Research Square

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Prevalence and grade of RLS in migraine: a prospective study of 251 migraineurs by synchronous test of c-TTE and c-TCD

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Abstract

Background

RLS is considered as a risk factor for migraine, but the correlation between the RLS and migraine remains controversial. To investigate the prevalence and Right-to left shunt (RLS) grade of PFO in patients with migraine (including migraine with aura and without) and assess the association between PFO and migraine.

Methods

Synchronous test of contrast transthoracic echocardiography (c-TTE) and contrast transcranial Doppler ultrasonography (c-TCD) was conducted in 251 patients with migraine, including 61 migraine with aura (MA) and 189 migraine without aura (MO) and 275 healthy adults. Among these patients, 25 patients with migraine and 14 healthy adults were evaluated by transesophageal echocardiography (TEE).

Results

(1). The prevalence of permanent RLS, total RLS and large RLS in migraine was significantly higher compared with controls ($P = 0.042$, < 0.001 and 0.001, respectively). (2). Compared with controls, the positive rate of total RLS and large RLS in MO was increased ($P = 0.004$ and 0.022 respectively), the positive rate of permanent RLS, total RLS and large RLS in MA was also increased ($P < 0.001$ for each of the comparisons). The positive rate of permanent RLS and large RLS in MA was significantly higher than in MO ($P = 0.004$ and 0.011 respectively). (3) The presence of large-size PFO (≥ 2.0 mm) of migraine was higher than that of controls ($P = 0.048$).

Conclusion

PFO is associated with increased migraine (especially with aura), when the PFO is permanent RLS, large RLS and large-size PFO (≥ 2.0 mm).

Background

The foramen ovale is an important fetal structure that closes after birth in most individuals but remains open as a patent foramen ovale (PFO) in approximately 25% of the healthy population [1]. PFO is the most common right-to left shunt (RLS), representing about 95% of all RLS [2]. The presence of PFO has been reported to be strongly associated with a number of disease processes, including cryptogenic stroke, transient ischemic attack, migraine headaches, peripheral arterial embolism, platypnea-orthodeoxia syndrome, and decompression sickness [3, 4]. Migraine is a chronic neurological disorder characterised by attacks of moderate or severe headache and reversible neurological and systemic symptoms, and is

one of the most prevalent and disabling medical illnesses in the world [5]. Migraines affect approximately 13% of the population aged 20 ~ 64 years, with one third of migraineurs having migraine with aura [6, 7]. Furthermore, it appears to be more severe and more prevalent in women [8]. In a meta-analysis, PFO is associated with a 2.5-fold increase in the prevalence of migraine and a 3.4-fold increase in the prevalence of migraine with aura [9]. Therefore, the identification of PFO in migraine patients is of great significance. Previous studies have found that contrast transthoracic echocardiography (c-TTE) and contrast transcranial Doppler ultrasonography (c-TCD) are simple, repeatable, and commonly used screening methods [10]. The purpose of this study was to evaluate the prevalence and shunt grade of PFO by synchronous test of c-TTE and c-TCD, and to explore the correlation between PFO and migraine.

Methods

Study population: 251 patients with migraine (age 14 ~ 74 years), who were diagnosed according to to the International Classification of Headache Disorders III- beta [11], were recruited from January 2018 to August 2019 in The First College of Clinical Medical Science, China Three Gorges University. The patients' medical history was recorded by clinical inquiry and telephone follow-up. Patients with migraine were divided into two subgroups: migraine with aura (MA, 61 cases) and migraine without aura (MO, 189 cases). We also accrued 275 healthy controls (age 14 ~ 81 years). Patients with arotid artery plaque, congenital heart disease, rheumatic heart disease, aortic dissection, malignant arrhythmia, hypercoagulability and other possible cerebrovascular events were excluded. Two experienced ultrasound technicians completed synchronous test of c-TTE and c-TCD. This study was approved by the ethics committee (No, HEC-KYJJ2020-002-01). All patients provided informed consent.

