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Transorbital Doppler with carotid siphon monitoring detects right-to-left shunt effectively

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ABSTRACT

Background: Transtemporal Doppler (TTD) with middle cerebral artery (MCA) is widely used for right-to-left shunt (RLS) detection. However, an alternative method for patients without suitable temporal bone windows should be established. The present study prospectively evaluated the effectiveness of transorbital Doppler (TOD) with carotid siphon (CS) monitoring in detecting RLS.

Methods: A total of 357 subjects with sufficient temporal bone windows underwent simultaneous TTD with MCA and TOD with CS. After injection of microbubbles, the numbers of artificial high-intensity signals were recorded at rest and after Valsalva maneuver.

Results: TOD with CS detected RLS in 146 patients. Sensitivity was 97.1%, specificity 95%, positive predictive value 92.5%, and negative predictive value 98.1%. The total positive rates for RLS detection by CS (40.9%) and MCA (37.8%) monitoring were comparable without significant difference, but TOD with CS detected significantly more grade 2 and 3 RLS than TTD with MCA (p = 0.001). The RLS rates of cryptogenic stroke patients was significantly higher than that of healthy controls, and RLS in cryptogenic stroke was remarkably higher than that in transient ischemia attack patients ($p < 0.05$). TOD with CS examined significantly more grade 2 and 3 RLSs than the MCA approach in the cryptogenic stroke patients ($p = 0.037$).

Conclusion: TOD with CS monitoring is able to detect RLS effectively in different populations including healthy subjects, cryptogenic stroke, transient ischemia attack, and migraine patients. In comparing to the TTD with MCA approach, TOD with CS monitoring could detect comparable rate of RLS, but more high grades of RLS.

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Transtemporal Doppler (TTD); middle cerebral artery (MCA); transorbital Doppler (TOD); carotid siphon (CS); right-to-left shunt (RLS); cryptogenic stroke

Background

High-degree right-to-left shunt (RLS) has been demonstrated to increase the risk of cryptogenic stroke [1–3], recurrent stroke [4–6], the number of silent ischemic brain lesions in divers [6], migraine with aura [7–9], and cerebral decompression sickness [10]. Patent foramen ovale (PFO) is considered as the most common cause of RLS. Percutaneous or surgical closure of PFO has been reported to decrease the recurrent ischemic strokes [11,12], improve migraine symptoms [13], and decrease the number of decompression cerebral ischemic events [14]. These facts further support the positive relation between high-degree RLS and the aforementioned pathologies.

Transesophageal echocardiography (TEE), contrast-enhanced transthoracic echocardiography (c-TTE), and contrast-enhanced transcranial Doppler (c-TCD) are the common methods to diagnose RLS. TEE is considered the ‘gold standard’ in RLS detection in clinic. However, TEE is semi-invasive and is not feasible in uncooperative patients. Swallowing a thumb-thick tube for TEE is uncomfortable, and sometimes necessitates sedation, both hamper the proper performance of Valsalva maneuver (VM). c-TTE has been reported with low sensitivity in RLS detection [15], and does not provide information on intracranial vessels thus have limited application in neurological clinics. The non-invasive transtemporal Doppler (TTD) with middle cerebral artery (MCA) has been widely used as a reliable screening method in detecting RLS [15,16]. However, one of the recognized limitations of TTD is the poor insonation through temporal window, particularly in women and older adults [17]. In stroke patients, the missing of transcranial bone window happens in 10–20% of population [18], especially in elders. Hu et al., reported in their study [19] that poor transtemporal acoustic window was found in 47.6% (female 66.6%) of the volunteers age 60 or older, and 17.2% (female, 33.3%) of the ones younger than 60. Furthermore, people of Asian origin and blacks have worse insonation rates through temporal windows

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than whites [20], leads to a more frequent failure in TTD examination.

