SELINUS UNIVERSITY OF SCIENCES AND LITERATURE DISTANCE LEARNING UNIVERSITY

IMPACT OF COMPLEX MORPHOLOGY OF MITRAL VALVE FOR TRANSCATHETER INTERVENTIONS FOR MITRAL COMPLICATIONS

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Impact of Complex Morphology of Mitral Valve for Transcatheter Interventions for Mitral Complications

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Table of Contents

Chapter 1: Cardiovascular Anatomy and Physiology

Cardiovascular system is a complex closed system responsible for maintaining homeostasis based on the controlled movement of blood throughout the huge network of the capillaries that permeate each and every tissues of the body [1]. The blood is the means of transportation for nutrients, other essential materials and also the disposal of the waste product for each and every cell of the body [2]. Numerous control mechanisms help to regulate and integrate the diverse functionality to supply nutrients to the specific areas of the body based on the need in order to maintain homeostasis. The cardiovascular system consists of the heart and connecting vasculature, from aorta to arterioles to capillaries to veins and to vena cava [3]. The heart is a muscular organ, comprising of four chambers: left and right atrium and left and right ventricle, which are separated by the septa and the valves that prevent the backflow of the blood [4].

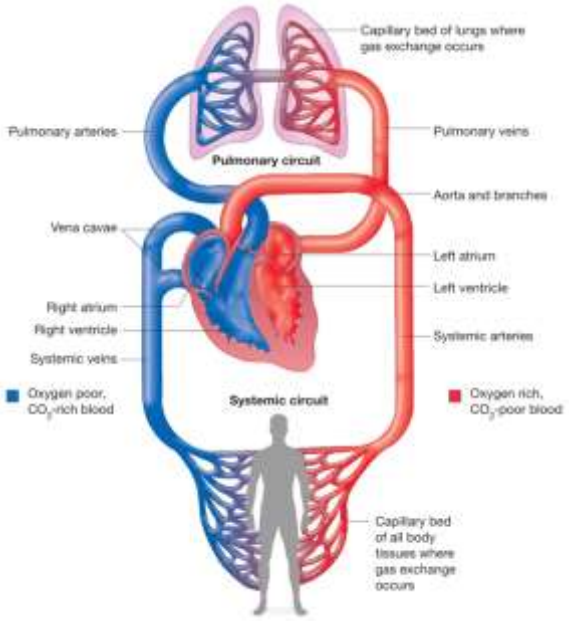

Figure 1 *Schematic of the circulatory system illustrating pulmonary circulation with oxygenation of the blood and systemic circulation delivering oxygen to the tissues and cells*[5]

1.1. Overview of research

Valvular disease is a common condition, the treatment of which is not always the most pragmatic. In certain scenarios, urgent intervention might be required. Usually, such interventions are impacted by the anatomical structures. Due to the complex three-dimensional structure of the mitral valve, it is more crucial that the valve has to be properly investigated for the transcatheter intervention. The creditability of the structures for their mechanical explanations has yet to be assessed.

1.2. Hypothesis and specific aims

The overall goal of this project is for understanding and summarizing multiple methodologies for assessing and analysing the complex morphology of the mitral valve (MV) in healthy human groups / participants and in patients having different types of cardiovascular diseases. The three-dimensional structural dynamics of the mitral valve is constantly changing throughout the life. The smallest change in the mitral valve orientation in a single cardiac cycle impact not only the complete anatomy but also any possibility of cardiovascular implants or the implanted ones. Therefore, understanding the biomechanics, the histological and functional behavior of the mitral valve might be key factor in cardiovascular anatomy and pathophysiology. Transcatheter interventions for the repair of the mitral valve has been considered as better and safer options as compared to open-heart surgeries for complete replacement of the affected valves. The applications and adjustments of the transcatheter interventions is highly impacted by the structural dynamics of the mitral valve. My overall objectives include: 1) Exploring the anatomical structure of the mitral valve; 2) Understanding the impact of the mitral anatomy to

transcatheter interventions; and 3) Integrating the literature to help improvise the clinical interventional procedures.

Specific aim 1: Exploring the anatomical structure of the mitral valve, including anatomical and biomechanical functionality and modelling. The inclusion of the MV structural dynamics and histology is explored in Chapters 2 and 3.

Specific aim 2: Understanding of the mitral anatomy to further support the evidence that its continual developing structure impacts any intervention which is investigated in Chapters 2, 3 and 4.

Specific aim 3: Integrating the available literatures to help improvise the clinical interventional procedures. Multiple existing theories are investigated for the dependency of the procedures which is elaborated in Chapters 4 and 5.

1.3. Thesis organization

The overall objective of this thesis is to integrate the available literature for providing the theoretical support to the prevailing clinical approaches in transcatheter interventions. This thesis is organized as follows. Chapter 1 provides the overview of the research and the structure of the thesis. Chapter 1 also gives a brief overview on the discussion about the cardiac and mitral valve anatomy and physiology. Chapter 2 presents further theoretical background mainly concentrated in the mitral valve diseases and cardiac interventions. Chapter 3 provides the summarized literature on the complex structural dynamics of the mitral valve; mitral valve biomechanics and

its complexity and possible impact on the transcatheter interventions. This chapter also provides the dependency of the transcatheter intervention on the mitral valve physiology and biomechanics.

Chapter 4 specifically demonstrates the research design and methods for the collection of the literature. Chapter 5 highlights the preliminary suppositions and implications as the result of the collected analyses. Chapter 6 presents the summarized case studies. Chapter 7 presents the expected findings and potential obstacles for this thesis. It also includes brief discussion on the future work that can be applied based on the updated literature reviews to enhance the current clinical approaches. Chapter 8 describes the significance and applicability of this thesis. It also includes a brief discussion about the future work that can be done to enhance the utility and potential of this method of integration of literature review.

2. Cardiovascular Anatomy and Physiology

Heart, a four chambered muscular pump, has a complex three-dimensional structure comprising of the four chambers, valve, aorta, arteries and veins. The strands and clumps of the specialized muscle containing myofibrils located throughout the heart initiate and distribute the impulses throughout the myocardium. The sinoatrial node is a small mass of specialized tissue beneath the epicardium generating the impulses near the opening of the venacava. The heart chambers are coordinated by these impulses so that they are more effective.

2.1. Location and dimension of the Heart

The position of the heart is in the thoracic cavity, medically in between the lungs in the space specifically known as the mediastinum where it is separated from other structures by a tough layer known as the pericardium. The heart is enclosed by the vertebrae from the dorsal side and the sternum and costal cartilages from the anterior side. The superior surface of the heart, called the base is connected to the superior and inferior venacavae, great arteries, aorta, pulmonary trunk and located at the level of the third costal cartilage. The apex or the inferior tip of the heart is located in between the junction of the fourth and the fifth ribs. The right chambers of the heart are anterior and the left chambers are posterior.

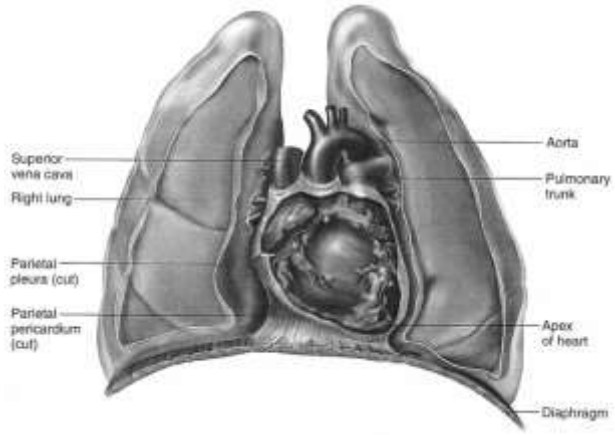

Figure 2 *Frontal section of the thoracic cavity with the lungs slightly retracted and open pericardial sac*[6]

A typical heart is around 12cm in length, 8cm in width and 6 cm in height and usually approximated with the size of the fist and the weight is around 250-300 grams. The size of the heart varies based on the individual, gender, exercise and many other factors. Active/ athletic people have larger heart that and pump blood more effectively. The size of the heart if not always reflective of the activity. Sometimes, the pathologies might also lead to increased size of the heart, for instance, hypertrophic cardiomyopathy.

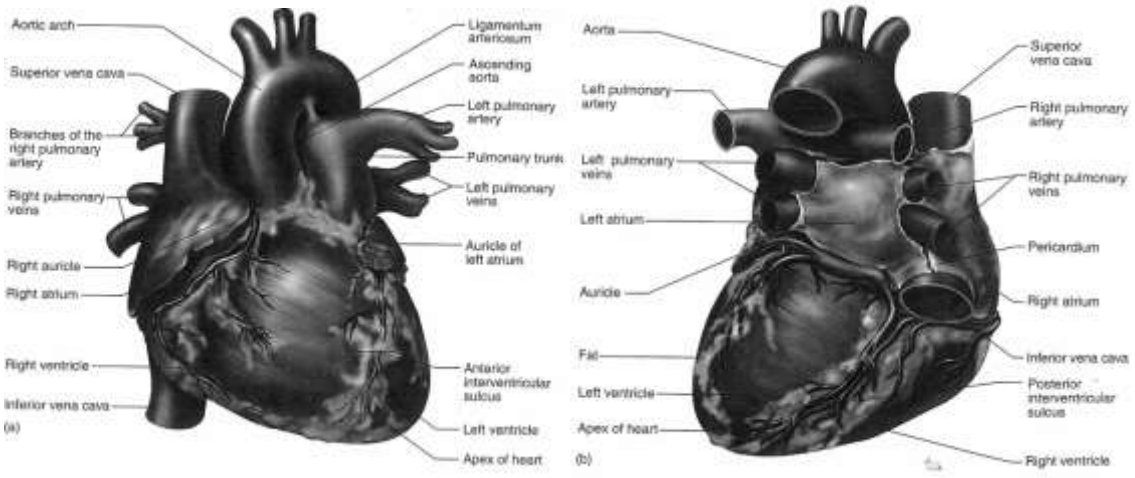

Figure 3 *External anatomy of the heart showing the (a) anterior aspect; and the (b) posterior aspect.*[6]

2.2. Chambers and Circulations of the Heart

The heart is composed of four chambers, two anterior are the left and right atria and the two inferiors are the left and right ventricle. The upper chambers, namely the atria, are the receiving chambers and the ventricles are the distributing/ pumping chambers. The upper chambers pump the blood to the ventricles which are much larger and have thicker walls to push the blood to the lungs (right ventricle) and the whole body (left ventricle). The pathway for the circulation of the blood to the lungs is via pulmonary pathway and the whole body is via systemic circulation. Pulmonary circulation is mainly for carrying the blood to the lungs to collect the oxygen and remove the carbon dioxide.

The right ventricle pumps deoxygenated blood to the pulmonary vein to the lungs where the carbon dioxide leaves the blood and the oxygen is collected for distribution throughout the body. Highly oxygenated blood is collected from the lungs by means of pulmonary capillaries to

pulmonary veins and to the left atrium. The blood will then pass through the mitral valve to the left ventricle to the systemic circulation where the oxygen is distributed throughout the body.

2.2.1. Ventricles

Right Ventricle pumps the blood from the right atrium via tricuspid valve to the pulmonary circulation. Several chordae tendineae, the strong strands of connective tissues, are associated with the flaps of the valves. These chordae tendinea are approximately 80% collagenous and elastic fibers and endothelium. Anterior, posterior and septal muscles correspond to three sections of the valves. With the contraction, the pressure within the ventricular chamber rises and blood flows from higher pressure to the lower pressure. The tension in the chordae tendineae and the papillary muscles is also generated to prevent the potential backflow. This tension prevent the backflow of the blood not only from the pulmonary trunk but also from the right ventricle to the right atrium.