Synchronous test of c-TTE and c-TCD: The test was performed with transthoracic echocardiography (TEE, Philips EPIQ7C, China, the probe model X5-1, frequency 1.0 ~ 5.0 MHz) and transcranial Doppler (TCD, Delica 9 PB, China, the probe frequency 2 MHz). Participants were lying comfortably in the left lateral position. ECG leads were connected to each individual in all groups. Single channel TCD and double depth monitoring were selected, and the middle cerebral artery (MCA) was observed through the right temporal bone window. Testing was performed during normal breathing and subsequently with the Valsalva maneuver (VM). The contrast agent was prepared using 8 mL saline solution, 1 mL air and 1 ml participant's blood, which was vigorously mixed between the two 10 mL syringes via a 3-way stopcock at least 30 times and then rapidly injected into the right antecubital vein. The first injection was performed during normal respiration. During VM, contrast agent was injected 5 s before the start of VM. This was produced by the patients blowing into a small soft plastic tube connected to the manometer device, patients then started the VM on the examiner's command and held it for 5 s.We assessed the effective VM by monitoring the peak flow velocity of the MCA Doppler spectrum was decreased by at least 25%, and the manometer device achieved and maintained a pressure of 40 mm Hg [12]. When TTE detected micro-bubbles signals (MES) in the left atrium within 3 ~ 5 cardiac cycles, and TCD detected more than 1 MES appeared within 10 seconds after VM, then we regarded the c-TCD results as positive. We assumed cardiac RLS passage through the PFO when both of them are positive.

TEE: Using Philips iU22 (the probe model S7-2, frequency 3.5 ~ 7.0 MHz). The patients were fasting (abstaining from all food and caloric drink) for 4 h, and oral administration of lidocaine glue was performed 10 minutes before the examination. The operator inserted probe about 30 ~ 35 cm away from the incisor. The integrity of the foramen ovale flap was observed at rest, by looking at whether there were fissures between the septum primum against the septum secundum, and whether there were color shunt observed by color Doppler. The height of PFO was measured by the maximum separation between the septum primum and septum secundum in the end-systolic frame, and a height ≥ 2 mm was defined as a large-size PFO [13]. The length of PFO tunnel was measured by the maximum overlap between the septum primum and septum secundum and a length ≥ 10 mm was defined as long-tunnel PFO [14]. (Fig. 1)

Image analysis: According to the grading standards formulated by Chinese College of Cadiovascular Physicians [15], the degree of shunt in c-TTE was quantified according to detected micro-bubbles in the left atrium: grade 0 = no occurrence of micro-bubbles; grade I = 1 ~ 10 micro-bubbles; grade II = 11 ~ 25 micro-bubbles; grade III = more than 25 micro-bubbles or left atrium nearly filled with micro-bubbles or left atrial opacity (Fig. 2). According to the number of MES, the classification of c-TCD was as follows: grade 0 = negative; grade I = 1 ≤ MES ≤ 10; grade II = MES > 10 and no curtain; grade III = curtain [16]. (Fig. 3) Grade I is defined as small shunt, grade II as moderate shunt, and grade III as large shunt. Total RLS including permanent RLS (RLS also occurred during rest) and provoked RLS (RLS occurred only after the VM).

Statistical analysis

All statistical analyses were performed using SPSS 19.0. Data were presented as (mean ± SD) for continuous variables and as frequency (n) and percentage (%) for categorical variables. Differences between the two groups were analyzed by the t-test for continuous variables, and the χ^2-test for categorical variables. Statistical significance was defined as a value of $P < 0.05$.

Results

Characteristics of controls and migraine

Characteristics of study participants in Table 1, there were no significant differences between the two groups.

Table 1
Characteristics of study participants

Characteristics	Controls(n = 275)	Migraine(n = 251)	*P* Value
Male/female,n	89/186	86/165	0.644
Age, years	43.2 ± 13.5	43.0 ± 13.7	0.861
BMI, Kg/m^2	22.74 ± 3.38	23.25 ± 3.33	0.445
Smoking, n(%)	16(5.82)	23(9.16)	0.226
Hypertension, n(%)	29(10.55)	24(9.56)	0.078
Diabetes mellitus, n(%)	7(2.55)	9(3.58)	0.488
Dyslipidemia, n(%)	5(1.82)	12(4.78)	0.055
High D-dimer, n(%)	1(0.36)	2(0.79)	0.510
silent brain infarcts, n(%)	19(6.91)	29(11.55)	0.065
deep white matter lesions, n(%)	6(2.18)	2(0.79)	0.195
Date are presented as mean ± SD or n (%) of patents			
BMI:body mass index (= calculated as weight in kilograms divided by height in meters squared)			

