Assessment of Peripheral Artery Tonometry in the Detection of Treadmill Exercise-Induced Myocardial Ischemia

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OBJECTIVES
We sought to assess the added diagnostic value of peripheral artery tonometric (PAT) measurements, based on finger pulsatile arterial volume changes, to standard 12-lead stress electrocardiography (ECG), for detecting exercise-induced myocardial ischemia, using single-photon emission computed tomography (SPECT) as the standard of comparison in a double-blinded, multicenter protocol.

METHODS
An automated algorithm for identifying myocardial ischemia from PAT was derived from 345 training cases. The PAT outcome was combined with the ECG result (ischemic, nonischemic, or equivocal), giving a PAT-enhanced value. A threshold of normality was determined to optimize agreement with the SPECT results in the training sample. The PAT-enhanced analysis was then validated in 616 subjects, only two of whom had technically unacceptable PAT studies.

RESULTS
In the validation cohort, receiver operating characteristic curve analysis of the PAT-enhanced diagnosis yielded an area under the curve of 0.72, a sensitivity of 63.5%, compared with 44.7% for ECG alone (p < 0.0001), and a specificity of 67.8% common to both ECG and PAT-enhanced diagnoses. Similar results were found in the training sample. Although over 10% of validation subjects had equivocal ECG results, with the aid of PAT, it was possible to provide diagnostic information for all but one subject.

CONCLUSIONS
Peripheral artery tonometry may be useful for improving the diagnosis of exercise-induced myocardial ischemia by both enhancing the sensitivity without impairing the specificity and increasing the percentage of definitive test results.

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Of all currently available noninvasive diagnostic techniques for detecting myocardial ischemia during exercise stress testing, electrocardiography (ECG) is the simplest and most widely used (1). The main limitation of ECG exercise testing is its relatively low accuracy (2). We postulated that an additional channel of physiologic information related to peripheral vascular responsiveness during exercise could supplement standard stress ECG and provide additional diagnostic value for the detection of exercise-induced myocardial ischemia. The basis for this speculation lies in earlier reports that myocardial ischemia induced by balloon inflation during percutaneous transluminal coronary angioplasty of major coronary arteries was found to be associated with increased systemic vascular resistance tightly linked to the induced ischemia (3). Further studies reported that increases in systemic vascular resistance were associated with myocardial ischemia (4,5).

Recent studies utilizing a specially designed device for measuring the peripheral artery tone of the finger—the peripheral artery tonometric (PAT) device, which was originally developed by one of the authors (Dr. Schnall) (6)—indicate that pulsatile blood volume through peripheral regions is subject to intense transient vasoconstriction during clinical events that involve activation of the sympathetic nervous system, such as the arousal phase from sleep apnea (6,7) and during rapid-eye-movement sleep (8).

In light of these findings, it was thought that finger vasomotor changes might provide appropriate hemodynamic information that could be associated with the occurrence of myocardial ischemia in clinically relevant situations.

In a recent study, a high concordance between exercise-induced, PAT-detected peripheral vasoconstriction and single-photon emission computed tomographic (SPECT) evidence of exercise-induced reversible myocardial hypoperfusion has been shown (9). Another study showed a significant difference between the PAT signal patterns of healthy volunteers and patients with documented coronary artery disease, where the latter group showed a higher incidence of vasoconstriction (10).
The goal of this study was to assess the possible additional diagnostic value of finger peripheral artery tone changes using a fully automated algorithmic system in combination with ECG, as compared with ECG alone, for detecting exercise-induced myocardial ischemia.

