Reliability of cerebral vasoreactivity assessment from the submandibular window

Yoko OKADA1, Kensuke SENZAKI1, Shiori KUWAGAKI1, Shu KONDO1, Satoko I. TAKEI1, Shiroh MIURA1, Masayuki OCHI1, Hirofumi OCHI1, Michiya IGASE2, Yasumasa OHYAGI1

1) Department of Neurology and Geriatric Medicine, Ehime University Graduate School of Medicine
2) Department of Anti-aging Medicine, Ehime University Graduate School of Medicine

Background and Purpose: Transcranial Doppler (TCD) is a noninvasive and effective technique for the measurement of cerebrovascular function. Measurement of breath holding index (BHI) in the middle cerebral artery is commonly performed to determine cerebrovascular reactivity. Nevertheless, a notable drawback of TCD is the absence of a transtemporal acoustic bone window. The submandibular window offers an alternative way to measure BHI. Here, we studied the diagnostic accuracy of cerebrovascular reactivity (CVR) in the internal carotid artery (ICA) as measured from the submandibular window.

Methods: Twenty-five volunteers (13 male, 12 female) with sufficient temporal acoustic bone windows were assessed. BHI was measured by mean blood velocities before and after breath holding. The correlation of BHI measured in ICA (BHIi) and ipsilateral middle cerebral artery (BHIm) was assessed.

Results: The mean age of the participants was 39.9 ± 13.7 years. The mean BHIm and BHIi values were 0.93 ± 0.29 and 0.92 ± 0.32, respectively. Spearman’s correlation coefficient between BHIm and BHIi was 0.665 (p = 0.0003). The cutoff point of the BHIi value for CVR impairment determined by BHIm was 0.71 (sensitivity 80.0%, specificity 80.0%).

Conclusion: Measuring BHI from the submandibular window may be a useful procedure in the case of temporal bone window insufficiency.

Keywords: breath holding index, transcranial Doppler, cerebrovascular reactivity, submandibular window, temporal bone window insufficiency

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ulus by CO₂. Inhalation of CO₂ or the breath-holding method is generally used to elevate the partial pressure of CO₂ in the blood. Assessment of CVR by TCD has been reported to be useful for risk prediction in patients with severe carotid artery stenosis or occlusion, regardless of whether the patients are symptomatic or asymptomatic. TCD provides real-time information on CBF based on ultrasound waves, which are emitted from a probe, transmit through the skull, and reflect the dynamic movement of red blood cells. Flow velocities estimated by the Doppler effect provide information on conditions such as vascular stenosis, recanalization after thrombolysis, vasospasm, and hyper-perfusion. Microembolic signals, known as MES or high intensity transient signals (HITS), are sudden short increases in Doppler signal intensity that are useful for detection of the right-to-left shunt, which is indicative of the risk of further stroke. Despite the usefulness of TCD, there are some limitations of its application. One obstacle in the clinical application of TCD is the insufficiency of the temporal acoustic bone window (TAW). In a previous report, the rate of insufficient TAW varied from 3% to 34%. Acquisition of TAW is affected by sex, age, race, and thickness and density of the temporal bone. Notably, the right-to-left cardiac shunt was also detected by TCD from the submandibular or suboccipital windows during acute ischemic stroke. Thus, such approaches may be complementary methods for patients with insufficient TAW. However, the assessment of CVR has rarely been compared with the approaches from different windows. To our knowledge, there is only one study that assessed CVR in the middle cerebral artery (MCA) and the internal carotid artery (ICA). Therefore, we investigated the accuracy of CVR of the ICA measured from the submandibular window in comparison with the traditional measurement of CVR of the MCA from the TAW in healthy volunteers using a breath-holding method.

Methods

1. Participants

Twenty-five adult volunteers (mean age 39.9 ± 13.7 years, 13 male participants and 12 female participants), who were living independently and had sufficient temporal bone windows, were enrolled in this study. CVR was analyzed in the participants using the procedure described in the following section. We interviewed all participants beforehand to assess the traditional cardiovascular risk factors and found hypertension and current smoking status in two participants, hyperlipidemia in one participant, and diabetes mellitus in none. The study protocol was in accord with the Declaration of Helsinki and approved by the local ethics committee of Ehime University. Informed consent was obtained before enrollment.

2. Ultrasound Assessment of Cerebrovascular Reactivity

We assessed CVR by measuring breath holding index (BHI) with TCD. BHI tests were performed in a quiet, air-conditioned (23–26°C) room. All participants were required to fast for 2 h before the examination and rest in the supine position for at least 10 min prior to the test, which was performed using a SONARA TCD System (Natus Neurology Incorporated, WI, USA). The transducer was held manually for the measurement of BHI.

First, we searched for the M1 segment (45–55 mm deep) of the MCA from the preauricular TAW above the zygomatic arch. The position of the probe was adjusted until a maximal and steady flow signal was obtained. Basal mean flow velocity (bVmean (cm/s)) before breath-holding for 30 s after a normal respiration and post-apnea Vmean (aVmean (cm/s)) after breath-holding were measured. Next, we examined the extracranial portion of the ipsilateral ICA from the submandibular window. The submandibular window is at the angle of jaw, and the flow signal of the ICA is usually at a depth of 40 mm from the probe, dorsolateral of the external carotid artery (ECA). The ICA is distinguished from the ECA by location and flow pattern.

