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Prevalence and extent of right-to-left shunt on contrast-enhanced transcranial Doppler in Chinese patients with migraine in a multicentre case-control study

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Abstract

Background: The association between RLS and migraine is still debated. The aim of this study is to investigate the prevalence and grade of RLS in Chinese patients with migraine and to evaluate the relationship between RLS and migraine.

Methods: A multi-center case-control study of contrast-enhanced transcranial Doppler was conducted in 931 consecutive patients with migraine (240 of 931 had migraine with aura and 691 of 931 were in the migraine without aura group) and 282 were healthy adults. Clinical trial no. NCT02425696.

Results: The prevalence of RLS was 63.8% and 39.9% in the migraine with aura group (MA+) and migraine without aura group (MA−), respectively, significantly higher than that of the healthy group (29.4%, $p < 0.001$; $p < 0.001$). The positive rate of large RLS in the MA+ group and MA− group was 32.1% and 16.5%, respectively, significantly higher than healthy group (6.4%, $p < 0.001$; $p < 0.001$). There was no difference among groups in terms of positive rate of permanent RLS ($p = 0.704$).

Conclusion: This multi-centre case-control study suggested that there is an association between RLS and migraine with and without aura, especially when the shunt is large.

Keywords

Right-to-left shunt, transcranial Doppler, patent foramen ovale, migraine

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Introduction

A right-to-left shunt (RLS) is an abnormal pathway between the venous and arterial circulations, and includes both intracardiac and extracardiac RLSs (1). 1 Intracardiac RLSs are usually related to patent

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foramen ovale (PFO) (2). Contrast-enhanced transcranial Doppler ultrasonography (c-TCD) is a clinically applicable and reproducible method of detecting RLSs, including both intracardiac and extracardiac RLSs.

Migraine is a common disabling neurovascular disorder. It has a high prevalence, 7.9% – 14% (3,4) in the western population and 9.3% in the Chinese population (5), and thus can be a great socioeconomic and personal burden. Moreover, about one-third of migraineurs have an occasional migraine with aura (MA+) (6). The pathogenesis of migraine is not well understood. Available data suggest that PFO is more common in patients with migraine, whereas other studies have reported that the prevalence of RLS is similar in patients with and without migraine (7,8).

The aim of the present study was to assess the prevalence and extent of RLS using c-TCD in Chinese patients with migraine (including migraine with and without aura) and compare them to the prevalence and extent of RLS in healthy controls. We then used these data to evaluate the relationship between RLS and migraine.

Methods

Study design

This multicentre case-control study on RLS in Chinese patients with migraine was performed from June 2015 to August 2016 in nine Chinese hospitals (see Appendix).

Study population

In this multicentre study, we enrolled consecutive participants with migraine aged 18 to 65 years. In total, 931 patients who fulfilled the criteria for migraine according to the International Classification of Headache Disorders III-beta (9) were included. A detailed clinical history was obtained from each patient via face-to-face interviews based on a questionnaire. Patients with migraine were divided into two groups: those without aura (MA−; 691 cases, 521 females, mean age: 40.98 ± 10.90 years) and those with aura (MA+; 240 cases, 174 females, mean age: 40.63 ± 11.25 years). Additionally, 282 healthy volunteers without a history of migraine were included as controls (199 females, mean age: 37.64 ± 11.50 years). Subjects were excluded from the study if they had severe arterial stenosis, an insufficient temporal window, inadequate cubital venous access, and/or were unable to perform the Valsalva manoeuvre (VM) because of severe heart or lung disease. The ethics board at each hospital approved the study (clinical trial no. NCT 02425696; https://clinicaltrials.gov/ct2/archive/NCT02425696). All subjects gave informed consent to participate in the study.

TCD procedure

A baseline TCD examination was performed with a TCD detector (EMS-9A; Delica, China). We used a hand-held 2-MHz probe at the left middle cerebral artery (MCA) with the participant lying comfortably in the supine position. An 18-gauge catheter was placed in the right antecubital vein. The medium was prepared by hand by mixing 9 mL of saline, 1 mL of air, and a drop of the participant's own blood (10). The medium was rapidly mixed back and forth 30 times between two 10-mL syringes that were connected by a three-way stopcock to create microbubbles (MBs). The procedure was performed three times: the first time during normal breathing and then two times during a 10 s VM that started 5 s after the initiation of medium injection (11). The patient was trained to inhale deeply and hold back expiration for 10 s, and then to release it to perform the VM; this corresponds to 15 s after the beginning of the medium injection (12). The highest single count of the number of MBs was taken as the estimate of shunt degree for each patient during two executions of a VM. The efficacy of the VM was identified by a reduction in the mean velocity in the MCA (13). RLS was diagnosed based on the presence of at least one MB during the 20 s c-TCD exam. An interval of at least 5 min from the last observed MB separated each test. An MB was defined sonically as a typical chirping sound, and visually by the presence of a spike-like form within the frequency spectrum and M-mode of the TCD detector.

