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CLINICAL/ORIGINAL PAPERS

Head-to-head comparison of real-time three-dimensional transthoracic echocardiography with transthoracic and transesophageal two-dimensional contrast echocardiography for the detection of patent foramen ovale

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Aims To assess the incremental value of real-time three-dimensional echocardiography (RT-3DTE) over contrast transthoracic echocardiography (TTE), compared with contrast transesophageal echocardiography (TEE) in the identification of patent foramen ovale (PFO).

Methods and results Eighty-one consecutive patients with history of migraine headache (MH) or unexplained cerebrovascular events (CE) were examined using RT-3DTE, contrast TTE, and contrast TEE in sequence. Feasibility of RT-3DE in patients with MH and CE was 98 and 91%, respectively. Mean time for 3D colour data set acquisition was 9 ± 5 min. PFO was diagnosed using contrast TEE in 36 patients (overall prevalence = 44%). Diagnostic accuracy of RT-3DE was significantly higher than that of contrast TTE: sensitivity 83 vs. 44%, $P < 0.001$; specificity 100 vs. 100%, $P7 =$ NS; positive predictive value 100 vs. 100%, $P =$ NS; negative predictive value 88 vs. 69%, $P < 0.01$; accuracy 93 vs. 75%, $P < 0.003$. Five of the six patients in whom RT-3DTE did not identify PFOs showed a defect diameter smaller than 2 mm.

Conclusion RT-3DTE is a feasible, accurate, and reproducible technique to detect PFO without the need of saline contrast injection. Its accuracy is superior to contrast 2D TTE and close to that of contrast TEE.

Keywords Echocardiography • Contrast • Three-dimensional echocardiography • Patent foramen ovale • Transesophageal • Cryptogenetic stroke • Divers

Introduction

The patent foramen ovale (PFO) may be detected by transthoracic (TTE) and transesophageal (TEE) echocardiography and by transcranial Doppler[1,2] in 25% of otherwise normal subjects (7% large PFOs at rest and an additional 20% were on Valsalva manoeuvre). Establishment of a strong association of cryptogenetic stroke with PFO in patients less than 55 years of age, and development of several novel procedures for PFO closure, including minimal-access surgery and percutaneous catheter closure, have increased the need for accurate detection and assessment of defect size, morphology, and spatial relationships.[3] At present, TEE associated with intravenous injection of agitated saline contrast (contrast TEE) represents the reference imaging technique for anatomical and functional definition of the interatrial septum and measurement of PFO size.[4] Sensitivity and specificity of contrast TEE for the detection of PFO have been reported to range between 68 and100% and between 70 and 100%, respectively.[5,6]

However, TEE is a semi-invasive procedure, and injection of agitated saline contrast may be complicated by symptomatic

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paradoxical air embolism.[7–11] Real-time three-dimensional transthoracic echocardiography (RT-3DTE) facilitates spatial recognition of intracardiac structures, potentially enhancing diagnostic accuracy of conventional, unenhanced TTE.[12]

The aim of the present study was to assess the incremental value of unenhanced RT-3DTE over contrast TTE, compared with contrast TEE, in the identification of PFO in patients with history of migraine headache (MH) or unexplained cerebrovascular ischaemic events (CE).

Methods

Study protocol

Between July 2007 and July 2008, we enrolled all consecutive patients in sinus rhythm and history of MH or CE who were referred to our Echolab for routine echocardiographic assessment. In patients with CE, the diagnosis of a cerebrovascular ischaemic event was based on the sudden onset of neurological deficits and the corresponding morphological findings at computer tomography or magnetic resonance study of the brain. In patients with MH, a neurologist made the diagnosis of MH with aura and frequent and refractory attacks as defined by the criteria of the International Headache Society.[13] Exclusion criteria included other cardiovascular defects, pregnancy, the presence of intracardiac thrombi, active endocarditis, coagulopathy, bacteriemia, or active infections, portal hypertension or pulmonary arteriovenous malformation. All patients underwent RT-3DE followed by contrast TTE and contrast TEE study in sequence. In addition, patients with MH underwent transcranial Doppler sonography too. All data were stored digitally in the hard disk of the ultrasound system and subsequently evaluated in random order by two independent observers (I.M. and S.G.), unaware of the results of contrast TEE. Presence or absence of PFO was assigned in case of agreement between the two observers. In case of disagreement, the patient group allocation was given by a third observer (S.L.).

The Ethics Committee of our Institution has approved the protocol, and all patients signed a written consent to be part of the study.

