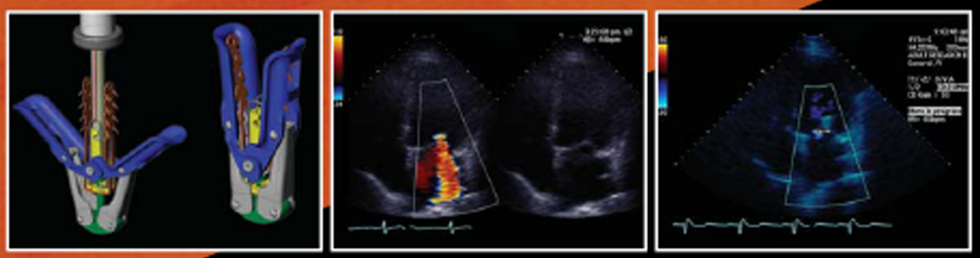
Percutaneous Mitral Leaflet Repair



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Percutaneous Mitral Leaflet Repair

Percutaneous Mitral Leaflet Repair:
MitraClip® Therapy for Mitral Regurgitation

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Foreword

Mitral regurgitation is a very serious medical condition that affects millions of patients in the United States and worldwide annually. Medical therapy is only marginally effective, but surgery for degenerative mitral regurgitation, in appropriate patients, is a tried and true therapy. However for functional mitral regurgitation, surgical intervention has its limitations and has generally been employed in conjunction with coronary artery bypass surgery or other valve operations, and less commonly as a stand-alone procedure.

Early in my career as a cardiac surgeon I took special interest in the mitral valve. I was intrigued by the elegant complexity and symphonic function of the mitral valve. After completing my cardiac surgery fellowship, I traveled the world to train with the "Masters of the Mitral Valve" including Alain Carpentier, Tirone David, Sir Madgi Yacoub, and Larry Cohen. I came away from this traveling fellowship with an even greater appreciation of the subtleties and complexities of the mitral valve apparatus. During this time I was exposed to the description of edge-to-edge mitral repair by Ottavio Alfieri and felt that it might provide an opportunity for a less invasive method for mitral repair. Given the need to open the heart for traditional annuloplasty or leaflet repair, a technique adaptable to beating heart surgery was attractive. In my animal laboratory at Columbia I created an approach for beating heart, "transapical edge-to-edge repair." We also demonstrated that the A2P2 coaptation point was the sweet spot, the "fulcrum" for the mitral valve apparatus. My team showed, using both mathematical fluid modeling and also in a sheep model, that stabilizing the A2P2 touch point reestablished effective coaptation of a dysfunctional mitral valve without compromising left ventricular function. We subsequently developed an approach for transapical edge-to-edge repair technique to facilitate off-pump mitral surgery. This pursuit of a less invasive approach led to a close association with Frederick St Goar's effort to develop an entirely percutaneous approach. I found the potential to move forward from a less invasive approach to mitral leaflet repair extremely exciting.

After more than a decade of development since these early concepts, percutaneous mitral valve repair totally has become, for selected patients, a reality. It's absolutely amazing.

This book represents the aggregation of the knowledge and experience accumulated with this approach during this exciting time of discovery. It has led to the creation of a new field and has fostered novel collaboration among cardiovascular specialties. It is especially exciting to see the accomplished path from open surgery, to beating heart surgical approaches, and finally to catheter-based therapy for a disease state that has resisted therapy for so many years and to appreciate the tremendous number of patients who will benefit from these efforts.

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My journey to develop and commercialize the MitraClip® system began more than 12 years ago. As president and CEO of Evalve, the start-up company that first developed and initially commercialized the technology, and later as general manager of the Structural Heart division of Abbott Vascular, I have had a unique vantage point to experience the challenges and opportunities involved in developing a first-in-class medical device.

Many people, including the distinguished coauthors of this book, took this journey with me. From the early bench tests and challenging preclinical studies, to first-in-human use and controlled clinical trials, this team of multidisciplinary leaders has provided wisdom, counsel, and perspective based on years of experience in cardiovascular medicine, interventional cardiology, cardiac surgery, echo-cardiology, pathology, and product development.

Mitral regurgitation is a progressive disease that continues to worsen when left untreated. Mitral regurgitation causes compensatory remodeling of the left ventricle, which results in reduced functional capacity, poor quality of life, repeat hospitalizations, and eventually in death from heart failure. Surgeons have successfully repaired the mitral valve to reduce mitral regurgitation in open, arrested heart surgery for over 50 years. However, many patients who are too sick to undergo traditional heart surgery continue to suffer from severe mitral regurgitation. The quest to help these patients through the development and application of the MitraClip® system, which has impacted more than 5000 patients and their families throughout the world, is chronicled in this book.

