Patent Foramen Ovale and Transcranial Doppler

V. Inchingolo[a]
M.A. Pacilli[b]
S. Gemma[a]
S. Mastroianno[b]
M. Impagliatelli[b]
C. Vigna[b]

Departments of Neurology[a] and Cardiology[b]
IRCCS "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo (FG), Italy

Patent foramen ovale (PFO) is an anatomical heart condition causing, mostly without symptoms, a right-to-left shunt (RLS) through the atrial septum, at level of the fossa ovale (1). In some cases, and via different mechanisms, PFO may be responsible for different pathological conditions. The PFO-related syndromes may be caused by paradoxical embolism or by toxic action on organs like the brain, from substances in the venous blood not properly filtered by the pulmonary circulation (2). Cerebral ischaemia and migraine (with aura particularly) are the most frequent PFO-related syndromes (3-13). Less frequent, but not less important in the clinical context, are peripheral embolisms (myocardium or limbs) (14), platypnoea-orthodeoxia (15), diver's embolism (16) and embolism during neurosurgery in the sitting position (17).
Contrast trans-oesophageal echocardiography (c-TEE) is considered the gold standard for diagnosis of PFO. It makes it possible to display the atrial septum, atrial cavities, the arrival of contrast medium after intravenous bolus administration and its RLS through the PFO (17). This method allows us to highlight an atrial septum aneurysm and to distinguish PFO from other anatomical conditions that cause left-to-right or bi-directional shunt, like defects and inter-atrial communications. A RLS is usually defined intra-cardiac when contrast microbubbles in the left atrium appear within three cardiac cycles of their appearance in the right atrium. Once this threshold is exceeded, we have to suspect an extra-cardiac shunt, like an arteriovenous fistula.
Due to the capacity of transcranial Doppler (TCD) to detect transiting particles with acoustic impedance different from that of blood in cerebral arteries, a RLS can be diagnosed with this tool (20-24) (Fig. 1). The TCD methodology in this field was standardised during the Consensus Conference in Venice in 1999 (25). It involves injecting, into an antecubital vein, a bolus consisting of a mixture of 0.9% saline solution and air (respectively 9 cc and 1 cc), obtained by passing them repeatedly between two syringes connected by a 3-way stopcock. It is appropriate to add about 0.5 cc of the patient's blood in order to obtain a more stable mixture.
Usually microbubbles are destroyed in their first pulmonary passage, as their diameter is greater than the

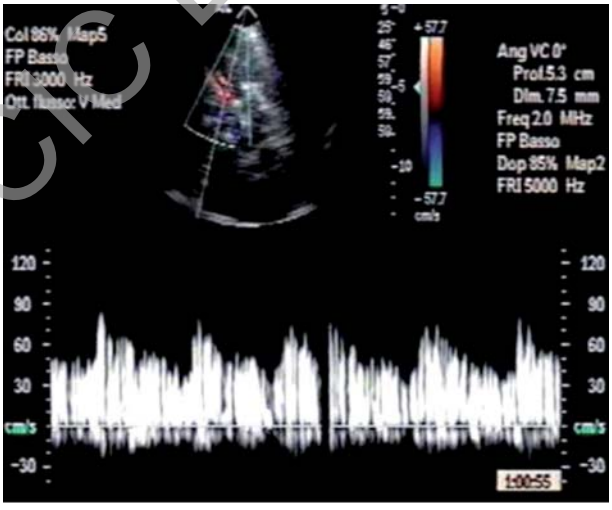

Fig. 1 - Contrast transcranial colour-coded Doppler detecting a high RLS at rest (high grade permanent shunt).

lumen of pulmonary capillaries. For this reason, no microembolic signal (MES) is detected in the cerebral arteries. On the contrary, in the presence of a PFO, some microbubbles jump the pulmonary filter and can be detected in form of MESs in the cerebral arteries (preferably the Doppler signal of the middle cerebral artery is monitored). These MESs are characterised by high intensity, unidirectionality, short duration (usually less than 300 msec.) and a typical noise ("chirping") (26).

