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# Outcomes of Complex Valve Surgery in Elderly Patients

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Abstract:

The number of elderly patients undergoing complex valve surgery for multiple valve disease is growing. Cardiac surgery in these patients is associated with a higher risk, as multiple co-morbidities are a frequent finding. This study reviews the short term outcomes of elderly patients undergoing cardiac surgery for multiple valve disease.

Keywords:

Multiple valve disease, elderly patients

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List of Abbreviations

| | |
|---|---|
| AM | Group of patients who underwent aortic and mitral valve surgery |
| AML | Anterior mitral leaflet |
| AMT | Group of patients who underwent aortic and mitral and tricuspid valve surgery |
| AR | Aortic regurgitation |
| AS | Aortic stenosis |
| AT | Group of patients who underwent aortic and tricuspid valve surgery |
| ATP | Adenosine triphosphate |
| AV | Aortic valve |
| AVR | Aortic valve replacement |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CAF | Comprehensive assessment of frailty score |
| CC | Creatinine clearance |
| CCS | Canadian cardiovascular society |
| CI | Confidence interval |
| CPB | Cardiopulmonary bypass |
| EROA | Effective regurgitant orifice area |
| EuroSCORE II | European System for Cardiac Operative Risk Evaluation II |
| FED | Fibroelastic disease |
| HF | Heart failure |
| LA | Left atrium |
| LF/LGAS | Low-flow/low-gradient aortic stenosis |
| LV | Left ventricle |
| LVEF | Left ventricular ejection fraction |
| LVOT | Left ventricle outflow tract |
| MICS | Minimally invasive cardiac surgery |
| MR | Mitral regurgitation |
| MS | Mitral stenosis |
| MT | Group of patients who underwent mitral and tricuspid valve surgery |
| MV | Mitral valve |

| | |
|---|---|
| MVA | Mitral valve area |
| MVD | Multiple valve disease |
| MVR | Mitral valve replacement |
| MVRp | Mitral valve repair |
| NYHA | New York Heart Association |
| OPR | Ontario province risk score |
| PCI | Percutaneous coronary intervention |
| PHT | Pressure half time |
| PISA | Proximal isovelocity surface area |
| PML | Posterior mitral leaflet |
| PROM | Predicted risk of mortality |
| PTFE | Polytetrafluoroethylene |
| QoL | Quality of life |
| ROS | Reactive oxygen species |
| RV | Right ventricle |
| SD | Standard deviation |
| SPAP | Systolic pulmonary artery pressure |
| TR | Tricuspid regurgitation |
| TTE | Transthoracic echocardiography |
| TV | Tricuspid valve |
| TVS | Triple valve surgery |

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# 1. Introduction

Mulitivalvular Disease (MVD) can be defined as the combination of stenotic or regurgitant lesions or both affecting more than one of the heart valves (Unger et al. 2016). Degenerative valve disease in the elderly often affects more than one heart valve, and this results in a complex clinical situation with several factors to be considered for optimal management. The increase in the proportion of elderly patients poses also additional challenges for the clinical management and leads to a higher intervention risk, as multiple co-morbidities are frequent in these patients.

## 1.1 Epidemiology

It has been reported that more than one in eight people aged 75 and older have a moderate or severe valve disease (Nkomo et al. 2006). The Euro Heart Survey (Iung et al. 2003) examined 5001 patients from 92 centres in 25 European countries. Native valve disease was reported in 71.9% of the total population. A total of 20.2% of these patients had MVD. In the group of patients suffering from MVD, 25.4% of them were older than 70 years. Lee et al. reviewed 623,039 patients undergoing cardiac valve surgery from 1993 to 2007 with 15.0% older than 80 years and 10.9% that underwent surgery for MVD. Out of these patients, 57.8% underwent surgery on the aortic and mitral valves, 31.0% on the mitral and tricuspid valves, 3.3% on the aortic and tricuspid valves, and 7.9% underwent triple-valve surgery. Their data also shows an incremental trend in the number of elderly patients undergoing valve surgery. From 1993-1997 11.0% of patients undergoing valve surgery were older than 80 years. This increased to 14.8% in 1998-2002 and was 16.9% in 2003-2007 ($p < 0.0001$) (Lee et al. 2011).

Mitral valve (MV) disease is the most common valvular pathology in the elderly, predominately resulting in mitral regurgitation (MR). Moderate to severe MR has been found in 9.3% in those aged more than 75 years. Aortic sclerosis affects one in four of patients older than 65 years in developed countries. The most common pathology of the aortic valve in the elderly population is aortic stenosis (AS) due to age-related calcific degeneration (Zakkar et al. 2016). The prevalence of AS increases with age; with an incidence of 0.2% at age 50-59, 1.3% at age 60–69, 3.9% at age 70–79 year old cohort and 9.8% at age 80–89 years (Nkomo et al. 2006, Iung et al. 2011, Seco et al. 2014).

## 1.2 Valvular Heart Disease

### 1.2.1 Mitral Valve Disease

#### 1.2.1.1 Mitral Valve Regurgitation

Mitral regurgitation (MR) is defined as systolic retrograde flow from the left ventricle to the left atrium. A lack of the normal systolic coaptation between the anterior and posterior mitral leaflet results in valvular incompetence. To better describe this pathology of the mitral valve, the causes and mechanisms of mitral regurgitation must be analysed (Enriquez-Sarano et al. 2009, Levine et al. 2015).

Causes of mitral valve regurgitation are generally classified as ischaemic (functional) and non-ischaemic (degenerative). Ischemic mitral regurgitation is associated with coronary artery disease. Non ischemic mitral regurgitation in an umbrella term which includes all types of degenerative valve disease, but also endocarditis. Mechanisms are grossly classified as functional or organic. Functional mitral regurgitation most often stems from valve deformation caused by ventricular remodelling based on ischemic heart disease, whereas organic mechanisms result from intrinsic valve lesions, which have been further classified by Carpentier as type I (normal valve movement, such as annular dilatation or leaflet perforation); type II (excessive movement, such as prolapse or flail); and type III (restrictive movement: IIIa—diastolic restriction such as rheumatic disease; IIIb—systolic restriction as in functional disease) (Enriquez-Sarano et al. 2009, Levine et al. 2015).

Degenerative processes play an important role in mitral regurgitation in the elderly. They exhibit two main pathologies: diffuse myxomatous degeneration (Barlow disease) and fibroelastic deficiency (FED). Barlow disease is associated with excess connective tissue, with redundant, thickened leaflets, marked annular dilatation, elongated and thin (sometimes ruptured) or thick (frequently calcified) chordae, disrupted collagen and elastic layers, that consist of excess acidic mucopolysaccharides. Fibroelastic deficiency is characterized by thin, translucent leaflets deficient in collagen, elastin, and proteoglycans with only moderate annular dilatation and with focal chordal elongation or rupture (Enriquez-Sarano et al. 2009, Levine et al. 2015).

Most patients with severe, chronic, primary mitral regurgitation remain asymptomatic for many years due to compensatory ventricular dilation. Symptoms of exertional dyspnoea and exercise intolerance develop slowly as the compensatory mechanisms are overwhelmed by the progressing volume overload, and irreversible left ventricular dysfunction occurs.

*Echocardiographic Considerations*

Echocardiography is the gold standard to diagnose valve disease. It provides essential information for further treatment. Transthoracic echocardiography (TTE) is indicated in patients with primary mitral regurgitation to evaluate the mitral valve apparatus and left ventricle function (LVEF). Several methods have been established to quantify mitral regurgitation using echocardiography. The size and the extent of the jet into the left atrium (LA) using colour flow doppler provides a good first impression, but is not recommended to quantify mitral regurgitation. An important parameter used for quantification is the vena contracta. Vena contracta is defined as the narrowest central flow region of a jet that occurs at, or just downstream to, the orifice of a regurgitant valve. Its width should be measured in a long-axis imaging plane perpendicular to mitral leaflet closure. However, there are limitations of this method. These include difficult or incorrect alignment of the imaging plane and the drawback that multiple jets cannot be considered. The PISA (proximal isovelocity surface area) method is based on the hydrodynamic principle that flow approaching a circular orifice forms concentric, hemispheric shells of increasing velocity just proximal to that orifice. The radius of the PISA is measured at mid-systole using the first aliasing velocity. Regurgitant volume and effective regurgitant orifice area (EROA) are obtained using standard formulas. The PISA method is based on the assumption of hemispheric symmetry of the velocity distribution proximal to the circular regurgitant lesion, which is problematic for eccentric jets, multiple jets, or complex or elliptical regurgitant orifices. Despite the obvious need to define MR severity, there is some disparity among the various available guidelines on grading the severity of MR. Integration of the various echocardiographic measurements and use of a systematic integrated approach will result in an accurate diagnosis and better decision making (Grayburn et al. 2012, Poelaert et al. 2016, Lancellotti et al. 2013, Nishimura et al. 2016)

1.2.1.2 Mitral Stenosis

Mitral stenosis (MS) causes obstruction at the level of the mitral valve during diastolic filling of the LV. The pathological process is caused by leaflet and/or chordal thickening and calcification, commissural fusion or shortening, chordal fusion or a combination of these processes (Jamieson et al. 2004). Rheumatic fever, which is the predominant aetiology of MS, has greatly decreased in industrialized countries. Nevertheless, MS still results in significant morbidity and mortality worldwide (Nkomo et al. 2006, Levine et al. 2015). Other rare causes are congenital deformities, which often present very early in infancy or childhood such as parachute mitral valve, double orifice

mitral valve, supramitral ring, infiltrating diseases like mucopolysaccharidosis, systemic diseases like Fabry's disease, systemic lupus erythematosus and rheumatoid arthritis, valve stenosis after mitral valve repair and disorders associated with abnormal serotonin metabolism as seen in carcinoid and methysergide treatment (Chandrashekhar et al. 2009).

Patients usually present with dyspnoea, often during exercise or in combination with disorders that increase heart rate. Other rare symptoms include haemoptysis, chest pain (often due to pulmonary hypertension), and pressure effects on adjacent structures, for example from a dilated left atrium. Atypical presentations include fatigue (spontaneous or with diuresis) with a low transmitral gradient and a syndrome of right heart failure with severe pulmonary arterial hypertension (Chandrashekhar et al. 2009).

Patients with isolated mitral annular calcification are typically asymptomatic for many years, but then develop symptoms of dyspnoea and exercise intolerance, similar to rheumatic mitral stenosis. Mitral stenosis due to mitral annular calcification becomes haemodynamically substantial when the calcification extends beyond the annulus and into the mitral leaflets, resulting in restricted leaflet motion (Nishimura et al. 2016).

*Echocardiographic Considerations*

Echocardiography is used to diagnose and judge stage of disease, assess concomitant mitral regurgitation, exclude conditions that mimic mitral stenosis. Both valve area and gradient can be accurately measured, but several measurements with more than one method are often needed to accurately estimate haemodynamics of the mitral valve. The area of the mitral valve orifice (MVA) can be estimated using the pressure half time (PHT), i.e. the time needed for the peak transvalvular pressure gradient to fall to its half value, in milliseconds. Once the pressure half time is known, the area of the mitral orifice can be calculated using an empirical formula (MVA = 220/PHT). The most reliable method to calculate valve area is planimetry with 2D echocardiography cross-section images, and even more reliability might be achieved with 3D echocardiography (Chandrashekhar et al. 2009, Lancellotti et al. 2013).