The transorbital, transforaminal, and submandibular approaches have all been described as alternative acoustic windows to the transtemporal window. The basilar [21,22], or vertebrobasilar [23] transforaminal approach was shown to have good specificity in detecting and grading RLS, but has less sensitivity than TTD. Moreover, transforaminal bone windows can also be insufficient, especially in older patients. The submandibular approach in monitoring extracranial internal carotid artery (ICA) and vertebral artery (VA) could overcome the problem of insufficient cranial bone windows, and was found to be comparable to the transtemporal approach in detecting the artificial high-intensity signals (HITS) in RLS [24]. However, the ICA monitoring encountered high swallowing artifacts (7.8%) [24]. Transorbital approach is used for insonation of distal ICA, mainly ophthalmic artery and carotid siphon (CS), and this window can be reliably insonated in all patients. CS is an S-shaped part of ICA, and the tortuous appearance with 1 going beyond a 180° bend has little interindividual variance [25], which makes it easy to identify and track by non-experts. Although transcranial Doppler (TCD) remains operator-dependent, TCD through the orbital window was evaluated as an easy test to perform [26]. In addition, TCD monitoring of ICA was considered a possible alternative to MCA monitoring [24,27]. The current study was aimed to assess the performance of transorbital Doppler (TOD) with CS for RLS detection and grading in comparing with simultaneous TTD with MCA.

Materials and methods

Participants

From January to December 2015, we prospectively evaluated 411 consecutive subjects from the Department of Neurology at our hospital for RLS detection. These include 80 healthy volunteers who received routine annual check-up at our hospital and do not have any presentations of neurological symptoms, and 331 patients with neurological diseases or symptoms (cryptogenic stroke, transient ischemic attack, migraine, and dizziness). Among the 331 patients, those who were unable to perform the standard Valsalva maneuver (VM) because of severe heart or lung disease, or cognitive or coordination impairment ($n = 25$) were excluded from our study. Patients who were examined with insufficient transtemporal window were excluded from the study ($n = 29$). 277 patients and the 80 healthy volunteers were enrolled and underwent TOD with CS and TTD with MCA monitoring simultaneously. The inclusion criteria for cryptogenic stroke patients were: (1). Diagnosed with ischemic stroke under WHO diagnostic criteria, and confirmed by CT/MRI; (2). Classified as the subtype of stroke of undetermined etiology in the TOAST system. The study procedure was approved by the ethics committee of Luoyang Central Hospital Affiliated to Zhengzhou University, and all participants provided written informed consent.

TOD and TTD protocol

The examinations were performed using the M-mode of EMS-9UA transcranial Doppler detector (Delica Inc, Shenzhen, China), and both right CS and MCA were monitored simultaneously. All participants were examined in left lateral decubitus and were asked to keep quiet and not to move their head. An 18-gage needle was inserted into patients' cubital vein. Mean flow velocity of the right MCA was recorded with a monitoring probe mounted in the head frame and placed on the right temporal window. The probe is placed above the zygomatic arch and anterior to the ear where the thinnest section of the squamous portion of the temporal bone is. The other probe (1.6 MHz) was simultaneously and manually positioned on the closed right eyelid for CS monitoring with the following attentions were paid when performing the procedure: (1). applied a sufficient amount of gel on the closed eyelid to minimize mechanical pressure, (2). instructed the subjects to turn their eyes away from the probe during the test and placed the probe on the lateral or superior orbital rim. No pressure was exerted onto the eye, and the acoustic amplitude is reduced to 10% of its original transmitting power for a safe but adequate visualization. The elbow joint of the operator's upper limb was fixed to not move to avoid probe movement. Doppler velocity analysis and compression tests allowed us to identify both arteries. Once the MCA and CS signal were confirmed by the carotid compression test, the positions of probes were registered. Initiating the registration from beginning and prolonging the registration until the end of monitoring were adopted to prevent movement distortion artifacts. A small sample volume of 8 mm in length and a low gain setting allowed discriminating signals from the background spectrum. The depth of monitoring was 40–55 mm and 65–70 mm for MCA and CS, respectively. After training patients on the VM, the test was performed at rest and during the VM twice, the strength of which was measured by the peak of the Doppler flow velocity curve. Artificial high-intensity signals (HITS) were produced according to a standard protocol: 9 mL/isotonic saline mixed with 1 mL/air (emulsified with blood) injected after 20 mixes as a bolus into the right cubital vein (three-way stopcock connector). VM started 5s after the injection, and lasted for 10s. A reduction during the VM of at least 30% of the mean blood flow velocities was considered as efficient and was reached in all patients.

