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The Left Atrial Appendage (LAA): Proximity of the Circumflex Artery and Evaluation of a Novel Method of Closure

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THE LEFT ATRIAL APPENDAGE (LAA): PROXIMITY OF THE CIRCUMFLEX
ARTERY AND EVALUATION OF A NOVEL METHOD OF CLOSURE

Thesis format: Monograph

by

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Graduate Program in Clinical Anatomy

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The School of Graduate and Postdoctoral Studies
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Abstract

The left atrial appendage (LAA) is an area of interest because of its thrombogenic potential in patients with atrial fibrillation. The current standard for LAA removal is epicardial excision, which may leave residual volume thereby undermining its effectiveness. Also, LAA surgery may injure the nearby circumflex artery. This investigation aims to measure the proximity of the circumflex artery to the LAA at various points, and evaluate pericardial patch exclusion as a novel method of LAA closure in a cadaveric model. After performing both procedures in all (n=27) hearts, epicardial excision left 24% of the original volume while pericardial patch exclusion left 4%. The circumflex artery was closest to the LAA at the 4 o'clock position. These results suggest that physicians should beware of the injuring the circumflex artery at 4 o'clock and that pericardial patch exclusion may be a viable alternative for surgical LAA closure in patients with atrial fibrillation.

Keywords

Left Atrial Appendage, Left Atrial Appendage Closure, Atrial Fibrillation, Pericardial Patch Exclusion, Epicardial Excision, Circumflex Artery.

Co-Authorship Statement

This thesis was written and completed by Bayan Malakouti-Nejad under the supervision of Dr. Michael Chu and the guidance of Dr. Marjorie Johnson. Experiments were designed and carried out jointly by Dr. Michael Chu, Dr. Jorge Catrip, Dr. Jeevan Nagendran, Katie Losenno, Dr. Marjorie Johnson, Eliot Winkler and Bayan Malakouti-Nejad. Analysis and interpretation of the data was mainly carried out by Bayan Malakouti-Nejad. Any manuscripts resulting from this thesis will be co-authored.

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Table of Contents

Abstract	ii
Co-Authorship Statement.....	iii
Acknowledgments.....	iv
Table of Contents	v
List of Tables	viii
List of Figures	ix
List of Abbreviations	x
List of Appendices	xi
Chapter 1	1
1 Introduction and Literature Review	1
1.1 Introduction.....	1
1.2 The Heart	1
1.2.1 Anatomy and Function.....	1
1.2.2 The Left Atrial Appendage	3
1.2.3 Coronary Circulation	5
1.3 Atrial Fibrillation	7
1.3.1 Introduction.....	7
1.3.2 Pathogenesis.....	7
1.3.3 Treatment	8
1.3.4 Significance of the Left Atrial Appendage	9
1.4 Surgical LAA Obliteration.....	10
1.4.1 Introduction.....	10
1.4.2 Percutaneous Occlusion Devices	11
1.4.3 LAA Exclusion	13

1.4.4	LAA Excision	15
1.4.5	Circumflex Coronary Artery.....	16
1.4.6	Pericardial Patch Exclusion of the LAA.....	17
1.5	Rationale Statement	17
1.6	Objectives	19
1.7	Hypothesis.....	19
Chapter 2	20
2	Methods.....	20
2.1	Subject Data.....	20
2.2	Study Design.....	22
2.3	Measurement of the LAA	22
2.4	Measurement of the Proximity of the Circumflex Artery.....	23
2.5	Surgical Techniques.....	24
Chapter 3	26
3	Results	26
3.1	Statistical Analysis.....	26
3.2	Measurements of the LAA.....	26
3.3	Proximity of the Circumflex Artery to the Base of the LAA	28
3.4	Residual Volume Left by Epicardial Excision and by Pericardial Patch Exclusion	
	30	
Chapter 4	32
4	Discussion	32
4.1	Interpretation of Results.....	32
4.2	Clinical Implications.....	32
4.2.1	Dimensions of the LAA.....	33
4.2.2	Proximity of the Circumflex Artery.....	33

4.2.3 Surgical Closure of the LAA	35
4.3 Strengths and Limitations	39
4.4 Future Directions	40
4.5 Conclusion	41
References.....	42
Appendix A: Rights and Permissions	51
Appendix B: Statement.....	58
Curriculum Vitae	59

List of Tables

Table 2.1.1 Subject Characteristics.....	20
Table 3.2.1 Mean length (mm), width (mm) and volume (mL), SD and range in all hearts (n=27), formalin fixed (n=18) and fresh frozen (n=9).....	26
Table 3.2.2 Mean LAA orifice major axis, minor axis and circumference (mm), SD and range in all hearts (n=27), formalin fixed (n=18) and fresh frozen (n=9)	26
Table 3.3.1 Mean distance from left main or circumflex artery to base of LAA (mm), SD and range at each point around clock-face (12:00 to 6:00).....	27
Table 3.3.2 Identity of the artery closest to the base of the LAA, left main (LM) or circumflex (Cx), at each point around the clock-face (12:00 to 6:00).....	28
Table 3.4.1 Mean volume (mL) \pm SD and residual volume (%) in the LAA prior to intervention, after conventional epicardial excision (CEE) and after pericardial patch exclusion (PPE), in all hearts (n=27), fixed specimens (n=18) and fresh specimens (n=9)...	29
Table 4.2.3 Comparison of four methods of LAA closure.....	39

List of Figures

Figure 1.2.2 The left atrial appendage (LAA).....	3
Figure 1.4.2 Three percutaneous LAA occlusion devices ⁵ . A) The PLAATO device, B) The Amplatzer Cardiac Plug and C) The WATCHMAN device.....	12
Figure 1.4.3 Staple and suture exclusion of the left atrial appendage (LAA) ⁵	14
Figure 1.4.4 Epicardial excision with oversew of the left atrial appendage ⁵	15
Figure 2.3.1 A) Measurements carried out on the LAA included length, width and volume, B) and measurements carried out on the LAA orifice included major axis, minor axis and circumference.....	22
Figure 2.4.1 Endocardial and epicardial view of clock-face arrangement used to orient the LAA orifice.....	23
Figure 2.5.1 Pericardial patch exclusion of the LAA, showing the original orifice and the patch sewn in place.....	24
Figure 2.5.2 Epicardial excision of the LAA, showing the original appendage, the excised portion and the remnant sewn shut.....	24
Figure 3.3.1 Mean distance from artery to the base of LAA (mm), ± 2 SD, at each point around clock-face (12:00 to 6:00).....	27
Figure 3.3.2 Identity of the artery closest to the base of the LAA, left main (LM) or circumflex (Cx), at each point around the clock-face (12:00 to 6:00).....	28
Figure 3.4.1 Mean volume (mL) \pm SE in the LAA prior to intervention, after conventional epicardial excision (CEE) and after pericardial patch exclusion (PPE), in all hearts (n=27), fixed specimens (n=18) and fresh specimens (n=9). (*) indicates significant difference in LAA volume (p<0.05).....	30

List of Abbreviations

LAA: Left Atrial Appendage

AF: Atrial Fibrillation

AV: Atrioventricular

TEE: Transesophageal Echocardiography

ANP: Atrial Natriuretic Peptide

BNP: Brain Natriuretic Peptide

RCA: Right Coronary Artery

LCA: Left Coronary Artery

LAD: Left Anterior Descending

SA: Sinatrial

LAAOS: Left Atrial Appendage Occlusion Study

LM: Left Main

Cx: Circumflex

CEE: Conventional Epicardial Excision

PPE: Pericardial Patch Exclusion

List of Appendices

Appendix A: Rights and Permissions	51
Appendix B: Statement	55

Chapter 1

1 Introduction and Literature Review

1.1 Introduction

The left atrial appendage (LAA), also called the auricle, is a remnant of the embryological development of the heart. It is an out-pocketing of the wall of the left atrium and has an orifice through which blood can enter and exit¹. The LAA has some physiological function, but its anatomy is most problematic for patients with atrial fibrillation (AF). Patients with AF have a dramatically increased risk of stroke due to blood clots that form as a result of their abnormal and irregular heartbeat². These patients are prescribed oral anticoagulants, namely warfarin, to help reduce this risk, but many of them cannot take warfarin long term³. The majority of blood clots in patients with AF form within the LAA, due to the stagnation and pooling of blood that occurs therein, so surgical resection of the appendage is an option for stroke risk reduction⁴. Surgical closure of the LAA can be done by exclusion or by excision. Exclusion involves suturing or stapling the orifice of the LAA closed so that blood no longer enters, effectively eliminating the appendage. Excision involves cutting the appendage off and suturing the remnant shut. Excision is the option most surgeons prefer, but it is difficult to achieve complete resection of the LAA⁵. A residual LAA stump, one that blood can still enter, has been shown to be possibly even more dangerous than an intact LAA⁶. Dr. Michael W.A. Chu, a cardiac surgeon at London Health Sciences Centre (LHSC), has developed an unpublished novel technique for LAA closure called pericardial patch exclusion that involves suturing a patch of the patient's pericardium over the LAA orifice. Any surgery on the LAA, whether performed endocardially or epicardially, runs the risk of damaging the circumflex coronary artery that runs in close proximity to the base of the appendage⁷.

1.2 The Heart

1.2.1 Anatomy and Function

The heart is a muscular organ that pumps blood through the circulatory system, providing tissues with oxygen and nutrients and removing metabolic waste products⁸. It

is located in the middle mediastinum of the thorax, sitting on the central tendon of the diaphragm⁹. It is situated between the right and left lungs, posterior to the sternum and costal cartilages and anterior to the oesophagus, descending aorta and thoracic vertebrae. In normal adults, the heart is roughly the size of a fist and weighs approximately 300 grams⁹.

It is enclosed in the pericardium, a double-membrane sac that provides protection to the heart, lubricates its rotational movement, and prevents it from overfilling⁸. The outer layer is the tough fibrous pericardium, which blends with the central tendon of the diaphragm and the walls of the great vessels leaving the heart. The inner layer, the serous pericardium, is itself made up of two layers. The parietal layer lines the inside of the fibrous pericardium, and the visceral layer sits immediately on top of the heart as the epicardium. These two layers are continuous with one another at the roots of vessels entering and leaving the heart⁹. The serous pericardium secretes a small amount of pericardial fluid into the space between its two layers – the pericardial space – that acts to reduce friction as the heart moves during its normal rhythm⁸.

The heart is made of four chambers, two atria located more superiorly and two ventricles inferior to them. The atria are relatively featureless chambers, in comparison to the ventricles, which receive blood from the body and the lungs and pump it to the ventricles. Their walls are thinner and mostly smooth, but also exhibit some comb-like muscular ridges called pectinate muscles⁹. Each atrium is separated from the ventricle by atrioventricular (AV) valves. The right AV valve has three cusps, while the left AV valve – the mitral valve – has two. The ventricles are separated from the great vessels leaving the heart by semilunar valves, a pulmonary valve on the right side and an aortic valve on the left side. Relative to the atria, the ventricles have much thicker walls, the interiors of which are covered in columns of muscle called trabeculae carneae⁹. The ventricles also contain papillary muscles, which connect to chordae tendineae, thin string-like tendons that attach to the cusps of the AV valves. During contraction of the ventricles, the papillary muscles contract and pull on the chordae tendineae, keeping the AV valve shut against intraventricular pressure and preventing backflow of blood into the atria⁸.

The right atrium receives deoxygenated blood from the body via the superior and inferior vena cava and sends it to the right ventricle through the right (tricuspid) AV valve. The right ventricle pumps blood through the pulmonary semilunar valve to the pulmonary trunk, which divides into the left and right pulmonary arteries taking blood to the lungs⁸. Once the blood is oxygenated it returns to the left atrium of the heart via four pulmonary veins, two from each lung. Blood then passes through the mitral valve to the left ventricle, from which it is pumped through the aortic semilunar valve into the aorta, taking it to the rest of the body⁸.

