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Assessment of peripheral endothelial function predicts future risk of solid-tumor cancer

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Abstract

Aims: Cardiovascular health metrics predict the risk not only of cardiovascular diseases but also of several types of cancers. Microvascular endothelial dysfunction can predict future cardiovascular adverse events, but the predictive value of microvascular endothelial dysfunction for future risk of solid-tumor cancer has not been characterized.

Methods: A total of 488 patients who underwent microvascular endothelial function assessment using reactive hyperemia peripheral arterial tonometry were included in this study. Microvascular endothelial dysfunction was defined as a reactive hyperemia peripheral arterial tonometry index $\leq$2.0.

Results: Of 221 patients with a baseline reactive hyperemia peripheral arterial tonometry index $\leq$2.0, 21 patients (9.5%) were diagnosed with incident solid-tumor cancer during follow-up, whereas of 267 patients with a baseline reactive hyperemia peripheral arterial tonometry index $>$2.0, 10 patients (3.7%) were diagnosed with incident solid-tumor cancer during follow-up ($p = 0.009$). Patients with a reactive hyperemia peripheral arterial tonometry index $\leq$2.0 had lower solid-tumor cancer-free survival compared to patients with a reactive hyperemia peripheral arterial tonometry index $>$2.0 (log-rank $p = 0.017$) (median follow-up 6.0 (3.0–9.1) years). Cox proportional hazard analyses showed that a reactive hyperemia peripheral arterial tonometry index $\leq$2.0 predicted the incidence of solid-tumor cancer, with a hazard ratio of 2.52 (95% confidence interval 1.17–5.45; $p = 0.019$) after adjusting for age, sex, and coronary artery disease, 2.83 (95% confidence interval 1.30–6.17; $p = 0.009$) after adjusting for diabetes mellitus, hypertension, smoking status, and body mass index $>30\,kg/m^2$, 2.79 (95% confidence interval 1.21–6.41; $p = 0.016$) after adjusting for fasting plasma glucose, systolic blood pressure, smoking status (current or former), and body mass index, and 2.43 (95% confidence interval 1.10–5.34; $p = 0.028$) after adjusting for Framingham risk score.

Conclusion: Microvascular endothelial dysfunction, as defined by a reactive hyperemia peripheral arterial tonometry index $\leq$2.0, was associated with a greater than two-fold increased risk of solid-tumor cancer. Microvascular endothelial dysfunction may be a useful marker to predict the future risk of solid-tumor cancer, in addition to its known ability to predict cardiovascular disease. Further research is necessary to develop adequate cancer screening strategies for patients with microvascular endothelial dysfunction.

Keywords

Cardiovascular diseases, cancer, vascular endothelium-dependent relaxation, microvessel abnormalities

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Introduction

Adherence to seven cardiovascular health metrics defined by the American Heart Association, including smoking, physical activity, obesity, dietary intake, total cholesterol, blood pressure, and blood sugar, not only decreases the risk of cardiovascular disease (CVD) but also the incidence of several malignancies.[1] Along the

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same lines, several well-known cardiovascular risk factors, including obesity, diabetes mellitus, and hypertension, increase the risk of both CVD and cancer.[2–4] Smoking is also associated with an increased incidence of solid-tumor cancer.[5] These commonalities may be explained, at least in part, by the fact that CVD and cancer share common underlying disease processes, such as chronic inflammation and oxidative stress.[6,7]

The endothelium is a prime site for the effects of cardiovascular risk factors. Thus, in reflecting the summative contribution of these risk factors that are associated with inflammation and oxidative stress, endothelial function can be viewed as an integrated index and sensitive marker of CVD risk.[8] There are two major non-invasive methods to evaluate peripheral endothelial function: flow-mediated dilatation (FMD) of the brachial artery and reactive hyperemia peripheral arterial tonometry (RH-PAT) of the index finger. Nitric oxide (NO) is a major contributor to the maintenance of systemic endothelial function, and therefore influences the pathophysiology of blood flow in both FMD and RH-PAT.[9] In contrast to FMD, which reflects macrovascular function, RH-PAT comprehensively evaluates the vascular reactivity of the microvasculature in the forearm. Importantly, previous observational studies have demonstrated an association between microvascular endothelial dysfunction (MED) and an increased incidence of CVD in individuals with minimal traditional cardiovascular risk factors, providing prognostic information above and beyond that provided by conventional cardiovascular risk factors.[10]

Given the similar pathological mechanisms that underpin cancer and CVD, we aimed to investigate the prognostic value of MED, measured using RH-PAT, for the future risk of incident cancer. In addition, given that microvascular endothelial function regulates blood supply in all solid-tumors, we excluded hematologic malignancies and focused particularly on solid-tumor cancers.

