Atherosclerosis 260 (2017) 87–93

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Preoperative cervical carotid artery contrast-enhanced ultrasound findings are associated with development of microembolic signals on transcranial Doppler during carotid exposure in endarterectomy

Kohki Oikawa [a], Tadayoshi Kato [b], Kazumasa Oura [b], Shinsuke Narumi [b], Makoto Sasaki [c], Shunrou Fujiwara [a], Masakazu Kobayashi [a], Yoshiyasu Matsumoto [a], Jun-ichi Nomura [a], Kenji Yoshida [a], Yasuo Terayama [b], Kuniaki Ogasawara [a, *]

[a] Department of Neurosurgery, Iwate Medical University School of Medicine, Morioka, Japan
[b] Department of Neurology and Gerontology, Iwate Medical University School of Medicine, Morioka, Japan
[c] Division of Ultrahigh Field MRI, Institute for Biomedical Sciences, Iwate Medical University School of Medicine, Morioka, Japan

ARTICLE INFO

Article history:
Received 21 January 2017
Received in revised form
27 February 2017
Accepted 17 March 2017
Available online 19 March 2017

Keywords:
Carotid endarterectomy
Ultrasound
Contrast enhancement
Microembolic signals

ABSTRACT

Background and aims: Emboli from the surgical site during exposure of the carotid arteries cause new cerebral ischemic lesions or neurological deficits after carotid endarterectomy (CEA). The purpose of the present study was to determine whether preoperative contrast-enhanced ultrasound findings of the cervical carotid arteries are associated with the development of microembolic signals (MES) on transcranial Doppler, during exposure of the arteries in CEA, and to compare the predictive accuracy of contrast-enhanced ultrasound findings with that of gray-scale median (GSM).

Methods: Seventy patients with internal carotid artery stenosis (≥70%) underwent preoperative cervical carotid artery ultrasound and CEA under transcranial Doppler monitoring of MES in the ipsilateral middle cerebral artery. Maximally enhanced intensities on the intraplaque and lumen time-intensity curves, respectively, were obtained from contrast-enhanced ultrasonography data, and the ratio of the maximal intensity (EI_p) of the intraplaque curve to that (EI_l) of the lumen curve was calculated. The GSM value of the plaque was also measured.

Results: The area under the receiver operating characteristic curve to discriminate between the presence and absence of MES during exposure of the carotid arteries was significantly greater for EI_p/EI_l than for GSM ($p = 0.0108$). Multivariate statistical analysis demonstrated that only EI_p/EI_l was significantly associated with the development of MES during exposure of the carotid arteries ($p = 0.0002$).

Conclusions: Preoperative contrast-enhanced ultrasound findings of the cervical carotid arteries are associated with development of MES on transcranial Doppler during exposure of the arteries in CEA, and the predictive accuracy of contrast-enhanced ultrasound is greater than that of GSM.

1. Introduction

Carotid endarterectomy (CEA) can prevent stroke in appropriately selected patients [1–3], but >70% of intraoperative procedure-related strokes are caused by cerebral emboli from the surgical site [4]. Emboli from the surgical site can be detected as microembolic signals (MES) on intraoperative transcranial Doppler (TCD) monitoring of the middle cerebral artery (MCA) [4–8]. Detection of MES during exposure of the carotid arteries has been shown to be significantly correlated with new ischemic lesions or neurological deficits following CEA [5–8]. Solid masses, such as thrombi, can be present on the surface of internal carotid artery (ICA) plaque, and carotid artery manipulation to expose them during the CEA procedure may result in the masses being dislodged, causing cerebral ischemic lesions [9]. It has been reported that intraplaque hemorrhage is related to a histologically disrupted plaque surface, which suggests that, under such conditions, thrombi are exposed to blood flow in carotid artery stenosis [10]. Histological neovascularization predicts carotid plaque vulnerability [11–13], and neovessels are

* Corresponding author. Department of Neurosurgery, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan.
E-mail address: kuogasa@iwate-med.ac.jp (K. Ogasawara).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.03.026

immature and fragile because local inflammatory damage and shear stress from the arterial lumen lead to collapse, causing intraplaque hemorrhage [12,14]. Thus, risk stratification for patients being considered for CEA can be improved by preoperative identification of plaque vulnerability based on the degree of neovascularization.

Cervical carotid artery ultrasound is widely used for bedside evaluation of the morphology of this artery, in particular, to characterize intraplaque components for determination of vulnerable plaques. A vulnerable plaque is generally seen as a hypoechoic plaque, but there is considerable overlap among components of plaque echogenicity, even with quantitative evaluation, such as with gray-scale median (GSM) [15,16]. Furthermore, plaque echogenicity does not always accurately predict the development of MES during CEA [8,17].

