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Transcranial color-coded sonography of vertebral artery for diagnosis of right-to-left shunts

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ABSTRACT

Background: It is unknown whether contrast transcranial color-coded sonography of vertebral artery monitoring via the foramen magnum window (cTCCS-VA) is useful to detect right-to-left shunt (RLS). We investigated whether cTCCS-VA can be proposed as an alternative to middle cerebral artery monitoring via the temporal bone window (cTCCS-MCA) for RLS detection, as compared with contrast transesophageal echocardiography (cTEE).

Methods: We evaluated 112 patients with ischemic stroke or transient ischemic attack. We compared the sufficiency of both acoustic windows in each age tertile. Then, we analyzed the accuracy of cTCCS in diagnosing an RLS for a patent foramen ovale (PFO) detected by cTEE.

Results: In the higher-age tertile, the foramen magnum window was significantly more sufficient than the temporal bone window (100% vs. 71%, $p < 0.001$). In 94 patients having both windows, diagnosis of an RLS using cTCCS-MCA revealed a specificity of 42%, and a sensitivity of 84%. Diagnosis of an RLS using cTCCS-VA revealed a specificity of 40%, and a sensitivity of 91%. Analysis of the subgroup with large PFOs revealed a specificity of 71% using both cTCCS-MCA and cTCCS-VA.

Conclusions: cTCCS-VA should play an important role in detecting an RLS, especially in elderly stroke patients having large PFOs.

1. Introduction

The presence of a patent foramen ovale (PFO) associated with a right-to-left shunt (RLS) is common in the general population. Results of echocardiographic and autopsy studies have indicated a prevalence of 10%–35% [1,2]. In selected populations (i.e., patients with stroke or transient ischemic attack (TIA)), the prevalence of PFOs is higher than it is in the general population, particularly in individuals with stroke of unknown etiology [3].

Various methods are used in clinical practice to detect a cardiac RLS. Although contrast transesophageal echocardiography (cTEE) is considered the reference standard technique [4,5], disadvantages of cTEE are that it is semi invasive and that it depends on the patient's cooperation and ability to swallow [6]. Contrast transcranial color-coded sonography (cTCCS) of middle cerebral artery (MCA) monitoring is a highly sensitive and non-invasive method for detecting an RLS [6,7]. However, when this procedure is incapable of detecting MCA because of an insufficient temporal bone window, it is not known whether or not cTCCS of vertebral artery monitoring via the foramen magnum window (cTCCS-VA) is useful for RLS detection. Thus, our aim is to investigate the applicability of cTCCS-VA as an examination for RLS in stroke patients.

2. Materials and methods

From October 2012 to March 2015, we prospectively enrolled consecutive patients with ischemic stroke or TIA who were examined by both cTCCS and cTEE in order to detect a PFO. All patients underwent a standardized stroke or TIA diagnostic work-up, which included magnetic resonance imaging (MRI) of the brain; electrocardiography; complete blood chemistry studies; complete ultrasonography of the extra- and intracranial arteries; cTCCS of MCA monitoring via the temporal bone window (cTCCS-MCA); cTCCS-VA; and cTEE. We routinely performed cTCCS within 48 h of admission, and we then performed cTEE within a week after the cTCCS.

Abbreviations: PFO, patent foramen ovale; RLS, right-to-left shunt; TIA, transient ischemic attack; cTEE, contrast transesophageal echocardiography; cTCCS, contrast transcranial color-coded sonography; MCA, middle cerebral artery; cTCCS-VA, contrast transesophageal echocardiography of vertebral artery monitoring via the foramen magnum window; MRI, magnetic resonance imaging; cTCCS-MCA, contrast transesophageal echocardiography of middle cerebral artery monitoring via the temporal bone window; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment; VM, Valsalva maneuver; MES, microembolic signals; CI, confidence intervals; cTCD, contrast transcranial Doppler.

