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● *Original Contribution*

A NEW METHOD OF MEASUREMENT OF CEREBRAL CIRCULATION TIME: CONTRAST-ENHANCED ULTRASONOGRAPHY IN HEALTHY ADULTS AND PATIENTS WITH INTRACRANIAL SHUNTS

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Abstract—Alterations in the cerebral circulation time (CCT) are observed in several cerebrovascular diseases. We designed a new method of global CCT measurement using gray-scale contrast-enhanced ultrasound and studied healthy Chinese adults and patients with intracranial shunts. Eighty-one healthy volunteers and eight patients with intracranial shunt disease were enrolled. The contrast agent Sonovue was used. Perfusion in the carotid artery and internal jugular vein bilaterally was recorded. Start and peak filling CCTs were calculated and analyzed. Imaging of carotid vessels was uncomplicated in all patients. The bilateral start CCT was 6.23 ± 1.39 s in healthy patients. There were no significant differences within subgroups and contrast-dosage groups. In the patient group, the mean start CCT was 3.0 ± 0.56 s. There was a significant difference between the control and patient groups ($p < 0.001$). This new method using gray-scale contrast imaging can measure CCT and cerebral blood volume accurately. It can be used to visualize blood flow differences in real time and is less dependent on the training of the operator. (E-mail: Duanyy@fmmu.edu.cn)

Key Words: **Cerebral blood flow measurement, Cerebral circulation time, Ultrasonography, Contrast enhancement.**

INTRODUCTION

Measurement of global cerebral circulation time (CCT) and global cerebral blood volume (CBV) is an approach used to diagnose many cerebrovascular diseases such as dural arteriovenous fistulas and vascular dementia (Bisdas et al. 2007). For years, digital subtraction angiography (DSA) has been considered the "gold standard" method for the measurement of CCT, but it is invasive and expensive.

Other diagnostic imaging procedures have been used for the measurement of CCT and evaluation of perfusion of cerebral blood flow (Celsis et al. 1985; Iseda et al. 2000; Liv et al. 2007; Yamamoto et al. 2004). With the development of contrast agents, more imaging methods are being used to measure CCT. The evaluation criteria vary with the method. Using single-photon emission computed tomography, Iseda et al. (2000) and Yamamoto et al. (2004) measured CCT respectively, as the time delay in a contrast bolus to the medial cerebral artery and away from the area feeding the medial cerebral artery. Liv et al. (2007) identified CCT as the delay in the peak time at which the contrast bolus reached the proximal M1 segment of the medial cerebral artery and longitudinal sinus, as well as that in the common carotid artery and internal jugular vein at the C-4 level, by application of contrast agent with 64-slice helical computed tomography (CT). Strictly speaking, 64-slice helical CT is neither continuous nor real-time dynamic imaging. In addition, radioisotope imaging and CT angiography have the shortcomings of being expensive and difficult to carry out and involving radiation exposure.

Transcranial ultrasound imaging with ultrasound contrast agents is an emerging method for evaluation of brain perfusion (Vicenzini et al. 2008). Doppler sonographic measurement of global CCT and CBV is a new diagnostic approach. It was recently described in healthy

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volunteers and patients with cerebrovascular disease. Schreiber's group (2002, 2003, 2005) undertook a series of studies measuring CCT extracranially as the time delay between enhancement in the distal internal carotid artery (ICA) and enhancement in the contralateral internal jugular vein (IJV) by transcranial Doppler (TCD). They recorded spectrum enhancement after injection of contrast agent (Levovist, Schering AG, Berlin, Germany), and calculated the CBV in normal volunteers and patients with cerebrovascular disease. Their results were promising, indicating that CCT decreased in patients with arteriovenous malformations and increased in patients with vascular dementia and Alzheimer's dementia. Compared with color Doppler ultrasound, TCD has shortcomings in the detection of cervical and intracranial vascular disease. These include the absence of 2-D image guidance and dependence on a high level of training for the investigator. Based on the method described by Schreiber et al. (2002), we designed a new method of measuring CCT and CBV in a group of normal adults and a small group of patients with intracranial arteriovenous shunts using a different contrast agent and an enhanced gray-scale ultrasonography system.

