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DISSERTATION

Endoscopic Minimally Invasive Cardiac Surgery

Endoskopische minimalinvasive Herzchirurgie

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von

Karel M. Van Praet
aus Aalst, Belgien

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1. Abbreviations and Acronyms

Abbreviation	Meaning
3D	Three-dimensional
3D-FE	Three-dimensional fully endoscopic
AF	Atrial fibrillation
AL	Anterior leaflet
AML	Anterior mitral leaflet
APHRS	Asia Pacific Heart Rhythm Society
AR	Aortic valve regurgitation
AS	Aortic valve stenosis
ASD	Atrial septal defect
AV	Aortic valve
AVN	Atrioventricular node
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
CO_2	Carbon dioxide
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTA	Computed tomography angiography
CWD	Continuous wave Doppler
DHZB	Deutsches Herzzentrum Berlin
DMR	Degenerative mitral valve regurgitation
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
EHRA	European Heart Rhythm Association
ERO	Effective regurgitant orifice
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
FED	Fibroelastic deficiency
FMR	Functional mitral valve regurgitation

FO	Foramen ovale
FTR	Functional tricuspid valve regurgitation
HD	High-definition
HRS	Heart Rhythm Society
IABP	Intra-aortic balloon pump
ICS	Intercostal space
ICU	Intensive care unit
IMR	Ischemic mitral valve regurgitation
IVC	Inferior vena cava
LA	Left atrium
LAA	Left atrial appendage
LHD	Left-sided heart disease
LOE	Level of evidence
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
MICS	Minimally invasive cardiac surgery
MIMVR	Minimally invasive mitral valve repair
MIMVS	Minimally invasive mitral valve surgery
MIS	Minimally invasive surgery
MR	Mitral valve regurgitation
MS	Mitral valve stenosis
MV	Mitral valve
MVR	Mitral valve repair
O_2	Dioxygen
OAC	Oral anticoagulation
OSA	Obstructive sleep apnea
PBV	Percutaneous balloon valvuloplasty
PFO	Patent foramen ovale
PISA	Proximal isovelocity surface area
PL	Posterior leaflet
PM	Papillary muscle
PMC	Percutaneous mitral commissurotomy

PML	Posterior mitral leaflet
PROM	Predicted risk of mortality
PS	Propensity score
PSM	Propensity score matching
PV	Pulmonary vein
RA	Right atrium
RCT	Randomized controlled trial
RLMT	Right lateral minithoracotomy
ROA	Regurgitant orifice area
RV	Right ventricle
Rvol	Regurgitant volume
SL	Septal leaflet
SMR	Secondary mitral valve regurgitation
SOLAECE	Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiologia
SPAP	Systolic pulmonary artery pressure
SVC	Superior vena cava
TEE	Transesophageal echocardiography
TEMVR	Totally endoscopic mitral valve replacement
TR	Tricuspid valve regurgitation
TRA	Tricuspid valve ring annuloplasty
TTE	Transthoracic echocardiography
TV	Tricuspid valve
VA	Video-assisted
VCW	Vena contracta width
VHD	Valvular heart disease

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4. Zusammenfassung

Einleitung: Ziel dieser Studie war der Vergleich der klinischen Ergebnisse zwischen der dreidimensionalen vollendoskopischen (3D-FE) und der videoassistierten (VA) minimalinvasiven Mitralklappenoperation bei Patienten mit degenerativer Mitralinsuffizienz (DMR).

Methodik: Von 2014 bis 2020 wurden insgesamt 710 Patienten mit Carpentier Typ II Mitralregurgitation (MR), die sich einer minimalinvasiven Mitralklappenreparatur unterzogen hatten (36,5% (n = 259) 3D-FE und 63,5% (n = 451) VA), zunächst in die Studie aufgenommen. Nach fünffacher multipler Imputation und anschließendem 1:1 Propensity Score (PS) Matching unter Berücksichtigung relevanter Ausgangsvariablen wurde eine ausgewogene Endkohorte von 484 Patienten gebildet. Alle klinischen Ergebnisparameter wurden auf einer Intention-to-treat-Basis analysiert.

Ergebnisse: In der gematchten Kohorte wies der 3D-FE-Ansatz eine signifikant längere Aortenquerklemmungszeit (3D-FE: 74min [63-89], VA: 60min [50-77]; p<0,001), eine längere kardiopulmonale Bypasszeit (3D-FE: 118min [103-142], VA: 86min [73-116]; p<0,001) und eine längere Gesamtoperationszeit (3D-FE: 179min [158-210], VA: 126min [110-169]; p<0,001) auf. Der 3D-FE-Ansatz war mit einer signifikant niedrigeren Rate an fehlgeschlagenen Mitralklappenreparaturen (3D-FE: 0,4% (n=1), VA: 2,0% (n=5); p=0,007) und Mitralklappenersatz (3D-FE: 0,8% (n=2), VA: 5,4% (n=13); p=0,008) verbunden. Beide Gruppen zeigten hervorragende Ergebnisse in Bezug auf Myokardinfarkt (3D-FE: 0,0% (n=0), VA: 1,2% (n=3); p=0,250), Schlaganfall (3D-FE: 1,7% (n=4), VA: 1. 7% (n=4); p=1.000), 30-Tage- (3D-FE: 0,0% (n=0), VA: 0,4% (n=1); p=1.000) und 1-Jahres-Mortalität (3D-FE: 0,8% (n=2), VA: 1,2% (n=3); p=1.000).

Schlussfolgerung: Der 3D-FE-Ansatz bei der minimalinvasiven Mitralklappenreparatur ist mit einer geringeren Rate an Reparaturversagen verbunden, allerdings zum Preis einer längeren Gesamtoperationszeit.

5. Abstract

Objectives: This study aimed to compare the clinical outcome between three-dimensional fully endoscopic (3D-FE) and video-assisted (VA) minimally invasive mitral valve (MV) surgery in patients with degenerative mitral regurgitation (DMR).

Methods: From 2014 to 2020, a total of 710 patients with Carpentier Type II mitral regurgitation (MR) undergoing minimally invasive mitral valve repair (36.5% (n = 259) 3D-FE and 63.5% (n = 451) VA) were initially included in the study. Five-fold multiple imputation followed by 1:1 propensity score (PS) matching considering relevant baseline variables provided a well-balanced final cohort of 484 patients. All clinical outcome parameters were analysed on an intention to treat basis.

Results: In the matched cohort, the 3D-FE approach showed significantly longer aortic cross clamp time (3D-FE: 74min [63-89], VA: 60min [50-77]; p<0.001), longer cardiopulmonary bypass time (3D-FE: 118min [103-142], VA: 86min [73-116]; p<0.001) and longer total operative time (3D-FE: 179min [158-210], VA: 126min [110-169]; p<0.001). The 3D-FE approach was linked with a significantly lower rate of failed MV repair (3D-FE: 0.4% (n=1), VA: 2.0% (n=5); p=0.007) and MV replacement (3D-FE: 0.8% (n=2), VA: 5.4% (n=13); p=0.008). Both groups showed excellent results in terms of myocardial infarction (3D-FE: 0.0% (n=0), VA: 1.2% (n=3); p=0.250), stroke (3D-FE: 1.7% (n=4), VA: 1.7% (n=4); p=1.000), 30-day (3D-FE: 0.0% (n=0), VA: 0.4% (n=1); p=1.000) and 1-year mortality (3D-FE: 0.8% (n=2), VA: 1.2% (n=3); p=1.000).

Conclusions: The 3D-FE approach in minimally invasive MV repair is associated with a lower rate of repair failure at the price of longer procedure related times.

6. Background

6.1. Introduction

Minimal scarring yet major heart surgery – most patients would endorse this principle. Since the mid-20th century, minimally invasive surgery (MIS) has been an integral part of some disciplines and has continually developed ever since. Dramatic developments in camera technology and specially designed instruments now afford a vast array of options, and in some surgical approaches it has become an indispensable part of everyday clinical practice[1]. Regarding cardiac surgery, the speed of these developments has had a powerful influence not only on clinical practice but also on the attitudes and expectations of cardiac patients[2]. As recent as the mid-1990s, access to the heart was achieved by partially opening the sternum or through a minithoracotomy[2]. However, surgeons are being asked more and more for a therapeutic approach that would leave the sternum untouched[2]. These increasing demands and advances in technology present a new challenge for the modern surgeon. Therefore, cardiac surgeons who want to meet this new challenge need to realize that greater technical skills for minimal incisions are mandatory[2].

About 2% of the population are affected by degenerative mitral valve (MV) disease[3]. It is a common disorder, and in cardiac surgery, mitral valve regurgitation (MR) is one of the most frequent heart valve diseases (HVD)[4]. Should patients undergoing a sternotomy suffer from comorbidities like morbid obesity, diabetes mellitus or even severe osteoporosis, the risk that wound healing would be hindered and delayed is significantly higher[2]. The minimally invasive techniques for MV surgery developed in the mid-1990s successfully offset some of the disadvantages associated with sternotomy and have since

been practiced worldwide[5]. Subsequently, four techniques have become apparent as recognized approaches to minimally invasive mitral valve repair (MIMVR):

- lower hemi-sternotomy,
- video-enhanced direct-vision right mini-thoracotomy,
- (totally) endoscopic right mini-thoracotomy (2D or 3D),
- robotic-assisted right mini-thoracotomy

There have been a number of observational studies and meta-analyses comparing MIS to sternotomy for MV surgery, however, problems with trial design and costs have hindered the implementation of larger randomised controlled studies with hard clinical outcomes[5 6 7 8 9 10 11]. Although the studies that were conducted illustrate increased operative times with MIS, it is clear that the postoperative length of stay is shorter, and with comparable mortality rates[12]. Notably, Vanermen et al. heralded the advancement of MIS port-access MV surgery in the year 2000, claiming it was on the threshold of becoming the surgery of the twenty-first century[13].

The benefits of MIMVS have long since been proven and it is currently a generally recognized alternative to the standard sternotomy procedure[14]. The clear advantages are not only the shortened hospital stay and rehabilitation, but also the reduced injury, blood loss, and need for transfusion[14]. With the aim of making surgical procedures even safer and less invasive[15], new techniques and technologies in heart surgery are continually developing and new chapters are being written. Great advancements are being made in the field of video-assisted minimally invasive cardiac surgery as the incisions through which it is possible to surgically treat VHD are getting smaller. Not only is the surgical outcome not jeopardized, but these advancements result in less aggravation and surgical trauma to the body as well as improved patient-centred outcome[15].

In the history of cardiothoracic and vascular surgery, the development of endoscopy has been long established as a milestone[16]. Cardiovascular surgeons have increasingly favoured endoscopic surgery in the treatment of congenital, valvular and coronary artery disease[16]. The use of the original two-dimensional (2D) imaging[16] as the basis of endoscopic cardiac surgery is now being surpassed by developments in three-dimensional high-definition (3D HD) video systems. This new 3D HD development with enhanced depth perception could well surpass the 2D system[16].

The developments in video-assisted technology have gone through many stages over the recent past, ranging from HD, 30° or 120° cameras to today's full 3D HD vision[17]. Zang et al. concluded that a 3D HD video system seems to be better in comparison to a 2D system when performing totally endoscopic mitral valve replacement (TEMVR), resulting in similar operative safety[16] and better surgical performance. Valuable in-depth particulars concerning the left ventricle (LV) and left atrium (LA) as well as structural information regarding the papillary muscles, MV leaflets, and chordae tendineae[16] are all provided by 3D HD technology in TEMVR surgery[17]. This promising technology is well worth promoting, yet there are technical challenges and a lengthy learning curve, meaning that the totally endoscopic video-assisted thoracoscopic approach to surgical treatment of MV disease is currently restricted to experienced surgeons[17].

There were outstanding results in the past when a fully endoscopic approach for MICS was implemented[14 18 19 20]. An essential part of these outcomes is patient satisfaction, which includes the cosmetic appeal and the desire for a better appearance as well as maximal healing of the scar tissue[21]. Consequently, surgeons are implementing periareolar incisions, which were first described as successful in reconstructive breast surgery. The periareolar approach is now performed as an alternative to the standard right lateral minithoracotomy (RLMT) in MICS[21].

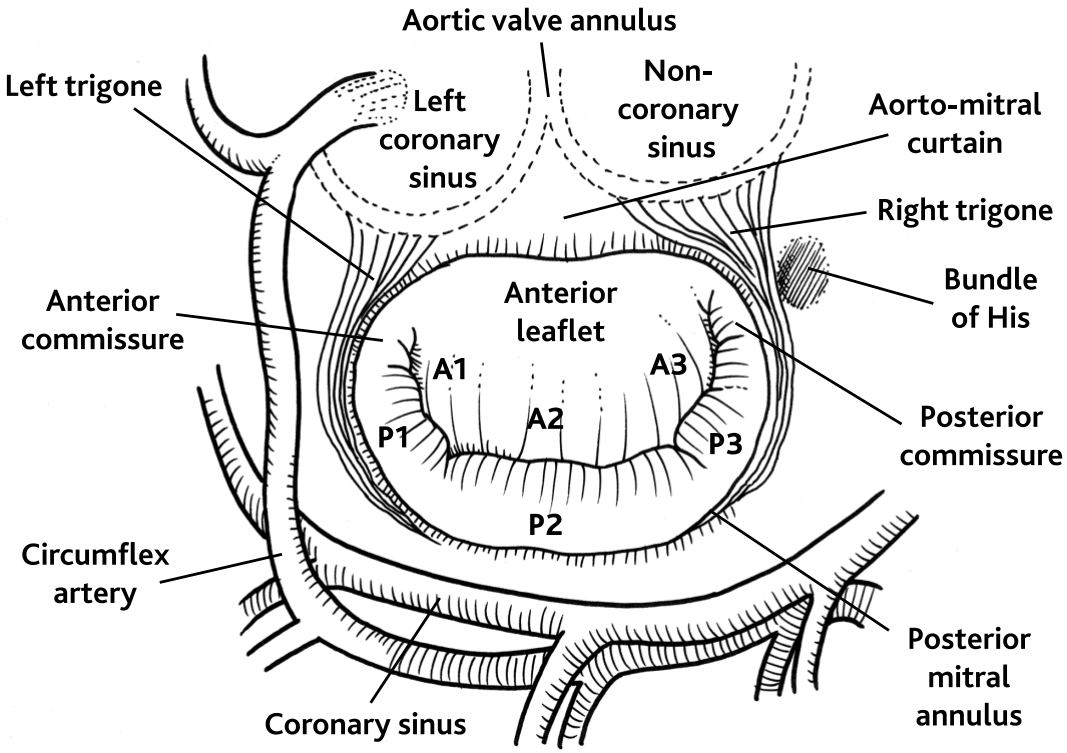
6.2. Valvular Heart Diseases

6.2.1. Mitral Valve

6.2.1.1. Mitral Valve Anatomy

The function of the mitral valve (MV) is to prevent blood from flowing backwards as it courses through the heart. Lying between the LA and the LV[35], it is one of four valves in the heart and is comprised of a complex geometry, as illustrated in Figures 1, 2 and 3, namely the posterior and anterior leaflets, the mitral annulus and the subvalvular apparatus[35]. The chordae tendineae and the papillary muscles (PM) make up the subvalvular apparatus and are introduced into the LV wall[35 36 37]. These composite structures work synchronously within the cardiac cycle to enable the contracting (systole) and relaxation (diastole) mechanisms[35 36].

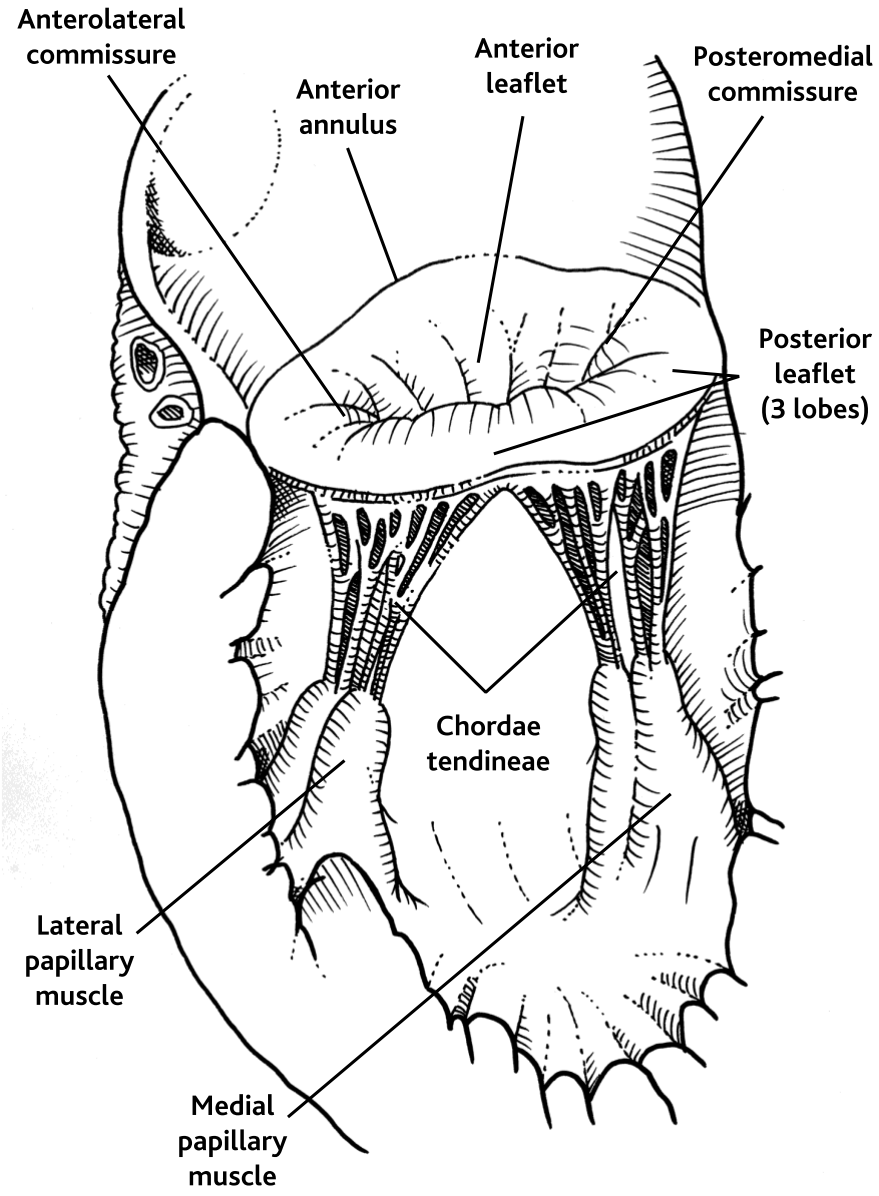
Figure 1: *The mitral valve; surgeon´s view from the left atrium.*



Mitral annulus and leaflets. The ring of fibrous tissue encircling the valvular orifice and the base of the valve is the annulus. As shown in Figure 1, it is secured in the left side of the heart [35 37] and adjoins the aortic valve, sharing a fibrous continuity with half of the non-coronary artery and left coronary artery cusps[35 38 39]. The anterior part of the mitral annulus is determined by this adjoining section of the aortic valve, and the left and right fibrous trigones outline its borders[35]. Regarding the posterior segment of the annulus, it is situated away from the trigones. During the cardiac cycle, the shape and diameter of the annulus fluctuate[35 37 40]. This dynamic structure becomes more circular in diastole and more three-dimensionally saddle shaped in systole, synchronous with the closure of the valve and coaptation of the leaflets[35 37 41 42]. The MV leaflets are a continual

band of tissue fractionated into posterior, anterior and commissural parts[35 36 37] (Figure 1). The posterior mitral leaflet (PML), as stated in prior studies on the human MV, is semilunar in shape when compared with the anterior mitral leaflet (AML) and has a relatively short radial length. The composition of the posterior leaflet consists of three minor semi-oval scallops, the central one of which is situated opposite the anterior leaflet and lies between the other two [35 38 43 37]. Alternatively, as shown in Figure 2, the structure of the anterior leaflet is longer and thicker and is more dome-shaped[35 37 38]. As the cardiac cycle goes into systole, the valve is closed as the free margins of both leaflets coapt[35 38]. In diastole, these free margins separate again and subsequently the valve opens[35 36]. Prior human MV studies also demonstrated that the tissue structures of both leaflets alter similarly depending on the region: in the clear zone, or the central part, the leaflets are smooth and thin, while as they gravitate towards the free margins (rough zone), or the region of coaptation, the tissue becomes rough and thick[35 36 41 37]. The rough zone is the central area for anchoring the chordae tendineae [35 37 44], although an attachment of the chordae is also present in the posterior leaflet near the annulus (known as the basal zone)[35 44 37]. There are four histological layers to both leaflets: the atrialis, the spongiosa, the fibrosa and the ventricularis layers[35]. The atrialis layer is topmost, next to the LA, and it is predominantly constituted of regulated elastic/collagen fibres[35]. The spongiosa is under the atrialis and constructed by way of an extracellular matrix of proteoglycans and glycosaminglycans as well as elastic fibres, and it makes up the main part of the free margins.[35]. The fibrosa is under the spongiosa and forms the central collagenous core (aligned) and is the crucial load-bearing layer of each leaflet.[35]. The last layer is the ventricularis and consists of a steady sheet of endothelial cells tucked with collagen and elastic fibres[35].