Echocardiography

All patients were examined using a commercially available GE Vivid7 (GE Healthcare, Horten, Norway) ultrasound system, equipped with standard probes: S3 for standard TTE, 3V for RT-3DTE, and T6 for multiplane TEE. TTE with colour Doppler was performed according to the standard practice guidelines.[14]

RT-3DTE imaging was obtained immediately after the end of the baseline two-dimensional study using standard apical and left parasternal approaches, plus the right parasternal approach with the patient placed in the right lateral decubitus position to obtain a 3D colour data set containing the entire interatrial septum.[15,16] The quality of RT-3DTE acquisitions was graded as satisfactory/good or insufficient/bad.

Afterwards, patients underwent contrast TTE and contrast TEE according to the standard protocols in our laboratory. Before performing contrast TEE, the heart and thoracic aorta were scanned for the presence of potential embolic sources. The interatrial septum was visualized both in the transverse midesophageal four-chamber view and in the longitudinal biatrial–bicaval view.

During both TTE and TEE studies, a bolus of agitated saline solution (9 mL saline and 1 mL air and blood mixture) was injected in the right cephalic vein while the patient was breathing quietly. Presence of PFO was diagnosed as a right-to-left interatrial shunt of at least one bubble

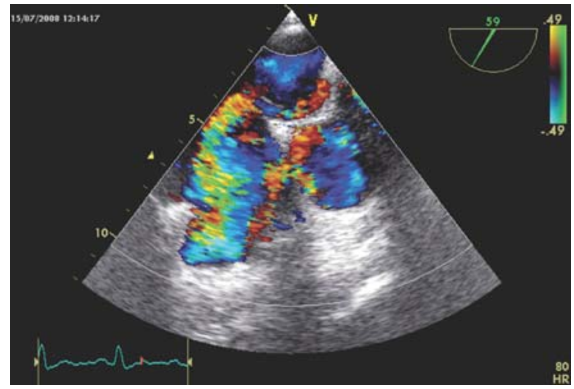

Figure 1 Colour Doppler transesophageal echocardiography study of interatrial septum at rest. The arrow indicates the passage of blood from right atrium (RA) into left atrium (LA). Separation of septum primum (SP) from septum secundum (SS) is clearly visualized and can be measured.

in the left atrium within 3–5 cardiac cycles after complete opacification of the right atrium,[17] with or without visualization of 'tunnel' by TEE-colour Doppler. After five heart beats from complete opacification of the right atrium, the patient was asked to perform the Valsalva manoeuvre according to the current protocols.[17] For bubbles appearing after the third heart beat, the origin from interatrial septum was checked at TEE.

The diameter of PFO was measured, using TEE, as the maximum separation between the septum primum and the septum secundum, during release of the Valsalva manoeuvre (*Figure 1*). Using RT-3DTE, PFO was identified as a flap of tissue overlying the foramen ovale with a small area of coloured flow (*Figure 2A–D*).

Statistical analysis

Continuous variables were summarized as mean ± SD. Categorical variables were reported as frequency (percentage) and compared by the χ^2 test. Statistical significance was assumed at a value of $P < 0.05$. The inter-observer agreement was measured by Cohen's kappa coefficient (k).

Results

Study population

During the study period, we enrolled 84 consecutive patients (78% females, 40 ± 11 years). Patients showed normal body size (Body mass index =25.2 ± 2.6 kg/m^2 and none was found to be affected by severe chronic pulmonary obstructive disease. All patients underwent successful contrast TTE and TEE (feasibility 100%). Three patients (3.6%) were excluded because quality of RT-3DTE acquisitions was graded insufficient/bad. The final study population consisted of 81 patients who were divided into two groups: 62 (84% females, age 38 ± 10 years) with MH and 19 (53% females, age 50 ± 11 years) with CE. As expected, patients with MH were significantly younger ($P < 0.0001$) and more frequently women ($P < 0.0001$) than CE patients.

