Appendage Obliteration to Reduce Stroke in Cardiac Surgical Patients With Atrial Fibrillation

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Background. **Left atrial appendage obliteration was historically ineffective for the prevention of postoperative stroke in patients with rheumatic atrial fibrillation who underwent operative mitral valvotomy. It is, however, a routine part of modern "curative" operations for nonrheumatic atrial fibrillation, such as the maze and corridor procedures.**

Methods. **To assess the potential of left atrial appendage obliteration to prevent stroke in nonrheumatic atrial fibrillation patients, we reviewed previous reports that identified the etiology of atrial fibrillation and evaluated the presence and location of left atrial thrombus by transesophageal echocardiography, autopsy, or operation.**

Results. **Twenty-three separate studies were reviewed, and 446 of 3,504 (13%) rheumatic atrial fibrillation patients, and 222 of 1,288 (17%) nonrheumatic atrial fibrillation patients had a documented left atrial thrombus. Anticoagulation status was variable and not controlled for. Thrombi were localized to, or were present in the left atrial appendage and extended into the left atrial cavity in 254 of 446 (57%) of patients with rheumatic atrial fibrillation. In contrast, 201 of 222 (91%) of nonrheumatic atrial fibrillation-related left atrial thrombi were isolated to, or originated in the left atrial appendage ($p < 0.0001$).**

Conclusions. **These data suggest that left atrial appendage obliteration is a strategy of potential value for stroke prophylaxis in nonrheumatic atrial fibrillation.**

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Obliteration of the left atrial appendage was first suggested as an adjunct to mitral valvotomy in the 1930s through the 1950s. At that time it was recognized that only approximately 50% of atrial thrombi were appendiceal in location [1–3]. It was suggested as early as 1950 that only approximately a 50% reduction in stroke risk could be expected from the procedure [4]. At the same time, Belcher and Somerville [3] noted that left atrial appendage thrombus was present in 64% of patients who embolized after mitral operation versus only 16% of those who did not have a clinical embolic event. They advocated surgical obliteration of the appendage when the organ was large. This was echoed by Halseth and associates [5] in a review of mitral commissurotomy in 1980. Smith and associates [6] noted that in 13 patients with postoperative embolism after open mitral valvotomy 3 patients had had the appendage surgically obliterated. In the rheumatic heart disease population appendage obliteration has not been studied in a randomized trial.

See also pages 515 and 565.

Present-day surgeons use the technique of appendage obliteration sporadically. At the Mayo Clinic two of ten cardiac surgeons routinely obliterate the appendage during mitral valve replacement and repair. Others use it only as part of the maze procedure developed by Cox [7], in which both right and left atrial appendages are obliterated as part of the standard operation. The relative contributions of appendage obliteration and return of left atrial contraction, which is 50% below normal by velocity measurements, and the proof of reduced stroke risk from the maze procedure are as yet undefined [8, 9]. If in the future a reduced rate of stroke is documented it may be impossible to determine whether restoration of sinus rhythm or left atrial appendage obliteration was the cause of reduced stroke incidence [10]. Other than the maze and corridor procedures, there is no documentation of routine obliteration of the appendage during cardiac operations in which atrial fibrillation (AF) of the nonvalvular or nonrheumatic type is present. This issue is of potential importance given the relatively higher prevalence of appendage thrombus location in this patient group, the high prevalence of AF in the general and elderly populations, and the fact that the average age of patients undergoing cardiac operation is increasing. No complications from left atrial appendage obliteration have been reported in series of patients undergoing the maze procedure, and transient anticoagulation is used only in those with persistent AF or those with a previous or perioperative thromboembolism [11, 12].

Atrial Fibrillation and Stroke

It has been estimated that 2.2 million United States citizens have either constant or intermittent AF. Epidemiologic data suggest that the risk of stroke is increased approximately fivefold in these individuals [13]. Recent placebo-controlled trials of antithrombotic therapy have confirmed an annual stroke rate of approximately 5% per year in placebo-assigned patients [14]. Silent cerebral infarctions are often demonstrated by computed tomog-

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raphy in patients with chronic AF and therefore, the true incidence of embolic stroke and chronic AF may actually be higher [15].

