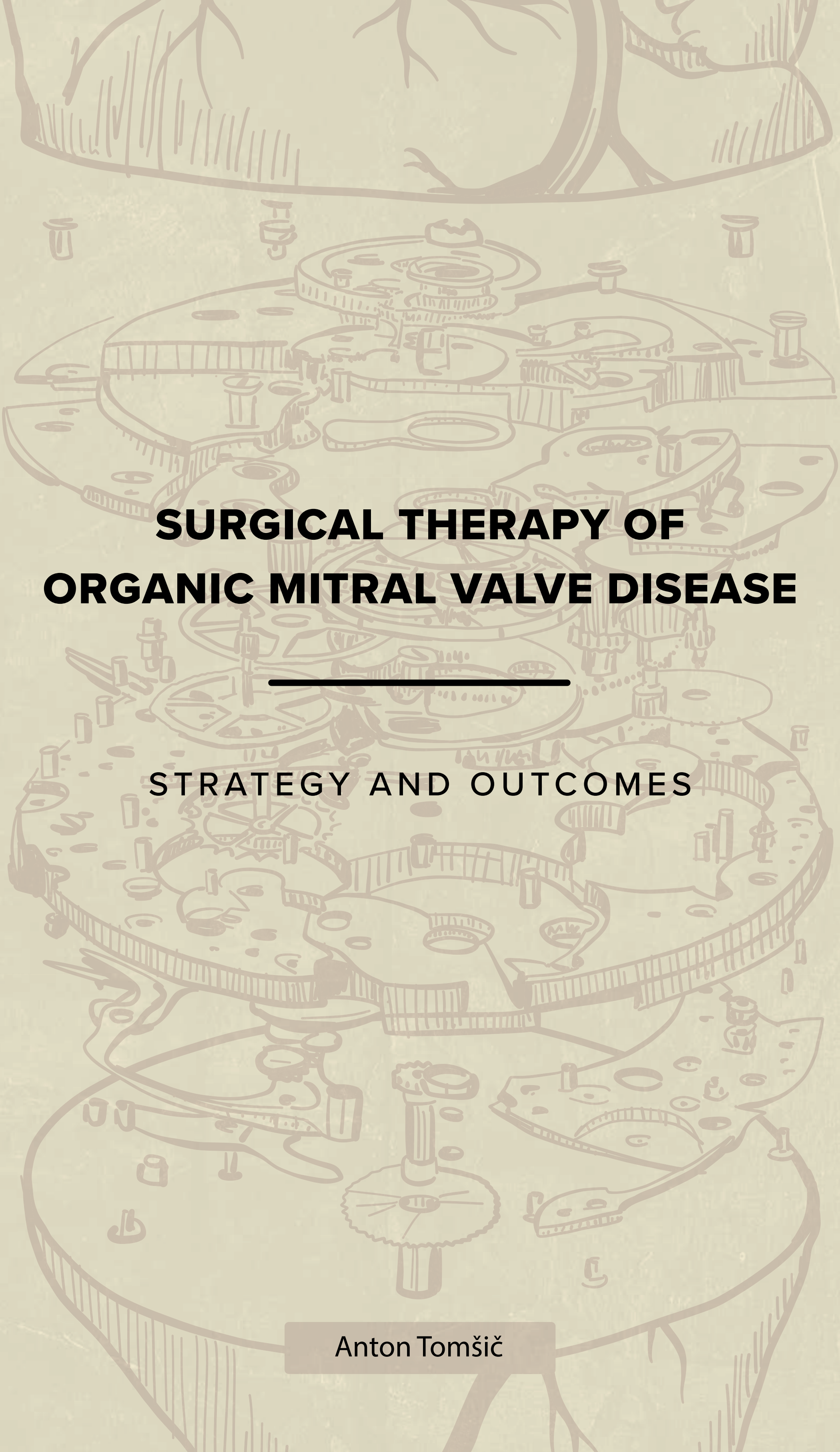
Surgical therapy of organic mitral valve disease: Strategy and outcomes

Tomsic, A.

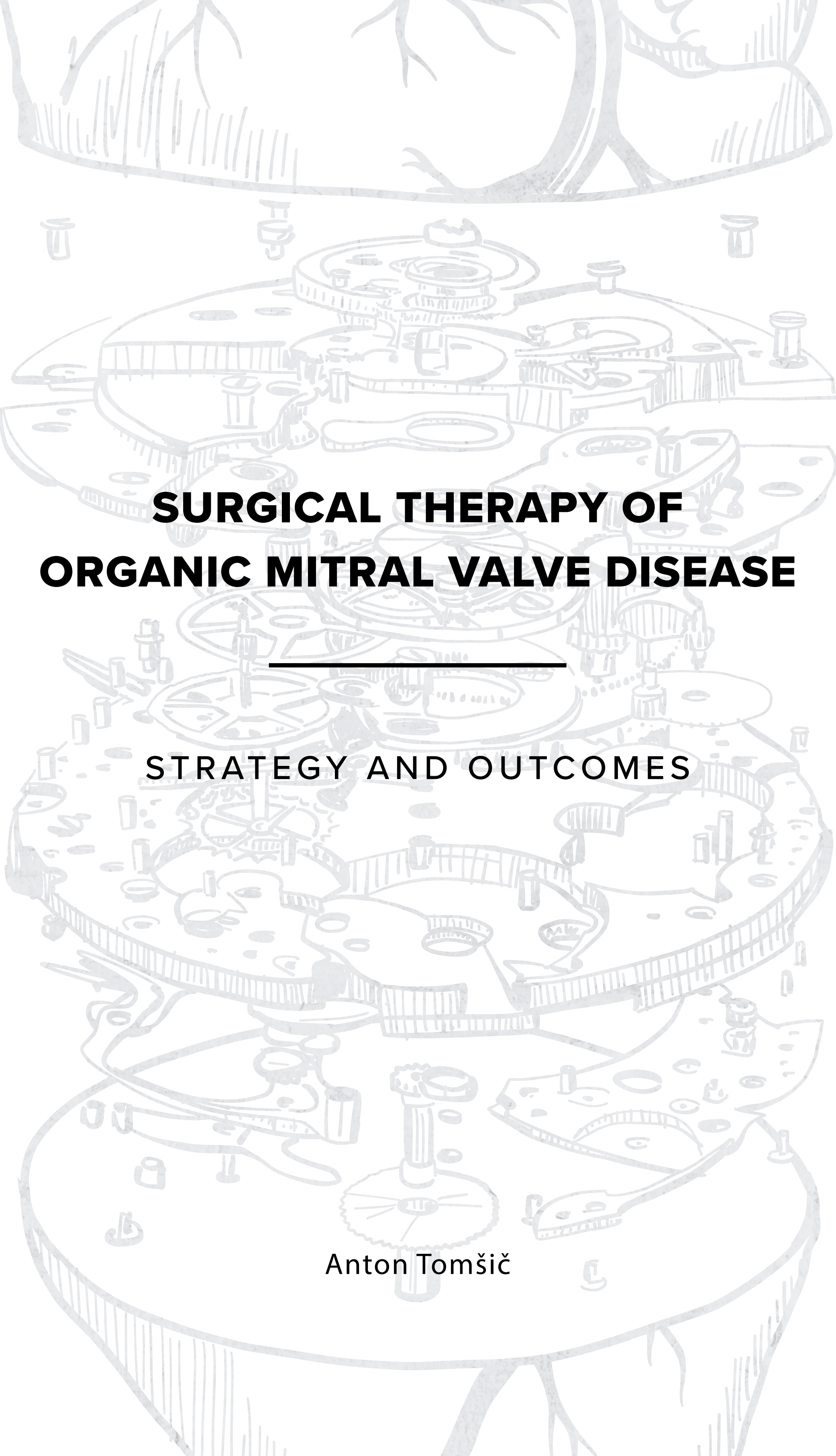
Author: Tomsic, A.
Title: Surgical therapy of organic mitral valve disease: Strategy and outcomes
Issue Date: 2021-02-18



SURGICAL THERAPY OF ORGANIC MITRAL VALVE DISEASE

STRATEGY AND OUTCOMES

Anton Tomšič



SURGICAL THERAPY OF ORGANIC MITRAL VALVE DISEASE

STRATEGY AND OUTCOMES

Anton Tomšič

COLOPHON

Cover design:	James Jardine | www.jamesjardine.nl
Layout:	James Jardine | www.jamesjardine.nl
Print:	Ridderprint | www.ridderprint.nl
ISBN:	978-94-6416-405-3

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Financial support for printing of this thesis by AtriCure B.V., Boehringer Ingelheim B.V., Canon Medical Systems Nederland, ChipSoft, Krijnen Medical Innovations B.V. and QP&S B.V. is gratefully acknowledged.

SURGICAL THERAPY OF ORGANIC MITRAL VALVE DISEASE: STRATEGY AND OUTCOMES

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. dr. ir. H. Bijl,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 18 februari 2021
klokke 15:00 uur

door

Anton Tomšič

Geboren te Ljubljana, Slovenië
in 1988

Promotor

Prof. Dr. R.J.M. Klautz

Co-promotores

Dr. M. Palmen
Dr. N. Ajmone Marsan

Leden promotiecommissie

Prof. Dr. M.J. Schalij
Dr. V. Delgado
Prof. G. El-Khoury, University Hospital Saint-Luc, Brussels
Prof. Dr. S.A.J. Chamuleau, Amsterdam UMC, Amsterdam

Za moje starše

TABLE OF CONTENTS

01

General introduction

INTRODUCTION

Organic or primary mitral valve disease is a group of diseases that primarily affects the mitral valve apparatus, directly resulting in valve dysfunction (either mitral valve regurgitation, stenosis or a combination of both). It is to be distinguished from functional or secondary mitral valve disease in which valve dysfunction is a consequence of wall motion abnormalities of the left ventricle [1, 2]. Both groups differ not only in terms of etiology but also in treatment considerations and patient prognosis [2-5].

The modern classification of mitral valve disease is based on the pioneering work of Carpentier [1] who proposed a functional classification of mitral valve diseases and provided a foundation for the subsequent developments in the field (**Table I**). It is important to understand that the type of classification does not directly imply a specific etiology and that various classification types can be seen in a single patient.

TABLE I. Carpentier's functional classification of mitral valve diseases.

Functional classification	Dysfunction (leaflet motion)	Lesion	Etiology
Type I	Normal	• Annular dilation • Leaflet perforation or tear • Vegetations	• Dilated cardiomyopathy • Endocarditis • Chronic atrial fibrillation
Type II	Excessive leaflet motion (prolapse)	• Chordae tendineae elongation or rupture • Papillary muscle elongation or rupture	• Degenerative mitral valve disease • Endocarditis • Trauma
Type III	Restricted leaflet motion		
Type IIIa	Restricted opening (diastolic motion) and closure (systolic motion)	• Leaflet thickening or retraction • Leaflet calcification • Chordal thickening, retraction or fusion • Commissural fusion	• Rheumatic heart disease • Carcinoid heart disease • Post-radiation
Type IIIb	Restricted closure (systolic motion)	• Left ventricular dilation or aneurysm • Papillary muscle displacement	• Dilated or ischemic cardiomyopathy

Since the beginning of cardiac surgery, significant changes in epidemiology, diagnosis and treatment of organic mitral valve disease have occurred. Rheumatic valve disease, that most commonly results in combined valve stenosis and, usually to a lesser extent, regurgitation, used to present the most common etiology [6]. To date, it remains an important health care problem in developing countries [7]. On the other hand, a significant decline in the incidence of rheumatic valve disease was observed in Western countries over the course of the 20th century. Over time, degenerative disease has become the leading cause of mitral valve dysfunction in these countries and, in Europe, nowadays presents the second most common valvular heart disease [8]. Due to the lack of contemporary population-based studies, the true prevalence of degenerative mitral valve disease in Europe is, however, hard to establish. Data from the United States of America demonstrate that significant (moderate or severe) mitral regurgitation affects 1.7% of the general North American population [9]. Contrary to aortic valve stenosis –the most common valvular heart disease in Europe that predominantly affects elderly patients [8]- the incidence of mitral regurgitation begins to rise in middle ages, potentiating its clinical and economic burden [7]. Surgical intervention in patients with degenerative mitral valve disease is nowadays linked to high repair and low mortality rates [10-12]. The high safety and effectiveness of surgical treatment for degenerative disease established in recent decades carries important consequences for treatment considerations in these patients, with a continuous lowering of the threshold for surgical intervention.

Contrary to degenerative mitral valve disease, infective endocarditis remains a complex disease with high morbidity and mortality rates that most commonly affects the mitral valve [13, 14]. In these patients, the mitral valve is infected by pathogens that cause tissue destruction and vegetation formation. This can result in detrimental effects on valve function, often resulting in rapid development of hemodynamically significant mitral regurgitation. Moreover, the disease often presents itself with complications of vegetation formation (with the risk of peripheral embolization) or destruction of surrounding structures (i.e. conduction system of the heart). According to recent publications on the incidence and prevalence of heart valve disease in the Netherlands [15, 16], infective endocarditis is a relatively rare disease, present in less than 2% of patients undergoing open-heart surgery (about 6% of patients who undergo surgical valve intervention). Despite the fact that infective endocarditis is a relatively rare disease, the high morbidity and mortality rates significantly potentiate its clinical significance. Moreover, a rise in the incidence of infective endocarditis has recently been reported [17, 18]. Underlying valve disease is a strong risk factor for the development of infective endocarditis and patients with yet undiagnosed degenerative mitral valve disease are at increased risk of developing this complication. Underlying degenerative mitral valve disease is present in about 40% of patients who undergo operation for active native infective endocarditis [19-21].

When left untreated, severe mitral valve disease will result in volume overload of the left ventricle and atrium (in case of valve regurgitation) and/or pressure overload of the left atrium (in case of valve stenosis). Over time this will result in the known complications of long-lasting severe mitral valve disease that include left ventricular dilation and functional decline, left atrial dilation, atrial fibrillation, elevated pulmonary artery pressures as well as functional and morphological changes of right heart chambers. The understanding of the effect of severe mitral regurgitation on cardiac function has progressed over time. An early report from the 1970s argued that sudden restoration of mitral valve competence will result in a deleterious effect on left ventricular function [22]. Nowadays, impaired left ventricular function is known to present a consequence of morphological and structural changes of the left ventricle that result from long-lasting volume overload [23-26]. Indeed, preservation of left ventricular function has become one of the leading arguments for early surgical intervention in the yet asymptomatic phase of mitral valve disease. Interestingly, a growing interest in an "early surgery" approach can lately be observed not only in cases of degenerative disease but mitral valve infective endocarditis as well [27]. While disease presentation and consequences of delaying surgery differ significantly between both etiologies and are hardly comparable, one could argue that improved understanding of mitral valve disease, increasing safety of cardiac surgery and growing surgical expertise are the major contributors to this trend in both cases.

Advancements in cardiac imaging techniques have improved our understanding of valve function and hereto related abnormalities, particularly in case of degenerative mitral valve disease. These advancements somehow challenge the basic concepts established by Carpentier and will be discussed in this thesis. Moreover, a large number of controversies regarding the optimal choice of valve repair techniques persist to date. Therefore, this thesis will focus on the timing, technical aspects and outcomes of mitral valve surgery in patients with either degenerative valve disease or native valve infective endocarditis.

THE MITRAL VALVE APPARATUS

Anatomy of the Mitral Valve

The mitral valve is a complex structure that anatomically and functionally connects the left atrium and left ventricle. It consists of mitral valve leaflets, chordae tendineae, papillary muscles and the mitral valve annulus, a part of the fibrous cardiac skeleton [28-30]. The latter is formed by condensation of collagenous connective tissue that serves as the anchor point for mitral leaflets. The superior part of the mitral valve annulus is attached to the muscles of the left atrium. On the inferior part, the annulus is attached to the left ventricle posteriorly and the aortic root anteriorly.

The mitral valve consists of two leaflets- the anterior and posterior mitral valve leaflet. Both leaflets are –as described by Carpentier [31]- divided into three segments: the A1/P1, A2/P2 and A3/P3 segments. The A1/P1 segments are adjacent to the anterolateral commissure and the A3/P3 to the posteromedial one. The posterior leaflet consists of three clearly defined scallops that are normally divided by distinct leaflet indentations. On the other hand, indentations on the anterior leaflet are usually absent and the division into respective segments is made by referring the parts of the anterior leaflet to the clearly distinguished segments of the posterior leaflet.

The base of the anterior mitral valve leaflet encompasses one-third of the mitral annular circumference [29]. At the level of the annulus, the anterior leaflet merges with the aortic-mitral continuity that fuses with the aortic root at the site of the left ventricular outflow tract (at the level of the left coronary and non-coronary sinus). This region of the annulus consists of fibrous tissue and is therefore less prone to dilation. The base of the posterior mitral valve leaflet encompasses the remaining two-thirds of the annular circumference [29]. The corresponding mitral valve annulus is mainly a muscular structure and therefore prone to dilation. While the height (distance between leaflet base and free edge) of the posterior leaflet is lower than the anterior one, both leaflets have comparable surface areas. The anterolateral and posteromedial commissures can be found at sides where both leaflets meet. The anatomy of these segments varies considerably [32]- they normally consist of a relatively well-defined leaflet segment that can be best identified by the presence of fan-shaped chordae tendineae. The latter normally originate from a separate papillary muscle head and provide support to the free edge of the commissural segment.

Normal mitral valve leaflets are thin, pliable and translucent. The leaflets have two distinct surfaces- the atrial and ventricular one. On the atrial leaflet surface, two zones can be distinguished in case of the anterior leaflet (the clear and rough zone) and three in case of the posterior leaflet (the basal, clear and rough zones) [28]. The rough zone of both leaflets corresponds to the surface area of leaflet coaptation.

Mitral valve leaflets are connected to papillary muscles –and hereby the left ventricle- by chordae tendineae. The chordae arise from papillary muscles and terminate at the:

1. Free edge of the mitral valve leaflets (*primary chordae*),
2. Ventricular surface of the mitral valve leaflets (*secondary chordae*),
3. Leaflet base (*tertiary or basal chordae*). These chordae are present only on the ventricular surface of the posterior leaflet.

Chordae tendineae arise from two distinct papillary muscle groups, the anterolateral and posteromedial group. The anterolateral papillary muscle group provides chordal support to the lateral part of the mitral valve (the anterolateral commissure, the A1/P1 segment and the lateral part of the A2/P2 segments). Accordingly, the posteromedial papillary muscle group provides chordal support the medial part of the mitral valve (the posteromedial commissure, the A3/P3 segments and the medial parts of the A2/P2 segments). At the time of valve repair, it is important to respect these anatomical relations.

Mitral Valve Mechanics

The mitral valve is a dynamic structure which's function results from contraction and relaxation of the left atrium and ventricle and the pressure changes that direct intra-cardiac blood flow. At the end of left ventricular isovolumetric relaxation, the pressure in the left atrium exceeds that of the left ventricle. This results in forward blood flow and diastolic filling of the left ventricle, preceded by passive mitral valve leaflet opening. As ventricular filling proceeds, ventricular pressure rises and atrial pressure falls, decreasing the blood flow driving pressure difference between both heart chambers. Blood flow through the mitral valve is normally biphasic [30]. Throughout the left ventricular systole, pulmonary venous flow fills the left atrium, stretching and, presumably, storing potential energy in the left atrial walls. This energy is available to assist in the initial diastolic left ventricular filling peak (termed E-wave). This is followed by partial closure of the mitral valve and later followed by a second filling peak (termed A-wave), occurring in late diastole [33]. Interestingly, experimental studies have suggested that left ventricular filling is relatively independent of left atrial contraction. The left atrium seems to serve only as a conduit for blood flow from the pulmonary veins into the left ventricle [34]. However, mitral valve opening does not seem to present a completely passive event as leaflet opening during the second filling peak seems to be enhanced by contraction of muscles in the annular portion of the anterior and posterior leaflets [34].

The systolic phase of the cardiac cycle starts with an isovolumetric contraction of the left ventricle. At the onset of ventricular contraction, the flow over the mitral valve is still very high and the valve is almost fully open [35]. The ensuing mitral valve closure mechanism is more complex than the mechanism of diastolic opening. Bellhouse et al. first proposed that the vortices formed during early left ventricular filling phase play a role in valve closure [36]. Reul et al., on the other hand, proposed that valve closure is not dependent on the formation of vortices but results from the systolic reversal of the atrio-ventricular pressure gradient with subsequent blood flow deceleration [33]. More recent studies, applying 4-dimensional cardiac magnetic resonance imaging, demonstrated that vortex formation is a biphasic event, occurring during the early as well as the late left ventricular filling phase [37]. The latter vortices, though weakened or absent in a proportion of individuals, could play a role in valve closure. Yellin et al. proposed that chordal tension, blood flow deceleration and vortices formation all play important roles in the mechanism of valve closure with chordal tension presenting a necessary condition for normal valve closure [38]. Hereby, the mechanism of valve closure in case of ectopic ventricular beats can be explained as well. The mechanism of valve closure thus most likely results from a combination of various mechanisms.

The three-dimensional leaflet form, that varies considerably throughout the cardiac cycle, is determined by chordae tendineae. It has been shown that the primary chordae are not constantly under tension; on the contrary, other types of chordae remain under tension throughout the whole cardiac cycle [34]. During valve closure, the chordae tendineae allow the mitral leaflets to engage their systolic form and, in the case of primary chordae, prevent leaflet prolapse. However, once the valve is fully closed, leaflet configuration is relatively independent, reflected by a low force exerted by the chordae during systole [39]. The leaflets do not function as passive structures but demonstrate, especially in case of the anterior leaflet, systolic stiffening that allows them to counterbalance the forces generated by the left ventricle. It has been shown that a significant force transfer occurs through the mitral valve-left ventricular interaction, enhancing left ventricular systolic performance [40]. This seems to be a function of papillary muscle shortening and contributes to as much as 10% of total left ventricular systolic force [40].

The shape of the normal mitral valve annulus resembles a saddle [41]. The anterior portion of the annulus, attached to the aortic root, presents the highest point. Extending posteriorly the annulus slopes down, reaching its lowest point at the area of the commissures. The posterior part of the annulus slopes up again but does not reach the height of the anterior part. Although a relatively simple structure, the movement of the annulus consists of complex three-dimensional changes, aimed at optimizing valve function. A sphincter-like movement of the annulus is initiated in late diastole, resulting in a reduction of the mitral valve annular area, promoting leaflet apposition and coaptation [41].

From early diastole to end-systole, the posterior two-thirds of the annulus contract, resulting in shortening of the posterior annular perimeter. Normally, the posterior annular perimeter is thus longest in diastole, resulting in a diastolic enhancement of the mitral valve area [42, 43]. Changes in the posterior annular length are not evenly distributed along the whole perimeter but occur primarily at annular sections that correspond to posterior leaflet indentations [34]. On the other hand, the anterior annular perimeter is shortest in diastole and reaches its maximal length in systole, resulting from systolic expansion of the aortic root that assists in left ventricular ejection [44]. The diastolic shortening of the anterior annular perimeter is several times smaller than the diastolic expansion of the posterior annular perimeter, resulting in a net increase of the mitral annular circumference during diastole. These cyclic changes in anterior and posterior annular perimeter length, and hereto related changes in the mitral valve annular area, are important to allow unobstructed diastolic trans-valvular blood flow. These characteristics of normal annular motion are important to appreciate in order to understand the changes in diastolic trans-valvular blood flow that occur after the implantation of an annuloplasty ring or band. Regardless of the type of device used, prosthetic annuloplasty will result in fixation of the maximal posterior annular perimeter.

In addition to the sphincter-like movement of the mitral valve annulus, systolic apposition of valve leaflets is augmented by early-systolic isovolumetric contraction of the left ventricle. This results in an upward and backward rotation of the anterior part of the annulus, ultimately displacing the anterior mitral valve leaflet posteriorly towards the posterior one. The elliptical mitral valve annulus also demonstrates cyclic changes in the ratio between the anterior-posterior and intra-commissural diameter. The shape of the annulus varies from more circular during the late-systole and diastole to more elliptical, with the shortest length of the anterior-posterior diameter, in mid-systole.

EVOLUTION OF MITRAL VALVE REPAIR

The first mitral valve repair was performed almost a century ago, in 1923, by dr. Elliot C. Cutler, a trainee of dr. Harvey E. Cushing, at the Peter Bent Brigham Hospital [45]. The patient was suffering from severe mitral valve stenosis of rheumatic origin. In a time when cardio-pulmonary bypass and cardiac echocardiography were both non-existent, dr. Cutler performed a bold blind commissurotomy by pushing a knife through the apex of the left ventricle. The patient survived the operation and made a remarkable recovery.

The first valve repair for pure mitral regurgitation was performed several decades later, in 1957, by one of the pioneers of cardiac surgery, dr. C. Walton Lillehei. Dr. Lillehei performed an annuloplasty under direct vision of the mitral valve [46]. At that time, the understanding of the causes of mitral regurgitation –cardiac echocardiography was first performed in 1953 while cardiac imaging was established as an important clinical tool only decades later- was still poorly understood and annular dilation was considered the primary cause of regurgitation. The pioneering spirit of the early days of mitral valve surgery, as well as cardiac surgery in general, resulted in rapid evolution of the field. In 1960, dr. Dwight C. McGoon was first to report a case of successful mitral valve repair due to a ruptured chorda by performing a triangular plication of the prolapsing leaflet in a patient with posterior leaflet prolapse [47]. In 1969, dr. Alain Carpentier introduced the concept of annular remodeling with the utilization of prosthetic annuloplasty rings [48]. The concept was characterized by: (I) restoring the normal systolic size and shape of the annulus without impairing leaflet motion, (II) sizing the ring on precise measurement of leaflet tissue and (III) stabilizing the annulus and eliminating the risk of recurrent deformation. Ever since, annuloplasty has become a cornerstone or surgical mitral valve treatment and failure to perform mitral annuloplasty at the time of valve repair has been recognized as one of the most important risk factors for the development of recurrent mitral regurgitation following an initially successful repair [49-51].

In 1983, Carpentier introduced a functional approach to understanding mitral valve disease in his seminal paper, *Cardiac valve surgery- the "French Correction"* [1]. The functional approach focuses on the analysis of leaflet motion, being either (I) normal, (II) increased, as with leaflet prolapse, or (III) diminished, as with leaflet restriction. In this paper, the concept of the "pathophysiological triad" was described that provided the basic knowledge needed to understand the complexity of mitral valve disease. By appreciating the underlying disease and consequent lesion that result in valve dysfunction, a systematical approach to valve repair, adaptable to various types of dysfunction, was established. Additionally, the basic principles of valve repair were proposed. These include (I) preservation or restoration of normal leaflet motion, (II) securing a large area of leaflet coaptation and (III) annular remodeling and stabilization. These principles are still valid today and are applicable to repair of other heart valves as well. Carpentier furthermore introduced a wide scope of valve repair techniques, with many of these being still in use today by surgeons worldwide [1, 31].

Several modifications as well as novel valve repair techniques have been introduced since then. These improvements have importantly impacted the current status of reconstructive mitral valve surgery, improving the reproducibility and durability of valve repair. Chordal replacement with polytetrafluoroethylene (Goretex®) sutures as neochords provided encouraging results in animal studies conducted by Vetter et al. [52] and Revuelta et al. [53]. In 1989, dr. Tirone David was first to describe the utilization of artificial neochords in patients with mitral valve prolapse [54]. Chordal replacement has initially proven to be particularly useful in patients with anterior leaflet prolapse, replacing other, technically more complex techniques [55, 56]. Perier et al. later demonstrated the versatility of artificial neochords in patients with posterior leaflet prolapse [57]. Use of neochords provides an alternative to technically more demanding leaflet resection techniques and nowadays presents a commonly used surgical repair technique in this setting.

In 1991, dr. Ottavio Alfieri first performed mitral valve repair by surgical edge-to-edge approximation of the anterior and posterior leaflets [58, 59]. The repaired valve resembled a congenital double orifice mitral valve anomaly but was in this context used as a repair technique for a complex valve abnormality. As the repair technique does not follow the basic principles of valve repair surgery proposed by Carpentier, focused on restoration of normal leaflet motion, this technique has sparked many debates on its suitability since the introduction [56]. However, the edge-to-edge technique combined with annuloplasty is a reproducible and popular repair alternative for complex mitral valve abnormalities in many centers experienced in reconstructive valve surgery and good-long term durability has been demonstrated [60, 61]. Moreover, it is an useful repair technique to treat systolic anterior motion of the anterior leaflet after valve repair for mitral regurgitation [62].

A combination of various repair techniques is nowadays commonly in use in experienced centers worldwide. Growing expertise has allowed valve repair rates in degenerative disease to reach levels well above 95% [10, 11, 50]. However, several mitral valve lesions remain a technical challenge and, often, complex repair techniques are necessary. In case of commissural leaflet prolapse, commissural closure, leaflet resection with reconstruction of the commissure and chordal replacement or shortening have been described to address this issue [63-65]. These techniques vary in technical difficulty and the effect the repair technique has on leaflet motion and valve function. In 1999, Dreyfus et al. described papillary muscle head repositioning as an alternative technique to treat commissural lesions [66]. To date, the technique remains seldom in use in this setting and late durability poorly explored.

Contrary to degenerative disease, valve repair in active infective endocarditis remains technically challenging and the benefits, when compared to valve replacement, less well defined. In 1990, Dreyfus et al. were the first to report promising results of valve repair in the setting of acute mitral valve endocarditis [67]. The presence of infected and destructed leaflet and subvalvular apparatus tissue makes valve repair particularly demanding. Furthermore, replacement of leaflet tissue with pericardial tissue (either autologous or heterologous) is often needed [19, 27, 67, 68]. Apart from the technical challenges of this maneuver, the use of pericardial patches incorporates a risk factor for recurrent valve dysfunction related to patch degeneration and calcification [69, 70]. Taking into account the high frequency of underlying valve disease seen in these patients, the common observation of annular abscess formation and high repair complexity, performing annuloplasty to reinforce the annulus and stabilize the repair seems meaningful. However, the use of prosthetic materials in the setting of active infection remains controversial due to the fear of bacterial colonization of the yet unendothelialized material. Many surgeons will therefore avoid prosthetic annuloplasty or perform annuloplasty with autologous pericardium [21, 71, 72]. It seems safe to say that the technical aspects of valve repair in native valve infective endocarditis need further investigation and that the benefits of mitral valve repair over replacement further establishment.

OBJECTIVES OF THIS THESIS

This thesis will focus on the timing and technical aspects of mitral valve surgery and their impact on the early and late patient- and valve-related results. In particular, we will focus on the persisting controversies surrounding valve repair surgery in the setting of acute mitral valve infective endocarditis, including the use of prosthetic materials and the value of valve repair in these patients. Moreover, we will focus on the application of the recently improved understanding of degenerative mitral valve disease pathology on the strategy of surgical mitral valve repair. Other technical aspects of valve repair surgery, including comparison of the results of valve repair surgery for posterior leaflet prolapse with different repair techniques and the value of papillary muscle head repositioning in cases of commissural prolapse, as well as the value of early surgery will be studied. The potential problems related to post-repair diastolic flow obstruction due to the fixation of the maximal posterior annular perimeter following prosthetic annuloplasty will be examined.

OUTLINE OF THIS THESIS

In **Chapter 2**, a novel, mitral valve sparing surgical technique in patients with extensive infective endocarditis of the aortic root and the aortic-mitral continuity in whom the infective process has progressed to include the mitral valve is described and the initial results are discussed.

Chapter 3 describes the results of an early-surgery oriented single-center experience in the treatment of patients with isolated native mitral valve infective endocarditis.

In **Chapter 4**, a novel concept of functional mitral valve leaflet prolapse in patients with Barlow's disease is presented. The implication of this concept on the surgical strategy is presented and the results studied.

In **Chapter 5**, the early and late results of a single-center, repair-all oriented approach to valve repair in Barlow's disease is described.

Chapter 6 describes the surgical technique and repair durability of papillary muscle head repositioning in the setting of commissural prolapse.

Chapter 7 provides a comprehensive overview of the surgical approach to excessive posterior mitral valve leaflet tissue and prolapse and compares the results of excessive leaflet height reduction by either tissue resection or shortening neochords.

In **Chapter 8**, the patient- and valve-related effect of mitral annular calcification on the results of a valve repair oriented approach in degenerative mitral valve disease is evaluated.

Chapter 9 describes the initial single-center experience with a novel, tissue-engineered bovine pericardial patch and examines the mid-term durability of this patch in mitral valve repair surgery.

Chapter 10 studies the risk factors and clinical consequences of elevated postoperative mitral valve gradient after an otherwise successful mitral valve repair with a full, semi-rigid annuloplasty ring.

Chapter 11 describes the early and late clinical outcome and the quality of life following mitral valve repair in asymptomatic patients with severe mitral regurgitation due to degenerative mitral valve disease.

REFERENCES

[1] Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg. 1983;86:323-37.

[2] Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg. 2017;52:616-64.

[3] DiBardino DJ, ElBardissi AW, McClure RS, Razo-Vasquez OA, Kelly NE, Cohn LH. Four decades of experience with mitral valve repair: analysis of differential indications, technical evolution, and long-term outcome. J Thorac Cardiovasc Surg. 2010;139:76-83; discussion -4.

[4] De Bonis M, Al-Attar N, Antunes M, Borger M, Casselman F, Falk V, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease. Eur Heart J. 2016;37:133-9.

[5] Enriquez-Sarano M, Schaff HV, Frye RL. Mitral regurgitation: what causes the leakage is fundamental to the outcome of valve repair. Circulation. 2003;108:253-6.

[6] Manjunath CN, Srinivas P, Ravindranath KS, Dhanalakshmi C. Incidence and patterns of valvular heart disease in a tertiary care high-volume cardiac center: a single center experience. Indian Heart J. 2014;66:320-6.

[7] Iung B, Vahanian A. Epidemiology of acquired valvular heart disease. Can J Cardiol. 2014;30:962-70.

[8] Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, 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.

[9] 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.

[10] Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. J Thorac Cardiovasc Surg. 2012;144:308-12.

[11] David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation. 2013;127:1485-92.

[12] Yazdchi F, Koch CG, Mihaljevic T, Hachamovitch R, Lowry AM, He J, et al. Increasing Disadvantage of "Watchful Waiting" for Repairing Degenerative Mitral Valve Disease. Ann Thorac Surg. 2015;99:1992-2000.

[13] Selton-Suty C, Celard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis. 2012;54:1230-9.

[14] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36:3075-128.

[15] Leening MJ, Siregar S, Vaartjes I, Bots ML, Versteegh MI, van Geuns RJ, et al. Heart disease in the Netherlands: a quantitative update. Neth Heart J. 2014;22:3-10.

[16] Surgery. BotNAfC-T. De Nederlandse dataregistratie hartchirurgie: resultaten van samenwerking tussen 16 Nederlandse hartchirurgische centra. Utrecht: Netherlands Association for Cardio-Thoracic Surgery (NVT); 2012.

[17] Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. Lancet. 2015;385:1219-28.

[18] Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol. 2015;65:2070-6.

[19] de Kerchove L, Price J, Tamer S, Glineur D, Momeni M, Noirhomme P, et al. Extending the scope of mitral valve repair in active endocarditis. J Thorac Cardiovasc Surg. 2012;143:S91-5.

[20] Jung SH, Je HG, Choo SJ, Song H, Chung CH, Lee JW. Surgical results of active infective native mitral valve endocarditis: repair versus replacement. Eur J Cardiothorac Surg. 2011;40:834-9.

[21] Ruttmann E, Legit C, Poelzl G, Mueller S, Chevtchik O, Cottogni M, et al. Mitral valve repair provides improved outcome over replacement in active infective endocarditis. J Thorac Cardiovasc Surg. 2005;130:765-71.

[22] Kirklin JW. Replacement of the mitral valve for mitral incompetence. Surgery. 1972;72:827-36.

[23] Quintana E, Suri RM, Thalji NM, Daly RC, Dearani JA, Burkhart HM, et al. Left ventricular dysfunction after mitral valve repair--the fallacy of “normal” preoperative myocardial function. J Thorac Cardiovasc Surg. 2014;148:2752-60.

[24] Suri RM, Schaff HV, Dearani JA, Sundt TM, Daly RC, Mullany CJ, et al. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. J Thorac Cardiovasc Surg. 2009;137:1071-6.

[25] Tribouilloy C, Rusinaru D, Szymanski C, Mezghani S, Fournier A, Levy F, et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. Eur J Echocardiogr. 2011;12:702-10.

[26] Ahmed MI, Gladden JD, Litovsky SH, Lloyd SG, Gupta H, Inusah S, et al. Increased oxidative stress and cardiomyocyte myofibrillar degeneration in patients with chronic isolated mitral regurgitation and ejection fraction >60%. J Am Coll Cardiol. 2010;55:671-9.

[27] de Kerchove L, Vanoverschelde JL, Poncelet A, Glineur D, Rubay J, Zech F, et al. Reconstructive surgery in active mitral valve endocarditis: feasibility, safety and durability. Eur J Cardiothorac Surg. 2007;31:592-9.

[28] Ho SY. Anatomy of the mitral valve. Heart. 2002;88 Suppl 4:iv5-10.

[29] McCarthy KP, Ring L, Rana BS. Anatomy of the mitral valve: understanding the mitral valve complex in mitral regurgitation. Eur J Echocardiogr. 2010;11:i3-9.

[30] Yoganathan AP, He Z, Casey Jones S. Fluid mechanics of heart valves. Annu Rev Biomed Eng. 2004;6:331-62.

[31] F. CAADHF. Carpentier's Reconstructive Valve Surgery. 1st edn. Philadelphia: Saunders, 2010.

[32] Gunnal SA, Farooqui MS, Wabale RN. Study of mitral valve in human cadaveric hearts. Heart Views. 2012;13:132-5.

[33] Reul H, Talukder N, Muller EW. Fluid mechanics of the natural mitral valve. J Biomech. 1981;14:361-72.

[34] Ingels NBKM. Mitral Valve Mechanics. 2015.

[35] Laniado S, Yellin EL, Miller H, Frater RW. Temporal relation of the first heart sound to closure of the mitral valve. Circulation. 1973;47:1006-14.

[36] Bellhouse BJ. Fluid mechanics of a model mitral valve and left ventricle. Cardiovasc Res. 1972;6:199-210.

[37] Elbaz MS, Calkoen EE, Westenberg JJ, Lelieveldt BP, Roest AA, van der Geest RJ. Vortex flow during early and late left ventricular filling in normal subjects: quantitative characterization using retrospectively-gated 4D flow cardiovascular magnetic resonance and three-dimensional vortex core analysis. J Cardiovasc Magn Reson. 2014;16:78.

[38] Yellin EL, Peskin C, Yoran C, Koenigsberg M, Matsumoto M, Laniado S, et al. Mechanisms of mitral valve motion during diastole. Am J Physiol. 1981;241:H389-400.

[39] Nielsen SL, Hansen SB, Nielsen KO, Nygaard H, Paulsen PK, Hasenkam JM. Imbalanced chordal force distribution causes acute ischemic mitral regurgitation: mechanistic insights from chordae tendineae force measurements in pigs. J Thorac Cardiovasc Surg. 2005;129:525-31.

[40] Askov JB, Honge JL, Jensen MO, Nygaard H, Hasenkam JM, Nielsen SL. Significance of force transfer in mitral valve-left ventricular interaction: in vivo assessment. J Thorac Cardiovasc Surg. 2013;145:1635-41, 41 e1.

[41] Lawrie GM. Structure, function, and dynamics of the mitral annulus: importance in mitral valve repair for myxamatous mitral valve disease. Methodist Debakey Cardiovasc J. 2010;6:8-14.

[42] Dagum P, Timek T, Green GR, Daughters GT, Liang D, Ingels NB, Jr., et al. Three-dimensional geometric comparison of partial and complete flexible mitral annuloplasty rings. J Thorac Cardiovasc Surg. 2001;122:665-73.

[43] Skov SN, Ropcke DM, Tjornild MJ, Ilkjaer C, Rasmussen J, Nygaard H, et al. The effect of different mitral annuloplasty rings on valve geometry and annular stress distributiondagger. Interact Cardiovasc Thorac Surg. 2017;24:683-90.

[44] Lansac E, Lim KH, Shomura Y, Goetz WA, Lim HS, Rice NT, et al. Dynamic balance of the aortomitral junction. J Thorac Cardiovasc Surg. 2002;123:911-8.

[45] Cutler EC, Levine SA. Cardiotomy and valvulotomy for mitral stenosis. The Boston Medical and Surgical Journal. 1923;188:p. 1023.

[46] Lillehei CW, Gott VL, DeWall RA, Varco RL. Surgical correction of pure mitral insufficiency by annuloplasty under direct vision. J Lancet 1957;77:446-9.

[47] McGoon DC. Repair of mitral insufficiency due to ruptured chordae tendineae. J Thorac Cardiovasc Surg. 1960;39:357-62.

[48] Carpentier A. [Reconstructive valvuloplasty. A new technique of mitral valvuloplasty]. Presse Med. 1969;77:251-3.

[49] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg. 2008;135:274-82.
[50] Johnston DR, Gillinov AM, Blackstone EH, Griffin B, Stewart W, Sabik JF, 3rd, et al. Surgical repair of posterior mitral valve prolapse: implications for guidelines and percutaneous repair. Ann Thorac Surg. 2010;89:1385-94.
[51] Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. J Thorac Cardiovasc Surg. 1996;111:718-29; discussion 29-30.
[52] Vetter HOB, J. H.; Factor S. M.; Malacuso F.; Frater R. W. M. Replacement of chordae tendineae of the mitral valve using the new expanded PTFE suture in sheep in E. Bodnar, M. Yacoub (Eds.), Biologic and Bioprosthetic Valves, Yorke Medical Books, New York (1986), pp. 772-785.
[53] Revuelta JM, Garcia-Rinaldi R, Gaite L, Val F, Garijo F. Generation of chordae tendineae with polytetrafluoroethylene stents. Results of mitral valve chordal replacement in sheep. J Thorac Cardiovasc Surg. 1989;97:98-103.
[54] David TE. Replacement of chordae tendineae with expanded polytetrafluoroethylene sutures. J Card Surg. 1989;4:286-90.
[55]\ David TE, Armstrong S, Ivanov J. Chordal replacement with polytetrafluoroethylene sutures for mitral valve repair: a 25-year experience. J Thorac Cardiovasc Surg. 2013;145:1563-9.
[56] David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. J Thorac Cardiovasc Surg. 2005;130:1242-9.
[57] Perier P, Hohenberger W, Lakew F, Batz G, Urbanski P, Zacher M, et al. Toward a new paradigm for the reconstruction of posterior leaflet prolapse: midterm results of the "respect rather than resect" approach. Ann Thorac Surg. 2008;86:718-25; discussion -25.
[58] G. AODBMLC. Edge-to-Edge Mitral Repair. Springer International Publishing, 2015.
[59] Fucci C, Sandrelli L, Pardini A, Torracca L, Ferrari M, Alfieri O. Improved results with mitral valve repair using new surgical techniques. Eur J Cardiothorac Surg. 1995;9:621-6 discuss 6-7.
[60] da Rocha ESJG, Spampinato R, Misfeld M, Seeburger J, Pfanmuller B, Eifert S, et al. Barlow's Mitral Valve Disease: A Comparison of Neochordal (Loop) and Edge-To-Edge (Alfieri) Minimally Invasive Repair Techniques. Ann Thorac Surg. 2015;100:2127-33; discussion 33-5.
[61] De Bonis M, Lapenna E, Del Forno B, Di Sanzo S, Giacomini A, Schiavi D, et al. Minimally invasive or conventional edge-to-edge repair for severe mitral regurgitation due to bileaflet prolapse in Barlow's disease: does the surgical approach have an impact on the long-term results? Eur J Cardiothorac Surg. 2017;52:131-6.
[62] Mascagni R, Al Attar N, Lamarra M, Calvi S, Tripodi A, Mebazaa A, et al. Edge-to-edge technique to treat post-mitral valve repair systolic anterior motion and left ventricular outflow tract obstruction. Ann Thorac Surg. 2005;79:471-3; discussion 4.
[63] Aubert S, Barreda T, Acar C, Leprince P, Bonnet N, Ecochard R, et al. Mitral valve repair for commissural prolapse: surgical techniques and long term results. Eur J Cardiothorac Surg. 2005;28:443-7.

[64] De Bonis M, Lapenna E, Taramasso M, Pozzoli A, La Canna G, Calabrese MC, et al. Is commissural closure associated with mitral annuloplasty a durable technique for the treatment of mitral regurgitation? A long-term (</=15 years) clinical and echocardiographic study. J Thorac Cardiovasc Surg. 2014;147:1900-6.
[65] Gillinov AM, Shortt KG, Cosgrove DM, 3rd. Commissural closure for repair of mitral commissural prolapse. Ann Thorac Surg. 2005;80:1135-6.
[66] Dreyfus G, Al Ayle N, Dubois C, de Lentdecker P. Long term results of mitral valve repair: posterior papillary muscle repositioning versus chordal shortening. Eur J Cardiothorac Surg. 1999;16:81-7.
[67] Dreyfus G, Serraf A, Jebara VA, Deloche A, Chauvaud S, Couetil JP, et al. Valve repair in acute endocarditis. Ann Thorac Surg. 1990;49:706-11; discussion 12-3.
[68] Evans CF, DeFilippi CR, Shang E, Griffith BP, Gammie JS. Fresh autologous pericardium for leaflet perforation repair in mitral valve infective endocarditis. J Heart Valve Dis. 2013;22:560-6.
[69] Fukunaga N, Matsuo T, Saji Y, Imai Y, Koyama T. Mitral Valve Stenosis Progression Due to Severe Calcification on Glutaraldehyde-Treated Autologous Pericardium: Word of Caution for an Attractive Repair Technique. Ann Thorac Surg. 2015;99:2203-5.
[70] Fukunaga N, Sakata R, Koyama T. Reoperative analysis after mitral valve repair with glutaraldehyde-treated autologous pericardium. Interact Cardiovasc Thorac Surg. 2017;25:912-7.
[71] Musci M, Hubler M, Pasic M, Amiri A, Stein J, Siniawski H, et al. Surgery for active infective mitral valve endocarditis: a 20-year, single-center experience. J Heart Valve Dis. 2010;19:206-14; discussion 15.
[72] Muehrcke DD, Cosgrove DM, 3rd, Lytle BW, Taylor PC, Burgar AM, Durnwald CP, et al. Is there an advantage to repairing infected mitral valves? Ann Thorac Surg. 1997;63:1718-24.

PART I

SURGICAL TREATMENT OF ACTIVE NATIVE MITRAL VALVE INFECTIVE ENDOCARDITIS

Infective endocarditis remains a deadly disease, associated with high mortality rates and severe complications [1]. It usually presents as a multi-system disease, a characteristic related on one hand to the wide scope of underlying morbidities typically present in these patients and on the other hand to the development of severe complications of infective endocarditis that often precede the diagnosis [2, 3]. Based on the variety and complexity of patients affected, a multidisciplinary approach is advised [1, 4].

Infective endocarditis most commonly affects left-sided heart valves, most commonly the mitral valve [3]. Surgical intervention during the index hospitalization is needed in about 50% of patients [3, 5]. The guidelines recommend surgical intervention in case of heart failure, signs of uncontrolled infection or for the prevention of peripheral embolization [1]. However, local practice and surgical expertise play a role in determination of the optimal treatment plan. For native mitral valve infective endocarditis, an early and repair-oriented surgical approach has been described in highly experienced centres [6]. In this setting, the threshold for surgery can be lowered to prevent further destruction of a repairable valve and the notion that, in the presence of severe mitral regurgitation, intervention will be necessary at some point in time.

In addition to the indication for intervention, the optimal surgical treatment modality as well as technical details of surgery remain a matter of discussion. Due to the presumed high risk of bacterial colonization of prosthetic materials in the setting of an active infection, it is believed that the use of prosthetic materials should be kept to a minimum. In case of mitral valve repair, prosthetic annuluplasty is therefore often omitted. A previous meta-analysis on the results of mitral valve repair and replacement in the setting of active infective endocarditis, however, demonstrated residual infection to be a rather uncommon event, occurring in only about 0.5% of patients who had undergone valve repair [7]. In a recent publication, Perrotta et al. rightfully speculated that residual infections are most likely related to incomplete resection of all macroscopically infected tissue [8]. Radical resection should therefore not be omitted, not even in an attempt to raise the likelihood of an initially successful repair. Residual infective endocarditis is thus possibly not related to the amount of prosthetic materials implanted but to the technical scrutiny of surgical intervention itself. Underlying mitral valve disease is present in about 40% of patients suffering from mitral valve endocarditis [3, 9-11] and the infective process often involves the mitral valve annulus. Complex leaflet as well as annulus repair techniques are often indicated to secure a durable repair after careful resection of all infected tissue has been performed. This provides theoretical background for annular stabilization to be performed in an attempt to support long-term repair durability.

Two recent large, multi-centre studies suggested valve repair to be related to improved overall survival when compared to valve replacement in the setting of active infective endocarditis [12, 13]. Such studies are, however, highly susceptible for selection bias, hard to statistically correct for in a multi-centre setting where the details of patient selection and repair techniques applied vary considerably. As patients receiving valve repair were likely in a better clinical condition with less extensive disease than patient undergoing replacement, the observed superiority might be unrelated to treatment modality. Moreover, on critical evaluation, the survival benefit of valve repair over replacement was largest in the early postoperative period when valve repair is less likely to provide a true survival advantage over valve replacement. Even in highly experienced centres, an absent late survival benefit, reflected by non-diverging survival curves after the early postoperative period, can be observed [6]. This could be related to a relatively high incidence of late reoperation following valve repair for active infective endocarditis [9, 14]. It is a generally accepted fact that the reintervention rate presents only the tip of the iceberg and that the actual prevalence of patients suffering from repair dysfunction will be considerably higher. The data on repair durability after valve repair for infective endocarditis remain scarce. Further refinement of patient selection, surgical repair technique and more liberal use of prosthetic annuloplasty could help improve repair durability in the setting of native infective endocarditis, resulting in a true survival benefit over valve replacement. Due to the theoretical risk of residual infection, the strategy of liberal use of prosthetic annuloplasty materials should be critically evaluated.

The relation of surgical volume and patients-related outcomes in mitral valve surgery remains a matter of debate. Recent studies suggest superior outcomes of surgery for mitral valve infective endocarditis in the hands of experienced surgeons and centres

[12, 13]. The relative low number of patients suffering from infective endocarditis, the high risk of surgery and the complexity of intra- and perioperative care all make the introduction of highly specialized endocarditis centres logistically feasible as well as clinically justified. In the following chapters, the results of a structured mitral valve endocarditis program in a tertiary institution will be evaluated.

REFERENCES

[1] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36:3075-128.

[2] Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016;387:882-93.

[3] Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG, Jr., Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169:463-73.

[4] Chambers J, Sandoe J, Ray S, Prendergast B, Taggart D, Westaby S, et al. The infective endocarditis team: recommendations from an international working group. Heart. 2014;100:524-7.

[5] Tornos P, Iung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Barwolf C, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart. 2005;91:571-5.

[6] Solari S, De Kerchove L, Tamer S, Aphram G, Baert J, Borsellino S, et al. Active infective mitral valve endocarditis: is a repair-oriented surgery safe and durable? Eur J Cardiothorac Surg. 2018.

[7] Feringa HH, Shaw LJ, Poldermans D, Hoeks S, van der Wall EE, Dion RA, et al. Mitral valve repair and replacement in endocarditis: a systematic review of literature. Ann Thorac Surg. 2007;83:564-70.

[8] Perrotta S, Jeppsson A, Frojd V, Svensson G. Surgical Treatment for Infective Endocarditis: A Single-Centre Experience. Thorac Cardiovasc Surg. 2017;65:166-73.

[9] de Kerchove L, Price J, Tamer S, Glineur D, Momeni M, Noirhomme P, et al. Extending the scope of mitral valve repair in active endocarditis. J Thorac Cardiovasc Surg. 2012;143:S91-5.

[10] Ruttmann E, Legit C, Poelzl G, Mueller S, Chevtchik O, Cottogni M, et al. Mitral valve repair provides improved outcome over replacement in active infective endocarditis. J Thorac Cardiovasc Surg. 2005;130:765-71.

[11] Jung SH, Je HG, Choo SJ, Song H, Chung CH, Lee JW. Surgical results of active infective native mitral valve endocarditis: repair versus replacement. Eur J Cardiothorac Surg. 2011;40:834-9.

[12] Toyoda N, Itagaki S, Egorova NN, Tannous H, Anyanwu AC, El-Eshmawi A, et al. Real-world outcomes of surgery for native mitral valve endocarditis. J Thorac Cardiovasc Surg. 2017;154:1906-12 e9.

[13] Lee HA, Cheng YT, Wu VC, Chou AH, Chu PH, Tsai FC, et al. Nationwide cohort study of mitral valve repair versus replacement for infective endocarditis. J Thorac Cardiovasc Surg. 2018;156:1473-83 e2.

[14] Musci M, Hubler M, Pasic M, Amiri A, Stein J, Siniawski H, et al. Surgery for active infective mitral valve endocarditis: a 20-year, single-center experience. J Heart Valve Dis. 2010;19:206-14; discussion 15.

02

Early and late results of surgical treatment for isolated active native mitral valve infective endocarditis

Anton Tomšič; Michel I.M. Versteegh; Nina Ajmone Marsan; Thomas J. van Brakel; Robert J.M. Klautz; Meindert Palmen

Interact Cardiovasc Thorac Surg. 2018;26(4):610-616

ABSTRACT

Background. Native mitral valve infective endocarditis (IE) is a complicated disease with high mortality and morbidity rates. Mitral valve repair is feasible when limited valve destruction is present. However, recurrent valve dysfunction and reintervention are common.

Methods. Between January 2000 and March 2016, 83 patients underwent surgery for isolated active native mitral valve IE. We applied an early surgery, valve repair-oriented approach with progressive utilization of patch techniques to secure a durable repair; repair was attempted in 67% of patients. Fifty-one (61%) patients underwent valve repair (including full ring annuloplasty in 94%) and 32 (39%) patients underwent mitral valve replacement.

Results. Early mortality was 13%. No cases of early recurrent IE occurred. Pre-discharge echocardiography demonstrated good repaired valve function in all but 1 patient with residual (moderate) regurgitation. The mean duration of follow-up was 3.7 years (interquartile range 1.5–8.4). For hospital survivors, 8-year overall survival rates were 92.4% (95% CI: 84.0%-100%) and 74.2% (95% CI: 53.8%-94.6%) for the mitral valve repair and replacement group, respectively. Propensity score-adjusted Cox regression analysis revealed no significant difference in survival between both groups (hazard ratio 0.359, 95% CI 0.107-1.200; P=0.096). Four reinterventions occurred, 2 in each group. Echocardiographic follow-up demonstrated excellent repair durability; no cases of mitral regurgitation and 1 case of mitral valve stenosis were seen.

Conclusions. Native mitral valve IE is linked to high mortality and morbidity rates. A durable valve repair is feasible in most patients and provides excellent mid-term durability. Mitral valve replacement is a reasonable alternative when a durable repair is not likely.

INTRODUCTION

Active infective endocarditis (IE) is a complex disease, associated with high mortality and morbidity rates [1], and most commonly affecting the mitral valve [2]. Dreyfus et al. were one of the first to demonstrate the feasibility of mitral valve repair (MVRep) in the setting of active IE [3]. A meta-analysis of early studies on the efficiency of MVRep in the setting of IE accordingly demonstrated that valve repair, feasible at the time in 39% of cases, is linked to decreased early and late mortality, reoperation, and recurrent endocarditis rates [4].

More recent reports have demonstrated that an aggressive approach to MVRep will enable MVRep to be performed in a majority of patients undergoing intervention in the acute phase of the disease [5, 6]. This is, however, highly dependent on the extent of valve destruction; uncontrolled infection in the active phase of IE with a delayed referral to surgery might make MVRep impossible after careful resection of all infected tissue is carried out. Furthermore, long-term operated valve dysfunction after MVRep in the setting of active IE remains a concern [5, 7, 8]. Late clinical and echocardiographic data in patients with isolated native active mitral valve IE remain limited.

The aim of this study was to explore our single-center experience in patients with isolated active native mitral valve IE. During the study period, we have utilized an early repair-oriented surgical approach with liberal utilization of prosthetic ring annuloplasty. We sought to determine the early and mid-term clinical and echocardiographic results of surgical treatment in this patient group.

METHODS

Study Population

Patients who underwent surgical mitral valve intervention between January 2000 and March 2016 were potentially eligible for this study. Inclusion criteria were active mitral valve IE and ≥18 years of age. Patients with prosthetic valve IE or multiple-valve endocarditis were excluded. Isolated native mitral valve IE was defined as IE limited to the mitral valve, regardless of the concomitant procedures performed.

During the study period, 303 patients underwent mitral valve operation for mitral valve IE. 113 of these were suffering for isolated active mitral valve IE; 30 of these had prosthetic valve IE. Of the remaining 83 patients eligible for this study, 51 (61%) underwent MVRep and 32 (39%) underwent mitral valve replacement (MVR). Five (6%) of the latter underwent MVR after an initial unsuccessful repair attempt.

Study Methods

Our Institutional Ethics Committee approved this study. Data on preoperative, operative and postoperative details were obtained from our computerized database. Follow-up clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through telephonic interviews. The median survival follow-up time was 3.7 years [interquartile range (IQR) 1.5 – 8.4; 100% complete]. The median follow-up time for valve-related events was 3.6 years (IQR 0.9 – 7.8; 96% complete). The median echocardiographic follow-up time was 3.8 years (IQR 1.8 – 7.3; 90% complete). Patient follow-up was closed in July 2016.

Pre- and Postoperative Care

Infective endocarditis was diagnosed according to the modified Duke criteria [9]. Active IE was defined as ongoing antibiotic treatment within 6 weeks of the initial diagnosis and/or macroscopic evidence of valve endocarditis and/or positive intraoperative valve cultures or pathological report. Empiric antibiotic therapy was started after IE was diagnosed and blood cultures harvested. Antibiotic therapy was adjusted according to the antibiogram.

Surgical therapy was performed according to the European guidelines recommendations; the indication for surgery included clinical signs of heart failure, signs of uncontrolled infection (signs of locally uncontrolled infections, infection with unfavorable microorganisms or persistent positive blood cultures, despite optimal conservative management) and prevention of embolism [1]. Additionally, early surgery was considered when severe mitral regurgitation (MR) due to valvular destruction was observed on echocardiography. In patients who did not meet these criteria, antibiotic therapy was initiated and repeated echocardiographic examination (usually after 5-7 days) was performed. If progression to severe MR was observed on repeated echocardiography, surgery was performed. In 36 (43%) patients from the final study cohort, severe MR was the only indication for surgical intervention. In these patients, surgery was performed to prevent further valve destruction that would likely prevent subsequent

MVRep. Surgery was performed within 14 days of the diagnosis in 50 (60%) of all patients. All surgeries were performed by experienced mitral valve surgeons. Because to the high risk of failed MVRep in patients undergoing intervention in the active phase of IE, the possibility of MVR was discussed preoperatively in all cases. The decision on the type of prosthesis used was based on a shared decision with the informed patient.

Following surgery, pathogen-specific therapy was continued for a minimum period of 6 weeks. Oral anticoagulation was initiated after the operation and was maintained for 3 months in case of MVRep with prosthetic ring implantation or biological valve implantation (target international normalized ratio: 2.0 – 3.0). In case of mechanical valve implantation (target international normalized ratio: 2.5 – 3.5) or in the presence of other indications, oral anticoagulation was continued indefinitely. All patients underwent transthoracic echocardiography prior to hospital discharge.

Surgical Procedures

All patients were operated through a median sternotomy using standard techniques for extracorporeal circulation with double venous cannulation. Antegrade warm and/or retrograde tepid blood cardioplegia was used for cardioprotection in all cases. Systemic hypothermia was used when retrograde cardioplegia was used or when an extended cross-clamp time was anticipated.

In all patients, radical excision of all macroscopically infected tissue was performed, without concern for the possibility of subsequent MVRep. Isolated resection of vegetations was performed in case of well-circumscribed vegetations that did not invade the leaflet tissue. Annular abscesses were evacuated and closed with autologous or heterologous pericardial patch. Annular decalcification was performed when needed. The operative area was rinsed with a rifampicine solution prior to performing valve repair or replacement.

Following resection, MVRep was attempted when a durable repair was considered feasible. In general, at least 1 normal commissure and two-thirds of normal free edges of the leaflets were considered the minimum requirement to attempt a repair. Small defects were closed directly with a 5-0 polypropylene suture. For the posterior mitral valve leaflet, annular plication or leaflet sliding plasty was performed in case of larger defects. When insufficient residual native posterior mitral valve leaflet tissue remained and in cases of larger anterior mitral valve leaflet defects, reconstruction with autologous or heterologous pericardial tissue was performed. Commissural reconstruction was performed with pericardial patch and/or leaflet sliding techniques. Commissural closure was additionally performed when indicated and the risk of high inflow gradient was minimal. Polytetrafluoroethylene neochords were implanted to support the neo free edge of reconstructed mitral leaflets and to treat residual leaflet prolapse.

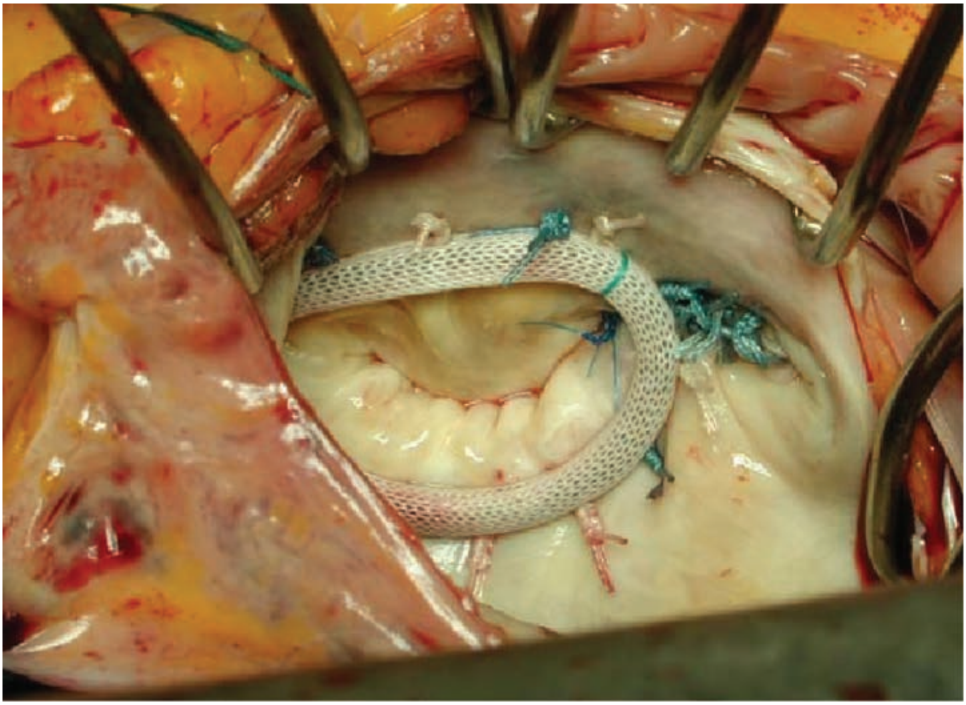


FIGURE 1. Intraoperative water test demonstrating restored valve competency.

Over the entire study period, pericardial patch techniques were progressively used to compensate for the lack of native valve tissue. Smaller defects were reconstructed with untreated autologous pericardium. Earlier in the series, bigger defects were reconstructed with glutaraldehyde-treated autologous or bovine pericardium; nowadays, we utilize decellularized bovine (CardioCel; AdmedusRegen Pty Ltd., Perth, WA, Australia) pericardium for extensive leaflet reconstruction. Ring annuloplasty was performed in all but 3 patients from the MVRep group; ring annuloplasty was deemed not necessary in patients with limited reconstruction and otherwise normal anatomy of the mitral valve. Intraoperative water-test was performed to asses any residual valve leakage (**Figure 1**).

