Mitral valve disease: A view on pathophysiology and management of the most common valve disease in the world

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Abstract

Objectives: Mitral valve disease is increasingly prevalent. Timely diagnosis and the choice of the right intervention are very important in the early stages, as valvular dysfunction often leads to cardiac failure and even sudden death. The focus of this paper is on the various pathologies of the mitral valve, their etiology, and clinical management. Methods: Mitral regurgitation (MR) can be managed surgically, percutaneously or medically. Treatment methods for primary MR include percutaneous mitral valve (MV) repair, MV replacement, minimally invasive mitral valve surgery (MIMVS), and more recently, robotics. Additionally, conventional sternotomy has been used for both MR and mitral stenosis. Nonetheless, ongoing clinical trials are a clear indicator that the management of valve diseases is continuously evolving. Results: Multiple studies favour MV repair via MIMVS, over conventional sternotomy or percutaneous approach. However, more data is needed to optimize patient selection. Robot assisted repair is a new alternative, but attention should be given to the steep learning curve and medical training of professionals wishing to perform this intervention. Cost effectiveness and possible side effects should be explored by clinical trials as well. While guidelines are fairly straightforward for primary MR, there is insufficient evidence to suggest that surgical treatment is advantageous for secondary MR. Management is usually pharmaceutical and aims to treat symptoms rather than cause. Conclusion: Mitral valve disease remains a medical challenge, but numerous research and clinical trials have been embarked upon to refine old methods and discover new ones to improve treatment success and procedural safety.

Introduction

Mitral valve disease affected approximately 5.8 million adults in the United States in 2016, with 5.49 million suffering from mitral regurgitation and 323 127 suffering from mitral stenosis. Mitral valve disease is prevalent across all age groups; however, it increases with age and affects 5.1% of elderly aged 65 and above.[1-3]The mitral valve has the most complex anatomy out of the four valves of the heart. It is also the valve most frequently causing disease. The three most common diseases of the mitral valve include mitral stenosis, mitral regurgitation, and mitral valve collapse.[4] Out of these, mitral regurgitation (MR) is by far the most frequently diagnosed and accounts for approximately 9.3% of over 75-year old, whereas mitral stenosis accounts for around 0.2%.[5]

Mitral regurgitation consists of two types: primary and secondary. Primary MR is a pathology of the mitral valve apparatus whereas secondary MR is a pathology of the left atrium or ventricle that ultimately affects the function of the mitral valve. Secondary MR can be further classified into ischemic or non-ischemic, depending on the cause, which will require different treatment plans.[6] Common causes of MR include annular calcification in the elderly, rheumatic fever, infective endocarditis, and left ventricular dilatation in functional mitral regurgitation. On the other hand, typical causes of mitral stenosis include rheumatic fever and

congenital causes.[7] In order to treat mitral valve diseases, a surgical attempt is the golden standard and aims to either restore function or to replace the valve. Where surgery is contraindicated, the transcatheter approach has proved to be a reliable option, especially for secondary mitral regurgitation.[8,9]

Understanding Mitral Valve Disease

Mitral Annulus Anatomy

Understanding mitral valve anatomy provides the foundation to appreciate its intrinsic valvular abnormalities. Continuing advancements in cardiac imaging allow for visualization over three dimensions.[10]

The mitral annulus is a junctional region between the left ventricle and the left atrium. It is saddle-shaped and will experience dynamic changes throughout the cardiac cycle (see Figure 1 for mitral valve anatomy).[11,12]

Annular diameter correlates with function and has shown to be impaired secondary to valve pathologies such as myxomatous disease and cardiomyopathies. With respect to myxomatous disease, the mitral annulus will dilate in all planes. The increase in diameter will inhibit regurgitation prevention mechanisms. In comparison, there is an isolated anterior-posterior enlargement with ischemic cardiomyopathy. Annular remodeling will vary depending on the pathophysiology of the underlying disease process.[13]

Physiological degrees of mitral annular incoherence have been isolated in "normal" patients and whether this represents early signs of dysfunction or a mere physiological variant is yet to be determined. However, it is important to appreciate that, histologically, the annulus is a non – continuous structure and its thickness will vary depending on the density of collagen.[14]

Mitral Stenosis

The physiological mitral orifice extent is between $4cm^2$ to $6cm^2$, the valve will open throughout the ventricular diastole to facilitate the blood filling of the left ventricle. Constriction less than $2cm^2$ can cause an impediment of blood flow to the ventricle thereby resulting in increased pressure exerted on the walls of the left atrium.[15] The main etiology of this constriction is rheumatic fever, where a group A beta-hemolytic streptococcus infects the patient in early life. The initial pharyngeal infection promotes the innate immune system to activate T and B cells. CD4+ T cells will promote the production of complementary IgG and IgM antibodies. However, the structural resemblance between the infectious material and human proteins results in tissue damage. From a cardiovascular perspective, antibody binding and dissemination of T cells will cause carditis.[16]

