DYNAMIC CEREBRAL AUTOREGULATION ASSESSMENT USING EXTRACRANIAL INTERNAL CAROTID ARTERY DOPPLER ULTRASONOGRAPHY

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Abstract—Transcranial Doppler ultrasonography of the middle cerebral artery (MCA) is frequently used to assess dynamic cerebral autoregulation (dCA); however, this is difficult in patients with poor temporal bone windows. In the study described here, we investigated the agreement and sensitivity of dCA indices determined from the extracranial internal carotid artery (ICA) and those determined from the MCA. Measurements for 32 stroke patients and 59 controls were analyzed. Measurement of the mean flow correlation index (Mx) and transfer function analysis based on spontaneous blood pressure fluctuation were simultaneously performed for the extracranial ICA and MCA. The mean values of Mx and phase shift did not significantly differ between the ICA and MCA (mean difference: Mx = 0.01; phase shift of very low frequency [VLF] = 0.7°, low frequency [LF] = 3.3° and high frequency = 4.5°), but the gains in VLF and LF in the ICA were significantly lower than those in the MCA (mean difference: gain of VLF = −0.13, gain of LF = −0.10). The intra-class correlation coefficient between the dCA indices of the ICA and MCA was favorable in Mx (0.76) and the phase shift of VLF (0.72). The area under the receiver operating characteristic curve for stroke diagnosis did not differ among the dCA indices. We conclude that dCA assessed from the ICA is as effective as that from the MCA, but the results are not interchangeable. (E-mail: naifangchi@tmu.edu.tw) © 2017 World Federation for Ultrasound in Medicine & Biology.

**Key Words:** Cerebral hemodynamics, Cerebrovascular diseases, Dynamic cerebral autoregulation, Transcranial Doppler ultrasonography.

INTRODUCTION

Cerebral autoregulation is a mechanism for maintaining adequate cerebral blood flow (CBF) in response to changes in cerebral metabolic needs or systemic hemodynamics (Powers et al. 1985). Dynamic cerebral autoregulation (dCA) in humans is measured by analyzing the correlation between changes in CBF and peripheral arterial blood pressure (ABP). Impaired dCA has been correlated with the severity and poor outcome of cerebrovascular diseases (Aries et al. 2010).

Studies have proven that transcranial Doppler ultrasonography (TCD) monitoring of blood flow velocity (BFV) in the middle cerebral artery (MCA) is an effective method for assessing dynamic changes in CBF, under the assumption of constant MCA diameter during the test (Lindegaard et al. 1987; Newell et al. 1994). The use of TCD to assess dCA on the basis of either spontaneous or induced CBF changes is valid and reliable (Brodie et al. 2009; Minhas et al. 2016). The success rate of trans-temporal insonation is affected by ethnicity, age, and thickness and density of temporal bone (Brunser et al. 2012; Kollar et al. 2004; Kwon et al. 2006; Wijnhoud et al. 2008). In studies in Western countries, the success rate of TCD is often...
90% (Brodie et al. 2009; Minhas et al. 2016; Ortega-Gutierrez et al. 2014), whereas in reports from Asian countries, the successful trans-temporal insonation rate is 60%–70% in middle-aged populations (Gao et al. 2002; Itoh et al. 1993; Kwon et al. 2006; Lien et al. 2001; Yagita et al. 1996). A high rate of TCD failure in aged individuals is detrimental to subject recruitment for studies on cerebrovascular or neurodegenerative diseases. Because high-quality Doppler signals can be obtained more easily from the extracranial internal carotid artery (ICA) than from the MCA, this may be an alternative for assessing dCA when trans-temporal insonation fails. Before the widespread use of TCD, the ICA flow volume measured with an electromagnetic flowmeter was used as a surrogate for CBF in assessing dCA (Lindegaard et al. 1987; Newell et al. 1994). The MCA is the main branch of the ICA, accounting for 80% of the flow volume in a hemisphere (Lindegaard et al. 1987). Under a drug-induced change in ABP, the average diameter change in both the ICA and MCA is less than 4% (Giller et al. 1993), and the change in BFV is consistent between the ICA and MCA (Liu et al. 2013). Accordingly, the BFV of the ICA may be used for assessing dCA, and the dCA determined from the BFV of the ICA may be similar to the dCA of the MCA, especially under spontaneous ABP fluctuations in resting states because no significant changes in the diameter of the ICA or MCA occur under this condition. Agreement of the autoregulation index between the ICA and MCA has been studied (Nogueira et al. 2016; Saeed et al. 2013), but only healthy volunteers have been tested. This study used both time- and frequency-domain analyses to compare the agreement, sensitivity, and specificity of ICA- and MCA-based dCA assessments for identifying patients with stroke.

