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Modified Right Heart Contrast Echocardiography Versus Traditional Method in Diagnosis of Right-to-Left Shunt: A Comparative Study

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Authors' Contribution:
A Study Design
B Data Collection
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Summary

Background: The purpose of this study was to evaluate the reliability, effectiveness, and safety of modified right heart contrast transthoracic echocardiography (cTTE) in comparison with the traditional method.

Material/Methods: We performed a modified right heart cTTE using saline mixed with a small sample of patient's own blood. Samples were agitated with varying intensity. This study protocol involved microscopic analysis and patient evaluation. 1. Microscopic analysis: After two contrast samples had been agitated 10 or 20 times, they underwent a comparison of bubble size, bubble number, and red blood cell morphology. 2. Patient analysis: 40 patients with suspected RLS (right- to-left shunt) were enrolled. All patients underwent right heart contrast echocardiography. Oxygen saturation, transit time and duration, presence of RLS, change in indirect bilirubin and urobilinogen concentrations were compared afterward.

Results: Modified method generated more bubbles ($P<0.05$), but the differences in bubble size were not significant ($P>0.05$). Twenty-four patients were diagnosed with RLS (60%) using the modified method compared to 16 patients (40%) with the traditional method. The transit time of ASb20 group was the shortest ($P<0.05$). However, the duration time in this group was much longer ($P<0.05$). Also, in semi-quantitative analysis mean rank of RLS was higher after injecting the modified contrast agent agitated 20 times ($P<0.05$).

Conclusions: Modified right heart contrast echocardiography is a reliable, effective and safe method of detecting cardiovascular RLS.

MeSH Keywords: Contrast Media • Echocardiography • Microbubbles

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Background

Cardiovascular right-to-left shunt (RLS) is increasingly more often recognized as an important condition associated with a number of pathological states, such as transient ischemic attack (TIA), cryptogenic stroke, migraine, platypnea-orthodeoxia syndrome and decompression sickness in scuba divers [1]. The most common shunt is the patent foramen ovale (PFO), a flap-valve defect in the interatrial septum, which is present in approximately 25% of individuals [2,3]. Other RLS's include atrial septal defect (ASD) and pulmonary arterio-venous malformation (PAVM) [4,5].

Detection and assessment of RLS by right heart contrast transthoracic echocardiography (cTTE) has become a routine diagnostic procedure in many echocardiographic labs.

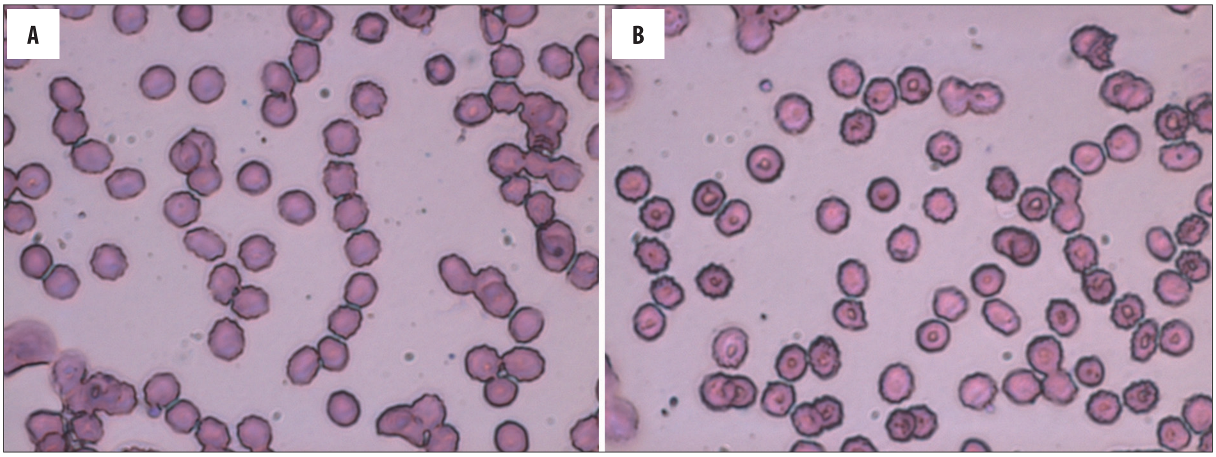

Figure 1. Microscopic appearance of red blood cells after agitating samples 10 (**A**) and 20 times (**B**). Blood red cell membranes visible in panel B are seriously damaged.