Genetic susceptibility to the development of acute rheumatic fever was initially considered in 1986. A 2011 systematic review seemed to confirm this hypothesis, suggesting heritability of 60%. Some studies have reported associations to class 2 HLA whilst other studies have discussed an association to non-HLA proteins, but a definite link is yet to be confirmed.[17-19]

Clinically, mitral stenosis will cause massive rises in left atrial pressure thereby resulting in reactive pulmonary hypertension. As the pressure remains elevated the atrium will begin to dilate in an attempt to accommodate the increasing volumes of blood. This dilation puts the patient at risk of atrial arrhythmias. This sequence of events will eventually result in congestive heart failure which is measurable via the New York Heart Association (NYHA) Classification.[15]

Mitral Regurgitation

Mitral regurgitation (MR) is a common valvular anomaly occurring in approximately 10% of the populace.[20] The disease can be divided into primary and secondary MR. Primary MR is the predominant form that will occur following myxomatous degeneration – which is the predominant aetiology, accounting for 2.5% of the world's population. Throughout the developing world, rheumatic heart disease remains widespread.[6]

Retrograde flow from the left ventricle into the left atrium results in a cyclic increase in left ventricular volume. Ultimately, ventricular remodeling occurs in an attempt to maintain cardiac output. Over time, as the ventricle hypertrophies, the actin-myosin cross-bridges will stretch, eventually derailing from the point of

optimal contractility, therefore, resulting in a gradual decrease in ejection fraction. As the ejection fraction deteriorates, the patient will experience heart failure symptoms.[21] Table 1 is a summary of the different types of mitral disease and their classification.

Endocarditis and its effects on mitral valve

Before the discovery of antibiotics, infective endocarditis was invariably fatal. Even with advancements in diagnosis and treatment, the in-hospital mortality rate for infective endocarditis is still high at 20% to 25%.[22] Studies have shown that early and late mortality rates were lower and event-free survival was greater in patients who went through mitral valve repair to treat acute endocarditis, as compared to those who underwent mitral valve replacement.[23] There is also a lower incidence of recurrent infections associated with mitral valve repair as compared to mitral valve replacement.[24] Therefore, patients with mitral valve endocarditis should be offered mitral valve repair whenever possible.[23] 89% of endocarditis patients who underwent mitral valve surgery are free from re-surgery at 5 years. This value decreases to 72% at 10 years post-operation. Patients who received mechanical valve replacements have a higher or equal rate of freedom from re-operation at 10 years compared with those who received biological valve replacements.[25] Native mitral valve endocarditis is relatively responsive to antibiotic treatment, therefore is likely to be cured pharmacologically. Prosthetic mitral valve endocarditis is, however, linked with poorer prognosis.[26]

Approaches for Treatment of Mitral Valve Disease

1. Percutaneous Mitral Valve Repair
2. Percutaneous Transluminal Mitral Valvuloplasty
3. Transcatheter Mitral Valve Replacement
4. Minimally Invasive Mitral Valve Surgery
5. Conventional Sternotomy

Percutaneous Mitral Valve Repair

Percutaneous mitral valve repair using the MitraClip (Abbott Laboratories, Menlo Park, California, USA) has been approved in 2008 in Europe and 2013 in the United States. Is one of the most common procedures performed today for patients with primary severe mitral regurgitation (MR) who are deemed unfit for surgery. This is usually the case for older patients with multiple co-morbidities.[7, 27-31]

The MitraClip device has 2 essential components: the clip delivery system and a guide catheter.[30] It enters the circulation through the femoral vein and is directed towards the heart. Transseptal puncture allows the advancement of the MitraClip to the left atrium. Moving through the mitral valve (MV), the apparatus reaches the left ventricle. The clip will grasp the leaflets, bringing them together, connecting the middle segment of the anterior leaflet to the one of the posterior leaflet. The MitraClip technology is based on Alfieri's surgical technique, thus creating a 'double orifice' MV. Before releasing the clip, assessment of the procedure via transesophageal echocardiogram (TEE) is required, as the MitraClip can be reopened and repositioned. This step also allows re-evaluation of mitral valve defect (if still present) and re-grading.[27,30-32]

