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EDITORIAL COMMENT

Obliteration of the Left Atrial Appendage for Prevention of Thromboembolism*

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Shaped like a wizard's hat but long considered functionally insignificant, the conical, trabeculated left atrial appendage (LAA) arises from the embryonic left atrium during the third week of gestation and extends superiorly from the anterolateral surface of the left atrium (1). This accessory chamber extends over an area of 3 to 6 cm^2, is more compliant than the atrium, and is actively contractile in normal hearts—filling and emptying in response to both ventricular and atrial dynamics (2,3). Receptors in the LAA influence heart rate, and granules secrete atrial natriuretic peptide, contributing to regulation of intravascular pressure and volume in response to stretch (3–7).

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The LAA is seldom imaged clearly by precordial echocardiography, but, through transesophageal echocardiography (TEE), the LAA has been recognized as a prime nidus of thrombus formation in patients with atrial fibrillation (AF) and, indeed, the leading source of cardiogenic stroke (8–10). When fibrillating, the LAA undulates at a rate >350 cycles/min, and outflow velocity is considerably reduced. With long-standing AF, the ejection velocity from the LAA often decreases to negligible levels, and the appendage dilates at least as quickly as the rest of the atrium in patients with chronic mitral valve disease, sometimes reaching an area of 12 cm^2. Communication with the atrial cavity increases proportionally, hypothetically facilitating the first stage of embolism by allowing a thrombotic mass to cross the orifice more easily.

In a meta-analysis of 23 studies in which the LAA was examined by TEE, autopsy, or direct intra-operative inspection, intracardiac thrombus was identified in 17% of patients with non-valvular AF and in 13% of cases in which AF was associated with valvular heart disease. These thrombi were located in the LAA in 91% of the patients with non-valvular AF, compared with 57% of those with valvular disease (11). In patients with mitral stenosis, stasis is generalized in both the atrium and the LAA, while, in cases of mitral regurgitation, the LAA may be more prone to this phenomenon than the body of the left atrium (12).

In patients with AF, several risk factors that predict thromboembolism in clinical studies correlate with reduced flow velocity in the LAA, accounting in part for their links to cardiogenic embolism (13,14). There are also strong correlations between reduced LAA flow velocity, thrombus formation, hypertension, and atheromatous disease of the aorta (15,16). Hypertension may be a key factor linking vascular lesions with the pathogenesis of thrombus in the appendage, and the consistent association of hypertension with stroke in AF patients may be attributed to atrial stasis or to associated disease of the vasculature supplying the brain. This may help explain why recent trials have not found control of the dysrhythmia and maintenance of sinus rhythm more effective than rate control and anticoagulation for prevention of adverse clinical outcomes in patients with AF (17,18).

At present, protection against ischemic stroke due to cardiogenic embolism in high-risk patients involves oral anticoagulation at a dose adjusted to maintain international normalized ratio between 2 and 3. Though highly effective, warfarin use is associated with a considerable risk of bleeding, including intracranial hemorrhage, which occurs at a rate of 0.5%/year. When the risk of bleeding or other impediment to anticoagulation outweighs the risk of ischemic stroke, removing or otherwise isolating the LAA represents a theoretically attractive alternative strategy for prevention of embolic events.

The LAA is relatively easy to exclude from communication with the left atrium at the time of cardiac surgery by ligation, plication, or amputation. The procedure, first applied in the 1930s to patients with rheumatic mitral stenosis (19), is now performed routinely in many centers and recommended in practice guidelines to reduce stroke risk in patients with valvular heart disease undergoing cardiac operation (20). The appendage is also routinely isolated during the Maze operation for treatment of refractory AF (21). With any of these techniques, there is a risk of incomplete exclusion, which has been reported on early (33%) and later (40%) postoperative TEE examinations (22).

Two articles in this issue of the *Journal* address elimination of the LAA for prevention of ischemic (presumably embolic) clinical events. Garcia-Fernandez et al. (23) report the outcome of LAA obliteration in patients with prosthetic mitral valves. Although the majority of the patients in their study had a cardiac rhythm other than sinus (presumably AF or flutter in most), the intensity of anticoagulation was not described, and the performance of LAA obliteration at the time of cardiac operation was not randomized. Even though prosthetic heart valves were potential sources of embolism in all cases, the LAA isolation procedure was

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associated with a reduced rate of ischemic events. Further study will be needed to establish whether incomplete ligation (2.9% in this report) compromises this protective effect.

The feasibility of less invasive approaches to isolating or removing the LAA has raised interest in applying this strategy to selected patients with AF who do not otherwise require cardiac surgery. Techniques for thoracoscopic ligation (24) and initial experience with catheter deployment of an implantable device to seal the mouth of the LAA have been described (25,26). As testimony to the limited function of the LAA in patients with chronic AF, its thoracoscopic removal from 437 patients appeared safe and unencumbered by clinical sequelae (24). Proof that one or another of these techniques is both effective and safe would provide a valuable alternative for patients unable to sustain systemic anticoagulant therapy. No such validation, however, has been produced to date. The logistical difficulties of mounting a proper randomized trial are compounded by considerable comorbidity in the subset of patients with AF who have risk factors for thromboembolism and contraindications to long-term anticoagulation.

In another article in this issue of the *Journal,* Blackshear et al. (27) describe their experience in 15 high-risk patients with AF and compare longitudinal outcomes of LAA exclusion with those of participants in the control groups of randomized trials of antithrombotic therapy for AF to derive the first estimates of the efficacy of this strategy as an alternative to anticoagulation. The patients had AF and one or more additional risk factors for stroke; anticoagulant therapy was either contraindicated or not sufficiently effective to eradicate LA thrombus demonstrated by TEE. After obliteration of the appendage by either surgical staples or snare under general anesthesia, there was a trend suggesting reduction in thromboembolism compared with historical cohorts over a median follow-up of 42 months, but statistical power to demonstrate proof of the concept was lacking in this small number of patients.

It is important to point out that the patients to whom the appendage exclusion procedure was applied differed from those in the earlier trials, who were deemed eligible for anticoagulation. Other advances in medical treatment may have also contributed to the apparent favorable outcome. The efficacy of the technique is presumably related to the completeness and permanence of elimination of blood flow into and out of the LAA. This was demonstrated by TEE at the time of intervention, but the durability of the effect was not confirmed by subsequent examinations.

Despite these limitations, this work is important as a test of how the concept that the pathogenesis of ischemic events in patients with AF is related to embolism of thrombus from the LAA can be exploited to clinical advantage. One reason for uncertainty is that many patients with AF harbor other forms of cardiovascular pathology, including hypertension and atherosclerosis. Patients with this common cardiac rhythm disturbance come cloaked in cardiovascular comorbidity that contributes to stroke risk and responds to antithrombotic therapy. Whether mechanical measures to intercede in this presumed mechanism will prove comparably effective and safer for some patients remains to be established as a therapeutic principle. We might swipe or seal the wizard's hat, yet the rabbit could still appear.

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