

Effect of Interventional Therapy Unexplained Dizziness and Relationship Between Dizziness Handicap Inventory and Right-to-Left Shunt Grading

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Objective: Unexplained dizziness remains a clinical challenge. Our previous studies have shown that unexplained dizziness may be related to patent foramen ovale (PFO). This study aims to explore whether the degree of shunt is correlated with the degree of unexplained dizziness and looking for the possible clinical intervention for patients with unexplained dizziness.

Methods: This study was a large single-center, prospective, controlled study. From March 2019 to March 2022, patients with unexplained dizziness and explained dizziness and healthy controls were recruited. Contrast-enhanced transcranial Doppler sonography (c-TCD) was performed to detect the existence of right-to-left shunt (RLS) and shunt grading. The dizziness handicap inventory (DHI) was completed to evaluate the dizziness. Unexplained dizziness patients with large amount of PFO were volunteered to receive medication treatment and transcatheter PFO closure and followed up six months.

Results: A total of 387 patients (132 unexplained, 123 explained and 132 controls) were enrolled. There was a statistical difference in the RLS grading with three groups ($p < 0.001$). The Spearman correlation coefficient of RLS grading and DHI scores in unexplained dizziness patients ($r=0.122$, $p=0.163$) and explained dizziness patients ($r=0.067$, $p=0.460$). In the unexplained group, there were 49 cases with massive grading RLS. Of which 25 patients received percutaneous PFO closure treatment and 24 cases received medication treatment. Followed up six months after treatment, the amount of DHI scores change in patients who received the percutaneous PFO closure was significantly higher than that in the medication treatment group ($p < 0.001$).

Conclusion: RLS may play an important role in unexplained dizziness. For unexplained dizziness patients, PFO closure may contribute to better outcomes. In the future, large-scale randomized controlled studies are still needed.

Keywords: unexplained dizziness, dizziness handicap inventory, DHI, patent foramen ovale, PFO, right to left shunt, RLS, contrast-enhanced transcranial Doppler sonography, c-TCD

Introduction

Dizziness is a common chief complaint in the general population, it has a prevalence of 22.9% and an incidence of 3.1% per year.¹ With the continuous advance of medical science and development of novel treatments, the world of dizziness has experienced a dramatic change. Even though an extensive battery of examinations and assessments, 5% of the patient's dizziness remain "unexplained", a particularly common and challenging problem in clinical practice.² The Dizziness Handicap Inventory (DHI) is one of the most popular questionnaires for assessment of the dizziness handicap. It is a useful, reliable, and valid measure of self-perceived handicap associated with dizziness. The original version of the DHI showed high internal consistency and test-retest reliability in a population of patients with dizziness of various etiologies.³⁻⁵ Take into account the differences in education and English level in China, we translated the Dizziness

Handicap Inventory (DHI) into Chinese. Poon DM⁶ has validated that the Chinese DHI retains high levels of reliability and validity as compared to the original DHI and has a moderate level of responsiveness.

Three patients with right-to-left shunt (RLS) accompanied by dizziness were reported in previous studies, and their symptoms improved significantly after surgery.⁷ The study linked RLSs to dizziness. The RLS refers to a blood shunt through the potential abnormal channel existing between systemic and pulmonary circulation, which is commonly seen in patients with patent foramen ovale (PFO).^{8,9} PFO is implicated in several complex conditions including cryptogenic stroke, migraine, platypnoea-orthodeoxia syndrome and decompression sickness in divers, and is generally found in approximately 25% of normal adults.^{10,11}

Our previous study has demonstrated that RLS especially large amount of RLS is related to unexplained dizziness and may be involved in the pathogenesis of unexplained dizziness.¹² In the present study, we have attempted to introduce novel insights into the pathophysiology of unexplained dizziness and explore the possible clinical intervention for treating unexplained dizziness and preventing the recurrence of unexplained dizziness.