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First, we evaluated the rate of sufficient temporal bone windows (cTCCS-MCA) and sufficient foramen magnum window (cTCCS-VA) for all patients. Then, in patients having only a sufficient foramen magnum window, we calculated the rate of RLS detection using only cTCCS-VA. Finally, after patients who had sufficient both temporal bone and foramen magnum windows (possible cTCCS-MCA and cTCCS-VA) were enrolled, the diagnostic accuracy of RLS detection was compared between cTCCS-MCA and cTCCS-VA as a diagnostic standard of cTEE findings (Fig. 1).

2.1. Clinical background

We defined the following clinical parameters for all of the patients: (1) age and gender (2) vascular risk factors including hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, and smoking, and (3) the pathological mechanisms of ischemic stroke or transient ischemic attack according to the criteria of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [8].

2.2. Ultrasonography

We performed cTCCS using an ultrasound unit (EUB-7500, Hitachi Medical Corporation, Tokyo, Japan) with a 2.0–4.0 MHz sector transducer. The MCA and the VA were identified, in accordance with previous reports [9,10]. Patients were examined in the right lateral decubitus position with the head in flexion to image the vertebral and basilar arteries (Fig. 2). This creates an easily accessible the foramen magnum window. Particular care was taken to identify an appropriate vertebral arteries in one scanning plane by tilting, rotating, or shifting the transducer. A Y-shaped color flow image of the vertebrobasilar junction can be visualized at 6–8 cm depth (Fig. 3A).

First, we performed cTCCS-MCA through the temporal bone window, and then cTCCS-VA was done through the foramen magnum window on the same day for all patients. Second, we reviewed the sufficiency of the acoustic windows for all patients. The sufficiency of acoustic window was defined as successful recording of MCA or VA. For example, when a patient had only a sufficient foramen magnum window, we conducted cTCCS-VA and canceled cTCCS-MCA. The patient was then registered as having received cTCCS-VA (sufficient foramen magnum window) and having an insufficient temporal bone window (ineligibility of cTCCS-MCA).

cTEE was performed within a week after cTCCS, using a 4–7-MHz transesophageal multiplanar probe (EUB-7500, Hitachi Medical Corporation, Tokyo, Japan). The patients received local pharyngeal anesthesia with lidocaine spray, without premedication. All studies were performed by expert sonographers (T.K., T.Y., A.A., and K.S.), and all examinations were recorded on a hard disk for subsequent review and analysis.

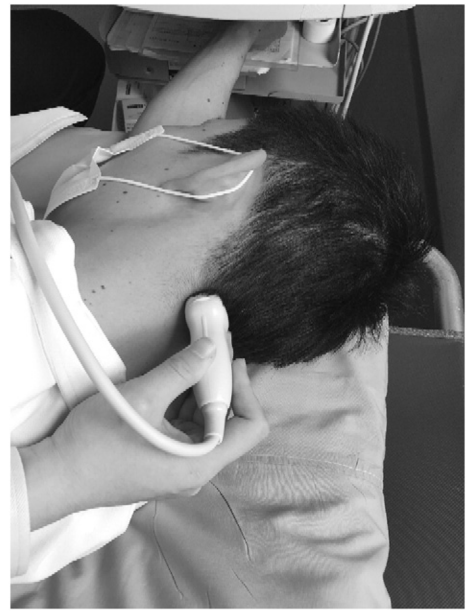

Fig. 2. Photograph of the location of the ultrasonic probe and right decubitus position of patient with the head in flexion.

2.3. Diagnosis of RLS by cTCCS

A contrast agent comprising a mixture of saline (9 mL) and air (1 mL) was prepared, which was agitated between two 10-mL syringes connected by a three-way stopcock. The contrast agent was then injected immediately as a bolus into the right anterior cubital vein with an 18-gauge intravenous catheter. The injections were performed under 2 conditions: (1) no Valsalva maneuver (VM) and (2) VM for 5 s, starting from 5 s after initiating introduction of the contrast agent. All patients were trained in the VM before the procedure. A total of 4 tests (1 test without VM and 3 with VM) were conducted using cTCCS-MCA and cTCCS-VA, respectively. The microembolic signals (MES) was defined as typical visible and audible, short-duration, high-intensity signals (Fig. 3B). When 1 or more MES were found on at least 1 of the 4 tests, we confirmed the presence of an RLS. The monitoring was continued for 90 s after injection of the contrast agent. If there were variations in the anatomy of the VA, we monitored the dominant VA.