Comparison of shunt type between controls and migraine: The prevalence of permanent RLS, total RLS and large RLS in migraine was significantly higher when compared with controls (respectively $P = 0.042$; $P < 0.001$; $P = 0.001$). (Table 2)

Table 2
Comparison of shunt type between controls and migraine

	Controls (n = 275)	Migraine (n = 251)	*P* Value
Permanent RLS, n(%)	17(6.18)	28(11.16)	0.042
Total RLS, n(%)	65(23.64)	98(39.04)	< 0.001
Small RLS, n(%)	31(11.27)	32(12.75)	0.602
Moderate RLS, n(%)	14(5.09)	23(9.16)	0.068
Large RLS, n(%)	20(7.27)	43(17.13)	0.001
Date are presented as n (%) of patents.			
RLS: right-to-left shunt.			

Comparison of shunt type between controls, MO and MA: Compared with controls, the positive rate of total RLS and large RLS in MO increased (respectively $P = 0.004$; $P = 0.022$), the positive rate of permanent RLS, total RLS and large RLS in MA increased (respectively $P < 0.001$; $P < 0.001$; $P < 0.001$). The positive rate of permanent RLS and large RLS in MA increased was significantly higher than in MA (respectively $P = 0.004$; $P = 0.011$). (Table 3)

Table 3
Comparison of shunt type between controls, MO and MA

	Controls (n = 275)	MO (n = 189)	MA (n = 61)	*P* Value[a]	*P* Value[b]	*P* Value[c]
Permanent RLS, n(%)	17(6.18)	15(7.93)	13(21.31)	0.402	< 0.001	0.004
Total RLS, n(%)	65(23.64)	68(35.98)	30(47. 54)	0.004	< 0.001	0.066
Small RLS, n(%)	31(11.27)	26(13.76)	6(9.83)	0.423	0.426	0.426
Moderate RLS, n(%)	14(5.09)	16(8.47)	7(11.48)	0.146	0.479	0.478
Large RLS, n(%)	20(7.27)	26(13.76)	17(27.87)	0.022	< 0.001	0.011
Date are presented as n (%) of patents.						
[a]*P* Value: Control VS MO, [b]*P* Value: Control VS MA, [c]*P* Value: MO VS MA						
Abbreviations: MA: migraine with aura; MO: migraine without aura. RLS :right-to-left shunts.						

PFO characteristics of TEE: The presence of large-size PFO (≥2.0 mm) of migraine increased than that of controls ($P = 0.048$). Length of PFO, long-tunnel PFO (≥ 10.0 mm) had no difference among the groups (respectively $P = 0.199$; $P = 0.095$). (Table 4)

Table 4
PFO characteristics of TEE

characteristics	Controls(n = 14)	Migraine(n = 25)	P Value
Large-size, ≥ 2.0 mm	1(7.14)	9(36.00)	0.048
Length of PFO, mm	7.25 ± 4.09	9.17 ± 4.05	0.199
Long-tunnel PFO, ≥ 10 mm	2(14.28)	10(40.00)	0.095
Date are presented as mean ± SD or n (%) of patents			

Discussion

RLS is an abnormal pathway between the venous and arterial circulations, and includes both intracardiac and extracardiac RLS. Intracardiac RLS are usually related to PFO, which has been described as a “back door to the brain” [17, 18]. Hagen et al's autopsy study on 965 normal hearts found that PFO had a prevalence of 27.3% for all age [19]. Therefore, PFO should be regarded as a normal structural variant even without paradoxical embolism or other discomfortable clinical conditions existed [20, 21]. Common detection methods of PFO include c-TTE, c-TCD and Contrast transesophageal echocardiography (c-TEE). Each of them has advantages and limitations in the diagnostics of a patient with stroke, but they should, in principle, be equivalent: they all detect RLS by MBs, either visually (TTE and TEE) or by Doppler shift (TCD). Therefore, provided that the technique and visualization is adequate, and the physiology behind the presence of the shunt (at rest or with the VM) is similar, there should be no significant difference in diagnostic accuracy [22]. C-TEE is regarded as the “gold standard” for the diagnosis of cardiac RLS [23].However, small PFO is hard to detect by TEE, and it may be difficult to perform the VM during TEE, especially in elderly patients with severe neurological deficits [24]. Besides, other less invasive techniques, such as TTE and TCD, have been improved and become preferred method to detect for PFO [12].

