INTRODUCTION

Embolism from atherosclerotic carotid stenosis is one of the most important causes of ischemic stroke.1 Simultaneously, hemodynamic impairments, including reduced cerebral blood flow (CBF) and cerebrovascular reserve (CVR), have been considered risk factors for the development of strokes in patients with carotid occlusive disease.2,9 Recently, several prospective randomized studies and a meta-analysis have shown that increased oxygen extraction fraction (OEF), which
indicates Power’s Stage II, termed misery perfusion, is an independent predictor for subsequent stroke in patients with symptomatic internal carotid artery (ICA) occlusion.\cite{1,12} Carotid artery stenting (CAS) is an effective endovascular alternative to carotid endarterectomy (CEA) for the prevention of ischemic stroke in patients with atherosclerotic carotid stenosis. In balloon-protected CAS, while the occurrences of ischemic complications are effectively reduced by blocking the anterograde carotid flow, it may simultaneously lead to cerebral hypoperfusion during the procedure. Thus, in some patients, the OEF is expected to increase to maintain the cerebral metabolic rate of oxygen when the cerebral perfusion pressure is critically reduced.\cite{28} As such, OEF could assist in the identification of patients with misery perfusion. However, to the best of our knowledge, the relationship between intraprocedural OEF during the temporary carotid occlusion in balloon-protected CAS and postprocedural microembolic infarctions (MIs) has not yet been examined.

We hypothesized that patients hemodynamically compromised by the blockage of the carotid flow during balloon-protected CAS could have increased OEF and, therefore, be at a higher risk of developing new MIs as revealed on postprocedural diffusion-weighted imaging (DWI). The aim of this study was to investigate whether increased OEF obtained by the classic blood sampling method, might be a risk factor for MIs following balloon-protected CAS.

MATERIALS AND METHODS

Patients

We conducted a retrospective study of patients with symptomatic (stenosis ≥50%, per North American Symptomatic Carotid Endarterectomy Trial [NASCET]) or asymptomatic (stenosis ≥80%, per NASCET) atherosclerotic carotid artery stenosis treated by CAS from April 2014 through March 2020 at our institute.\cite{2} A total of 129 consecutive patients with 132 carotid artery stenoses were treated by protected CAS. Among them, 103 patients (78.0%) were treated using distal balloon embolic protection. Five patients (4.9%) with manifestations of neurologic intolerance in the balloon test occlusion for 3 min before the procedures and 14 patients (13.6%) without measurement of OEF by blood sampling were excluded from the study. Finally, 84 patients (81.6%) were enrolled in this study. In 41 (48.8%) symptomatic cases, the CAS procedure was performed longer than 6 weeks after onset. Patients were classified into two groups based on the presence or absence of new MIs on the postprocedural DWIs.

Information, including patient characteristics, morphology of the carotid arteries, and procedural data, was obtained from each patient’s medical record. Reduced CBF was defined as a decrease of <80% from the contralateral side. Hemodynamic depression (HD) was defined as a decrease of <90 mmHg in systolic blood pressure and a decrease in the heart rate of <50 bpm. Written informed consent was obtained from all the patients.

OEF by blood sampling

OEFs were calculated, by measuring the amount of oxygen in the affected carotid artery and in the angiographically dominant side jugular bulb, just before the temporary occlusion (initial OEF) and reperfusion of the ICA (intraprocedural OEF) during the procedure and 15 min after the procedure (postprocedural OEF) [Figure 1]. Blood was anaerobically sampled with 7 IU heparinized syringes (2.5 mL) in the carotid artery through the arterial catheter and in the dominant jugular bulb through transfemoral venous access with a 100 cm 4F catheter (Glidecath, Terumo, Tokyo, Japan). The concentration of total oxygen was measured with a blood gas analyzer (ABL800 FLEX; Radiometer Medical ApS, Bronshoj, Denmark). Cerebral arteriojugular differences of oxygen (AVDO2) were calculated using the formula: AVDO2 = CaO2 – CvO2 where CaO2 is the arterial concentration of total oxygen and CvO2 is the venous concentration of total oxygen of the jugular bulb. OEF was calculated by the formula: OEF (%) = AVDO2/CaO2 × 100. The increase in OEF was calculated by the formula: increase in OEF = intraprocedural OEF – preprocedural OEF.

