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Peripheral Vascular Endothelial Dysfunction in Patients With Angina Pectoris and Normal Coronary Arteriograms

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Objectives. **We sought to determine endothelium-dependent vasodilator function in the brachial artery of patients with microvascular angina pectoris.**

Background. **Previous studies suggest the presence of endothelial dysfunction of the coronary microcirculation in patients with microvascular angina pectoris. It is not known whether endothelial dysfunction in these patients is a generalized process or whether it is confined to the coronary microcirculation only.**

Methods. **In 11 women (mean [±SD] age 60.1 ± 7.8 years) with microvascular angina (anginal pain, normal epicardial coronary arteries, positive exercise stress test), endothelium-dependent vasodilation was assessed in the brachial artery by measuring the change in brachial artery diameter in response to hyperemic flow. Results were compared with 11 age- and gender-matched patients with known three-vessel coronary artery disease and 11 age- and gender-matched healthy control subjects. In all subjects, the intima–media thickness (IMT) of the common carotid artery was also measured.**

Results. **Flow-mediated dilation (FMD) was comparable in patients with microvascular angina and coronary artery disease (1.9 ± 2.5% vs. 3.3 ± 3.3%, p = NS) but was significantly lower in patients with microvascular angina than in healthy control subjects (1.9 ± 2.5% vs. 7.9 ± 3%, p < 0.05). IMT was significantly lower in patients with microvascular angina than in those with coronary artery disease (0.64 ± 0.08 vs. 1.0 ± 0.28 mm, p < 0.05) and was comparable between patients with microvascular angina pectoris and healthy control subjects (0.64 ± 0.08 vs. 0.56 ± 0.14 mm, p = NS). IMT ≥0.8 mm was observed in 1 of 11 patients with microvascular angina, 1 of 11 control subjects and 10 of 11 patients with coronary artery disease.**

Conclusions. **These findings suggest that endothelial dysfunction in microvascular angina is a generalized process that also involves the peripheral conduit arteries and is similar to that observed in atherosclerotic disease. IMT could be helpful in discriminating patients with microvascular angina and atherosclerotic coronary artery disease.**

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Inadequate vasodilation in response to metabolic or pharmacologic stimuli characterizes patients with angina pectoris and normal results on coronary arteriography. Endothelium-dependent coronary vasodilation is specifically impaired in these patients in whom abnormal dilation of coronary microcirculation may contribute to myocardial ischemia (1,2). Supplementation of L-arginine, a precursor of endothelium-derived nitric oxide, improves defective endothelium-dependent vasodilation in patients with microvascular angina (3), indicating that endothelial dysfunction in these patients resulted from defective synthesis or release of nitric oxide, or both.

Endothelial dysfunction appears to be a generalized process. A close correlation between coronary artery endothelium-dependent vasomotor responses to acetylcholine and brachial vasodilator response to reactive hyperemia has been demonstrated in patients with coronary artery disease (4). The value of abnormal brachial dilation in predicting abnormal coronary endothelium is high in these patients. In patients with microvascular angina, an impaired forearm vasodilator response to ischemia has been observed (5), suggesting that the vascular involvement is not restricted to the coronary circulation but is part of a generalized vasomotor disturbance.

Intima–media thickness (IMT) of the common carotid artery has been suggested as a surrogate marker for coronary atherosclerosis. An association of coronary atherosclerosis status with IMT has been previously described (6). It is not known whether carotid IMT is also abnormal in patients with microvascular angina.

Thus, the present study sought to 1) determine whether endothelial dysfunction is present in peripheral conduit arteries of patients with microvascular angina, and 2) examine IMT in these patients.

Methods

Study patients. Eleven female patients with microvascular angina were included in the study (mean [±SD] age 60.1 ± 7.8

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Abbreviations and Acronyms
FMD = flow-mediated dilation
IMT = intima–media thickness
NID = nitrate-induced dilation

years, range 49 to 72). Diagnostic criteria for microvascular angina were typical angina pectoris during exercise or at rest, positive exercise stress test results, with ST segment depression ≥0.2 mV and normal epicardial coronary arteries. In eight patients, an exercise thallium-201 test was performed and showed reversible myocardial perfusion defects. No patient had a previous myocardial infarction or valvular heart disease. The control subjects were 11 healthy volunteers without anginal chest pain and normal results on the exercise stress test, matched for age and gender with the 11 patients with microvascular angina. A second control group included 11 patients with known coronary artery disease with no history of myocardial infarction and three-vessel disease on coronary angiography, matched for age and gender with the patients with microvascular angina. No patient or control subject had diabetes mellitus, and none were taking estrogen replacement therapy. All medications were withdrawn ≥48 h before the study. All patients and control subjects gave informed consent before entering the study. The clinical characteristics of the patients and control subjects are shown in Table 1.