This collective work provides a broad and deep knowledge of the origin, history, and rapid evolution of the MitraClip® therapy. The first MitraClip® procedure was performed more than eight years ago and it took five years from that first procedure to perform 300 procedures. As of January 2012, more than 300 procedures are performed every month. Over this time, technology in the catheterization laboratory has advanced providing better methods for imaging the procedure. For example, when the early MitraClip® procedures were performed, real-time three-dimensional transesophageal echocardiography was a research tool, but today this widely available technology is routinely used to help guide MitraClip® procedures. As the therapy continues

to advance at a fast pace, it is important that this text is available as a core reference on the MitraClip® system, as well a foundation for future learning on percutaneous mitral valve therapies.

All of the work described in this text also has a larger role to play in illuminating the critical junctures along the path of medical device innovation. For example, we see the importance of conducting multiple clinical studies to answer the many and evolving questions presented by a first-in-class therapy. Insight is gained into the need to compare new therapies to the gold standard of care (to clearly define the relative risks and benefits) while often in practice, adoption of a new therapy is primarily in patients for whom the standard of care is not an option.

Ultimately, the evidence presented in this book provides extensive support for the MitraClip® therapy as a therapeutic alternative for patients who currently have no good options for reduction of mitral regurgitation. I believe that the next generation of clinical and scientific advancement will expand the availability of the therapy to more patients as the clinical community works to ensure patients have options that best suit their needs.

Advancing healthcare technology is an exceptionally rewarding career. It is a privilege to witness the joy of patients and their families as they start life anew thanks to the hard work and dedication of many clinicians, scientists, and company employees. Improvement in patient care does not happen without clinical leaders who are tireless advocates for their patients. Dr Ted Feldman, without whom this book would not have been possible, is the very personification of this type of leader. For his guidance, leadership, clinical expertise, and friendship, I will always be grateful.

Ferolyn Powell
President & CEO Evalve, Inc. 1999–2009
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Preface

When, 20 years ago, I successfully performed an edge–to-edge repair for the first time on a patient with anterior leaflet segmental flail due to primary chordal rupture, I immediately had the perception that such a procedure could have an impact of some relevance in the treatment of patients with mitral regurgitation. As a matter of fact, the functional result in that case was perfect: the newly created double-orifice mitral valve was totally competent and the global mitral area was well above 3 cm^2 even after implantation of a prosthetic ring. Besides being effective, the edge-to-edge repair was extraordinarily simple. Only few minutes were required to correct a lesion which was considered complex and well known to be historically associated with suboptimal surgical results. At that time many surgeons used to replace the mitral valve when the anterior leaflet was involved in the mechanism producing mitral regurgitation. It was clear to me after that initial experience that a double orifice repair could be easily reproducible by every surgeon and therefore be a useful addition to the armamentarium of the techniques used for mitral valve reconstructive surgery.

In the following years our surgical experience expanded and the validity of the concept was repeatedly demonstrated in a variety of clinical subsets. Rigorous follow-up data were collected including echo findings at rest and under exercise, and highly satisfactory mid-term results were reported in patients who received the edge-to-edge repair in conjunction with annuloplasty. Simultaneously the pathophysiology of the operation was extensively studied using computer modeling methods. In well-selected patients without annular dilatation, the prosthetic ring was intentionally avoided without compromising the outcome, at least at mid term.

Our enthusiasm for the procedure, however, was always somehow mitigated by the skepticism of the surgical community. The main criticism was that the edge-to-edge repair was not reproducing the configuration of a normal mitral valve and was a sort of convenient short cut for those who were unable to properly reconstruct the mitral valve. The occurrence of mitral stenosis was considered a potential problem, and the long-term durability of a double-orifice mitral valve was questioned. On the other hand, our referring cardiologists could observe excellent results even in complex cases and had a positive attitude in regard to the edge-to-edge technique. Thanks to the pragmatism of these cardiologists, we have been able to develop one of the largest practices in Europe in the field of mitral valve repair.

The simplicity and the effectiveness of this type of mitral repair were particularly attractive to innovators exploring methods to correct mitral regurgitation percutaneously via transcatheter interventions. Several grasping devices have been developed and tested in animal experiments to approximate the mitral leaflets and duplicate the Alfieri stitch. The MitraClip® system currently widely used in the clinical practice is definitely the most effective and reproducible.

The role of the percutaneous clip procedure in the clinical practice is still controversial at this point in time. Data from the EVEREST studies and from the rapidly growing clinical experience in Europe provide useful information which can be the basis for some recommendations. It has been definitely shown that the clip procedure is relatively safe and generally well tolerated even by patients in poor clinical condition, with serious comorbidities and/or severe left ventricular dysfunction. On the other hand, the clip reduces mitral regurgitation not so effectively as mitral valve surgery, and recurrence or worsening of mitral regurgitation is more likely to occur in the follow-up. It has to be recognized, however, that in sick patients with severe mitral regurgitation, some reduction of mitral regurgitation is providing meaningful clinical benefit. The applicability of the clip procedure is limited, since precise echocardiographic criteria have to be respected to make a patient eligible. A less rigorous adherence to the criteria of eligibility could allow increased applicability. Mitral valve repair after an unsuccessful clip procedure has been reported in many patients, although the preferred surgical option cannot always be maintained and valve replacement is occasionally necessary.

