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Contrast transoesophageal echocardiography remains superior to contrast-enhanced cardiac magnetic resonance imaging for the diagnosis of patent foramen ovale

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Aims In 30–40% of patients with acute ischaemic stroke, the cause remains undefined (cryptogenic stroke). Contrast transoesophageal echocardiography (TEE) is considered the gold standard for patent foramen ovale (PFO) detection. Recently, however, cardiac magnetic resonance (CMR) has also been applied to detect PFO. In this study, we compared the diagnostic value of CMR and TEE in detecting PFO in a group of patients with apparently cryptogenic stroke.

Methods and results Twenty-five patients (age 50 ± 13 years, 16 males) with apparently cryptogenic ischaemic stroke underwent contrast-enhanced TEE and contrast CMR for detection of possible PFO. Both imaging studies were performed during Valsalva manoeuvre. PFO grading results were assessed visually both for TEE and for CMR, according to the entity of contrast passage in the left atrium (grade 0 = no PFO; grades 1, 2, and 3 = mild, medium, and wide PFO, respectively). TEE detected PFO in 16 patients (64%). Contrast-enhanced CMR identified a PFO in 7 (44%) of these patients. TEE showed a grade 1 PFO in five patients, a grade 2 PFO in eight patients, and a grade 3 PFO in three patients. Of these patients, CMR failed to identify PFO in all five patients with a grade 1 PFO, in one patient with a grade 2 PFO, and one patient with grade 3 PFO according to TEE. None of the nine patients without PFO at TEE was shown to have a PFO at CMR. When compared with TEE, the present methodology of CMR had a sensitivity of 50%, specificity of 100%, negative predictive value of 31%, and a positive predictive value of 100%.

Conclusion Our data suggest that TEE is the cornerstone imaging diagnostic test to detect and characterize PFO in patients with ischaemic stroke, and is shown to be better compared with the current CMR sequences.

Keywords Patent foramen ovale • Ischaemic stroke • Cardiovascular imaging

Introduction

Thirty to 40% of ischaemic strokes in patients <55 years of age have no identifiable cause (the so-called cryptogenic stroke).[1] Patent foramen ovale (PFO) is a haemodynamically insignificant interatrial communication present in >25% of the adult population.[2,3]

However, it has been difficult to non-invasively diagnose PFO *in vivo* until the development of echocardiography and the ability to image the interatrial communication during injection of saline contrast. With the use of contrast echocardiography, a strong association of apparently cryptogenic stroke with PFO has become evident in young (<55 years) patients,[4–6] and an association between the presence of PFO at echocardiography and

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apparently cryptogenic stroke has also recently been shown in older patients.[7]

Contrast-enhanced transoesophageal echocardiography (TEE) is now considered the reference test to detect PFO.[8–11] This method, however, is semi-invasive and is not tolerated by all patients. Recently, cardiac magnetic resonance (CMR) has been shown to be able to detect PFO.[12,13] There is a worldwide increase in the use of CMR to evaluate cardiac structure and function, and a paucity of data comparing CMR with TEE for the evaluation of PFO. Thus, in this study, we compared the results of CMR and TEE examinations with regard to PFO detection and grading in a group of patients with apparently cryptogenic stroke.

Methods

Patients

Seventy consecutive patients with age 18–75 years were admitted to our dedicated Stroke Unit with a diagnosis of acute ischaemic stroke or transient ischaemic attack between August 2006 and January 2007. The diagnosis was confirmed in all patients by cranial computed tomography, brain magnetic resonance imaging, or both. All patients underwent complete diagnostic workup with Doppler ultrasonography of the carotid and vertebral arteries with a 4–7 MHz linear-array scanner, standard electrocardiogram, and transthoracic echocardiography. In patients with suspected paroxysmal atrial fibrillation, a 24 h ECG Holter monitoring was also performed. The cause of stroke was established according to the modified TOAST criteria.[14] A definite mechanism of ischaemic stroke was identified in 45 patients. In 25 (35%) patients, the cause of the ischaemic stroke remained unknown despite the extensive diagnostic testing. This group underwent TEE and CMR to detect the presence of PFO. CMR and TEE were performed during the index admission after stroke, within 1 week of each other. Written informed consent was obtained from each patient or, if the patient was unable to provide consent, from the patient's relatives. The study was approved by the local ethics committee.