### 1.2.2 Aortic Valve Disease

#### 1.2.2.1 Aortic Regurgitation

Aortic regurgitation (AR) is caused by either intrinsic disease of the aortic cusps or from diseases affecting the ascending aorta. Intrinsic valvular problems include rheumatic, calcific, myxomatous disease, endocarditis, traumatic injury, and congenital abnormalities. Conditions affecting the ascending aorta that lead to aortic regurgitation include annular dilation and aortic dissection (secondary to blunt trauma or hypertension), mycotic aneurysm, cystic media necrosis, connective tissue disorders (Marfan's syndrome), and chronic hypertension. Aortic regurgitation (AR) is characterized by diastolic reflux of blood from the aorta into the left ventricle (LV) due to malcoaptation of the aortic cusps. This can be due to abnormalities of the aortic leaflets, their supporting structures (aortic root and annulus), or both (Bonow et al. 2016, Bekeredjian et al. 2005).

Chronic severe AR imposes a combined volume and pressure overload on the LV. The volume overload is a consequence of the regurgitant volume itself and is therefore directly related to the severity of the leak. The pressure overload results from systolic hypertension, which occurs as a result of increased total aortic stroke volume, because both the regurgitant volume and the forward stroke volume are ejected into the aorta during systole. Systolic hypertension can contribute to a cycle of progressive dilation of the aortic root and subsequent worsening of AR (Bekeredjian et al. 2005; Bonow et al. 2016). Among asymptomatic patients who have severe AR and normal LVEF at rest, progression to subnormal LVEF, overt heart failure (HF), or death occurs at a rate of 4.0% to 6.0% per year (Supino et al. 2006).

*Echocardiographic Considerations*

Transthoracic echocardiography provides useful information in patients with aortic regurgitation such as information about the cusp pathology, commissure variations and root morphology. Colour doppler is useful for localizing the site of regurgitation. Continuous wave doppler is used to determine the severity of AR by measuring the deceleration slope of the regurgitant jet by calculating the pressure half -time (PHT). It is the time required for the peak regurgitant pressure to decrease to half of its maximum value and is measured in milliseconds. The velocity of the regurgitant jet declines more rapidly in patients with severe AR because the larger regurgitant orifice allows a more rapid equilibration of the aortic and left ventricular pressures. Regurgitant volume and regurgitant fraction can also be used to evaluate the severity of AR. Regurgitant volume is the difference between the systolic flow across the aortic valve and "net forward" cardiac output. In the absence of

intracardiac shunts and mitral regurgitation, flow through the pulmonary artery or mitral valve is equivalent to net cardiac output (Lancellotti et al. 2013).

#### 1.2.2.2 Aortic Stenosis

The causes of Aortic Stenosis (AS) may be classified as calcific, congenital and rheumatic. The normal aortic valve consists of several layers of fibroblast-rich tissue, containing both collagen and elastin fibres, covered by a monolayer of endothelial cells. Calcific aortic stenosis is mainly caused by solid calcium deposits within the valve cusps and less by fusion of the commissures. Congenital aortic stenosis generally presents early. Children with AS either die in childhood or develop such severe symptoms which warrant aortic valve replacement. Rheumatic aortic valve stenosis is rarely seen in developed countries. Rheumatic aortic stenosis differs from calcific aortic stenosis in that it presents with commissural fusion (Rajamannan et al. 2007, Carabello et al. 2009, Zakkar et al. 2016).

The symptom triad of angina, syncope, and dyspnoea represents a late-stage consequence of chronic progressive left ventricular overload caused by worsening aortic stenosis, which usually has developed over several decades. Aortic stenosis is usually detected initially by auscultation that indicates the typical crescendo-decrescendo systolic ejection murmur radiating to the neck. In mild disease, the murmur peaks early in systole, S2 is physiologically split, and carotid upstrokes are normal (Carabello et al. 2009, Bonow et al. 2016).

Compensatory changes to maintain cardiac output, including increases in left ventricular wall thickness and contractility, are ultimately overwhelmed, resulting in the typical pathobiology of severely decreased diastolic compliance, sub endocardial ischaemia, exhausted myocardial contractile reserve followed by irreversible myocardial fibrosis, and baroreceptor-activated vasodilation. These changes contribute to further reductions in cardiac output and pulmonary congestion (Bonow et al. 2016).

The average survival after onset of symptoms is 3 years. Symptomatic patients with severe aortic stenosis who have not had aortic valve replacement have a mortality of 36–52%, 52–80% and 80–90% at 3, 5 and 10 years, respectively, following symptom onset (Rajamannan et al. 2007).

*Echocardiographic Considerations*

Echocardiography allows assessment of valve anatomy, leaflet motion, aortic valve area, and ventricular dimensions and function. Cardiac catherisation is no longer recommended for evaluation

of aortic stenosis. Doppler studies permit estimation of velocity and pressure gradients across the valve as well as calculating valve area. The velocity of blood across the stenotic aortic valve is directly related to the pressure difference between the left ventricle and aorta, and although the measurement is prone to error, maximum aortic jet velocity alone has been shown in several studies to be highly predictive of clinical outcome. The Continuity equation can also be used to calculate the aortic valve area based on the assumption that the stroke volumes proximal to and in the stenotic orifice are equal. 2-D planimetry can also be used to measure the aortic valve orifice. In some patients with preserved stroke volume index and severe aortic stenosis can present with low flow, low gradient aortic stenosis (LF/LGAS). This occurs in approximately 35.0 % of patients with severe AS. These patients have lower peak transaortic velocities and lower mean gradients compared with patients who have normal transaortic flow rates, despite having similar aortic valve area, similar dimensionless index, and similar LVEF. These features predispose to a clinical underestimation of the severity of AS in these patients (Stout et al. 2003, Awtry et al. 2011, Baumgartner et al. 2009, Nishimura et al. 2014).

### 1.2.3 Tricuspid Valve Disease

#### 1.2.3.1 Tricuspid Regurgitation

The function of the tricuspid valve is dependent of the interaction of the tricuspid annulus, leaflets papillary muscles, chordae, the function and morphology of the right heart. Any congenital or acquired abnormality affecting one of these structures leads to Tricuspid regurgitation (TR). Tricuspid regurgitation may be classified as primary and secondary. Primary Tricuspid regurgitation stems from abnormalities of the tricuspid valve apparatus, while secondary tricuspid regurgitation may result from annular dilation, pulmonary hypertension, and/or leaflet tethering in the setting of right- or left-sided heart disease. Tricuspid regurgitation occurs in 65-85% of the population, and approximately 8–10% of all TR is primary. A majority of tricuspid regurgitation diagnosed is usually functional and most often related to tricuspid annular dilatation and leaflet tethering due to right ventricular remodelling caused by pressure or volume overload (or both), myocardial infarction, or trauma (Arsalan et al. 2015, Rodés-cabau et al. 2016).

In cases of secondary TR, three phases maybe observed. In the first stage annular dilatation presents secondary to right ventricular (RV) enlargement. This leads to phase two where the annular dilation leads to lack of leaflet coaptation. With further progression of the disease, there is advanced RV dilatation and dysfunction. In advanced stages of TR, a progressive appearance of venous dilation,

with signs of right-sided heart failure, such as congestive liver failure, ascites, gut congestion with symptoms of dyspepsia or feeling of abdominal fullness and fluid retention with peripheral edema is seen. A decrease in cardiac output is responsible for an increase in exertional dyspnea and decreased functional capacity. (Huttin et al. 2016, Pozzoli et al. 2016)

In elderly patients, atrial fibrillation and disorders of right ventricle compliance can result in new onset of tricuspid regurgitation and often restoration of normal sinus rhythm may lead to marked reduction of tricuspid regurgitation. Cases of severe tricuspid regurgitation need to be surgically corrected in the setting of left sided valve disease. When it is left untreated, it is subsequently associated with adverse right ventricular remodeling and poor clinical outcomes (Pinney 2012, Rodés-cabau et al. 2016).

*Echocardiographic Considerations*

Transthoracic echocardiography is used to initially detect tricuspid regurgitation. However this can often prove challenging due to the unfavourable retrosternal position of the tricuspid valve, the high anatomical variability and difficulty in simultaneously visualizing all three leaflets. The method most often used to quantify the severity of the tricuspid regurgitation is usually visualisation of the colour flow jet. However once evidence of TR is established, transoesophageal echocardiography maybe used to establish a concrete diagnosis and provide detailed information on the Tricuspid valve and its sub-valvular apparatus. The method most often used to quantify the severity of the tricuspid regurgitation is usually visualisation of the colour flow jet (Huttin et al. 2016, Dreyfus et al. 2015).

### 1.2.3.2 Tricuspid Stenosis

Tricuspid Stenosis is a rare clinical entity and most often seen in conjunction with mitral stenosis in regions where rheumatic heart disease is predominant. Other causes of tricuspid stenosis include carcinoid syndrome, rare congenital malformations, valvular or pacemaker endocarditis and pacemaker induced adhesions, lupus valvulitis, and mechanical obstruction by benign or malignant tumors. Xenograft or mechanical prosthetic valve dysfunction, including thrombosis, can also result in obstruction.

*Echocardiographic Considerations*

The gold standard to diagnose tricuspid stenosis is an increase in transvalvular velocity recorded by continuous wave Doppler echocardiography. Tricuspid valve balloon valvuloplasty has limited

efficacy. Fibrinolytic therapy for prosthetic tricuspid valve thrombosis is usually regarded as first-line therapy (Baumgartner et al. 2009, Rodés-cabau et al. 2016).

### 1.2.4 Multivalvular Disease

Multivalvular disease (MVD) is the combination of stenotic or regurgitant lesions, or both, on two or more cardiac valves. Diagnosis of MVD is difficult because the hemodynamic interactions of one valvular pathology with another, which may alter the echocardiographic parameters that currently have been validated only in patients presenting with single valve disease (Unger et al. 2016, Unger et al. 2011).

There are several factors which impact the clinical presentation which include the valves involved, the severity of each lesion, chronicity of the valvular lesion and level of ventricular compliance. Due to interaction of one valve lesion with the other, treating one valve lesion may alter the severity of the other. Echocardiography can be used to quantify the severity of the stenotic or regurgitant valvular lesion and evaluation of valve anatomy and function. The quantification of stenotic lesions can be challenging by frequent occurrence of low-flow states with resulting 'pseudo normal' low gradients or 'pseudo severe' valve stenosis. Additionally haemodynamic interactions between the valve lesions which include changes in stroke volume and intracardiac pressure also affect the accuracy of data obtained (Unger et al.2016, Unger et al. 2011).