In case of an unsuccessful repair attempt, infection of a considerable proportion of the mitral valve and/or when durable valve repair was beleived impossible, MVR was performed. Whenever possible, the subvalvular apparatus was spared; later in our series, we have utilized polytetrafluoroethylene neochords to substitute the infected or ruptured chords and enable maintenance of the continuity between the left ventricle and the mitral annulus.

Study Endpoints

Postoperative mortality and morbidity endpoints were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery, and European Association for Cardio-Thoracic Surgery Guidelines [10]. Early mortality was defined as mortality within 30 days after the operation or during the index hospitalization. Residual and recurrent MR were defined as ≥moderate regurgitation.

Statistical Analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile ranges (IQR) when not normally distributed. Categorical data are presented as counts and percentages. The χ^2 and Fisher's exact tests were used for to analyze categorical variables. Independent-sample t-test and Mann-Whitney U-test (skewed data) were used to analyze continuous variables. Multivariable binary logistic regression analysis with a backward selection method was performed to identify the independent predictors of MVR. Variables showing a P-value of <0.10 on univariable analysis were included in the multivariable model.

For each patient, a propensity score was calculated from a multivariable logistic regression model on preoperative characteristics as independent variables with MVRep versus MVR as a binary dependent variable. Covariates included in the propensity score model were: female gender, age, hypertension, duration of antibiotic therapy (≥7 days), annular infection, *Staphylococcus aureus* infection, symptomatic MR, presence of degenerative mitral valve disease, haemodialysis, atrial fibrillation, previous cardiac surgery, impaired left ventricular function, critical preoperative state and aortic valve intervention. The propensity score was used as an independent variable in the multi-variable regression and Cox proportional hazards regression analysis to correct for baseline differences between the 2 groups. Odds ratios (ORs) and hazard ratios (HRs) are reported with 95% confidence intervals (CIs).

Survival and freedom from reintervention rates were estimated using the Kaplan-Meier method. The log-rank test was used for statistical comparison of the Kaplan-Meier curves. A double sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

RESULTS

Demographic Characteristics

Demographic characteristics are presented in **Table I**. A higher proportion of females was seen in the MVR group. Preoperative peripheral embolism was seen in 28 (34%) patients with no significant differences between both groups; in 20 patients this included emboli to the central nervous system. The frequency of annular infection between both groups failed to reach statistical significance. Interestingly, underlying degenerative mitral valve disease was more commonly observed in the MVRep group.

Intraoperative Details

Intraoperative details are shown in **Table II**. Multivariable analysis demonstrated underlying degenerative mitral valve disease as a predictor of successful MVRep (**Table III**). Of notice, annular infection or calcification and the timing of surgery were not predictive factors for MVR .

Early Mortality and Morbidity

There were no significant differences in the postoperative mortality and morbidity rates between the 2 groups (**Table IV**). When corrected for the propensity score, multivariable regression analysis demonstrated no effect of MVR versus MVRep on early mortality (OR: 2.010, 95% CI 0.372-10.863; P=0.41).

Early Echocardiographic Result

In the MVRep group, pre-discharge echocardiography demonstrated good function of the repaired valve in all but 1 patient in whom residual moderate MR was seen. Due to the poor clinical condition of this patient, no early reoperation was performed.

TABLE I. Baseline characteristics and intraoperative details.

	Mitral valve repair (n=51)		Mitral valve replacement (n=32)		
	n	**%**	**n**	**%**	**P-value**
Age (years)	55±14		60±13		0.11
Female sex	13	*26*	15	*47*	0.045
Hypertension	16	*31*	11	*34*	0.78
Chronic lung disease	3	*6*	5	*16*	0.25
Diabetes mellitus	6	*12*	8	*25*	0.12
Atrial fibrillation	6	*12*	2	*6*	0.48
Creatinine (mmol/l)	82 (IQR 66–100)		70 (IQR 55–102)		0.19
Preoperative hemodialysis	3	*6*	4	*13*	0.42
Previous cardiac surgery	2	*4*	2	*6*	0.64
Symptomatic mitral regurgitation	15	*29*	9	*28*	0.90
Critical preoperative state	5	*10*	5	*16*	0.50
Impaired left ventricular function	10	*20*	3	*9*	0.21
Peripheral embolism	16	*31*	12	*38*	0.57
Causative microorganism					0.35
Streptococcus species	33	*65*	15	*47*	
Staphylococcus species	9	*17*	10	*31*	
Staphylococcus aureus	8	*15*	8	*25*	
Enterococcus fecalis	5	*10*	5	*16*	
Other or culture negative	4	*8*	2	*6*	
Indication for surgery					
Heart failure	6	*12*	5	*16*	0.74
Uncontrolled infection	7	*14*	6	*19*	0.54
Prevention of embolism	16	*13*	17	*53*	0.049
Severe mitral regurgitation	41	*80*	12	*38*	<0.001
Preoperative antibiotic therapy duration (days)	13 (IQR 8–29)		9 (IQR 5–16)		0.034
≤7 days	12	*24*	13	*41*	0.098
Degenerative mitral valve disease	22	*43*	6	*19*	0.022
Annular infection	5	*10*	8	*25*	0.064
Annular calcification	5	*10*	7	*22*	0.20
Concomitant procedures					
Coronary artery bypass grafting	5	*10*	3	*9*	1.00
Aortic valve or root replacement	1	*2*	6	*19*	0.012
Tricuspid valve repair	6	*12*	4	*13*	1.00
Aortic cross-clamp time (min)	165 (IQR 120-184)		137 (IQR 112–239)		0.69
Cardiopulmonary bypass time (min)	203 (IQR 158-234)		175 (IQR152–243)		0.97

Continuous data are presented as means ± SD or medians with IQR.

TABLE II. Mitral valve repair and replacement details.

	Mitral valve replacement (n=32)					
	n	*%*				
Biological prosthesis	16	*50*				
Medtronic Mosaic*	9	*28*				
Perimount Magna***	7	*22*				
Mechanical prosthesis	16	*50*				
St. Jude Medical Regent**	16	*50*				
Prosthesis size (mm)						
27	5	*16*				
29	13	41				
31	11	*34*				
33	3	*9*				
	Mitral valve repair (n=51)					
Ring annuloplasty	48	*94*				
Physioring***	43	*90*				
Memo 3D****	3	*6*				
Medtronic CG Future*	1	*2*				
CarboMedics AnnuloFlex*****	1	*2*				
Ring annuloplasty size (mm)						
26-28	12	*24*				
30-34	27	*53*				
≥36	9	*17*				
Annular plication	21	41				
	AMVL		**PMVL**		**Commissures**	
	n	**%**	**n**	**%**	**n**	**%**
Resection	23	*45*	35	*69*	10	*20*
Reconstruction with auto-/xenologous pericardium (or commissural closure)	22	*43*	14	*28*	14	*28*
Neochords implantation	17	*33*	10	*20*	4	*8*
Chordal transposition	-		1	*2*	-	
Papillary muscle head repositioning	-		-		3	*6*
Vegectomy	3	*6*	5	*10*	1	*2*
Leaflet sliding plasty	-		8	*16*	-	
Identation closure	-		1	*2*	-	

Abbreviations: AMVL: anterior mitral valve leaflet; PMVL: posterior mitral valve leaflet
**Medtronic, Minneapolis, MN, USA; **St. Jude Medical, Little Canada, MN, USA; ***Edwards Lifesciences, Irvine, CA, USA; ****Sorin Group, Milan, Italy; *****CarboMedics, Austin, Tex, USA*

TABLE III. Univariable and multivariable analysis on predictors of mitral valve replacement.

	Univariable analysis			Multivariable analysis		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Annular infection	3.07	(0.90 – 10.40)	0.072	…	…	…
Annular calcification	2.58	(0.74 – 8.96)	0.14	…	…	…
Female sex	2.58	(1.01 – 6.59)	0.048	2.51	(0.95 – 6.60)	0.063
Age (years)			0.42	…	…	…
60 – 74.9	1.92	(0.65 – 5.65)	0.24	…	…	…
≥75	2.57	(0.42 – 17.05)	0.30	…	…	…
Staphylococcus aureus infection	1.79	(0.60 – 5.38)	0.30	…	…	…
Early surgery (≤7 days)	2.22	(0.85 – 5.79)	0.102	…	…	…
Degenerative disease	0.30	(0.11 – 0.87)	0.026	0.31	(0.11 – 0.91)	0.032
Peripheral embolism	1.31	(0.52 – 3.32)	0.57	…	…	…
Symptomatic mitral regurgitation	0.94	(0.35 – 2.50)	0.90	…	…	…
Preoperative hemodialysis	2.29	(0.48 – 10.96)	0.30	…	…	…
Critical preoperative state	2.18	(0.54 – 8.80)	0.28	…	…	…
Impaired left ventricular function	0.42	(0.11 – 1.68)	0.22	…	…	…
Commissural involvement	1.06	(0.36 – 3.16)	0.91	…	…	…

Hosmer-Lemeshow goodness-of-fit: 0.93; Nagelkerke R^2 square: 0.14
Abbreviations: CI: confidence interval; OR: odds ratio.

TABLE IV. Postoperative mortality and morbidity.

	Mitral valve repair (n=51)		Mitral valve replacement (n=32)		
	n	**%**	**n**	**%**	**P-value**
Early mortality	6	*12*	5	*16*	0.74
Mechanical circulatory support	2	*4*	1	*3*	1.00
Surgical re-exploration	10	*20*	3	*9*	0.21
Prolonged intubation (≥48 h)	15	*30*	6	*20*	0.28
Postoperative renal failure	9	*18*	6	*19*	0.89
Intensive care unit stay (days)	2 (IQR 1–7)		2 (IQR 1–5)		0.81
Postoperative stroke	1	*2*	0	*0*	0.39
Pacemaker implantation	0	*0*	2	*6*	0.15

Continuous data are presented medians with IQR.

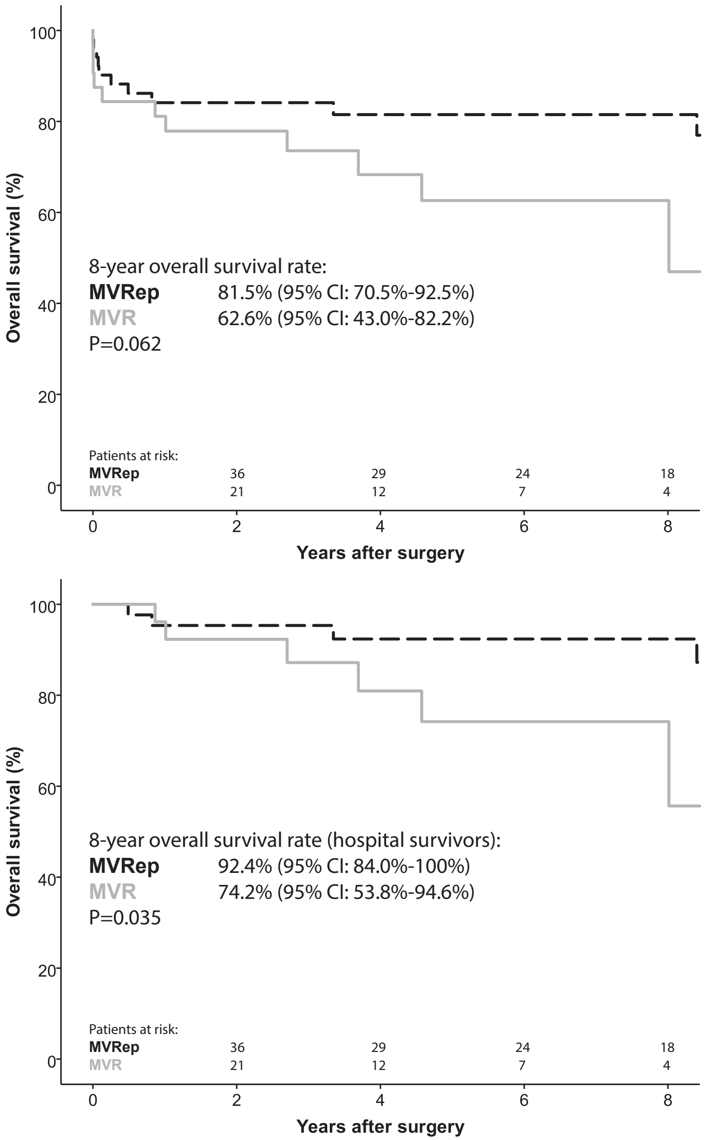


FIGURE 2. **Above**: Overall survival for all patients. **Below**: Overall survival excluding cases of early mortality.

Late Morbidity and Mortality

Fourteen late deaths occurred. There were 2 valve-related deaths (1 due to intracranial hemorrhage after previous mechanical valve replacement and 1 after transapical mitral valve-in-valve implantation), 1 death due to congestive heart failure, 5 sudden unexplained deaths, and 6 non-cardiac deaths. At 8 years after surgery, the overall survival rates were 81.5% (95% CI: 70.5%-92.5%) and 62.6% (95% CI: 43.0%-82.2%) for the MVRep and MVR group, respectively (P=0.062; **Figure 2**). For hospital survivors only, the 8-year overall survival rates were 92.4% (95% CI: 84.0%-100%) and 74.2% (95% CI: 53.8%-94.6%) for the MVRep and MVR group, respectively. Corrected for the propensity score, Cox regression analysis failed to demonstrate a statistical significance difference between the 2 groups (HR 0.359, 95% CI 0.107-1.200; P=0.096).

No thromboembolic events or episodes of recurrent IE occurred. Four patients experienced serious haemorrhagic complications (1 resulting in death). The most recent follow-up reported 58 patients to be alive: 85% were in NYHA functional class I and 15% were in NYHA functional class II (follow-up complete in 55 patients).

Freedom from Reintervention

Four patients needed mitral valve reintervention; 2 from the MVRep and 2 from the MVR group. At 8 years after surgery, the freedom from reintervention rates were 94.8% (95% CI: 87.7%-100%) and 94.7% (95% CI: 84.7%-100%) for the MVRep and MVR group, respectively (P=0.38) (**Figure 3**).

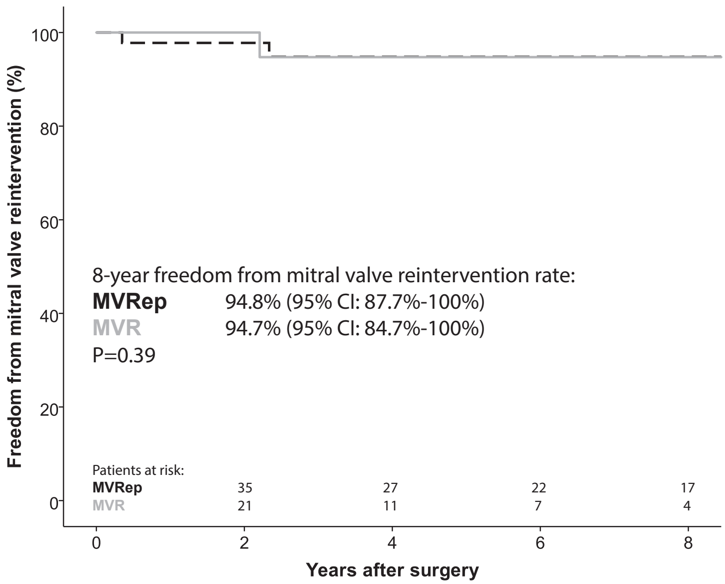


FIGURE 3. Freedom from operated valve reintervention.

In the MVR group, structural valve degeneration necessitating reintervention occurred in 2 patients, 2.5 and 10 years after (biological) valve implantation. The first patient underwent a re-MVR with a biologic prosthesis. The other patient underwent a trans-apical mitral valve-in-valve implantation and died in the early postoperative period [11].

In the MVRep group, reoperation was needed in 2 patients, 4 months and 2.5 years after initial repair. The first patient, discharged initially with residual, moderate MR, developed severe MR originating from the posterior commissure (commissural closure was performed during the initial operation). Following acute cardiac decompensation, an urgent MVR was performed. The other patient underwent an MVR after development of clinical and echocardiographic signs of mitral valve stenosis due to pannus formation. An annuloplasty ring size 26mm was implanted during the initial operation.

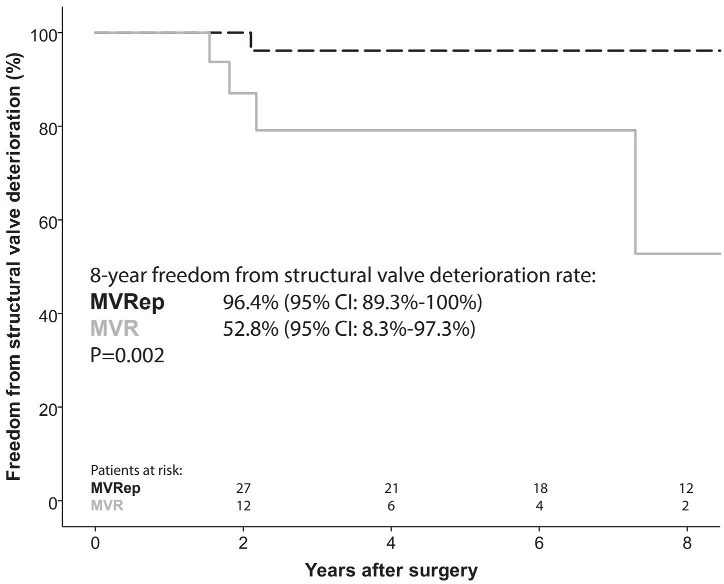


FIGURE 4. Freedom from structural valve deterioration.

Echocardiographic Follow-up

Following successful repair, 1 patient from the MVRep group developed mitral valve stenosis and underwent reintervention. No other cases of recurrent MR or mitral valve stenosis occurred in this group. For MVRep, the 8-year freedom from structural valve deterioration rate was 96.4% (95% CI: 89.3%–100%). Although the small number of patients at risk needs to be taken into account while interpreting the data, valve performance following valve repair showed better results than after MVR (**Figure 4**).

DISCUSSION

Surgical intervention for mitral valve IE has been linked to high early mortality and morbidity [5, 8, 12]. Similar early results were seen in our experience. We failed to demonstrate a significant effect of MVRep on early mortality. Our decision to perform valve repair or replacement was driven predominantly by the extent of valve destruction, and primary MVR did not negatively affect the early outcome.

Prompt surgical intervention was considered the standard of care when a patient was presented with a guideline-defined trigger for intervention [1]. However, a proportion of our patient cohort underwent operation without a guideline-defined trigger for surgical intervention. In these patients, early surgery was performed as ongoing tissue destruction would lower the probability of subsequent MVRep [3, 7]. Such strategy of early surgical intervention has enabled us to perform MVRep in 61% of all patients. In many patients with IE of the mitral valve, the diagnosis is commonly delayed, often resulting in significant tissue destruction prior to the initiation of antibiotic therapy. The duration of antibiotic therapy is therefore of little help to predict valve reparability. We reason that patients with newly diagnosed mitral valve IE should be presented to centers experienced in reconstructive valve surgery immediately after the diagnosis is established to further improve the probability of MVRep.

A high proportion of patients presented with a history of peripheral embolism and the central nervous system was involved in the majority of these. One week after the initiation of antibiotic therapy, the risk of peripheral embolism decreases substantially, challenging the need to perform surgery when prevention of peripheral embolism is the sole indication for surgery [13]. In patients with a recent neurological complication, surgery was historically postponed for 2-4 weeks to prevent further neurological deterioration resulting from the operation. Recent evidence has challenged such an approach, demonstrating that surgery within the first 2 weeks of a neurological event might be performed safely [14, 15]. In these patients an individualized approach is needed and the expected risk of further neurological deterioration needs to be weighed against the probability and expected clinical gain of MVRep.

Interestingly, underlying degenerative mitral valve disease with the presence of excessive leaflet tissue was predictive of successful MVRep. In our experience, MVRep is somehow technically less challenging in these patients as often there will be sufficient excessive native leaflet tissue to support a durable MVRep. The demonstrated durability of MVRep supports an aggressive repair approach even in the presence of active IE in patients with degenerative mitral valve disease.

The durability of MVRep in the setting of IE remains a concern [5, 7, 8, 16]. Combined with an early surgery strategy, our systematical approach to MVRep with progressive utilization of patch techniques has yielded encouraging mid-term repair durability. Previously, de Kerchove et al. reported a repair rate of 80% in a study on 137 patients with active mitral valve IE [5]. The authors demonstrated a remarkable level of surgical expertise and utilized several technical demanding techniques (e.g. partial homograft MVR) to secure such a high repair rate. While their repair rate exceeds the repair rate observed in our experience, the authors reported a freedom from mitral valve reoperation of only 89% at 8-years after surgery. In our experience, recurrent valve dysfunction was uncommon after successful valve repair (without residual MR), and only 1 reoperation was seen during the follow-up period. Based on the previously reported inferior results of partial homograft MVR and the known possibility of fibrosation and/or calcification of the implanted pericardial patches [17, 18], we are reluctant to perform valve repair when valve destruction is too severe. It seems that such an approach has enabled us to select patients in whom a durable valve repair was feasible. In cases of extensive destruction of the native mitral valve, MVR provides satisfactory results and should therefore be preferred to a complex repair with questionable durability. When the mitral valve is replaced, it is of paramount importance to preserve the left ventricular geometry by sparing the subvalvular apparatus (or replacing it with neochords).

Controversy on the use of prosthetic materials in the setting of active IE remains. This is partially caused by the fear of bacterial colonization prior to endothelization of prosthetic materials as well as by the fear of late prosthetic valve IE occurrence; both are associated with high mortality and morbidity [19]. Available evidence, however, suggest that the risk of residual IE is actually low [4]. We liberally utilize prosthetic ring annuloplasty in cases of active IE. In our experience, no residual cases or recurrences of IE were observed. This might partially be explained by rigorous resection of infected tissue consistently performed in our institution in combination with rinsing the operation field with a rifampicin solution. Irrespective of the underlying cause, our data confirm that prosthetic ring annuloplasty is safe in the setting of active IE, provided that radical resection of all infected tissue is performed.

Based on the demonstrated durability of MVRep seen in our experience, we believe that ring annuloplasty is an important prerequisite for successful valve repair. In most of these patients, the mitral valve annulus is diseased as well, either in the context of underlying degenerative valve disease or IE involving the annulus itself, and needs to be addressed. Furthermore, annuloplasty reduces the stress on reconstructed mitral valve leaflets and the tension on the subvalvular apparatus, improving the durability of valve repair. However, in case of a small, non-dilated mitral valve annulus, the possible advantages of ring annuloplasty should be weighed against the possible risk of mitral valve stenosis development. Our data also seem to suggest that in case of tissue resection and lack thereof for reconstruction, patch material should be used to reconstruct the leaflets. This should be preferred to annular plication and/or the implantation of a small ring.

It has been demonstrated that minimal invasive mitral valve surgery is feasible in patients with active mitral valve IE [20]. In our opinion, mitral valve surgery in this setting is complex in cases of both MVRep or MVR. Minimal invasive surgery should be performed only if radical resection and the probability of MVRep are not jeopardized. Further research is needed to establish the role of minimal invasive surgery in this setting.

LIMITATIONS

This is a retrospective single-center study with study limitations inherent to the study design. The limited number of patients at risk –our sample size compares fairly with other available studies- lowered the power of our statistical analyses. The findings of our study will need to be confirmed further. Furthermore, the proportion of patients with underlying degenerative disease was uneven between patients undergoing MVR and MVRep. The severity and duration of MR (possibly resulting in complications related to long-lasting MR) prior to the diagnosis of IE was unknown, making patients with underlying degenerative disease highly heterogenic and introducing a bias we were unable to statistically correct for. One could, however, assume that because of the asymptomatic patient status prior to the diagnosis of IE, the likelihood of long-standing severe MR that would result in irreversible changes is limited.

CONCLUSIONS

Native mitral valve IE is linked to high mortality and morbidity rates. The probability of residual IE occurrence is low and prosthetic ring annuloplasty is not contraindicated in these patients. MVRep in the setting of active IE provides excellent mid-term durability. MVR is a reasonable alternative for patients in whom a durable repair is not feasible.

REFERENCES

[1] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). European heart journal 2015;36:3075-128.

[2] Selton-Suty C, Celard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;54:1230-9.

[3] Dreyfus G, Serraf A, Jebara VA, Deloche A, Chauvaud S, Couetil JP et al. Valve repair in acute endocarditis. The Annals of thoracic surgery 1990;49:706-11; discussion 12-3.

[4] Feringa HH, Shaw LJ, Poldermans D, Hoeks S, van der Wall EE, Dion RA et al. Mitral valve repair and replacement in endocarditis: a systematic review of literature. The Annals of thoracic surgery 2007;83:564-70.

[5] de Kerchove L, Price J, Tamer S, Glineur D, Momeni M, Noirhomme P et al. Extending the scope of mitral valve repair in active endocarditis. The Journal of thoracic and cardiovascular surgery 2012;143:S91-5.

[6] Kanemitsu H, Nakamura K, Fukunaga N, Koyama T. Long-Term Outcomes of Mitral Valve Repair for Active Endocarditis. Circulation journal : official journal of the Japanese Circulation Society 2016;80:1148-52.

[7] de Kerchove L, Vanoverschelde JL, Poncelet A, Glineur D, Rubay J, Zech F et al. Reconstructive surgery in active mitral valve endocarditis: feasibility, safety and durability. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2007;31:592-9.

[8] Musci M, Hubler M, Pasic M, Amiri A, Stein J, Siniawski H et al. Surgery for active infective mitral valve endocarditis: a 20-year, single-center experience. The Journal of heart valve disease 2010;19:206-14; discussion 15.

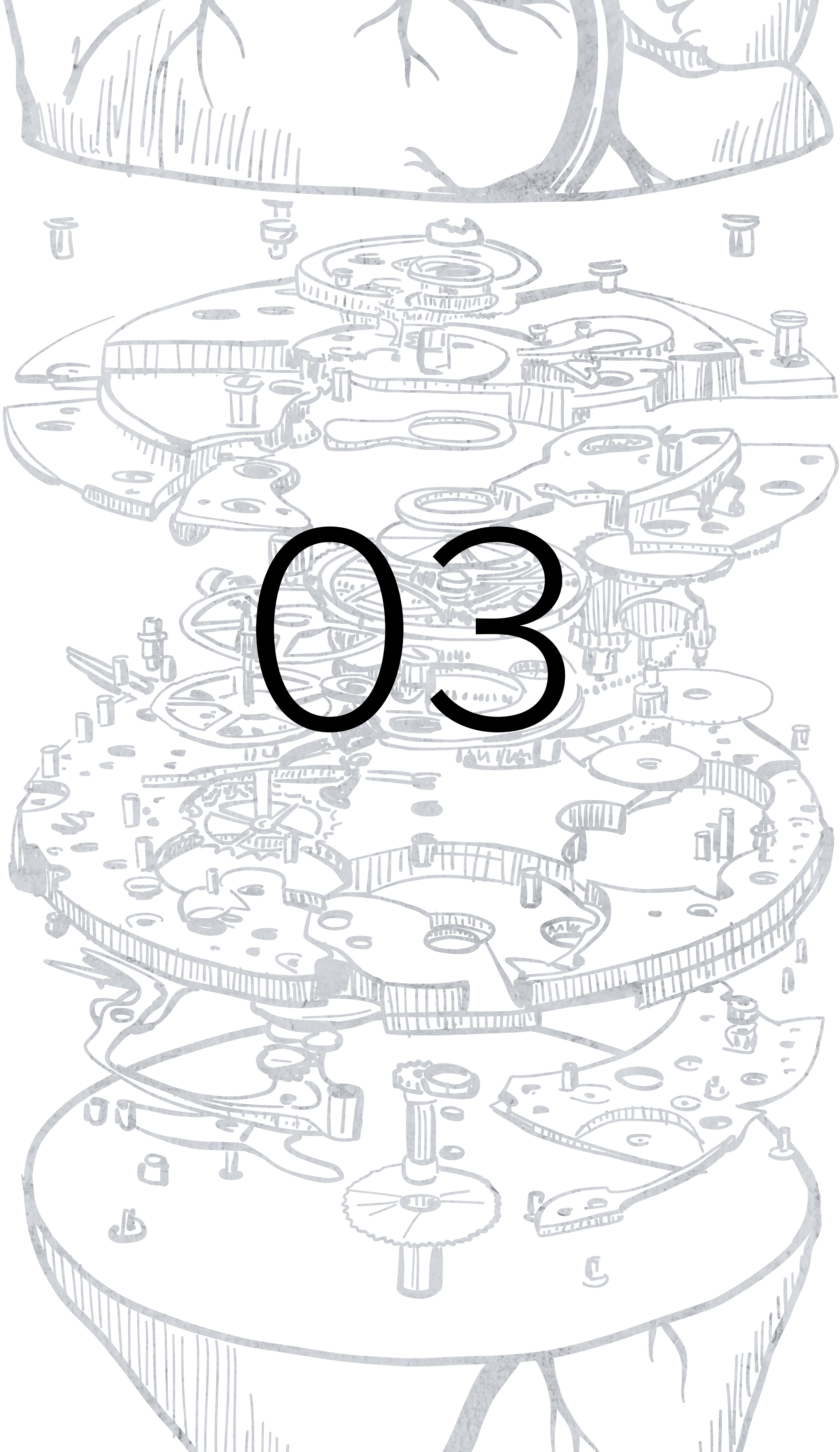
[9] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2000;30:633-8.

[10] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. The Journal of thoracic and cardiovascular surgery 2008;135:732-8.

[11] Tomšič A, Palmen M, Versteegh MI, van der Kley F, Siebelink HJ, Berendsen RR et al. Prosthesis Dislocation After Transapical Valve-In-Valve Mitral Valve Implantation. Can J Cardiol 2016;32:1576 e7-76 e9.

[12] Ruttmann E, Legit C, Poelzl G, Mueller S, Chevtchik O, Cottogni M et al. Mitral valve repair provides improved outcome over replacement in active infective endocarditis. The Journal of thoracic and cardiovascular surgery 2005;130:765-71.

[13] Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007;154:1086-94.
[14] Yoshioka D, Sakaguchi T, Yamauchi T, Okazaki S, Miyagawa S, Nishi H et al. Impact of early surgical treatment on postoperative neurologic outcome for active infective endocarditis complicated by cerebral infarction. The Annals of thoracic surgery 2012;94:489-95; discussion 96.
[15] Wilbring M, Irmscher L, Alexiou K, Matschke K, Tugtekin SM. The impact of preoperative neurological events in patients suffering from native infective valve endocarditis. Interact Cardiovasc Thorac Surg 2014;18:740-7.
[16] Shimokawa T, Kasegawa H, Matsuyama S, Seki H, Manabe S, Fukui T et al. Long-term outcome of mitral valve repair for infective endocarditis. The Annals of thoracic surgery 2009;88:733-9; discussion 39.
[17] Zegdi R, Khabbaz Z, Flecher E, Latremouille C, Noghin M, Chauvaud S et al. Management of commissural lesions in native mitral valve endocarditis: long-term results of valve repair and partial homograft replacement. The Journal of heart valve disease 2006;15:356-9.
[18] Fukunaga N, Sakata R, Koyama T. Reoperative analysis after mitral valve repair with glutaraldehyde-treated autologous pericardium. Interact Cardiovasc Thorac Surg 2017.
[19] Renzulli A, Carozza A, Romano G, De Feo M, Della Corte A, Gregorio R et al. Recurrent infective endocarditis: a multivariate analysis of 21 years of experience. arenzul@tin.it. The Annals of thoracic surgery 2001;72:39-43.
[20] Barbero C, Marchetto G, Ricci D, Mancuso S, Boffini M, Cecchi E, et al. Minimal access surgery for mitral valve endocarditis. Interact Cardiovasc Thorac Surg. 2017 Aug 1;25:241-245.



03

Extensive infective endocarditis of the aortic root and the aortic-mitral continuity:

A mitral valve sparing approach

Anton Tomšič; Adriaan W. Schneider; Meindert Palmen; Thomas J. van Brakel; Michel I.M. Versteegh; Robert J.M. Klautz

Eur J Cardiothorac Surg. 2017;51(6):1100-1107

ABSTRACT

Background. Severe cases of infective endocarditis (IE) of the aortic valve can cause aortic root destruction and affect the surrounding structures, including the aortic-mitral continuity, the anterior mitral valve leaflet and the roof of the left atrium. Reconstruction after resection of all infected tissue remains challenging. We describe our surgical approach and the mid-term results.

Methods. Between January 2004 and December 2015, 35 patients underwent surgery for extensive IE of the aortic valve with destruction of the aortic root, the aortic-mitral continuity and the mitral valve. Mean age was 60.4±13.7; 26/35 (74%) patients had prosthetic valve endocarditis. Four patients were in critical preoperative state. Median EuroSCORE II was 18.0% (interquartile range 11.0–26.7).

Results. Aortic root replacement was performed in 32 (91%) patients. The remaining patients underwent aortic valve replacement. Reconstruction of the aortic-mitral continuity and the roof of the left atrium were performed using a folded pericardial patch. In 28 patients (80%), mitral valve repair was performed. Postoperative mechanical circulatory support, acute kidney failure and surgical re-exploration were seen in 5 (16%), 10 (31%) and 4 (13%) patients, respectively. Early survival rate was 77% (27 patients). During a median follow-up of 29.8 months (interquartile range 6.4–62.9), 7 (26%) patients required reintervention (3-42 months after surgery); 4 were due to mitral incompetence, early in our experience.

Conclusions. Extensive IE of the aortic root with destruction of the surrounding tissues remains a complex disease with high morbidity and mortality rates. Our technique allows native mitral valve preservation but is technically challenging.

INTRODUCTION

Infective endocarditis (IE) presents a complex disease with in-hospital mortality rates ranging from 15% to 30% despite optimal antimicrobal and surgical therapy [1]. The prognosis is especially poor when periannular involvement, signs of heart failure and/or prosthetic valve endocarditis are present [1]. In cases of uncontrolled infection with progressive destruction of the adjacent structures and abscess formation urgent surgical intervention is indicated [1]. In particular, uncontrolled IE of the aortic valve can cause destruction of the aortic root and, subsequently, the aortic-mitral continuity and the mitral valve. Infection of the aortic-mitral continuity has been reported in 10.6% of cases of left-sided IE [2] and in 47.1% of patients with aortic root abscess [3]. In cases of left-sided double valve IE, aortic-mitral continuity reconstruction is needed in 28% [4]. This indicates that direct extension of the infective process is responsible for destruction of the mitral valve in a significant number of cases.

Independent of the extent of the disease, excision of all infected tissue is the cornerstone of surgical therapy for IE [1]. This is followed by reconstruction of all resected structures. Previously, double valve replacement with aortic-mitral continuity reconstruction has been described for cases of extensive IE of the aortic root with concomitant infection of the aortic-mitral continuity and the mitral valve [5]. Even in experienced centers such extensive surgical intervention is associated with a poor prognosis and the early mortality rate ranges from 10% to 32% [2, 5-8]. Surgical intervention, however, remains the only curative treatment option for most patients in this highly complex patient group. It has previously been demonstrated that in patients undergoing aortic valve surgery concomitant mitral valve repair rather than replacement is associated with improved long-term survival [9]. However, it is unclear whether a mitral valve sparing approach is an alternative for replacement in patients with extensive IE of the aortic root with involvement of the mitral valve.

In recent years, we have developed a surgical approach that allows preservation of the native mitral valve in such cases of extensive IE. The body of the anterior mitral valve leaflet (AMVL), the aortic-mitral continuity and the roof of the left atrium are reconstructed with pericardial patches and ring annuloplasty, followed by aortic valve or, preferably, root replacement. The aim of this study is to describe our surgical approach and assess the short- and mid-term safety and efficacy of this procedure.

METHODS

Study design

The study population consisted of all patients who underwent surgery for active IE of the aortic root with concomitant infection of the aortic-mitral continuity and the mitral valve between January 2004 and December 2015. By definition, this also included patients with previously replaced or repaired mitral valves. The study was approved by our Institutional Ethics Committee.

Clinical, operative and early outcome data were collected in our computerized database. Follow-up clinical and echocardiography data were collected in our outpatient clinic or by contacting the referring physicians and cardiologists, and/or by direct telephonic contact with the patients. Survival follow-up was 100% complete with a median follow-up time of 29.8 months [interquartile range (IQR) 6.4-62.9]. Follow-up on valve-related events was 94% complete. Recent echocardiography was available in 89% of patients with a median follow-up time of 26.2 months (IQR 7.4-70.2). Follow-up was closed on 7 March 2016.

Study endpoints

Data are reported according to the 2008 joint Society of Thoracic Surgeons, American Association for Thoracic Surgery, and European Association for Cardio-Thoracic Surgery Guidelines for reporting mortality and morbidity after cardiac valve interventions [10].

Surgical technique

All patients were operated through median (re-)sternotomy using standard techniques for extracorporeal circulation with double venous cannulation. Moderate systemic hypothermia, with a target core body temperature of 32°C, was used. Antegrade warm blood cardioplegia was used for cardioprotection in all cases and re-administered every 15-20 minutes.

The aortic valve and all macroscopically infected tissues were carefully removed and sent for microbacterial culture. This included all infected parts of the aortic annulus, the roof of the left atrium, the aortic-mitral continuity and all infected parts of the mitral valve (usually the anterior part of the mitral valve annulus and the body of the AMVL; **Figure 1A-D**). The operative area was rinsed with a rifampicin solution.

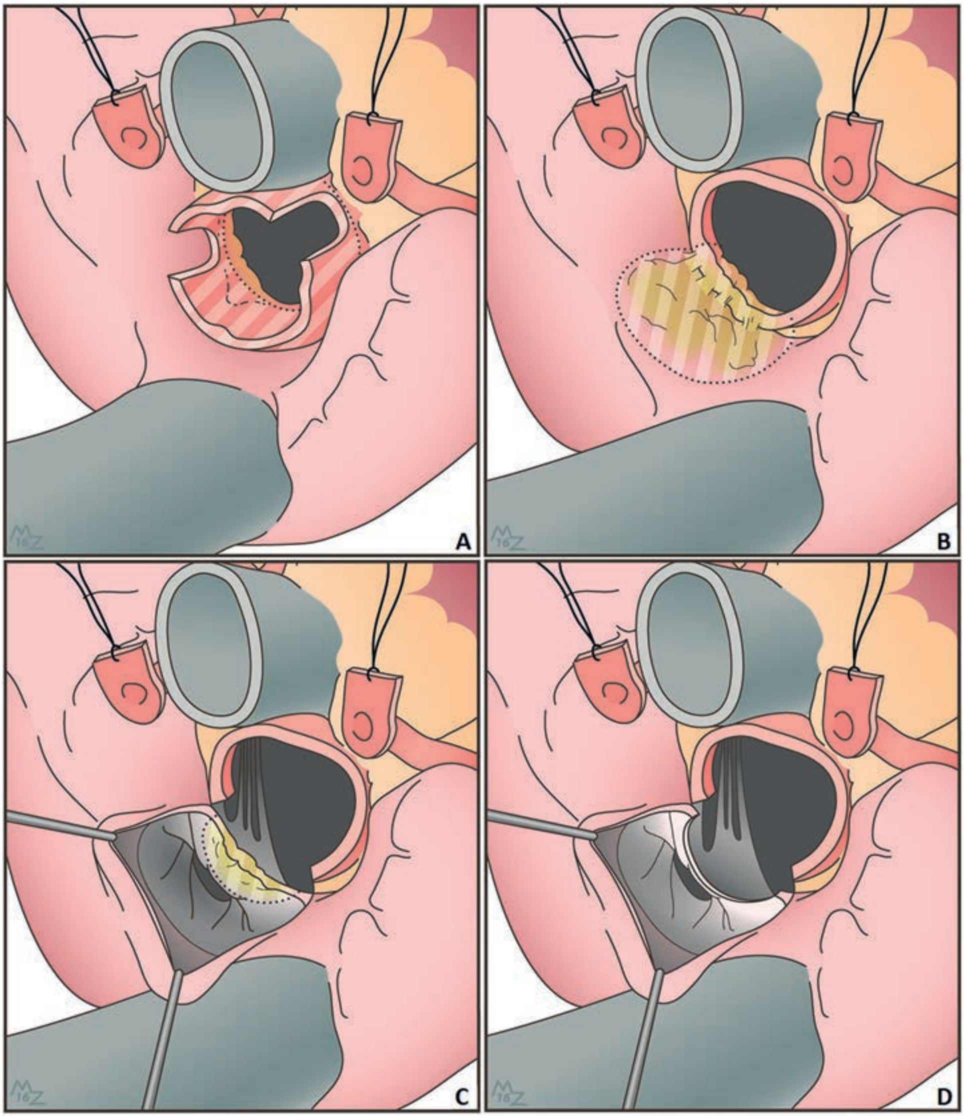


FIGURE 1. After removal of the infected aortic valve (native or prosthesis), all macroscopically infected tissues are carefully removed (**A-D**). For further explanation, please see the according text.

Reconstruction of the resected structures was performed with pericardial patch material (**Table I**). The mitral valve was reconstructed or replaced transseptally or, in most cases, through the roof of the left atrium/left ventricular outflow tract opening. If the free edge of the AMVL was intact and no infection of other parts of the mitral valve was present, an annuloplasty ring was first implanted in the remaining mitral valve annulus (typically from commissure to commissure). To determine the appropriate annuloplasty ring size, a sizer was placed on the remaining part of the mitral valve annulus with the intertrigonal distance serving as a guide for optimal size. The defect in the body of the AMVL was reconstructed using a pericardial patch, all the way up to the anterior part of the annuloplasty ring (**Figure 2A-B**). This patch was sewn in with a 5-0 polypropylene suture. The size of the patch was created in such a way that the newly reconstructed AMVL would roughly cover the implanted ring. For this reason, precise ring sizing is not crucial; in most cases (50%) we selected a ring size 32mm as that is the most prevalent size of the mitral valve in the Dutch population. In case of more extensive involvement of the mitral valve (destruction of the free edge or commissural involvement), the valve was excised. The sutures for the prosthetic mitral valve were placed in the remainder of the mitral valve annulus, usually covering two-thirds to three-quarters of the prosthesis.

Next, a folded pericardial patch was sutured with its fold to the annuloplasty ring (or valve in case of valve replacement), creating a double patch (**Figure 2C**). After unfolding, one part of the patch was used to reconstruct the roof of the left atrium and the other part to reconstruct the aortic-mitral continuity and the left ventricular outflow tract (typically from the former commissure between the left and non-coronary cusps all the way to the middle of the right coronary sinus; **Figure 2D-E**), using 4-0 polypropylene sutures. In most patients, the aortic root was then reconstructed with an aortic root prosthesis (**Figure 2F; Table I**) sutured in the left ventricular outflow tract with interrupted TiCron 4-0 sutures (Medtronic, Inc, Minneapolis, MN, USA). Coronary buttons were reimplanted using continuous 5-0 polypropylene sutures. The distal anastomosis (between the root prosthesis and the native aorta) was made using a continuous 4-0 or 5-0 polypropylene suture.

Pre- and postoperative care

Infective endocarditis was diagnosed according to the modified Duke criteria [11]. Empiric intravenous antibiotic therapy was initiated at the time of diagnosis; after causative pathogen identification this was adjusted accordingly (**Table II**). Intravenous antibiotic therapy was administered for at least 48 hours prior to surgery to ensure blood stream sterilization. Two (6%) patients, however, underwent operation within 48 hours of antibiotic therapy initiation due to rapid hemodynamic deterioration. Additionally, 2 patients received no preoperative antibiotic therapy as the diagnosis of active IE was established intraoperatively.

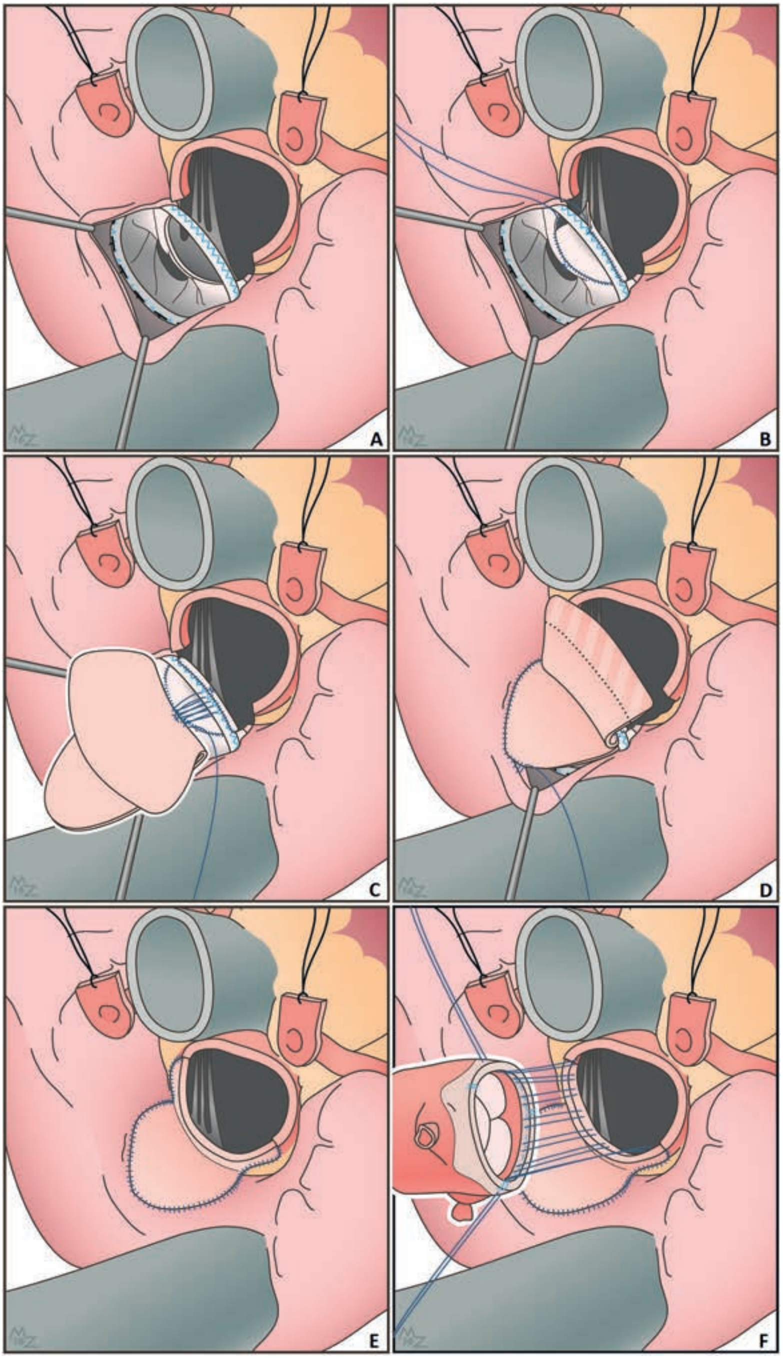


FIGURE 2. Following extensive resection of all infected structures, reconstruction of all affected structures is performed. For further explanation, please see the according text.

Postoperatively, pathogen specific intravenous antibiotic therapy was continued for a minimal duration of 6 weeks. Standard antithrombotic management consisted of oral anticoagulation for 3 months after surgery with a target international normalized ratio of 2.0-3.0. In patients with atrial fibrillation or a mechanical prosthesis in the aortic position, oral anticoagulation was continued indefinitely. In patients with a mechanical prosthesis in the mitral position, a target international normalized ratio range of 2.5-3.5 was applied.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed and medians with interquartile ranges (IQR) for skewed data. Categorical data are presented as counts and percentages. Freedom from time-related events was estimated using the Kaplan-Meier method. To assess the influence of our initial experience on the quality and durability of the procedure, we divided our study cohort in consecutive overlapping subgroups of 15 patients. In each subgroup, the freedom from reintervention was assessed individually using the Kaplan-Meier method. The results are presented graphically. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic characteristics

Demographic characteristics of all 35 patients and details on the extent of the disease are shown in **Table II**. Prosthetic valve endocarditis was seen in the majority of patients (74%). One patient underwent elective surgery and the diagnosis of low-grade prosthetic valve endocarditis was made intraoperatively. All other patients underwent urgent or emergent surgery. Most common indications for surgical intervention were evidence of uncontrolled infection and/or prevention of peripheral embolization. Four patients were in critical preoperative state. Preoperative peripheral embolization was seen in 5 patients: 3 cases to the brain and 2 to the spleen. Median EuroSCORE II was 18.0% (IQR 11.0–26.7).

TABLE I. Intraoperative details.

Aortic-mitral continuity and left atrium reconstruction	35 (100)
Right atrium reconstruction	5 (14)
Ventricular septum reconstruction	5 (14)
Aortic valve replacement	3 (9)
St. Jude Medical Regent*	3 (100)
Aortic root ± ascending aorta replacement	32 (91)
Stentless root prosthesis	24 (75)
Freestyle aortic root prosthesis**	17 (71)
Toronto aortic root prosthesis*	7 (29)
Composite tailored tissue graft	2 (6)
Perimount Magna***	1 (50)
Medtronic Mosaic**	1 (50)
Composite mechanical graft	5 (16)
St. Jude Medical Regent*	5 (100)
Homograft	1 (3)
Aortic arch replacement	1 (3)
Mitral valve repair	28 (80)
Physio Annuloplasty Ring***	24 (86)
No ring annuloplasty	4 (14)
Anterior leaflet reconstruction	26 (93)
Autologous pericardium	8 (31)
Xenologous pericardium	12 (46)
CardioCel****	6 (23)
Mitral valve replacement	7 (20)
St. Jude Medical Regent*	4 (57)
Medtronic Mosaic**	2 (29)
Perimount Magna***	1 (14)
Tricuspid valve repair	9 (26)
Physio Tricuspid Annuloplasty Ring***	3 (38)
MC3 Tricuspid Annuloplasty Ring***	3 (38)
De Vega annuloplasty	2 (25)
Commissuroplasty	1 (13)
Coronary artery bypass grafting	3 (9)
Aortic cross-clamp time (min)	300±77
Cardio pulmonary bypass time (min)	388±121

*Data are presented as n (%) and means ± standard deviations. *St. Jude Medical, Inc, St. Paul, MN, USA; **Medtronic, Inc, Minneapolis, MN, USA; ***Edwards Lifesciences, Irvine, CA, USA; ****AdmedusRegen Pty Ltd, Perth, WA, Australia*

TABLE II. Baseline characteristics.

Age (years)	60.4 ± 13.7
Female	6 (17)
Diabetes mellitus	2 (6)
Creatinine value	90 (IQR 75–112)
Preoperative rhythm	
Atrial fibrillation	10 (29)
Preoperative pacemaker	4 (11)
NYHA class	
I	25 (71)
II	2 (6)
III	6 (17)
IV	2 (6)
Left ventricular ejection fraction	
>50%	21 (60)
30-50%	13 (37)
<30%	1 (3)
Prosthetic valve endocarditis	26 (74)
Timing of surgery	
Elective	1 (6)
Urgent	30 (86)
Emergent	4 (11)
Previous cardiac surgery	26 (74)
Aortic valve replacement	26 (74)
Mitral valve repair	2 (6)
Mitral valve replacement	1 (3)
Diuretic therapy	
Oral	3 (9)
Intravenous	5 (14)
Critical preoperative state	4 (11)
Preoperative inotropic support	2 (6)
EuroSCORE II	18.0 (IQR 11.0–26.7)
Echocardiographic observation	
Perivalvular abscess	21 (60)
Vegetation	20 (57)
<10 mm	8 (23)
10-15 mm	2 (6)

TABLE II. Continued.

>15 mm	9 (26)
Unknown	1 (3)
Causative microorganism	
Staphylococcus aureus	5 (14)
Other *Staphylococcus* spp.	7 (20)
Streptococcus pneumoniae	2 (6)
Other *Streptococcus* spp.	10 (29)
Propionibacterium acnes	3 (9)
Culture negative	8 (23)
Antibiotic therapy duration (days)	10 (IQR 5–19)
<48 hours	4 (11)
Peripheral embolization	5 (14)
De novo total atrioventricular block	5 (14)
Indication for surgery	
Progressive heart failure	2 (6)
Prevention of peripheral embolization	7 (20)
Uncontrolled infection	35 (100)

Data are presented as n (%), means ± standard deviations or medians (interquartile range).

Intraoperative details

Details on the surgical procedures performed are shown in **Table I**. Aortic root replacement, with or without replacement of the ascending aorta, was performed in 32 (91%) cases. Three patients underwent aortic valve replacement. Of the 35 patients, 4 patients had previously undergone mitral valve surgery: 2 previous repairs and 2 replacements. One patient underwent a re-repair while the other 3 underwent valve replacement. Of the 31 patients with no history of previous mitral valve surgery, 27 (87%) underwent valve repair and 4 (13%) valve replacement.

Perioperative Mortality and Morbidity

There were 8 (23%) early deaths; 3 patients (9%) died intraoperatively and 5 (14%) patients died during the early postoperative period (**Table III**). All early deaths occurred in patients with prosthetic valve endocarditis; in-hospital mortality occurred in 2/4 patients in critical preoperative state. All intraoperative deaths were caused by uni- or biventricular failure with failure to wean from cardiopulmonary bypass. Uncontrolled bleeding was additionally present in 1. Other cases of early mortality were caused by multiple organ dysfunction syndrome caused by profound postoperative cardiogenic and/or distributive shock. Early mortality in the first and last 15 patients of the study cohort was 33% and 13%, respectively.

Postoperative complications are presented in **Table III**. Mechanical circulatory support was needed in 5 patients (4 of these died in the early postoperative period). Surgical re-exploration and postoperative acute kidney failure were seen in 4 (13%) and 10 (31%) patients, respectively.

TABLE III. Perioperative morbidity and mortality.

Mortality	
Early mortality	8 (23)
Intraoperative mortality	3 (9)
One-year mortality	10 (29)
Mechanical circulatory support	5 (16)
Prolonged intubation (>48 h)	6 (19)
Surgical re-exploration	4 (13)
Acute kidney failure	10 (31)
Pacemaker implantation	10 (36)
Intensive unit care stay (days)	3 (IQR 2–6)

Data are presented as n (%) and medians (interquartile range).

Late Mortality

During the follow-up period 5 additional deaths occurred, 2 within the first year after the operation. The 1-, 2- and 5-year survival rates were 69.4% [95% confidence interval (CI) 53.0–86.0%], 65.3% (95% CI 48.0–82.0%) and 65.3 (95% CI 48.0–82.0%), respectively (**Figure 3**). The cause of death was valve-related (following operated valve reintervention) in 1 patient, heart failure in 3 patients and unknown in 1 patient.

Infective Endocarditis Recurrence

No relapses or early recurrences of IE were seen. In 2 patients, late IE (29 months and 74 months after surgery) occurred. The first patient presented with echocardiographic evidence of IE (vegetations on both the aortic and mitral valve). The risk for operation was considered too high due to comorbidities and the high-risk of re-re-reoperation. The second patient presented without echocardiographic observations suggestive for

IE and the diagnosis was established by modified Duke criteria. The patient responded promptly to antibiotic therapy and due to the high-risk of re-re-reoperation no surgical intervention was performed. Both patients were alive at follow-up.

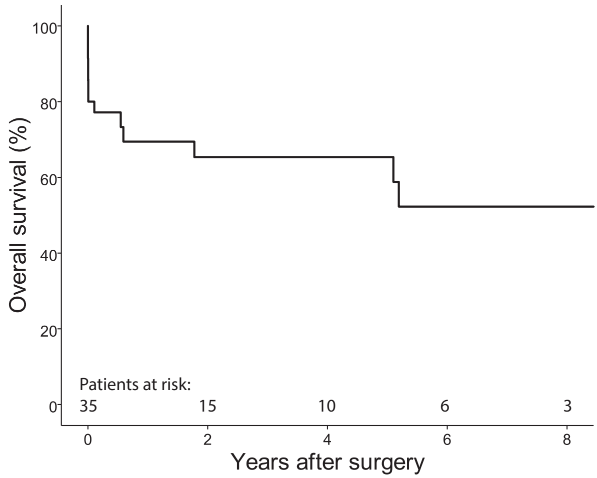


FIGURE 3. Survival curve for the whole study cohort.

Reintervention

Seven of the 27 hospital survivors underwent reintervention during the follow-up period (**Table III**). Freedom from reintervention rates at 1-, 2- and 5-years was 84.6% (95% CI 68.0–100.0%), 78.9% (95% CI 60.0–97.0%), and 51.2% (95% CI 23.0–80.0%), respectively (**Figure 4**). Within the first 15 hospital survivors of our series, reintervention was needed in 6 (mean follow-up: 82.5 ± 47.3 months; mean time to reoperation: 25.9 ± 16.5 months). In the last 15 hospital survivors, reintervention was needed in 1 [median follow-up: 9.6 months (IQR: 4.0–34.6); 89 days after initial operation].

Following mitral valve repair, 5 patients underwent mitral valve reintervention. In 4 patients recurrent MR was the primary indication for reoperation and in 2 of these no ring annuloplasty was performed during the initial operation. Paravalvular leakage of the aortic valve was the primary indication for reoperation in the remaining patient. Mitral valve replacement was concomitantly performed due to the presence of moderate MR. Two out of 3 patients that underwent aortic valve replacement during the initial operation needed reoperation due to the occurrence of a significant paravalvular leak.

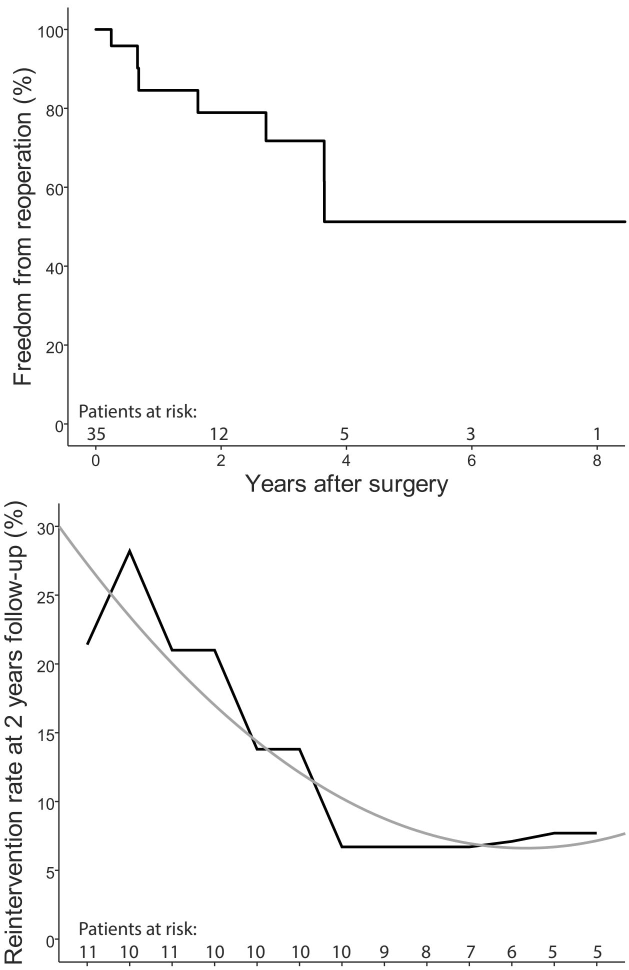


FIGURE 4. **Above**: freedom from operated valve reintervention. **Below**: 2 year freedom from operated valve reintervention trendline (hospital survivors; 27 patients).

Echocardiographic Follow-up

In patients who underwent mitral valve repair and did not undergo valve reintervention (n = 18), the latest echocardiography demonstrated none or mild MR in 14 (82%) and moderate MR in 3 (18%).

TABLE IV. Operated valve reintervention details.

	Time between initial surgery and reoperation	Year of initial surgery	Initial operation	Indication for reoperation	Recurrent MR mechanism	Procedure performed	Outcome
1	89 days	2013	AVR + MVR + AMC reconstruction + LA roof reconstruction	Paravalvular leakage (aortic valve) + moderate TR	…	Aortic root replacement + TVP	Survived
2	8 months	2004	Aortic root replacement + MVP + AMC reconstruction + LA roof reconstruction + VSD closure	Severe MR + severe TR	Patch dehiscence	MVP + TVP	Survived
3	8 months	2004	Aortic root replacement + MVP + AMC reconstruction + TVP + LA roof reconstruction	Severe MR	Patch defect + coaptation failure + annulus calcification	MVR	Survived
4	20 months	2007	AVR + MVP + AMC reconstruction	Paravalvular leakage (aortic valve) + moderate MR + severe TR	…	AVR + MVR + TVP	Died
5	33 months	2008	Aortic root replacement + MVP + AMC reconstruction	Severe MR	Ring + patch dehiscence	MVP	Survived
6	42 months	2004	Aortic root replacement + MVP + AMC reconstruction + LA roof reconstruction	LVOT reconstruction dehiscence with pseudo-aneurysm formation	…	Aortic root replacement	Survived
7	42 months	2009	Aortic root replacement + MVP + AMC reconstruction + LA roof reconstruction	Combined MV lesion	P1-AC prolapse + para-annular leak	TA-MVI	Survived

Abbreviations: AMC: aortic-mitral continuity; AVR: aortic valve replacement; LA: left atrium; LVOT: left ventricular outflow tract; MV: mitral valve; MVP: mitral valve plasty; MVR: mitral valve replacement; TA-MVI: trans-apical mitral valve implantation; TR: tricuspid regurgitation; TVP: tricuspid valve plasty; VS: ventricular septum

Late Clinical Outcome

Three thromboembolic events (2 transient ischemic attacks and 1 cerebrovascular accident) and no major bleeding events occurred. At most recent follow-up, 18 (86%) patients were in NYHA class I and 3 (14%) in NYHA class II.

DISCUSSION

In this study, we describe a single-center experience with patients suffering from extensive IE of the aortic root with concomitant infection of the aortic-mitral continuity and the mitral valve. Moreover, we describe a surgical technique that allows preservation of the native mitral valve when the destructive process is limited to the body of the AMVL, as is the case in many instances. The data presented demonstrate that mitral valve repair is feasible even in very severe cases of IE.

The early mortality rate of 23% seen in our series is comparable with mortality rates previously reported in similar cohorts [2, 7, 8]. This high early mortality rate reflects the presence of various risk factors, including prosthetic valve endocarditis, non-elective operation setting and critical preoperative state. During the course of the study, a decline in the early mortality rate was observed. We reason that this is a result of growing single-center experience and consequent improvements in the surgical technique and perioperative care. Following weaning from cardiopulmonary bypass, ventricular failure was often seen. This might reflect the long period of cardioplegic arrest, which is inevitable in these patients. Preoperatively, impaired left ventricular function was present in 63% of patients from the early mortality group. The limited number of patients and events, however, prevents further analysis of these observations.

As in other series, a large proportion of our patient cohort (74%) had prosthetic valve endocarditis [2, 7, 8]. The extent of disease in these patients reflects a delay in the diagnosis and treatment of IE after the initial onset of symptoms. Consequently, patients are referred for surgery when the infectious process has already advanced considerably. This observation emphasizes again that the awareness for IE in patients with prosthetic heart valves is mandatory to allow early intervention, prior to the development of extensive destruction of the surrounding structures [1].

We standardly utilize rigorous resection of all infected tissue in all cases of IE. A high proportion of patients needed reconstruction of cardiac structures beyond the aortic valve or root: i.e. the aortic-mitral continuity, the roof of the left atrium, and the mitral valve. This finding has not been reported uniformly by others [2, 7]. More extensive resection is partially responsible for the extensive aortic cross-clamp and cardiopulmonary bypass times observed in our cohort. However, we have been able to avoid bleeding complications related to poor patch anchoring in infection-ridden and devitalized tissues, previously described in 12% of cases; all such events resulted in intraoperative death [7]. Several studies have shown that residues or early recurrences of IE are a common complication in this patient group [2, 4, 6, 7]. Interestingly, in our experience this was not observed. Radical resection of all macroscopically infected structures combined with rinsing the operative area with rifampicin might provide sufficient protection from the occurrence of residual IE despite a large amount of prosthetic material implanted.

