4-30-2015

Establishing Anatomical Proximity between the Coronary Circumflex Artery and Mitral Valve Annulus: Implications for mitral valve surgery

Eliot Winkler
Western University, ewinkler@uwo.ca

ESTABLISHING ANATOMICAL PROXIMITY BETWEEN THE CORONARY CIRCUMFLEX ARTERY AND MITRAL VALVE ANNULUS: IMPLICATIONS FOR MITRAL VALVE SURGERY

(Thesis Format: Monograph)

by

Eliot Johnathon Winkler

Clinical Anatomy Graduate Program

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

Abstract

The circumflex artery (CX) lies in the left atrioventricular groove, running intimately parallel to the mitral annulus. Thus, unintentional damage to the CX can occur during mitral valve surgery, typically reported in hearts with a left dominant circulation. This study aims to elucidate the anatomical CX-annulus relationship with respect to dominance, and evaluate unintentional CX damage following three surgical repairs. Using cadaveric hearts (n=27), coronary circulation was dissected and dominance assigned. Following a left atriotomy, a clock face was overlaid on the mitral valve (12:00 positioned at A2 leaflet midline) and the CX-annulus distance was measured at each hour. The CX-annulus relationship was closest in left dominant hearts, with most (n=4) having a CX that hugged the posterior length of the annulus, diving deep at 3:00 (before the posterior commissure), a novel finding. Although surgical damage was independent of dominance, mitral valve repairs caused significantly greater severity of damage ($p<0.05$).

Keywords

Coronary circumflex artery, mitral valve annulus, coronary dominance, iatrogenic damage, mitral valve repair

Co-Authorship Statement

This thesis was completed by Eliot Winkler under the supervision of Drs. Marjorie Johnson and Michael Chu. Experiments were designed by M. Chu, and all data collection was performed by E. Winkler and Bayan Malakouti-Nejad. Analysis and interpretation of data was through a collaborative effort between E. Winkler, M. Johnson, and M. Chu. Parts of this thesis will be submitted as a manuscript for publication.

Acknowledgments

Dr. Marjorie Johnson, PhD for her invaluable assistance as my Graduate Affairs Committee member, her support in developing my methodology, and for always being so willing to help with problem-solving during the process. Thank you for your mentorship throughout this program and everything you have taught me.

Dr. Michael Chu, MD, FRCSC for the development of this research project, completing surgical interventions on the cadaveric hearts, and for always providing insight, support, and new opportunities throughout this project. Thank you for all of your mentorship throughout this process.

Bayan Malakouti-Nejad, BSc for being a reliable and hard-working research partner, and for being such an incredible friend and support system to me throughout my MSc.

Dr. Jeevan Nagendran, MD, PhD, FRCSC and Dr. Jorge Catrip, MD, FRCSC for sacrificing nights and weekends to complete the mitral valve surgeries on all of the cadaveric hearts, I am truly grateful.

Haley Linklater and Kevin Walker for their help setting up the Western Gross Anatomy Lab, acquiring demographic information from the donors, and for preparing the cadaveric specimens for my research to be completed.

To the donors and their families, I am forever indebted to the gracious and thoughtful gift your loved ones have provided. I want you to know that their selfless gesture has made a positive contribution to research that will improve the health of future patients.

My Clinical Anatomy colleagues for being a perpetual source of laughter, support, and love throughout the past two years, and for being my second family here in London.

My wonderful family, Mark Allison, and my outstanding friends for their constant support during my research, and for always showing interest no matter how many times they heard the same information.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AHSD – Arteriosclerotic heart disease

COLD – Chronic obstructive lung disease

COPD – Chronic obstructive pulmonary disease

CS – Coronary sinus

CT – Computed tomography

CVA – Cerebrovascular accident

CX – Coronary circumflex artery

FRCSC – Fellow of the Royal College of Surgeons of Canada

LA – Left atrium

LV – Left ventricle

MR – Mitral regurgitation

MS – Mitral stenosis

MV – Mitral valve

MVR – Mitral valve replacement

PMA – Percutaneous mitral annuloplasty

RFA – Radiofrequency ablation

RHD – Rheumatic heart disease

SI – Severity index

TEE – Transesophageal echocardiography

Chapter 1

1 Literature Review

1.1 Relevant Cardiac Anatomy

1.1.1 The Heart

The heart is a four-chambered muscular organ located in the middle mediastinum of the thorax. The heart is enclosed in pericardium, a double-walled fibroserous membrane that allows the heart to beat within a frictionless environment[1]. The wall of the heart consists of three layers, from superficial to deep they are: the epicardium, myocardium, and endocardium. The epicardium consists of a thin external layer of mesothelium, the myocardium is a thick middle layer of cardiac muscle, and the endocardium is an internal layer lining the membrane and valves[2]. The chief function of the heart is to pump blood through the vessels of the circulatory system.

The heart is comprised of four chambers, two atria and two ventricles, with the left and right atria located superior to the left and right ventricles. The right atrium receives oxygen-poor blood, which flows to the right ventricle where it is then pumped through the pulmonary arteries to be oxygenated in the lungs. Oxygen-rich blood returns to the left atrium (LA) of the heart via the pulmonary veins[1]. From here, oxygenated blood enters the left ventricle (LV) and is distributed to the systemic system via the aorta[1]. In order to regulate the movement of blood between

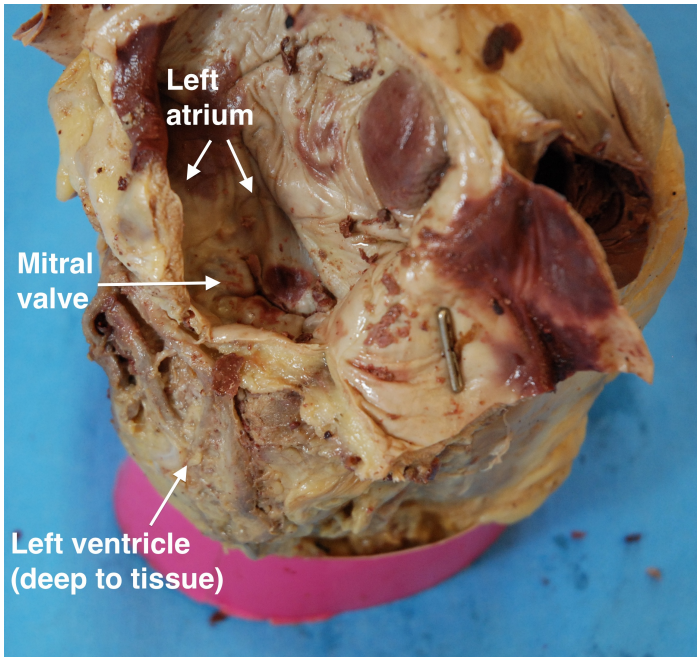

Figure 1.1.1. Posterior view of the heart. Left atrium has been opened to show the mitral valve, which separates the left atrium (superior) from the left ventricle (inferior).

chambers, valves sit between the atria and ventricle on the left and right side and are named the mitral and tricuspid valve, respectively[2] (Fig. 1.1.1). These valves are responsible for maintaining anterograde blood flow during ventricular contraction.

As the heart is a muscle, it requires its own blood supply, and receives vascularization from the only branches of the ascending aorta, the left and right coronary arteries[2]. Much like handedness, coronary circulation is assigned a dominance based on the contribution(s) of the left, right, or both coronary arteries to the posterior interventricular artery, resulting in left dominant, right dominant, or co-dominant circulation, respectively[3].

1.1.2 Coronary Circumflex Artery

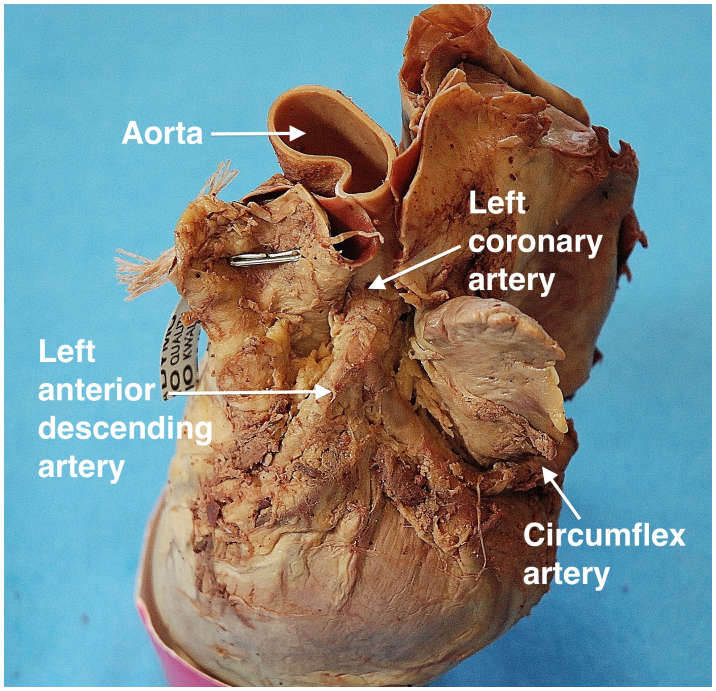

Figure 1.1.2. Left anterolateral view of the heart. The left coronary artery is a branch of the ascending aorta, and bifurcates to form the left anterior descending artery and the circumflex artery.

The coronary circumflex artery (CX) is a terminal branch of the left coronary artery (Fig. 1.1.2). The left coronary artery divides into the anterior interventricular artery (clinically known as the left anterior descending artery) and the CX, which courses towards the posterior aspect of the heart, traveling in the left atrioventricular groove[1] (Fig. 1.1.2). The CX gives off marginal branches along its course, and supplies the posterolateral left ventricle and anterolateral papillary muscles via septal branches[4]. In addition, the CX supplies the sinoatrial node, a specialized bundle of neurons known as the heart's pacemaker, in 38% of people via the sinoatrial nodal artery branch[1].

Following the atrioventricular groove, the CX has been documented to travel on the atrial side, however, occasionally dips onto the ventricular side of the groove[5]. Also traveling in the left atrioventricular groove is the coronary sinus (CS), collecting cardiac venous blood to be returned to the right atrium. The CX is dominant over the coronary sinus in only 0.9% of cases, meaning that the CS is the larger vessel in almost all cases[6]. Although the CS is larger, the CX is closer to the mitral valve 74.6% of the time[6]. Indeed, the CX crossed between the CS and the mitral annulus in 80% of cases[7]. It is well documented, however, that the anatomical relationship between these vessels changes within the cardiac cycle[6,7].

1.1.3 Mitral Valve Apparatus

The mitral valve (MV) apparatus is comprised of a fibrous annulus, anterior and posterior leaflets, atrial myocardium, ventricular myocardium, chordae tendinae, and papillary muscles[4]. The fibrous mitral annulus is part of the cardiac skeleton, which forms and anchors the valves to influence the forces exerted through them. The cardiac skeleton consists of four bands of connective tissue that encircle the bases of the pulmonary trunk, aorta, mitral, and tricuspid valves, and act to separate the atria from the ventricles[1]. The mitral annulus is a flexible structure that anchors the mitral valve attachments, and exhibits changes in its shape during the cardiac cycle[8]. It is oval in shape, with its inter-commissural length being larger than its anterior-posterior length[8]. Although large variation has been observed within and between patients in the annular structure, functionality remains the same[9].

The mitral annulus can be though of as a ring attached to the anterior and posterior mitral leaflets. The anterior (aortic) leaflet is broader than the posterior (mural) leaflet, and extends one-third around the annulus[8]. It is divided into three regions: A1, A2, and A3[8]. The anterior leaflet of the mitral valve is in fibrous continuity with the aortic valve, while the posterior annulus structure is primarily muscular[8]. The posterior leaflet has longer attachments, approximately two-thirds around the annulus, but is much narrower than the anterior leaflet[4]. The posterior leaflet has small indentations around its free edge, dividing it into three more definitive regions: P1, P2, and P3[8]. The P2 section is often variable in size, depending on overall annulus size[8]. There are two distinct areas

in which the leaflets come together at their insertion into the annulus, the anterior commissure and posterior commissure. The anterior commissure is located between A1 and P1, whereas the posterior commissure is located between A3 and P3 (Fig 1.1.3). The coaptation from the two leaflets helps maintain a low mechanical stress during ventricular systole[4,8].

