Eur J Echocardiography (2006) **7**, 147–154

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EUROPEAN SOCIETY OF CARDIOLOGY®

Comparison of transthoracic echocardiography using second harmonic imaging, transcranial Doppler and transesophageal echocardiography for the detection of patent foramen ovale in stroke patients

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Received 14 January 2005; received in revised form 22 April 2005; accepted 27 April 2005
Available online 31 May 2005

KEYWORDS
Patent foramen ovale;
Transthoracic echocardiography;
Transcranial Doppler;
Transesophageal echocardiography

Abstract *Aims:* The comparison of three imaging methods to determine which is the most accurate and reliable for the detection of right-to-left shunt.
Methods and results: One hundred and seven patients who were hospitalized for stroke underwent: a transthoracic echocardiography (TTE) using second harmonic, a transcranial Doppler (TCD) and a transesophageal echocardiography (TEE) from August 2003 to April 2004.

All studies were recorded on a videotape and were studied by a physician blinded to the study.

With TTE and TEE, we found 44 (41%) patent foramen ovales. All contrast tests were positive with TCD for these 44 patients.

For two patients, the contrast test was positive only with TTE and TCD. We found four false negative contrast tests with TTE.

Among the 63 patients who had a negative contrast test with TEE and TTE, the results were the same with TCD for 59 of them; we were not able to determine a cause for the four positive tests.

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doi:10.1016/j.euje.2005.04.007

Conclusion: This study confirms that transesophageal echocardiography has limitations in the diagnosis of patent foramen ovale.

In this study, the negative predictive value of transcranial Doppler was excellent. Therefore, this examination is able to exclude a patent foramen ovale with a high level of confidence.

Introduction

The foramen ovale normally closes at birth, however, a patent foramen ovale (PFO) is present in 10—25% of the general population according to autopsy and echocardiographic studies.[1—4]

A higher prevalence of PFO exists in subjects with ischemic stroke compared with healthy subjects, particularly in young patients (<55 years) with stroke of unknown origin.[5—8] Therefore, examination for a PFO is indicated in young patients with cryptogenic stroke.

PFO is implicated in other conditions as well, for example: migraine with aura,[9,10] platypnea—orthodeoxia,[11,12] and divers.[13,14]

Contrast transesophageal echocardiography (c-TEE), a semi-invasive technique, has been regarded as the gold standard for the detection of PFO.[15—17] But recent studies show that contrast transthoracic echocardiography (c-TTE) with second harmonic imaging and c-TEE have an equivalent efficacy[18—21] and that c-TEE is not perfect for this diagnosis.

Contrast transcranial Doppler (c-TCD) ultrasonography is an alternative method in the detection of right-to-left shunt.[22] The sensitivity and specificity compared with c-TEE appears to be high in several studies.[23—26] However, many of these studies were conducted before the standardization of c-TCD procedures for cardiac right-to-left shunt detection.[27] Therefore, the methodology differs in these c-TCD studies.

The aim of our study was to compare c-TTE with second harmonic imaging, c-TCD and c-TEE for the detection of PFO.

Methods

Patients

A total of 110 patients hospitalized for stroke or transient ischemic attack (TIA) were enrolled in this study from August 2003 to April 2004. Only 107 patients were included (40 women, 67 men) because three patients had insufficient temporal bone windows for the evaluation of c-TCD (ages of these patients were 72, 75 and 78 years old). The mean age was 56 years (age range, 22—78).

Fifty-three (50%) patients were less than 55 years.

Thirty-four patients presented with TIA and 73 presented with stroke.

Each patient underwent: a cerebral computed tomography, a 12 lead electrocardiogram, complete blood chemistry analysis and an ultrasonographic examination of supra-aortic arteries.

Among the 107 patients, 48 patients (45%) were cigarette smokers, 45 (42%) had arterial hypertension, 14 (13%) were diabetics, 33 (31%) had hyperlipidemia and 1 patient had an S protein deficiency.

A cause for stroke was found in 25 patients: 5 had auricular fibrillation, 2 had carotid artery dissection, 4 had cardiac systolic dysfunction, 2 had dilated cardiomyopathy, 1 with ejection fraction (EF) calculated at 25%, the other at 30%, 2 had ischemic cardiopathy, 1 had anterior akinesia with EF at 30%, and 1 had inferior dyskinesia and anterior hypokinesia with EF at 20%, and 14 had stenotic lesion in carotid and/or vertebrobasilar arteries.

