

An overlooked cause of cerebral ischaemic events

Ischaemic event or migraine? Think also patent foramen ovale

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Although the patent foramen ovale (PFO) has been convicted for causing stroke for the better part of 100 years [1], the medical community continues to turn a blind eye to it when finding and eliminating possible causes of stroke. Two recently published, blatant examples of this omission are the reasons for this editorial. In the first, an otherwise insightful and brilliantly described prospective, observational study examining the “one-year risk of stroke after transient ischemic attack or minor stroke”, a score was proposed to define the subsequent risk of stroke after an initial event [2]. The authors included about 4700 patients and followed them up for a median of 27 months. At 1 year, 274 events had occurred, whereof strokes accounted for the majority, followed by acute coronary syndromes (>10% of all events). One of the strongest predictors of stroke at 1 year was the finding of multiple acute cerebral infarctions on brain imaging. The presence of atrial fibrillation as a cause of stroke was reported and discussed, but the authors forgot to consider the PFO, and neither did an accompanying editorial [3].

It had been unequivocally shown that closure of the PFO with the Amplatzer technique infers benefit in patients with cerebral events [4–7]. Reduced mortality after PFO closure has even been shown in a comparative trial in which patients with or without device closure were followed up for more than 10 years. [6]. Not closing a PFO after an ischaemic event without a compelling explanation other than the documented

PFO increases the risk of a recurrent ischaemic event by about 1% per year. On the basis of the average age of such patients, this extrapolates to >30% for life.

All this has to be seen in the light of PFO closure as the simplest and safest procedure in interventional cardiology. Moreover, closing the PFO for stroke prevention confers collateral benefits such as protection against other paradoxical embolisms (myocardial infarction, visceral or systemic ischaemia) and migraine symptoms.

The link between PFO, connecting thrombosis, stroke and myocardial infarction was proved almost 20 years ago in a seminal paper [8]. It showed that the risk of dying in patients who had been admitted to hospital for deep venous thrombosis or pulmonary embolism was almost tripled by the mere presence of a PFO. The risk of simultaneously suffering a stroke was increased six-fold.

An article in the *Lancet* several years later completely ignored this link between venous thrombosis and PFO-associated events [9]. And, again, so did the accompanying editorial [10]. In this large Danish field study including 163 566 people followed up over 20 years, 25 199 patients with deep venous thrombosis and 16 925 patients with pulmonary embolism were identified. There was a startling incidence of coinciding stroke or myocardial infarction of about 3% in patients with pulmonary embolism (a clot had travelled through the right atrium) and 2% in patients with deep venous thrombosis only (fig. 1). This resulted in first-year risk hazard ratios of 2.2 (confidence interval 1.9–2.6) for stroke and 1.6 (1.4–1.9) for myocardial infarction after provoked venous thromboembolism. The respective risk hazard ratios for unprovoked venous thromboembolisms were 2.9 (2.3–3.7) and 2.6 (2.1–3.1) [9]. The PFO was not mentioned among the various, sometimes far-fetched, hypotheses on what could be a common cause of two such grave events happening in close sequence. The PFO is indeed the most likely explanation. It also explains why the hazard ratio in the patients with these combined events never completely receded to normal (fig. 1). Most of them must have a PFO, which engenders an overall increased risk of stroke and myocardial infarction. The authors' answer to our question

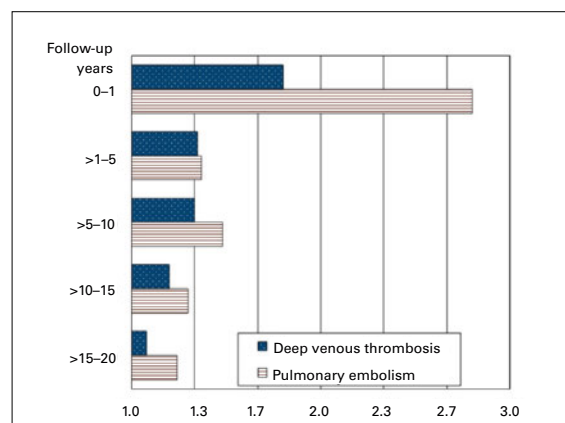


Figure 1: Relative risk for stroke or myocardial infarction in patients admitted for provoked venous thromboembolism.

Table 1: Cardiovascular risk in women with versus without migraine.

