Peripheral Arterial Responses to Treadmill Exercise Among Healthy Subjects and Atherosclerotic Patients

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Background—Peripheral cutaneous vascular beds, such as the fingertips, contain a high concentration of arteriovenous anastomoses, richly innervated by α-adrenergic nerve fibers, to control heat regulation. Nevertheless, for a variety of technical reasons, finger blood flow responses to exercise have not been well studied in health and disease. Hence, we compared finger pulse-wave amplitude (PWA) responses to exercise among 50 normal volunteers and 57 patients with atherosclerotic coronary artery disease (CAD) using a robust, modified form of volume plethysmography.

Methods and Results—PWA was quantified for each minute of exercise as a ratio relative to baseline. Exercise PWA responses were compared with clinical, hemodynamic, ECG, and myocardial single photon emission computed tomography parameters. Among normal subjects, 38 (76%) manifested vasodilation throughout exercise and 12 (24%) manifested initial vasodilation followed by vasoconstriction at high heart rate thresholds. None manifested vasoconstriction throughout exercise. By contrast, 20 CAD patients (35%) manifested progressive vasoconstriction from the onset of exercise, and 10 others (18%) manifested vasoconstriction at low heart rate thresholds (P<0.001 versus normals) after initial vasodilation with exercise. Patients exhibiting vasodilation versus vasoconstriction during exercise had similar clinical and exercise profiles, except for a greater use of ACE inhibitors and a greater level of achieved metabolic equivalents among the former (P<0.05 for both).

Conclusions—Half of our CAD patients manifested diminution in PWA that was consistent with peripheral arterial vasoconstriction during the early phases of treadmill exercise. Such paradoxical vasoconstrictive responses were not observed in normal subjects and, therefore, they may represent generalized vascular pathology secondary to atherosclerosis. (Circulation. 2001;103:2084-2089.)

Key Words: exercise • coronary disease • blood flow • body temperature regulation

Cutaneous vascular beds in peripheral regions (such as the fingers and toes) and nonperipheral regions (such as the limbs and body trunk) together govern thermoregulation. The peripheral cutaneous regions, however, are characterized by a unique anatomic structure, including a large number of arteriovenous anastomoses that are densely innervated by α-adrenergic fibers,1 no significant muscle mass, and lack of β-receptors.2 As a consequence, these cutaneous regions may afford a unique window into assessing the activation of the sympathetic nervous system. Such activation is characteristically manifested by profound diminution in finger blood flow during physiological stimuli as varied as cold stimulation and mental stress,3–5 the arousal state from sleep apnea,6 and REM sleep.7 Because the finger is particularly accessible for measurement, finger plethysmography is a convenient method for assessing such physiological phenomena. For a variety of technical reasons, however, finger plethysmography has found limited application in exercise stress testing.

The potential interest in studying peripheral cutaneous blood flow responses to exercise lies in the unique physiology governing this stressor. Because core body temperature increases during exercise, the central nervous system selectively decreases its tonicity to the peripheral cutaneous vascular beds, thereby promoting peripheral vasodilation and consequent heat loss.8 Thus, the increase in finger pulsatile blood volume is the expected physiological response to exercise, but it is not known if—and how—this response varies among healthy subjects and atherosclerotic patients. Accordingly, we evaluated peripheral thermoregulatory responses by means of a new plethysmographic device that is applicable for exercise use. The goals of the study were to compare exercise thermoregulatory responses among normal

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counterpressure also serves, in part, to unload arterial wall tension, thus improving the dynamic range of the arterial pulse excursions. Another device feature, the splitting of its distal cap, prevents the probe from generating a net force vector that would tend to push it away from the finger during its use. The probe components are connected by thin flexible tubing to isolated volume reservoirs to buffer pressure changes within the probe. A further volume reservoir that is not connected to the probe serves as a pressure reference. The pressure changes accompanying peripheral volume changes are fed to a personal computer, by which the signal is band pass-filtered (0.3 to 30 Hz), amplified, displayed, and stored.

**Exercise Protocol**
Patients were instructed to be off nitrates for 6 hours, calcium channel blockers for 24 hours, and β-blockers for at least 48 hours before testing. The Bruce exercise protocol\(^\text{11}\) was performed in a thermoneutral environment (21°C). Patients exercised to exhaustion, unless severe chest pain or hypotension intervened. Finger pulse-wave measurements were obtained continuously. Subjects were requested to lean the forearm of the monitored hand lightly on a padded supporting device attached to the treadmill’s side rail to minimize free hand movement.

