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Protocol for Optimal Detection and Exclusion of a Patent Foramen Ovale Using Transthoracic Echocardiography with Agitated Saline Microbubbles

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Agitated saline bubble studies in conjunction with echocardiography, in particular transesophageal echocardiography, are currently the principal means in the diagnosis of patent foramen ovale (PFO). We describe techniques and guidelines for the detection and exclusion of a PFO. The potential for misinterpretation of these bubble studies exists and therefore, several false positive and false negative scenarios are illustrated and discussed. (ECHOCARDIOGRAPHY, Volume 23, August 2006)

patent foramen ovale, *echocardiography*, *agitated saline contrast*, *Valsalva*

Patent foramina ovale are oblique slit-like defects resulting from incomplete fusion of the foramen ovale (septum primum) with the atrial septum (septum secundum). They occur in approximately 27–35% of people[1,2] and have been implicated in a variety of conditions such as paradoxical embolism and cryptogenic stroke,[3] migraines,[4–6] platypnea-orthodeoxia,[7] and gas venous-arterial embolism in divers.[8] Dynamically, they act like a valve that closes (like a door jam) on the left atrial side of the interatrial septum, due to the relatively higher left-sided pressures.

Bubble contrast studies in conjunction with transesophageal or transthoracic echocardiography have been the mainstay of patent foramen ovale (PFO) diagnosis. Techniques for the study have been described with variable detail in the literature.[9–11] False positive studies from transpulmonary crossing of microbubble have been discussed, but false negative studies, to a lesser extent.[12] The presence of left-sided heart disease, with an increased likelihood for elevated left atrial pressures, can decrease the detection of PFO by prevent-in right-to-left shunting.[13–14] We hereby describe our technique and guidelines for PFO detection and exclusion.

Methods

Using two-dimensional transthoracic echocardiography, the interatrial septum and atria are visualized. Suitable views may be the subcostal four-chamber, apical four chamber, or parasternal short axis. The most important consideration when planning to perform a bubble study is to visualize the left atrial aspect of the interatrial septum throughout the duration of the contrast opacification of the right atrium, and during the Valsalva or cough maneuver.

Two 10-mL syringes are attached to a three-way stopcock, one syringe filled with 9-mL saline (bacteriostatic saline works best) and (1 mL of air or air and blood mixture.[15–17] This setup is attached to an intravenous access line. The saline is rapidly pushed from the full syringe to the empty syringe at least 3–5 times in order to evenly mix in the air bubbles (agitate). This converts the clear saline to a whiter, partly opaque air/saline mixture. It is important to push the stopper to the absolute end of the syringe for maximal agitation

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and creation of adequate microbubbles. The agitated saline is then promptly injected into the patient's vein. The entire syringe is safely injected. If the access is via a central line, injection of 5 mL may suffice due to the more direct approach. Femoral vein injection of contrast seems to improve the PFO detection rate[18] because the flow from the inferior vena cava is presumably better angled to pass through a PFO. Gill and Quaife[9] frequently use intravenous lines in the feet for this purpose. However, longer venous transit times and spontaneous destruction of the microbubbles may offset some of these anatomic advantages. Also, Center for Disease Control Guidelines[19] makes a strong general recommendation to use upper rather than lower extremities for peripheral venous catheters, to minimize infection risk.

A satisfactory contrast injection should result in complete opacification of the right atrium. Agitated saline should be first injected without a Valsalva maneuver to look for a resting shunt. In a resting shunt, agitated saline crosses from the right into the left atrium without the need for a Valsalva maneuver. Such shunts have the highest morbidity.[20] The ideal time, from our experience, for complete opacification of the right atrium is at the end of the Valsalva maneuver when the interatrial septum transiently shifts toward the left atrium. This timing requires coordination between the sonographer, the patient, and the person injecting the microbubbles. The injection is performed while the patient is bearing down, and as the contrast is entering the right atrium the Valsalva is released and the image is thus optimized.