The examination is performed in basal conditions (patient at rest in the supine position) and, if negative, during the Valsalva manoeuvre (VM), in order to display a shunt not present at rest. Before test it is a good idea to train the patient in the proper execution of the VM and to monitor its effectiveness as progressive changes in peak flow velocity on Doppler spectrum. As established by the Consensus Conference group (25), the VM should start 5 seconds after the start of exposure to the contrast medium and should last 10 seconds. In daily clinical practice, however, it is noted that few patients are able to perform such a long VM. In our experience, and as reported by other authors (27), consistent results can be achieved with a shorter duration (5 seconds). On the basis of the number of MESs detected by TCD, we can classify the RLS as "mild", "medium" or "high", if there are, respectively, ≤ 10 MESs, >10 MESs without curtain (MESs individually countable on Doppler spectrum) and > 10 MES with curtain (MESs in such a number that they cannot be counted separately on Doppler spectrum, forming a continuum of increased signal). The RLS is also defined "permanent" if it is already present at rest and "latent" if it appears only after the VM. In doubtful cases (clinical history highly suggestive of PFO, but absent or not significant shunt), the test can be repeated in the standing position. In this way, there is more chance that a shunt will appear. But, in other cases, the reverse has been found.

The time between the start of the intravenous bolus exposure and the appearance of MESs is indicative of the route that microbubbles take to the cerebral arteries. In the case of a RLS through a PFO, this time is about 11 seconds. In the presence of a longer time (around 14 seconds) we would have to suspect an extra-cardiac shunt (e.g. pulmonary arteriovenous fistula). However, this difference, reported by Horner et al. (27), did not reach statistical significance. According to the Consensus Group (25), there is no unfailing cut-off time for distinguishing a cardiac from an extra-cardiac shunt.

If persistence of an opened foramen ovale is considered important for the passage of emboli from the venous circulation, a critical factor is undoubtedly the amount of blood reaching the brain. The greater the amount of blood flowing through the PFO and bypassing the pulmonary filter, the higher the probability of a clot reaching the brain. However, the amount of shunt reaching the brain does not always correlate with the size of the PFO measured with echocardiographic methods, primarily because there is no certain method for this measurement (2D measurement or measurement based on the number of bubbles appearing in the left atrium after contrast medium exposure). Moreover, 2D measurement tends to underestimate the size of PFO compared to balloon intra-cardiac measurements. This method also correlates with semi-quantitative c-TEE measurement only if the contrast medium is injected through the femoral vein (28). The amount of blood that is really diverted to the brain, under the same size of PFO, thus depends on other factors, like the orientation of the ostium cavale in the right atrium, the persistence of the Eustachian valve and the anatomy of the supraortic trunks. Hence the magnitude of the shunt should be measured directly in the cerebral arteries. The importance of quantification of shunt is reinforced by the observation that is precisely the magnitude of the shunt measured by TCD with contrast medium (c-TCD) that emerges as the main variable related to stroke (29) and its recurrence (30).

As established by the Consensus Conference (25), the classification of shunt is as follows: level I) no MES detected (no shunt); level II) 1-10 MESs (mild shunt); level III) > 10 MESs without curtain (medium shunt); level IV) > 10 MESs with curtain (high shunt). As mentioned above, the shunt is also defined as "permanent" or "latent", according to its appearance at rest or after the VM. By combining the 4-level shunt classification with the definition of the type of shunt (latent or permanent) it is possible to obtain a semi-quantitative six-level classification that more accurately reflects the "global entity" of the shunt: 0) absent, 1) mild latent, 2) medium latent, 3) high latent, 4) medium permanent, 5) high permanent (31). This classification provides a practical tool for comparing data and allows us to relate the shunt to patient clinical risk.