METHODS

Study population and test conditions. This was a prospective, multicenter study involving a total of 1,053 randomly selected subjects (820 males; mean age 56.2 ± 11 years) who were referred for diagnostic exercise myocardial perfusion SPECT imaging. These tests were independently performed at four medical centers: Sheba Medical Center, Tel Hashomer; Kaplan Medical Center, Rehovot, Israel; St. Luke’s-Roosevelt Medical Center, New York, New York; and Batey Medical Center, Bradenton, Florida. The study was approved by each hospital’s ethics committee. Patients gave informed, written consent after the purpose and nature of the study were explained. Patients with known nonischemic cardiomyopathy, chronic severe pulmonary disease (asthma or chronic obstructive pulmonary disease), or previous coronary artery bypass graft surgery were excluded. Patients on vasoactive drugs were instructed to stop taking calcium channel blockers for 24 h, and beta-blockers for at least 48 h before the test. Patients fasted for 3 h. Tests were performed at four medical centers: Sheba Medical Center, Tel Hashomer; Kaplan Medical Center, Rehovot, Israel; St. Luke’s-Roosevelt Medical Center, New York, New York; and Batey Medical Center, Bradenton, Florida. The study was approved by each hospital’s ethics committee. Patients gave informed, written consent after the purpose and nature of the study were explained. Patients with known nonischemic cardiomyopathy, chronic severe pulmonary disease (asthma or chronic obstructive pulmonary disease), or previous coronary artery bypass graft surgery were excluded. Patients on vasoactive drugs were instructed to stop taking calcium channel blockers for 24 h, and beta-blockers for at least 48 h before the test. Patients fasted for 3 h. Tests were performed at four medical centers: Sheba Medical Center, Tel Hashomer; Kaplan Medical Center, Rehovot, Israel; St. Luke’s-Roosevelt Medical Center, New York, New York; and Batey Medical Center, Bradenton, Florida. The study was approved by each hospital’s ethics committee. Patients gave informed, written consent after the purpose and nature of the study were explained. Patients with known nonischemic cardiomyopathy, chronic severe pulmonary disease (asthma or chronic obstructive pulmonary disease), or previous coronary artery bypass graft surgery were excluded. Patients on vasoactive drugs were instructed to stop taking calcium channel blockers for 24 h, and beta-blockers for at least 48 h before the test. Patients fasted for 3 h. Tests were performed in a thermally controlled environment (21°C to 23°C).

The efficacy analysis involved two stages; in both, the SPECT results served as a gold standard. In the first stage, a random sample of 314 subjects served as the training sample for developing the analysis algorithm. The remaining 708 subjects served as the validation set, 46 of whom were omitted from the analysis because of a nondiagnostic SPECT result. These trends were derived before, during, and after exercise. The SPECT results served as a gold standard. In the first stage, a random sample of 314 subjects served as the training sample for developing the analysis algorithm. The remaining 708 subjects served as the validation set, 46 of whom were omitted from the analysis because of a nondiagnostic SPECT result. These trends were derived before, during, and after exercise. The SPECT results served as a gold standard. In the first stage, a random sample of 314 subjects served as the training sample for developing the analysis algorithm. The remaining 708 subjects served as the validation set, 46 of whom were omitted from the analysis because of a nondiagnostic SPECT result. These trends were derived before, during, and after exercise. The SPECT results served as a gold standard.

The essential features of the PAT device are as follows: 1) a specialized probe and a computer-based system that pneumatically controls the probe and filters (0.3 to 30 Hz) and digitizes and records the PAT signal; 2) a uniform pressure field surrounding the whole of the distal part of the finger, including the finger tip; this facilitates a desirable arterial wall unloading effect, while inhibiting distal venous distention, which can cause veno-arterial-mediated vasoconstriction (11); 3) a proximal extension of the pressure field, which buffers the sensing region at the finger tip from extraneous and artifact signals such as perturbations in the venous system; and 4) an active clamp to the finger, due to the split thimble design. These features are illustrated in Figure 1.

Representative time courses of PAT signals are given in Figure 2. A normal PAT response (upper tracing) typically shows a progressive increase in the signal amplitude, whereas a progressive decrease (lower tracing) is the hallmark of a vasoconstrictive response, typically representing an abnormal PAT response.

PAT signal processing. Processing of the PAT signal involved the removal of noisy signals and the subsequent derivation of trends of pulse wave amplitude (PWA), heart rate, and a reflection coefficient parameter (k), describing wave propagation properties of the signal (12) and, thus, is related to the contractile properties of the arterial bed. These trends were derived before, during, and after exercise. A function of the percent predicted maximal heart rate and

Figure 1. Schematic diagram of the sensor’s structure. The sensor is partitioned into two separate sections that are independently pressurized. The sensor cap has a split thimble design that imparts a two-point clamping effect to lock the sensor to the finger tip while measuring pulsatile volume changes. The adjacent open-ended annular cuff provides a buffering effect against retrograde shock waves, to reduce noise, but is not used for sensing. Both compartments are designed to keep the venous transmural pressure negative to prevent venous pooling and distention and to ensure that only arterial volume changes are recorded.

Extended pressure field

Clamping & sensing region

Region of uniform pressure – finger in probe –

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Myocardial perfusion imaging. The SPECT imaging was performed using conventional methodology with either thallium-201 (3 to 4 mCi) or technetium-99m sestamibi (9 to 10 mCi at rest; 30 to 31 mCi at peak exercise). Standard SPECT myocardial scintigrams were independently assessed using standard techniques (13). Myocardial SPECT results were classified as normal, equivocal, or abnormal (reversible hypoperfusion).

