Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale

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Abstract

Aim Transesophageal echocardiography (TEE) is still considered as the reference method for the non-invasive detection of right-to-left shunts. Echocardiographic laboratories are spending most of their time performing TEE studies to exclude a thromboembolic cardiac disease. In a considerable proportion of these patients the question can be simplified to exclude a PFO. Replacing these TEE studies by TTE would result in a considerable gain in time and money.

We evaluated the value of transthoracic echocardiography with second harmonic imaging (TTE) (SH) and peripheral intravenous agitated saline solutions in the detection of patent foramen ovale (PFO) in a large cohort of patients.

Methods In 256 consecutive patients, TEE and TTE (SH) with the consecutive administration of three intravenous contrast injections of agitated saline injections before the release phase of the Valsalva manoeuvre were performed. Semi-quantification and timing of contrast passage were assessed during both imaging modalities. A shunt was present if at least one imaging modality showed microbubbles appearing in the left atrium. PFO was defined when these bubbles appeared early and arteriovenous pulmonary malformations were suspected if bubbles appeared late after the opacification of the right atrium. Shunts were considered important when >20 bubbles were present in one frame in the left atrium or left ventricle.

Results From the 256 patients, 60 presented a passage of contrast from the right to the left atrium in at least one imaging modality. PFO was detected by TEE in 53
patients and by TTE in 55 patients (sensitivity: 90.5% and specificity: 96.5% if TEE is accepted as the golden standard) \((p > 0.05)\). Considering only the important shunts TEE detected 39 important shunts and TTE 46 important shunts (sensitivity: 89.7% and specificity: 94.6%) \((p > 0.05)\).

AV pulmonary malformations were detected by TEE in 7 patients and by TTE in 10 patients (sensitivity: 85.7% and specificity: 98.3%) \((p > 0.05)\).

**Conclusions** In this large cohort of patients TTE (SH) is as accurate as TEE for the detection of PFO and late right-to-left shunts. If the only purpose of TEE is the detection of PFO such as in young cryptogenic stroke patients and in divers, TEE can be replaced by TTE (SH).

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**Introduction**

Transesophageal echocardiography (TEE) combined with contrast administration is considered as the method of choice in the diagnosis of patent foramen ovale (PFO) and pulmonary arteriovenous malformations.1

Because TEE studies are very time-consuming and considered as semi-invasive by the patient, we searched for a much easier, cheaper and less invasive technique to detect a PFO. Second harmonic imaging compared to fundamental mode imaging results in a much better image quality and a better visualisation of first and second generation contrast agents as well as free gas microbubbles.2 This is the reason why we assumed that transthoracic echocardiography with second harmonic imaging (TTE SH) in combination with the injection of an agitated saline solution can detect a right-to-left shunt as accurate as TEE.

**Methods**

Four different centers included 256 consecutive patients (153 males, 103 females with a mean age of 63 ± 14) referred to the echolaboratory for TEE. Motivation for TEE was stroke \((n = 181, 71\%)\), endocarditis \((n = 36, 14\%)\), valvular heart disease \((n = 13, 5\%)\), others \((n = 26, 10\%)\). Echocardiographic studies were performed with Toshiba Powervision 8000, VIVID 7, HP sonos 5500 with modalities for second harmonic imaging.

In all patients the study began with TTE. Three contrast injections were performed at low dynamic range and relative high gain settings to visualise even the most discrete contrast passage. Before contrast injections were performed attention was given to the presence of spontaneous and “snowstorm” contrast.3 The contrast injections of an agitated 10 ml physiologic saline solution were rapidly administrated through a right antecubital vein using an 18-gauge venous canula. Each injection was administrated just before the release phase of a Valsalva manoeuvre.4

The presence of an atrial septal defect or a patent foramen ovale was defined as the passage of contrast in the left cavities within the first four cardiac cycles after opacification of the right atrium. When contrast was seen in the left cavities after more than four cardiac cycles, it was considered as a passage of contrast through pulmonary arteriovenous malformation. Right-to-left shunts were considered as important when more than 20 microbubbles could be visualised during one frame. When there were less than 20 microbubbles the shunt was considered small.5,6

All studies were analysed on two different videotapes. TTE SH and TEE images were read separately and in a random order to avoid bias. Two independent readers estimated the contrast images and if there was no agreement a third reader was asked to achieve a consensus. Statistical analysis for comparing differences in severity and timing of contrast was performed with a \(\chi^2\) test.