Left Ventricle is the thickest of the heart chambers that is responsible pumping oxygenated blood to tissues via systemic circulation. With every contraction of the heart, the blood flows from the left ventricle to the systemic circulation via the aorta. On contrast-enhanced chest CT and cardiac MRI, when enlarged on axial slices to be ≥58 mm for male and ≥ 53mm for female. A healthy left ventricle comprises an inlet, apical trabecular, and an outlet portion without discreet anatomical borders [7]. The shape of the left ventricle approximates to a cone with the right ventricle hugging it which leads to the septal component to be curved. The left ventricular free wall is the thickest at the cardiac base and gets thinner towards the apex. The normal thickness at

the obtuse is 12-15mm (excluding trabeculations) when measured 1.5 cm from the mitral annulus.

2.2.2. Atria

Right Atrium is the receiving chamber of the heart in which the deoxygenated blood comes from the systemic circulation. The blood is drained in the right atrium via the superior and the inferior venacavae and the large coronary vein called the coronary sinus. Coronary sinus drains the deoxygenated blood from circulation of the heart myocardium or the systemic circulation from the heart to the right atrium.

Left Atrium, located on the left posterior side, acts as a holding chamber for blood coming from the lungs for distribution via the left ventricle. The left atrium has extremely essential for the increased interventional procedures via left atrium[8]. The left atrium consists of an appendage, a venous component and a vestibule, each having variations.

3. Surface features, layers and membranes

Cardiac muscle mass is formed by helix and surrounding circumferential wrap that assists in the mechanical functions [9]. The helically arranged chains of aggregated cardiomyocytes is validated by the histology. Pericardium or pericardial sac is the membrane that directly surrounds the heart including the roots of the major vessels and area closest to the heart. Pericardium has two sub-layers, the outer fibrous pericardium and the inner serous pericardium. The outer layer has tough, dense connective tissue and to protect the heart and to maintain the position of the heart in the

thoracic cavity. The inner layer of the pericardium is further divided into fibrous pericardium and the inner pericardium or the epicardium that is fused to the heart as a part of the heart wall.

The surface features of the heart are rather macroscopic and visible including the four chambers. Each of the atrium has leaflet-like extensions called the auricles which are thin-walled structures that can be filled with blood and then empty into atria or upper chambers of the heart. These are also referred to as atrial appendages. Coronary blood vessels are located in the fat-filled grooves known as sulcus, on the surface of the heart. The wall of the heart is distributed from the external to the internal in three divisions known as epicardium, myocardium and the endocardium. Myocardium is the thickest layer, made largely of the cardiac muscles with a framework of collagenous fibres. The complex swirling pattern of the muscles allows for the heart to pump blood effectively as compared to the linear pattern. As the left ventricle pumps the blood throughout the body, the myocardial muscles are thicker and better developed to generate higher pressure as compared to the right ventricles. The innermost layer, namely the endocardium lines the chambers and protects from direct contact with the blood. The endothelium of the endocardium and the coronary capillaries is very important in the regulations of the contraction of the myocardial muscles. Endothelia regulate cardiac muscle growth pattern.

The physical extension of the myocardium that separates the two atria are known as the septa, or more specifically intra-atrial septa which is also lined with the endocardium. There is an opening in the intra-atrial septa in the fetal heart known as foramen ovale that closes with age and a depression called Fossa Ovalis is left. The septum in between the two ventricles is known as the intra-ventricular septum and in between atria and ventricles is known as atrioventricular septum.

The bulk of the myocardium is formed by the contractile cardiac myocytes. Which produce the complex three-dimensional network, or syncytium, of anastomosing fibres. Each of the myocyte is surrounded by a fine network of fibrocollagenous connective tissue. The middle layer of the ventricular occupies 53-59% of the ventricular wall thickness and has characteristic muscle bundle. The myoarchitecture of the ventricular septum reflects the parietal wall of both the right and left ventricles, the major contribution coming from the middle layer of the left ventricle except at the apical portion where it is not present.

3.1. Heart Valve Structure and Function

The septa open in between the atria and the ventricles open by means of valves known as the atrioventricular valves, the semilunar valves open up to the pulmonary trunk and to the aorta is the aortic valve.

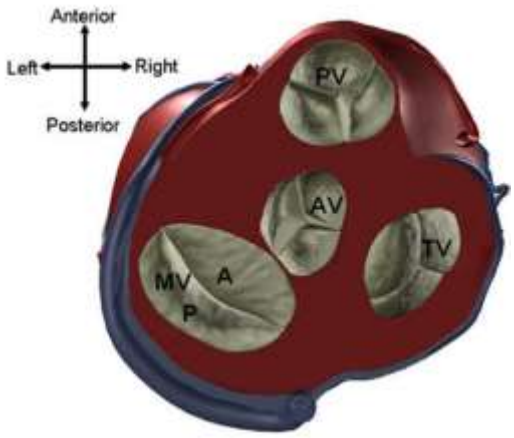

Figure 4 *Relative orientation of the heart valves*[10]

Mitral valve, also known as bicuspid valve or the left atrioventricular valve, is made up of two leaflets, attached to and supported by a ring of tough, fibrous tissue called the annulus. The

annulus is to maintain the proper shape of the valve supported by the tough, fibrous strings or the chordae tendineae and papillary muscle inside the walls of the ventricles or the papillary muscles.

Tricuspid valve has three leaflets, also known as cusps and separated the top right chamber (right atrium) from the bottom right chamber (right ventricle). Tricuspid valve opens to allow blood to flow from the right atrium to the right ventricle and prevents the backflow of blood from the right ventricle to the right atrium.

Pulmonary valve has three leaflets and separates the right ventricle from the pulmonary artery. Pulmonary valve opens to allow blood to be pumped from the right ventricle to the lungs (through the pulmonary artery) where it will received oxygen and prevents the back flow of blood from the pulmonary artery to the right ventricle.

Aortic valve has three leaflets unless in some congenital cases such as bicuspid aortic valve that separates the left ventricle from the aorta. The valve opens to allow the blood to leave the heart from the left ventricle through the aorta and the body and prevents the backflow of blood from the aorta to the left ventricle.

4. Summary

Evidently, there are many evidences that are still to be explored to ensure that the varied structural orientation of the mitral valve impact the interventions. The focus of this research is on the understanding of the mitral valve structural changes and biomechanical modelling.

Specifically, I will integrate all the essential information to elaborate on the projected hypothesis. This research will be based on the published literatures to simplify the methodology. Ultimately, it might help enhance patient management who require transcatheter interventions.

Chapter 2: Mitral Valve Anatomy and Pathophysiology

The complete anatomy of the mitral valve is extremely complicated structure the understanding of which requires multiple imaging methodologies. The anatomy of the mitral valve ensures the continual synchronicity of the opening and closure during the cardiac cycle [11]. The mitral valve opens during the diastole and closes during the systole. The mechanical integrity of the valve impacts the morphological changes leading to abnormal leaflet closure and regurgitation of the blood back to the left chamber causing loss of ventricular pressure and forward flow.

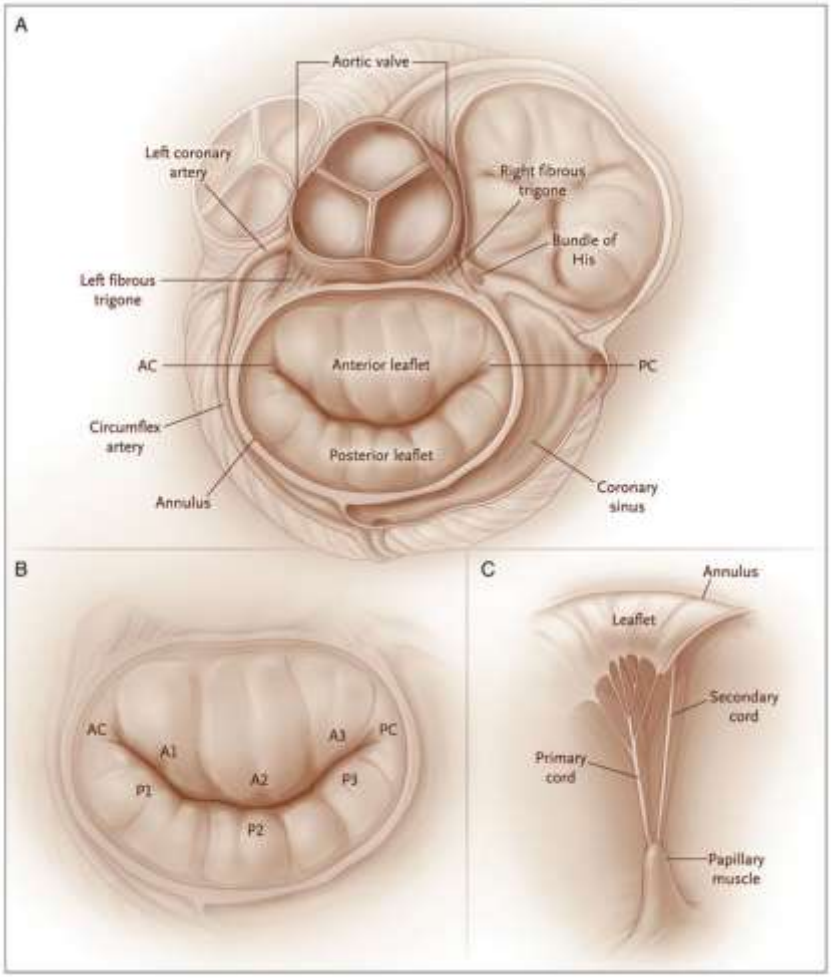

Figure 5 Mitral Valve and its surrounding structures. (A) Anterior and Posterior Commissure, (B) Mitralve valve leaflets,and (C) Primary chordae attached to valve free edge[12].

General Anatomy

The mitral valve complex is comprised of the annulus, the tendinous chords, the leaflets and the papillary muscles. The left atrial musculature is essential for inserting leaflets and myocardium to which papillary muscles are inserted [13]. The mitral valve (MV) is obliquely located immediately adjacent to the aortic valve (AV).

The left atrial wall is essential part of the mitral valve apparatus (MV) as the enlargement of the left atrium contributes to the mitral regurgitation. It is hypothesized that the atrial myocardium continues to the atrial surface of the mural leaflet making the leaflet vulnerable to being displaced when the atrial chamber enlarges.

Sectional Anatomy

Mitral valve anatomy is a complex three-dimensional arrangement of it component parts within the left ventricle. Multiple imaging technologies including echocardiography enhances us to visualize the entirety of the structure of the valve itself in each of the orthogonal planes of the left ventricle [14]. Imaging assessment allows the observation of the area of the valvular orifice. In imaging, the visualizations of the cardiac chambers are classified from short axis view, biplanar view, tri-planar view and four chamber views. In the two chamber views, the best view of the mode of closure of the leaflets and the level of the closure line relative to the atrioventricular junction is seen [15]. The prolapse, hooding and overshoot of each of the leaflets can be easily visualized and the aortic and the mural leaflets easily distinguished. The aortic leaflet can be observed best at an angle from the normal valve in the closed position.

Mitral Annulus

Left atrial wall and tendinous cords

The left atrial wall and the tendinous chords are not generally considered as the essential parts of mitral valve. However, multiple researches have claimed that the role of the atrial wall is much more significant due to the varying muscular extension. The amount of the muscular extension and contraction varies from heart to heart and from one location to another in the same heart. The variability of the insertion of the mural leaflet to the atrial myocardium can be observed. The distal edge of the atrial myocardium points the hinge at the anterior leaflet of the heart.

The string-like structures that attach the ventricular surface to the papillary muscles are the tendinous chords. The tricuspid valve has chordal attachments to the ventricular septum for differentiation from the mitral valve on cross-sectional echocardiography. The tendinous chords of the mitral valve are attached to papillary muscles and to the posterior-inferior wall to form tensor apparatus of the valve [16]. The chords from the apex of the papillary muscles attach with both the mural and the aortic leaflets of the mitral valve. The tendinous chords are classified in multiple ways. One of the classifications distinguishes the three orders; first order inserted on the free edge; second order insert into the ventricular surface and the third order attach to the mural leaflet. There are numerous first order chords that are delicate and often form networks. The second order chords form the rough zone beyond the free edge and thicker than that first order chords. The third chords arise directly from the ventricular wall and from small trabeculations [17]. Third order chords insert to the basal

portion of the leaflet and run only a short distance toward the free margin where webs are observed instead of chords. Individual cords such as commissural chords, strut chords, cleft chords based on the function. There are two commissural chords; leaflet and interleaflet supporting each free margin. These chords arise from a single stem and spread like a closing and opening fan allowing the adjacent leaflets to coapt and to move apart.