Assessment of exercise stress ECG. The ECG response during stress was considered ischemic if horizontal or downsloping ST-segment depression of ≥1 mm or upsloping ST-segment depression of ≥1.5 mm occurred at 0.08 s after the J point, relative to the baseline ECG. The response was considered equivocal if the ECG demonstrated 1.0 to 1.4 mm of upsloping or 0.5 to 0.9 of horizontal or downsloping ST-segment depression, relative to the baseline ECG.

PAT algorithm and statistical analysis. The objective of the PAT algorithm was to optimize agreement between the combined PAT responses/ECG results and the SPECT results. This was performed using a logistic regression model to generate an overall test value based on the PAT features of the training set signals, and then the ECG outcomes were classified as ischemic, nonischemic, or equivocal. When considered as independent predictors of the SPECT outcome, multivariate analysis showed that the PAT amplitude ratio was the most significant predictive factor, followed by ECG, percent maximal heart rate, and finally the $k_3$ value. A threshold of normality for the PAT-enhanced value was then determined to optimize agreement with the SPECT results in the training sample.

RESULTS

Sensitivity and specificity values and ROC curves at the specific ECG working points. Figure 3 shows the ROC curve for the PAT-enhanced determinations in the 616 validation subjects. The AUC for this sample was 0.72 ($p < 0.0001$). The same AUC value was also obtained for the
The receiver-operating characteristic (ROC) curve for the validation sample of 616 subjects in whom the peripheral arterial tonometer (PAT) outcome was used in combination with the electrocardiograph (ECG) result (PAT enhanced). The area under the curve (AUC) was 0.72. At a specificity value of 67.8%, the sensitivity of the combined PAT and ECG model was 62.4%, compared with 44.7% for ECG alone (p < 0.0001). The specificity value selected represents the specificity value of ECG for this study population. The ROC curve for the validation sample of 616 subjects in whom only the PAT outcome (PAT alone) was used. The AUC was 0.675. At a specificity value of 67.8%, the sensitivity of PAT was 58.4%, compared with 44.7% for ECG alone (p < 0.01).

The reference point marked on the ROC curve represents ECG specificity (67.8%) and allows the different sensitivity values for ECG, the PAT alone value, and the PAT-enhanced value to be compared at matching levels of specificity. At this specificity, ECG gave a sensitivity of 44.7%, whereas the sensitivity for the PAT-enhanced assessment was 63.5% (chi-squared statistic = 44.7, p < 0.0001) and that for PAT alone was 58.4% (chi-squared statistic = 7.67, p < 0.01). The sensitivity of the PAT diagnosis without ECG was not significantly different from the PAT-enhanced diagnosis. The PAT-enhanced ECG assessment increased the sensitivity by over 18%, while maintaining the specificity at a fixed value. When PAT was used alone, it increased the sensitivity by 14%, compared with exercise ECG alone. Very similar values were observed in the training sample, with a specificity of 70.1% and ECG sensitivity was 46.1%, whereas the sensitivity for PAT-enhanced assessment was 65.8% (chi-squared statistic = 13.24, p < 0.0003) and that for PAT alone was 52.6% (p = NS). The sensitivity of the PAT diagnosis without ECG was not significantly different from that of the PAT-enhanced diagnosis. These results are summarized in Table 1.

**Table 1. ECG, PAT Alone, and PAT-Enhanced Sensitivities and Specificities**

<table>
<thead>
<tr>
<th>Population</th>
<th>ECG</th>
<th>PAT Alone</th>
<th>PAT-Enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training groups (n = 290)</td>
<td>Sensitivity (%)</td>
<td>46.1</td>
<td>52.6*</td>
</tr>
<tr>
<td></td>
<td>Specificity (%)</td>
<td>70.1</td>
<td>70.1</td>
</tr>
<tr>
<td>Validation groups (n = 616)</td>
<td>Sensitivity (%)</td>
<td>44.7</td>
<td>58.4*</td>
</tr>
<tr>
<td></td>
<td>Specificity (%)</td>
<td>67.8</td>
<td>67.8</td>
</tr>
</tbody>
</table>

* p < 0.01 vs. ECG. † p < 0.0005 vs. ECG. ‡ p < 0.0001 vs. ECG.