**Results**

From the 256 patients, 60 patients presented a passage of contrast from the right to the left atrium in at least one imaging modality (Table 1). PFO was detected by TEE in 53 patients and by TTE in 55 patients (sensitivity: 90.5% and specificity: 96.5% if TEE is accepted as the golden standard) \((p > 0.05)\).

**Important and early shunting** was more often diagnosed by TTE SH than by TEE: 46 (18%) versus 39 (15%) (sensitivity: 89.7% and specificity: 94.6%) \((p > 0.05)\). Of the 46 important shunts seen on TTE SH, 5 were not visible on TEE, 6 shunts were diagnosed as small and 35 shunts were also
important on TEE (Table 1). This gives a positive predictive value of 76% (Fig. 1). On the other hand, of the 39 important shunts detected with TEE, there were 4 shunts diagnosed as small on TTE SH and not one was missed with TTE SH. This gives a high negative predictive value of TTE SH for important shunting (98%).

Small and early shunting was more often diagnosed by TEE than by TTE: 14 (0.5%) versus 9 (0.3%). Of the 14 small shunts on TEE, 5 were not seen with TTE SH. Of the 9 small shunts visualised on TTE SH 2 small shunts were missed by TEE.

Late shunting was detected by TEE in 7 patients and by TTE in 10 patients (sensitivity: 85.7% and specificity: 98.3%) (p > 0.05). Six late shunts were diagnosed with both studies. One shunt was seen on TEE and missed by TTE while four shunts detected with TTE were missed with TEE.

Discussion

This multicenter study with a population of more than 250 patients demonstrates that TTE SH in combination with an agitated saline injection has a high sensitivity (90.5%) and specificity (96.5%) taking TEE as the golden standard for the detection of right-to-left shunts.

In our study the negative predictive value for detecting early and important contrast passage with TTE SH is very high (98%). If we cannot detect a shunt on TTE there will be also no important shunt on TEE. As already shown in previous studies, small shunts are not of clinical importance. Because there are no false negatives for the detection of large PFO, TTE SH can be seen as a good screening technique for detecting PFO.

The positive predictive value is less high (still considering TEE as the golden standard), because five important shunts detected on TTE SH were not visible on TEE. This can be explained by the difficulty of performing a good Valsalva manoeuvre in the presence of an endoscope during TEE. Previous studies have already demonstrated that TEE can miss the diagnosis of right-to-left shunts. Both transcranial Doppler and color Doppler TEE studies showed in some patients the presence of a PFO by these alternative techniques although contrast TEE was negative.

If the only indication for TEE is the detection of PFO such as in young cryptogenic stroke patients without underlying heart disease and a minimal risk for cardio-embolic sources and in healthy divers with decompression sickness, TEE can be replaced by a much cheaper, more rapid and less invasive TTE SH approach. However, TEE will still be necessary in those patients with a high risk for trombo-emboligenic sources and in all patients without an available acoustic window by TTE SH.

References


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<th>Table 1 Early contrast passage: TTE SH versus TEE</th>
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>20 microbubbles = important shunt; <20 microbubbles = small shunt; 0 = no early shunt; p > 0.05.

Figure 1 Sensitivity, specificity, positive predictive value and negative predictive value of TTE SH versus TEE for the detection of early contrast passage (small and important shunts) and important early contrast passage. (PPV = positive predictive value, NPV = negative predictive value).
of right and left atrial pressure: implications for the
echocardiographic detection of persistent foramen ovale.  

5. Webster MW, Chancelor AM, Smith HJ, Swift DL, Sharp DN, 
Bass NM. Patent foramen ovale in young stroke patients.  

6. Van Camp G, Schulze D, Cosyns B, Vandenbossche JL.  
Relation between patent foramen ovale and stroke.  Am J  

7. Vandenbogaerde J, De Bleeker J, Decoo D, François K, 
Cambier B, Bergen JM, et al. Tansesophageal echo-Doppler in 
patients suspected of a cardiac source of peripheral emboli.  
Eur Heart J 1993;14:88–94.

8. Devuyyst G, Despland PA, Bogousslavsky J, Jeanrenaud X.  
Complementarity of contrast transcranial Doppler and con-
trast transesophageal echocardiography for the detection of 
patent foramen ovale in stroke patients.  Eur Neurol  