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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 Siores, 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 $\geq 50\%$ (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 $\geq 50\%$ 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}.

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Table 1. Demographic Characteristics of the 2 Study Groups

No. of Patients (N=287)	CAD Group (n=239)	NO-CAD Group (n=48)	P Value
Clinical variables			
Age, y	63.75±10.76	56.44±11.54	<0.01
Men	200 (83.68)	28 (58.33)	<0.01
Arterial hypertension	169 (67.78)	18 (37.50)	<0.01
Family history	103 (43.10)	2 (4.17)	<0.01
Dyslipidemia	187 (78.24)	18 (37.50)	<0.01
Diabetes mellitus	92 (38.49)	3 (6.25)	<0.01
Smoking	110 (46.03)	10 (20.83)	0.01
Previous medication			
ASA	184 (77)	13 (27.08)	<0.01
ADP inhibitors	89 (37.24)	5 (10.42)	<0.01
ACE	61 (25.52)	6 (12.5)	0.05
ARB	66 (27.62)	6 (12.5)	0.03
β-Blockers	108 (45.19)	9 (18.75)	<0.01
Statins	178 (74.48)	9 (18.75)	<0.01
Nitrates	37 (15.59)	2 (4.17)	0.04
Ca-antagonists	40 (16.74)	6 (12.5)	0.47

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.

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 (ΔT) of each carotid artery was assigned as the temperature of the segment under investigation minus the minimal temperature of each carotid. ΔT_{\max} was assigned as the maximum ΔT 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 χ^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) ΔT_{\max} , (2) IMT_{\max} , and (3) IMT_{\max} plus ΔT_{\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 ΔT 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%; $0.48\pm 0.39^\circ\text{C}$, $0.68\pm 0.44^\circ\text{C}$, $0.85\pm 0.49^\circ\text{C}$, and $0.87\pm 0.54^\circ\text{C}$; $P<0.01$; Figure).

In multivariate logistic regression analysis, ΔT_{\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, ΔT_{\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 ΔT_{\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; $P<0.01$).

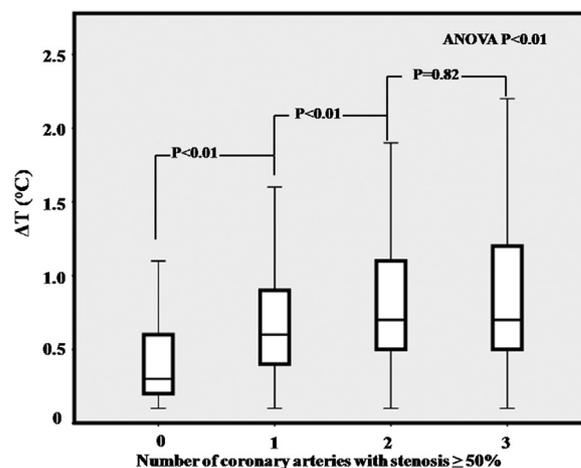


Figure. Temperature difference (ΔT) of carotid arteries of the study population according to the number of coronary arteries with stenosis $\geq 50\%$. Carotid arteries of patients with 3-vessel disease had the highest ΔT values.

Table 2. C-Statistic and NRI When Each Variable Is Added to a Baseline Model With Established Risk Factors

Model	C-Statistic	95% CI	P Value	NRI	95% CI
CAD					
IMT _{max}	0.880*	0.820–0.941	<0.01	0.721	0.022–0.973
ΔT_{max}	0.880*	0.818–0.941	<0.01	0.546	0.204–1.106
IMT _{max} + ΔT_{max}	0.882	0.819–0.945	<0.01	0.797	0.285–1.156
Multivessel CAD					
IMT _{max}	0.730†	0.672–0.788	<0.01	0.422	0.043–0.604
ΔT_{max}	0.716†	0.657–0.775	<0.01	0.577	0.254–0.726
IMT _{max} + ΔT_{max}	0.732	0.674–0.789	<0.01	0.440	0.237–0.708

ΔT indicates temperature difference; CAD, coronary artery disease; CI, confidence interval; IMT, intima-media thickness; and NRI, net reclassification improvement.

P value for comparison: *0.96 and †0.47.

In Table 2, the results of the c-statistic and NRI values of our prediction models are summarized. The NRI with the addition of ΔT_{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 ΔT_{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 ΔT_{max} , 0.880; P_{diff} =0.96) and multivessel CAD (c-statistic, 0.730 and 0.716; P_{diff} =0.47). Furthermore, the prediction model based on ΔT_{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.

