Clinical Investigations

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Usefulness of Peripheral Arterial Tonometry in the Detection of Mental Stress-Induced Myocardial Ischemia

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ABSTRACT

Background: Mental stress-induced myocardial ischemia (MSIMI) identifies a subset of coronary arterial disease (CAD) patients at increased risk for adverse cardiovascular events. Peripheral arterial vasoconstriction has been consistently reported as an underlying mechanism for ischemia development in this setting and as such affords a unique opportunity for the noninvasive detection of this phenomenon.
Hypothesis: We studied the usefulness of a peripheral arterial tonometry (PAT) technique in the detection of MSIMI. We sought to identify response patterns that would predict the development of MSIMI.
Methods: Participants were 211 patients with documented CAD. Mental stress testing was performed using a public speaking task. Rest-stress myocardial perfusion imaging was the gold standard for ischemia detection. PAT responses were assessed during the 2 phases of the stressful task (stress anticipation and the task performance) and were calculated as a ratio of stress to the resting pulse wave amplitude.
Results: Vascular response during the stress anticipation period (speech preparation) was more pronounced than during the actual speaking task (the mean preparation index was 0.64 ± 0.53; the mean speech index was 0.72 ± 0.60; $P < 0.001$). PAT response during speech preparation had modest accuracy for predicting MSIMI (area under the curve [AUC] was 0.63; 95% confidence interval [CI]: 0.53–0.74, $P = 0.015$). A PAT index of ≤ 0.52 was identified as the best cut off value for detecting MSIMI with a sensitivity of 76% and a specificity of 56%.
Conclusion: We identified a pattern of peripheral arterial response to mental stress that has a relatively modest accuracy in predicting MSIMI. Further research is needed to validate the findings of this study.

Introduction

Mental stress-induced myocardial ischemia (MSIMI) identifies a subset of coronary artery disease (CAD) patients at increased risk for adverse cardiovascular events.[1–8] Arguably, better detection of this phenomenon is expected to improve prognosis and treatment in the CAD population. MSIMI is usually asymptomatic and is rarely associated with the classic electrocardiographic (ECG) findings that define ischemia during exercise or pharmacologic stress testing.[1,8,9] To date, detection of this phenomenon has relied completely on radionuclide imaging which is expensive and requires special expertise and time consuming protocols. Thus any simple and inexpensive technique that could detect or predict ischemia development in this setting could prove to be important.

It has consistently been shown that MSIMI is specifically associated with peripheral arterial vasoconstriction.[9–13] This mechanism affords a unique opportunity for the noninvasive detection of this phenomenon. Peripheral arterial tonometry (PAT) is a noninvasive plethysmographic finger-mounted device that continuously measures the arterial pulse volume in the finger. It has been shown to accurately measure changes in the peripheral arterial blood flow and has diagnostic utility in various clinical conditions characterized by sympathetic nervous system activation and consequent peripheral vasoconstriction.[14–18]

In this study, we examined the usefulness of the PAT technique in the detection of MSIMI among a cohort of CAD patients. We sought to identify a response pattern that would best predict the development of MSIMI.

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Methods

Subjects

Participants in this study were recruited from outpatient clinics affiliated with university based medical centers. Eligibility criteria included age >18 years and a documented clinical diagnosis of CAD supported by: (1) angiographic evidence of >50% stenosis in 1 or more coronary arteries or previous percutaneous intervention or coronary artery bypass graft surgery (2) previous myocardial infarction documented by elevated troponin level in the range typical of infarction, Q-wave abnormalities on electrocardiography, or fixed perfusion abnormalities on nuclear scan, or (3) a positive radionuclide pharmacologic or exercise stress test. Patients were excluded if they had unstable angina or acute myocardial infarction within the 2 months preceding enrollment, had severe comorbid medical problems restricting life-expectancy to less than 5 years, were pregnant, or weighed over 400 pounds.

Study Design

The study protocol was approved by the University of Florida Institutional Review Board. Informed consent was obtained from all participants. Demographic and psychosocial characteristics were obtained prior to study procedures. Mental stress testing was performed after an overnight fast. β-Blockers, calcium-channel blockers, and long acting nitrates were withheld the night before testing. Peripheral arterial response was recorded continuously during the rest, stress, and 10 minutes into the recovery period. Myocardial perfusion imaging was also performed during the same testing session.