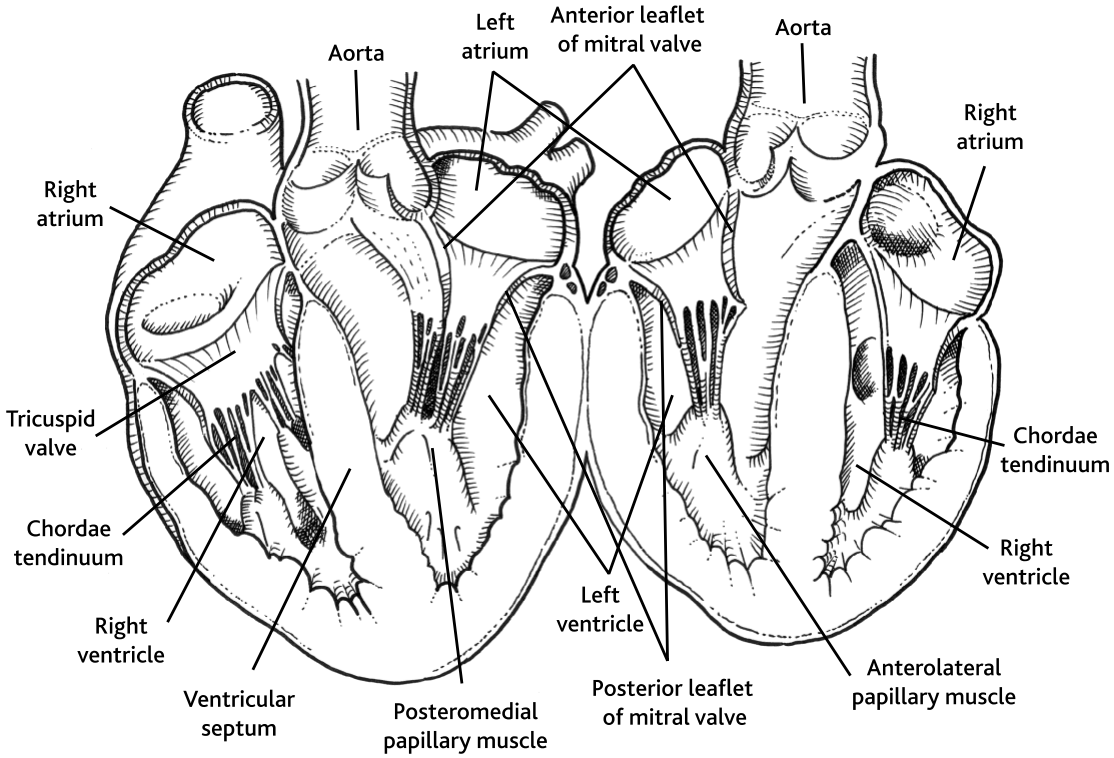
Figure 2: *Mitral valve anatomy; cross-sectional view through the left atrium and left ventricle.*



Subvalvular apparatus. As depicted in Figure 3, chord-like structures (known as chordae) emanate from the apex of the PMs, which are introduced into the leaflets[35 44 41]. Depending on the anatomical part of the LV wall they enter, the PMs are termed anterolateral and posteromedial, corresponding to the anterior and lateral parts of the

body [35]. The structures are dynamic in much the same way as the mitral annulus in that they change shape throughout the cardiac cycle[35]. With regard to their function however, previous studies offer differing opinions. Studies of dog MVs are, for example, contradictory: some declare that the opening of the MV is aided by the contraction/shortening of the PM, while coaptation is assisted by PM lengthening[35 45]; others assert that MV closing is dependent on the shortening of the PMs[35 46]. On the other hand, the chordae are defined by their size and their connection site; the marginal chordae, the thinnest in human MV, connect to the free edge of the leaflets, whereas the basal chordae, more expandable and thicker, are located between the free edges and the leaflet's connection to the annulus´ rough zone[35]. The largest and thickest of the basal chords, termed the strut chordae, are thought to have the highest tension and emanate from the apex of each PM and embed into the anterior leaflet[35 44 47 41 37 48]. Throughout the cardiac cycle, this insertion area goes through differing tensions and elasticity as the energy is transferred between the leaflets and the chordae[35 49]. The other chordae are the tertiary chordae, which attach to the lowest region of the posterior leaflet and stem from the LV wall[35 36 41]. The different types of chordae vary in function, according to past porcine and ovine studies. In systole, on the one hand, the marginal chordae ensure that the leaflets remain closed and therefore prevent MR. On the other hand, basal chordae are responsible for load transfer to the leaflets, and are able to prevent the marginal chordae from malfunction[35 50 51 52 53 48].

Figure 3: *Anatomy of the mitral valve and its subvalvular apparatus.*



6.2.1.2. Mitral Valve Regurgitation

6.2.1.2.1 Epidemiology, Pathophysiology and Grading of Mitral Regurgitation Severity

The definition of mitral valve regurgitation (MR) is the systolic backward flow of blood from the LV into the LA[54]. To a certain degree, a minor form of this heart valve disease can be found in healthy people[55]. However, as demonstrated in epidemiological data, regurgitation (moderate or severe) is the second most widespread form of VHD in Europe[54 56 4] and the most common valve disease in the USA[57]. As cases of rheumatic heart disease have decreased, the current increasing public health issue is MR[54 57]. In 2000, approximately 2-2.5 million people in the USA were affected with moderate or

severe regurgitation and, since it becomes more common with age, the prognosis will double for 2030 as the population grows and gets older[54 57]. Young adults appear to be afflicted with MR in countries burdened with rheumatic fever, yet there are no extensive epidemiological studies available[54 58].

The main cause of MR is malcoaptation between the AML and the PML and/or shrinkage of the coaptation area. Annular dilation or leaflet perforation cause Carpentier´s type I MV failure[59 60 61], and Carpentier´s type II MR failure is classified as when deteriorating leaflets or chordae tendineae cause changes that lead to sustained leaflet malfunction[59 62]. Carpentier´s type III failure is classified as when leaflet motion is restricted (leaflet tethering) and is caused by rheumatic disease or displacement of PMs secondary to LV dilatation[62 3].

Degenerative MR (DMR) (Carpentier´s type II MR), a non-ischemic primary MR, occurs when the primary components of the MV apparatus are deformed including: endocarditis induced- or traumatic chordae tendineae rupture (fibroelastic deficiency or FED), inflammatory changes, myxomatous leaflet disease, congenital leaflet cleft, calcification of the mitral annulus, and iatrogenic injury due to radiation or drugs[3]. It is more typical to encounter myxomatous degeneration (a redundancy of tissue that seems to be myxomatous after histopathological analysis) in younger patients and it is more commonly associated with mitral annulus dilatation[63]. Elderly patients are more susceptible to fibroelastic degeneration, which is defined by a single lesion without excess tissue[64], although the mitral annulus is found to be normal or slightly dilated[64] in these cases.

Changes in ventricular geometry may cause the mitral leaflet structures to retract or show tethering although the leaflets themselves remain intact. This is termed secondary MR (SMR) or functional MR (FMR). These changes occur when there is leaflet malcoaptation as a result of ischemic or dilated cardiomyopathy, myocarditis or other cardiac diseases

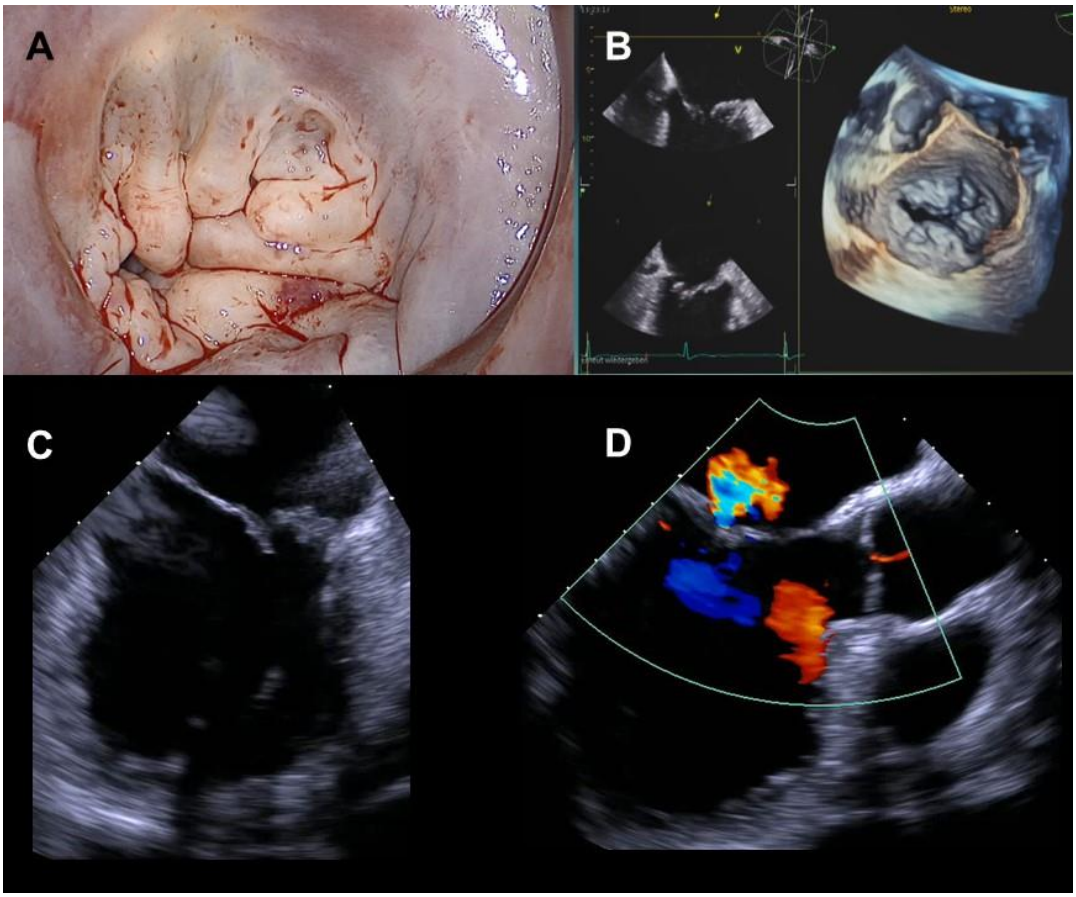
or causes of LV dysfunction[65]. Substantial changes in MV leaflet tissue (extracellular matrix changes) are illustrated in current studies as indications of structural leaflet remodelling and include increases in both thickness and length[66 67]. The LV remodelling as well as abnormalities in ventricular wall movement, shifting of the papillary muscles, or deformation of the mitral annulus are some of the latent dysfunctions that could be responsible for FMR[68 54 69].

Clinical data suggests that MR may be chronic or acute[65], and although ischemic MR (IMR) is often chronic and functional, acute ischemic MR can arise due to papillary muscle infarction and rupture. Regarding acute MR, the LA shows no escalating changes resulting from the sudden fluid volume excess[54], yet this causes an increase in pressure on the LA and pulmonary veins resulting in acute pulmonary edema[54].

Alternatively, chronic MR presents changes to the LA as it attempts to conform to the constant volume overload. This chronic form of IMR typically transpires about 7 days or more after myocardial infarction with abnormalities in LV wall motion. Should the volume overload continue over an extended time period, then the LV subsequently dilates and the cardiomyocyte performance diminishes, resulting in possible MV annulus dilatation and eventually chronic heart failure[54]. Patients who should be excluded from the chronic IMR group are those who suffer from primary MR due to leaflet pathology, either myxomatous or rheumatic[65]. These patients tend to have an improved life expectancy. Figure 4 illustrates pre-repair MR.

Figure 4. *Mitral valve regurgitation before surgical repair.*

A) *Intraoperative endoscopic view of the regurgitant mitral valve (view from the left atrium – surgeon´s view).* ***B)*** *Three dimensional image of the mitral valve also showing signs of significant coaptation deficits and mitral annular dilatation.* ***C)*** *Midesophageal long axis view of the mitral valve in systole without computational fluid dynamics*. ***D)*** *Native mitral valve in biplane view with computational fluid dynamics: coaptation gap leading to significant central regurgitation promoting a concentric jet. The full dimensions of the vena contracta are not entirely depicted in this image.*



For a summary of the quantitative, semi-quantitative, and qualitative parameters used in grading primary MR, see Table 1.

Table 1: *Grading the severity of chronic mitral valve regurgitation by echocardiography.*

(Adapted from W. Zoghbi et al. Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-dimensional and Doppler Echocardiography[70].)

	Mitral valve regurgitation severity[a]		
	Mild	**Moderate**	**Severe**
Structural			
MV morphology	**None or mild leaflet abnormality** (e.g. mild thickening, calcifications or prolapse, mild tenting)	Moderate leaflet abnormality or moderate tenting	**Severe valve lesions** (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation)
LV and LA size[b]	Usually normal	Normal or mild dilated	Dilated[c]
Qualitative Doppler			
Color flow jet area[d]	**Small, central, narrow, often brief**	Variable	Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence[e]	**Not visible, transient or small**	Intermediate in size and duration	**Large throughout systole**
CWD jet	Faint / partial / parabolic	Dense but partial or parabolic	Holosystolic / dense / triangular
Semiquantitative			

VCW (cm)	<0.3	Intermediate	≥0.7 (>0.8 for biplane)[f]
Pulmonary vein flow[g]	**Systolic dominance** (may be blunted in LV dysfunction or AF)	Normal or systolic blunting[g]	Minimal to no systolic flow / **systolic flow reversal**
Mitral inflow[h]	**A-wave dominant**	Variable	E-wave dominant (>1.2 m/sec)
Quantitative[ij]			
EROA, 2D PISA (cm^2)	<0.20	0.20-0.29	≥0.40 (may be lower in secondary MR with elliptical ROA)
RVol (mL)	<30	30-44	≥60 (may be lower in low flow conditions)
RF (%)	<30	30-39	≥50

ROA = regurgitant orifice area. LA = left atrium, atrial. LV = left ventricle, ventricular. CWD = continuous wave Doppler. VCW = vena contracta width. EROA = effective regurgitant orifice area. PISA = proximal isovelocity surface area. RVol = regurgitant volume.
Bolded qualitative and semi-quantitative signs are considered specific for their MR grade.
[a]All parameters have limitations, and an integrated approach must be used that weighs the strength of each echocardiographic measurement. All signs and measures should be interpreted in an individualized manner that accounts for body size, sex, and all other patient characteristics.
[b]This pertains mostly to patients with primary MR.
[c]LV and LA can be within the ‘‘normal’’ range for patients with acute severe MR or chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR.
[d]With Nyquist limit 50-70 cm/sec.
[e]Small flow convergence is usually <0.3 cm, and large is ≥1 cm at a Nyquist limit of 30-40 cm/sec. [f]For average between apical two- and four-chamber views.
[g]Influenced by many other factors (LV diastolic function, atrial fibrillation, LA pressure).
[h]Most valid in patients >50 years old and is influenced by other causes of elevated LA pressure. [I]Discrepancies among EROA, RF, and RVol may arise in the setting of low or high flow states. [j]Quantitative parameters can help subclassify the moderate regurgitation group.

