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Prediction of silent ischemic lesions after carotid artery stenting using integrated backscatter ultrasound and magnetic resonance imaging

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ABSTRACT

Objective: A major concern with carotid artery stenting (CAS) is the potential for cerebral embolism. The purpose of this study was to determine whether integrated backscatter (IBS) ultrasound and black-blood magnetic resonance imaging (BB-MRI) can predict the risk of a silent ischemic lesion after CAS.
Methods: We performed quantitative analysis of plaque characteristics in carotid arteries using IBS ultrasound and BB-MRI before CAS in 50 patients. We measured IBS values and the signal intensity ratio (SIR) from T1 weighted images of all plaques. We also performed diffusion-weighted (DWI) MRI of the brain before and after CAS.
Results: In the patient group that was positive ($n = 19$) for newly appearing ipsilateral silent ischemic lesions (NISIL), relative unstable component area (%UCA) evaluated by IBS analysis ($60.2 \pm 23.4\%$ and $35.3 \pm 19.2\%$, $p < 0.001$) and SIR (1.40 ± 0.19 and 1.18 ± 0.25, $p < 0.01$) in most stenotic lesions were higher than in the NISIL-negative group ($n = 31$). From the analysis of receiver operating characteristic curves, 50% of the %UCA measured by IBS and an SIR of 1.25 measured by BB-MRI were the most reliable cutoff values for predicting NISIL. In multivariate logistic regression analysis, the independent predictors of NISIL were SIR ($p = 0.030$), the CRP level ($p = 0.041$) and the %UCA measured by IBS ($p = 0.049$).
Conclusions: Quantitative tissue characterization of carotid plaques using IBS ultrasound and BB-MRI was useful to predict NISIL after CAS. The plaque components in carotid arteries should be evaluated by BB-MRI or IBS ultrasound before CAS to improve the clinical outcome of this procedure.

1. Introduction

Carotid artery stenting (CAS) has recently emerged as a potential alternative to carotid endarterectomy (CEA) [1] because it is a less invasive procedure and results in a shorter duration of hospitalization. A recent randomized controlled trial, SAPPHIRE showed that CAS had almost the same efficacy as CEA in high-risk patients [2,3]. Although many advantages of CAS have been reported, one of its disadvantages is the considerably high incidence of distal emboli during CAS, even though they are subclinical. Asymptomatic or silent ischemic lesions were detected by diffusion-weighted magnetic resonance imaging (DWI) more often in CAS than in CEA patients [4]. We and other investigators reported that analysis of carotid plaques using integrated backscatter (IBS) ultrasound or black-blood magnetic resonance imaging (BB-MRI) can identify the histological components of carotid plaques [5–7]. Plaque instability, such as lipid pool and intra-plaque hemorrhage is associated with an increased number of emboli after CEA or CAS [8,9]. Therefore, we hypothesized that it should be possible to predict embolism after CAS by applying IBS ultrasound and BB-MRI analysis to characterize the tissue components of carotid plaques. The aim of this study was to examine whether carotid plaque instability analyzed by IBS ultrasound and BB-MRI is associate with a higher risk of newly appearing ipsilateral silent ischemic lesions (NISIL) detected by DWI after CAS. An additional objective was to elucidate the usefulness of IBS and BB-MRI for the prediction of NISIL detected by DWI.

2. Methods

2.1. Study protocol

The subjects of the present study were 50 consecutive patients (45 men and 5 women) with high-grade carotid stenosis who were treated with CAS at Gifu University Hospital from October 2006 to April 2008. High-grade carotid stenosis was defined as a symptomatic carotid stenosis of >70% and asymptomatic carotid stenosis

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of >60% assessed with angiography, as recommended by the North American Symptomatic Carotid Endarterectomy Trial collaborators [10]. We assessed NISIL by DWI before and after CAS. At the same time, we performed quantitative analysis of plaque characteristics using IBS ultrasound and BB-MRI before CAS in all patients. The experimental protocol was approved by the institutional ethics committee of Gifu University Hospital and informed consent was obtained from all patients.

2.2. Integrated backscatter ultrasound imaging

Transverse and longitudinal scans of carotid plaques were performed using an ultrasound imaging system (SONOS 7500, Philips Medical Systems, Andover, MA). Conventional ultrasound images of the carotid artery and IBS values were easily acquired at the bedside using a 5–12 MHz transducer for all studies. We performed IBS measurements using cross-sectional images rather than longitudinal images because the same method was used in our previous study [5]. Regions-of-interest (ROIs) (0.6 mm × 0.6 mm) were set on the cross-sectional images. IBS values were measured in the cross-section with the greatest stenosis. IBS values in the near wall of the arteries (an angle span of 120° between −60° and +60°) were excluded from the analysis because of the erratic diffraction phenomena and the influence of angle dependency. That is, only IBS values in the far wall of the carotid plaques (an angle span of 240° between −120° and +120°) were measured by a neurosurgeon who was blinded to the BB-MRI findings. The IBS values of the far wall of the carotid artery plaques were corrected by subtracting the minimum IBS values of the vessel lumen just above the far wall. The details of our measurements have been previously reported [5]. Our definition of IBS values for each histological category was determined by comparing the histological images reported in our previous study (intra-plaque hemorrhage: $4 < \text{IBS} \leq 6$; lipid pool: $6 < \text{IBS} \leq 13$; fibrosis: $13 < \text{IBS} \leq 18$; mixed lesions: $18 < \text{IBS} \leq 27$; and calcification: $27 < \text{IBS} \leq 33$ dB) [5]. Unstable component was defined as the area of IBS values of intra-plaque hemorrhage and lipid pool ($4 < \text{IBS} \leq 13$). Relative unstable component area (%UCA: area of intra-plaque hemorrhage and lipid pool/area of plaque) was automatically measured in each plaque by computer software (T3D, Fortner Research LLC, Sterling, Virginia).