Although we still consider c-TEE the gold standard for diagnosing PFO, several observations support the conclusion that c-TCD and its recent evolution contrast transcranial colour-coded Doppler (c-TCCD) are techniques with adequate specificity and high sensitivity for this purpose. Various studies comparing these two methods have shown, for c-TCD, a sensitivity close to 100% and a specificity ranging from 60% to 100%. The benefits of c-TCD compared with c-TEE are: non-invasiveness, greater reliability of results in cases that require the VM (not always easy to perform for patients with a transoesophageal probe), and the ability to quantify the shunt directly in the target organ (the brain). The importance of quantification of RLS, reliable with c-TCD and less accurate with c-TEE, is demonstrated by a direct relationship between the en-

tity of the shunt measured by c-TCD and the risk of cryptogenic stroke (higher in patients with high grade shunt) (29,30). The main limitation of c-TCD is the difficulty to distinguish correctly the site of the shunt (32-35). In our and other institutions (30,36), c-TCCD is the first step when looking for PFO in patients with cryptogenic stroke and/or migraine with aura. It also contributes, through direct evaluation of the shunt in the target organ, to patient risk stratification; is also the best method for detecting residual shunts in patients undergoing percutaneous closure of PFO (37).

In cases of positive RLS, combining a trans-thoracic echocardiogram (TTE) and c-TCCD, almost completely fills the c-TCCD specificity gap compared to the gold standard. In this way, it is possible to diagnose a PFO with high diagnostic accuracy, avoiding patient discomfort. Basically, data concerning the presence or absence of the shunt and its entity can be obtained from c-TCCD and findings about the fossa ovale anatomy from TTE. c-TEE is mandatory in doubtful cases, with a poor thoracic window and when a clinical history indicates percutaneous closure of PFO (pre-operative fossa ovale anatomical study) (38,39).

Is desirable that c-TCD and c-TCCD be employed not only to look for RLS in routine clinical practice, but also in future clinical trials exploring the natural history of patients with stroke-related PFO or comparing different treatments for PFO.

References

1. Hagen PT, Scholz 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. Tembl J, Lago A, Sevilla T, Solis P, Vilchez J. Migraine, patent foramen ovale and migraine triggers. J Headache Pain 2007;8:7-12
3. Lechat P, Mas JL, Lascault G et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-52
4. Webster MW, Chancellor AM, Smith HJ et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-12
5. Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. Ann Intern Med 1992;117:461-465
6. Cabanes L, Mas JL, Cohen A et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993;24: 1865-1873
7. Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. Am Heart J 1995;130:1083-1088
8. Chant H, Mc Collum C. Stroke in young adults: the role of paradoxical embolism. Thromb Haemost 2001;85:22-29
9. Del Sette M, Angeli S, Leandri M et al. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998;8:327-330
10. Anzola GP, Magoni M, Guidani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999;52:1622-1625
11. Diener HC, Weimar C, Katsarava Z. Patent foramen ovale: paradoxical connection to migraine and stroke. Curr Opin Neurol 2005;18:299-304
12. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci (Lond) 2001;100:215-220
13. Schwaag S, Nabavi DG, Frese A, Husstedt IW, Evers S. The association between migraine and juvenile stroke: a case-control study. Headache 2003;43:90-95
14. Rigatelli GL, Rigatelli G, Rossi P, et al. Normal angiogram in acute coronary syndromes: The underestimated role of alternative substrates of myocardial ischemia. Int J Cardiovasc Imaging 2004;20:471-475
15. Zanchetta M, Rigatelli G, Ho SY. A mystery featuring right-to-left shunting despite normal intracardiac pressure. Chest 2005;128:998-1002
16. Cartoni D, De Castro S, Valente G et al. Identification of professional scuba divers with patent foramen ovale at risk for decompression illness. Am J Cardiol 2004;94:270-273
17. Zanchetta M, Onorato E, Rigatelli G, Pedon L, Zennaro M, Maiolino P. Can posterior fossa lesions be a place for preventive patent foramen ovale transcatheter closure? J Invasive Cardiol 2004;16:346-350
18. Schneider B, Zienkiewicz T, Jansen V, Hofmann T, Noltenius H, Meinertz T. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. Am J Cardiol 1996;77:1202-1209
19. Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME. The incidence of patent foramen ovale in 1,000 consecutive patients. A contrast transesophageal echocardiography study. Chest 1995;107:1504-1509
20. Itoh T, Matsumoto M, Handa N et al. Paradoxical embolism as a cause of ischemic stroke of uncertain etiology. A transcranial Doppler sonographic study. Stroke 1994;25:771-775
21. Jauss M, Kaps M, Keberle M, Haberbosch W, Dorndorf W. A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium for detection of patent foramen ovale. Stroke 1994;25: 1265-1267
22. Yeung M, Khan KA, Shuaib A. Transcranial Doppler ultrasonography in the detection of venous to arterial shunting in acute stroke and transient ischaemic attacks. J Neurol Neurosurg Psychiatry 1996;61:445-449