2.4. Diagnosis of PFO by cTEE

The contrast agent was injected under 2 conditions: (1) no VM and (2) injecting during the VM, and then releasing the VM when the

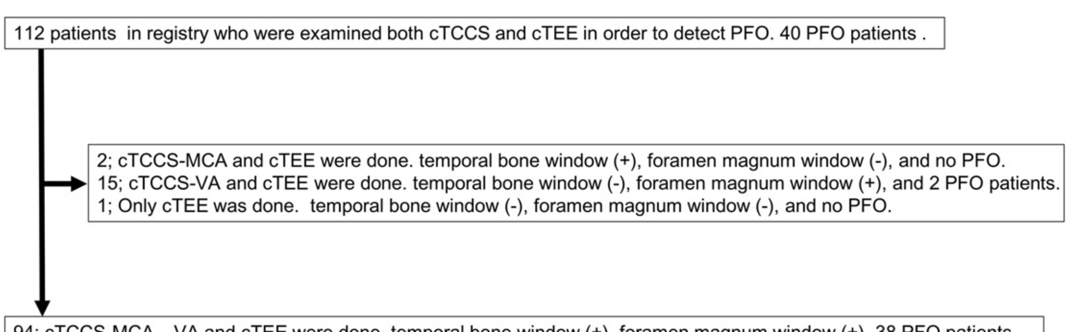

Fig. 1. Enrollment and assignment. One hundred and twelve patients were enrolled during the study period. Of these patients, 18 had insufficient temporal bone and/or foramen magnum windows. Ninety-four patients with sufficient both temporal bone and foramen magnum windows were assessed for diagnostic accuracy of right-to-left shunts. cTCCS, contrast transcranial color-coded sonography; cTEE, contrast transesophageal echocardiography; PFO; patent foramen ovale; cTCCS-MCA, contrast transcranial color-coded sonography of middle cerebral artery monitoring; cTCCS-VA, contrast transcranial color-coded sonography of vertebral artery monitoring.

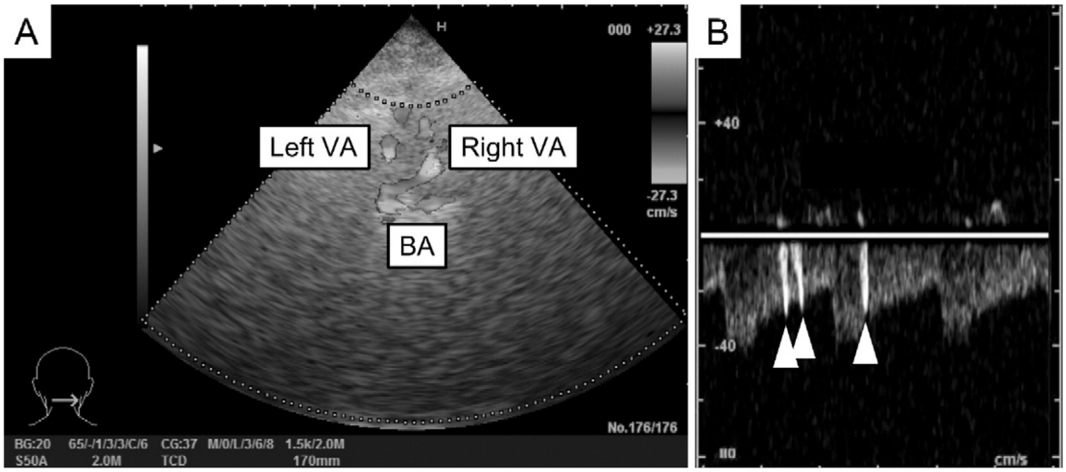

Fig. 3. Images by contrast transcranial color-coded sonography of vertebral artery recording. A) cTCCS can visualize the Y-shaped flow image of the vertebrobasilar junction. B) The microembolic signals (arrow heads) with high intensity signals are observed on the right vertebral artery. cTCCS, contrast transcranial color-coded sonography; VA, vertebral artery; BA, basilar artery.

