Periprocedural Evaluation and Management against Cerebral Hyperperfusion Syndrome after Carotid Artery Stenting in Japan: A Nationwide Questionnaire Survey

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Objective: Cerebral hyperperfusion syndrome (CHS) including intracranial hemorrhage (ICH) is a serious complication after carotid artery stenting (CAS). Therefore, neurointerventionalists in Japan commonly stratify the risk for CHS preprocedurally in CAS candidates using various imaging tests that are available, and sometimes performed preventive methods against CHS, such as staged angioplasty (SAP), undersized-balloon angioplasty followed by delayed CAS. In the current study, we used a nationwide questionnaire survey to clarify the current status of the periprocedural management against CHS and the 30-day outcomes of patients with a high risk of CHS after undergoing CAS or endovascular carotid revascularization procedures, such as SAP or stand-alone angioplasty. This study specifically analyzed the data for the periprocedural management against CHS.

Materials and Methods: Between June and August 2014, questionnaires were emailed to all of the neurointerventional specialists certified by the Japanese Society for Neuroendovascular Therapy (JSNET). If two or more specialist physicians belonged to an institute, a representative physician of the institute answered the questionnaire. This study focused on 14 items of the questionnaire that were directed at examining the preprocedural imaging tests done to evaluate the risk of CHS, the periprocedural management strategies used to prevent CHS, and the postprocedural imaging tests to detect hyperperfusion phenomenon, among others.

Results: Replies were obtained from 154 institutes which represented 336 JSNET-certified neurointerventional specialists. Preprocedural imaging tests done to evaluate the risk of CHS were performed in 144 institutes (93.5%), with single-photon emission CT (SPECT) the most used modality in 88.2% of the institutes. Acetazolamide challenge was performed in 114 (89.8%) of 127 institutes that used preprocedural SPECT evaluation. Of the institutes performing preprocedural CHS-risk evaluation, general anesthesia was administered during the procedure in 44.4%, periprocedural...
Introduction

Cerebral hyperperfusion syndrome (CHS) is known to be a serious complication that occurs after carotid revascularization procedures, such as carotid endarterectomy (CEA) or carotid artery stenting (CAS). CHS usually develops within several days after the carotid revascularization procedure due to excessive increases in cerebral blood flow (CBF) above the metabolic demands of the brain tissue. Sometimes, this can cause intracranial hemorrhage (ICH) with significant neurological sequelae.

The Japanese Society for Treatment at Neck in Cerebrovascular Disease (JASTNEC) Study retrospectively registered and examined 4494 Japanese patients who underwent CEA or CAS between April 2000 and March 2005. This study found the rates of CHS and ICH after CAS to be 1.1% and 0.7%, respectively, with the morbidity and mortality rates in patients with ICH after carotid revascularization procedure shown to be 65% and 26%, respectively.

The Japanese CAS survey that retrospectively registered 8092 patients who underwent CAS between January 2001 and December 2010 and reported finding the rate of ICH after CAS to be approximately 0.6%–0.7%.

Despite its low incidence, the devastating nature of ICH related to CHS has led to specific attempts by Japanese neurointerventionalists to determine methods for preventing CHS. As a result, the risk for CHS in CAS candidates is commonly evaluated using various imaging tests. Furthermore, potentially preventable procedures or management strategies against CHS have also sometimes been applied. These strategies have included the administration of edaravone (a free radical scavenging agent), general anesthesia during the procedure, and strict blood pressure control, among others. In 2009, Yoshimura et al. reported that the use of staged angioplasty (SAP), which consisted of undersized-balloon angioplasty followed by delayed CAS, was an especially promising method for preventing CHS. However, the penetration rate and efficacy of SAP in patients having a high risk of CHS in real clinical settings have yet to be thoroughly investigated.