**Assessment of Pulse-Wave Amplitudes**
Nonperiodic data related to incidental patient motion were removed from the pulse-wave tracings by electronic filtering. A region-of-interest was then defined between the beginning and end of exercise (Figure 2). Baseline amplitude was determined by averaging over the first 2 minutes of exercise. Average amplitude was then determined for each subsequent minute of exercise and expressed as a ratio compared with the baseline amplitude.\(^\text{10}\)

**Gated Myocardial Perfusion Imaging**
Gated SPECT imaging was performed using conventional methodology. Data were acquired after the injection of Tc-99m sestamibi (9 to 10 mCi at rest; 30 to 31 mCi at peak exercise) in 64 projections over a circular 180° orbit, with the scintillation camera set at a 140 keV energy peak with a 20% window, using a high resolution collimator and 2D Butterworth filter. Transaxial tomograms were reconstructed using back projection with a ramp filter. Resting left ventricular ejection fraction and volumes were calculated using a semiautomated volumetric algorithm.\(^\text{10}\)

**Assessment of Exercise Test Results**
The exercise ECG response was considered ischemic if horizontal or downsloping ST-segment depression ≥1 mm or upsloping ST-segment depression ≥1.5 mm occurred from the baseline ECG, when measured 0.08 s after the J point. Rest and exercise myocardial scintigrams were assessed semiquantitatively for each of 20 standardized myocardial segments in the apical, midventricular, and basal left ventricular regions. The presence of reversible hypoperfusion defined a scan as ischemic.
Statistical Analysis

All analyses used the summary minute-by-minute amplitude data. The amplitudes during exercise were expressed as a ratio relative to baseline amplitude; ratios >1 represented "vasodilation," ratios = 1 represented "no change," and ratios <1 represented "vasoconstriction." "Maximal" pulse wave amplitude was the maximum of all averaged minute-by-minute points during exercise. "End-exercise" amplitude ratio was that computed for the last minute of exercise. Clinical, hemodynamic, exercise ECG, and exercise SPECT results within CAD subgroups, divided by their peripheral blood flow responses to exercise, were compared using a Fisher's exact test for categorical variables and a t test for continuous measurements.

Results

Baseline Exercise Responses

Exercise duration averaged 9.6±1.9 minutes for volunteers, none of whom developed evidence of ischemia. Exercise duration averaged 8.2±2.5 minutes for the atherosclerotic patients (P<0.002 versus volunteers); 16 (28%) developed an ischemic response to exercise (2 abnormal clinical responses, 12 abnormal electrocardiographic responses, and 8 abnormal SPECT responses).

Exercise Pulse-Wave Amplitude Responses

By visual analysis, the temporal change in pulse-wave amplitude (PWA) with exercise ranged from progressive increases to progressive decreases, with some subjects showing a mixed pattern of an initially maintained or increased finger PWA during early exercise, followed by diminution in PWA later during exercise (Figure 3). The maximal PWA ratio during exercise (expressed as a percent relative to baseline) was significantly higher in the volunteers than in the patients (165±42% versus 118±42%, P<0.001), and the slope of PWA change during exercise was significantly more positive in the volunteers than in the patients (1.05±0.96 min⁻¹ versus 0.03±1.58 min⁻¹, P<0.001).

Individual PWA responses for the volunteers and patients are illustrated in Figure 4. Two basic temporal PWA patterns were observed in the volunteers: 38 (76%) manifested a rise in PWA during the course of exercise, and 12 (24%) had a fall in PWA below the baseline value at or before the end of exercise after an initial rise. Eleven volunteers (22%) manifested a transient diminution of PWA below the baseline at the very onset of exercise, before the characteristic rise began.

Figure 3. Characteristic patterns of PWA response to treadmill exercise (from top to bottom): a progressive increase in amplitude during exercise; a relatively flat amplitude response during exercise; a progressive decrease in amplitude during exercise; and a transition from an early increase to a late decrease in amplitude during exercise.

