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Original Article

In vivo correlation between morphological characteristics of coronary plaques and functional characteristics of carotid arteries in acute coronary syndrome

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Abstract: Background: Carotid artery temperature heterogeneity (ΔT) measured by microwave radiometry (MWR) has been associated with future cardiovascular events including acute coronary syndromes. The vulnerable plaques of the coronary arterial tree, that can be ideally depicted by intracoronary imaging such as optical coherence tomography (OCT) have anatomical characteristics such as the thin fibrous cap (TCFA), that make them vulnerable to rupture. The scope of the study was to assess the implication of the carotid artery temperature heterogeneity on the culprit coronary plaque morphology in patients presenting with acute myocardial infarction. Methods: 34 patients presented with an acute myocardial infarction were enrolled in the study. All patients underwent percutaneous coronary intervention (PCI) and OCT for the evaluation of the anatomical characteristics of the culprit lesion. After the completion of the PCI all patients underwent carotid ultrasound and MWR of both carotid arteries and thermal heterogeneity of the carotid arteries was assessed. Blood samples were collected for high sensitivity C-reactive protein (CRP) analysis. Results: Thirty four patients, 21 with STEMI (61.76%) and 13 (38.23%) with NSTEMI, were included in the study. Patients with ruptured plaques had significantly increased hsCRP compared to patients that did not have a ruptured plaque (14.41±4.02 vs 9.9±2.5, P<0.005). Thermal heterogeneity, was significantly increased in ruptured plaques compared to no ruptured ones (1.01±0.31 vs 0.51±0.14°C, P=0.001), and in plaques with TCFA compared to those without a TCFA (0.82±0.37 vs 0.60±0.05°C, P=0.001). Diabetes mellitus, ΔT and hsCRP, were entered in the multivariate analysis, from which DM (OR 4.12; 95% CI 0.77-22.07; P=0.07) and ΔT (OR for 0.1°C increase 1.43; 95% CI 1.03-1.98; P=0.03) remained in the final analysis, and only ΔT was independently associated with the presence of the TCFA. Regarding plaque rupture, STEMI, hsCRP, and ΔT were entered in the multivariate analysis from which hsCRP (OR 1.51; 95% CI 0.99-2.28; P=0.051) and ΔT (OR for 0.1°C increase 3.40; 95% CI 1.29-8.96; P=0.013) remained in the final analysis with the ΔT being the only variable.

Keywords: Inflammation, thermography, TCFA, plaque rupture, radiometry, OCT

Introduction

The vulnerable plaques of the coronary arterial tree, have anatomical characteristics such as the thin fibrous cap (TCFA), that make them prone to rupture in the presence of a specific stimulus such as the increased shear stress or inflammation. Inflammation is implicated both in the progression and the instability of atheromatic plaques [1-5]. Previous studies have demonstrated that both local and widespread (systemic) inflammatory activation are correlated with the temperature of the atheromatic plaques and the diffuse destabilization of atherosclerotic plaques [2, 3, 5-11].

Although it is well established that inflammation has a pivotal role in all phases of atherosclerosis, from the initiation of atherosclerosis in the early years of life to the culmination in acute coronary syndromes, the majority of these data are derived from nonspecific marker of systemic inflammation, present in all grades and kinds of inflammation [12-14]. Microwave

radiometry (MWR) that is an non-invasive method for assessing local inflammation by detecting the temperature of the tissues, has been associated to future coronary events or need for revascularization in a specific group of high risk patients, however no data exist regarding the possible direct relation to the morphological characteristics of the coronary arteries [15, 16].

Optical coherence tomography (OCT) due to its high resolution (~15 μm) can in vivo identify the majority of the morphological characteristics of coronary vulnerable plaques, including precise measurement cap thickness of the TCFA [4, 14, 17-19]. In patients with acute coronary syndrome, the presence of plaque rupture and TCFA detected by OCT has been related to systemic inflammatory markers as well as to metabolic syndrome [14, 20].

The scope of the study was to assess the implication of the carotid artery temperature heterogeneity on the culprit coronary plaque morphology on patients presenting with acute myocardial infarction.

Methods

Studied population

We enrolled 37 patients that underwent percutaneous coronary intervention (PCI) due to an acute myocardial infarction and had an identifiable denovo culprit lesion in a native coronary artery. The definition of non-ST-elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) was according to the current guidelines. More specific NSTEMI was defined as continuous chest pain in combination with the presentation of elevated levels of troponin T combined with the absence of ST-segment elevation ≥0.1 mV in ≥2 contiguous leads on 12-lead electrocardiogram. Exclusion criteria included cardiogenic shock, multivessel disease, previous CABG, and significant carotid artery stenosis. Also, patients treated with corticosteroids or nonsteroidal anti-inflammatory drugs, except for aspirin as well as patients with an inflammatory or neoplastic condition were excluded.

