Usefulness of Finger Blood Flow During Exercise as a Marker of Functionally Significant Coronary Heart Disease

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Potentially, the presence of abnormal peripheral vascular function during exercise could identify patients with more functionally severe coronary artery disease (CAD). If so, such patients could be expected to have a greater magnitude of exercise-induced ischemia. To test this hypothesis, we evaluated the degree of correlation between the peripheral pulse volume response to exercise and the magnitude of exercise-induced myocardial hypoperfusion among patients referred for clinical radioisotope imaging.

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We recruited 126 patients (mean age 61 ± 11 years, 112 men [89%]) with known CAD, based on angiography or prior myocardial infarction, referred for exercise myocardial perfusion single-photon emission computed tomography (SPECT) from 4 medical centers (St-Luke's Roosevelt Hospital, New York, New York; Batey Cardiology, Sarasota, Florida; Chaim Sheba and Kaplan Hospitals, Tel Aviv, Israel). No patient had a history of significant valvular disease or cardiomyopathy, prior coronary bypass surgery, or left bundle branch block. Eighty patients (62%) had prior myocardial infarction and 91 (73%) had prior coronary angioplasty. A referent group of 55 patients with a <5% likelihood of CAD (mean age 53 ± 10 years, 28 men [51%]) was also evaluated, identified by Bayesian analysis of age, sex, symptoms, risk factors, and exercise electrocardiographic results.[1] All patients gave informed consent.

Maximal treadmill exercise testing was conducted using the Bruce protocol in a thermoneutral environment (21°C to 22°C) in a fasting state. Patients complied with a request to discontinue taking nitrates for 6 hours, calcium channel blockers for 24 hours, and β blockers for ≥48 hours before symptom-limited exercise.

Myocardial perfusion SPECT imaging was performed using conventional methods. Tomographic images were acquired over a circular 180° arc after injection of either thallium-201 (2.8 to 3.2 mCi at peak exercise) or technetium-99m sestamibi (9 to 10 mCi at rest, 30 to 31 mCi at peak exercise). Transaxial tomograms were reconstructed at a pixel thickness of 6.4 mm using filtered back-projection with a ramp filter. Short-axis tomograms were re-oriented into vertical and horizontal long-axis slices of the heart.

Pulsatile finger pulse volume responses were assessed by peripheral arterial tonometry based on finger plethysmography (Itamar-Medical Inc., Caesaria, Israel), described in detail elsewhere.[2] The device contains 2 finger probes that serve as volume sensors coupled to a constant volume, variable pressure, computer-controlled pneumatic system. A constant near diastolic counter pressure of 70 mm Hg was applied within the probes to prevent venous pooling and retrograde venous blood perturbations. All compartments of the probe were collectively pressurized to the same level.

The exercise electrocardiographic response was considered ischemic if horizontal or downsloping ST-segment depression of ≥1 mm or ≥1.5 mm upsloping ST-segment depression occurred compared with baseline measured 0.08 second after the J point.

Radiotracer uptake was scored for each of 20 myocardial segments (6 segments within 3 groups of short-axis slices and 2 apical long-axis segments) using a 5-point score for reduced uptake: 0 = none; 1 = mild; 2 = moderate; 3 = severe; and 4 = absent. A summed reversibility score (SRS) was calculated as the difference between the sum of the 20-segment perfusion scores at stress minus the sum at rest. Ischemic SPECT responses were classified as mild (SRS = 2 to 5), moderate (SRS = 6 to 11), or severe (SRS >11).

Before data processing, nonperiodic data related to incidental patient motion were removed from the pulse wave tracings by digital signal processing. A computer software program then automatically determined pulse wave amplitude (PWA) values, with the baseline amplitude taken as the average of the PWAs at rest. The average amplitude was then determined for each minute of exercise and expressed as a ratio compared with baseline PWA.

The distribution of pulse wave amplitude and summed reversibility score were normalized using a logarithmic transformation. Continuous variables (mean ± SD) were compared using *t* tests. For comparison of >2 groups, a 1-factor analysis of variance was first performed, and if statistically significant (using $\alpha = 0.05$), paired comparisons were obtained. Categorical variables were compared using Fisher's exact test. Linear regression was applied to the minute-by-minute values for PWA during the exercise

