Optimization of patent foramen ovale detection by contrast transthoracic echocardiography using second harmonic imaging

Optimisation de détection du foramen ovale perméable par échocardiographie transthoracique avec contraste et seconde harmonique

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Summary
Background. — Patent foramen ovale is an anomaly responsible for paradoxical embolizations and cerebral ischemic events.

Aims. — We want to show second harmonic transthoracic echography sensitized by contrast agent perfusion is as well as transesophageal echography to patent foramen ovale detection.

Methods. — One hundred twenty one patients referred for transesophageal echocardiography for patent foramen ovale detection, underwent additive second harmonic transthoracic echocardiography with one of three randomized contrast agents: a mixture A of dextrose and air, mixture B of dextrose and air and blood, or mixture C of hydroxyethylamidon. The severity of atrial shunting was evaluated on recordings by semi-quantitative scoring. Intensity of contrast was also assessed by objective quantitative videodensitometry.

Results. — No difference was observed between the two techniques, nor between mixture A, B and C in terms of PFO detection during each exam. However, quantitative contrast analysis showed higher intensity with mixtures B and C with mixture A during transthoracic echography.

Conclusions. — When performed with a contrast agent, second harmonic transthoracic echocardiography and transesophageal echography are comparable when it comes to patent foramen ovale detection. Although the composition of the contrast agent does not appear to affect the rate of this detection, contrast quality in the right atrium during transthoracic exam is better with mixtures B and C than with mixture A.

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Mots clés
Foramen ovale perméable ; Accident ischémique cérébral ;

Resumé
Pré requis. — La perméabilité du foramen ovale est une anomalie responsable d’embolies paradoxales et d’accidents ischémiques cérébraux.

Buts. — Nous voulons démontrer que l’échocardiographie transthoracique en seconde harmonique avec produit de contraste est aussi efficace que l’échocardiographie transösophagienne pour diagnostiquer un foramen ovale perméable.

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Échographie transthoracique ;
Seconde harmonique ;
Échographie transeosophagienne ;
Agent de contraste.

Méthodes. — Cent vingt et un patients adressés pour recherche de foramen ovale perméable par échographie transeosophagienne ont aussi bénéficié d’une échographie transthoracique en seconde harmonique. Ces examens ont été sensibilisés par injection d’un des trois produits de contraste tiré au sort : produit A (Glucosé et air), produit B (Glucosé et air et sang), ou produit C (hydroxyéthylamidon). Un enregistrement vidéoéoscopique permettait de quantifier la sévérité du shunt atrial (score visuel semi quantitatif), et l’échogénicité du produit de contraste (score vidéo densitométrique numérisé).

Résultats. — Il n’y a pas de différence entre les deux méthodes pour la détection de foramen ovale perméable, quel que soit le contraste utilisé. L’analyse quantitative de l’échogénicité du contraste pendant l’examen transthoracique révèle une supériorité des produits B et C sur le produit A.

Conclusions. — L’échographie transthoracique en seconde harmonique avec injection de produit de contraste permet de détecter un foramen ovale perméable aussi bien que la voie transeosophagienne. Même si la composition du produit ne modifie pas ces résultats, les produits B et C ont une meilleure échogénicité que le produit A.

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Introduction

Patent foramen ovale (PFO) is an anomaly of the atrial septum, defined as the persistence of an anatomical duct between the right and the left atrium. It can lead to right-to-left shunting when pressure in the right heart cavities rises. PFO is implicated in numerous pathologies in which an embolism passes from the venous circulation to the systemic arterial circulation, leading to paradoxical embolization and cerebral ischemia [1, 2]. There is increasing interest in the investigation of PFO after ischemic cerebral events [3-5] because such events are the first cause of disability and the third cause of mortality in developed countries (with 25% being repeat events) [6, 7]. A multicenter prospective study on 581 male and female victims of idiopathic ischemic cerebral events showed that the incidence of recurrence on anti-platelet treatment was higher in those with PFO, especially when it is associated with an atrial septal aneurysm [8]. Furthermore, PFO can now be repaired by transcatheter septal occlusion and this has been shown to prevent recurrence. This enhances the worth of echocardiography before as well as during and after the procedure [9].

