Original Research

Bilateral Symmetry of Local Inflammatory Activation in Human Carotid Atherosclerotic Plaques

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Introduction: Only a few studies have investigated the structural and functional characteristics of carotid arteries bilaterally. Furthermore, there is controversy as to whether inflammation in paired vascular beds is a local or systemic phenomenon. We aimed to examine, in patients with coronary artery disease, whether intra-subject left and right carotid arteries have similar inflammatory status, as determined non-invasively by microwave radiometry (MWR).

Methods: Consecutive patients (n=200) with significant coronary artery disease were evaluated via an ultrasound echo-colour Doppler (US-ECD) study of both carotid arteries and temperature measurements with MWR. During thermography, thermal heterogeneity (ΔT) was defined as the maximum temperature along the carotid artery minus the minimum temperature.

Results: Mean ΔT was similar between the left and right carotid arteries (0.78 ± 0.48 vs. 0.84 ± 0.52˚C, p=0.12). Mean right intima–media thickness (IMT) was greater compared to mean left IMT (2.16 ± 1.20 vs. 1.93 ± 0.94 mm, p<0.01). In all carotids, there was a correlation between left and right carotid plaque ΔT (R=0.38, p<0.001) and between left and right IMT (R=0.48, p<0.001). Independent predictors for the presence of bilateral carotid plaques were found to be the extent of coronary artery disease, high ΔT, and therapy with angiotensin II receptor blockers; predictors for the presence of high ΔT bilaterally were bilateral carotid plaques, male sex, diabetes mellitus, and hypertension.

Conclusions: There is bilateral inflammatory activation in the carotid atherosclerotic lesions of patients with coronary artery disease. At this stage of carotid disease, arterial hypertension and diabetes mellitus are more strongly correlated with bilateral functional abnormalities in carotid plaques than with structural changes.

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Atherosclerosis of the carotid arteries is a major cause of stroke and transient ischemic attack.[1,2] The progression of atherosclerosis is partially influenced by risk factors such as sex, age, hypercholesterolaemia and hypertension.[3] Atherosclerotic plaques are exposed to the same predisposing factors in different arterial beds within the same patient. Thus, although a concordance between morphometric parameters may be observed symmetrically in carotid or iliac arteries, plaque inflammatory activation may be different.[3,4]

Previous *ex vivo* studies have shown that carotid plaques have an increased density of inflammatory cells, producing increased thermal heterogeneity.[5] Microwave radiometry (MWR) allows the *in vivo* non-invasive measurement of the temperature of carotid atherosclerotic plaques, reflecting their inflammatory status, as has been shown in recent studies.[6-8]

The aim of the present study was to evaluate, in patients with coronary artery disease, whether intra-subject left and right carotid arteries have a similar inflammatory status, as determined non-invasively by microwave radiometry, and to specify the independent predictors of bilateral functional and structural abnormalities in carotid arteries.

Methods

Study population

Consecutive patients undergoing coronary angiography for the evaluation of chest pain, electrocardiographic changes, and/or an increase in troponin levels, were prospectively enrolled in the study. Patients with coronary artery disease, as documented by coronary angiography (≥50% stenosis in one major epicardial vessel), underwent a standard carotid ultrasound examination followed by MWR measurement. The two measurements were performed blindly. Conventional risk factors for coronary artery disease and current medical therapy were recorded. Exclusion criteria for MWR were previous stroke or transient ischaemic attacks (TIA), vasculitis, non-atherosclerotic carotid artery disease and intermittent inflammatory, infectious, or neoplastic conditions. All participants provided informed consent and the study was approved by our institution's ethics committee.

Ultrasound imaging

Extracranial (common, internal, external) carotid arteries were examined with a high resolution B-mode ultrasound unit (Philips iEE33, Philips, Bothell, Washington), using the 7.5-MHz L9-3 linear probe. For signal detection the second harmonic technique was used. All data were collected and interpreted by experienced ultrasonographers (CM, DT). Both the internal and external carotid arteries were interrogated in transverse and longitudinal sections, as previously described.[6,7] The vertebral arteries were also studied with colour and power Doppler ultrasound. B-mode ultrasound was used to depict and evaluate atherosclerotic plaque morphology and plaque consistency, as well as to measure the intima–media thickness (IMT).