There are several different categorisation systems for RLSs (11,14–16). Based on the standards reported by Jauss et al. (11), Wessler et al. (14), and Xing et al. (16), we applied a five-level categorisation system according to the appearance of MBs in the TCD spectrum using unilateral MCA monitoring, as follows: grade 0 = negative; grade I = 1 ≤ MBs ≤ 10; grade II = 10 < MBs ≤ 25; grade III = >25 MBs and no curtain; and grade IV = curtain (where a single bubble cannot be identified) (Figure 1). We present the data for small (grade I), moderate (grade II), and large RLSs (grade III and grade IV). RLS was considered provoked if it occurred only after the VM and permanent if it also occurred during rest.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (Chicago, IL, USA). Differences between the groups were analysed using the chi-squared test. Continuous variables were compared with Student's

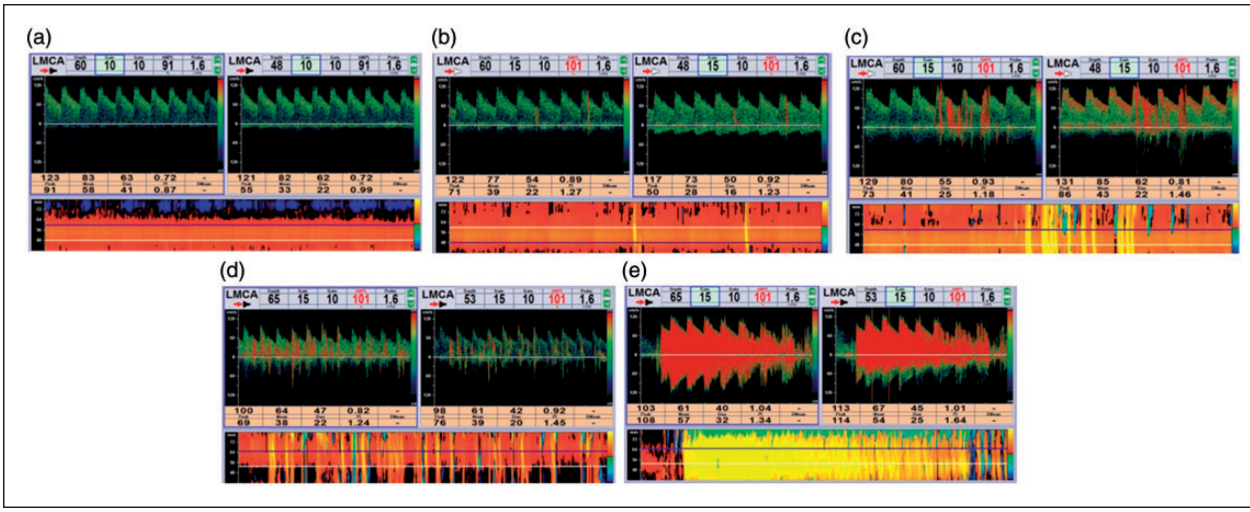

Figure 1. The five-level right-to-left shunt categorisation according to microbubble (MB) count in the contrast-enhanced transcranial Doppler spectrum using unilateral middle cerebral artery monitoring. Grade 0 = negative (a); Grade I = $1 \leq$ MBs ≤ 10 (b); Grade II = $10 <$ MBs ≤ 25 (c); Grade III = >25 MBs and no curtain (d); Grade IV = curtain (where a single bubble cannot be identified) (e).

Table 1. The overall prevalence and prevalence of permanent and provoked right-to-left shunt (RLS) in the migraine with aura group (MA+), migraine without aura group (MA−), and healthy control group.

Group	Overall prevalence of RLS (%/n)	Prevalence of permanent RLS (%/n)	Prevalence of provoked RLS (%/n)
MA+	63.8% (153/240)	60.1% (92/153)	39.9% (61/153)
MA−	39.9% (276/691)	62.0% (171/276)	38.0% (105/276)
Healthy control	29.4% (83/282)	67.5% (56/83)	32.5% (27/83)

t-tests; these variables are expressed as the mean ± the standard deviation. The level of significance was set at $p < 0.05$.