Mental Stress Procedure

Patients were initially placed in a temperature controlled (21 °C–23 °C), dark, and quiet room. They were put in a reclined position and rested for 30 minutes while their heart rate (HR) and blood pressure were obtained every 5 minutes using an electrocardiographic monitor and automatic oscillometric device (Dynamap Critikon Inc., Tampa, FL), respectively. Mental stress was then induced via a public speaking task performed in front of a small white-coated audience, as in prior research.[19,20] Participants were given a scenario describing a real life stressful event and asked to make up a realistic story around it. Participants were given 2 minutes to prepare their speech and 3 minutes to speak. They were told that their speech would be videotaped and evaluated later for content, quality, and duration of the speech. Hemodynamic measurements were obtained every minute during the preparation and the speech periods and at 1, 3, 5, and 10 minutes into the recovery period. Systolic blood pressure (SBP) and HR were used to calculate the pressure-rate product (PRP) value (PRP = SBP × HR).

Myocardial Perfusion Imaging

Myocardial perfusion imaging with 99mTc-sestamibi was used. At 1 minute into the speech a total dose of 20–30 mCi (based on patient's body weight) was injected. The timing of the injection was decided on the basis of the published evidence that adrenergic sympathetic response to mental stress usually occurs very quickly within the first minute of starting the stressful task.[9] Stress perfusion images were acquired 30–60 minutes later using photon emission computed tomography (SPECT) conventional methodology.[21] Resting images were obtained within 1 week of the stress test. The studies were interpreted by experienced nuclear cardiologists blinded to the condition (rest vs stress). Rest and stress images were visually compared for number and severity of perfusion defects using a scoring method from 0 to 4; with 0 being normal uptake and 4 no uptake. A summed difference score was calculated as the difference between summed stress and rest scores. Ischemia was defined as new or worsening perfusion defects during mental stress as compared to the resting baseline images with a summed difference score of ≥ 4.

Peripheral Arterial Tonometry Procedure

The PAT device (Itamar-Medical, Caesarea, Israel) was used to continuously measure pulse wave amplitude in the finger during rest and mental stress. The device was applied to the index finger. Attention was paid not to use the same extremity for blood pressure measurements. This device applies a constant pressure of 40–70 mm Hg to eliminate venous stasis and unload arterial wall tension within the finger. The device is connected via thin flexible tubing to an

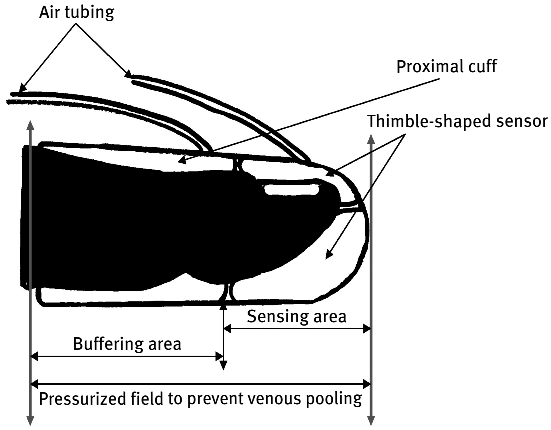

Figure 1. An illustrative diagram of the PAT device. The probe is divided into 2 separate sections that are independently pressurized. The sensing region is thimble shaped and imparts a 2 point clamping effect to hold it in place while measuring pulsatile volume changes. The adjacent annular cuff provides a buffering effect but is not used for measurement. The device is designed to keep the venous transmural pressure negative and prevent venous pooling in the probed part of the finger.

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isolated volume reservoir to buffer pressure changes within the probe. Another volume reservoir not connected to the probe serves as a pressure reference. The distal compartment of the device is connected to a pressure transducer which senses pulsatile fluctuations exerted by blood volume changes in the digital arteries. An illustrative diagram of the device is shown in Figure 1. The pressure changes were fed to a personal computer where the signal was filtered (0.3–30 Hz), amplified, stored, and analyzed. Noise was removed from the tracing by electronic filtering. The baseline pulse wave amplitude was determined by averaging over the last 3.5 minutes of the rest period. Areas that correspond to the preparation and the speech periods were identified in the tracing; average amplitudes were determined for each of the 2 segments by averaging over the corresponding 2 and the 3 minute periods, respectively (see Figure 2). Response during each of the 2 segments (preparation and speech indices, respectively) was then calculated as a ratio to the baseline (stress/rest). Device operation, signal recording, and analysis were done by one operator (DGL). The reproducibility of this measurement was examined in a small number of randomly selected patients (n = 20). Two observers independently analyzed the tracings and repeated the PAT measurements. Their results were almost identical ($r^2 \geq 0.997$, $P<0.001$). Representative PAT signals and the time course of the study are shown in Figure 2.

