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Assessment of carotid plaque echolucency in addition to plaque size increases the predictive value of carotid ultrasound for coronary events in patients with coronary artery disease and mild carotid atherosclerosis

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ABSTRACT

Objectives: This study examined whether combined ultrasound assessment of plaque size and echolucency in the carotid artery had an additive effect for predicting coronary events in patients with coronary artery disease (CAD). Ultrasound assessment of either plaque size or echolucency of carotid artery provides prognostic information on coronary events. Combined assessment of plaque size and echolucency of carotid artery has the advantage of obtaining both structural and compositional information in the same artery in a single session.

Methods and results: Ultrasound assessment of carotid plaque maximum intima-media thickness (plaque-IMTmax) and echolucency with integrated backscatter analysis was performed in 413 patients with CAD and carotid plaque. All study patients were followed up prospectively for 54 months or until the occurrence of a coronary event. During the follow-up period, 49 coronary events occurred including 2 cardiac deaths, 10 non-fatal acute myocardial infarctions and 37 recurrent and refractory unstable angina. Multivariate Cox hazards analysis showed plaque-IMTmax alone (HR 2.01, 95%CI 1.30–3.10), plaque echogenicity alone (HR 0.86, 95%CI 0.80–0.91) and combination of high plaque-IMTmax and low echogenicity on categorical data (HR 2.56, 95%CI 1.39–4.74) were independent predictors of coronary events. Analysis using *c*-statistics showed that plaque-IMTmax and plaque echolucency in combination had a significant incremental effect on the predictive value of the conventional risk factors for coronary events.

Conclusions: Combined ultrasound assessment of carotid plaque size and echolucency has an additive value for prediction of coronary events. Further studies need to evaluate the clinical utility of both ultrasound measurements for risk stratification in CAD.

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1. Introduction

Recent studies [1,2] suggest that plaque instability is not merely a local vascular occurrence, but instead exists simultaneously at multiple sites in the systemic vascular bed. It is therefore possible that instability of coronary plaque may be assessed by evaluating plaque characteristics in other vessels such as the carotid arteries. There is increasing evidence that atherosclerotic burden of systemic arteries predicts cardiovascular events and accordingly several non-invasive techniques have been developed to evaluate atherosclerotic burden in these vessels [3–12]. Ultrasound measurement of intima-media thickening (IMT) of the carotid artery has been shown to detect patients at a high risk of future cardiovascular events [3,4,8–12]. In addition, ultrasound measurement of echolucency of the carotid artery is capable of evaluating carotid plaque characteristics such as stability and composition and is therefore useful for identifying unstable carotid plaques [6,13–19]. Echolucent atherosclerotic plaques have been shown to be lipid-rich vulnerable lesions [16–19]. We have demonstrated previously that low integrated backscatter (IBS) values of carotid plaque, which indicate echolucency, predict future coronary events [5]. Fibrosis and calcification in the carotid plaque give a high IBS value, while deposition of lipid gives a low IBS value [17–19].

In general, although previous studies [4,5,7,13,14] have focused on a single parameter, recent studies [8–10] have reported a combination of vascular parameters may have an additive effect for

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predicting cardiovascular events. Assessment of IMT and plaque echolucency of the carotid artery has the advantage of obtaining both structural and compositional information within the same artery in a single session. We carried out this study to assess whether or not carotid maximum plaque IMT and plaque echolucency, detected by IBS analysis, had an additive effect for predicting coronary events in patients with coronary artery disease (CAD) that indicates advanced coronary atherosclerotic burden.

2. Methods

2.1. Study patients

This study screened 1432 consecutively enrolled patients with stable CAD who were admitted to the cardiology section of Yamanashi University Hospital, and all of them were examined with carotid ultrasound. The inclusion criteria included the presence of carotid intima-media thickness (IMT) ≥1.1 mm with protrusion of vessel wall into the lumen [14]. Patients with severe carotid stenosis (≥50%) were excluded in order to mitigate the direct threat to the cerebral circulation and a high risk of future ischemic stroke during the follow-up period. Among the screened patients, 41 patients met this exclusion criterion and were excluded. Other exclusion criteria were: (1) acute coronary syndrome, stroke, cardiogenic shock, pulmonary edema, major surgery, trauma or serious infectious disease within 4 weeks prior to enrollment, (2) neoplasm, significant hepatic or inflammatory disease, (3) chronic renal failure or serum creatinine level >2.5 mg/dL, congestive heart failure or left main trunk disease, (4) other serious diseases, (5) age >80 years old. Finally, this study enrolled 413 patients according to these inclusion and exclusion criteria. All the patients were ethnic Japanese and had stable CAD with an organic stenosis of >70% of the diameter of at least one major coronary artery (170 patients had single-vessel disease, 183 had two-vessel disease and 60 had three-vessel disease), no episodes of angina at rest and no changes in frequency of angina in response to sublingual nitroglycerin in the previous 3 months. The baseline characteristics of the study patients are summarized in Table 1. All the patients gave written, informed consent for this study at enrollment. This study was approved by the ethics committee of Yamanashi University Hospital.