1.2.2 The Left Atrial Appendage

The walls of both of the atria have a small out-pocketing that is the result of the embryological development of the heart. These out-pocketings are called the auricles or the atrial appendages¹. The left atrial appendage (LAA) is a long, tubular structure with an opening, called the LAA orifice, which opens into the left atrial cavity¹ (Figure 1.2.2). It is smaller than the right atrial appendage, and can have many lobes and bends¹⁰. During the embryological development of the heart, the pulmonary veins grow to form most of the wall of the left atrium and what began as the left atrial cavity forms the LAA. For this reason, the interior wall of the LAA contains an abundance of pectinate muscle, which is mostly absent from the rest of the left atrium¹.



Figure 1.2.2 The left atrial appendage (LAA).

Ernst and colleagues (1995), using resin casts of post-mortem LAAs, have noted great variability in the shape and size of the LAA, as well as its number of lobes and branches¹¹. Lacomis and colleagues (2007) used CT images to visualize the LAA and found broad variation between individuals in terms of LAA morphology, dimensions, angulation and motility¹². In live patients the LAA is typically visualized using transesophageal echocardiogram (TEE) or CT scan. However, because of the wide variation in the morphology of the LAA, especially in its number of lobes and complex branching

patterns, it is difficult to accurately image the LAA using these methods^{11,13}. A few

studies have attempted to describe the variability in LAA morphology by dividing them into categories. Di Biase and colleagues (2012) used MRI and CT imaging to describe 932 LAAs and assign them to one of four categories based on their shape: cactus, chicken wing, windsock and cauliflower¹⁴. The cactus LAA has a dominant central lobe with secondary lobes extending superiorly and inferiorly. The chicken wing LAA has an obvious bend in the middle portion and may fold back towards the heart. The windsock LAA has a single dominant lobe as its primary structure. Finally, the cauliflower LAA is relatively short with a complex internal structure¹⁴. Conversely, in the same year Shi and colleagues (2012) used angiography to image the LAA in 75 Chinese patients and divided them into eight categories, also based on their shape: tube, claw, sphere-like, tadpole, willow-leaf, sword, duckbill and irregular¹⁵. Besides the appendage itself, the LAA orifice has also been categorized based on shape. Wang and colleagues (2010) used CT to image 612 hearts and described five categories of the orifice. The majority were oval (69%), and the remainder were foot-like, triangular, water drop-like and round¹⁶. Studies like these serve to illustrate just how much one LAA differs from the next.

Despite this wide variation, there have been studies that have attempted to measure and describe the average dimensions of the left atrial appendage. In 1995, Ernst and colleagues measured casts of 220 post-mortem hearts and found the following mean LAA measurements: length of 30 mm, width of 31 mm, volume of 5.2 mL, orifice major axis of 21 mm and orifice minor axis of 15 mm¹¹. In 1996, Rubin and colleagues used TEE to evaluate the LAA in 100 patients and found a mean length of 51 mm and a mean width of 47 mm¹⁷. In 2003, Stollberger and colleagues attempted to compare TEE to post-mortem casts of the LAA in order to assess the accuracy of TEE. By TEE they found a mean length of 47.5 mm, width of 36.5 mm, orifice major axis of 23.3 mm and orifice minor axis of 16.8 mm. By cast they found a mean length of 30.8 mm, orifice major axis of 21.6 mm, orifice minor axis of 17.0 mm and volume of 7.0 mL¹³. In 2007, Lacomis and colleagues used CT imaging of 25 hearts to find a mean LAA length of 52.2 mm¹². Also in 2007, Su and colleagues made casts of 31 LAAs and found a mean length of 44.9 mm, orifice major axis of 17.4 mm and orifice minor axis of 10.9 mm⁷. Finally in 2012, after performing angiography to image the hearts of 75 patients, Shi and colleagues found a mean LAA length of 35.6 mm, LAA width of 18.5 mm and orifice major axis of

17.3 mm¹⁵. Veinot and colleagues studied 500 autopsied hearts in order to look at age related changes in the LAA. The study revealed that with age, the LAA orifice gets larger and the appendage increases in width, while its length remains relatively constant. Age and sex were the primary determinants of LAA dimensions, more so than patient height, weight and body surface area¹⁸.

While some believe that the LAA has minimal useful function¹⁹, it does play some physiological role. Tabata and colleagues (1998) have described the role of the LAA as a reservoir in the presence of pressure or volume overload, due to its increased dispensability compared to the rest of the left atrium²⁰. The LAA has also been described as an important source of atrial natriuretic peptide (ANP), which is released in response to increased blood volume and stimulates excretion of water, sodium and potassium. Bilateral atrial appendectomy in dogs has been found to eliminate the release of ANP and blunt renal excretion of sodium and water²¹. Rodeheffer and colleagues (1993) measured ANP levels in fresh tissue from human hearts and found that ANP concentration in the right and left atrial appendages was 40-fold higher than in the rest of the heart²². Cardiac surgeries that involve removal of the appendages attenuate ANP secretion post-operatively²³. In addition to ANP, the LAA is also a source of brain natriuretic polypeptide (BNP)²⁴.

1.2.3 Coronary Circulation

The heart is a muscle that requires oxygen and nutrients to function properly. Coronary circulation refers to the network of blood vessels that delivers blood to the myocardium, the muscle of the heart. Coronary arteries take oxygenated and nutrient-rich blood to the myocardium and coronary veins take deoxygenated and nutrient-poor blood away from the myocardium. These coronary vessels run just deep to the epicardium on the surface of the heart⁸.

The two main coronary arteries, right and left, originate from the very first part of the ascending aorta with their openings lying in the cusps of the aortic semilunar valves. As the heart relaxes just after the ventricles contract, blood fills the two main coronary arteries and the heart muscle is perfused⁸. The right coronary artery (RCA) originates

from the right aortic sinus and runs in the right coronary sulcus, which separates the right atrium from the right ventricle. The RCA gives off a small branch to the SA node near its origin, and later gives off a right marginal branch that runs down the right border of the heart towards the apex. It continues its course to the posterior of the heart in the coronary sulcus, and gives off another small branch to the AV node. In most hearts, the RCA terminates as the posterior interventricular artery, which runs in the posterior interventricular sulcus towards the apex of the heart⁸. The left coronary artery (LCA) originates from the left aortic sinus and emerges from behind the pulmonary trunk, running between it and the left atrial appendage, and divides into two major branches. The first branch is the anterior interventricular artery, also called the left anterior descending (LAD) artery. This artery runs towards the apex of the heart in the anterior interventricular sulcus. The second branch is the circumflex artery, which turns to the left and follows the left coronary sulcus towards the posterior of the heart, curving around the LAA. It gives off the left marginal artery, which runs down the left border of the heart towards the apex⁸.

Coronary dominance refers to an individual heart's pattern of coronary arteries, and specifically to whether the posterior interventricular artery arises from the RCA or the LCA. A heart is right dominant if the posterior interventricular artery arises from the RCA, left dominant if it arises from the circumflex artery of the LCA, and co-dominant if it receives contributions from both the RCA and LCA²⁵. A study of 110 Brazilian hearts found that 69% were right dominant, 12% were left dominant, and 19% were co-dominant²⁶. Another study, this one of the population of Assam, India, found that 70% were right dominant, 19% were left dominant, and 11% were co-dominant²⁷. According to these studies and others, the majority of individuals have right dominant coronary circulation. The network of coronary veins more or less accompanies the arteries and drains the myocardium of deoxygenated blood, returning it to the right atrium via the coronary sinus and the anterior cardiac veins⁸.

1.3 Atrial Fibrillation

1.3.1 Introduction

Atrial fibrillation (AF) is a condition that involves irregular or abnormal beating of the heart, known as arrhythmia. It is the most common form of arrhythmia, affecting approximately 350,000 Canadians²⁸, and 2-3% of the population of Europe²⁹. AF is characterized by a rapid and irregular heartbeat and fluttering of the two atria²⁵. The risk of developing it greatly increases with age, as well as with coincidence of high blood pressure, heart valve diseases, other underlying heart problems, and excessive alcohol consumption³⁰. In a longitudinal study of 5,201 patients over the age of 65, AF was diagnosed in 4.8% of women and 6.2% of men³¹. Lernfelt and colleagues (2014) looked at the incidence of AF in 2,629 elderly patients. They found that at 70 years of age 5.2% of men and 2.2% of women had AF, at 80 years 13.7% of men and 7.5 of women did, at 90 years 20.4% of men and 17.3% of women did, and at 100 years 33% of men and 26.8% of women had AF⁷⁵. Patients with AF can experience chest pain, shortness of breath, fatigue, dizziness and light-headedness. However, the main concern in these patients is a greatly increased risk of stroke due to turbulent blood flow and stasis of blood in the heart²⁵. Patients with AF have a fivefold increased risk of stroke over the general population². These patients experience approximately 17% of all ischemic stroke³², and roughly 35% of them will have a stroke during their lifetime⁴.

1.3.2 Pathogenesis

The beating of the heart is stimulated and controlled by the electrical conduction system of the heart. Electrical impulses spread throughout the muscle of the heart, exciting them and causing them to contract⁸. The impulse for a heartbeat originates in the sinoatrial (SA) node, also known as the pacemaker of the heart, located in the wall of the right atrium. From there, the signal spreads throughout the atria, stimulating them to contract. It reaches the atrioventricular (AV) node, which is located at the junction of the four heart chambers, where the signal is delayed for a fraction of a second to allow the ventricles to fill with blood. The signal is then sent down through the bundle of His and the bundle branches towards the apex of the heart. From the apex, the signal reaches the

myocardial cells via Purkinje fibres, stimulating contraction. This arrangement ensures that the ventricles contract from the bottom up, allowing efficient emptying of blood to the great vessels³³.

The normal functioning of the electrical conduction system of the heart ensures synchronized contraction of the myocardium, which is important for a couple of reasons. First, it causes smooth laminar flow of blood through the heart. Second, it results in complete filling and emptying of the hearts chambers, which helps keep blood moving and prevents pooling and stasis³³. In patients with atrial fibrillation, normal impulses from the SA node are overpowered by disorganized electrical impulses from elsewhere in the atria, most commonly from the roots of the left pulmonary veins³³. This causes the atria to beat rapidly, incompletely and irregularly. This fluttering of the atria causes turbulent blood flow through the heart, and since the atria do not empty completely, blood pools. Both of these factors lead to increased thrombogenesis, or blood clot formation in the atria. This is very dangerous because a blood clot in the left atrium can break off and embolize, and may travel to the brain and occlude one of those blood vessels, causing a stroke³³.

1.3.3 Treatment

There are many strategies for the treatment of atrial fibrillation, but they generally fall under a few categories. The first step is to return the patient's heart to normal sinus rhythm. This is called "rhythm control" and it can be done in two ways. The first is with medication; there are several drugs that can help re-establish sinus rhythm. The second is via electrical cardioversion, which involves delivering an electrical shock to the heart while the patient is under sedation. This temporarily stops the conduction system of the heart, and the hope is that when it restarts it is driven by the SA node again^{28,33,34}. The second step in AF treatment is "rate control". This entails decreasing the heart rate, since it is frequently elevated in AF due to the increased frequency of impulses to the AV node stimulating the ventricles. Medications used for this purpose include beta-blockers, calcium channel blockers and digoxin^{28,33,34}. If these strategies do not work, more permanent treatments are available. One of these treatments is catheter ablation, wherein a catheter is inserted into the femoral vein in the groin and threaded up to the heart. Once

in the atria, the catheter is used to deliver radiofrequency energy to ‘hot spots’ in the heart wall, which are parts of the wall that are generating the impulses that overpower the SA node. The radiofrequency energy ablates or scars the problem tissue, rendering it unable to evoke an electrical signal and allowing the SA node to generate its normal impulses^{28,33,34}. If all else fails, there is a surgical treatment for atrial fibrillation called the MAZE procedure, developed by Dr. James Cox and colleagues in 1987. The MAZE procedure involves making patterned incisions in the atrial walls, as well as removal of the atrial appendages. The resulting patterns of scar tissue block abnormal signal circuits and prevent the spread of disorganized signals, allowing the SA node to take over and restoring sinus rhythm^{28,33,34,35}.