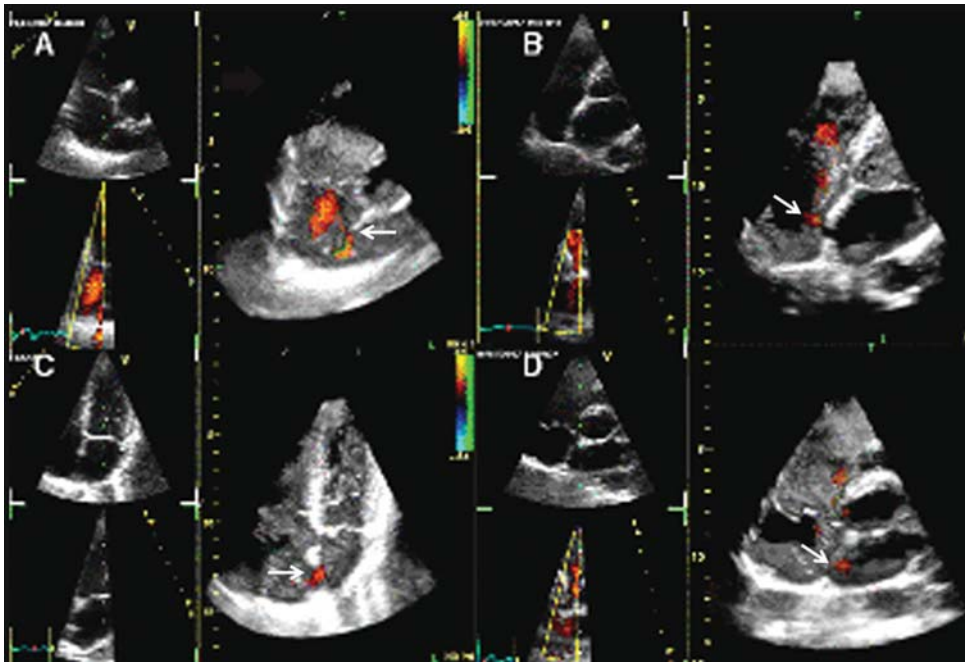

Figure 2 Four examples of real-time three-dimensional transthoracic echocardiographic visualization of patent foramen ovale (white arrows). Panels A and D, parasternal approach; Panels B and C, apical approach.

PFO was diagnosed using TEE in 36 patients (overall prevalence 44%): 29 among patients with MH (47%) and seven among patients with CE (37%; P = NS). Eight patients showed also atrial septum aneurysm and five patients showed a Chiari network.

Accuracy of real-time three-dimensional echocardiography

The feasibility of RT-3DTE in patients with MH and CE was 98 and 91%, respectively. The mean time of the RT-3DTE colour data set acquisition was 9 ± 5 min. All patients diagnosed to have PFO by RT-3DTE had positive shunt by colour Doppler.

There was a good agreement between the two observers in detecting PFO using RT-3DTE ($k = 0.82$).

Overall, the diagnostic accuracy of RT-3DE was significantly higher than that of contrast TTE: sensitivity 83 vs. 44%, $P < 0.001$; specificity 100 vs. 100%, P = NS; positive predictive value 100 vs. 100%, P = NS; negative predictive value 88 vs. 69%, $P < 0.01$; accuracy 93 vs. 75%, $P < 0.003$ (*Figure 3*).

In patients with MH, PFO were identified in 13/29 (45%) using contrast TTE and in 25/29 (86%) using RT-3DTE ($P < 0.001$). In patients with CE, PFOs were identified in three of seven (43%) using contrast TTE and in five of seven (71%) using RT-3DTE (P = NS). Sensitivity, specificity, positive and negative predictive value of contrast TTE and RT-3DTE in both MH and CE patients are summarized in *Table 1*. Average PFO diameter at contrast TEE was 2.2 + 1.5 mm in patients with MH, and 2.7 + 0.8 mm in patients with CE (P = NS). To assess the influence of PFO diameter on accuracy of RT-3DE, PFO diagnosed by contrast TEE were divided in tertiles according to the diameter of the defect. There was a significant relationship between the diameter of the

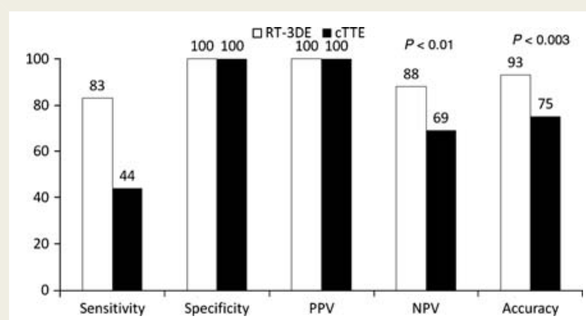

Figure 3 Accuracy of real-time three-dimensional (RT-3DE, white bars) and contrast two-dimensional (cTTE, black bars) transthoracic echocardiography in detecting patent foramen ovale in the overall study population. NPV, negative predictive value; PPV, positive predictive value.

PFO and the sensitivity of RT-3DE in diagnosing the defect (*Table 2*). Five of six (83%) of PFOs not identified by RT-3DTE showed a defect's diameter smaller than 2 mm.

Discussion

The results of the current study show that colour RT-3DTE is a feasible, accurate, and reproducible technique to detect PFO in patients with MH and CE. RT-3DE was significantly more accurate than contrast TTE, and it can avoid TEE and saline contrast injection in a sizable number of patients. Especially in those patients with larger PFO who are at higher risk of events and procedure

Table 1 Accuracy of contrast two-dimensional transthoracic and real-time three-dimensional echocardiography in detecting patent foramen ovale

		TEE		Sensitivity (%)	Specificity (%)	PPV (%)	PNV (%)	Accuracy (%)
		PFO+	PFO−					
MH								
TTE	PFO+	13	0	45	100	100	67	74
	PFO−	16	33					
RT-3DTE	PFO+	25	0	86	100	100	89	93
	PFO−	4	33					
CE								
TTE	PFO+	3	0	43	100	100	75	79
	PFO−	4	12					
RT-3DTE	PFO+	5	0	57	100	100	86	89
	PFO−	2	12					

MH, migraine headache; CE, cerebrovascular events; TTE, two-dimensional contrast transthoracic echocardiography; TEE, two-dimensional contrast transesophageal echocardiography; RT3-DTE, real-time three-dimensional transthoracic echocardiography; PFO, patent foramen ovale; PPV, predictive positive value; PNV, predictive negative value.