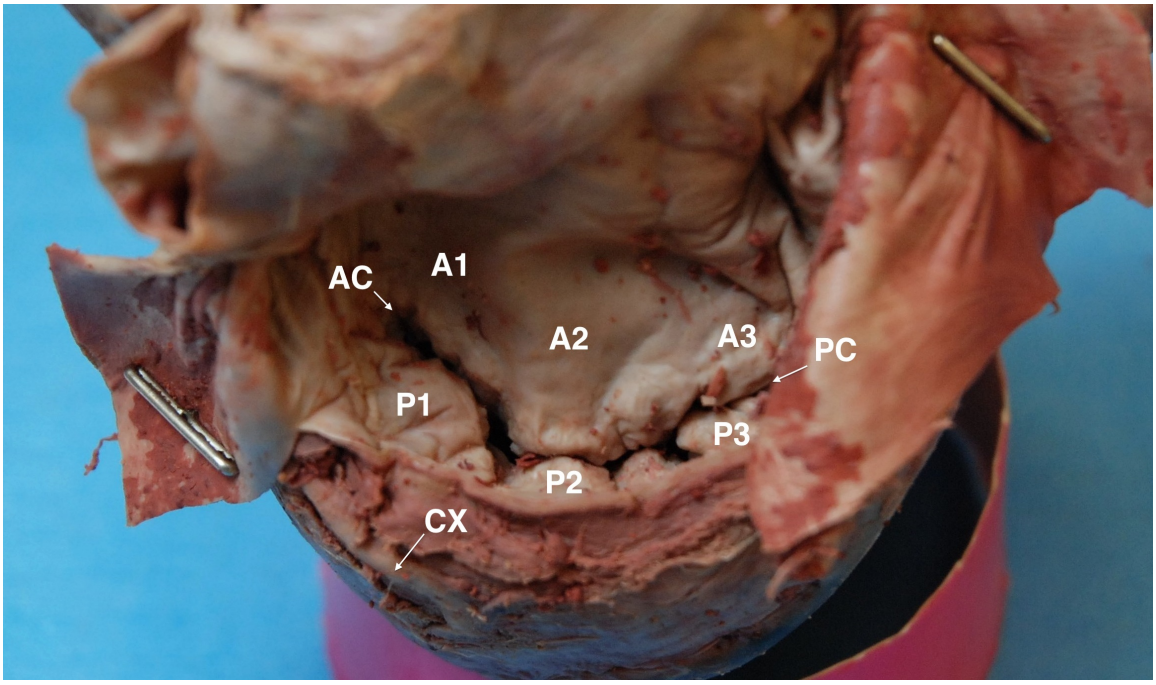

Figure 1.1.3. Superior view of the mitral valve. A1, A2, and A3 of the anterior leaflet and P1, P2, P3 of the posterior leaflet are shown. Between A1 and P1 lies the anterior commissure (AC) and between A3 and P3 lies the posterior commissure (PC). The circumflex artery (CX) can be seen on the posterior aspect.

The anterior and posterior leaflets of the mitral valve are anchored to papillary muscles within the left ventricle by the chordae tendinae[1]. Contraction of the papillary muscles pulls these tendinous cords taut prior to ventricular systole. By maintaining this tension throughout contraction, it allows the mitral valve leaflets to resist the developing pressure from the LV, and prevents the leaflets from being forced into the left atrium[1].

Together these components create the architecture responsible for maintaining mitral valve function and unidirectional blood flow between the left heart chambers.

Physiological deterioration of any structure(s) within this apparatus will result in a mitral valve pathology that must be corrected by mitral valve surgery.

1.2 Mitral Valve Surgery

1.2.1 Mitral Valve Disease

Mitral valve disease can be diagnosed by experienced physicians using a stethoscope to listen to heart sounds, or by using echocardiography[10]. In particular, a special type of echocardiography called transesophageal echocardiography (TEE) is most commonly used, where a small tube with an echo probe on the end is swallowed to assess the mitral valve from inside the esophagus[11,12]. Mitral valve disease is separated into two broad categories: mitral stenosis (MS) and mitral regurgitation (MR). Although MS accounts for <1% of cardiac diagnoses, MR due to MV prolapse affects approximately 5% of the population in the United States[10].

Mitral stenosis is a narrowing of the valve orifice, resulting in decreased blood flow from the left atrium to the left ventricle during ventricular diastole[13]. The primary cause of mitral valve stenosis is rheumatic heart disease (RHD)[13]. While incidences of RHD have fallen dramatically in developed countries, teenagers and adults in Africa, Asia, and the Middle East remain afflicted by this condition[14]. In addition, heavy mitral annular calcification extending beyond the leaflets has been determined to be a risk factor for MS[15]. MS can be corrected via a commissurotomy to remove scar tissue or calcium deposits, a valvuloplasty in which a balloon is inflated to open the valve[10], or using mitral valve replacement to insert a new non-stenotic valve[16]. As the left atrium stretches to accommodate the backup of blood in MS, the electrical pathways that keep the heart rhythm stable may be disturbed, causing abnormal or irregular heart rhythms known as atrial fibrillation[10].

Mitral regurgitation (also called mitral incompetence or mitral insufficiency) is a pathology in which blood flows backwards from the left ventricle to the left atrium during ventricular systole[14]. As a result of this retrograde flow, the heart must work harder to pump the same amount of blood to the systemic circulation. The primary cause of mitral regurgitation has been reported to be degenerative valve disease, wherein

chordal attachments to the mitral leaflets weaken or rupture[17]. Chordal elongation leads to systolic prolapse of one or both of the leaflets into the left atrium[14]. Chordal rupture produces a flail leaflet, which is more likely to cause MR than chordal elongation[14]. The anterior leaflet is less prone to dilation because of its continuity with the aortic valve, whereas in significant mitral regurgitation, the muscular annulus associated with the posterior leaflet dilates due to calcification[8]. In some patients, RHD, coronary artery disease, and dilated cardiomyopathy are attributed to the development of MR[13]. Chronic mitral regurgitation can cause the heart to compensate by increasing the size of the LV[10]. In addition, persistent retrograde blood flow into the left atrium may stretch the chamber, resulting in the same atrial fibrillation pathology observed in MS[14].

In cases of mitral valve disease, surgical intervention is often necessary to restore the valvular apparatus and heart functionality[13]. Replacing the mitral valve entirely or repairing the existing valvular structure through mitral valve surgery achieves restoration of function. Mitral valve surgery is a routine procedure, with 40% of valve operations being mitral valve related[18].

1.2.2 Mitral Valve Replacement

In cases where mitral valve repair is unable to be performed, such as in severe MR or MS, the diseased valve is replaced surgically with either a mechanical valve or a tissue valve. Mechanical valves carry the risk of blood clot formation, and therefore an anticoagulant (such as wafarain) is given in conjunction with this type of replacement[10]. Tissue valve replacements include use of bovine pericardial valves, porcine aortic valves, human dura mater or fascia lata valves[13]. However, tissue valves degenerate over time, and therefore must be replaced in a redo operation. Patient mortality following mitral valve replacement surgery is 3.8%, which doubles to 7.4% in said redo operations[19]. Complications associated with this surgery include atrioventricular groove rupture, CX injury, coronary sinus injury, posterior myocardial perforation, aortic valve cusp entrapment, mitral valve prosthesis leaflet entrapment, ventricular output failure, mechanical valve thrombosis, and/or late cardiac tamponade[20].

1.2.3 Mitral Valve Repair

Mitral valve repair has become the preferred alternative for almost all mitral valve pathologies[4]. The superiority of mitral valve repair over mitral valve replacement is a product of its low operative mortality, decreased valve related complications, preservation of mitral valve function, and improved left ventricular performance[21]. Hospital mortality for MV repair is <1% among advanced repair centres[22]. Complications may include residual mitral stenosis or regurgitation, persistent mitral regurgitation, left ventricular outflow obstruction, and/or hemolysis[20] – much fewer than MVR. The most common technique to repair mitral regurgitation is through a mitral valve annuloplasty, wherein a surgical device is sewn into the mitral annulus to restore mitral valve competence. By forcing the leaflets together, annuloplasty devices decrease annular diameter and increase leaflet coaptation[21]. This restores physiological form and function of the mitral apparatus and prevents future redilation[21].

In an attempt to avoid a median sternotomy, minimally invasive mitral valve repair has become an acceptable standard in some patients for correcting MR. A study of 1339 case reports found that 96% of patients were free from a redo operation 5 years post-repair when minimally invasive MV repair was employed[17]. Minimally invasive MV repair offers the benefits of improved cosmesis, less post-operative pain, less surgical tissue damage, and decreased risk of wound infection[17]. Methods to access the mitral valve using a minimally invasive approach include minithoracotomy, partial sternotomy, or robot-assisted procedures[23]. Percutaneous mitral annuloplasty (PMA) is a method currently under study[24] as a PMA via coronary sinus approach is associated with LV remodeling[6]. LV remodeling is essential to preventing continued dilation, which results in misaligned papillary muscles[4].

1.3 History of Iatrogenic Damage

1.3.1 Introduction

The coronary circumflex artery (CX) lies in the left atrioventricular groove, closely associated with the mitral valve annulus, and often hidden by epicardial fat and fibro-adipose tissue[5,18]. As a result, it is at risk for damage during mitral valve surgery. Iatrogenic damage to the CX can occur as a result of a fixation suture that kinks[25] or occludes[26,27] the artery, laceration of the vessel itself[28], sub-intimal hematoma[29], coronary artery spasm[29], cryoablation from the Maze procedure[30], or radiofrequency ablations to block tachycardia[5]. Following iatrogenic CX damage, patients often present with cardiogenic shock, ventricular arrhythmias, increased cardiac enzymes, and a difficulty weaning off bypass[31]. As a result, close attention to echocardiographic changes is imperative during the immediate post-operative period[32]. Ender *et al.* (2010) have reported a prevalence of iatrogenic damage in 1.8% of all mitral valve repair patients[33].

Regardless of the cause of iatrogenic damage, surgical correction must be completed in the intra-operative, or immediate post-operative, period. Restoration of blood flow is accomplished through a redo operation to remove misplaced stitches or complete a separate mitral valve replacement[28,29,32,34], saphenous bypass distal to the site of injury[30], or placement of a stent[35,36] or balloon angioplasty[37] to widen the lumen of the narrowed CX.

It is important to note that other surgical issues can present as iatrogenic damage to the CX. An air embolism can mimic CX occlusion[33], as some ST segment changes from echocardiography are transient due to intracardiac air following surgery[32]. Coronary embolism can also mimic mechanical injury of CX, producing similar post-operative symptoms[36]. A proper diagnosis can be made with TEE to ensure a correct treatment plan is implemented postoperatively[33].

1.3.2 Initial Surgical Case Reports

Cases of iatrogenic damage to the CX were first reported in three mitral valve replacement patients[38]. All three patients had occlusion of the proximal CX, caused by a

fixation suture approximately 3 cm from its origin, closest to the anterior commissure of the mitral valve. Danielson *et al.* (1967) concluded that iatrogenic damage relates to individual anatomical variation and the degree of calcification in each patient[38]. Indeed, Grande et al. (2006) suggested that heavy calcification of the mitral valve leaflets extending into the annulus and myocardium proves to be a risk factor for iatrogenic damage[15]. Following this initial report, Virmani *et al.* (1982) examined iatrogenic damage in three patients; two patients underwent mitral valve replacement and the third received mitral valve repair via annuloplasty[39]. All three patients were found to have an enclosing or obliterating suture in the proximal CX, approximately 2 cm from the origin. This study was the first to report coronary dominance in concert with iatrogenic damage, documenting that the CX was closest to the mitral valve in hearts with a left dominant or co-dominant circulation[39].

1.3.3 Coronary Dominance Research

The findings of Kaklikkaya & Yehinoglu (2003) were in accordance with the previous report from Virmani *et al.* (1982), establishing that the greatest risk of iatrogenic damage occurs in patients with a left dominant or co-dominant coronary circulation and affects the proximal third of the circumflex artery[40]. It has been shown that the proximal circumflex is wider in left dominant patients, thus increasing its likelihood of iatrogenic damage[41]. However, a report by Pessa *et al.* (2004) suggested that iatrogenic injury was independent of coronary dominance, showing that some right dominant hearts had a CX located very close to the mitral valve annulus[31]. It should be noted that Pessa *et al.* (2004) had a left dominance prevalence of 2.35% from a total of 85 fixed hearts, which is lower than literature reports where left dominance prevalence is approximately 10%[40].

Indeed, a few reports of iatrogenic CX damage in right dominant patients have been documented in the literature. One such case involved a mitral valve replacement resulting in partial injury of the CX, which developed into a vascular malformation due to local haemorrhage[28]. Additionally, sub-occlusion of the distal CX occurred in two separate right-dominant patients undergoing mitral annuloplasty to correct severe MR[15,35]. Distal CX occlusion also occurred in a right dominant heart as a result of torsion from nearby sutures following mitral valve repair to remedy a flail P2 segment[32].

Additionally, the CX can arise from the right coronary sinus. This retroaortic course can compress the CX following aortic valve replacements and can be compressed during exercise with aortic root expansion or as a result of the sharp takeoff angle of the vessel[42-44]. Coronary anomalies such as these, however, occur in only 1% of the population[45].

Although there is some evidence of iatrogenic damage in right dominant patients, the literature predominantly reports iatrogenic damage to the CX in patients with a left dominant or co-dominant coronary circulation. Tavilla & Pacini (1998) reported iatrogenic damage for a left dominant patient undergoing mitral valve repair to correct posterior leaflet prolapse[46], with a similar report documenting kinking in the middle third of the CX[25]. Subsequent to a mitral valve replacement, one patient had total occlusion of the proximal third of the CX[30]. Dramatic distortion of the CX occurred due to malposition of sutures placed in the P2 region[11], with similar entrapment seen in a recent case[37]. Annular decalcification and quadrangular resection of the posterior leaflet occluded the CX[47]. Misplaced sutures during P2 resection with an annuloplasty band caused complete occlusion of the CX in the P2 region[48]. One patient underwent a MVR following dehiscence of an annuloplasty band, experiencing total occlusion of the distal CX[32]. Another patient developed a left atrium fistula, as well as a single occlusion of the mid-CX, after mitral valve repair for severe regurgitation[34]. In 2012, Sheth *et al.* reported the first case of CX perforation as a result of MVR surgery[19]. Finally, a patient with co-dominant circulation experienced occlusion of the mid-distal CX due to an annuloplasty stitch from repair of a ruptured P2 segment[27].