Results

A total of 931 consecutive patients with migraine (236 males, 695 females; mean age: 40.89 ± 10.98 years) and 282 healthy volunteers (83 males, 199 females; mean age: 37.64 ± 11.50 years) were recruited. Of the 931 patients, 240 (25.78%) were in the MA+ group (174 females, mean age: 40.63 ± 11.25 years) and 691 (74.22%) were in the MA− group (521 females, mean age: 40.98 ± 10.90 years).

Of the patients with migraine (MA+ and MA−), the overall prevalence of RLS was 46.1% (429 of 931), and of the 429 patients with RLS, 61.1% had permanent RLS and 38.9% had provoked RLS. In the MA+ group, the overall prevalence of RLS was 63.8% (153 of 240), and of the 153 patients with RLS, 60.1% had permanent RLS while 39.9% had provoked RLS. In the MA− group, the overall prevalence of RLS was 39.9% (276 of 691), and of the 276 patients with RLS, 62.0% had permanent RLS and 38.0% had provoked RLS. The overall prevalence of RLS in the healthy group was 29.4% (83 of 282), and of the 83 individuals with RLS, 67.5% had permanent RLS and 32.5% had provoked RLS (Table 1). No significant differences in the prevalence of permanent RLS and provoked RLS were noted among the groups ($\chi^2 = 1.41$, $p = 0.70$).

Differences between the MA+ and MA− groups

No difference in age (40.63 ± 11.25 vs. 40.98 ± 10.90 years, $t = -0.43$, $p = 0.67$) or gender ($\chi^2 = 0.79$, $p = 0.37$) was found between the MA+ and MA− groups.

In the MA+ group, 36.3% of the patients (87 of 240) were grade 0 (negative), 23.3% (56 of 240) had an RLS of grade I, 8.3% (20 of 240) had an RLS of grade II, 17.1% (41 of 240) had an RLS of grade III, and 15.0% (36 of 240) had an RLS of grade IV (Figure 2a). Of the patients in the MA− group, 60.1% (415 of 691) were grade 0 (negative), 17.8% (123 of 691) had an RLS of grade I, 5.6% (39 of 691) had an RLS of grade II, 4.8%

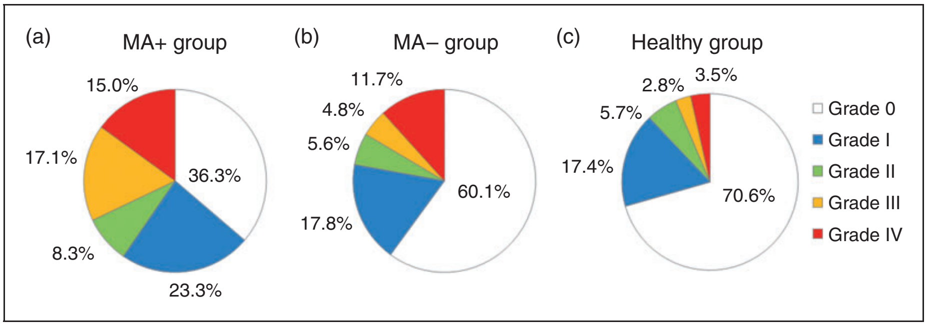

Figure 2. The percentage of the five right-to-left shunt (RLS) levels in the migraine with aura (MA+) (a), migraine without aura (MA–) (b), and healthy groups (c).

