A 10-year Institutional Review of Surgery for Structural Valve Dysfunction in the Developing World

by

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DECLARATION

I Chih-Yuan Chen, declare that:

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Signed: November 2017

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ABSTRACT

Background

Prosthetic heart valves do not fulfil the requirements for an ideal valve, resulting in the development of prosthetic dysfunction or complications over time. Structural valve dysfunction may be influenced by multiple components which include patient's factors, valve related factors and intraoperative factors. The inter-relation of these factors has a significant impact on morbidity and mortality associated with reoperative surgery for prosthetic valve dysfunction, particularly in a developing world where a large burden of communicable diseases together with lack of health care resources affect surgical outcome. In this study we examined the clinical records of the patients who underwent reoperative valve surgery to evaluate the clinical profile and factors that affect the surgical outcome after reoperation at a large tertiary referral center in a developing country.

Objectives

1) To describe the demographic profile of patients with malfunctioning prosthetic heart valves and define their clinical presentation

2) To describe the clinical presentation of valve dysfunction

3) To determine the possible mechanisms of mechanical and bioprosthetic valve failure

4) To determine the factors affecting the immediate surgical outcomes in subjects undergoing redo cardiac prosthetic valve surgery.

Materials and methods

A retrospective analysis of the clinical, perioperative and follow-up data of patients who underwent redo cardiac valve surgery for structural valve dysfunction between January 2005 and December 2014 at Inkosi Albert Luthuli Central Hospital, Durban, South Africa was undertaken. Patients were identified using the Speedminer software program which is a Data Warehouse software package used to store data collected on the hospital Medicom database. The file of each of patient who underwent redo cardiac prosthetic valve replacement for structural valve dysfunction was accessed and data were extracted on age, gender, potential risk factors for valve thrombosis, symptomatology, investigations including International normalized Ratio (INR) status and follow up. All patients were evaluated preoperatively by the cardiologist and the cardiothoracic surgical team and submitted for either an elective or emergency valve replacement. Excluded from the

study were those patients who underwent cardiothoracic surgery for nonvalvular reasons, i.e. coronary artery bypass surgery and congenital heart disease.

Results

During the ten year period (2005 to 2014) 2618 valve replacement operations were performed. During the same period 128 reoperations (4.9%) were performed in 113 patients (mean age 35.59 (SD±16.66) years). The majority of the patients were Black (72.6%) and female (75%). Fifteen patients (13.3%) were HIV infected and nine were pregnant.

Acute dyspnoea (NYHA class III 34.37% and class IV 21.88%) was the presenting feature in 72 patients (56.25%). Clinical presenting features of an obstructed valve (flash pulmonary oedema with or without clinically audible prosthetic valve clicks) were documented in the clinical records of 44 of the 128 (34.4%) reoperations. In seventeen instances subjects presented with acute onset of cardiac failure (13.3%) and in eleven the presentation was characterised by signs of low cardiac output state (5.3%). There were no clinical indicators of an obstructed valve in the remaining 56 (43.8%). Of these 56 patients: 38 presented with change in effort tolerance and 18 where asymptomatic.

Valve dysfunction was detected by echocardiography and confirmed fluoroscopically in 71/128 cases (55.47%). In the remaining patients the diagnosis was made either at fluoroscopy (11.72%) or on echocardiography (32.81%). The ejection fraction (EF) was severely impaired (EF<40%) in 7.08% of patients. The mean left atrial size was 52.28mm and mean pulmonary systolic pressure 45mmHg (range 26-104).

Mechanical valve dysfunction was documented in 110/128 reoperations (obstructed valve (100) and prosthetic infective endocarditis (10). In almost two thirds of instances with obstructed mechanical prostheses levels of anticoagulation achieved were poor (INR<2.0); 30/110 (27.27%) were within therapeutic ranges of 2-4 and 9/110 (8.18%) was >4.0. HIV status did not influence the outcome of surgery and did not appear to be the main mechanism of valve obstruction. The bioprosthetic valve group comprised the remaining 18 of 128 reoperations. In this group 13/18 patients had structural valve deterioration with periprosthetic leaks, and remaining 5 had prosthetic infective endocarditis (aortic root abscess (1) and annular dehiscence (4).

Emergency surgery was performed in 54.7% of the study population, of which 60.2% were in the mitral position. There was a total of 13 early in-hospital deaths (11.5%) of which one “on table” death was due to a low cardiac output state (LCOS). Postoperative mortality was related to prosthetic endocarditis (5/13) and high grade dyspnoea at presentation (7/13). Multivariate analysis revealed that bypass time >3.5 hours (HR 5.58, 95%CI 1.24-24.95), cross clamp time >120 minutes (HR 4.48, 95%CI 1.25-18.73), and third time redo operations (HR 4.26, 95%CI 1.23-14.75) were the independent predictors for early in-hospital mortality.

Conclusion

Our study shows a 4.9% reoperation rate after the previous valve replacement surgery with 11.5% perioperative mortality. Our results confirm that reoperative surgery is associated with significant morbidity and mortality. More than half the patients presented acutely for mechanical valve obstruction which was due to inadequate levels of anticoagulation and required emergency surgery. Early mortality was related to poor NYHA class at presentation and to the presence of infective endocarditis. An important finding of this study was the high rate of valve obstruction associated with poor anticoagulation in patients who received the Cryolife On-X valve. They had a shorter interval to valve obstruction requiring redo valve replacement compared to the other mechanical prostheses.

Chapter 1: Introduction

Acquired cardiac valvular disease

Acquired valvular disease affects different populations in the context of a country's development and may be subdivided into rheumatic, degenerative and post traumatic causes.(1-3) Whereas degenerative heart disease is common in the western world rheumatic heart disease is still the predominant reason for heart valve surgery and prosthesis implantation in the developing countries. Rheumatic valve disease has almost completely been eradicated in the industrialized countries due to the improvement of medical treatment, access to medical care and socio-economic status.(2) The disease is only limited to the population of immigrants from developing countries but the most common heart valve entity in the developed world is degenerative valvular disease, as there is an increase in life expectancy in the developed world due to multi-factorial reasons. In our context, degenerative valve disease is observed in the Caucasian and Asiatic populations with better socio-economic status, lifestyle in urbanization and increased life expectancy.(3)

Rheumatic valvular disease

Rheumatic valvular disease remains a challenge in the developing world due to inadequate access to health care due to poor infrastructure in the health system,

vast rural areas with a large catchment area per primary health care clinic; furthermore, inadequate funding for basic medicines and a large burden of communicable diseases which determine preferential policy directives from the Department of Health that exclude rheumatic fever and heart valvular diseases.

Although the incidence of rheumatic valvular disease has been on a downward trend throughout the developing world, it is still a major contributing factor for heart valve disease in children and young adults requiring repeated hospital admissions, which result in valve replacement.(2, 3) Rheumatic heart disease (RHD) results from untreated complications of rheumatic fever, which is commonly associated with group-A streptococcal infection during childhood. The antibodies form against the initial infection and cross-react with proteins in the heart valve creating an autoimmune reaction. The inflammatory responses from the autoimmune reaction lead to destruction of the heart valves. Nine to thirty-nine percent of patients who contract acute rheumatic fever develop associated valve deficiency two to ten years after the initial febrile episode, creating a bimodal age distribution with peaks in late childhood and early adulthood. Twenty percent of patients with RHD will die before the age of five, and eighty percent before they reach 25 years old. One of the most common long term manifestations of RHD is chronic valve deformity, occurring in twenty-five to forty percent of chronic RHD patients, many of whom require valve surgery when the disease is severe.(4-6)

Emerging valve disease and the influence of HIV infection

There are new forms of heart valve disease that have emerged over the last 20 years. The three main sources of these emerging valve diseases are 1) new infectious diseases such as HIV infection 2) drug-related diseases resulting from specific drug effects on a particular valve which has only been observed in the developed world and 3) new types of idiopathic disease (e.g. antiphospholipid syndrome).(2) In our setting, the epidemic of HIV infection has been associated with concomitant heart disease. Although HIV is not a direct cause of the heart valve disease, the immunocompromised state may be predisposed to systemic infection that subsequently results in an infective endocarditis. (2) Furthermore, a significant number of subjects who were receiving highly active antiretroviral therapy (HAART) with early generation drugs (e.g. stavudine) may develop the complication of lipodystrophic syndrome and atherosclerotic heart disease leading to degenerative valvular diseases.(7-10)

The presence of concomitant retroviral disease has resulted in challenges in the management of valve disease, many of whom with advanced heart disease present for surgery. The true incidence of combined retroviral and heart disease in Southern Africa has not been well studied. The Heart of Soweto study shared some information about the spectrum of heart disease and risk factors in a black urban

population in South Africa. This study identified 1593/4162 subjects with newly diagnosed cardiovascular disease over a one year period (Jan-Dec 2006). Overall retroviral disease was identified in 74/1593 (5%). No data was given on cardiac complications related to HIV infection such as tuberculous-related pericardial disease and left ventricular dysfunction related to HIV infection. (11) Retroviral disease in valve disease category comprised 4%.

Our study was conducted in the eThekwini municipality of the province of KwaZulu-Natal (KZN), which is one of the nine provinces in the Republic of South Africa with a total land surface area of 94361 square kilometres and a population of 10.26 million people. The population of KZN is composed of black African (86.6%), Indian or Asian (7.4%), Caucasian (4.2%) and Mixed Ancestry (1.4%). The Province of KZN is currently facing a large communicable disease burden in combination with a high rate of retroviral disease. The prevalence of HIV infection is highest (59%) in the age group older than 24 years with a lower prevalence in the age group of 30-34 years.(11, 12) It is therefore not surprising that many patients with chronic RHD have concomitant HIV infection. This province is managing the largest Anti-Retroviral Treatment program (ART) in the country, with the number of patients on ART increasing exponentially from 408238 (2010/2011) to 840738 (2012/2014).