In this study, the incidence of permanent and total RLS in migraine was higher than that of controls. In addition, compared with controls, the positive rate of RLS in both MA and MO increased ($P < 0.05$), this is consistent with Yang et al's study [25]. It suggested that PFO associated RLS may be associated with migraine (MA and MO). However, Yang only used c-TCD to evaluate the positive rate of RLS, which was difficult to determine the anatomic origin of intracranial MES, in other words, it can’t exclude extracardiac RLS, and to some extent it affects the accuracy of the results.[12] However, c-TTE can make up for c-TCD’s deficiency and has advantages on the judgment of intracardiac RLS, therefore the results are expected to be more accurate. The mechanism of PFO causing migraine is unknown, possible causes being coughing, straining to defecate, during the VM, and lifting heavy objects which can cause right atrial pressure (RAP) to be increased and exceed the left atrial pressure (LAP), making it easier for RLS to go through a PFO, MES and metabolite products from venous circulation enter the intracranial artery and cause brain stimulation [12]. Nozari et al [26] showed in mice that small particulate or air emboli injected into the carotid artery were able to evoke a cortical spreading depression (CSD) without causing ischemia. This study suggested that abnormal microembolism and ischemia may provide a trigger for migraine [27–29]. In addition, the correlation between PFO and migraine may be related to genetics. A recent report documented that the occurrence of atrial shunt was consistent with autosomal dominant inheritance to some families with aura migraine [30].

In this study, the proportion of large shunt in the MA group and the MO group were increased (especially in MA) compared with controls, suggesting that the correlation between PFO and migraine may be related to large shunt. Larger RLS may increase migraine probability, suggesting a “neuronal threshold” above which migraine is triggered. Jesurum et al’s [31] reported a follow-up study of 67 migraineurs’ migraine symptoms after transcatheter PFO closure, which use migraine relief (> 50% reduction in frequency) as the endpoint, migraineurs with aura were 4.5 times more likely to experience migraine relief than migraineurs without aura. Although some patients have RLS shunt, there was no statistically significant

difference in migraine symptom relief between the complete group and the incomplete group (77% vs 83%, $P = 0.76$). In conclusion, migraine relief may occur despite residual RLS after transcatheter PFO closure, which may suggest a reduction in RLS burden below a neuronal threshold that triggers migraine. Some scholars have reported that migraineurs with RLS were associated with impairment of dynamic cerebral autoregulation (dCA). Guo et al [32] divided 66 migraine patients into the RLS group (n = 30) and the non-RLS group (n = 36). It was found that phase difference (PD) of patients in the RLS group were significantly lower than those in the non-RLS group ($P < 0.001$), and The PD in the large RLS group was significantly lower than that of the small RLS group ($P < 0.01$) and non-RLS group ($P < 0.001$), dCA was impaired in migraineurs with large RLS, and this may represent a potential mechanism linking RLS and migraine. Transcatheter PFO closure has recently become an effective therapy for improving migraine symptoms and reducing ischemic events. It is essential to analyze PFO characteristics and identify high-risk PFO. Compared with controls, the prevalence of large-size PFO (≥ 2.0 mm) increased ($P = 0.048$), length of PFO, long-tunnel PFO (≥ 10.0 mm) was no difference among groups (respectively, $P = 0.199$, $P = 0.095$). It was suggested that PFO may cause migraine related to the large-size PFO. This may be due to an increased risk of paradoxical embolism in large PFO [33].

These discovery of a possible link between migraine and PFO remains controversial. As a rule, embolic events show an unpredictable hemispheric distribution, while migraine pain is typically lateralized, often periodic and predictable, like menstrual migraine. Moreover, patients with PFO combined with migraine experienced a decrease in headache symptoms with age [30]. Whether the relationship between PFO and migraine is causal or symbiotic remains to be studied.

Our study may have some limitations: first, some of the studied subjects were outpatient patients, which may have selection bias. Secondly, the diagnostic method of PFO is c-TEE. Due to invasive examination and difficulty in VM, only some patients have completed c-TEE.

Conclusion

PFO is associated with increased migraine (especially with aura), when the PFO is permanent RLS, large RLS and large-size PFO (≥ 2.0 mm).

