



● *Clinical Note*

## CONTRAST-ENHANCED COLOR-CODED DOPPLER SONOGRAPHY IN MOYAMOYA DISEASE: A RETROSPECTIVE STUDY

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**Abstract**—The purpose of this study was to validate the feasibility of contrast-enhanced transcranial Doppler sonography (CE-TCCD) in the diagnosis of Moyamoya disease (MMD). CE-TCCD data on patients with MMD were analyzed. The CE-TCCD data were classified qualitatively into four patterns by two independent investigators: normal vascular color Doppler signal (pattern 1), augmented color Doppler signal with identifiable vascular structure (pattern 2), confluent color Doppler signal filling more than two-thirds of the display frame without identifiable vascular structure (pattern 3) and confluent color Doppler signal filling full display (pattern 4). To investigate the validity, we compared the CE-TCCD data with traditional transcranial Doppler data and Suzuki grades on cerebral angiography. A total of 32 CE-TCCD studies from 16 MMD patients (male 37.5%, median age 48) were included in this study. The CE-TCCD findings were distributed across patterns 1 (n = 3), 2 (n = 12), 3 (n = 10) and 4 (n = 7) and were correlated with the Suzuki grades ( $p < 0.005$ ) and hemodynamic parameters. Inter-rater reliability was promising (Cronbach  $\alpha = 0.883$ ). The CE-TCCD test provides distinctive patterns in MMD, according to their stage of progression. CE-TCCD patterns seem to be a reliable and valid means for the evaluation of MMD. (E-mail: [okyunmi@korea.ac.kr](mailto:okyunmi@korea.ac.kr)) © 2018 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.

**Key Words:** Moyamoya disease, Transcranial doppler, Ultrasound contrast agent, Diagnosis.

### INTRODUCTION

Moyamoya disease (MMD) is a cerebrovascular condition characterized by progressive stenosis or occlusion of the terminal internal carotid or middle cerebral arteries with abnormal basal collaterals (Suzuki and Takaku 1969). The diagnosis of MMD is challenging because the only diagnostic gold standard test is invasive transfemoral catheter-based cerebral angiography (TFCA), which is not suitable for a screening test (Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis and Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases 2012).

Transcranial Doppler (TCD) or transcranial color-coded Doppler sonography (TCCD) is a non-invasive test for the evaluation of intracranial cerebral vasculature (Zipper

and Stolz 2002). Ultrasound contrast agents (UCAs) composed of microbubbles have become an available tool for evaluating vascular systems (Cosgrove 2006; Dietrich et al. 2012). UCAs can intensify weak vascular signals and improve the visualization of intracranial arteries in patients with a poor temporal window through which conventional TCD cannot detect cerebral blood flow. Conventional TCD or TCCD can detect major basal cerebral arteries including the circle of Willis. However, in MMD patients, the middle cerebral artery or intracranial internal carotid artery disappears and is replaced by aberrant basal collateral vessels. We hypothesized that the signal of weak basal collateral vessels could be augmented by the use of UCAs in MMD patients. Therefore, based on the hypothesis that CE-TCCD can visualize basal collaterals in MMD, we studied CE-TCCD findings for patients with MMD.

### METHODS

We identified patients who were diagnosed with MMD and underwent CE-TCCD at the Korea University Guro Hospital between January 2015 and January 2016. The

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diagnosis of MMD was made when TFCA revealed characteristics of steno-occlusive disease of the anterior circulation with basal collateral flow, after excluding other causes of steno-occlusive disease (Research Committee 2012). The study protocol was approved by the institutional review board of the Korea University Guro Hospital (KUGH 16195). Given the retrospective design of this study, the board allowed us to proceed with the analysis without obtaining informed consent from the patients.

We rated the angiographic findings according to the Suzuki criteria, which classify the angiographic stage of MMD as narrowing of the carotid fork (stage I); initiation of the MMD (dilated major cerebral artery and a slight moyamoya vessel network, stage II); intensification of MMD (disappearance of the middle and anterior cerebral artery, and thick and distinct moyamoya vessels, stage III); minimization of the moyamoya (disappearance of the posterior cerebral artery and narrowing of individual moyamoya vessels, stage IV); reduction of the moyamoya (disappearance of all main cerebral arteries from the internal carotid artery system, further minimization of the moyamoya vessels and an increase in the collateral pathways from the external carotid artery system, stage V); and disappearance of the moyamoya (disappearance of the moyamoya vessels, with cerebral blood flow derived only from the external carotid artery and the vertebrobasilar artery systems, stage IV), and compared them with the CE-TCCD findings (Suzuki and Takaku 1969).

