Original Article

Evaluation of Digital Thermal Monitoring as a Tool to Assess Perioperative Vascular Reactivity

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***Aim*: The inflammatory response following tissue injury after major surgery is known to affect endothelial function and vascular reactivity. In this study we evaluated the utility of bedside Digital Thermal Monitoring (DTM) as a surrogate for evaluating vascular function in the postoperative period.**
***Methods*: Ischemia-induced reactive hyperemia variables were measured in sixty patients scheduled for major thoracic surgery using DTM (VENDYS 5000BC; Endothelix, Inc., Houston, TX, USA) at baseline and at 24, 48, 72 hours, and day 5 postoperatively. Furthermore, baseline DTM variables (TR, aTR and AUCTR) and postoperative kinetics of these variables were compared among patients with and without preoperative chemo-radiation and cardiovascular risk factors.**
***Results*: There were no significant differences in the DTM parameters measured at baseline and on each of the studied postoperative days. Compared to the baseline, the lowest measures of all variables were observed 24 hrs postoperatively and the highest measures of all variables were observed at 72 hrs. Patients with abdominal obesity and smoking had lower DTM values than the rest of the study group.**
***Conclusions*: In our study, DTM as measured by the VENDYS 5000BC DTM system (Endothelix, Inc.) did not reveal significant changes in ischemia-induced reactive hyperemia (vascular reactivity) between the baseline and after surgery in the postoperative period. Patients with certain cardiovascular risk factors (abdominal obesity, smoking) had a significant lower DTM signal. Whether this novel non-invasive technique is able to serve as a perioperative diagnostic tool for patients in a clinical setting warrants further study.**

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Key words; Perioperative vascular reactivity, Non-invasive technology, Digital-thermal monitoring, Reactive hyperemia

Introduction

The link between systemic inflammation and acute endothelial dysfunction is increasingly recognized as one of the key factors in the pathogenesis of postoperative cardiovascular complications. Importantly, this acute inflammation and ensuing endothelial dysfunction might be amenable to pharmacologic intervention[1)] if robust, reliable, reproducible and simple measures to evaluate endothelial function are readily available. Clinical studies have shown that endothelial dysfunction is manifested by impaired vascular reactivity, which can be measured by assessing flow mediated dilation (FMD) using non-invasive techniques such as brachial artery reactivity testing (BART)[2-4)]. While FMD is a non-invasive measure-

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ment of vascular reactivity and endothelial-dependent vasomotion[5], this technique is dependent on technical expertise and expensive ultrasound equipment, thereby restricting it to a vascular research laboratory and therefore being of limited clinical utility in the perioperative setting.

DTM is a new non-invasive, FDA-approved method of assessing vascular reactivity that is currently under evaluation for the assessment of peripheral vascular function[6]. Similar to the FMD technique, DTM uses ischemia-induced reactive hyperemia as a stimulus to induce changes in vascular reactivity and increased blood flow. The proposed advantage of DTM is that expensive and labor-intensive ultrasound technology used to study changes in brachial artery diameter (FMD) is replaced by simple fingertip thermocouple probes that measure reactive hyperemia by fingertip thermal changes. The interest in DTM, therefore, is that this technique is simpler and more suitable for point of care testing. In addition, such point of care testing technology has the potential to facilitate research into the perioperative kinetics of vascular reactivity and endothelial function following surgery to the bed side, especially in the postoperative period where patients are often restricted to the postoperative recovery area (e.g. ICU or surgical floor).

In the current study we tested the hypothesis that surgical trauma is associated with impaired vascular reactivity in the immediate postoperative period (primary endpoint), as measured by a decrease in DTM temperature rebound variables: temperature rebound (TR), adjusted temperature rebound (aTR) and area under the curve of TR (AUC_{TR}). The secondary endpoint was the association of preoperative risk factors for cardiovascular disease with a decrease in DTM variables.

Materials & Methods

Following Institutional Review Board approval and patients' informed consent, an observational pilot study was conducted to assess reactive hyperemia-derived DTM variables at the preoperative visit (baseline) and at 24, 48, 72 hours, and day 5 postoperatively in sixty consecutive patients undergoing major thoracic surgery, including any intrapleural procedure with an expected blood loss >500 mL (e.g. esphagectomy, pneumonectomy or lobectomy). The study was carried out at The University of Texas M. D. Anderson Cancer Center in Houston, Texas, USA.

Exclusion criteria included: patients under the age of 18; patients deemed unsatisfactory for surgery after the pre-anesthetic evaluation; and patient's baseline fingertip temperature below 27℃ at the beginning of the DTM examination.