Following resection of all infected tissues, several options to reconstruct the aortic root are available. We have previously described our experience with the Medtronic Freestyle stentless porcine bioprosthesis (Medtronic, Minneapolis, MN, USA) in such cases [12]. This prosthesis was used in 17 (49%) patients in this study cohort with satisfactory results; it currently presents our standard choice in these patients. Standard aortic valve replacement was performed in 3 patients; 2 of these developed a clinically significant paravalvular leak and underwent reoperation. In the presence of an aortic root abscess, aortic root replacement, as advocated by the European guidelines [1], seems justified.

During the study period, we have systematically utilized mitral valve repair despite the presence of an extensive infectious process. Mitral valve repair was deemed impossible when the infection proceeded to include more than only the anterior portion of the valve. Ring annuloplasty provides annular stabilization and serves as a guide for the appropriate size of the pericardial patch needed to reconstruct the AMVL. However, a significant proportion of patients undergoing valve repair needed reintervention due to recurrent MR. All mitral valve reinterventions occurred during our early experience with this procedure. Several risk factors might have predisposed to the high reintervention rate during this period. First, ring annuloplasty was not performed in 2 patients who later underwent mitral valve reintervention. Second, in 8 patients, untreated autologous pericardial tissue -commonly used early in our experience- was used to reconstruct the AMVL; 3 of these patients later underwent reintervention. Untreated autologous pericardium appeared to be prone to tissue degeneration that resulted in patch retraction and valve dysfunction. We currently utilize pretreated decellularized bovine pericardium when performing this procedure; superior handling and improved durability are of particular benefit in this setting. In the absence of these risk factors good valve repair durability was established.

Our data suggest that growing single-center experience importantly impacts the clinical outcome of this patient group, known for high early morbidity, mortality and reintervention rates [2, 8]. This makes us believe that these patients should be presented to an experienced endocarditis team early in the course of the disease. We currently utilize an aggressive approach and tend to proceed with surgical intervention as soon as blood stream sterilization is secured. In most patients, prosthetic valve endocarditis was present and conservative management alone is unlikely to result in full recovery. Moreover, further progression of tissue destruction could make mitral valve repair impossible.

LIMITATIONS

This is a retrospective single-center study with a limited number of patients. However, our study included the biggest cohort of such extensive cases of active IE reported to date. We included only patients with active IE to ensure a homogenous patient population. Due to limited numbers of patients and events, we have not been able to directly compare clinical outcomes of patients who underwent mitral valve repair rather than replacement. The assumed clinical benefits of mitral valve repair are based on the available literature. Nevertheless, the presented surgical technique is a reasonable alternative in cases of-extensive IE with acceptable early and late outcomes.

CONCLUSIONS

Infective endocarditis of the aortic root with extension into the aortic-mitral continuity and the mitral valve remains a complex disease with high mortality and morbidity rates. To ensure optimal prognosis, early referral to experienced centers is mandatory. The described reconstructive technique allows mitral valve preservation when the destructive process is limited to the anterior part of the valve. Provided that radical resection of all infected tissue is performed, the risk of early IE recurrence is low. However, surgery is technically challenging, reflected in our experience by a significant number of reinterventions. Nevertheless, a technically sound procedure will result in a satisfactory result with good valve repair durability.

REFERENCES

[1] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.

[2] Forteza A, Centeno J, Ospina V, Lunar IG, Sanchez V, Perez E et al. Outcomes in aortic and mitral valve replacement with intervalvular fibrous body reconstruction. Ann Thorac Surg 2015;99:838-45.

[3] Leontyev S, Borger MA, Modi P, Lehmann S, Seeburger J, Doenst T et al. Surgical management of aortic root abscess: a 13-year experience in 172 patients with 100% follow-up. J Thorac Cardiovasc Surg 2012;143:332-7.

[4] Sheikh AM, Elhenawy AM, Maganti M, Armstrong S, David TE, Feindel CM. Outcomes of double valve surgery for active infective endocarditis. J Thorac Cardiovasc Surg 2009;138:69-75.

[5] David TE, Kuo J, Armstrong S. Aortic and mitral valve replacement with reconstruction of the intervalvular fibrous body. J Thorac Cardiovasc Surg 1997;114:766-71; discussion 71-2.

[6] De Oliveira NC, David TE, Armstrong S, Ivanov J. Aortic and mitral valve replacement with reconstruction of the intervalvular fibrous body: an analysis of clinical outcomes. J Thorac Cardiovasc Surg 2005;129:286-90.

[7] Davierwala PM, Binner C, Subramanian S, Luehr M, Pfannmueller B, Etz C et al. Double valve replacement and reconstruction of the intervalvular fibrous body in patients with active infective endocarditis. Eur J Cardiothorac Surg 2014;45:146-52.

[8] Kim SW, Park PW, Kim WS, Sung K, Lee YT, Jun TG et al. Long-term results of aortomitral fibrous body reconstruction with double-valve replacement. Ann Thorac Surg 2013;95:635-41.

[9] Saurav A, Alla VM, Kaushik M, Hunter CC, Mooss AV. Outcomes of mitral valve repair compared with replacement in patients undergoing concomitant aortic valve surgery: a meta-analysis of observational studies. Eur J Cardiothorac Surg 2015;48:347-53.

[10] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008;33:523-8.

[11] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.

[12] Schneider AW, Hazekamp MG, Versteegh MI, Bruggemans EF, Holman ER, Klautz RJ et al. Stentless bioprostheses: a versatile and durable solution in extensive aortic valve endocarditis. Eur J Cardiothorac Surg 2016;49:1699-704.

PART II

BARLOW'S MITRAL VALVE DISEASE

An association between a mid-systolic click accompanied by late systolic murmur and mitral regurgitation was first demonstrated by Barlow and colleagues in 1963 by means of cine-ventriculography [1]. In a subsequent analysis of 90 patients, Barlow and colleagues speculated that these auscultatory signs are caused by abnormal leaflet motion, occurring as a consequence of invariably lengthened, functionally lengthened or ruptured chordae tendineae [2]. Interestingly, the authors also proposed that the voluminous aspect of mitral valve leaflets is a secondary abnormality, occurring as a consequence of excessive leaflet stress.

Carpentier and colleagues later characterized Barlow's mitral valve disease as the most severe form of degenerative mitral valve disease [3]. The least extensive form was termed fibroelastic deficiency (FED), characterized by thin mitral valve leaflets and, usually, single-scallop prolapse due to chordal rupture. The scope of degenerative mitral valve diseases is marked by an increasing amount of excessive leaflet tissue and a growing number of affected segments. Patients with Barlow's disease are usually younger than patients with other types of degenerative mitral valve disease. The diagnosis is often established in the first 2 or 3 decades of life by abnormal cardiac auscultation on physical examination. Echocardiographic and surgical examination will reveal voluminous, thickened and myxomatous degenerated mitral valve leaflets with prominent annular dilation [4]. Thickened chordae tendineae, that may be elongated or ruptured, are frequently observed. Extensive annular calcification, involving predominantly the posterior annulus, may also occur, often at a later stage of disease. Typically, large annuloplasty rings will be needed to complement valve repair.

Carpentier proposed that excessive tissue is responsible for the billowing of leaflet belly regions into the left atrium during systole while leaflet prolapse will result from chordal or papillary muscle elongation or rupture [3]. Recent improvements in cardiac imaging have provided a more detailed insight in the physiology and pathology of Barlow's disease and suggest that abnormal leaflet motion can occur as a consequence of functional annular abnormalities. Moreover, resolution of these abnormalities by means of annular remodeling and stabilization could allow abnormal leaflet motion to be effectively corrected.

Disease extensiveness, with multi-scallop prolapse and voluminous leaflets, make valve repair in the context of Barlow's disease particularly challenging. Moreover, late results of valve repair for Barlow's disease are inferior to the results of valve repair for other types of degenerative disease, with recurrent mitral regurgitation occurring significantly more often [5]. Interestingly, patients with Barlow's disease seem to be particularly prone to repair failure in cases when annuloplasty is not performed. This suggests that the contribution of annular abnormalities differs between various type of degenerative valve disease.

In accordance with these observations, Hutchins and colleagues reported in 1986 that the mitral annulus fibrosus in patients with Barlow's disease structurally differs from the annulus fibrosus of healthy individuals or patients with other types of degenerative disease [6]. In particular, posterior annular displacement, a separation between the atrial wall–mitral valve junction and the left ventricular attachment, was observed in 92% of patients in whom other macroscopic characteristics of Barlow's disease were also present. The authors suggested that the mitral valve annulus could be the primary abnormality in these patients and possibly directly responsible for excessive leaflet motion. Consistent with the observations made by Barlow and colleagues, the authors proposed that excessive leaflet stress could present the stimulus for increased production of mitral leaflet tissue. The observations made by Hutchins and colleagues do not seem to have been widely accepted as other authors have challenged their findings [7]. For a long time, myxomatous degeneration of mitral valve tissue was thus believed to be a primary abnormality and associations with other connective tissue disorders, including Marfan syndrome, were made.

In Barlow's disease, annular morphology and motion throughout the cardiac cycle differ significantly from the ones seen in other types of degenerative mitral valve disease. Besides more pronounced annular dilation, poorer annular contraction and saddle-shape attenuation with abnormal annular enlargement in late systole have been described [8, 9]. This description of excessive late systolic annular motion is surprisingly consistent with the mechanism of valve dysfunction proposed by Hutchins and colleagues nearly three decades earlier. It seems crucial to differentiate between structural and functional abnormalities of the mitral valve annulus.

Myxomatous leaflet degeneration is nowadays believed to be a result of excessive leaflet stress, resulting in activation of valve interstitial cells. These cells have recently been proposed to play the leading role in the development of various types of heart valve disease [10]. While valve interstitial cells are of crucial importance to maintain physiological valve structure and function, valve injury or increased mechanical stress has been shown to promote differentiation of quiescent valve interstitial cells into activated ones [11]. In the activated form, the cells will increase matrix synthesis and up-regulate expression of matrix-remodeling enzymes. Under conditions of excessive mechanical stress, that in Barlow's disease occurs due to excessive annular motion, leaflets can be expected to grow progressively. This process is not seen only in patients with Barlow's disease, but has also been demonstrated in patients with ischemic as well as atrial functional mitral regurgitation where compensatory leaflet lengthening has been described [12, 13]. This adaptive leaflet growth could partially compensate for increasing mitral annular area and explain why in patients with Barlow's disease even prominent annular dilation will not always be accompanied by severe mitral regurgitation [9]. Interestingly, myxomatous degeneration is not seen in other types of mitral valve disease where, as mentioned, adaptive leaflet growth occurs as well. As mechanical stress is the promotor valve interstitial cells activation in all cases, one has to speculate that the response to stress is not uniform but possibly related to patient- and disease-specific characteristics.

The observed abnormalities carry important consequences for the strategy of surgical mitral valve repair. In particular, the contribution of annular dynamics on mitral valve leaflet motion needs to be appreciated when valve repair strategy is formed. Recently, Klautz and colleagues proposed the concept of functional leaflet prolapse that adds to the understanding of valve abnormalities in Barlow's disease [14]. The absence of normal structural support of the mitral valve complex results in a late-systolic out- and downward movement ("*curling*") of the mitral valve annulus (**Figure 1**). Consequently, abnormal late-systolic displacement of the papillary muscle tips towards the left atrium will result in abnormal leaflet motion of the mitral valve leaflets. In such cases, it is important to make a differentiation between actual leaflet prolapse and functional leaflet prolapse. In functional leaflet prolapse the leaflet arises above the plane of the annulus as assessed by echocardiography. However, during surgical valve analysis, the leaflet does not rise above the plane of the reference point.

As discussed, Carpentier proposed that excessive leaflet motion in degenerative mitral valve disease always occurs as a consequence of subvalvular apparatus abnormalities [3]. Any abnormal leaflet motion should be addressed at the time of valve repair to resolve excessive leaflet stress and secure a durable repair. Understanding the contribution of abnormal annular dynamics should allow for a simplified valve repair to be performed without failing to achieve the basic goals of valve repair. Application of these concepts to valve repair surgery is to date, however, unstudied. The following chapters will therefore focus on the application of these pathological principles of Barlow's disease to valve repair strategy and explore the results hereof.

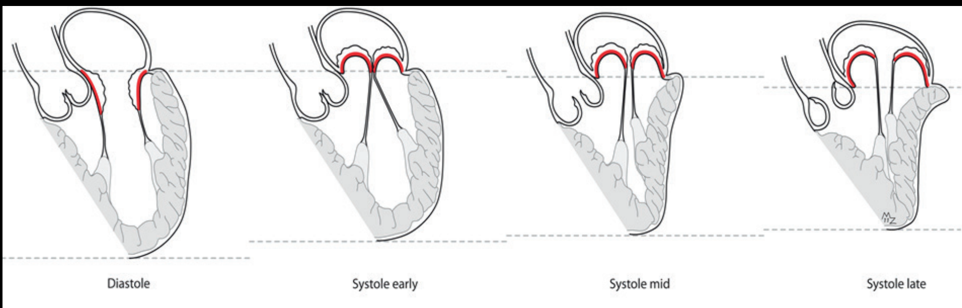


FIGURE 1. Pathological late-systolic movement of mitral valve annulus in Barlow's disease directly results in functional leaflet prolapse.

REFERENCES

[1] Barlow JB, Pocock WA. The significance of late systolic murmurs and mid-late systolic clicks. Md State Med J 1963;12:76-7.

[2] Barlow JB, Bosman CK, Pocock WA, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clicks. An analysis of 90 patients. Br Heart J 1968;30:203-18.

[3] Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg 1983;86:323-37.

[4] Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J 2010;31:1958-66.

[5] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135:274-82.

[6] Hutchins GM, Moore GW, Skoog DK. The association of floppy mitral valve with disjunction of the mitral annulus fibrosus. N Engl J Med 1986;314:535-40.

[7] Angelini A, Ho SY, Anderson RH, Davies MJ, Becker AE. A histological study of the atrioventricular junction in hearts with normal and prolapsed leaflets of the mitral valve. Br Heart J 1988;59:712-6.

[8] Apor A, Nagy AI, Kovacs A, Manouras A, Andrassy P, Merkely B. Three-dimensional dynamic morphology of the mitral valve in different forms of mitral valve prolapse - potential implications for annuloplasty ring selection. Cardiovasc Ultrasound 2016;14:32.

[9] Clavel MA, Mantovani F, Malouf J, Michelena HI, Vatury O, Jain MS et al. Dynamic phenotypes of degenerative myxomatous mitral valve disease: quantitative 3-dimensional echocardiographic study. Circ Cardiovasc Imaging 2015;8.

[10] Liu AC, Joag VR, Gotlieb AI. The emerging role of valve interstitial cell phenotypes in regulating heart valve pathobiology. Am J Pathol 2007;171:1407-18.

[11] Tamura K, Jones M, Yamada I, Ferrans VJ. Wound healing in the mitral valve. J Heart Valve Dis 2000;9:53-63.

[12] Dal-Bianco JP, Aikawa E, Bischoff J, Guerrero JL, Handschumacher MD, Sullivan S et al. Active adaptation of the tethered mitral valve: insights into a compensatory mechanism for functional mitral regurgitation. Circulation 2009;120:334-42.

[13] Kim DH, Heo R, Handschumacher MD, Lee S, Choi YS, Kim KR et al. Mitral Valve Adaptation to Isolated Annular Dilation: Insights Into the Mechanism of Atrial Functional Mitral Regurgitation. JACC Cardiovasc Imaging 2017.

[14] Klautz RJ, Tomšič A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in Barlow's disease: the concept of functional prolapse. Multimed Man Cardiothorac Surg 2016;2017.

04

Mitral valve repair in Barlow's disease with bileaflet prolapse:

The effect of annular stabilization on functional mitral valve leaflet prolapse

Anton Tomšič; Yasmine L. Hiemstra; Daniella D. Bissessar; Thomas J. van Brakel; Michel I.M. Versteegh ; Nina Ajmone Marsan; Robert J.M. Klautz ; Meindert Palmen

Interact Cardiovasc Thorac Surg. 2018;26(4):559-565

ABSTRACT

Background. Barlow's disease is the most severe form of degenerative mitral valve disease, commonly characterized by bileaflet prolapse. Abnormal mitral annular dynamics is typically present and results in functional mitral valve leaflet prolapse that may be addressed with annular stabilization alone.

Methods. Between January 2001 and December 2015, 128 patients with Barlow's disease and bileaflet prolapse underwent valve repair. This included anterior mitral valve leaflet (AMVL) repair in 70 patients while 58 patients were identified as having functional prolapse and underwent no specific AMVL repair. During the course of the study, the proportion of patients undergoing specific AMVL repair decreased (77% in the first and 33% in the second 64 patients). Semi-rigid ring annuloplasty was performed in all cases. The median clinical and echocardiographic follow-up duration was 6.5 years (IQR 2.9-10.5; 93.9% complete) and 4.7 years (IQR 2.2-10.2; 94.4% complete), respectively.

Results. Early mortality was 1.6%. Postoperative echocardiogram demonstrated no residual mitral regurgitation in all but 1 patient (AMVL repair group). There was no significant difference in the overall survival rate at 6 years after operation between both groups. At 6 years, the freedom from recurrent ≥Grade 2+ MR rate was 90.7% (95% CI 82.9%-98.5%) and 89.1% (95% CI 75.8%-100%) for patients with and patients with no AMVL repair, respectively (P=0.43). Three patients required late mitral valve reintervention, all from the AMVL repair group.

Conclusions. Annular stabilization can effectively resolve functional prolapse of the AMVL. Careful discrimination between functional and true AMVL prolapse allows for a technically less challenging operation that provides excellent repair durability.

INTRODUCTION

Degenerative mitral valve disease is the second most common valve disease in Western countries [1]. Surgical repair is the established treatment of choice as it provides optimal results in terms of survival and freedom from valve-related events [2, 3]. However, in the setting of Barlow's disease, extensive valve degeneration with bileaflet prolapse is typically present. Additionally, leaflet, annular or subvalvular apparatus calcifications are frequently seen. These characteristics make valve repair particularly challenging [4, 5].

The aetiology of Barlow's disease remains poorly understood. Recently, quantitative 3D echocardiography studies have enabled a better insight into the characteristics of degenerative mitral valve disease [6, 7]. These studies have shown that Barlow's disease is characterized by diminished annular saddle shape and abnormal annular dynamics with pathological overstretching of the mitral valve annulus towards end-systole. Consequently, late-systolic functional mitral valve leaflet prolapse will occur [8]. However, functional prolapse is often accompanied by true leaflet prolapse due to ruptured or elongated chordae tendineae, making intraoperative surgical analysis critical. Functional prolapse can be identified by an echocardiographic prolapse of the anterior mitral valve leaflet (AMVL) that cannot be confirmed during surgical valve analysis. Stabilization of the mitral valve annulus can resolve functional leaflet prolapse by preventing abnormal annular dynamics.

The aim of this study was to explore the frequency of the need for specific AMVL repair in a subgroup of patients with bileaflet prolapse secondary to Barlow's disease. Moreover, we compare the durability of mitral valve repair in patients who did to patients who did not undergo AMVL repair.

METHODS

Study population

Between January 2001 and December 2015, 661 consecutive adult (≥18 years of age) patients underwent surgical intervention for mitral regurgitation (MR) due to degenerative mitral valve disease at our institution. Patients with accompanying active infective endocarditis were excluded. Barlow's disease was defined according to preoperative, echocardiographic and intraoperative characteristics that included excessive myxomatous bileaflet degeneration, annular dilatation and posterior displacement of the mitral valve annulus [9, 10]- and was present in 181 (27%) patients. On preoperative echocardiography, bileaflet prolapse was defined as the free edge of both leaflets over-riding the plane of the mitral valve orifice at the end of systole and was present in 132 (73%) patients (**Figure 1**). Mitral valve repair was performed in 128 (97%) of these patients who present the current study cohort.

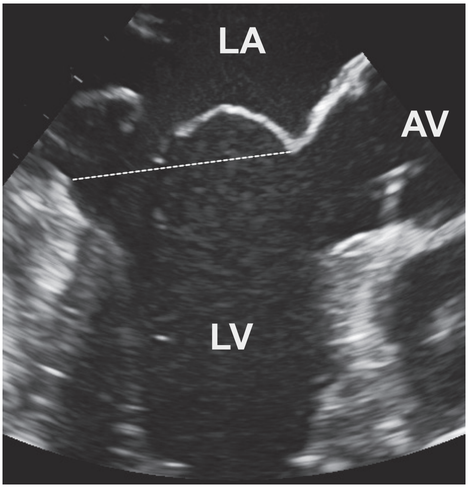


FIGURE 1. Preoperative echocardiography in a patient with Barlow's disease- the free edge of both leaflets overrides the plane of the displaced mitral valve annulus (dotted line) during systole. In this patient, anterior mitral valve leaflet prolapse was treated by annular stabilization alone.

Study methods

Our Institutional Medical Ethic Committee approved this study. Pre-, intra- and postoperative data were collected from our computerized patient registry. Follow-up clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through questionnaires to patients. The median survival follow-up time was 6.6 years [interquartile range (IQR) 3-10.5; 98.4% complete, 2 patients were lost to follow-up due to emigration]. The median follow-up time for valve-related events was 6.5 years (IQR 2.9-10.5; 93.9% complete). The median echocardiographic follow-up time was 4.7 years (IQR 2.2-10.2; 94.4% complete). Patient follow-up was closed in December 2016.

Surgical procedure

During the study period, a repair-all strategy was applied, and eventual mitral valve replacement was only performed in case of an unsatisfactory intraoperative result of valve repair. Median sternotomy (n=117), partial sternotomy (n=9), or lateral mini-thoracotomy was performed (n=6). Standard cannulation techniques with central or peripheral cannulation (according to the surgical approach utilized) and intermittent blood cardioplegia for cardioprotection were used in all cases.

Thorough echocardiographic and surgical valve analysis was performed to discriminate between functional and true AMVL prolapse. On preoperative echocardiography, late-systolic overstretching of the mitral valve annulus in the anterior-posterior diameter with progressive displacement of both mitral valve leaflets towards the left atrium will be seen in these patients. Early in our experience, unaware of the phenomenon of functional prolapse, all leaflets that were over-riding the plane of the mitral valve orifice during valve closure on preoperative echocardiography were considered to be prolapsing and treated accordingly. Growing understanding on the contribution of annular abnormalities to valve morphology and functional prolapse has led us to focus more attention on the length and integrity of the chordae providing support to the AMVL. When primary chordae tendineae are ruptured, the indication for AMVL repair will be clear- this is, however, not often the case. When prolapse of all segments of the AMVL is seen on preoperative echocardiography/surgical analysis, this suggests that the prolapse will likely be functional in nature. In some patients, the lack of a reference point during surgical valve analysis makes the discrimination between functional and true AMVL prolapse challenging. In these patients, a "posterior mitral valve leaflet (PMVL) repair first" approach was applied. Subsequent water test allowed us to determine whether any true AMVL prolapse was present. A single 2-0 TiCron (Medtronic, Inc, Minneapolis, MN, USA) suture was placed in the posterior part of the mitral valve annulus (at mid-point) and was kept under traction when the water-test was performed. This simulated the presence of an annuloplasty ring and prevented deformation (migration of the posterior part of the mitral annulus towards the apex of the left ventricle) of the floppy mitral valve annulus. In case of a satisfactory water test, no additional repair on the AMVL was performed, despite the echocardiographic findings.

An overview of the surgical techniques utilized is shown in **Table I**. Commissural prolapse was treated predominately by papillary muscle head repositioning. For PMVL prolapse, quadrangular resection with annular plication (earlier in our series) or leaflet sliding techniques (later in our series) was used when excessive tissue in height and width was present. When the amount of excessive tissue in width was less pronounced, a triangular resection or non-resection techniques with shortening polytetrafluoro-ethylene neochords were used. True AMVL prolapse was treated predominantly with polytetrafluoroethylene neochords. Full, semi-rigid ring annuloplasty was performed in all cases. Ring sizing was based on the surface area of the AMVL and did not differ between both groups. Prior to 2010, Physio ring (Carpentier Edwards Lifesciences, Irvine, CA, USA) was our primary choice. Since 2010, Physio II ring (Carpentier Edwards Lifesciences, Irvine, CA, USA) has been our standard choice in the setting of degenerative mitral valve disease.

All patients underwent pre-discharge echocardiography to confirm the success of valve repair. Oral anticoagulation with a target international normalized ratio of 2.0-3.0 was continued up to 3 months after surgery. In the presence of other indications (e.g. atrial fibrillation), oral anticoagulation was continued indefinitely.

Study endpoints

Postoperative mortality and morbidity end points were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery, and European Association for Cardio-Thoracic Surgery Guidelines [11]. Early mortality was defined as mortality within 30-days after the operation or during the index hospitalization.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile ranges (IQR) when not normally distributed. Categorical data are presented as counts and percentages. The χ^2 and Fisher's exact test were used to analyze categorical variables. Independent sample t-test and Mann-Whitney U-test (skewed data) were used to analyze continuous variables. Survival and events rates were summarized using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional-hazards regression analysis was used to analyze the effect of no AMVL repair on recurrent MR. With no AMVL repair forced into the model, the remaining variables were selected using a backward selection method. Variable retention in the model was set at a P-value of 0.10. The following variables were included: sex, left ventricular ejection fraction ≤60%, atrial fibrillation, annular plication, annular calcification, height of leaflet coaptation, commissural prolapse and type of ring annuloplasty. A double-sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using the IBM Statistics for Windows, version 23.0 (SPSS, Inc., IBM Corporation, Armonk, NY, USA).

TABLE I. Intraoperative details of mitral valve repair.

		AMVL repair (n=70)	No AMVL repair (n=58)	P-value
Annulus	Ring annuloplasty	100 (70)	100 (58)	1.0
	Ring annuloplasty size	36 (IQR 34-40)	36 (IQR 34-38)	0.49
	Annular plication	51 (36)	12 (7)	<0.001
	Decalcification	13 (9)	16 (9)	0.67
Annuloplasty type	Physio ring*	75 (53)	34 (20)	<0.001
	Physio II ring*	21 (15)	62 (36)	
	Simulus semi-rigid**	1 (1)	2 (1)	
	CG future**	0 (0)	2 (1)	
	Duran ring**	1 (1)	0 (0)	
PMVL	Resection	90 (63)	81 (47)	0.15
	Triangular	4 (3)	17 (10)	
	Quadrangular	86 (60)	64 (37)	
	Sliding plasty	71 (50)	78 (45)	0.43
	Neochords	27 (19)	35 (20)	0.37
	Chordal transfer	1 (1)	0 (0)	1.00
	Indentation closure	16 (11)	26 (15)	0.16
AMVL	Resection	3 (2)	0 (0)	
	Neochords	94 (66)	0 (0)	
	Chordal shortening	1 (1)	0 (0)	
	Chordal transfer	1 (1)	0 (0)	
Commissures	Commissural closure	10 (7)	5 (3)	0.31
	Neochords	1 (1)	0 (0)	1.00
	Papillary muscle head repositioning	17 (10)	54 (38)	<0.001
Aortic cross-clamp time (min)		182 (IQR 150-221)	147 (IQR 122-176)	<0.001
Cardiopulmonary bypass time (min)		227±56	199±54	0.013
Leaflet coaptation height (mm)		9.5 (IQR 8.0-10.0)	8.0 (IQR 7.0-9.0)	<0.001

*Data are presented as % (n) or medians with IQR. Abbreviations: AMVL: anterior mitral valve leaflet; PMVL: posterior mitral valve leaflet; PTFE: polytetrafluoroethylene. * Edwards Lifesciences, Irvine, CA, USA; ** Medtronic Inc., Minneapolis, MN, USA.*

RESULTS

Baseline characteristics and intraoperative details

Baseline characteristics of the whole patient cohort are shown in **Table II**. Anterior mitral valve leaflet repair was performed in 70 (55%) patients while no AMVL repair was performed in 58 (45%) patients. The frequency of AMVL repair decreased progressively over time (**Figure 2**); during the first half of the study period AMVL repair was performed in 49/64 (77%) patients and during the second half in 21/64 (33%) patients.

There were a statistically significant higher number of female patients and higher preoperative creatinine values in the AMVL repair group. No other differences between both groups were seen. Anterior mitral valve leaflet repair was performed by implantation of polytetrafluoroethylene neochords in the majority of patients. As expected, longer aortic cross clamp and cardiopulmonary bypass times were seen in the AMVL repair group.

Early outcomes

Early mortality was 1.6% (2 patients). The causes of death were multiorgan dysfunction syndrome following severe postoperative distributive shock and perioperative myocardial infarction resulting in acute biventricular heart failure. In general, more postoperative complications were observed in the AMVL repair group (**Table III**). This partially reflects the improvements in perioperative management implemented during the study period that include the introduction of blood saving protocols and improvements of cardio-pulmonary bypass techniques. Consequently, lower surgical re-exploration (16% vs. 2%, P=0.007) and postoperative kidney failure rates (4% vs. 0%, P=0.25) were seen in the no AMVL repair group.

There were no significant differences in the early echocardiographic results between both groups (**Figure 3**). Postoperative echocardiography demonstrated none or trivial MR in 107 (83%) patients, mild MR in 20 (16%) patients and moderate-to-severe residual MR in 1 (1%) patient. The latter patient, who underwent AMVL repair during the initial operation, underwent early reoperation on postoperative day 8. Valve replacement was performed due to concerns on the long-term durability of a re-repair in this patient. Sufficient height of leaflet coaptation was observed in both groups, even though the height of coaptation was significantly lower in the no AMVL repair group. No hemodynamically significant systolic anterior motion was observed in any of the patients.

TABLE II. Baseline characteristics.

	Overall (n=128)	AMVL repair (n=70)	No AMVL repair (n=58)	P-value
Age (years)	58.4±14.5	58.3±12.9	58.5±16.2	0.95
Female sex	43 (55)	57 (33)	31 (22)	0.004
Body surface area	1.89±0.23	1.94±0.20	1.84±0.25	0.009
Chronic lung disease	6 (7)	6 (4)	5 (3)	0.89
Atrial fibrillation	38 (48)	44 (31)	29 (17)	0.081
Creatinine (mmol/l)	81 (IQR 73-90)	84 (IQR 76-94)	77 (IQR 67-85)	0.002
NYHA class				0.76
I	37 (47)	34 (24)	40 (23)	
II	53 (68)	54 (38)	52 (30)	
III-IV	10 (13)	12 (8)	8 (5)	
Critical preoperative state	1 (1)	1 (1)	0 (0)	1.0
Left ventricular function				0.51
>60%	72 (92)	74 (52)	69 (40)	
30-60%	28 (36)	26 (18)	31 (18)	
Left ventricular diameter				
End-diastolic	54.4±6.3	54.9±6.8	53.8±5.6	0.35
End-systolic	32.8±6.0	32.3±6.4	32.1±5.5	0.30
Left atrial diameter	44.1±8.6	45.1±9.2	42.9±7.8	0.12
Annular calcification	17 (22)	16 (11)	19 (11)	0.63
Concomitant procedures				
Tricuspid valve repair	48 (61)	43 (30)	53 (31)	0.23
Radiofrequency ablation	31 (40)	36 (25)	26 (15)	0.23
Coronary artery bypass grafting	9 (12)	10 (7)	9 (5)	0.79
Aortic valve replacement or repair	2 (3)	1 (1)	3 (2)	0.45

Data are presented as % (n) and means ± SD or medians with IQR. Abbreviations: AMVL: anterior mitral valve leaflet; NYHA: New York Heart Association.

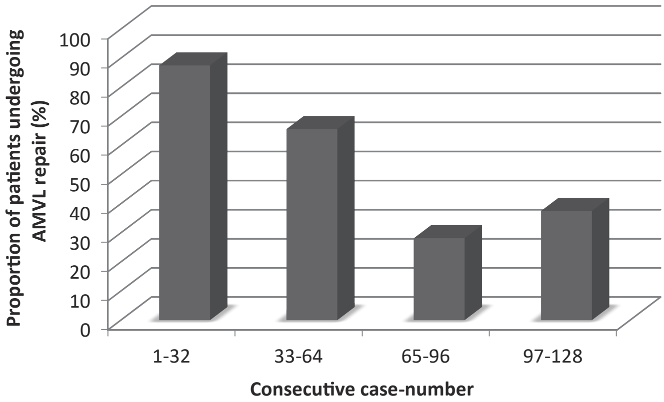


FIGURE 2. The proportion of consecutive patients undergoing AMVL repair during 4 consecutive phases of the study.

TABLE III. Postoperative complications.

	AMVL repair (n=70)	No AMVL repair (n=58)	P-value
Early mortality	3 (2)	0 (0)	0.50
Prolonged intubation	13 (9)	5 (3)	0.14
Permanent stroke	1 (1)	2 (1)	0.89
Renal failure	4 (3)	0 (0)	0.25
Surgical re-exploration	16 (11)	2 (1)	0.007
Early valve reintervention	1 (1)	0 (0)	1.0

Data are presented as % (n). Abbreviations: AMVL: anterior mitral valve leaflet.

Late mortality and morbidity

There were 16 late deaths. The cause of death was cardiac related in 9 patients (congestive heart failure in 1, acute type A dissection in 1, sudden unexplained in 4, ventricular tachycardia in 1 and intracranial hemorrhage in 2) and non-cardiac in 7 patients. At 6-years after surgery, the overall survival rate was 93.3% (95% CI 87.4%-99.2%) and 86.6% (95% CI 76.0%-97.2%) for patients undergoing AMVL repair and for patients in whom no AMVL repair was performed, respectively (P=0.48; **Figure 4**).

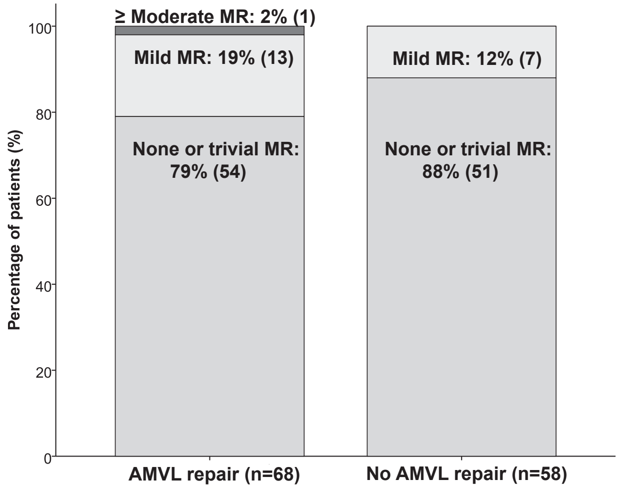


FIGURE 3. Early echocardiographic results.

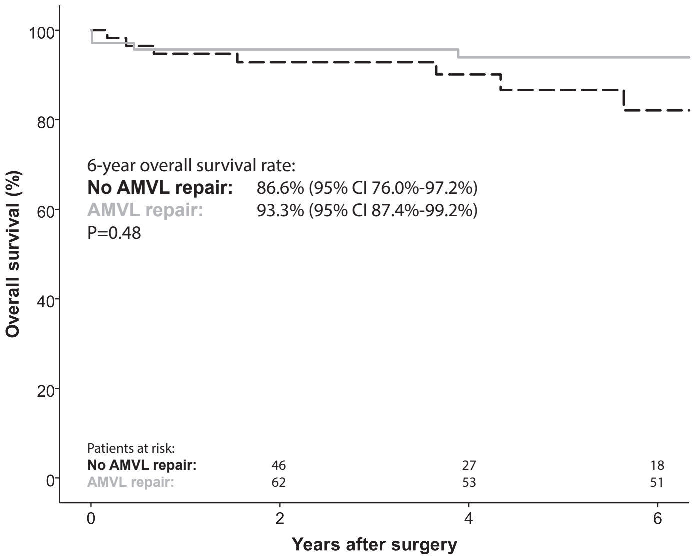


FIGURE 4. Overall survival.

No episodes of infective endocarditis occurred. There were 6 thromboembolic events (4 transient ischemic attacks and 2 cerebrovascular accidents) and 3 severe bleeding episodes (2 resulting in death). At most recent follow-up, 71% patients alive at follow up were in NYHA functional class I, 23% in NYHA functional class II and 6% in NYHA functional class III.

Echocardiographic follow-up

Recurrent (≥Grade 2+) MR was seen in 14 patients. The overall 1- and 6-year freedom from recurrent MR rates were 98.2% (95% CI 95.7%-100%) and 90.6% (95% CI 84.1%-97.1%), respectively. At 6-years after surgery, the freedom from recurrent MR rates were 90.7% (95% CI 82.9%-98.5%) and 89.1% (95% CI 75.8%-100%) for patients undergoing AMVL repair and for patients in whom no AMVL repair was performed, respectively (P=0.43; **Figure 5**). Cox regression analysis failed to demonstrate any significant effect of no AMVL repair on recurrent MR (**Table IV**). At most recent follow up, 88% of patients showed ≤mild MR, 10% moderate MR and 2% severe MR.

TABLE IV. Cox proportional-hazards regression analysis on predictors of recurrent MR (≥Grade 2+).

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P-value	Hazard ratio	95% confidence interval	P-value
No AMVL repair	1.669	0.513-5.424	0.40	1.367	0.349-5.352	0.65
Sex (female)	0.587	0.196-1.757	0.34			
Left ventricular ejection fraction ≤60%	0.484	0.107-2.187	0.35			
Atrial fibrillation	1.444	0.484-4.309	0.51			
Annular plication	1.205	0.381-3.803	0.75			
Height of leaflet coaptation (mm)	0.913	0.603-1.383	0.67			
Annular calcification	3.306	1.006-10.870	0.049	4.119	1.165-14.566	0.028
Commissural prolapse	0.475	0.144-1.568	0.22			
Ring annuloplasty type*						
Physio II ring	3.289	0.602-17-954	0.17	2.611	0.466-14.641	0.28
Other	322.005	22.061-4699.909	<0.001	438.878	28.965-6649.834	<0.001

** Physio ring listed as reference category. Abbreviations: AMVL: anterior mitral valve leaflet.*

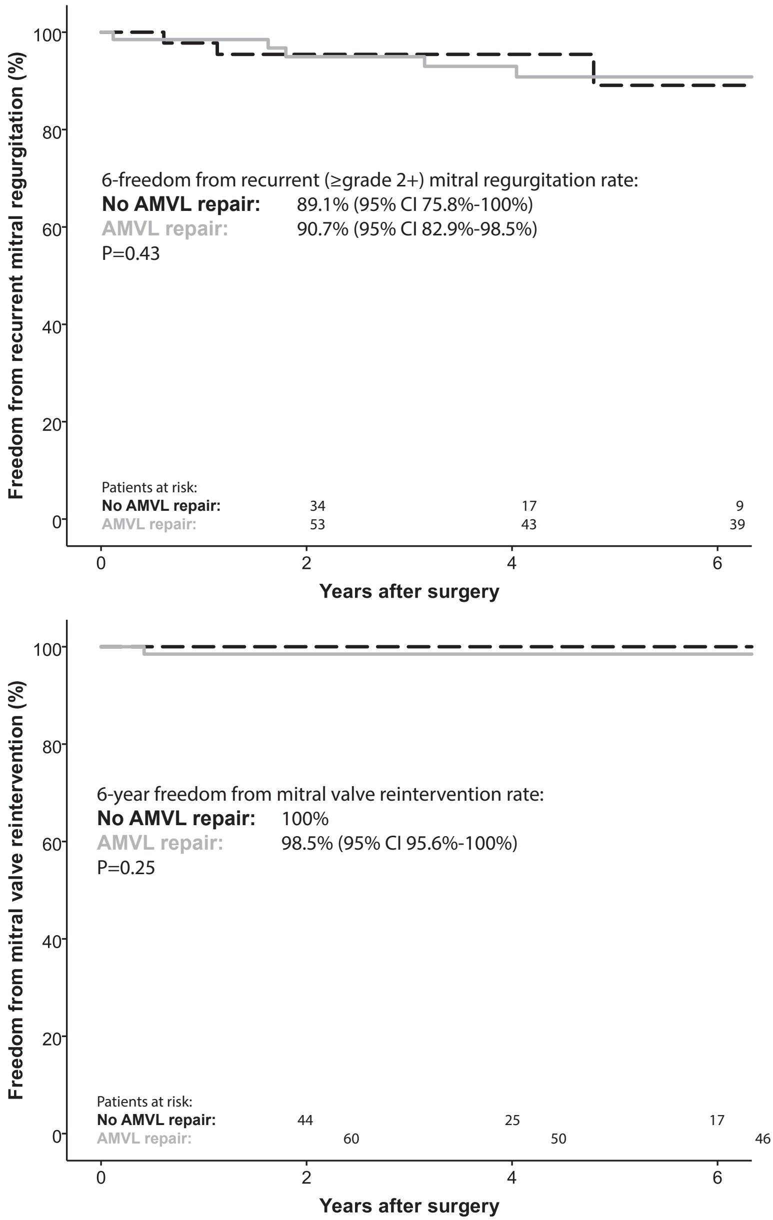


FIGURE 5. **Above:** freedom from recurrent moderate (≥2+) mitral regurgitation. **Below:** freedom from mitral valve reintervention.

Late mitral valve reintervention

Three patients underwent late mitral valve reintervention, all due to recurrent MR. All patients underwent AMVL repair during the initial operation. The mechanism of recurrent MR was suture dehiscence at the PMVL (after previous quadrangular resection) in 1; *de novo* AMVL prolapse and PMVL restriction in 1 and ventricular dilatation secondary to severe aortic valve insufficiency in 1. Upon reoperation, 2 mitral valve re-repairs and 1 valve replacement were performed. All patients survived the reoperation. The 1-and 6-year freedom from operated valve reintervention rate was 99.2% (95% CI 97.6%-100%) for both. There was no significant difference in the freedom from late mitral valve intervention rates between both groups (P=0.25; **Figure 5**).

DISCUSSION

Our study demonstrates that mitral valve annuloplasty successfully resolves functional prolapse of the AMVL in patients with Barlow's disease and bileaflet prolapse. We also found that functional AMVL prolapse -without true leaflet prolapse- affects the majority of these patients. Annuloplasty will provide annular stabilization and prevent abnormal annular dynamics that otherwise significantly contribute to valve dysfunction. Furthermore, addressing the functional prolapse of the AMVL with annular stabilization alone provides excellent valve repair durability.

The mitral valve annulus is a dynamic structure that plays an important role in the normal functioning of the mitral valve. Complementary to annular dilatation, abnormal annular dynamics is additionally present in Barlow's disease and is characterized by poor early systolic annular contraction and saddle shape accentuation [6, 7, 10, 12]. In late-systole an abnormal late-systolic annular enlargement with enlargement of the anterior-posterior and intercommissural diameters further occurs [6, 7]. Annular changes are readily present even in the absence of severe MR [6]. This pathological annular movement directly results in an absence of physiologic systolic mitral valve area reduction, impairs mitral valve leaflet apposition and promotes valve regurgitation. Posterior mitral annulus displacement is a prominent structural abnormality in patients with Barlow's disease [10, 13] that provides a possible explanation for the described abnormalities. Moreover, paradoxical systolic displacement of the papillary muscles towards the left atrium has been described [14-16]. This further contributes to the occurrence of mitral valve leaflet billowing and/or prolapse. Altogether, these observations demonstrate that the mitral valve annulus is the primary substrate of functional leaflet prolapse in Barlow's disease.

Annuloplasty presents an essential component of surgical mitral valve repair [2, 17]. In Barlow's disease, the aim of prosthetic annuloplasty is not only annular remodeling but also prevention of abnormal annular dynamics and restoring the physiological systolic annular saddle shape. The effect of surgical annuloplasty on mitral valve morphology was characterized by De Paulis et al. who described their experience in 40 selected patients with Barlow disease's and a central regurgitant jet in whom valve repair was established by semi-rigid band annuloplasty alone [18]. Following repair, intraoperative echocardiography revealed marked changes in the morphology of the mitral valve as a reduction of the mitral valve annulus with re-establishment of leaflet coaptation in the left ventricle and increased leaflet coaptation height were observed. Moreover, paradoxical systolic displacement of the papillary muscle was resolved as a marked increase of the distance between the papillary muscle tip and the mitral annular plane was seen. Similarly, Ben Zekry et al. were able to successfully perform mitral valve repair with ring annuloplasty alone in 24 patients with Barlow's disease [19]. Following annular stabilization, comparable changes of the mitral valve morphology were observed.

Because of extensive annular abnormalities and functional consequences hereof, bileaflet prolapse is a common observation in patients with Barlow's disease and has previously been reported in up to 75% of these patients [5, 20-22]. The frequency of bileaflet prolapse in our study cohort is comparable to these reports. In the context of bileaflet prolapse due to Barlow's disease, AMVL repair is performed almost uniformly in centers experienced in reconstructive mitral valve surgery [5, 20, 21]. This reflects the approach to AMVL prolapse early in our experience.

Over time, our understanding on the contribution of abnormal mitral annular dynamics to mitral valve dysfunction in Barlow's disease has grown. The effect of annular stabilization on functional leaflet prolapse has led us to adopt a conservative approach to AMVL prolapse in this setting. This is reflected by a decreasing percentage of patients undergoing specific AMVL repair during the study period. The selection of patients for inclusion in this study was made on careful assessment of the preoperative echocardiogram, and all patients demonstrated bileaflet prolapse. The diagnosis of Barlow's disease was further confirmed intraoperatively in all cases. The study cohort therefore presents a homogenous population and the observed decrease presents a direct effect of the newly implemented repair approach.

Valve repair in Barlow's disease remains technically challenging. This is also reflected by our experience as various techniques were utilized to secure valve competency. In Barlow's disease, excessive leaflet tissue and thickened chordae tendineae are typically seen [9]. Valve degeneration will affect all valve segments, often making the valve appear prolapsing on all levels. In such cases, the differentiation between surgical and functional prolapse needs to be made with respect to the morphological changes that follow annular stabilization [8, 18]. While this will resolve the functional, it will not resolve true leaflet prolapse, normally occurring due to chordal elongation and/or rupture. Although ruptured chordae can be easily identified intraoperatively, the identification of elongated chordae can be difficult, especially when the reference point in the PMVL is difficult to establish. In these cases, PMVL repair and annular stabilization (with annuloplasty sutures) are first performed and only in that phase, the AMVL can be properly assessed. As mentioned earlier, a water test is helpful to understand the motion of the AMVL. This test has to be properly performed with adequate filling of the ventricle.

In our more recent experience, AMVL repair was still needed in about one-third of patients. When possible, addressing AMVL prolapse with annuloplasty alone will result in a technically less challenging procedure and helps reduce the length of cardiopulmonary bypass. Moreover, it prevents the inadvertent implantation of neochords that are too short and might cause leaflet restriction. During the follow-up period, we failed to observe any difference in the incidence of recurrent MR between both groups. Moreover, no patient from the no AMVL repair group needed mitral valve reintervention during the follow-up period. These observations demonstrate that annular stabilization provides an effective resolution of the functional prolapse at mid-term and that future chordal elongation will not occur if excessive leaflet strain will be resolved by a sound repair. Studies with longer follow-up duration are needed to confirm our findings. Interestingly, papillary muscle head repositioning for commissural prolapse was performed more commonly in the no AMVL repair group. In these cases, the papillary muscle head providing support to the commissural region was identified and repositioned, thereby preventing the free edge of this segment to prolapse in systole. This has some effect on the motion of the para-commissural segments of the AMVL. However, this could not resolve the prolapse of the whole AMVL that is typically observed in cases of functional mitral valve leaflet prolapse.

We regularly perform excessive PMVL tissue resection to reduce excessive leaflet tissue height and width. In our opinion, sliding of the PMVL can effectively simultaneously addresses both issues. When only limited excessive tissue is present, though rarely seen in Barlow's disease, non-resection techniques present an alternative. A central regurgitant jet seen on preoperative echocardiography might suggest that MR could occur solely as a consequence of abnormal annular dynamics with functional prolapse of both mitral valve leaflets. This can potentially be addressed by annular stabilization only [18, 19]. A proportion of patients undergoing PMVL repair in our cohort might therefore have undergone valve repair with ring annuloplasty alone. On the basis of the studies by De Paulis et al. and Ben Zekry et al., this does however result in a mentionable risk of systolic anterior motion [18, 19]. Large annuloplasty rings combined with leaflet height reduction are effective at preventing this complication [23]. The performance of PMVL height reduction seems therefore important and is, in our opinion, essential as has previously been advocated to prevent systolic anterior motion [24].

LIMITATIONS

This is a single-centre study in a selected group of patients with Barlow's disease. Our surgical approach has evolved during the study period. This resulted in some differences in the surgical techniques performed between both groups. However, both groups demonstrated satisfactory long-term repair durability that compare favorably with the results previously described in the literature. The difference in the surgical techniques preformed does, therefore, not obscure our results. The duration of clinical and echocardiographic follow-up was limited to mid-term results. The long-term durability of mitral valve repair in this setting will need to be confirmed in the future.

CONCLUSIONS

Mitral valve repair in Barlow's disease with bileaflet prolapse is technically challenging. The strategy of surgical mitral valve repair should take into account the contribution of the mitral valve annulus to the expressed valve dysfunction and the changes in mitral valve morphology that follow annular stabilization. Functional prolapse of the AMVL can effectively be treated by annular stabilization alone. Discrimination between functional and true prolapse allows for a simplified valve repair that provides excellent long-term repair durability.

REFERENCES

[1] Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW 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] David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation 2013;127:1485-92.

[3] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA 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.

[4] Anyanwu AC, Itagaki S, Chikwe J, El-Eshmawi A, Adams DH. A complexity scoring system for degenerative mitral valve repair. J Thorac Cardiovasc Surg 2016;151:1661-70.

[5] Jouan J, Berrebi A, Chauvaud S, Menasche P, Carpentier A, Fabiani JN. Mitral valve reconstruction in Barlow disease: long-term echographic results and implications for surgical management. J Thorac Cardiovasc Surg 2012;143:S17-20.

[6] Clavel MA, Mantovani F, Malouf J, Michelena HI, Vatury O, Jain MS et al. Dynamic phenotypes of degenerative myxomatous mitral valve disease: quantitative 3-dimensional echocardiographic study. Circ Cardiovasc Imaging 2015;8.

[7] Apor A, Nagy AI, Kovacs A, Manouras A, Andrassy P, Merkely B. Three-dimensional dynamic morphology of the mitral valve in different forms of mitral valve prolapse - potential implications for annuloplasty ring selection. Cardiovasc Ultrasound 2016;14:32.

[8] Klautz R, Tomsic A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in Barlow's disease: the concept of functional prolapse. Multimed Man Cardiothorac Surg 2016;2017.

[9] Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J 2010;31:1958-66.

[10] Eriksson MJ, Bitkover CY, Omran AS, David TE, Ivanov J, Ali MJ et al. Mitral annular disjunction in advanced myxomatous mitral valve disease: echocardiographic detection and surgical correction. J Am Soc Echocardiogr 2005;18:1014-22.

[11] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732-8.

[12] Grewal J, Suri R, Mankad S, Tanaka A, Mahoney DW, Schaff HV et al. Mitral annular dynamics in myxomatous valve disease: new insights with real-time 3-dimensional echocardiography. Circulation 2010;121:1423-31.

[13] Hutchins GM, Moore GW, Skoog DK. The association of floppy mitral valve with disjunction of the mitral annulus fibrosus. N Engl J Med 1986;314:535-40.

[14] Sanfilippo AJ, Harrigan P, Popovic AD, Weyman AE, Levine RA. Papillary muscle traction in mitral valve prolapse: quantitation by two-dimensional echocardiography. J Am Coll Cardiol 1992;19:564-71.

[15] Lawrie GM. Barlow disease: Simple and complex. J Thorac Cardiovasc Surg 2015;150:1078-81.

[16] Lawrie GM, Earle EA, Earle NR. Nonresectional repair of the barlow mitral valve: importance of dynamic annular evaluation. Ann Thorac Surg 2009;88:1191-6.

[17] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135:274-82.

[18] De Paulis R, Maselli D, Salica A, Leonetti S, Guerrieri Wolf L, Weltert L et al. Mitral repair with the sole use of a semi-rigid band in a sub-population of patients with Barlow's disease: a 4-year follow-up with stress echocardiography. Interact Cardiovasc Thorac Surg 2015;21:316-21.

[19] Ben Zekry S, Spiegelstein D, Sternik L, Lev I, Kogan A, Kuperstein R et al. Simple repair approach for mitral regurgitation in Barlow disease. J Thorac Cardiovasc Surg 2015;150:1071-7 e1.

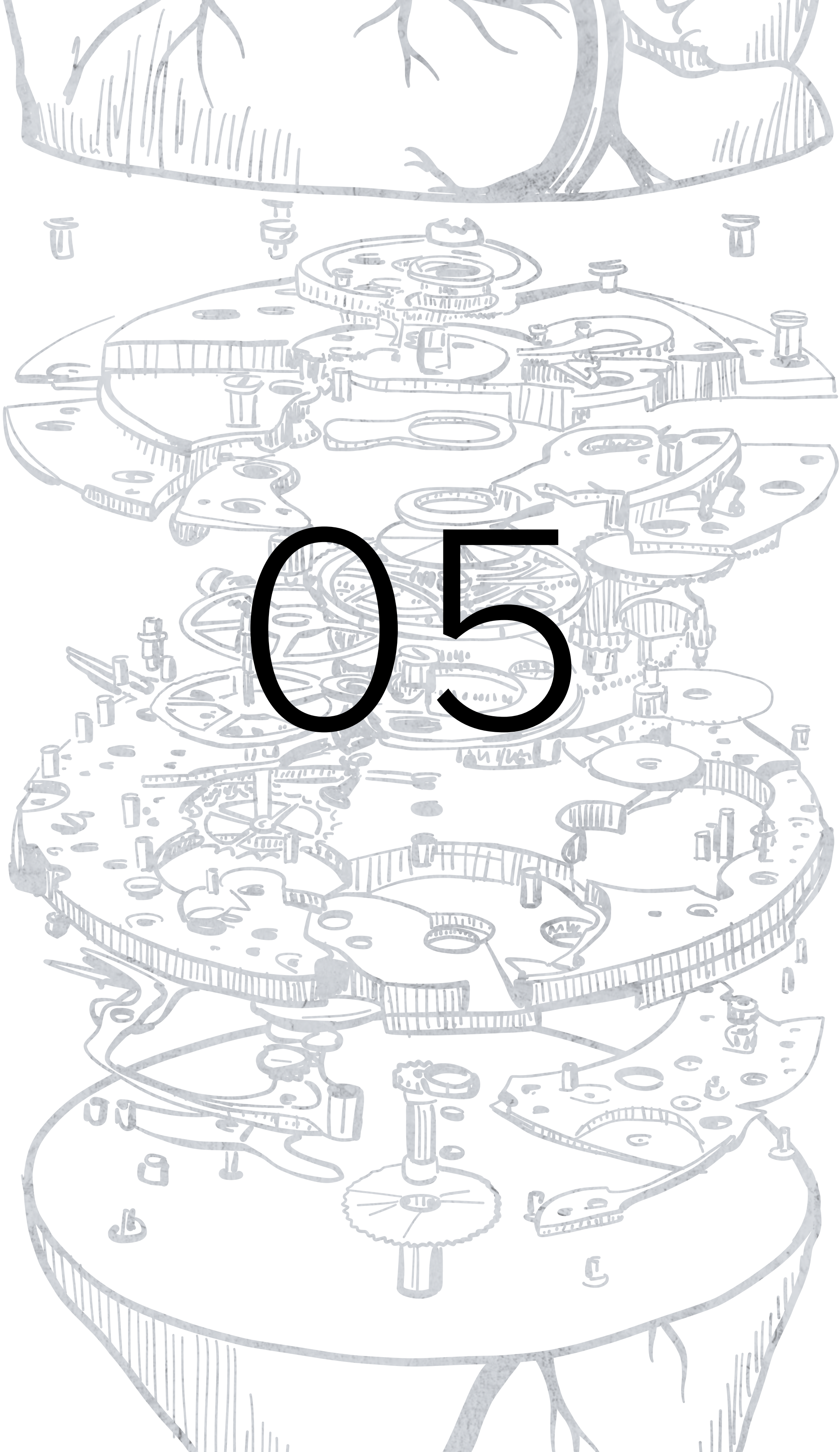
[20] Newcomb AE, David TE, Lad VS, Bobiarski J, Armstrong S, Maganti M. Mitral valve repair for advanced myxomatous degeneration with posterior displacement of the mitral annulus. J Thorac Cardiovasc Surg 2008;136:1503-9.

[21] Borger MA, Kaeding AF, Seeburger J, Melnitchouk S, Hoebartner M, Winkfein M et al. Minimally invasive mitral valve repair in Barlow's disease: early and long-term results. J Thorac Cardiovasc Surg 2014;148:1379-85.

[22] De Bonis M, Lapenna E, Del Forno B, Di Sanzo S, Giacomini A, Schiavi D et al. Minimally invasive or conventional edge-to-edge repair for severe mitral regurgitation due to bileaflet prolapse in Barlow's disease: does the surgical approach have an impact on the long-term results?dagger. Eur J Cardiothorac Surg 2017.

[23] Adams DH, Anyanwu AC, Rahmanian PB, Abascal V, Salzberg SP, Filsoufi F. Large annuloplasty rings facilitate mitral valve repair in Barlow's disease. Ann Thorac Surg 2006;82:2096-100; discussion 101.

[24] Varghese R, Itagaki S, Anyanwu AC, Trigo P, Fischer G, Adams DH. Predicting systolic anterior motion after mitral valve reconstruction: using intraoperative transoesophageal echocardiography to identify those at greatest risk. Eur J Cardiothorac Surg 2014;45:132-7; discussion 37-8.



05

Early and long-term outcomes of mitral valve repair for Barlow's disease:

A single-centre 16-year experience

Anton Tomšič; Yasmine L. Hiemstra; Stephanie L. van der Pas; Hein Putter; Michel I.M. Versteegh; Thomas J. van Brakel; Nina Ajmone Marsan; Robert J.M. Klautz; Meindert Palmen

Interact Cardiovasc Thorac Surg. 2018;26(5):783-789

ABSTRACT

Background. Following mitral valve repair for Barlow's disease, recurrent mitral regurgitation (MR) is believed to occur frequently and is mainly attributed to disease progression.

Methods. Between 1/2000 and 12/2015, 180 patients (40% female, mean age 58.7±13.5 years) with Barlow's disease underwent mitral valve repair. To provide a longitudinal assessment of mitral valve repair durability, a multistate model for interval censored observations (4 states- 1: grade 0/1+ MR, 2: grade 2+ MR, 3: grade 3+/4+ MR; 4: reintevention/death) was built. The mechanism of recurrent MR was assessed echocardiographically.

Results. Early mortality was 1.7%. After hospital dismissal, 6 late reinterventions were performed. With death as competing risk, the 10-year overall reintervention-free survival and reintervention rates were 79.8% (95% CI 72.7%-87.6%) and 4.5% (95% CI 2.0%-10.2%), respectively. Echocardiographic follow-up was available for 165 (93%) of hospital survivors with a total of 480 examinations. The incidence of both recurrent grade 2+ and grade 3+/4+ MR was relatively low up to 10 years after surgery. Grade 2+ MR did not always progress to higher regurgitation grade during the follow-up period. Grade 3+/4+ regurgitation was highly associated with valve-related morbidity and mortality. Recurrent MR (≥grade 2+) was predominantly related to the technical aspects of valve repair.

Conclusions. Despite the complex valve abnormalities seen in patients with Barlow's disease, mitral valve repair can be performed with good early and late outcomes and low rates of recurrence of MR up to 10-years after surgery. Early and late valve repair durability is good and remains stable over time, suggesting that underlying disease progression has limited clinical significance.

INTRODUCTION

Barlow's disease presents the most severe form of degenerative mitral valve disease and is characterized by severe annular, leaflet and subvalvular abnormalities. Improved understanding of valve dysfunction and growing surgical expertise nowadays allows for restoration of mitral valve competency in the majority of these patients [1, 2]. However, recurrent mitral regurgitation (MR) remains a concern even in the hands of experienced surgeons [3, 4].

Surgical valve repair strategy in Barlow's disease differs from the repair strategy in other forms of degenerative disease as it needs to take into account the profound annular abnormalities seen in these patients [5-8]. Even when corrected for known surgical risk factors for recurrent MR, Flameng et al. have previously demonstrated that recurrent MR occurs at a linearized rate of 2.9% per year for patients with Barlow's disease [3]. The authors proposed that Barlow's disease carries an inherent tendency to disease progression even after a successful valve repair. Other authors have later reached similar conclusions [2]. On the contrary, it has previously been proposed that valve degeneration occurs as a consequence of abnormal mechanical stress that will, in genetically predisposed individuals, result in activation of valve interstitial cells and extracellular matrix remodelling [9]. Mitral valve repair should therefore also aim to eliminate any excessive stress to the mitral valve apparatus. Disease progression after an initially successful valve repair is thus possibly inherent to the technique of valve repair rather than disease itself. To provide further insight into repaired valve performance, the application of longitudinal data analysis rather than time-to-event methods has been advised [10]. This could provide further understanding of the course of disease following successful valve repair.

The aim of this study was to explore the early and late patient- and valve-related outcome of mitral valve repair in patients with Barlow's disease. Moreover, we aim to gain in-depth information on mitral valve repair performance by analysing echocardiographic follow-up data in a longitudinal data analysis model for repeated echocardiographic measurements.

METHODS

Study population

Between January 2000 and December 2015, 684 consecutive adult patients underwent surgical intervention for MR due to degenerative mitral valve disease at our institution. Patients with accompanying active mitral valve infective endocarditis were excluded. 185 (27%) patients demonstrated both echocardiographic and surgical characteristics of Barlow's disease. These included excessive leaflet tissue, bileaflet myxomatous degeneration and mitral annular disjunction [6, 11]. Mitral valve repair was attempted in all cases and successfully performed in 181 (98%) patients. Excluding 1 patient that underwent valve repair with the edge-to-edge technique, 180 patients who underwent valve repair present the final study cohort.

Study methods

Pre-, intra-, and postoperative data were collected from our computerized patient registry. Follow-up clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through patient questionnaires. Our Institutional Medical Ethic Committee approved this study. Patient follow-up was closed in February 2017. Details on patient follow-up are provided in **Supplementary material A**.

Surgical procedure

During the study period, a repair-all strategy was applied and eventual valve replacement was only performed in case of an unsatisfactory intraoperative result of valve repair. Median sternotomy (n=157), partial sternotomy (n=13) or lateral mini-thoracotomy was performed (n=10). Standard cannulation techniques with central or peripheral cannulation (according to the surgical approach utilized) and intermittent warm blood cardioplegia for cardioprotection were used in all cases.

We have previously reported our surgical repair strategy in patients with Barlow's disease [7]. This includes discrimination between true and functional leaflet prolapse that occurs in patients with Barlow's disease as a consequence of profound annular motion abnormalities. In such cases, echocardiographic evidence of anterior mitral valve leaflet (AMVL) prolapse in a combination with annular displacement and abnormal annular motion suggests that AMVL prolapse can be resolved by annular stabilization alone. The final discrimination between true and functional leaflet prolapse is made during surgical valve analysis.

Commissural prolapse was treated predominately by papillary muscle head repositioning. To treat posterior mitral valve leaflet (PMVL) prolapse and excessive tissue, quadrangular resection with annular plication (earlier in our series) or leaflet sliding techniques (later in our series) was used when excessive tissue in height and width was present. Alternatively, a triangular resection combined with shortening polytetrafluoroethylene neochords were used to correct for excessive leaflet in width and height, respectively. True AMVL prolapse was treated predominantly with polytetrafluoroethylene neochords. Full, semi-rigid ring annuloplasty was performed in all but 1 patient who underwent a full, flexible ring implantation. Ring sizing was based on the surface area of the AMVL.

Intraoperative and predischarge echocardiography were performed by an experienced echocardiographists to confirm the success of valve repair. Oral anticoagulation with a target international normalized ratio of 2.0-3.0 was continued up to 3 months after surgery. In the presence of other indications, oral anticoagulation was continued as indicated.

