Importance of Contrast Transthoracic Echocardiography for Evaluating Large Right-to-Left Shunt in Patent Foramen Ovale Associated with Cryptogenic Stroke

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Abstract

Transcatheter closure of patent foramen ovale (PFO) is an effective therapy for preventing cryptogenic stroke (CS). The identification of high-risk PFO, which is more likely to be linked to CS, is essential. This study aimed to assess the accuracy of contrast transthoracic echocardiography (TTE) for evaluating large right-to-left (RL) shunt. We enrolled 119 patients with or without CS who were confirmed to have PFO. The severity of RL shunt evaluated by contrast TTE and transesophageal echocardiography (TEE) was classified as follows: small (<10 microbubbles), moderate (10–20 microbubbles), and large (>20 microbubbles). With contrast TTE, large RL shunt was observed in 94 (79%) of 119 patients, including 66 of 74 with CS and 28 of 45 without CS. With contrast TEE, large RL shunt was observed in 33 (28%) patients, including 26 with CS and 7 without CS. Contrast TTE showed large RL shunt more frequently than contrast TEE ($p < 0.01$). Large RL shunt evaluated by contrast TTE had a sensitivity of 89% and an accuracy of 70% for the association with CS, whereas large RL shunt evaluated by contrast TEE had a sensitivity of 35% and an accuracy of 56%. Accuracy was significantly greater in contrast TTE than in contrast TEE ($p = 0.02$). In conclusion, contrast TTE identified large RL shunt more frequently. Large RL shunt evaluated by contrast TTE provided greater accuracy for the association with CS. Our findings suggest that contrast TTE is valuable for evaluating large RL shunt as high-risk PFO.

Introduction

Patent foramen ovale (PFO) is linked with various diseases, including cryptogenic stroke (CS) [1–6]. Since randomized trials have demonstrated that transcatheter closure of PFO reduces the recurrence of stroke at higher rates compared to medical therapy [7–9], the relationship between PFO and CS has become increasing interest. The prevalence of PFO is approximately 25% in the general population [10]. Thus, the diagnosis of high-risk PFO, which is more likely to be linked to CS, is important.

Large right-to-left (RL) shunt is effective to stratify PFO for an increased risk of CS. Contrast transesophageal echocardiography (TEE) remains the standard reference for assessing the severity of RL shunt [11, 12], but contrast TEE often has the difficulty in accurately evaluating large RL shunt due to an insufficient Valsalva maneuver. Whereas, contrast transthoracic echocardiography (TTE) has been reported to be useful for PFO detection with a high sensitivity and specificity [13]. Contrast TTE can obtain an adequate Valsalva maneuver. Therefore, contrast TTE may be effective to accurately evaluate large RL shunt. This study aimed to assess the accuracy of contrast TTE compared to TEE for evaluating large RL shunt associated with CS.

Methods

Study population

A total of 119 patients with or without CS who were confirmed to have PFO were enrolled. Presence of PFO was confirmed by TEE and cardiac catheterization. Patients with CS were proven to have cerebral

infarction by magnetic resonance imaging. CS was diagnosed by a neurologist based on the exclusion of all other identifiable causes of stroke, such as large artery atherosclerosis, cardioembolism, small vessel disease, and arterial dissection, using brain and carotid imaging, electrocardiography, and echocardiography. All patients provided written informed consent for examination. The study was approved by the ethics committee of our institution.

Contrast TTE

TTE using a 2.5- to 3.5-MHz probe with harmonic imaging (iE33 with an S5-1 probe; Philips Medical Systems, Best, The Netherlands, and Artida with a PST-25BT probe; Canon Medical Systems, Otawara, Japan) was performed. TTE images were obtained in an apical four-chamber view or a subcostal four-chamber view. Gain settings were individually adjusted to optimize visualization of the interatrial septum and agitated saline contrast. Saline contrast was produced by 1 mL air, 1 mL blood, and 8 mL saline, and was agitated between two 10 mL syringes connected with a three-way stopcock. Contrast TTE with a spontaneous Valsalva maneuver was performed at two times. Agitated saline contrast was injected from an antecubital vein during the strain phase of the Valsalva maneuver, and the Valsalva maneuver was released immediately after opacification of the right ventricle. TTE images were digitally stored. The maximum number of microbubbles appearing in the left ventricle was counted in a single frame. The severity of RL shunt was classified into three groups by independent cardiologists who were unaware of the status of the patient. Large RL shunt was defined as >20 microbubbles, moderate RL shunt was defined as 10-20 microbubbles, and small RL shunt was defined as <10 microbubbles.