Because the biggest concern and most serious potential complication for patients with atrial fibrillation is the formation of blood clots and embolization to the brain, most AF patients are prescribed blood thinners, or anticoagulants, to prevent thrombogenesis^{28,33,34}. Warfarin, brand name Coumadin, is used in most cases and is the gold standard. One study found that warfarin consistently decreases the risk of stroke in AF patients by 68%³⁶. Another meta-analysis of studies looking at stroke risk reduction in AF patients found that therapy with adjusted-dose warfarin reduces the relative risk of stroke by 62%³⁷.

1.3.4 Significance of the Left Atrial Appendage

The LAA has been recognized as a major site of origin for thrombi in patients with AF. In 1969, Aberg reviewed 642 patients with AF and found that 43 thrombi and 29 systemic emboli originated in the LAA vs. 22 thrombi and 16 systemic emboli from the rest of the left atrium³⁸. Stoddard and colleagues (1995) performed TEE in 317 AF patients and found thrombi in the LAA of 21% of them³⁹. In 1995, Manning and colleagues performed TEE in 233 patients with AF who were not on long-term anticoagulation, and found that after a period of 48 hours of atrial fibrillation, 15% of these patients had left atrial thrombus and all but one of those were in the LAA⁴⁰. In 1996, Blackshear and Odell published possibly the most cited paper regarding the prevalence of thrombi in the LAA. They performed a meta-analysis of previous studies and found that in patients with rheumatic AF, 57% of thrombi originated in the LAA, and

in patients with non-rheumatic AF, 91% of thrombi originated therein⁴. From these studies it is clear that in patients with atrial fibrillation, blood clots form in the LAA more often than anywhere else in the heart. It has been found that LAA function and morphology may play a role in increasing the risk of thrombogenesis. The poor pumping function of the LAA⁴¹ and its complex shape⁴² lead to stasis of blood within the appendage, which leads to clotting. The right atrial appendage may be a site of thrombogenesis as well, however it is less likely and less of a concern. The right atrial appendage is generally more broad and shorter than its counterpart on the left atrium, so blood does not pool as much, making it a less conducive environment for blood clot formation. Also it is important to note that a thromboembolism from the right atrium would lead to pulmonary embolism, while one from the left atrium leads to stroke. While pulmonary embolism is still a serious condition, it is not nearly as devastating as a stroke, so thrombogenesis in the right atrial appendage is less of a concern than in the LAA.

1.4 Surgical LAA Obliteration

1.4.1 Introduction

While oral anticoagulation with warfarin is the gold standard treatment for atrial fibrillation, it is not always used. One meta-analysis posited that warfarin might not be effective for long-term use because anticoagulation therapy is difficult to sustain in elderly patients due to increased risk of bleeding and the drug's narrow therapeutic window³⁷. A review article in 2000 stated that warfarin was underused and put forward several reasons as to why this is the case. It found that a patient's age, perceived lack of embolic risk, and haemorrhage risk all influence a physician's decision to not prescribe warfarin. Many physicians also consider it impractical and inconvenient to monitor a patient's warfarin levels as necessary³. Cohen and colleagues (2000) found that warfarin use falls short of recommendations and cited old age, language difficulties, patient disability, and insufficient awareness of its benefits as causes for the reluctance of physicians to treat patients with warfarin⁴³. An important reason for the underuse of warfarin is the risk of complications. Patients with increased age (65+ years), diabetes mellitus, and those who take more than three drugs per day are at an increased risk of complications from warfarin use⁴⁴. It is important to note that it is these older patients

who are most likely to develop atrial fibrillation and require treatment with warfarin in the first place. In one study, of all AF patients who were at moderate to high risk of stroke and were not a high bleeding risk, only 53% received warfarin therapy. Further, among patients who did receive warfarin, only 40% were adherent⁴⁵. So even though it is effective at reducing stroke risk in patients with AF, for several reasons warfarin cannot be used in many cases.

Because the majority of thrombi occurring in patients with atrial fibrillation originate in the LAA, surgical closure of the appendage is a viable alternative when warfarin cannot be administered⁴. Johnson and colleagues (2000) evaluated prophylactic removal of the LAA for any patient undergoing open-heart surgery in order to reduce stroke risk due to potential future development of atrial fibrillation. They found it safe and effective and recommended the procedure¹⁹. In fact, closure of the LAA has been found to be non-inferior to warfarin for prevention of stroke in patients with AF⁴⁶. Closure of the LAA is often done concomitantly with other cardiac surgeries. It is relatively easy and safe, and has minor risks and huge potential benefits. Surgical LAA obliteration is recommended in the American College of Cardiology/American Heart Association Guidelines for patients undergoing mitral valve surgery⁴⁷, and many studies have been carried out evaluating LAA closure during operations involving the mitral valve^{6,48,49}. The MAZE procedure for treatment of atrial fibrillation involves resection of the atrial appendages³⁵. Sueda and colleagues developed a procedure for left atrial ablation in patients with chronic AF associated with mitral valve disease, which also involves excision of the LAA⁵⁰. Finally, LAA closure has also been performed in conjunction with coronary artery bypass grafting⁵¹. LAA closure can be done surgically, via exclusion or excision, or percutaneously with an occluding device.

1.4.2 Percutaneous Occlusion Devices

In recent years, devices to occlude the LAA that are introduced percutaneously have been developed. A catheter is used to deliver the device into the venous system and threaded up to the right atrium. From there the atrial septum is punctured and the device is delivered into the LAA in order to close it off from the rest of the left atrium. The three most prominent examples of these devices are the PLAATO device, the WATCHMAN

device and the Amplatzer Cardiac Plug. The PLAATO device (Figure 1.4.2A) consists of a self-expanding nitinol cage, with a diameter range of 15-32 mm, that expands to fill the volume of the LAA. It also has three rows of anchors along its struts to help fix it in place⁵². The WATCHMAN device (Figure 1.4.2C) also consists of a self-expanding nitinol frame with fixation barbs, and is covered by a permeable polyester fabric. It comes in diameters of 21, 24, 27, 30 and 33 mm⁵³. The Amplatzer Cardiac Plug (Figure 1.4.2B) is another nitinol mesh structure, but it is made of a distal lobe and a proximal disk with polyester patches sewn on, connected by a short waist. It acts like a pacifier with the distal lobe in the LAA and the proximal disk covering the orifice. It also has stabilizing hooks and comes in lobe sizes of 16-30 mm, in 2 mm increments⁵⁴.

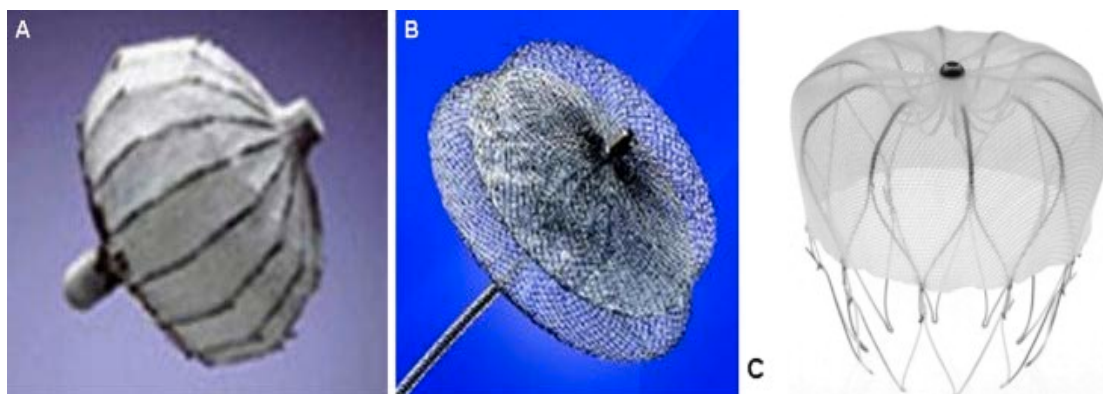


Figure 1.4.2 Three percutaneous LAA occlusion devices⁵. A) The PLAATO device, B) The Amplatzer Cardiac Plug and C) The WATCHMAN device.

These devices seem like a promising solution for LAA closure, but there are many studies pointing out some of their drawbacks. In 2007, Onalan and Crystal reviewed data from the three aforementioned devices, and found a relatively high rate of complications. Out of 313 patients occluded with the PLAATO device, there were eight cases of pericardial effusion and nine cases of cardiac tamponade. With the WATCHMAN device, out of 66 patients there were five cases of pericardial effusion and two cases of device embolization. The Amplatzer Cardiac Plug was used in 16 patients, with one case of device embolization. In total, among these three devices, there were 31 major complications in 395 patients (8%)⁵⁵. Holmes and Schwartz noted that percutaneous LAA occlusion devices carry potential procedural risks including air embolism from the placement of large sheaths, device embolization, pericardial effusion and vascular access

events. They concluded that the most significant complication is pericardial effusion, which can in rare cases lead to tamponade⁴⁷. Another review looked at two studies done with the WATCHMAN device, and found that procedure or device related adverse events occurred within a week of device implantation in 6.5% of cases in one study and in 3.7% in the other. This included incidences of serious pericardial effusion in 5.0% and 2.2% of cases⁵⁶. Yet another review, done last year, evaluated total adverse event rates for these three devices. The adverse event rate for the PLAATO device, the WATCHMAN device and the Amplatzer Cardiac Plug was 5.4%, 13.6% and 23.5%, respectively⁵⁷. The most common complication with the PLAATO device is tamponade. With the WATCHMAN device, device embolization is a concern. The Amplatzer Cardiac Plug carries a risk of pericardial effusion, device thrombosis and embolization, and procedural stroke⁵⁸. It is important to note that the PLAATO device is no longer clinically available for LAA occlusion⁵⁹. So while these devices show promise as a relatively simple method for LAA occlusion, there are some disadvantages. Firstly, much more work needs to be done to ensure their safety. Secondly, it has been shown that their stroke reduction rates are more modest than initially reported, putting into question their effectiveness for patients with AF⁵⁸. Finally, these devices have a uniform shape while the morphology of the LAA is extremely variable, limiting their ability to fully occlude the appendage. Currently, surgical LAA closure is still a better option than percutaneous device occlusion.