Valsalva Maneuver

Performance of a Valsalva maneuver, i.e., expiratory effort against a closed glottis, or asking the patient to cough during echocardiography, will facilitate passage of blood through a PFO, should it exist, by momentarily altering the left/right atrial pressure gradient. This causes the septum primum, on the left side of the atrial septum, to transiently lift up and open the septae.

An acceptable Valsalva maneuver in this context is one in which the interatrial septum is seen to shift to the left, most dramatically upon the release phase of Valsalva. The patient may need several practice attempts. The examiner will ask the patient to bear down "as if about to have a bowel movement" for 5–10 seconds. This maneuver is commonly not maintained long enough to result in septal shifting. The examiner in our labs may assist the patient by firmly pressing over the abdomen and asking the patient to use their abdominal muscles to push back against the examiner's hand. Performing a satisfactory Valsalva may be difficult during transesophageal echocardiography (TEE) and is dependent on the level of sedation. In such cases the patient can be asked to cough forcefully several times. It may be helpful to perform the agitated bubble study toward the end of the transesophageal examination when the patient is less sedated. As with the Valsalva maneuver, the critical component remains the confirmation of atrial septal shifting.

Guidelines for PFO Detection

Our guidelines for PFO diagnosis are presented (Table I). Finding 1 in Table I (actual visualization of bubbles crossing the atrial septum) is sufficient for the diagnosis of a PFO, but is only occasionally noted. In other words, if this is fulfilled, then the others are not necessary. The presence of findings 2–4 is to ensure the use of adequate technique. So, ideally, should also be fulfilled. Upon the release of an adequate Valsalva maneuver, there should be an atrial septal shift to the left. This must be achieved to confirm an adequate study prior to considering the study as "negative" and falsely eliminating the possibility of a PFO. We believe that the common practice of less strict criteria has contributed to the lower echo detection rate in the published literature than what is known via autopsy data.

Illustrative Case Examples

Figure 1 initially appears to be positive for the detection of a PFO. There is right atrial dense opacification followed by the appearance of bubbles in the left heart. It will also be observed that the septum has not shifted. The

TABLE I

Findings Suggestive of Patent Foramen Ovale

1. Right atrial bubbles are shown by step-frame review to enter the left atrium via the interatrial septum (even if after 3–5 cardiac cycles)
2. Right atrial dense opacification (including region immediately adjacent to septum)
3. Interatrial septal shift to the left
4. Bubbles seen in the left atrium

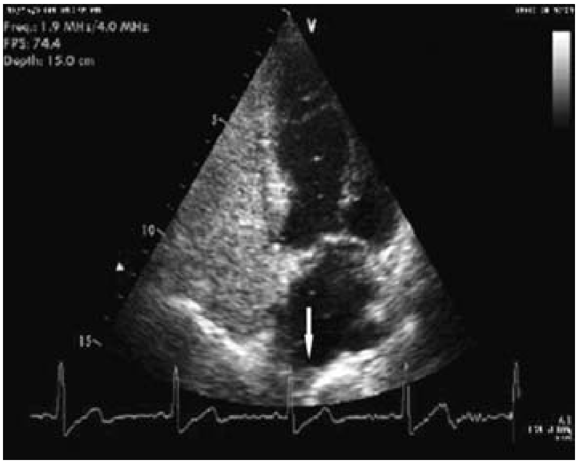


Figure 1. *Potential false positive study. 2D echocardiogram, apical four-chamber view after agitated saline bubble injection. The RA is densely opacified. The atrial septum is midline (not shifted). Few bubbles are seen in left atrium and ventricle arising from the right superior pulmonary vein (arrow).*

