Title page

Full title: Mitral Valve Pathology

Joseph D WESTABY[a], Mary N SHEPPARD[a]

[a]Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George's University of London, London, SW17 0RE

The cardiovascular pathology laboratories at St George's University of London are funded by Cardiac Risk in the Young.

We have no conflicts of interest to declare.

Corresponding author: Dr Joseph Westaby, Department of Cardiovascular Pathology, Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George's University of London, London, SW17 0RE.

Tel: 0208725 5112; Fax: 020 8725 5139; Email: jwestaby@sgul.ac.uk

Abstract

The mitral valve is composed of leaflets, cords and papillary muscles which must work in combination for the valve to function properly. The valve leaflets have three distinct layers, the atrialis, the spongiosa and the fibrosa. Pathological changes affecting these structures may result in either stenosis or regurgitation of the valve and their consequential clinical symptoms and signs.

The appearance of the valve changes with increasing age. Age related changes include thickening of the valve leaflet substance, fatty streaks of the leaflets, nodular thickening along the lines of coaptation and atrio-ventricular junctional orifice calcification.

Diseases affecting the mitral valve include prolapse, rheumatic disease, infectious endocarditis, non-bacterial thrombotic endocarditis, hypertrophic cardiomyopathy and congenital disease. Both prolapse and rheumatic disease show valve leaflet thickening with calcification, while prolapse shows myxomatous degeneration. Both infectious endocarditis and non-bacterial thrombotic endocarditis show vegetations on the atrial leaflet surfaces. These two conditions may only be distinguished on histology as a diagnosis of non-bacterial thrombotic endocarditis should only be made when the valve is devoid of bacterial colonies and acute inflammation.

Advances in mitral valve interventions, both surgical and transvascular, are discussed along with their complications.

Key words: Mitral valve, pathology, histology, rheumatic disease, endocarditis, prolapse, floppy mitral valve, valve replacement

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 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 which attach to the papillary muscles located infero-septally and supero-laterally within the left ventricle (Fig 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 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 90mm to be abnormal and indicative of dilatation. Each leaflet is inspected for evidence of thickening, infection, 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 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 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 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 3). Nodular thickenings present along and below the lines of coaptation of both the aortic and mural leaflets (Fig 3). These occur due to the repeated trauma of the leaflets closing against each other. [1] Calcification of the atrio-ventricular junctional orifice of the mitral valve is extremely common with increasing age and is strongly associated with cardiovascular disease. [2, 3, 4] 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 4A&B). [5] In severe cases, large nodules are observed which may ossify or contain cartilage with extramedullary haematopoiesis. These nodules can extend into the underlying left ventricular myocardium and form a large mass (Fig 4A). They do not usually result in mitral stenosis.

The size of the mitral apparatus is mainly determined by the size of the atrio-ventricular junctional orifice 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 atrio-ventricular junctional orifice. Like proximal aortic dilation results in aortic regurgitation, this enlargement of the atrio-ventricular junctional orifice 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 atrio-ventricular junctional orifice, again pulling the mitral leaflets apart and resulting in functional regurgitation.

Functional regurgitation may occur in the absence of atrio-ventricular junctional orifice dilatation. Left ventricular remodelling can result in 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 which 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 Anischkow 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 5A). From the ventricular aspect, a funnel shape appearance may be seen (Fig 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. In the acute stages of the rheumatic process as a result of the myocardial insult, basal ventricular dilatation occurs and the oedematous thickened leaflets do not coapt properly and give rise to significant mitral regurgitation in the absence of stenosis. This is seen particularly in the child with rheumatic disease.

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.

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 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 destruction of the leaflets (Fig 6A). The infection may result in ulceration, aneurysm formation, rupture and perforation of the valve leaflets (Fig 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.

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 occurs most commonly in the brain, spleen, kidneys, lungs and mesentery whilst abscesses occur in the kidneys, liver and spleen. [6] 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 7A). There is necrosis of the valvar leaflets and abscess formation which can also directly involve the myocardium (Fig 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. [7] The vegetations form along the lines of coaptation (Fig 8A). On histology, the vegetations consist of fibrin and platelet thrombi which are lacking an inflammatory infiltrate (Fig 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.

Congenital mitral valve disease

Congenital mitral valve anomalies may be categorised into supravalvar, valvar and subvalvar. There may also be a mixed picture. [8]

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

Valvar anomalies include those affecting the atrio-ventricular junctional orifice and leaflets. The atrio-ventricular junctional orifice 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 which attach to the right ventricle may be observed, in cases of atrioventricular septal defect. [9]

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 chronic rheumatic disease has declined.

Mitral valve prolapse includes different degrees of atrio-ventricular junctional orifice dilation, leaflet expansion and ballooning, and chordal dysfunction.

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 9A&B). It has also been described as myxomatous due to this texture (Fig 9B).

The aetiology is complex and has 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 9A). These diseases affect transforming growth factor beta signalling, which plays a key role in the development of valves. [10] A number of familial forms have been described including myxomatous mitral valve prolapse 1, 2 and 3 as well as an X linked forms. [11, 12] 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 potentially due to the inability of the maldeveloped leaflet to share the load generated in the systemic circulation. [13] As mitral valve clefting develops through malembryogenesis, mitral valve prolapse may arguably, be referred to as a congenital disease.

Macroscopically the leaflets appear rubbery and oedematous with diffuse thickening (Fig 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 surface area resulting in ballooning into the atrium (Fig 9A&B). Ballooning is challenging to assess in the post mortem state but a height of 2mm above the AV junction has been used as a criterion. There is elongation of the cords which may also appear thinned and can rupture. The atrio-ventricular junctional orifice is commonly dilated beyond 90mm.