**Sensitivity and specificity of PAT and ECG by demographic and clinical features.** Table 2 summarizes the specificity and sensitivity results when comparing dichotomous groupings of patients based on certain demographic and clinical features of the patient population. None of the comparisons were statistically significantly different, suggesting that the PAT-enhanced diagnosis provided similar results for the opposing sides of each category. The ECG sensitivity and specificity results were also not significantly different in any of these comparisons.

Comparative ECG sensitivity and specificity values show that the diagnostic advantage of PAT-enhanced analysis over ECG alone was consistent throughout the range of clinical and demographic subgroups studied.

**Diagnostic value of PAT versus ECG.** Nondiagnostic or equivocal outcomes of ECG were frequent occurrences in this study, as were SPECT equivocal findings. Overall, 17.5% of the ECG tests failed to provide a definitive diagnosis (10.9% equivocal, 6.5% nondiagnostic), whereas SPECT was equivocal in 6.4% of the subjects, and PAT was nondiagnostic in only 0.3% of the subjects and equivocal in none.

**DISCUSSION**

We assessed the diagnostic value of adding a novel technique, based on the measurement of vasomotor responses of the finger, to standard 12-lead ECG scoring for detecting exercise-induced myocardial ischemia.

**Possible significance of finger vasomotor responses during circulatory adjustments to exercise.** The major peripheral vascular change associated with exercise-induced myocardial ischemia was the degree of vasoconstriction. The mechanism for vasoconstriction during exercise is poorly understood. Previous studies of the interaction between exercise and thermal stress have shown that skin blood flow regulation is affected by both baroregulatory and thermoregulatory homeostatic requirements (14). As the core temperature increases, skin vessels dilate (15). In the face of impaired myocardial contractility due to ischemia, a tendency of peripheral vasoconstriction to increase peripheral resistance is important for maintaining BP, but, however, would result in reduced heat dissipation (14).

The palmar surfaces of the hands and fingers are important sites of thermoregulation (16–18) and may be better
suited for measuring exercise-related vasomotor changes versus generalized systemic vascular changes. Goldberg et al. (19) showed that exercise-induced myocardial ischemia occurs amid an overall reduction in systemic vascular resistance, so it is probable that measuring total peripheral resistance could fail to identify the transition of peripheral vascular tone in the manner demonstrated by finger PAT (9,10). Therefore, it appears that the choice of the peripheral site for vascular tone measurement is crucial to the appropriate determination of myocardial ischemia during exercise.

Other factors affecting finger PWA during exercise. Several other factors can have immediate short-term effects on finger blood flow. These include local finger temperature changes, heating or cooling of the torso, and other large body masses. Because the studies were performed in a temperature-controlled environment, it is unlikely that any of these factors could have played a significant role or have selectively biased the ischemic patients.

Reductions in systemic BP or local finger BP are also improbable causes of finger PWA during exercise, because it was found that during exercise, diastolic BP was generally maintained and systolic BP generally showed large work load-related increases. Thus, the pulse pressure at the more distal finger vasculature was at least maintained if not increased. Because the amplitude of the pulsatile volume change recorded by PAT is a function of both the effective pulse pressure and the local vascular compliance, it is most likely that a reduction in compliance (i.e., vasoconstriction) was the cause of the reduction in the pulsatile volume amplitude.

Clinical implications. Our validated results showed that the PAT device contributed to an approximately 40% increase in diagnostic sensitivity over ECG, with no loss of specificity. This benefit was quite consistent in referred populations with substantially different ECG sensitivity levels (42.6% in Israel vs. 61.9% in the U.S.). It was also consistent among populations with substantially different positive SPECT prevalences (40.7% in Israel vs. 11.0% in the U.S.) and between patients taking cardiac medications (49.8% vs. 21.4%) and those not taking cardiac medications. The PAT-enhanced diagnosis also proved to be very robust, as it was able to provide a diagnosis in virtually all subjects and facilitated the conversion of equivocal ECG results to definitive diagnoses, without impairing the specificity.

In contrast to imaging methods and, to some extent, ECG, the PAT method has two limitations: 1) it is not configured to provide information on the site of coronary pathology, as it does not actually derive information from the myocardium itself; and 2) it currently does not provide an index of the severity of disease. Further studies are required to address these issues. Application of the PAT method would be possible, however, in virtually any clinical exercise stress testing setting, because the analysis is automatic and entirely user-independent, and the device is extremely simple to use.