Measurements of IMT were performed in 3 segments of 20 mm along each carotid artery. For this purpose, the middle segment was the region of common carotid bifurcation (bifurcation segment), which was defined as the last cross section encompassing a single common carotid artery lumen and was used as a marker. The other two segments were defined as the regions 20 mm proximal and 20 mm distal to the bifurcation region. The proximal was described as the common carotid artery segment and the distal as the internal carotid artery segment. The maximum IMT for each segment was calculated from 3 pre-selected images. The segment of each carotid artery with the highest IMT value was designated as "the segment under investigation". The respective value was also used in the statistical analysis.

Carotid plaques were identified as focal echogenic thickenings with a minimal intimal plus medial thickness ≥1.2 mm.[9] To assess plaque echogenicity the Gray–Weale classification was used, as previously described (Type I-V). We considered Types I and II as fatty plaques, Types III and IV as mixed plaques, and Type V as calcified plaques. We used the classification previously described by considering fatty plaques as heterogeneous and mixed and calcified as homogeneous.[6,7,10-12] The plaque surface was considered regular when it was smooth, and irregular if a variation ≥0.3 mm was observed on the surface of the plaque with a depth of 1 mm.[13]

Microwave radiometry measurements

The MWR measurements were performed with the RTM 01 RES microwave computer-based system (Bolton, UK) that measures temperature from internal tissues at microwave frequencies. MWR measurements were obtained at least 10 minutes after the ultrasound examination in order to avoid any influence on temperature from palpation or the ultrasound study. The basic principles of MWR have been described previously.[6,7,14] The MWR system possesses an antenna with a sensor that filters all possible microwaves or radiofrequency waves that may be present in the room's vicinity and may cause interference with the sensor. The diameter of the antenna is 3.9 cm. The sensor of the antenna 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.

Temperature measurements were performed for each carotid artery at the "segment under investigation". To ensure that matching cross-sections were compared between ultrasound and MWR, the measurements were performed at each segment, as previ-

ously defined in ultrasound imaging, starting from the proximal common carotid artery and moving distally, based on markers located under the guidance of ultrasound. We analysed segments of 20 mm in length, as MWR measured temperature in a length of 2 cm. Thus, we avoided overlapping or missing areas by MWR. All measurements of the carotid artery were performed at room temperature (20-24˚C). Measurements at each of the 3 segments were obtained 3 times to assess the reproducibility of the method (overall, 9 measurements by each operator). The temperature of each segment used for further analysis was the mean of the 3 temperatures. The measurements were compared to study the intra-observer variability. The differences in the mean temperature in each segment measured by each operator were compared to study the inter-observer variability. The method has been validated previously.[7] The temperature variables used in the statistical analyses were the temperature of the "segment under investigation" and the minimal temperature across the carotid artery. Therefore, the temperature difference (ΔT) was assigned as the temperature of the segment under investigation minus the minimum temperature of each carotid (reference temperature). ΔT≥0.90˚C was assigned as high ΔT, in accordance with previous observations.[6]

Statistical analysis

The statistical analysis was performed using commercially available software (SPSS Inc., version 20, Chicago, Il, USA). Quantitative data are presented as rates or mean values ± SD. Probability values are two-sided from the Student t-test for continuous variables. Non-continuous values were compared by chi-square test. Pearson's correlation coefficient was used to analyse the correlation of ΔT and IMT in the left and right carotid arteries. Multiple logistic regression analysis was used to determine independent factors predicting the presence of carotid plaques or high local inflammation, as measured by ΔT, in carotid arteries. A two-tailed value of $p<0.05$ was considered statistically significant throughout.

Results

Baseline demographic and clinical characteristics

In the screening process, we included 246 patients who were evaluated for coronary artery disease. Of these, 200 patients met the inclusion criteria and 400 carotid arteries were analysed. Significant carotid artery stenosis (≥70%) was found in 22 patients (11%). Four patients (2%) had unilateral carotid artery occlusion. Patient demographics and clinical data are summarised in Table 1.