Leaflet chords are of different forms, the most common are the rough zone chords. Some chords typically split into three chords after the origin from the papillary muscles. Two chords insert to the rough zone and one chord insert to the free margin of the leaflet. Rough zone chords in the mural leaflets are usually shorter and thinner as compared to the ones found in the aortic leaflet. Cleft chords are found in the mural leaflet which are miniature version of commissural chords with branches in between adjacent segments into the free margin. Aortic leaflet has muscularized chords averaging 3mm in diameter.

Papillary muscles and left ventricular wall

Papillary muscles are the muscular components of the mitral valve apparatus. The papillary muscle includes a portion of the adjacent left ventricular wall as a functional unit. Papillary muscles are the starting point for the tendinous chords. The locations and orientations of the papillary muscles are impacted by the alterations in the size and shape of the left ventricle. The apical and middle thirds of the left ventricular wall are the normal location for the rising of the papillary muscles. Groups of papillary muscles are arranged fairly close together with some of the muscles fused at the bases or have bridges of muscular or fibrous continuity. Parachute malformations might occur in cases of extreme fusion that

might lead to valvular stenosis. The anterolateral and posteromedial positions are occupied by two groups of which the anterolateral muscles from the circumflex are smaller. The right coronary artery most often supplied the posteromedial papillary muscles. Infarction of the adjoining ventricular wall leads to the rupture of a papillary muscles. Rupture of the entire papillary muscle or a group will involve torrential regurgitation given that half the support of each leaflet will be lost. The rupture of the papillary muscle is similar to breakage of the major chord. The affected free edge doesn't meet with the other leaflet and moves to the left atrial cavity during systole.

Valvular complications

Most of the valvular complications are mainly identified by the murmur, which is identified by the assessment of the heart sound by stethoscope. A murmur is an irregular sound like a woosh that is noisy when blood is flowing from one chamber of the heart to the other with a bit of backflow. The presence of the murmur should be investigated as all of them are not equally harmful. Some of the possible causes of the murmurs include the narrowing /stiffening of the valve (namely stenosis), backflow of the blood from one of the valves (regurgitation), improperly closing leaflets (prolapse), and improperly formed or missing valve (atresia). Some of the valve problems can be linked with birth defects including aortic valve stenosis, Ebstein's anomaly, Pulmonary valve stenosis, Bicuspid aortic valve. Some of the aging-related diseases including degenerative valve disease, calcification due to aging, mediastinal radiation therapy. Infective endocarditis, injury and Rheumatic fever are some of the related illnesses and conditions that can also trigger valve problems and lead to leak

of blood backward or fail to open completely. These conditions make the heart work harder and lessen its ability to pump blood throughout the systemic circulation.

Mitral Valve complications

Mitral Valve Regurgitation

Mitral valve regurgitation is a condition caused by mitral valve prolapse in which the flaps of the mitral valve don't close tightly, leading the blood to leak backwards into the left atrium, which, when not treated can lead to damage of the heart muscles. The leaky mitral valve increased the blood pressure in the left atrium and that might lead to increase in pressure in the pulmonary veins leading from lungs to the heart [18]. The most common symptom of mitral valve regurgitation is palpitations in severe cases. With increase in severity, the heart may enlarge in size to maintain the forward blood flow causing heart failure usually reflected as shortness in breath during exertion, coughing, congestion around the heart and lungs and swelling of the legs and feet (edema). The enlarged left atrium produces rapid and disorganized movement also known as atrial fibrillation that reduces the blood's pumping ability. The fibrillating atrium is not able to pump blood efficiently and quivers and so increased the risk for the blood clot formation resulting in stroke.

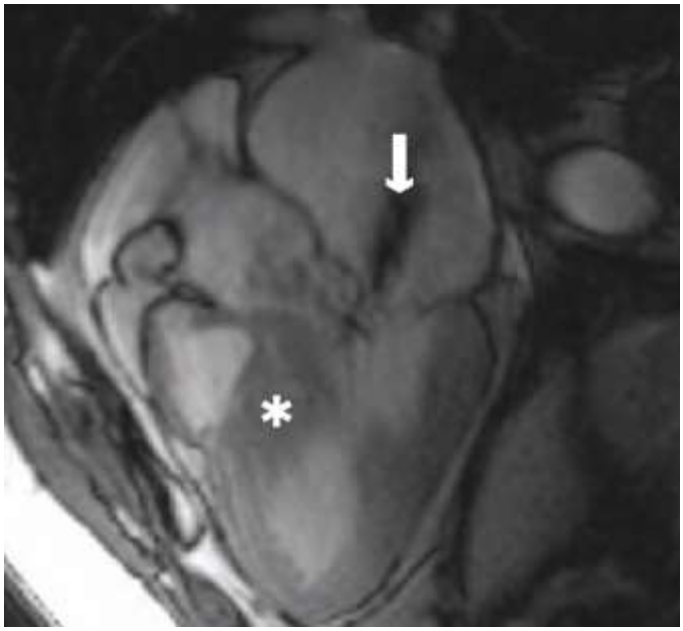

Figure 6 62 year old male with posteriorly directed dephasing jet of mitral regurgitation due to hypertrophic obstructive cardiomyopathy [19].

Mitral valve regurgitation leads to increased blood pressure in the left atrium and hence the pulmonary system or heart-to-lungs system. In a normal healthy adult, the pulmonary artery pressure is 8-20mm Hg at rest and in cases of hypertension, this pressure increases over 25-30 mm Hg. Some of the most common symptoms of the pulmonary hypertension (PAH) include shortness of breath during routine activity, fatigue, chest pain, racing heartbeat, pain in upper right side of abdomen and decreased appetite.

Pulmonary hypertension is usually classified under five groups. Group 1 pulmonary hypertension are known to have no known cause and are usually inherited, possibly caused by drugs or toxins. Some of these pulmonary hypertensions are caused by conditions such as connective tissue damage, HIV infection, liver disease, congenital heart disease, sickle cell disease, or schistosomiasis or any other conditions that affect

veins and small blood vessels of the lungs. Group 2 is associated with the mitral valve or left heart diseases including the mitral valve regurgitation which is the most common cause of pulmonary hypertension. Group 3 pulmonary hypertension is related to the lung problems such as chronic obstructive pulmonary disease and interstitial lung disease, and other sleep related diseases. Reason for the occurrences of the group 4 PAH includes blood clots in the lungs or blood clotting in general lungs-to-heart pathway. Group 5 PAH is triggered by other complications such as blood disorders including polycythemia vera and essential thrombocythemia, systemic disorders including sarcoidosis and vasculitis, metabolic disorders including thyroid and glycogen storage disease, and other conditions such as kidney disease and tumors that have direct and indirect influence over the pulmonary arteries.

Mitral Valve Stenosis

Mitral valve stenosis or the mitral stenosis is the narrowing of the heart's mitral valve. When the valve is abnormal, it doesn't open completely and blocks the blood flow into the main pumping chamber of the left ventricle. Mitral valve stenosis usually leads to tiredness, short of breath and other problems. The main cause of the mitral valve stenosis is an infection known as Rheumatic fever causing scarring the mitral valve and leading to serious heart complications. Other conditions include congenital diseases, mitral annular calcification, SLE and carcinoid syndrome.

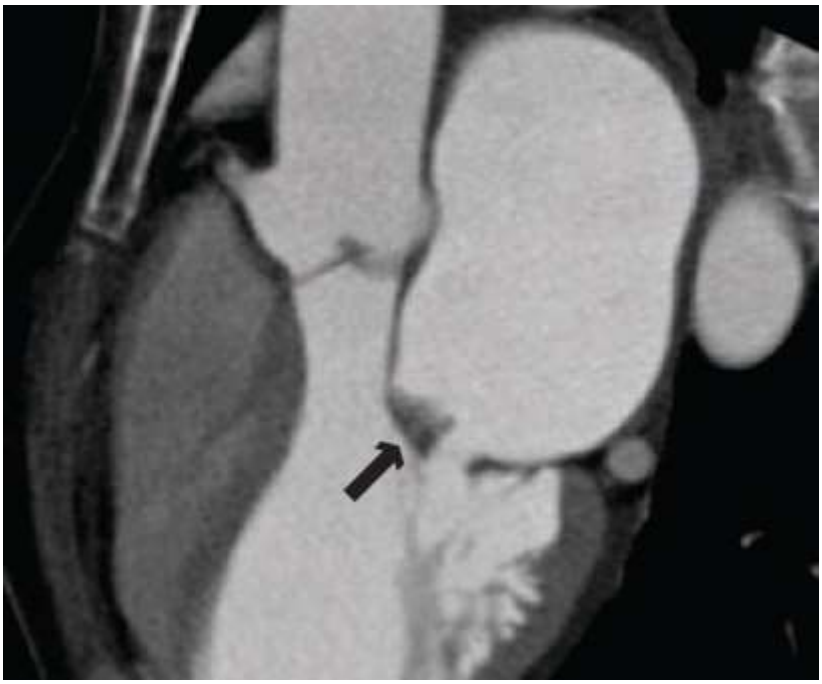

Figure 7 62 year old female with rheumatic mitral stenosis. Thickened anterior and posterior leaflets with commisural fusion/calcification [19].

Symptoms of the mitral valve stenosis include shortness of breath, fatigue, swollen feet or legs, heart palpitations, dizziness/ fainting, coughing up blood, chest discomfort. The symptoms observed during the heart examination are heart murmur, fluid buildup in the lungs and irregular heart rhythms.

The pathology of the mitral valve is observed in the valve, physiology and changes in the left atrium. Mitral valve leaflets get stiff, the leaflets start to thicken, distort and fuse during the progression of the disease. The impact of the rheumatic fever to the heart is only in 10 - 40% of the first attacks.

Aortic Valve Complications

The aortic valve directs the blood flow from left ventricle to the systemic circulation or the rest of the body. The aortic root refers to the aortic valve from its position at the left ventricular outlet to its junction with the ascending portion of the aorta. The aorta is actually the direct continuation of the left ventricular outflow tract. Aorto-ventricular junction is the junction between the left ventricular structures and aortic valvular sinus representing the anatomic junctions. The basal attachments of the leaflets within the left ventricle forms a virtual ring known as the annulus. During the development of the heart, the adjacent valvular leaflets and sinuses are excavated from fused distal parts of proximal cushions forming one sinus and leaflet of the aortic valve, together with adjacent sinus and leaflet of pulmonary valve.

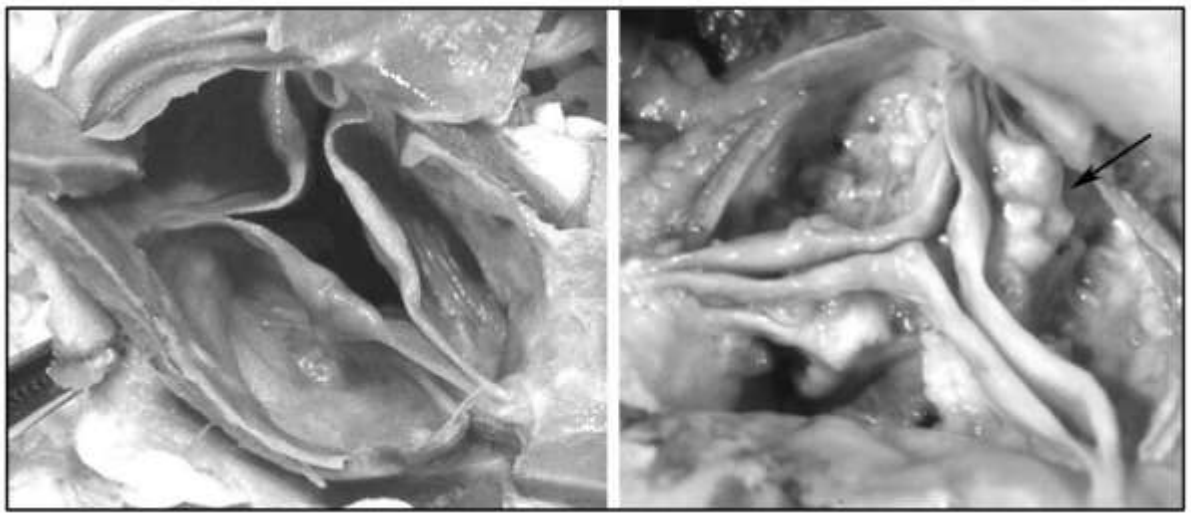

Figure 8 Images of minimally diseased aortic valve and a severely calcified aortic valve. Arrow pointing to lipo-calcific changes to the aortic side although the commissures are squared [20].