1.4.3 LAA Exclusion

Exclusion of the LAA is the first of two broad categories of surgical LAA obliteration. The idea is to close off, or exclude, the LAA from the rest of the left atrium, effectively eliminating it and its thrombogenic potential⁵. The orifice of the LAA is closed using sutures or surgical staples (Figure 1.4.3). In 1984 and 1988, two separate automatic surgical staplers were introduced for exclusion of the LAA. Both studies reported adequate appendage obliteration and no complications^{60,61}. The LAA orifice can also be sewn closed from within the left atrium using a pursestring suture⁶², and encircling suture⁵¹, or a double row of running suture^{48,51,63}. More recently, a device called the AtriClip has been introduced for LAA exclusion in patients undergoing median sternotomy. The AtriClip is carefully placed over the LAA and clips it shut. It has

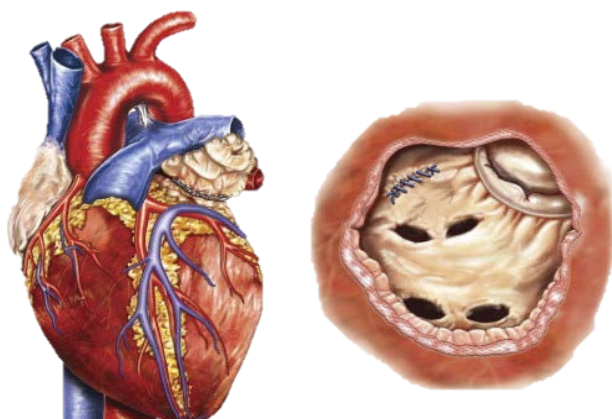


Figure 1.4.3 Staple and suture exclusion of the left atrial appendage (LAA)⁵.

successfully closed the LAA in 67 of 70 (96%) patients⁶⁴. In 2012 a similar device, called the TigerPaw system, was introduced to epicardially exclude the LAA and was deemed safe after use in 60 patients⁶⁵.

However, LAA exclusion is not successful if post-operatively there is still some blood flow between the LAA

and the left atrium. The presence of residual flow across the suture or staple line makes the operation a failure, since if the LAA remains a potential site of thrombogenesis⁵. Lynch and colleagues described six cases of patients who had undergone LAA exclusion by pursestring closure and subsequently experienced recanalization and high-velocity blood flow between the LAA and left atrium, as detected by TEE⁶². In 2000, Katz and colleagues used TEE to assess residual blood flow between the LAA and left atrium in 50 patients who had undergone LAA suture exclusion. They found that 18 of these patients (36%) had incomplete LAA closure, and suggested that residual flow between the incompletely excluded LAA and the left atrium may produce a setting for stagnant blood within the appendage and may be a mechanism for thrombogenesis⁴⁸. Another study assessed LAA exclusion, by surgical staple and by suture, in patients undergoing coronary artery bypass grafting. It found that exclusion was successful in only 24 of 33 (72%) patients who had undergone staple exclusion, and in 5 of 11 (45%) patients who had undergone suture exclusion⁵¹. Schneider and colleagues (2005) evaluated six patients who underwent LAA exclusion by TEE and found that only one of them had a completely ligated LAA post-operatively. They also noted that incomplete closure results in blood stagnation in the LAA and increased likelihood of clot formation⁶³. Finally, in 2008 Kanderian and colleagues conducted another study assessing the success of both staple and suture exclusion by TEE. Only 17 of 73 (23%) suture LAA exclusions were successful, and out of 12 staple exclusions, none were a success⁶⁶. There has been speculation as to why exclusion of the LAA fails so often, with the main cause being dehiscence of the sutures or staples due to tension from the LAA orifice as it attempts to

return to its original shape. These discouraging results illustrate the fact that current exclusion methods are not ideal for completely ligating the LAA.

1.4.4 LAA Excision

Excision of the LAA is the second broad category of surgical LAA obliteration. It involves cutting off and removing the LAA completely and sewing the remnant shut⁵ (Figure 1.4.4). In 1949, Madden published one of the first reports on removal of the LAA after performing it in two patients⁶⁷. Johnson and colleagues (2000) performed LAA excision in 391 patients and recommend prophylactic LAA removal whenever a patient's chest is open, in order to prevent potential thromboemboli from future development of atrial fibrillation¹⁹. An amputating stapler device can be used to excise the LAA and staple the remnant closed^{66,68}, but it is more commonly performed with scissors⁶⁶. In 2010, Roth and colleagues introduced a technique for LAA excision that involved using a piece of the patient's pericardium to reinforce the remnant in order to increase the safety of the procedure⁶⁹.

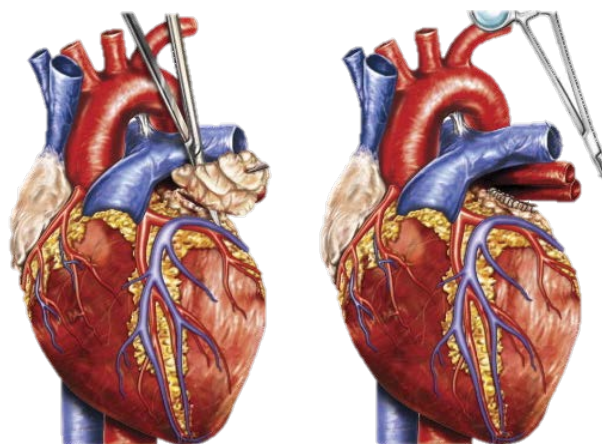


Figure 1.4.4 Epicardial excision with oversew of the left atrial appendage⁵.

Because the appendage is fully removed and not just excluded, residual flow between the LAA and the left atrium is not a concern in LAA excision. In an editorial comment in

2011, Sievers noted that LAA excision has better outcomes than exclusion and mentioned that he has switched his technique for surgical LAA obliteration to complete excision⁷⁰. Also in 2011, Chatterjee and colleagues published a review of LAA occlusion techniques. In the review they mention that epicardial excision with oversew is the most effective technique for surgical LAA closure, and that it is their method of choice⁵.

Despite excision being the current gold standard for surgical obliteration of the LAA, it is still not always successful. Excision is considered to be a failure if it fails to

remove the entire appendage and leaves a residual stump. Crystal and colleagues (2003) first put the criterion for what constitutes a residual stump forward in the Left Atrial Appendage Occlusion Study (LAAOS)⁷¹. Their criterion was a remnant LAA 1 cm in length or longer, and this was based on the rationale that the smallest appendages are 2 cm long and a greater than 50% reduction in its volume would be necessary to reduce stroke risk. Now throughout the literature, a residual stump of 1 cm or greater is considered a failure⁶⁶. This is important because one study found that residual stump left after LAA excision is potentially even more dangerous, in terms of stroke risk, than the initial appendage⁶. A reason for this is not cited, but there is speculation as to why this is the case. The idea is that in an intact LAA thrombi form in the tip and are rarely dislodged, while in a shallower residual stump, thrombi form near the orifice and are much more likely to be dislodged by the flow of blood through the heart and embolize. In one study of 52 patients who underwent LAA excision, a residual stump greater than 1 cm was present in 14 of them, resulting in a success rate of 73%⁶⁶. Therefore, while LAA excision is the current gold standard, and generally much more successful than exclusion, it can still leave a residual stump limiting its effectiveness and presenting a potential danger to patients.

1.4.5 Circumflex Coronary Artery

As mentioned earlier, the circumflex artery is a branch of the left main coronary artery, as is the anterior interventricular artery. After it branches, it curves down and around the base of the LAA epicardially, running in the left coronary sulcus towards the posterior of the heart⁸. It supplies blood to the left atrium and the posterolateral part of the left ventricle⁸. Because of its close proximity to the base of the LAA, it has been noted several times that the circumflex artery is in danger of being injured during surgery on the appendage, epicardially and even endocardially^{7,10,12,72}. Because of its area of supply, damage to this artery would interrupt blood flow to the left atrium and part of the left ventricle, causing significant damage. Although the potential danger is recognized, no comprehensive measurements of the distance between the artery and the LAA have been made.

1.4.6 Pericardial Patch Exclusion of the LAA

All of the current surgical options for LAA closure have their drawbacks, and in many cases these disadvantages can put patients at great risk. It is important that a safe and effective technique of completely closing the left atrial appendage is found, in order to reduce stroke risk in patients with atrial fibrillation. The ideal LAA surgical closure method would fulfill certain criteria. Firstly, it would fully and completely eliminate the appendage, leaving no residual stump. Secondly, it would not allow residual communicative blood flow between the LAA and the left atrial cavity. Thirdly, it would be able to be performed with minimal strain on the patient, and with minimal chance of perioperative and post-operative complications. Fourthly, it would not require the patient to be on medication post-operatively. Finally, it would comfortably suit the size and shape of any individual's left atrial appendage.

With this in mind, Dr. Michael W.A. Chu MD, FRCSC, a cardiac surgeon at London Health Sciences Centre in London, Ontario, Canada, has developed a novel method of surgical LAA obliteration called 'pericardial patch exclusion' that shows promise in being able to completely close the LAA. The technique involves resecting a piece of the patient's pericardium and shaping it to the individual's LAA orifice. The patch is then sewn over the orifice using a running suture, excluding the appendage from the rest of the left atrium. The idea is that this technique can overcome the failures of conventional excision and exclusion. It should not leave any residual LAA volume, since the patch covering the orifice is level with the atrial wall. Also, there will hopefully be no residual blood flow between the appendage and the left atrium since the patch does not deform the LAA orifice, reducing the potential for dehiscence of the sutures. Using a cadaveric model we can assess residual LAA volume left by these methods, but we cannot assess blood flow across the patch or the suture line.

1.5 Rationale Statement

This research aims to fulfill three goals. The first is to provide an anatomical description of the left atrial appendage in order to guide the development of more effective closure methods. Percutaneous devices that are currently used to close the LAA

work by expanding and filling the appendage and blocking off the orifice. However, these devices are available in a limited range of sizes, which may exclude some individuals. Determination of the range of LAA and LAA orifice sizes may provide valuable information to help ensure that all patients have closure devices available to them.

The second aim is to determine the distance between the circumflex coronary artery and the LAA at specific points around its base. The circumflex is in danger during any LAA surgery, but little is known about the specific regions that require most attention, or how far the artery is from the base of the LAA. These results will give physicians an idea of which areas require more care and attention, and will hopefully reduce the incidence of injury to the artery. Also, the branching of the left main coronary artery to the LAD and the circumflex occurs at a variable position. Measuring at which point this branching is most likely to occur will provide useful information in terms of how extensive ischemic injury may be when damage occurs at a certain point.

The third and final aim is to evaluate the novel pericardial patch exclusion method of LAA closure in comparison to conventional epicardial excision, with regards to residual volume left in the appendage after each operation. Epicardial excision is the current gold standard for surgical LAA closure. However, it often leaves a potentially thrombogenic residual stump. Pericardial patch exclusion shows promise in fully eliminating the LAA. Pericardial patch exclusion, if it leaves little or no residual LAA volume, may be a viable option for surgical LAA closure, and may help reduce stroke risk in patients with atrial fibrillation.

1.6 Objectives

Using a cadaveric model, the objectives of this investigation are:

1. To provide a full and accurate description of the anatomical dimensions of the left atrial appendage (LAA) to accommodate the development of more effective closure methods.
2. To track the course of the circumflex artery around the base of the LAA and to measure its proximity at various points. This will give surgeons a better idea in which area the circumflex artery is in greatest danger of being injured, and where to be most careful, during LAA operations.
3. To assess the residual volume left in the LAA by conventional epicardial excision and by the novel pericardial patch exclusion technique, as compared to the initial LAA volume. This will help determine if pericardial patch exclusion is a more effective method for eliminating the LAA, and whether it is a viable option for surgical LAA closure.

1.7 Hypothesis

With regards to the third objective of this project, it is hypothesized that the novel pericardial patch exclusion technique will leave less residual volume in the left atrial appendage than conventional epicardial excision.

Chapter 2

2 Methods

2.1 Subject Data

A total of 27 adult cadaveric hearts were harvested from specimens in the Human Anatomy Lab at Western University in accordance with the Anatomy Act of Ontario and Western's Committee for Cadaveric Use in Research, approval #15052013. Of these 27 cadaveric, 18 (67%) were from specimens fixed with a 10% formalin solution, and nine (33%) were from fresh frozen specimens. Mean age of all 27 specimens was 77.1 ± 12.5 (53-97) years and consisted of 18 (67%) male and 9 (33%) female donors. Mean age of the formalin fixed specimens (n=18) was 79.8 ± 12.3 (53-97) years and consisted of 11 (61%) male and 7 (39%) female donors. Mean age of the fresh frozen specimens (n=9) was 71.8 ± 12.5 (55-87) years and consisted of 7 (78%) male and 2 (22%) female donors. Full subject data is available in Table 2.1.1

Table 2.1.1 Subject characteristics.

