Original Paper

# Vascular Function Measured by Fingertip Thermal Reactivity Is Impaired in Patients With Metabolic Syndrome and Diabetes Mellitus

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*Digital thermal monitoring (DTM) of vascular function has already been shown to correlate well with coronary artery calcium (CAC) score and coronary artery disease. To determine its utility in the metabolic syndrome (MS) and diabetes mellitus (DM), 233 asymptomatic patients with DM/MS but without coronary artery disease underwent DTM during and after 5 minutes of supra-systolic arm cuff inflation, as well as CAC. Post-cuff deflation adjusted temperature rebound (aTR) was lower in MS and DM compared with the normal group. The odds ratio of lowest vs upper 2 tertiles of aTR was 2.3 for MS and 3.5 for DM compared with the normal group, independent of age, sex, and risk factors. The area under the receiver operating characteristic curve to predict CAC ≥100 was 0.69 for metabolic status (DM/MS), 0.79 for aTR, and 0.87 for both. This study demonstrates that vascular dysfunction measured by DTM is associated with DM/MS and could potentially be used to detect asymptomatic individuals with increased subclinical atherosclerosis.* J Clin Hypertens (Greenwich). *2009;11:678–684.* ©*2009 Wiley Periodical, Inc.*

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Vascular function measured by inducing reactive hyperemia is related to atherosclerosis-induced clinical events in a variety of cardiovascular conditions,[1] including established coronary artery disease, multiple risk factors, obesity,[2] metabolic syndrome (MS),[3,4] and diabetes mellitus (DM).[5,6] However, currently available tests for endothelial dysfunction are too difficult, expensive, and variable for routine clinical use.[7] Fingertip digital thermal monitoring (DTM) of vascular function during cuff-occlusive reactive hyperemia is a new noninvasive and operator-independent test that has previously been shown to predict cardiovascular disease.[8] The present study was designed to correlate the extent of vascular dysfunction measured by DTM with the degree of glucose intolerance and with the extent of subclinical atherosclerosis in asymptomatic adults with normal glucose tolerance, MS or DM.

## METHODS

The study population consisted of 233 asymptomatic patients (35 years and older) with normal glucose tolerance, MS, or DM who underwent a coronary artery calcium (CAC) scan. Patients with established cardiovascular disease, diabetic retinopathy, end-stage renal disease, and Reynaud's syndrome were excluded. Body mass index, hip circumference, blood pressure, fasting blood glucose, and lipid profile were obtained by standard techniques. DTM of vascular function was performed at the same visit. Risk factors were determined and Framingham risk estimation was calculated to assess the risk of developing total coronary disease events (angina, myocardial infarction, or cardiovascular death) over the next 10 years.[9] MS was defined by the presence of at least 3 of the following criteria[10]: (1) waist circumference >102 cm (men) and >88 cm (women); (2) serum triglycerides ≥150 mg/dL; (3) high-density lipoprotein cholesterol levels of <40 mg/dL (men) and <50 mg/dL (women); (4) fasting glucose ≥100 mg/dL; or (5) blood pressure of at least 130/85 mm Hg or treated hypertension.

### Digital Thermal Monitoring of Vascular Function

After an overnight fast and abstinence from tobacco, alcohol, caffeine, or vasoactive medications, the patients' blood pressure in the left arm was recorded in a sitting position 15 minutes before the DTM test. After remaining at rest in a supine position in a room with temperature 22 to 24°C for 30 minutes, patients underwent DTM of both hands during 3 minutes stabilization, 5 minutes cuff inflation to 50 mm Hg greater than systolic blood pressure, and 5 minutes deflation. These measurements were obtained using an automated, operator-independent protocol. DTM thermal probes designed to minimize the area of skin-probe contact and fingertip pressure were attached to the pulp of the index finger, and thermal changes were traced continuously and digitalized automatically using a computer-based thermometry system with 0.01°F thermal resolution and an automated compressor for measurement of blood pressure and controlled occlusion hyperemia. The equations for post-occlusive adjusted temperature rebound (aTR) and area under the curve (AUC) are shown in Figure 1. The coefficients of variation of DTM after a 1 day interval measured by Bland-Altman model for the AUC and aTR were 4.8% and 4.5%, respectively.

