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Original Research Article

Relations between digital thermal monitoring of vascular function, the Framingham risk score, and coronary artery calcium score

Naser Ahmadi, MD[a], Fereshteh Hajsadeghi, MD[a], Khawar Gul, MD[a], Jackson Vane, MS[a], Nudrat Usman, MD[a], Ferdinand Flores, BS[a], Khurram Nasir, MD, MPH[b], Harvey Hecht, MD[c], Morteza Naghavi, MD[b], Matthew Budoff, MD[a]*

[a]Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, 1124 West Carson Street, RB2, Torrance, CA 90502, USA; [b]Society for Heart Attack Prevention and Eradication, Houston, TX, USA and [c]Lenox Hill Hospital, New York, NY, USA

KEYWORDS:
Coronary artery calcium score;
Coronary artery disease;
Digital thermal monitoring;
Framingham risk score

BACKGROUND: Digital thermal monitoring (DTM) of vascular function was shown to correlate with the presence of known coronary artery disease (CAD).

OBJECTIVE: We evaluated whether DTM can identify at-risk, asymptomatic patients with significant coronary artery calcium (CAC) or increased Framingham risk score (FRS).

METHODS: Two hundred thirty-three consecutive asymptomatic subjects (58 ± 11 years; 62% men) without known CAD underwent DTM, CAC, and FRS calculation. DTM measurements were obtained during and after a 5-minute suprasystolic arm-cuff occlusion. After cuff-deflation temperature rebound (TR) and area under the temperature curve (AUC) were measured and correlated with FRS and CAC.

RESULTS: TR was lower in patients with FRS $>$ 20% and CAC $\geq$ 100 as compared with FRS $<$ 10% and CAC $<$ 10, respectively ($P < 0.05$). After adjustment for age, sex, and traditional cardiac risk factors, the odds ratio of the lowest compared with the upper 2 tertiles of TR was 3.96 for FRS $\geq$ 20% and 2.37 for CAC $\geq$ 100 compared with low-risk cohorts. The area under the receiver operating characteristic (ROC) curve to predict CAC $\geq$ 100 increased significantly from 0.66 for FRS to 0.79 for TR to 0.89 for TR + FRS.

CONCLUSIONS: Vascular dysfunction measured by DTM strongly correlates with FRS and CAC independent of age, sex, and traditional cardiac risk factors and was superior to FRS for the prediction of significant CAC.

Introduction

Peripheral vascular dysfunction, assessed noninvasively through reactive hyperemia procedures, is an independent predictor of cardiovascular events.[1–4] Fingertip digital vascular function during cuff-occlusive reactive hyperemia is a

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* Corresponding author.
E-mail address: mbudoff@labiomed.org