Eighty-two (77%) patients had cryptogenic stroke, 38 (46%) patients in this group were below 55 years.

Thirty-two patients (30%) had a history of migraine, 12 migraine sufferers had associated aura.

Investigations with echocardiography

All examinations are recorded on VHS-tapes which were then reviewed by an other experienced echocardiographer.

A contrast test was done for each examination: an 18-gauge needle was placed into the antecubital vein. Two 10-mL syringes were prepared: one containing 9 mL of saline solution and the other containing 1 cc of air.

The contents of both syringes were rapidly mixed until a homogenous solution was obtained

(contrast solution). The solution was then rapidly injected or bolused.

The test was executed twice without Valsalva manoeuvre and twice with Valsalva manoeuvre which lasted at least 10 s. The Valsalva manoeuvre was performed 5 s after the injection of the contrast agent.

Transthoracic echocardiography (TTE)

TTE was performed with an imaging system (SONOS 5500, Philips Medical System, Andover, Mass) with a 3-MHz probe.

A patent foramen ovale was diagnosed if at least one micro-bubble (MB) was detected in the left atrium within three cycles following the appearance of the contrast in the right atrium. The shunt was considered small when less than 10 MB were seen, medium (Fig. 1) when more than 10 were present and large if all the left atrium was opaque.

Transcranial Doppler (TCD)

TCD was performed with a SONOS 5500 (Philips Medical System, Andover, Mass) with a 3-MHz large band probe. The temporal window was used. Patients were in the supine position. The side of the cranium with the superior temporal window was chosen.[28]

The middle cerebral artery was identified with colour Doppler and the Doppler sample volume was placed in the middle cerebral artery.

The contrast test was executed. The test was deemed positive if at least one ''hit'' was recorded on the TCD trace within 40 s after the injection.

The results were classified as follows: 0 hit test negative, 1—10 hits small shunt, >10 hits but without ''curtain'' effect: medium shunt (Fig. 2) and >10 hits with ''curtain'' effect (when the hits were so numerous as to be no longer distinguishable separately): large shunt (Fig. 3).

Transesophageal echocardiography (TEE)

TEE was realized by an experienced echocardiographer who was blinded to the results of the two others examinations.

TEE was performed with a SONOS 5500 (Philips Medical System, Andover, Mass) with a 4—7 MHz transesophageal multiplane probe.

For this examination, a local pharyngeal anaesthesia was induced with adequate amounts of 0.02% oral lidocaine. If necessary, patients were sedated with 5 mg of intravenous midazolam. The patients were properly instructed how to perform a Valsalva manoeuvre and the target was to obtain a collapse of the right atrium during Valsalva manoeuvre.

The contrast test was carried out. A patent foramen ovale was diagnosed when at least one MB was detected in the left atrium within three cycles following the appearance in the right atrium. The quantification was the same as with TTE (Fig. 4 for large shunt).

When a patent foramen ovale was diagnosed, a lower extremity venous Doppler was done as well.

Statistical analysis

To determine if the results between the three methods were significantly different, the primary analysis of the shunt detection results was carried out using the Cochran test (p values of less than 0.05 were considered statistically significant). The

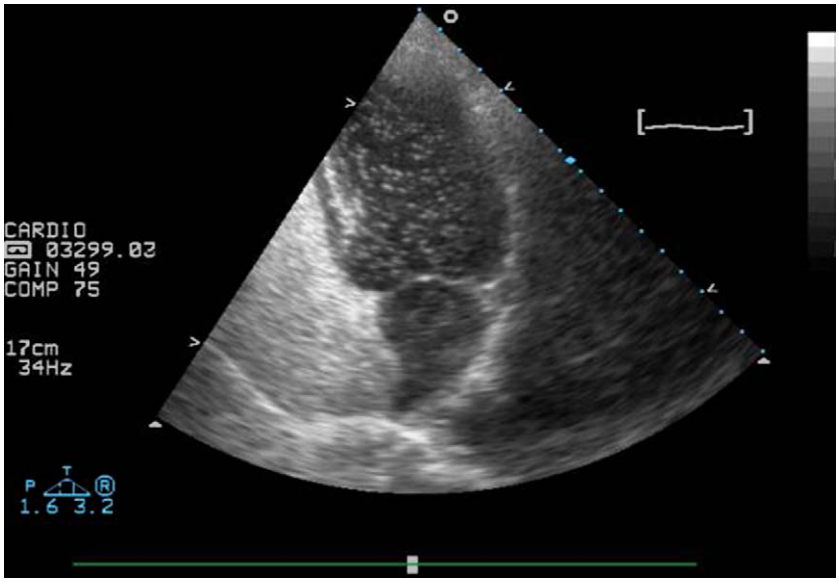

Figure 1 Medium shunt with transthoracic echocardiography.

