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Peripheral Arterial Tonometry: A Diagnostic Method for Detection of Myocardial Ischemia Induced during Mental Stress Tests: A Pilot Study

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Summary

Background: Mental stress testing is considered a reliable method for diagnosing patients with coronary heart disease (CHD) who may be at risk for future events. It has been shown recently that myocardial ischemia induced during mental stress tests is specifically associated with peripheral arterial vasoconstriction.

Hypothesis: The study was undertaken to test the diagnostic capability of peripheral arterial tonometry (PAT) to detect peripheral arterial vasomotor changes.

Methods: We monitored pulsatile finger blood volume changes using a specially designed finger plethysmograph, PAT that can detect peripheral arterial vasomotor changes. Equilibrium radionuclide angiography (ERNA) was simultaneously performed in 18 male patients at rest and during a mental arithmetic stress test with harassment. All patients had previously diagnosed coronary disease and positive exercise tests. Myocardial ischemia was diagnosed by ERNA when global ejection fraction fell ≥ 8% during mental stress or new (or worsened) focal wall motion abnormalities occurred. Peripheral arterial tonometry tracings were considered abnormal when the pulse wave amplitude decreased by ≥ 20% from baseline.

Results: In 18 patients there were 16 usable studies. In eight patients, both ERNA and PAT were abnormal, and in six patients the tests were negative by both methods. In two cases, the results were discordant. Therefore, when considering an abnormal PAT tracing as indicative of mental stress-driven myocardial ischemia, concordance of the two methods was 88%.

Conclusion: The use of PAT may facilitate both clinical testing and research during mental stress.

Key words: mental stress, myocardial ischemia, blood flow, exercise, coronary heart disease, peripheral arterial tonometry, radionuclide ventriculography

Introduction

Mental stress-induced ischemia, which occurs in 30–60% or more of patients with stable coronary artery disease (CAD), is predictive of future cardiac events, including myocardial infarction and death;[1–4] risk ratios for adverse cardiac events associated with mental stress ischemia fall in the range of 2.5–3 Thus, better detection of mental stress-related ischemia should lead to more adequate treatment and improved prognosis in patients with CAD.

Mental stress testing induces both demand- and supply-related myocardial ischemia.[5, 6] However, while the majority of subjects with CAD experience angina and/or ischemic electrocardiogram (ECG) changes during exercise,[7–9] during mental stress testing < 20% of subjects experience either one of these ischemic signals.[10–12] Thus, detection of mental stress-induced ischemia relies almost totally on radionuclide assessment. Unfortunately, conventional radionuclide technology is expensive. Therefore, despite certain advantages of mental stress tests, the subject remains of limited interest except to a few devoted cardiologists and psychologists.

A National Institutes of Health (NIH) task force on behavioral research recently issued recommendations that included the encouragement of new technologies to "identify . . . pathophysiological characteristics of individuals who are predisposed to and at greatest risk of acute behaviorally triggered events."[13] In the pilot study findings reported here, we introduce a method, peripheral arterial tonometry (PAT), that may

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allow mental stress testing to be more widely available in the future, and report its correlation with radionuclide ventriculography. It should be noted that of the authors, JS, RPS, and AC are employees of and have a financial interest in Itamar-Medical, which manufactures the tonometric device used in this experiment.

Goldberg *et al.*[8] reported that ischemia induced during mental stress testing is characterized by a unique and rapid rise in systemic vascular resistance that is also associated with peripheral arterial vasoconstriction.[14] In addition, Grote *et al.* firmly established an association between PAT changes and sympathetic output by demonstrating that PAT measures correlated with norepinephrine release.[15] Because of these observations linking myocardial ischemia with the constriction of the peripheral arterial vasculature, we tested the diagnostic capability of PAT in detecting myocardial ischemia, utilizing equilibrium radionuclide angiography (ERNA) as the standard for ischemia in 18 male patients with stable CAD.