Contrast-enhanced TCCD was performed on two machines (12 patients with ProSound Alpha7 premier [Hitachi-Aloka Medical, Tokyo, Japan; using UST-52105, 1.25–5 MHz phase array sector probe, display rate 13 Hz] and 4 patients with Affiniti 70 (Philips Ultrasound, Bothell, WA, USA; using S5-1 phased array sector probe)) using contrast harmonic imaging at a low mechanical index (1.1). Before starting the CE-TCCD examination, intravenous access was obtained through the right medial cubital vein with a 22-gauge intravenous catheter. After at least 5 min of rest in the supine position, transcranial Doppler sonographic examination was performed for the middle cerebral, anterior cerebral, posterior cerebral, vertebral and basilar arteries. For comparison with CE-TCCD patterns, we determined the following hemodynamic parameters of the middle cerebral arteries on both sides: mean flow velocity (MFV), peak systolic velocity (PSV), end-diastolic velocity (EDV), pulsatility index (PI) and resistance index (RI). As hemodynamic parameter values varied greatly in patients with MMD, the parameters on the side with the highest MFV were obtained as representative.

The CE-TCCD images were obtained using a low-frequency sector probe on a temporal window. Before the start of UCA (SonoVue, Bracco, Milan, Italy) infusion, color Doppler was turned on, and the color gain was set at minimum to avoid exaggerated vascular signals. Before

UCA infusion, we checked the best visible temporal window. While the probe was manually maintained over the temporal window, 2 mL of activated UCA was infused in a bolus, followed by saline flushing. All these procedures were recorded using a movie recorder with which the machines were equipped. CE-TCCD findings were classified into four groups: normal vascular pattern (pattern 1: normal), augmented color Doppler signal with identifiable vascular structures (pattern 2: augmented), confluent color Doppler signal filling more than two-thirds of the display frame without identifiable vascular structures (pattern 3: confluent), confluent color Doppler signal filling the complete display (pattern 4: full) (Fig. 1). The CE-TCCD findings were classified by two independent vascular neurologists who were blind to the clinical information (W.K.S. and C.W.C.).

Inter-rater reliability was tested using Cronbach's  $\alpha$ . To test the validity of CE-TCCD, the correlation with Suzuki grade was computed using Kendall's rank correlation coefficient ( $\tau$ ). The association of CE-TCCD patterns with hemodynamic parameters, including PSV, EDV, MV, PI and RI, was tested using linear regression analyses.

## RESULTS

During the study period, a total of 32 CE-TCCD studies (patients, 16; males, 37.5%; median age, 48 y; range, 19–64 y) were included (Table 1). The patients presented with several cerebrovascular diseases including ischemic stroke ( $n = 8$ ), intracerebral hemorrhage ( $n = 1$ ), transient ischemic attack ( $n = 4$ ) and headache without focal neurologic symptoms ( $n = 2$ ). Of the 16 patients, 6 (37.5%) were classified as “probable MMD” given the unilateral involvement. The distribution of Suzuki grades was as

Table 1. Baseline characteristics of the patients ( $n = 16$ )

Age	46.06 ± 12.40
Sex, male	6 (37.5%)
Hypertension	6 (37.5%)
Diabetes mellitus	6 (37.5%)
Smoking	0 (0%)
Dyslipidemia	3 (18.9%)
Total cholesterol, mg/dL	174.64 ± 51.70
Low-density lipoprotein cholesterol, mg/dL	112.31 ± 51.23
High-density lipoprotein cholesterol, mg/dL	47.13 ± 13.59
Triglycerides, mg/dL	158.31 ± 98.92
Presenting symptoms	
Ischemic stroke/transient ischemic attack	
Transient ischemic attack	4 (25%)
Border zone infarction	3 (18.8%)
Single subcortical infarction	1 (6.3%)
Diffuse multifocal infarction	2 (12.5%)
Posterior circulatory territorial infarction	1 (6.3%)
Hemorrhagic stroke (thalamic intracerebral hemorrhage)	1 (6.3%)
Headache	3 (18.8%)
No symptom/sign	1 (6.3%)

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