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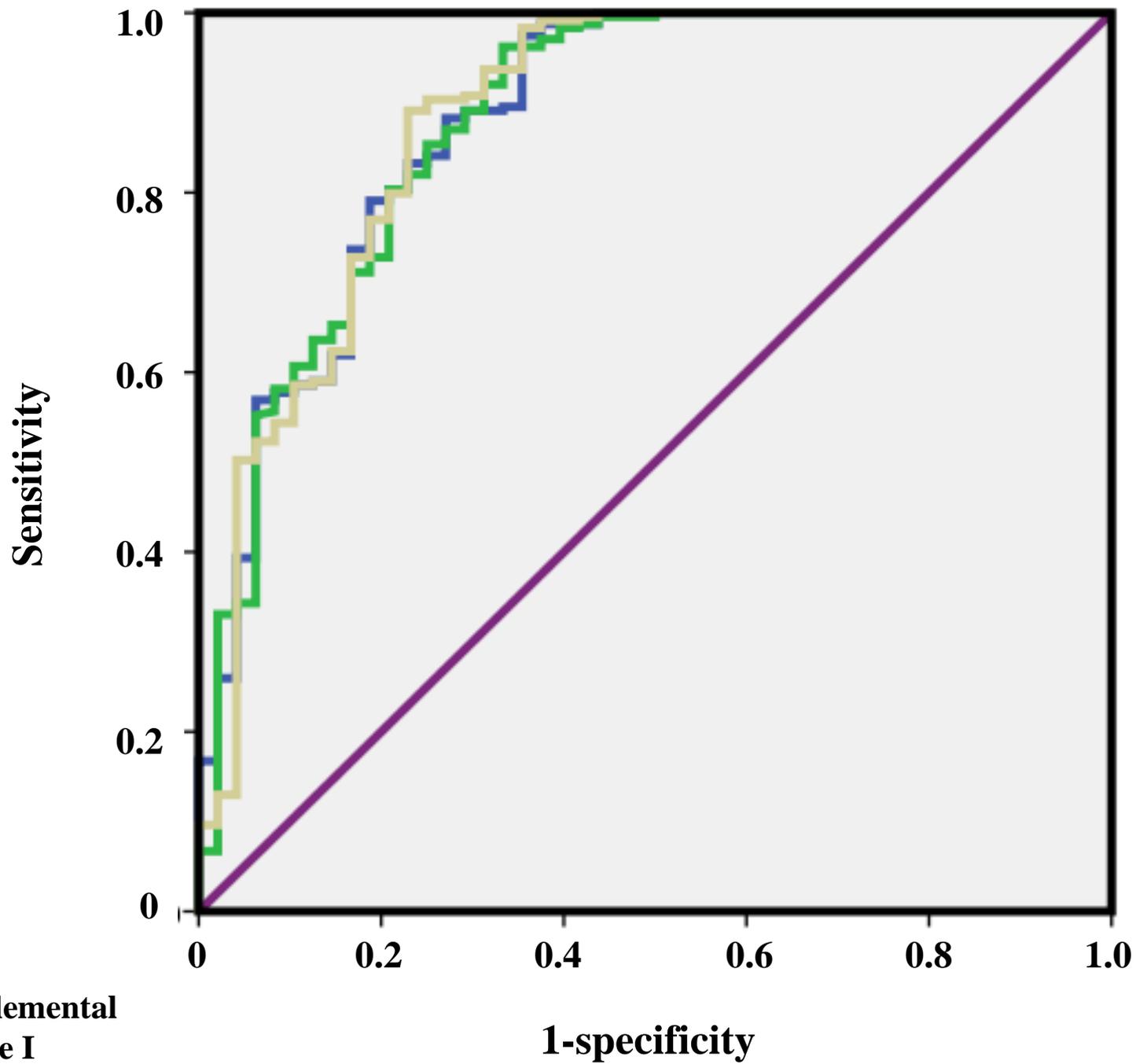
Disclosures

None.