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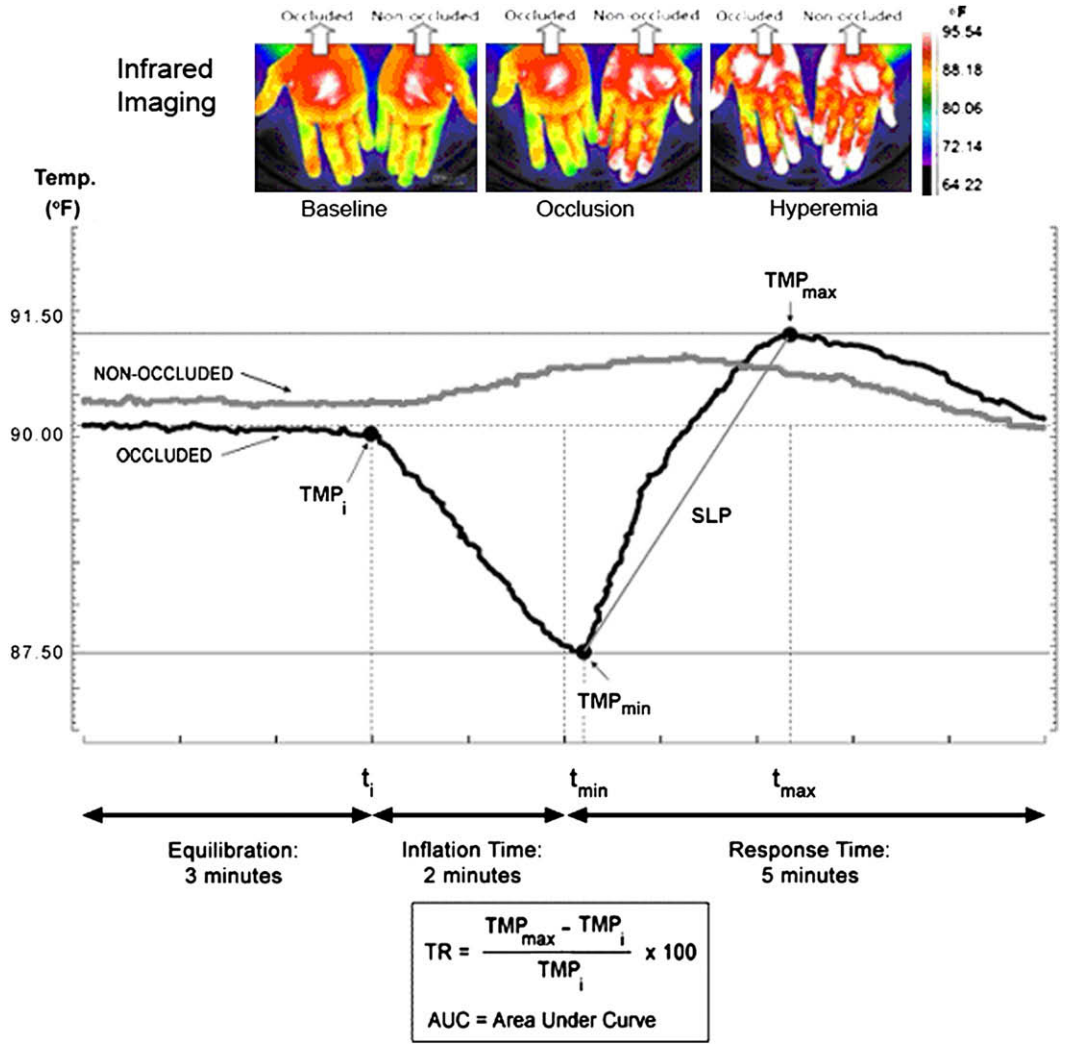

Figure 1 Fingertip skin temperature changes before and during postocclusive reactive hyperemia as shown by infrared imaging and DTM.

new noninvasive and operator-independent test that was previously shown to predict the extent of coronary artery disease (CAD).[5,6] Coronary artery calcification (CAC) is an anatomic disease marker that was correlated with the presence and extent of CAD.[7] The present study was designed to determine the correlation of vascular dysfunction measured by digital thermal monitoring (DTM) with the Framingham risk score (FRS) for 10-year CAD and the extent of subclinical atherosclerosis measured by CAC in asymptomatic adults.

Methods

Subjects and study design

The study population consisted of 233 consecutive asymptomatic patients (age > 35 y) who underwent CAC scanning and DTM. Subjects with established cardiovascular disease, stroke, diabetic retinopathy, end-stage renal disease, Raynaud syndrome, infection, cancer, immunosuppression, systemic inflammation status, or end-stage liver disease 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 FRS was calculated to assess the risk of developing total coronary disease events (angina, myocardial infarction, or cardiovascular death) over the next 10 years.[8]

CAC scanning

CAC was detected using an E-Speed electron beam scanner (GE-Imatron, South San Francisco, CA). The coronary arteries were imaged with 30–40 contiguous 3-mm slices during end-diastole using electrocardiographic (ECG) triggering during a 35-sec breathhold. CAC was considered present in a coronary artery when a density of >130 Hounsfield units (HU) was detected in ≥3

Table 1 Relation between CAC, cardiovascular risk factors, and DTM of vascular function

