Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke

Konstantinos Toutouzas, MD*; Georgios Benetos, MD*; Maria Drakopoulou, MD; Christina Deligianni, MD; Konstantinos Spengos, MD; Christodoulos Stefanadis, MD; Elias Siores, Bsc, Msc, PhD; Dimitrios Tousoulis, MD

Background and Purpose—Microwave Radiometry (MWR) allows in vivo noninvasive assessment of internal temperature of tissues. The aim of the present study was to evaluate in patients with ischemic stroke and bilateral carotid plaques (1) whether ipsilateral carotid arteries exhibit higher temperature differences (ΔT), as assessed by MWR; (2) the predictive accuracy of MWR in symptomatic carotid artery identification.

Methods—Consecutive patients with recent acute anterior circulation ischemic stroke because of large artery atherosclerosis were included in the study. Carotid arteries of all patients were evaluated by carotid ultrasound and MWR.

Results—In total, 50 patients were included in the study. Culprit carotid arteries had higher ΔT compared with nonculprit (0.93±0.58 versus 0.58±0.35°C; P<0.001). The addition of ΔT to a risk prediction model based only on ultrasound plaque characteristics increased its predictive accuracy significantly (c-statistic: 0.691 versus 0.768; Pdiff=0.05).

Conclusions—Culprit carotid arteries show higher thermal heterogeneity compared with nonculprit carotid arteries in patients with acute ischemic stroke and bilateral carotid plaques. MWR has incremental value in culprit carotid artery discrimination. (Stroke. 2015;46:272-274. DOI: 10.1161/STROKEAHA.114.007526.)

Key Words: acute stroke ♦ carotid atherosclerosis ♦ inflammation

Limited studies have investigated symptomatic patients with bilateral carotid plaques. In this specific population, 18F fluoro-ß-glucose positron emission tomography–computed tomography examination has demonstrated higher inflammation in symptomatic plaques compared with the contralateral.1,2 Thus, inflammation seems to play a major role in progression and destabilization of the culprit plaque in patients with symptomatic carotid stenosis.

Recent studies with a new method, microwave radiometry (MWR), revealed that in vivo noninvasive temperature measurements of carotid plaques can be obtained, reflecting plaque inflammatory activation.3 Because higher plaque inflammation is associated with plaque vulnerability in carotid arteries,2,4 we hypothesized that in patients with acute ischemic stroke, culprit carotid arteries will exhibit higher temperature compared with the contralateral carotid arteries.

The aim of the present study was to investigate in patients with acute ischemic stroke and bilateral carotid plaques (1) whether the culprit carotid artery has higher inflammation as detected by MWR compared with the contralateral artery and (2) the predictive accuracy of MWR in culprit carotid artery identification.

Study Population
Consecutive patients with large vessel atherosclerosis as cause of acute anterior circulation ischemic stroke were included in the study. Patients with history of paroxysmal or persistent atrial fibrillation were excluded. All eligible patients after initial assessment (electrocardiography, brain computed tomography imaging, and carotid ultrasound) underwent MWR measurements of both carotid arteries within the first 24 hours. Patients underwent second brain imaging with MRI during their hospital stay to exclude lacunar infarcts and transient ischemic attacks. All cases with other certain or probable cause of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, after an extensive diagnostic work up reviewed by C. Deligianni and K. Spengos, were excluded from further analysis.2 The ipsilateral to cerebral ischemia carotid artery was assigned as culprit. All patients provided informed consent for their participation. The study has been approved by our institution’s ethical committee.

Ultrasound Imaging
Carotid artery ultrasound imaging was performed as previously described.15,6 Both extracranial carotid and vertebral arteries were examined with a high resolution B-mode ultrasound unit (Philips iEE33 ultrasound machine, Philips, Bothell, Washington), using a 7.5-MHz transducer. Carotid plaques were defined according to previously used definitions.9

Methods

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Three segments of 20 mm were considered along each carotid artery. The middle segment was the region of common carotid bifurcation (bifurcation segment) and was used as a marker. The segment of each carotid artery with the highest plaque thickness was designated as target segment for the following MWR measurements.

