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Impact of surgical techniques used for mitral valve repair on hemodynamic performance

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Impact of surgical techniques used for mitral valve repair on hemodynamic performance

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

Background Mitral regurgitation (MR) has many etiologies; the most common is degenerative disease. If not corrected, severe MR may cause left and right ventricular heart failure. Mitral valve (MV) repair is the gold standard for treatment of MR. All repair techniques include MV annuloplasty, but various techniques are employed to repair the valvular apparatus. The classical technique of leaflet resection is associated with excellent results, but repair using artificial chordae is gaining popularity and has been shown to achieve similar results.

Aims (1) Does MV repair with artificial chordae correct the morphology and function of the MV better than leaflet resection? (2) How common are MR at rest and systolic anterior motion (SAM) when these techniques are compared at rest and during physical exercise? (3) To what extent is the right ventricular function restored in patients with chronic MR after MV repair? (4) Is MV repair preferable for the surgical treatment of MV infective endocarditis?

Methods Study I: Retrospective study conducted in two centers that compares the results of MV repair using two different surgical techniques.

Studies II and III: Prospective studies of resting and exercise echocardiography in patients that had undergone MV repair with either artificial chordae or leaflet resection. Study III compares the hemodynamics and left ventricular function of the repaired MV. Study IV evaluates the right ventricular function at rest and during exercise.

IV: Retrospective study of long term outcomes of patients with MV infective endocarditis (IE) who underwent surgical repair in Lund with different surgical techniques.

Results and importance

I: Both evaluated techniques for repair the MV were associated with good long-term survival and low incidence of recurrent MR, reoperation, IE and thromboembolism. No significant differences were detected between the groups.

II: Both surgical techniques were associated with low pressure gradients over the MV at rest and during exercise without any significant difference between the groups. The left ventricular function was well preserved and both groups had good exercise capacity.

III: At follow up, patients who underwent mitral valve repair had significantly worse RV function at rest and peak exercise than did healthy individuals.

IV: Mortality following surgery for mitral IE is high. Independent predictors of poor outcome are the preoperative symptoms of persisting fever, clinical stroke and heart failure and infection with *S. aureus*, diabetes mellitus, renal failure and age. The surgical method (i.e. repair or prosthesis implantation) did not influence survival of IE.

Key words: mitral valve repair, artificial chordae, outcome, right ventricular function, infective endocarditis.

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Impact of surgical techniques used for mitral valve repair on hemodynamic performance

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LUND UNIVERSITY

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Cardiothoracic Surgery

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Dedicated to my wonderful wife, Hanna
and my precious daughters,
Lilja Hrönn and Helena Rut

”Delays have dangerous ends”
William Shakespeare

Contents

List of Publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals (I-IV).

I. **Ragnarsson S**, Sjögren J, Sanchez R, Wierup P, Nozohoor S. Polytetrafluoroethylene neochordae is noninferior to leaflet resection in repair of isolated posterior mitral leaflet prolapse: a multicentre study. Interact Cardiovasc Thorac Surg. 2014 Oct;19(4):577-83. doi: 10.1093/icvts/ivu225. Epub 2014 Jul 6.

II. **Ragnarsson S**, Sjögren J, Stagmo M, Wierup P, Nozohoor S. Assessment of mitral valve repair with exercise echocardiography: artificial chordae versus leaflet resection. Semin Thorac Cardiovasc Surg. 2016, In Press.

III. **Ragnarsson S**, Sjögren J, Stagmo M, Wierup P, Nozohoor S.Late Right Ventricular Performance after mitral valve repair assessed by exercise echocardiography. Submitted.

IV. **Ragnarsson S**, Sjögren J, Stagmo M, Wierup P, Nozohoor S.Clinical Presentation of Native Mitral Valve Infective Endocarditis Determines Long-Term Outcome after Surgery. J Card Surg. 2015 Sep;30(9):669-76. doi: 10.1111/jocs.12591. Epub 2015 Jun 29.

In addition, unpublished results related to Study IV are presented in this thesis.

Populärvetenskaplig sammanfattning (Summary in Swedish)

I Sverige utförs ungefär 6000 hjärtoperationer årligen, varav de flesta är kranskärlsoperationer och klaffoperationer. Den vanligaste klaffoperationen är aortaklaffbyte följt av mitralklaffoperationer. Mitralklaffen reglerar blodflödet som kommer från vänster förmak till vänster kammare igenom sina två klaffsegel. Det främre och bakre klaffbladet möts och klaffen stängs när vänster kammare pumpar blodet vidare genom kroppspulspådern. Klaffbladen förhindras att åka upp i vänster förmak av strängar som kallas *chordae tendinae.* Alla ändringar i klaffapparaten som gör att ytan där främre och bakre klaffbladet möts blir mindre eller upphör leder till läckage i klaffen. Eftersom klaffläckaget släpper tillbaka en del av blodet till vänster förmak får vänster kammare utföra ett dubbelarbete för att kunna tillgodose kroppen med det blod den behöver. Många olika sjukdomar kan orsaka läckage i mitralklaffen. Den vanligaste sjukdomen är degenerativ sjukdom, det vill säga att klaffen blir trasig. Ett annat exempel är infektion i klaffen. Kirurgisk behandling av dessa klaffsjukdomar är fokus i denna avhandling.

Degenerativ sjukdom leder till att *chordae* eller klaffbladen blir trasiga. Då åker antingen det främre eller det bakre av klaffbladen upp i vänster förmak och ytan där klaffbladen möts upphävs, så kallad prolaps. Läckaget gör att hjärtat med tiden sviktar och patienten upplever andfåddhet och nedsatt kondition. Patienter som drabbas av sjukdomen är oftast i medelåldern och har många år kvar att leva. Det enda sättet att upphäva denna process är med en hjärtoperation där man i första hand försöker reparera klaffen. Om operationen lyckas kan man leva lika länge som om man aldrig hade drabbats av sjukdomen. I de fall det inte går att reparera klaffen får man byta klaffen.

Den vanligaste metoden som används för att laga klaffen är så kallad resektionsplastik som innebär att man tar bort den delen av klaffseglet som åker upp i vänster förmak och syr sedan ihop dess friska kanter. På senare tid har flera centra börjat använda sig av ett enklare sätt att reparera klaffen. Med denna metod förstärker man den del av seglet som läcker med syntetiska strängar (*chordae*) som ser till att klaffen inte åker upp i förmaket. Denna metod kan vara enklare att lära sig och tillämpa jämfört med resektionsplastik. Tidigare forskning har redan visat att den nya metoden är lika säker som den vanliga metoden och att den är lika effektiv i att förhindra återinsjuknande i läckage i klaffen.

Denna avhandling består av fyra delarbeten som på olika sätt studerar de kirurgiska metoder som används för att reparera en läckande mitraklaff. I delarbete I utfördes en jämförelse av patientgrupper som opererades med de två olika teknikerna mellan 1998 och 2012. Resultaten visade att reparation med syntetiska *chordae* var jämförbar med den klassiska resektionsmetoden: överlevnad var god i båda grupperna, risken för att behöva opereras om och risken för att återfå läckage var låg och jämförbar mellan grupperna.

I delarbete II inkluderades 56 patienter som tidigare hade genomgått mitralklaffoperation, varav 24 med syntetiska *chordae* och 32 med resektionsplastik metoden. Patienternas hjärta undersöktes både i vila och under pågående cykling på en motionscykel. Vi studerade hur mitralklaffen fungerar när hjärtat belastas och får pumpa stora mängder blod. Resultaten visade att båda metoderna ger fina flödesförhållanden i vila och arbete och att arbetsförmågan var liknande i bägge grupperna.

I delarbete III jämfördes de 56 patienter som undersöktes i delarbete II med hjärtfriska individer i syfte att undersöka hur högerkammarens funktion ser ut efter reparation i mitralklaffen. Jämfört med friska individer, hade de opererade patienterna betydligt sämre funktion i högerkammaren. Patienter med mitralinsufficiens vars vänsterkammare blivit förstorade innan operation hade sämre högerkammarfunktion vid uppföljningen. Vår slutsats blev att det är viktigt att operera patienter med mitralinsufficiens i god tid innan de utvecklar sänkt högerkammarfunktion.

I delarbete IV undersöktes 100 patienter som opererades mellan 1998 och 2014 för infektion i mitralklaffen (endokardit). Syftet var att se vilken betydelse vissa symptom som patienterna hade innan operation för långtidsöverlevnad. Symptomen som vi var intresserade av var stroke, ihållande feber och hjärtsvikt. Vi delade patienterna i grupper beroende på hur många av symptomen de hade: inga, ett symptom eller två till tre. Överlevnaden var sämre hos patienter som hade symptom innan operation och ännu sämre hos dem som hade två till tre symptom. Andra faktorer som var associerade med sämre överlevnad var *S. aureus* infektion, högre ålder, diabetes och njursvikt. Långtidsöverlevnad hos de som genomgick klaffbyte och klaffreparation var lika.

Abbreviations

18F-FDG PET/CT	^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography
AC	artificial chordae
ACE	angiotensin converting enzyme
AHA/ACC	American Heart Association / American College of Cardiology
AF	atrial fibrillation
AVR	aortic valve replacement
ARB	angiotensin II receptor blocker
BMI	body mass index
BSA	body surface area
C-sept	distance from the coaptation line to the septum
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CW	continuous wave Doppler
ePTFE	extended polytetrafluoroethylene
EROA	effective regurgitant orifice area
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FAC	fractional area change
IE	infective endocarditis
IQR	interquartile range
LA	left atrium
LR	leaflet resection
LV	left ventricular
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVIDd	left ventricular internal dimension end diastole
LVPWd	left ventricular powterior wall end diastole
LVOT	left ventricular outflow tract

MR	mitral regurgitation
MRI	magnetic resonance imaging
MSCT	multislice computer tomography
MV	mitral valve
NVE	native valve endocarditis
NYHA	New York Heart Association
PASP	pulmonary artery systolic pressure
PML	posterior mitral leaflet
PVE	prosthetic valve endocarditis
RV	right ventricle
RVSP	right ventricular systolic pressure
SAM	systolic anterior motion
SD	standard deviation
SE	standard error
TAPSE	tricuspid annular plane systolic excursion
TEE	transesophageal echocardiography
TR	tricuspid regurgitation
TR max PG	tricuspid regurgitation maximum pulse gradient
TTE	transthoracic echocardiography
TVI	time—velocity integral
S’	tissue Doppler-derived systolic velocity of the annulus

Introduction

Mitral valve regurgitation

Mitral valve regurgitation (MR) is the most common valvular problem in the Western world, and its incidence increases with advancing age (1, 2). It is the second most common cause of valvular surgery in Europe after aortic valve stenosis (2). Mitral regurgitation arises when the normal systolic coaptation between the anterior and posterior mitral leaflets is reduced or eliminated (3). In 1983, Alain Carpantier and colleagues described a useful functional classification of MR in the report, "Cardiac valve surgery—the "French correction" (4) that is shown in Figure 1. In type I MR, the leaflets have normal motion; in type II, there is excessive leaflet motion (prolapse into the left atrium). Type III has restricted leaflet motion: IIIa in diastole and IIIb in systole.

MR is caused by various conditions and can be categorized as either organic MR or functional MR depending on whether the insufficiency is due to intrinsic pathology in the mitral valve or originates in the left ventricle (LV)(3). Causes of organic MR include degenerative mitral valve (MV) disease, infective endocarditis (IE), rheumatic valve disease, papillary muscle rupture due to ischemia, and trauma (3). Functional MR can result from any condition that causes cardiomyopathy producing annular dilatation or chronic ischemia with LV remodeling; both of these conditions restrict MV leaflet motion (3).

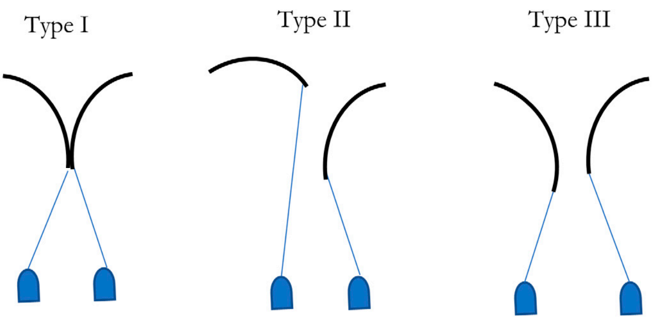

Figure 1: Carpantier Classification of mitral insufficiney. Type I har normal leaflet motion. Type II has excessive leaflet motion. Type III has restricted leaflet motion.

Degenerative mitral valve disease

Definition

Because the incidence of rheumatic heart disease has decreased in industrialized countries, degenerative MR is now the most common etiology (1, 2). The prevalence of degenerative MR is distributed evenly among individuals in each decade of age from 30 years to 80 years and has an equal gender distribution (5). Patients that undergo surgery for degenerative MR are usually middle-aged with a male predominance (6). Degenerative MR is usually due to leaflet prolapse (Type II according to Carpentier's classification) and rarely due to isolated mitral annular calcification (3). The anatomical lesions that cause leaflet prolapse include myxomatous degeneration of the leaflet tissue, chordal rupture, and chordal elongation. Isolated posterior leaflet prolapse is the most common pathology (Figure 2), accounting for between 50% and 80% of all cases, whereas anterior leaflet pathology is seen in 10 to 15% and bileaflet prolapse in 10 to 35% (3, 6, 7). Cases seen at referral centers for mitral valve surgery tend to have a larger proportion of anterior leaflet and bileaflet pathology than cases seen in less specialized centers.

Surgery

Mitral valve replacement

Mitral valve replacement involves implanting either a biological or mechanical prosthesis into the mitral annulus. Classically, all leaflet tissue and chordae tendinae were removed before the new prosthesis was implanted. Strategies that preserve valvular tissue, and thus, conserve chordal attachments of the mitral apparatus to the LV wall (8), have achieved better preservation of LVEF and better survival (9). Recently, complex mitral valve pathologies are more often treated with repair; therefore, mitral valve replacement for degenerative disease has become less frequent (10). The current guidelines of the European Society of Cardiology recommend mitral valve repair "whenever possible" for surgical treatment of degenerative MR (11). Likewise, American College of Cardiology / American Heart Association (AHA/ACC) guidelines recommend MV repair in preference to MV replacement in treatment of posterior leaflet, anterior leaflet, and bileaflet pathology (12).

Leaflet resection

The classical method of posterior leaflet repair with quadrangular resection was first described by Alain Carpantier (4). As shown in Figure 2, it entails resecting the diseased prolapsing segment from the leaflet edge to the annulus and closing the defect with sutures and performing either sliding plasty of the remaining leaflet or annular plication. The repair is reinforced with an annuloplasty ring. This technique is associated with very good durability and long-term outcomes (13, 14). Posterior leaflet prolapse is a common pathology; the widespread use of the standardized and reproducible method of quadrangular resection has produced excellent long-term results (15). Failure to implant an annuloplasty ring is associated with a risk of late reoperation (15). To reduce the number of secondary cordae tendineae that are resected during leaflet resection and to avoid reconstruction of the mitral annulus, the less extensive triangular resection has gained popularity (16, 17).

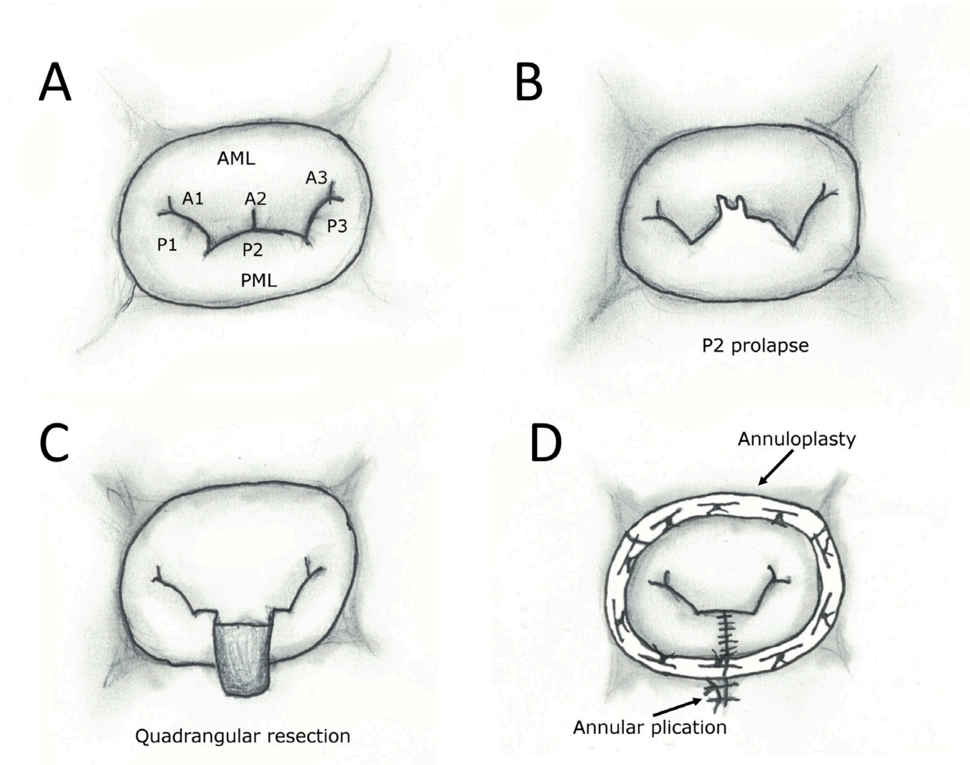

Figure 2: (A) Mitral valve, the surgeon's view. AML, anterior mitral leaflet; PML, posterior mitral leaflet. (B) Prolapse and flail of segment P2 of the posterior mitral leaflet. (C) The defect in the posterior mitral leaflet after a quadrangular resection of P2 has been performed. (D) Complete mitral valve repair for P2 prolapse with quadrangular resection, annular plication, and ring annuloplasty.