Percutaneous coronary intervention and imaging

All patients with NSTEMI underwent PCI and OCT study within 12 h since symptom onset. Similarly STEMI was defined as continuous chest pain combined with elevation of the ST-segment more than 0.1 mV in more than 2 contiguous leads on the ECG. Patients with STEMI were deferred to the catheterization laboratory immediately upon hospital arrival and underwent OCT study before performance of primary PCI. We used the combination of the diagnostic coronary angiography, the ECG findings or the local wall motion abnormalities in order to identify the culprit lesion. We used the LightLab OCT wire (Image-wire™; LightLab Imaging, Westford, MA) to perform the OCT study. Acquired images were analyzed by 2 independent investigators using previously validated criteria for OCT plaque characterization [21, 22].

Microwave radiometry imaging

The MRW measurements were performed with the RTM 01 RES microwave computer based system (Bolton, UK) as previously described [1, 23, 24]. Microwave radiometry measurements were obtained within 12 hrs after PCI and they were guided by carotid ultrasound. The carotid arteries were scanned from their point of origin, throughout their whole length. The external and the internal carotid artery were assessed in both transverse and longitudinal sections, while the plaque morphology and plaque consistency were estimated by using B-mode ultrasound. Carotid plaques were categorised as fatty, mixed or calcified according to previously published criteria [24]. We excluded patients with significant carotid stenosis.

The basic principles of MRW have been previously described [1, 24-26]. Microwave radiometry has an antenna with a sensor that measures with an accuracy of 0.20°C the 'volume under investigation' as a rectangular area of 3 cm in width, 2 cm in length, and 3-7 cm in depth depending on the water content of the body. Segments of 20 mm in length, were analysed as MRW measured temperature in a length of 2 cm. In order to obtain the measurement the antenna was held for 10 sec at this position for 10 sec, which is the necessary time for the receiver to integrate the microwave emission and to convert the measured signal to temperature by a microprocessor. Temperature difference (ΔT), that actually shows the thermal heterogeneity of the specific tissue was calculated as the temperature of the segment under investigation minus the minimal temperature of each carotid (reference temperature).

Table 1. Baseline Characteristics of the studied population

	Plaque rupture (n=20)	Non-rupture (n=14)	*p*-value
Age (years)	61.9±6.7	63.5±8.1	0.52
Gender (male); n, (%)	17 (85.0)	12 (85.7)	0.99
Hypertension; n, (%)	11 (55.0)	5 (37.71)	0.44
Diabetes mellitus; n, (%)	8 (40.0)	6 (42.85)	>0.99
Dyslipidaemia; n, (%)	8 (40.0)	7 (50.0)	0.72
Active smoking; n, (%)	6 (30.0)	6 (42.85)	0.48
Family history of CAD; n, (%)	7 (35.0)	5 (35,71)	0.96
Statins	10 (50.0)	7 (50.0)	0.98
ACE inh or ARBs	8 (40.0)	7 (50.0)	0.77
Clinical syndrome; n, (%)			0.08
ST-elevation myocardial infarction	15 (75.0)	6 (42.9)	
Non-ST-elevation myocardial infarction	5 (25.0)	8 (57.1)	

CAD: coronary artery disease, ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker.

Table 2. Type of carotid artery plaques stratified according to optical coherence findings at the coronary arteries. Percentages are in brackets

	No plaque (n=11)	Fatty plaques (n=7)	Mixed plaques (n=9)	Calcified plaques (n=7)	*P* value
Rupture	6 (54.54)	5 (71.42)	5 (55.55)	4 (57.14)	P=0.89
No Rupture	5 (45.45)	2 (28.57)	4 (44.44)	3 (42.81)	

All patients signed an informed consent form. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research and ethical committee (152/202-13).

Statistical analysis

Statistical analysis was performed with SPSS 25 statistical software (SPSS Inc., Chicago, Illinois). Quantitative data are presented as rates or mean value ± SD. Probability values are two-sided from the Student t-test for continuous variables were compared and Analysis of variance (ANOVA) test for more than 2 categories. Non-continuous values were compared by χ^2 test. A value of $P<0.05$ was considered significant.

Results

Baseline characteristics, and univariate analysis

Our study included 34 patients with acute myocardial infarction, 13 patients (38.23%) with NSTEMI and 21 with STEMI (61.76%). **Table 1** depicts the baseline characteristics of the studied population. There was no significant deference between the baseline characteristics of patients with ruptured and patients with no ruptured coronary plaque.

