Published in final edited form as:
Vasc Med. 2009 May ; 14(2): 143–148. doi:10.1177/1358863X08098850.

Digital thermal monitoring of vascular function: a novel tool to improve cardiovascular risk assessment

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Abstract

Digital thermal monitoring (DTM) of vascular function during cuff-occlusive reactive hyperemia relies on the premise that changes in fingertip temperature during and after an ischemic stimulus reflect changes in blood flow. To determine its utility in individuals with and without known coronary heart disease (CHD), 133 consecutive individuals (age 54 ± 10 years, 50% male, 19 with known CHD) underwent DTM during and after 2 minutes of supra-systolic arm cuff inflation. Fingertip temperatures of the occluded and non-occluded fingertips were measured simultaneously. Post-cuff deflation temperature rebound (TR) was lower in the CHD patients and in those with an increased Framingham risk score (FRS) compared to the normal group. After adjustment for age, sex, and cardiac risk factors, TR was significantly lower in those with CHD compared to those without CHD ($p < 0.05$). This study demonstrates that vascular dysfunction measured by DTM is associated with CHD and an increased FRS, and could potentially be used to identify high-risk patients.

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Keywords

coronary heart disease; digital thermal monitoring; endothelial function; Framingham risk score; reactive hyperemia; vascular reactivity

Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States.[1] More than half of first coronary events, including sudden cardiac death, occur in asymptomatic individuals, highlighting the importance of detecting individuals at risk prior to an adverse event.[2] Current national guidelines recommend an office-based assessment as the initial step to identify CHD risk including a lipid profile and Framingham 10-year CHD risk estimation.[3] Recent reports have demonstrated that peripherally determined endothelial dysfunction is strongly associated with cardiovascular disease.[4–6] Fingertip digital thermal monitoring (DTM) during cuff-occlusive reactive hyperemia is a new non-invasive method of vascular function assessment based on the premise that changes in fingertip temperature during and after an ischemic stimulus reflect changes in blood flow and endothelial function. The current study investigates the ability of DTM to identify high-risk patients.

Methods

The study population consisted of 133 consecutive individuals (age 54 ± 10 years, 50% male) who underwent DTM during and after 2 minutes of supra-systolic arm cuff inflation. The study protocol and consent form were approved by a local Investigational Review Board (IntegReview Austin, TX, USA). Individuals over 35 years old were eligible to participate. Patients with diabetic retinopathy, peripheral vascular disease, underlying infection, cancer, immunosuppression, and end-stage renal or liver disease were excluded.

Demographics, medical history and medication were recorded. A history of cigarette smoking was considered present if a participant was a current smoker. Weight, height, and blood pressure were determined for each individual. Blood pressure (mmHg) was obtained with a mercury sphygmomanometer in a sitting position after approximately 5 minutes using the auscultatory methods of the American Heart Association protocol. Established CHD was based on a confirmed history of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention or angina. Blood samples were obtained after an overnight fast; total cholesterol (TC) and triglycerides (TG) were determined using standard enzymatic methods. High-density lipoprotein (HDL) cholesterol was measured after precipitation of apo B containing particles with phosphotungstate. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Diabetes was defined as fasting glucose > 126 mg/dl or the use of hypoglycemic medication. The Framingham risk score (FRS) was used to assess the risk of developing total coronary disease events (angina, myocardial infarction or CHD death) over the next 10 years as previously. Diabetes mellitus was classified as high risk (FRS ≥ 20%).[3]

Digital thermal monitoring of vascular function

After an overnight fast and abstinence from tobacco, alcohol, caffeine, or vasoactive medications, the left arm blood pressure was recorded in a sitting position 15 minutes before the DTM test (Omron HEM 705 CP semi-automated sphygmo-manometer; Bannockburn, IL, USA). After resting in a supine position in an ambient temperature of 22–24°C for 30 minutes, DTM of both hands was performed during 3 minutes of stabilization, 2 minutes of cuff inflation to 50 mmHg greater than systolic blood pressure, and 5 minutes of deflation. These measurements were obtained using an automated, operator-independent protocol

(VENDYS-5000; Endothelix Inc., Houston, TX, USA). 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 VENDYS software with a computer-based thermometry system, 0.01°C thermal resolution and an automated compressor for measurement of blood pressure and controlled occlusion hyperemia. The equations for post-occlusive temperature rebound (TR) and nadir to peak (NP), as well as changes in vascular function in both the occluded and non-occluded extremity are shown in Figure 1. The coefficients of variation (CV) of DTM after a 1-day interval measured by the Bland Altman model for NP and TR were 6.4% and 4.5%, respectively. There was a strong correlation between DTM obtained during and after 2-minute and 5-minute arm cuff occlusions (TR: $r = 0.89$, $p = 0.0001$; NP: $r = 0.83$, $p = 0.0001$).