Abbreviations

RLS: Right-to left shunt; PFO: Patent foramen ovale; c-TTE: Contrast transthoracic echocardiography; c-TCD: Contrast transcranial Doppler ultrasonography; MA: Migraine with aura; MO: Migraine without aura; TEE: transesophageal echocardiography; MCA: Middle cerebral artery; VM: Valsalva maneuver; MBs: Micro-bubbles signal; RA: Right atrium; LA: Left atrium

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Yichang Central People's Hospital(No, HEC-KYJJ2020-002-01).

Consent for publication

All patients provided informed consent, they all give their consent for publication.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Finding

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Authors' contributions

QZ and RLcontributed to the study concept and design, the diagnosis of the patients and the acquisition, analysis and interpretation of data and drafted the manuscript. JZ contributed to the study concept and design, ZD andYC contributed to the data acquisition. All authors read and approved the final manuscript.

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Figures

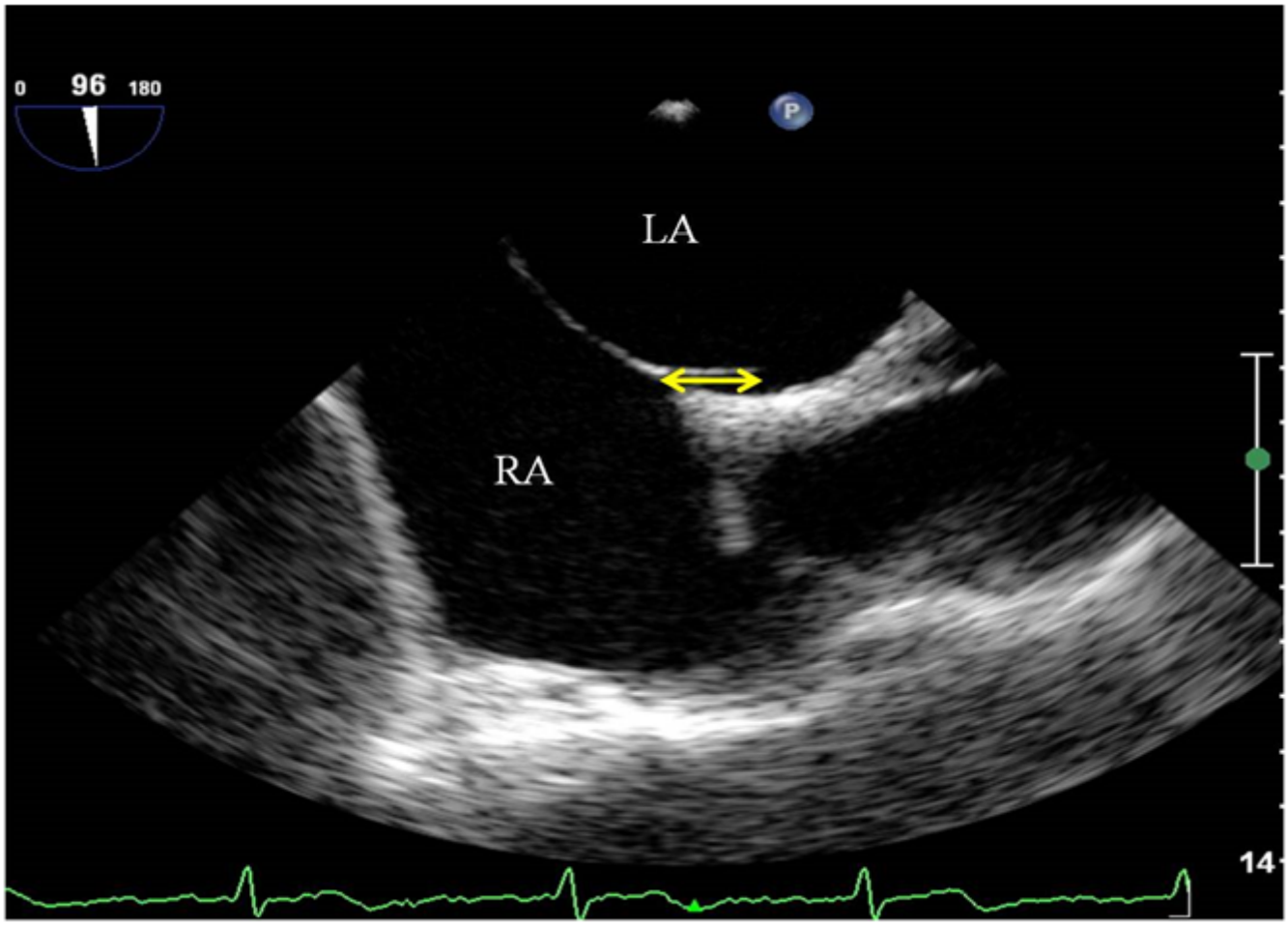

Figure 1

The septum primum against the septum secundum by TEE. RA : right atrium, LA : left atrium