6.2.1.2.2 Progression of Mitral Valve Regurgitation

Mitral valve regurgitation severity (calculated as effective regurgitant orifice (ERO) area)[71] and the warranting volume overload (calculated as regurgitant volume (RVol)) are the main areas defining MR, although LV systolic pressure, as the driving force, and LA compliance also play an important role[54 70]. When the disease is acute, ventricular energy is mainly converted into potential energy (LA pressure V-wave) in the regurgitant orifice as a result of the lack of resistance in the LA[54 72]. When the regurgitation is chronic, the enlarged LA is resistant, the V-wave is usually small, and ventricular drive is transformed mostly into kinetic energy (large RVol)[54]. Atrial enlargement and increased compliance is more than likely the explanation for abatement in atrial pressure and an improved clinical situation after acute MR causing heart failure in the first place[54]. It is important to recognise the dynamic[54 73] nature of the ERO as it can expand or decrease as a result of increased loading and contractility[54 74]. A valve prolapse can exacerbate this, causing the area to continually expand throughout systole[54 75 76]. In FMR, the ERO area is dynamic during systole with a large area during short isovolumic contractions and relaxation phases[54 76]. With reduced loading, or administration of inotrope medication, this type of MR is also dynamic[77] and could subsequently disappear following these interventions. Exercise, on the other hand, nearly always causes changes in the ERO area[54 78]. The RVol development of the organic disease in the long term is about 5 to 7 mL per year. This is determined by ERO area development which is caused by annular enlargement or new lesions[54 79]. In this way, MR is self-sufficient and leads to LA and annular enlargement which then consequentially causes an enlarged ERO area[54]. LV and LA enlargement as well as volume overload with increased preload are the causes of any LV and LA outcomes of organic MR[54]. Although there are normal or increased vascular

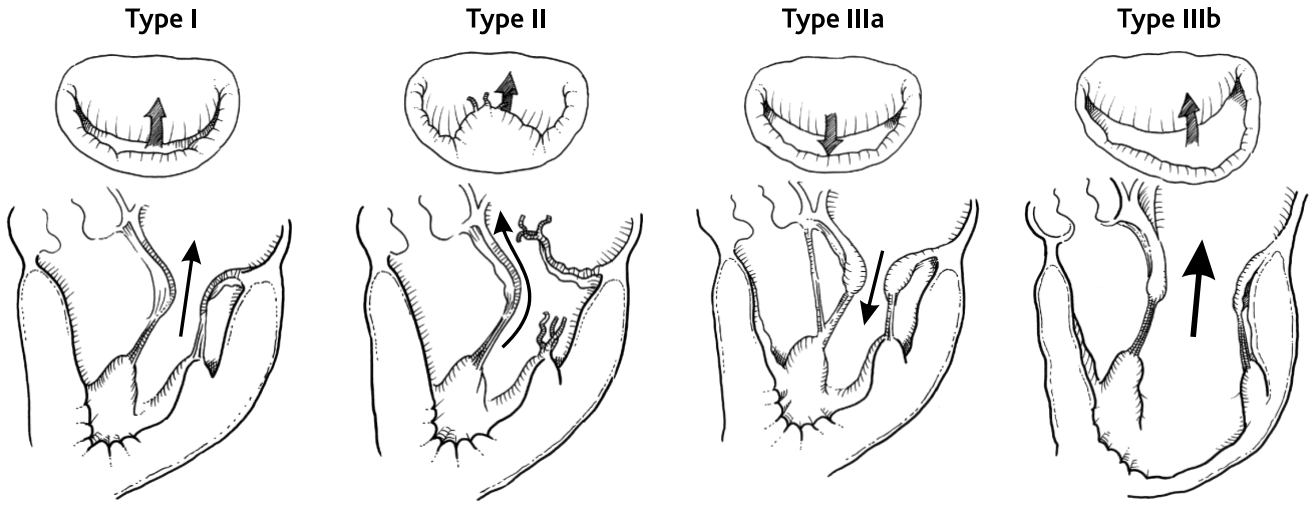
resistances, impedance to ejection is reduced, yet myocardial afterload (end-systolic wall stress), i.e. the force against which the LC contracts, is normal with an LV end-systolic volume that is slightly increased to normal[54 80]. For that reason, altered LV function might co-exist with high or normal EF in the organic disease[54 81], although borderline normal EF, between 50–60%, already implies overt LV dysfunction[54 82]. Large end-systolic dimensions are an immediate sign for LV dysfunction[83 84], although a large ejection volume can often conceal this and is only discovered through surgical elimination of MR. The postoperative EF drop is about 10% on average [54 85 86]. It is more complicated to define diastolic ventricular dysfunction, although the capacity for exercise appears to be curtailed[54 87]. Due to LV dysfunction preceding the regurgitation, the physiology of FMR is even more complex than that of organic MR[54] yet pulmonary hypertension[88] and heart failure are the result of increased LA pressure caused by FMR[54 89 90]. It is not clear if functional regurgitation leads to remodelling and dysfunction, although high mortality in connection with increased MR severity is a clear indication that this may be the case[54 91 92 93].

6.2.1.3. Carpentier´s Classification of Mitral Valve Dysfunction

Alain Carpentier et al. developed the most typically applied classification system for MV disease[35 94]. Also known as the ‘pathosphysiologic triad’, MV dysfunctions are divided into three categories as depicted in Figure 5, each of which are founded on the position of the leaflet edges with respect to the MV annular plane and all of which lead to clinical MR[35]. ***Type one (I)*** applies to normal leaflet movement and has links to annular dilation or leaflet perforation; ***type two (II)*** refers to excessive leaflet movement generally as a

result of elongation or rupture of the chordae tendineae and/or the papillary muscles; and ***type three (III)*** characterizes restricted leaflet movement as the subvalvular apparatus is retracted (***type IIIa***) or with displacement of the PMs and LV dilatation, creating apical displacement (tethering) of the papillary muscles (***type IIIb***)[35].

Figure 5: *Alain Carpentier´s functional classification of mitral valve disease.*



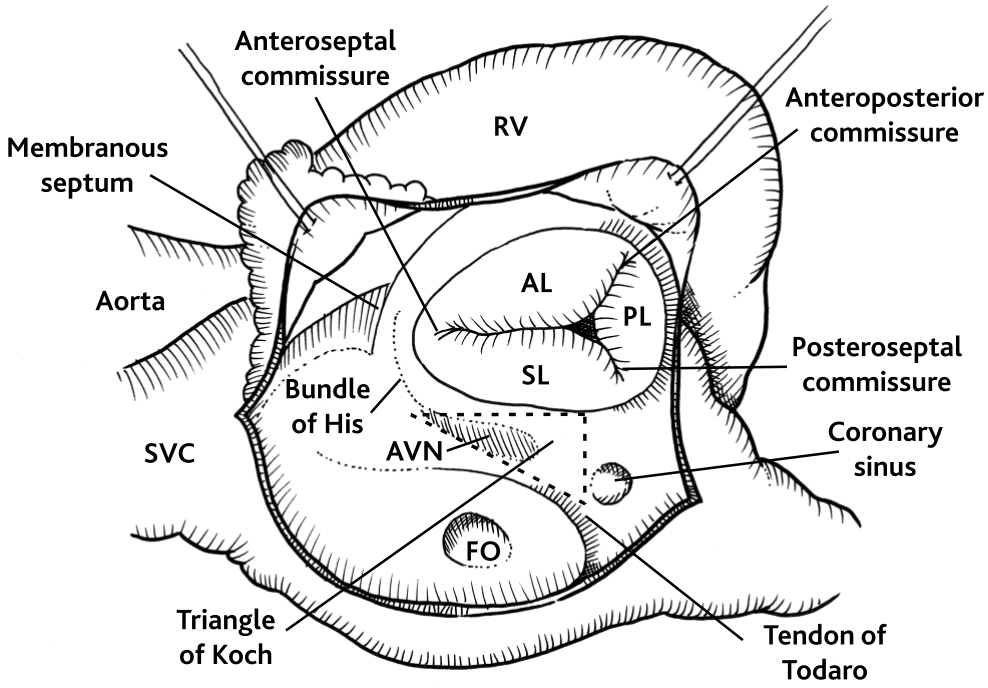
6.2.2. Tricuspid Valve

6.2.2.1. Tricuspid Valve Anatomy

The tricuspid valve (TV) complex includes 3 leaflets (septal, posterior, and anterior), two papillary muscles, the chordae tendinae, the right ventricular (RV) and right atrial (RA) myocardium and the tricuspid annulus[95], all of which contribute to the cohesive and coordinated function of the TV. As illustrated in Figure 6, the complex nonplanar structure of the TV ring (annulus) is flatter and asymmetric in shape compared to the mitral annulus, which is more in the form of a saddle[95]. The proximity of the TV annulus to the right

(fibrous) trigone and the interventicular septum means that it is relatively fixed[95]. In the third dimension, the peak of the TV annulus is (in the direction of the right atrium) located in an anteroposterior location, and the most inferior point (in the direction of the right ventricle) in a mediolateral orientation[95]. For the duration of the cardiac cycle, there can be an approximate 30% change in the TV annular area[95].

Figure 6: *Tricuspid valve anatomy; surgical view from the right atrium.*



6.2.2.2. Tricuspid Valve Regurgitation

6.2.2.2.1 Epidemiology and Grading of Tricuspid Valve Regurgitation Severity

The Framingham Heart Study includes some echocardiographic data indicating a general prevalence of 8% of moderate or greater TR[96 97]. This rate escalates with age, though the findings do not clearly outline why, and despite female longevity, women are 4.3 times more likely to suffer from significant TR than males[96]. A history of myocardial infarction

and heart failure were unsurprisingly associated with higher rates of TR [96]. There is a shortage of epidemiological facts and statistics from economically developing countries[96], and in certain areas rheumatic heart disease is widespread, notably south Asia and sub-Saharan Africa[96]. The rate of chronic rheumatic heart disease is as high as 14.3/1000 in areas of Sub-Saharan Africa[96] [58]. That approximately 9% of patients with chronic rheumatic heart disease are associated with TR is indicated in the echocardiographic data, 93% of whom suffer from significant TR[96] [98]. The implication of these data, therefore, is that there are approximately 1.2 cases of rheumatic TR per 1,000 patients in these regions[96].

Moderate or acute TR is apparent in 35% of patients suffering from clinical heart failure, influencing long-term survival expectations[96] [99] [100]. A great deal of interest was aroused recently by a report stating that 27% of patients in one series had mild TR at best at the time of left-sided valve surgery [96] [101].

The quantitative, semi-quantitative, qualitative, and structural parameters used in grading primary TR are listed in Table 2. Figure 7 depicts pre-repair TR.

Table 2: *Grading the severity of chronic tricuspid valve regurgitation by echocardiography.*

(Adapted from W. Zoghbi et al. Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-dimensional and Doppler Echocardiography[70].)

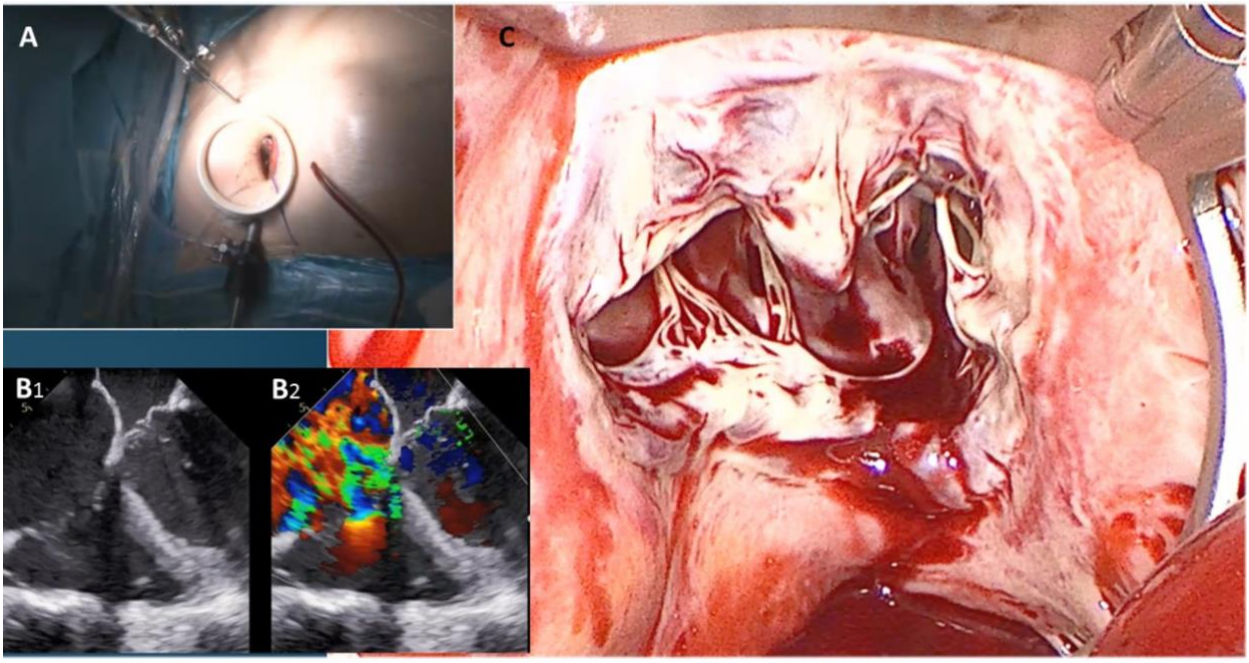
	Tricuspid valve regurgitation severity		
Parameters	**Mild**	**Moderate**	**Severe**
Structural			
TV morphology	**Normal or mildly abnormal leaflet**	Moderately abnormal leaflet	**Severe valve lesions** (e.g., flail leaflet, severe retraction, large perforation)
RV and RA size	Usually normal	Normal or mild dilatation	Usually dilated[a]
Inferior vena cava diameter	Normal <2 cm	Normal or mildly dilated 2.1-2.5 cm	Dilated >2.5 cm
Qualitative Doppler			
Color flow jet area[b]	**Small, narrow, central**	Moderate central	**Large central jet** or eccentric wall-impinging jet of variable size
Flow convergence zone	**Not visible, transient or small**	Intermediate in size and duration	**Large throughout systole**
CWD jet	**Faint / partial** / parabolic	Dense, parabolic or triangular	Dense, often triangular
Semiquantitative			
Color flow jet area (cm^2)[b]	Not defined	Not defined	**>10**
VCW (cm)[b]	<0.3	0.3-0.69	**≥0.7**
PISA radius (cm)[c]	≤0.5	0.6-0.9	**>0.9**
Hepatic vein flow[d]	Systolic dominance	Systolic blunting	**Systolic flow reversal**

			Tricuspid
Tricuspid inflow[d]	**A-wave dominant**	Variable	E-wave >1.0 m/sec
Quantitative			
EROA (cm^2)	<0.20	0.20-0.39[e]	**≥0.40**
RVol (2D PISA) (mL)	<30	30-44[e]	>45

RA = right atrium, atrial. RV = right ventricle, ventricular. CWD = continuous wave Doppler. VCW = vena contracta width. PISA = proximal isovelocity surface area. EROA = effective regurgitant orifice area. RVol = regurgitant volume.
Bolded signs are considered as specific for their TR grade.
[a]RV and RA size can be within the ‘‘normal’’ range in patients with acute severe TR.
[b]With Nyquist limit >50-70 cm/sec.
[c]With baseline Nyquist limit shift of 28 cm/sec.
[d]Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).
[e]There are little data to support further separation of these values.

Figure 7: *Tricuspid valve regurgitation before surgical repair.*

A) *Intraoperative endoscopic minimally invasive setup.* ***B1)*** *Native tricuspid valve in biplane view without computational fluid dynamics: coaptation gap leading to significant central regurgitation promoting a concentric jet. The full dimensions of the vena contracta are not entirely depicted in this image.* ***B2)*** *Native tricuspid valve in biplane view with computational fluid dynamics: coaptation gap leading to significant central regurgitation promoting a concentric jet. The full dimensions of the vena contracta are not entirely depicted in this still image* ***C)*** *Intraoperative endoscopic view on the regurgitant tricuspid valve (view from the right atrium – surgeon´s view). Please note the large central coaptation deficit.*



6.2.2.2.2 Pathophysiology and Progression of Tricuspid Valve Regurgitation

Traditionally, the aetiology of TR breaks down into primary and secondary causes[96]. Intrinsic valvular disease, either congenital or acquired, is the cause of primary TR and constitutes only 8-10% of all severe TR[96 100 102]. Isolated acquired primary TR, which is rare but still recognized, also tends to affect other valves due to the pathology of rheumatic disease[96]. A blunt chest trauma, typically seen in high-energy road traffic accidents, can also be a rare cause of TR [96] and is associated with delayed presentation[96 103]. Chordal rupture is typically caused by the acute rise in RV cavity pressure as well as papillary muscle or leaflet tears [96 103 104].

Annular dilatation can typically lead to functional or secondary tricuspid valve regurgitation (FTR) which is caused by RV dysfunction and enlargement, itself a result of left-sided heart disease (LHD) from myocardial or valvular causes, right heart infarction or RV volume and pressure overload, the latter being a result of pulmonary hypertension or other cardiomyopathies[95]. There are three phases of FTR[95]. The first phase is dilation of the RV resulting in TV annulus dilation[95], which mainly transpires in the anterior and posterior portions correlating to the free wall of the ventricle. Due to the close anatomical connection with the fibrous skeleton of the heart[95], dilation of the septal segment is uncommon. The morphology of the TV annulus changes as it dilates. It develops in a planar and circular way, and in this phase the degree of annular dilation dictates TR severity[95]. During the second phase, as the RV and TV annulus further dilate, substantial FTR is evident due to poor leaflet coaptation[95]. In the final phase, progressive RV distortion and eccentricity cause further TV annular dilatation and leaflet tethering[95]. Chronic volume overload, causing late progressive RV dysfunction and remodelling, can often lead to PM displacement, further contributing to TR[95].

6.3. Surgical Treatment of Valvular Heart Disease

There are international guidelines for patients with diseased MVs and/or TVs determining when surgery should be indicated[105 106], although diagnostic tests need to be made to secure the degree of VHD. The key tool used to assess the severity is echocardiography. It is used to evaluate the possibility of repairing the valve as well as the mechanism and severity of MR, mitral valve stenosis (MS), TR, and tricuspid valve stenosis (TS), and its consequences for the LV (remodelling and/or function), the RV, the LA and pulmonary circulation[105].

The exact recommendations for MV and TV interventions for MR and/or TR can be found in Tables 3, 4 and 5. These guidelines for VHD management were published jointly in 2021 by the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS)[107].

6.3.1. Indications for Intervention in Mitral Valve Disease

The second most common VHD in Europe is MR and the therapeutic procedure is determined by the underlying mechanism (secondary or primary)[107]. Indications for surgery in severe primary MR and chronic severe FMR are illustrated in the following Tables 3 and 4 of recommendations, respectively.

Table 3: *Recommendations on indications for intervention in severe primary mitral valve regurgitation.*

(Adapted from Vahanian et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease[107]*.)*

Recommendations	**Class**[a]	**Level**[b]
Mitral valve repair is the recommended surgical technique when the results are expected to be durable.	I	B
Surgery is recommended in symptomatic patients who are operable and not high risk.	I	B
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥40 mm and/or LVEF ≤60%).	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <40mm and LVEF >60%) and atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension[c] (SPAP at rest >50mmHg).	IIa	B
Surgical mitral valve repair should be considered in low-risk asymptomatic patients with LVEF >60%, LVESD <40 mm[d] and significant LA dilatation (volume index ≥60 mL/m^2 or diameter ≥55 mm) when performed in a Heart Valve Centre and a durable repair is likely.	IIa	B
TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by the Heart Team, and for whom the procedure is not considered futile.	IIb	B

BSA = body surface area; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary artery pressure. TEER = transcatheter edge-to-edge repair.
[a]Class of recommendation.
[b]Level of evidence.
[c]If an elevated SPAP is the only indication for surgery, the value should be confirmed by invasive measurement.
[d]Cut-offs refer to average-size adults and may require adaptations in patients with unusually small or large stature.

Table 4: *Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation.*

(Adapted from Vahanian et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease[107]*.)*

Recommendations	**Class**[a]	**Level**[b]
Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team.	I	B
Patients with concomitant coronary artery or other cardiac disease requiring treatment		
Valve surgery is recommended in patients undergoing CABG or other cardiac surgery.	I	B
In symptomatic patients, who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics[c], PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered.	IIa	C
Patients without concomitant coronary artery- or other cardiac disease requiring treatment		
TEER should be considered in selected symptomatic patients not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment[d].	IIa	B
Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team.	IIb	C
In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider, in selected cases, a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for a ventricular assist device or heart transplant [d].	IIb	C

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; GDMT = guideline-directed medical therapy; SMR = secondary mitral regurgitation; PCI = percutaneous coronary intervention; TAVI = transcatheter aortic valve implantation; TEER = transcatheter edge-to-edge repair.
[a]Class of recommendation.
[b]Level of evidence.
[c]LVEF, predicted surgical risk, amount of myocardial viability, coronary anatomy/target vessels, type of concomitant procedure needed, TEER eligibility, likelihood of durable surgical repair, need of surgical mitral replacement, local expertise.
[d]COAPT criteria (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation).

