Prediction of the Cerebral Hyperperfusion Phenomenon after Carotid Endarterectomy Using a Transit Time Flowmeter

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Abstract

The purpose of this study was to investigate the relationship between the cerebral hyperperfusion phenomenon (CHP) and carotid artery flow volume as measured by a transit time flowmeter during carotid endarterectomy (CEA). We retrospectively investigated 74 patients who underwent both transit time flowmetry and single photon emission computed tomography (SPECT). The flow volumes of the internal carotid artery (ICA) before and after the endarterectomy were recorded during surgery as the pre- and the post-ICA (mL/min), respectively. We defined the difference between the pre- and the post-ICA as the ΔIC (mL/min). Two independent board-certified neurosurgeons analyzed the asymmetry index (affected side/contralateral side) of regional qualitative cerebral blood flow before and after the CEA respectively. We defined the CHP as an excessive increase in this asymmetry index between preoperative and postoperative SPECT. The CHP was observed in five of the 74 patients (6.8%). The pre-ICA of the CHP cases was significantly lower than that of the non-CHP cases (in mL/min, median 29 vs. 97; P = 0.01). The ΔIC of the CHP cases was significantly higher than that of the non-CHP cases (in mL/min, median 154 vs. 50; P = 0.002). The cut-off value of the ΔIC was 81 mL/min (sensitivity 100%, specificity 78.3%, area under the curve 0.912). The findings of this study suggest that the ΔIC is associated with the CHP. The transit time flowmeter is useful to predict the CHP during surgery.

Key words: carotid endarterectomy, cerebral blood flow, hyperperfusion, transit time flowmeter

Introduction

The aim of carotid endarterectomy (CEA) is the removal of plaque to prevent future cerebral infarction. This benefit exists only when complication rates are kept at a low level. One of the main issues after CEA is the cerebral hyperperfusion phenomenon (CHP), which is defined as major excessive increase in the ipsilateral cerebral blood flow above the metabolic demands of the brain tissue after CEA.1) This phenomenon results from failure in normal cerebral autoregulation secondary to longstanding decreased perfusion pressure. This failure results in the cerebral arterioles being maximally dilated and the arterioles subsequently losing their ability to constrict when normal perfusion pressure is restored by CEA.2) Most patients have slight abnormal signs such as ipsilateral headache, or eye and face pain in the early phase of the CHP. However, if the CHP is not recognized and not adequately treated, life-threatening symptoms such as seizures or focal neurological signs related to cerebral edema or intracranial hemorrhage can occur. These symptoms are called “cerebral hyperperfusion syndrome.” It is reported that the incidence of cerebral hyperperfusion syndrome ranges from 0.2% to 18.9%.1–4) It is important to detect the CHP as soon as possible to prevent hyperperfusion syndrome. In a previous report, single photon emission computed tomography (SPECT), positron emission tomography (PET), and perfusion-weighted magnetic resonance imaging (MRI)5) studies were used in the management...
of the CHP; however, such studies are characterized by substantial costs and technical complexity. Transcranial Doppler is also used during surgery, but the transcranial method still poses considerable technical difficulties because of poor insertion of the cranial window. Among these devices for predicting cerebral hyperperfusion syndrome, the transit time flowmeter has high potential. Use of a transit time flowmeter provides real-time immediate feedback about the flow volume or change in the flow volume during surgery. However, we are not aware of studies describing transit time flowmetry associated with the CHP during surgery. The purpose of this study, therefore, was to investigate the relationship between the CHP and carotid artery flow volume measured by transit time flowmetry during surgery.

Methods

Patient selection

The study participants were patients who underwent both transit time flowmetry during surgery and SPECT immediately after surgery at the Tsukuba Medical Center Hospital, Ibaraki, Japan between December 2005 and February 2014. This study was approved by the Institutional Review Committee of the Tsukuba Medical Center Hospital (approval number: retrospective study 2018-038), and informed consent was obtained.

