General Introduction and Outline of the Thesis

GENERAL INTRODUCTION

Mitral valve and regurgitation

Valvular regurgitations are among the most frequent heart diseases [1,2] and mitral regurgitation (MR) is considered the most common valve disease with a prevalence of 2-3% having significant regurgitation in the general population [2]. MR is defined as systolic regurgitation of blood from the left ventricle (LV) to the left atrium (LA) and results from incomplete mitral valve (MV) closure and a pressure gradient between the LV and LA. Incomplete MV closure results from dysfunction of one of the components of the MV apparatus, which includes the mitral annulus, leaflets, chordae tendineae, papillary muscles and the underlying LV wall (Figure 1).

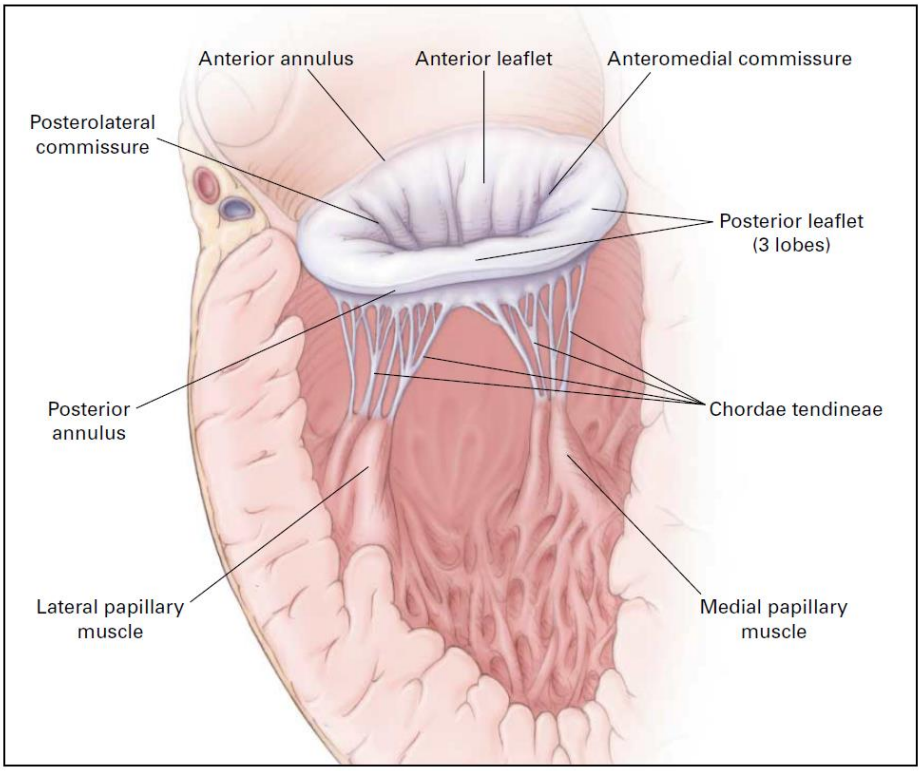

Figure 1. Mitral valvular apparatus. *Reproduced with permission from Otto CM. Evaluation and management of chronic mitral regurgitation.* N Engl J Med. *2001;345:740-746, Copyright Massachusetts Medical Society.*

The mitral annulus is a highly complex saddle-shaped anatomical and functional entity, which is directly related to hemodynamic changes subsequent to muscle contraction of the LV, LA and motion of the aortic root throughout the cardiac cycle [3]. It plays an important

role in leaflet coaptation, in unloading MV closing forces and in promoting LA and LV filling and emptying. Enlargement of the annulus is mostly seen secondary to LV cavity dilatation in dilated cardiomyopathy or in remodeling as result of scar formation after myocardial infarction [4]. Primary mitral annular remodeling is also seen in patients with MV prolapse or atrial fibrillation [5,6].

The leaflet part of the MV apparatus consists of two leaflets with a larger and usually thicker anterior leaflet with a trapezoid or dome-shape. The posterior leaflet is crescent-shaped with a shorter radial length but longer circumferential base that is attached to the posterior mitral annulus [7]. Both leaflets can be dived into three parts with a lateral (A1/P1), central (A2/P2) and medial scallop (A3/P3), with demarcating indentations and slits only seen in the posterior leaflet (Figure 2). Additional commissural leaflet tissue can be found at the anterolateral and posteromedial commissures.

