Aus der Klinik für Herz-, Thorax- und Gefäßchirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

# Minimally Invasive Surgery versus Median Sternotomy in Native Mitral Valve Endocarditis: A Propensity Score Matched Comparison

Minimalinvasive Chirurgie versus mediane Sternotomie
für native Mitralklappenendokarditis:
Ein Propensity Score Matched Vergleich

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 3. März, 2023

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# Abbreviations and Acronyms

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| ADP | Adenosine diphosphate |
| AML | Anterior mitral leaflet |
| ARB | Angiotensin-receptor blocker |
| AV | Aortic valve |
| AVR | Aortic valve replacement |
| BMI | Body mass index |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CBA | Catheterization-based assist device |
| CK | Creatine kinase |
| CK-MB | Creatine kinase muscle-brain type |
| CPB | Cardiopulmonary bypass |
| CTA | Computed tomography angiography |
| CVA | Cerebrovascular accident |
| CVD | Cerebrovascular disease |
| DHZB | *Deutsches Herzzentrum Berlin*, German Heart Center Berlin |
| DRG | Diagnosis-related group |
| ECG | Electrocardiogram |
| ECMO | Extracorporeal membrane oxygenation |
| EF | Ejection fraction |
| ESC | European Society of Cardiology |
| EuroSCORE | European System for Cardiac Operative Risk Evaluation |
| FFP | Fresh frozen plasma |
| Fr | French |
| HACEK | Haemophilus, aggregatibacter, cardiobacterium hominis, eikenella corrodens, kingella. Refers to a group of gram-negative bacterial endocarditis pathogens. |
| IABP | Intra-aortic balloon pump |
| ICD | Implantable cardioverter defibrillator |
| ICU | Intensive care unit |
| IE | Infective Endocarditis |
| LAD | Left anterior descending |

| | |
|---|---|
| LVOT | Left ventricular outflow tract |
| MIMVS | Minimally invasive mitral valve surgery |
| MIS | Minimally invasive surgery |
| MS | Median sternotomy |
| MV | Mitral valve |
| NVE | Native valve endocarditis |
| NYHA | New York Heart Association |
| PAD | Peripheral artery disease |
| PCI | Percutaneous coronary intervention |
| PML | Posterior mitral leaflet |
| PROM | Predicted risk of mortality |
| PVE | Prosthetic valve endocarditis |
| RBC | Red blood cells |
| REDCap2 | Research Electronic Date Capture 2 |
| STS | Society of Thoracic Surgeons |
| TIA | Transient ischemic attack |
| TMVr | Transcatheter mitral valve repair |
| TMVR | Transcatheter mitral valve replacement |
| TRALI | Transfusion-related acute lung injury |
| TTE | Transesophageal echocardiogram, echocardiography |
| TTE | Transthoracic echocardiogram, echocardiography |
| VIS | Vasoactive-inotropic score |

# Preface

The results of the present work were published in:
Kofler M, Van Praet KM, Schambach J, Akansel S, Sündermann S, Schönrath F, Jacobs S, Falk V, Kempfert J. Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison. European Journal Cardio-Thoracic Surgery. 2021 August 18

# Abstract English

**BACKGROUND**. Minimally invasive mitral valve surgery (MIMVS) via a right anterolateral thoracotomy is an established alternative to the conventional median sternotomy (MS), providing clinical benefits because it is less invasive. However, there is limited evidence regarding the role of MIMVS in left-sided infective endocarditis, which often leads to complex pathology of the mitral valve. Some centers still consider endocarditis a relative contraindication for MIMVS. Patients with native mitral valve endocarditis are often critically ill with high rates of morbidity and mortality following surgery.

**METHODS**. Operative and postoperative outcomes of two propensity score matched patient groups undergoing surgical treatment for native mitral valve infective endocarditis at *Deutsches Herzzentrum Berlin* were retrospectively compared. 154 patients were included, 112 patients received a MS and 42 received MIMVS.

**RESULTS**. Propensity score matching resulted in 39 matched pairs with balanced preoperative characteristics. There were no significant differences in cardiopulmonary bypass- and aortic cross-clamp time, however overall operative time was shorter for the MIMVS group (median MIMVS 138 minutes, MS 187 minutes, $p=0.005$). MIMVS patients needed less red blood cell transfusions (median MIMVS 1 unit, MS 4 units, $p<0.001$) and less fresh frozen plasma transfusions (median MIMVS 0 units, MS 1 unit, $p=0.001$), no significant difference was found in platelet transfusions. First reported postoperative creatine kinase was similar, though postoperative creatine kinase-muscle brain type was higher for MIMVS (MIMVS 74.94 units per liter, MS 88.85 units per liter, $p=0.036$). There was no difference in revisions for bleeding ($p>0.999$). Ventilation time was reduced in the MIMVS group (median MIMVS 708 minutes, MS 1440 minutes, $p=0.024$) and reintubation rates were lower for MIMVS (MIMVS 5.1%, MS 25.6%, $p=0.021$). Intensive care unit stays were comparable ($p=0.061$). Postoperative Vasoactive Inotrope Scores, inotrope exposure times, renal complication rates, multi organ failure, and mechanical support rates were similar among both groups. There was no significant difference in 30-day mortality and 1-year mortality. Overall survival was similar for both groups ($p=0.970$) and reoperation rates were lower for MIMVS group ($p=0.019$).

**CONCLUSION**. This study shows that MIMVS for native valve infective endocarditis provides clinical benefits when compared to MS. These included shorter ventilation times, lower rates of transfusion of red blood cell units and fresh frozen plasma units, and less reoperations for patients treated with MIMVS. This study shows that minimally invasive mitral

valve surgery is a safe alternative for surgical treatment of native mitral valve infective endocarditis compared to the conventional sternotomy approach.

# Abstract German

**HINTERGRUND**. Minimalinvasive Mitralklappenchirurgie (MIMVS) über einen rechte anterolaterale Thorakotomie ist eine etablierte Alternative zur konventionellen medianen Sternotomie (MS), welche aufgrund geringerer Invasivität klinische Vorteile bietet. Die Rolle von MIMVS bei linksseitiger infektiöser Endokarditis ist jedoch noch nicht ausreichend geklärt. Endokarditis kann zu komplexen Pathologien der Mitralklappe führen. Daher betrachten manche Zentren infektiöse Endokarditis noch als Kontraindikation für MIMVS. Patienten mit nativer Mitralklappenendokarditis sind oftmals in kritischem Zustand und haben hohe Morbiditäts- und Mortalitätraten nach operativer Versorgung.

**METHODEN**. Operative und postoperative Behandlungsergebnisse von zwei Propensity Score Matched PatientInnengruppen die für native Mitralklappenendokarditis am *Deutschen Herzzentrum Berlin* operativ versorgt wurden wurden retrospektiv verglichen. 154 PatientInnen wurden eingeschlossen, davon erhielten 112 eine MS und 42 MIMVS.

**ERGEBNISSE**. Nach Propensity Score Matching wurden 39 PatientInnenpaare mit balancierten präoperativen Charakteristika identifiziert. Es gab keine signifikanten Unterschiede in kardiopulmonaler Bypass- und Aortenklemmzeit, jedoch waren Gesamtoperationszeiten für die MIMVS Gruppe kürzer (Median MIMVS 138 Minuten, MS 187 Minuten, p=0.005). MIMVS Patienten brauchten weniger Erythrozytenkonzentrate (Median MIMVS 1 Einheit, MS 4 Einheiten, p<0.001) und weniger frisch gefrorene Plasma Transfusionen (median MIMVS 0 Einheiten, MS 1 Einheit, p=0.001), es gab keinen signifikanten Unterschied in Thrombozytenkonzentraten. Es gab keinen Unterschied in der ersten postoperativen Creatinkinase, jedoch war die erste postoperative Creatinkinase-Muscle Brain Typ für MIMVS höher (MIMVS 74.94 Einheiten pro Liter, MS 88.85 Einheiten pro Liter, p=0.036). Es gab keinen Unterschied in Revisionen für Blutungen (p>0.999). Für MIMVS waren Ventilationszeit kürzer (Median MIMVS 708 Minuten, MS 1440 Minuten, p=0.002) und Reintubationsraten geringer (MIMVS 5.1%, MS 25.6%, p=0.012). Der Aufenthalt auf Intensivstation war für beide Gruppen ähnlich (p=0.061). Postoperative Vasoactive-Inotrope Scores, Inotropikatherapiedauer, renale Komplikationen, Multiorganversagen und mechanische Unterstützungsraten waren in beiden Gruppen ähnlich. Es gab keinen signifikanten Unterschied in 30-Tage-Mortalität und 1-Jahres-Sterblichkeit. Gesamtüberleben war für beide Gruppen ähnlich (p=0.970) und die Reoperationsrate für MIMVS geringer (p=0.019).

**FAZIT**. Diese Studie zeigt, dass MIMVS für native Mitralklappenendokarditis klinische Vorteile gegenüber MS bietet. In der postoperativen Behandlung waren dies vor allem kürzere Ventilationszeit, geringere Raten an Erythrozytenkonzentrattransfusionen und frisch gefrorene Plasma Transfusionen sowie weniger Reoperationen für MIMVS Patienten. Dies zeigt, dass MIMVS eine sichere Behandlungsalternative für native Mitralklappenendokarditis ist im Vergleich zur konventionellen MS.

# 1. Introduction

Infective Endocarditis (IE) is an infection of the endocardium affecting the valves, endocardial surface, or intracardiac devices like pacemakers (1). Despite many advances in modern medicine, left-sided IE in particular is still associated with a high mortality of 20-30% (2). This condition bears the worst short-term outcome of all cardiovascular diseases (2). Management of IE is complex, requiring the long-term use of antibiotics. Around half of these patients eventually need surgical treatment (3). The objective in surgery is to remove vegetations, clear abscesses, repair or replace damaged valves, and restore cardiac function (3).

The following dissertation focuses on native mitral valve (MV) IE. Traditionally, a conventional median sternotomy (MS) is used for surgical access of the MV (4). Minimally invasive mitral valve surgery (MIMVS) began being developed in the 1990s (5). In 1998, the first MIMVS with video-assisted visualization was performed (5). The following years brought further technological improvements and the accumulation of expertise in the surgical technique.

At the German Heart Center Berlin (*Deutsches Herzzentrum Berlin*, DHZB), the first minimally invasive surgery (MIS) for the MV was performed on October 8, 2014. Since then, surgeons at the DHZB have performed 1,106 MIMVS as of December 31, 2019.

Although MIMVS has been successfully implemented for many years, its role in the treatment of IE is not yet well established (4). Some centers still consider IE a relative contraindication for MIS (6). However, the reported advantages of MIS like reduced transfusions, postoperative atrial fibrillation and time to recovery are a compelling reason to extend its indications to IE, especially because these patients have high morbidity and mortality rates to begin with (6). Surgeons at the DHZB have been performing MIS for MV IE since January 12, 2015.

The following dissertation compares MIMVS versus conventional MS surgery for IE of the native MV. Propensity score matching was used to increase the comparability of both groups (MIMVS vs. MS).

## 1.1. Infective Endocarditis

### 1.1.1. Epidemiology

Infective endocarditis has a prevalence of 11.6 per 100,000 citizens in Germany, making it a rare disease (7,8). However, in Germany the prevalence is rising between 2-10% each year while in-hospital mortality remains steady at around 17% (7). Furthermore, despite the advances in diagnosis, therapy, and surgical treatment during the last decades, mortality has not significantly changed within the last four decades (9). This stands in contrast to reductions in the mortality of other cardiovascular diseases like myocardial infarction thanks to advancements in modern medicine (10).

These epidemiological developments may be explained by several trends, the most evident being the aging population both in Germany and worldwide (11). The increase in healthcare-associated endocarditis cases also plays a significant role (3). Intravascular devices, catheters, and surgical wounds are examples of entry ports and breeding grounds for pathogens in healthcare-associated endocarditis (3). These medical causes have also resulted in a change of the bacterial spectrum, shifting towards more staphylococcus aureus infections (3). Furthermore, cases of rheumatoid endocarditis which tend to affect younger adults have decreased, in turn increasing the proportion of older patients (3). Naturally, these developments apply to highly developed countries (11). Less developed countries still see more younger patients, who may have rheumatic or uncorrected congenital heart disease, and more culture-negative endocarditis (12).

### 1.1.2. Etiology and Pathophysiology

Healthy valvular endothelium is typically not able to be colonized by pathogens (11). In order for IE to occur, several predisposing factors must come together (11). First, the surface of the cardiac valve must be altered so that bacteria or other pathogens are capable of attaching and colonizing (11). This endothelial damage can be caused by turbulent blood flow due to preexisting valve damage or after rheumatic endocarditis, mechanical damage by electrodes or catheters, or repeated solid particle injection during intravenous drug use (11). The damage enables the growth of fibrin-plated deposits that overlie damaged interstitial edema, first described by Gross and Friedberg as “nonbacterial thrombotic endocarditis” (13).

The next predisposing factor is bacteremia with an organism that can attach to and colonize valve tissue (11). Different organisms have different mechanisms of attachment; some may bind to the nonbacterial thrombotic endocarditis while others bind directly to endothelial cells (11). Bacteremia with organisms not apt for attachment typically does not lead to endocarditis, explaining why transient bacteremia during activities like teeth brushing and dental procedures is no longer considered a risk factor for IE (11,14). Once the organism begins colonization, it creates the vegetation by burying itself in fibrin, platelets and other serum molecules, forming a solid protective matrix (11). The growth of these vegetations, thereby damaging and destroying valves, as well as the formation of abscesses, are what lead to valvular insufficiency and even cardiac dysfunction.

Valvular surgery alters the endothelial surface, can cause turbulent flow and provides another possible surface for bacterial colonization. This explains why previous valve repair or replacement is considered a risk factor for IE (15).

### 1.1.3. Clinical Presentation

Patients with IE typically present with signs of chronic inflammation, rapid worsening of valvular dysfunction and/or symptoms caused by embolic events (16). Common organs to be affected by embolization are the brain, spleen, lung, kidney, and skin (17). Valvular dysfunction may lead to early or progressing congestive heart failure, presenting as exertion or rest dyspnea or pulmonary edema (16,18). Signs of chronic inflammation include B symptoms, anemia, leukocytosis, and thrombocytosis (16). They may also present with fever of unknown origin, or rarely immunologic phenomena like Osler's nodes or Janeway lesions (2).

The first sign of IE is usually a positive blood culture, though many times endocarditis may be blood culture negative (16). Infective endocarditis is classified based on its acuity into acute, subacute or chronic, and based on the affected valve into native (NVE) or prosthetic valve endocarditis (PVE) (16). This study examines only cases of acute or subacute NVE.

### 1.1.4. Diagnosis

As IE presents in many different and unspecific ways, it can be hard to diagnose. Historically, the most important diagnostic tools were Osler's criteria, the Beth Israel criteria and the Duke criteria (19). In 2000, the Duke criteria were revised and published as modified

Duke criteria (20). These modified Duke criteria are generally used today and recommended in the current guidelines for the diagnosis of IE (14).

The modified Duke criteria use clinical, echocardiographic and biological findings to determine whether a patient has 'definite IE', 'possible IE' or 'rejected IE' (14). A clinician allocates a patient's findings to major and minor criteria and makes the diagnosis (14). Major criteria regard blood cultures and imaging findings, while minor criteria evaluate predisposing factors, fever, vascular phenomena, immunological phenomena and more indecisive microbiological evidence (14). The major and minor criteria as well as the diagnostic conclusions are shown in **Tables 1 and 2** below.

**Table 1**: Definition of infective endocarditis according to the modified Duke criteria.

| **Definite IE** |
|---|
| Pathological criteria<br>• Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or<br>• Pathological lesions; vegetation or intracardiac abscess by<br>• histological examination showing active endocarditis<br>Clinical criteria<br>• 2 major criteria; or<br>• 1 major criterion and 3 minor criteria; or<br>• 5 minor criteria |
| **Possible IE** |
| • 1 major criterion and 1 minor criterion; or<br>• 3 minor criteria |
| **Rejected IE** |
| • Firm alternate diagnosis; or<br>• Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or<br>• No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or<br>• Does not meet criteria for possible IE, as above |

*Note.* Adopted from 2015 ESC Guidelines for the management of infective endocarditis (14).

**Table 2**: Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis.

| **Major Criteria** |
|---|
| 1. Blood cultures positive for IE<br>a. Typical microorganisms consistent with IE from 2 separate blood cultures:<br>• Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus; or |

- Community-acquired enterococci, in the absence of a primary focus; or

b. Microorganisms consistent with IE from persistently positive blood cultures:
   - ≥2 positive blood cultures of blood samples drawn >12 h apart; or
   - All of 3 or a majority of ≥4 separate cultures of blood (with and last samples drawn ≥1 h apart); or

c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody antibody titre >1:800

2. Imaging positive for IE
   a. Echocardiogram positive for IE:
      - Vegetation;
      - Abscess, pseudoaneurysm, intracardiac fistula;
      - Valvular perforation or aneurysm;
      - New partial dehiscence of prosthetic valve.
   b. Abnormal activity around the site of prosthetic valve implantation detected by $^{18}$F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.
   c. Definite paravalvular lesions by cardiac CT

**Minor Criteria**

1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.
6. CT

*Note.* Adopted from 2015 ESC Guidelines for the management of infective endocarditis (14).

### 1.1.5. Treatment

The 2015 ESC Guidelines for the management of infective endocarditis outline the optimal treatment algorithm for IE, based on antimicrobial therapy and surgery (14). When a patient is admitted to the hospital and IE is suspected, the first step is to obtain at least two blood cultures (14). In Germany, a blood culture for IE consists of 2 aerobic and 2 anaerobic samples drawn from two different sites, i.e. left and right arm, under sterile conditions (21). The blood should not be drawn from indwelling venous catheters or cannulae as these are not considered sterile (14). After blood cultures are obtained, patients receive a calculated antimicrobial therapy (14). Once a microbe is identified, the antimicrobial therapy is adjusted

according to the microbe's resistances and sensitivities (14). If the blood culture is negative but IE is still suspected, the initial calculated antimicrobial therapy is continued (14).

For NVE, antibiotic therapy should last from two to six weeks while it should last at least six weeks for PVE (14). Bactericidal antibiotic regimens are preferred to bacteriostatic therapy because a patient's immune system is often not sufficiently effective in fighting pathogens at the bradytroph valvular tissue (14). Furthermore, though not resistant, many endocarditic bacteria are tolerant to antibiotics (14). This means that the antibiotic drug inhibits their growth but does not kill them (14). Especially dormant and slow-growing bacteria are therefore hard to eradicate, which is why these microbes require the administration of antibiotics for such a long duration (14).

In any case, the primary focus of IE should be identified before surgery (14). If the focus is extracardiac, i.e. an infected catheter or tooth, it should be eradicated before the end of antibiotic therapy and before surgery (14). However, this may not be feasible in urgent surgical settings (14).

As mentioned above, around half of the patients with IE end up receiving a surgical intervention during the course of treatment (3). There are three major indications for cardiac surgery: heart failure, uncontrolled infection, and prevention of embolism (14). **Table 3** summarizes the European Society of Cardiology (ESC) guidelines indications and timing of surgery in left-sided valve endocarditis. Previous studies have shown that early surgery significantly reduces in-hospital and mid-term mortality as well as risk of embolic events (22,23).

**Table 3**: Indications and timing of surgery in left-sided valve infective endocarditis (native valve endocarditis and prosthetic valve endocarditis).

| Indications for surgery | Timing |
|---|---|
| 1. Heart failure | |
| Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock | Emergency |
| Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance | Urgent |
| 2. Uncontrolled Infection | |
| Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation) | Urgent |

| | |
|---|---|
| Infection caused by fungi or multiresistant organisms | Urgent/ elective |
| Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci | Urgent |
| PVE caused by staphylococci or non-HACEK gram-negative bacteria | Urgent/ elective |
| 3. Prevention of embolism | |
| Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy | Urgent |
| Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk | Urgent |
| Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm) | Urgent |
| Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery | Urgent |

*Note.* Adopted from 2015 ESC Guidelines for the management of infective endocarditis (14).

The timing of surgery is classified by urgency (14). Emergency surgeries are those which must be performed within 24 hours, urgent surgeries within a few days, and elective surgeries after at least 1-2 weeks of antibiotic treatment (14).

## 1.2. Mitral Valve Surgery

The MV is located between the left atrium and left ventricle. During diastole, oxygenated blood moves from the left atrium to the left ventricle (LV), passing through the opened MV. During systole, the MV closes to prevent blood flowing back into the left atrium, forcing the blood out of the left ventricular outflow tract (LVOT) and through the opened aortic valve (AV). Malfunction of the valve can affect the entire heart and circulatory system.