Table 1
Baseline clinical characteristics of the study patients.

	Study patients (n = 413)
Age (yrs)	62 ± 14
Male gender, n (%)	325 (79)
Hypertension, n (%)	162 (39)
Smoking, n (%)	149 (36)
Diabetes mellitus, n (%)	153 (37)
Multivessel CAD, n (%)	243 (59)
Family history of CAD, n (%)	103 (25)
LDL-cholesterol (mg/dL)	119 ± 30
HDL-cholesterol (mg/dL)	47 ± 11
Hemoglobin A1c (%)	6.0 ± 0.9
C-reactive protein (mg/L)	2.5 ± 4.2
Systolic blood pressure (mm Hg)	131 ± 21
LVEF (%)	54 ± 12
Medication use, n (%)	
Beta-blocker	150 (36)
Calcium antagonist	256 (62)
ACEI or ARB	241 (58)
Sulfonyl urea	100 (24)
Aspirin	413 (100)
Thienopyridine	392 (95)
Statin	283 (69)
Fibrate	70 (17)
Ultrasound parameters	
Plaque-IMTmax (mm)	2.7 ± 0.7
Calibrated IBS (dB)	−16.1 ± 4.6
Averaged calibrated IBS (dB)	−15.0 ± 4.1

Data are expressed as the mean value ± SD or number (%) of patients. Hypertension, blood pressure ≥140/90 mm Hg or taking anti-hypertensive medication; Smoking, ≥10 cigarettes/day for ≥1 year; Diabetes mellitus, according to the criteria of the American Diabetic Association or taking anti-diabetic medication; multivessel CAD, organic stenosis of more than 2 major coronary arteries; LVEF, left ventricular ejection fraction on echocardiography; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

2.2. Follow-up study

After baseline data were obtained at our hospital, 413 patients were followed up prospectively every month at a hospital by the patients' primary physicians for a period of up to 54 months or until the occurrence of a coronary event. All these patients received the standardized medical therapy outlined in Table 1. The study endpoint was any major coronary event, including cardiac death, non-fatal myocardial infarction or recurrent and refractory angina pectoris requiring coronary revascularization. Details of collection and check of the follow-up data are described in the online supplemental data.

2.3. Carotid ultrasound evaluation

Details of carotid ultrasound evaluation are described in the online supplemental data. Briefly, a carotid ultrasound examination was performed on all eligible patients at the screening visit of the study using an 11.0 MHz, linear-array transducer (SONOS-5500, Phillips, Andover, MA, USA) [5,6,20]. Atherosclerotic plaques were defined as lesions with a focal IMT of 1.1 mm or greater, with a localized protrusion of the vessel wall into the lumen [5,6,20,21]. Maximum IMT (Plaque-IMTmax) was defined as the greatest axial thickness among all plaques in the carotid arteries. The degree of carotid stenosis was determined using both B-mode imaging and color flow (% area stenosis) and duplex ultrasonography in which peak systolic velocity >130 cm/s was classified as ≥50% stenosis.

We measured the IBS values of all carotid atherosclerotic plaques, as described in our and other earlier reports [5,6,18,20]. For each plaque, conventional high-resolution and B-mode images were obtained, followed by the acquisition of 60 IBS images. Atherosclerotic plaques were analysed using the manual definition mode to outline the region of interest (ROI). The average power of the IBS signal within the ROI was measured and displayed in decibels (dB) for a total of 60 frames. We adopted the adventitia as the reference object and then expressed the relative IBS values of the intima-media and adventitia (calibrated IBS = intima-media IBS value–adventitia IBS value) (Supplementary Fig. 1). In each patient, the plaque with the lowest calibrated IBS value was selected from all the carotid plaques with IMT ≥1.1 mm in each patient, and its calibrated IBS value was expressed as calibrated IBS and was used for the most part of analyses. In a separate analysis, we calculated average of calibrated IBS (averaged calibrated IBS) of all the carotid plaques with IMT ≥1.1 mm in each patient. A lower IBS value reflects more echolucent plaque.

2.4. Laboratory examination

Venous blood was obtained from all study patients after a 12 h overnight fast at the time of enrollment into the study. Levels of high density lipoprotein cholesterol (HDL-cholesterol) and low density lipoprotein cholesterol (LDL-cholesterol) in fasting serum were measured as described previously [20]. C-reactive protein (CRP) levels in the fasting plasma were assayed by rate nephelometry (Dade Behring, Marburg, Germany).

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