Considering all the above, the ideal candidate for the clip procedure could be an inoperable or high-risk symptomatic patients with severe mitral regurgitation (organic or functional), fulfilling the echocardiographic criteria of eligibility. In my opinion, for the time being, patients who can be offered mitral valve surgery with an acceptable risk should not be considered for percutaneous interventions. Along with rapid advancements in technology and progresses in imaging modalities, indications are expected to expand in the near future. Improvements in the first-generation device will take place, and some of the intrinsic limitations of the current system will be abolished. Furthermore, new sophisticated imaging modalities will be introduced and facilitate the procedure. Importantly, an effective catheter-based annuloplasty technique (not available at present) is badly needed to enhance the effectiveness and the durability of the clip procedure.

From a historical perspective, I think that the most important merit of the edge-to-edge technique was to make percutaneous mitral repair possible.

Ottavio Alfieri MD

Acknowledgments

I am grateful, especially to our first U.S. MitraClip® patient. He presented with dyspnea after being treated for 10 years, with a then new and relatively untested coronary therapy called rotational atherectomy. He sought me out because he wanted "whatever is newest" for his recurrent symptoms. Immediately upon laying a stethoscope on his chest and hearing a 4/6 murmur of new mitral regurgitation I recognized the serendipity of his presentation. It is the rare patient who seeks to be the first for a novel therapy, and this man launched all that has led to this comprehensive book on MitraClip®.

Ted Feldman MD

1 Anatomy of the mitral valvular complex

Nicolas M. Van Mieghem, Jackie S. McGhie, and Margot M. Bartelings

INTRODUCTION

> "*…mitral insufficiency begets mitral insufficiency….*"
> *Jesse E. Edwards and Howard B. Burchell, 1958* (1).

The mitral valvular apparatus is the complex anatomical and functional entity (2) that separates the left atrium from the left ventricle. The both famous and infamous Belgian anatomist and physician Andreas Vesalius described the bicuspid left atrioventricular valve as resembling a bishop's mitre, hence the term mitral valve (3). The mitral valve as such (the annulus with two leaflets) is encapsulated within surrounding structures: the left atrium, the left ventricle, the aortic valve, the papillary muscles, the tendinous cords, and the cardiac central fibrous body. In 1972, Perloff and Roberts introduced the concept of the "mitral apparatus" to underscore this essential and harmonious structural relationship (2).

One or more flaws in the machinery can impair adequate mitral valve functioning. The pathophysiology can be functional, structural, or mixed. Inadequate apposition and coaptation of the mitral leaflets during systole will result in mitral regurgitation, whereas obstruction to diastolic forward flow into the left ventricle marks mitral stenosis. In all age groups, mitral regurgitation is the most common valvular disorder with a global prevalence of 1.7%, increasing to 10% in the ≥75-year olds (4). Practical knowledge of the anatomy of the mitral valvular apparatus forms the base of understanding the pathophysiology of mitral valve disorders in general and mitral regurgitation in particular and is an evident prerequisite for successful treatment of mitral valve pathology.

The Mitral Valvular Complex

Adequate mitral valve closure requires alignment and contact of the two mitral leaflets in one single plane (apposition and coaptation). An optimal annulus size, a geometrically correct orientation of the papillary muscles with the tendinous cords attached and the closing forces generated by the left ventricle catalyze this sophisticated process. From an anatomical perspective the mitral apparatus is intimately related to surrounding structures like the electrical conduction system, the aortic valve, the coronary sinus (CS), and the left circumflex coronary artery. Evidently this integrated anatomy is relevant for surgical and catheter-bound mitral valve therapies (5).

The Mitral Annulus

The mitral annulus is D-shaped and is defined by the confluence of the fibrous cardiac skeleton and mitral valvular tissue on the one hand and left atrial and ventricular myocardium on the other (6). It has a longer intercommissural and a shorter aortic-mural (septal-to-lateral) axis. From a three-dimensional (3D) perspective it has a non-planar configuration with elevated anteroseptal and posterolateral segments toward the atrium and complementary depressed medial (septal) and anterolateral segments (at the commissures) toward the ventricle, giving the annulus its typical "saddle shape" appearance (Fig. 1.1) (7–9). The mitral valve is located posterior and inferior to the aortic valve, which can be regarded as the centrepiece of the heart. The left and non-coronary leaflets (often inappropriately called cusps) of the aortic valve and the anterior (aortic) leaflet of the mitral valve form continuity. This so-called aortic-mitral curtain is bordered by fibrous expansions, the left and right fibrous trigones (Fig. 1.2). The cardiac skeleton is formed by the fusion of both the membranous septum (interventricular and atrioventricular) and the aortic-mitral curtain and houses the bundle of His, which is the prolongation of the atrioventricular node and represents the main connection of the atrial and ventricular electrical conduction system (10).

