



## EDITORIAL COMMENT

# Patent foramen ovale: Seeing through the mist<sup>☆</sup>

## Foramen ovale patente: uma visão através da neblina



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In 1877 Connheim was the first to describe paradoxical embolism through a patent foramen ovale (PFO), a phenomenon that has since been documented in numerous autopsy and echocardiographic studies. Besides migration of thrombi through the septal defect, other mechanisms have been proposed that implicate PFO in cardioembolic phenomena, including increased vulnerability to atrial arrhythmias and local thrombus formation.<sup>1</sup>

Various studies have demonstrated an association between PFO and cryptogenic stroke, but others have questioned the causal nature of this relationship.<sup>2–4</sup> The figures show the importance of this link: around 25% of the general population have PFO, and around 40% of ischemic strokes are cryptogenic (of undetermined cause); PFO is a plausible mechanism that might explain many of them.

But with such a common finding as PFO, how can its guilt or innocence be established, particularly regarding ischemic stroke? Distinguishing association from causality is always a challenge, but in this context is crucial.

The three randomized trials comparing percutaneous PFO closure with medical treatment<sup>5–7</sup> showed no benefit for either strategy, but they have significant limitations. The most important are low statistical power due to the small number of patients and events, crossover between study arms, variability in inclusion criteria, medical therapies and types of closure device, and the criteria used to define and assess events. It is striking that in two of these studies it took more than ten years to randomize even these small numbers of patients.

However, subsequent analyses of these trials have helped to clarify certain points, such as the existence of alternative explanations for recurrent stroke in CLOSURE I<sup>8</sup> and evidence of long-term benefit in the closure arm of the RESPECT trial.

Meta-analyses have also shown contradictory results, although they generally favor percutaneous closure.<sup>9,10</sup>

The lack of solid evidence means that international medical societies do not recommend percutaneous PFO closure, although guidelines from national societies in some countries give indications for its use. In the American Heart Association/American Stroke Association guidelines for stroke prevention,<sup>11</sup> percutaneous closure may be considered in patients with PFO and deep vein thrombosis.

The article by Paiva et al.<sup>12</sup> in this issue of the *Journal* describes the first prospective observational study in Portugal of patients undergoing percutaneous PFO closure following stroke. Some of the results merit particular

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attention. The population consisted of relatively young adults with few comorbidities, indicating that their referral for the technique was appropriate. The rate of serious device- or intervention-related complications was low, and the follow-up was long, which is essential to assess adverse effects in a condition like PFO. Some of the study limitations are pointed out by the authors, but there are other important points: it is difficult to estimate relative risk reductions in a study group by using historical data from a meta-analysis as a control; transesophageal echocardiography was not used for analysis of events in the study population, but transthoracic echocardiography has known limitations in assessing residual shunt and the presence of intracavitary or device-related thrombi; and concomitant medical therapy may have had a significant impact on the results. The authors of observational studies must always seek alternative explanations for their findings, which in the present case was particularly difficult.

Three randomized trials are currently under way in this area: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE), Device Closure versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale (DEFENSE-PFO), and GORE® HELEX® Septal Occluder/GORE® Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients – The Gore REDUCE Clinical Study. However, the relatively small number of patients being randomized and the low rate of predicted events in this population mean that these trials are unlikely to resolve the question of the value of percutaneous PFO closure for secondary prevention of ischemic cerebrovascular events.

While we await for further evidence to guide us, there are certain points to bear in mind when deciding on the appropriate therapeutic option.

Firstly, it is important to remember that a diagnosis of cryptogenic stroke should only be made after a thorough and extensive diagnostic workup to identify the cause, involving a multidisciplinary team in which specialists in neurology, internal medicine and imaging play central roles. Neuroradiological imaging is essential to identify patterns suggestive of a cardioembolic source, which cardiologists are not trained to assess.<sup>13</sup> The anatomical characteristics of the PFO are another potential aid to decision-making; some studies have identified markers of increased risk, including the size of the PFO and of the shunt, spontaneous shunt at rest (without Valsalva maneuver), and the presence of atrial septal aneurysm.<sup>14</sup> Finally, the RoPE study investigators<sup>15</sup> developed a 10-point index to identify patients most likely to benefit from percutaneous closure, assigning 1 point for each of the following: absence of four clinical variables (diabetes, hypertension, smoking, and prior stroke or transient ischemic attack); imaging evidence of the presence of cortical stroke; and age, with 1 point assigned for each decade under 70 years (5 points for those aged <30 years). The higher the score, the greater the likelihood of an ischemic event being related to the PFO. It is important to validate this index in further studies and analyses.

To summarize, the selection of patients likely to benefit from percutaneous PFO closure for secondary prevention should be on an individual basis, following an extensive

multidisciplinary diagnostic workup. Only in this way is it possible to ensure consistency in treatment, safety in outcomes and optimization of resources.

## Conflicts of interest

The author has no conflicts of interest to declare.

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