

Original Article

Advantages of contrast-enhanced transcranial doppler conducted via two-channels, compared to a single-channel

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Received November 16, 2018; Accepted March 13, 2019; Epub June 15, 2019; Published June 30, 2019

Abstract: The purpose of the current study was to evaluate the advantages of contrast-enhanced transcranial doppler (c-TCD) conducted via two-channel mode, compared to single-channel mode. The parallel test method of diagnostic testing was adopted. Two-channel c-TCD was conducted and interpreted via three different methods, comparing differences between the effects of conducting c-TCD via two-channel mode and single-channel (either left or right) mode. Conditions were set so that the appearance of microbubble signals in either channel was the golden diagnostic criteria for right to left shunts. Diagnostic sensitivity of single-channel c-TCD mode was evaluated. Diagnostic consistencies and positive rates were compared between single-channel and two-channel modes. A total of 242 cases were enrolled in this study. Diagnostic sensitivities of left and right single-channel mode were 77.46% and 76.06%, respectively, under a resting state. They were 95.31% and 96.88%, respectively, after the Valsalva maneuver (VM). Under a resting state, diagnostic consistencies were general between two-channel and left channel modes and between two-channel and right channel modes (Kappa value = 0.740, 0.724, respectively; $P < 0.001$). After VM, both diagnostic consistencies were good (Kappa value = 0.894, 0.928, respectively; $P < 0.001$). After VM, although diagnostic consistencies were good, positive rates of two-channel c-TCD mode were significantly higher than those in both left and right single-channel c-TCD modes (79.34% vs. 75.62%, $P = 0.004$; 79.34% vs. 76.86%, $P = 0.031$; respectively). Two-channel c-TCD mode had higher positive rates than single-channel mode, especially in patients with small right to left shunts or poor coordination of VM.

Keywords: Contrast enhancer, right to left shunt, transcranial doppler

Introduction

Contrast-enhanced transcranial doppler (c-TCD) has been widely applied as a sensitive method for detection of right to left shunts (RLS) [1]. However, there are different ways to conduct c-TCD, in practice. These include detection via vertical or recumbent position, administering contrast enhancers at different time points after the Valsalva maneuver (VM), and detection via single-channel or two-channels. Effects of different body positions and administration times of contrast enhancers have been demonstrated in some studies [2-7]. The consensus concerning RLS detection with transcranial Doppler sonography and contrast agents at the Fourth Meeting of the European Society of

Neurosonology and Cerebral Hemodynamic suggests that c-TCD should be performed bilaterally, if available [8]. However, a lot of clinical ultrasound centers use single-channel c-TCD, simplifying the detection process in practice. One meta-analysis showed no significant differences in positive detection of RLS between c-TCD via unilateral and bilateral middle cerebral arteries [1]. However, in studies cited by this meta-analysis, patients were given contrast enhancers each time they underwent c-TCD in different modes. As the productive effects of contrast enhancers may vary, results of c-TCD may be affected significantly. Moreover, injecting contrast enhancers separately, for different modes, might lead to certain bias. The current study often observed

microbubble (MB) signals appearing only in one channel during the two-channel c-TCD examination. Thus, it remains uncertain whether single-channel or two-channel c-TCDs have different effects for detection of RLS. To answer this question, the current study reviewed cases in which patients received c-TCD via both middle cerebral artery channels. The current study then summarized characteristics of MB signals in the two channels, adopting the parallel test to analyze potential advantages of conducting c-TCD via two-channel mode, compared to single-channel mode.

Materials and methods

Patients

Selected patients underwent c-TCD in Shenzhen People's Hospital, between January 2017 and December 2017.

Inclusion criteria: (1) Underwent two-channel c-TCD; (2) Had ischemic strokes and received c-TCD for detection of RLS; (3) Aged 18 to 45 years old; (4) Bilateral temporal windows were good; (5) Adopted the supine position during c-TCD; (6) Effective VM was conducted; (7) Bilateral middle cerebral arteries were set as the two channels of c-TCD, while depths of distance ≥ 10 mm were set for both channels; and (8) The blood flow spectrum and MB signal could be clearly distinguished on c-TCD images.