As many as 61-90% of patients suffering from aortic stenosis have a concomitant mitral regurgitation, with moderate or severe mitral regurgitation being found in 13-74% of patients. Aortic stenosis leads to an increased afterload, which then leads to hypertrophic left ventricle remodelling along with left ventricular dilatation and systolic dysfunction. This often leads to a secondary mitral regurgitation due to dilatation of the mitral annulus and decreased coaptation of the mitral leaflets. This is often more pronounced in elderly patients who also suffer from advanced coronary artery disease, which also contributes to the development of a functional mitral regurgitation. A severe stenosis of the aortic valve can also result in a more severe mitral regurgitation due to an increase in the pressure gradient between the left ventricle and left atrium ,thereby increasing the regurgitant volume for any given regurgitant orifice. On the other hand, the presence of mitral regurgitation can also affect the presentation of aortic stenosis by resulting in a 'low-flow, low-gradient' state by decreasing the net forward stroke volume and thereby a lower transaortic pressure gradient (Galli et al. 2014, Unger et al. 2016).

A combination of a stenotic aortic and mitral valve is rarely seen for two reasons, first due to the decline of rheumatic heart disease over the years and secondly due to the fact that the co-existence of two stenosed left sided heart valves leads to an intolerable hemodynamic situation which warrants immediate treatment. The clinical findings are often those caused by the so called 'upstream lesion', which in this case would be the stenotic aortic valve, however the more proximal lesion (i.e. the mitral stenosis) can also cause symptoms such as haemoptysis, pulmonary oedema and peripheral embolization. In cases of severe aortic and mitral stenosis, there is a great reduction in the net forward cardiac output, thereby decreasing the flow velocities and pressure gradients across both valves, which can lead to underestimation of the severity of both the stenotic lesions. In elderly patients mitral stenosis may be degenerative in nature, caused by progressive mitral annular calcification involving the base of the leaflets. Due to advancements in healthcare fewer rheumatic cases have been reported and the number of cases of degenerative valve disease are on the rise. Rheumatic mitral Stenosis (MS) is usually associated with 'diastolic doming' and symmetric fusion of the commissures. On the other hand degenerative MS results from progressive annular calcifications which starts at the base of the leaflets, which then leads to a gradual decrease in the functional valvular orifice, without commissural fusion. When the AS and MS are equally severe, the most common clinical presentation involves hemoptysis and pulmonary edema. Underestimation of the severity of the degree of AS in these cases, can cause acute left ventricular failure and 'flash' pulmonary edema, when the protective mitral stenosis is treated (Unger et al. 2016, Unger et al. 2010, Unger et al. 2011).

Concomitant aortic and mitral regurgitation leads to a severe volume overload. When there is a dominant aortic regurgitation systolic hypertension and eccentric left ventricular wall hypertrophy may be seen. Premature mitral valve closure limits the regurgitant flow in severe acute aortic regurgitation, which is however not present in cases of chronic aortic regurgitation. This leads to severe left ventricular dysfunction. On the other hand mitral stenosis combined with aortic regurgitation produces opposite left ventricular loading conditions, which means that the LV end-diastolic and end-systolic volumes are lower than when the lesions were to occur by themselves. This impacts the clinical picture by reducing the severity of the aortic regurgitation and may lead to underestimation of the severity of the two pathologies (Gaasch et al. 2008, Galli et al. 2014, Unger et al. 2016).

Tricuspid valve lesions are rarely primary in nature and mainly occur in conjunction with left sided valve lesions, which dominate the clinical picture. The development of tricuspid regurgitation in the setting of left sided valve disease leads to further right ventricular dilatation and dysfunction, more

tricuspid annular dilatation, and further loss of coaptation and thus a more severe tricuspid regurgitation. There are several studies which show that correction of just left sided valve disease isn't sufficient treatment for tricuspid regurgitation and that concomitant tricuspid annuloplasty is associated with improved outcomes (Jeong et al. 2014, Mascherbauer et al. 2010, Dreyfus et al. 2015).

## 1.3 Surgical Techniques

Cardiac surgery is highly complex and carries with it a high risk of complications and mortality. This is especially true for valvular heart surgery, which requires careful preparation and high level of specialisation. Intraoperative transoesophageal echocardiography (TEE) also plays an important role in the success of valvular heart surgery. Median sternotomy is the most common method of approach to the heart, as it provides good exposure of the aorta and allows de-airing and defibrillation with ease. With advances in minimally invasive cardiac surgery (MICS), other approaches have been developed which include partial sternotomy (parasternal or transternal incision), mini-thoracotomy, video assisted using port-access technology and robotically assisted (Iribarne et al. 2011, Wheatley et al. 2005).

Cardiopulmonary bypass (CPB) is established before any manipulations on the heart to avoid cardiovascular instability and the risk of dislodging atrial thrombi. Routine cardiopulmonary bypass is established with aortic cannulation and single or bicaval venous cannulation. When bicaval is required, the cephalad cannula is placed through the right atrial appendage and directed into the superior vena cava. Blood is gravity drained from the heart and lungs in polyvinyl chloride tubing to a reservoir and then oxygenated using a gas-exchanger and then returned to the arterial system. This ensures a clear, blood less and motionless surgical field. Cardiopulmonary bypass is established with moderate hypothermia (32° C) and is followed by cross clamping the ascending aorta above the coronary ostia and proximal to the aortic cannula, thus isolating the coronary circulation and preventing blood entering the heart (Wheatley et al. 2005, Machin et al. 2006).

This is followed by administering cardioplegia by an anterograde approach via the aortic root or direct coronary ostium access. Cardioplegia can be defined as a technique involving single multiple infusions into the aortic root or into the coronary vasculature of a hypo- or normothermic solution designed to arrest the heart and also to protect the myocardium during aortic cross-clamping with global ischemia. It can be administered as a cold crystalloid cardioplegia, cold blood cardioplegia or warm blood cardioplegia. Using blood as the delivery vehicle to administer cardioplegia has significant advantages which include prevention of osmotic swelling, improved capillary distribution and maintenance of an optimal pH. Due to its high potassium concentration the cardioplegia causes a reduction in the myocardial membrane potential, leading to inactivation of sodium channels. This results in the suppression of the myocardial action potentials and finally in diastolic arrest (Machin et al. 2006).

The reperfusion phase follows the valvular intervention. During the reperfusion phase, the hibernating myocardial cells are brought back to their previous working condition. In this phase it is of utmost importance to rapidly convert ventricular fibrillation and to eliminate residual air in the heart chambers and coronary arteries. Once de-airing is complete and echocardiographic imaging shows optimal valvular function the aortic cross-clamp is released and the patient is weaned from the cardiopulmonary bypass. This is then followed by haemostasis and closure of the chest wall.

In general there are two types of procedures which may be performed i.e. valve repair and valve replacement. In cases of valve replacement a valve prosthesis is used. These prostheses may be mechanical or biological. Previous designs of mechanical valves prostheses include, caged ball valves and monoleaflet valves. Today, most mechanical heart valves are bileaflet valves. They are made of two semilunar disks attached to a rigid valve ring by small hinges. Biological valves may be sub-classified as stented, stentless and percutaneous bioprostheses. Stented porcine bioprosthetic valves consist of 3 porcine aortic valve leaflets cross-linked with glutaraldehyde and mounted on a supporting stent. Pericardial valves are fabricated from sheets of bovine pericardium mounted inside or outside a supporting stent. Stentless bioprostheses are created using complete porcine aortic valves or fabricated from bovine pericardium. Percutaneous valves are used in special procedures such as transcathether aortic valve implantation (TAVI). The choice of a mechanical valve has its advantages and disadvantages. Mechanical valves are durable, with minimal loss of structural integrity over time. The negative attributes are due to the higher risk of valvular thrombosis and thromboembolism associated with the mechanical valves, which in turn necessitates long-term anti-coagulant therapy with the concomitant risk of bleeding. The principle advantage of implantation of a bioprosthesis is related to its lack of thrombogeneity. The low risk of thromboembolism, voids the need for permanent anticoagulation, which consequently results in a lower incidence of hemorrhagic events. The main disadvantage associated with the bioprostheses is their propensity to undergo structural valvular deterioration, which often necessitates re-operation. This is especially pronounced in younger patients (Pibarot et al. 2009).

### 1.3.1 Mitral Valve Surgery

Surgery of the mitral valve can be broadly classified as repair or replacement. Mitral valve repair involves the alteration of the defective valve geometry enabling it to continue performing under normal physiological loads. Whereas mitral valve replacement involves the implantation of a valve prosthesis, which may be biological (bovine or porcine) or mechanical. The choice of procedure

depends upon the cause of the mitral regurgitation, the anatomy of the mitral valve, and the degree of left ventricle dysfunction. The advantages of mitral valve repair over mitral valve replacement include improved long-term survival, a better preservation of left ventricular function, and greater freedom from endocarditis, thromboembolism and anticoagulant-related haemorrhage (Gillinov et al. 2003).

When mitral valve surgery is planned, bicaval cannulation is required to ensure good exposure and drainage. A left atriotomy incision is made starting behind the inter-atrial groove at the junction of the right superior pulmonary vein and the left atrium, which is then extended superiorly toward the left atrial roof and inferiorly in front of the inferior pulmonary vein and behind the inferior vena cava. Other approaches to the mitral valve include the superior approach through the atrial roof, and the transeptal approach. An atrial retractor is then used to secure an optimal view of the mitral valve (Wheatley et al. 2005).

There are several techniques of mitral valve repair. These include quadrangular resection, sliding leaflet repair, chordal replacement, chordal transposition and annuloplasty. Quadrangular resection is used to treat prolapse of the posterior mitral leaflet (PML). In this technique the posterior leaflet with diseased chordae is resected, the annulus is plicated, and an annuloplasty is then performed to complete the repair. The sliding leaflet repair is a variation of the quadrangular resection technique and aims to reduce the height of the posterior leaflet, thereby moving the point of systolic leaflet coaptation posteriorly. This reduces the incidence of left ventricle outflow tract (LVOT) obstruction caused by systolic anterior motion (SAM) of the anterior leaflet of the mitral valve. For prolapse of the anterior mitral leaflet (AML) chordal transfer or chordal replacement techniques can be applied.

Chordal transfer involves the identification of unsupported regions of AML and then suturing it to a part of the PML. Chordal replacement involves the use of Polytetrafluoroethylene (PTFE) sutures and the neochordae are affixed to the fibrous portion of the papillary muscle and then passed through the leaflet one or more times and securely knotted. Ring annuloplasty is performed using a ring measured during surgery to fit the mitral annulus and is used to reduce the annulus diameter in order to bring the leaflets together and reduce orifice area thus preventing regurgitation. The ring size is determined by measuring the inter-trigonal distance, inter-commissural distance and surface of the anterior leaflet during surgery ( Gillinov et al. 2003, Gillinov et al. 2004).

Mitral valve replacement is performed when repair of the mitral valve is not feasible. The native mitral valve is then excised and care is taken not to damage the mitral annulus and papillary muscle. For the implantation of a valve prosthesis, sutures with pledgets are used. Sutures are inserted 3-5

mm apart and the pledgets can be positioned on the atrial or ventricular side. The sutures emerge just below the annulus at the junction of fibrous tissue with myocardium. Care must be taken not to damage the circumflex artery and the aortic valve. After completion of the mitral valve repair or replacement, the left atriotomy is closed with a continuous monofilament suture.