Methods

Study population

In this observational cohort study, we enrolled 687 patients who visited the Mayo Clinic between January 2006–February 2014 and underwent endothelial function testing using the EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel) for the assessment of chest pain and/or cardiovascular risk. The decision to assess endothelial function was at the clinical discretion of the evaluating physician. Patients with a known hematological malignancy and those with less than 90 days of follow-up were excluded. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board. All patients provided written informed consent for participation in the current study.

Assessment of microvascular endothelial function

RH-PAT was used to evaluate microvascular endothelial function using methods described previously.[10,11] In brief, the study protocol included a five-minute baseline measurement, followed by a five-minute period during which a blood pressure cuff was inflated around the study participant's test arm with a pressure of 60 mm Hg above baseline systolic blood pressure or 200 mm Hg, followed by a six-minute peripheral arterial tonometry (PAT) recording period after deflation of the cuff. The RH-PAT ratio was defined as the average pulse wave amplitude (PWA) for a one-minute period beginning one minute after pressure cuff deflation divided by the average PWA during a 3.5-minute baseline period before pressure cuff inflation. The RH-PAT ratio on the test arm was indexed to the PAT ratio of the contralateral arm, which was used as an internal control. Per clinical protocol, patients were instructed to stop all vasoactive medications, including calcium channel blockers, β blockers, and long-acting nitrates, for at least 24 h prior to endothelial function testing, and allowed to use short-acting nitrates as needed for chest pain relief up to six hours prior to testing. A calculated RH-PAT index $\leq$2.0 is a clinically used cut-off value for diagnosis of MED at Mayo Clinic, and was also equivalent to the median value of RH-PAT index in this study.[12] If more than one test was performed in a given patient, only the first test was included in the final analysis.

Clinical assessment

Clinical history, laboratory data, and current medications were collected from detailed chart review by an investigator blinded to RH-PAT data. Data were collected on the following parameters: (a) sex, age, body mass index (BMI), and traditional CVD risk factors (smoking status and obesity (BMI$>$30 kg/m^2)), (b) dyslipidemia, defined by a documented history of hyperlipidemia, treatment with lipid-lowering therapy, a low-density lipoprotein (LDL) cholesterol level above the target ($<$130 mg/dl for low risk patients, $<$100 mg/dl for moderate-high risk patients, $<$70 mg/dl for very high risk, and $<$55 mg/dl for extreme high risk patients based on 10-year atherosclerotic CVD risk),[13] high-density lipoprotein (HDL) cholesterol $<$ 40 mg/dl in men or $<$50 mg/dl in women, or triglycerides $>$150 mg/dl, (c) type 2 diabetes mellitus, defined as a documented history of or treatment for type 2 diabetes,

(d) hypertension, defined as a documented history of or treatment for hypertension, (e) coronary artery disease, defined as more than 50% luminal stenosis in any coronary arteries diagnosed by coronary angiography or computed tomography coronary angiography, and (f) a diagnosis of a solid-tumor cancer before and after the baseline RH-PAT test. Information about the primary site and date of cancer diagnosis was also collected, as was information regarding survival.