To clarify the current status of the periprocedural management used to prevent CHS and the 30-day outcomes of patients with a high risk of CHS after undergoing CAS or endovascular carotid revascularization procedures such as SAP or stand-alone angioplasty, we conducted a nationwide questionnaire survey. The name used for this study was the STrategy of Optimal carotid revascularization for high-risk Patients of Cerebral Hyperperfusion Syndrome (STOP CHS) study.

The questionnaire, which was divided into two parts, was used to collect data between October 2007 and March 2014. The first part examined the periprocedural practice policy of each participating institute for the candidates undergoing elective endovascular carotid revascularization procedures. The second part examined the 30-day outcomes of patients at high risk for CHS who underwent elective endovascular carotid revascularization procedures.

In this paper, data from the first part of the questionnaire were examined to clarify the current status of the periprocedural management used for preventing CHS after endovascular carotid revascularization in Japan.

Materials and Methods

Between June and August 2014, questionnaires were emailed to all of the neurointerventional specialists that had been certified by the Japanese Society for Neuroendovascular Therapy (JSNET). If two or more specialist physicians belonged to the same institute, one representative physician from the institute was chosen to answer the questionnaire.

Keywords ▶ carotid artery stenting, cerebral hyperperfusion syndrome, questionnaire survey, staged angioplasty
After completion of the questionnaires, the answer sheets were re-emailed to the office of the study committee.

The elective endovascular carotid revascularization procedure was defined as a procedure that include either regular CAS, first-stage angioplasty of SAP, or stand-alone angioplasty for atherosclerotic carotid stenosis 48 hours or more after the last symptom, if symptomatic. In accordance to the diagnostic criteria used at each of the participating institutes, risk of CHS was stratified into two levels: average and high. In the current analysis, the term “preprocedural” indicated “before the procedure” and “before the revascularization of the affected artery during the procedure,” while “after the procedure” and “after the revascularization of the affected artery during the procedure” were applied to the term “postprocedural.”

As shown in Table 1, the first part of the questionnaire consisted of 14 items. If a respondent answered “no” to Question 2, then the responses to the subsequent questions were not required. Questions 4 and 12 were required for the respondents who answered “yes” for Questions 3 and 11, respectively. With the exception for Question 1, which required an integral number, all of the questions were multiple choice. Multiple answers were allowed for Questions 3, 4, 11, and 12.

### Results

#### Questionnaire response rate

Replies were obtained from 154 institutes. The respondents’ institutes included a total of 336 (the median number per institute, 2; interquartile range, 1–3) out of all of the 952 JSNET-certified neurointerventional specialists. Consequently, the responses covered the experiences with 35.3% of the JSNET-certified specialists.

#### Preprocedural imaging tests used to evaluate the risk of CHS

A total of 144 institutes (93.5%) performed some kind of preprocedural imaging test to evaluate the risk for CHS. Table 2 shows the performance rates for each of the preprocedural imaging modalities used for CHS-risk evaluation. The most frequently found imaging modality for evaluating CAS candidates was the single-photon emission computed tomography (SPECT), which was used in 127 institutes (88.2%). The radionuclide tracers used to measure the CBF in SPECT included iodine-123-labeled N-isopropyl-p-iodoamphetamine (I-123-IMP) in 105 institutes (82.7% of the SPECT-performing institutes) and technetium-99m-labeled ethyl cysteinate dimer (Tc-99m-ECD) in 38 institutes (29.9%). The second most frequent imaging modality was cerebral MRA, which was used in 48 institutes (33.3%). Perfusion-weighted MRI (including arterial spin labeling [ASL]) and CT perfusion were performed in 16% and 13% of the institutes, respectively.

Among the 127 institutes with preprocedural SPECT evaluation, acetazolamide challenge was performed in 114 institutes (89.8%), routinely (88 institutes) or on a case-by-case basis (26 institutes). Out of the 144 institutes that used preprocedural imaging evaluation to determine the risk of CHS, 122 institutes (84.7%) performed the acetazolamide challenge. In 8 out of these 122 institutes, xenon CT was used instead of SPECT.