1.3.4 Circumflex-Annulus Anatomical Relationship

In addition to the aforementioned studies by Kaklikkaya & Yehinoglu (2003) and Pessa (2004), several other anatomical studies have been completed to elucidate the circumflex-annulus relationship. A morphometric study completed on the mitral annulus used 8 points around the annulus to measure the distance to the CX, finding that the CX was closest at the anterior commissure, a distance of 3.3 mm away[9]. In recent studies there has been an increase in the prevalence of using computed tomography (CT) software to image and measure this relationship. Using cardiac multidetector CT, the CX was judged to run between the coronary sinus and annulus in 80% of 36 hearts (25

healthy, 11 with severe MR)[7]. In addition, cardiac CT of 70 hearts (40 healthy, 30 with severe MR) showed that a global minimum of <5 mm was common in left dominant patients, and that in these patients the CX was closest at the anterior commissure[5]. Multi-slice CT of 320 PMA patients showed that the CX was located closer to the annulus than the coronary sinus in 74.6% of cases[6]. These results were further supported by a study of 65 fixed cadaveric hearts, in which the CX was found to be closer to the annulus than the coronary sinus, and the CX was observed to overlap the coronary sinus in 70% of cases at the anterior commissure, a frequent site for iatrogenic injury[49].

Chapter 2

2 Introduction

2.1 Background and Motivation

As previously discussed, mitral valve repair has become the preferred alternative to prosthetic valve replacement for almost all mitral valve pathologies[4]. Although mitral valve repair has fewer complications than mitral valve replacement[20], one serious potential complication is iatrogenic occlusion of the circumflex artery, occurring in approximately 1.8% of all mitral valve repair patients[41]. The circumflex artery lies within the left atrioventricular groove, running intimately parallel to the posterior aspect of the mitral annulus. Clinically, this groove is filled with fibro-adipose tissue, making it difficult for surgeons to visualize the corresponding spatial orientation of these vessels[5]. In addition, surgical sutures for MV repair are placed intra-annularly at an angle perpendicular to the CX, thus increasing susceptibility of iatrogenic damage.

Many surgical case reports have cited this complication in left dominant coronary networks, and to the best of our knowledge, only five have documented iatrogenic damage in a right dominant coronary system[15,28,32,35,36]. However, previous anatomical studies have debated whether coronary dominance has an effect on this anatomical relationship, with some suggesting that left or co-dominant circulation exhibits a closer relationship that predisposes patients to a higher risk for damage[40], and others concluding damage is independent of dominance[31]. The latter has been contradicted by a wealth of case reports documenting iatrogenic damage in left dominant systems.

The purpose of this study is to further elucidate the link between coronary dominance and the CX-annulus relationship in a clinically relevant context. By centering our study methodology around standardized cardiothoracic landmarks, anatomical results can easily be interpreted by anatomists and surgeons alike. Ideally, information obtained from surgical interventions will be integrated with anatomical findings, providing further insight into reducing iatrogenic damage of the CX in future mitral valve surgeries.

2.2 Study Objectives

1. Establish a standardized anatomical distance of the circumflex artery to the mitral valve annulus.

2. Evaluate iatrogenic damage resulting from mitral valve repair and replacement surgical techniques.

2.3 Hypothesis

It is hypothesized that the coronary circumflex artery will be located closer to the mitral valve annulus in left dominant or co-dominant hearts, thus making these hearts more susceptible to iatrogenic damage during surgical intervention.

Chapter 3

3 Methods

3.1 Subject Data

For the purpose of this study, 18 (67%) fixed and 9 (33%) fresh cadaveric human hearts were harvested from specimens in the Human Anatomy Lab at the University of Western Ontario. Cadaveric use is in accordance with the Anatomy Act of Ontario and Western's Committee for Cadaveric Use in Research, ethics approval #15052013. Fixed hearts were perfused with a 10% formalin solution to ensure preservation. Fresh-frozen hearts were removed from fresh, non-perfused cadaveric specimens and subsequently frozen in the morgue until they required thawing to perform necessary measurements and surgeries. Mean age was 77.2 ± 12.7 (age range 53-97) years with the study population consisting of 18 (67%) males and 9 (33%) females. Cause of death varied among donors. A detailed list containing all subject data is included in Table 3.1.1.

Table 3.1.1. Subject characteristics (n=27).

Preservation	Gender	Age	Cause of Death
Fixed (n=18)	Male	84	Cardiac Arrest, Congestive Heart Failure, Coronary Artery Disease
	Male	93	Bladder Cancer, COPD
	Male	63	Cardiac Arrhythmia, Complicating Chronic Obstructive Pulmonary Disease
	Female	78	Diffuse Metastatic Cancer (unknown primary), Ulcerative Colitis
	Female	90	Pneumonia, Progressive Supranuclear Palsy
	Female	75	Multiple Myeloma, Chronic Renal Failure
	Male	85	Cerebrovascular Accident, COPD, Peripheral Vascular Disease
	Female	76	Non-Alcoholic Liver Cirrhosis, Non-Alcoholic Steatohepatitis, Atrial Fibrillation, ASHD
	Male	62	Metastatic Melanoma, Melanoma
	Female	93	Breast Cancer, Parkinson's Disease
	Male	97	Dehydration, Bowel Obstruction, Fecal Impaction, CVA, Hypertension
	Male	87	Fractured Left Hip, Cancer of the pancreas
	Male	69	End Stage Chronic Obstructive Lung Disease
	Female	89	CVA, COLD, Congestive Lung Failure
	Male	53	Carcinoma of the Bladder
	Female	73	Breast Cancer
	Male	80	Parkinson's Disease, illegible, Ischemic Heart Disease
	Male	90	Pneumonia, Depression, Ischemic Heart Disease
Fresh-Frozen (n=9)	Male	55	Possible Pneumonia, Severe COPD, Oxygen Dependency, Lung Cancer
	Male	79	Coronary Artery Disease, Diabetes, Syncope, Transient Ischemic Attacks, Sudden Cardiac Arrest
	Male	87	Coronary Artery Disease, Congestive Heart Failure, Atrial Fib, Hypertension
	Female	70	Brain Metastases, Lung Cancer, Breast Cancer
	Male	65	Cardiac Arrest, Coronary Artery Disease, Hypertension, Bladder Cancer
	Male	84	Acute Uremia, Dementia, Chronic Obstructive Lung Disease
	Male	66	Acquired Brain Injury
	Female	55	Pneumonia, Right Pan Coast Lung Tumor
	Male	85	Cancer of the Lung, Dementia

3.2 Study Design

The following methodology was performed on all hearts within this study (n=27). The CX was dissected from epicardial fat and differentiated from the coronary sinus in

the left atrioventricular groove. Methodology for establishing coronary dominance was consistent with the National Heart, Lung, and Blood Institute's definition used in previous studies[15,40], wherein contributions from the left and/or right coronary artery to the posterior interventricular artery results in left, co-dominant, or right dominance, respectively[3].

A left atriotomy was performed in which a longitudinal incision was made down the midline of the posterior atrial wall, between the pulmonary veins, abutting at the level of the mitral annulus. Subsequent perpendicular incisions at the inferior aspect of the longitudinal incisions created two flaps that exposed the mitral valve leaflets and annulus (Fig. 3.2.1).

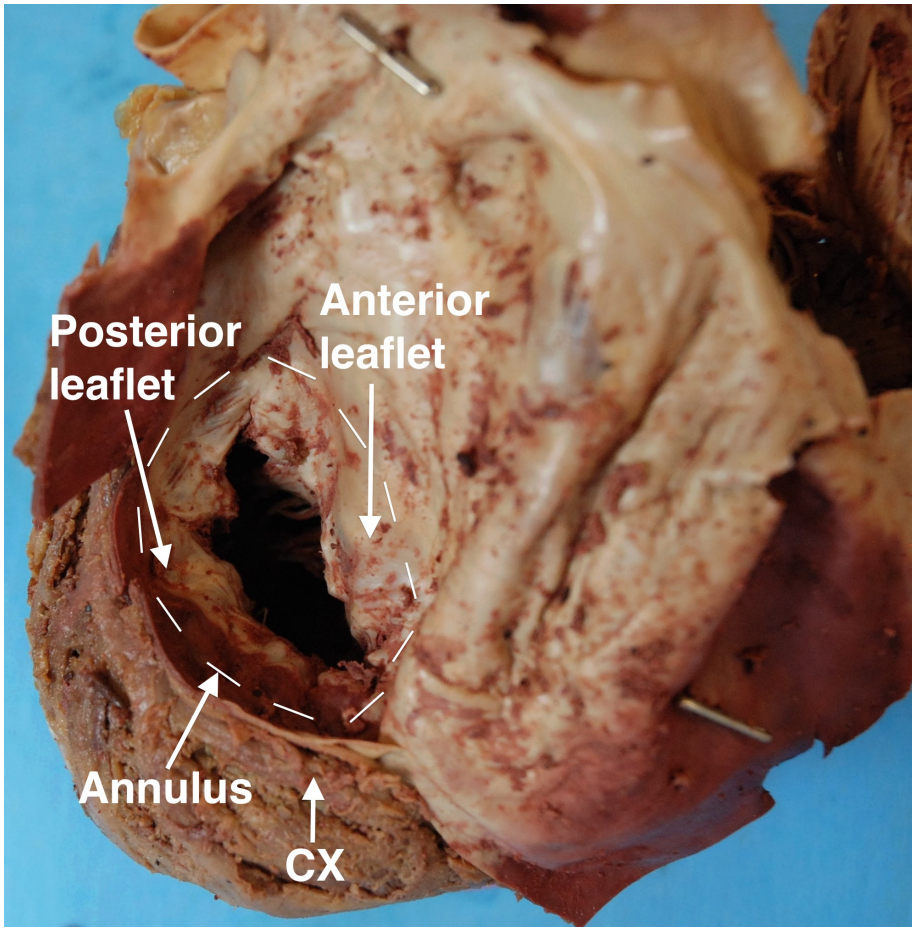

Figure 3.2.1. Superior anterolateral view of the mitral valve annulus and leaflets, exposed following left atriotomy.

3.3 Measurement Techniques

Following a left atriotomy, three measurements were performed to characterize the mitral valve annulus: anterior-posterior length, inter-commissural length, and circumference. Anterior-posterior length was measured from A2 leaflet midline to P2 leaflet midline and inter-commissural length was measured from the anterior commissure to the posterior commissure (Fig. 3.3.1A). Annulus circumference was measured by using a string to outline the annulus, followed by measuring the resulting length of string.

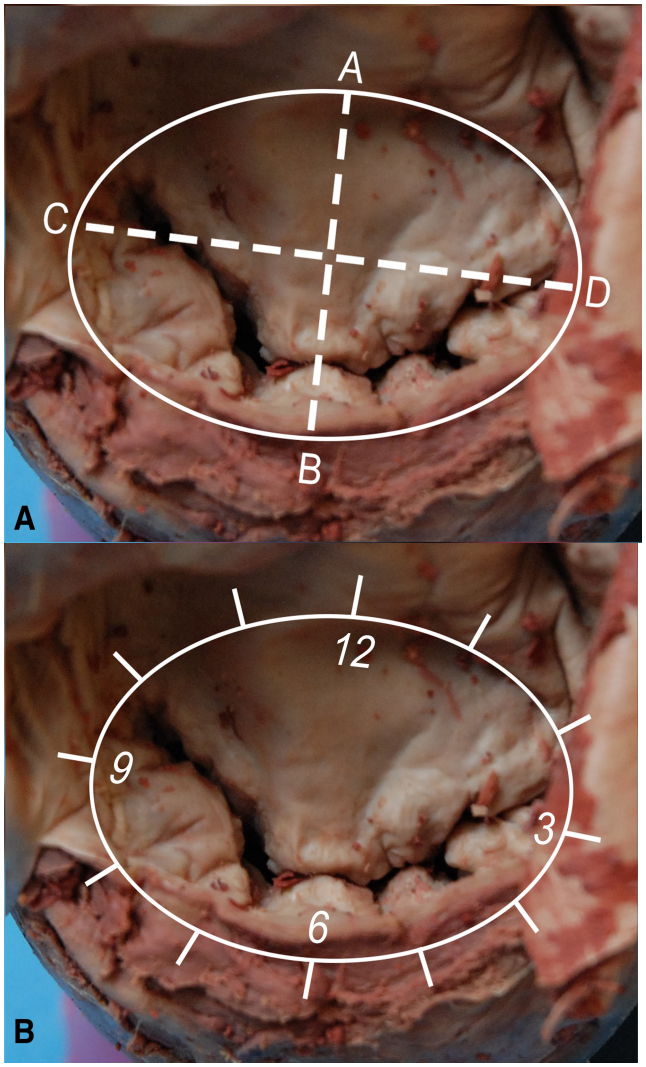

Figure 3.3.1. A. The mitral annulus was measured across the anterior-posterior dimension (A-B) and the inter-commissural dimension (C-D). Circumference was measured using string, as described in the methods. **B.** Distance between the circumflex artery and the annulus was measured at each hour on a surgically relevant clock face.