METHODS

Ethical approval of the study protocol

All participants or their legal guardians gave written informed consent. The protocol was approved by the Human Patients Review Committee of the Fourth Military Medicine University (Xi'an, China).

Subjects

Healthy volunteers. Eighty-one healthy volunteers were enrolled in this study as the control group and underwent routine medical examinations in our hospital (50 males, 31 females; age range: 33–72 y; mean age: 48 ± 13 y). No patients had cerebral vascular risk factors based on their histories. No abnormal presentations were observed in the physical examination, laboratory tests (lipid profile, blood glucose) or imaging evaluation (CT or magnetic resonance imaging of the head) in all volunteers. Patients with a history of smoking and hypertension were excluded. All volunteers underwent carotid color Doppler ultrasound imaging before measurement of CCT. Patients with carotid plaques or stenoses were excluded.

Patient group. Eight patients (6 males, 2 females; age range: 24–68 y; mean age: 45 ± 14 y) with intracranial shunt disease confirmed by DSA were enrolled. Six of the eight patients were diagnosed as having an arterial venous malformation, one subject had a carotid-cavernous fistula and one had a dural arteriovenous fistula. All parameters relating to the procedure and measurement were the same as for the control group. CCT results for the patients were compared with the values for the control group.

Ultrasound protocol

Detection of cervical vessels and measurement of blood flow. All patients were required to rest ≥5 min in the supine position. A small electronic sphygmomanometer was set on the non-injected wrist to measure real-time heart rate and blood pressure. An ultrasonographic scanner with color Doppler capabilities was used (Logiq 9, General Electric, Fairfield, CT, USA). The pre-contrast examination was conducted using a high-frequency linear transducer (M12-L, 5.0–10.0 MHz) to obtain images of the ICA and vertebral arteries (VAs) and then measure blood flow volume (BFV). The imaging depth was set at 40–60 mm. The inner diameter (R) was measured. The sampling position for the ICA was 1.5 cm above the bifurcation of the common carotid artery and, for VAs, the middle segment between C-3 and C-4. We used dual-functional color-coded Doppler flow mode for the identification and measurement of vessels. Pulse repetition frequency of color-coded flow was 30–50 cm/s. The angle was corrected to $<45^{\circ}$, and measurements were made in the longitudinal plane. Three heart cycles were measured and averaged. The mean blood flow velocity (V) of the ICA and VA bilaterally was calculated using the software within the machine. BFV was calculated using the formula (Zwiebel 2004)

$$\mathrm{BFV} = \pi * (\mathrm{R}/2)^2 * V * 60$$

where $\pi = 3.14$; R = inner diameter of vessels (mm); $R/2$ = radius (mm); and V = mean blood flow velocity (mm/s). Global cerebral blood flow volume (CBF) is the sum of the BFVs for all four vessels.

All examinations and measurements described above were done directly on-line by one experienced ultrasonographer (Y. L. Yang).

Protocol for ultrasonic contrast imaging. Recommendations arrived at by consensus were followed in a standardized approach to the use of ultrasonic contrast agents (Nedelmann et al. 2009). A scanning transducer (4C, 3.0–5.0 MHz, Logiq 9, General Electric) was chosen to image the common carotid artery (CCA) and IJV bilaterally as the target plane (Fig. 1). A clinically approved ultrasonic microbubble contrast agent (SonoVue, Bracco, Milan, Italy) was used. The contrast agent was prepared according to the manufacturer's instructions. Briefly, 5 mL of physiologic (0.9%) saline solution was added to the vial, and the vial shaken for 25–30 s to form a suspension. After the target plane was determined,