Morphological and Functional Assessment of Carotid Plaques Have Similar Predictive Accuracy for Coronary Artery Disease

Konstantinos Toutouzas, MD; Georgios Benetos, MD; Maria Drakopoulou, MD; Archontoula Michelongona, MD; Charalampia Nikolaou, MD; Constantina Masoura, MD; Konstantinos Stathogiannis, MD; Constantina Aggeli, MD; Eleftherios Tsiamis, MD; Elias Siories, BSc, MSc, PhD; Christodoulos Stefanadis, MD

Background and Purpose—Microwave radiometry allows noninvasive in vivo measuring of internal temperature of tissues reflecting inflammation. In the present study, we evaluated the predictive accuracy of this method for the diagnosis of coronary artery disease (CAD).

Methods—Consecutive patients (n=287) scheduled for coronary angiography were included in the study. In carotid arteries of both groups, the following measurements were performed: (1) intima-media thickness (IMT max) and (2) temperature measurements by microwave radiometry (ΔT max). C-statistic and net reclassification improvement were used to compare the prediction ability of the markers IMT max and ΔT max for the presence of CAD and multivessel CAD.

Results—Of 287 patients, 239 had stenoses ≥50% (CAD group), and 48 did not have significant stenoses (NO-CAD group). ΔT max was an independent predictor for the presence of CAD and multivessel CAD, showing similar predictive accuracy to intima-media thickness, as assessed by c-statistic and net reclassification improvement.

Conclusions—Local inflammatory activation, as detected by microwave radiometry, has similar predictive accuracy to intima-media thickness for the presence and extent of CAD. (Stroke. 2013;44:2607-2609.)

Key Words: carotid arteries ■ coronary artery disease ■ inflammation ■ microwaves

Carotid intima-media thickness (IMT) has been widely used as a surrogate marker for coronary artery disease (CAD).1–4 The increase of IMT in carotid arterial wall reflects morphological alterations and does not provide information on the functional changes. Microwave radiometry (MR) is a new method and allows in vivo noninvasive measurement of the temperature of carotid atherosclerotic plaques, reflecting their inflammatory status.5–7

In the present study, we aimed to (1) examine whether the inflammation of carotid artery wall, as assessed by MR, correlates with the presence of CAD, and (2) compare the predictive value of the morphological and functional assessment of carotid plaques in CAD detection.

Methods

Study Population

Consecutive patients undergoing coronary angiography were prospectively enrolled in the study. Significant CAD was defined as diameter lumen stenosis of ≥50% in ≥1 major coronary artery. Multivessel CAD was defined as the presence of significant stenoses in ≥2 major coronary arteries.

All patients underwent carotid ultrasound examination followed by MR measurements, performed by specialists blinded to angiographic results. All participants provided informed consent, and the study was approved by our institution ethical committee.

Ultrasound Imaging

The ultrasound protocol included scanning of both carotid arteries from their point of origin throughout their whole length using a 7.5-MHz transducer (Philips iEE33; Philips, Washington). IMT measurements 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 and was used as a marker. The regions 20 mm proximal and 20 mm distal to the bifurcation region defined the 2 other segments, namely the common carotid artery segment and the internal carotid artery segment, respectively. The highest IMT value of all segments of both carotid arteries was defined as IMT max.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002462/-/DC1.

Correspondence to Konstantinos Toutouzas, MD, First Department of Cardiology, Hippokration Hospital, 26 Karaoli and Dimitriou str, Holargos, 15562 Athens, Greece. E-mail ktoutouz@gmail.com

© 2013 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.113.002462

2607
MR Measurements
RTM-01-RES, a microwave computer-based system (Bolton, United Kingdom), was used for the performance of MR measurements. The system measures temperature from internal tissues at microwave frequencies. The basic principles of MR have been described previously.5,6
Temperature measurements were performed at each carotid artery over the previously defined segments (20 mm each). The method has been validated as described previously.6 Temperature difference ($\Delta T$) of each carotid artery was assigned as the temperature of the segment under investigation minus the minimal temperature of each carotid. $\Delta T_{max}$ was assigned as the maximum $\Delta T$ value of both carotid arteries.

Statistical Analysis
Data were analyzed using commercially available software (version 20, SPSS Inc; Chicago, IL). $P$ values are 2-sided from the Student $t$ test when continuous variables were compared and ANOVA test when there were >2 categories. Noncontinuous values were compared by $\chi^2$ test. A $P$ value of <0.05 was considered significant. Multiple logistic regression analysis was used to determine independent predictors for CAD. We considered the addition of the following markers: (1) $\Delta T_{max}$, (2) IMT $max$, and (3) IMT $min$ plus $\Delta T_{max}$ on established risk factors (sex, age, dyslipidemia, arterial hypertension, diabetes mellitus, smoking, and family history), and we compared the respective prediction models with the use of Harrell c-statistic and net reclassification improvement (NRI).

Results
We included a total of 287 patients (Table 1). Of those 287 patients, 239 (83.3%) had significant CAD (CAD group), and 48 patients did not have significant coronary artery stenoses (NO-CAD group); 103 patients (35.89%) had 1-vessel CAD, 90 patients (31.36%) had 2-vessel disease, and 46 patients (16.03%) had 3-vessel disease.