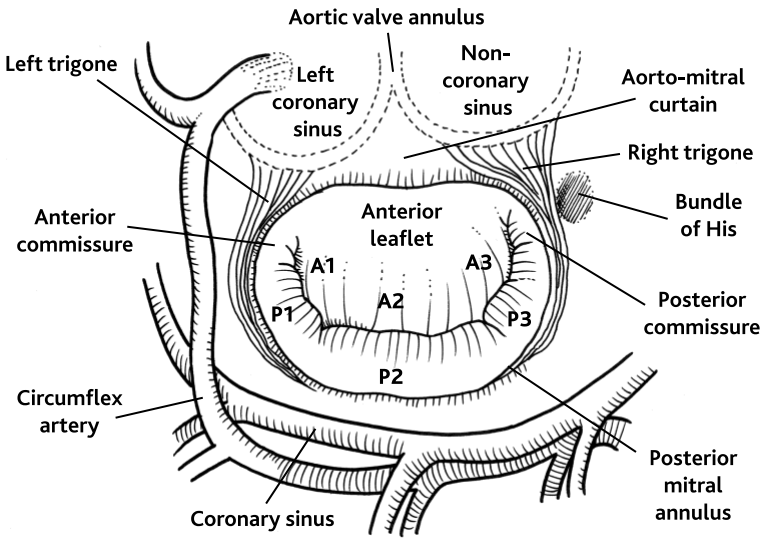
### 1.2.1. Anatomy

The origin of the word mitral is “mitre” in Latin, which means bishop’s or pope’s hat (17). The MV’s structure and leaflets bear resemblance to its front and back parts that rise to the top and form a peak. The valve is bicuspid, consisting of an anterior mitral leaflet (AML) on the aortic side and a posterior mitral leaflet (PML) on the mural side (24). Both leaflets are attached to the ovoid-shaped mitral annulus which consists of fibrous tissue (25). The annulus

is thinnest at the posterior leaflet insertion site, making this area prone to dilation (25). The AML is semicircular, attaching to one third of the annular circumference (25). The quadrangular PML takes up the remaining two thirds (25). The PML usually has three scallops separated by clefts, which allow an anatomical differentiation into an anterolateral (P1), middle (P2), and posteromedial (P3) segment (25). The opposing sections of the AML are termed A1, A2, and A3 respectively (25).

**Figure 1** below shows a view from the left atrium of the MV. Leaflet scallops A1-A3 and P1-P2 are labelled as described above. The aorto-mitral curtain labels the tissue between the AV and the MV. Above the aorto-mitral curtain, the AV annulus is represented, as well as the left coronary sinus and the non-coronary sinus. Towards the left sinus, the left trigone is shown, which is a part of the fibrous cardiac skeleton (26). The right trigone is shown below the non-coronary sinus, respectively. The bundle of His is the point of electrical transfer from the atrium to the ventricles (26). The left main coronary artery begins from the left coronary sinus. After a short segment, the left circumflex artery branches off. It runs next to the coronary sinus along the coronary sulcus towards the back of the heart (24). Here, it is in close proximity to the mitral annulus. The posterior mitral annulus is labelled representatively.

**Figure 1**: Mitral valve, view from the left atrium.




Collagenous leaflet extensions called chordae tendinae connect the leaflets to the papillary muscles in the LV (25). Primary chordae insert at the edge of the leaflets, secondary chordae on the ventricular side of the leaflet, and tertiary chordae connect the leaflet base (25). These insertions are important to prevent prolapse, reduce tension, and increase stability (25).

The chordae of both valves are attached to either the anterolateral or the posteromedial papillary muscle (25). Physiologic myocardial perfusion is important in the function of these muscles, therefore also important for proper valvular function (25).

In clinical examination, the MV projects onto the left anterior chest wall (27). The valve is left parasternal in the fourth intercostal space (27). It is typically best heard on auscultation in the fifth intercostal space in the left medioclavicular line (27).

### 1.2.2. Preoperative Diagnostics

As described by Reilly (28), patients should undergo a comprehensive preoperative evaluation before any major surgical procedure. The goal is to provide an assessment of short- and long-term risks of morbidity and mortality from surgery (28). Furthermore, other health factors that may influence the probability of adverse events from surgery may be addressed (28). The preoperative evaluation can also elicit risk factors and health issues that need treatment regardless of surgery (28).

First, a surgeon should acquire a comprehensive and up-to-date patient history (28). Special attention should be paid to comorbid conditions like diabetes, liver, or renal disease, prior anesthesia or surgeries, cigarette smoking, alcohol use, functional capacity, and medications and allergies (28). In a following physical examination, all body systems should be evaluated (28). Auscultation of the heart serves to discover pathologic heart sounds or murmurs (28). It is also important to pay close attention to pulmonary findings (28). These may be linked to potential heart failure and may impact the surgery or postoperative course (28). The head and neck should be carefully examined for anesthesia planning (28).

The New York Heart Association (NYHA) functional classification plays a significant role in functional, cardiac, and pulmonary evaluation (18). This classification is used to grade the symptomatic syndrome of heart failure, which typically encompasses fatigue, breathlessness, and swollen ankles (18). These clinical findings are caused by structural or functional cardiac abnormalities, leading to reduced cardiac output and higher intracardiac pressures at rest or stress (18). **Table 4** below shows the four NYHA categories used. Higher NYHA scores are associated with a higher risk of ventricular dysfunction and adverse outcomes (29).

**Table 4**: New York Heart Association functional classification based on severity of symptoms and physical activity.

| | |
|---|---|
| Class I | No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations. |
| Class II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations. |
| Class III | Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations. |
| Class IV | Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased. |

*Note.* Adopted from 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (18).

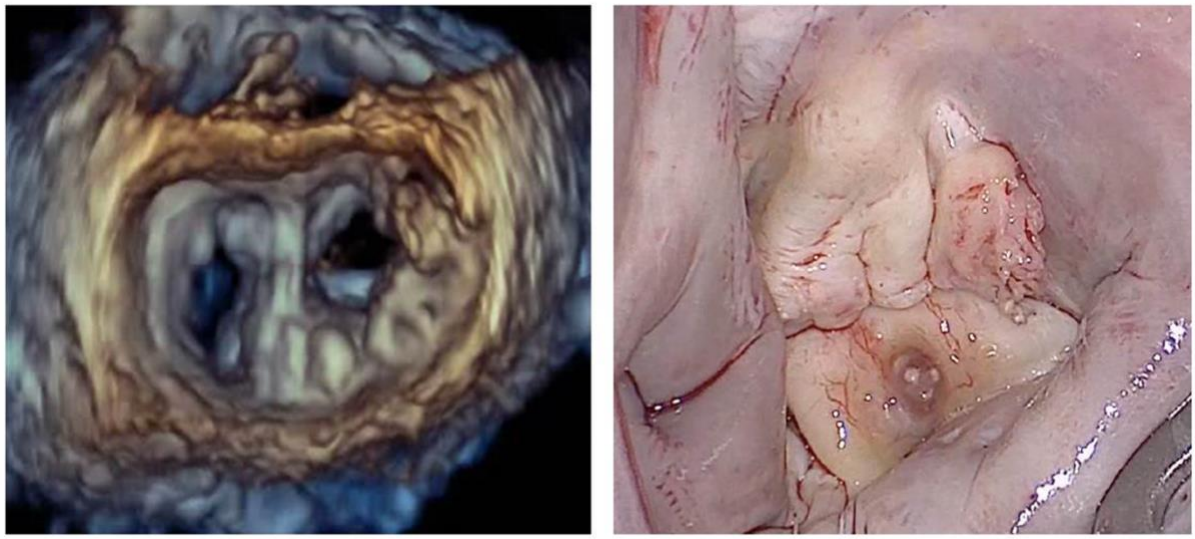
Basic preoperative laboratory studies should be ordered to check electrolytes, renal function, blood count, clotting, and liver function (28).

A preoperative electrocardiogram (ECG) should be acquired to establish a baseline before surgery (29). Since many cardiac patients have abnormalities in their preoperative ECG like atrial fibrillation, this can be helpful for comparing a postoperative ECG (29). Abnormalities in the ECG may require further preoperative diagnostics for a comprehensive understanding of a patient's cardiac disease.

Echocardiography must also be performed to evaluate all cardiac valves, ejection fraction (EF) and ventricular function (29). In IE, echocardiography is used for diagnosis, prognostic assessment, follow-up under antibiotic therapy, documentation of surgical treatment, and to evaluate the risk of embolism (14). A transthoracic (TTE) or transesophageal echocardiogram (TEE) is done.

**Figure 2** on the following page shows TEE findings of MV IE as well as the corresponding intraoperative view. The AML shows a vegetation and the PML shows beginning perforation.

**Figure 2**: Preoperative mid-esophageal 4D mitral valve view TEE depicting MV IE vegetations (left); the surgeon's intraoperative real-time totally endoscopic view of the MV affected by IE via a 3D 30° thoracoscope during MIS (right) (30).



*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

The TEE also plays an important role intraoperatively in assessing valvular function after repair or replacement (14).

Performing a coronary angiography in patients at risk for coronary artery disease may be an important part of cardiac assessment before surgery (28). The procedure helps surgeons understand the distribution of coronary artery disease, the systolic and diastolic function of the heart, pulmonary hypertension, valvular abnormalities and other pathologies like a persisting foramen ovale (31). The 2017 ESC/EACTS guidelines on the management of valvular heart disease recommend coronary angiography for men over the age of 40, post-menopausal women, patients with a history of coronary artery disease, patients with suspected myocardial ischemia, and patients with one or more cardiovascular risk factors (32). For other patients, coronary angiography is not recommended for standard preoperative diagnostics (32). Coronary revascularization by catheter or bypass graft solely to reduce surgical risk is also not recommended (28).

Preoperative computed tomography angiography (CTA) from the upper thoracic aperture to the trochanter minor delivers valuable information for planning MIS procedures (33). The most important anatomic structures to be considered from the CTA are the aorta, iliac arteries,

femoral arteries, and subclavian arteries, as well as the sternum and ribcage(33,34). These images allow the surgeon to ensure there are no vascular or structural contraindications for MIS, like ascending aortic disease, severe MV calcification, or other anatomical abnormalities (33). The preoperative CTA is also used to confirm the correct intercostal spaces to access the MV (34).

### 1.2.3. Surgical Risk Assessment Scores

To assess perioperative and postoperative mortality as well as the risk of complications, several risk scores of differing complexities are used in cardiac surgery, the most widely adopted being the European System for Cardiac Operative Risk Evaluation Score II (EuroScore II) and Society of Thoracic Surgeons (STS) Score (35).

#### *1.2.3.1. Society of Thoracic Surgeons Score*

The STS Score is predominantly used in the United States and is based on an extensive database of cardiac surgery patient outcomes in the United States (36). The risk score is continually adjusted to improve accuracy (37). The last update to the STS Score was published in 2018 and was based on patient data from July 2011 to June 2014 (38). A limitation of this score is that it cannot be used for all cardiac surgeries, but only for isolated coronary artery bypass graft (CABG), isolated AV replacement, isolated MV replacement, isolated MV repair, CABG with AV replacement or CABG with MV repair or replacement (37). The advantage of this scoring system is that it not only includes mortality as the predicted risk of mortality (PROM), but also other important outcomes including renal failure, permanent stroke, prolonged ventilation, deep sternal wound infection, reoperation, morbidity or mortality, short length of stay, and long length of stay (38). Furthermore, this score explicitly takes IE into account as a preoperative patient characteristic which is why it was chosen for the risk assessment in this dissertation (37).

**Table 5** below shows the patient characteristics considered in the STS Score.

**Table 5**: Patient characteristics included in the STS Score.

| | |
|---|---|
| Operation type<br>Age<br>Ejection fraction | Illicit drug use<br>Alcohol consumption (drinks per week)<br>Recent pneumonia |

| | |
|---|---|
| Body mass index<br>Body surface area<br>Sex<br>Renal function (dialysis/creatinine)<br>Hematocrit<br>White blood cell count<br>Platelet count<br>ADP receptor inhibitor usage/timing of discontinuation<br>Hypertension<br>Immunosuppressive therapy within 30 days<br>Steroids within 24 hours<br>Glycoprotein IIb/IIIa inhibitor within 24 hours<br>Inotropes within 48 hours<br>Preoperative IABP<br>Shock/ECMO/CBA<br>PAD<br>Left main disease<br>Proximal LAD<br>Aortic root abscess in AVR/AVR+CABG<br>Mitral stenosis<br>Aortic stenosis<br>Mitral insufficiency<br>Tricuspid insufficiency<br>Aortic insufficiency<br>Arrhythmia and type<br>Endocarditis<br>Chronic lung disease<br>CVD/CVA/TIA<br>Carotid stenosis<br>Previous carotid surgery | Mediastinal radiation<br>Cancer diagnosis within 5 years<br>Diabetes/diabetes control method<br>Number of diseased vessels<br>Myocardial infarction history/timing<br>Cardiac presentation on admission<br>Race/ethnicity<br>Status<br>ACE/ARB inhibitor within 48 hours in nonelective operation<br>Heart failure class and timing<br>Recent smoker/timing<br>Family history of CAD<br>Home oxygen<br>Sleep apnea<br>Liver disease<br>Unresponsive neurologic status<br>Syncope<br>Previous CABG<br>Previous aortic valve procedure<br>Previous mitral valve procedure<br>Previous transcatheter valve replacement/percutaneous valve repair<br>Previous other valve procedure<br>Number of previous cardiovascular surgeries<br>Previous ICD<br>PCI history/timing<br>Previous any other cardiac intervention<br>Payer/insurance type<br>Tricuspid valve repair performed concomitantly<br>Time trend (surgery date) |

*Note.* Adopted from The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2–Statistical Methods and Results (39)

Notably, this score includes some intraoperative characteristics, like the use of an intra-aortic balloon pump (IABP), catheter based assist device, and extracorporeal membrane oxygenation (ECMO) (39). Other scoring systems used were limited to preoperative characteristics. These intraoperative and postoperative factors were equally taken into account in this study as the scores were calculated retrospectively.

#### *1.2.3.2. European System for Cardiac Operative Risk Evaluation Score II*

The European System for Cardiac Operative Risk Evaluation Score II (EuroSCORE) was developed and validated for major cardiac procedures using a CABG as a baseline (40). Other procedures are represented as factors of CABG procedures and include isolated non-CABG procedures, two major procedures, and three or more major procedures (40). Infective endocarditis or other crucial determinants in operative outcome of the disease are not represented in the EuroSCORE II score. This explains why the EuroSCORE II tends to underestimate preoperative risk and have suboptimal calibration in the infective endocarditis population (41). Therefore, it was not included for the patient population in this dissertation.

#### *1.2.3.3. De Feo Score*

Scores specific to IE surgery risk have also been developed, including the De Feo (42), STS-IE (36), PALSUSE (43), RISK-E (35) and Costa-Score (44). There is no clear consensus on which risk score is best for IE, though the 2015 ESC guidelines mention the De Feo and STS-IE score (14). Since the De Feo Score is mentioned in these guidelines, is well-known among these scores and yields a simple point score that works well for matching the populations, it was in this retrospective analysis.

The De Feo Score quantifies the endocarditis-specific preoperative risk profile of patients (42). It was developed and validated for NVE (42), which corresponds with the patient population in examined in this dissertation. The authors De Feo et al. (42) intended for this risk score to be used alongside the EuroSCORE and STS Score to more specifically assess preoperative risk. Consequently, the STS and De Feo Score were calculated and later used for matching in this analysis. The STS Score captures the patient's general preoperative risk of mortality and the De Feo Score takes prognostic clinical determinants specific to IE into account (37,42). Overall, the STS and De Feo Scores are good preoperative discriminants of mortality and morbidity in IE (45).

**Table 6** below shows the preoperative characteristics considered in the De Feo Score. Each of these characteristics is weighted with points ranging from 5 to 13 (42). If a factor is not present, no point is given for that category (42).

**Table 6**: Independent preoperative predictors of mortality (logistic regression analysis) and the deriving De Feo scoring system for mortality prediction in native valve IE.

| Characteristic | Score |
|---|---|
| Age 40-49 years | 5 |
| 50-59 years | 7 |
| 60-69 years | 9 |
| 70-79 years | 11 |
| ≥80 years | 13 |
| Renal failure | 5 |
| NYHA class IV | 9 |
| Ventilatory support | 11 |
| Positivity of latest pre-op. blood culture | 5 |
| Perivalvular involvement | 5 |

*Note.* Adopted from The Need for a Specific Risk Prediction System in Native Valve Infective Endocarditis Surgery (42).

The points for renal failure were given if a patient had preoperative creatinine >2mg/dL (42). Of the NYHA scores, only class IV yielded additional points (42). Ventilatory support was defined as patients who were preoperatively intubated and on mechanical ventilation or who needed ventilatory support with noninvasive measures (42). Positivity of latest preoperative blood culture added points if a patient was not able to reach blood culture negativity through antibiotic treatment before surgery (42). Finally, perivalvular involvement referred to annular abscess or aortocavitary fistulas (42).

The given points from each category are then added up, resulting in a sum of 0 to 48 points (42). The more points reached, the higher the mean predicted mortality (42). The De Feo Score also allocates point ranges to risk group classes. 0-5 points are Class 1, 7-13 points are Class 2, 14-19 points are Class 3, and ≥20 points are Class 4 (42). Class 1 has a mortality of 1 ± 0.7%; Class 2 3.7±1.6%; Class 3 12±5%; Class 4 43%±18% (42).

*1.2.3.4. Vasoactive-Inotropic Score*

Another score calculated for this dissertation is the Vasoactive-Inotropic Score (VIS). The VIS is the most investigated and reported score to quantify pharmaceutical cardiovascular support in intensive care medicine (46). It is calculated by adding the dose in µg/kg/min of the most important inotropes and vasopressors and weighting each medication with a factor from

1 to 10,000 to account for differences in strength (47). This is the formula for the VIS used in this study:

VIS = dopamine dose (µg/kg/min) +
dobutamine dose (µg/kg/min) +
100 x epinephrine dose (µg/kg/min) +
100 x norepinephrine dose (µg/kg/min) +
10,000 x vasopressin dose (U/kg/min) +
10 x milrinone dose (µg/kg/min)

(47)

The VIS makes the administration of pharmaceutical circulatory support quantifiable and comparable. It is used in clinical trials either as a baseline characteristic or an outcome. In this study, the VIS was calculated directly postoperatively to compare circulatory support between the MIMVS and MS group.

### 1.2.4. Principles in Cardiac Surgery

#### *1.2.4.1. Cardiopulmonary Bypass*

Cardiopulmonary bypass (CPB) was a major advancement in cardiac surgery, allowing for the first time for complex intracardiac procedures requiring more time to be performed (48). The first surgery under CPB was performed by John H. Gibbon, Jr., the inventor of the heart-lung machine, in 1953 (48). Since then, major advances in the heart-lung machine like the development of new oxygenators minimizing blood trauma and the introduction of protamine to antagonize heparinization have made the machine much safer, laying the foundation for modern cardiac surgery (49).

Before placing a patient on CPB, up to 300U/kg Heparin are administered in order to reach and maintain an activated clotting time of 400 to 480ms (49). Then, the surgeon attaches inflow and outflow cannulae to the heart-lung machine using tubes (49). The blood enters the machine via the venous reservoir (49). The venous blood is gathered through central cannulation of the vena cava or peripheral femoral cannulation, which is popular in MIS (49). Other inflows can also lead blood from the cardiotomy and from cardiac vents (49). A pump moves the venous blood to the oxygenator, where carbon dioxide is eliminated and oxygen is

added (49). A heat exchanger is integrated into the oxygenator, allowing the patient's body temperature to be closely monitored and controlled intraoperatively (49). Before returning to the patient, the blood passes through an arterial filter and bubble trap. The arterial cannula, placed in the aorta in central cannulation or in the femoral arteries in peripheral cannulation, complete the cardiopulmonary circuit (49). A system for cardioplegia administration is often incorporated into the heart-lung machine, allowing for an elegant transition to and from bypass (49).

As mentioned above, there are different options for arterial and venous cannulation which are used depending on the procedure, atherosclerotic vascular changes, and patient habitus (50). For arterial cannulation in MIS, the peripheral common femoral artery, axillary artery, or central ascending aorta may be selected (50). The most common arterial cannulation site for MIS is peripheral, namely the femoral artery (50). Either the right or left femoral artery is chosen, though surgeons at DHZB prefer the left artery for less interference with peripheral venous cannulation (see below paragraph). The artery can either be cannulated directly or percutaneously (50). Percutaneous cannulation can avoid groin complications like infection, hematoma, or lymphocele and is therefore preferred in obese patients who are at higher risk (50,51). Femoral artery cannulation provides retrograde cerebral perfusion which has previously been associated with a higher risk of stroke (52). This may be considered in procedural planning, especially in the elderly population who is already at higher risk of stroke and if abdominal aortic calcifications are present (52).

The axillary artery is the alternative peripheral cannulation site which has the advantage of antegrade perfusion (50). Cannulation of the ascending aorta in MIS is similar to cannulation in MS (50). However, access and visibility is limited due to the small incisions (50). Both of these cannulation sites provide antegrade cerebral perfusion, which may be preferred in patients with risk factors for stroke (52).

Venous cannulation in MIS is achieved either via the peripheral right femoral artery or via central bicaval cannulation (50). In peripheral cannulation, the right femoral artery is preferred because it has a more direct alignment with the inferior vena cava (50). Percutaneous cannulation is most popular since it has a low rate of groin complications (50). Central venous cannulation of the superior and inferior vena cava is necessary in some MIS procedures, and not typically necessary for MIMVS (50).

For CPB in MS procedures, central arterial and venous cannulation is the standard approach (53). First, the aorta is cannulated, and then the superior and inferior vena cava are cannulated separately (53).

Temperature management is also achieved via modern CPB systems. The surgeon may decide to keep the patient's body temperature in normothermia (36°C), mild hypothermia (32-35°C), or moderate hypothermia (28-32°C) (54). In cardiac procedures using CPB, hypothermia enables a lower flow rate in the heart lung machine to adequately sustain the patient through a lower metabolic rate (54). The advantage of lower flow is that there is less need for venous drainage as the venous return decreases and therefore a better view. In general, hypothermia is cytoprotective, protecting the brain against possible perioperative brain ischemia as well as the myocardium (54). If hypothermia is used, the patient's temperature is lowered intraoperatively using the heart lung machine after bypass begins (54). The warming process begins 10 to 15 min before the aortic cross-clamp is released (54).