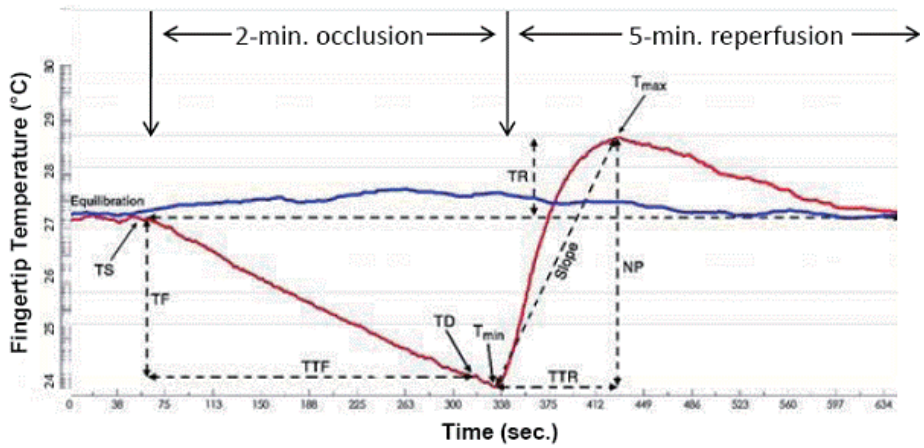
Preoperative surgical and cardiovascular risk was assessed using the ASA Physical Status Classification System[7], Lee Modified Cardiac Risk Index[8], and in patients who met the criteria for metabolic syndrome[9]. Cardiovascular risk factors included obesity (BMI >30 kg/m^2), abdominal obesity (waist circumference: men >102 cm, women >88 cm), dyslipidemia (triglycerides ≥150 mg/dL, HDL cholesterol: men <40 mg/dL, women <50 mg/dL, diabetes mellitus (fasting glucose >110 mg/dL or diabetes medication on the physician chart) or coronary artery disease (positive coronary angiography, status post-myocardial ischemia/infarction).

DTM in this study was conducted using a VENDYS 5000BC DTM system (Endothelix, Inc., Houston, TX, USA). This FDA-approved device consists of a computer-based thermometry system (0.006℃ thermal resolution), with two special thermocouple fingertip probes designed to minimize the area of skin-probe contact and fingertip pressure. A standard sphygmomanometer cuff and a compressor unit to control cuff inflation and deflation are included to facilitate the occlusion-hyperemia protocol. The baseline test was conducted with the patient at rest for 30 minutes in the supine position, in a quiet, dimmed room with ambient temperature of 24℃ to 26℃, whereas the postoperative DTM measurements were conducted on the surgical ward. VENDYS DTM probes are affixed to the index finger of each hand and after a period of stabilization of basal skin temperature (defined as stabilization within a 0.05℃ threshold) the temperature is measured in the index fingers of both hands (of which the right arm only is subjected to occlusion-hyperemia) with an automated, operator-independent protocol. The right upper arm cuff is rapidly inflated to ≥50 mmHg above systolic pressure for 2 minutes, and then rapidly deflated to invoke reactive hyperemia distally. Thermal tracings are measured continuously and digitized automatically using a computer-based thermometry system with 0.006℃ thermal resolution. Dual channel temperature data are simultaneously acquired at a 1 Hz sample rate.

The primary variables and DTM-derived measures, related to thermal debt and recovery, were recorded and calculated. In addition, postoperative complications in all patients were collected and correlated to the changes in measured and derived DTM variables (see legend of **Fig. 1**.

Primary variables:

TR Temperature rebound (TR): maximum temperature (T_{max}) − start temperature (T_S)



Temperature (T in °C)	Time (t in sec)	Vital signs	Derived Measures
T_S Starting temperature immediately prior to cuff inflation	t_i = Time of cuff inflation	**sBP** Systolic blood pressure (noninvasive)	**TR** Temperature rebound (T_{max} - T_S)
T_{min} Lowest temperature (nadir) observed during cuff inflation	t_{min} = Time to T_{min}	**dBP** Diastolic blood pressure (noninvasive)	**aTR** Adjusted TR (TR/T_S)
T_{max} Highest rebound temperature observed after cuff deflation	t_{max} = Time to T_{max}	**meanBP** Mean blood pressure (calculated)	**AUC_{TR}** Area under the curve between T_{min} and T_{max}
		HR Heart rate	**TF** Temperature Fall = T_S - T_{min}
			TD Deflation Temperature
			tTF Time taken to reach temperature fall
			tTR Time taken to reach temperature rebound (TR)
			NPT Nadir to peak temperature gain (T_{max} - T_{min})
			SLP Slope (NP/time to reach TR)

Fig. 1. Representative example of a temperature-time trace in response to occlusion-hyperemia.