Methods

Patients

This study was a large single-center, prospective, controlled study. It was carried out in the Second Affiliated Hospital of Nanchang University. From March 2019 to March 2022, 132 “unexplained” dizziness patients and 121 patients with explained dizziness were enrolled, additionally, 132 healthy volunteers without dizziness were recruited as normal controls. All patients recruited for the study voluntarily and signed an informed consent form. The ethics committee of the Second Affiliated Hospital of Nanchang University approved our research protocol [approval number (2019) 009].

We did a series of examinations (such as Dix–Hallpike maneuver, pure tone audiometry, an orthostatic hypotension test, a videonystagmography, caloric test parameters, video head impulse-test results, or vestibular-evoked potential measure of otolith function, carotid ultrasound, transcranial Doppler sonography, brain magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), 24-hour dynamic electrocardiogram, echocardiography) on all patients with dizziness and detailed medical history inquiry, routine laboratory examinations, psychological/psychiatric evaluations, etc. After the burden of diagnosis and evaluation, the patient’s dizziness remains “unexplained”, which was considered for inclusion in the study. Also, the Valsalva maneuver is required, as it is the basis for determining whether RLS exists or not. Nevertheless, with a definite diagnosis of dizziness, including benign positional paroxysmal vertigo (BPPV), vestibular neuritis, vestibular migraine, Meniere’s disease, bilateral vestibular dysfunction, vestibular paroxysm, orthostatic hypotension, stroke, cerebellar ataxia, sudden deafness, cervical spondylosis, cardiogenic dizziness and combined tumor, endocrine, blood system, liver or kidney failure, patients with psychiatric disorder (such as suicide idea, addict, etc.) and other possible dizziness diseases have been excluded from our study, as well as pregnant woman and pulmonary arteriovenous malformation (PAVF), patent ductus arteriosus (PDA) also have been excluded.

Procedure

Contrast-Enhanced Transcranial Doppler Sonography

All enrolled cases underwent c-TCD to determine the existence and shunt grading of RLS at resting state and after Valsalva maneuver (VM), respectively. The c-TCD protocol used a 2-MHz probe through a single-channel dual-depth mode with a sampling volume of 8 mm and a dual depth difference of 10 mm to monitor the middle cerebral artery (MCA) and the vertebral artery (VA) in patients with poor temporal window. Agitated microbubble saline solution (1 milliliter of air, 9 milliliters of saline, and 0.2 milliliters of venous blood) was injected into the antecubital vein through an 18-gauge trocar. Microbubble injection was performed 1 time at rest and 2 times during the Valsalva maneuver. Besides, each interval was at least 2 min. The Valsalva maneuver held for at least 5 to 10 seconds. Efficacy of the Valsalva maneuver was identified by a reduction of the mean velocity in the MCA or VA at least 25%. The magnitude of RLS was determined by detecting and calculating within 25s after the agitated normal saline was injected. Patients were divided into 5 levels: grade 0, normal or negative; Grade I, $1 \leq \text{MBs} \leq 10$; grade II, $10 < \text{MBs} \leq 25$; grade III, >25 MBs and no curtain; and grade IV, curtain where a single bubble cannot be identified. Grade I is a mild shunt, grade II is

a moderate shunt, and grade III and IV are massive shunts. RLS was considered latent if it occurred only after VM and permanent when it occurred also at rest.

c-TCD was performed by the same doctor with more than 10 years of working experience (Neuroelectrophysiology, Vascular Ultrasound Specialist). The agitated normal saline was injected by the same experienced nurse (Clinical Nurse Specialist). The higher shunt grading of RLS that was detected via c-TCD at resting state and after VM was used as the result of RLS grading in each case.^{13–15} Patients with RLS (+) require Transesophageal echocardiography (TEE) or right heart catheterization to support the diagnosis of PFO. A standardized protocol was used to perform TEE by experienced echocardiographers and cardiologists.¹⁶

Dizziness Handicap Inventory Score

All patients were asked to complete the dizziness handicap inventory score (DHI). The DHI contains 25 items; a “yes” response yields a score of 4 points, “sometimes” gives 2 points and “no” 0 points. The total scores range from 0 (no impairment) to 100 (severe impairment). Scores between 0 and 30 represent mild or no symptoms, 31–60 moderate impairment and 61 to 100 points indicate severe symptoms. The scale is further sub-grouped into a 7-item physical scale (maximum score 28), a 9-item emotional scale (maximum score 36) and a 9-item functional scale (maximum score 36).