Statistical analysis

Continuous variables are expressed as mean ± SD. Descriptive statistics were used to summarize study participant characteristics. Tests of significance between groups were determined by using Student's *t*-test with the level of significance set at $p < 0.05$ (two-tailed). Chi-squared analysis was used to test for differences between dichotomous variable groups. Multiple linear regression models were used to further examine the relationship of DTM-derived measures with CHD, which were significant in univariate analysis. Two sets of multivariable models were examined in a hierarchical fashion: (1) adjusted for age and sex, (2) adjusted for age, sex, systolic blood pressure, body mass index (BMI), LDL, HDL, TG, diabetes mellitus, smoking, and cholesterol-lowering and blood pressure medications. The results were reported as regression coefficients (representing change in DTM measures) with the presence of reported CHD as measures of effect using the above models. All statistical analyses were performed using STATA (Austin, TX, USA).

Results

A total of 133 individuals (age 54 ± 10 years, 50% male, 25% hypertensive, 14% with a history of CHD, and 44% with a family history of premature CHD) were studied. The mean lipid values were within the NCEP guideline range (Table 1). Demographic and clinical characteristics of the study population according to the presence and absence of CHD are shown in Table 1. The CHD cohort had more men and a more frequent history of smoking, hypertension, hypercholesterolemia, diabetes, family history of premature CHD, and increased FRS. The CHD and non-CHD cohorts were similar in age, BMI, and lipid profile. Neither initial temperature (TMPi) nor temperature fall (TF) was significantly different between these groups ($p > 0.5$). TR was 62% lower among those with CHD compared to those without CHD (0.6 ± 0.9 vs 1.6 ± 1.7, $p = 0.0003$). Post-cuff deflation area under the curve (AUC) and slope of TR at 30, 60, and 90 seconds were studied and found to be similarly correlated with TR and NP among those with CHD as compared to those without CHD (data not shown in the table).

As shown in Table 2, in multivariate analysis after adjustment for age and sex (model 1), DTM of vascular function was lower among those with compared to those without CHD (TR: $p = 0.047$; NP: $p = 0.023$). DTM of vascular function remained significantly lower among those with clinical CHD, after adjustment for cardiac risk factors and medication use (model 2). In addition, the results remained similar after adjustment for FRS (model 3).

In the fully adjusted model (model 2), logistic regression analyses demonstrated odds ratios for CHD of the lowest tertile versus two upper tertiles of 3.05 (95% CI, 1.04–8.94, $p = 0.042$) for TR, and 2.83 (95% CI, 0.92–8.73; $p = 0.070$) for NP. In a sub-analysis, TR decreased with increasing CHD risk from the lowest to highest FRS to the established CHD

(Figure 2). Similar relationships were observed in both sexes. In addition to decreased TR in the occluded arm in the CHD cohort, the post-cuff deflation TR in the non-occluded arm, the contra-lateral fingertip, was lower in the CHD cohort than in the cohort without CHD (0.9 ± 1.2 vs 1.7 ± 1.8, $p = 0.02$). These differences remained significant after adjustment for age and sex (regression coefficient –0.55, $p = 0.03$).

Discussion

The present study demonstrates that fingertip TR as measured by DTM is inversely related to increasing cardiovascular risk independent of age, sex and other cardiac risk factors. Furthermore, vascular reactivity of the non-occluded arm after deflation of the contra-lateral extremity decreased in known CHD compared to the lower risk cohort.

Reactive hyperemia after a period of ischemia is a physiologic response of the vasculature and endothelial system that results in rapid increases in local blood flow and temperature.[7–10] The response to the reactive hyperemia is strongly dependent on the degree of endothelium-derived nitric oxide release following local ischemic stress.[11,12] Recent studies have highlighted that reactive hyperemia in peripheral vessels is attenuated in individuals with coronary vascular dysfunction compared to those with normal vascular function, and may partly explain its association with known CHD.[6] In addition, a recent 1-year follow-up study of 267 patients with peripheral arterial disease revealed an odds ratio for CHD events of 2.7 (95% CI 1.2–5.9, $p = 0.018$) in individuals with reduced versus normal hyperemic flow, independent of age, sex and traditional CHD risk factors.[4]