	Adjusted hazard ratio	95% confidence interval
Major cardiovascular disease	1.50	1.33–1.69
Myocardial infarction	1.39	1.18–1.64
Stroke	1.62	1.37–1.92
Angina or coronary revascularization	1.73	1.29–2.32
Cardiovascular mortality	1.37	1.02–1.83

as to why the PFO was not mentioned in the report was that a few case records had been screened for the mention of a PFO, but these spot checks had yielded nothing. Of course, a PFO will not be mentioned if it has not been looked for specifically. We suggested then that they recontacted the patients with these combined events for a transoesophageal echocardiogram (TOE), on the assumption that the majority of them would have a PFO. However, there allegedly was no money for this. We offered to help with finding a funding source only to learn that it would not be possible, anyhow, to identify and recontact these patients. This was quite surprising only a short while after their outcomes had been published in a reputable journal.

At about the same time, a report on 2040 individuals in the Framingham Offspring Study described silent cerebral infarctions documented by magnetic resonance imaging, irrespective of the gender, in about 7% of people at the age of 30–49 years, 8% at the age of 50–59 years, 10% at the age of 60–69 years and 15% at the age of 70–89 years [11]. Suspected reasons for this observation were presented. The PFO was not among them.

A paper in *Neurology* about stenoses and occlusions of brain-supplying arteries in young stroke patients examined the status of afferent vessels [12]. A long list of possible problems in these vessels was presented. However, embolic vessel occlusion due to paradoxical embolism through a PFO was not mentioned.

In an article in the *New England Journal of Medicine*, the risk for thrombotic stroke and myocardial infarction with hormonal contraception was examined in 1626158 Danish women, representing 14251063 person-years of observation [13]. They found a risk increase of up to 1.7 for stroke or myocardial infarction associated with hormonal contraception in otherwise mostly healthy women. Again, a multitude of possible explanations for this were enumerated, but a higher rate of venous thrombosis and paradoxical embolism in the presence of a PFO was scotomised.

The second recent publication prompting this editorial appeared in the *British Medical Journal*. It dwelt on migraine and the risk of cardiovascular disease in women and reported a prospective cohort study of 115541 participants the Nurses' Health Study II [14]. They

were aged 25–42 years, free of angina or cardiovascular disease, and 15% of them suffered from migraine. They were followed up from 1989 to 2011. Their adjusted cardiovascular hazard ratio compared with the control background without migraine is listed in table 1. Endothelial dysfunction or abnormal vascular reactivity were indicated in an accompanying editorial and the possibility was raised that these women might benefit from preventive therapy with a statin and acetylsalicylic acid, although the latter had proved to increase the overall risk for myocardial infarction in women [15]. The PFO was again left oblivion. It provides a likely explanation for the issue at stake and can be remedied easily, obviating the need for long-term preventive drugs. PFO closure can also improve symptoms, particularly regarding migraine with aura [16].

It has to be kept in mind that a PFO can be sought quite easily with transthoracic echocardiography. TOE has a higher yield, but the small PFOs seen only with TOE may be negligible. A PFO can also be easily closed at the cost of a few 1000 Swiss francs and the procedure is virtually devoid of complications or follow-up problems. This warrants searching for a PFO as an integral part of any work-up after stroke or transient ischaemic attack, myocardial infarction with an aspect of embolic coronary occlusion, embolic visceral or peripheral artery occlusion, and severe migraine, in particular migraine with aura. At worst, preventive PFO closure (also referred to as mechanical vaccination [17]) provides no protection in cases where no events would have happened. At best, it saves the patient's life or prevents one or several important events during the remainder of the patient's life, and thereby possible dire sequelae known to many stroke patients. Twenty-seven PFOs needed to be closed to prevent one stroke within 5 years in a randomised trial [5]. With a conservative assumption of a risk reduction with increasing age because of the increasing pressure in the left atrium reducing right to left shunts through a PFO, that would lead to a number needed to treat of five PFO closures in 65-year-old patients, with two PFOs needing to be closed to prevent one stroke in 20-year-old patients. And this does not consider factors aggravating the risk of paradoxical embolism with age, such as the ever increasing risk of venous thrombosis [18] and the enhanced and prolonged Valsalva manoeuvres during defecation and micturition.

Disclosure statement

BM: Consultant and speaker fees from St. Jude Medical. FN: Research grants to the institution and consultant and speaker fees from St. Jude Medical.

References

The full list of references is included in the online version of the article at www.cardiovascmed.ch

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