	SEX	AGE	CAUSE OF DEATH
Formalin Fixed	M	84	Cardiac Arrest, Heart Failure, Coronary Artery Disease
	M	93	Bladder Cancer, COPD
	M	63	Cardiac Arrhythmia, Complicating COPD
	F	78	Diffuse Metastatic Cancer, Ulcerative Colitis
	F	90	Pneumonia, Progressive Supranuclear Palsy
	F	75	Multiple Myeloma, Chronic Renal Failure
	M	85	Cerebrovascular Accident, COPD, Periph Vascular Disease
	F	76	Non-Alcoholic Liver Cirrhosis, Atrial Fibrillation, ASHD
	M	62	Metastatic Melanoma, Melanoma
	F	93	Breast Cancer, Parkinsons Disease
	M	97	Dehydration, Bowel Obstruction, Fecal Impaction, CVA
	M	87	Fractured Left Hip, Cancer of the pancreas
	M	69	End Stage Chronic Obstructive Lung Disease
	F	89	CVA, COLD, Congestive Lung Failure
	M	53	Carcinoma of the Bladder
	F	73	Breast Cancer
	M	80	Parkinsons Disease, illegible, Ischemic Heart Disease
M	90	Pneumonia, Depression, Ischemic Heart Disease	
Fresh Frozen	M	55	Possible Pneumonia, Severe COPD, Lung Cancer
	M	79	Coronary Artery Disease, Diabetes, Sudden Cardiac Arrest
	M	87	Coronary Artery Disease, Congestive Heart Failure, A Fib
	F	70	Brain Metastases, Lung Cancer, Breast Cancer
	M	65	Cardiac Arrest, Coronary Artery Disease, Bladder Cancer
	M	84	Acute Uremia, Dementia, Chronic Obstructive Lung Disease
	M	66	Acquired Brain Injury
	F	55	Pneumonia, Right pan coast Lung Tumor
M	85	Cancer of the Lung, Dementia	

2.2 Study Design

The study protocol was carried out on all (n=27) cadaveric hearts. The hearts were dissected epicardially in order to expose the circumflex artery, and the posterior aspect of the wall of the left atrium was cut in order to expose the left atrial cavity and visualize the LAA orifice. Various dimensions of the LAA and the LAA orifice were then measured. Next, the proximity of the circumflex artery was measured at six points around the base of the LAA. Finally, the hearts underwent pericardial patch exclusion and epicardial excision, after each of which residual volume was measured.

2.3 Measurement of the LAA

The length of each LAA was measured from the centre of the base to the most distal tip. Width was measured at the widest part of the appendage, perpendicular to the axis of length (Figure 2.3.1A). The measurements carried out on the LAA orifice were the length of the major axis, length of the minor axis and circumference (Figure 2.3.1B). The LAA orifice is oval in shape, so the major axis is its longest diameter (in the vertical plane) and the minor axis is its shortest diameter (in the horizontal plane). LAA volume was also measured. All measurements except for LAA orifice circumference and LAA volume were made once with a ruler and once with a digital Vernier caliper (Precise Digital Caliper, 6 inch, model 210-2373), each by two raters. LAA circumference was measured to the nearest 1 cm with a string and ruler by two different raters. LAA volume was measured to the nearest 0.1 mL twice, once by filling it to the orifice with water and recording the volume of water used, and again by filling it to the orifice with agarose gel, waiting for the gel to harden, then removing the gel and submerging it in water and recording the volume change of the water.

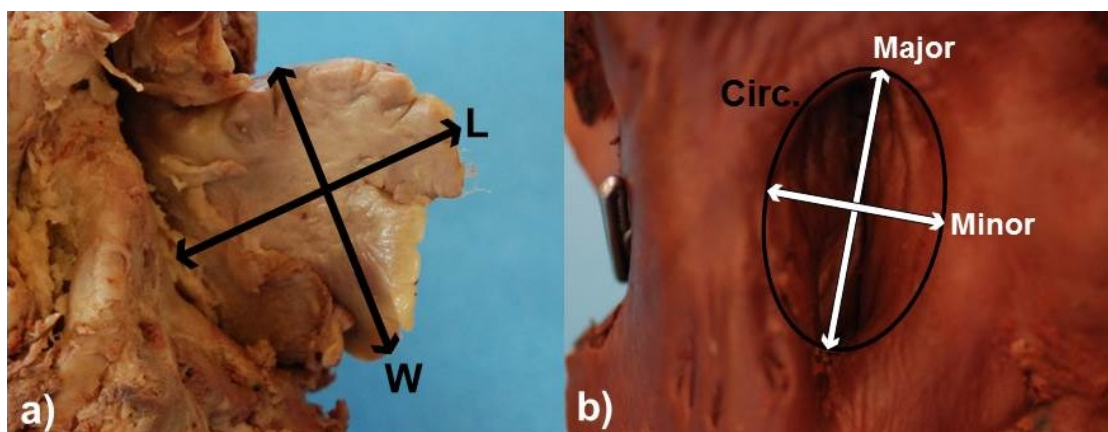


Figure 2.3.1 A) Measurements carried out on the LAA included length, width and volume, B) and measurements carried out on the LAA orifice included major axis, minor axis and circumference.

2.4 Measurement of the Proximity of the Circumflex Artery

When viewing the LAA orifice from inside the left atrial cavity, surgeons use an imaginary superimposed clock face to refer to different positions around its edge. The clock face is arranged so that the 12 o'clock and 6 o'clock positions lie at either end of the major axis, and 3 o'clock and 9 o'clock lie at either end of the minor axis. When translated from the endocardial aspect of the heart to the epicardial side, the clock face is flipped and ends up arranged in a counter clockwise orientation (Figure 2.4.1). This reflected clock, from 12 o'clock to 6 o'clock, was drawn around the base of the LAA with a marker as accurately as possible. The distance from the base of the LAA at each of these seven equidistant points (12, 1, 2, 3, 4, 5 and 6 o'clock) to the nearest edge of the circumflex artery, or the left main coronary artery prior to the branching of the circumflex, was measured. All measurements were made once with a ruler and once with a digital Vernier caliper (Procise Digital Caliper, 6 inch, model 210-2373), each by two raters.

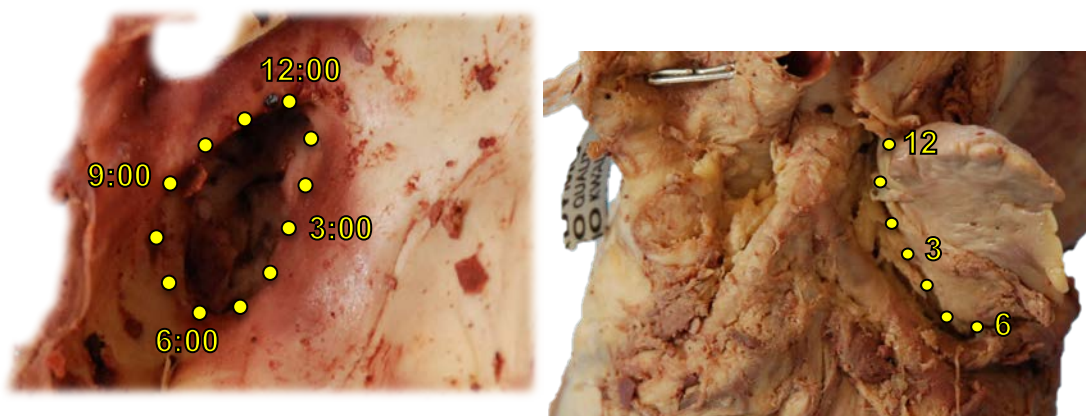


Figure 2.4.1 Endocardial and epicardial view of clock-face arrangement used to orient the LAA orifice.

2.5 Surgical Techniques

All surgeries were performed by board certified cardiac surgeons. Pericardial patch exclusion was performed first. Excess pericardial tissue was obtained from the Human Anatomy Lab at Western University, and patches were cut to the shape of each individual LAA. The patches were then sewn over the orifice of the LAA using a running 4-0 prolene suture. After the patch was in place, residual volume in the appendage was measured in the same way initial LAA volume was, once with water and once with agarose gel. After volume was measured, the suture was cut and the patch was removed. Conventional epicardial excision was then performed on each heart. Using scissors, the LAA was resected as close as possible to its base without risking coronary injury or hemorrhage. The remnant stump was then sutured shut using a running 4-0 prolene suture. After the excision was complete, residual volume was once again measured by water and by agarose gel.

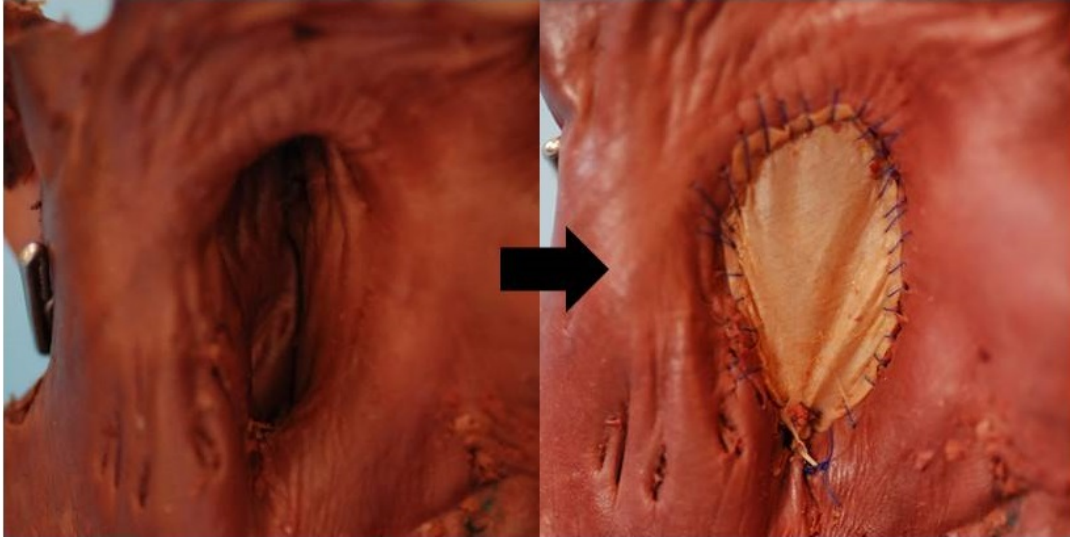


Figure 2.5.1 Pericardial patch exclusion of the LAA, showing the original orifice and the patch sewn in place.