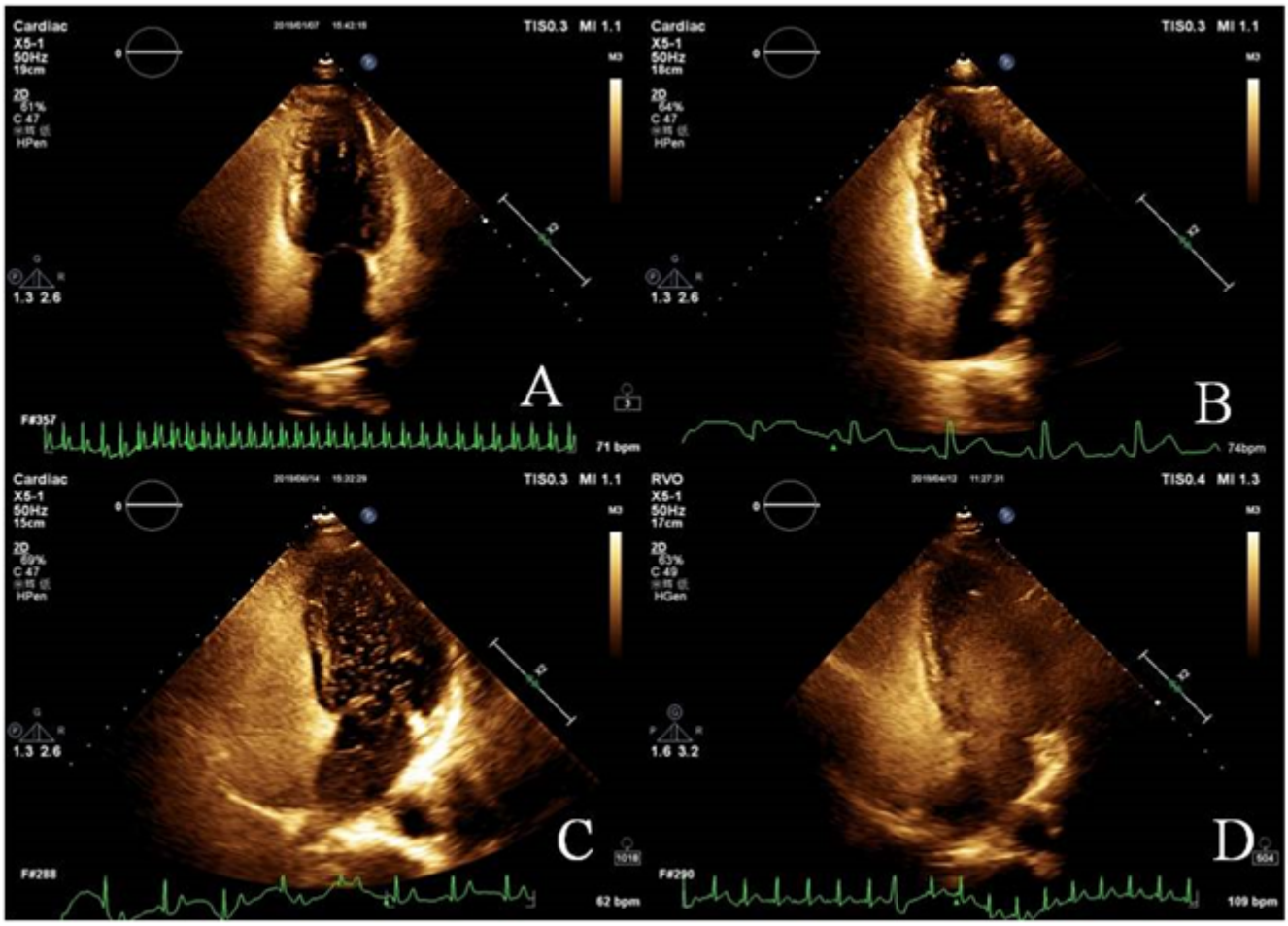

Figure 2

Quantification of RLS by c-TTE. (A): grade 0, no occurrence of micro-bubbles. (B): grade I, 1~10 micro-bubbles. (C): grade II, 11~25 micro-bubbles. (D): grade III, more than 25 micro-bubbles or left atrium nearly filled with micro-bubbles or left atrial opacity.