right atrium was filled with the contrast agent. A total of 4 tests (1 test without the VM and 3 with the VM) were done with cTEE. When at least 1 microbubble was seen in the left atrium within 3 cardiac cycles from the appearance of microbubbles in the right atrium in at least 1 of 4 cTEE tests, we diagnosed the patient as having a PFO [11]. We classified the cTEE findings of a PFO into 3 subgroups: no PFO (no microbubble); small PFO (1–29 microbubbles); and large PFO (≥30 microbubbles), using a modification of the criteria defined by Cabanes et al. [12].

2.5. Statistical analysis

We calculated the rate of sufficient temporal bone windows (cTCCS-MCA) and sufficient foramen magnum windows (cTCCS-VA) for all patients, and compared the sufficient rate of the acoustic windows with age tertiles using Fisher's exact test. We enrolled patients with sufficient both temporal and foramen magnum windows. Then, we calculated the specificity, sensitivity, and accuracy rates of cTCCS-MCA and cTCCS-VA in detecting an RLS according to "gold standard" of PFO diagnosis by cTEE for these patients. The Fisher's exact test was used for cross tables. We analyzed the concordance rate along with the 95% confidence intervals (CI) of RLS detection for cTCCS-MCA and cTCCS-VA with the use of κ statistics. A p value < 0.05 was considered to represent a statistically significant difference. Data were analyzed using SPSS for Windows, version 22.

Written informed consent was obtained from patients and their families to participate in the study, which proceeded in accordance with the Declaration of Helsinki.

3. Results

We enrolled 112 patients (85 males (76%) and 27 females (24%)) during the study period (Fig. 1). Table 1 shows the baseline characteristics. The mean age was 59 years (age range, 26–82 years), 18 (16%) patients had TIA, and 94 (84%) patients had ischemic stroke. We were unable to classify 47 of the 94 (50%) stroke patients according to the previously mentioned categories (Table 1).

Table 1
Patient characteristics.

Clinical data	Value
Total no. of patients	112
Male[a]	85 (76)
Age (y)	
Mean	59
Range	26–82
Vascular risk factors[a]	
Hypertension	69 (62)
Dyslipidemia	51 (46)
Diabetes mellitus	33 (29)
Atrial fibrillation	9 (8)
Smoking	74 (66)
Diagnosis[a]	
Transient ischemic attack	18 (16)
Ischemic stroke	94 (84)
Pathologic mechanism of ischemic stroke (n = 94)[b]	
Large artery atherosclerosis	5 (5)
Small-vessel occlusion	14 (15)
Cardioembolism	13 (14)
Other	16 (17)
Undetermined cause	47 (50)

[a] Data are numbers of patients, and numbers in parentheses are percentages.
[b] Pathologic mechanism is assessed by ischemic stroke patient number, and numbers in parentheses are percentages.