Artificial chordae

Chordae tendineae have been replaced since the advent of cardiac surgery using materials such as silk, nylon, and either autologous or xenograft pericardium (18). Chordal replacement with artificial chordae was first introduced experimentally in sheep by Frater and colleagues (19) using the newly available expanded polytetrafluorethylene sutures (ePTFE) (Gore-Tex®, WL Gore & Associates, Flagstaff, AZ). They were first used in humans for repair of anterior leaflet prolapse (20). However, since then, these sutures have been used extensively for repair of posterior leaflet and bileaflet prolapse (21-24). They have proven to be particularly useful to repair prolapse of multiple leaflet scallops (23).

The ePTFE sutures have several biological advantages, including the fact that they become endothelialized and are non-thrombogenic (18). Artificial chordae produce an anatomical repair and maintain the important relationship between the valve leaflet and the subvalvular apparatus (25). The use of artificial chordae was shown to be associated with excellent long-term results (23, 24, 26) and even more superior results in posterior leaflet prolapse than in anterior leaflet prolapse (23).

More than 40 different techniques for the use of artificial chordae in degenerative MV disease are described in the medical literature (25). The simplest technique first passes the ePTFE suture through the papillary muscle. Then both arms of the suture are passed through the leaflet and a knot is tied on the atrial side (27). Tirone David described his method of using artificial chordae that passes the ePTFE suture successively through the papillary muscle and free margin of the leaflet to create several pairs of artificial chordae (18). One of the challenges of using artificial chordae is to create the correct length of artificial chordae (26). Several techniques have been developed to address this issue. The Leipzig Heart Center developed the loop technique, which has become a well-known and established technique that addresses this issue (28). A ruler is used to measure the desired chordal length. Then, one to several loops of ePTFE suture of this pre-determined length is tied securely using a felt pledget that is then attached to a papillary muscle.

Other resectional repair methods

Other more complex repair methods include chordal shortening, to treat elongated chordae tendinae, and chordal transfer (4, 29). The chordal shortening method was shown to be associated with higher repair failure rates than artificial chordae (30), and chordal transfer is more technically demanding than artificial chordae (31).

Edge-to-edge repair

Alfieri et al. introduced the Edge-to-edge repair to correct MR due to different etiologies (32, 33). The posterior and anterior leaflet edges are sutured together to form a double-orifice valve without causing mitral valve stenosis (33). The method is reproducible, simple, and was shown to be associated with a freedom from reoperation of 89 ± 3% at 17 years after surgery (34) .

Minimally invasive mitral valve surgery

Minimally invasive approach is gaining popularity. The most common incision is right minithoracotomy, but occlusion of the aorta and cannulation approaches vary between centers (35). Minimally invasive mitral valve repair was shown to be feasible for the repair of complex MV pathologies and can achieve low perioperative complication rates and very good durability (36, 37). Robotic assisted mitral valve surgery, used in some centers, has been followed by short-term results comparable to those of conventional mitral valve repairs (38).

Transcatheter mitral valve repair

Various transcatheter repair of MR are being developed. The most thoroughly studied method uses the MitraClip® (Abbot, Chicago, IL) to treat MR of various etiologies in patients who are not surgical candidates (39, 40). The method is based on the Edge-to-edge concept proposed by Alfieri (32). The transcatheter method is less effective in reducing MR (40) and, among patients with degenerative disease, should only be considered for those not suitable for surgery.

Evaluation

Clinical assessment

Clinical examination usually reveals the first signs of MR: systolic thrill, loud systolic murmur, a third heart sound, early diastolic rumble, and atrial fibrillation (3). Chest radiography may indicate cardiomegaly and left-atrial enlargement. Although sensitive, these signs are not specific enough to warrant MV surgery (11, 12).

Echocardiography

Echocardiography is the primary approach to assessment of patients with MR. Echocardiography must include an assessment of MR severity, causative mechanisms, anatomy (including calcification), repairability, and consequences (41). Identifying patients with severe MR is of great importance, due to clinical consequences, and because these patients often will eventually require surgery.

Current guidelines of the European Society of Cardiology for the management of heart valve disease (11) recommend evaluating MR with qualitative, semiqualitative and quantitative methods. The qualitative assessment should include thorough assessment of all scallops of the posterior and anterior leaflets (42). All departures from normal valve morphology, such as whether there is a flail leaflet, ruptured papillary muscle, or large coaptation defect should be evaluated and described. The density of the continuous wave (CW) Doppler should be noted; any abnormalities of the color flow regurgitant jet should be described; and whether the jet reaches the posterior wall should be evaluated (11).

The semi-quantitative assessment includes measurement of the vena contracta width (≥7mm in severe MR), systolic pulmonary vein flow reversal, E wave dominance during inflow (≥1.5 m/s), and the ratio of time-velocity integral (TVI) mitral/TVI aortic (>1.4 in severe MR). The quantitative measurements include the size of the effective regurgitant orifice area (EROA), which should be ≥40 mm^2; regurgitant volume, which that should be ≥60 mm^2; and the size of the left atrium and left ventricle (11).

Transthoracic echocardiography (TTE) is recommended as the first-line echocardiography study for MR (41). Transesophageal echocardiography (TEE) should be used when TTE is inconclusive or further diagnostic work-up is needed. Three-dimensional TEE or TTE may provide additional information in complex mitral valve lesions. TEE should be used intraoperatively to assess the results of MV surgery and to guide further surgical correction when necessary (11).

Indication and timing of surgery

Severe degenerative MR confers a poor prognosis if left untreated (43, 44). In asymptomatic severe MR, the estimated 5-year death rate was reported to be 22 ± 3% (3). Current guidelines recommend surgery for all patients that have symptomatic severe MR (11, 12). MV repair has been shown to restore life expectancy to normal except in patients with impaired LV function or severe symptoms of heart failure before surgery (6). Despite the lack of a prospective randomized study comparing mitral valve replacement and mitral valve repair, current guidelines recommend mitral valve repair over replacement (11, 12). The recommendations are primarily based on single center observational studies that use crude statistical adjustments to control for differences between patient characteristics in the treatment groups. MV repair was shown to produce superior outcomes for operative mortality, left ventricular function, valve-related complications, and long term survival (7). A recent prospective multicenter registry study of patients that underwent either mitral valve replacement or mitral valve repair showed that MV repair was associated with lower operative mortality, longer long-term survival, and fewer valve-related complications than was MV replacement (7). The same holds true for elderly patients. Among octogenarians who underwent MV surgery for degenerative disease, MV replacement was associated with shorter survival and proved to be an independent predictor of early mortality (45).

Because referral centers with high-volumes of mitral valve surgery have reported over 95% repairability with excellent clinical results (6, 10, 26), international guidelines have been changed; they now recommend surgery even in asymptomatic patients who have signs of LV remodeling due to chronic severe MR (11). LVEF < 60% or LVESD >45 mm are defined as echocardiographic indicators of LV remodeling (11). The

AHA/ACC guidelines recommend surgical referral for asymptomatic patients with severe MR and signs of LV remodeling if the surgery is performed at a Heart Valve Center of Excellence, which is defined in the guidelines (46). Accordingly, it is now the aim of some centers to repair 100% of mitral valves that need surgery for degenerative MR (10).

Outcome measures

Survival

Length of survival is an important indicator of the success of cardiac surgery. However, short-term and long-term survival are dependent on the patient's preoperative status. Predictors of poor surgical outcome are symptoms, age, atrial fibrillation, severity of MR (especially EROA), pulmonary hypertension, left atrial dilatation, large left ventricular end-systolic dimension (LVESD), and low LVEF (3, 11, 43). In the modern era of mitral valve surgery, in-hospital mortality in high-volume centers has become low and is reported to be approximately 1% (6, 7, 47-50). Surgical volume seems to be an important factor for better results from MV surgery. There is high center-to-center variability in the proportion of MV that are repaired; low-volume centers perform repairs significantly less often than high-volume centers (51). Furthermore, the in-hospital mortality of mitral valve repair in the United States varies from 1% in high-volume centers to 3% in low-volume centers (51). Studies reporting long-term mortality report five-year survival ranging between 85% and 97% (7, 10, 13, 52), 10-year survival between 65% and 90% (7, 13, 14, 52), and 20-year survival of approximately 45% (14).

Systolic anterior motion (SAM)

Systolic anterior motion of the mitral valve is a known complication of MV repair (53, 54). SAM is detected by intraoperative TEE following MV repair and is reported to occur in 4% of cases (55). It can cause LV outflow obstruction, and residual MR is usually present (56). Risk factors for SAM are a small left ventricle, tall posterior leaflet, anteriorly displaced coaptation line (measured by the distance from the coaptation line to the septum, C-sept), and enlarged interventricular septum (55, 57). The best way to prevent hemodynamically significant SAM is to be aware of the aforementioned risk factors and to use a large annuloplasty ring or a posterior band instead of a complete ring and to move the coaptation line away from the septum. However, when detected, SAM can be resolved in most patients using non-invasive measures, such as fluid administration, beta-blockade and vasoconstriction (57). If these measures are not sufficient, useful surgical strategies include edge-to-edge repair, posterior leaflet height reduction techniques, replacing the annuloplasty ring with a larger one, and valve replacement (55, 56).

Freedom from reoperation and recurrent MR

The durability of MV repair has classically been reported as freedom from reoperation. The various methods of mitral valve repair have been shown to influence reoperation frequencies. The classical method of quadrangular resection with annuloplasty was the first method shown to produce excellent long-term results and low risk of reoperation (14, 15). However, MV repair using artificial chordae has also been associated with low rates of reoperation (58). Studies of long-term freedom from reoperation following MV surgery have reported that freedom from reoperation at five-years ranges between 93% and 98% (7, 13), 10-year freedom from reoperation between 89% and 98% (7, 13, 14, 58), and 15-year freedom from reoperation between 87% and 97% (7, 13, 14).

Reporting reoperation rates is known to underestimate the frequency of MR recurrence following MV repair (59). Therefore, reporting recurrent MR in outcome studies of MV repair is important. Studies of long-term freedom from recurrence of moderate to severe MR (≥2+ MR) following MV surgery have reported freedom from recurrent ≥2+ MR at five-years to be approximately 95% (6, 7, 10), at 10-years between 90% and 95% (6, 7, 58), and at 15-years to be approximately 80% (6).

Left ventricular function

The most commonly used method to evaluate left ventricular function is the left ventricular ejection fraction (LVEF), which is usually measured using the Simpson's method. In severe MR and normal left ventricular function, LVEF is high due to the afterload reduction and regurgitant volume that flows retrogradely through the insufficient mitral valve. However, LVEF is still a useful marker of LV function in patients with MR (44). A drop in LVEF below 60% is associated with worse survival following surgery (44). Postoperative LV function is largely determined by preoperative LV function.

Right ventricular function

The RV has complex geometry, and its function is difficult to evaluate using two-dimensional imaging. The most easily available and widely used parameter to measure RV function is tricuspid annular plane systolic excursion (TAPSE) (60). TAPSE measures the longitudinal contraction pattern of the RV. Other indices of RV function are tissue Doppler-derived systolic velocity of the annulus (S'), which also measures the longitudinal contraction pattern of the RV, and the fractional area change (FAC) (60) Right ventricular (RV) dysfunction is a common finding in patients referred for MV surgery due to degenerative disease (61). RV dysfunction is caused by a complex interaction with the remodeled and enlarged LV and the interventricular septum (61). Postoperative RV dysfunction is common following MV surgery for degenerative disease (62). Poor postoperative RV function is associated with early and late mortality, but the poor RV function seems to reflect poor preoperative condition (63). More information on the long-term RV performance following MV surgery is needed.

The role of exercise echocardiography

Stress echocardiography is predominantly used in three settings: in the event of symptoms without severe valvular pathology, in asymptomatic severe valvular pathology, or in valve disease with reduced LV function (64). In certain situations, such as asymptomatic degenerative MR, the use of serial stress testing may provide objective evidence of a stress-associated decline before subjective symptoms are reported (65). Stress echocardiography is performed with either the intravenous administration of dobutamine or with physical exercise. Exercise echocardiography is the more physiological alternative, but may be associated with inferior image quality. The echocardiography can be performed directly following physical exercise on a treadmill or exercise bike, or *during* exercise on a supine exercise bike. The test provides information about the patient's physical capacity along with data about the valvular and ventricular function during physical exercise. According to Garbi et al., "the predicted maximum workload for healthy subjects is 2.5 W/kg in women and 3.0 W/kg in men between 21 and 30 years of age, minus 10% for each added decade" (64).

A handful of studies have used exercise echocardiography following MV surgery. At least two studies have evaluated MV gradients following MV surgery for functional MR with exercise echocardiography (66, 67). Studies that used exercise echocardiography to evaluate hemodynamics following surgery for degenerative MV disease (68, 69), have not compared the hemodynamics of different surgical techniques used for repair of PML prolapse.

Studies of leaflet resection vs. artificial chordae

At the time when Study I of this thesis was being planned, few reports had compared leaflet resection (LR) with artificial chordae (AC) for treatment of PML prolapse. A retrospective study by Lange et al. reported similar short-term and mid-term mortality in patients who had undergone LR and AC for isolated posterior mitral leaflet prolapse (47). The study also reported high freedom from reoperation rates at four years in the LR group (96±1%) and in the AC group (99±1%) (47). However, length of follow-up was short in the AC group.

A large retrospective study by Seeburger et al. of patients who underwent minimally invasive MV surgery for PML prolapse showed that AC were associated with significantly larger mitral orifice area (3.3 ± 0.3 cm^2) than those who had undergone LR (3.0 ± 0.8 cm^2, $p < 0.001$) and with lower mean pressure gradient (2.7 ± 1.7 mm Hg versus 3.1 ± 1.7 mm Hg, respectively, $p = 0.03$) (70). At five years after surgery, freedom from reoperation was 98.7% in the AC group compared with 93.9% in the LR group (log-rank test, $p = 0.005$) (70).

Falk et al. performed a prospective randomized trial comparing minimally invasive MV surgery using AC versus LR for treatment of PML prolapse (48). The study showed excellent short term outcome (48). Intraoperative TEE showed a longer coaptation line in the AC group compared with the LR group and. This did not translate into a between-group difference in the grade of MR at one year follow-up (48). Other echocardiographic measurements at one year follow-up did not detect any significant difference in LVEF, MV orifice area, or transvalvular gradients (48).

Infective endocarditis

Epidemiology and pathogenesis

In industrialized countries, the annual incidence of infective endocarditis ranges between 3 and 9 cases per 100,000 persons (71). The male:female ratio is greater than 2:1. Infective endocarditis occurs when bacteria with specialized adherence properties enter the bloodstream (bacteremia) and attach to damaged cardiac endothelium. Despite the increase in surgical treatment, one year-mortality of IE remains 20-30% (72). A nationwide registry study from Sweden showed that mortality risk, relative to the general population, remains increased for a long time following IE (73). Excluding the first year, the relative mortality risk was 2.2 times higher in patients with IE than in the general population (73).

Infective endocarditis has shifted from being a disease of young adults with congenital heart defects or rheumatic heart disease to being a disease of elderly patients with comorbidities (72). Likewise, the microbiology has changed from being primarily due to bacteria from the oral cavity to being mostly caused by *S. aureus* (74). Hemodialysis, diabetes mellitus, and intravascular devices are the main factors associated with *S. aureus* IE (75).

Diagnosis

The Modified Duke's Criteria are used to confirm the diagnosis of IE (76). These criteria are a list of clinical, microbiological and echocardiographic findings (76). To fulfill the criteria for "definitive IE", the patient should fulfill 2 major criteria; 1 major criterion and 3 minor criteria; or 5 minor criteria. The diverse clinical presentation of IE requires that the index of suspicion is high enough to trigger adequate work-up with blood cultures and imaging (77).

The primary imaging modality for IE is echocardiography (77). The imaging is rapid and in many cases diagnostic but is highly dependent on experience (77). TTE is usually performed first but TEE must be performed in cases where TTE is negative but a high index of suspicion for IE remains, because both sensitivity and specificity of TEE are much higher than those of TTE for detecting vegetations and abscesses (77). TEE should also be performed when TTE is positive to evaluate complications. If the negative initial echocardiographic examination is negative but suspicion of IE remains, TTE/TEE should be repeated in 5-7 days (77).