The need for valve replacement surgery

Of all the valve diseases that require intervention in our context, the majority are due to long standing chronic rheumatic valve disease while degenerative aortic valve disease accounts for the remaining few requiring surgeries. Regardless of the aetiology, long standing valve disease results in several pathophysiological sequelae that affect the functioning of the cardiac chambers. In brief, left-sided valve disease will have an impact on the function of the left atrium and the left ventricle. Stenotic mitral valve lesions create a pressure overload in the left atrium with resultant pulmonary hypertension and right ventricular dysfunction/failure while aortic stenosis imposes a pressure load on the left atrium and the left ventricle. In contrast, regurgitant lesions create a volume overload in the atrium and ventricle. Severe valve disease impairs effort tolerance, has an impact on quality of life and life expectancy. Left untreated it results in irreversible ventricular dysfunction, making it crucial to identify and treat the disease early with an appropriate timing for valve replacement surgery when the native valve disease become severe. A serious challenge with valve replacement surgery is the potential need for reoperation in the future due to prosthetic valve dysfunction. The decision to replace a native heart valve therefore requires a consideration of several factors, including the site and type of valve to be inserted, adherence to a strict

anticoagulation protocol, as well as an understanding of the ideal characteristics of the artificial prosthetic replacement valve.

The Ideal cardiac prosthesis

Since the artificial prosthetic valve is a foreign material inserted into the cardiac chamber and blood is constantly interacting with the prosthetic interface with the potential for thrombus formation, reduction of trauma of blood as it passes through the prosthetic material is crucial. The ideal valve is characterised by high durability since it has to function at 40 million cycles per year with minimal turbulence in the central orifice, and its internal design has to be such that the washout jet prevents thrombus formation over the hinge mechanism of the prosthetic valve.

Advantage and disadvantage of each type of prosthesis

Prosthetic valves may be classified into mechanical or biological, based on the composition of the valve leaflets. The major difference between them is the need for anticoagulation: biological (tissue) valves have properties that are similar to the human heart valve and therefore long term anticoagulation is not indicated when a biological valve is inserted at surgery but a drawback of the tissue valve is its limited durability. In contrast, the major drawback of the mechanical valve is the

mandatory need for anticoagulation therapy to prevent blood clotting and prosthetic valve thrombosis. Anticoagulation calls for frequent regular monitoring of blood coagulant activity (international normalised ratio (INR)) at a health facility to ensure adequate levels of anticoagulation without increasing the risk of bleeding, all of which affect the individual's lifestyle and have an impact on quality of life after valve surgery.

Figure 1. Different type of mechanical valves. A. Hufnagel design; B. Starr-Edward caged-ball design; C. Medtronic Hall single tilting disc design; D. St. Jude mechanical bi-leaflet design; E. Carbomedics Carbo-seal Valsava design.

Mechanical prosthesis (Figure1)

The evolution of mechanical heart valves started with the Starr-Edwards ball-and-cage valve in 1962 and led to the development of the Kay-Shirley caged-disc valve in 1965. Significant improvement in the design of the valve was made in the early 1970s with single tilting-disc valve and this was followed by the St. Jude Medical bi-leaflet mechanical heart valve in the late 70s which became the gold standard for

the most of its peers. Although there are several mechanical valves with different profiles, no ideal mechanical prosthesis has been designed to date. The bi-leaflet, mono-leaflet and the ball-and-cage valves (Fig. 1B-D) have stood the test of the time as they have proven to be functional prostheses.

Modern mechanical valves have several advantages in design: they have a lower profile and provide a larger effective valve orifice. They are associated with less structural deterioration in the younger population and have a longer life span.(13, 14) The pyrolytic carbon discovered in late 1960s was found to be most suitable material for the mechanical heart valve because of its superior biocompatibility, resistance to wear and tear and lower thrombogenicity. The pyrolytic carbon or titanium-coated pyrolytic carbon composition of the leaflets provides better longevity compared to the earlier polycrystalline type of metal used as it is less prone to impact and fraction tear with subsequent fatigue failure.(13, 15)

The bi-leaflet valve is thought to have less thrombogenicity and trauma to the blood with good haemodynamic flow through the artificial orifice. There have been numerous other attempts to improve the bi-leaflet design, which has resulted in various bi-leaflet mechanical valves in the current market. (1, 13, 15)

Biological prosthesis (Figure 2)

The biological valve is derived from either bovine or porcine tissue; its life span after implantation has improved with the newer generation of valve preservation techniques. Biological valves may be mounted on a stent (Figure 2. A and B) or inserted without a stent (Fig 2 C).(16) Biological valves are implanted in older patients and/or in patients where anticoagulation is contraindicated; they have resulted in a reasonable outcome with a lower mortality. Biological valves are not implanted in patients who are considered unsuitable for open heart surgery. In such patients, transcatheter aortic valve implantation (TAVI), a percutaneous catheter-deployed biological valve is indicated. This procedure has gained popularity particularly in the developed world where there is a growing population of septuagenarians and octogenarians.

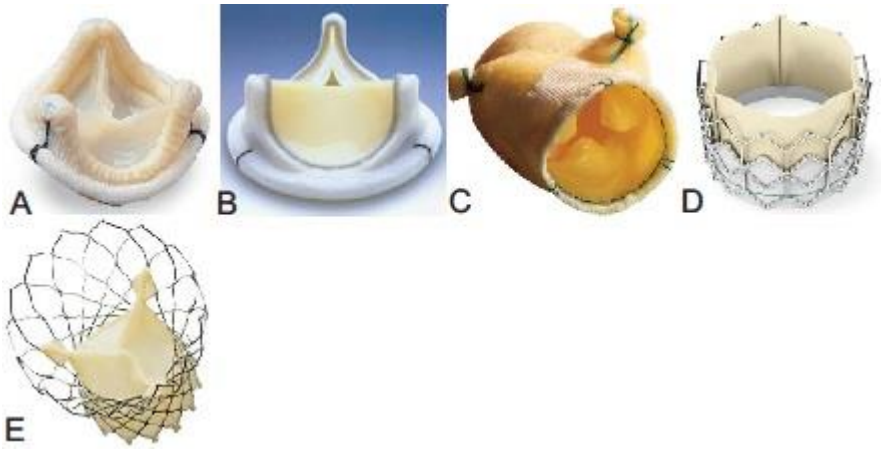

Figure 2 The different types of biological cardiac prosthetic valves. A. stented porcine valve (Medtronic mosaic); B. stented bovine pericardial valve (Carpentier-Edwards Magna); C. Stentless porcine bio-prosthetic valve (Medtronic Freestyle); D. percutaneous bioprosthesis expanded over a balloon (Edwards Sapien); E. percutaneous self-expandable percutaneous bioprosthesis (CoreValve).

Choice of biological vs mechanical valve implantation

There are multiple factors influencing the cardiac surgeon's decision to implant a particular type of valve prosthesis, among them being the need for anticoagulation and the potential risk of complications thereafter. The surgeon takes into consideration several patient factors such as age, life expectancy, patient preference, the indications and contraindications for anticoagulation therapy, comorbidities and lastly access to a health care facility where patient's INR may be monitored and adjusted in necessary. Although the American College of Cardiology/ American Heart Association and European College of Cardiology have published guidelines on anticoagulation for prosthetic valves these recommendations can only serve as a guide in developing countries where

anticoagulation poses a major challenge because of difficulty in access to a health care facility for INR monitoring with a potential risk for thrombosed mechanical prostheses leading to catastrophic consequence for the patient.(17-19)

A brief guideline for the choice of mechanical prosthesis is based on the following considerations:

1) The informed patient wants a mechanical valve with no contraindication for long term anticoagulation.

2) The patient is already on long term anticoagulation for a previous mechanical prosthesis implantation, cardiac rhythm abnormality and high risk of thromboembolisation.

3) The patient is at risk of rapid biological valve structural deterioration (young age, hyperparathyroidism and renal failure)

4) The patient is younger than 65 years of age with a good life expectancy

5) Easy access to local health facilities where the INR can be monitored and adjusted accordingly (critical factor for developing countries)

The choice of a biological valve selection is based on the following factors:

1) The informed patient wants a biological cardiac valve

2) Good quality of anticoagulation is not available (contraindications, high risk of bleeding, compliance issue, lifestyle factors, and poor or no access to a health care facility in the rural region.)

3) The patient is older than 65 years of age with limited life expectancy

4) The female patient is in child-bearing age. Biological heart valves tend to undergo rapid structural deterioration in this younger, child bearing age group for which they may return for redo valve surgery within a short space of time.

