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Thermal heterogeneity of carotid arteries as a novel biomarker in patients with diabetes mellitus assessed for coronary artery disease

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ABSTRACT

Background: Vulnerable plaque plays crucial role in prognosis of diabetes mellitus (DM). Microwave radiometry (MWR) allows measurement of the temperature of tissues, thus indirectly reflecting inflammation, a characteristic of atherosclerotic plaque stability. Aim of the study was to evaluate the relation of carotid artery inflammation with glycemic control and presence of coronary artery disease (CAD).
Methods: We included 112 patients (65 ± 9 years, 30 ± 5 kg/m^2, 74 DM and 38 non-DM, with a 2:1 ratio) that were referred for scheduled coronary angiography (CA) for evaluation of their clinical condition. We measured thermal heterogeneity, expressed as temperature difference (ΔT) along each carotid artery, with MWR and maximum temperature difference between the 2 carotid arteries (ΔTmax).
Results: Patients with DM presented higher ΔTmax comparing to patients without DM (0.91 ± 0.29 vs 0.71 ± 0.25 °C, $p < 0.001$). Glycaemia over time was associated with thermal heterogeneity of carotids (HbA1c: *<6.5*: 0.78 ± 0.23, HbA1c: *6.5–7*: 0.87 ± 0.24, HbA1c: *7–8*: 0.99 ± 0.30, HbA1c: *>8*: 1.15 ± 0.35 °C, $p = 0.003$). Patients with CAD presented higher ΔTmax comparing to patients with normal CA (0.93 ± 0.24 vs 0.68 ± 0.25 °C, $p < 0.001$) and patients that underwent coronary revascularization presented higher ΔTmax (0.95 ± 0.25 vs 0.76 ± 0.26 °C, $p < 0.001$). A ΔTmax ≥ 0.9 (received by ROC analysis) was an independent predictor for revascularization in DM patients (odds ratio 3.29, 95% CI: 1.07–10.16; $p = 0.039$) when adjusted for sex, age and the established risk factors of CAD.
Conclusion: Local inflammatory activation of carotid arteries is more pronounced in patients with DM and is associated with the glycemic control. Carotids' thermal heterogeneity is associated with need for revascularization supporting its predictive value in DM patients assessed for CAD.

1. Introduction

Diabetes mellitus (DM) is established as one of the significant risk factors of coronary artery disease (CAD) that affects cardiovascular events and mortality [1]. Vulnerable plaques seem to play a crucial role in cardiovascular outcomes [2], while glycemic status and presence of DM is associated with more pronounced vulnerable plaque characteristics [3,4], probably linked to the unfavorable outcomes. Early identification of vulnerable atherosclerotic plaques in order to intervene in level of primary and secondary prevention could dramatically change outcomes of cardiovascular disease.

Microwave radiometry (MWR) is a new non-invasive method allowing measurement of the temperature of tissues, thus indirectly reflecting inflammation, a characteristic of vulnerable plaques [5]. This method can designate thermal heterogeneity (TH) of carotid arteries [6,7], which, unlike structural characteristics and degree of luminal stenosis, assesses the inflammatory activation within the plaque [8]. TH of carotids has been found to be predictive of the presence and extend of CAD [9], and is significantly attenuated in patients with CAD and DM [10]. However, the relationship of TH with glycemic control and its impact on the need for coronary revascularization has not been investigated so far.

We aimed to assess the relation of carotid artery inflammation with: a) glycemic control and b) coronary revascularization, in patients with DM undergoing coronary angiography for CAD assessment.

2. Methods

2.1. Study population

We prospectively evaluated 112 patients that were referred to our department for scheduled diagnostic coronary angiography (CA) for evaluation of their clinical status, without including patients with myocardial infraction. Patients were enrolled with a 2:1

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ratio (DM: non-DM) in order to better investigate the effects of glycemic control in DM patients.

All patients were evaluated for temperature difference (ΔT) along each carotid artery with MWR. Patients' baseline, clinical characteristics and medications are presented in Table 1. All participants gave informed consent to participate in the study, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study was approved by the ethics committee of the institution.