BHI in the MCA (BHIm) and in the ICA (BHII) was calculated independently in each vessel as the ratio of bVmean/aVmean, which reflects vasoactivation in response to CO₂ (Fig.1). BHI was given by the following formula, and values less than 0.69 were considered abnormal.

\[
BHI = \frac{[(aVmean - bVmean) \times 100]}{bVmean \times T}
\]

\(T = \) duration of apnea (s)

3. Statistical analysis

Values are expressed as the mean ± standard deviation (SD) for continuous variables, and as the number and proportion (%) for categorical variables.

We initially examined the differences in BHI and other TCD parameters between the MCA and ICA using the Mann–Whitney U test. We then assessed the correlation...
of parameters with paired Spearman’s analysis. The optimal cutoff point of BHIi for the impairment of CVR determined by BHIm was obtained from the receiver operating characteristics (ROC) curve.

All analyses were performed using commercially available statistics software (JMP ver. 10.0; SAS Institute, Cary, NC, USA), and \( p < 0.05 \) was considered statistically significant.

**Results**

No insufficient submandibular windows were identified in the present study. Table 1 shows the comparison of BHI and other TCD parameters between the MCA and ICA. The mean ± SD of BHI (in MCA vs. ICA: 0.93 ± 0.06 vs. 0.92 ± 0.06, \( p = 0.6622 \)), heart rate (HR) before breath-holding (71.0 ± 3.0 vs. 74.6 ± 3.7, \( p = 0.7708 \)), and HR after breath-holding (69.2 ± 1.9 vs. 68.7 ± 1.9, \( p = 0.9303 \)) were not different between MCA and ICA. Flow velocities were lower in the ICA than in the MCA.

Correlations of BHI and other parameters between the MCA and ICA are shown in Table 2. Significant positive correlations were found in BHI and heart rate. We also demonstrated the correlation of BHI values between the MCA and ICA on a scatter plot (Fig.2). A positive linear correlation was observed between BHIm and BHIi (\( r_s = 0.67, p = 0.0003 \)). Mean BHI values were not different between male and female participants (BHIm: male 0.89 ± 0.23 vs. female 0.98 ± 0.34, \( p = 0.5315 \), BHII: 0.89 ± 0.31 vs. 0.95 ± 0.35, \( p = 0.6828 \)). Mean age was higher in the impaired CVR group (49.6 ± 15.1 years, \( n = 5 \)) compared with the normal CVR group (37.5 ± 12.5 years, \( n = 20 \)), but the observed difference was not statistically significant.

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**Table 1** Comparison of cerebrovascular reactivity between MCA and ICA

| Parameter | MCA         | ICA         | \( p \)  |
|-----------|-------------|-------------|---------|
| BHI       | 0.93 ± 0.06 | 0.92 ± 0.06 | 0.6622  |
| Basal EDV | 25.2 ± 2.0  | 17.7 ± 2.0  | 0.0320 * |
| Mean (cm/s) | 41.2 ± 2.5  | 29.0 ± 2.5  | 0.0015 **|
| PSV (cm/s)| 66.3 ± 3.7  | 47.6 ± 3.7  | 0.0013 **|
| HR (beats/min) | 71.0 ± 3.0  | 74.6 ± 3.0  | 0.7708  |
| Post-apnea EDV | 33.9 ± 2.6  | 25.2 ± 2.6  | 0.0478 * |
| Mean (cm/s) | 53.0 ± 3.3  | 37.4 ± 3.3  | 0.0019 **|
| PSV (cm/s)| 79.5 ± 4.5  | 55.8 ± 4.5  | 0.0007 **|
| HR (beats/min) | 69.2 ± 1.9  | 68.7 ± 1.9  | 0.9303  |

BHII, breath holding index; MCA, middle cerebral artery; ICA, internal carotid artery; EDV, end-diastolic velocity; PSV, peak systolic velocity; HR, heart rate.

*\( p < 0.05 \), **\( p < 0.01 \).

**Fig.1** Representative raw traces of blood velocity during the breath-holding test. Flow velocity increases according to the elevation of end tidal CO2 partial pressure while breath holding.

**Table 2**

| Parameter | MCA | ICA | \( p \)  |
|-----------|-----|-----|---------|
| Vmean     | 100 | 100 | 0.6622  |
| Basal Vmean | 60  | 60  | 0.6622  |
| Post-apnea Vmean | 45  | 45  | 0.6622  |
| Breath-holding time (s) | 31.5 ± 0.7 | 31.0 ± 0.7 | 0.4583 |

Vmean, mean flow velocity; bVmean, basal mean flow velocity; aVmean, post-apnea mean flow velocity; T, apnea time.
significant \((p = 0.071)\). None of the other vascular risk factors correlated with BHI in either the MCA or ICA groups.