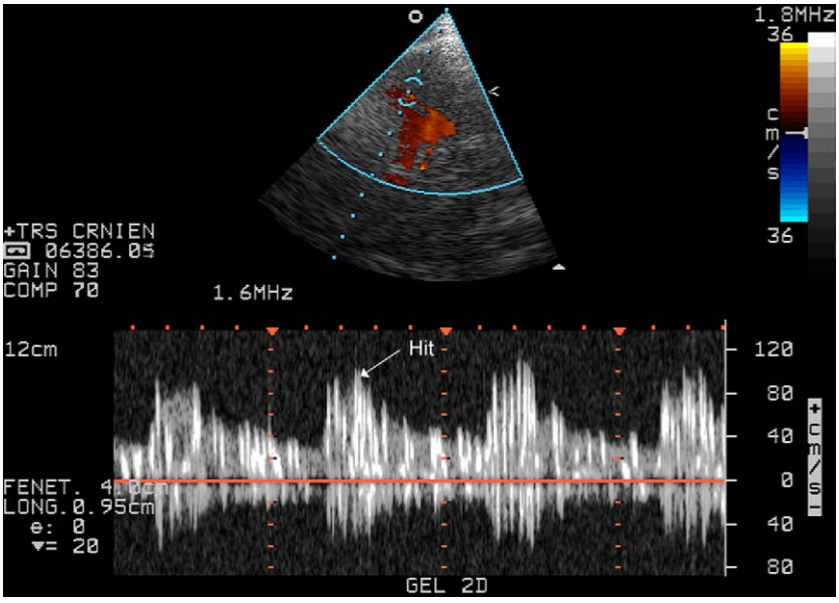

Figure 2 Medium shunt with transcranial Doppler.

Wilcoxon test was then used to compare the results of each examination with another (*p* values of less than 0.0167 were considered statistically significant (with the correction of Bonferroni)). The data studied for these two tests were the presence or absence of shunt with Valsalva manoeuvre in each examination.

Data of the quantification of the shunt were analyzed by the Friedman test (*p* values of less than 0.05 were considered statistically significant).

Results (Table 1)

With TTE

Thirty-eight (35%) patients had a PFO, 18 (47%) of these patients were discovered without Valsalva's manoeuvres:

- without Valsalva, 5 patients had a small shunt, 11 a medium shunt and 2 a large shunt;

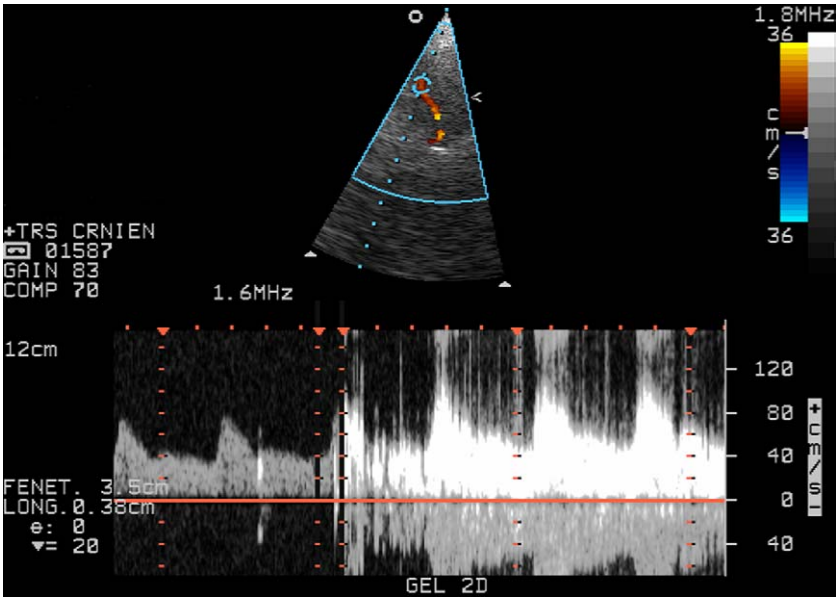

Figure 3 Large shunt with transcranial Doppler.

