# Incomplete surgical ligation of the left atrial appendage – time for a new look at an old problem

# Arash Aryana, Rohit Bhaskar

Mercy General Hospital and Dignity Health Heart and Vascular Institute, Sacramento, California, USA

*Correspondence to:* Arash Aryana, MS, MD, FACC, FHRS. Department of Cardiology and Cardiovascular Surgery, Mercy General Hospital, Dignity Health Heart and Vascular Institute, 3941 J Street, Suite #350, Sacramento, CA 95819, USA. Email: a\_aryana@outlook.com.

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# "We can't solve problems by using the same kind of thinking we used when we created them."—Albert Einstein

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting an estimated 6 million individuals in the US (1). In patients with non-valvular AF, the risk of ischemic stroke/systemic embolization is nearly 5-fold greater after adjusting for all other risk factors (1). The left atrial appendage (LAA) has been identified as a common site of thrombus formation in patients with AF (2). As such, the LAA has been targeted for surgical closure using a variety of techniques for over 6 decades, a practice that is frequently performed in conjunction with mitral valve and AF surgery (3,4). However, surgical LAA exclusion can often yield incomplete LAA closure (5,6) which may in turn be associated with increased risk of thromboembolism (7). The latest studies have suggested a possible improvement in the rate of successful LAA closure using contemporary exclusion techniques such as endoscopic stapling or external clipping (8,9). However, these investigations have been uncontrolled and non-randomized. In fact, in a recent prospective randomized controlled study of patients undergoing AF surgery with concomitant LAA closure, Lee et al. (10) discovered that incomplete surgical LAA closure continues to remain a frequent and under-recognized clinical entity irrespective of closure technique.

## LAA closure: rationale and techniques

Stroke constitutes the most common fatal and disabling neurological disease of the adult life, and it also remains the most serious complication of AF (1). It has been postulated that loss of atrial contraction in the setting of AF leads to reduced flow velocities within the LAA, thereby promoting stasis and thrombus formation inside this structure (11). Certainly, this notion is consistent with the findings from a systematic review of the literature which found that in patients with non-valvular AF, 89% of intracardiac thrombi were localized to the LAA (2). As a result, over the last few decades, a variety of surgical techniques have been implemented to eliminate the LAA (3), and more recently several percutaneous options have also been devised (12). The surgical techniques fall broadly into two categories: (I) surgical exclusion or (II) surgical excision. Within the exclusion realm, are running or mattressed sutures with or without felt pledgets placed either on the epicardial or more commonly on the endocardial surface of the LAA (3). In the excision domain, the most common techniques consist of stapled excision or removal and oversew (3). But despite long-standing clinical experience, the success of surgical LAA closure has yet to be systematically evaluated. Additionally, the criteria for complete LAA closure have not been clearly defined. In various studies, they have ranged from a "lack of an anatomical structure remaining between the mitral valve base and the left superior pulmonary vein" versus

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a "residual stump measuring <1 cm" or mere absence of "persistent flow into the LAA following surgical exclusion" as seen on transesophageal echocardiography (4,5,13). Consequently, the reported incidence of incomplete LAA closure fluctuates widely among different studies, varying anywhere from 10% to 80% (14). Nonetheless, the highest success rate appears to be most commonly achieved with surgical excision (4,13).

# "Problems are the price you pay for progress."—Wesley Branch Rickey

## Incomplete LAA closure

In a prior study, the authors evaluated the incidence of incomplete LAA closure following surgical suture ligation performed in conjunction with mitral valve or Maze surgery in a cohort of non-valvular AF patients, as well as the risk of stroke/systemic embolization in those with incomplete versus complete LAA closure (7). We found an incomplete LAA closure in 35% of the cohort which was similar to that previously reported in the literature (5,6,13). Previously, Katz and colleagues (5) also evaluated 50 patients who underwent surgical LAA ligation in association with mitral valve surgery and similarly reported evidence of incomplete LAA closure in 36% of their cohort. The incidence of incomplete LAA closure was also investigated in the Left Atrial Appendage Occlusion Study (LAAOS) (13). The authors concluded that complete LAA occlusion proved challenging and highly operator-dependent, with postoperative transesophageal echocardiography demonstrating incomplete LAA exclusion in 34% of patients subjected to either suture ligation or stapler closure. Likewise, Kanderian and colleagues (6) examined patients who underwent LAA exclusion by direct surgical excision, stapler, or suture ligation and discovered an incompletely excluded LAA in 45% of the entire cohort (27% with excision, 77% with suture and 100% with stapler closure). Several explanations have been proposed for the relatively high incidence of incomplete LAA exclusion observed following surgical suture ligation (3). First, shallow suture bites used to avoid the adjacent circumflex coronary artery may be to blame. Second, incomplete LAA closure could also result from the failure to extend the running sutures to the most distal edge of the LAA orifice. Presence of a mitral valvular annuloplasty ring or prosthesis can sometimes pose technical difficulties in this regard. Lastly, the LAA ostium itself can occasionally exhibit complicated anatomical shapes

and configurations creating further technical challenges in achieving complete LAA closure.