Contrast-enhanced ultrasound can generate real-time images of microbubbles as intravascular tracers that penetrate the plaque from the vessel lumen or adventitial side through neovessels [18–20]. In particular, second-generation contrast agents containing less soluble gases, such as Sonazoid (GE Healthcare, Oslo, Norway), are stable *in vivo* and provide stable contrast because they are highly compressible and facilitate detection of small and low-flow vessels, such as neovessels in carotid plaques [14,18]. Recent studies demonstrated that visual or quantitative evaluation of the contrast effect using contrast-enhanced ultrasound enabled the histopathological assessment of neovascularization of the carotid plaque, suggesting that the high contrast effect in plaque may reliably predict the presence of rich neovessels, plaque rupture, and intraplaque hemorrhage [12,14,18,21,22].

The purpose of the present study was to determine whether preoperative contrast-enhanced ultrasound findings of the cervical carotid arteries are associated with development of MES on TCD during exposure of the arteries in CEA and to compare the predictive accuracy of contrast-enhanced ultrasound findings with that of GSM.

2. Patients and methods

2.1. Study design

The present study was a prospective observational study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The institutional ethics committee reviewed and approved the protocol, and all patients or their next of kin provided their written, informed consent prior to the patients' participation.

2.2. Inclusion criteria of patients

Patients with ipsilateral ICA stenosis $\geq$70% determined according to the below-mentioned method with useful preoperative residual function (modified Rankin scale score, 0–2) and who underwent CEA of the carotid bifurcation in our institution were included. Patients with previous allergic reactions to Sonazoid or eggs [14], those who did not undergo preoperative contrast-enhanced ultrasound, and those without reliable TCD monitoring throughout the entire operation because of failure to obtain an adequate bone window were excluded.

2.3. Angiography and measurement of the degree of ICA stenosis

All patients underwent angiography with arterial catheterization, and the degree of ICA stenosis was determined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [3] and based on the comment of Fox et al. [23], as follows [24]. The distal ICA was measured beyond the bulb, where the walls are parallel and no longer tapering. To prevent underestimation of percentage stenosis for the distal ICA with reduced axial diameter due to near occlusion, if the diameter of the coaxial section of the distal ICA was at least 80% smaller than the diameter on the contralateral side, the diameter of the contralateral distal ICA was substituted for calculating the degree of stenosis of the affected ICA. If the contralateral ICA was occluded or stenotic (>70%) and the diameter of the distal ICA on the affected side was less than the diameter of the distal external carotid artery, the diameter of the distal external carotid artery was substituted for calculating the degree of stenosis of the affected ICA. The required diameter of each artery was measured on the workstation.

2.4. Pre-, intra- and postoperative management

Antiplatelet therapy was given to all patients until the morning of the day of CEA. The procedure was performed under general anesthesia with an operative microscope through a skin incision by only one senior neurosurgeon blinded to preoperative ultrasound findings, as well as intraoperative TCD findings. The neurosurgeon continued the procedure regardless of the intraoperative TCD findings. During anesthesia, standard electrocardiography, direct arterial blood pressure measurements through an intra-arterial catheter, pulse oximetry, and capnography were routinely monitored. During carotid artery exposure, the increase in systolic blood pressure was in principle maintained at least 10% above the preoperative value [23]. A vasodilator (nicardipine or nitroglycerin) or a vasoconstrictor (theoadrenalin) was administered intravenously as needed. Intraluminal shunts or patch grafts were used in none of these procedures. Heparin (5000 IU) was given as a bolus before ICA clamping.

2.5. Cervical carotid artery ultrasound and data processing

Cervical carotid artery ultrasound was performed on the affected side using an ultrasound scanner (VOLSON E8 EXPERT, GE Healthcare, Milwaukee, WI) with a 9L probe (3.1–7.9 MHz) by one investigator, three days before surgery, and all images were stored on the hard disk drive of the scanner. First, a carotid plaque was identified on B-, color Doppler-, and pulse Doppler-mode images. Next, contrast-enhanced ultrasonography was performed using a coded phase inversion mode (frame rate, 30 frames/s; image depth, 4–5 cm; transit focus, 3–4 cm) with a low mechanical index (0.1–0.2). Data were continuously recorded from 10 s before an intravenous bolus injection (0.01 ml/kg body weight) of a contrast agent (Sonazoid, Daiichi-Sankyo/GE, Tokyo, Japan) over 70 s (Fig. 1A). A low mechanical index was used for the minimal destruction of the microbubbles produced by the contrast agent.

Raw data of contrast-enhanced ultrasonography were transferred to the workstation. One investigator, who was blinded to patient information, manually placed multiple circular regions of interest (ROIs) within the carotid plaque on the sagittal section of a coded phase inversion image so that ROIs extended all over the plaque and were located near the lumen of the carotid artery (Fig. 1B). Regions with acoustic shadows due to calcification were excluded from the ROIs. The same investigator also manually placed a circular ROI at each of the proximal and distal portions within the lumen of the carotid artery on the same image (Fig. 1B). Time-intensity curves of the intraplaque and lumen ROIs were generated from the raw data using echo analyzing software (VolMap445 ver.1.1.2a2, YD, Ikoma, Nara, Japan). Each original time-intensity curve was output as a csv file by the software. Using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), time-intensity curves were averaged with respect to intraplaque ROIs