#### Periprocedural management for patients with a high risk of CHS

As seen in Fig. 1, patients with an average risk for CHS during the endovascular carotid revascularization...
procedure were routinely given general anesthesia in 20 institutes (13.9%), while those with a high risk for CHS were administered general anesthesia routinely or on a case-by-case basis in 64 institutes (44.4%).

The periprocedural management strategies for patients with a high risk of CHS included the use of intravenous edaravone administration in 75 institutes (52.1%), strict blood pressure control in 132 institutes (91.7%), and avoiding postprocedural anticoagulant therapy in 91 institutes (63.2%) (Table 3).

### Modality and timing of postprocedural imaging tests during detection of the hyperperfusion phenomenon

Out of the 144 institutes that used preprocedural imaging evaluation to determine the risk of CHS, 143 (99.3%) performed postprocedural imaging tests in order to detect the hyperperfusion phenomenon. SPECT was the primary imaging modality used in 112 of the institutes (78.3%). At approximately half of these institutes, SPECT was performed on the day following the endovascular procedure. The second leading modality was the use of near-infrared spectroscopy (NIRS) in 44 institutes (30.8%), with these institutes performing the procedure during the endovascular procedure (Table 4).

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**Table 2** Preprocedural imaging tests to evaluate the risk of cerebral hyperperfusion syndrome after endovascular carotid revascularization

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Single-photon emission computed tomography</td>
<td>127 (88)</td>
</tr>
<tr>
<td>I-123-IMP</td>
<td>105/127 (83)</td>
</tr>
<tr>
<td>Tc-99m-ECD</td>
<td>38/127 (30)</td>
</tr>
<tr>
<td>Tc-99m-HMPAO</td>
<td>3/127 (2.4)</td>
</tr>
<tr>
<td>I-123-IMZ</td>
<td>1/127 (0.8)</td>
</tr>
<tr>
<td>Positron-emission tomography</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Perfusion-weighted magnetic resonance imaging/artrial spin labeling magnetic resonance imaging</td>
<td>23 (16)</td>
</tr>
<tr>
<td>Perfusion CT</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Xenon CT</td>
<td>10 (6.9)</td>
</tr>
<tr>
<td>Transcranial Doppler ultrasonography/transcranial color-coded duplex ultrasonography</td>
<td>13 (9.0)</td>
</tr>
<tr>
<td>Near-infrared spectroscopy</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Cerebral magnetic resonance angiography</td>
<td>48 (33)</td>
</tr>
<tr>
<td>Others</td>
<td>1* (0.7)</td>
</tr>
</tbody>
</table>

*Global cerebral oxygen extraction fraction (OEF) determined by the classic blood sampling method. I-123-IMP: iodine-123-labeled N-isopropyl-4-iodoamphetamine; I-123-IMZ: iodine-123-labeled iomazenil; Tc-99m-ECD: technetium-99m-labeled ethyl cysteinate dimer; Tc-99m-HMPAO: technetium-99m-labeled hexamethyl-propylene amine oxide

**Table 3** Periprocedural management strategies for patients with a high risk for cerebral hyperperfusion syndrome

<table>
<thead>
<tr>
<th>Management strategies</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural administration of edaravone</td>
<td>75 (52)</td>
</tr>
<tr>
<td>Routine</td>
<td>66 (46)</td>
</tr>
<tr>
<td>Case-by-case basis</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>Periprocedural strict blood pressure control</td>
<td>132 (92)</td>
</tr>
<tr>
<td>Routine</td>
<td>121 (84)</td>
</tr>
<tr>
<td>Case-by-case basis</td>
<td>11 (7.6)</td>
</tr>
<tr>
<td>Postprocedural intravenous anticoagulant therapy</td>
<td>53 (37)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>44 (31)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>None</td>
<td>91 (63)</td>
</tr>
</tbody>
</table>

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**Fig. 1** Type of anesthesia in accordance with the risk of CHS. CHS: cerebral hyperperfusion syndrome
The penetration rate of SAP

During the study period, 39 respondents (27.1%) either attempted or performed SAP in patients with a high risk of CHS.