Figure 4. Individual PWA responses to exercise (expressed as a percent relative to baseline) among healthy volunteers (top) and patients with documented coronary atherosclerosis (bottom). Definition of each pattern is summarized along top of figure. Left panels represent PWA responses that tended to increase during exercise; middle panels represent PWA responses that peaked and then declined before peak exercise; and right panels represent PWA responses that declined throughout exercise. Top right panel is blank because such responses were not observed in volunteers.
Three temporal patterns of PWA were observed among the atherosclerotic patients: 27 (47%) manifested a rise in PWA during exercise, 10 (18%) exhibited an initial rise followed by a fall before the end of exercise, and 20 (35%) manifested a fall in amplitude from the onset of exercise that worsened progressively during exercise. For the volunteers and patients who manifested an initial rise followed by a fall in amplitude, the onset of the transition occurred at significantly lower thresholds among the patients than in the controls (120±11 bpm versus 162±21 bpm, *P*<0.01; 77±11% versus 88±12% of maximal predicted heart rate, *P*<0.01; and 5.2±1.5 versus 7.4±2.3 minutes, *P*<0.05). Among the patients, the frequency of PWA falling below the initial baseline value increased progressively with increasing percent of maximal predicted heart rate; by contrast, amplitudes below the baseline value were uncommon in volunteers at <90% of maximal predicted heart rate (Figure 5).

**Evaluation of Predictors**

To identify potential clinical predictors of finger blood flow responses to exercise, we compared a number of clinical parameters among the CAD patients, who were divided into 2 groups: the 20 patients who manifested PWA exercise responses consistent with initial and progressive vasoconstriction were 1 group, and the 37 patients who manifested responses consistent with initial vasodilation were the other. As shown in the Table, there was a significant difference between these 2 groups with respect to the use of ACE inhibitors and the achieved level of metabolic equivalents, each of which was greater among the patients manifesting vasodilation.

**Discussion**

Our results indicate significant differences in the peripheral vasodilator responses to exercise among healthy normal volunteers and patients with proven atherosclerotic CAD. Finger PWA rose progressively throughout exercise in the volunteers, but in ∼25% of such subjects, there was a late reversal, with declines in PWA beginning at a mean heart rate of 162±21 bpm. In contrast, >33% of the CAD patients manifested a fall in PWA from the onset of exercise. These falls, which were not observed among normal volunteers, were characteristically progressive in nature and worsened throughout the exercise period. Other CAD patients manifested falls in finger PWA that began at substantially lower heart rate thresholds compared with the late falls observed in some of the volunteers. Consequently, the finger pulse wave responses to exercise among the CAD patients were quite heterogeneous. Clinical and exercise parameters did not differ among the CAD patients manifesting vasoconstrictor and vasodilator responders, except for a greater use of ACE inhibitors and the achieved level of metabolic equivalents.
inhibitors and higher achieved peak metabolic equivalents among the vasodilators.

Potential Explanations
Because peripheral cutaneous vascular regions, such as the fingers and toes, are densely innervated by α-adrenergic nerve fibers, local vasoconstrictive responses are characteristic elicted during activation of the sympathetic nervous system. Exercise, however, is a unique stimulus in that heat stress causes central-mediated withdrawal of vasoconstrictor outflow to peripheral vascular beds. Accordingly, the peripheral arteriovenous plexuses increase in size and come closer to the skin surface, thus facilitating heat loss. Of note, α-adrenergic stimulation is still present during exercise, so the peripheral vascular regions are under the influence of competitive stresses during exercise: heat stress (favoring peripheral vasodilation) and α-adrenergic stimulation (favoring peripheral vasoconstriction). Thus, it can be reasoned that any condition that alters this competitive balance in favor of α-adrenergic stimulation might favor the elicitation of a paradoxical increase in cutaneous finger blood flow with exercise. One condition previously shown to alter this competitive balance in favor of peripheral vasoconstriction during exercise is diminished cardiac output, as seen in patients with heart failure. However, because few patients in our study had abnormal left ventricular function at rest or the induction of myocardial ischemia during exercise, other factors must also be operative in mediating abnormal peripheral vascular responses to exercise. The potential role of nitric oxide–mediated vasodilation within peripheral arteries is of particular interest in this regard, because many CAD patients manifest concomitant peripheral endothelial dysfunction. It was previously demonstrated that the effects of circulating catecholamines are enhanced in the presence of peripheral endothelial dysfunction, but it is presently unknown whether nitric oxide helps facilitate the vasodilatory effects of heat stress or retard the vasoconstrictive effects of sympathetic stimulation at the level of cutaneous finger arterioles. The higher use of ACE inhibitors among CAD patients manifesting finger vasodilation is consistent with this possibility given their amelioration of endothelial dysfunction, but many finger vasodilators were also not on ACE inhibitor therapy. Alternatively, consideration could focus on whether central-mediated processes contributed to our findings.