Exclusion criteria: (1) c-TCD was performed in a single-channel or single-depth; (2) Either of the temporal windows was poor; (3) The blood flow spectrum and MB signal could not be clearly distinguished on c-TCD images; and (4) Detected to have aortic atheromas and intracardiac tumors or clots via transthoracic echocardiography procedures.

Process and results of c-TCD

The current retrospective study used monitoring probes to conduct two-channel c-TCD under a resting state and after VM. Moreover, c-TCD was conducted on all patients by the same neurologist, with more than 5 years relevant experience. One milliliter of air, 9 mL of normal saline, and one drop of back venous blood were used to constitute the agitated saline solution with blood (ASb). This such solution was used as the

contrast enhancer. It was injected into all patients by the same experienced nurse [9]. The neurologist that performed the c-TCD and the nurse that administered the injections did not participate in data collection and statistical analysis. Mouth pressure gauging was performed by patients reaching 40 mmHg and sustaining for 10 seconds, deemed as indicative of effective VM [10]. When c-TCD was conducted under a resting state, MB signals were counted appearing in the two channels 20 seconds after the elbow vein was injected with ASb. When c-TCD was conducted after VM, VM was performed for 5 seconds after injecting ASb. MB signals appearing in the two channels at 20 seconds after the injection were counted [9]. Results of c-TCD were classified, according to the following criteria: 1) No MB signal as grade I, representing no RLS; 2) 1-10 MB signals appeared in either channel as grade II, representing small RLS; 3) 11-25 MB signals appeared in either channel as grade III, representing medium RLS; 4) More than 25 signals appeared in either channel as grade IV, representing large RLS; and 5) When MB signals of the two channels were not identical, the larger signal count was chosen for classification of results [11].

Study protocol

The current retrospective investigative study was approved by the Ethics Committee of Shenzhen People's Hospital. Informed consent was obtained from enrolled patients or legal relatives before receiving c-TCD. Other related data was extracted for research purposes. Multifunctional transcranial Doppler equipment (Delica MVU-6300, made in China) was used. The lowest recognition threshold for embolus was set at 3 dB. Probe frequency of c-TCD was set at 1.6 MHz. Sampling volume was set at 10-12 and gain was set at 5-18. All enrolled patients received transthoracic echocardiography, carotid artery ultrasonography, and head magnetic resonance angiography procedures. Digital subtraction angiography procedures were performed when necessary.

The parallel test method of diagnostic testing was adopted. For each c-TCD case enrolled, results from two-channel c-TCD were extracted in three different ways, representing the results of three different modes of conducting c-TCD.

Two-channel c-TCD, compared to single-channel

Table 1. Features of MB signals in the two channels of c-TCD under a resting state

		MBs appeared in either LMCA or RMCA (n, %)		Total
		Yes	No	
MBs appeared in LMCA (n,%)	Yes	110 (45.46%)	0	110 (45.46%)
	No	32 (13.22%)	100 (41.32%)	132 (54.54%)
Total (n,%)		142 (58.68%)	100 (41.32%)	242
Kappa value		0.740		
p value of Kappa test		< 0.001		
p value of McNemar test		< 0.001		
		Yes	No	
MBs appeared in RMCA (n,%)	Yes	108 (44.63%)	0	108 (44.63%)
	No	34 (14.05%)	100 (41.32%)	134 (55.37%)
Total (n,%)		142 (58.68%)	100 (41.32%)	242
Kappa value		0.724		
p value of Kappa test		< 0.001		
p value of McNemar test		< 0.001		

Note: MBs: microbubble signal; LMCA: left middle cerebral artery; RMCA: right middle cerebral artery; Contrast-enhanced Transcranial Doppler: c-TCD; n: the number of case.