Red line represents the temperature trace of ischemic/hyperemic (right) arm, while the blue line represents that of the control (left) arm.

aTR Adjusted TR (TR/ T_S)
AUC_{TR} Area under the curve between minimum temperature (T_{min}) and T_{max}

Statistical Methods

Descriptive statistics were used to summarize the patients' demographic, clinical, and DTM-derived measures. The distribution of DTM-derived measures does not satisfy the normality assumption. Pairwise comparisons between each of the post-operative DTM measurements and baseline were implemented using a non-parametric bootstrap method with a statistical level of 0.05. Comparisons between the lowest DTM measurements at 24 h and the highest DTM measurements at 72 h were carried out using the same method. Univariate analysis via a non-parametric Wilcoxon method was used to evaluate the impact of comorbidities on the difference between the baseline DTM measurements and their lowest (highest) DTM measurements at 24 h (72 h), respectively. These comorbidities include: preoperative radiation (yes or no), preoperative chemotherapy (yes or no), hypertension (yes or no), diabetes mellitus (yes or no), obesity (yes or no), abdominal obesity (yes or no), smoking (never or smoker), coronary artery disease (yes or no), and Lee cardiac index (2 or 3).

$P<0.05$ was considered to indicate statistical significance. Statistical analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Sixty patients scheduled for major thoracic surgery who met the eligibility criteria were enrolled in the study. Three of these patients were excluded from the study because the procedure was aborted for surgical reasons, and 45% of the measured DTM tests in the postoperative period at various time points were invalid and not used in the analysis due to low starting fingertip temperature (<27℃).

Baseline Characteristics

The preoperative (baseline) patient and clinical characteristics of the study population are summarized in **Table 1**. Among 57 patients, the median age was 63 years old, and 63% were men. There were 6 (10.5%) obese patients and 16 (28.1%) patients with abdominal obesity. Twenty (37%) patients had a Lee cardiac index of 3 and the rest had a Lee cardiac index of 2. In terms of comorbidities, 12 (21.1%) had coronary artery disease, 33 (57.9%) had hypertension, 10 (17.5%) had diabetes mellitus, and 28 (49.1%) had dyslipidemia. In terms of treatment, 25 (43.9%) had taken statins, 17 (29.8%) had taken beta-blockers, 6 (10.5%) had taken ACE inhibitors, and 5 (8.8%) had taken AT2 inhibitors.

Table 1. Baseline characteristics

		All Patients ($n=57$)
		N (%)
Age, years	Median (range)	63 (28,80)
Male sex		36 (63.2%)
Race or ethnic group†	Black	7 (12.3%)
	Hispanic	4 (7%)
	White	46 (80.7%)
ASA	2	5 (8.8%)
	3	51 (91.2%)
Lee cardiac index	2	37 (64.9%)
	3	20 (35.1%)
Preoperative radiation therapy	No	37 (64.9%)
	Yes	20 (35.1%)
Preoperative chemotherapy	No	30 (52.6%)
	Yes	27 (47.4%)
Obesity‡	No	51 (89.5%)
	Yes	6 (10.5%)
Abdominal obesity‡‡	No	41 (71.9%)
	Yes	16 (28.1%)
Smoking	Never	17 (29.8%)
	Smoker	40 (70.2%)
Coronary artery disease	No	45 (78.9%)
	Yes	12 (21.1%)
Hypertension	No	24 (42.1%)
	Yes	33 (57.9%)
Diabetes mellitus	No	47 (82.5%)
	Yes	10 (17.5%)
Dyslipidemia	No	29 (50.9%)
	Yes	28 (49.1%)
Statin	No	32 (56.1%)
	Yes	25 (43.9%)
Beta-blocker	No	40 (70.2%)
	Yes	17 (29.8%)
ACE inhibitor	No	51 (89.5%)
	Yes	6 (10.5%)
AT2 inhibitor	No	52 (91.2%)
	Yes	5 (8.8%)

ASA = American Society of Anesthesiologists physical status classification system; AT2 = antagonist;
† Race was self-reported
‡ BMI >30 kg/m^2
‡‡ Waist circumference >102 cm (men), >88 cm (women)

