# Patent Foramen Ovale and Cryptogenic Stroke: Where Do we Go From Here

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Ischemic stroke is the third most common cause of death and the leading cause of functional incapacity in western countries. Despite an exhaustive study of the etiology of stroke, according to internationally accepted etiological criteria the cause of this disease is classified as undetermined in up to 30%-40% of patients in databases on stroke. This proportion is even higher in young patients. Persistence of patent foramen ovale (PFO) has been implicated as a potential cause of paradoxical embolism and, particularly, cerebral embolism in stroke of unknown cause (cryptogenic stroke).[1-10] When the cause of stroke is a right-to-left shunt (RLS) through a PFO the health of the patient may be seriously compromised. There are 100 000 cases of stroke in Spain of which 30% are of indeterminate origin. Given that RLS/PFO is detected in a third of these cases, then 10 000 cases of ischemic stroke could be associated with RLS/PFO each year. Permanent closure (by adhesion of the septum primum to the atrial septum) normally occurs in the first 3 months of life, but the foramen ovale remains patent in a substantial number of people. Patent foramen ovale is detected in 27%-35% of normal hearts at autopsy, in 10%-26% of normal individuals with contrast transesophageal echocardiography (c-TEE) and in 25%-35% using contrast transcranial Doppler (c-TCD) ultrasonography. The diameter of the PFO in autopsy examinations of normal hearts ranges from 1 to 19 mm, with a mean of 4.9 mm. The pathological relevance of these small diameters is apparent if we consider that an embolus of 1 mm is sufficient to occlude a major cortical arterial branch, and that an embolus of 3 mm occludes the trunk of the middle cerebral artery causing massive hemispherical infarction. But PFO as a potential cause of stroke is still controversial, as Dr. Mesa et al emphasized in their work published in this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA.[11] Points of contention include the physiopathological mechanism implicated, the factors that determine a greater risk of stroke and the diagnostic test of choice.

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The presence of a RLS is, in itself, not an appropriate factor for predicting the risk of stroke because up to 30% of the healthy population has RLS. Different studies have analyzed the characteristics associated with a greater risk of ischemic stroke finding that the larger diameter of the PFO, and particularly, the more pronounced the shunt, the greater the risk. A mean of 13.9 microbubbles are detected in the left atrium in patients with cryptogenic stroke compared to 1.6 microbubbles in patients stroke of unknown cause. But patent foramen ovale is often detected in patients with an established cause of stroke (atrial fibrillation, carotid stenosis) and factors traditionally associated with paradoxical embolism in patients with PFO and stroke (such as a previous history of thrombophlebitis, clinical criteria, ECG or echocardiographs showing pulmonary hypertension and, particularly, the onset of stroke symptoms associated with maneuvers that increase the pressure in right heart cavities, such as coughing or Valsalva maneuver) are often absent. Thus, the etiopathogenic role of PFO in stroke has been questioned, particularly in older patients, who constitute the largest group at risk of stroke and also the group associated with the most number of other vascular risk factors. Surprisingly, the importance of the diameter of the PFO and, particularly, the size of the RLS have received little attention in the literature despite being factors often proposed as determining the pathogenic potential of the PFO. De Castro suggested the importance of the size of the RLS in PFO because patients with PFO and cryptogenic stroke with ischemic lesions in the c-TCD had more microbubbles in the left atrium than patients with no lesions in the c-TCD.[4] Our group has conducted an extensive prospective study

which included more than 200 consecutive patients with acute phase stroke and a group of 100 healthy volunteer controls. We demonstrated that the increase in risk of stroke is due to a massive shunt in patients with cryptogenic stroke, while there was no increase in risk in those with a lesser shunt (<25 signals in c-TCD). A massive shunt increased the risk of ischemic stroke 3.5 fold and the risk of cryptogenic stroke 12 fold (95% CI, 3.2-34.5).[5] Dr. Mesa et al complemented these results by showing greater mobility of the septum at the location of the fossa ovalis and extensive passage of contrast as markers of risk of stroke.[11]

But what is notable in these studies, and for the question of cryptogenic stroke and PFO in general, is the enormous variability in the techniques used. In view of these results, the importance of the size of the shunt seems obvious. The absence of specific and validated risk factors demands some effort to standardize the technique, whether c-TEE or c-TCD. Patterns or markers of risk could then be identified and reproduced by different work groups, thus allowing multicenter studies to be conducted analyzing the risk of recurrence. Such studies will definitively determine whether a more or less aggressive therapy is appropriate in the patient who has suffered cryptogenic stroke.