### Coronary Calcium Scanning

The studies were performed with an E-Speed electron beam scanner. Coronary arteries were imaged with rapid acquisition of 30 to 40 contiguous images of 3-mm slice thickness without gap during end-diastole using electrocardiographic triggering during a single 35 second breath hold. CAC was quantified using the previously described Agatston scoring method.[11]

### Statistical Analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS Institute, Chicago, IL). All continuous data are presented as a mean value ± standard deviation, and all categorical data are reported as a percentage or absolute number. Student *t* tests and chi-square tests were used to assess differences between groups. The association between DTM and metabolic status was analyzed by multivariable logistic regression analyses. The dependent variable, metabolic status, was analyzed as a categorical variable, and trichotomized as normal glucose tolerance, MS or DM. These analyses were adjusted for demographics, age, sex, and conventional cardiovascular risk factors. The results are reported as odds ratios for the logistic regression. SAS 9.13 software (SAS Institute, Inc, Cary, NC) was used to compare significance between different receiver operating characteristic (ROC) curves. The study protocol and consent form were approved by the Institutional Review Board Committee Board of Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA.

## RESULTS

Characteristics of the 233 asymptomatic study participants are shown in Table I. The frequency of hypertension and hypercholesterolemia increased from normal glucose tolerance to MS to DM. In addition, vascular dysfunction (measured by DTM), Framingham risk estimation, and CAC increased with the severity of metabolic status from normal glucose tolerance to MS to DM. There were no significant statistical differences between the normal glucose tolerance, MS, and DM cohorts in sex, smoking status, and family history of premature cardiovascular disease, height, and full lipid profiles.

One-way analysis of variance showed a significant negative linear trend between the mean DTM of vascular reactivity and the number of Adult Treatment Panel III (ATP III) metabolic diagnostic criteria present in each patients (Figure 2). aTR and AUC, DTM indices of vascular reactivity, were significantly reduced from normal glucose tolerance to MS to DM in both sexes (Figure 3) (aTR was not shown in the Figure). To investigate independent