Transesophageal echocardiography

TEE was performed with a 5 MHz phased multiplane probe (Philips, iE 33). A dose of 0.02 mg of lidocaine (Xylocaine, AstraZeneca) was administered by spray in the pharynx for local anaesthesia, with no systemic sedation in order to maintain ability to adequately perform the Valsalva manoeuvre. A commercially available intravenous contrast agent (D-galactose, Echovist, Schering) was used in order to standardize the size and echogenicity of microbubbles for the detection of PFO. Echo-contrast was administered as a bolus of 10 mL via an antecubital vein during Valsalva strain and release phase while visualizing the two atria in the 90° bicaval view. TEE images were analysed by two experienced cardiologists. Atrial septal aneurysm was defined as movement of the atrial septum >10 mm.[5,24] The presence of PFO was defined by right-to-left shunting of bubbles within three cardiac cycles of Valsalva release. A semi-quantitative grading system was allocated as follows[15]: grade 0 = no evidence of contrast agent passage from the right to the left atrium; grade 1 = passage of three to nine microbubbles from the right to the left atrium; grade 2 = passage of 10–30 microbubbles from the right to the left atrium; and grade 3 = passage of >30 microbubbles from the right to the left atrium (i.e. complete opacification of left atrium due to shunting of contrast). Differences were resolved by consensus.

Cardiac magnetic resonance

CMR was performed on a 1.5 T scanner (Signa Excite II, GE Medical Systems, Buc, Paris), using the combination of a six-channel body-phased-array coil and a two-channel spine-phased-array coil was used with vector-ECG gating. A protocol was developed to detect PFO anatomy and dynamic shunting using the following sequences; steady-state free precession imaging was performed in two long-axis planes, a four-chamber stack and short axis stack (TR 2.8/TE 1.2 /Flip 55°/TI 325/matrix 256 × 256/slice thickness 5 mm, slice gap 0 mm) to assess the anatomy of the inter-atrial septum. Subsequent sequences were prescribed from the reference SSFP planes where the fossa ovalis was best visualized in order to provide two orthogonal views of the fossa ovalis; usually a four-chamber and modified atrial short-axis view. A fast-cine gradient echo sequence with a long TE was performed to detect turbulent jets (TR 15.4/TE 12.0/flip 20°/matrix 256 × 256). Contrast-enhanced perfusion imaging was then performed using a hybrid fast-gradient echo saturation recovery planar true-FISP sequence (TR 2.9/TE 1.3/flip 36°/TI 119/matrix 128 × 128/slice thickness 6 mm, slice gap 1 mm, temporal resolution three phases per R–R interval). During Valsalva manoeuvre, using respiratory bellows to monitor respiration, 10 mL of gadopentetate dimeglumine (Magnevist, Schering) was infused at 6 mL/s by a power injector into an antecubital vein followed by a 20 mL saline solution. Phase-contrast flow mapping was then performed to detect significant intra- and extra-cardiac shunts that may account for apparently cryptogenic stroke (such as anomalous pulmonary venous drainage or intrapulmonary arterovenous malformations).

Contrast-enhanced perfusion images were analysed by two radiologists and one cardiologist with SCMR level-3 expertise in cardiac imaging, who were blinded to the TEE results, with differences resolved by consensus. Visual assessment was performed for the presence of PFO anatomy and coexistent atrial septal aneurysm on SSFP and perfusion images during Valsalva manoeuvre. A semi-quantitative grading score was used as for TEE, to assess right-to-left shunting prior to contrast reaching the pulmonary veins: grade 0 = no contrast enhancement in the left atrium; grade 1 = mild contrast enhancement close to the atrial septum; grade 2 = only slight contrast enhancement in the body of the left atrial cavity; and grade 3, bright contrast enhancement in the entire left atrium before the contrast agent entered the pulmonary veins. Quantitative assessment was performed by placing a region-of-interest in the right atrium (RA), and another in the left atrium along the border of the fossa ovalis. Analysis of time-intensity curves was performed as described previously.[16] PFO was indicated when there was a clear peak in the left atrial signal at the same time as the right atrial signal was visible on time–intensity curve, implying the presence of a right-to-left shunt (*Figure 1*).

