Percutaneous closure of patent foramen ovale

The association of patent foramen ovale (PFO) with morbidity in adulthood, especially cryptogenic stroke in young patients (who present a three- to fourfold prevalence of PFO) has now been known for twenty years [1, 2]. Since then various special anatomical features have been described which predispose to morbidity in patients with patent foramen ovale, including atrial septal aneurysm [3], large PFO size [4], prominent eustachian valve [5] and thrombogenic state [6, 7].

In the last 20 years of active search for PFO-associated diseases a number of morbidities have been more or less conclusively shown to be associated with PFO:

- cryptogenic stroke and transitory ischaemic attacks (TIAs)
- transitory global amnesia
- peripheral arterial embolism
- myocardial infarction with normal coronary arteries
- decompression illness in divers and pilots
- migraine with aura
- platypnoea-orthodeoxia syndrome
- stroke/TIA associated with pulmonary embolism and/or prothrombotic states
- hypoxia in sleep apnoea, COPD and bronchial asthma or after LVAD implantation
- ischaemic colitis
- recurrent brain abscess
- left heart valvular disease in carcinoid syndrome

While in the early days interventional closure systems were used that were not specifically designed, developed or adapted for PFO closure, a growing number of more specific PFO closure systems using very different technologies and implantation techniques have been developed and evaluated within the last ten years. The spectrum covers umbrella devices, radiofrequency application and suture techniques, and ranges from systems with relatively large amounts of bulky foreign material to minimised, very soft and thin systems and even biodegradable devices.

For most associated morbidities it is not yet definitely known what the statistical benefit of PFO closure in a valid cohort of patients might be. Still, outcomes in individual cases are very intriguing and highly suggestive of major benefit from PFO closure in various pathologies, prompting patients and their physicians to refuse randomisation into clinical trials and thus rendering the results of these trials less accurate, whatever the final result may be.

However, the answer to the question whether the intervention favourably influences the natural course of PFO-associated disease mainly depends on two factors: the likelihood that the association is a causal relationship; and the probability that the intervention involves a considerably lower short and long term complication rate as compared to the natural disease course.

The list of potential complications is long and some of them are fairly disquieting:

- device embolisation (0.5–1.0%)
- thrombotic material on device (0.4–0.6%)
- thromboembolism and recurrences (0–4.9%)
- atrial fibrillation (2–4% in the first few weeks; may be unrelated to closure)
- perforation/arrosion (0–0.5%)
- pulmonary embolism (more probable in thrombophilia)
- air embolism
- atrioventricular block
- residual shunts (0–35%)
- retroperitoneal bleeding
- sudden death
- retropharyngeal haematoma (intubation trauma)
- compromise of AV valves
- partial obstruction of superior vena cava
- haemolysis
- silent cerebral microemboli [8]

To date not one randomised trial has furnished proof of the benefit of PFO closure.

The best database exists for PFO and cryptogenic stroke. The vast majority of clinically indicated PFO closures were performed for presumed paradoxical brain embolism as the only or the most likely pathophysiology causing TIA or stroke in the patient's individual history. The recurrence rate of stroke or TIA in patients with PFO and atrial septal aneurysm (ASA) was 4.4 events per year in the initial study by Mas [9] or 4.8% in the Lausanne study [10], while the recurrence rate in PFO without ASA is reported to be in the range of 1–1.5% per year. While acknowledging that up to 25% of cryptogenic strokes recur within 4 years, the 2007 Food and Drug Administration Circulatory System Devices Panel regarded the data on the association between PFO and stroke overall, as well as cryptogenic stroke, as controversial [11]. Thus PFO closure is still a matter for debate even for the leading indication, and therefore the question of safety is of key importance when discussing the rationale of PFO closure. At present the rate of serious complications is reported to lie in the range of 1.5%, limiting any major benefit within the first year in patients with simple PFO.

Long term benefits and complications beyond one year are more difficult to evaluate, and the evaluation is further complicated by the fact

that the recurrence rate after PFO closure in cryptogenic stroke is by no means 0%, while admittedly it is reduced to about half the event rate in retrospective comparative data analyses. Only one study reported a very low recurrence rate, which it explains by the consequent exclusion of patients with even mild atherosclerosis who were included in all the other series. This study, providing a carefully selected and exquisitely homogeneous patient population, was meant as a trial proofing of the concept that paradoxical emboli can be avoided by PFO closure. It reported an annual recurrence rate of only 0.16% [12, 13].

Most investigators advise two imaging techniques for safe placement of the PFO occluder, and several reports exist in which intracardiac echocardiography is preferred as the second imaging tool in addition to fluoroscopy. In this issue of the journal the authors propose dispensing with echocardiography altogether and using fluoroscopy as the only guidance for device implantation. They ensure proper implantation by applying contrast through the delivery sheath into the right atrium after implantation and before release of the device.

Simplifying surgical and interventional techniques can lead to improved standards of care, easier adjustment to measures of quality control, a focus on key issues of procedure, improvements in aspects of teaching and, last but not least, more economical use of resources. Whether or not simplification of techniques finally brings benefit or harm for the patient can best be decided in the light of the early and late results and complication rates. Also to be evaluated is whether the proposed change of technique is applicable to all types of device.

Wahl and coworkers present one of the largest monocentric series of patients who underwent PFO closure [14]. Overall they report a residual shunt rate of 12%. For the device used in the largest subgroup, comprising 83% of all patients in whom PFO closure was performed, a residual shunt rate of 10% with the AGA Medical PFO occluder is reported at a minimum of 6 months post implantation, a point of time when a definite result is usually achieved.

Residual shunt rate is one of the most important parameters for checking the effectiveness of therapy, since residual shunt is associated with an at least 3- to 4-fold increase in the recurrence rate [15–19]. Hence every effort should be undertaken to minimise residual shunts. With some new devices allowing the configuration to be adapted during implantation on the basis of anatomy (eg the Premere Device) transoesophageal echocardiography is very helpful, while in more fixed configuration devices such as the Amplatzer PFO devices this may be less important or even unimportant. The rate of residual shunts at six months reported by Wahl lies within the upper range of rates that have been reported from trials mainly using the AGA PFO occluder, and some groups have reported considerably lower residual shunt rates [13, 20].

Further, the adjunctive information from online transoesophageal echocardiography during implantation may make it possible to use the smallest device feasible, thus improving the complete closure rate (which is negatively correlated to device size even in the series by Wahl in this issue) and simultaneously reduce the long term myocardial or aortic arrosion rate.

The overall rate of major procedural complications has been reported to approximate 1.5% [21] in ten published studies, while Wahl reports 2.2%. However, his rate also included periprocedural complications without long term sequelae, which have so far been underreported by others. Thus the overall procedure itself is apparently safe even without TEE or intracardiac echocardiography.

However, for the occluders above 30 mm in diameter the procedural complication rate rose to 6.6% and the residual shunt rate to 26%, and in patients with atrial septal aneurysms the six months shunt rate rose to 17%, indicating that larger PFOs and patients with ASA may be particularly prone to procedural complications and the risk of only partially successful implantations. In these subgroups, and also with newer devices, it may be advisable to perform online transoesophageal or intracardiac echocardiography.

Nonetheless the study by Wahl et al. shows that, for simple PFO closures with the AGA medical PFO occluder, safe occlusion is possible using fluoroscopy as the only imaging tool.

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