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## SCIENTIFIC EDITORIAL

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

Optimisation de la détection du foramen ovale perméable par échocardiographie transthoracique en mode harmonique

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The pathological role of patent foramen ovale (PFO) is increasingly suggested in a number of clinical situations such as paradoxical embolism, refractory hypoxaemia, platypnoea-orthodeoxia syndrome, decompression sickness in divers, and migraine with aura and stroke. The association between PFO and cryptogenic stroke has been recognized for many years and confirmed in a recent meta-analysis [1]. Therapeutic trials are ongoing to test prospectively the safety and efficacy of PFO closure techniques or medical therapy for stroke recurrence. Because of these potential therapeutic implications, accurate identification of PFO is crucial. However, the best way to identify PFO remains the subject of debate [2].

Although the cornerstone of diagnosis of PFO is the identification of right-to-left shunt after contrast injection, different imaging techniques are proposed such as transoesophageal echocardiography (TEE), transthoracic echocardiography (TTE) and transcranial Doppler (TCD). In this issue of the journal, Lefevre et al [3] studied, with contrast harmonic TTE (HTTE) and TEE, 121 patients referred for detection of PFO. They compared the performance of three randomized contrast agents: a mixture of dextrose and air (DA); dextrose, air and blood (DAB); and hydroxyethylamidon (HEA). Identification of PFO was studied both semiquantitatively and quantitatively using video densitometry. Their study addresses several important issues concerning PFO detection.

### What is the best technique to detect a PFO: TEE or TTE?

Among echocardiographic techniques, TEE with a contrast study has long been considered the method of reference for diagnosis of PFO. TEE is far superior to fundamental TTE due to the high quality of visualization of atrial septum and the capacity to specify accurately the location of right-to-left shunt through the PFO [4]. However, the superiority of TEE over TTE for PFO detection has been challenged since the introduction of harmonic imaging during TTE. Harmonic imaging dramatically improves the imaging quality and provides better visualization of contrast agents due to the specific acoustic properties of microbubbles. Several recent studies have demonstrated that HTTE with contrast is as accurate as TEE in detecting PFO [5-10]. Some even suggest that HTTE should be the new reference technique for PFO detection [9].

Kuhl et al [5], in their study of 111 patients with a cerebral ischaemic event, compared three echocardiographic methods for PFO detection using a polygelatin contrast agent. This study was the first to show that HTTE provides results that are similar to TEE in detecting PFO, and are better than fundamental TTE. The severity of contrast visibility was significantly higher for HTTE compared to fundamental TTE and was similar to TEE. Five other

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recent studies demonstrated similar results, showing high sensitivity and specificity of contrast with agitated saline contrast injection for detecting right-to-left shunts as compared to contrast TEE [6-10]. Van Camp et al [6], emphasized the very high negative predictive value of contrast HTTE for detecting early and important right-to-left shunts. The results of the study by Lefevre et al [3] are consistent with these previous studies, confirming that TEE and HTTE have a comparable yield for the detection of PFO. Using DAB as the contrast agent, and TEE as the reference method, the sensitivity for PFO detection was 100% and the specificity 95.6%. This study also confirms the very high negative predictive value – 100% – of HTTE for the detection of PFO.

Therefore, HTTE can now be considered as an alternative to TEE for the detection of PFO if TEE is to be carried out only for this purpose. This should be the case in divers with decompression sickness, in patients before spinal surgery, and in young patients with stroke without underlying heart disease and a minimal risk for cardioembolic sources [9]. Owing to the high negative predictive value of HTTE contrast study with adequately performed Valsalva manoeuvre, a negative study should obviate the need for TEE in these cases.

HTTE has many advantages. It is non-invasive and can be easily repeated. It gives the opportunity to perform good provocative manoeuvres (Valsalva and cough test), which are sometimes difficult to perform during TEE, especially after sedation, and probably explain some of the false negative studies encountered. In a recent study involving 1435 patients with ischaemic stroke, the presence or absence of PFO could not be determined in 32.1% because bulging of the septum could not be demonstrated during TEE in patients with a negative contrast study despite aggressive manoeuvres to elevate right atrial pressure [11]. Therefore, a negative TEE does not eliminate the presence of a PFO, and it is recommended to perform HTTE with provocative manoeuvres to definitely exclude a PFO.

Indeed, TEE remains the best method to study the atrial septum and to confirm the exact location of a right-to-left shunt. It should be noted also that false positive results can occur with HTTE and the two techniques are recognized as complementary [8].

## Role of contrast agents

The study by Lefevre et al [2] adds new information by examining the role of contrast agents in the detection of PFO. The choice of echo contrast agent could be relevant because different agents may have different acoustic properties that translate into a higher sensitivity for detection of atrial shunts. In a previous study in 34 patients undergoing HTTE and TEE, Buttignoni et al [12] showed that oxypolygelatine solution (Gelifundol) was superior to saline for the assessment of a PFO when using transthoracic contrast echocardiography, visually and by acoustic densitometry. In the study by Lefevre et al [2], contrast quality in the right atria during HTTE and quantitative analysis were better with DAB or HEA than with DA. However, in this study the composition of contrast agent appeared not to modify the rate of detection of PFO.

Although not specifically addressed in their study, the question of whether or not to replace the well established and inexpensive agitated saline contrast protocol with other contrast agents is open. In favour of contrast agents such as hydroxyethylamidon, galactose microparticle and polygelatin solutions are the better quality of opacification and the absence of transpulmonary passage. Although the late appearance of a large quantity of bubbles in the left atrium after four or more cardiac cycles is generally thought to be related to arteriovenous malformation, the late appearance of a small amount of microbubbles is relatively frequently observed with harmonic imaging after saline injection and may induce false positive results [13]. Another potential advantage of these agents is the absence of large air microbubbles, as it has been shown recently that after saline injection, transient ischaemic cerebral manifestations may occur after massive right-to-left shunt during the Valsalva manoeuvre, probably due to air embolism (14; personal unpublished data).

## Quantification of PFO

Another question addressed in the paper by Lefevre et al [3] is the issue of quantification of the right-to-left shunt. Generally, PFO detection is based on a visual assessment of the number of contrast bubbles appearing in the left atrium at rest or during provocative manoeuvres. A significant shunt is generally defined by the appearance of more than 20 to 30 bubbles in the left atrium. However, these cut-off values are somewhat arbitrary and the reproducibility of this semiquantification is far from perfect [15]. Furthermore, the magnitude of contrast shunting does not necessarily correlate with the true anatomical size of the PFO [2]. Although quantitative analysis has the potential to improve PFO detection, the sensitivity of detecting PFO is dependent on a variety of factors including the echocardiographic technique, the site of injection, the number of injections, and more importantly the quality of provocative manoeuvres [2]. Furthermore, the intensity of contrast passage varies from time to time in an individual patient. Therefore, the question as to whether the use of a more homogeneous microbubble solution and quantification improve the reproducibility of right-to-left shunt detection remains to be demonstrated.

In conclusion, the paper by Lefevre et al highlights the current limitations of PFO detection techniques and the need to continue working in a way that optimizes and standardizes PFO identification and quantification.

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