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TABLE 1 Comparison of Clinical Data in Patient Groups			
	CAD Likelihood		
Variables	<5% (n = 55)	100% (n = 126)	p Value (overall test)
Age (yrs)	53 ± 9	60 ± 11	<0.001
Men	28 (51%)	112 (89%)	<0.001
Angina pectoris	6 (10%)	45 (36%)	0.001
Acute myocardial infarction	0	78 (62%)	<0.001
Percutaneous coronary intervention	0	92 (73%)	<0.001
Systemic hypertension	9 (16%)	40 (32%)	0.045
Diabetes mellitus	3 (5%)	17 (14%)	0.129
High cholesterol	21 (38%)	78 (62%)	0.004
Currently smoker	9 (16%)	32 (26%)	0.182
Resting parameters			
Body mass index (kg/m^2)	26.7 ± 4.3	27 ± 3.7	0.735
Rest heart rate (beats/min)	69 ± 10	74 ± 14	0.030
Rest systolic blood pressure (mm Hg)	124 ± 15	132 ± 17	0.001
Rest diastolic blood pressure (mm Hg)	80 ± 9	81 ± 8	0.531
Medication use			
Statins	6 (12%)	44 (35%)	0.001
Angiotensin-converting enzyme inhibitors	2 (4%)	20 (16%)	0.015
Calcium antagonists	2 (4%)	19 (15%)	0.041
β blockers	1 (2%)	50 (40%)	<0.001
Exercise parameters			
Exercise time (min)	9 ± 2	8 ± 2	0.002
Peak metabolic equivalents	12 ± 2	11 ± 3	0.004
Peak heart rate (mm Hg)	159 ± 14	147 ± 13	<0.001
Peak systolic blood pressure (mm Hg)	166 ± 22	172 ± 18	0.116
Peak diastolic blood pressure (mm Hg)	84 ± 8	84 ± 8.6	0.934
Peak mean arterial pressure (mm Hg)	125 ± 14	128 ± 11	0.189
Ischemic electrocardiogram	10 (18%)	10 (31%)	0.101
Exercise chest pain	0	2%	0.554
SPECT			
Ischemic SPECT	0	43%	<0.001
Summed reversibility score	0.5 ± 1.4	4.8 ± 8	<0.001
Number of reversible defects	0.1 ± 0.2	1.6 ± 2.9	<0.001

period to determine the slope for PWA change over the temporal course of exercise. Hierarchical logistic regression models were developed using SPECT ischemia as the dependent variable. The independent variables were added in the following sequence: clinical, then exercise test, and then PWA variables. Receiver-operating characteristic curves were constructed for each model, and the areas under these receiver-operating characteristic curves were compared using the method of Hanley and McNeil[3] to determine the incremental discriminant accuracy at each hierarchical step.

The distribution of clinical and exercise variables in patients with low CAD likelihood and those with known CAD is summarized in Table 1. As expected, the low likelihood patients had a lower frequency of anginal symptoms and better exercise test performance.

Representative PWA responses to exercise are shown in Figure 1. The mean slope of the PWA response during exercise was positive among the low CAD likelihood subjects but negative in the CAD group (11 ± 109 vs −57 ± 167 minutes^{-1}, p = 0.006). Among patients with a low likelihood of CAD, male and female subjects manifested similar values for the mean slope of PWA response during exercise (17 ± 93 vs 5 ± 124 minutes^{-1}, p = 0.73) and the mean PWA ratio at peak exercise (152 ± 76 vs 129 ± 54, p = 0.16), and similar mean heart rates at the time when PWA ratios began to fall below baseline during exercise (143 ± 25 vs 147 ± 28, p = 0.77).

Classification of CAD patients according to terciles of peak exercise PWA response revealed progressively greater exercise SPECT abnormalities with diminishing PWA ratios (Figure 2). Figure 3 shows the individual peak exercise PWA ratios among patients with CAD, grouped according to the presence and magnitude of ischemic SPECT responses. Patients with nonischemic SPECT responses manifested the highest mean PWA and the highest variation in individual PWA values. In contrast, patients with severe ischemic SPECT responses manifested the lowest PWA values and least variation. Among patients with ischemic SPECT, there was a statistically significant correlation between the logarithmically transformed summed reversibility score and the logarithmically transformed PWA ratio (r = −0.37, p <0.001). Among patients grouped by PWA terciles, those with the lowest PWA ratios manifested higher systolic and diastolic blood pressures during exercise, and those with the highest PWA ratios had higher peak heart rates (Table 2).

PWA ratio was the most potent predictor of an ischemic SPECT response to exercise by multivariate analysis (p <0.001). More importantly, hierarchical analysis showed that PWA provided a significant increment of information in addition to that provided by the clinical and exercise data with respect to the prediction of SPECT ischemia (Figure 4).