### 1.3.2 Aortic Valve Surgery

The aortic valve can be approached by a complete median sternotomy or by a partial upper sternotomy. After establishing cardiopulmonary bypass a transverse aortotomy is performed and the leaflets are excised. Next the calcified annulus is debrided. After measurement of the diameter of the aortic annulus an appropriate valve prosthesis is selected for implantation. Following this pledgeted horizontal sutures are placed through the native aortic annulus and the sutures are brought through the prosthetic valve ring. Then the valve is seated and the sutures are securely knotted. Recently there has been a rise in the use of sutureless heart valves. These valves are first crimped together and then expanded in situ. When the valve is sewn in place or appropriately positioned, the transverse aortotomy is closed, and aortic cross-clamp is removed, followed by myocardial reperfusion.

Valve sparing operations are considered in cases of functional aortic regurgitation. This normally occurs when there is dilatation of the sinotubular junction and ascending aorta. This is treated with dacron tube prosthesis and results in coaptation of the valve leaflets with no or only trace insufficiency. In some cases additional annuloplasty may also be considered (Ribeiro et al. 2000).

### 1.3.3 Tricuspid Valve Surgery

In most cases, tricuspid valve repair is favoured over replacement, however, for complex lesions, specific surgical repair techniques may be required and replacement maybe superior to repair. Replacement is mostly performed in patients with primary tricuspid regurgitation (Arsalan et al. 2015).

Isolated tricuspid valve surgery has been rarely reported in the literature. Tricuspid valve surgery is generally performed along with left sided valve surgery. After right heart isolation, a standard oblique atriotomy is performed parallel to the AV groove to approach the tricuspid valve. Tricuspid valve surgery can be performed without cross clamping the aorta during the reperfusion time.

The main goal of tricuspid valve repair is the restoration of leaflet coaptation. The well-known De Vega annluplasty involves the plication of the posterior and anterior portion of the annulus,

preserving the septal portion, with a double continuous suture. There have been modifications to the De Vega technique which involve the use to intermittent pledgets. This procedure has been associated with good results, however, it has also been reported that the DeVega annuloplasty or its modifications may render the valve mildly stenotic. Annuloplasty is performed by using pledgeted sutures and ring. It has been shown that suture annuloplasty is inferior to ring annuloplasty.The atriotomy is then closed with a polypropylene suture using a double layer closure (McGee et al. 2008, Antunes et al. 2007, Muraru et al. 2016).

## 1.4 Multiple Valve Surgery

### 1.4.1 Mitral and Tricuspid Valve Surgery

As degenerative valve disorders increase in frequency as the population ages, degenerative mitral regurgitation (MR) has become the most common cause of mitral valve (MV) surgery. However, a consistent number of patients develop significant functional tricuspid regurgitation (TR) following MVrp, and significant TR has been reported as being responsible for an increase in mortality late after MV surgery (Kitai et al. 2016).

Mitral valve dysfunction results in left atrial and pulmonary arterial hypertension, flattening and dilation of the tricuspid annulus, and secondary functional tricuspid regurgitation (TR). Once the normal three-dimensional shape of the tricuspid annulus flattens owing to left-sided pressure and volume overload, tricuspid remodeling may occur over time and lead to progression of TR despite correction of mitral pathology. That has led to a trend of performing tricuspid valve repair even in the setting of none-mild TR when significant tricuspid annular dilation exists (Badhwar et al. 2016, Dreyfus et al. 2015).

Badhwar et al. reviewed 88,473 patients undergoing mitral valve surgery using the STS (Society of Thoracic Surgeons) database and analysed patients who underwent concomitant tricuspid valve surgery. They concluded that the performance of concomitant tricuspid valve repair at the time of mitral operation was associated with an increase in morbidity along with a twofold increase in pacemaker rate, but was not associated with an elevated risk adjusted operative mortality (Badhwar et al. 2016).

A study of 200 patients undergoing reoperative procedures on left sided heart valves with moderate-to-severe tricuspid regurgitation by Gosev et al. compared the outcomes of the cases with tricuspid valve intervention (n= 75) with those without (n=125). Although the group with Tricuspid valve intervention had a higher operative risk, the operative mortality and postoperative rates of right ventricle (RV) dysfunction did not differ between the two groups. However, there were more cases of new RV dysfunction in the group without tricuspid valve intervention (Gosev et al 2015).

The standard surgical technique of tricuspid valve repair for functional TR is tricuspid annuloplasty, which has a favorable effect on mortality in comparison with a suture technique, such as De Vega's or Kay's technique. Gosev et al. also suggest that tricuspid ring annuloplasty yields better results than TV suture repair alone (Gosev et al 2015).

Another study of 645 consecutive patients on the benefit of concomitant tricuspid valve annuloplasty by Chikwe et al. found that tricuspid annuloplasty was independently associated with freedom from late moderate TR and was an independent predictor of recovery of right ventricular function (Chikwe et al. 2015).

A systemic review of the literature by Zhu et al. found 561 articles on the topic of concomitant tricuspid valve surgery in patients undergoing left-sided valve disease. They reviewed 12 selected articles to provide the best clinical evidence to determine if concomitant Tricuspid valve surgery was beneficial. They concluded that although a concomitant tricuspid valve intervention prolongs the duration of the surgery, it can be considered as a low-risk procedure and it did not significantly increase the perioperative mortality and morbidity when left-sided valve disease is corrected simultaneously. They also found no statistically significant increased risks of concomitant TV surgery with regard to major complications such as bleeding, stroke, renal failure, respiratory insufficiency, low cardiac output syndrome, myocardial infarction, neurological deficit, wound infection and pericardial effusion (Zhu et al. 2015).

### 1.4.2. Aortic and Mitral Valve Surgery

Barreiro et al. identified 408 consecutive elderly patients who underwent isolated Aortic valve replacement (AVR), and then classified these patients in to two groups on the basis of the severity of the concomitant mitral regurgitation (MR). Actuarial survival at 1, 5, and 10 years for the group with no MR to mild MR was 93.8%, 73.3%, and 40.1% versus 92.3%, 58.2%, and 14.6% for the group with moderate to severe MR at the time of the AVR. Their follow-up data suggested an improvement in MR in 81.8% of the patients presenting with functional MR. Mitral regurgitation persisted or worsened in 65.4% of patients with degenerative mitral valve disease (Barreiro et al. 2005).

A study by Kilic et al. of 41,417 patients undergoing concomitant MV surgery and AVR included 72.0% MV replacements and 28.0% MV repairs. They reported a 29.0% postoperative morbidity rate in both groups, MV repair versus replacement, concomitant with AVR. They found that after risk adjustment, MV repair was associated with lower odds of in-hospital mortality (Kilic et al. 2015).

Another study by Hamamoto et al. compared the morbidity and mortality of 379 patients after aortic and mitral valve replacement versus aortic valve replacement and concomitant mitral valve repair. A 15 year follow-up showed that survival was similar in both the groups (Double valve replacement

81±3% and the AVR+MVRp 79±7%). However, the freedom from mitral valve reoperation at 15 years was significantly better for the double valve replacement group (54±5%) as compared with the AVR and MVRp group (15±6%). Due to their younger patient cohort (mean age 54.1±9.7 years) they recommended double valve replacement with mechanical valves based on the lower incidence of valve failure and a similar rate of thromboembolic complications as compared with AVR and MVRp (Hamamoto et al. 2003).

A systemic review of literature by Harling et al. found 17 studies and included 3053 patients undergoing aortic valve replacement for aortic stenosis with co-existing mitral regurgitation. They found an improvement in the severity of mitral regurgitation following aortic valve replacement in 55.5% of patients, whereas 37.7% remained unchanged, and 6.8% worsened. Improved long-term survival was seen at 3, 5 and 10 years in absent-mild mitral regurgitation when compared with moderate-severe mitral regurgitation in all groups. Reverse remodeling was demonstrated by a significant reduction in left-ventricular end-diastolic diameter and left-ventricular mass, while no significant change was seen in left-ventricular end-systolic diameter, septal thickness or left atrial volume. They concluded that despite left ventricle remodeling, concomitant moderate-severe mitral regurgitation adversely affected both early and late mortality following aortic valve replacement (Harling et al. 2011).

A meta-analysis by Saurav et al. compared the outcomes of mitral valve repair versus mitral valve replacement in patients undergoing simultaneous aortic valve replacement. They found the early (in hospital and up to 30 days post-surgery) mortality and late (>30 days post-surgery) mortality were significantly lower in patients who underwent mitral valve repair as compared to those undergoing mitral valve replacement. The MV reoperation rate, thromboembolism (including valve thrombosis) and major bleeding rates were found to be comparable between the two groups (Saurav et al. 2015).

Therefore, the mitral valve disease accompanying aortic valve disease should not be left untreated. There is some evidence to suggest that mitral valve repair is superior to mitral valve replacement in the setting of aortic valve disease, but this is still a matter of debate.

### 1.4.3. Aortic, Mitral and Tricuspid Valve Surgery

Simultaneous aortic, mitral and tricuspid valve surgery is a complex procedure which requires exceptional surgical skills. This is often referred to as 'triple valve surgery' in the literature. Some of the factors which make this procedure so complex include advanced nature of the valvular lesions and tendency towards decompensation, prolonged cardiopulmonary bypass and increased myocardial ischemic time.

Minimally invasive cardiac surgery using right antero-lateral thoracotomy or partial upper sternotomy with unilateral J-shaped extension has been performed successfully for double valve surgeries (Pope et al. 2014, Cosgrove et al. 2015) . However, a minimally invasive approach to triple valve surgery has not been used in clinical practice. A report on minimally invasive triple valve surgery performed through a right anterior thoracotomy showed no significant postoperative complications but a very high 30-day mortality rate (50.0%) (Elmahdy et al. 2013). Hence, the standard approach to triple valve disease remains the median sternotomy.

Prosthesis related complications such as endocarditis, thromboembolism, anticoagulation-related hemorrhage, and paravalvular leaks have also been reported to be higher compared with single valve replacement (Shinn et al. 2009, Lio et al. 2014). As reported for isolated mitral or tricuspid valve surgery, repair is often preferred to replacement and has been associated with better outcomes, even in triple valve surgery. A multicenter registry report which included 8,021 patients by Suri et al. emphasized that mitral and tricuspid valve repair in patients undergoing triple valve surgery was associated with better outcomes as compared to mitral and tricuspid valve replacement (Suri et al. 2014).

Lio et al report that the mortality rate for concomitant aortic, mitral and tricuspid valve surgery ranges between 2.5 and 25% and that the long-term survival after triple valve surgery is reduced, with survival rates at 5 and 10 years of 75–82 and 61–75%, respectively (Lio et al. 2014). Peterss et al. reported similar findings in their review of elderly patients undergoing triple valve surgery and reported satisfactory postoperative quality of life (Peterss et al. 2012). Therefore, even though concomitant aortic mitral and tricuspid valve surgery is a complex procedure and associated with relevant risks, the patient's age alone should not be a contraindication for triple valve surgery.

## 1.5 Cardiac Surgery in the Elderly

Life expectancy has increased during recent decades leading to a growing older population, with 16.0% of the western European population being over 65 years of age (Huber et al. 2007). The number of patients older than 70 years requiring cardiac surgery has increased 7-fold and in those older than 80 years 24-fold, respectively, in the past 17 years. In Germany, the average age of cardiac surgical patients increased from 1990 to 2007 from 55.8 years to 68.8 years; the proportion of patients older than 80 being 9.8% (Friedrich et al. 2009).