23. Zanette EM, Mancini G, De Castro S, Solaro M, Cartoni D, Chiarotti F. Patent foramen ovale and transcranial Doppler. Comparison of different procedures. Stroke 1996;27:2251-2255
24. Droste DW, Silling K, Stypmann J et al. Contrast transcranial doppler ultrasound in the detection of right-to-left shunts: time window and threshold in microbubble numbers. Stroke. 2000;31:1640-1645
25. Jauss M, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. Cerebrovasc Dis 2000;10:490-496
26. Spencer MP, Thomas GI, Nicholls SC, Sauvage LR. Detection of middle cerebral artery emboli during carotid endoarterectomy usin transcranial Doppler Ultrasonography. Stroke 1990;21:415-423
27. Horner S, Ni XS, Weihs W et al: Simultaneous bilateral contrast transcranial Doppler monitoring in patients with intracardiac and intrapulmonary shunts. J Neurol Sci 1997;150:49-57
28. Schuchlenz HW, Wehis W, Beitzke A, Stein JI, Gamillscheg A, Rehak P. Transesophageal echocardiography for quantifying size of patent foramen ovale in patients with cryptogenic cerebrovascular events. Stroke 2002;33:293-296
29. Serena J, Segura T, Perez-Ayuso MJ, Bassaganyas J, Molins A, Davalos A. The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. Stroke 1998;29:1322-1328
30. Anzola GP, Zavarise P, Morandi E, Rozzini L, Parrinello G. Transcranial Doppler and risk of recurrence in patients with stroke and patent foramen ovale. Eur J Neurol 2003;10:129-135
31. Vigna C, Inchingolo V, Giannatempo GM et al. Clinical and brain magnetic resonance imaging follow-up after percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. Am J Cardiol 2008;101:1051-1055
32. Droste DW, Kriete JU, Stypmann J et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: comparison of different procedures and different contrast agents. Stroke 1999;30:1827-1832
33. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol 2001;38:613-623
34. Blersch WK, Draganski BM, Holmer SR et al. Transcranial duplex sonography in the detection of patent foramen ovale. Radiology 2002;225:693-699
35. Heckmann JG, Niedermeier W, Brandt-Pohlmann M, Hilz MJ, Hecht M, Neundörfer B. Detection of patent foramen ovale. Transesophageal echocardiography and transcranial Doppler sonography with ultrasound contrast media are 'supplementary, not competing, diagnostic methods'. Med Klin (Munich) 1999;94:367-370
36. Rigatelli G, Braggion G, Chinaglia M et al. Setting up a multidisciplinary program for management of patent foramen ovale-mediated syndromes. J Interv Cardiol 2006;19:264-268
37. Anzola GP, Morandi E, Casilli F, Onorato E. Does transcatheter closure of patent foramen ovale really "shut the door?" A prospective study with transcranial Doppler. Stroke 2004;35:2140- 2144
38. Konstantinides S, Just H. Patent foramen ovale: conservative or surgical therapy? Z Kardiol 2000;89:63-71
39. Waight DJ, Cao QL, Hijazi ZM. Closure of patent foramen ovale in patients with orthodeoxia-platypnea using the amplatzer devices. Catheter Cardiovasc Interv 2000;50:195-198