Mitral Valve Disease

Basic Sciences and Current Approaches to Management

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It is with very fond memories that I dedicate my contribution in this book to three important mentors: Matthias Paneth, at Royal Brompton Hospital, who inspired me with humour and professionalism; Dr. Craig Miller for his commitment to the basic science of valve function and a good friend; and Professor Alain Carpentier, whose rigorous approach to the understanding and management of mitral valve disease has been an inspiration to multiple generations of mitral valve surgeons. Also, to my surgical colleagues at Royal Papworth hospital during the last thirty five years who have at all times been supportive, challenging and kind. A magnificent bunch of imaginative reprobates

Francis C. Wells

Early in my career, I was impressed by the Foreword to one of the books written by the late philosopher Freddie Ayer. He commented that it was always the comments of his strongest critic that proved most valuable when he was contemplating how best to establish his own concepts. I have exactly the same feelings with regard to my

good friend Richard Van Praagh. Although we have rarely seen eye to eye on the best way to describe the cardiac components, I would not have honed most of my concepts without his stringent criticisms, for which I thank him most sincerely.

Robert H. Anderson

Preface

The abbreviators[1] *(of works) do harm to knowledge and to love, for the love of anything is the offspring of knowledge, love being more fervent in proportion as knowledge is more certain. And this certainty springs from a complete knowledge of all of the parts which united compose the whole of the thing which ought to be loved*. Leonardo da Vinci W.19084r. Royal library, Windsor.

These words of Leonardo beautifully encompass the reason for this book. A full and complete knowledge, understanding and love of the basic science appertaining to the mitral valve must enable the caring professional to strive towards the very best management.

The left atrioventricular valvar complex, usually known as the mitral valve, is coming of age. The physiological and structural complexity of this, the lynchpin of cardiac function, is now widely appreciated. The details of development, the structural change in response to uneven pressure distribution, cellular signalling incurring structural change and the genetic determination of diseased states, are less so.

Whilst libraries and journals are replete with information on the imaging, diagnosis and surgical management of the lesions encountered in the setting of the diseased mitral valve, this book sets out to provide up-to-date information on these and other areas of basic science, in an attempt to serve as easy reference for those with an interest. In addition, we have encouraged a standardisation of terminology in the descriptions of the valvar components to enhance communication between specialists involved in the care of patients suffering from mitral valve disease.

A thorough understanding of all aspects of the valve must enhance the therapeutic approach to its malfunction. In particular, the embryological development and morphology of the valve can, and should, shape decisions on the optimal surgical approach. A particularly hot topic of discussion at the moment is the reality or otherwise of what has been referred to as leaflet disjunction. A detailed analysis of the hinging of the mural leaflet at the atrioventricular junction reveals that this term is not helpful in reaching for a true understanding of the functional impact of variations in leaflet origin on the presence or absence of mitral regurgitation and leaflet

[1] The name abbreviation was given to the secretaries at the chancery of the Vatican, who impeded Leonardo's work during his stay at the pleasure of the Medici pope whilst working on the anatomy and physiology of the heart, and in writing these words, he may have had them in mind.

prolapse. Further work is needed in this area if we are to engage in truly informed discussions.

The editors are two veritable Shropshire Lads (one born in the sight of Bredon Hill and the other of the Wrekin). Our paths first crossed whilst working at Royal Brompton Hospital and both of us were heavily influenced by the sage of cardiac surgery, Dr John Kirklin of the University of Alabama. His scientific approach to our specialty was groundbreaking and set standards of care through knowledge that remain a paragon of intellectual cardiac surgery.

It is our hope that this book may make a significant contribution to encouraging a much wider appreciation of the importance of a sound understanding of the basic sciences pertaining to this wonderfully complex structure, a true wonder of nature.

Cambridge, UK — Francis C. Wells
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Contents

The Mitral Valve: A Brief History

1

Francis C. Wells

The left atrioventricular valve acquired its "mitral" designation through a description by the great renaissance anatomist Andreas Vesalius. In his seminal text De Humani Corporis Fabrica Libri Septum (first edition:1543), he wrote the following. "At the root of the circle of the venous artery (the left atrium), a membranous circle [valvar atrio-ventricularis sinistra] originates from the substance of the heart (the atrioventricular junction) and goes inward into the space of the left ventricle, when it descends a little way into the space of the ventricle it splits into two membranous processes resembling in shape those of the right ventricular membranes being however of only two rather than three on the right side. They are greater in strength than those in the right ventricle. Because the membranous circle of the venous artery (left atrium) is split into only two membranes you would not be wrong in comparing them to a Bishop's Mitre if you compare the part encircling the head to the membranous circle and its processes to the front and the back points of the Mitre" [1].

Vesalius described the function of these membranes of the heart as bodies that are present to prevent regurgitation of material (sanguis). His description is fully recognisable in modern parlance. Outwith the now correct nomenclature, that of the aortic and mural leaflets, Vesalius describes the two leaflets as facing the right and the left sides of the left ventricle. He correctly describes the arching distribution of cordal insertions leaving the underside of the leaflets and inserting into the muscle of the left ventricle. He described how the cords are stabilised by fleshy projections from the ventricular wall (musculus papillares anteriores and posteriores), which we call the antero-superior and infero-lateral papillary muscles. He contrasts his description and comparison to an up-turned Bishop's Mitre to that of Galen, who described the leaflets as being like arrowheads projecting downwards into the ventricular cavity [2]. Thus, as elsewhere in his text, Vesalius reveals a deep knowledge of prior anatomical writings, especially those of the great natural philosophers,

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Hippocrates (460–375 BCE), Aristotle (385–323 BCE), Erasistratus (304–250 BCE), and Galen (129–c.200 AD). Interestingly, there is no mention of the work of that other great renaissance man, Leonardo da Vinci. Thirty years earlier he had extensively written and illustrated his studies on the structure and function of the heart and the valves of the heart. This ground-breaking work, although recognised as important by the few who saw it, was confined to the pages of personal notes never published, underscoring the importance of publishing work for peer review and discussion.

The first known descriptions of the heart begin with an Egyptian papyrus from about 3,000 BCE in which there is a description of the heart and great vessels. The ancient Egyptian understanding of the heart was very much based on the interconnection of mysticism, religion, and spirituality of the human form. Its central importance in the balance of the mind and body is manifest in the assessment of a life by comparing the weight of the feather of Maat with the heart of the deceased, which was laden with the burdens of their lifestyle and moral failures. Maat is the concept of universal balance and harmony, personified in the goddess of that name. It is thus clear that the heart was more than an anatomical structure.

A canon of medicine from around 2,600 BCE ascribed to the legendary Chinese Emperor Huang Ti, recognised that the heart and pulse regulate the blood, which according to this manuscript flows in a continuous circle and never stops. The Greek anatomist and royal physician to Selenicus, Nicator of Syria, founded the school of anatomy in Alexandria with Heroditus. He described the valves of the heart [3]. He also concluded that the heart was not the centre of sensation but was a pump.

Aristotle made mention of the valves of the heart in his books de Respiratione and de partibus Animalium 3, referenced by William Harvey in his masterpiece “de Motu Cordis.” Aristotle called them nerves, with little further comment. Hippocrates, in contrast, wrote as follows “The hidden membranes and fibres spread throughout the chambers like cobwebs especially around the orifices. There are filaments implanted into the walls of the chambers as well. The author believes these to be guy ropes and stays of the heart as well as the foundation of the arteries.” These ultra-modern comments resonate with our modern understanding of the importance of the mitral valvar complex in supporting left ventricular function.

Much of the work of these academic giants has been passed down to us through the work of Avicenna. Abu Ali Sina or Ibn Sina was a Persian polymath. He is regarded as one of the most important and influential physicians, astronomers, and thinkers of the Islamic Golden age. Many of his writings have survived and revealed the heavy influence of Hippocrates. His “Canon of Medicine” is regarded as the founding text of medieval and early modern medicine. Without his extensive discourses on Hippocrates and Galen much of the work of those giants may never have been recognised as they are today.

The Renaissance anatomist Alessandro Benedetti, born in Parma in 1450, physician of Verona and Padua, and surgeon to the Venetian army, described the valves as uni-directional gates. He called them “valvulae,” from the Latin “valva,” a leaf of a folding door. He also began to distinguish the heart as a capacitance pump receiving blood, rather than contributing blood on the basis of the uni-directional control of

the flow of the valves. He recognised the importance of the strength of the mitral valve, which he described as the strongest of all of the heart valves. He was responsible for the construction of the first-ever anatomy theatre in Padua, where he carried out his instructional dissections.

Sandwiched between these early renaissance anatomists and Andreas Vesalius, as already emphasised, is the unpublished and largely undiscovered work of the Florentine polymath Leonardo da Vinci. Living from1452 until 1519 and a self-educated natural philosopher, Leonardo set about a very detailed comparative anatomical study of the heart begun in Milan, continued at the family home of his apprentice and long-time travelling companion Francesco Melzi, and completed during his move to Rome in the employment of the Pope. Leonardo spent a year in the Melzi family home, a villa overlooking the river Adda just nineteen miles from Milan. There he was able to pursue his many interests in geology, hydrology, and anatomical dissection. In the absence of human material on which to work, Leonardo invested his efforts in animal dissection, extending his understanding of comparative anatomy. This investment of energy into animal dissection reveals his insistence that all natural forms are diagrams of the forces acting upon them, which was an Aristotelian mantra. On this basis, he argued that physiological function could be deduced from form, whatever the setting. The chapter in this book on the comparative anatomy of the mitral valve (The Atrioventricular valve in the animal kingdom, Bjarke Jensen) reveals the appropriateness of comparisons across species in modern times. Thus the heart, the body's pump, would reveal its secrets through an understanding of hydrology, architecture, and structural form in a way that can be transposed to other settings.

In March of 1513, Giovanni de Medici was elected Pope. He became Pope Leo X; He was the son of Lorenzo "the magnificent" de Medici, the Florentine ruler who had patronised Leonardo whilst in Florence, and recommended him to the Sforza court in Milan, perhaps helping him to escape the hubris of two court appearances for homosexuality. This latter move to Rome allowed Leonardo to recommence his dissection on human cadavers, an activity that it is suggested caused his removal from the employ of Giovanni following an occupational dispute based on the jealousy of a German mirror maker, with whom Leonardo was sharing quarters in the Villa Belvedere within the Vatican. He was returning to a fraternity very familiar to him in the company of Bramante, Michelangelo, and Raphael; not all of them happy relationships. Comparisons of his output whilst in the employ of the Pope with those of his younger competitors became unfavourable in the eyes of his employer. It is during this time that his anatomical studies became very modern, indeed considered "post-modern" at that time. He had moved beyond descriptive anatomy to applied anatomy or as we would term it today, physiological thought.

Leonardo's study of anatomy had endured through much of his life, with the first evidence appearing in his drawing of the fluid systems of the body probably done around 1482 (RL 12597).[1] In this drawing, the heart is depicted in Galenic form as

[1] RL refers to Royal Library catalogue numbering of the manuscript pages held in the possession of the British Royal Family in the Library at Windsor.

a two-chambered structure. A note to the side of the drawing states "Cut through the middle of the heart, liver and lung and the kidneys so that you can represent the vascular tree in its entirety." This statement of intent came to fruition three decades later with Leonardo's in-depth study of the internal organs. In these later studies, his approach to understanding the body moved definitively from anatomical structure to how form informed function. The centrepiece of this work was an extensive study of the heart. Virtually all of the drawings from these studies reveal the anatomy of the Ox heart. Whilst Leonardo's seminal work on the Aortic valve is well known, his important observations on the mitral valve are less recognised. His drawings of the mitral and tricuspid valves reveal his exceptional ability to look, see, and understand the structures under examination. This, coupled with his unique ability as a draughtsman, has left us with some of the most remarkable drawings that impart functional knowledge as well as structural information. Innovation was Leonardo's middle name. The techniques that he described to allow appropriate viewing of the working heart are yet another example of his genius, and his ability to apply lateral thought. By injecting the hearts with hot wax, and waiting for it to set, and the heart to seize in rigour mortis, he was able to demonstrate the form of this three-dimensional structure as in working life. Thus, he was able to visualise the cordal array beneath the valve as if it was under tension (Fig. 1.1: RL 19119 recto). His drawings of this are truly ground-breaking.

This chapter is not sufficient to discuss Leonardo's work on the heart in its entirety along with its internal anatomy and physiology, but a fuller description can be found in "The Heart of Leonardo" by this author [4]. In the course of this work, Leonardo correctly described the anatomical structure of the mitral valve and its component parts. His drawings of the ventricular aspect of the valve reveal the arching cordal insertions spreading out to distribute the forces applied to the valve; their insertion into the papillary muscles, shown as extensions of the trabeculated myocardium and their arcading nature into the three principle types, primary secondary and tertiary cords[2,3] (Fig. 1.2). He spent considerable efforts describing the nature of the necessary surfaces of coaptation of the leading edges of the leaflets (see Fig. 1.2). He even indicated measurement of this height; a factor we know is critical to normal valvar function.[4] His engineering sense allowed him to think about the interaction of valve and ventricle. There is a tiny sketch of ropes and pulleys in the middle of a summary page of drawings of the Ox heart indicating his acknowledgement of the interplay of forces between valve and ventricle, the so-called atrioventricular loop, which is vital in maintaining normal ventricular function[5] (Fig. 1.3a, b). He also studied extensively the tricuspid valve and went so far as to describe making a paper

[2] RL 19078 (detail).

[3] RL 19080 recto.

[4] RL 19080 recto & RL 19074 recto.

[5] RL 19074 verso.

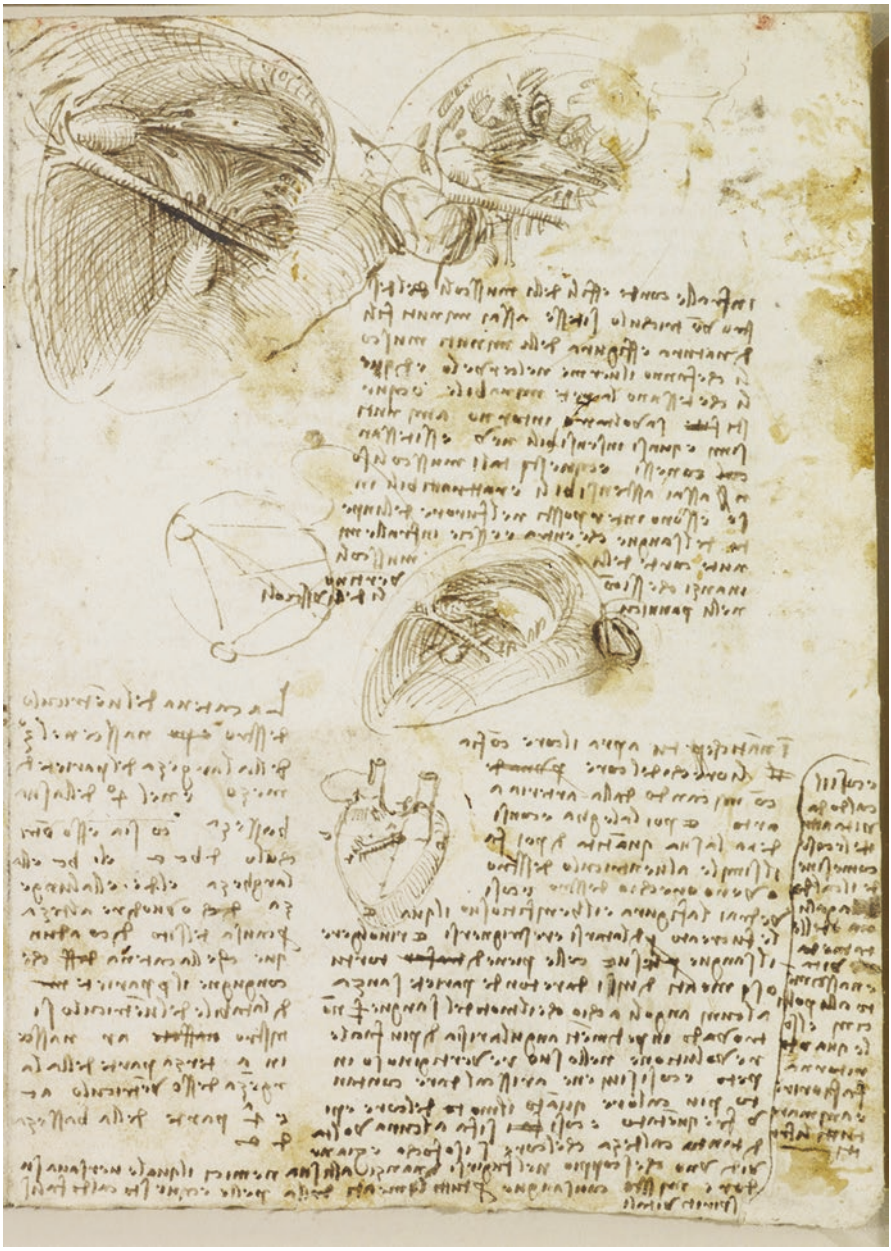

Fig. 1.1 RL 19119 recto. The right ventricle and the Tricuspid valve with the moderator band after distension with hot wax. (Lent by Her Majesty The Queen. Royal collection © Her Majesty Queen Elizabeth II)

Fig. 1.2 RL 19080 recto. Detailed drawings of the Mitral valve by Leonardo visualising the cordal arrays, the mitral valve complex and coaptation of the leaflets as well as the relationship between the aortic and mitral valves. (Lent by Her Majesty The Queen. Royal collection © Her Majesty Queen Elizabeth II)

model to demonstrate leaflet movement (Fig. 1.3c).[6] In describing the function of the cords in preventing eversion of the leaflets allowing mitral regurgitation, he invoked the metaphor of the sails on a sailing boat.[7] As the ropes (Cords) from the Capstan (Papillary muscles) prevent the sail (the leaflets) from being blown inside out, so the Cords support the Mitral leaflets preventing regurgitation.

These observations were not published and thus are not considered in the wider canon of anatomical literature. Of course, with practical applications of this level of knowledge being half a millennium away, it is difficult to know how it might have been applied. We should also remember that Leonardo was seen as something as an upstart in the Academic community of the time as a result of his lacking a classical education. This reflected his artistic training, which was seen as a lowly profession

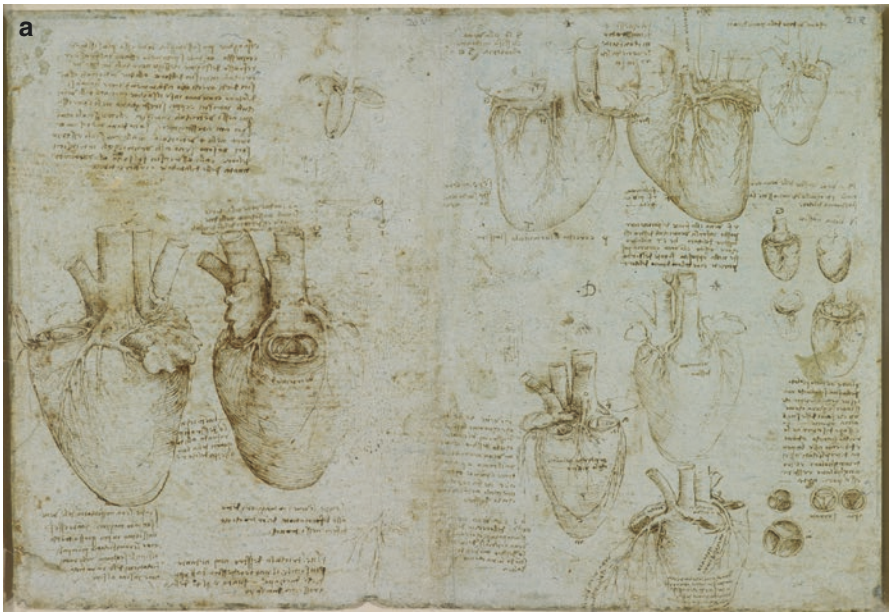

Fig. 1.3 (**a**) RL 19074 verso. (Lent by Her Majesty The Queen. Royal collection © Her Majesty Queen Elizabeth II). (**b**) Detail of RL 19074 verso. A geometrical sketch to illustrate the forces acting on the leaflets and cords of the Mitral valve. (Lent by Her Majesty The Queen. Royal collection © Her Majesty Queen Elizabeth II). (**c**) RL 19704 recto. Detailed analysis of the Tricuspid valve. This includes a description of making a model of the valve for teaching purposes. (Lent by Her Majesty The Queen. Royal collection © Her Majesty Queen Elizabeth II)

[6] RL 19116 verso.

[7] Madrid manuscript II f. 121 verso.

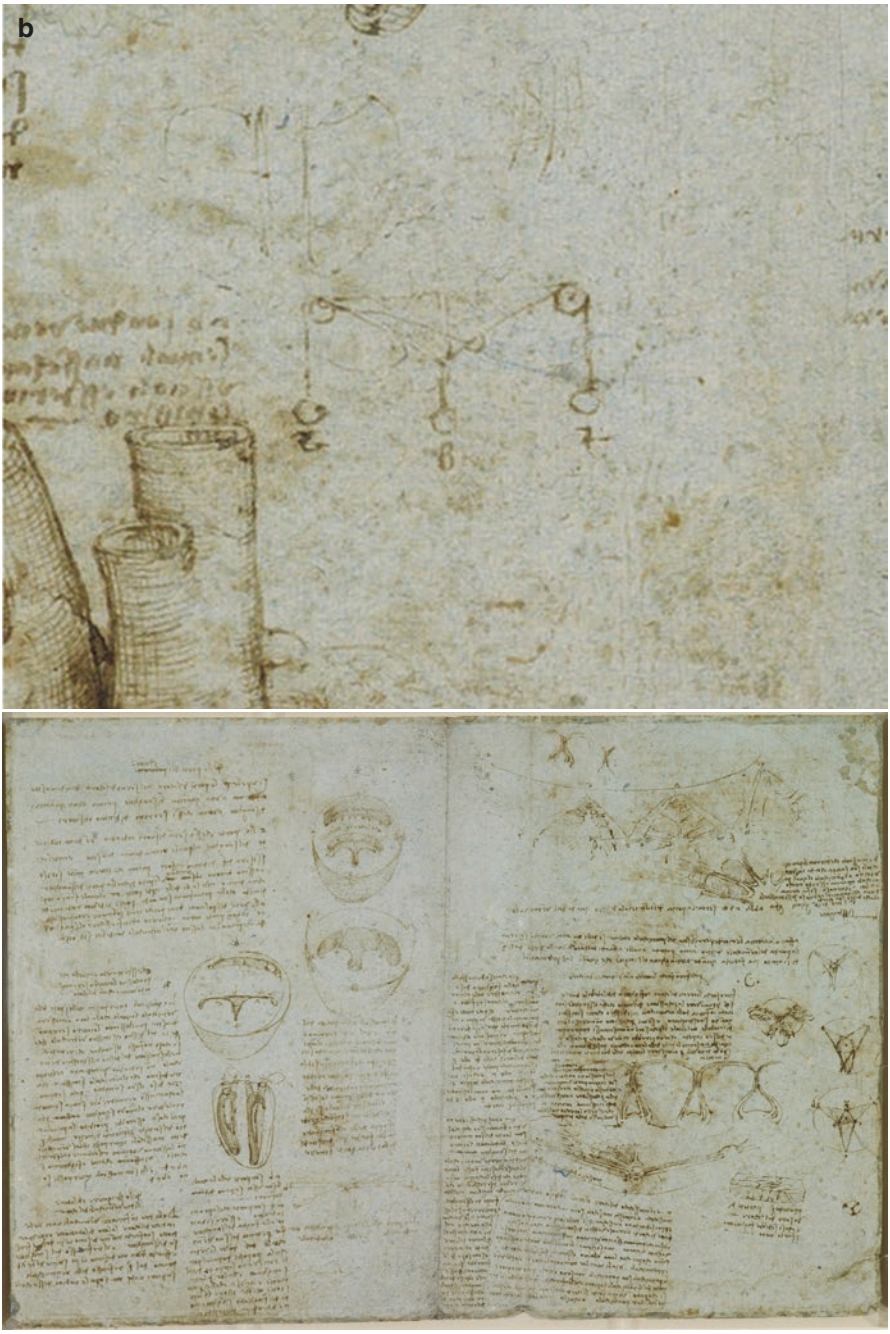

Fig. 1.3 (continued)

at the time. We can but marvel at his genius today, as the relevance of his observations unfurls with our own developing knowledge.

As mentioned earlier, William Harvey, who lived from 1578 through 1657, introduced his discussion of the atrioventricular valves by alluding to the fact that Aristotle had considered the cords and papillary muscles to be nerves in the heart. Aristotle was aware that muscles could not contract without the presence of nerves, and abstracted this thought to the heart. Harvey described the presence of "tendons and fleshy twigs with very many fibrous connections within the ventricle, of which some apart are stretched with divers motions and are partly hidden in furrows with deep ditches about them in the walls and mediastinum, and they are like a kind of little muscles which are superadded to the heart as auxiliaries for the further expulsion of the blood, that like the diligent and artificial provision of tackling in a ship they might help the heart contracting itself everyway and might squeeze more blood more fully and forcibly out of the ventricles.[8]

Harvey discussed the comparative anatomy of the atrioventricular valves, and detailed the necessity of the left ventricle having the thickest muscle by the nature of the work that it has to do delivering blood to the whole of the body rather than just to the lungs. He described the mitral valve as having the appearance of a "mitre" but without referencing the use of this name to the work of Vesalius. Whether it is an independent observation of his, or an absence of attribution, we cannot know. The omnipresence of religion at those times, however, may have been the stimulus for both men to use this term. His colourful terminology for the right atrioventricular valve describes it as having three forked portals, with the left-sided valve as having only two, and hence mimicking the Bishop's Mitre. This, he suggested, allows tighter closure than the right valve. He describes the cords of the valve being tendons that reach far out, even to the conus of the ventricle, through its middle "that they may be most exactly shut." Harvey had significant difficulty in getting his theory of the circulation accepted and support sprung from a perhaps unexpected quarter. René Déscartes, the great French philosopher, mathematician, and scientist, whilst opposing Harvey's ideas of ventricular function, recognised in a mechanistic discussion that the presence of the atrioventricular valves could allow only unidirectional flow, supporting the premise of the continuous circulation that was still being rejected by many important physicians and scientists of the time. In a letter to Beeverwijck he wrote, "the valves prevent the blood from backing up "in agreement with the laws of mechanics.".[9] Déscartes dispute with Harvey was over the cause of the movement of the heart. Descartes maintained that cardiac movement was caused by the flow of the blood, whereas Harvey maintained the Aristotelian position, namely that the heart was a muscle, and hence the progenitor of movement. This position was then reinforced by the work of Richard Lower, of whom more later,

[8] The Anatomical Excercises of Dr. William Harvey. De Motu Cordis 1628. The first English text of 1653, newly edited by Geoffrey Keynes. Chapter XVII. P. 107. Issued by the Lustar press on the quadricentennial of the birth of Dr William Harvey. Limited to 1578 copies.

[9] Letter to Beverwijk, July 5, 1643, AT IV 5.

who demonstrated that the heart continued to beat after removal from the body of an animal.

Harvey then conceded that his own investigations of the internal structure of the heart were incomplete, but that he intended to return to it when he had the time. It is interesting, especially in the context of this book, that he recognised the importance of understanding both the embryology of the heart and its comparative anatomy. In this, he compared himself with the approach of Aristotle, who studied the developing chicken's embryo and the initial pulsation of the heart visible in the foetal stage.[10]

A further interesting observation from Harvey's writing in de Motu Cordis is the fact that he used boiling of the heart to unravel the aggregated cardiomyocytes, commenting that all anatomists from Galen on had used this technique. His observations on the mitral and tricuspid valves, however, were scant, and simply define their presence as proof of maintenance of the forward and onward flow of the blood. His use of the presence of valves as underscoring the truth of the circulation is focussed on the work of Acquapendente (Hieronymous Fabricius from Acquapendente and, Italy 1533–1619) and Realdo Colombo (1516–1559) on the presence and function of valves within the peripheral veins and the valve at the entrance of the inferior caval vein to the right atrium.

Enter Dr. Richard Lower, a physician and scientist who was trained in part by the great Thomas Willis, of the circle of Willis. Lower had a stellar career. He worked extensively on the potential for transfusion of blood, and on the structure and function of the heart. In his latter years, he acted as royal physician to King Charles II in his final illness. In 1669, he published his own magnum opus "Tractus de Corde" [5]. In this publication Lower fulfilled Harvey's promised, but never delivered, further description of the structure and movement of the heart. He discussed the function of the papillary muscles and valvar leaflets in a modern fashion [6]. An example of his gift with words is as follows describing the tricuspid valve, "Thus when the apex of the heart is drawn nearer to the base in each systole the papillae also move upwards and slacken their fibres (Cords) to very loose reins; the membranes to which they are attached follow suit and hanging loose are driven upwards like bellying sails by the expulsion of blood at each systole of the heart. In consequence of this they close the opening of the heart so exactly that not even the smallest drop can flow back into the auricle but is expelled into the lungs where no such hindrance bars its way. But while the apex is drawn nearer the base at each Systole of the Heart and the papillae slacken their fibres in diastole the apex goes back again and draws down with it the papillae and their fibres. Hence the membranes are likewise withdrawn and uncover at once the entrance into the heart, opening the doors, as it were, to the inflow of blood from the auricle [7]." These words evoke those of Leonardo 150 years earlier. As did Leonardo, he went on to suggest that the presence of the papillary muscles prevented the leaflets from reaching the walls of the ventricle so that they were able to return to the closed position more easily rather than be trapped against the walls by the flowing blood. This ingenious proposition is not considered today, but is probably relevant to the normal valvar function. Lower described

[10] Ibid., Chapter XVII, page 113.

passing a pipette into the ventricle through the apex and injecting water under pressure to demonstrate the closure of the valve. He also described the injection of water across the valve to demonstrate full and complete closure, as we use in surgery today when testing the repaired valve during the operation. Lower then emphasised the greater strength of the valvar apparatus on the left side of the heart to accommodate the much higher left ventricular systolic pressure.

Three great eighteenth-century anatomists, William Cheselden, (The Anatomy of the Humane Body 1713), John Hunter, 1728–1793 (A Treatise on the Blood Inflammation and Gun-shot wounds 1794), and his brother William Hunter 1718–1783 (Lecture notes on Anatomy), each wrote about the valves of the heart, but each of their descriptions was limited to the simple anatomical statement of parts and the physiological function of preventing regurgitation of ventricular blood in systole.

By the middle of the nineteenth century Henry Gray had produced his Magnus opus "Anatomy Descriptive and Surgical', known ever since simply as "Gray's anatomy." The first edition reproduces the simple descriptions of the mitral valve to be found in the works of the previous century. This has continued until recent times, with some minor additions regarding valvar and commissural closure.

It was not until meaningful surgical procedures become available, and the truly intimate relationship between the valve and ventricular function became appreciated, that the anatomical descriptions of the mitral valve really took on a functional aspect. In 1964, Dr. Walton Lillehei, a major cardiac surgical pioneer based in Minneapolis, recognised that, when the mitral valve was simply cut away from the ventricle, disrupting all of the support of the tension apparatus provided by the left ventricle, patients suffered progressive left ventricular failure no matter how successful the replacement valvar surgery had been. This resulted in the death within 5 years of surgery of around half of the patients undergoing surgery. In his seminal paper on this subject, Lillehei wrote the following, "Early in our series with this valve, we experienced a post-operative mortality significantly higher than anticipated when compared with that of patients having reconstructive procedures in similar functional status. The mortality in this early experience with the ball valve was mainly due to "low cardiac output" syndrome associated with apparent excellent prosthesis function [8]."

The functional anatomy of the valve began to be seriously appreciated around this time, with sophisticated experiments on the movements of the valve [9]. Strikingly, in the absence of replacement prostheses, the early attempts at surgery on the valve had been through reconstruction. It was in stark contrast to these early promising results that the detrimental effect of complete excision of the valve became apparent. It was not until another three decades had past, however, that through the excellent work of surgeons such as Dwight McGoon at the Mayo clinic and Alain Carpentier at l'hopital Broussais in Paris the true superiority of mitral valvar preservation and reconstruction became apparent.

One of the earliest descriptions of the mitral valve as an interconnected complex was by Perloff ad Roberts [10]. In their words, "The Mitral apparatus is a complex, finely coordinated mechanism that can be deranged by a multiplicity of acquired

and congenital disorders and requires for its competence the functional integrity of the anatomic elements working in delicate concert. These anatomic elements are: 1. Posterior left atrial wall, 2. The annulus, 3. Leaflets, 4. Chordae tendineae, 5. Papillary muscles, and 6. Left ventricular wall."

And so, it is today that we really have come to appreciate the sophisticated physiology, interplaying with its complex anatomy that the mitral valve has really come of age. Truly understanding it and its central role in normal cardiac function has become an exciting specialism all of its own. It may be thought of as the lynchpin of efficient ventricular function. Just as the mitral crown sits on top of the head of the Church, so does its biological counterpart sit as the prince of all the internal organs.[11]

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[11] "The heart is as it were a Prince in the Commonwealth, in whose person is the first and highest government everywhere; from which as from the original and foundation, all power in the animal is derived, and doth depend." The Anatomical exercises of Dr. William Harvey de Motu Cordis 1628. From the first English text 1653. Translation by Geoffrey Keynes.

Anatomical Development of the Left Atrioventricular Valvar Complex

2

Robert H. Anderson, Wouter H. Lamers, Jill P. J. M. Hikspoors, Damian Sanchez-Quintana, and Timothy J. Mohun

Introduction

Elsewhere in this book, the reader will find an excellent and erudite account of the morphogenetic aspects of mitral valvar development (see Chap. 9). In that chapter, Bill Chaudhry and Deborah Henderson provide "an overview explaining how genes and genetic pathways control the formation and remodelling of the mitral valve." Their intention is to provide the link between the details of morphological development as provided in this chapter, and the approaches taken by clinical geneticists, as summarised in Chap. 10. Our knowledge of the morphological changes accompanying the development of the valvar complex, however, fall short when compared with the amazing advances made recently in deciphering the genetic cues which underscore the changes in valvar architecture. As we will show, we are able to chart the changes that occur as the endocardial cushions formed in the atrioventricular canal become remoulded to form the leaflets of the mitral valve. We are also able to observe the compaction of the trabecular components of the ventricular walls to form its papillary muscles. Details of formation in the human or murine heart of the tendinous cords, in contrast, and knowledge of the subdivision of the developing mural leaflet into the so-called "scallops," are thus far lacking. For this very reason, there are very few previous descriptions that

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warrant citation in the context of this book The best we can currently achieve, therefore, in regard to the human heart, is to provide an account of the changes revealed by examination of the serial histological sections available from the human embryos archived in the Human Developmental Biology Resource. We are able to compare the findings from these sections from those available from a small series of human fetuses obtained between 11 and 30 weeks of development. These findings, as we will show, are particularly significant in regard to the ongoing discussions of the relevance of so-called "disjunction." The information available from the serially sectioned human embryos has now been greatly expanded by the availability of the interactive pdf's that permit interrogation of the temporal changes in anatomy seen a series of embryos reconstructed from Carnegie stages 9 through 23 [1]. We have also been able to compare the changes seen in the human heart with those occurring in the murine heart as revealed by examination of three-dimensional datasets produced using the recently developed technique of episcopic microscopy [2]. The latter findings are significant not only because, as we will show, they are comparable with the findings obtained from the human heart, but also because much of the information derived with regard to molecular biology has accrued from investigation of murine hearts.

The Initial Stages of Development

The heart tube first becomes recognised as a linear entity within the pericardial cavity at around 4 weeks of human development, this being represented by stage 10 in the categorisation based on the series of embryos held at the Carnegie Institute. At this early stage, the embryo itself has not "bent" to produce its recognisable shape. In consequence, the pericardial cavity is found close to its cranial end. Within the pericardial cavity, there is a solitary endocardial tube, receiving venous inflow from the vitelline and umbilical venous tributaries, and extending cranially to feed the aortas. The larger part of the endocardial tube at this stage will form little more than the cavity of the definitive left ventricle (Fig. 2.1). As development proceeds, the material is added to the developing heart at its venous and arterial poles from the so-called second heart field, which is part of the heart-forming area of the embryo itself. The initial components, which form the putative left ventricle, are derived from the first heart field. With the addition of the new material over the subsequent two to three days of development, it becomes possible, by Carnegie stage 12, to recognise the ventricular loop. The apical components of the left and right ventricles can then be seen to be "ballooning" from its inlet and outlet ends. At this stage, the embryo has also developed venous tributaries within its body, and the developing atrial chambers can now be recognised. The junction between the developing atrial and ventricular components is seen as the atrioventricular canal, which is supported exclusively above the cavity of the developing left ventricle. The embryo has itself begun to bend, and is more recognisable as a developing homunculus, with the pericardial cavity now in the cervical region (Fig. 2.2).

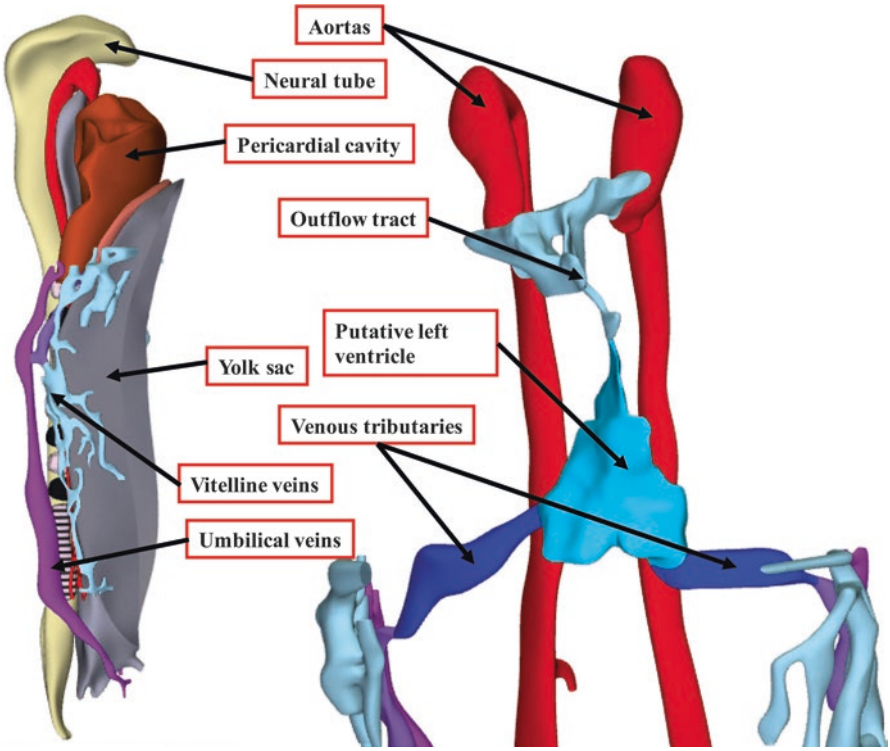

Fig. 2.1 The images show reconstructions of a human embryo at Carnegie stage 10. The left-hand panel shows the overview of the embryo, while the right-hand panel shows the lumen of the developing heart tube as segmented within the pericardial cavity

Throughout the period of development to this stage, the lumen of the developing heart tube has been lined by cardiac jelly. Within the atrioventricular canal, the jelly has conglomerated to form two cushions. These entities lie edge-to-edge, in superior and inferior positions, and guard the newly formed common atrioventricular orifice. The arrangement is well seen in human embryos at Carnegie stage 14, when the embryo is around 5 weeks old (Fig. 2.3). Although the newly formed cushions lie edge-to-edge within the atrioventricular canal, they have yet to fuse. The arrangement does produce right and left atrioventricular orifices, even though the canal myocardium remains supported as a common entity above the cavity of the left ventricle. The next crucial stage of development is seen by Carnegie stage 16, which has involved an additional two to three days of development. By then, expansion of the atrioventricular canal has brought the cavity of the right atrium into direct communication with the cavity of the developing right ventricle (Fig. 2.4). The ventricular walls, at this stage, are made up mainly of a trabecular meshwork. The myocardium of the atrioventricular canal still provides direct myocardial continuity throughout the junctions between the atrial walls and the relatively thin compact layer of the ventricular walls. The primary atrial septum

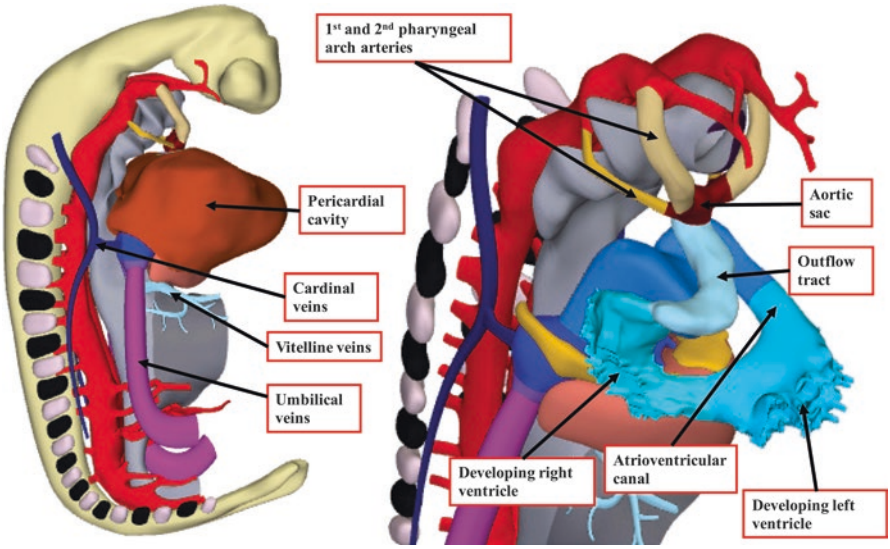

Fig. 2.2 The images show reconstructions from a human embryo at Carnegie stage 12. The left-hand panel shows an overview of the embryo itself. The right-hand panel shows the lumen of the developing heart, which remains a solitary tube. By this stage, it is possible to recognise a ventricular loop, and evidence is seen of the forming ventricular apical components. The atrioventricular canal, also recognisable at this stage, opens exclusively into the developing left ventricle

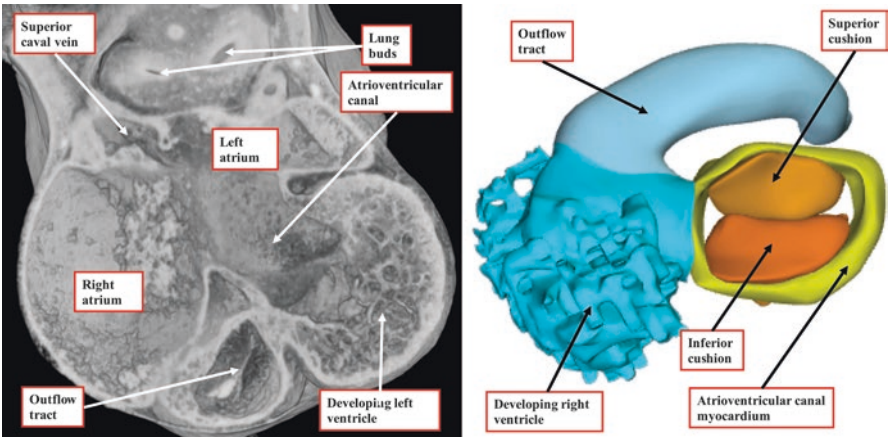

Fig. 2.3 The left-hand image is a section from an episcopic dataset prepared from a human embryo at Carnegie stage 14. The cut is taken across the long axis of the atrioventricular canal, showing how it connects exclusively at this stage with the developing left ventricle. The right-hand panel is from an interactive pdf made by reconstructing a human embryo at the same stage. The cavity of the left ventricle has been removed, permitting visualisation of the cushions now formed within the canal, which is viewed in its short axis from the apex of the developing left ventricle

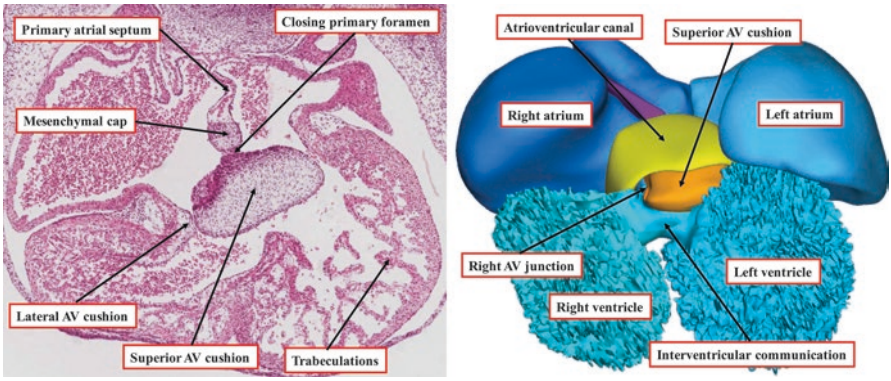

Fig. 2.4 The left-hand panel shows a "four chamber" histological section, stained with hematoxylin and eosin, and prepared from a human embryo at Carnegie stage 16. The right-hand panel shows a reconstructed human embryo at the same stage of development. Expansion of the atrioventricular (AV) canal, still a common entity, has produced direct communication between the cavities of the developing right atrium and right ventricle. Note the appearance of a lateral cushion in the right atrioventricular junction. A similar lateral cushion is also present in the left atrioventricular junction, although not seen in the section. The section shows how the growth of the primary atrial septum, with a mesenchymal cap on its leading edge, is obliterating the primary atrial foramen

has now grown to separate the cavities of the right and left atrial chambers, with the mesenchymal cap carried on its leading edge fusing with the atrioventricular cushions to obliterate the primary atrial foramen. Another key structure has also appeared by this stage of development. This is the vestibular spine [3], also known as the dorsal mesenchymal protrusion [4]. First described by Wilhelm His Senior in the nineteenth century, this important structure was subsequently forgotten for over 100 years. It is now recognised to play the crucial role in anchoring the primary atrial septum to the atrial surface of the atrioventricular cushions, this being the process that binds together the cushions [5]. The right and left atrioventricular orifices are then able to expand as the cushions themselves fuse along their facing surfaces. The influence of the spine is well seen at Carnegie stage 18 when the embryo is about 6 weeks old. The atrioventricular cushions have now fused along their facing surfaces. The vestibular spine, in turn, has fused along their atrial surfaces. The spine, along with the mesenchymal cap, is now beginning to musculariseThis process will form the anterior buttress of the atrial septum [6], binding at the same time the primary atrial septum to the fused atrioventricular cushions (Fig. 2.5). By this stage of development, the atrioventricular canal myocardium is becoming sequestrated on the atrial aspect of the newly forming insulating tissues of the atrioventricular junctions. The compact component of the ventricular walls is also beginning to thicken, with the trabeculations compacting to form the papillary muscles of the developing atrioventricular valvar complexes. At this stage, however, the compacting trabeculations extend from the ventricular walls to the

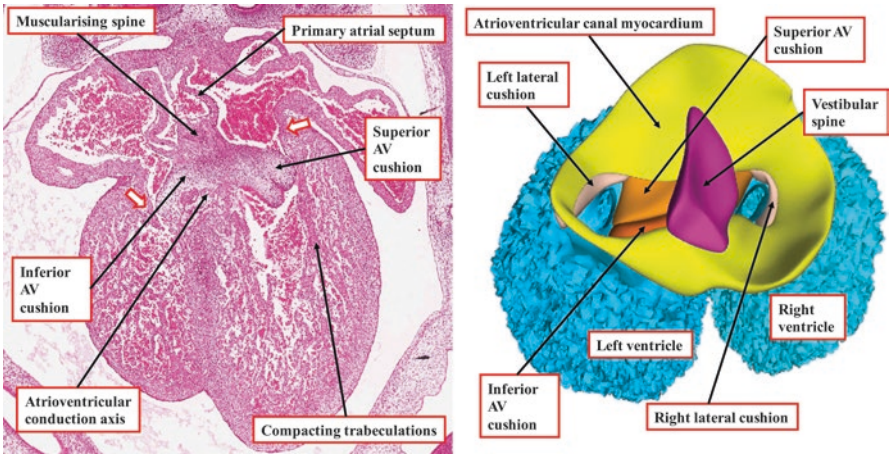

Fig. 2.5 The left-hand panel is a histological section, again stained with hematoxylin and eosin, taken in "four chamber" fashion, through a human embryo at Carnegie stage 18, representing around six weeks of development. The right-hand panel is a reconstruction from an interactive pdf showing the same stage of development. In the right-hand panel, the atrioventricular canal myocardium is viewed from above, with the vestibular spine shown in purple. The spine, shown muscularising in the left-hand panel, binds together the central parts of the atrioventricular junctions, permitting subsequent expansion of both atrioventricular orifices. As seen in the left-hand panel, the atrioventricular canal myocardium itself is now becoming sequestrated on the atrial side of the insulating plane of the atrioventricular junctions. It will become the vestibules of the mitral and tricuspid valves (white arrows with red borders). The larger part of the fused cushions remains positioned above the cavity of the left ventricle. The left ventricular trabeculations are now compacting at the ventricular side of the cushions and will form the papillary muscles

edges of the atrioventricular cushions. The lateral cushions in both atrioventricular orifices remain relatively small. The bulk of the cushions themselves, furthermore, remain within the cavity of the left ventricle, with the rightward margins of both cushions draping themselves across the crest of the muscular ventricular septum. This arrangement is well seen at a comparable stage of murine development (Fig. 2.6).

The arrangement of the relationship between the fusing superior and inferior cushions and the left lateral cushion, at this stage of development, is also comparable to the situation seen in congenitally malformed hearts with deficient atrioventricular septation and a common atrioventricular junction [5]. As is the case in the congenitally malformed hearts, the outflow tract to the developing aortic root at this stage is cranial to the superior atrioventricular cushion. With ongoing normal development, of course, the aortic root becomes committed to the left ventricle. This does not occur, however, until there is the closure of the embryonic interventricular communication [7]. This process is the consequence of the construction of a shelf in the roof of the right ventricle [8]. The shelf is formed from the proximal margins of additional cushions, which have by now developed throughout the length of the myocardial outflow tract. It is this

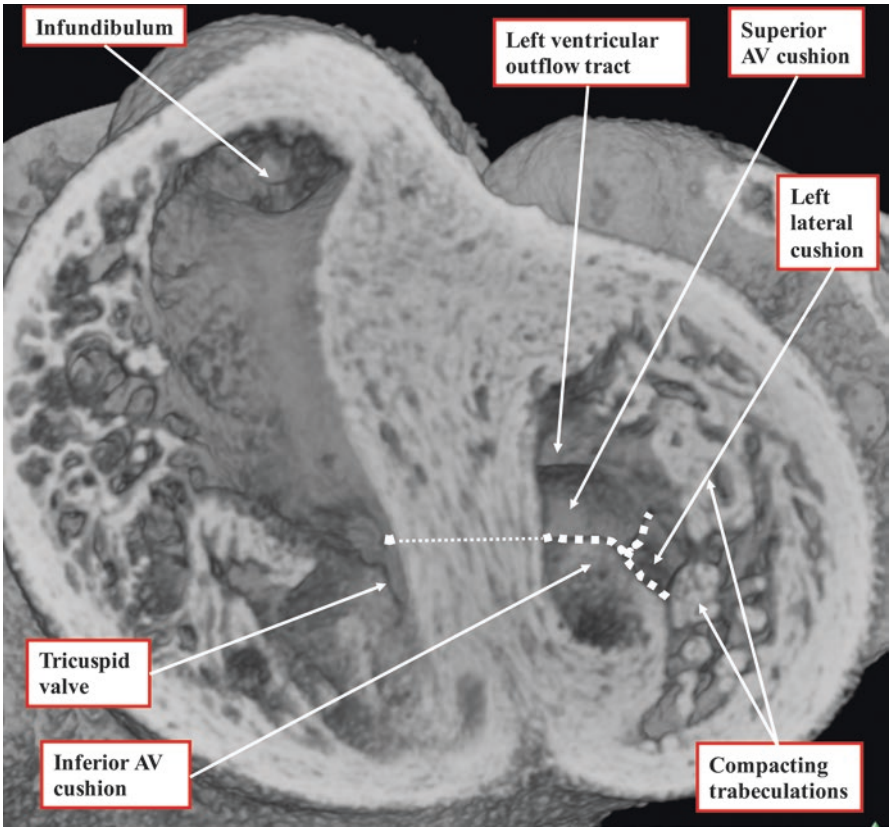

Fig. 2.6 The image is from an episcopic dataset prepared from a mouse embryo sacrificed at embryonic day 12.5. The ventricular mass has been sectioned in its short axis, and the base is viewed from the apex. The developing aortic root remains positioned at this stage above the cavity of the right ventricle, so the left ventricle still ejects its blood through the embryonic interventricular communication, which is cranial to the superior atrioventricular (AV) cushion. As in the human heart (Fig. 2.5), the bulk of the fused cushions is positioned above the cavity of the left ventricle. The arrangement produced by the apposition between the edges of the fused superior and inferior cushions and the left lateral cushion (white dashed lines) replicates the arrangement of the left atrioventricular valve found in the setting of the atrioventricular septal defect with the common atrioventricular junction. The rightward margins of the cushions have draped themselves over the crest of the ventricular septum, and will form the septal leaflet of the tricuspid valve, which also has contributions from both the major cushions, as shown by the thin dashed white line

process that converts the secondary embryonic communication, as seen at Carnegie stage 18, into the definitive left ventricular outflow tract (Fig. 2.7). The initial, or primary, interventricular communication is present at the stage at which the atrioventricular canal is supported exclusively above the cavity of the developing left ventricle. At this initial stage, the outflow tract was supported exclusively by the developing right ventricle (Fig. 2.3). With the expansion of the atrioventricular canal, as shown in Fig. 2.4, the dorsal, or peritricuspid,

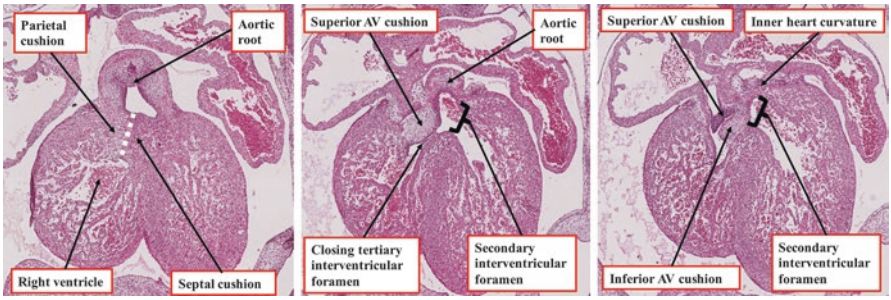

Fig. 2.7 The figure is made up of additional histological sections from the dataset used to prepare Fig. 2.5. The images show how the secondary embryonic interventricular communication present at this stage of development becomes remodeled to form the left ventricular outflow tract. The left-hand panel is a cranial section, showing how the proximal cushions within the outflow tract have fused (white dashed line) and muscularised to form a shelf that separates the aortic roof from the cavity of the right ventricle. There is an additional communication between the aortic root and the cavity of the right ventricle, as shown in the middle panel. This is eventually closed by the right-sided tubercles of the two atrioventricular (AV) cushions, which are seen fused together in the right-hand panel. This process closes the tertiary interventricular communication, with the tissues derived from the fused atrioventricular cushions becoming the membranous part of the ventricular septum

boundaries of this primary foramen become remodeled to form the right atrioventricular orifice. The interventricular communication that remains at this stage, therefore, as shown in the right-hand panel of Fig. 2.4, can be considered as the secondary interventricular foramen. It is the boundaries of this channel that are eventually remodeled to form the left ventricular outflow tract (Fig. 2.7). The space that is then closed to complete ventricular septation is the tertiary communication. It is the persisting intermediate part of the primary foramen. It is closed by the formation of so-called tubercles, which are the rightward margins of the major atrioventricular cushions. The process is well seen in murine hearts at the comparable stage of development to Carnegie stage 18 in the human heart. This is when the developing mouse is on the 14th day of development (Fig. 2.8).

It is shortly after these stages, in both the human and murine hearts, that the tertiary interventricular communication is closed by the tubercles of the atrioventricular cushions, thus completing the process of cardiac septation. Even at this stage of development, nonetheless, the aortic root, although now only in communication with the cavity of the left ventricle, remains positioned above the cavity of the right ventricle. In the developing human heart, this closure of the tertiary communication takes place after around seven to eight weeks of development. This is represented by stages 19 through 23 of the Carnegie system. By Carnegie stage 19, when the communication is beginning to close, the communication is between the cavity of the right ventricle and the aortic root. Strictly speaking,

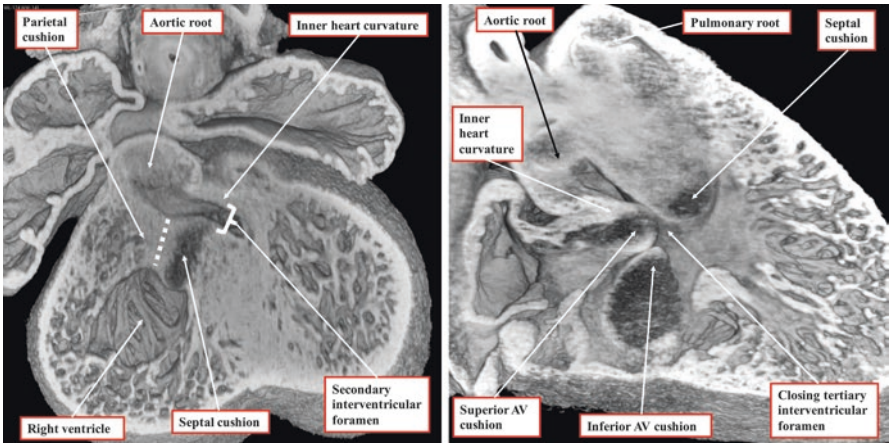

Fig. 2.8 The images are taken from an episcopic dataset prepared from a developing mouse embryo sacrificed at embryonic day 13.5. The left-hand panel shows a frontal section through the ventricular mass. It shows how the proximal parts of the atrioventricular cushions have fused (white dashed line) to build a shelf in the roof of the right ventricle, which separates the subaortic and subpulmonary channels, but also separates the aortic root from the ventricular cavity. By this process, the secondary interventricular communication existing at that time is converted into the left ventricular outflow tract. Note the muscularisation of the parietal cushion, but that the attachment of the septal cushion to the muscular ventricular septum has yet to muscularise. The right-hand panel is a sagittal section through the same dataset. It shows that a further communication exists between the aortic root and the cavity of the right ventricle. This is the tertiary communication. It is being closed by the formation of swellings, known as "tubercles," from the rightward margins of the atrioventricular cushions. Note that, at this stage, the myocardial inner heart curvature interposes between the developing leaflets of the aortic and atrioventricular valves

therefore, it is an aortic outflow-right ventricular communication. Only when the persisting foramen is closed does the new septal components itself become an interventricular structure. And, from that stage onwards, it then becomes possible to recognise the building blocks of the mitral valvar complex (Fig. 2.9).