The monitored Doppler spectra were stored, and the artificial HITS were analyzed auditory and measured visually according to the consensus four-level categorization [28]: Negative –No HITS. Grade 1 –1-10 HITS. Grade 2 – >10 HITS but no curtain effect. Grade 3 – Curtain effect (shower of HITS which does not allow to distinguish and to count them). The maximum number of HITS in each case (i.e. either during normal breathing or during the VM) recorded in the MCA was taken as the estimate of shunt extent in the MCA. Estimates of shunt extent in the CS were obtained the same way. Tests were performed consecutively; each test required approximately 3 min, and there was an interval of at least 5 min between tests. Two experienced ultrasound technologists were designated to assess the respective shunt extent of the MCA and CS in all subjects. The four-level categorization according to HITS count has been used to estimate the size of PFO [28], i.e. 1–10 microbubbles (grade 1) – small PFO; >10 microbubbles (grade 2 and 3) – large PFO.

Statistical analysis

Statistical analysis was performed with SPSS 21.0 software (SPSS Inc., Chicago, IL, U.S.A.). The chi-square test with Bonferroni correction was used to compare positive rates of RLS detection. McNemar's test was used to compare RLS detection between CS and MCA monitoring. Bowker's test was used for comparisons of the shunt extents between CS and MCA. Statistical significance was set at $p < 0.05$.

Results

In total, both TOD with CS and TTD with MCA monitoring were recorded for 357 participants (192 men, 165 women) aged 25–70 years (mean age, 52.5 ± 7.6 years), including 183 with cryptogenic stroke (51.3%), 38 with transient ischemic attack (10.6%), 32 with migraine (8.9%), 24 patients presenting with dizziness (6.7%), and 80 healthy subjects without any symptoms (22.4%) (Table 1). The age and gender were not different among different groups ($p > 0.05$).

Table 1. Demographic and clinical characteristics of the participants underwent simultaneous transtemporal Doppler (TTD) with middle cerebral artery (MCA) and transorbital Doppler (TOD) with carotid siphon (CS) monitoring.

Disease or Symptoms	Age (Yr)	Gender (M/F)	Smoking history	Alcohol history
Healthy subjects (*n* = 80)	56.4 ± 7.7	43/37	21 (26.25%)	13 (16.25%)
Cryptogenic stroke (*n* = 183)	53.4 ± 6.4	96/87	56 (30.60%)	32 (17.49%)
Transient ischemic attack (n=38)	52.0 ± 6.7	21/17	11 (28.95%)	7 (18.42%)
Dizziness (*n* = 24)	49.6 ± 7.1	14/10	7 (29.16%)	4 (16.67%)
Migraine (*n* = 32)	50.7 ± 6.2	14/18	9 (28.12%)	7 (21.88%)
F/χ^2	1.256	1.473	0.710	0.536
P	0.532	0.831	0.950	0.970

Positive rate and degree of RLS detection in all subjects

At rest, positive rates for RLS detection in MCA and CS monitoring were 15.7% and 17.9%, respectively, and during VM testing, the positive rates in MCA and CS monitoring were 38.9 and 40.9%, respectively. There were no significant difference between the MCA and CS monitoring (Table 2) ($P > 0.05$, for both conditions). Taken the MCA measurement as the standard, the sensitivity (97.1%) and specificity (95%) of CS monitoring were both high. The positive prediction value was 92.5%, and negative prediction value was 98.1%. Grade 3 RLSs were detected in 8.9 and 10.9% of the 357 patients who underwent the MCA and CS monitoring, respectively. Grade 2 RLSs were detected in 8.1 and 10.1% patients in MCA and CS monitoring, respectively. The CS monitoring approach detected significantly more high grades RLS (grade 2 + 3) than the MCA monitoring ($p = 0.001$) (Figure 1). When discarding patients who with both approaches had no-HITS or 'curtain' effects, Pearson's correlation between the number of HITS of MCA and CS was highly significant at rest ($r = 0.747$; $p < 0.01$) and after VM ($r = 0.865$; $p < 0.01$).

