PFO and the Heart
More Than Meets the Eye*

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Knowledge and timber shouldn’t be much used till they are seasoned.

—Oliver Wendell Holmes (1)

As with many things in evolution, some structure or physiology that is beneficial during development can be detrimental at a later period. Thus, a patent foramen ovale (PFO), a cornerstone of embryonic circulation, can have undesirable consequences if it continues to be patent, as is the case in up to 25% of normal adults. A large body of circumstantial evidence including epidemiologic association, case-control series, and rare reports that have shown an actual embolus traversing the PFO links PFO to cryptogenic strokes (2). Much of this evidence, however, is only of the suggestive variety. Given the difficulty in generating clearly definitive data, a lot of the addition to the literature has been just more data of the same kind. The article by Wöhrle et al. (3) in this issue of JACC, although in the same vein, takes a novel detour and adds important information.

They studied left ventricular late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) in 74 patients with a cryptogenic stroke, a PFO, and no history of coronary artery disease (CAD). Of these patients, 10% had LGE, involving a small amount of myocardium (7%), and the presence of LGE did not affect left ventricular size or function. Occlusive CAD was excluded in 7 of 8 patients with LGE. Coronary microembolization often results in small foci of focal mid-myocardial LGE (4), depending on particle size. LGE, in this study, resembled the more common CAD pattern and indicated possibly a single event with a larger embolus than seen after coronary interventions. It was not clear whether the patients were enrolled consecutively or chosen selectively from their entire cohort; and thus, the likely size of the problem among all patients with PFO and cryptogenic strokes, remains unclear. Bubble shunts were severe (in >80% of patients) and atrial septal aneurysm was present in 64% of the subjects.

Even with the caveats mentioned, this article is an important contribution to the PFO literature. It adds to the growing body of evidence that a PFO has multiple, potentially adverse, consequences that are often not noticed. Although a plethora of literature addresses stroke in patients with a PFO, no systematic study has evaluated embolism in other organ systems. Although occasional reports of systemic embolism do exist, they are not very common. Emboli often tend to be small, and in many instances may be clinically silent, and only detected (5) at pathology. Our failure to detect these, in say the kidney or the heart, might be a limitation of our methods, particularly in asymptomatic subjects and may require wider use of sophisticated imaging methods. Recent data suggest that diffusion-weighted CMR can reveal many silent central nervous system emboli in patients with a PFO and a pulmonary embolism (6). Thus, cardiac damage, presumably from paradoxical emboli in the current study, is more confirmatory data that a PFO may allow multi-organ embolization. Unfortunately, this investigation did not provide longer term follow-up data and it would be very interesting to study the significance of these small foci of LGE. Minor cardiac injury, evidenced by troponin leaks and often regarded as unimportant in the past, has significant influence on long-term morbidity and mortality (e.g., after
coronary intervention and in chronic heart failure). The potential threat of a PFO would be much greater if there was a longer term downside to foci of minor LGE. Lack of a control group in this study makes it even harder to gauge the importance of LGE. One would expect a very low prevalence of LGE in this age group with no cardiac history. However non-CAD–related factors, such as vigorous exercise, influence LGE. One study (7) found up to a 4% prevalence of LGE in presumably healthy controls (57 ± 6 years) presenting for screening. The timing of the LGE study is important. Device clots and nearly a 9% rate of subclinical central nervous system emboli (8) were described in the periprocedural period, and these too could have influenced cardiac LGE if both closure and CMR were done in close temporal proximity. Finally, the group as a whole was at higher risk of embolization with severe shunting and high prevalence of atrial septal aneurysm (9,10). We should, therefore, be careful about generalizing these findings to the garden variety PFO population.

Second, given the additional reason to consider PFOs to be dangerous, the authors hint that cardiac LGE may be another reason to close a PFO in patients with cryptogenic stroke. This contention, although logical, is not supported by this study, and expanding indications for closure based on these types of studies is premature. The PFO literature has been full of controversy (11,12), circumstantial evidence, and interventional recommendations, based solely on expert opinion. Physician unease and patient emotion about strokes (13) is often used to justify aggressive interventional therapy. Who should be treated and how, are not based on strong, high-quality data and remain a matter of intense debate and opinion. Some studies question the association between PFO and strokes (14,15). Moreover cryptogenic stroke patients receiving medical treatment have similar rates of recurrent events, whether they have a PFO or not (16) and a recent meta-analysis confirms this (17). Finally, a third of the PFOs may be an innocent bystander in patients with cryptogenic stroke (18). Thus, although the risk of a PFO remains uncertain, there is a small but finite risk to closures, even in experienced hands (19); some adverse events such as an increased incidence of atrial fibrillation (20) might even make the embolic risk a bit higher. The exact risk-benefit ratio of closing a PFO will not be evident until we complete good-quality randomized clinical trials but our track record in doing this is not very encouraging (21); many physicians seem to have made up their minds about the right course of action and find it easier to just perform “off-label” PFO closure. It is, therefore, clearly not prudent to use “2-territory embolization,” detectable only with high-quality imaging, as an indication to intervene in patients with PFOs at this time. Nearly 40% of ischemic strokes in younger patients have no identifiable cause (22) and nearly half of these patients have an associated PFO (23). More sophisticated imaging (24,25) will identify even more patients who might be offered closure under this new paradigm. Clearly, we have not reached that level of evidence even in PFO and cryptogenic stroke, let alone in anything even more expansive. We need to wait for high-quality data before recommending this option.

This neat study, with intriguing evidence of paradoxical embolism into the heart, adds to the fascinating story of PFOs and their adverse impact. It also encourages the introduction of better imaging to detect currently unidentified pathology. Any deeper conclusion, especially regarding therapy, must await more data. A similar study with appropriate controls and longer term outcome data for any marker of subclinical embolization might be a good start. Whether we ever use such a paradigm for introducing interventional therapy should depend on a much higher level of proof.

Addendum
Since this paper was submitted, the Closure I trial, a randomized study comparing PFO closure with STARFlex versus current medical therapy, failed to show any significant benefit for PFO closure on preventing recurrent TIA or strokes (NMT Medical Press Release: Preliminary results of CLOSURE I PFO/stroke trial; Business Wire: June 17, 2010). More complete trial data were unavailable at this time and are expected to be released later this year. A number of other trials, however, are continuing and will provide a clearer picture down the road.
Editorial Comment

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Bibliography


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