After the operation, patients receive clopidogrel for 30 days and aspirin for the next 6 to12 months.[27] Procedural success is highly dependent on patient factors. TEE along with transthoracic echocardiography is used for patient screening and ensures that anatomic requirements are met for a feasible MitraClip repair. Calcification of more than 80% of leaflet area, short leaflets, and low baseline MV area are common disqualifiers from the procedure, while orifice area greater than 70.8 mm^2 or mitral valve area less than 3 cm^2 were indicators of clip failure.[33]

Although considered safer than surgical treatment for severe primary MR, percutaneous repair still has its risks. Common postoperative complications include atrial fibrillation and acute kidney injury, as well as partial detachment of the clip. Mitral stenosis or full displacement of the clip have occurred in less than 5% of cases. The EVEREST II trial, which proved the efficacy of MitraClip in 2010 and gained its approval in the US, also highlighted that nearly 20% of patients needed another operation within a year.[27,32]

Since 2019, the MitraClip has been approved in the USA for secondary functional MR as well.[27] Ongoing clinical trials in Europe (RESHAPE-HF2) and Canada (EVOLVE-MR) are considering the effectiveness of promoting this treatment for functional MR, after another two anticipated clinical trials, COAPT and MITRA-FR, had conflicting results (mainly due to different selection criteria).[34-36] Cardioband (Edwards Lifesciences, Irvine, California) percutaneous annuloplasty procedure is currently used in Europe for the treatment of this condition.[33]

Nevertheless, the first line of management of secondary MR remains pharmacological therapy: angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics, providing symptom relief.[37] Tsang et al. paper on recent advances in the management of mitral valve disease argued that doctors are more reticent in offering interventional therapy such as mitral valve repair or replacement, in the absence of clear guidelines (in the US, replacement is still favored, sparing the sub-valvular apparatus, while in Europe repair is considered first). This could adversely affect outcomes for patients.[13] Case studies are expected to be published in the coming years (especially from the USA) and careful documentation of medical decisions and considerations would be advisable. Over time, the conduction of longitudinal studies should also shed some light on the issue.

PASCAL Transcatheter mitral valve repair system is a newer device that is used for percutaneous repair of MR. It hopes to fill in the gap left by the MitraClip and help patients who do not meet the anatomic criteria for the procedure. PASCAL is still developing, although an initial clinical trial including 23 patients has yielded favourable results. The CLASP study was shortly commenced, which gained CE marking approval after 98% out of the 62 patients had an MR grade of two or under at 6 months follow-up. More randomized controlled trials are needed before the procedure becomes widely available.[13,38,39]

Percutaneous Transluminal Mitral Valvuloplasty

Percutaneous transluminal mitral valvuloplasty (PTMV) changed the approach of cardiothoracic surgeons to mitral stenosis. The technique was developed by Inoue in 1984 but has since been refined. Anatomically, PTMV is of greatest use in patients with the pliability of the mitral valve, clear of substantial calcification or fibrosis.[40,41.] Suitability of this technique for mitral stenosis can be determined through the application of Abascal's echocardiographic scoring system. Also known as the Wilkins score, it is essential in its application as it can predict mitral regurgitation following an intervention. The criteria evaluate four key aspects to valvular morphology outlined in Table 2. With respect to the Wilkins criteria, a higher score specifies a more progressed disease and a reduced chance of success with this technique. Surgical mitral valve replacement is recommended for patients in those in which PTMV is not anatomically optimal.[42] The surgical basis is via balloon valvuloplasty, this balloon is applied crossing the mitral valve thereby improving leaflet excursion and orifice diameter. The operation is critical in the treatment of rheumatic heart disease as it fractures the rheumatic fusion that has developed. It is also a reliable therapy management option for pregnant women.[43]

The 1984 paper by Inoue and colleagues was revolutionary as the technique developed allowed mitral commissurotomy without thoracotomy. Post-operative complications following thoracotomy, in patients who are already cardiopulmonary compromised, create a very vulnerable situation for the patient. The initial study consisted of six patients, five of which were successfully managed with this new technique. The procedure was unable to be performed in the remaining patient due to technical difficulties. Interestingly, the Wilkins score was only implemented in 1990, 6 years following this study.[44]

The balloon is introduced through the saphenous vein and will ascend into the mitral orifice. Across the mitral orifice, the balloon is partially inflated, when fully expanded the balloon will separate the fused commissures via expansile propulsion. Surgically, the balloon is buoyed via a nylon micromesh and changes shape in three stages, depending on the degree of inflation. The micromesh is essential for the shape adaptation that the balloon experiences.[44]Despite medical advances, the basic premise of this technique has remained the same. As of 2016 Adhikari and colleagues described a similar approach.[45] In selected patients, PTMV is now the treatment of choice and is associated with less than a 1% mortality. With any operation, the risk of embolism is always appreciable. However, pre-operative application of transesophageal echocardiography aids in the

identification of left atrial thrombi and therefore has limited risk of embolic stroke to 1.1% - 5.4%.[46]