Variables	CAC < 10 (n = 109)	11 ≤ CAC ≤ 99 (n = 46)	CAC ≥ 100 (n = 78)	*P* value
Sex (male), % (n)	49 (57)	71 (33)	63 (49)	0.001
Current smoker, % (n)	35 (38)	38 (17)	45 (35)	NS
Hypertension†, % (n)	31 (31)	49 (23)	62 (48)	0.0001
Antihypertensive medication†, % (n)	67 (50)	88 (20)	89 (43)	0.0001
Hypercholesterolemia‡, % (n)	46 (46)	56 (26)	57 (44)	NS
Lipid-lowering medication‡, % (n)	50 (47)	80 (21)	85 (37)	0.001
Diabetes mellitus§, % (n)	13 (12)	19 (9)	32 (25)	0.008
Antidiabetic medication§, % (n)	80 (18)	79 (7)	77 (19)	0.006
Family history of CHD‖, % (n)	40 (41)	44 (20)	51 (40)	NS
Age (y), mean ± SD	52 ± 10	57 ± 9	58 ± 9	0.0001
Body mass index (kg/m^2), mean ± SD	26.9 ± 4	28.4 ± 4.8	28.9 ± 5.2	NS
Waist circumference (inch), mean ± SD	35.9 ±3.6	38.4 ±3.5	38.6 ± 3.9	0.004
Hip circumference (inch), mean ± SD	40.28 ±4.6	41.5 ±5	41.5 ± 4	NS
Systolic blood pressure (mm Hg), mean ± SD	131.6±14	132±15	136 ± 16	NS
Diastolic blood pressure (mm Hg), mean ± SD	77 ± 5	75 ± 4	77 ± 4	NS
Heart rate (beats/min), mean ± SD	68 ± 4	68±5	69±5	NS
Fasting blood glucose (mg/dL), mean ± SD	101 ± 7	102 ± 8	106 ± 10	NS
Total cholesterol (mg/dL), mean ± SD	204 ± 44	182 ± 45	190± 55	0.02
HDL-C (mg/dL), mean ± SD	54 ± 20	43 ± 13	51 ± 19	0.02
LDL-C (mg/dL), mean ± SD	119 ± 38.8	106 ± 41	104 ± 38	0.02
Triglycerides (mg/dL), mean ± SD	149 ± 11	164 ± 20	156 ± 13	NS
FRS, mean ± SD	6.9 ± 3.2	9.8 ± 5	11.6 ± 4.5	0.0001
TR, mean ± SD	1.82 ± 0.19	1.43 ± 0.28	1.01 ± 0.23	0.03
AUC, mean ± SD	462 ± 35	432 ± 33	366 ± 21	0.01
	FRS ≤ 10% (n = 143)	10 < FRS < 20% (n = 32)	FRS > 20% (n = 58)	*P* value
TR, mean ± SD	1.7 ± 0.18	1.4 ± 0.3	0.85 ± 0.2	0.04
AUC, mean ± SD	460 ± 37	431 ± 20	384 ± 28	0.04

CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, nonsignificant ($P > 0.05$).

†Self-reported diagnosis of hypertension, prescribed antihypertensive medication, or current systolic blood pressure > 140 mm Hg or diastolic > 90 mm Hg (>130/80 mm Hg if diabetic).

‡Self-reported diagnosis of high cholesterol, prescribed lipid-lowering medication, or current total cholesterol > 200 mg/dL.

§Self-reported diagnosis of diabetes (type 1 or 2) or prescribed antidiabetic agents.

‖First-degree relative; female < 65 y, male < 55 y.

contiguous pixels (>1 mm^2) overlying that coronary artery and quantified.[9]

DMT of vascular function

After an overnight fast and abstinence from tobacco, alcohol, caffeine, and vasoactive medications, the left arm blood pressure was recorded in a sitting position 15 minutes before the DTM test (Omron HEM 705 CP semiautomated sphygmomanometer, Bannockburn, IL). After remaining at rest in a supine position in a room with temperature 22°C to 24°C for 30 minutes, DTM of both hands was obtained during 3 minutes of stabilization, 5 minutes of cuff inflation to 50 mm Hg greater than systolic blood pressure, and 5 minutes of deflation using an automated, operator-independent protocol (VENDYS-5000; Endothelix Inc, Houston, TX). DTM 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 VENDYS software (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 postocclusive temperature rebound (TR) and area under the curve (AUC) are shown in Figure 1.

Intratest variability was assessed in 18 subjects without CAC (age 35 ± 4 y; 74% men) in 2 tests performed 24 hours apart. Day-to-day intrasubject variability was 6.2% for baseline temperature, 8.7% for mean blood pressure, and 11.4% for heart rate. The coefficient of repeatability of TR and AUC were 2.6% and 2.8%, respectively.