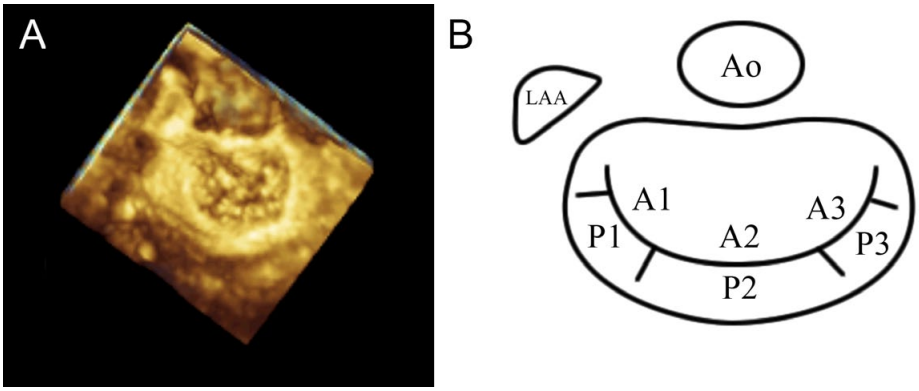

Figure 2.
A. En-face view of a normal mitral valve with 3D echocardiography
B. Schematic representation of the anterior (A1/A2/A3) and posterior (P1/P2/P3) mitral valve scallops. LAA: left atrial appendage, Ao: aorta

The leaflets are connected with the papillary muscles and the LV wall by chordae tendineae. From each papillary muscle, chordae attach to the ipsilateral half of both MV leaflets. The primary chords attach to the free margins of the leaflets and secondary chordae insert close to the rough zone of the leaflets. The tertiary chords arise directly from the LV wall or from the trabeculae carnae and insert exclusively into the posterior leaflet [8]. Primary and secondary chordae have different functions with primary chordae to maintain leaflet apposition and secondary chordae to maintain normal LV size and geometry [9]. Elongation or rupture of the primary chordae leads to significant MR. Secondary chordae rarely rupture and are not critical to maintaining coaptation [7].

Two papillary muscles are present: the anterolateral and posteromedial. Their location is variable, but they are most commonly attached to the middle third of the LV wall avoiding

the interventricular septum and are designated by their projected relationship to the lateral and medial mitral commissures [10]. In most cases, the lateral papillary muscle has a single head and dual blood supply whereas the medial papillary muscle has commonly two heads and single blood supply by the right coronary artery or the circumflex, based on coronary dominance [7].

According to etiology and pathophysiology, MR can be divided somewhat artificially into a primary or organic and a secondary or functional categories [11,12]. In primary lesions, one or more of the components of the MV itself are deranged. Acute MR will occur in case of traumatic, papillary muscle rupture usually associated with a myocardial infarction or infective endocarditis with leaflet perforation or chordal rupture. With the reducing prevalence of rheumatic fever and increased lifespan nowadays degenerative MV disease, leading to leaflet prolapse due to chordal elongation or rupture, is the most common etiology for primary chronic MR in Europe [1]. Barlow's disease with myxomatous degeneration is seen more in a younger population whereas older populations more often present with fibro-elastic deficiency in which lack of connective tissue leads to chordal rupture. Other less common causes of primary chronic MR are infective endocarditis, connective tissue disorders, congenital cleft and radiation heart disease. In secondary lesions geometric and/or functional changes of the LV are the core of the problem with idiopathic cardiomyopathy and coronary artery disease as main causes. MR results from tethering (apical and lateral papillary muscle displacement, annular dilatation) and reduced closing forces due to LV dysfunction (reduced contractility and/or LV dyssynchrony) [11].

In 1983 Carpentier distinguished in his classical report about the pathophysiologic classification of the MV three types of pathology on the basis of a functional approach: in type I there is a normal leaflet motion, type II is associated with increased leaflet motion and type III is associated with restricted leaflet motion [13]. More recently, Shah and Raney proposed an updated classification based on echocardiography in order to provide a more comprehensive and detailed assessment of MV disorders which may be more relevant to modern MV repair techniques [14,15].

