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Female gender is independently associated with increased carotid temperatures in patients with coronary artery disease

Georgios Benetos [a,1,2], Konstantinos Toutouzas [a,*,1,2], Ioannis Matsoukis [a,2], Maria Drakopoulou [a,2], Fotini Mitropoulou [a,2], Iosif Koutagiar [a,2], Charalampia Nikolaou [a,2], Konstantinos Stathogiannis [a,2], Elias Siores [b,2], Dimitris Tousoulis [a]

[a] First Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece
[b] Centre for Materials, Research and Innovation, University of Bolton, Bolton, UK

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ABSTRACT

Background: Limited are the data regarding the sex differences in functional carotid artery characteristics. Microwave Radiometry (MWR) is a new noninvasive method, which measures in vivo instantly the internal temperatures of tissues, reflecting inflammation. The aim of the present study was to investigate whether in patients with coronary artery disease (CAD), gender related differences apply in carotid plaque functional characteristics, as assessed by MWR.

Methods: Consecutive patients with significant CAD were included in the study. All patients underwent evaluation of both carotid arteries by 1) ultrasound and 2) MWR. During ultrasound common carotid IMT and plaque thickness were assessed according to Mannheim consensus. During MWR measurements, temperature difference (ΔT) was assigned as maximal temperature along the carotid artery minus minimum. ΔT ≥0.90 °C was assigned as high ΔT.

Results: In total 364 patients with significant CAD were included in the study. Of these 54 were female and 310 were male. Max plaque thickness and cclMT were similar between males and females (2.38 ± 1.16 vs. 2.46 ± 1.12 mm, $p = 0.63$ and 0.944 ± 0.172 vs. 0.942 ± 0.169 mm, $p = 0.96$). Carotid arteries of females showed higher ΔT values (1.16 ± 0.48 vs 0.87 ± 0.45 °C, $p < 0.001$). Interestingly, females had more commonly high ΔT values bilaterally (35.2% vs 15.5%, $p = 0.001$). In multivariate analysis, female sex was independently associated with bilateral high ΔT, when adjusted to potential covariates (OR = 2.78, 95% CI = 1.42–5.45, $p = 0.003$).

Conclusions: In patients with CAD, sex specific differences apply in functional but not in structural carotid artery characteristics. Whether this discrepancy has prognostic significance, remains to be clarified in future studies.

1. Introduction

Carotid atherosclerosis represents a major cause of stroke. Recent reports show differences in the incidence, prevalence and severity of ischemic strokes between the two genders [1]. In specific, women suffer from stroke in older age than men, but the total lifelong incidence is higher in females. Interestingly, stroke related mortality and morbidity appears to be higher in women [2]. Moreover, carotid endarterectomy, as the basic therapy for critical carotid stenosis, shows greater long-term benefit in men than women, both for symptomatic and asymptomatic stenosis [3,4].

Despite these major differences, few studies have addressed gender-related differences in pathophysiology of carotid atherosclerosis and most of our knowledge regarding this topic is derived from coronary arteries [5–7]. Pathological studies have revealed a significantly more vulnerable carotid plaque phenotype in men compared to women. Indeed, inflammatory cell infiltration and intraplaque hemorrhage are more prominent in male carotid endarterectomy specimens [8–10]. In contrast, women show in vivo more intense intraplaque neovascularization, as assessed by contrast enhanced ultrasound [11]. Limited are the data, however, in regard to sex differences in functional characteristics of carotid arteries.

Microwave radiometry (MWR) allows in vivo noninvasive measurement of the temperature of carotid atherosclerotic plaques, reflecting their inflammatory status, as it has been shown in recent studies [12–18]. More importantly, MWR measurements have been

* Corresponding author at: Hippokration General Hospital, 114 Vas. Sofias ave, Athens, Greece.
E-mail address: ktoutouz@gmail.com (K. Toutouzas).
[1] These authors contributed equally to the manuscript.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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associated with vulnerable carotid plaque characteristics, including plaque neovascularization [15].

In the present study, we aimed to investigate in patients with significant coronary artery disease (CAD), whether: 1) sex related differences apply in carotid plaque temperatures, as assessed by MWR and 2) differences are evident in carotid morphological characteristics, as assessed by ultrasound.

2. Methods

2.1. Study population

Consecutive patients with significant coronary artery disease-CAD (≥50% stenosis in at least one major epicardial vessel), undergoing coronary angiography due to stable angina or variant acute coronary syndromes, were prospectively enrolled in the study.

During their stay in the hospital, all patients underwent ultrasound evaluation of both carotid arteries followed by MWR measurements performed by specialists blinded to angiographic results. Patients with any cerebrovascular disease, previous stroke or transient ischemic attacks, vasculitis, non-atherosclerotic carotid artery disease, intermittent inflammatory, infectious or neoplasmatic conditions, or patients that were treated with corticosteroids or/and NSAD (except aspirin) were excluded from the study.

Medical history, conventional risk factors for coronary artery disease and current medical therapy were recorded in all patients. Data from the angiography were used to identify the percentage of arterial stenosis and the number of coronary vessels involved. Written informed consent was obtained from each patient. The study protocol was approved by the hospital's Ethics Committee.