In order to report anatomical data in a clinically relevant context, a standardized clock face used in cardiothoracic surgery was visually overlain on the mitral valve annulus. 12:00 was placed at the A2 leaflet midline and 6:00 at the P2 leaflet midline, with the anterior and posterior commissures located at approximately 10:00 and 2:00, respectively (Fig 3.3.1B). The distance between the CX edge and the mitral valve annulus was measured at each hour on the clock face where the artery was present. All measurements were performed by two separate raters to the nearest 0.01 mm using a digital vernier caliper and averaged for a final value.

3.4 Mitral Valve Surgeries

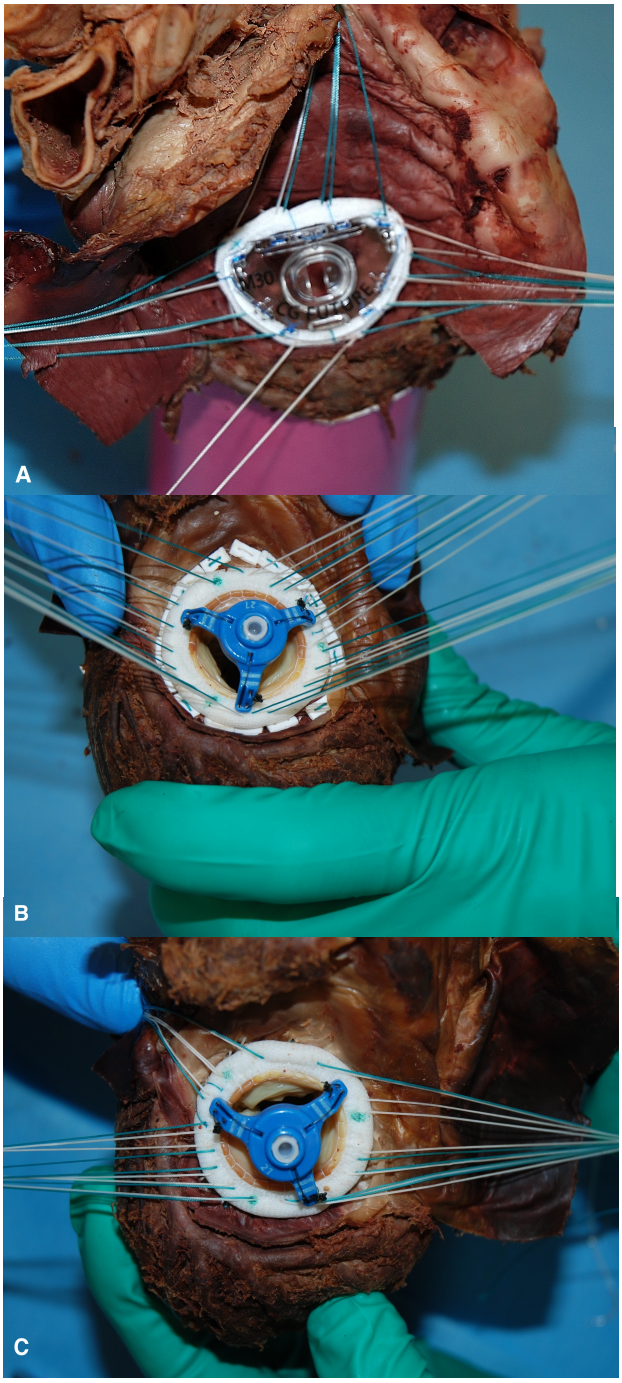

Figure 3.4.1. Three surgical procedures performed on all hearts. **A.** Mitral valve repair via annuloplasty ring. **B**. Mitral valve replacement with everting sutures. **C.** Mitral valve replacement with inverting sutures.

Following anatomical measurements, three different surgical repairs were performed on each heart: a mitral valve repair, a mitral valve replacement with everting sutures, and a mitral valve replacement with inverting sutures. A total of 81 procedures (3 x n=27) were completed. Mitral valve repair was completed using an annuloplasty ring. Mitral valve replacements were completed using everting plegeted sutures (pledgets placed on the atrial side of the MV) or inverting plegeted sutures (pledgets placed on the ventricular side of the MV; Fig 3.4.1). Three cardiothoracic surgeons certified by the Fellow of the Royal College of Surgeons Canada (FRCSC) collectively performed the 81 surgeries completed in this study.

After each surgical repair, damage to the CX was assessed at each hour it was present on the MV clock face using a four-point index, increasing in severity from 1 to 4 (Fig 3.4.2). A value of 1 indicated no damage to the CX, while a value of 4 indicated complete occlusion of the CX. The detailed severity index (SI) is outlined in Table 3.4.1.

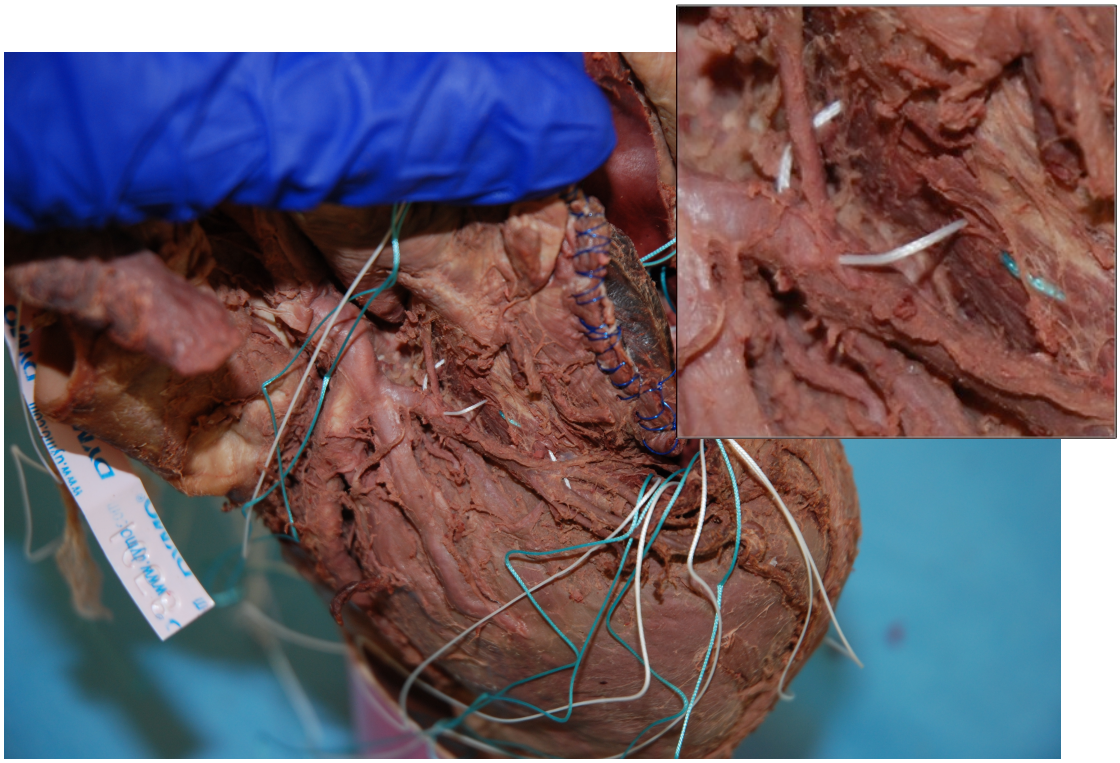

Figure 3.4.2. Following each surgical intervention, severity of iatrogenic damage to the CX was assessed at each hour of the clock face the artery was present using a four-point index. SI value seen in the inset was 3, indicating laceration to the CX.

Table 3.4.1. Severity index used for quantifying damage done to the circumflex artery.

Index Value	Description of Damage
1	There is no risk of the suture damaging the artery
2	The suture is in the tissue adjacent to the artery
3	The suture has pierced the edge of the artery
4	The suture has encircled and occluded the artery

3.5 Statistical Analyses

All data analyses were completed with SPSS software version 22[50]. Continuous data are presented as mean ± SD, unless otherwise specified. For ease of interpretation, the one co-dominant heart in our study has been grouped with the left dominant hearts as it exhibits a contribution from the left coronary artery to coronary dominance.

Due to the evident trend and small group size of left dominant hearts (n=5), this data was removed to perform anatomical statistical analysis. As a result, only right dominant hearts (n=22) were used in statistical analysis of the CX-annulus relationship. Following a Shapiro-Wilks test, data was shown to not have a normal distribution for 5/7 clock hours ($p<0.05$). Therefore, a non-parametric Kruskal-Wallis H test was performed to determine statistically significant differences in the CX-annulus distance between clock hours. A Wilcoxon signed-rank post-hoc test with Bonferroni correction was completed to assess statistically significant differences between specific clock hours. Statistical power (1-β) of this test was calculated using the G*Power 3 software program[51]. Inter-rater reliability was calculated to determine absolute agreement between the two raters across all anatomical measurements. Inter-rater reliability was significant, with an absolute agreement value of 0.996 ($p<0.001$).

Right (n=22) and left (n=5) dominant hearts were then combined for surgical data analysis, as observation of the data yielded no common trends in frequency or severity of damage between coronary dominance. As surgical interventions used ordinal data to rank the risk of damage to the CX, non-parametric assessments were required to test for statistical significance. A Friedman test was used to calculate significant differences in iatrogenic damage across the three different surgical interventions. Following this, Wilcoxon signed-rank post-hoc tests with Bonferroni correction were used in order to identify significance between specific surgeries. To determine significant differences in iatrogenic damage levels between clock hours within each surgical intervention, a Kruskal-Wallis H test was performed, followed by a Wilcoxon signed-rank post-hoc test with Bonferroni correction for each of the three surgeries.

Chapter 4

4 Results

4.1 Mitral Valve Annulus Characterization

Males had larger average values across all mitral valve measurements compared to females, most notably in terms of annulus circumference (Table 4.1.1). Across all hearts (n=27), average anterior-posterior length was found to be 19.62 ± 4.89 mm, with an average inter-commissural length of 37.18 ± 4.71 mm, and an average annulus circumference of 101.23 ± 13.61 mm.

Table 4.1.1. Anatomical characterization of the mitral valve.

Heart Groups	Anterior-posterior length (mean [mm] ± SD)	Inter-commissural length (mean [mm] ± SD)	Annulus circumference (mean [mm] ± SD)
Male, Fixed (n=11)	23.87 ± 4.59	38.09 ± 3.81	106.72 ± 11.72
Male, Fresh (n=7)	16.83 ± 1.40	40.14 ± 4.64	107.75 ± 11.49
Female, Fixed (n=7)	16.59 ± 3.23	33.38 ± 4.49	87.47 ± 10.13
Female, Fresh (n=2)	16.64 ± 0.74	35.13 ± 1.49	96.40 ± 5.94
Total (n=27)	19.62 ± 4.89	37.18 ± 4.71	101.23 ± 13.61

4.2 Circumflex Artery-Annulus Relationship

4.2.1 Overall Circumflex Artery-Annulus Relationship

At almost all hours on the mitral clock face, the average distance between the CX and the mitral valve annulus was shorter in fresh hearts compared to fixed hearts (Table 4.2.1). In terms of gender differences, females had shorter average distances than males across all hours (Table 4.2.1). The CX was closest to the mitral valve annulus across all hearts (n=27) at the 8:00 position, with an average proximity of 1.91 ± 2.01 mm. The frequency of coronary dominance in our study was 22 (81.5%) right dominant, 4 (14.8%) left dominant, and 1 (3.7%) co-dominant.

Table 4.2.1. Mean distance (mm ± SD) between the circumflex artery and the mitral valve annulus at each hour on the standardized mitral valve clock face.

	11:00 (mean [mm] ± SD)	**10:00 (mean [mm] ± SD)**	**9:00 (mean [mm] ± SD)**	**8:00 (mean [mm] ± SD)**	**7:00 (mean [mm] ± SD)**	**6:00 (mean [mm] ± SD)**	**5:00 (mean [mm] ± SD)**	**4:00 (mean [mm] ± SD)**	**3:00 (mean [mm] ± SD)**
Fresh, Left Dom.* (n=2)	-	7.79 ± 0.22	1.29 ± 0.75	0.46 ± 0.35	0.42 ± 0.02	0.40 ± 0.16	0.53 ± 0.02	0.56 ± 0.27	1.44 ± 0.96
Fixed, Left Dom. (n=3)	-	11.48 ± 1.13	3.46 ± 3.73	1.90 ± 2.18	1.30 ± 0.97	1.21 ± 0.49	1.14 ± 0.81	1.25 ± 0.87	1.90 ± 1.77
Fresh, Right Dom. (n=7)	12.77 ± 7.86	10.09 ± 3.91	2.01 ± 2.37	0.90 ± 0.82	1.10 ± 1.10	1.28 ± 1.18	1.03 ± 0.20	1.18 ± 0.00	-
Fixed, Right Dom. (n=15)	-	8.51 ± 3.48	3.64 ± 1.54	2.57 ± 2.29	3.53 ± 3.24	5.35 ± 5.38	3.68 ± 2.58	4.80 ± 3.86	-
Total (n=27)	12.77 ± 7.86	9.10 ± 3.40	3.02 ± 2.10	1.91 ± 2.01	2.42 ± 2.76	3.40 ± 4.49	2.19 ± 2.22	2.67 ± 3.14	1.67 ± 1.19

*One heart showing co-dominance has been included with the fresh, left dominant heart group for statistical purposes, due to the presence of a contribution from the left coronary artery to the posterior inter-ventricular artery.