**Microwave Radiometry Measurements**

A microwave computer-based system (RTM 01 RES, Bolton, UK) was used for the performance of MWR measurements. The system measures temperature from internal tissues at microwave frequencies. Basic principles of MWR have been previously described. MWR measurements were performed at both culprit and nonculprit carotid arteries over the segments previously defined in ultrasound imaging, including the target segments. Temperature difference ($\Delta T$) of each carotid artery was assigned as the temperature of the target segment minus the minimal temperature of each carotid (reference temperature) as previously determined.

**Statistical Analysis**

Probability values are 2-sided from the Student $t$ test or Wilcoxon test for continuous variables, depending on the normal or not distribution of the variables (SPSS Inc., Chicago, IL, USA). Noncontinuous values were compared by $\chi^2$ test. A value of $P<0.05$ was considered significant. Multiple logistic regression analysis was used to determine those factors which are independently associated with culprit carotid arteries.

Several prediction models were also considered for culprit carotid artery identification and were compared with the use of Harrell’s c-statistic as measure of discrimination: (1) traditional risk factors plus plaque thickness (sex, age, smoking, dyslipidemia, arterial hypertension, diabetes mellitus, and family history), (2) traditional risk factors plus $\Delta T$, 3) traditional risk factors plus plaque thickness plus $\Delta T$.

**Results**

In total, 100 carotids from 50 patients with anterior cerebral circulation ischemic stroke with bilateral carotid plaques on the ground of large artery atherosclerosis were included in final analysis (Table 1).

Max plaque thickness in culprit carotid arteries was higher compared with nonculprit carotid arteries (3.76±2.03 versus 2.53±1.09 mm; $P<0.001$). By multivariate logistic regression analysis, culprit carotid arteries had higher max plaque thickness compared with nonculprit, after adjustment for sex, age, vascular risk factors, and $\Delta T$ values (odds ratio, 1.60; 95% confidence interval, 1.12–2.28; $P=0.01$).

Culprit carotid arteries had higher $\Delta T$ compared with asymptomatic carotid arteries (classification based on clinical criteria; 0.93±0.58 versus 0.58±0.35°C; $P<0.001$; Figure). By multivariate logistic regression analysis, culprit carotid arteries exhibited higher $\Delta T$ values compared with nonculprit, after adjustment for sex, age, vascular risk factors, and max plaque thickness (odds ratio, 5.94; 95% confidence interval, 1.56–22.63; $P=0.01$).

In Table 2 are summarized the results of c-statistics of the various models. The addition of $\Delta T$ to the model of traditional risk factors+plaque thickness increased the predictive ability of the model significantly.

**Discussion**

In the present study, we showed that in patients with acute atherothrombotic stroke and bilateral carotid artery disease (1) culprit carotid arteries have increased plaque thickness and higher inflammatory activation compared with nonculprit...
arteries and (2) ΔT offers incremental predictive value in culprit carotid artery identification.

The findings with MWR regarding the inflammatory status of the culprit carotid artery are in accordance with the studies using 18F fluoro-d-glucose positron emission tomography—computed tomography. Indeed, recent studies with limited number of patients with acute ischemic stroke have shown that inflammatory activation interferes significantly in plaque progression and destabilization.¹²⁴

The addition of a functional characteristic in the diagnostic algorithm, such as an accurate marker of local inflammation, increased the diagnostic accuracy of the culprit plaque.

Quantification of plaque inflammation could potentially significantly to primary and secondary prevention of stroke. Indeed, functional carotid artery assessment, additionally to morphological characteristics, could better stratify patients in risk for stroke. Although 18F fluoro-d-glucose positron emission tomography scan is the most accurate non-invasive method for detection of local inflammation, radiation exposure and other technical issues hamper its wide application, especially for serial evaluations. Thus, a new noninvasive method, simple in application, such as MWR, would be a useful tool in primary and secondary prevention.

Study Limitations
All patients had ipsilateral to the cerebral symptoms carotid plaques, where the events were attributed. However, other sources of atheroemboli, such as the aortic arch, cannot be excluded because our patients did not undergo transeosophageal echocardiography.

Conclusions
In patients with acute ischemic stroke and bilateral carotid plaques, MWR offers incremental predictive value in culprit carotid artery identification.

Disclosures
None.

References
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