Aetiology of prosthetic valve failure

- Biological valve failure

After implantation, the conventional stented bioprosthesis has a failure rate of 10-30% in the first 10 years and 20-50% at 15 years.(13) Certain host and valve related factors may influence the rate of biological valve deterioration:

1) Host-related factors

The age of the patient at the time of implantation has a strong influence of the rate of the biological valve deterioration; early failure usually occurs in the younger age group under 40 years of age (20-30%) and to a lesser degree in the in older age over 70 years of age (<10%).(13, 17, 18, 20-22) Structural deterioration is more frequent in the mitral position because of exposure to high mechanical stress during systole. Structural deterioration of the aortic valve is more common in subjects with systemic hypertension because of the chronic elevation in the diastolic pressure. Pibarot and colleagues had described three pathophysiological mechanisms that contribute to bioprosthetic valve degeneration. Degenerative, immune and atherosclerotic processes act in concert to cause valve deterioration over time. **(Fig.3)**

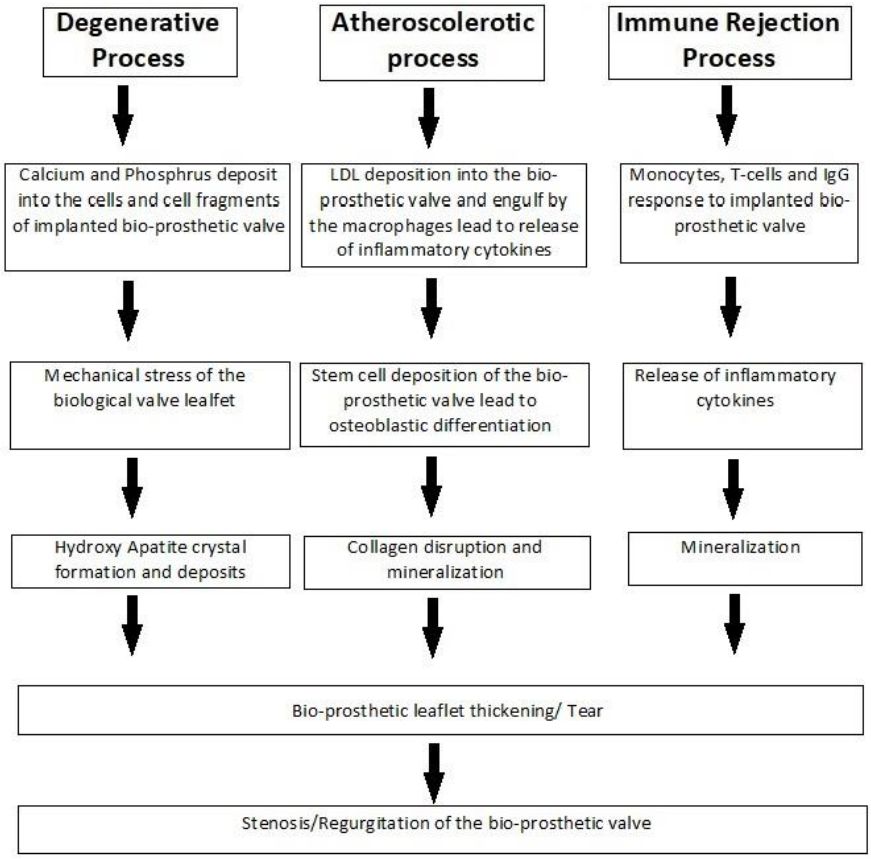

Figure 3. Possible mechanism for structural deterioration of the bio-prosthetic valve. Adapted from Pibarot P and Dumesnil JG. Circulation 2009.(13)

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2) Valve-related factors

Early generation biological valves used formaldehyde for fixation that resulted in early degeneration of bioprosthesis several years after implantation. This preservation technique employs chemical crosslinking to diminish the antigenicity of the xenogenic material (calf pericardial tissue) to further improve its stability and prevent autolysis. The disadvantage of glutaraldehyde fixation is that it decellularizes the valve and causes calcium influx which interacts with phosphorus

in the cell membrane to cause calcium phosphate crystal deposits. This is one of many reasons accounting for biological valve dysfunction and failure. In contrast, the new generation biological valve has undergone a chemical treatment at very low pressure, with surfactant and heat treatments, as well as modification of the stent design to decrease the rate of biological prosthesis deterioration and dysfunction.(13, 16, 21)

- **Mechanical valve failure**

Current problems associated with mechanical valves are the following:

1) Structural dysfunction

   The repetitive cardiac cycle may cause fatigue to the valve material that subsequently leads to fracture of the valve leaflets.(15)

2) Valve thrombosis and embolism

   The opening and closing of the mechanical prosthesis cause stasis and turbulence of the blood flow at the region of the implantation, which leads to platelets activation and thrombus formation. The common region of thrombus formation is the hinge mechanism where high shear stress and varying frequency of contact contribute to activation of platelets and

stagnation of blood flow. Blood clots may form at this point, enlarge and embolize to the peripheral organs.(15)

3) Pannus formation

Once the mechanical prosthesis has been implanted the human body will continue to epithelialize the sewing ring which is direct contact with the native valve annular tissue. This process varies with time, and as fibrosis builds up in the sewing ring it may result in overgrowth of fibrosis from the native annulus into the orifice of the mechanical valve. This causes turbulence in the blood flow and activates the clotting cascade, a process that contributes to leaflet dysfunction and obstruction. (Fig 4)

4) Bleeding and haemorrhage

The efficacy of anticoagulation with the coumarin anticoagulant warfarin, is monitored by measuring the INR level which requires a monthly blood sample to be taken at a health care facility and warfarin dose to be adjusted by the health care practitioner. The absorption and metabolism of this drug is influenced by several factors, particularly liver function, diet, concomitant drug usage and alcohol intake, all of which have an effect of the level of INR, resulting in a narrow index of safety. If the INR level falls too low then the

individual may prone to valve thrombosis, and if the INR is too prolonged it makes the individual more prone to bleeding upon minimal contact force.

5) Endocarditis

The mechanical valve has a sewing ring which made of Teflon, polyester or Dacron which serves as a nidus for bacterial colonization during any transient bacteraemia, leading to infection of the endocardium of the heart and predisposes to prosthetic valve endocarditis during episodes of bacteraemia.

In summary, potential problems exist with implantation of an artificial heart valve, whether it is biological or mechanical. Host immune responses to foreign material implanted in the native valve position may cause the biological prosthesis to deteriorate with time, resulting in valve calcification and the eventual development of a stenotic lesion. The valve may become infected, resulting in leaflet perforation and leaflet destruction, or infection of the sewing ring leading to valve dehiscence and severe regurgitation.

Problems with the mechanical prosthesis may result in stenosis or regurgitation. Structural failure or fracture, thrombus formation at the hinge mechanism or pannus ingrowth may result in a single leaflet becoming stuck in an open position,

or infective endocarditis may lead to periprosthetic valve dehiscence. All the above-mentioned conditions may lead to a regurgitant lesion; thrombus formation at hinge mechanism or pannus ingrowth affect the hinge mechanism causing in one or both leaflets to become stuck in the closed/semi-closed position and a resultant stenotic ± regurgitant lesion. (Fig 4)

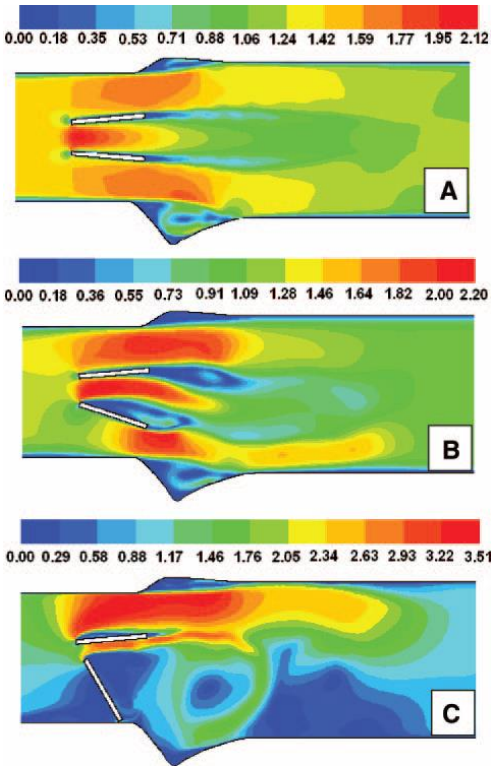

Figure 4. Effect of prosthetic valve dysfunction on blood flow, the dynamics Numerical simulation showing the flow velocity distribution in bileaflet mechanical valves at a cardiac output of 5 L/min. A, Normally functioning bileaflet prosthesis. The flow velocity within the central orifice is higher than that in the lateral orifices. Accordingly, the peak gradient across the central orifice is 19 mm Hg, which is higher than the actual peak transprosthetic gradient (10 mm Hg). B, Mild prosthesis dysfunction with 25% restriction in the opening of 1 leaflet. The peak gradient is 20 mm Hg. C, Severe prosthesis dysfunction with 1 leaflet blocked in the closed position. The peak gradient is 50 mm Hg. Courtesy of Drs Othman Smadi and Lyes Kadem, Concordia University, Montreal, Québec, Canada. Pibarot and Dumesnil Selection and Management of Prosthetic Valves 1039

Challenges associated with redo cardiac surgery

After replacement, patients who develop prosthesis failure due to different aetiologies will require replacement of the underlying failed valve prosthesis (redo cardiac surgery). The redo heart valve replacement differs from the first-time surgery as the surgical outcome will be determined by several factors:

1. The patient's preoperative clinical condition and associated comorbidities. The most common presentation is a thrombosed mechanical valve which may result in the patient presenting *in extremis* in a shocked state, with low cardiac output state (LOCS) and multiple organ failure.

2. The current status of left ventricular function which may or may not be affected by the intrinsic valvular prosthesis dysfunction.

3. Any previous concomitant coronary artery bypass graft done and its patency. For instance, the left internal mammary graft to left anterior descending artery may lie behind the sternum.

4. Closure of the pericardium from previous surgery. If the pericardium was not closed then enlargement of the right atrium due to the underlying valve prosthesis dysfunction exposes this chamber to potential injury upon chest re-entry.

5. The presence of epicardial adhesions to pericardium that have resulted from previous surgery. Occasionally freeing the heart from previous cannulation sites

adhesion may result in injury to the great vessels or cardiac chambers and lead to massive haemorrhage.