The very close agreement between ECG sensitivity and specificity values for the training and validation populations shows that the independent findings were consistent, thus lending support to the accuracy of the determined ECG performance relative to thallium SPECT in this study. The

Table 2. Sensitivities and Specificities of Stress ECG and PAT Based on Demographic Data and Clinical Features

<table>
<thead>
<tr>
<th>Site</th>
<th>n</th>
<th>Prevalence of Ischemia on SPECT (%)</th>
<th>PAT-Enhanced Sensitivity (%)</th>
<th>ECG Sensitivity (%)</th>
<th>PAT-Enhanced Specificity (%)</th>
<th>ECG Specificity (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>616</td>
<td>32.1</td>
<td>63.5</td>
<td>44.7</td>
<td>68.0</td>
<td>67.8</td>
<td>NS</td>
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<tr>
<td>U.S.</td>
<td>181</td>
<td>11.0</td>
<td>85.7</td>
<td>61.9</td>
<td>72.0</td>
<td>65.8</td>
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<tr>
<td>Israel</td>
<td>435</td>
<td>40.7</td>
<td>60.8</td>
<td>42.6</td>
<td>65.5</td>
<td>69.0</td>
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<td>Normal</td>
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<td>26.2</td>
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<td>49.4</td>
<td>67.1</td>
<td>67.1</td>
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<tr>
<td>Abnormal</td>
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<td>38.5</td>
<td>64.3</td>
<td>41.1</td>
<td>68.7</td>
<td>68.7</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>497</td>
<td>38.4</td>
<td>63.9</td>
<td>45.5</td>
<td>67.0</td>
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<td>Female</td>
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<td>5.0</td>
<td>50.0</td>
<td>16.7*</td>
<td>70.8</td>
<td>67.3</td>
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<td>Age range (yrs)</td>
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<td>&lt;21–65</td>
<td>481</td>
<td>31.0</td>
<td>61.1</td>
<td>46.3</td>
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<td>69.3</td>
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<td>39.6</td>
<td>72.4</td>
<td>62.1</td>
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<td>Cardiac medications</td>
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<tr>
<td>No</td>
<td>384</td>
<td>21.4</td>
<td>62.2</td>
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<td>232</td>
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<td>Risk factors</td>
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<td>0–1</td>
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<td>41.7</td>
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<td>39.6</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>≤30</td>
<td>492</td>
<td>31.9</td>
<td>61.8</td>
<td>43.9</td>
<td>68.1</td>
<td>67.2</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;30</td>
<td>124</td>
<td>32.2</td>
<td>70.0</td>
<td>47.5</td>
<td>67.9</td>
<td>70.2</td>
<td></td>
</tr>
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</table>

*The female SPECT-positive sample comprises only six cases.

BMI = body mass index; ECG = electrocardiogram; NS = not significant (for both ECG and PAT-enhanced comparisons of sensitivity and specificity); PAT = peripheral artery tonometry; SPECT = single-photon emission computed tomography.
close agreement between PAT-enhanced sensitivity and specificity values for the two independent patient populations in this study demonstrates the robust nature of the measurement.

The relative sensitivity of ECG for the detection myocardial ischemia by SPECT imaging was relatively low in this study; moreover, it varied by nearly 20% between the Israeli and U.S. subpopulations. We have previously noted that “apparent” test accuracy can vary markedly according to the presence and magnitude of various pre-test and post-test referral biases (20,21). The effect of referral bias is also present when evaluating the apparent accuracy of exercise ECG testing in a population referred for stress radionuclide testing, as there is a preferential tendency to refer either ‘‘nondefinitive” or discordant exercise ECG test responders for radionuclide stress testing. Such referral could tend to result in an underestimation of the true sensitivity of exercise ECG relative to SPECT evidence of ischemia. Furthermore, differences in clinical practice in Israel versus the U.S. could serve to accentuate the potential effects of referral bias, although this would require more prospective studies to evaluate it formally. The differences in test sensitivity among male and female subjects that was observed in this study were probably also secondary to the impact of referral bias, as the female population in our study constituted a subgroup in which the prevalence of SPECT ischemia was much lower than that in our male population. The limited number of females with SPECT-positive results in this study further precludes the drawing of firmer conclusions.

Conclusions. In light of: 1) the improved performance of the combined ECG and PAT analysis over ECG alone; 2) the increased yield of definitive outcomes; 3) the robustness of the combined ECG and PAT analysis; and 4) the benign and simple nature of the PAT technique, we believe that this approach may have a useful contributory role in the diagnosis of exercise-induced myocardial ischemia.

Acknowledgment
We thank Barry L. Zaret, MD, from Yale University, for reviewing this manuscript and offering very helpful advice.

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