Furthermore, a review conducted by Satya and colleagues highlighted how PTMV resulted in an estimated doubling of the mitral valve area coupled with a 50% decrease in the transmitral gradient. Long term follow-up highlighted continued functional enhancement with survival rates >80% at 10 years post-operation.[47]

A randomized controlled trial completed by Reyes and colleagues compared open mitral commissurotomy to PTMV. The study focused upon sixty patients with severe mitral stenosis, none of which were lost to follow up. Even though long-term results were similar and both techniques maintained a desired mitral valve area three years post-intervention, more desirable results were achieved through PTMV (2.4 $\pm$0.6 cm^2, vs. 1.8 $\pm$0.4 cm^2). Restenosis rates were similar in both groups and less than 40% had cardiovascular symptoms three years post-operation. The trial emphasized the potential complications with PTMV, but also noted superior hemodynamic results and faster recovery due to the eradication of the need for a thoracotomy. This led to a suggestion that those who are anatomically favorable should undergo PTMV rather than open commissurotomy.[48]

Transcatheter Mitral Valve Replacement

Multiple studies acknowledge that surgical repair of the MV is the preferred method of management in both primary and secondary MR, however, not all patients qualify for it.[7,13,27,31.]

Transcatheter mitral valve replacement (TMVR) is a relatively new therapy, a little over 500 patients receiving it to date worldwide. It is not as advanced as transcatheter aortic valve replacement due to the complexity of the MV and its anatomical structure: asymmetric annulus, intricate subvalvular apparatus, and located in close proximity to the left ventricle, subsequently being affected by changes in the left ventricular function.[49]

Similar to transcatheter MV repair, TMVR is accomplished using TEE guidance. In early studies, a left mini-thoracotomy was required to gain access to the left ventricle. Once inside, the device is directed up to the left atrium and aligned over the mitral annulus. A specific target area is identified and the new valve will be deployed, while the delivery system will be retracted.[50] Most of TMVR procedures still use this technique, as only 4 reported devices were technically successful using a transfemoral-transseptal approach, the first-in-human trial using the Sapien M3 valve publishing its results in 2019. Ten patients received the procedure and success was recorded in nine of them (one patient reported recurrent MR due to paravalvular leak).[51,52]

The valves can be mechanical or bioprosthetic and around 70% of patients who undergo mitral valve replacement will receive a bioprosthetic valve. Conversely, mechanical valves are believed to be more resilient as multiple studies report a much lower mortality rate, despite the need for anticoagulation therapy.[31,53,54]The same studies, however, highlighted the worryingly high rates of complications and postoperative mortality. Systematic reviews place the mortality rate anywhere between 10 to 60% after one year, while the risk of developing heart failure can be as high as 31%.[49,51,53,55] Tendyne prosthesis (Abbott Structural, Santa Clara the US) is the first TMVR device to gain CE approval in January 2020, but the evolution of TMVR systems is far from rapid, due to the strict selection criteria of ongoing clinical trials, which affect results by diminishing the external validity of the studies and their transferability to real-life clinical scenarios .[49,51]

Minimally Invasive Surgery

Surgical mitral valve repair is the gold standard for treating primary MR and around 95% of patients being treated in designated centres while the remaining 5% who are not suited for surgery, will be considered for one of the aforementioned transcatheter interventions. Its effectiveness on secondary MR is still disputed and current European guidelines encourage pharmacological management.[56]

Traditionally, surgical repair/replacement of the mitral valve was done via median sternotomy. In order to minimise mortality and morbidity, various minimally invasive approaches have been developed, but undoubtedly the most common approach is right minithoracotomy.[56-58] A small incision is made in the 4^{th} intercostal

space, providing access to the heart. The intervention requires access to femoral vessels for peripheral cannulation and connection to a cardiopulmonary bypass machine (CPB). TEE is used for guidance. Wolfe et al present in great detail the surgical technique and the four pillars of a successful minimally invasive mitral valve surgery (MIMVS): adequate cannulation and perfusion, good view of the mitral valve, thorough cardiac protection and procedure match to specific pathology and aetiology of MV defect.[58]

For correction of degenerative MR, one of the most prevalent MV pathologies, great results have been recorded using a non-resectional repair technique and implantation of new chordae using the loop technique, accompanied by ring annuloplasty for better resilience in the long-term. MV repair in the case of endocarditis is based on the removal of infected tissue and the use of a pericardial patch or repair using primary suturing, along with artificial chordae implant and ring annuloplasty. Annuloplasty with a closed, undersized ring is also used in the operation for ischemic MR.[57, 59,60]