Study endpoints

Postoperative mortality and morbidity endpoints were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery and European Association for Cardio-Thoracic Surgery Guidelines [10]. Early mortality was defined as mortality within 30-days after the operation or during the index hospitalization. The severity of MR was evaluated using a multiparametric integrative approach, including qualitative and quantitative assessments as currently recommended [12]. The severity of MR was graded on a 4-grade scale: 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe) and 4+ (severe). To explore the mechanism of mitral valve repair failure, echocardiograms were re-evaluated by a cardiologist experienced in cardiac echocardiography (N.A.M.). Pseudoprolapse was defined as a condition in which the free edge of one mitral valve leaflet was displaced above the free edge of the opposing leaflet in systole without overriding the plane of the annulus. Early recurrent MR was arbitrarily defined as ≥Grade 2+ MR observed within the first 2 years after the initial operation. Late recurrent MR was defined as ≥Grade 2+ MR observed later than 2 years after the initial operation.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile ranges (IQR) when not-normally distributed. Categorical data are presented as counts and percentages. The cumulative incidences of reintervention and death were estimated using the Aalen-Johansen estimator [13]. For the remaining analyses, a multistate model for interval-censored observations was built [14]. The start of the follow-up for the multistate model was set at 3 months after the operation. The following four states were defined: 'Grade 0 or 1+ MR', 'Grade 2+ MR', 'Grade 3+ or 4+ MR', and the terminal state 'reintervention/death' (**Figure 1**). This type of multistate model is designed for situations where patients can move back and forth between states (i.e. echo grades) and where the times at which a patient changes state (e.g. moves from Grade 2+ to Grade 3+) are not exactly observed. The hazards of transitioning between the states were taken to be constant, after tests for a change in hazard at 1.5 or 2 years were not significant. In the unadjusted analyses, none of the seven hazards were assumed to be equal to each other. For the adjusted analyses, three hazards were allowed: deterioration (moving to a higher state), improvement (moving to a lower state) or reintervention/death (moving to the terminal state). First, univariate analyses at the 15% level were performed. Then, a multivariate model was made, in which covariates were constrained to only have an effect on those hazards on which they had a significant effect in the univariate analyses. The multistate models were estimated using the MSM package in R [15].

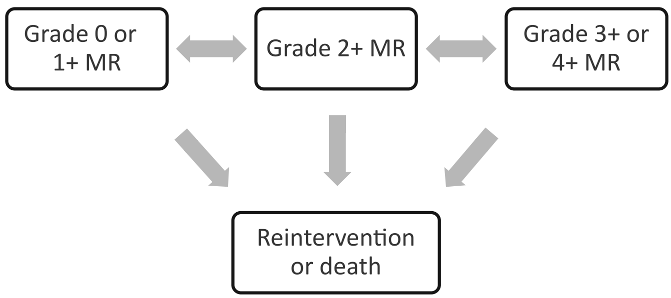


FIGURE 1. Multistate model design. State 'reintervention/death' presents a terminal state while transitions between other states are freely allowed.

RESULTS

Baseline characteristics

Baseline characteristics of the whole study cohort are presented in **Table I**. At admission, the majority of patients were symptomatic and a history of atrial fibrillation was present in more than one-third of patients. Left ventricular functional impairment or left ventricular dilatation were present less often. The vast majority of patients demonstrated echocardiographic evidence of bileaflet prolapse, and in a relatively high proportion of patients, mitral annular calcification was seen. The majority of patients underwent elective surgery.

Early results

Intraoperative details on mitral valve repair and concomitant procedures performed are provided in **Table II**. Early mortality was 1.7% (3 patients, **Table III**). The cause of death was multiorgan failure in 2 patients and perioperative myocardial infarction in 1 patient. All of the deceased patients were symptomatic and had a history of atrial fibrillation. No major postoperative complications occurred in most (81.7%) patients.

Postoperative resting mitral valve gradient was 3.26±1.42 mmHg and was significantly lower in patients in whom no annular plication was performed (2.92±1.22 mmHg and 3.93±1.56 mmHg, $P<0.001$). No significant systolic anterior motion was present in any of the patients. In 2 (1.1%) patients, significant residual MR (≥Grade 2+) was observed on predischarge echocardiography (**Supplementary material B**) and both underwent early reoperation. One patient showed residual AMVL prolapse and underwent reoperation on postoperative day 8. Valve replacement was performed as a durable repair was deemed unlikely due to a severely degenerated and malformed AMVL. The second patient showed residual PMVL prolapse and underwent mitral valve re-repair on postoperative day 8.

Late clinical outcome

There were 22 late deaths. The cause of death was valve-related in 10 (intracranial bleeding in 2; death following mitral valve reoperation in 1; end-stage heart failure with recurrent MR in 1; sudden unexplained death in 6) and cardiac- but not valve-related in 3 (myocardial infarction in 1; type A aortic dissection several years after the initial procedure in 1; end-stage heart failure in 1) patients. The cause of death was not cardiac-related in 9 patients.

TABLE I. Baseline characteristics.

	N = 180
Age	58.7±13.5
Sex (female)	72 (40.0)
NYHA class	
I	69 (38.3)
II	87 (48.3)
III-IV	24 (13.4)
Preoperative atrial fibrillation	66 (36.7)
Hypertension	58 (32.2)
Renal impairment	
Moderate (CC 85-50 ml/min)	80 (44.4)
Severe (CC <50 ml/min)	5 (2.8)
Extracardiac arteriopathy	1 (0.6)
History of TIA or CVA	4 (2.2)
Chronic lung disease	11 (6.1)
Diabetes mellitus	2 (1.1)
Non-elective surgery setting	3 (1.7)
Critical preoperative state	1 (0.6)
Left ventricular ejection fraction	
>60%	127 (70.6)
30%-60%	53 (29.4)
Left ventricular end-systolic diameter >45mm	12 (6.7)
Pulmonary hypertension (sPAP >50mmHg)	7 (3.9)
Leaflet prolapse	
None	4 (2.2)
Isolated anterior	5 (2.8)
Isolated posterior	24 (13.3)
Bileaflet	147 (81.7)
Mitral annular calcification	32 (17.8)

Data are presented as n (%). Abbreviations: CC: creatinine clearance; CVA: cerebrovascular accident; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure; TIA: transient ischaemic attack.

TABLE II. Intraoperative details.

	N=180
Mitral valve annulus	
Annular plication	61 (33.9)
Decalcification	26 (14.4)
Annuloplasty ring size	36 (IQR 32-38)
Anterior mitral valve leaflet	
Resection	3 (1.7)
Neochords	83 (46.1)
Chordal transfer	1 (0.6)
Chordal shortening	1 (0.6)
Posterior mitral valve leaflet	
Resection	150 (83.3)
Sliding plasty	132 (73.3)
Neochords	55 (30.6)
Chordal transfer	2 (1.1)
Chordal shortening	1 (0.6)
Papillary muscle head repositioning	2 (1.1)
Identation closure	35 (19.4)
Commissures	
Anterior commissure	26 (14.4)
Papillary muscle head repositioning	19 (10.6)
Commissuroplasty	6 (3.3)
Neochords	1 (0.6)
Posterior commissure	65 (36.1)
Papillary muscle head repositioning	57 (31.7)
Commissuroplasty	7 (3.9)
Neochords	1 (0.6)
Aortic cross-clamp time (min)	153 (IQR 137-200)
Cardiopulmonary bypass time (min)	203 (IQR 174-250)
Second pump run	14 (7.8)
Concomitant procedures	
Tricuspid valve repair	95 (52.8)
Radiofrequency ablation	56 (31.1)
Coronary artery bypass grafting	16 (8.9)
Aortic valve intervention	5 (2.8)
Thoracic aorta replacement	2 (1.1)

Data are presented as n (%).

TABLE III. Postoperative complications

	N = 180
Early mortality	3 (1.7)
Sternal wound infection	0 (0)
Prolonged intubation (>24h)	20 (11.1)
Renal failure	5 (2.8)
Permanent stroke	2 (1.1)
Early reoperation	19 (10.5)
Re-exploration for bleeding and/or cardiac tamponade	17 (9.4)
Early valve reoperation	2 (1.1)

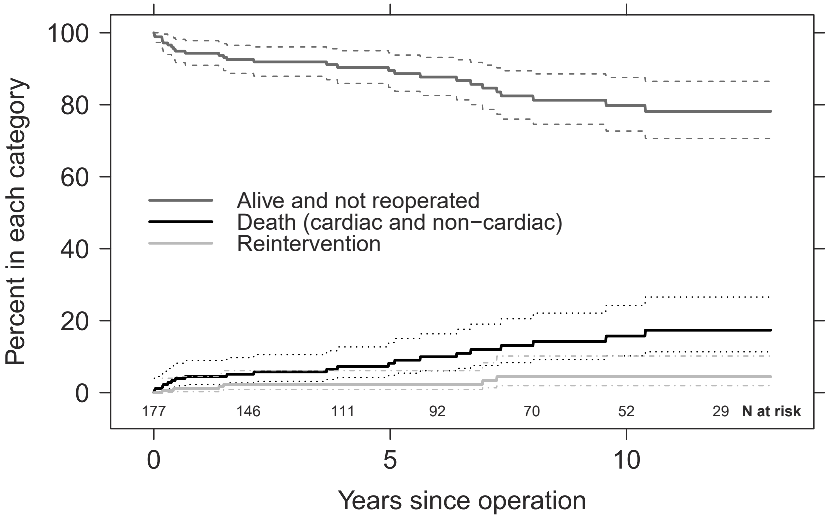
Data are presented as n (%).

Following hospital discharge, 6 late reinterventions were performed. The cause of reintervention was prosthetic valve endocarditis in 1, suture line defect of the PMVL in 1, recurrent MR in 3 and secondary MR in 1. Taking all-cause death and mitral valve reintervention as competing risks, the 5- and 10-year cumulative incidence of reintervention-free survival were 89.5% [95% confidence interval (CI) 84.8%-94.4%] and 79.8% (95% CI 72.7%-87.6%), respectively (**Figure 2**).

Eleven patients experienced a thromboembolic event. Five of these were cerebrovascular accidents and 6 were cerebral transient ischaemic attacks. No events were fatal. Six patients experienced serious haemorrhagic complications resulting in death in 2 patients (intracranial bleeding in both cases). There was 1 episode of infective endocarditis (occurring 1 month after the initial intervention), resulting in a reoperation.

Late echocardiographic outcome

Figure 3 shows the time-related changes in the percentage of patients in various states over time. As expected, patients alive and free from reintervention demonstrated good repair durability up to 10 years after the initial operation. Interestingly, Grade 2+ MR did not always progress with time but remained stable or even regressed with time (upon any of the following echocardiographic measurements; **Supplementary material C**). When stratifying patients based on the observed severity of MR, the reintervention-free survival probability was best for patients without any significant MR (**Supplementary material C**). All transitions form state 1 to state 4 were deaths. All transitions from state 3 to state 4 were valve-related events: 5 were reinterventions and 1 was valve-related death (end-stage heart failure with recurrent MR).



	5-year cumulative incidence		10-year cumulative incidence	
		95% confidence interval		95% confidence interval
Reintervention	2.3%	0.9%-6.1%	4.5%	2.0%-10.2%
Cardiac death	4.9%	2.5%-9.6%	10.0%	5.8%-17.2%
Non-cardiac death	3.3%	1.4%-8.0%	5.8%	2.7%-12.5%
Alive without reintervention	89.5%	84.8%-94.4%	79.8%	72.7%-87.6%

FIGURE 2. Competing risk of outcomes. Time related parametric estimates with 95% confidence intervals (dashed lines) are presented for the following mutually exclusive categories: death (red), reintervention (blue) and patients alive without reintervention (green).

Multivariate analysis demonstrated only male gender as a statistically significant protective factor (hazard ratio 0.32, 85% CI 0.11-0.91) against repaired valve functional deterioration (**Supplementary material D**). In particular, PMVL resection (no leaflet resection was performed in a relatively small number of patients in whom only excessive tissue in height was present and treated by implanting shortening neochords) or the presence of annular calcification did not affect repaired valve performance. Multivariate analysis demonstrated only advanced patient age (>60 years old; hazard ratio 3.21, 85% CI 1.16-8.85) as a significant risk factor for transition to state 4.

	5-year cumulative incidence		10-year cumulative incidence	
		95% confidence interval		95% confidence interval
Grade 0/1+ MR	79%	63% - 85%	67%	39% - 75%
Grade 2+ MR	7%	0% - 10%	6%	0% - 10%
Grade 3+/4+ MR	2%	0% - 3%	2%	0% - 3%
Death or reintervention	13%	8% - 37%	25%	18% - 61%

FIGURE 3. Multistate model demonstrating the time from the initial operation dependent percentage of patients in each of the predefined states.

Mechanism of recurrent MR

Echocardiographic assessment revealed that recurrent MR was most commonly related to the technical aspects of valve repair (**Table IV**). Early recurrent MR was seen in 11 patients. This was caused by residual prolapse/billowing and suture line defect in 5 and 1 patient, respectively. Leaflet restriction –usually combined with pseudoprolapse of the opposite mitral valve leaflet- was the cause in 4 patients while the cause of recurrent MR was not clear in 1 patient.

TABLE IV. The mechanism of recurrent MR in patients in whom ≥grade 2+ MR was seen at any point during the follow-up period.

Case	Year of surgery	AMVL	PMVL	Time to first observation		Last observation		Reintervention	Time to reintervention (years)
				MR grade	Years	MR grade	Years		
1	2001	Prolapse	-	2+	0.5	4+	1.1	Yes (MVR)	1.5
2	2002	Restriction (left ventricular dilatation)	Restriction (left ventricular dilatation)	3+	1.8	2+	7.3	Yes (aortic root replacement + restrictive mitral annuloplasty)	7.3
3	2002	-	Suture line defect	4+	0.1	4+	0.1	Yes (re-repair)	0.6
4	2004	Not clear	Not clear	2+	2.0	2+	11.0	No	-
5	2004	Residual billowing (insufficient leaflet coaptation)	-	2+	1.8	2+	10.7	No	-
6	2005	Restriction	Pseudoprolapse	4+	1.0	4+	1.0	Yes (MVR)	1.4
7	2009	-	Restriction	3+	1.2	3+	1.2	No	-
8	2010	-	Restriction	2+	1.6	2+	1.6	No	-
9	2012	Pseudoprolapse (possibly neochord too long)	-	2+	1.5	2+	2.5	No	-
10	2013	Pseudoprolapse (possibly neochord too long)	-	3+	1.0	3+	2.8	No	-
11	2014	Prolapse	-	2+	1.1	2+	2.5	No	-
12	2003	Thickened leaflet	Restriction + thickened leaflet	2+	8.5	2+	12.5	No	-
13	2004	Unknown	Unknown	2+	7.3	2+	8.8	No	-

TABLE IV. Continued.

Case	Year of surgery	AMVL	PMVL	Time to first observation		Last observation		Reintervention	Time to reintervention (years)
				MR grade	Years	MR grade	Years		
14	2004	Restriction	Relatively short but mobile (loss of coaptation)	2+	8.9	3+	12.6	No	-
15	2006	Pseudoprolapse	Restriction (possibly due to the repositioned papillary muscle)	2+	3.5	4+	7.0	Yes (MVR)	7.0
16	2006	-	Pseudoprolapse	2+	5.8	2+	5.8	No	-
17	2007	Restriction	Decreased mobility	2+	6.1	2+	8.7	No	-
18	2008	-	Prolapse	3+	4.7	4+	5.7	No	-
19	2008	Restriction	Pseudoprolapse	3+	8.1	3+	8.8	No	-
20	2012	Pseudoprolapse	Restriction	2+	3.1	2+	3.1	No	-

Abbreviations: AMVL: anterior mitral valve leaflet; MR: mitral regurgitation; MVR: mitral valve replacement; PMVL: posterior mitral valve leaflet.

Late recurrent MR was seen in 9 patients. A combination of leaflet restriction with or without pseudoprolapse of the opposite leaflet presented the most common cause of repair failure. In 1 patient, valve analysis upon reoperation revealed that leaflet restriction was likely caused by the repositioned papillary muscle head. Recurrent prolapse (evidence of chordae rupture was also seen on echocardiography) as the sole cause of repair failure was seen in only 1 patient. Of notice, leaflet thickening as the cause of recurrent MR was seen in 1 patient only.

DISCUSSION

Our study demonstrated that a systematic valve repair strategy in Barlow's disease, utilizing a combination of leaflet resection techniques, subvalvular apparatus manipulation, neochords implantation and annular stabilization, is highly reproducible and will allow valve repair to be performed in nearly all patients. Recurrent MR –occurring early or late- was most commonly related to the technical aspects of valve repair and not disease progression. Furthermore, once occurring, Grade 2+ MR did not always progress with time during the follow-up period.

We adhere to an early surgery approach in all patients with degenerative mitral valve disease and advise surgery to asymptomatic patients with severe MR, regardless of the expected repair complexity. This is in line with the recommendations of the American Heart Association/American College of Cardiology on the management of valvular heart disease [16]. On the other hand, the recently updated guidelines from the European Society of Cardiology/European Association of Cardio-Thoracic Surgery advise considering surgery in asymptomatic patients only when favourable anatomy (flail leaflet) or significant left atrial dilatation is present [17]. The high proportion of patients in whom successful valve repair with a documented good result was feasible is believed to support an early surgical approach even in patients with complex valve pathology. It is, however, imperative that such patients are referred to centres with sufficient experience in reconstructive valve surgery.

The majority of patients underwent valve repair through standard full-sternotomy with –especially later in our series- limited midline skin incision (approximately 10-15 cm in length). Previous studies have demonstrated favourable results of the minithoracotomy approach to valve repair in patients with Barlow's disease [18, 19]. However, this includes significant modifications of the mitral valve repair technique when compared to our technique. We remain reluctant to utilize the edge-to-edge repair technique in patients with degenerative mitral valve disease because this technique has been demonstrated to have a profound effect on diastolic transvalvular mitral valve gradients [20]. We have to acknowledge, however, that patients with Barlow's disease usually present with large valve orifice areas and large annuloplasty rings –making functional mitral valve stenosis unlikely to occur regardless of the repair technique utilized- are utilized to complement valve repair. In our opinion, the decision on the type of approach should be based on the decision of the informed patient and projected repair complexity. Surgical approach should not determine the strategy of mitral valve repair.

Interestingly, female gender had a negative effect on valve repair durability. Our study is not the first to report such findings and further studies are needed to explore the underlying causes of such observations [21]. Our results further suggest that even Grade 2+ MR after mitral valve repair might remain stable for years. In line with this observation, the time-related probability of death or reintervention seemed only moderately higher once Grade 2+ MR was observed. There are several possible explanations for these findings. Such observations can be partially explained by the fact that grading of the severity of MR is based on arbitrarily defined grades while the amount of regurgitant flow presents a continuous biological parameter. The severity of MR is dependent on various factors that can present an extrinsic and reversible cause of repaired valve function deterioration [10]. On the other hand, it should be acknowledged that the follow-up time in our patients was limited. In these patients, the severity of MR might progress in the future and necessitate reoperation. Taking this into consideration, close follow-up should be advised in all patients while further research is needed to assess the clinical significance of our findings. On the other hand, the occurrence of ≥Grade 3+ MR was clearly related to valve-related morbidity and mortality. Importantly, the underlying mechanism needs to be taken into account when assessing the expected clinical significance and prognosis of "recurrent MR". Our observations should therefore be interpreted with caution.

In a previous study on 348 patients (including 83 patients with Barlow's disease) who underwent successful valve repair for degenerative mitral valve disease, Flameng et al. have shown that recurrent MR (>2/4 MR) occurs most commonly because of recurrent leaflet prolapse or leaflet thickening [3]. They hypothesized that even after a sound surgical repair, disease progression presents an inherent characteristic of Barlow's disease. We argue that valve repair that successfully resolves any excessive stress on the mitral valve leaflets and subvalvular apparatus should provide good repair durability even in cases of Barlow's disease. To assure a stable, durable valve repair, a large surface area of leaflet coaptation without any residual malaposition of the mitral valve leaflets –that would result in unwanted tension to the leaflets and chordae tendineae- needs to be achieved. Annular stabilization is of utmost importance in these patients as annular abnormalities (diminished annular saddle shape and abnormal motion) increase the strain exerted to the mitral valve leaflets. Ring annuloplasty with a suitable annuloplasty device that mimics the normal systolic annular saddle shape can resolve these issues. This is supported by the fact that leaflet thickening was an uncommon observation in our experience, despite the fact that this has been reported to present the most common mechanism of repair failure in patients with degenerative disease [22]. The very low rate of disease progression as a cause of failure underlines that these operations stabilize the disease and could therefore be advised even to asymptomatic patients.

In our experience, the most common mechanism of recurrent MR was leaflet restriction, usually combined with pseudoprolapse of the opposite leaflet. Hypothetically, this could present a consequence of leaflet resection. Contrary to this speculation, leaflet resection did not predict worsening of repaired valve function on multivariate analysis. We speculate that resection will not *per se* induce clinically significant leaflet restriction. However, excessive leaflet resection might well induce leaflet restriction and eventually result in pseudoprolapse of the opposite leaflet. Loss of sufficient leaflet coaptation height will induce excessive residual strain on the mitral valve leaflet(s), indicating instability of valve repair in the long term. This would explain the similarity in the mechanism of early and late recurrent MR seen in our experience. It also suggests that even late recurrent MR can be directly related to the technical aspects of valve repair. Furthermore, insufficient height of leaflet coaptation might result from other technical aspects of valve repair (inadequate ring sizing) and might in patients with Barlow's disease result from the inability to prevent abnormal annular motion. In our opinion, this provides a possible argument for the utilization of semi-rigid instead of flexible annuloplasty devices in these patients. However, the effect of various annuloplasty devices on annular motion in patients with Barlow's disease needs to be studied further.

LIMITATIONS

Our study is retrospective in nature and therefore subject to the inherent weaknesses of a retrospective analysis. The valve repair technique has somehow evolved throughout the study period (i.e. abandonment of the annular plication technique) and might have affected the results. We reason that this could have only a limited effect on repair durability. Furthermore, our results in terms of repaired valve performance are based on our experience only and the observations might not be applicable to other techniques of valve repair. Lastly, MR severity was –based on the accepted recommendations- scored on a graded scale. Such simplification inevitably results in a loss of possibly relevant information regarding repaired valve durability. However, analysing MR severity on a continuous scale would be statistically very complex to conduct and interpret.

CONCLUSIONS

Despite the complex valve abnormalities seen in patients with Barlow's disease, mitral valve repair can be safely performed with good early and late outcomes. Early surgical intervention seems justified, despite the complexity of valvular abnormalities normally observed. Early repair failure is largely related to the technical aspects of valve repair. Late deterioration of repaired valve function occurs infrequently and also appears inherent to the surgical technique, suggesting that underlying disease progression has limited clinical significance.

REFERENCES

[1] Adams DH, Anyanwu AC, Rahmanian PB, Abascal V, Salzberg SP, Filsoufi F. Large annuloplasty rings facilitate mitral valve repair in Barlow's disease. Ann Thorac Surg 2006;82:2096-100; discussion 101.

[2] Jouan J, Berrebi A, Chauvaud S, Menasche P, Carpentier A, Fabiani JN. Mitral valve reconstruction in Barlow disease: long-term echographic results and implications for surgical management. J Thorac Cardiovasc Surg 2012;143:S17-20.

[3] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135:274-82.

[4] Newcomb AE, David TE, Lad VS, Bobiarski J, Armstrong S, Maganti M. Mitral valve repair for advanced myxomatous degeneration with posterior displacement of the mitral annulus. J Thorac Cardiovasc Surg 2008;136:1503-9.

[5] Clavel MA, Mantovani F, Malouf J, Michelena HI, Vatury O, Jain MS et al. Dynamic phenotypes of degenerative myxomatous mitral valve disease: quantitative 3-dimensional echocardiographic study. Circ Cardiovasc Imaging 2015;8.

[6] Eriksson MJ, Bitkover CY, Omran AS, David TE, Ivanov J, Ali MJ et al. Mitral annular disjunction in advanced myxomatous mitral valve disease: echocardiographic detection and surgical correction. J Am Soc Echocardiogr 2005;18:1014-22.

[7] Klautz RJ, Tomšič A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in Barlow's disease: the concept of functional prolapse. Multimed Man Cardiothorac Surg 2016;2017.

[8] Apor A, Nagy AI, Kovacs A, Manouras A, Andrassy P, Merkely B. Three-dimensional dynamic morphology of the mitral valve in different forms of mitral valve prolapse - potential implications for annuloplasty ring selection. Cardiovasc Ultrasound 2016;14:32.

[9] Rabkin E, Aikawa M, Stone JR, Fukumoto Y, Libby P, Schoen FJ. Activated interstitial myofibroblasts express catabolic enzymes and mediate matrix remodeling in myxomatous heart valves. Circulation 2001;104:2525-32.

[10] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732-8.

[11] Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J 2010;31:1958-66.

[12] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.

[13] Aalen OO, Johansen S, xf, ren. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. Scandinavian Journal of Statistics 1978;5:141-50.

[14] Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389-430.

[15] H. Jackson C. Multi-State Models for Panel Data: The msm Package for R. 2011.

[16] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA et al. 2017 AHA/ACC Focused Update of the 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 Clinical Practice Guidelines. Circulation 2017;135:e1159-e95.

[17] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.

[18] da Rocha ESJG, Spampinato R, Misfeld M, Seeburger J, Pfanmuller B, Eifert S et al. Barlow's Mitral Valve Disease: A Comparison of Neochordal (Loop) and Edge-To-Edge (Alfieri) Minimally Invasive Repair Techniques. Ann Thorac Surg 2015;100:2127-33; discussion 33-5.

[19] De Bonis M, Lapenna E, Del Forno B, Di Sanzo S, Giacomini A, Schiavi D et al. Minimally invasive or conventional edge-to-edge repair for severe mitral regurgitation due to bileaflet prolapse in Barlow's disease: does the surgical approach have an impact on the long-term results?dagger. Eur J Cardiothorac Surg 2017.

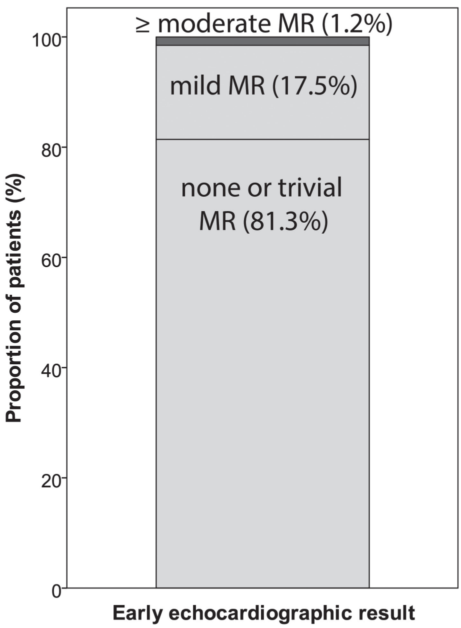
[20] Jahren SE, Hurni S, Heinisch PP, Winkler B, Obrist D, Carrel T et al. Transvalvular pressure gradients for different methods of mitral valve repair: only neochordoplasty achieves native valve gradients. Interact Cardiovasc Thorac Surg 2017.

[21] Chan V, Chen L, Elmistekawy E, Ruel M, Mesana TG. Determinants of late outcomes in women undergoing mitral repair of myxomatous degeneration. Interact Cardiovasc Thorac Surg 2016;23:779-83.

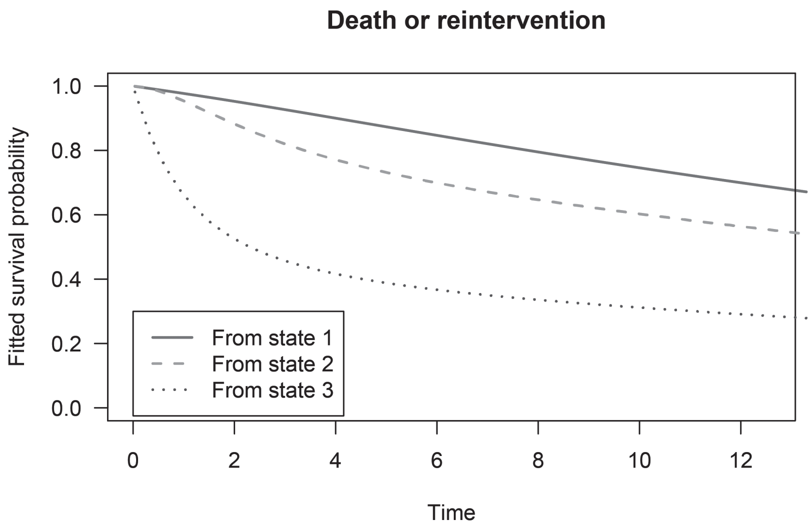
[22] Chan V, Elmistekawy E, Ruel M, Hynes M, Mesana TG. How Does Mitral Valve Repair Fail in Patients With Prolapse?-Insights From Longitudinal Echocardiographic Follow-Up. Ann Thorac Surg 2016;102:1459-65.

Median survival follow-up was 7.4 (IQR 3.9-11.7; range 0-17.0) years and was 98.9% complete (2 patients were lost to survival follow-up due to emigration). Median clinical follow-up time for valve-related events (including mitral valve reintervention, thromboembolic events, haemorrhagic complications and infective endocarditis) was 6.6 (IQR 2.9-10.9; range 0-16.2 years) years. Clinical follow-up was 91% complete (the ratio of total observed person time to potential person time of follow-up to the closing date of the study). Echocardiographic follow-up was available for 165 (93.2% of hospital survivors) patients with a total of 480 (2.9/patient) examinations available and a median follow-up time of 5.4 (IQR 2.3-10.4) years.

SUPPLEMENTARY MATERIAL A. Details on patient follow-up.



SUPPLEMENTARY MATERIAL B. Early echocardiographic outcome. Residual mitral regurgitation was seen in 2 patients- both underwent early reoperation (during the initial hospitalization).



SUPPLEMENTARY MATERIAL C. Fitted probability of transition to state 4 (reintervention or death) after entering state 1 (grade 0+/1+ MR, red solid line), state 2 (grade 2+ MR, green dashed line) or state 3 (grade 3+/4+ MR, blue dotted line).

One year after entering state 2, a typical patient had the probability of 29% of being in state 1 (MR regression to Grade 0+/1+), 54% of being in state 2 (Grade 2+ MR), and the probability of 12% of being in state 3 (Grade 3+/4+ MR). The probability of an event (death/reintervention) within 1 year was 5%. After 10 years, the probability that this patient was in state 1 was 53%, in state 2 was 5% and in state 3 was 2%. The probability of an event (death/reintervention) within 10 years was 40%.

Within the group of patients in whom echocardiographic follow-up was available, 20 transitions to state 4 (death/reintervention) were observed. The time-related probability that a patient was in state 1 (Grade 0/1+ MR) before transition to state 4 was relatively constant for the follow-up period with an estimated value of 64%. Of the observed transitions to state 4, 14/20 (70%) originated from state 1. The estimate of 64% is different because the multistate model accounts for the possibility that a patient moved to another state between the time of the last echo and the time of transitioning to state 4. All of these events were deaths: valve-related (intracranial bleeding) in 1, type A dissection in 1, sudden, unexplained in 6 and non-cardiac related in 6. The time-related probability that a patient was in state 2 (Grade 2+ MR) before transition to state 4 was negligible as no direct transitions from state 2 to state 4 were observed. The time-related probability that a patient was in state 3 (Grade 3+/4+ MR) before transition to state

4 was relatively stable with an estimated value of 36%. This accounted for 6/20 (30%) transitions. All of these transitions were valve-related events: 5 were reinterventions and 1 was valve-related death (end-stage heart failure with recurrent MR).

SUPPLEMENTARY MATERIAL D. Univariate and multivariate analysis of risk factors for deterioration or improvement of mitral valve repair function and reintervention/death.

	Univariate analysis			Multivariate analysis		
	Deterioration	**Improvement**	**Death or reintervention**	**Deterioration**	**Improvement**	**Death or reintervention**
Age (>60)	1.94 (0.96-3.91)	1.37 (0.60-3.15)	3.34 (1.60-6.98)*			3.21 (1.16-8.85)*
Gender (male)	0.32 (0.15-0.68)*	0.40 (0.17-0.92)*	0.70 (0.35-1.41)	0.32 (0.11-0.91)*	0.49 (0.14-1.67)	
Atrial fibrillation						
Paroxysmal	3.74 (1.33-10.48)*	5.05 (1.64-15.50)*	1.74 (0.74-4.07)	1.67 (0.46-6.02)	2.66 (0.66-10.81)	
Chronic	1.09 (0.40-3.00)	0.73 (0.15-3.52)	3.25 (1.48-7.17)*			2.12 (0.77-5.83)
LVEF ≤60%	0.16 (0.05-0.51)*	N/A	1.88 (0.93-3.80)	0.29 (0.07-1.24)		
LVESD >45mm	0.57 (0.10-3.33)	N/A	2.57 (0.96-6.89)			
Annular calcification	2.29 (0.96-5.49)	0.71 (0.15-3.44)	0.99 (0.36-2.76)			
Leaflet prolapse						
Bileaflet	1.31 (0.21-8.13)	1.91 (0.33-11.23)	N/A			
Isolated posterior	0.78 (0.10-6.22)	N/A	N/A			
Isolated anterior	6.55 (0.80-53.87)	2.84 (0.23-34.90)	N/A			
PMVL resection	0.71 (0.29-1.76)	2.63 (0.77-9.02)	0.83 (0.28-2.47)			

Abbreviations: LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; PMVL: posterior mitral valve leaflet.
**statistically significant*

PART III

TECHNICAL ASPECTS OF MITRAL VALVE SURGERY

Increasing surgical expertise and technical modifications have made mitral valve repair feasible in a wide variety of diseases and, nowadays, valve repair is successfully performed even in very complex cases. Nevertheless, several controversies persist to date, ranging from the optimal selection of repair techniques in specific lesions to the problem of elevated post-repair gradient following an otherwise successful valve repair.

In the case of posterior mitral valve leaflet prolapse, several techniques are available to address this lesion. In general, these techniques can be divided into resection and non-resection techniques. Two recent meta-analyses have allegedly demonstrated superiority of chordal replacement over leaflet resection techniques [1, 2]. Such results do, however, need to be interpreted with caution and put into proper clinical perspective. To achieve the desired goal of reconstructive mitral valve surgery, including restoration of normal leaflet motion, leaflet prolapse as well as excessive leaflet tissue need to be addressed. Excessive leaflet tissue in height (redundancy of leaflet tissue from the annular edge to leaflet free edge plane) as well as excessive tissue in width (redundancy of leaflet tissue in the horizontal plane) need to be appropriately corrected.

Resection and non-resection techniques are not fully interchangeable as the chordal replacement techniques are unable to address excessive leaflet tissue in width. Residual excessive leaflet motion has, in a virtual mitral valve model [3], been shown to result in excessive leaflet stress and might predispose to late repair failure. Therefore, it needs to be addressed at the time of valve repair [4]. With posterior leaflet lesions, the presence and extent of (I) excessive leaflet tissue in height, (II) excessive leaflet tissue in width and (III) abnormal leaflet motion will guide the optimal repair strategy and secure the best results. Generic division into distinctive repair groups with ensuing head-to-head comparison is thus unlikely to provide relevant clinical information but is more likely to result in an unjustified preference for the utilization of a single repair technique. The debate should rather be focused on the utilization of various repair techniques for a specific indication.

An important observation made by the meta-analyses comparing leaflet resection and non-resection techniques was the significantly higher post-repair mitral valve gradient following valve repair with leaflet resection techniques [1, 2]. Non-resection techniques have been proposed to better preserve diastolic leaflet motion while leaflet resection techniques have been proposed to provide diastolic blood flow obstruction. In light of these findings, a prospective randomized clinical trial comparing the results of mitral valve repair with leaflet resection or leaflet preservation (The CAMRA CardioLink 2 trial) is currently being performed [5]. Such observations and results, however, need to be critically assessed before definitive conclusions can be made. The contribution of posterior leaflet motion on diastolic blood flow is less than the contribution of anterior leaflet motion. Moreover, the technical execution of posterior leaflet resection likely plays a crucial role in the preservation of diastolic leaflet movement. In the absence of excessive leaflet tissue, excessive resection of the leaflet free edge might indeed hinder diastolic leaflet opening and result in unwanted flow obstruction and higher post-repair gradients [6, 7]. Even in the presence of excessive leaflet tissue, similar can be expected if excessive leaflet resection is performed. On the other hand, it cannot be expected that a properly sized leaflet resection in the presence of excessive leaflet tissue will result in similar problems. Leaflet resection with subsequent restoration of leaflet continuity might cause leaflet stiffening at the level of the suture line. Nevertheless, this is probably unlikely to have clinically significant consequences.

The problem of elevated post-repair gradients and the clinical consequences hereof have recently gained widespread interest. In addition to the previously mentioned speculation that leaflet resection might result in higher post-repair gradients, controversies regarding the effect of the type of annuloplasty device implanted (in particular full-ring versus partial flexible band) on post-repair gradients have recently emerged [8-10]. Again, the observations being made need to be understood in the light of the limitations of the studies performed. Importantly, previous studies have shown that, in normal hearts, the diastolic mitral valve annular area is primarily related to the length of the posterior annular perimeter that lengthens during diastole [11]. As annuloplasty devices are sized to systolic valve configuration and lack elasticity, the posterior annular perimeter will not be able to lengthen in diastole, preventing the physiologic attenuation of mitral annular area to occur. This is clearly unrelated to the type of device implanted. More importantly, the effect of annuloplasty device on anterior leaflet motion should be appreciated as the type of device implanted might restrict the diastolic opening angle and hereby obstruct diastolic blood flow [12]. In addition to the risk factors for elevated post-repair gradients, the clinical importance hereof needs to be re-evaluated [13].

The type of repair technique used to perform valve repair in specific lesions might additionally have an important effect on post-repair gradients. Several studies have demonstrated a negative effect of the edge-to-edge technique on post-repair gradients [6, 9]. On the other hand, in case of complex lesions such as commissural prolapse, the edge-to-edge technique might provide a technically appealing alternative, avoiding other, more complex maneuvers and lowering the risk of unsuccessful repair. However, even in the setting of commissural prolapse, concerns on the appropriateness of this technique have been raised [14]. Alternatively, papillary muscle head repositioning can be performed, providing that the continuity of the subvalvular apparatus is preserved [15]. The patient- and valve-related results of this technique remain, however, scarcely studied.

Mitral annular calcification remains a challenging entity despite growing surgical expertise. In patients with degenerative mitral valve disease it can be expected that the weight of the problem will decrease as a result of earlier referral for surgery. In these patients, annular calcification is a multi-phase process that is believed to develop as a result of excessive mechanical stress exerted by the annulus [16]. Early surgery might therefore constrain disease progression by reducing excessive annular stress and thus eliminating the underlying pathological substrate. Nevertheless, a proportion of patients will present with advanced annular calcification. A repair-all strategy in these patients is questionable as even in experienced centres the results of valve repair for complex valve abnormalities might not be superior to the results of valve replacement [17]. The repair all strategy in these patients needs further evaluation.

In reconstructive mitral valve surgery, the underlying disease might render native leaflet tissue unsuitable for a durable valve repair to be performed. This is commonly seen in patients with infective endocarditis where valve replacement remains performed in many cases. In selected patients, however, leaflet patch reconstruction might offer an alternative to valve replacement. In such cases, destructed native leaflet tissue is replaced by autologous or heterologous tissue. However, the materials used differ from native leaflet tissue and have been shown to be prone to retraction and calcification [18-20]. Moreover, in the case of heterologous materials, an immune response to the implanted tissue can occur and result in repair failure [21, 22]. While valve repair with patch techniques offers a promising alternative to valve replacement, patch degeneration can limit the expected clinical benefit of valve repair and has, in the case of certain patch materials, even been shown to result in an unacceptably high rate of valve reintervention [21]. Therefore, new patch alternatives as well as critical evaluation of their performance in the setting of reconstructive valve surgery are needed.

These aspects of reconstructive mitral valve surgery will be studied and discussed in the following chapters.

REFERENCES

[1] Mazine A, Friedrich JO, Nedadur R, Verma S, Ouzounian M, Juni P et al. Systematic review and meta-analysis of chordal replacement versus leaflet resection for posterior mitral leaflet prolapse. J Thorac Cardiovasc Surg 2018;155:120-28 e10.

[2] Mihos CG, Yucel E, Santana O. A systematic review and meta-analysis of chordal replacement versus leaflet resection for isolated posterior mitral valve prolapse. J Cardiovasc Surg (Torino) 2017;58:779-86.

[3] Choi A, McPherson DD, Kim H. Biomechanical evaluation of the pathophysiologic developmental mechanisms of mitral valve prolapse: effect of valvular morphologic alteration. Med Biol Eng Comput 2016;54:799-809.

[4] Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg 1983;86:323-37.

[5] Chan V, Chu MWA, Leong-Poi H, Latter DA, Hall J, Thorpe KE et al. Randomised trial of mitral valve repair with leaflet resection versus leaflet preservation on functional mitral stenosis (The CAMRA CardioLink-2 Trial). BMJ Open 2017;7:e015032.

[6] Jahren SE, Hurni S, Heinisch PP, Winkler B, Obrist D, Carrel T et al. Transvalvular pressure gradients for different methods of mitral valve repair: only neochordoplasty achieves native valve gradients. Interact Cardiovasc Thorac Surg 2018;26:248-55.

[7] Tomšič A, Klautz RJM, Palmen M. eComment. Posterior mitral valve leaflet prolapse: one term, several different meanings. Interact Cardiovasc Thorac Surg 2018;26:256.

[8] Mesana TG, Lam BK, Chan V, Chen K, Ruel M, Chan K. Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: potential affect on surgical strategy. J Thorac Cardiovasc Surg 2013;146:1418-23; discussion 23-5.

[9] Murashita T, Greason KL, Suri RM, Daly RC, Joyce LD, Stulak JM et al. Mitral valve gradient after valve repair of degenerative regurgitation with restrictive annuloplasty. J Thorac Cardiovasc Surg 2016;151:106-9.

[10] Ma W, Shi W, Wu W, Ye W, Kong Y, Zhu D et al. Elevated gradient after mitral valve repair: The effect of surgical technique and relevance of postoperative atrial fibrillation. J Thorac Cardiovasc Surg 2018.

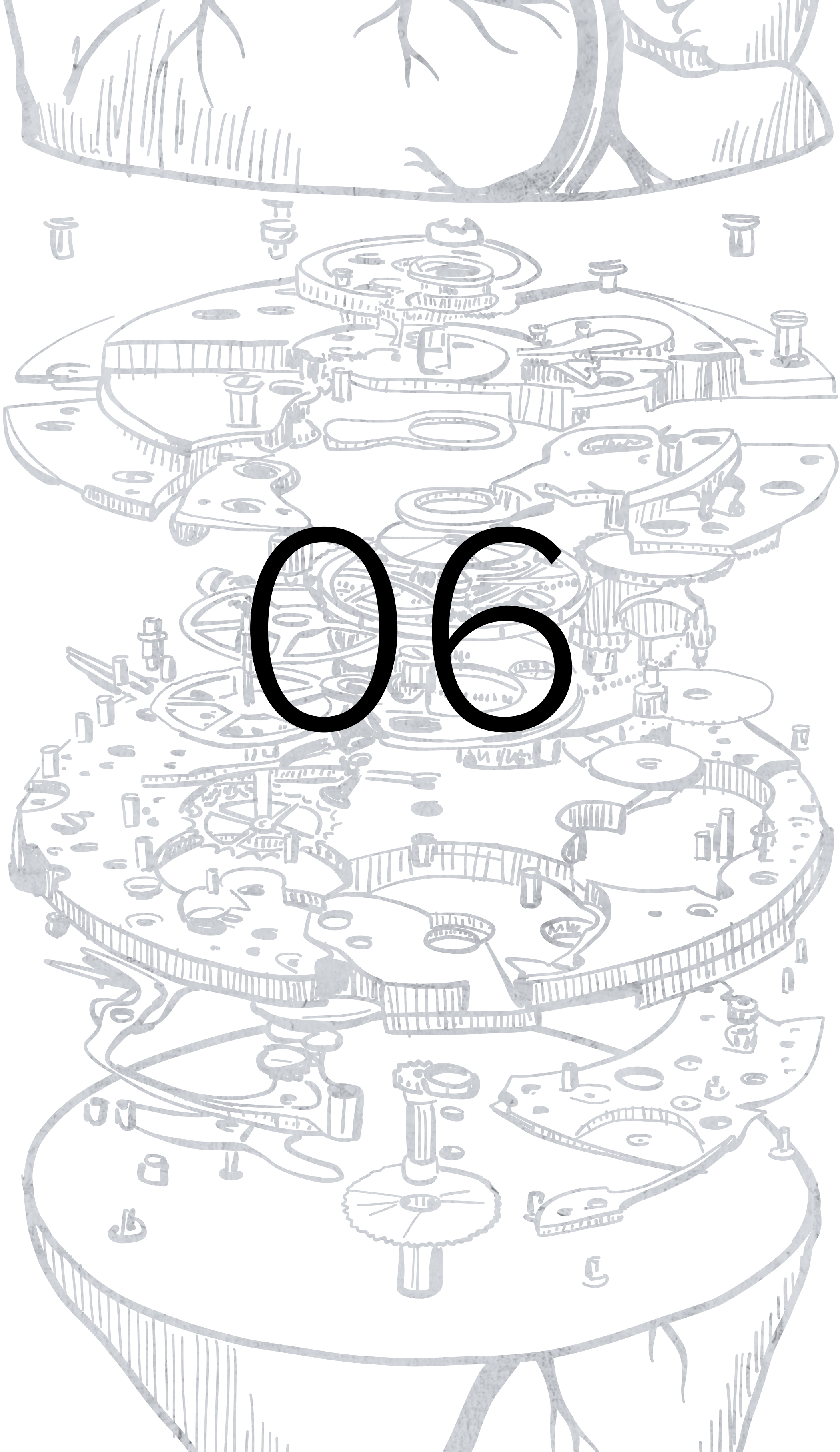
[11] Dagum P, Timek T, Green GR, Daughters GT, Liang D, Ingels NB, Jr. et al. Three-dimensional geometric comparison of partial and complete flexible mitral annuloplasty rings. J Thorac Cardiovasc Surg 2001;122:665-73.

[12] Bothe W, Kvitting JP, Swanson JC, Goktepe S, Vo KN, Ingels NB et al. How do annuloplasty rings affect mitral leaflet dynamic motion? Eur J Cardiothorac Surg 2010;38:340-9.

[13] Tomšič A, Palmen M, Klautz RJM. The devil is in the details, not the ring. J Thorac Cardiovasc Surg 2019.

[14] Dreyfus GD, Aubert S. Should mitral valve prolapse, even though commissural, be treated by suturing both leaflets together? Ann Thorac Surg 2006;81:2339; author reply 39-40.

[15] Dreyfus G, Al Ayle N, Dubois C, de Lentdecker P. Long term results of mitral valve repair: posterior papillary muscle repositioning versus chordal shortening. Eur J Cardiothorac Surg 1999;16:81-7.
[16] Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. J Thorac Cardiovasc Surg 1996;111:718-29; discussion 29-30.
[17] Gillinov AM, Blackstone EH, Nowicki ER, Slisatkorn W, Al-Dossari G, Johnston DR et al. Valve repair versus valve replacement for degenerative mitral valve disease. J Thorac Cardiovasc Surg 2008;135:885-93, 93 e1-2.
[18] Fukunaga N, Matsuo T, Saji Y, Imai Y, Koyama T. Mitral Valve Stenosis Progression Due to Severe Calcification on Glutaraldehyde-Treated Autologous Pericardium: Word of Caution for an Attractive Repair Technique. Ann Thorac Surg 2015;99:2203-5.
[19] Fukunaga N, Sakata R, Koyama T. Reoperative analysis after mitral valve repair with glutaraldehyde-treated autologous pericardium. Interact Cardiovasc Thorac Surg 2017;25:912-17.
[20] David TE. Invited Commentary. Ann Thorac Surg 2017;103:120-21.
[21] Kelley TM, Jr., Kashem M, Wang H, McCarthy J, Carroll ND, Moser GW et al. Anterior Leaflet Augmentation With CorMatrix Porcine Extracellular Matrix in Twenty-Five Patients: Unexpected Patch Failures and Histologic Analysis. Ann Thorac Surg 2017;103:114-20.
[22] Zaidi AH, Nathan M, Emani S, Baird C, del Nido PJ, Gauvreau K et al. Preliminary experience with porcine intestinal submucosa (CorMatrix) for valve reconstruction in congenital heart disease: histologic evaluation of explanted valves. J Thorac Cardiovasc Surg 2014;148:2216-4, 25 e1.



06

Papillary muscle head repositioning for commissural prolapse in degenerative mitral valve disease

Anton Tomšič; Robert J.M. Klautz; Thomas J. van Brakel; Nina Ajmone Marsan; Michel I.M. Versteegh; Meindert Palmen

Interact Cardiovasc Thorac Surg. 2018;27(1):124-130

ABSTRACT

Background. Surgical correction of commissural mitral valve prolapse can be challenging. Several surgical techniques, including commissural closure, leaflet resection with sliding plasty and chordal replacement, remain commonly in use. Conversely, papillary muscle head repositioning remains uncommonly utilized for the treatment of commissural prolapse.

Methods. Between January 2003 and December 2015, 518 patients underwent primary mitral valve repair for severe degenerative mitral valve regurgitation at our institution. Among these, 116 patients had non-isolated commissural prolapse (14 anterolateral, 82 posteromedial, and 20 bicommissural prolapse). Eighty-eight patients underwent papillary muscle head repositioning and presented the study cohort.

Results. Mean patient age was 62.8±12.5 years and 32 (36%) patients were female. Postoperative echocardiography showed no residual mitral regurgitation in all but 1 (1%) patient in whom Grade 2+ regurgitation was seen. The freedom from late reintervention rates at 5 and 10 years were 96.1% (95% CI 91.8%-100%), and 92.7% (95% CI 86.4%-99.0%), respectively. Upon reoperation, no recurrent commissural prolapse was observed. Echocardiographic follow-up demonstrated excellent valve repair durability. The freedom from Grade ≥2+ mitral regurgitation rates at 5 and 10 years were 92.6% (95% CI 86.3%-98.9%) and 86.1% (95% CI 76.7%-95.5%), respectively.

Conclusions. Papillary muscle head repositioning for the treatment of commissural mitral valve prolapse is a reproducible and reliable technique that provides excellent long-term results.

INTRODUCTION

Mitral valve repair for degenerative mitral valve disease provides good early and late outcomes [1]. As a result of widespread utilization of standardized techniques to address specific lesions, the reproducibility and durability of valve repair for degenerative mitral valve disease have improved over time. However, commissural prolapse remains technically challenging and several techniques, including commissural closure, leaflet resection with sliding and chordal replacement, have been described to address this issue [2-8].

When the subvalvular apparatus is preserved and prolapse is a consequence of chordal or papillary muscle elongation, papillary muscle head repositioning presents an alternative to these techniques [9]. Dreyfus et al. originally described this technique and demonstrated its excellent durability [10, 11]. Additionally, the versatility of this technique was described as it can be applied to any prolapsing segment of the mitral valve, provided that the subvalvular apparatus is of sufficient quality. In the setting of commissural prolapse, papillary muscle head repositioning offers the advantage of preserving the largest possible mitral valve orifice area. Surprisingly, based on the current literature, the technique seems largely underutilized [2-7]. To date, data on the early and late results of this technique in the setting of commissural prolapse remain scarce.

The aim of this study was to analyze the results of a papillary muscle head repositioning-oriented approach to commissural prolapse. We analyze (I) the feasibility of papillary muscle head repositioning for commissural prolapse and (II) the early and late clinical and echocardiographic outcomes.

METHODS

Patients

Between January 2003 and December 2015, 518 consecutive patients without a history of previous cardiac surgery underwent mitral valve repair for mitral regurgitation (MR) due to degenerative mitral valve disease at our institution. Commissural prolapse (limited- involving the commissural scallop only and measuring ≤5mm of leaflet margin; extensive- involving the commissural leaflet and either 1 or both paracommissural areas) was defined as described by Carpentier et al. [12].

One hundred and sixteen patients had non-isolated commissural prolapse- 14 anterolateral, 82 posteromedial, and 20 bicommissural prolapse (total number of commissural lesions= 136). In 11 cases, commissural prolapse was caused by chordae rupture or fibrosis, rendering papillary muscle head repositioning technically not feasible. In the remaining 125 commissural lesions, this was successfully addressed with papillary muscle head repositioning in 102 (82%) cases (**Table I**). Papillary muscle head repositioning was unsuccessfully attempted (residual prolapse) in 2 patients with prolapse of the anterolateral commissure; in both patients, commissural closure was performed instead. Because of anatomical reasons (n=1), calcification or fibrosis of the commissural segment (n=3) or according to surgeon preference (n=17), papillary muscle head repositioning was not attempted and another technique was used. In the latter cases, only limited commissural prolapse (without prolapse of the adjacent parts of the anterior and/or posterior mitral valve leaflet) was present that was suitable for correction by either the magic stitch technique or very limited commissural closure.

TABLE I. Overview of the site of commissural lesion (number of lesions=125) and surgical techniques used to address this for patients (n=105) with an intact subvalvular apparatus.

	Papillary muscle head reposition	Commissural plasty	PTFE neochords implantation	Papillary muscle shortening
Posteromedial commissure (n=73)	63 (86)	6 (8)	2 (3)	2 (3)
Anterolateral commissure (n=12)	6 (50)	5 (42)	1 (8)	0 (0)
Bicommissural (n=20)				
Posteromedial commissure (n=20)	18 (90)	2 (10)	0 (0)	0 (0)
Anterolateral commissure (n=20)	15 (71)	4 (20)	1 (5)	0 (0)
Combined (n=125)	102 (82)	17 (13)	4 (3)	2 (2)

Data are presented as n (%). Abbreviations: PTFE: polytetrafluoroethylene.

Eighty-eight patients in whom papillary muscle head repositioning was performed to address commissural prolapse presented the final study cohort. This includes 5 patients with bicommissural prolapse in whom this technique was combined with a different technique on the contralateral commissure. The preoperative patient characteristics are listed in **Table II**; in the final study cohort, 14 (16%) patients demonstrated limited commissural prolapse only.

TABLE II. Baseline characteristics.

Characteristic	Value (N=88)
Age (years)	62.8±12.5
Female gender	32 (36)
NYHA class	
I	30 (34)
II	43 (49)
III/IV	15 (17)
Atrial fibrillation	38 (43)
Renal impairment	
Moderate (CC 50-85 ml/min)	42 (48)
Severe (CC <50 ml/min)	5 (6)
Hypertension	44 (50)
Chronic lung disease	7 (8)
History of TIA or CVA	5 (6)
Peripheral vascular disease	1 (1)
Diabetes mellitus	4 (5)
Left ventricular end-diastolic diameter (mm)	57.3±7.2
Left ventricular end-systolic diameter (mm)	34.7±6.8
Impaired left ventricular ejection fraction (≤60%)	29 (33)
Range of commissural prolapse	
Extensive commissural prolapse	74 (84)
Limited commissural prolapse	14 (16)

Data are presented as n (%). Abbreviations: CC: creatinine clearance; CVA: cerebrovascular accident; NYHA: New York Heart Association; TIA: transient ischemic attack.

The study was approved by our Institutional Ethics Committee. Preoperative, intraoperative and postoperative data were prospectively collected in our computerized database and retrospectively analyzed. Intraoperative transesophageal and postoperative transthoracic echocardiography was standardly performed by an experienced cardiologist to document the intraoperative and postoperative result of mitral valve repair. Follow-up data were collected through clinical visits at our institution or affiliated clinics and hospitals and through questionnaires to patients.

Study endpoints

Early mortality was defined as mortality within 30-days after the operation or during the index hospitalization. Postoperative mortality and morbidity endpoints were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery, and European Association for Cardio-Thoracic Surgery Guidelines [13]. The severity of MR was evaluated using a multi-parametric integrative approach, including qualitative and quantitative assessments as currently recommended [14]. The severity of MR was graded on a 4-grade scale: Grade 1+ (mild), Grade 2+ (moderate), Grade 3+ (moderate-to-severe) and Grade 4+ (severe). The follow-up echocardiograms were re-evaluated by an experienced cardiologist (N.A.M.) for cases in which any significant MR was observed.

Surgical technique

All patients were operated through median sternotomy using standard techniques for extracorporeal circulation with ascending aortic and bicaval cannulation. Intermittent antegrade and retrograde warm blood cardioplegia was used for cardiac protection. The mitral valve was exposed via the trans-septal approach in most patients.

The technique of papillary muscle head repositioning has previously been described by Dreyfus et al. [10, 15]. We have previously shown the technical execution of this technique in patients with commissural prolapse [16]. In short, the papillary muscle head providing chordal support to the prolapsing commissure can be identified by the presence of fan-like chordae terminating at the free edge of the commissural scallop (**Figure 1**). First, the corresponding portion of the muscle head is split vertically. The desired amount of downward displacement towards the apex of the left ventricle corresponds to the height of prolapse determined on surgical analysis. Thereafter, a pericardial pledgeted 4-0 polypropylene U suture is placed in the mobilized papillary muscle head. This is then resutured to the base of the remaining papillary muscle head.

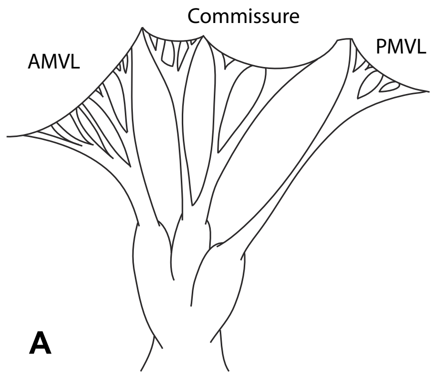


FIGURE 1. Schematic presentation of the papillary muscle head repositioning technique.

Additional mitral valve repair techniques and procedures performed are presented in **Table III**. Posterior mitral valve leaflet prolapse was addressed with quadrangular resection combined with posterior annulus plication (early in our series) or leaflet sliding technique (later in our series). Residual posterior mitral valve leaflet prolapse was addressed with the implantation of neochords. When the extent of excessive tissue was less pronounced, a more limited (triangular) resection and/or implantation of neochords were performed. Anterior mitral valve leaflet prolapse was addressed predominantly with the implantation of neochords. Ring annuloplasty was performed in all cases.

Statistical analysis

Continuous data are presented as mean ± standard deviation for normally distributed data or median and interquartile range (IQR) when not normally distributed. Categorical data are presented as counts and percentages. Survival and freedom from time-related events were estimated using the Kaplan-Meier method. Statistical analysis was performed using the IBM Statistics for Windows, version 23.0 (SPSS, Inc., IBM Corporation, Armonk, NY, USA).

TABLE III. Intraoperative data.

Variable	Value
Commissure (number of lesions=125)	
Papillary muscle head repositioning	120 (96)
Commissural plasty*	4 (3)
PTFE neochords*	1 (1)
Posterior mitral valve leaflet	
Triangular or quadrangular resection	22 (75)
Chordal shortening	1 (1)
Chordal transfer	3 (3)
PTFE neochords	23 (26)
Leaflet sliding	50 (57)
Indentation closure	13 (15)
Anterior mitral valve leaflet	
Triangular resection	1 (1)
Chordal shortening	1 (1)
Chordal transfer	2 (2)
PTFE neochords	45 (51)
Annulus	
Posterior annulus plication	36 (41)
Annular decalcification	9 (10)
Annuloplasty	88 (100)
Annuloplasty	
Physio ring[a]	68 (78)
Physio II ring[a]	16 (18)
Carpentier Classic[a]	1 (1)
Memo 3D[b]	2 (2)
Simulus semi rigid[c]	1 (1)
Annuloplasty ring size (mm)	
24-30	9 (10)
32-36	54 (50)
38-40	25 (40)
Concomitant procedures	
Tricuspid valve repair	53 (60)
Radiofrequency ablation for atrial fibrillation	35 (40)
Coronary artery bypass grafting	18 (21)
Aortic valve or root intervention	5 (6)
Ascending aorta replacement	3 (3)

*Data are presented as n (%). * In 5 patients with bi-commissural prolapse, papillary muscle head repositioning was combine with a different technique on the contralateral commissure. [a] Edwards Lifesciences, Irvine, CA, USA. [b] LivaNova, London, UK. [c] Medtronic, Inc, Minneapolis, MN, USA.*

RESULTS

Early clinical and valve-related results

There were 2 (2.3%) early deaths. The cause of death was multiple organ dysfunction syndrome, which developed as a consequence of severe postoperative distributive shock in 1 patient and periprocedural myocardial infarction resulting in acute biventricular failure in 1 patient.

Postoperative transthoracic echocardiography showed none or trivial MR in 73 (85%), mild (Grade 1+) MR in 12 (14%) and moderate (Grade 2+) MR in 1 (1%) patient. In the latter patient, who refused early reoperation, residual regurgitation was a consequence of posterior mitral valve leaflet restriction. Hemodynamically significant systolic anterior motion of the anterior mitral valve leaflet was absent in all patients.

Late clinical results

The median survival follow-up was 9.7 years (IQR 5.0-11.8) and was 99% complete (1 patient was lost to follow-up because of emigration). There were 18 late deaths. The cumulative actuarial survival rates at 1, 5, and 10 years were 94.3% [95% confidence interval (CI) 89.4%-99.2%], 89.2% (95% CI 82.5%-95.9%), and 74.3% (95% CI 64.1%-84.5%), respectively (**Figure 2**). The cause of death was end-stage heart failure in 1 patient (poor left ventricular function without significant recurrent MR was seen in this patient), intracranial bleeding in 1 patient, sudden unexplained death in 6 patients and ventricular fibrillation in 1 patient. One patient died due to an acute type A aortic dissection, 8 years after the initial operation. The patient underwent an emergent reoperation at another institution and died during the reoperation. The cause of death was not cardiac related in 8.

There were 5 thromboembolic events, 2 cerebrovascular accidents and 3 transient ischemic attacks. Four severe bleeding events occurred, including 1 case of intracranial bleeding resulting in death. In this patient, atrial fibrillation was the indication for long-term oral anticoagulation, and intracranial bleeding occurred at a supra-therapeutic international normalized ratio value. No cases of operated valve endocarditis occurred.

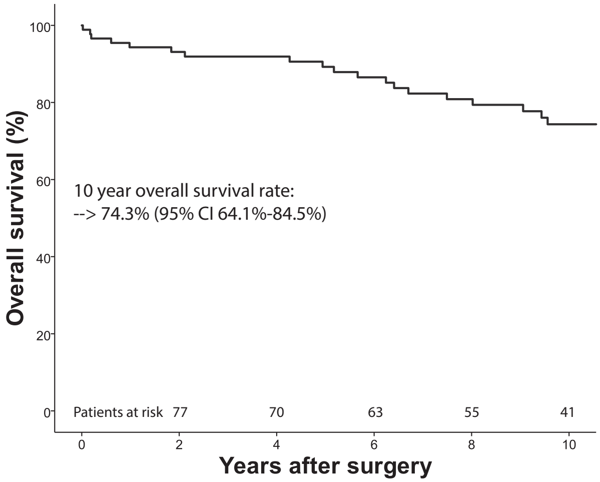


FIGURE 2. Overall survival.

Freedom from reintervention and recurrent mitral regurgitation

Five patients required late mitral valve reintervention during the follow-up period. The freedom from late reintervention rates at 1, 5, and 10 years were 98.7% (95% CI 96.2%-100%), 96.1% (95% CI 91.8%-100%), and 92.7% (95% CI 86.4%-99.0%), respectively (**Figure 3**). The indication for reintervention was recurrent MR in 4 patients and mitral valve stenosis in 1 patient (**Table IV**). Upon reoperation, no cases of recurrent commissural prolapse were documented. However, in 1 patient, in whom recurrent MR was a consequence of a combined *de novo* anterior mitral valve leaflet prolapse and posterior mitral valve leaflet restriction, surgical inspection revealed that posterior mitral valve leaflet restriction was partially caused by traction from the repositioned papillary muscle head. This observation was not encountered in any other patient.