6. Time interval to cardiopulmonary bypass. The time taken to free the heart and place the patient onto the heart-lung machine for haemodynamic support may compromise ventricular function.

Postoperative complications usually directly relate to patient's preoperative profile (age, gender, preoperative clinical status and associated comorbidities); intraoperative techniques (pump time, aortic cross clamp time, type of cardioplegia used, amount of inotropic support and systemically induced corporeal cooling), all of which contribute to the patient's postoperative state.

In summary, valve surgery in the developing world present unique challenges related to the underlying disease aetiology and profile, as well as the choice of prosthetic valve for implantation. The effects of associated comorbidities such as HIV infection on blood coagulability and ventricular function may have an influence on outcome of valve replacement surgery.(23) The nature and design of prosthetic valves may account for structural valve dysfunction occur over time (usually 7-8 years after implantation of the biological valve) while the major problem with

mechanical valves relate to the need for anticoagulation. Furthermore, surgical techniques become more challenging during redo cardiac valve surgery, which influence the operative surgical morbidity and predispose to postoperative complications and mortality. (24, 25)(Table 1)

Table 1. Complications associated with redo cardiac valve prosthetic surgery

Possible complications associated with redo cardiac valve prosthetic surgery
1. lower cardiac output state (LCOS)
2. right ventricular failure and tricuspid regurgitation
3. pulmonary hypertension
4. thromboembolism (CVA)
5. neurological disturbance
6. renal failure
7. arrhythmia and conduction abnormalities
8. termination of pregnancy
9. haemorrhage due to anticoagulation agent
10. re-thrombosed valve
11. prosthetic endocarditis

Chapter 2: Overview and Literature Review

Morbidity and mortality associated with cardiac valve reoperation

Since the introduction of heart valve replacement surgery in 1960 (Dwight Harken) it has become clear that the benefits of valve surgery are not infrequently overshadowed by morbidity and mortality associated with anticoagulation and prosthetic valve thrombogenicity. Despite advances in valve design that are associated with improved haemodynamics and less thrombogenicity, valve dysfunction remains a lifelong risk in these patients. Reoperation for the cardiac prosthetic dysfunction is associated with significant early mortality. Lytle and colleagues (27) documented 1000 consecutive redo cardiac valve surgery in 897 patients from 1958 to 1984 at the Cleveland clinic, Ohio, USA. Their series had shown an overall early mortality at 12.1%. The early mortality for first operation for aortic and mitral valve was around 10% but increased to 14% with multiple valve reoperations and significant higher in tricuspid reoperation at 20%. There was a proportional increase in mortality with the number of reoperations. There was a high mortality for 3-5 reoperations in the aortic valve (33%), mitral valve (50%) and multiple valves (67%). (26) A larger series was published by Dr Piehler and co-workers from three institutions over a thirty year period (1963 to 1992) (Mayo clinic, Birmingham Veterans Affairs Medical Center, St. Vincent Hospital and Medical Center and the Oregon Health Sciences University).(28) There were 2246

reoperations in 1984 patients (1395 Male and 851 female). The age ranges from 1.5 to 88 years with mean of 52 years ± 16 years at the time of redo cardiac valve surgery. The unadjusted early mortality was 10.8%. The commonest cause of reoperation was a periprosthetic leak without evidence of infective endocarditis (600/2246), degeneration of bioprosthesis (558/2246), pannus ingrowth (121/2246) and device thrombosis (75/2246). (27) Other studies comprising a sample size over 100 patients undergoing redo cardiac valve surgery in the last 20 years showed an early mortality between 4% (Luciani)(28) and 13.1% (Sener)(29). These data show a varying mortality rate for reoperative cardiac valve surgery across institutions. Factors that affected postoperative mortality included the patient's preoperative clinical condition, intraoperative technical factors and postoperative intensive care unit management.

Series	Study duration	Patients	Valve Position	Valve Type	Early Mortality (%)
Lytle et al, 1986 (26)	1958–1984	897	AV, MV, TV	B	12.1
*Deviri et al, 1991 (30)	1980-1989	100	AV, MV	M	12.3
Bortolotti et al, 1994 (31)	1966–1992	549	AV, MV	B	11
Piehler et al, 1995 (27)	1963–1992	1984	AV, MV	B	10.8
Tyers et al, 1995 (32)	1975–1992	708	AV, MV, TV	B	11
Sener et al, 1995 (29)	1984–1993	154	AV, MV	B	13.1
Akins et al, 1998 (33)	1985–1997	400	AV, MV	T	7.8
Jamieson et al, 2003 (18)	1975–1999	463	MV	T	7.1
*Taljaard et al, 2003 (34)	1991-2001	32	AV, MV	M	64.7
Luciani et al, 2006 (28)	1997–2002	290	AV, MV	B	4
Tang et al, 2007 (35)	1997–2002	743	AV, MV, TV	B	9.4
*Current series	2005-2014	128	AV, MV, TV	B	11.5

Table 2. Results of reoperative valve surgery compared to South African studies*

AV= aortic valve; MV= mitral valve; TV= tricuspid valve; B= both (tissue and mechanical); T= tissue; M= mechanical.

An early mortality is defined as intraoperative death, and postoperative death (intensive care unit, high care and ward admission) within 30 days of the surgery.

i. Prosthesis type and the Site of implantation

Tang et al reviewed 743 patients who underwent mitral and /or aortic valve redo surgery in Toronto between 1990 to 2005. There were 236 mechanical and 507 biological prostheses. Twenty percent of those with mechanical valves underwent urgent surgery compared to 12% with biological valves. Severe dyspnoea (NYHA III to IV) was the presenting feature in 87% with mechanical and 81% with biological

valves. The mechanical group was much younger and had less concomitant Coronary Artery Bypass Grafts (CABG) at the time of first valve replacement. Retroviral status was not described in the study population.(35)

The site of valve implantation had some bearing on the rate of prosthetic valve deterioration. Tang et al. showed that 371 out of 507 biological valves explanted were in aortic position and 175 out of 507 were in mitral position.(35) The biological valve in the aortic position seemed to deteriorate more rapidly in the presence of systemic hypertension, LV hypertrophy, poor LV function and patient prosthetic mismatch. These conditions are associated with a high pressure gradient over the aortic valve leading to high diastolic closure stress over the biological leaflets predisposing to structural valve dysfunction (SVD). Persistent left ventricular hypertrophy after bioprosthetic aortic valve replacement also had a higher incidence of structural valve deterioration (SVD) requiring reoperation (HR 2.38 (95% CI 1.61,3.51; $P<0.001$).(22) In contrast, causes of SVD in the mitral position were young age, renal failure and hyperparathyroidism.(13, 18, 21, 22) Similar findings were reported in the Veterans Affairs 15year randomized trial by Hammermeister et al who found a higher rate of reoperation for bioprosthetic aortic valve replacement.(36)

In another large study Ruel et al. studied 3233 subjects who had undergone 3856 operations over 32 years duration in Ottawa, Canada. After excluding 291 (9.0%) who were lost to follow-up completely after valve replacement, and a further 350 patients (10.8%) who were only lost to follow-up later with a mean of 4.7±4.3 years after valve replacement the group studied the remaining group of 2348 patients. Actual freedom from all-cause reoperation at 10, 15 and 20 years was 96.2, 94.1, and 93.8% for aortic mechanical valves and 96.4, 94.8, and 94.2% for mitral mechanical valves. Freedom from all-cause reoperation was 76.1, 61.4, and 59.6% for aortic bioprosthetic valves, and 79.8, 63.3, and 57.6% for mitral bio-prosthetic valves. The range of ages for the aortic and mitral valve reoperation were similar (48.3-75.5 aortic and 46.8-71.6 mitral). Redo surgery with valves implanted at the aortic and mitral position were described at the 20 years follow up: mechanical (6.2% in aortic vs 5.8% mitral) and biological prosthesis (42.4% in mitral vs 40.4% aortic). There was a higher rate of reoperation for the bioprosthetic valve group rather than mechanical valve group due to structural valve deterioration.(19) These authors showed that the site of valve implantation and the age of the patients did not affect the outcome of reoperation.

Rizzoli et al. from Isituto Chirurgia Cardiovasculare, University of Padova, Italy, studied 755 patients who underwent 863 re-operations between 1st January 1970-

1995. Operative age was 53.08 ±13.77 (range, 10 to 83 years). There were 289 mechanical prostheses VS 60 biological in aortic position and 441mechanical VS 164 biological in mitral position. The mitral position had a higher reoperation rate for both biological and mechanical prostheses groups.

Bortolotti et al. from Isituto Chirurgia Cardiovasculare, University of Padova, Italy, studied 330 patients who underwent first reoperation of 351 bioprostheses which composed of 88 patients who underwent surgery in the aortic position, 221 mitral, 21 mitral and aortic between 1970-1990. The primary indication was structural valve deterioration (87%), followed by periprosthetic leaks (7%) and endocarditis (6%). This group had a high reoperation rate in the mitral position compared to the aortic position for the bioprosthetic valves.(42)

In another study Tyers et al. studied 708 reoperations out of 5499 previous primary valve operations over a 17 year period: 3.4% was redo for mechanical prostheses and 16% was redo for biological valve failure. The cumulative follow-up prior to mechanical prosthesis replacement was 105 patient-years (mean follow up 2.4 ± SD 2.2 years; range of 5 days to 7.3 years). In contrast, the follow-up for the biological valve implantation was 5,429 patient-years (mean follow up 8.2 years ±

SD 3.8 years; range 10 days to 18.3 years). In this study the mechanical valve was associated with early reoperation. This study did not provide the patients' preoperative surgical condition which may have been a significant factor for postoperative morbidity and mortality.(32)

ii. Mechanical valve reoperation: valve obstruction

Possible factors that are associated with early mechanical valve reoperation and related complications are summarised in the studies discussed below. The most devastating complication, valve obstruction, is associated in the majority cases with a typical clinical presentation characterized by the acute onset of dyspnoea or pulmonary oedema with or without cardiogenic shock.(18, 25, 37-40)

Two South African studies that have evaluated mechanical valve obstruction, have shown varying postoperative morbidity and mortality for reoperation. Deviri et al. studied 100 patients presenting with mechanical valve obstructions over 9 years duration at Baragwanath Hospital, University of Witwatersrand and showed that 46 presented with class III to IV dyspnoea (47.9%) and 24 with low cardiac output state and shock (25%). Eight patients were completely asymptomatic (8.3%). All patients

underwent urgent operation once the diagnosis of obstruction was made.(30) The early mortality rate was 12.3%.