Carotid ultrasound analysis

The mean IMT of all carotid arteries (n=400) was 2.04 ± 1.09 mm. Mean right IMT was greater than mean left IMT (2.16 ± 1.20 vs. 1.93 ± 0.94 mm, $p<0.01$; Figure 1). In all carotids, there was a correlation between left and right IMT ($p<0.001$, $R=0.48$).

Carotid plaques were identified in 313 (78.25%) carotid arteries. In 133 (66.5%) patients bilateral carotid artery disease was found, in 47 (23.5%) patients unilateral carotid artery plaques were detected, and in 20 (10%) patients carotid disease was not observed. In patients with carotid plaques (n=180, 90%), there was a correlation between left and right IMT ($R=0.40$, $p<0.001$). Mean right IMT was greater than mean left IMT (2.30 ± 1.19 vs. 2.05 ± 0.91 mm, $p<0.01$).

Fifty two plaques (16.61%) were characterised as fatty, 181 (57.83%) as mixed, and 80 (25.56%) as cal-

Table 1. Demographic characteristics.

Number of patients (n)	200	
Clinical variables:		
Age (years)	64.15 ± 10.53	
Male sex	164	(82)
Hypertension	142	(71)
Family history	88	(44)
Dyslipidaemia	156	(78)
Diabetes	76	(38)
Smoking	91	(45.50)
Previous medication:		
ASA	158	(79)
ADP-inhibitors	72	(36)
ACE	56	(28)
ARB	50	(25)
b-blockers	91	(45.50)
Statins	153	(76.50)
Nitrates	30	(15)
Ca-antagonists	32	(16)
Previous cardiac history:		
CABG	27	(13.50)
PCI	61	(30.50)
Multi-vessel coronary artery disease (≥2 vessel disease)	112	(56)

All values are expressed as mean ± SD or n (%).
ASA – acetylsalicylic acid; ACE – angiotensin-converting enzyme inhibitors; ARB – angiotensin II receptor blockers; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft.

cified. Eighty-one plaques (25.88%) had an irregular surface, while 232 (74.12%) had a regular surface. There were heterogeneous plaques in 71 (22.68%) carotid arteries and homogeneous plaques in 242 (77.32%).

Vessel-based analysis

By multiple logistic regression analysis, the number of coronary arteries with significant stenoses (odds ratio [OR]: 1.45, 95% confidence interval [CI]: 1.00-2.12, p=0.05), age (OR: 1.03, 95%CI 1.01-1.06, p=0.02) and ΔT value (OR: 6.34, 95%CI: 2.94-13.65, p<0.01) were found to be independent predictors for the presence of carotid plaque (IMT≥1.2 mm).

Patient-based analysis

By multiple logistic regression analysis, the number of coronary arteries with significant stenoses (OR: 1.55, 95%CI 1.00-2.40, p=0.05), the presence of high ΔT (≥0.90˚C) in both carotid arteries (OR: 3.47, 95%CI: 1.34-9.00 p=0.01) and therapy with angiotensin receptor blockers (ARB) (OR: 0.39, 95%CI: 0.20-0.76 p=0.01) were found to be independent predictors for the presence of carotid plaque bilaterally (IMT≥1.2 mm).

Microwave radiometry analysis (MWR)

The mean ΔT of all carotids (n=400) was 0.80 ± 0.49˚C. Mean ΔT was similar in the left and right carotid arteries (0.78 ± 0.48˚C vs. 0.84 ± 0.52˚C, p=0.12; Figure 1). In all carotids, there was a correlation between left and right carotid plaque ΔT (R=0.38, p<0.001; Figure 2). In all carotid arteries, there was a correlation between ΔT and IMT (R=0.25, p<0.001).

In patients with carotid plaques (n=180), there was a correlation between left and right ΔT (R=0.37, p<0.001). Mean ΔT was similar in the left and right carotid arteries (0.80 ± 0.49˚C vs. 0.87 ± 0.53˚C, p=0.08).