In the recent study of 28 patients undergoing AF surgery with concomitant LAA closure using contemporary techniques, Lee et al. (10) found evidence of "early failure" in 1 patient subjected to endocardial suture ligation (13%), 6 patients treated with stapled excision (60%) and 2 patients using surgical excision (20%). Moreover, during immediate follow-up, 4/7 patients treated with endocardial suture ligation (57%) were further discovered to have developed incomplete LAA closure, of whom 3 patients (43%) exhibited greater than mild LAA flow as assessed by transesophageal echocardiography. In contrast, no other patients treated with stapled or surgical excision exhibited incomplete LAA closure during immediate follow-up (P=0.03). On the other hand, at 3 months, one more patient treated with endocardial suture ligation (14%) was additionally found to have an LAA "stump" (defined as the presence of residual LAA measuring >1 cm in maximum length), as compared to 2/8 patients (25%) subjected to stapled closure and 3/6 patients (50%) treated with surgical excision (P=0.35). As such, the overall failure rate of LAA surgical closure was 57%, including 63% using endocardial suture ligation, 60% with stapled excision, and 50% with surgical excision (P=0.85). In this study, none of the patient had a stroke during follow-up. However, no reliable conclusions may be reached regarding the safety associated with incomplete LAA closure based on the findings of this study due to its minimal follow-up duration of only 3-6 months.

#### Stroke risk

Prior studies have suggested that presence of incomplete LAA closure may predict an increased risk of thromboembolism (6,7,14). Garcia-Fernandez and colleagues (4) evaluated 58 patients who underwent surgical LAA ligation and reported a lower incidence of embolic events at 6 years in those who underwent LAA ligation (3% vs. 17%; P=0.01). Additionally, a multivariate analysis found that absence of LAA ligation served as an independent predictor for thromboembolic events (odds ratio of 6.7). When identification of incomplete LAA closure was taken into account together with the absence of complete LAA closure, the estimated embolic risk further increased to 11.9-fold (4). A number of other studies have also reported a remarkably high embolic event rate following surgical LAA closure. For instance, in

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LAAOS (13), of the 52 patients who underwent concurrent LAA surgical exclusion and coronary artery bypass surgery at least 12% developed thromboembolic events post-LAA closure, including 12 strokes and 13 transient ischemic attacks. Although the overall incidence of incomplete LAA closure in this study was 34%, a relationship between embolic event rates and presence/absence of incomplete LAA closure was unfortunately never examined. Similarly, Bando and colleagues (15) evaluated 812 patients who underwent mitral valve surgery and surgical LAA ligation. They determined that 72 patients (9%) experienced a late stroke. Among these, 65% had received LAA ligation. But once again the incidence of incomplete LAA closure among the stroke patients was not explored. Katz and colleagues (5) discovered spontaneous echocardiographic contrast or frank thrombus within the incompletelyclosed LAAs of 9/18 (50%) patients while not receiving oral anticoagulation therapy, and reported stroke/systemic embolization in 4 of these patients (22%). Lastly, in the study by Kanderian and colleagues (7), the prevalence of thrombus identified within the incompletely-closed LAA was quite remarkable including 46% with suture and 67% with stapler closure, which accompanied a prominent, late stroke/systemic embolization rate of 15% in patients with incomplete LAA closure. But unfortunately, none of these studies included a comparator arm or an estimated hazard risk to better characterize the actual risk associated with incomplete LAA closure.

## Limitation of conventional risk stratification scores

In a prior study (7), the authors examined the incidence of stroke/systemic embolization in patients with incomplete LAA closure and we found that despite a significantly higher rate of long-term oral anticoagulation administered to those with incomplete LAA closure, there was an incidence of stroke/systemic embolization that was 8-times higher in patients with incomplete (16%) as compared to those with complete LAA (2%) closure. Furthermore, this was independent of the stroke/systemic embolization risk determined by conventional risk stratification schemes. That is, the CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc risk scores were in fact similar for those with incomplete LAA closure and associated stroke/systemic embolization (CHADS<sub>2</sub>: 2.0, CHA<sub>2</sub>DS<sub>2</sub>VASc: 4.0) versus those with complete LAA closure and without stroke/systemic embolization (CHADS<sub>2</sub>: 2.0, CHA<sub>2</sub>DS<sub>2</sub>VASc: 3.9), suggesting that conventional risk stratification schema may not offer an