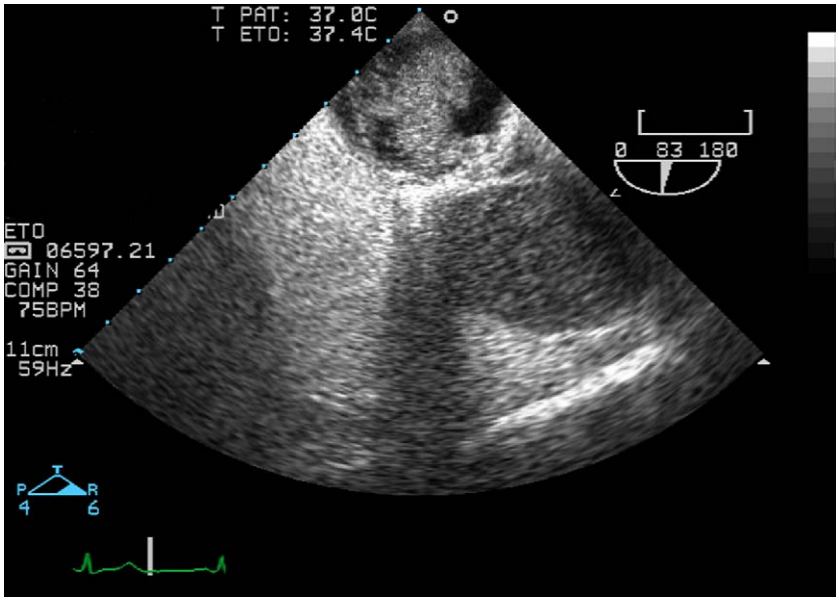

Figure 4 Large shunt with transesophageal echocardiography.

- with Valsalva, 2 patients presented a small shunt, 15 a medium shunt and 21 a large shunt.

With DTC

Forty-eight (45%) patients had a positive contrast test and 31 (65%) of these were found without Valsalva's manoeuvres:

- without Valsalva, 9 patients presented a small shunt, 18 a medium shunt and 4 a large shunt;
- with Valsalva, 7 patients had a small shunt, 17 a medium shunt and 24 a large shunt.

With TEE

Forty-two (39%) PFO were diagnosed, 14 (13%) of these without Valsalva's manoeuvres:

- without Valsalva, 3 patients presented a small shunt, 9 a medium shunt and 2 a large shunt;
- with Valsalva, 3 patients had a small shunt, 22 a medium shunt and 17 a large shunt.

All 42 patients with a PFO detected by TEE had a positive contrast test with TCD.

Two patients had a positive contrast test with TTE and TCD but a negative one with TEE. These 2 patients had been sedated before TEE by midazolam.

Forty-four patients were diagnosed with PFO either by TTE or by TEE.

For 4 patients, only the TCD found a right-to-left shunt. There was a doubt about an intracardiac shunt for these patients. In these 4 patients, the shunt was detected with Valsalva's manoeuvre: two were small, one medium and the last was large.

Eighteen (47%) PFOs were found in patients less than 55 years.

Table 1 Results with Valsalva manoeuvre

	Transthoracic echocardiography	Transcranial Doppler	Transesophageal echocardiography
Small shunt	2	7	3
Medium shunt	15	17	22
Large shunt	21	24	17
Total	38	48	42
Wilcoxon test	$p = 0.004$	$p = 0.015$	

Concerning the patients with migraine, PFO was detected in 18 cases (56% of them); 6 of them had migraine with aura.

Statistical analysis

Comparison of methods

Test of Cochran

This test found a statistically significant difference ($p = 0.02$) between the three methods in the detection of the shunts.

Test of Wilcoxon

A statistically significant difference was evident between the results of TCD and TTE ($p = 0.004$), and between TCD and TEE ($p = 0.015$). However, between results of TTE and TEE there was no statistically significant difference ($p = 0.599$).