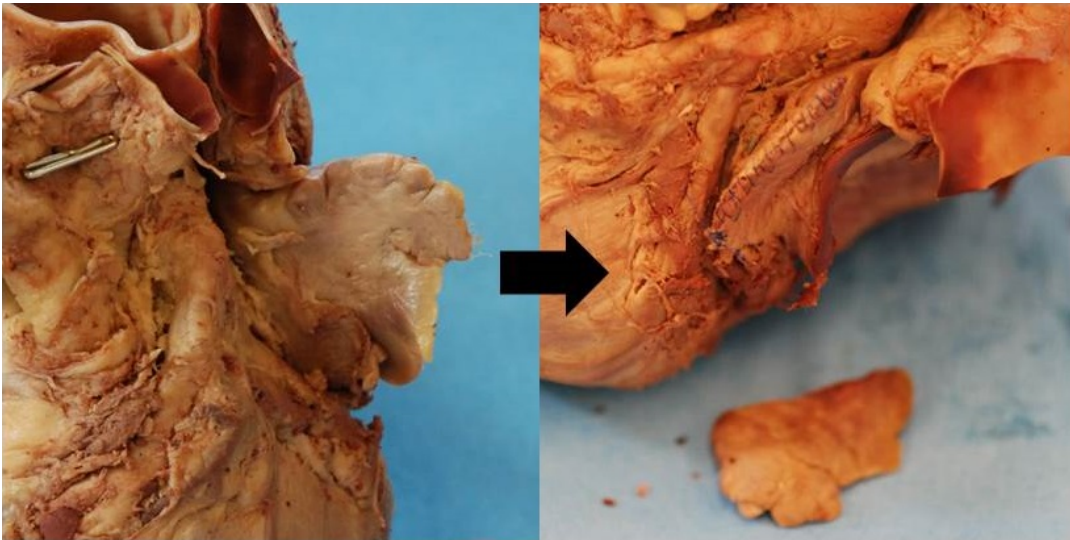


Figure 2.5.2 Epicardial excision of the LAA, showing the original appendage, the excised portion and the remnant sewn shut.

Chapter 3

3 Results

3.1 Statistical Analysis

Data were imported and analyzed using SPSS software version 22 (IBM Corp., Armonk, NY, USA, 2013). Continuous data are presented as mean \pm SD. A nonparametric one-way ANOVA was performed to determine if the residual volumes left by the two LAA closure methods were different, and p values < 0.05 were considered significant. Most measurements were made by digital Vernier caliper to the nearest 0.01 mm as well as by ruler to the nearest 1 mm. Because of this discrepancy, parallel-forms reliability was performed in order to determine the agreement between the two methods. The resulting reliability was 0.993, so it was deemed appropriate to proceed using only the data from the digital Vernier caliper measurements. Inter-rater reliability was 0.994. Parallel-forms reliability was done to compare the volume measurement with water and with agarose gel and the reliability was 0.997.

3.2 Measurements of the LAA

The mean length, width and volume of the LAA are shown in Table 3.2.1. Along with the overall information (n=27), the data is separated into formalin fixed specimens only (n=18) and fresh frozen specimens only (n=9). This is done to show general trends; no statistical analysis was carried out regarding the differences between the groups.

Table 3.2.1 Mean length (mm), width (mm) and volume (mL), SD and range in all hearts (n=27), formalin fixed (n=18) and fresh frozen (n=9).

	All Hearts (n=27)			Formalin Fixed (n=18)			Fresh Frozen (n=9)		
	<i>Length (mm)</i>	<i>Width (mm)</i>	<i>Volume (mL)</i>	<i>Length (mm)</i>	<i>Width (mm)</i>	<i>Volume (mL)</i>	<i>Length (mm)</i>	<i>Width (mm)</i>	<i>Volume (mL)</i>
Mean	41.06	29.13	4.02	38.84	30.86	3.17	45.49	25.67	5.73
SD	12.80	8.01	4.01	9.50	8.25	3.70	17.54	6.58	4.26
Minimum	23.34	15.76	0.25	24.15	20.67	0.55	23.34	15.76	0.25
Maximum	78.69	52.26	16.80	58.02	52.26	16.80	78.69	34.21	13.30

The mean dimensions of the LAA orifice, major axis length, minor axis length and circumference, are shown in Table 3.2.1. Again, the information (n=27) is stratified into fixed (n=18) and fresh (n=9) specimens to show general trends.

Table 3.2.2 Mean LAA orifice major axis, minor axis and circumference (mm), SD and range in all hearts (n=27), formalin fixed (n=18) and fresh frozen (n=9).

	All Hearts (n=27)			Formalin Fixed (n=18)			Fresh Frozen (n=9)		
	<i>Major Axis (mm)</i>	<i>Minor Axis (mm)</i>	<i>Circum. (mm)</i>	<i>Major Axis (mm)</i>	<i>Minor Axis (mm)</i>	<i>Circum. (mm)</i>	<i>Major Axis (mm)</i>	<i>Minor Axis (mm)</i>	<i>Circum. (mm)</i>
Mean	23.03	14.20	64.39	22.79	12.08	58.94	23.50	18.44	75.28
SD	5.94	5.52	22.24	5.72	3.76	13.86	6.68	6.20	31.62
Minimum	11.93	6.51	28.00	14.85	6.54	39.00	11.93	6.51	28.00
Maximum	37.57	28.98	128.50	37.57	22.30	86.50	34.65	28.98	128.50

3.3 Proximity of the Circumflex Artery to the Base of the LAA

The mean distance from either the left main coronary artery or the circumflex artery to the base of the LAA at each point around the clock-face is shown in Table 3.3.1. The artery was closest to the base of the LAA at the 3:00, 4:00 and 5:00 positions. The mean distance of the artery to the LAA, \pm two SD, is also shown in Figure 3.3.1.

Table 3.3.1 Mean distance from left main or circumflex artery to base of LAA (mm), SD and range at each point around clock-face (12:00 to 6:00).

	12:00	1:00	2:00	3:00	4:00	5:00	6:00
Mean (mm)	15.31	11.44	8.89	6.90	5.94	6.54	8.38
SD (mm)	4.44	3.57	2.50	1.92	1.29	1.87	2.16
Minimum (mm)	8.81	6.60	5.43	3.86	3.92	3.75	5.16
Maximum (mm)	22.73	18.47	13.89	10.55	9.29	11.78	12.49

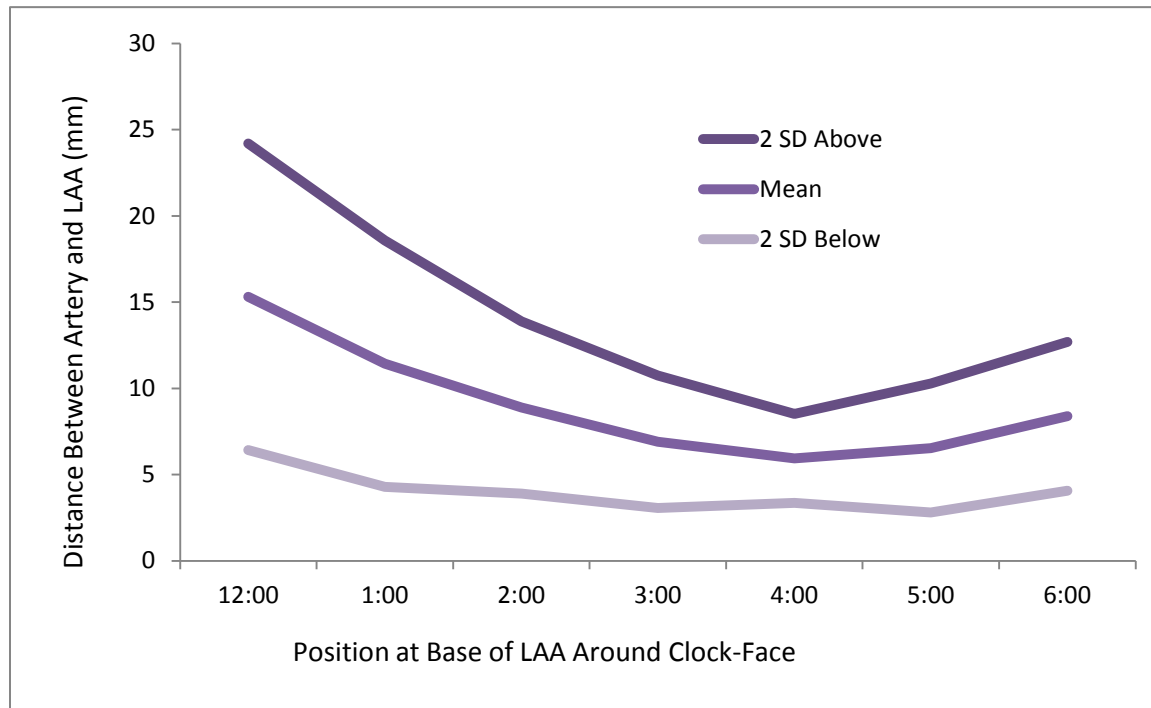


Figure 3.3.1 Mean distance from artery to the base of LAA (mm), \pm 2 SD, at each point around clock-face (12:00 to 6:00).

Whether the artery that was closest to the base of the LAA at each point around the clock-face was the left main coronary artery (LM) or the circumflex artery (Cx) is shown in Table 3.3.2. At 12:00 and 1:00, the artery closest to the LAA was usually the left main. At 2:00 and 3:00, the artery closest to the LAA was most often the circumflex. At 4:00, 5:00 and 6:00, the artery closest to the LAA was always the circumflex. This information is also shown in Figure 3.3.2.

Table 3.3.2 Identity of the artery closest to the base of the LAA, left main (LM) or circumflex (Cx), at each point around the clock-face (12:00 to 6:00).

	12:00	1:00	2:00	3:00	4:00	5:00	6:00
# Closer to LM	23	18	8	3	0	0	0
# Closer to Cx	4	9	19	24	27	27	27
<i>Closer to LM</i>	85.2 %	66.7 %	29.6 %	11.1 %	0 %	0 %	0 %
<i>Closer to Cx</i>	14.8 %	33.3 %	70.4 %	88.9 %	100 %	100 %	100 %

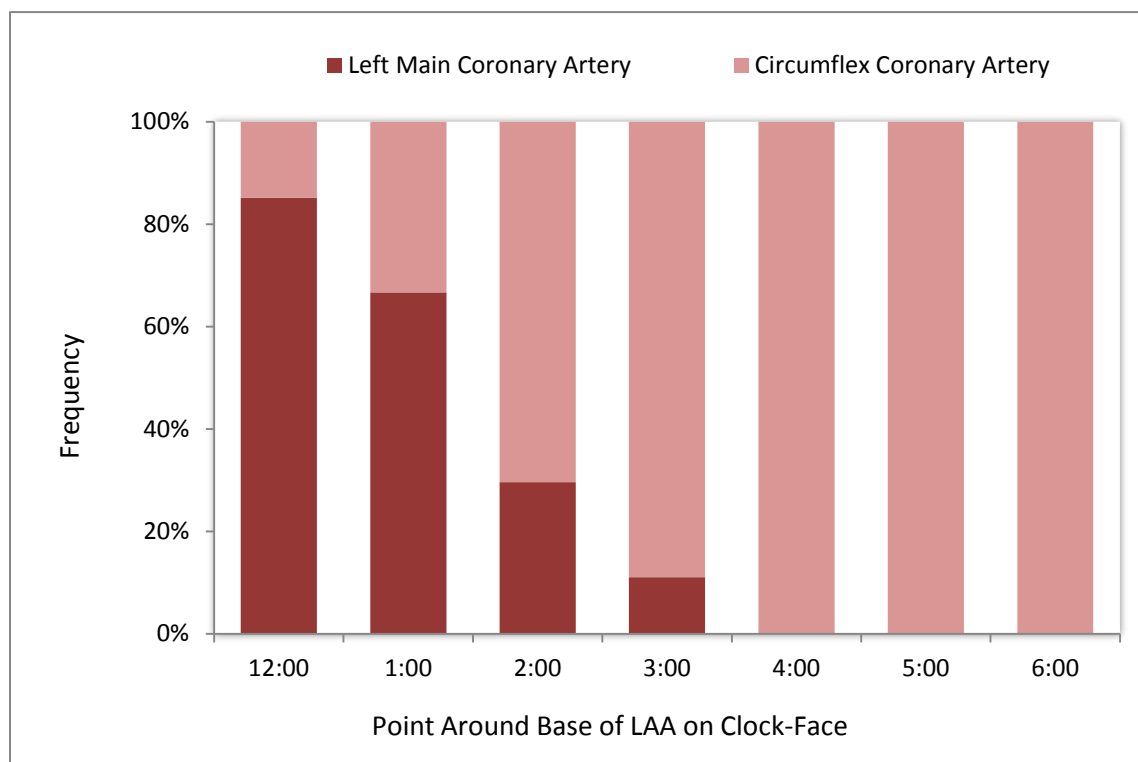


Figure 3.3.2 Identity of the artery closest to the base of the LAA, left main (LM) or circumflex (Cx), at each point around the clock-face (12:00 to 6:00).