Statistical analysis

All statistical analyses were performed with SPSS version 15.0 (SPSS Inc, Chicago, IL). All continuous data

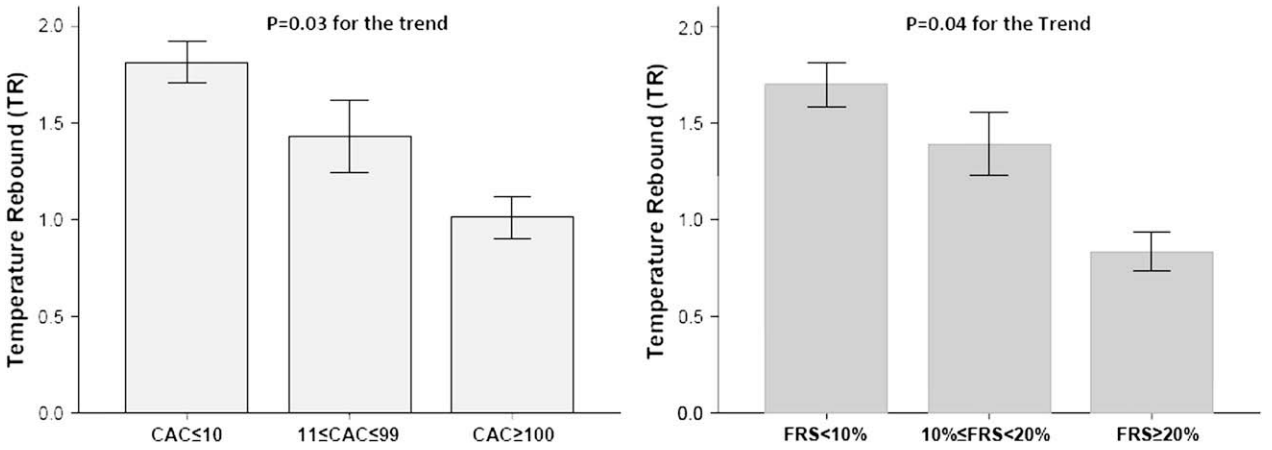

Figure 2 (*Right*) DTM of vascular function decreased proportionally with increasing CAC, and (*left*) DTM of vascular function decreased proportionally with increasing FRS.

are presented as a mean value ± SD, 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 CAC was analyzed by multivariable logistic regression analyses. CAC was classified according to the calcium score groupings of <10, 11–99, and ≥100. These analyses were adjusted for demographics, age, sex, and traditional cardiac risk factors. The results are reported as odds ratios (ORs) for the logistic regression. SAS 9.13 software (SAS Institute, Cary, NC) was used to compare ROC curve areas. The study protocol and consent form were approved by the Institutional Review Board Committee of the Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA.

Results

Characteristics of the 233 asymptomatic study participants are shown in Table 1. The frequency of hypertension, diabetes, and FRS rose with increasing CAC. Significant CAC was more common in men and in older age groups. TR and AUC were significantly and progressively lower among groups of increasing CAC score (Fig. 2 right). Similarly, TR and AUC significantly and progressively worsened as the FRS increased from <10% to 10%–20% to >20% (Fig. 2 left).

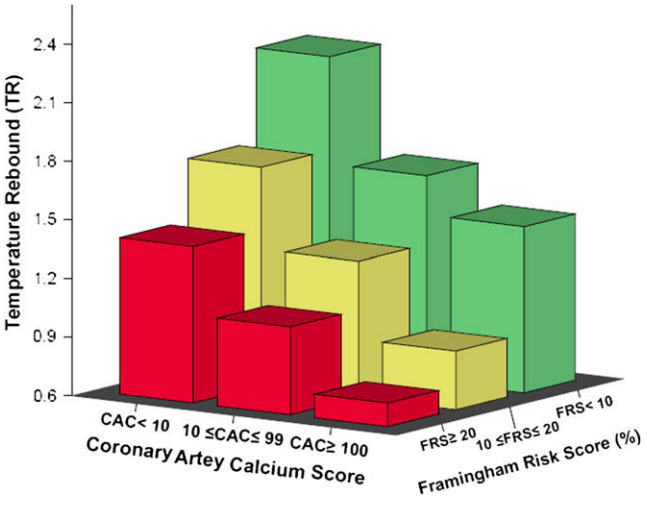

Figure 3 DTM of vascular function is reduced with the increase in FRS and CAC score.