The median echocardiographic follow-up time was 8.7 years (IQR 3.1-10.7) and was available in 91% of patients. Eleven (14%) patients developed recurrent MR during the follow-up period; at last follow-up echocardiography, 4 (5%) patients demonstrated Grade 2+ MR and 7 (9%) patients demonstrated ≥Grade 3+ MR. The freedom from ≥Grade 2+ MR rates at 1, 5, and 10 years were 97.5% (95% CI 94.0%- 100%), 92.6% (95% CI 86.3%- 98.9%), and 86.1% (95% CI 76.7%-95.5%), respectively. The freedom from ≥Grade 3+ MR rates at 1, 5, and 10 years were 98.7% (95% CI 96.2%-100%), 93.8% (95% CI 87.9%-99.7%), and 91.9% (95% CI 84.8%-98.9%), respectively (**Figure 3**). Four of the

7 (57%) patients in whom recurrent, ≥grade 3+ MR was seen underwent mitral valve reoperation. The other 3 (43%) patients were still alive and free from reoperation at the time of last follow-up.

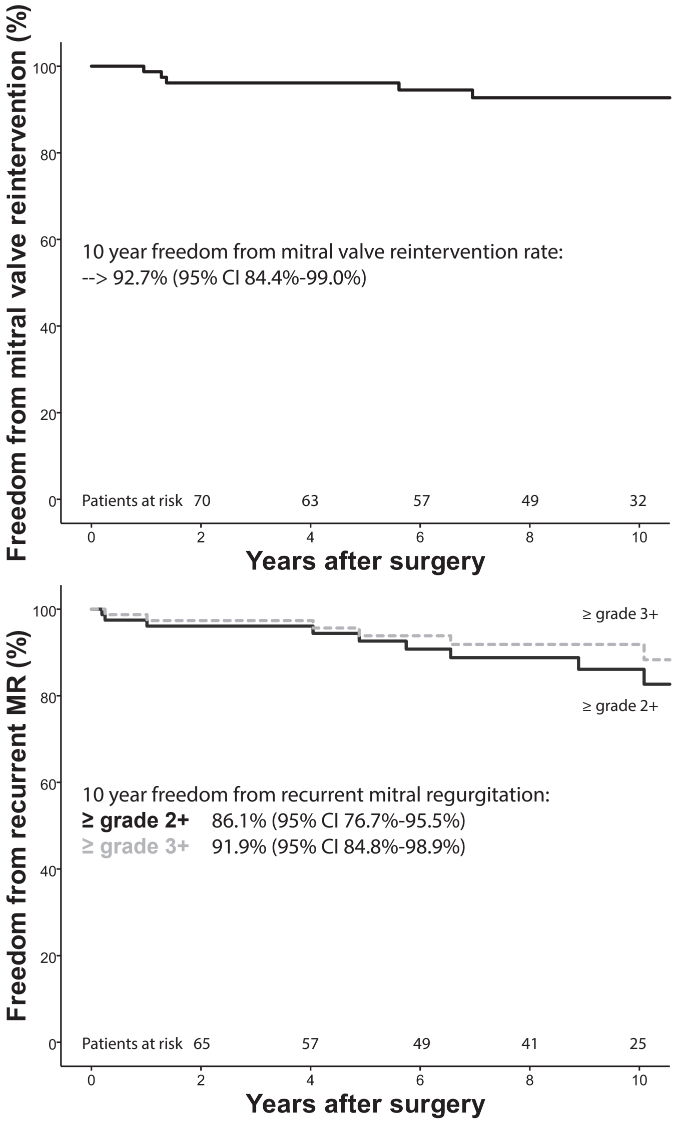


FIGURE 3. **Above:** freedom from late mitral valve reintervention. **Below:** freedom from ≥Grade 2+ and ≥Grade 3+ recurrent mitral regurgitation.

TABLE IV. Details on late reoperation.

	Year of initial surgery	Time to reoperation (years)	Indication for reoperation	Perioperative findings	Procedure performed	Outcome
1	2005	5.6	Recurrent MR	Ring dehiscence	MV re-repair	Survived
2	2005	1.4	Recurrent MR	AMVL restriction + PMVL pseudoprolapse	MV replacement	Survived
3	2005	1.0	Recurrent MR	PMVL restriction	MV replacement	Survived
4	2006	7.0	Recurrent MR	AMVL pseudoprolapse + PMVL restriction (partially a consequence of traction from the repositioned papillary muscle head)	MV replacement	Survived
5	2010	1.3	Mitral valve stenosis	Severe pannus formation	MV re-repair	Survived

Abbreviations: AMVL: anterior mitral valve leaflet; MR: mitral regurgitation; MV: mitral valve; PMVL: posterior mitral valve leaflet

Of the 14 patients with only isolated commissural prolapse, follow-up echocardiography was available in 13 [93%, mean follow-up 6.4 (IQR 3.0-9.5) years]. No recurrent MR was seen in any of these patients. One patient underwent late reoperation due to mitral valve stenosis, developing as a consequence of severe pannus formation.

DISCUSSION

Our data demonstrate that papillary muscle head repositioning presents a reproducible and reliable option for the treatment of commissural prolapse in patients with degenerative mitral valve disease. Furthermore, this technique can be used to address the majority of commissural lesions in these patients.

The technique of papillary muscle head repositioning was originally described by Dreyfus et al [11, 15]. They have compared the results of posterior papillary muscle head repositioning (n=60) against chordal shortening (n=40) in the posterior paramedial and paracommissural area in patients with non-isolated anterior mitral valve leaflet prolapse. At a mean follow-up of 26.4±24.2 months, excellent repair durability with low reoperation rates were reported with the papillary muscle head repositioning technique

[11]. Surprisingly, despite the documented good long-term results and versatility of this technique, this does not seem to be commonly in use to treat commissural lesions [2-5, 8].

We currently utilize papillary muscle head repositioning as the technique of choice for commissural prolapse in degenerative mitral valve disease. Due to evident reasons, this technique cannot be performed when the native chordae are ruptured or otherwise considered unsuitable for a durable repair. In these patients, we tend to address commissural prolapse with either commissural plasty or chordal replacement. In the absence of any of these observations, papillary muscle head repositioning is technically feasible in the vast majority of patients with degenerative mitral valve disease. In our experience, papillary muscle head repositioning was relatively less often performed at the level of the anterolateral commissure when compared to the posteromedial one. This is due to the fact that prolapse is normally less extensive at the level of the anterolateral commissure, making commissural prolapse at the anterolateral commissure repairable with a single magic stitch or very limited commissural closure. Hampered by the retrospective study design, we reason that the demonstrated percentage of patients in whom papillary muscle head repositioning was feasible in our experience is likely underestimated. The technique does necessitate a certain level of expertise, in particular at assessing the amount of leaflet prolapse and corresponding amount of papillary muscle head displacement needed. In our experience, all operations were performed by experienced mitral valve surgeons. Importantly, the technique was reproducible and a steep learning curve was observed even in surgeons previously unfamiliar with this technique.

In degenerative mitral valve disease, commissural prolapse is almost always accompanied by prolapse of the adjacent segments of the anterior and/or posterior mitral valve leaflet, an observation supported by our data and others as well [5, 12]. This prevented us to study the feasibility and durability of papillary muscle head repositioning only in cases of isolated commissural prolapse. However, as such cases are very rare, papillary muscle head repositioning should be seen as a technique complementary to other techniques performed to secure valve competency. Directly addressing the commissural region as a functional whole is an advantage of the papillary muscle head repositioning technique when compared to other techniques.

Previous studies have demonstrated changes in biochemical and mechanical properties of the myxomatous mitral valve chordae [17, 18]. In particular, increased glycosaminoglycan content is responsible for the characteristic thickened appearance of the degenerated chordae. This also negatively alters their mechanical characteristics, causing them to fail at lower loads than normal mitral valve chordae [17]. As papillary muscle head repositioning includes preservation of these degenerated chordae, concerns on their long-term durability are justified. Clinical and echocardiographic follow-up in our patients demonstrated a low incidence of mitral valve reintervention and recurrent MR. Recurrent commissural prolapse was absent in all patients who underwent late reoperation. This makes us believe that despite impaired mechanical properties, chordae tendinae of degenerated mitral valves are suitable for a long-lasting repair. Our results, therefore, support the durability of the papillary muscle head repositioning technique previously described by Dreyfus et al. [10, 11, 15]. Furthermore, our results provide additional evidence on the long-term durability, reproducibility and versatility of this technique. Upon reoperation, retraction of the posterior mitral valve leaflet occurred secondary to excessive traction from the repositioned papillary muscle head in 1 patient. This could present a consequence of fibrotic changes of the papillary muscle following its mobilization and manipulation. As this was not seen in any other patient, we reason that the risk of developing this complication is low.

Commissural closure has been proposed as a technically non-challenging option to address commissural prolapse [3, 8]. De Bonis et al. previously reported their experience with 125 patients undergoing commissural closure with annuloplasty for isolated commissural prolapse [3]. They demonstrated excellent valve repair durability. Furthermore, follow-up echocardiography demonstrated low mean resting mitral valve gradients and no patients needed mitral valve reintervention for mitral valve stenosis during the follow-up period. On the other hand, others have reported modifications of this technique as recurrent MR can occur due to leaflet tearing [19]. Commissural closure will inevitably distort normal leaflet motion and induce excessive stress on the sutures and mitral valve leaflets. This implies that the technique –while considered technically not challenging- requires a certain level of expertise and might only be suited for cases of limited commissural prolapse. Commissural prolapse, on the other hand, most commonly occurs in combination with prolapse of the anterior and/or posterior mitral valve leaflet and is typically seen in patients with forme fruste or Barlow's disease.

Commissural closure inevitably results in a significant reduction of the circumference of the mitral valve opening area, leading to a 30% to 40% reduction of the mitral valve orifice area and possibly favoring dynamic mitral valve stenosis [8, 9]. Papillary muscle head repositioning, on the other hand, restores normal leaflet motion, allows for a good surface area of leaflet coaptation, and does not reduce the mitral valve orifice area [9]. This provides a clear advantage over the commissural closure technique. It has previously been demonstrated that annuloplasty itself can cause exercise-induced mitral valve stenosis in cases of low indexed ring orifice area [20]. Efforts to preserve the maximal mitral valve orifice area seem to be justified.

As an alternative to papillary muscle head repositioning, leaflet resection with or without leaflet sliding can be performed to treat commissural prolapse. Shimizu et al. reported their experience with 122 patients with commissural prolapse [5]; leaflet resection was performed in 111 (91%) patients and was accompanied by leaflet sliding in 43 (35%) of these. They demonstrated good long-term valve repair durability with low reoperation and recurrent MR rates. We rarely utilize this technique in the setting of commissural prolapse in degenerative mitral valve disease as it is technically more challenging than other options that provide comparable results. However, in the uncommon cases of annular and leaflet calcification at the height of the commissural region, leaflet resection with sliding or commissural reconstruction might be unavoidable.

In case of ruptured native chordae tendineae, chordal replacement presents a reasonable primary alternative repair technique. This technique has documented good long-term durability and is also suitable as a primary strategy to address commissural prolapse in the setting of degenerative mitral valve disease [21]. In cases of degenerative mitral valve disease (and particularly Barlow's disease where commissural prolapse is most frequently present), the commissure is usually affected as a functional whole and leaflet prolapse expands to the adjacent parts of the anterior and/or posterior leaflet segments. As chordal replacement is targeted at resolving leaflet prolapse of only a limited length of the leaflet free edge, multiple neochords would be needed to address this issue. Therefore, we prefer to utilize papillary muscle head repositioning as a primary treatment strategy in this setting as a single maneuver can effectively resolve the issue. This characteristic also provides an additional benefit over surgical techniques (e.g. small leaflet resection or leaflet foldoplasty) that focus on the commissure only. As another alternative, chordal shortening can be performed in cases where native chordae are intact and considered suitable for a durable valve repair. This technique, however, is technically challenging, making it less attractive than the papillary muscle head repositioning technique [11].

In this study, we have focused only on patients who demonstrated commissural prolapse during echocardiographic and surgical valve analysis. In a small proportion of patients, there were some doubts regarding the extensiveness of changes in the commissural region. Typically very limited prolapse was seen in these patients and papillary muscle head repositioning was not primarily considered or performed. In several of these cases, residual commissural prolapse or billowing was seen on the saline test and addressed with commissural plasty or implantation of neochords as this needs to be resolved to secure optimal repair durability. Papillary muscle head repositioning presents a valuable technique in these cases as well and an aggressive approach to billowing of the commissures seems in our opinion justified.

LIMITATIONS

This is a single-center study with limitations inherent to the study design. Papillary muscle head repositioning was not initially considered in all patients with commissural prolapse. Therefore, the true feasibility of this technique might be underestimated. Not all patients were followed-up prospectively at our institution after undergoing surgery, resulting in differences in the frequency of clinical and echocardiographic follow-up. To overcome this shortcoming, echocardiographic studies in cases where any significant MR was reported were reassessed for regurgitation severity by an experienced cardiologist. We reason that any recurrent commissural prolapse would result in ≥Grade 2+ recurrent MR and thus be detected during follow-up. Due to the low number of patients in whom commissural abnormalities were addressed with repair techniques other than papillary muscle head repositioning, a comparison between both groups was not feasible. The durability of papillary muscle head repositioning seen in our experience is however in line with previous studies on this matter and supports the previously demonstrated good results of this technique.

CONCLUSIONS

Papillary muscle head repositioning is a reproducible technique that can effectively resolve commissural prolapse in in the majority of patients with degenerative mitral valve disease. The technique provides excellent long-term durability and the occurrence of recurrent commissural prolapse is highly unlikely.

REFERENCES

[1] David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation 2013;127:1485-92.

[2] Aubert S, Barreda T, Acar C, Leprince P, Bonnet N, Ecochard R et al. Mitral valve repair for commissural prolapse: surgical techniques and long term results. Eur J Cardiothorac Surg 2005;28:443-7.

[3] De Bonis M, Lapenna E, Taramasso M, Pozzoli A, La Canna G, Calabrese MC et al. Is commissural closure associated with mitral annuloplasty a durable technique for the treatment of mitral regurgitation? A long-term (</=15 years) clinical and echocardiographic study. J Thorac Cardiovasc Surg 2014;147:1900-6.

[4] Lapenna E, De Bonis M, Sorrentino F, La Canna G, Grimaldi A, Torracca L et al. Commissural closure for the treatment of commissural mitral valve prolapse or flail. J Heart Valve Dis 2008;17:261-6.

[5] Shimizu A, Kasegawa H, Tabata M, Fukui T, Takanashi S. Long-term outcomes of mitral valve repair for isolated commissural prolapse: up to 17-year experience. Ann Thorac Surg 2015;99:43-7.

[6] Mathieu P, Dagenais F, Saez De Ibarra JI, Baillot R. Surgical treatment of commissural prolapse: case report and review of the options. J Heart Valve Dis 2004;13:142-4.

[7] Morimoto H, Tsuchiya K, Nakajima M, Akashi O, Kato K. Mitral valve repair for extended commissural prolapse involving complex prolapse. Asian Cardiovasc Thorac Ann 2007;15:210-3.

[8] Gillinov AM, Shortt KG, Cosgrove DM, 3rd. Commissural closure for repair of mitral commissural prolapse. Ann Thorac Surg 2005;80:1135-6.

[9] Dreyfus GD, Aubert S. Should mitral valve prolapse, even though commissural, be treated by suturing both leaflets together? Ann Thorac Surg 2006;81:2339; author reply 39-40.

[10] Dreyfus GD, Souza Neto O, Aubert S. Papillary muscle repositioning for repair of anterior leaflet prolapse caused by chordal elongation. J Thorac Cardiovasc Surg 2006;132:578-84.

[11] Dreyfus G, Al Ayle N, Dubois C, de Lentdecker P. Long term results of mitral valve repair: posterior papillary muscle repositioning versus chordal shortening. Eur J Cardiothorac Surg 1999;16:81-7.

[12] Carpentier A, Adams, DH, Filsoufi, F. Reconstructive Valve Surgery. 1st. edn: Saunders, 2010.

[13] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008;33:523-8.

[14] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.

[15] Dreyfus GD, Bahrami T, Alayle N, Mihealainu S, Dubois C, De Lentdecker P. Repair of anterior leaflet prolapse by papillary muscle repositioning: a new surgical option. Ann Thorac Surg 2001;71:1464-70.

[16] Klautz RJ, Tomšič A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in Barlow's disease: the concept of functional prolapse. Multimed Man Cardiothorac Surg 2016;2017.
[17] Barber JE, Ratliff NB, Cosgrove DM, 3rd, Griffin BP, Vesely I. Myxomatous mitral valve chordae. I: Mechanical properties. J Heart Valve Dis 2001;10:320-4.
[18] Grande-Allen KJ, Griffin BP, Calabro A, Ratliff NB, Cosgrove DM, 3rd, Vesely I. Myxomatous mitral valve chordae. II: Selective elevation of glycosaminoglycan content. J Heart Valve Dis 2001;10:325-32; discussion 32-3.
[19] Higuchi K, Koseni K, Inaba H, Osawa H, Kinoshita O, Takamoto S. Reinforced edge-to-edge commissural closure with mitral valvuloplasty. J Card Surg 2007;22:137-8.
[20] Doi K, Yamano T, Ohira S, Yamazaki S, Numata S, Yaku H. Annuloplasty Ring Size Determines Exercise-Induced Mitral Stenosis Severity after Valve Repair. J Heart Valve Dis 2015;24:744-51.
[21] David TE, Armstrong S, Ivanov J. Chordal replacement with polytetrafluoroethylene sutures for mitral valve repair: a 25-year experience. J Thorac Cardiovasc Surg 2013;145:1563-9.

07

Excessive leaflet tissue in mitral valve repair for isolated posterior leaflet prolapse- leaflet resection or shortening neochords?

A propensity score adjusted comparison

Anton Tomšič, Yasmine L. Hiemstra, Thomas J. van Brakel, Michel I.M. Versteegh, Nina Ajmone Marsan, Robert J.M. Klautz, Meindert Palmen

J Cardiovasc Surg (Torino). 2019;60(1):111-118

ABSTRACT

Background. Chordal replacement techniques are progressively used to treat posterior mitral valve leaflet (PMVL) prolapse while leaflet resection remains commonly in use to address excessive leaflet tissue. For excessive tissue in height, shortening neochords can be used alternatively. Use of chordal replacement techniques has been suggested to result in lower diastolic transvalvular gradients, higher freedom from reoperation and improved left ventricular function.

Methods. From 1/2005 to 12/2016, 150 patients underwent valve repair for isolated PMVL prolapse with excessive tissue. Excessive tissue in height was treated by leaflet resection (n=99) or shortening neochords (n=51). Excessive tissue in width was always resected. Logistic regression was used to generate propensity scores for risk-adjusted comparison.

Results. Two patients died postoperatively. In the Neochords group, resection of excessive tissue in width was still needed in 28 (55%) cases. Postoperative echocardiography demonstrated residual (≥2+) mitral regurgitation in 2/150 patients (Resect group). No differences in anuloplasty ring size, postoperative diastolic transvalvular gradients or left ventricular function were observed. Median clinical follow-up duration was 4.4 (IQR 2.0-7.0; 98% complete) years. There was no inter-group difference in overall survival or freedom from reintervention. Mean echocardiographic follow-up was 3.0 (IQR 1.2-5.4; 93% complete) years. In the matched population, the 6-year freedom from recurrent mitral regurgitation rates were 91.3% (95% CI 81.9%-100%) and 97.2% (95% CI 91.9%-100%) for the Resect and Neochords group, respectively (P=0.43).

Conclusions. Both leaflet resection and shortening neochords provide a valuable tool to address excessive PMVL height. Repair durability is excellent regardless of the technique utilized.

INTRODUCTION

Mitral valve (MV) repair for isolated posterior MV leaflet (PMVL) prolapse due to degenerative valve disease is highly reproducible and nowadays feasible in almost all cases [1-4]. Cases of isolated PMVL prolapse vary in the extent of excessive leaflet tissue and the status and quality of native chordae tendineae [5]. Mitral valve repair techniques used to treat PMVL prolapse are adapted to these specific characteristics.

The MV repair techniques described by Carpentier focused on PMVL resection to address leaflet prolapse as well as excessive leaflet tissue [6]. Soon thereafter, David was first to demonstrate that extended polytetrafluoroethylene neochords can be used to correct leaflet prolapse occurring due to elongated or ruptured native chordae tendineae [7]. Perier et al. later demonstrated the versatility of chordal replacement techniques in patients with PMVL prolapse by showing that neochords can effectively address not only leaflet prolapse but also excessive PMVL tissue in height [8]. Two recent systematic reviews and meta-analyses speculated that chordal replacement techniques will allow implantation of larger annuloplasty rings and result in improved postoperative left ventricular (LV) function, lower diastolic transvalvular gradients and higher freedom from reoperation when compared to PMVL resection techniques [9, 10]. Such speculations are, however, based on highly heterogeneous patient groups that vary in the extent of excessive tissue. Furthermore, leaflet resection techniques have evolved as annular plication has largely been abandoned while the indication for leaflet resection has shifted primarily to addressing excessive tissue.

The aim of this study was to explore the results of a structured approach to PMVL prolapse and excessive tissue in cases of isolated PMVL prolapse. We further aim to analyze the results of either leaflet resection or implantation of shortening neochords to treat excessive leaflet tissue in height and analyze the early- and mid-term results of both techniques in a propensity score matched analysis.

METHODS

Patients

Between January 2005 and December 2016, 520 patients underwent surgical intervention for severe degenerative MR at our institution. Of these, 185 patients presented with isolated PMVL prolapse and excessive tissue in height and underwent MV repair. Excluding patients who underwent annular plication (n=22) or reduction of excessive PMVL height with a combination of techniques (n=13), 150 patients present the final study cohort. Preoperative, intraoperative and postoperative data were retrospectively collected from our computerized database. Follow-up survival, clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through questionnaires to patients. The study was approved by our Institutional Ethics Committee.

Study endpoints

Early mortality was defined as mortality within 30-days after the operation or during the index hospitalization. Postoperative mortality and morbidity endpoints were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery and European Association for Cardio-Thoracic Surgery Guidelines [11]. The severity of MR was evaluated using a multi-parametric integrative approach, including qualitative and quantitative assessments, as currently recommended [12]. MR severity was graded on a 4-grade scale: grade 1+ (mild), grade 2+ (moderate), grade 3+ (moderate-to-severe) and grade 4+ (severe). Residual and recurrent MR were defined as MR ≥grade 2+. Diastolic transvalvular gradient was calculated using continuous wave Doppler.

Surgical technique

During the study period, a systematic approach to PMVL abnormalities was applied. The PMVL was assessed for the presence of prolapse and quality of the subvalvular apparatus. Thereafter, the affected segment(s) of the PMVL was assessed for excessive leaflet tissue in height and width.

Valve repair was tailored to the extent of leaflet tissue and 3 scenarios were possible (**Figure 1**). When no excessive leaflet tissue was present only abnormal PMVL motion was to be addressed. This was always corrected with implantation of non-shortening neochords. When excessive leaflet tissue was present, this was addressed accordingly. First, the PMVL was assessed for the presence of excessive issue in height and/or width (**Figure 2**). Excessive leaflet tissue in width was assessed by folding the PMVL into the LV. When wrinkling of the affected segment was seen (that would result in PMVL wrinkling at the level of leaflet coaptation and/or leaflet billowing after valve repair was accomplished), this was treated by leaflet resection in all cases (taking into account that

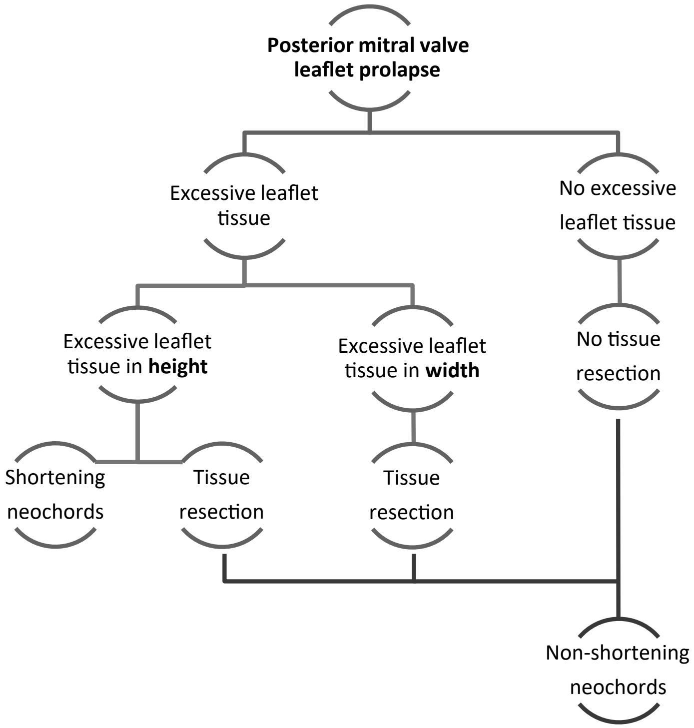


FIGURE 1. A systematic approach to excessive posterior mitral valve leaflet tissue. The leaflet is assessed for the presence of excessive tissue in width and/or height. Excessive tissue in width is always resected. Excessive tissue in height can be treated by either tissue resection or implantation of shortening neochords. Non-shortening neochords are used to resolve any remaining leaflet prolapse.

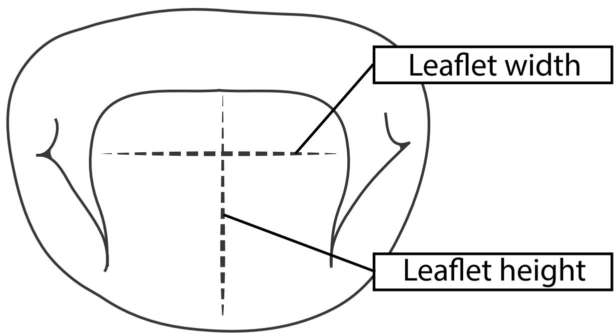


FIGURE 2. Schematic presentation of excessive leaflet tissue of the posterior mitral valve leaflet; excessive tissue in height needs to be distinguished from excessive tissue in width.

neochords cannot address excessive leaflet tissue in width). Redundant leaflet tissue in height was assessed by PMVL inspection- leaflet height ≥20 millimeters was considered excessive. This was address by:

1. Leaflet resection- **Resect group**. Typically, this was combined with resection of excessive tissue in width, resulting in a quadrangular resection of the PMVL. Leaflet integrity was restored by suturing the leaflet remnants together with a 5-0 polypropylene suture and combined with leaflet sliding at the level of leaflet base. This was combined with the implantation of non-shortening neochords –aimed at resolving residual prolapse- in 42 (42%) patients.
2. Shortening neochords- **Neochords group**. In these cases, neochords were used to bring the free edge of the prolapsed area to a lower level, as previously described by Perier et al. [8]. Shortly, neochords were implanted to the free edge of the prolapsing leaflet segment. The length of these was shortened to bring the prolapsed segment under the plane of the annulus and thereby compensate for excess in leaflet height. The final length of these chords was determined on water-test. This was combined with limited triangular leaflet resection (typically shortening the free edge of the affected segments for a few millimeters with care taken to avoid excessive tissue resection that would likely hamper diastolic PMVL motion) to address excessive tissue in width in 28 (55%) patients.

Semi-rigid ring annuloplasty was performed in all cases. Intraoperative echocardiography was performed by an experienced cardiologist to document the result of valve repair.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians (IQR) when not normally distributed. Categorical data are presented as counts and percentages. In the unmatched patient cohort, comparisons between the two groups were performed using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test (skewed data) for continuous variables. Propensity score matching was used to balance the covariates due to the non-randomised study design. For each patient, a propensity score was calculated from a multivariable logistic regression model with covariates as independent variables and group allocation as a binary dependent variable. Patients were matched in a 1:1 matching fashion with a calliper width of 0.10. Covariates included in the propensity score model were: age, gender, body surface area, mean preoperative diastolic transvalvular gradient, annular calcification, LV function, hypertension, and EuroSCORE II. The P-value of the Hosmer-Lemeshow test and the c-statistic of the propensity score model were 0.609 and 0.722, respectively. McNemar's test (categorical variables), paired Student's t-test (normally distributed continuous variables), and Wilcoxon signed-ranked test (skewed continuous variables) were performed for the comparison between the matched groups. Survival and freedom from time-related events were estimated using the Kaplan-Meier method and compared using the log-rank test (stratified for the propensity score in the matched population). Statistical analysis was performed using the IBM Statistics for Windows, version 25.0 (SPSS, Inc., IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline characteristics

Baseline characteristics of the unmatched and matched patient populations are presented in **Table I**. Prior to propensity score matching, a higher incidence of annular calcification was seen in the Resect group (14% vs. 2%, P=0.018). Propensity score matching effectively eliminated any significant differences between both groups and yielded 47 well matched patient pairs.

Early mortality and morbidity

There was 1 death in the Resect and 1 death in the Neochords group. The first patient died due to cardiogenic shock with multi-organ failure. The latter patient (who underwent minimal invasive surgery) failed to wean form cardio-pulmonary bypass due to acute biventricular failure, presumably due to inadequate intraoperative cardioprotection. In general, no statistically significant differences in the early clinical outcomes were observed between both groups in the unmatched and matched patient population (**Table II**).

TABLE I. Baseline characteristics.

	Unmatched population			Matched population		
	Resect group (n=99)	**Neochords group (n=51)**	**P-value**	**Resect group (n=47)**	**Neochords group (n=47)**	**P-value**
Age	64.1±11.0	62.4±12.1	0.70	62.9±12.3	62.4±12.1	0.85
Gender (female)	38 (38)	11 (22)	0.038	12 (26)	10 (21)	0.77
Body surface area	1.95±0.23	1.94±0.24	0.79	1.94±0.19	1.96±0.23	0.57
NYHA class			0.13			0.49
I	27 (27)	19 (37)		13 (28)	17 (36)	
II	50 (50)	27 (53)		28 (59)	25 (53)	
III-IV	22 (22)	5 (10)		6 (13)	5 (11)	
Hypertension	40 (40)	13 (26)	0.070	16 (34)	13 (28)	0.51
Atrial fibrillation	27 (27)	13 (26)	0.82	10 (21)	13 (28)	0.68
Previous cardiac surgery	2 (2)	2 (4)	0.49	0 (0)	2 (4)	0.16
Renal impairment			0.87			0.75
Moderate (CC 85-50 ml/min)	44 (44)	21 (41)		19 (40)	19 (40)	
Severe (CC <50 ml/min)	7 (7)	3 (6)		4 (9)	3 (6)	
History of TIA/CVA	6 (6)	3 (6)	0.97	4 (9)	2 (4)	0.69
Chronic lung disease	11 (11)	6 (12)	0.91	4 (9)	4 (9)	1.00
Diabetes mellitus	2 (2)	0 (0)	0.55	1 (2)	0 (0)	1.00
Pulmonary hypertension (≥50 mmHg)	15 (15)	9 (18)	0.69	5 (11)	9 (20)	0.39
EuroSCORE II	1.73 (IQR 0.93-3.05)	1.36 (IQR 0.89-2.12)	0.33	1.54 (IQR 0.81-2.79)	1.36 (IQR 0.89-2.27)	0.74
Annular calcification	14 (14)	1 (2)	0.018	3 (6)	1 (2)	0.50
Concomitant procedures						
Tricuspid valve repair	51 (51)	19 (37)	0.097	27 (57)	31 (34)	0.027
RF-ablation	22 (22)	9 (18)	0.51	8 (17)	9 (19)	1.00
CABG	20 (20)	7 (14)	0.33	9 (19)	7 (15)	0.77
AVR	3 (3)	1 (2)	0.70	2 (4)	1 (2)	1.00
Thoracic aorta replacement	1 (1)	1 (2)	0.63	1 (2)	1 (2)	1.00

Data are presented as n (%), means ± standard deviation or medians (interquartile range). Abbreviations: AVR: aortic valve replacement; CABG: coronary artery bypass grafting; CC: creatinine clearance; CVA: cerebrovascular accident; NYHA: New York Heart Association; TIA: transient ischemic attack.

TABLE II. Postoperative complications.

	Unmatched population			Matched population		
	Resect group (n=99)	**Neochords group (n=51)**	**P-value**	**Resect group (n=47)**	**Neochords group (n=47)**	**P-value**
Mortality	1 (1)	1 (2)	1.0	0 (0)	1 (2)	1.00
Prolonged intubation (>24 hours)	11 (11)	1 (2)	0.050	4 (9)	1 (2)	0.38
Early reoperation	7 (7)	2 (4)	0.44	3 (6)	1 (2)	0.63
Surgical re-exploration	5 (5)	2 (4)	0.76	2 (4)	1 (2)	1.00
Early valve reoperation	2 (2)	0 (0)	0.55	1 (2)	0 (0)	1.00
Renal failure	0 (0)	1 (1)	0.34	0 (0)	1 (2)	1.00
Permanent stroke	1 (1)	2 (4)	0.27	1 (2)	2 (4)	1.00

Data are presented as n (%).

Early valve-related results

Residual MR was seen in 2/150 (1.3%) patients (Resect group). Both underwent early reoperation. The cause of residual MR was residual PMVL prolapse and residual excessive tissue with PMVL billowing and residual leakage through an open indentation. A MV re-repair was performed in both cases. All other patients demonstrated ≤mild residual MR and no systolic anterior motion on pre-discharge echocardiography.

Interestingly, no significant difference in the size of annuloplasty ring implanted was observed between both groups (**Table III**). Sufficient height of leaflet coaptation was achieved in both groups. There were no significant differences in the postoperative LV end-diastolic diameter and LV ejection fraction between both groups in both the matched and unmatched population.

Late results

Median survival follow-up duration was 4.2 (IQR 1.9-6.8) years and was 99% complete (2 patients were lost to follow-up due to emigration). During the follow-up period, 12 late deaths occurred. The cause of death was cardiac related in 5 (intra-cerebral hemorrhage in 2, heart failure in 1 and sudden unexplained in 2) and non-cardiac related in 7 patients. At 6 years after surgery, the overall survival rate for the unmatched population was 92.5% (95% CI 86.6%-98.4%) and 80.1% (95% CI 61.5%-98.7%) for the Resect and Neochords group, respectively (P=0.24; **Figure 3**). In the propensity score matched patient population, the 6-year overall survival rate was 93.2% (95% CI 85.8%-100%) and 79.7% (95% CI 61.1%-98.3%) for the Resect and Neochords group, respectively (P=0.20; **Figure 3**).

TABLE III. Valve-related results of mitral valve repair.

	Unmatched population			Matched population		
	Resect group (n=99)	**Neochords group (n=51)**	**P-value**	**Resect group (n=47)**	**Neochords group (n=47)**	**P-value**
Preoperative						
Diastolic transvalvular gradient (mmHg)	2.10 (IQR 1.54-2.98)	1.64 (IQR 1.15-2.78)	0.045	2.03 (IQR 1.53-2.86)	1.64 (IQR 1.15-2.78)	0.62
LVEDD (mm)	55±7	55±6	0.99	55±6	55±7	0.71
LVEF (%)	66.2±7.7	63.6±8.3	0.081	64.5±7.7	63.5±8.4	0.56
Annuloplasty ring size	34 (IQR 32-36)	34 (IQR 32-36)	0.15	34 (IQR 31-36)	32 (IQR 32-36)	0.29
Leaflet coaptation height (mm)	7.7±1.6	8.6±1.7	0.002	8.0 (IQR 7.0-8.0)	8.0 (IQR 8.0-9.0)	0.15
Postoperative						
Diastolic transvalvular gradient (mmHg)	3.31±1.41	3.19±1.11	0.64	3.33 (IQR 2.46-4.23)	3.22 (IQR 2.61-3.86)	0.35
LVEDD (mm)	51 (IQR 45-55)	52 (IQR 46-57)	0.12	49 (IQR 45-54)	52 (IQR 46-58)	0.070
LVEF (%)	55.4±7.4	53.7±7.6	0.19	55.4±7.7	54.2±7.7	0.35

Data are presented as means ± standard deviation or medians (interquartile range). Abbreviations: IQR: interquartile range; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter.

Clinical follow-up was 90% complete with a median follow up of 3.4 (IQR 1.7-6.2) years. There was 1 late MV reintervention (Resect group) due to severe MR, performed 7.8 years after the initial operation as a consequence of infective endocarditis. A successful MV re-repair was performed. The 6-year freedom from MV reintervention was 100% for both the Resect and Neochords group in both the unmatched and matched patient population. A second episode of infective endocarditis occurred during the follow-up period (Neochords group) that was treated conservatively.

Median echocardiographic follow-up was 3.0 (IQR 1.2-5.4) years and was available in 93% of patients. In the unmatched patient population, the 6-year freedom from recurrent MR rates were 86.9% (95% CI 77.3%-96.5%) and 97.4% (95% CI 92.5%-100%) for the Resect and Neochords group, respectively (P=0.42; **Figure 4**). For the propensity score matched population, the 6-year freedom from recurrent MR rates were 91.3% (95% CI 81.9%-100%) and 97.2% (95% CI 91.9%-100%) for the Resect and Neochords group, respectively (P=0.43, **Figure 4**).

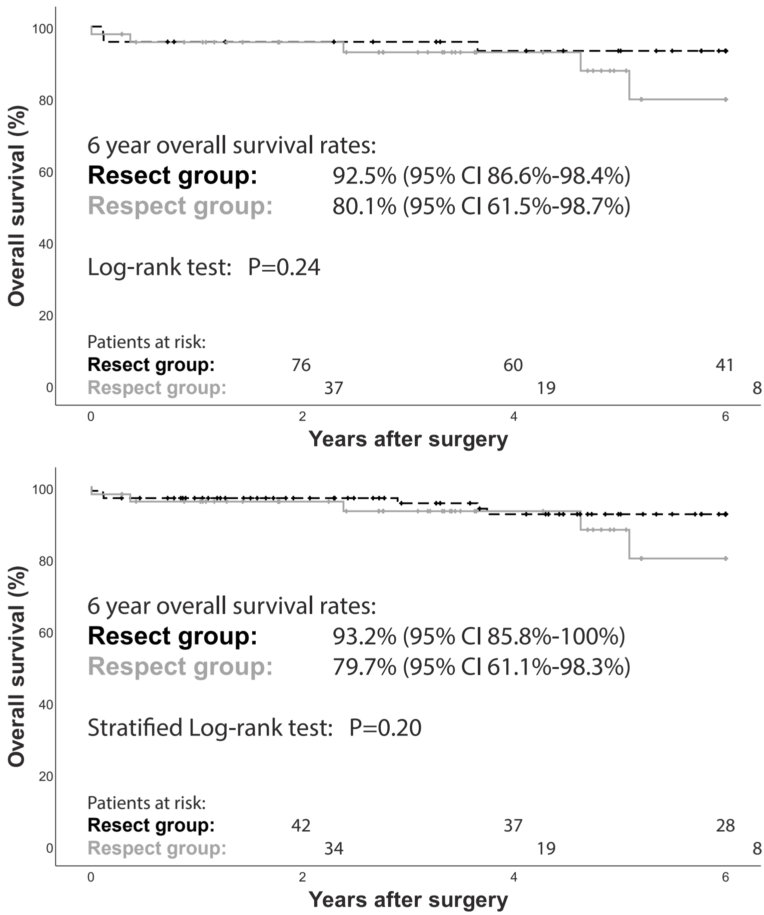


FIGURE 3. Overall survival for the Resect and Neochords groups (above: unmatched patient population, below: propensity score matched patient population).

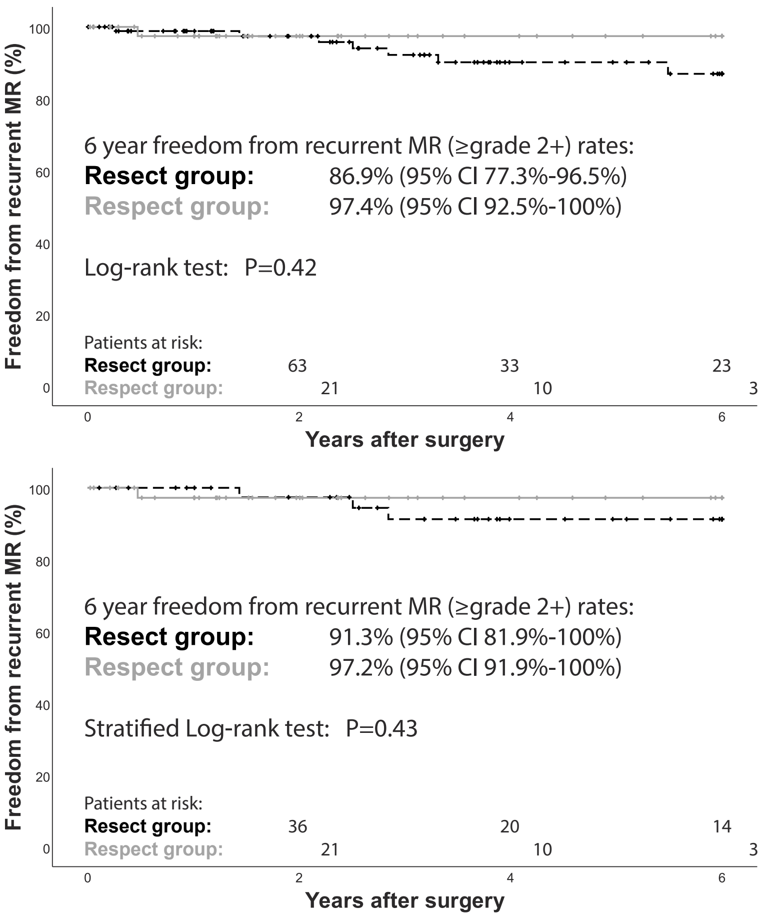


FIGURE 4. Freedom from recurrent mitral regurgitation (≥grade 2+) for the Resect and Neochords groups (above: unmatched patient population, below: propensity score matched patient population).

DISCUSSION

Our results demonstrate that in case of a structured approach to PMVL abnormalities, tailored to valve specific characteristics, leaflet resection and chordal replacement techniques are often used concomitantly. Excessive PMVL tissue in height can effectively be treated by either leaflet resection or implantation of shortening neochords. The choice of repair technique will not affect early or late repair performance, postoperative LV function or diastolic transvalvular gradients.

With the widespread utilization of chordal replacement techniques, leaflet resection techniques are nowadays used less commonly than before [13]. When leaflet prolapse/flail is not accompanied by excessive leaflet tissue, leaflet resection is best avoided and chordal replacement has readily become the preferred repair strategy. This helps avoid the disadvantages of annular plication that is believed to alter LV morphology and function [14]. Such cases should, however, be distinguished from cases when PMVL prolapse/flail is accompanied by excessive leaflet tissue. In such cases, the aim of valve repair is to (I) resolve any leaflet prolapse, (II) address excessive leaflet tissue in height and (III) address excessive tissue in width.

To address excessive PMVL tissue in width, leaflet resection or plication remain the only surgical options. Care should be made to avoid *excessive* leaflet resection with excessive shortening of the free margin of the PMVL. This has been shown to result in elevated transvalvular gradients (data are often derived from an *ex vivo* model of acute MR without excessive leaflet tissue where any resection will be excessive) and leaflet resection should always be made with respect to preservation of leaflet mobility [15-17]. As demonstrated by our results, when PMVL resection is performed purely to treat excessive leaflet tissue, additional neochords to correct leaflet prolapse are often needed and help prevent excessive resection.

Our study was the first to select only patients with PMVL prolapse and excessive tissue in height and aimed to address the unanswered question on whether leaflet resection of shortening neochords provide comparable results in this setting. Perier et al., who introduced the "*Respect rather than Resect*" paradigm, did report in the initial experience that leaflet resection –aimed at reducing excessive tissue in width- was still performed in one third of patients in whom leaflet prolapse and/or excessive tissue in height were otherwise addressed with chordal replacement techniques [8]. Too often, the results of their study are misinterpreted and used as an argument to support a chordal replacement PMVL repair only. As we selected only patients with excessive leaflet tissue, the high proportion of patients in the Neochords group who additionally underwent leaflet resection in width comes to no surprise. Addressing excessive leaflet tissue is important to secure long-term repair stability and durability. While clinical data to support such statements are currently lacking, Choi et al. have previously shown –in a virtual MV model- that excessive PMVL tissue will result in excessive leaflet stress [18].

This promotes activation of valve interstitial cells with ensuing myxomatous degeneration (often referred to as disease progression) and should therefore be reduced to minimum [19].

It has been suggested that chordal replacement techniques will allow annuloplasty ring oversizing and result in lower diastolic transvalvular gradients when compared to leaflet resection techniques [9, 10, 20]. In our opinion, such observations need to be interpreted with care. When no excessive PMVL tissue in height is present, oversizing the annuloplasty ring will inevitably lead to insufficient height of leaflet coaptation. In these patients, small annuloplasty ring size might indeed present a true clinical problem as functional MV stenosis might ensue [21]. Moreover, when leaflet prolapse with excessive leaflet height is present at a single segment, the same problem (insufficient height of leaflet coaptation) will occur at the level of non-affected segments. In our opinion, oversizing of the annuloplasty ring is feasible only in cases where excessive tissue in height is present at all segments of the PMVL. In these patients, large rings are usually needed to complement valve repair, making clinically significant elevated transvalvular gradients unlikely the occur. This is partially reflected by the somehow larger annuloplasty ring sizes used in our experience in the Resect group. We reason that this is probably related to our preference to perform tissue resection when a large amount of excessive PMVL tissue is present.

Several studies have suggested that chordal replacement might lead to improved postoperative LV function when compared to leaflet resection because of better preservation of the mitral-ventricular continuity [1, 4, 9, 22]. However, the demonstrated (statistically significant) difference of about 3% makes us question the clinical significance of such observations [1]. In all of the studies that seem to support this idea, a proportion of patients in whom leaflet resection was performed also underwent mitral annular plication. This likely presents the cause of LV functional decline and, when avoided, the reason here for is likely eliminated. To the best of our knowledge, there is no available data that support the theory that a properly sized leaflet resection without annular plication will disturb the mitral-ventricular continuity. The questionable and, indeed present, limited benefit of performing PMVL repair exclusively with chordal replacement techniques should be weighed against the concerns that arise by systematically not addressing excessive PMVL leaflet tissue.

Our results are in line with previous studies that have demonstrated excellent MV repair durability for patients with isolated PMVL prolapse [3, 8]. We believe that such outcomes are a result of a structured approach to PMVL prolapse that aims to resolve any leaflet prolapse, addresses excessive leaflet tissue and secures annular remodeling and stabilization [3, 8, 23].

LIMITATIONS

This is an observational single center study with limitations inherent to the study design. We have performed propensity score matching to compensate for the lack of patient randomization. Furthermore, the number of patients included in the study was limited, somehow limiting the value of the results presented. Moreover, the resect techniques were more commonly in use early and chordal replacement techniques later in the predefined study period. This might have had an effect on the perioperative outcomes related to the improvements in perioperative care. Our results (in particular freedom from recurrent MR and MV reintervention) will have to be validated in properly powered, larger scale studies with longer follow-up in the future. However, this was the first study to truly compare the resect and shortening neochords techniques in a contemporary setting, hereby eliminating study bias attributable to addition of patients with annular plication or no excessive leaflet tissue.

CONCLUSIONS

A structured approach to PMVL prolapse and excessive leaflet tissue provides excellent repair performance. Excessive PMVL tissue in height can effectively be addressed by both leaflet resection or shortening neochords techniques with comparable results. The decision on which technique to use is best adapted to other valve characteristics, including presence of annular calcification and the presence/amount of excessive tissue in width.

REFERENCES

[1] Falk V, Seeburger J, Czesla M, Borger MA, Willige J, Kuntze T, et al. How does the use of polytetrafluoroethylene neochordae for posterior mitral valve prolapse (loop technique) compare with leaflet resection? A prospective randomized trial. J Thorac Cardiovasc Surg. 2008;136(5):1205.

[2] Lange R, Guenther T, Noebauer C, Kiefer B, Eichinger W, Voss B, et al. Chordal replacement versus quadrangular resection for repair of isolated posterior mitral leaflet prolapse. Ann Thorac Surg. 2010;89(4):1163-70.

[3] Perier P, Stumpf J, Gotz C, Lakew F, Schneider A, Clausnizer B, et al. Valve repair for mitral regurgitation caused by isolated prolapse of the posterior leaflet. Ann Thorac Surg. 1997;64(2):445-50.

[4] Seeburger J, Falk V, Borger MA, Passage J, Walther T, Doll N, et al. Chordae replacement versus resection for repair of isolated posterior mitral leaflet prolapse: a egalite. Ann Thorac Surg. 2009;87(6):1715-20.

[5] Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J. 2010;31(16):1958-66.

[6] Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg. 1983;86(3):323-37.

[7] David TE. Replacement of chordae tendineae with expanded polytetrafluoroethylene sutures. J Card Surg. 1989;4(4):286-90.

[8] Perier P, Hohenberger W, Lakew F, Batz G, Urbanski P, Zacher M, et al. Toward a new paradigm for the reconstruction of posterior leaflet prolapse: midterm results of the "respect rather than resect" approach. Ann Thorac Surg. 2008;86(3):718-25.

[9] Mazine A, Friedrich JO, Nedadur R, Verma S, Ouzounian M, Juni P, et al. Systematic review and meta-analysis of chordal replacement versus leaflet resection for posterior mitral leaflet prolapse. J Thorac Cardiovasc Surg. 2018;155(1):120-128.

[10] Mihos CG, Yucel E, Santana O. A systematic review and meta-analysis of chordal replacement versus leaflet resection for isolated posterior mitral valve prolapse. J Cardiovasc Surg (Torino). 2017;58(5):779-86.

[11] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg. 2008;135(4):732-8.

[12] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802.

[13] Mihaljevic T, Pattakos G, Gillinov AM, Bajwa G, Planinc M, Williams SJ, et al. Robotic posterior mitral leaflet repair: neochordal versus resectional techniques. Ann Thorac Surg. 2013;95(3):787-94.

[14] David TE, Omran A, Armstrong S, Sun Z, Ivanov J. Long-term results of mitral valve repair for myxomatous disease with and without chordal replacement with expanded polytetrafluoroethylene sutures. J Thorac Cardiovasc Surg. 1998;115(6):1279-85.

[15] Da Col U, Di Bella I, Bardelli G, Koukoulis G, Ramoni E, Ragni T. Triangular resection and folding of posterior leaflet for mitral valve repair. J Card Surg. 2006;21(3):274-6.

[16] Dreyfus GD, Corbi P, Rubin S, Aubert S. Posterior leaflet preservation in mitral valve prolapse: a new approach to mitral repair. J Heart Valve Dis. 2006;15(4):528-30.

[17] Padala M, Powell SN, Croft LR, Thourani VH, Yoganathan AP, Adams DH. Mitral valve hemodynamics after repair of acute posterior leaflet prolapse: quadrangular resection versus triangular resection versus neochordoplasty. J Thorac Cardiovasc Surg. 2009;138(2):309-15.

[18] Choi A, McPherson DD, Kim H. Biomechanical evaluation of the pathophysiologic developmental mechanisms of mitral valve prolapse: effect of valvular morphologic alteration. Med Biol Eng Comput. 2016;54(5):799-809.

[19] Rabkin E, Aikawa M, Stone JR, Fukumoto Y, Libby P, Schoen FJ. Activated interstitial myofibroblasts express catabolic enzymes and mediate matrix remodeling in myxomatous heart valves. Circulation. 2001;104(21):2525-32.

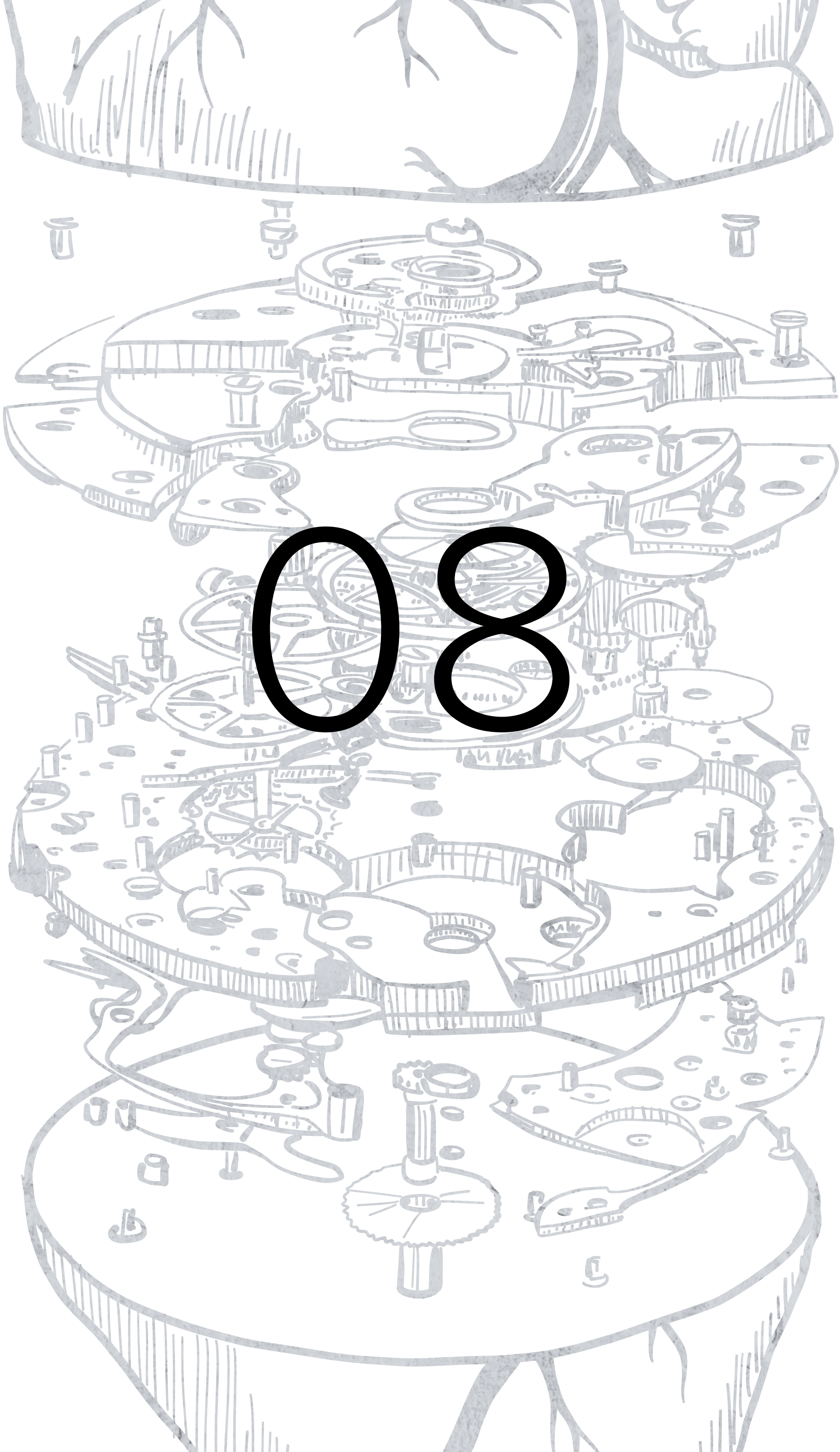
[20] Chua YL, Pang PY, Yap YP, Abdul Salam ZH, Chen YT. Chordal Reconstruction versus Leaflet Resection for Repair of Degenerative Posterior Mitral Leaflet Prolapse. Ann Thorac Cardiovasc Surg. 2016;22(2):90-7.

[21] Mesana TG, Lam BK, Chan V, Chen K, Ruel M, Chan K. Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: potential affect on surgical strategy. J Thorac Cardiovasc Surg. 2013;146(6):1418-23.

[22] Imasaka K, Tayama E, Tomita Y. Left ventricular performance early after repair for posterior mitral leaflet prolapse: Chordal replacement versus leaflet resection. J Thorac Cardiovasc Surg. 2015;150(3):538-45.

[23] Johnston DR, Gillinov AM, Blackstone EH, Griffin B, Stewart W, Sabik JF, 3rd, et al. Surgical repair of posterior mitral valve prolapse: implications for guidelines and percutaneous repair. Ann Thorac Surg. 2010;89(5):1385-94.

08



Initial experience and early results of mitral valve repair with CardioCel pericardial patch

Anton Tomšič; Daniella D. Bissessar; Thomas J. van Brakel; Nina Ajmone Marsan; Robert J.M. Klautz ; Meindert Palmen

Ann Thor Surg. 2018;106(4):1241-1244

ABSTRACT

Background. To assess the performance of a tissue engineering process-treated bovine pericardium patch (CardioCel) in the setting of reconstructive mitral valve surgery.

Methods. Between 3/2014 and 4/2016, 30 patients (57.2±14.3 years, 27% female) underwent mitral valve leaflet repair with a CardioCel patch.

Results. Perioperative mortality was 7% (2 patients, non-graft-related). In 28 remaining patients, pre-discharge echocardiography demonstrated good repaired valve function. At a mean follow-up of 1.7±0.9 years, 3 additional deaths occurred (2 due to infective endocarditis, 1 non-cardiac related). On follow-up echocardiography [follow-up time 1.7±0.8 years, available for 26/28 (93%) hospital survivors], recurrent regurgitation was seen in 2 patients (both infective endocarditis) and 1 underwent reoperation (no infection at the level of patch repair was observed). In the remaining patients, the most recent echocardiogram demonstrated ≤mild regurgitation and stable gradients. The thickness and echodensity of the implanted patch on follow-up echocardiograms were comparable with postoperative echocardiograms.

Conclusions. Initial results of the CardioCel patch in mitral valve repair surgery are satisfactory. The resistance to infection and late degeneration will need to be assessed in the future.

TECHNOLOGY

Mitral valve (MV) repair is preferred over replacement when good repair durability can be expected. Patch techniques are widely used to replace destructed leaflet tissue or augment valve leaflets in cases of relative tissue deficiency [1,2]. Concerns on the durability of patch materials used in reconstructive MV surgery have been raised [1-3]. In recent years, the CardioCel (Admedus Regen Pty Ltd, Perth, WA, Australia) bovine pericardial patch has become our material of choice for patch repair of the MV. Following harvesting, the CardioCel is subjected to a complex preservation process including decellularization, molecular cross-linking with ultra-low glutaraldehyde concentrations and anti-mineralization treatment with the ADAPT process [4]. No data on the performance of CaridoCel in adult patients undergoing MV repair are available. Therefore, we explored our initial experience and early clinical and echocardiographic results of MV repair with the CardioCel patch.

TECHNIQUE

Patients and surgical procedures

A retrospective chart review of patients who underwent MV repair between 3/2014 and 4/2016 at our institution was performed. Patients in whom the CardioCel patch was used for leaflet reconstruction or augmentation were included in this study.

A large patch to augment/reconstruct the body of the AMVL was implanted in 11 patients; the indication was progression of the infectious process from an aortic root abscess to the AMVL (n=6), hypertrophic obstructive cardiomyopathy (n=3), and rheumatic valve disease (n=2). In 13 patients, a smaller patch, not expanding beyond the scope of a single leaflet segment, was implanted. In 2 patients, a larger patch, used to reconstruct an A1-A2 segment defect of the AMVL, was implanted. In another 2 patients, reconstruction of the anterolateral commissure was performed while in the last 2 patients, multiple CardioCel patches were used to repair both leaflets.

In case of AMVL leaflet repair, the patch was used to repair the leaflet body in all cases. In cases of PMVL, in selected patients the patch was also used to reconstruct the leaflet free-edge. The patch was implanted using running 5-0 monofilament polypropylene sutures. When used to reconstruct a leaflet free-edge, neochords were implanted to prevent leaflet prolapse. The neochords were implanted in a standard fashion; each end of the neochord was first passed through the implanted patch twice (2-3millimetres from the free-edge). Thereafter, the length was adjusted to bring the leaflet to the desired height, corresponding to the height of the adjacent segments. The neochords were tied during the final water-test. Full, semi-rigid ring annuloplasty was performed in 28/30 patients. Intraoperative transoesophageal echocardiography was routinely performed. All patients underwent a transthoracic echocardiographic examination prior to hospital discharge.

Study endpoints and follow-up

Perioperative mortality was defined as mortality within 30-days after the operation or during the index hospitalization. Study endpoints were defined according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions [5].

The function of the repaired MV and implanted CardioCel patch was assessed with transthoracic echocardiography. Mitral regurgitation (MR) severity was evaluated using a multi-parametric integrative approach, including qualitative and quantitative assessments –as recommended [6]- and graded on a 4-grade scale: mild/moderate/moderate-to-severe/severe. Residual and recurrent MR were defined as ≥moderate. Mean diastolic MV gradient was calculated using continuous-wave Doppler. Additionally, patch function and morphology were assessed. This included patch thickness, mobility (1=comparable to normal leaflet tissue, 2=decreased mobility, 3=no movement) and echodensity (0=comparable to normal tissue, 1=moderately elevated, 2=elevated).

Regular clinical and echocardiographic follow-up was performed at our outpatient clinic. All echocardiograms were reviewed by an experienced cardiologist (N.A.M.). Our institutional Ethical Committee approved the study.

Statistical analysis

Continuous data are presented as means ± standard deviation or medians and inter-quartile ranges (IQR). Categorical data are presented as counts and percentages. Pre-discharge and follow-up variables were compared with the Wilcoxon signed-rank test and paired samples Student's t-test. Statistical analysis was performed using IBM SPSS Statistics, version 23.0 (SPSS, Inc., IBM Corporation, Armonk, NY, USA).

CLINICAL EXPIRIENCE

Patient characteristics and early clinical results

Baseline characteristics are presented in **Table I**. In cases of active MV IE, non-elective surgery shortly after the initiation of antibiotic therapy [median number of 12 (IQR 8-19) days following the definitive diagnosis] was performed. The timing of surgery was determined by our endocarditis team. There were no intraoperative and 2 (7%) early postoperative deaths. The cause of death was multi-organ failure and malignant hearth rhythm disturbance. In both patients the last available post-operative echocardiography demonstrated good repaired valve function.

TABLE I. Baseline characteristics.

	N=30
Age (years)	57.2±14.3
Gender (female)	8 (27)
Etiology	
Infective endocarditis	
Active	15 (50)
Healed	5 (17)
Rheumatic valve disease	3 (10)
Hypertrophic obstructive cardiomyopathy	3 (10)
Degenerative	4 (13)
Atrial fibrillation	8 (27)
NYHA class	
I	7 (23)
II	12 (40)
III-IV	11 (37)
Dialysis	2 (7)
Previous cardiac surgery	6 (20)
Diabetes mellitus	6 (20)
Chronic lung disease	4 (13)
Left ventricular function	
Good (LVEF >50%)	23 (67)
Moderate (LVEF 30%-50%)	7 (23)

Data are presented as n (%) unless specified otherwise. Abbreviations: LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Early echocardiographic results

On pre-discharge echocardiography, no residual MR was observed and the mean diastolic MV gradient was 4.1±1.6mmHg (**Table II**). Pre-discharge echocardiography demonstrated a certain impairment of leaflet mobility (interpreted as related to the repair itself and not a consequence of early changes in patch integrity) at the level of patch repair in 4 patients.

TABLE II. Mitral valve function and patch characteristics determined on pre-discharge and follow-up echocardiography. Only data of patients with follow-up echocardiography available are presented (n=26).

	Preoperative echocardiography (n=26)	Pre-discharge echocardiography (n=26)	Follow-up echocardiography (n=26)	P-value*
Mitral regurgitation grade				0.41
None/trivial	1 (4)	16 (62)	17 (65)	
Mild	8 (31)	10 (38)	7 (27)	
Moderate	5 (19)	0 (0)	0 (0)	
≥Moderate-to-severe	12 (46)	0 (0)	2 (8)	
Mean diastolic mitral valve gradient (mmHg)	2.41±1.38	4.11±1.59	3.82±1.64	0.45
Patch thickness (mm)	-	3.7±0.9	3.9±1.1	0.16
Patch echodensity				0.18
Normal	-	12 (50)	10 (33)	
Moderately elevated	-	12 (50)	13 (44)	
Elevated	-	0 (0)	1 (3)	

**Comparing pre-discharge and follow-up echocardiographic variables.*

Follow-up results

Follow-up was 97% complete (1 patient lost to follow-up due to migration) with a mean follow-up of 1.7±0.9 years. There were 3 late deaths; 2 were valve-related (both multi-organ failure as a complication of MV IE) and 1 was non-cardiac related. Clinical follow-up was 94% complete with a mean follow-up of 1.7±0.8 years. There were 2 [2/28 (7%) patients at risk] episodes of IE (at 2 months and 1.7 years), both resulting in severe MR (**Table III**) and 1 patient underwent reoperation. No other reinterventions were performed.