### 1.5.1 Age Related Changes in the Elderly

Cardiac surgery in the elderly is challenging for several reasons, including advanced atherosclerosis, impaired diastolic heart function, renal insufficiency, reduced lung compliance and respiratory muscle strength. Other noteworthy risk factors for surgery in the elderly include age-related central and peripheral impairment of the nervous system, poor nutritional status, anaemia and altered pharmacokinetics of several drugs (Seco et al. 2014, Friedrich et al. 2009).

Ageing affects the cardiovascular system of the patients. There are relevant changes in the systemic vasculature, heart musculature, heart valves and coronary circulation. With age there is a dilation of the great vessels and thickening of the arterial walls. This is mainly due to changes in the wall matrix and increase in elastolytic and collagenolytic activity and in smooth muscle tone. Such changes result in increased vascular stiffness, systemic vascular resistance and afterload, which may cause myocardial hypertrophy leading to reduced heart function (Nicolini et al. 2014).

The ageing process results in decreased mechanical and contractile efficiency, stiffening of myocardial cells, mural connective tissue and valves, decreased number of myocytes, increased myocyte size, increased rate of myocyte apoptosis, and blunted adrenoceptor-mediated contractile and inotropic response. On an intracellular level, with ageing there is a decrease in regulatory autophagy in the heart muscle. Autophagy provides a cytoprotective role by the removal of toxic protein aggregates, damaged mitochondria and harmful reactive oxygen species (ROS) and intracellular infectious pathogens. Autophagy not only contributes to cell survival but is involved in organismal lifespan. Reduced autophagy results in the build-up of senescent mitochondria in the heart muscle. The senescent mitochondria exhibit reduced ATP production and increased ROS generation. The end result of these processes is the production of pro-inflammatory cytokines. The secretion of the cytokines from cardiomyocytes recruits macrophages and neutrophils and then

amplifies the inflammatory responses which injure the cardiomyocytes. This leads to progression of heart failure in elderly patients (Nicolini et al. 2014, Linton et al. 2015, Nishida et al. 2015).

There are some changes in our basic understanding of the ageing process. Calcific changes of the aortic valve as seen in cases of aortic stenosis were originally considered a degenerative process. However newer evidence suggests that it is an active and complex process involving lipoprotein deposition, chronic inflammation, and osteoblastic transition of valvular interstitial cells resulting in active leaflet calcification. There have also been several investigations on the ultrastructure of the mitral valve, which has changed our understanding of the biomechanics and structure of the mitral valve and its leaflets. The ageing of the mitral valve is no longer deemed a simple wear and tear process. There have been studies that show marked reduction in cellularity, disoriented collagen fibres, and increased elastin fibres with severely reduced mucopolysaccharides in valves of patients aged ≥60 years (Lindman et al. 2016, Levine et al. 2015).

In elderly patients postsurgical stress, both physical and psychological, can lead to an imbalance in autonomic, endocrine, metabolic, and immune functions. Depending on the patient's preoperative physiologic reserve and comorbid conditions, additional clinical challenges may impose further alterations in the stress response and, thus, the recovery process (Kim et al. 2014).

### 1.5.2 Cardiac Surgery in Elderly

There is increasing evidence that older patients benefit from cardiac surgery. Huber et al. report that octogenarians after cardiac surgery, exhibit a better quality of life and a considerable increase in their emotional well-being, as well as an increase in their functional status. Activity and mobility improved in coronary and valve disease with nearly 80.0 % of the patients feeling no or only little limitation in their daily activity (Huber et al. 2010). In their analysis of 84 reoperative cases (72.6% male, mean age 81.9±1.9 years) in octogenarians, Deschka et al. show considerably increased mortality rates (in-hospital mortality 32.1%), but also an excellent functional status and quality of life of the survivors (Deschka et al 2014).

A 5 year prospective study of survival, functional outcome, living arrangements, daily activities and leisure engagements in 300 octogenarians after cardiac surgery by Chaturvedi et al. showed good results. The 30-day survival was 84.3%, the overall 1- and 5-year survival was 76.6% and 57.8%, respectively. At the time of the last follow up, activities within the social and cognitive domains were maintained. Another study of 112 elderly patients (75-89 years) undergoing reoperations reported

the freedom from valve-related mortality and morbidity to be 86%±4% at 5 years and the operative mortality for valve reoperations was 10.7% (Chaturvedi et al. 2010).

However, another study by Johnson et al. of 7726 patients (65.0% male, 6.8% octogenarians) undergoing cardiac surgery over a time range of seven years suggested that age alone influences outcomes after cardiac bypass or valve surgery. They reported that elderly patients had a higher risk for death, longer hospital stay, more neurologic complications, and were more likely to undergo a reoperation due to bleeding complications. The demographics in terms of diabetes mellitus, urgency of the procedure, prior myocardial infarction, time since last myocardial infarction, cerebrovascular history, chronic obstructive pulmonary disease, or pump time did not differ between octogenarians and non-octogenarians (Johnson et al. 2005).

A systemic review of 44 studies of 9236 patients by Abah et al. analysed the existing evidence regarding postoperative quality of life (QoL) of older people following cardiac surgery. They report that QoL following cardiac surgery in octogenarians improves in the majority of patients. However, they also found an apparent decrease in QoL in 8–19% of octogenarians following cardiac surgery (Abah et al. 2015).

A review by Menezes et al. on the usefulness of cardiac rehabilitation in the elderly also provides some valuable insights into this issue. They cited several studies which substantiated the benefits of cardiac rehabilitation on a number of physiologic parameters and clinical factors including exercise capacity, inflammation, glucose control, autonomic function, behavioural characteristics, quality of life, congestive heart disease and mortality after a major cardiovascular event. Their study shows that with cardiac rehabilitation quality of life could be restored in elderly patients (Menezes et al. 2014).

Therefore, it could be suggested that advanced age or the need for reoperation in elderly patients is not a contraindication to conventional surgical intervention. Flawless surgery, meticulous hemostasis, excellent myocardial protection, and perfect anesthesiological management are basic requirements for cardiac surgery in elderly patients.

# 2. Methods

A retrospective review of our institutional database identified 311 patients who underwent multiple valve surgery between January 2011 and May 2016 at our institution. Of these patients 119 were aged 75 years or older. Patients who underwent minimally invasive multiple valve surgery via a right anterolateral thoracotomy and a mini-sternotomy were excluded from this study. Patients who underwent pulmonary valve surgery were also excluded. We then divided the patients into four groups, based on the valves that were operated namely, aortic and mitral valve surgery (AM), mitral and tricuspidal valve surgery (MT), aortic and tricuspidal surgery (AT) and aortic, mitral and tricuspid valve Surgery (AMT).

The study adhered to the ethical guidelines of the 1975 Declaration of Helsinki. Because this was a retrospective chart review of parameters collected as part of routine patient care, our institutional review board waived the need of informed consent for use of the data for scientific purposes.

We calculated the perioperative mortality using the EUROScore II model collecting the data from our institutional database. The EuroSCORE II is an update of the older logistic EuroSCORE and is based on an updated data set and adjusted to take into consideration the modern advancements in cardiac surgery. The following parameters were collected to calculate the EUROScore II (Nashef et al. 2012):

- Age
- Gender
- Renal impairment: Assessed on basis of creatinine clearance (CC) calculated by the Cockcroft–Gault formula and further sub classified as follows:
    - Normal (CC>85 ml/ min)
    - Moderate (50<CC <85 ml/min)
    - Severe (CC<50 ml/min)
    - Dialysis (regardless of CC)
- Extracardiac arteriopathy : If the patients had one or more of the following :
    - Claudication
    - Carotid occlusion or >50% stenosis
    - Amputation for arterial disease
    - Previous or planned intervention on the abdominal aorta, limb arteries or carotids

    - Poor mobility: If patients experienced severe impairment of mobility secondary to musculoskeletal or neurological dysfunction.
- Previous cardiac surgery: If patients had one or more previous major cardiac operation involving opening the pericardium.
- Chronic lung disease.
- Active endocarditis: If patients were still on antibiotic treatment for endocarditis at the time of surgery.
- Critical preoperative state: If patients had any one or more of the following occurring preoperatively in the same hospital admission as the operation:
    - Ventricular tachycardia or fibrillation or aborted sudden death
    - Cardiac massage
    - Ventilation before arrival in the anaesthetic room
    - Inotropes
    - Intra-aortic balloon counterpulsation or ventricular-assist device before arrival in the anaesthetic room
    - Acute renal failure (anuria or oliguria <10 ml/h).
- Insulin dependent diabetes.
- NYHA Class: New York Heart Association (NYHA) classification of dyspnoe:
    - I: no symptoms on moderate exertion
    - II: symptoms on moderate exertion
    - III: symptoms on light exertion
    - IV: symptoms at rest
- Stable angina: If the patients could be classified as having Canadian cardiovascular Society (CCS) class 4 angina (inability to perform any activity without angina or angina at rest)
- Left ventricular function (LVEF): LVEF acquired from echocardiography, further classified as:
    - good (LVEF 51% or more)
    - moderate (LVEF 31 –50%)
    - poor (LVEF 21–30%)
    - very poor (LVEF 20% or less)
- Recent myocardial infarction: If patients had a myocardial infarction within 90 days before operation.

- Pulmonary hypertension: Systolic pulmonary artery pressure (SPAP) acquired by echocardiography, further sub classified as :
    - Moderate: Systolic pulmonary artery pressure (31-55 mm Hg)
    - Severe: Systolic pulmonary artery pressure (>55mm Hg)
- Urgency of operation: Classified as follows:
    - Elective: routine admission for operation
    - Urgent: patients not electively admitted for operation but who require surgery on the current admission for medical reasons and cannot be discharged without a definitive procedure
    - Emergency: operation before the beginning of the next working day after decision to operate
    - Salvage: patients requiring cardiopulmonary resuscitation (external cardiac massage) en route to the operating theatre or before induction of anaesthesia.
- Weight of the intervention: This implies the extent or size of the intervention with the baseline being isolated Coronary Artery Bypass Grafting procedure (CABG), more complex procedures are associated with more risk and classified in three categories:
    - Isolated non-CABG major procedure (e.g. single valve procedure, replacement of ascending aorta, correction of septal defect, etc.)
    - Two major procedures (e.g. CABG +AVR), or CABG + mitral valve repair (MVRp), or AVR+replacement of ascending aorta, or CABG+MAZE procedure, or AVR+MVR, etc.);
    - Three major procedures or more (e.g. AVR+MVR+CABG, or MVR+CABG+tricuspid annuloplasty, etc.), or aortic root replacement when it includes AVR or repair and coronary re-implantation and root and ascending replacement.
- Surgery on the thoracic aorta

Echocardiography was performed routinely by qualified personnel, preoperative echocardiographic data was collected and the grade of the valvular pathology was graded from I to IV. Left ventricular ejection fraction was calculated according to Simpson's biplanar method.

We searched our two institutional databases THGQIMS and ICUData by IMESO® – GmbH to collect the data. An in depth analysis of the intensive care history of the patients revealed the postoperative complications. The data was analysed using the IBM Statistical Package for the Social

Sciences (SPSS) version 20. Data were expressed as percentages and means ± standard deviation (SD).