Table 2. Digital thermal monitoring (DTM) parameters*

Parameters	Time	n	Measurement	Comparison	*p*-value†	Comparison	*p*-value
TR	Baseline	52	0.24 ± 0.58				
	24 h PO	44	0.06 ± 0.52	Baseline v. 24 h PO	1.0		
	48 h PO	41	0.37 ± 0.99	Baseline v. 48 h PO	1.0		
	72 h PO	38	0.45 ± 0.77	Baseline v. 72 h PO	1.0	24 h v. 72 h PO	0.04
	5 d PO	27	0.32 ± 0.64	Baseline v. 5 dh PO	1.0		
aTR	Baseline	52	0.65 ± 0.5				
	24 h PO	44	0.52 ± 0.56	Baseline v. 24 h PO	1.0		
	48 h PO	41	0.8 ± 1.02	Baseline v. 48 h PO	1.0		
	72 h PO	38	0.84 ± 0.8	Baseline v. 72 h PO	1.0	24 h v. 72 h PO	0.16
	5 d PO	27	0.6 ± 0.56	Baseline v. 5 dh PO	1.0		
AUC_{TR}	Baseline	52	116 ± 109				
	24 h PO	44	83.5 ± 101	Baseline v. 24 h PO	1.0		
	48 h PO	41	132 ± 176	Baseline v. 48 h PO	1.0		
	72 h PO	38	140 ± 149	Baseline v. 72 h PO	1.0	24 h v. 72 h PO	0.17
	5 d PO	27	120 ± 118	Baseline v. 5 dh PO	1.0		

PO = post-operation, TR = temperature rebound, aTR = adjusted temperature rebound, AUC_{TR} = area under the curve of temperature rebound
*Plus-minus values are the means ± SE; †Multiple comparisons based on a non-parametric bootstrap method

DTM - Perioperative Kinetics

Each of the three DTM parameters, TR, aTR, and AUC_{TR}, at baseline and each of the four postoperative time points, 24 h, 48 h, 72 h, and day 5, are summarized using the mean ± standard error in **Table 2**. For each of the DTM parameters, when comparing baseline measurements and each of the postoperative measurements, there was no statistical significance based on the non-parametric bootstrap method (p = 1.0 for all comparisons). When comparing the lowest DTM measurements at 24 h versus the highest DTM measurements at 72 h, there was a significant difference between the 24 h and 72 h TR measurements (p = 0.04), but not for aTR (p = 0.16), or AUC_{TR} (p = 0.17).

DTM and Comorbidities

When stratified by comorbidities, there were no differences in the baseline DTM measurements between patients with cardiovascular risk factors and those who did not have any risk factors, or between those who received preoperative chemo-radiation and those who did not (**Table 3**).

There were no differences in TR measurements between baseline and 24 h postoperatively (lowest measured DTM variables, $p \geq 0.05$; **Table 4a**). For aTR, patients who had abdominal obesity had a significantly lower difference between baseline and 24 h postoperatively than those without abdominal obesity (p = 0.02). Similarly, patients who had abdominal obesity had a significantly lower difference between baseline and 24 h postoperative AUC_{TR} than those without abdominal obesity (p = 0.03). Patients with a history of smoking (current or former) had a significantly lower TR difference between baseline and 72 h postoperatively than never-smokers (p = 0.02, **Table 4b**).

Discussion

In this prospective, observational pilot study, we assessed the utility of DTM using a VENDYS 5000BC DTM system (Endothelix, Inc.) as a point of care testing device to study the kinetics of vascular reactivity (ischemia-hyperemia-dependent vasomotion) following major thoracic surgery at the bedside in post-surgical units. We were not able to find a significant difference between baseline DTM measurements before surgery and each of the postoperative measurements. Low average baseline (pre-op) aTR values in the present study population with multiple comorbidities may have contributed to our inability to detect a significant decline of TR values after surgery.

We observed a significant difference of TR at 72 h postoperatively (highest recorded values) when compared to TR at 24 hrs (lowest recorded values, compared to baseline; p = 0.04); but this effect was not present for aTR (p = 0.16), or AUC_{TR} (p = 0.17). Patients with abdominal obesity had lower aTR and AUC_{TR} values (baseline-24 h; p = 0.02 and p = 0.03) and patients with a history of smoking (current or for-