Positive rate and degree of RLS detection in cryptogenic stroke patients

In the cryptogenic stroke patients, the positive rates for RLS detection in MCA and CS monitoring were 20.8 and 22.4% at rest, and 49.2% vs. 51.4% during VM testing ($P > 0.05$, for both conditions). The sensitivity (97.8%) and specificity (91.6%) of CS monitoring were both high. The positive prediction value was 93.6%, and negative prediction value was 97.8%. In comparing with health controls ($n = 80$), the positive RLS rate of the cryptogenic stroke patients under VM condition was significantly higher (49.5% vs. 17.5%, $\chi^2 = 23.37$, $p < 0.001$). Grade 3 RLSs were detected in 8.2 and 14.3% of the 183 patients who underwent the MCA and CS monitoring, respectively. Grade 2 RLSs were 10.4% and 9.3% for each approach. The CS monitoring detected significantly more high grade RLSs than the MCA approach ($p = 0.037$). Pearson's correlation between the number of HITS of MCA and CS was highly significant at rest ($r = 0.756$; $p < 0.05$) and after VM ($r = 0.813$; $p < 0.05$).

Comparison of the RLS positive rate between the healthy control, cryptogenic stroke, migraine and transient ischemia attack groups

As shown in Table 3, the positive rates of RLS detection in healthy control, cryptogenic stroke, transient ischemia attack, migraine and dizziness groups were 17.5%

(14/80), 49.2% (90/183), 23.7% (9/38), 37.5% (12/32), and 20.8% (5/24), respectively, under VM condition by the MCA monitoring approach. When performing the χ^2 test for multiple comparisons with Bonferroni correction, the RLS rate of cryptogenic stroke patients was significantly higher than that of healthy controls, and RLS in cryptogenic stroke was remarkably higher than that in transient ischemia attack patients ($p < 0.05$). For each disease group and even the healthy control group, the positive rates for RLS detection had no significant difference between the MCA and CS monitoring at rest

Table 2. Comparison of right-to-left shunt (RLS) detection rate by transtemporal Doppler (TTD) with middle cerebral artery (MCA) and transorbital Doppler (TOD) with carotid siphon (CS) monitoring, in all subjects.

Rest condition		CS	
		Positive (17.9%)	Negative
MCA	Positive (15.7%)	51	5
	Negative	13	288
VM testing		CS	
		Positive (40.9%)	Negative
MCA	Positive (38.9%)	135	4
	Negative	11	207