4.2.2 Right Dominant Circumflex Artery-Annulus Relationship

A Kruskal-Wallis H test showed a statistically significant difference in distance between clock hours ($X^2(7) = 42.804$, $p<0.05$, $(1-\beta)=0.748$). A Wilcoxon signed-rank post-hoc test with Bonferroni correction showed a significant difference in distances between the 10:00 position and all positions between 9:00-5:00 (Z scores and adjusted *p* values reported in Table 4.2.2). Interestingly, the average distance at 10:00 was closer than in left dominant hearts (Fig. 4.2.1). Fixed right dominant hearts displayed the largest average distances across the 9:00-4:00 positions (Table 4.2.1). Two fresh right dominant hearts had a circumflex artery that was present at the 11:00 position, averaging 12.77 ± 7.86 mm from the mitral valve (Table 4.2.1).

Table 4.2.2. Results of the Wilcoxon signed-rank test for differences in CX-annulus distance between clock hours in right dominant hearts (n=22).

Pairwise Comparison	Z Score	*p* value	Adjusted *p* value (Bonferroni correction)
9:00-10:00	-3.920	<0.0001	0.006*
8:00-10:00	-5.569	<0.0001	<0.0001*
7:00-10:00	-5.047	<0.0001	<0.0001*
6:00-10:00	-4.041	<0.0001	0.004*
5:00-10:00	-3.432	0.001	0.04*

**p* values were deemed to be statistically significant (<0.05).

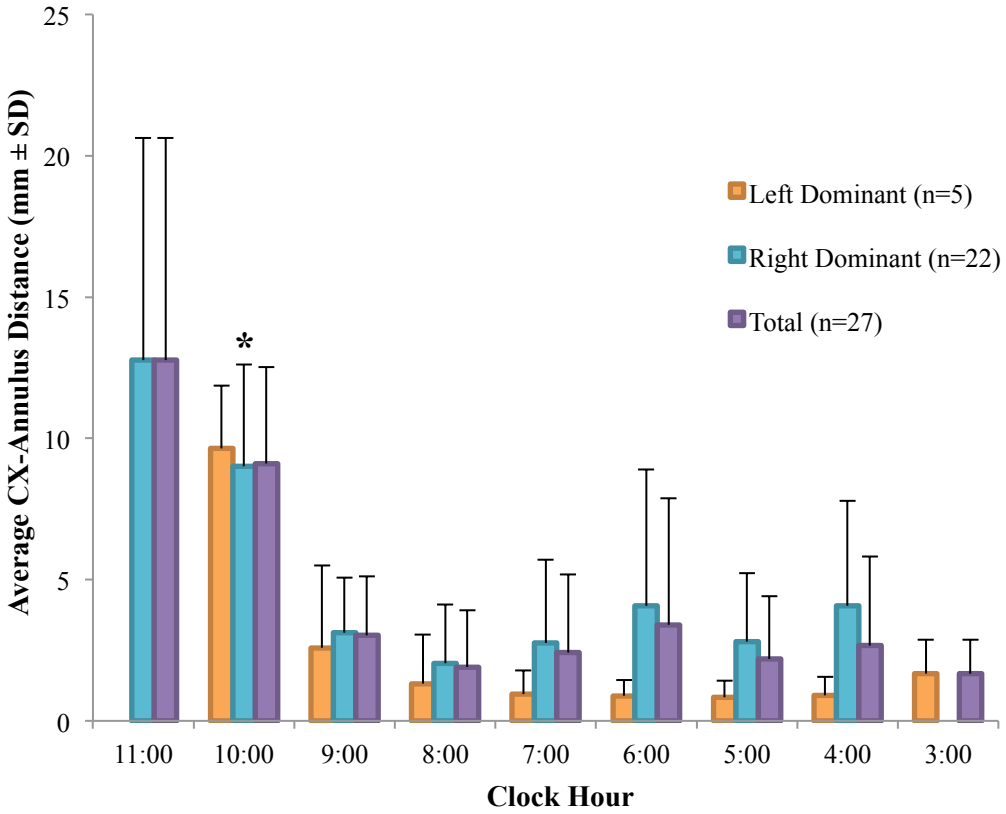

Figure 4.2.1. Average CX-annulus distance (mm ± SD) across all mitral valve clock hours for left dominant (n=5), right dominant (n=22), and total (n=27) hearts. The asterisk indicates a clock hour that is significantly different from other hours (p<0.05).

4.2.3 Left Dominant Circumflex Artery-Annulus Relationship

Fresh left dominant hearts showed the shortest average distances between the circumflex and the mitral valve at all hours, except 10:00 (Table 4.2.1). Additionally, most left dominant (n=3) and one co-dominant (n=1) heart had a circumflex artery that

hugged the mitral valve annulus along the posterior aspect, reaching the 3:00 position before diving deep to perfuse cardiac tissue. At 3:00, the average distance between the CX and the mitral valve annulus in these hearts was 1.67 ± 1.19 mm, closer than the proximity of 1.91 ± 2.01 mm previously seen at the 8:00 position across all hearts (Fig. 4.2.1). All fresh, left dominant hearts (n=5) had an average distance of <1 mm between the 8:00-4:00 position, with the closest average distance being 0.40 ± 0.16 mm at 6:00 (Table 4.2.1).

4.3 Surgical Interventions

4.3.1 Mitral Valve Repairs

A Friedman test of severity of damage across surgeries yielded a borderline statistically significant result ($X^2(2) = 5.953$, $p=0.051$). Wilcoxon signed-rank post hoc tests conducted with a Bonferroni correction applied showed a significant difference in severity of damage between mitral valve repairs and mitral valve replacements with everting sutures ($Z = -2.518$, $p<0.0167$). Mitral repairs resulted in damage between the 7:00-9:00 positions, with the greatest risk of injury at 9:00 (Fig. 4.3.1). There was potential suture injury to the circumflex artery occurring 3/27 (11%), 5/27 (19%), and 6/27 (22%) of the time at 7:00, 8:00, and 9:00, respectively. A Kruskal-Wallis H test yielded a statistically significant difference in severity of damage between clock hours in mitral valve repairs ($X^2(8) = 16.505$, $p<0.05$). Wilcoxon signed-rank tests yielded statistically significant differences between 9:00 and 8:00 compared to other clock hours (Z scores and adjusted *p* values reported in Table 4.3.1), however, following a Bonferroni correction these differences were no longer statistically significant. Across all sutures at the 9:00-7:00 positions, partial thickness (value of 3) of the CX was observed 7/81 (9%) of the time. Indeed, half (7/14) of the potential injuries recorded (SI value>1) from all MV repairs were assigned an SI value of 3.

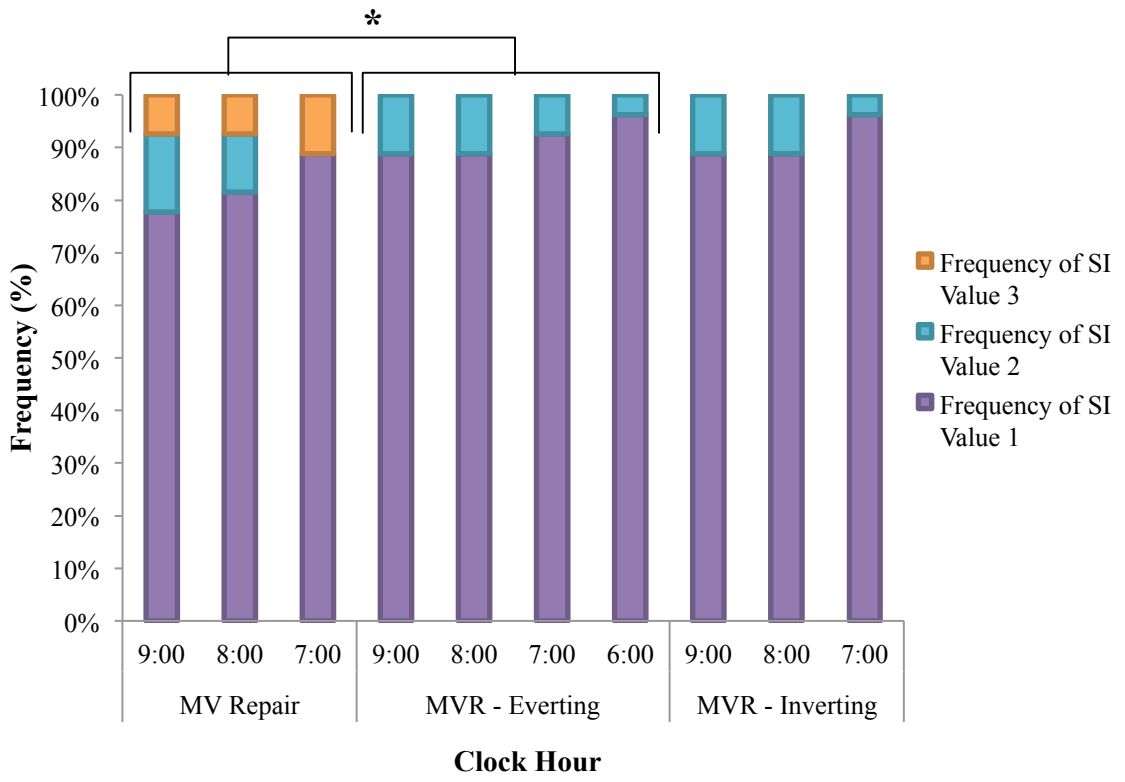

Figure 4.3.1. Frequency (%) of SI values documented at affected hours across all three mitral valve surgeries. The asterisk indicates a significant difference in the severity of damage between two surgeries (p<0.05).

Table 4.3.1. Results of the Wilcoxon signed-rank test for differences in severity of damage between clock hours in mitral valve repairs.

Pairwise Comparison	Z Score	*p* value	Adjusted *p* value (Bonferroni correction)
10:00-9:00	2.800	0.005	0.337
6:00-9:00	-2.743	0.006	0.402
5:00-9:00	-2.279	0.023	1
4:00-9:00	-1.999	0.046	1
10:00-8:00	2.348	0.019	1
6:00-8:00	-2.299	0.021	1

4.3.2 Mitral Valve Replacements with Everting Sutures

Mitral valve replacement with everting sutures had potential damage occurring between the 6:00-9:00 positions, with the greatest risk of injury at 8:00 and 9:00 (Fig. 4.3.1). There was potential suture injury to the CX occurring 1/24 (4%), 2/27 (7%), 3/27 (11%), and 3/27 (11%) of the time at 6:00, 7:00, 8:00, and 9:00, respectively. A Kruskal-Wallis H test did not yield a statistically significant difference in severity of damage

between clock hours in mitral valve replacement with everting sutures ($X^2(8) = 6.458$, p=0.596). All potential injuries observed in this surgery were a result of a suture piercing the tissue adjacent to the CX (SI value of 2).

4.3.3 Mitral Valve Replacements with Inverting Sutures

Mitral valve replacement with inverting sutures had potential damage occurring between the 7:00-9:00 positions, with the greatest risk of injury at 8:00 and 9:00 (Fig. 4.3.1). There was potential suture injury to the CX occurring 1/27 (4%), 3/27 (11%), and 3/27 (11%) of the time at 7:00, 8:00, and 9:00, respectively. A Kruskal-Wallis H test did not yield a statistically significant difference in severity of damage between clock hours in mitral valve replacement with inverting sutures ($X^2(8) = 7.994$, p=0.434). All potential injuries observed in this surgery were a result of a suture piercing the tissue adjacent to the CX (SI value of 2).

4.3.4 Summary of Surgical Results

The greatest frequency and recorded severity of damage was seen in mitral valve repairs. Complete occlusion of the CX (SI value of 4) was never observed across all three surgeries. The CX was most likely to be damaged at the 9:00 position, with a total of 12/81 (15%) recorded instances of potential damage across all three surgeries (Fig. 4.3.1). Potential CX damage (SI value>1) was not observed at the 3:00-5:00, 10:00, or 11:00 positions.

Chapter 5

5 Discussion

5.1 Anatomical Significance

Characterization of the mitral valve annulus resulted in values consistent with the literature. The fibrous annulus is variable between patients and the anterior-posterior dimension tends to be very short in some cases[9], with the shortest value in our study recorded at 11.89 mm. The anterior-posterior dimension is estimated to typically be 75% of the inter-commissural dimension[52], although this ratio was determined to be 53% across all hearts (n=27) in our study (19.62 mm to 37.18 mm). Males had larger values than females across all MV measurements, a sex difference frequently observed in anatomical research.