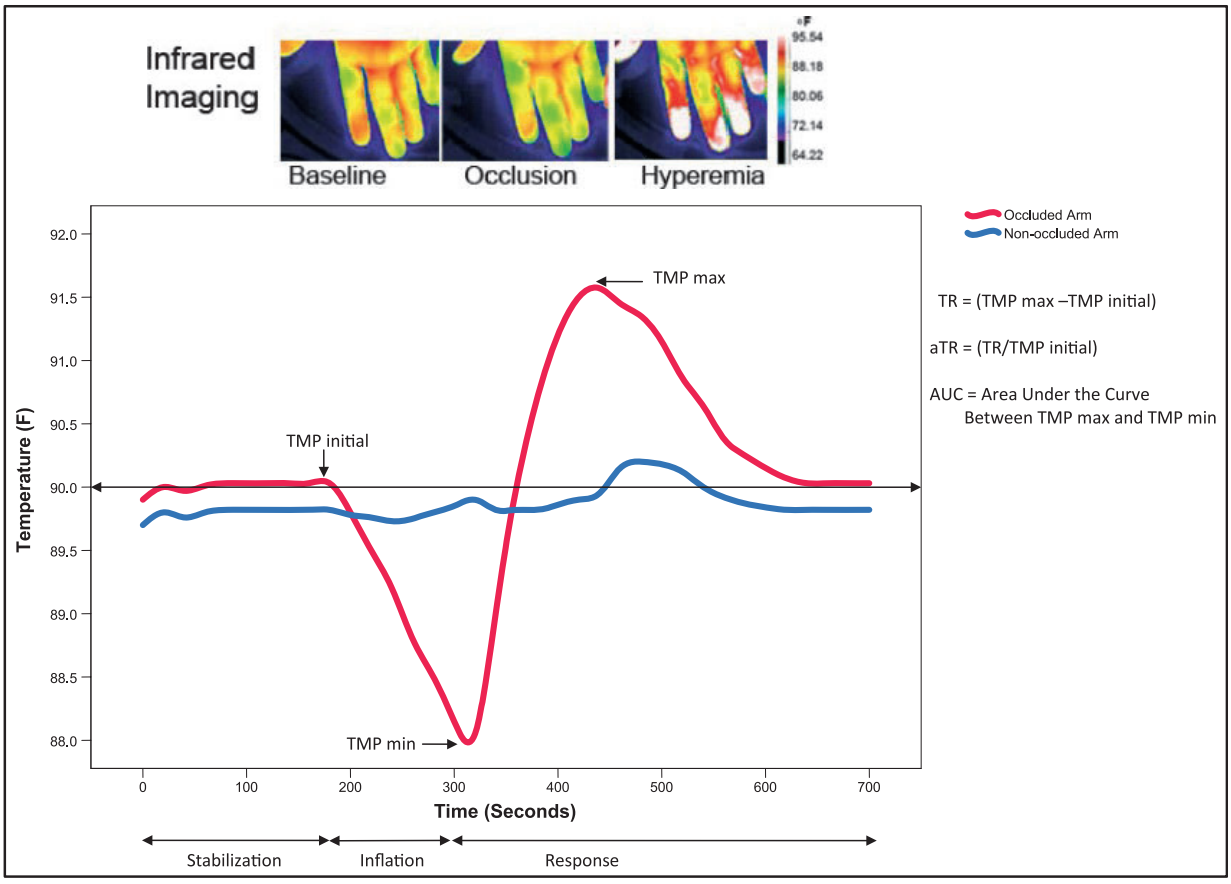


*Figure 1. Skin temperature (TMP) changes during cuff-reactive hyperemia, as shown by infrared imaging and digital thermal monitoring.*

determinants of the severity of metabolic status, stepwise multivariate logistic regression models were produced (Table II). After adjustment for age, sex, and other cardiac risk factors by logistic regression, the odds ratio of the lowest vs 2 upper tertiles of aTR was 2.3 (95% 1.4–4.6, *P*=.03) in MS and 3.5 (95% 1.5–8.4, *P*=.006) in DM as compared with normal glucose tolerance. In addition to aTR being lower in MS and DM compared with normal glucose tolerance patients, it was even more reduced when CAC exceeded 100 in those with MS or DM (Figure 4).

ROC curves were constructed to assess the ability of a combination of clinical and metabolic variables to predict significant CAC. The AUC for the 3 proposed models are summarized in Figure 5. The presence/absence of DM or MS (model I), presence/absence of vascular dysfunction (2 upper tertiles vs lowest tertile of aTR) (model II), and both (model III), added significantly to the AUC (*P*<.0001). In model III, the addition of vascular dysfunction to metabolic status significantly increased the AUC (*P*=.0001) in comparison to model I.

## DISCUSSION

The current study demonstrates that vascular dysfunction measured by DTM increases in proportion to the severity of glucose intolerance in patients with no prior history of coronary artery disease and is closely related to the number of metabolic components of the ATP III criteria Furthermore, ROC curves derived from clinical and metabolic criteria demonstrated that the addition of vascular dysfunction to metabolic status has an incremental value in predicting the burden of coronary atherosclerosis as measured by CAC.

### Vascular Function and Metabolic Status

Vascular function is considered an integral part of the inflammatory-proliferative disease process in response to known cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, and smoking.[12,13] In the MS, atherogenic

**Table I.** Relationship Between Metabolic Status, Cardiovascular Risk Factors, and DTM Variables

| Variables | Normal Glucose Tolerance n=106 | Metabolic Syndrome n=81 | DM n=46 | *P* Value |
|---|---|---|---|---|
| Sex (Male) | 62% (65) | 68% (55) | 52% (24) | .2 |
| Smoking | 33% (35) | 47% (38) | 43% (19) | .1 |
| Hypertension[a] | 37% (39) | 54% (43) | 61% (28) | .003 |
| Antihypertensive medication[a] | 86% (33) | 87% (37) | 73% (20) | .04 |
| Hypercholesterolemia[b] | 52% (55) | 62% (50) | 39% (18) | .03 |
| Lipid-lowering medication[b] | 61% (34) | 72% (36) | 97% (17) | .03 |
| Family history of CHD[c] | 53% (56) | 39%(32) | 46% (21) | .1 |
| Age, y | 55±11 | 60±11 | 62±9 | .001 |
| Height, in | 67.5±4.3 | 67.8±4.3 | 68±4.1 | .8 |
| Weight, lb | 176±20 | 191±16 | 182±17 | .03 |
| BMI, kg/m$^2$ | 27.8±4.3 | 30.1±3.9 | 30.2±4.5 | .003 |
| Waist circumference, in | 36±4 | 40.2±3.1 | 38±3 | .001 |
| Hip circumference, in | 40.1±3 | 42.5±3.8 | 41.3±4 | .003 |
| SBP, mm Hg | 128±10 | 136±9 | 135±8 | .001 |
| DBP, mm Hg | 76±4 | 78±5 | 79±5 | .7 |
| Heart rate, beats per min | 68±4 | 68±4 | 68±5 | .6 |
| Fasting blood sugar, mg/dL | 92±5 | 105±3 | 110±12 | .001 |
| Total cholesterol, mg/dL | 188±27 | 191±22 | 197±24 | .3 |
| HDL-C, mg/dL | 50±10 | 48±8 | 47.8±8 | .4 |
| LDL-C, mg/dL | 111±17 | 112±19 | 117±25 | .6 |
| Triglycerides, mg/dL | 135±17 | 155±20 | 160±22 | .2 |
| CAC score | 94±18 | 221±52 | 407±81 | .0001 |
| 10-Year CHD risk, FRE % | 7.1±3 | 10.8±4 | 14.1±4.6 | .0001 |
| DTM of vascular reactivity in occluded arm | | | | |
| aTR | 2±0.23 | 0.93±0.17 | 0.91±0.2 | .001 |
| AUC | 465±51 | 439±39 | 333±45 | .008 |