All surgical procedures have been performed through a full median sternotomy with cardiopulmonary bypass and single aortic cross-clamp technique. Biological and/or mechanical prostheses were implanted with standard techniques. The choice of valve prosthesis was made according to the most recent guidelines on valve surgery, age of the patients, associated comorbidities, and surgeon and/or patient preferences. Valve repair, if possible, was preferred over replacement.

We also retrospectively collected the data of our routine follow up and were able to determine the 30 day mortality.

# 3. Results

From January 2011 to May 2016, we operated 311 patients with more than one diseased heart valve, of whom 119 patients (38.3%) were older than 75 years. 55.0% of these patients were males.

The mean EUROScore II estimated the operative mortality to be 17.3±15.1% in the AM group, 13.3±5.0% in the AT group, 16.8±14.3% in the MT Group and 15.7±18.2% in the AMT group. The highest EUROScore II in the whole group was 72.6% and the lowest was 2.0%.

| | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) |
|---|---|---|---|---|
| Mean age (years) | 78.7±3.1 | 77.4±2.9 | 77.5±2.2 | 79.0±2.6 |
| Median age (years) | 78 | 77 | 78 | 79 |
| Male (%) | 54.5 | 80.0 | 44.4 | 69.2 |
| Euro Score II (%) | 17.3±15.1 | 13.3±5.0 | 16.8±14.3 | 15.7±18.2 |
| Max | 72.1 | 20.1 | 60.5 | 72.6 |
| Min | 3.3 | 8.3 | 2.0 | 2.5 |
| Endocarditis (%) | 4 (9.3) | 0 | 4 (8.9) | 2 (7.7) |
| | | | | |

Table 1: Patient details

Analysis of the concomitant risk factors showed a high percentage of patients suffering from arterial hypertension (83.2%, n=99), diabetes mellitus type II (35.3%, n=42), chronic renal failure (40.7%, n=58) and atrial fibrillation (62.2%, n=74). Patients with atrial fibrillation were further sub-classified into chronic (43.7%, n=52) and paroxsysmal (18.5%, n=22) atrial fibrillation groups. Other concomitant diseases included hyperlipidemia (35.3%, n=42), hypothyroidism (10.9%, n=13), hyperthyroidism (7.6, n=9) and hyperuricemia (11.8%, n=14). A total of 18.5% (n=22) of the population suffered from chronic obstructive pulmonary disease (COPD).

| | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) |
|---|---|---|---|---|
| Arterial Hypertension (%) | 39 (90.7) | 5 (100.0) | 36 (80.0) | 19 (73.1) |
| Diabetes Mellitus (%) | 20 (46.5) | 0 (0.0) | 18 (40.0) | 4 (15.4) |
| NIDDM (%) | 8 (18.6) | 0 (0.0) | 8 (17.8) | 3 (11.5) |
| IDDM (%) | 12 (27.9) | 0 (0.0) | 10 (22.2) | 1 (3.8) |
| Chronic Renal Failure (%) | 25 (58.1) | 2 (40.0) | 23 (51.1) | 8 (30.8) |
| Hyerlipidemia (%) | 19 (44.2) | 2 (40.0) | 12 (26.7) | 9 (34.6) |
| Hypothyroidism (%) | 5 (11.6) | 1 (20.0) | 7 (15.6) | 0 (0.0) |
| Hyperthyroidism (%) | 1 (2.3) | 1 (20.0) | 6 (13.3) | 1 (3.8) |
| Hyperuricemia (%) | 6 (14.0) | 1 (20.0) | 4 (8.9) | 3 (11.5) |
| COPD (%) | 5 (11.6) | 0 (0.0) | 12 (26.7) | 5 (19.2) |
| | | | | |
| Atrial Fibrillation (%) | 19 (44.2) | 4 (80.0) | 32 (71.1) | 19 (73.0) |
| Chronic (%) | 11 (25.6) | 4 (80.0) | 21 (46.7) | 16 (61.5) |
| Paroxsysmal (%) | 8 (18.6) | 0 (0.0) | 11 (24.4) | 3 (11.5) |
| | | | | |
| Coronary Artery Disease (%) | 28 (65.1) | 4 (80.0) | 18 (40.0) | 12 (46.1) |
| Single Vessel Disease (%) | 5 (11.6) | 2 (40.0) | 2 (4.4) | 2 (7.7) |
| Double Vessel Disease (%) | 10 (23.2) | 2 (40.0) | 3 (6.7) | 1 (3.8) |
| Triple Vessel Disease (%) | 13 (30.2) | 0 (0.0) | 13 (28.9) | 9 (34.6) |
| | | | | |

Table 2: Concomitant diseases: NIDDM: non-insulin-dependent diabetes mellitus, IDDM: insulin-dependent diabetes mellitus, COPD: chronic obstructive pulmonary disease

Echocardiographic analysis revealed varying lesions and their severity. In our cohort we found aortic stenosis (Total- 43.7%, Grade I˚- 1.9%, Grade II˚- 3.8%, Grade III˚- 82.7%, Grade IV˚- 11.5%), aortic regurgitation (Total- 26.1%, Grade I˚- 12.9%, Grade II˚- 35.5%, Grade III˚- 41.2%, Grade IV˚- 9.7%), mitral regurgitation (Total- 89.9%, Grade I˚- 0.9%, Grade II˚- 15.0%, Grade III˚- 68.2%, Grade IV˚- 15.9% ), tricuspid regurgitation (Total- 67.2%, Grade I˚- 6.25%, Grade II˚- 47.5%, Grade III˚- 36.3%, Grade IV˚- 10.0%). Mitral stenosis was a rare finding occurring in only 5.9% of cases.

Endocarditis was found the main indication for surgery in 8.4% of cases (AM-9.3%, MT-8.9%, AMT-7.7%). The mean left ventricular ejection fraction (LVEF) was 47.0±11.7. Further analysis revealed that 18.3% of the patients had an LVEF between 10-30%, 45.8% of the patients had an LVEF between 30-50% and 35.8% had an LVEF more than 55%. Pulmonary hypertension was found in 28.3% of the patients.

A total of 76.5% of the patients were operated electively, 72.1% in the AM group, 73.3% in the MT group and 84.6% in the AMT group, while all patients undergoing aortic and tricuspid valve surgery were operated electively. In 18.5% of the cases the operation was urgent and 5.0% of the cases were considered to be emergency procedures. Among these surgeries 9.2% of the cases were redo-procedures.

The prevalence of coronary artery disease (CAD) was also evaluated (52.1%, n=62). Among these patients, triple vessel disease was found in 29.4% (n=35) of the patients. Double vessel disease was found in 13.4% (n=16) and single vessel disease 9.2% (n=11) of our patient cohort. Coronary artery bypass grafting (CABG) was performed all of these cases in addition to valve surgery.

The aortic valve was in the majority of cases replaced while aortic valve repair was performed on one patient. Biological prostheses were implanted in the most cases. The tricuspid valve was almost exclusively reconstructed (94.7%, n=72). There were 4 cases in the mitral and tricuspid valve group where the tricuspid valve was replaced with a biological valve. The mitral valve was reconstructed and replaced in almost equal proportions. Mitral valve reconstruction was performed in 53.9% of the patient cohort. Biological mitral valve prostheses were in 70.0% (n=35) of the mitral valve replacements, whereas mechanical valves were implanted in 30.0% (n=15) of the cases.

| | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) |
|---|---|---|---|---|
| Aortic valve replacement (%) | 42 (97.7) | 5 (100.0) | - | 26 (100.0) |
| Aortic valve repair (%) | 1 (2.3) | 0 (0.0) | - | 0 (0.0) |
| Mitral valve replacement (%) | 18 (41.9) | - | 19 (42.2) | 13 (50.0) |
| Mitral valve repair (%) | 25 (58.1) | - | 26 (57.8) | 13 (50.0) |
| Tricuspid valve repair (%) | - | 5 (100.0) | 41 (91.1) | 26 (100.0) |
| Tricuspid valve replacement (%) | - | 0 (0.0) | 4 (8.9) | 0 (0.0) |
| | | | | |

Table 3: Individual procedures in the sub groups

| | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) |
|---|---|---|---|---|
| Biological aortic valve (%) | 35 (81.4) | 5 (100.0) | - | 24 (92.3) |
| Mechanical aortic valve (%) | 7 (16.3) | 0 (0.0) | - | 2 (7.7) |
| Biological mitral valve (%) | 11 (25.6) | - | 13 (28.9) | 11 (42.3) |
| Mechanical mitral valve (%) | 7 (16.3) | - | 6 (13.3) | 2 (7.7) |
| Biological tricuspid valve (%) | - | 0 (0.0) | 4 (8.9) | 0 (0.0) |
| Mechanical tricuspid valve (%) | - | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | | | | |

Table 4: Type of valve prosthesis implanted

| | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) |
|---|---|---|---|---|
| No concomitant procedure (%) | 16 (37.2) | 2 (40.0) | 30 (66.7) | 14 (53.8) |
| CABG (%) | 26 (60.4) | 2 (40.0) | 15 (33.3) | 10 (38.5) |
| Ao. asc (%) | 1 (2.3) | 1 (20.0) | 0 (0.0) | 1 (3.8) |
| CABG and Ao. asc (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (3.8) |
| | | | | |

Table 5: Concomitant procedures; CABG- Coronary Artery Bypass Graft, Ao. asc- concomitant replacement of the ascending aorta, CABG and Ao. asc- concomitant replacement of the ascending aorta and CABG procedure.

The mean operation time was 288.5±86.2 min in the AM group, 285.0±53.9 min in the AT group, 279.6±100.1 min in the MT group and 346.4±130.7 min in the AMT group. The mean cardiopulmonary Bypass (CPB) time was 181.3±60.6 min in the AM group, 169.8±21.7 min in the AT group, 178.4±77.8 min in the MT group and 234.2±91.8 min in the AMT group. The mean cross-clamp time was 129.1±42.9 min in the AM group, 100.8±31.4 mins in the AT group, 103.0±38.1 min in the MT group and 150.2±42.4 min in the AMT group.

The postoperative main postoperative complications were re-sternotomy (16.0%, n=19), postoperative ischemic stroke (6.7%, n=8), prolonged mechanical ventilation and tracheotomy (10.1%, n=12), acute kidney injury (15.1%, n=18), nosocomial pneumonia (15.1%, n=18) and heparin induced thrombocytopenia type II (9.2%, n=11).

| Complication | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) | Total (n=119) |
|---|---|---|---|---|---|
| Re-sternotomy (%) | 6 (13.9) | 0 (0.0) | 9 (20.0) | 4 (15.4) | 19 (15.9) |
| Adverse neurological events (%) | 2 (4.7) | 0 (0.0) | 4(8.9) | 2 (7.7) | 8 (6.7) |
| Pacemaker implantation (%) | 10 (23.3) | 0 (0.0) | 8 (17.8) | 4 (15.4) | 22 (18.5) |
| Surgical site infections (%) | 4 (9.3) | 0 (0.0) | 5 (11.1) | 1 (3.9) | 10 (8.4) |
| PMV and Tracheotomy (%) | 3 (6.9) | 0 (0.0) | 7 (15.6) | 2 (7.7) | 12 (10.1) |
| Acute kidney injury (%) | 7 (16.3) | 0 (0.0) | 6 (13.3) | 5 (19.2) | 18 (15.1) |
| Pneumonia (%) | 3 (6.9) | 0 (0.0) | 11 (24.4) | 4 (15.4) | 18 (15.1) |
| Heparin induced thrombocytopenia type II (%) | 5 (11.6) | 0 (0.0) | 2 (4.4) | 4 (15.4) | 11 (9.2) |
| | | | | | |

Table 6: Postoperative complications, PMV- prolonged mechanical ventilation.