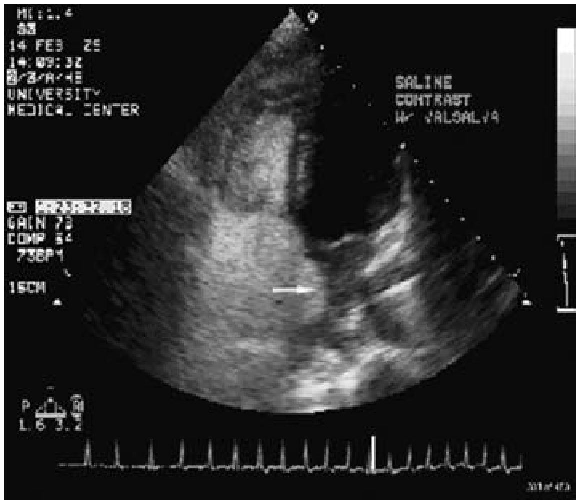


Figure 2. *A definite PFO (small). 2D echocardiogram, apical four-chamber view after agitated saline bubble injection. Dense opacification of the right atrium, interatrial septal shift toward the left atrium, and bubbles seen crossing septum.*

lack of septal shifting does indeed decrease the chance of bubble passage through a potential PFO, but is not mandatory if bubbles are seen within the LA. Importantly, the witnessed bubbles were seen, by step-frame analysis, to emerge from the right superior pulmonary vein (RSPV) and not the interatrial septum. This patient had a pulmonary arterial-venous shunt.

Caution needs to be raised when using this methodology since the actual opening of the PFO may extend to the base of the interatrial septum and could be confused with the RSPV. Therefore, multiple saline injections may be needed to clearly demonstrate the origin of the shunt. When questions remain, a TEE may need to be performed since the actual PFO opening and pulmonary veins are clearly demonstrated as separate origins. Both of the patient examples in Figures 2 and 3 show true positive studies that fulfill both our diagnostic criteria. With careful step-frame analysis, the first bubbles seen within the LA were observed at the middle of the shifted septum. Figure 3 represents a PFO with the LA opacified as densely as the RA, consistent with a larger degree of shunting.

Figure 4 shows three images obtained in sequence. Initially (Fig. 4A), contrast has fully opacified the right atrium, but the septum has yet to shift. No bubbles are seen to cross the septum, so the study is negative so far. Subsequently (Fig. 4B), the septum has begun to move to the left and bubbles are seen to cross over. The passage of bubbles across the septum can be confirmed using step-frame analysis. All diagnostic criteria for PFO detection have been fulfilled and the study is positive. Even as the septum begins to return to its original position (Fig. 4C), bubbles continue to cross the PFO. This reinforces our view that finding 1 in Table I

