EDITORIAL COMMENT

Patent Foramen Ovale, Guilty But Only as a Gang Member and for a Lesser Crime*

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In the third century (1,2) of arguing whether a patent foramen ovale (PFO), caught repeatedly in the act of begetting paradoxical thromboembolism (PTE) (3–5), poses a significant threat, some facts seem straightforward; some do not. A PFO is required before birth. The fetal right ventricle is not capable of pumping all of the blood through the collapsed lungs. Birth changes this, as the passage through the lungs becomes mandatory and is facilitated by decreased pulmonary vascular resistance. The Eustachian valve (6)(Fig. 1) or a Chiari’s network (7)(ridge or transatrial membrane, respectively, canalizing the blood from the inferior vena cava onto the PFO) are no longer required. On the contrary, they are now counterproductive, impeding fusion of the PFO that should occur at this stage. If these anatomical structures persist and remain directed onto a PFO, they constitute significant risk factors. The same holds true for an atrial septal aneurysm (ASA). This misnomer is used to describe a thin-walled, flaccid, and undulating portion of the septum primum in the region in which it is overlaying the septum secundum on the left side, the site that is supposed to fuse after birth (Fig. 2). Individuals with an ASA have a higher prevalence of a PFO, proved again by Meissner et al. (8) in this issue of the Journal and trivial to every handyman knowing that it is difficult to glue two structures together that are constantly moving to and from each other. The PFO with an ASA also is likely to open more often and more widely. A curtain will yield more easily to a draft than a solid door ajar.

The PFO and its accomplices have been under tightening scrutiny as a remediable cause for PTE (9–16). Initially, it was the ASA that caught the attention, when transthoracic echocardiography became capable of demonstrating it in patients with otherwise-unexplained cerebral vascular embolic accidents. Its role in PTE was confirmed in individual reports (17) as well as in meta-analyses (18). In the era before transesophageal echocardiography improved the sensitivity to document a PFO, the ASA was assumed to produce embolism even in the absence of a PFO. This misconception has since been discarded for good (17). Correspondingly, it has been shown that closure of the PFO in patients with an ASA removes the clinical relevance of the latter (19).

The importance of the isolated PFO remains controversial. In limited patient cohorts observed for only a few years, the risk of a recurrent cerebrovascular event after an index event appears not significantly increased by the presence of a PFO (17). This issue’s survey on 577 random participants (≥45 years) of the Stroke Prevention: Assessment of Risk in a Community (SPARC) study with PFO screening by a single echocardiographer duplicates this impression (8). Even when looking specifically at large-size PFOs, a significant risk for cerebrovascular events could not be detected. The number of such individuals was, however, small (n = 63). The prevalence of an ASA was 1.1% (5 of 437 subjects) in subjects without PFO and 4.3% (6 of 140 subjects) in those with PFO. The fact that an ASA increases the risk of persistence of the foramen ovale was confirmed with a significance of 0.028. Cerebrovascular events, including transient ischemic attacks (TIAs), occurred in 41 subjects (approximately 1.4 events per 100 observation years, assuming a five-year mean observation period). The cohort with a PFO were afflicted by 12 such events (1.7 per 100 observation years). Subjects without a PFO were afflicted by 29 such events (1.3 per 100 observation years). The actuarial event-free survival at five years was 91% with and 93% without a PFO (not significant). It was 81% for subjects with an ASA and 93% for those without. This nearly four-fold risk difference reached statistical significance (p = 0.048) after correction for baseline variables, albeit based on two events only. Surprisingly, these two events happened in the six patients with ASA but no PFO, projecting their risk at seven times that of the rest of the study population, whereas the risk of an ASA with a PFO was nonexistent. Small numbers must account for these findings, in stark contrast to current knowledge and logic.

The classical stroke risk factors, such as previous myocardial infarction, atrial fibrillation, and diabetes, proved their assumed doom in this survey. A previous venous thromboembolism was not identified as a risk factor, which again turns the focus away from the PFO. However, the case against the PFO is far from an acquittal. A meta-analysis had yielded an association of PFO with all strokes with an odds ratio of 3, which increased to 5 if only cryptogenic strokes were considered. The odds ratios for ASA admittedly were more drastic (16 and 24, respectively) (18). The noncorrelation with the size of the PFO in this study may be due to limited numbers or insensitive assessment methods. It contradicts previous art. Anatomic PFO size (6), amount of provoked shunting (20), and the presence of spontaneous right-to-left shunt (21) all proved to be significantly linked to cryptogenic stroke.