Results

Table 1 summarizes the clinical characteristics of all patients admitted to the Stroke Unit; age 22–85 years (mean, 62 ± 13 years), 44 males (63%). Twenty-five patients with apparently cryptogenic stroke were analysed by TEE and CMR. Overall, TEE detected the presence of a PFO in 16 (64%) patients with apparently cryptogenic stroke. CMR identified a PFO in 9 (36%) of these patients. Three patients with PFO had atrial septal aneurysm, which was concordantly identified on SSFP CMR sequences (*Figure 2*). However, CMR failed to identify seven patients with PFO seen on TTE; this included five patients with TEE grade 1

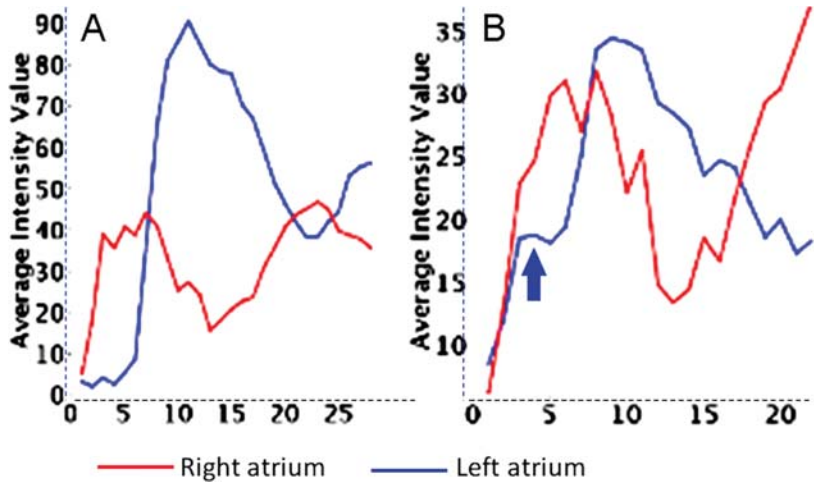

Figure 1 Cardiac MRI time-signal intensity curves. A region of interest is placed in the right atrium (red curve) and left atrium (blue curve), adjacent to the fossa ovalis, in order to detect inter-atrial shunt. Fast gradient echo images are acquired rapidly during infusion of gadolinium contrast and time-intensity curves generated. (*A*) Negative result, with a peak of contrast intensity in the right atrium separate from the subsequent peak in the left atrium. (*B*) Positive result, with an early peak in the left atrium (arrow) signifying transit of contrast material from the right to the left across a PFO.

Table 1 Main clinical characteristics of enrolled patients

	Apparently cryptogenic stroke	Ischaemic stroke	*P*
Patients (*n*)	25	45	
Age (years)	50 ± 13	60 ± 6	0.0001
Sex (%)			
Males	15 (60%)	30 (67%)	
Females	10 (40%)	15 (33%)	
Risk factors			
Smoking	5 (20%)	23 (51%)	0.03
Hypercholesterolaemia	11 (44%)	28 (62%)	0.05
Hypertension	6 (24%)	27 (60%)	0.0001
Type 2 diabetes	5 (20%)	23 (51%)	0.004
Systolic blood pressure (mmHg)	142 ± 11	148 ± 17	0.06
Diastolic blood pressure (mmHg)	76 ± 9	84 ± 8	0.003
HR (bpm)	74 ± 10	79 ± 6	0.01
Weight (kg)	73 ± 4	75 ± 3	0.0001
Height (cm)	169 ± 5	170 ± 3	0.003
BMI (kg/m^2)	25.4 ± 2.0	25.7 ± 1.3	0.01

HR, heart rate; BMI, body mass index.

PFOs, one with grade 2 PFO, and one with grade 3 PFO (*Table 2*). Furthermore, in patients in whom PFO was shown by both TEE and CMR, the latter tended to underestimate the degree of the interatrial shunt using the semi-quantitative grading score of contrast-enhanced images and time–intensity curves (*Table 2*). In the nine patients without evidence of PFO on TEE, there was no evidence of PFO on CMR. All patients had normal haemodynamic data with no significant intra- or extra-cardiac shunts detected by volumetric analysis of phase-contrast CMR curves. The fast-cine gradient echo sequence with long TE did not detect any turbulent jets, which is not surprising given the transient nature and small volume of PFO flow.

When compared with TEE as a 'gold standard' for the detection of PFO, the present methodology of CMR had a sensitivity of 50%, specificity of 100%, negative predictive value of 31%, and a positive predictive value of 100% (*Figure 3*).