Abbreviations: aTR, adjusted temperature rebound; AUC, area under the curve; BMI, body mass index; CAC, coronary artery calcium; CHD, coronary heart disease; DBP, diastolic blood pressure; DM, diabetes mellitus; DTM, digital thermal monitoring; FRE, Framingham (10-year) risk estimation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure. [a]Self-reported diagnosis of hypertension, prescribed antihypertensive medication, or current SBP >140 mm Hg or DBP >90 mm Hg (>130/80 mm Hg if diabetic). [b]Self-reported diagnosis of high cholesterol, prescribed lipid-lowering medication, or current total cholesterol >200 mg/dL. [c]First-degree relative; male <65 years, female <55 years.

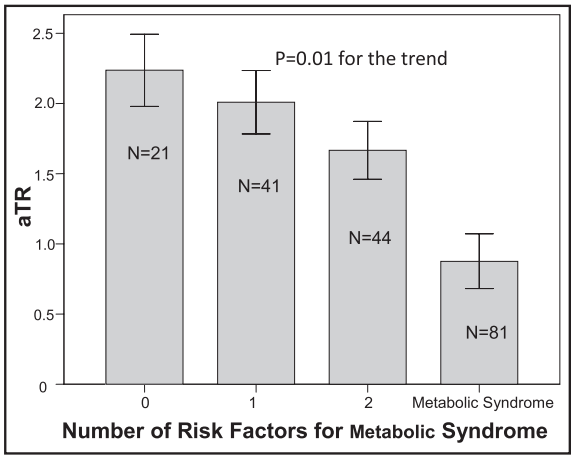


*Figure 2. Adjusted temperature rebound (aTR) (mean ± standard error) in relation to the number of Adult Treatment Panel III (ATP III) diagnostic metabolic criteria present in each patient.*

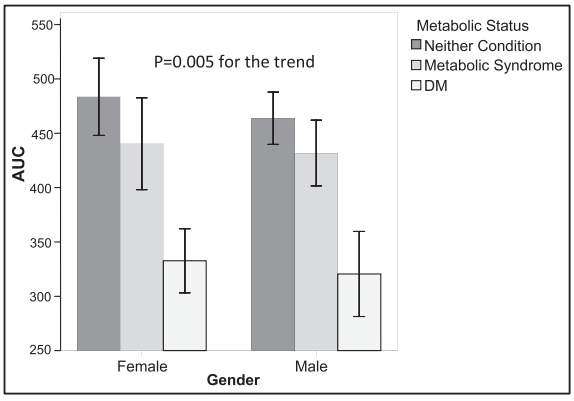


*Figure 3. Area under the curve (AUC) (mean ± standard error) in relation to the severity of metabolic status in both sexes. DM indicates diabetes mellitus.*

**Table II.** Multivariate Logistic Regression Model Demonstrating Increasing Likelihood of Vascular Dysfunction With Increasing Severity of Metabolic Status

| Model | Normal Glucose Tolerance | Metabolic Syndrome | Diabetes Mellitus |
|---|---|---|---|
| Adjusted for age, sex (n=233) | | | |
| Odds of AUC | 1.0 (Referent) | 2.7 (1.2–5.9), *P*=.009 | 3.7 (1.4–9.8), *P*=.007 |
| Odds of aTR | 1.0 (Referent) | 1.9 (1.1–3.8), *P*=.02 | 3.2 (1.2–7.1), *P*=.003 |
| Adjusted for age, sex, hypercholesterolemia, hypertension, cigarette smoking, family history of cardiovascular disease (n=233) | | | |
| Odds of AUC | 1.0 (Referent) | 2.5 (1.1–5.9), *P*=.02 | 4.0 (1.4–11.5), *P*=.01 |
| Odds of aTR | 1.0 (Referent) | 2.3 (1.4–4.6), *P*=.03 | 3.5 (1.5–8.4), *P*=.006 |

Dependent variables: neither condition, metabolic syndrome, and diabetes mellitus. Models: indices of digital thermal monitoring vascular reactivity. Odds of area under the curve (AUC): lowest vs 2 upper tertiles of AUC. Odds of adjusted temperature rebound (aTR): lowest vs 2 upper tertiles of aTR.