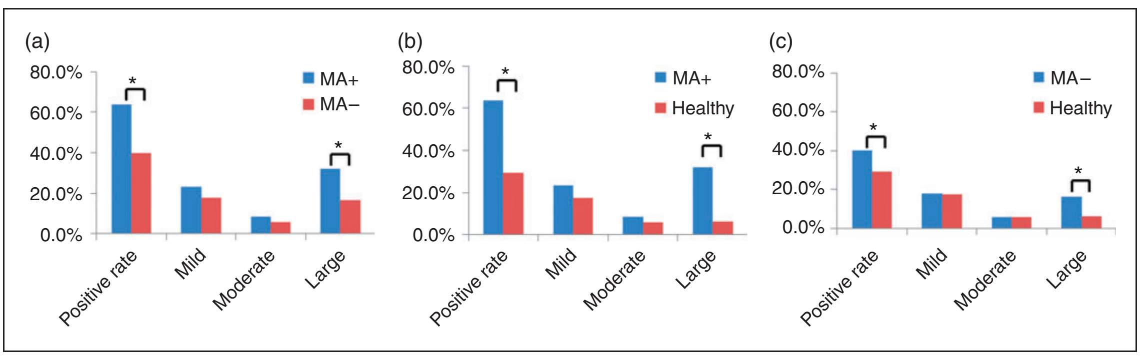

Figure 3. The overall prevalence of right-to-left shunt (RLS) as well as the prevalence of small RLS, moderate RLS, and large RLS in the various groups. The overall prevalence of RLS and prevalence of large RLS in the migraine with aura group (MA+) were significantly higher than were those in the migraine without aura (MA–) group (a) and healthy group (b). The overall prevalence of RLS and prevalence of large RLS in the MA– group were significantly higher than were those in the healthy group (c). *$p < 0.001$.

(33 of 691) had an RLS of grade III, and 11.7% (81 of 691) had an RLS of grade IV (Figure 2b). The overall prevalence of RLS (63.8% vs. 39.9%, $\chi^2 = 40.64$, $p < 0.001$) and the prevalence of large RLSs (32.1% vs. 16.5%, $\chi^2 = 26.54$, $p < 0.001$) were significantly higher in the MA+ group than they were in the MA– group. However, the prevalences of moderate-sized and small shunts were similar between the MA+ and MA– groups (8.3% vs. 5.6%, $\chi^2 = 2.17$, $p = 0.14$; 23.3% vs. 17.8%, $\chi^2 = 3.51$, $p = 0.06$; Figure 3a)

Differences between the MA+ and healthy groups

Subjects in the healthy group were slightly younger than were those in the MA+ group (40.63 ± 11.25 vs. 37.64 ± 11.50 years, t = 2.99, $p = 0.003$), but no significant difference in gender was noted between the two groups ($\chi^2 = 0.24$, $p = 0.63$).

In the healthy group, 70.6% (199 of 282), 17.4% (49 of 282), 5.7% (16 of 282), 2.8% (8 of 282), and 3.5% (10 of 282) of the individuals were grade 0 (negative), grade I, grade II, grade III, and grade IV, respectively (Figure 2c). Compared to the healthy group, the MA+ group had a significantly higher overall prevalence of RLS (63.8% vs. 29.4%, $\chi^2 = 61.64$, $p < 0.001$) and a significantly higher prevalence of large RLSs (32.1% vs. 6.4%, $\chi^2 = 57.53$, $p < 0.001$; Figure 3b).

Differences between the MA– and healthy groups

Subjects in the healthy group were younger than were those in the MA– group (40.98 ± 10.90 vs. 37.64 ± 11.50 years, t = 4.27, $p < 0.001$), but no difference in gender was noted between the two groups ($\chi^2 = 2.43$, $p = 0.12$).

The MA– group had a significantly higher overall prevalence of RLS than did the healthy group (39.9% vs. 29.4%, $p = 0.002$). In addition, large shunts were found significantly more often in patients with MA– than in healthy individuals (16.5% vs. 6.4%, $\chi^2 = 17.47$, $p < 0.001$). In contrast, the percentages of moderate and small shunts were similar in both the MA– and healthy groups (5.6% vs. 5.7%, $p = 0.99$ and 17.8% vs. 17.4%, $p = 0.88$, respectively; Figure 3c).

Discussion

In this multicentre case-control study, the main finding was that the prevalence of RLS was significantly higher in Chinese migraineurs (including both MA+ and MA−) than it was in healthy controls. Hence, there appears to be a close relationship between RLS and MA− as well as between RLS and MA+. In addition, the proportion of large shunts was significantly larger in migraineurs with and without aura than it was in healthy controls. Such findings suggest that the presence of an RLS, especially a large RLS, is associated with migraine.

The prevalence of RLS in both migraineurs and healthy individuals varies. In the current multicentre study, we used c-TCD and found that 29.4% of the general Chinese population had an RLS. The prevalence of RLS we detected in our healthy population was similar to that reported previously in a study on 965 autopsy specimens, which found the prevalence of PFO to be 27.3% (17), with PFO comprising about 95% of all RLSs (18).

