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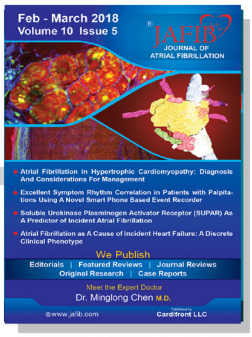

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Surgical Closure of the Left Atrial Appendage: The Past, The Present, The Future

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Abstract

Occlusion of the left atrial appendage (LAA) may protect against stroke in patients with atrial fibrillation. While percutaneous LAA closure devices have demonstrated efficacy in stroke reduction, surgical LAA occlusion has been performed with mixed results to date. Although surgical exclusion via internal sutures or noncutting stapler is ineffective due to recanalization of the LAA, surgical excision and certain exclusion devices including the AtriClip device are effective methods to achieve complete closure of the LAA. No data currently exists to support routine, prophylactic LAA closure at the time of cardiac surgery, but this practice may benefit certain patients at high risk for stroke. The currently enrolling Left Atrial Appendage Occlusion Study (LAAOS) III is the largest study to date designed to assess the efficacy of LAA occlusion for stroke prevention. The results of this trial will inform future clinical practice regarding stroke prevention with surgical LAA occlusion for patients with atrial fibrillation. Meanwhile, the ATLAS trial is investigating the efficacy of LAA occlusion in surgical patients who do not have atrial fibrillation but are at increased risk for developing it post-operatively.

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder of clinical significance[1]. AF is one of the leading etiologies of cardiogenic is chemic strokes, increasing the risk for stroke by five-fold as compared to patients without AF[2]. Over 2.5 million people in the United States are currently diagnosed with AF[3], and every hour approximately 15 of these patients will suffer from a stroke[4]. In patients with nonvalvular AF, the most common site for thrombus formation is the left atrial appendage (LAA), which accounts for >90% of detected thrombi[5],[6]. The LAA can be categorized into one of four groups based upon its anatomy on CT scan (cactus, cauliflower, chicken wing, and windsock), and cauliflower LAA has been associated with increased risk for stroke in patients with nonvalvular AF[7]. Thus, targeted interventions to occlude the LAA have been proposed in an effort to reduce the risk for stroke in patients with AF[8],[9],[10]. Our aim is to review the various methods of surgical LAA closure and their efficacy, surgical closure devices that are both currently available and under-development, and finally the evidence in support of LAA closure in a variety of patients. Although the particular morphology of the LAA may be an important consideration for placement of endo-luminal devices, it has little effect on surgical closure.

Disclosures

JJS has no potential conflicts of interest to report.

JRE reports that he is a paid consultant and a member of the speakers bureau for Atricure.

Key Words

Left Atrial Appendage Occlusion, Atrial Fibrillation, Cardiac Surgery.

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Methods of Surgical Closure and Efficacy

A variety of surgical approaches to LAA occlusion have been proposed, including suture exclusion (via endocardial or epicardial ligation), suture excision, stapler exclusion/excision with or without suture reinforcement, snares/suture loops, epicardial exclusion clips, and others still currently under development. All of these techniques have the primary goal of complete exclusion of the LAA in order to prevent thrombus formation. Nearly two decades ago, the completeness of LAA endocardial ligation was evaluated systematically for the first time with surprising results: in patients that had undergone mitral valve surgery and LAA exclusion, transesophageal echocardiography (TEE) was done for cause and identified incomplete exclusion in 36% of patients, half of whom also had spontaneous echo contrast or thrombus in the remaining LAA and 22% of whom had suffered a thromboembolic event after their initial surgery[11]. Although this may represent a select population because TEE was done for cause, these results called into question the assumption that surgical closure is routinely complete and highlighted the need for surveillance of completeness of LAA exclusion, which must be applied for all proposed techniques.