A contrast agent (CA) that cannot cross the pulmonary capillary system is required. Although different kinds of CAs have been used in the past, agitated saline (AS) is the simplest and cheapest medium that does not produce side effects. In their studies on transcranial Doppler examination previous researchers added a small sample of patients' own blood into the saline (ASb) in order to increase the number of microbubbles [6]. However, to the best of our knowledge, few studies comparing these methods comprehensively by using cTTE were reported [7]. The aim of our study was to compare the reliability, effectiveness, and safety of modified (ASb) cTTE with traditional (AS) method.

Material and Methods

Patients

This study was approved by the Ethics Committee of Shandong Chest Hospital, and all patients gave written informed consent before cTTE. 40 consecutive patients admitted to our hospital from Mar 1st, 2014 to Dec 10th, 2014 were enrolled. This group included 18 men and 22 women (mean age: 41±14 years); 18 with history of cryptogenic stroke (18/40, 45%), 10 with history of TIA (10/40, 25%), 8 with migraine (8/40, 20%), and 4 with orthodeoxia (4/40, 10%).

Microscopic image evaluation

Two types of CA (modified (ASb): 8ml saline + 1ml blood +1ml air, and traditional (AS): 9ml saline +1ml air) were agitated 10 or 20 times, and subsequently underwent microscopic examination (Olympus BX51, Japan) to evaluate bubble size, bubble number, and red blood cell morphology.

Echocardiographic protocols and image evaluation

All cTTE examinations were carried out by experienced sonographers using Philips iE Elite (Philips, Medical Systems, Eindhoven, The Netherlands). Echocardiographic standard protocols based on the recommendations of the American Society of Echocardiography were followed to assess the chamber size, cardiac structure and function [8–10]. The cTTE was performed in a semi-Fowler's position. Each study participant was subject to assessment using the following four methods: injection of saline agitated 10 times (AS10), saline agitated 20 times (AS20), saline mixed with blood and agitated 10 times (ASb10), and saline mixed with blood and agitated 20 times (ASb20). The apical 4-chamber view was visualized in each patient assessed with those four methods, intervals between each examination was at least 5 minutes.

Before the infusion, CA was agitated by pushing the mixture between two 10-ml syringes 10 or 20 times through a three-way venous line. A Valsalva maneuver (VM) was maintained for at least 5 seconds after infusion of CA. Time interval from the injection to the first appearance of air bubbles in the right heart (transit time, TT) and the time interval between of first bubble appearing in the right heart to the disappearance of the last bubble (duration time, DT) were calculated. Images were analyzed frame by frame, and RLS was semi-quantified into 4 grades: grade 0 – no RLS, grade 1 – mild RLS (1–10 bubbles in the left atrium), grade 2 – moderate RLS (11–25 bubbles in the left atrium), and grade 3 – severe RLS (more than 25 bubbles in the left atrium or opacification of the left atrium) [11,12]. Appearance of microbubbles in the left atrium after 3 beats from opacification of the right atrium is suggestive of PAVM [13]. Fluctuations in oxygen saturation were monitored, and the RLS was compared using different methods, indirect bilirubin and urobilinogen change after the cTTE.

Statistical analysis

Statistical analyses were performed using commercially available statistical software (SPSS version 19.0; SPSS, Inc., Chicago, IL). Bubble size, bubble number, TT, and DT differences were assessed by one-way ANOVA, followed by a post hoc comparison using Bonferroni test. Changes in oxygen saturation, indirect bilirubin and urobilinogen after cTTE were compared with paired Student's t-test. Semi-quantified results of different methods of RLS diagnosis were assessed with Kruskal-Wallis test. $P<0.05$ was considered statistically significant.