Transesophageal echocardiography (TEE) used to be the gold standard for diagnosis and follow-up after PFO repair [10-14] but since second harmonic imaging improved ultrasound image quality, transthoracic contrast echocardiography using second harmonic imaging (2HTTE) is becoming a diagnostic alternative for PFO detection, especially as sensitivity can be enhanced by using a contrast agent [15,16]. In the present study 2HTTE is compared with TEE in the diagnosis of PFO, and the ability of three contrast agents — dextrose solution and air (DA), dextrose solution and air and blood (DAB) and hydroxyethylamidon solution (HEA) — to sensitize shunt detection is also compared.

Methods

Population and study design

We included 130 successive patients referred to our echocardiography laboratory for TEE to investigate PFO after a systemic ischemic event, or before an atrial fibrillation ablation procedure. There was no limitation by age, gender, or ultrasonic window. All patients gave their consent for the injection of contrast agent. From a randomization table, we allocated one of the three contrast agents (DA, DAB or HEA) to each patient. Each patient was given a 2HTTE examination with the selected contrast agent followed by TEE with the same contrast agent. The two examinations were carried out by the same investigator. All examinations were recorded on videotapes and simple-blind reviewed by an independent examiner. In cases of disagreement, a third examiner resolved the issue. The video-recordings were digitalized for objective analysis of the contrast intensity in the right atrium. This study was approved by an Institutional Review Board.

Instrumentation

Two ultrasound systems were used, namely a Sequoia 256 System® with a 2.5-5 MHz transthoracic probe and a transesophageal multipurpose probe (Acuson, Mountain View, California, USA), and a Sound System 5500® with a 2.5-5 MHz transthoracic probe and a transesophageal multipurpose probe (Hewlett Packard, Andover, Massachusetts, USA).

Standard 2HTTE and TEE procedures were performed for each patient in accordance with American Society of Echocardiography guidelines. More specifically, when the interatrial septum was visualized both in 2HTTE (apical four-chamber view) and TEE (two-atrial view), contrast agent was manually injected through a 18G catheter into a peripheral vein of the right arm. The contrast agents were prepared as follows:

- DA: 9 mL of 5% dextrose solution, shaken with 1 mL of ambient air;
- DAB: 8 mL of 5% dextrose solution, and 1 mL of patient blood, shaken with 1 mL of ambient air;
- HEA: 10 mL of hydroxyethylamidon without shaking.

Each contrast agent was injected at rest during a cough manoeuvre for both 2HTTE and TEE.

Data analysis

The existence of a right-to-left atrial shunt was defined by the detection of contrast bubbles in the left atrium within three cardiac cycles of opacification of the right atrium. A semi-quantitative evaluation of the shunt was made by the echocardiographer on the basis of the number of bubbles in the
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left atrium: no bubbles (grade 0), 1-10 bubbles (grade 1), 11-30 bubbles (grade 2), more than 30 bubbles (grade 3).

Echocardiograms were digitized before and after contrast agent injection and quantitative digital analysis of contrast intensity was performed off-line using special software. To eliminate ultrasound artefacts compensate for differences in gain settings and isolate the ultrasound signal coming from the contrast agent, we calculated a “relative variation of intensity” (RVI):

\[
RVI = \frac{(\text{maximal contrast value}) - (\text{value without contrast})}{(\text{value without contrast})}
\]

Statistical analysis

The Chi² test was used to compare the homogeneity of the three groups. A Kappa test was used to calculate the agreement between 2HTTE and TEE. If \( \kappa \) was less than 0.4, the agreement was poor; if it was between 0.4 and 0.59, agreement was moderate; if it was between 0.6 and 0.79, agreement was good; and if it was above 0.79, the agreement was very good. Digitized contrast intensities were compared using the Mann-Whitney test. All tests were two-tailed and a p value <0.05 was considered significant.