TABLE III. Details on cases of operated valve infective endocarditis.

	Underlying etiology	Patch use	Time-to-event	Echocardiographic observations	Intraoperative observations	Outcome
1	Rheumatic valve disease	AMVL augmentation	2 months	Annuloplasty ring dehiscence and vegetations; severe MR	Annuloplasty ring dehiscence and vegetations; no signs of patch infection	Died after reoperation
2	Native valve endocarditis	AMVL reconstruction (A3 segment)	1.7 years	Vegetations on the AMVL; severe MR	N/A	Died prior to reoperation

Abbreviations: AMVL: anterior mitral valve leaflet; MR: mitral regurgitation.

Follow-up echocardiographic results

Follow-up echocardiography was available for 26/28 (93%) hospital survivors with a mean follow-up of 1.7±0.8 years. Recurrent MR occurred in 2 (8%) patients and the cause was IE in both. In the remaining patients, the latest echocardiography demonstrated none/trivial and mild MR in 17 (65%) and 7 (27%) patients, respectively (**Table II**).

On latest echocardiography, the mean diastolic MV gradient did not differ from the pre-discharge values (4.1±1.6mmHg vs. 3.8±1.6mmHg, P=0.45). Similarly, no significant differences in patch thickness were observed (3.7±0.9mm vs. 3.9±1.1mm, P=0.16). In patients in whom impaired leaflet mobility at the level of patch repair was seen on pre-discharge echocardiography (n=4), a comparable result was seen on follow-up echocardiography. Newly observed decreased leaflet mobility at the level of patch repair was seen in 2 patients with no increased echodensity or leaflet thickening. Slightly increased echodensity of the implanted patch was noticed in 4 patients without any significant patch thickening.

COMMENT

This is the first study to explore the results of MV repair with the CardioCel pericardial patch in adult patients with good early valve repair performance demonstrated, implying good patch biocompatibility and resistance to early degeneration.

Heterologous materials are antigenic and decellularization is essential to secure biocompatibility. Novel decellularized heterologous patch materials have recently been introduced. In case of decellularized porcine intestinal submucosa (CorMatrix, Cardiovascular, Atlanta, GA, USA), Kelley et al. reported poor results after MV repair with AMVL augmentation with the CorMatrix patch [3]. Within 1 year after implantation, patch-related reoperation was needed in 7/25 patients (average time-to-discovery of recurrent MR was 192±105 days) due to an intense inflammatory reaction to the implanted patch. Similar worrying results were described by Gerdisch et al. who explored their experience with the CorMatrix patch in 19 MV repair cases [7]. At a median follow-up of 10.9 months, patch-related reoperation was needed in 2 patients. These results all question the suitability of heterologous bioscaffolds in MV repair surgery.

Our initial intraoperative experience with CardioCel was favourable as this material combines off-the-shelf availability and good handling. Moreover, our results demonstrate good biocompatibility and resistance to early patch degeneration (shrinkage). Nevertheless, 2 patients experienced operated valve IE. In one patient this occurred within 2 months after operation with the infection limited to the yet unendothelialized prosthetic ring. The other patient did not undergo reoperation and an infection of the implanted patch could not be excluded. In previous reports on the use of CardioCel in the paediatric population, no observations similar to ours were made [8]. Data on the performance of CardioCel in reconstructive valve surgery in adult patients are to date absent and resistance to infection will need to be reassessed in the future.

Upon echocardiographic follow-up, a slight increase in patch thickness was observed (0.2 mm, n.s.). This might be related to a controlled process of patch endothelialization and collagen layer formation that has previously been observed in juvenile sheep models where CardioCel was used for valve repair [9].

The cost-efficiency of the CardioCel patch needs to be considered. We were able to demonstrate good early results of MV repair with the CardioCel patch; compared to materials prone to early degeneration, a lower number of reoperations will compensate for the higher price. On the other hand, data on long-term performance of CardioCel will need to be awaited to compare the cost-efficiency to other patches where late (and not early) degeneration might present a problem (e.g. glutaraldehyde-treated autologous pericardium).

Due to the single-center study design and limited follow-up duration, this study has inevitable limitations. We have performed this study to asses our initial experience and explore the early performance (biocompatibility and resistance to early degeneration) of a novel material. Future clinical and echocardiographic follow-up is crucial in these patients.

In conclusion, the initial experience with tissue engineered CardioCel pericardial patch in MV repair is promising. Our results demonstrate good early patch performance. The resistance to infection and late degeneration will need to be further explored in the future.

REFERENCES

[1] Fukunaga N, Sakata R, Koyama T. Reoperative analysis after mitral valve repair with glutaraldehyde-treated autologous pericardium. Interact Cardiovasc Thorac Surg 2017.

[2] Tomšič A, Schneider AW, Palmen M, van Brakel TJ, Versteegh MIM, Klautz RJM. Extensive infective endocarditis of the aortic root and the aortic-mitral continuity: A mitral valve sparing approach. Eur J Cardiothorac Surg 2017;51(6):1100-1107.

[3] Kelley TM, Jr., Kashem M, Wang H et al. Anterior leaflet augmentation with cormatrix porcine extracellular matrix in twenty-five patients: Unexpected patch failures and histologic analysis. Ann Thorac Surg 2017;103(1):114-120.

[4] Neethling WM, Glancy R, Hodge AJ. Mitigation of calcification and cytotoxicity of a glutaraldehyde-preserved bovine pericardial matrix: Improved biocompatibility after extended implantation in the subcutaneous rat model. J Heart Valve Dis 2010;19(6):778-785.

[5] Akins CW, Miller DC, Turina MI et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008;33(4):523-528.

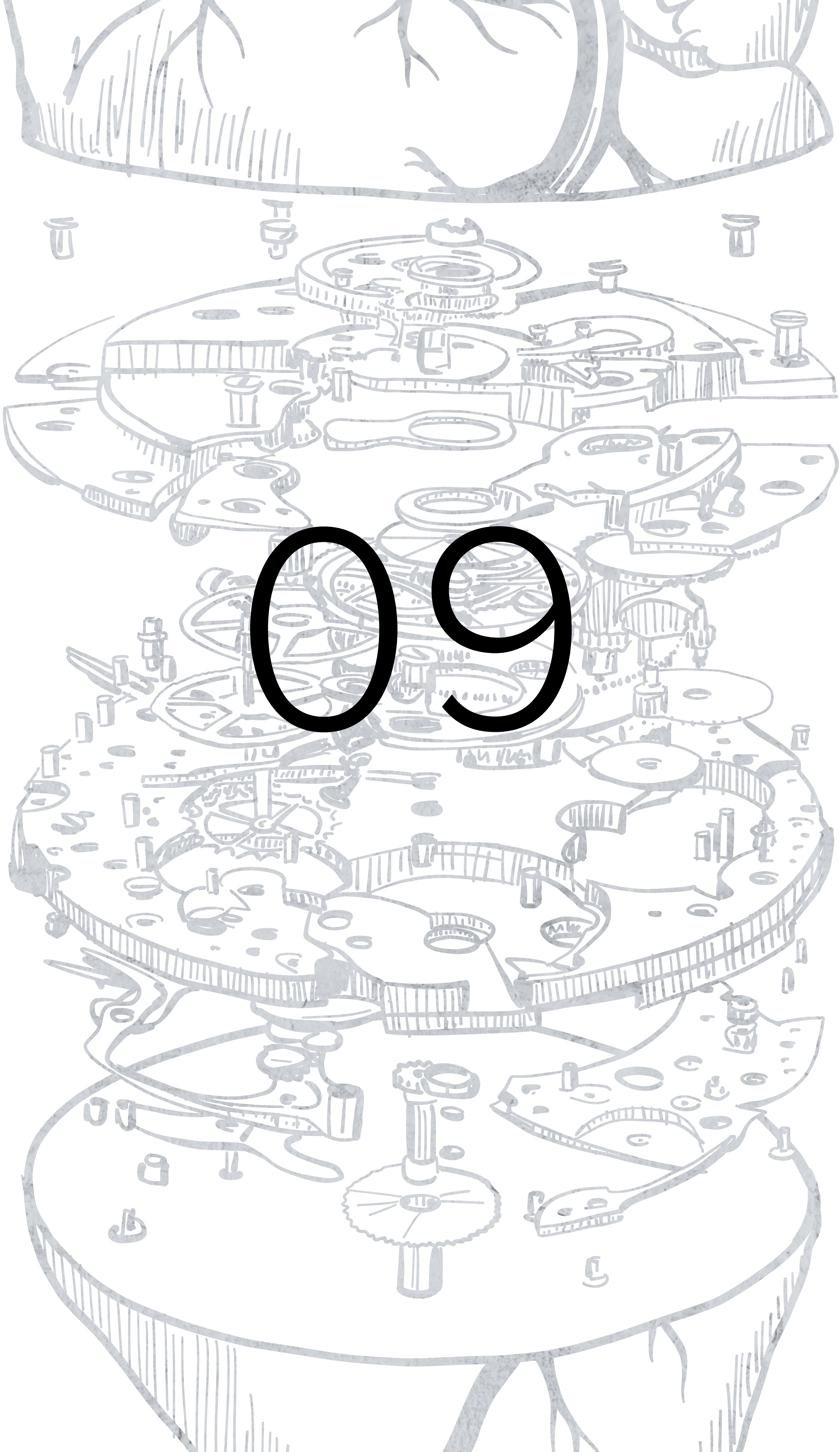
[6] Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography. J Am Soc Echocardiogr 2003;16(7):777-802.

[7] Gerdisch MW, Shea RJ, Barron MD. Clinical experience with CorMatrix extracellular matrix in the surgical treatment of mitral valve disease. J Thorac Cardiovasc Surg. 2014 Oct;148(4):1370-8.

[8] Neethling WM, Strange G, Firth L, Smit FE. Evaluation of a tissue-engineered bovine pericardial patch in paediatric patients with congenital cardiac anomalies: Initial experience with the adapt-treated CardioCel(r) patch. Interact Cardiovasc Thorac Surg 2013;17(4):698-702.

[9] Brizard CP, Brink J, Horton SB, Edwards GA, Galati JC, Neethling WM. New engineering treatment of bovine pericardium confers outstanding resistance to calcification in mitral and pulmonary implantations in a juvenile sheep model. J Thorac Cardiovasc Surg 2014;148(6):3194-3201.

09



Outcomes of valve repair for degenerative disease in patients with mitral annular calcification

Anton Tomšič; Yasmine L. Hiemstra; Thomas J. van Brakel; Michel I.M. Versteegh; Nina Ajmone Marsan; Robert J.M. Klautz; Meindert Palmen

Ann Thorac Surg. 2019;107(4):1195-1201

ABSTRACT

Background. The risk factors for the development of mitral annular calcification (MAC) in degenerative mitral valve disease and the effect it may have on patient- and valve-related outcomes require further evaluation.

Methods. Between 1/2002 and 12/2015, 627 patients underwent mitral valve surgery for degenerative disease. MAC was seen in 75 (12%) patients; 73 (97%) underwent valve repair (6 without annuloplasty ring implantation) while 2 (3%) underwent valve replacement after an unsuccessful repair attempt.

Results. MAC was linked to patient age, female gender and degenerative disease subtype. Early mortality was comparable between patients with and without MAC [3/75 (4%) vs. 10/552 (2%), P=0.20]. In patients with MAC, 1/3 deaths was directly related to annular decalcification and reconstruction. Early repair failure was more common in patients with MAC [8/75 (11%) vs. 17/552 (3%), P=0.006]. During follow-up, no differences in overall survival or freedom from late reintervention were observed. However, at 8 years after surgery, freedom from recurrent mitral regurgitation was worse in patients with MAC. In these patients, repair failure was linked to non-use of ring annuloplasty. For patients with MAC in whom annular decalcification and annuloplasty were performed, repair durability was comparable to patients without MAC.

Conclusions. Mitral valve surgery in degenerative disease accompanied by MAC is safe. Optimal surgical strategy includes annular decalcification (when this would prevent implantation of an annuloplasty ring) and ring annuloplasty and will lead to results similar to patients without MAC. However, when the annulus is not addressed, repair performance is hampered. For these patients, alternative repair techniques should be explored in the future.

INTRODUCTION

Mitral valve (MV) surgery in the presence of mitral annular calcification (MAC) presents a technical challenge. Although valve replacement in patients with MAC is already demanding, repairing a MV in the presence of MAC is even more challenging. Therefore, valve replacement will still often be performed primarily or after an unsuccessful repair attempt [1-5]. Theoretically, the best results are to be expected when complete annular decalcification is performed.

In patients with degenerative MV disease, MAC is rather commonly encountered [5-7]. The risk factors for the development of MAC in the setting of degenerative MV disease remain poorly understood. At the time of surgical intervention, several specific complications, including damage to the circumflex artery and disruption of the atrioventricular groove, may result from annular decalcification [4,8]. Consequently, a modified surgical strategy with limited or even without annular decalcification is often chosen. This could lead to suboptimal results, especially in the case of valve repair without annuloplasty [9-12]. However, the effect of such technical modifications as well as outcomes of MV repair in patients with degenerative MV disease, in whom an aggressive repair-all strategy is advocated, and MAC remain insufficiently explored.

The aim of this study was to explore the predictors of MAC in patients with degenerative MV disease, explore the effect of MAC on patient- and valve-related outcomes, and to determine the risk factors for repair failure in patients with MAC.

METHODS

Study population

Between 1/2002 and 12/ 2015, 627 consecutive adult (≥18 years of age) patients underwent surgical intervention for MR due to degenerative MV disease at our institution. Patients with active MV infective endocarditis or other aetiologies were excluded. The presence and severity of MAC was based on intraoperative analysis and graded qualitatively. MAC was present in 75 (12%) of these patients. Mild MAC (calcification of less than one-third of the annulus circumference) was present in 30 (40%) patients, moderate in 27 (36%) and severe (calcification of more than two-thirds of the annulus circumference) in 18 (24%) patients. The distribution of MAC is shown in **Figure 1**.

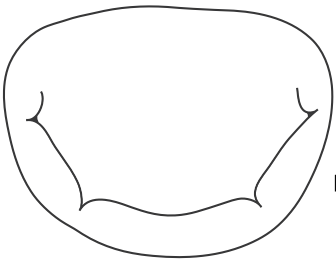


FIGURE 1. Distribution of MAC.

Study methods

Our Institutional Medical Ethic Committee approved this study. Pre-, intra-, and post-operative data were collected from our prospective computerized patient registry. Follow-up clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through patient questionnaires. Patient follow-up was closed in February 2017. Survival follow-up was 99% complete with a median duration of 6.4 (IQR 3.5-10.3) years. Follow-up on clinical events was 90% complete with a median duration of 5.9 (IQR 2.8-9.8) years [90% complete for patients with MAC with a median follow-up duration of 4.65 (IQR 2.09-8.49) years and 90% complete for patients without MAC with a median follow-up duration of 5.63 (IQR 2.55-9.86) years].

Surgical procedure

MV repair was performed by experienced MV surgeons and valve repair was attempted in all cases. The MV was carefully inspected to determine the site of leaflet prolapse and the presence and degree of MAC. In brief, the anterior MV leaflet prolapse was primarily addressed with chordal replacement. In the case of posterior MV leaflet involvement, leaflet resection with or without annular plication (early study period) or leaflet sliding was performed to address excessive leaflet tissue in width or height, or both. Residual prolapse was addressed with chordal replacement. Alternatively, shortening neochords were implanted to treat excessive posterior MV leaflet height. Commissural prolapse was addressed predominantly with papillary muscle head repositioning. Ring annuloplasty was considered in all patients, including patients with MAC.

In 14 (19%) patients with limited MAC, the presence of MAC was not expected to prevent annuloplasty ring implantation or influence leaflet mobility after repair and no decalcification was performed. In 55 (73%) patients with MAC, en bloc decalcification of the calcified annulus was performed after leaflet detachment. In cases of extensive annular decalcification, annular reconstruction was performed by the "sliding atrium technique" or, especially in cases of extensive MAC with extension into the left ventricular wall, by patch implantation to restore the continuity between the left atrium and ventricle and cover the exposed annular tissue and the underlying atrioventricular groove. Bioglue (CryoLife, Atlanta, GA, USA) was used in 6 of the latter patients to reinforce the atrioventricular groove. The remnant of the leaflet was reattached to the "new" annulus; in case of "sliding atrium technique" several millimetres into the left atrium and, in case of patch reconstruction of the posterior annulus, to the suture-line of the patch and left atrium. A ring was subsequently implanted just beyond the new leaflet insertion.

In 6/75 (8%) patients with MAC, no annular decalcification was performed despite the presence of severe MAC. These patients were typically older (mean age 80.6±2.1 years, range 77.2-83.3) with MAC usually expanding into the wall of the left ventricle. The decision not to perform annular decalcification was based on the presumable high risk of this maneuver that would also result in significant prolongation of the cardiopulmonary bypass and aortic cross-clamp times. Ring annuloplasty was not performed in any of these patients.

Study endpoints

Postoperative mortality and morbidity end points were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery and European Association for Cardio-Thoracic Surgery Guidelines [13]. Early mortality was defined as mortality within 30-days after the operation or during the index hospitalization. Residual and recurrent MR were defined as ^{3}Grade 2+ MR.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile ranges (IQRs) when not normally distributed. Categorical data are presented as counts and percentages. Comparisons between the two groups were performed using the chi-square test or Fisher's exact test for categorical variables and Student's t test or Mann-Whitney U test (skewed data) for continuous variables. Survival and events rates were summarized using the Kaplan-Meier method and compared using the log-rank test. A multivariable regression and Cox proportional-hazards regression analysis were used to analyze the predictors of MAC and recurrent MR in patients with MAC, respectively. Variables were selected using a backward selection method. Variable retention in the model was set at a P-value of 0.10. A double-sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using the IBM Statistics, version 23.0 (SPSS, Inc., IBM Corporation, Armonk, NY, USA) and GraphPad Prism (GraphPad Software, LA Jolla, CA, USA).

RESULTS

Risk factors for MAC

Multivariable regression analysis demonstrated increasing patient age (OR 1.032, 95% CI 1.008-1.057, P=0.008), female gender (OR 2.105, 95% CI 1.271-3.485, P=0.004) and Barlow's disease (OR: 2.117, 95% CI 1.250-3.584, P=0.005) as significant risk factors of MAC (**Supplemental material A**). Surprisingly, in this specific group, systemic hypertension (OR 0.583, 95% CI 0.346-0.981, P=0.042) demonstrated a protective effect against MAC. Notably, no link between renal impairment and MAC was observed.

Baseline characteristics and early results

Baseline characteristics of the entire patient population are presented in **Table I**. Patients with MAC were older, a higher proportion was females and Barlow's disease was more commonly seen.

In general, more postoperative complications were seen in patients with MAC (**Table II**). There was no statistically significant difference in the early mortality rates between patients with and without MAC. Of the 3 early deaths in patients with MAC, 1 was directly related to annular decalcification. In this patient with left coronary artery dominance, postoperative compression of the left circumflex coronary artery resulted in fatal ventricular failure. Autopsy revealed hematoma formation under the pericardial patch that was used to reconstruct the posterior part of the annulus after decalcification. The 2 remaining patients died of multi-organ failure.

TABLE I. Baseline patient characteristics.

	MAC (n=75)	No MAC (n=552)	P-value
Age (years)	70.8 (IQR 63.3-77.4)	66.6 (IQR 58.2-74.2)	0.012
Gender (female)	42 (56)	190 (35)	<0.001
NYHA			0.69
I	21 (28)	155 (28)	
II	39 (52)	262 (48)	
III-IV	15 (20)	133 (24)	
Hypertension	28 (38)	272 (50)	0.058
Atrial fibrillation			0.10
Paroxysmal	16 (21)	100 (18)	
Chronic	19 (25)	92 (17)	
Renal impairment			0.054
Moderate (CC 50-85)	35 (47)	264 (48)	
Severe (CC <50)	15 (20)	59 (11)	
Extracardiac arteriopathy	1 (1)	10 (2)	0.77
History of TIA or CVA	6 (8)	28 (5)	0.29
Diabetes mellitus	2 (3)	26 (5)	0.43
Chronic lung disease	9 (12)	47 (9)	0.31
Previous cardiac surgery	2 (3)	19 (4)	0.73
LVEF ≤60 %	18 (24)	149 (27)	0.57
LVESD ≥45 mm	6 (8)	62 (6)	0.51
Pulmonary hypertension (sPAP >50 mmHg)	10 (13)	75 (14)	0.94
Aetiology			0.024
FED/FED+	37 (49)	346 (63)	
Forme fruste/Barlow's disease	38 (51)	204 (37)	
EuroSCORE II	2.15 (IQR 1.31-4.29)	1.86 (IQR 0.97-3.59)	0.043

Abbreviations: CVA: cerebrovascular accident; CC: creatinine clearance; FED: fibroelastic deficiency; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MAC: mitral annular calcification; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure; TIA: transient ischaemic attack.

Early repair failure in patients with MAC

Early repair failure was seen in 8 (11%) and 17 (3%) patients with and without MAC (P=0.006, **Table II**). In patients with MAC, early repair failure occurred readily during the operation in 4 patients and was detected on postoperative echocardiography (with intraoperative echocardiography demonstrating ≤Grade 1+ MR) in the remaining 4 patients (**Table III**).

TABLE II. Early results.

	MAC (n=75)	No MAC (n=552)	P-value
Mortality	3 (4)	10 (2)	0.20
Prolonged intubation	11 (15)	65 (12)	0.48
Surgical reexploration	13 (18)	42 (8)	0.006
Stroke	2 (3)	3 (1)	0.11
Renal failure	2 (3)	24 (4)	0.76
Failed repair	8 (11)	17 (3)	0.006
Valve replacement	2 (3)	7 (1)	0.30
Early reintervention	3 (4)	8 (2)	0.14
Residual MR (≥2+)	6 (8)	10 (2)	0.007

Abbreviations: MAC: mitral annular calcification; MR: mitral regurgitation.

TABLE III. Details on residual MR in patients with MAC.

	Year of surgery	Age at operation	Residual MR mechanism	Annu-loplasty	Annular decalci-fication	Early reoperation
1	2002	71.8	Systolic anterior motion	1	0	Replacement
2	2002	83.3	Residual PMVL prolapse	0	0	Re-repair
3	2002	73.9	Mechanism not clear	1	0	-
4	2012	81.6	Lack of leaflet coaptation, intraoperative Grade 2+ MR	0	0	-
5	2012	67.3	Residual PMVL prolapse	1	1	Re-repair
6	2013	79.1	Lack of leaflet coaptation, intraoperative Grade 2+ MR	0	0	-

Abbreviations: MR: mitral regurgitation; PMVL: posterior mitral valve leaflet..

When the early results of valve repair in 55 patients with MAC, in whom both annular decalcification and annuloplasty were both performed, were compared with patients without MAC, no statistically significant difference in the early valve repair failure rate was observed (**Table IV**). Despite the lack of statistical significance, the incidence of valve repair failure was twice as high in the presence of MAC.

For 6 patients with MAC and no annuloplasty, residual MR was seen in 3 patients and the remaining 3 patients were discharged with no residual MR (**Table V**).

TABLE IV. Early valve repair results in patients with MAC in whom annular decalcification and annyloplasty were performed.

	Decalcification (n=55)	No MAC (n=552)	P-value
Failed repair	3 (6)	17 (3)	0.42
Valve replacement	2 (4)	7 (1)	0.19
Early reintervention	1 (2)	8 (2)	0.58
Residual MR (≥2+)	1 (2)	10 (2)	1.00

Abbreviations: MAC: mitral annular calcification; MR: mitral regurgitation.

TABLE V. Early and late results of patients with MAC who underwent MV repair without annuloplasty.

	Year of surgery	Age at operation	Annular decalci-fication	Early/late reoperation	Residual/recurrent MR
1	2002	83.3	0	Early	Residual MR
2	2002	82.2	0	-	Recurrent MR (0.9 years)
3	2003	77.6	0	-	No follow-up echocardiography available
4	2007	79.8	0	-	Recurrent MR (2.8 years)
5	2012	81.6	0	-	Residual MR (intraoperative)
6	2013	79.1	0	-	Residual MR (intraoperative)

Abbreviations: MR: mitral regurgitation.

Late results

During the follow-up period, 139 late deaths occurred, including 75 cardiac-related deaths. At 8 years after surgery, the overall survival rates were 69.2% (95% CI 54.4%-80.0%) and 78.7% (95% CI 74.4%-82.4%) for patients with and without MAC (P=0.093, **Figure 2**). In patients with MAC, 16 late deaths occurred. The cause of death was cardiac-related in 14 patients: myocardial infarction in 1, heart failure with recurrent MR in 1 and sudden unexplained death in 12 patients.

There were 19 (3%) late reinterventions, 1 (1%) in patients with MAC and 18 (3%) in patients without MAC. In the former patient, the indication for reoperation was recurrent MR and, upon reoperation, valve replacement was performed. The 8-year freedom from MV reintervention rates were 98.3% (95%CI 88.7%-99.7%) and 95.3% (95%CI 92.2%-97.2%) for patients with and patients without MAC (P=0.42, **Figure 3**).

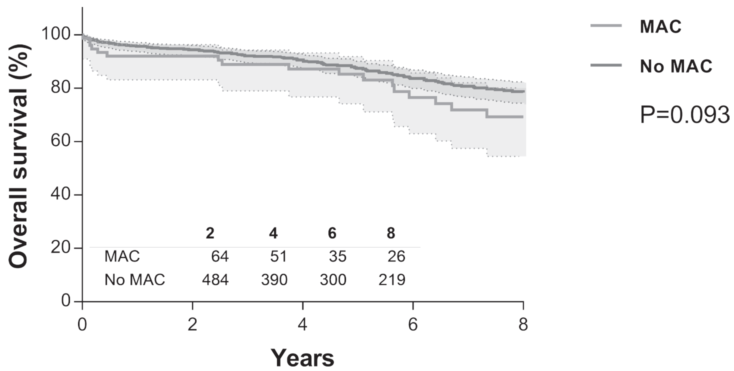


FIGURE 2. Overall survival.

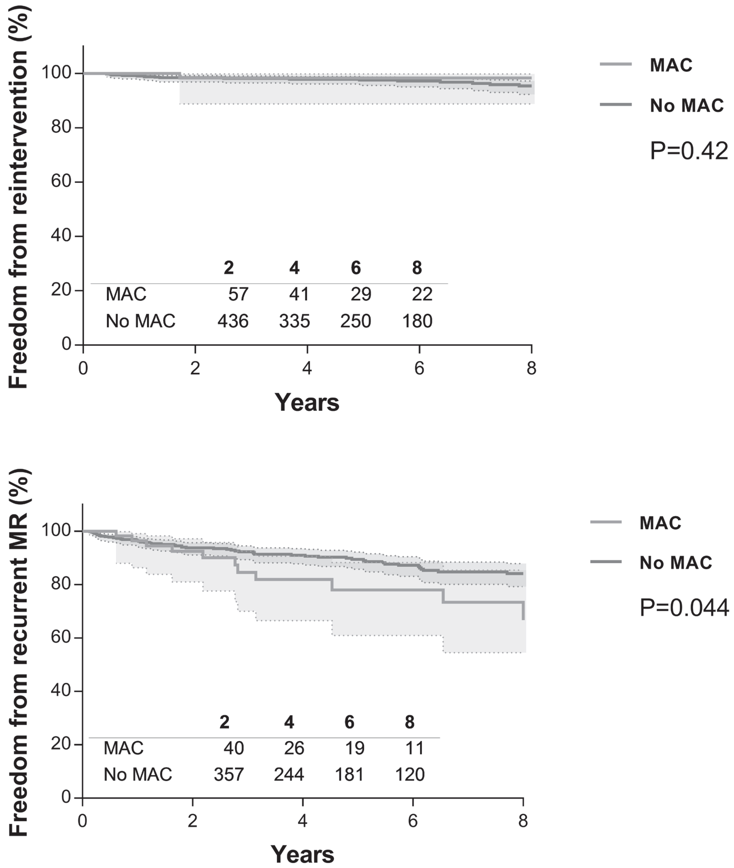


FIGURE 3. Freedom from late mitral valve reintervention (above) and recurrent MR (below).

The median echocardiographic follow-up time was 3.8 years (IQR 1.7-7.7; available for 92% of hospital survivors). Recurrent MR occurred in 74 (12%) patients, 12 (18%) from the MAC and 62 (11%) from the no-MAC group. The 8-year freedom from recurrent MR rates were 73.4% (95% CI 54.5%-85.4%) and 84.7% (95% CI 80.0%-88.4%) for patients with and without MAC (P=0.044, **Figure 3**).

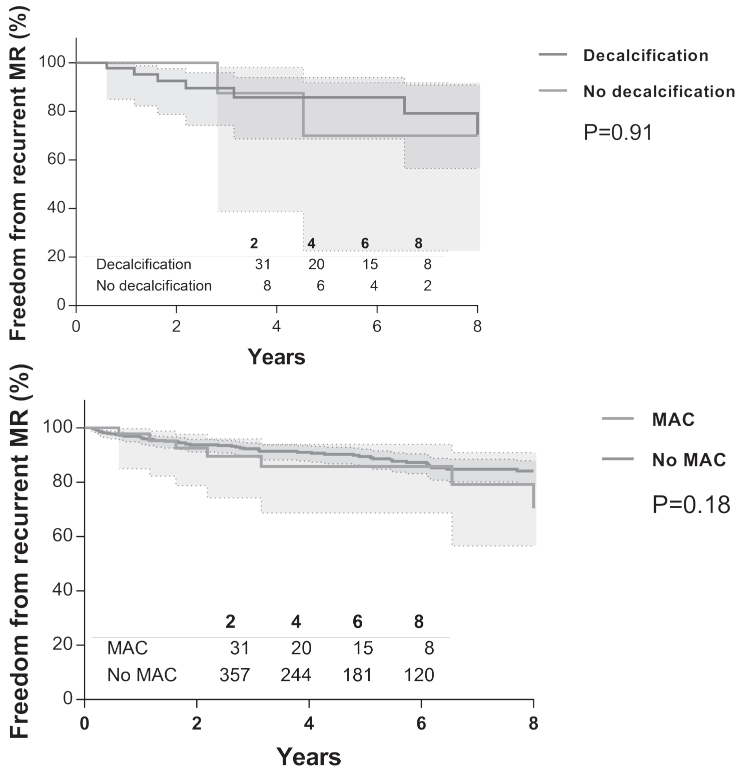


FIGURE 4. Freedom from recurrent MR in patients with MAC and annuloplasty ring implantation in whom annular calcification was or was not performed (above). Freedom from recurrent MR in patients without MAC and patients with MAC in whom annular decalcification and annuloplasty were performed (below).

Mitral valve repair performance in patients with MAC

For patients with MAC, Cox proportional-hazards regression analysis revealed non-use of ring annuloplasty (HR 17.092, 95% CI: 2.745-106.405, P=0.002) and postoperative mild MR (HR 6.291, 95% CI: 1.616-24.491, P=0.008) as risk factors for recurrent MR

(**Supplemental material B**). For the 69 patients in whom annuloplasty was performed, no significant difference in valve repair durability was observed between patients in whom annular decalcification was and was not performed (P=0.64, **Figure 4**).

For 3 patients with MAC in whom annuloplasty was not performed and no residual MR was seen on postoperative echocardiography, follow-up echocardiography was available for 2 patients. In both patients, recurrent MR occurred early after the initial operation, at 0.9 and 2.8 (**Table V**).

When the durability of valve repair in the 55 patients with MAC in whom both annular decalcification and annuloplasty were performed was compared with patients without MAC, no significant difference in the freedom from recurrent MR was observed (P=0.18, **Figure 4**).

DISCUSSION

Risk factors for the development of MAC in the general population include patient age, female gender, systemic hypertension and chronic kidney disease [14-16]. We did not observe a correlation between chronic kidney disease and MAC. This may be explained by the fact that chronic kidney disease was seldom present in our population. Our results suggest that the type of degenerative MV disease (Barlow's disease vs. FED) plays a role in the pathoetiology of MAC. This is contrary to the recent results by Fusini et al. [5]. As described by Carpentier et al., development of MAC in degenerative MV disease is a prolonged, multi-phase process of annular degeneration that is initiated by excess tension exerted on the MV annulus [17]. Emerging evidence on the primary involvement of the MV annulus and the typical prolonged history of valve disease in patients with Barlow's disease provide explanations for our findings.

The patients with MAC in our study were older with a higher proportion of women. Both characteristics have been identified as risk factors for perioperative mortality in patients undergoing valve operations [18]. Despite this, perioperative mortality remained comparable between both groups. Of note, in of 55 patients with MAC in whom annular decalcification was performed, 1 death was directly related to annular decalcification itself. Left coronary artery dominance was present and fatal postoperative ischemia developed after an initial hemodynamic stable period without electrocardiographic or echocardiographic signs of ischemia. The delayed presentation was likely related to the fact that the circumflex artery was compromised by hematoma formation and not annuloplasty suture placement. Although damage to the circumflex artery after MV repair is relatively uncommon, a recent case-series including 6 patients demonstrated the detrimental consequences of such an event as severe left ventricular dysfunction developed in 4 of 6 patients [19]. Early recognition is of utmost importance to prevent serious complications and should, in case of annular decalcification, be suspected even when signs of ischemia are initially absent.

When valve repair is performed, only limited MAC, which does not compromise normal leaflet motion and the performance of annuloplasty, can be left in place with annuloplasty sutures passed around the calcified proportion of the annulus. Again, extra care should be taken to avoid circumflex artery injury, especially if unremoved MAC is present at the area of the anterolateral commissure where the artery lies in the vicinity [19].

In our experience, repair failure occurred more commonly in patients with MAC. Our results are similar to the results of a study by Chan et al. of 625 patients with degenerative MV disease in whom MAC in various extent was present in 119 (19%) [6]. In their experience, intraoperative conversion to valve replacement was needed in 5 of 119 patients (4%) with MAC. However, technical difficulty of valve repair in these patients depends on the extent of MAC. On one hand, limited and even moderate MAC in these patients is a manageable problem that might not even necessitate annular decalcification. On the other hand, extensive MAC is linked to higher valve replacement rates even in the setting of degenerative MV disease and, when left untreated, a technically imperfect repair.

When the freedom from MV reintervention rates were compared, no differences were observed between patients with and without MAC, but repair durability was worse in patients with MAC. This can only partially be explained by differences in patient characteristics, because female sex has previously been identified as a risk factor for recurrent MR following valve repair [20].

When exploring the results of valve repair in patients with MAC only, non-use of ring annuloplasty emerged as the predominant risk factor for recurrent MR. Moreover, valve repair durability was not different between patients without MAC and patients with MAC in whom annular decalcification and annuloplasty were performed. On one hand, this suggest that should a technically sound repair be performed, valve repair durability in degenerative MV disease will not be hampered by the presence of MAC despite the technical challenges of annular decalcification that necessitates leaflet mobilization and reimplantation. On the other hand, this stresses out the importance of annular remodeling and repair stabilization in these patients. An interesting observation was that when annuloplasty was performed in patients with MAC, repair durability did not differ between patients in whom annular decalcification was or was not performed. This suggests that mild MAC that does not hamper leaflet motion or annuloplasty ring implantation might be left in place.

When MAC is left untouched in a severely calcified annulus, progressive annular dilatation after repair is unlikely to occur. The high incidence of residual or recurrent MR seen in patients cases of valve repair without ring annuloplasty is likely to result from insufficient height of leaflet coaptation resulting from the absence of annular remodeling. To compensate for insufficient leaflet coaptation, anterior MV leaflet or posterior MV leaflet, or both, augmentation can be performed. Although a leaflet-only repair resulted in poor results in our experience and is related to poor results with the edge-to-edge technique in patient with MAC as well [9], leaflet augmentation resolves the shortage of leaflet coaptation that other repair techniques fail to address. Combined with a fixed, calcified annulus this might result in a stable repair. As we learned about the poor results of valve repair without ring annuloplasty in MAC, we have started using this technique in selected patients with severe MAC in whom annular decalcification would be challenging to perform. The results of this repair technique will need to be explored in the future and it should be seen as a repair alternative only in carefully selected cases.

MV replacement is a logical alternative in patients in whom annular decalcification is considered too risky and repair durability might be hampered. However, severe drawbacks should be acknowledged. Implanting a valve prosthesis in a non-decalcified annulus can be challenging and is likely to result in paravalvular leakage. Moreover, in the absence of decalcification, a smaller size prosthesis is likely to be implanted, resulting in a risk of prosthesis-patient mismatch development. To partially compensate here for, the prosthesis can be implanted in an intra-atrial position [12]. However, the high risk of paravalvular leakage will persist. In our experience, annular decalcification was considered too risky to perform only in older patients. To decrease the risk of prosthesis-patient mismatch development, a mechanical prosthesis (with larger orifice areas than bioprostheses of comparable size) would be preferred. The use of mechanical prostheses in elderly patients is linked to increased valve-related morbidity and mortality [21].

In patients with severe MAC in whom annular decalcification is undesirable, trans-catheter MV implantation presents a less invasive alternative. Early experience in patients with MAC shows that this is linked to high early morbidity and mortality rates [22]. For the time being, trans-catheter MV implantation in these patients should be seen as a bail-out procedure to be reserved only for patients in whom surgical intervention is considered too high-risk.

LIMITATIONS

This is a single center study of a retrospective cohort of patients with limitations inherent to the study design. Considering the fact that ring annuloplasty is performed routinely in patients with degenerative MV disease at our institution, the decision not to perform annuloplasty ring implantation was individually based.

CONCLUSIONS

MAC in patients with degenerative MV disease is linked to patient age, gender and subtype of degenerative disease. In this selected population, MV intervention is reasonably safe to perform despite the presence of MAC. Early repair failure is more likely to occur and is predicted by non-use of ring annuloplasty. Nevertheless, repair durability is comparable to patients without MAC when a technically sound repair is performed. New repair techniques should be explored in patients in whom annuloplasty ring implantation is not performed.

REFERENCES

[1] Price J, Glineur D, De Kerchove L, El Khoury G. Mitral Valve Repair is Feasible Following Extensive Decalcification and Reconstruction of the Atrioventricular Groove. J Heart Valve Dis 2015;24:46-52.

[2] Uchimuro T, Fukui T, Shimizu A, Takanashi S. Mitral Valve Surgery in Patients With Severe Mitral Annular Calcification. Ann Thorac Surg 2016;101:889-95.

[3] d'Alessandro C, Vistarini N, Aubert S, Jault F, Acar C, Pavie A et al. Mitral annulus calcification: determinants of repair feasibility, early and late surgical outcome. Eur J Cardiothorac Surg 2007;32:596-603.

[4] Feindel CM, Tufail Z, David TE, Ivanov J, Armstrong S. Mitral valve surgery in patients with extensive calcification of the mitral annulus. J Thorac Cardiovasc Surg 2003;126:777-82.

[5] Fusini L, Ghulam Ali S, Tamborini G, Muratori M, Gripari P, Maffessanti F et al. Prevalence of calcification of the mitral valve annulus in patients undergoing surgical repair of mitral valve prolapse. Am J Cardiol 2014;113:1867-73.

[6] Chan V, Ruel M, Hynes M, Chaudry S, Mesana TG. Impact of mitral annular calcification on early and late outcomes following mitral valve repair of myxomatous degeneration. Interact Cardiovasc Thorac Surg 2013;17:120-5.

[7] Anyanwu AC, Itagaki S, Chikwe J, El-Eshmawi A, Adams DH. A complexity scoring system for degenerative mitral valve repair. J Thorac Cardiovasc Surg 2016;151:1661-70.

[8] Salhiyyah K, Kattach H, Ashoub A, Patrick D, Miskolczi S, Tsang G et al. Mitral valve replacement in severely calcified mitral valve annulus: a 10-year experience. Eur J Cardiothorac Surg 2017.

[9] Maisano F, Caldarola A, Blasio A, De Bonis M, La Canna G, Alfieri O. Midterm results of edge-to-edge mitral valve repair without annuloplasty. J Thorac Cardiovasc Surg 2003;126:1987-97.

[10] Morisaki A, Kato Y, Takahashi Y, Shibata T. Mitral valve repair without mitral annuloplasty with extensive mitral annular calcification. Interact Cardiovasc Thorac Surg 2014;19:1080-2.

[11] Kato Y, Hattori K, Bito Y, Kotani S, Inoue K, Shibata T. Simple supra-annular prosthesis insertion for dialysis patients with extensive mitral annular calcification. J Heart Valve Dis 2011;20:180-3.

[12] Atoui R, Lash V, Mohammadi S, Cecere R. Intra-atrial implantation of a mitral valve prosthesis in a heavily calcified mitral annulus. Eur J Cardiothorac Surg 2009;36:776-8.

[13] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008;33:523-8.

[14] Savage DD, Garrison RJ, Castelli WP, McNamara PM, Anderson SJ, Kannel WB et al. Prevalence of submitral (anular) calcium and its correlates in a general population-based sample (the Framingham Study). Am J Cardiol 1983;51:1375-8.

[15] Fox CS, Larson MG, Vasan RS, Guo CY, Parise H, Levy D et al. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. J Am Soc Nephrol 2006;17:521-7.

[16] Kanjanauthai S, Nasir K, Katz R, Rivera JJ, Takasu J, Blumenthal RS et al. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2010;213:558-62.

[17] Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve anulus: pathology and surgical management. J Thorac Cardiovasc Surg 1996;111:718-29; discussion 29-30.

[18] Rankin JS, Hammill BG, Ferguson TB, Jr., Glower DD, O'Brien SM, DeLong ER et al. Determinants of operative mortality in valvular heart surgery. J Thorac Cardiovasc Surg 2006;131:547-57.

[19] Coutinho GF, Leite F, Antunes MJ. Circumflex artery injury during mitral valve repair: Not well known, perhaps not so infrequent-lessons learned from a 6-case experience. J Thorac Cardiovasc Surg 2017;154:1613-20.

[20] Chan V, Chen L, Elmistekawy E, Ruel M, Mesana TG. Determinants of late outcomes in women undergoing mitral repair of myxomatous degeneration. Interact Cardiovasc Thorac Surg 2016;23:779-83.

[21] Jamieson WR, von Lipinski O, Miyagishima RT, Burr LH, Janusz MT, Ling H et al. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after mitral valve replacement. J Thorac Cardiovasc Surg 2005;129:1301-8.

[22] Guerrero M, Dvir D, Himbert D, Urena M, Eleid M, Wang DD et al. Transcatheter Mitral Valve Replacement in Native Mitral Valve Disease With Severe Mitral Annular Calcification: Results From the First Multicenter Global Registry. JACC Cardiovasc Interv 2016;9:1361-71.

SUPPLEMENTAL MATERIAL A. Univariable and multivariable logistic regression analysis on risk factors for MAC.

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age (continuous)	1.024	1.001-1.046	0.038	1.032	1.008-1.057	0.008
Sex (female)	2.411	1.479-3.931	<0.001	2.105	1.271-3.485	0.004
Hypertension	0.620	0.376-1.021	0.060	0.583	0.346-0.981	0.042
Atrial fibrillation						
Paroxysmal	1.432	0.770-2.664	0.26			
Chronic	1.848	1.022-3.342	0.042			
Renal impairment						
Moderate (CC 50-85)	1.204	0.699-2.072	0.50			
Severe (CC <50)	2.308	1.145-4.655	0.019			
Aetiology (Barlow's disease)	1.742	1.073-2.828	0.025	2.117	1.250-3.584	0.005
Extracardiac arteriopathy	0.738	0.093-5.852	0.77			
History of TIA or CVA	1.642	0.656-4.108	0.29			
Diabetes mellitus	0.559	0.130-2.404	0.43			
Chronic lung disease	1.479	0.693-3.158	0.31			
History of coronary artery disease	0.609	0.312-1.192	0.15			
LVEF ≤60 %	0.850	0.484-1.491	0.57			
Aortic valve intervention	1.613	0.687-3.788	0.27			

Hosmer-Lemeshow goodness of fit: 0.21

SUPPLEMENTAL MATERIAL B. Cox proportional-hazards regression analysis on risk factors for recurrent MR in patients with MAC.

	Univariable analysis			**Multivariable analysis**		
	Odds ratio	**95% confidence interval**	**P-value**	**Odds ratio**	**95% confidence interval**	**P-value**
Age (continuous)	1.027	0.973-1.084	0.33			
Sex (female)	1.311	0.392-4.384	0.66			
Hypertension	0.924	0.242-3.530	0.91			
Atrial fibrillation						
Paroxysmal	1.823	0.435-7.645	0.41			
Chronic	2.079	0.548-7.884	0.28			
Renal impairment						
Moderate (CC 50-85)	2.600	0.530-12.752	0.24			
Severe (CC <50)	4.238	0.697-25.750	0.12			
Aetiology (Barlow's disease)	1.222	0.387-3.855	0.73			
Site of leaflet prolapse						
Isolated anterior	1.012	0.121-8.438	0.99			
Bileaflet	0.991	0.301-3.263	0.99			
Annular decalcification	0.588	0.177-1.957	0.39			
Non-use of ring annuloplasty	17.000	3.081-93.812	0.001	17.092	2.745-106.405	0.002
Postoperative mild MR	6.257	1.694-23.106	0.006	6.291	1.616-24.491	0.008

10

Risk factors and clinical significance of elevated mitral valve gradient following valve repair for degenerative disease

Anton Tomšič; Yasmine L. Hiemstra; Bardia Arabkhani; Bart J.A. Mertens; Thomas J. van Brakel; Michel I.M. Versteegh; Nina Ajmone Marsan; Robert J.M. Klautz ; Meindert Palmen

Eur J Cardiothorac Surg. 2020;57(2):293-299

ABSTRACT

Background. The risk factors and clinical effect of elevated mitral valve gradients after valve repair for degenerative valve disease remain insufficiently understood.

Methods. Between January 2004 and December 2015, 484 patients underwent valve repair for degenerative disease. A true-sized full annuloplasty ring was implanted in all cases. We analysed the effect of preoperative and intraoperative factors on the post-repair gradient. Additionally, we explored the effect of post-repair gradient on long-term outcomes.

Results. On linear regression analysis, post-repair mitral valve gradients were associated with patient age (coefficient=-0.110, standard error=0.005, P=0.034), body surface area (coefficient=0.905, standard error=0.340, P=0.008), implanted annuloplasty ring size (coefficient=-0.181, standard error=0.018, P<0.001), and the use of Physio I ring (coefficient=0.414, standard error=0.122, P=0.001). On multivariable analysis, post-repair mitral valve gradient was not associated with overall survival [hazard ratio (HR) 1.034, 95% confidence interval (CI) 0.889-1.203, P=0.66] or freedom from atrial fibrillation (HR 0.849, 95% CI 0.682-1.057, P=0.14), but did emerge as a risk factor for mitral valve reintervention (HR 1.378, 95% CI 1.033-1.838, P=0.029). Two out of 11 reinterventions were performed due to mitral valve stenosis and in both patients, high post-repair gradients were seen readily on predischarge echocardiography.

Conclusion. Following valve repair for degenerative mitral valve disease, elevated gradients occur even when true-sized annuloplasty is performed. The late clinical results of valve repair with elevated post-repair gradient are impaired and further studies are needed to explore preventive measures aimed at resolving the issue.

INTRODUCTION

Surgical mitral valve (MV) repair is the treatment of choice for mitral regurgitation (MR) due to degenerative disease with high valve reparability, repair durability and freedom from reoperation rates readily established [1, 2]. When the results of MV repair are examined in further detail, the problem of elevated post-repair gradients, following an otherwise successful repair without residual regurgitation, has emerged as a subject of debate [3-5].

The problem of elevated post-repair MV gradients was initially described in patients after restrictive mitral annuloplasty for ischemic MR [4] but may also be of clinical importance in patients with degenerative MR [3, 5]. To justify the growing enthusiasm for early surgery of yet asymptomatic patients with degenerative MR, optimal patient- and valve-related results are needed. Data on the risk factors and clinical impact of elevated MV gradients following valve repair for degenerative disease remain scarce.

The aim of this study was to analyse the risk factors of elevated post-repair MV gradients and the effect here of on patient- and valve-related outcomes in a cohort of patients who underwent successful MV repair for degenerative disease.

METHODS

Patients

All adult patients (≥18 years of age) who underwent surgical intervention (n=528) for MR due to degenerative disease between January 2004 and December 2015 at our institution were eligible for inclusion. We excluded patients with a history of previous cardiac surgery (n=18) and patients in whom MV replacement was performed (n=9). Of the remaining 501 patients, 17 additional patients were excluded for the following reasons: early mortality (n=6), non-use of annuloplasty ring (n=4) or missing predischarge echocardiogram (n=7). The final study cohort compromised 484 patients who all underwent successful MV repair with a complete annuloplasty ring.

Measurements of MV gradients were acquired from continuous wave Doppler acquisitions of the diastolic inflow of the MV. Mean MV gradient was calculated as the average of 3 and 5 cycles or patients in sinus rhythm and atrial fibrillation, respectively. All acquisitions were performed according to a standardized protocol of our echo lab to ensure data reproducibility. All measures were performed by experienced echocardiographists.

Study endpoints

All endpoints were defined according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions [6]. Primary endpoints included all-cause mortality and freedom from MV reintervention. Secondary endpoints included freedom from atrial fibrillation. We excluded other types of atrial tachycardias (e.g. atrial flutter or incisional atrial tachycardia) because of etiological differences associated with the development post-repair atrial tachycardias [7]. Only patients in preoperative sinus rhythm (n=312) were included in the latter analysis.

Surgical technique and perioperative care

When indicated, anterior MV leaflet prolapse was addressed with chordal replacement. Posterior MV leaflet prolapse was addressed with a combination of leaflet resection and chordal replacement techniques. The decision on which technique to use was based on the extent of leaflet prolapse and excessive tissue in height and/or width. Earlier in this series, annular plication was more frequently used to help restore the continuity of the posterior MV leaflet. Later, leaflet sliding techniques were employed. Commissural prolapse was primarily addressed with papillary muscle head repositioning.

All patients included in the current study underwent full annuloplasty ring implantation. Ring sizing was standardly based on the surface area of the anterior MV leaflet and was not influenced by the type of anterior and/or posterior MV leaflet repair technique used. No over- or downsizing was performed in any of the patients.

Intraoperative transoesophageal echocardiography was performed by an experienced cardiologist to document the intraoperative result of MV repair. Additionally, predischarge transthoracic echocardiography (performed on postoperative day 4-7) was performed to exclude any significant residual MR. Systolic anterior motion was observed in 2 patients and treated conservatively. Oral anticoagulation was initiated for a period of 3 months with a target Internationalized Normalized Ratio of 2.0-3.0. In presence of other indications, the target Internationalized Normalized Ratio range and treatment duration were adjusted accordingly.

Follow-up

Preoperative, intraoperative and postoperative data were retrospectively collected from our computerized database. Follow-up survival, clinical and echocardiographic data were collected through regular clinical visits at our institution or affiliated clinics and hospitals, and through questionnaires to patients. Patient follow-up was based on the available recommendations [8]. Records pertaining to reported office visits, echocardiography and rhythm information, operations, cardioversions, catheter ablation or hospitalizations were obtained and analysed. Rhythm follow-up was based on electrocardiograms obtained during regular follow-up. Additional rhythm monitoring (e.g. 24-h Holter monitoring) was performed on clinical grounds (e.g. complaints of heart palpitations) and the indication for this was left at the discretion of the attending cardiologist. A total of 1126 (mean 2.3/patient, range 0-8) follow-up echocardiograms were available for analysis. The study was approved by our Institutional Ethics Committee Follow-up was completed in February 2017.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile range (IQR) when not normally distributed. Categorical data are presented as counts and percentages. The distribution of variables was evaluated using the Kolmogorov-Smirnov test.

A univariable and multivariable linear regression model, with post-repair MV gradient as a dependent continuous variable, was built to explore the factors associated with post-repair MV gradient. Variable inclusion was based on the previously established effect on MV gradient. To assess for the presence of violations in model assumptions, residuals were plotted versus fitted values and investigated graphically. Univariable and multivariable Cox proportional hazards regression analysis was used to explore risk factors for the occurrence of time-to-event outcomes. Based on known clinical validity and taking into account the ratio of events to risk factors, the following factors were included in respective multivariate models: *for mortalit*y: age, gender, chronic pulmonary disease, renal impairment, left ventricular function, symptomatic MR, atrial fibrillation and post-repair MV gradient; *for reintervention*: anterior MV leaflet repair and post-repair MV gradient; and *for atrial fibrillation*: age, tricuspid valve repair, preoperative left atrial diameter and post-repair MV gradient. Cubic third-degree splines were used to adjust for possible non-linear association of mean MV gradient with time-to-event outcome in the proportional hazards model. The Wald test was used to test for the presence of a non-linear effect. In addition to P-value-based hypothesis testing, non-linearity of mean MV gradient was assessed graphically by plotting the fitted splines for mean MV gradient, together with 95% confidence intervals (CIs) on the log-hazard scale versus mean MV gradient.

To study the evolution of mean MV gradients during the follow-up period, a mixed-model based linear regression analysis of MV gradient on follow-up time which accounts for repeated within-patient observation was carried out. To account for potential heteroscedasticity or non-normality, bootstrap-based standard errors were investigated. In addition, a *post hoc* exploration of model residuals was explored to investigate these same model assumptions as well as the linearity assumption of MV gradient decent versus follow-up time. No evidence of serious model deviations was found and hence the regular standard errors and hypothesis test are reported.

All tests were 2-tailed and a P-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM Statistics for Windows, version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) and R, version 3.5.1 using the Survival package, version 2.43-3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics and MV repair details

Baseline characteristics of the whole study group is presented in **Table I**. Median patient age was 66.5 (IQR 57.8-73.8) years and the majority of patients were male. The repair and procedure details are presented in **Table II**. A full-ring was used in all patients; the majority of patients (n=456; 94.2%) underwent either a Physio I (n=223; 46.1%) or Physio II (n=233; 48.1%) ring (Edwards Lifesciences, Irvine, CA, USA) implantation. In 42 (8.7%) patients, a ring size 30 or smaller was implanted.

TABLE I. Baseline characteristics.

	n=484
Age (years)	66.5 (IQR 57.8-73.8)
Gender (female)	171 (35.3)
Body surface area (m^2)	1.93±0.22
NYHA	
I	146 (30.2)
II	243 (50.2)
III-IV	95 (19.6)
Hypertension	221 (45.7)
Atrial fibrillation	172 (35.5)
Renal impairment (mL/min/1.73 m^2)	
Moderate (CC 50-85)	226 (46.7)
Severe (CC <50)	41 (8.5)
Diabetes mellitus	22 (4.5)
Chronic lung disease	42 (8.7)
Mitral annular calcification	49 (10.1)
Echocardiographic characteristics	
LVEF ≤60%	134 (27.7)
LVEDD (mm)*	54±7
LVESD (mm)*	33±7
LAD (mm)*	45.0 (IQR 40.0-49.0)
EuroSCORE II	1.76 (IQR 0.99-3.24)
Degenerative disease subtype	
Barlow's disease	140 (28.9)
Forme fruste Barlow's disease	51 (10.5)
Site of leaflet prolapse	
Posterior leaflet	299 (61.8)
Single scallop prolapse	234 (48.3)
Anterior leaflet	41 (8.5)
Bileaflet	144 (29.7)

*Data are presented as n (%) and means ± SD or medians (IQR). Abbreviations: CC: creatinine clearance; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure. *Available for ≥95% of patients.*

TABLE II. Mitral valve repair details.

	n=484
Mitral valve annulus	
Plication	102 (21.1)
Anterior mitral valve leaflet repair (neochords)	125 (25.8)
Posterior mitral valve leaflet	
Resection	321 (66.3)
Leaflet sliding	222 (45.9)
Neochords	206 (42.6)
Chordal transfer	9 (1.9)
Indentation closure	85 (17.6)
Commissural repair	111 (22.9)
Annuloplasty ring type	
Physio I ring	223 (46.1)
Physio II ring	233 (48.1)
Other	28 (5.8)
Annuloplasty ring size	
≤28	42 (8.7)
30	62 (12.8)
32	112 (23.1)
≥34	268 (55.4)
Intraoperative mitral valve gradient (mmHg)	1.66 (IQR 1.16-2.40)
Concomitant procedures	
Tricuspid valve repair	321 (51.4)
Radiofrequency ablation for atrial fibrillation	148 (30.6)
Coronary artery bypass surgery	96 (19.8)
Aortic valve intervention	28 (5.8)

Data are presented as n (%) and medians (IQR).

Post-repair MV gradient

A moderate positive correlation (r=0.356, n=391, P<0.001) between the intraoperative and predischarge MV gradient was seen (**Supplementary material, Figure S1**). The haemodynamic results of valve repair are demonstrated in **Table III**. As expected, post-repair MV gradients decreased with the size of annuloplasty ring implanted (**Figure 1**).

TABLE III. Postoperative echocardiographic results.

	n=484
Predischarge mitral valve gradient (mmHg)	3.46±1.43
Predischarge heart rate (min^{-1})	80±15
Predischarge stroke volume (ml)*	74 (IQR 58-93)
Predischarge cardiac index (L/m^2)*	5.7 (IQR 4.6-7.4)
Predischarge haemoglobin value (mmol/L)	6.4±0.8

*Data are presented as means ± standard deviations and medians (IQR). *Available for ≥90% of patients.*

On linear regression analysis, increasing patient age (coefficient -0.11, standard error 0.005, P-value 0.034) and annuloplasty ring size (coefficient -0.181, standard error 0.018, P-value<0.001) were correlated with lower post-repair MV gradients (**Table IV)**. On the other hand, increasing body surface area (coefficient 0.905, standard error 0.340, P-value 0.008) and, interestingly, use of the Physio I ring (coefficient 0.414, standard error 0.122, P-value <0.001) were correlated with higher post-repair MV gradients. The linear regression model demonstrated good fit with no evidence of heteroscedasticity or non-linearity (**Supplementary material, Figure S2**).

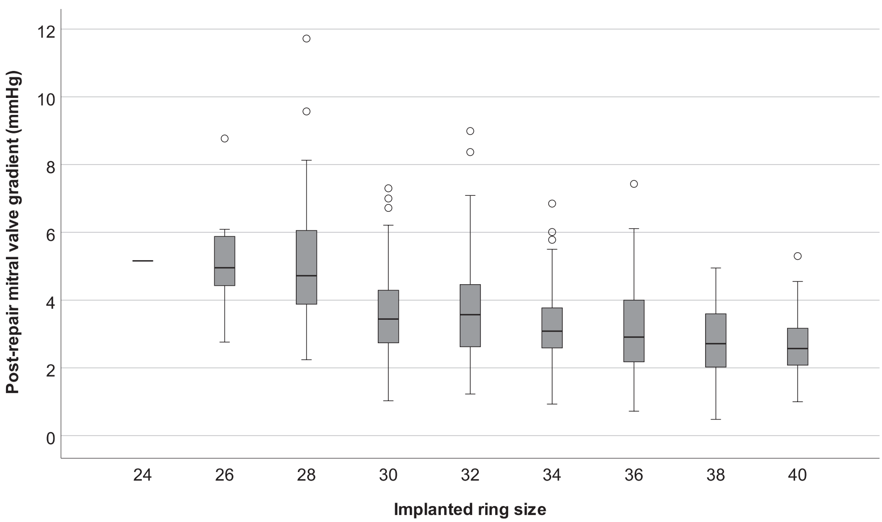


FIGURE 1. Post-repair resting mitral valve gradients in relation to the implanted annuloplasty ring size. Smallest size rings (≤size 28) had the most pronounced effect on post-repair gradients. The middle horizontal line presents the median and the upper and lower borders of the box present the upper and lower quartiles. The upper and lower whiskers present the maximum and minimum values of non-outliers. Extra dots present the outliers.

TABLE IV. Univariable and multivariable linear regression analysis on risk factors associated with post-repair mitral valve gradients.

	Univariable analysis			Multivariable analysis		
	Coefficient	Standard error	P-value	Coefficient	Standard error	P-value
Gender (female)	0.114	0.137	0.40	0.069	0.153	0.65
Age (years)	0.000	0.006	0.98	-0.110	0.005	0.034
Body surface area	0.294	0.302	0.33	0.905	0.340	0.008
Atrial fibrillation	-0.137	0.136	0.32	-0.008	0.121	0.95
Posterior mitral annular plication	0.347	0.160	0.030	0.109	0.155	0.48
Annular decalcification	-0.682	0.223	0.002	-0.235	0.195	0.23
PMVL resection	0.028	0.139	0.84	0.188	0.126	0.14
PMVL indentation closure	-0.154	0.172	0.37	-0.123	0.149	0.41
Annuloplasty ring size	-0.164	0.017	<0.001	-0.181	0.018	<0.001
Annuloplasty ring type						
Physio I ring	0.486	0.129	<0.001	0.414	0.122	0.001
Postoperative blood haemoglobin value	-0.288	0.082	<0.001	-0.301	0.071	<0.001
Postoperative heart rate	0.029	0.004	<0.001	0.024	0.004	<0.001

Abbreviations: AMVL: anterior mitral valve leaflet; PMVL: posterior mitral valve leaflet.

Late clinical results

From cubic spline-based analyses, no evidence of non-linearity for post-repair MV gradient was found for all time-to-event outcomes (**Supplementary material, Figures S3-S5**). Hence, post-repair MV gradient was entered into the Cox proportional hazards regression analysis models as a continuous variable for all subsequent analyses.

During a median follow-up period of 5.8 (IQR 3.4-9.3) years (99.5% complete, 2 patients were lost to follow-up due to emigration), 84 patients died. When corrected for patient age, gender, chronic pulmonary disease, renal impairment, left ventricular function, symptomatic MR and atrial fibrillation, post-repair MV gradient was not associated with patient survival (HR 1.034, 95% CI 0.889-1.203, P=0.66; **Supplementary material, Table S1**).

Follow-up on clinical related events was 90% complete with a mean duration of 5.2 (IQR 2.7-8.8) years. When adjusted for patient age, tricuspid valve repair and preoperative left atrial diameter, post-repair MV gradient was not associated with late atrial fibrillation occurrence (HR 0.849, 95% CI 0.682-1.057, P=0.14; **Supplementary material, Table S1**).

When adjusted for anterior MV leaflet repair, post-repair MV gradient was associated with a higher risk of MV reintervention (HR 1.378, 95% CI 1.033-1.838, P=0.029; **Supplementary material, Table S1**). A total of 11 late reinterventions were performed. The indication for reintervention was recurrent MR in 9 patients and elevated MV gradient in the remaining 2 patients. In both of the latter patients, a post-repair gradient of ≥5 mmHg (5.88 mmHg and 5.23 mmHg, respectively) was seen on pre-discharge echocardiography, despite an acceptable gradient seen on intraoperative echocardiography (2.53 mmHg and 4.23 mmHg, respectively). In the first of the latter patients, an annuloplasty ring size 26 was initially implanted and a re-repair due to heart failure symptoms (no significant MR or other explanation for this observation were found) was performed 1.3 years after the initial operation. Upon reoperation, the annuloplasty ring was explanted, resolving the problem of elevated gradient. In the other patient, an annuloplasty ring size 32 was implanted during the initial operation. Severe pannus formation occurred and the patient underwent a valve replacement 1.1 years after the initial operation.