Table 1. Clinical Characteristics of Patients and Control Subjects

Pt or Subj No.	Age (yr)/Gender	Chol	TG	Smoking	HTN
MVA					
1	57/F	212	135	+	−
2	72/F	190	98	−	+
3	64/F	225	142	−	−
4	68/F	200	116	−	−
5	64/F	234	162	−	+
6	52/F	188	92	−	−
7	55/F	218	122	−	−
8	62/F	245	158	−	−
9	51/F	198	141	−	+
10	49/F	225	92	−	−
11	68/F	232	115	+	−
Mean	60.18	215	124		
SD	±7.80	±19	±24		
Normal					
1	56/F	185	143	−	−
2	74/F	230	85	−	−
3	62/F	198	115	−	+
4	70/F	232	161	+	−
5	64/F	192	95	−	−
6	51/F	217	105	+	−
7	55/F	238	168	−	−
8	62/F	218	96	+	−
9	50/F	222	107	+	−
10	50/F	186	110	−	+
11	68/F	197	168	−	−
Mean	60.18	210	123		
SD	±8.40	±19	±31		
CAD					
1	57/F	227	168	−	+
2	71/F	218	105	−	+
3	63/F	236	175	−	−
4	69/F	196	117	+	−
5	64/F	187	132	−	+
6	53/F	227	145	+	+
7	56/F	238	89	−	−
8	61/F	245	115	−	+
9	51/F	234	127	+	+
10	50/F	204	96	−	−
11	68/F	215	178	+	+
Mean	60.27	220	131		
±SD	±7.39	±18	±31		

CAD = patients with three-vessel coronary artery disease; Chol = cholesterol; F = female; HTN = hypertension; M = male; MVA = patients with microvascular angina; Normal = normal subjects; Pt = patient; Subj = subject; TG = triglycerides; + = yes; − = no.

Study protocol. *Brachial artery endothelial function study.* Each subject was studied in the morning, after abstaining from alcohol, caffeine and tobacco as well as food within 8 h before the study. High resolution echocardiography–Doppler ultrasound (Acuson 128XP) with a 7.0-MHz transducer was used to measure the flow velocity and diameter of the right brachial arteries. In all studies, scans were taken at rest, during reactive hyperemia (endothelium-dependent stimulus to vasodilation), again at rest and after sublingual nitroglycerin (endothelium-independent vasodilation). The intraobserver and interobserver variabilities for repeated measurements are 0.1 ± 0.12 and 0.08 ± 0.19 mm, respectively, in our laboratory. When reactive hyperemia studies were performed on 2 separate days, the mean difference in brachial vasodilator response in absolute terms was 1.1 ± 1%.

Each subject rested quietly for 10 min before the scan. When a satisfactory position was found, the skin was marked, a scan was recorded at rest, and arterial flow velocity was measured using a pulsed Doppler signal at 60° angle in the center of the artery. Blood flow through the brachial artery was altered with an occluding cuff placed in the forearm ~8 cm distal to the site of brachial artery measurement (7). By inflating the cuff to 250 to 300 mm Hg, distal circulation arrest was obtained, and flow was reduced through the brachial artery measured proximal to the cuff. By deflating the cuff after 5 min of inflation, flow through the brachial artery was increased (reactive hyperemia). The brachial artery was scanned continuously 30 s before and 90 s after cuff deflation. Ten minutes later, a second rest scan was recorded. Nitroglycerin (400 μg) was then administered sublingually, and the artery was scanned 5 min later.

All images were recorded on super-VHS videotape and later analyzed by two observers (J.L., C.P.) who did not know the identity of the subject or the scan sequence. Artery diameter measurements were made at end-diastole (peak of R wave on the electrocardiogram) using electronic calipers. Five cardiac cycles were analyzed, and measurements were averaged. Brachial artery diameter measurements after reactive

hyperemia were taken 60 s after cuff deflation. Flow-mediated dilation (FMD) was calculated as the percent increase in arterial diameter during hyperemia versus the corresponding rest value. Brachial artery diameter measurements after nitroglycerin were taken 5 min after nitroglycerin administration. Nitrate-induced dilation (NID) was calculated as the percent increase in arterial diameter after nitroglycerin versus the corresponding rest value.