Table 3. Univariate analysis of baseline DTM measures by comorbidities

Comorbidity	TR				aTR			AUC_{TR}		
	N	Mean	Median	p^*	Mean	Median	p^*	Mean	Median	p^*
Preoperative radiation										
No	31	0.14	−0.04		0.60	0.56		101.60	86.74	
Yes	18	0.36	0.31	0.10	0.66	0.71	0.43	123.06	110.19	0.28
Preoperative chemotherapy										
No	25	0.17	−0.04		0.64	0.56		108.29	86.86	
Yes	24	0.28	0.13	0.30	0.61	0.61	0.87	110.73	104.86	0.59
Hypertension										
No	21	0.24	0.08		0.64	0.55		105.05	92.49	
Yes	28	0.21	0.20	0.83	0.61	0.63	0.92	112.81	94.69	0.94
Diabetes mellitus										
No	40	0.16	0.05		0.57	0.56		96.13	90.11	
Yes	9	0.51	0.61	0.05	0.88	0.77	0.12	168.85	151.92	0.08
Obesity										
No	43	0.18	0.07		0.59	0.56		98.68	86.86	
Yes	6	0.51	0.56	0.12	0.90	0.94	0.20	186.94	202.04	0.09
Abdominal obesity										
No	36	0.18	0.05		0.58	0.53		94.50	84.57	
Yes	13	0.34	0.33	0.23	0.75	0.70	0.27	150.97	151.67	0.07
Smoking										
Never	16	0.18	0.01		0.65	0.64		118.23	93.91	
Smoker	33	0.24	0.11	0.54	0.61	0.61	0.89	105.25	92.49	0.79
Coronary artery disease										
No	40	0.26	0.13		0.64	0.61		112.36	96.29	
Yes	9	0.05	−0.04	0.39	0.55	0.56	0.65	96.70	86.74	0.65
Lee cardiac index										
2	32	0.16	0.09		0.67	0.61		112.15	93.47	
3	17	0.35	0.30	0.27	0.54	0.55	0.55	104.47	92.49	0.97

TR = temperature rebound, aTR = adjusted temperature rebound, AUC_{TR} = area under the curve of temperature rebound. p^*: p-value was based on a non-parametric Wilcoxon method.

mer) had a significantly lower TR difference between baseline and 72 h postoperatively than never-smokers ($p = 0.02$, **Table 4b**). There were no significant consistent changes in vascular reactivity correlating with the incidence of the other perioperative cardiovascular comorbidities or neoadjuvant radiochemotherapy.

Impairment of vascular reactivity is a precursor for cardiovascular disease and precedes the morphological changes associated with atherosclerosis in the blood vessels[9, 13, 20, 21] and the clinical manifestations of its associated complications (e.g. myocardial infarction, stroke)[10, 11]. Furthermore, any transient inflammatory burden or systemic inflammatory state also adversely affects endothelium-dependent vascular function with a consequent increased risk for cardiovascular complications[1, 12]. In the perioperative context, inflammatory mediator release associated with surgical trauma has been shown to impair vascular function and correlate with both the duration and extent of major surgery[1, 12-15]. This effect may be additive to the underlying endothelial dysfunction that is inherent in certain surgical patients as a result of their preoperative co-morbidity burden and thus may play a significant role in certain perioperative complications (e.g. perioperative myocardial infarction, poor wound healing, ALI, sepsis)[13, 15, 16]. Importantly, this acute inflammation and ensuing endothelial dysfunction might be amenable to pharmacologic intervention[1] if robust, reliable, reproducible and simple measures to evaluate endothelial function are readily available.

Studies have reported a direct and positive correlation between impaired flow-mediated dilation (FMD) of the brachial artery and the increased inci-

Table 4a. Univariate analyses of DTM measurement differences between baseline and 24 h (lowest DTM measurements) by comorbidities