Treatment in Large Amount Grading with Unexplained Dizziness

Patients with large amount of RLS through TEE or right heart catheterization were confirmed PFO. Volunteered to receive medication treatment (antiplatelets) and percutaneous closure of PFO. Oral administration of aspirin 100mg/d plus clopidogrel 50–75mg/d within 6 months after operation. Six months later, aspirin 100mg/d was administered orally until 1 year after surgery.¹⁷ DHI score follow-up through outpatient or telephone calls was assessed after 6 months.

Statistical Analysis

Data measurements assumed a normal distribution are expressed as $x \pm s$. Statistical analysis of categorical data was carried out by Pearson’s chi-square and Fisher’s exact tests. For the comparison of multiple groups of data, post hoc testing was used to judge the differences between groups according to the adjusted standardized residuals. To detect the difference between the two groups of continuous variables, Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test the data for a normal distribution, an independent sample *t*-test was used for the normally distributed variables, and the Mann–Whitney *U*-test was used for variables that did not conform to a normal distribution. Spearman correlation coefficient was used to analyze the correlation between the DHI scores and RLS grading. The chi-square/ χ^2 test was used for categorical variables and single-factor classification data. $p < 0.05$ was considered statistically significant. All tests were conducted by IBM SPSS Statistics 25.0 software (SPSS, Chicago, IL, USA).

Results

Patient Demographic and Clinical Characteristics at Baseline

Within the time frame, a total of 387 patients (177 males, 210 females) completed c-TCD at the Department of Neuroelectrophysiology in our hospital were enrolled, of which, 132 unexplained dizziness patients, 123 patients with explained dizziness, and 132 healthy controls. The mean age was 41.14 ± 14.06 , 56.23 ± 12.17 , and 39.33 ± 8.85 years, respectively. There was no statistical difference between gender in the three groups ($\chi^2 = 2.821$, $p = 0.244$). There was no statistical difference between age in patients with unexplained dizziness patients and healthy controls ($t = 1.252$, $p = 0.212$). However, there was a statistical difference between age in patients with explained dizziness patients and healthy controls ($t = 12.60$, $p < 0.001$), and in patients with unexplained dizziness and explained dizziness ($t = -9.123$, $p < 0.001$). There was no statistical difference between DHI scores in patients with unexplained dizziness patients and explained dizziness patients ($t = -0.715$, $p = 0.475$). The demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1 Patient Demographic and Clinical Characteristics at Baseline

Groups/ Variables	Unexplained Dizziness	Explained Dizziness	Healthy Controls	t/χ^2	p value
Sex (female, %)	79 (59.85%)	61 (49.59%)	70 (53.03%)	2.821	0.244
Age (mean $\pm$ SD)	41.14 $\pm$ 14.06	56.23 $\pm$ 12.17	39.33 $\pm$ 8.85	118.598*	0.000
RLS (%)	79 (59.85%)	34 (27.64%)	32 (24.24%)	43.14	0.000
DHI	36.83 $\pm$ 11.40	37.89 $\pm$ 12.45	–	–0.715	0.475

Notes: All values retain the last three decimal places. –, not available; *, Mann–Whitney U-test.

Abbreviations: RLS, right-to-left shunt; DHI, dizziness handicap inventory score.