Peripheral PWA and Blood Pressure Changes
Decreases in finger PWA during exercise were not associated with differences in brachial arterial blood pressure responses to exercise, suggesting a dissociation between peripheral finger blood flow responses and more central blood pressure changes. Of note in this regard, a different physiology governs the vascular responses within the forearm and other proximal vascular regions because of the presence of significant muscle mass, β-receptors, and an active cutaneous vasodilator system within these regions, which is not found in cutaneous peripheral regions. By contrast, the arteriovenous anastomoses found in the finger region are absent in these more proximal vascular beds. That these arteriovenous anastomoses govern a unique vascular response is evidenced by findings demonstrating that the progressive increase in arteriovenous anastomoses from hand to proximal finger phalanges and then distal finger phalanx are accompanied by a progressive increase in the magnitude of vasoconstriction to physiological stimuli as well. Consequently, forearm blood flow shows little vascular response to stimuli that produce profound vasoconstriction in the fingers.

Peripheral pulse-wave responses to exercise were not further compared with peripheral arterial blood pressure responses at the finger level in our study, but it has been demonstrated that peripheral arterial blood pressure at the finger level is maintained during exercise among CAD patients. Doupe et al demonstrated that transient reductions in finger blood flow can occur without causing a reduction in peripheral blood pressure in nonexercise settings. Other studies have found that transient decreases in peripheral PWA during anesthesia are not associated with significant effects on peripheral arterial blood pressure, when measured simultaneously. Given that pulse pressure usually increases substantially during exercise, thus inducing an increase in the finger pulse waveform, a selective, sympathetically mediated decrease in regional vascular compliance represents the most likely explanation for those patients manifesting reductions in finger PWA during exercise in our study.

Implications for Exercise Efficiency
Zeles et al previously postulated that sympathetically mediated cutaneous vasoconstriction during exercise inhibits heat loss among patients with congestive heart failure, perhaps explaining the heat intolerance observed in such patients. Our observations further raise the issue of whether CAD patients manifesting peripheral vasoconstriction in the absence of left ventricular dysfunction are also subject to impaired heat loss. Second, given that the achieved metabolic equivalent level was lower among CAD patients manifesting peripheral vasoconstriction, prospective study may be indicated to determine whether such peripheral vasoconstrictors are subject to diminished exercise efficiency.

Limitations
Peripheral arterial tonometry measures pulsatile changes in volume rather than flow. Although previous studies have demonstrated a correspondence between these 2 measures, caution should be exerted in substituting one as a measure for the other. Although the assessment of PWA by peripheral arterial tonometry is relatively free of artifacts when individuals are monitored at rest, the recordings are subject to technical artifact if there is undue patient motion during exercise. These technical artifacts can be readily identified, however, because they generally do not resemble characteristic pulse-waves. Various factors that may have affected finger blood flow responses to exercise were not evaluated in this study, such as the role of baroreflex and chemoreflex function or the presence of autonomic nervous system dysfunction, which may be assessed, in part, by measuring beat-to-beat variations of finger PWA in the frequency domain. In addition, our findings were evaluated in a limited sample of CAD patients, including mostly nonische-
mic patients and those with normal resting left ventricular function. Thus, an evaluation of sicker CAD cohorts would seem to be indicated. In addition, evaluating other factors, such as age, hypertension, and diabetes mellitus, would also be of interest.

Conclusions
Using a newly modified volume plethysmographic device, we discovered that a substantial percentage of CAD patients manifest a progressive diminution in finger blood PWA during exercise. Because normal individuals maintain or increase finger PWA with exercise, these paradoxically vasoconstrictive responses may reflect generalized peripheral vascular pathology secondary to atherosclerosis.

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