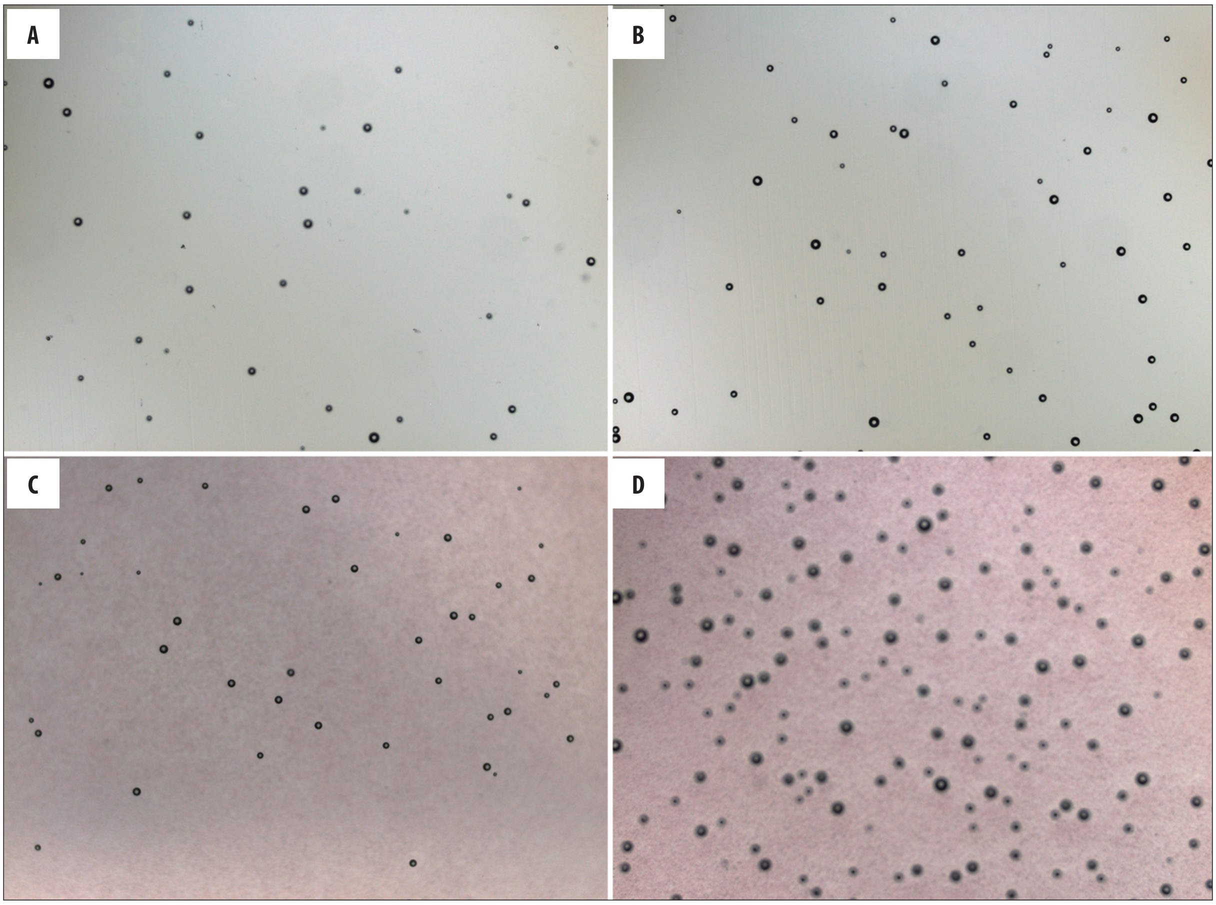

Figure 2. Microbubbles generated with different methods (**A–D** represent AS10, AS20, ASb10, and ASb20, respectively). As demonstrated, saline with blood agitated 20 times generated more microbubbles than other methods.

Results

Microscopic image evaluation

The red blood cell membranes were severely damaged after being agitated 20 times (Figure 1). The ASb20 group generated the largest number of microbubbles (F=73.529, P=0.006), while the bubble size did not show much difference (F=1.373, P=0.451) (Figures 2, 3, Table 1).