Methods

Eighteen men aged 45–75 years (mean age 61 years), who were in stable clinical condition and who had had positive thallium exercise stress tests in the preceding 12 months, were selected for this study. All subjects had clinical CAD and met Diamond and Forrester's criteria for ≥ 90% post-test probability for CAD.[16] Relevant clinical data are presented in Table I. Beta-blocking agents were discontinued 48 h before and calcium antagonists and long-acting nitrates 24 h before the tests. After signing written consent, the patients were placed in a supine position on the radionuclide test table.

TABLE I Clinical data of study patients

Patient No.	Age	Medication	History of MI	History of angina
1	46	BB	No	Yes
2	75	Nit	Yes	No
3	55	BB, Nit	Yes	No
4	63	BB, Nit, Ca++	Yes	No
5	53	BB, Nit, Ca++	Yes	No
6	65	BB, Nit, Ca++	Yes	Yes
7	67	BB	No	No
8	64	BB	Yes	No
9	74	BB	Yes	No
10	56	None	Yes	No
11	63	BB	Yes	No
12	58	BB, Nit, Ca++	No	Yes
13	60	BB, Nit	Yes	Yes
14	54	BB, Nit	No	Yes
15	74	BB, Nit	No	Yes
16	58	BB, Ca++	No	Yes

Abbreviations: MI = myocardial infarction, BB = beta blocker, Nit = long-acting nitrate, Ca++ = calcium channel blocker.

Peripheral Arterial Tonometry Technique

Peripheral arterial tonometry sensors were mounted on two nonadjacent fingers of the left hand. The most abnormal tracing was utilized for analysis. Each thimble-shaped sensor (patent pending) was connected via two air-conducting tubes to a computer-based main system that controlled and sensed the pressure in the probe[17] (Fig. 1). The probe, which is based on the principle of finger plethysmography, consists of two separate contiguous pneumatic compartments that are inflated with air for maintaining a uniform pressure field of 40–70 mm of mercury around the digit. The distal compartment, which encloses the distal phalanx and fingertip, is connected to a pressure transducer within the main system, which senses pulsatile pressure changes induced by the volume changes of the pulsating digital arteries. In the main system, the signal is amplified and band-pass filtered between 0.3 and 30 Hz. The proximal compartment encompassing the middle phalanx acts as a venous tourniquet to inhibit retrograde venous shock-wave propagation into the distal measurement site.

As a consequence of the constant near diastolic pressure inside the probe, the PAT output reflects the pulsatile oscillations of the digital arterial vasculature. The ability to eliminate venous pooling and to encompass the fingertip under pressure distinguishes the PAT probe from classical digital venous occlusion plethysmographs in which the volume change accompanying venous pooling is, in fact, the monitored parameter.

The PAT response is considered positive for myocardial ischemia when there is sustained reduction of the recorded pulse wave amplitudes (PWA) of > 20% from the premental stress baseline (Fig. 2). This definition of abnormality was based on previous work in which PAT was tested versus thallium single-photon emission computed tomography (SPECT) in exercise stress testing. A receiver operator characteristic (ROC) analysis to optimize sensitivity and specificity set this threshold to a 20% reduction in PWA.[18]

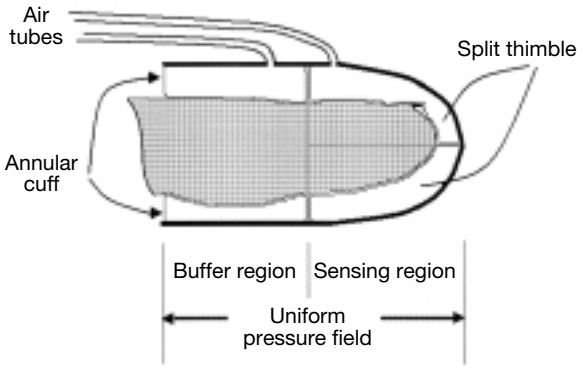

FIG. 1 Cross-sectional view through the volumetric peripheral arterial tonometry finger probe. Note split thimble construction of front part of probe (cap) and independent contiguous annular cuff (annulus). Entire cap region constitutes volumetric sensing region. Air-tubes connect the compartments to a remote control console for signal transduction, processing, and data acquisition.