Statistical Analysis

Results were expressed as means±SD for continuous variables and frequencies and percentages for categorical variables. Stress hemodynamic responses were calculated as the difference between the stress and rest measurements. Statistical differences between groups were determined using a Student *t* test for normally distributed and Mann-Whitney test for non-normal distribution data. Differences between categorical variables were determined using χ^2 analyses. Statistical significance was considered as $P<.05$. Considering radionuclide perfusion imaging as the gold standard for detection of MSIMI, receiver operator characteristic (ROC) curves were constructed for each PAT index using SPSS statistical software (SPSS Inc., Chicago, IL). Coordinate points of the curves were used to identify the best cut off value that predicted ischemia on perfusion imaging.

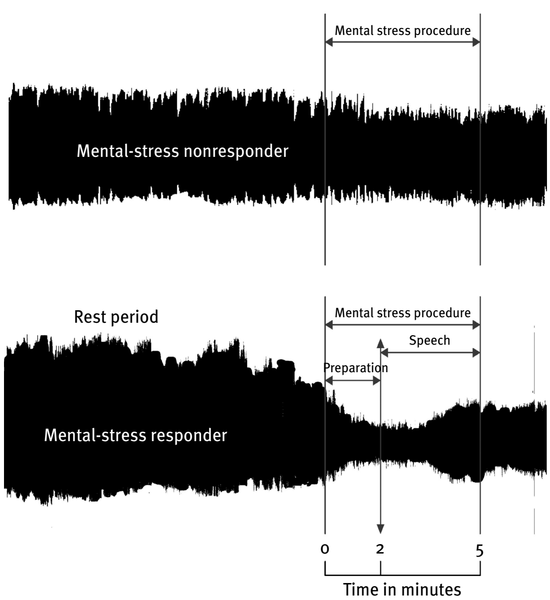

Figure 2. Representative examples of PAT tracings. The top tracing shows a patient with no significant response to mental stress. The bottom tracing shows significant peripheral arterial response to mental stress.

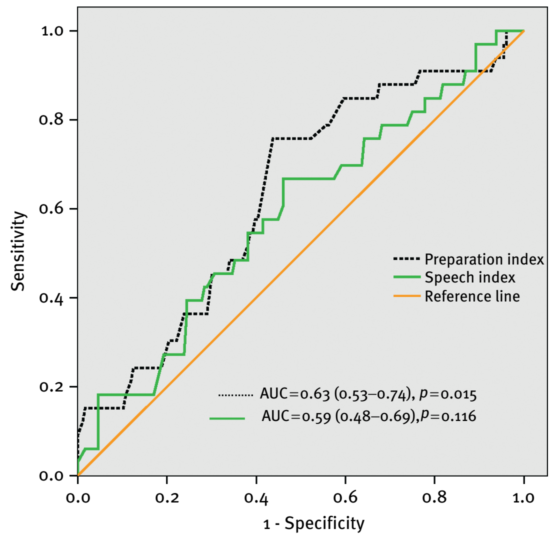

Figure 3. Receiver operator characteristics (ROC) curve with sensitivity and 1-specificity for the 2 PAT indices. The diagonal line is the reference with 50% sensitivity and 50% specificity. The positive actual state for the presence of mental stress-induced myocardial ischemia (MSIMI) was considered as summed difference score >3 on myocardial perfusion imaging. A preparation index of ≤ 0.52 was the best predictive cut off value, identifying patients with MSIMI with a sensitivity of 76% and specificity of 56%. Area under the curves (AUC) with confidence intervals and *P* values are also shown.

Results

Patient Characteristics and Baseline Data

A total of 211 patients were studied, of which 77 (37%) were females. Mean age was 64±9 years. The majority (89%) were white. All participants had CAD. Demographic and clinical characteristics of the study population are described in Table 1.