**METHODS**

*Patients and measurements*

This study was approved by the Institutional Review Board of Taipei Medical University. Patients with ischemic stroke in the MCA territory were recruited within 1 wk of onset from the neurology ward at Taipei Medical University Shuang Ho Hospital. Controls without a history of stroke were recruited from the health management center at the same hospital. Written informed consent was obtained from all participants.

In each patient, the stroke location was confirmed through magnetic resonance imaging. Electrocardiography, extracranial carotid Doppler ultrasonography and transcranial color-coded Doppler ultrasonography were performed in all patients; those with poor bilateral temporal windows, atrial fibrillation or ICA or MCA diameter stenosis >50% were excluded. A total of 91 patients, comprising 32 patients with stroke (age, 59 ± 10 y; 29 men) and 59 controls (age, 49 ± 14 y; 20 men), were enrolled for the final analysis. In all patients, the National Institutes of Health Stroke Scale (NIHSS) was applied on the day of dCA measurement.

The dCA measurements were recorded in spontaneously breathing patients placed in a supine position with their heads elevated at 30°; signal recording was initiated after 15 min of rest, and a stable end-tidal CO2 was confirmed through capnography (Nellcor N85, Medtronic, Fridley, MN, USA). The BFVs in the ipsilateral ICA and MCA were simultaneously recorded using a Doppler monitor (MultiDop-T, Compumedics DWL, Singen, Germany) with two 2-MHz probes and a custom-made head frame (Fig. 1a). In stroke patients and controls, affected side (right = 20, left = 12) and right-side measurements were recorded, respectively. In the controls, if insonation failed on the right side, then left-side measurements were recorded (tested side: right = 55, left = 4). The depth
of insonation was 40–50 mm in the ICA and 50–60 mm in the MCA, and sample volume length was 5–10 mm for both the ICA and MCA (Fig. 1b). ABP was continuously recorded through finger plethysmography (Finometer Pro, Finapres, Enschede, Netherlands). In each subject, the BFVs of the ICA and MCA and the ABP were digitally recorded simultaneously for 5 min at a sampling rate of 50 Hz using a laptop equipped with a data acquisition device (NI USB-6221 BNC, National Instruments, Austin, TX, USA) and signal processing software (DataDemon, DynaDx, Mountain View, CA, USA). The Finapres device has a known delay of 1 s between signal acquisition and analogue output. Therefore, it is necessary to measure the delay and synchronize the devices before the test (Claassen et al. 2016). We synchronized the Finapres device and Doppler monitor by aligning the artificial noises produced at the Finapres finger sensor and ultrasound probe at the same time.