6.3.2. Indications for Intervention in Tricuspid Valve Disease

For symptomatic patients (despite receiving medical therapy), TV intervention is done concomitantly during procedures for left-sided valve disease[107]. Making the choice between repairing or replacing the TV depends on TV anatomy and is a question of surgical expertise - however, the main hinderance facing TV repair is when leaflet tissue is not flexible [107]. As illustrated in Figure 8, the preferred technique of TV repair includes ring annuloplasty using the Edwards Physio Tricuspid ring.

The preferred valve prosthesis type is a biological prosthesis, due to its long durability and because mechanical valves have a higher risk for thrombosis[107]. Indications for surgery in TV disease are shown in Table 5 below.

Figure 8: *Endoscopic minimally invasive tricuspid valve repair using an isolated annuloplasty technique.*

A1) Midesophageal long axis view in systole without computational fluid dynamics after successful tricuspid valve annuloplasty. ***A2)*** Midesophageal long axis view in systole with computational fluid dynamics after successful tricuspid valve annuloplasty: no signs of paravalvular leakage or residual insufficiency. ***A3)*** *Three-dimensional transesophageal echocardiographic reconstruction of the surgically repaired tricuspid valve.* ***B)*** *Intraoperative endoscopic view of the repaired tricuspid valve (isolated annuloplasty) in systole: no signs of residual tricuspid valve insufficiency****.***

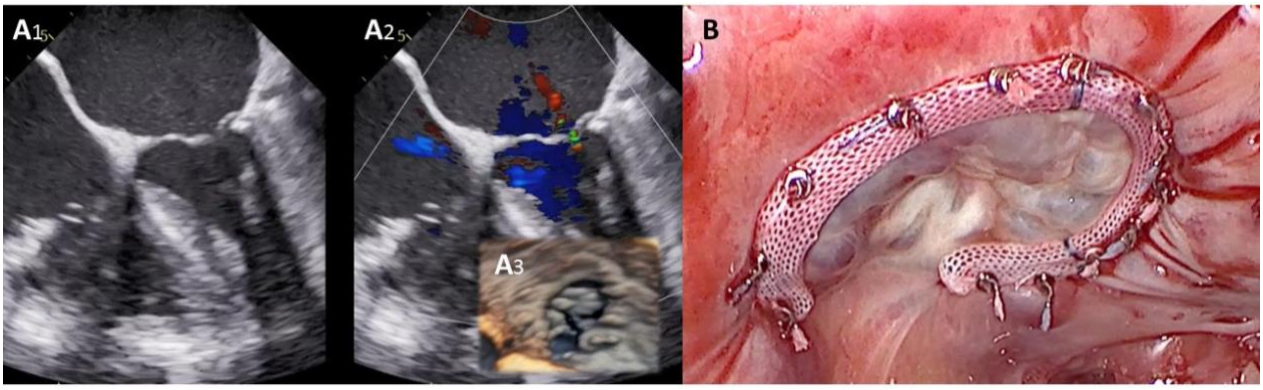


Table 5: *Recommendations on indications for intervention in tricuspid valve disease.*

(Adapted from Vahanian et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease[107]*.)*

Recommendations	Class[a]	Level[b]
Recommendations on primary tricuspid valve regurgitation		
Surgery is recommended in patients with severe primary tricuspid valve regurgitation undergoing left-sided valve surgery.	I	C
Surgery is recommended in symptomatic patients with severe isolated primary tricuspid regurgitation without severe RV dysfunction.	I	C
Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery.	IIa	C
Surgery should be considered in asymptomatic or mildly symptomatic patients with isolated severe primary tricuspid regurgitation and RV dilatation who are appropriate for surgery.	IIa	C
Recommendations on secondary tricuspid valve regurgitation		
Surgery is recommended in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery.	I	B
Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with a dilated annulus (≥40 mm or >21 mm/m^2 by 2D echocardiography) undergoing left-sided valve surgery.	IIa	B
Surgery should be considered in patients with severe secondary tricuspid regurgitation (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension[c].	IIa	B
Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease[d].	IIb	C

2D = two-dimensional; LV = left ventricular; PMC = percutaneous mitral commissurotomy; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]In patients with previous surgery, recurrent left-sided valve dysfunction needs to be excluded.
[d]Transcatheter treatment can be performed according to Heart Team at experienced valve centres in anatomically eligible patients in whom an improvement of quality of life or survival can be expected.

6.3.3. Indications for Combined and Multiple-Valve Diseases

6.3.3.1. Multiple-Valve Diseases

The same heart valve can contain stenosis and regurgitation. Different conditions can present disease of multiple valves, particularly in congenital and rheumatic heart valve disease, but in degenerative heart valve disease this is less common[107]. Due to the lack of facts and statistics on combined or multiple-valve disease[107], it is not possible to make evidence-based suggestions. The following are common notions for the treatment of combined or multiple-valve disease:

• The predominant VHD - either stenosis or regurgitation - will determine the management. Should there be a balance of both regurgitation and stenosis, the basis for intervention indications should be objective consequences and symptoms rather than on the indices of severity of stenosis or regurgitation[107]. In this setting, the Doppler pressure gradient mirrors the global haemodynamic load (stenosis and regurgitation) of the valve lesion[107].

• Each valve lesion should be assessed individually as well as the interaction between the different valve lesions[107]. An example is the following: AS severity could be underestimated due to associated MR, because a lower stroke volume due to MR

decreases the flow across the aortic valve and hence the gradient across the AV[107]. Because of this, the necessity to incorporate different measurements in the analysis is highlighted (including heart valve area assessment) and that includes, where possible, methods that are not so dependent on loading circumstances (planimetry for example)[107].

• Analysis of the reverberations of distinct valve lesions (i.e., presence of LV dilatation or dysfunction or symptoms) have been the basis for intervention indications. Non-severe diverse lesions linked with LV impairment could also be grounds for intervention[107].

• The Heart Team should make the decision to treat several heart valves after exact assessment of heart valve lesions and their interaction with other lesions. The decisions should also consider other factors such as age, comorbidities, and the risk of combined procedures[107]. The risk of further intervention and the development of untreated valve disease should be equated with the risk of combined intervention[107].

• The presence of other VHD should be influential in the choice of the appropriate surgical technique or interventional procedure[107].

6.3.3.2. Combined Diseases: Atrial Fibrillation

The most common application of surgical ablation in the past was as a concomitant operation during CABG or heart valve surgeries[108]. Previous consensus recommendations as well as facts and statistics from multiple studies were grouped together to get IIa level of evidence (LOE) C recommendations[108 109]. However, these recommendations went on to say, "*It is advisable that all patients with documented atrial fibrillation referred for other cardiac surgeries undergo a left atrial or biatrial procedure for atrial fibrillation at an experienced center, unless it "...will add significant risk..."*[109]. This procedural grouping is evident in more recent AHA/ACC/HRS guidelines, though more

current randomized comparisons are also included. These determine that the LOE recommendation for surgical ablation together with another cardiac surgical procedure is a IIa LOE B [108]. The success of durable rhythm control and the number of surgical ablation surgeries have consistently risen[108].

Concomitant open cardiac surgeries, in which a left atriotomy is carried out for the main procedure, regularly involve patients receiving MV replacement or repair, with or without concomitant TV replacement or repair, or the surgical closure of an ASD[108]. MV replacement has been superseded by MV repair for primary MR and does not require lifelong anticoagulation[108]. In this way, the necessity for continual anticoagulation or medicinal treatment for atrial fibrillation can be reduced by successful surgical ablation concomitant to MV repair[108]. The rate of concomitant cardiac surgical procedures in patients with atrial fibrillation at the time of MV operations has inclined from 52% to 62%[108]. Before performing surgical ablation, surgeons are expected to acquire the necessary training because this, as well as the preoperative AF duration and LA size, can influence the outcome. Based on the collective experience of specialists as well as other literature[108], it is recommend that surgical ablation is performed at the time of concomitant open atrial procedures, such as MV surgery in patients with symptomatic AF (Table 6)[108].

Table 6: *Indications for surgical ablation of atrial fibrillation.*

(Adapted from Calkins et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation[108]*.)*

Recommendation		**Class**	**LOE**
Indications for concomitant open (*e.g.* mitral valve) surgical ablation of atrial fibrillation			
Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication.	Paroxysmal: surgical ablation is recommended.	I	B-NR
	Persistent: surgical ablation is recommended.	I	B-NR
	Long-standing persistent: surgical ablation is recommended.	I	B-NR
Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication.	Paroxysmal: surgical ablation is recommended.	I	B-NR
	Persistent: surgical ablation is recommended.	I	B-NR
	Long-standing persistent: surgical ablation is recommended.	I	B-NR
AF = atrial fibrillation; LOE = Level of Evidence; Level of Evidence B-NR: data derived from one or more non-randomized trials or meta-analysis of such studies.			

There is no effect on adjusted short-term survival, although surgical ablation of AF combined with MV surgery may reduce the incidence of AF [107]. After surgical ablation, it has been noted that the number of pacemakers that were implanted rose (9.5% versus 7.6% in the group with no surgical ablation and AF)[107]. Should a patient be expecting cardiac surgery, concomitant AF ablation may be a consideration in the attempt to evaluate benefits and risk factors; the advantage of relief from atrial arrhythmias being

weighed up against the recurrence risk factors, which include years in atrial fibrillation, renal dysfunction, age, (left) atrial dilatation, and other cardiovascular risk factors[107]. Recommendations for the management of AF in VHD are summarized in Table 7.

Table 7: *Recommendations on management of atrial fibrillation in patients with native valvular heart disease.*

(Adapted from Vahanian et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease[107].)

Recommendations	**Class**[a]	**Level**[b]
Surgical interventions		
Concomitant AF ablation should be considered in patients undergoing valve surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (LA dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors).	IIa	A
LAA occlusion should be considered to reduce the thromboembolic risk in patients, with AF and a CHA_2DS_2VASc score ≥2 undergoing valve surgery.	IIa	B
AF = atrial fibrillation; LA = left atrial; LAA = left atrial appendage. [a]Class of recommendation. [b]Level of evidence.		

6.3.4. Technical Aspects of Cardiothoracic Surgery

6.3.4.1. Cardiopulmonary Bypass

The introduction of the cardiopulmonary bypass (CPB) heralded a new era in cardiac surgery. For the first time in history, complex cardiac operations which necessitate more time were able to be conducted. John H. Gibbon Jr., the creator of the CPB machine, was the first to perform surgery utilizing CPB in 1953[110]. The development of the heart-lung machine since that time has established the bedrock for, and safety of, cardiac surgery today. This includes the introduction of protamine to antagonize heparinization and the development of oxygenators that minimize blood trauma, which have improved the safety of CPB[111].

In order to preserve and achieve an activated clotting time (ACT) of 400 to 480 ms, up to 300 U/kg Heparin are administered before placing the patient on CPB[111]. Then, by way of tubes, the surgeon can attach outflow and inflow cannulae to the CPB machine and the blood enters the CPB through a venous reservoir. Blood can be gathered or drained through central cannulation of the vena cava or peripheral femoral cannulation, although blood can also be drawn from cardiac vents and from the cardiotomy sucker. Venous blood is then pumped to the oxygenator. The oxygenator is not only where CO_2 is extracted and O_2 is added, but also where the patient's body temperature is controlled and monitored throughout the operation via the integrated heat exchanger. The blood then transfers through an arterial filter and bubble trap prior to being led back to the patient. The CPB circuit is concluded by placing the arterial cannula in the aorta (central cannulation) or in the femoral artery (peripheral cannulation). The CPB machine often has an integrated system for cardioplegia administration[111].

6.3.4.2. Cardioplegic Cardiac Arrest

With the administration of cardioplegia, the heart is safeguarded during ischemia. It also provides a bloodless operative field and affords more time to carry out complex procedures[112]. Cardioplegia also provides a flaccid myocardium upon which operational procedures may be carried out[112]. Cardioplegia typically exists as a high potassium crystalloid or blood solution[112]. The heart is arrested in diastole as a result of the high extracellular potassium concentration in the heart which depolarizes the resting cardial cells membrane potential[113]. Cellular metabolism and electrical activity is then decreased, substantially lowering the necessity for oxygen in the myocardium[113]. Further ischemic times can be obtained by using ice to cool the myocardium, hence the administration of cardioplegia should also be carried out at lower temperatures[112].

Firstly, the aorta is occluded via external (transthoracic) cross-clamping or by way of endo-aortic balloon occlusion and, with the administration of cardioplegia, the heart swiftly placed into cardiac arrest. There are two systems whereby the cardioplegic solution can be dispensed; antegradely via the coronary arteries or retrogradely through the coronary sinus. To guarantee the heart remains in cardiac arrest and to safeguard the provision of electrolytes and metabolites, the cardioplegia solution is dispensed every few minutes[112]. Two types of cardioplegia were administered in the cases examined in this dissertation, namely: intra-cellular crystalloid Bretschneider's (i.e., Custodiol) cardioplegia or extra-cellular crystalloid del Nido's cardoplegia.

The introduction of reperfusion hot shots is preferred by some surgeons, which entails the administration of warm blood cardioplegia at the conclusion of the operation. This shot of warm blood cardioplegia is given to hinder myocardial metabolic derangement[114 115].

6.3.4.3. Intraoperative Monitoring

The type of access used in the surgery is immaterial when discussing intraoperative monitoring – nearly all cardiac surgeries, including MV surgery, demand diligent observation throughout the procedure. Fundamental measurements identify arrhythmias, ischemia, or cardiac fibrillation[116], and are made by using pulse oximetry and ECG. Arterial blood samples and blood pressure monitoring are both managed using an arterial line[116]. By placing a central venous line, the central venous pressure (CVP) can be monitored, and if necessary, cardiovascular drugs can be administered[116].

It is essential to apply transesophageal echocardiography (TEE) as it aids monitoring of myocardial and valvular function as well as supporting the positioning of catheters and cannulas. Additionally, TEE enables direct comparison of the surgical result both before and after the procedure, and is critical regarding port access MIS[116]. The latter point demonstrates that cases presenting TEE contraindications are therefore not suitable for MIMVS[116].

Ventilation is usually supplied in MICS by a double-lumen endotracheal tube, which enables the right lung to be deflated while simultaneously ventilating the left lung[116]. Access to the MV is greatly improved through this measure[116].

6.3.5. Minimally Invasive Heart Valve Surgery

Detailed information regarding the set-up of the two most relevant minimally invasive heart valve surgery procedures that are significant to this dissertation as well as their contrasting technical aspects can be found in paragraphs 7.2.3. Past literature published by our group provided thorough and detailed descriptions of these approaches[4 17 28 30 117 118 33].

6.4. Risk Assessment in Cardiac Surgery

Estimation of peri- and postoperative morbidity and mortality in cardiac surgery is carried out using risk scores, and the individual risk calculations are based on the evaluation of large databases. The three most common scores are listed below.

6.4.1. EuroSCORE

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is an additive score where cardiac surgery risk factors of an individual patient are calculated and graded, resulting in an estimated mortality[119]. Developed by the EACTS between 1995 and 1999, the EuroSCORE model has been widely tested and accepted in Europe and North America[120]. By using an online calculator, the EuroSCORE is ascertained for each patient based on his or her preoperative data[121].

6.4.2. EuroSCORE II

By basing its information on CABG data, the EuroSCORE II was able to be advanced, validated and authorized for other major cardiac procedures[122]. These comprise isolated non-CABG procedures, two major cardiac operations, and ≥ three major cardiac procedures[122].

6.4.3. Society of Thoracic Surgeons score

The Society of Thoracic Surgeons (STS) score, primarily used in the United States, is founded on a cardiac surgical procedures patient outcomes database[123], also from the United States, and is constantly being updated and honed for exactness and precision[124] (the most recent update was based on patient data from July 2011 to June 2014 and was published in 2018[125]). The disadvantage of this score is the restricted number of cardiac surgeries for which it can be applied. These surgeries are: isolated surgical MV replacement, isolated surgical AV replacement, isolated surgical MV repair, isolated CABG, and CABG with surgical MV repair or replacement or with AV replacement[124]. There are, however, a wide range of advantages including the predicted risk of mortality (PROM), and the risk of other important outcomes including mortality or morbidity, permanent stroke, prolonged mechanical ventilation, renal failure, deep sternal wound infection, hospital length of stay, and reoperation [125]. This risk assessment tool was chosen for this dissertation because it specifically observes relevant preoperative patient characteristics[124].

Unlike other scoring systems, this system also features intra-operative patient characteristics, including the use of a catheter-based assist device, extra-corporeal membrane oxygenation (ECMO), and an intra-aortic balloon pump (IABP)[126]. In this study, the scores were quantified respectively, so that the intraoperative and postoperative factors were given equal precedence.

7. Three-Dimensional Fully Endoscopic versus Video-Assisted Minimally Invasive Mitral Valve Surgery: a Matched Comparison

7.1. Study Objectives

MIMVS is not only beneficial with regard to pleasing cosmetic results; there are also clear clinical advantages over median sternotomy. These include ventilation time, postoperative pain, length of stay (not only in intensive care unit (ICU) but also total hospital stay) and transfusion of blood products[9 22 23 24]. With all factors taken into consideration, most centers would opt for minimally invasive MV repair through right (antero)lateral minithoracotomy[25 26 27] due to the encouraging perioperative outcomes, exceptional rates of reparability, long-lasting durability and long-term survival. Regarding the visualization of the procedures, technological improvements in mitral valve repair (MVR) have progressed from a video-assisted (VA) to a three-dimensional fully endoscopic (3D-FE) approach and involve even smaller, less obtrusive skin incisions[4]. However, there is minimal analytical data available detailing a comparison of the two approaches. As a result, our aim is to investigate differences between 3D-FE and VA minimally invasive surgery in terms of MV repair rate and clinical outcome in patients with degenerative mitral valve disease, using a propensity score (PS) matched analysis.