Hemodynamic Responses to Mental Stress

Mental stress induced significant changes in all hemodynamic variables (SBP, diastolic blood pressure, HR, and PRP, all *P* values<0.001), see Table 2. Comparing responses during the preparation and speech periods, all hemodynamic

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Table 1. Demographic and Clinical Characteristics of Study Population

Variables	Frequency/Mean (n = 211)
Mean age (years)	64±9
Gender (males)	134 (64%)
Ethnicity (white)	186 (89%)
(African American)	13 (6%)
Previous MI	39 (19%)
Abnormal coronary angiogram	138 (65%)
Abnormal exercise or pharmacologic stress test	74 (35%)
Previous CABG	74 (35%)
Previous PCI[a]	91 (43%)
Smoking past or current	147 (70%)
Hypertension	167 (79%)
Diabetes	63 (33%)
History of angina	137 (65%)
Hyperlipidemia	190 (90%)
β-blockers	160 (76%)
ACE inhibitors	110 (52%)
Calcium channel blockers	45 (21%)
Mean resting LVEF[b] (%)	56±14
Mean body mass index	30±6

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Values expressed as either mean±SD or frequency (%).

variables were significantly higher during the speech compared to the preparation period (P <0.001). This is detailed in Table 2.

PAT and Mental Stress-Induced Ischemia

Reduction in pulse wave amplitude during the 2 minute speech preparation period was significantly more pronounced than during the speaking task (P <0.001). This is shown in Table 2. MSIMI occurred in 34 (16%) of the 211 patients. The mean preparation index was significantly lower in patients who developed MSIMI (mean±SD = 0.49±0.34) than in those who did not (mean±SD = 0.66±0.56; P = 0.013). No differences in the speech index were observed between patients with and without MSIMI (P = 0.12). This information is shown in Table 2.

ROC curves were constructed for each of the PAT indices, the preparation index had modest accuracy in predicting MSIMI (AUC of 0.63; 95% CI: 0.53–0.74, P = 0.015). The predictive power of the speech index was not better than chance (AUC of 0.59; 95% CI: 0.48–0.69, P = 0.116). Using coordinate points of the curves the best cut off PAT value for detecting MSIMI was identified as ≤ 0.52. The sensitivity and specificity for this definition were 76% and 56% for the preparation index and 55% and 60% for the speech index, respectively. The 2 ROC curves are shown in Figure 3. Positive and negative predictive values were 25% and 93% for the preparation index and 20% and 87% for speech index, respectively.

Discussion

In this study we examined the peripheral vascular response to mental stress in a cohort of CAD patients using a novel PAT technique. Our findings suggest that arterial vasoconstrictive response to mental stress is more pronounced during the anticipatory stress period than during the actual task performance. This response pattern with an approximately 50% reduction in pulse wave amplitude from rest to stress predicted the development of MSIMI with a sensitivity of 76% and specificity of 56%. This study provides further insight into the mechanisms underlying the development of mental stress-induced ischemia, namely peripheral vascular responses. Additionally the findings of this study have potential practical clinical application by identifying a response pattern that modestly predicts the development of MSIMI.

Peripheral vasculature in the human finger has a unique anatomic feature with a large number of arteriovenous anastomoses innervated by a rich supply of α-adrenergic fibers.[22] This structure is subject to intense transient vasoconstriction during events that involve activation of the sympathetic nervous system.[23] This affords a unique opportunity for assessing the peripheral vascular response to mental stress. Several studies have reported the consistent association between increased peripheral systemic vascular resistance and the development of myocardial ischemia in this setting.[8–10] This mechanism leads to increased pressure-rate product and consequently myocardial blood supply-demand mismatch. The PAT measures changes in the peripheral blood volume and it has diagnostic utility in various clinical conditions characterized by sympathetic nervous system stimulation such as obstructive sleep apnea and exercise-induced myocardial ischemia.[14–17,24]

The accuracy of the PAT technique reported in this study is equivalent to those reported in other studies. Chouraqui et al studied the accuracy of a similar technique in predicting exercise-induced myocardial ischemia.[24] PAT alone had a sensitivity of 58% and a specificity of 68%. When an ECG-PAT enhanced algorithm is used, the sensitivity and specificity improved to 64% and 68%, respectively. This approach was not possible in our study because MSIMI is rarely associated with electrocardiographic changes.