IMT measurement. B-mode ultrasound imaging was performed using the same ultrasound machine (128XP Acuson, 7.0-MHz linear array transducer). The scanning method used was similar to that proposed by Salonen and Salonen (8) and Blankenhorn et al. (9). The common carotid arteries were studied in longitudinal planes with anterior, lateral and posterior approaches. The image was focused on the posterior wall, and images of the distal 10 mm of the common carotid artery were recorded from the approach showing the greatest distance between the lumen–intima interface and media–adventitia interface. All scans were recorded on super-VHS videotapes for subsequent analysis. Mean IMT was calculated as the average of 10 measurements made manually in each carotid by means of electronic calipers. Measurements were made by consensus of two observers (J.L., C.P.) unaware of the identity of the subject.

Statistical evaluation. Results are expressed as mean value ± SD. Differences between cholesterol, triglycerides, brachial artery vasodilator responses and IMT were evaluated and analyzed by one-way analysis of variance. If this test was positive, the Student-Newman-Keuls test was performed to evaluate differences among the three groups. A p value <0.05 was considered statistically significant.

Results

Patients. Table 1 shows the clinical characteristics of patients and control subjects. All participants were women, and age was well matched among the three groups. There were no significant differences in cholesterol and triglyceride levels and smoking habits and arterial hypertension were comparable in all groups.

Brachial artery diameter. Baseline brachial artery diameter was comparable in patients with microvascular angina (3.7 ± 0.5 mm), patients with coronary artery disease (3.5 ± 0.6 mm) and healthy control subjects (3.5 ± 0.6 mm). The time-averaged flow velocity during peak reactive hyperemia, a measure of the stimulus for dilation was similar in all three groups (71 ± 19 cm/s in patients with microvascular angina, 73 ± 23 cm/s in patients with coronary artery disease, 76 ± 10 cm/s in healthy control subjects) (Table 2).

FMD. FMD was 1.9 ± 2.5% in patients with microvascular angina (range −3% to 6%), significantly lower than that in healthy volunteers (7.9 ± 3%, range 3% to 12%, $p < 0.05$) and comparable to that observed in patients with three-vessel coronary artery disease (3.3 ± 3.3%, range 0% to 10%, p = NS) (Fig. 1). In a subset of six patients with microvascular angina without risk factors for atherosclerosis, FMD was 1.5 ± 2.7%, significantly lower than that in a subset of five normal healthy volunteers without risk factors (FMD 7.2 ± 2.7%, $p < 0.01$).

Table 2. Vessel Size and Time-Averaged Velocity at Reactive Hyperemia in Study Participants

Group	Vessel Size (mm)	Time-Averaged Velocity at Reactive Hyperemia (cm/s)
MVA	3.7 ± 0.5	71 ± 19
Normal	3.5 ± 0.6	76 ± 10
CAD	3.5 ± 0.6	73 ± 23

Data presented are mean value ± SD. Abbreviations as in Table 1.

Nitrate-induced dilation. Nitrate-induced dilation (NID) was 22 ± 13% in patients with microvascular angina (range 6% to 40%) and did not differ significantly from that in healthy control subjects (24 ± 7%, range 12% to 39%, p = NS) or patients with three-vessel coronary artery disease (18 ± 7%, range 3% to 33%, p = NS) (Fig. 2).

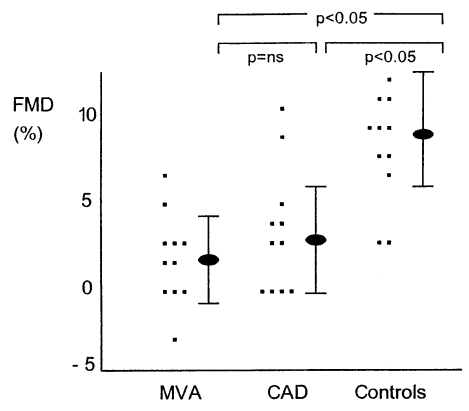
IMT. IMT was 0.64 ± 0.08 mm in patients with microvascular angina (range 0.5 to 0.7), significantly lower than that in patients with three-vessel coronary artery disease (1.0 ± 0.28 mm, range 0.6 to 1.6, $p < 0.05$) and comparable to values observed in healthy volunteers (0.56 ± 0.14 mm, range 0.4 to 0.8, p = NS).