Results

Population

The number of examinations provided at least 30 randomized elements per contrast agent. We retained 121 patients out of 130 for analysis of agreement, and 116 for RVI analysis. Three examinations were stopped (because of acute left heart failure, chest pain and systemic systolic hypertension); three cases could not be analyzed because of missing items, and eight of the videotape tablerecords were incomplete. Overall, there was 7%-10% exclusion, which is unusual for a prospective study.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the population after randomization according to contrast agents.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dextrose and air</td>
</tr>
<tr>
<td>Randomized patients (n, %)</td>
<td>41 (33.9)</td>
</tr>
<tr>
<td>Age (years±sd)</td>
<td>56.3±13.8</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>Indication (n, %)</td>
<td>Definitive ischemic cerebral event</td>
</tr>
<tr>
<td></td>
<td>Atrial arythmia ablation</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic cerebral event</td>
</tr>
<tr>
<td></td>
<td>Distal leg ischemic event</td>
</tr>
<tr>
<td>Echocardiograph (n, %)</td>
<td>Sonos 5500</td>
</tr>
<tr>
<td></td>
<td>Sequoia 256</td>
</tr>
<tr>
<td>Ultrasound window (n, %)</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Bad</td>
</tr>
</tbody>
</table>

The main characteristics of the population are listed in table 1. The three groups were comparable in terms of age, gender, indication for TEE, and ultrasound transthoracic window (which was good in 67%, medium in 27%, and poor in 6%).

Agreement between 2HTTE and TEE, irrespective of contrast agent

TEE detected 22 PFO out of 121 patients (18.2%), while 2HTTE detected 23 PFO (19%), including 19 of the 22 PFO detected with TEE (table 2). There were four false positives and three false negatives. The agreement between TEE and 2HTTE was 94.2%, with a coefficient of agreement \( \kappa \) of 0.81 (very good agreement). Taking TEE as the reference, 2HTTE had a sensitivity of 86.4%, a specificity of 96%, a positive predictive value of 82.6%, and a negative predictive value of 96.9%.

Qualitative agreement between 2HTTE and TEE, according to contrast agent

Dextrose solution and air (DA)

Out of 41 patients, we detected 6 PFO with TEE (14.6%) and 5 PFO with 2HTTE (12.2%) (table 3A). There were one false positive and two false negatives. Agreement was 92.7% with
a coefficient of agreement $\kappa$ of 0.683 (good agreement). Thus using the DA contrast agent, 2HTTE had a sensitivity of 66.7%, a specificity of 97.1%, a positive predictive value of 80%, and a negative predictive value of 94.4%.

Dextrose solution and air and blood (DAB)

TEE detected 10 PFO (30.3%) while 2HTTE detected 11 PFO (33.3%) (table 3B). There was only one false positive and no false negatives. Agreement between 2HTTE and TEE was the highest of the three (97%), with a coefficient of agreement of 0.930 (very good). With DAB, 2HTTE exhibited a sensitivity of 100%, a specificity of 95.6%, a positive predictive value of 90.9%, and a negative predictive value of 100%.

Hydroxyethylamidon (HEA)

Out of 47 patients, we detected 6 PFO with TEE (12.7%) and 7 with 2HTTE (14.9%), giving one false negative and two false positives (table 3C). The agreement between these two techniques was 93.6%, with a coefficient of agreement of 0.732 (good agreement). With HEA, 2HTTE exhibited a sensitivity of 83.3%, a specificity of 95.1%, a positive predictive value of 71.4%, and a negative predictive value of 97.5%.

DAB was the contrast agent that gave the best agreement (97%) between 2HTTE and TEE. The Kappa test produced an agreement between these two examinations of only 89.3%, with $\kappa=0.67$ (good agreement).

Semi-quantitative agreement between 2HTTE and TEE, irrespective of contrast agent

For 108 patients out of 121 (89.2%), 2HTTE was able to evaluate the shunt correctly compared to TEE irrespective of the semi-quantitative grade of PFO (table 4). Nevertheless we had 4 false positives and 3 false negatives. In addition, among the 22 cases of PFO, there were 9 cases (40.9%) for which the semi-quantitative evaluation of the shunt differed between 2HTTE and TEE. The Kappa test produced an agreement between these two examinations of only 89.3%, with $\kappa=0.67$ (good agreement).