In the Left Atrial Appendage Occlusion Study (LAAOS), 77 patients undergoing coronary artery bypass grafting at increased risk for stroke were randomized to LAA occlusion via suture ligation or stapler (n=52) versus control (n=25)[12]. During this pilot study, 20% of patients randomized to LAA occlusion had appendage tears requiring intraoperative suture repair. Eight weeks postoperatively,

TEE revealed that suture exclusion had been successful in only 45% of patients, and stapler exclusion was successful in only 72% of patients. Failure was defined as residual flow into the appendage or residual "neck" greater than 1cm. Despite the limited success in achieving complete occlusion, three factors led the authors to conclude the LAA occlusion deserved further evaluation in larger studies: (1) LAA occlusion did not significantly prolong cardiopulmonary bypass time or increase postoperative complications including bleeding and AF, (2) a learning curve of 4 cases, after which success rates doubled from 43% to 87%, was identified, and (3) only 2.6% of patients experienced a periprocedural stroke and no further strokes occurred at mean 1 year follow-up.

Given the findings of the LAAOS study and others, the Cleveland Clinic retrospectively reviewed TEEs of patients with prior surgical LAA closures at their center to determine which technique was most effective in achieving complete closure[13]. Among 137 patients, only 40% of closures were deemed to be successful. However, surgical excision (73% success) significantly outperformed both suture exclusion (23%) and stapler exclusion (0%). This is because when the appendage is left intact, over time the sutures or staples closing the orifice gradually erode through the wall of the appendage allowing it to reopen. And even when surgical excision did not achieve complete exclusion, no thrombi were detected in these patients.

Additional evidence in favor of surgical excision was provided by Lee and colleagues, who demonstrated that, although the overall risk for late neurologic events in patients undergoing AF surgery was low, surgical excision was associated with a lower risk for stroke or transient ischemic attack (TIA) as compared to all other LAA occlusion techniques including suture ligation and stapler exclusion/excision (0.2% vs 1.1%; p = 0.001)[14]. Based upon these retrospective findings, the authors then designed a pilot prospective randomized controlled trial to compare 3 surgical LAA occlusion techniques in 28 patients: internal suture ligation, stapler excision, and surgical excision[15]. The overall failure rate in this trial, defined as persistent stump >1cm or persistent flow between the left atrium and LAA on TEE, was 57%, with no significant differences among the groups. Importantly, early (intraoperative) failure was noted in 32% of patients, allowing for reintervention during the index surgery. Nevertheless, the findings of this study led Gillinov to conclude in his editorial commentary that surgeons' confidence in LAA occlusion is misplaced and that device-based management of the LAA may represent a solution to the shortcomings of surgical management[16].

Surgical Closure Devices

Due to the shortcomings of traditional surgical techniques for LAA occlusion, several surgical devices have been developed. Ironically, all of these devices are designed to occlude, rather than excise, the LAA, despite the previously presented evidence in favor of excision among the traditional techniques. The effectiveness of these devices depends primarily on their ability to sustain a high occlusion pressure as compared to suture ligation and stapling. Although the Tiger Paw System (Maquet Medical Systems, Wayne, NJ) initially received FDA 510(k) clearance in 2013, the FDA issued a Class I recall of the device in 2015 after reports of LAA tears leading to adverse events and death during use of the device[17]. Other devices such as the Cardioblate Closure Device (Medtronic, Fridley, MN) and the Sierra Ligation System (Aegis Medical Innovations, Inc., Vancouver, BC)are still considered investigational[18]. The most robust clinical experience currently available involves the AtriClip device (Atricure, Dayton, OH), designed as a parallel, self-closing clamp with cloth covering that exerts uniform pressure at the base of the LAA. This device aims to achieve atrophy of the LAA due to occlusion pressure with additional proposed advantages over traditional techniques including rapid deployment, the ability for reorientation and reapplication, electrical isolation of the LAA (to potentially reduce LAA arrhythmogenicity), and minimal risk for tears, bleeding, and circumflex artery injuries[19].