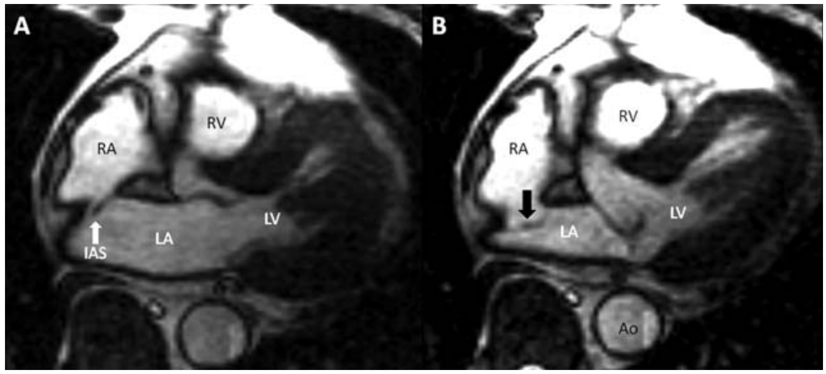

Figure 2 Cardiac MRI of atrial septal aneurysm. SSFP high five-chamber chamber view showing bulging of the atrial septum during the cardiac cycle from right (*A*) to left (*B*), consistent with atrial septal aneurysm. A diastolic frame with fossa ovalis [white arrow = (B) systolic frame showing deviation of the fossa ovalis towards the left (black arrow)]. RA, right atrium; RV, right ventricle; IAS, inter-atrial septum; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract.

Table 2 **Comparison between TEE and CMR grading scores**

	TEE			
CMR	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Grade 0	9	5	1	1
Grade 1	0	0	4	1
Grade 2	0	0	3	0
Grade 3	0	0	0	1

Discussion

This study shows that TEE more frequently identifies the presence of PFO in patients with apparently cryptogenic stroke, compared with CMR. When PFO is detected by CMR, it was shown to be accurate with a high specificity and a positive predictive value. However, the sensitivity of CMR for PFO was low, with a number of false negatives and a subsequently poor negative predictive value.

Until recently, the diagnosis of PFO had not been possible using CMR because of insufficient spatial and temporal resolution and the absence of a measurable shunt volume. Recent technical advances, however, might have improved the diagnostic accuracy of CMR. Mohrs *et al.* assessed the diagnostic role of dynamic contrast-enhanced MR in 15 patients with and 5 patients without PFO; CMR was able to correctly diagnose all patients with and without PFO and there was a good correlation of grading scores between CMR and TEE.[12] Nusser *et al.*, in a larger series of 75 patients undergoing percutaneous PFO closure, demonstrated that contrast-enhanced MRI was inferior to TEE for the detection of right-to-left shunting, in agreement with our result.[16]

The present data suggest that CMR is less sensitive than TEE for the diagnosis of PFO, failing to identify all patients with grade 1 PFO at TEE examination. Moreover, in our population, both semi-quantitative and quantitative analyses of CMR underestimated the amount of flow across the PFO when compared with TEE. This finding may have clinical relevance because PFO patients with large shunts have been shown to have a higher risk for paradoxical embolisms than those with small shunts.[17–20] Therapeutic strategies may also be guided by the severity of the shunt across the PFO.[10,21]

In those cases where CMR was able to detect PFO with good accuracy, the sequences that were found most helpful were SSFP analysis of atrial septal anatomy and the presence of aneurysm, and the real-time perfusion sequence during contrast administration allowing visualization of contrast entering the left atrium through the PFO. Time–intensity curves were useful to support the visual analysis. The long-TE fast gradient echo sequence did not add further information in the identification of PFO, but is a useful technique in the evaluation of larger turbulent jets, such as mitral or aortic regurgitation.

A number of possible explanations may explain the discrepancies between CMR and TEE in the assessment of PFO. First, there may be variation in the adequate performance of the Valsalva manoeuvre, which is the most effective way to induce dynamic right-to-left atrial shunting.[22] If the patient does not perform Valsalva manoeuvre correctly, a PFO can be missed.[23] The Valsalva release phase is a precise moment in which right atrial pressure exceeds left atrial pressure allowing right to left.[24] This time point is readily seen on TEE by visualizing the decrease in RA size followed by sudden movement of the inter-atrial septum during release phase; this real-time monitoring is not possible during CMR examination. The exact timing of Valsalva release may have been missed on CMR even with the use of respiratory bellows. Real-time free-breathing sequences are available, but at the cost of significantly lower spatial resolution. During TEE, repeated contrast injections may be performed, with some evidence that a greater number of injections (5–10 repeated injections) significantly increase the sensitivity to detect PFO,[25] whereas in the present series CMR perfusion imaging involved a single infusion of the gadolinium-based agent. Repeated contrast