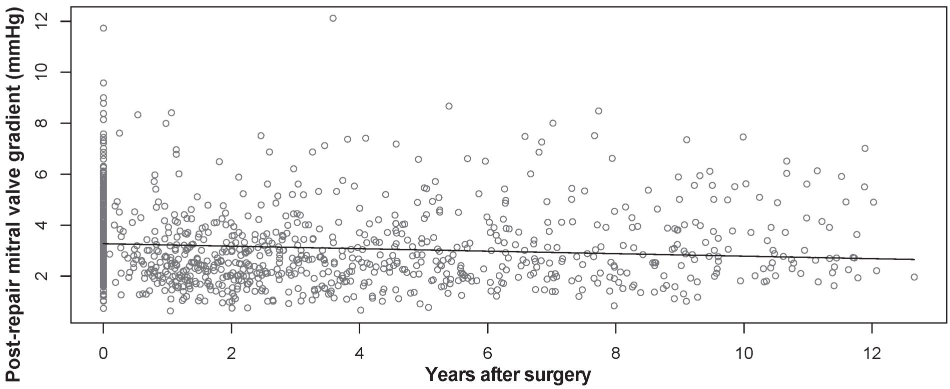


FIGURE 2. Longitudinal changes in mean resting mitral valve gradients. During the follow-up period, a slight decrease, when compared with the predischarge post-repair mean mitral valve gradient, can be observed.

Late echocardiographic results

On mixed-model linear regression analysis on the evolution of mean MV gradient during the follow-up period, a slight decline in MV gradients was seen (estimate=-0.05, 95% CI = -0.07- -0.02, P<0.001) during the follow-up period (**Figure 2**).

DISCUSSION

The results of our study are in line with previous studies, and demonstrate that, following valve repair for degenerative disease, high post-repair gradients are of important clinical relevance. However, repair technique (in particular posterior MV leaflet resection) did not show a significant effect on post-repair gradients and no effect of post-repair gradients on the occurrence of late atrial fibrillation was observed.

The mechanism of elevated post-repair MV gradients is poorly understood, but is in our opinion related to fixation of the posterior annular perimeter length. Indeed, in an adult sheep model, Dagum et al. have shown that cyclic changes in the MV annular area, reaching a maximum in late diastole, are correlated with length changes of the posterior annular perimeter [9]. After implantation of a true-sized partial or complete flexible annuloplasty device, complete fixation of the MV annular area, posterior and anterior annular perimeters throughout the cardiac cycle was observed. Similarly, Bothe et al. reported that MV annuloplasty results in a significant reduction of the maximal MV opening area [10], independent of the type of annuloplasty device used (partial or full ring; flexible, semi-rigid or rigid). Moreover, the Physio I ring (as well as the majority of other full rings implanted) did not impair posterior MV leaflet motion. Additionally, while the Physio I ring did increase the excursion of the annular and belly region of the anterior MV leaflet, it did not affect the excursion of the anterior leaflet at the leaflet edge. No effect on anterior leaflet motion was seen after the implantation of a partial Cosgrove-Edwards band (Edwards Lifesciences, Irvine, CA, USA). Their results suggest that no diastolic flow obstruction due to changes in anterior leaflet motion is to be expected after implantation of the majority of annuloplasty devices tested.

In a study on 107 patients after MV repair for degenerative disease, Mesana et al. suggested that full rings may be associated with higher post-repair gradients when compared to partial bands [5]. Their results need to be interpreted with caution as the Duran ring (Medtronic Inc., Minneapolis, MN, USA), notoriously prone to significant pannus formation [11, 12], was used in most patients who underwent full ring implantation. As MV gradients were measured several years after the initial operation, the high gradients observed in this group are most likely related to pannus formation and not implanted annuloplasty device type. Murashita et al. explored post-repair gradients in 1147 patients after MV repair for degenerative disease [13]. In most patients, a standard 63 mm flexible band was implanted, irrespective of annular perimeter length or anterior leaflet size. In the first median follow-up period (124.5 days after operation), a mean gradient of 3.7±1.6 mmHg was reported that declined to a mean gradient of 3.3±1.8 mmHg in the second median follow-up period (600 days after operation). The gradients in the first median follow-up period seem somehow higher than early post-repair gradients observed in our population. On longitudinal analysis, a decline similar to the one observed by Murashita et al. was also observed in our population. While clearly limited, amongst others, by the unadjusted differences in patient populations, such observations challenge the alleged superiority of partial bands in terms of post-repair gradients. On the other side, excessive shortening of the posterior annular perimeter (resulting from downsizing described by the authors) is bound to have resulted in smaller MV areas than would have been achieved with a true-sized ring.

The results of our analyses suggest that the post-repair gradient is partially associated with patient characteristics (relation of patient age and body surface area to post-repair gradient likely reflect the relation of these parameters to systemic metabolic needs and hereto related cardiac output). Moreover, our results demonstrate that the choice of annuloplasty device used might affect post-repair gradients. This likely correspondent to the differences in the ratio between the anterior-posterior diameter (reflecting anterior MV leaflet surface area to which the ring is sized) and the length of the "posterior perimeter" of the annuloplasty ring between different annuloplasty devices. We are unaware of any studies demonstrating that the increased saddle shape of the Physio II ring is related to improved diastolic MV opening properties when compared to annuloplasty devices with less pronounced saddle-shape. Because of the lack of evidence, we cannot exclude the possibility that the Physio II ring results in superior diastolic opening properties of the anterior leaflet that might explain our observation. For the time being, this should, however, be seen as a theory and properly designed studies will need to be conducted in the future.

In a recent meta-analysis, Mazine et al. have speculated that in cases of posterior MV leaflet prolapse, chordal replacement techniques will result in lower MV gradients when compared to leaflet resection techniques [14]. Our results failed to demonstrate any significant effect of posterior leaflet resection on post-repair gradient. This is likely related to the fact that we primarily used leaflet resection techniques to address excessive posterior MV leaflet tissue and structurally avoided excessive resection. Should this be avoided, no significant shortening of the posterior leaflet free edge, that could at least theoretically limit diastolic leaflet mobility, is to be expected. Functional MV stenosis should not present a reason not to perform adequate leaflet resection when this is indicated, an opinion previously emphasized by our group and others [15-18].

We did not observe any effect of elevated MV gradients on freedom from atrial fibrillation. On the contrary, elevated post-repair MV gradient was identified as a risk factor for late atrial fibrillation occurrence in recent studies by Kawamoto et al. [19] as well as Ma et al. [20]. We included only patients in sinus rhythm who did not undergo any ablation procedures, a characteristic that could provide an explanation for the differences observed between our results and the results by Kawamoto et al. [19]. More importantly, we differentiated between atrial fibrillation and other types of atrial tachycardias as the mechanisms associated with the development of different atrial tachycardias after MV operations are known to fundamentally differ [7]. To adjust for potential unadjusted bias, future studies should include information on the type of incision made to expose the MV when exploring the effect of other factors on early and late atrial tachycardias. Previous studies also demonstrated that an elevated post-repair MV gradient impairs left atrial reverse remodelling [21]. Nevertheless, atrial fibrillation is most likely related to left atrial fibrosis that develops because of long-standing volume overload prior to the operation and is present even in patients in preoperative sinus rhythm [22]. More studies, with longer follow-up, are also needed to explore weather left atrial reverse remodelling in the presence of elevated post-repair gradient is decreased or only delayed. The results of our study do, however, suggest that the clinical burden of elevated post-repair gradient might be lower than previously suggested.

The observation that the risk of reintervention might be related to post-repair MV gradient has not previously been reported. The incidence of reoperation for MV stenosis after previous repair is known to be low [13, 23] but reflects only the patients most affected by this condition. Other studies have additionally shown that high post-repair gradients will result in decreased exercise tolerance and quality of life [3, 5]. We followed the established concepts of valve repair for degenerative disease that include annular remodelling and stabilization. As fixation of the maximal posterior perimeter length, and hereto related maximal MV area, are likely inevitable with any type of annuloplasty device used, elevated post-repair gradients might not be avoidable in all patients. Omitting annuloplasty device implantation is controversial as this is known to result in a higher risk of recurrent MR [24]. Possibly, new annuloplasty device design and identification of patients in whom annular characteristics are sufficiently preserved to support valve sufficiency in the long-term even without annular stabilization would help reduce the burden of this problem.

LIMITATIONS

This is a single-centre retrospective study with study limitations inherent to the study design. The results are applicable to the type of MV repair techniques described only and further studies are needed to evaluate the effect or other repair techniques (e.g. edge-to-edge repair) and annuloplasty devices on the occurrence of elevated post-repair gradients. During the study period, the MV repair techniques have evolved with, in particular, annular plication being performed less often. As the type of leaflet repair did not affect the sizing of the annuloplasty device implanted, no relevant effect on the results presented is to be expected. Moreover, the number of reinterventions was low and prevented us to explore the risk factors for MV reintervention specified to the indication for reintervention (i.p. recurrent MR vs. elevated MV gradient). While we failed to identify a relation between post-repair MV gradient and survival or atrial fibrillation, we cannot exclude the possibility that a correlation does exist but we were unable to detect it due to an insufficient number of patients and events. Our results should thus be seen as hypothesis forming and will need to be confirmed in future studies. We have performed cubic spline analyses but failed to identify a cut-off value that would ease the identification of patient a risk for complications related to elevated post-repair MV gradient in the clinical setting. Identification of a cut-off value should be pursued in future studies. Nevertheless, in line with previous studies, our results do support the efforts aimed at securing the lowest possible post-repair MV gradient.

CONCLUSION

Following MV repair with a semi-rigid annuloplasty ring, increased resting MV gradients are not uncommon. This is, among others, related to the implanted ring size and patient body surface area. Elevated post-repair MV gradients might result in poorer freedom from reintervention due to the added risk of reintervention for MV stenosis while survival and incidence of late atrial fibrillation development do not seem to be affected.

REFERENCES

[1] Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. J Thorac Cardiovasc Surg 2012;144:308-12.

[2] David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation 2013;127:1485-92.

[3] Chan KL, Chen SY, Chan V, Hay K, Mesana T, Lam BK. Functional significance of elevated mitral gradients after repair for degenerative mitral regurgitation. Circ Cardiovasc Imaging 2013;6:1041-7.

[4] Magne J, Senechal M, Mathieu P, Dumesnil JG, Dagenais F, Pibarot P. Restrictive annuloplasty for ischemic mitral regurgitation may induce functional mitral stenosis. J Am Coll Cardiol 2008;51:1692-701.

[5] Mesana TG, Lam BK, Chan V, Chen K, Ruel M, Chan K. Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: potential affect on surgical strategy. J Thorac Cardiovasc Surg 2013;146:1418-23; discussion 23-5.

[6] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732-8.

[7] Lukac P, Hjortdal VE, Pedersen AK, Mortensen PT, Jensen HK, Hansen PS. Atrial incision affects the incidence of atrial tachycardia after mitral valve surgery. Ann Thorac Surg 2006;81:509-13.

[8] Butchart EG, Gohlke-Barwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, et al. Recommendations for the management of patients after heart valve surgery. Eur Heart J 2005;26:2463-71.

[9] Dagum P, Timek T, Green GR, Daughters GT, Liang D, Ingels NB, Jr., et al. Three-dimensional geometric comparison of partial and complete flexible mitral annuloplasty rings. J Thorac Cardiovasc Surg 2001;122:665-73.

[10] Bothe W, Kvitting JP, Swanson JC, Goktepe S, Vo KN, Ingels NB, et al. How do annuloplasty rings affect mitral leaflet dynamic motion? Eur J Cardiothorac Surg 2010;38:340-9.

[11] Chung CH, Kim JB, Choo SJ, Kim KS, Song H, Song MG, et al. Long-term outcomes after mitral ring annuloplasty for degenerative mitral regurgitation: Duran ring versus Carpentier-Edwards ring. J Heart Valve Dis 2007;16:536-44; discussion 44-5.

[12] Suh YJ, Chang BC, Im DJ, Kim YJ, Hong YJ, Hong GR, et al. Assessment of mitral annuloplasty ring by cardiac computed tomography: Correlation with echocardiographic parameters and comparison between two different ring types. J Thorac Cardiovasc Surg 2015;150:1082-90.

[13] Murashita T, Greason KL, Suri RM, Daly RC, Joyce LD, Stulak JM, et al. Mitral valve gradient after valve repair of degenerative regurgitation with restrictive annuloplasty. J Thorac Cardiovasc Surg 2016;151:106-9.

[14] Mazine A, Friedrich JO, Nedadur R, Verma S, Ouzounian M, Juni P, et al. Systematic review and meta-analysis of chordal replacement versus leaflet resection for posterior mitral leaflet prolapse. J Thorac Cardiovasc Surg 2018;155:120-8.

[15] Tomšič A, Hiemstra YL, van Brakel TJ, Versteegh MI, Ajmone Marsan N, Klautz RJ, et al. Excessive leaflet tissue in mitral valve repair for isolated posterior leaflet prolapse-leaflet resection or shortening neochords? A propensity score adjusted comparison. J Cardiovasc Surg (Torino) 2019;60:111-8.

[16] Antunes MJ. Revisiting posterior mitral leaflet prolapse: Resect, respect, or resect with respect? J Thorac Cardiovasc Surg 2018;155:602-3.

[17] Tomšič A, Klautz RJM, Palmen M. Respect versus resect: Two different repair techniques or two different tools in the toolbox? J Thorac Cardiovasc Surg 2018;155:600-1.

[18] Dreyfus GD, Dulguerov F, Marcacci C, Haley SR, Gkouma A, Dommerc C, et al. "Respect when you can, resect when you should": A realistic approach to posterior leaflet mitral valve repair. J Thorac Cardiovasc Surg 2018;156:1856-66 e3.

[19] Kawamoto N, Fujita T, Fukushima S, Shimahara Y, Kume Y, Matsumoto Y, et al. Functional mitral stenosis after mitral valve repair for Type II dysfunction: determinants and impacts on long-term outcome. Eur J Cardiothorac Surg 2018;54:453-9.

[20] Ma W, Shi W, Wu W, Ye W, Kong Y, Zhu D, et al. Elevated gradient after mitral valve repair: The effect of surgical technique and relevance of postoperative atrial fibrillation. J Thorac Cardiovasc Surg 2018. [Epub ahead of print]

[21] Marsan NA, Maffessanti F, Tamborini G, Gripari P, Caiani E, Fusini L, et al. Left atrial reverse remodeling and functional improvement after mitral valve repair in degenerative mitral regurgitation: a real-time 3-dimensional echocardiography study. Am Heart J 2011;161:314-21.

[22] Corradi D, Callegari S, Maestri R, Ferrara D, Mangieri D, Alinovi R, et al. Differential structural remodeling of the left-atrial posterior wall in patients affected by mitral regurgitation with or without persistent atrial fibrillation: a morphological and molecular study. J Cardiovasc Electrophysiol 2012;23:271-9.

[23] Becker TM, Grayburn PA, Roberts WC. Mitral Valve Repair for Pure Mitral Regurgitation Followed Years Later by Mitral Valve Replacement for Mitral Stenosis. Am J Cardiol 2017;120:160-6.

[24] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135:274-82.

SUPPLEMENTARY MATERIAL

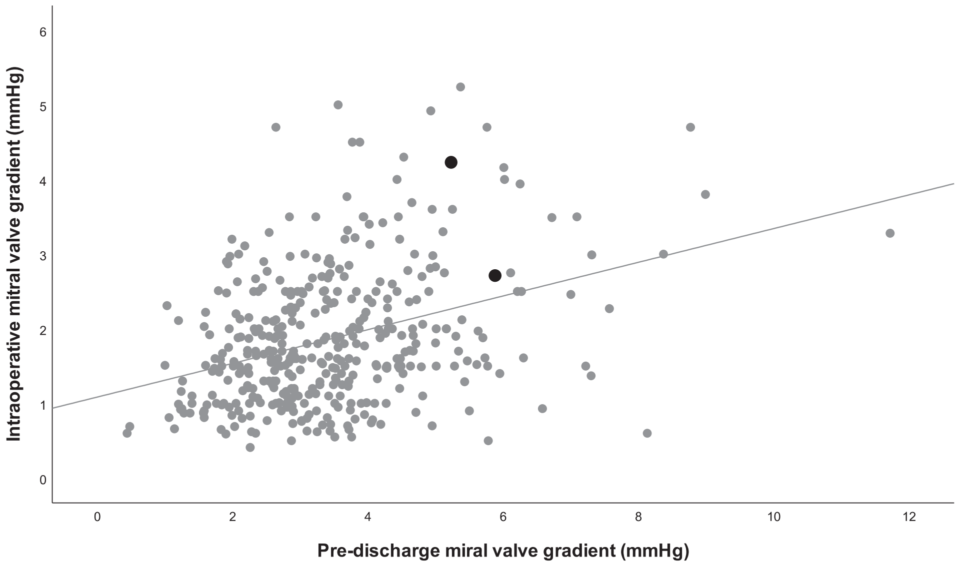


FIGURE S1. Pearson's correlation analysis demonstrated a moderate positive correlation (r=0.356, n=391, P<0.001) between the intraoperative and pre-discharge post-repair MV gradient. Patients in whom a late reintervention was performed a highlighted in red. An intraoperative gradient of 2.53 mmHg and 4.23 mmHg, and pre-discharge gradient of 5.88 mmHg and 5.23 mmHg, respectively, was present in these patients.

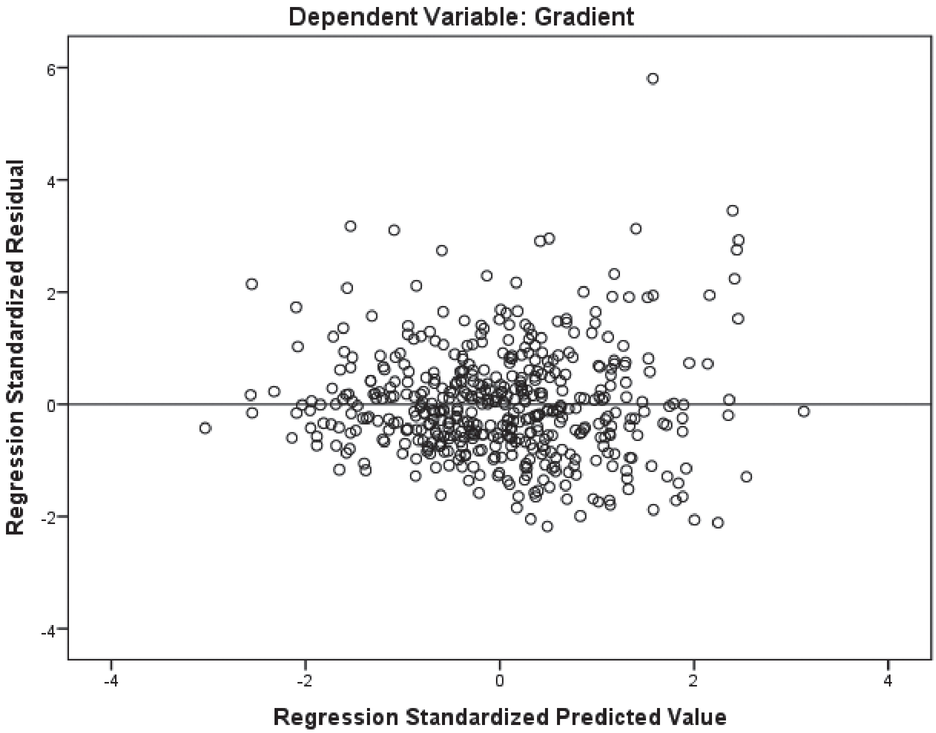


FIGURE S2. Model fit analysis for the linear regression analysis model on the risk factors associated with post-repair mitral valve gradient.

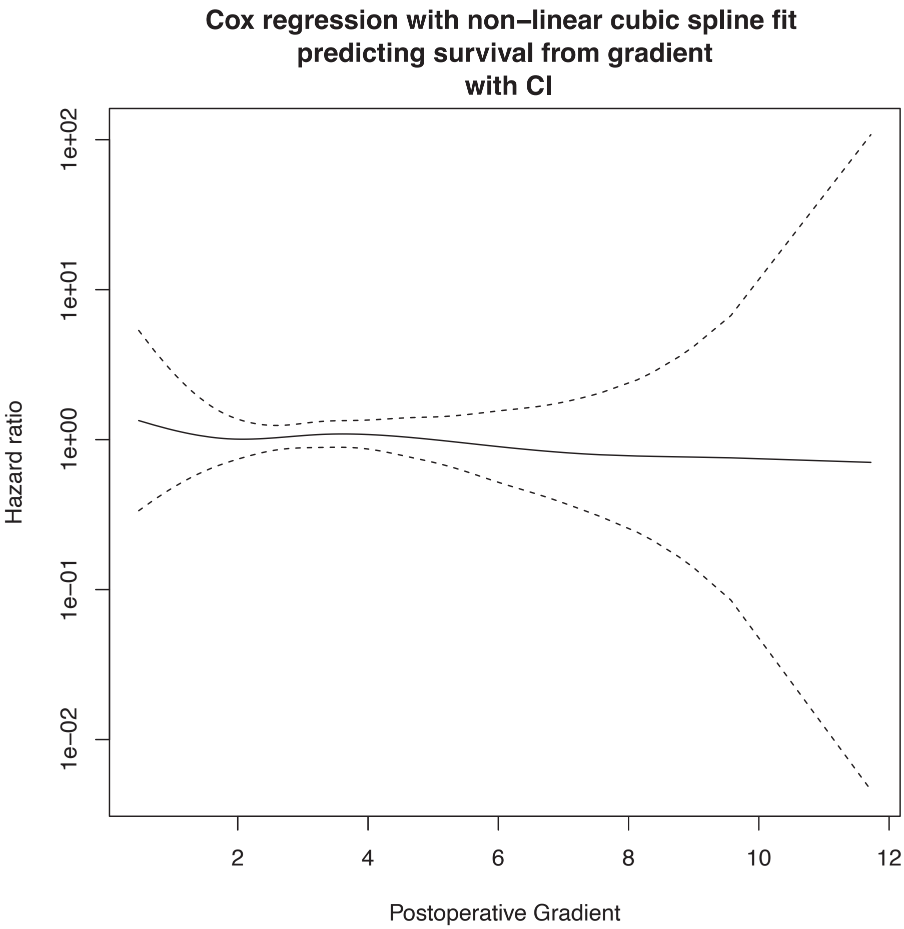


FIGURE S3. Univariate cubic spline regression analysis for the outcome mortality. No evidence of for non-linearity was found. Test for non-linearity: P=0.68.

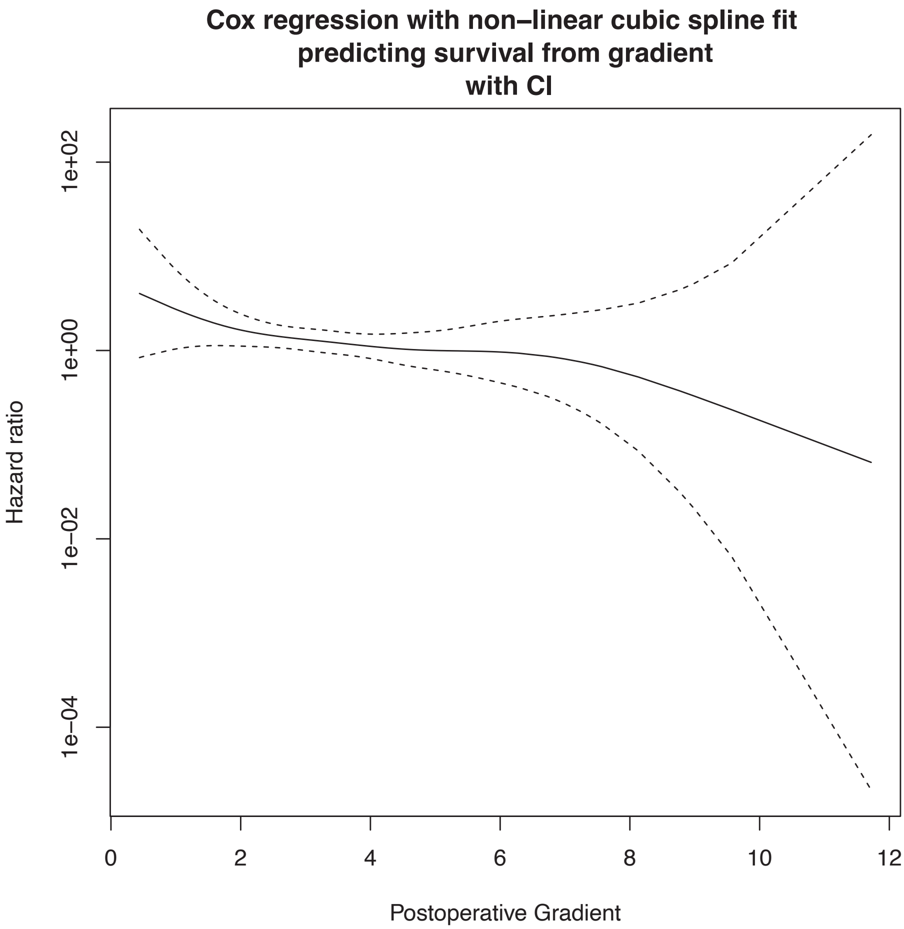


FIGURE S4. Univariate cubic spline regression analysis for the outcome atrial fibrillation. No evidence of for non-linearity was found. Test for non-linearity: P=0.56.

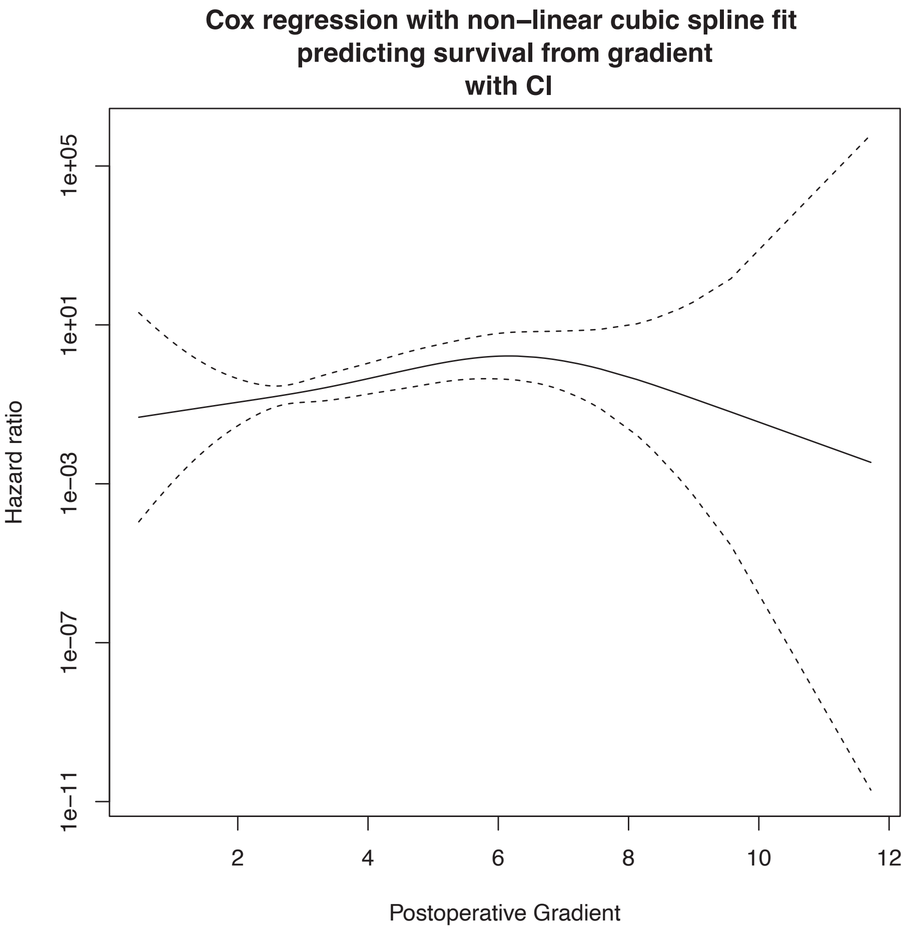


FIGURE S5. Univariate cubic spline regression analysis for the outcome reintervention. No evidence of for non-linearity was found. Test for non-linearity: P=0.30.

TABLE S1. Univariate and multivariate Cox proportional hazards regression analysis results for time-to-event outcomes of interest. Post-repair mitral valve gradient was included as a continuous variable.

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
All-cause mortality						
Age (continuous)	1.084	1.058-1.111	<0.001	1.065	1.033-1.098	<0.001
Gender (female)	1.322	0.852-2.050	0.21	0.826	0.508-1.342	0.44
Chronic obstructive pulmonary disease	2.654	1.463-4.813	0.001	1.992	1.078-3.682	0.028
Impaired left ventricular function	1.608	1.025-2.524	0.039	1.515	0.952-2.410	0.080
Renal impairment						
Moderate (CC <85 ml/min)	2.824	1.626-4.906	<0.001	1.533	0.825-2.851	0.18
Severe (CC ≤50 ml/min)	5.641	2.905-10.954	<0.001	1.834	0.793-4.243	0.16
Atrial fibrillation	2.148	1.399-3.299	<0.001	1.362	0.867-2.139	0.18
Symptomatic mitral regurgitation	1.814	1.051-3.131	0.032	1.020	0.574-1.811	0.95
Postoperative mitral valve gradient (continuous)	0.970	0.834-1.128	0.69	1.034	0.889-1.203	0.66
Atrial fibrillation						
Age (continuous)	1.082	1.048-1.116	<0.001	1.085	1.048-1.123	<0.001
Tricuspid valve repair	1.737	0.964-3.132	0.066	1.193	0.648-2.196	0.57
Left atrial diameter (continuous)	1.018	0.973-1.064	0.44	1.035	0.986-1.087	0.16
Postoperative mitral valve gradient (continuous)	0.831	0.668-1.034	0.097	0.849	0.682-1.057	0.14
Mitral valve reintervention						
Anterior mitral valve leaflet repair	0.910	0.241-3.444	0.89	0.964	0.255-3.646	0.96
Postoperative mitral valve gradient (continuous)	1.380	1.035-1.840	0.028	1.378	1.033-1.838	0.029

Abbreviation: CC: creatinine clearance; CI: confidence interval; HR: hazard ratio.

PART IV

TIMING OF SURGERY IN DEGENERATIVE MITRAL VALVE DISEASE

The timing of surgery for patients suffering from asymptomatic severe degenerative mitral valve regurgitation is a matter of controversy. This is reflected by the European and North American guidelines; the European guidelines recommend surgery in asymptomatic patients only in the presence of certain additional characteristics (e.g. left atrial volume index ≥60 ml/m2 body surface area or flail leaflet). On the other hand, the North American guidelines advocate a more aggressive approach and recommend surgery for all asymptomatic patients with severe mitral valve regurgitation, provided that the expected repair rate is high, expected mortality low and patients are operated on in heart valve centre [1, 2]. Even in Europe, several experienced centres have reported their results with surgical management of completely asymptomatic patients, challenging the recommendations made by the respective guidelines [3-5].

The discrepancy in the recommendations is based on the ongoing discussion on weather completely asymptomatic severe mitral regurgitation presents a rapidly evolving disease or not. In a study by Rosenhek and colleagues, performing close clinical and echocardiographic follow-up in 132 asymptomatic patients, the authors argued against early surgery [6]. Their conclusion was based on the fact that after a follow-up of 8 years, more than 50% of the whole study cohort remained free of an indication for surgery. In a recent update from the same research group, reporting the results of a "*watchful waiting*" approach in 280 completely asymptomatic patients [7], the overall survival of the study cohort did not differ from the overall survival of the age- and gender-matched general population. Nevertheless, 2 deaths due to heart failure (both occurring in elderly patients who opted voluntarily not to attend further follow-up visits) as well as 2 sudden deaths were observed. As acknowledged by the authors, comparing the survival rates to the general population is challenging as referral bias and superior treatment of cardiovascular and other pathologies could provide an explanation for such observations.

Contrary to the active surveillance proposed by Rosenhek and colleagues, other groups advise a much more aggressive approach to asymptomatic severe mitral regurgitation.

This is related to the growing pool of evidence suggesting that severe mitral regurgitation is not a benign condition but will lead to progressive and irreversible structural and morphological changes of the heart and result in an excess of hereto related morbidity and mortality [2, 8-12]. Nevertheless, it should be acknowledged that the amount of evidence supporting an early surgery approach remains scarce.

The highest level of evidence derives from the international multi-centre MIDA registry and a single-centre prospective registry from South Korea. In a recent publication from the MIDA registry, Suri and colleagues concluded that, in patients with severe mitral regurgitation due to flail leaflet, early surgery is associated with greater long-term survival and a lower risk of heart failure when compared to initial medical management, with no difference in new-onset atrial fibrillation [13]. However, the authors excluded only patients with class I indications for surgery from their study cohort and a Class II indication was present in almost 30% of patients undergoing early surgery. No clear conclusions regarding the value of early surgery in completely asymptomatic patients can therefore be drawn from their analyses. Moreover, the observation that early surgery is not effective at preventing the occurrence of late atrial fibrillation is disappointing. The latter is known to occur in a substantial percentage of patients even after adequate resolution of volume overload related to mitral regurgitation [14]. This is most likely related to left atrial fibrosis that develops because of long-standing volume overload prior to the operation and is present even in patients in preoperative sinus rhythm [15]. The value of early surgery for the prevention of late atrial fibrillation will need to be evaluated in the future. Lastly, surgical intervention is related to early and late complications and might, in example, predispose to the occurrence of incisional atrial tachycardia's.

The reports from the remaining prospective registry from Kang and colleagues provide a better insight into the value of early surgery in completely asymptomatic patients as the authors excluded patients with Class II indications from their analyses [16]. In their earlier report, early surgery was shown to improve overall survival while the more recent report failed to show a beneficial effect of early surgery on overall survival despite the lower incidence of cardiac-related deaths with early surgery. The authors did find early surgery to be related to a lower occurrence of a predefined composite endpoint of operative mortality, cardiac death, repeat mitral valve surgery or hospitalization due to congestive heart failure [17].

Irrespective of the position taken, the protagonists of either an active surveillance or early surgery oriented approach seem to agree that patients with severe mitral regurgitation are best of being followed-up or operated on early in experienced heart valve centres. More studies are clearly needed to better define the results of the former or the latter approach.

REFERENCES

[1] Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg 2017;52:616-64.

[2] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA et al. 2017 AHA/ACC Focused Update of the 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 Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252-89.

[3] van Leeuwen WJ, Head SJ, de Groot-de Laat LE, Geleijnse ML, Bogers AJ, Van Herwerden LA et al. Single-centre experience with mitral valve repair in asymptomatic patients with severe mitral valve regurgitation. Interact Cardiovasc Thorac Surg 2013;16:731-7.

[4] Coutinho GF, Garcia AL, Correia PM, Branco C, Antunes MJ. Negative impact of atrial fibrillation and pulmonary hypertension after mitral valve surgery in asymptomatic patients with severe mitral regurgitation: a 20-year follow-up. Eur J Cardiothorac Surg 2015;48:548-55; discussion 55-6.

[5] Coutinho GF, Garcia AL, Correia PM, Branco C, Antunes MJ. Long-term follow-up of asymptomatic or mildly symptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular function. J Thorac Cardiovasc Surg 2014;148:2795-801.

[6] Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238-44.

[7] Zilberszac R, Heinze G, Binder T, Laufer G, Gabriel H, Rosenhek R. Long-Term Outcome of Active Surveillance in Severe But Asymptomatic Primary Mitral Regurgitation. JACC Cardiovasc Imaging 2018;11:1213-21.

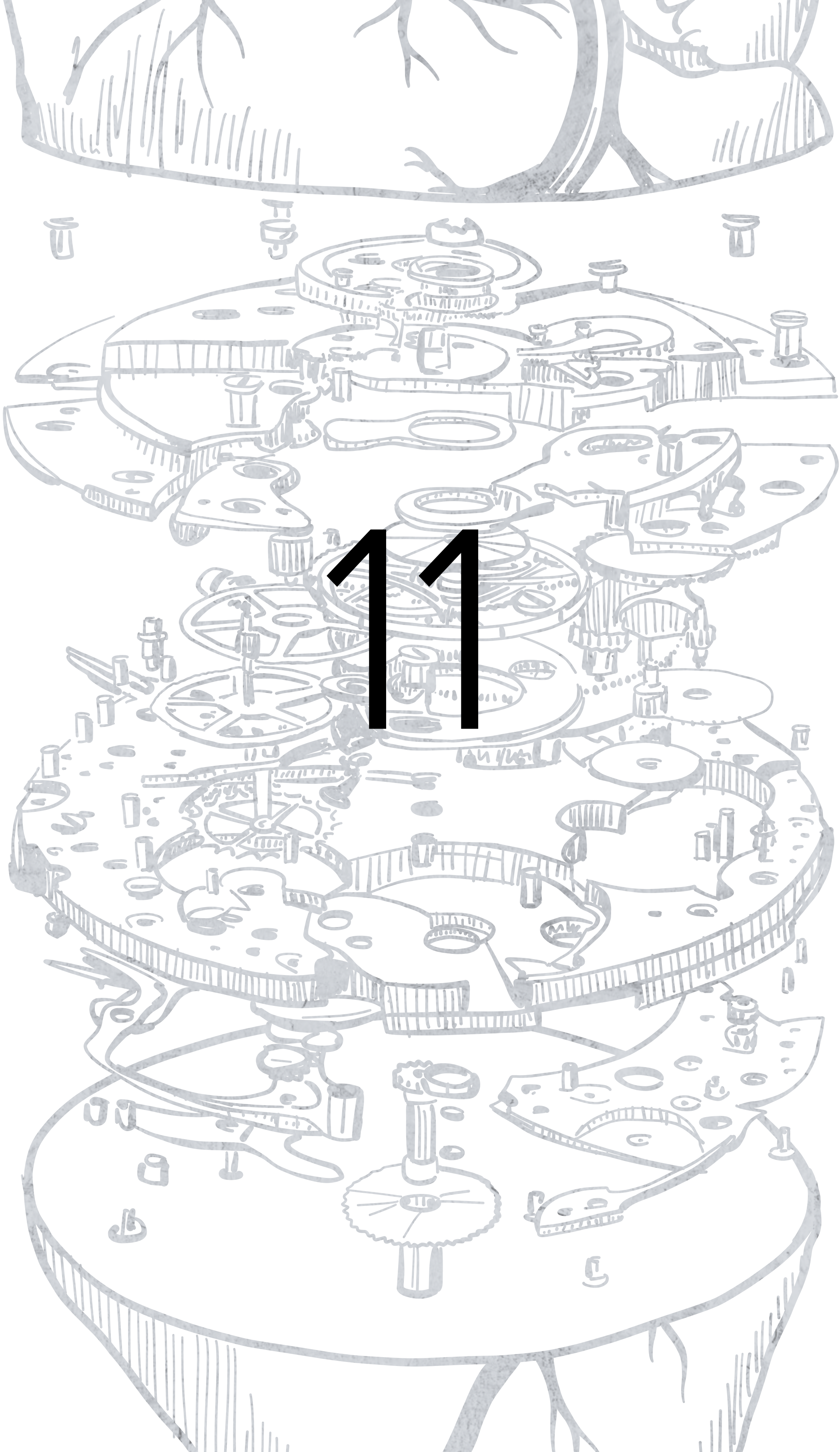
[8] Tribouilloy C, Rusinaru D, Szymanski C, Mezghani S, Fournier A, Levy F et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. Eur J Echocardiogr 2011;12:702-10.

[9] Suri RM, Schaff HV, Dearani JA, Sundt TM, Daly RC, Mullany CJ et al. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. J Thorac Cardiovasc Surg 2009;137:1071-6.

[10] Quintana E, Suri RM, Thalji NM, Daly RC, Dearani JA, Burkhart HM et al. Left ventricular dysfunction after mitral valve repair--the fallacy of "normal" preoperative myocardial function. J Thorac Cardiovasc Surg 2014;148:2752-60.

[11] Griffin BP. Timing of surgical intervention in chronic mitral regurgitation: is vigilance enough? Circulation 2006;113:2169-72.
[12] Ahmed MI, Guichard JL, Soorappan RN, Ahmad S, Mariappan N, Litovsky S et al. Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function. J Thorac Cardiovasc Surg 2016;152:1059-70 e2.
[13] Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos JF et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA 2013;310:609-16.
[14] Stulak JM, Suri RM, Dearani JA, Sundt TM, 3rd, Schaff HV. When should prophylactic maze procedure be considered in patients undergoing mitral valve surgery? Ann Thorac Surg 2010;89:1395-401.
[15] Corradi D, Callegari S, Maestri R, Ferrara D, Mangieri D, Alinovi R et al. Differential structural remodeling of the left-atrial posterior wall in patients affected by mitral regurgitation with or without persistent atrial fibrillation: a morphological and molecular study. J Cardiovasc Electrophysiol 2012;23:271-9.
[16] Kang DH, Kim JH, Rim JH, Kim MJ, Yun SC, Song JM et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation 2009;119:797-804.
[17] Kang DH, Park SJ, Sun BJ, Cho EJ, Kim DH, Yun SC et al. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. J Am Coll Cardiol 2014;63:2398-407.

11



Long-term results of mitral valve repair for severe mitral regurgitation in asymptomatic patients

Anton Tomšič; Yasmine L. Hiemstra; Fabienne M.A. van Hout; Thomas J. van Brakel; Michel I.M. Versteegh; Nina Ajmone Marsan; Robert J.M. Klautz; Meindert Palmen

J Cardiol. 2018;72(6):473-479

ABSTRACT

Background. In asymptomatic patients with severe degenerative mitral valve regurgitation (MR), early surgery is often performed in experienced centers. The patient- and valve-related results and the quality of life after surgery in these patients remain insufficiently explored.

Methods. Between 1/2000 and 12/2015, 83 asymptomatic patients (mean age 56.6±12.6 years, 21 female) without any complications related to long-lasting MR underwent early surgery. Follow-up clinical and echocardiographic data and health-related quality of life assessment (SF-36) were studied and matched to the general population.

Results. Repair rate was 100% and early mortality was 0%. Residual MR (≥grade 2+) was seen in 1 (1%) patient who underwent a successful re-repair while 4 (5%) patients needed permanent pacemaker implantation. At a median follow-up of 7.6 (IQR 4.1-11.9) years, 6 late deaths occurred. The 10-year overall survival rate was 91.5% (95% CI 84.2%-98.8%) and was comparable to the general population. The health-related quality of life (84% complete) did not differ from the general population. One patient underwent late reintervention. Median echocardiography follow-up was 5.2 years (IQR 2.4-10.4; 98% complete). The 10-year freedom from recurrent MR rate (≥grade 2+) was 86.7% (95% CI 76.1%-97.3%). The 10-year freedom from any atrial tachycardia rate was 68.7% (95% CI 55.2%-82.2%) while 7 (8%) patients underwent late pacemaker implantation.

Conclusions. Early surgical intervention in asymptomatic patients with severe MR can be performed safely and restores normal life expectancy and quality of life. However, the frequency of late arrhythmias and pacemaker implantation is high and needs further evaluation.

INTRODUCTION

Surgical mitral valve (MV) repair is the treatment of choice for severe mitral regurgitation (MR) due to degenerative disease [1, 2]. The timing of surgery in asymptomatic patients without echocardiographic evidence of left ventricular (LV) functional decline or dilatation remains a matter of debate. Previously, Rosenhek et al. have advised a watchful waiting approach with close clinical and echocardiographic follow-up [3]. They have shown that even in the presence of severe MR, survival free of an indication for surgery at 8 years can be as high as 55±6%. However, others have shown that severe MR follows a more progressive and malignant course and have recommended an early surgery approach to decrease the early and late valve-related morbidity and mortality rates [4-9].

Current guidelines recommend early surgery only when the risk of surgery is low and expected probability of a durable valve repair is high [1, 2]. In centers experienced in reconstructive MV surgery, the results of valve repair for degenerative disease have progressively improved and a durable repair will nowadays be possible in almost all of these patients, regardless of repair complexity [10-12]. This has encouraged a more aggressive early surgery approach and a growing number of patients undergo surgery prior to the development of symptoms or before meeting other criteria for surgical intervention. However, patients are potentially exposed to perioperative morbidity and mortality, unanticipated valve replacement with proven negative influence on long-term survival [13], and the possibility of valve repair failure. The early and late outcomes of valve repair in completely asymptomatic patients with severe MR due to degenerative valve disease remain insufficiently explored.

The aim of this study was to explore the patient- and valve-related results of surgical intervention for severe MR in truly asymptomatic patients with degenerative valve disease. We aim to explore the clinical and echocardiographic outcomes of these patients and to compare the overall survival and quality of life to the age- and gender-matched general population.

METHODS

Patients

Between January 2000 and December 2015, 684 consecutive patients underwent surgical intervention for degenerative MV disease at our institution. For the purpose of this study we included only elective asymptomatic patients [New York Heart Association (NYHA) class I] without any clinical or echocardiographic complications related to long-lasting MR. The latter included LV dilatation (LV end systolic diameter ≥45 mm), reduced LV ejection fraction (≤60%), pulmonary hypertension (resting systolic pulmonary artery pressure >50 mmHg or ≥60 mmHg during exercise) or history of atrial fibrillation (AF). Patients with symptomatic coronary artery disease were excluded as this would have affected the timing of surgery. On the other hand, patients with asymptomatic coronary artery disease in whom coronary artery bypass grafting was performed due to an abnormal preoperative coronary angiogram were not excluded.

Only patients referred for surgery due to an asymptomatic heart murmur detected unexpectedly during physical examination for reasons of life-insurance acceptance or work-related check-up that warranted further investigation were included. During the study period, we recommended surgery to all asymptomatic patients with severe MR referred to our institution. All valves were deemed repairable, regardless of the expected repair complexity.

Follow-up

Preoperative, intraoperative, and postoperative data were prospectively collected in our computerized database and retrospectively analyzed. Follow-up survival, clinical, and echocardiographic data were collected through clinical visits at our institution or affiliated hospitals, and through questionnaires obtained from patients. Approximately one-half of all follow-up echocardiographic studies were performed at our institution and the other half in affiliated hospitals. Whenever the report from an outside laboratory indicated ≥Grade 2+ MR, the study was reviewed in our hospital. The study was approved by our Institutional Ethics Committee.

Study endpoints

Early mortality was defined as mortality within 30-days after the operation or during the index hospitalization. Postoperative mortality and morbidity endpoints were defined according to the joint Society of Thoracic Surgeons, American Association for

Thoracic Surgery, and European Association for Cardio-Thoracic Surgery Guidelines [14]. Additional endpoints included freedom from any atrial tachycardia (AT; further divided in freedom from AF, and other AT), hospitalization for heart failure, and pacemaker implantation. Severity of MR was quantitatively assessed according to current recommendations using a multi-parametric approach and including the effective regurgitant orifice area (using proximal isovelocity surface area method) and regurgitant volume measurements [15]. MR severity was graded as: 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe). Residual and recurrent MR were defined as ≥Grade 2+ MR.

Quality of life assessment

The health-related quality of life assessment was conducted using the SF-36 quality of life questionnaire. It contains questions clustered in 8 domains: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social functioning, emotional role functioning, and general mental health. Raw scores are calculated as the sum of (re-coded) scale items and transformed to a 0 to 100 scale. The domains are then summarized to form 2 summary measures, the Physical Component Score and Mental Component Score. The scales are obtained by summing the domains together within a component. Thereafter, the scores are divided by the range of scores and transformed into a scale. The mean score of both components is 50 with a standard deviation (SD) of 10. Higher scores represent better health status. The study by Aaronson et al. was used to compare the health-related quality of life between the general Dutch population and the study population [16].

Surgical technique

Surgery was performed through median sternotomy (n=68), lateral mini thoracotomy (n=11), or hemi-sternotomy (n=4). Antegrade and/or retrograde warm blood cardioplegia was used for cardioprotection in all cases. When longer cardiopulmonary bypass times were anticipated, mild systemic hypothermia was applied. Blood cardioplegia was administered in intervals of 15 or 20 (in case of hypothermia) minutes. In the vast majority of patients (n=77), the MV was exposed transseptally.

Repair techniques used included chordal replacement for anterior MV leaflet prolapse. Commissural prolapse was treated predominantly by papillary muscle head repositioning. For the posterior MV leaflet, a combination of resection and neochords techniques, aimed at resolving leaflet prolapse and excessive tissue in height and/

or width, were used. Earlier in the study period, annular plication was performed in selected patients. Intraoperative echocardiography was performed by an experienced cardiologist to analyze the result of valve repair.

Prior to 2004, tricuspid valve (TV) repair was performed only when ≥moderate tricuspid regurgitation was present on preoperative echocardiography. Since 2004, this was performed also in the presence of significant tricuspid annulus dilatation (≥40 mm or ≥21 mm/m^2 body surface area), regardless of the amount of regurgitation.

Pre-discharge echocardiography was performed in all patients. Oral anticoagulation was initiated for the first 3 months after surgery with a target international normalized ratio of 2.0-3.0. In the absence of other indications, oral anticoagulation was discontinued thereafter.

Statistical analysis

Continuous data are presented as means ± standard deviation for normally distributed data or medians and interquartile ranges (IQR) when not normally distributed. Categorical data are presented as counts and percentages. Survival and freedom from time-related events were estimated using the Kaplan-Meier method. Age- and gender-matched survival in the general population were calculated using the Dutch population life tables (http://statline.cbs.nl/). Statistical analysis was performed using the IBM Statistics for Windows, version 23.0 (SPSS, Inc., IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline characteristics and surgical procedure

The median patient age was 56.6±12.6 years and the majority of patients were male (**Table I**). Overall, the proportion of patients with any significant comorbidities and the estimated risk of surgical mortality were low. Mitral valve repair rate was 100%. The details on surgical techniques used are shown in **Table II**. Intraoperative echocardiography demonstrated no significant residual MR in all cases.

TABLE I. Baseline characteristics.

	N=83
Age (years)	56.6±12.6
Gender (female)	21 (25)
Hypertension	31 (37)
Renal impairment	
Moderate (CC 85-50 ml/min)	26 (31)
Severe (CC <50 ml/min)	1 (1)
History of TIA or CVA	2 (2)
Chronic lung disease	3 (4)
Diabetes mellitus	1 (1)
Echocardiographic characteristics	
Left ventricular ejection fraction (%)	69±5
Left ventricular end diastolic diameter (mm)	54±6
Left ventricular end systolic diameter (mm)	32±5
Systolic pulmonary artery pressure (mmHg)	28±7
Site of leaflet prolapse	
Isolated posterior	50 (60)
Flail leaflet	21 (25)
Bileaflet	25 (30)
Flail leaflet	5 (6)
Isolated anterior	7 (9)
Flail leaflet	6 (7)
None	1 (1)
Annular calcification	7 (8)
EuroSCORE II	0.86 (IQR 0.59-1.08)

Data are presented as N (%) and means ± standard deviation or medians (IQR). Abbreviations: CC: creatinine clearance; CVA: cerebrovascular accident; TIA: transient ischemic attack.

TABLE II. Intraoperative details.

	N=83
Mitral valve annulus	
Plication	25 (30)
Decalcification	6 (7)
Annuloplasty	83 (100)
Anterior mitral valve leaflet	
PTFE neochords	27 (33)
Posterior mitral valve leaflet	
Resection	
Triangular	17 (20)
Quadrangular	47 (37)
Sliding plasty	44 (53)
PTFE neochords	31 (37)
Chordal transfer	1 (1)
Papillary muscle head repositioning	1 (1)
Identation closure	13 (16)
Commissures	
Anterior commissure	
Papillary muscle head repositioning	2 (2)
Commissuroplasty	2 (2)
Posterior commissure	
Papillary muscle head repositioning	14 (17)
Papillary muscle shortening	1 (1)
Commissuroplasty	7 (8)
PTFE neochords	1 (1)
Concomitant procedures	
Tricuspid valve repair	28 (34)
Coronary artery bypass grafting	6 (7)
Second pump run	4 (5)
Cardiopulmonary bypass time (min)	176 (IQR 145-202)
Aortic cross-clamp time (min)	139 (IQR 115-158)

Data are presented as N (%) and medians (IQR). Abbreviations: IQR: interquartile range; PTFE: polytetrafluoroethylene.

Early outcomes

There was no early mortality. No major complications occurred in the majority of patients (**Table III**). In 1 (1%) patient, pre-discharge echocardiography demonstrated residual, grade 3+ MR due to residual posterior MV leaflet prolapse. The patient underwent a MV re-repair on postoperative day 10 and the further postoperative course was uneventful. Furthermore, postoperative permanent pacemaker implantation was needed in 4 (5%) patients (due to complete heart block in 3 and atrial flutter with symptomatic bradycardia in 1). Postoperative pacemaker implantation was more commonly performed in patients with concomitant TV repair (3/28 versus 1/55), albeit the difference was statistically not significant (p=0.074). The incidence of pacemaker implantation in patients undergoing prophylactic TV repair was highest soon after the indication for TV repair was extended to isolated annular dilatation in 2004 and 2005 (2/3 cases of pacemaker implantations in this group). From 2006 on, pacemaker implantation was needed in 1/19 patients in whom concomitant TV repair was performed.

TABLE III. Postoperative complications.

	N=83
Early mortality	0 (0)
Deep sternal wound infection	0 (0)
Prolonged intubation (>24h)	1
Renal failure	0 (0)
Permanent stroke	0 (0)
Early reoperation	6 (7)
Early valve reoperation	1 (1)
Re-sternotomy for other causes	0 (0)
Subxyphoidal pericardiotomy	5 (6)
ICU stay (days)	1 (IQR 1-2)
Permanent pacemaker implantation	4 (5)
Postoperative supraventricular tachycardia	37 (45)

Data are presented as N (%) and medians (IQR). Abbreviations: ICU: intensive care unit; IQR interquartile range.

Late mortality

Median survival follow-up was 7.3 years (IQR 3.7-11.9; 654 total follow-up years) and was 99% complete (1 patient was lost to follow-up due to emigration). Six late deaths occurred and the cause of death was cardiac-related in 3 patients; all of these were sudden, unexplained deaths. The most recent follow-up echocardiography revealed no significant MR and good LV function in 2 and no significant MR and mildly impaired LV function without any significant MR in 1 of these patients. The 5- and 10-year overall survival rates were 95.4% (95% CI 90.3%-100%) and 91.5% (95% CI 84.2%-98.8%), respectively. Overall survival was comparable to the age- and gender-matched general population (**Figure 1**).

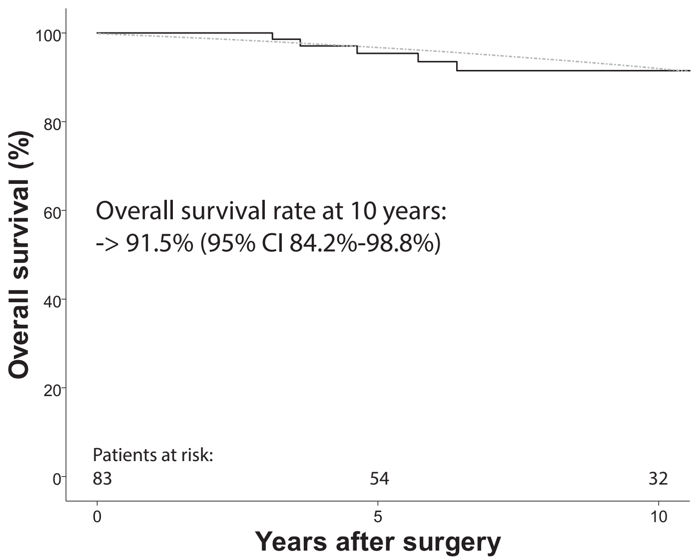


FIGURE 1. Overall survival of patients with asymptomatic severe mitral valve regurgitation (solid line) compared to the age- and gender-matched general population (dashed line).

Late morbidity

Clinical follow-up was 93% complete [median follow-up duration 7.0 (IQR 3.2-11.2) years]. Valve-related morbidity included 6 thromboembolic events (1 cerebrovascular accident and 5 transient ischemic attacks); 2 severe bleeding events (1 of these patients was on oral anticoagulation with an international normalized ratio level of 4.5 at the time of the event); and 2 hospitalizations for heart failure. The linearized event rates were 1.0%/patient year for thromboembolic events, 0.34%/patient year for hospitalization for heart failure, and 0.34%/patient year for severe bleeding event.

De novo ATs occurred often during the follow-up period and the freedom from any AT rates at 5- and 10-years after surgery were 84.8% (95% CI 76.4%-93.2%) and 68.7% (95% CI 55.2%-82.2%), respectively (**Figure 2**). At the time of last follow-up (mean patient age 64.0±12.8 years), the prevalence of AF was 12%. The 10-year freedom from AF rate was 84.1% (95% CI 73.7%-94.5%). The 10-year freedom from other ATs rate was 81.0% (95% CI 69.0%-92.9%). Following hospital discharge, 7 (8%) patients underwent late pacemaker implantation. The indication for permanent pacemaker implantation was brady-tachy syndrome in 4, total atrioventricular block in 2, and sinoatrial node dysfunction in 1.

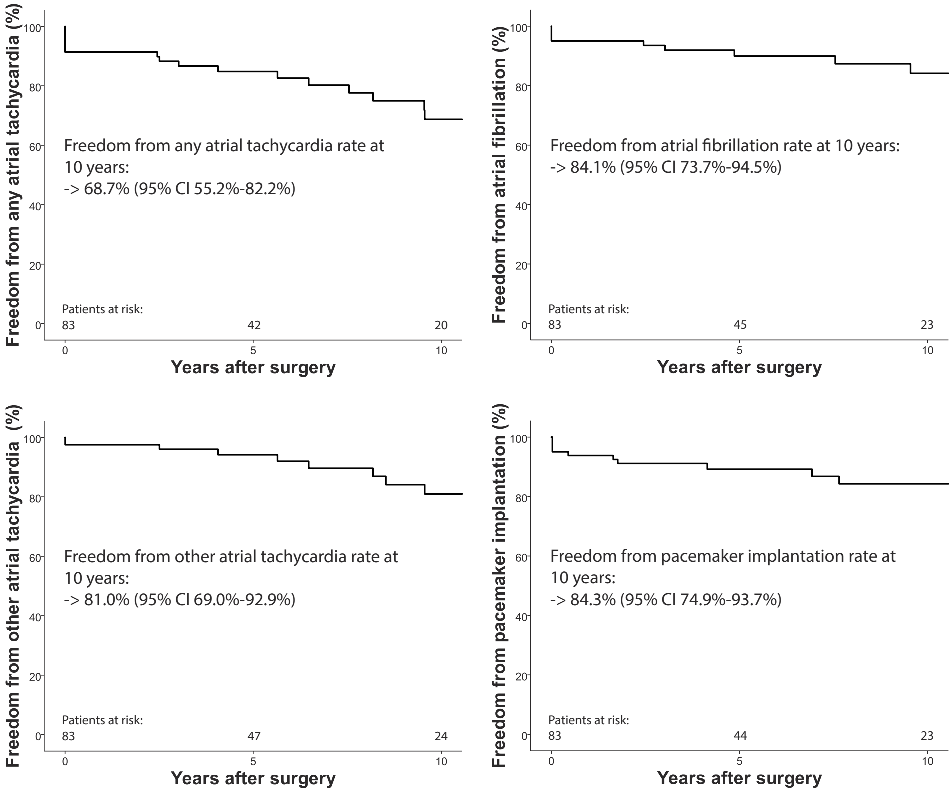


FIGURE 2. Freedom from late morbidity: (A) freedom from any atrial tachycardia; (B) freedom from atrial fibrillation; (C) freedom from other types of atrial tachycardia; (D) freedom from pacemaker implantation.

At the time of last follow-up, 64 (85%) patients were in NYHA class I, 10 (14%) in NYHA class II, and 1 (1%) in NYHA class III. Recurrent MR was present in 2/11 of symptomatic patients, providing an explanation for their status. The remaining causes that could possibly explain the symptomatic status were: impaired LV function (mildly in 3 and moderately in 1) in 4/9, AT in 4/9 and functional MV stenosis (postoperative mean MV pressure gradient ≥5 mmHg) in 3/9 patients.

During the follow-up period, 1 late MV reintervention was performed. Recurrent MR was first detected 7 years after the initial operation. A few years prior to this observation, the patient underwent pacemaker implantation that resulted in almost exclusive right ventricular pacing and led to LV dyssynchrony, dilatation, and functional decline. Biventricular pacing failed to resolve the issue. Echocardiography demonstrated posterior MV leaflet restriction with pseudo-prolapse of the anterior leaflet at the height of the posterior commissure. A MitraClip (Abbott Vascular, Santa Clara, CA, USA) implantation (9.1 years after the initial operation) was performed. At last echocardiographic follow-up, no significant MR was present.

Late echocardiographic outcome

The mean echocardiographic follow-up time was 5.2 (IQR 2.4-10.4) years and was 98% complete. Freedom from recurrent (≥Grade 2+) MR rate at 5- and 10-years after surgery was 95.6% (95% CI 90.7%-100%) and 86.7% (95% CI 76.1%-97.3%), respectively (**Figure 3**). At the time of last echocardiographic follow-up, no significant MR (≤Grade 1+) was seen in 74 (91%) patients, Grade 2+ MR in 5 (6%), and ≥Grade 3+ MR in 2 (3%) patients, the latter including the patient who later underwent MitraClip implantation.

Quality of life

A total of 65 patients (84% complete for patients alive at follow-up, mean follow-up time 7.2±4.3 years) completed the SF-36 quality of life questionnaire. One questionnaire had to be discarded due to insufficient data. The mean patient age at the time of follow-up was 64.3±12.1 years and 16/64 (25%) patients were female. Compared to the general age- and sex-matched population, the study population performed better in several individual domains of the SF-36 quality of life assessment (**Table IV**). The Physical and Mental Component Scores were comparable to the matched population.

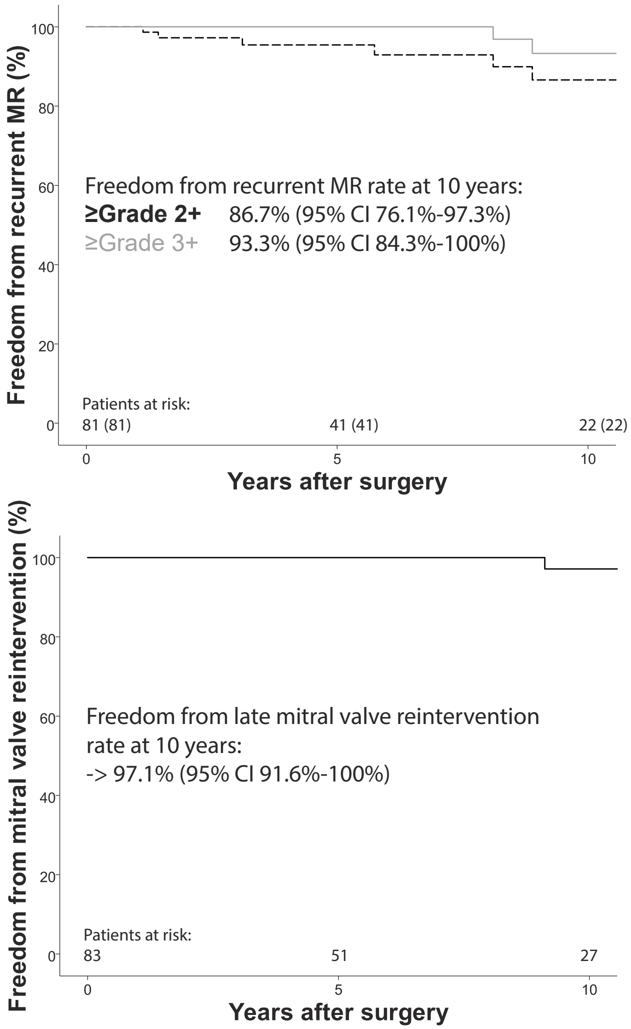


FIGURE 3. **Above:** freedom from recurrent (freedom from ≥Grade 2+ and ≥Grade 3+ mitral regurgitation are presented separately; patients at risk for freedom form ≥Grade 3+ mitral regurgitation are presented in brackets) mitral regurgitation. **Below:** freedom from late mitral valve reintervention.

TABLE IV. The results of the SF-36 quality of life questionnaire compared to the age- and gender-matched general population derived from the study of Aaronson et al. [16].

	Study population (n=64)		Matched general population		
	Mean	**SD**	**Mean**	**SD**	**P-value**
PF	83.1	22.2	77.1	22.6	0.001
RP	75.8	39.6	70.8	39.1	0.13
BP	84.9	23.2	70.9	24.2	<0.001
GH	65.5	23.3	65.0	19.7	0.72
VT	69.4	17.5	69.2	18.9	0.62
SF	87.5	18.9	82.8	22.5	0.014
RE	87.5	28.2	82.6	32.3	<0.001
MH	82.3	13.2	75.7	17.8	<0.001
PCS	49.5	10.3	46.8	10.2	/
MCS	52.1	6.8	50.8	9.8	/

Abbreviations: PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SD: standard deviation; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component score; MCS: mental component score.