Approximately 35% of patients with AF will have a stroke during their lifetime. The prevalence of AF increases with age and doubles for each decade after age 55; by the ninth decade of life AF is the most important new factor for stroke [13]. Besides aging, the stroke risk in patients with AF is also increased in the presence of cardiovascular diseases, most notably rheumatic mitral stenosis or prosthetic cardiac valves. Among patients with nonrheumatic or nonvalvular atrial fibrillation, a history of previous thromboembolism, hypertension, diabetes, and echocardiographic left ventricular dysfunction and left atrial enlargement increase the risk of stroke [14, 16, 17], whereas mitral regurgitation appears to decrease the risk [18].

Five randomized trials of warfarin versus placebo have demonstrated a reduction in stroke rate by approximately two thirds in warfarin-treated patients [14]. Mortality was reduced by approximately one third. Warfarin was associated with a rate of intracranial hemorrhage of less than 1% per year. In warfarin-treated patients, approximately 50% of the strokes occurred in individuals who had inadvertent therapeutic lapses, or required temporary or permanent cessation of therapy [14, 19], a finding that parallels the experience in patients with valvular prostheses [20, 21]. Although this underscores the efficacy of warfarin in those who can take it and remain on it, it points out that the need to temporarily stop giving warfarin in cases of minor bleeding or noncardiac surgical procedures exposes patients to a significant risk for stroke. More than 50% of the AF population is age 75 or older [19] and it has been estimated that 20% or more have a contraindication to warfarin [22]. These findings provide justification for considering left atrial appendage obliteration during cardiac operations, if evidence is available that implicates thrombus in the appendage as the principle cause of embolic events.

Left Atrial Appendage Thrombus in Atrial Fibrillation

It has long been assumed that most embolic events in patients with AF, both rheumatic and nonrheumatic, occur as a consequence of left atrial, and especially left atrial appendage thrombi with thromboembolism. Before the availability of warfarin, Viko and colleagues [23] noted a reduction in embolic events in quinidine-treated patients with mitral stenosis. In the modern era, the widespread application of transesophageal echocardiography has provided insight into the prevalence and location of intraatrial thrombi in AF patients. When compared with surgical examination of the left atrium, transesophageal echocardiography has been estimated to be 100% sensitive, 99% specific, and have a 91% positive predictive value with a negative predictive value of 100% [24]. Manning and associates [25] performed transesophageal echocardiography on 233 patients with atrial fibrillation of more than 48 hours duration who were not on chronic anticoagulation before hospitalization. Thirty-four (15%) had a left atrial thrombus detected, and all but one of these was located in the appendage. In another series [26] of 272 patients with nonrheumatic AF the prevalence of thrombus was 8% (all in the appendage), but anticoagulation status was not specified.

We combined findings from studies in the settings of operation, autopsy, or transesophageal echocardiography in an attempt to estimate the relative frequency with which thrombi are found in the appendage or body of the left atrium in patients with AF. These data are presented in Tables 1 and 2. No attempt was made to control for anticoagulation status. In this collection of previous re-

Table 1. Review of Published Reports Detailing the Frequency and Site of Thrombus Location in Patients With Nonrheumatic Atrial Fibrillation

Setting	No. of Patients	Thrombus Location: LA Appendage	Thrombus Location: LA Cavity	Reference No.
TEE[a]	317	66	1	40
TEE	233	34	1	25
Autopsy	506	35	12	39
TEE	52	2	2	28
TEE	48	12	1	41
TEE and Operation	171	8	3	24
SPAF III TEE Study	359	19	1	42
TEE	272	19	0	26
TEE	60	6	0	43
Total	1,288	201	21	

[a] 5% of this cohort had mitral stenosis or a prosthetic mitral valve.

LA = left atrium; SPAF III = Stroke Prevention in Atrial Fibrillation Trial; TEE = transesophageal echocardiography.