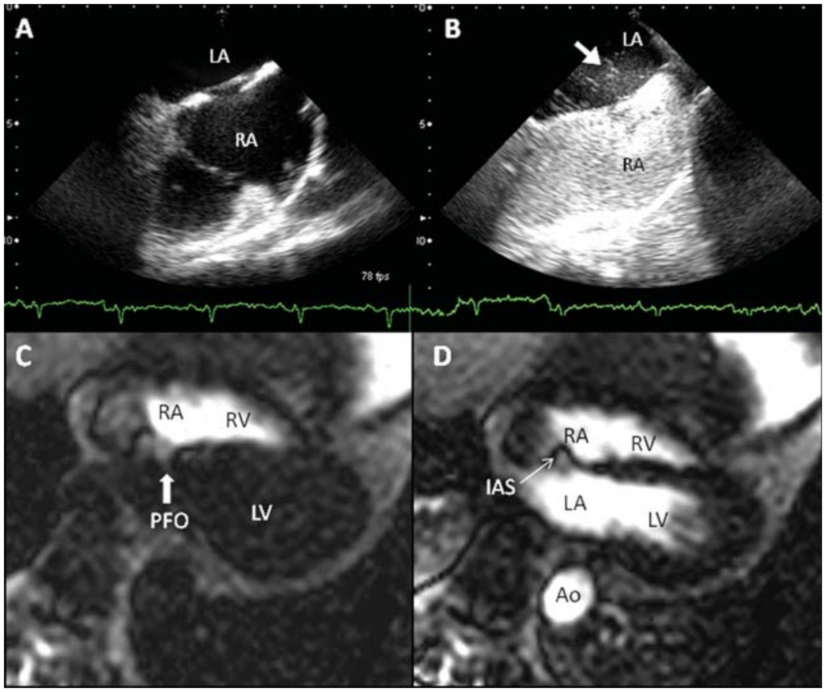

Figure 3 Comparison of TEE and CMR images in a patient with PFO. (*A*) TEE 90° view of the atrial septum. (*B*) TEE contrast injection at the moment of Valsalva release reveals passage of a large number of bubbles from right to left (arrow), assessed as a grade 2 shunt. (*C*) CMR fast gradient echo perfusion sequence four-chamber view, showing contrast filling the right atrium, with a jet of contrast crossing a patent foramen ovale into the left atrium (arrow). (*D*) The same four-chamber image three frames later, showing contrast filling the left heart via the pulmonary veins and opacifying the aorta. The position of the inter-atrial septum is clearly seen (arrow) and can be compared with the visualization of the jet in the previous frame. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PFO, patent foramen ovale; IAS, inter-atrial septum.

injection is also possible utilizing CMR (dependent on dose, patient body weight, and presence of preserved renal function); however, this would be confounded by the interaction with contrast present in the blood pool and returning to the LA via the pulmonary veins. A larger, single contrast bolus during CMR would increase the overall contrast transit time, and might improve the chance of matching the presence of right atrial contrast with Valsalva release during CMR. The current fast-gradient echo sequences for CMR perfusion imaging have significantly reduced temporal resolution when compared with TEE, and may therefore not be sensitive enough to detect rapid and short-lived passage of blood across a PFO prior to contrast obscuring the left atrium. Partial volume artefact from contrast filling the RA may also obscure the detection of small right-to-left shunts. Lastly, there may be minor theoretical differences in the rheology of galactose-based echo contrast and gadolinium-based CMR contrast.

We acknowledge the limitations of this small cohort. The prevalence of PFO in this population admitted to the stroke unit is slightly higher than that reported in previous studies,[7] which may reflect the selection bias or play of chance. The comparison of grading between CMR and TEE is subjective and semi-quantitative. The use of TEE as a comparator and a reference has inherent limitations, but is appropriate for comparison of CMR to the existing standard of TEE for PFO diagnosis. Lastly, the temporal and spatial resolutions of CMR sequences are continually improving.

The relevance of detecting a PFO in a patient with first-onset apparently cryptogenic stroke is still under debate. Recent prospective population studies by Meissner *et al.* (Olmsted County)[26] and Rundek *et al.* (Northern Manhattan)[27] question whether patients with a PFO have a higher risk of first embolic events than those without PFO. Certainly, the current guidelines do not support the closure of PFO in patients with first-onset apparently cryptogenic stroke, stating that 'although numerous observational studies have suggested a strong association between PFO and cryptogenic stroke, a causal relationship has not been convincingly established'.[28]

Conclusions

Compared with TEE, contrast CMR appears to be less sensitive for the diagnosis of PFO and underestimates the degree of the shunt. This issue is clinically relevant in the context of increasing CMR utilization world-wide, and the growing numbers of interventions performed for PFO closure. The present data suggest that, at present, the TEE performed by experienced operators remains the 'gold-standard' imaging technique to assess the presence, anatomic characteristics, and degree of dynamic shunting in PFO.

Conflict of interest: none declared.

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