Echocardiographic Image evaluation

None of the 40 subjects presented with side effects. 24 patients were diagnosed with RLS (60%) after examination with the modified method, while in 16 patients RLS (40%) was demonstrated using the traditional method. These four methods differed significantly with respect to the effectiveness of detection of RLS (H=65.11, P=0.003), group ASb20 exhibiting the highest (Figure 4, Table 2). Among the RLS-positive patients, 3 were suspected to have PAVM; others were considered to have intra-cardiac RLS. Moreover, there were statistically significant differences in TT and DT (TT: F=40.125, P=0.001; DT: F=41.25, P=0.003). ASb20 was characterized by the shortest TT and the longest DT (Figure 3). There was not much difference with regard to change in oxygen saturation, indirect bilirubin and urobilinogen concentrations after cTTE (all P>0.05) (Table 3).

Discussion

Results of our study demonstrated that modified CA, which had been agitated 20 times, generated more microbubbles than other contrast agents. Among patients with suspected RLS ASb20 also yielded more positive results, characterized by higher grading, shorter TT, and longer DT. Furthermore, physiological parameters did not show significant differences after cTTE.

In addition to agitated saline several solutions, such as Dextrose and Echovist, have been used as CAs for RLS detection [1]. Previous studies showed good specificity and sensitivity with respect to RLS detection [14,15]. Droste et al. found that a galactose-based CA generated more bubbles, which was probably due to generation of more stable microbubbles than by AS alone [15]. A modified cTTE examination showed the same effect on microbubbles as in previous research [6,7]. However, our study focused on TTE, not TCD. Moreover, we combined microscopic examination together with clinical evaluation.

From this study, we may conclude that greater agitation produces more microbubbles. At the same time, the effect of agitation can be augmented by addition of blood to stabilize the bubbles. However, agitation cannot be increased without limits. Red blood cells could be seriously damaged in the presence of more vigorous agitation. In this study,

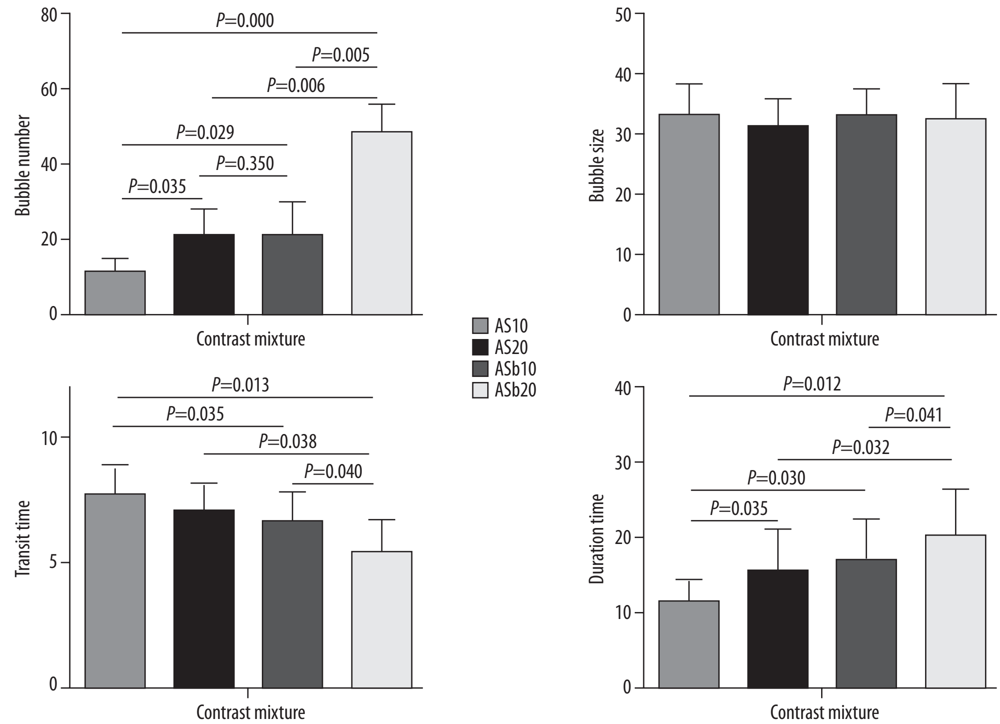

Figure 3. Comparison of the four methods according to the number of bubbles, bubble size, TT, and DT. Statistically significant differences were noted.