adequate risk assessment in this situation. On the other hand, incomplete LAA closure itself was found to be an independent predictor of stroke/systemic embolization (odds ratio of 21.0, 95% confidence interval: 1.9-232, P=0.01) with a time-dependent hazards ratio of 8.9 (95% confidence interval: 1.0-81; P=0.05) and an annualized risk of ~12% per 100-patient-years of follow-up. The latter annualized risk was nearly 3-times higher than that predicted by conventional risk stratification schemes, and almost equivalent to a CHADS<sub>2</sub> score of 5 (actual score =2) or a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 9 (actual score =4). Given the physiologic differences between an incompletely-closed versus a non-ligated LAA, it is possible that conventional stroke risk stratification schemes do not accurately predict the patient risk in the setting of such an entity. The same is for instance also true of patients with valvular (rheumatic) AF in whom the risk of stroke is nearly 17-fold greater, and virtually independent of the CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score (2). As such, these findings support the notion that the presence of incomplete LAA closure may in fact be "worse" than no closure at all (7,13). Though at this time the reason for this is not entirely clear, it is conceivable that incomplete LAA closure could be associated with a reduced flow state and increased stasis/stagnation within the "stenotic" LAA, thereby promoting a higher thromboembolic risk.

## Other implications

Similar to the surgical experience, manifestation of incomplete LAA occlusion following various types of endocardial and epicardial percutaneous LAA closure has been well-described (16-20). As with surgical techniques, there is limited data available on the long-term prognosis of incomplete percutaneous LAA closure. Additional research and investigation in this area is clearly warranted. Furthermore, it may be plausible to ask whether in LAA closure trials a potential benefit derived from complete LAA closure could in part be offset by the presence of incomplete LAA closure. LAAOS III-a large, randomized prospective trial designed to compare the efficacy of LAA closure for stroke prevention using excision versus stapled closure, to no closure at all (21)-may ultimately address this issue. For now, the findings from the PRAGUE-12 study (22) seem to provide preliminary support in favor of complete LAA closure. This study found that the incidence of stroke among those who underwent LAA surgical excision in conjunction with AF surgery was 2.7% at 1 year, as compared to 4.3% in the control arm. Although this difference did not

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reach statistical significance, this was likely related to the study's moderately-small sample size and short-term followup. Indeed, these findings are promising and provide further justification to investigate a clearer role for complete LAA closure in reducing the risk of stroke/systemic embolization in patients with AF.

## Need for anticoagulation

In a prior study conducted by the authors (7), all cases of stroke/systemic embolization in the setting of incomplete surgical LAA closure occurred in patients not receiving oral anticoagulation suggesting that long-term anticoagulation therapy may be essential to effectively reduce the embolic risk within this patient population. This also gives credence to the idea that at least certain patients with persistently elevated embolic risk and intolerance to long-term oral anticoagulation may be considered for closure of the incompletely-excluded LAA using alternate strategies (23). Another unresolved clinical dilemma pertains to the management of patients with incomplete LAA closure who remain in sinus rhythm. Indeed, there have been sporadic reports on the occurrence of LAA thrombus even in patients who remain in sinus rhythm. In a series of consecutive patients with stroke/systemic embolization and absence of significant carotid arterial stenosis, Labovitz and colleagues (24) found that 5% of patients in sinus rhythm demonstrated LAA thrombi. Similarly, Vigna and colleagues (25) reported an atrial thrombus in 14% of patients with dilated cardiomyopathy who were in sinus rhythm. These data suggest that the LAA may perhaps even serve as a source of thromboembolism in the absence of AF. For now, in the authors' opinion, all patients with incomplete LAA closure should preferably be treated with long-term oral anticoagulation therapy regardless of presence or absence of postoperative AF.

In summary, great strides have been made in surgical LAA exclusion over the past 6 decades as a means of stroke risk reduction in patients with AF. But despite this, incomplete LAA closure remains an important clinical dilemma. Given the potential for undesirable consequences associated with this entity, the incidence of incomplete LAA closure may be considered an important quality marker in those who undergo this procedure. Nevertheless, screening for incomplete LAA closure following surgical exclusion is presently not addressed by the practice guidelines. Additionally, many insurance payers in the US do not

recognize or permit routine surveillance studies. As such, further research and investigation is clearly much needed to better address the long-term prognosis and management of patients with incomplete LAA closure.

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# Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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