Currently, the association between RLS and migraine is still being debated. To date, some studies have reported that the prevalence of RLS in patients with MA+ is 2.5-fold greater than that found in healthy control subjects (19), while other studies determined that the prevalence of RLS is similar in both patients with and without migraine (8,20). In 1999, Anzola et al. (7) studied 113 patients with MA+, 53 patients with MA−, and 25 controls without migraine using c-TCD. The study reported that the prevalence of PFO was 48%, 23%, and 20% in the patients with MA+, patients with MA−, and non-migraine controls, respectively. The study concluded that the patency of PFO was significantly associated with MA+ (MA+ vs. MA−, $p = 0.002$; MA+ vs. non-migraine controls, $p = 0.001$) (7). In 2005, Dalla Volta et al. (21) studied 334 patients with migraine and determined that 61.9% (161 of 260) of the patients with MA+ and 16.2% (12 of 74) of the patients with MA− were PFO carriers, as determined by c-TCD. Their results also confirmed a link between MA+ and RLS (21). In our study of 240 patients with MA+, we used c-TCD to detect RLS. The MA+ and healthy control groups were significantly different in term of the prevalence of RLS, as were the MA+ and MA− groups. Our findings support previous observations of a link between MA+ and RLS, especially between MA+ and large RLSs.

Our data also suggested that the prevalence of RLS in MA− was significantly higher than that in healthy controls, although this finding differs from the results of previous studies (5,7). For instance, the abovementioned study by Anzola et al. (6) concluded that the patency of PFO was associated with MA+ but not with MA− . In a previous single-centre study performed by our team in 2012 (5), 158 of 217 Chinese migraineurs were diagnosed with MA−; while the prevalence of RLS in the subjects with MA− was higher than that in healthy controls (36.1% vs. 28.0%), no significant difference was found between the groups ($p > 0.05$) (5). However, considering that the number of subjects with MA− was limited in that single-centre study, the difference in prevalence of RLS may not have contributed significantly to the overall relationship between RLS and MA−. In the present multicentre study, we recruited more patients with MA− (691) and observed that the prevalence of RLS in these patients was significantly higher than that in healthy controls, suggesting that RLS may be related to both MA− and MA+.

In terms of the relationship between the size of the RLS and migraine, Schwerzmann et al. (19) analysed shunts with trans-oesophageal echocardiography and found that large shunts were more common in patients with MA+. Another study demonstrated that large RLSs were significantly more prevalent in both MA+ and MA− patients than they were in patients without migraine (22). Here, in addition to the increased overall shunt prevalence, large shunts were more prevalent in migraineurs both with and without aura than they were in healthy individuals. Meanwhile, moderate and small-sized shunts were equally prevalent in migraineurs and healthy controls. Hence, it is possible that an RLS, especially a large RLS, is associated with migraine. Moreover, we also noticed that the prevalence of permanent RLS did not differ among the groups. These findings suggest that the size of the RLS (large) rather than the type (permanent and provoked) is associated with migraine.

Based on these findings, it has been speculated that RLS may be involved in the pathogenesis of migraine. However, the mechanisms underlying the association between migraine and RLS remain controversial. One possible mechanism is that a vasoactive biochemical (e.g., serotonin or venous micro-emboli), bypassing the pulmonary filter through an RLS, could eventually favour such neurovascular events (e.g., cortical spreading depression), which may trigger migraine attacks (23). Furthermore, dynamic cerebral autoregulation, which is known to be impaired in patients with MA+, may be a potential mechanism linking migraine and RLS (24).

To our knowledge, the present multicentre case-control study on >1,100 Chinese participants involved more migraineurs than previous c-TCD studies. Moreover, we enrolled healthy subjects as a control group to determine differences in the prevalence and extent of RLS between migraineurs and healthy controls. The data from our study support that the presence of an RLS, especially a large shunt, may be a risk factor for migraineurs both with and without aura. However, our study does have some limitations. In the present study, we tried to match the migraine group in terms of age and gender to the healthy controls. Unfortunately, as we enrolled consecutive migraineurs and most of the healthy volunteers consisted of staff and students from the nine hospitals, the mean age of the healthy group was lower than that of the migraineurs. Despite this, no difference in gender was noted among the groups. The mean age of all groups was within 35–40 years, although no studies have indicated that age or sex has an effect on RLS prevalence. We therefore assumed that it was acceptable to combine the consecutive data from the nine hospitals. Here, we used c-TCD to detect RLSs of any aetiology because it is non-invasive and safe. RLSs include intracardiac RLSs such as PFO and extracardiac RLSs such as pulmonary arteriovenous fistula. Further studies are needed to explore the proportion of patients with PFO and pulmonary arteriovenous fistula, especially given the possible therapeutic option of closing the PFO in patients with MA+ to reduce attack frequency and prevent stroke.