3.4 Residual Volume Left by Epicardial Excision and by Pericardial Patch Exclusion

The mean volume of the LAA prior to any intervention, mean volume after conventional epicardial excision and mean volume after pericardial patch exclusion is shown in Table 3.4.1. This data is also stratified further into formalin fixed specimens and fresh frozen specimens. This information is also shown in Figure 3.4.1.

Table 3.4.1 Mean volume (mL) \pm SD and residual volume (%) in the LAA prior to intervention, after conventional epicardial excision (CEE) and after pericardial patch exclusion (PPE), in all hearts (n=27), fixed specimens (n=18) and fresh specimens (n=9).

		Original LAA	After CEE	After PPE
All Hearts (n=27)	<i>Volume (mL)</i>	4.02 \pm 4.01	0.95 \pm 1.02	0.17 \pm 0.08
	<i>% Residual</i>	-	23.63 %	4.23 %
Formalin Fixed (n=18)	<i>Volume (mL)</i>	3.17 \pm 3.70	1.11 \pm 1.13	0.19 \pm 0.10
	<i>% Residual</i>	-	35.02 %	5.99 %
Fresh Frozen (n=9)	<i>Volume (mL)</i>	5.73 \pm 4.26	0.62 \pm 0.71	0.14 \pm 0.05
	<i>% Residual</i>	-	10.82 %	2.44 %

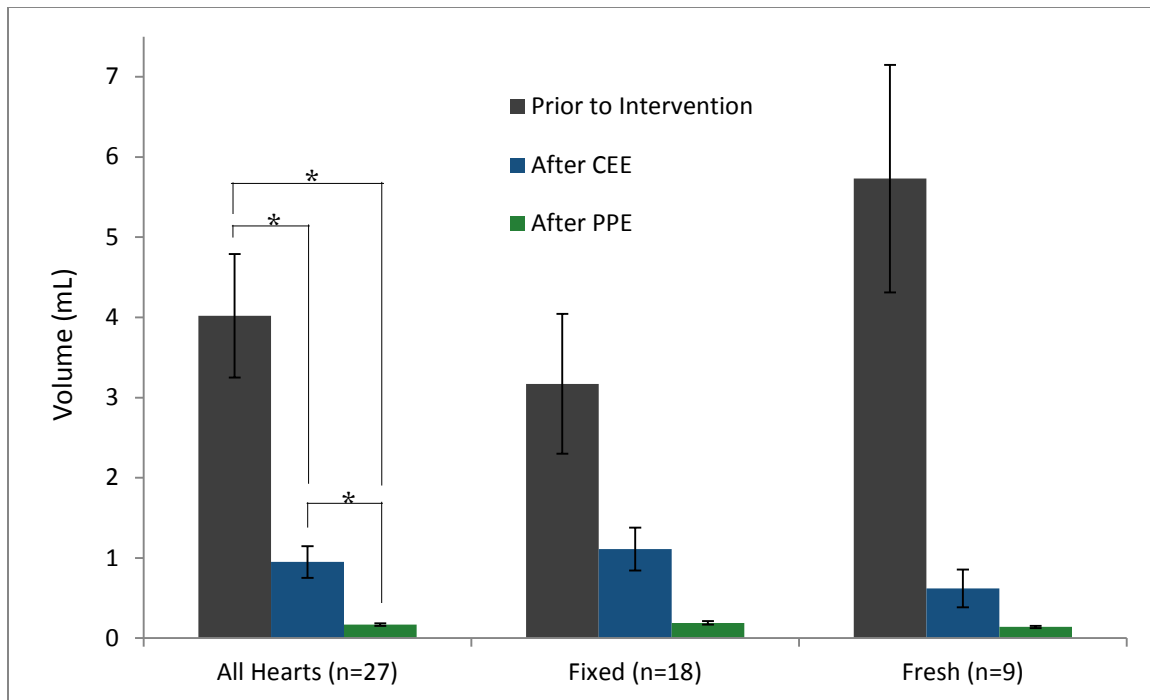


Figure 3.4.1 Mean volume (mL) \pm SE in the LAA prior to intervention, after conventional epicardial excision (CEE) and after pericardial patch exclusion (PPE), in all hearts (n=27), fixed specimens (n=18) and fresh specimens (n=9). (*) indicates significant difference in LAA volume ($p < 0.05$).

There was a significant effect of LAA condition (prior to intervention, after CEE, or after PPE) on volume in the LAA [$\chi^2(2)=57.35$; $p < 0.05$; $1-\beta > 0.8$]. Post hoc comparisons indicated that the mean volume of the LAA prior to intervention, the mean LAA volume after CEE, and the mean LAA volume after PPE were all significantly different. Therefore, conventional epicardial excision left a significantly greater residual volume in the LAA than pericardial patch exclusion did. The data for the two stratified groups (formalin fixed specimens and fresh frozen specimens) was not analyzed because of a lack of power due to small sample sizes.

Chapter 4

4 Discussion

4.1 Interpretation of Results

This investigation aimed to use a cadaveric model to fulfill three objectives regarding the left atrial appendage (LAA). The first objective was to produce a description of the anatomical dimensions of the appendage. According to the results of this study, the mean length of the LAA was 41.06 ± 12.80 mm, the mean width was 29.13 ± 8.01 mm, and the mean volume was 4.02 ± 4.01 mL. In terms of the LAA orifice, the mean major axis diameter was 23.03 ± 5.94 mm, the mean minor axis diameter was 14.20 ± 5.52 mm, and the mean circumference was 64.39 ± 22.24 mm.

The second objective was to measure the distance from the circumflex coronary artery to the base of the LAA at various points. The results showed that the artery was furthest away from the LAA at the 12 o'clock position, with a mean distance of 15.31 ± 4.44 mm. Moving around the base of the LAA in a counter-clockwise direction, the artery got progressively closer to the appendage. It reached its closest proximity at the 4 o'clock position, with a mean distance of 5.94 ± 1.29 mm. From then on the distance began to grow once again.

The third objective was to evaluate a novel method of LAA closure in comparison to current standards. The novel method, pericardial patch exclusion, was hypothesized to leave less residual LAA volume than the conventional epicardial excision technique. The mean volume remaining in the LAA following epicardial excision was 0.95 ± 1.02 mL. Pericardial patch exclusion left a mean residual volume of 0.17 ± 0.08 mL, which is significantly smaller ($p < 0.05$). These results are in accordance with our hypothesis.

4.2 Clinical Implications

The LAA is an area of great interest in cardiac surgery because of its implications with stroke risk in patients with atrial fibrillation (AF). Because of this, the findings of this study have numerous clinical implications.

4.2.1 Dimensions of the LAA

There have been several studies to note the great variability in the size and shape of the LAA^{11,12,14,15}, and that variety has been found in this investigation of 27 cadaveric hearts as well. The length of the LAA ranged from 23.34 mm to 78.69 mm, the width ranged from 15.76 mm to 52.26 mm, and the volume ranged from 0.25 mL to 16.80 mL. The major axis of the orifice ranged from 11.93 mm to 37.57 mm, the minor axis ranged from 6.51 mm to 28.98 mm, and the circumference ranged from 28.0 mm to 128.5 mm. These huge ranges are indicative of the considerable differences from one LAA to the next. This is of clinical importance because percutaneous LAA occlusion devices function by expanding and filling the appendage. They must completely fill the LAA and fully cover the orifice in order to be effective. The three most prominent such devices are the PLAATO device, the WATCHMAN device and the Amplatzer Cardiac Plug. These devices are available in different sizes, and are sized to the LAA orifice diameter of each patient. The PLAATO device comes in diameter sizes that range from 15-32 mm⁵². The WATCHMAN device comes in a diameter range of 21-33 mm⁵³. The Amplatzer Cardiac Plug is available in sizes ranging from 16-30 mm⁵⁴. So these devices are only designed to safely fit in a LAA orifice that is no smaller than 15 mm and no larger than 33 mm. However, in this study alone, orifice diameter ranged from 7 mm to 38 mm. It is likely that there are a considerable number of individuals for whom these devices would either be too small or too large, negatively affecting their effectiveness and their safety. This information may serve to drive the development of LAA occlusion devices with a larger selection of sizes to fit more patients. Conversely, surgical techniques of LAA closure are not limited by appendage size. Pericardial patch exclusion, notably, is designed to be customizable to the size of each individual LAA orifice.

4.2.2 Proximity of the Circumflex Artery

The close proximity of the circumflex coronary artery to the base of the LAA places it in danger during operation on the appendage^{7,10,12}. This is not only true for operations that take an epicardial approach such as excision. It is also true for endocardial

operations, such as suture or staple exclusion, and even implantation of percutaneous closure devices⁷². Part of this investigation included measuring the distance from the edge of the artery to the base of the LAA at seven different points. Cardiac surgeons use a clock-face arrangement to refer to different parts of the LAA orifice, and this clock-face was transferred over to the epicardial aspect of the heart. The seven points of measurement were determined from the 12 o'clock through 6 o'clock positions. The results, as found in Table 3.3.1, indicate that the artery is relatively far from the LAA at the 12 o'clock position, but begins to get closer at 1 and 2 o'clock. The artery is closest at 3, 4 and 5 o'clock, but then begins to course away again at 6 o'clock. This suggests that during any intervention on the LAA, special care must be taken when the 3, 4 or 5 o'clock positions are involved. These are the points at which the circumflex artery is at greatest risk.

Moreover, as seen in Figure 3.3.1, the mean distance of the artery was plotted on a line graph along with a line indicating the mean minus two standard deviations and a line indicating the mean plus two standard deviations. This was done because 95% of values lie within two standard deviations from the mean. So this line graph represents a "95% zone" wherein an artery would be expected to lie in 95% of cases. Paying special attention to the line representing the mean minus 2 SD, one can see that although on average the artery is a comfortable distance from the base of the LAA at 12, 1 and 2 o'clock, the 95% zone extends to much closer. In fact, the only real safe zone lies within 3 mm of the base of the LAA. This is also very important for physicians to consider. Although they may rightfully expect to encounter the artery at 3, 4 and 5 o'clock, they must also be prepared to see it as close as 4 mm from the LAA at other points. Previous studies have mentioned the risk of injuring the circumflex artery during LAA surgeries^{7,10,12}, but none have attempted to directly measure the proximity of the artery to the base of the LAA. This is the first investigation to track the distance from the artery to the appendage at various points, using surgical nomenclature to provide a clinically relevant account of its course around the LAA.

Furthermore, it is not always the circumflex artery proper that is closest to the base of the LAA; sometimes it is the left main coronary artery. As seen in Table 3.3.2 and

Figure 3.3.2, at the 12 and 1 o'clock positions the artery that was closest to the LAA was most often the left main. At 2 and 3 o'clock one was more likely to see the circumflex artery, and from 4 to 6 o'clock it was always the circumflex that was closest. This has implications with regards to the interruption of blood supply in the event of injury to the artery. Damage near the 12, 1 and 2 o'clock positions would be more likely to involve the left main artery, and that would affect blood flow through the anterior interventricular, or left anterior descending (LAD), artery as well as the circumflex. The circumflex artery supplies blood to the left atrium and the posterolateral left ventricle. The LAD supplies blood to the IV septum, the apex of the heart, and approximately half of the left ventricle⁸. Therefore, during an operation on the LAA, damage to the artery after the 2 o'clock position would likely affect blood flow to the left atrium and the posterolateral aspect of the ventricle. Conversely, damage to the artery prior to this point may affect blood flow to the left atrium, the entire left ventricle and part of the IV septum, producing a much more dire situation.