In our study, fresh-frozen hearts displayed consistently shorter distances compared to fixed hearts. This indicates that the fixation process changes the relationship between the CX and the annulus, perhaps due to a shortening of the myocardium length, or through distortion of the vessel as a result of congealed blood. Fixed hearts have proven to be a viable model for examining this anatomical relationship[31,49], and are therefore included in the interpretation of our results.

There is much debate regarding the frequency of coronary dominance within the population. Reports range from 58% right dominant, 10% left dominant, and 32% co-dominant[40], to 81.17% right dominant, 2.35% left dominant, and 16.47% co-dominant[31]. The coronary dominance frequency reported in our study is consistent with that of Angelini and colleagues (2002), where upon reviewing 1,950 coronary angiograms established the frequency of coronary dominance as 89.1% right dominant, 8.4% left dominant, and 2.5% co-dominant within their study population[45].

The CX is frequently documented as closest to the annulus at the anterior commissure[5,9], with many case reports detailing occlusion of the CX at this same point[26,38,39,53]. Due to this close relationship to the anterior commissure, and the

observation that the proximal CX tends to be wider in left dominant hearts[41], many case reports highlight the proximal CX as the area with the greatest risk for iatrogenic damage[30,35,40,54]. In our study, the distances at the anterior commissure (10:00 position) were not the closest reported distances across all hours. In fact, the 10:00 position was significantly different ($p<0.05$) from all other hours in right dominant hearts, indicating that the CX was much further from the annulus at this hour compared to the rest. Interestingly, 10:00 was the only hour in which the CX was closer to the annulus in right dominant hearts compared to left dominant hearts. Indeed, some have argued that damage is independent of dominance at the P1 leaflet[54]. However, average distances dramatically decreased at the 9:00 position, indicating a closer approach of the CX to the mitral annulus between the 10:00 and 9:00 positions. This transition zone between the 10:00 and 9:00 positions may in fact be the area where iatrogenic damage was observed in the aforementioned case studies, although damage may have been documented as being at the AC. The closest relationship across all hearts (n=27) was at 8:00, with a distance of 1.91 ± 2.01 mm, and is consistent with reports of damage or occlusion to the proximal circumflex artery[19,26,28,30,35,42,54.]

The notion that coronary dominance has an effect on the proximity of the CX to the mitral annulus has been deliberated in previous anatomical studies. Kaklikkaya & Yenigolu (2003) concluded that distances between the CX and the fibrous annulus have a direct relationship with coronary dominance. In their study, left dominant circulation had distances closer than both right and co-dominant hearts, with the circumflex being as close as 1 mm to the annulus in some cases. This is consistent with our data, where the average distance between the circumflex and the mitral annulus was <1 mm from the 8:00-4:00 position across all fresh left dominant hearts. Moreover, an average distance of <1 mm was only seen at the 8:00 position in fresh right dominant hearts.

However, Pessa *et al.* (2004) concluded that the circumflex-annulus distance is not related to the pattern of coronary network dominance. To the best of our knowledge, there are only 5 reports documenting iatrogenic damage in a right dominant system[15,28,32,35,36]. Pessa and colleagues (2004) reported right dominant hearts with a minimum distance of 1.01 mm between the CX and the annulus. This is in stark contrast

to the results from our study, in which fixed, right dominant hearts had the largest average distances between the 9:00-4:00 positions, indicating that right dominant hearts would be at a lower risk for iatrogenic damage during surgery. Indeed, left dominant hearts were consistently closer to the mitral annulus than right dominant hearts across all hours except 10:00. In two fresh, right dominant hearts, the circumflex artery had branched quite proximally from the left coronary artery origin, and was present at the 11:00 position, averaging 12.77 ± 7.86 mm away from the mitral annulus. These results support the notion that left dominant hearts should exhibit a closer CX-annulus relationship.

Left dominant hearts had shorter average distances between the CX and the annulus across all hours in our study, except 10:00. Virmani *et al.* (1982) found that in their three case reports, the left or co-dominant hearts had a CX consistently closer than right dominant hearts, as close as 3-3.5 mm from the annulus. In addition, Kaklikkaya & Yehinoglu (2003) found that the circumflex was always closer than right or balanced dominance at all five points measured around the mitral valve annulus. Moreover, Ghersin and colleagues (2013) displayed that patients with left dominant circulation had smaller global minimum distances between the circumflex artery and the annulus.

The single closest average proximity across all hearts was 0.40 ± 0.16 mm at 6:00 in fresh left dominant hearts. This is consistent with a report by Ghersin *et al.* (2013) where the left dominant CX had a secondary zone of closeness located at approximately 6:00 (midline of the P2 leaflet). Indeed, Kaklikkaya & Yeniglou (2003) discovered that only in left dominant circulation was the circumflex artery located at 6:00 in their cadaveric hearts. Spencer *et al.* (2014) showed that the circumflex artery wraps around the posterior aspect of the mitral valve further in left dominant circulation. Moreover, damage at the P2 leaflet was most frequent in left dominant hearts, indicating that a left dominant system maintains a closer circumflex-annulus relationship[54]. These reports support our findings of a left dominant circumflex artery traveling further along the posterior aspect of the mitral valve. However, our finding of the circumflex artery reaching 3:00 in left dominant and co-dominant hearts, just posterior to the posterior commissure, has been previously unreported in the literature. At 3:00 the average

distance was 1.67 ± 1.19 mm, closer than the shortest distance seen across all hearts at 8:00 (1.91 ± 2.01 mm).

This novel finding advocates for cautionary suture placement in areas formerly considered to be at low risk for damage during mitral valve surgery. Mitral valve repair and arrhythmia surgery utilizes a left atrial isthmus ablation line that crosses the posterior aspect of the mitral annulus at approximately 4:00/5:00, where it is well believed to be a safety zone for CX ablation (Fig. 5.1.1). Our study refutes this by indicating ablation would be augmented in patients with a left dominant circulation. Recognition of this risk of CX damage is evident in modified techniques in which radiofrequency ablation (RFA) is performed between the left pulmonary veins and mitral annulus more distally over the atrioventricular groove after the terminal CX has left the groove[55]. One report detailed a case in which stenosis of the CX was due to multiple RFA procedures: an initial procedure that resulted in thinning of the tissue surrounding the CS (shortening the CX-CS distance), and a subsequent redo procedure that caused CS ablation and the resulting CX stenosis[56]. Another clinical study of mitral isthmus ablation showed acute sub-clinical injury of the CX in 28% of cases, with shorter distances between the CS and CX associated with a

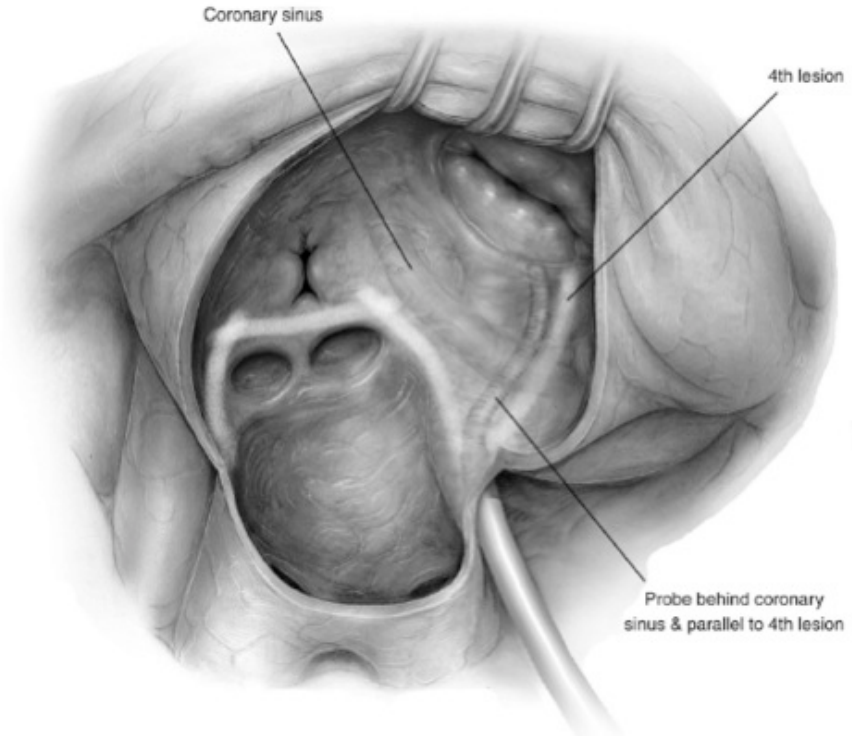

Figure 5.1.1. Cardiac ablation of the mitral valve isthmus between the 4:00/5:00 position in a procedure to correct atrial fibrillation. This ablation would put left dominant hearts in our study at a greater risk of damage, due to the close relationship between the CX and annulus until the 3:00 position. Picture used with permission from Dr. Michael Chu (2011).

greater risk of injury[57]. Indeed, caution in using excess radiofrequency energies during percutaneous RFAs has been advocated in recent studies[5,49]. Measures such as preoperative coronary angiography are imperative for assessing the coronary dominance pattern of the patient[36,58] and implementing additional caution in left or co-dominant patients, especially in light of our findings.

5.2 Clinical Significance

Differences in suturing techniques between mitral valve repair and replacements are responsible for putting the CX at a greater or lesser risk of injury, respectively. MV repair sutures are placed intra-annularly at an angle that often runs parallel to the CX. However, the suture-CX orientation changes at the hour where the CX approaches or departs from the mitral valve. Approach across all types of coronary dominance occurs most often at the anterior commissure (10:00 position), a site where occlusion is frequently documented[26,38,39,53]. Departure of the vessel in left dominant hearts in our study was mostly at the 3:00 position, however, the departure hour is variable in right dominant hearts. Therefore, in left dominant hearts, this change of orientation is seen at the 10:00 position and again at the 3:00 position (Fig.

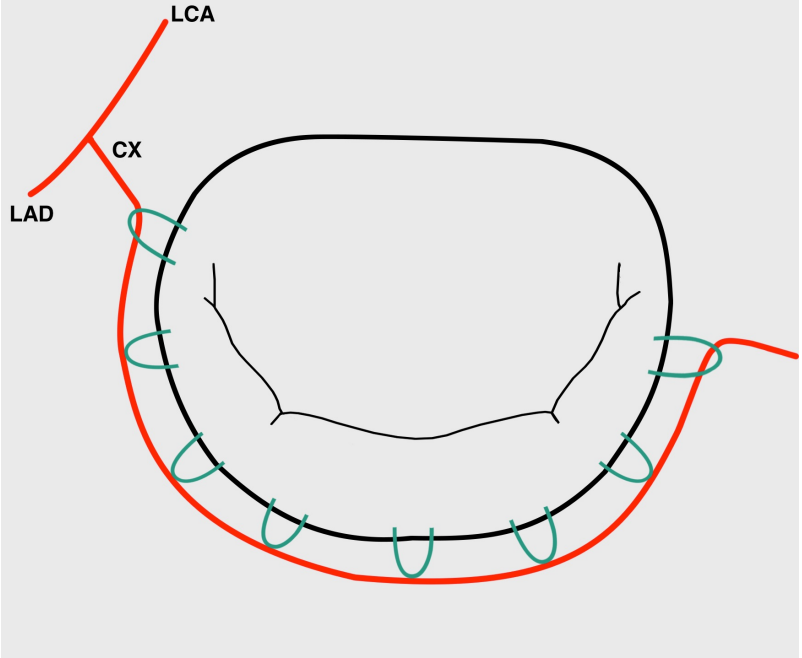

Figure 5.2.1. Placement of intra-annular sutures during mitral valve repair with annuloplasty ring. Sutures run parallel to the CX, however, this orientation changes to be perpendicular at 10:00 and 3:00 as the vessel approaches or departs from the annulus, respectively. As a result, complete occlusion of the CX may be seen at the 10:00 and/or 3:00 position (LCA=left coronary artery, LAD=left anterior descending artery).

5.2.1). As a result, kinking (SI value of 2) or sub-occlusion (SI value of 3) of the vessel would be observed around all hours of the mitral annulus, except where the perpendicular orientation of the CX may lead to a complete occlusion (SI value of 4). The combination of suture depth and the perpendicular angle seen at CX approach or takeoff results in the increased frequency of iatrogenic damage reported following MV repairs. Indeed, it is recommended that these intra-annular sutures be placed inwards of the leaflets, especially at the anterior commissure (10:00 position)[12,54,59].

Mitral valve replacements (regardless of type), however, have sutures that run perpendicular to the CX, but are not placed as deep within the mitral annulus. Although sutures run perpendicular around the entire annulus, the shallow depth is responsible for the lack of complete occlusion (SI value of 4) seen following mitral valve replacements. Instead, misplaced sutures are more likely to run in the tissue adjacent to the artery and distort the vessel upon tightening, causing kinking of the CX (SI value of 2). Complete occlusion of the CX following MVR becomes a greater risk in the case of redo operations, in which deeper tissue bites must be taken to compensate for calcification of the annulus or tissue infection. As a result, the perpendicular orientation of the suture now placed at a greater depth within the annulus may cause complete occlusion at any hour the CX is present.