7.2. Material and Methods

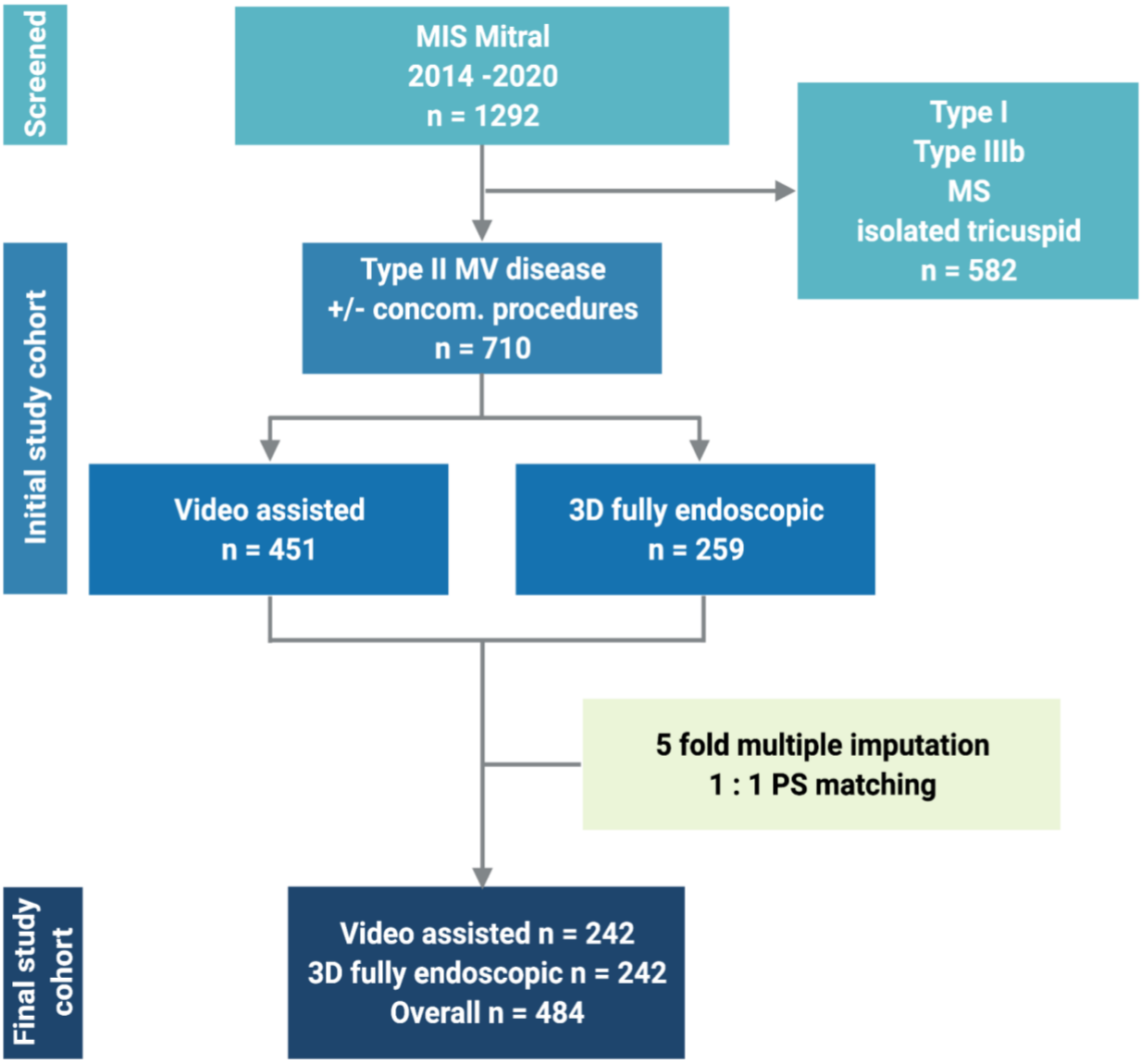
7.2.1. Study Design

This retrospective single-center study performed at the German Heart Center Berlin (*Deutsches Herzzentrum Berlin (DHZB)*) in Berlin, Germany, was approved by the local ethics committee and complies with the Declaration of Helsinki (ethics approval number: EA2/063/19).

7.2.2. Study Population and Patient Enrolment

As illustrated in Figure 9, from 2014 to 2020, a total of 1,292 patients scheduled to undergo minimally invasive mitral or tricuspid valve surgery embedded in our institutional electronic database were screened for eligibility regarding inclusion criteria. We excluded patients with the primary intention of MV replacement or tricuspid valve repair (n = 582). The initial study cohort of 710 patients (63.5% (n = 451) VA and 36.5% (n = 259) 3D-FE) with Carpentier type II severe MR was used to perform 5-fold multiple imputation and consecutive 1:1 propensity score (PS) matching, providing a final cohort of 484 patients (242 matched pairs). The indication for MV surgery was confirmed by the Interdisciplinary Heart Team and was based on current guidelines[107].

Figure 9: *Study design: 3D fully endoscopic versus video-assisted MIMVS - a matched comparison.*



7.2.3. Surgical Strategy and Techniques of Minimally Invasive Mitral Valve Repair

As illustrated in Figure 10, all patients were operated on via anterolateral minithoracotomy by accessing the chest through the 4th intercostal space (ICS). In VA and female 3D-FE patients, a straight skin incision was performed at the lateral chest wall in the sub-mammary fold, while suitable male 3D-FE patients were treated through a semicircular periareolar incision around the nipple. In both groups, soft tissue was retracted by dedicated wound protectors (Alexis®, Applied Medical), while in the VA group additional spreading of the ribs using a minithoracotomy retractor (ValveGate™, Geister) was applied, in order to facilitate procedural steps through direct vision. The pericardium was opened with an incision approximately 4cm anterior of the phrenic nerve. Cardiopulmonary bypass was installed through the femoral vessels. Cannulas were placed after thorough identification of guide wires in transesophageal echocardiography (TEE). In patients with contraindications for femoral cannulation or retrograde arterial perfusion based on preoperative computed tomography scan, axillary arterial cannulation was applied. Cardiac arrest was induced by retrograde cardioplegia following clamping of the aorta ascendens using either a transthoracic Chitwood clamp (3th ICS) or via endoballoon (Intraclude®, EdwardsLifescience). For VA patients, a 0° thoracoscope was placed in the 2nd ICS, while a 3D 30° thoracoscope (Aesculap Einstein Vision) in the 3rd ICS was used for 3D-FE surgery (Figure 10). Exposure of the mitral valve was enabled by means of a left atrial retractor applied through a parasternal incision in projection to the right upper pulmonary vein. Techniques of mitral valve repair included ring annuloplasty and placement of artificial chordae (NeoChord Inc.) for prolapsing segments (q.v. Figure 11). After closing of the LA, temporary pacemaker wires were mounted at the

right ventricle on the arrested heart. Intraoperative TEE was used to confirm successful mitral valve repair in all patients.

Figure 10: *Periareolar endoscopic high-definition three-dimensional MICS setup.*

Legend: A. *A soft-tissue retractor without additional rib-spreading is used for exposure.* ***B.*** *A three-dimensional screen is used.* ***C.*** *The surgeon operating on the mitral valve totally endoscopically with 3D glasses. Peripheral cardiopulmonary bypass with endoaortic balloon occlusion clamping.* ***D.*** *Mitral valve ring annuloplasty.*

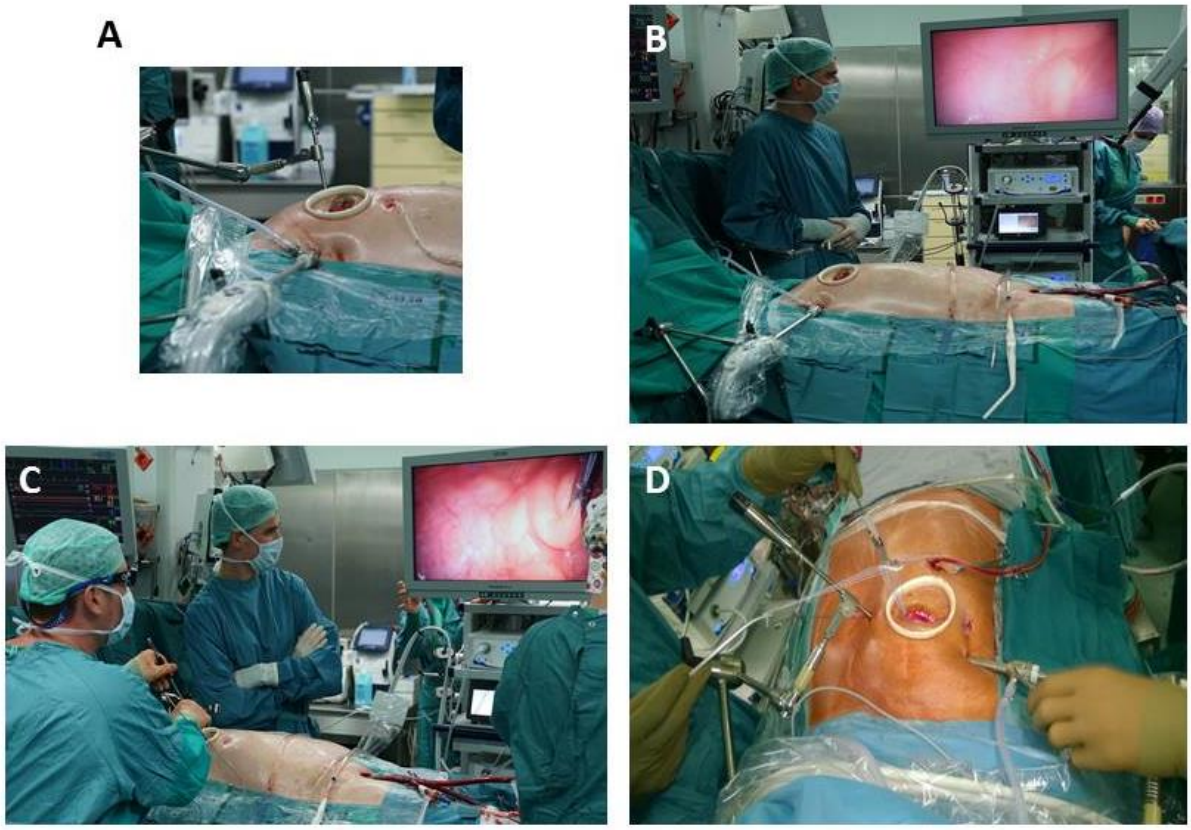
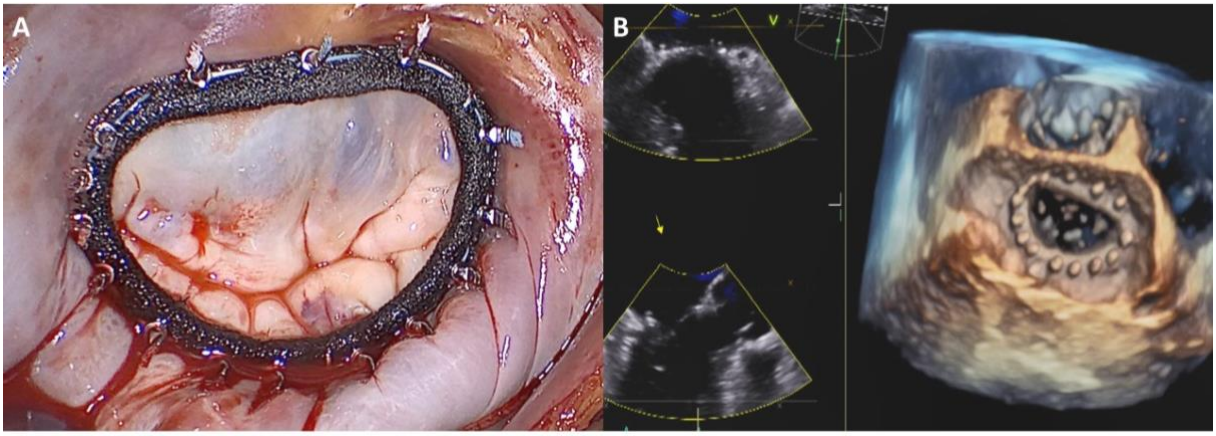


Figure 11: *Endoscopic minimally invasive surgical mitral valve repair.*

A) *Intraoperative endoscopic view of the repaired mitral valve (view from the left atrium – surgeon´s view).* ***B)*** *Three-dimensional transesophageal echocardiographic image of the surgically repaired mitral valve, also showing no signs of residual regurgitation.*



7.2.4. Data Reconstruction

In an effort to systematically collect procedural and patient data, an online secured web platform - Research Electronic Data Capture 2 (REDCap2) - was utilized (see Addendum). Using this software, each patient obtained an anonymized identification number. Data on preoperative status, epidemiological facts and statistics, perioperative management, procedural characteristics, postoperative results, and mortality was collected.

7.2.5. Definition of Important Clinical Endpoints

Patients with attempted MVR and the necessity for second aortic cross clamping due to residual MV regurgitation with consecutive MV replacement were considered as failed repair. Mitral valve replacement was considered as endpoint, since all patients in the matched cohort were judged as “likely-reparable” by the Interdisciplinary Heart Team on the basis of preoperative TEE.

7.2.6. Statistics

7.2.6.1. Propensity Score Matching

In general, for comparing therapies in medicine, an RCT (randomized controlled trial) is used[127]. An RCT assures an even distribution of unknown and known patient characteristics to the treatment- and control-group[128]. Preferably, bias is reduced, and conclusions and/or presumptions can be made about treatment effects[128]. Yet, RCTs are not always suited to the analysis of therapeutic effects, as they may be insufficient, inappropriate, impossible, or unnecessary[128].

As an alternative, non-randomized, retrospective investigations can be used to evaluate treatment modalities[128]. The principal issue these studies have is a lack of internal validity[128]. Because patients are not randomly allocated to the treatment- or control-group, the study groups may manifest systematic differences in known and unknown

characteristics[128]. Those dissimilarities make it unfavourable to attribute variations in outcome to the treatment[128].

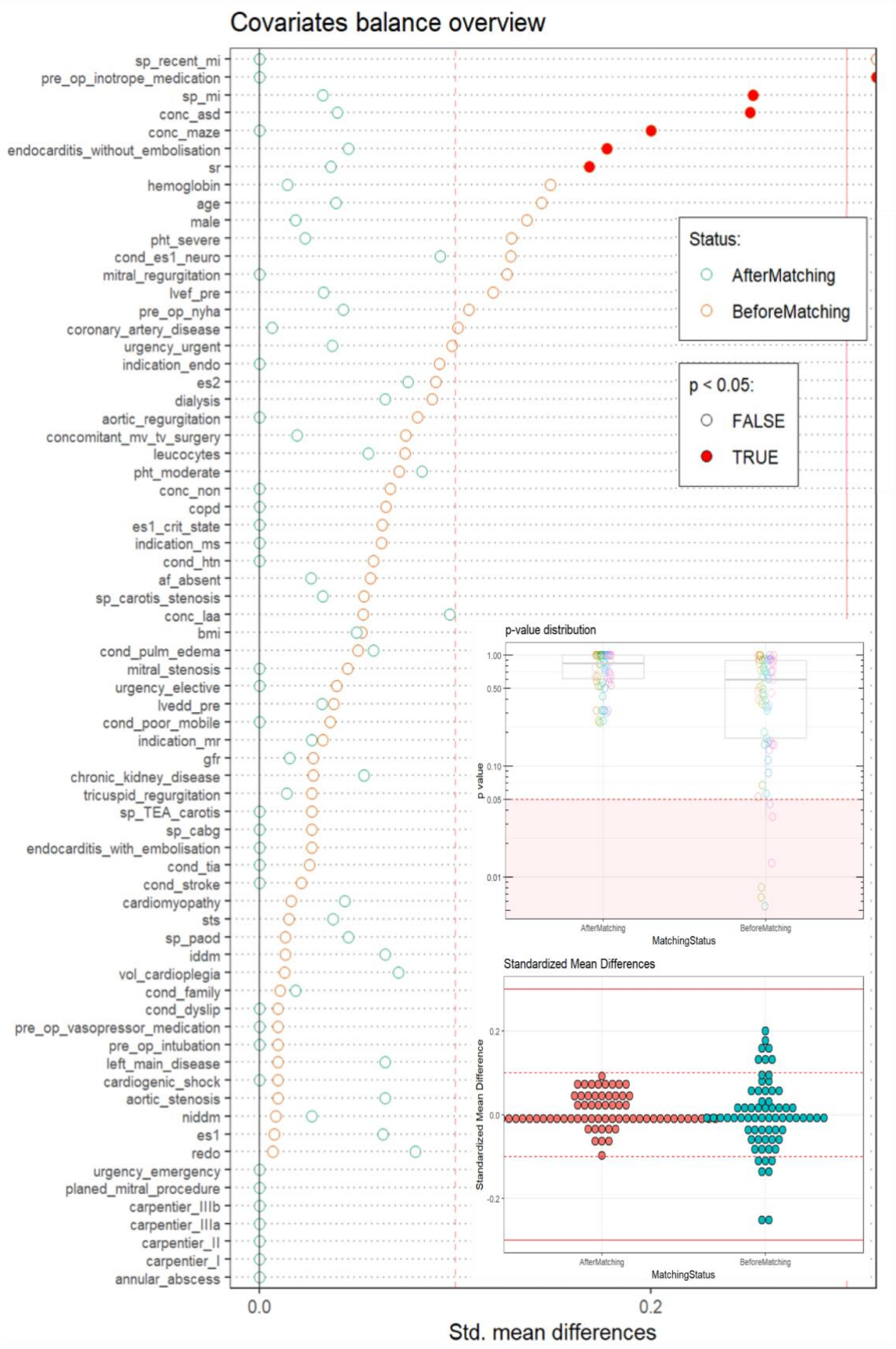
Fortunately, there are statistical techniques that can account for this. Multiple regression models are among the most commonly utilized[128]. This technique controls for contrasting characteristics in a linear way[128]. Propensity score matching (PSM) is more accurate when linearity cannot be presumed and is non-parametric[128].

The propensity score is defined as the probability that a patient will be allocated to the intervention group[128], in this case MIMVS. In 1-to-1 randomized studies, this is 0.5 for each patient[128]. However, in a non-randomized analysis, this probability is unknown and dependent on the patient characteristics[128]. Applying a logistic regression model with MIMVS as the dependent variable and (preoperative) patient characteristics as the independent variable, propensity scores were determined for each patient[128].

Aiming to make comparisons between the control- and treatment-group, patients from both study arms were matched based on similar levels of propensity scores. Patient pairs were allocated to one another 1-to-1 by making use of the nearest neighbor matching method.

PSM automatically results in a reduction in study group size through elimination of patients who do not have a match with an equivalent score. Nevertheless, the resulting smaller groups of patients are analogous enough to compare results with negligible bias. In our study, 5-fold multiple imputation and nearest-neighbour 1-to-1 PSM balanced the cohort regarding 69 important risk factors and potential confounders. Figure 12 shows the covariates balance overview and PSM quality.

Figure 12: *Covariates balance overview.*



7.2.6.2. Statistical Analysis

Continuous variables are depicted as median with interquartile range (IQR), while categorical variables are shown as frequencies with corresponding percentages. Five-fold multiple imputation of covariates, followed by nearest-neighbour 1:1 PS matching including all variables listed in **Figure 12**, was performed to balance both groups in terms of risk factors and potential confounders[129]. Diagnostics of PS matching were performed by investigating the standardized mean difference of individual variables. In line with current recommendations, a standardized mean difference of ≤ 0.1 was considered to preclude residual imbalance[130]. Differences in continuous data were assessed using the Wilcoxon signed-rank test with continuity correction. Proportions were compared using McNemar's test. A two-sided p-value of <0.05 was considered as statistically significant. For statistical analyses, R Version 4.0.0 (R Development Core Team (2019). R: A Language and Environment for Statistical Computing) and SPSS Statistics (version 25, IBM, Armonk, NY, USA) were used. Data reporting and statistical analyses were performed according to the statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery[131].

7.3. Results

7.3.1. Patient Cohort before and after Propensity Score Matching

Figure 12 shows the covariates balance overview of the unmatched and matched population.

7.3.2. Periprocedural and Clinical Outcomes

Matching diagnostic and baseline characteristics. After PS matching, all variables included in the matching showed a standardized mean difference ≤ 10%, indicating adequate covariate balance (Figure 12). The overall matching efficiency was 93.4%. Further details of baseline characteristics of the unmatched and matched cohorts are illustrated in Figure 12.