2.2. Ultrasound imaging

A high-resolution B-mode ultrasound unit (iE33 xMATRIX, Philips Healthcare, Bothell, WA, USA), with a 7.5 MHz transducer was used to examine both carotid arteries (common, internal, external) throughout their whole length, in transverse and longitudinal sections. Ultrasound imaging procedures and specific definitions of the examined parameters were previously described [19,20]. In brief, ultrasound measurements were performed over three segments of 20 mm in length. Carotid bifurcation was the middle segment and was used as a marker. Carotid plaque thickness (PT) and the common carotid artery intima-media thickness (ccIMT) were measured according to Mannheim consensus [21]. In specific, ccIMT was measured at the last 10 mm of the distal wall of common carotid at region without plaque. The highest value of ccIMT and PT for both carotid arteries was assigned as ccIMTmax and PTmax respectively.

Atherosclerotic plaque morphology, echogenicity, consistency, surface contour and heterogeneity were also defined. Gray–Weale classification was used for plaque echogenicity evaluation (Types I–V) [22]. Based on this, plaques were described, according to the morphology, as fatty (Type I–II) mixed (Type III–IV) and calcified (Type V), or according to the heterogeneity, as heterogeneous (Type I–II) and homogeneous (Type III–V) [23]. The plaque was also defined as regular if its surface was smooth or irregular if a rupture variated between 0.3 mm and 0.9 mm was observed on the surface of any plaque [24]. All data were collected and interpreted by experienced ultrasonographers. In case of disagreement, data were evaluated by a third one, and the final decision was extracted by the research team.

2.3. Microwave radiometry measurements

A microwave computer-based system (RTM 01 RES, Bolton, United Kingdom) that detects temperature from internal tissues at microwave frequencies was used to measure carotid plaque temperature [25,26]. The basic principles, the technical and functional characteristics of MWR device have been previously described [12–17]. In brief, MWR measurements were obtained over the previously defined segments, at least 10 min after the ultrasound examination in order to avoid any influence on temperature from palpation or the ultrasound study. Carotid plaque temperature was the median value of three repeated measurements after setting vertically the transducer on the specific segment for 10 s. This procedure was repeated over all the previously defined from the ultrasound segments, starting from the distal to the proximal segment. [20,27]. During MWR measurements, temperature difference (ΔT) was defined as maximal temperature along the carotid artery minus minimum. ΔT ≥0.90 °C was assigned as high ΔT according to previous observations [15]. ΔTmax was assigned as the maximal value of the ΔTs of both carotid arteries [19].

2.4. Statistical analysis

Carotid artery and patient based analysis were performed to determine the impact of gender on morphological and functional carotid artery characteristics.

Quantitative data are presented as rates or mean values ± SD, while qualitative variables as absolute and relative frequencies. Probability values were two-sided from the Student t-test for continuous variables. Non-continuous values were compared by chi square test. All risk factors examined for interactions. The data were thereafter analyzed using both standard logistic and linear regression as well as multiple logistic and linear regression analysis in order to determine those factors which are independently associated with ΔT. The variables examined in the prediction models made to reveal any correlation between gender and ΔT, were known cardiovascular disease risk factors (smoking, dyslipidemia, arterial hypertension, diabetes mellitus, and family history), demographic characteristics (gender, age), severity of coronary heart disease (number of vessels), plaque thickness and medication. A two-tailed value of $p < 0.05$ was considered statistically significant throughout. Statistical analyses were performed using commercially available software (SPSS, version 20, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline demographic and clinical characteristics

A total of 728 arteries from 364 patients with significant CAD were included in the analysis. Of these patients, 310 were male and 54 were

Table 1
Demographic characteristics of the study population.

N = 364	Male (N = 310)	Female (N = 54)	p
Clinical variables			
Age	63.99 ± 10.77	65.89 ± 10.34	0.23
Dyslipidemia	230 (74.2%)	46 (85.2%)	0.08
Smoking	153 (49.4%)	18 (33.3%)	0.03
Diabetes mellitus	109 (35.2%)	25 (46.3%)	0.12
Hypertension	205 (66.1%)	40 (74.1%)	0.25
CAD family history	134 (43.2%)	31 (57.4%)	0.05
Medication			
Aspirin	213 (68.7%)	39 (72.2%)	0.61
ADP blockers	112 (36.1%)	20 (37%)	0.90
Statin	207 (66.8%)	40 (74.1%)	0.29
ACE inhibitors	89 (28.7%)	10 (18.5%)	0.12
Angiotensin II receptor antagonist	79 (25.5%)	15 (27.8%)	0.72
Nitrates	41 (13.2%)	11 (20.4%)	0.17
B-Blockers	136 (43.9%)	32 (59.3%)	0.04
Ca channel blockers	53 (17.1%)	15 (27.8%)	0.06
CAD severity			
One vessel CAD	118 (38.1%)	20 (37%)	0.11
Two vessels CAD	119 (38.4%)	22 (40.7%)	
Three vessels CAD	73 (23.5%)	12 (22.2%)	