Correlation between FRS, DTM of vascular function, and CAC

The TR was strongly and inversely correlated with the FRS ($r = -.071$, $P = 0.008$) and CAC ($r = -0.81$, $P = 0.004$). TR was lower in each FRS category as the CAC increased; similarly, TR was significantly lower in each CAC category at higher FRS (Fig. 3). The lowest TR was noted in the combination of the highest CAC and FRS groups; however, TR was observed to be lower in the setting of high CAC than increased FRS (Fig. 3).

After adjustment for age, sex, and traditional cardiac risk factors by logistic regression, the OR of the lowest compared with the 2 upper tertiles of TR was 2.37 in CAC ≥ 100 and 3.96 in FRS > 20% compared with CAC < 10 and FRS < 10%, respectively (Tables 2 and 3). The association between decreased TR and significant CAC remained robust even after adjustment for FRS (Table 2). No significant differences were observed between CAC < 10 and 10–99 as well as FRS < 10 and 10–20 in DTM vascular function after adjustment for age, sex, and traditional cardiac risk factors.

ROC curves were constructed to assess the ability of a combination of clinical variables to predict CAC ≥ 100. The AUCs for three proposed models are summarized in Figure 4. The addition of TR was superior to the FRS (AUC ± SD = 0.79 ± 0.03 compared with 0.66 ± 0.04; $P = 0.033$). The addition of TR to FRS significantly improved the AUC compared with FRS alone (AUC ± SD = 0.89 compared with 0.66; $P = 0.0001$) and provided the largest contribution to predict CAC ≥ 100.

Table 2 Association between DTM of vascular function and the extent of CAC

Model	CAC < 10 OR (95% CI)	CAC ≥ 100 OR (95% CI)	*P* value
Adjusted for age, sex (n = 187)			
AUC	1.0 (referent)	5.7 (2.4–13.4),	0.0001
TR	1.0 (referent)	2.53 (1.2–5.4),	0.01
Adjusted for FRS (n = 187)			
AUC	1.0 (referent)	4.68 (2.09–10.32)	0.0001
TR	1.0 (referent)	2.06 (1.1–4.2)	0.01
Adjusted for age, sex, hypercholesterolemia, diabetes, hypertension, obesity, cigarette smoking, family history of CVD (n=187)			
AUC	1.0 (referent)	5.28 (2.18–12.7)	0.0001
TR	1.0 (referent)	2.37 (1.06–5.27)	0.03

CVD, cardiovascular disease. OR for DTM variables determined as lowest tertile compared with upper 2 tertiles (multivariate logistic regression analysis).

Discussion

The current study shows a strong inverse relation between vascular dysfunction measured by DTM and increased cardiovascular risk in asymptomatic patients as determined by FRS and CAC. Furthermore, TR was independently more predictive of CAC ≥ 100 than as FRS, as well as adding significantly to the FRS.

Prior studies

Dorbala et al[10] studied the relation between coronary vasodilator reserve and FRS in subjects without clinical CAD and showed that subjects with intermediate-risk scores (10%–20%) had higher coronary vascular resistance. Witte et al[11] in a meta-regression analysis of 211 articles reported that, in patients with low FRS, each 1% increase in FRS was associated with a decrease in flow-mediated dilation by 1.42% (95% CI, 0.65–2.19); however, flow-mediated dilation was not related to FRS in intermediate and high FRS groups. In contrast, Ijzerman et al[12] studied 46 healthy subjects who underwent postocclusive reactive hyperemia test with laser Doppler flowmetry and showed that skin microvascular dysfunction was associated with increased FRS in both sexes. Ramadan et al[13] showed that decreased brachial flow-mediated vasodilation measured through reactive hyperemia procedure is associated with the degree of CAD. Similarly, Kuvin et al[14] reported that reactive hyperemia peripheral arterial tonometry was inversely correlated with the extent of CAD risk and the presence or absence of CAD.