Statistical analysis

Continuous variables distributed normally were expressed as the mean ± standard deviation (SD), and those with a skewed distribution were expressed as the median with interquartile range (IQR). Categorical variables were expressed as frequency (percentage). Enrolled patients were divided into two groups–those with MED (RH-PAT index $\leq$2.0) and those without MED (RH-PAT index > 2.0). For between-groups comparisons, the unpaired *t*-test was used for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed variables, and χ^2 test (and Fisher's exact test) for categorical variables. Kaplan-Meier methods were used to estimate solid-tumor cancer-free survival rates. The difference among groups was analyzed using the log-rank test. For all tests a p value < 0.05 was considered statistically significant. Univariate analyses were performed to show the association between MED and incident solid-tumor cancer, with additional stratification by sex and presence of cardiovascular risk factors. Univariable and multivariable Cox proportional hazards analyses were performed to estimate the independent prognostic power. In multivariable analysis, four covariate sets were investigated: (a) RH-PAT index $\leq$2.0, age, sex, and coronary artery disease, (b) RH-PAT index $\leq$2.0, diabetes mellitus, hypertension, smoking status (current), and BMI >30 kg/m^2, (c) RH-PAT index $\leq$2.0, systolic blood pressure, smoking status (current or former), and BMI, and (d) RH-PAT index $\leq$2.0 and 10-year CVD risk calculated by Framingham risk score.[14] These covariates sets were chosen for clinical relevance. Receiver operating characteristics analysis was performed with two logistic regression models: (a) 10-year CVD risk, and (b) 10-year CVD risk and RH-PAT index. We evaluated the discriminatory power of RH-PAT index for solid-tumor cancer when adding RH-PAT index to the conventional CVD risk score by calculating net reclassification improvement and integrated discrimination improvement. All statistical analyses were performed using JMP Pro software (SAS Institute, Inc., Cary, North Carolina, USA) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Between January 2006–February 2014, 687 patients underwent endothelial function testing at the Mayo Clinic using the EndoPAT 2000 device for the assessment of chest pain and/or cardiovascular risk. Five patients who developed hematological malignancies (two patients with RH-PAT index $\leq$2.0 and three patients with RH-PAT index >2.0) and 194 patients with a follow-up period <90 days were excluded, leaving a total of 488 patients. Excluded patients with a follow-up period < 90 days were younger and had fewer comorbidities than patients with a follow-up period $\geq$90 days (Supplemental Material Table 1). Patients (mean age 53.5 ± 13.1 years old) were followed up for a maximum of 12 years (median 6.0 (3.0–9.1) years) at the Mayo Clinic from the date of the index microvascular endothelial function test. Two hundred and twenty-one patients (45.3%) had MED (defined as a RH-PAT index $\leq$2.0) and 267 patients (54.7%) had normal microvascular endothelial function (RH-PAT index >2.0). Table 1 outlines the baseline characteristics of the study sample categorized according to normal versus abnormal microvascular endothelial function. A higher proportion of patients with MED were men. Patients with MED were significantly more likely to be obese and have traditional cardiovascular risk factors, such as diabetes mellitus and dyslipidemia. Patients with MED were also more likely to be treated with aspirin, statins, and metformin. White blood cell count was significantly higher in patients with MED compared to those without MED ($p = 0.019$). The prevalence of a pre-existing diagnosis of a solid-tumor cancer was not different between the groups at baseline (Table 1). Comparison of baseline characteristics between patients with MED and those without MED among patients with a follow-up period < 90 days demonstrated a similar pattern to the studied population showing a higher prevalence of diabetes mellitus, dyslipidemia, and obesity (Supplemental Material Table 2).

Impact of MED on the incidence of a new solid-tumor cancer diagnosis

A total of 31 patients (6.4%) were diagnosed with solid-tumor cancer during the follow-up. The diagnosis of solid-tumor cancer was more frequent in patients with MED than in those without MED (9.5% vs 3.7%, $p = 0.009$) (Table 2). All-cause mortality was not different between patients with MED and patients without MED (3.6% vs 3.0%, $p = 0.70$). Cardiovascular mortality was the leading cause of death in patients with MED accounting for 62.5% of deaths, compared to

Table 1. Baseline clinical characteristics comparing patients with normal versus abnormal microvascular endothelial function using the reactive hyperemia peripheral arterial tonometry (RH-PAT) index (follow-up duration ≥90 days).