Thin cap fibro atheroma (TCFA) was present in 31 patients (91.1%), significantly more in ruptured plaques compared in non-ruptured plaques (100% vs 78.85%, P=0.03). There was no association between the type of carotid plaque and the presence of coronary artery rupture (**Table 2**). Similarly there was no significant association between the type of carotid plaque and thermal heterogeneity detected by MWR (**Figure 1**). Patients with ruptured plaques had significantly increased hsCRP compared to patients that did not have a ruptured plaque (14.41±4.02 vs 9.9±2.5, P<0.005). Thermal heterogeneity expressed as Mean ΔT, was significantly increased in ruptured plaques compared to no ruptured ones (1.01±0.31 vs 0.51±0.14°C, P=0.001), and in plaques with TCFA compared to those without a TCFA (0.82±0.37 vs 0.60±0.05°C, P=0.001) (**Tables 3** and **4**).

Predictors of plaque rupture and presence of TCFA

Diabetes mellitus, ΔT and hsCRP, were entered in the multivariate analysis, from which DM (OR 4.12; 95% CI 0.77-22.07; P=0.07) and ΔT (OR

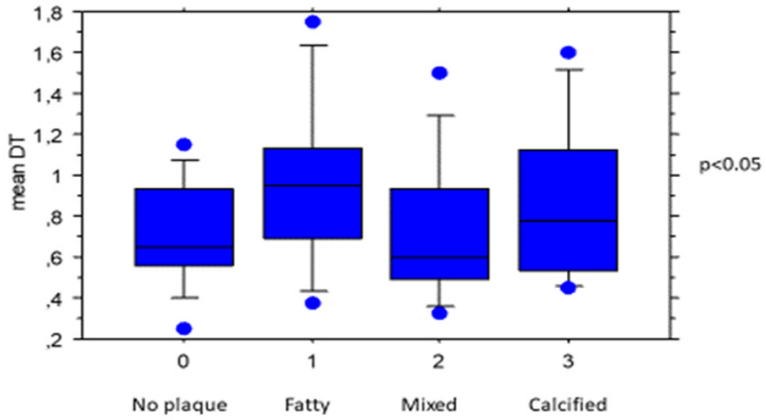

Figure 1. Mean ΔT values of carotid plaques detected by microwave radiometry compared to the type of carotid plaque.

Table 3. Correlation of TCFA with the demographic factors and inflammatory markers

	OR	95% CI	*p*-value
Male gender	0.41	0.04-4.15	0.45
Age (years)	1.04	0.94-1.14	0.47
STEMI	1.25	0.30-5.27	0.76
DM	3.00	0.70-12.88	0.14
Hypertension	0.48	0.12-0.54	0.38
Dyslipidaemia	0.38	0.16-1.31	0.36
Smoking	0.48	0.10-2.29	0.36
Family history of CAD	1.00	0.25-4.08	0.99
ΔT (for 0.1°C increase)	1.37	1.02-1.84	0.04
hsCRP	1.20	0.98-1.46	0.07

CAD: Coronary artery disease, TCFA: Thin cap fibroatheroma, STEMI: ST elevation myocardial infarction, DM: Diabetes mellitus.

for 0.1°C increase 1.43; 95% CI 1.03-1.98; P=0.03) remained in the final model, with ΔT being the only variable independently associated with the presence of the TCFA. Similarly regarding plaque rupture, STEMI, hsCRP, and ΔT were entered in the multivariate analysis from which hsCRP (OR 1.51; 95% CI 0.99-2.28; P=0.051) and ΔT (OR for 0.1°C increase 3.40; 95% CI 1.29-8.96; P=0.013) remained in the final model, with the ΔT being the only variable independently associated with the presence of rupture.

Discussion

The main finding of the study is that in patients with myocardial infarction, there is an association between the morphological characteristics of the vulnerable plaque with the functional characteristics of the carotid arteries. According to our results, local inflammation expressed as thermal heterogeneity and detected by MRW was found to be an independent predictor of the presence of TCFA or ruptured plaque in the coronary arteries of patients admitted with acute coronary syndrome.