#### *1.2.4.2. Cardioplegic Cardiac Arrest*

Cardioplegia temporarily stops the heart for cardiac procedures (55). This protects the heart during periods of ischemia, provides a flaccid myocardium which can be operated on, allows the drainage of blood in operative field, and gives enough time to perform complex procedures (55). Most commonly, cardioplegia is a high potassium medium, administered as a crystalloid or blood solution (55). The resulting high extracellular potassium concentration in the heart depolarizes the resting cardiac cells membrane potential, arresting the heart in diastole (55). This reduces cellular metabolism and electrical activity, dramatically reducing the myocardium's oxygen demand (56). Additional cooling of the myocardium with ice can warrant even longer ischemic times, in which case the cardioplegia may also be administered at lower temperatures (55).

After the aorta is occluded via cross-clamping or balloons (see sections 2.3.1., 2.3.2.), the heart is quickly put into cardiac arrest using cardioplegia (55). The cardioplegic solution can be administered antegrade via the coronary arteries or retrograde via the coronary sinus (56). During the procedure, most solutions are administered every few minutes to ensure sufficient cardiac arrest and an adequate supply of electrolytes and metabolites (55).

In the cases examined in this dissertation, either Calafiore's blood cardioplegia, the intracellular crystalloid Bretschneider's (also known as Custodiol or HTK) cardioplegia or the extracellular crystalloid Del Nido's cardioplegia were used (56).

Some surgeons choose to administer ‘hot shots’ before the reperfusion phase. A ‘hot shot’ is the administration of warm blood cardioplegia at the end of the procedure to prevent myocardial metabolic derangement (57,58).

#### *1.2.4.3. Intraoperative Monitoring*

Mitral valve surgery, like virtually all cardiac surgeries, requires careful intraoperative monitoring, regardless of which mode of surgical access is selected. The most basic measurements include pulse oximetry and intraoperative ECG monitoring to detect arrhythmias, ischemia, or fibrillation (31). An arterial line is used for blood pressure monitoring and for arterial blood sampling (31). A central venous line is placed to monitor central venous pressure and administer cardiovascular drugs if needed (31).

Transesophageal echocardiography helps monitor myocardial and valvular function, aids in positioning catheters and cannula, and allows for a direct before and after comparison of the surgical result (31). Intraoperative TEE is crucial for port access MIS (31). Therefore, patients with contraindications for TEE are practically not apt for MIMVS (31).

For a minimally invasive approach, a double-lumen endotracheal tube is typically used for ventilation (25). This allows for deflation of the right lung while ventilating the left lung, allowing for better access to the MV (25).

### 1.2.5. Surgical Approach

As forementioned, the indications for IE surgery include heart failure through progressing valvular and tissue damage, uncontrolled infection, and a high risk of embolism (14). The objectives of surgery are the removal of infected tissue and implants, remove vegetations, debride paravalvular infection and cavities, and restore cardiac function and valvular integrity (59). All affected structures should be resected without concern of the feasibility of vale repair (60).

For valvular dysfunction, endocarditis leads to insufficiency rather than stenosis (1). Alain Carpentier’s functional classification as a pathophysiologic triad for mitral regurgitation can be used to accurately describing valvular dysfunction (61). Type I mitral regurgitation describes a normal leaflet motion, where there is either annular dilation or leaflet perforation causing the insufficiency (61). In type II regurgitation, leaflet prolapse causes insufficiency

due to chordal elongation/rupture or papillary muscle elongation/rupture (61). A Carpentier type III regurgitant MV has restricted leaflet motion (61).

#### *1.2.5.1. Endocarditic Lesions*

The presence of a mitral annular abscess caused by IE is an important determinant of disease severity to consider before surgery (62,63). An annular abscess means that the infection is not just limited to the leaflets, chordae or papillary muscles (62). When a prosthesis is introduced, it may remain in contact with diseased tissue, even if careful debridement was performed (62). This can lead to valve dehiscence, paravalvular leakage, and even reinfection (62).

At the DHZB, the presence of a mitral annular abscess is an important criterion in deciding which surgical approach to select. Typically, if an annular abscess can be detected preoperatively, this is a contraindication for MIMVS. This is not only because these patients usually have complex endocarditic pathologies. The left circumflex artery branches off from the left main coronary artery and runs along the coronary sulcus to the back of the heart (24). Here, the circumflex artery is very close to the mitral annulus. During surgical annuloplasty or valvular replacement, the circumflex artery may be injured (25). If a bypass of the circumflex artery should then become necessary, the surgeon would have to convert to a MS because this procedure is not possible via a right anterolateral minithoracotomy approach.

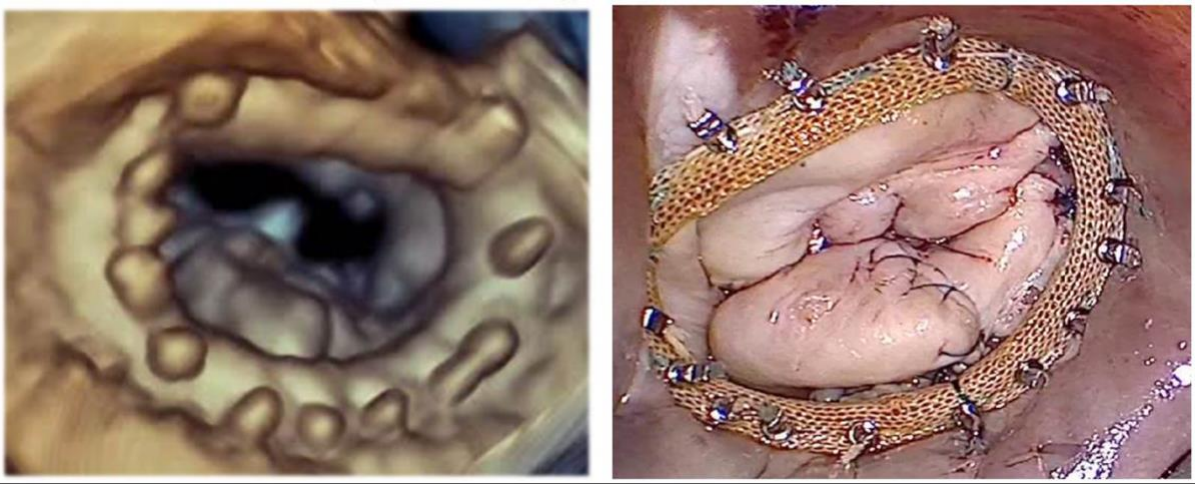
#### *1.2.5.2. Mitral Valve Repair*

Mitral valve repair is the surgical strategy of choice not only in IE, but in most other MV pathologies as well (14). To treat IE, all infected or inflamed tissue should be resected carefully (64). The resected tissue can be replaced with an autologous or a bovine pericardial patch, or it can simply be sutured (25). If chordae are infected or ruptured, they may be replaced by artificial chordae (25).

In many cases, an annuloplasty is necessary to restore normal shape and stabilize the MV (64). Flexible or semirigid rings may be used (65). The ring sizing is determined intraoperatively following the principles of Carpentier (65).

**Figure 3** shows an intraoperative TEE and endoscopic view after MV repair (30). Here, a annuloplasty was performed and the PML was reconstructed. See **Figure 2** under 1.2.2. for the TEE and intraoperative images of this MV before repair.

**Figure 3**: Postoperative mid-esophageal 4D MV view TEE depicting a repaired MV (left); intraoperative real-time totally endoscopic view of a repaired MV via a 3D 30° thoracoscope during MIS (right) (30).



*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

*1.2.5.3. Mitral Valve Replacement*

The 2015 ESC guidelines recommend repairing the MV whenever possible, especially if disease is limited to the valve (14). If the valve is too extensively destroyed, severe calcification or fibrosis of the leaflets is present, or the patient has severe ischemic disease, a repair may not be feasible (25). In that case, replacement with a biological or mechanical valve is indicated (25). This decision may need to be made intraoperatively, sometimes after a failed MV repair. In case of valve replacement, the physician must decide if a patient should receive a biological or mechanical valve (25). Factors to consider include anticoagulation, durability, recipient age and life expectancy, and patient preference (25).

To prepare for valve replacement, the anterior leaflet must be transferred or completely resected as it will otherwise obstruct the LVOT (25). The posterior leaflet is usually left intact and used to support the valve replacement sutures (25).

The following biologic prosthetic MVs are used at the DHZB; product name is listed first and brand name is in parenthesis: Hancock™ II (Medtronic), Epic™ (St. Jude Medical/Abbott) Biomitral (BioIntegral Surgical), Carpentier-Edwards Bioprosthesis Mitral Model (Edwards Lifesciences).

The following mechanic MVs are used at the DHZB: SJM™ Masters Series Mechanical Heart Valve (St. Jude Medical/Abbott), Open Pivot™ (Medtronic).

## 1.3. Study Objectives

### 1.3.1. Current literature on minimally invasive mitral valve surgery for infective endocarditis

To date, there are no other studies directly comparing MIMVS to MS for IE. Overall, only limited data is available on the role of MIMVS in IE (4,66,67).

A 2021 systemic review of MIMVS for IE by Shih et al. including 5 case series without comparison groups and 1 cohort study provides an overview of the current literature on this topic (67). The reviewers found a MV repair rate of 32.5%, conversion to sternotomy in 1.8%, average in-hospital mortality of 9.4%, average length of hospital stay of 21.6 days, 30-day survival of 89.1% and 1-year survival of 79.3% (67). These findings come from a highly selected group of patients who may present with more favorable characteristics than patients who do not receive a minimally invasive procedure (67). Since IE is a complex pathology poor prognosis, these findings need to be compared to MS for IE to fully evaluate the efficacy of MIMVS (67).

### 1.3.2. Minimally invasive mitral valve surgery versus median sternotomy

Minimally invasive surgery has gained increasing popularity in Germany, with rates for isolated minimally invasive mitral procedures rising from 13.1% in 2004 to 53.6% in 2019 (68). In North America, approximately one in three isolated mitral operations is performed using a less invasive approach (69). Most of these procedures are carried out in higher volume centers (69).

The following sections describe the literature around comparability, benefits, uncertainties, and drawbacks around MIMVS described in present literature. It is of note that

these findings apply to MIMVS in general, not specifically to MIMVS versus MS for IE. They are the foundation of the study objectives of this dissertation.

#### *1.3.2.1. Comparability of minimally invasive mitral valve surgery to median sternotomy*

Previous meta-analyses comparing MIMVS to MS have shown similar rates of mortality for both procedures (52,69,70). A comprehensive 2011 meta-analysis by Cheng et al. showed that the mortality rate for MIMVS versus MS was comparable at 30 days, 1 year, 3 years, and 9 years (71).

High surgeon procedural volume is an important factor for both minimally invasive and conventional MV surgery (69). In both procedures it is associated with a reduction in mortality (69). High volume in MIMVS was also shown to reduce the risk of stroke and early readmission (69).

An analysis by Hawkins et al. showed that MIMVS shows excellent results and a favorable resource utilization profile (72). Although surgical costs are higher, they are offset by decreased transfusions and ancillary costs like ventilation time (72).

#### *1.3.2.2. Benefits of minimally invasive mitral valve surgery*

Minimally invasive mitral valve surgery has many well-established benefits. The video-assisted technique can provide better visualization of the mitral valve (73). Apart from improved cosmesis, postoperative transfusion rates, ventilation time, ICU stay, and hospitalization time are all reduced (52,71,74–76) Some of these advantages are linked to preserving sternal integrity in MIS (74). However, most of this evidence is based on more routine procedures for mitral regurgitation.

In an analysis by Nissen et al., MIMVS showed higher MV repair rates across multiple pathologies, a reduced rate of stroke, renal dysfunction, pacemaker implantation, atrial fibrillation, and reduced length of hospital stay (69).

#### *1.3.2.3. Uncertainties and drawbacks of minimally invasive mitral valve surgery*

Minimally invasive surgery is technically more demanding for the surgeon (77). The treatment of IE, as a less prevalent disease of the MV, is not yet fully established in MIS. Some

centers still consider a relative contraindications for MIS, among with aortic calcification, right ventricular dysfunction, and severe mitral annulus calcification (6). At specialized centers with experienced surgeons, MV repair or replacement in IE is feasible and may provide superior outcomes compared to the more invasive conventional MS approach.

Casselman et al. showed that cross-clamp, CBP and procedure times may be increased in MIMVS (71). However, ventilation time, ICU length of stay and hospital stay were still reduced, indicating that these increases in procedural time do not have serious effects on patient outcomes (71).

Groin complications due to cannulation in MIMVS, like lymphocele, arterial bleeds, and infection, have become rare (78). The DHZB and other centers use vascular closure devices like the MANTA to further improve hemostasis (51).

The meta-analysis by Cheng et al. showed a significant increase in risk of stroke up to 30 days post-procedure for MIMVS in comparison to conventional MS (71). In the subsequent subgroup analysis of endoaortic and transthoracic clamping, endoaortic clamping was associated with the higher rates of stroke (71). Studies only using transthoracic clamps did not show a higher risk of stroke (71).

Schneider et al. showed that the risk of cerebral micro-embolisms for the duration of the procedure is not increased for MIMVS, suggesting that reported strokes occur mainly after the surgical procedure (79). A 2015 study by Casselmann et al. showed a low risk (0.8%) of postoperative stroke in MIMVS using endoaortic balloon clamping (80). Reported postoperative stroke rates for MIMVS range from 0.6% to 4.4% (80). The authors suggest that these findings could be linked to the experience and procedure volume, both of which were high in their selected centers (80). Another propensity-score matched study comparing MIMVS to MS in 2404 procedures also showed no increase in postoperative stroke for MIMVS, though this study did not describe how many cases used transthoracic versus endoaortic balloon clamping (81). Nonetheless, a consensus on whether MIMVS has a higher risk for postoperative stroke remains to be established.

### 1.3.3. Repair rates in minimally invasive mitral valve surgery

Surgical mitral valve repair is generally preferred to replacement whenever feasible due to better patient outcomes (14,82). This also applies to the surgical treatment of IE (82).

Nissen et al. demonstrated that MIMVS is independently associated with higher MV repair rates compared to a conventional MS (69). The etiology of MV disease impacts repair rates (83). Whilst degenerative leaflet prolapse and isolated annular dilation have high repair rates, rheumatic disease has a low repair rate (83).

Aside from higher repair rates, MIMVS also has a high success rate (84). In a 4-year study by Casselman et al., 187 patients who underwent MIMVS were examined (84). Only two patients required conversion to sternotomy to complete the repair (84). Of course, these findings apply particularly to experienced centers. In this study, 99.5% of patients were free from reoperation at 30 days, 97.1% at 1 year and 93.3% at 4 years (84). In a study by Seeburger et al. examining 1,339 patients who underwent minimally invasive MV repair, freedom from reoperation was 96.3% at 5 years.

### 1.3.4. Endpoints

The **main hypothesis (primary endpoint)** of this dissertation is:

- MIMVS provides clinical benefits over MS in patients with IE of the native MV

# 2. Materials and Methods

## 2.1. Study Design

This is a retrospective analysis of patient data regarding MIMVS and conventional MS for native MV IE surgery performed at the DHZB from 2009 to 2019 (30).

Since the patients were not randomly assigned to either surgical procedure, propensity score matching was used. The propensity scores for both patient populations were calculated according to preoperative and planned procedural characteristics. This method helps minimize selection bias inherently present (30).

Patients with similar propensity scores were then compared using suitable statistic tests to evaluate perioperative events as well as postoperative morbidity and mortality (30).

Before collecting patient data, the research proposal of this project was verified by the Ethics Committee of the *Charité – Universitätsmedizin Berlin*. They expressed no concerns in the pursuit of the project or publication of its results. This is documented in the ethics vote (*Ethikvotum*) number EA2/027/19 (30).

## 2.2. Patient Identification

The patients examined in this retrospective analysis were recruited by filtering MV procedures from all operations at the DHZB during the given time periods. These patients were then filtered by diagnosis-related groups (DRGs). All patients who had a primary or secondary diagnosis of ‘endocarditis’, ‘active endocarditis’, ‘florid endocarditis’ or ‘infectious endocarditis’ were selected. Only patients with native valve endocarditis were included, prosthetic valve endocarditis cases were excluded. 154 patients with acute or subacute MV IE operated on from 2009 to 2019 were included in the study (30).

The decision to allocate these IE patients to surgery was in line with current ESC guidelines and made by a dedicated interdisciplinary ‘Endocarditis-Team’ at *DHZB* (14). Patients undergoing MIMVS were operated by one of three experienced minimally invasive surgeons. Patients undergoing MS were operated by a wider range of surgeons at *DHZB*, including the three experienced minimally invasive surgeons (30).

To ensure the patients who received MV repair or replacement were comparable, MS patients who received procedures not feasible via the MIMVS approach were excluded. By

carefully reading operation reports, patients with MV procedures who also received AV procedures, pulmonary valve procedures, CABG, or a Morrow operation (ventricular septal myomectomy in case of LVOT obstruction) were excluded. Infectious involvement of the AV or pulmonary valve was also an exclusion criterion, even if the valve was not repaired or replaced during the operation. MS patients who received concomitant operations feasible in MIS like tricuspid valve procedures remained included (30).

In total, 42 patients who received MIMVS and 112 patients who received a MS for IE of the native MV were included (30).

## 2.3. Surgical Procedures

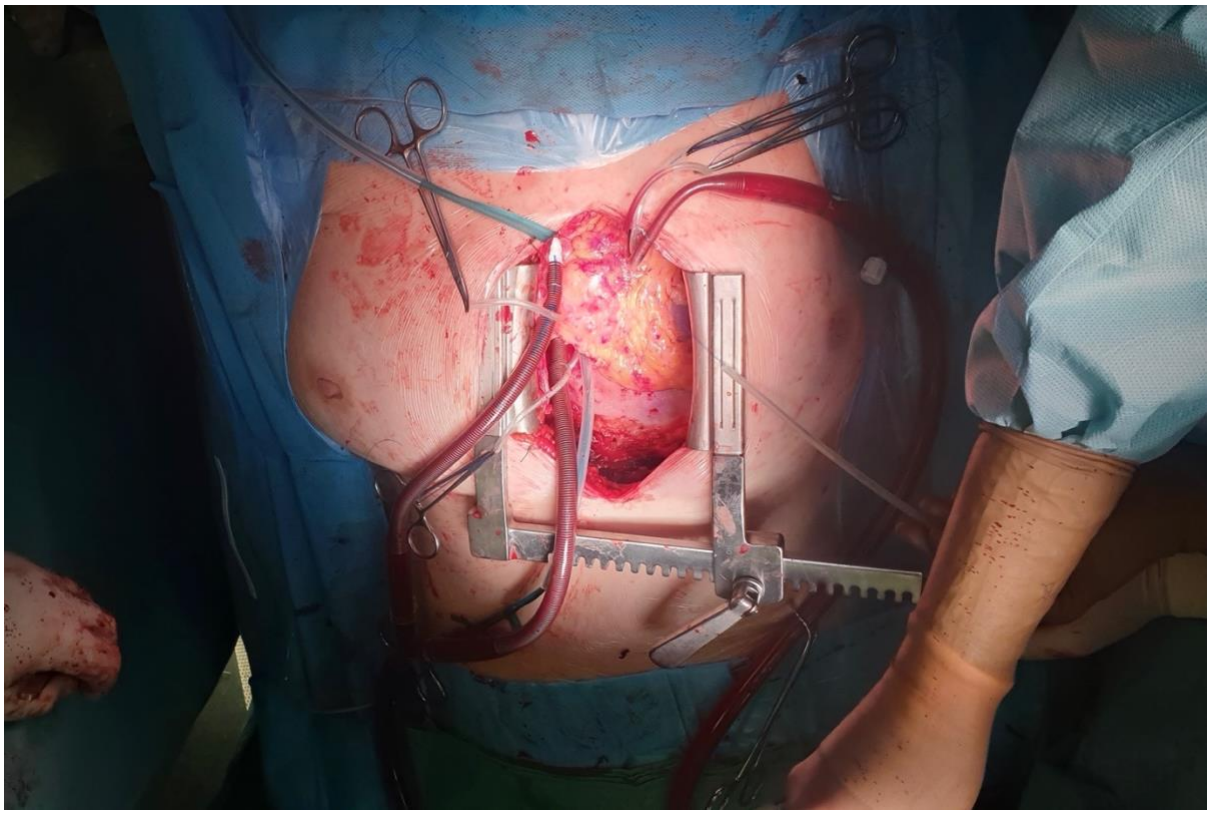
### 2.3.1. Median Sternotomy

To date, the most common surgical approach in MV surgery is still the conventional full, MS (85). It offers full view and access to almost all cardiac structures (25). To begin, the patient lies intubated and draped in a supine position (53,86). A TEE may be performed directly before surgery to confirm the pathology and left to standby to aid in evaluating cardiac function during the procedure (31). The skin incision is made, reaching from the suprasternal notch to the xyphoid process (86). The sternum is laid free, its midline marked, and opened with the saw, being diligent to avoid injury to the pleura, pericardium, thymus, brachiocephalic vein, or peritoneum (86). Ostial bleeding is limited by applying bone wax (86).