In the second study, a ten year evaluation of prosthetic valve obstruction at Tygerberg hospital between 1991 and 2001, Taljaard et al. showed that in 25 out of 34 events the patients presented with class III to IV dyspnoea (74%): 91% were in pulmonary oedema and 26% had a low cardiac output state. In this study three patients were asymptomatic and one tested HIV positive. Emergency operation (within 24 hours) was performed in 50% of cases, while 42% underwent elective surgery.(34) The overall mortality was 64.7%. These studies showed that early surgical intervention was associated with a lower postoperative mortality rate.

iii. Influence of native valve disease on prosthesis dysfunction

To what extent the underlying preoperative native valve disease may contribute to future prosthetic valve dysfunction has not been studied. One reason is that younger subjects with rheumatic disease would receive a mechanical prosthesis due to its good life span while the older population with concomitant ischaemic coronary artery disease are likely to receive a biological prosthesis. (11, 14-16) Predisposing factors to thrombosis include the native valve position, the degree of

left ventricular dysfunction, the degree of the left atrial enlargement, and the presence of atrial fibrillation (AF). Systemic thromboembolism is much less common with aortic compared to mitral valve disease. It is usually associated with coexisting mitral valve disease and atrial fibrillation. It may be the presenting manifestation in more than 10% of the patients with mitral stenosis. The presence of AF increases the risk of systemic thromboembolism by 3-7 times (33-36), and even higher up to an 18-fold as estimated in the Framingham study. (37, 38) The incidence of systemic embolism is between 1-5% per year for mitral disease.(33, 34, 36, 39, 40)

iv. Mechanical vs bioprosthesis and the influence of age

The age of the patient when the biological valve is implanted is important since younger patients have a more active immune system which reacts to the residual animal antigen on the surface of the biological valve, leading to a humoral and cellular response. The response of various cellular compartments may release inflammatory cytokines and result in mineralization of the leaflets explaining why the biological prosthesis is prone to structural valve dysfunction (SVD) much faster in the young population.(13, 18, 37) The rate is between 20-30% in patients under 40 years and under 10% in the elderly (>70yr). As the leaflets lose their flexibility they may become thickened, resulting in a stenotic lesion, or they be subject to tears which result in a regurgitant lesion.(13)

In the Veterans Administration outcome study 15 years after valve replacement Hammermeister et al. reported showed that the all-cause mortality after aortic valve replacement was 13% lower in the mechanical valve group compared to bioprosthetic group, but this finding was not demonstrated in the mitral position. Biological valve structural failure occurred more frequent under age 65years (aortic 26% vs mitral 44%) compared to older subjects over 65years (aortic 9%: mitral 6%). The mechanical prosthesis across age groups showed no mechanical structural failure in both positions.(36)

In their study on the determinants of reoperation Ruel et al. showed that the mean ages for aortic, mitral and double valve replacement were 61.9 ± 13.6, 59.2 ± 12.4, 58.5±12.4 ($P < 0.05$), respectively; freedom from all-cause reoperation at 10, 15 and 20 years was 96.2, 94.1 and 93.8% for aortic mechanical valves, and 76.1, 61.4 and 59.6% for aortic bio-prosthetic valves. Similar data were reported for the mitral position: 96.4, 94.8 and 94.2% for mitral mechanical valves, and 79.8, 63.3 and 57.6% for mitral bio-prosthetic valves. This study demonstrated that structural valve deterioration accounted for the much higher rate of reoperation in the bioprosthetic group.(22)

In contrast, recent studies have shown that improvements in the design of the mechanical prosthesis, the material used, and better flow dynamics have led to the construction of mechanical heart valves that are more durable, easily implantable and associated with less thrombogenicity. The incidence of valve dysfunction due to intrinsic structural dysfunction is reported to be rare with the newer generation bi-leaflet mechanical valves.(13, 15) Whereas the early generation mechanical prosthesis had low but significant rate of stress or fatigue fracture this problem seems to be less in the newer generation more durable pyrolitic carbon leaflets.

v. Valve size:

In a report of 3014 valve operations performed from 1970-1997 Rizzoli et al. described 334 reoperations with 290 first operations, 27 second operations, 6 third operations and 1 fourth operation. This group showed that reoperations occurred in 71 patients with an aortic prosthesis less than 21mm and in 184 patients with a mitral prosthesis less than 27mm: 39% of reoperations were for prosthetic valve dehiscence, 13% for pannus in-growth and 8% of valve thrombosis. (25) In their multivariate analysis of factors predisposing to prosthetic thrombosis they identified the mitral and tricuspid position as incremental risk factors. A novel finding was the protective effect of larger size of prosthesis greater than 27mm diameter; this could be explained by more regular transvalvular flow and reduction

in the risk of the thrombosis in the mitral prosthesis. Large prosthetic size (>27mm), Sorin tilting disk prosthesis and bileaflet prostheses were associated with 67%, 69% and 83% risk reduction respectively. (24)

Patient-prosthesis mismatch (PPM) has been identified as a factor that may predispose to structural valve deterioration of the biological valve and to thrombosis of the mechanical prosthesis. Jamieson et al. have shown that a lower freedom from reoperation was associated with a larger body surface area (Hazard ratio ((HR))1.84 per meter square increase in BSA).(19) Ruel and colleagues have shown that a larger bioprosthesis size in the aortic position was associated with an increased freedom from reoperation for structural valve deterioration (HR 0.82 per increase of one valve size independent of BSA)(23). They also showed that the ratio of prosthesis size/BSA below the 10^{th} percentile valve of cohort studied was associated with HR 1.79. This relationship did not exist for the mitral bioprosthesis. They found that a higher patient-prosthesis mismatch in the aortic position resulted in more rapid structural valve deterioration of the bioprosthesis and necessitated earlier reoperative surgery. These data emphasize the importance of correct valve size at the first operation in preventing the sequelae associated with PPM.

vi. Blood stasis and systemic embolism

Early studies have shown that a low cardiac output state prior to surgical replacement for native valve disease is an important risk factor for systemic embolism.(41-43) Also, poor contractility of the left ventricle with slower circulation within the cavity contributes to stasis of the blood flow, predisposing to thrombosis formation. This is commonly observed in the infarcted anterolateral and apical walls of the left ventricle which become hypokinetic or akinetic with resultant thrombus formation in the apical segment. A similar mechanism is probably operative in patients with impaired left ventricular function who undergo mechanical prosthesis implantation.

Left atrial size and AF are two of the major contributing factors to the systemic thrombus formation and commonly associated with a large atrium in the mitral valvular disease. The left atrial appendage is the most common site of the thrombus formation due to the abnormal rhythm causing the stasis of the blood in the most peripheral part of the atrium. Szekely et al. have shown that one third of emboli occurred in the first month and two thirds occurred within 12 months of onset of AF. The incidence increases with age. (43, 44)

vii. HIV status

The effect of the Human Immunodeficiency Virus (HIV) in relation to the chronic inflammatory process and an increase in vascular thrombogenicity has recently been documented (41,42). Funderburg and Lederman et al. have shown that the HIV infected individuals have an increased risk of arterial and venous thromboembolism. They found that HIV infected patients who are receiving HAART had 2 to 10 fold greater risk of developing venous thrombosis and 2 fold greater risk of developing myocardial infarction.(41,42) Although the exact aetiology has not been identified. It has been hypothesized that chronic inflammation triggers the coagulation pathway and increases the viscosity of blood in these patients. There is also some evidence that HIV disease may contribute to anticoagulation failure, a factor that may contribute to prosthesis dysfunction.

Chong et al. evaluated the outcome of 22 patients with HIV infection who underwent primary cardiac valve replacement during 1990-1999. The mean age of the study population was 37.2 years with male dominance (15/22). Fifty percent (11/22) of the patient had mechanical valve, 7 had bioprostheses and 4 had homografts. Intravenous drug abuse was reported at 16/22 patients. Although they had a 94% survival at one month this reduced to 50% at 5 years. The poor late survival was due to progression of HIV disease and continuation of risk prone

behaviour.(23) This study did not document the treatment status of their patients and did not examine the mechanism of late death after valve replacement.

The Department of Health (DOH) in KwaZulu-Natal, South Africa has already implemented its High Active Anti-Retroviral Disease Treatment (HAART) program since 2012. Although surgery may be carried out successfully in HIV infected subjects (23) the effect of HAART rolls out program after valve replacement is yet to be determined.