The arrangement in which the compacted trabeculations of the ventricular walls merged with the ventricular margins of the atrioventricular cushions has remained through the stages of development from Carnegie 19 through 21. Over the same period, furthermore, there has been little obvious additional expansion of the atrioventricular orifices, although the sectioned hearts are usually contracted. Reconstructions show, nonetheless, that even by Carnegie 23, when the ventricular septum has been completed by the formation of the membranous septum, the aortic root remains largely positioned above the cavity of the right ventricle (Fig. 2.10). Thus, the mitral valve, during the stages from Carnegie 19 through 23, has developed its presumptive aortic and mural leaflets, but throughout these stages, the developing leaflets are of comparable length. The aortic

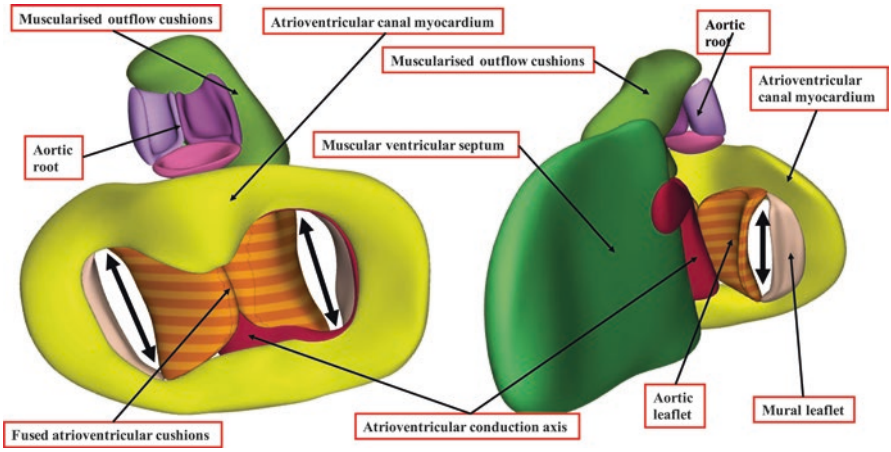

Fig. 2.9 The reconstructions are prepared from an interactive pdf made from a human embryo reconstructed at Carnegie stage 23, representing around 8 weeks of development, when ventricular septation has been completed by the formation of the membranous septum. The left-hand panel shows that, although the atrioventricular cushions have fused, there has been the minimal inferior expansion of the atrioventricular valvar orifices. The aortic root, now separated by the shelf formed by muscularisation of the proximal outflow cushions, remains positioned largely above the cavity of the right ventricle. The right-hand panel, representing the view from the apex of the left ventricle, shows how at this stage there has been no "wedging" of the aortic root between the developing mitral valvar complex and the muscular ventricular septum

leaflet of the valve, however, has much great depth, being formed from the larger part of the major atrioventricular cushions. As we have already shown, is also possible, over this period, to recognise the contributions made by both of the major atrioventricular cushions to the membranous part of the ventricular septum. This fibrous part of the septum, eventually, will be separated by delamination of the septal leaflet of the tricuspid valve into interventricular and atrioventricular components [9]. During this initial period of development, nonetheless, there has not been any delamination of the septal leaflet. It is possible to recognise the contributions made by the superior and inferior atrioventricular cushions to the aortic leaflet of the mitral valve. Should this fusion fail, the result is often described as a "cleft." This is an inappropriate term, since it is not the consequence of the "cleaving" of a previously formed entity, but rather the failure of fusion of the building blocks of the aortic leaflet. Should the heart retain its original common atrioventricular junction, then the left atrioventricular valve retains its trifoliate configuration [5], as shown in Fig. 2.6. The so-called "cleft" is then an obvious zone of apposition between the left ventricular components of the leaflets derived from the superior and inferior cushions. After separation of the junctions in the context of normal development, the site of fusion of the two cushions "points" towards the space that will become the subaortic outflow tract (Fig. 2.11).

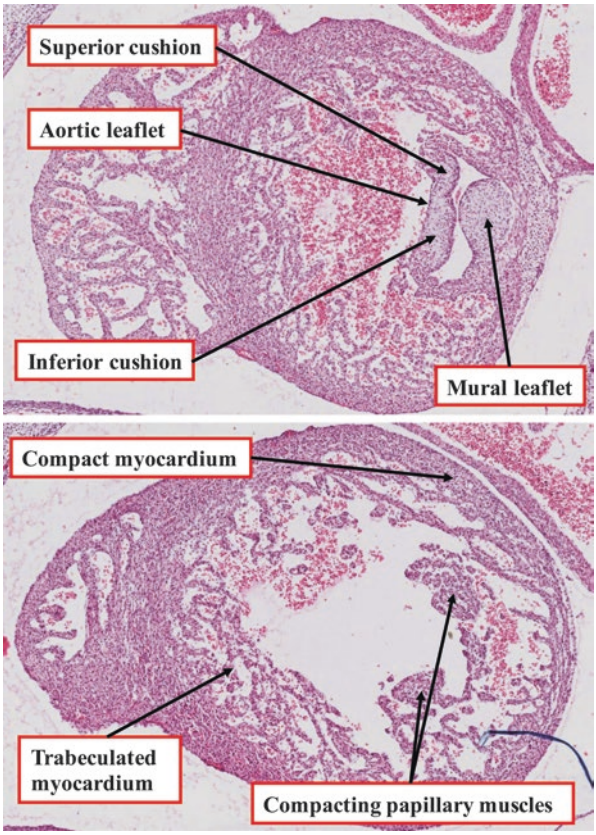

Fig. 2.10 The images show short-axis sections through the left ventricle in a human embryo at Carnegie stage 23. The upper panel shows how the distal left ventricular margins of the superior and inferior atrioventricular cushions have almost completed their fusion to produce the aortic leaflet of the mitral valve. The mural leaflet at this stage, however, is small. It will subsequently be developed in relation to the lateral cushion of the left atrioventricular junction. The lower panel, from the same dataset, shows how the ventricular trabeculations are compacting to produce the papillary muscles

The expansion of the left atrioventricular junction, such that the mural leaflet increases in length, is not seen until 11 to 12 weeks of development. Even at 9 weeks of development, the myocardium of the papillary muscles extends to the margins of the developing valvar leaflets, with no evidence of formation of tendinous cords, nor the expansion of the mural leaflet. These changes have become recognisable by 12 weeks of development [10]. Only at this stage does it become possible to distinguish between the papillary muscles, the tendinous cords, and the leaflets. It is also possible to recognise the formation of the basal cords, supported by the miniaturised papillary muscles, on the ventricular aspect of the developing mural leaflet. As yet, to the best of our knowledge, investigations have yet to be conducted to establish the processes by which the mural leaflet becomes separated into its component parts, or how the different tendinous cords achieve their definitive structure (Fig. 2.12). It is also not until relatively late in development that there is the interruption of the myocardial continuity in

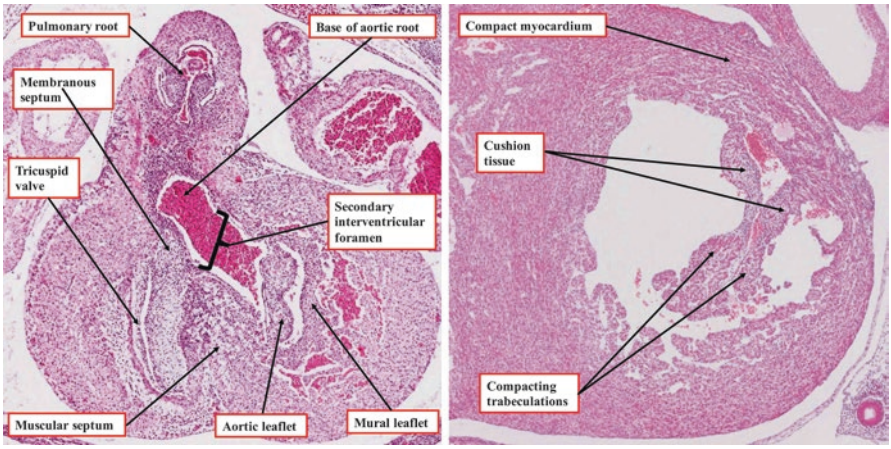

Fig. 2.11 The left hand image shows a section in the short axis of the ventricular mass from a human embryo at Carnegie stage 21. The section is stained with haematoxylin and eosin. The atrioventricular cushions have fused to form the aortic leaflet of the mitral valve, although it remains possible to recognise the contributions made by the superior and inferior cushions. The secondary interventricular foramen is becoming transformed into the subaortic outflow tract subsequent to closure of the tertiary foramen by the tubercles of the atrioventricular cushions, which are now recognisable as the membranous septum. The ventricular trabeculations forming the papillary muscles extend to the margins of the cushions at this stage, an arrangement maintained also at Carnegie stage 23, as shown in the right-hand panel, from a different embryo again stained with haematoxylin and eosin

the mural atrioventricular junction between the left atrial vestibular myocardium and the crest of the left ventricular wall. As we demonstrated in Fig. 2.9, the muscular continuity is still present at Carnegie stage 19 and remains at Carnegie stage 23. By 11 weeks of fetal development, fibro-adipose tissue has accumulated in the atrioventricular groove and is prominent throughout the mural junction. It is the conjunction between these external tissues of the atrioventricular grooves and the cushion tissues that provide the scaffold for the formation of the mural leaflet, which must eventually sever the initial myocardial connections [11]. The precise mechanics of the process of separation, and the timing at which separation becomes complete, have still to be established. The fact that epicardially derived cells contribute to the mural leaflets of both the mitral and tricuspid valves, nonetheless, is strong evidence showing that ingrowth across the developing junction is the major factor in severing the initial myocardial continuity [12]. Persistence of the initial myocardial connections produces the substrate for Wolff-Parkinson-White syndrome. In that regard, it may well be significant that, as shown in Fig. 2.9, the myocardial accessory connections are formed on the epicardial aspect of the fibrous hinge of the mural leaflet of the mitral valve [13]. The mechanism and timing of the formation of the hinges of the mural leaflet, however, are as yet unknown. These

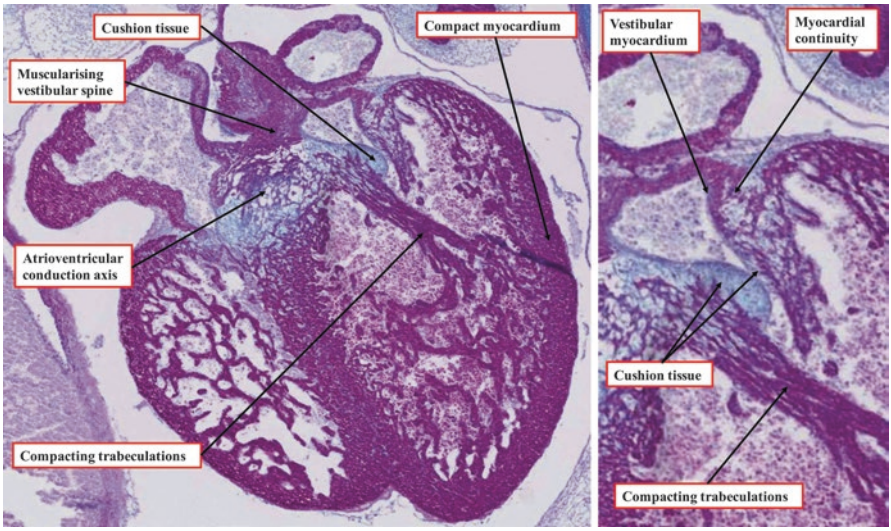

Fig. 2.12 These images of a "four chamber" section through a human embryo at Carnegie stage 19, representing around 7 weeks of development, are stained with the periodic acid Schiff technique, which shows fibrous tissues in blue and myocardium in purple. As is shown in the left-hand panel, the trabecular layers of the myocardial walls have now compacted to form the papillary muscles, which attach to the ventricular margins of the atrioventricular endocardial cushions. The section also shows how the atrioventricular conduction axis is "penetrating" through the developing plane of atrioventricular insulation. The connections between the conduction axis and the muscularising tissues of the vestibular spine will form the atrioventricular node. The right-hand panel is a higher magnification of the same section, showing the building blocks of the mitral valve. At this stage, however, there is still myocardial continuity across the mural atrioventricular junction, although the atrioventricular canal myocardium is becoming sequestrated to form the left atrial vestibule

changes are important as we seek to understand the significance of so-called "disjunction" of the mural leaflet and its significance to mitral valvar prolapse. Already at 11 to 12 weeks of development, we can recognise the different arrangements of hingeing of the mural leaflet within the left atrioventricular junction. In parts of the junction, the leaflet is hinged between the atrial and ventricular myocardial components (Fig. 2.13—left-hand panel). At other parts, the separation between the myocardial components is such that the leaflet is hinged from the atrial vestibule, leaving a collar of fibrous tissue within the junction (Fig. 2.13—middle panel). This is the arrangement that, in the postnatal heart, is now being interpreted to represent "disjunction." At still other points in the same junction, the fibrous separation is such that the leaflet is hinged from the crest of the left ventricular wall (Fig. 2.13—right-hand panel). In the light of these developmental changes, it is hardly surprising that so-called "disjunction" can be found as a ubiquitous feature of not only individuals with mitral valvar prolapse, but also of the normal arrangement (Fig. 2.14).

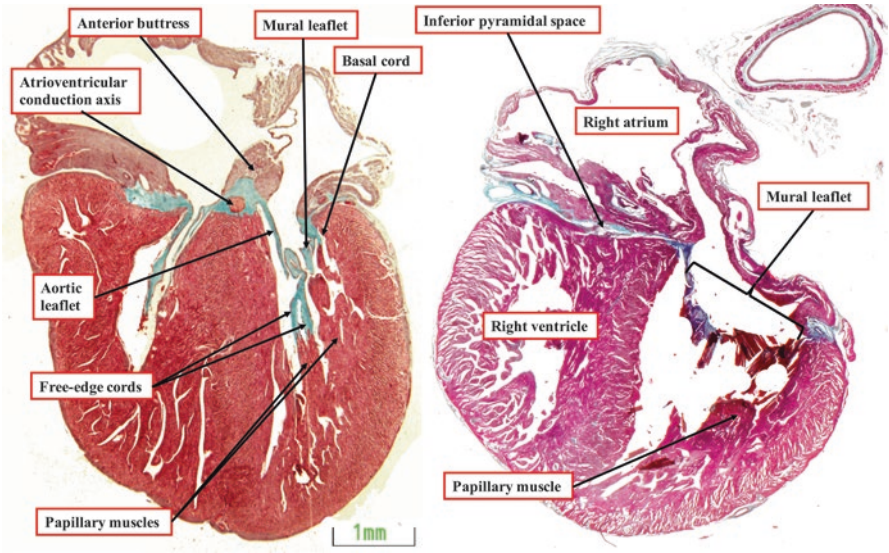

Fig. 2.13 The images are "four chamber" sections from fetuses at 11 weeks (left-hand panel) and 11 to 12 weeks (right-hand panel) development. Both sections are stained with the trichrome technique, which colours myocardium as red-brown, and fibrous tissue green. The left-hand image shows that the insulating tissues of the atrioventricular junctions are now well-formed, and the tendinous cords can now be recognised interposing between the papillary muscles and the leaflets. The right-hand panel, cut in a more oblique plane, shows that both atrioventricular junctions have expanded between eight weeks and 12 weeks of development, producing the elongated mural leaflet of the mitral valve, and the inferior pyramidal space

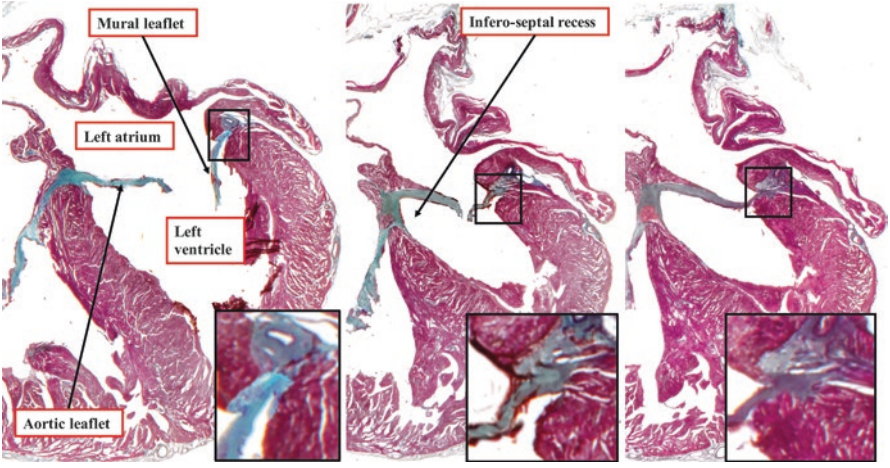

Fig. 2.14 The images show serial "four chamber" sections made through a heart obtained from a human fetus at 11 to 12 weeks of development. The insets show the arrangements of hingeing of the mural leaflet of the mitral valve at various points around the left atrioventricular junction, with the areas of enlargement shown as the boxes in the main panels. The left-hand panel shows "neutral" hingeing between the atrial and ventricular myocardial walls. The middle panel shows hingeing from the atrial vestibule, with this arrangement said to represent "disjunction" when found in the postnatal heart. The right-hand panel shows hingeing from the crest of the ventricular wall

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How Should We Describe the Mitral Valve and Its Component Parts?

3

Robert H. Anderson and Francis C. Wells

Introduction

It is axiomatic that a coherent account of the optimal means of describing the surgical approach to diseases of the mitral valve requires that the discussants use uniform words when offering their own opinions. It is our intention to achieve such uniformity as we edit the contributions to this volume. Ideally, nonetheless, we should also be sure that those contributing to the book are comfortable with our own preferred terms for description. With this in mind, therefore, we have prepared this initial chapter in which we discuss the reasons underscoring our own preferences, since there is no question but that opinions are many and varied with regard to the words that might be used to describe the valve and its components. We have shared the chapter with our contributors, and taken note of any major problems they may have encountered with regard to our initial suggestions. This version of the chapter is the one that has determined the style and words to be used in the remainder of the book.

The Mitral Valve

The valve in the normal heart, which guards the left atrioventricular junctions, is described as being "mitral" because of its perceived likeness to the episcopal mitre. This likeness is best appreciated when the closed valve is viewed from its ventricular aspect. The similarity with the religious headgear, specifically the Bishop's mitre, is then striking (Fig. 3.1). The valve has also been described as the "bicuspid" valve,

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Fig. 3.1 The mitral valve is shown in its closed position, and is viewed having opened the left ventricle along its sternocostal surface. The similarity between the ventricular view of the valve and the Episcopal mitre is striking

comparing it in this fashion with the tricuspid valve, which guards the right atrioventricular junction. Nowadays, this term is hardly ever used in the clinical setting, although some do still describe the leaflets of the valve using the word "cusp." We dislike the use of this word in this context. As we will describe, we use the word "leaflet" to describe the moving components of not only the atrioventricular valves, but also the arterial valves as they are a broad expanse of tissue that can be likened to a broad leaf, and not just a point of contact. It is in the description of the arterial valves, however, that "cusp" is more usually found in modern day accounts of valvar morphology and function. This is also less than perfect, since when used in its vernacular meaning, a "cusp" is a point or elevation. We presume that the word was used to describe the leaflets of the arterial valves because of their likeness to the surfaces of the molar teeth when viewed in their closed positions, again from the ventricular aspect (Fig. 3.2). The term "cusp," however, has subsequently become ambiguous, since many now use the word to describe the sinuses of the arterial roots, rather than the leaflets. And, as we have already indicated, the word was also used traditionally to describe the leaflets of the atrioventricular valves. Some, indeed, would now seek to distinguish the leaflets of the two sets of valves by using "cusp" to described the moving parts in the context of the arterial valves, whilst using "leaflet" in the setting of the atrioventricular valves. We find this a confusing distinction, not least since the valve guarding the atrioventricular junction is universally described as the "tricuspid valve." Fortunately, we have no such problems in describing the valve guarding the left atrioventricular junction, since this is equally universally now known as the mitral valve. It is important, nonetheless, to recognise that the valve guarding the left half of the common atrioventricular junction in the setting of deficient atrioventricular septation is not a "mitral" valve. This valve is a trifoliate structure, with the space

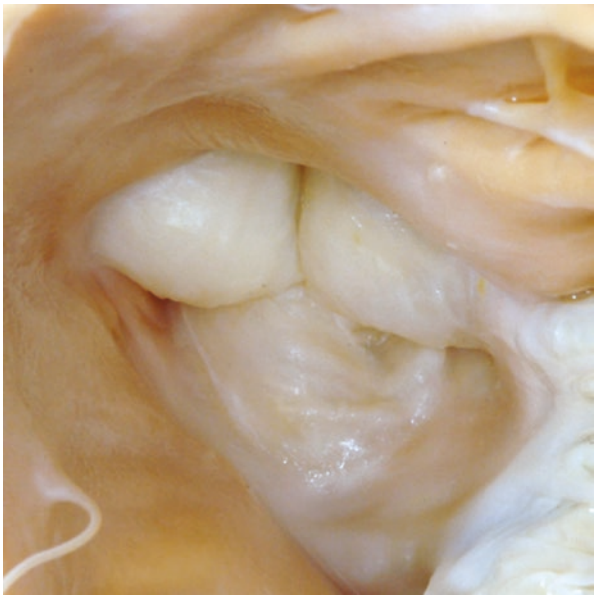

Fig. 3.2 The leaflets of the normal aortic valve are shown in their closed position, as with the mitral valve in Fig. 3.1 viewed from the aspect of the left ventricle. This time, it is the similarity to the surfaces of the molar teeth that is striking. We presume it was this similarity that underscored the naming of the leaflets as "cusps." We consider it better to describe the moving parts, as with the moving parts of the atrioventricular valves, as "leaflets"

between the left ventricular components of the two leaflets which bridge the ventricular septum and reside in the left ventricle being a zone of apposition (Fig. 3.3). The space is not a "cleft" in an otherwise normal mitral valve. When subsequently discussing these significant differences in morphology elsewhere in our book, we will describe the valve found in the congenitally malformed hearts as the morphologically left atrioventricular valve, recognising that, on occasion, it can be right-sided when there is left-handed ventricular topology.

The Mitral Valvar Complex

When considered in its entirety, the mitral valve can conveniently be defined as the structure guarding the morphologically left atrioventricular junction. And, as we have discussed, the entity is now universally recognised when described as the mitral valve. It can only function properly, however, when all its components are working in harmony. This means that we must also provide uniform definitions for its working parts. The concept of the valvar complex was popularised in the 1970s by Perloff and Roberts [1]. In this regard, it should be noted that Lillehei, much earlier, had recognised simple excision of the valvar leaflets and their supporting tendinous cords resulted in early heart failure [2] This permitted him to infer that these components, including the support provided by the left ventricle, functioned as a unit. He had noted that removing the key ventricular support interrupted the harmonious function of the complex. Since these descriptions, the notion of the valvar complex has stood well the subsequent passage of time. The parts of the

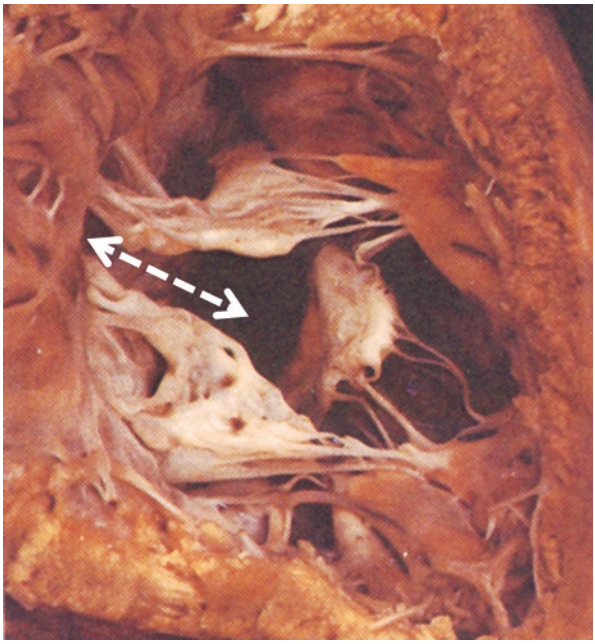

Fig. 3.3 The left atrioventricular valve from a heart with deficient atrioventricular septation, or atrioventricular septal defect with common atrioventricular junction, also known as an "atrioventricular canal malformation," is shown as viewed from the apex of the left ventricle. The valve is trifoliate and bears no resemblance to the episcopal mitre (compare with Fig. 3.1). Although often considered a "cleft," the space shown by the double-headed white arrow is the zone of apposition between the left ventricular components of the two leaflets of the common valve that bridge the ventricular septum. It is incorrect to describe this valve as being "mitral"

complex are, first, the annulus, when defined on the basis of the fibro-adipose tissues supporting the leaflets within the atrioventricular junction. The further components are the leaflets, supported by the tendinous cords and the papillary muscles, with the latter two parts also well described as the tension apparatus (Fig. 3.4).

The Valvar Annulus

The so-called annulus is the junction of the atrial and ventricular myocardial masses, and also the point of origin of the leaflets. When viewed from its atrial aspect, the junction itself is ovoid (Fig. 3.5). As can be seen from the section shown in Fig. 3.4, the antero-superior part of the annulus is an area of fibrous continuity between the leaflets of the mitral and aortic valves. The postero-inferior part, in contrast, is itself a component of the junction between the left atrial myocardium and the parietal wall of the left ventricle. By virtue of these anatomic differences, we differentiate between the two parts of the annulus, and by extension the leaflets they support, as being aortic in contrast to the mural. We will describe the specific structure of the two parts of

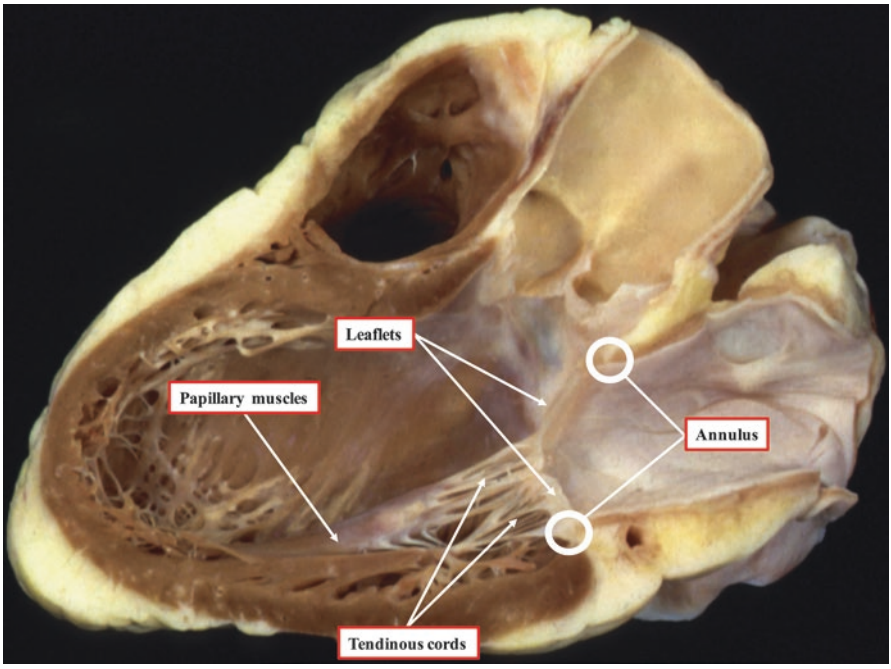

Fig. 3.4 The parasternal long axis cut through the left side of the heart serves well to show the components of the mitral valvar complex. We will discuss in detail to the naming of, and controversies surrounding, the different parts of the complex as shown in the section

the annulus in our more detailed account of anatomy provided in Chap. 4. Suffice to state, at this point, that it is exceedingly rare, if at all, to find a complete fibrous "ring" surrounding and supporting the leaflets of the valve. It is also the case, however, that the support provided to the mural leaflet, in most individuals, takes the form, at some point within the junction, of a curtain. This fibrous curtain, or collar, then separates the atrial vestibule from the crest of the ventricular wall. Such an arrangement rarely, if ever, is found supporting the entirety of the mural leaflet. Failure to recognise that such a feature is part of the normal anatomy, however, has lead in the past, and again recently, to it being nominated as "disjunction." We will emphasise in our account that this is no more than a variation of the normal arrangement. We have seen no convincing evidence to suggest that its presence underscores prolapse of any part of the mural leaflet.

The Valvar Leaflets

It is description of the leaflets that continues to be the most contentious area relating to the mitral valve. As already explained, it is our preference to describe the moving parts of the valvar complex as leaflets rather than "cusps." As shown above, we then distinguish the paired leaflets of the valve as being aortic and mural. Most textbooks

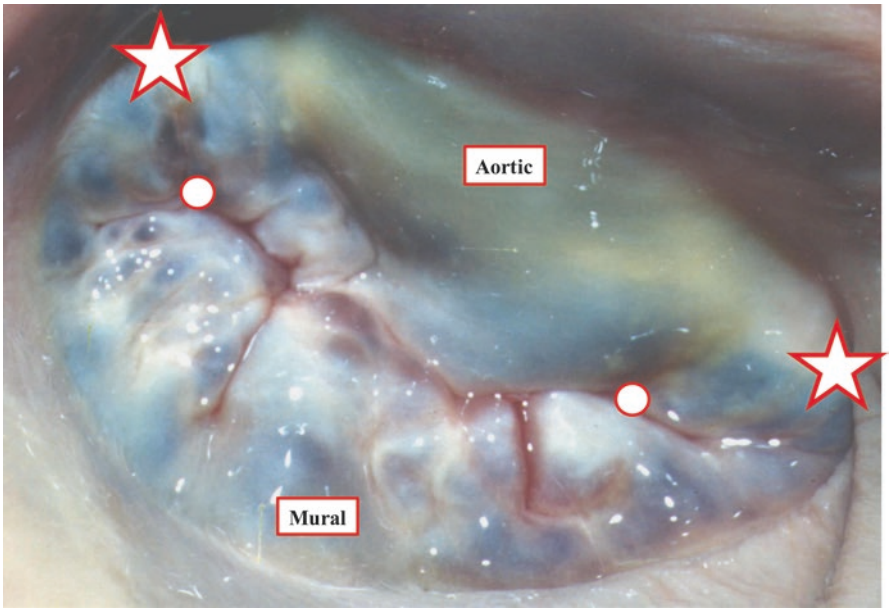

Fig. 3.5 The closed leaflets of the mitral valve are viewed from the atrial aspect. The "annulus" is delimited by the attachment of the atrial myocardium at the atrioventricular junction. It has two components, delimited by the stars. The anterior part, on its ventricular aspect, is in continuity with the leaflets of the aortic valve, whilst the posterior part is supported by the free parietal wall of the left ventricle. By virtue of these differences, we describe the two parts as being aortic and mural. As can be seen, this also permits the leaflets to be named as being aortic and mural. Note, however, that the ends of the solitary zone of apposition between the leaflets, shown by the white dots with red borders, do not extend to the annulus

describe the leaflets as being "anterior" and "posterior." When seen in the context of the heart within the body, however, these adjectives are not completely accurate. This is because, when assessed in attitudinally appropriate fashion, the left atrioventricular junction, and the papillary muscles supporting the leaflets anchored by the annulus within the junction, are positioned obliquely relative to the orthogonal planes of the body (Fig. 3.6).

As medical students learn when they are first introduced to human anatomy, all structures within the body should be described in the context of the subject standing upright in the so-called "Anatomical Position." It is unfortunate that, for centuries, anatomists have disregarded this key rule of human anatomy when describing the heart. Thus, the heart is usually removed from the body and positioned on its apex when described in anatomical textbooks. It is assessment in this "Valentine" position that permits the components of the left atrioventricular junction and by extension the leaflets of the mitral valve, to be described as being "anterior" and "posterior." Increasingly, however, clinicians are viewing the components of the valve as revealed by techniques of imaging that show the valvar complex as it resides within the body. And surgeons, of course, other than when transplanting the

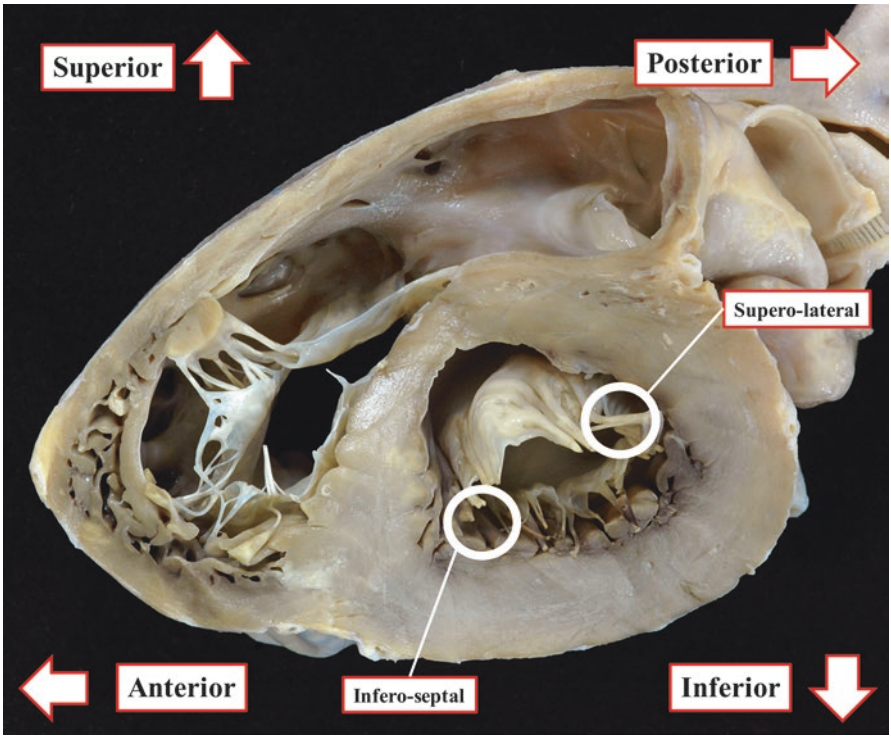

Fig. 3.6 The image shows the short axis of the ventricular mass, with the heart placed in attitudinally appropriate position. The ends of the zone of apposition between the leaflets of the mitral valve, and the papillary muscles that support them, are located in infero-septal and supero-lateral positions. It is a mistake to describe these features as being "postero-medial" and "antero-lateral," as is the current practise

organ, view the heart within the body. Throughout our book, therefore, we will describe the components of the heart as they are seen in attitudinally appropriate position. When considering the leaflets of the valve, nonetheless, such potential controversies in the description are removed when the leaflets are described simply as being aortic and mural (Fig. 3.5).

It is in distinction of the sub-components of the leaflets that the greatest controversy continues to exist. There are also problems in describing the way that the leaflets meet. As can be seen from Fig. 3.5, when viewed in their closed position there is but a solitary line showing the zone of apposition between the two leaflets. It is another rule of anatomy that structures with two moving parts, such as the lips, or the eyelids, close along a solitary zone of apposition. When using strict anatomical definitions, such a junction between two parts is called a "commissure." It has become conventional in clinical cardiology, nonetheless, to describe the ends of the solitary zone of apposition between the leaflets of the mitral valve as the paired "commissures." This convention is unlikely to change. With this in mind, therefore, we will describe the junction between

the leaflets as their zone of apposition, retaining the terms "commissures" to describe the two ends of the zone. We will still obey the rules of attitudinal nomenclature when distinguishing between the commissures. Thus, they will be described, along with the papillary muscles which support them, as occupying infero-septal and supero-lateral positions (Fig. 3.6). When viewing the relationship of the line of closure within the overall annulus, it can be seen that the zone of apposition does not reach to the margins of the atrioventricular junction. Instead, there are two segments of leaflet tissue interposed between the commissures and the annulus. These are the so-called "commissural" leaflets. Some have suggested that these parts should be accorded the status of leaflets, and the valve therefore considered to possess four rather than two leaflets [3]. We consider it better simply to consider the valve as possessing its aortic and mural leaflets, with the commissural leaflets being subsections of the overall skirt of leaflet tissue arranged so as to permit the valve to close in competent fashion. It is this arrangement of closure of the leaflets that underscores the much greater problem of description—namely whether the mural leaflet of the valve is best assessed in terms of three "scallops." As with the convention regarding the ends of the zone of apposition being named as "commissures," it is now the case that clinical cardiologists uniformly accept the concept that the mural leaflet of the valve is, indeed, arranged in the form of three scallops, named P1 through P3 by Carpentier [4]. It should be noted that, although it is often found to be the case, the three portions are not predicated upon the site of the clefts or indentations but are simply dividing the leaflet into three approximately equal portions for ease of description. By extension, the aortic leaflet against which the scallops co-apt is divided into three parts, A1 through A3. In most normal valves, as shown in Fig. 3.5, this convention works well. As was pointed out by Victor and Nayak, however, the arrangement of three scallops within the mural leaflet is not universal. Indeed, when examining a large series of normal valves, it is common to find indentations of varying height in the mural leaflet. We presume that these represent relatively arrested outward growth of the valvar leaflets as they are moulded during development from the atrioventricular endocardial cushions. The presence of these indentations allows the valvar orifice to open to a surface area that is wider than the annular orifice at rest, thus accommodating increased rates of flow and volumes at the extremes of exercise. Victor and Nayak compared this situation to the pleats found in a lady's skirt, or a Scotsman's kilt, which are there to allow ease of movement [5]. As is then recognised by any surgeon who has operated on patients with deformed mitral valves, the "regular" arrangement is frequently broken. It remains the fact, nonetheless, that analysis of the mural leaflet typically begins with an assessment of its presumed tripartite normality, so we will respect this convention in our descriptions. It then remains to remember that the so-called "P1" scallop is positioned supero-laterally, whilst it is the "P3" scallop that is located infero-septally.

The Tendinous Cords

The first point to emphasise with regard to our definitions for this part of the valvar complex is that, throughout our book, we will be using English as opposed to Latin terminology, since American English has now become common usage in of the

scientific world. Apart from anything else, the use of American English permits us to avoid the introduction of grammatical solecisms such as "caval flow," which is often used to describe flow through the "superior vena cava." The flow, of course, is venous rather than caval. The mistake of describing it as "caval" is readily avoided when describing the superior caval vein. It is for these reasons that we describe the tendinous cords, rather than the "chordae tendineae." And for those wondering why we have dropped the "h" from cords, this is because the anatomical entities are more akin to the cords of a window blind rather than the chords, or groups of notes, played on the piano or guitar! The categorisations offered for the cords that attach the leaflets of the atrioventricular valves to their supporting papillary muscles are many and varied. We restrict ourselves to the description of free edge or primary cords, and strut and basal cords, which can be considered as secondary. The primary cords attaching to the free edges of the leaflets are often further distinguished in terms of "commissural" and "cleft" cords, depending on their patterns of branching [6], but it can be very difficult to distinguish these differences. Suffice it to say that the so-called "commissural cords," better described as appositional cords, extend from the tips of the papillary muscles. They branch so as to supply the free edges of both the aortic and mural leaflets. The so-called "cleft" cords, in contrast, supply the adjacent margins of different parts of the mural leaflet. Where there are deep clefts, they extend into the depths of the cleft, and occasionally to the reflection of the components at the atrioventricular junction. The strut cords are the cords that splay out onto the underside of the aortic leaflet, where they are attached to the ventricular aspect of the leaflet away from its free edge. The basal cords support the ventricular aspect of the components of the mural leaflet, often with their own miniature heads (Fig. 3.7).

Fig. 3.7 As seen from the left-hand side, the panels show the features of free edge, strut, and basal cords of the mitral valve. Note that the cord arising from the tip of the papillary muscle in the left-hand panel itself branches to supply the free edges of both the aortic and mural leaflets of the valve. This is a so-called "commissural" cord

The Papillary Muscles

These are the muscles that give rise to the free edge and strut cords of the tendinous apparatus (Fig. 3.7). For the mitral valve, there are paired papillary muscles, although each muscle can have several heads [7]. The most important point to note when describing the papillary muscles is their location when the heart is within the chest. At the moment, it is customary to describe the muscles as being "postero-medial" and "antero-lateral." This is a consequence of the inappropriate fashion, popular for centuries, of describing the heart in "Valentine" fashion having removed it from the chest during either cadaveric dissection or during an autopsy. As shown in Fig. 3.6, when the heart is viewed in attitudinally appropriate fashion, the muscles are located infero-septally and supero-laterally. This is the fashion in which they will be described in our book. It should also be noted that each papillary muscle provides tendinous cords to both of the leaflets of the mitral valve.

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The Anatomy of the Mitral Valve

4

Robert H. Anderson, Shumpei Mori, Justin T. Tretter, Damian Sanchez-Quintana, and Diane E. Spicer

Introduction

As we indicated in the introduction to this book, the mitral valve is best considered in terms of a "complex." From the outset of cardiac surgery, as pointed out in our chapter describing the history of the valve, perceptive surgeons have appreciated that all parts of the complex must work in harmony if the valve is to function properly. It was Perloff and Roberts, however, who introduced the formal notion of the valvar complex [1]. As also explained elsewhere in our book (See Chap. 3), it is now our intention to expand their approach so as to consider the complex as an atrioventricular entity (Fig. 4.1). Our account of the anatomical arrangement of the components of the complex is very much based on our own experiences. We recognise, in this respect, that controversies still abound with regard to each of its parts. There are multiple paradoxes that may well explain these ongoing disagreements and debates.

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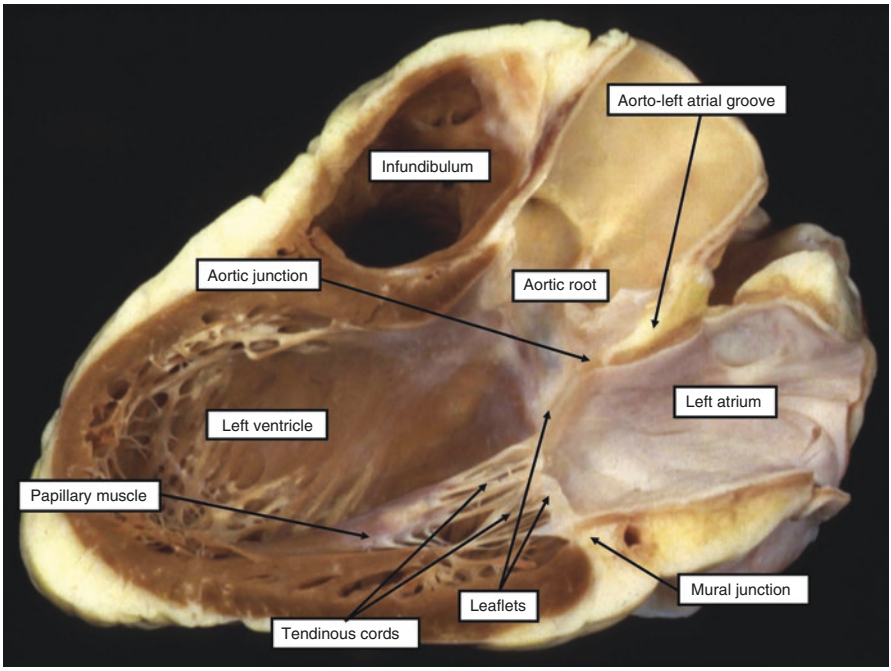

Fig. 4.1 The heart has been sectioned in its long axis so as to produce a section comparable with the parasternal long-axis view as obtained by echocardiographers. The section is photographed from its left side. The image shows the components of the left atrioventricular junctional complex, namely the left atrial walls, the aortic and mural components of the left atrioventricular junction, the valvar leaflets, their supporting tendinous cords, the papillary muscles (only the infero-septal muscle is seen in this cut) and the supporting ventricular myocardium

If the surgeon is properly to treat the abnormal valves confronting him or her in the operating room, he or she must have full information regarding the normal arrangement. This makes it important to recognise the paradoxes. The first paradox is that, while surgeons see many more mitral valves than do morphologists, the valves requiring their attention are usually abnormal rather than normal. We must extrapolate, therefore, from the normal features with which we are confronted as anatomists so as to account for the abnormal findings with which the surgeon is confronted. The second paradox is that, unlike morphologists, the surgeon has limited access to all the components of the junctional complex. From the standpoint of function, the hidden parts are likely to be of just as much significance as those that are obvious to the surgical view. We are fortunate, therefore, that the morphological details can now be shown in exquisite detail by virtual dissection of computed tomographic datasets, not only of the living heart but also autopsied specimens. Virtual dissection of the living heart has the inestimable value that the valvar components can be assessed as they are located in their normal positions within the chest. This then highlights the third paradox. As anatomists, we teach our students that all structures should be described as they are located within the body. It is surprising, therefore, that anatomists have ignored this basic rule for centuries when describing the heart

in "Valentine" fashion [2]. Throughout this chapter, therefore, as with the remainder of our book, we will be describing the components of the left atrioventricular junction complex in the attitudinally appropriate fashion. As far as is possible, we will also orientate our illustrations in this way.

What Is the Mitral Valve?

The normal mitral valve guards the morphologically left atrioventricular junction. It is a well-recognised fact that the atrioventricular valves "belong" to their ventricles. In congenitally corrected transposition, for example which is characterised by the discordant arrangement of the atrioventricular connections, the mitral valve is a right-sided structure when the atrial chambers are usually arranged. The valve then guards the junction between the morphologically right atrium and the discordantly connected morphologically left ventricle. In this chapter, of course, we are concerned with the normal left-sided mitral valve. Its alternative name is the bicuspid valve. Hence, it has two components within the skirt of leaflet tissue that opens and closes within the left atrioventricular junction. We presume it was the perceived similarity of the arrangement of those two components, when viewed from the ventricular aspect, to the episcopal mitre that underscored the usual naming of the valve (Fig. 4.2).

As we emphasised in our chapter on definitions (see Chap. 3), there is a marked difference between this bifoliate pattern of normal closure and the trifoliate arrangement seen in the heart with atrioventricular septal defects in the setting of a common atrioventricular junction. That is why the left atrioventricular valve in the latter setting should not be described as being "mitral." As suggested above, we presume it was the view from the apex of the left ventricle that promoted the notion that the bifoliate valve would better be described as being mitral (Fig. 4.2). Nowadays, the valve is seen more frequently in the parasternal long-axis section as obtained by the echocardiographer. This view encapsulates the reasons why the structure is best analysed in terms of a junctional complex (Fig. 4.1). The components of the complex are the atrial vestibules, the atrioventricular junction itself, the valvar leaflets, the tendinous cords, and the papillary muscles, with the papillary muscles themselves supported by the inferior or diaphragmatic wall of the left ventricle. When viewed in the short axis of the left ventricle, the mitral valve differs from the tricuspid valve in lacking any tension apparatus directly attached to the muscular ventricular septum (Fig. 4.2). This is because an extensive infero-septal recess of the subaortic outflow tract interposes between the curtain of leaflet tissue and the endocardial surface in the inferior component of the muscular ventricular septum (Figs. 4.3 and 4.4) [3].

The presence of the recess has a marked influence on the well-recognised "off-setting" of the hinges of the leaflets of the mitral versus the tricuspid valve. This characteristic sign, used by echocardiographers to distinguish between the valves, and by inference, the ventricles supporting them, does not become visible until the transition is reached between the inferior part of the muscular ventricular septum and the parietal inferior wall of the left ventricle (Fig. 4.5). The hinge of the mural leaflet of the mitral valve then forms the leftward border of

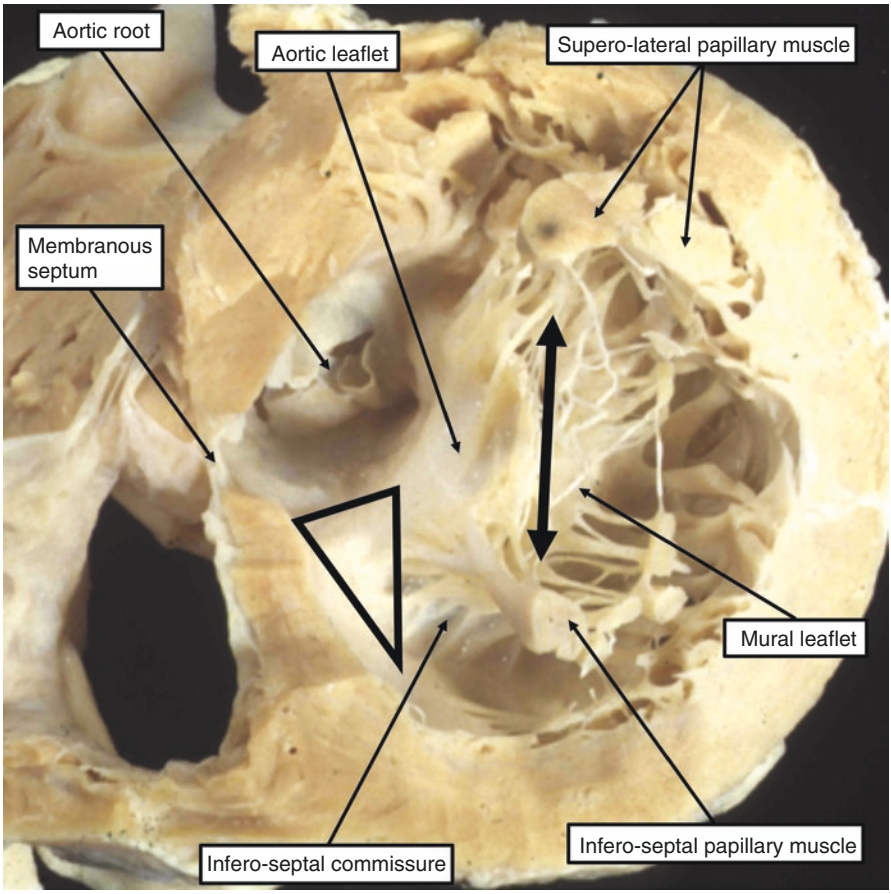

Fig. 4.2 The ventricular mass has been sectioned in its short axis, and photographed looking towards the base. The leaflets of the mitral valve come together along a solitary zone of apposition (double-headed black arrow), producing an arrangement reminiscent of the episcopal mitre. Note the extensive recess that interposes between the aortic leaflet of the valve and the left ventricular septal surface (black open triangle). This is the infero-septal recess of the aortic root. Note also that, when viewed in attitudinally appropriate fashion, as shown in this image, the ends of the zone of apposition between the leaflets, and the supporting papillary muscles, are positioned infero-septally and supero-laterally

the inferior pyramidal space. The atrioventricular node is found within the floor of the triangle of Koch at the level of the transition between the apex of the inferior pyramidal space and the inferior extent of the septal recess (Fig. 4.6). It is because of the juxtaposition of these two spaces that the penetrating component of the conduction axis, usually described as the bundle of His, has such a short course as it extends from the atrial to the ventricular components of the heart. As we have emphasised, there is marked individual variation in all

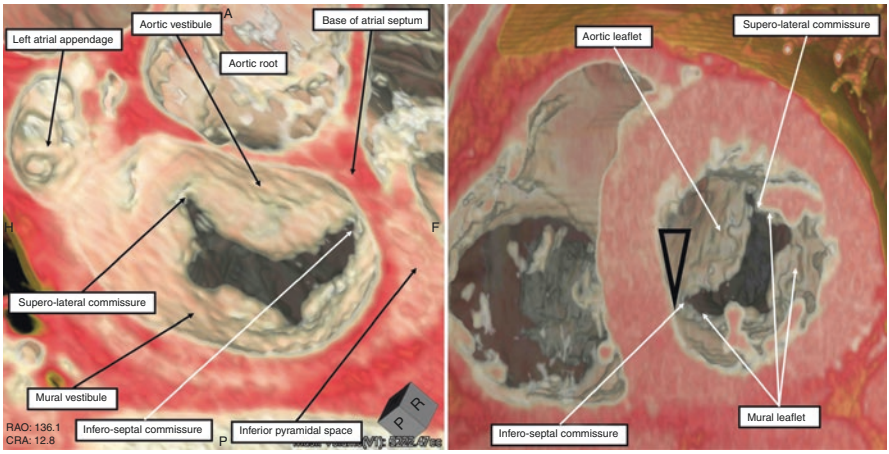

Fig. 4.3 The computed tomographic scans of the living heart reinforce the image of the valve as shown by the anatomical section shown in Fig. 4.2. The ability to section the three-dimensional dataset, however, means that it is possible to show the heart as seen from the atrial aspect (left-hand panel) and the ventricular aspect (right-hand panel). Comparing the two images shows that the infero-septal recess of the aortic root (black open triangle in right-hand image) undermines the base of the atrial septum, as shown in the left-hand image

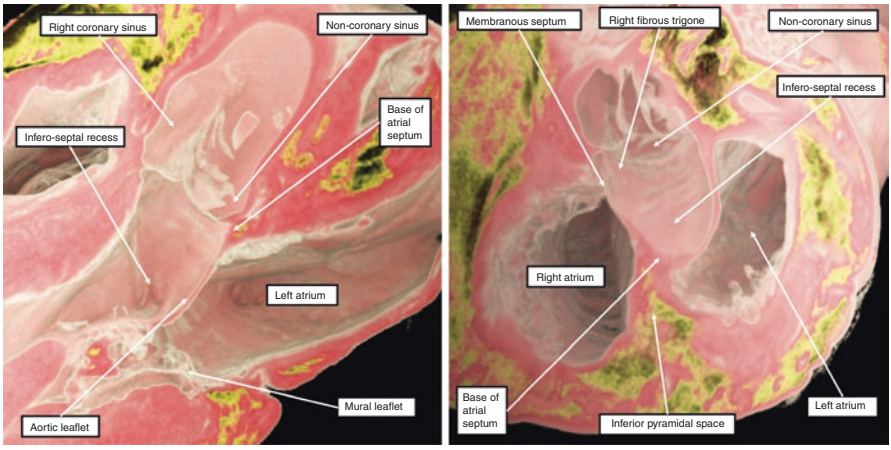

Fig. 4.4 These magnetic resonance imaging scans are made from a formalin-fixed autopsy specimen of a normal heart. They show how multiple sections can be taken to show the anatomy of features otherwise difficult to appreciate, in this instance the infero-septal recess of the subaortic outflow tract. The left-hand panel is a tilted section simulating the long-axis echocargraphic plane, while the right-hand panel is taken on the short axis of the atrioventricular junctions. The right-hand panel shows particularly well how the recess interposes between the right and left atrioventricular junctions, and undermines the base of the atrial septum. It also shows how the apex of the recess overlaps the apex of the inferior pyramidal space

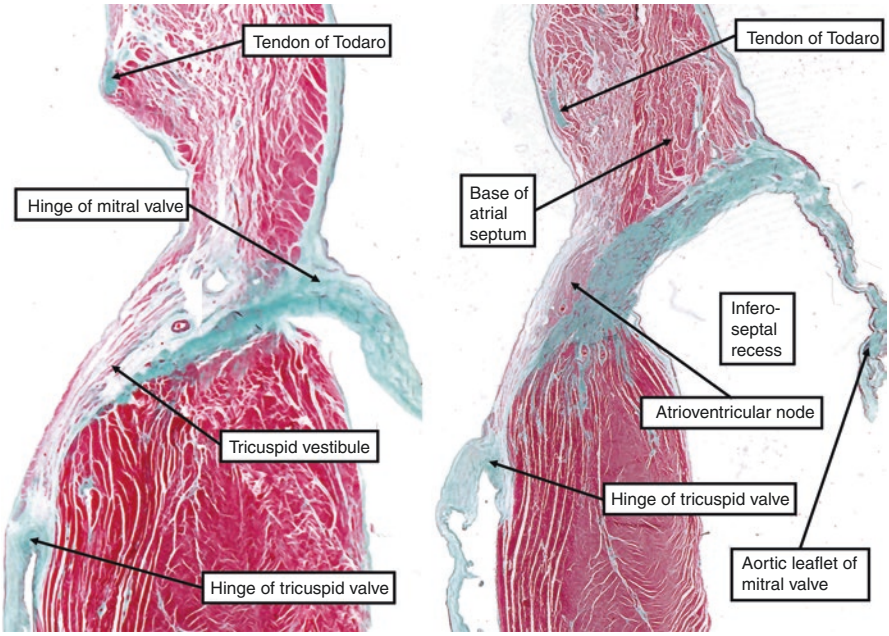

Fig. 4.5 The images, oriented in "four chamber" fashion, with the atrial chambers positioned superior to the ventricles, show two histological sections through the septal component of the atrioventricular junctions. The left-hand panel is taken at the base of the triangle of Koch, while the right-hand panel is through the middle of the triangle. The sections show how the off-setting of the hinges of the leaflets of the atrioventricular valves is found only at the base of the triangle (left-hand panel). As shown in the right-hand panel, the section taken superiorly confirms how the infero-septal recess of the aortic root undermines the base of the atrial septum, interposing between the aortic leaflet of the mitral valve and the septal surface of the left ventricle. Note the location of the atrioventricular node as seen in the right-hand panel. The node is carried on the atrial aspect of the fibrous insulating tissue, which produces continuity between the leaflets of the mitral and tricuspid valves

components of the junctional complex. We will address the extent of these variations, and their potential surgical significance, as they relate to each of the components.