In carotid arteries with plaques (n=313), fatty plaques had higher ΔT compared to mixed and calcified plaques (1.23 ± 0.55˚C vs. 0.87 ± 0.44˚C vs. 0.67 ± 0.49˚C, respectively, p<0.01). Plaques with an irregular surface had higher ΔT compared to plaques with a regular surface (1.20 ± 0.45˚C vs. 0.76 ± 0.48˚C, p<0.01). Heterogeneous plaques had higher ΔT compared to homogeneous plaques (1.22 ± 0.56˚C vs. 0.77 ± 0.44˚C, p<0.01).

Vessel-based analysis

By multiple logistic regression analysis, the plaque texture (fatty) (OR: 1.98, 95% CI: 1.00-3.95, p=0.05), plaque surface (regular) (OR: 0.12, 95%CI: 0.06-0.25, p<0.01), plaque echogenicity (OR: 0.24, 95%CI 0.08-0.74, p=0.01) and hypertension (OR: 2.66, 95%CI: 1.28-5.55, p=0.01) were found to be independent predictors for high carotid ΔT.

Patient-based analysis

By multiple logistic regression analysis, male sex (OR:

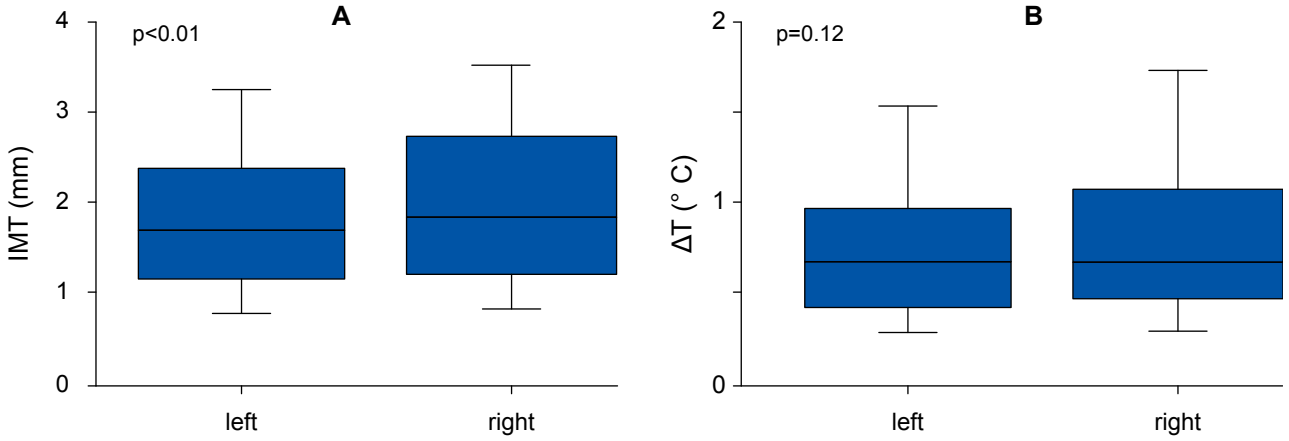

Figure 1. Intima-media thickness (IMT) in the left and right carotid arteries of the study population. A. Mean right IMT was greater than mean left IMT (p<0.01). B. Temperature difference (ΔT) in left and right carotid arteries. Mean ΔT was similar between left and right carotid arteries. The bottom of the box represents the first quartile, the top of the box represents the third quartile, and the line in the box represents the median value.