Table 1. Microscopic analysis.

	AS10	AS20	ASb10	ASb20
Bubble number	11.00±4.06	20.60±7.39	21.30±8.44	48.30±7.72
Bubble size (μm)	33.00±5.47	31.40±4.76	33.25±4.56	32.19±6.36

AS10 – saline agitated 10 times; AS20 – saline agitated 20 times; ASb10 – saline with blood agitated 10 times; ASb20 – saline with blood agitated 20 times.

all patients presented with stable physiological parameters, which reflected the safety of the modified method. However, it is unclear whether there are any side effects when the agent is agitated more than 20 times or after repeated cTTE examinations.

Venous source of thrombosis, transiently raised right atrial pressure during the neurological event, and the presence of PFO constitute the "PFO triad" [16]. Many pathological states, such as cryptogenic stroke, TIA, migraine, platypnea-orthodeoxia syndrome, or decompression sickness affecting scuba divers are associated with the presence of PFO. The possible mechanism might involve migration of thrombus, air bubble, fat embolus, or chemical substances from the venous system into the left heart through an intra- or extra-cardiac shunt, a PFO in particularl [17]. Thus, detection of RLS is the key to treatment. Right heart contrast echocardiography is a novel technique enabling RLS detection and its semi-quantitative assessment [11]. The recently published AHA/ASA guideline for prevention of stroke in patients with stroke and TIA recommended that any patient with PFO, who had suffered ischemic stroke or transient ischemic attack, may receive antiplatelet or warfarin therapy in order to minimize the risk of stroke recurrence [18]. If patients have moderate to severe RLS due to PFO or ASD, they are referred for closure the device implantation [18,19].

Although the effectiveness of RLS detection varied with CA composition and degree of agitation in our study, controversy still exists. Lefèvre J et al. found that composition of the contrast agent did not appear to affect the rate of detection of PFO, while contrast quality in the right atrium during TTE was better with mixtures of dextrose with air and blood, or hydroxyethylamidon mixture, than a combination of dextrose and air [20]. If CA composition and agitation affect the outcomes of semi-quantification, then the results negative in traditional cTTE might be positive in modified cTTE technique. According to our experience, even some healthy adults have mild RLS as assessed with modified cTTE. If there is a connection between RLS and clinical events, then to what degree does the presence of RLS affect clinical events? Further research is needed to answer this question.