Characteristics	Total $n = 488$	RH-PAT index ≤2.0 $n = 221$	RH-PAT index >2.0 $n = 267$	p Value
Age, years	52.8 ± 13.1	52.1 ± 13.3	53.4 ± 12.9	0.25
Sex, *n* (%)				
Women	293 (60.0)	121 (54.8)	172 (64.4)	0.03
Men	195 (40.0)	100 (45.2)	95 (35.6)	
Race, *n* (%)				
Caucasians	448 (91.8)	203 (91.9)	245 (91.8)	0.97
Non-Caucasians	40 (8.2)	18 (8.1)	22 (8.2)	
Comorbidities, *n* (%)				
Hypertension	229 (46.9)	108 (48.9)	121 (45.3)	0.43
Diabetes mellitus	48 (9.8)	35 (15.8)	13 (4.9)	<0.001
Dyslipidemia	352 (72.1)	171 (77.4)	181 (67.8)	0.02
Chronic kidney disease	72 (16.4)	35 (17.2)	37 (15.7)	0.68
Coronary artery disease	106 (21.7)	56 (25.3)	50 (18.7)	0.08
Smoking, *n* (%)				
Current	25 (5.1)	12 (5.4)	13 (4.9)	0.96
Former	157 (32.1)	71 (32.1)	86 (32.2)	
Never	306 (62.7)	138 (62.4)	168 (62.9)	
Laboratory data				
LDL-C, mg/dl	106.6 ± 40.0	105.1 ± 38.3	107.8 ± 41.6	0.49
HDL-C, mg/dl	57.3 ± 17.7	54.2 ± 17.5	60.0 ± 17.5	0.001
Triglyceride, mg/dl	109 (78–157)	118 (80–177)	107 (77–147)	0.06
FPG, mg/dl	96 (90–104)	98 (92–106)	94 (89–102)	0.001
HbA1c, %	5.5 (5.2–6.0)	5.6 (5.2–6.3)	5.4 (5.2–5.9)	0.28
Creatinine, mg/dl	0.93 ± 0.23	0.94 ± 0.25	0.93 ± 0.21	0.58
WBC count, $\times 10^9$/l	6.67 ± 2.14	7.20 ± 2.35	6.26 ± 1.87	0.019
Neutrophil/WBC	0.60 ± 0.09	0.61 ± 0.11	0.59 ± 0.08	0.35
BMI, kg/m^2	28.4 ± 6.0	29.9 ± 6.4	27.3 ± 5.3	<0.001
Systolic BP, mm Hg	122.8 ± 16.9	122.6 ± 16.6	122.9 ± 17.2	0.86
Diastolic BP, mm Hg	74.8 ± 10.0	74.2 ± 10.0	75.3 ± 9.9	0.24
RH-PAT index	2.07 (1.71–2.52)	1.69 (1.47–1.82)	2.49 (2.21–2.79)	<0.001
Medications, *n* (%)				
Aspirin	251 (51.4)	125 (56.6)	126 (47.2)	0.04
Statin	217 (44.6)	109 (49.3)	108 (40.6)	0.05
Metformin	29 (5.9)	23 (10.4)	6 (2.3)	<0.001
Pioglitazone	4 (0.8)	3 (1.4)	1 (0.4)	0.23
ACEi/ARB	131 (26.8)	71 (32.1)	60 (22.5)	0.02
CCB	104 (0.21)	59 (26.7)	45 (16.9)	0.008
β Blocker	160 (32.8)	80 (36.2)	80 (30.0)	0.14
Long-acting nitrate	74 (15.2)	49 (22.2)	25 (9.4)	<0.0001
10-year CVD risk, %	7.3 (3.3–13.2)	7.3 (3.9–15.6)	6.7 (3.3–11.7)	0.094
Previous solid cancer, *n* (%)	64 (13.1)	26 (11.8)	38 (14.2)	0.42

ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Table 2. Incident solid-tumor cancer and death during follow-up.

Characteristics	Total $n = 488$	RH-PAT index ≤ 2.0 $n = 221$	RH-PAT index > 2.0 $n = 267$	p Value
Incident solid cancer, n (%)	31 (6.4)	21 (9.5)	10 (3.7)	0.009
Cancer type, *n* (%)				
Breast	6	4 (19.0)	2 (20.0)	
Lung	5	4 (19.0)	1 (10.0)	
Prostate	3	2 (9.5)	1 (10.0)	
Colorectal	1	1 (4.8)	0 (0.0)	
Cervix	1	0 (0.0)	1 (10.0)	
Skin	15	10 (4.8)	5 (50.0)	
All cause death, n (%)	16 (3.3)	8 (3.6)	8 (3.0)	0.70
Cause of death, *n* (%)				
Cardiovascular	6	5 (62.5)	1 (12.5)	
Cancer-related	3	1 (12.5)	2 (25.0)	
Others/unknown	7	2 (25.0)	5 (62.5)	

RH-PAT: reactive hyperemia peripheral arterial tonometry.

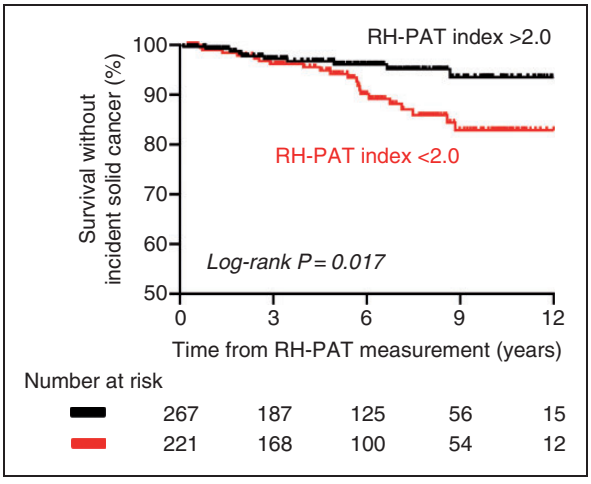

Figure 1. Comparison of solid-tumor cancer-free survival between patients with normal versus abnormal microvascular endothelial function as measured using the reactive hyperemia peripheral arterial tonometry (RH-PAT) index. Patients with microvascular endothelial dysfunction had a lower solid-tumor cancer-free survival compared to those with normal microvascular endothelial function at baseline (log-rank $p = 0.017$).