Factors influencing surgical outcome of redo valve surgery

i. Perioperative risk and mortality

Early experiences have shown a high postoperative mortality rate in patients with obstructed mechanical prosthesis who present with the NYHA class IV symptoms. Improvements in medical technology, surgical techniques, anaesthesia and perioperative care as well as earlier detection of the thrombosed valve prostheses have had a significant impact on morbidity and improvement on the postoperative mortality.(37)

Locally, Deviri E and co-workers et al. have shown a mortality of 4% for patients with NYHA class I, II, III and a much higher mortality of 17.5% for patients presenting with NYHA class IV symptoms in 100 patients who underwent 106 valve replacements for obstructed mechanical cardiac prostheses at the University of Witwatersrand Hospital in Johannesburg between 1980 to 1989.(30) Taljaard and Doubell et al. also showed a very high mortality for patients presenting with NYHA class IV symptoms. They studied 32 patients who presented in 34 occasions with prosthetic valve obstruction at Tygerberg hospital between 1991-2001. Two thirds of their subjects presented with NYHA class IV symptoms and poor INR control and their operative outcome was poor with a high overall mortality of 64.7%.(34)

The rapidity of onset of valve dysfunction and perioperative risk factors also have a bearing on the outcome. Rizzoli et al. showed those subjects with prosthetic valve thrombosis who had severe perioperative risk factors had lower survival (49% at 30 days and 18% at 17 years) compared to subjects who had pannus ingrowth into the prosthetic valve with high perioperative risk factors (94% at 30 days and 74% at 17 years).(25) This can be explained by the acute haemodynamic instability associated with thrombosis of the mechanical prosthesis as opposed to a more insidious onset of leaflet malfunction due to pannus ingrowth that allows the left ventricle and the left atrium time to compensate for the change in haemodynamics.(31)

ii. Influence of LV function on outcome and survival

LV dysfunction may be present from at the time of the first valve implantation and is related to duration of the underlying native valve lesion prior to surgical correction. To what extent this affects prosthetic valve function has not been fully established. Morishita et al. analysed the long term results and risk factors for long term survival rate after valve re-replacement for the prosthetic valve dysfunction in subjects under 70 years. Subjects with an EF < 0.39 at the time of surgery had lower survival rate (83-98% at 1yr and 31-56% 5 yrs) compared to those with EF> 40% (96-98% at 1yr and 90-94% at 5yrs). This study identified higher NYHA class, male predominance and tricuspid regurgitation as factors that affected the hospital death and long term survival, while NYHA IV and lower left ventricular ejection were independent predictors of early in-hospital morbidity and mortality as well as long term survival.(31)

In Morishita et al's study 7 patients out of 107 with LV dysfunction had an EF that was less than 39%. This group had 83% one-year survival and a 5-year survival was 31%, as compared to a 96% and 90% survival respectively in the group with normal ventricular function. In this study advanced NYHA and lower EF were independent predictors of late deaths, having a negative effect on the long term survival.(45)35

Similarly, Taljaard and Doubell et al. showed a high early mortality was associated with high NYHA class and LV dysfunction at Tygerberg hospital. Those patients who presented in cardiogenic shock had 100% mortality, and only 4 out of 25 patients who were severely symptomatic (NYHA III and IV) survived.(34) Of the 20 who died 4 deaths occurred on the surgical table for emergency surgery and 11 had an early in-hospital mortality; Ten of the 11 patients who presented with NYHA class IV dyspnoea succumbed. Similarly, in Deviri et al's study, 11 out of 63 patients (17.5%) who had NYHA class IV symptoms and underwent emergency redo valve replacement surgery demised in the perioperative phase.(30)

Rationale for this study

Inkosi Albert Luthuli Central Hospital based in the province of KwaZulu-Natal serves a population with an unique set of circumstances with regard to socio-economic status, distribution of healthcare service, and the large burden of communicable and non-communicable disease. These factors may have a significant impact on patients undergoing valve surgery as well as the outcome of patients undergoing reoperations for valve dysfunction. Furthermore, the choice of mechanical and biological valves has changed recently based on availability and cost. The effects of

all these factors, including the retroviral status of subjects who are presented for cardiac valve replacement surgery have not been evaluated. What potential effect the retroviral status has on coagulability and valve function has not been studied. This study plans to assess the clinical profile and factors that determine the surgical outcome of those patients undergoing reoperation for prosthetic valve dysfunction.

Chapter 3: Aims, Materials and Methods

Aims

To evaluate the pre, intra and postoperative data of all the patients who underwent redo valve replacement for cardiac prosthetic valve dysfunction.

Hypothesis

Re-operative valve surgery is associated with considerable morbidity and mortality.

Objectives

1. To describe the demographic profile and clinical presentation of patients with prosthetic valve dysfunction.

2. To determine the possible mechanisms and aetiology of prosthetic valve dysfunction.

3. To determine whether human immunodeficiency virus infection is associated with prosthetic valve dysfunction

4. To determine the immediate surgical outcome and early in-hospital mortality at a large referral centre.

Materials and methods

A retrospective analysis of the perioperative and follow-up data of patients who underwent redo cardiac valve replacement for structural valve dysfunction between January 2005 to December 2014 at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa was undertaken. Excluded from the study were all subjects who underwent cardiothoracic surgery for nonvalvular reasons, i.e. coronary artery bypass surgery. Patients were identified using the Speedminer software program. Speedminer is a Data Warehouse and Business Performance Management software package, used by IALCH since 2006 to manage, process and categorise the data collected on its Medicom database. The file of each of patient who underwent redo cardiac prosthetic valve replacement for structural valve dysfunction was accessed and data were extracted on age, gender, potential risk factors for valve thrombosis, symptomatology, investigations including INR status as well as follow up decisions. Investigations were recorded together with subsequent admissions and reviewed diagnoses during follow up.

The study group comprised all those who underwent redo valve surgery for structural mechanical and biological valve dysfunction. Valve dysfunction requiring surgery was defined as any impairment in valve function leading to prosthetic valve stenosis/blockage or regurgitation. Patients referred from a peripheral hospital with

suspected valve dysfunction (history of previous heart valve replacement and the clinical features of cardiac failure, dyspnoea, haemoptysis, pulmonary oedema and a low cardiac output state) were evaluated by the cardiologist at IALCH and valve dysfunction confirmed on transthoracic echocardiography and/or fluoroscopic screening. The clinical presentation, transthoracic echocardiogram, fluoroscopic screening and blood investigations were reviewed by the cardiologist and cardiothoracic surgeon prior to surgery.

Surgical Procedures

Surgery was performed via a sternal re-entry with division of retrosternal mediastinal adhesions to expose the pericardium and free the heart from adhesions due to previous surgery. Cardio-pulmonary bypass was instituted and systemic hypothermia induced with cardioplegic arrest using blood or crystalloid solution employed for myocardial protection. Once the heart was mobilised the dysfunctional prosthesis was explanted with preservation of the annulus, and tissue submitted for culture to guide antibiotic therapy in suspected infective endocarditis. The size of the annulus was measured and the new valve implanted with pledgeted Ethibond sutures. The patient's presenting condition, duration of cardiopulmonary bypass and cross clamp time, as well as the postoperative use of inotropic support were recorded as potential contributors to postoperative morbidity and mortality.

Immediate outcome was analysed by evaluating data in the first 30 days for postoperative morbidity and mortality, and thereafter at the 6 weeks and six month follow-up visits postoperatively. Left ventricular function as assessed by ejection fraction and cardiac chambers were compared pre and postoperatively to determine whether any change in ventricular function correlated with clinical symptomatology and outcome.

Statistical analysis

Statistical Package for the Social Sciences (SPSS version 18.0) was used for analysis of data and a 95% level of confidence estimated; a global significance level of $\dot{\alpha}$ = 5% was chosen.

Descriptive statistics (expressed as the mean +/- standard deviation) were used for the following parameters: age, gender, functional class of dyspnoea, comorbidities, previous native valve disease, previous prosthesis implanted, duration between previous surgery to the redo prosthesis replacement, transthoracic echocardiogram parameters (ejection fraction, end diastolic dimension, end systolic dimension, size of left atrium and aortic root, pulmonary systolic pressure) and blood biochemistry (pre-op INR, full blood count and serum electrolytes).

Odds ratios were calculated to evaluate the strength of associations between the demographics, clinical presentation, risk factors and valve dysfunction. The chi-squared and Fishers exact test was used to compare categorical variables and the Student's unpaired t-test was used for continuous variables, to assess the significance of any difference in risk between the two groups (those with mechanical and biological valves). A p-value <0.05 was regarded as significant. Binary logistic regression analysis was used to control for confounding factors when assessing the independent relationships between risk factors for valve thrombosis and the outcome variable (valve dysfunction). Multivariate analysis was used to assess the effect of clinical criteria and other risk factors on the likelihood of prosthetic malfunction. Actuarial survival curves were calculated by the Kaplan-Meier failure estimate method, and the log-rank test was used to compare subgroups. A p-Value of less than 0.05 was considered significant.

Chapter 4: Results

Number of Valve replacements

During the ten-year period (2005 to 2014) 2618 valve replacement operations were performed and 2618 valves implanted into aortic, mitral and tricuspid positions. (Table 2) There were 165 biological valves implanted and the remainder were mechanical valves as follows: Cryolife On-X 2151, Medtronic Mechanical 177 (Advantage 150, ATS 27), Saint Jude 124 and Carbomedics Sorin 1. A total of 128 reoperations (4.9% of 2618 replacement operation) were performed in 113 patients during this period with an average number of 12.8 reoperations per year. The highest number of reoperations (22) were performed in 2014. Of the 128 reoperations 94 (73.43%) had one reoperation; 23 patients had two; 9 patients had three and 2 had four operations during the ten year period.