Imaging assessment

Characteristics of the carotid artery lesion were evaluated on digital subtraction angiography and magnetic resonance imaging (MRI). The degree of stenosis was measured on angiography using the NASCET criteria.\cite{3} The characteristics of the carotid plaque were described using T1-weighted black-blood MRI.\cite{30} We measured the signal intensity ratio (SIR) with manual operator defined regions of interest drawn over the entire plaque in the carotid area with the greater degree of stenosis. We used the sternocleidomastoid muscle as the reference tissue on the T1-weighted image. The SIR was calculated as follows: signal intensity of the entire plaque/signal intensity of the reference tissue. The total volume of carotid plaque was quantified automatically by calculating the total number of pixels drawn manually of regions of interest in consecutive multidetector computed tomography images with workstation (Ziostation2, Ziosoft, Tokyo, Japan). The degree of collateral circulation in the circle of Willis was evaluated on magnetic resonance angiography, based on the presence or absence of an anterior connection (between the targeted and contralateral ICAs through the anterior communicating and A1 portion of the anterior cerebral arteries) and the presence or absence of a
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Figure 1: Oxygen extraction fraction measurement flow diagram.

posterior connection (between the targeted ICA and basilar artery through the posterior communicating and P1 portion of the posterior cerebral arteries). Pre- and postprocedural DWIs were performed 1 week prior and 24 h after the CAS and analyzed by independent neuroradiologists. The MRI device used in this study was the Achieva Nova Dual 1.5T (Philips, Rastatt, Germany). DWI was performed using a spin-echo echo-planar sequence with the following parameters: b values 1000 s/mm², repetition time/echo time/excitation 3000 ms/90 ms/2, matrix 127 × 128, FOV 230 × 230 mm, section thickness 6 mm with intersection gap 0.6 mm, and 22 slices. CBF was measured by single photon emission computed tomography (SPECT) with ¹²³I-labeled N-isopropyl-p-iodoamphetamine.

Endovascular procedure

The patients were premedicated with 100 mg of acetylsalicylic acid and 75 mg of clopidogrel or 200 mg of cilostazol for at least 14 days before the procedure without a loading dose. The procedures were performed with femoral (n = 43, 51.2%) or brachial access (n = 41, 48.8%) under local anesthesia. Systemic heparinization was achieved with target activated clotting times between 300 s and 350 s during the procedure. A distal balloon (Carotid GuardWire PS; Medtronic, Santa Rosa, CA, USA) with and without proximal balloon protection was used in 9 and 75 cases, respectively. Closed-cell stents (Carotid Wallstent Monorail Endoprosthesis; Boston Scientific Corp., Natick, MA, USA) were used mostly (n = 75, 89.3%), and the open-cell stents (Precise; Cordis Corporation, Miami Lakes, FL, USA) were used for cases of tortuous or calcified lesions (n = 9, 10.7%). After postdilation, routine aspiration of debris was performed. Finally, the balloon protection device was retrieved. After the completion of CAS, heparin was not reversed until its effect disappeared spontaneously. During the procedure, blood pressure, heart rate, and neurological symptoms were closely monitored. Atropine sulfate was prophylactically administered just before predilation in all cases. Patients with periprocedural HD were initially given intravenous fluids. Intravenous vasopressor therapy (e.g., dopamine) was administered in those with persistent hypotension despite intravenous fluids.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation, and comparisons of these variables between the groups were performed using the Mann–Whitney U or Wilcoxon signed-rank tests. Categorical variables are reported as percentages and were compared using Fisher's exact probability test. Factors predictive in univariate analysis (P < 0.05) were entered into a backward multivariate logistic regression analysis; P < 0.05 was considered statistically significant. The correlation coefficients (r) > 0.5 were considered statistically significant. All statistical analyses were performed with “EZR (Easy R)” software.[18]

RESULTS

Of the 84 patients studied, balloon-protected CAS was successfully completed in all the cases with no manifestations of neurologic symptoms, and intraprocedural angiography revealed no evidence of distal embolization in the intracranial
circulation. Overall, new MIs as revealed on postprocedural DWIs were observed in 37 patients (44.0%). Among them, 14 (37.8%) patients had accompanied MIs in the contralateral cerebral hemisphere as well. The average number of MIs on DWI was 3.0 (range, 1–7). Most of all the new MIs were small round spots located in the watershed zone. No adverse events, such as major or minor stroke, myocardial infarction, or death, were noted in the periprocedural period.

Baseline characteristics of the patients, morphological findings of the vascular structures, and procedural factors were summarized and compared [Tables 1 and 2]. The DWI-positive group was significantly older than the DWI-negative group (75.9 vs. 72.8, respectively, P = 0.014).

In the morphological factors, the SIR was significantly higher in the DWI-positive group compared to that in the DWI-negative group (1.78 vs. 1.52, respectively, P = 0.003). There were no significant differences with respect to total plaque volume, pre- and post-CAS stenotic rate, and the frequency of the presence of anterior and posterior connections.