IMT ≥0.8 mm was observed in 1 of 11 patients with microvascular angina, 1 of 11 healthy volunteers and 10 of 11 patients with three-vessel coronary artery disease (Fig. 3).

Discussion

In the present study we examined vascular endothelial and smooth muscle function in the large vessels of patients with microvascular angina by means of a simple noninvasive method that is known to enable accurate and reproducible assessment of the vascular responses to flow increase and nitrates (7,10). In animals, flow-dependent dilation is endothelium dependent and is mediated by nitric oxide (11,12). The

Figure 1. FMD in patients with microvascular angina (MVA), control subjects and patients with coronary artery disease (CAD). **Ovals** = mean value; **vertical lines** = standard deviation.



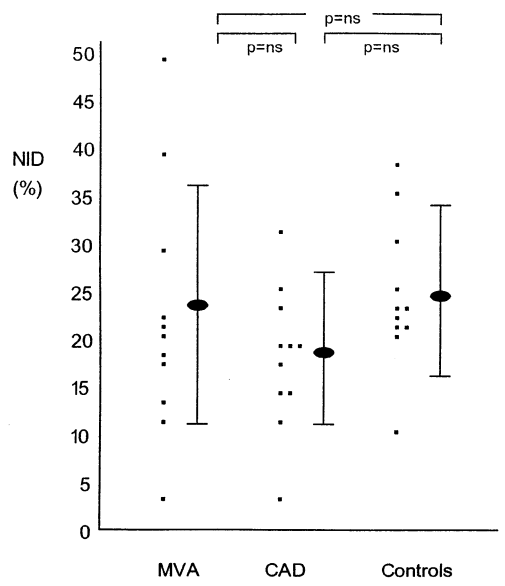
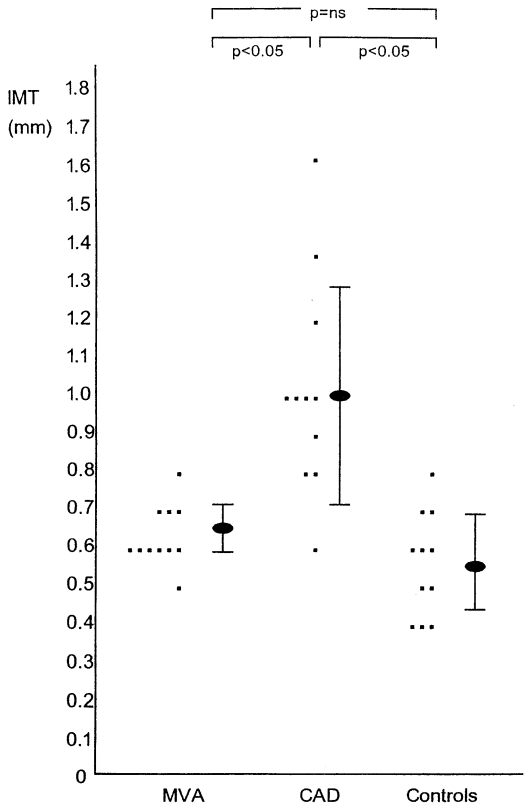


Figure 2. NID in patients with microvascular angina (MVA), control subjects and patients with coronary artery disease (CAD). Symbols as in Figure 1.

same mechanism is essential for FMD of large human arteries (13). Hence, this test can be used as an estimate of the capacity of human endothelial cells to release nitric oxide in response to a physiologic stimulus as well as an estimate of endothelial dysfunction in diseased states. To distinguish endothelial from intrinsic smooth muscle dysfunction, we used nitroglycerin, an endothelium-independent vasodilator. Nitrates cause smooth muscle relaxation, acting directly by increasing cyclic guanosine monophosphate levels of smooth muscle cells.

Figure 3. IMT in patients with microvascular angina (MVA), control subjects and patients with coronary artery disease (CAD). Symbols as in Figure 1.



Endothelial function in patients with microvascular angina. The results of the present study in the brachial artery clearly indicate the presence of endothelial dysfunction in patients with microvascular angina comparable to that observed in patients with extended atherosclerotic heart disease. It has been previously shown (1,2) that acetylcholine-induced vasodilation of coronary microcirculation is impaired in microvascular angina. Microvascular endothelial dysfunction may contribute to the reduced vasodilator reserve during atrial pacing and anginal chest pain in these patients. Some degree of abnormal response of epicardial coronary arteries to acetylcholine was also present in the majority (71%) of the patients with microvascular angina (2). Intracoronary infusion of L-arginine (3) markedly improved endothelium-dependent vasodilation of the coronary microcirculation in these patients, suggesting that impaired acetylcholine-induced endothelium-dependent vasodilation of the coronary microcirculation in patients with microvascular angina resulted from defective synthesis or release of nitric oxide, or both.