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Moreover, compelling echocardiographic documents of thrombi straddling the PFO (3–5) and strokes or myocardial infarctions in healthy young people with nothing but an ominously gaping PFO cannot be dispensed lightly. Admittedly, the yearly recurrence rates of a cryptogenic stroke in the presence of a PFO under medical treatment with acetylsalicylic acid or warfarin reported from 16% to 3% (12,22,23) may have been overly pessimistic considering that, typically, people age <55 years were studied. Yet, including TIAs it had been 10% with and 8%, respectively, without a PFO in a substudy of the Warfarin Aspirin Recurrence Stroke Study (WARSS) (24) with a mean age of 63 years, comparable with the 67 years in the survey by Meissner et al. (8).

The potential of a PFO to cause harm increases with age parallel to the occurrence of venous thromboembolism (25,26). Correspondingly, WARSS only showed a significant correlation between PFO and cryptogenic stroke recurrence in patients ≥65 years but not in those ages 55 to 64 years (26).

Another hard-to-overlook piece of evidence for the potential of evil of a PFO in the presence of venous thrombosis is the fact that the stroke rate in patients admitted for clinically apparent pulmonary embolism was 13% with and only 2% without a PFO (p = 0.02) with a mortality of 33% and 14%, respectively (p < 0.01) (27). Moreover, analyzing the benefit of closing the PFO percutaneously in contrast to medical treatment in a meta-analysis of nonrandomized trials, the annual rate of stroke was reduced from 3.1% to 0.4%, that of TIA from 2.6% to 1.4%, and that of either from 5.8% to 1.9% (p < 0.05 for all) (23).

Assuming the role of the prosecutor with the PFO on trial, one could cast in front of the jury the evidence of a Mayo Clinic autopsy series (28). The almost linearly decreasing prevalence of a PFO with age could indicate a selective mortality rather than a tendency for spontaneous closure of the PFO as assumed by the authors. That would call for early detection and closure of all PFOs or at least the ugly ones, before venous thrombosis kicks in during early adulthood. Cross your heart, if a simple vaccination against the PFO was available, would you not recommend it for everybody or, if it was not completely free of side effects, advocate early screening and vaccination in case of a documented PFO?

In the want of such a vaccination, general screening, at least for large PFOs associated with an ASA, appears pressing every time one is confronting a young person with irreparable damage from a stroke that has to be considered paradoxical for lack of any plausible cause short of the PFO found in the aftermath. It has to be conceded that there is more to cryptogenic systemic embolism than a PFO as such is not found in all cases. If there is no PFO or other right-to-left passage, perhaps the pulmonary venous bed
should be suspected. It constitutes one of the remaining blind spots in modern medicine. Lacking techniques to check for pulmonary venous thrombi and in light of extremely simple, safe, and reliable percutaneous, catheter-based methods to close a PFO permanently in <15 min with the awake patient being incapacitated for <2 h, we will continue to be tempted to pound on the nail with this elegant hammer. We just have to make sure that we pound on nothing but nails (e.g., PPOs that deserve this denomination), not to fall into Mark Twain’s category of men with a hammer for whom everything looks like a nail to pound upon.

Notwithstanding, the report of Meissner et al. (8) provides an important hint to the fact that ongoing randomized trials on this subject with target patient numbers of 500 to 1,500 and follow-up periods of just a couple of years may be blatantly underpowered. They risk falling short of showing that a good thing is a good thing. While waiting for their results after perhaps expanded recruitment and extended follow-up, we better keep the PFO in custody using match-controlled, nonrandomized data for justification (29,30). It is more likely than not that, in the end, the PFO will be convicted, even though only as a member of a gang (i.e., ASA, Eustachian valve, Chiari’s network, venous thrombosis, right atrial pressure overload, hypercoagulability) and for a lesser crime.

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