In the procedural factors, the mean duration of carotid occlusion and activated clotting time were not significantly different between the two groups. Initial, intraprocedural, and postprocedural OEFs were 36.0 ± 6.7%, 46.2 ± 8.9%, and 38.2 ± 6.7% in the DWI-positive group and 38.1 ± 6.4%, 40.3 ± 7.2%, and 38.4 ± 6.5% in the DWI-negative group, respectively. The intraprocedural OEF and the increase in OEF were significantly higher in the DWI-positive group compared with that in the DWI-negative group (P = 0.005 and < 0.001, respectively). Moreover, in the DWI-positive group, the intraprocedural OEF was significantly higher compared with the initial or postprocedural OEFs [Figure 2a]. There were no significant differences in OEFs in the DWI-negative group [Figure 2b]. The multivariate logistic regression analysis is shown in [Table 3]. The SIR and intraprocedural OEF were significantly associated with the development of new postprocedural MIs with an odds ratio of 3.85 and 1.08, respectively. There were no correlations between the number of MIs and the SIR [r = 0.186, P = 0.299, Figure 3a], and there was a high correlation between the number of MIs and the increase in OEF [r = 0.724, P < 0.001, Figure 3b].

**DISCUSSION**

Cerebral ischemic events are one of the most frequent complications of CAS. Rates of 32.8–51.0% have been reported for subclinical MIs after protected CAS.[3,8,24] Ischemic stroke following CAS has been associated with old age, characteristics of the carotid plaque and aorta, and the type of stent and protection devices.[3,8,24] In addition, several investigators have demonstrated that decreased preprocedural CBF and CVR, obtained using computed tomography perfusion scan, MRI, positron emission tomography (PET), and SPECT, were significant predictors of postprocedural MIs in CAS.[13,16,19,27] It has been hypothesized that in cases of

| Table 1: Baseline characteristics and analysis of risk factors for postprocedural cerebral MIs. |
|---------------------------------------------------------------|
| **Variables** | **Total (n=84)** | **Postprocedural MI** | **P-value** |
| | | **Present (n=37)** | **Absent (n=47)** |
| Patient demographics | | | |
| Age, mean (SD) | 742 (5.4) | 75.9 (4.0) | 72.8 (6.0) | 0.014 |
| Male, n (%) | 71 (84.5) | 31 (83.8) | 40 (85.1) | 1 |
| Medical comorbidities, n (%) | | | |
| Hypertension | 62 (73.8) | 28 (75.7) | 34 (72.3) | 0.806 |
| Diabetes mellitus | 28 (33.3) | 13 (35.1) | 15 (31.9) | 0.818 |
| Dyslipidemia | 27 (32.1) | 13 (35.1) | 14 (29.8) | 0.643 |
| Coronary artery disease | 23 (2.74) | 7 (18.9) | 16 (34.0) | 0.145 |
| Smoking | 40 (47.6) | 14 (37.8) | 26 (55.3) | 0.128 |
| Previous stroke history | 41 (48.8) | 15 (40.5) | 26 (55.3) | 0.195 |
| Morphological factors | | | |
| Left side, n (%) | 40 (47.6) | 17 (45.9) | 23 (48.9) | 0.828 |
| Signal intensity ratio | 1.63 (0.41) | 1.78 (0.41) | 1.52 (0.38) | 0.003 |
| Total plaque volume, mm³ (SD) | 568.2 (269.1) | 532.0 (267.5) | 586.1 (244.9) | 0.406 |
| Presence of anterior connection, n (%) | 60 (71.4) | 26 (70.3) | 34 (72.3) | 1 |
| Presence of posterior connection, n (%) | 51 (60.7) | 24 (64.9) | 27 (57.4) | 0.51 |
| Pre-CAS stenosis rate (SD) | 78.2 (12.4) | 77.4 (12.5) | 78.5 (11.1) | 0.796 |
| Post-CAS stenosis rate (SD) | 19.7 (18.9) | 18.2 (16.3) | 20.6 (19.9) | 0.791 |
| ContraIateral stenosis rate (SD) | 25.2 (29.6) | 25.4 (25.8) | 25.1 (31.1) | 0.621 |
| Reduced cerebral blood flow, n (%) | 10 (11.9) | 5 (13.5) | 5 (10.6) | 0.743 |

CAS: Carotid artery stenting, MIs: Microembolic infarctions, SD: Standard deviation
lower cerebral perfusion, the microembolic load is less likely to clear from the vascular bed, resulting in postprocedural MIs at, in particular, the poorly perfused area of the brain.\[5\] This mechanism showing impaired clearance of emboli was supported by the “washout theory” proposed by Caplan and Hennerici.\[5\] Especially, under the critical decrease of cerebral perfusion, the OEF increases to maintain cerebral oxygen metabolism because the oxygen supply is diminished due to reduced CBF.\[5\] Increased OEF was previously reported to be a significant risk factor for subsequent stroke in patients with carotid occlusive disease.\[7,11,12\] However, the relationship between intraprocedural OEF during temporary carotid occlusion in balloon-protected CAS and postprocedural MIs has been unclear.