Presently, complementary imaging modalities have an increasing role in the diagnostic work-up of patients with suspected and confirmed IE. Multislice computer tomography (MSCT) can reveal coronary anatomy in cases were coronary angiography carries high risk and show the extent and consequences of perivalvular involvement (78). Magnetic resonance imaging (MRI) is particularly useful in detecting cerebral lesions (79, 80). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and other functional imaging modalities play a valuable role in patients suspected with prosthetic valve IE (81). To decrease the number of patients with possible or rejected IE where there is still high index of suspicion, the above mentioned new imaging modalities were incorporated into the European Society of Cardiology (ESC) 2015 modified criteria for the diagnosis of infective endocarditis (77).

Indication and timing of surgery

Surgery for IE is associated with better short- and long-term results than antibiotic therapy alone (82). Early surgery (during the active phase) is associated with better outcomes than surgery during the late phase (after a completed course of intravenous antibiotics) (83). However, surgery during the active phase confers high risk and should be justified with features indicating that treatment with antibiotics alone is unlikely to be successful. The current guidelines recommend surgery for patients with signs of heart failure, uncontrolled infection or to prevent embolism (77).

Urgent surgery, defined as surgery within a few days or less than one week, is recommended in cases with aortic or mitral native valve endocarditis (NVE), prosthetic valve endocarditis (PVE) with severe regurgitation, obstruction causing symptoms of heart failure, or echocardiographic signs of poor hemodynamic tolerance; such cases must by treated by urgent surgery (77). In case of refractory pulmonary edema or cardiogenic shock, emergency surgery (within 24 hours) is recommended (77). Urgent surgery is recommended in patients with locally uncontrolled infection (abscess, false aneurysm, fistula, or enlarging vegetation) and in patients infected with multiresistant organisms or fungi. Patients with aortic or mitral NVE or PVE with persistent vegetations ≥10 mm after ≥1 embolic episode despite appropriate antibiotic therapy must also be treated by urgent surgery.

Despite the above recommendations, the optimal timing of valve surgery in patients with IE remains unclear. In a randomized trial involving patients with severe left-sided infective endocarditis and a large vegetation, but no other indication for emergency surgery at randomization, the incidence of the composite endpoint of in-hospital death or embolic events within the first 6 weeks after randomization was significantly lower among patients assigned to surgery within 48 hours after randomization than among those assigned to usual care (3% vs. 23%); the benefit was driven by fewer embolic events (84). The study included a young population with relatively little comorbidity. More randomized studies on the effect of early surgical intervention for IE are needed.

The timing of surgery of patients with ischemic lesions following embolism has previously been unclear. Ischemic cerebral lesions are associated with worse outcome (85). However, most patients with cerebral lesions die of sepsis and not of hemorrhagic transformation of the cerebral lesion (85). Surgery should, therefore, not be delayed in cases of ischemic lesions of the brain without hemorrhage (77).

Surgical techniques used in mitral valve infective endocarditis

Surgery in IE should remove infected tissue, foreign material, and hardware; debride and clear cavities and paravalvular infection; restore the anatomy and function of the heart including its valves; and remove any threatening source of embolism (86).

In mitral valve IE, perivalvular infections commonly require reconstruction of the annulus with an autologous or bovine pericardial patch (87). When there is extensive tissue destruction, MV replacement is usually performed either with a biological or mechanical valve prosthesis. When tissue destruction is not extensive and when the surgeon has experience in mitral valve surgery, MV repair may be performed.

Dreyfus et al. described several methods of MV repair of IE, including using Carpentier's methods and pericardial patch reconstructions of the leaflets (88). Kerchove et al. described a repair rate >80% using both non-patch and patch techniques with a 62% survival at 8 years (89). Non-patch techniques included triangular or quadrangular resection, artificial chordae, and chordal transfer. Patches were used in 61%; valve repair failure rates did not differ significantly between non-patch and patch techniques (89).

The value of performing MV repair instead of MV replacement is not fully understood for IE. The comparison is difficult using retrospective cohorts, and many studies have reported series with few patients (90). However, a systematic review of 24 studies with 1,194 patients who underwent mitral valve surgery for IE showed that in-hospital and long-term mortality were significantly lower after mitral valve repair than after valve replacement (91). The crude in-hospital mortality was 2.3% versus 14.4% ($p < 0.0001$), and long-term mortality was 7.8% versus 40.5%. Meta-regression analysis showed that MV repair was associated with longer short-term and long-term survival than was MV replacement (91).

Aims

Study I

To evaluate clinical outcomes, including cardiac events, of patients who underwent mitral repair with either artificial chordae or traditional resection techniques of mitral valve repair at two centers in a strictly homogenous population with severe mitral valve regurgitation due to isolated degenerative posterior leaflet prolapse.

Study II

The aim of this study was to determine how preservation of leaflet structure using artificial chordae compares with the widely-adopted technique of leaflet resection in terms of long-term hemodynamic outcomes evaluated by exercise capacity and by echocardiography at rest and during peak exercise.

Study III

The aims of this study of patients who underwent isolated mitral valve repair for chronic MR due to posterior leaflet prolapse were: (1) evaluate the RV function in these surgical patients relative to healthy controls; (2) determine whether the RV function and response to exercise differ according to different surgical techniques of mitral valve repair; and (3) evaluate whether exercise capacity is associated with RV function.

Study IV

The aim of this study was to examine whether preoperative clinical presentation is a significant determinant of late outcomes in patients undergoing surgery for isolated native mitral valve IE.

Material and Methods

Patients and study design

Study I

Patients

A retrospective study was conducted of 224 consecutive patients who underwent isolated mitral valve repair for MR due to isolated posterior leaflet prolapse between January 1998 and May 2012 at the Department of Cardiothoracic Surgery at Skane University Hospital, Lund, Sweden (n=203) and Varde Heart Centre, Varde, Denmark (n=21). The nine patients who required mitral valve replacement due to unsuccessful repair were excluded as well as 14 patients who underwent both artificial chordae and resection repair. The remaining 201 patients who comprised the study population had undergone posterior mitral leaflet (PML) repair with either artificial chordae (n=55) or leaflet resection (n=146).

Surgical techniques

The access, cannulation techniques and methods of attaining cardioplegic arrest are described in Study I. The resection techniques used in the leaflet resection group were: quadrangular resection with annular plication in 68% (n = 100), quadrangular resection with sliding plasty in 25% (n = 36), triangular resection in 5% (n = 7), and leaflet resection with chordal transfer in 2% (n = 3: two quadrangular resections and one triangular resection). Artificial chordae were created with CV4 ePTFE sutures (Gore-Tex®, WL Gore & Associates, Flagstaff, AZ). The suture was first placed in the fibrous part of the papillary muscle (Figure 3). Then, both arms of the suture were placed in the posterior leaflet edge and back through the leaflet edge from the atrial to the ventricular side. The leaflet was drawn down into the ventricle so that the prolapse was eliminated and the knot tied on the ventricular side. This process created one pair of artificial chordae. Usually, two pairs of artificial chordae were created, one pair originating from each papillary muscle.

Follow-up

The following postoperative endpoints were evaluated: all-cause mortality at 30 days, 60 days and 90 days after surgery, reoperation due to recurrent MR, freedom from moderate or greater MR, freedom from new-onset chronic atrial fibrillation, freedom from endocarditis, freedom from arterial embolism, freedom from valve thrombosis, freedom from any major bleeding event requiring hospitalization, and freedom from the composite endpoint of major adverse events. A major adverse event was defined as any of the following: death, reoperation for any cause, re-admission due to heart failure, endocarditis, thromboembolism, or pacemaker implantation. Follow-up was performed in February 2013 and was 100% complete for survival (1,184 patient-years; mean 5.9±3.9 years).

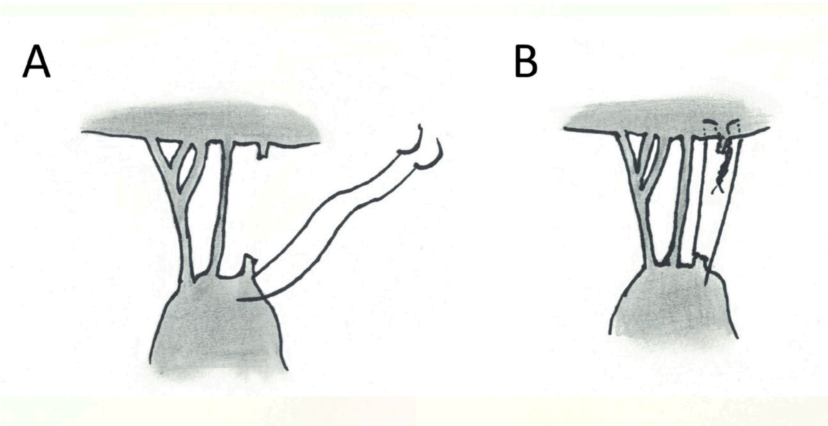

Figure 3: A schematic presentation of the placement of artificial chordae (A) The ePTFE suture is placed in the fibrous part of the papillary muscle. (B) Completed insertion of a pair of artificial chordae

Study II

Patients

Between January 2005 and January 2014, 154 patients underwent primary repair for isolated PML prolapse due to degenerative disease. A total of 79 patients were excluded (Figure 4). The remaining 75 patients were invited to participate. Fifty-nine patients consented to participate and 56 patients comprised the final study population. Of these, 24 patients had undergone repair with artificial chordae (AC) and 32 with leaflet resection (LR).

Surgical techniques

Five patients in the AC group had minithoracotomy compared with none in the LR group (p = 0.01). Artificial chordae were placed as described for Study I. Resection techniques employed in the LR group were quadrangular resection with either annular plication, sliding plasty, or triangular resection.

Clinical follow-up and exercise echocardiography

This prospective study collected clinical data, determined subjective functional capacity using the Duke Activity Status Index questionnaire (92), measured exercise capacity, and performed resting echocardiography and peak exercise echocardiography. We postulated that, compared with repair using leaflet resection, PML repair with artificial chordae is associated with a lower MV pressure gradient at rest and during peak exercise, which were primary endpoints. Secondary endpoints included pulmonary artery pressure, LV function and remodeling at rest; and exercise duration, maximum exercise capacity, residual MR and pulmonary artery pressure during physical exercise.

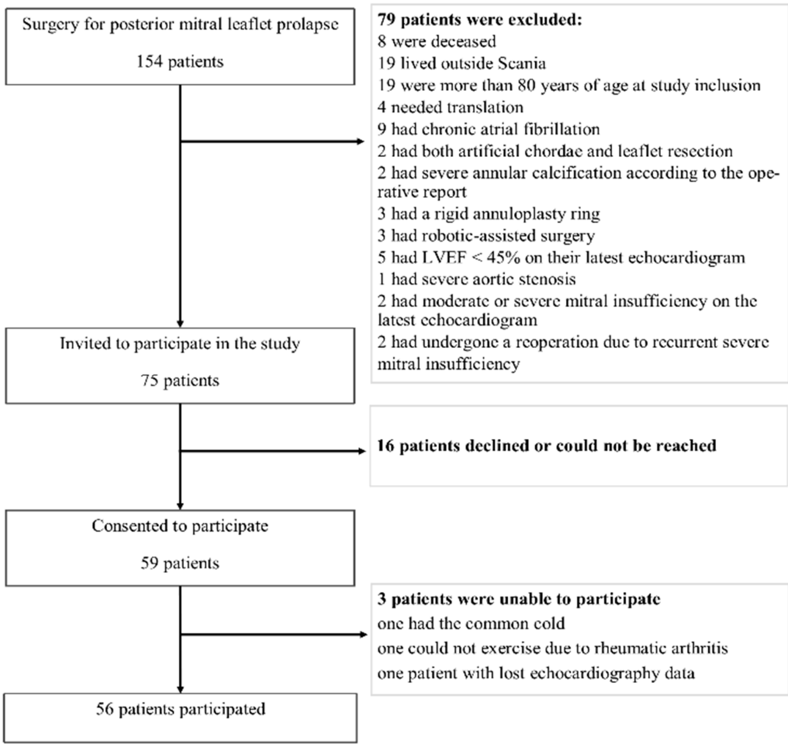

Figure 4: Flow diagram of patient enrollment for Study II.

Study III

The study included the same 56 patients that were included in Study III. Each of the 56 study patients was matched with an individual from the National Registry of those living in Skane County with the same age and sex. Fourteen individuals consented to participate. One person could not exercise due to back pain resulting in a control group of 13 individuals. Clinical data were collected prospectively. Using transthoracic echocardiography, measurements of RV function were obtained at rest and at peak exercise. RV function was assessed using TAPSE and RV S'. RV systolic dysfunction was defined as an TAPSE value of <16 mm or as an S' was value of <10 cm/s.

Study IV

Study population

Between April 1998 and January 2014, 146 mitral valve procedures for active native mitral valve IE were performed in 142 patients meeting the Duke criteria [9] for IE at the Department of Cardiothoracic Surgery at Skane University Hospital, Lund, Sweden. Exclusion criteria were: mitral prosthetic endocarditis (n=20), concomitant aortic prosthetic endocarditis (n=6), and concomitant infective endocarditis of another native valve (aortic valve, n=18). Two patients were excluded due to a previously implanted pacemaker system. The final study population consisted of the remaining 100 patients.

Follow-up and grouping according to clinical symptoms

Clinical data were obtained from the department's database and patient records. Data on microbiology, echocardiograms, time of symptom onset and the initiation of intravenous antibiotics were retrieved from patient records. All patients had undergone preoperative TTE and, in most patients, TEE was also performed. Patients were screened for the following preoperative clinical symptoms: clinical stroke due to cerebral embolism, congestive heart failure, and uncontrolled bacteremia at the time of surgery. We categorized patients into three groups, A, B, and C, based on presenting symptoms. Patients with none of the three clinical symptoms were classified as Group A, patients with any one of the clinical symptoms constituted Group B, and patients with any two or all three clinical symptoms were classified as Group C. The primary endpoint was all-cause postoperative mortality. Secondary endpoints were reoperation due to recurrent IE in the mitral valve or prosthesis, structural valve deterioration, and non-structural valve deterioration. Follow-up was performed in March 2014, was 100% complete for survival and encompassed 469 patient-years (mean follow-up was 4.7±4.2 years, median 3.8 years, interquartile range [IQR] 0.8-7.7 years).

Unpublished results

In this thesis, unpublished results from a retrospective study of all consecutive patients with left-sided native valve endocarditis, who underwent surgery in Lund between January 1998 and December 2015, are presented. The 279 consecutive identified patients included: 117 patients with isolated mitral valve endocarditis (group M), 140 patients with isolated aortic valve endocarditis (group A), and 22 patients with mitral and aortic valve endocarditis (group MA). Clinical data obtained from the department's database and patient records included microbiology results, echocardiograms, and time of symptom onset and the time when the Duke's criteria for definitive IE were fulfilled. Follow-up of survival was performed using the Swedish Population Registry; follow-up for the outcomes of recurrent endocarditis and reoperation was performed using the electronic patient records in Skåne County. Follow-up was performed in September 2016 and was 100% complete for survival (mean follow-up was 5.9 ± 4.8 years, median 4.8 years, IQR 1.8 - 9.5 years).

Ethical aspects

All studies were performed according to the principles of the Helsinki Declaration of Human Rights and were approved by the Regional Ethical Review Board in Lund, Sweden. Study IV was also approved at the University of Southern Denmark. Written informed consent was obtained from the patients of Study II and III and from the healthy controls in Study III.

Statistical analysis

Results for categorical data are given as proportions. Continuous variables with normal distributions are expressed as the mean ± SD, whereas non-parametric continuous variables are expressed as the median and IQR. Student's t-test was used to evaluate normally distributed continuous variables, whereas the Mann-Whitney U test was used for non-parametric continuous variables. The paired samples T-test was used to compare measurements obtained at baseline and at peak exercise in Studies II and III. The chi-squared test was used for categorical variables, except when the expected frequency was below five, in which case Fisher's exact test was used. A simple linear regression was used to assess the correlation between exercise capacity and RV function. In studies I and IV, event rates ±1 standard error (SE) were estimated, plotted using the Kaplan-Meier method, and compared using the log-rank test. In Study IV, the risk-adjusted survival was assessed with Cox's proportional hazard regression analysis; the inclusion criterion for each independent variable was p<0.25, and the limit for forward inclusion was p<0.05. In the unpublished results, all known and plausible covariates where entered in the univariable and multivariable Cox's proportional hazard regression analysis.

Statistical analyses were performed and survival graphs plotted using the statistical software package SPSS (IBM, Armonk, NY): Version 21.0 in Studies I, II, and IV and Version 22.0 in Study IV. Microsoft ® Excel 2016MSO (Microsoft, Redmond, WA) was used to plot graphs for Study II and III.

Results

Study I

Preoperative and intraoperative data

New York Heart Association (NYHA) functional classes III-IV were significantly more frequent in the leaflet resection group than in the artificial chordae group (p=0.03). Other preoperative characteristics did not differ significantly between the groups (Table 1). The duration of surgery was shorter in the artificial chordae group than in the the leaflet resection group. All patients received an annuloplasty with a mean ring size of 33±4 mm in the artificial chordae group and 31±3 mm in the resection group (p=0.001).