Table 2. Features of MB signals in the two channels of c-TCD after VM

		MBs appeared in either LMCA or RMCA (n, %)		Total
		Yes	No	
MBs appeared in LMCA (n,%)	Yes	183 (75.62%)	0	183 (75.62%)
	No	9 (3.72%)	50 (20.66%)	59 (24.38%)
Total (n,%)		192 (79.34%)	50 (20.66%)	242
Kappa value		0.894		
p value of Kappa test		< 0.001		
p value of McNemar test		0.004		
		Yes	No	
MBs appeared in RMCA (n,%)	Yes	186 (76.86%)	0	186 (76.86%)
	No	6 (2.48%)	50 (20.66%)	56 (23.14%)
Total (n,%)		192 (58.68%)	50 (20.66%)	242
Kappa value		0.928		
p value of Kappa test		< 0.001		
p value of McNemar test		0.031		

Note: VM: valsalva maneuver.

These included left single-channel mode, in which left middle cerebral artery (LMCA) channels were analyzed, right single-channel mode, in which right middle cerebral artery (RMCA) channels were analyzed, and two-channel mode, in which bilateral middle cerebral artery channels were simultaneously analyzed. Conditions were set such that the appearance of MB signals in either channel was the golden diagnostic criteria for RLS. This parallel test avoided bias derived from injecting contrast

enhancers repetitively three different times. Productive effects of contrast enhancers may vary between different injections, even if injected by the same nurse.

For each enrolled case, this study retrospectively observed the appearance of MB signals in bilateral channels of c-TCD after injection of the contrast enhancer. For left single-channel c-TCD mode and right single-channel c-TCD mode, the appearance of MB signals in the respective single middle cerebral artery channel was defined as the positive result. For two-channel c-TCD mode, the appearance of MB signals in either middle cerebral artery channel was defined as the positive result. Next, this study evaluated whether two-channel c-TCD mode was more likely to detect MB signals than single-channel mode. Furthermore, this study compared diagnostic consistencies and positive rates between single-channel and two-channel c-TCD modes.

Statistical analysis

Related data of cases was extracted by two data collectors, repetitively. The two copies of data were checked by the same data inspector. If there were any unqualified data (based on the exclusion criteria) or inconsistent data, it would be checked, corrected, and removed. SPSS 24.0 was used for statistics analysis. McNemar's test was used to compare positive rates of c-TCD modes and Kappa test was used to evaluate diagnostic consistencies of different c-TCD modes (Kappa value ≥ 0.75 representing good consistency, $0.4 \leq$ Kappa value $<$

Two-channel c-TCD, compared to single-channel

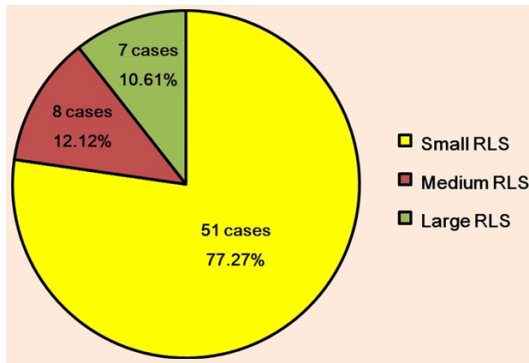


Figure 1. Classification of RLS for patients whose MB signal appeared only in one channel.

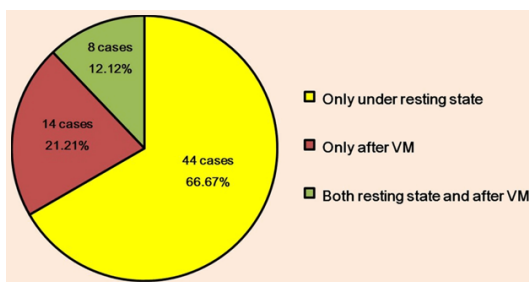


Figure 2. Examination conditions of c-TCD for patients whose MB signal appeared only in one channel.

0.75 representing general consistency, and Kappa value < 0.4 representing poor consistency). Significance level was set at $P < 0.05$.

Results

A total of 242 cases, meeting inclusion criteria, were enrolled. The average age of patients was 35.89 ± 5.23 years.

Under a resting state, 142 cases were positive in two-channel c-TCD mode, 110 cases were positive in left single-channel c-TCD mode, and 108 cases were positive in right single-channel c-TCD mode. Moreover, 100 cases were negative in all three c-TCD diagnostic modes.

