
Editorial comment

How cryptic is a cryptogenic stroke?

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A most dramatic event in a patient life is the occurrence of stroke, which, when cryptogenic, turns out to be a disturbing event for the physician as well. The word cryptogenic comes from the ancient Greek and means “of unknown origin”.

In this issue of the Journal Butera et al.¹ report their experience in transcatheter closure of patent foramen ovale (PFO) after a cryptogenic stroke. In this study, carried out by expert operators, neither complications nor recurrence of events occurred during follow-up. Although this study is a welcome piece of information, is the evidence strong enough to suggest a generalized treatment by transcatheter closure of the PFO in all patients with cryptogenic stroke? In other words is stroke clearly related to the presence of PFO? This study is not randomized, thus we cannot know what could have been the fate of the same patients if treated in a more conservative way. The authors do not report the therapy taken by these patients, if they were treated by oral anticoagulants, this might explain the absence of recurrence of stroke. Furthermore the follow-up of the study was 1 year, but patients with recurrence of events prior to PFO closure had had recurrence of the ischemic events at least 24 months after the first stroke¹, suggesting that the follow-up was probably too short. More importantly no attempt was made to screen these patients for the presence of thrombophilic disease and the authors only report a generic absence of thromboembolic source. The cause of a stroke may be multiple, from local, intracranial, thrombus formation or spasm, distal embolization from aortic atheromatous plaques or debris, which can be very difficult to diagnose if not carefully searched for by transesophageal echo-

cardiography, carotid plaques or cardiac sources, the latter easier to diagnose by ultrasounds. Inherited or acquired thrombophilic disease, including antiphospholipid syndrome, activated protein C and protein S resistance, and hyperhomocysteinemia may also be involved. Other causes may be paroxysmal atrial fibrillation (which is more common in patients with PFO²) and atrial septal aneurysm which was found by Agmon et al.³ to be associated with PFO in 56% of cases. Hypertension and even migraine have been found to be significantly associated with a cryptogenic stroke⁴, and if the association with hypertension seems reasonable, the association with migraine might suggest a role for spasm.

The finding of a PFO, which is so common in the normal population to reach an incidence of about 30%⁵, has been considered for a long time an innocent, trivial, remnant of our fetal life. The possibility of making a diagnosis *in vivo* noninvasively by means of transesophageal echocardiography has shown that a cryptogenic stroke is more frequent in the presence of a PFO. The PFO theory is founded on this association, and not on a cause-effect relationship. Of note, PFO is not enough to cause a stroke. One should also assume the simultaneous presence of a venous thromboembolism (not demonstrated in this study, as well as in many other studies on cryptogenic stroke), and of a right-to-left shunt (which is not physiological, it may occur during Valsalva maneuver or other rare conditions raising the right atrial pressure over the left atrial one). This remarkable coincidence of events is very rare. Only few studies⁶ have carefully studied the presence of coagulation abnormalities, which have been found in up to 31% of patients

with cryptogenic stroke. Yet physicians are more impressed by images, like a hole in the septum, than by elusive biochemical or biomolecular defects.

Thus a cryptogenic stroke is probably more cryptogenic than currently accepted. PFO may represent the embolic source in some of the patients with cryptogenic stroke, but certainly the search for the cryptic causes should be more accurate than usually performed in the presence of a PFO. For these reasons, studies like that of Butera et al. in this issue of the Journal are welcome and important clinical and technical advancement. However the transcatheter closure of PFO should be considered in the wide scenario of the unknown causes of stroke, and should be utilized by expert operators only in well selected cases. Randomized studies with long follow-up will, hopefully, provide more objective information on the optimal management of patients with PFO and cryptogenic stroke.

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