Our results reflect this surgical difference in suturing technique, as mitral valve repairs are the only surgical technique that resulted in sutures directly damaging the CX due to laceration (SI value of 3). Furthermore, mitral valve repairs experienced the greatest frequency of damage across all three surgeries ($p<0.05$), with a total of 14/149 (10%) misplaced sutures. Our surgical findings are supported by the cardiothoracic surgery literature, as many documented cases of iatrogenic damage to the CX are observed following MV repairs. Case reports have documented kinking[11,59], sub-occlusion or damage[15,27,35-37,48,53], or complete occlusion[25,26,32,34,35,39,41,46,54] of the CX. The majority of these documented cases used an annuloplasty ring as their repair method, consistent with the MV repair technique used in our study, and therefore comparable for interpretation of our results.

As novel mitral valve repair techniques are developed, in conjunction with the results of this study, the frequency of iatrogenic damage to the CX should decrease. Cikirikcioglu *et al*. (2011) completed a study to assess the safety of a novel biodegradable annuloplasty ring and found that sutures were placed at a safe distance from the anterior commissure, P2 segment, and posterior commissure[60], though there was an absence of left dominant hearts in their study. Similarly, a recent study using an open, flexible annuloplasty ring allowed for annular sutures to be avoided at the anterior aspect of the annulus while still facilitating physiological movement during the cardiac cycle[44]. Novel devices such as these allow MV repair to remain superior to replacement, especially in terms of its early and late results[4].

Mitral valve replacement surgery remains a viable option for patients where MV repair is not feasible. Mitral valve replacements exclusively had SI values no greater than 2, meaning misplaced sutures only entered the tissue adjacent to the vessel. This is indicative of the suturing technique, where sutures run parallel to the vessel, and are unlikely to cause complete occlusion of the CX. Our results are consistent with the literature, as the few reports of iatrogenic damage following mitral valve replacements are due to kinking of the artery[18], or partial occlusion or damage[19,28,58], with complete occlusion documented only twice in the past 30 years[30,32]. This is in stark contrast to the wealth of literature documenting complete occlusion of the CX following MV repair within the same time period. Complete occlusion of the CX was previously documented in early mitral valve replacements[38,39], although improved imaging techniques, as well as the advent of mitral valve repair, has dramatically reduced this occurrence.

Damage occurred to the CX between the 9:00-7:00 hours in all three surgeries, with mitral valve repair consistently having the greatest average SI value of damage. In mitral valve replacement with everting sutures, damage occurred more distally on the CX, between the 9:00-6:00 region. The risk of damage is greater in the proximal third of the CX[40], which is consistent with the hours experiencing damage in our study. Previous literature supports our findings, frequently reporting the proximal circumflex as being damaged or distorted[19,26,28,30,35,42,54]. Research suggests that distortion of the CX occurs most often at the P1 segment and is independent of dominance[54]. This is consistent with

our results, as many SI values of 2 were seen at approximately 9:00 and 8:00, both located within the P1 segment, in both left and right dominant hearts. An SI value of 2 indicates that the suture has entered the tissue adjacent to the CX, and would theoretically kink the vessel when that suture was tightened. In fact, due to the increased presence of SI values of 2 within our study, this indicates that the CX may be injured more frequently than appreciated, and may reflect a reporting bias within the literature. The same research from Calafiore and colleagues (2010) proposes that occlusion of the CX occurs most often at the P2 segment and in left dominant hearts. Consistent with our findings, the 7:00 position, located in the P2 region, experienced the greatest amount of sub-occlusions (SI value of 3) in MV repair surgery.

However, contradictory to Calafiore *et al.* (2010), we found no pattern between coronary dominance and severity of damage. Across all three surgeries, 2/5 (40%) left dominant hearts and 10/22 (45%) right dominant hearts experienced potential iatrogenic damage (SI values>1). Sub-occlusion of the CX (SI value of 3) occurred more frequently in right dominant hearts compared to left dominant hearts. Despite left dominant hearts maintaining a closer CX-annulus relationship, and traveling further posteriorly to the 3:00 position on the annulus, they do not seem to be at a higher risk for iatrogenic damage compared to right dominant. Of course, our small population size of left dominant hearts (n=5) may attribute to the trend seen here. Although the anterior commissure has been implicated as the site most often damaged[49,53], we did not see any damage to the 10:00 position across all three surgical interventions. In addition, we did not see damage to the 3:00 position in left dominant hearts following MV repair, although we would expect to as a result of the perpendicular orientation of the CX (Fig. 5.2.1). This may be attributed once again to the small sample size of left dominant hearts (n=5) within this study.

While the CX was never completely occluded across all three techniques (index value of 4), this may reflect the fact that vessels lying within the left atrioventricular groove are hidden by epicardial fat intraoperatively[18], making them more susceptible to complete occlusion due to decreased visibility. Furthermore, the sutures used in this study were smaller than those utilized in a true surgical setting, potentially decreasing the prevalence of observed CX injuries. Absence of complete occlusion may also be

attributed to the skills, training, and expertise of the cardiothoracic surgeons in our study, as iatrogenic damage to the CX may be more frequent in novice surgeons or at less experienced repair centres.

5.3 Strengths and Limitations

There are many strengths associated with our study it in terms of experimental design and relevant findings. This study is the first of its kind to use a combined anatomical and surgical approach in assessing potential iatrogenic damage to the CX following mitral valve surgery. One advantage to using cadaveric hearts was the assessment of anatomical relationships and completion of multiple procedures on the same heart, with that specimen serving as its own control. This proves beneficial, as it is unfeasible to perform multiple procedures within a live patient for the purpose of a study. Furthermore, analysis of damage across case reports would have yielded a complex study design with too many variables to control for. This study also afforded the opportunity to examine the CX-annulus relationship in a surgical context relevant for cardiothoracic surgeons. By implementing the mitral valve clock face, our anatomical and surgical results can be readily interpreted by cardiothoracic surgeons and anatomists alike.

Our study also had several limitations. The number of left dominant hearts studied (n=5) is a large limitation to this study. Although four of these hearts displayed a clear anatomical trend, it would be advantageous to increase the sample size to assess trend consistency and statistical significance. Although we attempted to increase sample size, the harvested cadaveric hearts from the 2014-2015 donors yielded no left dominant hearts, a finding not surprising, as only 10% of the population has left dominant circulation[45]. As surgeries were completed on cadaveric hearts, another limitation is the absence of post-operative physiological changes associated with iatrogenic damage to the CX. It is assumed sutures adjacent to or piercing the CX would distort or lacerate the vessel, respectively, although we cannot assess these results physiologically. Finally, this study may have been limited by human error in two respects. Firstly, we tried our best to skeletonize the coronary circulation without distorting any of the corresponding vessels, although we cannot state definitively this did not occur. Secondly, while we may have

experienced human error performing our anatomical measurements, our inter-rater reliability had an absolute agreement value of 0.996 (p<0.001).

5.4 Conclusions

The results of this study support previous anatomical findings that maintain left dominant hearts exhibit a closer CX-annulus relationship. As a result of this investigation, an anatomical trend has been discovered in which the majority of left dominant hearts had a CX that traveled posteriorly around the mitral valve annulus to the 3:00 position, diving into the myocardium before reaching the posterior commissure. These novel findings hold clinical importance for atrial fibrillation surgery, as cardiac ablation procedures are completed between the 4:00-5:00 position, putting patients with left dominant CXs at a greater risk for iatrogenic damage.

Across surgical repairs, iatrogenic damage appears to be independent of coronary dominance. Mitral valve repairs exhibited the greatest severity and frequency of damage, likely due to intra-annular sutures placed perpendicular to the CX. Damage was seen across the 9:00-6:00 positions, with 9:00 being at the highest risk for damage, consistent with a wealth of case reports documenting kinking or occlusion of the proximal CX following mitral valve surgery.

Future studies should continue investigating anatomical trend of left dominant or co-dominant hearts reaching the 3:00 position on the mitral valve by increasing sample size. In addition, as the anterior leaflet is in fibrous continuity with the aortic valve, future studies should investigate how the aortic valve is implicated following the same three mitral valve surgeries.

Bibliography

1. Moore, K. L., Agur, A. M. R., & Dalley, A.F. (2011). *Essential Clinical Anatomy / Atlas of Anatomy*. Lippincott Williams & Wilkins.

2. Whitaker, R. H. (2014). Anatomy of the heart. *Medicine*, *42*(8), 406–408.

3. U.S. National Heart, Lung, and Blood Institute. Proposal and manual of operations for collaborative studies in coronary artery surgery: contract no. I-HV-32973. National Heart, Lung, and Blood Institute, Washington, DC; 1975. In: Kirklin JW, Barratt-Boyes BG. *Cardiac surgery: morphology, diagnostic criteria, natural history, techniques, results, and indications*. New York: Churchill Livingstone Inc.; 1993. p. 18–20.

4. Ferrao de Oliveira, J. M., & Antunes, M. J. (2006). Mitral valve repair: better than replacement. *Heart*, *92*(2), 275–281.

5. Ghersin, N., Abadi, S., Sabbag, A., Lamash, Y., Anderson, R. H., Wolfson, H., & Lessick, J. (2013). The three-dimensional geometric relationship between the mitral valvar annulus and the coronary arteries as seen from the perspective of the cardiac surgeon using cardiac computed tomography. *European Journal of Cardio-Thoracic Surgery*, ezt152.

6. Młynarski, R., Młynarska, A., & Sosnowski, M. (2013). Anatomical variants of left circumflex artery, coronary sinus and mitral valve can determine safety of percutaneous mitral annuloplasty. *Cardiology Journal*, *20*(3), 235–240.

7. Choure, A. J., Garcia, M. J., Hesse, B., Sevensma, M., Maly, G., Greenberg, N. L., … Kapadia, S. R. (2006). In Vivo Analysis of the Anatomical Relationship of Coronary Sinus to Mitral Annulus and Left Circumflex Coronary Artery Using Cardiac Multidetector Computed Tomography: Implications for Percutaneous Coronary Sinus Mitral Annuloplasty. *Journal of the American College of Cardiology*, *48*(10), 1938–1945.

8. McCarthy, K. P., Ring, L., & Rana, B. S. (2010). Anatomy of the mitral valve: understanding the mitral valve complex in mitral regurgitation. *European Heart Journal - Cardiovascular Imaging*, *11*(10), i3–i9.

9. Eto, M., Morita, S., Nakashima, Y., Nishimura, Y., & Tominaga, R. (2014). Morphometric study of the human mitral annulus: guide for mitral valve surgery. *Asian Cardiovascular & Thoracic Annals*, *22*(7), 787–793.

10. Turi, Z. G. (2004). Mitral Valve Disease. *Circulation*, *109*(6), e38–e41.

11. Meursing, D. F., Boonswang, N. A., Dobrilovic, N., & Wait, M. A. (2006). Perioperative Myocardial Infarction Secondary to Dynamic Circumflex Coronary

Artery Occlusion after Mitral Valve Repair. *Texas Heart Institute Journal*, *33*(1), 85–87.

12. Czesla, M., Götte, J., Weimar, T., Ruttkay, T., & Doll, N. (2013). Safeguards and pitfalls in minimally invasive mitral valve surgery. *Annals of Cardiothoracic Surgery*, *2*(6), 849–852.

13. Ismail, I., & Haverich, A. (2010). Pathology and Classification of Mitral Valve Disease. In R. S. Bonser, D. Pagano, & A. Haverich (Eds.), *Mitral Valve Surgery* (pp. 21–29). Springer London. Retrieved from http://link.springer.com/chapter/10.1007/978-1-84996-426-5_2

14. Ray, S., Beynon, R., & Borg, A. (2006). Mitral valve disease. *Medicine*, *34*(6), 226–230.

15. Grande, A. M., Fiore, A., Massetti, M., & Viganò, M. (2008). Iatrogenic Circumflex Coronary Lesion in Mitral Valve Surgery. *Texas Heart Institute Journal*, *35*(2), 179–183.

16. Pomar, J. L., & Pereda, D. (2010). Mitral Stenosis. In R. S. Bonser, D. Pagano, & A. Haverich (Eds.), *Mitral Valve Surgery* (pp. 117–129). Springer London. Retrieved from http://link.springer.com/chapter/10.1007/978-1-84996-426-5_12

17. Seeburger, J., Borger, M. A., Falk, V., Kuntze, T., Czesla, M., Walther, T., … Mohr, F. W. (2008). Minimal invasive mitral valve repair for mitral regurgitation: results of 1339 consecutive patients. *European Journal of Cardio-Thoracic Surgery*, *34*(4), 760–765.

18. Schyma, C., Kernbach-Wighton, G., & Madea, B. (2012). Kinking of a coronary artery as a rare complication in mitral valve replacement. *Forensic Science International*, *221*(1–3), e30–e33.

19. Sheth, H., Swamy, R. S., & Shah, A. P. (2012). Acute myocardial infarction and cardiac arrest due to coronary artery perforation after mitral valve surgery: successful treatment with a covered stent. *Cardiovascular Revascularization Medicine*, *13*(1), 62–65.