The substantial change in size and shape of the aortic valve cusps and leaflets that occur during the cardiac cycle are facilitated by a highly complex internal microarchitecture. The

layered structure of the aortic valve is formed by a dense collagenous layer close to the outflow surface to provide the primary strength component, the central core of loose connective tissue and an elastin layer below the inflow structure. The main components include valvular endothelial cells (VECs), the valvular interstitial cells (VICs), and extracellular matrix (ECM), including collagen, elastin and glycosaminoglycans.

The aortic valve is the cardiac centerpiece and forms the bridge between left ventricle and ascending aorta. The main component comprising the sinuses of Valsalva, the fibrous interleaflet triangles, and the valvular leaflets. Portions of fibrous aortic root are exposed to ventricular pressures, these being superior portions of interleaflet triangles. Aortic sinuses of Valsalva are the spaces between the laminal surface of the three bulges on the aortic root and their respective valvular leaflets.

Cardiac Interventions

Cardiac intervention is a non-surgical interventional procedure used to open narrowed arteries to improved blood flow in the heart. Interventional procedures includes all the techniques from opening the coronaries arteries for the supply of the blood to the myocardium and to treat the severe valve issues. Coronary/ Cardiac Interventions include various techniques such as balloons, cutters, lasers, suckers, filters, stents, grinders, and many other tools. The cardiac intervention is a choice of treatment for single/ double vessel lesions. Percutaneous Coronary Intervention (PCI) is a procedure to treat severe blockages (> 99%) of the coronary arteries also known as Chronic Total Occlusion PCI. The assessment of the cardiac electrical system for the irregular rhythms, EP study, is a non-surgical

procedure that involves inserting catheters into a blood vessel in the wrist or groin and guiding to the heart with special X-Ray machine. Other interventional procedure includes radiofrequency ablation that uses an electrode catheter to destroy abnormal electrical tissues using arrythmia, cardioversion to deliver electrical shock to the heart to convert irregular hearth rhythm.

PCI is a basic procedure used for the diagnostic cardiac catheterization and coronary angioplasty. PCI starts with the vascular access by the method of similar techniques used for the insertion of arterial sheath through the arm or leg with Seldinger's method.

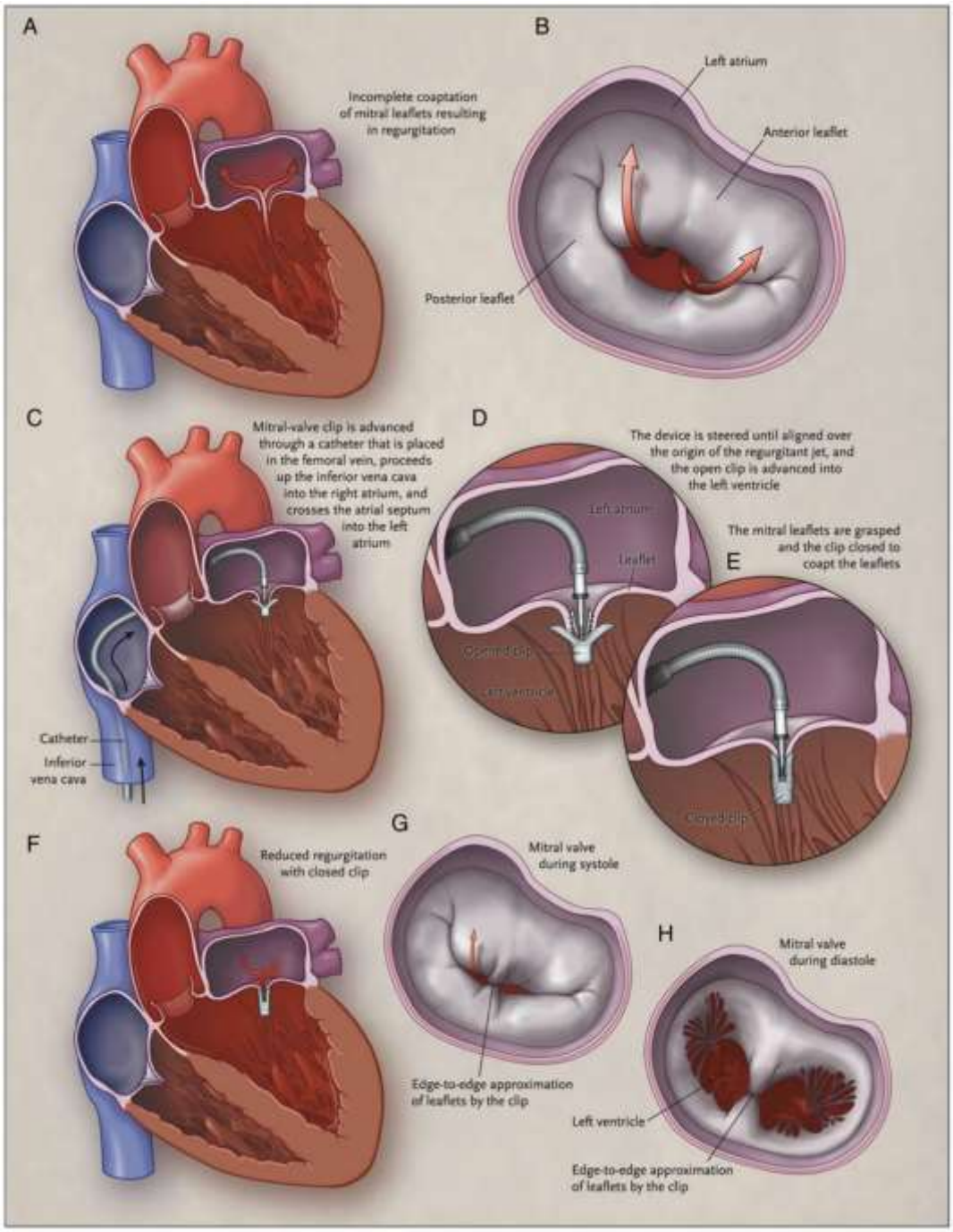

Figure 9 Repair of mitral valve with MitraClip. (A & B) Incomplete leaflet coadaptation, (C) MitraClip passed through mitral orifice (D & E) Mitraclip grasp the leaflet edges, (F) device locked and then released, (G & H) double orifice created [12].

Transcatheter Aortic Valve Interventions (TAVI)

Transcatheter Aortic Valve Interventions (TAVI) is a minimally invasive procedure also known as transcatheter aortic valve replacements (TAVR) and is a less invasive procedure that is designed to replace a disease aortic valve. Aortic Valve Procedures do surprisingly well even in elderly patients with survival in one large population of patients older than 80 years at 89% and 69% after 1 to 5 years [21]. Percutaneous intervention is the most common method, the cut-down procedure is useful in case of the calcified or stenosed vessel. The use of the venous access for the purpose of accessing ventricular temporary pacing wire. An example is ballooning of the calcified aortic valve that is considered to fracture the calcific deposits.

Transcatheter Mitral Valve Repair (TMVR)

Transcatheter mitral valve repair with the devices allows for the repair of the leaky mitral valve using one or more small clip-like devices placed on the valve percutaneously via femoral venous access that is performed on beating heart. Studies have shown that the transcatheter mitral valve repair is effective in treatment of mitral regurgitation[22]. TMVR has less pain, shorter hospital stay and a quicker overall return to normal life and activities as compared to the surgery. Multiple devices have been approved by FDA and are CE certified to be used in the TMVR procedure and thousands of operations happen every year [23].

Transcatheter Mitral Valve Replacement (TMVR)

Transcatheter Mitral Valve Replacement (TMVR) is mainly targeted for older patients with degenerative calcified Aortic Stenosis (AS) accessed mostly via transfemoral route [24]. The first in-human transcatheter mitral valve replacement was conducted at Center for Heart Valve Innovation, St. Paul's Hospital, Vancouver, Canada between August 2017 and August 2018. The transeptal transcatheter mitral valve replacements system secure the native mitral valve leaflets between the dock and the frame. The TMVR study concluded that trans-septal TMVR is feasible with an early procedural success rate of 90%; results were achieved across a variety of mitral regurgitation etiologies, both functional and degenerative (chordal, leaflet, calcification); the procedure is substantially safe with minimal complications in high-risk cohort and no deaths at 30 days; and earlier discharge with possible median length of stay of 1.5 days.

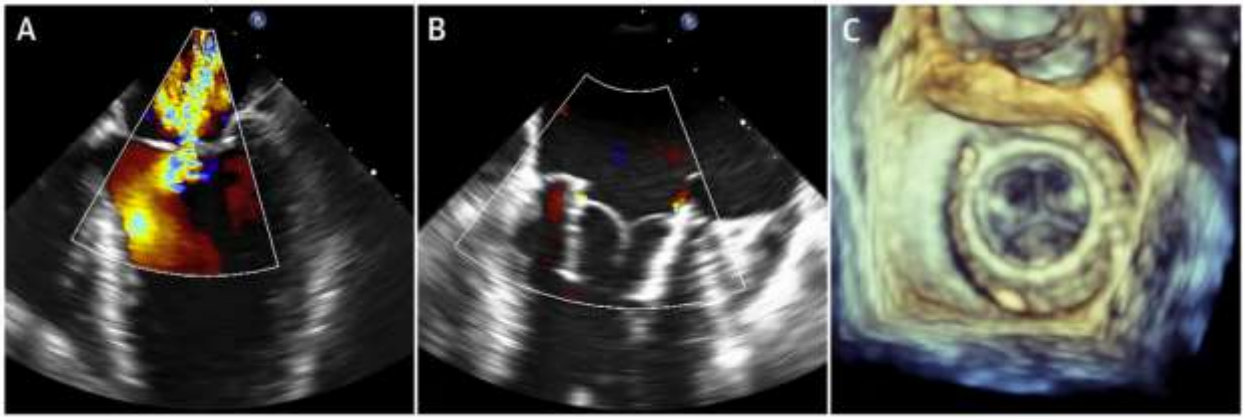

Figure 10 (A) Severe mitral regurgitation at baseline. (B) No mitral regurgitation following percutaneous trans-septal TMVR. (C) 3D imaging from the left atrial aspect [24].

Summary

The mitral valve is often considered to be a dynamic structure that evolves throughout the lifespan. The valve opens and closes based on the pressure change and responds in an intricate and dynamic manner to flow changes during the regular cardiac cycle by structurally adapting to the complex haemodynamic environment. Their dynamic features usually lead to the obstruction in the insertion of the prosthetic valves to overcome issues such as durability, thrombogenicity, haemolysis, calcification and many more. Deriving from the durable leaflets, the changes in the mechanical strength and hemodynamic response of the valve, might lead to increase in belly stress, shear stress and strain on the leaflet free edge. Prosthetic valve development will never identically replicate the characteristics of the native valve. However, the main goal is the combine the knowledge and move towards fully functional, hemodynamically long-term sustainable prosthesis that is capable of regulating systemic blood flow in one direction.