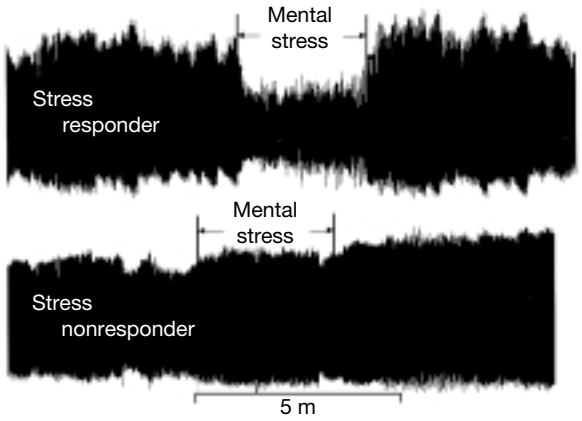

FIG. 2 Time course of peripheral arterial tonometry (PAT) responses during mental stress testing. Top: Example of a positive mental stress responder. Note the sharp sustained reduction in PAT amplitude throughout the entire period of applied mental stress. Upon completion of stress, PAT rapidly reverts to the pre-stress baseline level. Bottom: Example of a mental stress nonresponder. Note the absence of sustained PAT amplitude changes throughout the period of applied mental stress. Slight PAT signal variability appears to be unrelated to the mental stress.

Radionuclide Technique

Red cells were first labeled with sodium pyrophosphate. After patients had been at rest and heart rate and blood pressure had stabilized for at least 15 min, 20 to 30 mCi of 99m technetium pertechnetate were injected. The gamma camera was positioned as close as possible to the patient's chest and approximately in the 45° left anterior oblique view to provide the best septal separation between left and right ventricles. A baseline 12-lead ECG together with an ERNA rest study were obtained. Mental stress was then commenced by asking the patient to perform serial seven subtractions under moderate harassment starting at the number 3,000. The mental stress image commenced at the beginning of the serial subtractions and continued until an adequate radionuclide count density was achieved. The duration of the stress, which was determined by the rate at which the required 4–5 million counts were accumulated, was between 1.5 and 4.5 min. Therefore, the mental stress results represent an average of the response during mental stress. The images were acquired using an SPX4 gamma camera (Elscint, Haifa, Israel) with a low-energy medium sensitivity collimator, set at 140 keV with a 20% window. The data were obtained in a phase mode according to the method reported by Standke *et al.*[19] The computer program calculated a left ventricular and a regional ejection fraction by a fully automated method. Ischemia was defined according to Psychophysiological Investigations of Myocardial Ischemia (PIMI) criteria as a mental stress-associated reduction of ≥ 8% in the global ejection fraction compared with baseline at rest, or as a new or worsening focal wall motion abnormality. Images were interpreted by two experienced observers (DSS, AA) and discrepancies resolved by consensus. Wall motion abnormality was scored on a scale of 0–3 with 0 = normal, 1 = mild abnormality, 2 = moderate, and 3 = severe. Ischemia was diagnosed on the basis of wall motion abnormality only if both observers felt it was at least moderate in severity.

Results

Figure 2 shows a typical PAT tracing. In all 18 cases, PWA recorded by PAT began to change within 4–5 s after the transition from rest to stress.

In 18 patients there were 16 usable studies. Two studies had to be discarded because of excessive artifact (defined as occupying > 5% of the tracing). The ERNA procedure indicated that nine subjects experienced myocardial ischemia during stress: ischemia was diagnosed in four of these subjects on the basis of both worsened wall motion abnormalities compared with rest and a > 8% reduction in ejection fraction during stress, and in the other five solely on the basis of wall motion changes unaccompanied by reduction in ejection fraction. In eight subjects, both the PAT tracing and the ERNA were abnormal, that is, the PAT PWA decreased by > 20% from baseline during mental stress and the ejection fraction during ischemia decreased by ≥ 8%. In six patients, the tests were negative by both methods. In one case, the PAT was negative while ERNA was positive, and in one the PAT was positive while ERNA was negative. Thus, using ERNA results as the standard of reference, there was one false positive and one false negative PAT. Concordance was therefore 88%. Table II shows the ERNA and PAT results for each subject studied.