The Left Atrioventricular Junction

When viewed from the atrial aspect, the left and right atrioventricular junctions, along with the aortic root, take on an obvious shamrock configuration. The diverging inferior components of the atrioventricular junctions are separated by the tissues of the inferior pyramidal space, with the artery to the atrioventricular node extending between the right atrial vestibule and the crest of the left ventricular cone in this area (Fig. 4.7). When viewed from the ventricular aspect, the orifice overlaps with the aortic root within the circular configuration of the short axis of the left

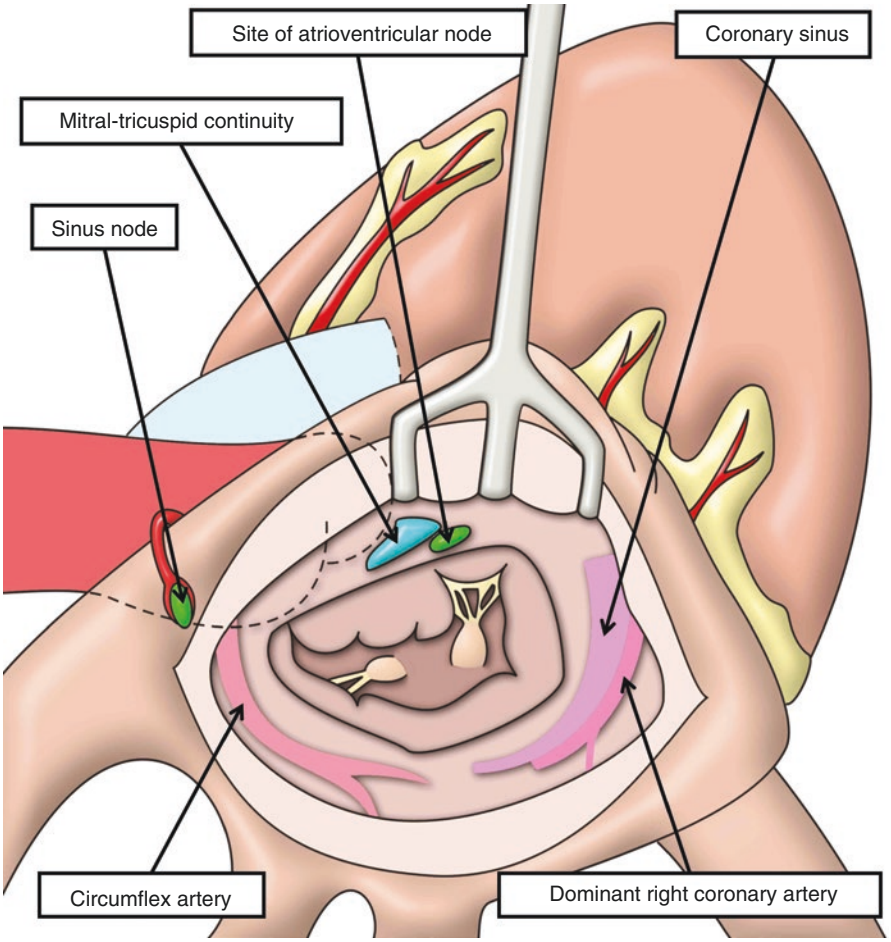

Fig. 4.6 The drawing shows the view of the mitral valvar orifice as would be seen by the surgeon. The atrioventricular node carried on the area of fibrous continuity between the leaflets of the mitral and tricuspid valves that forms the roof of the infero-septal recess (see Figs. 4.4 and 4.5), is located at the transition from the septal to the parietal components of the left atrioventricular junction

ventricular cone. This view shows well how the infero-septal recess of the aortic root extends towards the crux, separating the leaflets of the mitral valve from the septal surface of the left ventricle (Figs. 4.2, 4.3, and 4.4). When viewed from the atrial aspect, the left atrial myocardium is seen to insert into the atrioventricular junction at the margins of the ovoid orifice, forming the left atrial vestibule (Fig. 4.8). Anteriorly, the vestibular myocardium is related directly to the aortic root, with the atrial wall separated from the non-coronary aortic valvar sinus by the aorto-left atrial groove (Fig. 4.9—upper panel). Posteriorly and inferiorly, the vestibule forms the atrial part of the mural component of the junction (Fig. 4.9—lower panel). Within the mural junction, the circumflex artery and the coronary sinus are

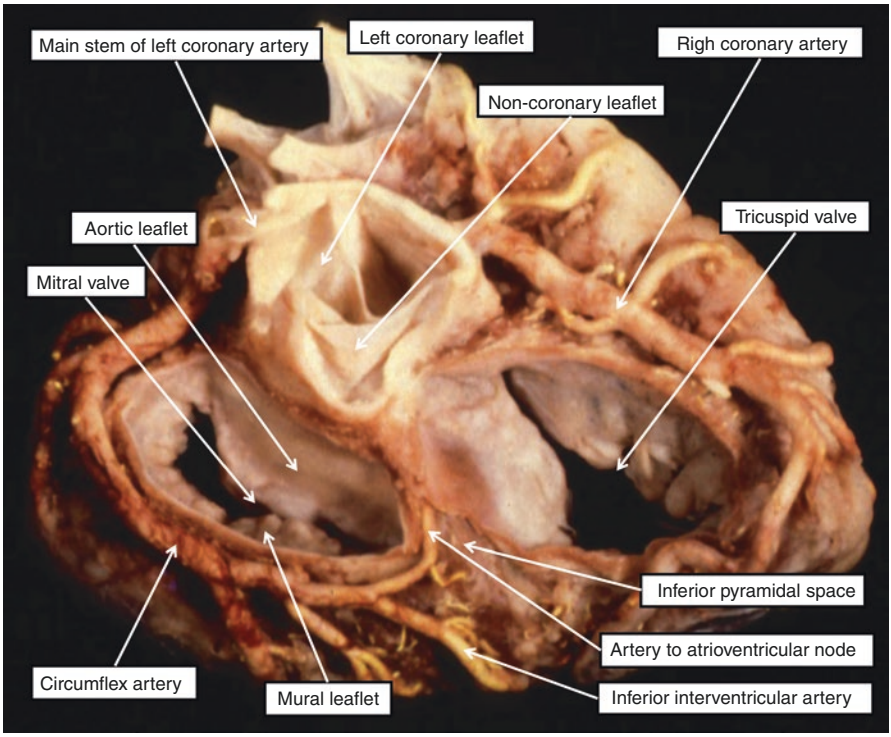

Fig. 4.7 The heart is viewed from above having removed the arterial roots down to the level of the semilunar hinges of the arterial valves, and the atrial myocardium to reveal the vestibules of the mitral and tricuspid valves. The dissection shows well the relationship between the aortic leaflet of the mitral valve and the non-coronary and left coronary leaflets of the aortic valve. In this heart, the circumflex coronary artery was dominant. Note that the artery to the atrioventricular node extends through the inferior pyramidal space, which separates the diverging inferior margins of the left and right atrioventricular junctions

surrounded by the fibro-adipose tissue that fills the left atrioventricular groove. In most individuals, who have the right coronary arterial dominance, the circumflex artery has a limited course within the junction. When the circumflex artery is dominant, a feature found in around one-tenth of the population, then it is much more closely adherent to the hinge of the mural leaflet of the valve (Fig. 4.7). The coronary arteries are usually located deeper within the groove, and closer to the endocardial surfaces, than are the venous structures (Fig. 4.10). The coronary sinus itself, nonetheless, retains an intimate relationship with the hinge of the mural leaflet of the valve (Fig. 4.9—lower panel, Fig. 4.10). Although echocardiographers typically use the so-called "off-setting" of the hinges of the leaflets of the mitral and tricuspid valves as a feature with which to distinguish them, in reality, the leaflets of the mitral valve have a very limited attachment to the left ventricular surface of the inferior part of the muscular ventricular septum.

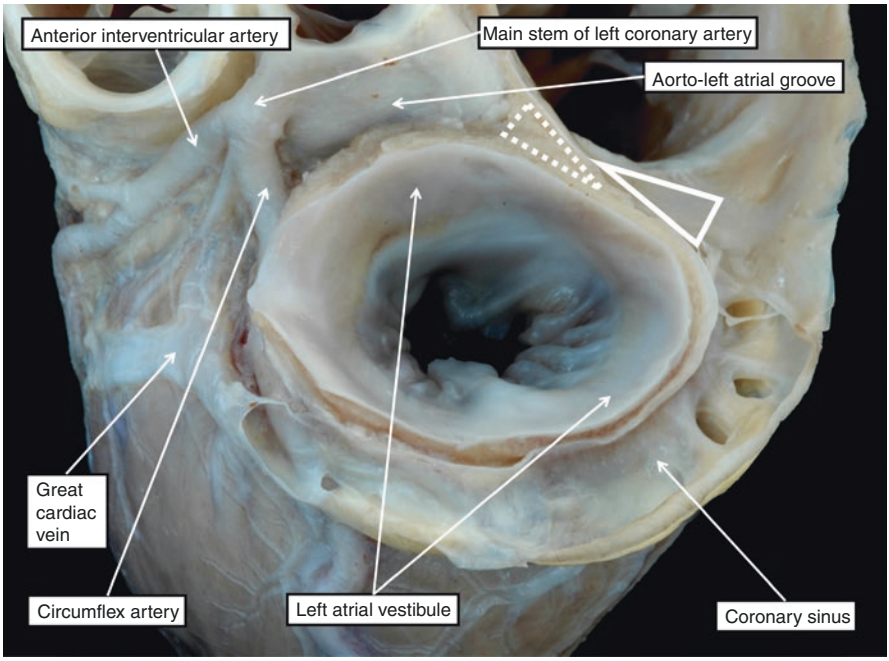

Fig. 4.8 The dissection has been made by removing the walls of the left atrium, but leaving the vestibule. The vestibular myocardium supporting the aortic leaflet of the mitral valve is separated from the aortic root by the cavity of the transverse pericardial sinus. This is best described as the aorto-left atrial groove. Note how the apex of the triangle of Koch (white triangle) overlaps the inferior extent of the infero-septal recess, shown by the white triangle with dashed lines. It is this relationship that permits the bundle of His to pass from the apex of the triangle to reach the crest of the muscular ventricular septum

As we have already emphasised, this is because of the presence of the deep infero-septal recess of the left ventricular outflow tract (Fig. 4.3). Inferior to the infero-septal end of the zone of apposition between the aortic and mural leaflets, the hinge of the mural leaflet arises from the leftward boundary of the inferior pyramidal space. This space is filled by a superior continuation of the fibro-adipose tissue of the inferior atrioventricular groove. This tissue interposes between the atrial floor of the triangle of Koch and the myocardial crest of the septal component of the ventricular cone. We used to describe this area as a muscular atrioventricular septum. We now know that because of the presence of the fibro-adipose tissue within the inferior pyramidal space, it is an open sandwich rather than a true septum (Fig. 4.11). The cavity of the infero-septal recess interposes beneath the septal component of the junction between the leaflets of the mitral valve and the left ventricular surface of the muscular ventricular septum. This subtle feature is not readily obvious to the surgeon, nor even to the anatomist, without special dissections made to show its location (Fig. 4.12). As we have shown, however, the extent of the recess is revealed by interrogation of computerised tomographic datasets (Fig. 4.4). The key

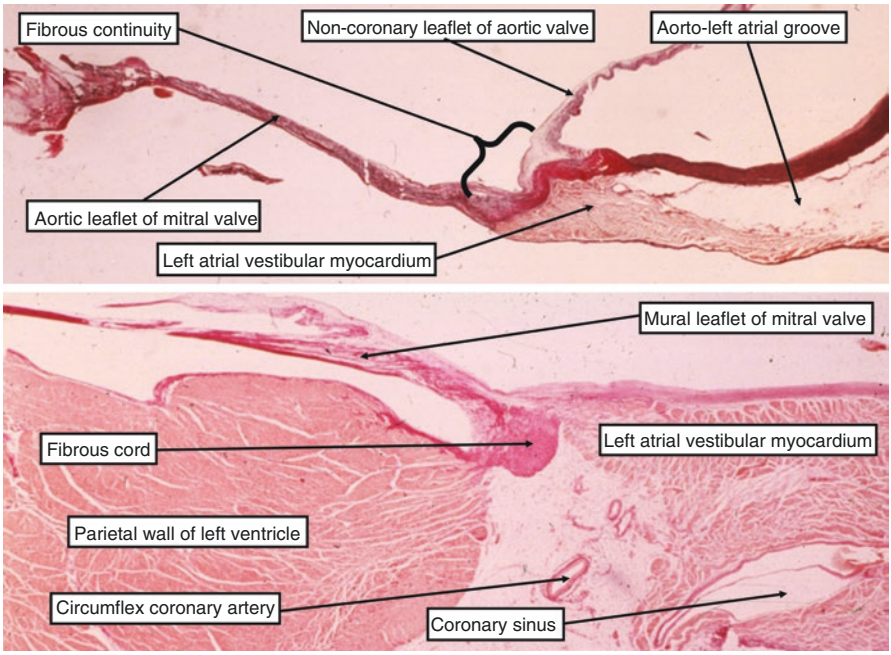

Fig. 4.9 The histological sections are taken through the vestibules of the left atrium inserting into the hinges of the aortic (upper panel) and mural (lower panel) leaflets of the mitral valve

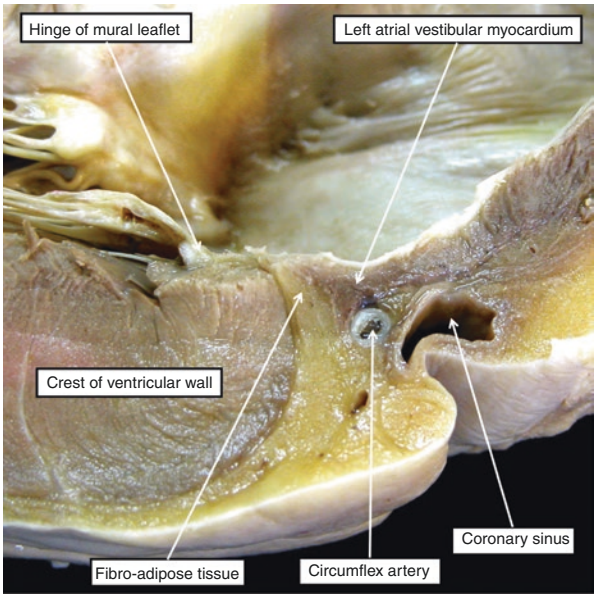

Fig. 4.10 The image shows a gross anatomical section across the mural component of the left atrioventricular junction. It is not possible to recognise any entity that corresponds to a so-called "annulus." Insulation is provided by the fibro-adipose tissues filling the atrioventricular groove

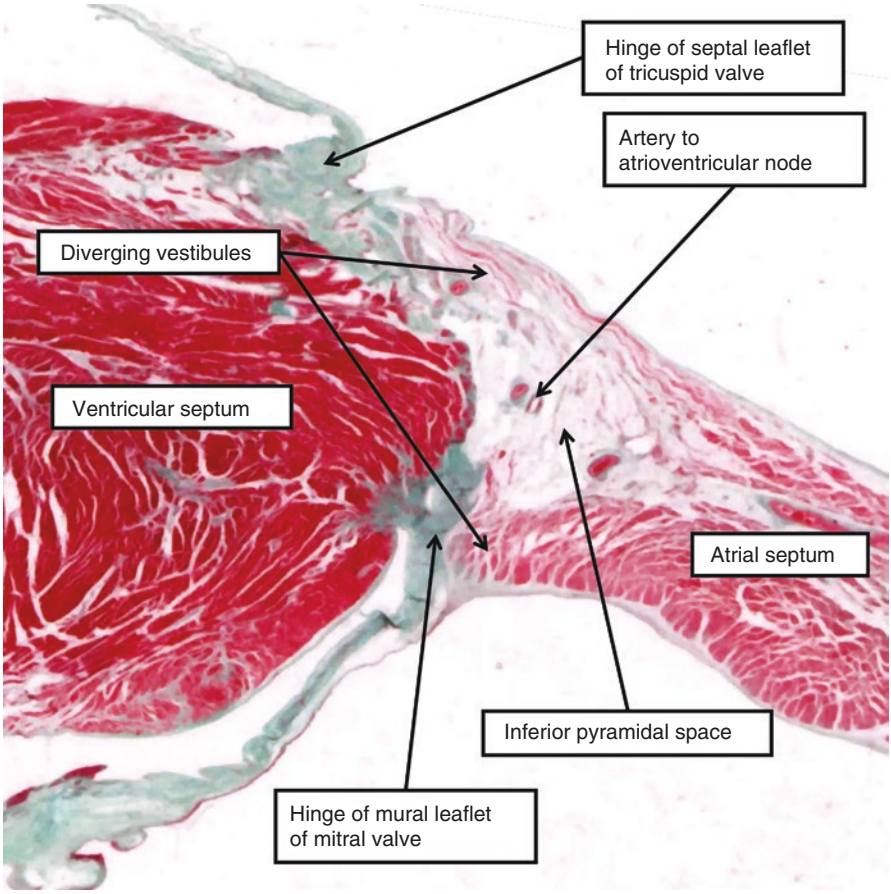

Fig. 4.11 The histological section, which is now orientated to match the arrangement seen in the parasternal long-axis section, with the cavities of the right-sided chambers shown to the top, reveals how the fibro-adipose tissues of the inferior pyramidal space interpose between the diverging vestibules of the atrioventricular junctions and the crest of the muscular ventricular septum. Note the atrioventricular nodal artery within the fibro-adipose tissues filling the space

structure to be found within the septal component of the junction is the atrioventricular node. Extensions from the node run into the parietal vestibules of both the mitral and tricuspid valves. Fortunately for the cardiac surgeon, the presence of the recess produces a distance between the node and the likely site for placement of sutures by those replacing the mitral valve. Care should be taken, nonetheless, to avoid placing sutures too deeply within the septal part of the vestibule. Respect should also be paid to the location of the circumflex artery, particularly when it is the dominant coronary artery (Figs. 4.6 and 4.7) [4].

It is often thought that a discrete fibrous "annulus" is part of the parietal component of the left atrioventricular junction. A recent editorial, for example

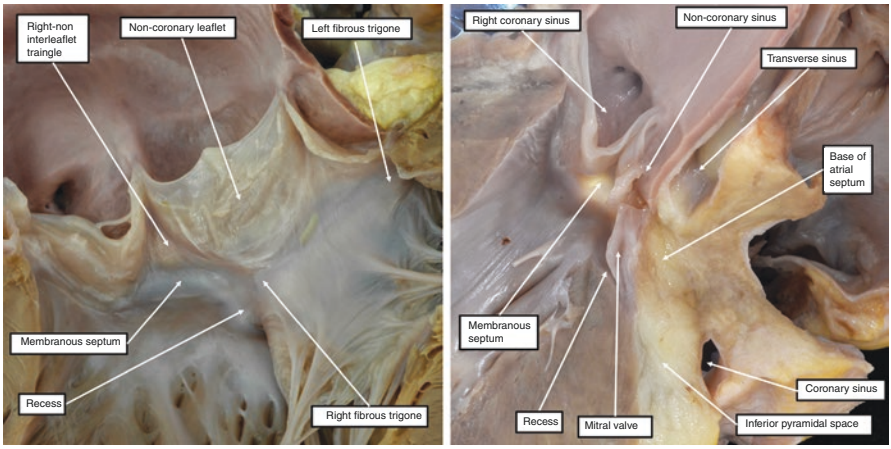

Fig. 4.12 The images show the location of the infero-septal recess of the aortic root. The left panel is a photograph of the aortic root taken from the front. It shows the recess extending towards the crux between the aortic leaflet of the mitral valve and the septal surface of the left ventricle. The right-hand panel is a section made through a different heart parallel to the septal surface and through the base of the atrial septum. The recess is seen between the leaflet of the mitral valve and the ventricular septum

suggested that the alleged entity "originates at the fibrous trigones, which sit at the junction between mitral and aortic valves and extends as an ellipse attached posteriorly to the left atrium and anteriorly to the left ventricle" [5]. This is rarely, if ever, the case [6]. The strongest part of the atrioventricular junction is the area of fibrous continuity found anteriorly between one of the leaflets of the mitral valve and the left and non-coronary leaflets of the aortic valve (Fig. 4.9—upper panel). It is because of this relationship that we name the leaflet of the mitral valve as being "aortic." The area of fibrous continuity is then thickened at its rightward and leftward ends to form the fibrous trigones. These thickenings anchor the aortic-mitral unit to the crest of the left ventricular myocardial cone (Fig. 4.12—left-hand panel). The anchorage provided by the right fibrous trigone is itself part of the roof of the infero-septal recess. This overall area of fibrous tissue then extends inferiorly as a fibrous plate at the apex of the inferior pyramidal space (Fig. 4.4). Within the mural atrioventricular junction, however, the support provided to the hinge of the mural leaflet varies markedly at different parts within the same individual. At some points, the fibrous tissue can be cord-like (Fig. 4.9—lower panel). At other points it can be shelf-like, forming a curtain between the vestibular atrial myocardium and the crest of the left ventricular wall (Fig. 4.13—upper panel). At still other parts of the junction, even in the same individual, it is possible to find areas with the absence of any fibrous tissue supporting the mural leaflet (Fig. 4.10).

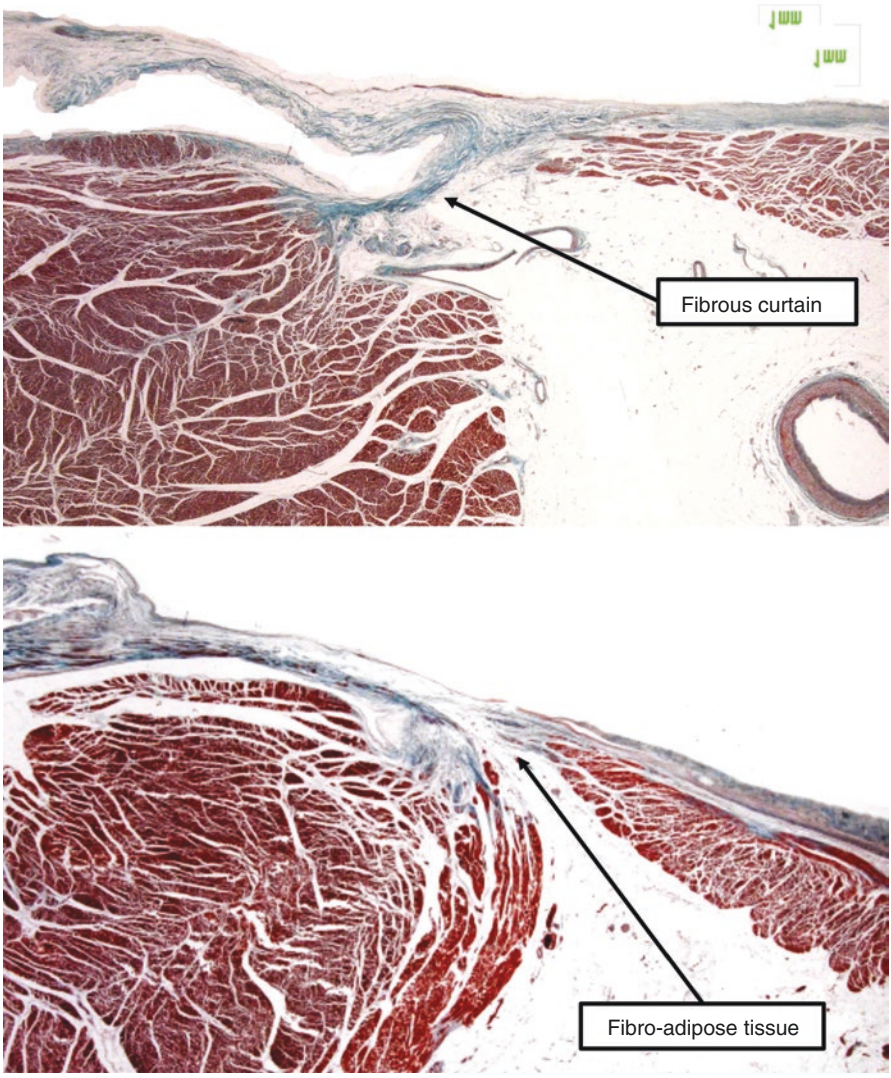

Fig. 4.13 The images are histological sections showing the different fashion in which the mural leaflet of the mitral valve can be anchored within the left atrioventricular junction. In Fig. 4.8, we have already illustrated a cord-like component anchoring the leaflet. The upper panel of this figure shows a curtain-like collar of fibrous tissue anchoring the leaflet to the base of the atrial vestibular myocardium, while the lower panel shows, as in Fig. 4.9, an absence of any fibrous tissue within the junction, the leaflet being hinged from the crest of the ventricular wall. These different arrangements can be found at different parts of the mural leaflet in the same individual

The leaflet is then hinged from the crest of the ventricular wall (Fig. 4.13—lower panel). It is the exception, therefore, rather than the rule, to find a complete fibrous structure, be it cord-like or curtain-like, which supports the hinge of the mural leaflet throughout the extent of the parietal atrioventricular junction. It is quite some time now since we demonstrated the lack of such continuous support for the hinge of the mural leaflet of the mitral valve within the left atrioventricular junction [6]. Our investigation at that time had been performed because of the suggestion that a feature termed "disjunction" might underscore prolapse of the mural leaflet [7, 8]. We found, however, that the feature described as "disjunction" was just as frequent in the normal heart as in the hearts we studied from patients with prolapsing mitral valves. We have summarised the findings from this investigation in Fig. 4.14. The fact that the variability we found in the support provided to the mural leaflet of the mitral valve was comparable in hearts obtained from normal individuals and those with prolapse now achieves new significance. This is because the notion involving so-called "disjunction" as underscoring prolapse of the mural leaflet has resurfaced, albeit with no mention made of our own previous investigation [9]. Our investigation of living datasets has confirmed, nonetheless, our previous findings using histology. The findings subsequent to the interrogation of computed tomographic datasets show that so-called "disjunction" is no more than the curtain-like support provided to the mural leaflet at different parts of the junction in most normal individuals (Figs. 4.15, 4.16, and 4.17). As yet,

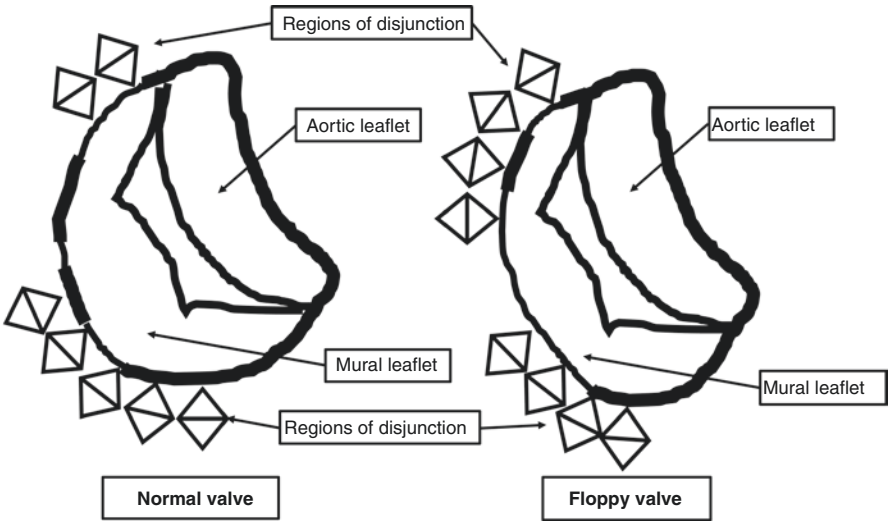

Fig. 4.14 In this figure, we summarise the findings from a previous study in which we explored the significance of so-called "disjunction." In this study [6], we compared the junctional arrangement in seven normal individuals with six hearts obtained from patients having prolapsing leaflets or so-called "floppy" mitral valves. In the drawing, we show the findings from two of the hearts, illustrating how the finding of so-called disjunction could be just as extensive in the normal hearts as in those with floppy leaflets. There was also comparable variability in the thickness of the fibrous hinges of the mural leaflets, shown by the width of the black lines

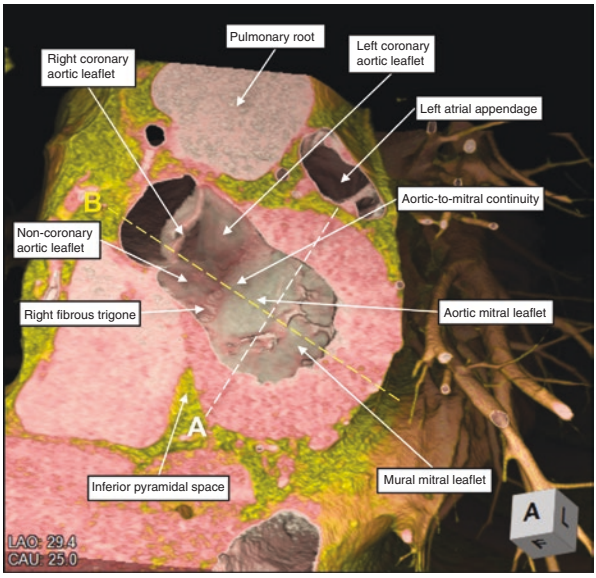

Fig. 4.15 The image is taken from a computerised tomographic dataset taken during systole in an 82-year old normal individual undergoing analysis for suspected coronary arterial disease. It shows an oblique cut through the short axis of the base of the left ventricle. Further cuts were taken along the planes A and B to show the anatomy of the hinges of components of the mural leaflet of the mitral valve

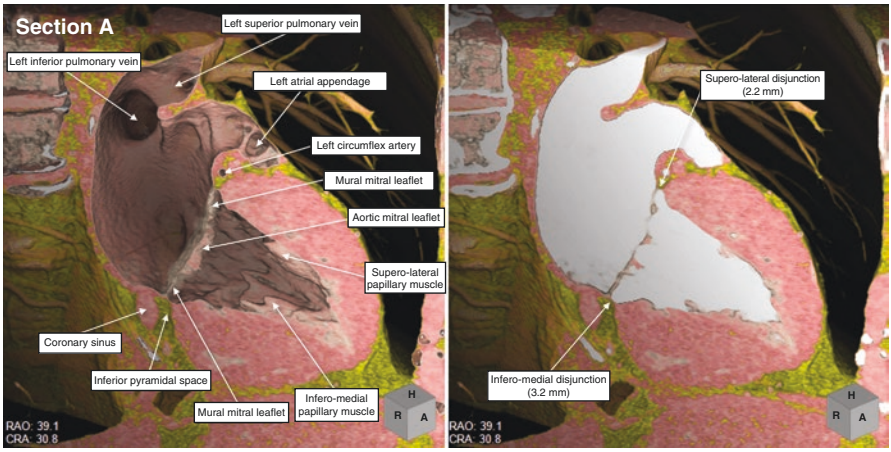

Fig. 4.16 The image shows the findings from the cut along plane A as indicated in Fig. 4.15. There is so-called "disjunction" at the two ends of the hinge of the mural leaflet of the mitral valve

therefore, there is no evidence of which we are aware positively to implicate the finding of so-called "disjunction" as the cause of mitral valvar prolapse. As was indicated by the editorialist placing emphasis on the so-called annulus [5], "new and careful physiological studies with multiple timed comprehensive measurements" will be required to resolve this issue. This will require careful comparisons with normal findings, assessing the overall hinge of the leaflet as shown in Figs. 4.15, 4.16, and 4.17.

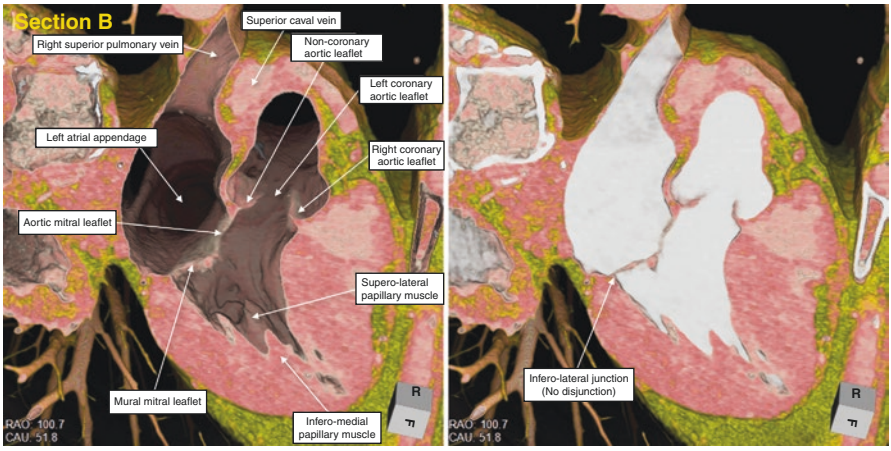

Fig. 4.17 This image shows the findings regarding the arrangement of the hinge of the mural leaflet in its central component, with the cut taken along the plane B as indicated in Fig. 4.15. There is no "disjunction" along the support of the middle part of the mural leaflet

The Valvar Leaflets

The skirt of leaflet tissue suspended from the left atrioventricular junction closes along a solitary zone of apposition between its two components. These components are typically described as being "anterior" and "posterior." When viewed in attitudinally appropriate fashion, these adjectives are rarely completely accurate. Because of this inaccuracy, it is our preference to describe the leaflets as being aortic and mural. It is then possible, in almost all instances, to recognise the ends of the zone of apposition between these two components. For anatomists, it is the zone of apposition itself which would best be described as the "commissure." This is the area over which the moving components abut. For better or worse, conventional wisdom dictates that it is the ends of this zone of apposition that clinicians recognise as the "commissures." So as to avoid confusion, we will simply describe these areas as the ends of the zone of apposition. When viewed attitudinally, they are positioned infero-septally and supero-laterally (Figs. 4.2 and 4.3). The ends of the zone of apposition do not reach the atrioventricular junction. Between the ends of the zone of apposition and the junction itself are found the commissural components of the skirt of leaflet tissue. On occasion, these can be extensive (Fig. 4.18). This can then create problems in determining for certain which area is the zone of apposition.

In the normal heart, it is very unusual for the aortic component of the skirt of valvar tissue to be anything other than a solitary entity. On occasion, nonetheless, this part of the valve can retain the components from which it is developed. This is known as congenital "clefting", although the leaflet, in this setting, will never have been a solitary entity. In some instances, minor degrees of so-called "clefting" can be recognised in otherwise normal valves. Although the aortic leaflet of the valve is usually a solitary entity, this is never the case for the remainder of the skirt of leaflet

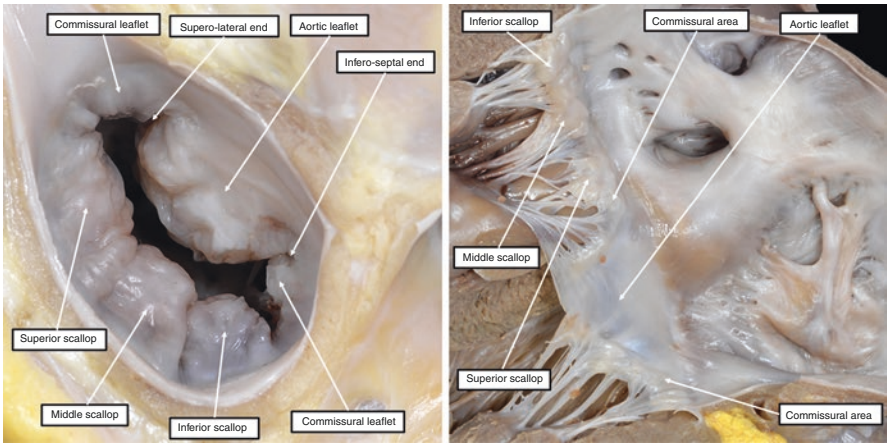

Fig. 4.18 The images show typical mitral valves as seen in the autopsy room with an intact atrioventricular junction (left-hand panel), and when opened through the inferior end of the zone of apposition between the leaflets (right-hand panel). Note the presence of an extensive commissural leaflet at the inferior end of the zone of apposition in the heart shown in the left-hand panel. This creates a potential problem in distinguishing between the end of the zone of apposition itself and the "cleft" between the commissural leaflet and the inferior scallop of the mural leaflet

tissue. The fact that the mural leaflet is never a unitary entity has spawned several approaches for describing its components. Some authorities have suggested that the mural leaflet can be considered as possessing three parts, which themselves should be considered as separate leaflets in a quadrifoliate valve [10]. More usually, these components are recognised as the valvar "scallops." It is this latter notion that provided the basis of valvar description popularised by Carpentier and his colleagues [11]. Others have pointed to the frequent presence of relatively discrete areas of leaflet tissue at the ends of the zone of apposition, promoting these parts as the commissural leaflets [12]. Victor and Nayak had commented that, in reality, there were frequently numerous slits along the mural component of the skirt. Such slits, which can be compared to pleats in a skirt or kilt, are necessary to permit the extensive mural leaflet to fit snugly against the aortic component when the valve is in its closed position [13]. Analysis of large numbers of normal hearts then shows that there is no uniform pattern [14]. The presence of three scallops in the mural leaflet, along with smaller commissural segments, is no more than the usual finding. Variations are frequent, meaning that specific description of the individual arrangement is better than procrustean classification. The area of the two leaflets, nonetheless, irrespective of the manner of division of the mural leaflet, is more-or-less the same. The aortic leaflet, which guards no more than one-third of the overall circumference of the junction, is deep, whereas the mural leaflet, guarding the remaining two-thirds, is shallow (Fig. 4.19). Irrespective of the variability in the specific arrangement of the mural leaflet, it is now conventional to describe the three scallops as representing P1, P2, and P3, with P1 being the supero-lateral scallop [11]. The opposing parts of the aortic leaflet are then typically recognised as being A1, A2, and A3 (Fig. 4.20).

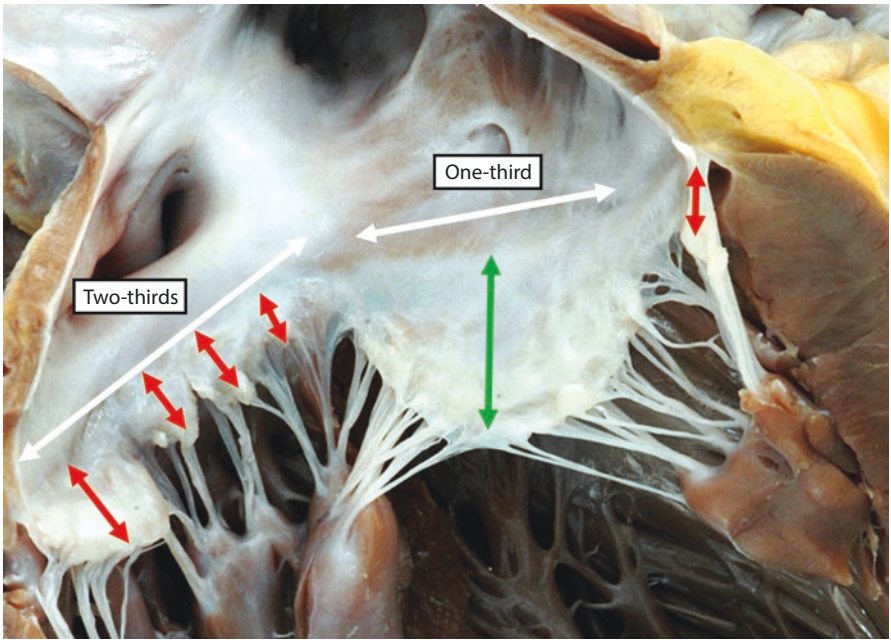

Fig. 4.19 The left atrioventricular junction has been opened by making a cut close to the inferior end of the zone of apposition between the leaflets, and the skirt of leaflet tissue opened to show the arrangement of the component parts. The aortic leaflet, which guards around one-third of the circumference of the orifice, is deep (green double-headed arrow), whereas the components making up the mural leaflet are all relatively shallow (red double-headed arrows)

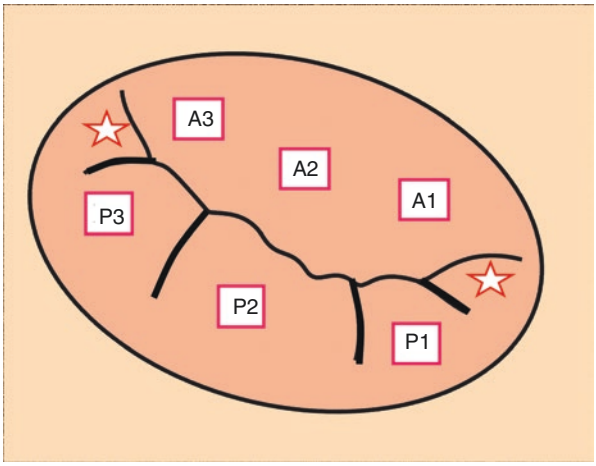

Fig. 4.20 The drawing shows the conventional approach to naming the components of the mitral valve, with P1 through P3 showing the scallops of the mural leaflet, and A1 through A3 the components of the aortic leaflet against which they abut. Note also, however, the presence of the commissural leaflets (stars)

The Tendinous Cords

Just as with the leaflets, the best way of describing the tendinous cords, or "chordae tendineae" has also proved controversial. It has long been suggested that "orders" of cords can be recognised. Others have suggested the need to differentiate between "commissural" cords and "cleft" cords [15]. As explained in our introductory chapter, we take a much simpler approach, not least because the branching of the cords makes it impossible to distinguish between the variants alleged to be "cleft" as opposed to "commissural." We distinguish between free-edge cords, strut cords, and basal cords. The key feature of normality is that the support provided by cords attached to the free edges should be uniform for all parts of the aortic and mural leaflets (Figs. 4.18 and 4.19). It was suggested quite some time ago now that lack of such uniform support was one of the features that promoted prolapse of components of the mural leaflet [16, 17]. We see no reason to doubt this proposition. The strut cords are the force-bearing entities attached in aggregated fashion to the ventricular surface of the aortic leaflet of the valve (Fig. 4.12). They show marked individual variation, as do the basal cords attached to the ventricular aspect of the mural leaflet. Each of the basal cords is usually attached on the ventricular side to its own miniature papillary muscle.

The Papillary Muscles

The major papillary muscles of the mitral valve are positioned so as to provide greatest support to the ends of the solitary zone of apposition between the leaflets. It follows, therefore, that they are located infero-septally and supero-laterally (Fig. 4.3—right-hand panel). It is a mistake to account for the muscles as being antero-medial and postero-lateral, as continues to be the usual description of clinicians. This approach reflects the bad habit of describing the heart as if removed from the body and positioned on its apex, the so-called "Valentine" approach. Each papillary muscle receives tendinous cords from both of the leaflets. Both muscles tend to have several heads. The presence of the infero-septal recess means that, unlike the tricuspid valve, there are no papillary muscles arising directly from the muscular ventricular septum. At their bases, the muscles are then supported by a zone of trabecular myocardium, attaching them to the compact walls of the left ventricle. This presence of trabecular myocardium can be exaggerated in the presence of so-called non-compaction, which is much better described as excessive trabeculation [18]. For this reason, the bases of the papillary muscles should be avoided by those seeking to assess the thickness of the compact and trabecular components of the walls.

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The Surgical Utility of a Detailed Knowledge of the Basic Sciences Pertaining to the Mitral Valve

5

Francis C. Wells

The confusions which occupy us arise when language is like an engine idling, not when it is doing its work.

Philosophy is a battle against the bewitchment of our intelligence by means of our language

—Ludwig Wittgenstein [1]

Thus wrote Ludwig Wittgenstein in his "Philosophical Investigations" (1973). The point that is to be made is that the language that is chosen to describe lesions etc., can rapidly become ingrained and reproduced without thought. It then gets passed on from generation to generation of cardiac surgeons and accepted as truth unquestioned, leading to unchallenged paradigms, which become translated into therapies that may not be wholly appropriate. One of the principle reasons behind this book on the basic sciences is to present the disease of the mitral valve in the light of what is known and where the gaps in knowledge remain, and to question dogma where it is not matched with evidence.

It is common practice to teach and inform aspiring practitioners of Mitral valve surgery along didactic lines. This is understandable when it is appreciated that we are dealing with human lives and that the practice of cardiac surgery outside of well-defined parameters, can lead to death or severe morbid complications. The practice of mitral valve surgery is at once on at least two levels, first, the safe orchestration of the procedure to obviate the potential complications of operating inside the heart of a fellow human being and second to carry out a procedure which requires a creative eye and a degree of insight less essential in many other procedures. It is to the eternal credit of Professor Alain Carpentier that he described a structured approach to the valve allowing a logical format that for the majority of cases produced a functionally competent valve [2, 3].

Others had been developing techniques for Mitral valve reconstruction at the same time, largely driven by the absence of satisfactory replacement devices in the

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mid-1950s onwards into the late 1960s. Pioneers such as McGoon at the Mayo clinic, Wooler, Kay and Paneth all developed techniques that could be applied to selective lesions of the valve. The McGoon valvuloplasty was directed at isolated mural leaflet prolapse and dealt with it by a triangular imbrication or excision of the billowing excess leaflet with significant success [4].

What Carpentier brought to the table was a functional classification of the leaking mitral valve that is now the mantra of all interested in this subject. The trilogy of dilated orifice and/or leaflet perforation, excessive leaflet motion and restricted leaflet motion continues to practically sub-divide the lesions which in turn leads towards surgical solutions laid out and defined by Professor Carpentier. All of that holds true to this day, almost 40 years since its presentation to cardiac surgeons at large, through the 1984 American association of thoracic surgeon's guest lecture, known now as "the French Correction" [4]. His presentation on that occasion and the paper that followed was prescient in many ways not least the prophesising of robotic surgery for the conduct of the operation.

However, the techniques described therein result largely in a fixed mural leaflet and hence a mono-leaflet valve. The addition of a complete rigid annuloplasty ring immobilises the base of the heart just as does a replacement prosthesis. In fact, this can lead one to ask the difference between a well-seated tissue prosthetic valve with complete sub-valve preservation and this kind of repair. That contention has never been tested in a randomised prospective trial. One wonders at the potential outcome.

Others, led by Carlos Duran have championed the use of a flexible band/ring to allow flexing of the atrioventricular junctional complex [5].

A further development was the lateral thought of Dr. Robert Frater (of the Montefiore hospital in the Bronx New York, New York), to reconstruct the leaflet cords using Goretex© [6] sutures [7]. The Gortex becomes covered in fibrous and endothelial tissue. The gaps in the structure of ePTFE sutures encourage the attachment of host tissue, This was verified in an Ovine model [8], and confirmed in human studies [9]. This move towards artificial cord use has transformed the world of mitral valve repair. It allows the retention of the natural length of the mural and aortic leaflets and the retention of the normal orifice area. It is now the preferred method for many surgeons and has had a significant impact on the development of minimal access to mitral valve surgery.

Surgical reconstruction of the valve has now reached a degree of refinement such that all and any combination of lesions can be addressed through a combination of techniques. There is still a place for leaflet resection, whether triangular, quadrangular or variations of sliding techniques. The free-thinking approach to the use of leaflet support with neo-cords, resection of excessively billowing portions of leaflet, and orifice dimension adjustment with the use of annuloplasty rings (preferably flexible bands in my opinion) gives rise to a toolbox of techniques that can be used in virtually any situation confronting the true Mitral valve surgeon. A full working knowledge and familiarity with all of the above and additional techniques such as the reduction of leaflet height with local base of leaflet resections, leaflet advancement using pericardium and various types of commissuroplasty separate the mitral journeyman from the specialist mitral surgeon.

All of this knowledge is enhanced when combined with a deep working knowledge of the basic sciences of the atrioventricular valve and its role in normal heart function. This is the rationale for this book.

When setting up a case for surgery it is invaluable to spend time inspecting the valve in detail, a "golden 5 minutes" in which to learn and to understand the lesions of each individual valve. Inspection at this level reveals many things that even the best ultrasound and MRI examinations cannot reveal; the presence of secondary and tertiary lesions often lost through echo drop-out and the anatomy of the papillary muscles which is very difficult to identify on echocardiographic examination. Here a sound working knowledge of the embryology and anatomy of the adult valve is key to understanding the lesions and the best way to deal with them.

Knowledge at this level also encourages the re-examination of taught dogma. The classification of valve pathology into fibro-elastic deficiency and myxomatous disease with the Barlow's valve at the extreme of the spectrum, whilst edifying the type of lesion, it does little to inform the mechanism of their development. It is of interest that in the so-called fibro-elastic deficient group the part of the leaflet that is prolapsed (most often P2) is the only thickened part of the valve leaflets. The rest being homogeneous in appearance. In the paper describing the comparative histopathological analysis of mitral valves in Barlow disease and fibro-elastic deficiency (FED) the glaring error is that the only parts of the valve examined histologically in the FED group are those resected at surgery [10]. It is the author's experience that the remainder of the valve is usually functionally normal. This is also borne out by the fact that in Carpentier's own data the repaired valves in this group have at least an 80% 20-year functional survival [11]. If it was a disease of the valve as a whole, other parts would surely degenerate and fail over this time period and that is not the case in practically all reported series.

It is my contention that what we are seeing is the result of an excessively loaded portion of the valve in a congenitally malformed valve. If we think of the valve as a force-field at end systole bearing pressures of up to 200 mm Hg on extreme exercise if the leaflets cannot spread that load around the whole valve then these pressure points will be traumatised over time. If we then look at the histological changes in this light, we see that they correspond to trauma-induced change with collagen disruption and the laying down of myxoid tissue, all changes seen around excessively traumatised joints.

Thus, the presence of deep interruptions in the mural leaflet which in almost all of these valves occurs, exposes these segments to a load that is isolated and traumatic. In addition, we commonly see in these patients highly abnormal papillary muscle arrangements that also prevent the normal load sharing of the normal valve. Hence in summary what we are seeing is a valve that cannot deal with the systolic stresses that a normal valve is able to do.

Pre-operative imaging focusses upon the leaflet lesions and is excellent at recognising the three groups of lesions described by Carpentier. However direct inspection is superior in all but functional aspects. If the surgeon focusses upon what the actual visible lesions are rather than looking for those described in the cardiologist's report, a better understanding of the real situation is forthcoming. The actual

anatomy of the valve around the prolapsing segment usually reveals interesting additional lesions, such as interruptions in leaflet growth rendering what many refer to as deep clefts (which are in fact interruptions in leaflet growth), highly abnormal papillary muscles, and calcification. The complete understanding of the valve will often lead to a modified approach to the repair. This may also prevent early recurrence that can be the case if other lesions are missed, or the height of coaptation is irregular and all of the leaflet(s) are not fully supported.

Hence the broadest understanding of the atrioventricular valve complex and its particular morbid anatomy is essential to optimise the reconstruction of the valve in each individual case.

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The Atrioventricular Valve in the Animal Kingdom

6

Bjarke Jensen

Introduction

The atrioventricular valve is as old as the vertebrates, approximately half a billion years [1]. All vertebrates have atrial and ventricular chambers, and the junction between these chambers is always guarded by an atrioventricular valve [2, 3]. Between vertebrates, there are more than 100-fold difference in heart rate, and more than a tenfold difference in solitary ventricular or left ventricular systolic pressure [4]. For breathing, fish rely on the gill circulation, which is placed in series with the systemic circulation. Amniotes, in contrast, rely on the lung circulation for breathing, which is in parallel to the systemic circulation. Amniotes, therefore, have septated hearts, including a septated atrioventricular junction [5, 6] (Fig. 6.1). Also, just as the chamber walls are subjected to the tension revealed by the law of Laplace [7], bigger animals have thicker valves [8], and so valvar morphology scales with chamber volumes. Given all these factors, we can immediately appreciate that the atrioventricular valvar apparatus varies substantially between vertebrates [9] (Fig. 6.2). In this chapter, I review key aspects of evolutionary trends in form and function of the atrioventricular valve. I then detail differences and similarities of the gross morphology of the atrioventricular valve, which is solitary in some setting, but morphologically left in the setting of ventricular septation. Finally, I survey mammals, focusing on species with extreme left ventricular pressure, as in the giraffe, or large stroke volume as in the elephant.

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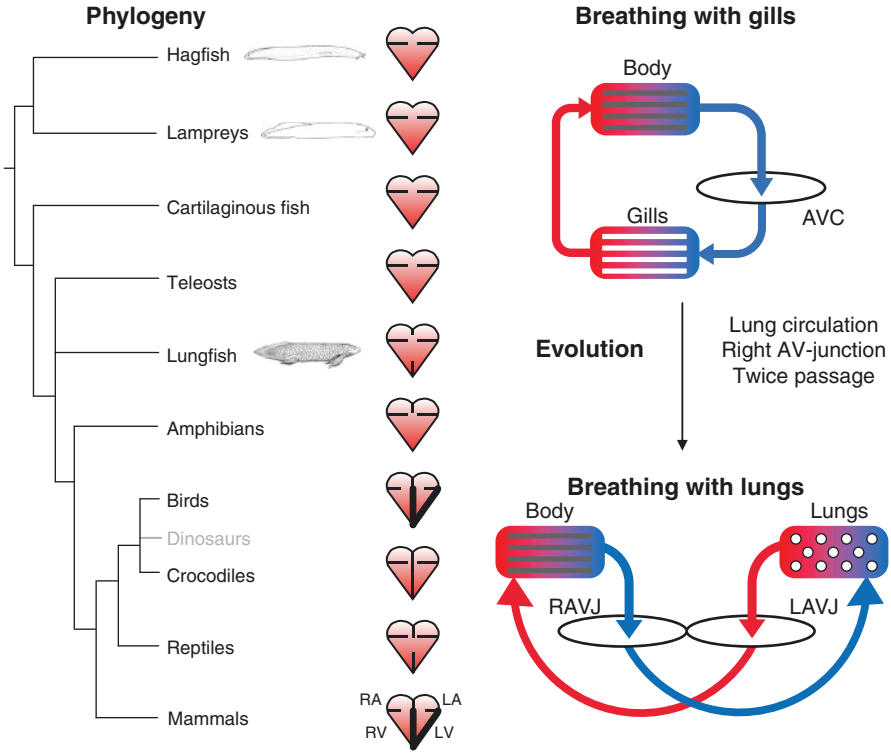

Fig. 6.1 In the phylogeny of vertebrates, the evolution of breathing of air with lungs associated with a remodeling of the atrioventricular canal (AVC) towards a distinct right atrioventricular junction (RAVJ). When breathing with lungs, each erythrocyte has to pass the heart twice for each passage of a systemic capillary. The atrioventricular junction of lung breathers, therefore, is approximately twice as large as in fishes. Cartoons of fishes are reprinted from Wikipedia courtesy of Creative Commons Licensing. Birds and mammals are characterized by a thick-walled left ventricle (LV). AVC, atrioventricular canal; LA, left atrium; LAVJ, left atrioventricular junction

Major Evolutionary Trends

The Primitive Atrioventricular Valve

The jawless fishes, hagfish and lampreys, represent the oldest lineage of living vertebrates. Their hearts comprise a single atrium and a single ventricle, separated by a myocardial atrioventricular canal in which is hinged a bifoliate atrioventricular valve [3] (Fig. 6.3a). The myocardium of the atrioventricular canal is typically dispersed by collagen, but a plane of fibro-adipose tissue is not seen and as such there is not an annulus for the valvar leaflets to hinge on. Of the leaflets, one is approximately cranial while the other is caudal. Younger lineages of fish, which include sharks and bony fishes, have a basically comparable atrioventricular valve, although

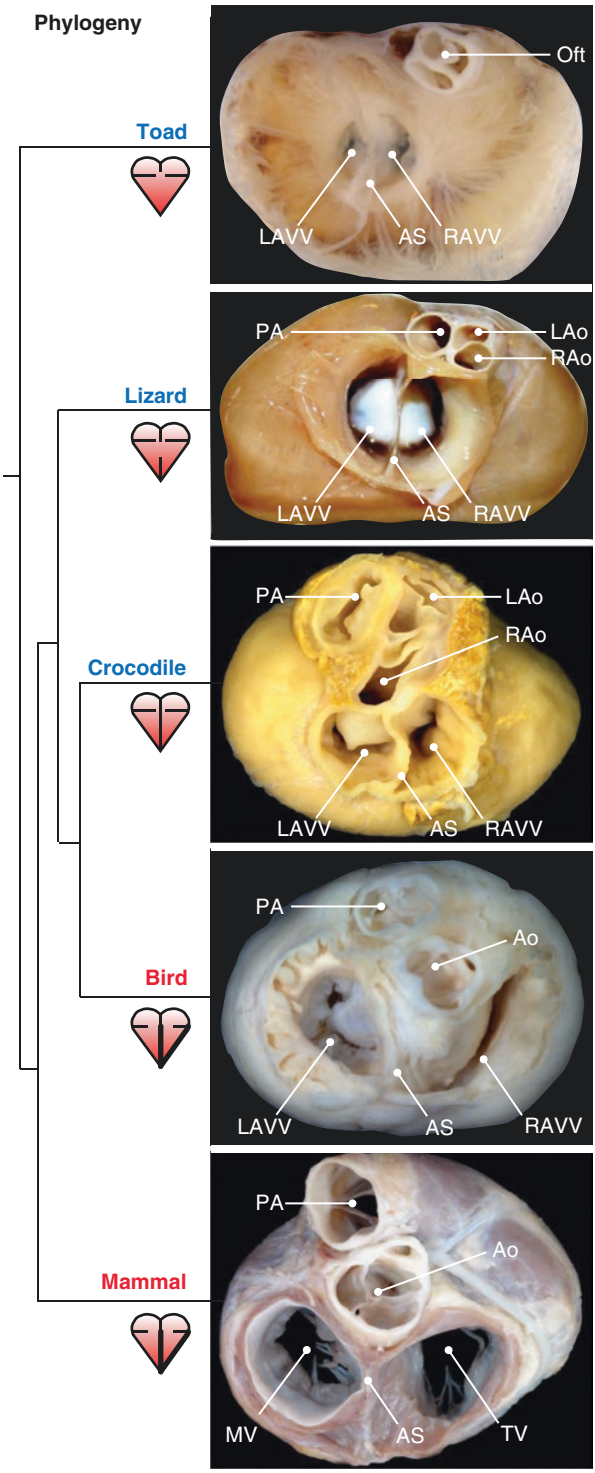

Fig. 6.2 The ventricular base of tetrapods. In the animals with full ventricular septation (Crocodile, Bird, Mammal), notice the remodeling of the atrioventricular valve to multiple leaflets and the positional change of the aortic base (RAo and Ao) compared to animals without full ventricular septation (Toad and Lizard). In the warm-blooded animals (Bird and Mammal), notice that the atrioventricular orifices are proportionally larger than in the cold-blooded animals (Toad, Lizard, Crocodile). The images of toad and lizard are adapted from [10], the images of crocodile and mammal (human) are adapted from [11], and the image of bird (chicken) is adapted from [12]. Ao, aorta; AS, atrial septum; LAo, left aorta; LAVV, left atrioventricular valve; MV, mitral valve; RAo, right aorta; RAVV, right atrioventricular valve; oft, outflow tract; PA, pulmonary artery; TV, tricuspid valve

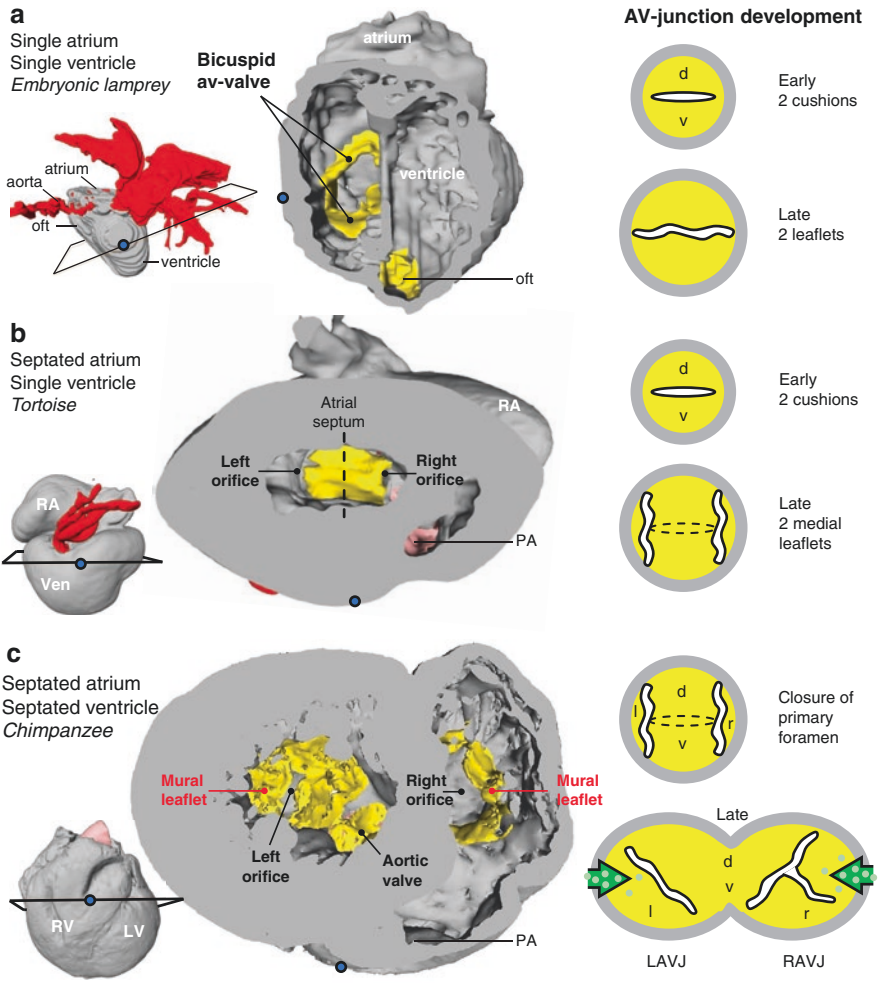

Fig. 6.3 Anatomy of the atrioventricular junction in relation to atrial and ventricular septation. (**a**) 3D model of embryonic heart of a lamprey, based on histological sections from the Dorhn collection, made in Amira as previously described [13]. It shows the bifoliate atrioventricular valve with a cranial and a caudal leaflet. Cartoons on the right conceptualize the manner of development. In all vertebrates, the embryonic (Early) atrioventricular canal is dominated by a dorsal (d) and a ventral (v) cushion. (**b**) 3D model of the heart of a tortoise which has a full atrial septum (based on MRI, adapted from [10]), showing the large medial atrioventricular valve with in the atrioventricular junction that is separated into a left and right orifice. This valve forms from the merger of the embryonic dorsal and ventral cushions (right-hand cartoon). (**c**) 3D model of the heart of a chimpanzee, which has a full atrial and ventricular septum, based on MRI, adapted from [14], showing large mural leaflets. The mural leaflets develop from lateral cushions, that are diminutive when the primary foramen closes (l, left cushion; r, right cushion). In late parts of embryogenesis and fetal development, the mural leaflets will grow with a substantial contribution from epicardial-derived cells (green arrows). (Color Figure Online)

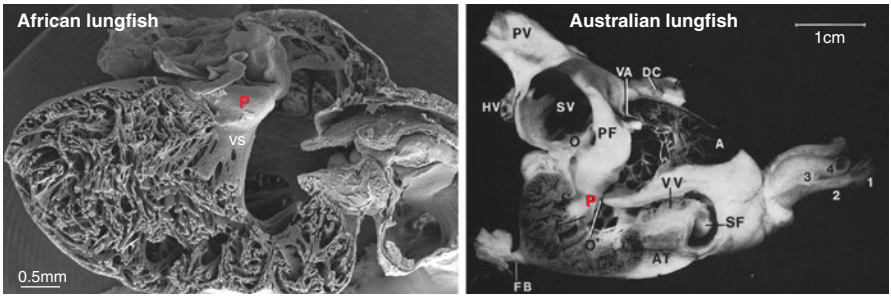

Fig. 6.4 The peculiar plug-shaped atrioventricular valve (P) of the lungfishes. Notice the highly trabecular architecture of the ventricle (vs, ventricular septum). Image of the African lungfish is adapted from [17] and the image of the Australian lungfish is adapted from [18]

some divergence is found. In zebrafish, for example, there appears to be three major leaflets and a minor fourth leaflet [15, 16]. There is considerable variation between fishes whether the margins of the leaflets are so-to-say free, or anchored in the ventricular trabecular meshwork by strands of connective tissue. It is never possible, however, to find papillary muscles when defined as thick and free-standing trabeculations [3]. The Dipnoi bony fishes, which include lungfishes, belong to a sister group to the lineage within which evolved land-living vertebrates that breathe air with lungs. Lungfish, arguably, have the most peculiar atrioventricular valve of any vertebrate (Fig. 6.4). It has no leaflets. Instead, it is plug-shaped, having a spherical central cushion that sits on the crest of the partial ventricular septum [19]. Atrial regurgitation, then, is avoided when the atrioventricular muscle contracts against the plug [17, 20]. Despite the apparent oddity of the atrioventricular valve of adult Dipnoi, its own early development bears considerable resemblance to the early stages of development as seen in mammals [9, 21].