The current study demonstrated that fingertip TR as measured by DTM decreased in individuals with known CHD, as well as in asymptomatic patients with a worsening CHD risk profile (Figure 2). These findings are consistent with a prior report which demonstrated a linear reduction across FRS quartiles in 46 healthy individuals in endothelium-dependent and -independent vasodilation in skin, as well as delayed recruitment of skin capillaries after arterial occlusion.[13] Similarly, reduced peak dilation after 2 minutes of cuff occlusion was associated with increasing FRS in 842 asymptomatic women[14] and vascular function measured by peripheral arterial tonometery (RHPAT) was lower in individuals with known CHD.[15]

In addition to post-deflation TR in the occluded arm, there was reduced post-deflation TR in the non-occluded arm after deflation of the contra-lateral occluded extremity in patients with established CHD. The exact mechanism is unknown, but the independence of TR decline in the occluded versus non-occluded extremities (Figure 1) suggest a neurovascular response in the non-occluded arm.

Possible study limitations include the 2-minute cuff inflation compared to the traditional 5-minute protocol for vascular function assessment. However, an excellent correlation of DTM indices of vascular function between 2-minute and 5-minute arm cuff occlusions, and also consistent responses during and after the 2-minute and 5-minute cuff occlusion reactive hyperemia test,[16] were demonstrated. In addition, the contribution of inflammatory markers was not evaluated. Despite these potential limitations, significant differences between those with and without known CHD were detected.

In summary, the significant independent inverse relationship between DTM-measured vascular function and CHD risk supports the addition of digital thermal monitoring to existing non-invasive modalities for the assessment of vascular function. Prospective studies are needed to determine the association between DTM-measured vascular dys-function and future CHD events, as well as whether treatment directed towards improving vascular function measured by DTM will reduce events.

Acknowledgments

Craig Jamieson is an employee and major shareholder (> $10,000) of Endothelix. Morteza Naghavi and Khawar Gul are cofounders of Endothelix and major shareholders of the company. Craig Hartley, Ralph Metcalfe, and Harvey Hecht are members of the Endothelix scientific advisory board. Naser Ahmadi, Khurram Nasir and Zhiying Wang are consultants to Endothelix. This study was sponsored by Endothelix Inc.

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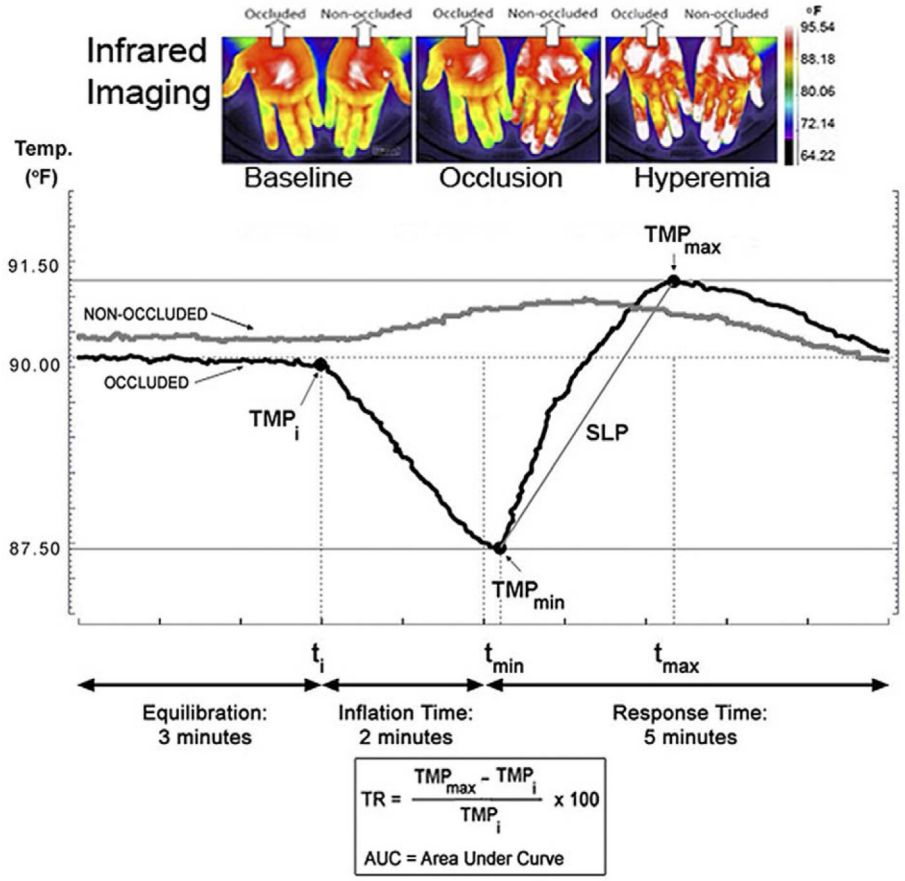
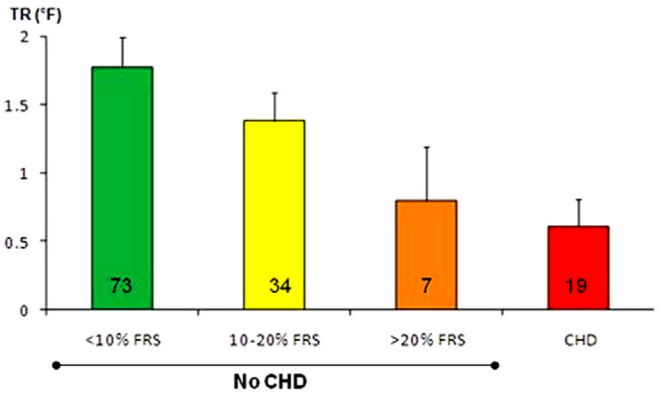