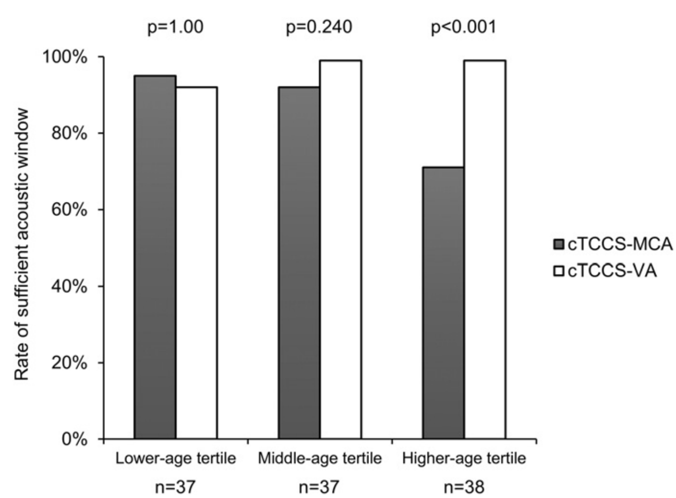

Fig. 4. Rates of sufficient acoustic windows in stratified age tertiles. With higher age, the rate of sufficient temporal bone windows decreased, while the rate of sufficient foramen magnum windows increased. The foramen magnum windows in the higher-age tertile were significantly more sufficient than the temporal bone windows (100% vs. 71%, p < 0.001). Gray bar: cTCCS-MCA (temporal bone window); white bar: cTCCS-VA (foramen magnum window). cTCCS-MCA, contrast transcranial color-coded sonography of middle cerebral artery monitoring (temporal bone window); cTCCS-VA, contrast transcranial color-coded sonography of vertebral artery monitoring (foramen magnum window).

Table 2
Comparison between cTCCS-MCA via the temporal bone window and cTEE.

		cTEE		
		No PFO (0 microbubble)	Small PFO (1–29 microbubbles)	Large PFO (≧30 microbubbles)
cTCCS-MCA	RLS− (no microembolic signal)	47	18	4
	RLS+ (≧1 microembolic signal)	9	6	10

Note: Small or large PFO discriminating from no PFO when cTCCS-MCA detects RLS: specificity 42% (95% CI, 31–51%), sensitivity 84% (95% CI, 77–90%), accuracy 67% (95% CI, 58–75%). Large PFO discriminating from no or small PFO: specificity 71% (95% CI, 48–88%); sensitivity 81% (95% CI, 77–84%), accuracy 80% (95% CI, 73–85%).
cTCCS-MCA, contrast transcranial color-coded sonography of middle cerebral artery monitoring; cTEE, contrast transesophageal echocardiography; RLS, right-to-left shunt; PFO, patent foramen ovale.

In the 112 patients, the overall incidence of PFOs was 36% when using cTEE. The rate of sufficient temporal bone windows was lower than that of the foramen magnum windows (96 of 112, 85% on temporal bone vs. 109 of 112, 97% on foramen magnum) despite no statistical significant difference ($p = 0.373$). After we classified the patients into age tertiles (lower-age tertile: 26–52 years; middle-age tertile: 53–65 years; higher-age tertile: 66–82 years), the rate of sufficient temporal bone windows gradually decreased as their age advanced (Fig. 4). The foramen magnum windows in the higher-age tertile were significantly more sufficient than the temporal bone windows (100% vs. 71%) ($p < 0.001$). In regard to patients having only a sufficient foramen magnum window (i.e., no temporal bone window), cTCCS-VA was able to detect an RLS in 2 of 15 patients (13%) (Fig. 1).

After we had registered 94 patients with sufficient temporal bone and foramen magnum windows, we analyzed the diagnostic accuracy of RLS for cTCCS-MCA and cTCCS-VA (Fig. 1). cTEE detected a small PFO (1–29 microbubbles) in 24 patients and a large PFO (≥30 microbubbles) in 14 patients (totaling 40%), whereas cTCCS-MCA and cTCCS-VA detected an RLS (≥1 MES) in 25 patients (27%) and 20 patients (21%), respectively. The sensitivities of RLS diagnosis using cTCCS-MCA and cTCCS-VA were sufficiently high in our series (Tables 2 and 3), and there was moderate concordance of RLS diagnosis between cTCCS-MCA and cTTCS-VA ($\kappa = 0.45$, 95% CI, 0.23–0.62). When discriminating large PFOs from small or no PFOs, the RLS diagnostic accuracy of cTCCS-MCA and cTCCS-VA increased, and the concordance of RLS diagnosis between cTCCS-MCA and cTCCS-VA improved significantly ($\kappa = 0.88$, 95% CI, 0.64–0.97).