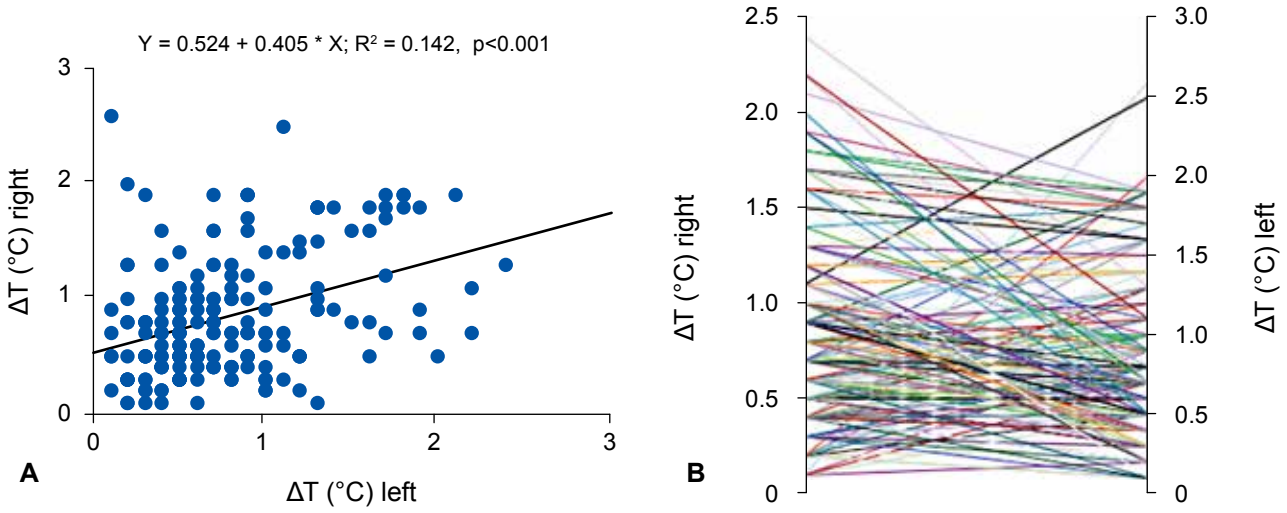

Figure 2. Correlation of temperature differences (ΔT) between the left and right carotid arteries. A. There was a positive correlation between the left and right carotid artery ΔT (R=0.38, p<0.001) (panel A). B. Temperature differences (ΔT) between the left and right carotid artery of each patient.

0.35, 95%CI 0.15-0.83, p=0.02), the presence of carotid plaques bilaterally (OR: 3.18, 95%CI 1.18-8.27, p=0.02), diabetes mellitus (OR:2.16, 95%CI 1.02-4.59, p=0.04) and hypertension (OR=2.92, 95%CI 1.02-8.41, p=0.05) were found to be independent predictors for bilateral high ΔT (Tables 2 and 3).

Table 2. Univariate logistic regression analysis for independent predictors of bilateral high thermal heterogeneity.

Factor	p	OR	95% CI
Male sex	0.01	0.35	0.16–0.77
No. of diseased vessels	0.05	1.59	1.004–2.52
Diabetes mellitus	0.01	2.40	1.19–4.85
Hypertension	0.01	3.47	1.28–9.36
Bilateral carotid plaque	0.01	3.49	1.39–8.80

OR – odds ratio; CI – confidence interval.

Table 3. Multivariate logistic regression analysis for independent predictors of bilateral high thermal heterogeneity.

Factor	p	OR	95% CI
No. of diseased vessels	0.26	1.34	0.80–2.22
Diabetes mellitus	0.04	2.16	1.02–4.59
Hypertension	0.05	2.92	1.02–8.41
Bilateral carotid plaque	0.02	3.18	1.18–8.27
Male sex	0.02	0.35	0.15–0.83

Abbreviations as in Table 2.

Discussion

This study demonstrated the following: 1) local atherosclerotic plaque inflammation is similar in the left and right carotid arteries; 2) carotid plaques bilaterally are observed more frequently in patients with extensive coronary artery disease who are not taking ARB; and 3) local inflammation is more prominent in patients with extensive coronary artery disease, diabetes mellitus and arterial hypertension.

