cm segment were averaged to obtain mean vessel diameter.

Statistical Analysis

Hemodynamic and angiographic data are presented as mean±SEM. For paired analyses within groups, statistical analyses were performed using Student's t test for parametric data and the Wilcoxon Signed Rank test for nonparametric data. Between-group analysis was performed using the unpaired t test for parametric data and the Wilcoxon Rank Sum test for nonparametric data. Statistical significance was accepted at the 95% confidence level (p<0.05).

Results

Participant Characteristics

The clinical characteristics of the six control subjects and the 11 patients with atherosclerosis are provided in Table 1. Age, sex distribution, fasting serum total cholesterol level, heart rate, and basal mean blood pressure were not significantly different between the two groups. Although there was a greater number of smokers and diabetic individuals in the atherosclerotic group, this difference did not reach statistical significance.

Responsiveness of Calf Resistance Vessels in Control Subjects

Venous occlusion strain-gauge plethysmography was used to measure calf blood flow in order to calculate calf vascular resistance. Basal calf blood flow in the control subjects was 1.6±0.2 ml/100 ml tissue/min, and calf vascular resistance was 63±10 units. Basal values for calf blood flow and calf vascular resistance were reestablished between interventions and did not differ significantly from each other. Intra-arterial infusion of methacholine increased calf blood flow to 5.6±1.5 ml/100 ml/min (p<0.005) and decreased calf vascular resistance to 22±5 units (p<0.01). Methacholine did not alter either mean blood pressure (95±5 versus 95±7 mm Hg, p=NS) nor heart rate (62±5 versus 64±4 beats/min, p=NS). Sodium nitroprusside increased calf blood flow to 3.3±0.3 ml/100 ml/min (p<0.005) and decreased calf vascular resistance to 28±3 units (p<0.01). Sodium nitroprusside did not alter blood pressure or heart rate. Phenylephrine decreased calf blood flow to 0.7±0.1 ml/100 ml/min (p<0.05) and increased calf vascular resistance to 120±20 units (p<0.01) in control subjects. Neither mean blood pressure nor heart rate changed from basal values during the phenylephrine infusion.

Responsiveness of Calf Resistance Vessels in Atherosclerotic Patients

Plethysmography was not performed in one atherosclerotic subject because of technical difficulties. Basal calf blood flow in the atherosclerotic patients was 2.2±0.3 ml/100 ml tissue/min, and calf vascular resistance was 55±9 units. These values were not significantly different from those observed in the control group. In the patients with atherosclerosis, methacholine did not change calf blood flow (3.2±0.9 ml/100 ml tissue/min, p=NS) nor did it decrease calf vascular resistance (59±14 units, p=NS). Sodium nitroprusside increased calf blood flow to 3.8±0.5 ml/100 ml tissue/min (p<0.002) and decreased calf vascular resistance to 29±4 units (p<0.01). Neither methacholine nor sodium nitroprusside altered mean blood pressure or heart rate. Phenylephrine decreased calf blood flow to 0.7±0.1 ml/100 ml tissue/min (p<0.05) and increased calf vascular resistance to 120±20 units (p<0.01). Phenylephrine increased mean blood pressure to 117 mm Hg (p<0.05) but did not affect heart rate.

The relative effects of each intervention on calf vascular resistance in the control and atherosclerotic groups are illustrated in Figure 1. Whereas metha-
choline induced vasodilation in calf resistance vessels of control subjects, no vasodilation occurred in the patients with atherosclerosis (−64±11% versus 6±18%, p<0.01). The vasodilator responses to the intra-arterial infusion of sodium nitroprusside were comparable in both groups (−51±5% versus −42±4%, p=NS). Furthermore, vasoconstrictor responsiveness to the intra-arterial phenylephrine infusion was similar in the calf resistance vessels of control subjects and atherosclerotic patients (105±30% versus 108±22%, p=NS).