Further evidence is provided by the present data that endothelial dysfunction in patients with microvascular angina is not confined to the coronary microcirculation but also extends to large peripheral conduit arteries. It has been previously proposed (5,14,15) that some patients with limited microvascular vasodilator capacity may present a more generalized disorder, leading to an attenuated hyperemic response to transient forearm ischemia, esophageal motility abnormalities or bronchoconstrictor responses to metacholine inhalation. Morphologic changes of subcutaneous small arteries have been described (16) in patients with microvascular angina, although no significant functional abnormalities were associated with the observed structural changes in vitro. These results suggest that there is a generalized abnormality in the vascular tree in microvascular angina rather than one confined to the heart. It is also known that endothelial dysfunction is a generalized process, not necessarily confined to vascular beds with clinically overt atherosclerosis. The brachial vasodilator response to reactive hyperemia was closely related to the coronary vasodilator response to acetylcholine (4) and to the extent of coronary atherosclerosis (17) in patients with atherosclerotic heart disease. Botker et al. (18) using the same technique were unable to detect differences in flow-mediated vasodilation between patients with microvascular angina and control subjects. They reported a percent diameter change of the brachial artery in response to reactive hyperemia in these patients of 2.7%, a value similar to that observed in our study (1.9%). Although their control subjects also showed an abnormal response to hyperemic flow (FMD 4.2%) that was significantly lower than the normal values observed in our study as well as in previous studies (7,19); the apparently abnormal

response of the control group might preclude a significant difference in FMD between patients with microvascular angina and control subjects in that study (18).

The response to nitroglycerin was normal in our patients with microvascular angina, suggesting a selective endothelial dysfunction rather than a disorder of smooth muscle cell responsiveness. Quyyumi et al. (2) also showed that microvascular coronary dilation caused by sodium nitroprusside was not abnormal in patients with microvascular angina, indicating that the vasodilator defect in the coronary microcirculation was not caused by smooth muscle dysfunction.

It is noticeable that in our study, patients with microvascular angina presented with the same degree of endothelial dysfunction in peripheral arteries as patients with extended coronary artery disease. It has been reported (4,7) that the brachial dilator response to reactive hyperemia is blunted in patients with coronary artery disease compared with that in control subjects without coronary disease; the response to nitroglycerin appears to be normal in these patients.

B-mode ultrasound of the carotid circulation has been proposed as a useful measure for clinical screening of patients with chest pain syndromes and for use in clinical trials. Autopsy studies have shown that the extent of extracranial carotid and coronary atherosclerosis is well correlated (20,21). Common carotid IMT is correlated with traditional vascular risk factors (22); is higher in the presence of aortic, femoral or carotid plaque (21); may predict the likelihood of acute coronary events (8); and is significantly although weakly correlated with the extent and severity of coronary artery disease (23). In 1990 Craven et al. (24) compared subjects with severe coronary artery disease (one or more vessels with ≥50% stenosis) with subjects having no coronary disease and found that IMT was greater in patients. In our study, the two groups with and without coronary atherosclerosis could be discriminated on the basis of carotid IMT. A thickness >0.8 mm was helpful in discriminating these two groups with a similar degree of endothelial dysfunction in the conduit arteries.

Limitations of the study. Some of our patients and control subjects had coronary risk factors that may influence endothelial function and IMT (22,25,26). However, it is unlikely that the presence of risk factors influenced the present results because the incidence of factors such as smoking and hypertension was similar in the three groups, whereas the levels of cholesterol and triglycerides were comparable. Furthermore, in a subset of patients with microvascular angina without risk factors for atherosclerosis, FMD was lower than that in a subset of healthy control subjects without risk factors. A second limitation is that all patients were women, and thus conclusions may not extend to the male population; nevertheless, there is a female prevalence among patients with microvascular angina (27,28). Finally, these findings do not apply to women who are premenopausal; however, the majority of patients with microvascular angina are postmenopausal women (28,29).

Conclusions. The present study demonstrated that in patients with microvascular angina, endothelial dysfunction is a generalized process involving the peripheral conduit arteries and is similar to that observed in atherosclerotic heart disease. Common carotid IMT measurement might be a useful method for discriminating patients with microvascular angina and atherosclerotic coronary artery disease.

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