12.5% of deaths in patients without MED. Only one solid-tumor cancer-related death (12.5%) occurred in patients with MED, while two deaths (25.0%) occurred in patients without MED (Table 2). MED at baseline was significantly associated with decreased solid-tumor cancer-free survival with the divergence in survival curves becoming apparent after six years (log-rank $p = 0.017$) (Figure 1). The association between MED and incident solid-tumor cancer was prominent in men, patients with hypertension, dyslipidemia, and significant coronary artery disease, and patients without diabetes mellitus, current smoking, and obesity (Table 3). Univariate Cox proportional hazard ratio analysis demonstrated that MED, aging, and male sex were significantly associated with an increased risk of incident solid-tumor cancer (hazard ratio (HR) of RH-PAT index ≤ 2.0 2.43, 95% confidence interval (CI) 1.14–5.16; $p = 0.021$, HR age 1.51, 95% CI 1.12–2.06; $p = 0.009$, HR male sex 2.20, 95% CI 1.07–4.48; $p = 0.031$), but coronary artery disease and 10-year CVD risk were not associated with an increased risk of incident solid-tumor cancer (Table 4). Patients with coronary artery disease were significantly older, more predominantly men, and had more comorbidities (Supplemental Material Table 3). A RH-PAT index ≤ 2.0 was a robust predictor of an increased risk of incident solid-tumor cancer after adjustment for coronary artery disease and non-modifiable risk factors such as age and sex (multivariate set 1), modifiable risk factors, such as diabetes mellitus (or fasting plasma glucose level), hypertension (or systolic blood pressure), current smoking (or current/former smoking), and BMI $> 30\,kg/m^2$ (or BMI) (multivariate set 2 and 3), and 10-year CVD risk (multivariate set 4) ((1) adjusted HR 2.52, 95% CI 1.17–5.45; $p = 0.019$, (2) adjusted HR 2.83, 95% CI 1.30–6.17; $p = 0.009$, (3) adjusted HR 2.79, 95% CI 1.21–6.41; $p = 0.016$, (4) adjusted HR 2.43, 95% CI 1.10–5.34; $p = 0.028$) (Table 5). The RH-PAT index was significantly lower in patients who developed incident solid-tumor cancer during follow-up compared to patients who did not develop incident solid-tumor cancer

Table 3. The association between abnormal microvascular endothelial function and incident solid-tumor cancer.

Stratified by	No. of patients with RH-PAT index ≤ 2.0 /all patients (%)	No. of patients with incident solid-tumor cancer /all patients (%)	Odds ratio	95% CI	*p* Value
All individuals	221/488 (45.3)	31/488 (6.4)	2.70	(1.24–5.86)	0.009
Sex					
Male	100/195 (51.3)	18/195 (9.2)	3.70	(1.17–11.69)	0.018
Female	121/293 (41.3)	13/293 (4.4)	1.69	(0.56–5.19)	0.35
Hypertension					
(–)	113/259 (43.6)	14/259 (5.4)	0.97	(0.33–2.87)	0.95
(+)	108/229 (47.2)	17/229 (7.4)	9.60	(2.14–43.02)	0.0004
Dyslipidemia					
(–)	50/136 (36.8)	10/136 (7.4)	2.80	(0.75–10.43)	0.11
(+)	171/352 (48.6)	21/352 (6.0)	2.80	(1.06–7.41)	0.031
Diabetes mellitus					
(–)	186/440 (42.3)	27/440 (6.1)	2.45	(1.10–5.49)	0.025
(+)	35/48 (72.9)	4/48 (8.3)			
Coronary artery disease					
(–)	165/382 (43.2)	21/382 (5.50)	1.81	(0.75–4.41)	0.18
(+)	56/106 (52.8)	10/106 (9.4)	9.38	(1.14–77.0)	0.013
Current smoking					
(–)	209/463 (45.1)	29/463 (6.3)	2.88	(1.28–6.47)	0.008
(+)	12/25 (48.0)	2/25 (8.0)	1.09	(0.06–19.62)	0.95
BMI					
$<30\,kg/m^2$	124/320 (38.8)	24/320 (7.5)	3.48	(1.44–8.40)	0.004
$\geq 30\,kg/m^2$	96/166 (57.8)	7/166 (4.2)	1.87	(0.35–9.92)	0.46

BMI: body mass index; CI: confidence interval; RH-PAT: reactive hyperemia peripheral arterial tonometry.