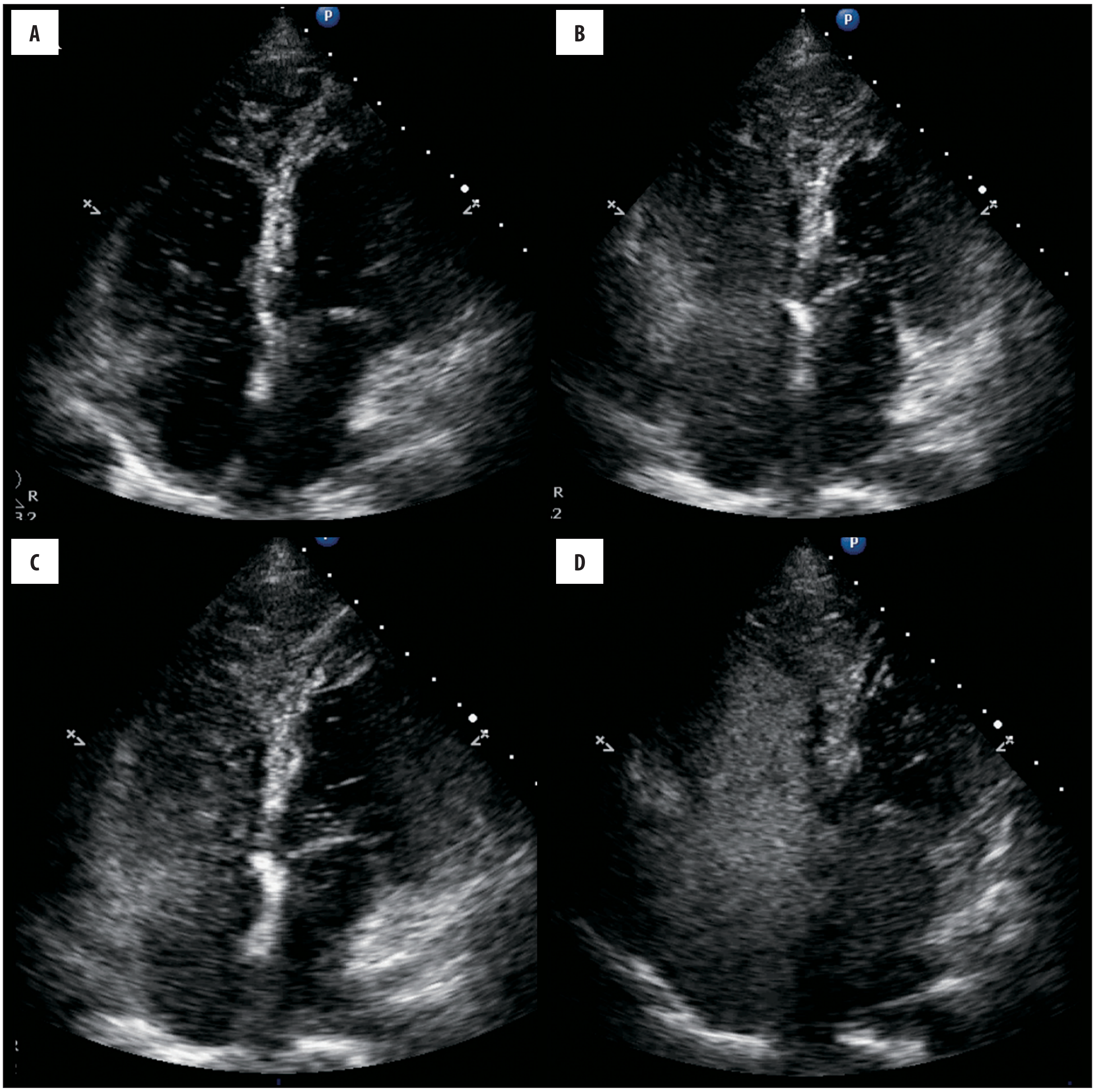

Figure 4. Right heart contrast TTE performed using different methods. Pictures **A–D** correspond to AS10, AS20, ASb10, and ASb20 contrast agents. Mild RLS was visualized with AS 10, while ASb20 demonstrated left atrium opacification.

Table 2. cTTE analysis.

	AS10	AS20	ASb10	ASb20
TT (s)	7.68±1.29	6.98±1.17	6.56±1.32	5.37±1.31
DT (s)	11.23±3.25	15.36±5.87	16.76±5.68	20.18±6.18
RLS positive (%)	11 (27.5%)	16 (40.0%)	21 (52.5%)	24 (60.0%)
Grade 0	29	24	19	16
Grade 1	10	13	14	4
Grade 2	1	3	7	12
Grade 3	0	0	0	8

Table 3. Physiological parameter before and after cTTE.

	Before cTTE	After cTTE	*t*	*P*
Oxygen saturation (%)	99.43±6.29	98.89±5.48	0.554	0.573
Indirect bilirubin (μmol/L)	16.64±4.93	16.268±5.16	–1.826	0.098
Robilinogen (μmol/L)	0.54±0.37	0.55±0.48	–0.329	0.698

There were also several limitations to our study. Firstly, right heart time-intensity curve was not analyzed to compare various methods objectively. Secondly, sample size was not large enough and the incidence of RLS was not representative. Nonetheless, this study contributes to improvement and standardization of right heart contrast echocardiography.

Conclusions

In conclusion, the modified cTTE using a mixture of saline and blood agitated 20 times is a safe, reliable, and effective method for detection of RLS. Moreover, effectiveness of RLS detection varied with a type of contrast agent and intensity of agitation. Semi-quantification using modified cTTE method and its relationship to clinical events nees further research.

Conflict of interest

None.

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