Figure 1.
Skin temperature changes during cuff-reactive hyperemia, as shown by infrared imaging and digital thermal monitoring (DTM). (SLP, slope.)



	<10% FRS	10-20% FRS	>20% FRS	CHD	P value
Temperature Rebound (TR)	1.8	1.4	0.8	0.6	p = 0.002
Nadir to Peak (NP)	4.0	3.5	3.0	2.8	p = 0.01

Figure 2.
Temperature rebound (TR) correlates with the Framingham risk score and coronary heart disease.

Table 1

Demographic characteristics of the study participants

	CHD *n* = 19	No CHD *n* = 114	*p*-value
Age (years)	58 ± 10	53 ± 10	NS
Sex (female)	42	51	NS
Current smoker	10	4	NS
Systolic blood pressure (mmHg)	136 ± 2021	132 ± 19	NS
Diastolic blood pressure (mmHg)	82 ± 12	83 ± 12	NS
Hypertension[a]	53	20	0.002
Hypertension medication	42	17	0.011
Total cholesterol (mg/dl)	227 ± 38	241 ± 44	NS
HDL-C (mg/dl)	57 ± 21	60 ± 18	NS
LDL-C (mg/dl)	142 ± 43	148 ± 43	NS
Triglycerides (mg/dl)	164 ± 77	189 ± 120	NS
Cholesterol-lowering medication	32	10	0.008
Diabetes mellitus[b]	26	8	0.015
Family history of CHD[c]	74	40	0.006
BMI (kg/m^2)	29 ± 5	27 ± 5	NS
Heart rate (beats/minute)	68 ± 11	73 ± 11	NS
Temperature initial (TMPi) (°F)	88.8 ± 6.3	89.8 ± 4.2	NS
Temperature fall (TF) (°F)	2.2 ± 1.1	2.2 ± 1.0	NS
Temperature rebound	0.6 ± 0.9	1.6 ± 1.7	0.0003
Nadir to peak (NP) (°F)	2.8 ± 0.9	3.8 ± 1.6	0.0005

Values presented as mean ± SD or %.

CHD, coronary heart disease (self-reported history of heart attack, coronary bypass grafting, angioplasty or stenting followed by physician reconfirmation); NS, non-significant ($p > 0.05$).

For definitions of other abbreviations, please refer to main text.

[a]Self-reported diagnosis of hypertension, prescribed medication for hypertension, or current blood pressure >140 mmHg systolic or >90 mmHg diastolic (>130/80 mmHg if diabetic).

[b]Self-reported diagnosis of diabetes (type 1 or 2) or prescribed medication for diabetes.

[c]First-degree relative: female <65 years, male <55 years.

Table 2

Relationship between DTM of vascular function and coronary heart disease in adjusted analysis

	No CHD	CHD regression coefficients (95% CI)	*p*-value
TR (temperature rebound)			
Model 1	0 (ref group)	–0.98 (–1.76, –0.20)	0.014
Model 2	0 (ref group)	–1.13 (–2.08, –0.18)	0.020
Model 3	0 (ref group)	–0.91 (–1.73, –0.08)	0.033
NP (nadir to peak)			
Model 1	0 (ref group)	–0.84 (–1.60, –0.08)	0.030
Model 2	0 (ref group)	–1.00 (–1.91, –0.11)	0.029
Model 3	0 (ref group)	–0.79 (–1.58, –0.08)	0.048

Regression coefficients represent mean differences in TR & NP after adjusting for covariates.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, BMI, cigarette smoking status, diabetes, systolic blood pressure, anti-hypertensive medications, LDL, TG, HDL, BP medications and lipid-lowering medications.

Model 3: adjusted for FRS, BP medications and lipid-lowering medications.

For definitions of abbreviations, please refer to main text.