(1.79 (1.59–2.23) vs 2.08 (1.72–2.54), $p = 0.026$) (Figure 2). The discriminatory accuracy for incident solid-tumor cancer significantly improved after adding RH-PAT index to the 10-year CVD risk calculated by Framingham CVD risk score (integrated discrimination improvement 0.0119, 95% CI 0.0009–0.023; $p = 0.035$, net reclassification improvement 0.4381, 95% CI 0.0865–0.7898; $p = 0.015$) (Supplemental Material Table 4).

Discussion

In the current study we show that patients with MED had a greater than two-fold increased risk of developing incident solid-tumor cancer compared to those without MED at baseline, even after adjusting for co-variables. In addition, individuals with MED had a lower solid-tumor cancer-free survival compared to individuals with normal microvascular endothelial function at baseline. Thus, the current study supports the concept that MED may predispose to the development of cancer and/or may act as a surrogate marker of risk for the development of cancer.

MED as an integrated marker of risk factors

Evidence to date suggests that several proatherogenic stimuli trigger inflammation and reactive oxygen species (ROS) production in endothelial cells, and that excess oxidative stress plays a crucial role in the pathologic manifestations of atherosclerosis.[15] Meanwhile, inflammation and genotoxic stress induce apoptosis via ROS production, and ROS-induced DNA damage may play an essential role in the development of cancer.[16–18] Chronic inflammation and excess oxidative stress are two of the underlying biological processes for both atherosclerotic CVDs and cancer. The fact that anti-inflammatory treatment targeting interleukin-1β reduced not only major cardiovascular events post-myocardial infarction but also lung cancer incidence and mortality in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) further supports this notion.[19] Previous studies have shown that a decreased RH-PAT index is associated with increased inflammatory cytokines and oxidative stress markers.[20,21] Furthermore, we previously reported an inverse correlation between RH-PAT index and white

Table 4. Univariate Cox proportional hazard ratio analysis for the incidence of solid-tumor cancer.

	Univariate		
Variable	HR	95% CI	*p* Value
RH-PAT index ≤2.0	2.43	(1.14–5.16)	0.021
RH-PAT index, unit increase	0.52	(0.26–0.98)	0.043
Age, 10-year increment	1.51	(1.12–2.06)	0.009
Male sex	2.20	(1.07–4.48)	0.031
White race	2.43	(0.33–17.83)	0.38
Diabetes mellitus	1.36	(0.48–3.89)	0.57
Fasting plasma glucose, mg/dl	0.99	(0.96–1.01)	0.37
HbA1c, %	1.32	(0.39–3.00)	0.57
Hypertension	1.26	(0.62–2.56)	0.52
Systolic BP, mm Hg	1.01	(0.98–1.02)	0.61
Diastolic BP, mm Hg	1.02	(0.98–1.06)	0.37
Dyslipidemia	0.71	(0.33–1.51)	0.37
LDL-C, mg/dl	0.46	(0.04–3.73)	0.49
HDL-C, mg/dl	0.99	(0.97–1.02)	0.77
Triglyceride, mg/dl	1.00	(0.99–1.00)	0.14
Coronary artery disease	1.68	(0.79–3.58)	0.18
Current smoking	1.11	(0.26–4.64)	0.89
Current or former smoking	1.40	(0.69–2.85)	0.34
BMI ≥ 30 kg/m^2	0.57	(0.24–1.31)	0.19
BMI, kg/m^2	0.96	(0.89–1.02)	0.23
10–year CVD risk, %	1.03	(0.99–1.07)	0.14

BMI: body mass index; CI: confidence interval; CVD: cardiovascular disease; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; RH-PAT: reactive hyperemia peripheral arterial tonometry.

blood cell count, which is consistent with the current observation showing increased white blood cell count in patients with MED.[22] MED may therefore indicate these conditions in any given individual, although in the current study we did not address the direct association between oxidative stress markers and RH-PAT index. Conventional cardiovascular risk factors,

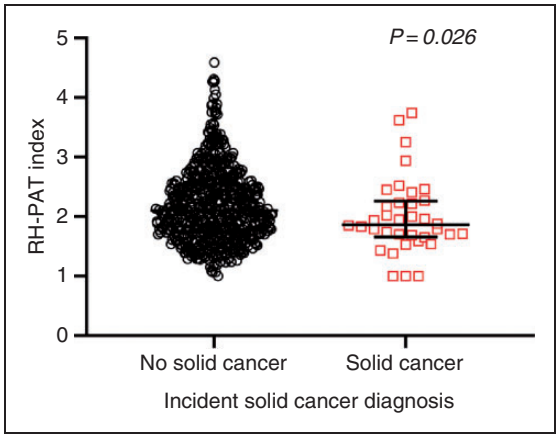

Figure 2. Comparison of reactive hyperemia peripheral arterial tonometry (RH-PAT) index between patients with and those without incident solid-tumor development. Scatter plot and median with interquartile range of the RH-PAT index comparing patients with and those without incident solid-tumor cancer development during follow-up. Patients with incident solid-tumor cancer during follow-up had a significantly lower RH-PAT index at baseline compared to those without incident solid-tumor cancer (1.79 (1.59–2.23) vs 2.08 (1.72–2.54), $p = 0.026$).