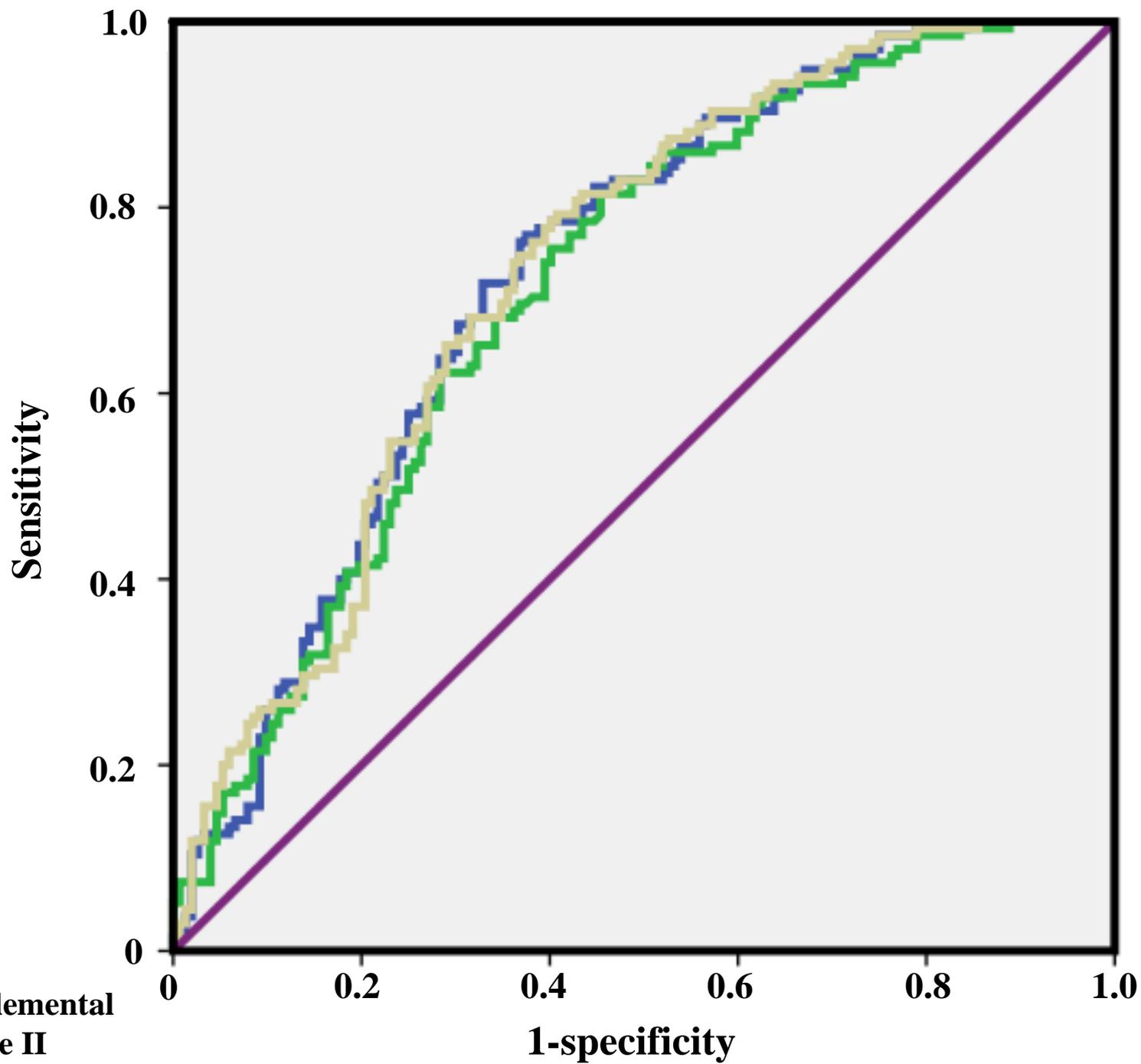
References

- Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607.
- Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM, et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. *Eur Heart J*. 2007;28:2094–2101.
- Kotsis VT, Pitiriga VCh, Stabouli SV, Papamichael CM, Toumanidis ST, Rokas SG, et al. Carotid artery intima-media thickness could predict the presence of coronary artery lesions. *Am J Hypertens*. 2005;18(5 pt 1):601–606.
- Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis*. 2012;220:128–133.
- Toutouzas K, Drakopoulou M, Aggeli C, Nikolaou C, Felekos I, Grassos H, et al. In vivo measurement of plaque neovascularisation and thermal heterogeneity in intermediate lesions of human carotid arteries. *Heart*. 2012;98:1716–1721.
- Toutouzas K, Grassos C, Drakopoulou M, Synetos A, Tsiamis E, Aggeli C, et al. First in vivo application of microwave radiometry in human carotids: a new noninvasive method for detection of local inflammatory activation. *J Am Coll Cardiol*. 2012;59:1645–1653.
- Toutouzas K, Grassos H, Synetos A, Drakopoulou M, Tsiamis E, Moldovan C, et al. A new non-invasive method for detection of local inflammation in atherosclerotic plaques: experimental application of microwave radiometry. *Atherosclerosis*. 2011;215:82–89.

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: IMT_{max}, Green line: ΔT_{max} , Brown line: IMT_{max}+ ΔT_{max} , 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: IMT_{max}, Green line: ΔT_{max} , Brown line: IMT_{max}+ ΔT_{max} , Purple line: Reference line.