Table 3. Valve replacement surgery during 2005-2014

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
MVR*	124	148	113	127	116	85	119	114	97	94
AVR*	31	36	31	24	31	29	38	55	46	44
TVR*	0	0	0	0	1	0	0	0	0	2
DVR*	38	49	58	57	36	44	44	44	47	57
OMV*	0	0	1	0	0	0	0	0	0	0
Tricuspid valve replacement	0	0	1	0	0	1	0	0	0	1
CABG+MVR*	5	8	8	5	5	4	5	4	1	2
CABG+AVR*	1	8	5	6	5	2	9	10	6	7
CABG+DVR*	1	1	1	2	0	2	1	0	0	0
Modified Bentall	1	3	5	3	3	3	6	4	2	4
operations	201	253	223	226	199	172	223	231	199	215
valves implanted	240	303	281	283	235	216	267	275	246	272
reoperations	14	15	9	15	7	8	13	18	7	22

*** Abbreviation for table 2: MVR=Mitral Valve Replacement, AVR=Aortic Valve Replacement, DVR=Double Valve Replacement (AVR+MVR), TVR=Triple Valve Replacement (AVR+MVR+Tricuspid Valve replacement), OMV=Open Mitral Valvotomy, CABG=Coronary Artery Bypass Grafts.**

Demographic data and premorbid disease profile

The demographic data of the 113 patients at the time of first presentation for reoperation at IALCH are shown in table 5. The most frequent premorbid native valve morphology prior to the first valve operation was mitral valve disease (62.5%), followed by left-sided double valve disease (23.44%) and aortic valve disease (11.72%) (table 4). Over a quarter (26.19%) had redo surgery within 2 years of previous valve surgery, with the remaining patients presenting at variable periods thereafter.

Table 4: Premorbid native valve disease and previous surgery

Previous native valvular disease	**Reop=128**	%
Aortic stenosis (AS) (SAM)	9	7.03
Aortic regurgitation (AR)(sinus of Valsalva)	8	6.25
Mitral stenosis (MS)	39	30.47
Mitral regurgitation (MR)(+ASD)	41	32.03
Double valve disease (Aortic + Mitral)	30	23.44
Tricuspid regurgitation	1	0.78
Interval between previous and current operation		
0-2 years	33	26.19
2-10 years	59	38.89
>10 years	44	34.92

The overall mean age at reoperation was 35.59 (SD±16.66) years with the 64.6% of the patients being under the age of 40 years (table 5). The median age for the

mechanical valve group was 30 years (mean 31.4, 95% CI 28.7-34) and the median for biological group was 54 years (mean 52.8, 95% CI 44.9-60.6). Most reoperations were performed in Black African subjects (72.6%) and three quarters of the subjects were female. Fifteen subjects (13.3%) were HIV infected and all received mechanical prosthetic valves: thirteen subjects were female and two were male. Anticoagulation was poorly maintained (INR<2) in 61.81% of patients.

Table 5. Demographic data

Characteristic	n=113	%
Age		
<=18	20	17.7
19-30	29	25.7
31-40	24	21.2
41-50	14	12.4
>50	26	23
Race		
Black	82	72.6
Mixed Ancestry	3	2.6
Indian	19	16.8
Caucasian	9	8.0
Gender		
Female	74	65.5
Male	39	34%
HIV status		
Negative	98	86.7
Positive	15	13.3

Clinical presentation at reoperation

High grade dyspnoea was the presenting feature in 72 subjects (56.24%) (Table 6): 34.37% were NYHA class III and 20.31% class IV. Two subjects (1.56%) arrived at the referral hospital intubated. Low grade dyspnoea (NYHA class I and II) was present in 56 out of 128 (43.75%) subjects. Ninety-eight subjects (76.6%) were in sinus rhythm, most of the remainder (18.6%) being in AF.

Clinical presenting features of an obstructed valve (flash pulmonary oedema with or without clinically audible prosthetic valve clicks) were found in the clinical records of 44 of the 128 (34.4%) reoperations. In seventeen instances subjects presented with acute onset of cardiac failure and in eleven the presentation was characterised by signs of low cardiac output state: syncope and pre-syncope (3.13%), cardiogenic shock (4.69%) and total circulatory arrest (0.78%). There were no clinical indicators of an obstructed valve in the remaining 56 (43,8%) records. These patients presented with a change in effort tolerance (n=38) while the remaining 18 subjects were complete asymptomatic; valve obstruction in these cases was detected during the routine evaluation at the Department of Cardiology follow-up clinic.

Table 6. Clinical features prior to reoperation

Characteristic	Reop=128	%
NYHA Class		
I	11	8.59
II	45	35.16
III	44	34.37
IV	26	20.32
IV-intubated	2	1.56
Rhythm		
Sinus rhythm	98	76.56
Atrial fibrillation	22	17.19
Atrial flutter	3	2.34
Heart block	5	3.91
Clinical presentation		
Asymptomatic	18	14.06
Pulmonary oedema	44	34.38
Change in effort tolerance (NYHA I-III)	38	29.69
Acute heart failure	17	13.28
Syncope and pre-syncope	4	3.13
Total circulatory arrest	1	0.78
Cardiogenic shock	6	4.68
Associated conditions		
Chest pain	9	
Sternal wound infection	1	
Recurrent anaemia	2	
Infective endocarditis	15	
Pregnancy	9	

Signs of prosthetic valve endocarditis were present in 15 cases (11.72%), in whom two weeks of IV antibiotics were administered prior to their surgery. Nine subjects experienced anginal type chest pain. Nine subjects were pregnant all of whom had sub-therapeutic anticoagulation levels with INR<2 (range 0.68-1.9) with valve obstruction and received mechanical valves during gestation from 12 to 32 weeks. The mean haemoglobin was 11.84g/dl (range 6.6 to 16.8 g/dl); two patients had haemolytic anaemia. The serum creatinine was >120 µg/l in 17 patients (13.28%).

Table 7: INR levels in patients with obstructed mechanical prostheses

International Normalized Ratio (INR)	N=110	%	p value
0-2	68	61.81	
2-4	31	28.19	
>4	11	1	<0.00001
Mean INR (SD)	2.36	2.39	
Confidence Level (95.0%)	0.43		

The level of anticoagulation in subjects with malfunctioning mechanical prostheses was poor. In almost two thirds of instances with obstructed prostheses levels of

anticoagulation achieved were poor (INR<2.0); 28.19% were within the therapeutic ranges of 2-4 and 1% >4.0 ($p<0.0001$) (Table 7).

Diagnosis of valve dysfunction

In over half the patients, (71/128; 55.47%) valve dysfunction was detected transthoracic echocardiography and confirmed fluoroscopically. In the remaining patients, the diagnosis was made either at fluoroscopy (11.72%) or on echocardiography (32.81%). Echocardiography was performed in 113/128 instances prior to redo cardiac valve surgery. The EF was mildly impaired (EF 40-49%) in 24.78% and severely impaired (EF<40%) in 8 (7.08%) patients. The mean left atrial size was 52.28mm and mean pulmonary systolic pressure 45mmHg (range 26-104) preoperatively, and fell to 49.4mm and 40 mmHg respectively at the six-week follow up visit.

Table 8: Comparison of pre and postoperative echocardiographic findings

Echocardiogram data	Preoperative		Postoperative	
EF	**N=113**	**%**	**N=92**	**%**
>=60	30	26.55	19	20.65
50-59	47	41.59	41	44.57
40-49	28	24.78	23	25
<40	8	7.08	9	9.78
LVEDD (mm)				
Mean (SD)	49.87 (10.40)		49.42 (12.82)	
Range	27 - 80		34 - 96	
LVESD (mm)				
Mean (SD) mm	34.55 (8.20)		32.29 (8. 67)	
Range (mm)	20-78		22 - 71	
Left atrial size mm				
Mean (SD)	52.58 (14.95)		49.41(12.90)	
Range	25 - 120		33- 101	
Aortic root size (mm)				
Mean (SD)	28.16 (6.31)		29.15 (7.72)	
Range	14 - 56		18 -56	
PAS (mmHg				
Mean (SD)	45.08 (13.25)		40.15 (12.13)	
Range	23-104		21 - 78	

Surgical procedures

The surgical procedures performed are shown in table 9. Emergency surgery was performed in 70/128 reoperations (54%); elective reoperation was performed for the remaining 58 events. The most common redo valve operations were performed in mitral position (62.5%), followed by the aortic (21.09%) and redo double valve replacement (14.06%). Most valve prostheses were replaced with mechanical valves (78.90%) and 19.54% had biological cardiac prostheses implanted. Two patients had suture repair of the para-annular leaks due to misplacement of the annular sutures at the first operation.

Seventeen reoperations were performed and mechanical prostheses implanted in 15 (13.27%) patients who were HIV infected. Eleven presented with high grade dyspnoea (NYHA III-IV) at a mean age 29.5 year. Seven patients were on HAART and 8 patients were not. Anticoagulation was poorly controlled (INR<2) in 15/17 (88.24%). Thirteen underwent emergency surgery for stuck mechanical prostheses. The operative mortality included one CVA, one peripheral vasculopathy related retroviral disease and two had termination of pregnancy due to intra-uterine death; the rest made an uneventful recovery.

The bioprosthetic valve excised at the redo cardiac prosthetic valve replacement comprised 14.29% of the total number of reoperations. Overall the Carpentier-Edward (mean surgical interval 17.5 years) and Medtronic Hancock (mean surgical interval 10.5 years) were the commonest bioprosthetic valves replaced (11.91%). (Table 10) The three most common mechanical valves replaced were the CryoLife On-X, St. Jude and Carbomedics Sorin which accounted for 30.16%, 29,37% and 20,64% of the explanted mechanical valves respectively.