Procedure related outcome according to operative approach. The 3D-FE approach was associated with a significantly longer aortic cross clamp time (3D-FE: 74min [63-89], VA: 60min [50-77]; p<0.001) (Figure 13), a longer cardiopulmonary bypass time (3D-FE: 118min [103-142], VA: 86min [73-116]; p<0.001) (Figure 14) and a longer total operative time (3D-FE: 179min [158-210], VA: 126min [110-169]; p<0.001) (Figure 15) when compared to the VA approach. The rate of failed MV repair (3D-FE: 0.4% (n=1), VA: 2.0% (n=5); p=0.007) (Figure 16) and the rate of MV replacement (3D-FE: 0.8% (n=2), VA: 5.4% (n=13); p=0.008) (Figure 17) was higher in the VA group, while the reconstructive strategy in terms of neochord placement either in the anterior or posterior leaflet as well as the use of an isolated ring for MV repair did not differ between both groups. Details regarding the procedure related outcomes of the matched cohort are displayed in Table 8.

Table 8: *Operative Outcomes*

	Video-assisted	**3D fully endoscopic**	**Significance**
Variables	**n = 242**	**n = 242**	**p - value**
Aortic cross-clamp time, *min*	60 [50-77]	74 [63-89]	<0.001
Cardioplulmonary bypass time, *min*	86 [73-116]	118 [103-142]	<0.001
Operative time, *min*	126 [110-169]	179 [158-210]	<0.001
Mean transvalvular gradient, *mmHg*	3 [2-4]	3 [2-4]	0.202
Failed MV repair	5 (2.0)	1 (0.4)	0.007
MV replacement	13 (5.4)	2 (0.8)	0.008
Neochords posterior leaflet	191 (78.9)	194 (80.2)	0.828
Neochords anterior leaflet	38 (15.7)	52 (21.5)	0.146
Isolated ring	15 (6.3)	13 (5.4)	0.845
Conversion to sternotomy	1 (0.4)	3 (1.2)	0.625
Continuous variables are depicted as median with interquartile range, categorical variables are presented as frequency with corresponding percentage. MV = mitral valve.			

Figure 13: *Aortic cross-clamp time in minutes.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*

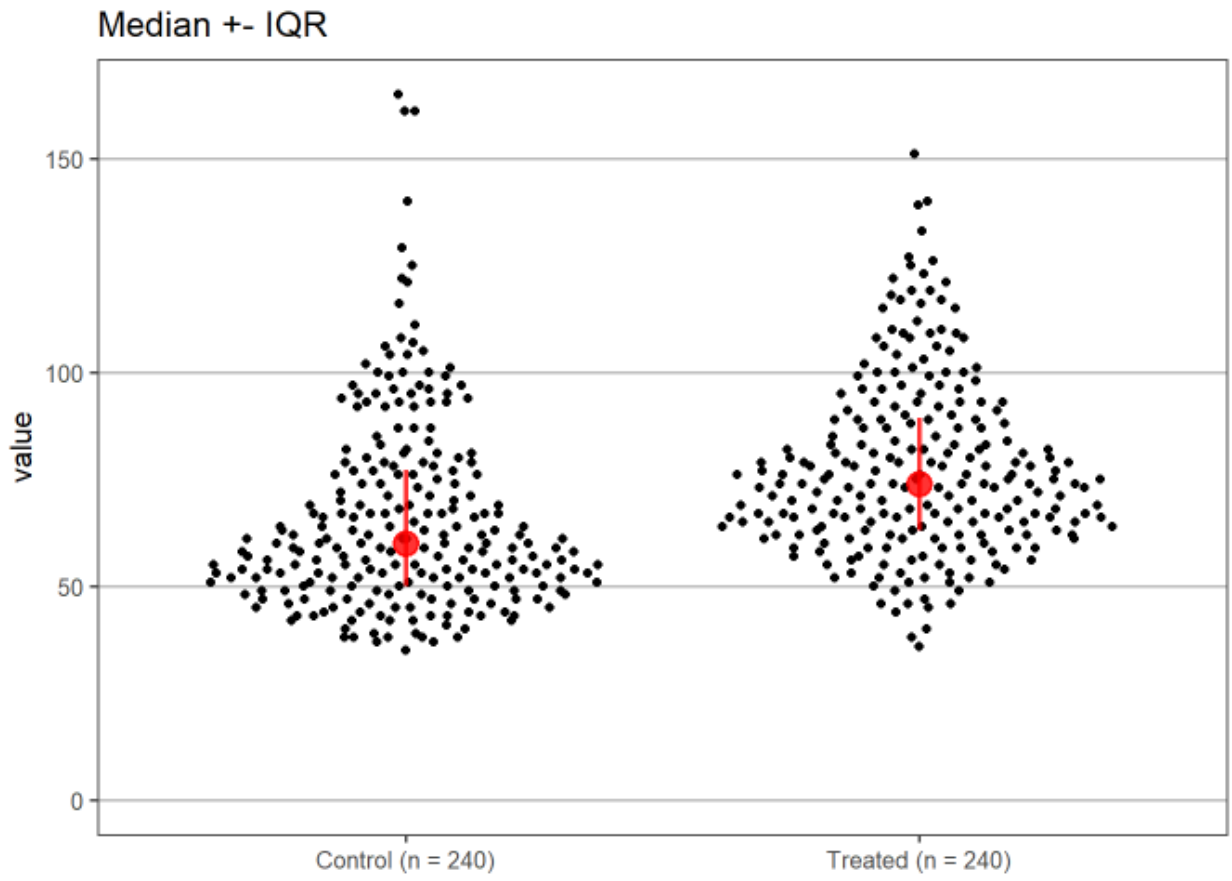


Figure 14: *Cardiopulmonary bypass time in minutes.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*

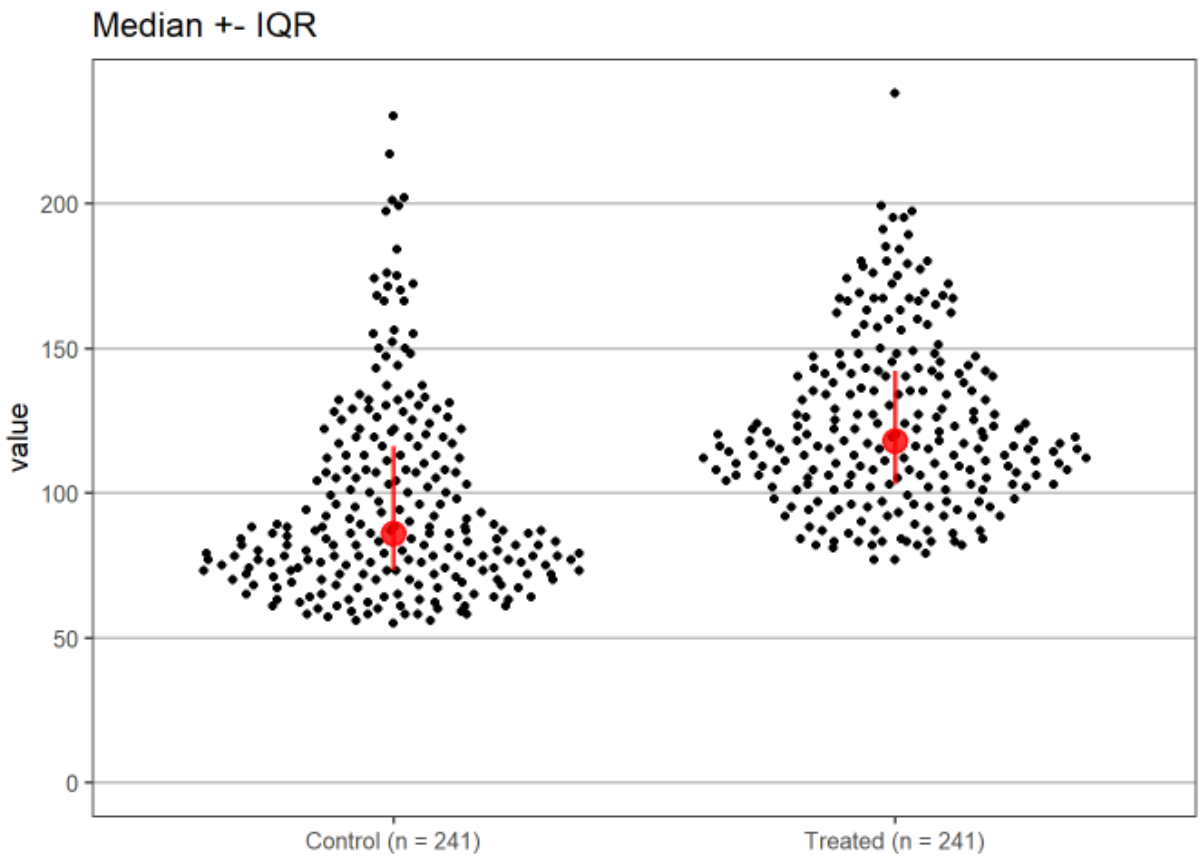


Figure 15: *Operative time in minutes.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*

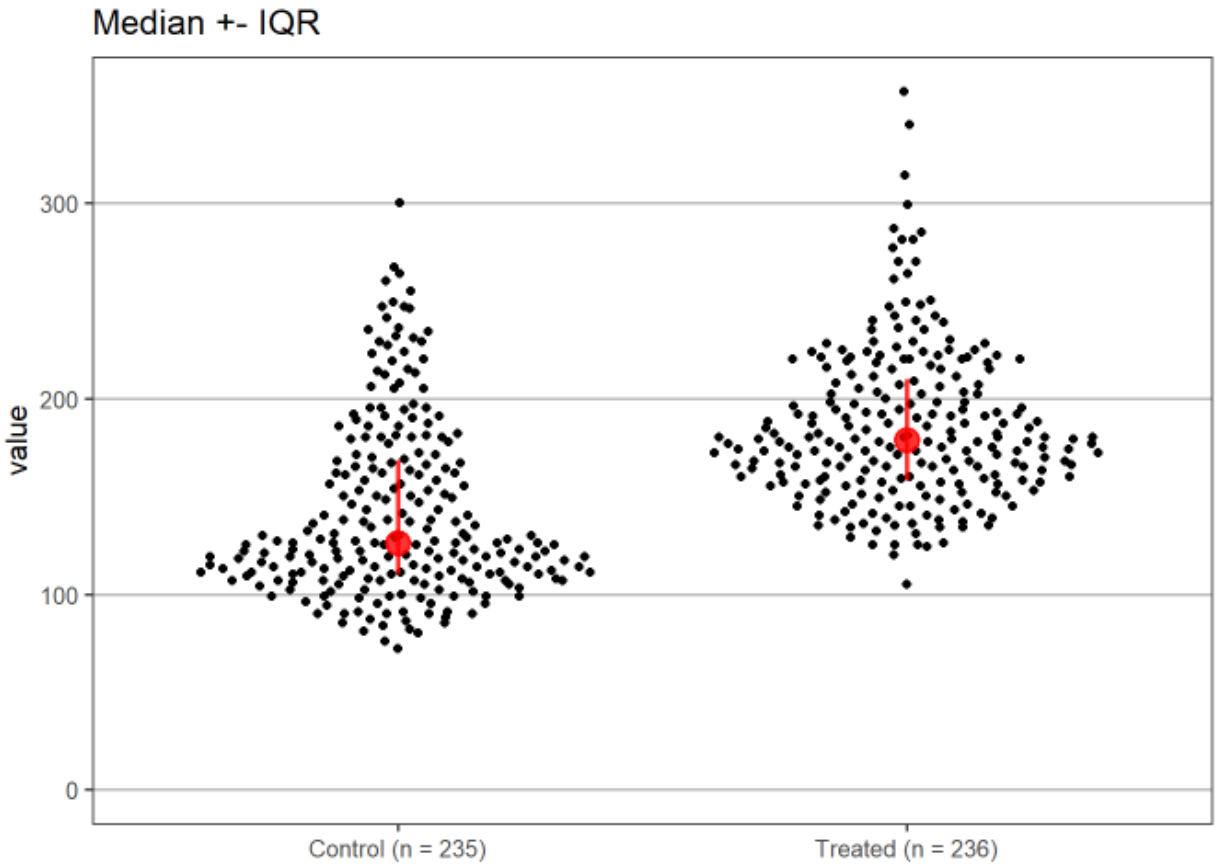


Figure 16*: Failed mitral valve repair.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*

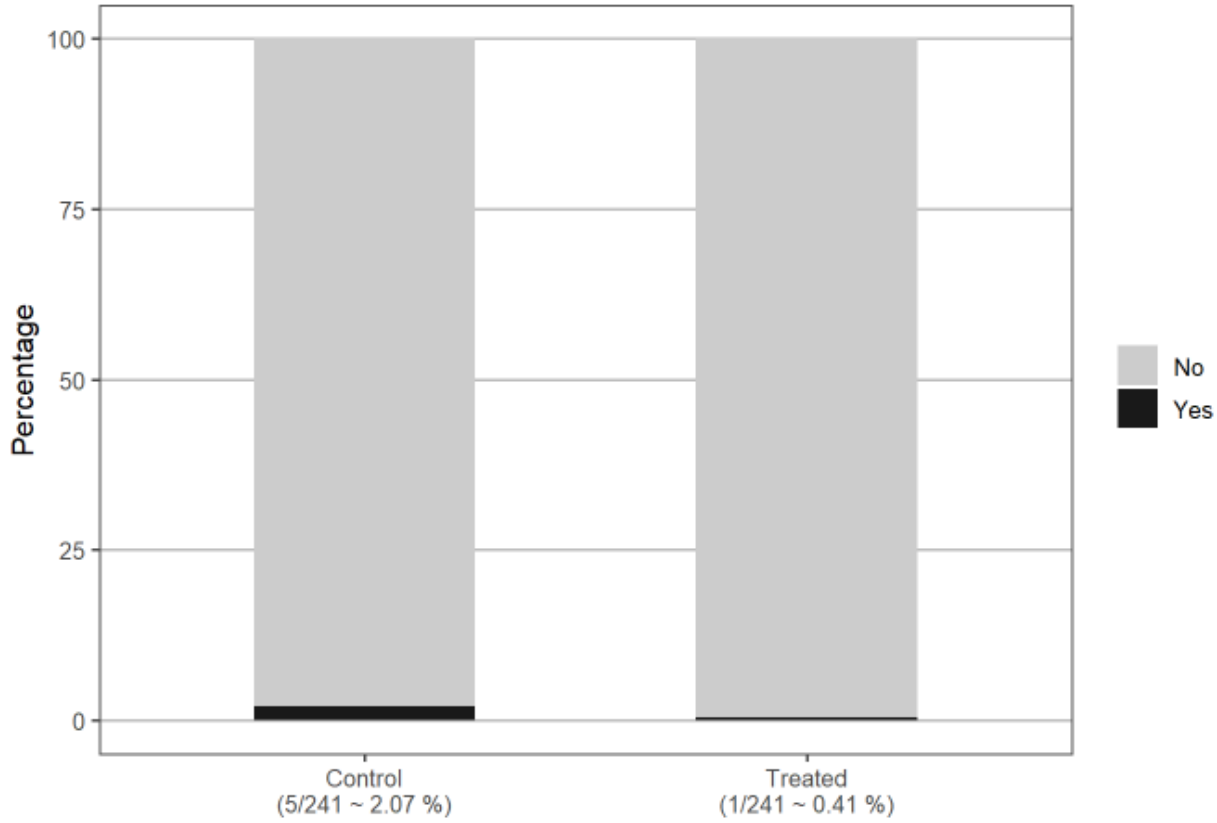
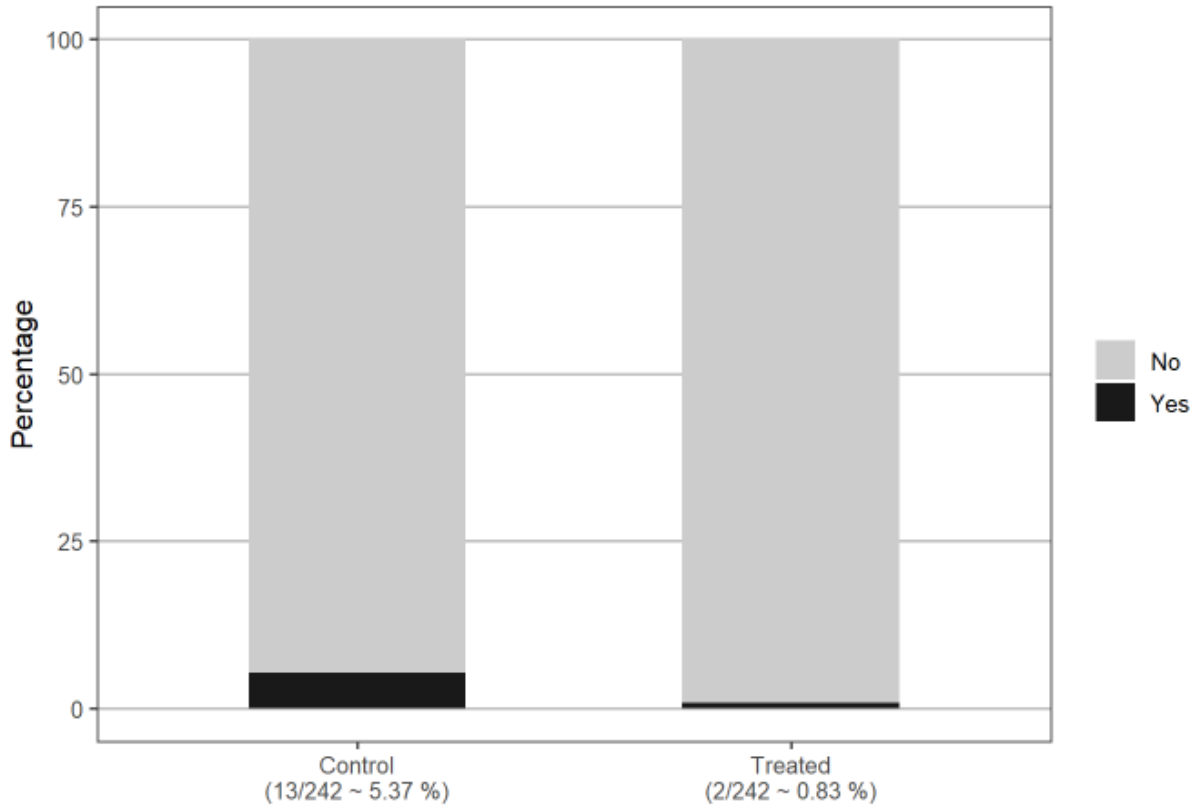


Figure 17: *Mitral valve replacement.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*



Postoperative outcome. Both groups showed similar rates of major cardiac and cerebrovascular events like myocardial infarction (3D-FE: 0.0% (n=0), VA: 1.2% (n=3); p=0.250), stroke (3D-FE: 1.7% (n=4), VA: 1.7% (n=4); p=1.000) (Figure 18) and 30-day mortality (3D-FE: 0.0% (n=0), VA: 0.4% (n=1); p=1.000) (Figure 19). The proportion of patients needing red-blood-cell, fresh-frozen-plasma or platelet transfusion was similar in both groups, with an equal rethoracotomy rate of 5.8% (n = 14) in both groups (p = 0.512). Mid-term follow-up revealed a 1-year mortality of 0.8% (n=2) in the 3D-FE group

compared to 1.2% (n=3) in the VA group (p=1.000) (Figure 20). Further details on the postoperative outcomes of the matched cohort are depicted in Table 9.