Table 2. Review of Published Reports Detailing the Frequency and Site of Thrombus Location in Patients With Rheumatic Atrial Fibrillation

Setting	No. of Patients	Thrombus Location: LA Appendage	Thrombus Location: LA Cavity	Reference No.
Operation	581	26	17	38
Autopsy	136	12	11	39
Operation	818	20	23	27
TEE	50	12	4	28
Operation	21	6	0	29
Operation	293	11	10	30
TEE/Operation	110	13	8	31
TEE/Operation	19	5	0	32
TEE	20	1	1	33
Operation	581	25	16	34
Autopsy	26	13	5	4
TEE	260	17	16	36
Operation	80	33	13	37
Autopsy	509	60	68	35
Total	3,504	254	192	

LA = left atrium; TEE = transesophageal echocardiography.

ports, 57% of atrial thrombi in rheumatic mitral valve disease occurred in the appendage [27–39], whereas in nonrheumatic AF 91% of left atrial thrombi were located in the atrial appendage [24–26, 28, 39–42; Halperin J, unpublished data]. In this analysis, thrombi that were present in the appendage but extended into the body of the atrium were designed as apendiceal thrombi. Localization of atrial thrombi in AF does not prove the etiology of embolic events. Nonetheless, these prevalence data and the efficacy of warfarin prophylaxis are consistent with the view that approximately 75% of embolic events in AF result from atrial thrombi, and perhaps 25% of events may be due to intrinsic carotid or cerebral vascular disease [43]. Twelve percent of elderly AF patients have cervical carotid artery stenosis [44]. If 75% to 90% of AF-associated atrial thrombi are confined to the atrial appendage, then more than 50% of thromboemboli in chronic AF occur as a consequence of left atrial appendage thrombi.

Left Atrial Appendage Thrombus in Patients in Sinus Rhythm

In the series of Manning and associates [25], abnormal left ventricular function was an independent risk factor for atrial thrombus in patients with AF.

Other data suggest that patients with significant left ventricular dysfunction may be at risk for left atrial thrombus formation while in sinus rhythm. In a series of consecutive patients with stroke, transient ischemic attack, or systemic embolization and no carotid stenosis of 50% or greater, Labovitz and associates [45] noted that 5% of patients in sinus rhythm demonstrated left atrial appendage thrombi. In 8 of 58 patients with dilated cardiomyopathy who were in sinus rhythm, an atrial thrombus was noted [46]. In a series of 70 patients with dilated cardiomyopathy reported by Siostrzonek and associates [47], 11 of 13 atrial thrombi were in the appendage, although the number of thrombi in patients with sinus rhythm was not specified. These and other data suggest that the atrial appendage may be a source of embolic material in the absence of AF [48]. If obliteration of the left atrial appendage is proved to reduce stroke in AF patients and it is free of other complications, its use may be extended.

Atrial Fibrillation and Cardiac Operation

Tables 3 and 4 list the prevalence of preoperative AF versus total numbers of operations by type of operation and by age at Mayo Clinic Rochester for two decades. Historically, AF is rare among patients undergoing bypass grafting, but its prevalence increases in the elderly population. In the large series from the Cleveland Clinic, 0.5% of patients less than 65 years of age, 1.5% of those aged 65 to 74 years, and 4.1% of those aged 75 years undergoing coronary artery bypass grafting had preoperative AF [49]. Glower and associates [50] from Duke reported that 5% of those over 80 years of age undergoing coronary bypass grafting had preoperative AF. Data from recent consecutive patient series demonstrate an even higher prevalence of AF in patients undergoing any general cardiac operation, 13% in the series of Davila-Roman and associates [51]. The Mayo experience and other data suggest that AF is common before valvular operations. Saour and associates [20] noted a prevalence of 21% of preoperative AF in consecutive young patients (approximate mean age, 25 years) undergoing valve replacement operation. In an anticoagulation study after valve replacement operation, 45% of the study population had AF [52]. Sixty-four percent of patients who underwent mitral valve replacement in the series of Jegaden and associates [21] had preoperative AF.

Table 3. Number and Percentage of Patients With Preoperative Atrial Fibrillation Undergoing Cardiac Operation at the Mayo Clinic

Cardiac Operation	No. of Patients With AF	Total Operations	Percentage
Valve and CABG	279	1,696	16.5
Valve alone	1,978	6,447	30.7
CABG	180	11,738	1.5
Total	2,437	19,881	12.3

AF = atrial fibrillation; CABG = coronary artery bypass grafting.