Quantitative echogenicity of contrast agents

RVI was higher with DAB (3.6±1.6) than with DA (2.6±1) ($p=0.02$) (figure 2). RVI was also higher with HEA (3.7±2.1) than with DA (2.6±1) ($p=0.02$). On the other hand, there was no difference in RVI between DAB and HEA ($p=0.8$). Similarly, we obtained identical results in a pairwise comparison of the medians, and there was no difference in RVI between DAB and HEA ($p=0.79$) (results not shown). DAB and HEA developed higher contrast gain than did DA.

There was little discordance between the two investigators after the second reading of each examination. In only 6 TTE examinations out of 121 (4.9%) was there doubt about whether or not there was an interatrial shunt and in all these cases, the ultrasonographic window was either poor or medium. In TEE, there was doubt in 2 cases out of 121 (1.6%). This is a lower discordance rate than that reported in other studies, perhaps due to differences in the power of the echographic or recording systems used. There were

![Figure 1](image1.png)

**Figure 1.** Qualitative agreement between TTE and TEE according to the contrast agent: DAB gave better agreement (97%) than DA (92.7%) or HEA (93.6%).

* $p<0.05$ from DA.

![Figure 2](image2.png)

**Figure 2.** Box and whisker plot. For each contrast agent, the horizontal line and the written value represent the median (50th percentile) RVI. The box extends from the 25th percentile to the 75th percentile. Whiskers correspond to minimal and maximal adjacent values. There was a higher contrast gain with DAB or HEA than with DA.
6 cases of discordance among the 22 shunts (27.3%) hinging on the semi-quantitative measurement of the shunt, (similar to the reported rates).

Furthermore, there was no difference in echograph use with the different contrast agents.

### Discussion

Systemic ischemic events, particularly in the brain, usually require a Doppler echocardiographic examination to detect an embolic process. However, reliable and complete diagnosis does not seem possible using just transthoracic echocardiography in fundamental imaging mode and invasive TEE is practised [12, 14, 17-19]. There has been considerable interest in developing less invasive techniques such as 2HTTE, which we evaluated here for detection of PFO. 2HTTE does not necessitate sedation of the patient, does not require evaluation by paramedical personnel, and is quicker. There is no contraindication for 2HTTE. We choose the cough manoeuvre for shunt sensitization because it is easier than the Valsalva maneuver. Our results demonstrate that 2HTTE is useful as it gives good agreement with TEE ($\kappa=0.81$), especially when DAB is used as the contrast agent ($\kappa=0.93$). False positive and false negative results may occur with intrapulmonary shunts. Furthermore, in a video-densitometric study, we obtained higher intensity images with DAB and HEA than with DA.

**Table 4** Semi-quantitative agreement between TTE and TEE. Out of 22 PFOs, 13 (59.1%) were evaluated with the same precision by TTE and TEE.

<table>
<thead>
<tr>
<th>All contrast agents</th>
<th>TEE no shunt grade 0</th>
<th>TEE shunt grade 1</th>
<th>TEE shunt grade 2</th>
<th>TEE shunt grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTE no shunt Grade 0</td>
<td>95</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TTE shunt grade 1</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TTE shunt grade 2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>TTE shunt grade 3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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2HTTE has now supplanted fundamental TTE imaging for left ventricular echographic measurements as well as for endocardial definition or dobutamine stress echocardiography [20-22]. However, few studies have focussed on 2HTTE in PFO detection [20-22]. In the study of Kühl et al. on 111 patients with ischemic cerebral embolic events, 52 showed evidence of a right-to-left atrial shunt with 2HTTE compared with only 32 with fundamental imaging ($p<0.001$) and 51 with TEE ($p=ns$) [23]; furthermore the severity score of the shunt did not differ between 2HTTE and TEE (61.6±80.2 bubbles versus 43.9±54.3 bubbles; $p=ns$). In the study of Madala et al. on 64 patients referred for TEE after ischemic cerebral attack, TEE identified 9 PFO; for 2HTTE the sensitivity was 100% and the specificity was 82%, whereas for fundamental TTE sensitivity and specificity were 78% and 100% respectively [24]. Ha et al. showed that 2HTTE using contrast agents was superior to TTE using fundamental imaging for detecting PFO in 136 successive patients referred for the investigation of a cardiac embolism source. The two methods had comparable sensitivity and specificity [25]. Our randomized prospective study on 121 patients also referred for PFO detection by TEE, indicated that 2HTTE was effective with a very good agreement of 94.2% ($\kappa=0.81$) with the TEE results. The sensitivity, specificity, positive predictive value, and negative predictive value, were respectively 86.4%, 96%, 82.6%, and 96.9%.