Contrast TEE

TEE using a 5-MHz multiplane probe (iE 33 with an X7-2t probe; Philips Medical Systems) was performed under local anesthesia. If needed, intravenous sedation was administered at the time of probe insertion. The severity of RL shunt was evaluated at the end of the routine examination when a patient was less sedated to enable performance of the spontaneous Valsalva maneuver. Agitated saline contrast was injected during the strain phase of the Valsalva maneuver, and the Valsalva maneuver was released immediately after opacification of the right atrium. The Valsalva maneuver was considered effective if leftward bulging of the interatrial septum was observed. Contrast injection was repeated at two times. The maximum number of microbubbles appearing in the left atrium was counted in a single frame. Similar to contrast TTE, the severity of RL shunt was classified into three groups: large RL shunt (>20 microbubbles), moderate RL shunt (10–20 microbubbles), and small RL shunt (<10 microbubbles).

Variability

Inter- and intra-observer differences were analyzed in all TTE and TEE images. The severity of RL shunt was evaluated by two blinded observers and by a single observer at two different times. Percentage agreement was used to assess the inter- and intra-observer variabilities.

Statistical analysis

Data are presented as mean $\pm$ standard deviation for continuous variables and as number and percentage for categorical variables. The sensitivity, specificity, and accuracy of large RL shunt of contrast TTE and TEE for the association with CS were analyzed. Accuracy was defined as (true positive) + (true negative) / total in sample. Comparisons were analyzed using the Fisher's exact test. Statistical analysis was performed using JMP version 14.0 (SAS Institute Inc., Cary, NC, USA), and significance was defined as $p < 0.05$.

Results

Patient characteristics

The mean age of patients was 48 ± 15 years, and 63 patients were male. Seventy-four patients had CS, and 45 patients did not have CS.

Large RL shunt

With contrast TTE, large RL shunt was observed in 94 (79%) of 119 patients, including 66 of 74 patients with CS and 28 of 45 patients without CS, moderate RL shunt was observed in 14 (12%) patients, and small RL shunt was observed in 11 (9%) patients. With contrast TEE, large RL shunt was observed in 33 (28%) of 119 patients, including 26 of 74 patients with CS and 7 of 45 patients without CS, moderate RL shunt was observed in 37 (31%) patients, and small RL shunt was observed in 49 (41%) patients (Figure 1). Contrast TTE showed large RL shunt more frequently than contrast TEE ($p < 0.01$).

Differences in the severity of RL shunt between contrast TTE and TEE are shown in Table 1. Contrast TTE showing a greater severity of RL shunt than contrast TEE was observed in 74 (62%) patients, including 34 patients with large RL shunt on TTE and moderate RL shunt on TEE, 29 patients with large RL shunt on TTE and small RL shunt on TEE, and 11 patients with moderate RL shunt on TTE and small RL shunt on TEE. The same severity of RL shunt between contrast TTE and TEE was observed in 42 (35%) patients. Contrast TTE showing a less severity of RL shunt than contrast TEE was observed in 3 (3%) patients. Figure 2 shows a representative case demonstrating the difference in the severity of RL shunt between contrast TTE and TEE. Only a few microbubbles appeared in the left atrium with contrast TEE, but large RL shunt (>20 microbubbles) was observed with contrast TTE.

The sensitivity, specificity, and accuracy of large RL shunt of contrast TTE and TEE for the associated with CS are shown in Table 2. Large RL shunt evaluated by contrast TTE had a sensitivity of 89%, a specificity of 38%, and an accuracy of 70%. Large RL shunt evaluated by contrast TEE had a sensitivity of 35%, a specificity of 84%, and an accuracy of 54%. The accuracy of large RL shunt of contrast TTE was significantly greater than that of contrast TEE ($p = 0.02$).

Reproducibility

There were 99% agreement in the classification of RL shunt of contrast TTE and TEE by two blinded observers, and 98% agreement by a single observer assessing twice.

Discussion

The major findings of the present study were: 1) contrast TTE showed large RL shunt more frequently than contrast TEE, and 2) large RL shunt evaluated by contrast TTE had greater accuracy for the association with CS compared to that evaluated by contrast TEE. To the best of our knowledge, this is the first study to show the efficacy of contrast TTE for evaluating large RL shunt associated with CS.

Since randomized trials, such as the RESPECT, REDUCE, and CLOSE trials, have demonstrated the benefits of transcatheter closure for the reduction of stroke [7–9], transcatheter closure of PFO is expected to increase as a therapeutic option. PFO is common, but not all PFOs are the same. It is necessary to diagnose high-risk PFO, which is more likely to be linked to CS. Larger RL shunt carries a greater potential for transseptal passage of thrombus. Large RL shunt is a particularly important risk factor for an increased likelihood of CS [14–16]. Furthermore, the RESPECT and REDUCE trials revealed that the effect of transcatheter PFO closure for preventing CS was increased in patients with large RL shunt [7, 8]. The CLOSE trial included patients with large RL shunt or atrial septal aneurysm, and demonstrated that transcatheter closure was superior, with a lower rate of stroke (in fact, no stroke at all), compared to medical therapy [9]. With the advent of transcatheter closure of PFO, patient selection has become important. Large RL shunt is useful to identify patients who obtain greater benefit from transcatheter closure. Therefore, accurate assessment of large RL shunt is essential.