In the EXCLUDE trial, 70 patients at risk for AF and stroke after cardiac surgery underwent LAA occlusion with the Atriclip device[20]. Patients were assessed with transesophageal echocardiography intraoperatively and with CT scan at 3 months. Success was defined as Occlusion with no residual neck > 1cm and no leaks or migration. Device success was achieved in >95% of cases, and no device-related adverse events or perioperative mortalities occurred. After 3 months, >98% of patients undergoing TEE or computed tomography (CT) imaging had complete LAA exclusion. The first long-term results for the AtriClip device evaluated 40 patients with AF undergoing elective cardiac surgery with planned concomitant ablation and AtriClip placement[21]. Although 10% of patients suffered early, non-device-related mortality, the remaining 36 patients were serially evaluated with computed tomography (CT) at 3, 12, 24, and 36 months. With a 3.5 year mean duration of follow-up, 100% of clips were found to be stable without any displacement, and no intracardial thrombi, LAA perfusion, nor LAA stump were detected. Most importantly, no strokes, TIAs, or other neuro events (aside from a single, unrelated TIA 2 years postoperatively in a patient with a carotid plaque) were reported. Very recently, a totally thoracoscopic approach for AtriClip placement has been reported with a 94% success rate at 3-months as evaluated by CT, proving the feasibility of performing LAA occlusion as a stand-alone procedure in select patients[22]. Further studies of AtriClip and other LAA occlusion devices are on the horizon and will certainly be informative regarding the safety and effectiveness of these devices.

When Should LAA Be Closed?

Given that the LAA serves as the primary source of thrombus in patients with AF who suffer from stroke, closure of the LAA has been proposed as a logical way to prevent adverse neurological events in certain patients. Indeed, the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial was the first to demonstrate the non-inferiority of "local" occlusion of the LAA by any device versus warfarin anticoagulation in patients with nonvalvular AF[23]. In patients with a contraindication to anticoagulation, the percutaneously placed Watchman device has been shown to reduce strokes by 77% (1.7% vs 7.3% expected byCHADS2 score)[24], and the now-discontinued percutaneous PLAATO device reduced stroke rate by 55% (3.8% vs 6.6% expected)[25].

LAA closure in patients with AF?

Both randomized controlled trials and registry data for percutaneous LAA occlusion devices are increasingly supporting a role for percutaneous LAA occlusion as an alternative to anticoagulation in

select patients[26], but these data cannot automatically be extrapolated to surgical LAA ligation. An early meta-analysis of the composite effectiveness of a variety of surgical LAA occlusion techniques concluded that there was insufficient evidence to support LAA occlusion in patients with AF undergoing cardiac surgery, primarily due to limited success rates (55-65%) and some evidence suggesting incomplete occlusion may actually increase the risk for adverse neurological events[27]. On the other hand, individual reports had provided evidence in favor of effective stroke reduction after LAA ligation, even if incomplete (6.7-fold risk reduction for incomplete ligation vs 11.9-fold risk reduction for complete ligation vs no ligation)[28]. Thus, the early experience with surgical LAA occlusion suggested that while complete LAA ligation may be beneficial, the complications associated with the procedure were not insignificant and the rate of successful closure (and therefore stroke protection) were, at best, limited.

With further investigation, however, accumulating evidence began to support the practice of surgical LAA excision or exclusion in conjunction with surgical ablation for AF for longitudinal thromboembolic morbidity prevention. This practice ultimately received a Class IIA recommendation (level of evidence C, "limited data") in the 2017 Society of Thoracic Surgeons (STS) clinical practice guidelines[29]. The primary study cited in support of this recommendation was an updated meta-analysis that demonstrated significant reductions in stroke at 30-days (0.95% vs 1.9%, p=0.005) and at latest follow-up (1.4% vs 4.1%, p=0.01) in patients with AF undergoing LAA occlusion during cardiac surgery versus those with AF not undergoing this additional procedure at the time of surgery[30]. LAA occlusion was also associated with a significant reduction in all-cause mortality (1.9% vs 5% at latest follow-up, p=0.0003) in this study.