Chapter 3: Mitral Valve Structural Dynamics

The recent developments in the biotechnology and tissue engineering have enabled the creation of more durable mitral valves when compared with the conventional homograft and xenografts. Most of the recent studies are more focused on the ovine mitral valve allografts in order to develop the scaffolds for subsequent implantation in the future modelling simulating the clinical homogenic model. As cryopreserved human pulmonary valve allografts have shown that there is reduction in the reoperation rate and have optimal haemodynamics [25]. The modelling and simulation of the mitral valve is essential for the derivation of the gross anatomy of the mitral valve structure and model the geometry and forces required to support the load.

Mitral valve lies between the left atrium where the oxygenated blood is collected from the lungs and the left ventricle that pumps the blood to the systemic circulation. The design of the mathematical modelling of the mitral valve that qualitatively matches the anatomical structure and produces physiological flows in the realistic physiological tension and morphology. Multiple design-based approaches have been devised in order to compute the tension needed the support the load of each of the cardiac cycle. Mitral valve tissue is anisotropic and extremely heterogenous that has large fiber bundles having varying thickness and fiber orientations. The understanding of the designing of the realistic mitral valve, hence, is essential.

Mitral Valve Model construction

Mitral valve is composed of mitral leaflets and a set of chordae tendineae and papillary muscles. The anterior and the posterior leaflets cover uneven fraction of the ring which has to be considered for the construction of the model. The free edges of the leaflets are attached to the chordae tendineae that seamlessly blend into surrounding leaflet tissue.

Preliminary assumption

The primary assumption behind the model construction is that closed valve achieves a state of mechanical equilibrium in order to support the static pressure load. Differential equations are associated in order to derive the configuration and the forces supported[26]. Theoretical anatomy and physiology imply the following assumptions in order to model the geometry.

1. Valves are made from fibers that exert tension only in their own directions.
2. Leaflets have tensile force to support only uniform pressure load.
3. The two families of the fibers are under tension at any point internal to the leaflet, one is oriented radially and the other circumferential.
4. Leaflets are supported by chordae tendineae which anchors two papillary muscles that only have tensile forces.

Problem derivation

The general dynamics of the mitral valve is based on the hypothesis that for every cardiac cycle the valve closes 0.2s with inertia-elastic timescale of pressurised valve to be in order of 10^{-4}s. The leaflet is represented as unknown parametric surface in $\mathbb{R}^3$ with tension exerted by

constant(u) and variable (v) fibers. The following equation represents the total pressure force on an arbitrary patch of the leaflet.

$$\int_{v_1}^{v_2} \int_{u_1}^{u_2} p\big(X_u(u,v) \times X_v(u,v)\big)\ du\ dv \qquad (1)$$

The parameters u and v are dimensionless and hence based on the fundamental theorem of calculus and as integrand is 0, tensions S and T have units of forces in the following equations.

$$p\big(X_u(u,v) \times X_v(u,v)\big) + \frac{\partial}{\partial}\left(S\frac{X_u}{|X_u|}\right) + \frac{\partial}{\partial}\left(T\frac{X_v}{|X_v|}\right) = 0 \qquad (2)$$

The functions are periodic, the equation is closed and can only be solved when the variable fibers are continuous, piecewise linear with slopes ±1 or 0. Three hypothesis were assessed out of which these set of equations most clearly defined.

Formulation and modelling trees for fibers and tendineae

Based on the defined equations, the valve ring has boundary condition and chordae tendineae are inherently discrete and modelled as tree of fibers[27]. The geometrical positions of the chordae tendineae as gathered in the histological samples were not as significant as previously assumed in discretization of the pressure. The tension in the chordal tree is categorized in each generation in the Cartesian grid. Binary branching structure in the real mitral valve apparatus has been well categorized and secondary and tertiary chordae have been investigated[28]. Primary chordae is considerably sufficient in the calculation of the exerted pressure on the complete mitral apparatus[29].

Formulation of mitral valve model

Nonlinear differential equilibrium equations are thus derived using Newton's method with line search[30]. The leaflets and chordae have closed geometry, pressurized configuration based on the

solution of the pre-defined equations. The intersection of the free edges is essential to avoid the leakage and insertion of the structure in the fluid to essential for understanding of the dynamics of the fluid-structure interaction. Tensions in chordae usually exceeds the maximally allowed fiber tension with radial tension lower near the free edge and circumferential tension highest at the anterior free edge that cannot be captured by materials having uniform material properties.

Derivation of fluid elasticity model

The geometry and the tensions of the pressurized model are used by studies to assign a physical law to the valves. The derived functions have been used in modelling of the soft tissues when the tension is 0 for zero and negative strains and exponential increase at collagen fibers slignment[31]. The fluid elasticity model was derived from the assessment of the porcine mitral valve that was stained with van Gieson's picrofuchsin. Literature strongly claim that large leaflets have two distinct fiber families, that support observation of radial and circumferential fibers in chordae.

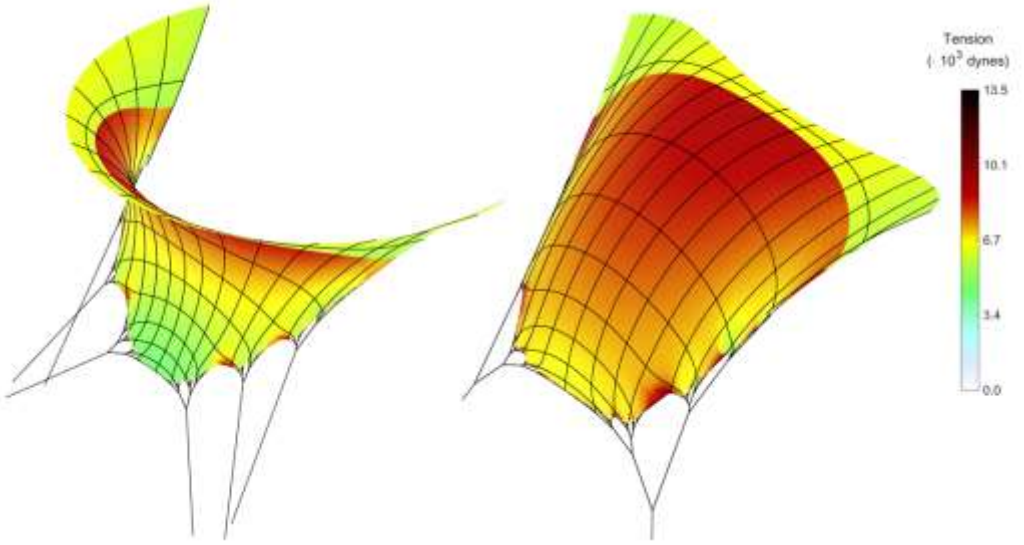

Figure 11 *Closed geometry of the model valve showing the total tension including the radial and circumferential tensions.*[30]

Fluid-structure interaction

The fluid-structure interaction is based on the immersed-boundary formulation derived from the literature[32]. The exertion of force per unit volume is calculated by integral over any finite volume of time. Dirac delta function has been adopted as the most efficient mathematical tool for the representation of the singular force field. Eulerian description of viscous incompressible fluid allows for the dependency on the variables that are functions of fixed Cartesian coordinates. Thus derived mitral valve function, is simulated in the computer test chamber and mounted to model partition in order to assess model's functions and associated flows with pressure difference across the chamber.

In the simulation, ventricular pressure rapidly rises at ventricular systole and a large negative pressure difference occurs at mitral valve. This closure transient is immediately followed by oscillation in the flow that decays rapidly, and the mitral flow stabilizes near zero. In early diastole, the negative pressure difference during ventricular systole is in the order of 100 mmHg that might lead to failure[33]. The interaction is observed in real time and slow motion to show the views during early filling, mid-diastole, atrial systole, the valve in process of closing immediately after the start of each of the cycles with peak flow Reynold number to be 2700.

Mitral Valve Biomechanics

The complicated structure of the mitral valve for allowing the unidirectional flow of the blood between the left atrium and left ventricle has larger surface area as compared to the aortic valve. Mitral valve dysfunction include stenosis, obstructions, regurgitations that can lead to commonly

identified cardiac valvular lesions which is a major medical problem[34]. As much as 5% of the people have some range of mitral valve prolapse eventually leading to mitral valve regurgitation. Studies have shown that mitral valve regurgitation following myocardial infarction doubles the risk of death of post myocardial infarction[13,35] and any disease resulting in altered stress in the valve can influence the MV disease progression and repair robustness[36–38]. Mitral valve has been less studied as compared to aortic valve due to its complex morphology. However, various computational 2-dimensional and 3-dimensional models have been designed.

Structure-based models

Structure-only finite element 2D and 3D models have been used to simulate the biomechanics and physiology of the valvular diseases[27,39]. Transversely isotropic strain-energy function model was used to predict the mechanical difference in MV function of healthy heart as compared to the cardiomyopathic heart. MV surgical intervention were modelled based on this method to study the effect of the annuloplasty procedure, and biomechanical response to the Alfieri stitch technique, mitral annular contraction, neochordal replacement and implantation based on model construction, constitutive law, and validation and verification. Image-based geometry reconstruction of the complex MV apparatus is accurate, fast and reliable for clinical translations. Recent studies are more focused on the 2D and 3D fast developing clinical imaging modalities derived from CT, ECHO, and MRI. Subject -specific MV modelling adopts anisotropic behaviors for hyper-elastic consecutive material models. Hence, different valvular components are classified based on generated data and sources. Data generated from the imaging modalities are extremely different and non-linear as compared to the material response ex vivo while considering the stress distribution in the anterior leaflet, papillary muscle and the ring.

Fluid-structure interaction-based models

Transvalvular pressure difference between the left atrium and the left ventricle mostly drive the mitral valve structure, pressure distribution and strength. Structure-based models are mostly accurate when the valves are either completely closed or completely open. Hence, a fluid-structure interaction (FSI) -based model is essential for the estimation of the pressure at each point of the cardiac cycle. Vortex formation has been observed to assist in mitral valve closure at end- diastole[40]. Fluid-based models are usually best described using Eulerian formulation and solid-only models are based on Langrangian formulations[41,42]. Arbitrary-Langrangian-Eulerian (ALE) formulation is mainly applied to moving structural boundary to simulate the flow through mechanical heart valves. A comparison study between FSI analysis using immersogenometric variational framework and structural-only simulations concluded that the valvular leaflet deformation from FSI modelling is better physiological realism. Fluid-coupled 3D computational model was designed to simulate normal and pathological mitral function inferred that changing anisotropy of the valvular properties can alter valve function and increased MV stiffness can lead to changes in the peak frequency and heart sound. Authors in groups have studied a full three-dimensional FSI model of polyurethane bioprosthetic MV devised on the basis of classical immersed boundary methods that successfully predicted the dynamic performance.

Coupled MV-LV models

Simplified boundary conditions are applied in order to mimic motions of the ventricular dynamics. Coupled MV-LV conditions have been implemented in a couple of studies as there is strong coupling between MV and LV, however MV dynamics is affected by cyclic deformation

of mitral leaflets, chordae and the papillary muscles. The saddle-shaped and asymmetrical mitral annuloplasty ring. Cardiac simulator known as the Dassault Systemes's living heart project simulated the mitral regurgitation and to assess the impact of surgically induced. The MV-LV model was the first 3D FSI model based on MR images and included the LV contraction, non-linear soft tissue mechanics, and FSI within the IB/FE framework. The model showed that the flow patterns are strongly afflicted by the LV deformations. Despite the strong coupling between the MV and LV dynamics, the modelling studies have still to be further investigated in order to substantiate the impact of the MV physiology over any intervention.