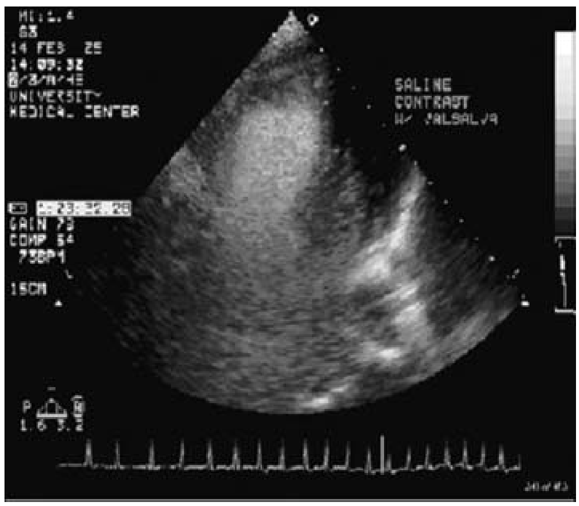
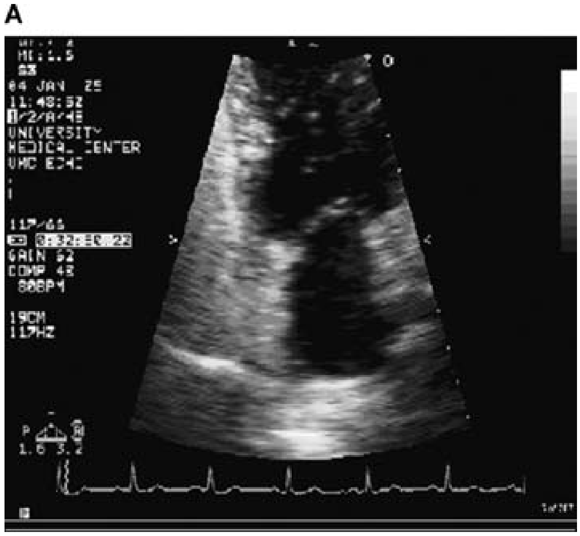
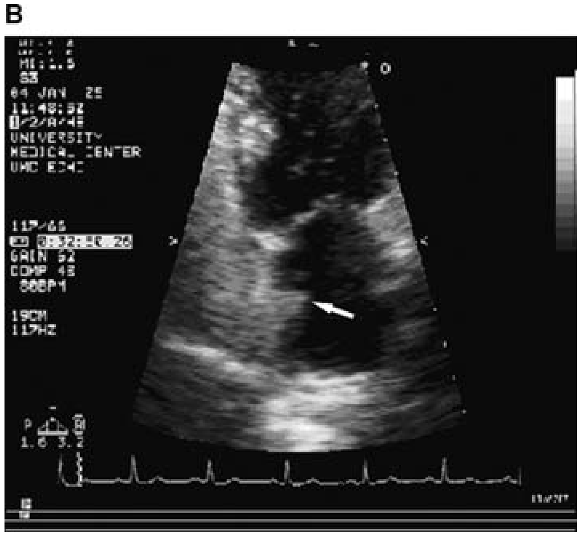


Figure 3. *A definite PFO (severe shunting). 2D echocardiogram, apical four-chamber view after agitated saline bubble injection. Dense right atrial opacification, septal shift, and severe shunting across the septum.*





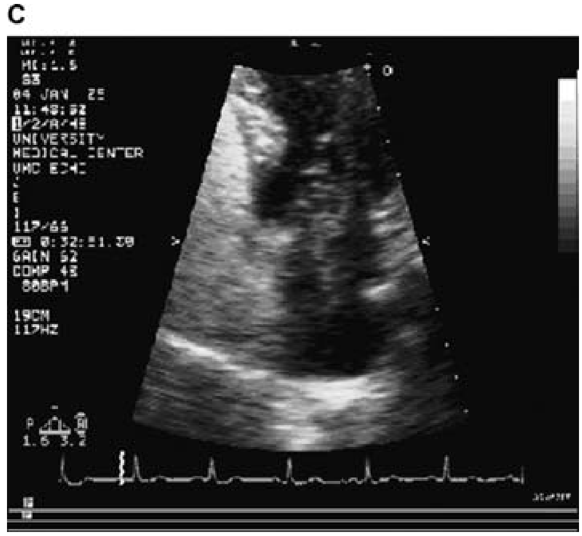


Figure 4 **A**. *Temporal sequence of septal shifting. Figures 4A–4C. 2D echocardiogram, apical four-chamber view after agitated saline bubble injection. Right atrial dense opacification prior to optimal response to Valsalva and septal shifting.* **B**. *With successful Valsalva, the septum is noted to shift leftward. This optimally displaces the atrial septae in preparation for bubble shunting.* **C**. *Because the bubbles were seen to adequately persist in the RA, shunting across the septum was readily visualized confirming the high likelihood for a PFO. Note that by this time the septum has returned to its midline, nonshifted position.*

(visualization of a septal shunt by step-frame analysis) alone is sufficient for PFO diagnosis. The practical implication is that if a study fails to capture images depicting right atrial opacification and interatrial septal shift (Fig. 4A and 4B), but does capture right atrial microbubbles crossing the interatrial septum into the left atrium (Fig. 4C), the study is positive.