Comorbidity	TR				aTR			AUC_{TR}		
	N	Mean	Median	p^*	Mean	Median	p^*	Mean	Median	p^*
Preoperative radiation										
No	24	−0.07	−0.09		−0.00	0.03		−15.95	0.00	
Yes	15	−0.33	−0.20	0.22	−0.15	−0.13	0.29	−41.10	−34.53	0.24
Preoperative chemotherapy										
No	21	0.03	0.12		−0.08	0.00		−23.48	0.00	
Yes	18	−0.41	−0.24	0.05	−0.04	0.00	0.99	−28.12	−24.49	0.68
Hypertension										
No	16	−0.21	−0.20		−0.12	0.00		−38.81	−17.61	
Yes	23	−0.15	−0.08	0.56	−0.02	0.00	0.70	−16.45	−15.50	0.74
Diabetes mellitus										
No	33	−0.14	−0.12		−0.04	0.04		−22.69	−11.51	
Yes	6	−0.37	−0.44	0.17	−0.16	−0.26	0.40	−41.73	−59.44	0.45
Obesity										
No	34	−0.17	−0.19		−0.05	0.00		−22.39	−13.50	
Yes	5	−0.19	−0.08	0.98	−0.17	−0.09	0.57	−47.58	−44.45	0.41
Abdominal obesity										
No	27	−0.15	−0.17		0.05	0.05		−5.94	0.00	
Yes	12	−0.22	−0.36	0.59	−0.32	−0.37	0.02	−69.92	−88.41	0.03
Smoking										
Never	11	−0.23	−0.20		−0.25	0.04		−68.67	−34.53	
Smoker	28	−0.15	−0.15	0.65	0.01	0.00	0.54	−8.71	−13.50	0.37
Coronary artery disease										
No	30	−0.24	−0.20		−0.10	0.00		−38.59	−19.61	
Yes	9	0.04	−0.17	0.49	0.06	0.10	0.52	17.60	33.75	0.29
Lee cardiac index										
2	25	−0.02	−0.07		0.02	0.04		−13.75	−8.87	
3	14	−0.45	−0.38	0.06	−0.21	−0.26	0.12	−46.82	−52.78	0.24

TR = temperature rebound, aTR = adjusted temperature rebound, AUC_{TR} = area under the curve of temperature rebound. p^*: p-value was based on a non-parametric Wilcoxon method.

dence of immediate and long-term postoperative adverse events following vascular surgery[17, 18]. While FMD is a non-invasive measurement of vascular reactivity and endothelial-dependent vasomotion[6], this technique is dependent on technical expertise and expensive ultrasound equipment, thereby restricting it to a vascular research laboratory and therefore being of limited clinical utility in the perioperative setting. DTM, a novel non-invasive technique, utilizing the principle of reactive hyperemia, has also been shown to correlate with Doppler flow velocity[19], a parameter used in the BART technique. Recent studies investigating DTM showed that impaired vascular reactivity correlated with the extent of myocardial perfusion defect[20] and was found in patients with metabolic syndrome and diabetes mellitus[21]; however, these latter observations were made in a static setting, with measurements at a single time point. We therefore studied the utility of DTM in the dynamic postoperative setting after patients had undergone major thoracic surgery.

Interestingly, we found a lower DTM signal in patients with cardiovascular risk factors such as abdominal obesity (aTR and AUC_{TR}) and smoking (TR). These results are consistent with previous studies that found impaired vascular function and increased cardiovascular risk in patients with these comorbidities[22, 23]; however, cardiovascular complications associated with chemotherapy were not associated with lower DTM values in our study. Chemotherapy is known to impair cardiovascular function and the mechanisms include the production of reac-

Table 4b. Univariate analyses of DTM measurement differences between baseline and 72 h (highest DTM measurements) by comorbidities

Comorbidity	TR				aTR			AUC_{TR}		
	N	Mean	Median	p^*	Mean	Median	p^*	Mean	Median	p^*
Preoperative radiation										
No	22	0.12	0.15		0.21	0.03		19.40	3.21	
Yes	12	0.24	0.20	0.65	0.27	0.00	0.79	24.15	0.00	0.99
Preoperative chemotherapy										
No	20	0.22	0.15		0.25	0.00		27.51	0.00	
Yes	14	0.07	0.17	0.90	0.20	0.10	0.92	11.88	6.01	0.97
Hypertension										
No	11	0.00	0.13		0.01	0.00		−20.80	0.00	
Yes	23	0.24	0.21	0.66	0.33	0.05	0.44	41.10	6.42	0.42
Diabetes mellitus										
No	29	0.15	0.21		0.22	0.00		20.10	0.00	
Yes	5	0.24	−0.02	0.70	0.28	−0.24	0.96	26.72	−119.10	0.63
Obesity										
No	29	0.12	0.13		0.19	0.00		18.74	0.00	
Yes	5	0.41	0.57	0.56	0.48	0.79	0.50	34.62	68.72	0.77
Abdominal obesity										
No	24	−0.04	0.11		0.13	0.00		5.89	0.00	
Yes	10	0.64	0.42	0.13	0.47	0.51	0.44	57.51	80.33	0.64
Smoking										
Never	10	0.63	0.58		0.80	0.75		117.93	110.99	
Smoker	24	−0.03	0.00	0.02	−0.01	−0.12	0.05	−19.28	−20.57	0.06
Coronary artery disease										
No	26	0.15	0.20		0.27	0.13		24.72	9.06	
Yes	8	0.20	−0.03	0.86	0.10	−0.33	0.46	9.24	−78.89	0.49
Lee cardiac index										
2	20	0.12	0.17		0.17	0.00		7.45	0.00	
3	14	0.22	0.16	0.77	0.32	−0.10	0.90	40.54	−29.66	0.74

TR = temperature rebound, aTR = adjusted temperature rebound, AUC_{TR} = area under the curve of temperature rebound. p^*: p-value was based on a non-parametric Wilcoxon method.

tive oxygen species and oxidative stress, apoptosis of cardiomyocytes, and structural and functional changes in cardiac myofibrils[24].