Dynamic cerebral autoregulation analysis

Before dCA analysis, the acquired data were inspected manually. Severe artifacts shorter than three beats were removed and replaced by linear interpolation, and severe artifacts longer than three beats were excluded from analysis, according to the recommendations of a white paper from the International Cerebral Autoregulation Research Network (CARNet) (Claassen et al. 2016). In the present study, the time domain of dCA was analyzed as the mean flow correlation index (Mx). In brief, Pearson correlation coefficients between 20 consecutive 3-s periods (a total of 1 min) of mean BFV and ABP were calculated, and five correlation coefficients of 5 min were averaged as the Mx (Czosnyka et al. 1996; Reinhard et al. 2003). In patients with favorable dCA, change in CBF is presumably independent of change in ABP; accordingly, Mx = 0 represents intact dCA, whereas Mx = 1 represents absent dCA. The Mx in stroke patients was higher than that in healthy controls (Reinhard et al. 2005, 2008). Frequency-domain analysis of dCA was performed through transfer function analysis (TFA), according to the recommendations of CARNet (Claassen et al. 2016). In TFA, phase shift, gain and coherence between the BFV and ABP waveforms at very low frequency (VLF, 0.02–0.07 Hz), low frequency (LF, 0.07–0.20 Hz) and high frequency (HF, 0.20–0.50 Hz) were calculated. In the transfer function between ABP and CBF, gain reflects the damping effect of dCA on the magnitude of ABP oscillations. A low gain represents an efficient dCA. Furthermore, in patients with intact dCA, the changes in CBF are usually restored faster than those in ABP, resulting in a phase shift between the waveforms of CBF and ABP (van Beek et al. 2008). In stroke patients, the phase shift between CBF and ABP is lower than that in healthy controls (Petersen et al. 2015; Reinhard et al. 2008).

Statistical analysis

The agreement and intra-individual correlation between the dCA indices assessed from the ICA and MCA were calculated using Bland–Altman plots and the intra-class correlation coefficient (ICC), respectively. The average value of each dCA index was compared between the ICA and MCA through a paired t-test. Agreement between the ICA and MCA was compared among all participants (n = 91), controls (n = 59) and stroke patients (n = 32). Moreover, patients with stroke usually have impaired dCA; therefore, we used the receiver operating characteristic (ROC) curve to compare each dCA index between the ICA and MCA for identifying stroke patients. The data are expressed as means ± standard deviations (SD), and p < 0.05 was considered to indicate statistical significance. Statistical data were analyzed using SPSS Statistics for Windows (Version 18.0, IBM, Armonk, NY, USA) and MedCalc statistical software (Version 16.8, MedCalc Software, Ostend, Belgium).

RESULTS

The demographic data of patients and controls are summarized in Table 1. Bland–Altman plots for dCA indexes are presented in Supplementary Figures S1–S13. The mean difference ±95% agreement in the Bland–Altman plots and the ICC of each dCA index between the ICA and MCA are summarized in Table 2. Mean differences in Mx, phase shift and coherence of all frequency bands between the ICA and MCA did not significantly differ from zero. The paired t-test revealed small but significant differences in the mean coherence of VLF in controls and the mean coherence of LF in patients with stroke between the ICA and MCA. Both gain (cm/s/mm Hg) and normalized gain (%/mm Hg) of ICA are significantly lower than those of MCA at VLF and LF. Moreover, compared with the LF band, the range of 95% agreement was larger in phase shift, but smaller in coherence in the HF band.

Table 1. Demographic data of the participants

<table>
<thead>
<tr>
<th>Value</th>
<th>Stroke(+) (n = 32)</th>
<th>Stroke(−) (n = 59)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>59 ± 10 (37–70)</td>
<td>49 ± 14 (20–72)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>29 (91%)</td>
<td>20 (34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (78%)</td>
<td>14 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (50%)</td>
<td>10 (17%)</td>
<td>0.001</td>
</tr>
<tr>
<td>NIHSS (range)</td>
<td>3 ± 3 (0–15)</td>
<td></td>
<td></td>
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<tr>
<td>Stroke etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAA</td>
<td>10 (31%)</td>
<td></td>
<td></td>
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<tr>
<td>SVD</td>
<td>22 (69%)</td>
<td></td>
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</tr>
</tbody>
</table>

LAA = large artery atherosclerosis; NIHSS = National Institutes of Health Stroke Scale; SVD = small vessel disease.