Discussion

Our present study is the first to have specifically examined the status of the periprocedural evaluation and the management of patients undertaken in order to prevent CHS after endovascular carotid revascularization in Japan. This analysis was based on the responses from a little more than one-third of all of the JSNET-certified neurointerventional specialists.

Preprocedural imaging tests to evaluate the risk of CHS

Preprocedural imaging tests for identification of patients at high risk for CHS were performed in almost all of the participating institutes (93.5%). An anesthesiologists’ survey for perioperative management policy of CEA was conducted in the United States in 2012 and showed that preoperative risk stratification for CHS was only performed by 60% of 664 respondents.10) Thus, this study attempted to confirm that Japanese neurointerventionalists paid special attention to prevent CHS after endovascular carotid revascularization procedures. SPECT was the primary imaging modality used in 88.2% of the institutes with preprocedural imaging evaluation for the risk of CHS, while acetazolamide challenge was performed in almost all of the institutes with preprocedural SPECT evaluation (89.8%). Several Japanese studies reported finding that the detection of a significant decrease in the cerebrovascular reactivity (CVR) in response to acetazolamide and CBF at the resting stage by preprocedural SPECT could be used to predict the postprocedural hyperperfusion phenomenon and CHS.11–15) The findings reported by Oshida et al.15) especially showed that the prediction accuracy of CVR to acetazolamide was superior to that of CBF at the resting stage. The Japanese Guidelines for the Management of Stroke 200916) (edited by the Japanese Stroke Society [JSS]) and the Practice Guidelines for Neuroendovascular Therapy 200917) (edited by the Japanese Registry of Neuroendovascular Therapy investigators), have respectively described the clinical implications of the preprocedural evaluation of the cerebral hemodynamics using SPECT for the superficial temporal artery-middle cerebral artery bypass surgery and CAS. In line with these guidelines, the present study revealed that Japanese neurointerventionalists widely performed preprocedural assessments of the risk of CHS using SPECT in conjunction with the acetazolamide challenge.

In June 2014, which was after the end of the current study survey period, it was reported that acute congestive heart failure and acute pulmonary edema occurred after intravenous acetazolamide administration, with this information then placed in the drug package insert. As a result, four Japanese academic societies including the JSS recommended that physicians should obtain informed consent from patients prior to use, in addition to preparing an emergency care system that could be used during SPECT examinations. In April 2015, the Guidelines for Appropriate Use of Acetazolamide were published.18) After these recommendations and the suggested guidelines were approved by the four societies, it was felt that there was a reduction in the performance rate of the preprocedural SPECT evaluations. Therefore, further studies that clarify the practice status of the preprocedural risk evaluation for CHS will need to be updated.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>N=143</th>
<th>Day of procedure</th>
<th>Timing of imaging test, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During procedure</td>
<td>1</td>
</tr>
<tr>
<td>SPECT</td>
<td>112 (78)</td>
<td>0</td>
<td>15 (13)</td>
</tr>
<tr>
<td>PET</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Perfusion MRI/ASL</td>
<td>30 (21)</td>
<td>0</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Perfusion CT</td>
<td>25 (18)</td>
<td>0</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Xenon CT</td>
<td>8 (5.6)</td>
<td>0</td>
<td>1 (13)</td>
</tr>
<tr>
<td>TCD/TCCD</td>
<td>18 (13)</td>
<td>6 (33)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>NIRS</td>
<td>44 (31)</td>
<td>35 (80)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Cerebral MRA</td>
<td>3 (2.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>3 (2.1)</td>
<td>3 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Global cerebral oxygen extraction fraction (N = 1), C-arm conebeam CT perfusion (N = 1), two-dimensional perfusion angiography (N = 1).