While we studied the kinetics of endothelial function throughout the perioperative period and showed a similar nadir to that shown by Tonetti *et al.*[24], we did not quantify the intensity of systemic inflammation using a laboratory assay of the cytokines. The extent of perioperative inflammation, as measured by an increase of pro-inflammatory cytokines, and its correlation to impaired reactivity, as measured by DTM, needs to be investigated in future studies. Lastly, we observed in our study that patients with abdominal obesity showed a decrease of one of the DTM variables postoperatively, although there were no differences in the baseline measurements when compared to their cohorts without obesity. This might have been related to the impaired endothelial function in these patients in the face of perioperative stress related to cytokine release, although at this point this is purely speculative as we did not measure the cytokine levels in correlation with the DTM measurements in the postoperative period.

A major limitation of the technique is that we had to exclude a number of DTM tests due to low fingertip starting temperature (<27℃) at various time points. Contributory factors could be the fact that DTM is highly dependent on ambient room temperature. Other factors that may have impacted the low starting temperature in some patients may include vasoconstriction, which results from a cuff placed too tightly around the arm, leading to false TF and TR

values, stressors such as the white coat effect[25, 26], myogenically mediated vasoconstriction, a rise in intravascular pressure or even direct damming of venous outflow and capillary outflow obstruction[27]. Another issue that remains unresolved is the extent to which a neurovascular response contributes to reactive hyperemia. Infrared imaging of the control hand during DTM testing revealed this phenomenon of a neurovascular effect that could possibly lead to blunting of the temperature response to reactive hyperemia. Evaluation of the temperature data for the left finger, functioning as a control, might have additional value for observation, although its interpretation has not been fully explored. Further, a limitation of our study protocol that may have contributed to the relatively low TR values is the fact that 2-minute arm cuff occlusion was used to induce reactive hyperemia, whereas more recent DTM protocols use 5-minute occlusion. As a general observation from previous DTM tests, a 2-minute aTR value can be converted to a 5-minute value by multiplying by a factor of 1.4.

In summary, we cannot conclude that this device in the version tested is a useful point of care testing tool to study perioperative reactive hyperemia; however, the analysis highlights some interesting data that can fuel interest to refine the current technology. The improvement of DTM for non-invasive assessment of endothelium-dependent vascular dysfunction is of significant importance for perioperative patient risk assessment because there is a need to detect patients with subclinical micro-vascular dysfunction. This group of patients usually presents to the perioperative setting with cardiovascular co-morbidities, including hypertension, obesity, history of smoking, hyperlipidemia, and neo-adjuvant chemo-radiotherapy that may impair perioperative micro-vascular function. Without any symptoms or history of cardiac events these patients are often are classified as ASA 2 patients, underestimating the underlying risk for complications related to micro-vascular dysfunction (e.g. wound healing).

Therefore, further studies are warranted regarding: 1) if technology to quantify vascular reactivity is warranted in the clinical setting to make decisions regarding therapeutic interventions (preoperative optimization) to improve post surgical outcomes, 2) such technology should be inexpensive, portable, robust, reliable and reproducible, and 3) if known preoperative co-morbidities (chemo-radiation) and cardiac risk factors (obesity, smoking) associated with impaired vascular function can be easily quantified and modified prior to surgery.

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Conflict of Interest

The authors report no conflicts of interest.