Table 2 Accuracy of real-time three-dimensional echocardiography in detecting patent foramen ovale according to the diameter of the defect

PFO diameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
0–2 mm	76	100	100	88	91
2.1–5.4 mm	89	100	100	98	98
5.5–8 mm	100	100	100	100	100

Abbreviations as in *Table 1*.

complications. Finally, we have also shown that there is a relationship between the size of the PFO and accuracy of RT-3DE, and false-negative cases are limited to patients with small (<2 mm) size PFO.

PFO is an oblique, slit-like defect resulting from incomplete fusion of septum primum (the foramen ovale) with septum secundum (the atrial septum). It is a relatively common finding in the healthy population, with an overall prevalence of 27% in autopsy studies.[1] The PFO role in paradoxical thromboembolism has been confirmed by individual reports and meta-analysis,[18] but a significant effect in severe migraine remains to be demonstrated.[19] Finally, PFO size may be an independent risk factor for recurrent CE.[6,18] Therefore, in young patients with cryptogenetic stroke, accurate assessment of atrial septum anatomy and detection or exclusion of PFO presence and its size are of paramount importance to address management.[18]

Currently, TEE associated with intravenous injection of agitated saline contrast represents the reference imaging technique for anatomical and functional definition of the interatrial septum and measurement of PFO size. However, TEE is a semi-invasive procedure burdened with patient discomfort, procedural risk, and significant time consumption,[20] and injection of agitated saline contrast may be complicated by symptomatic paradoxical air embolism.[7–11]

The risk of side effects of contrast TEE appears to be low.[7] Nevertheless, several cases of neurological deficiency have been already described after agitated saline contrast TEE with Valsalva manoeuvres. In a study of decompression sickness and interatrial shunts, Wilmshurst *et al.*[8] described four patients with symptoms such as syncope, confusion, or faintness following this procedure. Holcomb *et al.*[10] described two patients with PFO presenting with acute and focal neurological deficits after this procedure. The first one developed a right-lower quadrant anopsia with hand numbness and ataxia. The second one exhibited lower extremity numbness and central blindness. Srivastava and Undesser[9] reported three cases of transient ischaemic attack after contrast TEE diagnosis of right-to-left shunt. Therefore, another echocardiographic technique that is accurate in detecting PFO from transthoracic approach and without the need of contrast injection would be desirable.

RT-3DE allows fast acquisition of dynamic pyramidal data sets that encompasses the most part of the heart. Acquired data sets can be sliced in several planes and rotated allowing the observer to visualize cardiac structures like interatrial septum 'en face' from both the left and the right side with better understanding of its anatomy and its spatial relationship with adjacent structures. Addition of 3D colour Doppler flow mapping allows to visualize shunt jets in relation to the anatomy of the interatrial septum and to locate exactly the origin of the jet and the size of the defect. Our results show that transthoracic RT-3DE is a feasible, accurate, and reproducible technique to screen patients with CE and MH without the use of contrast.

Limitations of live RT-3DE include patient and technology issues. Patients must have an adequate acoustic window. In our experience, RT-3DE assessment of interatrial septum was feasible, especially via the right parasternal or subcostal windows. The most useful approach is the right parasternal one with the patient in the right lateral decubitus position, since in this way there is a perpendicular ultrasound path to the atrial septum. In all patients, an attempt was made to utilize this window in addition to the conventional apical, left parasternal, and subcostal views. Another limitation of RT-3DE is that the current technology provides a suboptimal spatial and temporal resolution. When imaging smaller defects that have dynamic shunts or shunts elicited only with Valsalva manoeuvre/coughing, RT-3DE accuracy may sometimes be hampered by this frame rate. In our patient's cohort, all false-negative cases except one showed a PFO diameter of less than 2 mm.

Conclusions

Spatial and functional anatomy of the interatrial septum can be visualized with RT-3DE colour technique to accurately detect PFO with a small additional time compared with usual TTE. The technique does not require the injection of agitated saline solution, and it is reproducible and accurate in comparison to contrast TEE, except in small (i.e. less than 2 mm) PFOs. In these cases, contrast TEE remains the gold standard for detection of PFO. Potential of RT-3DE to be used as a screening tool to detect PFO in divers and in patients with cryptogenetic stroke has to be evaluated in multicenter trials.

Conflicts of interest: none declared.

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