Fibroelastic tissue extends from the fibrous trigones to mark the virtual annulus; anteriorly, it is a semicircular solid structure. From a pathological perspective this rigid structure makes the anterior annular segment resistant to dilatation but also more vulnerable to so-called skip or direct extension lesions from aortic valve endocarditis given its continuity with the aortic valve. Especially in its posterior aspects several blanks in the annular structure are filled with atrial myocardium and adipose tissue. Hutchins et al. introduced the term "disjunction" to define this absence of a complete cord-like ring of connective tissue encircling the atrioventricular junction (11). The absence of a well-formed fibrous cord in this particular position opposite the aortic-mitral curtain explains its predilection for annular dilation and calcification resulting in a disproportional increase in the aortic-mural (septal-to-lateral) diameter. The virtual annulus is not a static structure; during systole it exhibits a sphincteric contraction, which can reduce the annular surface by up to 25% and a translational excursion toward the apex, reflecting the propagation of the ventricular torsion at the base of the heart (12–15).

Mitral Leaflets

The mitral valve is bicuspid. What is classically referred to as the anterior mitral leaflet is closely related to the aortic valve and the septum, hence the alternative term "aortic leaflet" (2,3,10). As a corollary, the posterior mitral leaflet is also called the "mural leaflet." The anterior leaflet is long with a narrow base that encloses one-third of the annular circumference. It separates the inflow and outflow tracts of the left ventricle. The posterior leaflet is short but has a wide base that extends over

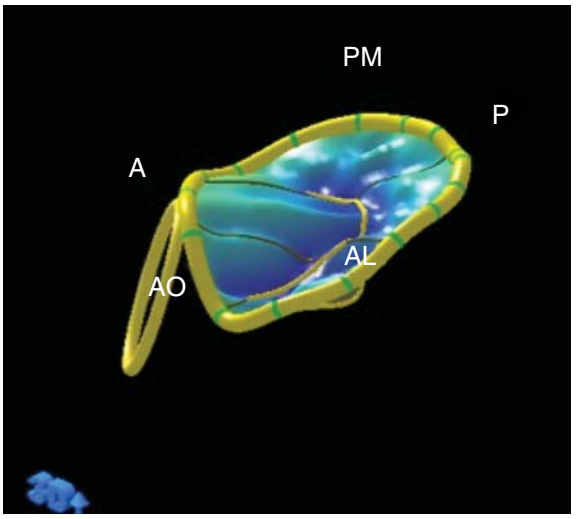

Figure 1.1 Three-dimensional echocardiographic illustration of the "mitral annulus" demonstrating the saddle shape. The anteroseptal (A) and posterolateral (P) segments toward the atrium are elevated whereas the complementary medial (septal) (PM) and anterolateral segments (AL) (at the commissures) toward the ventricle are depressed. *Abbreviations*: Ao, aorta.

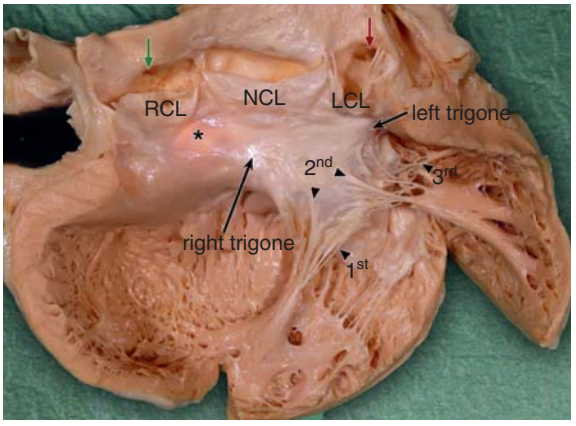

Figure 1.2 The aortic-mitral curtain. *: membranous septum. RCL: right coronary leaflet with ostium of the right coronary artery (*green arrow*). NCL: non-coronary leaflet. LCL: left coronary leaflet with ostium of left main stem (*red arrow*). Arrowheads 1st, 2nd, 3rd: primary, secondary, tertiary cords.

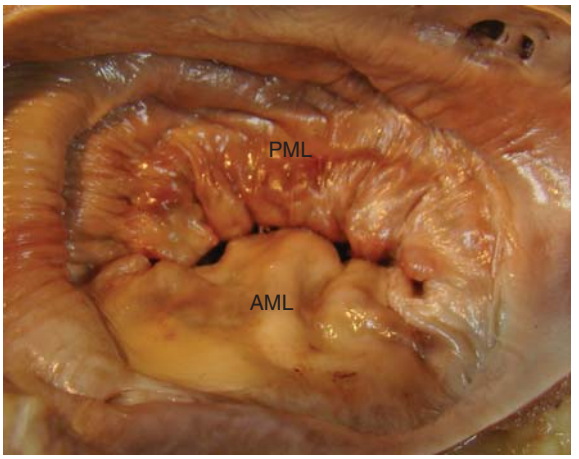

Figure 1.3 View on the closed mitral valve (systolic position) from a left atrial perspective. The anterior mitral leaflet (AML) has a longer surface with a shorter base and encloses one-third of the annular circumference. The posterior mitral leaflet (PML) is short but extending over two-thirds of the annular circumference.