Next, the ability of BHII to predict impaired CVR determined by BHIM was assessed through the analysis of ROC curves. The area under the curve using BHII to predict the impaired CVR was 0.83. A BHII level of 0.71 resulted in 80.0% sensitivity and 80.0% specificity (Fig.3).

**Table 2** Correlation of cerebrovascular reactivity between MCA and ICA

|               | r_s       | p       |
|---------------|-----------|---------|
| BHI           | 0.67      | 0.0003  | **    |
| Basal EDV (cm/s) | −0.05  | 0.8223  |       |
| Mean (cm/s)   | −0.18     | 0.3818  |       |
| PSV (cm/s)    | −0.18     | 0.3849  |       |
| HR (beats/min)| 0.58      | 0.0026  | **    |
| Post-apnea EDV (cm/s) | −0.04  | 0.8358  |       |
| Mean (cm/s)   | −0.08     | 0.7096  |       |
| PSV (cm/s)    | −0.14     | 0.4976  |       |
| HR (beats/min)| 0.52      | 0.0078  | **    |

BHI, breath holding index; MCA, middle cerebral artery; ICA, internal carotid artery; EDV, end-diastolic velocity; PSV, peak systolic velocity; HR, heart rate; \(r_s\), Spearman’s rank correlation coefficient.

\(*p < 0.05, \,**p < 0.01.\)

**Discussion**

In the present study, we evaluated the usefulness of an alternative submandibular window approach to assess CVR in place of the TAW approach, which is difficult to perform in some patients. We found a correlation between BHII and BHIM, and the cutoff value of the BHII for CVR impairment was 0.71, which was quite similar to that of BHIM. In general, there is no insufficiency of the submandibular window; thus, measuring BHI from the submandibular window should be a valuable method when
the TAW approach is insufficient.

TCD provides rapid information regarding the cerebrovascular hemodynamic state. To analyze these flow signals via the TAW, a sufficient amount of ultrasound beam must pass through the temporal bone. Acquisition of the TAW is affected by age, sex, race, thickness and texture of the temporal bone, and soft tissue thickness of the temporal area. The rate of success in recording blood flow signals decreases in Asian and African populations, women, and older adults. The incidence of sufficient TAW presence was 77.1% in Japanese participants. Additionally, sufficient TAW was present in only 17.0% of women aged 70 years or older.

Four major acoustic TCD windows are known: 1) the TAW, 2) the transorbital window, 3) the submandibular window, and 4) the suboccipital window. From the TAW, the MCA, anterior and posterior cerebral artery, ICA terminus, and posterior communicating artery are detectable, and this window is the most commonly used in TCD examinations. The transorbital window can be used to examine the carotid siphon and the ophthalmic artery. Although no harmful effects have been reported in transorbital TCD, the power of output should be reduced to 10% (or less than 17 mW/cm²) to protect the crystalline lens. The submandibular approach is generally employed for evaluation of the distal cerebral ICA. The vertebral and basilar arteries can be detected by the suboccipital (transforaminal) approach with a direct insonation through the foramen magnum. Each method has unique advantages for the analysis of different arteries and indications and may complement the insufficiency of TCD from other windows. The transorbital, submandibular, and suboccipital windows have been reported for alternative use when the TAW is insufficient. Topçuoglu et al. reported that submandibular ICA recording was as sensitive and specific as TAW recording for detection of the right-to-left shunt. However, to our knowledge, there have been no previous reports comparing TCD methods through different windows for the assessment of CVR. A previous report demonstrated good reproducibility of the BHI in the ICA siphon from the transorbital window, but there was no significant decrease in the BHI corresponding to ICA stenosis, which may be due to fixation instability and the tortuous shape of the ICA siphon. Flow velocities often change at the curvature or stenotic lesion, and a proximal ICA stenotic lesion may affect CVR measurement from the cervical segment. The submandibular window may have better stability than the transorbital window. However, in the present study, we did not evaluate stenosis by cervical ultrasound, computed tomography, or magnetic resonance angiography. Use of the submandibular window to detect the ICA is an easier method compared with use of the TAW because of the lack of bone transition. However, it is important to avoid artifacts of respiratory and neck movement.

Although CVR is a useful biomarker for the risk of cerebrovascular events, it is important to note the limitations of CVR measurement by TCD. Cerebral blood velocity is an accurate indicator of CBF changes when the diameter of the blood vessels is constant. In a previous 7-T MRI study, MCA diameter did not alter during small deviations in the end tidal CO₂ partial pressure (Pₑ-CO₂) from normocapnia, but dilation was observed at higher Pₑ-CO₂ values. The blood flow velocity changes measured by TCD underestimate underlying changes in CBF under high hypercapnic conditions. In contrast, there are no previous reports regarding diameter changes of the ICA in response to CO₂ levels under similar procedures. Further investigation is needed to understand the implications of the assessment of CVR in the ICA.

TCD is a non-invasive and cost-effective tool, and the breath-holding test is simple and common in CVR examination. Use of the submandibular window is an easier method than use of the TAW for the measurement of CVR. We propose the use of the submandibular window as an alternative method in the event of insufficient TAW.

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**Conflicts of interest**

The authors declare that they have no conflicts of interest.

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