20. Mulholland, M. W., & Doherty, G. M. (2011). *Complications in Surgery*. Lippincott Williams & Wilkins.

21. Aybek, T., Risteski, P., Miskovic, A., Simon, A., Dogan, S., Abdel-Rahman, U., & Moritz, A. (2006). Seven years' experience with suture annuloplasty for mitral valve repair. *The Journal of Thoracic and Cardiovascular Surgery*, *131*(1), 99–106.

22. De Bonis, M., & Bolling, S. F. (2012). Mitral valve surgery: wait and see vs. early operation. *European Heart Journal*, ehs248.

23. Gillinov, A. M., & Mihaljevic, T. (2010). Minimally Invasive Mitral Valve Surgery. In R. S. Bonser, D. Pagano, & A. Haverich (Eds.), *Mitral Valve Surgery* (pp. 105–115). Springer London. Retrieved from http://link.springer.com/chapter/10.1007/978-1-84996-426-5_11

24. Montant, P., Pasquet, A., Khoury, G. E., & Vanoverschelde, J.-L. (2010). Chronic Mitral Regurgitation. In R. S. Bonser, D. Pagano, & A. Haverich (Eds.), *Mitral Valve Surgery* (pp. 31–42). Springer London. Retrieved from http://link.springer.com/chapter/10.1007/978-1-84996-426-5_3

25. Mantilla, R., Legarra, J. J., Pradas, G., Bravo, M., Sanmartín, M., & Goicolea, J. (2004). Percutaneous Coronary Intervention for Iatrogenic Occlusion of the Circumflex Artery After Mitral Anuloplasty. *Revista Española de Cardiología (English Edition)*, *57*(7), 702–704.

26. Aubert, S., Barthélémy, O., Landi, M., & Acar, C. (2008). Circumflex coronary artery injury following mitral annuloplasty treated by emergency angioplasty. *European Journal of Cardio-Thoracic Surgery*, *34*(4), 922–924.

27. Postorino, S., Buja, P., Grassi, G., Millosevich, P., Barbierato, M., Venturini, A., … Raviele, A. (2011). Mitral valve repair complicated by iatrogenic coronary artery lesion treated with percutaneous coronary intervention: *Journal of Cardiovascular Medicine*, *12*(3), 180–181.

28. Mulpur, A. K., Kotidis, K. N., & Nair, U. R. (2000). Partial circumflex artery injury during mitral valve replacement: Late presentation. *Journal of Cardiovascular Surgery*, *41*(2), 333–4.

29. Ziadi, J., Mleyhi, S., Denguir, R., & Khayati, A. (2014). Iatrogenic occlusion of the circumflex artery and left ventricle pseudoaneurysm after mitral annuloplasty. *Journal of Cardiology Cases*, *9*(3), 104–105.

30. Nakajima, H., Ikari, Y., Kigawa, I., Kitamura, T., Hatori, M., Tooda, E., … Hara, K. (2005). Rapid Diagnosis and Management of Intraoperative Myocardial Infarction During Valvular Surgery: Using Intraoperative Transesophageal Echocardiography Followed by Emergency Coronary Artery Bypass Grafting Without Coronary Angiography. *Echocardiography*, *22*(10), 834–838.

31. Pessa, C. J. N., Gomes, W. J., Catani, R., Prates, J. C., & Buffolo, E. (2004). Anatomical relashionship between the posterior mitral valve annulus and the coronary arteries: implications to operative treatment. *Revista Brasileira de Cirurgia Cardiovascular*, *19*(4), 372–377.

32. Varela, N. L., Pulido, J. N., Lynch, J. J., Mauermann, W. J., & Rehfeldt, K. H. (2011). Acute Coronary Syndrome After Mitral Valve Surgery: A Rare Complication Secondary to Mechanical Occlusion of the Circumflex Artery. *International Anesthesiology Clinics*, *49*(2), 32–41.

33. Ender, J., Gummert, J., Fassl, J., Krohmer, E., Bossert, T., & Mohr, F. W. (2008). Ligation or distortion of the right circumflex artery during minimal invasive mitral valve repair detected by transesophageal echocardiography. *Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography*, *21*(4), 408.e4–5.

34. Somekh, N. N., Haider, A., Makaryus, A. N., Katz, S., Bello, S., & Hartman, A. (2012). Left Circumflex Coronary Artery Occlusion after Mitral Valve Annuloplasty. *Texas Heart Institute Journal*, *39*(1), 104–107.

35. Wykrzykowska, J., Cohen, D., & Zimetabum, P. (2006). Mitral annuloplasty causing left circumflex injury and infarction: novel use of intravascular ultrasound to diagnose suture injury. *The Journal of Invasive Cardiology*, *18*(10), 505–508.

36. Vaquerizo, B., Serra, A., & García-Picart, J. (2011). Perioperative ST-segment Elevation Myocardial Infarction during Mitral Valve Annuloplasty: Role of Early Angiography. *Journal of Clinical & Experimental Cardiology*, *02*(05).

37. Eshelbrenner, C., & Ahmed, S. H. (2012). Concomitant Anomalous Right Coronary Artery and Iatrogenic Left Circumflex Artery Entrapment, Treated Successfully With Percutaneous Coronary Intervention. *JACC: Cardiovascular Interventions*, *5*(11), 1185–1186.

38. Danielson, G. K., Cooper, E., & Tweeddale, D. N. (1967). Circumflex coronary artery injury during mitral valve replacement. *The Annals of Thoracic Surgery*, *4*(1), 53–59.

39. Virmani, R., Chun, P. K., Parker, J., & McAllister, H. A. (1982). Suture obliteration of the circumflex coronary artery in three patients undergoing mitral valve operation. Role of left dominant or codominant coronary artery. *The Journal of Thoracic and Cardiovascular Surgery*, *84*(5), 773–778.

40. Kaklikkaya, I., & Yeginoglu, G. (2003). Damage to coronary arteries during mitral valve surgery. *The Heart Surgery Forum*, *6*(6), E138–142.

41. Ender, J., Selbach, M., Borger, M. A., Krohmer, E., Falk, V., Kaisers, U. X., … Mukherjee, C. (2010). Echocardiographic Identification of Iatrogenic Injury of the Circumflex Artery During Minimally Invasive Mitral Valve Repair. *The Annals of Thoracic Surgery*, *89*(6), 1866–1872.

42. Veinot, J. P., Acharya, V. C., & Bedard, P. (1998). Compression of anomalous circumflex coronary artery by a prosthetic valve ring. *The Annals of Thoracic Surgery*, *66*(6), 2093–2094.

43. Vaishnava, P., Pyo, R., Filsoufi, F., & Sharma, S. (2011). Compression of an Anomalous Left Circumflex Artery After Aortic and Mitral Valve Replacement. *The Annals of Thoracic Surgery*, *92*(5), 1887–1889.

44. Bakker, R. C., Bouma, W., Hamer, I. J. W., Natour, E., & Mariani, M. A. (2014). Mitral Valve Repair in a Patient with an Anomalous Left Coronary Artery. *Journal of Cardiac Surgery*, *29*(6), 782–784.

45. Angelini, P., Velasco, J. A., & Flamm, S. (2002). Coronary Anomalies Incidence, Pathophysiology, and Clinical Relevance. *Circulation*, *105*(20), 2449–2454.

46. Tavilla, G., & Pacini, D. (1998). Damage to the circumflex coronary artery during mitral valve repair with sliding leaflet technique. *The Annals of Thoracic Surgery*, *66*(6), 2091–2093.

47. Acar, C. (2007). Re: Injury to the circumflex coronary artery following mitral valve repair. *European Journal of Cardio-Thoracic Surgery*, *32*(5), 818–818.

48. Zegdi, R., Jouan, J., Fabiani, J.-N., & Deloche, A. (2007). Injury to the circumflex coronary artery following mitral valve repair. *European Journal of Cardio-Thoracic Surgery*, *31*(4), 740–740.

49. Spencer, J. H., Prahl, G., & Iaizzo, P. A. (2014). The Prevalence of Coronary Sinus and Left Circumflex Artery Overlap in Relation to the Mitral Valve. *Journal of Interventional Cardiology*, *27*(3), 308–316.

50. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

51. Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191.

52. Barker, T. A., & Wilson, I. C. (2010). Surgical Anatomy of the Mitral and Tricuspid Valve. In R. S. Bonser, D. Pagano, & A. Haverich (Eds.), *Mitral Valve Surgery* (pp. 3–19). Springer London. Retrieved from http://link.springer.com/chapter/10.1007/978-1-84996-426-5_1

53. Murugesan, C., Raghu, B., & Rao, P. V. (2011). Transesophageal Echocardiographic Diagnosis and Management of Circumflex Artery Injury Following Mitral Valve Repair. *Cardiology Research*, *2*(2), 90–92.

54. Calafiore, A. M., Iacò, A. L., Varone, E., Bosco, P., & Di Mauro, M. (2010). Distortion of the proximal circumflex artery during mitral valve repair. *Journal of Cardiac Surgery*, *25*(2), 163–165.

55. Fayad, G., Modine, T., Le Tourneau, T., Decoene, C., Azzaoui, R., Al-Ruzzeh, S., … Warembourg, H. (2003). Circumflex artery stenosis induced by intraoperative radiofrequency ablation. *The Annals of Thoracic Surgery*, *76*(4), 1291–1293.

56. Takahashi, Y., Jaïs, P., Hocini, M., Sanders, P., Rotter, M., Rostock, T., … Haïssaguerre, M. (2005). Acute Occlusion of the Left Circumflex Coronary Artery During Mitral Isthmus Linear Ablation. *Journal of Cardiovascular Electrophysiology*, *16*(10), 1104–1107.

57. Wong, K. C. K., Lim, C., Sadarmin, P. P., Jones, M., Qureshi, N., Bono, J. D., … Betts, T. R. (2011). High incidence of acute sub-clinical circumflex artery "injury" following mitral isthmus ablation. *European Heart Journal*, *32*(15), 1881–1890.

58. Morin, D., Fischer, A., Sohl, B., & Sadeghi, H. (1982). Iatrogenic Myocardial Infarction - A Possible Complication of Mitral Valve Surgery Related to Anatomical Variation of the Circumflex Coronary Artery. *The Thoracic and Cardiovascular Surgeon*, *30*(03), 176–179.

59. Gomes, W. J. (2008). Injury to the circumflex coronary artery following mitral valve repair: a rather opposite strategy. *European Journal of Cardio-Thoracic Surgery*, *33*(5), 948–949.

60. Cikirikcioglu, M., Cherian, S., Stimec, B., Theologou, T., Myers, P. O., Fasel, J., & Kalangos, A. (2011). Morphologic and angiographic analysis to assess the safety of a biodegradable mitral annuloplasty ring. *The Journal of Heart Valve Disease*, *20*(2), 199–204.

Curriculum Vitae

Name: Eliot Johnathon Winkler

Post-secondary Education and Degrees:

The University of Western Ontario
London, Ontario, Canada
B.Sc. Honors Specialization in Biology, Major in Physiology
2008-2013

The University of Western Ontario
London, Ontario, Canada
M.Sc. Clinical Anatomy
2013-2015

Honours and Awards:

AAA Travel Award
2015

Gabriel G. Altmann Research Award in Clinical Anatomy
2014

Western Graduate Research Scholarship
2013-2015

Related Work Experience:

Teaching Assistant
The University of Western Ontario
2013-2015
- Mammalian Histology 3309
- Systemic Human Anatomy 3319
- Medical Imaging for Clinical Anatomy 9567L
- Gross Anatomy for Dentistry
- Gross Anatomy for Medicine (Years 1 and 2)

Anatomy Outreach Instructor
The University of Western Ontario
2013-2015
- Anatomy and Radiology Contouring Bootcamp
- Clinical Anatomy Outreach Program

Conference Presentations:

Winkler EJ, Malakouti-Nejad B, Johnson M, Catrip J, Nagendran J, Kiaii B, Chu MWA. (2015). Establishing Anatomical Proximity Between the Coronary Circumflex Artery and the Mitral Valve Annulus: Implications for Transcatheter Mitral Valve Repair. Poster

Presentation at the International Society for Minimally Invasive Cardiothoracic Surgery, Berlin, Germany.

Winkler EJ, Malakouti-Nejad B, Johnson M, Catrip J, Nagendran J, Chu MWA. (2015). Establishing Anatomical Proximity Between the Coronary Circumflex Artery and the Mitral Valve Annulus: Implications for Mitral Valve Surgery.

- Poster Presentation at the American Association of Anatomists Meeting at Experimental Biology, Boston, MA.
- Poster Presentation at the Department of Anatomy and Cell Biology Annual Research Day, London, ON.

Publications:

Winkler EJ, Malakouti-Nejad B, Johnson M, Catrip J, Nagendran J, Chu M. (2015). Establishing Anatomical Proximity Between the Coronary Circumflex Artery and the Mitral Valve Annulus: Implications for Mitral Valve Surgery. The FASEB Journal, 29(1 Supplement), 552.7.

Malakouti-Nejad B, **Winkler EJ,** 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.

Certifications and Professional Memberships:

Western Certificate in University Teaching and Learning
2015

American Association of Anatomists Graduate Student Member
2014-2015