ASL: arterial spin labeling; NIRS: near-infrared spectroscopy; PET: positron-emission tomography; SPECT: single-photon emission computed tomography; TCD: transcranial Doppler ultrasonography; TCCD: transcranial color-coded duplex ultrasonography
Perfusion imaging tests using CT or MRI have been reported to be useful tools for predicting the hyperperfusion phenomenon and CHS.\textsuperscript{19,20} The present study found that the penetration rates for these modalities consisted of a little under 20% of the participating institutes. There were some institutes using ASL. ASL is a perfusion imaging method that does not require gadolinium contrast. Therefore, this method can be used to evaluate the risk of CHS in patients with moderate to severe renal impairment. Uchihashi et al.\textsuperscript{21} examined the ASL and SPECT methods in patients with cerebrovascular occlusive diseases and reported finding good agreement between the two modalities. ASL can be more frequently used as a promising modality to predict CHS without an acetazolamide challenge.

Kuroda et al.\textsuperscript{22} utilized single slab 3D time-of-flight MRA by 3.0 Tesla imaging equipment to analyze the signal intensity of the middle cerebral artery of the affected side and found it to be a simple, noninvasive screening tool that can be used to predict CHS. Thus, physicians of institutes in which SPECT or perfusion imaging tests are unavailable may use MRA findings as a way to evaluate the risk of CHS.

Periprocedural management for patients with a high risk of CHS

The present study found that 44.4% of the institutes provided general anesthesia during the endovascular revascularization procedures for the high-risk patients versus only 13.9% for the average-risk patients. The preventive efficacy of the use of general anesthesia during CAS or CEA has yet to be definitively clarified. However, it is assumed that anesthetic agents such as propofol or barbiturates are neuroprotective as they decrease CBF and the brain metabolism. In fact, these agents have been used as preventive or therapeutic agents against the hyperperfusion phenomenon or CHS.\textsuperscript{12,23} Furthermore, the use of general anesthesia during the procedure may help to prevent the development of CHS when the asymptomatic hyperperfusion phenomenon occurs immediately after revascularization due to the smooth transition into continuous general anesthesia or conscious sedation after the procedure. As a result, this could help to provide strict blood pressure control.

Edaravone, which is a free radical scavenging agent, has been approved and is widely used in Japan as a neuroprotective drug for acute ischemic stroke. The present study revealed more than half of the responding institutes used periprocedural edaravone administration in spite of the off-label use. This is likely due to the fact that Ogasawara et al.\textsuperscript{24} reported that periprocedural administration of edaravone reduced the occurrence of the postprocedural hyperperfusion phenomenon in patients who underwent CEA.

The JASTNEC study reported that the periprocedural strict blood pressure control was negatively associated with the occurrence of ICH in patients with CHS after CEA (adjusted odds ratio, 0.035; 95% confidence interval, 0.002–0.542), but not in patients after CAS.\textsuperscript{7} In patients with CHS who were under strict blood pressure control, there was a lower proportion that subsequently developed ICH (38% (8/21)) as compared to those who were free from ICH (60% (6/10)). However, due to the small sample size, the difference between the groups was not found to be significant (p = 0.4414). Abou-Chebl et al.\textsuperscript{25} reported that there was a reduction in the incidence of CHS in patients undergoing CAS when they routinely received strict blood pressure control (n = 560, the rate of CHS = 0.5%) versus the pre-strict-blood-pressure-control period (n = 266, the rate of CHS = 1.9%, p = 0.12). In addition, the authors also found that there was a significant reduction in the incidence of ICH from the pre-strict-blood-pressure-control period (1.1%) to the strict-blood-pressure-control period (0%, p = 0.032). There was an especially marked reduction in the rates of CHS and ICH in the high-risk patients of CHS that were defined as being with hypertensive, having a diameter stenosis of 90% or more, or having poor collaterals; 29.4% to 4.2% (p = 0.006), and 17.6% to 0% (p = 0.006), respectively. This demonstrates the preventive efficacy of the periprocedural strict blood pressure control against CHS. Our present study also found that periprocedural strict blood pressure control was performed in almost all of the institutes that provided CAS in a real clinical setting.