Table 9: *Postoperative Outcomes*

	Video-assisted	**3D fully endoscopic**	**Significance**
Variables	**n = 242**	**n = 242**	**p - value**
Mitral regurgitation ≥ grade 1	10 (4.1)	14 (5.8)	0.541
PLT transfusion	15 (6.2)	17 (7.1)	0.850
RBC transfusion	27 (11.2)	33 (13.7)	0.512
FFP transfusion	9 (3.7)	9 (3.7)	1.000
Rethoracotomy	14 (5.8)	14 (5.8)	1.000
Respiratory failure	3 (1.2)	4 (1.7)	1.000
Delirium	6 (2.5)	4 (1.7)	0.753
Stroke	4 (1.7)	4 (1.7)	1.000
Myocardial infarction	3 (1.2)	0 (0.0)	0.250
Intensive care unit stay, *days*	1 [1-2]	1 [1-2]	0.760
30-day mortality	1 (0.4)	0 (0.0)	1.000
1-year mortality	3 (1.2)	2 (0.8)	1.000
Continuous variables are depicted as median with interquartile range, categorical variables are presented as frequency with corresponding percentage. FFP = fresh frozen plasma; ICU = intensive care unit; PLT = platelets; RBC = red blood cells.			

Figure 18: *Postoperative stroke.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*

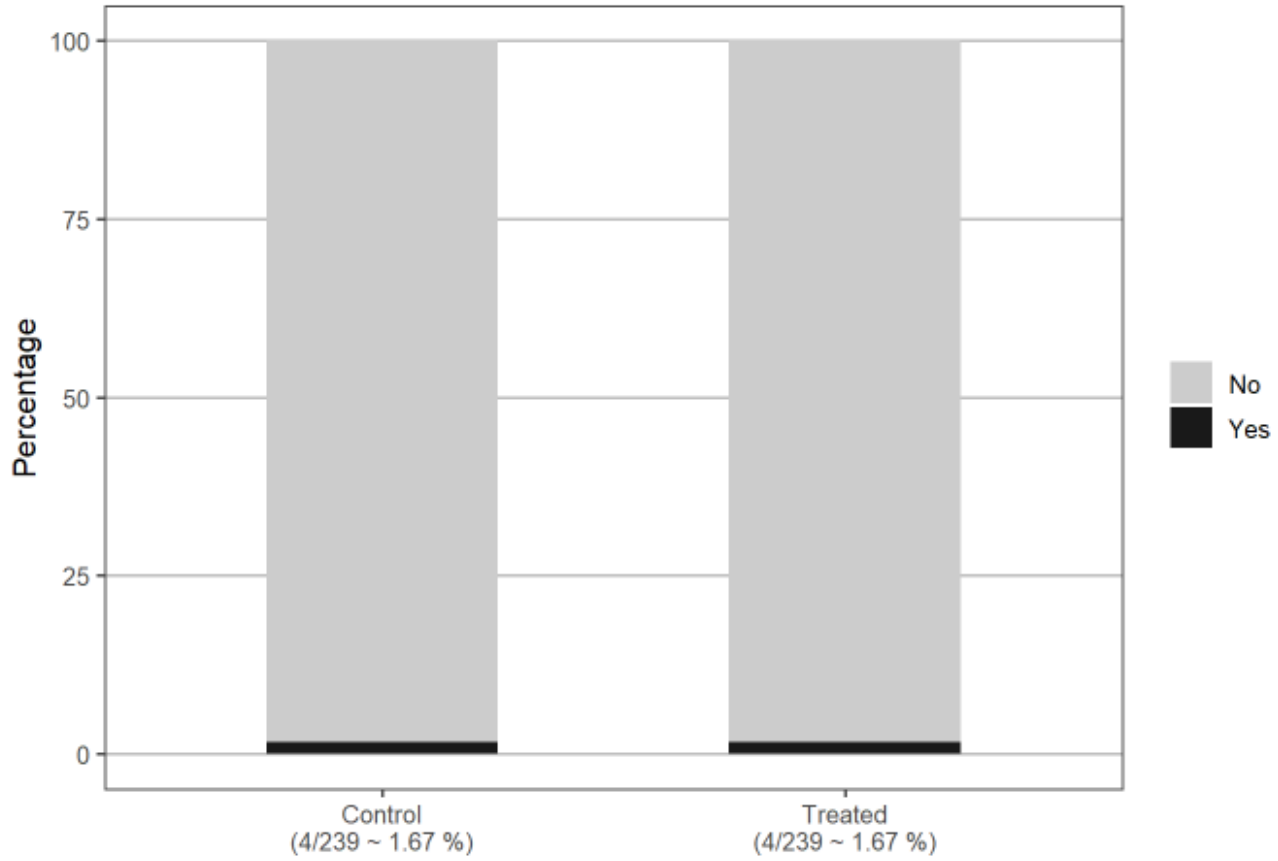


Figure 19: *Thirty-day mortality.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*

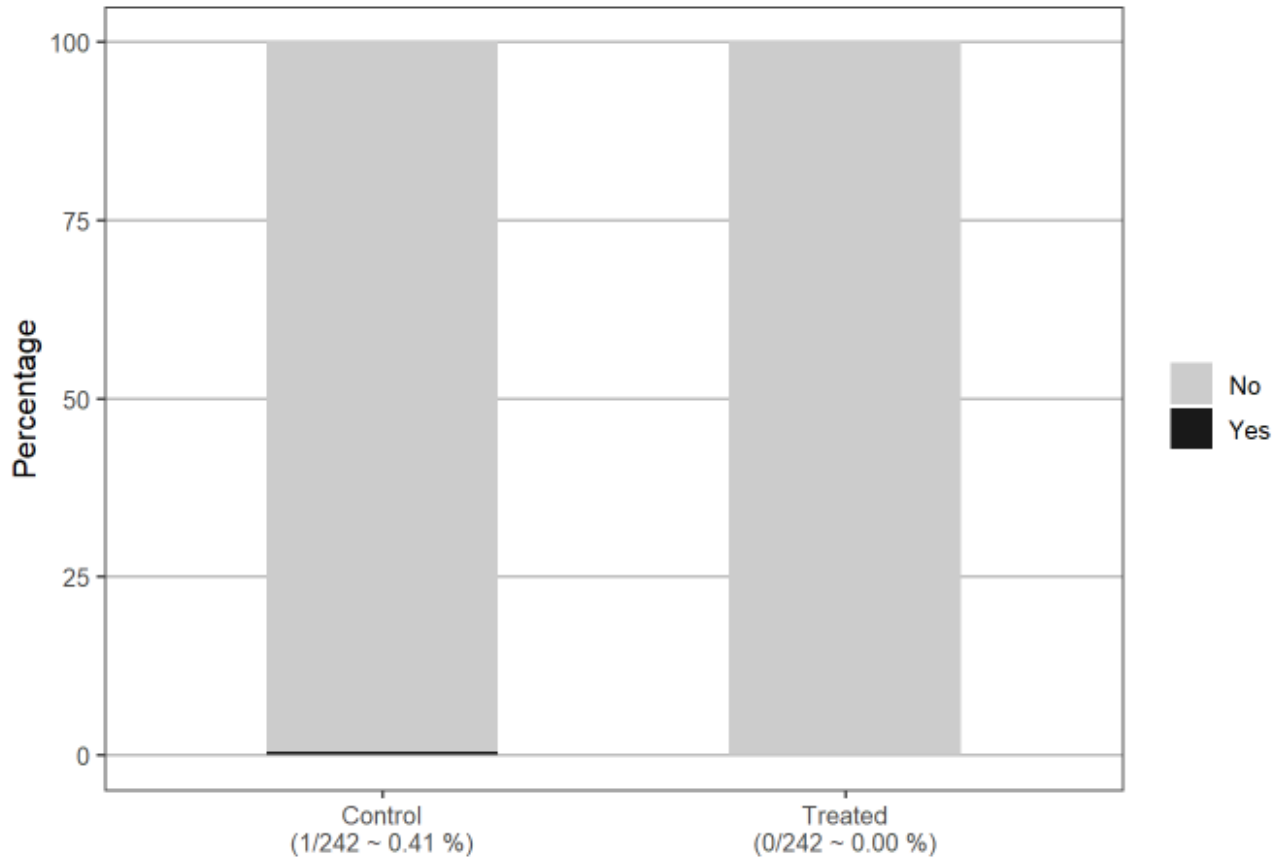
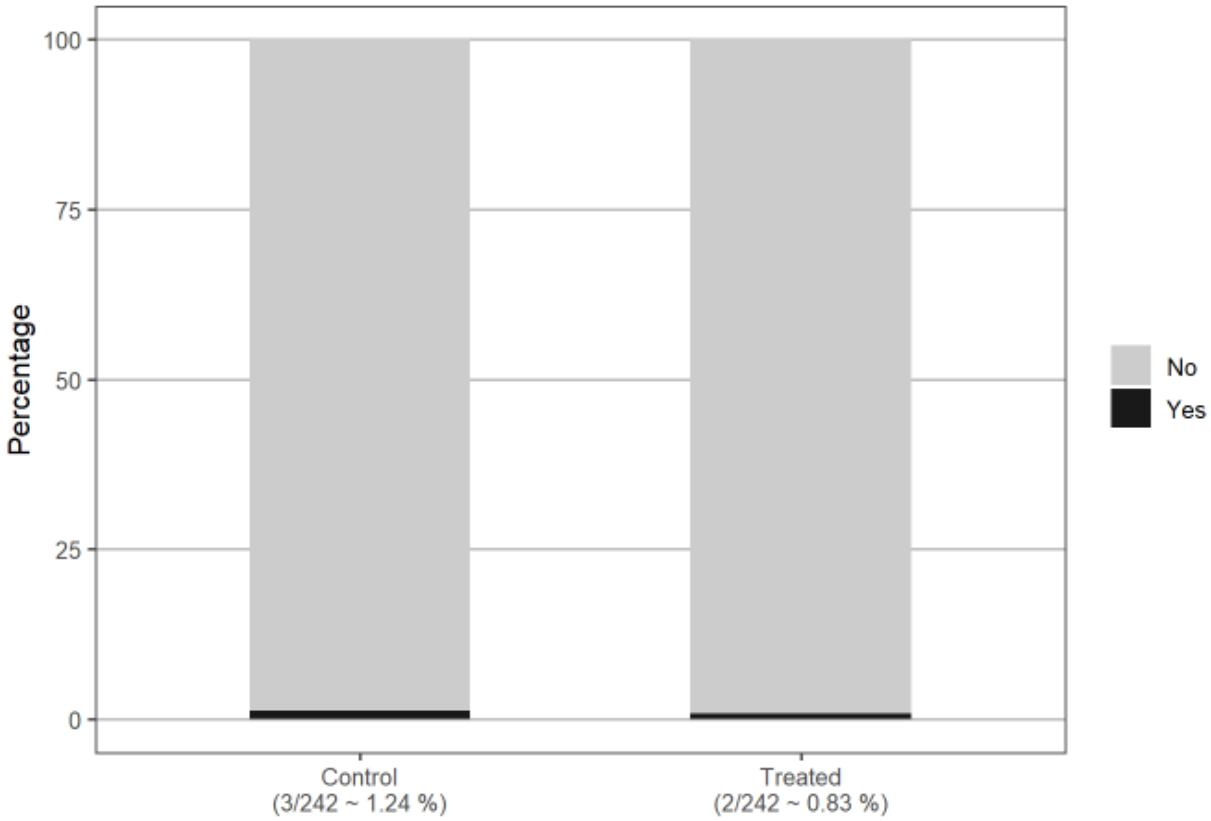


Figure 20: *One-year mortality.*

Legend: *Control = video-assisted; Treated = 3D fully endoscopic.*



7.4. Discussion

This study highlights the outcome of patients undergoing minimally invasive surgery due to Carpentier type II MR using either a 3D-FE or a VA approach.

The main findings are: (1) the rate of MV repair failure and the rate of MV replacement is lower in patients treated with a 3D-FE approach; (2) procedure related times are significantly shorter in patients undergoing VA mitral valve repair; (3) both approaches provide excellent results in terms of postoperative major cardiac and cerebrovascular events. Taken together, our report provides evidence for relevant benefits regarding MVR in patients treated using the 3D-FE approach, at the price of longer operative times.

Implementing right anterolateral minithoracotomy as an access for MV surgery turned out to provide excellent exposure of the MV, leading to a further reduction of invasiveness through maintaining full sternal integrity[132]. These advantages led to a widespread adoption of anterolateral minithoracotomy as the preferred access in minimally invasive mitral valve surgery, despite existing data suggesting longer operative times when compared to partial sternotomy and full sternotomy[133]. A previous study comparing non-rib-spreading- and rib-spreading minithoracotomy provided evidence for less postoperative pain, shorter ICU stay, shorter hospital length of stay and shorter operation time in patients treated using the 3D-FE non-rib-spreading approach[134]. The results regarding operative time contrast with our findings, when considering that the 3D-FE approach was associated with significantly longer procedure related times in our cohort. Although the results from the previous report were based on a PSM analysis, the shorter operative time in the non-rib-spreading 3D-FE group was probably derived from learning curve effects, as argued by the authors. It is also important to emphasize that in spite of the longer operative times in the 3D-FE group described in the present study, the required

standards in a “Heart Valve Centre” in terms of postoperative major cardiac and cerebrovascular events were achieved with both techniques[135].

Mitral valve repair according to visualisation strategy. Our findings regarding the success rate of MVR need to be interpreted keeping in mind that all patients considered for PS matching were judged as “likely repairable” by the Heart Team, based on preoperative echocardiography. The overall repair rate of 97% confirms minithoracotomy as excellent access for minimally invasive MVR and is in line with previously published reports[136]. However, it needs to be pointed out that the rate of failed MV repair and the need for MV replacement was significantly lower in the 3D-FE group. These findings are underlined by the fact that the reconstructive techniques in terms of neochord placement in the anterior and the posterior MV leaflet, as well as the use of isolated annuloplasty rings due to Barlow’s disease with a central jet and lack of chordal rupture, were similar between both groups[137]. The high-definition 3D visualisation provides excellent depth perception which facilitates MV analysis and may contribute to a more precise neochord placement within the leaflets. A significant affection of the described results induced by learning curve effects is not likely, since the surgeons involved had already obtained a high level of expertise prior to the refereed study period and were exposed to MVR with a high annual case load[138].

7.4.1. Study Limitations

The following limitations may have affected our findings and the consequently drawn conclusions*:* (a) although we performed PS matching considering several clinically relevant risk factors and potential confounders, a residual bias induced by the retrospective study design cannot be entirely precluded; (b) the provided results refer to

Carpentier type II patients only, and an extrapolation to other forms of MV disease, where longer procedure related times may significantly influence postoperative outcome, should be performed with caution; (c) our findings regarding the success of MVR refer to perioperative outcome only, so that future studies comparing the long-term repair durability of 3D-FE and VA, ideally using a randomized study design, are warranted.

7.5. Conclusion

In summary, the present report extends the currently available literature by providing detailed insights on the characteristic advantages of 3D-FE and VA minimally invasive MVR, referring to a head-to-head comparison using a large and well-balanced sample size. Three-dimensional fully endoscopic surgery provides excellent visualization of valvular and subvalvular structures. Both approaches, video-assisted and 3D-fully-endoscopic, are suitable for providing good results in terms of hard clinical endpoints. Three-dimensional fully endoscopic MIMVS is associated with higher repair rates. In degenerative mitral valve regurgitation, 3D fully endoscopic surgery shows higher repair rates compared to the video assisted approach. In our cohort, the 3D-fully-endoscopic approach was associated with a lower rate of failed MV repair and MV replacement, at the price of longer operative times.