A common viewpoint is that bubbles must appear in the LA within 3–5 cardiac cycles of their appearance in the RA to diagnose a PFO and that bubbles appearing in the LA beyond five cycles suggest transpulmonary shunting. There is little published data to support this. Also, this view is flawed for two reasons. Indeed, bubbles may not cross a PFO until after 3–5 cycles. This delay can be explained by a hypodynamic circulation, by dilated, fibrillating atria, or a delay in atrial shunting. Furthermore, bubbles traversing a sizeable pulmonary shunt may get to the left atrium within the 3–5 cycles and create a false positive interpretation (Fig. 5). Arteriovenous shunting is most common in patients with liver disease.[21,22] Transpulmonary shunting can be resolved by carefully following bubble movements with frame-by-frame analysis or independently assessing each pulmonary vein origin for bubble entry during a TEE bubble study. If a PFO is found, the extent of shunting can be approximated and there is some evidence that the size of the PFO[23,24] in addition to shunting at rest[20] are markers of a worse outcome and predictors of stroke

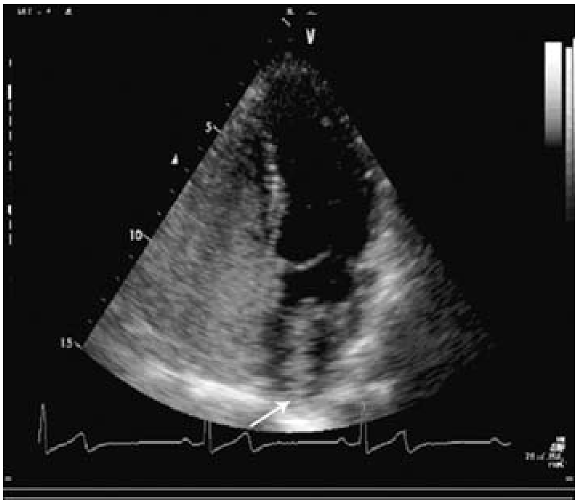


Figure 5. *Large pulmonary AV fistula. 2D echocardiogram, apical four-chamber view after agitated saline bubble injection. Optimal dense opacification of the right atrium is noted. The septum is midline. Microbubbles are seen to emerge from the right superior pulmonary vein (arrow) and these occurred very early after contrast injection (within three cardiac cycles).*

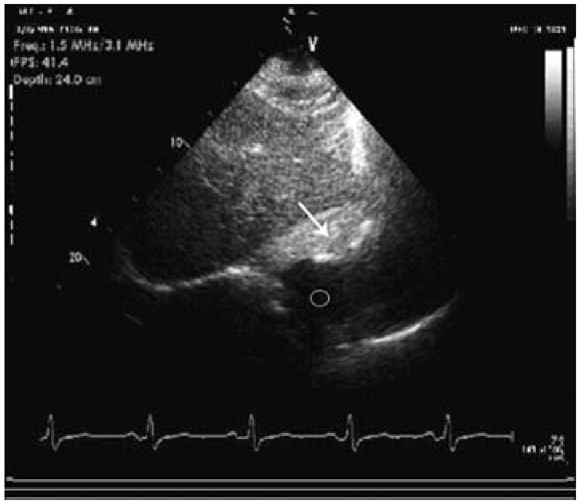


Figure 6. *Potential false negative study. 2D echocardiogram subcostal long-axis view after agitated saline bubble injection. The densely opacified RA cavity (arrow) partially masks the more distal left atrial cavity (circle). This finding reduces the chance of visualizing any bubbles within the LA.*

recurrence. PFO size measurements are not discussed in this paper.