References

1) Vallance P, Collier J, Bhagat K: Infection, inflammation, and infarction: does acute endothelial dysfunction provide a link? Lancet, 1997; 349: 1391-1392
2) Korkmaz H, Onalan O: Evaluation of endothelial dysfunction: flow-mediated dilation. Endothelium, 2008; 15: 157-163
3) Guthikonda S, Sinkey CA, Haynes WG: What is the most appropriate methodology for detection of conduit artery endothelial dysfunction? Arterioscler Thromb Vasc Biol, 2007; 27: 1172-1176
4) Oida K, Ebata K, Kanehara H, Suzuki J, Miyamori I: Effect of cilostazol on impaired vasodilatory response of the brachial artery to ischemia in smokers. J Atheroscler Thromb, 2003; 10: 93-98
5) Deanfield JE, Halcox JP, Rabelink TJ: Endothelial function and dysfunction: testing and clinical relevance. Circulation, 2007; 115: 1285-1295
6) Gul KM, Ahmadi N, Wang Z, Jamieson C, Nasir K, Metcalfe R, Hecht HS, Hartley CJ, Naghavi M: Digital thermal monitoring of vascular function: a novel tool to improve cardiovascular risk assessment. Vasc Med, 2009; 14: 143-148
7) Dripps RD, Lamont A, Eckenhoff JE: The role of anesthesia in surgical mortality. JAMA, 1961; 178: 261-266
8) Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation, 1999; 100: 1043-1049
9) Alberti KG, Zimmet P, Shaw J: Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med, 2006; 23: 469-480
10) Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature, 1993; 362: 801-809
11) Werns SW, Walton JA, Hsia HH, Nabel EG, Sanz ML, Pitt B: Evidence of endothelial dysfunction in angiographically normal coronary arteries of patients with coronary artery disease. Circulation, 1989; 79: 287-291
12) Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J: Treatment of periodontitis and endothelial function. N Engl J Med, 2007; 356: 911-920

13) Burnham E, Moss M: Progenitor cells in acute lung injury. Minerva Anestesiol, 2006; 72: 369-374
14) Hunt BJ, Jurd KM: Relation between endothelial-cell activation and infection, inflammation, and infarction. Lancet, 1997; 350: 293
15) Rafat N, Hanusch C, Brinkkoetter PT, Schulte J, Brade J, Zijlstra JG, van der Woude FJ, van Ackern K, Yard BA, Beck G: Increased circulating endothelial progenitor cells in septic patients: correlation with survival. Crit Care Med, 2007; 35: 1677-1684
16) Kawano N, Emoto M, Mori K, Yamazaki Y, Urata H, Tsuchikura S, Motoyama K, Morioka T, Fukumoto S, Shoji T, Koyama H, Okuno Y, Nishizawa Y, Inaba M: Association of endothelial and vascular smooth muscle dysfunction with cardiovascular risk factors, vascular complications, and subclinical carotid atherosclerosis in type 2 diabetic patients. J Atheroscler Thromb, 2012; 19: 276-284
17) Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Menzoian JO, Vita JA: Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. Circulation, 2002; 105: 1567-1572
18) Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO, Vita JA: Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol, 2003; 41: 1769-1775
19) McQuilkin GL, Panthagani D, Metcalfe RW, Hassan H, Yen AA, Naghavi M, Hartley CJ: Digital thermal monitoring (DTM) of vascular reactivity closely correlates with doppler flow velocity. Conf Proc IEEE Eng Med Biol Soc, 2009; 1: 1100-1103
20) Ahmadi N, Usman N, Shim J, Nuguri V, Vasinrapee P, Hajsadeghi F, Wang Z, Foster GP, Nasir K, Hecht H, Naghavi M, Budoff M: Vascular dysfunction measured by fingertip thermal monitoring is associated with the extent of myocardial perfusion defect. J Nucl Cardiol, 2009; 16: 431-439
21) Ahmadi N, Hajsadeghi F, Gul K, Leibfried M, DeMoss D, Lee R, Flores F, Nasir K, Hecht H, Naghavi M, Budoff MJ: Vascular function measured by fingertip thermal reactivity is impaired in patients with metabolic syndrome and diabetes mellitus. J Clin Hypertens (Greenwich), 2009; 11: 678-684
22) Mathieu P: Abdominal obesity and the metabolic syndrome: a surgeon's perspective. Can J Cardiol, 2008; 24 Suppl D: 19D-23D
23) Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE: Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet, 1992; 340: 1111-1115
24) Monsuez JJ, Charniot JC, Vignat N, Artigou JY: Cardiac side-effects of cancer chemotherapy. Int J Cardiol, 2010; 144: 3-15
25) Ogedegbe G: White-coat effect: unraveling its mechanisms. Am J Hypertens, 2008; 21: 135
26) Tsai PS: White-coat effect and blood pressure reactivity. Int J Cardiol, 2008; 126: 273; author reply 274-275
27) Edwards CM, Marshall JM, Pugh M: The cutaneous vasoconstrictor response to venous stasis is normal in subjects with primary Raynaud's disease. Clin Auton Res, 1999; 9: 255-262