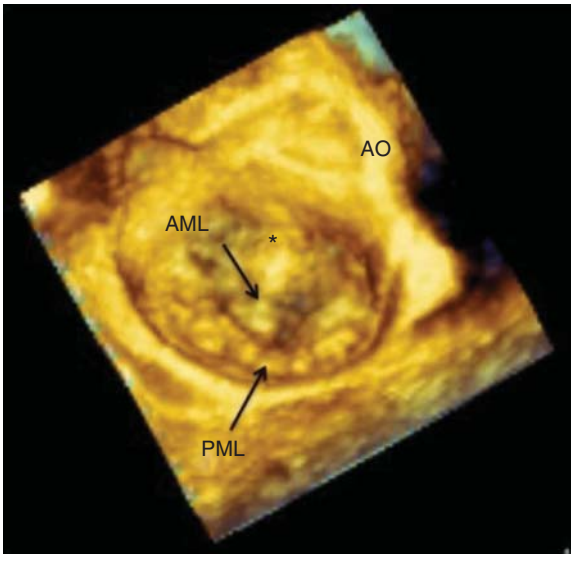

Figure 1.4 Three-dimensional echocardiographic reconstruction illustrating the "surgical view." The zone of apposition has an oblique orientation relative to the orthogonal planes of the body and is recognized as the "mitral smile." Ao: aorta. *: aortic-mitral curtain (fibrous continuity).

two-thirds of the annular circumference (Fig. 1.3). The surface area of both leaflets together is 2.5 times the area of the annular orifice. In systole, normal mitral valve leaflets coapt over a height of, on an average, 8 mm giving an "overlapping reserve" or "coaptation reserve" in case of annular dilation. The zone of apposition has an oblique orientation relative to the orthogonal planes of the body and is recognized as the "mitral smile" by short axis echocardiography (Figs. 1.3 and 1.4). It is bordered by the posteromedial and anterolateral commissures. Slits in the posterior leaflet create three scallops. Together with the commissures these indentations are areas with less and thinner leaflet material contributing to a more flexible posterior leaflet and complying with the dynamic motions of the annulus (the so-called sphincter mechanism).

Aortic-Mitral Curtain

As mentioned earlier the aortic-mitral curtain is formed by the confluence of the left and non-coronary leaflets of the aortic

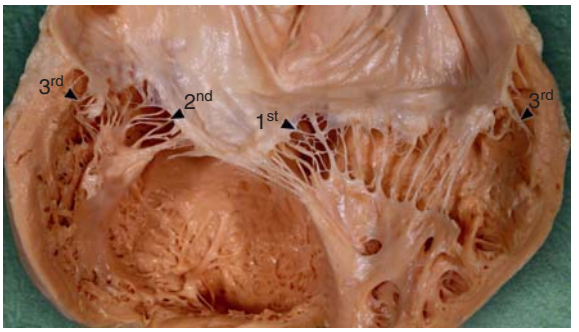

Figure 1.5 Atrial aspect of the mitral valve with three generations of cords. Arrowheads 1st, 2nd, 3rd: primary, secondary, tertiary cords.

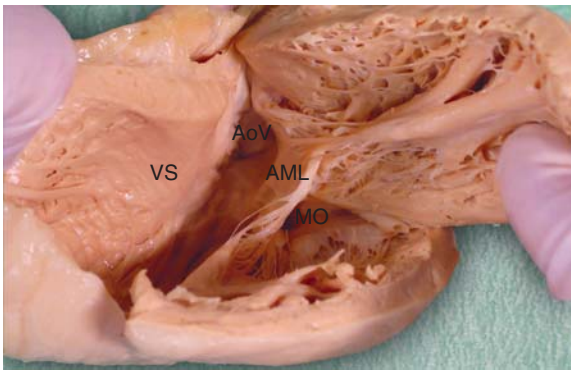

Figure 1.6 The left ventricular outflow tract is sandwiched between the ventricular septum (VS) and the anterior mitral leaflet (AML). *Abbreviations*: AoV, aortic valve; MO, mitral orifice.

valve and the anterior (aortic) leaflet of the mitral valve. It is underpinned by strut (principal) cords, which connect the papillary muscles and the anterior mitral leaflet and contribute to its virtually inert state throughout the cardiac cycle (15). As such, the aortic-mitral curtain functions as an anchor and hinge point for the aortic and mitral valve dynamics. Animal experiments and 3D transoesophageal echocardiography studies in humans elegantly demonstrated the coupled reciprocal behavior of the aortic and mitral annulus (16,17). The mitral valve annulus reaches its maximum area in early diastole when the aortic annulus area is minimal. Conversely, the aortic annulus obtains its maximal surface area in open position in systole when the mitral annulus area is the smallest area. Furthermore, during systole the angle between the aortic and mitral annulus decreases due to a flexion motion of both structures around the inert anchoring of the aortic-mitral curtain. Both principles may hypothetically optimize left ventricular contraction since the aortic annulus contraction facilitates mitral annulus expansion and vice versa and the geometric changes in systole (the "aortic-mitral flexion") may optimize ejection of blood toward the aorta. If the tension of the strut cords is released, the aortic-mitral curtain angulation (approximately 90°) is dissolved and the aortic and mitral annuli are drawn together which may impact LV geometry and performance.