Table 5. Multivariate Cox proportional hazard ratio analysis for the incidence of solid-tumor cancer.

	Multivariate 1			Multivariate 2			Multivariate 3			Multivariate 4		
Variable	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
RH-PAT index ≤2.0	2.52	(1.17–5.45)	0.019	2.83	(1.30–6.17)	0.009	2.79	(1.21–6.41)	0.016	2.43	(1.10–5.34)	0.028
Age, 10-year increment	1.57	(1.14–2.16)	0.006									
Male sex	2.01	(0.94–4.31)	0.073									
Coronary artery disease	0.84	(0.36–1.95)	0.69									
Diabetes mellitus				1.09	(0.36–3.36)	0.88						
Hypertension				1.53	(0.72–3.24)	0.27						
Current smoking				1.34	(0.31–5.73)	0.69						
BMI ≥30 kg/m^2				0.39	(0.16–0.96)	0.041						
FPG, mg/dl							0.99	(0.96–1.02)	0.47			
Systolic BP, mm Hg							1.01	(0.99–1.04)	0.21			
Current/former smoking							1.24	(0.58–2.80)	0.54			
BMI, kg/m^2							0.93	(0.86–1.07)	0.087			
10-year CVD risk, %										1.02	(0.98–1.06)	0.21

BMI: body mass index; BP: blood pressure; CI: confidence interval; CVD: cardiovascular disease; FPG: fasting plasma glucose; HR: hazard ratio; RH-PAT: reactive hyperemia peripheral arterial tonometry.

such as hypertension, diabetes mellitus, current smoking status, and obesity individually were not found to be independent predictors of incident solid-tumor cancer in the current analysis. Furthermore, even 10-year CVD risk was not an independent predictor of incident solid-tumor cancer. Nevertheless, previous reports have demonstrated that these factors may also induce chronic inflammation and oxidative stress, leading to CVD and be associated with carcinogenesis in large-scale epidemiological studies.[4,7,23,24] This observation may indicate that MED, as a marker of vascular health, provides an integrated index of risk that is superior to that provided by individual factors and Framingham CVD risk score.

MED-induced tissue hypoxia can affect carcinogenesis

Endothelial function plays a critical role in regulating blood supply in response to ischemia and metabolic demands. Thus, endothelial dysfunction may impose a risk of chronic hypoxia to perfusing tissue.[25,26] Chronic hypoxia can induce genetic instability through the alteration of DNA damage-associated checkpoints and decreased DNA repair.[27] Furthermore, hypoxic human cells increase their glucose uptake as a consequence of the metabolic shift from aerobic respiration to anerobic glycolysis, resulting in accumulation of various glycolytic metabolites such as uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) and uridine diphosphate glucuronic acid (UDP-GlcUA).[28,29] UDP-GlcNAc and UDP-GlcUA are used to synthesize hyaluronic acid, which has been linked to cancer development.[30] Tissue hypoxia also stimulates angiogenesis via hypoxia-inducible factor 1 (HIF-1).[31] Angiogenesis through the action of HIF-1 and subsequent activation of vascular endothelial growth factor (VEGF) is a common pathway in atherogenesis and carcinogenesis.[32] In this context, endothelial dysfunction might increase the risk of solid-tumor cancer by potentially leading to chronic tissue hypoxia, although the precise molecular processes involved require further clarification.

Interpretation and outcome of RH-PAT index results

Our data demonstrate that MED characterized as a low RH-PAT index was associated with a greater than two-fold increased risk of future solid-tumor cancer development (Figure 1, Tables 4 and 5). Although the median baseline RH-PAT index was significantly lower in patients with incident solid-tumor cancer during follow-up compared to that in patients without incident solid-tumor cancer, there was a notable overlap between the two groups (Figure 2). Therefore, it is difficult to determine a clear cut-off value of the RH-PAT index to predict the incidence of future solid-tumor cancer development. Nevertheless, the current study shows that MED measured using RH-PAT acts as an indicator of risk for the future development of solid-tumor cancer, and could therefore be used to identify patients who require more aggressive screening (Supplemental Material Table 4). This in turn could allow for the detection of pre-malignant disease, or cancer in the early stages of its natural history, that may still be amenable to curative therapy, or potentially to identify individuals at risk in whom lifestyle interventions and therapeutic approaches targeting vascular health could be recommended. However, further studies are needed to clarify whether any therapy targeting endothelial dysfunction could reduce the risk of incident solid-tumor cancers.