Conditions were set such that the appearance of MB signals in either of the two channels was the golden diagnostic criteria for RLS. Under a resting state, diagnostic sensitivity was 77.46% for left single-channel mode and 76.06% for right single-channel mode. Diagnostic consistencies between two-channel c-TCD mode and two single-channel c-TCD modes were all general under a resting state (Kappa value = 0.740

for two-channel mode and left single-channel mode, Kappa value = 0.724 for two-channel mode and right single-channel mode; $P < 0.001$). According to the results of McNemar's test, the positive rate of two-channel c-TCD mode was significantly higher than two single-channel c-TCD modes under a resting state (58.68% vs. 45.46%, $P < 0.001$; 58.68% vs. 44.63%, $P < 0.001$) (Table 1).

After VM, 192 cases were positive in two-channel c-TCD mode, 183 cases were positive in left single-channel c-TCD mode, and 186 cases were positive in right single-channel c-TCD mode. A total of 50 cases were negative in all three c-TCD diagnostic modes. Conditions were set such that the appearance of MB signals in either of the two channels was the golden diagnostic criteria for RLS. After VM, diagnostic sensitivity was 95.31% for left single-channel mode and 96.88% for right single-channel mode. Diagnostic consistencies between two-channel c-TCD mode and two single-channel c-TCD modes were all good after VM (Kappa value = 0.894, 0.928 respectively; $P < 0.001$). Although diagnostic consistency was good, results of McNemar's test showed that the positive rate of two-channel c-TCD mode was still significantly higher than two single-channel c-TCD modes after VM (79.34% vs. 75.62%, $P = 0.004$; 79.34% vs. 76.86%, $P = 0.031$) (Table 2).

Regarding detection of MB signals in all enrolled cases, 66 cases showed MB signals in only one channel, including 34 cases only in LMCA channel and 32 cases only in RMCA channel. In the c-TCD of these 66 cases, 77.27% (51 cases) were small RLS, 12.12% (8 cases) were medium RLS, and 10.61% (7 cases) were large RLS (as shown in Figure 1). Additionally, in the c-TCD of these 66 cases, MB signals appeared only under a resting state for 44 cases, accounting for 66.67%, and only after VM for 14 cases, accounting for 21.21%. Both under a resting state and after VM, MB signals appeared in 8 cases, accounting for 12.12% (as shown in Figure 2). The above results reveal that MB signals appearing only in one middle cerebral artery channel may be more likely to occur under a resting state and for small RLS cases.

In this study, there were 4 cases with severe narrowing of the left carotid artery and 1 case with severe narrowing of the right carotid artery.