We determined the interobserver variability of %UCA from 20 recordings in which %UCA was measured by two observers in randomly selected carotid cross-sections. The interobserver variability of %UCA was 1.0 ± 3.4%. The interobserver correlation coefficient was 0.99 ($p < 0.001$). Likewise, we determined intraobserver variability of %UCA from 20 recordings in which %UCA was measured twice by one observer in randomly selected carotid cross-sections. The intraobserver variability of %UCA was 0.4 ± 3.4%. The intraobserver correlation coefficient was 0.99 ($p < 0.01$).

2.3. MRI black-blood imaging

BB-MRI was performed using a 1.5-T system (Intera Achieva Nova Dual, Philips Medical Systems, Best, The Netherlands) equipped with standard neck array coils. Fat suppression was used to reduce the signal from subcutaneous tissues, and a zero-filled interpolation technique was used to reduce pixel size and minimize partial-volume artifacts. Plaque imaging was performed in the oblique section at three parts including the minimal lumen area. The parameters for T1 weighted images (T1WI) were: cardiac gated, double inversion recovery two-dimensional (2D) turbo spin-echo (TSE) under spectral pre-saturation with inversion recovery (SPIR) (TSE factor: 7, echo time [TE]: 10 ms, repetition time [TR]: 1 × R–R interval (duration of the interval from the center of one R wave to the center of the following R wave on an electrocardiogram), 256 × 80% (recon 512) matrix; and a scan time of 1 min, 13 s. The signal intensity of plaques was compared with that of the adjacent sternocleidomastoid muscle (SCM) by a radiologist who was blinded to the ultrasound findings. We calculated the ratio of the signal intensity of carotid plaques to that of SCM and defined this as the signal intensity ratio (SIR).

It has been reported that lipid-rich necrotic cores appear as areas of high signal intensity in T1WI of BB-MRI, whereas they appear as areas of variable signal intensity in T2WI of BB-MRI [7]. In time-of-flight (TOF) images, lipid-rich necrotic cores appear as areas of moderate intensity, but fibrous tissue shows moderate-to-low signal intensity as well. Since T1WI of BB-MRI shows the borders of intimal plaques more clearly than TOF images. We employed the SIR in T1WI to discriminate tissue components of carotid plaques rather than using T2WI or TOF images.

We determined interobserver variability of SIR from 20 recordings in which SIR was measured by two observers in randomly selected carotid cross-sections. The interobserver variability of SIR was 1.2 ± 3.9%. The interobserver correlation coefficient was 0.98 ($p < 0.001$). Likewise, we determined intraobserver variability of SIR from 20 recordings in which SIR was measured twice by one observer in randomly selected carotid cross-sections. The intraobserver variability of SIR was 0.1 ± 3.2%. The intraobserver correlation coefficient was 0.98 ($p < 0.01$).

2.4. Carotid artery stenting procedure

Aspirin (100 mg) and clopidogrel (75 mg) or ticlopidine (100 mg) or cilostazol (200 mg) were given for a minimum of 7 days prior to the procedure. All stent procedures were performed under local anesthesia via the percutaneous transfemoral route. The procedures were carried out by an experienced neurointerventional team. A heparin bolus of 100 U/kg was given immediately before the intervention to increase the activated clotting time (ACT) to a minimum of 300 s. A 6F, 90-cm catheter sheath was guided from the femoral artery to the ipsilateral common carotid artery proximal to the stenosis. Two different types of embolic protection devices were used: Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA) ($n = 44$) and Angioguard (Johnson & Johnson, Cordis, Minneapolis, MN) ($n = 6$). In all patients, pre-dilation of the internal carotid lesion was done using a 3.5- or 4-mm balloon catheter. Two types of stents were placed in the stenotic lesion: Precise (Johnson & Johnson, Cordis, Minneapolis, MN) ($n = 42$) or Wallstent (Boston Scientific, Natick, MA) ($n = 8$). Post-dilation was performed with a 4.5- or 5-mm balloon catheter. Fasting plasma concentration of total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, triglycerides and C-reactive protein were measured by standard laboratory methods within three days before CAS.

2.5. Detection of a silent ischemic lesion by MRI

The baseline MRI was obtained after diagnostic angiography and prior to CAS in all patients. The period between the baseline DWI and CAS was 10 ± 8 days. During this period, there were no new ischemic events such as transient ischemic attacks or strokes. The second DWI was performed within 48 h after CAS. The MRI studies consisted of DWI with the echoplanar method under the following conditions: TR/TE 2060/67.0: slice thickness, 5 mm: spacing, 1.5 mm: b value, 1000 s/mm^2: and FOV, 24 cm. NISIL were counted by comparing the first and second DWI.

2.6. Statistical analysis

Continuous values were expressed as the mean ± SD. Categorical data were summarized as percentages and compared using a Fisher's exact test. Comparisons of continuous variables between the cohorts were performed with unpaired Student's t-