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 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. If there is cordal rupture then the leak is pan-systolic.

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 atrio-ventricular junctional orifice dilatation. Cordal elongation or rupture, atrio-ventricular junctional orifice and papillary muscle calcification may be present. This is classic MVP, with the 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 atrio-ventricular junctional orifice. In symmetric form, leaflet tips meet at a common point on the atrio-ventricular junctional orifice. 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 characterized 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 a "degenerative process" he associated with thinned and ruptured cords. This is in life called non-classic MVP with mitral valve leaflet thickness of 0 mm to 5 mm and typically involves a single segment of the posterior leaflet with cordal rupture. One or more cords, usually to a single segment, are ruptured, causing prolapse of the unsupported segment. Unruptured cords are often thinned. However, the normally coapting leaflets on either side of the prolapse segment have cords which appear normal. Leaflets are thin, sparse, and of normal height, the exception being the prolapsing segment, which may display thick and excess tissue. Rather than a diffuse "degenerative disease", this is suggestive of a more localised process confined to a single segment potentially

mediated by the deep clefts frequently seen either side. [13] Any degree of atrioventricular orifice dilatation may be seen in MVP whereas, in Barlow's disease they are all > 40% larger than normal.

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 infero-septal 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 10B). [14, 15]

The histological appearances of the floppy valve (Fig 10A) are 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-organized 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. [16] 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 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. [17]

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 accident. [18]

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 need for anticoagulation due to the risk of thrombosis (Fig 12B). Modern bileaflet valves have good long-term durability.

For mitral regurgitation, the valve is repaired utilising artificial cords. Resection of the prolapsed segments is now much less common with a move toward a "respect vs resect" approach. [19] An annuloplasty ring may be inserted if required (Fig 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 12C).

Complications of valve replacement which may be seen at post mortem include thrombosis, paravalvular leak, endocarditis and pannus (Fig 13A&B). [20]

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. Thorough pathological analysis with serial sectioning of both prolapsing and non-prolapsing leaflets of the prolapsing mitral valve and comparing to normal valve leaflets would establish whether "fibroelastic deficiency" exists as an entity. 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.

References

1. Pomerance, Ariela. "Ageing changes in human heart valves." British Heart Journal 29.2 (1967): 222.

2. van't Klooster, Cilie C., et al. "Multifocal cardiovascular calcification in patients with established cardiovascular disease; prevalence, risk factors, and relation with recurrent cardiovascular disease." IJC Heart & Vasculature 27 (2020): 100499.

3. Fox, Caroline S., et al. "Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study." Circulation 107.11 (2003): 1492-1496.

4. Kanjanauthai, Somsupha, et al. "Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA)." Atherosclerosis 213.2 (2010): 558-562.

5. Pomerance, Ariela. "Pathological and clinical study of calcification of the mitral valve ring." Journal of Clinical Pathology 23.4 (1970): 354-361.

6. Guerrero, Manuel L. Fernández, et al. "Infective endocarditis at autopsy: a review of pathologic manifestations and clinical correlates." Medicine 91.3 (2012): 152-164.

7. Lopez, J. Antonio, et al. "Nonbacterial thrombotic endocarditis: a review." American heart journal 113.3 (1987): 773-784.

8. Mitruka, Surindra N., and John J. Lamberti. "Congenital heart surgery nomenclature and database project: Mitral valve disease." The Annals of thoracic surgery 69.3 (2000): 132-146.

9. Séguéla, Pierre-Emmanuel, Lucile Houyel, and Philippe Acar. "Congenital malformations of the mitral valve." Archives of cardiovascular diseases 104.8-9 (2011): 465-479.

10. Le Tourneau, Thierry, et al. "Genetics of syndromic and non-syndromic mitral valve prolapse." Heart 104.12 (2018): 978-984.

11. Gasser, S., H. Reichenspurner, and E. Girdauskas. "Genomic analysis in patients with myxomatous mitral valve prolapse: current state of knowledge." BMC cardiovascular disorders 18.1 (2018): 41.

12. Le Tourneau, Thierry, et al. "Genetics of syndromic and non-syndromic mitral valve prolapse." Heart 104.12 (2018): 978-984.

13. Ring, Liam, et al. "The prevalence and impact of deep clefts in the mitral leaflets in mitral valve prolapse." European Heart Journal–Cardiovascular Imaging 14.6 (2013): 595-602.

14. Basso, Cristina, et al. "Arrhythmic mitral valve prolapse and sudden cardiac death." *Circulation* 132.7 (2015): 556-566.

15. Garbi, Madalina, Patrizio Lancellotti, and Mary N. Sheppard. "Mitral valve and left ventricular features in malignant mitral valve prolapse." Open heart 5.2 (2018) 14-16.

16. Sabater-Molina, M., et al. "Genetics of hypertrophic cardiomyopathy: A review of current state." Clinical genetics 93.1 (2018): 3-14.

17. Maron, Martin S., et al. "Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy." Circulation 124.1 (2011): 40-47.

18. Forteleoni, Antonietta et al. “Traumatic mitral valve regurgitation: a case report and state-of-the-art review.” Journal of cardiovascular medicine (Hagerstown, Md.) vol. 20,10 (2019).

19. Cohen, Brian D., et al. "Contemporary Management of Mitral Valve Disease." Advances in Surgery 54 (2020): 129-147.

20. Dinarevic, S., et al. "Left ventricular pannus causing inflow obstruction late after mitral valve replacement for endocardial fibroelastosis." Pediatric cardiology 17.4 (1996): 257-259.