Right-to-Left Shunt and Grading in Patients from Different Groups

The RLS-positive [RLS (+)] patients detected by c-TCD were 59.85%, 27.64%, and 24.24%, respectively. Patients with RLS (+) continue to complete TEE or right heart catheterization. We found one diagnosed with PAVF and one with PDA. There was a statistical difference between the proportion of RLS in patients with unexplained dizziness and those with explained dizziness and healthy controls ($\chi^2=43.14$, $p<0.001$). There was a statistical difference in the RLS grading with these groups ($\chi^2=57.194$, $p<0.001$). The grading of RLS in three groups is shown in Table 2. The RLS grading in patients with unexplained dizziness was significantly higher than that in patients with explained dizziness ($\chi^2=31.398$, $p<0.001$). The RLS grading in patients with unexplained dizziness was significantly higher than healthy controls ($\chi^2=43.606$, $p<0.001$). There was no statistical difference between RLS grading in patients with explained dizziness and healthy controls ($\chi^2=1.419$, $p=0.701$).

Association Between Right-to-Left Shunt Grading and DHI Scores

Based on the DHI scores, the total scores range from 0 (no impairment) to 100 (severe impairment). Scores between 0 and 30 represent mild or no symptoms, 31–60 moderate impairment and 61 to 100 points indicate severe symptoms. The DHI scores grading from different groups are shown in Figure 1. The Spearman correlation coefficient of RLS grading and DHI scores in unexplained dizziness patients ($r=0.122$, $p=0.163$) and explained dizziness patients ($r=0.067$, $p=0.460$), respectively, are shown in Figure 2. There was no correlation between DHI score and RLS grading.

Comparison of Treatment in Large Amount Grading Group

In the unexplained group, there were 49 cases with massive grading RLS confirmed PFO. Of which 25 patients received percutaneous PFO closure treatment and 24 cases received medication treatment. Age ($t=-0.718$, $p=0.476$), gender ($\chi^2=0.027$, $p=0.869$) and DHI scores ($t=-0.54$, $p=0.592$) showed no statistically significant difference between cases receiving percutaneous PFO closure and medication treatment at baseline. In the percutaneous PFO closure and medication treatment group, the DHI scores were statistically significant difference between baseline and 6 months after treatment ($t=17.712$, $p<0.001$; $t=4.49$, $p<0.001$, respectively). Followed up six months after treatment, the DHI scores were statistically significant difference between patients receiving the percutaneous PFO closure and medication treatment ($t=-12.466$, $p<0.001$, as show in Table 3). Table 4 and Figure 3 show the treatment effect estimates. The DHI

Table 2 Right-to-Left Shunt and Grading in Patients from Different Groups

Groups/ Variables	RLS+ (%)	RLS Grading				DHI	χ^2	p value
		Negative	Mild	Moderate	Massive			
Unexplained dizziness	79(59.85)	53(40.15)	19(24.05)	11(13.92)	49(62.03)	36.83 $\pm$ 11.40	31.398	0.000
Explained dizziness	34(27.64)	89(72.36)	14(41.18)	7(20.59)	13(38.23)	37.89 $\pm$ 12.45	1.419	0.701
Healthy controls	32(24.24)	100(75.76)	17(53.13)	6(18.75)	9(28.12)	–	43.606	0.000
t/χ^2	43.14	57.194				1.53	–	
p value	0.000	0.000				0.128		

Notes: All values retain the last three decimal places. –, not available.

Abbreviations: RLS, right-to-left shunt; DHI, dizziness handicap inventory score.