Data from the Coronary Artery Surgery Registry have suggested a dramatically increased mortality rate during follow-up among patients operated on with AF; however, several variables including the number of diseased coronary arteries and presence of congestive heart failure were greater in the AF group. The study did not indicate specifically whether or not stroke was the principal cause of increased mortality during follow-up [53], nor did a separate report on stroke after coronary bypass in the Coronary Artery Surgery Registry list AF as a risk factor [54].

Atrial fibrillation is extraordinarily common in the postoperative period among cardiac surgical patients. It occurs in approximately 32% coronary artery bypass grafting patients and 50% to 60% of valve operations. Stroke risk is increased from 1.4% to 3.3% by the presence of AF isolated to the postoperative period [55, 56]. The rate of atrial appendage thrombus in this setting is unknown.

Techniques of Left Atrial Appendage Obliteration

The procedure for appendage obliteration in the maze procedure is excision with suture closure [7]. Elsewhere

Table 4. Percentage of Patients at Various Ages With Preoperative Atrial Fibrillation Undergoing Cardiac Operation

Cardiac Operation	< 60 Years	61–70 Years	71–80 Years
Valve and CABG	17.1	16.7	16.8
Valve alone	18.8	30.8	27.9
CABG	0.8	2.6	4.0
Total	8.3	9.2	10.6

CABG = Coronary artery bypass grafting.

DeSesa and associates [57] have recommended external staples as being preferable, as less tissue bunching and potential nidus for thrombus formation were noted. Hellerstein and co-workers [58], in an experimental procedure, described simple cross-clamping with suture ligation and excision. No data presented suggest that complications related to the procedure have occurred in humans. Concerns include the possibility that obliteration without removal may lead to postoperative pyrexia, pericarditis, bleeding, or dehiscence. The possibility that small thrombi may form at the suture line and subsequently embolize must also be considered.

Proving the Value of Atrial Appendage Obliteration in Atrial Fibrillation

It has been estimated that 50% to 75% of patients with AF receive either aspirin or warfarin [22]. Stroke risks in individuals with AF vary between 1% and 4% per year for those receiving warfarin, to 4.5% to 7% per year for those untreated [14], to 12% per year for those with a previous stroke who cannot or will not take warfarin [14, 19, 43]. A conservative estimate is that obliteration of the left atrial appendage would further reduce the risk of stroke by 50%. If all patients undergoing cardiac operation entered a randomized trial, using stroke as a primary end point and assuming that at the end of 2 years 4% of the nonobliterated group and 1% of the obliterated group will have developed at least one stroke or systemic embolic event, using a one-sided t test with 0.90 power and a significance level of 0.05, 462 patients per group would be required to detect this difference. Obviously, the sample sizes would be significantly reduced in a subgroup of patients who could not or would not take warfarin and included patients with prosthetic valves or rheumatic disease.

Summary

When used to reduce postoperative embolism in patients with rheumatic mitral stenosis, atrial appendage obliteration was not judged to be uniformly successful [59] and its subsequent use has been sporadic and governed by intuition alone. The presence and magnitude of stroke risk associated with AF in nonanticoagulated patients has been determined to be approximately 4.5% to 12% per year in nonrheumatic and 15% per year in rheumatic AF patients. The efficacy of warfarin in preventing strokes in AF is now well established, and serious bleeding is now comparatively rare in younger patients, but a persistent problem in the one-half of the total AF population who are aged 75 years and older. The safety of warfarin may improve with the use of low (international normalized ratio, 1.4 to 2.7) therapeutic dose and the use of international normalized ratio monitoring [14, 43]. Temporary cessation of warfarin in patients who take it, and contraindications to use of warfarin result in strokes that might be prevented if prior appendage obliteration was used as an adjunct to cardiac operation and chronic anticoagulation. Nonrheumatic AF is far more common than rheumatic AF at present, and the great majority of intraatrial thrombi in nonrheumatic AF occur in the appendage. Randomization of all AF patients undergoing cardiovascular operation to left atrial appendage obliteration versus nonobliteration is a reasonable strategy to assess the risks and benefits of left atrial appendage obliteration as an adjunctive stroke prevention strategy. Because the risk of stroke in patients with AF and previous thromboembolism is 12% per year, a randomized trial of surgical appendage obliteration in those unable to take warfarin may also be justified.

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