In Japan, argatroban has only been approved for acute atherothrombotic stroke and heparin-induced thrombocytopenia. However, despite the uncertainty of its efficacy, postprocedural intravenous anticoagulant therapy using argatroban or unfractionated heparin has been used in approximately 60%–70% of the elective endovascular procedures performed for atherosclerotic stenosis such as CAS and intracranial angioplasty/stenting.\textsuperscript{26} The present study demonstrated that more than half of the participating institutes adopted a reasonable practice policy, an avoidance of postprocedural anticoagulation, in patients with a high risk for CHS.

Postprocedural imaging tests to detect the hyperperfusion phenomenon

The postprocedural imaging tests used to detect the hyperperfusion phenomenon included SPECT in 78.3%, NIRS in
30.8%, and MR perfusion in 21%. NIRS was primarily performed during the actual procedure (79.5%), while SPECT and MR perfusion were performed on the day following the procedure in approximately half of the institutes that performed each of the imaging modalities (53.6% and 56.7%, respectively). The JASTNEC study examined the onset of CHS and ICH after CAS and reported that it peaked on 1.5 ± 2.3 postprocedural days and within 12 hours, respectively. Because CHS and ICH develop during the relatively early phase after the procedure, it appears to be necessary to begin monitoring the cerebral hemodynamic status immediately after the procedure or revascularization of the affected artery during the procedure in order to prevent the development of CHS and ICH in patients with asymptomatic hyperperfusion phenomenon. Thus, the efficacy of NIRS, which was the second most common modality used to detect the hyperperfusion phenomenon in this study, may be promising. The low penetration rate of TCD (<10%) in this study was thought to reflect the fact that most of the Japanese neurointerventionalists were neurosurgeons and that insonation through the temporal bone window was limited in elderly Asian (Japanese) people. There were two institutes that performed the X-ray angiography perfusion analysis using the application that was bundled with their angiography equipment. Both Terada et al. and Fujimoto et al. have reported finding that the X-ray angiography perfusion analysis for detecting hyperperfusion after revascularization during CAS was effective, and thus, can be considered to be a promising modality for detecting hyperperfusion.

The penetration rate of SAP

The present study is the first to examine the penetration rate for SAP. Our results revealed that the penetration rate of SAP for patients with a high risk of CHS among the participating institutes was 27.1%. In a subsequent analysis of the second part of our questionnaire survey, we are planning to compare and report the treatment results between patients who underwent SAP versus those who underwent regular CAS.

Limitations

The limitations of our current study include the fact that the response rate was limited to a little more than one-third of the JSNET-certified neurointerventional specialists. Furthermore, the actual number of patients who underwent each of the pre-, peri-, and postprocedural imaging modalities or management strategies is as of yet unknown. Similarly, we did not collect any information regarding the diagnostic criteria used to stratify the risk of CHS at each of the institutes. Finally, since the Japanese Guidelines of Appropriate Use of Acetazolamide were not published until April 2015, this means there could be differences between practices collected at the surveyed period and the period after the publication of these guidelines. To further clarify the effective imaging modalities and management strategies that are used to prevent CHS after the endovascular carotid revascularization procedure, we are currently planning to conduct further multicenter observational studies.

Conclusion

In Japan, the majority of the neurointerventionalists preprocedurally evaluate the risk for CAS candidates developing CHS by primarily using SPECT in conjunction with the acetazolamide challenge. In addition, SAP was attempted or performed in 27.1% of the participating institutes. The present study is the first to specifically examine the current Japanese practices that are used to prevent the occurrence of CHS after endovascular carotid revascularization procedures. We plan to conduct further multicenter observational studies in order to definitively clarify the periprocedural management necessary to prevent CHS after endovascular carotid revascularization procedures in patients with a high risk for CHS.

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