Evolutionary Conservation of the Atrioventricular Canal and Valve

Whereas cardiac anatomy and physiology has been investigated in a high number of vertebrates, the expression of genes has been investigated in much fewer species. It is clear from lamprey to human, nonetheless, that a core set of evolutionary conserved transcription factors, such Gata4, Tbx5, and Tbx20, are crucial for proper development of the chambers [22, 23]. The atrioventricular canal, then, results from a program of repression of chamber myocardium that is effectuated by factors such as the growth factor Bmp2, and the downstream transcription factors Tbx2 and Tbx3 [24, 25]. Several of these factors, and many others, are also of great importance to the proper formation of the atrioventricular cushions and valvar leaflets [26]. While there is a growing picture of the evolutionary conserved mechanisms

involved in the formation of the atrioventricular canal and its valve [27, 28], it is probably fair to say that much less is known of what drives differences between species and groups [29].

The Atrioventricular Valve Is Modified by Full Atrial Septation

The earliest land-living vertebrates were amphibians. Extant amphibians have a solitary ventricle and, dependent on the species, an atrium in which the state of the atrial septum can vary from almost absent to full [14, 30]. Typically, the atrioventricular valve is bifoliate, again with dorsal and ventral leaflets, which are caudal and cranial in fishes [31]. The change to the dorsal-ventral arrangement seen in tetrapods reflects the cranial position of the atriums relative to the ventricle, rather than the dorsal position found in fishes [31]. The bifoliate arrangement is modified when there is full atrial septation, which is the case in anuran amphibians such as frogs and toads, and in amniotes, represented by reptiles, birds, and mammals [32]. In the development of these animals, the dorsal and ventral cushions of the embryonic atrioventricular canal merge with the mesenchymal cap of the forming atrial septum [33] (Fig. 6.3b). Consequently, the atrioventricular canal becomes divided such that separate orifices are provided for the left and right atrial inflows. The atrioventricular canal is then guarded by a single, dome-shaped valve, which is concave on its ventricular side (Fig. 6.3b). Most of this valve is anchored dorsally and ventrally in smooth-surfaced and atrioventricular canal-like myocardium, the so-called bulboauricular lamellas, rather than papillary muscles [13]. Compared to human, this setting is not much different from the fifth week of gestation, when the primary atrial septum has merged with the dorsal and ventral atrioventricular cushion, and the ventricular septum is not yet fully formed [33, 34]. In the formed reptiles, this valve is so dynamic that it reaches deep into the ventricle in diastole, thus sealing off the equivalent of the primary interventricular foramen of the embryonic human [10].

The Atrioventricular Junction Expands Rightwards with Full Ventricular Septation

A full ventricular septum only develops in crocodylians and birds, which are grouped together with dinosaurs in the archosaur clade, and in mammals [31, 35]. This development associates with a very noticeable remodeling of the ventricular base. In early ventricular septation, the septum is a midline structure, whereas the atrioventricular canal is positioned on the left. Then, the atrioventricular canal undergoes a rightward expansion, thus providing a direct connection between the right atrium and the developing right ventricle [36, 37]. Consequently, the atrioventricular canal becomes proportionally much wider, from about a third of ventricular width to approximately half of ventricular width in human, mouse, and chicken. In the rat snake, and anole lizards, which do not form a full ventricular septum, the width of the atrioventricular canal remains approximately a third of ventricular width throughout gestation [21].

Even in monitor lizards, the atrioventricular canal does not expand rightwards, despite the ventricular septation being sufficiently developed but not yet full, such that, in systole, the low-pressure right ventricle becomes separated from the high-pressure left ventricle [38]. The pronounced rightward expansion of the atrioventricular canal, therefore, along with a smaller concomitant leftward expansion, is closely related to full ventricular septation. The expansion, furthermore, necessitates the development of large parietal, or mural, leaflets.

These mural leaflets become apparent in development as expanding lateral cushions [39] (Fig. 6.3c). At first, the cushions are on the parietal aspect of a myocardial floor, or "gully." This gully is more pronounced on the right, and the right atrioventricular mural leaflet in birds is predominantly myocardial [40] (Fig. 6.2). In crocodylians, this valve has some myocardium, and a muscular parietal valve was likely the primitive condition in the mammalian lineage [9, 13]. In mouse, as in humans, the mural leaflets are developed from an endocardial cushion. By approximately 12 days of development in the mouse, epicardially derived cells start to migrate into the cushion, and this lineage will make up a substantial fraction of the formed leaflet [41, 42] (Fig. 6.3c, green arrows). This migration also contributes to the formation of a fibro-adipose annulus. In crocodylians, the atrioventricular myocardial continuity is disrupted ventrally. In mammals and birds, it is only the conduction axis that is spared [43, 44].

Anecdotal observations suggest that the avian left atrioventricular valve is trifoliate rather than bifoliate and mitre-like as in mammals [9, 45–47], and a substantial cleft can be seen in the mural leaflet of the chicken heart shown in Fig. 6.2. Furthermore, Benninghoff describes the left atrioventricular valve of the monotreme mammals as having 3 leaflets [9]. This suggests that a trifoliate valve is the primitive condition and, conversely, that the bifoliate mitre-like valve is a specialization. The pertinent information on birds and monotreme mammals, however, is sparse and as has been demonstrated in the introductory chapter of this volume, the counting of leaflets can be highly ambiguous. The salient feature, then, is the appearance of the zone or zones of apposition [48]. To the best of my knowledge, it has not been assessed in birds and monotreme mammals whether the closed valve has a solitary zone of apposition, which would in effect make it bifoliate, or whether there is second zone of apposition, which would make it trifoliate.

Full ventricular septation not only impacts on the atrioventricular junction, but also on the position of the base of the aorta [49]. Because the embryonic single outflow tract, subsequent to the process of looping, is supported by the developing right ventricle, the aortic channel must shift leftwards to achieve its ultimate connection with the left ventricle. This process, achieved by building a shelf in the roof of the right ventricle, is followed by a shift of the aortic root into the space between the left and right atrioventricular junctions, a movement that is referred to as wedging [34]. In some mammals, the wedging can be so extreme that the aorta is effectively between the left and right atrioventricular junctions (Fig. 6.5). In consequence, the left and right atrioventricular junctions become dispersed from each other by the growth of the base of the atrial septum, formation of the central fibrous body and, in birds in particular, by myocardialization of the ventricular membranous septum [12].

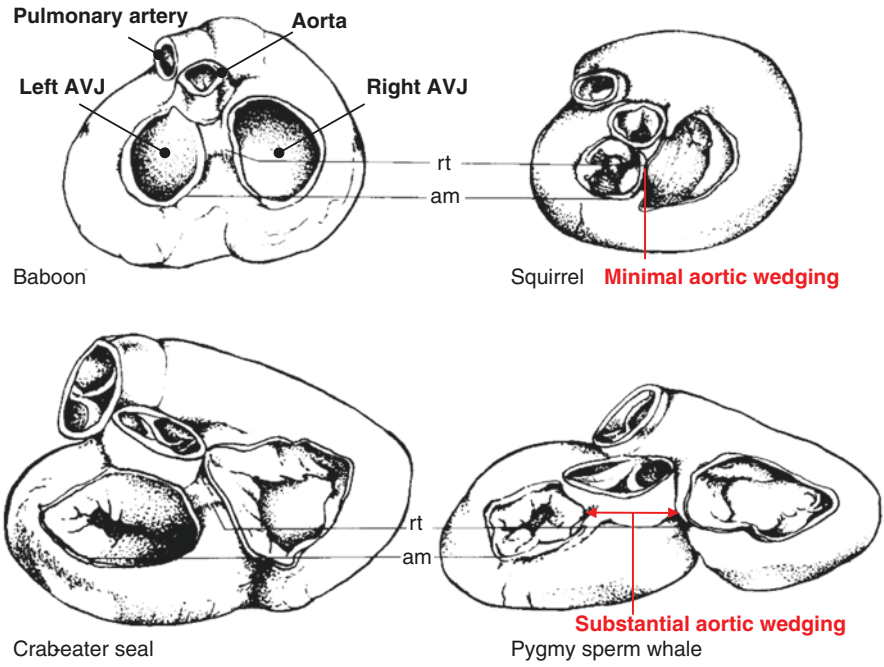

Fig. 6.5 Aortic wedging in mammals and separation of the left and right atrioventricular junctions. Adapted from [50], with original labels of right trigone (rt), or central fibrous body, and atrial muscle (am)

Flow Across the Atrioventricular Valve Increases Manifold with Warm-Bloodedness

Ventricular filling in fishes, amphibians, and reptiles is thought to be much dependent on the contraction of the atriums [5, 51], although recent experiments on alligators showed the persistence of a substantial cardiac output even when atrial appendages were ligated [52]. In contrast, most of the filling of the ventricles in mammals occur before atrial contraction. This remains the case even during exercise in which heart rate is much elevated and filling time is much reduced [53]. On Doppler echocardiography, this is revealed as a greater atrioventricular flow rate prior to the P wave of the electrocardiogram than during the PR interval, often expressed as an E/A ratio of approximately 1.5 (Dog [54]; Rabbit [55]; Mouse [42]; Human [56]; Sheep [57]; Wolf [58]; Human, Chimpanzee, and Gorilla [59]; Cat [60]). Less data exists for birds, but surprisingly, similar measurements in the Racing pigeon reveal very substantial active filling, with an E/A ratio of less than 1 [47]. In Fig. 6.6, I illustrate that, when we compare the warm-blooded mammals to the cold-blooded reptiles, cardiac output is greatly elevated in mammals. This difference reflects the fact that, in mammals, the heart rate is

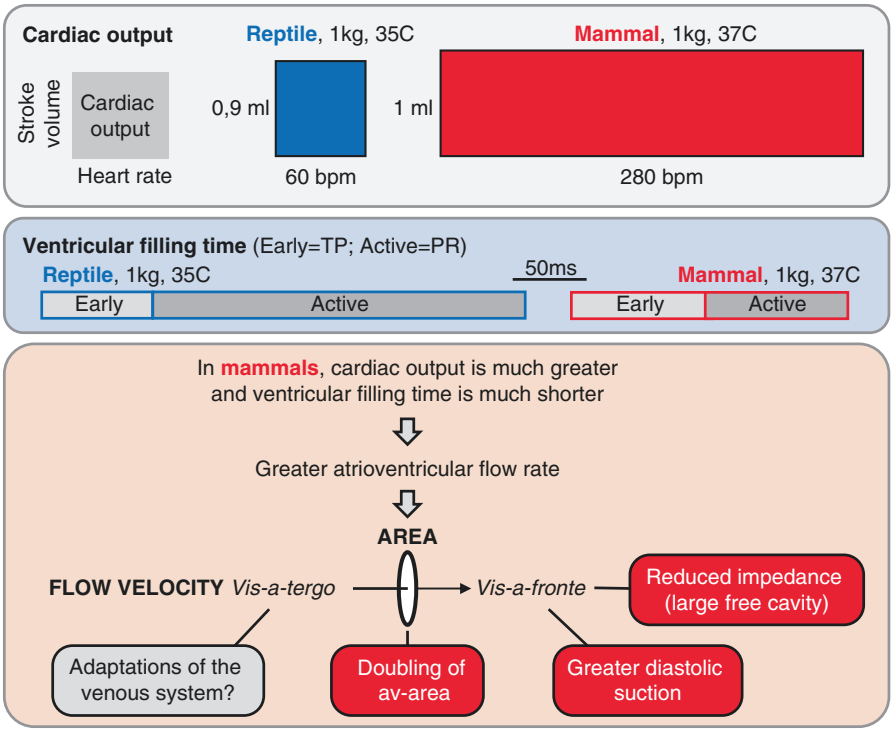

Fig. 6.6 In the evolution of the warm-blooded mammals from cold-blooded reptilian ancestors, cardiac output and heart rate became much increased (top scheme). Ventricular filling time, shown here as the TR interval on the electrocardiogram, in mammals is much shorter than in reptiles (middle scheme). Consequently, the mammalian atrioventricular flow rate in diastole is much greater and this is facilitated by at least 3 parameters (lower scheme, red boxes); an approximately doubling of the atrioventricular orifice [13], greater diastolic ventricular suction [61, 62], and a tremendous reduction in number of ventricular trabeculations giving a much reduced impedance to blood flow [63]. Values for heart rate, TR, early filling (E, or TP interval), and active filling (A, or PR interval) are from [64] in which values for mammals were taken from [65] and the values for reptiles are the averages of the values of ball pythons, green iguanas, and American alligators. (Color Figure Online)

much elevated, with ventricular filling time being much shorter, in particular the active part. In Fig. 6.6, these intervals correspond to the electrocardiographically derived TR and PR intervals respectively. Consequently, the atrioventricular flow rate is much greater in mammals. This is facilitated by the greater atrioventricular orifices mentioned above, and additionally by a greater diastolic suction of the ventricles [61, 62] and a reduction in impedance to filling by the tremendous reduction in the number of ventricular trabeculations [63]. The heart, however, cannot pump more blood than the venous return, and the venous system of mammals may operate at a greater mean circulatory filling pressure along with other adaptations of the venous system [66].

Thick Compact Walls and Large Papillary Muscles with Multiple Tendinous Cords Evolved Together

Already Benninghoff emphasized that a defining difference between the hearts of cold-blooded and warm-blooded vertebrates was the tremendous reduction in the number of ventricular trabeculations, together with a reciprocal thickening of the compact ventricular wall [9]. A similar difference can also be observed in the atrial walls [64]. The consequence is that the chamber cavities change from a so-called spongy appearance to one that is dominated by a large central cavity devoid of structures (Fig. 6.7, also see Fig. 6.4) [67]. In mammals and birds, the papillary muscles are the only prominent myocardial structures in the cavities. In the right ventricle, the septomarginal trabeculation and the moderator band may also be prominent, but this varies between species [50]. The appreciable distance between the tips of the papillary muscles and the margins of the atrioventricular valvar leaflets is bridged by cords of connective tissue, the tendinous cords. Thus, while strands of connective tissue may anchor the parts of the atrioventricular valvar leaflets in the cold-blooded vertebrates [3, 68], their atrioventricular valve is mostly anchored in myocardium near the atrioventricular canal, and the connective tissue strands are far less prominent and typically less numerous than in warm-blooded vertebrates (Fig. 6.7).

Blood Vortices in the Left Ventricle of Warm-Blooded Vertebrates

The large ventricular cavities in warm-blooded vertebrates allow for blood vortices to form during diastole and isovolumetric contraction [69–71]. Their formation is likely further facilitated by the greater blood flows and shorter duration of cardiac phases when compared to cold-blooded vertebrates [64] (Figs. 6.6 and 6.7d). In contrast, in cold-blooded vertebrates, most erythrocytes will have to pass numerous intertrabecular spaces in diastole and systole. Hence, blood effectively settles, or sequesters, during the long isovolumetric contraction (Fig. 6.7c) [5, 10]. Consequently, the ventricular side of the atrioventricular valve may experience quite different regimes of shear stress in the course of one cardiac cycle in warm-blooded vertebrates when compared to cold-blooded vertebrates. Recent studies on regeneration in zebrafish have developed atrioventricular valve-specific inducible cell-death [72]. Such model systems could be important in unraveling differences and similarities in atrioventricular valvar homeostasis between cold- and warm-blooded vertebrates, for example, concerning shear stress.

Summary of Major Evolutionary Trends

The primitive setting is an atrioventricular valve with two leaflets. The evolution of breathing with lungs introduced a pulmonary circulation. Within the heart, the systemic and pulmonary circulation became separated by the atrial and ventricular septums. When the atrial septum is full, there is the merger of the dorsal and ventral

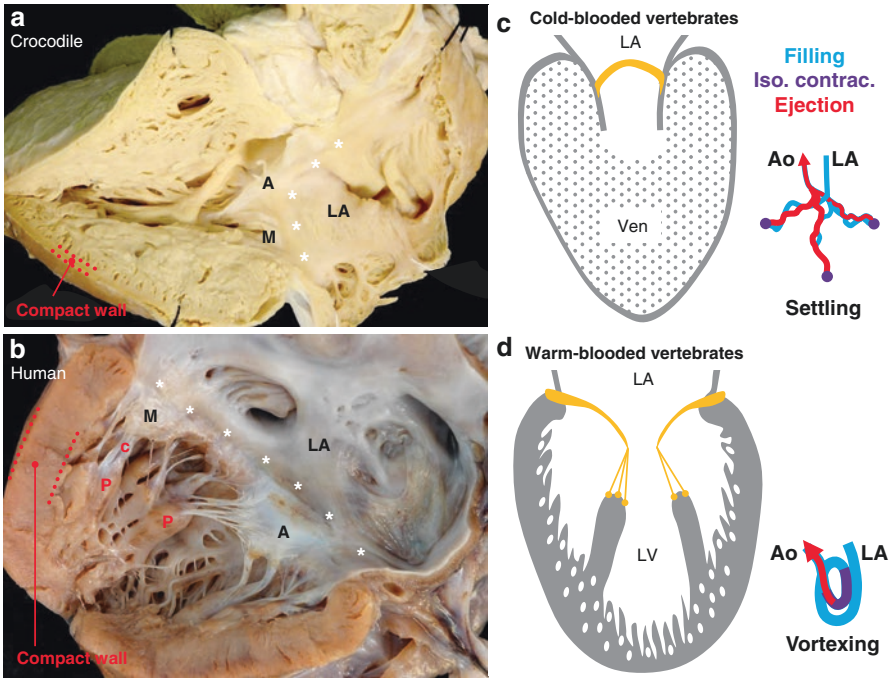

Fig. 6.7 Left ventricle mural architecture and atrioventricular valvar anchoring. (**a**–**b**) Left side of the heart of a crocodile (**a**) and human (**b**). Although the crocodile and human atrioventricular junctions are alike due to the smooth-walled vestibule (asterisks) and a bifoliate mitral valve (A, aortic leaflet; M, mural leaflet), the human (mammal) heart is readily distinct by the much thicker compact wall and the large papillary muscles (examples labeled with P) from which numerous long tendinous cords anchor the margins of the mitral valve (example labeled with c). (**c**) In the cold-blooded vertebrates (fishes, amphibians, and reptiles), the atrioventricular valve (orange) is anchored in atrioventricular canal-like myocardium. The ventricular cavity is spongy because of a gargantuan number of fine trabeculations. The right-most colored line diagram conceptualizes that erythrocytes have to pass multiple intertrabecular spaces during filling (**blue line**) before settling during the long isovolumetric contraction (**purple dot**). During ejection, multiple intertrabecular spaces have to be passed again before the major arteries are reached (**red arrow**) and because the pressure gradient has a different orientation in diastole (atria-ventricle) and systole (ventricle-arteries) it is conceivable that erythrocytes will pass different intertrabecular spaces in diastole and systole. (**d**) In the warm-blooded vertebrates (mammals and birds), the atrioventricular valvar leaflets (orange) are hinged at the atrioventricular junction, with their margins anchored by multiple tendinous cords to multiple large and prominent papillary muscle. The ventricular cavity is mostly free of any structures. Consequently, much of the incoming blood maintains momentum and forms vortices (line drawing). Images A-B are adapted from [11]. (Color Figure Online)

atrioventricular cushions, which function as primordial leaflets. This leads to the development of separate left and right atrioventricular orifices. Full ventricular septation associates with a pronounced expansion of the atrioventricular canal. This expansion associates with the development of large mural valvar leaflets and a fibro-adipose annulus. The independent evolution of warm-bloodedness in mammals and birds has in both instances lead to a substantial increase in atrioventricular flow

rates. This is facilitated by greater venous return, larger atrioventricular orifices, greater diastolic suction, and large cavities of predominantly compact muscle. Few ventricular trabeculations persist in mammals and birds, with some of these growing substantially to form papillary muscles. Much of this evolutionary change relates back to increments in metabolic rate, which in turn relates back to increased cardiac output, and perhaps more specifically the efficacy of oxygen transport.

The Left Atrioventricular Valve at the Extremes

The mitral valve of the giraffe is arguably challenged formidably, as it has to guard the left atrium from left ventricular blood with a pressure that is well above 200 mmHg in systole [73, 74]. Using echocardiography, it has been shown that giraffes have a small stroke volume for an animal of its size [75]. This could indicate mitral valvar regurgitation. Similar cardiac outputs, from which stroke volume could be calculated, however, have been calculated from echocardiography and the inert gas rebreathing technique. We can presume, therefore, that the giraffe mitral valve is efficient. Unsurprisingly then, histology of leaflets of mitral valves obtained from 12 giraffes did not show any overt pathologies [8]. And, when compared to valves of calves with a similar body mass, which have normal mammalian blood pressures [76], the giraffe leaflets were only slightly thicker and richer in collagen (Fig. 6.8). To the best of my knowledge, therefore, the mitral valve of giraffes is challenged formidably, but it is not qualitatively different from the mitral valve of similar-sized mammals [50]. Indeed, it likely operates at similar efficiency as other mammals. A comparable analysis can be made for birds. The ostrich has the highest systemic arterial blood pressure among birds, which already have higher blood pressures than mammals [7, 78]. Yet their left atrioventricular valve is not conspicuously different from the left atrioventricular valve of other birds [12]. While there is not much known about the mitral valves in the largest mammals, it is clear that they have very large stroke volumes, at least several liters, yet the mitral valve in elephants, for example, is not overtly different from the mitral valve of other mammals [50, 77].

Summary

The evolution from the primitive atrioventricular valve of the solitary ventricle to the bifoliate mitral valve of the left ventricle involved several changes, including the formation of an aortic leaflet, a mural leaflet, large tendinous cords, and papillary muscles, and a remodeling of the atrioventricular canal. It is not clear whether these events are developmentally distinct processes, or whether they are causally related. For example, there is no known exception to the rule that full ventricular septation and the aortic leaflet develop together, which suggests they are causally related. On the other hand, the normal formation of the mural leaflet not only coincides with full ventricular septation, but it also involves the addition of epicardially derived cells.

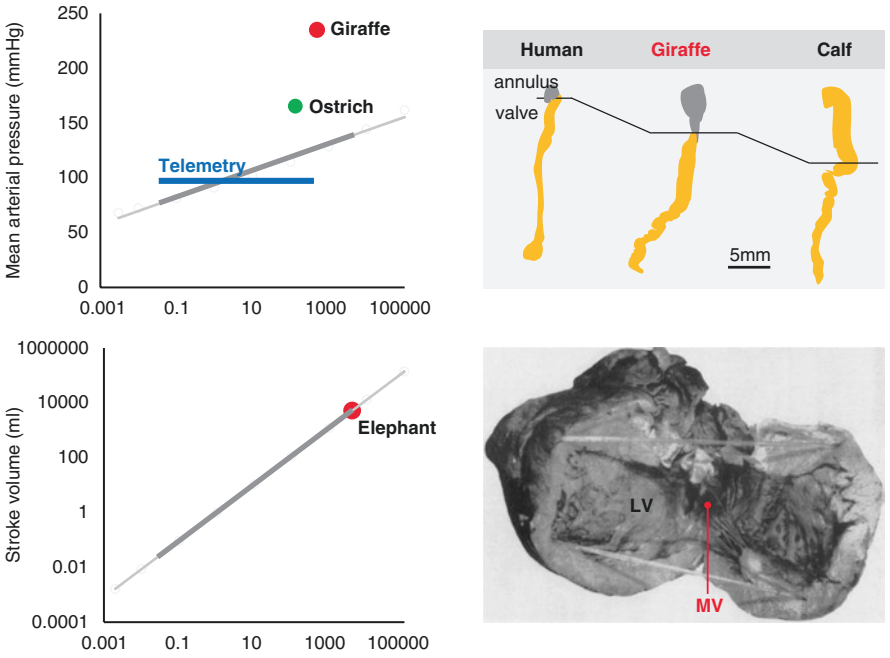

Fig. 6.8 The mitral valve of mammals with extreme left ventricle physiology. The two graphs show the equation-determined relation (adapted from [7]) between physiological parameters and body mass in mammals, with dark gray showing the relation within the range of body mass the equations are based on, the light gray showing the full range of mammalian body weight. In the blood pressure graph (top), the blue line shows the relation for awake mammals with telemetric measurements, adapted from [76]. The top-right image schematizes the histology of the mitral valve leaflet (Grey is myocardium, orange is connective tissue), shows that the giraffe leaflet is a bit thicker than that of human and calf (adapted from [8]). The mitral valve of elephants (image adapted from [77]) has not been studied in detail, but there is nothing in the literature to suggest that it is qualitatively different from the mitral valve of other mammals

This indicates a multi-factorial mechanism behind the formation of the mural leaflet. Also, some developments may be subordinate to other processes. The formation of tendinous cords and large papillary muscles, for example, may be secondary consequences to the increase in cavity size and concomitant greater growth of the compact wall. From a functional perspective, it is intriguing that birds may be quite reliant on atrial contraction for active ventricular filling, as in cold-blooded vertebrates. In mammals, in contrast, the passive filling is dominant. It is further intriguing that the left atrioventricular valve of birds may be trifoliate rather than bifoliate. Given that birds have greater cardiac outputs and systemic blood pressures than mammals of comparable sizes, more studies with direct comparisons of physiological parameters of mammals and birds could be very rewarding.

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The Atrioventricular Complex: Function and Dysfunction

7

Francis C. Wells

Introduction

The Mitral valve is so much more than a singular structure. A better term for it is the Mitral valve complex, or more precisely the left atrioventricular valve complex (A-V complex), the term "complex" perhaps first coined by J. K. Perloff and W. C. Roberts in 1972 [1]. This left A-V valve complex consists of the left atrial wall (e), the mural mitral valve leaflet (b), the tendinous cords (c), the papillary muscles (d), and the postero-superior and infero-basal left ventricular free wall (g). In addition, the Aortic leaflet (a), for most of its circumferential length, becomes the Aorto-Mitral curtain (f), which forms just over one-third of the circumference of the left ventricular outflow tract and in turn merges with the ventricular side of the aortic valve (Fig. 7.1).

At the conjunction of the Aortic, Tricuspid, and Mitral valves lies a condensation of connective tissue that is at its most dense as a result of the forces that are exerted at this point through the cardiac cycle. This region is referred to, by some authorities, as the central fibrous body of the heart, from which more dense condensation of the membrane runs part way around the antero-superior circumference of the Mitral valve. These variable but incomplete extensions were first described by Henle J. and were referred to as the left and right fila of Henle 1873 [2]. In some species cartilage or even bone may be found at these most dense areas of membranous condensation, reflecting the stress and strain exerted at these regions through the cardiac cycle. Contrary to dogma, the atrioventricular junction (annulus) is not a complete fibrous ring around the orifice of the valve, but simply the boundary between atrium and ventricle; there is no formal discrete structure that can be defined as the annulus. For most of its circumference, it contains fat and superiorly

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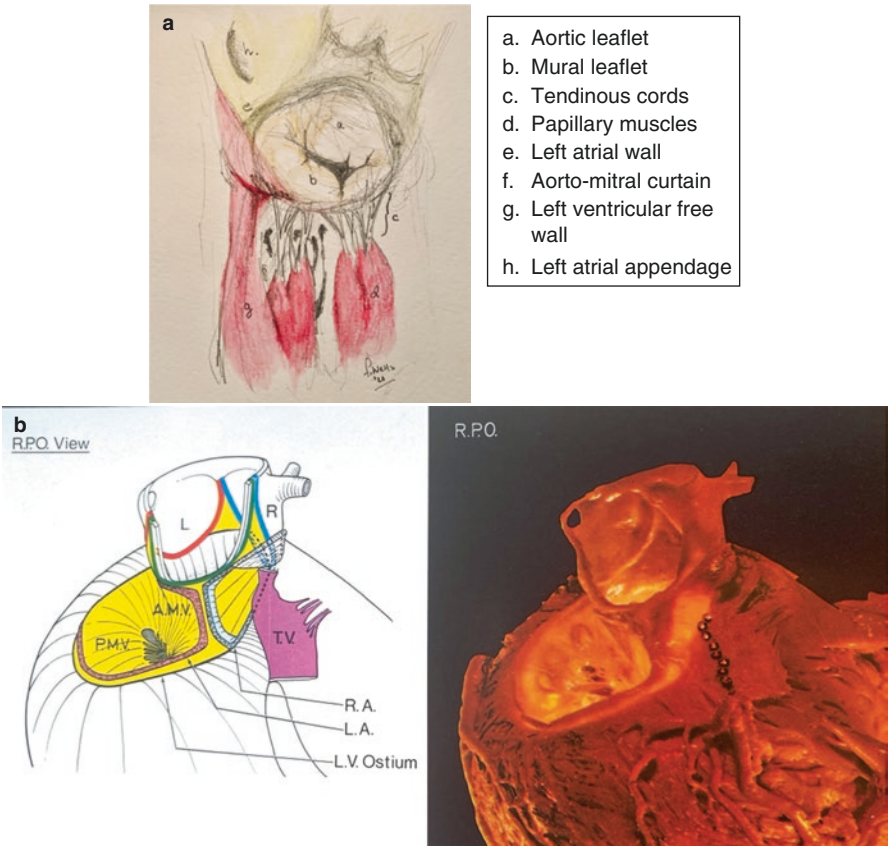

Fig. 7.1 (**a**) The Mitral valve complex [FCW sketch]. *a*. Aortic leaflet, *b*. Mural leaflet, *c*. Tendinous cords, *d*. Papillary muscles, *e*. Left Atrial wall, *f*. Aorto-Mitral curtain, *g*. L.V. free wall, *h*. L.A. appendage. (**b**) Anatomical demonstration of the same attitudinal region as in the sketch. These images reveal the innate saddle shape of the aorto-mitral curtain and the aortic leaflet/aorto-mitral curtain continuity and atrial convexity of the LV outflow tract impressed upon this structure. [Figure 46-1&2 McAlpine WA. Heart and Coronary arteries]. (**b**) The saddle shape of the Aortic leaflet and the Aorto-mitral curtain of the mitral valve. Anatomical demonstration of the same attitudinal region as in sketch. These images reveal the innate saddle shape of the aorto-mitral curtain and the aortic leaflet/aorto-mitral curtain continuity and atrial convexity\ of the LV outflow tract impressed upon this structure. [Figure 46-1&2 McAlpine WA. Heart and Coronary arteries]

the Circumflex coronary artery and inferiorly the coronary sinus has relatively close proximity. For most of this junction, the fibrous extension from the antero-superior Trigone does not form a complete ring, more of which later [3]. Thus a better description of this region is the atrioventricular junction, which is more complex than the use of the simple term annulus implies.

For normal physiological function, each of the components of the atrioventricular complex must be structurally and functionally normal. The use of the more comprehensive descriptive term, the atrioventricular complex that we refer to as the

Mitral valve, is important in trying to help physicians and surgeons make sense of the lesions that are encountered. Indeed, the atrioventricular valvar complex is really a machine in the strict sense of the definition of that word. That is, an apparatus using or applying mechanical power, having several parts, each with a definite function, and *together* performing certain kinds of work; or an instrument that transmits a force or directs its application [4].

The key to the maintenance of this machine's function is the way that the leaflets of the valve meet at the commissure.[1] As is well established the leaflets do not close edge-to-edge. They meet and, supported by the primary cords, they coapt over a height of 5–8 mms (Fig. 7.2a & b). Just as the keystone is the vital component of an arch, so coaptation[2] is for the full and pressurised closure of the Mitral valve. Each normal closed and fully developed leaflet forms a somewhat complex sinusoidal shape as it extends from the left atrial wall or aorto-mitral curtain, into the body of the leaflet and then turning downward into the ventricle where it meets its counter-part (Fig. 7.2c).

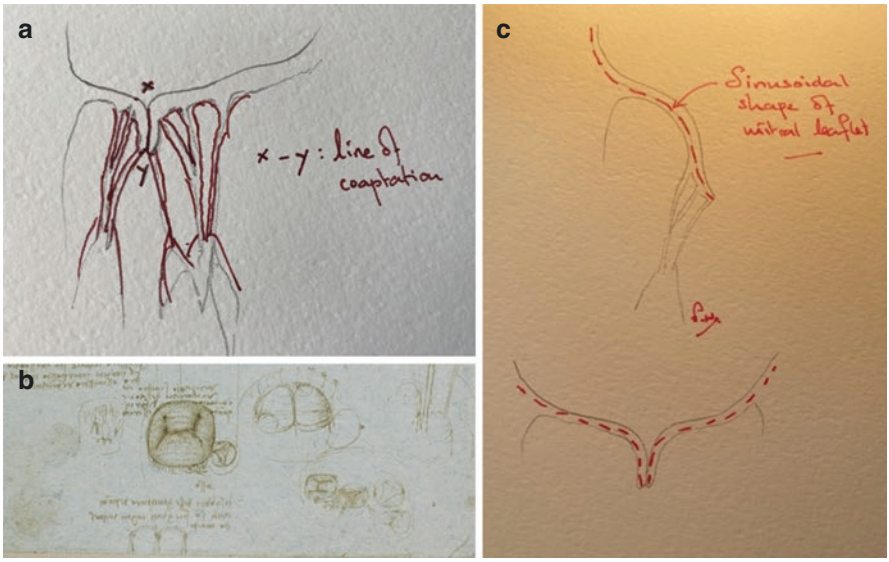

Fig. 7.2 (**a**) Sketch showing atrioventricular valve coaptation. [FCW] (**b**) Detail from RL 19080 recto revealing coaptation of the mitral valve. [Copywrite Her Majesty the Queen. Royal Collection Windsor]. (**c**) Schematic representation of the Sinusoidal shape of the coapting Mitral leaflets. [FCW]

[1] The line of coaptation of the leaflets throughout the closure line is correctly named the commissure, not just the marginal junctions.

[2] Coaptation: derived from the Latin, coaptare meaning to fit closely together.

Disrupt any part of the mechanism of a machine complex and the machine cannot function normally. As so often is the case in failing machinery, the failure of one part will lead to a slow and steady, or on occasions, a catastrophic failure of the whole. So it is in the heart, disruption of any part of the atrioventricular complex can lead to a slow or catastrophic failure of valve and heart function. Left atrial dilatation, as a result of atrial fibrillation, will often lead to distraction of the atrial/ventricular junction, drawing the mural leaflet away from coaptation with the aortic leaflet and slowly developing mitral regurgitation [5]. In contrast, papillary muscle rupture, as a result of myocardial infarction, will usually lead to catastrophic and life-threatening pulmonary oedema and rapid onset left ventricular failure with a high mortality. Between these extremes is the most common form of atrioventricular dysfunction, caused by slowly worsening mitral valve leaflet prolapse, with progressive left atrial and ventricular volume loading and heart failure. As a result of increasing wall stress, this more chronic form of *disease* of the valve incurs fibrous tissue deposition within the left ventricular myocardium, worsening the prognosis for the patient and reducing the chance of a full recovery of ventricular function. In this chapter we will explore the functional aspects of the structure of the left atrioventricular valve and the importance of each component in its performance.

The Atrioventricular Complex Through the Cardiac Cycle

The normal Mitral valve is a highly dynamic structure. It is subject to significant and complicated movement in all components, under rapid pressure changes, throughout the cardiac cycle. The valve has to achieve all of this with surfaces that have to prevent surface thrombus formation, with an average life span of 70 + years. A challenge, which to date, no man-made structure has been able to reliably reproduce.

Let us begin at the end of *systole*. At this point, the left ventricular muscle is maximally contracted with significant twisting of the apex from the base as well as the apex being pulled upward toward the base. The papillary muscles are tensioned and the atrioventricular valve is tightly closed with full leaflet coaptation. The Aortic valve is beginning to close with the leaflets beginning to unfurl as a result of the vortices in the aortic sinuses. As muscular tension abates, *diastole begins*, the ventricle begins to untwist and to fill with blood from the left atrium across the opening Mitral orifice. The mass of blood entering the ventricle accelerates the untwisting of the chamber. As the dilatation of the ventricle accelerates a suction effect is created further enhancing the flow of blood from the atrium to ventricle. The Mitral valve leaflets are opening with the longer Aortic leaflet guiding the flow of blood towards the apex [6]. Vortices have begun above the valve leaflets by the end of systole which then roll down into the ventricle and as the blood reaches the apex of the ventricle larger vortices develop which begin to float the leaflets away from the ventricular walls and upwards towards each other [7, 8]. Leonardo suggested that the bulk of the Papillary muscles prevent the mitral mural leaflet from reaching the ventricular wall which enables the blood to get behind it and begin to billow the leaflet towards

coaptation which fits with modern understanding of the vortices getting behind the skirts of the valve and drifting the leaflets towards each other.[3] The veracity of this suggestion has been borne out by recent studies. Left atrial contraction drives the final blood flow into the ventricle across the valve further stretching the left ventricular myocardium, recruiting the innate elastic recoil that exists in the myocardial walls.

A particular property of the Mitral valve during diastole, that enhances maximum flow under all conditions [9], is the ability of the atrioventricular junction to dilate beyond the orifice area at which the leaflets fully coapt. This occurs as the oxygen and nutrient demands of exercise are met by an increasing cardiac output and thus, venous return. The heart evolved through times when we as a species relied upon being able to go from rest to maximum exercise quickly, when chasing our prey, or escaping the preying jaws of the sabre-toothed Tiger! To carry the machine/mechanical analogy further, we can compare the exercise-driven dilating atrioventricular orifices to the wide exhausts on sports cars to allow exiting of burnt gases as speedily as possible to allow the following cycle of fuel ignition and energy release. The atrioventricular orifice changes its circumference by up to 40% through the cardiac cycle.

In addition to the expansile A-V junction, the leaflets have developed in such a way, that there are interruptions in leaflet continuity of varying depth, to allow it to open rather like the pleats of a lady's skirt, thereby, allowing greater freedom of movement, and in this case, enhanced flow of blood to the ventricle. These normal interruptions have supportive cords that extend into their depths revealing that they must be interruptions in development of the atrioventricular cushions (Fig. 7.3 cords to the depth of the mural leaflet interruptions). The terminology used to name these interruptions has been various, with the common use of the word cleft to describe them. Cleft is the past participle of the verb to cleave and endorses the idea of a splitting or cutting of the tissues which is not the case. Indentations, (implying a dentate appearance with the notches seen along a dental line) does not quite match the bluntness or the depth of these normal interruptions, found in development.

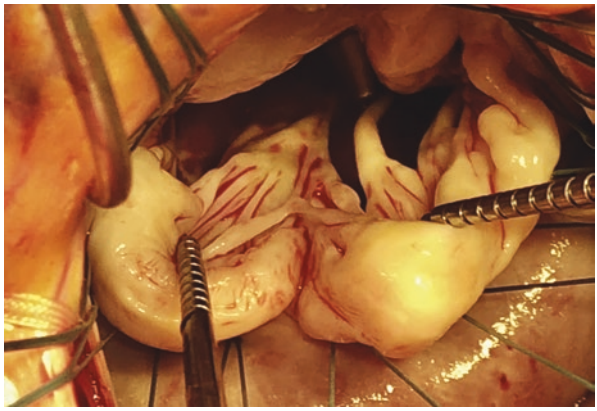

Fig. 7.3 Tendinous cords extending into the depths of the abnormally deep clefts

[3] Leonardo da Vinci. Windor Royal Library. Royal Collection RL 19073 recto.

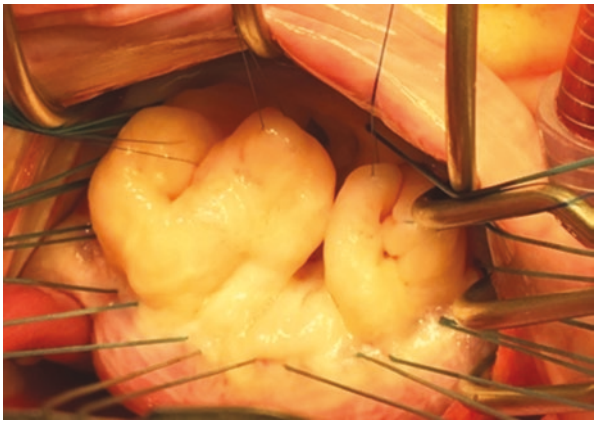

Fig. 7.4 Deficient leaflet development at the centre of the P2 region

Perhaps a better term is a recess but the word interruption implies not only the anatomical finding but also the probable aetiology. Interruptions of normal depth do not reach as deeply as the A-V junction and usually extend for no more than one-third of the height of the leaflet. Thinking back to the embryology of the valve it raises the question that these leaflet interruptions are where the atrioventricular cushions have not grown as far forwards as the part on either side (Fig. 7.4, Deficient leaflet development at the centre of the P2 region).

It is true to say that the detailed knowledge of the full development of the components of the mitral valve remains unknown. Therefore, any description of the detailed development has to remain in the world of speculation at the moment. However, if one is to, in a sense, reverse engineer what is found at surgery in patients with mitral valve prolapse, certain tentative conclusions may be drawn. The detailed development of the valve apparatus is enormously complex. The development of the papillary muscles from the non-compacted myocardium is a highly complex process and it is to be expected that nature gets it wrong from time to time. Similarly, the development of the tendinous cords and their relationship to the leaflet and the papillary muscles is yet another example of the huge complexity of the development of this structure. Hence interruptions in the advancement of the atrioventricular cushions would give rise to the recesses found at surgery. As the development of the cords and the papillary muscles must be a conjoined process it is not at all surprising to find that the cords reach to the very depths of the interrupted leaflets. Variations from the normal horseshoe-shaped papillary muscles are also to be expected and are regularly found. These anatomical variations will disrupt the normal distribution of forces around the conjoined aortic and mural leaflets.

It is common to find the extension of the opposing portion of the Aortic leaflet in valves where the mural leaflet is underdeveloped (Fig. 7.5a & b, Overgrowth of Aortic leaflet to match under-development of the mural leaflet). If this assumption of abnormal development with severe retardation in growth of parts of the A-V cushions is true then it will likely lead to the morbid anatomy of deep interruptions in the leaflet reaching to the atrioventricular junction of the orifice. Here we see that

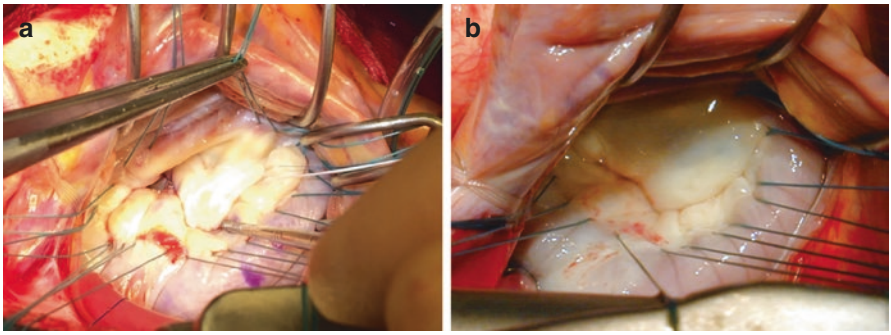

Fig. 7.5 (**a** & **b**) Overgrowth of Aortic leaflet to match under-development of Mural leaflet

the cords reach into the depths of these undeveloped leaflet interruptions indicating a retardation of growth of these parts of the leaflets (Fig. 7.4). These are features that we commonly find in the regurgitant valve, more of which later.

At the end of the diastole, the ventricular muscle begins to contract with a twisting motion and the conical ventricle shortens from apex to base. The papillary muscles are tensioned, exerting a restraining force on the tendinous cords, which in turn prevent eversion of the mitral leaflets as they begin to move towards coaptation. It is the primary cords that prevent eversion of the valve leaflets and as the force on the leaflets grow, the secondary cords come into play, spreading the load through their arching extensions extending onto the underside of the leaflets. This area of cordal distribution on the ventricular side of the valve has become known as the "rough zone" (Fig. 7.6). This is not a good name as it is not rough in the true meaning of that word. The leaflet is covered with endothelium and thus inherently smooth but has the rippled, raised insertions of the tendinous cords as they merge with the leaflet tissue. These arching terminations of the secondary cords spread the load of the pressurised ventricle. As the intra-ventricular pressure continues to rise the area of coaptation of the two leaflets develops over 0.5–0.8 cms. At this point in the cycle, the load is transferred from the primary cords to the secondary cords, the primary cords, even vibrating in these later stages of systole. They have done their job in preventing prolapse of the leaflet. This differentiation of primary and secondary cords is not absolute but relative as there is some residual fusion of the two cordal types near the edge of the leaflet. At this point, the blood continues to swirl in vortices under the now almost completely closed valve developing the coaptation of the leaflets until complete closure is achieved.

Once the leaflets meet and coaptation is complete the energy expended in ventricular contraction can be spent on driving the blood along the left ventricular outflow tract and out into the aorta. From the time of complete closure of the Mitral leaflets the force of intra-ventricular pressure is exerted on the underside of the valve leaflets which then becomes in engineering terms a *force field*. They have to distribute this energy evenly across both leaflet surfaces to prevent undue strain in local parts. The valve has grown and developed with these stresses continuously

at work, shaping them and forming the response to stress. The leaflets bear the strain through several mechanisms.

The key component is the surfaces of coaptation, that are present in a fully closed normal valve. This coaptation has developed through the restraint of the primary cords preventing leaflet prolapse. The closing of the sphincter-like muscle at the base of the ventricle enhances this closure pushing the leaflets towards each other further supporting coaptation. The load is further shared through the tendinous cords and the tensed papillary muscles through to the ventricular muscle wall and back to the base of the heart at the atrioventricular junction. The distribution of the tendinous cords, arising from the two main horseshoe-shaped papillary muscles spatially arranged around each end of the commissure (closure line) of the leaflets is vital in load sharing. It will be noted that the two leaflets are not completely separated at the ends of the commissures and this allows the load to be shared between them at these junctional regions. The tendinous cords are most dense in these regions.

The secondary tendinous cords arch across the underside of the leaflets spreading the load evenly as do the arches under the roof in a large building (Fig. 7.6: So-called rough zone underneath the Aortic leaflet [Bovine specimen]).

In the normal arrangement, the direction of tension from leaflet to papillary muscle is vertical. Imagine walking to the airport carrying your luggage at 45 degrees to your body! It could not be maintained for long. And so it is with the papillary muscles and the tendinous cords. Abnormal development of the Papillary muscles causing the insertion of the cords at an angle from the vertical puts undue strain on them further increasing the likelihood of stretch and rupture. The Papillary muscles as with all other parts of the atrioventricular complex are liable to congenital malformation. A description of papillary muscle variations can be found in a paper by Roberts and Cohen [10]. The most common extreme version is the parachute mitral valve where all of the cords arise from one papillary muscle head. Whilst this can produce regurgitation it usually produces stenosis.

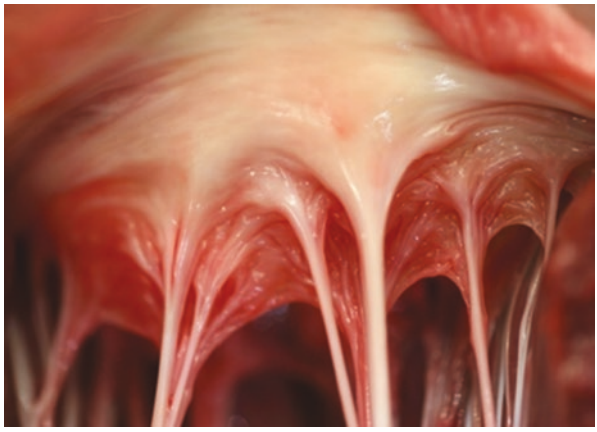

Fig. 7.6 So-called rough zone underneath the Aortic leaflet [Bovine specimen]

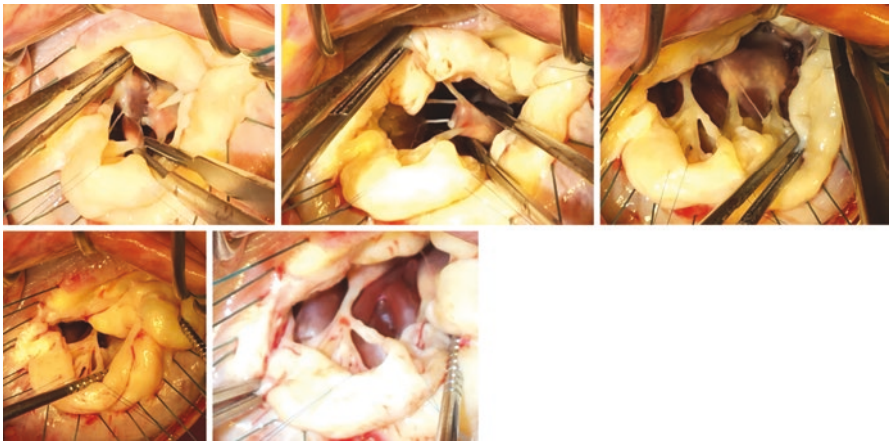

Fig. 7.7 Intraoperative photographs of abnormal papillary muscle morphology

It would appear that condensations of the non-compacted myocardium give rise to the Papillary muscles. (see the chapter on development R H Anderson et al) Therefore, it is not surprising to find a multitude of possibilities arising from abnormal development. Some variations observed at the surgery are shown in Fig. 7.7. When operating on these valves it is striking how frequently one sees these forms of abnormality. Papillary muscle malalignment can be through abnormal embryogenesis giving rise to the kinds of abnormalities illustrated in Fig. 7.7, or through left ventricular distortion through ischaemic lesions or other cardiomyopathies resulting in functional mitral regurgitation. A proper appreciation of papillary muscle geometry is important in approaching mitral valve reconstruction.

As systole develops, the pressure inside the left ventricular outflow tract (LVOT) increases, and the pliable aorto-mitral curtain, which forms one-third of the LVOT, naturally takes up a cylindrical shape. Also the junction of the A-M curtain flexes on the aortic leaflet that then turns upwards as the leaflets close in coaptation. This is how the so-called *Saddle shape* of the valve develops [11]. The aorto-mitral curtain forming the "pommel" of the saddle and the aortic leaflet the seat of the saddle (Fig. 7.1b). These forces have helped to shape the aortic leaflet and maintenance of its three-dimensional shape through which the strain of ventricular closure is distributed. The fundamental importance of this distinct morphology is discussed by Salgo IS, Gorman JH, and colleagues. They point out how the curvature of the Aortic leaflet reduces mechanical stress [12]. Of significant interest is the fact that this observation seems to hold across mammalian species. They suggest quite reasonably that their data strongly suggest that nature conserves the 3-dimensional geometric changes brought about by the highly dynamic sphincter-like closure of the basal ventricular muscle and the conformation of the aorto-mitral curtain, which alters the orifice surface area dimensions by up to 40% [13]. The annulus (the ring orifice) is a descriptive term rather than a singular and identifiable structure. It responds to these pressure and force changes rather than exerting them. The

dynamism of the atrioventricular orifice and the leaflet morphology is well demonstrated in an exhaustive MRI study of the mitral orifice and leaflets by Shuan Leng and colleagues [14]. The normal annular dynamics were significantly reduced in patients with mitral regurgitation over valves in the normal group. This reflects the basal dilatation of the ventricle in response to increasing volume overload with the progression of the mitral regurgitation.

There is the suggestion that by mapping the saddle shape in a complete annuloplasty ring and re-imposing it on the orifice of the valve that this can impart improved physiological morphology. Contrary to this thought is the fact that by leaving the inter-trigonal space (aorto-mitral curtain) free of device, as in a C band (Trigone to Trigone) the annulus can and will take up naturally the saddle shape for the reasons described previously. Miller and colleagues demonstrated with three-dimensional computer modelling that "regardless of their three dimensional shape, rigid and complete annuloplasty rings, but not a partial flexible band, increased maximum principal anterior mitral leaflet strains predominantly in the belly and edge regions in the normal beating Ovine heart [15]." Thus emphasising the natural tendency of this dynamic conformation of the Aortic leaflet to the pressurised ventricle and outflow tract to allow the optimal configuration.

The stress and strain found within the Mitral valve during isovolumetric contraction have been studied in vivo in both animals and man. Several studies have demonstrated the beautiful adaptation of this structure to the forces that are exerted upon it in all stages of the cardiac cycle [16, 17]. Moreover, the histological adaptation to the distributed stresses on the leaflets has been shown to occur as well [18]. The authors of this paper (Blomme et al. [18]) demonstrated that CTGF (a profibrotic growth factor promoting the synthesis of extracellular matrix (ECM) components) is up-regulated in many pathological processes involving mechanically challenged organs, promotes ECM accumulation and is considered as a hallmark of fibrotic diseases. They demonstrate that abnormal perception and responsiveness of valvular interstitial cells to mechanical stress may induce an inappropriate adaptative remodelling of the valve progressively leading to a myxomatous mitral valve. The authors were able to show that mechanical stretching induced the nuclear translocation of myocardin-related transcription factor-A (MRTF-A) which forms a transcriptional complex with SRF to promote the expression of target genes, notably CTGF.

Recently Calafiore et al have made the case for structural remodelling of the mitral valve through molecular stimulation and cellular change as a result of altered forces and flow on ischaemic mitral valves [19]. It is becoming ever more clear that restoration of a normal force distribution throughout the valve leaflets, cords, and papillary muscles as well as restoring normal flow patterns is the key to sustainable return to normal mitral valve function and structural remodelling.

Piecing all of this information together it would appear that the abnormal formation of the mitral valve complex will lead to the abnormal distribution of the forces that act upon it throughout the cardiac cycle and that these abnormal forces will bring about pathological stress and strain distribution in the leaflets, cords, and papillary muscles. These excess forces in areas of the valve that are not well supported can and almost certainly do lead to the changes that are seen histologically with collagen and elastin disruption and the laying down of

myxoid material. Fundamentally the valvular interstitial cells (VIC's) control the nature of the extracellular matrix. Their phenotype is regulated by signals from the environment and thus in turn, they are responsible for the homeostasis in normal circumstances and remodelling of the ECM in pathological states of abnormal stress and strain [20–22].