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As part of its heat regulating role, finger blood flow is highly regulated by the autonomic nervous system,[4,5] making this vascular region highly sensitive to the effect of many physiologic stimuli such as painful or emotional stimuli,[5–9] or the effects of physiologic processes such as sleep apnea and REM sleep.[10,11] In addition, because digital blood flow may be regulated by endothelial factors, such as nitric oxide,[12–14] evaluation of finger blood flow during provocative stress may be of interest among patients with CAD. Our results indicate that a substantial number of patients with CAD have a decrease in finger pulse volume with exercise. In contrast, using a variety of techniques, previous studies have demonstrated that finger blood flow or pulse volume characteristically increases during exercise among normal subjects.[2,4,5]

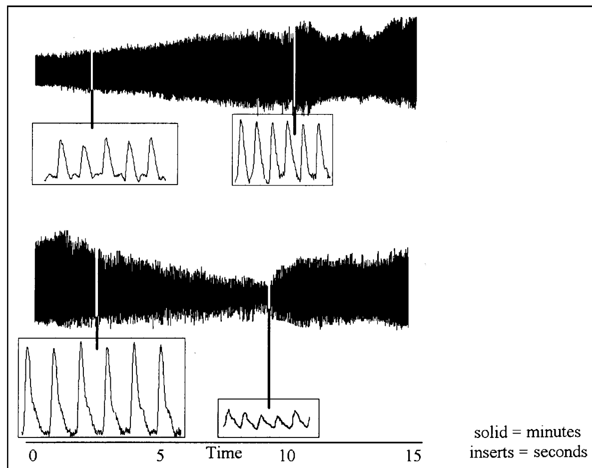

FIGURE 1. Examples of opposing finger PWA responses to exercise stress. *Top,* progressively increasing signal amplitude patterns; *bottom,* a progressively decreasing signal amplitude pattern. *Black images* represent the condensed trend plot for finger PWA amplitude throughout the rest, exercise, and postexercise period on a time scale of minutes (paper speed of 25 mm/s). *Inserts* show samples of the signals near the onset *(left)* and at the peak of exercise *(right)* for both examples. Expanded data are shown on a time scale of seconds (paper speed of 1 mm/s).

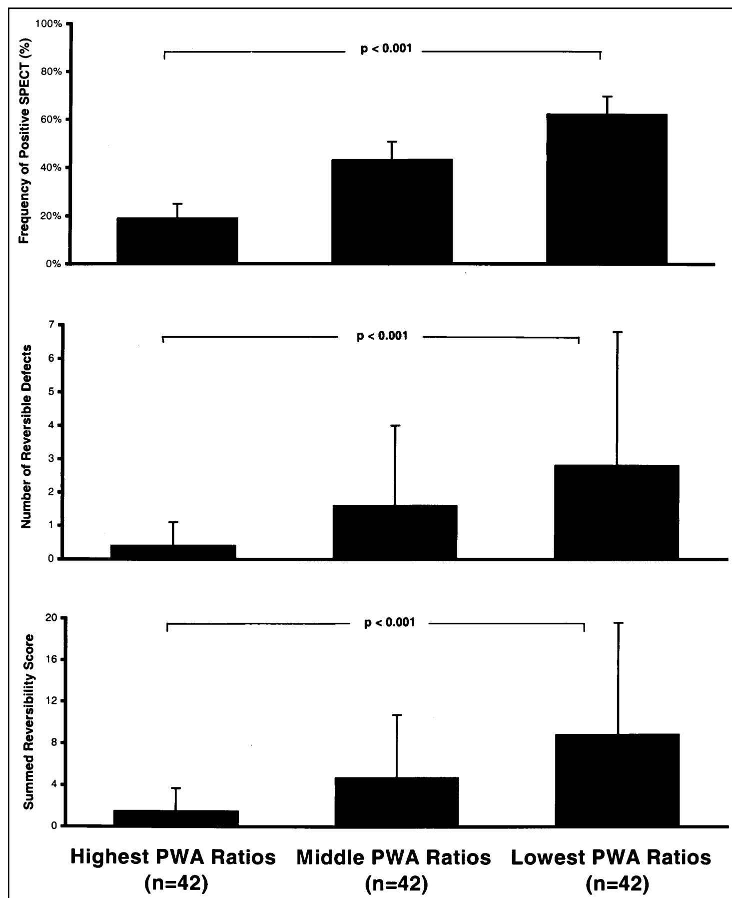

FIGURE 2. Frequency of ischemic perfusion studies *(top)*, mean number of exercise-induced reversible perfusion defects *(middle)*, and summed reversibility scores *(bottom)* during SPECT imaging among patients with CAD, divided by peak exercise PWA values into 3 terciles, highest on the *left* and lowest on the *right.*