The patient is now heparinized before cannulation to prevent embolic complications (53). The pericardium is opened using a vertical incision which is two thirds towards the left side of the heart (53). This allows easier retraction of the right sided pericardium and optimal visibility of the left atrium (53). During the conventional MS approach, central aortic cannulation of the distal ascending aorta or proximal aortic arch is chosen for the arterial component (50,53). Venous drainage is achieved by placing a central bicaval cannula (50). The CPB machine is started.

**Figure 4** shows the intraoperative setting at this point. The median sternotomy is performed and the chest is held open with a sternal retractor. The arterial and venous cannulae are inserted and the patient is perfused using CPB.

**Figure 4**: Intraoperative view of a male patient undergoing conventional MV surgery via a MS using central bicaval venous cannulation and central arterial cannulation of the distal ascending aorta for cardiopulmonary bypass.



Once bypass perfusion begins, the aorta is clamped using a normal transthoracic clamp (53). For myocardial protection and stopping the heart, cardioplegic solution is administered antegrade via a cannula in the aortic root and/or retrograde through the coronary sinus (53,55). For most sternotomy MV surgery at DHZB, Calafiore is administered antegrade.

To expose the mitral valve, Sondengaard's atrial groove is located and a standard left atriotomy is performed 4 to 6 centimeters below the landmark (53). Self-holding Cooley-hooks are used to present the MV. The valve is then examined carefully, paying close attention to the anulus, leaflets, and chordae, and taking findings of the intraoperative TEE into account. The principles of IE MV repair and replacement which follow next are described in 1.2.5.

After the MV repair or replacement is finished, the left atrium is closed with single-layer sutures (53). The heart is vented in antegrade and retrograde fashion (49). Once all the air is removed, the aortic clamp is released and the coronary arteries are reperfused with the patient's blood (49). The heart begins beating again.

Another intraoperative TEE control should confirm proper function of the MV as well as the other cardiac valves (53). If the TEE is satisfactory, the reperfusion phase starts by beginning to take patient off CPB (53). A left atrial catheter is placed to monitor pressure and extracardiac pacemaker electrodes are sewn onto the right atrium and/or right ventricle (53). Catecholamines and sequential pacing with the epicardial leads may aid the reperfusion process, depending on the patient's cardiac function (31). Meanwhile, the left atrial pressure is monitored to optimize hemodynamic performance (87). Once the heart-lung machine is no longer supporting circulation, the patient is decannulated and protamine is administered to reverse the effects of heparinization (31).

To end the procedure, the surgeon places chest drains through epigastric stab incisions and pleural drains through the fifth or sixth intercostal space if necessary. The sternum is then closed with stainless steel wires (86). The wire tips are covered by the presternal fascia, the subcutaneous tissue is closed with absorbable sutures, and finally the skin is closed using staples or subcuticular sutures (86). Sterile bandages are applied and the patient is moved to the intensive care unit (ICU) or recovery room.

### 2.3.2. Minimally Invasive Surgery

To begin a MIS procedure for MV repair or replacement, the patient is placed in a modified lateral decubitus position (64). This elevates the right hemithorax, therefore facilitating access to the intercostal spaces (31). In MIS, a double-lumen tube or bronchial blocker is used (53). This allows the right lung, at the access port, to be deflated, while only the left lung is ventilated (31).

After heparinization, the right or left femoral vein and artery are cannulated in Seldinger's technique. A 25 French (Fr) venous cannula is advanced until it is inside the superior vena cava (88). Intraoperative TEE is used to confirm the correct position (88). For arterial cannulation, a 21 or 23 Fr cannula is placed over a wire positioned in the true aortic lumen (88). Again, TEE is crucial for confirming the correct position (88). In MIS, arterial cannulation can also be performed in the ascending aorta or axillary artery, though this is not the standard at the DHZB (50). Once cannulation is complete, CPB begins.

Now the right anterolateral minithoracotomy is performed, a 3 to 4 cm incision in the inframammary crease for female patients or above the nipple for male patients (64). Alternatively, a truly minimally invasive periareolar "nipple-cut" approach can be used in male

patients (64). The thorax is then entered through the third or fourth intercostal space (25). Additional visibility and operating space is gained by using a soft-tissue retractor, avoiding additional rib spreading, and a retractor if needed (88). A 10 mm camera port is inserted for video-assisted fully endoscopic monitoring (64). Either a 2D or 3D 30° high definition thoracoscope is inserted through the port (64). Both systems are used at the DHZB, dependent on the surgeon. For 3D visualization, the surgeons must wear 3D glasses when viewing the monitor (64).

Carbon dioxide is insufflated at 2 liters per minute through the camera port, aiding in pressing the right lung away from the operating field (53,88). To gain access to the pericardial sack, the right hemidiaphragm is sometimes retracted by a suture in the tendinous dome which is then brought out of the thorax through the right sixth or seventh intercostal space (88). A lengthwise pericardiotomy is performed 2 to 3 cm ventral of the phrenic nerve, reaching from the aorta to the diaphragm (88). Percutaneous retraction sutures of the pericardial leaves ensure an unobstructed view of the heart (53). A stab incision in the fourth right parasternal intercostal space is added for the atrial retractor, securing the right atrium with a suture (64).

Next, the aorta is blocked using either a Chitwood transthoracic clamp or an Intraclude balloon occlusion system (64). The balloon occlusion system is an aortic endoclamp that is advanced in place via the femoral arterial bypass canula (88). It should lie in the ascending aorta, cranial to the coronary arteries and caudal to the right subclavian artery. Under TEE control, the balloon is inflated, blocking the aorta (89). The balloon has a central lumen that can provide antegrade cardioplegia or vent the aortic root (33). In case the balloon occlusion system is used, bilateral radial arterial catheters must be placed before procedure start to ensure the endoballoon does not move distally, obstructing the aorta's branches (89).

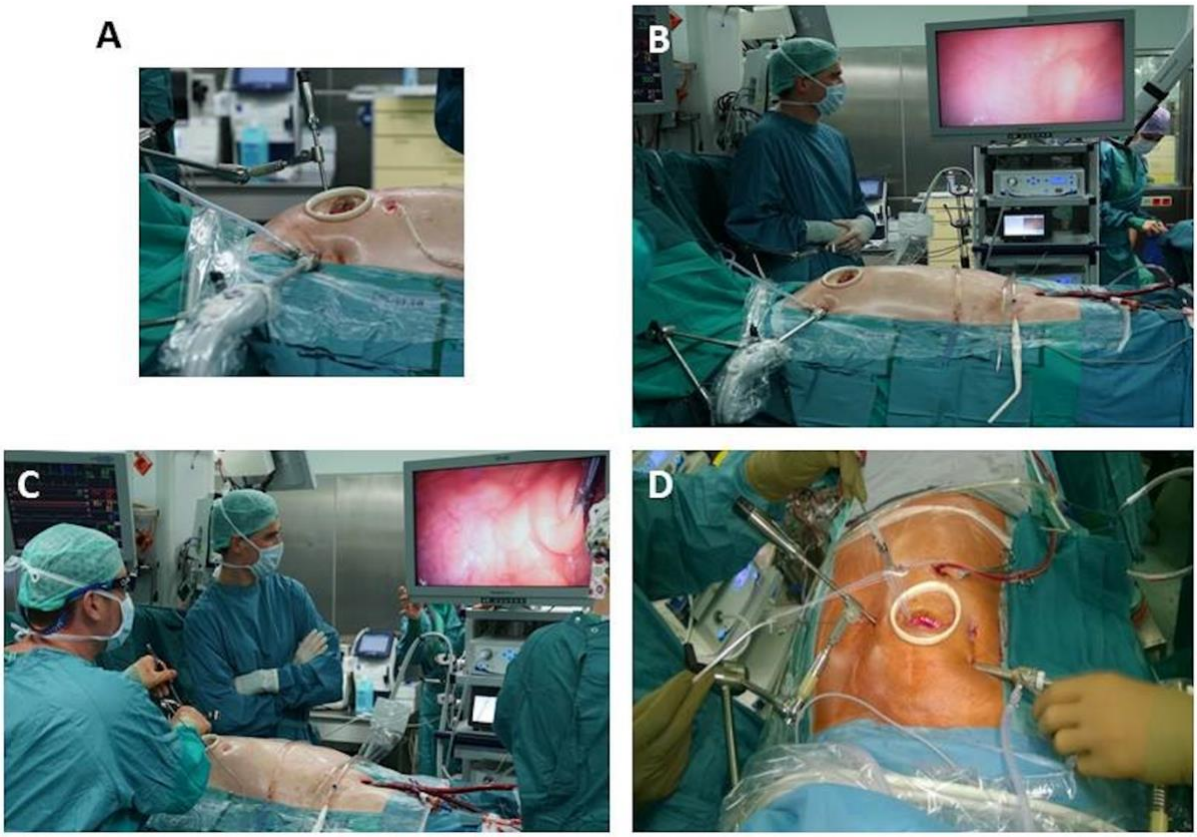
Alternatively, a Chitwood transthoracic clamp can be used, in which case aortic cannulation is necessary for the application of cardioplegia (33). Next, cardioplegia is administered antegrade via the endoballoon or a cardioplegia catheter in case of clamping (33). If necessary, the anaesthesiologist may also introduce an endovascular catheter to the coronary sinus to administer retrograde cardioplegia (52). At the DHZB, Del Nido or Bretschneider cardioplegic solution are used in MIMVS.

Next, the left atrium is opened ventrally to the right pulmonary veins via a standard left atriotomy (53). A left atrial vent and a left atrial retractor are used for optimal exposure of the MV (53). The MV is inspected closely, then repaired or replaced as described in 1.2.5.

**Figure 5** below shows an overview of the operative setup. Image A shows a lateral view of the retractor and the endoscope. Images B and C show the process of fully endoscopic visualization of the MV.

Image D shows the intraoperative setting during MV repair in MIS. A soft tissue retractor is inserted using the less invasive sternal sparing periareolar approach. Peripheral cannulation was used for CPB which are only visible in pictures B and C. Here, a Physio II annuloplasty ring is being lowered onto the annulus of the MV after being sutured.

**Figure 5**: Complete setup for fully endoscopic high definition 3D MIMVS as performed by Prof. Dr. Jörg Kempfert and his team at DHZB.




*Note.* Adopted from Minimally Invasive Surgical Mitral Valve Repair: State of the Art Review (64).

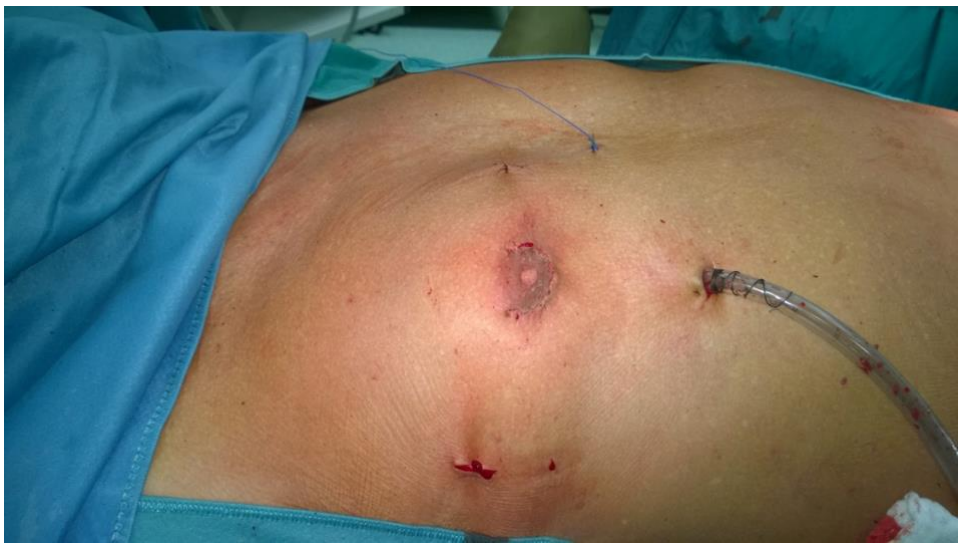
Once complete, the surgeon ensures all leaflets move normally and in case of a prosthetic valve confirms that it is sewn in well (53). The quality of the MV repair or replacement is assessed by injecting a saline solution into the ventricle (53). If the valve is fully competent, no leakage occurs in this static test (53). The left atrium is then closed using a continuous suture. Before the last knot is secured, the left atrium is vented. To ensure removal of all

residual air, the vent must be placed across the valve ensuring that venting holes are in the atrium and ventricle (88). Epicardial pacing wires are sewn to the right ventricle and/or right atrium while the heart is still compressed and on bypass (88).

Now, some surgeons administer “hot shots” via the aortic root (57,58). After the aortic root is vented, the endoaortic balloon is deflated or the transthoracic clamp removed, allowing reperfusion (88). As the heart begins contracting again, the patient can slowly be taken off CPB (88). Protamine is administered, reversing the effects of heparin, and the femoral cannula are removed (88).

After decannulation the epicardium is sutured back together. The camera and port are removed and the thoracic wall is closed in layers. At the end of the procedure, sterile bandages are applied and the patient is moved to the ICU or recovery room. **Figure 6** below shows the intraoperative findings of a patient directly after completion of the MIMVS procedure using the periareolar approach. The periareolar incision was closed using a subcutaneous suture and a drainage tube was placed. The remaining stab incisions were closed with intracutaneous sutures.

**Figure 6**: Postoperative view of a male patient after applying the periareolar approach in MIMVS.



*Note.* Adopted from Minimally Invasive Surgical Mitral Valve Repair: State of the Art Review (64).

## 2.4. Data Collection

In order to systematically collect the patient and procedural data, the online secure web platform Research Electronic Data Capture 2 (REDCap2) was used. Within the software, each patient received an anonymized identification number. Data on epidemiologic data, preoperative status, procedural characteristics, perioperative management, postoperative outcome, and mortality was gathered.

## 2.5. Collected Data

All the data for this study was gathered from electronic and paper files at the DHZB. The electronic files and data were accessed from the clinical software used at DHZB, including *medfolio*, *m.life*, *Lauris*, and *IntelliSpace*. This software gave access to medical letters, operation reports, CPB protocols, periprocedural echocardiographic reports, laboratory values, and electrocardiograms. For patients who received their operation before October 15, 2012, this information was gathered from the paper files stored at DHZB's central archive. Some of this older patient data was additionally supplemented with data extracted from older clinical software provided from medical controlling at DHZB.

Epidemiologic parameters recorded included: age at the day of operation, sex, DHZB hospitalization dates, prior hospitalization time, discharge destination, last contact, and lost to follow-up.

Preoperative parameters recorded included: body mass index (BMI), NYHA class, EF, creatinine level in mg/dl. Preexisting conditions recorded were insulin-dependent diabetes mellitus, arterial hypertension, coronary artery disease, atrial fibrillation, history of previous open-heart surgery, history of dialysis. De Feo Score and STS PROM scores were retrospectively calculated and recorded. Endocarditis-related preoperative conditions recorded were embolic events, acute versus subacute endocarditis, and bacterial species. Preoperative treatment with inotropes was also recorded. Operative concomitant procedures and MV repair versus replacement were analyzed additionally.

Intraoperative outcome data gathered included primary access (sternotomy or right anterolateral thoracotomy), concomitant procedures, overall operative time, CPB time, cross-clamp time, and MV repair versus replacement rates.

Postoperative treatment data encompassed ICU time, ventilation time, transfusion of red blood cell (RBC) units, transfusion of fresh frozen plasma (FFP) units, transfusion of platelet units, surgical reexploration (revision) for bleeding, inotrope exposure time, reintubation after extubation, readmission to the ICU, mechanical support on IABP or ECMO. The VIS was calculated for timing directly postoperatively as well as the postoperative amount of time inotrope medications were administered. Postoperative data on creatine kinase (CK) and creatine kinase muscle-brain type (CK-MB) was gathered.

## 2.6. Statistical Methods

### 2.6.1. Data Preparation

Due to the retrospective study design, some selection bias in which patients received MIMVS and conventional MS is inherently present. The differences in patient characteristics result from being assigned to the MIMVS 'treatment' group or the MS 'control' group in a not randomized manner. Median sternotomy is the standard of care in patients with IE of the native MV and is often chosen in more critical situations. This results in different preoperative clinical characteristics for the conventional MS group. This is illustrated in **Table 7** showing the baseline characteristics of the unmatched population in 3.1.1.

### 2.6.2. Propensity Score Matching

The gold standard for comparing therapies in medicine is a randomized controlled trial (90). A randomized controlled trial guarantees an even distribution of all known and unknown patient characteristics to the intervention and control group (91). Ideally, bias is minimized, and inferences can be made about therapeutic effects (91). However, randomized controlled trials are not always suited to analyze treatment effects, as they may be impossible, inappropriate, insufficient, or unnecessary (91).

Alternatively, non-randomized, often retrospective studies can be used to evaluate therapies (91). The main issue these studies have is a lack in internal validity (91). Since patients are not randomly assigned to the control or intervention group, the groups may show systematic differences in known and unknown patient characteristics (91). These differences make it difficult to attribute differences in outcome to the intervention (91).

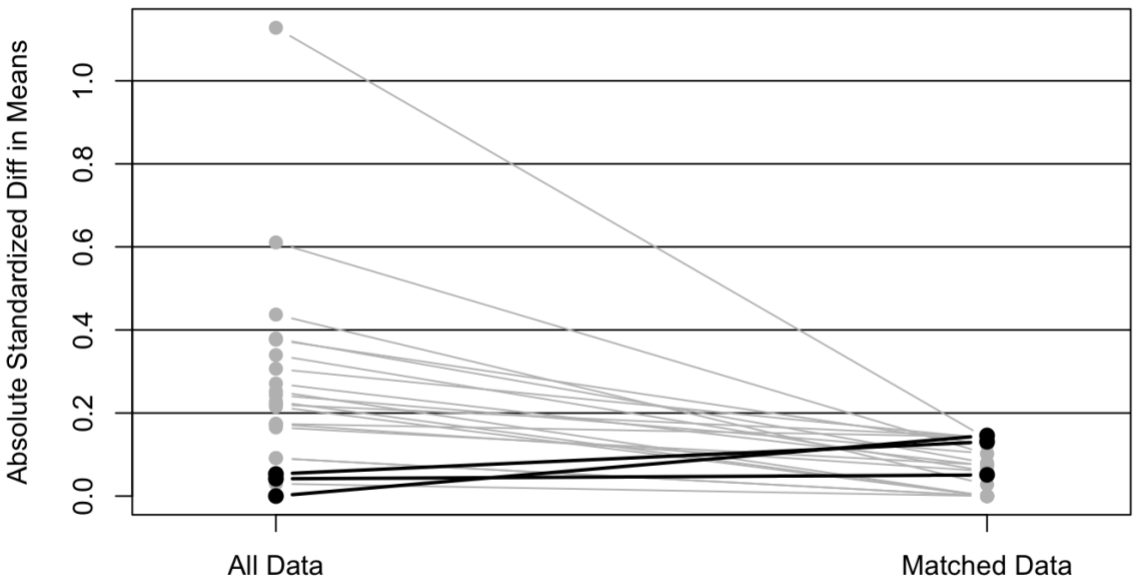
Thankfully, there are statistic methods that can account for this. Multiple regression models are among the most common used (91). This method controls for different characteristics in a linear fashion. The propensity score method is more accurate when linearity cannot be assumed and non-parametric.

The propensity score is defined as the probability that a patient will be allocated to the intervention group, in this case MIMVS. In 1:1 randomized studies, this is 0.5 for each patient (91). In a non-randomized study, however, this probability is unknown and dependent on the characteristics of the patient (91). Using a logistic regression model with the patient's preoperative characteristics as the independent variable and MIMVS as the dependent variable, propensity scores were calculated for each patient (91).

Next, in order to make comparisons between the treatment and control group, patients from both groups were matched based on similar levels of propensity scores. Patient pairs were assigned to one another in 1:1 using the nearest neighbor matching technique. Adjustment for endocarditis severity was performed by the dedicated De Feo Score (30).

The resulting matching quality according to standardized difference in means is shown in **Figure 7** below.

**Figure 7**: Propensity score matching quality according to standardized difference in means (30).



*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

The final model for the propensity score included the following variables: age, female sex, BMI, preoperative NYHA>2, EF <60%, previous cardiac surgery, insulin dependent diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, preoperative dialysis, last preoperative creatinine in mg/dl, STS PROM Score, De Feo Score, subacute endocarditis, staphylococcus aureus as causative organism, preoperative inotrope support, and concomitant procedures during MV repair or replacement.

These variables were carefully chosen to best reflect determinants of postoperative outcome. Staphylococcus aureus infection, periannular involvement as reflected in the De Feo Score, and heart failure are established prognostic risk factors (92). Variables that could determine treatment allocation were avoided in matching.

Propensity score matching inevitably leads to a reduction in study group size through exclusion of patients who do not have a match with a similar score. However, the resulting smaller groups of patients are similar enough to compare postoperative outcomes with minimal bias.

### 2.6.3. Statistical Analysis

After matching, the perioperative and postoperative results of the treatment (MIMVS) and control (MS) group were compared. Scalar valuables were compared using the Mann-Whitney-U test and t-test. The confidence interval was 95% and p-values <0.05 were considered statistically significant. Nominal valuables were compared using the Chi-square test (a=0.05) (30).

### 2.6.4. Data Analysis Software Instruments

Propensity score matching was performed using R software (version 4.0.0, The R Project for Statistical Computing, Austria) version 3. Statistical analysis and tests were done using IBM SPSS Statistics (version 25, IBM, Armonk, NY, USA).