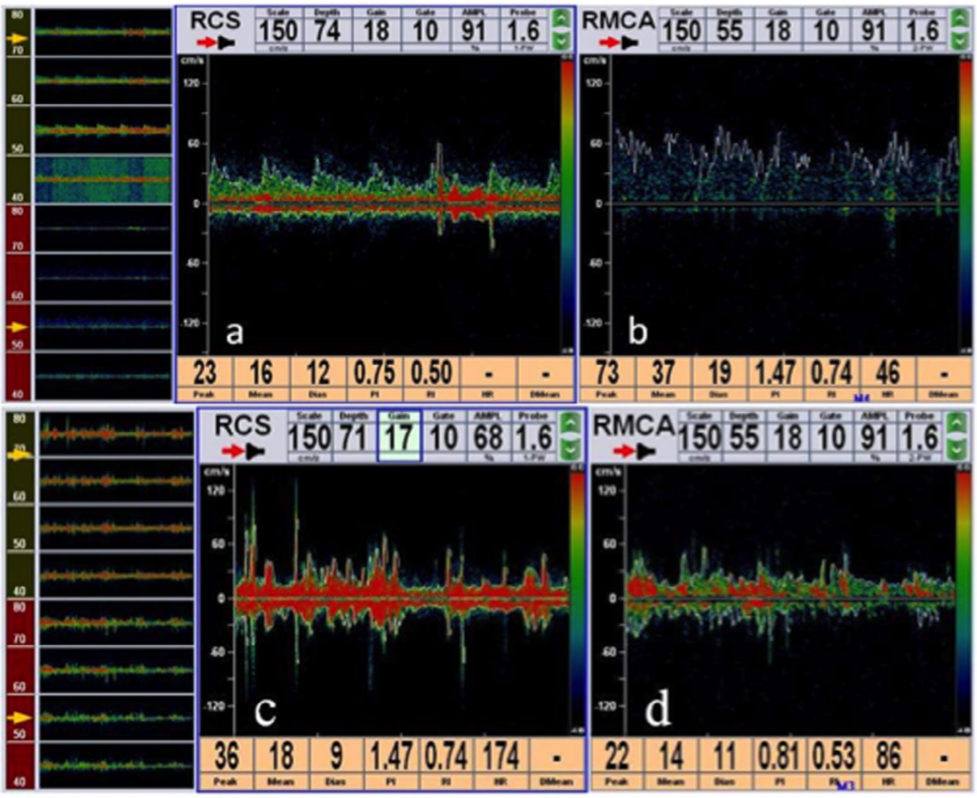

Figure 1. Representative HITS spectras detected by TTD with right MCA (RMCA) and TOD with right CS (RCS) on same patients. (a). Grade 1 RLS detected by TOD with CS approach on patient 1, (b). Grade 0 RLS detected by TTD with MCA approach on patient 1, (c). Grade 3 RLS detected by TOD with CS approach on patient 2, (d). Grade 2 RLS detected by TTD with MCA approach on patient 2.

Table 3. Comparison of the right-to-left shunt (RLS) rate using the transtemporal Doppler (TTD) with middle cerebral artery (MCA) monitoring approach under VM condition.

	Healthy controls	Cryptogenic stroke	Transient ischemic attack	Migraine	Dizziness
RLS positive	14	90	9	12	5
RLS negative	66	93	29	20	19
Total	80	183	38	32	24
Overall chi-sq test χ^2			30.433		
P			0.000		

Chi-Sq pairwise multiple comparison	1 vs. 2	1 vs. 3	1 vs. 4	1 vs. 5	2 vs. 3	2 vs. 4	2 vs. 5	3 vs. 4	3 vs. 5	4 vs. 5
χ^2	23.369	0.296	5.129	0.137	8.271	1.490	6.866	1.579	0.068	1.802
Bonferroni adjusted *P*	0.01	0.587	0.24	0.711	0.04	0.222	0.09	0.209	0.794	0.179

Notes: 1: Healthy controls; 2: Cryptogenic stroke; 3: Transient ischemic attack; 4: Migraine; 5: Dizziness.

and VM condition. Regarding the sensitivity and specificity of the TOD with CS monitoring approach, the healthy controls (85.7% sensitivity and 92.4% specificity) and the transient ischemia attack group (87.9% sensitivity and 93.2% specificity) were both high when taking the MCA measurement as the standard, and there were no significant difference between the transient ischemic attack patients vs. the control subjects.

Discussion

The novel finding of the present study is that the transorbital approach in monitoring right CS is able to detect RLS with high selectivity and specificity, especially in the cryptogenic stroke and migraine patient populations. There are several advantages of the TOD with CS approach. Firstly, there were no absent orbital windows in our series of patients. Secondly, the CS is easy to identify and track, even during the VM, due to its anatomic characteristics and inter-individual uniformity; although the probe for CS monitoring was manually positioned in our study, it's easy for us to reproducibly position the probe and monitor the CS in all the patients. Thirdly, the left lateral decubitus was optimal for RLS detection, due to the anatomic location of right atrium and PFO, which have less affects on the performance of VM [29–31]; and such position is also convenient for the operation. The limitation on poor insonation through TTD window is difficult to overcome technically [32]. In view of the data that TOD with CS detected comparable rate of RLS as TTD with MCA from our study on 357 subjects, it's appropriate to conclude that TOD with CS is suitable to be an emerging RLS screening method without the problem on missing transcranial bone windows.