Limitations

This study has a number of limitations. First, because of the retrospective observational cohort design, it is challenging to derive causal associations from the current study. Second, despite collecting clinical data from detailed chart review, misclassification of cancer and undetected incident cancer may have occurred. Of note, however, the clinical data were collected by an investigator blinded to the RH-PAT data. Third, diet and nutrition are significant determinants that influence both CVD and cancer development. For example, red meat raises the risk of CVD by increasing the plasma level of trimethylamine-N-oxide, as well as the risk of colorectal cancer.[33,34] Nevertheless, we could not adjust for the influence of diet and nutrition due to lack of data. Similarly, we could not adjust for alcohol consumption, which is also a known risk factor for CVD as well as a number of solid-tumor cancers. However, only two patients in this study had a documented history of heavy alcohol consumption that could play a role in disease development, and thus the effect of excess alcohol intake was not accounted for. Fourth, patients with MED had more comorbidity and were taking more medications, such as aspirin, statins, metformin, and antihypertensive medications, which may have drawn more medical attention to these patients, resulting in higher levels of incidental detection of solid-tumor cancers. Also, the direct effects of medications on incident solid-tumor cancer could not be ignored. Aspirin and statins have been identified as protective against colorectal cancer, while metformin is protective against breast, colon, liver, pancreas, prostate, endometrium, and lung cancer.[35–37] Given that (a) these medications were more prevalent among MED patients who, as compared to patients without MED, developed more solid-tumor cancers during the follow-up period,

and (b) these medications were shown to reduce the risk of incident solid-tumor cancer, the significant effect of MED on incident solid-tumor cancer risk might be underestimated and therefore even larger than that observed in this study. On the contrary, pioglitazone and angiotensin-converting enzyme inhibitor might be associated with an increased risk of bladder cancer and lung cancer, respectively.[38,39] However, none of the patients studied developed bladder cancer, and all five patients who developed lung cancer were not treated with angiotensin-converting enzyme inhibitor. Fifth, while the CANTOS trial reported high sensitivity C-reactive protein and interleukin 6 as surrogate markers to predict future risk of lung cancer in post-myocardial infarction patients treated with canakinumab,[19] the lack of these inflammatory and oxidative stress biomarkers in the majority of study population limits our ability to meaningfully evaluate the possible mechanistic link of inflammation and/or oxidative stress to MED and its association with incident solid-tumor cancer. However, we have previously shown the association between local inflammatory and/or oxidative stress markers such as F2-isoprostanes, myeloperoxidase, and lipoprotein-associated phospholipase A2 and coronary endothelial dysfunction.[40–42] Furthermore, increased serum high sensitivity C-reactive protein was associated with coronary MED which could be noninvasively assessed with RH-PAT index.[43,44] Our data indicating the close association between MED and increased white blood cell count, which has been linked to the increased risk of cancer,[24] could partly explain the underlying chronic inflammation. Finally, though we calculated the predictive value of the RH-PAT index using a multivariable analysis, we could not adjust for all the variables due to the small numbers of events in our sample. Nevertheless, an RH-PAT index $\leq$2.0 remained an independent predictor of new solid-tumor cancer development after adjusting for variables shown to be relevant to both cancer and CVD in previous studies. Also, we could not estimate the predictive value of the RH-PAT index for the individual types of solid-tumor cancers due to the small numbers of events. However, given that adherence of cardiovascular health metrics reduced the rates of incident combined cancer, MED could be viewed as a comprehensive risk marker of incident solid-tumor cancers.[1]

Conclusions

In conclusion, MED defined by an RH-PAT index $\leq$2.0 predicts incident solid-tumor cancers. Abnormal peripheral vasoreactivity should thus alert clinicians not only to the risk of CVD but also to that of malignancy in any given individual. This risk prediction appears to precede the development of disease by more than five years. Whether improvement in MED translates into reduction of incident CVD and cancer remains to be determined. Similarly, the mechanism underlying this association needs to be defined in future studies.

Author contribution

TT, JDS, and AL contributed to the conception and design of the work. TT, JDS, RT, and SG contributed to the acquisition, analysis, or interpretation of data for the work. TT, JDS, and MTC drafted the manuscript. JH, LOL, and AL critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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