TABLE II Equilibrium radionuclide angiography and peripheral arteral tomography results for the study subjects

Patient No.	Rest EF	Rest WMA	Stress EF	Stress WMA change	Stress result	ERNA index	PAT result	PAT match
1	58	No	63	No WMA	−	> 1	−	True −
2	31	Yes	25	Worsened	+	0.4	+	True +
3	50	Yes	38	Worsened	+	> 1	−	False −
4	36	Yes	38	Same	−	> 1	−	True −
5	44	Yes	45	Same	−	0.72	+	False +
6	51	Yes	52	Worsened	+	0.57	+	True +
7	68	No	59	New	+	0.37	+	True +
8	39	Yes	20	Worsened	+	0.7	+	True +
9	37	Yes	39	Same	−	0.89	−	True −
10	37	Yes	37	Same	−	> 1	−	True −
11	46	Yes	46	Worsened	+	0.7	+	True +
12	57	No	56	New	+	0.43	+	True +
13	38	Yes	45	Same	−	> 1	−	True −
14	46	No	52	No WMA	−	> 1	−	True −
15	50	No	46	New	+	0.48	+	True +
16	52	No	42	New	+	0.14	+	True +

Abbreviations: EF = left ventricular ejection fraction, WMA = wall motion abnormality, ERNA = equilibrium radionuclide angiography, PAT = peripheral arterial tonometry, + = positive, − = negative.

Discussion

According to Burton[20] and Dorlas and Nijboer,[21] a decrease in PWA in finger plethysmography is diagnostic of peripheral vasoconstriction. Jain *et al.*[14] stated that a major factor responsible for the mental stress-induced fall in left ventricular ejection fraction in their studies was a peripheral vasoconstriction response. In the studies reported by Goldberg *et al.*[8] from the PIMI investigators, a rise in calculated systemic vascular resistance was the single most reliable and most highly correlated physiologic response associated with mental stress ischemia.

The concordance between PAT and ERNA results in this report is 88%, but was calculated according to the PAT threshold that was determined for assessing exercise-induced ischemia and according to the PIMI radionuclide criteria derived from mental stress-induced ischemia. It should be noted that three of the five patients, in whom a true positive finding of mental stress ischemia was based on a change in wall motion abnormality but not on a reduction in ejection fraction, had experienced a previous myocardial infarction. It is possible that in some of these patients a dilatation of an infarct-derived regional scar during stress may have been misinterpreted as a worsening of a wall motion abnormality, in which case the concordance between PAT and ERNA results may be slightly lower than reported.

Recently, perfusion myocardial imaging during mental stress has been reported as a sensitive and reproducible technique for detecting myocardial ischemia associated with mental stress testing.[22] Further work with the PAT device should be undertaken utilizing perfusion imaging since it has been shown to be more reproducible than ERNA testing. Nevertheless, the results reported in this study are very promising and warrant further investigation. Another potential limitation of our work as performed relates to the timing of the measurement. We defined the onset of mental stress as the beginning of the public speaking task. However, previous authors such as Legault *et al.*[11] have monitored the preparation period prior to mental stress by means of a radionuclide vest device and found that, in normal individuals, left ventricular ejection fraction increases during the preparation period, as does pressure–rate product. This seems to indicate that the stressful period may actually begin before the onset of the active task with psychological and physiologic changes that anticipate the stress to come. More work is necessary to better define the protocol that will turn out to be optimal for eliciting and detecting mental stress ischemia.