Quantification of the shunts

Test of Friedman

There was a statistically significant difference between the methods in the quantification of the shunts ($p = 0.017$).

Discussion

The prevalence of PFO was 41% in our study group and was highest for the patients with cryptogenic stroke aged below 55 years (47%). This agrees with previous studies which find a prevalence of 55% of PFO, for the patients below 55 years with a cryptogenic stroke.[5]

The sensitivity of the TCD was excellent in our study. The negative predictive value was 100%. The statistical analysis showed statistical difference between results of TCD and the other two examinations.

Yet for four patients, the contrast test was positive only with TCD. Other previous studies also found more positive contrast tests with TCD.[29]

This can be explained by

- the presence of low shunts not detected by TEE and TTE;
- shunts outside of the heart, especially in the lung: small intrapulmonary shunts could cause positive contrast test with TCD which cannot be distinguished from shunts across a PFO[30];
- possibility of false positive contrast test with TCD.

We could not distinguish between these possibilities in this study.

The sensitivity of TTE was lower than with TEE in this study, although this difference did not reach statistical significance.

TTE is limited in patients who have decreased echogenicity, and Valsalva's manoeuvre led to a further decrease in image quality.

In two cases, the PFO was detected with TTE but not with TEE, therefore we did not consider TEE as the gold standard examination for the PFO detection. This prevented us from calculating the specificity. The limits of TEE in the diagnosis may have been due to the sedation, which hinders the ability to perform the Valsalva manoeuvre (which is frequently necessary to elicit a right-to-left shunt).

TCD had a perfect sensitivity in this study. This method is non-invasive and the quantification is easier than with TTE and TEE. But because of the absence of visualization of the cardiac cavities, there is a doubt about false positive cases. The use of TCD is limited in the older patients, where sometimes the temporal window is calcified, preventing the use of TCD.

Consequently, when the only objective is the detection of a PFO, TCD in association with TTE could replace TEE.

For the etiologic diagnosis, when there is an ischemic stroke, the echocardiographer is looking for another embolic cause. In our study, we did not find more embolic cause with TEE than with TTE in patients less than 55 years.

Several studies have shown that for the patients in sinus rhythm and with a normal TTE, more particularly in patients <45 years, the interest of TEE is in the search of a PFO and an atrial septal aneurysm.[31,32] Therefore, with the progress of TTE with the second harmonic, some recommend not to perform a TEE for young patients in sinus rhythm with a normal TTE.[33]

The limitations of TTE are the analysis of aortic's arch, visualization of smaller tumours and detection of atrial septal aneurysms.

The prevalence of migraine sufferers in our study was high (30%) in this population of patients with ischemic stroke. The prevalence is higher than that in the previous studies,[19] but the population is small. The prevalence of PFO in the migraine sufferer is 56%. There seems to be a relation between migraine and presence of PFO.[34,35] But these studies, like ours, have been done with a small population. A larger study group would be required to investigate this relation.

Lower extremity venous Dopplers had only found 5 cases of thrombus present among PFO carriers. These results agree with results of previous studies that used phlebography.[8,36] A paradoxical embolus cannot be excluded by the

absence of deep venous thrombosis in the legs. Indeed, the clot can either migrate or deep venous thrombosis can be found in the pelvic area and consequently the venous Doppler appears normal.

Conclusion

The diagnosis of PFO is important in the work-up of a stroke, especially in cryptogenic stroke, which has a high prevalence of PFO and atrial septal aneurysm. Transesophageal echocardiography is considered to be the gold standard to find a defect of the inter-atrial septum. Our study, which compared transthoracic echocardiography with second harmonic imaging, transcranial Doppler and transesophageal echocardiography in the detection of patent foramen ovale in patients with stroke, has shown that transcranial Doppler in association with transthoracic echocardiography, can accurately and reliably detect cases of patent foramen ovale. We confirmed that transesophageal echocardiography is susceptible to false negative cases in the detection of patent foramen ovale. These limitations may be due to the sedation, which hinders the Valsalva manoeuvre. Therefore, the detection of patent foramen ovale can be done without transesophageal echocardiography, a semi-invasive examination. However, transesophageal echocardiography remains important for the diagnosis of other embolic etiology.

Acknowledgements

We acknowledge Dr Patrick Beliveau and Dr Carlos Brun.

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