Tendinous Cords and Papillary Muscles

The mitral valve leaflets are connected to the left ventricular free wall like a parachute (2,3,10). Fibro-elastic collagen-bound tendinous cords (chordae tendineae) arise from the papillary muscles, bifurcate several times, and attach to the ventricular side of both leaflets (18). The cords intermingle within the fibrous components of leaflets, annulus, and even trigones. The thinnest part is near the insertion site on the leaflets and is the predilection site for chordal rupture. There are three orders of tendinous cords (Figs. 1.2 and 1.5): the primary or marginal cords insert on the free margin of the leaflets to prevent marginal prolapse, align the coaptation zone, and maintain leaflet apposition during valve closure; secondary or intermediate cords attach onto the ventricular surface to preclude billowing and distribute tension on the leaflet tissue. Among the secondary cords, the stay, strut, or principal cords are longer and thicker and insert on the ventricular surface of the anterior mitral leaflet ensuring direct continuity between the LV myocardium through the papillary muscles and the mitral annulus at the fibrous trigones. These struts are under continuous tension and contribute to LV geometry and angulation between the aortic and mitral annulus through the aortic-mitral curtain (see the previous section) (15). Tertiary or basal cords originate directly from the ventricular wall and attach exclusively to the posterior leaflet contributing to ventricular geometry and annular fortification (Figs. 1.2 and 1.5).

There are two papillary muscles entrenched into the apical to middle thirds of the left ventricular free wall, each with a variable number of composing subdivisional heads. The classic and somewhat simplified paradigm is that the blood supply to the anterolateral papillary muscle is provided by one or more branches of the left circumflex or diagonal branches, whereas the posteromedial papillary muscle is supplied by a single branch of the left circumflex or right coronary artery depending on coronary dominance. Due to its single vascular supply, the posteromedial papillary muscle in particular is susceptible to coronary ischemia.

Left Atrium and Left Ventricle Integration

From the previous description, it is clear that the myocardium of the left atrium and ventricle is intimately connected to the mitral valve. The term disjunction has already been proposed to mark the fact that rather than being separated by an anatomic cord-like structure, myocardium hinges directly to the valvular tissue (11). More specifically, this disjunction is apparent at the posterior segment where the left atrial posterior wall hinges directly onto the posterior leaflet. This particular continuity might render the posterior leaflet more vulnerable to being displaced in the case of left atrial enlargement hypothetically causing annular dilatation and valvular malcoaptation (2). The insertion of the left atrial myocardium follows the general contour of the annulus. This does

not hold true (3,18) for the left ventricular myocardium, which at the level of the aortic-mitral curtain doesn't hinge onto the anterior leaflet nor to the annular structure per se; so the left ventricular outflow tract gets sandwiched between the ventricular septum and the anterior mitral leaflet (Fig. 1.6). The free wall of the left ventricle on the other hand is directly connected to the posterior leaflet through the mural or tertiary cords and hinges onto the anterolateral commissure. Finally, the papillary muscles can be viewed as extensions of the apical to lateral left ventricle wall and are connected to the ventricular surface and the free edge of both mitral leaflets through the tendinous cords. Given the tight interdependence with the ventricular free wall and the unique arrangements of the different components, changes in ventricular geometry can have serious consequences for the mitral valve dynamics (19,20). Left ventricular free wall dyskinesia can change the orientation of the tertiary (basal) cords with a tethering effect on the valve leaflets. And yet more global left ventricular dilatation can displace the papillary muscles in an apical direction creating tenting of the mitral leaflets. The result will be a malcoaptation of the mitral leaflets and eventually mitral regurgitation.

Coronary Venous and Arterial Anatomy

It's not our aim to give a comprehensive review of the coronary venous and arterial circulation. Rather, we would present relevant anatomical data illustrating the complex relationship between the coronary vasculature and the mitral valve annulus.