To investigate cerebral hemodynamics, PET and SPECT are useful for measuring OEF, but it is impractical to use because it is complicated, expensive, and unsuitable for real-time evaluation of cerebral hemodynamics during the procedure. In contrast, blood sampling for OEF calculation is simple and available, although the technique is slightly invasive. Hattori et al. demonstrated that the OEF on PET, using a short inhalation of O–O₂, was correlated with the blood sampling OEF in healthy human volunteers.\[14\] This method has been frequently and effectively used as a tool to monitor the cerebral hemodynamics in patients with severe traumatic brain injuries.\[21\] Iwata et al. recently reported the usefulness of increased OEF, obtained by blood sampling after CAS, to anticipate cerebral hyperperfusion syndrome. To the best of our knowledge, this is the first study to describe the association between cerebral ischemic events and the OEF, by the blood sampling method, during carotid occlusion in balloon-protected CAS.\[15\]

In this study, the intraprocedural OEF in the DWI-positive group significantly increased due to the ICA occlusion and showed a significantly high value compared to that of the DWI-negative group. In addition, an increase in OEF statistically correlated with the number of new MIs on postprocedural DWIs. As increased intraprocedural OEF could be considered the result of the metabolic compensation for the reduction of the CBF due to the targeted ICA occlusion, our results suggest that there could be patients hemodynamically compromised by carotid flow blockage during balloon-protected CAS, and they could be at risk for the development of periprocedural cerebral ischemia.

Table 2: Baseline characteristics and analysis of risk factors for postprocedural cerebral MIs.

| Variables                                               | Total (n=84) | Postprocedural MI Present (n=37) | Absent (n=47) | P-value |
|---------------------------------------------------------|--------------|---------------------------------|---------------|---------|
| Periprocedure                                           |              |                                 |               |         |
| Transfemoral approach, n (%)                            | 43 (51%)     | 17 (45.9)                       | 26 (55.3)     | 0.51    |
| Proximal and distal balloon protection, n (%)           | 9 (10.7%)    | 5 (13.5)                        | 4 (8.5)       | 0.498   |
| Closed-cell stent, n (%)                                | 75 (89.3%)   | 33 (89.2)                       | 42 (89.4)     | 1       |
| Hemodynamic depression, n (%)                           | 27 (32.1%)   | 11 (29.7)                       | 16 (34.0)     | 0.815   |
| Carotid occlusion duration, min (mean±SD)               | 16.9±3.8     | 16.7±3.7                        | 17.1±3.6      | 0.556   |
| Activated clotting time, sec (mean±SD)                  | 305±35       | 315±32                          | 302±34        | 0.78    |
| DEF                                                     |              |                                 |               |         |
| Initial OEF, % (mean±SD)                                | 37.2±6.6     | 36.0±6.7                        | 38.1±6.4      | 0.128   |
| Intraprocedural DEP, % (mean±SD)                        | 42.9±8.5     | 46.2±8.9                        | 40.3±7.2      | 0.005   |
| Increase in OEF, % (mean±SD)                            | 5.8±8.1      | 10.2±9.9                        | 2.3±3.9       | <0.001  |
| Postprocedural OEF, % (mean±SD)                         | 38.3±6.5     | 38.2±6.7                        | 38.4±6.5      | 0.717   |

MIs: Microembolic infarctions, OEF: Oxygen extraction fraction, SD: Standard deviation

Table 3: Multivariate analysis of factors associated with postprocedural cerebral microembolic infarctions.

| Variables                | Adjusted OR | 95% CI      | P-value |
|--------------------------|-------------|-------------|---------|
| Age                      | 1.09        | 0.97        | 1.21    | 0.144 |
| SIR                      | 3.85        | 1.09        | 13.7    | 0.037 |
| Intraprocedural OEF      | 1.08        | 1.01        | 1.16    | 0.022 |