Short-term outcomes

Thirty-day and 90-day mortality was 0.5% (1/201). Two patients required early reoperation due to recurrent severe MR (postoperative day 1 and 24). Both patients were in the leaflet resection group. Re-exploration for bleeding was not performed on any of the patients that underwent right minithoracotomy. Among the 185 patients that underwent median sternotomy, eight patients (4.3%) required re-exploration for bleeding and a deep sternal infection developed in one patient (0.5 %). The incidence of short-term complications did not differ significantly between the groups.

Long-term survival

The linearized incidence of overall mortality was 1.8% per patient-year. As shown in Figure 5A, five-year survival was 98.2±1.8% in the artificial chordae group and 93.9±2.1% in the resection group (log rank, p=0.67). Survival was 80.3 ±4.5% at 10 ten years in the leaflet resection group.

Table 1. Preoperative patient characteristics and perioperative data by type of MV repair

	Artificial chordae n = 55	Leaflet resection n = 146	P value
Age in years	60.5±11.4	61.2±11.6	0.69
Females	14 (25.5%)	44 (30.1%)	0.51
Hypertension	10 (18.2%)	26 (17.8%)	0.91
Diabetes mellitus	1 (1.8)	1 (0.68)	0.47
COPD	4 (7.3)	7 (4.8)	0.35
NYHA class III-IV	22 (44.0)	90 (61.6)	0.03
Chronic AF[a]	4 (7.0)	10 (6.9)	0.57
BMI [kg/m2]	25.6±3.5	25.3±3.8	0.19
S-creatinine [μmol/L]	81.0±17.4	80.4±20.7	0.85
Logistic EuroSCORE	3.6±4.4	4.4±4.2	0.28
Multiple segment disease	8 (14.5%)	35 (24.0%)	0.14
1 segment	47 (85.5%)	111 (76.0%)	
2 segments	7 (12.7%)	33 (22.6%)	
3 segments	1 (1.8%)	2 (1.4%)	
Mini-thoracotomy	14 (25.5%)	0	<0.001
CPB time (min)	110±37	124±30	0.01
Cross-clamping (min)	80±28	91±24	0.008
Ring size (mm)	33±4	31±3	0.001
Commissuroplasty	4 (7.3%)	4 (2.7%)	0.22
Suture of cleft	25 (45.5%)	5 (3.4%)	<0.001

Dichotomous variables are given as n (%) and continuous variables are expressed as mean ± SD. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association.

[a]One patient had a pacemaker implanted preoperatively

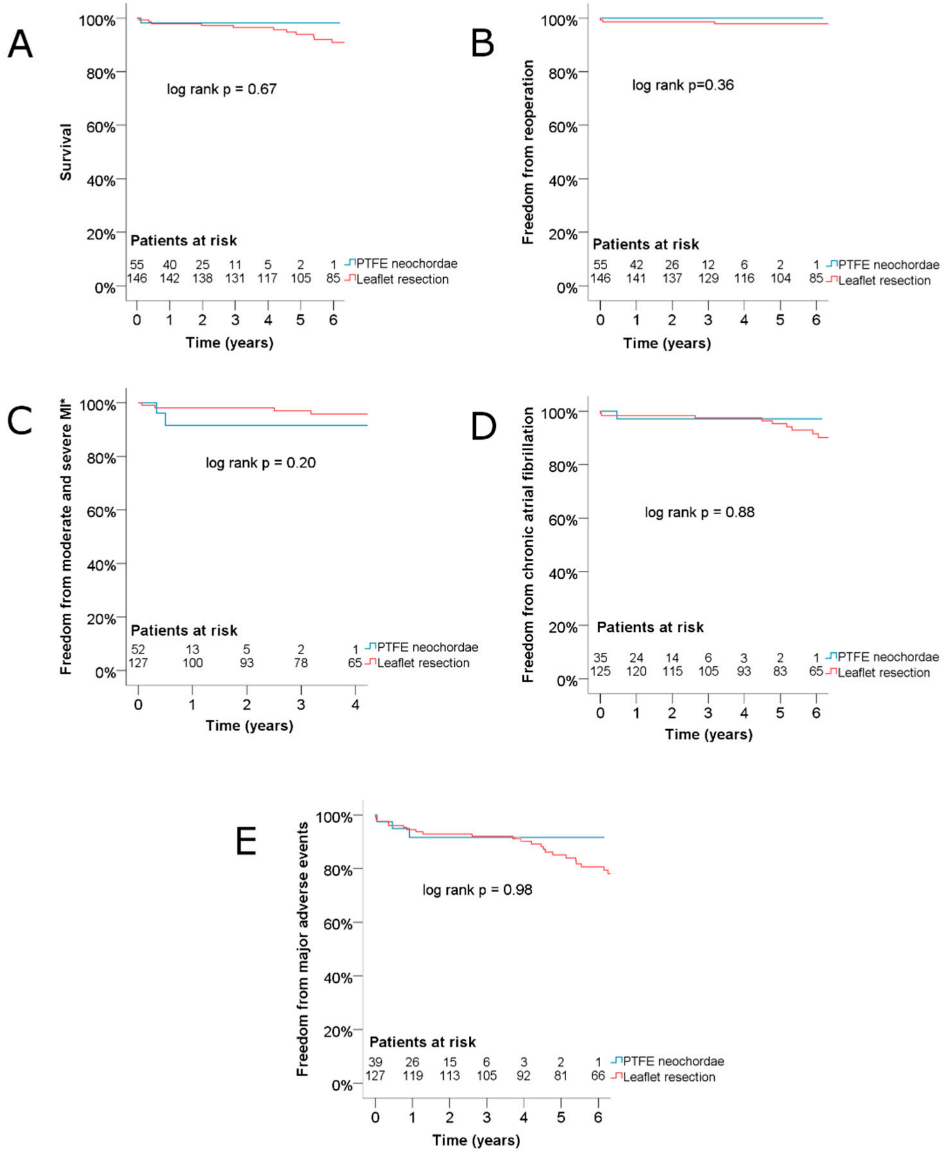

Figure 5 Kaplan Meier estimates of (A) survival, (B) freedom from reoperation, (C) freedom from moderate to severe MR, (D) freedom from chronic atrial fibrillation and (E) freedom from any major adverse event. *MI, mitral insufficiency

Freedom from adverse events

One patient in the leaflet resection group required a late reoperation (3.2 years after surgery) due to recurrent severe MR. Freedom from all-cause reoperation was 100% in the artificial chordae group and 97.9±1.2% in the resection group (log rank, p=0.36), Figure 5B. At five years, freedom from recurrent moderate or severe mitral regurgitation was 91.9±5.5% in the artificial chordae group and 95.8±2.1% in the resection group (log rank, p=0.20), Figure 5C.

Freedom from new onset chronic atrial fibrillation five years following surgery was 97.1±2.8% in the artificial chordae group compared with 95.3±2.1% in the leaflet resection group (log rank, p=0.88), Figure 5D. In both groups, freedom from non-structural dysfunction at five years was 100%. Freedom from endocarditis at five years was 100% in the artificial chordae group, compared with 98.5±1.1% in the resection group (log rank, p=0.45). Freedom from arterial embolism at five years was 100% in the artificial chordae group compared with 92.3±2.5% in the resection group (log rank, p=0.22). All embolisms were cerebral and resulted in ischemic strokes. In both groups, freedom from valve thrombosis at 5 years was 100%. Freedom from a major bleeding event in the artificial chordae group was 100% after both one year and five years, compared with 99.2 ± 0.8% after one year and 98.2±1.3% after five years in the resection group (p=0.54)

Freedom from the composite endpoint "major adverse events" at five years was 91.6±4.7% in the artificial chordae group compared with 85.1±3.4% in the leaflet resection group (log rank p=0.98), Figure 5E.

Study II

Preoperative and operative data

Preoperative patient characteristics and operative data are shown in Table 2. The mean age at surgery, gender distribution, and Logistic EuroSCORE of the two study groups were comparable. Seven different surgeons carried out the procedures. In the artificial chordae group, 5 patients underwent minithoracotomy, whereas in the resection group, none underwent minithoracotomy (p = 0.01). The resection techniques employed and the annuloplasty ring types are shown in Table 2. The mean ring size was significantly larger in the artificial chordae group (32.5 ± 2.6) than in the leaflet resection group (30.6 ± 2.6), p = 0.01). The mean time on cardiopulmonary bypass and the mean aortic cross clamp time were both shorter in the artificial chordae group than in the resection group (p = 0.003).

During the interval between surgery and the exercise echocardiography test, none of the patients in the study were hospitalized due to heart failure. Four patients were admitted due to atrial fibrillation that presented after the initial postoperative discharge. During follow up, one patient experienced an ischemic stroke, and four patients experienced transient ischemic attacks.

Table 2. Comparision of preoperative patient characteristics and operative data by type of MV repair.

	Artificial chordae (n = 24)	**Resection (n = 32)**	**P value**
Age at surgery, years	60.2 ± 10.5	59.8 ± 9.3	0.89
Female gender	7 (29%)	10 (31%)	0.86
NYHA class III-IV	9 (37%)	15 (47%)	0.48
LVEF < 50%	3 (13%)	0	0.07
Pulmonary artery hypertension >60 mmHg	8 (33%)	9 (28%)	0.68
Logistic EuroSCORE	3.1 ± 1.7	2.9 ± 1.5	0.69
Right minithoracotomy	5 (21%)	0	0.01
Ring type			0.004
Cosgrove-Edwards		3 (13%)	
Duran band	15 (63%)	31 (97%)	
Physio II	6 (25%)	1 (3%)	
Affected scallop			
P1	2 (8%)	1 (3%)	0.57
P2	24 (100%)	31 (97%)	1.0
P3	4 (17%)	4 (13%)	0.71
Prolapse of 2 or 3 scallops	6 (25%)	3 (9%)	0.15
Type of resection			
Quadrangular resection, annular plication		25 (78%)	
Quadrangular resection, sliding plasty		4 (13%)	
Triangular resection		3 (9%)	
Ring size	32.5 ± 2.6	30.6 ± 2.6	0.01
Ring size indexed to BSA	16.5 ± 2.0	15.9 ± 2.4	0.40
Cardiopulmonary bypass time	98 ± 31	120 ± 23	0.003
Cross-clamp time	74 ± 24	91 ± 19	0.003

Dichotomous variables are given as n (%) and continuous variables are expressed as mean ± SD.
BSA, body surface area according to DuBois formula.

Functional status

The median follow-up interval, from surgery to the exercise test, was significantly longer in the resection group (median 7.5 years, IQR 6.0-9.2 years, mean 7.5 years) than in the artificial chordae group (median 2.8 years, IQR 1.6-3.3 years, mean 2.8 years; $p < 0.001$). The mean age at the time of exercise echocardiography of the patients was 67.5 ± 9.3 and 63.0 ± 10.4 years, in the resection and artificial chordae groups, respectively ($p = 0.09$), Table 3. The mean Duke Activity Status Index score was similar in the two groups: 53 ± 7 points in the artificial chordae group and 51 ± 12 in the leaflet resection group ($p = 0.48$).

Table 3.
Comparison of clinical assessments, pulse and blood pressure measurements from exercise echocardiography by type of MV repair.

	Artificial chordae (n = 24)	**Resection (n = 32)**	**P value**
Clinical assessment			
Age at test, years	63.0 ± 10.4	67.5 ± 9.3	0.09
Time since surgery, years	2.8 (1.6-3.3)	7.5 (6.0-9.2)	<0.001
Atrial fibrillation	0	0	
NYHA Class I / II / III / IV	20 / 4 / 0 / 0	26 / 5 / 1 / 0	
Duke activity status index	53 ± 7	51 ± 12	0.48
BSA (m^2)	1.96 ± 0.18	1.94 ± 0.23	0.71
Baseline heart rate and blood pressure			
Pulse	73 ± 12	76 ± 11	0.40
Systolic BP, mm Hg	133 ± 15	140 ± 15	0.13
Measurements during exercise			
Exercise, max pulse	127 ± 19	129 ± 20	0.58
Exercise, max systolic BP, mm Hg	174 ± 38	174 ± 24	0.97
Exercise duration, min	9.4 ± 3.8	8.8 ± 3.3	0.55
Maximum exercise capacity, Watts	136 ± 43	131 ± 40	0.65
Maximum exercise capacity indexed to BSA (Watts/m^2)	67 ± 18	67 ± 18	0.94

Dichotomous variables are given as n (%), continuous variables are expressed as mean ± SD, unless they are nonparametric, in which case they are expressed as median with interquartile range in parentheses. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; BSA, body surface area according to DuBois formula; NYHA, New York Heart Association classification.

Exercise hemodynamics

As shown in Table 3, the groups did not differ significantly in exercise duration or peak exercise workload in Watts. Resting and exercise hemodynamics in the study groups are displayed in Table 4. In the artificial chordae group, one patient had severe MR at rest and during exercise. This patient has subsequently undergone reoperation with additional artificial chordae that successfully repaired the mitral valve. As shown in Figure 6, the mean MV gradient increased from 3.0 ± 1.3 mmHg at rest to 8.7 ± 3.7 during exercise in the artificial chordae group ($p < 0.001$) and from 3.0 ± 1.0 to 11.3 ± 8.7 in the resection group ($p < 0.001$). One patient in the AC group had an MV gradient > 15 mm Hg at during exercise. The mean MV gradients did not differ significantly between groups at rest ($p = 0.90$) or during exercise ($p = 0.21$). We did not detect a difference in the estimated RVSP at rest ($p = 0.46$) or during exercise ($p = 0.84$) between groups.

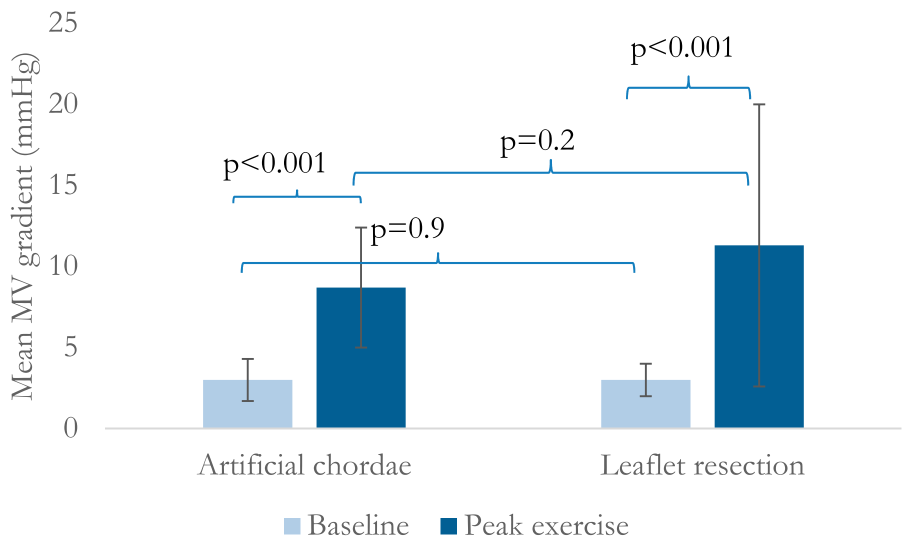

Figure 6: Comparision of mean mitral valve pressure gradient at rest (baseline, light blue bar) and during peak exercise (dark blue bar) by study group. Horizonatal blue lines indicate two-way comparisons.

Systolic anterior motion

Systolic anterior motion (SAM) was detected in five patients. A review of echocardiography studies performed following surgery and prior to discharge revealed SAM movements of chordae and anterior leaflet tissue in three patients but no increase in left ventricular outflow tract (LVOT) gradients and no MR. SAM was more common in the artificial chordae group (n = 4, 17%) than in the resection group (n = 1, 3%) but the difference was not significant ($p = 0.15$). Patients with SAM did not have hemodynamically significant MR at rest or at peak exercise. The resting peak LVOT gradient in patients with SAM was 4.7 ± 1.3 mmHg and 6.2 ± 3.0 mmHg ($p = 0.25$) in patients without SAM. During peak exercise, the patients with SAM had a peak LVOT gradient of 10.8 ± 2.8 mmHg, whereas those without SAM had 11.1 ± 3.9 mmHg ($p = 0.88$).