In a paper addressing the spectrum of normality of the Mitral valve relevant to Mitral prolapse, as long ago as 1979, Becker and De Wit wrote, " If one considers the fact that the Mitral valve sustains considerable pressures for a prolonged time, one may perhaps speculate on the effects of an irregular distribution of cordal support on leaflets". This is to be found in valves from patients in increasing age and they defined them as ballooning deformities. They go on to point out that study of the body of the leaflets from these conditions, reveal an increase in mucopolysaccharides, probably an expression of tissue injury [23]. One of the central tenants of their paper is that "minor variations in architecture of the cordal apparatus may leave some parts of the leaflets less well supported than others, a phenomenon which could then result in deformity of the leaflet at that particular site." Furthermore, they note that these abnormalities are most commonly found at the site of the posteromedial commissure and related parts of the mural leaflet. In summary, they state that, weakening of the central core of the leaflet, may act as a final common pathway to a process of chronic injury and in some cases, a floppy and ultimately prolapsing valve leaflet [24].

This assertion that unbalanced forces on a biological structure will lead to a change in cellular signalling and thence to a change in leaflet morphology and thence to a failure of valve structural integrity is a modern take on sage intelligent deduction. In a now lesser known work, (but still recognised by significant minds in Science and the Arts as among the finest academic books of the twentieth century), On Growth and Form [25], D'Arcy Thompson, its polymath author, powerfully makes the case in his words that the form of any objects in nature are diagrams of the forces that act upon them. In other words, "that in general no organic form exists save as are in conformity with physical and mathematical laws." He declared that physiology is vastly strengthened and enlarged by making use of the chemistry and of the physics of the age. All should be supported by mathematical explanation. These ultra-modern thoughts are coming to pass in the modern scientific age as the understanding of the regurgitant/degenerating mitral valve evolves. He wrote in his beautiful Edwardian prose, "For the harmony of the world is made in Form and Number, and the heart and soul and all the poetry of Natural Philosophy are embodied in the concept of mathematical beauty." He alludes to the power of measurement and understanding in a biblical quote from Isiah wherein he sates "Who has measured the waters in the hollow of his hand and metered out heaven with the span, and comprehended the dust of the earth in a measure and weighed the mountains in scales and the hills in a balance.".[4] These profound statements recognise the fundamental determination of structure by natural forces, normal or abnormal on the structure in question. Let us then consider the impact of abnormal morphology of the valve on its structure and function.

[4] Isiah. Chapter 40 verse 12. The Old Testament. King James's bible.

The Malfunctioning Mitral valve

We have discussed the normal structure and function of the left-sided atrioventricular complex, the Mitral valve, and the great importance of normal structural integrity and form. Let us now consider the impact of the abnormal morphology that is to be found in the malformed valve which leads to an inability to control the normal unidirectional flow of blood. As stated at the beginning of this chapter failure of any component of the atrioventricular complex will lead to various degrees of incompetence.

The most common lesion presenting to the cardiologist/surgeon is that of Mural leaflet prolapse. This is accompanied by cordal elongation and frequently cordal rupture (Fig. 7.8).

As discussed earlier, closer inspection of the valve will almost always reveal accompanying papillary muscle abnormalities and/or deep interruptions on either side of the prolapsing segment. If we think of the need to distribute forces evenly across the closed and tensioned valve it is easily visualised that deep recesses, extending to the atrioventricular junction and abnormal papillary muscle distribution will prevent normal force distribution.

In addition, it is common to find that the prolapsing portion is much taller (sometimes x2 or x3) than the height of the rest of the mural leaflet (Fig. 7.9)

At the commissural ends, there may be a significant paucity of cordal support usually associated with papillary muscle abnormalities and leaflet prolapse (Fig. 7.10)

All of these and many other combinations of abnormalities will confront the mitral valve surgeon who should be versed in all of the possible techniques of repair and reconstruction to reach a 95% repair rate which should be possible in the modern state of knowledge.

As these are all congenital developmental lesions and the valve is so complex any combination of anatomical abnormalities may be encountered. The degenerative component in the leaflet histology is a result of sustained maldistribution of forces on the valve leaflets and not a primary disease process.

Fig. 7.8 Ruptured cord. Note the excess height of the leaflet and the deep clefts on either side

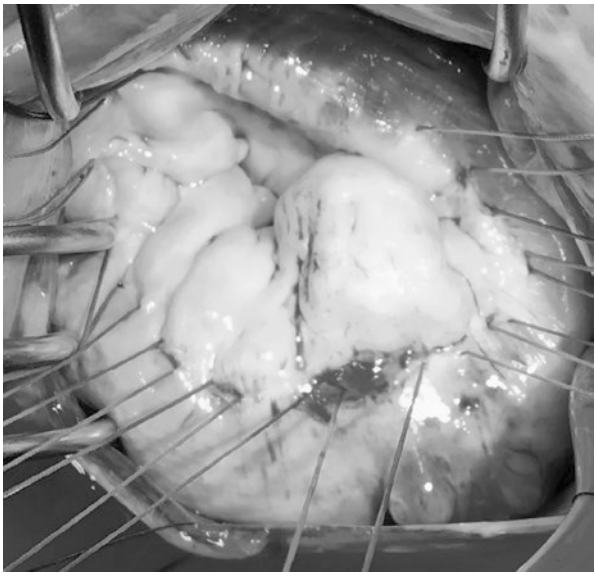

Fig. 7.9 Eccentric excessive height of the mural leaflet in the P3 region. Note the scalloping of the P1/P2 regions also turning the mural leaflet into four segments

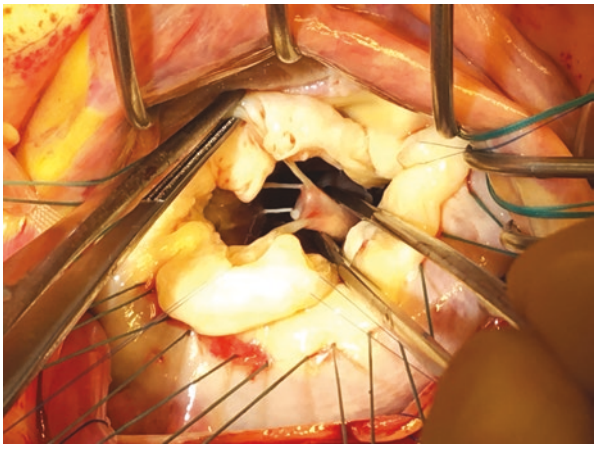

Fig. 7.10 Antero-superior commissural prolapse with highly abnormal papillary muscle and a significant paucity of cords

Conclusions

The mitral valve complex is one of the most complicated developmental processes that the body has to undertake. Its many components and the mode of embryogenesis is such that it should surprise no one that nature makes mistakes that lead to the lesions that we find inside the heart at surgery. The increased frequency of these lesions within families reinforces the congenital nature of these lesions. The fact that the "degenerative" changes and the manifestation of these morphogenic problems do not present until later in life fits with the presented hypothesis that it is the congenital malformation that is the primary lesion in these valves and not a later and

secondary disease process as has been suggested by some. The inability to distribute the exerted forces of systolic closure lead to the morphological cahnges encountered in the prolapsing segments of the valve.

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Mitral Valve Pathology

8

Joseph D. Westaby and Mary N. Sheppard

Text

As it has been well described in other chapters, we will only briefly revisit the anatomy and function of the mitral valve. It is important to understand the normal valve anatomy and its function, in order to understand the pathological changes that occur.

It is composed of two leaflets, the aortic and mural leaflets (Fig. 8.1a). These two leaflets press together to close at the zone of coaptation, as well as meeting at the commissures at either end of the leaflet. The valves are hinged by numerous tendinous cords that attach to the papillary muscles located inferoseptally and superolaterally within the left ventricle (Fig. 8.1b). The cords are inserted into the ventricular aspect of both leaflets giving a rough appearance below the line of apposition, seen particularly in the aortic leaflet. The valve is supported by a saddle-shaped fibrous annulus which serves as a support structure for the valve.

The mitral valve is a complex structure with leaflets, cords, and papillary muscles working together to function properly. It serves as a one-way door between the left atrium and ventricle of the normal heart, allowing blood to flow through in diastole and preventing it from going back by closing in systole. In systole, the valve closes and the leaflets are tightly apposed preventing regurgitation of blood from the left ventricle into the atrium. In diastole, the leaflets drop into the left ventricle opening and allowing the passage of blood from the left atrium into the left ventricle.

In the post mortem setting, the valve is inspected from the left atrium and its circumference is measured as this is important when it comes to functional regurgitation. We consider a circumference of more than 90 mm to be abnormal and indicative of dilatation. Each leaflet is inspected for evidence of thickening, infection,

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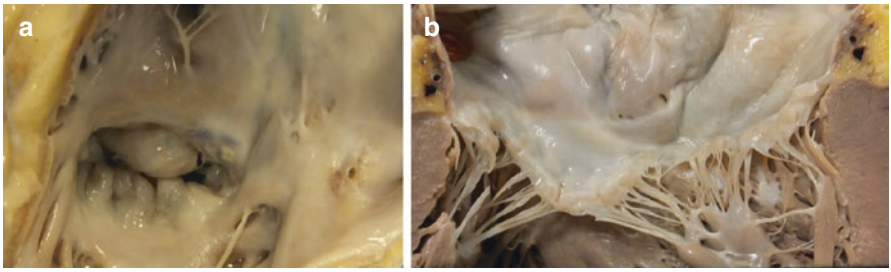

Fig. 8.1 The normal mitral valve. (**a**) The normal mitral valve viewed from the left atrium showing the aortic and mural leaflets in apposition. Note, the three segments divided by indentations in the mural leaflet. (**b**) The normal mitral valve in a heart has been opened up through the lateral wall of the left ventricle and atrium to divide the mitral valve between the two leaflets with the cords attached to the papillary muscles. Note, the scalloped indented nature of the mural leaflet between cords. Because of the cordal insertion on the ventricular surface, there is a rough thickened area below the line of apposition in the aortic leaflet which increases with age

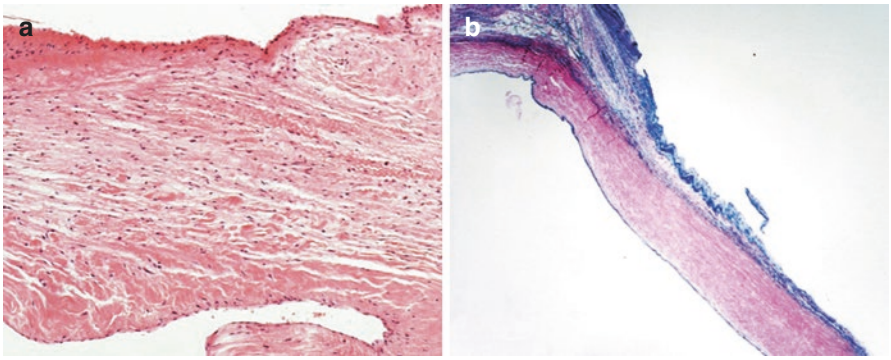

Fig. 8.2 Histology of the normal mitral valve. (**a**) A haematoxylin and eosin stained section. The atrialis is located at the top of the image, with the paler spongiosa located centrally and the fibrosa at the base. (**b**) An elastic-Van Geison stain with the elastin fibres appearing black and collagen appearing red. Note, the multiple layers of elastin fibres in the atrialis and the dense collagen of the fibrosa

vegetations, perforations, and calcification. From the ventricular side, the papillary muscles and cords are inspected for thickening, vegetations, fusion, or rupture.

Normal Histology

The mitral valve is lined by endothelium and the underlying structures may be subdivided into three components; the atrialis, the spongiosa, and the fibrosa (Fig. 8.2a). The atrialis lies on the atrial side of the valve and is composed of elastic and collagen fibres. The spongiosa, which underlies the atrialis, is composed of basophilic extracellular matrix consisting of proteoglycans and glycosaminoglycans, with

occasional elastic fibres. This hydrophilic composition draws in water resulting in expansion and swelling of the layer allowing it to act as a protective buffer at zones of impact. This gives it a paler appearance when compared to the other layers of the valve. The fibrosa lies on the ventricular aspect of the valve and consists of densely packed collagenous fibres which provide the major structural support of the leaflets (Fig. 8.2b).

Age-Associated Changes

With increasing age, one sees a thickening and loss of translucence of the mitral valve leaflets. Whilst in those under 20 years of age, the leaflets are thin and translucent, in those over 50 years of age the leaflets appear opaque and thicker. The ventricular surface of the aortic leaflet often develops yellow lipid deposits which appear as fatty streaks macroscopically (Fig. 8.3). Nodular thickenings present along and below the lines of coaptation of both the aortic and mural leaflets (Fig. 8.3). These occur due to the repeated trauma of the leaflets closing against each other [1]. Calcification of the annulus of the mitral valve is extremely common with increasing age and is linked to coronary artery disease. This process starts at the angle of the leaflets and the ventricular endocardium which may merge to form a bar along the atrioventricular junction and extend rarely into the valve leaflet (Fig. 8.4a & b) [2]. In severe cases, large nodules are observed which may ossify or contain cartilage with extramedullary haematopoiesis. These nodules can extend

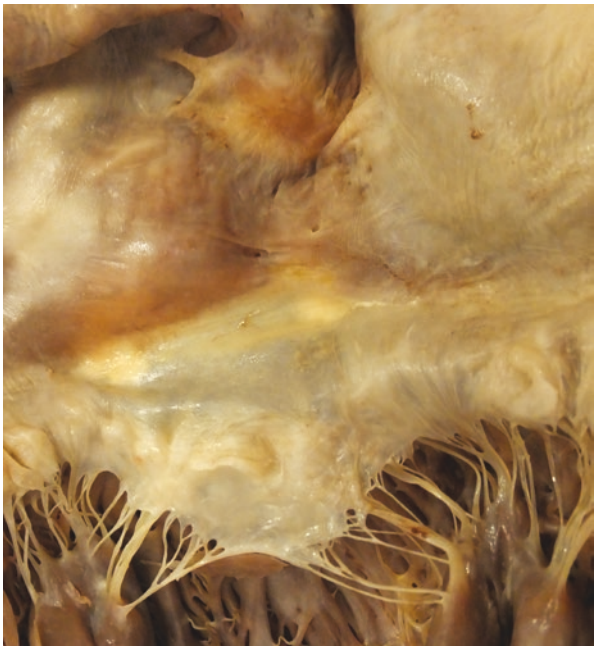

Fig. 8.3 Age-related changes of the mitral valve. Nodular thickening along the lines of coaptation (black arrow) and lipid deposition are shown within the valve leaflets (yellow arrow)

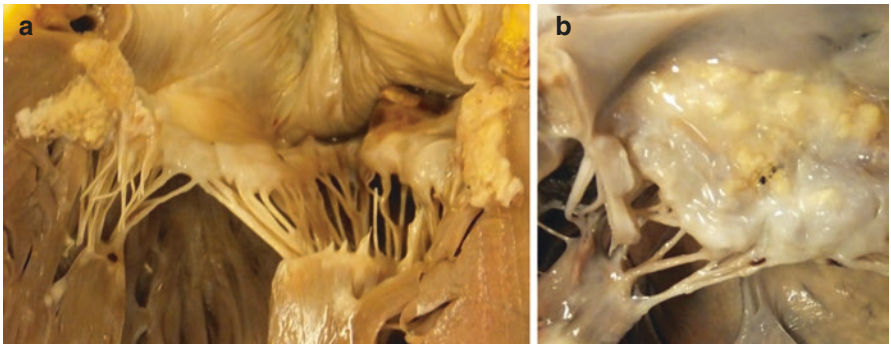

Fig. 8.4 Advanced annular calcification. (**a**) Extensive nodular calcification affecting the annulus and extending into the subendocardium. (**b**) Nodular calcification extending from the annulus into the aortic valve leaflet

into the underlying left ventricular myocardium and form a large mass (Fig. 8.4a). They do not usually result in mitral stenosis.

The size of the mitral apparatus is mainly determined by the size of the annulus which, in life, can be reduced by up to 50% in systole when compared to diastole. Dilation of the left ventricle, such as in left-sided cardiac failure or dilated cardiomyopathy, leads to an increase in the circumference of the annulus. Like proximal aortic dilation results in aortic regurgitation, this enlargement of the annulus pulls the mitral leaflets apart resulting in, what is referred to clinically as, functional regurgitation. This highlights the importance of taking a measurement of the circumference of the valve at post mortem where mitral regurgitation is suspected. Similarly, atrial dilation may result in an increase in the circumference of the annulus, again pulling the mitral leaflets apart and resulting in functional regurgitation.

Functional regurgitation may occur in the absence of annular dilatation. Left ventricular remodelling can result in the radial displacement of the papillary muscles upsetting the normal anatomy of the valvular apparatus. This displacement pulls the cords apart resulting in malcoaptation.

Rheumatic Disease

Rheumatic disease may result in both regurgitation or stenosis. The underlying cause is group A haemolytic streptococcus which is thought to lead to the development of autoantibodies against a glycoprotein present in the valves and cardiac connective tissue. The disease causes pericarditis, myocarditis, and a valvulitis but the long-term damage mainly affects the valves.

The specific lesion that is seen is the Aschoff nodule within the myocardium. These are foci of predominantly lymphocytes with occasional plasma cells and activated macrophages present in the interstitium. The macrophages have abundant eosinophilic cytoplasm with a round nuclei with a band of condensed chromatin

which has the appearance of a "caterpillar" and are named Anitschkow cells. These inflammatory foci surround areas of collagen necrosis.

There are thought to be three phases to the Aschoff nodule. An early phase that shows exudative and degenerative changes in collagen. This is followed by an intermediate phase where the collagen fibres swell and fragment and there is an influx of Anitschkow cells and surrounding giant cells. This, finally, progresses to dense collagenous scar tissue.

In the acute setting the mitral valve shows slight thickening with subtle "vegetations" found along the lines of coaptation as tiny brown smooth lesions. It is important to note these are not the prominent vegetations of endocarditis but, rather, a deposition of fibrin on the surface of the leaflet with swelling. Microscopically, there is a lymphohistiocytic valvulitis with Aschoff nodules.

The pericardium and myocardium usually recover but repeated damage to the valve leaflets results in fibrosis and calcification of the leaflets with commissural fusion. The mitral valve takes on a "fish mouth" or "slit" like appearance due to these changes when viewed, in situ, from the atrial perspective, reducing the size of the orifice (Fig. 8.5a). From the ventricular aspect, a funnel shape appearance may be seen (Fig. 8.5b). This result from cordal shortening, fusion and retraction with leaflet extension to the papillary muscles and may pull the valve leaflets apart resulting in malcoaptation and regurgitation. Most commonly it results in mitral stenosis with a hugely dilated left atrium. The regurgitant or stenotic mitral valve usually leads to dilation of the left atrial cavity. A thickened patch in the left atrium corresponding to the jet of mitral regurgitation may develop. This focal endocardial thickening is known as a McCallum patch and histologically appears fibrous with a chronic inflammatory infiltrate.

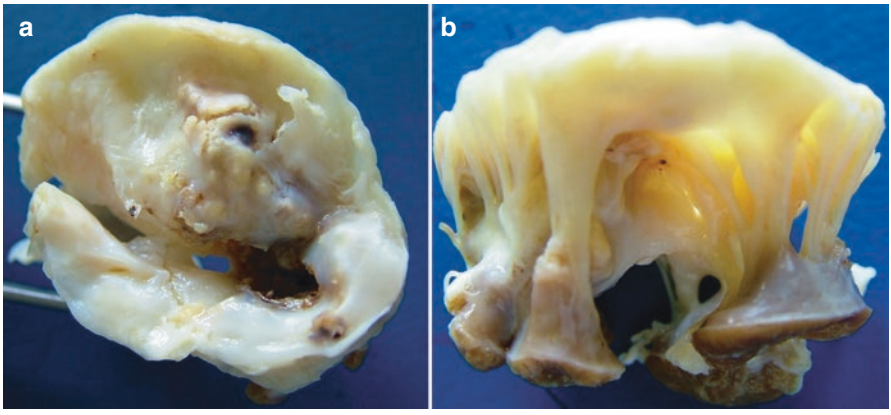

Fig. 8.5 Chronic rheumatic disease of the mitral valve. (**a**) An excised valve viewed from the atrial aspect showing ulceration and calcification. Note, the "slit" or "fish mouth" appearance of the orifice. (**b**) An excised valve viewed below from the ventricular aspect. Note, the "funnel" like appearance with fusion and thickening of the cords

Mural thrombus may be found within the left atrial appendage or the cavity with any form of cardiac failure. They particularly occur in mitral stenosis due to the marked atrial dilation. These thrombi can embolise and lead to distal infarction particularly in the cerebral circulation. This highlights the importance of thorough macroscopic examination, including opening and examining the appendages, in these cases.

Histologically in chronic rheumatic disease, the leaflets show diffuse fibrous and fibroelastic thickening with progressive loss of discernible valve layers. There is also new vessel formation. There may or may not be chronic inflammation with a predominance of lymphocytes. Leaflet calcification often develops later at the commissures, spreads onto the leaflets, and may ulcerate through the valve leaflet (Fig. 8.5a).

Infective Endocarditis

Endocarditis is defined as an inflammation of the endocardium which may occur throughout the chambers of the heart but usually occurs on the valve surface and often involves the left-sided valves because they have a higher systemic pressure. Classically, vegetations are seen on the atrial leaflet surfaces which range in size from subtle rough patches to large fungating masses involving the entire valve leaflets with the destruction of the leaflets (Fig. 8.6a). The infection may result in ulceration, aneurysm formation, rupture, and perforation of the valve leaflets (Fig. 8.6b). The infection can extend out as perivalvar abscesses which can erode into the myocardium and can result in fistula formation. The cords and papillary muscles may also be affected with vegetations resulting in necrosis and rupture of the cords.

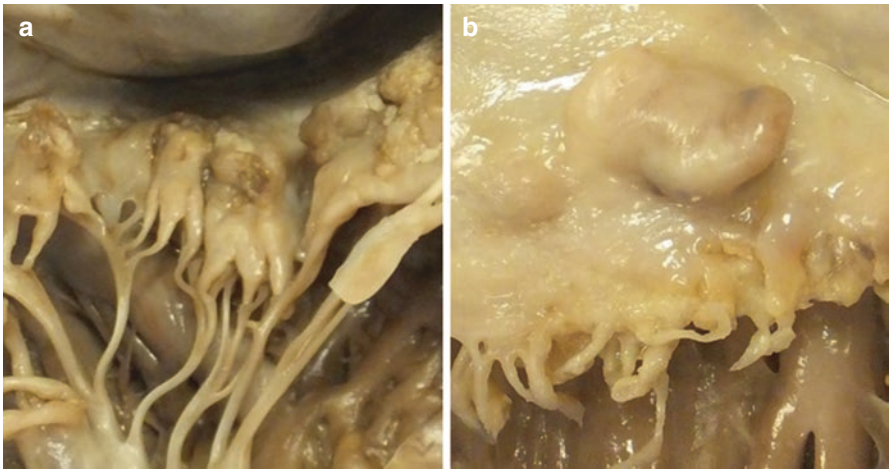

Fig. 8.6 Infective endocarditis affecting the mitral valve. (**a**) Numerous vegetations on the atrial surface of the leaflets. (**b**) An outpouching or aneurysm on the aortic leaflet surface with marked thickening of the cords

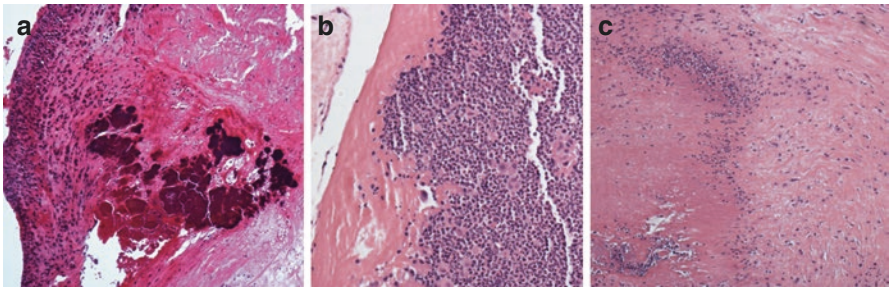

Fig. 8.7 Photomicrographs of infective endocarditis. (**a**) Dark bacterial colonies are present in and on the valve substance. (**b**) A dense acute inflammatory infiltrate composed predominantly of neutrophils. (**c**) Necrosis of the valve substance

The vegetations may embolise resulting in both local and systemic complications. Septic embolisation to the coronary artery with blockage results in acute transmural myocardial infarction which can cause sudden cardiac death. Smaller septic emboli may lodge in intramural vessels and cause small septic infarcts and abscesses. Systemic embolisation can result in distal organ infarction, abscesses, mycotic aneurysms, Janeway lesions, and Osler nodes. Infarctions occur most commonly in the brain, spleen, kidneys, lungs, and mesentery whilst abscesses occur in the kidneys, liver, and spleen [3]. White centred retinal haemorrhage may be seen in the eye called Roth spots. Histologically these are predominantly composed of fibrin as part of a fibrin platelet thrombus at the site of haemorrhage.

Viewed microscopically, the vegetations are composed of fibrin and platelets with an acute inflammatory infiltrate and bacterial colonies (Fig. 8.7a). There is necrosis of the valvar leaflets and abscess formation which can also directly involve the myocardium (Fig. 8.7b & c). It is essential that neutrophils and leaflet necrosis as well as organisms should be observed for a diagnosis of infective endocarditis. The most common causes of infective endocarditis are staphylococcal and streptococcal bacteria with *staphylococcus aureus* and streptococcus viridans predominating.

Non-Bacterial Thrombotic Endocarditis

This is a condition, in which, there are usually small vegetations present on the atrial surface of the valve leaflets but, they are devoid of bacterial aggregates and acute inflammation as seen in infective endocarditis. The condition is also referred to as marantic endocarditis and is associated with neoplastic, autoimmune, or vascular disease [4]. The vegetations form along the lines of coaptation (Fig. 8.8a). On histology, the vegetations consist of fibrin and platelet thrombi which are lacking an inflammatory infiltrate (Fig. 8.8b). The valve substance may appear normal or show minor alterations in the collagen and elastin fibres. Gram stain should be used to exclude the presence of bacterial colonies.

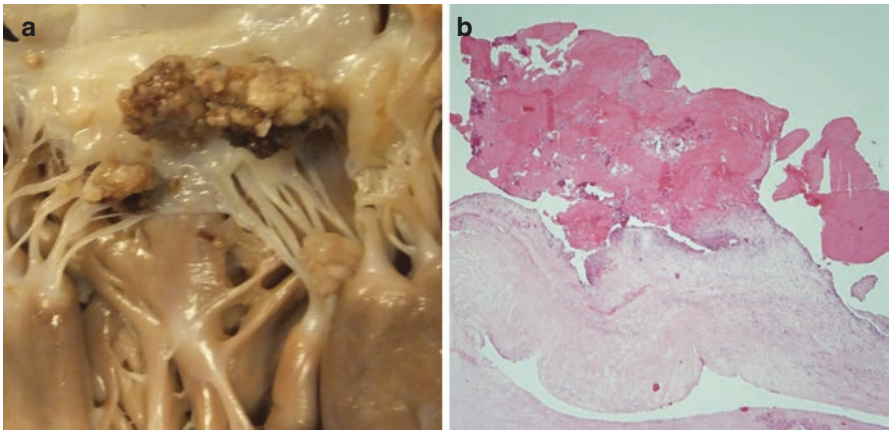

Fig. 8.8 Non-bacterial thrombotic endocarditis. (**a**) A large vegetation is attached to the valve leaflet. (**b**) Microscopically the vegetation is composed of fibrin and devoid of bacteria and an acute inflammatory infiltrate

Mitral Valve Prolapse

Mitral valve prolapse (MVP), also known as floppy mitral valve syndrome, systolic click-murmur syndrome, billowing mitral leaflets, and myxomatous disease is a valvular disorder which rises steadily with age. This is now the most common cause of isolated mitral regurgitation in patients undergoing mitral valve repair in the developed world, where the chronic rheumatic disease has declined.

Degenerative mitral valve disease includes different degrees of annular dilation, leaflet expansion, and ballooning, and chordal dysfunction. It encompasses two broad categories, fibroelastic deficiency (FED) and Barlow disease (BD). The name floppy valve was given to the condition by surgeons who noted that the cusps were large and voluminous and soft to feel, quite unlike the typical retracted hard cusps of rheumatic disease (Fig. 8.9a & b). It has also been described as myxomatous due to this texture (Fig. 8.9b).

The aetiology is complex and is thought to have a genetic component. Those with connective tissue diseases, such as Loeys-Dietz and Marfan's syndromes, are well recognised to have prominent myxomatous change in their mitral valve (Fig. 8.9a). These diseases affect transforming growth factor-beta signalling, which plays a key role in the development of valves [5]. A number of familial forms have been described including myxomatous mitral valve prolapse 1, 2, and 3 as well as an X linked forms [5, 6]. It has been noted that mitral valve clefts occur significantly more frequently in those with mitral valve prolapse. These occur in or adjacent to areas affected by prolapse to a greater extent and increased number of clefts is also associated with more extensive prolapse. This suggests a role in the development of mitral valve prolapse [7].

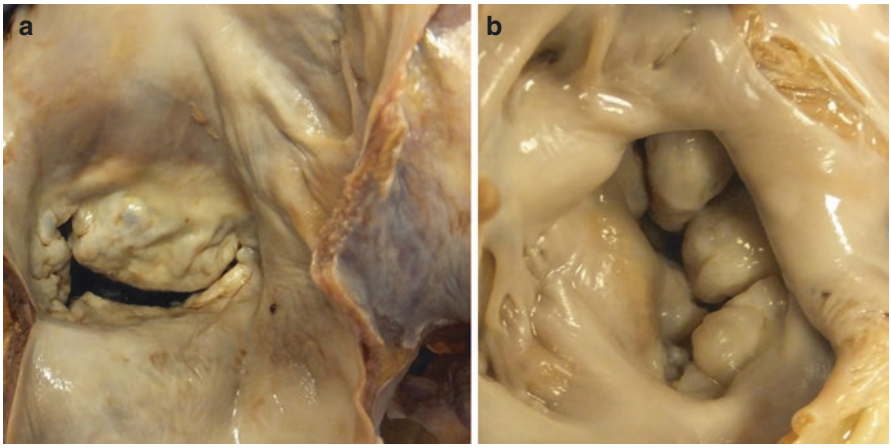

Fig. 8.9 Mitral valve disease in Marfan's syndrome. (**a**) The mitral valve viewed from the atrium showing ballooning and expansion of the aortic leaflet up above the atrioventricular junction. Note also, the generalised thickening of the leaflets. (**b**) The mitral valve viewed from the atrium showing ballooning and expansion of all three segments of the mural leaflet. Note, the thickened appearance of the leaflets

Macroscopically the leaflets appear rubbery and oedematous with diffuse thickening (Fig. 8.9b). The changes can be variable in one or both leaflets. The leaflets are divided into segments clinically and the severity of the disease shows variation from segment to segment with P2 of the mural leaflet most commonly and most severely affected. The leaflets may show increase in the surface area resulting in ballooning into the atrium (Fig. 8.9a & b). Ballooning is challenging to assess in the post mortem state but a height of 2 mm above the AV junction has been used as a criterion [8]. There is elongation of the cords which may also appear thinned and can rupture. The annulus is commonly dilated beyond 90 mm.

Prolapse is defined as displacement of some portion of one or both leaflets of the valve during systole up into the left atrium in living patients (Fig. 8.10a). Prolapse is a strange word for what is an upward movement, but it is used clinically. In a proportion of subjects with mitral cusp prolapse, regurgitation develops at the end of systole. MVP is further subdivided into non-classic and classic based on the thickness of the mitral valve leaflets. Fibroelastic deficiency and Barlow's disease have been considered as both ends of the spectrum of degenerative mitral valve disease.

Barlow's disease is the most severe form of myxoid degeneration of all components of mitral valve apparatus. Barlow in 1970s coined the term *billowing mitral leaflet syndrome* to describe the billowing of mitral leaflets as seen on echocardiography. Barlow's disease is defined according to the criteria described by Carpentier as: bileaflet prolapse > 2 mm; billowing valve with excess tissue and thickened leaflets ≥ 3 mm; and severe annular dilatation. Chordal elongation or rupture, annular and papillary muscle calcification may be present. This is classic MVP, with the

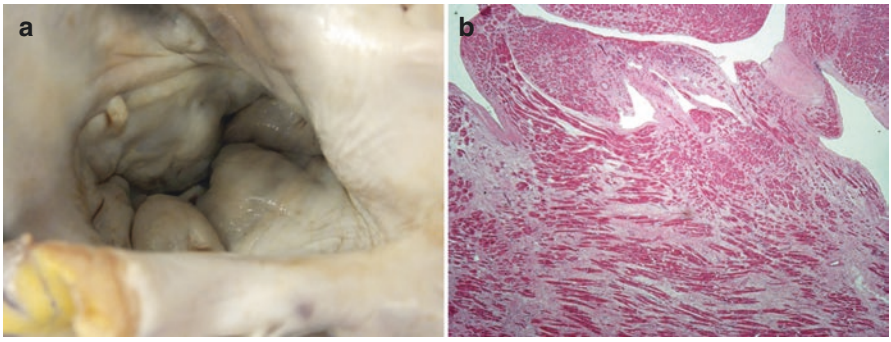

Fig. 8.10 Mitral valve prolapse. (**a**) Prominent ballooning of the leaflets up into the atrium. (**b**) Marked left ventricular inferior wall subendocardial fibrosis. This fibrosis may act as a substrate for arrhythmia in these individuals

mitral valve leaflet thickness being more than 5 mm. Classic MVP is further subdivided into symmetric and asymmetric based on the point at which leaflets' tips join the mitral annulus. In symmetric form, leaflet tips meet at a common point on the annulus. In asymmetric form, one leaflet is displaced toward the atrium with respect to the other. Classic asymmetric MVP is also further subdivided into flail and non-flail subtypes. In flail subtype, prolapse occurs when a leaflet tip turns outward, becoming concave toward the left atrium causing mitral valve deterioration. The flail leaflet has a higher prevalence of mitral regurgitation than non-flail form and varies from tip eversion to chordal rupture. Carpentier characterised the surgical lesions seen in Barlow's disease and was the first to differentiate it from another category of mitral valve prolapse where there was no billowing or excess tissue. Carpentier used the term *fibroelastic deficiency* to describe this degenerative process, which is associated with thinned and ruptured cords and typically involves a single segment of the posterior leaflet. This is in life called non-classic MVP with mitral valve leaflet thickness of 0 mm to 5 mm. Cordal rupture is the classical lesion of fibroelastic deficiency. One or more chords, usually to a single segment, are ruptured, causing prolapse of the unsupported segment. Unruptured cords are often thinned. Leaflets are thin, sparse, and of normal height, the exception being the prolapsing segment, which may display thick and excess tissue. Annular dilation is present but less prominent than in Barlow's disease.

The natural history of MVP is heterogenous and largely determined by the severity of the prolapse. The overall prognosis for MVP is good. Most asymptomatic individuals are not aware that they have MVP and do not require treatment. Large-scale surveys of fit young individuals show that minor degrees of cusp prolapse without regurgitation are commonplace and can be regarded as minor physiological anomalies. Complications associated with MVP include infective endocarditis, mitral valve regurgitation with cardiac failure, arrhythmias, transient ischemic event, or systemic embolism. The major predictor of mortality in MVP is the degree of mitral valve regurgitation and ejection fraction. About 5–10% of patients develop severe regurgitation; with poor ventricular function and atrial fibrillation.

Spontaneous rupture of the mitral cords may occur, resulting in acute regurgitation and cardiac failure. Patients with redundant leaflets are also at high risk of sudden death. The mortality rate of patients with severe mitral regurgitation is 6–7% per year. Young women with mild floppy change but abnormal resting ECG, prolonged Q-T interval, family history of sudden death or complex ventricular arrhythmias are at a greater risk of sudden death. There is prolapse of both leaflets with fibrosis in the posterobasal wall and posteromedial papillary muscle in many cases leading to the concept of a cardiomyopathy linked to MVP. The inferior free wall of the left ventricle can show replacement fibrosis in the subendocardium and midwall in close proximity to the inferoseptal papillary muscle. This damage has been postulated to occur through additional strain being placed by the ballooned leaflet on the cords, papillary muscle, and free wall. This fibrosis may potentially act as a substrate for arrhythmia explaining sudden cardiac death in a subset of affected individuals (Fig. 8.10b) [9, 10].

The histological appearances of the floppy valve (Fig. 8.10a) are the expansion of the spongiosa layer and infiltration of the solid fibrosa with loosely arranged myxomatous tissue. These myxoid areas are cellular, with many spindle-shaped fibroblastic cells. The collagen and elastin fibrils become fragmented. There is a high content of acid mucopolysaccharide and glycosaminoglycans and an increased number of mast cells, but the cusp is not vascularized or inflamed. The atrial and ventricular surfaces of the leaflet are often covered by a well-organised new layer of fibrous tissue containing elastic laminae. Mechanical trauma to the endocardial surface causes division of fibroblastic cells in the superficial zones of the cusp and leads to this surface fibrous thickening. This secondary, nonspecific fibrous response is seen in almost every abnormal valve and should not be confused with the primary disease process. Small platelet thrombi are common on the leaflet surface due to mechanical trauma.

Hypertrophic Cardiomyopathy Related Mitral Valve Disease

Hypertrophic cardiomyopathy is one of the most common inherited heart disease with an estimated prevalence of 1 in 500. It is now well a well characterised condition known to originate from mutations in the genes that encode sarcomeric proteins, the most common of which is cardiac myosin binding-protein C [11]. In 25% of cases, there is left ventricular outflow tract obstruction which is due to the anterior mitral valve leaflet contacting against the hypertrophied interventricular septum in systole.

In those with left ventricular outflow tract obstruction, an “impact lesion” can be observed which corresponds to the thickened edge of the anterior leaflet of the mitral valve (Fig. 8.11a & b). It has been suggested that elongation of the anterior leaflet of the mitral valve precedes the development of left ventricular hypertrophy supporting the theory that mitral valve abnormalities seen in hypertrophic cardiomyopathy are due to both the primary gene defect and the development of asymmetric left ventricular hypertrophy [12].

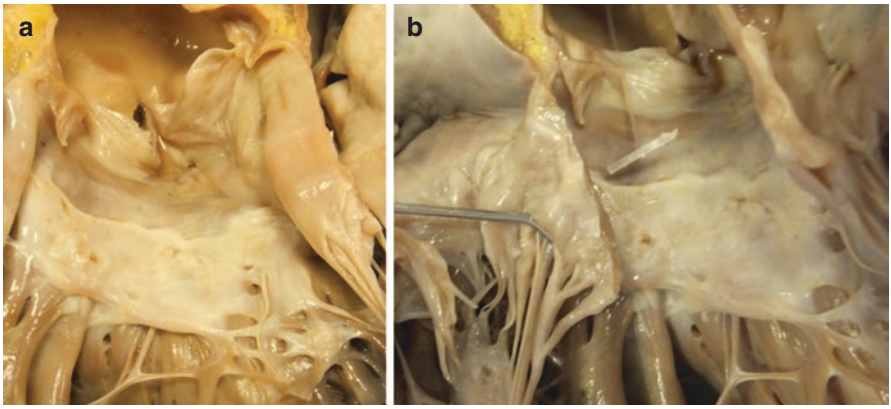

Fig. 8.11 The mitral valve in hypertrophic cardiomyopathy. (**a**) A thickened subendocardial patch present on the interventricular septum just inferior to the aortic valve known as an "impact lesion." (**b**) Thickening of the aortic leaflet of the mitral valve corresponding to the "impact lesion." This is due to systolic contact of the aortic mitral leaflet with the hypertrophied interventricular septum

Congenital Mitral Valve Disease

Congenital mitral valve anomalies may be categorised into supravalvar, valvar, and subvalvar. There may also be a mixed picture [13].

There is a single congenital supravalvar anomaly known as a mitral ring which is described as a circumferential ridge of tissue that ranges from a thin membrane to a thick fibrous ridge.

Valvar anomalies include those affecting the annulus and leaflets. The annulus may show hypoplasia, dilatation, or deformation. The leaflets may show hypoplasia/agenesis, clefting, excessive tissue, or a double orifice.

Subvalvar anomalies incorporate those that affect the cords and the papillary muscles. The cords may show agenesis, shortening, or elongation. The papillary muscles may show hypoplasia/agenesis and shortening. There may be unifocal attachment of the cords to a single papillary muscle which results in the so-called "parachute" mitral valve. Additionally, a straddling mitral valve, in which cords that attach to the right ventricle may be observed, in cases of the atrioventricular septal defect [14].

Trauma

Traumatic mitral valve regurgitation is rare with a variable clinical presentation depending on which component is damaged. Papillary muscle trauma usually presents with acute failure whilst presentation with damage to the cords may be delayed. The most common cause is blunt chest trauma due to road traffic accidents [15].

Papillary Muscle Rupture in Ischaemic Heart Disease

Papillary muscle rupture of the mitral valve is a rare complication of ischaemic heart disease. It most frequently occurs secondary to acute myocardial infarction involving the papillary muscle which results in rupture and severe regurgitation. The patient presents with acute heart failure which may lead to cardiogenic shock and sudden cardiac death. Classically, blockage of the inferior intraventricular artery, previously known as the posterior descending artery, results in a myocardial infarction of the inferior left ventricular wall and septum which involves the inferoseptal papillary muscle. The superolateral papillary muscle has a dual blood supply from the left anterior descending coronary artery and either the marginal or diagonal branch of the circumflex coronary artery therefore, the inferoseptal papillary muscle is more commonly affected.

Mitral Valve Replacement

For most patients undergoing mitral valve replacement for mitral stenosis, the valve is mechanical and is usually a bileaflet tilting disc valve with the need for anticoagulation due to the risk of thrombosis (Fig. 8.12b). Modern bileaflet valves have good long-term durability.

For mitral regurgitation, the valve is repaired with resection of the prolapsed segments and the insertion of an annuloplasty ring if required (Fig. 8.12a). More recently use of a clip called the mitraclip in patients who cannot undergo surgical repair is used as well as transarterial mitral valve replacement with a bioprosthetic valve (TAMI) (Fig. 8.12c).

Complications of valve replacement which may be seen at post mortem include thrombosis, paravalvular leak, endocarditis, and pannus (Fig. 8.13a & b) [16].

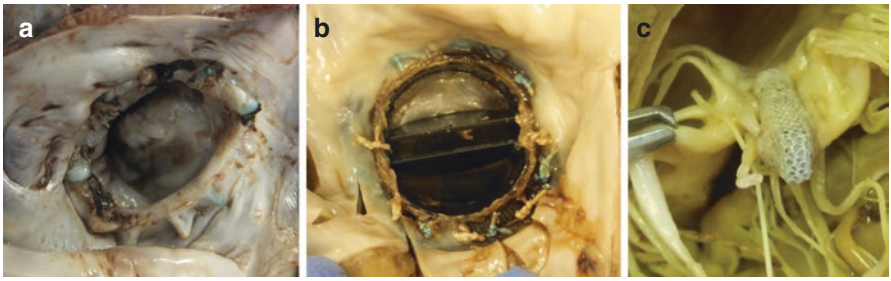

Fig. 8.12 Surgical interventions. (**a**) An annuloplasty ring used to reshape and strengthen the natural valve annulus. (**b**) A bileaflet mechanical heart valve used to replace the native mitral valve. (**c**) A transcatheter mitral valve repair with a mitral valve clip (Mitraclip) used to minimise regurgitation

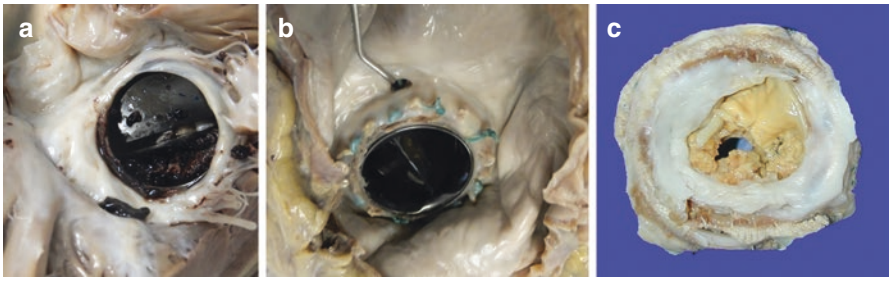

Fig. 8.13 Surgical complications. (**a**) Mechanical valve thrombosis. Note, the thrombus adhered to the surface of the mechanical valve leaflet showing colour variation. (**b**) Paravalvular leak. A fistula has formed between the left atrium and left ventricle in this individual with a mechanical mitral valve replacement and Marfan's syndrome. (**c**) Pannus and endocarditis. Pannus (dense collar of collagen) projects inwards from the bioprosthetic ring. Underlying this, on the leaflet surfaces pale soft friable vegetations are present

Future Work

The aetiology of mitral valve prolapse is complex. Further genome wide analysis in individuals affected by this disease and the establishment of the role of growth factors would increase our understanding of the pathogenesis and molecular pathways leading to the disease. The use of mouse models of congenital clefting would allow the role of these lesions in the disease to be established. Functional studies to assess the efficacy of blocking the transforming growth factor-beta pathway in preventing disease progression could facilitate the development of novel therapeutic options.FundingThe cardiovascular pathology laboratories at St George's University of London are funded by Cardiac Risk in the Young.

Conflict of Interest We have no conflicts of interest to declare.

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Morphogenetic Aspects of Mitral Valve Development

9

Bill Chaudhry and Deborah J. Henderson

Introductory Remarks

The purpose of this chapter is to provide an overview explaining how genes and genetic pathways control the formation and remodelling of the mitral valve in order to link the clinical and morphological observations on the development of the mitral valve in Chap. 9, with the approaches taken by clinical geneticists expounded in Chaps. 10 and 11.

The mitral and tricuspid valves develop at the junction between the atriums and ventricles from local expansions of sub-endocardial extracellular matrix known as endocardial cushions. Similar swellings are involved in arterial valve formation and outflow tract septation. Whilst the basic underpinning mechanisms that explain how the atrioventricular valves form have been known for some time [1–3], these are less well understood for the arterial valves. It has become clear that, although there are similarities in the development processes that lead to the formation of the atrioventricular and arterial valves, at least some of the cell lineages and morphogenetic mechanisms are different [4]. Notably, for both sets of valves, key gaps in our understanding remain, particularly relating to remodelling of the valve leaflets from their endocardial cushion precursors (Fig. 9.1). Although the majority of the early processes involved in mitral valve development are thought to be very similar to that for the tricuspid valve, subtle differences in embryonic cell lineage contributions, gene expression, and exposure to different haemodynamic forces, may influence their differential maturation and the disorders they incur. In this chapter, we focus on the molecular genetic factors that influence atrioventricular valve development. We highlight reported differences between the mitral and tricuspid valves that may account for their differential development, physiology, and function. By necessity,

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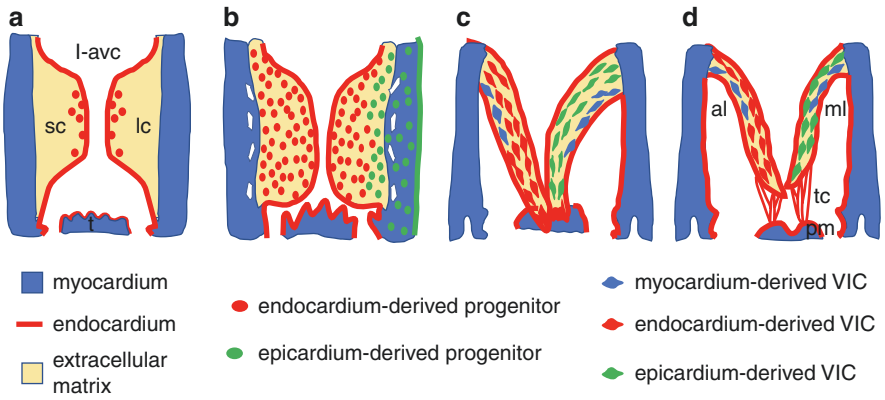

Fig. 9.1 Development of the mitral valve (**a**) At 3 weeks the endocardial cushions—the precursors of the mitral valve leaflets—are first seen in the left side of the atrioventricular canal. At this stage, they are composed of extracellular matrix and undifferentiated mesenchymal cells derived from the endocardium. The myocardium associated with the cushion tissue begins to break down. (**b**) By 4–5 weeks of gestation, these endocardial cushions have expanded and mesenchymal cells derived from the embryonic epicardium have migrated into the atrioventricular myocardium and the lateral cushion. (**c**) Between 10–13 weeks of gestation, the leaflets remodel and their tips associate with the trabeculations—this step is poorly understood. (**d**) By 15 weeks the leaflets have remodelled further and the tendinous cords have become apparent. These are in continuity with the papillary muscles that have remodelled from the trabecular myocardium of the left ventricle. Al = aortic leaflet, l-avc = left atrioventricular canal, mc = mural leaflet; pm = papillary muscle; t = trabeculae; tc = tendinous cords

the majority of this experimental information comes from experiments in the mouse, and occasionally the chicken. The close similarity in cardiovascular development between these organisms and ourselves [5, 6], nonetheless, means that as we begin to analyse human embryos, we are finding that the same genes and processes are involved in all these higher vertebrates.

Patterning of the Atrioventricular Canal

In human embryos, the heart initially forms at approximately day 18 or Carnegie stage (CS)8, equivalent to embryonic day (E) 7.5–8 in the mouse, as a simple midline tube of endocardial cells surrounded by atrial and ventricular cardiomyocytes. These cardiomyocytes originate from progenitors that originate in an area of anterior embryonic mesoderm known as the first heart field and sometimes called the cardiac crescent. Later, a closely related group of progenitor cells, known as the second heart field (SHF), add on to the forming heart tube and contribute to the atriums, right ventricle, and outflow tract (reviewed in [7–10]). As the atrial and ventricular portions of the initial primitive (or primary) heart tube expand or "balloon" to form recognisable chambers (reviewed in [11, 12]), the cells at their junction give rise to the atrioventricular canal, where the mitral and tricuspid valves will form.

The early genes expressed in the atrioventricular canal promote valve development but repress atrial and/or ventricular chamber identity. Conversely, genes expressed in the atrial and ventricular chambers enhance the development of contractile cardiomyocytes and repress atrioventricular canal identity (reviewed in [11, 12]). This early atrioventricular canal patterning occurs at around day 23 of human development (CS10–11 or E9.5–E10.5 in mouse). It is dependent on the signalling molecule bone morphogenetic protein 2 (BMP2), secreted by the myocardium (Fig. 9.2). Knock out mouse experiments show that the absence of *Bmp2* in the myocardium leads to a failure to specify the atrioventricular canal as being different from the rest of the chamber myocardium [13, 14]. Conversely, if *Bmp2* expression is artificially expanded throughout the primary heart tube, an atrioventricular canal-like phenotype is seen throughout the ventricular chamber [15]. Bmp2 activates several T-box transcription factors that bind to the regulatory regions of target genes and can either activate or repress their expression. *Tbx2* and *Tbx3* act to maintain the primitive myocardial phenotype, suppressing chamber development in both the atrioventricular region and in the developing outflow tract [16–18]. As with loss of *Bmp2*, loss of *Tbx2* results in the failure to form a distinct atrioventricular canal, with the almost complete failure of cushion, and by extension valve, formation. Another T-box family member, *Tbx20*, is strongly expressed in the forming cardiac chambers but is not expressed in the atrioventricular canal. It has opposing actions to *Tbx2*. It activates chamber-specific genes, but is also a *Tbx2* repressor

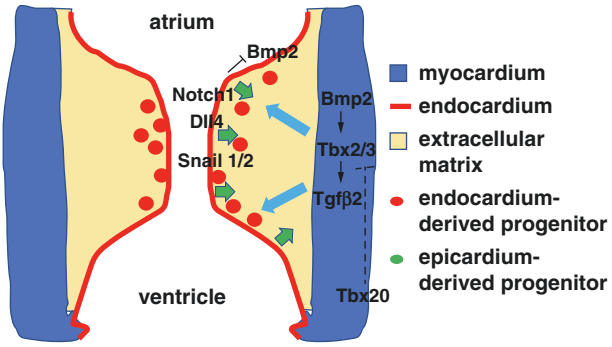

Fig. 9.2 Atrioventricular canal patterning occurs at around day 23 of human development. Bone morphogenetic protein 2 (Bmp2), secreted by the myocardium activates several T-box transcription factors that bind to the regulatory regions of target genes and can either activate or repress their expression. *Tbx2* and *Tbx3* act to maintain the primitive myocardial phenotype and suppress chamber development in both the atrioventricular region and in the developing outflow tract. *Tbx20* is strongly expressed in the forming cardiac chambers but is not expressed in the atrioventricular canal. It has opposing actions to *Tbx2* and activates chamber-specific genes but is also a *Tbx2* repressor, repressing any tendency to develop atrioventricular canal identity. The Notch pathway (including Dll4) plays an essential role in confining expression of *Bmp2* to the myocardium of this region. This activates Snail 1/2, which are required for the transformation of the endocardial cells into mesenchyme that populates the cushion. Genetic disruptions that completely inactivate these genes will either result in a failure to properly pattern the atrioventricular canal or to form the chambers and lead to early embryonic death

[19–22], inhibiting any tendency to develop atrioventricular canal identity. Thus, an adversarial signalling network involving *Bmp2* and *Tbx2/3* is required to specify the atrioventricular myocardium [13, 16], which is restricted from extending into the chambers by *Tbx20*.

The Notch pathway provides direct signalling between endothelial and myocardial cells and is active in the atrioventricular canal. It has comprehensively been shown that its expression in the endocardium of the atrioventricular canal plays an essential role in confining expression of *Bmp2* to the myocardium of this region [23, 24]. Abnormal activation of Notch1 signalling throughout the entire endocardium of the heart produces a similar effect to ectopic *Bmp2* expression. In contrast, expression of activated Notch1 in the atrioventricular canal myocardium represses *Bmp2* and *Tbx2* and results in failure to form the atrioventricular endocardial cushions [24, 25]. Any genetic disruptions that completely block these genes will either result in a failure to properly pattern the atrioventricular canal or to form the chambers and lead to early embryonic death. If subtly disrupted, however, these genes may still have relevance to mitral valve malformations and disease. For example Follistatin-like 1 (Fstl1) is a secreted glycoprotein that regulates *Bmp2* and *Tgfβ1* (reviewed in [26]). Knock out of this gene in the mouse endocardium resulted in the persistence of *Tgfβ1* and *Bmp2* expression in neonatal valves. With ongoing endothelial-to-mesenchymal transformation, the valves become enlarged and myxomatous, leading to severe mitral regurgitation and death between 2–4 weeks after birth [27]. Importantly, the tricuspid valves were spared.

Extracellular Matrix

The heart tube has a layer of the extracellular matrix, known as cardiac jelly, which separates the inner endocardial layer from the outer myocardial layer. The next stage in the development of the mitral valve is the appearance of localised acellular expansions of this cardiac jelly within the atrioventricular canal. These are the endocardial cushions. Even at this early stage, they act as valves to prevent retrograde blood flow as the ventricles contract. Initially, superior and inferior atrioventricular cushions are seen, which separate the atrium from the inlet component of the ventricular loop. A pair of smaller "lateral" cushions, precursors of the atrioventricular mural leaflets, form subsequent to the development of the right ventricle and expansion of the atrioventricular canal [5, 28]. The extracellular matrix in the atrioventricular cushions is mainly composed of hydrophilic proteoglycan molecules, the most abundant of which are versican and hyaluronan. Mice lacking versican [29] or hyaluronan synthase-2 (Has2), the enzyme required for the production of hyaluronan [30], die shortly after heart looping. This is almost certainly because it is not possible to achieve sufficient cardiac output without adequate endocardial cushion bulk to prevent retrograde flow within the heart (reviewed in [31]). In addition to a mechanical role, hyaluronan and versican, together with a number of other molecules (such as cartilage link protein; [32]) form a scaffold that modulates cell signalling processes. They control the activity of other extracellular matrix molecules by

sequestering latent forms or cleaving them to create activate ones. For example hyaluronan can act together with the epidermal growth factor (EGF) family of growth factor receptors, ErbB2/B3, to stimulate Ras-dependent intracellular signalling. This signalling is required for the formation of the cushion mesenchyme and thus the development of the endocardial cushions [30, 33]. Enzymes that control the breakdown of this extracellular matrix can have profound effects on development, but also on ongoing valve homeostasis. For example ADAMTS5 is a metalloprotease produced by the developing valve endocardium that cleaves aggrecan and versican. *Adamts 5*-knock out mice have enlarged heart valves during the latter stages of foetal life, which manifests as myxomatous valve disease in adult animals. These phenotypes appear to relate to reduced versican cleavage within the developing and mature valve leaflets [34]. In human genetic studies, mutations in *ADAMTS5* have been linked with a range of valve problems, including bicuspid aortic valve [35]. Proteoglycan accumulation is a hallmark of human myxomatous valve disease. Extrapolating from the animal studies, it is possible that ineffective aggrecan/versican cleavage during valve development might underlie later myxomatous disease in adulthood, suggesting that this disease of ageing could have origins in foetal life.

Endocardial-to-Mesenchymal Transformation

The entry of cells into the atrioventricular cushions is required for their development into valve primordiums. The main source of cells is the layer of endocardial cells lining the atrioventricular canal. To invade the cushions, these cells lose attachments with surrounding endocardial cells. This means they change from an epithelial to a mesenchymal phenotype, and hence are able to migrate into the cushions. This important role for endocardial-to-mesenchymal transformation (EndMT) in cushion formation was first described in the last century [36]. Compared to other aspects of mitral valve development, it is relatively well understood [37, 38]. Notably, a very similar genetic cascade is activated in cancer, which is responsible for local tumour invasion and metastasis. As with those molecules that are involved in initial patterning of the atrioventricular canal, marked deficiency or loss of the molecules that control EndMT frequently result in failure to form the endocardial cushions and early embryonic death.

The crucial signals for initiating EndMT are Bmp2 and transforming growth factor-beta 2 (TGFβ2), secreted by the atrioventricular myocardium (reviewed in [39, 40]). Notch1 signalling in the endocardium, via its receptor Delta-like 4 (Dll4; [41, 42]), works together with Bmp2 to regulate *Snail* and *Slug* transcription factors. It is *Snail* and *Slug* (*Snail* 1 and 2) that down-regulate the expression of vascular endothelial cadherin (VE-cadherin), an adhesion molecule that maintains intercellular junctions in endothelial tissue and allows cells to escape the endocardial monolayer [41, 43–45]. It also upregulates the expression of genes required for cell migration and invasiveness (reviewed in [46]). The ingress of cells by EndMT must be controlled. Thus, whilst vascular endothelial growth factor (VEGF) is important in initial induction of EndMT, it facilitates replication of endothelial cells and then

controls its resolution [47, 48]. VEGF does this by activating *Nfatc1* (another transcription factor) to limit the extent of EndMT [49]. *Nfatc1* maintains proliferation of the endocardium during EndMT and valve sculpting, but also suppresses the expression of the *Snail* transcription factors [50]. The extent of signalling crosstalk between these various pathways is poorly characterised. This remains an important unexplored aspect of the regulation of both arterial and atrioventricular valve development. Low-level EndMT is also thought to be essential for maintaining valve integrity throughout the life. Evidence of such activity can be found in 1–2% of valve endocardial cells in healthy adults [51]. These cells may be required to renew the valve interstitial cell population and thus replenish the extracellular matrix that is needed in mature valves for their durability. Hence subtle defects in the regulation of EndMT may be relevant to human mitral valve disease. Maladaptive EndMT has been shown to occur subsequent to myocardial infarction, in conjunction with thickening of the mitral valve leaflets [52].