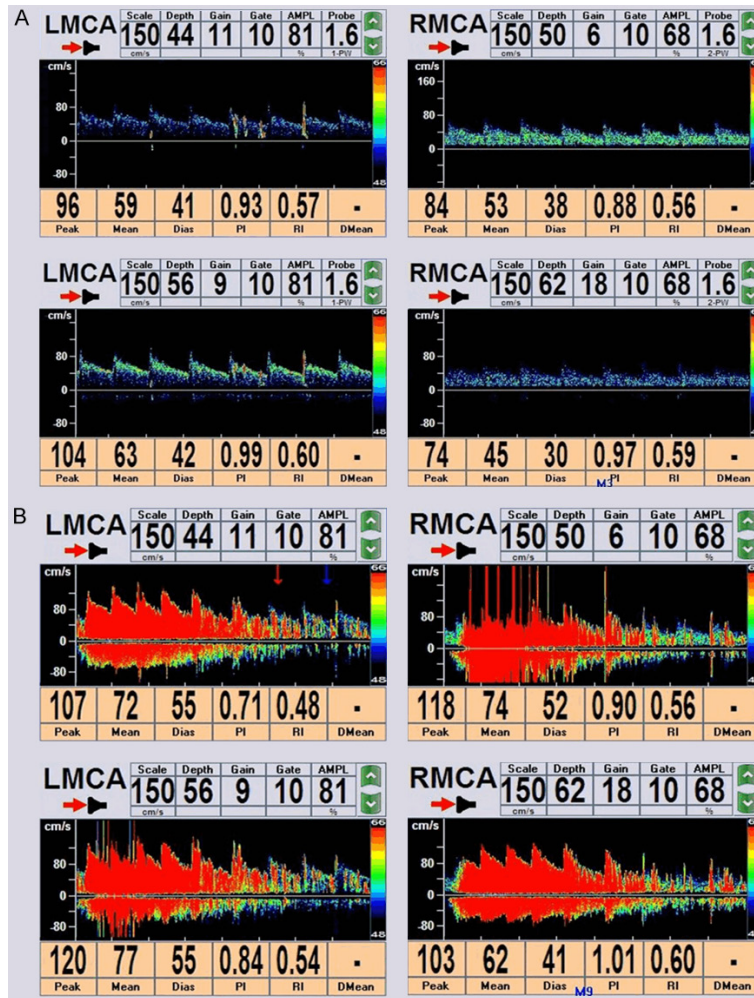


Figure 3. Case 1: (A) 38-year-old male patient with ischemic stroke was conducted two-channel c-TCD. Graph (A) shows 5 MB signals appeared only in LMCA channel under resting state. Graph (B) shows more than 25 MB signals were detected in either middle cerebral artery channels after VM.

Under two-channel c-TCD mode, no MB signals appeared in the channel with severely narrowed carotid arteries on that side for these 5 cases. MB signals did appear in other channels, indicating small RLS either under a resting state or after VM for these 5 cases.

Discussion

RLS is a common etiological mechanism for cryptogenic strokes, young strokes, migraines, syncope, and unexplained vertigo. Thus, it is very important to emphasize positive rates of screening technology for RLS. Positive rates of all c-TCD modes were relatively high for young patients with strokes and suspected to be combined with RLS in this study, using retrospective analysis. This also confirms the importance of c-TCD for detection of RLS.

A previous meta-analysis showed no significant differences in positive detection for RLS between c-TCD via unilateral and bilateral middle cerebral artery [1]. Thus, c-TCD is usually conducted via monitoring single-channel mode for convenience purposes. However, in studies cited by the meta-analysis, patients were given contrast enhancers each time, undergoing c-TCD in different modes. As the productive effects of contrast enhancer may vary and affect results of c-TCD significantly, it was considered that injecting contrast enhancers separately for different modes might lead to certain bias. Furthermore, the Neurological Ultrasound Center conducted c-TCD, adopting bilateral middle cerebral artery channels mode. It was observed that MB signals appeared only in one channel. Thus, it was speculated that single-channel c-TCD mode might miss MB signals that would only appear in the other channels. Thus, positive rates would be reduced for diagnosis of RLS.

This study showed that the positive rate of single-channel

c-TCD mode was significantly lower than two-channel c-TCD mode, both under a resting state and after VM. The main reason might be that RLS was small for some patients. In these cases, the MB induced by RLS could not only be shunted into anterior circulation arteries but also into posterior circulation arteries from subclavian arteries. Thus, when the RLS is small, single-channel c-TCD mode is likely to fail detection. MB might randomly shunt into other undetected arteries. In this study, among cases in which MB signals appeared only in single-channel mode, small RLS accounted for 77.27% (as shown in **Figure 1**), supporting the above hypothesis. VM can open the oval foramen, closed under a resting state, and increase the amount of RLS [12]. In this study, among cases in which MB signals appeared only in one channel, c-TCD conducted under a resting