An international consensus has recently been reached to provide the necessary standardization using c-TCD as the technique of choice.[6] The methodology is evaluated paying particular attention to the use of the Valsalva maneuver and the contrasts used for the detection of RLS. Mesa et al[11] use the femoral route for administration of ultrasonographic contrast, which increases the sensitivity of c-TEE in particular because the inferior vena cava drains alongside the PFO. The technique is not very practical though, and maybe too invasive for routine evaluation of RLS through the PFO in day-to-day clinical practice. The use of an antecubital vein is standardized and can determine the presence and size of a right-to-left shunt.[5,6] The standardization of the method must also consider the echo contrast used. The most assessable, safe and easy to use in daily clinical practice is saline contrast. This is easily prepared and used, and has the advantage of being a standardized technique both in its preparation and the evaluation of RLS.[5,6] Use of commercial contrasts does not provide any particular advantages and, in any case, we should give priority to contrasts that do not cross the pulmonary bed (Echovist®) and those that help indicate the presence of PFO or intra- or extracardiac RLS.

The aim of having an appropriate standardized technique available is to provide correct therapeutic guidance. The therapy used will ultimately depend on two variables: the risk associated with therapeutic intervention and the risk of recurrence of stroke in patients with RLS/PFO. The few studies that have analyzed this risk were generally retrospective, did not include a control group with no RLS/PFO or enrolled few patients. A French group, led by Mas, have recently presented the results of the only prospective study of recurrence of stroke published until present which, using a similar methodology to that of the PICSS study, shows an increase in risk only in patients with PFO in association atrial septal aneurysm (ASA) compared to those free of these anomalies (15.2% vs 4.2%).[7] These results are similar to those obtained in our group in the follow-up of 143 patients for a mean of 600 days, comparing the risk of recurrence in patients with massive RLS («shower» and «curtain» patterns) with patients with small-moderate or no RLS (16.7% vs 4.2%).[8] These two studies, supported by evidence from the retrospective studies mentioned earlier, emphasize the need to implement more effective therapeutic measures in high risk patients, that is, those with a massive shunt, especially when associated with an ASA.

Our knowledge of risk groups is increasing, but the ideal treatment for a patient who has suffered cryptogenic stroke with PFO as a potential cause remains undefined. Options include established antiplatelet treatment, surgery and anticoagulant treatment. Intravascular closure of PFO through placement of an umbrella device has been proposed recently, but the technique is not without risk, and there are currently no materials available that do not deteriorate and lose their effectiveness over time. An interesting meta-analysis synthesized the results from 5 retrospective secondary prevention studies that used at least 2 therapeutic options (antiplatelet treatment, warfarin or surgery). A pooled data analysis of these studies was performed. Anticoagulant treatment was concluded to be better than antiplatelet treatment (OR=0.37; 95% CI, 0.23-0.60) and comparable to PFO occlusion (OR=1.19; 95% CI, 0.62-2.27) in the prevention of recurrences of ischemic stroke.[9] These results do not agree with the only prospectively performed clinical trial, the PICSS study (Patent Foramen Ovale in Cryptogenic Stroke),[10] a branch of the WARSS trial that analyzed the efficacy of antiplatelet treatment versus anticoagulant treatment (warfarin) in the prevention of recurrences in patients who suffered cryptogenic stroke. This study found no differences in efficacy between the two treatments whether assessed globally or stratified by the size of the PFO or the presence or absence of ASA.

Despite the results from the PICSS study, the therapeutic approach proposed by our group consists of providing conservative treatment for patients with cryptogenic stroke: antiplatelet treatment if a RLS/PFO of any size is detected and anticoagulant treatment (international normalized ratio=1.5-2.5) if a massive RLS («shower» and «curtain» patterns) is detected associated with ASA. The indication of endovascular treatment should be reserved for young patients with secondary prevention failure after anticoagulant treatment or in those who might benefit but in whom

such treatment is contraindicated. However, prospectively designed studies are needed to support these recommendations.

Not only have the treatment and risk associated with a PFO/RLS to be established but also the cause of the stroke. RLS/PFO is present from birth so why doesn't cerebral infarction happen earlier? Why are recurrences not more common? Suggestions have included states of hypercoagulability that may be transitory at times, venous insufficiency that increases with age, the coexistence of other cardiac factors that cause stroke such as ASA or atheromatosis of the aortic arc, increase in the size of RLS/PFO with age and predisposition to cardiac arrhythmias in patients in whom PFO/ASA are a marker for such a predisposition. However, none of these suggestions have been proven, probably because a large study population would be needed with multicenter studies and a standardized methodology. A multicenter study is currently in progress in Spain with the use of c-TCD and C-TEE (CODICIA study). The study has enrolled 300 patients and is currently in follow-up phase (http://rt00242i. eresmas.net/index.htm).

Until results from this study are available, both c-TEE and c-TCD should be used together if we wish to adequately assess the clinical relevance of a RLS through the PFO or any other intra- or extracardiac right-left communication. C-TCD is more sensitive for detection of a right-to-left shunt than c-TEE, particularly for extracardiac shunts, whereas c-TEE is more specific, detecting ASA associated with PFO or other heart conditions that may cause stroke. We cannot emphasize enough that the finding of PFO may just be that, a finding. We should therefore complete the etiological study of cryptogenic stroke, particularly in a young patient. The near future will probably show us which path to take at the crossroads, indicating the risk markers and the most suitable therapeutic option for cryptogenic stroke, and the condition will become less cryptogenic.

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