Guidelines for PFO Exclusion

We strongly believe that all echo conditions listed in Table II must ideally be satisfied in order to rule out a PFO with adequate certainty. We insist on a septal shift because it reassures the examiner that the mean right atrial pressure has transiently exceeded that of the left atrium. Without this transient pressure differential, passage of blood (and bubbles) is unlikely to occur with elevated left atrial pressures or through a PFO, and a study may be falsely interpreted as negative (Fig. 6). This concept is supported by patients with large atrial septal defects where, despite the absence of septal tissue, microbubbles commonly remain in the right atrium throughout the cardiac cycle, provided the right-sided pressures are normal. Given this fact, it is not surprising that the much smaller PFO shunts require transient shifts in atrial pressures and this is best witnessed by transient interatrial septal shifting.

TABLE II

Findings that Help Exclude Patent Foramen Ovale

1. Right atrial dense opacification (especially adjacent to the septum), and
2. Transient leftward shifting of the interatrial septum, but
3. No bubbles in the left atrium seen to emerge through the interatrial septum, or
4. Bubbles noted in LA only after 3–5 cardiac cycles after the transient septal shift

Although subcostal imaging planes are frequently recommended during the investigation of atrial septal defects, for a perpendicular alignment of the Doppler, this window is not ideal for the investigation of smaller PFOs. Since an optimal bubble study creates dense opacification of the right atrium—which is in the near-field on subcostal imaging planes—this view may result in an attenuation artifact that blocks the adequate visualization of a small amount of microbubbles in the left atrium (farfield) (Fig. 6). Therefore, in our experience it is preferable to use another echo window which provides continuous imaging of the LA side of the atrial septum during bubble enhancement of the RA.

It is imperative to have complete right atrial dense opacification (exclusion) to firmly rule out a PFO. Not uncommonly, noncontrasted blood filling the RA via the inferior vena cava will mix with the contrasted blood entering via the superior vena cava (seen more readily with TEE)

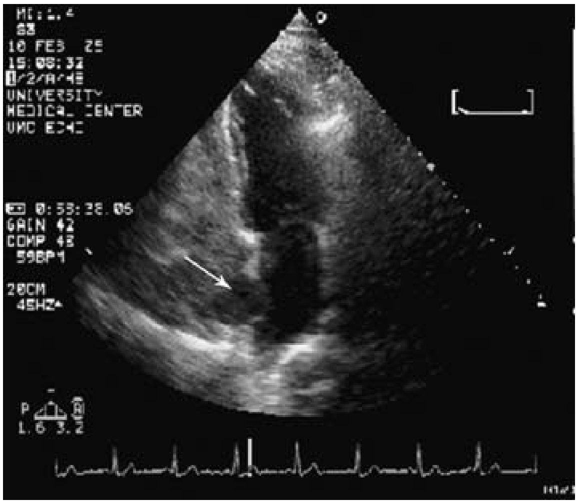


Figure 7. *Potential false negative study. 2-D echocardiogram, apical four-chamber view after agitated saline bubble injection. Although contrast is visualized within the RA cavity and the septum is shifted leftward, an echo-free space is noted along atrial septum (arrow). This reduces the sensitivity of recognizing a PFO since this noncontrasted blood may shunt across a PFO and not be seen within the LA.*

and results in a "contrast-free zone" along the atrial septum. This creates a scenario where the noncontrasted blood may actually "shunt" through a PFO but is not recognized in the LA. This should be noted and avoided with a more rapid or larger volume (or both) repeat microbubble injection. If the RA opacification remains incomplete, the echo interpreter cannot be certain that a PFO is not present and the study should be concluded as indeterminate (or suboptimal), but not negative (Fig. 7).

Conclusions

The diagnosis and exclusion of a PFO is highly variable with both operator and reader dependence. It is hoped that our guidelines will help to standardize the performance and interpretation of PFO and improve the diagnosis of this common finding that has a growing clinical significance due to percutaneous closure options. Furthermore, we believe these methods will help reduce the gap between the known incidence of PFO and the current published echocardiographically detected PFO rate.