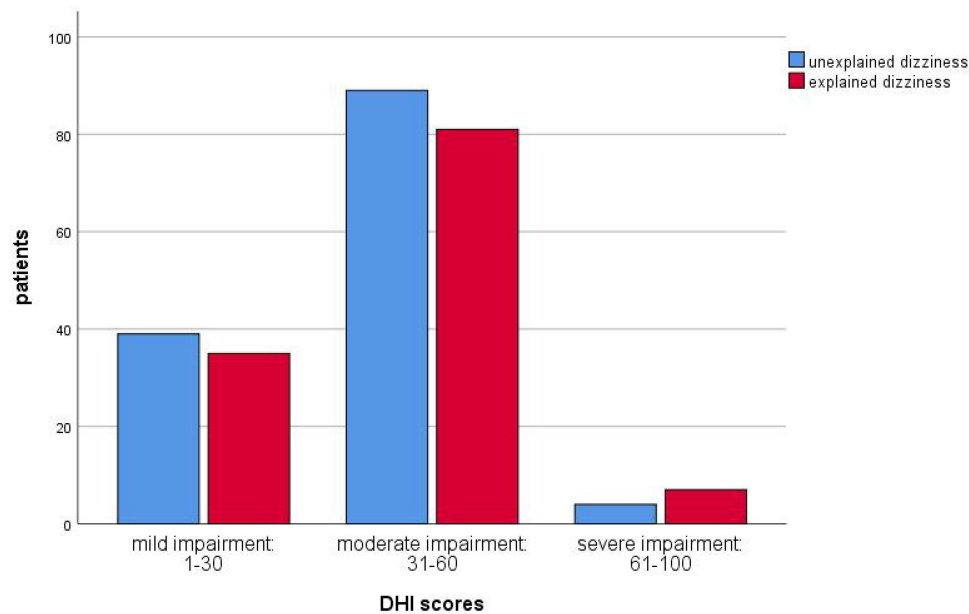


Figure 1 The DHI scores in patient with unexplained dizziness and explained dizziness.

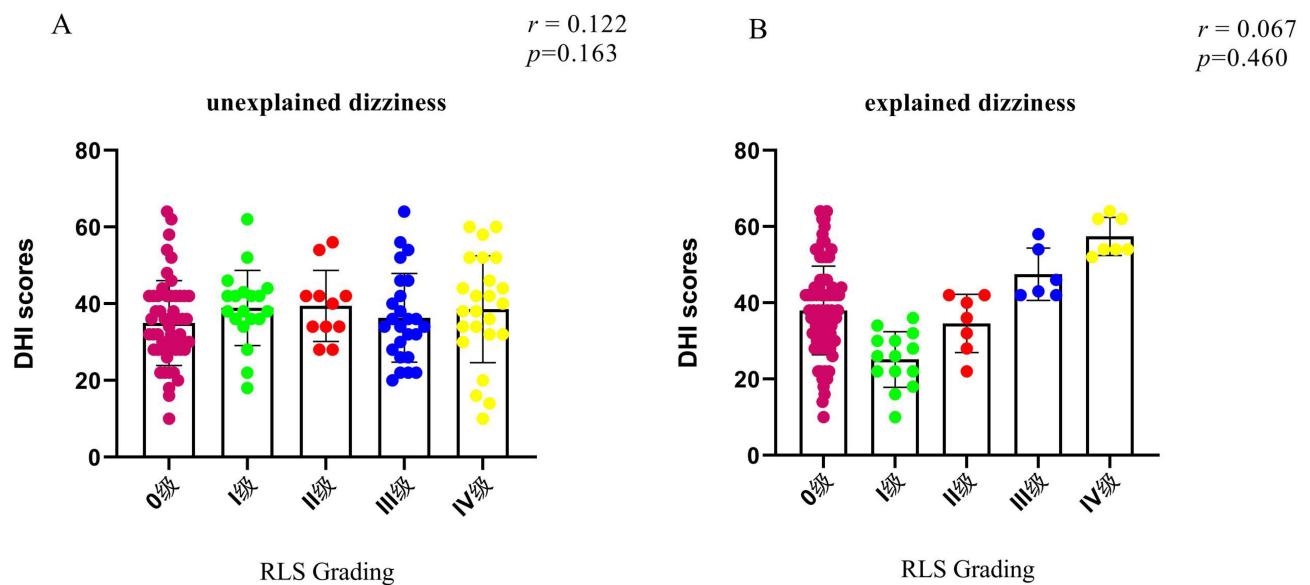


Figure 2 (A) The Spearman correlation coefficient of RLS grading and DHI scores in unexplained dizziness patients. **(B)** The Spearman correlation coefficient of RLS grading and DHI scores in explained dizziness.

scores were statistically significant difference between patients receiving the percutaneous PFO closure and medication treatment ($t=9.157$, $p<0.001$, MD 26.35, 95% CI 20.71–31.99).