In a venous system where there is plenty of interindividual variability, consistent entities are the anterior interventricular vein (AIV), the great cardiac vein (GCV) and the CS (20,21). In general, the AIV originates at the lower or middle third of the anterior interventricular groove (22). It follows the groove toward the base of the heart and then turns posterior at the atrioventricular groove to enter the GCV. The GCV wraps around the left atrioventricular groove to fuse with the oblique left atrial vein (remnant of the embryonic left superior vena cava) to become the CS. The middle cardiac vein (MCV) runs along the posterior interventricular groove to empty into the CS close to its orifice in the right atrium. The orifice of the CS in the right atrium is slightly posterior to the atrioventricular bundle and is guarded by a thin semicircular valve, the thebesian valve, which may have a cribriform, muscular, fibrous, or fibromuscular morphology and composition (Fig. 1.7) (20). The AIV and MCV are accompanied by the left anterior descending artery and posterior descending artery respectively (23). The CS and the GCV have a more unpredictable course relative to the left circumflex artery (LCX) and its marginal branches. There is a vast literature on the complex interrelation between the CS-GCV, the LCX and the mitral annulus (MA) (20,21,24–26). Several imaging modalities each with their pros and cons have proved to be useful in examining this particular anatomy: venography, 3D echocardiography, multislice CT, electron-beam CT, and cMRI. On top of this there is also valuable pathology data available (20).

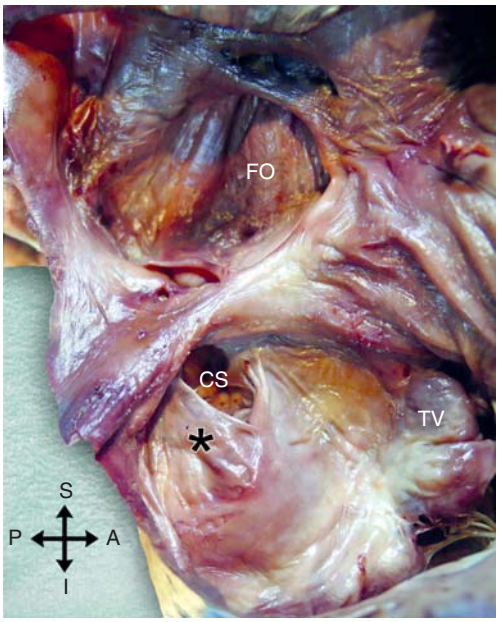

Figure 1.7 Right atrial view on the trial septum. The orifice of the coronary sinus (CS) in the right atrium is guarded by the Thebesian valve (asterisk). *Abbreviations*: FO, foramen ovale; TV, tricuspid valve.

Unfortunately, there is no standardized method of measuring or reporting, which makes it virtually impossible to extrapolate quantitative data from one study to the other and from one imaging technology to the other. Nonetheless, some general principles can be extracted.

The location of the CS relative to the MA changes along its course. In the majority of cases (90–100%), the body of the CS is adjacent to the posterior left atrial wall, well above and cranial to the deeper laying MA (Fig. 1.8) (21,24,27). It is closest to the lateral segment of the MA (at the corresponding P2 level) and furthest from the commissures. With significant mitral regurgitation (particularly in ischemic cardiomyopathy) the CS gets lifted away from the lateral MA segment, and conversely moves closer to the commissures (21,25). This coincides with the flattening of the "3D saddle shaped" annulus and the increase in the septal-to-lateral annular diameter (11). As the CS nears its ostium and accepts several branches, its caliber grows. The CS always runs in close vicinity to the LCX (distance CS-LCX 1. 3 ± 1. 0 mm (21) to 2.7 ± 1.0 mm (25)). The LCX is overcrossed by the CS/GCV in 60–80% of the time (Fig. 1.9). The crossing point relative to the CS ostium, the length of the overlapping segment, the length of the parallel course as well as the distance of the CS–LCX crossing point to the MA is highly variable. The AIV on its turn overcrosses a diagonal or ramus branch in up to 16% of cases according to the pathology study by Maselli (20).

CONCLUSIONS

The mitral valve is part of a broader mitral valvular complex. Normal valvular mechanics require a sophisticated interaction

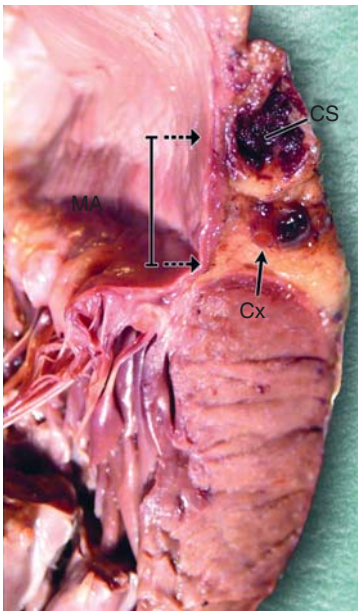

Figure 1.8 The coronary sinus (CS) is located well above and cranial to the deeper laying mitral annulus (MA). The distance is indicated by the dotted arrows. *Black arrow*: left circumflex artery (LCX).