4.2.3 Surgical Closure of the LAA

For patients with AF, the vast majority of blood clots that form in the heart come from the LAA⁴. Because of this, surgical closure of the LAA can be performed, and is done either by exclusion or by excision. Excision is the more popular method^{5,70}, but it can leave a stump with residual volume within, which may be even more thrombogenic and dangerous⁶. A novel method of LAA closure, called pericardial patch exclusion, has been developed in order to overcome this. The patch of pericardium is sutured over the patient's LAA orifice flush with the left atrial wall, so it should leave very little residual volume, if any. In this investigation, 27 cadaveric hearts underwent both conventional epicardial excision (CEE) of the LAA as well as pericardial patch exclusion (PPE) to evaluate which method left less residual volume. CEE was found to have reduced the volume of the LAA to 0.95 ± 1.02 mL (24% of the original), while PPE reduced the LAA volume to 0.17 ± 0.08 mL (4% of the original). Therefore, PPE left a significantly smaller residual LAA volume than CEE, suggesting that it may improve stroke risk in patients with AF.

While the formalin fixation process does not change the size of tissues, it does change their properties. Formalin acts by cross-linking proteins in the treated specimens, and because of this tissue that has been fixed with formalin is generally stiffer and less compliant than fresh tissue. Fresh cadaveric tissue is more comparable to the live tissue that would be encountered in surgery. For this reason, the data from the surgical interventions was stratified into two groups, fixed specimens (n=18) and fresh specimens (n=9). While the same trends that are seen in the overall group (n=27) are seen in both stratified groups, the difference in residual volume left after CEE and after PPE is smaller in the fresh specimen group. CEE managed to remove more of the LAA in this group, probably due to the compliant nature of the tissue. Also, due to the nature of the study, the LAA was more visible and more accessible than it would be in a real surgery. Due to the small sample size of the fresh group, analysis was not carried out on the difference between CEE residual volume and PPE residual volume because there was not enough power to detect significance. According to power a priori power calculations, a sample size of 15 fresh specimens would be required to achieve the power to detect significance. So the collapsed overall results are considered.

According to the results of this investigation, pericardial patch exclusion left a very minimal residual LAA volume of 0.17 ± 0.08 mL. However, the patch that was sewn over the orifice of the LAA appeared to be completely level with the wall of the surrounding left atrium. It is possible that because volume was measured using water and agarose gel, the residual volume that was observed was the result of the surface tension of these materials. Therefore, it may be the case that the actual residual volume left by pericardial patch exclusion was negligible, and that the LAA was virtually eliminated.

Besides leaving less residual volume than epicardial excision, the pericardial patch exclusion technique of LAA closure has several other advantages. One is that it can be performed either via sternotomy or with a minimally invasive approach, using a right minithoracotomy. Epicardial excision on the other hand can only be done via sternotomy. This is important because surgical occlusion of the LAA is often done concomitantly with mitral valve repair⁴⁸, and mitral valve repair is frequently performed via a right minithoracotomy approach⁷³.

The tissue of the left atrium, and especially of the LAA, is very delicate and friable. This can lead to tearing of the tissue and bleeding in LAA operations^{5,61,69}. The fact that the LAA is not resected in pericardial patch exclusion nearly eliminates the risk of bleeding. Furthermore, the pericardium has previously been used as reinforcement for the thin and easily torn LAA tissue during excision procedures⁶⁹. Similarly, our use of pericardium in the patch exclusion technique may attenuate the risk of bleeding from the delicate atrial tissue.

Another advantage of pericardial patch exclusion over epicardial excision is that it leaves the appendage on the heart. The LAA plays an important role in the control of natriuresis through the secretion of atrial natriuretic peptide^{21,22,74}. The fact that PPE leaves the LAA intact and attached might be beneficial because it may help maintain homeostatic regulation of natriuresis and diuresis.

While excision of the LAA is deemed unsuccessful if there is a residual stump, exclusion methods are deemed unsuccessful if blood flow persists between the LAA and the left atrial cavity across the suture or staple line as detected post-operatively by transesophageal echocardiography (TEE) post-operatively^{48,66}. Current exclusion techniques have a higher rate of failure than excision techniques⁵, and this failure may be the result of a couple of factors. Exclusion of the LAA involves bringing two sides of the orifice together and pursing the tissue of the left atrium. This may place tension on the sutures or staples as the orifice naturally begins to return to its original shape, causing dehiscence and recanalization of the LAA⁶². Additionally, because of the proximity of structures such as the circumflex artery that may be injured intra-operatively, shallow suture bites are often taken in order to avoid damaging these structures⁵. This may also lead to the dehiscence that leads to failure of LAA exclusion. Both of these obstacles are overcome by the pericardial patch exclusion technique. Because the patch is cut to the shape of the LAA orifice, the left atrial tissue does not become pursed or bunched, eliminating tension placed on the sutures. Also, owing to the longer suture line and lack of tension, smaller suture bites are more effective at holding the patch in place.

In recent years there has been development of several percutaneous LAA occlusion devices. While these devices show promise in effectively occluding the LAA, there are many potential risks with their use including device embolization, pericarditis, pericardial effusion, cardiac tamponade, and LAA tearing^{55,58}. Also, their actual stroke reduction rates are more modest than anticipated⁵⁵. As such, more investigation must be done before these devices can be used as reliable and effective alternatives to surgical closure of the LAA. The pericardial patch exclusion technique carries far fewer risks than these devices. Since the pericardium is not thrombogenic, as the percutaneous devices are, patients do not have to be placed on dual antiplatelet therapy post-operatively to prevent clotting. Also percutaneous occlusion devices rely on expanding and filling the LAA, but do not take into account the variable morphology of the appendage. Pericardial patch exclusion on the other hand involves covering the LAA orifice, making it suitable for any appendage morphology.

All LAA closure methods have their strengths and their weaknesses. Four of these methods are compared in Table 4.2.3. In terms of the difficulty of performing each procedure, excision and exclusion are relatively easy to perform, while implantation of percutaneous devices and pericardial patch exclusion are more difficult. Excision and percutaneous device closure carry a risk of bleeding, while this risk is negligible for both conventional and pericardial patch exclusion. Infection and erosion are only a concern for percutaneous devices. Patients undergoing percutaneous device closure must remain on dual antiplatelet therapy for six months to prevent thrombogenesis from the device. This is not a concern in the other three methods. Finally, the approach that must be taken for each of the techniques is important. Percutaneous devices are introduced via catheter. The other three methods can be done after a sternotomy. However, only conventional and pericardial patch exclusion can be done with a minimally invasive approach. Looking at the risks and benefits of pericardial patch exclusion, it can be noted that the only disadvantage is that it is more difficult to perform. Aside from that, it seems to be a superior LAA closure technique.

Table 4.2.3 Comparison of four methods of LAA closure.

	Conventional Epicardial Excision	Conventional Endocardial Exclusion	Percutaneous Device Closure	Pericardial Patch Exclusion
Difficulty	+	+	+++	+++
Risk of Bleeding	++	low	+	low
Risk of Infection	0	0	++	0
Risk of Erosion	0	0	++	0
Requirement of Additional Medications	0	0	++	0
Approach	Sternotomy	Sternotomy, Minimally Invasive	Percutaneous	Sternotomy, Minimally Invasive

4.3 Strengths and Limitations

There are several important strengths to this investigation. The use of cadaveric specimens allowed for direct measurements of the dimensions of the LAA, the proximity of the circumflex artery, and residual volume left after intervention. Almost all previous studies on LAA closure have relied on TEE to evaluate operational success, but because of the complex morphology and branching pattern of the LAA, TEE may not be completely accurate¹³. Also, the use of a cadaveric model made it possible for both interventional methods, CEE and PPE, to be performed in each specimen. This allowed each heart to serve as its own control, and effectively doubled the sample size. If a cadaveric model were not used, only one of the two intervention techniques could have been performed in each heart, requiring twice as many subjects to obtain the same results. Another strength of this study is that it is the first to measure the exact distance from the circumflex artery to the base of the LAA, and did so in terms understood by all cardiac surgeons.

This investigation also had some limitations that must be addressed. The first is the sample size of 27 cadaveric hearts. This relatively small sample size limits the robustness of the findings. Furthermore, the properties of fresh cadaveric tissue are more indicative of live tissue, but only nine fresh cadaveric hearts were available for this study. Another limitation is that the use of a cadaveric model precluded the assessment of residual blood flow or leakage between the LAA and the left atrium, which is the mechanism of failure for LAA exclusion techniques. Finally, this study data may have been limited by human error with respect to all of the measurements carried out.

4.4 Future Directions

The main priority of future investigations like this one should be access to a greater number of specimens. Increasing the sample size would increase the robustness and validity of the findings. This is especially true for fresh frozen specimens, since they are more comparable to state of the heart in a live patient. If more fresh specimens were involved in this study, it would likely be possible to detect a significant difference in the residual volume left by CEE and that left by PPE. Further investigation into the effectiveness of the pericardial patch exclusion method and its viability as an alternative to current standards of surgical LAA closure will have to involve evaluation of the technique in live patients. This would allow for assessment of persistent blood flow between the LAA and the left atrial cavity across the patch by transesophageal Doppler echocardiography or CT. Consideration of PPE as an improvement on current methods of LAA exclusion depends on the absence of post-operative flow between the atrium and the appendage. Furthermore, assessment of the patch itself after a period of time will allow appraisal of the integrity of the pericardial tissue and judgment of its ability to withstand the pattern of blood flow through the heart. Long-term follow up in AF patients who have had PPE done will allow for the evaluation of the procedure's ability to reduce stroke risk, which is the goal of any surgical LAA closure. Definitive stroke risk reduction has not been demonstrated for any of the previously discussed forms of LAA closure, but this may eventually be possible. Finally, it may be useful to use resin casting of the LAA in order to gain an appreciation of its internal features. Knowledge of the

internal aspect of the appendage, such as its common branching patterns and number of lobes, may lend itself to the development of more effective occlusion devices.

4.5 Conclusion

The left atrial appendage (LAA) is of great clinical consequence for thrombogenesis in patients with atrial fibrillation (AF), so there is interest in its surgical closure. Current closure techniques are not ideal, and may even put the patient at greater stroke risk than before. A novel method of LAA closure, pericardial patch exclusion, aims to improve upon current methods and completely eliminate the appendage. Any operation on the LAA poses the risk of injury to the circumflex artery, which runs in close proximity to the base of the appendage. This investigation demonstrates that i) the circumflex artery is closest to the base of the LAA at the 4 and 5 o'clock positions and ii) that the novel pericardial patch exclusion technique is significantly more effective at eliminating the LAA than conventional epicardial excision. Pericardial patch exclusion of the LAA shows promise in completely eliminating the LAA, and may be a viable alternative to currently employed surgical techniques. The technique may give surgeons a better tool to help reduce the risk of stroke in patients with atrial fibrillation.

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2013-2015

- Systemic Human Anatomy
- Mammalian Histology
- Gross Anatomy for Medicine Yrs. 1 & 2
- Gross Anatomy for Physical Therapy

Publications:

Malakouti-Nejad, B., Winkler, E., Johnson, M., Catrip, J., Losenno, K., & Chu, M. (2015). Evaluation of Two Methods of Left Atrial Appendage (LAA) Closure and its Proximity to the Circumflex Artery. *The FASEB Journal*, 29(1 Supplement), 552.6.