# 3. Results

## 3.1. Patient Characteristics

In total, 154 patients were included in this retrospective analysis. This group included 42 patients who received MIMVS and 112 patients who received a conventional MS for surgical treatment of IE of the native MV (30).

### 3.1.1. Before Propensity Score Matching

**Table 7** below shows the demographic and preoperative characteristics of the treatment and control group before propensity score matching. Most patients in this analysis were treated via MV replacement.

Continuous variables are depicted as mean with standard deviation; categorical variables are presented as frequency with corresponding percentage. For the unmatched population, group differences were tested using the t-test of independent samples. The chi-square test was used to compare proportions (30).

**Table 7**: Baseline characteristics of the unmatched population (30).

| Baseline characteristics of the **unmatched population** | | | |
|---|---|---|---|
| | **MIMVS** | **MS** | **p value** |
| **Variables** | **n = 42** | **n = 112** | |
| Age, years | 56.29 (17.23) | 61.38 (13.52) | 0.056 |
| Female Sex | 18 (42.9) | 43 (38.4) | 0.749 |
| Body mass index, kg/m$^2$ | 25.64 (6.00) | 26.76 (6.41) | 0.329 |
| NYHA class < II | 23 (54.8) | 59 (52.7) | 0.961 |
| Ejection fraction < 60% | 4 (9.5) | 27 (24.1) | 0.074 |
| Previous open-heart surgery | 2 (4.8) | 15 (13.4) | 0.217 |
| Insulin-dependent diabetes mellitus | 6 (14.3) | 16 (14.3) | >0.999 |
| Arterial hypertension | 23 (54.8) | 63 (56.2) | >0.999 |
| Coronary artery disease | 7 (16.7) | 21 (18.8) | 0.949 |
| Atrial fibrillation | 8 (19.0) | 33 (29.5) | 0.272 |

| | | | |
|---|---|---|---|
| Dialysis | 2 (4.8) | 16 (14.3) | 0.175 |
| Creatinine, mg/dl | 1.24 (0.93) | 1.51 (1.21) | 0.198 |
| MV dedicated STS PROM, % | 5.32 (4.70) | 9.96 (10.61) | 0.007 |
| De Feo Score | 10.95 (7.70) | 16.67 (9.36) | 0.001 |
| Embolic events | 17 (40.5) | 59 (52.7) | 0.243 |
| Subacute endocarditis | 8 (19.0) | 15 (13.4) | 0.533 |
| Staphylococcus aureus | 11 (26.2) | 41 (36.6) | 0.305 |
| Preoperative inotropes | 2 (4.8) | 18 (16.1) | 0.112 |
| Concomitant procedures | 7 (16.7) | 27 (24.1) | 0.439 |
| Planned MV replacement | 32 (76.2) | 99 (88.4) | 0.101 |

*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

Overall, the preoperative state of the MS group was more critical. They had significantly higher preoperative risk scores, reflected as the STS PROM score, and a higher endocarditis-specific surgical risk, reflected as the De Feo Score.

There were no significant differences ($p > 0.05$) in age, sex, BMI, high NYHA class, left ventricular EF, previous open-heart surgery, Insulin-dependent diabetes mellitus, arterial hypertension, atrial fibrillation, dialysis, creatinine, embolic events, acute vs. subacute endocarditis, staphylococcus aureus as causative organism, preoperative inotropes, concomitant procedures, and planned MV replacement. All of these characteristics reflect surgical risk as well. Although each individual factor of these was insignificantly different, the cumulative effect still reflects that the MS patients were more ill before surgery than their MIMVS counterparts.

### 3.1.2. After Propensity Score Matching

**Table 8** below shows the demographic and preoperative characteristics of the treatment and control group after propensity score matching. Propensity score matching resulted in 39 patients from each group.

Continuous variables are depicted as mean with standard deviation; categorical variables are presented as frequency with corresponding percentage (30).

Since propensity score matching produces pairs that are no longer completely independent from another, statistic tests that account for this interrelation should be used (93). In this study, continuous variables for the matched population were compared using the paired t-test or the signed Wilcoxon test. McNemar's test was used to compare bivariate endpoints. The log-rank test was used to assess differences in survival and freedom from reoperation; the results were depicted in Kaplan-Meier curves (30).

**Table 8**: Baseline characteristics of the matched population (30).

| Baseline characteristics of the **matched population** | | | |
|---|---|---|---|
| | **MIMVS** | **MS** | **p value** |
| **Variables** | **n = 39** | **n = 39** | |
| Age, years | 56.44 (17.01) | 58.10 (15.37) | 0.542 |
| Female Sex | 16 (41.0) | 16 (41.0) | >0.999 |
| Body mass index, kg/m$^2$ | 25.73 (6.16) | 26.64 (6.27) | 0.441 |
| NYHA class < II | 21 (53.8) | 22 (56.4) | >0.999 |
| Ejection fraction < 60% | 4 (10.3) | 3 (7.7) | >0.999 |
| Previous open-heart surgery | 2 (5.1) | 2 (5.1) | >0.999 |
| Insulin-dependent diabetes mellitus | 6 (15.4) | 8 (20.5) | 0.791 |
| Arterial hypertension | 22 (56.4) | 22 (56.4) | >0.999 |
| Coronary artery disease | 7 (17.9) | 5 (12.8) | 0.774 |
| Atrial fibrillation | 7 (17.9) | 7 (17.9) | >0.999 |
| Dialysis | 2 (5.1) | 3 (7.7) | >0.999 |
| Creatinine, mg/dl | 1.24 (0.96) | 1.41 (1.18) | 0.334 |
| MV dedicated STS PROM, % | 5.46 (4.81) | 5.16 (3.85) | 0.793 |
| De Feo Score | 11.28 (7.79) | 12.23 (7.35) | 0.467 |
| Embolic events | 16 (41.0) | 18 (46.2) | 0.815 |
| Subacute endocarditis | 7 (17.9) | 6 (15.4) | >0.999 |
| Staphylococcus aureus | 11 (28.2) | 11 (28.2) | >0.999 |
| Preoperative inotropes | 2 (5.1) | 4 (10.3) | 0.687 |
| Concomitant procedures | 6 (15.4) | 5 (12.8) | >0.999 |
| Planned MV replacement | 30 (76.9) | 31 (79.5) | >0.999 |

*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

The matched population was predominantly male (59%), in their mid-fifties, and slightly overweight. Their EF was largely intact with only around 10% of patients showing an EF of ≤60% in both groups. About one fifth of patients in each group had a marked limitation or inability for physical activity without discomfort at NYHA ≥3. Only 5% of patients had previous open-heart surgery. Equally distributed comorbidities were arterial hypertension in 56% and atrial fibrillation in 17.9% for both patient groups.

Since the p values were all ≥ 0.05, the groups were balanced and none of the remaining differences were significant. MIMVS patients had a slightly higher rate of coronary artery disease (17.9% versus 12.8% in MS group) and a slightly lower rate of preoperative dialysis (5.1% versus 7.7% in MS group) as well as slightly lower creatinine levels (mean of 1.24mg/dl opposed to 1.41mg/dl in MS group).

The MV dedicated STS PROM Score reflecting similar preoperative risk profiles was very close for both groups after matching. MIMVS patients had a predicted risk of mortality of 5.46% (SD ±4.81) and MS patients 5.16% (±3.85). The De Feo Score which standardized the severity of endocarditis was 11.28 points (±7.79) in MIMVS and 12.23 (±7.35) in MS.

Further matching parameters related to endocarditis included preoperative embolic events (in 41% of MIMVS, 46.2% of MS patients), subacute as opposed to acute endocarditis (subacute in 17.9% of MIMVS, 15.4% of MS patients), and staphylococcus aureus infection (in 28.2% of both MIMVS and MS patients).

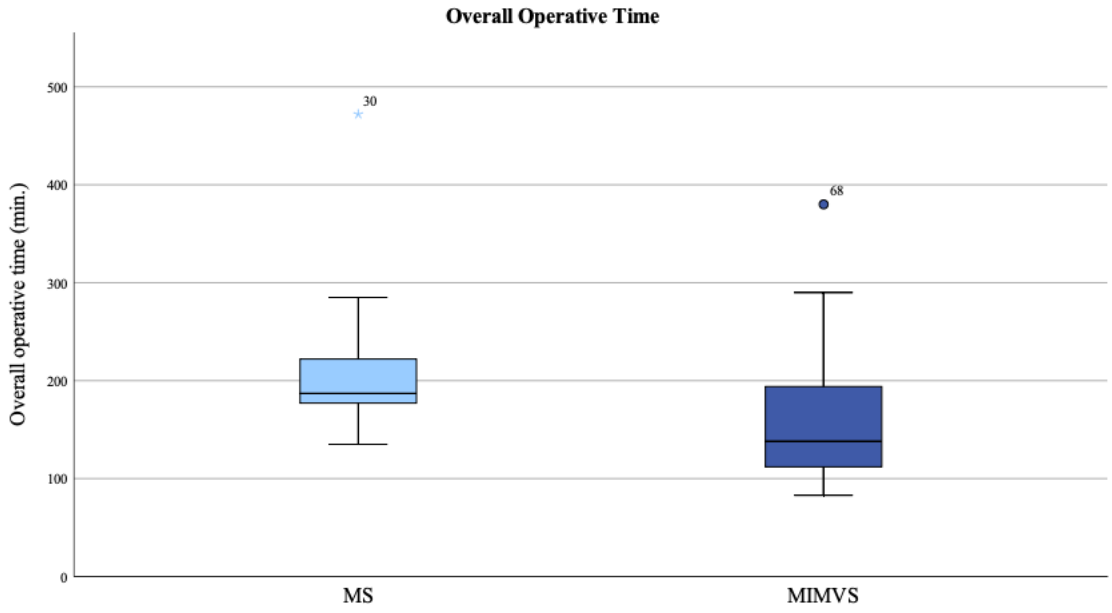
After matching, MIMVS patients still needed less inotropes in comparison to conventional MS patients (5.1% opposed to 10.3%). However, slightly more concomitant procedures were performed in the MIMVS group (15.4% opposed to 12.8%). Planned MV replacements were performed in the majority of patients instead of repairs and the rate was similar for both groups (MIMVS 76.9% replacements, MS 79.5% replacements).

## 3.2. Operative Outcomes

There was a significant (p=0.005) difference between overall operative times. For MIMVS patients the median operative time was 138 minutes (interquartile range 112-196) and

for MS patients it was 187 minutes (175-230). The overall median operative time for both patient groups was 180 minutes (134.75-211) (30). This is depicted in **Figure 8** below.

**Figure 8**: Overall operative time in minutes.




There were no significant differences in CPB time or aortic cross clamp time between the matched MIMVS and MS (p=0.563, p=0.780, respectively). MIMVS patients had a median CPB time of 96 minutes (interquartile range 77-138) whilst MS patients had a median of 99 minutes (88-127). For aortic cross clamping time, MIMVS patients had a median of 64 (54-90) and MS patients 65 (59-83) (30). These results are shown in **Figures 9** and **10**.

**Figure 9**: Cardiopulmonary bypass time in minutes.

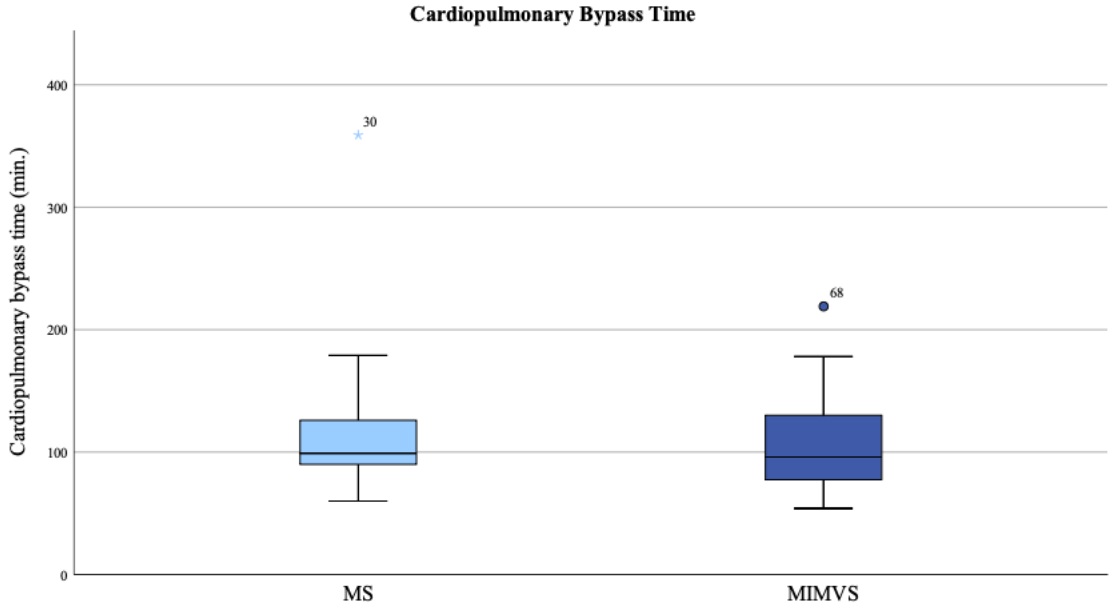
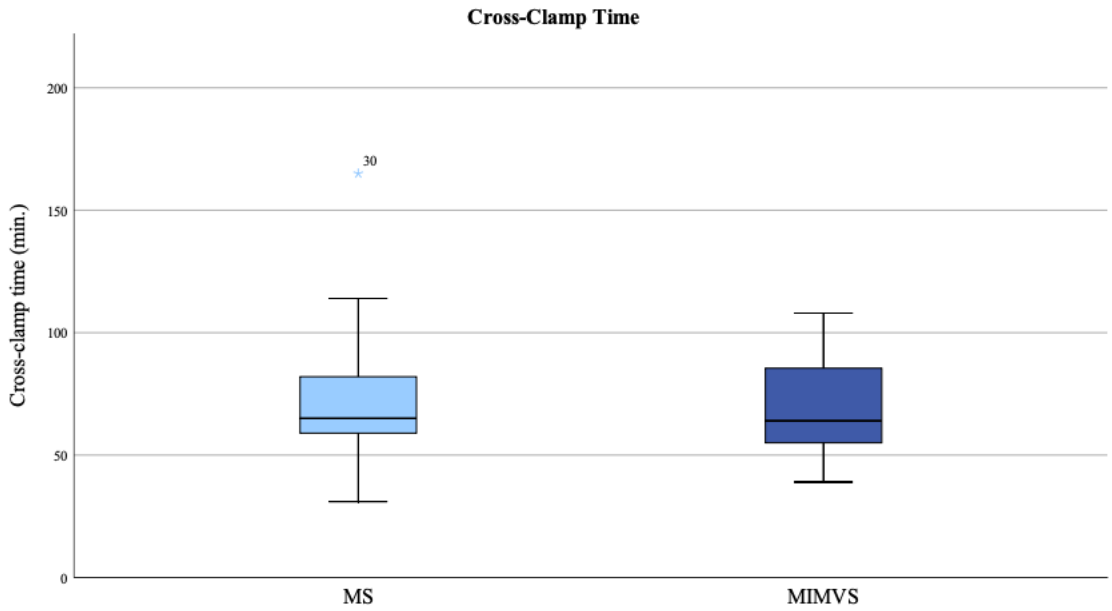



**Figure 10**: Cross-clamp time in minutes.




## 3.3. Postoperative Outcomes

The postoperative course of both patient groups was evaluated for the duration of their stay at the DHZB as well as after transfer to another hospital. Most patients were transferred to the *Paulinenkrankenhaus* (Berlin) for further postoperative care, a close partnering hospital of the DHZB.

### 3.3.1. Procedural Outcomes

Minimally invasive mitral valve surgery patients needed a median of 1 RBC transfusion (interquartile range 0-4) as opposed to 4 RBC transfusions in MS patients (interquartile range 2-10) (p=0.001). Minimally invasive mitral valve surgery patients also needed no FFP transfusions (median 0, interquartile range 0-0) whilst MS patients needed a median of 1 unit (interquartile range 0-5) (p=0.002). There was no significant difference in platelet transfusions; MIMVS patients received a median of 0 (interquartile range 0-0) and MS patients received 0 (interquartile range 0-2) as well (p=0.365) (30).

CK and CK-MB were recorded postoperatively within 2 hours of leaving the operating room as laboratory markers for myocardial injury after cardiac surgery. CK is the level of all four subtypes combined; myocardium-brain, skeletal muscle, brain, and mitochondrial type. The first reported postoperative CK within two hours after leaving the operating room was 630 at median (standard deviation±554.98) for MIMVS patients and 465.79 (±252.36) for MS patients (p=0.152). With the upper cutoff at 167 U/l for women and 190 U/l for men, CK was elevated for both groups without significant differences. Postoperative CK-MB was significantly different (p=0.036) at mean 74.94 (±55.97) for MIMVS and 88.85 (±51.73) for MS patients. CK-MB was elevated in both groups (median 74.94 U/l for MIMVS and 88.85 U/l for MS) with the upper cutoff at 25 U/l for both sexes.

Patients who underwent MIMVS had similar rates of surgical revisions (re-explorations) for bleeding (p>0.999). 12.8% of the group (5 of 39) needed a revision opposed to 10.3% (4 of 39) of the MS group (30).

### 3.3.2. Pulmonary Outcomes

Patients who underwent MIMVS were ventilated for a median time of 708 minutes (interquartile range 429-1236) whilst MS patients were ventilated for a median of 1440 minutes (interquartile range 659-4411). This is a significant finding (p=0.024), with MS patients needing invasive ventilation for almost twice as long as MIMVS patients (30).

Furthermore, 25.6% of MS patients (10 of 39) needed to be reintubated during postoperative care, opposed to only 5.1% of MIMVS patients (2 of 39) (p=0.021) (30).

Tracheotomy rates were similar amongst both groups; 7.7% of MIMVS (3 of 39) patients and 12.8% of MS (5 of 39) patients received this intervention (p=0.727) (30).

### 3.3.3. Cardiovascular Outcomes

The postoperative VIS score was 9 at median for MIMVS patients (interquartile range 5-20) and 10 for MS patients (interquartile range 3-22), bearing no significant difference (p=0.856).

Postoperative inotrope exposure time was also similar. Minimally invasive mitral valve surgery patients received inotropes for a median of 8.2 hours after the procedure (interquartile range 4.3-13.1) whilst MS patients were exposed for 7.2 hours (interquartile range 2.5-21.6) (p=0.417).

Low cardiac output rates were similarly low at 5.1% (2 of 39) for MIMVS and 2.6% (1 of 39) for MS patients (p>0.999) (30). Pacemaker implantation was necessary for 2.6% (1 of 39) of MIMVS and 7.7% (3 of 39) of MS patients (p=0.625).

Postoperative stroke was reported in one MIMVS patient (2.6%), no MS patients had this complication (0%) (p not applicable) (30).

### 3.3.4. Intensive Care Medicine Outcomes

Overall, the ICU stay was similar for MIMVS patients (median 1 day, interquartile range 1-4) and MS patients (median 3 days, interquartile range 1-9) (p=0.061) (30).

Readmission to ICU rates were also similar across both groups; 17.9% of MIMVS patients (7 of 39) were readmitted versus 23.1% (9 of 39) of MS patients (p=0.791) (30).

Postoperative mechanical support rates, which included IABP or ECMO, were insignificantly higher (p=0.500) for MIMVS patients at 7.7% (3 of 39) than for MS patients at 2.6% (1 of 39).

There was no significant difference in postoperative renal complications, which included renal insufficiency, renal failure, and postoperative dialysis; 44.4% of the MIMVS group (12 from 39) and 55.6% of the MS group (15 of 39) were affected, bearing an insignificant difference (p=0.475). Hemodialysis was necessary in 2.6% of MIMVS (1 of 39) and 7.7% of MS (3 of 39) patients (p=0.625).

No myocardial infarctions were reported in either group.

Multi organ failure was also not significantly different among the groups; 7.7% of MIMVS patients (3 of 39) and 12.8% (5 of 39) of MS patients had this complication (p=0.687).