As noted below, the superficial femoral artery was occluded in three patients; therefore, drug delivery to the calf must have occurred by way of the patent deep femoral artery. Reduced drug delivery possibly affected the vasoactive responses in these individuals. To ensure that the data derived from these patients did not skew the overall analysis, a subset analysis was performed on the remaining patients. Again we found that methacholine reduced calf vascular resistance in control subjects but not in atherosclerotic patients (−64±11% versus 18±23%, p<0.01), whereas the vasodilative response to sodium nitroprusside (−51±5% versus −44±5%, p=NS) and the vasoconstrictive responses to phenylephrine (105±30% versus 99±22%, p=NS) were comparable in each group.

**Conduit Vessel Responsiveness**

The baseline diameter of the superficial femoral artery in control subjects was 7.5±0.8 mm; in the atherosclerotic subjects it was 6.0±0.5 mm. These apparent differences did not reach statistical significance. In control subjects methacholine increased the diameter of this vessel to 9.0±1.1 mm (p<0.05), sodium nitroprusside increased it to 8.9±1.1 mm (p<0.05), and phenylephrine reduced it to 6.3±0.7 mm (p<0.05).

Three of the 11 subjects with atherosclerosis had a proximal occlusion of the superficial femoral artery; therefore, the diameter of this vessel could not be determined in those individuals. Of the remaining eight subjects, seven had angiographic evidence of atherosclerosis but had no lesions that exceeded 70% of the vessel diameter. When compared with baseline measurements, no significant increase in vessel diameter was observed during the intra-arterial infusion of methacholine (6.0±0.5 mm, p=NS). Furthermore, there was no significant change in the diameter of the superficial femoral artery during the sodium nitroprusside (6.0±0.5 mm, p=NS) or phenylephrine (5.6±0.4 mm, p=NS) infusions.

The responses of the superficial femoral artery to each pharmacological intervention in control subjects and atherosclerotic patients are compared in Figure 2. The vasodilator responses to methacholine (20±4% versus 1±4%, p<0.05) and sodium nitroprusside (19±4% versus 5±4%, p<0.05) were blunted in the patients with atherosclerosis. Moreover, the vasoconstrictor response to phenylephrine was depressed in the atherosclerotic group (−15±1% versus −1±5%, p<0.05).

**Flow-Mediated Vasodilation in Conduit Vessels**

The effect of increases in blood flow on conduit vessel diameter was examined in control subjects and atherosclerotic patients during reactive hyperemia. As shown in Figure 3, reactive hyperemia produced a substantial increase in calf blood flow in both control subjects (from 1.6±0.2 to 11.1±2.9 ml/100 ml tissue/min, p<0.05 versus baseline) and atherosclerotic patients (from 2.2±0.3 to 10.0±1.5 ml/100 ml tissue/min, p<0.001 versus baseline). The magnitude of the increase in blood flow was not significantly different between the two groups. In the control subjects, the superficial femoral artery dilated (from 7.5±0.8 to 8.2±0.3 mm, p<0.05) during reactive hyperemia (Figure 4). In contrast, despite the comparable increase in blood flow, no significant change in the diameter of the superficial femoral artery was observed in the atherosclerotic patients (from 6.0±0.5 to 6.1±0.5 mm, p=NS). These data are consistent with the impaired vasodilator responses observed during pharmacological interventions.

**Discussion**

To our knowledge, this is the first in vivo study to report vasodilator function in peripheral conduit and...
reported that acetylcholine causes vasodilation in coronary resistance vessels. The patients in that study had no angiographic evidence of coronary atherosclerosis and thus are similar in that aspect to our control group. We cannot extrapolate our findings in the calf resistance vessels of atherosclerotic subjects to other regions of circulation because vascular smooth muscle sensitivity to endothelium-dependent vasodilators may differ in different vessels.