Included variables

The demographic and procedural data were collected from the hospital charts and evaluated retrospectively. Symptomatic patients with carotid stenosis of ≥50% and asymptomatic patients with carotid stenosis of ≥80% underwent CEA, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Each patient’s medical records were reviewed to collect information about the following factors: age, sex, systemic comorbidity, symptomatic case, contralateral stenosis, radiological imaging, intraoperative blood pressure and end-tidal CO$_2$ (EtCO$_2$), and clinical outcome. We defined the contralateral carotid stenosis of ≥70% as a significant contralateral stenosis.

Transit time flowmeter

The transit time flow volume was measured using a hand-held flow probe system (MediStim, Oslo, Norway). This probe consists of two small piezoelectric crystal transducers in a common tip and a small reflector bracket mounted opposite the crystals. It can hold a blood vessel between the crystal transducers and the reflector. An ultrasound signal is emitted from one crystal transducer to the other via the reflector. The time required for the ultrasound signal to pass through the blood is longer upstream than downstream and this difference is directly proportional to the volume of the blood flow (Fig. 1a). The blood flow volumes are expressed in mL/min.

Treatment protocol

All patients underwent CEA under general anesthesia, using an intraluminal shunt, and without patch angioplasty. After exposing the common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA), the perivascular probe was attached to the CCA (Fig. 1b). The flow volume was recorded after clamping of both the ECA and the superior thyroid artery. The volume reached a steady-state within a few seconds, and we assumed this recorded value as the flow volume of the ICA (Fig. 1c). The respective flow volumes of the ICA before and after endarterectomy were defined as the pre-ICA (mL/min) and the post-ICA (mL/min). We also defined the difference between the post- and the pre-ICA as the ΔIC (mL/min). These flow volumes were recorded under stable conditions. Anesthesiologists kept the blood pressure and the EtCO$_2$ constant.

We measured the resting cerebral blood flow (CBF) by $^{99m}$Tc-ethyl cysteinate dimmer ($^{99m}$Tc-ECD) SPECT before the CEA and immediately after the surgery after the recovery from general anesthesia. To increase objectivity, two independent board-certified neurosurgeons analyzed the asymmetry index (affected side/contralateral side) of regional qualitative CBF before and after the CEA respectively. In case of significant stenosis or occlusion of the contralateral ICA, we analyzed the asymmetry index by using the ipsilateral cerebellar hemisphere as a reference (affected cerebral hemisphere/ipsilateral cerebellar hemisphere). We defined the CHP as an excessive increase in this asymmetry index between preoperative and postoperative SPECT. When the CHP occurred, strict blood pressure control was applied with or without general anesthesia.

Statistical analysis

The continuous data were expressed as means ± standard deviations (SDs) or as medians with the interquartile range. Differences between patients with the CHP and those without the CHP were assessed using the chi-square test and the Mann–Whitney U test. Differences were considered significant at a level of $P < 0.05$. The receiver operating characteristic (ROC) curve of sensitivity and specificity was used to assess the particular cut-off value for the flow volume with regard to the CHP. The statistical tests were performed using SPSS version 25 (IBM Japan, Tokyo, Japan).
Prediction of Hyperperfusion Using a Transit Time Flowmeter

Results

Demographic characteristics
During the study period, 109 patients underwent CEA. Among them, 74 patients underwent both transit time flowmetry and SPECT. Of those 74 patients, 67 (91%) were men and seven (9%), women. The mean patient age was 70.2 ± 7.7 years (median 70 years). Thirty-nine patients (53%) were symptomatic before surgery. The average of the degree of ICA stenosis was 73% (interquartile range, 67–81) according to the method of the NASCET. Seven patients (9%) had ≥70% stenosis of the contralateral ICA (Table 1). Systolic blood pressures at the time of the pre- and post-ICA measurement were 115 mmHg (interquartile range, 105–120) and 110 mmHg (interquartile range, 100–120), respectively, and those values does not differ significantly \((P = 0.15)\). EtCO\(_2\) at the time of the pre- and post-ICA measurements were 34 mmHg (interquartile range, 32–37) and 34 mmHg (interquartile range, 31–36.25), respectively, and those values did not differ significantly \((P = 0.52)\).