A variety of contrast agents have been employed for echocardiographic examinations to highlight right and left heart cavities [26]. Several studies have concluded that injection of contrast agent optimized detection of a cardiac shunt [19, 27, 28]. We tested three contrast agents in both 2HTTE and TEE: DA solution, in routine use in our department; DAB solution (as the addition of blood has been used with success in other circumstances [29, 30]); and HEA solution as its physicochemical characteristics appeared well suited for second harmonic imaging. We did not test saline because its chemical composition is too similar to that of blood to generate enough contrast. A polygelatin solution employed in two studies published while our study was underway gave excellent opacification of the right cardiac cavities. Kuhl et al. used a polygelatin solution (Gelifundol, Biotest Pharma) [23], while Tan et al. showed that agitated colloid was superior to saline for opacification of right heart chambers in 25 successive patients [31].

Our TTE results show that DAB gives the best agreement with TEE, with a similar PFO diagnosis rate (97%, i.e. only 3% of overestimated error) and a negative predictive value of 100%. We noted a better contrast/noise ratio with DAB than with the other two contrast agents. Thus, with this contrast agent, an absence of atrial right-to-left shunt on 2HTTE would obviate the need for TEE to investigate PFO. It should be borne in mind that PFO detection is seldom the
only reason for performing TEE which is of value in the search for other causes of systemic embolism, such as an intracardiac tumor, thrombi or thoracic aortic disease.

**Limitations**

As in other applications, the ultrasound window limits the usefulness of 2HTTE, especially in subjects with respiratory diseases. But we demonstrate relevance of 2HTTE even in subjects with a medium ultrasound window. TEE diagnosed only 22 PFO (18.2%) in our population, which is lower than the usual prevalence in the general population [32] or in the population of stroke patients [1, 33-35], low-powering our study. This can be accounted for by the fact we only had 63% ischemic events in our population; indeed, the indication of TEE before ablation of atrial fibrillation reduced the potential number of patients with PFO. The right atrium was selected for acquisition of the digitized pictures as the contrast agent concentrates in this cavity after injection into the peripheral venous circulation, and also because this is the site that is most often analysed in studies on contrast agents [29, 30]. Even if there is not yet a real-life clinical application, calculation of the relative variation of intensity effectively eliminated measurement errors due to background acoustic noise and differences in gain settings from one examination to another. Complementary studies with larger samples should show higher clinical relevance. The main error in this phase of the study stemmed from the positioning of the sampling window to measure the contrast intensity: the 10 mm window was positioned arbitrarily by the investigator on the least echogenic zone of the right atrium after injection, then on its most echogenic zone after injection. As mean or median, DAB and HEA were much more echogenic than DA, which is the most echogenic zone after injection. As mean or median, DAB and HEA were much more echogenic than DA, which is the most echogenic zone after injection. As mean or median, DAB and HEA were much more echogenic than DA, which is the most echogenic zone after injection.

**Conclusion**

When performed using a contrast agent, TEE and 2HTTE had comparable yields for PFO detection. Thus, PFO could be initially investigated using 2HTTE with DAB as the contrast agent, with a sensitivity of 100%, a specificity of 95.6%, a positive predictive value of 90.9%, and a negative predictive value of 100%. In stroke patients, TEE is usually required to explore the atrial septum as well as the left atrial auricle and the thoracic aorta. However, in selected patients such as those studied before spinal surgery or after PFO closure, PFO can be reliably diagnosed by 2HTTE.

**References**


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