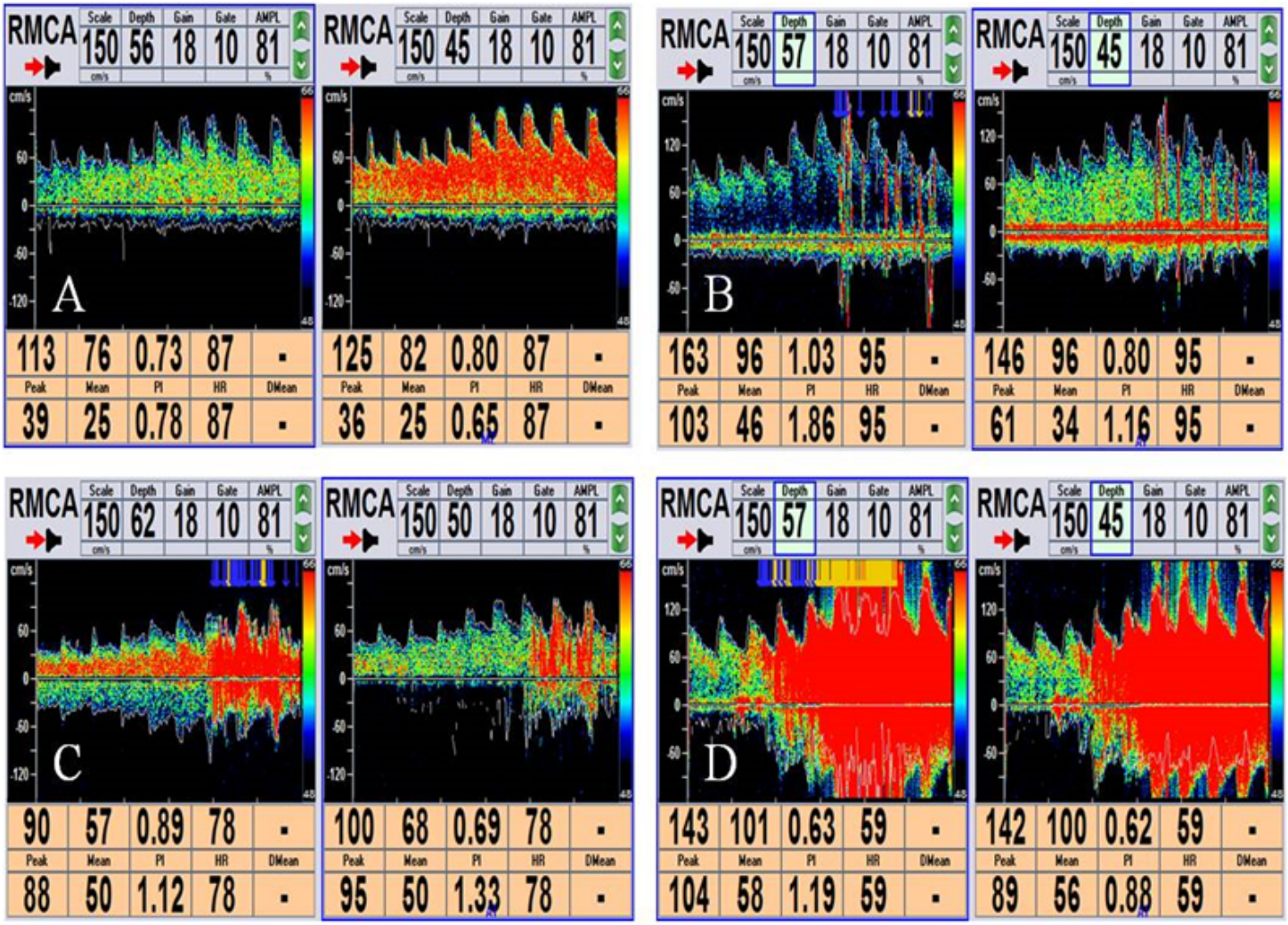

Figure 3

Quantification of RLS by c-TCD. (A): grade 0, negative. (B): grade I, 1≤ MES ≤10. (C): grade II, MES >10 and no curtain. (D): grade III, curtain.