Discussion

Dizziness is the most common reported medical complaints affecting 15–35% of the adult population.^{18,19} According to the Classification of Vestibular Disorders of the Barany Society, dizziness is defined as a nonvertiginous sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion.²⁰ It is usually combined with the clinical manifestations of impaired vision and somatosensory and proprioceptive organs, and it is affected by many factors.^{21,22} Diagnosis is usually difficult because these complaints are nonspecific and the differential diagnosis is broad.

Table 3 Comparison of Treatment in Large Amount Grading Group

Groups	Baseline (Age)	Baseline (Female)	Baseline (DHI)	6 Months (DHI)	T-test	
					t	p value
Percutaneous PFO Closure	46.52±13.67	14 (56%)	37.44±10.39	1.84±2.70	17.712	0.000
Medication Treatment	49.25±13.35	14 (58.33%)	38.92±8.63	29.67±10.61	4.49	0.000
t/χ^2	-0.718	0.027	-0.54	-12.466		
p value	0.476	0.869	0.592	0.000		

Abbreviations: PFO, patent foramen ovale; DHI, dizziness handicap inventory.

Table 4 The Treatment Effect Estimates in Large Amount Grading Group

Groups	Mean ± SD (DHI)	MD (95% CI) (DHI)	T-test	
			t	p value
Percutaneous PFO Closure	35.6±10.05	26.35 (20.71–31.99)	9.157	0.000
Medication Treatment	9.25±10.09			

Abbreviations: PFO, patent foramen ovale; MD, Mean Difference; SD, Standard Deviation; CI, Confidence Intervals (Lower Limit-Upper Limit).

Our previous study has found that PFO and age were related to unexplained dizziness, RLS especially large amount of RLS is related to unexplained dizziness.¹² In this article, we demonstrated that age especially young people is related to unexplained dizziness once again, and the proportion of RLS in patients with unexplained dizziness was significantly higher than in those with explained dizziness and healthy controls. We also found that there was statistical significance in RLS grading with three groups. Large shunts account for the most in the unexplained dizziness patients, suggesting that RLS might play an important role in the pathogenesis of unexplained dizziness. PFO-mediated hypoxemia occurs when deoxygenated venous blood from the right atrium enters and mixes with oxygenated arterial blood in the left atrium. The presence of right-to-left cardiac shunting can exacerbate the degree of hypoxemia in patients with valsalva maneuver.^{23,24} We have discussed the possible mechanisms in our previous study.¹² Of course, their pathophysiology remains to be further elucidated, and more basic research is needed to confirm this hypothesis in the future.

The Dizziness Handicap Inventory (DHI) score was computed from a 25-item scale that assesses an individual's perception of handicap due to dizziness encompassing emotional, functional and physical burden. It is the most widely used self-reported measurement of patients with dizziness. Due to its strong validity and test/retest

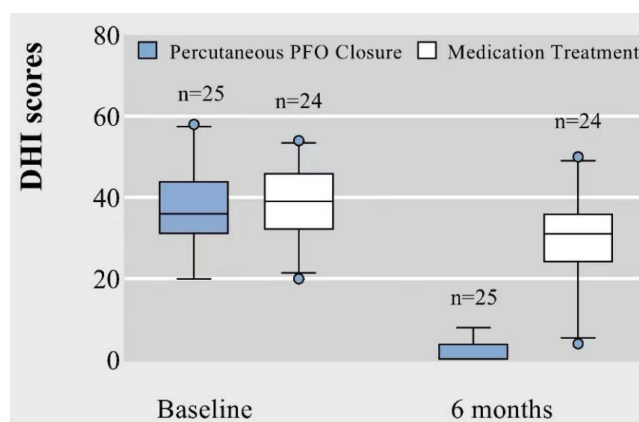


Figure 3 Box plots of raw data for DHI at baseline and six months. Data are median (central line), interquartile range (box margins), adjacent values (whiskers), and outliers (dots).