Table 4.
Comparison of resting and exercise hemodynamics by type of MV repair

	n[a]	Artificial chordae n (%) or Mean ± SD	n[a]	Resection n (%) or Mean ± SD	P value
Resting measures					
Any mitral regurgitation	24	6 (25%)	32	4 (13%)	0.30
Mild		5 (21%)		4 (13%)	
Moderate		0		0	
Severe		1 (4%)		0	
SAM	24	4 (17%)	32	1 (3%)	0.15
Cardiac output, L/min	18	4.1 ± 1.5	22	3.6 ± 1.3	0.29
Indexed LA volume, mL/m^2	21	35.3 ± 11.7	24	35.9 ± 11.0	0.86
LV ejection fraction, 4 chamber, %	20	63.2 ± 3.5	31	61.2 ± 6.0	0.24
LV ejection fraction, biplane, %	18	59.7 ± 3.5	22	58.8 ± 5.3	0.55
LVIDd, mm	23	45.2 ± 5.5	30	45.7 ± 5.4	0.75
LVPWd, mm	23	12.1 ± 2.1	30	12.1 ± 1.6	0.96
Peak mitral gradient, mm Hg	22	7.6 ± 3.6	30	7.6 ± 2.7	0.99
Mean mitral gradient, mm Hg	22	3.0 ± 1.3	30	3.0 ± 1.0	0.90
Peak aortic gradient, mm Hg	22	5.2 ± 1.5	30	6.9 ± 3.5	0.032
TR, Maximum velocity	19	2.5 ± 0.3	23	2.4 ± 0.3	0.47
RVSP, mm Hg	19	24.5 ± 5.8	23	23.2 ± 5.3	0.46
Peak exercise measures					
Any mitral regurgitation (grade 1-4)	24	7 (29%)	32	4 (13%)	0.18
Mild		6 (25%)		4 (13%)	
Moderate		0		0	
Severe		1 (4%)		0	
SAM	24	4 (17%)	32	1 (3%)	0.15
Mean mitral gradient, mm Hg	20	8.3 ± 3.4	31	11.3 ± 8.7	0.21
Peak aortic gradient, mm Hg	18	10.9 ± 3.7	28	11.2 ± 4.0	0.56
RVSP	11	39.3 ± 12.0	18	36.8 ± 12.1	0.84

Dichotomous variables are given as n (%) and continuous variables are expressed as mean ± SD.
LA, left atrium; LV, left ventricular; LVIDd, left ventricular end-diastolic internal dimension; LVPWd, left ventricular posterior wall dimension; RVSP, right ventricular systolic pressure; SAM, systolic anterior motion; TR, tricuspid regurgitaion anumber of available measurements.

Study III

Study participants

Preoperative patient characteristics and operative data are shown in Table 5. The demographics and clinical assessment of the study participants at the time of follow-up are shown in Table 2. The mean ages of the study group and control group were similar ($p = 0.63$) at the time of the study and the proportions of females in both groups were the same ($p = 1$). The participants' self-rated functional capacities, according to the Duke Activity Status Index, were similar in both groups ($p = 0.26$). The use of beta-blockers and use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers were more frequent in the study group than the control group ($p = 0.01$ and $p = 0.03$, respectively).

Table 5.
Preoperative patient characteristics and operative data

Preoperative characteristics of the study group	**n=56**
Age at surgery (years)	60.0±9.7
Female gender	17 (30%)
NYHA class III-IV	24 (43%)
LVEF <50%	3 (5.4%)
PASP >60 mm Hg	17 (30%)
Logistic EuroSCORE	3.0±1.6
Operative data	**n=56**
Ring type	
Cosgrove-Edwards® Mitral annuloplasty system	3 (5.4%)
Duran Ancore® band	46 (82%)
Physio II® semi rigid ring	7 (12.5%)
Affected scallop	
P1	3 (5.4%)
P2	55 (98%)
P3	8 (14.3%)
Prolapse of 2 or 3 scallops	9 (16%)
Type of repair	
Leaflet resection	32 (57%)
Artificial chordae	24 (43%)
Ring size (mm)	31.4±2.7
CPB time (min)	110±29
Cross-clamp time (min)	84±23

Dichotomous variables are given as n (%), continuous variables are expressed as mean ± SD.
CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction, PASP, pulmonary artery systolic pressure.

Exercise capacity

The study group had a maximum exercise capacity of 133 ± 41 Watts, whereas the control group had a maximum exercise capacity of 154 ± 47 Watts, but the difference was not significant (p=0.12). The exercise duration in the two groups did not differ significantly (0.33). The maximum heart rate was 128 ± 20 beats per minute in the study group and 129 ± 18 beats per minute in the control group (p = 0.9) (Table 6).

Table 6. Comparison of clinical assessment, heart rate, blood pressure and measurements from exercise echocardiography between study and control groups

	Study group (n = 56)	Control group (n = 13)	P value
Clinical assessment			
Age at assessment (years)	65.5±10.0	64.0±9.7	0.63
Female gender	17 (30%)	4 (30%)	1.0
NYHA I / II / III / IV	46 / 9 / 1 / 0	12 / 1 / 0 / 0	
Short form assessment (Duke Activity Status Index)	52±10	55±4	0.26
BSA according to DuBois formula (m^2)	1.95±0.21	2.0±0.18	0.47
Current medications			
Beta blocker	35 (63%)	3 (23%)	0.01
Calcium channel blocker	7 (13%)	0	0.33
ACE inhibitor or ARB	21 (38%)	1 (8%)	0.03
Resting heart rate and blood pressure			
Atrial fibrillation	0	0	
Resting heart rate (BPM)	75±11	74±11	0.74
Resting systolic BP (mm Hg)	137±15	138±13	0.9
Measurements during exercise			
Maximum heart rate (BPM)	128 ± 20	129 ± 18	0.87
Maximum systolic BP (mm Hg)	174 ± 31	181 ± 45	0.48
Duration (min)	9.1 ± 3.5	11.1 ± 4.1	0.33
Maximum effort (Watts)	133 ± 41	154 ± 47	0.12

Dichotomous variables are given as n (%), continuous variables are expressed as mean ± SD, unless they are nonparametric, in which case they are expressed as median (IQR). ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; BSA, Body Surface Area; NYHA, New York Heart Association.

[a]number of available measurements.

Table 7. Comparison of resting and exercise haemodynamics between study and control groups

Measure	n[a]	Study group (n = 56)	n[a]	Control group (n = 13)	P value
Baseline measures					
Any mitral regurgitation	56	10 (18%)	13	0	0.19
Mild		9 (16%)		0	
Moderate		0		0	
Severe		1 (2%)		0	
SAM	56	5 (9%)	13	0	1.0
Indexed LA volume, mL/m^2	45	35.7 ± 11.2	0		
LVEF (%)	51[b]	62.0 ± 6.0	6[a]	59.7 ± 3.1	0.29
LVIDd (mm)	53	45.5 ± 5.4	11	43.7 ± 6.5	0.31
LVPWd (mm)	53	12.1 ± 1.8	11	11.3 ± 1.1	0.17
Mean mitral valve gradient (mm Hg)	52	3.0 ± 1.1	2	0.7 ± 0.1	0.005
E / e'	48	15.9 ± 4.3	11	7.1 ± 2.9	<0.001
Peak aortic gradient (mm Hg)	53	6.1 ± 2.9	12	9.4 ± 10.2	0.042
TR max PG (mm Hg)	42	23.8 ± 5.5	3	22.1 ± 4.0	0.54
Interventricular septal movement (mm)	48	7.0 ± 1.3	10	8.9 ± 2.0	<0.001
TAPSE (mm)	52	16.7 ± 3.3	12	24.4 ± 4.3	<0.001
S' (cm/s)	55	10.6 ± 2.6	12	14.3 ± 2.5	<0.001
Peak exercise measures					
Any mitral regurgitation (grade 1-4)	56	11 (20%)	13	0	0.11
Mild		10 (18%)		0	
Moderate		0		0	
Severe		1 (2%)		0	
SAM	56	5 (9%)	13	0	1.0
Mean mitral gradient (mm Hg)	51	10.1 ± 7.2	0		
Peak aortic gradient (mm Hg)	46	11.1 ± 3.8	12	17.2 ± 13.9	0.01
TR max PG (mm Hg)	29	38.8 ± 11.9	4	23.9 ± 9.4	0.03
TAPSE (mm)	40	19.8 ± 4.2	12	34.6 ± 3.8	<0.001
S', (cm/s)	33	14.5 ± 6.7	13	20.7 ± 5.1	0.005

Dichotomous variables are given as n (%), continuous variables are expressed as mean ± SD, unless they are nonparametric, in which case they are expressed as median (IQR).

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; BSA, body surface area according to DuBois formula; LVIDd, left ventricular internal diameter end diastole; LVPWd, left ventricular posterior wall end diastole; NYHA, New York Heart Association classification; S', Tissue doppler-derived systolic velocity of the annulus; SAM, systolic anterior mortion; TAPSE, tricuspid annular plane systolic excursion; TR max PG, Tricuspid regurgitation maximum pulse gradient.

[a]Number of available measurements; [b]According to Simpson's method. The remaining participants did not have sufficient image quality for the Simpson's method but all had normal ejection fractions based on visual judgment.

Right ventricular function

The echocardiographic measures at rest and peak exercise are shown in Table 7. Resting TAPSE was significantly lower in the study group (16.7 ± 3.3 mm) than in the control group (24.4 ± 4.3 mm, $p<0.001$). Based on TAPSE assessed at rest, 33% (17/52) of the study group had RV dysfunction (TAPSE <16 mm), whereas none of the control group had RV dysfunction.

The mean increase in TAPSE during exercise was lower in the study group, 3.1 ± 4.0 mm, than the control group, 9.7 ± 5.4 mm ($p <0.001$) (Figure 7). TAPSE increased by a factor of 1.21 ± 0.25 during exercise in the study group compared with 1.43 ± 0.31 in the control group ($p = 0.013$). In the study group, there was no correlation between baseline TAPSE and maximum exercise capacity (R = 0.064, R-square = 0.004) nor between TAPSE at peak exercise and maximum exercise capacity (R = 0.097, R-square = 0.009). At rest, the interventricular septal movement was significantly lower in the study group than in the control group (7.0±1.3 versus 8.9±2.0, respectively; $p < 0.001$).

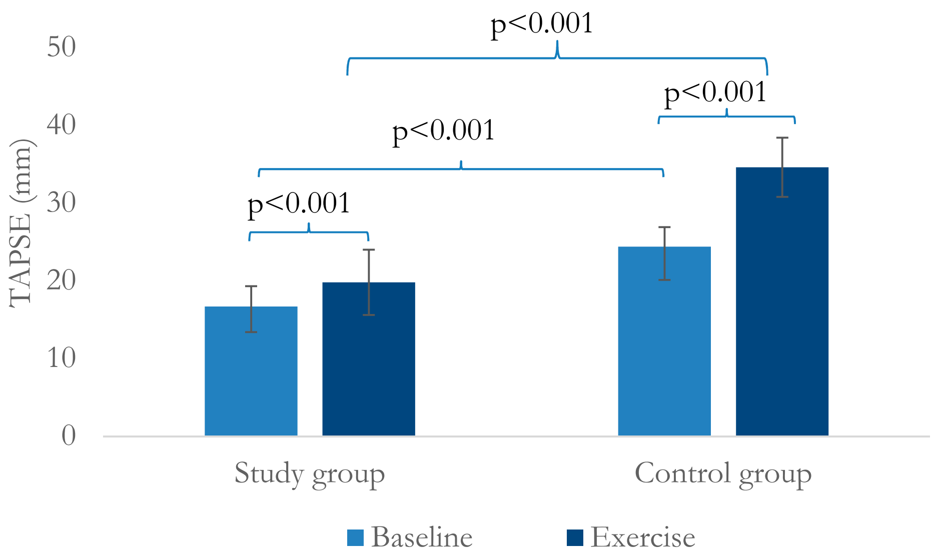

Figure 7: Comparision of tricuspid annular plane systolic excursion (TAPSE) at rest (baseline, light blue bar) and during peak exercise (dark blue bar) between study and control groups. Horizonatal blue lines indicate two-way comparisons.

Resting RV S' was lower in the study group, 10.6 ± 2.6 cm/s, than in the control group, 14.3 ± 2.5 (p <0.001). Based on S' value, 44% (24/55) of the study group had RV dysfunction (S' value <10 cm/s), whereas none of the control group had RV dysfunction. As shown in Figure 8, S' increased significantly in both groups during exercise. At peak exercise, S' was lower in the study group, 14.5 ± 6.7 cm/s, than in the controls, 20.7 ± 5.1 cm/s (p = 0.005).

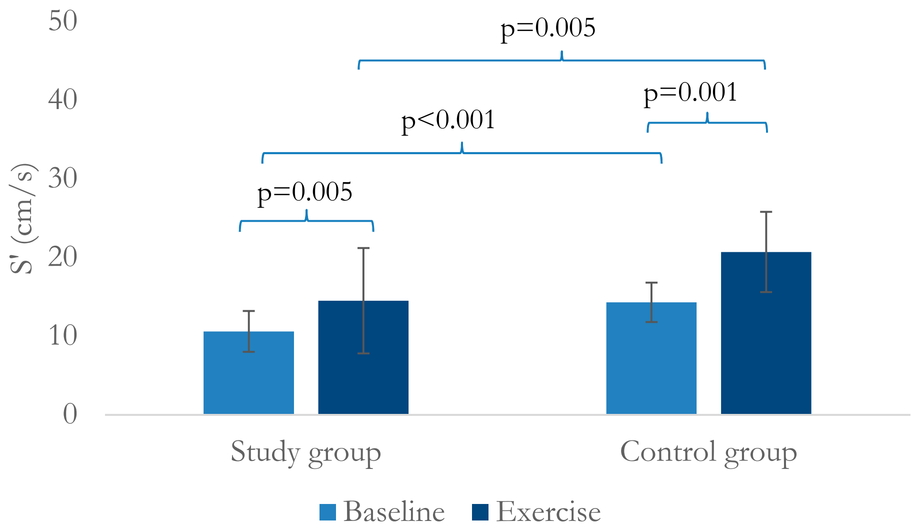

Figure 8: Comparision of RV S' at rest (baseline, light blue bar) and during peak exercise (dark blue bar) between study and control groups. Horizonatal blue lines indicate two-way comparisons.

Preoperative LV dilatation (LVIDs ≥40 mm) was present in 34% of the patients. At follow up, patients with preoperative LV dilatation had at rest a mean TAPSE of 14.8 ± 2.4 mm compared with 17.2 ± 3.4 mm in those with normal LV size (p=0.037). However, during peak exercise the difference in mean TAPSE did not remain significant. Preoperatively, 17 patients (30%) had an estimated pulmonary artery systolic pressure ≥60 mm Hg. No study patient had pulmonary hypertension during the exercise test. In the study group, 42 (75%) patients had tricuspid regurgitation permitting measurement of the pressure gradient. The peak gradient over the tricuspid valve (TR max PG) at rest was 24±6 mm Hg. The TR max PG could be measured in three patients (8%) in the control group; the mean was 22±4 mm Hg. At peak exercise the TR max PG remained unchanged in the control group; however, in the study group it increased significantly from resting value to 39±12 mm Hg (p <0.001).

Artificial chordae vs. leaflet resection

The median follow-up interval, from surgery to the exercise test, was significantly longer in the resection group (median 7.5 years; IQR 6.0-9.2 years; mean 7.5 years) than in the artificial chordae group (median 2.8 years; IQR 1.6-3.3 years; mean 2.8 years; $p < 0.001$). Baseline TAPSE did not differ between the artificial chordae and leaflet resection groups (Table 8). However, at peak exercise, TAPSE was significantly higher in patients repaired using artificial chordae than in patients who underwent leaflet resection (21.7±3.8 mm vs. 18.6±4.0, respectively; $p = 0.02$). The absolute increase in TAPSE with exercise in the artificial chordae group was 4.8 ± 3.8 mm Hg compared with 2.1 ± 3.9 mm Hg in the resection group ($p = 0.04$). TAPSE increased by a factor of 1.30 ± 0.22 in the artificial chordae group compared with 1.15 ± 0.26 in the resection group ($p = 0.07$). S' was similar in both groups at baseline. At peak exercise, S' was higher in the artificial chordae group than in the leaflet resection group, but the difference was not significant ($p = 0.14$).

Left ventricular size and function at rest

The left ventricular end-diastolic internal dimension (LVIDd) was 46 ± 5 mm in the study group and 44 ± 7 mm in the control group ($p = 0.31$). The left ventricular ejection fraction (LVEF) was 62 ± 6 in the study group and 60 ± 3 in the control group ($p = 0.29$). The mean left ventricular filling pressure, assessed with E/e', was significantly higher in the study group than in the control group (15.9±4.3 versus 7.1±2.9, respectively: $p < 0.001$).

Table 8:
Right ventricular function at rest and during peak exercise according to type of mitral valve repair.

	n[a]	Leaflet resection (LR)	n[a]	Artificial chordae (AC)	n[a]	Control group	P values
Resting							
TAPSE (mm)	30	16.4 ± 3.4	22	17.0 ± 3.1	13	24.4 ± 4.3	AC vs. LR, 0.52 LR vs. control, <0.001 AC vs. control, <0.001
S' (cm/s)	32	10.8 ± 3.1	23	10.4 ± 1.8	12	14.3 ± 2.5	AC vs. LR, 0.54 LR vs. control, <0.001 AC vs. control, 0.001
Exercise							
TAPSE	25	18.6 ± 4.0	15	21.7 ± 3.8	12	34.6 ± 3.8	AC vs. LR, 0.02 LR vs. control, <0.001 AC vs. control, <0.001
S' (cm/s)	18	13.0 ± 3.8	15	16.5 ± 8.9	13	20.7 ± 5.2	AC vs. LR, 0.14 LR vs. control, <0.001 AC vs. control, 0.14

Variables are given as n (%), continuous variables are expressed as mean ± SD
AC, artificial chordae; LR, leaflet resection; TAPSE, tricuspid annular plane systolic excursion; S', Tissue Doppler-derived systolic velocity of the annulus.
[a]Number of available measurements.