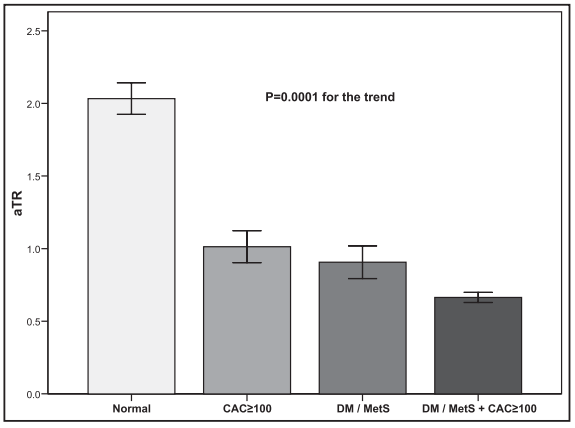


*Figure 4. Adjusted temperature rebound (aTR) (mean ± standard error) in relation to the severity of metabolic status and significant coronary artery calcium (CAC). DM indicates diabetes mellitus; MS, metabolic syndrome.*

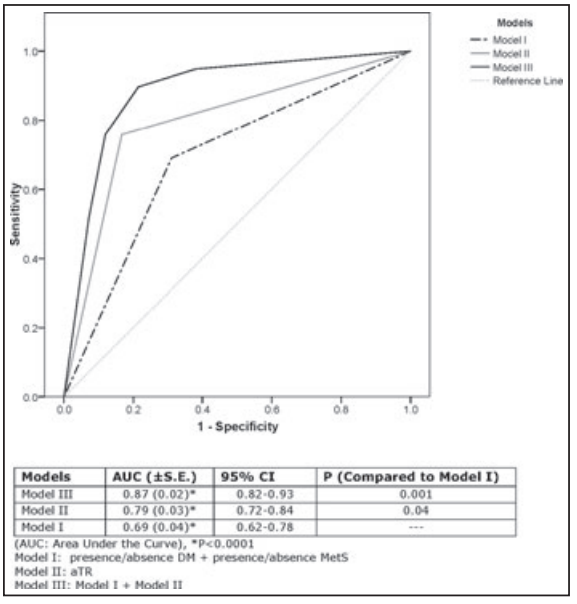


*Figure 5. Receiver operating characteristic curves for 3 models created to assess the ability of a combination of clinical variables to predict significant subclinical coronary atherosclerosis, as measured by coronary artery calcification (CAC ≥100), among asymptomatic individuals. aTR indicates adjusted temperature rebound; CI, confidence interval; DM, diabetes mellitus; MS, metabolic syndrome.*

vascular changes begin prior to the onset of overt diabetes.[14,15] DTM measures both cutaneous microvascular reactivity as well as vascular reactivity in deep tissue that results in increased blood flow to the fingers due to reactive hyperemia. Studies have shown that cutaneous microvascular reactivity may be directly mediated via nitric oxide pathways, and cardiovascular pharmacologic and nonpharmacologic therapies may improve skin microvascular reactivity.[16–27]

O'Neal and colleagues[28] compared intimal-medial thickness and pulse wave conduction velocity in unstenosed arteries of the lower limb in 156 patients with and without type 2 diabetes and showed that they increased with the number of risk factors for MS, as well as DM. In addition, Melikian and colleagues [29] investigated the determinants of vascular function in 100 asymptomatic nondiabetics with and without the MS and found that brachial artery flow-mediated dilation decreased proportionally with the increase of risk factors for MS and DM as well. These results concur with those of the present study, which has additionally demonstrated that the extent of vascular dysfunction is not only dependent on the number of ATP III MS criteria present for each individual but also on the severity of the metabolic status.

**Vascular Function and Subclinical Atherosclerosis**

The volume of CAC is an excellent marker of overall atherosclerotic burden,[30–35] which correlates with both the total plaque burden and the presence of obstructive disease. In addition, there are numerous studies confirming the extraordinary predictive

power of CAC for clinical events in asymptomatic patients.[36,37] The excellent correlation of DTM with CAC in this study as demonstrated by the ROC curves (Figure 5, Table II) confirms the ability of this technology to identify higher risk patients. Moreover, the significantly lower aTR associated with the combination of CAC >100 and MS and DM, adds further to the strength of DTM to discriminate risk, even among those with MS and DM.

## CONCLUSIONS

The current study, demonstrating the correlation of vascular dysfunction measured by DTM with the degree of metabolic disorder and the burden of subclinical atherosclerosis, suggests that DTM may be used to identify patients at higher risk for coronary artery disease.

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