DISCUSSION

Our results demonstrate that early surgery in asymptomatic patients with severe MR, prior to the occurrence of complications related to long-standing MR, is safe and valve repair is feasible in all cases, regardless of repair complexity. After successful repair, the life expectancy and quality of life are comparable to the general population, making early intervention justified.

Surgical MV repair is the gold standard for treatment of severe MR due to degenerative MV disease. The documented high repair rates and good repair durability have motivated surgeons to advise early surgery in asymptomatic patients prior to the occurrence of complications related to long-standing severe MR [4-6, 17]. The recently updated European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines for the management of valvular heart disease remain, however, conservative when it comes to early surgery for severe asymptomatic degenerative MR [1]. Clearly, early surgery should be performed exclusively when the expected risk of surgery is low and the probability of valve repair (without residual MR) is high.

According to the guidelines, however, surgery in asymptomatic patients without clinical or echocardiographic complications of long-standing MR should only be considered when favorable anatomy (flail leaflet) is present [1]. On the other hand, the recently updated American Heart Association/American College of Cardiology valvular heart disease guidelines advise considering surgery irrespective of the projected valve repair complexity [2]. Importantly, the North American guidelines recognize progressive increase in LV size or decrease in LV function on serial echocardiographic studies as early markers of disease progression. This is in line with recent evidence that postoperative (irreversible) LV functional decline will occur often even in patients with "preserved" LV function (ejection fraction >60%) [18] and is to be attributed to chronic oxidative stress that causes disruption of the cardiomyocyte cytoskeletal-mitochondrial architecture in these patients [19].

The rationale behind early surgical intervention is that restoring MV competence will prevent otherwise inevitable morphological and functional changes of the LV and left atrium and the consequences thereof. However, the risks of open-heart surgery are not negligible and the potentially detrimental effects of unexpected valve replacement need to be taken into account. A recent report from the Mitral regurgitation International DAtabase (MIDA) registry clearly demonstrated long-term superiority of valve repair over replacement in terms of survival and freedom from valve-related complications [13]. Valve replacement in an asymptomatic patient is probably more detrimental for the long-term patient prognosis than a watchful waiting approach. It has been shown that the probability of valve repair is highly variable and depends on center and surgeon experience [20]. When an early surgery approach is chosen, patients should be referred to a center with sufficient experience in reconstructive valve surgery and documented good results.

During the study period, we have applied an early surgery approach in asymptomatic patients, irrespective of projected repair complexity. Typically, these patients are young and vital and the expected perioperative morbidity and mortality will nearly always be low. It should be kept in mind that a prolonged history of asymptomatic MR will most often be observed in patients with complex valve abnormalities [21], as also observed in this study. Only 25% of patients had a pathology that could be classified as isolated "*flail posterior leaflet*". As nowadays a durable valve repair is feasible in the majority of patients with complex lesions [10, 22], we reason that the complexity of valve repair should not result in a delayed referral to surgery. Currently, no randomized clinical trials aimed at resolving the issue of the timing of surgery in severe primary MR are available. The evidence to support the early surgery approach derives from a very limited number of prospective registries and, largely, retrospective studies. Moreover, these often include patients with either favorable pathology (flail leaflet) or define early surgery solely as the absence of Class I indications for surgery, as in the case of a report from the MIDA registry [23]. On the other hand, a multi-center prospective registry reported by Kang et al. included 610 consecutive patients with severe organic MR irrespective of valve morphology who underwent either early surgery (n=235; repair rate 94%) or conventional treatment (n=375; watchful waiting) and reported superior results with the early surgery approach [24].

Early and late permanent pacemaker implantation was needed in 4 and 7 of our patients, respectively. The incidence of early pacemaker implantation was higher in patients with concomitant TV repair, although the absolute number of patients is very low and no definite conclusion can be drawn. In a recent study, Jouan et al. encountered similar observations and highlighted the problem of increased rates of high-grade heart conduction disorders and pacemaker implantations related to concomitant TV repair in patients undergoing MV surgery [25]. In our experience, the majority of early pacemaker implantations was needed early after the indication for concomitant TV repair was extended to isolated annular dilatation. Hereafter, the incidence of early pacemaker implantation in this group declined and was comparable to previous reports [25, 26]. Comparing the incidence of pacemaker implantation between patients with and without an indication for concomitant TV repair is somehow misleading due to more advanced disease progression in patients with TV annular dilatation.

The most commonly observed late morbidity was ATs. Compared with the data from the Rotterdam study [27], the prevalence of AF in our study cohort was 5.7 times higher when compared to age- and gender-matched general Dutch population. As the vast majority of patients demonstrated good valve repair function, recurrent MR does not provide a possible explanation for this finding. Likely, this occurred due to the fact that asymptomatic but hemodynamically significant MR was present for a prolonged period prior to the diagnosis and resulted in irreversible functional changes to the left atrium. In a study of 573 patients in sinus rhythm who underwent surgery for severe MR, Stulak et al. demonstrated that new-onset late AF is common after MV surgery with a cumulative risk of occurrence of 23% at 10 years after surgery [28]. Comparable results were also reported by Suri et al. in an analysis of 902 asymptomatic patients with severe MR from the MIDA registry who, interestingly, failed to demonstrate any beneficial effect of early surgery on the occurrence of new AF when compared to watchful waiting [23]. These results are all in line with our observations and bring to question whether prophylactic rhythm intervention should be performed at the time of MV surgery. Better documentation of the likely presence of occult AF prior to surgery might identify patients in whom ablation might readily be indicated.

In our experience, other types of ATs were also common. The occurrence of such rhythm abnormalities can be explained by surgical trauma and scarring at surgical incision or cannulation sites that provide a substrate for re-entry tachycardias and thus present a direct consequence of surgical intervention [29, 30]. To the best of our knowledge, this topic has been poorly studied to date and the incidence observed in our study is difficult to evaluate critically. Enriquez et al. studied the electrophysiological mechanisms and outcomes of catheter ablation in 67 patients presenting with ATs after previous MV surgery [29]. Interestingly, the left atrium was the chamber of origin more commonly in patients after previous concomitant surgical AF ablation. On the other hand, right-sided ATs were more common in patients with right atriotomy scars. Additionally, a study by Lukac et al. found that the superior transseptal approach created a corridor of slow conduction between the right atriotomy scar and the tricuspid annulus that might predispose to the occurrence of right-sided ATs [31]. Due to the absence of studies designed to assess the freedom from late ATs, the clinical significance of these observations is unknown. In a recent review of literature, Boulemden et al. evaluated the effect of the type of atrial approach to the mitral valve and found no difference on outcomes when left atriotomy was compared to the transseptal approach [32]. Nevertheless, the majority of studies available for inclusion in the review explored only the freedom from early rhythm abnormalities. We standardly use the transseptal approach during MV surgery and this prevented us from comparing the effect of the type of incision used on the incidence of ATs. As ATs significantly affect the quality of life and necessitate oral anticoagulation, more research is needed on how these are to be prevented.

LIMITATIONS

This is a single-center experience with limitations inherent to the study design. Our study was a single-arm study that did not include a comparable cohort of patients with asymptomatic severe MR in whom no early surgery would be performed. Moreover, no data on preoperative health-related quality of life was available. To overcome these drawbacks, the results were compared to the age- and gender-matched general population. The rhythm follow-up was conducted by the referring cardiologists; systematic follow up with 24-hour Holter monitoring might have revealed additional, clinically silent rhythm disturbances.

CONCLUSIONS

Early surgical intervention for asymptomatic patients with severe MR is safe and a durable valve repair is achievable regardless of repair complexity. Furthermore, following successful early surgery, the life expectancy and quality of life are comparable to the general population. However, even after a successful valve repair, the frequency of ATs and pacemaker implantation is high and warrants further evaluation.

REFERENCES

[1] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease: The Task Force for 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 2017;38:2739-91.

[2] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 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 Clinical Practice Guidelines. Circulation 2017;135:e1159-e95.

[3] Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238-44.

[4] Gillinov AM, Mihaljevic T, Blackstone EH, George K, Svensson LG, Nowicki ER, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? Ann Thorac Surg 2010;90:481-8.

[5] Goldstone AB, Patrick WL, Cohen JE, Aribeana CN, Popat R, Woo YJ. Early surgical intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a systematic review and meta-analysis. Ann Cardiothorac Surg 2015;4:220-9.

[6] Yazdchi F, Koch CG, Mihaljevic T, Hachamovitch R, Lowry AM, He J, et al. Increasing disadvantage of "watchful waiting" for repairing degenerative mitral valve disease. Ann Thorac Surg 2015;99:1992-2000.

[7] David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation 2013;127:1485-92.

[8] Suri RM, Aviernos JF, Dearani JA, Mahoney DW, Michelena HI, Schaff HV, et al. Management of less-than-severe mitral regurgitation: should guidelines recommend earlier surgical intervention? Eur J Cardiothorac Surg 2011;40:496-502.

[9] Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, et al. Clinical outcome of mitral regurgitation due to flail leaflet. N Engl J Med 1996;335:1417-23.

[10] Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. J Thorac Cardiovasc Surg 2012;144:308-12.

[11] Goldstone AB, Cohen JE, Howard JL, Edwards BB, Acker AL, Hiesinger W, et al. A "repair-all" strategy for degenerative mitral valve disease safely minimizes unnecessary replacement. Ann Thorac Surg 2015;99:1983-90.

[12] Perier P, Hohenberger W, Lakew F, Batz G, Diegeler A. Rate of repair in minimally invasive mitral valve surgery. Ann Cardiothorac Surg 2013;2:751-7.

[13] Lazam S, Vanoverschelde JL, Tribouilloy C, Grigioni F, Suri RM, Avierinos JF, et al. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: analysis of a large, prospective, multicenter, international registry. Circulation 2017;135:410-22.

[14] Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008;33:523-8.
[15] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.
[16] Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.
[17] van Leeuwen WJ, Head SJ, de Groot-de Laat LE, Geleijnse ML, Bogers AJ, Van Herwerden LA, et al. Single-centre experience with mitral valve repair in asymptomatic patients with severe mitral valve regurgitation. Interact Cardiovasc Thorac Surg 2013;16:731-7.
[18] Quintana E, Suri RM, Thalji NM, Daly RC, Dearani JA, Burkhart HM, et al. Left ventricular dysfunction after mitral valve repair--the fallacy of "normal" preoperative myocardial function. J Thorac Cardiovasc Surg 2014;148:2752-60.
[19] Ahmed MI, Guichard JL, Rajasekaran NS, Ahmad S, Mariappan N, Litovsky S, et al. Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function. J Thorac Cardiovasc Surg 2016;152:1059-70 e2.
[20] Chikwe J, Toyoda N, Anyanwu AC, Itagaki S, Egorova NN, Boateng P, et al. Relation of mitral valve surgery volume to repair rate, durability, and survival. J Am Coll Cardiol 2017; pii: S0735-1097(17)30677-0.
[21] Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J 2010;31:1958-66.
[22] Tomšič A, Hiemstra YL, van der Pas SL, Putter H, Versteegh MIM, van Brakel TJ, et al. Early and long-term outcomes of mitral valve repair for Barlow's disease: a single-centre 16-year experience. Interact Cardiovasc Thorac Surg 2018;26:783-9.
[23] Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos JF, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA 2013;310:609-16.
[24] Kang DH, Park SJ, Sun BJ, Cho EJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for asymptomatic severe mitral regurgitation: a propensity analysis. J Am Coll Cardiol 2014;63:2398-407.
[25] Jouan J, Mele A, Florens E, Chatellier G, Carpentier A, Achouh P, et al. Conduction disorders after tricuspid annuloplasty with mitral valve surgery: Implications for earlier tricuspid intervention. J Thorac Cardiovasc Surg 2016;151:99-103.
[26] Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg 2005;79:127-32.
[27] Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949-53.

[28] Stulak JM, Suri RM, Dearani JA, Sundt TM, 3rd, Schaff HV. When should prophylactic maze procedure be considered in patients undergoing mitral valve surgery? Ann Thorac Surg 2010;89:1395-401.

[29] Enriquez A, Santangeli P, Zado ES, Liang J, Castro S, Garcia FC, et al. Postoperative atrial tachycardias after mitral valve surgery: Mechanisms and outcomes of catheter ablation. Heart Rhythm 2017;14:520-6.

[30] Markowitz SM, Brodman RF, Stein KM, Mittal S, Slotwiner DJ, Iwai S, et al. Lesional tachycardias related to mitral valve surgery. J Am Coll Cardiol 2002;39:1973-83.

[31] Lukac P, Hjortdal V, Pedersen AK, Jensen HK, Mortensen PT, Hansen PS. The superior transseptal surgical approach to mitral valve creates slow conduction. Pacing Clin Electrophysiol 2006;29:719-26.

[32] Boulemden A, Nadarajah D, Szafranek A, Richens D. Atrial approaches to the mitral valve: is there a difference in postoperative rhythm disturbance and permanent pacemaker implantation? Interact Cardiovasc Thorac Surg 2018 Apr 7. [Epub ahead of print]

12

General discussion and future perspectives

The aim of this thesis was to assess the current status of reconstructive mitral valve surgery for organic mitral valve disease. Moreover, a detailed assessment of the results presented may help establish the clinical value of pathophysiological concepts of mitral valve disease, which should be respected when the optimal treatment plan is constructed. While the focus of this thesis was largely based on the technical details of mitral valve surgery, it should be acknowledged that the results of surgical treatment for organic mitral valve disease are largely influenced by perioperative clinical decision making. Therefore, the perioperative aspects of mitral valve surgery, in particular the timing of surgery, were studied as well. The results presented will hopefully encourage further research in this field and may contribute to further refine the concept of a patient tailored approach in organic mitral valve disease.

MITRAL VALVE INFECTIVE ENDOCARDITIS

Chapter 2 and **Chapter 3** focus on the results of mitral valve surgery in mitral valve infective endocarditis in various real-world clinical scenarios. The relatively high mortality rate seen is in line with the results previously reported [1-3]. This is primarily related to the poor clinical condition and severe comorbidities that these patients normally present with. The advocated policy of preoperative antibiotic treatment of at least 48 hours whenever feasible to secure bloodstream sterilization and radical resection of infected tissue combined with rinsing the operative field with a rifampicin solution resulted in an absence of residual infections despite liberal utilization of prosthetic materials. This is an important observation as prosthetic mitral valve annuloplasty remains commonly omitted despite the fact that underlying mitral valve disease is often present, the annulus is often affected by the infective process or a complex repair is performed. A durable repair was established in the majority of patients and the reoperation rate reported is lower than the reoperation rates reported previously [1, 2, 4]. Moreover, a low incidence of recurrent mitral regurgitation was seen on follow-up echocardiography. It can reasonably be assumed that liberal utilization of prosthetic annuloplasty contributed to the satisfactory valve repair durability observed.

The described intraoperative approach to mitral valve repair, with valve replacement performed without attempting valve repair when the infectious process had resulted in destruction of a larger proportion of the valve, likely plays a crucial role in optimizing the clinical results of these patients. Despite the general belief that mitral valve repair will provide superior clinical results to valve replacement, it should be acknowledged that good valve repair durability is an absolute prerequisite to achieve this. Critical intraoperative assessment of the possibility of a durable valve repair to be performed will help identify patients in whom a clinical benefit of valve repair can be expected while avoiding the downsides of prolonged aortic cross clamp and cardiopulmonary bypass time. A durable repair in the presence of extensive valve destruction is highly unlikely and a repair attempt should best be avoided. It is safe to assume that optimal perioperative management combined with a structured surgical approach are essential to achieve good clinical results in these patients.

The overall survival benefit of valve repair in infective endocarditis is to date poorly established. In previous studies, the survival benefit was often driven by an early (occurring within the first year after surgery) advantage, characterized by diverging survival curves, followed later by a parallel course of survival curves [5]. During the early postoperative period overall survival is less likely to be affected by treatment modality (repair versus replacement) and more likely to be affected by patient characteristics. This raises concerns on the true value of valve repair over valve replacement in active infective endocarditis. A tendency to superior overall survival with valve repair, when compared to valve replacement, was observed in **Chapter 2**. Interestingly, the survival curves were divergent also beyond the early postoperative period. Due to small sample size, no statistical significance was observed. The survival benefit of a systematic approach to mitral valve repair in infective endocarditis will need to be evaluated further in properly designed and powered studies.

BARLOW'S MITRAL VALVE DISEASE

Chapter 4 and **Chapter 5** focused on the pathophysiological concepts of Barlow's disease, the implications these are to have on valve repair strategy and the outcome of surgical intervention. Several important conclusions can be drawn from the results presented. First, the concept of disease progression is effectively challenged by observing that repair failure after an initially successful repair is primarily related to the technical aspect of surgery, as presented in **Chapter 5**. It is important to understand that this not only provides an implication for the technical aspects of valve surgery but also raises questions on the effect of the timing of surgery on degenerative disease progression. Optimal surgical repair will include annular stabilization while obtaining a large surface area of leaflet coaptation and will also resolve excessive leaflet stress. A stable valve repair is likely to restrain disease progression that primarily occurs as a consequence of abnormal annular dynamics, the pathophysiologic cornerstone of Barlow's disease [6-8]. Previous studies have demonstrated the feasibility of valve repair with the sole use of annuloplasty in Barlow's disease [6, 9]. With the development of trans-catheter techniques of mitral valve annuloplasty, trans-catheter repair could become a therapeutic option in the future for carefully selected patients, even prior to the occurrence of severe regurgitation. This would not only restrain disease progression but also prevent the development of the consequences of severe mitral valve regurgitation.

The described concept of functional leaflet prolapse challenges the appropriateness of any, surgical or trans-catheter, repair technique that fails to systematically address the mitral valve annulus. Recently, off-pump mitral valve repair with implantation of neochords has been described as a treatment option for patients with degenerative mitral valve disease [10]. Studies have shown that the results of this repair technique are inferior in the presence of bileaflet prolapse that most commonly occurs in the presence of Barlow's disease. One can assume that the underlying reason for repair failure in these cases is not the presence of bileaflet prolapse itself but the failure to address abnormal annular motion present in Barlow's disease, as also described recently [11].

An important and to date unanswered question is the effect of the type of annuloplasty device (semi-rigid or flexible, full or partial) on valve repair durability. As previously demonstrated, the clinical importance of annular remodeling and stabilization varies across different types of degenerative mitral valve disease. Patients with Barlow's disease seem to be most prone to the development of recurrent mitral regurgitation in the absence of annuloplasty [12]. This is likely related to the fact that annular dynamics in Barlow's disease differ significantly from those seen in fibroelastic deficiency [8, 13]. In patients with Barlow's disease there are no theoretical advantages of preserving annular dynamics by implantation of a partial and/or flexible annuloplasty device. Moreover, lack of more rigid annular stabilization could affect the diastolic and systolic valve leaflet configuration and movement, and fail to resolve excessive leaflet stress.

TECHNICAL ASPECTS OF MITRAL VALVE REPAIR

In **Chapter 6** to **Chapter 10**, several controversies in reconstructive mitral valve surgery are studied. As discussed, the results presented in this thesis support the concept of a patient tailored approach to mitral valve repair.

The problem of elevated mitral valve gradient after an otherwise successful valve repair without residual regurgitation is of particular interest. While several ideas, including avoidance of leaflet resection and use of partial and flexible annuloplasty devices, have recently been proposed to avoid this complication [14-17], there are insufficient theoretical foundations as well as clinical evidence to support their implication in general practice. **Chapter 7** describes a structured approach to excessive leaflet tissue in patients with degenerative mitral valve disease. The results demonstrate the safety and efficiency of both, resection and non-resection techniques, and suggest that valve repair is best fitted to valve-related characteristics. Interestingly, no effect of posterior leaflet resection on post-repair gradients was observed.

As discussed in **Chapter 10**, the problem of elevated post-repair gradient is most likely related to the implantation of a prosthetic annuloplasty device. This is not likely related to device undersizing, normally avoided in valve repair for organic mitral valve disease, but to annular stabilization itself which fixates the mitral valve in a systolic configuration. Any device implanted will disable the otherwise physiologic lengthening of the posterior annular perimeter during the diastolic phase of the cardiac cycle. To prevent the occurrence of an elevated post-repair gradient, the fixation hereof should thus ideally be avoided. However, as this can only be achieved by omitting annular remodeling and stabilization, this can be expected to come at the price of higher recurrent valve regurgitation rates [12, 18]. Projecting the known results of valve repair surgery on individual basis is challenging and in highly selected patients with preserved annular dynamics and morphology, annloplasty could possibly be omitted. In the presence of a high risk of elevated post-repair gradient (typically in the case of a small anterior leaflet, necessitating implantation of a small annuloplasty device), the decision not to implant an annuloplasty device could potentially be justified.

Impaired systolic annular function, consisting of annular flattening, dilation and diminished systolic contraction, is frequently present in patients with non-Barlow's degenerative valve disease. In these patients, impaired annular function likely presents a consequence of long-standing mitral regurgitation. Early valve repair, prior to the development of annular dysfunction, could present a durable treatment option even without an annuloplasty device implantation. This would allow off-pump valve repair with the implantation of artificial neochords where leaflet repair is usually not combined with concomitant annuloplasty to be performed [10]. However, taking into account the established impressive results of valve surgery for degenerative disease achieved in experienced centres [19], one has to question the clinical value of omitting cardiopulmonary bypass that comes with the price of no direct valve exposure. In the future, thorough understanding of the pathophysiology of mitral valve disease will guide a personalized valve repair strategy and possibly identify patients in whom off-pump valve repair will present an appropriate treatment option.

In line with the efforts aimed at preserving the maximal mitral valve orifice area, addressing commissural prolapse with papillary muscle head repositioning seems the most reasonable choice. As presented in **Chapter 6**, this technique is highly reproducible and reliable when the integrity of the subvalvular apparatus is preserved. The very long-term results of this technique are still lacking. However, the available results, including the results in cases of leaflet prolapse at other valve regions than the commissures [20, 21], are sufficient to conclude that even myxomatous degenerated chordae are of sufficient quality to support a durable repair. A thorough understanding of normal mitral valve function supports this observation, as primary chordae are crucial in guiding optimal systolic leaflet position but actually experience very little stress during the whole cardiac cycle.

In **Chapter 8**, the results of mitral valve repair with a tissue-engineering process treated bovine pericardial patch are studied. The results demonstrate good patch performance at early follow-up without any signs of echocardiographically detectable patch degeneration. While such results are promising, detailed late follow-up will be needed before any conclusions on the suitability of this material in reconstructive mitral valve surgery can be made. Availability of a reliable patch material to allow partial replacement of a diseased leaflet would enable an increased number of patients to benefit from the known advantages of valve repair. An example are patients with mitral annular calcification in whom valve repair without annular decalcification and ring annuloplasty is prone to repair failure, as demonstrated in **Chapter 9**. The disproportion between the dilated and calcified annulus and the mitral valve leaflets make valve repair without annular remodeling unstable due to the insufficient height of leaflet coaptation. As an alternative, and to compensate for the relative shortage of leaflet tissue, patch augmentation of the anterior leaflet can be performed. The results of this repair technique will, however, need to be further evaluated in the future.

TIMING OF SURGERY IN DEGENRATIVE MITRAL VALVE DISEASE

The safety and efficacy of early surgery in patients with severe degenerative mitral valve disease described in **Chapter 11**. Nevertheless, a number of patients experienced complications related to surgery, in particular supraventricular heart rhythm and conduction abnormalities. While these complications did not seem to effect the overall survival rates and health-related quality of life, both being comparable to the age- and gender-matched general population, they do provide space for further improvement of clinical results in these patients.

To date, the evidence for early surgery in the presence of asymptomatic severe mitral valve regurgitation remains relatively low. While pathological studies, demonstrating macro- end microscopic cardiac changes even in completely asymptomatic patients, do provide solid theoretical grounds to support early surgery [22, 23], one should not neglect the variety of clinical results in relation to surgeon and centre experience [24]. In addition to the benefits related to the resolution of continuous volume overload, an early surgery approach must also overcome the possible complications related to the procedure itself to prove itself superior to a watchful waiting approach. While the expected morbidity and mortality of surgical mitral valve intervention is nowadays low, previous studies have suggested that in asymptomatic patients with severe mitral regurgitation, survival and quality of life can remain comparable to the general population also when an watchful waiting approach is applied [25]. Further studies as well as further refinement of the results of mitral valve repair for degenerative disease are needed to guide a solid evidence based approach to the timing of surgery in these patients.

REFERENCES

[1] de Kerchove L, Price J, Tamer S et al. Extending the scope of mitral valve repair in active endocarditis. J Thorac Cardiovasc Surg 2012;143(4 Suppl):S91-95.

[2] Musci M, Hubler M, Pasic M et al. Surgery for active infective mitral valve endocarditis: A 20-year, single-center experience. J Heart Valve Dis 2010;19(2):206-214; discussion 215.

[3] Ruttmann E, Legit C, Poelzl G et al. Mitral valve repair provides improved outcome over replacement in active infective endocarditis. J Thorac Cardiovasc Surg 2005;130(3):765-771.

[4] Shimokawa T, Kasegawa H, Matsuyama S et al. Long-term outcome of mitral valve repair for infective endocarditis. Ann Thorac Surg 2009;88(3):733-739; discussion 739.

[5] Toyoda N, Itagaki S, Egorova NN et al. Real-world outcomes of surgery for native mitral valve endocarditis. J Thorac Cardiovasc Surg 2017;154(6):1906-1912 e1909.

[6] De Paulis R, Maselli D, Salica A et al. Mitral repair with the sole use of a semi-rigid band in a sub-population of patients with barlow's disease: A 4-year follow-up with stress echocardiography. Interact Cardiovasc Thorac Surg 2015;21(3):316-321.

[7] Klautz RJ, Tomšič A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in barlow's disease: The concept of functional prolapse. Multimed Man Cardiothorac Surg 2016;2017.

[8] Clavel MA, Mantovani F, Malouf J et al. Dynamic phenotypes of degenerative myxomatous mitral valve disease: Quantitative 3-dimensional echocardiographic study. Circ Cardiovasc Imaging 2015;8(5).

[9] Ben Zekry S, Spiegelstein D, Sternik L et al. Simple repair approach for mitral regurgitation in barlow disease. J Thorac Cardiovasc Surg 2015;150(5):1071-1077 e1071.

[10] Colli A, Manzan E, Aidietis A et al. An early european experience with transapical off-pump mitral valve repair with neochord implantation. Eur J Cardiothorac Surg 2018.

[11] Colli A, Besola L, Bizzotto E et al. Mechanisms of recurrent regurgitation after transapical off-pump mitral valve repair with neochord implantationdagger. Eur J Cardiothorac Surg 2019.

[12] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135(2):274-282.

[13] Apor A, Nagy AI, Kovacs A, Manouras A, Andrassy P, Merkely B. Three-dimensional dynamic morphology of the mitral valve in different forms of mitral valve prolapse - potential implications for annuloplasty ring selection. Cardiovasc Ultrasound 2016;14(1):32.

[14] Mazine A, Friedrich JO, Nedadur R et al. Systematic review and meta-analysis of chordal replacement versus leaflet resection for posterior mitral leaflet prolapse. J Thorac Cardiovasc Surg 2018;155(1):120-128 e110.

[15] Chan KL, Chen SY, Chan V, Hay K, Mesana T, Lam BK. Functional significance of elevated mitral gradients after repair for degenerative mitral regurgitation. Circ Cardiovasc Imaging 2013;6(6):1041-1047.

[16] Mesana TG, Lam BK, Chan V, Chen K, Ruel M, Chan K. Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: Potential affect on surgical strategy. J Thorac Cardiovasc Surg 2013;146(6):1418-1423; discussion 1423-1415.

[17] Ma W, Shi W, Wu W et al. Elevated gradient after mitral valve repair: The effect of surgical technique and relevance of postoperative atrial fibrillation. J Thorac Cardiovasc Surg 2018.

[18] Johnston DR, Gillinov AM, Blackstone EH et al. Surgical repair of posterior mitral valve prolapse: Implications for guidelines and percutaneous repair. Ann Thorac Surg 2010;89(5):1385-1394.

[19] Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: Implications for future guidelines. J Thorac Cardiovasc Surg 2012;144(2):308-312.

[20] Dreyfus G, Al Ayle N, Dubois C, de Lentdecker P. Long term results of mitral valve repair: Posterior papillary muscle repositioning versus chordal shortening. Eur J Cardiothorac Surg 1999;16(1):81-87.

[21] Dreyfus GD, Aubert S. Should mitral valve prolapse, even though commissural, be treated by suturing both leaflets together? Ann Thorac Surg 2006;81(6):2339; author reply 2339-2340.

[22] Ahmed MI, Gladden JD, Litovsky SH et al. Increased oxidative stress and cardiomyocyte myofibrillar degeneration in patients with chronic isolated mitral regurgitation and ejection fraction >60%. J Am Coll Cardiol 2010;55(7):671-679.

[23] Ahmed MI, Guichard JL, Soorappan RN et al. Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function. J Thorac Cardiovasc Surg 2016;152(4):1059-1070 e1052.

[24] Anyanwu AC, Bridgewater B, Adams DH. The lottery of mitral valve repair surgery. Heart 2010;96(24):1964-1967.

[25] Zilberszac R, Heinze G, Binder T, Laufer G, Gabriel H, Rosenhek R. Long-term outcome of active surveillance in severe but asymptomatic primary mitral regurgitation. JACC Cardiovasc Imaging 2018;11(9):1213-1221.

13

General discussion and future perspectives (Dutch)

Het doel van dit proefschrift is het evalueren van de huidige status van reconstructieve mitralisklepchirurgie bij organisch mitraliskleplijden. De focus ligt met name op de technische operatieve gegevens die in de verschillende studies verzameld zijn en geëvalueerd. Daarnaast wordt de pathofysiologie van mitraliskleplijden in de uitgevoerde studies uitgebreid beschreven, aangezien dat van invloed is op het klinische beloop en het plannen van een optimale chirurgische behandelstrategie. De resultaten van chirurgische interventie voor organisch mitraliskleplijden worden voor een belangrijk deel beïnvloed door de perioperatieve klinische besluitvorming. Daarom zijn ook perioperatieve aspecten meegenomen in de uitgevoerde studies, welke met name gericht zijn op de timing van chirurgische interventie. Op basis van dit proefschrift blijkt het noodzakelijk om verder onderzoek te verrichten om een optimale patiëntgerichte benadering voor organisch mitraliskleplijden te bewerkstelligen.

INFECTIEUZE MITRALISKLEPENDOCARDITIS

In **Hoofdstuk 2** en **Hoofdstuk 3** worden de resultaten van chirurgische interventie bij infectieuze mitralisklependocarditis beschreven in verschillende klinische scenario's. De relatief hoge mortaliteit is overeenkomstig met eerder gepubliceerde resultaten [1-3]. Dit is primair gerelateerd aan de matige klinische conditie en uitgebreide comorbiditeiten waar deze patiënten zich gebruikelijk mee presenteren. Het toegepaste beleid bestaat preoperatief uit 48 uur antibiotisch behandelen om sterilisatie van de bloedbaan te bewerkstelligen. Vervolgens wordt het geïnfecteerde weefsel chirurgisch radicaal gereseceerd waarbij het operatiegebied gereinigd wordt met rifampicineoplossing. Dankzij dit beleid was geen recidief of residuale infectie bij alle patiënten ondanks liberaal gebruik van prothesemateriaal. Gebaseerd op deze belangrijke bevinding lijkt het mogelijk en veilig om bij actieve endocarditis een ring annulusplastiek in het kader van een complexe mitraliskleprecontructie te verrichten. Dit wordt vaak niet wordt uitgevoerd vanwege angst voor recidief infectie in aanwezigheid van actieve infectie. Echter komt onderliggend mitraliskleplijden in deze populatie vaak voor met, wordt betrokkenheid van de annulus bij het infectieuze proces vaak gezien of wordt een complexe reconstructie verricht. Op basis van deze gronden heeft verrichten van een annulusplastiek wel de voorkeur in deze patiënten. De studies in deze hoofdstukken laten zien dat bij de meerderheid van de patiënten een duurzame reparatie kon worden uitgevoerd met een lager aantal re-operaties dan in de literatuur beschreven is [1, 2, 4]. Bovendien werd een lage incidentie van recidief mitralisklepinsufficiëntie gezien. Vanwege het laagdrempelig toepassen van annulusplastiek tijdens operaties kan worden aangenomen dat de reparaties in deze specifieke doelgroep zijn verduurzaamd.

Indien het infectieuze proces geresulteerd heeft in uitgebreide destructie van de natieve klep, wordt er mitralisklepvervanging verricht zonder initiële poging tot reparatie, volgens de beschreven gestructureerde intra-operatieve aanpak. Het is een algemene aanname dat mitralisklepreparatie, in vergelijking met klepvervanging, een superieur klinisch resultaat geeft op de lange termijn. Echter moet de reparatie technisch mogelijk zijn en is een goede duurzaamheid van de reparatie een absolute voorwaarde om een goede uitkomst te bewerkstelligen. Daarom is kritische beoordeling van de mogelijkheid van een duurzame klepreparatie noodzakelijk, waarbij patiënten worden geselecteerd voor reparatie waarbij een klinisch voordeel wordt verwacht en waarbij mogelijke negatieve effecten, zoals een langere aortaklemtijd en cardiopulmonale bypass tijd, vermijdt kunnen worden. Indien er sprake is van uitgebreide destructie van de natieve mitralisklep, is het nastreven van een duurzame klepreparatie vrijwel onmogelijk en kan een poging tot reparatie het beste vermeden worden. Kortom, een doordacht perioperatief beleid in combinatie met een structurele chirurgische aanpak is essentieel om een optimaal klinisch resultaat te behalen.

Tot op heden is er weinig bewijs dat een overlevingsvoordeel van klepreparatie bij patiënten met infectieuze mitralisklependocarditis aantoont. Eerdere studies beschrijven vooral een toename in overleving op basis van het eerste postoperatieve jaar na de operatie, waarbij de overlevingscurve in de vroege fase een divergerend verloop heeft en in de latere fase een parallel verloop laat zien[5]. In de vroege periode lijkt de overleving minder beïnvloedt te worden door de soort procedure (reparatie versus vervanging) en in meerdere mate door patiëntkenmerken. Hierdoor blijft de ware superioriteit van klepreparatie boven klepvervanging bij een actieve infectieuze endocarditis twijfelachtig. De resultaten beschreven in **Hoofdstuk 2 laten een neiging naar een verbeterde overleving zien in patiënten die een klepreparatie hebben ondergaan**. De overlevingscurves in dit hoofdstuk hadden een divergerend verloop, ook na de vroege postoperatieve periode. Echter, door de kleine populatie kan deze bevinding niet statistisch onderbouwd worden. De klinische waarde van een systematische benadering voor mitralisklepreparatie bij infectieuze endocarditis moet daarom verder geëvalueerd worden in gestandaardiseerde studies met de juiste populatiegrootte.

ZIEKTE VAN BARLOW

Hoofdstuk 4 en **Hoofdstuk 5** richten zich op het pathofysiologische concept achter de ziekte van Barlow, het effect hiervan op de mitralisklepreparatie strategie en de uitkomsten van chirurgische interventie. Allereerst wordt de ziekteprogressie ter discussie gesteld; Hoofdstuk 5 beargumenteerd dat het falen van een klepreparatie na een initieel succesvolle chirurgische reparatie primair gerelateerd is aan technische aspecten van de operatie. Dit heeft niet alleen betrekking op de chirurgisch technische aspecten van klepchirurgie, maar ook dat ziekteprogressie een potentieel effect heeft op de optimale timing van chirurgische interventies. Optimale chirurgische klepreparaties bestaan onder andere uit stabilisatie van de annulus en het creëren van een groot oppervlak van klepbladcoaptatie waardoor de overmatige stress op de klepbladen zal normaliseren. Een stabiele klepreparatie zal de progressie van de ziekte van Barlow beperken. Deze progressie wordt hoofdzakelijk veroorzaakt door abnormale annulus dynamiek, wat de pathofysiologie van deze ziekte kenmerkt [6-8]. Eerdere studies hebben aangetoond dat klepreparatie waarbij enkel annuloplastiek wordt toegepast haalbaar is bij een Barlowklep [6, 9]. Met de opmars van endovasculaire technieken voor annuloplastiek kan endovasculaire mitralisklepreparatie in de toekomst een therapeutische optie worden voor een zorgvuldig geselecteerde groep patiënten, zelfs voordat er ernstige regurgitatie optreedt. Dit zou niet alleen ziekteprogressie tegengaan, maar zo kunnen ook de consequenties van ernstige mitralisklepinsufficiëntie voorkomen worden.

Het beschreven concept van functionele klepbladprolaps stelt het toepassen van reparaties, zowel chirurgisch als endovasculair, waarbij de annulus niet systematisch wordt meegenomen, ter discussie. Recent is off-pump mitralisklepreparatie met implantatie van kunstmatige neochordae beschreven als behandeloptie voor patiënten met een degeneratieve mitralisklepaandoening [10]. Echter hebben eerdere studies aangetoond dat de resultaten van off-pump mitralisklepreparaties inferieur zijn indien er prolaps van beide klepbladen aanwezig is, wat meestal het geval is bij de ziekte van

Barlow. Al met al lijkt het waarschijnlijker dat reparaties falen indien de abnormale annulus beweging niet behandeld wordt, en dat de oorzaak niet ligt in het al dan niet aanwezig zijn van prolaps van beide klepbladen [11].

Een belangrijke, en tot op heden onbeantwoorde kwestie, is het effect van het type annuloplastiekprothese (semi-rigide of flexibel; geheel of partieel) op de duurzaamheid van de klepreparatie. Tussen de verschillende soorten degeneratieve mitralisklepaandoening varieert de invloed van remodellering en stabilisatie van de annulus op de klinische uitkomst. Patiënten met de ziekte van Barlow lijken het meest gevoelig te zijn voor het ontwikkelen van recidief mitralisklepinsufficiëntie in de afwezigheid van annuloplastiek [12]. Dit is vermoedelijk gerelateerd aan het feit dat de dynamiek van de annulus bij ziekte van Barlow verschilt van de annulus dynamiek in patiënten met fibroelastische deficiëntie [11, 12]. Bij patiënten met ziekte van Barlow bestaat er theoretisch gezien geen voordeel van het behouden van de annulusdynamiek door implantatie van partiele en/of flexibele annuloplastiekprothese. Bovendien kan het gebrek aan rigide annulus stabilisatie de diastolische en systolische configuratie van de klepbladen beïnvloeden, wat kan resulteren in residuele overmatige stress op de klepbladen.

TECHNISCHE ASPECTEN VAN MITRALISKLEPREPARATIE

Hoofdstuk 6 tot en met **Hoofdstuk 10 beschrijven verschillende discussiepunten** binnen de reconstructieve mitralisklepchirurgie. Zoals eerder benoemd pleiten de resultaten van dit proefschrift voor een patiënt specifieke benadering van mitralisklepreparatie.

Het belangrijkste probleem is het bestaan van een verhoogde gradiënt over de mitralisklep na een succesvolle klepreparatie zonder resterende insufficiëntie. De recente theorieën over het voorkomen van deze complicatie stellen dat klepbladresecties vermeden moeten worden en partiële of flexibele annuloplastiekprotheses gebruikt moeten worden. Echter is het bewijs, zowel theoretisch als klinisch, ontoereikend, waardoor deze adviezen nog niet geïmplementeerd zijn in de dagelijkse praktijk. **Hoofdstuk 7** beschrijft een structurele benadering voor behandeling van excessief klepweefsel bij patiënten met een degeneratieve mitralisklepaandoening. In de resultaten wordt de veiligheid en de efficiëntie van klepreparaties ofwel met klepbladresectie, ofwel zonder resectie, aangetoond. Daarbij moet het type klepreparatie afgestemd worden op de karakteristieken van de klep. Een interessante bevinding in deze studie was dat resectie van het achterste klepblad geen effect had op de postoperatieve gradiënt.

Zoals besproken in **Hoofdstuk 10** is het ontstaan van de postoperatieve gradiënt meest waarschijnlijk gerelateerd aan de implantatie van een annuluoplastiekprothese. Dit is niet gerelateerd aan het verkleinen van de annulus met een "undersized" ring, wat sowieso vermeden moet worden bij klepreparaties voor organische mitralisklepaandoening, maar aan het feit dat verrichten van annuloplastiek de mitralisklep fixeert in een systolische configuratie. Elke geïmplanteerde prothese belemmert de normaal aanwezige fysiologische verlenging van de achterste annulaire perimeter gedurende de diastole. Om een verhoogde postoperatieve gradiënt te voorkomen zou idealiter fixatie aldaar vermeden moeten worden. Echter, dit kan alleen bereikt worden door af te zien van annulus stabilisatie en remodellering, waartegenover een hogere incidentie van recidiverende mitralisklepinsufficiëntie staat [12, 18]. In theorie zal er bij geselecteerde patiënten, met behoudt van morfologie en dynamiek van de mitralisklepannulus, afgezien kunnen worden van een annuloplastiek. Bij een hoog risico op een verhoogde postoperatieve gradiënt, meestal in het geval van een kleine voorste klepblad waarbij implantatie van een klein annuloprothese noodzakelijk is, kan de beslissing om af te zien van annuloplastiek mogelijk worden gerechtvaardigd.

Beperkte systolische functie van de annulus, bestaande uit afvlakking van de annulus, dilatatie en verminderde systolische contractie, is bij patiënten met een degeneratieve mitralisklepaandoening (geen ziekte van Barlow) vaak aanwezig. Bij deze patiënten is de verminderde functie van de annulus een gevolg van langer bestaande mitralisklepinsufficiëntie. Vroegtijdige klepreparatie, uitgevoerd voordat ernstige en irreversibele functionele afwijkingen van de annulus ontstaan, kan mogelijk een duurzame oplossing zijn, ook zonder het uitvoeren van een annuloplastiek. Hierbij kan ook off-pump klepreparatie met implantatie van kunstmatige neochordae mogelijk gemaakt worden [10]. Echter, gezien de reeds bereikte, indrukwekkende resultaten van klepchirurgie bij een degeneratieve aandoening in gespecialiseerde centra [19] is het maar de vraag of het verstandig is om cardiopulmonaire bypass achterwege te laten waardoor er geen direct zicht meer is op de mitralisklep. In de toekomst kan gepersonaliseerde mitralisklepreparatie nagestreefd worden gebaseerd op begrip van de pathofysiologie van mitralisklepdegeneratie. Daarbij zal de patiëntselectie zodanig worden dat off-pump klepreparatie in sommige gevallen een passende behandelingsoptie wordt.

Herstel van de commissurale prolaps middels repositie van de papillairspierkop lijkt de optimale keuze om maximale mitralisklepopening te behouden. In **Hoofdstuk 6** wordt deze techniek beschreven als goed reproduceerbaar en betrouwbaar, indien het subvalvulaire apparaat nog intact is gebleven. Alhoewel resultaten op zeer lange termijn nog ontbreken, laten de beschikbare data zien dat zelfs myxomateus gedegenereerde chordae voldoende sufficiënt zijn voor een duurzame reparatie. Dit wordt ondersteund door de eerder gedocumenteerde resultaten van klepreparaties waarbij gebruik gemaakt wordt van papillairspierkop repositie bij prolaps van het klepblad, ook indien deze een andere oorsprong heeft dan vanuit de commissuur [20, 21]. Het begrip van de normale mitralisklepfunctie ondersteund deze bevinding, aangezien de primaire chordae een cruciale rol spelen in het optimaal positioneren van de klepbladen tijdens de systole, waarbij de spanning op deze chordae gedurende de gehele cardiale cyclus laag blijft.

Hoofdstuk 8 beschrijft de uitkomsten van mitralisklepreparatie waarbij gebruik gemaakt is van "tissue-engineering process treated bovine pericardial patch". Het gebruik van deze patch laat goede resultaten zien zonder echografisch aantoonbare degeneratie. Deze bevindingen zijn weliswaar veelbelovend, maar de resultaten op lange termijn moeten worden afgewacht voordat er conclusies getrokken kunnen worden over het gebruik van deze patch tijdens reconstructieve mitralisklep chirurgie. De beschikbaarheid van betrouwbaar patchmateriaal voor het deels vervangen van aangedaan klepblad kan in een groter aantal patiënten de mogelijkheid verschaffen voor klepreparatie, wat de eerder genoemde voordelen met zich mee brengt. Zoals beschreven in Hoofdstuk 9 is het noodzakelijk om bij patiënten met een gecalcificeerde mitralisannulus tijdens klepreparatie annulus decalcificatie toe te passen en een ring te plaatsen om recidief mitralisklepinsufficiëntie te voorkomen. Zonder annulus remodellering zorgt de discrepantie tussen de gedilateerde en gecalcificeerde annulus en de hoogte van de mitralisklepbladen voor een instabiele reparatie vanwege tekort aan klepbladcoaptatiehoogte. Patch augmentatie van het voorste klepblad zonder annulus decalcificatie en remodellering zou een alternatief kunnen bieden. Augmentatie zorgt in theorie voor compensatie van het relatief te kort aan klepbladweefsel. De uitkomsten van deze techniek dienen echter verder geëvalueerd te worden.

TIMING VAN CHIRURGISCHE INTERVENTIE BIJ DEGENERATIEVE MITRALISKLEPAANDOENING

De veilige en effectieve toepassing van vroege chirurgische interventie bij patiënten met ernstig aangedane degeneratieve mitralisklep worden beschreven in **Hoofdstuk 11**. Complicaties van deze ingreep bestonden met name uit supraventriculaire aritmieën en geleidingsstoornissen. Alhoewel dit geen effect lijkt te hebben op de overleving en kwaliteit van leven in vergelijking met leeftijdsgenoten van hetzelfde geslacht, is er ruimte voor verdere verbetering van de postoperatieve klinische resultaten.

Het bewijs voor vroege interventie bij asymptomatische patiënten met ernstige mitralisklepinsufficiëntie blijft vooralsnog relatief beperkt. Enkele pathologisch georiënteerde studies laten micro- en macroscopische veranderingen van het hart zien, zelfs bij compleet asymptomatische patiënten, wat vroeg chirurgisch ingrijpen rechtvaardigt [22, 23]. Echter is variatie in klinische resultaten gerelateerd aan bekwaamheid van de chirurg en het behandelend centrum [24]. Een vroeg chirurgische interventie moet niet alleen volumeoverbelasting reduceren maar ook superior zijn ten opzichte van conservatieve behandeling, gezien de mogelijkheid op procedure-gerelateerde complicaties. Ondanks de tegenwoordig lage morbiditeit en mortaliteit van chirurgisch behandelen van de mitralisklep, laten eerdere studies zien dat de overleving en kwaliteit van leven bij asymptomatische patiënten met ernstige mitralisklepinsufficiëntie vergelijkbaar kan zijn met de gezonde populatie. Bij deze patiënten kan dan ook gekozen worden voor een "watchful waiting" benadering waarbij gewacht wordt tot de patiënten symptomen of andere triggers voor interventie ontwikkelen [25]. Voor het bepalen van de optimale timing om mitralisklep chirurgie toe te passen, wat verbeterde resultaten kan opleveren, is aanvullend onderzoek noodzakelijk.

REFERENTIELIJST

[1] de Kerchove L, Price J, Tamer S et al. Extending the scope of mitral valve repair in active endocarditis. J Thorac Cardiovasc Surg 2012;143(4 Suppl):S91-95.

[2] Musci M, Hubler M, Pasic M et al. Surgery for active infective mitral valve endocarditis: A 20-year, single-center experience. J Heart Valve Dis 2010;19(2):206-214; discussion 215.

[3] Ruttmann E, Legit C, Poelzl G et al. Mitral valve repair provides improved outcome over replacement in active infective endocarditis. J Thorac Cardiovasc Surg 2005;130(3):765-771.

[4] Shimokawa T, Kasegawa H, Matsuyama S et al. Long-term outcome of mitral valve repair for infective endocarditis. Ann Thorac Surg 2009;88(3):733-739; discussion 739.

[5] Toyoda N, Itagaki S, Egorova NN et al. Real-world outcomes of surgery for native mitral valve endocarditis. J Thorac Cardiovasc Surg 2017;154(6):1906-1912 e1909.

[6] De Paulis R, Maselli D, Salica A et al. Mitral repair with the sole use of a semi-rigid band in a sub-population of patients with barlow's disease: A 4-year follow-up with stress echocardiography. Interact Cardiovasc Thorac Surg 2015;21(3):316-321.

[7] Klautz RJ, Tomšič A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in barlow's disease: The concept of functional prolapse. Multimed Man Cardiothorac Surg 2016;2017.

[8] Clavel MA, Mantovani F, Malouf J et al. Dynamic phenotypes of degenerative myxomatous mitral valve disease: Quantitative 3-dimensional echocardiographic study. Circ Cardiovasc Imaging 2015;8(5).

[9] Ben Zekry S, Spiegelstein D, Sternik L et al. Simple repair approach for mitral regurgitation in barlow disease. J Thorac Cardiovasc Surg 2015;150(5):1071-1077 e1071.

[10] Colli A, Manzan E, Aidietis A et al. An early european experience with transapical off-pump mitral valve repair with neochord implantation. Eur J Cardiothorac Surg 2018.

[11] Colli A, Besola L, Bizzotto E et al. Mechanisms of recurrent regurgitation after transapical off-pump mitral valve repair with neochord implantationdagger. Eur J Cardiothorac Surg 2019.

[12] Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in barlow disease versus fibroelastic deficiency. J Thorac Cardiovasc Surg 2008;135(2):274-282.

[13] Apor A, Nagy AI, Kovacs A, Manouras A, Andrassy P, Merkely B. Three-dimensional dynamic morphology of the mitral valve in different forms of mitral valve prolapse - potential implications for annuloplasty ring selection. Cardiovasc Ultrasound 2016;14(1):32.

[14] Mazine A, Friedrich JO, Nedadur R et al. Systematic review and meta-analysis of chordal replacement versus leaflet resection for posterior mitral leaflet prolapse. J Thorac Cardiovasc Surg 2018;155(1):120-128 e110.

[15] Chan KL, Chen SY, Chan V, Hay K, Mesana T, Lam BK. Functional significance of elevated mitral gradients after repair for degenerative mitral regurgitation. Circ Cardiovasc Imaging 2013;6(6):1041-1047.

[16] Mesana TG, Lam BK, Chan V, Chen K, Ruel M, Chan K. Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: Potential affect on surgical strategy. J Thorac Cardiovasc Surg 2013;146(6):1418-1423; discussion 1423-1415.

[17] Ma W, Shi W, Wu W et al. Elevated gradient after mitral valve repair: The effect of surgical technique and relevance of postoperative atrial fibrillation. J Thorac Cardiovasc Surg 2018.

[18] Johnston DR, Gillinov AM, Blackstone EH et al. Surgical repair of posterior mitral valve prolapse: Implications for guidelines and percutaneous repair. Ann Thorac Surg 2010;89(5):1385-1394.

[19] Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: Implications for future guidelines. J Thorac Cardiovasc Surg 2012;144(2):308-312.

[20] Dreyfus G, Al Ayle N, Dubois C, de Lentdecker P. Long term results of mitral valve repair: Posterior papillary muscle repositioning versus chordal shortening. Eur J Cardiothorac Surg 1999;16(1):81-87.

[21] Dreyfus GD, Aubert S. Should mitral valve prolapse, even though commissural, be treated by suturing both leaflets together? Ann Thorac Surg 2006;81(6):2339; author reply 2339-2340.

[22] Ahmed MI, Gladden JD, Litovsky SH et al. Increased oxidative stress and cardiomyocyte myofibrillar degeneration in patients with chronic isolated mitral regurgitation and ejection fraction >60%. J Am Coll Cardiol 2010;55(7):671-679.

[23] Ahmed MI, Guichard JL, Soorappan RN et al. Disruption of desmin-mitochondrial architecture in patients with regurgitant mitral valves and preserved ventricular function. J Thorac Cardiovasc Surg 2016;152(4):1059-1070 e1052.

[24] Anyanwu AC, Bridgewater B, Adams DH. The lottery of mitral valve repair surgery. Heart 2010;96(24):1964-1967.

[25] Zilberszac R, Heinze G, Binder T, Laufer G, Gabriel H, Rosenhek R. Long-term outcome of active surveillance in severe but asymptomatic primary mitral regurgitation. JACC Cardiovasc Imaging 2018;11(9):1213-1221.

LIST OF PUBLICATIONS

van Wijngaarden AL, Tomšič A, Fortuni F, Delgado V, Bax JJ, Klautz RJM, Marsan NA, Palmen M. Mitral valve repair for isolated posterior mitral valve leaflet prolapse: the effect of respect and resect techniques on left ventricular function. Under review.

Hiemstra YL, Tomšič A, Gripari P, van Wijngaarden AL, van der Pas SL, Palmen M, Klautz RJM, Pepi M, Bax JJ, Delgado V, Marsan NA. Evolution from mitral annular dysfunction to severe mitral regurgitation in Barlow's disease. Interact Cardiovasc Thorac Surg. 2020. Accepted, awaiting publication.

Tomšič A, Arabkhani B, Schoones JW, Etnel JRG, Marsan NA, Klautz RJM, Palmen M. Prosthesis-patient mismatch after mitral valve replacement: A pooled meta-analysis of Kaplan-Meier-derived individual patient data. J Card Surg. 2020. Epub ahead of print.

Tomšič A, Klautz RJM. What we see depends on what we look for. Eur J Cardiothorac Surg. 2020;58(5):1105.Defauw RJ, Tomšič A, van Brakel TJ, Klautz RJM, Palmen M. A structured approach to native mitral valve infective endocarditis: is repair better then replacement? Eur J Cardiothorac Surg. 2020;58(3):544-550.

Diephuis E, de Borgie C, Tomšič A, Winkelman J, van Boven WJ, Bouma B, Eberl S, Juffermans N, Schultz M, Henriques JP, Koolbergen D. Continuous postoperative pericardial flushing method versus standard care for wound drainage after adult cardiac surgery: A randomized controlled trial. EBioMedicine. 2020;55:102744.

Tomšič A, Hiemstra YL, Arabkhani B, Mertens BJA, van Brakel TJ, Versteegh MIM, Marsan NA, Klautz RJM, Palmen M. Risk factors and clinical significance of elevated mitral valve gradient following valve repair for degenerative disease. Eur J Cardiothorac Surg. 2020;57(2):293-299.

Hiemstra YL, Tomšič A, van Wijngaarden SE, Palmen M, Klautz RJM, Bax JJ, Delgado V, Ajmone Marsan N. Prognostic Value of Global Longitudinal Strain and Etiology After Surgery for Primary Mitral Regurgitation. JACC Cardiovasc Imaging. 2020;13(2):577-585.

Tomšič A, Palmen M, Klautz RJM. The devil is in the details, not the ring. J Thorac Cardiovasc Surg. 2019;157(5):e249-e250.

Tomšič A, Hiemstra YL, van Brakel TJ, Versteegh MIM, Marsan NA, Klautz RJM, Palmen M. Outcomes of Valve Repair for Degenerative Disease in Patients With Mitral Annular Calcification. Ann Thorac Surg. 2019;107(4):1195-1201.

Tomšič A, Hiemstra YL, van Brakel TJ, Versteegh MI, Ajmone Marsan N, Klautz RJ, Palmen M. Excessive leaflet tissue in mitral valve repair for isolated posterior leaflet prolapse-leaflet resection or shortening neochords? A propensity score adjusted comparison. J Cardiovasc Surg (Torino). 2019;60(1):111-118.

van der Wall SJ, Olsthoorn JR, Heuts S, Klautz RJM, Tomšič A, Jansen EK, Vonk ABA, Sardari Nia P, Klok FA, Huisman MV. Antithrombotic therapy after mitral valve repair: VKA or aspirin? J Thromb Thrombolysis. 2018;46(4):473-481.

Tomšič A, Klautz RJM, Palmen M. Off-pump mitral valve repair: is less really more? Eur J Cardiothorac Surg. 2018;54(6):1147-1148.

Bissessar D, Tomšič A, van Brakel T, Klautz R, Palmen M. Bileaflet pericardial patch repair for rheumatic mitral valve disease. Multimed Man Cardiothorac Surg. 2018 Jan 25;2018:http://mmcts.org/tutorial/884.

Tomšič A, Bissessar DD, van Brakel TJ, Marsan NA, Klautz RJM, Palmen M. Initial Experience and Early Results of Mitral Valve Repair With CardioCel Pericardial Patch. Ann Thorac Surg. 2018;106(4):1241-1244.

Tomšič A, Hiemstra YL, van Hout FMA, van Brakel TJ, Versteegh MIM, Marsan NA, Klautz RJM, Palmen M. Long-term results of mitral valve repair for severe mitral regurgitation in asymptomatic patients. J Cardiol. 2018;72(6):473-479.

Tomšič A, Klautz RJM, Palmen M. Mitral valve infective endocarditis: putting the puzzle pieces together. Eur J Cardiothorac Surg. 2018;54(1):199.

Tomšič A, Klautz RJM, van Brakel TJ, Ajmone Marsan N, Versteegh MIM, Palmen M. Papillary muscle head repositioning for commissural prolapse in degenerative mitral valve disease. Interact Cardiovasc Thorac Surg. 2018;27(1):124-130.

Tomšič A, Klautz RJM, Palmen M. Respect versus resect: Two different repair techniques or two different tools in the toolbox? J Thorac Cardiovasc Surg. 2018;155(2):600-601.

Tomšič A, Klautz RJM, Palmen M. eComment. Posterior mitral valve leaflet prolapse: one term, several different meanings. Interact Cardiovasc Thorac Surg. 2018;26(2):256.

Tomšič A, Hiemstra YL, van der Pas SL, Putter H, Versteegh MIM, van Brakel TJ, Ajmone Marsan N, Klautz RJM, Palmen M. Early and long-term outcomes of mitral valve repair for Barlow's disease: a single-centre 16-year experience. Interact Cardiovasc Thorac Surg. 2018;26(5):783-789.

Tomšič A, Versteegh MIM, Ajmone Marsan N, van Brakel TJ, Klautz RJM, Palmen M. Early and late results of surgical treatment for isolated active native mitral valve infective endocarditis. Interact Cardiovasc Thorac Surg. 2018;26(4):610-616.

Tomšič A, Arabkhani B, Schoones JW, van Brakel TJ, Takkenberg JJM, Palmen M, Klautz RJM. Outcome reporting for surgical treatment of degenerative mitral valve disease: a systematic review and critical appraisal. Interact Cardiovasc Thorac Surg. 2018;26(4):566-572.

Tomšič A, Hiemstra YL, Bissessar DD, van Brakel TJ, Versteegh MIM, Ajmone Marsan N, Klautz RJM, Palmen M. Mitral valve repair in Barlow's disease with bileaflet prolapse: the effect of annular stabilization on functional mitral valve leaflet prolapse. Interact Cardiovasc Thorac Surg. 2018;26(4):559-565.

Tomšič A, Schneider AW, Palmen M, van Brakel TJ, Versteegh MIM, Klautz RJM. Extensive infective endocarditis of the aortic root and the aortic-mitral continuity: a mitral valve sparing approach†. Eur J Cardiothorac Surg. 2017;51(6):1100-1107.

Tomšič A, Li WW, de Mol BA. Reply to Prestipino et al. Eur J Cardiothorac Surg. 2017;51(2):401-402.

Klautz RJ, Tomšič A, Palmen M, van Brakel TJ, Perier P. Optimal surgical mitral valve repair in Barlow's disease: the concept of functional prolapse. Multimed Man Cardiothorac Surg. 2016 Dec 6;2017.

Tomšič A, Li WW, van Paridon M, Bindraban NR, de Mol BA. Infective Endocarditis of the Aortic Valve with Anterior Mitral Valve Leaflet Aneurysm. Tex Heart Inst J. 2016;43(4):345-9.

Tomšič A, Palmen M, Versteegh MI, van der Kley F, Siebelink HJ, Berendsen RR, Schalij MJ. Prosthesis Dislocation After Transapical Valve-In-Valve Mitral Valve Implantation. Can J Cardiol. 2016;32(12):1576.e7-1576.e9.

Tomšič A, Schotborgh MA, Manshanden JS, Li WW, de Mol BA. Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. Eur J Cardiothorac Surg. 2016;50(5):849-856.

CURRICULUM VITAE

Anton Tomšič was born on 11 April 1988 in Ljubljana, Slovenia. After graduating from high school (Gimnazija Vič, Ljubljana, Slovenia), he started Medical school in 2006 at the Medical faculty of Ljubljana. He finished his studies in 2012 and obtained his medical degree in 2013 after passing the Slovenian medical board exam. In 2014, he moved to The Netherlands where he started working as a resident at the Department of Cardio-Thoracic Surgery at University Hospital Amsterdam. In the same year he obtained the Educational Commission for Foreign Medical Graduates certification. In 2015 he started working as a resident at the Department of Cardio-Thoracic Surgery at University Hospital Leiden. Paralel to his residency, he started a PhD project under supervision of prof. dr. Robert J.M. Klautz, which resulted in this thesis. Since July 2018 he is in training for cardio-thoracic surgeon at the Department of Cardio-Thoracic Surgery at University Hospital Leiden.

DANKWOORD

Ten eerste wil ik alle patiënten bedanken die deel hebben genomen aan dit onderzoek. Daarnaast wil ik iedereen die aan de totstandkoming van dit proefschrift heeft bijgedragen heel hartelijk bedanken. In het bijzonder wil ik bedanken;

Prof. Dr. R.J.M. Klautz, beste Professor, ik wil u van harte bedanken voor de kansen die u mij heeft geboden. U heeft mij vanaf het begin van mijn ANIOS en promotie tijd in het LUMC gesteund en de mogelijkheid gegeven om mijzelf verder te ontwikkelen als dokter, wetenschapper en persoon. Ik heb veel van u geleerd en ben blij om dat te kunnen blijven doen.

Dr. M. Palmen, beste Meindert, ik heb enorm genoten van onze samenwerking de afgelopen jaren. Jij wist mij altijd de weg te wijzen, hebt mij gesteund in de uitvoer van alle ideeën die ik kon bedenken en je hebt altijd tijd vrijgemaakt voor onderzoeksoverleg. Je enthousiasme en energie zijn besmettelijk en ik hoop dat onze samenwerking nog lang zal blijven bestaan.

Dr. Ajmone Marsan, beste Nina, door jouw is dit proefschrift een echt multidisciplinair werk geworden. Ik waardeer de samenwerking die we hebben opgebouwd enorm, evenals je bereidheid om altijd al je kennis met ons te willen delen. Je vermogen om thoraxchirurgen te begrijpen is uitzonderlijk.

Alle collega's van de afdelingen Thoraxchirurgie en Cardiologie van het LUMC evenals alle collega's van verwijzende ziekenhuizen die bij het onderzoek betrokken waren, dank voor de samenwerking en jullie hulp de afgelopen jaren.

Lieve collega assistenten van het afdeling Thoraxchirurgie, bedankt voor de prettige samenwerking door de jaren. Beste Adriaan, may the best men win.

Lieve paranimfen, beste Sabrina en Bardia, wij hebben wel wat meegemaakt in onze assistentetijden! Samen zijn we door "ups-and-downs" gegaan en ik ben jullie ontzettend dankbaar voor jullie steun en adviezen. Ik waardeer dat jullie deze dag aan mijn zijde staan.

Er zijn veel vrienden die ik niet allemaal persoonlijk kan bedanken. Leven is een roller coaster en ik ben trots dat we die samen beleven!

Draga mami in ata, ta knjiga je rezultat vajinega truda in ljubezni, ki sta mi jo izkazala v vseh teh letih. Odločitve, ki so pripeljale do končnega uspeha, niso vedno bile lahke. Vajino razumevanje in podpora sta mi dajala moč skozi vse te čase in nas skupaj pripeljale do željenega cilja. Dragi Pavel, bratska ljubezen je nerazdružljiva in hvala ti za ves tvoj trud in oporo. Moji širši druzini- vesel sem, da lahko te trenutke delim z vami!