The role of inflammation in the initiation of atherosclerosis and triggering of an ACS is still a challenging topic in current pathophysiology. Although its role in both situations is well established, its actual mechanism is still the subject of current research. The most acceptable theory for the initiation of an ACS, involves the destabilization of the endothelium and the stable plaque, and the final rupture or erosion of the plaque that has become vulnerable. The local activation of inflammatory cascade in the pathogenesis of ACS results in the final initiation and promotion of thrombus formation. Similarly the theory of widespread inflammation comes to support the hypothesis that destabilization and thrombus formation are promoted and maintained by both innate and adaptive immune responses through complex interactions [27]. The recent finding that systemic inflammation has an unfavourable effect on in hospital complications and mortality of patients with acute coronary syndrome and no signs of congestive heart failure, has targeted it as a recent promising therapeutic strategy for ACS patients [28]. Although some recent clinical trials on anti-inflammatory treatments in patients presenting with ACS have showed satisfactory results; most of them have failed to complete resolve the mystery from the theoretical aspect into quantifiable benefits [29]. In most of the studies, inflammatory activation has been assessed by several nonspecific pro-inflammatory cytokines and in-

Table 4. Correlation of plaque rupture with the demographic factors and inflammatory markers

	OR	95% CI	*p*-value
Male gender	0.94	0.14-6.55	0.95
Age (years)	0.97	0.88-1.07	0.50
STEMI	4.00	0.93-17.30	0.06
DM	1.13	0.28-4.50	0.87
Hypertension	0.32	0.21-0.39	0.010
Dyslipidaemia	1.50	0.38-5.95	0.56
Smoking	1.75	0.42-7.29	0.44
Family history of CAD	1.00	0.26-0.39	0.99
ΔT (for 0.1°C increase)	3.61	1.47-8.89	0.005
hsCRP	1.42	1.11-1.81	0.005

CAD: Coronary artery disease, STEMI: ST elevation myocardial infarction, DM: Diabetes mellitus.

flammatory markers with hsCRP to the most popular and widely used marker.

According to the current knowledge, there is a correlation between the morphological and functional characteristics (thermal heterogeneity and inflammation) of the coronary vulnerable plaque indicating a direct role of inflammation on the destabilization of the vulnerable plaque, however these studies were performed with the use of invasive techniques IVUS, OCT or intravascular thermography [30-34]. Moreover systemic inflammation has been correlated to coronary plaque vulnerability by using nonspecific markers of inflammation such as CRP. In the current study we investigated the role of local and systemic inflammation on the coronary plaque destabilization and initiation of a myocardial infarction. For the first time we correlated in vivo, two relatively new modalities, OCT and MWR. Optical Coherence tomography is the optimal method for the identification of the anatomical characteristics of the coronary vulnerable plaque as it has the highest resolution for the detection of plaque rupture, thin cap fibroatheroma and thrombus, and MWR can noninvasively measure the functional characteristics of peripheral arteries, such as thermal heterogeneity in the carotid arteries.

We also correlated the findings of the two techniques with hsCRP, in order to link the functional and morphological characteristics of the arterial plaques with the most commonly used inflammatory marker. Although OCT is an invasive method that requires the catheterization of the patient, microwave radiometry is a safe, noninvasive method that can be applied as an outpatient, which does not need hospitalization and requires minimal learning curve and skills.

Our study showed that, carotid inflammation was the only independent predictor of plaque rupture and presence of TCFA, while hsCRP was predictor of both TCFA and plaque rupture only in the univariate analysis. In contrast to previous studies performed with the use of intravascular imaging, we showed that carotid thermal heterogeneity performed with a noninvasive method such as MWR has better accuracy compared to hsCRP in predicting the presence of the characteristics of vulnerable plaque such as TCFA and plaque rupture [20, 35]. This can be attributed to the fact that CRP is a non specific inflammatory marker, while MWR can assess local inflammation in the arterial system that probably has more specificity compared to CRP in detecting inflammatory activation in the arteries [1, 26, 36]. The anatomical characteristics of the carotid plaques had no relation either to the presence of coronary rupture or to the presence of thermal heterogeneity indicating that this local inflammatory activation is possible to reflect a panarteritis rather than an isolated local event caused by a carotid plaque. This difference compared to previous studies can be explained from the exclusion of patients with carotid artery stenosis and from the increased percentage of patients with no carotid plaques that reached 33% of the studied population [19]. Moreover, recent studies performed with MWR and PET/CT in patients with carotid endarterectomy confirmed that carotid artery structural changes cannot predict inflammatory process and this is in concordance with the results of the current study [36].

Clinical implication: The better correlation of carotid inflammation with the presence of TCFA compared to systemic hsCRP may contribute to the early recognition of patients that have vulnerable coronary plaques that are prone to rupture. By using the non invasive method of MWR we may also recognize a subgroup of patients with high risk for ACS that require more aggressive therapy based on medications that have anti-inflammatory effect such as statins. This

possible favorable prognostic effect should be examined in large, prospective randomized studies.

In conclusion, carotid thermal heterogeneity is associated with the presence of TCFA and plaque rupture in patients with acute myocardial infarction. Large scale randomized studies are necessary to further support this hypothesis.

Disclosure of conflict of interest

None.

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