Cerebral hyperperfusion phenomenon
The CHP was observed in five of the 74 patients (6.8%). The interobserver agreement between two independent neurosurgeons concerning the CHP was 100%. No hemorrhagic changes or seizures relating to the CHP occurred within the observation period. New postoperative ischemic lesions in the ipsilateral hemisphere on DWI developed in 13 patients (17.6%). All of them were an asymptomatic single spotty lesion. The ratio of the symptomatic stenosis was higher in the CHP cases \((n = 5/5, 100\%)\) than

Table 1   Patients’ backgrounds

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, (n)</th>
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<tbody>
<tr>
<td>Patients, (n)</td>
<td>74</td>
</tr>
<tr>
<td>Male, (n) (%)</td>
<td>67 (91)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>70.2 ± 7.7</td>
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<tr>
<td>Hypertension, (n) (%)</td>
<td>67 (91)</td>
</tr>
<tr>
<td>Diabetes mellitus, (n) (%)</td>
<td>28 (38)</td>
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<tr>
<td>Hyperlipidemia, (n) (%)</td>
<td>43 (58)</td>
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<tr>
<td>Coronary artery disease, (n) (%)</td>
<td>36 (49)</td>
</tr>
<tr>
<td>Contralateral stenosis, (n) (%)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Symptomatic stenosis, (n) (%)</td>
<td>39 (53)</td>
</tr>
<tr>
<td>NASCET (%), median (IQR)</td>
<td>73 (67–81)</td>
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</table>


Fig. 1   (a) Schematic drawing of the principle of the transit time flowmeter. Two transducers generate ultrasound. The solid arrow represents the upstream signal, and the dotted arrow, the downstream signal. The flow volume is measured by the time difference between the downstream (T2) and the upstream (T1) signals. (b) Intraoperative image of carotid endarterectomy. The external carotid artery (white arrow) is clamped by a clip and the superior thyroid artery (arrow head) is temporary occluded by a silk thread. The perivascular probe (*) is attached to the common carotid artery and measures the flow volume. (c) We assume this recorded value as the flow volume of the internal carotid artery.
in the non-CHP cases \((n = 34/69, 49\%)\); however, the difference was not significant \((P = 0.06)\). The ratio of contralateral stenosis was also higher in the CHP cases \((n = 2/5, 40\%)\) than in the non-CHP cases \((n = 5/69, 7\%)\); however, the difference was not significant \((P = 0.07)\). No significant difference was found between the CHP and non-CHP cases in the degree of stenosis \((median 75 vs. 73\%; P = 0.41)\). The overall mean value of the pre-ICA was 92 mL/min \((interquartile range, 49.75–140.75)\). Nor were any significant differences found between the CHP and the non-CHP cases were 29 mL/min \((interquartile range, 7.5–69)\) and 97 mL/min \((interquartile range, 58–143)\), respectively, and those values differed significantly \((P = 0.01)\). The \(\Delta IC\) of the CHP and the non-CHP cases were 154 mL/min \((interquartile range, 101–231.5)\) and 50 mL/min \((interquartile range, 29–77)\), respectively, and those values differed significantly \((P = 0.001)\) \((Table 2 and Fig. 2)\). By ROC analysis of the \(\Delta IC\) and the CHP \((Fig. 3)\), the area under the curve \((AUC)\) value was 0.912, and the cut-off value of the \(\Delta IC\) was 81 mL/min \((sensitivity and specificity of 100\% and 78.3\%, respectively)\). If the \(\Delta IC\) was higher than this cut-off value, the occurrence rate of the CHP was 25\% \((n = 5/20)\) and if the \(\Delta IC\) was under this cut-off value, the occurrence rate of the CHP was 0\% \((n = 0/54)\). The rate of flow volume increase \([\Delta IC/Pre-ICA \times 100 \%(\%)]\) also differed significantly between the CHP and the non-CHP cases \((P = 0.002)\).