Echocardiography

The MV was the first of the four cardiac valves to be evaluated with echocardiography. Over the last fifty years conventional two-dimensional (2D) echocardiography has served as a valuable clinical tool and is still the imaging modality of choice for the diagnosis and management of MR [11,12]. For accurately assessing MV morphology, 2D transthoracic echocardiography (TTE) and transesophageal echocardiography (TOE) are often used. Although 2D-echocardiography is a non-ionizing and cost-effective technique, the cardiologist has to reconstruct mentally the complex structure of the heart, resulting in geometrical assumptions, which in turn could underestimate the validity of clinical findings. With the introduction of three-dimensional (3D) echocardiography there is now a feasible technique

for rapid and accurate identification of MV pathology and in some studies it has been shown to be superior to 2D in patients with MR [16,17].

MR severity depends on the degree of leaflet malcoaptation: it can range from trace to severe and increases over time [18]. Echocardiographic assessment of MR severity consists primarily of colour Doppler flow imaging. To quantify MR severity, measurement of the vena contracta (Figure 3A) and proximal isovelocity surface area (PISA) (Figure 3B) are recommended [19]. The vena contracta is measured as the narrowest width of the MR jet just distal to the leaflet tips. It is a simple linear measurement of the regurgitant orifice and is relatively independent of loading conditions. Three-dimensional measurements of the vena contracta may be more accurate, in particular in asymmetric regurgitant orifices seen in functional MR, because the effective regurgitant orifice area is now measured without geometric assumptions [20]. The PISA method is based on a geometric assumption of a hemispherical flow shape distal to the regurgitant orifice. Just as the vena contracta, the PISA method is also subject to research in 3D echocardiography [21]. However, all these 3D approaches have not yet found their way into clinical routine application.

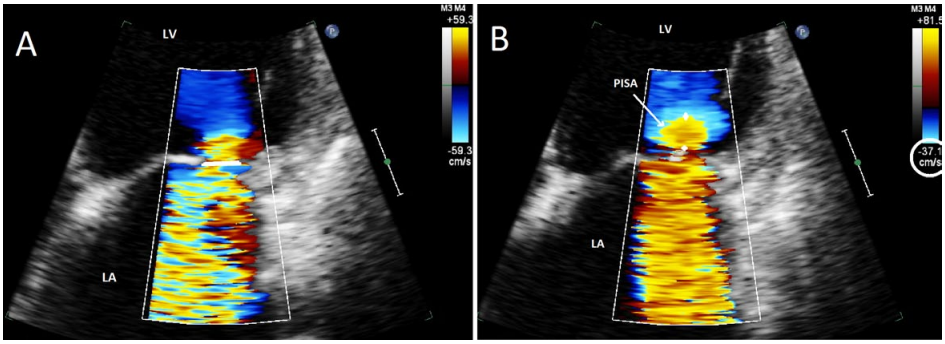

Figure 3.
A. Vena contacta measurement (white line)
B. PISA method: measurement of the radius (between white dots) to calculate the PISA after optimizing by decreasing the depth, narrowing the sector, using zoom mode and adjusting the aliasing limit to a value between 20-40 cm/s with shifting the baseline downward. LV: left ventricle. LA: left atrium.

Surgical and percutaneous treatment of MR

In multiple studies impaired long-term survival in patients with MR has been reported, which led to a worldwide consensus and acceptance of surgical repair of the MV to prevent LV dysfunction and mortality [11,12,22]. Through preservation of normal valvular tissue and the subvalvular apparatus, MV repair optimizes postoperative LV function and is preferred over MV replacement. Compared with MV replacement, MV repair has a lower surgical mortality risk and provides better survival, in particular in patients with degenerative MV disease [23,24]. In MV surgery for secondary MR, MV repair was considered the gold standard, but reports of high recurrence rates raised doubts. Comparing MV repair with replacement

Acker et al. observed no significant difference in left ventricular reverse remodeling or survival at 12 months [25].

MV repair may combine different techniques as annuloplasty, resection, sliding plasty or chordal replacement according to etiology. Repair of disease of the anterior leaflet is more challenging than repair of disease of the posterior leaflet, mostly prolapse, with the anterior leaflet to be more important to retain geometry and mobility.