reliability, the DHI has become the “gold standard” against which similar scales have been compared. We did not investigate the clinical characteristics (age of onset, duration, and detailed medical therapy) of dizziness in participants in this study. Instead, we assessed the severity of dizziness using the DHI, to investigate the association with RLS grading, regardless of the types of dizziness. We found that there was no correlation between the RLS grading and DHI total scores among unexplained dizziness patients and explained dizziness. We thought the possible reason is that the DHI total scores represent the degree of dizziness and quality of life of vestibular disorders. It is highly correlated with patients’ psychological status. It was subgrouped into three content domains evaluating specific functional, emotional or physical problems associated with an individual’s reaction to balance function impairment. The DHI is likely multidimensional in nature, but that the dimensions are substantially different from the functional, emotional, and physical disability subscales. Items of the DHI do not evaluate the otological or neurovegetative symptoms which mostly accompany to vestibular symptoms and do not assess the effects of dizziness on self-care activities.^{4,25} Furthermore, we only calculate the total scores, we should calculate subscale scores to assess the physical manifestations, functional impact, and emotional Impact of dizziness on the dizzy patient.

PFO closure has demonstrated its effect in CS patients with PFO,^{26–29} and three randomized studies^{30–32} and meta-analyses have addressed the issue of percutaneous closure as therapy for migraine.^{33–37} Although current guidelines do not include unexplained dizziness as a surgical indication for PFO, our study found that percutaneous PFO closure on unexplained dizziness patients with massive grading shunt may contribute to better outcomes. Previous study reported that there are complications of PFO closure, such as increase in the risk of new-onset atrial fibrillation,³⁸ atrial perforation with tamponade,³⁹ and the potential long-term risk of aortic root dilatation⁴⁰ and subsequent erosions caused by the implanted device as well as the potential formation of thrombi on the device.^{41,42} Nevertheless, our patients in this study did not have any complications discussed above. The possible reason is that the sample size for PFO closure is small.

However, it is undeniable that the study has several limitations: 1) this is a single-center study; we should expand the sample size for further analysis and verification; 2) we cannot be sure that we included all risk factors for unexplained dizziness, and there might be some factors of which clinicians are not aware; 3) we did not research the medical therapy for dizziness with the percentage of patients and distribution across severity; 4) PFO closure was performed on a voluntary basis at the patients’ preference. This could have generated placebo effect. We focus our work on the research and investigation of the clinical characteristics of PFO-related dizziness in the future, and a well-designed study (transcatheter PFO closure or a sham procedure) with long-term follow-up is necessary to investigate the detailed contribution between PFO closure and medical treatment in patients with unexplained dizziness.

Although there are some limitations in our study, it is undeniable that we should pay more attention to the presence of PFO in patients with unexplained dizziness. PFO closure may contribute to better outcomes in unexplained dizziness patients with large amount of shunt. Of course, our findings should be cautiously generalized to all populations with dizziness.

Conclusions

This study showed that RLS might play an important role in the pathogenesis of unexplained dizziness. PFO closure may contribute to better outcomes in unexplained dizziness patients with large amount of shunt. c-TCD could be incorporated into an assessment tool to appraise and guide interventions for unexplained dizziness in clinical practice. In the future, for patients with refractory and recurrent unexplained dizziness, the evaluation, intervention, and prognosis of RLS would be worthy of further exploration.

Data Sharing Statement

The data used during the study are available from the corresponding author by request.

Statement of Ethics

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University [approval number (2019) 009]. All patients recruited for the study voluntarily and signed an informed consent form. The procedures obey institutional guidelines.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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