Contrast TEE is used for the assessment of RL shunt. The amount of RL shunt evaluated by contrast TEE has reportedly been associated with CS [14, 15], however several studies have shown that the distribution of RL shunt is not linked to CS [11, 17, 18]. These conflicting results could be explained by differences in the performance of the Valsalva maneuver. The Valsalva maneuver increases intrathoracic pressure and decreases venous return and left atrial pressure during the strain phase. Rebound venous return after the release increases right atrial pressure and the gradient between right and left atrial pressures, leading to opening of the flap-like foramen ovale and facilitating RL shunt. Thus, an adequate Valsalva maneuver is essential to assess the severity of RL shunt in patients with PFO.

Contrast TEE has technical limitations in the accurate assessment of RL shunt. The Valsalva maneuver is insufficient due to probe insertion. Under sedation, the Valsalva maneuver itself is difficult to perform. The fasting state causes a lower right atrial pressure, leading to a reduction in the right and left atrial pressure gradient with the Valsalva maneuver. Thus, contrast TEE could result in an underestimation of the severity of RL shunt [19]. Whereas, contrast TTE has increasingly been utilized for the detection of PFO. The diagnosis of PFO has greatly improved with high sensitivity and specificity [13, 20]. Contrast TTE has an advantage in that patients are able to adequately perform the Valsalva maneuver. On the basis of these findings, contrast TTE can be reliable for evaluating RL shunt. Additionally, TTE is simple to use, easily available, and low cost [21–23]. In clinical practice, contrast TTE could be used to assess RL shunt with an increased risk of CS and to select patients for transcatheter closure.

The present study had some limitations. First, the number of patients was small. Second, the severity of RL shunt depended on the degree of Valsalva maneuver. However, the assessment of RL shunt was

uniform because contrast TTE and TEE with the Valsalva maneuver were performed at a single institution. Finally, the efficacy of large RL shunt of contrast TTE was not assessed in an independent population. The accuracy in this study represented a best-case scenario.

In conclusion, contrast TTE can identify large RL shunt more frequently than contrast TEE. Large RL shunt evaluated by contrast TTE provides greater accuracy for the association with CS. Contrast TTE can be valuable for evaluating large RL shunt associated with CS in patients with PFO, and may be effective for stratifying patients who should undergo transcatheter PFO closure.

Declarations

Funding: The authors received no financial support.

Conflicts of interest: The authors have no relationships relevant to the contents of this paper to disclose.

Availability of data: This study is based on data from our institution. The data are available from the corresponding author on reasonable request.

Code availability: Not required.

Authors' contributions: All authors contributed to the collection of data, discussion and interpretation of the data, and the writing of the report. All authors reviewed and approved the manuscript for submission. The study was designed by YT, RN, TA, and HI. The analysis was performed by YT. The manuscript was written by YT.

Ethics approval: This study was approved by the ethical committee of our institution.

Consent to participate: Informed consent was obtained before entering this study.

Consent for publication: Not required.

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Tables

Table 1 Severity of RL shunt between contrast TTE and TEE

	Contrast TEE			
Contrast TTE	Small	Moderate	Large	Total
Small	9 (8%)	1 (1%)	1 (1%)	11 (9%)
Moderate	11 (9%)	2 (2%)	1 (1%)	14 (12%)
Large	29 (24%)	34 (29%)	31 (26%)	94 (79%)
Total	49 (41%)	37 (31%)	33 (28%)	119 (100%)
<i>RL</i> right-to-left, <i>TEE</i> transesophageal echocardiography, <i>TTE</i> transthoracic echocardiography				

Table 2 Large RL shunt of contrast TTE and TEE for the association with CS

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Contrast TTE	89%	38%	70%	68%	70%
large RL shunt					
Contrast TEE	35%	84%	79%	44%	54%
large RL shunt					
CS cryptogenic stroke, RL right-to-left, TEE transesophageal echocardiography, TTE transthoracic echocardiography					

Figures

Figure 1

RL shunt evaluated by contrast TTE and TEE Contrast TTE shows large RL shunt more frequently than TEE.

Figure 2

Representative case Contrast TEE (left) shows small RL shunt with a few microbubbles appearing (arrow) in the left atrium, whereas contrast TTE (right) shows large RL shunt with >20 microbubbles appearing (arrow) in the left ventricle. LA left atrium, LV left ventricle, RA right atrium, RV right ventricle