The development of unilateral carotid artery disease is known to be affected by the risk factors for atherosclerosis.[15-17] Only a few studies have investigated the presence of bilateral carotid artery disease. Previous findings suggested that atherosclerosis of the human carotid arteries is generally a bilateral disease.[3,4] Indeed, several surrogate markers for atherosclerosis have high correlation coefficients for left versus right carotid artery volumes.[4] Thus, the moderate level of symmetry of wall volumes in carotid arteries suggests that the development of atherosclerosis is partially controlled by systemic factors, but local factors may also play an important role. Interestingly, in femoral arteries a concordance has been found in morphometric parameters, but not in plaque inflammation.[3] Atherosclerotic plaques of patients with advanced disease, such as those who undergo endarterectomy, may not exhibit a degree of lesion symmetry.[4]

The administration of ARB had a protective effect in the presence of bilateral carotid plaques. Several experimental and clinical trials have established the key role of the renin–angiotensin system in the pathogenesis of atherosclerosis, demonstrating that agents that inhibit the renin–angiotensin system confer a cardiovascular benefit beyond the reduction of blood pressure

alone. The anti-atherosclerotic and anti-inflammatory effects of ARB are well documented and cannot be explained solely in terms of their antihypertensive effect. These actions are specifically mediated through the inhibition of angiotensin type I receptor.[18,19]

In addition, hypertension and diabetes mellitus affected the inflammation in both carotids. There is compelling evidence to support an association between hypertension and vascular inflammation, linking hypertension with an increase in several proinflammatory markers.[19,20] In a recent study, hypertension was an independent predictor of carotid wall inflammation in patients with coronary artery disease, as determined by ^{18}F-fluoro-deoxyglucose uptake, although the majority of patients were under statin therapy, as in the current study.[21]

The association of diabetes mellitus with the local inflammatory activation of human atherosclerotic plaques is supported by previous data.[22-24] It appears that, in patients with intermediate carotid plaque stenosis, diabetes mellitus and arterial hypertension, functional abnormalities may be more profound than structural changes. Indeed, the majority (87%) of the study population had a mean IMT of 1.97 ± 0.96 mm, and in this specific group the presence of these two risk factors was highly predictive of the presence of bilateral inflammation.

In this early phase of the disease, arterial hypertension and diabetes mellitus appear to be the most important factors affecting bilateral functional alterations in carotid arteries. The detection of functional changes in the carotids may 1) be a warning for the early detection of carotid structural changes, 2) provide prognostic information about coexisting coronary artery disease, and 3) potentially predict patients with ocular ischaemic events or strokes.

Specific comments

Mean ΔT were statistically different between subgroups, although an overlap was observed in ΔT values. Even in the subgroups with a large overlap the differences were more than the sensitivity of the method (0.20˚C). Moreover, in the vessel-based analysis, the results of previous studies, demonstrating the correlation of ΔT with the plaque type,[7] were confirmed with trivial overlap. Thus, the complex pathophysiological substrate influencing the inflammatory status in diabetes mellitus and arterial hypertension, could explain the overlap in the patient-based analysis demonstrated in previous studies.[25]

A correlation was found in ΔT between the left and right carotids, although in the individual analysis this was not present in all patients (Figure 2B). However, the correlation was statistically significant as a large number of patients were included.

The IMT was used to evaluate the atherosclerotic disease in the carotids. Despite the possible limitations of IMT measurement, the maximal IMT was well correlated with the inflammatory activation in the vessel wall, as evaluated by MWR. In these measurements, the IMT also included plaques, as described in previous studies that investigated the overall atherosclerosis in carotid arteries.[26-28]

The evaluation of coronary artery disease was based on the angiographic presence of stenosis (>50%). Invasive imaging modalities could increase the number of patients with extensive coronary artery disease. Thus the sensitivity of MWR measurements could only be underestimated based on the angiographic criteria. However, clinically the most widely used method for evaluating coronary artery disease is still coronary angiography. Finally, we cannot draw any conclusion regarding the effect of statin treatment, as the majority of the patients were already being treated.

Conclusions

There is bilateral inflammatory activation in the intermediate carotid lesions of patients with coronary artery disease. The extent of the coronary artery disease predicts both structural and functional changes in carotid plaques. At this state of carotid disease, arterial hypertension and diabetes mellitus are more strongly correlated with the bilateral functional abnormalities in carotid plaques than with the structural changes.

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