8. References

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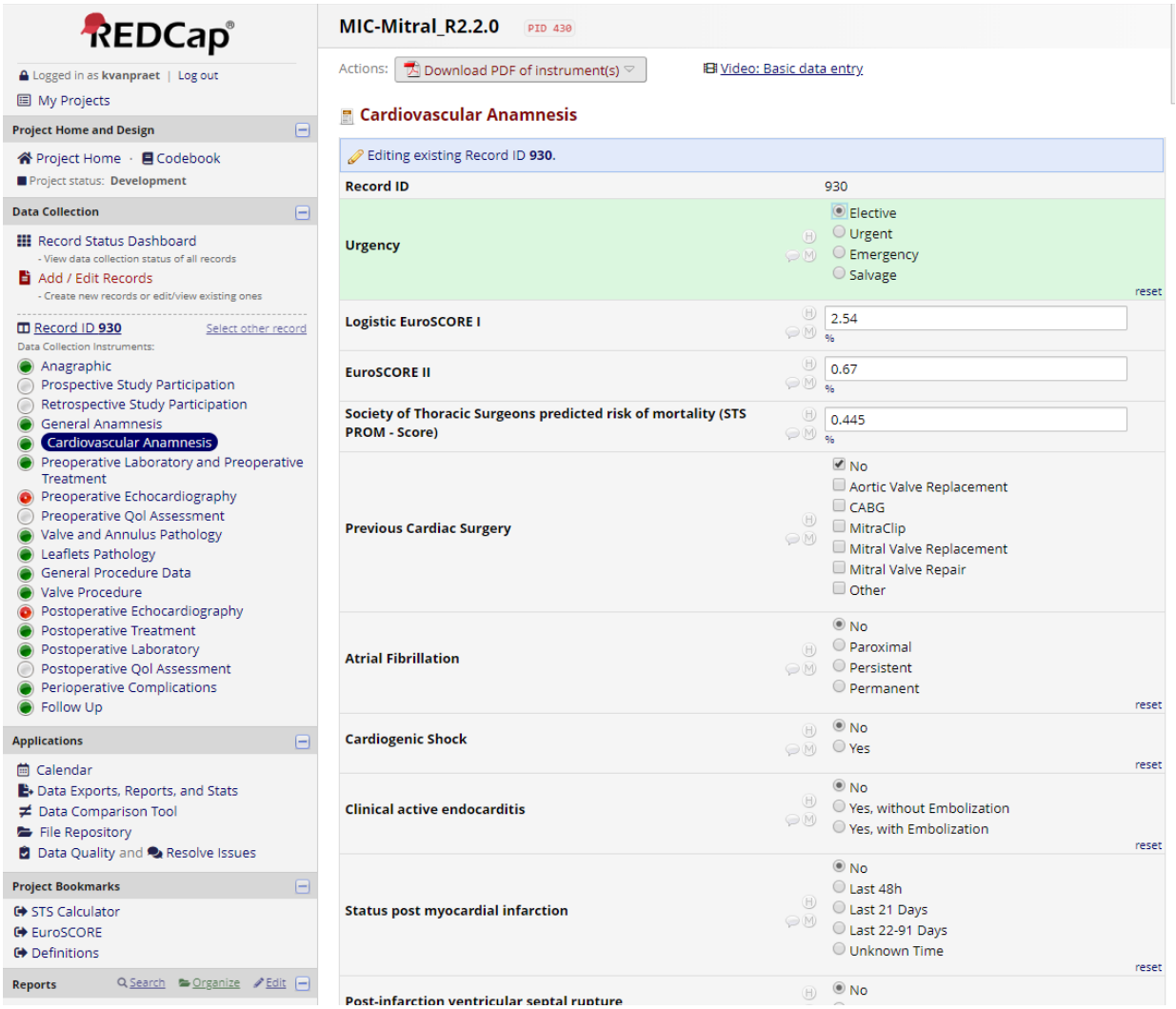
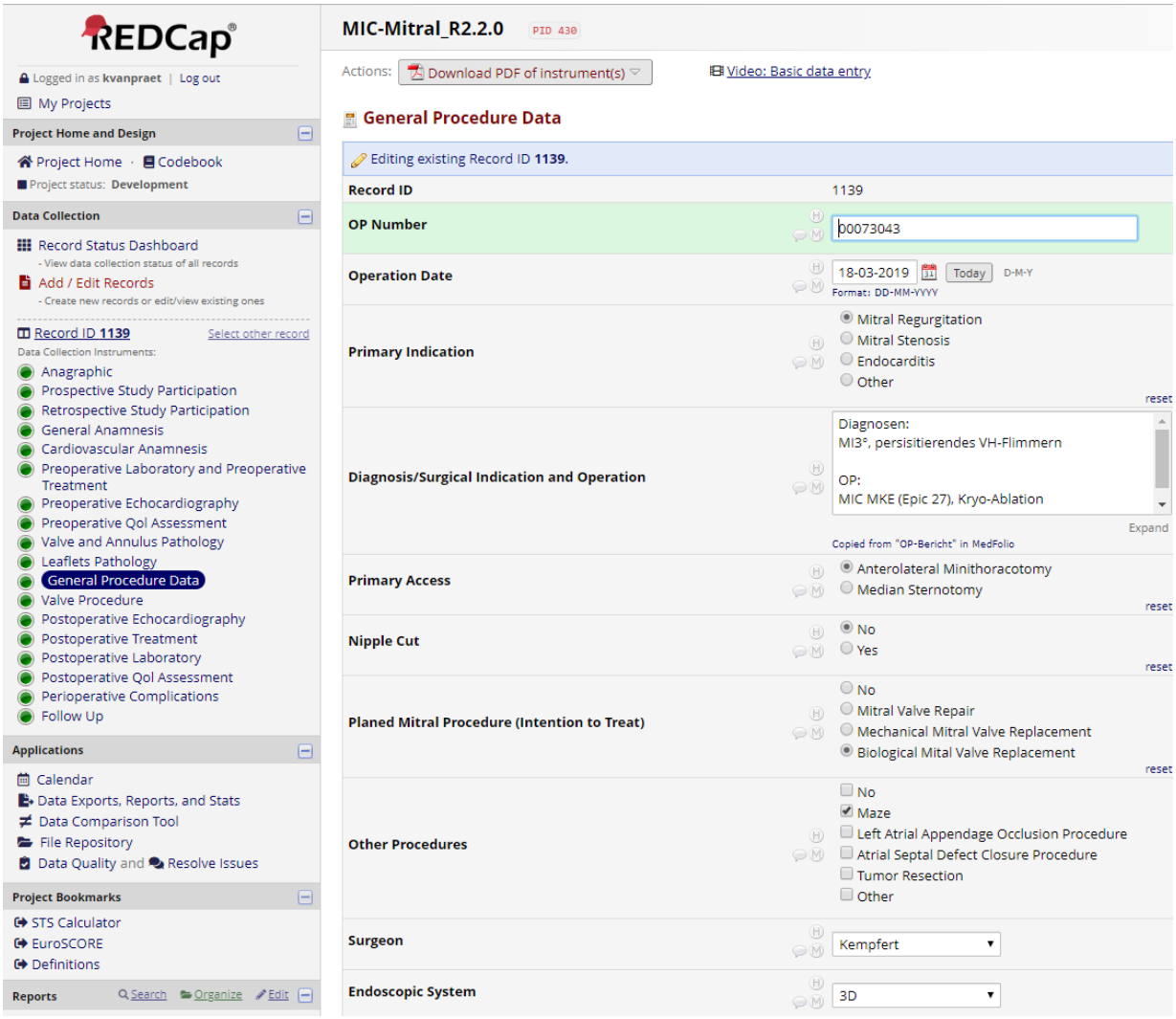
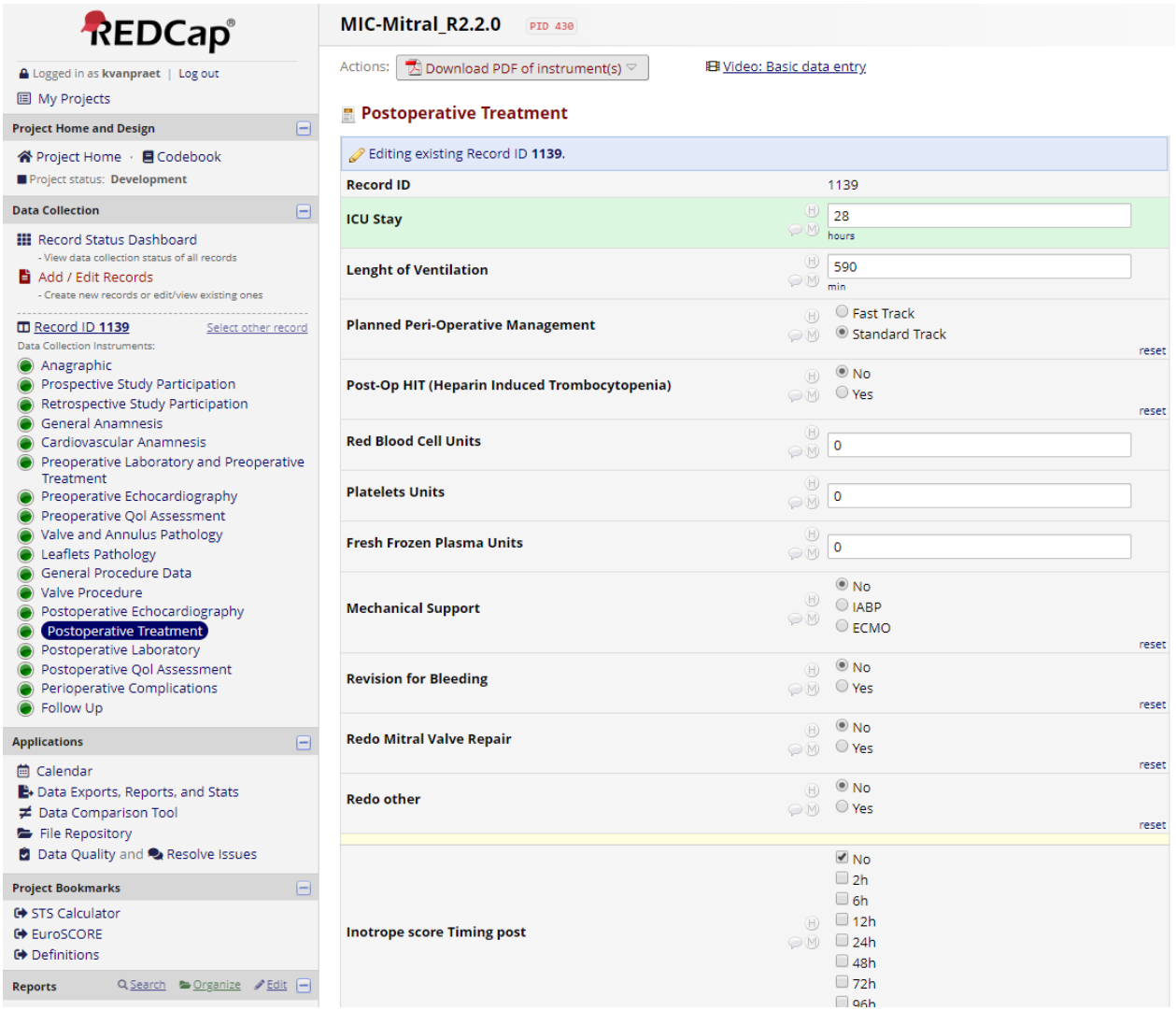
9. Addendum

9.1. Screenshots from our online secure web platform Research Electronic Data Capture 2 (REDCap2):




REDCap
Logged in as kvanpraet | Log out
My Projects
Project Home and Design
Project Home · Codebook
Project status: Development
Data Collection
Record Status Dashboard
- View data collection status of all records
Add / Edit Records
- Create new records or edit/view existing ones
Record ID 1139
Select other record
Data Collection Instruments:
Anagraphic
Prospective Study Participation
Retrospective Study Participation
General Anamnesis
Cardiovascular Anamnesis
Preoperative Laboratory and Preoperative Treatment
Preoperative Echocardiography
Preoperative QoI Assessment
Valve and Annulus Pathology
Leaflets Pathology
General Procedure Data
Valve Procedure
Postoperative Echocardiography
Postoperative Treatment
Postoperative Laboratory
Postoperative QoI Assessment
Perioperative Complications
Follow Up
Applications
Calendar
Data Exports, Reports, and Stats
Data Comparison Tool
File Repository
Data Quality and Resolve Issues
Project Bookmarks
STS Calculator
EuroSCORE
Definitions
Reports
Search
Organize
Edit
MIC-Mitral_R2.2.0
PID 430
Actions:
Download PDF of instrument(s)
Video: Basic data entry
General Procedure Data
Editing existing Record ID 1139.
Record ID
1139
OP Number
00073043
Operation Date
18-03-2019
Today
D-M-Y
Format: DD-MM-YYYY
Primary Indication
Mitral Regurgitation
Mitral Stenosis
Endocarditis
Other
reset
Diagnosis/Surgical Indication and Operation
Diagnosen:
MI3°, persisitierendes VH-Flimmern
OP:
MIC MKE (Epic 27), Kryo-Ablation
Expand
Copied from "OP-Bericht" in MedFolio
Primary Access
Anterolateral Minithoracotomy
Median Sternotomy
reset
Nipple Cut
No
Yes
reset
Planed Mitral Procedure (Intention to Treat)
No
Mitral Valve Repair
Mechanical Mitral Valve Replacement
Biological Mital Valve Replacement
reset
Other Procedures
No
Maze
Left Atrial Appendage Occlusion Procedure
Atrial Septal Defect Closure Procedure
Tumor Resection
Other
Surgeon
Kempfert
Endoscopic System
3D


REDCap
Logged in as kvanpraet | Log out
My Projects
Project Home and Design
Project Home · Codebook
Project status: Development
Data Collection
Record Status Dashboard
- View data collection status of all records
Add / Edit Records
- Create new records or edit/view existing ones
Record ID 1139
Select other record
Data Collection Instruments:
Anagraphic
Prospective Study Participation
Retrospective Study Participation
General Anamnesis
Cardiovascular Anamnesis
Preoperative Laboratory and Preoperative Treatment
Preoperative Echocardiography
Preoperative QoI Assessment
Valve and Annulus Pathology
Leaflets Pathology
General Procedure Data
Valve Procedure
Postoperative Echocardiography
Postoperative Treatment
Postoperative Laboratory
Postoperative QoI Assessment
Perioperative Complications
Follow Up
Applications
Calendar
Data Exports, Reports, and Stats
Data Comparison Tool
File Repository
Data Quality and Resolve Issues
Project Bookmarks
STS Calculator
EuroSCORE
Definitions
Reports
Search
Organize
Edit
MIC-Mitral_R2.2.0
PID 430
Actions:
Download PDF of instrument(s)
Video: Basic data entry
Postoperative Treatment
Editing existing Record ID 1139.
Record ID
1139
ICU Stay
28
hours
Lenght of Ventilation
590
min
Planned Peri-Operative Management
Fast Track
Standard Track
reset
Post-Op HIT (Heparin Induced Trombocytopenia)
No
Yes
reset
Red Blood Cell Units
0
Platelets Units
0
Fresh Frozen Plasma Units
0
Mechanical Support
No
IABP
ECMO
reset
Revision for Bleeding
No
Yes
reset
Redo Mitral Valve Repair
No
Yes
reset
Redo other
No
Yes
reset
Inotrope score Timing post
No
2h
6h
12h
24h
48h
72h
96h

10. Eidesstattliche Versicherung

„Ich, Karel M. Van Praet, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Endoskopische minimalinvasive Herzchirurgie / Endoscopic Minimally Invasive Cardiac Surgery 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

11. Curriculum Vitae

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

12. List of Publications

- Karel M Van Praet, Gaik Nersesian, Markus Kofler, Simon H Sündermann, Axel Unbehaun, Volkmar Falk, Jörg Kempfert. **Right Antero-Lateral Mini-Thoracotomy Surgical Aortic Valve Replacement.** Surg Technol Int. 2022 May 27;41:sti41/1597. doi: 10.52198/22.STI.41.CV1597.

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- Karel M. Van Praet, Gaik Nersesian, Matteo Montagner, Serdar Akansel, Dirk Eggert-Doktor, Markus Kofler, Simon H. Sündermann, Volkmar Falk, Jörg Kempfert. **Endoaortic balloon occlusion in minimally invasive mitral valve surgery.** Multimed Man Cardiothorac Surg. 2022 Apr 5;2022. doi: 10.1510/mmcts.2022.017

- Karel M. Van Praet, Gaik Neresian, Marian Kukucka, Emanuel Heil, Markus Kofler, Volkmar Falk, Jörg Kempfert, Christoph Klein, Axel Unbehaun. **Percutaneous transseptal transcatheter mitral valve-in-valve implantation under endovascular cerebral protection.** Multimed Man Cardiothorac Surg. 2022 Apr 5;2022. doi: 10.1510/mmcts.2022.015

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- Michel Pompeu Sá, Basel Ramlawi, William A Gray, John H. Malin, Jef Van den Eynde, Serge Sicouri, Gianluca Torregrossa, Christoph Klein, Emanuel Heil, Simon H. Sündermann, Anna Emmerich, Jörg Kempfert, Markus Kofler, Volkmar Falk, Axel Unbehaun, Karel M. Van Praet. **Transcatheter mitral valve implantation in the ongoing structural heart revolution.** J Card Surg. 2022 Mar 27. doi: 10.1111/jocs.16431.

- Serdar Akansel, Markus Kofler, Simon H. Sündermann, Karel M. Van Praet, Volkmar Falk, Jörg Kempfert. **Partial ring annuloplasty in the management of mitral annular calcification.** J Card Surg. 2022 Apr 2. doi: 10.1111/jocs.16439.

- Reinhard Fuchs, Karel M. Van Praet, Richard Bieck, Jörg Kempfert, David Holzhey, Markus Kofler, Michael A Borger, Stephan Jacobs, Volkmar Falk, Thomas Neumuth. **A system for real-time multivariate feature combination of endoscopic mitral valve simulator training data.** Int J Comput Assist Radiol Surg. 2022 Mar 16. doi: 10.1007/s11548-022-02588-1

- Karel M. Van Praet, Markus Kofler, Simon H. Sündermann, Jörg Kempfert. **Endoaortic Balloon Occlusion During Minimally Invasive Mitral Valve Surgery.** Innovations (Phila). 2022 Mar 11;15569845221083047. doi: 10.1177/15569845221083047

- Karel M. Van Praet, Gaik Nersesian, Markus Kofler, Emmanuel Heil, Axel Unbehaun, Christoph Klein, Joerg Kempfert, Volkmar Falk, Jin-Hong Gerds-Li, Christoph Starck. **Minimally invasive approach to the treatment of atrial fibrillation: Concomitant Convergent and LARIAT procedure.** Multimed Man Cardiothorac Surg. 2022 Feb 14;2022. doi: 10.1510/mmcts.2022.005

- Antonia van Kampen, Markus Kofler, Alexander Meyer, Maria Gerber, Simon H. Sündermann, Karel M. Van Praet, Serdar Akansel, Matthias Hommel, Volkmar Falk, Jörg Kempfert. **Aortic valve replacement via right anterolateral minithoracotomy - preventing adverse events during the initial learning curve.** J Cardiovasc Surg (Torino). 2021 Nov 26. doi: 10.23736/S0021-9509.21.11981-0

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- Markus Kofler, Karel M. Van Praet, Julie Schambach, Serdar Akansel, Simon Sündermann, Felix Schönrath, Stephan Jacobs, Volkmar Falk, Jörg Kempfert. **Minimally invasive surgery versus sternotomy in native mitral valve endocarditis: a matched comparison.** Eur J Cardiothorac Surg. 2021 Aug 18;ezab364. doi: 10.1093/ejcts/ezab364

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- ICVTS-2022-100122 - **Periareolar Endoscopic Minimally Invasive Cardiac Surgery: Postoperative Scar Assessment Analysis**, Cardiac general, Original Article (received: 18.02.2022).

Manuscripts accepted for publication:

- JCR112921-2996 – **Transcatheter Aortic Valve Implantation in a Patient with Criss-Cross Heart**, Congenital Heart Disease, Case Report (received 2021-12-03). Decision letter: accepted for publication in ***JACC:Case Reports*** on Friday June 10th, 2022.

Bookchapters accepted for publication:

Publisher: **Springer** Nature Switzerland AG
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- **Endo-Aortic Balloon Occlusion in Minimally Invasive Atrioventricular Surgery.** Karel M. Van Praet, Markus Kofler, Axel Unbehaun, Volkmar Falk, Jörg Kempfert.
- **Cannulation Techniques in Minimally Invasive Mitral Valve Surgery.** Karel Van Praet, Markus Kofler, Jörg Kempfert.

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- **Chirurgische Mitralklappenrekonstruktion.** [Article in German]. Antonia van Kampen, Karel Van Praet, Stephan Jacobs.
- **Chirurgische Therapie der Trikuspidalklappenendokarditis.** [Article in German]. Karel Van Praet, Antonia van Kampen, Markus Kofler, Jörg Kempfert.
- **Chirurgischer Mitralklappenersatz.** [Article in German]. Antonia van Kampen, Karel Van Praet, Stephan Jacobs.
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- **Transkatheter Verfahren zur Behandlung der Trikuspidalklappeninsuffizienz.** [Article in German]. Karel Van Praet, Antonia van Kampen, Markus Kofler, Axel Unbehaun.
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14. Bescheinigung Statistik

CHARITÉ

CharitéCentrum für Human- und Gesundheitswissenschaften

Charité | Campus Charité Mitte | 10117 Berlin

Institut für Biometrie und klinische Epidemiologie (iBikE)

Direktor: Prof. Dr. Geraldine Rauch

Postanschrift:
Charitéplatz 1 | 10117 Berlin
Besucheranschrift:
Reinhardtstr. 58 | 10117 Berlin

Tel. +49 (0)30 450 562171
geraldine.rauch@charite.de
https://biometrie.charite.de/

Name, Vorname: Van Praet, Karel

Emailadresse: vanpraet@dhzb.de
Matrikelnummer: 225193
PromotionsbetreuerIn: Prof. Dr. med. Jörg Kempfert

Promotionsinstitution / Klinik: Deutsches Herzzentrum Berlin

- Klinik für Herz-, Thorax- und Gefäßchirurgie

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CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN Institut für Biometrie und Klinische Epidemiologie Campus Charité Mitte Charitéplatz 1 | D-10117 Berlin Sitz: Reinhardtstr. 58