Open chest procedures with a full sternotomy are the gold standard for MV surgery, but over the last few years the use of minimally invasive techniques for MV repair with a partial sternotomy approach or with minimally invasive, video-assisted, surgery through the right thoracic cavity have steadily increased. These techniques are associated with equivalent mortality and major morbidity, but with superior cosmetics, faster recovery, reduced hospital costs and lower risk of atrial fibrillation and bleeding [26]. Especially in young and in asymptomatic patients these arguments help to convince these patients to undergo MV repair [27].

For patients at high risk for surgical treatment there are currently also percutaneous alternatives. Although numerous percutaneous annuloplasty techniques are being tested in clinical trials [28], the MitraClip® system is the main technique used in clinical practice. By a transseptally introduced catheter system, a metallic clip covered with a polyester fabric is guided towards the MV. The clip is able to grasp and approximate the free edges of the MV leaflets, analogue to the surgical Alfieri stich technique [29]. The clip can be removed or re-positioned if the immediate result is not satisfactory, or an additional clip can be implanted. The safety, feasibility and echocardiographic results of this MitraClip® system were demonstrated in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) trials [30,31]. Also, in real-world registries good clinical outcomes have been described, particularly the COAPT and MITRA-FR trials are relevant in this regard and will be discussed in the final chapter of this thesis, but questions about the most appropriate patient population to treat and at what time to treat still need to be answered [32-34].

OUTLINE OF THE THESIS

The aims of this thesis are to investigate the role of echocardiography in identification of MR mechanism and quantifying MR severity and to evaluate MR outcome. For this purpose, the thesis is divided into three main parts.

Identification of MR mechanism

A new, updated echocardiographic classification of MR mechanisms with special attention to the added value of three-dimensional (3D) echocardiography is described in **Chapter 2**. The optimal echocardiographic measurement of mitral annulus size, one of the main

mechanisms of MR, is discussed in **Chapter 3**. In **Chapters 4** and **5** the role of new echocardiographic techniques such as 2D xPlane imaging and 3D echocardiography for the evaluation of the site and extent of MV prolapse is discussed.

Quantification of MR severity

To determine the severity and need for intervention, quantification of MR is recommended. In **Chapter 6** errors in calculating MR volume according to present methods are discussed. In **Chapter 7** the gap between guidelines and real-world practice in echocardiographic quantification of MR in patients referred for MV surgery is discussed.

Evaluation of MR outcome

In this part of the thesis we report outcome of MR treated conservatively, with MV surgery and the MitraClip® system. The results of optimization of heart failure therapy on secondary moderate-to-severe MR is reported in **Chapter 8**. Outcome after minimal or conventional MV surgery in asymptomatic and symptomatic patients with MR is reported in **Chapters 9** and **10**. The role of the anatomy of the MV complex and outcome after transcatheter MV intervention with the MitraClip® system is discussed in **Chapters 11** and **12**. Finally, in **Chapter 13** we reflect on and discuss the most important findings of this thesis.