Study IV

Patient characteristics

Patient characteristics and clinical data are presented in Table 9. Three patients had IE due to ongoing intravenous drug abuse, one in group A and two in group B. The median time interval from symptom onset to the initiation of intravenous antibiotic therapy was 3 days (IQR 1-10). The median time interval from the initiation of antibiotic therapy to surgery was 10 days (IQR 5-19). Three patients underwent surgery within 48 hours of the initiation of antibiotic therapy, and 11 patients within 72 hours. There was no significant difference in the time from the initiation of antibiotic therapy to surgery in Groups A, B, and C.

Microbiology

Causative microorganisms were identified in blood cultures in 95 patients (Table 10); *S. aureus* accounted for the IE of 42 patients. The five patients with negative blood cultures also had negative tissue cultures. The time interval between initiation of antibiotic therapy to surgery was shorter in patients with *S. aureus* infection than in patients infected with other pathogens ($p<0.001$). There was no significant difference in the frequency of *S. aureus* between Groups A, B, and C ($p=0.5$).

Indications for mitral valve surgery

Almost half of the patients (n=48) had congestive heart failure. Six patients were ventilated using positive-pressure due to pulmonary edema, and two had an intra-aortic balloon pump inserted preoperatively. Thirty-six patients had documented septic embolism. Cerebral embolism was present in 22 patients, whereas six patients had peripheral arterial embolism to the extremities, four had ocular emboli, one had an embolus to the kidney, one an embolus to a vertebral disc, one a silent brain embolus, and one had an embolus to the skin of the torso. Eight patients had persistent fever despite appropriate antibiotic therapy.

Table 9.
Preoperative patient characteristics, indications, and operative data

	Total (n=100)	Group A (n=35)	Group B (n=53)	Group C (n=12)
Patient characteristics				
Age (years)	61.4±13.6	58.7±16.3	61.4±13.6	61.4±13.6
Female	51 (51%)	19 (54%)	25 (47%)	7 (58%)
Surgical acuity[a]	29 (29%)	8 (23%)	17 (32%)	4 (67%)
Days from symptom onset until start of intravenous antibiotic therapy	3.0 (1.0-10)	3.0 (2.0-5.0)	3.0 (1.0-21)	4.5 (1.0-6.5)
Days from symptom onset until surgery	20 (8.3-32)	14 (9.0-30)	21 (8.5-38)	18 (7.0-44)
Days from start of intravenous antibiotics to surgery	10 (5.0-18)	9.0 (5.0-12)	11 (4.5-20)	12 (6.0-35)
Severe mitral regurgitation	61 (61%)	15 (43%)	36 (68%)	10 (83%)
Healthcare-associated IE	12 (12%)	6 (17%)	5 (9%)	1 (8%)
Known mitral valve pathology or heart murmur	11 (11%)	4 (11%)	7 (13%)	0
Positive preoperative blood cultures	95 (95%)	35 (100%)	50 (94%)	10 (83%)
Staphylococcus aureus infection	42 (42%)	14 (40%)	21 (40%)	7 (58%)
Diabetes mellitus	24 (24%)	9 (26%)	13 (25%)	2 (17%)
Preoperative dialysis	5 (5%)	3 (9%)	1 (2%)	1 (8%)
Left ventricular ejection fraction < 50%	13 (12%)	2 (6%)	7 (14%)	3 (25%)
Logistic EuroSCORE (%)	17 (9.1-37)	12 (6.9-31)	17 (9.7-39)	29 (18-57)
Indications for surgery				
Congestive heart failure	48 (48%)	0	38 (72%)	10 (83%)
All cause embolization	36 (36%)	8 (23%)	19 (36%)	9 (75%)
Uncontrolled bacteremia	8 (8%)	0	1 (2%)	7 (58%)
Abscess on echocardiography	4 (4%)	1 (3%)	3 (6%)	1 (8%)
Large vegetation	64 (64%)	24 (69%)	32 (66%)	8 (67%)
Operative data				
Annular involvement	22 (12%)	4 (11%)	12 (23%)	6 (50%)
Annular reconstruction	8 (8%)	1 (3%)	4 (8%)	3 (25%)
Mitral valve repair	41 (41%)	21 (60%)	16 (31%)	4 (33%)
Ring size	28.6±2.1	28.4±1.6	29.0±2.6	28.0±2.6
Valve size	27.3±2.0	27.1±1.7	27.7±2.1	26.0±1.1
Concomitant CABG[b]	16 (16%)	6 (17%)	9 (17%)	1 (8%)
Concomitant AVR[b]	8 (8%)	1 (3%)	5 (9%)	2 (17%)
Cardiopulmonary bypass time (min)	126 (99-161)	123 (98-150)	122 (96-166)	156 (132-200)
Aortic cross clamp time (min)	90 (70-117)	84 (68-108)	87 (68-110)	116 (93-136)

Intraoperative findings

Mitral valve repair was attempted in 48 patients and was successful in 85% (41/48). In patients in who repair was successful, the following methods were used: 8 patients had a simple removal of a vegetation or infected tissue material without the need of leaflet resection; 22 patients had leaflet resection, the posterior leaflet alone was resected in 20 patients, and both the anterior and posterior leaflets was resected in two patients; 10 patients underwent leaflet reconstruction with either bovine or autologous pericardium (the anterior leaflet in four patients and posterior leaflet in seven patients). Mechanical prostheses were implanted in 35 (59%) of the 59 patients who underwent valve replacement.

Four of the 22 patients (18%) with perivalvular involvement underwent mitral valve repair. One third of the patients with positive *S. aureus* culture (n=14/42) had perivalvular involvement, whereas perivalvular involvement was seen in 14% (8/58) of the remaining patients (p=0.02). Annular reconstruction was carried out in one patient who underwent repair and seven patients who underwent valve replacement. Autologous pericardium was used for the reconstruction in four patients; bovine pericardium in three patients, and a flip-over of the anterior mitral leaflet was performed in one patient.

Table 9, footnotes

Dichotomous variables are expressed as number of patients and percentage in parentheses. Continuous normally distributed variables are expressed as mean ± standard deviation. Continuous non-parametrically distributed variables are expressed as median with interquartile range in parenthesis. AVR, aortic valve replacement; CABG, Coronary artery bypass grafting; IE, infective endocarditis. aOperated within 24 hours from being accepted for surgery bFour patients had both CABG and AVR.

Table 10.
Microbiology

Pathogen	Number (%)
Staphylococcus aureus	42 (42%)
MRSA[a]	1 (1%)
Coagulase-negative staphylococci	4 (4%)
Enterococcus faecalis	5 (5%)
Oral streptococci	23 (23%)
Other streptococci	8 (8%)
HACEK group[b]	5 (5%)
Escherichia coli	4 (4%)
Abiotrophia defectiva	1 (1%)
Aerococcus urinae	1 (1%)
Shewanella algae	1 (1%)
Candida albicans	1 (1%)
Negative cultures	5 (5%)

[a]Methicillin-resistant *Staphylococcus aureus*, [b]*Haemophilus species* (n=3), *Aggregatibacter aphrophious* (n=1), *Cardiobacterium hominis* (n=1,) *Eikenella corrodens* (n=0), *Kingella kingae* (n=0).

Outcome

The overall 30-day mortality was 5% (n=5); 0% in Group A; 8% in Group B (n=4); and 8% in Group C (n=1); and did not differ significantly between groups (p=0.24). The overall 90-day mortality was 11% (n=11); 3% in Group A (n=1); 15% in Group B (n=8); and 17% in Group C (n=2); and did not differ significantly between groups (p=0.16). Long-term survival of Groups A, B, and C are shown in Figure 9. The overall five-year survival in the study population was 67.4±5.1%, compared with 92.5% in the Swedish background population. Survival at five years was 87.0±6.1% in Group A, 62.6±7.1% in Group B, and 33.8±15.2% in Group C. Long-term survival of Group C was significantly shorter than that of Group A (log rank p=0.001).

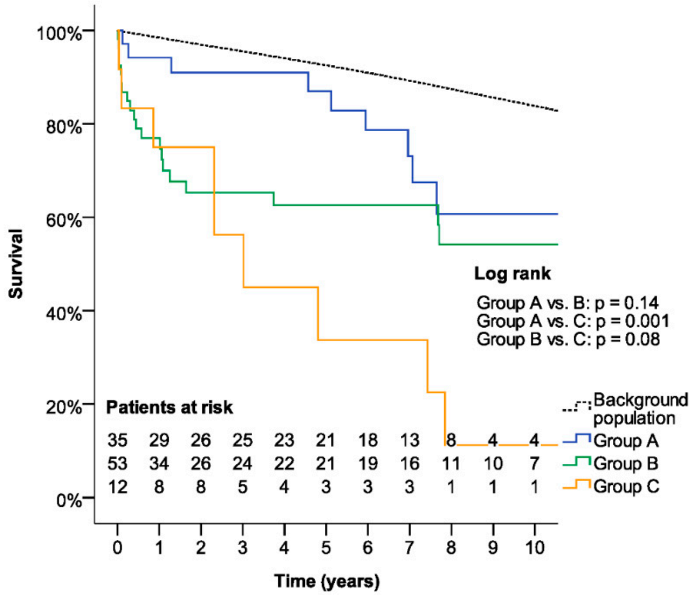

Figure 9: Kaplan-Meier estimates of survival for Groups A, B, and C

The Kaplan-Meier estimate of survival for patients with *S. aureus* IE compared with IE with other pathogens is presented in Figure 10. The five-year survival for *S. aureus* IE was 48.4±8.3% compared with 81.3±5.7% for IE due to other pathogens (log rank p<0.001). After the exclusion of patients who died within 90 days of surgery, the one-year survival of *S. aureus* IE was 86.8±6.1% compared with 96.3±2.6% for IE due to other pathogens, whereas the five-year survival for *S. aureus* IE was 63.5±9.4% compared with 82.8±5.6% in IE with other pathogens (log rank p=0.03). The Kaplan-Meier estimate of survival for patients with mitral valve repair compared with mitral valve replacement is presented in Figure 11. Patients who underwent MV repair had a five-year survival of 76.1±7.0%, compared with 60.7±7.1% in patients in whom the valve was replaced (log rank p=0.30).

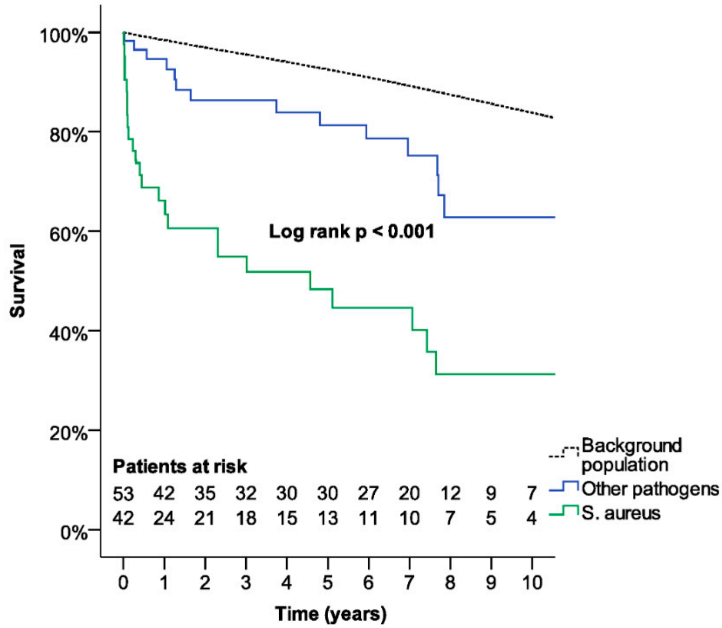

Figure 10: Kaplan-Meier estimates of survival for patients with *S. aureus* infective endocarditis (IE) compared with those with IE resulting from other pathogensFreedom from reoperation.

There were no early reoperations (<30 day). Five patients underwent reoperation during the follow-up period. Three of these underwent primary mitral valve repair and were reoperated due to perivalvular abscess (day 53 after primary surgery), perivalvular regurgitation in the area of a covered perivalvular abscess (day 226), and mitral stenosis (day 1403). The remaining two patients were reoperated for prosthetic endocarditis (day 313 and day 730). Three were intravenous drug users: one died one year after surgery, one required reoperation due to prosthetic endocarditis at two years, and one required surgery of the aortic valve due to recurrent endocarditis four years postoperatively. The overall freedom from reoperation was 92.6±3.3% at five-years.

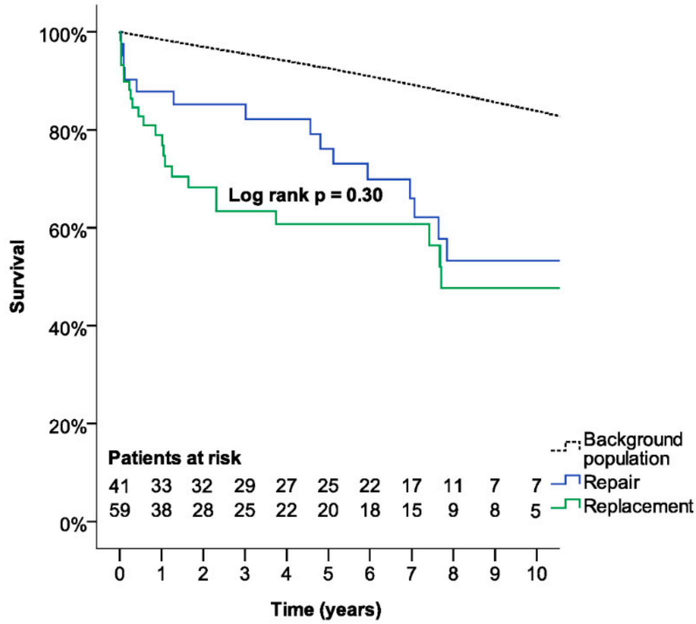

Figure 11: Kaplan-Meier estimates of survival for patients who underwent mitral valve repair compared with those who underwent mitral valve replacement

Prognostic factors for survival

The independent predictors of long-term survival following IE were: clinical presentation group (Group A = reference group), HR=2.37 (95% CI 1.02-5.50) for Group B, and HR=4.07 (95% CI 1.56-10.6) for Group C; age, HR= 1.04 per 1-year increment (95% CI 1.01-1.07); diabetes mellitus, HR= 4.31 (95% CI 2.28-8.51); preoperative renal failure requiring dialysis, HR= 4.58 (95% CI 1.50-14.0); and *S. aureus* IE, HR= 3.43 (95% CI 1.71-6.87), Table 3.

Table 11.
Results of univariate and multivariate Cox regression analysis

	Univariable Cox regression			Multivariable Cox regression		
Variable	**HR**	**(95% CI)**	**p**	**HR**	**(95% CI)**	**p**
Congestive heart failure	2.89	(1.46-5.75)	0.002			
Embolic stroke	1.01	(0.46-2.21)	0.98			
Uncontrolled bacteremia	1.94	(0.76-5.00)	0.17			
Preoperative clinical presentation			0.02			0.014
Group A	1	(ref.)		1	(ref.)	
Group B	1.82	(0.83-4.00)		2.37	(1.02-5.50)	
Group C	3.77	(1.49-9.53)		4.07	(1.56-10.6)	
Age, per 1-year increment	1.03	(1.00-1.05)	0.03	1.04	(1.01-1.07)	0.014
Female gender	1.66	(0.87-3.18)	0.13			
Diabetes mellitus	3.97	(2.07-7.61)	<0.001	4.31	(2.28-8.51)	<0.001
Renal failure requiring dialysis	3.07	(1.19-7.90)	0.02	4.58	(1.50-14.0)	0.008
Known mitral disease	0.64	(0.20-2.07)	0.45			
Mode of acquisition			0.46			
Community (ref.)	1	(ref.)				
Healthcare-associated	1.76	(0.80-3.88)				
Intravenous drug use	1.18	(0.16-8.76)				
Staphylococcus aureus vs. other pathogens	3.72	(1.82-7.62)	<0.001	3.43	(1.71-6.87)	0.001
Time from start of i.v. antibiotics until surgery[a]	1.01	(0.99-1.03)	0.23			
Time from symptom onset until surgery[a]	0.98	(0.97-1.003)	0.12			
Annular involvement[b]	2.79	(1.43-5.45)	0.003			
Leafletb			0.96			
Anterior (ref.)	1	(ref.)				
Posterior	1.15	(0.41-3.21)				
Both	1.02	(0.51-2.04)				

CI, confidence interval; HR, hazard ratio; ref., reference value; i.v., intravenous.
[a]per 1-day increment, [b]according to operative report.

Unpublished results

Patients in Group M were older than patients in group A (Table 12). In Group M 52% of the patients were females compared with 22% in Group A. Pulmonary hypertension was more common in Group M (14%) than in group A (6%, p=0.043).