Age was compared with the Mann–Whitney U-test; proportions of sex, hypertension and diabetes were compared with Fisher’s exact test. Age and NIHSS were expressed as mean ± standard deviation.
The ICC between the ICA and MCA was favorable (≥0.6) for the MX, phase shift of VLF, coherence of all frequency bands, and normalized gain of LF; and was poor (<0.4) for the gain of all frequency bands. In addition, compared with the LF band, the ICC was smaller in phase shift but larger in coherence in the HF band. The results remained unchanged when agreement and ICC were separately tested among controls and stroke patients (Table 2).

The area under the receiver operating characteristic curve (AUC) for each dCA index used in
identifying patients with stroke is listed in Table 3. Sensitivity and specificity in identifying patients with stroke were favorable for the Mx (AUC of ICA and MCA = 0.680 and 0.709, respectively) and phase shift of VLF (AUC of ICA and MCA = 0.615 and 0.508, respectively), but did not significantly differ from random guesses (AUC = 0.5) for the phase shift of LF or HF, gain of all frequency bands and normalized gain in all frequency bands. No significant differences were observed in the AUCs of all dCA indices between the ICA and MCA. Thus, the sensitivity and specificity of dCA indices for identifying patients with stroke did not differ between the ICA and MCA.

**DISCUSSION**

The mean values of Mx, phase shift and coherence of all frequency bands did not significantly differ between the ICA and MCA. In addition, the AUCs for identifying patients with stroke did not significantly differ in the Mx and phase shift of all frequency bands. Therefore, in the study of stroke, the dCA index determined from the BFV of the ICA is very close to and as valid as that of the MCA.

### Table 3. Comparison of sensitivity and specificity of stroke diagnosis between dCA indices assessed from the ICA and MCA

<table>
<thead>
<tr>
<th></th>
<th>VLF (0.02–0.07 Hz)</th>
<th>LF (0.07–0.20 Hz)</th>
<th>HF (0.20–0.50 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase shift (°)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>0.680 (0.574–0.774)*</td>
<td>0.707 (0.596–0.803)*</td>
<td>0.616 (0.499–0.724)</td>
</tr>
<tr>
<td>MCA</td>
<td>0.709 (0.604–0.799)*</td>
<td>0.712 (0.601–0.808)*</td>
<td>0.570 (0.453–0.681)</td>
</tr>
<tr>
<td><strong>Gain (cm/s/mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>0.615 (0.502–0.720)</td>
<td>0.537 (0.423–0.649)</td>
<td>0.530 (0.414–0.643)</td>
</tr>
<tr>
<td>MCA</td>
<td>0.512 (0.400–0.623)</td>
<td>0.502 (0.390–0.617)</td>
<td>0.538 (0.423–0.651)</td>
</tr>
<tr>
<td><strong>Normalized gain (%/mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>0.534 (0.421–0.644)</td>
<td>0.504 (0.391–0.617)</td>
<td>0.590 (0.473–0.699)</td>
</tr>
<tr>
<td>MCA</td>
<td>0.601 (0.487–0.707)</td>
<td>0.588 (0.473–0.696)</td>
<td>0.600 (0.483–0.708)</td>
</tr>
</tbody>
</table>

Sensitivity/specificity (optimal criterion).
ICA Mx = 0.560 (0.73 (~>0.43).
MCA Mx = 0.780/0.56 (~>0.34).
ICA VLF phase shift = 0.57/0.83 (~<51°).
MCA VLF phase shift = 0.65/0.77 (~<54°).

AUC = area under the receiver operating characteristic curve; CI = confidence interval; dCA = dynamic cerebral autoregulation; HF = high frequency; ICA = internal carotid artery; LF = low frequency; MCA = middle cerebral artery; Mx = mean flow correlation index; SD = standard deviation; VLF = very low frequency.

* p < 0.05, AUC = 0.5.
determined from the MCA. However, the mean values of gain and normalized gain differed between the ICA and MCA; therefore, the dCA behavior of the ICA differs from that of the MCA.