Postoperative third-degree atrioventricular block resulted in 18.5% of patients and they implanted pacemakers. A MAZE procedure was performed in 17.7% of the patients, of whom 33.3% maintained sinus rhythm at the time of discharge.

The mean intensive care unit (ICU) stay in the AM group was 9.1±10.9 days ranging from 1 to 60 days, in the AT group it was 2.8±2.5 days ranging from 1 to 7 days, in the MT group it was 11.5±19.9 days ranging from 1 to 119 days and in the AMT group it was 9.8±9.6 ranging from 1 to 40 days. The mean mechanical ventilation time in the AM group was 85.5±191.6 hours ranging from 6 to 1128 hours, in the AT group it was 11.0±4.3 hours ranging from 7 to 18 hours, in the MT group

it was 164.0±489.8 hours ranging from 6 to 2856 hours and in the AMT group it was 76.5±189.5 hours ranging from 6 to 960 hours.

The mean total hospital stay in the AM group was 18.4±14.0 days, in the AT group it was 13.0±3.1 days, in the MT group it was 21.9±23.8 days and in the AMT group it was 16.5±8.5 days.

| | OP time (min) | CPB time (min) | CC time (min) | RP time (min) |
|---|---|---|---|---|
| Aortic and mitral valve surgery (n=43) | 288.5±86.2 | 181.3±60.6 | 129.1±42.9 | 42.6±24.8 |
| Aortic and tricuspid valve surgery (n=5) | 285.0±53.9 | 169.8±21.7 | 100.8±31.4 | 42.0±12.0 |
| Mitral and tricuspid valve surgery (n=45) | 279.6±100.1 | 178.4±77.8 | 103.0±38.1 | 48.7±35.3 |
| Aortic mitral and tricuspid valve surgery (n=26) | 346.4±130.7 | 234.2±91.8 | 150.2±42.4 | 70.6±66.7 |
| | | | | |

Table 7: Operative times: OP time- Total duration of surgery, CPB time- Duration of cardiopulmonary bypass, CC time- Duration of aortic cross clamping, RP time- Duration of reperfusion phase.

| | Aortic and mitral valve surgery (n=43) | Aortic and tricuspid valve surgery (n=5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n=26) |
|---|---|---|---|---|
| Total Hospital Stay (days) | 18.4±14.0 | 13.0±3.1 | 21.9±23.8 | 16.5±8.5 |
| ICU Stay (days) | 9.1±10.9 | 2.8±2.5 | 11.5±19.9 | 9.8±9.6 |
| Intubation Time (hrs) | 85.5±191.6 | 11.0±4.30 | 164.0±489.8 | 76.5±189.5 |

Table 8: Total hospital stay, ICU stay and intubation time.

The 30 day mortality was 4.2% with a total in-hospital mortality of 7.6%. The main causes of mortality were sepsis and multi-organ failure (3.4%), cardiogenic shock (2.5%) and low output syndrome (1.7%).

| | 30 Day Mortality (%) | In Hospital Mortality (%) |
|---|---|---|
| Aortic and Mitral Valve Surgery (n=43) | 3 (7.0) | 3 (7.0) |
| Aortic and Tricuspid Valve Surgery (n=5) | 0 (0.0) | 0 (0.0) |
| Mitral and Tricuspid Valve Surgery (n=45) | 1 (2.2) | 5 (11.1) |
| Aortic, Mitral and Tricuspid Valve Surgery (n=26) | 1 (3.9) | 1 (3.9) |
| Total (n=119) | 5 (4.2) | 9 (7.6) |
| | | |

Table 9: Thirty day and In-hospital Mortality

| Cause | Aortic and mitral valve surgery (n= 43) | Aortic and tricuspid valve surgery (n= 5) | Mitral and tricuspid valve surgery (n=45) | Aortic, mitral and tricuspid valve surgery (n= 26) | Total (n =119) |
|---|---|---|---|---|---|
| Sepsis and multi-organ failure % | 1 (2.3) | 0 (0.0) | 2 (4.4) | 1 (3.9) | 4 (3.4) |
| Cardiogenic shock % | 2 (4.7) | 0 (0.0) | 1 (2.2) | 0 (0.0) | 3 (2.5) |
| Low output syndrome % | 0 (0.0) | 0 (0.0) | 2 (4.4) | 0 (0.0) | 2 (1.7) |
| | | | | | |

Table 10: Causes of mortality

# 4. Discussion

Over the years there has been an increase in the number of elderly patients referred for cardiac surgery. Cardiac surgery is associated with an elevated level of risk, especially in multi-morbid elderly patients. This risk is further increased in elderly patients suffering from multiple valve disease. There are several factors influencing surgical success including preoperative physiologic reserve and comorbid conditions, as well as the nature and interactions of the valve lesions (Kim et al. 2014).

Due to lack of quantifiable measures of the varying effect aging has on an individual and in turn the cellular and tissue aging process, we are at present unable to determine a patient's biological age. Therefore chronological age is the only parameter which can be used to characterise the ageing process in a patient (Friedrich et al. 2009). There have been several studies on cardiac surgery in elderly patients. However, among these studies there is a discrepancy on the matter of a fixed age cut-off to define an elderly patient. A review by Wiedemann et al. also addressed this issue and reported that in literature the so called cut-off can range from 65 to 80 years of age. For their review they defined an elderly patient as older than 70 years of age (Wiedemann et al. 2010). There have been several other studies which have presented the outcomes of cardiac surgery in octogenarians (Chaturvedi et al. 2010, Abah et al. 2015, Huber et al. 2007, Deschka et al. 2014). They have reported that cardiac surgery can be performed in these patients and that age is not a contraindication for cardiac surgery. For the purpose of our study a cut off of 75 years has been used. This ensures that the patients in our cohort are correctly placed in the geriatric spectrum.

Preoperative determination of the risks associated with cardiac surgery are of utmost importance. This is often required to ascertain if the risks associated with the surgery outweigh the benefits, this even more important when the patient being operated is of advanced age. The two standard models to determine perioperative risk are the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II and the Society of Thoracic Surgeons Predicted Risk of Mortality (PROM) score. These risk assessment methods have limitations. It has been reported that the EuroSCORE II typically overestimates perioperative risk, whereas the STS score has been reported to underestimate perioperative risk in frail patients (Sepehri et al. 2014, Sündermann et al. 2011).

The first working model of the logistic EuroSCORE was launched in 1999. However the algorithm relied heavily on homogeneity between the study group on which it was designed and the patient cohort undergoing modern era cardiac surgery. Therefore this required new calibration of the

algorithm, which resulted in the EUROScore II. A validation study by Barili et al. demonstrated that it was a good predictor of perioperative mortality (Barili et al. 2013). The Society of Thoracic Surgeons Predicted Risk of Mortality (PROM) score also determines the 30-day mortality, and was developed using the STS database. It calculates the risk of mortality for five different procedures including 1) isolated primary coronary artery bypass grafting (CABG), 2) isolated aortic valve replacement (AVR), 3) isolated mitral valve repair (MVRp) or replacement (MVR), 4) combined CABG and AVR and, 5) CABG and MV Repair or MVR. There are other lesser known risk scores such as the Parsonnet, Cleveland Clinic, French, Pons, and Ontario Province Risk (OPR) scores. Comparing the above mentioned scoring systems, a study by Geissler et al. found that the EuroSCORE algorithm yielded the highest predictive value in their patient population (Geissler et al. 2000).

Although there have been revisions in the available risk predicting algorithms such as the EuroSCORE II and others, these models are still limited in their ability to predict postoperative outcomes because of their reliance on chronological age and medical diagnoses taking into consideration the biological status of an elderly patient.

Clegg et al. describe frailty as a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability (Clegg et al. 2013). The prevalence of frailty in people older than 65 years is high, ranging from 7 to 16·3%. The prevalence increases with age, and is greater in women than in men (Mañas et al. 2015).

Sündermann et al introduced the Comprehensive Assessment of Frailty (CAF) score which takes into consideration age-related factors in addition to clinical and laboratory data to quantify the perioperative risk in elderly people undergoing elective cardiac surgery. The CAF takes into account the “biological age “in addition to conventional scoring items of elderly patients to assess the operative risk prior to elective cardiac surgery. Their results show that it is necessary and possible to use a score containing mainly factors concerning the biological age and frailty of a patient to calculate the perioperative risk. However there is still further scope for improvement to develop an optimal frailty algorithm. This will help to select patients for surgery and improve outcomes in patients at highest risk of adverse sequelae (Sepehri et al. 2014, Sündermann et al. 2011).

Degenerative processes play an important role in the progression of valvular heart disease. Peterss et al. analysed 90 elderly patients who underwent concomitant Aortic, mitral and tricuspid valve surgery. They classified the causes of valvular heart disease in their patient’s as 70.0% degenerative

disease, 19.0% endocarditis and 11.0% rheumatic, with 24.0% undergoing cardiac redo-surgery (Peterss et al. 2012). In our cohort we had 8.4% operations due to endocarditis, and 91.6% of the operations due to degenerative valve disease. There were no cases of rheumatic valve disease and 9.24% of patients undergoing reoperations. It is may also be noted that a part of the degenerative heart valves may be a sequelae of rheumatic heart disease.

In this study we retrospectively calculated the EuroSCORE II to estimate to risk of mortality. The risk of mortality ranged from 2.0% to 72.6% in our cohort. Although the EuroSCORE II does not consider biological age of the patient, we see that there is a great variation in the state of health in elderly patients. Due to the retrospective nature of this study the CAF score or other frailty scores were not calculated preoperatively.

The number of patients with coronary artery disease (CAD) has increased over the last decades. The management of these patients is also complex due to greater severity of coronary lesions and the higher global risk profile. In our cohort we see a large number of patients with coronary artery disease (52.1%) and among them a large number of patients (56.5%) had triple vessel disease. This resulted in concomitant coronary artery bypass graft (CABG) procedure in a large part of the patient cohort. In an analysis of collaborative trials that included over 7,000 patients by Flather et al., age had an influence on the comparative results of CABG versus PCI on mortality. In this analysis, older patients had better outcomes when they underwent CABG compared with PCI, while younger patients tended to have more favourable outcomes with PCI (Flather et al. 2012, Rezende et al. 2016). In our cohort 44.5% (n=53) of all patients underwent concomitant CABG Procedures. Among these patients the total mortality was 4.2% (n=5).