DTM vascular function

The present study is consistent with the association of cuff occlusion–induced vascular dysfunction with atherosclerosis. However, large variations in intersession flow-

Table 3 Association between DTM of vascular function and the extent of FRS

Model	FRS < 10% OR (95% CI)	FRS > 20% OR (95% CI)	*P* value
Adjusted for age, sex (n=201)			
AUC	1.0 (referent)	2.7 (1.4–7.2)	0.01
TR	1.0 (referent)	4.1 (1.94–10.3)	0.0001
Adjusted for age, sex, hypercholesterolemia, diabetes, hypertension, obesity, family history of CVD (n = 201)			
AUC	1.0 (referent)	2.3 (1.1–4.6)	0.03
TR	1.0 (referent)	3.96 (1.89–8.28)	0.0001

CVD, cardiovascular disease. Odds ratio for DTM variables determined as lowest tertile compared with upper 2 tertiles (multivariate logistic regression analysis).

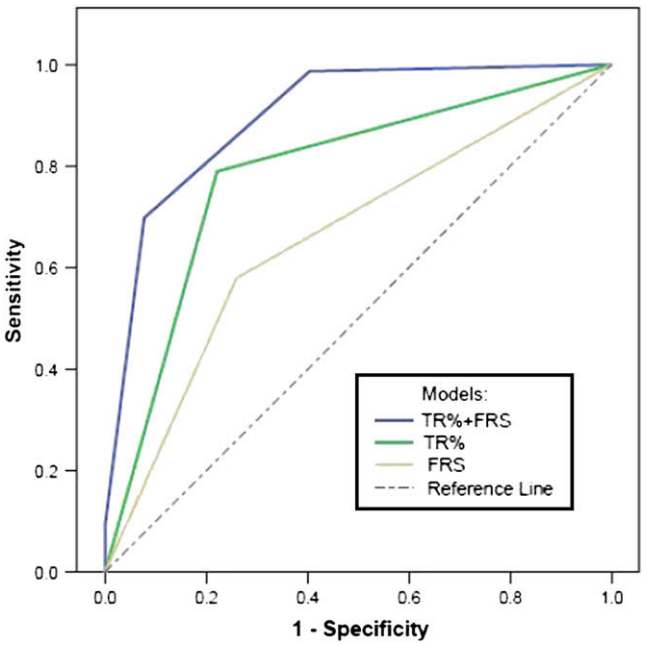

Figure 4 ROC curves for 3 models created to assess the ability of a combination of clinical variables to predict significant subclinical coronary atherosclerosis as measured by CAC ($\geq$100) among asymptomatic patients. AUC ($\pm$SD) for 3 models created to assess the ability of a combination of clinical variables to predict significant subclinical coronary atherosclerosis as measured by CAC ($\geq$100) among asymptomatic patients.

mediated vasodilation responses (range, 1%–84%)[15] and reactive hyperemia peripheral arterial tonometry (14.8%–15.9%)[16,17] severely limit their use in an individual patient. In contrast, DTM, by virtue of its standardized, operator-independent, automated technique, is associated with low coefficients of variation for studies performed 1 day apart (4.8% and 4.5% for AUC and TR, respectively), and thus appears more suitable for clinical use and tracking changes in patients over time.

In the asymptomatic population, FRS and CAC are the acknowledged measurements of cardiovascular risk.[18,19] The excellent correlations between vascular dysfunction measured by DTM and FRS, and, in particular, the superior independent and incremental value of DTM for predicting high CAC, support the potential use of this new technique for risk stratification in the asymptomatic population.

Limitations of the study

The present study has several limitations. Only asymptomatic patients who underwent CAC were included. Our study showed the correlation between DTM of vascular function and CAC. However, additional evaluations, including outcome studies, are needed to evaluate whether measuring DTM of vascular function can provide additive value to predict outcome and could be used as a cost-effective screening test for cardiovascular risk stratification. Given these limitations, our results require large patient population studies in different ethnic groups from other centers for confirmation.

Conclusion

The current study shows the correlation of vascular dysfunction measured by DTM with the increased burden of cardiovascular risk factors as measured by the FRS, and the burden of subclinical atherosclerosis as measured by the CAC score. It also shows that the addition of vascular dysfunction measured by DTM to the FRS provides incremental value to predict high-risk coronary artery calcification. Prospective studies are needed to determine the association between DTM-measured vascular dysfunction and future CHD events, as well as whether treatment directed toward improving vascular function measured by DTM will reduce events.

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