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**Table 2** Characteristics of patients with and without cerebral hyperperfusion phenomenon

<table>
<thead>
<tr>
<th></th>
<th>Cerebral hyperperfusion phenomenon ((n = 5))</th>
<th>Non-cerebral hyperperfusion phenomenon ((n = 69))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, (n)%</td>
<td>5 (100)</td>
<td>62 (90)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (\text{years}), median (IQR)</td>
<td>69 (64.5–76.5)</td>
<td>70 (65–75.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>Symptomatic stenosis, (n)%</td>
<td>5 (100)</td>
<td>34 (49)</td>
<td>0.06</td>
</tr>
<tr>
<td>Contralateral stenosis, (n)%</td>
<td>2 (40)</td>
<td>5 (7)</td>
<td>0.07</td>
</tr>
<tr>
<td>NASCET (%), median (IQR)</td>
<td>75 (67–94.5)</td>
<td>73 (67–81)</td>
<td>0.41</td>
</tr>
<tr>
<td>Pre-ICA (\text{mL/min}), median (IQR)</td>
<td>29 (7.5–69)</td>
<td>97 (58–143)</td>
<td>0.01</td>
</tr>
<tr>
<td>Post-ICA (\text{mL/min}), median (IQR)</td>
<td>170 (158.5–257)</td>
<td>150 (102–205.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>(\Delta IC) (\text{mL/min}), median (IQR)</td>
<td>154 (101–231.5)</td>
<td>50 (29–77)</td>
<td>0.001</td>
</tr>
<tr>
<td>(\Delta IC/Pre-ICA \times 100 %(%)), median (IQR)</td>
<td>500 (253–11200)</td>
<td>48 (27–110)</td>
<td>0.002</td>
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</table>

**Discussion**

Our study demonstrated that intraoperative carotid artery transit time flowmetry was useful in predicting the CHP. The pre-ICA of the CHP cases was significantly lower than that of the non-CHP cases and the \(\Delta IC\) of the CHP cases was significantly higher than that of the non-CHP cases. The cut-off value of the \(\Delta IC\) predicting the CHP was 81 mL/min.

The incidence of cerebral hyperperfusion syndrome was reported to range from 0.2% to 18.9\%\(^{1–4}\). It varied according to the various definitions of hyperperfusion syndrome and the hyperperfusion

**Fig. 2** Box-and-whisker plot of the \(\Delta IC\) in the cerebral hyperperfusion phenomenon cases and non-cerebral hyperperfusion phenomenon cases. IC, internal carotid.

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\(\Delta IC\): internal carotid blood flow measured after endarterectomy, \(\Delta IC\) \(\text{mL/min}\) = Post-ICA – Pre-ICA.
phenomenon, which are not standardized. We focused on the excessive increase in the CBF asymmetry index between preoperative and postoperative SPECT. The onset of hyperperfusion syndrome was reported within several hours to several days. Once hyperperfusion syndrome occurs, it is difficult to control. Some studies indicated that nearly 30% of patients with hyperperfusion syndrome remain partly disabled, and mortality rates of 50% have been reported. Therefore, it is important to detect the CHP as soon as possible to prevent cerebral hyperperfusion syndrome. In our study, larger blood flow volume increases during the CEA procedure, ΔIC, were associated with the postoperative CHP. This association between the ΔIC and the CHP was statistically significant and well adapted to the pathophysiology of failed autoregulation. The sensitivity and specificity were 100% and 78.3%, respectively, and the AUC was 0.912. Since this AUC is over 0.8, we regard the ΔIC as a good diagnostic tool.

Larger blood flow volume increases indicate dysautoregulation leading to the CHP. If the CHP is suggested by the transit time flowmeter, we can promptly and adequately start intervention such as intraoperative strict control of blood pressure and postoperative continuation of general anesthesia at an early stage of hyperperfusion.