4. Discussion

We evaluated the presence of RLS in stroke patients because paradoxical brain embolisms due to RLS are one of the most important mechanisms of cryptogenic strokes. Because the prevalence of paradoxical brain embolisms in the elderly is similar to that in young patients [13], we should pay attention to detecting an RLS in elderly as well as young patients in order to investigate the mechanism of stroke. Interestingly, our finding that the rate of sufficient temporal bone windows decreases in elderly subjects is in line with a previous report by Itoh et al. [14] Actually, by using cTCCS-VA, we were able to detect RLS in 13% of patients without sufficient temporal windows. Therefore, we consider that cTCCS-VA should play an important role in detecting RLS, especially in elderly stroke patients.

cTCCS-VA and cTCCS-MCA are useful for RLS detection in subjects with both sufficient temporal bone and foramen magnum windows. Our results are partially in concordance with previous reports of contrast transcranial Doppler (cTCD)-MCA and cTCD-VA [15]. However, cTCCS allows more accurate location of the VA as compared with TCD, because the sonographer is better able to recognize anatomic landmarks and the spatial course of the arteries as color flow images, which is helpful for vessel identification. When a less experienced sonographer conducts TCD, precise evaluation for tortuous and hypoplastic intracranial vertebral arteries may be difficult [16]. If applicable, we recommend that RLS should be detected using cTCCS-VA instead of cTCD-VA.

The specificity and accuracy increased in cTCCS-MCA and cTCCS-VA after analysis of the diagnostic large PFO subgroup. This finding is in line with a previous report by Kobayashi et al. [17] It is clinically important to detect large PFOs, which are associated with stroke recurrence in patients with paradoxical brain embolisms [18]. Thus, we should initially conduct cTCCS for cryptogenic stroke patients, instead of the relatively invasive cTEE.

Our study has several limitations. First, the relatively small number of study subjects might have been a factor in the incidence of large PFOs. Second, stroke patients with severe neurological deficits who were unable to undergo cTEE were not enrolled in our series. Finally, 4 expert sonographers were unable to independently and blindly perform cTEE after cTCCS.

In conclusion, cTCCS has potential for RLS detection, and cTCCS-VA should be performed first in order to evaluate the stroke mechanism in elderly patients.

Conflicts of interest

The authors declare that they have no conflict of interest.

Table 3
Comparison between cTCCS-VA via the foramen magnum window and cTEE.

		cTEE		
		No PFO (0 microbubble)	Small PFO (1–29 microbubbles)	Large PFO (≧30 microbubbles)
cTCCS-VA	RLS− (no microembolic signal)	51	19	4
	RLS+ (≧1 microembolic signal)	5	5	10

Note: Small or large PFO discriminating from no PFO when cTCCS-VA detects RLS: specificity 40% (95% CI, 29–46%), sensitivity 91% (95% CI, 84–96%), accuracy 70% (95% CI, 62–76%). Large PFO discriminating from no or small PFO: specificity 71% (95% CI, 49–87%), sensitivity 88% (95% CI, 84–90%), accuracy 85% (95% CI, 78–90%).
cTCCS-VA, contrast transcranial color-coded sonography of vertebral artery monitoring; cTEE, contrast transesophageal echocardiography; RLS, right-to-left shunt; PFO, patent foramen ovale.

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None.

References

[1] S.N. Konstadt, E.K. Louie, S. Black, T.L. Rao, P. Scanlon, Intraoperative detection of patent foramen ovale by transesophageal echocardiography, Anesthesiology 74 (1991) 212–216.

[2] D.C. Fisher, E.A. Fisher, J.H. Budd, S.E. Rosen, M.E. Goldman, The incidence of patent foramen ovale in 1, 000 consecutive patients. A contrast transesophageal echocardiography study, Chest 107 (1995) 1504–1509.