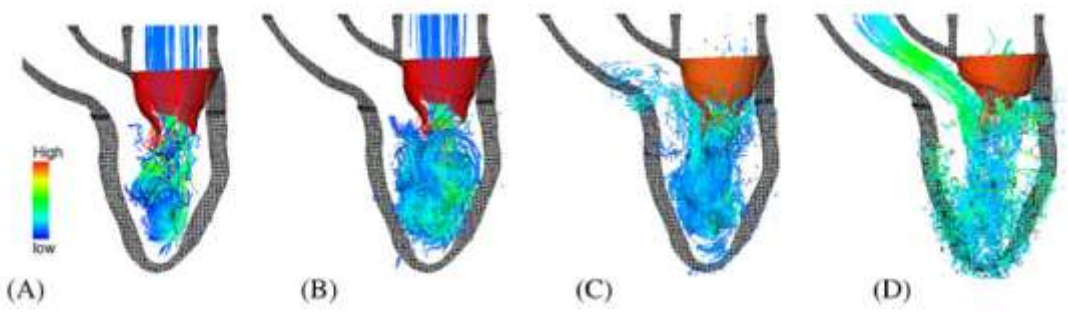

Figure 12 *Integrated MV-LV model streamlines (A) early diastolic filling, (B) late diastolic filling, (C) MV closing; and (D) middle of systolic ejection.*[28,43]

Biomechanical Functional Physiology

The investigation of the biomechanical solutions is essential to avoid geometrical mitral valve configuration abnormalities in ischemic mitral regurgitation. The ability of the mitral valve is to withstand the demanding mechanical power and environment of the heart and achieving lifelong durability of the inserted valves[44]. MV and AV are most prone to regurgitation due to degenerative valve diseases, calcifications and myocardial infarctions. The abnormal reversal of the blood flow from the left ventricle to the left atrium results in abnormality and weakening

with increased deposition of collagen and proteoglycans. The coordinated movement of the different structures of the heart including the endothelial and interstitial cells that maintain homeostatic state essential for the normal rhythm. Mitral regurgitation leads patient to undergo repair or replacement mainly ring annuloplasty to restore normal size and function.

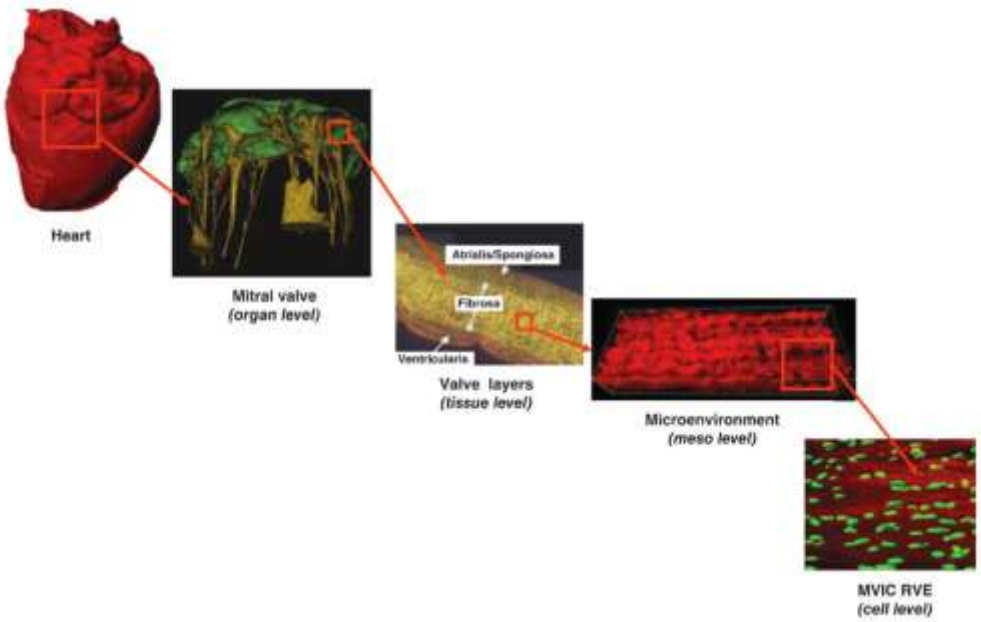

Figure 13 *Heart valve biomechanics at multi-scale level (cell, tissue and organ).*[44]

Flow dynamics

Imaging modalities including MR and CT are implemented to capture flow patterns produced in vicinity of the fresh valves and computational methods are used for investigation of the hemodynamics. Flow visualisation demonstrated that the fluid exits from the stenotic valve as an asymmetric, angulated jet with decreasing diameter with the degree of stenosis under regular physiological conditions (HR = 70/min; Systolic duration = 300 ms; Mean Aortic pressure = 90-100 mm Hg). With the increase in the stenosis, the flow dynamics is more disturbed and based on the jet-type flow-field, doppler anemometry data is revealed. Doppler echocardiography enhances the hemodynamics properties to be used to assess the MV pathologies. Stenosis is

defined as the total or partial obstruction of the valve orifice usually initiated by rheumatic fever, endocarditis, ankylosing spondylitis, atrial myxoma, and Lutembacher syndrome.

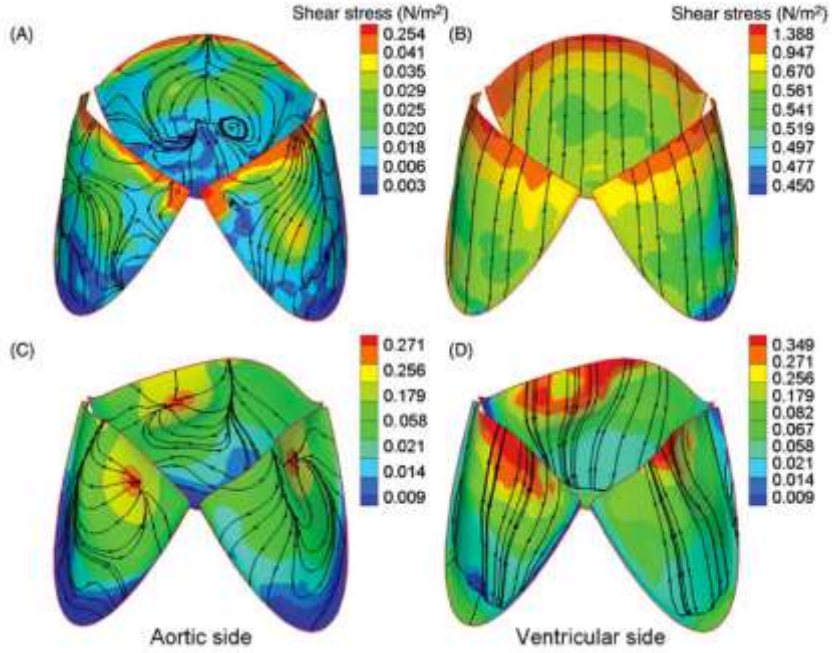

Figure 14 *Friction streamline and shear stress magnitude plots on aortic and ventricular sides of leaflets during fully closed and open conditions.*[44]

Diseased Valve dynamics

Pathological changes in the vascular endothelial cell-mediated responses have been associated with diseases such as atherosclerosis, thrombosis, stroke, and hypertension. Valvular diseases have not only been triggered due to dysfunctional change in the cellular proliferation and extracellular matrix organization but also the histopathological alterations at cellular and tissue level. Hemodynamic flow across the endothelial tissues is the main player in the injury and subsequent dysfunction in degenerated valves. Endothelia on opposing sides of the valves are subjected to extremely different hemodynamics that can be linked to distinctly different patterns

of focal calcification on the atrial side of the MV[45,46]. Fibroblasts during disease or injury usually acquires the secretory myofibroblast-like phenotype with alpha-smooth muscle actin as principle indicatory of valve interstitial cells.

Tensile biomechanics

The deeper understanding of the pathophysiological tissue remodelling of MV healthy and diseased tissues is based on the development of the accurate soft tissue remodelling. Novel meso-scale (10-100 µm) model has been developed for MV leaflets tissues based in distinct collagen and elastin fiber networks within each tissue layer[31]. Substantial layer- specific stress variation and atrialis layer contributed to the radial stress component and the mechanical response of the circumferential direction was mainly due to elastin in ventricularis at lower stress. The ability to discern minute changes in stiffness at low stress-strain and to assess contributions and interactions of the individual layers of multi-layered structures. Pathological changes in the endothelial cell-mediated responses have been associated with atherosclerosis, thrombosis, stroke and hypertension. Valve Interstitial Cells (VIC) impart extremely essential role in the valve tissue haemostasis and pathophysiology by maintaining structural integrity of the tissues by protein synthesis and enzymatic degradation for durability.

Computational approaches and tissue engineering

Predictive mitral valve computational models have been investigated and included in the development of the constitutive models based on numerical modelling and experimental biomechanics. The valvular movement and the transient vibrations are constructed by dynamic non-linear fluid-coupled finite element model of valve leaflets. Material changes leads to the

altered leaflet anisotropy which however, preserved the overall valve function and had significant valvular functions. Finite-element modelling also considered the changes in the collagen fiber content and orientation to the mechanical loading condition within engineered mitral valve constructs supporting the hypothesis that the collagen fibers oriented with principal strain directions increased the fiber stretch. Left ventricular wall stands as a structural element in the mitral valve which incorrectly assumes that the papillary muscles are fixed in space. Mechanical stimuli have significant impact not only in the organ but also cellular and tissue level as physiological function can occur in multiple scales[33]. Hence, multi-scale modelling has been adopted in order to characterize the healthy and the diseased heart which are supported by extensive tools. However, very few of them support at all the three scales. Cellular-scale model predicts the cellular deformation, and the tissue-level model enables analysis of the functional predictions. Integration of the computational model linked with the experimental data comprehends the distinct phases in the development by use of observation, fitting and validation[47,48].

Summary

Physiological functions occur at multiple length scales and at different orders of the cardiac cycles. Biomechanical study is hence essential for understanding the physiological and the pathological changes in the stress and hence the impact of any kind of intervention. Unidirectional flow of the blood might seem extremely basic however requires extremely complicated assessment with minimal fluid and energy loss. High tensile strength to resist the pressure and low flexural rigidity for passive interaction with surrounding blood is speculated at the tissue level. Hence, multi-level investigation is required for transcatheter intervention.

Chapter 4: Literature Review

Mitral valve disease, specifically Mitral Valve Regurgitation is the second most common valvular disease after aortic stenosis. Mitral valve regurgitation is responsible for 20% of the patients with heart failure and 12% patient with myocardial infarction. The causes of myocardial infarction are classified into structural and functional including degeneration of leaflets or chordae, LV and annular dilation [49]. Transcatheter procedures for the regurgitation of the mitral valve are based on the mechanisms that are targeted towards mitral remodelling or repair. Annular remodelling can either be obtained from directly entering the systemic circulation or by placing the device through the fossa ovalis[43]. The devices are placed across the coronary sinus which exert pressure including Mitral Contour System (Contour System), Monarc System (American Medical Systems), and PTMA (Viacor). MitraClip and Mitral Contour System are the mostly used devices.

MitraClip devices are more inclined to use edge-to-edge repair technique and has 3 components, namely, a guide catheter (22-French near the interatrial septum and 24-French proximally), a delivery system and a clip implant[50]. A guide catheter is advanced to the left atrium from the femoral vein after the transseptal puncture via a femoral approach. The clip insertion is assisted by the fluoroscopic and TEE guidance, while being advanced into the left ventricle at the regurgitation orifice. The arms of the clip are withdrawn to grasp the leaflets and creates a double orifice.

Careful preprocedural imaging[51] is crucial for the success of the procedures. Also, understanding the mechanism of mitral regurgitation is important. In order to determine the technique to be

used, edge-to-edge or indirect annuloplasty techniques. From the clinical perspective, echocardiography or CT or MRI plays a vital role in evaluating for the factors involving in the procedures. Echocardiography is a robust technique for the assessment of the severity of the mitral regurgitation and has improved identification of the mechanism and accuracy in mitral valve regurgitation. CT and echocardiography play important roles in the assessment of the anatomy and evaluation of the mechanism. CT is used for systematic evaluation of the mitral annulus for the calcification. CT -derived indexes in assessment of the anatomy and geometry of mitral valve including distance between papillary muscles, sphericity index of the mitral valve where increased sphericity index refers the patient without functional regurgitation. The distance between the left circumflex artery and coronary sinus might imply that there is chance of compression with coronary sinus-based devices.