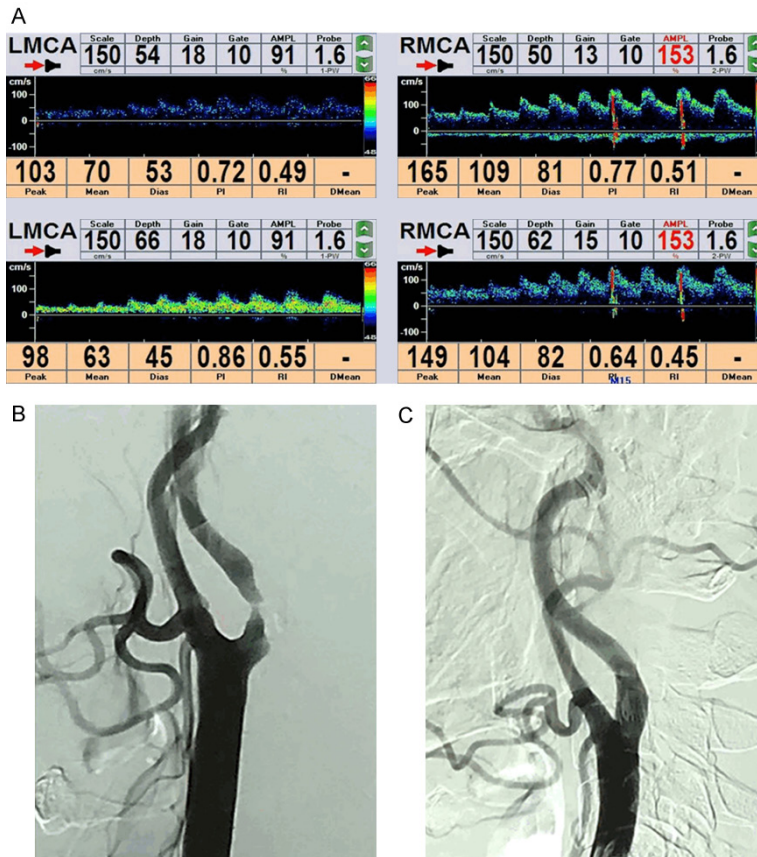


Figure 4. Case 2: (A) 43-year-old male patient with ischemic stroke combined with left severely narrowed internal carotid artery, was conducted two-channel c-TCD. Graph (A) shows in the c-TCD of this case, after VM, no MB signal was detected in the LMCA channel, while 3MB signals were detected in the synchronous RMCA channel. Graph (B) shows left internal carotid artery was severely narrowed. Graph (C) shows right internal carotid artery was normal.

state accounted for 66.67% (as shown in **Figure 2**), confirming the hypothesis. As shown in **Figure 3**, a 38-year-old male patient with ischemic stroke underwent two-channel c-TCD. The 5 MB signals appeared only in the LMCA channel under a resting state. However, more than 25 MB signals were detected in both middle cerebral arteries channels after VM. This case also confirms the above hypothesis.

In addition, in the c-TCD, it was very interesting that, if the carotid artery was severely narrowed on one side, MB signals could not be detected in the middle cerebral artery channel on that side. Small RLS was detected on the normal side at the same time. It was speculated that, if MB passed the severely narrowed carotid artery on one side, it might disintegrate due to mechanical friction or prolonged passing time of blood flow. Thus, it could not be detected in

the middle cerebral artery channel of c-TCD on that side. As shown in **Figure 4**, a 43-year-old male patient with ischemic strokes combined with a severely narrowed left internal carotid artery underwent two-channel c-TCD. The c-TCD of this case after VM showed no MB signals in the LMCA channel. However, 3 MB signals were detected in the synchronous right middle cerebral artery (RMCA) channel. Moreover, c-TCD was conducted mainly for youth ischemic strokes. the number of cases with severely narrowed carotid arteries was limited. Thus, this phenomenon needs further specially-designed studies for examination. To further prove the viewpoint, the current study presented a special case not included in enrolled cases. As shown in **Figure 5**, a 41-year-old male patient with ischemic strokes combined with a severely narrowed left internal carotid artery underwent two-channel c-TCD. The right temporal window of this patient was poor. Thus, c-TCD was performed under resting state via two-

channels, simultaneously, including left common carotid artery and LMCA channels. In the c-TCD, 8 MB signals were detected in the left common carotid artery channel, but no MB signals were detected in the synchronous LMCA channel. This case also confirmed the present hypothesis.