Sources of Mitral Valve Interstitial Cells

A number of different cell lineages clarified using Cre-driven enhancer mouse lines (Fig. 9.3; reviewed in [53]), have been shown to contribute to the developing atrioventricular valves.

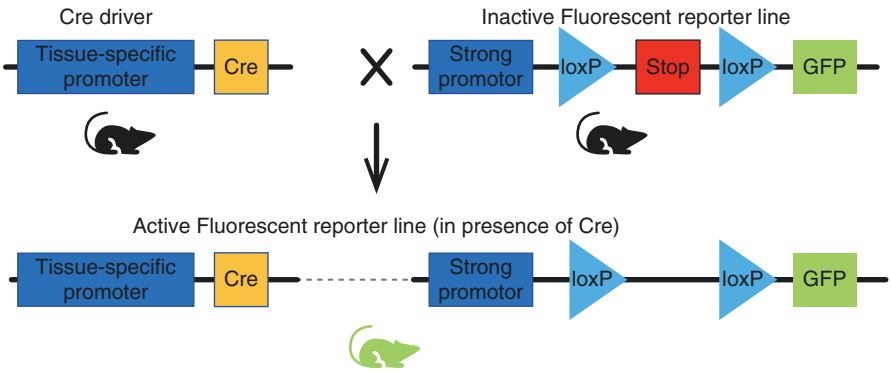

Fig. 9.3 Cell lineage tracing using Cre-lox mice. Distinct cell lineages can be tracked using genetically modified mouse strains. One line of mice is created in which the enzyme Cre recombinase is linked to a tissue-specific gene promoter. This results in the expression of Cre only in the tissue of choice. In a second mouse line, a gene that encodes a fluorescent marker, for example green fluorescent protein (GFP) is placed downstream of strong promoter. The presence of a Stop sequence, flanked by loxP sites (the recognition sites for Cre recombinase), prevents the GFP from being expressed. When these two lines of mice are crossed together, Cre recombinase is expressed only in the cells/tissue where the tissue-specific promoter is expressed. This results in recombination of DNA at the loxP sites and removal of the Stop sequence. This allows the strong promoter to drive expression of GFP only in the cells (and their progeny from later divisions) where the tissue-specific promoter is expressed

Endocardial Cells

Endocardium, the endothelium of the heart, originates from at least two sources. The majority of the endocardium found in the atrioventricular region, which undergoes EndMT to enter the valve interstitium [54, 55], derives from the first heart field. A small population, in both the endocardial and interstitial components, comes from the second heart field [SHF; [56]]. It is not known if these different origins are of biological importance. A particularly interesting subset of cells are restricted to the cushion/valve endocardium and are labelled by the *Nfatc1en-Cre* driver [50]. The labelled endocardial cells do not undergo EndMT to enter the valve. Although it remains uncertain, it has been suggested that this population is essential for maintaining the integrity of the valve endocardium itself.

Second Heart Field-Derived Mesenchyme

As development proceeds, the atrial and ventricular septal structures fuse with the atrioventricular cushions at the crux of the heart. An additional second heart field-derived structure, the vestibular spine or dorsal mesenchymal protrusion), fuses with the atrioventricular cushions to bring about atrial and atrioventricular septation [57, 58]. Deficiency of the spine, brought about by disruption of the SHF, is associated with atrioventricular septal defects. A subset of atrioventricular septal defects exhibit abnormal valve development, the most severe of which have a solitary atrioventricular valve orifice with bridging leaflets. The development of this abnormality is a current topic of research, as it remains unclear how much of the valve abnormality is the result of a shared requirement of SHF cells for the development of the vestibular spine and the mitral valve, and how much is a secondary consequence of the atrioventricular septal defect.

Epicardial-Derived Cells

The heart is covered with a layer of cells (the epicardium) that mainly originate from the region of the developing diaphragm (reviewed in [59, 60]). These cells attach to the heart surface and invade, being at this stage known as epicardial or epicardium-derived cells, to provide most of the cardiac fibroblasts, along with the smooth muscle cells of the coronary arteries. In the mouse, the epicardium and epicardial-derived cells can be specifically labelled by *Wt1*^{ERT2}*-Cre* or by *Tbx18-Cre* drivers. Studies have shown that in the mural leaflet of the mitral valve, which is derived from the lateral cushions, epicardially derived cells give rise to the majority of the valve interstitial cells, replacing the original cells that entered by EndMT [61–63]. In contrast, epicardially derived cells make only a minor contribution to the aortic leaflet of the mitral valve. The biological relevance of this difference, if any, remains unknown.

Neural Crest Cells

These multipotent progenitor cells migrate from the neural tube early in development. They are important in forming the peripheral nervous system, pigment cells, and many of the bones in the head. They are also essential for septation of the outflow of the heart, making a major contribution to the outflow tract cushions and valves [64]. They make only a minor contribution, however, to the cells populating the atrioventricular valves [65, 66]. A specific role in the mitral valve remains unclear, although their persistence in adult valves suggests that they may have one.

Bone Marrow-Derived Cells

Studies in humans after bone marrow transplantation surprisingly revealed that cells of haematopoietic lineage appear in adult heart valves [67]. Recently this has been investigated in mice [68]. Lineage tracing has shown that, whereas at birth only ~5% of atrioventricular valve cells are of the leukocyte lineage, this rises to close to 20% within the mitral valve by two months of age [69]. Moreover, their gene expression profile changes considerably during the postnatal period [70]. The specific function of these bone marrow-derived cells remains unclear, but they appear to be macrophages and dendritic cells rather than endocardial cells or valve interstitial cells. Recently, it has been shown that they play critical roles in valve remodelling [71]. Importantly, these bone marrow-derived cells are increased in myxomatous mitral valves in both mice and humans [72, 73]. Very little is known about their function either during development, normal homeostasis, or in pathological situations. It is clearly important to evaluate whether any of these specific progenitor populations have specific roles in health and disease.

Mitral Valve Growth and Maturation

Once the endocardial cushions have formed, and been populated by interstitial cells, they undergo growth and remodelling in order to acquire the structure of mature valve leaflets. The gross morphological changes that occur as the valve develops are described in Chap. 8. Maturation and thinning of the endocardial cushions to form valve leaflets is characterised by both downregulation of cell proliferation and transition from an undifferentiated mesenchymal phenotype to differentiated valve interstitial cells (VIC). Higher levels of cell proliferation may persist at the distal ends of the valve primordiums. The active growth in these regions may be important to form sculpted leaflets [54]. Growth and fusion of the superior and inferior atrioventricular endocardial cushions are driven by proliferation of newly formed mesenchymal cells in response to signals from the endocardium [74]. Although the processes coordinating cushion growth and fusion, as opposed to early cushion formation, are not well understood, studies in mice have shown that transcription

factors including *Sox9, Twist1,* and *Tbx20* [75–77] are active in this process. They drive the high levels of cell proliferation found in the remodelling valves. Deletion of these factors in the mouse embryo results in failure to form proper valve primordiums. Deletion of EGFR and HB-EGF in mice results in enlargement of the atrioventricular cushions due to excessive proliferation in cushion mesenchyme [78], suggesting that HB-EGF-EGFR signalling is also required to modulate mesenchymal proliferation [79, 80]. Jagged1 signalling via Notch1 is also thought to limit the extent of mesenchymal proliferation in the endocardial cushions by positively regulating HB-EGF/EGFR [42].

Other pathways have been implicated in valve remodelling because of human syndromes associated with mitral valve malformation. The BMP and/TGFβ signalling pathway, as previously discussed, seems to be particularly important in growth and remodelling of the leaflets. This pathway has been shown to be abnormal in both Loeys-Dietz and Marfan syndromes. Mice lacking the Bmp-specific inhibitor Smad6 or the BMP antagonist Noggin [81, 82], have enlarged valve leaflets associated with increased proliferation. In contrast, loss-of-function models for BMP and TGF family members and their receptors have reduced cell proliferation in the atrioventricular cushions and hypoplastic valves (reviewed in [40]). Whilst mutations in *TGFBR2* and *SMAD3* are directly implicated in Loeys-Dietz syndrome (reviewed in [83]), the fibrillin (*FBN1*) mutations causing Marfan syndrome may indirectly cause mitral valve prolapse. Fibrillin is a large structural protein that contributes to the functional integrity of connective tissue and normally sequesters latent TGFβ binding proteins. Thus, *FBN1* mutations may interfere with this regulation of TGFβ signalling. Ras signalling has also been implicated in regulating cushion mesenchyme. Mitral valve prolapse is a common feature in Noonan's syndrome, which is caused by gain-of-function mutations of *PTPN11*. Conversely, loss-of-function mutations in Ras-pathway components such as *Nf1* (the gene mutated in Neurofibromatosis type I), result in hypercellular valves, suggesting that the Ras signalling pathway negatively regulates cushion mesenchyme proliferation (reviewed by [33]).

As in earlier stages of development, therefore, a number of molecules are implicated in regulating the proliferation of cells in the atrioventricular cushions and are essential for their normal development. As with EndMT, the interplay between these genes and gene products is underexplored. It is likely to be important for understanding how mitral and tricuspid valves develop and respond to postnatal insults, stresses, and ageing.

Release of the Leaflets and Formation of the Tension Apparatus

This is the area of mitral valve formation that is probably least well understood. After the period of endocardial cushion expansion, the primordium of the mural leaflet has to remodel in order to be freed from the ventricular wall. The fused major cushions must also remodel to achieve their mature flexible forms. Whilst the lateral cushion is initially adhered to the myocardium, this changes over time (between the

10th and 13th week of human development) to leave a free, mobile leaflet attached to the ventricular wall by tendinous cords and papillary muscles [84–86]. At least in the mouse heart, it has been suggested that this process involves programmed cell death in the region between the myocardial wall and the cushion, which creates space between them, freeing the developing leaflet from the myocardium [55]. It is clear that the papillary muscles are myocardial in origin [55] and form by compaction of the pre-existing trabeculations which form from the innermost layer of the myocardium [87]. The processes by which the tendinous cords create the union between the papillary muscles and the leaflets currently remains unknown (see Chap. 4).

Extracellular Matrix (ECM) and Valve Remodelling

The cells present within the matrix are important for the regulation of ECM biosynthesis and its turnover within the valve leaflets. Indeed, the ECM of the remodelling valves is very similar to that found in developing cartilage and bone (reviewed in [88]). It shares many of the same transcriptional regulators, such as *Sox9* and *Scleraxis*, and modulating proteins, for example ADAMTS5. These genes play slightly different roles than at earlier stages. For example whilst *Sox9*, a master regulator of cushion mesenchyme and cartilage formation, is necessary for early interstitial cell proliferation, later it promotes the expression of cartilage matrix proteins such as aggrecan in the remodelling leaflets [54, 75]. Similarly, NFATc1/Calcineurin signalling is important for the transition from growth to remodelling in the cushion/valve endocardium [49, 89] and regulates expression of RANKL and Cathepsin K. These proteins are required for transcriptional activation of bone matrix remodelling enzymes during osteoclast differentiation in the bone. They presumably play a similar role in the highly similar ECM of the developing valves [90]. Periostin promotes the differentiation of both endothelial- and epicardial-derived mesenchyme while blocking the emergence of other cell types, especially cardiomyocytes. It is also required for fibrous maturation of the atrioventricular leaflets and their supporting apparatus [91, 92]. The transcriptional regulator, *Scleraxis*, appears to be particularly important for regulating ECM in the remodelling valves [93]. It is first expressed in the atrioventricular endocardial cushions just prior to remodelling. It becomes more widely expressed as remodelling progresses, and is also retained in the adult valves [54]. *Scleraxis* is specifically expressed in the developing tendinous cords of the valve leaflets in the chicken embryo, although this does not seem to be the case in the mammalian heart [54, 93]. *Scleraxis* regulates the expression of a number of ECM molecules found in the remodelling atrioventricular valve leaflets and its loss in mice results in thickened atrioventricular valve leaflets. Abnormal ECM deposition is characterised by an increase in cartilage-associated proteins such as Sox9, cartilage oligo matrix protein, and cartilage link protein, and a downregulation of tendon-associated proteins such as Collagen XIV [93]. *SCHLERAXIS* is upregulated in human myxomatous mitral valve leaflets, suggesting that these pathways are clinically relevant.

In diseased valves, there is aberrant recruitment of endocardial and interstitial cells, along with the transition of a subset of interstitial cells into myofibrobasts expressing alpha-smooth muscle actin. These cells, together with the expression of matrix metalloproteases and proinflammatory cytokines, result in a degraded and disarrayed matrix in the leaflets and tendinous cords, which can become calcified (recently reviewed in [94, 95]). These structural changes are associated with the aberrant re-expression of early valve mesenchymal and chondrogenic progenitor markers. They have been related to the reactivation of foetal transcriptional programmes [96–99]. These data may go some way to explain why cardiac valves appear to be predisposed to abnormal accumulation of ECM proteins associated with myxomatous degeneration and calcification. Indeed, matrix Gla protein, encoded by the *MGP1* gene, is downregulated in developing bone in order to allow calcification but is maintained in developing heart valves [100]. Loss of *MGP1* in mice results in calcification of the heart valves in the neonatal period, perhaps showing that prevention of calcification of the maturing leaflets is an active process.

The Lamellar Mitral Valve Structure

In addition to the deposition of cells and ECM proteins, the emergence of a lamellar structure is seen in human valves before birth [101], and probably begins in the second trimester [102]. In the mouse heart, lamination starts between E15.5 and E18.5 (reviewed in [103]), but in both cases, there is still considerable remodelling after birth. Extracellular proteins are generally secreted by the valve interstitial cells. Turnover of these molecules continues throughout life. The relative thicknesses of the layers vary between the leaflets of the mitral valve. They also vary within each leaflet from their hinges to the free edge [104].

During the stratification process, collagen fibrils (mainly types I and III) become circumferentially oriented and densely packed at the ventricular side of the leaflet to form the fibrous layer that provides tensile strength to the leaflet [105, 106]. Notably, the valve interstitial cells are connected to the extracellular matrix, including the collagen, via integrin receptors on their surfaces. Disruption of these interactions can result in valve calcification, although it remains unclear whether this results from direct anti-calcification roles for integrins or is secondary to valve-extracellular matrix interactions (reviewed in [107]). Filamin A is a non-muscle actin-binding protein that organises filamentous actin into orthogonal networks and stress fibres. It anchors membrane proteins to the actin cytoskeleton, and provides a scaffold for cytoplasmic and nuclear signalling proteins. Mutations leading to a dysfunctional FLNA protein have been identified in myxomatous valvar dystrophy [108]. They may affect signalling pathways that modulate cellular migration and mechanical stress responses during development [95].

Proteoglycans, particularly hyaluronan, versican, biglycan, and decorin, are the main components of the middle spongy layer of the leaflet. The distribution of these molecules differs in regions exposed to different stresses. Hyaluronan and versican are abundant in the compressive regions of the leaflets. Biglycan, in contrast, is most

abundant in the centre of the aortic leaflet, which is a tensile region. It is less abundant in the tendinous cords, also tensile, and the free edge of the aortic leaflet, which is compressive. It is least abundant in the compressive mural leaflet [109]. The atrial side of the mitral valve leaflets is largely made up of elastin. Different compositions of glyocosaminoglycan (GAG) side chains attached to the core protein molecules are also found in different parts of the valve and its tension apparatus, correlating again with compressive and tensile regions. Notably, the relative amounts of these molecules change as the valves age [109, 110]. Dysregulation and imbalance of the ECM components appear to be a general feature of valve disease regardless of aetiology. For example myxomatous disease is characterised by loose collagen, increased proteoglycan, and reduced elastin content with altered fibre orientation in all valve layers (reviewed in [95]).

Both gene expression and cell differentiation are involved in establishing the laminar structure of the valve tissue. For example Wnt/β-catenin signalling primes the cushion mesenchyme to respond to patterning cues that promote the proteoglycan-rich spongiosa layer and restrain the boundaries between the tendinous cords and the leaflets [111]. As well as genetic regulation of the stratification process, it has also been suggested that mechanical stimuluses are important for the alignment of collagen fibres in the developing and maturing leaflets [112]. The patterning of the extracellular components of the leaflets align with blood flow, which may suggest that hemodynamic forces acting via the valve endocardium are driving the process.

Cilia and Cell Polarity in the Mitral Valve

Recently, there has been a major interest in the role of cilia in valve development and maintenance, largely because of the association between mutations in cilia-associated genes and valve defects, including mitral valve prolapse. This has come about because of the identification of several cilia-related genes, including Daschous1 (*DCHS1*), Desert hedgehog (*DHH*), and *DZIP1* [113–115] in familial cases of mitral valve prolapse. Primary cilia are small projections of membrane with a microtubule core that are implicated in cell signalling and mechano-sensation. There is considerable evidence to show that the presence of cilia is temporally and spatially regulated during valve formation and that they are maintained on the surface of the valve interstitial cells, although not on the endocardium, during adult life. This absence from the valve endocardium suggests that their role is unlikely to be related to the detection of shear stress. *DCHS1* is a component of a cellular signalling pathway that regulates cell polarity and migration. *DCHS1* deficiency in patient cells, and in cells carrying one mutated allele of the *Dchs1* gene in mice, was sufficient to result in altered migration and cellular arrangement of valve interstitial cells [113]. These studies suggest that interstitial cell organisation, and the pathways that regulate this process, are critical determinants of valve development and that disruption may result in disease [95]. Although the precise and potentially multiple roles of cilia in valve development and maintenance remain unclear, they have been implicated in modulating the extracellular matrix, restraining calcification and

responding to inflammatory signals. Mouse models of *Dzip1* have suggested that the mitral valve prolapse seen in adult mice is a result of developmental defects, apparent from mid-embryogenesis, that result in abnormalities is extracellular matrix production and dysmorphic valve leaflets [114]. Whilst several families have been described with mutations in these genes, they currently explain only a small proportion of cases of mitral valve prolapse, with the causes of the majority of sporadic or familial forms of mitral prolapse remaining unclear.

Conclusions and Perspectives

Despite many important advances to our understanding of the aetiology of valve disease, treatment still relies primarily on surgical intervention. There are currently no available curative or palliative medicines. Any future opportunities for therapeutic intervention will require a better knowledge of the mechanisms leading to congenital malformation of the atrioventricular valves that predispose to adult disease. Developmental transitions from proliferation and expansion of the endocardial cells, to remodelling and elongation of the valves leaflets and supporting tension apparatus, likely involve extensive crosstalk between canonical developmental pathways, for example BMP/TGFβ, Wnt, Notch, and mechanotransduction pathways elicited by blood flow, that remain relatively poorly understood. The generation of novel models using conditional null-mice and delineation of the individual contributing valve cell types will help unravel the mechanisms involved in the post-EMT development of the AV valves. Exome sequencing and studies of structural variation in predisposed individuals may also be important for future pharmacological strategies aimed at maintaining physiological heart function to slow, and maybe eventually prevent, disease.

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Genetics of Mitral Valve Disease

10

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Introduction

Mitral valve prolapse (MVP) is a common disorder, with a prevalence of 2–3% in the general population. It is the most common cause of primary mitral regurgitation requiring surgery [1], making the underlying etiology of this condition of significant interest. As a familial pattern is observed in up to half of cases [2, 3], much work has sought to determine the underlying heritable components that may contribute to this condition. In this chapter, we focus on the genetics of mitral valve prolapse, providing a broad outline of the loci known to be associated with syndromic and non-syndromic forms of MVP, a historical perspective of how some of these loci came to be identified, and a discussion of how these findings have led to novel frameworks for our understanding of at least subsets of patients with this condition. Elucidating the genetic underpinnings of MVP will further our understanding of the biological basis of this disease, and may allow earlier detection of asymptomatic individuals and prediction of disease progression.

Given its prevalence, MVP would be predicted to be a complex polygenic disease trait that adheres to the common disease-common variant hypothesis. Based on the latter, common heritable diseases in the population result from underlying genetic contributors (changes in coding or regulatory sequences of genes or variants) that are also common in the population [4]. According to this model, individual variants

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at disease-influencing genes confer a small additive or multiplicative susceptibility to the expression of the disease phenotype [4]. However, as is the case with many common diseases, a subset of MVP cases cluster tightly within families and follow a Mendelian pattern of inheritance suggesting the presence of rare variants with strong effects on disease pathogenesis [3]. Mendelian inheritance patterns relevant to non-syndromic MVP include autosomal and X-linked dominant, both of which are characterized by a single mutated copy of the causative gene is sufficient to yield the disease phenotype with the latter characterized by the absence of male-to-male transmission. Towards this end, classic genetic linkage analysis led to the earliest detection of the chromosomal locations of disease genes associated with MVP. More recent studies have leveraged next-generation sequencing technologies whose higher throughput have afforded the ability to perform genome-wide association studies (GWAS) as well as the interrogation of all coding sequences (whole-exome sequencing) in affected individuals.

Histology and Pathophysiology of MVP

MVP is characterized by a slow and progressive increase in the length and area of mitral valve tissue leading to thickening of the leaflets, their prolapse in systole beyond the mitral annulus into the left atrium, and associated mitral regurgitation. The extracellular matrix (ECM) constitutes the fibro-skeleton of a normal mitral valve. Normal mitral valve leaflets demonstrate three distinct tissue layers on histologic examination: the atrialis (composed of elastic fibers and directed towards the atrial-facing surface) provides elasticity, the spongiosa (composed of an interwoven network of glycosaminoglycans and proteoglycans within a spongy elastin network making up the middle layer) provides flexibility, and the fibrosa (composed of collagen fibers and directed towards the ventricle) provides tensile strength [5]. MVP is histologically characterized by myxomatous degeneration, a consequence of ECM dysregulation. In myxomatous valves an accumulation of proteoglycans leads to expansion of the spongiosa layer, structural alterations in all collagen components of the valve leaflets, and structurally abnormal chordae containing increased amounts of glycosaminoglycans [6–8].

Genetic Basis of Syndromic MVP

Syndromic MVP (Table 10.1) refers to those etiologies of disease that are thought to be secondary or associated with an identifiable disorder.

MVP as Part of Connective Tissue Disorders

The vast majority of known syndromic forms of MVP can be broadly associated with defects in the transforming growth factor β (TGF-β) superfamily signaling

Table 10.1 Loci or causative genes associated with syndromic and non-syndromic mitral valve prolapse

Syndromic		
Marfan Syndrome	*FBN1*	
Loeys-Dietz Syndrome	*TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD3*	
Juvenile Polyposis Syndrome	*SMAD4*	
Ehlers-Danlos Syndrome	>20 genes (*COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *ADAMTS2*, *FKBP14*, *PLOD1*, *TNXB*)	
Trisomy 18 (Edwards syndrome)	Chr 18	
Trisomy 13 (Patau syndrome)	Chr 13	
Klinefelter syndrome	Chr X	
Tetralogy of Fallot	*JAG1*, *GATA6*, *TBX1*, *GATA4*, *NKX2-5*	
Non-Syndromic		
X-linked Mitral Valve Dystrophy	Chr X	*FLNA*
Autosomal Dominant MVP (MMVP2)	Chr 11	*DCHS1*
Autosomal Dominant MVP (MMVP3)	Chr 13	*DZIP1*
Autosomal Dominant MVP (MMVP1)	Chr 16	–

pathway or important components of the ECM. The TGF-β signaling pathway involves numerous cytokines acting through specific cell-surface receptors to mediate diverse cellular processes including cell proliferation, differentiation, and apoptosis via a number of intracellular signaling molecules [9] while the ECM describes highly dynamic non-cellular component of all tissues and organs that both physically scaffolds cellular constituents and initiates the biochemical and biomechanical cues necessary for appropriate tissue morphogenesis, homeostasis, and physiologic function [10]. Indeed, the ECM and TGF-β signaling pathway are themselves intimately linked, a relationship that is perhaps best exemplified in the context of Marfan syndrome, an autosomal dominant systemic connective tissue disorder that results from mutations in the ECM protein fibrillin-1 [11–13] resulting in cardiovascular, skeletal, and ocular manifestations in affected individuals. TGF-β isoforms are synthesized as precursor proteins that are proteolytically processed and secreted by cells in an inactive form as large latent complexes (LLCs) which are then sequestered by ECM proteins, including fibrillin-1, and rapidly released by proteases in response to physiologic or pathologic cues [14]. In Marfan syndrome, a reduction in fibrillin-1 is thought to result in deficient LLC sequestration and a concomitant excess of TGF-β signaling as has been demonstrated in mouse models of this disease [15]. MVP is frequently seen in patients with Marfan syndrome, with studies describing a widely varied prevalence from 28–80% [16–20]. Furthermore, Marfan syndrome mice demonstrate postnatally acquired myxomatous changes in the architecture of the mitral valve that correlate temporally with increased TGF-β signaling, a phenotype that can be rescued *in vivo* by TGF-β antagonism consistent with a causal mechanism [21]. Loeys-Dietz syndrome is another connective tissue disorder that shares many cardinal features of Marfan syndrome, including an increased

prevalence of MVP [22, 23], and results from mutations in several TGF-β signaling pathway members including TGF-β receptors 1 and 2 (*TGFBR1* and *TGFBR2*), the downstream TGF-β signaling pathway effector mothers against decapentaplegic homolog 3 (*SMAD3*), as well as the cytokines TGF-β 2 and TGF-β 3 (*TGFB2* and *TGFB3*) [24–26]. Mutations in other downstream effectors of TGF-β signaling pathways are also associated with MVP including mothers against decapentaplegic homologue 4 (*SMAD4*) which causes juvenile polyposis [27].

Syndromic forms of MVP are also associated with diseases that result from mutations in critical components of the ECM. Ehlers-Danlos syndrome is characterized by musculoskeletal (hypermobility of joints and muscle hypotonia), cutaneous (elastic and fragile skin), and cardiovascular (vascular aneurysms and valvular lesions) abnormalities [28]. Notably, the clinical Ehlers-Danlos syndrome results from mutations in at least 20 different genes including several different collagen types (*COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*) as well as enzymes that process, fold, or interact with collagen (*ADAMTS2*, *FKBP14*, *PLOD1*, *TNXB*) [29]. At least two large cohort studies of over 200 patients with Ehlers-Danlos syndrome have identified an MVP prevalence of approximately 6% [30, 31]. Notably, neither of these studies classified individuals by the causative molecular lesion for their Ehlers-Danlos syndrome raising the possibility that MVP disproportionately affects a subset of these patients. There is also data suggesting a genetic association between other connective tissue diseases and MVP including pseudoxanthoma elasticum [32], Larsen-like syndrome [33], and Williams-Beuren syndrome [34]. In the case of pseudoxanthoma elasticum, a more recent report using modern imaging technologies has questioned the strength of this genetic association with MVP given its presence in only 3 of 67 patients [35].

MVP as Part of Complex Congenital Heart Disease

Several aneuploidies characterized by multiorgan system anomalies including complex congenital heart disease feature mitral valve architectures that share features common to non-syndromic forms of MVP. Trisomy 18 (Edwards syndrome), which includes micrognathia, rocker-bottom feet, biliary atresia, and profound intellectual disability, is associated with a number of cardiac lesions (atrial and ventricular septal defects, tetralogy of Fallot, double-outlet right ventricle, coarctation of the aorta, bicuspid aortic and pulmonary valves) [36]. Mitral valve abnormalities were noted to be relatively common (66%) in one study of 41 postmortem cases [37] in which the leaflets were noted to be redundant and myxomatous with absent or underdeveloped papillary muscles. Trisomy 13 (Patau syndrome) is characterized by polydactyly, cleft lip and palate, hypotelorism, and microphthalmia as well as congenital cardiac defects including atrial and ventricular septal defects, patent ductus arteriosus, and hypoplastic left heart syndrome [36]. Description of mitral valve morphology in these patients is relatively limited, with a single study of echocardiographic evaluation in 14 patients demonstrating evidence of mitral valve dysplasia and absence of a papillary muscle [38]. Klinefelter syndrome

results from the presence of an additional X chromosome (47,XXY) with affected patients demonstrating a tall stature, small tetes, and delayed puberty with the most common cardiac manifestations being MVP, a patent ductus arteriosus, and atrial septal defects [36]. However, the association between Klinefelter syndrome and MVP has proven more controversial. Two early patient series describing echocardiographic analyses in Klinefelter syndrome reported MVP in approximately 55% of subjects [39, 40], However more recent and larger studies utilizing modern echocardiographic equipment have failed to reproduce these results, with no evidence of MVP identified in 94 patients with Klinefelter syndrome [41, 42]. The association of MVP with isolated congenital heart disease has also been studied. Tetralogy of Fallot, the most common cyanotic congenital heart defect [43], is associated with good long-term survival following palliation, thus allowing for assessment of MVP in adult patients. A single cohort study in 324 adult tetralogy of Fallot patients identified an 8% prevalence of systolic mitral valve abnormalities, with 4.6% demonstrating MVP [44].

Genetic Basis of Non-Syndromic MVP

Pedigree Studies

There is a long-standing appreciation that a subset of non-syndromic MVP (i.e., MVP not associated with other disorders) is inherited in a familial pattern with pedigrees demonstrating both autosomal dominant and X-linked patterns of inheritance with variable penetrance dependent upon both age and sex [45, 46]. Genetic linkage analysis, a powerful tool that allows for detection of the specific chromosomal location of disease genes, led to the identification of four loci associated with non-syndromic MVP [47]. It is important to note that within the category of non-syndromic MVP, two specific phenotypes have been described in the surgical literature [48]. Barlow's disease is associated with diffuse myxomatous degeneration leading to prolapse of most leaflet scallops into the left atrium during systole, severe mitral annular enlargement, and elongated chordae along with histologic evidence of disrupted collagen and elastic layers. Fibroelastic deficiency, on the other hand, is associated with thinned leaflets, mild-to-moderate mitral annular dilation, and thin chordae with histologic evaluation demonstrating decreased connective tissue. Indeed, Barlow's disease and fibroelastic deficiency are themselves associated with different natural histories with the former noted in patients presenting for surgery at young to middle-ages in which chordal rupture is rarely present and the latter in patients present at older age with chordal rupture after a shorter clinical history. These linkage analyses yielded three loci for autosomal dominant non-syndromic MVP and one for X-linked MVP, aptly named myxomatous mitral valve prolapse 1-3 (MMVP1, MMVP2, MMVP3) and X-linked myxomatous valvular dystrophy (XMVD) [47] (Table 10.1).

The earliest description of familial clustering in MVP came in 1969 upon the identification of a pedigree in St. Louis, MO wherein all male members in three

generations of this family exhibited congenital mitral insufficiency, suggesting a X-linked inheritance pattern [49]. Almost 30-years later, a five-generation pedigree of French origin consisting of 92 individuals in which 21 affected individuals had both MVP and a mild form of hemophilia A (a hereditary bleeding disorder that at the time had a known X-linked recessive pattern of inheritance) allowed for the rapid chromosomal mapping of XMVD to an 8 centimorgan region of the Xq28 telomeric region [50]. Detailed clinical features of this pedigree identified full-penetrance in affected males with some moderately affected female patients [51]. This region was later more finally mapped to a 2.5 megabase region with the screening of candidate genes ultimately leading to the identification of a P637Q missense mutation in filamin-A (*FLNA*) as the causative allele. Analysis of three other independent families identified two other missense mutations (G288R and V711D) and a 1944 kilobase in-frame genomic deletion removing exons 16–19 further supporting this conclusion [52]. *FLNA* encodes filamin-A, a large cytoplasmic protein that can function as a molecular tether, linking ECM-bound cell-surface integrins with the actin cytoskeleton [53, 54]. Filamin-A has also been demonstrated to regulate TGF-β signaling by associating with the known downstream TGF-β signaling effector mothers against decapentaplegic homologs 2 (SMAD2) [55]. Homozygous loss of murine *Flna* allele results in mid-gestational embryonic lethality with affected animals demonstrating severe cardiac malformations [56, 57]. Interestingly, immunohistochemical expression analysis of filamin-A in mice demonstrates robust expression during embryogenesis and early postnatal life with significantly reduced expression in the adult [58, 59], suggesting a potential developmental basis in this genetically distinct non-syndromic MVP phenotype. Indeed, tissue-specific deletion of *Flna* in the developing murine atrioventricular valves results in a myxomatous mitral valve phenotype by 2-months of age, a phenotype that likely results from a developmental error in how extracellular matrix is assembled and organized during fetal development [59].

Another family with an autosomal dominant pattern of MVP inheritance was described in 2003 upon identification of the proband as a volunteer in a course teaching echocardiographic imaging [60]. Echocardiograms and DNA were obtained for 28 individuals from this pedigree of Western European descent with 12 diagnosed with MVP, 3 with an intermediate phenotype, and the remaining 13 being unaffected. Linkage analysis revealed that the locus for autosomal dominant MVP in this family lied in a 4.3 centimorgan region on chromosome 11p15.4, which was at that time designated "MMVP2" given that it was the second such locus described. This region spanned approximately 4.45 megabases and, at the time, included several large gaps in sequence coverage and at least 46 genes [60]. The causative mutation was described 12 years later after 4 affected individuals in this pedigree underwent tiled capture and high-throughput sequencing of genomic DNA spanning 2.1 megabases within this locus yielding 4,891 single nucleotide variants and insertion/deletion polymorphisms which, upon filtering for rare variants shared among all affected members of the pedigree, yielded three heterozygous protein coding variants [61]. Two lied in *DCHS1*, a member of the cadherin superfamily of proteins (P197L and R2513H), and one in *APBB1*, the amyloid-beta A4 precursor protein-binding family B member 1 (R481H). In vivo functional assays performed

in zebrafish and mice supported DCHS1 as the causative allele which was confirmed by the identification of two additional families in which MVP segregated with a novel DCHS1 protein variant (R2330C). *DCHS1* is the human homologue of the drosophila gene *dachsous* (*ds*), which serves as a core component of the Wnt/planar cell polarity (PCP) signaling pathway which establishes cell orientation within the epithelial plane [62]. Mice homozygous for inactivating mutations of murine *Dchs1* results in neonatal mortality with multiorgan dysfunction [63]. However, adult *Dchs1* heterozygous mice exhibit mitral valve prolapse that phenocopied what was identified in the originally described proband (pronounced involvement of an elongated posterior leaflet that shifts coaptation anteriorly) with histologic analysis confirming leaflet thickening and myxomatous degeneration [60, 61] (Fig. 10.1). Evaluation valve morphology during embryonic development revealed dose-dependent alterations in the shape and anatomical patterning of the mitral valve, again consistent with a developmentally based disease that progresses over the lifespan of affected individuals.

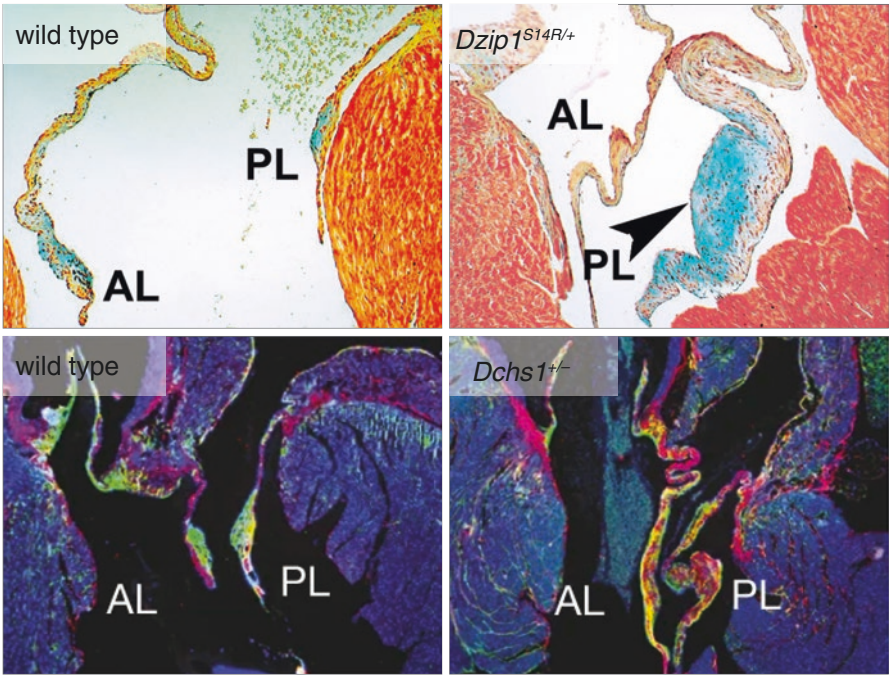

Fig. 10.1 Murine models of non-syndromic mitral valve prolapse recapitulate anatomic and histopathologic findings of human disease. Histologic examination of 6-month old mice heterozygous for a *Dzip1* missense allele identified in non-syndromic familial mitral valve prolapse (MVP) demonstrate dysmorphic posterior leaflets (PL) when compared with wild type littermate controls. Similarly, immunohistochemical analyses of 9-month old mice that are haploinsufficient for *Dchs1* (another allele associated with non-syndromic familial MVP) demonstrate myxomatous degeneration and expansion of proteoglycan expression when compared with wild type littermate controls. (AL = anterior leaflet; red = collagen, green = proteoglycan)

A third family of 46 individuals demonstrating MVP with an autosomal dominant pattern of inheritance was described in 2005 [64]. The proband in this third-generation pedigree of Western European descent was a dentist who self-referred for family analysis of MVP, with 43 individuals undergoing echocardiography and DNA sampling (9 of whom were affected). In this case, linkage analysis narrowed the causative locus to an 8.2 megabase candidate region on chromosome 13q31.3–q32.1 then designated "MMVP3" as it was the third such locus described in the literature. Importantly, this study was the first to demonstrate that minimal displacement or "prodromal" (no diagnostic leaflet displacement beyond the mitral annulus, but with a leaflet closure/coaptation pattern shifted anteriorly resembling that of patients with fully expressed MVP) valve morphologies that were previously classified as normal variants share the same underlying genetic substrate [64]. A subsequent study exploring the role of primary cilia in MVP assessed the linked 8.2 megabase region for candidate genes with known functions in ciliogenesis or cilia signaling, leading to the identification of DAZ-interacting protein 1 (*DZIP1*). Subsequent whole-exome sequencing of four affected individuals from this pedigree revealed a single missense variant in DZIP1 that affects both expressed isoforms (S70R/S24R), representing the only coding change within the linkage interval that segregated with the disease phenotype [65]. As human *DZIP1* and mouse *Dzip1* are highly conserved at the amino acid level, the missense variant identified in this family was introduced into the endogenous murine locus to assess the phenotypic consequences *in vivo*. Adult mice heterozygous for this *Dzip1* missense variant develop myxomatous mitral valves and functional MVP. Further biochemical and molecular analysis on these mutant animals suggested that this *Dzip1* missense variant represents a loss-of-function allele resulting in dysregulation of ECM-associated pathways [65] (Fig. 10.1).

The first genetic locus identified to segregate in an autosomal dominant pattern with MVP ("MMVP1") paradoxically remains the only locus with an unidentified causal gene to date (Table 10.1). The study describing MMVP1 systematically screened first-degree relatives of 17 patients who underwent MV repair yielding 4 pedigrees of varied ethnicities (Ashkenazi Jewish, western France, and eastern France) with a total of 79 subjects undergoing echocardiography and blood sampling, 25 of whom were affected [66]. Genetic linkage studies narrowed the locus to a 5 centimorgan region of chromosome 16 (16p11.2–16p12.1). The causative allele in this setting remains to be identified. The 5 centimorgan region defined by the sequence tag sites D16S3068 and D16S420 identified from these pedigrees span a region of approximately 1.3 megabases [66]. This region contains at least eight protein coding genes along with several long intergenic non-coding RNAs.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) test genetic variants across the genomes of many individuals to identify genotype-phenotype associations and have revolutionized the fields of complex disease genetics, leading to the identification of novel

disease susceptibility genes and biological pathways [67]. As genetic variants are present along a spectrum of allele frequencies and effect sizes, GWAS is best suited for the identification of common variants with small effects, intermediate frequency variants with moderate effects, or highly penetrant rare mutations. Rare variants with small effect sizes are difficult to detect by GWAS while common variants with large effects are not commonly seen in complex disease traits [67]. GWAS in the context of MVP, consisting of a meta-analysis including 2,864 cases and 9,218 controls, identified 6 risk loci that are robustly associated with MVP [68]. These 6 loci implicated four intergenic (*IGFBP5-TNS1*, *SETD4-CBR1*, *PITBNB-MN1,* and *PCNX-SIPA1L1*) and two intronic regions (*LMCD1* and *SMG6*). These candidates were narrowed from an initial list of 53 genes that were located within 500 kilobases to 1 megabase from the lead associated single nucleotide polymorphism (SNP) by taking into account proximity to the SNP, level of cardiac expression, proximity to previously identified GWAS signals for cardiovascular traits, and a biological link with mitral valve or cardiac development [68]. This study highlighted functional data for two of these genes: LMCD1 (a transcription factor known to repress the activity of the critical cardiac transcription factor GATA6) knockdown in zebrafish embryos caused regurgitation of the single atrioventricular valve of the two-chamber heart in these animals while Tensin 1 (a protein that localizes to focal adhesions and interacts with actin) showed sustained expression by immunohistochemistry during murine valve morphogenesis with adult *Tns1*$^{-/-}$ mice demonstrating enlarged mitral valves with evidence of myxomatous degeneration. A follow-up study sought to utilize the same data to identify additional loci that despite not having met the stringent GWAS statistical thresholds ($P < 5 \times 10^8$) may still have biological relevance for MVP by applying computational pathway enrichment tools [69]. This led to the identification of GLIS family zinc finger 1 (*GLIS1*), a Kruppel-like zinc finger protein containing transactivation and repressor functions as a potential susceptibility gene for MVP, supported by its expression of murine *Glis1* in developing valvular endothelial and interstitial cells [69].

Mitral Valve Prolapse: An Unrecognized Ciliopathy?

Primary cilia are microtubule-based solitary organelles that extend from the surface of most vertebrate cell types to receive and process molecular and mechanical signaling cues [70]. Long regarded as an "evolutionary vestige," the primary cilium has emerged an essential signaling hub that coordinates a variety of signaling pathways including those regulated by Hedgehog, G protein-coupled receptors, Wnt, TGF-β, and receptor tyrosine kinases to control developmental processes, tissue plasticity, and organ function [71]. Primary ciliary dysfunction underlies a pleiotropic group of disease and syndromic disorders termed ciliopathies which may affect a number of different organs in the body (e.g., Bardet-Biedl syndrome, Leber's congenital amaurosis, and polycystic kidney disease). Indeed, an association between MVP has long been appreciated in the context of autosomal dominant polycystic kidney disease (ADPKD) [72]. ADPKD patients

have a 10-fold increase in rates of MVP compared with the general population [73, 74]. Furthermore, unbiased forward genetics approaches in mice have revealed a critical role for the cilium and cilia transduced signaling pathways in the pathogenesis of congenital heart disease [75]. As our collective understanding of the biology associated with causative genes for MVP increases, there is a growing body of evidence to support that some forms of non-syndromic MVP are ciliopathies. All three of the known causative genes identified from large linkage analyses for non-syndromic MVP (*DCHS1*, *DZIP1*, and *FLNA*) are intimately involved in ciliogenesis or ciliary function (Fig. 10.2). *DCHS1* (the causative gene identified at the MMVP2 locus) encodes Dachsous-1, a component of the primary cilium. In the context of the MMVP3 locus, the determination that *DZIP1* was the causative allele emanated from a series of experiments exploring the hypothesis that primary cilia may contribute to valvulogenesis [65]. These

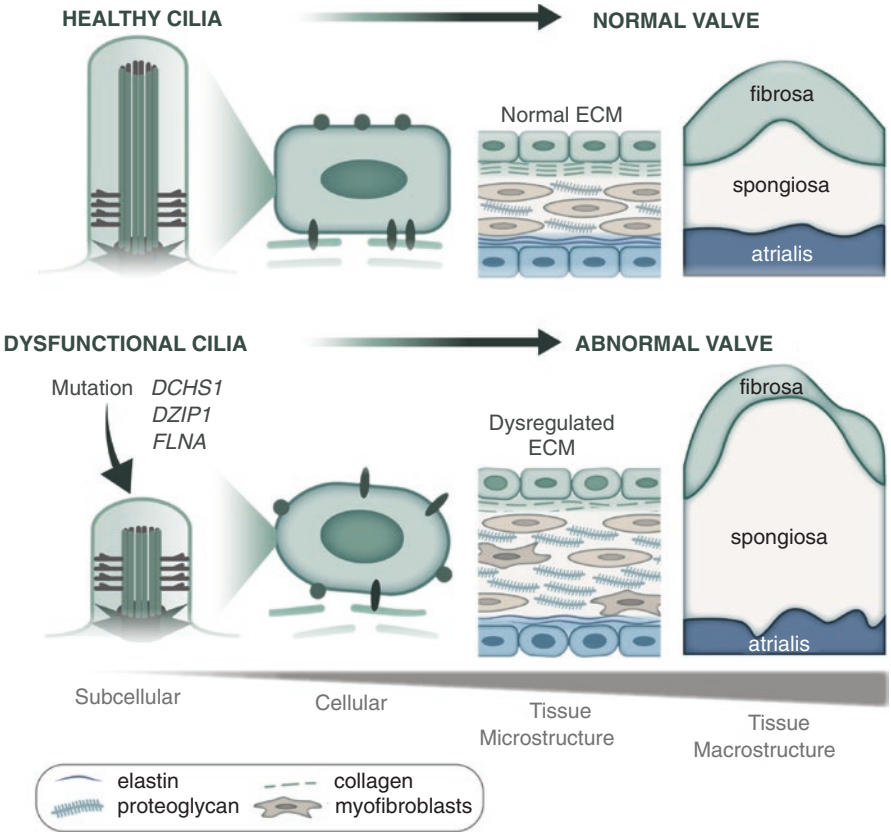

Fig. 10.2 Mitral valve prolapse as a ciliopathy. Primary cilia play a critical role during normal cardiac valvular morphogenesis. Three of the four loci identified as being causative for familial non-syndromic mitral valve prolapse (*DCHS1*, *DZIP1*, and *FLNA*) are all involved in ciliogenesis or ciliary function

studies found that primary cilia are robustly expressed on mesenchymal cells within valve primordia with their length changing over the course of development concomitant with the type of ECM produced within the mitral valves. In fact, the way that *DZIP1* was identified as the causative allele amongst the 16 genes in the MMVP3 locus was through its known role in ciliogenesis and cilia signaling [65]. At the time of its discovery as the causative allele at the *XMVD* locus, *FLNA* was known to associate with downstream effectors of the TGF-β signaling pathway, overactivity of which was thought to contribute to the increased incidence of MVP in Marfan syndrome patients. Subsequent studies have since shown that filamin-A directly interacts with meckelin, a transmembrane receptor that localizes to the primary cilium and basal body (the protein structure at the base of the cilium) [76]. *MKS3*, the gene that encodes meckelin, is mutated in Meckel-Gruber syndrome, a ciliopathy characterized by renal cystic dysplasia, hepatic developmental defects, and severe neurodevelopmental anomalies. Interestingly, studies exploring this filamin-a/meckelin interaction have demonstrated that loss of filamin-A leads to defects in basal body positioning and ciliogenesis [76]. *GLIS1*, the aforementioned gene identified through additional bioinformatic analyses of previously published GWAS data for MVP, has also been suggested to have a potential role in ciliogenesis [77]. A mechanistic basis for how defective ciliary function may lead to MVP was best illustrated by tissue-specific knockout of the ciliogenic gene intraflagellar transport protein 88 (ift88) from endothelial-derived mesenchymal cells in mice *in vivo*. Ift88-loss led to the loss of primary cilia, valve enlargement, and a molecular signal demonstrating robust activation of ECM gene pathways consistent with early stages of myxomatous degeneration [65].

Future Perspectives

Technological Advances

While significant progress has been made in our understanding of the genetic basis for MVP, there remains much to be discovered. Technological advances have played an important role in our ability to accelerate efforts to identify the molecular underpinnings of these diseases which, to date, have yielded important insights into the genes and pathways that ultimately result in an MVP phenotype and a growing recognition that this disease results from primary pathologic insults that occur during development. These findings further underscore that MVP is not a single disease, but instead exists along a phenotypic spectrum wherein a degree of dosage sensitivity conferred by individual risk alleles collectively drive alterations in highly stereotyped and regulated morphogenetic events during cardiac development, likely through a core group of signaling pathways, to yield a mature phenotype that may meet the diagnostic criteria for MVP or instead yield a "prodromal" intermediate [64].

Indeed, technological innovations have changed enormously our approach to understanding the genetic basis of complex disease. Complex and iterative linkage analyses are no longer required as the cost, throughput, and availability of DNA sequencing has significantly reduced the barriers to the application of these cutting-edge technologies. One group recently utilized an exome slice methodology wherein 101 probands with MVP underwent sequencing of the coding regions of 522 genes associated with cardiac development and/or disease [78]. This study found 1 individual with a likely pathogenic mutation in *DCHS1* along with an additional 10 probands with likely pathogenic mutations in six different genes that have been associated with cardiomyopathies (*DSP*, *HCN4*, *MYH6*, *TMEM67*, *TRPS1*, and *TTN*). Increasing the yield of studies of this nature necessitates that unbiased interrogations of coding or non-coding DNA sequences in affected and unaffected populations be linked with very careful clinical phenotyping of each individual. Towards that end, the specificity of echocardiographic diagnosis for MVP was increased significantly upon an improvement of our understanding of the three-dimensional shape of the mitral valve [79, 80]. As echocardiographic imaging technologies continue to improve yielding higher resolution images and the ability to render multi-dimensional projections of cardiac anatomy, we may be able to better categorize MVP into subtypes that will yield a greater signal-to-noise ratio in subsequent unbiased genomic interrogations. Whole-exome sequencing, a methodology wherein the entire protein coding DNA sequence of an individual genome is defined, in carefully phenotyped pedigrees has the ability to reveal novel modes of inheritance for MVP. Oligogenic patterns of inheritance have been suggested in hypertrophic cardiomyopathy [81] and recently shown in the context of left ventricular noncompaction cardiomyopathy [82]. It is also interesting to note that, even within families with non-syndromic MVP who share the same underlying causative genetic lesion, the phenotypic spectrum of disease presentation is quite varied suggesting the existence of unlinked enhancer and/or suppressor loci. Our ability to systematically identify and define these modifier loci will have important prognostic implications for MVP patients with the potential to inform clinical care decisions.

Genetic Discoveries Outside of Coding Regions

A critical challenge in understanding the genetic underpinnings of all inherited disease lies in the assessment of genetic variation outside of coding regions of the genome. As outlined, the most significant loci identified in the GWAS performed for MVP were within intergenic regions of the genome. While intergenic variants from GWAS can lead to incredible discoveries regarding gene regulation and disease pathogenesis [83, 84], examples of this nature are exceedingly rare. Although sequencing the entire genome of an individual has become a relatively straightforward undertaking both in terms of cost and availability, we remain in the nascent stages of our ability to interpret the consequences of variants in non-coding sequences.

Genetic Basis of Sudden Cardiac Death Risk in MVP

Another important finding associated with MVP whose genetic etiology requires further evaluation is the increased risk for sudden cardiac death, which is roughly twice that observed in the general population [85, 86]. Although much of this risk can be attributed to left ventricular dysfunction secondary to severe mitral regurgitation [87], life-threatening ventricular arrhythmias can be seen in MVP patients with even trivial to mild mitral regurgitation [88]. A recent case report described familial segregation of a truncating variant in *FLNC*, which encodes filamin-C (An actin-binding protein necessary for the structural integrity of the sarcomere in cardiac and skeletal muscle cells) with both MVP and ventricular arrhythmias [89]. *FLNC* mutations have been associated with dilated cardiomyopathy [90, 91], hypertrophic cardiomyopathy [92], and restrictive cardiomyopathy [93–95], but not with valvular abnormalities. Whether both the MVP and ventricular arrhythmia phenotypes result from a single genetic lesion as is suggested by this report, or instead results from cosegregation of an independent risk modifier remains to be determined. Uncovering the genetic predisposition to ventricular arrhythmias and sudden cardiac death in the setting of MVP is an important area for future investigation.

Conclusions

MVP is a common, highly heritable phenotype and is associated with important clinical sequelae including severe mitral regurgitation and sudden cardiac death. Multiple genes have been identified from pedigree investigations and GWAS studies of individuals with MVP and have been linked to abnormal valve embryogenesis and cell differentiation, ultimately leading to ECM dysregulation and myxomatous degeneration of the mitral valve. As our collective understanding of the biology associated with causative genes for MVP increases, there is a growing body of evidence to support that some forms of non-syndromic MVP are ciliopathies. Indeed, all three of the known causative genes identified from large linkage analyses for non-syndromic MVP (*DCHS1*, *DZIP1*, and *FLNA*) are intimately involved in ciliogenesis or ciliary function. Genetic discoveries overall have exponentially accelerated our understanding of MVP. However, many questions remain unanswered in relation to MVP pathophysiology, clinical progression, and therapeutic options. Future studies are needed to address these important issues.

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Genetics and Genetic Counselling Relevant to Mitral Valve Prolapse

11

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Introduction

Mitral valve prolapse (MVP) is the most prevalent valvular abnormality worldwide, with atrial displacement of either the posterior, anterior, or both leaflets, and is usually benign without any long-term sequelae [1]. In some cases, it results in sufficient incompetence manifesting with symptoms, or the regurgitation is severe to warrant intervention because of secondary structural abnormalities, and in some cases, there is an association with ventricular arrhythmias and sudden cardiac death (SCD) [2, 3]. Multiple studies show a familial component in approximately one-third of cases prompting research into genetic heritability [4, 5]. The observed family history can be higher in MVP associated with other syndromic (usually monogenic) conditions, such as aortopathies, connective tissue diseases, and dilated cardiomyopathy. Herein we describe the genetics of MVP and aspects of counselling for probands and family members [4–6].

Genetics

Broadly speaking the clinically relevant genetics of MVP can be considered in the context of one of the following 4: (1) Syndromic conditions without connective tissue disease; (2) Syndromic conditions with connective tissue diseases (CTD);

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(3) MVP and arrhythmia in genes associated with non-ischaemic cardiomyopathies or ion channel diseases; and (4) Multi-factorially inherited with certain single nucleotide polymorphisms (SNPs) [7]. Each of these associations can manifest with a range of phenotypes, including multi-system involvement where MVP is one component, or with predominantly cardiovascular (CV) manifestations, or as a result of cascade clinical family screening. The patient can thus take very different trajectories and the patient journey can mean contact with cardiologists and cardiac surgeons may be late when the clinical and genetic evaluation has already taken place, or, may be early in the disease where CV manifestations are the only features, and this should prompt an evaluation to ensure there are no syndromic associations and no features of CTD. Clinical guidelines acknowledge the high familial pattern of MVP, which may be genetic for e.g. trisomies 18 (Edwards syndrome), 13 (Patau syndrome), and 15, or Mendelian CTD which are usually autosomal dominant. However, in the absence of these syndromes and CTDs, MVP can still show a familial pattern, and guidelines recommend cascade clinical evaluation of family members [8, 9].

The current known genes and single nucleotide polymorphisms are summarized in Fig. 11.1 [7].

Syndromes associated with connective tissue disease include Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Williams-Beuren syndrome, Pseudoxanthoma elasticum, Larsen-like syndrome, and Borrone dermato-cardioskeletal syndrome. These are discussed in Chap. 10 on genetics and reviewed elsewhere [7].

Familial MVP

In addition to the high observed prevalence of MVP in syndromic genetic conditions, isolated familial forms of MVP have long been recognised. The first published report suggested an X-linked recessive inheritance with only male phenotypic expression in a 3-generational family with polyvalvular disease [10]. Subsequent familial studies have suggested 60% heritability, with notable age- and sex-dependent phenotypic expression and reduced penetrance. These studies support autosomal dominant inheritance, with linkage studies identifying three loci: MMVP1, MMVP2, and MMVP3.

MMVP1 was identified through linkage study mapping to chromosome 16p12.1–p11.2, although the gene and protein remain elusive [11].

MMVP2 in a 5-generation family mapped to locus 11p15.4, following which a missense variant (p.R2513H) in the *DCHS1* gene was discovered in the same family. This variant was found in an unrelated family who also expressed MVP. The gene product is a signal peptide belonging to the cadherin family with loss of function impairing cell polarity during valve development in mice [12].

MMVP3 was identified in a 3-generation family with MVP and linkage to chromosome 13q31.3–q32.1 [8]. The gene and protein were unknown until a recent publication describing a deleterious missense mutation in a cilia gene, *DZLP1* [13].