Mitral valve and sub-valvular anatomy and mechanism of regurgitation is quantified by the CT and echocardiography. The dynamic information of the mitral valve leaflets are provided by the echocardiography and the best anatomical definition of the valvular and sub-valvular apparatus is provided by the CT. The anatomy of the valve leaflets is assessed for pro-lapsed and flail segments with echocardiography.

Mitral valve and annulus assessment is done with CT by means of following steps:

1. CT images are scrolled to the level of the mitral valve. Cross hairs are placed in the center of the mitral valve on the axial image.

2. Image is rotated in the longitudinal place such that the reference lines are parallel to the interventricular septum and across the apex of the left ventricle showing the center of the mitral valve.
3. Image is rotated in the sagittal image such that the reference line crosses the left ventricular apex.

2 Theoretical Background

Transcatheter mitral valve replacement (TMVR) implies multiple benefits over MV repair devices [52]. Due to the mitral valve complex structure, creating the mitral valve repair device tailored to all the anatomical structures due to the diversity and intricacy of mitral valve diseases. The one valve fits all concept for the TMVR devices for predictable MR reduction with upgrading procedures. Mitral valve repair devices usually provide higher safety profiles and less impact to native anatomy. The main points considered for the design are that the valve has to be crimped, have anchoring system, must not have Left Ventricular Outflow Tract (LVOT) obstruction, reduction of stagnation flow, maximization of the mitral annulus scaling and mitral orifice shape and made for established TMVR surgical approaches. Designing the TMVR prosthetics devices with high technical implantation success is required for superior performance.

3 Clinical Implications

Valve anchoring techniques[52] must be utilized in order to overcome the limitation of the TAVR due to the absence of the calcification and smaller annular region. Multiple anchoring techniques have been proposed and developed using the tethers to archive counteracting axial forces; native

leaflet grasping to fixate the prosthetics in place; atrial and ventricular flanges in order to grasp the MV annulus and leaflets; docking systems in order to allow radial forces sufficient enough for fixation. MV is subjected to high pressures of around 120 mmHg during the systolic phase when the valve closed so the late migration of the TMVR devices is of concern. The dynamic motion over the cardiac cycle should be considered as a newly protruding anterior mitral valve leaflet due to the implanted TMVR devices may create LVOT obstruction, or device dislodgement if the system utilizes the leaflet capturing, under high systolic pressure[40].

TMVR devices need to ensure that the native mitral valve annulus apply proper sealing required in order to prevent the leakage through the interface of the valve stent and the native annulus, also known as paravalvular leakage. The TAVR procedures and designs are currently essential for the assessment of the transaortic approach.

4 Summary

The success rate for the TAVR for the treatment of aortic valve and TMVR for the mitral valve. MitraClip^{TM} for the mitral regurgitation has improvised and streamlined the progress and development of the catheter-based technologies. TMVR is potentially going to be new option for the treatment of the MR patients with perceived risk. TMVR systems are designed with increased as an viable option to be used in the perceivable future.

Chapter 5: Preliminary Suppositions and Implications

Mitral valve is complete and usually involves the synchronous involvement of several anatomical structure that include chordae tendinea, valvular leaflets, mitral annulus, papillary muscles for the unidirectional passage of the blood from left atrium to the right atrium. The mitral valve is saddle-shaped structures that is composed of the fibro collagenous tissue attached with the mitral leaflets. Mitral regurgitation is mainly caused by the failure in the complete coaptation and adequate symmetrical apposition of both mitral leaflets.

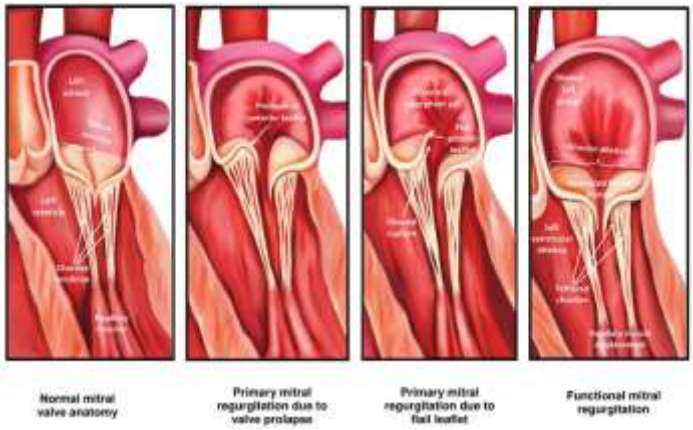

Figure 15 *Mitral valve apparatus and etiologies of mitral regurgitation*[53]

Early Clinical Results

Application of Transcatheter Mitral Valve Replacement (TMVR) has emerged as a potential alternative for the treatment of severe mitral regurgitation in patients[54]. Clinical characteristics and the procedural results have been analyzed previously. TMVR is considered as a feasible, less invasive alternative treatment for the treatment of the severe mitral regurgitation in patient with increased prohibitive surgical risk. Conventional mitral valve surgery have been the standard of care for the patient with the symptomatic severe mitral regurgitation. A fraction of the patient having severe mitral regurgitation are eligible for the TMVR procedure. A comprehensive

review of the published data describing the multiple outcomes from the TMVR systems was also available. A gradual increase in use of the transfemoral- transeptal approach and improved patient selection will be essential. Standardized data abstraction sheets are used for extraction of the data inferring clinical characteristics, procedural results, and mid and post- surgical outcomes.

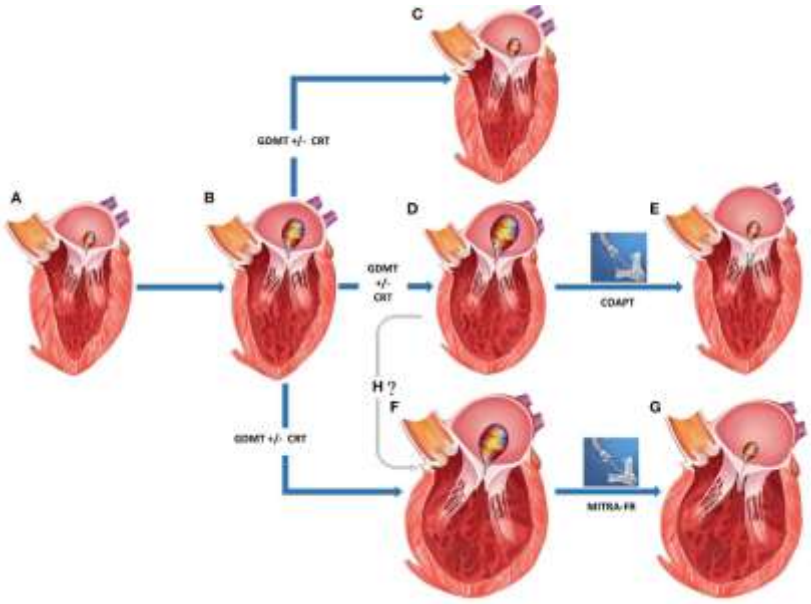

Figure 16 *Optimal timing for the mitral valve intervention in functional MR showing the natural history of functional MR with progression in severity of MR over time accompanied by left ventricular dysfunction, ventricular dilation, progressive symptoms, and worsening survival*[53].

The baseline clinical characteristics for the TMVR include the age range, gender, STS-PROM score (%), etiology of mitral regurgitation, NYHA classification and cardiac pathological history and status. The cardiac pathological data and history includes LV ejection fraction, Diabetes mellitus, hypertension, atrial fibrillation, coronary artery disease, prior myocardial infarction, prior coronary artery bypass surgery, prior valve intervention/ surgery, chronic renal insufficiency, chronic obstructive pulmonary disease, prior stroke of TIA, pulmonary

hypertension and hospitalization for HF within past year. Vast procedures are implied under general anesthesia and transesophageal echocardiographic guidance. TMVR was mostly applied by transapical approach. Most of the commercial transcatheter mitral valve replacement devices have self-expanding frame, 3 bovine leaflets, variable anchoring mechanism. TMVR was associated with very high success rate in the valve implantation, associated with excellent hemodynamic results, low rate of the significant residual MR, low transvalvular mitral gradient after the procedure, high rates of periprocedural complications, improved functional class and low mortality rate.

The mitral valve apparatus is a complex dynamic structure and multiple important anatomical aspects should be considered. TMVR was designed to address issues such as lack of calcified / rigid mitral valve, saddle-shaped large dynamic annulus, irregular leaflet geometry, LV outflow tract proximity, and sub-valvular apparatus. Recent researches have shown efficacy for TMVr with MitraClip system for treating secondary MR. Comparison of the mitral repair is done with mitral replacement. Clinical outcomes assessment of the MitraClip percutaneous therapy trail was used for the demonstration of the cardiac health and well-being. This is less invasive method as compared to the other concurrent procedures.

TMVr patient assessment

A retrospective observational cohort study was performed on patients including those who underwent TMVr. A follow-up echocardiography on the basis of specific parameters, clinical characteristics and procedural characteristics is applied in order to assess the patients after the

TMVr[55]. Significant concomitant improvement in the mitral regurgitation is mediated by the reduction of the systolic pressure by the means of TMVr.

Systemic Review

International conference presentations and published researches have reported TMVr system datasets. A huge set of records were identified 2477 via Pubmed, 5752 from EMBASE and 131 from International conferences. A whole list of transcatheter mitral valve replacement devices were assessed based on the publications. Most patients were recorded at the age of 75 years of age and at New York Heart Association and exhibited at least one episode of heart failure. Mortality rate was also observed and recorded. However, existing indications included coronary artery diseases, prior coronary bypass grafting, atrial fibrillation and chronic renal insufficiency.

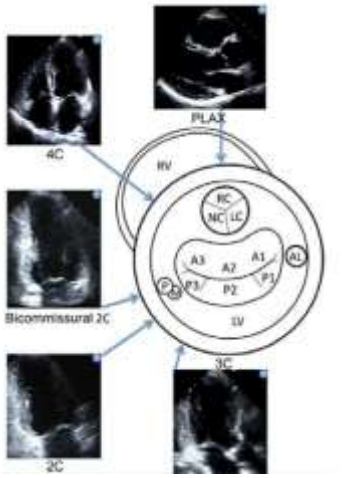

Figure 17 *Central schematics showing left ventricle in short view seen from apex with extrapolating echo beams*[56].

Post-procedural data were collected at 30-days of the surgery. The surgeries were conducted under general anesthesia and by means of transoesophageal echocardiographic guidance. The most common method for the insertion was the transapical approach and resulted in very high success rate of 91.7%. Conversion to open-heart surgeries were also observed in sub-group of

patients triggered by valve malposition, device embolization or migration and minimal mortality rate. The selection of elderly patients is standard as the complications arise after a certain age-group. Global Pilot Study also emphasized on the exclusion criteria which included severe LV dysfunction, large annular dimensions, high risk of LF outflow tract obstruction, sever mitral annular or leaflet calcification, previous aortic or mitral valve surgery, severe tricuspid valve regurgitation. The surgery is less invasive as compared to conventional surgery for treatment of severe MR in patients having high surgical risks and might drastically increase therapeutic options for specific patient group.

Pre-procedural planning – Role of CT

Transcatheter mitral valve repair and replacements have both been assisted by the transcatheter mitral valve interventions[57]. Mitral valve diseases can be classified as primary mitral regurgitation caused by primary valvular defect and secondary mitral regurgitation is also known as the functional regurgitation. Functional regurgitation is mainly caused by the distortion of the supporting apparatus due to dilated or ischemic cardiomyopathy. Primary mitral regurgitation is due to myxomatous or degenerative change. The anatomy of the leaflets and tendinous chord is preserved in the secondary regurgitation. Inferolateral wall infarction and subsequent adverse remodelling leads to the posterior leaflet tethering and eccentric MR with posteriorly directed jet.