REFERENCES

1. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-43.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.
3. Silbiger JJ. Anatomy, mechanics, and pathophysiology of the mitral annulus. Am Heart J 2012;164:163-76.
4. Silbiger JJ. Mechanistic insights into ischemic mitral regurgitation: echocardiographic and surgical implications. J Am Soc Echocardiogr 2011;24:707-19.
5. Ennezat PV, Marechaux S, Pibarot P, Le Jemtel TH. Secondary mitral regurgitation in heart failure with reduced or preserved left ventricular ejection fraction. Cardiology 2013;125:110-7.
6. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. II. Abnormalities in mitral valve prolapse. Circulation 1982;65:713-9.
7. Dal-Bianco JP, Beaudoin J, Handschumacher MD, Levine RA. Basic mechanisms of mitral regurgitation. Can J Cardiol 2014;30:971-81.
8. Silbiger JJ, Bazaz R. Contemporary insights into the functional anatomy of the mitral valve. Am Heart J 2009;158:887-95.
9. Obadia JF, Casali C, Chassignolle JF, Janier M. Mitral subvalvular apparatus: different functions of primary and secondary chordae. Circulation 1997;96:3124-8.
10. Victor S, Nayak VM. Variations in the papillary muscles of the normal mitral valve and their surgical relevance. J Card Surg 1995;10:597-607.
11. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012;33:2451-96.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
13. Carpentier A. Cardiac valve surgery--the “French correction”. J Thorac Cardiovasc Surg 1983;86:323-37.
14. Shah PM, Raney AA. Echocardiography in mitral regurgitation with relevance to valve surgery. J Am Soc Echocardiogr 2011;24:1086-91.
15. Shah PM, Raney AA. New echocardiography-based classification of mitral valve pathology: relevance to surgical valve repair. J Heart Valve Dis 2012;21:37-40.
16. Ben Zekry S, Nagueh SF, Little SH, et al. Comparative accuracy of two- and three-dimensional transthoracic and transesophageal echocardiography in identifying mitral valve pathology in patients undergoing mitral valve repair: initial observations. J Am Soc Echocardiogr 2011;24:1079-85.
17. Grewal J, Mankad S, Freeman WK, et al. Real-time three-dimensional transesophageal echocardiography in the intraoperative assessment of mitral valve disease. J Am Soc Echocardiogr 2009;22:34-41.
18. Enriquez-Sarano M, Basmadjian AJ, Rossi A, Bailey KR, Seward JB, Tajik AJ. Progression of mitral regurgitation: a prospective Doppler echocardiographic study. J Am Coll Cardiol 1999;34:1137-44.
19. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.

20. Thavendiranathan P, Phelan D, Thomas JD, Flamm SD, Marwick TH. Quantitative assessment of mitral regurgitation: validation of new methods. J Am Coll Cardiol 2012;60:1470-83.
21. Buck T, Plicht B. Real-Time Three-Dimensional Echocardiographic Assessment of Severity of Mitral Regurgitation Using Proximal Isovelocity Surface Area and Vena Contracta Area Method. Lessons We Learned and Clinical Implications. Curr Cardiovasc Imaging Rep 2015;8:38.
22. Gillinov AM, Mihaljevic T, Blackstone EH, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? Ann Thorac Surg 2010;90:481-8.
23. Shuhaiber J, Anderson RJ. Meta-analysis of clinical outcomes following surgical mitral valve repair or replacement. Eur J Cardiothorac Surg 2007;31:267-75.
24. Dayan V, Soca G, Cura L, Mestres CA. Similar survival after mitral valve replacement or repair for ischemic mitral regurgitation: a meta-analysis. Ann Thorac Surg 2014;97:758-65.
25. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23-32.
26. Yanagawa B, Latter D, Verma S. Year in review: mitral valve surgery. Curr Opin Cardiol 2016;31:148-53.
27. Ramzy D, Trento A. Minimal invasive mitral valve surgery does make a difference: Should it be the gold standard for mitral valve repair? Trends Cardiovasc Med 2015;25:466-8.
28. Kelley C, Lazkani M, Farah J, Pershad A. Percutaneous mitral valve repair: A new treatment for mitral regurgitation. Indian Heart J 2016;68:399-404.
29. Alfieri O, De Bonis M. The role of the edge-to-edge repair in the surgical treatment of mitral regurgitation. J Card Surg 2010;25:536-41.
30. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol 2009;54:686-94.
31. Mauri L, Foster E, Glower DD, et al. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol 2013;62:317-28.
32. Stewart MH, Jenkins JS. The Evolving Role of Percutaneous Mitral Valve Repair. Ochsner J 2016;16:270-6.
33. Stone G, Abraham W, Lindenfeld J, et al. TCT-627 Cardiovascular Outcomes Assessment of MitraClip Therapy in Heart Failure Patients with Functional Mitral Regurgitation (The COAPT Trial): Baseline Characteristics and Preliminary 30-Day and 1-Year Outcomes of the Roll-In Cohort. J Am Coll Cardiol 2016;68:B255.
34. Obadia JF, Armoiry X, Iung B, et al. The MITRA-FR study: design and rationale of a randomised study of percutaneous mitral valve repair compared with optimal medical management alone for severe secondary mitral regurgitation. EuroIntervention 2015;10:1354-60.