2.2. Microwave radiometry measurements

The MWR measurements were performed with the RTM 01 RES microwave computer-based system (Bolton, UK). The system measures the temperature of internal tissues at microwave frequencies. The basic principles of MWR have been previously described [7,9]. MWR system has an antenna with two sensors: one for microwaves and the other for infrared. The microwave sensor filters all possible microwaves or radiofrequency waves that may be present in the room vicinity and cause interference with the sensor. The antenna detects microwave radiation at 2–5 GHz. The volume under investigation is a rectangular area 3 cm wide, 2 cm long and 3–7 cm in depth. The second sensor takes infrared measurements from the skin for calibrating the microwave sensor reading.

The segments analyzed were about 20 mm in length, starting from the proximal common carotid artery and moving distally, thus avoiding overlapping or missing areas by MWR. The microwave antenna of the device was placed at a 90° angle to the skin. After setting vertically the transducer, carotid temperature measurements were performed three times on each segment (overall, 9 measurements). The temperature of each segment used for further analysis was the mean of the 3 temperatures. This method has been validated as previously described [6,7]. The temperature difference (ΔT) for each carotid artery was defined as the temperature of the segment with the highest temperature minus the lowest temperature for each carotid (reference temperature), as previously described [7,9]. In the statistical analysis, "ΔTmax" was defined as the maximum ΔT value of both carotid arteries.

2.3. Laboratory tests

The laboratory tests included an evaluation of glycemic control based on fasting glucose and glycated haemoglobin (HbA1c) and other tests measuring total cholesterol and fractions, triglycerides, urea, creatinine, transaminases, and blood count. High-sensitivity troponin T (TnT-hs) was analyzed only in 37 patients, because only during the last period of the study the high sensitivity assay was available. HbA1c values were obtained from all patients (DM and non DM).

Table 1
Baseline characteristics and medication.

	Total (n = 112)	DM (n = 74)	Non-DM (n = 38)	p Value
Clinical characteristics				
Age, years	65 ± 9	66 ± 9	63 ± 9	0.08
Body mass index, kg/m^2	30 ± 5	30 ± 5	30 ± 5	0.89
Gender, m/f	70/42	44/30	26/12	0.57
Hypertension	85 (76)	59 (80)	26 (68)	0.19
Dyslipidaemia	71 (63)	51 (69)	22 (58)	0.25
Family history	14 (13)	7 (10)	7 (18)	0.18
Smoking (current)	38 (34)	23 (31)	15 (40)	0.64
CAD history	28 (25)	19 (26)	9 (24)	0.82
DM duration, years	–	11 ± 9	–	
Coronary angiography				0.26
1-vessel CAD (%)	25	26	24	
2-vessel CAD (%)	17	16	17	
3-vessel CAD (%)	18	23	11	
Medication				
ASA	42 (38)	28 (38)	14 (37)	0.94
ADP receptor inhibitor	27 (24)	19 (25)	8 (20)	0.55
ACE-i/ARB	73 (65)	49 (66)	24 (63)	0.75
Calcium antagonist	22 (20)	16 (22)	6 (17)	0.57
b-blocker	68 (61)	45 (61)	23 (60)	0.92
Diuretics	48 (43)	33 (44)	15 (40)	0.70
Statins	72 (64)	55 (74)	17 (46)	**0.01**
Laboratory tests				
Glucose, mg/dl	142 ± 59	161 ± 66	102 ± 16	<**0.001**
Haemoglobin A1c, %	6.6 ± 1.4	7.1 ± 1.5	5.5 ± 0.4	<**0.001**
Haemoglobin, g/dl	13.6 ± 1.8	13.4 ± 1.7	14.1 ± 1.8	**0.05**
Creatinine, mg/dl	1.0 ± 0.6	1.1 ± 0.8	0.9 ± 0.2	0.13
AST, U/L	24 ± 15	25 ± 18	21 ± 7	0.29
ALT, U/L	23 ± 16	24 ± 18	21 ± 10	0.33
Total cholesterol, mg/dL	167 ± 37	163 ± 38	178 ± 30	0.12
LDL cholesterol, mg/dL	91 ± 31	88 ± 30	98 ± 36	0.30
HDL cholesterol, mg/dL	44 ± 13	42 ± 11	51 ± 16	**0.01**
Triglyceride, mg/dL	146 ± 73	151 ± 80	130 ± 47	0.28

DM: Diabetes mellitus; CAD: Coronary artery disease; ASA: Acetylsalicylic acid; ADP: Adenosine diphosphate; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blockers; AST/ALT: Aspartate/alanine transaminase; LDL/HDL: low-density/high-density lipoprotein; Values are mean ± SD.
Bold indicates significance of $p < 0.05$.