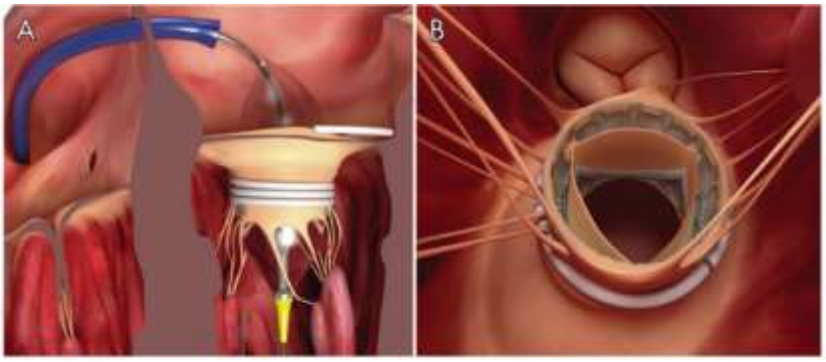

Figure 18 *Deployment of transseptal transcatheter mitral valve replacement system. (A) 4-chambered view and (B) enface view from LV apex* [56].

Application of 3D Echocardiography for modeling

The feasibility of Transesophageal echocardiography (TEE) and Trans-pericardial echocardiography (TPE) has been actively implied as a model of choice in the pre-clinical studies of the valves. The recent application of the CT-Scanning for pre-procedural planning is evolving as well.

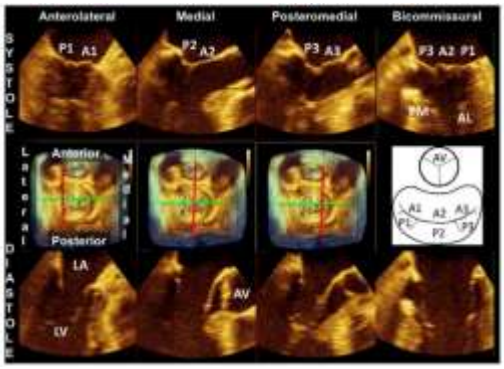

Figure 19 *Upper panel (2D Echo views of precisely known orientation; Middle panel (3D-rendered surgical view of MV); Lower panel (Same slice planes in diastole with Mv open)*[56].

Preliminary implantation outcomes

Small devices designed to treat secondary mitral regurgitation which might have different etiologies and patient-specific anatomy. Even with high technical challenges for TMVI which

might include left ventricular outflow tract obstruction and valvular MR. 3D transesophageal echocardiography and multi-slice computed tomography (CT). 2D and 3D guided echocardiography was performed. All the involved patients were successfully implanted with no mortality but with minimal issues[54].

Replacement options for native mitral valve diseases

The surgical and the percutaneous replacement of mitral valve impact the overall performance of the left ventricle and hence the complete systemic circulation. Percutaneous heart valve replacements were initially designed for aortic valve, which are highly impacted by the calcification. The differences between the surgical aortic and mitral valve replacement are controlled by the valve-in-vale settings. The valve -in-valve procedures for mitral valve, the main issues can be interference with the left ventricle outflow tract. Multiple TMVR devices have been designed for the treatment of the MR. However, some of them are still in the early experimental phase but most of them have over 96% success rate. Some devices have already reached in the clinical feasibility study. Devices already in market include CardiAQ-EVOQUE, Tiara, FORTIS, Tendyne, Intepid, Caisson, HighLife, SAPIEN M3, Cardiovalve, Cephea, AltaValve, Navigate with consistent improvements.

Current Marketed Devices and implications

Some transcatheter mitral valve implantation under development are enlisted as:

- Fortis (Edwards Lifesciences): First-in-man study underway
- Tiara (Neovasc): First-in-man study underway
- TAVI-TA (CardiAQ)/ TAVI-TF (CardiAQ): First-in-man study completed

- Caisson TMVR (Caisson): Preclinicals underway
- Medtronic TMVR (Medtronic): In development
- Highlife Mitral Valve Replacement (HighLife): Pre-clinicals underway
- Medtronic TMVR (Medtronic): Pre-clinicals underway
- Navigate TMVR (NCSI): Clinical implants have occurred.
- MitrAssist Valve (MitraAssist): Preclinicals underway
- Tendyne/ Lutter TMVR (Tendyne): First-in-man study underway
- Cardiovalve (Valtech): Preclinicals underway

Figure 20 *Curent trancatheter mitral valve replacement devices. (A) CardiAQ/EVOQUE, (B) Tiara, (C) FORTIS, (D) Tendyne, (E) Intrepid, (F) Caisson, (G) HighLife, (H) SAPIEN, (I) Cardiovalve, (J) NaviGate*[58].

Impact on Commercialization

The investigations have been used for the determination that increased growth in the cardiac surgery and benefits of the clinical outcomes might have impacted the commercialization of the TMVR. The complementary transcatheter and surgical therapies might be implemented successfully. It has been essential to note that the transcatheter patients have distinct clinical characteristics.

Transcatheter intervention possibilities

Open-heart surgery is being established as the gold-standard for the treatment of mitral repair and regurgitation, as an alternative to therapeutic options. A number of cases of Transcatheter mitral valve implantation in calcified valve cases. TMVI is trying to bring the concept of 'one-valve-fits-all' due to better predictability of the mitral regurgitation. However, due to design complications, the implications are both catastrophic and lower safety profile. Functional mitral regurgitation have higher recurrences due to consistent remodelling or poor patient selection. Fluoroscopic and echocardiographic imaging guidance are used in pre-procedural planning and post-procedural confirmation. The haemodynamic function of the valve to ensure the forward cardiac output, thus preserving the structural and functional integrity of the LV[59]. Contractility of the base of the valve is the key contributor in the cardiac motion and the output. Mitral valve is essential in the inflow-outflow of the ventricular tracts, preserving energy loss and optimizing fluid-structure interaction. Surgical practices currently considered complementary to each other. Valve replacements are used for replacing the disease state with healthier options, mainly prostheses. The replacement and repair surgeries have their own advantages in restoring life-expectancy with surgical repair.

The comparative assessment of the mitral valve repair and replacement is based on surgical experience. Valve replacements are comparatively easier to perform so surgeons are more inclined towards valve replacements. However, in valve replacements, the post-surgical requirements are higher including but not limited to need for anti-coagulation, risk of thromboembolism, prosthetic endocarditis, impaired LV function. The valve replacement requires an ideal prosthetic valve that should have simple and reproducible implant which has

very high immediate success rate without any post-surgical mitral regurgitation; absence of transvalvular gradient and peri-valvular regurgitation; no LCx obstructions, coronary sinus, LVOT obstruction; low infection rates; durable; no acute of delayed embolization; ability to modify based on the cardiac cycle[60–63]. However, there is no such mitral valve yet. Improved prosthetics also require the correct selection of patients and continuous research and development of the new devices.

Summary

The delay in evolution of TMVR is mainly due toe the anatomical and pathophysiological reasons for preference of MV repair over replacement. The structural change of the mitral valve in the functional mitral regurgitation leading to more spherical is due to dilation in the annular region. The left atrial entanglement and dilation in mitral annulus has been considered as the primary mechanism of mitral leaflet coaptation [53]. Chronic compensated and decompensated stages occur over years by evolution of mitral regurgitation depending upon the severity and cardiac structural changes.

Current Indications and Future Directions

Management strategies for mitral regurgitation have been under discussion based on multiple criteria[53]. Intervention is the only option after the trigger of the mitral regurgitation. The decision of the intervention is complicated by the multiple factors. Pre-procedural imaging-based evaluations are recommended and followed for the safe positioning of the clip. Technical and technological advances have been very beneficial in the field of the microinvasive cardiac valvular operations. Approaches were assisted by the percutaneous or transapical transcatheter valve repair and replacement. COAPT and MITRA-FR in degenerative MR highly enhanced the

understanding of the intervention in the functional MR. The benchmark for the future trails in the field of the percutaneous mitral repair are acquired from COAPT. The MitraClip data has been set as the main source of data for future applications including consistent evolution of the 2D/3D echocardiography and fluoroscopic imaging.

Chapter 6: Summarized Case Studies

The frequency of incidence of the cardiovascular diseases in U.S. adults was one in three (approximately 71.3 million)[64]. Despite age being the main factor in the cardiovascular diseases, 65% of patients are under the age of fifty-five. Heart disease and stroke are encountered as the first and the third main cause of the death in the United States. In terms of hospitalization for heart disease and stroke, cardiovascular diseases remain the leading cause of short-term stays. Cardiovascular diseases have also been the costliest diseases in the United States based on continual care, hospitalization, and medications.

Studies on transcatheter valve implantations and was not inferior to the surgical valve replacement[65].The study was followed-up the next year as well in order to assess the mortality and adverse events[66]. The transcatheter procedures were associated with the improvement in the quality of life, however the results are varied by cohort. Also, the procedure is cost-effective for eligible candidates. The assessed outcomes included rate of emergent conversion to surgery, valve embolization, multiple valve insertions, deaths; cardiovascular complications, rehospitalizations, length of intensive care unit stay, improvement in quality of life, stroke, myocardial infarction, valvular fibrillation, PAR, vascular injuries, improvement in symptoms, renal functions and many more. The first-year assessment concluded that the mortality rate of is similar to that of the surgical procedures. This suggested that the transcatheter method is more cost-effective for selected patients. This was further supported by the follow-up assessment in the following year.

Annular displacement distance and velocity in patients with FMR were observed to be reduced as compared to the normal values[67]. The assessment of the 3D and dynamic changes of the mitral valve anatomy by means of the 3D tracking software. Degenerative MR was observed by means of the 3D annular area compared to normal values. The study in which the patients had decreased annular displacement distance and velocity which illustrated the interdependence between dynamic behavior of mitral valve and the etiology of the FMR.

Studies have also shown that MVR is usually preferred in the case of MR and is technically simpler and more reproducible for reduction of MR [68,69]. Transcatheter valve replacements assessment was done in a 75-year old woman who are repeatedly admitted for the heart failure mainly in the context of recurrent severe tricuspid regurgitation[70]. The transthoracic echocardiography was performed for the assessment and presented with a moderately dilated right ventricle with preserved function. The patient was implanted Edwards balloon-expandable valve as it has emerged as the potential alternative to surgery for high-risk patients with recurrent symptomatic severe regurgitation. A 23-mm Edwards balloon was inflated in the ring to assess the movement of the balloon and wire by the use of the CT-scan. The regurgitation remained severe even after the implantation and due to the oval shape, rigidity and the open configuration of the ring, the valve was imperfectly positioned. After multi-disciplinary investigation, surgical teams were involved in the replacement of the valve on the fourth day.

Chapter 7: Expected Findings and Potential Obstacles

The improvisation of the transcatheter interventions based on the understanding of the mitral valve complex has significant potential. The multi-modal approach of understanding the mitral valve complex has been observed to be the most successful. Due to the exposure of multiple complexities in the valve itself, the importance of understanding not only the anatomy but the pathology as well is important. The efficient and the reproducible style of intervention is also based on the mitral anatomy. Multiple modalities are applied for understanding and then implementing the methodologies.

Any interventional methodologies have multiple consequences including post-interventional complications and might also lead to death. Hence, the perception of the structure and physiology is essential. This thesis also provided information on the multiple modelling methodologies. However, the main obstacle is that the existing methodologies do not completely replicate the mitral valve under systolic and diastolic pressure.

Chapter 8: Discussion and Significance

The potential obstacles discussed in multiple sections of this thesis can only be tackled by the continual improvisation in the understanding of the mitral valve at different phases of the cardiac cycle. During the cardiac cycle, there is not only physiological but there are also chemical, elastic and other changes based on the surrounding structures including the ventricular wall. Failure of any surrounding structure to operate at a perfect pace might add stress on the mitral valve leading to its failure. Hence, thorough investigations are ongoing for that understanding and has significant potential in the interventional methodologies. This thesis is only trying to incorporate all those ideas to help upgrade the patient safety in the interventional methodologies.

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