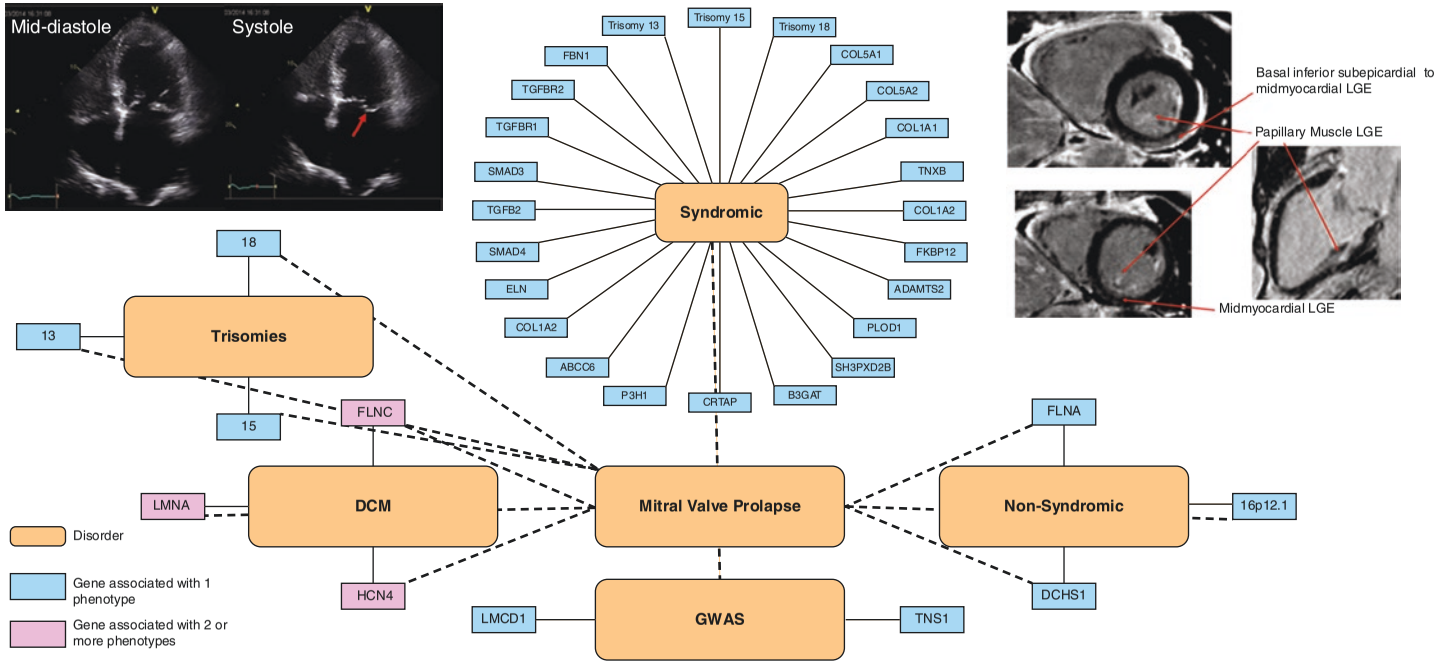

Fig. 11.1 Schematic of the complexities of MVP genetics [7]. The implicated genes have been organized into those associated with syndromic conditions and a higher frequency of MVP than that seen in the general population, those associated with familial non-syndromic forms, and genome-wide association studies. The red arrow on the apical four-chamber two-dimensional echo tracing in late systole shows the posterior mitral valve leaflet prolapsing into the left atrium. The red arrows on the T1 late gadolinium enhancement images point to areas of hyperenhancement indicating fibrosis in cases of MVP with ventricular arrhythmias

The authors functionally validated their findings in a mouse model which developed myxomatous MVP as an adult, and then validated findings in a large human cohort of MVP with a GWAS study, identifying cilia gene variants.

In a family with X-linked inheritance, there was a P637Q mutation in the *FLNA* gene [14]. More recently, families with muscular dystrophy and MVP have been described. The type of MV prolapse is unusual and may be unique to *FLNA*-related MVP: myxomatous leaflets with paradoxical restriction of leaflet motion in diastole.

Cardiomyopathies and Ion Channelopathies (FLNC, LMNA, HCN4, *SCN5A*)

Genetics of non-ischaemic dilated cardiomyopathy (DCM) is complicated with wide phenotypic expression, with a certain subset having a higher propensity for arrhythmia [15]. These arrhythmia prone DCMs have been recognized as left-dominant arrhythmogenic cardiomyopathies, as well as being described as arrhythmogenic DCM. Recently, left ventricular non-compaction (LVNC) and sinus node dysfunction with MVP have been described in persons with *HCN4* variants [16]. The *FLNC* gene encodes for gamma filamin which crosslinks actin filaments—defects in FLNC cause skeletal myopathy and truncating variants have recently been recognized as causing arrhythmias and DCM. The frequency of MVP and the association with SCD, MVP, and cardiomyopathy-related genes are unknown and an active area of research. Recently *SCN5A* and *LMNA* pathogenic variants were reported in unrelated families with arrhythmic MVP [17, 18]. Recognized risk factors for sudden cardiac death in MVP include the following: female sex, family history of sudden death, documented ventricular tachycardia, ventricular premature complexes, syncope, T wave inversion in the inferior leads, fibrosis (at post-mortem or on cardiac MRI with late gadolinium enhancement of the papillary muscles, basal LV segments), Pickelhaube sign (on lateral wall tissue Doppler), high strain, mitral annular disjunction, curling and paradoxical septal annular expansion. Thus, it is foreseeable that MVP with arrhythmia and structural abnormalities, a family history of sudden cardiac death, may become an indication for clinical genetic testing.

Sporadic and Common MVP

The vast majority of MVP is multi-factorially inherited, and do not meet clinical indications for genetic testing. Genome-wide association studies have been performed, given the large familial component observed, and have identified 7 significant loci [19, 20]. Of these, two candidate genes were discussed: *TNS1* on Chr2 and *LMCD1* on Chr3 [21]. Both genes have plausibility with a role in valvular development, although further genomic and functional studies are essential to discern their implication in the genetic risk of MVP, and to identify causal genes in the remaining associated loci. More powerful association studies are likely to

identify additional risk loci and serve to build MVP polygenic risk score with potential clinical use.

Genetic Counselling

Counselling is a crucial component prior to any form of genetic testing to ensure relevant aspects are discussed *a priori* to requesting tests, rather than addressing potential issues that can arise after the test results are returned. The increased availability of multiple private companies offering clinical tests and direct-to-consumer tests have made availability better than it has ever been. This coupled with decreasing costs and a patient-driven desire to know have increased demand for genetic counselling. This is usually provided by genetic counsellors, who are specialized healthcare professionals with dual training in medical genetics and counselling, bridging the gap of genetic testing and interpretation for probands, family members, and clinicians (Table 11.1). However, the increased demand on genetic counsellor services means these are not always available and counselling can be delivered by any competent member of an inherited cardiovascular clinic. In addition to providing expertise in cardiac genetics and psychosocial aspects of counselling, genetic counsellors often also re-evaluate genetic test results at follow-up for variants which

Table 11.1 Summary of roles of genetic counselling services

Risk assessment	• Collect detailed medical and multi-generational family history • Assess the risk of inherited cardiovascular conditions in probands and family
Education	• Describe features, risk factors, and genetics of inherited cardiovascular conditions • Discuss screening, prevention, and management options relevant to the suspect conditions(s)
Genetic testing	• Identify and coordinate appropriate genetic test options • Discuss the benefits and limitations of genetic tests • Address concerns over out-of-pocket costs and insurance (private or state) coverage • Address concerns over "luxury" insurance and potential discrimination
Result interpretation	• Review literature, curation panel data, and laboratory information to provide accurate, contemporary information • Collaborate with providers to apply genetic information to probands and family members
Result disclosure	• Explain genetic test results and implications for patient and family • Provide written documentation for probands, families, and providers
Patient-centered counselling	• Address patient and family concerns regarding the condition • Discuss implications for family planning and reproductive options when relevant • Facilitate family communication about diagnosis and testing options • Identify resources for additional support and information

Modified from Arscott et al. [22]

Table 11.2 Benefits of including a genetic counsellor in the inherited cardiovascular conditions team

Domain	Selected examples
Clinical efficiency	Time saving for the busy cardiologist (before, during, and after the clinic): • Request and review appropriate family records (autopsy reports, genetic test results, screening evaluations, etc.) • Facilitate efficient genetic testing (appropriate sample, paperwork, billing process) • Navigate post-mortem genetic testing cases (sample retention, communication with coroners, DNA banking, etc.)
Keeping current	Ongoing knowledge of changes in: • Genetic testing options • Dynamic interpretation of genetic variant • Availability of appropriate research studies • Updated practice guidelines for inherited arrhythmias
Specific expertise	Contributes unique knowledge to care team: • Gene/variant level knowledge • Familiarity with scenarios affecting test selection • Communicating detailed genetic test results • Awareness of family planning options
Interpersonal communication	Enhanced connection with patient family: • Communicate with patients and other members of the multidisciplinary team • Establish rapport with patients and their families • Demonstrate an understanding of family and cultural values with regard to genetic testing • Instill confidence in care team and increase adherence to recommendations • Empower families to play active role in their care
Patient support	Serve as patient advocate: • Promote informed decision making • Assessment of competency to consent, supporting vulnerable people (e.g. children and those with mental health issues) • Provide psychosocial counselling • Identify and refer to local and national support resources • Facilitate communication for appropriate family care (written letters, referrals to other specialized centres, etc.)
Liability	Reduce liability for the health care team: • Provide and document informed consent for genetic testing; document genetic testing results and recommendations • Integrate family history and genetic testing information into patient care • Discuss concerns regarding genetic discrimination, particularly with predictive genetic testing

Modified from Spoonamore and Ware [23]

may have been re-classified, as well as providing input to variant curation panels. Clinical practice guidelines, consensus, and scientific statements incorporate genetic counselling into their recommendations to provide these additional services (Table 11.2).

Definition of Genetic Counselling

The National Society of Genetic Counsellors defines genetic counselling as the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease [24]. The process integrates the following:

- Collection of detailed family history; its interpretation to assess the risk of disease occurrence or recurrence.
- Education of the probands and family regarding inheritance, testing, management, minimizing risk, resource availability, and research.
- Counselling to promote informed choice and where applicable interventions.

Genetic counselling can occur at differing time points including pre-conception and older age. Most consultations will be outpatient based involving cardiologists, paediatrics, and sometimes the obstetrician (for pre-conception or prenatal).

Generation of Referrals for Genetic Counselling

Clinical genetic testing for isolated MVP is not recommended. However, there are a number of scenarios where genetic testing may be indicated:

- Patient with MVP and suspected syndromic conditions.
- As part of evaluation for suspected aortopathies and connective tissue disorders in both probands and family members.
- Probands with MVP and other structural abnormalities such as a cardiomyopathy.
- Probands with MVP who have survived a cardiac arrest.
- Pathology services evaluating sudden unexpected death cases with MVP.
- Family members of patients with sudden death where aortopathy, connective tissue disease, inherited arrhythmia or cardiomyopathy suspected, which may have MVP.

Clinical Evaluation of Family Members

Clinical cascade evaluation can be done with focused clinical examination auscultating for mid-systolic click and pan-systolic murmur. Echocardiography, once expensive and difficult to obtain is now widely available. A limited study with two views parasternal long axis and apical 4 chamber can be sufficient to assess for MVP in an adult adequately hydrated patient. Handheld ultra-sound can make this very easy to do rapidly, without sending patients to cardiac echocardiography laboratory, and can be done in outpatient settings. The main reasons guidelines do not recommend evaluation of family member's is the cost-effectiveness, lack of data supporting use. Guidelines do recommend family members of patients with bicuspid aortic valve are evaluated but do not mention MVP [25, 26]. However, it is our usual practice to take a minimum three-generational family history, explain to the patient the familial nature of both MVP and sudden cardiac death, and recommend adult first-degree family members undergo a single clinical evaluation for MVP. Guidelines may change to reflect this in the future as increasing evidence is published.

What Should Be Included in Counselling

Genetic counselling usually involves three phases: pre-test counselling, testing, and interpretation of results, which are best delivered in a centre with experience in diagnosis, management, and prognostication of inherited cardiovascular conditions. The discussion should include a comprehensive medical and family history (including multi-generational pedigree, obtaining medical records, clinical test results, post-mortem reports, and death certificates) advantages and disadvantages of proceeding with genetic testing, availability of types of genetic tests, risks and benefits of each type of test, incidental findings and return of results, and options for research studies where no pathogenic variant is found (Table 11.1). Once this has taken place and appropriate time provided to process information, the appropriate test can be selected and biospecimens provided (usually blood sample but cheek swabs are reliable alternative).

Once test results are back, a follow-up visit should be arranged, and return of results should take place, as agreed prior to sending biospecimens. For example, if whole exome sequencing is used, and agreed to not disclose incidental findings, then this should not be brought up. The return of results is usually limited to pathogenic or likely pathogenic results. However, a great proportion of tests are returned under the variant of uncertain or unknown significance (VUS) and these are not usually disclosed. Disclosure can require that this be placed on the medical records. Reclassification of variants should be discussed which may include research-based functional studies as well as testing selected family members to determine co-segregation of the variant with phenotype. This is a powerful tool to aid with variant reclassification of VUS to benign or pathogenic. Thus, the role of the genetic counsellors and genetic testing in a multidisciplinary inherited cardiovascular conditions clinic occurs at different stages on the patient's journey (Fig. 11.2).

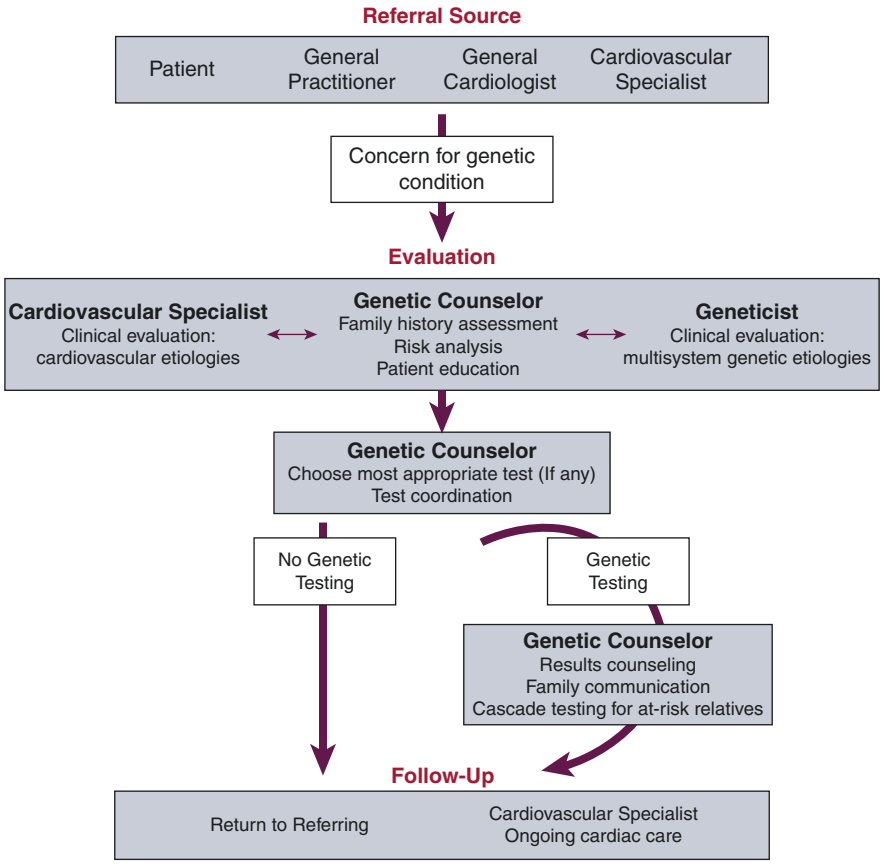

Fig. 11.2 Main roles of genetic counsellors (modified from Arscott et al. [22])

Types of Genetic Tests

The types of genetic tests available is dependent on appropriate local laboratory services, as well as services offered by private companies. This ranges from classic Sanger sequencing (one nucleotide at a time) to next generation (massively parallel) sequencing which can be a targeted panel, whole exome (WES), or whole genome sequencing (WGS). Dependent on the country, not all next generation WES or WGS are approved for clinical testing, and validation with a clinical test is sometimes required. In the USA, a clinical test has to be Clinical Laboratory Improvement Amendments (CLIA)-approved, and in the UK has to be in a Clinical Pathology Accreditation (CPA)-approved laboratory. The over-arching principle in selecting a genetic test is based on pre-test probability. Whilst, requesting an increasing number of candidate genes may intuitively increase the likelihood of identifying a causative pathogenic variant, it also increases the likelihood of genetic noise and VUS. Thus,

the selection of the type of genetic test has to be carefully balanced understanding the breadth and depth of commercial tests available.

There is also a large discrepancy with test results depending on the vendor, the technique, the sequencing platform, and variant classification. In 2015, the American Council of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) proposed classification of variants into 5 classes: Pathogenic (Class 5) >95%, Likely Pathogenic (Class 4) >90%, Variant of Uncertain significance (Class 3) 10–90%, Likely Benign (Class 2) <10% and Benign (Class 1) <5% [27]. The laboratory will provide a classification but this is often with a disclaimer that requires additional evaluation and should be interpreted in the clinical context i.e. requires accurate phenotyping of the probands family members. Thus, clinicians will reclassify the variant based on additional data, and many genetic counsellors contribute actively to variant classification in multidisciplinary clinics.

Most hospitals and private companies now use next generation technologies and focus on a selected panel of tests. For MVP, this will be driven by the associated syndromic, aortopathy, connective tissue disease and in rare cases with a personal and/or family history of sudden cardiac death. Best practice is to confirm any genetic sequence identified with next generation tests with Sanger sequencing. Laboratories also commonly offer tests for larger chromosomal deletions or duplications, which can be missed by typical polymerase chain reaction-based sequencing approaches.

If a candidate gene or panel test returns negative, then there are a number of options for further genetic testing. Again, this will be driven by the suspected clinical phenotype with regards to MVP. The first line is to do an extended panel which can usually be done with the same initial sample. If this returns negative, then approaches include WES and WGS. Whole exome sequencing includes all of the approximately 20,000 human genes and represents approximately 2% of the human genome. This can be combined with "parent-proband trios" to help narrow down the list of candidates to *de novo* mutations. The approach can also be used with one affected family member and an unaffected parent to perform a 'trio' to triangulate down to candidate variants seen in the affected individuals and absent in the unaffected individual. With MVP this can be used for cases where MVP and arrhythmia are frequent as recently identified in a family with MVP and a novel truncating variant in the *FLNC* gene which cosegregated with the disease [28].

When WES does not yield a candidate variant, WGS approaches can be used. Although WES implies all of the exome is sequenced, this is not the case, as enrichment steps target approximately 96–98% of the WES. Thus, WGS will cover the entire exonic regions and intronic regions that may be involved with exonic splicing. However, WGS has lower depth of coverage (this refers to the number of times a genomic region is read or sequenced). For WES the minimum standard, 30x, which refers to the number of times a nucleotide is read during sequencing to avoid sequencing errors. The coverage varies between laboratories and the platform used.

Utilizing WES or WGS can lead to large amounts of VUS being identified which are not clinically meaningful without functional validation, which becomes near impossible for a single case with hundreds of VUSs. Analysing the entire WES or WGS can also increase the likelihood of incidental findings, some of which are

actionable. The ACMG updated a policy on reporting of incidental findings in 2016, which includes 59 actionable genes, many of which are related to cardiomyopathies and Aortopathies [29]. These scenarios emphasize the importance of thorough pre-test evaluation, counselling, and informed consent, so that potential scenarios, outcomes, and impact on management to the individual and family have been thoroughly prepared for.

Conclusions

The vast majority of MVP cases are multi-factorially inherited and no indications for clinical genetic testing exist. Patients may undergo direct-to-consumer tests, which may identify some recognized SNPs associated with MVP. It is important to note that the yield is highly dependent on the type of GWAS testing chip used. Given MVP is associated with aortopathies and connective tissue diseases, this is the most likely way that patients with MVP will be referred for genetic testing. In some familial cases with an arrhythmia component and/or SCD history, these may have dual pathologies of MVP with a form of non-ischaemic cardiomyopathy and propensity for arrhythmia. These cases either as survivors of SCD events, or family members with a relative with MVP and SCD, may seek out genetic testing. The evaluation of these cases should be at specialist centres with expertise in deep phenotype. The selection of genetic tests available should then be carefully considered, with pre-test genetic counselling, explaining the complexities, potential results, implications for management to the probands and family members. Ideally the process should be delivered with the assistance of genetic counsellors; however, where this is unavailable, this can be provided by clinicians competent and experienced with inherited cardiovascular conditions.

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Assessment of Mitral Valve Function: The Valve and The Ventricle

12

Madalina Garbi and Francis C. Wells

The function of the mitral valve is assessed primarily with echocardiography, a readily available imaging modality that provides qualitative and quantitative morpho-functional data [1]. The understanding of the mitral valve has been progressively advanced by echocardiography, because it allows live observation of the valve and heart in motion, by comparison with the fixed end-diastolic state observed at the time of surgery and the fixed end-systolic state-observed post-mortem by anatomists and pathologists. Further morpho-functional information can be provided by cardiac magnetic resonance imaging and cardiac computed tomography.

Characterisation of Mitral Valve Function

The assessment of the mitral valve function begins with characterisation of the dysfunction as regurgitation, stenosis, or mixed. The assessment of mitral regurgitation begins with the assessment of anatomic integrity of the valve components, to define the type of regurgitation: primary or secondary. Often a primary and a secondary mitral regurgitation component coexist, because of dilatation of the left ventricle and/or of the left atrium as a result of a degree of primary mitral regurgitation. When both a primary and a secondary mitral regurgitation component coexist, the mitral regurgitation is classified and managed as primary. This is because of the fundamental role of valve intervention in the management of primary mitral regurgitation, whilst the management of secondary mitral regurgitation begins with medical treatment. Primary mitral regurgitation is a disease of the mitral valve, which fails to prevent back-flow in systole and consequently affects the left ventricle and the left

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atrium. On the contrary, secondary mitral regurgitation is a disease of the left ventricle or/and of the left atrium that can affect the function of the mitral valve. This chapter will focus on primary mitral regurgitation.

In primary mitral regurgitation, one or more valve components have abnormal morphology and function. Morphologic abnormalities of the mitral valve leaflets are characteristic not only for the primary nature of the regurgitation but also for the specific aetiology of the disease.

Degenerative mitral valve disease is the most common cause of primary mitral regurgitation [2] and it comprises mitral valve prolapse and/or flail mitral valve leaflet as regurgitant lesions. The congenital aberrations in the formation of the mitral valve related with this condition are described in the chapters on mitral valve development. In degenerative mitral valve disease two-dimensional (2D) or three-dimensional (3D) transthoracic or transoesophageal echocardiography can detect focal or extensive thickening of one or both mitral valve leaflets, systolic displacement within the left atrium (prolapse) of one or more scallops together with the respective coaptation point, elongation of cords and/or ruptured cords with consequent flail leaflet segment having the leaflet tip everted in the left atrium in systole. It is important to highlight that systolic displacement of leaflet tissue into the left atrium without concomitant displacement of the coaptation point does not represent valve prolapse; if leaflet coaptation is preserved, it only represents functionally insignificant bowing of the leaflet. This is referred to as billowing of the leaflet and is classically seen in mitral valve with Barlow Disease, though it is commonly seen in the isolated mural leaflet prolapse also (Fig. 12.1). The extent of leaflet abnormalities in "degenerative" mitral valve disease covers a wide spectrum and abnormalities of dimensions, shape, and function of the atrio-ventricular junction, known as "mitral valve annulus," may coexist (Fig. 12.2). Flail leaflet segments are often seen in valves with otherwise normal leaflet thickness, preserved shape of the annulus, and annular dilatation of a lesser degree. Similarly, focal leaflet thickening and prolapse of one only mitral valve scallop can present with preserved saddle shape of

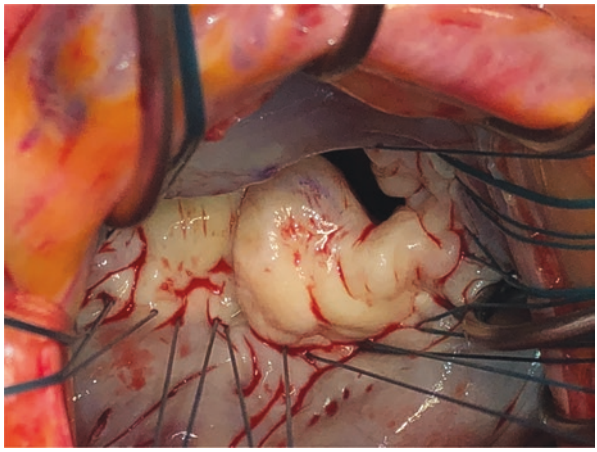

Fig. 12.1 Mitral valve with significant billowing of the mural leaflet with excessive amounts of tissue in the belly of the leaflet, as seen at the time of surgery from the left atrium (surgical view)

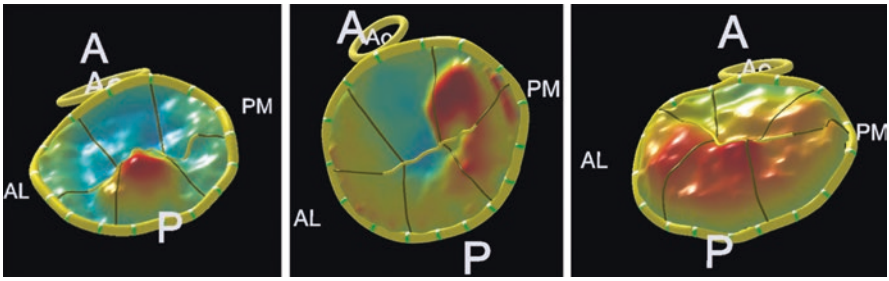

Fig. 12.2 Three-dimensional echocardiography mitral valve model demonstrating the spectrum of mitral valve leaflet pathology in degenerative mitral valve disease. The left-sided image demonstrates mural (posterior) mitral valve leaflet prolapse at the central scallop P2. The central image demonstrates more extensive prolapse involving particularly the medial scallop of the mural (posterior) leaflet P3, the medial commissure, and the medial scallop of the aortic (anterior) leaflet A3. The right-sided image demonstrates extensive mitral valve tissue redundancy and prolapse of both leaflets and all scallops as well as of both commissures, as well as a remodelled, circular and flat, mitral valve annulus corresponding to Barlow Disease

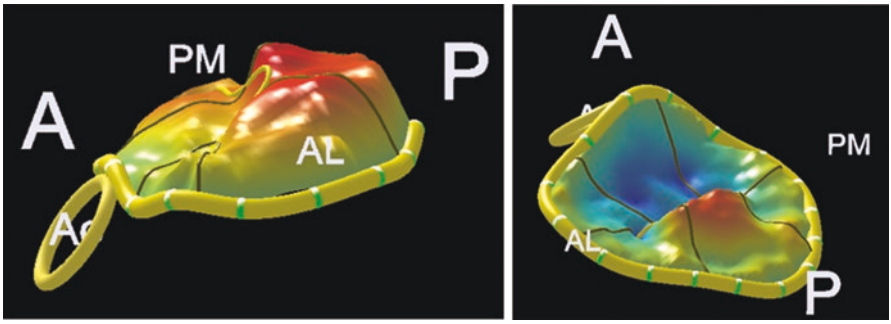

Fig. 12.3 Three-dimensional echocardiography mitral valve model demonstrating the preserved saddle shape of the mitral valve annulus in patient with limited mitral valve prolapse at P2 (right-sided image) and flattened remodelled annulus in patient with Barlow Disease (left-sided image)

the mitral valve annulus (Fig. 12.3). Prolapsing scallops have redundant tissue and/or elongated redundant cords. The scallop most likely to prolapse is the central scallop of the mural (posterior) leaflet; this scallop has the largest circumferential length and the least support [3]. Paucity of cords and/or papillary muscle displacement as well as interruption in the leaflet development which prevents the leaflet from being able to spread the load it is subjected to contribute to the higher incidence of prolapse of this scallop. Extensive leaflet thickening and prolapse of both leaflets and all scallops is usually associated with dilatation, circular remodelling, and flattening of the mitral valve annulus, with loss of the saddle shape (Barlow Disease of the mitral valve) [4] (Fig. 12.3). A dynamic annular saddle shape is needed to evenly distribute the stress and strain in the aortic mitral valve leaflet in

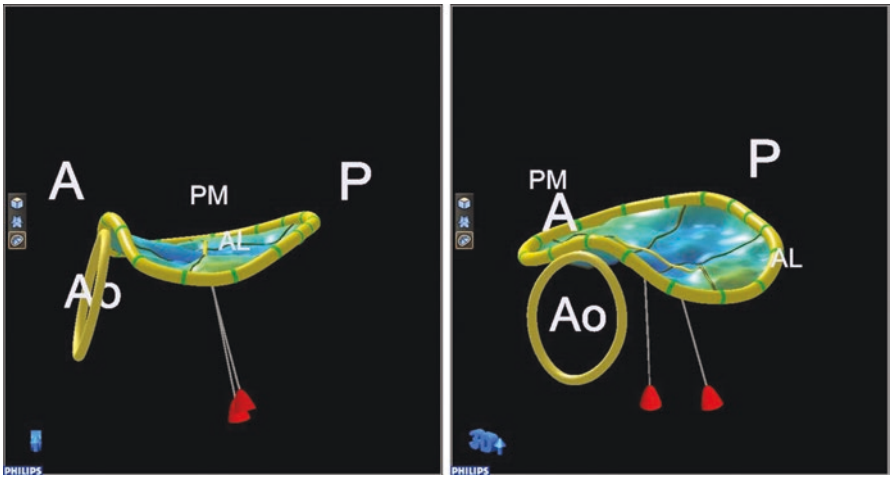

Fig. 12.4 Three-dimensional echocardiography mitral valve model demonstrating the normal saddle shape of the mitral valve annulus, meant to ensure a smaller projected mitral valve area for the mitral valve leaflets to cover in systole and less leaflet stress. The annulus bends in systole, accentuating the saddle shape and further reducing the projected mitral valve area

systole; it is also needed to reduce the atrio-ventricular junction area to be covered by the mitral valve leaflets in systole, facilitating effective leaflet coaptation (Fig. 12.4). This dynamic shape is the result of the increase in pressure in the left ventricular outflow tract which is cylindrical, resulting in antero-posterior annulus bending accentuating the saddle shape in systole. The systolic reduction in the atrio-ventricular junction area is also due to contraction of atrial muscular fibres at end-diastole, similar to a sphincter mechanism. The sphincter mechanism is lost in atrial fibrillation with the loss of atrial depolarisation, explaining worsening or primary mitral regurgitation severity during atrial fibrillation and also explaining the development of atrial-secondary mitral regurgitation during paroxysms of atrial fibrillation, in patients without primary mitral valve disease. Similarly, flattening of the mitral valve annulus throughout the cardiac cycle in extensive forms of mitral valve prolapse (Barlow Disease) contributes to the mitral regurgitation severity. An accurate assessment of the mitral valve annulus linear dimensions (antero-posterior and intercommissural), circumference, and area can be obtained with cardiac computed tomography (Fig. 12.5).

The dilatation of the mitral valve annulus as part of the degeneration of the valve or as consequence of left atrial dilatation as a result of mitral regurgitation with or without coexistent atrial fibrillation, opens up deep indentations or clefts in between the scallops of the mural (posterior) mitral valve leaflet and these can contribute to mitral regurgitation. Three-dimensional echocardiography facilitates the detection of regurgitant indentations and clefts (Fig. 12.6). Where surgical resection of the prolapsing portion of the leaflet is employed the subsequent suturing together of the cut leaflet edges will pull on the edges of the indentations and this will produce a secondary leak if not attended to.

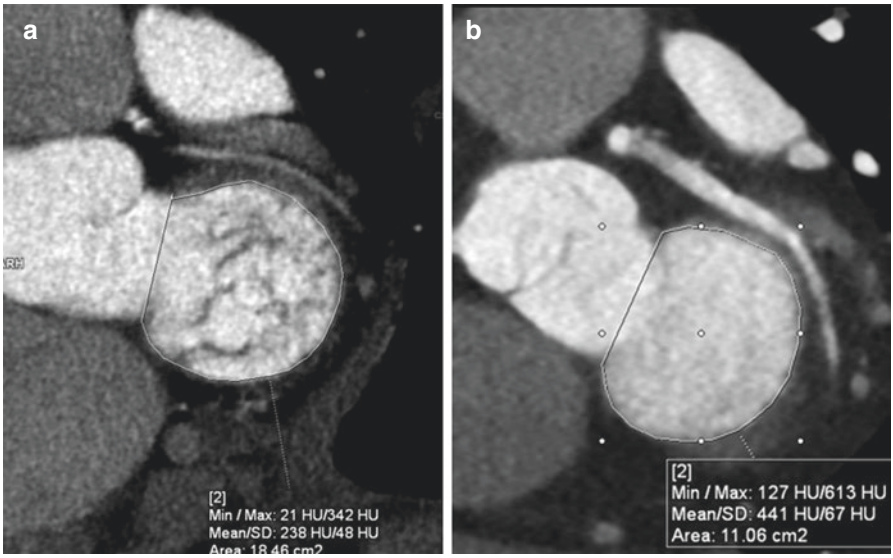

Fig. 12.5 Cardiac computed tomography assessment of the mitral valve annulus. The annulus on the right-sided image is normal in dimensions and shape, whilst the annulus on the left-sided image is dilated and circularly remodelled with increased antero-posterior diameter (Barlow Disease). (Image courtesy of Dr. Jonathan Weirmccall, Royal Papworth Hospital)

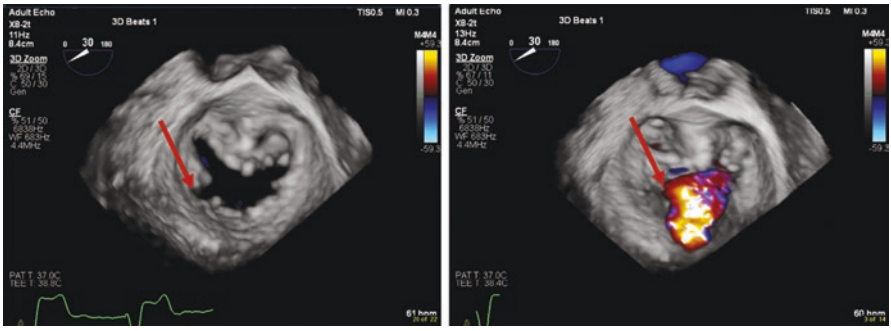

Fig. 12.6 Three-dimensional echocardiography datasets demonstrating cleft in between the lateral and the central scallops of the mural (posterior) leaflet (left-sided image) contributing to the mitral regurgitation mechanism (right-sided image demonstrates enhancement of regurgitation at the level of the cleft)

Mitral annular calcification, known abbreviately as MAC, is often present not only with advanced age but also in younger individuals with Barlow Disease. Mitral annular calcification alone can be the cause of mitral regurgitation with or without associated mitral stenosis as part of a calcific degeneration of the mitral valve similar with the calcific degeneration of the aortic valve resulting in aortic stenosis. When present, in any of the above-mentioned scenarios, mitral annular calcification

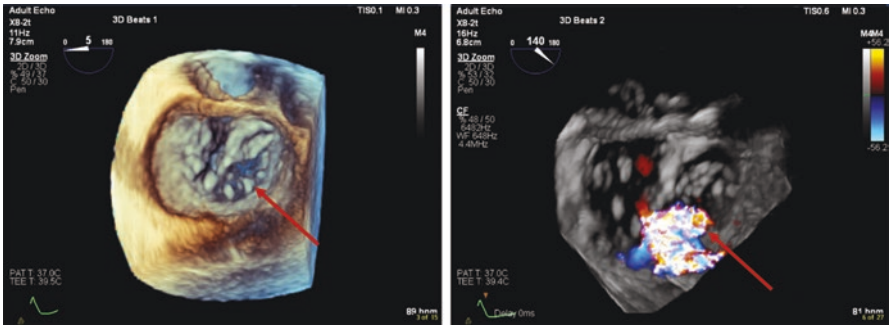

Fig. 12.7 Three-dimensional echocardiography datasets demonstrating retraction of the posterior mitral valve leaflet at the level of the medial scallop of the mural (posterior) leaflet P3 in patient with prolapse of the aortic (anterior) mitral valve leaflet central scallop A2 shown by red arrow in the left-sided image, accentuating the mitral regurgitation on the medial aspect (shown by the red arrow in the right-sided image

contributes to the mitral regurgitation mechanism by impacting the dynamic properties of the mitral valve annulus and by infiltrating and provoking retraction of adjacent mitral valve leaflet tissue and consequently restricting the coaptation of the respective leaflet in systole (Fig. 12.7). The degree and extent of mitral annular calcification can be assessed with three-dimensional echocardiography (Fig. 12.8) and, more precisely, with cardiac computed tomography (Fig. 12.9).

Although the term "mitral valve annulus" simply describes the atrio-ventricular junction rather than a distinct mitral valve structural component, mitral annular disjunction is often reported on imaging (cardiac magnetic resonance or echocardiography) in patients with degenerative mitral valve disease, with or without significant mitral regurgitation. Measurements of "mitral annular disjunction" actually represent measurement of the leaflet prolapse depth, or, in other words, measurements of the systolic displacement of the prolapsing leaflet within the left atrium. Pronounced prolapse, extensive around the valve circumference and with a large prolapse depth is common in patients with Barlow Disease, explaining the more common reports of "mitral annular disjunction" in these patients (Fig. 12.10).

Mitral regurgitation is the result of ineffective coaptation of the leaflets. A Doppler calculated effective regurgitant orifice area equal to or larger than 0.4 cm^2 defines severe mitral regurgitation. A regurgitant orifice of this size can easily form in a patient with prolapse of one only mitral valve scallop at end-systole, when the prolapsing scallop is displaced within the left atrium and, consequently, the length of the coaptation of this scallop with the respective scallop of the opposite leaflet is reduced, becoming inefficient. Furthermore, large or multiple regurgitation jets can form in complex extensive mitral valve prolapse involving more than one scallops. However, in case of excessive tissue redundancy, despite prolapse of both leaflets and all scallops, an effective coaptation length can be preserved up to late during the

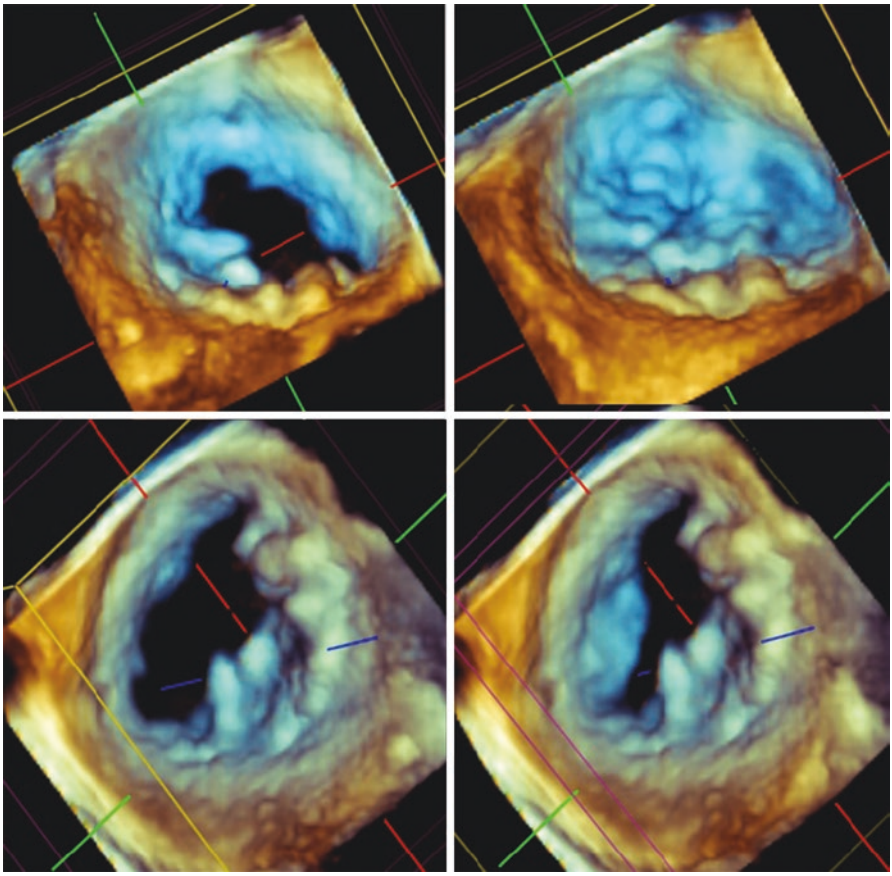

Fig. 12.8 Three-dimensional TOE images of circumferential mitral valve annulus calcification in different diastolic frames and with different angles of interrogation

course of the disease, often with only moderate mitral regurgitation present centrally in the valve as a result of circular remodelling of the mitral valve annulus with antero-posterior diameter increase. This is often the case in patients with Barlow Disease (Fig. 12.11).

The regurgitant orifice is usually not visible in mitral valve prolapse, it is only suggested by the existence of a regurgitant jet and, when feasible, highlighted by the three-dimensional-guided two-dimensional cross-section through the vena contracta of the regurgitant jet representing the effective regurgitant orifice area. More often, the effective regurgitant orifice area is not measured on colour-flow 3D guided 2D planimetry but calculated with the Doppler PISA method, based on the assumption of a circular orifice.

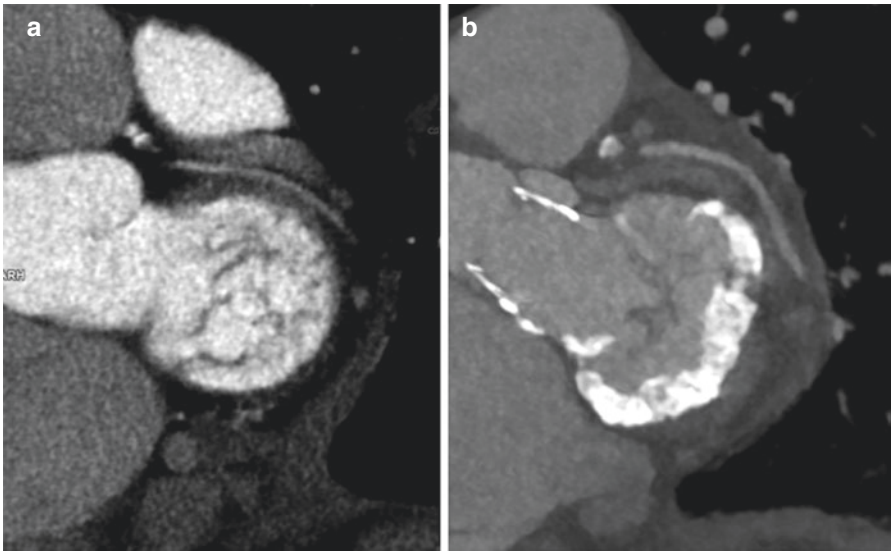

Fig. 12.9 Cardiac computed tomography demonstrating Barlow mitral valve without (left) and with (right) mitral annulus calcification. (Image courtesy of Dr. Jonathan Weirmccall, Royal Papworth Hospital)

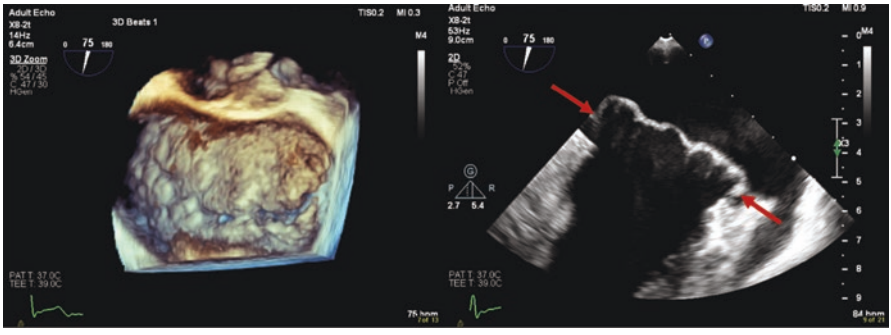

Fig. 12.10 Barlow disease assessment with three-dimensional TOE on the left-sided image demonstrating large annulus exceeding the ability of the sector to fully include. Assessment with two-dimensional TOE on the right-sided image demonstrates posterior leaflet atrialisation in systole with large prolapsing height shown by red arrows

In case of a flail mitral valve leaflet scallop, a true, visible, anatomic regurgitant orifice is formed, with complete lack of coaptation of the flail scallop with the respective scallop of the opposite leaflet (Fig. 12.12). Consequently, the mitral regurgitation is always severe in the case of a flail mitral valve leaflet, although the appearance of the regurgitant jet can be misleading, with the jet being concealed as a result of eccentricity and often also truncated as a result of high left atrial pressure, particularly early after the rupture of a cord.

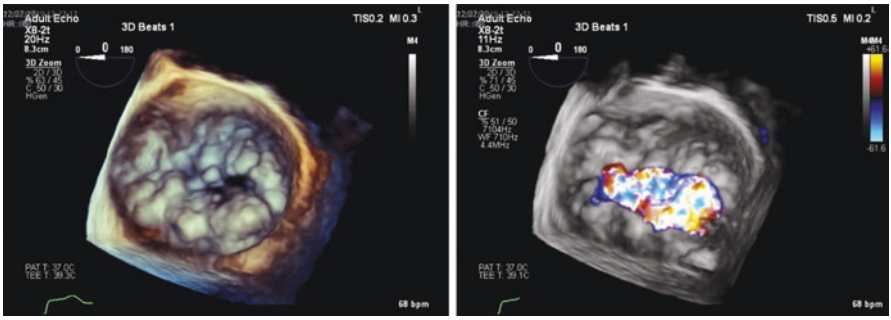

Fig. 12.11 Three-dimensional TOE surgical view (left atrial aspect of the mitral valve) in patient with Barlow Disease late in the course of the disease with mitral regurgitation (right-sided image) more pronounced centrally however extending along the coaptation line at this stage

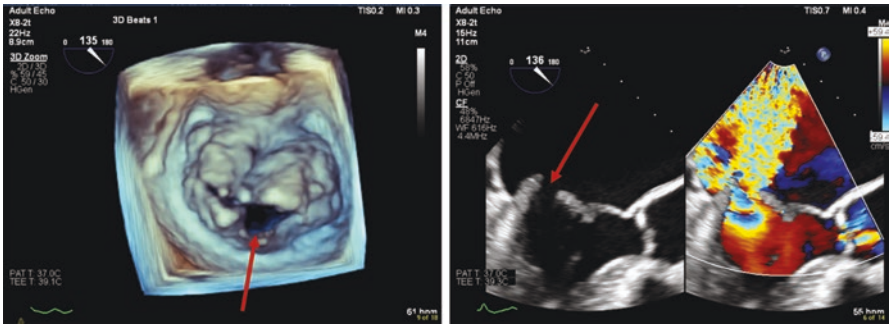

Fig. 12.12 The left-sided image is a three-dimensional TOE surgical view demonstrating anatomic orifice created by flail mural (posterior) leaflet central scallop P2 in patient with Barlow Disease, shown with red arrow. The right-sided image demonstrates the same lesion in two-dimensional TOE long-axis view, with the tissue discontinuation shown with red arrow; torrential mitral regurgitation as a result of this lesion is also observed

Assessment of Mitral Regurgitation Severity

The severity of mitral regurgitation can be qualitatively estimated or quantified [5]. As already mentioned, the degree of mitral regurgitation is estimated from the inspection of the mitral valve regurgitant lesion and of the regurgitant jet. Severe mitral regurgitation is diagnosed in the case of flail mitral valve leaflet. Severe mitral regurgitation is also suspected when the regurgitant jet follows the left atrial wall up to the pulmonary veins and even returns towards the mitral valve as a result of a Coanda effect (Fig. 12.13). The regurgitant jet comprises a flow convergence zone (resulting from the acceleration of the blood flow just before the abnormal,

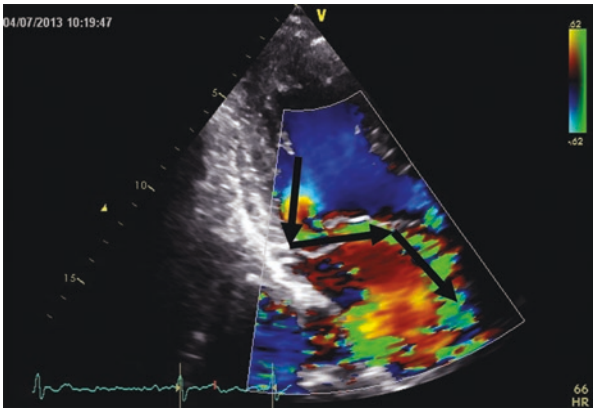

Fig. 12.13 Two-dimensional transthoracic apical long-axis view demonstrating severe mitral regurgitation in patient with flail mural (posterior) mitral valve leaflet with Coanda effect of the jet. There is also extreme flow constriction invalidating the PISA method, as demonstrated by the black arrows showing change in direction in between the three components of the jet

regurgitant orifice), a laminar flow zone (vena contracta or narrow neck, present just after the regurgitant orifice), and a flow divergence zone (resulting from the expansion of the jet within the left atrium). The flow divergence zone has been used for estimation of mitral regurgitation severity, just based on inspection or based on the calculation of the percent of the left atrium area covered by the area of the jet. However, the expansion of the flow divergence zone within the left atrium depends on left atrial pressure and left atrial compliance, not only on mitral regurgitation severity; the divergence zone can be truncated or significantly diminished in case of high left atrial pressure as, for example in acute mitral regurgitation (Fig. 12.14) and it can expand disproportionately to the degree of mitral regurgitation in case of a compliant, enlarged left atrium. The vena contracta is a much more reliable qualitative or semi-quantitative measure of mitral regurgitation severity, depending on the size of the regurgitant orifice [6]. Vena contracta can be measured using two-dimensional or three-dimensional colour-flow Doppler echocardiography. In case of an asymmetric regurgitant jet, with large difference in between diameters in different two-dimensional views, the vena contracta area obtained with the help of three-dimensional echocardiography is more accurate (Fig. 12.15). The vena contracta area is measured on 3D-guided 2D planimetry and represents the effective regurgitant orifice area, alternatively quantified using the PISA method.

Existence of systolic flow reversal in the pulmonary veins detected on transthoracic or transoesophageal echocardiography is a strongly specific sign of severe mitral regurgitation (Fig. 12.16).

The severity of mitral regurgitation is also typically estimated from the Continuous Wave Doppler signal density and intensity of the regurgitant jet.

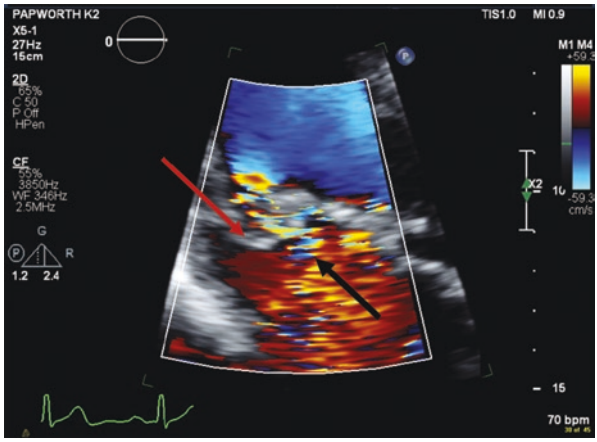

Fig. 12.14 Colour-flow Doppler mapping of mitral regurgitation jet in patient with acute mitral regurgitation due to flail posterior mitral valve leaflet (red arrow). The mitral regurgitation is severe and acute and, consequently, the left atrial pressure is high and the jet is truncated as for not more than mild mitral regurgitation

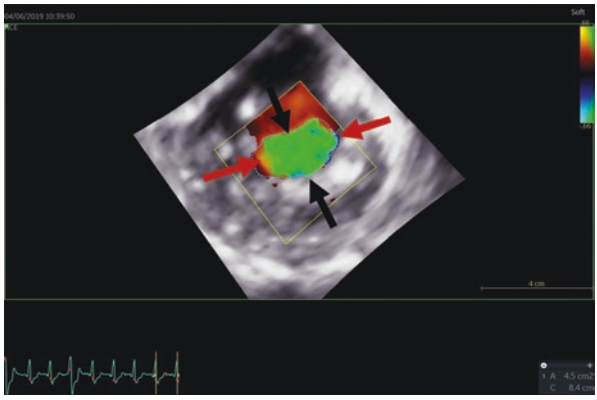

Fig. 12.15 Vena contracta area (3D-guided 2D cross-section at the level of the vena contracta) in patient with large difference in linear dimensions in between two-dimensional echocardiography planes (small antero-posterior diameter in between the black arrows and large commissural diameter in between the red arrows)

However, in both mitral valve prolapse and flail mitral valve leaflet the signal envelope can be incomplete, either because the regurgitant jet is eccentric or because the regurgitation is end-systolic.

Quantification of mitral regurgitation severity with PISA method (Fig. 12.17) assumes a circular regurgitant orifice, constant flow rate throughout systole, and no flow constriction of the regurgitant jet (Fig. 12.18), practically assuming that the central axis of the convergence zone, of the vena contracta and of the divergent zone of the jet are aligned in a straight line without direction change. Cautious interpretation of results is required in degenerative mitral regurgitation, because all these assumptions can be more or less untrue both in the case of flail mitral valve leaflet

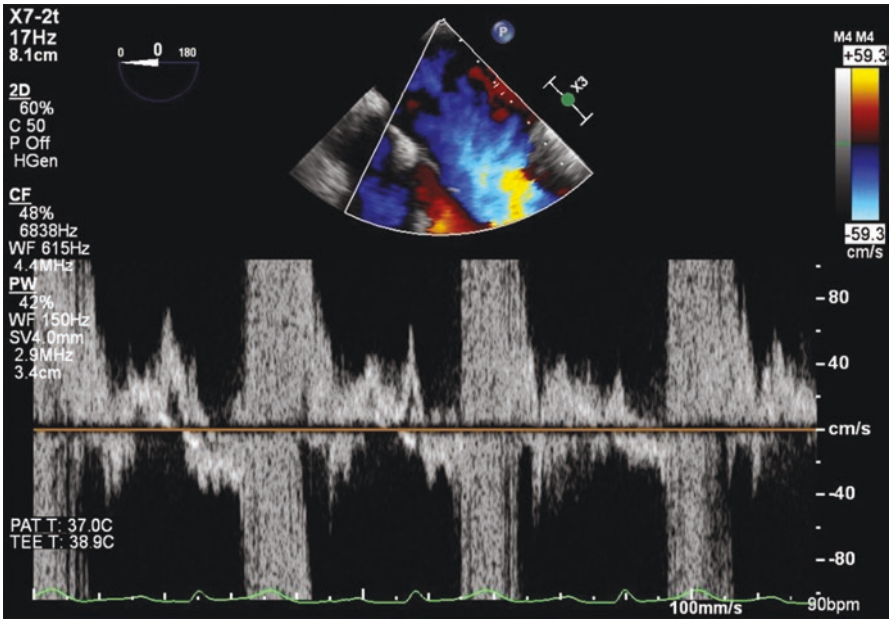

Fig. 12.16 Pulsed-wave Doppler signal demonstrating systolic flow reversal in the left upper pulmonary vein on TOE in patient with severe mitral regurgitation

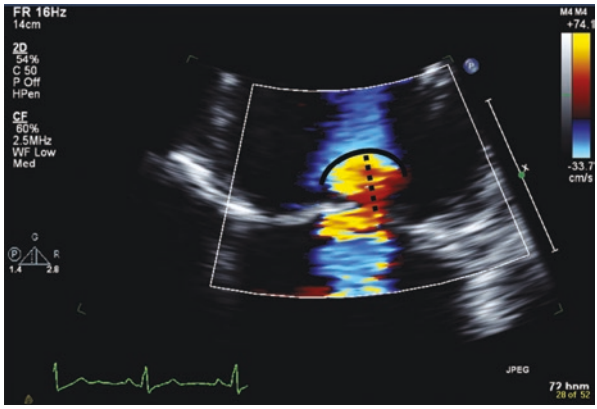

Fig. 12.17 Colour-flow two-dimensional transthoracic echocardiography demonstration of mitral regurgitation quantification with PISA method, measuring the proximal isovelocity radius of the jet

and in the case of mitral valve prolapse. The jet of mitral regurgitation due to flail mitral valve leaflet can have extreme flow constriction (Fig. 12.13). Mitral regurgitation due to mitral valve prolapse can be a strictly end-systolic phenomenon, with large variation of flow rate during systole.

Quantification of mitral regurgitation can be also performed by subtracting the forward flow from the total left ventricular stroke volume to obtain the regurgitant volume and subsequently calculate the regurgitant fraction. The regurgitant fraction

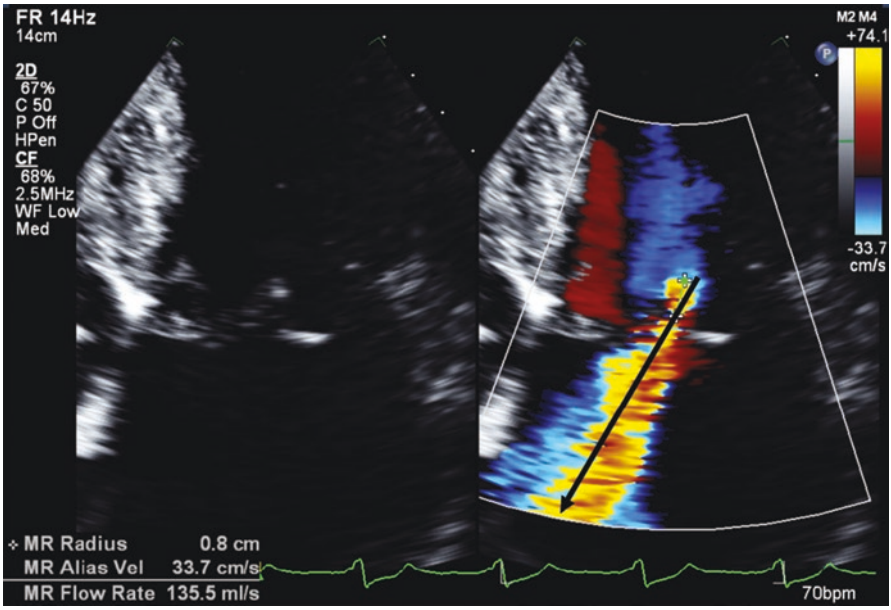

Fig. 12.18 Colour-flow Doppler two-dimensional transthoracic echocardiography in patient with mitral valve prolapse with no flow constriction of the regurgitant jet—the black arrow shows alignment of the three components of the regurgitant jet

is not only a measure of mitral regurgitation severity, it is also a measure of the potential impact that primary mitral regurgitation may have on the left ventricle, better reflecting the specific haemodynamic state. This type of quantification can be obtained using Doppler echocardiography or cardiac magnetic resonance imaging [7, 8] (Fig. 12.19).

Increase in degenerative mitral regurgitation severity during supine bicycle exercise echocardiography predicts the development of symptoms [9], important for an early mitral valve repair strategy in patients with low surgical risk in conditions of the high likelihood of successful and durable repair.