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Table 2. Comparison of Hemodynamic and PAT Responses During the Preparation and the Speech Periods

	Resting Period	Preparation Period	Speech Period	*P* Value
PAT index (all patients)		0.64±0.53	0.72±0.60	<0.001
PAT index by MSIMI groups				
MSIMI (n = 34)		0.49±0.34[a]	0.58±0.40[b]	[a]$P = 0.013$
No Ischemia (n = 177)		0.66±0.56[a]	0.75±0.62[b]	[b]$P = 0.12$
SBP mm Hg	120±18	146±23	162±26	<0.001
DBP mm Hg	65±9	83±12	93±14	<0.001
HR beats/min	61±10	73±14	79±16	<0.001
Pressure-rate product	7264±1609	10642±2814	12943±3641	<0.001

Values expressed as mean±SD.
[a]*P* value for comparing the preparation index between patients with and without MSIMI.
[b]*P* value for comparing the speech index between patients with and without MSIMI.
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; MSIMI, mental stress-induced myocardial ischemia; PAT, peripheral arterial tonometry; SBP, systolic blood pressure.

Our findings in this study indicated that the preparation index is significantly lower than the speech index, suggesting a more profound vasoconstrictive response during the stress anticipation (speech preparation) period compared to the actual speaking task. Additionally we found that this pattern was more predictive of MSIMI compared to the speech response. There is published evidence that stress anticipation may in fact be as or sometimes more stressful than the actual task performance.[25,26] Legault et al studied the time course of hemodynamic and myocardial functional responses during mental stress by means of a radionuclide vest device. They showed that ischemic response to a speech stressor was sudden, starting in the preparation period, and was maintained during the actual speaking task.[27] Other studies have also shown that epinephrine responses to mental stress peak very quickly within 1 minute of starting the stressful task.[13] However, in our study, HR and BP reactivity did not show the same response pattern as the PAT. Both HR and BP responses were higher during the speech compared to the preparation periods, suggesting that PAT measurements are not directly reflective of HR and BP changes. This is not surprising as PAT does not measure pressure; instead it measures peripheral blood volume. Hence changes in peripheral blood volume may not necessarily reflect changes in HR or BP. Another potential reason for this discrepancy is the BP measurement techniques used in this study. Using the traditional sphygmomanometeric brachial BP technique may miss rapid changes that would only be captured by beat-by-beat measurements.

The peripheral arterial tone is maintained by a constant balance of opposing vasodilative and a vasoconstrictive forces.[23] There is evidence that the effect of circulating catecholamines is enhanced in the presence of endothelial dysfunction.[28,29] This response is mediated via reduced nitric oxide activity in the dysfunctional endothelium.[29] Several studies have established the deleterious effects of mental stress on endothelial function.[30] This may potentially explain the underlying vascular mechanisms for MSIMI. Although the PAT technique used in this study does not directly measure endothelial function, it provides a direct assessment of the vascular response to mental stress.

Limitations

The PAT approach described in this article has very low positive predictive value. The negative predictive value was, however, very high at 93%. These findings suggest that the utility of this technique is limited and may only be useful if the test is negative.

Blood flow in the human finger is subject to modulation by several environmental, local, and systemic factors.[22] Although our study attempted to control for some of these factors, for example, performing the study procedures in a temperature-controlled environment, it is possible that other exogenous or local factors may have influenced our results. Patients were asked to withhold their antianginal medications the night before testing. However, some medication effects may have remained during the testing procedures. Also, baseline disease severity was heterogeneous in this population and might have affected our results.

The prevalence of MSIMI in this study was 16%; this is lower than the rates reported in other studies.[1–8] The ischemia detection methods used in those studies were different. While we used perfusion SPECT imaging, most previous studies used radionuclide ventriculography.[1,3,5–9,12,13] We have shown that the detection of MSIMI using SPECT

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imaging has good reproducibility.[31] It is also possible that the lower rate of ischemia observed in this study is due to differences in patients' inclusion criteria. Specifically, our study did not require a positive exercise stress test or a coronary stenosis beyond a certain severity for inclusion, while most of the previous studies did. Additionally, the modest accuracy of the PAT technique in detecting MSIMI among our asymptomatic, low risk population suggests that its accuracy may in fact be higher if tested among high risk CAD patients.

Conclusion

In this study we identified a peripheral arterial response that has a relatively modest accuracy for the detection of MSIMI. Further research is needed to validate the findings of this study in different populations. It is possible that using the PAT technique in conjunction with other signals of ischemia may improve its diagnostic accuracy.

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