It is well established that mitral valve repair has better results in terms of lower operative mortality, superior quality of life, higher long-term survival, and greater freedom from reoperation as compared to mitral valve replacement in patients with degenerative mitral regurgitation (Nicolini et al. 2014). A meta-analysis by Vassileva et al. on the short-term and long-term survival of patients who underwent mitral valve repair and replacement also reported similar findings. Their analysis suggests a significantly increased likelihood of both short-term mortality (summary odds ratio 2.667 (95% confidence interval (CI) 1.859-3.817)) and long-term mortality (summary hazard ratio 1.352 (95% CI 1.131-1.618)) in patients undergoing mitral valve replacement as compared to those undergoing mitral valve repair (Vassileva et al. 2011). Of greater interest is whether elderly patients profit greater from mitral valve repair or replacement, as the problems of tissue fragility and annular/ valvular calcification are more pronounced in the elderly. Therefore surgeons may tend to perform a

less time consuming mitral valve replacement with a biological valve prosthesis rather than attempting a long and tedious mitral valve repair. A study of 117 consecutive patients undergoing mitral valve surgery older than 75 years by Ailawadi et al. showed that mitral valve replacement in these patients resulted in a higher rate mortality than mitral valve repair (23.4% versus 7.1%, p=0.01) or as compared with either operation in a control group of young patients (p<0.0001) (Ailawadi et al. 2008). A systemic review of literature by Ghoreishi et al. also addressed the same question. They too report that mitral valve replacement is associated with higher rates of operative mortality [pooled OR 3.97; 95% confidence interval (CI) 1.59–9.86, P=0.003] and more postoperative complications (pooled OR 2.35; 95% CI 1.34–4.09, P=0.003) than mitral valve repair among elderly patients (Ghoreishi et al. 2013). In our cohort, mitral valve reconstruction was performed in 53.9% of the whole group (AM -58.1%, MT-57.8%, AMT-50.0%). As stated earlier, the decision to treat mitral valve lesions in the elderly population is a difficult one. There are cases in which repair is possible, but in cases where replacement is the quicker and safer option, it should be the procedure of choice. The total mortality in cases of mitral repair was 3.4% (n=4), in cases of mitral valve repair the total mortality was 4.2% (n=5) in cases of mitral valve replacement.

The choice of the prosthesis is also an important decision in elderly patients, mainly due to concerns of compliance with anticoagulation, cerebrovascular accidents, bleeding and structural valve degeneration and need for reoperation. In their review Kaneko et al. concluded that the current literature supports the use of biological prosthetic valves in patients aged >60 years (Kaneko et al. 2013). In our cohort 20.2% (n=24) of patients received mechanical prosthesis, with a majority of patients receiving a biological valve prosthesis. The mitral valve was repaired and replaced in almost equal proportions. This indicates that the choice of repair over replacement needs to be a patient dependent one. We also see that in most cases the tricuspid valve was repaired with only 3.4% (n=4) patients receiving biological prosthesis.

The 30 day mortality in our cohort was 4.2% with a total in-hospital mortality of 7.6%. Noack et al. analysed 487 consecutive patients who underwent triple valve surgery (TVS) with a mean age of 70.3 ± 9.3 years and a logistic EuroSCORE of 17.4±17.1% (ranging from 1–95%). They reported a 30-day mortality of 16.1% and the long-term survival at 1 year and 5 years was 71.8% and 54.6% respectively. They ratified their seemingly high 30-day mortality by suggesting higher surgical risk in their elderly patients, larger number of comorbidities and concomitant procedures, and worse preoperative status (Noack et al. 2013). A similar retrospective, observational, cohort study of 106 patients by Lio et al. who underwent TVS reported findings from a younger population (mean age of 68.6±9.5 years (range 28–85 years)) with an in-hospital mortality of 5.6%. Their 5- and 10-year

survival rates were 85.0±3.0 and 65.0±9.0%, respectively (Lio et al. 2014). Another study by Peterss et al. which only included patients who underwent aortic, mitral and tricuspid valve surgery reported a 30 day mortality of 16.0% (Peterss et al.2012). Large registries such as The Society of Thoracic Surgeons Database, in North America and The German Society of Thoracic and Cardiovascular Surgery report a stable in-hospital mortality rate of 13.0% in patients with TVS without concomitant procedures (Noack et al. 2013, Beckmann et al. 2015, Lee et al. 2011).

Pagni et al. reported in his study on triple valve surgery on 131 patients (mean age 67.2±13.4 years) a 30-day and hospital mortality of 10.6% (n=14), the main causes of which were low cardiac output in 6.1% (n=8), sepsis in 3.1% (n= 4), acute respiratory distress syndrome in 0.8% (n=1), stroke in 0.8 % (n=1), and associated multisystem organ failure in 6.1% (n=8) patients (Pagni et al. 2014). In our cohort mortality was attributed to sepsis and multi-organ failure (3.4%), cardiogenic shock (2.5%) and low-output-syndrome (1.7%). Among the 9.24% (n=11) of patients who underwent reoperations, the in-hospital mortality was 18.2% (n=2).

Chaturvedi et al. reviewed 300 consecutive octogenarians (mean age 82.6 years) who underwent cardiac surgery. The 30-day survival was 84.3% and the overall 1- and 5-year survival reported was 76.6%and 57.8%, respectively. They also studied the functional outcome, living arrangements, daily activities and leisure engagements of these patients and reported satisfactory outcomes. At two years follow up 63.9% of the patients were classified autonomous, 31.7% semiautonomous, and 4.3% dependent. At the time of first follow up, 76.4% of the patients were at home, 19.2 % in a residence, and 4.3% of the patients were in a supervised setting. They also reported that almost all patients were involved in leisure activities in the social (98.9%), cognitive (98.4%), and physical (93.1%) domains (Chaturvedi et al. 2010). Another study by Abah et al systematically reviewed the postoperative quality of life in octogenarians after cardiac surgery. They analysed forty-four studies that involved cardiac surgery in octogenarians, of which nine were prospective. They reported an improvement in the overall quality of life. Although this study does not involve a follow up, it is noteworthy that elderly patients do enjoy a better quality of life after valvular heart surgery (Abah et al. 2015). Our study does not include a follow up analysis and clearly focused on short term outcome. Therefore we cannot provide data on quality of life that will be evaluated in ongoing studies.

In conclusion our study demonstrates the feasibility of complex multiple valve surgery in elderly patients. The EUROscore II obviously overestimates the risk of these patients. Since it is not part of the clinical routine to evaluate frailty of elderly patients partly due to the lack of a standardised frailty scoring system, further prospective trials are required. Postoperative mortality was seen to be

in the same range as in several other studies. However, significant complication rates demand a careful patient selection and preoperative conditioning.

Limitations:

Being a retrospective single centre study this study has its limitations. The number of patients is quite small especially in the AMT group. This can be due to the fact that older patients are often undergo several interventional and minimally invasive procedures before conventional surgery is considered or that they are too decompensated or frail to be operated. Another significant limitation is that there has been no consideration of biological age or frailty in this study. Quality of life has also not been factored into this study due to its retrospective nature and its focus on short term outcomes. A further follow up analysis is mandatory.

# 5. Summary

Degenerative valve disease in the elderly often affects more than one heart valve, and this results in a complex clinical situation with several factors to be considered for optimal management. The increase in the proportion of elderly patients poses also additional challenges for the clinical management and leads to a higher intervention risk, as multiple co-morbidities are a frequent finding in these patients.

We reviewed the outcome of patients older than 75 years of age, who underwent complex multiple valve surgery at our institution. A retrospective review of our institutional database showed that from January 2011 to May 2016, we operated on 311 patients with more than one diseased heart valve, of whom 119 patients (38.3%) were older than 75 years (mean age 78.3±2.7 years). The mean EUROScore II estimated the operative mortality to be 16.5±15.1%. Concomitant bypass surgery was performed in 54 patients (45.4%).

The 30 day mortality was 4.2% with a total in-hospital mortality of 7.6%. The main causes of mortality were sepsis and multi-organ failure (n=4), cardiogenic shock (n=3) and low output syndrome (n=2). Postoperative atrioventricular block III with pacemaker implantation occurred in 18.3% of patients. The main postoperative complications were re-sternotomy 16.0%, cerebro-vascular events, acute kidney injury 15.1%, nosocomial pneumonia 15.1% and heparin induced thrombocytopenia type II 9.2%.

In conclusion this study demonstrates the feasibility of complex multiple valve surgery in elderly patients. Perioperative risk may be overestimated by the EUROScore II and emphasis should be shifted from the chronological to biological ages. Postoperative mortality was seen to be in the same range as several other studies. Further prospective studies are required with a longer follow-up and evaluation of quality of life.

# 5. Zusammenfassung

Degenerative Herzklappenkrankheiten bei älteren Patienten treten häufig bei mehreren Herzklappen gleichzeitig auf. Dies führt zu einer komplexen klinischen Situation, deren Faktoren für ein optimales Management in Betracht gezogen werden müssen. Die Zunahme des Anteils älterer Patienten stellt auch zusätzliche Herausforderungen für das klinische Management dar und führt zu einem höheren Interventionsrisiko, da bei diesen Patienten Komorbiditäten häufig auftreten.

Wir haben eine retrospektive Analyse von hochbetagten Patienten mit komplexer Herzklappenchirurgie durchgeführt und deren frühpostoperatives Outcome untersucht. Es wurden Patienten eingeschlossen, die zwischen Januar 2011 und Mai 2016 am Universitätsklinikum Magdeburg operiert wurden. In dem Untersuchungszeitraum wurden bei insgesamt 311 Patienten komplexe Mehrfacheingriffe durchgeführt. Insgesamt 119 Patienten (38,3%) waren Patienten älter als 75 Jahre (Durchschnittsalter 78,3±2,7 Jahre). Der Durschnitts-EUROScore II war 16,5±15,1%. Bei 54 Patienten (45,4%) wurde simultan eine Bypassoperation durchgeführt.

Die 30-Tage Mortalität lag bei insgesamt 4,2% und die Krankenhausmortalität lag bei 7,6%. Die Hauptursachen für die Mortalität waren Multiorganversagen bei Sepsis (n=4) sowie kardiogener Schock (n=3) und low output syndrome (n=2). Bei 18,3% der Patienten kam es zu einem anhaltendem postoperativen AV-Block III° mit nachfolgender Schrittmacherimplantation. Weiter Komplikationen waren Rethorakotomie bei Blutung (16,0%), cerebrale Ischämie (7,0%), akutes Nierenversagen (15,1%), Pneumonie (15,1%) und heparininduzierte Thrombozytopenie Typ II (9,2%).

Zusammenfassend können wir feststellen, dass auch bei älteren Patienten Mehrfachklappen-Operationen mit vertretbarem Risiko durchführbar sind. Der Euroscore II überschätzt das perioperative Risiko dieser Patienten. Die Mortalitätsraten waren vergleichbar mit andere Studien. Die höhere Komplikationsrate erfordert eine sehr sorgfältige Indikationsstellung.

# 6. References


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Ehrenerklärung

Ich erkläre, dass ich die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur

Promotion eingereichte Dissertation mit dem Titel „Outcomes of Complex Valve Surgery in Elderly Patients“ in der Klinik für Herz- und Thoraxchirurgie ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe. Bei der Abfassung der Dissertation sind Rechte Dritter nicht verletzt worden.

Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation herzustellen und zu vertreiben.

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| | |
|---|---|
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