Carotid arteries of patients with NO-CAD (n=96; 16.72%) had lower $\Delta T$ compared with patients with 1-vessel CAD (n=206; 35.89%), 2-vessel disease (n=180; 31.36%), and 3-vessel disease (n=92; 16.03%; 0.48±0.39°C, 0.68±0.44°C, 0.85±0.49°C, and 0.87±0.54°C; $P<0.01$; Figure).

In multivariate logistic regression analysis, $\Delta T_{max}$ was an independent predictor for the presence of CAD when adjusted for sex, age, statin use, and established risk factors (odds ratio, 3.80; 95% confidence interval, 1.27–11.37; $P=0.02$). Furthermore, in the same model, $\Delta T_{max}$ was an independent predictor for the presence of multivessel CAD (odds ratio, 1.98; 95% confidence interval, 1.16–3.37; $P=0.01$).

By receiver-operating curve analysis, we obtained a good predictive capacity of $\Delta T_{max}$ for CAD (area under the curve, 0.766; 95% confidence interval, 0.686–0.847; $P<0.01$) and for multivessel CAD (area under the curve, 0.660; 95% confidence interval, 0.597–0.722; $P<0.01$).

Table 1. Demographic Characteristics of the 2 Study Groups

<table>
<thead>
<tr>
<th></th>
<th>CAD Group (n=239)</th>
<th>NO-CAD Group (n=48)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63.75±10.76</td>
<td>56.44±11.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Men</td>
<td>200 (83.68)</td>
<td>28 (58.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>169 (67.78)</td>
<td>18 (37.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history</td>
<td>103 (43.10)</td>
<td>2 (4.17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>187 (78.24)</td>
<td>18 (37.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>92 (38.49)</td>
<td>3 (6.25)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>110 (46.03)</td>
<td>10 (20.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>184 (77)</td>
<td>13 (27.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ADP inhibitors</td>
<td>89 (37.24)</td>
<td>5 (10.42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ACE</td>
<td>61 (25.52)</td>
<td>6 (12.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>ARB</td>
<td>66 (27.62)</td>
<td>6 (12.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>108 (45.19)</td>
<td>9 (18.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Statins</td>
<td>178 (74.48)</td>
<td>9 (18.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nitrates</td>
<td>37 (15.59)</td>
<td>2 (4.17)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ca-antagonists</td>
<td>40 (16.74)</td>
<td>6 (12.5)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ASA, acetylsalicylic acid; ARB, angiotensin II receptor blockers; Ca-antagonists, calcium antagonists; and CAD, coronary artery disease.

Figure. Temperature difference ($\Delta T$) of carotid arteries of the study population according to the number of coronary arteries with stenosis ≥50%.
In Table 2, the results of the c-statistic and NRI values of our prediction models are summarized. The NRI with the addition of $\Delta T_{\text{max}}$ was higher for the prediction of multivessel CAD compared with the NRI after addition of IMT_{max}. For the presence of CAD, NRI was greater for IMT_{max} compared with $\Delta T_{\text{max}}$.

### Discussion

This study demonstrated that: (1) patients with CAD had increased local inflammation in carotid plaques compared with subjects without significant CAD; (2) this local inflammatory activation increased proportionally to the extent of CAD as detected by angiography; and (3) inflammation as detected by MR in carotid plaques was an independent predictor for the presence and extent of CAD.

In the current study population, risk prediction models, on the basis of structural or functional markers, showed similar predictive accuracy for CAD (c-statistic IMT_{max}, 0.880; c-statistic $\Delta T_{\text{max}}$, 0.880; $P_{\text{diff}}=0.96$) and multivessel CAD (c-statistic, 0.730 and 0.716; $P_{\text{diff}}=0.47$). Furthermore, the prediction model based on $\Delta T_{\text{max}}$ showed higher NRI value compared with IMT_{max} for multivessel CAD prediction (0.577 and 0.422, respectively). Whether these findings are reproducible in low-risk asymptomatic populations should be examined further. Possibly, the functional assessment in an earlier stage of the disease could increase the predictive value of current imaging modalities.

### Conclusions

Local inflammatory activation of carotid arteries, as assessed by MR, correlates with the presence and extent of CAD.

### Acknowledgments

We thank Dr Demosthenes Panagiotakos for his substantial contribution in the statistical analysis of the data.

### Disclosures

None.

### References

Morphological and Functional Assessment of Carotid Plaques Have Similar Predictive Accuracy for Coronary Artery Disease

Konstantinos Toutouzas, Georgios Benetos, Maria Drakopoulou, Archontoula Michelonga, Charalampia Nikolaou, Constantina Masoura, Konstantinos Stathogiannis, Constantina Aggeli, Eleftherios Tsiamis, Elias Siores and Christodoulos Stefanadis

Stroke. 2013;44:2607-2609; originally published online July 25, 2013;
doi: 10.1161/STROKEAHA.113.002462

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/9/2607

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/07/25/STROKEAHA.113.002462.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL
Supplemental Figure I
Supplemental Figure II
**Supplemental Figure I:** Area Under the Receiver Operator Characteristic Curves of the various prediction models for the presence of coronary artery disease. Blue line: IMTmax, Green line: ΔTmax, Brown line: IMTmax+ΔTmax, Purple line: Reference line.

**Supplemental Figure II:** Area Under the Receiver Operator Characteristic Curves of the various prediction models for the presence of multivessel-coronary artery disease. Blue line: IMTmax, Green line: ΔTmax, Brown line: IMTmax+ΔTmax, Purple line: Reference line.