Less perioperative complications (especially blood loss), decreased chances of surgical wound infection, as well as a shorter recovery period, have been the main advantages of MIMVS.[57,61,62] Operative survival rate in multiple retrospective studies has been 100% and mortality rate at 30-day follow up is between 0.2 to 4.8%, depending on patient profile, higher mortality being recorded for patients undergoing MIMVS with concomitant tricuspid valve repair or coronary artery bypass grafting.[60,63,64] Disadvantages of MIMVS, compared to standard sternotomy, include longer CPB time and increased risk of stroke during or immediately after intervention (almost 2.6% of patients have reported ischemic strokes).[59]

Conventional Sternotomy

Median sternotomy has been the preferred approach in mitral valve surgery for many years. It involves an incision due to complications such as inevitable blood loss, transfusion, and a higher risk of surgical site infections, MIMVS has gained ground as a first choice instead.[65,66] Sundermann et al. meta-analysis reports similar rates of mortality, but a clear advantage of MIMVS over conventional sternotomy when it comes to postoperative care and hospital stay.[66] Nonetheless, some surgeons argue that median sternotomy allows for better exposure and possibly even fewer complications.[67]

All in all, the efficacy of conventional sternotomy is comparable to that of MIMVS and ongoing clinical trials are still trying to provide the medical community with a definite answer.[68]

Future directions

This paper focused on percutaneous mitral valve repair with the MitraClip device, which is the only percutaneous technology accepted by the US Food and Drug Administration (FDA). However, there are other approaches to edge-to-edge mitral valve repair under development, such as PASCAL, valve clamp, and mitral stitch. The PASCAL mitral valve repair system adopts a transseptal approach. It involves a 22-French guide with a maneuverable catheter and an implanted catheter. It achieves its best position via a central spacer created to occupy the regurgitant orifice area, along with two paddles and two clasps that hold separate valve leaflets.[1,2] Such techniques, which aim to resolve the challenges posed by existing techniques, are currently being studied.[3]

The various advantages of minimally invasive surgery over conventional techniques have made minimally invasive surgery thrive in the past few years. However, there are still many difficulties associated with it, such as the restricted field of view, decreased maneuverability of the instruments, increased skill requirement, and higher costs.

Robots have been used in an attempt to solve some of the aforementioned challenges, and some success has been seen with the da Vinci SP (Intuitive Surgical, Sunnyvale, California, USA) robotic system.[69] However, the utility of robotic systems is still unable to prove significant improvements clinically. One study comparing robotic approach against minimally invasive surgery, found that robotic intervention had higher rates of transfusion (15% compared to 5% rates in MIMVS), as well as higher chances of developing atrial fibrillation post-surgery. Moreover, it is immensely expensive, which further strains the resources of the NHS.[70]

Ways to enhance the success of minimally invasive surgery and reduce its postoperative complications need to be explored further. The paper by Gillinov et al. analysing robotic mitral valve repair in 1000 patients described a decrease in stroke risk (which is originally linked to long CPB time) after the first 500 cases, from 2% to 0.8%. This sheds a light on the importance of the learning curve among surgeons and how this may pose an impediment in adopting robotic mitral valve surgery as a conventional approach.[71]

Conclusion

Understanding the management of mitral valve diseases is ever-evolving with satisfactory outcomes through minimally invasive and percutaneous approaches. Future studies, perhaps, could focus on long term results of such approaches and patient selection methods.

Human Studies: No ethical approval required as no patient information was shared

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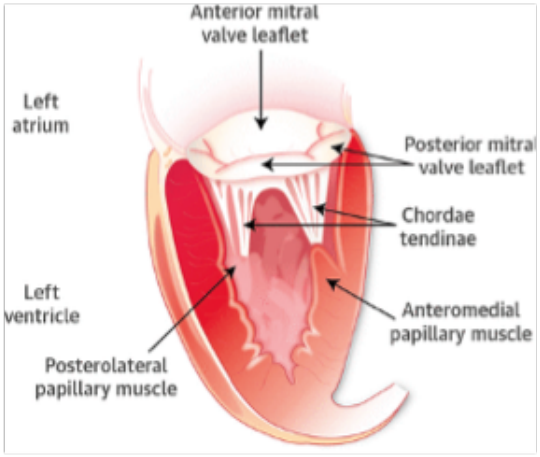

Figure 1: Mitral valve anatomy from Asgar et al. *Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations.*[12]