**Abnormal Vasodilator Function in Peripheral Atherosclerotic Vessels**

We found that atherosclerotic involvement of the superficial femoral artery renders this conduit vessel relatively unresponsive to pharmacological vasodilator stimuli (methacholine and sodium nitroprusside) and to the α₁-adrenergic agonist phenylephrine. Thus, abnormalities in vasomotion could not be confined to impaired release of an endothelium-derived relaxing factor but must involve the inability of vascular smooth muscle to respond to vasoactive stimuli. Several investigators have reported impaired vasodilation and even paradoxical vasoconstriction of atherosclerotic coronary conduit vessels after acetylcholine infusion, whereas infusion of nitroglycerin caused vasodilation. These findings contrast with ours in that the atherosclerotic coronary vessel manifested only impaired endothelium-dependent vasodilation. This may reflect the possibility that coronary atherosclerosis is less extensive than that involving the superficial femoral artery or that different regions of circulation were studied. Our findings are similar to those recently reported in Wanatabe rabbits; segments of aorta severely affected by atherosclerosis demonstrate reduced relaxation responses to both acetylcholine and nitroglycerin and decreased contractile responses to phenylephrine. Our group data showed no significant effect of sodium nitroprusside in the superficial femoral artery, but in several individuals the vessel did dilate, particularly in those whose angiography revealed only mild luminal irregularities of the vessel. Higher doses of sodium nitroprusside would possibly induce limb vasodilation in our patients' atherosclerotic vessels. In fact, one group of investigators did report that the dose–response curve for sodium nitroprusside was shifted to the right in atherosclerotic human coronary arteries.

**Flow-Mediated Vasodilation of Conduit Vessels**

Recent evidence suggests that the endothelium plays a crucial role in flow-mediated vasodilation of conduit vessels. Reactive hyperemia causes an increase in blood flow through large conduit vessels to accommodate the dilated resistance vessels. However, the reactive hyperemic blood flow in our control subjects was only half of that observed in previous studies of normal subjects. The participants' apprehension and anxiety during the study could have produced local neurohormonal influences on vasmotor tone. Moreover, the brief duration of ischemia may not have allowed maximum vasodilation of re-
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**Limitations of Study**

We presume that abnormal endothelium-dependent vasodilation in the resistance vessels of atherosclerotic patients is a consequence of impaired synthesis, release, or transport of endothelium-derived relaxing factor because the vasodilator response to methacholine was blunted. The possibility that methacholine acts by inhibiting presynaptic and postsynaptic junctions of autonomic pathways cannot be excluded; however, this possibility is unlikely because previous studies have shown that acetylcholine at comparable doses exerts its effects predominantly by acting locally on vascular receptors and that these actions are not altered by autonomic blockade. Furthermore, because our subjects were not pretreated with a prostaglandin synthesis inhibitor, the impaired vasodilation in the resistance vessels of atherosclerotic individuals may have been caused by a decreased production of prostacyclin or increased release of a vasoconstriction prostanoid substance. However, this possibility is also unlikely because, as previous studies have shown, cyclooxygenase inhibitors do not interfere with the vasodilator responses to acetylcholine.

In conclusion, peripheral ischemia and claudication are not only the result of atherosclerotic obstructions to regional blood flow but also may be secondary to altered vascular reactivity of resistance and conduit vessels. Impaired endothelium-dependent relaxation of resistance vessels occurs even in patients with mild atherosclerosis. Atherosclerotic involvement of conduit vessels affects the smooth muscle and renders these vessels relatively unresponsive to vasoactive agents. Furthermore, the atherosclerotic conduit vessels cannot dilate in response to increases in flow. Thus, in patients with peripheral atherosclerosis a series of abnormalities consisting of unresponsive, possibly rigid conduit vessels that feed resistance vessels with abnormal vasodilatory function may all contribute to the development of claudication.

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**References**


KEY WORDS • atherosclerosis • blood flow • endothelium-derived relaxing factor • vasodilation
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