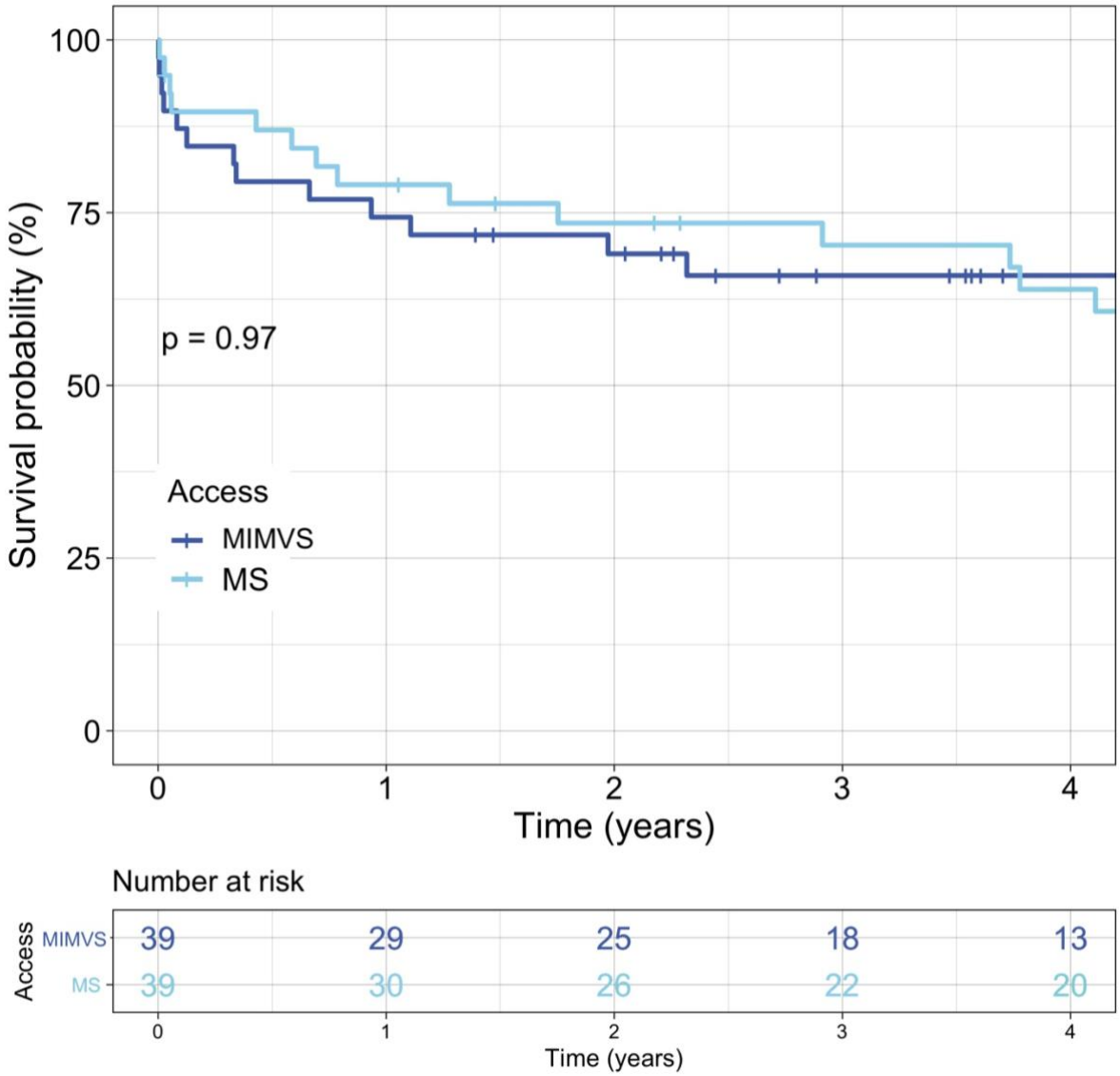
## 3.4. Follow-up endpoints

There was no significant difference in mortality between the two groups. Minimally invasive mitral valve surgery patients had a 30-day mortality of 10.3% (4 of 39) and a 1-year mortality of 23.1% (9 of 39). Median sternotomy patients had 10.3% (4 of 39) at 30 days and 25.6% (10 of 39) at 1 year (p=0.375, p=0.792 respectively) (30).

The median follow-up duration for both populations was 3.5 years (interquartile range 1-6 years). Survival and freedom from reoperation were compared for all patients up to April 2021 and are depicted in the Kaplan Meier graphs in **Figures 12** and **13** below (30).

Postoperative survival among both groups showed no significant difference (p=0.97).

**Figure 11**: Kaplan-Meier survival probability with number at risk (30).

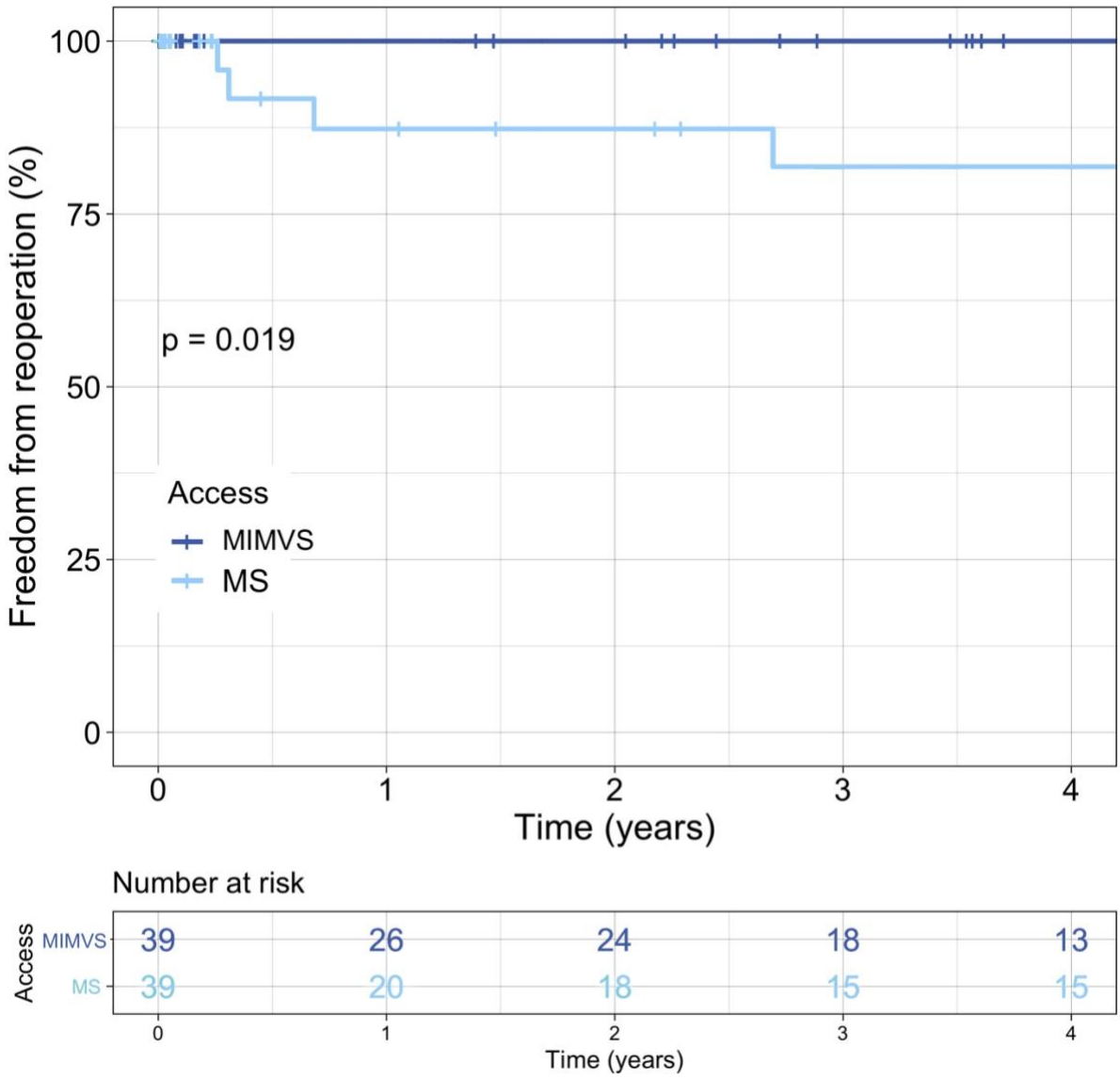


*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

Postoperative freedom from reoperation was significantly higher for MIMVS patients. None of the 39 patients in the MIMVS group underwent a reoperation for revision opposed to 6 of 39 MS patients (p=0.019) (30).

The reasons for reoperation were mainly the recurrence of IE to the prosthetic MV leaflets, occurring in 3 of the patients. One patient had a prosthetic leaflet infection as well as paravalvular leakage, another had an isolated infective paravalvular leakage, and the final patient had a paravalvular leakage without signs of infection (30).

**Figure 12**: Kaplan-Meier freedom from reoperation with number at risk (30).



*Note.* Adopted from Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison (30).

# 4. Discussion

## 4.1. Operative Outcomes

An interesting finding in this study was the shorter overall operative times for the MIMVS group. This stands against previous concerns around MIS for IE because of the usually increased operating times in MIS (4). Minimally invasive procedures generally utilize smaller incisions, cause no sternal interference leading to blood marrow bleeding, and require minimal dissection, suggesting less blood loss during the procedure (5). Intraoperatively, this could result in a surgeon needing to spend less time controlling bleeds and coagulating, therefore reducing procedure time.

Incidentally, the MIMVS endocarditis patients in this study needed less RBC and FFP transfusions. Several studies comparing MIMVS to MS have shown less bleeding and the need for less transfusions for the minimally invasive approach (70,71,74,94). Less transfusions for the MIMVS group may also be explained by improved hemostatic monitoring in more recent years. The conventional MS group included patients from 2009-2019. Patients whose procedure dated further back may have had slightly different postoperative treatment because of protocol changes in therapeutic schemes at the DHZB over time.

Notably, there were no significant differences in CPB and cross-clamp times between the groups. Since MIMVS patients typically go on bypass earlier in the procedure, i.e., before opening the thoracic cavity, this is a compelling finding. This needs to be interpreted under the light of the high case load of surgeons performing MIMVS at DHZB. This may also explain the shorter operation times for MIMVS at DHZB. Nonetheless, CPB and cross-clamp time remain important prognostic factors in a patient's postoperative course, shorter times yielding a better prognosis (95).

Overall, MV repair is associated with longer clamping than replacement because of the surgical complexity (96). A possible explanation for shorter aortic cross-clamp times in the MIMVS group could be a lower number of repairs compared to the MS group. However, propensity score matching resulted in no significant differences in repair rates between the two groups (9 repairs in MIMVS, 8 repairs in MS, for 39 patients in each respective group). Though this does not explain the reduced clamp time in this study, this could partially explain the longer cross-clamp and overall operative times reported in other studies. Some studies comparing MIMVS to MS have more repairs in the MIMVS group than replacements (5).

The most likely explanation for the shortened cross-clamp and CPB times as well as the shorter overall operative times for MIS procedures is the high case load and experience of surgeons performing MIMVS at the DHZB. In the period of this study, three highly trained and specialized surgeons exclusively performed the MIMVS procedures (30).

## 4.2. Postoperative Outcomes

### 4.2.1. Procedural Outcomes

As mentioned earlier, MIMVS patients needed less RBC and FFP transfusions which could be linked to less intraoperative bleeding. Since there were no significant differences in revisions for bleeding, these were likely not influenced by surgical reexploration.

Elevated levels of CK and CK-MB were found for both MIMVS and MS patients within 2 hours postoperatively. This suggests the presence of ischemic injury of the cardiac muscle after surgery. A statistically significant difference in CK-MB between the groups (MIMVS mean 74.94 U/l, MS mean 88.85 U/l) was registered. However, this difference is most likely too subtle to indicate a clinically relevant difference in ischemic myocardial stress in surgery.

### 4.2.2. Pulmonary Outcomes

Two important findings for pulmonary outcomes were ventilation time and the need for reintubation after extubating. The median ventilation time for MS patients was approximately 24 hours and for MIMVS patients 12 hours. Minimally invasive mitral valve surgery patients may have needed less time on the ventilator because this procedure causes less trauma to the chest cavity since the integrity of the thorax has an impact on postoperative lung function. A reduction in ventilation time has also been reported in other studies comparing MIMVS to a conventional full MS (5). The present work suggests that these findings may be transferable in the IE setting. The rate of tracheotomies was not elevated. This aligns with our findings since a tracheotomy is typically only performed if the patient is expected to need mechanical ventilation for more than 21 days (97).

Less transfusion of RBC and FFP units may also have contributed to a reduction in the risk of transfusion-related acute lung injury (TRALI) in the MIMVS group, resulting in better postoperative pulmonary function. During TRALI, a patient develops acute pulmonary edema

within 6 hours after transfusion of blood products, usually due to antibodies (98). A total higher number of blood products administered is a risk factor in developing TRALI. In this study, the MS group may have had more of these complications due to their increased number of transfusions. This could in turn have led to more reintubations and increased ventilation time.

### 4.2.3. Cardiovascular Outcomes

The calculated VIS and postoperative inotrope administration time gave insights to the cardiovascular stability of MS and MIMVS patients after their procedures. The fact that no significant differences were noted suggests that both methods of access are similarly challenging to the patient's cardiovascular stability. Previous studies have shown that VIS is a predictor for adverse outcomes in adult cardiothoracic surgery (99). The odds ratio increases linearly with higher VIS scores (99). More research is necessary to transfer these findings to the active and subacute IE population. The nature of their disease and the possibility of sepsis already makes them more likely to receive vasoactive medication.

Rates for low cardiac output and pacemaker implantation were also similar among the populations. This is an additional indicator for safety and comparability to MS when using MIMVS to treat IE.

As described in 1.3.2.3., there is still controversy around the risk of stroke in MIMVS procedures. Literature suggest that this risk may be attributed to the use of endoaortic clamping (71). oN inferences can be made about risk of postoperative stroke from our findings since the event only occurred once in the patient population.

### 4.2.4. Intensive Care Medicine Outcomes

Intensive Care Unit stay was insignificantly higher for MS patients ($p=0.061$). A shorter ICU stay has been demonstrated in MV surgery for non-IE patients in a meta-analysis by Sündermann et al. comparing right lateral minithoracotomy to MS (70). These findings may not be replicable in an IE population because of endocarditis-specific risk factors like sepsis. In this study, readmissions to the ICU were also similar for MIMVS and MS patients.

There was also no difference in postoperative renal function, hemodialysis, multi-organ failure, supporting that the procedures were equally safe.

## 4.3. Follow-up Outcomes

There were no significant differences in 30-day, 1-year, and follow-up mortality between the groups. This aligns with findings comparing MS to MIMVS in non-IE patients, e.g. in a meta-analysis by Sündermann et al. (70). Other propensity score matched studies also showed similar early mortality rates for MIMVS compared to MS (52). However, the population size in this study of 72 patients is a too small population size to produce reliable assumptions about mortality.

This study did show a significant reduction in reoperations for the MIMVS group. Although most reoperations were linked to reinfection, no inferences could be made on why this was the case for more MIS than MIMVS patients. This was especially surprising given that the patient populations were balanced for endocarditis complexity using the De Feo Score. A possible explanation could be an overall higher rate of wound and mediastinal infections in MIS patients linked to a larger wound area, which may in turn increase the risk of prosthetic MV infection. These findings also need to be seen in the light of a shorter follow-up period than for sternotomy patients. Further, reoperation rates may be affected by surgeon skill since all MIMVS procedures were performed by 3 highly experienced minimally invasive surgeons (30).

All in all, these findings show that both MIMVS and MS are good treatment options for the critical situation of IE with acceptable outcomes. Both procedures are equally safe and tolerable to the patient. MIMVS yields benefits in the intensive care setting directly after surgery and can decrease reoperation rate. Still, the choice of whether to use MIMVS or MS as an approach to MV IE needs to be made via a careful, individual, interdisciplinary evaluation (30).

## 4.4. Other Minimally Invasive Approaches to the Mitral Valve

The right anterolateral minithoracotomy is not the only minimally invasive procedure available for MV surgery. Generally speaking, there are transcatheter and surgical approaches for MV repair and replacement.

There are many efforts in developing procedures and devices for transcatheter mitral valve replacement (TMVR) and repair (TMVr). The MV's complex architecture and various etiologies for mitral regurgitation have complicated these aspirations. For TMVr, the only

widely adopted procedure is the MitraClip, which permanently opposes the AML and PML, creating a double orifice and ideally reducing mitral regurgitation. Some other procedures aiming in performing an annuloplasty were developed but not widely implemented due to lack of clinical efficacy (6). The implementation of TMVR also faces difficulties, some of these including the asymmetrical MV anulus geometry, its constant movement, its proximity to the AV and LVOT, calcification, and anatomic variability. Some centers use valves designed for transcatheter AV replacement in an off-label approach in patients who have had previous MV surgery. Specific TMVR are in development, some of which are implanted off-pump via a ministernotomy (6).

Though these catheter approaches are promising for MV surgery in general, the removal of vegetations and clearing of abscesses will not be possible. Therefore, most of the above mentioned transcatheter techniques will not be options to treat IE, even if these procedures can repair or replace damaged valves and restore cardiac function.

Aside from the right anterolateral minithoracotomy approach for MIS, the MV can also be accessed via a partial upper or lower sternotomy. These modes of access can easily be extended into a full MS and can also bring advantages in postoperative pain and cosmesis. However, these partial sternotomies are preferred for AV access in IE rather than for MV access (100).

## 4.5. Limitations

The findings from this study come from a relatively small, single-center analysis. The retrospective study design naturally limits the size of the patient population and the data available for analysis. Furthermore, it induces a selection bias, in this case leading to a healthier patient population for MIMVS. The propensity score matching minimized this bias as much as possible. A prospective randomized controlled study is still superior (30).

Propensity score matching has its own limitations. To begin, the preoperative characteristics of the study patients could only be adjusted for variables that were recorded. Also, not all preoperative characteristics could be included in the matching as this would have excluded too many patients. In this study, it was attempted to find a compromise by including the most important epidemiologic data as well as composite scores to reflect more complex characteristics. The De Feo Score quantified the severity of IE and the STS Score summarized the preoperative risk profile. The factors that were not taken into matching can only be

accounted for in a randomized study design. The use of multiple testing in data analysis after the propensity score matching is a further limitation of this study. The reported outcomes suggest a trend of better patient outcomes for MIMVS. However, RCTs will be necessary to fully prove these findings (30).

The procedures analyzed were performed by multiple surgeons. For the MIMVS group, 3 experienced surgeons performed all the procedures. The surgeons for the MS group were broader and more included these 3 who performed MIMVS. This makes a severe biasing effect unlikely. The surgeon's case volume, experience, and skill may still influence the findings (30).

Furthermore, the overall characteristics of the study group were shifted towards a less critically ill preoperative state. This is because of the preoperative characteristics of the available MIMVS, which the control MS patients were adjusted to. The majority of more critically ill MS patients did not find a match in the MIMVS group during the propensity score analysis. This means that the findings in this paper apply to IE MIMVS patients who are in a less critical preoperative state. In order to extend these findings to more emergent cases of MV IE, further studies are necessary. When technically complex MV pathologies like annular involvement are expected, MIMVS may not be the appropriate surgical approach (30).

The findings relating to blood products, especially RBC units, are dependent on clinical practice at *DHZB* regarding the indication for transfusion. These are subject to predefined cut-offs, e.g. hemoglobin for RBC unit transfusion. Naturally, individual decisions due to clinical condition of the patient also influence the decision to administer blood products. This may have influenced the findings in this study. Since both MS and MIMVS were affected by these individual decisions, a severe impact is not likely.

Another limitation is that MV repair versus replacement rates were not analyzed. There is extensive evidence that MV repair leads to better outcomes than MV replacement (100). Therefore, surgeons strive to repair the MV instead of implanting a prosthetic valve whenever possible (30). In this study, repair versus replacement was included in the propensity score matching to account for this difference in outcome. Our research question was focused on the direct postoperative setting.

## 4.6. Outlook

Minimally invasive procedures are gaining popularity with physicians and patients. Patients expect an evolution towards minimally invasive procedures and no longer expect open surgical procedures as the standard of care. Physicians used to be trained in MIMVS only after

learning conventional open sternotomy surgery. This dogma is slowly shifting. The endoscopic camera view allows both the surgeon and trainee an excellent visualization of the MV. This allows the trainee as surgical first assistant to become more familiar with the procedure they are learning and allows the cardiac surgeon who is teaching the procedure to supervise with more accuracy (5). In other surgical fields, like general surgery, a keyhole approach is used as a standard for many procedures. Complimented by the improvement and further evolution of technical instruments, the future of cardiac surgery will surely shift to less invasive procedures whenever possible.

# 5. Conclusion

This retrospective study compared the MIMVS approach to the conventional MS approach for native MV repair or replacement in patients with IE. Propensity score matching was used to adjust for differences in preoperative state. Operative and postoperative outcomes were compared and evaluated for both groups.

The study showed that MIMVS for IE of the native MV provides clinical benefits when compared to conventional MS. This included shorter ventilation times, less RBC and FFP transfusions, and less reoperations.

The findings from this first direct comparison of MIMVS to MS contribute towards the discussion of the implementation of MIMVS for IE of the native MV. Considering IE as a contraindication for MIMVS per se should be reevaluated. Instead, guidelines should reflect the complexity of the disease and carefully consider a patient's preoperative status and the state of the disease. Minimally invasive mitral valve surgery should be considered a first-line surgical approach for eligible patients with MV IE.

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# 7. Supplement

Supplement 1: Instruments used for data acquisition.