Previous studies examining catecholamine changes in the peripheral blood during mental stress have revealed very early rises in epinephrine and norepinephrine consistent with rapid changes in sympathetic tone. Becker *et al.*[23] showed that in normal men the blood level of epinephrine was increased by 110% above pretest level at 1 min after onset of mental stress and regressed to only 40% over baseline at the termination of stress 4 min later. Furthermore, norepinephrine also rose 40% from baseline to the first minute of stress.

Mental stress has been reported to produce both increases in heart rate and blood pressure, with a greater and more rapid rise in blood pressure than in heart rate.[5, 6] In some cases, decreases in myocardial oxygen supply due to vasoconstriction occur.[24, 25] Also, blood flow changes secondary to mental stress have been related to an endothelial-mediated mechanism, and recently an endothelin blocker has been shown to reverse the abnormal endothelial function assessed during mental stress.[26] Myocardial ischemia elicited by mental stress testing has been shown to be associated not only with epicardial coronary artery abnormalities, but also with dysfunction of the coronary microcirculation.[27]

Conclusion

Regardless of the mechanism producing ischemia in the individual patient, it is likely that sympathetic stimulation is a common contributing factor and is probably the most important mechanism for alteration in the PWA as measured by the PAT device. This preliminary report of pilot study results showing a high degree of correlation between abnormalities of the PWA measured by the PAT device and radionuclide-measured ischemia is highly promising for the future clinical utility of this new device.

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Images in Cardiology: Persistent Left and Absent Right Superior Vena Cava Documented by Magnetic Resonance Imaging

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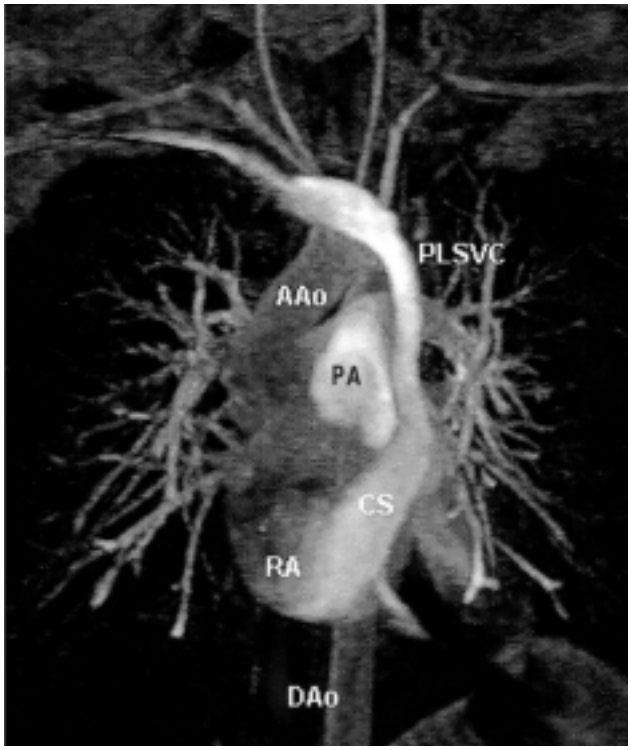

Transthoracic echocardiography of a 52-year-old man who presented with persistent atrial fibrillation revealed dilatation of the coronary sinus suspicious of an anomalous persistent left superior vena cava. Transesophageal echocardiography was contraindicated due to a known large Zenker's diverticulum. Therefore, contrast-enhanced magnetic resonance imaging was performed and the diagnosis of a persistent left superior vena cava leading via the enlarged coronary sinus to the right atrium was confirmed. Persistent left superior vena cava occurs in 2–4% of all congenital cardiac defects but coexisting absent right superior vena cava, as in this case, is rare. Usually, a right superior vena cava is at least rudimentarily detectable.

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FIG. 1 Magnetic resonance imaging in a patient with persistent left and absent right superior vena cava. AAo, ascending aorta; CS, coronary sinus; DAo, descending aorta; PA, pulmonary artery; PLSVC, persistent left superior vena cava; RA, right atrium.