References

1. Hagen PT, Scolz DG, Edwards WD: Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;59:17–20.
2. Thompson T, Evans W: Paradoxical embolism. *Q J Med* 1930;23:135–152.
3. Webster MW, Chancellor AM, Smith HJ, et al: Patent foramen ovale in young stroke patients. *Lancet* 1988;2:11–12.
4. Finsterer J, Sommer O, Stiskal M, et al: Closure of a patent foramen ovale: Effective therapy of migraine and occipital stroke. *Int J Neurosci* 2005;115(1):119–127.
5. Schwerzmann M, Wiher S, Nedeltchev K, et al: Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology* 2004;62(8):1399–1401.
6. Sztajzel R, Genoud D, Roth S, et al: Patent foramen ovale, a possible cause of symptomatic migraine: A study of 74 patients with acute ischemic stroke. *Cerebrovasc Dis* 2002;13(2):102–106.
7. Seward JB, Hayes DL, Smith HC, et al: Platypnea-orthodeoxia: Clinical profile, diagnostic workup, management, and report of seven cases. *Mayo Clin Proc* 1984;59:221–231.
8. Moon RE, Camporesi EM, Kisslo JA: Patent foramen ovale and decompression sickness in divers. *Lancet* 1989;1:513–514.
9. Gill EA Jr, Quaife RA: The echocardiographer and the diagnosis of patent foramen ovale. *Cardiol Clin* 2005;23:47–52.
10. Djaiani G, Phillips-Bute B, Podgoreanu M, et al: The association of patent foramen ovale and atrial fibrillation after coronary artery bypass graft surgery. *Anesth Analg* 2004;98:585–589.
11. Fisher DC, Fisher EA, Budd Jh, et al: The incidence of patent foramen ovale in 1000 consecutive patients. *Chest* 1995;107:1504–1509.
12. Kerut EK, Norfleet WT, Plotnick GD, et al: Patent foramen ovale: A review of associated conditions and the impact of physiological size. *[Review] J Am Coll Cardiol* 2001;38(3):613–623.
13. Siostrzonek P, Lang W, Zangeneh M, et al: Significance of left-sided heart disease for the detection of patent foramen ovale by transesophageal contrast echocardiography. *J Am Coll Cardiol* 1992;19:1192–1196.
14. Movsowitz HD, Movsowitz C, Jacobs LE, et al: Negative air-contrast test does not exclude the presence of patent foramen ovale by transesophageal echocardiography. *Am Heart J* 1993;126(4):1031–1032.
15. Fan S, Nagai T, Luo H, et al: Superiority of the combination of blood and agitated saline for routine contrast enhancement. *J Am Soc Echo* 1999;12(2):94–98.
16. Droste DW, Reisener M, Kemény V, et al: Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts. *Stroke* 1999;30:1014–1018.
17. Steiner M, Di Tullio M, Rundek T, et al: Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 1998;29:944–948.
18. Gin KG, Huckell VF, Pollick C: Femoral vein delivery of contrast medium enhances transthoracic echocardiographic detection of patent foramen ovale. *J Am Coll Cardiol* 1993;22(7):1994–2000.
19. O'Grady NP, Alexander M, Dellinger EP, et al: Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2002;23:759–769.

20. De Castro S, Cartoni D, Fiorelli M, et al: Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;31:2407–2413.
21. Vedrinne J, Duperret S, Bizollon T, et al: Comparison of transesophageal and transthoracic contrast echocardiography for detection of an intrapulmonary shunt in liver disease. *Chest* 1997;111:1236–1240.
22. Naeije R: Hepatopulmonary syndrome and portopulmonary hypertension. *Swiss Med Weekly* 2003;133:163–169.
23. Homma S, DiTullio MR, Sacco RL, et al: Characteristics of patent foramen ovale associated with cryptogenic stroke. A biplane transesophageal echocardiographic study. *Stroke* 1994;25:582–586.
24. Schuchlenz HW, Weihs W, Horner S, et al: The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med* 2000;109:456–462.

Supplementary Material

The following supplementary material is available for this article online: Movie Clips: Figures 1 and 5, Figures 2 and 3, Figures 4a-c, Figure 7.