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Limb Stress-Rest Perfusion Imaging With Contrast Ultrasound for the Assessment of Peripheral Arterial Disease Severity

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OBJECTIVES We hypothesized that stress-rest perfusion imaging of skeletal muscle in the lower extremity with contrast-enhanced ultrasound (CEU) could evaluate the severity of peripheral arterial disease (PAD).

BACKGROUND Perfusion imaging may provide valuable quantitative information on PAD, particularly in patients with diabetes in whom microvascular functional abnormalities are common.

METHODS Study subjects included 26 control subjects and 39 patients with symptomatic PAD, 19 of whom had type 2 diabetes mellitus. A modified treadmill exercise test was performed to determine exercise time to development of claudication. Multilevel pulse-volume recordings and ankle-brachial index (ABI) at rest and post-exercise ABI were measured in both extremities. Microvascular blood flow in the gastrocnemius and soleus muscles was measured at rest and after 2 min of calibrated plantar-flexion exercise.

RESULTS During exercise, claudication did not occur in normal subjects and occurred earlier in PAD patients with diabetes than without (median time 1.2 min [95% confidence interval (CI) 0.6 to 2.5] vs. 3.0 min [95% CI 2.1 to 6.0], $p < 0.01$). Compared to control subjects, patients with PAD had lower skeletal muscle blood flow during plantar-flexion exercise and lower flow reserve on CEU. After adjusting for diabetes, the only diagnostic tests that predicted severity of disease by claudication threshold were CEU exercise blood flow and flow reserve (odds ratios 0.67 [95% CI 0.51 to 0.88; $p = 0.003$] and 0.64 [95% CI 0.46 to 0.89, $p = 0.008$], respectively). A quasi-likelihood information analysis incorporating all non-invasive diagnostic tests indicated that the best models for predicting severity of disease were the combination of diabetes and either exercise blood flow or flow-reserve on CEU.

CONCLUSIONS Perfusion imaging of limb skeletal during exercise and measurement of absolute flow reserve can provide valuable information on the severity PAD. This strategy may be useful for evaluating the total impact of disease in patients with complex disease or those with coexisting functional abnormalities of flow regulation. (J Am Coll Cardiol Img 2008;1:343–50) © 2008 by the American College of Cardiology Foundation

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Many noninvasive ethods commonly used for diagnosing peripheral arterial disease (PAD) rely on the detection of pressure gradients, such as the ankle-brachial index (ABI) and Doppler-derived flow velocity, or on abnormal pulse volumes caused by stenosis. Although these methods have performed quite well for the detection of moderate-to-severe disease in symptomatic patients, they also have well-recognized limitations. Resting pressure gradients do not develop until inflow vessel stenosis becomes relatively severe (1,2). Current diagnostic methods are also poorly suited to evaluating the impact of diffuse or multilevel disease and the influence of collateral flow. They also provide little information on abnormal microvascular functional responses that can limit flow responses to exercise. A method for evaluating skeletal muscle perfusion and perfusion reserve during exercise would potentially be valuable for quantifying the total impact of the complex pathophysiologic processes in patients with limb ischemia, particularly in those with diabetes in whom distal arterial disease and abnormal microvascular functional responses are common (3,4). Perfusion assessment could also play a valuable role in the development and testing of therapies designed to increase tissue perfusion.

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index
CEU = contrast-enhanced ultrasound
DM = diabetes mellitus
PAD = peripheral arterial disease
PVR = pulse volume recording
VI = video intensity

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Noninvasive imaging techniques that commonly are used to evaluate myocardial perfusion in those with suspected coronary artery disease have not routinely been used in PAD largely because of practical considerations of cost and time. There is also the need for quantitative information because regional heterogeneity in tracer uptake cannot be used for diagnosis. Contrast-enhanced ultrasound (CEU) is a quantitative perfusion imaging technique that has recently been applied to study skeletal muscle flow responses to exercise, hyperinsulinemia, and exogenous growth factor therapy (5–7) and to quantify abnormal microvascular responses in patients with insulin resistance (8). In this study, we hypothesized that stress-rest perfusion imaging of leg skeletal muscle with CEU could be used to detect PAD and evaluate its severity, and would be of particular value in patients with diabetes mellitus (DM).

METHODS

Study population. The study was approved by the Human Investigation Committee. We studied 26 consecutively recruited control subjects and 39 patients with documented PAD, of whom 19 had type 2 DM. All participants gave written informed consent. Control subjects were excluded for a history of coronary artery disease, hypertension moderate or greater in severity (>140/90 mm Hg), dyslipidemia, history of diabetes, or first-degree relatives with diabetes determined on a prestudy evaluation. Control subjects were also excluded if body weight was >10% over ideal. Patients with PAD were enrolled if they had classic symptoms of claudication and a history of at least one abnormal diagnostic test (ABI, pulse volume recording [PVR], Doppler ultrasound, or angiography). Exclusion criteria for PAD subjects were angina, congestive heart failure, ischemic ulcers of the lower extremity, or inability to perform walking exercise. Diabetes mellitus was defined by fasting blood glucose ≥126 mg/dl on 2 or more studies and microangiopathic complications were defined by either recent eye examination (performed within 1 year on all patients) and/or proteinuria.

Protocol. Blood was drawn in the fasting state and ABI measurement and PVRs were performed for both legs. A modified upright treadmill walking exercise test was performed to determine the time to development of claudication and claudication-limited exercise time. Exercise was performed at a walking speed of 2.0 mph with an initial of grade of 0% that increased by 2% every 3 min (9). Pulmonary oxygen consumption and minute ventilation were measured by a metabolic sensor system (VMax29, SensorMedics; Cardinal Health, Dublin, Ohio). Subjects were instructed to report the onset of claudication for each limb. Exercise was continued for 20 min unless terminated as the result of intolerable claudication or other limiting symptoms. Immediate postexercise ABIs were measured. Subjects underwent stress-rest CEU perfusion imaging of the calf plantar-flexor muscles on a separate day.

ABI and PVR. For ABI measurements, systolic blood pressure of the brachial, dorsalis pedis, and posterior tibialis arteries were measured bilaterally at rest and immediately after treadmill exercise in the supine position (10). For each leg, the lowest calculated ABI from either dorsalis pedis or posterior tibialis was used. Bilateral lower-extremity PVRs were measured in the supine position by pneumoplethysmography (1058-C Vascular Mini-

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