Table 12. Comparision of preoperative characteristics of patients that underwent surgery for left-sided IE in Lund according to valve affected by IE

Variable	**Total n = 279**	**Mitral and Aortic Valve (MA) n=22**	**Mitral Valve (M) n=117**	**Aortic Valve (A) n=140**	**P-value (M vs A)**
Age	58.4 ± 14.4	56.3 ± 12.9	61.9 ± 14.1	55.8 ± 14.4	.001
Sex (female)	96 (34.4%)	4 (18.2%)	61 (52.1%)	31 (22.1%)	<.000
Emergency[a]	85 (33.5%)	5 (25.0%)	33 (30.8%)	47 (37.0%)	.322
NYHA class (%)					
I	38 (15)	3 (15)	14 (14)	21 (16)	
II	52 (21)	4 (20)	18 (18)	30 (23)	
III	84 (34)	8 (40)	42 (42)	34 (27)	
IV	74 (30)	5 (25)	26 (26)	43 (34)	
NYHA III or IV	158 (63.7%)	13 (65.0%)	68 (68.0%)	77 (60.2%)	.105
LVEF <50%	70 (26.1%)	10 (45.5%)	14 (12.4%)	46 (34.6%)	<.001
PASP >60 mmHg	24 (9.1%)	1 (4.8%)	15 (13.6%)	8 (6.0%)	.043
Renal Failure	28 (10,6%)	3 (14.3%)	14 (12.7%)	11 (8.3%)	.255
IHD	65 (23.3%)	5 (22.7%)	28 (23.9%)	32 (22.9%)	.839
COPD	23 (8.7%)	2 (9.5%)	9 (8.2%)	12 (9.0%)	.816
Diabetes Mellitus	49 (17.8%)	3 (13.6%)	26 (22.2%)	20 (14.7%)	.122
PVD	23 (8.7%)	1 (4.8%)	11 (10.0%)	11 (8.3%)	.640
EuroSCORE I	10.0 ± 3.9	10.9 ± 4.3	10.1 ± 3.6	9.7 ± 4.2	.464
Time from symptoms to diagnosis (days)	11 (4.3 – 27)	18 (4 – 51.5)	8 (3 – 15)	16 (6.8 – 30)	<.001
Time from antibiotics to diagnosis (days)	2 (0 – 5)	1,5 (0 – 3)	2 (0 – 6)	2 (0 – 4.3)	.868
Time from antibiotics to surgery (days)	7 (3 – 15)	9,5 (5 – 19.5)	7 (3 – 14.3)	7 (3 – 14.3)	.943
Time from diagnosis to surgery (days)	4 (1 – 10)	7 (2 – 16.5)	4 (2 – 10.5)	3 (1 – 8)	.036
Indications for surgery					
Heart failure	192 (68.8%)	15 (68.2%)	53 (45.3%)	124 (88.6%)	<.001
Embolism	112 (40.7%)	10 (45.5%)	47 (40.2%)	55 (40.4%)	.965
Large vegetation	169 (61.2%)	13 (59.1%)	78 (66.7%)	78 (56.9%)	.112
Persisting infection	28 (10.3%)	3 (13.6%)	8 (6.8%)	17 (12.7%)	.123
Abscess formation	39 (14.1%)	4 (18.2%)	6 (5.1%)	29 (21.0%)	<.001

Dichotomous variables are expressed as number of patients and percentage in parentheses. Continuous normally distributed variables are expressed as mean ± standard deviation. Continuous non-parametrically distributed variables are expressed as median with interquartile range in parenthesis. COPD, chronic pulmonary obstructive disease; EuroSCORE, European system for cardiac operative risk evaluation; LVEF, left ventricular ejection fraction; IHD, ischemic heart disease; NYHA, New York Heart Association classification; PASP, pulmonary artery systolic pressure; peripheral vascular disease.
[a]Surgery started before 8 AM the following morning.

Staphylococcus aureus was more frequent in Group M (47%, n = 55) than in Group A (21%, n = 30; P <.001), Table 13. The median time from symptom onset to surgery in group M was 8 days (IQR 3-15) compared with 16 days (IQR 6.8-30) in group A (P <0.001). However, among the subgroup of patients with S. *aureus* endocarditis the difference did not persist, so this more rapid progression in group M may have been caused by the greater frequency of *S. aureus* in group M. The median time from diagnosis to surgery was 4 days (IQR 2-10.5) in group M compared with 3 days (IQR 1-8) in group A (p= .036).

The most common indication for surgery was heart failure, which was twice as common in Group A (89%) as in Group M (45%, p<0.001), Table 12. Preoperative investigations showed that abscess formation was present in 21% (n=29) of Group A compared with 5% (n=6) of group M (p<0.001).

Table 13 Microbiology

Pathogen	Total (n=279)	Mitral and Aortic Valve (n=22)	Mitral Valve (n=117)	Aortic Valve (n=140)
Staphylococcus aureus	92 (33.0%)	7 (31.8%)	55 (47.0%)	30 (21.4%)
Coagulase-negative Staphylococci	18 (6.5%)	2 (9.1%)	4 (3.4%)	12 (8.6%)
Streptococcus bovis	5 (1.8%)	1 (4.5%)	-	4 (2.9%)
Viridans Streptococci	66 (23.7%)	8 (36.4%)	24 (20.5%)	34 (24.3%)
Streptococcus pneumoniae	7 (2.5%)		1 (0.9%)	6 (4.3%)
Beta-Haemolytic Streptococci	25 (9.0%)	1 (4.5%)	9 (7.7%)	15 (10.7%)
Enterococcus faecalis	25 (9.0%)	3 (13.6%)	6 (5.1%)	16 (11.4%)
HACEK	6 (2.2%)		5 (4.3%)	1 (0.7%)
Other gram-negative bacteria	6 (2.2%)		5 (4.3%)	1 (0.7%)
Other pathogens	8 (2.9%)		3 (2.6%)[a]	5 (3.6%)
Negative culture	20 (7.2%)		5 (4.3%)	15 (10.7%)

[a]1 patient with *Candida albicans.*

HACEK, *Haemophilus species*, *Aggregatibacter aphrophious*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Surgical interventions were performed on the mitral valves of the 139 patients in Group M and Group MA. Mitral repair was attempted in 65 patients and 58 (89.2%) of these were successful. When MV repair was not successful, a mitral valve prosthesis was implanted. Of the 81 patients who underwent mitral valve replacement, 54.3% (n = 44) received a mechanical valve, and 45.7% (n = 37) received a biological valve. Thirteen patients (9%) required annular reconstruction due to paravalvular involvement.

The 162 patients in Group A and Group MA underwent surgery for endocarditis affecting the aortic valve. Aortic valve replacement with a biological valve was performed in 66 patients, and a mechanical valve was used in 60 patients. The remaining 36 patients underwent an aortic root procedure using a homograft (n = 22), a Bentall procedure with a biological (n = 4) or mechanical (n = 7) valve, or a Ross-type procedure (n = 3).

The 90-day mortality was similar among the subgroup of patients who underwent surgery within 48 hours from diagnosis within group M and group A (6% and 7%, respectively, P = 0.8). However, among patients who underwent surgery >48 hours after diagnosis, the 90-day mortality was greater, 15%, in group M than in group A, 6% (P = .04).

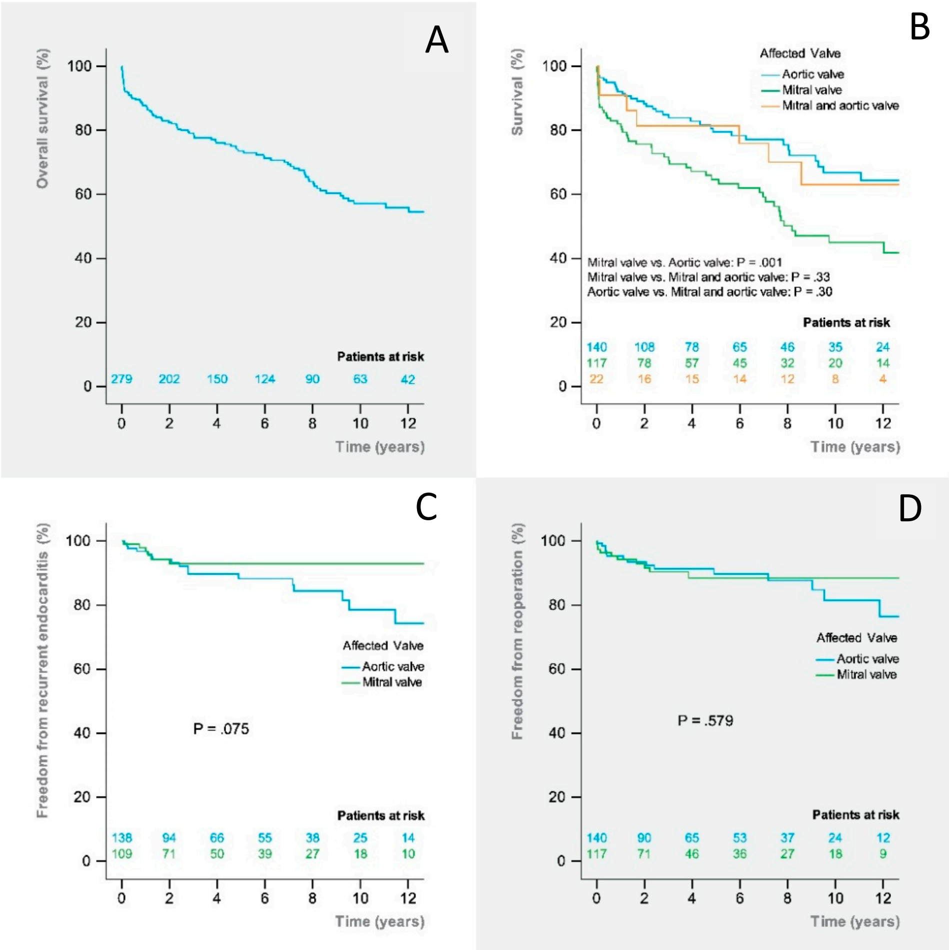

Figure 12: Kaplan-Meier estimates of (A) overall survival following surgery; (B) survival comparing Groups MA, M and A; (C) freedom from recurrent endocarditis comparing Group A and Group M; and (D) freedom from all-cause reoperation comparing Group A and Group M.

The five-year survival in group M was 65±5% compared with 78±4% in group A (log rank, P = .001) (Figure 12). There was no significant difference detected in freedom from recurrent endocarditis or freedom from reoperation when Group A and Group M were compared. Among patients with mitral valve endocarditis (group M and group MA), 5-year survival was 80% in those who underwent mitral valve repair compared with 59% in those who underwent mitral valve replacement (P = 0.01) (Figure 13).

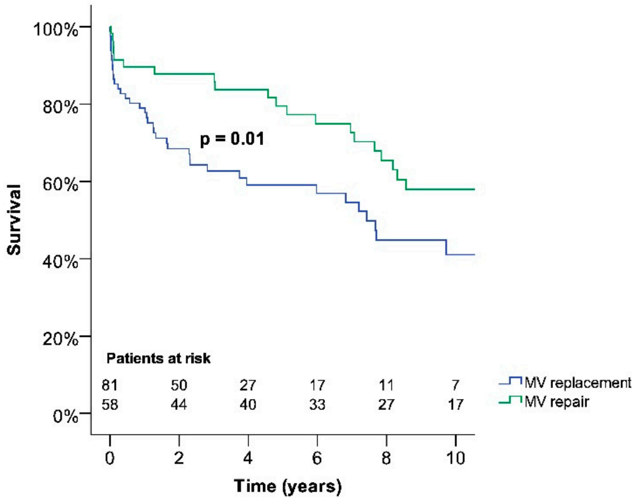

Figure 13: Kaplan-Meier estimates of (A) survival of patients with S. *aureus* endocarditis comparing Group A and Group M and (B) survival of patients with non-*S. aureus* endocarditis comparing Group A and Group M. NVE, native valve endocarditis.

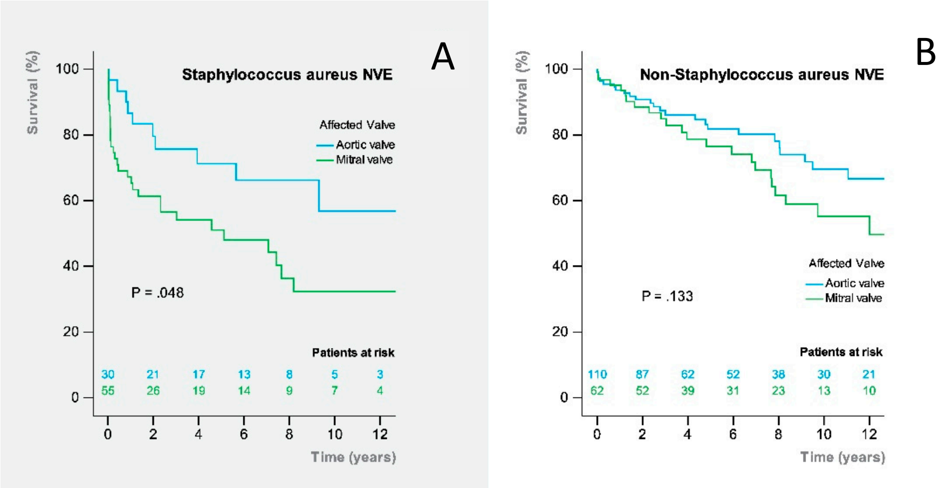

Figure 14: Kaplan-Meier estimates of (A) survival of patients with S. *aureus* endocarditis comparing Group A and Group M and (B) survival of patients with non-*S. aureus* endocarditis comparing Group A and Group M. NVE, native valve endocarditis.

Among patients with *S. aureus* endocarditis, the five-year survival was 71±9% in Group A compared with 51±7% in Group M (p = 0.048) (Figure 14A). In patients with non-*S. aureus* endocarditis, the difference in survival between groups A and M was not statistically significant (Figure 14B). Independent risk factors of long-term survival were mitral valve endocarditis, *S. aureus*-infection, age, diabetes mellitus, and intravenous drug use.

Table 14

Results of univariate and multivariate Cox regression analysis, left sided endocarditis.

	Univariable Cox regression			Multivariable Cox regression		
Risk Factor	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.03	1.01 – 1.04	.001	1.03	1.01 – 1.05	.001
Sex (female)	1.53	1.02 – 2.31	.040	1.18	0.75 – 1.84	.476
Diabetes mellitus	3.07	1.96 – 4.81	<.001	2.74	1.67 – 4.49	<.001
Congestive heart failure	1.04	0.67 – 1.62	.859	1.25	0.74 – 2.11	.399
Preoperative hemodialysis	2.52	1.27 – 5.04	.009	1.94	0.89 – 4.23	.098
Stroke	1.30	0.78 – 2.18	.320	1.11	0.62 – 1.99	.730
Staphylococcus aureus	2.45	1.64 – 3.67	<.001	1.62	1.00 – 2.62	.048
Mitral valve IE	1.98	1.30 – 3.01	.001	2.16	1.27 – 3.66	.004
Intravenous drug use	1.83	0.89 – 3.78	.103	3.73	1.45 – 9.60	.006
Uncontrolled infection	1.53	0.81 – 2.88	.190	1.53	0.81 – 2.88	.190
Surgery within 48 hours of diagnosis	1.11	0.73 – 1.69	.631	0.96	0.61 – 1.53	.871
Abscess (observed intraoperatively)	1.35	0.89 – 2.04	.162	1.40	0.87 – 2.26	.164

CI, confidence interval; HR, hazard ratio; IE, infective endocarditis.

Discussion

This thesis explores the importance of surgical techniques on hemodynamic performance, and the outcome following mitral valve surgery for degenerative disease and infective endocarditis. Infective endocarditis is an infection in the tissues of the heart valves and surrounding structures, which is associated with high early mortality (71, 74). The epidemiology of IE has changed dramatically over the last few decades, as older patients with more comorbidities experience the disease, and that is now frequently caused by aggressive bacteria such as *S. aureus.* Degenerative MR, on the other hand, is usually a chronic condition that can be asymptomatic for many years but can eventually lead to atrial fibrillation, pulmonary hypertension, LV failure, and a shortened life-span (3). If the condition is treated surgically before the development of LV failure and pulmonary hypertension, life-expectancy is restored (6). Reports from almost twenty years ago, showed excellent long-term results following mitral valve repair (15, 93). However, surgical strategies have continued to evolve and more complex lesions are being treated with higher success rates (94). A large prospective international multicenter registry study has showed that over the 35-year study period, surgical strategy has changed significantly (7). During the early era, posterior leaflet prolapses were treated with leaflet resection, while anterior leaflet prolapse was treated with chordal shortening, chordal transfer, or commissural annuloplasty. In the modern era, fewer and more limited resections are performed in the posterior leaflet and artificial chordae have become a standard technique in repairing both leaflets (7).

"Respect rather than resect"

The purpose of any surgical technique in MV repair should be to maximize the valve orifice area and restore physiological valve dynamics. The use of AC is an effective, simple and reproducible means of achieving that goal (25). The rationale behind using AC instead of LR in PML prolapse, is that the technique maximizes the orifice area, does not require reconstruction of the mitral annulus, resection of secondary chordae is unnecessary, and the technique allows the treatment of multiple prolapses (25, 50, 58, 95, 96). The expression "respect rather than resect" has been coined to highlight the essence of the AC technique (50).