OEF: Oxygen extraction fraction, SIR: Signal intensity ratio of carotid plaque
Near-infrared spectroscopy and transcranial Doppler (TCD) are also suitable for real-time monitoring during CAS. Near-infrared spectroscopy in CAS has a significant advantage in the measurement of cerebral hemodynamics, which is ease of use. Placement of the sensor on the forehead is fast and easy, and real-time data reflecting changes in cerebrovascular hemoglobin saturation appear immediately. However, the major disadvantage of regional oxygen saturation is that it can measure only a small, limited area of the frontal cortex.[17] Orlandi et al. performed TCD monitoring during CAS and also demonstrated that the MCA blood flow velocity values were significantly lower in patients with new postoperative neurological deficits than in those without.[27] Ogasawara et al. reported the interrelation between MCA blood flow velocity and microembolic signals on TCD during CEA, and concluded that low MCA flow velocity was additive in predicting the development of new postoperative MIs on DWI after CEA.[25] Because low flow velocity on TCD suggests poor cerebral perfusion, these reports indicated the cerebral ischemic event could be more frequently developed in cases accompanying impaired CBF during the procedure. These studies were consistent with our results and the hypothesis that hypoperfusion increases the susceptibility to cerebral infarction by impairing washout of emboli from the cerebral circulation.[5] HD could also lead to a temporary reduction in cerebral perfusion and contribute to postprocedural cerebral ischemia.[20] The international carotid stenting study (ICSS)-MRI substudy showed that in patients who were treated by CAS, the occurrence of periprocedural HD was associated with a >3 times higher number of new MIs compared with patients without HD, and suggested that avoidance of periprocedural HD could maintain the cerebral perfusion and reduce the risk of MIs during CAS.[1] In the present study, the frequency of intraprocedural HD was not associated with postprocedural MIs. It is speculated that the difference of the HD criteria in our study was not as strictly definitive as in the ICSS-MRI substudy.[1] Moreover, the HD duration was not evaluated in either study. For future studies, intensive analysis with a uniform definition, including severity and duration of HD, is warranted.
The association between advanced age and the risk of ischemic events after CAS compared with CEA has been reported in many multicenter randomized controlled trials. Vascular tortuosity, severe calcification, or unstable plaque may contribute to the underlying mechanisms of CAS in elderly patients and may increase the risk of new MIs during the procedure. These observations correspond with our results. Furthermore, in a previous study, advanced age was found to be associated with lower CVR, obtained by xenon computed tomography scans with acetazolamide challenge, in patients with severe carotid stenosis. Although the mechanism of reduced CVR estimated before the procedure could differ from that of increased OEF during carotid occlusion in CAS, both parameters could indirectly indicate the poor collateral perfusion. The collateral perfusion to the cerebral hemisphere on the occluded ICA side mostly depends on the presence of anterior and posterior connections. In this study, no significant differences in the ratio of the anterior and posterior connections were found between the two groups. Thus, the CBF on the occluded ICA side might be closely related to the vessel diameters of the anterior and posterior connections.

The characteristics of the carotid lesions, including the degree of stenosis, volume, and vulnerability, were reported to be the most important risk factors of postprocedural MIs after CAS. Actually, multivariate analysis in this study revealed that high SIR was significantly associated with the development of postprocedural MIs. In addition, increased OEF alone was also statistically significant factor in multivariate analysis. However, increased OEF alone is unlikely to develop cerebral infarction. Both embolic materials from atheromatous lesions and increased OEF, indicating hemodynamic impairment to aggravate cerebral ischemia, are thought to contribute to increase development of the MIs in balloon-protected CAS. In general, throughout all CAS procedures, microembolic signals on TCD could be detected in almost all the patients. In other words, embolic materials could be generated during the catheter manipulations in almost all the CAS patients. Therefore, the multivariate analysis might statistically provide increased OEF as an independent predictor of postprocedural MIs.

Prior studies have demonstrated that the SIR is a noninvasive, non-contrast angiographic tool to evaluate CBF. Moreover, it can be provided by both perfusion CT and single-photon emission computed tomography (SPECT), which are more practical than PET. We have already reported that SIR estimated before the procedure was associated with the number of new MIs on postprocedural DWI. It is suggested that the SIR could be a replacement for PET or SPECT in evaluating cerebral hemodynamics. However, it may prove useful in the real-time evaluation of intraprocedural cerebral hemodynamics during balloon-protected CAS.

CONCLUSION

Increased intraprocedural OEF during balloon-protected CAS, obtained by the blood sampling method, was associated with an increased incidence of new MIs and correlated with the number of new MIs on postprocedural DWI. This suggests that patients hemodynamically compromised by the blockage of carotid flow during balloon-protected CAS could be at risk for the development of periprocedural cerebral ischemia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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