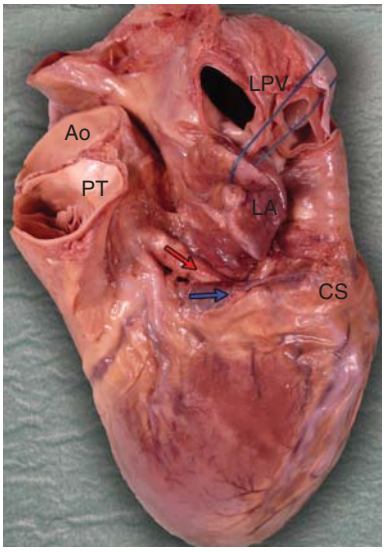

Figure 1.9 The left trial appendage (LA) is pulled away to expose the coronary sinus (CS)/great cardiac vein (*blue arrow*), which crosses the left circumflex artery (*red arrow*). *Abbreviations*: Ao, aorta; LPV, left pulmonary veins; PT, pulmonary trunk.

of the different valve components and the adjacent left ventricular and atrial myocardium.

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2 The pathophysiology of mitral regurgitation

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INTRODUCTION

Incompetence of the mitral valve allows a portion of left ventricular (LV) stroke volume to be regurgitated into the left atrium (LA), necessitating an increased volume output to make up for that lost to regurgitation. In addressing the pathophysiology of mitral regurgitation (MR) it is mandatory to distinguish between primary (organic) MR and secondary (functional) MR. In primary MR there is disease of one or more components of the mitral valve causing the valve to leak, allowing blood to flow back into the LA during systole. Regurgitation, in turn, places a hemodynamic overload upon the LV which, if severe and prolonged, leads to LV damage, heart failure, and eventual death. This pathophysiology is relatively straightforward. It is valve disease that leads to negative sequelae and restoration of valvular competence is curative if performed in a timely manner.

The pathophysiology of secondary or functional MR is far more complex. Here, it is the disease of the ventricle caused by myocardial infarction or cardiomyopathy that causes regional wall motion abnormalities, ventricular dilatation, papillary muscle displacement, and annular dilatation which in turn cause a normal mitral valve to leak. Thus, the main problem is not the MR itself but rather severe LV damage to which MR is added as a secondary pathology. Because restoration of mitral competence cannot cure the underlying ventricular pathology, the role of such therapy is much less clear than it is for primary MR.

PRIMARY MR

The Stages of Primary MR

Acute MR

Acute severe MR as might occur with the rupture of a chorda tendina or with leaflet destruction in infective endocarditis imparts a sudden volume overload on the LA and LV (Fig. 2.1A) (1). The volume overload on the LV increases preload (sarcomere stretch), maximizing utilization of the Frank–Starling mechanism (2) which increases LV's pumping ability and also causes a small increase in the end diastolic volume. At the same time the new low impedance pathway for ejection into the LA reduces LV afterload. The increased preload and decreased afterload, both act in concert with sympathetically increased contractility to increase the total LV stroke volume. However, because a large portion of the total stroke is ejected into the LA instead of the aorta, forward output falls. At the same time the small LA is overfilled, causing high LA filling pressure, resulting in pulmonary congestion. Thus, the patient with acute severe MR experiences heart failure, yet LV muscle function is normal or even increased.

Chronic Compensated MR

Many patients with acute MR require immediate surgery to relieve heart failure by correcting the leaking valve. However, if severe MR develops more gradually allowing for LV and LA adaptation, the patient may enter a chronic compensated phase (Fig. 2.1B). In this phase eccentric cardiac hypertrophy develops, leading to a large increase in LV end diastolic volume, allowing for increased LV total and forward stroke volume. Increased LV radius increases the systolic wall stress from its reduced level in the acute phase to normal in this phase. However, increased preload in conjunction with normal contractile function still maintains a higher-than-normal ejection fraction. In this phase the LA has also enlarged, allowing it to receive the regurgitant volume at a lower filling pressure. Thus, compensated with normal forward output and left-sided filling pressures, the patient may be entirely symptom free despite severe MR.

Chronic Decompensated MR

While chronic severe MR may be tolerated for several years, most patients progress to the decompensated stage in about five years (3,4). In this stage persistent severe MR has caused both substantial myocardial damage and pronounced LV remodeling leading to LV contractile dysfunction. The loss of contractile force impairs LV shortening so that the end systolic volume increases. This increase is compounded by abnormally high afterload. Although MR is often believed to unload the LV by way of the ejection pathway into the LA, this tendency is offset by the increase in the radius term of the Laplace equation for wall stress (σ, afterload): $\sigma = P \times r/2th$ where P = LV systolic pressure, r = LV radius, and th = LV thickness. Thus in decompensated MR, afterload is increased not decreased as is often held (5). In turn LV filling pressures are increased and forward stroke volume decreases. In most cases these adverse changes lead to heart failure symptoms. However, even though contractile dysfunction has occurred, increased preload may maintain LV ejection fraction in the "normal" range, potentially falsely reassuring the clinician that the patient is still compensated (6).

THE MECHANISMS OF LEFT VENTRICULAR DYSFUNCTION

An obvious question arises from the above discussion: What are the mechanisms that transit the LV from its compensated to the decompensated state? Are these mechanisms a property of the LV chamber, the myocytes comprising the chamber, or some combination of both?