At the Department of Cardiothoracic Surgery at Skåne University Hospital in Lund, leaflet resection has currently become a much less frequent repair method, while artificial chordae have become the standard means of repairing both anterior and posterior leaflet prolapse. We felt that it was important to evaluate our experience of this technique and compare the clinical results and outcome of the two techniques in the setting of isolated PML prolapse.

In Study I, we found that MV repair for PML prolapse, with both artificial chordae and leaflet resection, were associated with excellent survival: the AC group had 98 ±2% five-year survival and the LR group 94 ± 2% (p=0.67). The incidence of short-term complications did not differ between the groups. The rate of reoperation was low. At five years, none were reoperated in the AC group and the freedom from reoperation in the LR group was 98 ± 1 %. Using artificial chordae seems to be an effective and safe method of repairing PML prolapse. Other studies comparing AC and LR in the treatment of PML prolapse have also shown comparable one and five-year survival in both groups, congruent to our results (47, 48, 70, 97). The freedom from reoperation was low in both groups as reported in previous studies (47, 48, 70, 97).

The use of AC permits the repair of complex MV pathologies, including multi-segment prolapses, with relatively short aortic cross-clamp times (23). Study I only included patients with PML prolapse. In the AC group 15% had prolapse of two or three segments. The aortic cross-clamp times were significantly lower in the AC group compared with the LR group, which indicates that the technique is not complex and time-consuming. Other centers have reported similar cross-clamp times in the use of AC (22, 47, 48, 58).

The mean ring size in group AC was significantly larger than in group LR. This finding has also been observed in other studies comparing AC and LR in the treatment of PML prolapse (47, 70, 97) and is most likely explained by the fact that annular reconstruction is not required when implanting artificial chordae.

As Seeburger et al. point out, the use of AC has facilitated advances and the adaptation of minimally invasive MV surgery (70). Minimally invasive MV surgery through a right minithoracotomy and the use of either thoracoscopy or robotic assistance is increasingly used in the treatment of degenerative MR, including complex disease (38, 52, 98). A recent propensity-matched analysis of patients that either had median sternotomy or right minithoracotomy with 97 patients in each arm, showed very low operative mortality in both groups and equally durable results (99). In Study I, fourteen patients in the AC group underwent MV repair through a right minithoracotomy. Since then, minimally invasive mitral surgery with robotic assistance has been introduced at our department.

Hemodynamics following mitral valve repair

Study II was designed to compare the hemodynamics of patients that have undergone MV repair with either AC or LR. The left ventricular function was well preserved and similar in both groups. The mean mitral gradient at rest was the same in both groups (AC, 3.0 ± 1.3 mm Hg; LR 3.0 ± 1.0 mm Hg; p = 0.90). Seeburger et al. reported that, following surgery, AC was associated with lower resting mean MV pressure gradients (3.1 ± 1.7) compared with LR (2.7 ± 1.7, p = 0.03). Similar results were found in a recent study by Chua et al. (97). This small difference is unlikely to have any clinical importance. Furthermore, in the prospective randomized trial by Falk et al. (48), the MV gradients were even lower in both groups with no significant difference between the treatment groups (AC, 2.3 ± 1.0; LR, 2.6 ± 1.4) (48). Murashita et al. have recently published a study on hemodynamic outcomes of 1147 patients that underwent MV repair for degenerative MR (100). The majority of the patients were treated with triangular resection and a posterior band annuloplasty. The mean mitral valve gradient was 3.1 ± 1.4 mm Hg in the operating room and 3.5 ± 1.6mmHg at the last follow-up (100). In summary, MV repair with both AC and LR result in low resting MV gradients after surgery.

Both groups had high results on the Duke Activity Scale Index, indicating acceptable exercise capacity. The maximum heart rate was around 130 beats per minute in both groups, indicating that the patients exerted themselves adequately. The mean exercise capacity in both groups exceeded 130 Watts with no statistical difference detected. Likewise, the maximum pulse and the exercise duration was similar in both groups. The mean MV gradients increased significantly in each group but a significant difference was not detected between the groups at peak exercise (AC 8.7 ± 3.7 mmHg; LR, 11.3 ± 8.7; p = 0.21). According to Garbi et al., gradient thresholds for severe mitral stenosis on exertion are established as >15 mm Hg (64), which exceeds the MV gradients measured at peak exercise in both groups in Study II. Only one outlier in the AC group and none in the LR group had an MV gradient >15 mm Hg. Thus, our findings suggest that neither method of MV repair for PML prolapse is associated with MV stenosis.

Chan et al. performed exercise echocardiography on patients following MV repair for degenerative disease and divided the cohort into two groups according to the mean resting MV gradient (68). The group that had MV gradients of >3 mm Hg, also had higher MV gradients at peak exercise, and higher pulmonary artery systolic pressures at rest and at peak exercise compared with those who had a resting MV gradient that was ≤3 mm Hg (68). The group with high resting MV gradients had a maximum exercise capacity of 101 ± 40 Watts compared with 122 ± 51 Watts in the group with low resting MV gradients, which both compare unfavorably to the 130 Watts that both groups in Study II exhibited.

A total of five patients had SAM at rest and during exercise. SAM was more common in the AC group compared with the LR group, although a significant difference was not detected. SAM has been reported as a cause of late MV repair failure (101). In Study II, all patients who had SAM demonstrated low LVOT gradients at rest and during exercise with no hemodynamically significant MR. These finding suggests that SAM without elevated LVOT gradients at rest, are unlikely to cause LVOT obstruction during exercise. In a recent study, 34 patients that had SAM immediately postoperatively, but were successfully treated with beta-blockers and fluid hydration, underwent symptom-limited exercise echocardiography (69). Two of these patients had SAM at rest with LVOT obstruction that increased with exercise. The remaining 32 patients had no SAM nor LVOT obstruction (69). It follows that patients who have had MV repair, and exhibit SAM movement without LVOT obstruction at rest, are unlikely to suffer hemodynamic consequences of SAM during exercise. On the other hand, those who have SAM and a raised LVOT gradient at rest, are likely to experience increased LVOT obstruction during exercise.

The main finding in Study III is that patients who underwent MV repair due to PML prolapse had significantly worse RV function, as measured with the longitudinal indices of TAPSE and S', than healthy controls at long-term follow-up. One-third of the study patients had RV systolic dysfunction as indicated by TAPSE. Hyllén et al. showed that RV dysfunction was detected in 61% six months after MV surgery for degenerative disease (62). TAPSE has been shown to related to both early and late death (63). However, poor postoperative RV function seems to be a surrogate for poor preoperative condition (63). In Study III, preoperative LV dilatation (LVIDs ≥40 mm) was associated with lower TAPSE at follow-up. Results from a multicenter registry study showed that, in MR due to flail leaflets, LVESD ≥ 40 mm is independently associated with increased mortality after mitral surgery (102).

During exercise, there was an increase in RV function as measured by TAPSE and S'. However, the increase was proportionally greater in the healthy controls compared with the study group. Despite having markedly lower than expected measures of longitudinal right ventricular function, the patients in the study group had good exercise capacity with a maximum workload of 133 ± 41watts. Although the exercise capacity of the study group was slightly lower than the exercise capacity of the control group, the between-group difference was not statistically different. Poor RV function was not associated with impaired maximum exercise capacity.

These findings may reflect an underestimation of RV function in patients that have undergone pericardiotomy. A few studies have supported this notion. Raina et al. showed that after cardiac surgery, there is a loss of longitudinal shortening of the RV and a relative increase in transverse shortening despite normal global RV function (103). A study on 99 patients that underwent coronary artery bypass grafting (CABG), showed that TAPSE was significantly reduced three months after surgery, despite improved exercise capacity (104). The authors suggested that, following CABG, TAPSE probably lacks clinical significance. Finally, Tamborini et al. examined 40 patients with TAPSE and S' on one hand, and three-dimensional right ventricular ejection fraction (RVEF) on the other hand (105). The results showed that, despite significantly reduced TAPSE and S' after surgery, RVEF remained constant (105). New accessible methods of assessing RV function following cardiac surgery are needed.

Mitral valve infective endocarditis

Infective endocarditis is a heterogenous disease that is caused by different pathogens, it can result in various complications and cannot be treated by any single specialty. Reducing mortality requires multimodal approach, including improvements in how often and in what way cultures are taken, the use of antibiotic therapy in accordance to international guidelines, improved imaging diagnostics, timely surgery when indicated, and better follow-up. Major causes of death in IE are heart failure, stroke, sepsis and multiorgan failure (72). In addition, a significant proportion of mortality in IE is because of sudden death (72). Preventing these deaths requires an acceleration of the diagnosis process and risk stratification, prompt antibiotic treatment, and transfer of high -risk patients to tertiary-care facilities (72).

Numerous predictors of survival have been identified in previous studies, including clinical, biological, and echocardiographic factors. The results presented in this thesis show that simple clinical signs that can be detected bedside, such as clinical stroke, persisting fever, and congestive heart failure, are associated with poor long-term outcome. These findings are in line with previous studies on left-sided endocarditis demonstrating that the clinical signs of abnormal mental status and congestive heart failure are associated with 6-month mortality (106). Several studies have showed that stroke is a predictor of poor survival in left sided IE (80, 107, 108). In addition to the clinical signs of stroke, uncontrolled infection, and congestive heart failure; *S. aureus*, renal failure requiring dialysis, diabetes mellitus and age were identified as independent predictors of long-term mortality. These findings are consistent with previous studies (74, 109-111).

In Study IV, the early mortality in patients with mitral valve IE was very high. Sheikh et al. published a study on 104 patients operated for isolated MV endocarditis over a period of 27 years (87) with an in-hospital mortality of 8.7% and a five-year survival was 73 ± 5%. These are similar findings to those of Study IV. The short-term mortality was even more pronounced in the subgroup of *S. aureus* mitral valve IE. Interestingly, the unpublished results show that the proportion of patients with *S. aureus* was much higher in the mitral valve IE group compared with the aortic valve IE group.

The unpublished results in this thesis show that, despite a shorter time from symptom onset to diagnosis and a higher proportion of *S. aureus* in patients with mitral IE compared with aortic valve IE, patients with mitral valve IE had a longer time interval from diagnosis to surgery than did those with aortic valve IE. It is not possible to draw any conclusions as to why this is the case, considering the retrospective nature of the data. However, most surgeons feel comfortable doing aortic valve replacement while fewer surgeons perform MV surgery on a daily basis. It is important that this does not delay surgery. In the case of complicated IE were urgent surgery is warranted, surgical intervention may nevertheless be delayed. A study by Delahaye et al. showed that 8/19 patients that had severe heart failure or persisting fever either had delayed surgery or no surgery at all (112).

The implementation of a formalized multidisciplinary Endocarditis Team is an important improvement in the diagnosis and treatment of patients with IE (77). In Italy, the implementation of such a team was shown to be associated with a dramatic reduction in in-hospital (28% vs. 13%; p = 0.02) and 3-year (34% vs. 16%; p = 0.0007) mortality (113). In France, the 1-year mortality of patients with IE was reduced from 18.5% to 8.2% (p = 0.008) with the introduction of a multidisciplinary team (114). A multidisciplinary Endocarditis Team was formed at Skåne University Hospital at the end of 2016 and since January 1st 2017, patients in Skåne county with IE are referred to the multidisciplinary team at Skåne University Hospital in Lund for evaluation.

Both Study IV and the unpublished results compare MV repair to replacement in the setting of mitral valve IE. Study IV included 100 patients with isolated mitral valve endocarditis, while the unpublished results included 17 additional patients with isolated mitral valve IE operated in recent history as well as 22 patients with aortic and mitral valve endocarditis. In Study IV, there was a trend towards better survival among patients operated with MV repair compared with MV replacement. However, Figure 13 in the unpublished results, shows a significantly better long-term survival among the 58 patients that had MV repair over the 81 patients that had MV replacement. This is a crude analysis and should be interpreted with caution. According to a meta-analysis by Feringa et al., MV repair was associated with favorable in-hospital and long-term mortality, the rate of reoperation, and cerebrovascular events, compared with MV replacement (91). In addition, meta-regression analysis demonstrated that MV repair was associated with better outcome than MV replacement.

Limitations

The limitations of Study I and Study IV in this thesis are that they are retrospective observational studies. The inclusion periods were long which may have led to treatment biases that can evolve over the years. In studies I-III, the median follow-up time of patients with artificial chordae was shorter than for patients who had leaflet resection. Study II and III included a prospective cohort of patients who were selected from a retrospective cohort of patients operated for PML degenerative MV disease at our clinic. Inclusion biases may have occurred since a relatively small proportion of patients were included in the study from the original cohort. The studies may have been underpowered to show differences in the occurrence of rare events. Study III included a control group of patients that had not undergone sternotomy and pericardiotomy.

However, having a control group that has undergone sternotomy may introduce bias from the surgical interventions the group has undergone. Furthermore, only longitudinal indices of RV function were used (TAPSE and S'). These indices of RV function are not validated for evaluation of RV function during exercise. The echocardiographic data for several variables, especially during peak exercise, was not complete due to the image quality.

Conclusions

Study I

Artificial chordae are non-inferior to leaflet resection for PML prolapse. Both techniques have comparable early and mid-term postoperative outcomes with low mortality, and a low incidence of reoperation and recurrent mitral regurgitation.

Study II

The data indicate that repair of PML prolapse with either artificial chordae or leaflet resection techniques is followed by low MV gradients both at rest and during peak exercise and that no with no differences were detected between the study groups. Both repair methods appear to be associated with good exercise capacity and favorable long-term hemodynamics.

Study III

Patients that have undergone MV repair due to PML prolapse have significantly reduced RV function compared with healthy controls at long-term follow-up as measured by TAPSE and S'. TAPSE was similar in both types of repair at rest but a slightly higher TAPSE was observed in the AC group than in the LR group at peak exercise. Preoperative LV dilatation was associated with lower TAPSE at follow-up. Although the impaired RV function did not correlate to poorer exercise capacity, we believe that early surgical referral for MV repair is important to preserve long-term RV function and clinical outcome.

Study IV

Survival after surgery for native mitral valve IE was independently influenced by the presence of preoperative embolic stroke, congestive heart failure or uncontrolled bacteremia alone or in combination in addition to *S. aureus* as the causative pathogen. Therefore, delaying surgical treatment may increase the probability and severity of preoperative complications and consequently postoperative mortality. The unpublished results related to Study IV show the time interval from diagnosis to surgery is greater in patients with mitral valve IE compared with aortic valve IE. When patients operated after 48 hours from diagnosis was compared according to the valve affected by IE, patients with mitral valve IE had significantly higher 90-day mortality compared with those with aortic valve IE.

Future perspectives

Artificial chordae are associated with excellent short-term results and long-term durability. There are many different techniques in placing AC and it is uncertain which of these techniques are most effective and durable. In our center, we place comparatively few pairs of AC and we do not have a quantitative method of determining AC length. A study comparing different AC techniques would be valuable and might increase the overall success rate of AC in MV repair for degenerative disease.

Isolated MV repair is increasingly being performed with minimally invasive techniques using a right minithoracotomy instead of full sternotomy. Minimally invasive MV repair is associated with fewer blood transfusions, less pain, shorter intensive care unit and hospital stay, lower risk of surgical site infections and improved cosmetics compared with the median sternotomy approach (99). An additional motivating factor in adopting a minimally invasive approach would be if it resulted in better hemodynamics and exercise capacity. Therefore, an attractive study would be to compare MV repair through sternotomy with right minithoracotomy using exercise echocardiography.

The present thesis showed that RV function at long-term follow-up after MV surgery for degenerative disease, is impaired using longitudinal indices. Recent data suggests that longitudinal indices are poor indicators of RV function as the longitudinal contraction pattern changes with pericardiotomy. Comparing patients that undergo MV repair through median sternotomy with patients that undergo right minithoracotomy, where the pericardial incision is more limited, might show superior RV function with the latter approach. Additionally, a study on RV function following MV repair using other indices, such as FAC and three-dimensional RV ejection fraction might lead to different conclusions regarding long-term RV function following MV repair.

Infective endocarditis is a very heterogenous disease and due to its nature, interventional studies on patients with IE are difficult to carry out. The present thesis only presented data on patients with native valve endocarditis that underwent surgery. More data is needed on the treatment of IE in Sweden, including the proportion that undergo surgery and the timing of surgery. An effective way to study IE, is by using large registries and pooling data from different centers. A nation-wide study with data from the Swedish Cardiac Surgery Registry and the Swedish Endocarditis Registry has gotten ethical approval by the Regional Ethical Review Board in Lund (Reference number 2016/601) is underway.

The results presented in this thesis about IE show that the subgroup of patients with *S. aureus* mitral valve endocarditis have very high early mortality rates. Predictors influencing short-term and long-term mortality in *S. aureus* MV endocarditis need to be identified so that one may have a better chance of reducing the number of early deaths.

The appropriate timing of surgery in different settings of infective endocarditis is unclear. More prospective studies on urgent surgery vs standard therapy are needed.

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