We also analyzed the rate of flow volume increase [ΔIC/Pre-ICA × 100 (%)]. The rates of the CHP and the non-CHP cases were 500% (interquartile range, 253–11,200) and 48% (interquartile range, 27–110), respectively (P = 0.002). However, especially in the CHP cases, this rate was too high to clinically imagine the usefulness. This is because the pre-ICA of the CHP cases was very low. Consequently, the rate of increase [ΔIC/Pre-ICA × 100 (%)] became too high. According to the above results, we think the ΔIC is clinically more useful than the increase rate [ΔIC/Pre-ICA × 100 (%)].

Single photon emission computed tomography, PET, and perfusion-weighted MRI are used to detect the CHP; however, these examinations carry the risk that patients may have to enter the examination room soon after surgery. Measurement of regional cerebral O₂ saturation by near-infrared spectroscopy (NIRS) is also used. NIRS allows noninvasive, continuous real-time detection of indirect information about cerebral oxygenation with sensors placed on the forehead. This device can mainly detect the changes in the forehead region, but consequently the CHP in the regions outside the sensors’ coverage area, such as the middle cerebral artery area, is not well detected. Transcranial devices are also used during surgery; however, the detection rate of intracranial blood flow is low, particularly for elderly female patients, due to thickening of the skull or increased aeration caused by osteoporotic change, and the measurement value is highly dependent on a laboratory technician.

Some previous articles reported the relationship between carotid artery flow increase and cerebral hyperperfusion as shown by an electromagnetic blood flowmeter, but this device is affected by the surrounding magnetic field, conductance, and angle of the probe. Because of these weak points, the cut-off values of electromagnetic blood flowmeters vary depending on the study and range from 200 to 330 mL/min. These threshold values are relatively higher than that of our study. Because there is no other previous report about transit time flowmetry related to cerebral hyperperfusion, it is difficult to confirm the validity of our threshold. However, the transit time flowmeter is superior to the electromagnetic blood flowmeter from the viewpoint of accuracy and reproducibility.

Although transit time flowmeters are not common in the field of neurosurgery, they are widely used for graft assessment during cardiovascular surgery and have been recommended by the joint 2010 European Association for Cardio-Thoracic Surgery and European Society of Cardiology guidelines. The transit time flowmeter is convenient and its measurement results are sufficiently valid, exact, and reproducible in in vivo and in vitro studies.
This device can measure blood flow even if the diameter of the blood vessel is not known. The measurement is not influenced by the flow velocity distribution in the blood vessel nor by the angle of the probe. \(^{17}\) Measurement of blood flow by the transit time flowmeter generally takes 10–20 s. In terms of these technical features, the transit time flowmeter is superior to electromagnetic or Doppler flowmeters. The transit time flowmeter carries the potential risk of embolic complication. However, the incidence of an ischemic new lesion was almost the same as that of a previous study without using the transit time flowmeter. \(^{18}\) Recently, use of a transit time flowmeter during cerebral aneurysmal surgery, cranial bypass surgery, and carotid endarterectomy has been demonstrated. \(^{19–22}\) This is the first report about the CHP after CEA using a transit time flowmeter. Among the various procedures for predicting the CHP, the transit time flowmeter has high potential to improve postoperative management of CEA.

**Limitations**

A limitation of our study was the definition of the CHP. As mentioned above, the definition of cerebral hyperperfusion syndrome and the CHP vary according to the report. There is no absolute definition of the CHP, and in this study, we examined an excessive increase in the CBF asymmetry index between preoperative and postoperative CBF asymmetry index. In our hospital, we used \(^{99m}\)Tc-ECD SPECT and did not measure the quantitative value earlier in the study. To increase objectivity, two independent board-certified neurosurgeons analyzed the asymmetry index. The number of the CHP cases was small, and this study was performed retrospectively. Nevertheless, our study provides important clinical implications for the postoperative management of CEA.

**Conclusion**

Intraoperative transit time flowmetry of internal carotid arterial blood flow was useful in predicting the cerebral hyperperfusion phenomenon, and the cut-off value of the ΔIC was 81 mL/min.

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**Conflicts of Interest Disclosure**

The authors declare that they have no conflict of interest.

**References**


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