*Confidential*



## Anagraphic / General information

| | |
|---|---|
| Record ID | _____ (Internal REDCap authentification number) |
| Patient ID | _____ |
| Case ID | _____ |
| Surname | _____ |
| Name | _____ |
| Street | _____ |
| City | _____ |
| Postal code | _____ |
| Federal land | _____ |
| Gender | ○ Male<br>○ Female |
| Birth Date | _____ (Format: DD-MM-YYYY) |
| Age | _____ (Years) |
| Admission Date | _____ (Format: DD-MM-YYYY) |
| Hospitalized Prior to DHZB? | ○ Yes<br>○ No |
| Hospitalized since | _____ |
| Discharge Date | _____ (Format: DD-MM-YYYY) |

| | |
|---|---|
| Hospitalization Time | _____ (Days) |
| Hospitalisation days before admission DZHB | _____ |
| Discharge Destination | ◯ PKH<br>◯ Rehabilitation<br>◯ Home<br>◯ Other Hospital<br>◯ Death |
| Other hospital discharge date | _____ |
| PKH Admission Date | _____ (Format: DD-MM-YYYY) |
| PKH Discharge Date | _____ (Format: DD-MM-YYYY) |
| PKH Hospitalization Time | _____ (Days) |
| Did the patient take part in the prospective randomized mitral valve ring annuloplasty (Physio II versus Memo 4D) study? | ◯ No<br>◯ Yes |
| Did the patient take part in the retrospective randomized mitral valve ring annuloplasty (Physio II) study? | ◯ No<br>◯ Yes |
| General Patients Related Comments | _____ |

# General Anamnesis

Height

_____
(m)

Weight

_____
(kg)

Body Surface Area

_____
(m2)

Body Mass Index

_____
(kg/m2)

Ethnic Group

- ◯ Caucasic
- ◯ Asian
- ◯ Hispanic
- ◯ Black

**Pre-Existing Conditions**

| | No | Yes | Not Available |
|---|---|---|---|
| Hypertension | ◯ | ◯ | ◯ |
| Dyslipidemia | ◯ | ◯ | ◯ |
| Familiarity | ◯ | ◯ | ◯ |
| Poor Mobility | ◯ | ◯ | ◯ |
| Pulmonary Edema | ◯ | ◯ | ◯ |
| TIA (resolves within 24 hours) | ◯ | ◯ | ◯ |
| Stroke (CVA that lasts for greater than 24 hours) | ◯ | ◯ | ◯ |
| Neurological disease (ESI definition) | ◯ | ◯ | ◯ |

Event description (what, when)

_____

Preop neurologic complications

_____
(what? when? association to IE?)

Brain haemorrhage

- ◯ Yes
- ◯ No

(=intrazerebrale Blutung, Blutung in das Hirnparenchym)

Smoke

- ◯ No
- ◯ Ex-Smoker
- ◯ Active Smoker

| | |
|---|---|
| Diabetes Mellitus type 1 | ◯ No<br>◯ Oral Therapy<br>◯ Insuline |
| Diabetes Mellitus type 2 | ◯ No<br>◯ Diet<br>◯ Oral Therapy<br>◯ Insuline |
| Pre-Op Critical State | ◯ No<br>◯ Yes<br>(VT or VFib or aborted sudden death, preoperative CPR, preoperative ventilation before anaesthetic room, preoperative inotropes or IABP, preoperative acute renal failure (anuria or oliguria < 10ml/hr)) |
| Heart failure? | ◯ Yes<br>◯ No<br>(Herzinsuffizienz? Anhand LVEF: normal über 52%, leichte HI 41-51%, mittel 30-40%, schwer unter 30%) |
| Heart failure onset | ◯ recent (e.g. since endocarditis diagnosis)<br>◯ preexisting |
| Pre-Op NYHA | ◯ I<br>◯ II<br>◯ III<br>◯ IV<br>(I: Herzkrankheit (objektiver Nachweis einer kardialen Dysfunktion) ohne körperliche Limitation; II: Beschwerden bei min. mittelschwerer körperlicher Belastung (zB 2 Stockwerke Treppen); III: Beschwerden bei leichter körperlicher Belastung (zB ein Stockwerk); IV: Beschwerden in Ruhe) |
| Chronic Lung Disease (STS Definition) | ◯ No<br>◯ Mild (60-75% FEV1)<br>◯ Moderate (50-59% FEV1 or Steroids)<br>◯ Severe (FEV1 < 50% and CO2 > 50 mmHg)<br>◯ Yes, (unknown severity) |
| Chronic Kidney Disease | ◯ No<br>◯ Yes |
| Chronic Kidney Disease Stadium | ◯ 1<br>◯ 2<br>◯ 3<br>◯ 4<br>◯ 5<br>(Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m 2); Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m 2); Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m 2); Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m 2) Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m 2 or dialysis)) |

| | |
|---|---|
| Acute renal failure | ○ Yes<br>○ No<br>(as clinical complication of IE) |
| Dialysis | ○ No<br>○ Yes |
| Cancer | ○ No<br>○ Yes |
| Immunocompromised state | ○ No<br>○ Yes |
| HIV | ○ No<br>○ Yes |
| Previous endocarditis | ○ No<br>○ Yes |

**ECG / Only fill out heart rhythm**

| | |
|---|---|
| Heart rate | _____<br>(bpm) |
| PQ-Time | _____<br>(ms) |
| QRS-Time | _____<br>(ms) |
| QT/QTc | _____<br>(number/number ms) |
| Heart Rhythm | ☐ Other<br>☐ Sinus Rhythm<br>☐ Atrial Fibrillation<br>☐ Atrial Flatter<br>☐ Pacemaker<br>☐ Left bundle branch block<br>☐ Right bundle branch block<br>☐ AV-Block I<br>☐ AV-Block II<br>☐ AV-Block III<br>☐ Ventricular tachycardia<br>☐ Ventricular extrasystole |
| Other heart rhythm | _____ |
| Pre-Op Clinical History Comments | _____ |

# Cardiologic Anamnesis

| | |
|---|---|
| Urgency | ◯ Elective<br>◯ Urgent<br>◯ Emergency<br>◯ Salvage<br>(elective: within 1-2 weeks (antibiotic treatment before); urgent: within 7d; emergency: within 24h; salvage: within hours) |
| Logistic EuroSCORE I | _____<br>(%) |
| EuroSCORE II | _____<br>(%) |
| STS PROM mvr Model | _____<br>(%) |
| STS PROM isolated MVR | _____<br>(%) |
| Previous Cardiac Surgery | ☐ No<br>☐ Aortic Valve Replacement bio<br>☐ Aortic Valve Replacement mech<br>☐ CABG<br>☐ MitraClip<br>☐ Mitral Valve Replacement bio<br>☐ Mitral Valve Replacement mech<br>☐ Mitral Valve Repair<br>☐ Other |
| Other Previous Cardiac Surgery | _____ |
| Surgery date | _____ |
| **Rhythm** | |
| Pre-Op Rhythm | ◯ Sinus Rhythm<br>◯ Atrial Fibrillation<br>◯ Pacemaker<br>◯ Other Arrhythm |
| Atrial Fibrillation | ◯ No<br>◯ Paroximal<br>◯ Persistent<br>◯ Permanent |

| **Shock** | |
|---|---|
| Cardiogenic Shock | ◯ No<br>◯ Yes |
| Septic shock | ◯ Yes<br>◯ No |

| **Endocarditis** | |
|---|---|
| Clinical active endocarditis | ◯ No<br>◯ Yes, without Embolization<br>◯ Yes, with Embolization |
| Embolization organ | ☐ Brain<br>☐ Lung<br>☐ Spleen<br>☐ Other |
| Symptom severity of embolization | ◯ asymptomatic<br>◯ mild<br>◯ severe |
| Embolization when? | ☐ before surgery<br>☐ after surgery |
| Embolization date | _____ |
| Diagnosis Date Endocarditis | _____ |
| Endocarditis state | ◯ acute (rapidly progressive infection)<br>◯ subacute<br>◯ chronic (low-grade fever, non-specific symptoms) |

| **Heart disease** | |
|---|---|
| Status post myocardial infarction | ◯ No<br>◯ Last 48h<br>◯ Last 21 Days<br>◯ Last 22-91 Days<br>◯ Unknown Time |
| Post-infarction ventricular septal rupture | ◯ No<br>◯ Yes |
| Coronary Artery Disease | ◯ No<br>◯ One Vessel<br>◯ Two Vessels<br>◯ Three Vessels |
| Left main coronary artery disease | ◯ No<br>◯ Yes |

**Vascular Disease**

| | No | Yes | Not Available |
|---|---|---|---|
| Carotid TEA / other carotid artery intervention | ○ | ○ | ○ |
| Carotid Stenosis > 50% | ○ | ○ | ○ |
| Peripheral artery disease | ○ | ○ | ○ |

Pulmonary hypertension

- ○ No
- ○ Moderate (sysPAP 31-55 mmHg)
- ○ Severe (sysPAP >55 mmHg)

Cardiomyopathy

- ○ No
- ○ Dilatative
- ○ Hypertrophic
- ○ Ischemic
- ○ Other
- ○ Restrictive

Cardiomyopathy comments

_____

# Lab and Preop Treatment

| | |
|---|---|
| **m.life Labor > Chemie** | |
| Fever within 72h preop? | ◯ Yes<br>◯ No<br>(Fever: Temp =/> 38) |
| LDH | _____<br>(U/L) |
| Creatinine | _____<br>(mg/dL) |
| GFR | _____<br>(mL/min/1.73m2) |
| CRP | _____ |
| **m.life Labor > Bb+Koag** | |
| WBC (Leucocytes) | _____<br>(K/µL) |
| Hemoglobin | _____<br>(g/dL) |
| Hematocrit | _____<br>(%) |
| Platelets | _____<br>(K/µL) |
| **m.life Labor > Blutgase (arteriell)** | |
| ABG lactate level | _____<br>(mg/dL) |

| **Preop inotropics (nur Zeit einfüllen wenn es welche gab, Mengen nicht)** | |
|---|---|
| Total Inotrope exposure time preop | _____ (total time in h) |
| Pre-OP inotrope medication | ◯ No<br>◯ Yes |
| Pre-OP vasopressor medication | ◯ No<br>◯ Yes |
| Dopamine 2h | _____ (mcg/kg/min) |
| Dobutamine 2h | _____ (mcg/kg/min) |
| Epinephrine 2h | _____ (mcg/kg/min) |
| Inotrope score 2h | _____ |

| **Intensivmedizin** | |
|---|---|
| Pre-Op ICU treatment | ◯ No<br>◯ Yes |
| Pre-OP intubation | ◯ No<br>◯ Yes |
| Pre-OP CPR within the last 48h | ◯ No<br>◯ Yes |

# Preop Echo

| | |
|---|---|
| Pre-OP echo modality | ◯ TTE<br>◯ TEE |
| Pre-OP echo date | _____<br>(Format: DD-MM-YYYY) |
| Left ventricular ejection fraction grade (LVEF) | ◯ < 30%<br>◯ 30% - 50%<br>◯ > 50% |
| LVEF in numbers: | _____<br>(%) |
| Right Ventricle Ejection Fraction (RVEF) | _____<br>(%) |
| Tricuspid Annular Plane Systolic Excursion (TAPSE) | _____<br>(mm) |
| Left Ventricle End-Diastolic Diameter (LVEDD) | _____<br>(mm) |
| Left-Ventricle End-Systolic Diameter (LVESD) | _____<br>(mm) |
| LV Mass | _____<br>(g) |
| Septal thickness | _____<br>(mm) |
| Left atrial area | _____<br>(cm2) |
| Left atrial diameter | _____<br>(mm) |
| Mitral vena contracta | _____<br>(mm) |
| Mitral valve area (PHT) | _____<br>(cm2 (derived from PHT)) |

Right ventricular systolic pressure

_____
(mmHg)

General pre-OP echo comments

_____

# Valve And Anulus Pathology

**Valve Assessment**

**(Grades definition: No-Trace: AI/MI/TI < 1; Mild: AI/TI/MI = 1, Mild, Trace-to-Mild; Moderate: AI/TI/MI = 1-2 and = 2, Mild-to-Moderate, Moderate; Severe: AI/TI/MI = 2-3 and > 3, Moderate-to-Severe, Severe)**

| | No-Trace | Mild | Moderate | Severe |
|---|---|---|---|---|
| Aortic Stenosis | ○ | ○ | ○ | ○ |
| Aortic Regurgitation | ○ | ○ | ○ | ○ |
| Tricuspid Stenosis | ○ | ○ | ○ | ○ |
| Tricuspid Regurgitation | ○ | ○ | ○ | ○ |
| Mitral Stenosis | ○ | ○ | ○ | ○ |
| Mitral Regurgitation | ○ | ○ | ○ | ○ |

Mitral valve type

○ Native
○ Prosthetic, biological
○ Prosthetic, mechanical
(The preoperative mitral valve type (which is infected))

Carpentier Class

○ Not Applicable
○ I
○ II
○ IIIa
○ IIIb

Mitral Annular Calcification

○ No
○ Anterior
○ Posterior
○ Anterior + Posterior
○ Yes, location unknown

Mitral Annulus Dilatation

○ No
○ Anterior
○ Posterior
○ Anterior + Posterior
○ Yes, location unknown

Annular Diameter

_____
(mm)

Mitral IIIb Notes

_____

| **Endocarditis - valvular effects** | |
|---|---|
| Mitral Valve Endocarditis | ◯ No<br>◯ Yes |
| Vegetations | ☐ No<br>☐ Anterior Mitral Leaflet<br>☐ Posterior Mitral Leaflet<br>☐ Bileaflet<br>(Infected mass attached to an endocardial structure or on implanted intracardiac material. // Echo: Oscillationg or non-oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material) |
| Vegetation largest size in cm | _____ |
| Perforation | ☐ No<br>☐ Anterior Mitral Leaflet<br>☐ Posterior Mitral Leaflet<br>☐ Bileaflet<br>(Interruption of endocardial tissue continuity- // Interruption of endocardial tissue continuity traversed by color-doppler flow) |
| Annular Abscess | ◯ No<br>◯ Yes |
| Other abscess | ◯ Yes<br>◯ No<br>(Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen. // Echo: thickened, non-homogenous perivalvular area with echodense or echolucent appearance) |
| Pseudoaneurysm | ◯ Yes<br>◯ No<br>(Perivalvular cavity communicating with the cardiovascular lumen // Echo: Pulsatile perivalvular echo-free space, with color-doppler flow detected) |
| Fistula | ◯ Yes<br>◯ No<br>(Communication between two neighboring cavities through a perforation. // Echo: Color-doppler communication between two neighboring cavities through a perforation) |
| Valve aneurysm | ◯ Yes<br>◯ No<br>(Saccular outpoucing of valvular tissue. // Saccular bulging of valvular tissue) |

| | |
|---|---|
| Dehiscence of a prosthetic valve | ◯ Yes<br>◯ No<br>(Echo: Paravalvular regurgitation identified by TTE/TOE, with or without rocking motion of the prosthesis) |

**Endocarditis - general**

| | |
|---|---|
| Blood Culture | _____ |
| Organism category | ☐ Staphylococcus aureus<br>☐ Fungi<br>☐ Non-HACEK Gram-negative bacilli<br>☐ HACEK Gram-negative bacilli<br>☐ Streptococcus<br>(HACEK = Haemophilus parainfluenzae/paraphrophilus/influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Klingella kingae/dentrificans) |
| When was organism identified? | ◯ Before surgery (blood cultures)<br>◯ During surgery (path.)<br>◯ After surgery (blood cultures)<br>◯ Never identified<br>◯ Information not given |
| When was last blood culture before surgery? | _____ |
| Last blood culture preop positive or negative? | ◯ Negative<br>◯ Positive |
| Intraoperative MiBi | ◯ Negative<br>◯ Positive |
| Endocarditis on other Valves | ◯ No<br>◯ One other Valve<br>◯ Two other Valves |
| General Valvular Pathology Comments | _____ |

# Leaflets Pathology

| | |
|---|---|
| Leaflet Fibrosis | ○ No<br>○ Anterior Mitral Leaflet<br>○ Posterior Mitral Leaflet<br>○ Bileaflet |
| Leaflet Calcification | ○ No<br>○ Anterior Mitral Leaflet<br>○ Posterior Mitral Leaflet<br>○ Bileaflet |
| Anterior Mitral Leaflet Calcification Site | ☐ A1<br>☐ A2<br>☐ A3 |
| Posterior Mitral Leaflet Calcification Site | ☐ P1<br>☐ P2<br>☐ P3 |

**Leaflet Motion**

| | Normal | Decreased/Restriction | Increased/Prolapse | Increased/Flail |
|---|---|---|---|---|
| Anterior Mitral Leaflet | ○ | ○ | ○ | ○ |
| A1 | ○ | ○ | ○ | ○ |
| A2 | ○ | ○ | ○ | ○ |
| A3 | ○ | ○ | ○ | ○ |
| Posterior Mitral Leaflet | ○ | ○ | ○ | ○ |
| P1 | ○ | ○ | ○ | ○ |
| P2 | ○ | ○ | ○ | ○ |
| P3 | ○ | ○ | ○ | ○ |

| | |
|---|---|
| Anterior Mitral Leaflet Cleft | ○ No<br>○ Yes |
| Posterior Mitral Leaflet Cleft | ○ No<br>○ Yes |
| Posterior Mitral Leaflet Cleft Localization | ☐ P1/P2<br>☐ P2/P3 |

# General Procedure Data

| | |
|---|---|
| OP Number | _____ |
| Operation Date | _____ (Format: DD-MM-YYYY) |
| Primary Indication | ◯ Mitral Regurgitation<br>◯ Mitral Stenosis<br>◯ Endocarditis<br>◯ Other |
| Diagnosis/Surgical Indication and Operation | _____ (Copied from "OP-Bericht" in MedFolio) |
| Sepsis | ◯ Yes<br>◯ No<br>(Sepsis at time of procedure?) |
| Primary Access | ◯ Anterolateral Minithoracotomy<br>◯ Median Sternotomy |
| Decision to median sternotomy | ◯ Planned primary median sternotomy<br>◯ Secondary median sternotomy due to intraoperative complications |
| Nipple Cut | ◯ No<br>◯ Yes |
| Planed Mitral Procedure (Intention to Treat) | ◯ No<br>◯ Mitral Valve Repair<br>◯ Mechanical Mitral Valve Replacement<br>◯ Biological Mital Valve Replacement |
| Other Procedures | ☐ No<br>☐ Maze<br>☐ Left Atrial Appendage Occlusion Procedure<br>☐ Atrial Septal Defect Closure Procedure<br>☐ Tumor Resection<br>☐ Other |
| Other Procedure Data Comment | _____ |
| Surgeon | ◯ Falk<br>◯ Kempfert<br>◯ Jacobs<br>◯ Other |
| Surgeon name | _____ |

| | |
|---|---|
| Endoscopic System | ○ 2D<br>○ 3D |
| Operation Time | _____<br>(min) |
| Cardio Pulmonary By-Pass Time | _____<br>(min) |
| Cross-Clamp Time | _____<br>(min) |
| Aortic Clamp Type | ○ Chitwood Transthoracic Clamp<br>○ Endoaortic Clamping/Intraclude Balloon<br>○ Fibrillation<br>○ Beating-heart |
| Arterial Cannulation site | ☐ Right femoral artery<br>☐ Left femoral artery<br>☐ Right axillary artery<br>☐ Central Cannulation<br>☐ Other |
| Cardioplegia Type | ○ Custodiol (Brettschneider)<br>○ Del Nido<br>○ Other |
| Other Cardioplegia Type | _____ |
| Cardioplegia | _____<br>(mL) |
| Cardioplegia Dosis | ○ 1<br>○ 2<br>○ 3<br>○ 4<br>○ 5 |
| 1. Cardioplegia Dosis | _____<br>(ml) |
| 2. Cardioplegia Dosis | _____<br>(ml) |
| 3. Cardioplegia Dosis | _____<br>(ml) |

| | |
|---|---|
| 4. Cardioplegia Dosis | _____ (ml) |
| 5. Cardioplegia Dosis | _____ (ml) |
| Intra-OP temperature | _____ (°C) |
| Conversion to Sternotomy | ☐ No<br>☐ Pulmonary Adhesions<br>☐ Bleeding<br>☐ Failed Repair<br>☐ Typ-B Dissection<br>☐ Type-A Dissection<br>☐ AV-Disruption |
| Urine output | _____ (mL) |
| Sodium max | _____ (mmol/L) |
| Sodium min | _____ (mmol/L) |
| Potassium max | _____ (mmol/L) |
| Potassium min | _____ (mmol/L) |
| Magnesium max | _____ (mmol/L) |
| Magnesium min | _____ (mmol/L) |
| Glucose | _____ (mg/dL) |
| Hemoglobin | _____ (g/dL) |

| | |
|---|---|
| Dopamine | _____ (µg/kg/min) |
| Dobutamine | _____ (µg/kg/min) |
| Epinephrine | _____ (µg/kg/min) |
| Inotrope Score | _____ |
| Hemofiltration | ○ Yes ○ No ○ Unknown |
| Hemofiltration Volume | _____ (mL) |