The LAAOS II study, designed as a pilot randomized investigation into LAA occlusion in patients with AF undergoing cardiac surgery demonstrated two key findings relevant to the question of performing LAA closure in patients with preoperative AF[31]. First, among a nearly 2,000 patient cross-section of cardiac surgery candidates, >10% had preoperative AF and nearly half of these met eligibility for randomization. Second, LAA closure was demonstrated to be safe after 51 patients had been randomized to occlusion vs no occlusion, as no detectible differences in mortality or major adverse cardiovascular and cerebrovascular events among the groups at 1-year.

Due to the success of this pilot study, the LAAOS III trial has been initiated to assess the impact of LAA occlusion on the incidence of ischemic stroke or TIA detected by neuroimaging and/or systemic arterial embolism in patients with AF and CHA_2DS_2-VASc ≥2 undergoing cardiac surgery on cardiopulmonary bypass[32]. This multicenter, international trial is randomizing a target goal of 4,700 patients to LAA occlusion versus no occlusion at the time of cardiac surgery. Although amputation with double-layered linear closure of the LAA is the preferred and recommended technique for occlusion, stapler or other FDA-approved device closure of the LAA will also be permitted. Of note, purse-string closure of the LAA is not a permissible technique for patients enrolled in LAAOS III. As of the beginning of 2017, over 2,800 patients had been enrolled with an evenly-distributed case-mix of concomitant surgery (unpublished data; with permission, R. Whitlock).

LAA closure in patients without AF?

While there is evidence to support the practice of LAA occlusion in patients with AF undergoing cardiac surgery, the practice of prophylactic LAA closure in patients without AF undergoing cardiac surgery does not appear to be effective. A recent large-scale, propensity-matched analysis of prophylactic LAA closure demonstrated that this practice was actually associated with an increase in early, postoperative AF (adjusted odds ratio 3.88) and did not decrease the risk of stroke or mortality[33].

Although routine LAA ligation in all-comers is contraindicated, further study is required to determine whether prophylactic LAA closure may be efficacious in certain patient groups at high risk for developing postoperative AF. For example, both the $CHADS_2$ and the CHA_2DS_2-VASc score have been demonstrated to predict the occurrence of postoperative AF following cardiac surgery:[34] could these scores be used to assign LAA closure to select patients? The first LAAOS study, during which routine LAA closure was performed in patients at increased risk for AF ($CHADS_2$>2), served as a pilot investigation into this very question .Because successful closure was achieved in only 45% of cases, it is difficult to conclude from this data that LAA closure should be performed routinely in patients without AF, even if they may be at high risk for developing postoperative AF; however, a significant learning curve was identified, whereby surgeons achieved nearly 90% success after their first four cases.

Due to this promising signal of significantly increased efficacy of LAA closure after a brief learning curve, a large-scale randomized trial investigating prophylactic LAA closure in patients without preoperative AF at high risk for the development of postoperative AF is also currently underway. The ATLAS trial is randomizing patients without a documented history of AF but who are at high risk for the development of postoperative AF(CHA_2DS_2-VASc ≥2 and HASBLED >3) who are undergoing elective cardiac surgery to LAA exclusion with the AtriClip or no concomitant AtriClip placement. The primary objective of this study is to compare the incidence and impact of postoperative AF among the two treatment arms. Interestingly, a prespecified secondary analysis of this trial is to evaluate the healthcare resource utilization (length of stay, re-admission, and costs of care for AF) in each study group. The ATLAS study intends to enroll 2,000 patients at up to 40 sites throughout the United States.

Conclusion

The LAAOS III and ATLAS trials will be the largest trials to investigate the efficacy of LAA occlusion for stroke prevention at the time of cardiac surgery in patients with AF and without AF at the time of surgery, respectively. The results of these trials are eagerly anticipated. Previous experience suggests that traditional surgical exclusion techniques are ineffective due to recanalization of the LAA. Surgical excision is effective if a cul-de-sac is not left behind by the surgeon. The AtriClip device also appears to be an effective method for LAA occlusion. There is currently no data to support routine, prophylactic LAA closure in an all-comer cardiac surgery patient population, but, with time, select patient populations who stand to benefit from this practice may be identified.

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