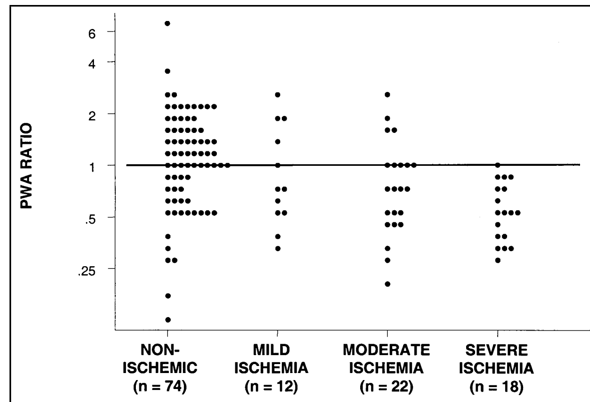

FIGURE 3. Distribution of finger PWA ratios at peak exercise among patients with CAD, divided into nonischemic patients, and those with mild, moderate, and severe ischemia based on the summed SPECT reversibility scores. The mean values for finger PWA decreased progressively among the 4 groups: 130 ± 90, 105 ± 73, 88 ± 50, 53 ± 22 (p <0.001).

Thus, the induction of a decrease in finger pulse volume during exercise among patients with CAD is a paradoxical response, perhaps governed in part by endothelial factors.

Among patients with CAD, those manifesting a reduction in finger PWA during exercise had significantly larger summed SPECT reversibility scores, indicating induction of substantial ischemia. However, finger PWA reduction during exercise also occurred often in the absence of ischemia, indicating that this occurrence is not a specific marker for myocardial ischemia. Nevertheless, there was a graded relation between the magnitude of exercise-induced myocardial hypoperfusion and reduction of finger PWA. Because the magnitude of exercise-induced hypoperfusion is related to cardiac events in an exponential fashion,[15] these results suggest that CAD patients with a decrease in finger pulse volume with exercise may also be at higher risk for cardiac events. However, a prospective study in larger number of patients is needed to assess this possibility as well as to further explore the predictive relation between myocardial ischemia and finger blood flow responses to exercise. In addition, extension of our study to include more diverse patient subgroups such as diabetics and more female patients with CAD would also be of interest.

Finger pulse volume during exercise was the most potent predictor of ischemia on exercise SPECT by multivariate analysis. Even more relevant, however, was its ability to add additional information to that already provided by conventional clinical variables in a stepwise hierarchical analysis.

TABLE 2 Exercise Test Performance Among Patients With CAD Grouped by PWA Ratio

	PWA Ratios			
Variables	Highest (n = 42)	Middle (n = 42)	Lowest (n = 42)	p Value
Exercise time (min)	8 ± 2	8 ± 2	8 ± 2	0.659
Peak metabolic equivalents	11 ± 3	11 ± 3	10 ± 3	0.312
Peak heart rate (beats/min)	151 ± 14	144 ± 18	146 ± 10	0.026
Peak systolic blood pressure (mm Hg)	169 ± 16	168 ± 19	178 ± 20	0.038
Peak diastolic blood pressure (mm Hg)	82 ± 8	83 ± 8	87 ± 9	0.031
Ischemic electrocardiogram	13 (31%)	9 (23%)	16 (38%)	0.391
Exercise chest pain	0	0	3 (7%)	0.106

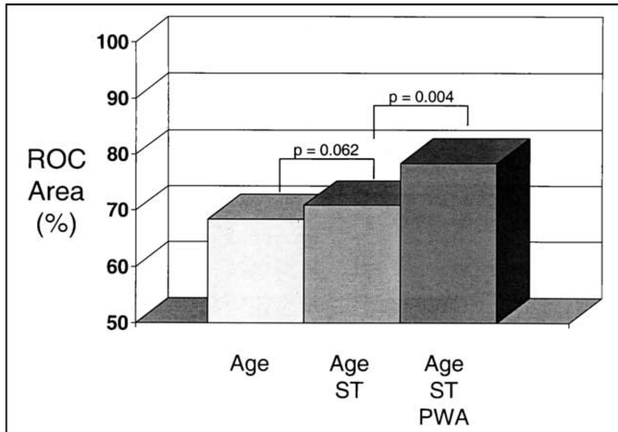

FIGURE 4. Incremental increase in receiver-operating characteristic (ROC) curve area for the prediction of myocardial ischemia (by SPECT) based on a forced hierarchical analysis. Among clinical variables, age was the only significant predictor and was forced into the model first. The exercise ST segment (ST) was then forced in as a second variable. Peak exercise PWA response was then introduced as an additional variable to age and sex, adding significantly to the prediction of myocardial ischemia by receiver-operating characteristic analysis.

In conclusion, patients with CAD often have a paradoxical decrease in finger blood flow during exercise, with the greatest frequency of paradoxical responses concentrated among CAD patients manifesting relatively severe degrees of inducible myocardial hypoperfusion. Among clinical and exercise test variables, the finger blood flow response to exercise was the most potent predictor of exercise-induced myocardial hypoperfusion by multivariate analysis.

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