# Valve Procedure

| | |
|---|---|
| Mitral Valve Procedure (Actually Performed) | ◯ No<br>◯ Mitral Valve Repair<br>◯ Biological Mitral Valve Replacement<br>◯ Mechanical Mitral Valve Replacement |
| Tricuspid Procedure | ◯ No<br>◯ Tricuspid Valve Repair<br>◯ Tricuspid Valve Replacement |
| Isolated Mitral Valve Ring Repair | ◯ No<br>◯ Yes |
| Mitral Valve Repair Attempts | ◯ 0<br>◯ 1<br>◯ 2<br>◯ 3 |
| Leaflet Repair | ☐ Anterior Mitral Leaflet Reconstruction<br>☐ Posterior Mitral Leaflet Reconstruction<br>☐ Quadrangolar Resection<br>☐ Triangular Resection<br>☐ Anterior Mitral Leaflet Neochordae Implantation<br>☐ Posterior Mitral Leaflet Neochordae Implantation<br>☐ Plication<br>☐ Edge-to-Edge Repair<br>☐ Cleft Closure |
| AML Chordae Lenght | _____<br>(mm) |
| PML Chordae Lenght | _____<br>(mm) |
| Mitral Annuloplasty Type/Model | ◯ No<br>◯ Physio-II<br>◯ Cosgrove Band<br>◯ Edwards McCarthy Adams Etlogix<br>◯ Other |
| Other Mitral Annuloplasty Type/Model | _____ |
| Ring Size | _____ |
| Prosthesis Type | ◯ Bio Hancock<br>◯ Bio SJM Epic<br>◯ Mech SJM<br>◯ Medtronic Mitral<br>◯ Bioprosthesis Edwards Rinder<br>◯ Other<br>◯ BioIntegral |

| | |
|---|---|
| Other Prosthesis Type | _____ |
| Prosthesis Size | _____ (mm) |
| Intraop Mitral Valve Sizing | _____ (mm) |
| Intra-Op Downsizing | ◯ No<br>◯ Yes |
| Tricuspid Valve Repair Model | ◯ No<br>◯ Cosgrove Band<br>◯ PhysioTricuspid<br>◯ Carpentier Edwards<br>◯ Other |
| Other Tricuspid Valve Repair Model | _____ |
| Tricuspid Valve Annuloplasty Size | _____ |
| Tricuspid Valve Repair - Neochordal Loop | ◯ No<br>◯ Yes |
| Tricuspid Valve Replacement Size | _____ |
| Concomitant Minimally Invasive MV Surgery and TV Surgery | ◯ No<br>◯ Yes |
| Intra-Op TEE Residual Mitral Regurgitation | ◯ No-Trace<br>◯ Mild<br>◯ Moderate<br>◯ Severe<br>(No-Trace: MI< 1; Mild: MI=1, Trace-to-Mild, Mild; Moderate: MI=1-2 and =2, Mild-to-Moderate, Moderate; Severe: MI=2-3 and >=3, Moderate-to-Severe, Severe) |
| Residual Mitral Regurgitation Reason | _____ |
| Intra-Op TEE Residual Tricuspid Regurgitation | ◯ No-Trace<br>◯ Mild<br>◯ Moderate<br>◯ Severe<br>(No-Trace: TI< 1; Mild: TI=1, Trace-to-Mild, Mild; Moderate: TI=1-2 and =2, Mild-to-Moderate, Moderate; Severe: TI=2-3 and >=3, Moderate-to-Severe, Severe) |

| | |
|---|---|
| Residual Tricuspid Regurgitation Reason | _____ |
| Hot Shots | ◯ No<br>◯ Yes |
| Intra-Op TEE Systolic Anterior Movement (SAM) | ◯ No<br>◯ Light Functional SAM<br>◯ Relevant SAM |
| Intra-Op TEE Comments | _____ |
| Rhythm after de-clamping | ◯ Other<br>◯ Sinus Rhythm<br>◯ Atrial Fibrillation<br>◯ AV-Block 1<br>◯ AV-Block 2<br>◯ Av-Block 3<br>◯ Asystole<br>◯ Atrial flatter<br>◯ Ventricular Tachycardia<br>◯ Ventricular Fibrillation |
| Other Rhythm | _____ |
| Reperfusionszeit | _____<br>(min) |
| LV SD Volume before clamping | _____ |
| RV SD Volume before clamping | _____ |
| LV SD Volume after clamping | _____ |
| RV SD Volume after clamping | _____ |

# Postop Echo

| | |
|---|---|
| Post-Op Echo Modality | ○ TTE<br>○ TEE |
| Post-Op Echo Date | _____<br>(Format: DD-MM-YYYY) |

**Post-Op Valve Assessment**

**No-Trace: AI/MI/TI< 1; Mild: AI/MI/TI=1, Trace-to-Mild, Mild; Moderate: AI/MI/TI=1-2 and =2, Mild-to-Moderate, Moderate; Severe: AI/MI/TI=2-3 and >=3, Moderate-to-Severe, Severe**

| | No-Trace | Mild | Moderate | Severe |
|---|---|---|---|---|
| Aortic Regurgitation_post | ○ | ○ | ○ | ○ |
| Mitral Regurgitation_post | ○ | ○ | ○ | ○ |
| Tricuspid Regurgitation_post | ○ | ○ | ○ | ○ |

| | |
|---|---|
| Postoperative Mitral Valve Quality | ☐ No insufficiencies<br>☐ Paravalvular insufficiency<br>☐ Transvalvular insufficiency |
| Left Ventricle Ejection Fraction Grade (LVEF) post | ○ < 30 %<br>○ 30 - 50 %<br>○ > 50 % |
| If Available, LVEF in numbers post: | _____<br>(%) |
| Right Ventricle Ejection Fraction (RVEF) post | _____<br>(%) |
| Left Ventricle End Diastolic Diameter (LVEDD) | _____<br>(mm) |
| Right Ventricle End Diastolic Diameter (RVEDD) post | _____<br>(mm) |
| Left Ventricle End Systolic Diameter (LVESD) post | _____<br>(mm) |
| Systolic Pulmonal Arterial Pressure (sysPAP) post | _____<br>(mmHg) |
| LV Mass post | _____ |

| | |
|---|---|
| Septal thickness post | _____ |
| Left Atrial Diameter post | _____ (mm) |
| Mitral dpMittel post | _____ (mmHg) |
| General Post-Op Echo Comments post | _____ |

# Postop Treatment

| | |
|---|---|
| ICU Stay | _____ (hours) |
| ICU Stay in hours | _____ |
| Lenght of Ventilation | _____ (min) |
| Planned Peri-Operative Management | ◯ Fast Track<br>◯ Standard Track |
| Post-Op HIT (Heparin Induced Trombocytopenia) | ◯ No<br>◯ Yes |
| Red Blood Cell Units (EK) | _____ |
| Platelets Units (TK) | _____ |
| Fresh Frozen Plasma Units (FFP) | _____ |
| Mechanical Support | ◯ No<br>◯ IABP<br>◯ ECMO |
| **Op. Revision** | |
| Revision for Bleeding | ◯ No<br>◯ Yes |
| Revision for Bleeding Date | _____ (PLEASE note the MM-DD-YYYY format) |
| Redo Mitral Valve Repair | ◯ No<br>◯ Yes |
| Redo Mitral Valve Repair Date | _____ (PLEASE note the MM-DD-YYYY format) |
| Redo other | ◯ No<br>◯ Yes |
| Other Re-OP cause | _____ |

| **Postop Inotropics** | |
|---|---|
| Total Inotrope exposure score timing post | _____ (in h) |
| Post-OP Rhythm | ◯ Other rhythm<br>◯ Sinus rhythm<br>◯ Atrial fibrillation<br>◯ Pacemaker |
| Electrical cardioversion | ◯ Yes ◯ No ◯ Unknown |
| Number of electrical cardioversions | _____ (n) |
| Heart Rhythm 1. postop ECG (upon arrival at the ICU) | ☐ Other<br>☐ Sinus Rhythm<br>☐ Atrial Fibrillation<br>☐ Atrial Flatter<br>☐ Pacemaker<br>☐ Left bundle branch block<br>☐ Right bundle branch block<br>☐ AV-Block I<br>☐ AV-Block II<br>☐ AV-Block III<br>☐ Ventricular tachycardia<br>☐ Ventricular extrasystole |
| Other heart rhythm 1. postop ECG | _____ |
| Heart rate 1. postop ECG | _____ (bpm) |
| PQ-Time 1. postop ECG | _____ |
| QRS-Time 1. postop ECG | _____ |
| QT/QTc 1. postop ECG | _____ |
| Heart Rhythm 2. postop ECG (upon discharge) | ☐ Other<br>☐ Sinus Rhythm<br>☐ Atrial Fibrillation<br>☐ Atrial Flatter<br>☐ Pacemaker<br>☐ Left bundle branch block<br>☐ Right bundle branch block<br>☐ AV-Block I<br>☐ AV-Block II<br>☐ AV-Block III<br>☐ Ventricular tachycardia<br>☐ Ventricular extrasystole |

| | |
|---|---|
| Other heart rhythm | _____ |
| Heart rate 2. postop ECG | _____ (bpm) |
| PQ-Time 2. postop ECG | _____ |
| QRS-Time 2. postop ECG | _____ |
| QT/QTc 2. postop ECG | _____ |
| **Postop. Enzymes (Labor > Chemie > Enzyme)** | |
| 1. CK-Value | _____ |
| 1. CK-Value: hours after the Procedure | _____ (h) |
| 1. CK-MB Value | _____ |
| 1. CK-MB Value: hours after the procedure | _____ (h) |
| Post-OP Coronary Angiography (PCA) | ○ No<br>○ Yes |
| PCA: hours after the procedure | _____ (h) |
| Post-OP Coronary Angiography Report | _____ |
| Post-OP Circumflex Artery Revascularization with PTCA/PCI | ○ No<br>○ Yes |

| **Pulmonal Treatment** | | | |
|---|---|---|---|
| | No | Yes | Not Available |
| Tracheotomy | ○ | ○ | ○ |
| Pleural Draiage | ○ | ○ | ○ |
| Re-Intubation after Extubation | ○ | ○ | ○ |

| **Wards** | |
|---|---|
| Re Admission to ICU | ○ No<br>○ Yes |
| Where did the Patient go immediately after the Operation? | ○ AWR<br>○ IPS 1 |
| Reanimation | ○ No<br>○ Yes |
| General Post-Op Comments | _____ |

# Postop Vasoactive Inotropic Score

| **Vasoactive Inotropic Score (VIS) directly postop** | |
|---|---|
| Dopamine dose (µg/kg/min) VIS postop | |
| Dobutamine dose (µg/kg/min) VIS postop | |
| Adrenaline dose (µg/kg/min) VIS postop | |
| Noradrenaline dose (µg/kg/min) VIS postop | |
| Milrinone dose (µg/kg/min) VIS postop | |
| Vasopressin dose (IU/h) VIS postop | |
| VIS postop total | |

| **Vasoactive Inotropic Score (VIS) MAXIMUM (within 24h postop)** | |
|---|---|
| Dopamine dose (µg/kg/min) VIS max | |
| Dobutamine dose (µg/kg/min) VIS max | |
| Adrenaline dose (µg/kg/min) VIS max | |
| Noradrenaline dose (µg/kg/min) VIS max | |
| Milrinone dose (µg/kg/min) VIS max | |
| Vasopressin dose (IU/h) VIS max | |
| VIS max 24h | |

# Postop Laboratory

| **Last post-op lab available** | |
|---|---|
| Last Post-Op Blood Control | _____ (PLEASE note the MM-DD-YYYY format) |
| Leucocytes post | _____ (/nL) |
| Hemoglobin post | _____ (g/dL) |
| Creatinin post | _____ (mg/dL) |
| eGFR post | _____ (ml/min/1,73m2)) |

| **m.life Labor > Chemie eGFR** | |
|---|---|
| 1. eGFR: hours after procedure | _____ (h) |
| 1. eGFR post | _____ |

| **m.life Labor > Chemie** | |
|---|---|
| 1. Creatinine: hours after procedure | _____ (h) |
| 1. Creatinine post | _____ |
| 1. LDH: hours after procedure | _____ (h) |
| 1. LDH post | _____ |

**m.life Labor > Bb+Koag**

1. Hematocrit: hours after procedure

_____ (h)

1. Hematocrit post

_____

1. Platelets: hours after procedure

_____ (h)

1. Platelets post

_____

**m.life Labor > Blutgase (arteriell)**

1. Glucose: hours after procedure

_____ (h)

1. Glucose post

_____

1. Lactate: hours after procedure

_____ (h)

1. Lactate post

_____

1. pH: hours after procedure

_____ (h)

1. pH post

_____

# Perioperative Complications

| | |
|---|---|
| Pain Score after OP | _____ (0-10) |
| Pain Score at discharge | _____ (0-10) |
| Multi Organ Failure | ○ No ○ Yes |

**MACCE (Major Adverse Cardiac and Cerebrovascular Events)**

| | No | Yes | Not Available |
|---|---|---|---|
| Death | ○ | ○ | ○ |
| Myocardial Infarction | ○ | ○ | ○ |
| Stroke | ○ | ○ | ○ |

**Post-Op Cardiac Complications**

| | No | Yes | Not Available |
|---|---|---|---|
| Atrial Fibrillation | ☐ | ☐ | ☐ |
| New Onset Atrial Fibrillation | ☐ | ☐ | ☐ |
| 1st Grade AV-Block | ☐ | ☐ | ☐ |
| 2nd Grade AV-Block | ☐ | ☐ | ☐ |
| 3rd Grade AV-Block | ☐ | ☐ | ☐ |
| New Onset Left Bundle Branch Block (LBBB) | ☐ | ☐ | ☐ |
| Bradycardia | ☐ | ☐ | ☐ |
| Atrial Flutter | ☐ | ☐ | ☐ |
| New Onset Atrial Flutter | ☐ | ☐ | ☐ |
| Non-Substained Ventricular Tachycardia | ☐ | ☐ | ☐ |
| Asystole | ☐ | ☐ | ☐ |
| New Onset Right Bundle Branch Block (RBBB) | ☐ | ☐ | ☐ |
| Peri-op PM Implantation | ☐ | ☐ | ☐ |
| Low Cardiac Output Syndrome | ☐ | ☐ | ☐ |

| | |
|---|---|
| Hematothorax | ○ No ○ Yes |
| Sepsis | ○ No ○ Yes |
| Gastrointestinal Complications | ○ No ○ Yes |

| | |
|---|---|
| Respiratory Post-Op Complications | ☐ No<br>☐ Post-Op Diaphragmatic Cupola Elevation<br>☐ Respiratory Failure<br>☐ Post-Op (Broncho-) Pneumonia<br>☐ Respiratory insufficiency |
| Renal Complications | ☐ No<br>☐ Post-Op Renal Failure<br>☐ Post-Op New Dialysis<br>☐ Renal insufficiency |
| Adequate wake (adäquate Wachreaktion) | ○ Yes<br>○ No |
| Post-Op Sympthomatic Neuropsychotic Syndrome | ○ No<br>○ Yes |
| Delirium score label | ☐ Acute onset and fluctuating course<br>☐ Inattention<br>☐ Disorganized thinking<br>☐ Altered level of consciousness |
| Delirium Score | _____ |
| Neurologic complications | ○ No<br>○ Paresis |
| CT scan available | ○ No<br>○ Yes |
| Wound Infection | ☐ No<br>☐ Thoracic Wound<br>☐ Inguinal Wound<br>☐ Thoracic Wound + Inguinal Wound<br>☐ Sternal Wound |
| Canulation Site Complications | ☐ No<br>☐ Canulated Femoral Artery Dissection<br>☐ Post-Op Femoral Artery Bleeding<br>☐ Inguinal Lynph Fistula<br>☐ Canulated Limb Ischemia<br>☐ Canulated Limb Compartment Syndrome<br>☐ Canulated Limb Neuropathy |

# Follow Up

| | |
|---|---|
| Last Contact | _____ (Format: DD-MM-YYYY) |
| Lost To Follow Up | ◯ No<br>◯ Yes |
| Survival Time | _____ (Days) |
| Death | ◯ No<br>◯ Yes |
| Date of Death | _____ (PLEASE note the DD-MM-YYYY format) |
| Reason of Death | ◯ Cardiac<br>◯ Non-Cardiac<br>◯ Other |
| Other Death Reason Comment | _____ |
| 30d Mortality | _____ |
| 1y Mortality | _____ |
| DHZB Hospital Mortality | _____ |
| PKH Hospital Mortality | _____ |

# Scores

[skript_mic]

| **De Feo Score** | | |
|---|---|---|
| Score Age | | _____ (At the time of the surgery) |
| Used calculated value | [age] | |
| Score Renal Failure | | _____ (If creatinine >2mg/dl) |
| Used calculated value | [creatinin] | |
| Score NYHA class IV | | _____ (Preop NYHA) |
| Used calculated value | [pre_op_nyha] | |
| Score Ventilatory Support | | _____ |
| Used calculated value | [pre_op_intubation] | |
| Score Positivity of latest preop blood culture | | _____ |
| Used calculated value | [preop_culture_posneg] | |
| Score Perivalvular involvement | | _____ |
| Used calculated value \| Annular Abscess [annular_abscess]Used calculated value \| Other Abscess [other_abscess]Used calculated value \| Pseudoaneurysm [pseudoaneurysm]Used calculated value \| Fistula [fistula] | | |
| Final De Feo Score | | _____ |
| Final Class De Feo Score | | _____ |

| **ANCLA Score** | |
|---|---|
| Score Anemia | _____ |
| Used calculated value \| Gender [gender]Used calculated value \| Hemoglobin [hemoglobin] | |
| Score NYHA class IV | _____ |
| Used calculated value | [pre_op_nyha] |
| Score Critical state | _____ |
| Used calculated value | [pre_op_critical_state] |
| Score Large intercardiac destruction | _____ |
| Used calculated value \| Perforation [perforation]Used calculated value \| Annular Abscess [annular_abscess]Used calculated value \| Other Abscess [other_abscess]Used calculated value \| Pseudoaneurysm [pseudoaneurysm]Used calculated value \| Fistula [fistula]Used calculated value \| Valve aneurysm [valve_aneurysm]Used calculated value \| Anterior Mitral Leaflet Cleft [aml_cleft]Used calculated value \| Posterior Mitral Leaflet Cleft [pml_cleft] | |
| Score Surgery on thoracic aorta | _____ |
| Used calculated value | [other_procedure_data_comme] |
| Final ANCLA Score | _____ |

| **Anatomic Score** | |
|---|---|
| Score Vegetations | _____ |
| Used calculated value \| No [vegetations(0)]Used calculated value \| AML [vegetations(1)]Used calculated value \| PML [vegetations(2)]Used calculated value \| Bileaflet [vegetations(3)] | |
| Score Perforation | _____ |
| Used calculated value \| No [perforation(0)]Used calculated value \| AML [perforation(1)]Used calculated value \| PML [perforation(2)]Used calculated value \| Bileaflet [perforation(3)] | |
| Score Annular Abscess | _____ |
| Used calculated value | [annular_abscess] |

| | | |
|---|---|---|
| Scores Leaflet Motion | | |
| | (Type) | |
| Used calculated value \| AML [posterio_mitral_leaflet] | [anterior_mitral_leaflet]Used calculated value \| PML | |
| Final Anatomic Score | | |

# 8. Eidesstattliche Versicherung

„Ich, Julie Schambach, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: **Minimally Invasive Surgery versus Sternotomy in Native Mitral Valve Endocarditis: A Propensity Score Matched Comparison / Minimalinvasive Chirurgie versus Sternotomie für native Mitralklappenendokarditis: Ein Propensity Score Matched Vergleich** selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

# 9. Anteilserklärung an etwaigen erfolgten Publikationen

Julie Schambach hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Kofler M, Van Praet KM, Schambach J, Akansel S, Sündermann S, Schönrath F, Jacobs S, Falk V, Kempfert J. Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison. European Journal Cardio-Thoracic Surgery. 2021 August 18

Beitrag im Einzelnen: Datenerfassung aus den digitalen und analogen Akten des DHZB, statistische Auswertung der gematchten Populationen mit SPSS, Analyse der Ergebnisse, Review und Editing.

_____

Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

_____

Unterschrift des Doktoranden/der Doktorandin

# 10. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

# 11. List of Publications

As of March 2022

1. Kofler M, Van Praet KM, Schambach J, Akansel S, Sündermann S, Schönrath F, Jacobs S, Falk V, Kempfert J. Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison. European Journal Cardio-Thoracic Surgery. 2021 August 18

# 12. Acknowledgements

First and foremost, I would like to express my sincere gratitude to my doctoral supervisor Prof. Dr. med. Jörg Kempfert who defined the subject of this research. His innovative surgical work in the field of minimally invasive surgery for mitral valve endocarditis laid the foundation for my dissertation. I am incredibly grateful to have had the opportunity to contribute to this emerging field.

I would also like to thank Dr. Markus Kofler and Mr. Karel Van Praet. Their expertise and guidance helped me in the research and writing of this thesis. They were both important mentors who supported me in all respects, from our first meeting to the submission of this dissertation. Their guidance and input made this dissertation possible.

I thank Prof. Dr. med. Volkmar Falk, the director of Heart, Thorax and Vascular Surgery at DHZB, for giving me the opportunity to perform research in his department. Further, I am grateful for the help I received from the employees at DHZB. To name a few: Ursi Wacker, Thomas Haese, Susanne Filbrich, Hans-Peter Brickwede, and Enkhsaikhan Bernd.

Finally, I would like to thank my family and friends. I am grateful for my parents Gabriele and Stephan's continuous support and encouragement throughout this meaningful period of my life. I would like to thank my friends for cheering me on and offering their advice and company.

# 13. Confirmation by Accredited Statistician

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Zur Vorlage bei der
**Promotionskommission** der
Charité – Universitätsmedizin Berlin

Berlin, den 3. November 2021

**Bescheinigung nach § 8 Abs. 2a PO 2017**

Sehr geehrter Frau Schambach,

hiermit bestätige ich Ihnen zum Zwecke der Vorlage beim Promotionsbüro der Charité die erfolgte Beratung zu Ihrem Promotionsprojekt. Die Durchführung und Beschreibung der statistischen Methoden der mir vorgelegten Schrift ist in Art und Umfang für die Erarbeitung adäquat. Nach Einsicht in Datenbank und der mir vorgelegten Beschreibung von Methoden und Berechnungen sehe ich eine sorgfältige und detaillierte statistische Bearbeitung, die eine Darstellung der betrachteten Populationen einschließlich einer *propensity-score-matching* Analyse beinhalten. Das Ethikvotum zur Arbeit liegt Ihnen vor.
Im heutige Beratungsgespräch wurden die Primärdaten der Arbeit nicht mit begutachtet. Ergänzend erfolgte eine Beratung zu deskriptiven Statistik, p-Wert Adaptation, zu Abbildungen sowie dem a priori explorativen Charakter von observationalen (retrospektiven) Studien.

Ich wünsche Ihnen für die Zukunft alles Gute.

[redacted]

Priv.-Doz. Dr. med. Sascha Tafelski
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