The Left Ventricle in Primary Mitral Regurgitation

Accurate quantification of mitral regurgitation severity is important for clinical decision making and timing of intervention [10]. In the majority of cases, the severity of mitral regurgitation progresses gradually during the course of disease [11], in parallel with the progression of morphological abnormalities [12]. Correspondingly, in the majority of cases, the negative impact of mitral regurgitation on the left ventricle commences when the regurgitation is severe, beginning as a compensatory mechanism [13]. To compensate for the stroke volume that retrogradely escapes within the left atrium as a result of mitral valve incompetence, the left ventricle

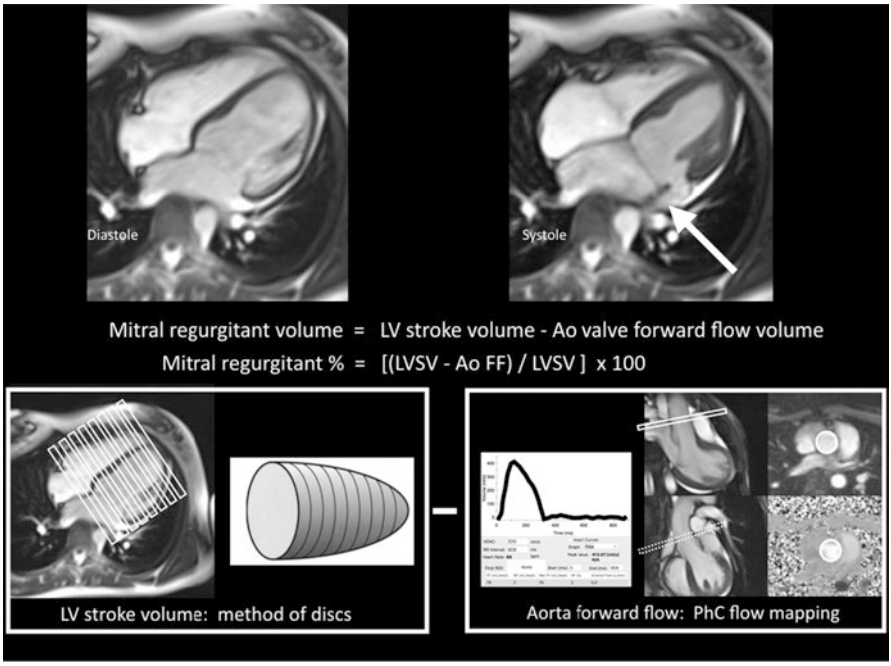

Fig. 12.19 Cardiac magnetic resonance imaging demonstrating assessment of mitral regurgitation severity based on left ventricular total stroke volume and the forward stroke volume through the aortic valve. (Image courtesy of Dr Marina Hughes, Royal Papworth Hospital)

dilates to increase the global stroke volume and, consequently, to maintain the forward stroke volume in systole. However, dilatation implies architectural changes and loss of bullet shape, leading to drop in left ventricular systolic efficacy and decompensation (Fig. 12.20). Mitral valve intervention should be offered before significant left ventricular ejection fraction drop; in the absence of symptoms, current heart valve disease management guidelines recommend valve intervention in severe mitral regurgitation when the ejection fraction of the left ventricle drops below 60%.

Whilst the succession of events described above takes place in the majority of cases, there are two major exceptions to the rule: the first is the case of severe mitral regurgitation as a result of chord rupture with flail mitral valve leaflet scallop and the second is mitral regurgitation in Barlow Disease.

In case of rupture of chord, the severe mitral regurgitation is acute and leads to the acute significant rise in left atrial pressure with consequent acute decompensation despite a hyperdynamic left ventricle that had no time to dilate. Mitral valve intervention may be necessary in the acute phase to treat heart failure, or symptoms may settle on medical treatment, transitioning to a chronic severe mitral regurgitation state. Because patients with acute mitral regurgitation secondary to a flail

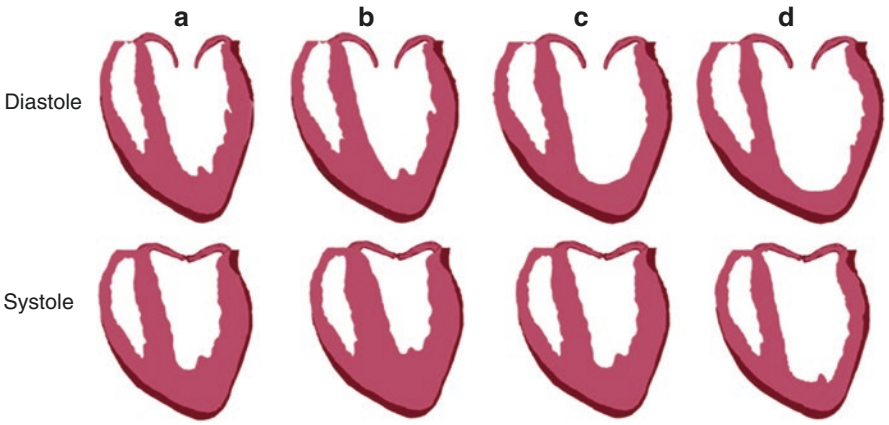

Fig. 12.20 Illustration of the effect of severe mitral regurgitation on the left ventricle. Image (**a**) demonstrates a normal left ventricle. Image (**b**) demonstrates left ventricle in acute mitral regurgitation, when the cavity is only mildly dilated (see diastole) and the function is hyperdynamic (reduced cavity size in systole). Image (**c**) demonstrates left ventricle in chronic severe mitral regurgitation with progressive cavity dilatation (see diastole) but preserved ejection fraction. Image (**d**) demonstrates left ventricle in case of decompensation—drop in ejection fraction (larger cavity at end-systole)

leaflet scallop tend to be older and to have severe comorbidities, it is good to consider a conservative medical management attempt initially, in case of high surgical risk, high anaesthetic risk or poor suitability for transcatheter edge to edge repair.

In Barlow Disease, the left ventricular systolic function can drop in parallel with the increase in mitral regurgitation severity, likely because of coexistent myocardial involvement [14]. Therefore, a delicate situation may be reached when non-severe mitral regurgitation coexists with moderate left ventricular systolic dysfunction, situation likely to benefit from mitral valve intervention, although not addressed by current heart valve disease management guidelines.

Assessment of Left Ventricular Systolic Function

Accurate assessment of left ventricular systolic function is important in mitral regurgitation, to avoid late intervention. Serial assessment to detect left ventricular systolic function drop during follow-up of chronic severe mitral regurgitation is usually performed with echocardiography and mainly based on ejection fraction [15]. The outcomes evidence that informs current guidelines comes from two-dimensional echocardiography-derived ejection fraction; however three-dimensional echocardiography and cardiac magnetic resonance imaging have less error, less interobserver variability, and higher reproducibility than two-dimensional echocardiography for the assessment of left ventricular ejection fraction. Low error, low

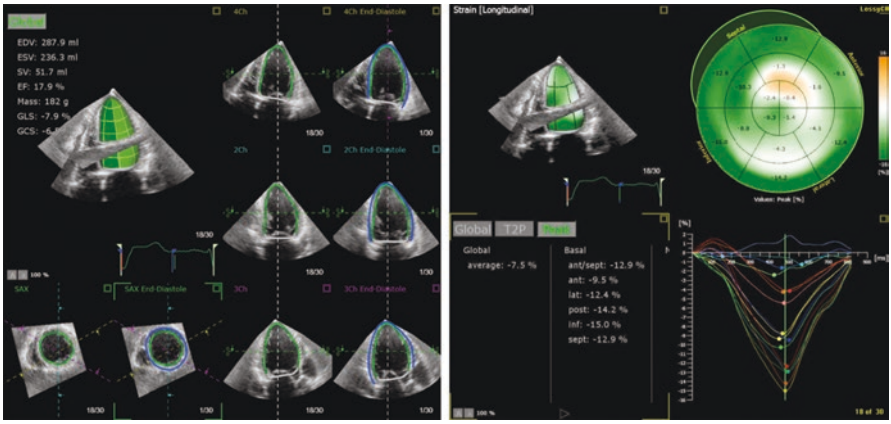

Fig. 12.21 Three-dimensional echocardiography assessment of left ventricular ejection fraction and global longitudinal strain for follow-up of mitral regurgitation

interobserver variability, and high reproducibility are needed for accurate serial assessment of the left ventricle, to allow detection of a small drop in systolic performance. Consequently, despite paucity of outcomes data, three-dimensional echocardiography and cardiac magnetic resonance imaging are increasingly used in clinical practice for follow-up of patients with primary mitral regurgitation (Fig. 12.21).

Barlow Disease poses an added challenge to all left ventricular ejection fraction assessment methods, including cardiac magnetic resonance imaging. This is because the prolapsing volume, the volume of blood entrapped within the mitral valve leaflets at end-systole, volume of blood displaced beyond the atrio-ventricular continuity and within the left atrium, is not included in the end-systolic volume of the left ventricle. (Fig. 12.22) This results in an erroneously smaller measured end-systolic volume and, consequently, an erroneously higher calculated ejection fraction of the left ventricle. Therefore, the diagnosis of left ventricular systolic dysfunction can be delayed.

A left ventricular ejection fraction within normal range and above the threshold currently indicating mitral valve intervention (>60%), can be falsely reassuring in primary mitral regurgitation. This is because the left ventricle ejects the regurgitant volume within a low-pressure chamber (the left ventricle) rather than within the high-pressure systemic circulation and thus deconditions, partially explaining the initial drop in ejection fraction following mitral regurgitation correction. A second explanation could be the irreversible disruption of the cardiomyocyte desmin-mitochondrial sarcomeric architecture in patients with severe mitral regurgitation diagnosed on myocardial biopsy samples obtained at the time of mitral valve surgery with immunohistochemistry and cardiomyocyte ultrastructure transmission electron microscopy [16]. In patients with severe mitral regurgitation, the drop in left ventricular ejection fraction as well as the development of symptoms can be predicted by the loss of contractile reserve, defined as the failure of the left

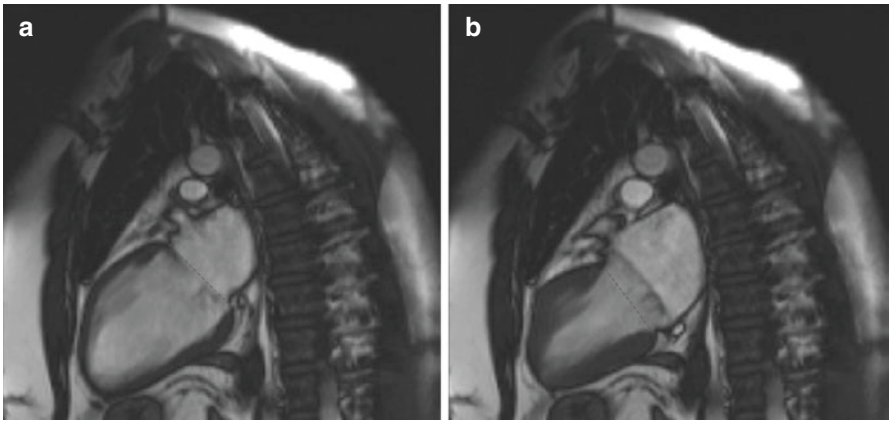

Fig. 12.22 Cardiac magnetic resonance imaging assessment of the left ventricular ejection fraction in Barlow disease. Image (**a**) represents end-diastolic frame and image (**b**) represents end-systolic frame. The green dotted line marks the left ventricular cavity border with the left atrium for purposes of ejection fraction assessment. At end-systole, the volume of blood entrapped within the mitral valve leaflets is excluded from the end-systolic volume of the left ventricle

ventricular ejection fraction to increase during supine bicycle exercise echocardiography [17, 18]. It can be also predicted by an estimated systolic pulmonary artery pressure >50 mmHg during echocardiography at rest [19, 20] or >60 mmHg during supine bicycle exercise [21, 22], both associated with worse outcome.

A more refined assessment of left ventricular systolic function than the ejection fraction, assessment able to detect subtle changes, and subclinical systolic function drop is provided by global longitudinal strain [23] (Fig. 12.21). Being a reproducible measure of longitudinal systolic myocardial deformation (shortening), the global longitudinal strain is a better predictor of postoperative outcome in severe mitral regurgitation. Furthermore, the increase in global longitudinal strain during supine bicycle exercise echocardiography is a better measure of left ventricular contractile reserve than the increase in left ventricular ejection fraction and it predicts event-free survival in patients with asymptomatic severe mitral regurgitation [24–27].

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Arrhythmias in Mitral Valve Prolapse

13

Noel G. Boyle

Abbreviations

cMRI	Contrast-enhanced magnetic resonance imaging
EPS	Electrophysiology Study
HR	Hazard ratio
LGE	Late gadolinium enhancement
MAD	Mitral annular disjunction
MR	Mitral regurgitation
MVP	Mitral valve prolapse
NSVT	Non-sustained ventricular tachycardia
PVC	Premature ventricular complex
RR	Relative risk
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

First described in 1966, mitral valve prolapse (MVP) has been as a recognized clinical syndrome for over 50 years [1]. The initial report of Barlow and Brosman included five patients with midsystolic clicks and late systolic murmurs, confirmed by phonocardiography. Using left ventricular "cineangiocardiography" in four patients, the authors demonstrated that these clinical findings were linked to

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"aneurysmal" protrusion of the posterior mitral leaflet into the left atrium due to abnormalities of the mitral tendinous chords—all before the first application of echocardiography to diagnose MVP in 1971 [2].

Initially regarded as a benign finding without significant arrhythmic complications, this changed in 1970s with multiple reports of arrhythmic associations. While MVP predisposes to both atrial and ventricular arrhythmias, this chapter will focus on the prevalence, mechanisms, and management of ventricular arrhythmias in MVP.

Early Studies of Arrhythmias in MVP

While the condition was initially labeled as "benign," reports of cardiac arrest and sudden death, some associated with exercise, appeared as early as 1968 [3]. In an exercise study of patients with MVP, post-exercise multifocal ventricular ectopy was seen in 25% and proposed by Barlow and colleagues as the potential mechanism for cardiac arrest [4]. Furthermore, they reported success using propranolol to suppress this exercise-induced ventricular ectopy. The importance of syncope as a precursor to sudden death was also soon recognized in these patients [5].

In a study of 24-hour ambulatory monitoring in 24 patients with MVP published in 1975, Winkle at al. found frequent PVCs in 50%, and complex ventricular arrhythmias including VT in 20%; 60% demonstrated PACs and SVT was recorded in 30% [6]. There was a poor correlation between symptoms and recorded arrhythmias, but 24-hour monitoring was more sensitive for arrhythmia detection than stress testing. The same group also reported a group of seven patients (5F, 2M—ages 21–61 years) who presented with sustained VT or resuscitated cardiac arrest and were found to have MVP as the only underlying structural cardiac abnormality [7].

The first controlled study of MVP patients with cardiac monitoring was reported by De Maria and colleagues in 1976. During 10 hours of ambulatory monitoring in 31 MVP patients and 40 controls, premature ventricular contractions, supraventricular arrhythmias, and bradyarrhythmias occurred in 58%, 35%, and 9% of MVP patients compared to 15%, 8% and 5% in normal subjects, respectively—all statistically significant differences [8]. Based on the available data in 1977, Levy and colleagues estimated the annual risk of sudden death attributable to MVP alone (without mitral regurgitation (MR)) as 1.9 per 100,000 patients [9]. This compared with an annual risk of sudden death of 22 per 100,000 in the adult US population at that time.

Population Studies

In the first study to report on the natural history in clinically diagnosed patients (midsystolic click and late systolic murmur or both- documented by phonocardiography) published in 1977, 53 patients were followed at the University of North Carolina for a mean of 13.7 years. MVP was implicated as a cause of sudden death

in two patients and resuscitated VF arrest in a third—giving a sudden death/cardiac arrest rate of 5.2% [10]. Nishimura et al. reported in 1985 the first longitudinal study in patients followed at the Mayo Clinic who had (minimally symptomatic) MVP documented by echocardiography [11]. In 237 patients followed for a mean of 6.2 years (range 1–10.2) the sudden death rate was 2.5%, with overall survival similar to that of a matched control population. Of the six patients who died suddenly, four were men (ages 57–70 years) and two were women (ages 31, 49 years); three patients had no prior history of ventricular arrhythmias, while three had previously documented ventricular arrhythmias (One was on propranolol, two on class I antiarrhythmic drugs).

In the same decade, a European study from Amsterdam reported on 300 patients (164 F, mean age 42.2 years) with a clinical diagnosis of MVP, followed for an average of 6.1 years [12]. Sudden death occurred in three patients, with documented ventricular fibrillation in two. Notably, non-sustained ventricular tachycardia was seen in 56 patients—all were successfully managed medically, predominantly with beta-blockers. Overall, significant complications, including arrhythmias, endocarditis, progressive regurgitation requiring surgery and cerebrovascular accident occurred in 100 of the 300 patients. An accompanying editorial entitled "Prolapse Paranoia" pointed out that this was a single-center study of a referral population of symptomatic patients (in contrast to the Mayo Clinic 1985 study) and lacked a control group [13]. The lack of a consensus on the echocardiographic findings at that time was also noted.

The first large study to give a true population prevalence of MVP was the Framingham study report in 1999, where 2-D echocardiography was applied to a population of 3491 (1845 F) subjects [14]. The reported prevalence of MVP was 2.4%, with one case of atrial fibrillation, three of syncope, and no cases of cardiac arrest. In the same issue of the New England Journal of Medicine, Nishimura and McGoon provided valuable insight into the diagnosis of primary MVP, which they indicated required redundant and thickened leaflets, and is generally found in patients with connective tissue syndromes and in older men [15]. A further follow-up study from the Framingham population in 2015 of 3679 generation three subjects, showed an MVP prevalence of 1% with familial clustering (OR was 2.5 with parental MVP) [16]. However, the association with ventricular arrhythmias and cardiac arrest remained uncertain with case series and mostly data from hospital-based cohorts.

The Oregon Sudden Unexpected Death Study, which has tracked all out-of-hospital cardiac arrests in the metropolitan Portland area (population 1 million), found a 2.3% prevalence of MVP (17/729) in patients who suffered sudden cardiac arrest (SCA) between 2002–2014 and had a prior echocardiogram [17]. Compared to the general SCA population, MVP patients were younger (60.9 versus 69.9 years) and had fewer traditional cardiac risk factors including hypertension, diabetes and coronary disease. Five of the 17 patients (~30%) were female. Mitral regurgitation was present in 14 (82%) and was severe in 10 (59%). The prevalence of MVP in this population was remarkably similar to the value of 2.4% reported in the Framingham study in 1999, suggesting that the prevalence of MVP in SCA patients may be similar to the general population.

Recent Studies of Arrhythmias in MVP

In 2013, Sriram and coworkers described a "malignant" subset of MVP patients who experienced life-threatening arrhythmias, characterized by female gender, bileaflet MVP, biphasic inverted T waves, and complex ventricular ectopy [18]. In a cross-sectional study of 24 patients with resuscitated idiopathic out-of-hospital cardiac arrest followed at the Mayo Clinic, 10 (42%) of these (9F, 1M) had bileaflet MVP. ECGs showed biphasic or inverted T waves, predominantly in the inferior leads, and PVCs in seven of these 10 patients. The PVCs showed an intriguing morphology pattern of outflow tract alternating with papillary muscle or fascicular foci. NSVT was also seen in these patients.

Basso and associates reported on a registry 650 young adults, age < 40 years, with sudden cardiac death (SCD) from the Veneto region of Italy in 2015 [19]. Forty-three patients (26F, mean age 32 years) with MVP and SCD were identified. MVP accounted for 7% of all fatal events and 13% in females. In 12 cases where an ECG was available, ten had T wave inversion in the inferior leads and all had right bundle pattern ventricular arrhythmias, indicating a left ventricular focus. In a parallel study of 30 living patients followed at the University of Padua with complex ventricular arrhythmias, mitral valve bileaflet thickening was seen in 70%. Evidence of late gadolinium enhancement (LGE) at the papillary muscle bases and lateral wall on contrast magnetic resonance imaging (cMRI) was present in 93%, corresponding with histological findings of myocardial fibrosis of the inferobasal left ventricular wall and papillary muscle in the SCD pathological study (Fig. 13.1).

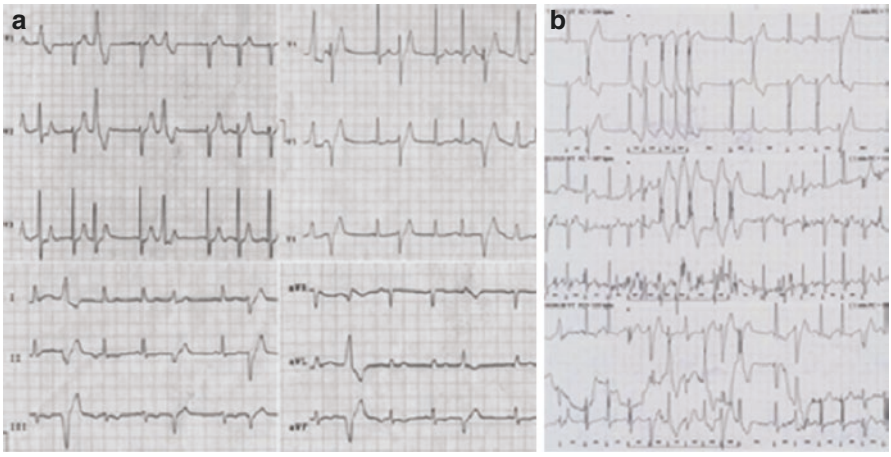


Fig. 13.1 Sudden cardiac death in a 36-year-old woman with in vivo diagnosis of mitral valve prolapse. (**a**) The 12-lead basal ECG at the time of admission to the emergency department for palpitations. Single and coupled ventricular premature beats with right bundle branch block morphology are present; note the negative T wave on the e inferior leads. (**b**) Non-sustained ventricular tachycardia is also recorded on the 24-hour Holter ECG. (**c**) Myxomatous degeneration of both leaflets of the mitral valve with elongated chordae is visible on gross examination. (**d** and **e**) Histology shows severe myxoid thickening of the posterior mitral valve leaflet and myocardial fibrosis of the left ventricular inferobasal wall (**d**) and papillary muscle (**e**). From: Basso C et al. Arrhythmic mitral valve prolapse and sudden cardiac death. Circulation 2015;132:556–566

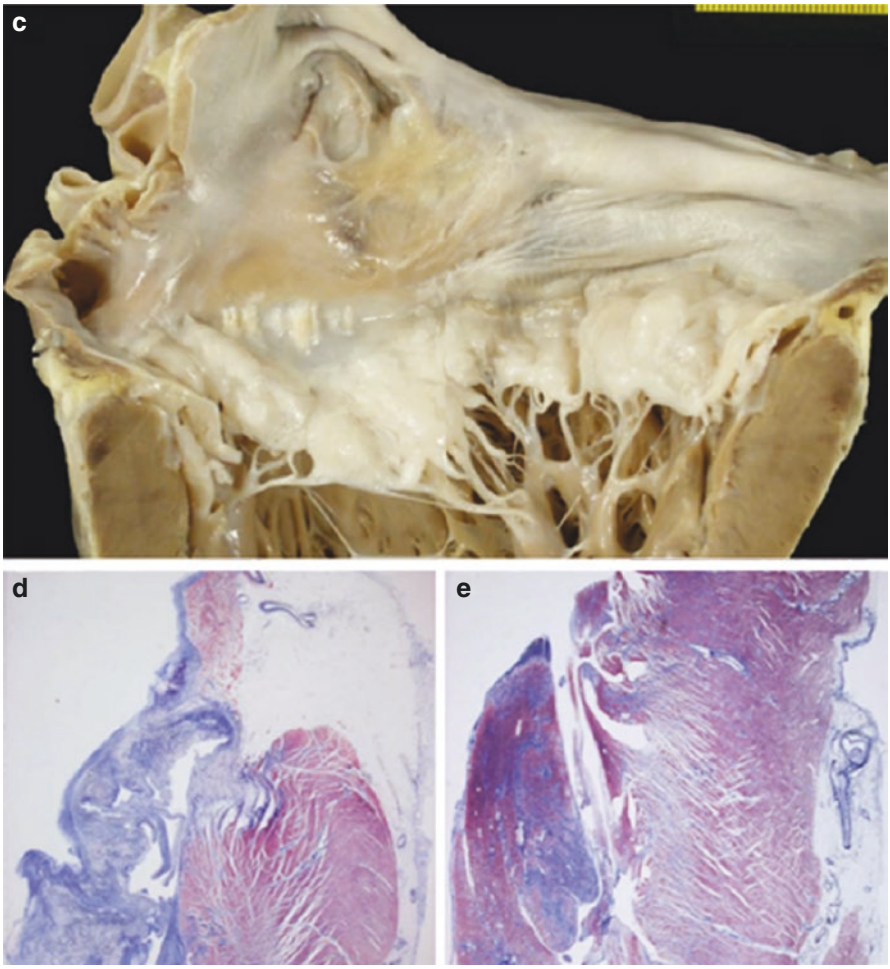
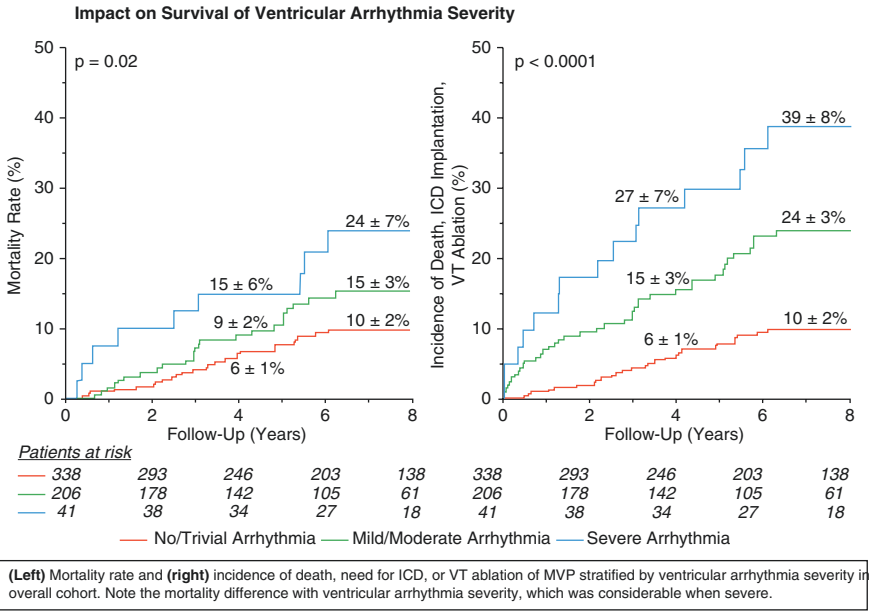


Fig. 13.1 (continued)

A new report published from the Mayo Clinic group updates their study population findings to 2020 [20]. A cohort of 595 patients (278 F; mean age 65 years), diagnosed with MVP between 2003 and 2011, were followed for an average of 8 years. Ventricular ectopy was common, and defined as: mild in 43% (PVC burden >5%), moderate in 27% (NSVT with rates 120 to <180/min.), and severe in 9% (NSVT rates >180/min.). Overall mortality at follow-up was 10% for no arrhythmia or PVCs<5%, 15% for the mild or moderate arrhythmia group, and 24% for the severe arrhythmia group ($p < 0.02$) (Fig. 13.2). Arrhythmic MVP was independently associated with mitral annular disjunction (MAD), mitral leaflet redundancy, and repolarization abnormalities on the ECG. After adjustment for MVP characteristics, severe arrhythmia was associated with higher rates of mortality, ICD implantation, or VT ablation (HR = 4.7).



(Left) Mortality rate and **(right)** incidence of death, need for ICD, or VT ablation of MVP stratified by ventricular arrhythmia severity in overall cohort. Note the mortality difference with ventricular arrhythmia severity, which was considerable when severe.

Fig. 13.2 Impact of ventricular arrhythmia severity on survival in mitral valve prolapse. Ventricular arrhythmias were defined as: No/Trivial—PVC burden, 5%; Mild- PVC burden >5% and VT runs <=120 bpm; Moderate—VT runs 120–179 bpm; Severe—VT runs >180 bpm or sustained VT/VF. ICD = implantable cardioverter-defibrillator; PVC = premature ventricular complex; VT = ventricular tachycardia; VF = ventricular fibrillation. From Essayagh B. et al. Presentation and outcome of arrhythmic mitral valve prolapse. JACC 2020;76:637–49

Arrhythmia Risk Stratification

ECG Findings

T wave abnormalities, particularly biphasic T waves in the inferior leads is found in up to 40% of unselected MVP patients and in 80% of patients with SCD [19, 21]. Premature ventricular contractions are also a common finding occurring in 40–80% of MVP patients, with ventricular couplets in 65%, complex (multiform) PVCs in 50%, and NSVT in 35% [6, 9, 22]. In their initial description of the "malignant" bileaflet MVP syndrome, Sriram at al. reported alternating outflow tract PVCs with papillary muscle/fascicular PVCs in 80% and also NSVT in 80% of patients with bileaflet MVP and cardiac arrest compared with 10–20% of cardiac arrest survivors without MVP [18].

The authors postulate that this particular pattern of PVCs may be potential triggers for VF. QT prolongation may be an additional risk factor for some patients [23].

Echocardiography

Echocardiography remains the gold standard for diagnosis of MVP, and may provide information to help in the risk stratification for arrhythmias and SCD [24].

Classic MVP is defined as superior displacement of the mitral leaflets of 2 mm or more above the mitral annulus during systole, in the parasternal long-axis view. This may occur with (classic) or without (non-classic) thickening of the mitral leaflets (5 mm or greater—measured during diastole), and with or without MR. The use of echocardiography for risk stratification has yielded mixed results. Some studies have found that MV leaflet >5 mm thickness was associated with an increased risk of ventricular arrhythmias and SCD [11, 25].

Bileaflet MVP has been proposed to carry increased risk compared to single leaflet MVP, but studies have found conflicting results likely due to a result of selection bias. In the 2013 Mayo Clinic analysis of 24 young patients who survived out-of-hospital cardiac arrest, from a database of 1200 patients evaluated at a "Genetic Heart Rhythm Clinic" from 2000–2009, bileaflet MVP was found in 10 (42%). However, in an echocardiography database study of 18,786 patients from the same institution in 2016, while bileaflet MVP was associated with higher rates of ventricular tachycardia, there was no statistically significant difference in the rates of ventricular fibrillation/SCD or ICD implantation between the bileaflet and single leaflet MVP groups [26]. In the 2015 Italian study from Basso at the University of Padua, which included 30 clinical patients with complex arrhythmias (NSVT(27), sustained VT (1) or VF(2)), bileaflet MVP was present in 70% compared with 36% in a group of control subjects [19].

Mitral regurgitation has also been reported in several studies to be an additional marker for all forms of ventricular arrhythmias. An early study from 1985 found that ventricular tachycardia occurred in 35% of patients with MVP who had moderate or severe MR compared with a rate of 5% in MVP patients without MR. [22] A study reported in 2010 from Turkey, found that moderate to severe MR was the only independent predictor of ventricular arrhythmias (RR: 8.4) in a cohort of 58 MVP patients [27].

More recently, measurements of lateral mitral annular velocities have been proposed as an additional marker. In a study of 278 patients with myxomatous bileaflet MVP, those with a peak systolic annular velocity >16 cm/s were more likely to have malignant ventricular arrhythmias (67%) versus those with a velocity <=16 cm/s (22%) [28]. The pattern of the high-velocity systolic signal resembles that of a spiked helmet and has been labeled the "Pickelhauble sign".

Initially in autopsy studies in the 1980s, mitral annular disjunction (MAD) describes a separation between the atrial wall- mitral valve junction and the top of the left ventricular free wall, to which it would normally be attached (Fig. 13.3) [29, 30]. The first echocardiographic to carefully evaluate for MAD from Carmo and associates in Portugal in 2010 reported a diagnosis of mitral annular disjunction (MAD) in 21 of 38 patients with myxomatous MVP by transthoracic echocardiography [31].

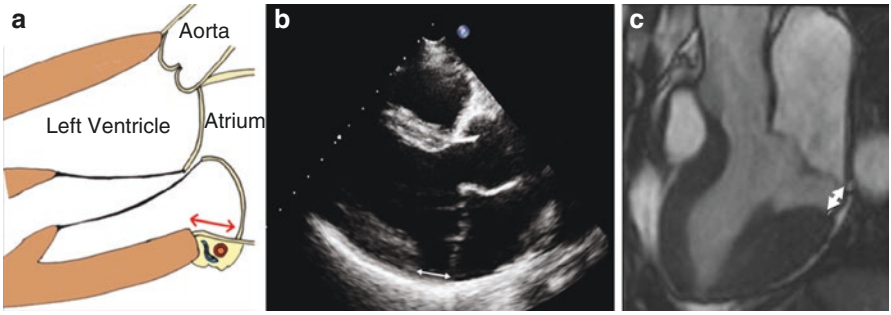


Fig. 13.3 Measurement of mitral annular disjunction (MAD). (**a**) Schematic representation of transthoracic echocardiography, parasternal long-axis view: the length of MAD is measured from the left atrial wall–MV posterior, leaflet junction to the top of the LV posterior wall during end-systole (double-headed gray arrow). (**b**) Two-dimensional transthoracic echocardiography, parasternal, long-axis view, showing a bileaflet MVP and posterior MAD (white line) measured during end-systole. (**c**) Cine CMR, 3-chamber, systolic frame, long-axis view: MVP patient with MAD measured from the left atrial wall–posterior MV leaflet junction to the top of the LV inferobasal wall during end-systole (double-headed white arrow). LV indicates left ventricular; MAD, mitral annulus disjunction; MV, mitral valve; and MVP, mitral valve prolapse. Adapted from: Carmo P et al. Mitral annular disjunction in myxomatous mitral valve disease: a relevant abnormality recognizable by transthoracic echocardiography, Cardiovasc Ultrasound. 2010;8:53–60, and Basso C. at al. Mitral valve prolapse, ventricular arrhythmias, and sudden death. Circulation 2019;140:952–64

Further, the severity of the MAD correlated with the occurrence of NSVT on Holter monitoring, and MAD >8.5 mm was a strong predictor for NSVT.

Cardiac Magnetic Resonance Imaging

In the combined clinical and pathologic Italian registry study by Basso et al. from 2015, late gadolinium enhancement (LGE) at CMRI was found in 93% of 30 patients with complex ventricular arrhythmias versus 14% of control subjects [19]. The LGE was localized to the papillary muscles in 25 patients (83%) and on the LV inferobasal segment under the posterior leaflet in 22(73%). In the accompanying autopsy study of 43 patients with MVP and SCD, left ventricular fibrosis was detected at the level of the papillary muscle in all patients and the inferobasal wall in 88%. Another MRI imaging approach used post-contrast T1 times, which are reduced in fibrosis. Bui et al., in a retrospective study of 23 patients with ventricular arrhythmias and MVP, found all patients has reduced T1 times, while only 36% has evidence of LGE [32].

In a US multicenter study reported in 2018, comparing 365 MR patients (177 with MVP and 177 non-MVP), LV fibrosis confirmed by LGE was more prevalent in the MVP group (36.7% versus 6.7%: $p < 0.001$) [33]. Arrhythmic events, defined as sustained VT, syncope with inducible VT or SCD were seen in eight patients (4.5%) of the MVP cohort versus one patient (0.8%) in the non-MVP group. The highest arrhythmic event rate was seen in MVP patients with fibrosis (7.7%).

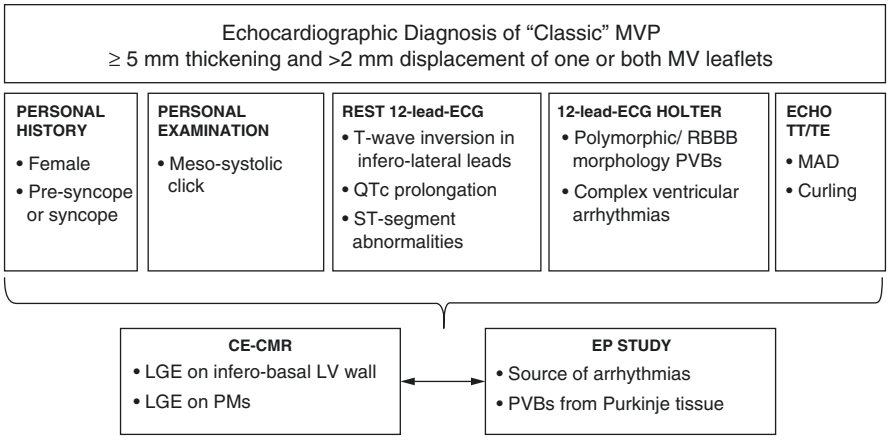


Fig. 13.4 Risk stratification for arrhythmic MVP by clinical profile and diagnostic tests. CE indicates contrast enhanced; CMR, cardiac magnetic resonance; EP, electrophysiologic; LGE, late gadolinium enhancement; LV, left ventricular; MAD, mitral annulus disjunction; MV, mitral valve; MVP, mitral valve prolapse; PM, papillary muscle; PVB, premature ventricular beat; RBBB, right bundle branch block; TE, transesophageal; and TT, transthoracic. Curling is defined as a posterior motion of the posterior mitral ring on the adjacent myocardium. From Basso et al. Mitral valve prolapse, ventricular arrhythmias, and sudden death. Circulation 2019; 140: 952–64

Analysis of an Australian national database of autopsies in cardiac arrest patients yielded 71 cases of SCD in isolated MVP patients [34]. LV fibrosis was present in 79% of cases versus 38% of matched controls.

Further studies from the University of Padua group in 2016 provided robust evidence that mitral annular disjunction (MAD) was strongly associated with arrhythmic MVP. In a follow-up study of 36 patients with arrhythmic MVP and LGE on MRI, MAD was present in all patients (mean distance 4.8 mm) versus 20% of controls (mean distance 1.8 mm) [35]. In addition, "curling" of the mitral annulus (defined as a systolic motion of the posterior mitral ring on the adjacent myocardium) was also seen in all patients and there was a linear relationship between the depth of curling and the length of MAD. An approach to MVP diagnosis and risk stratification combining echocardiography with ECG, Holter, and MRI findings is shown in Fig. 13.4.

Electrophysiology Testing

In a 1984 study from Morady et al. in 1984 found that in a subset of 20 MVP patients with syncope or presyncope, and PVCs or NSVT, polymorphic NSVT was induced in 8, monomorphic sustained VT in 2 and VF in 3 [36]. A similar study in 1985 from Rosenthal and associates found that 14 of 20 patients with MVP were inducible for ventricular arrhythmias compared to 1 of 12 controls. Nine of the 14 patients were induced with standard stimulation protocols (up to 3 ventricular

extrastimuli to right ventricular apex), and five with more "aggressive" stimulation protocols [37]. Given the general unreliability of EP studies in non-ischemic cardiomyopathies, EP testing as a risk stratifier has largely been abandoned in MVP patients [38].

Mechanisms of VT/VF and Sudden Cardiac Death in MVP

The pathologic pattern of mitral annular disjunction ("MAD") was first described in an autopsy case report of SCD in a clinically diagnosed case of MVP with documented ventricular arrhythmias in 1981 [29]. The pattern was then described as "floppy mitral valve" with a depiction of an elongated mitral atrioventricular junction and the valve attached to the atrial musculature. In a 1986 NEJM paper, reporting a pathological study of 900 adult hearts, Hutchins et al. reported that 25 (3%) had a typical floppy valve and 23 (92%) of these showed a displaced mitral attachment which they labeled "disjunction of the mitral annulus fibrosis." [30] The further postulated that this anatomical variation resulted in excessive mobility resulted in mechanical stress leading to the myxomatous degeneration of the leaflet.

In 2016, Marra, Basso, and colleagues reported that MAD was associated with basal—mid LV hypertrophy and fibrosis and was found in all their 36 cases with arrhythmic MVP [35]. They then postulated that because of abnormal contractility produced by MAD, the mechanical stretch is transmitted by the papillary muscles resulting in increased wall stress in the papillary muscle and inferobasal wall leading to hypertrophy and fibrosis—as evidenced by LGE on cMRI and fibrosis on postmortem histology. The genesis of malignant arrhythmias in MVP may result from a combination of substrate (fibrosis) and trigger (mechanical stretch) causing premature ventricular beats (PVCs) [39]. Indeed animal experiments over 30 years ago found that papillary muscle traction resulted in earlier local ventricular activation, prolonged functional refractory period, and altered QRS morphology in an experimental canine open-chest model [40]. Further the addition of a transient modulator such as elevated sympathetic or decreased vagal tone resulting in calcium loading in the sarcoplasmic reticulum and delayed afterdepolarizations in the Purkinje fibers produces the setup for sustained ventricular arrhythmias in the vulnerable patient [41]. (Fig. 13.5)

The central role of MAD in the genesis of ventricular arrhythmias was further highlighted in a 2018 Norwegian study [42]. The study population consisted on 116 patient who had MAD confirmed by echocardiography; 84 of the patients also undergoing a CMR. Ninety (78%) of the patients has MVP and 26(22%) did not have MVP. Sustained VT or cardiac arrest occurred in 7% of the "MAD with MVP" patients and in 31% of the "MAD without MVP" patients. The authors concluded that MAD itself was the arrhythmic entity, rather than MVP.

However, the pathologic connection of mitral annular disjunction and MVP has been questioned. In a study by Angelini and colleagues of 13 hearts, 7 normal and 6 with "floppy" mitral valves, varying degrees of disjunction at the mitral annulus was found in seven of 7 normal hearts and five of 6 with floppy mitral valves [43, 44]. A study by Konda and associates reported in 2017, found that in an echocardiography database of 1439 patients, 125 (8.7%) cases had MAD, while only 15 (1%) had

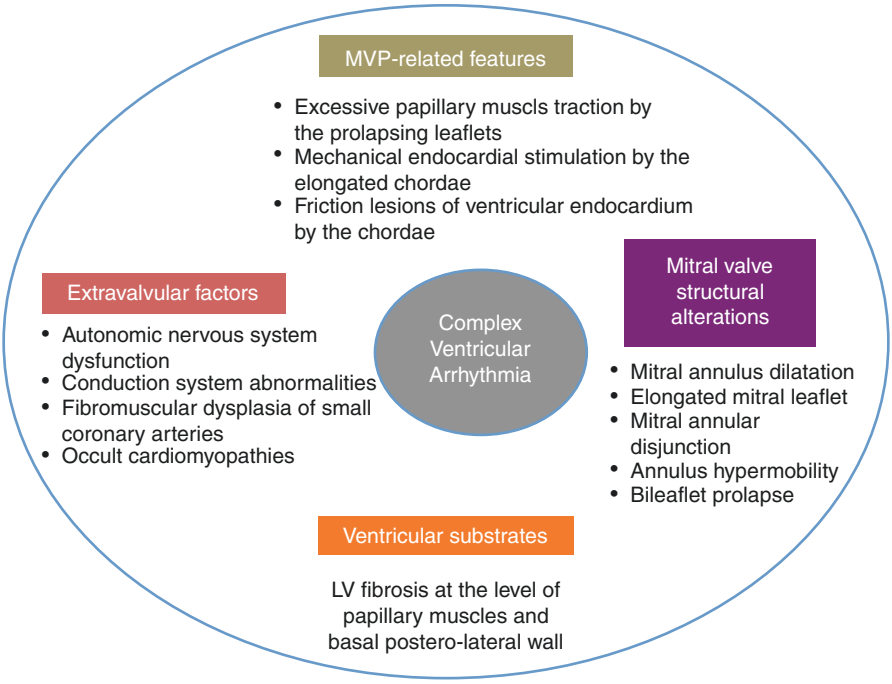


Fig. 13.5 Mechanisms of ventricular arrhythmias in mitral valve prolapse (MVP) patients with preserved left ventricular (LV) ejection fraction and no or trivial mitral regurgitation. From Lancellotti P and Garbi M. Malignant mitral valve prolapse: substrates to ventricular remodeling and arrhythmias. Circulation CV Imaging 2016;9:1–3

Table 13.1 Comparison of the pathologic study of Hutchins et al. (1988) and the Echocardiographic study of Konda at al. (2017)

	Hutchins et al. (n = 900) [Pathologic—1988]	Konda et al. (n = 1439) [Echocardiographic—2017]	p-value
MAD (+) MVP (+)	23 (2.6%)	15 (1.0%)	0.005
MAD (+) MVP (−)	42 (4.7%)	110 (7.6%)	0.005
MAD (−) MVP (+)	2 (0.2%)	38 (2.7%)	<0.0001
MAD (−) MVP (−)	833 (92.5%)	1276 (88.7%)	0.002

MAD: Mitral annular disjunction; MVP: mitral valve prolapse
Adapted from Konda et al. The Analysis of Mitral Annular Disjunction detected by Echocardiography and Comparison with previously reported Pathologic Data. J. Echocardiography 2017;15:176–185

mitral valve prolapse [45]. Overall MVP was more common in the group without disjunction (2.7%) versus the group with disjunction (1%; $p < 0.005$) [Table 13.1]. This is the opposite of the findings of the 1986 Hutchins et al. pathology study which were 0.2% versus 2.6% respectively [30]. The authors suggest the limited

resolution of echocardiography (2 mm), and also that only the posterior valve area is well seen by echocardiography, may explain the differences. Further comparison of this study with the Hutchins study found a significantly larger number of patients had MAD, but no floppy mitral valve: 7.6% versus 4.7% respectively. In both studies, MAD was more common in patients without mitral valve prolapse. More recently, the concept of mitral annular disjunction as a pathologic entity in itself has also been queried. In an editorial accompanying the 2020 Mayo Clinic database study [20], Garbi and Garweg also point out that echocardiography and MRI may not be able to distinguish actual disjunction at the mitral annulus from the prolapsing height of the mitral valve leaflet in systole [46]. More detailed anatomical and imaging studies will be needed to clarify this question.

Treatment Options

Medical Therapy

Beta-blockers are the first line agents for the management of ventricular ectopy and NSVT in patients with MVP [47]. However, there are few studies in the literature and no randomized trails. In a 1977 study of sixteen symptomatic MVP patients, Winkle and associates found that only 6 patients (37%) had symptomatic improvement with propranolol, while 44% were unchanged and 19% had symptomatic deterioration; however PVC burden was reduced by three-quarters in 56% of patients [48]. Studies have shown increased sympathetic activity assessed by heart rate variability parameters, particularly in symptomatic patients with MVP and normalization with metoprolol therapy [49, 50]. Patients are generally advised to avoid stimulants that may increase catecholamine levels, such as caffeine, alcohol, and illicit substances. If there is evidence that an arrhythmia is exercise induced, then patients' exercise activity should be adjusted accordingly.

Catheter Ablation

In some cases of PVC induced VT or VF, triggers can be mapped to the papillary muscles or the fascicular conduction system. In these sites, Purkinje potentials usually precede the PVC triggers [51]. However only case series with small numbers from tertiary referral centers are available. In a Mayo Clinic series of 14 patients with MVP and ventricular ectopy (13F, mean age 34 years, six with a prior cardiac arrest and an ICD)—all patients had at least one papillary muscle or ventricular ectopic focus [52]. Symptomatic ventricular ectopy was reduced in 12 of 14 patients; however, one patient developed a VF storm within 24 hours of the ablation procedure. At an average of 15 months of follow-up, repeat ablation was needed in six patients and two of the cardiac arrest patients received appropriate shocks. The University of Pennsylvania EP group reported a series of 25 patients (16F, mean age 55 years, prior cardiac arrest in 4 patients) with MVP and PVCs mapped to the

papillary muscles [53]. Complete PVC elimination was achieved in 19 patients and significant reduction in the PVC burden in two, with an average follow-up of 31 months. There were no differences in patients with and without VF and five of six patients with a reduced EF recovered normal LV function. However, the limitations of ablation in these patients become apparent with more prolonged follow-up. In a small series of 15 patients who were followed for a mean of 9 years post initial ablation at UCSF, ventricular ectopy was multifocal in 5 cases; all five underwent repeat ablation with new clinically dominant foci were found in three [54]. Five of the 15 (33%) developed recurrence of VT/VF and underwent ICD implantation.

Implantable Cardioverter Defibrillators (ICDs)

Implantable defibrillator placement is indicated for secondary prevention in patients with sustained VT, VF, or resuscitated SCD [47]. There insufficient data to guide the use of ICD in primary prevention, and the implications of inducible sustained VT or VF at EP testing are uncertain as discussed above [6, 36, 37]. In some centers, this may be the basis for a recommendation for ICD implantation [41].

Mitral Valve Repair

The effect of mitral valve repair surgery on ventricular arrhythmias in MVP appears to be age related. In a series of 32 patients who underwent mitral valve repair at the Mayo Clinic from 1993 to 2012, age < 60 years, mitral valve repair was associated with a reduction in postoperative ventricular ectopy [55]. In a subset of 8 patients with implanted ICDs preoperatively, ICD shocks for sustained VT or VF decreased from 0.95 to 0.19 per person-year, pre- and post-surgery [56]. This suggests that early surgery may modify the ventricular substrate; however, older patients are more likely to have diffuse fibrosis and other comorbid conditions contributing to ventricular ectopy [41].

Conclusions

Significant progress has been made in the last decade in understanding the arrhythmic substrate of MVP and in defining the features of a “malignant” MVP arrhythmic syndrome. MVP is associated with a spectrum of ventricular arrhythmias from unifocal PVCs to VF and SCD. The mechanism appears to be a combination of the substrate (myocardial fibrosis and hypertrophy; mitral annular disjunction), triggers (mechanical stretch generating PVCs from Purkinje fibers), and autonomic modulating factors. Further studies will be needed to refine risk stratification, identify the genetic patterns for various patient subgroups, and to develop new therapies to intervene early in the condition and prevent progression and development of ventricular arrhythmias [57, 58].

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The Organisation of Specialist Valve Care Provision

14

Madalina Garbi and Francis C. Wells

Optimal diagnosis, surveillance, and timing of intervention for patients with heart valve disease is provided in heart valve clinics by heart valve disease specialists [1]. Because the assessment are mainly based on echocardiography, heart valve disease specialists running the clinics are experts in echocardiography. The clinics also comprise nurse specialists and echocardiography physiologists adequately taught and trained in heart valve disease [2]. Heart valve disease surveillance in these clinics provides better adherence to guidelines, better patient experience, and the rigorous expert use of echocardiography techniques, including three-dimensional echocardiography and valve stress echocardiography. Furthermore, when needed, patients are promptly referred for cardiac magnetic resonance imaging and cardiac computed tomography, integrating all imaging results for clinical decision making.

Although the data is controversial it is likely that optimal surgical results in heart valve disease are obtained in heart valve centres of excellence with high volumes of surgery in the hands of surgeons with expertise in heart valve disease [3, 4]. Studies which are reported as being contrary to this, with lower volume centres and without specialist groups, are likely confounded by the lack of all-inclusive data and greater use of valve replacement in the more complex lesions, but this data is impossible to penetrate. Decisions that are reached by multidisciplinary teams involving heart valve disease specialists, imaging specialists, surgeons, and interventional cardiologists are likely to give a more consistent level of excellent care with an ability to adapt to new developments than those without. Heart Valve Centres of Excellence are required to have expertise in all aspects of heart valve disease intervention, to publish their results regularly, and to have structured staff training programmes for periprocedural care, programmes overseen by national or international professional societies [3].

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Degenerative mitral regurgitation requires specific expertise in mitral valve disease for optimal diagnosis, management planning, and the optimal timing of intervention [5, 6]. The heart valve disease specialist assessing degenerative mitral valve patients in the valve clinic and making follow-up plans should have deep understanding of mitral valve morphology and the impact of valve morphology on mitral valve repair success rate. In recent years it has become clear that the timing of surgical intervention is key to the protection of left ventricular function [5]. Surveillance for surgical timing should include detailed serial assessment of the left ventricle to detect early, at subclinical stage, a potential drop in systolic performance. It should also include valve stress echocardiography for the assessment of symptomatic patients with non-severe mitral regurgitation as well as for the assessment of asymptomatic patients with severe mitral regurgitation [7]. For patients in the first category, valve stress echocardiography with supine bicycle exercise can demonstrate an increase in the severity of mitral regurgitation on exertion in 30% of patients. For patients in the second category, supine bicycle exercise can demonstrate low exercise tolerance and the existence of symptoms concealed by sedentary habits, as well as low left ventricular contractile reserve or pathological rise in systolic pulmonary artery pressure during exercise.

Mitral valve surgery for degenerative mitral regurgitation or other pathology requires mitral valve surgeons—cardiothoracic surgeons with expertise in mitral valve surgery [8]. The higher likelihood of successful and durable mitral valve repair in the hands of high-volume mitral valve surgeons is well demonstrated and recognised [5, 8]. The results of mitral valve repair should be published per centre and per individual surgeon, including the rates of residual regurgitation and reoperation matched to the preoperative mitral valve morphology and patient risk [3]. Heart Valve Centres of Excellence are required to have a multidisciplinary Mitral Valve Team, comprising at least one surgeon with special advanced expertise in mitral and tricuspid valve repair and a cardiologist with specialist expertise in mitral valve disease, usually also specialist in echocardiography; the mitral valve team should also include specialists in other imaging modalities (cardiac magnetic resonance and cardiac computed tomography) and interventional cardiologists with expertise in transcatheter mitral valve intervention [9]. Imaging and clinical data of degenerative mitral regurgitation patients should be reviewed by the expert mitral valve team in regard with the suitability of the mitral valve morphology for surgical repair. In the hands of high-volume mitral valve surgeons and in Heart Valve Centres of Excellence with very low perioperative mortality, patients with mitral valve morphology highly likely to result in successful and durable repair can have mitral valve surgery early in the course of the disease, without waiting for symptoms, left ventricular systolic dysfunction or pulmonary hypertension to occur [5]. Standards for Heart Valve Centres of Excellence in general and in particular for rates of success and mortality regarding surgical mitral valve repair have been recently published by the European Society of Cardiology Working Group on Valvular Heart Disease and by the European Association for Cardiothoracic surgery [9]. Only degenerative mitral regurgitation patients with very low life expectancy and/or very high surgical risk should be considered for transcatheter mitral regurgitation edge-to-edge repair,

transcatheter implantation of neo-chords, or other transcatheter techniques. Transcatheter procedures should be only offered for symptoms and not early, for prognostic benefit.

Despite this knowledge, a significant number of patients are deprived of the chance of mitral valve reconstruction as so many patients are managed outside specialist centres. Several recent papers continue to reveal widely varying repair rates in the USA as revealed through the records of Medicare data [10]. The average repair rate remains around 60% outside of specialist centres.

In conclusion, undoubtedly in the modern world degenerative mitral regurgitation is best managed through well organised and properly funded specialist valve centres from which valuable data can be gleaned and developments implemented for the best possible patient experience.

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Correction to: The Anatomy of the Mitral Valve

Robert H. Anderson, Shumpei Mori, Justin T. Tretter, Damian Sanchez-Quintana, and Diane E. Spicer

The original version of this chapter was inadvertently published with a figure repeated twice. The chapter has been updated with the correct figures.

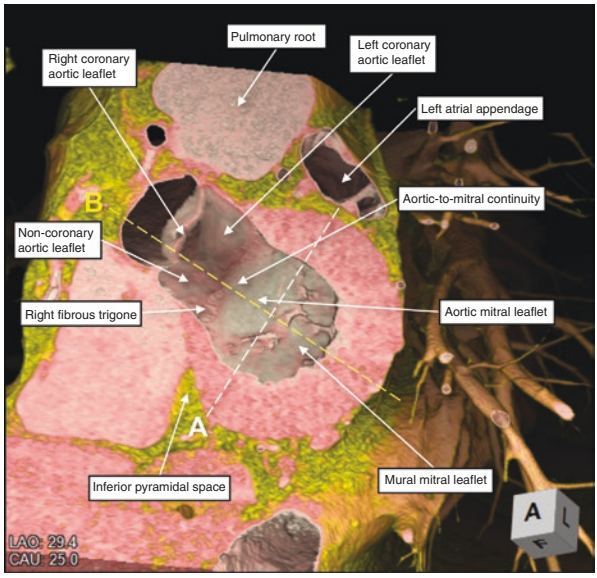

Fig. 4.15 The image is taken from a computerised tomographic dataset taken during systole in an 82-year old normal individual undergoing analysis for suspected coronary arterial disease. It shows an oblique cut through the short axis of the base of the left ventricle. Further cuts were taken along the planes A and B to show the anatomy of the hinges of components of the mural leaflet of the mitral valve

The updated online version of the chapter can be found at https://doi.org/10.1007/978-3-030-67947-7_4

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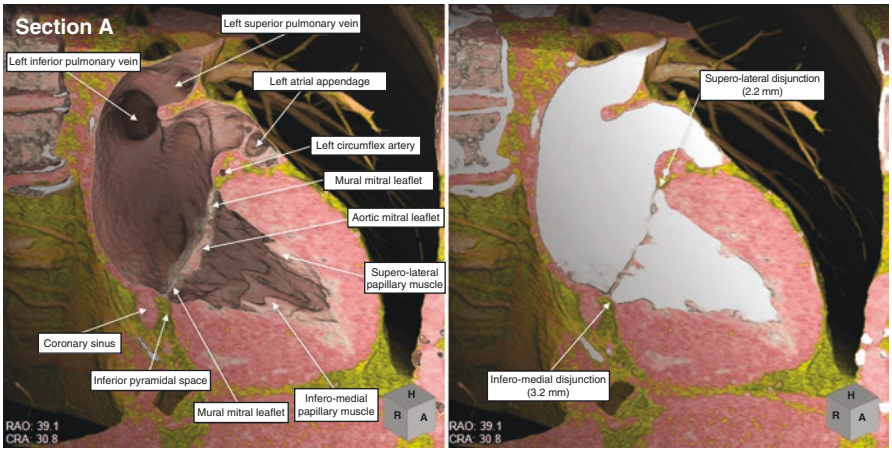

Fig. 4.16 The image shows the findings from the cut along plane A as indicated in Fig. 4.15. There is so-called "disjunction" at the two ends of the hinge of the mural leaflet of the mitral valve

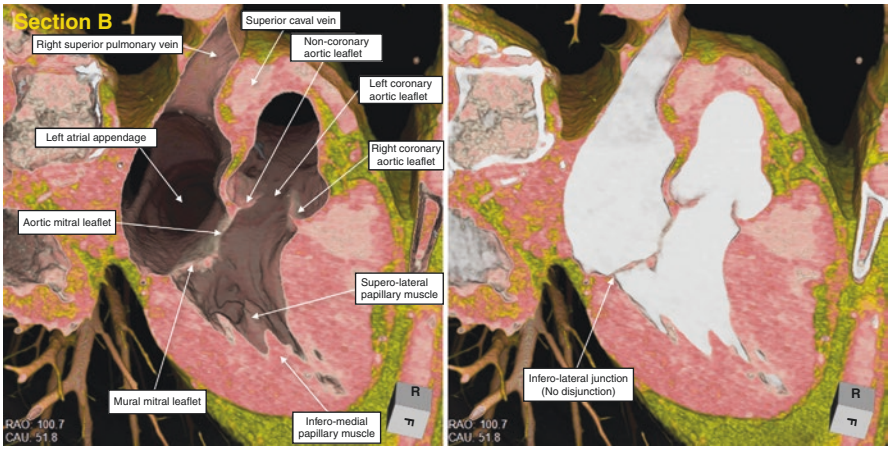

Fig. 4.17 This image shows the findings regarding the arrangement of the hinge of the mural leaflet in its central component, with the cut taken along the plane B as indicated in Fig. 4.15. There is no "disjunction" along the support of the middle part of the mural leaflet

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