We analyzed the RLS detection rates in several populations, i.e. cryptogenic stroke patients (n = 183), migraine patients (n = 32), patients with transient ischemic attack (n = 38) or dizziness (n = 24), and healthy volunteers (n = 80). RLS positive was detected in ~50% of the cryptogenic stroke patients and ~38% of migraine patients, with comparable detection rates by both TTD and TOD monitoring approaches. The RLS positive rates are significantly higher than that in the healthy subjects, which is ~18% in our study. However, patients with transient ischemic attack or dizziness were examined with 20–23% of RLS in our study, and didn't show any difference when comparing with the healthy controls. It has been shown that RLS is associated with increased risk of cryptogenic stroke [1–3] and migraine [7–9], but no established evidence links RLS with transient ischemic attack or dizziness. In patients with cryptogenic strokes, PFO can be detected in more than 50%, whereas its prevalence in the general population is about 25% [33]. Migraine attack is associated with a higher prevalence of PFO than among the general population [34]. The presumed mechanism is paradoxical embolism of venous thrombotic material across the atrial right to left shunt. Although the relationship and relevance of PFO with cryptogenic stroke and migraine are well established, our data on the comparison between the two monitoring approaches confirmed that TOD with CS is a reliable method in detecting RLS in different populations.

We noticed that the TOD with CS approach examined more grade 2 and 3 RLSs than the TTD with MCA approach, and even in the same patient, the CS monitoring detected more HITS than the MCA monitoring (Figure 1). This detection discrepancy may due to two anatomic properties of CS, (1). CS bifurcates into anterior cerebral artery (ACA) and MCA, which leads to the split-flow of microbubbles from CS into ACA and MCA, thus the microbubbles flow though MCA may be less than those of CS; (2). the S shape of CS leads to a distinct reduction of vessel pulsatility and flow velocity of this section [25], which may reduce the background noise and enable a better resolution of the detection. However, the HITS numbers between CS and MCA monitoring were highly correlated in our study, indicating a similar clinical significance of CS monitoring in HITS detection. Large PFO has been shown to present in a higher proportion of patients with cryptogenic stroke [2]. Our study enrolled 183 cryptogenic stroke patients; the CS monitoring detected about 25% patients with large PFO among those with RLS. This result is concordant with a recent report [35], and indicates the effectiveness of this approach in clinic application.

Same as previously reported, our study also approved that the TOD approach is safe for the eye [19,36–38]. There were no complications or adverse effects occurred in our study patients. In addition to detect RLS, the TOD approach has been validated as a valid alternative to TTD for detecting microembolic signals in patients with no suitable temporal acoustic window [39]. So this approach could be applied more broadly in clinic as an alternative to the TTD approach in RLS and microemboli screening in subjects with poor transcranial bone windows.

Limitations

Although the TOD with CS approach examined more grade 2 and 3 RLSs than the TTD with MCA approach, the international consensus on RLS grading is based on microbubble detection in MCA but not other vessels in considering the hemodynamics variance among different vessels [28]. Thus, this grading criteria is not applicable to the CS monitoring. In addition, the 'gold standard' TEE approach was not applied to confirm the RLS and measure the size of PFO, which warrants future studies to justify the clinical application of the TOD approach.

Author contributions

Conceived and designed the study: ZD, ZY and JL.

Performed the study: ZD, BS, CM, YL.
Analyzed the data: ZD, YD, DS, SL.
Wrote the paper: ZD and JL.

Disclosure statement

No potential conflict of interest was reported by the authors.

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