In conclusion, our data from the multicentre study suggests that there is an association not only between RLS and MA+, but also between RLS and MA−, especially when the shunt is large. Besides, in terms of the prevalence of mild RLS, moderate RLS and permanent RLS, there is no difference between healthy population and migraineurs with and without aura.

Clinical implications

- RLS, especially large RLS, is associated with migraine with aura as well as migraine without aura. RLS may be involved in the pathogenesis of migraine.
- Detection of right-to-left shunt should be considered in patients with migraine.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Nedeltchev K and Mattle HP. Contrast-enhanced transcranial Doppler ultrasound for diagnosis of patent foramen ovale. *Front Neuro Neurosci* 2006; 21: 206–215.
2. Del Sette M, Angeli S, Leandri M, et al. Migraine with aura and right-to-left shunt on transcranial Doppler: A case-control study. *Cerebrovasc Dis* 1998; 8: 327–330.
3. Henry P, Auray JP, Gaudin AF, et al. Prevalence and clinical characteristics of migraine in France. *Neurology* 2002; 59: 232–237.
4. Burch RC, Loder S, Loder E, et al. The prevalence and burden of migraine and severe headache in the United States: Updated statistics from government health surveillance studies. *Headache* 2015; 55: 21–34.
5. Yu S, Liu R, Zhao G, et al. The prevalence and burden of primary headaches in China: A population-based door-to-door survey. *Headache* 2012; 52: 582–591.
6. Rasmussen BK. Epidemiology of headache. *Cephalalgia* 2001; 21: 774–777.
7. Anzola GP, Magoni M, Guindani M, et al. Potential source of cerebral embolism in migraine with aura: A transcranial Doppler study. *Neurology* 1999; 52: 1622–1625.
8. Kahya Eren N, Bulbul NG, Yakar Tuluce S, et al. To be or not to be patent: The relationship between migraine and patent foramen ovale. *Headache* 2015; 55: 934–942.
9. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.
10. Hao N, Liu K, Guo ZN, et al. Comparison of two contrast agents for right-to-left shunt diagnosis with contrast-enhanced transcranial Doppler. *Ultrasound Med Biol* 2014; 40: 2317–2320.
11. Jauss M and Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. *Cerebrovasc Dis* 2000; 10: 490–496.
12. Guo YZ, Gao YS, Guo ZN, et al. Comparison of different methods of Valsalva maneuver for right-to-left shunt detection by contrast-enhanced transcranial doppler. *Ultrasound Med Biol* 2016; 42: 1124–1129.
13. Zanette EM, Mancini G, De Castro S, et al. Patent foramen ovale and transcranial Doppler. Comparison of different procedures. *Stroke* 1996; 27: 2251–2255.
14. Wessler BS, Kent DM, Thaler DE, et al. The RoPE score and right-to-left shunt severity by transcranial doppler in the CODICIA study. *Cerebrovasc Dis* 2015; 40: 52–58.
15. Yang Y, Guo ZN, Wu J, et al. Prevalence and extent of right-to-left shunt in migraine: A survey of 217 Chinese patients. *Eur J Neurol* 2012; 19: 1367–1372.
16. Xing YQ, Guo YZ, Gao YS, et al. Effectiveness and safety of transcatheter patent foramen ovale closure for migraine (EASTFORM) trial. *Sci Rep* 2016; 6: 39081.

17. Hagen PT, Scholz DG and Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; 59: 17–20.
18. Ailani J. Migraine and patent foramen ovale. *Curr Neurol Neurosci Rep* 2014; 14: 426.
19. Schwerzmann M, Nedeltchev K, Lagger F, et al. Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology* 2005; 65: 1415–1418.
20. Garg P, Servoss SJ, Wu JC, et al. Lack of association between migraine headache and patent foramen ovale: Results of a case-control study. *Circulation* 2010; 121: 1406–1512.
21. Dalla Volta G, Guindani M, Zavarise P, et al. Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. *J Headache Pain* 2005; 6: 328–330.
22. Anzola GP, Morandi E, Casilli F, et al. Different degrees of right-to-left shunting predict migraine and stroke: Data from 420 patients. *Neurology* 2006; 66: 765–767.
23. Beda RD and Gill EA Jr. Patent foramen ovale: Does it play a role in the pathophysiology of migraine headache? *Cardiol Clin* 2005; 23: 91–96.
24. Guo ZN, Xing Y, Liu J, et al. Compromised dynamic cerebral autoregulation in patients with a right-to-left shunt: A potential mechanism of migraine and cryptogenic stroke. *Plos One* 2014; 9: e104849.

Appendix

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