The smaller gain and normalized gain of the ICA, compared with those of the MCA, reflect a smaller change in the BFV of the ICA than in that of the MCA under spontaneous ABP change; this difference may be physiologic or technical. The larger cross-sectional area of the ICA compared with that of the MCA results in a smaller absolute BFV change, which could explain the smaller absolute gain, but not the smaller normalized gain of the ICA compared with that of the MCA. In studies of dCA, the diameter of the vessel is presumably constant, and the Doppler-recorded BFV represents the CBF, which is not exactly the true condition. After ABP changes, both the ICA and MCA exhibit a small (<4%) change in diameter (Giller et al. 1993), but it is not clear whether the magnitude of this change varies between the ICA and MCA, which may account for the difference in gains between them. In addition, the Doppler-recorded BFV is measured by depicting the envelope of the whole Doppler spectrum, which represents the maximum but not the mean BFV in the vessel. BFV is fastest in the middle of the vessel and slowest at the vessel wall (Tortora and Derrickson 2012), and the relation between maximum and mean BFV could depend on vessel diameter. Therefore, the difference between measured BFV and mean BFV in the ICA may be different from that in the MCA, which in turn results in a difference in gains between the ICA and MCA. However, in ROC curve analysis, neither gain nor normalized gain was valid for identifying patients with stroke. In previous studies on dCA in stroke, gain has not been reported (Petersen et al. 2015; Reinhard et al. 2008) or has not been reported to differ between stroke patients and controls (Reinhard et al. 2005). Therefore, the importance of gain in stroke is not clear and warrants further investigation. Increased Mx and decreased phase shift have been associated with stroke (Petersen et al. 2015; Reinhard et al. 2005, 2008).

In the present study, ROC curve analysis revealed a favorable sensitivity and specificity of Mx and phase shift of VLF for identifying stroke patients. In a study of traumatic brain injury, the Mx and phase shift of VLF were effective in predicting favorable and poor outcomes (Liu et al. 2015). Therefore, Mx and phase shift are the substantial dCA indices in neurologic diseases.

In a study on dCA test–retest reliability (Ortega-Gutierrez et al. 2014), the mean differences in Mx and phase shift of LF (0.06–0.12 Hz) between test and retest were close to zero, and the range of 95% agreement was approximately ±0.3 for Mx, ±30° for the phase shift of LF and ±1.5 cm/s/mm Hg for the gain of LF. In addition, the test–retest ICC was 0.456 for Mx, 0.632 for the phase shift of LF and 0.635 for the gain of LF. Thus, a substantial variation was observed in each dCA index at a different timing, even within the same artery. The mean difference, 95% agreement range and ICC of the aforementioned test–retest reliability study were close to the values of ICA–MCA agreement tests performed in the present study; hence, the difference in dCA between the ICA and MCA at the same time point may not exceed the natural dCA fluctuation in the same artery.

This study has some limitations. First, the conclusions apply only to Mx and TFA determined from spontaneous CBF and ABP fluctuations. This study did not evaluate dCA under induced ABP changes, such as the Valsalva maneuver or thigh cuffs, and the consistency in diameter and BFV changes between the ICA and MCA under induced ABP changes remains unclear. Second, the agreement between the ICA and MCA was tested in healthy volunteers and ischemic stroke patients, but the consistency between the ICA and MCA remains uncertain for other diseases. Third, more than 90% of the stroke patients were male, so whether the agreement between the ICA and MCA is applicable to female patients remains unclear. The dCA assessed from the ICA under induced ABP changes and in diseases other than stroke warrants further investigation. Last, the advantage of a higher success rate for extracranial Doppler scanning applies only to the Asian population.

**CONCLUSIONS**

Assessment of dCA through extracranial ICA Doppler ultrasonography is a suitable approach because of its high success rate in practice, especially in the Asian population. Moreover, the Mx, phase shift and coherence of ICA are consistent with those of TCD with the same validity in studies of stroke. However, gain and normalized gain differ between the ICA and MCA, which implies that the two arteries have different dCA behavior. Therefore, although the dCA assessed from the ICA is close to and as valid as that from the MCA, the results are not interchangeable.

**SUPPLEMENTARY DATA**

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ultrasmedbio.2017.02.003.

**REFERENCES**