2.4. Coronary angiography

Angiograms were assessed independently by 2 experienced interventional cardiologists. CAD was defined as angiographic atherosclerotic involvement of >50% in at least 1 major coronary artery or its major branches. The severity of CAD was assessed from the number of involved coronary vessels with significant luminal obstructions.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation. Before analysis, all continuous variables were tested by Kolmogorov-Smirnov test showing normal distribution. Group means of continuous variables were compared by unpaired Student's *t*-test. ΔTmax values between HbA1c and CAD categories (known without progression, known with disease progression and first diagnosis) were compared using one-way analysis of variance (ANOVA).

Correlations between variables were obtained and tested by Pearson's correlation coefficient after tested for normality curves. The cut-off value for ΔTmax to predict presence of CAD was based on receiver operating characteristic (ROC) curve analysis. Multiple logistic regression analysis was used to determine independent predictors for coronary revascularization in presence of CAD. The lowest level for statistical significance was set at $p < 0.05$.

3. Results

We included a total of 112 patients, 74 DM patients (44 males, 66 ± 9 years, 30 ± 5 kg/m^2) and 38 patients without DM (26 males, 63 ± 9 years, 30 ± 5 kg/m^2, Table 1).

Patients with DM presented significantly higher TH comparing to patients without DM (0.91 ± 0.29 vs 0.71 ± 0.25 °C, $p < 0.001$). Glycaemia control over time was associated with TH of carotid arteries in DM patients (*HbA1c < 6.5%*: 0.78 ± 0.23, *HbA1c 6.5–7%*: 0.87 ± 0.24, *HbA1c 7–8%*: 0.99 ± 0.30, *HbA1c > 8%*: 1.15 ± 0.35 °C, $p = 0.003$ ANOVA, Fig. 1). A significant correlation between HbA1c and ΔTmax was found in patients with DM ($r = 0.50$, $p < 0.001$), while in non-DM patients HbA1c was not found to be correlated with ΔTmax ($r = 0.09$, $p = 0.63$).

Patients with CAD presented higher ΔTmax comparing to patients with normal CA (0.93 ± 0.24 vs 0.68 ± 0.25 °C, $p < 0.001$, Fig. 2). This finding was confirmed also for both patient subgroups: a) DM patients with CAD presented higher ΔTmax than DM without CAD (0.96 ± 0.25 vs 0.77 ± 0.26 °C, $p = 0.005$), b) non-DM patients with CAD presented higher ΔTmax than non-DM patients without CAD (0.85 ± 0.23 vs 0.54 ± 0.18 °C, $p < 0.001$). Another notable finding is that

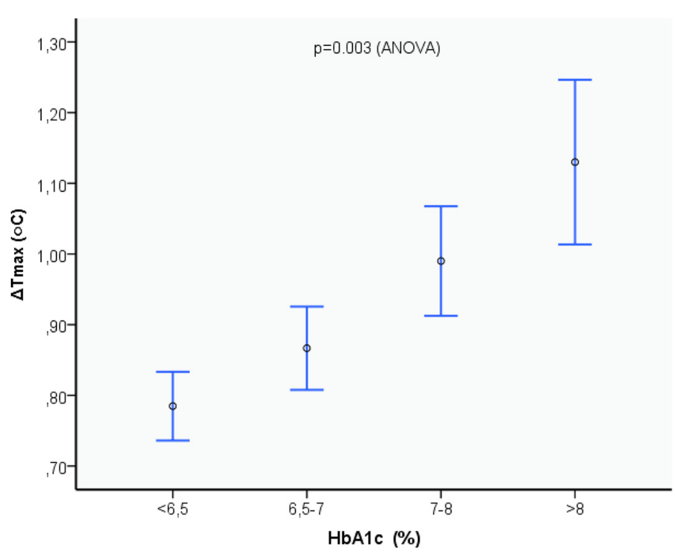

Fig. 1. Hba1c levels and thermal heterogeneity of carotid arteries. (Bars are mean ± SE).

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