[3] M. Di Tullio, R.L. Sacco, A. Gopal, J.P. Mohr, S. Homma, Patent foramen ovale as a risk factor for cryptogenic stroke, Ann. Intern. Med. 117 (1992) 461–465.

[4] A.C. Pearson, A.J. Labovitz, S. Tatineni, C.R. Gomez, Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology, J. Am. Coll. Cardiol. 17 (1991) 66–72.

[5] E.K. Louie, S.N. Konstadt, T.L. Rao, P.J. Scanlon, Transesophageal echocardiographic diagnosis of right to left shunting across the foramen ovale in adults without prior stroke, J. Am. Coll. Cardiol. 21 (1993) 1231–1237.

[6] W.K. Blersch, B.M. Draganski, S.R. Holmer, H.J. Koch, F. Schlachetzki, U. Bogdahn, et al., Transcranial duplex sonography in the detection of patent foramen ovale, Radiology 225 (2002) 693–699.

[7] R. Belvis, R.G. Leta, J. Marti-Fabregas, D. Cocho, F. Carreras, G. Pons-Llado, et al., Almost perfect concordance between simultaneous transcranial Doppler and transesophageal echocardiography in the quantification of right-to-left shunts, J. Neuroimaging 16 (2006) 133–138.

[8] H.P. Adams Jr., B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, et al., Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment, Stroke 24 (1993) 35–41.

[9] T. Tsuchiya, M. Yasaka, T. Yamaguchi, K. Kimura, T. Omae, Imaging of the basal cerebral arteries and measurement of blood velocity in adults by using transcranial real-time color flow Doppler sonography, Am. J. Neuroradiol. 12 (1991) 497–502.

[10] M. Kaps, G. Seidel, T. Bauer, B. Behrmann, Imaging of the intracranial vertebrobasilar system using color-coded ultrasound, Stroke 23 (1992) 1577–1582.

[11] M.A. de Belder, L. Tourikis, G. Leech, A.J. Camm, Risk of patent foramen ovale for thromboembolic events in all age groups, Am. J. Cardiol. 69 (1992) 1316–1320.

[12] L. Cabanes, J. Coste, G. Derumeaux, X. Jeanrenaud, C. Lamy, M. Zuber, et al., Interobserver and intraobserver variability in detection of patent foramen ovale and atrial septal aneurysm with transesophageal echocardiography, J. Am. Soc. Echocardiogr. 15 (2002) 441–446.

[13] M. Handke, A. Harloff, M. Olschewski, A. Hetzel, A. Geibel, Patent foramen ovale and cryptogenic stroke in older patients, N. Engl. J. Med. 357 (2007) 2262–2268.

[14] T. Itoh, M. Matsumoto, N. Handa, H. Maeda, H. Hougaku, H. Hashimoto, et al., Rate of successful recording of blood flow signals in the middle cerebral artery using transcranial Doppler sonography, Stroke 24 (1993) 1192–1195.

[15] M. Del Sette, L. Dinia, D. Rizzi, A. Sugo, B. Albano, C. Gandolfo, Diagnosis of right-to-left shunt with transcranial Doppler and vertebrobasilar recording, Stroke 38 (2007) 2254–2256.

[16] J. Krejza, R.W. Baumgartner, Clinical applications of transcranial color-coded duplex sonography, J. Neuroimaging 14 (2004) 215–225.

[17] K. Kobayashi, Y. Iguchi, K. Kimura, Y. Okada, Y. Terasawa, N. Matsumoto, et al., Contrast transcranial Doppler can diagnose large patent foramen ovale, Cerebrovasc. Dis. 27 (2009) 230–234.

[18] T. Fukuoka, T. Dembo, H. Nagoya, Y. Kato, O. Yasuko, I. Deguchi, et al., Factors related to recurrence of paradoxical cerebral embolism due to patent foramen ovale, J. Neurol. 259 (2012) 1051–1055.