Finally, it was hypothesized that changing intracranial arteries pathway could be a possible cause for MB signals appearing only in one channel of c-TCD. For example, when one side of the internal carotid artery is occluded, the blood flow signal detected on that side of the middle cerebral artery channel may be supplied by the contralateral anterior circulation or the same lateral posterior circulation. Compared to the normal middle cerebral artery, blood flow in the changed middle cerebral artery has an extended path and many small arteries needed

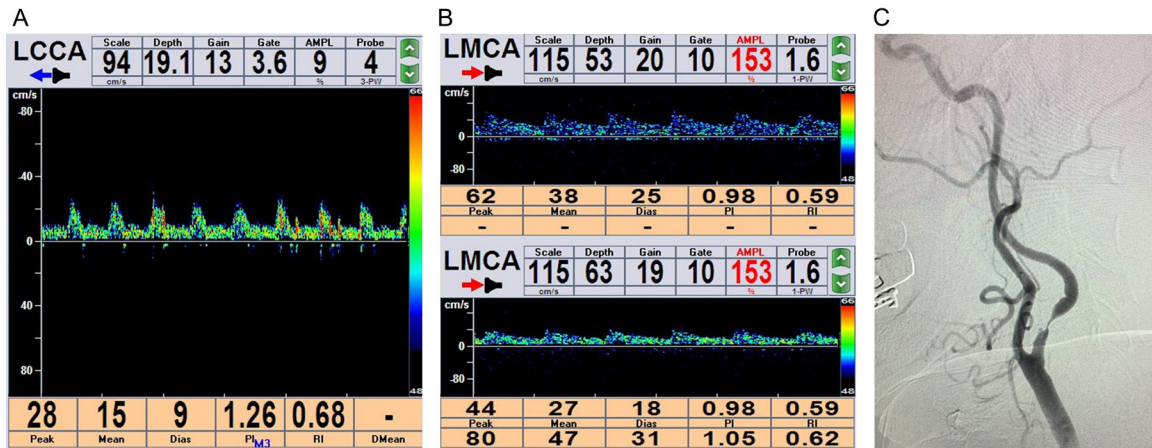


Figure 5. Case 3: This case was not included in enrolled cases. (A) 41-year-old male patient with ischemic stroke combined with left severely narrowed internal carotid artery, for poor right temporal window, c-TCD was conducted under resting state via simultaneous two-channel including left common carotid artery and LMCA channels. Graph (A) shows 8 MB signals were detected in the left common carotid artery channel. Graph (B) shows no MB signal was detected in the synchronous LMCA channel. Graph (C) shows left internal carotid artery was severely narrowed.

to pass through. Thus, the MB might arrive later or may disintegrate before arrival. However, since this study was retrospective, there was no evidence to prove this hypothesis.

In this study, conditions were set such that the appearance of MB signals in either of the two channels was the golden diagnostic criteria for RLS. Diagnostic sensitivity of single-channel c-TCD mode under a resting state was less than 80%. Consistency between single-channel and two-channel c-TCD modes was also moderate. However, after VM, although results had relatively high consistency, the positive rate of two-channel c-TCD mode was significantly higher than single-channel c-TCD mode. Therefore, as a screening technology for RLS, two-channel is superior to single-channel c-TCD.

Conclusion

Two-channel c-TCD mode had higher positive rates than single-channel c-TCD mode for diagnosis of RLS, especially in patients with small RLS or poor coordination on VM. However, given the retrospective nature of this study, most enrolled cases lacked complete data concerning causes and stratification analyses. Future prospective studies and detailed analyses for special cases are necessary, comparing c-TCD with c-TCD, simultaneously, combining contrast-enhanced transthoracic or transesophageal echocardiography procedures.

Acknowledgements

This study was funded by the Medical Research Funding Project of Guangdong Province (item number: A2018176), San Ming Cultivating Funding Project of Shenzhen People's Hospital (item number: SYLY201711), and Science and Technology Innovation Committee Project of Shenzhen (item number: JCYJ201506051034-20338). This study was registered with the Chinese Clinical Research Registry Center (registration number was ChiCTR1800016064).

Disclosure of conflict of interest

None.

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