The surgical interval to reoperation showed that biological valves had a much longer interval to reoperation compared to the mechanical valve which averaged between 10-17.5 years to reoperation due to poor anticoagulation. (Fig 5) The lowest interval (1 year) to reoperation was with the CryoLife On-X mechanical valve and highest was the Bjork-Shiley mechanical (40 years). The St. Jude and the Carbomedics Sorin had similar intervals to reoperation (9.5 and 8 years respectively). Analysis of the INR showed poor anticoagulation for all three explanted valves (Cryolife ON-X, St. Jude and Carbomedics Sorin) with levels of INR<2 in almost 60%.

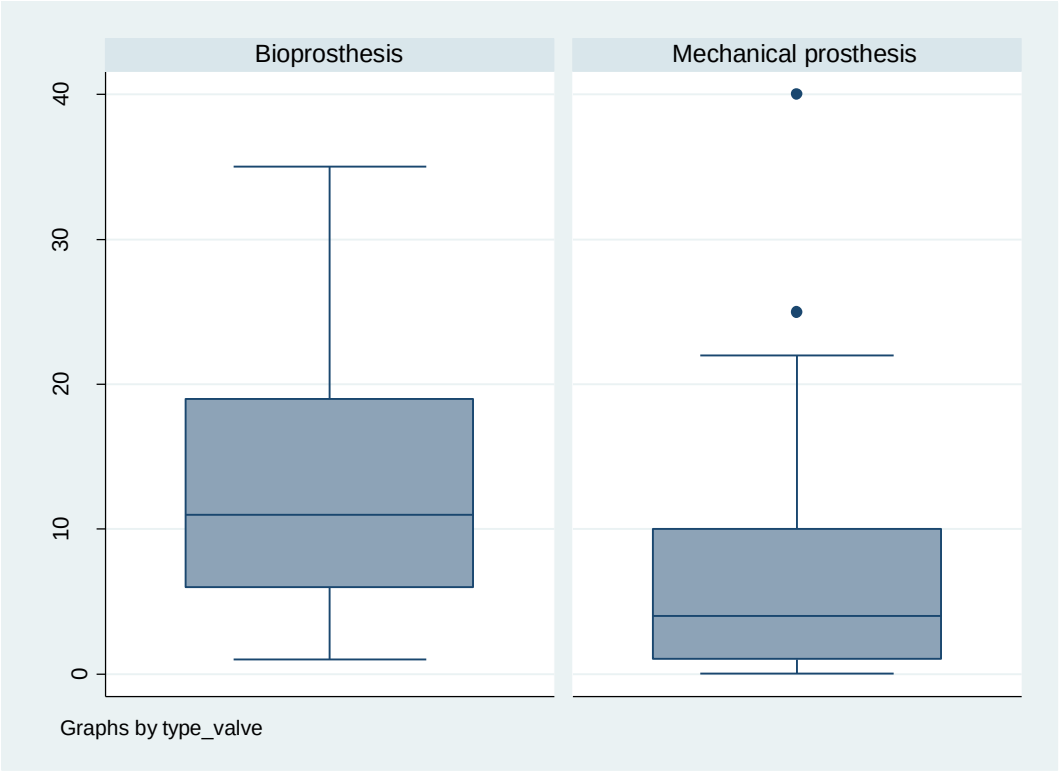

Figure 5. Time to reoperation: bioprosthesis had a longer interval to reoperation compared to the mechanical prosthesis.

Table 9: Operative procedures

Type of surgery	N=128	%
Elective	58	45.31
Emergency	70	54.69
New prosthesis implanted	**N=126**	
Biological prosthesis	25	19.54
Mechanical prosthesis	101	78.90
Surgical Procedure		
Redo AVR*	27	21.09
Redo MVR	80*	62.50
Mitral prosthetic repair for leaks	2	1.56
Redo tricuspid valve replacement	1	0.78
Redo DVR	18**	14.06

*Three subjects underwent additional procedures: tricuspid annuloplasty (1), CABG (1) and repair of aortic false aneurysm 91). ** Five subjects underwent additional procedures: Subaortic membrane resection (1), CABG (1) and aortic root enlargement (3).

Table 10: Valve type and years in surgical interval to redo cardiac valve surgery

Explanted Valve	N=126	Reoperation (%)	Time (*p50) to reoperation (yr)
Bioprosthesis (18)		14.29%	
Glycar bioprosthesis	1	0.79	8
Carpentier-Edwards	7	5.56	17.5
Medtronic Hancock	8	6.35	10.5
Homograft	1	0.79	35
Edward Perimount	1	0.79	2
Mechanical (108)		85.71%	
Carbomedics Sorin	26	20.64	8
St. Jude	37	29.37	9.5
Cryolife On-X	38	30.16	1
Medtronic Hall	3	2.38	2
Medtronic Advantage	1	0.79	5
Bjork-Shiley	1	0.79	40
Medtronic ATS	2	1.59	2.67

*p50= median years of surgical interval to reoperation p =0.0027

The diagnosis of an obstructed mechanical valve was confirmed at operation and the mechanism of obstruction identified intraoperatively (table 12). In the Cryolife ON-X group 30/38 patients had a thrombosed valve with a median surgical interval of one year whereas the St. Jude group had 11/37 patients with median surgical

interval of 9.5 years and Carbomedics Sorin group had 13/26 patients with median surgical interval of 8 years (table 10). The St. Jude and Carbomedics Sorin groups both had higher median surgical interval since valve deterioration had a more insidious progression due to pannus ingrowth (see below).

Table 11: Characteristic of three major mechanical cardiac prosthesis valve explanted

	ON-X (n=38)	%	St. Jude (n=37)	%	Sorin (n=26)	%
INR Level						
INR <2	24	63.16	22	59.46	16	61.54
INR>2	14	36.84	15	40.54	8	38.46
Valve pathology						
Thrombosed valve (clot + organized thrombus)	30	78.95	11	29.73	13	50.00
Pannus ingrowth	1	2.63	14	37.84	7	26.92
Mixed (pannus+thrombus)	1	2.63	5	13.51	6	23.08
Prosthetic endocarditis	2	5.26	4	10.81	0	0
Paraprosthetic leaks	4	10.53	3	8.11	0	0

Operative findings

The mechanistic aetiology of valve dysfunction is described in table 12. Obstruction by blood clot affecting a single leaflet or both leaflets of mechanical prostheses was the predominant finding (75/128) and categorised as fresh clot (34/128), organized

thrombus and mixture of pannus (20/128), fresh clot and organized thrombus (21/128). Isolated pannus in-growth causing single mechanical leaflet dysfunction (19/128) and infective endocarditis (annular dehiscence, vegetations and para-prosthetic leaks and root abscess) (13/128) were the other two causes of mechanical valve dysfunction. In those who had biological prosthetic valves the main findings were leaflet perforation, calcification and para-valvular leaks. In two cases misplacement of the annular suture resulted in a para-valvular leak.

Table 12: Operative findings

Mechanical prosthesis	N=128	%
Obstruction of single leaflet with fresh clots	25	19.53
Obstruction of single leaflet with organized thrombus	15	11.72
Obstruction of single leaflet with pannus in-growth	19	14.84
Obstruction of single leaflet with both fresh clots, organized thrombus and pannus in-growth	12	9.37
Paravalvular leak due to suture placement	2	1.56
Obstruction of both leaflets with fresh clots	9	7.03
Obstruction of both leaflets with organized thrombus	5	3.91
Obstruction of both leaflets with fresh clots, organized thrombus and pannus in-growth	8	6.25
Obstruction of single leaflet with infective endocarditis and para-prosthetic leaks	3	2.34
Aortic root abscess	1	0.78
Infective endocarditis with vegetations and para-prosthetic leak	9	7.03
Stitch leaks	2	1.56
Biological Prosthesis		
Calcified bioprosthesis and perforation of leaflets	1	0.78
Calcified bioprosthesis with para-prosthetic leaks	12	9.38
Aortic root abscess	1	0.78
Annular dehiscence and para-prosthetic leak	4	3.12

Operative morbidity and postoperative complications

The mean aortic cross clamp time was 107 minutes (range 36-360 minutes). The total duration of bypass time ranged was 158 minutes (range 74-465 minutes). Most patients (74%) had Crystalloid St. Thomas II cardioplegic solution to establish cardiac electro-mechanical arrest and 32 (25%) had cold blood cardioplegic solution. The remaining patient had right atrial exclusion with snaring of both vena cavae (without cardioplegic arrest) to replace the tricuspid prosthesis. Systemic corporeal cooling was employed as part of the myocardial protection strategy but the deep hypothermic cardiac arrest was used in one case with prosthetic infective endocarditis and an aortic root false aneurysm requiring repair, as well as debridement and reconstruction of the mitral annulus.

Table 13 shows that the number of patients requiring inotropic support. Low dose inotropic support was employed in 51.55% of the subjects post operatively and the remainder received high dose adrenaline with/without an additional inotrope. Three patients with postoperative severe left ventricular dysfunction required support with the Intra-Aortic Balloon Pump (IABP); all survived the surgery and were discharged home.

Table 13: Factors influencing the Operative morbidity

Duration of aortic cross clamp time (minutes)		
Mean (SD)		**107 (51)**
Range		36 – 360
Duration of bypass time (minutes)		
Mean (SD)		158 (65)
Range		74 – 465
Type of cardioplegia	**N=128**	**%**
No cardioplegia used	1	0.78
Blood cardioplegia	32	25.00
Crystalloid St. Thomas II solution	95	74.22
Systemic corporeal cooling (degrees Celsius)		
Nasal temperature probe		
Mean (SD)		29.14 (2.81)
Range		16.1 –35.8
Bladder temperature probe		
Mean (SD)		29.45 (2.40)
Range		18.7 – 35.4
Postoperative inotropic requirement	**N=128**	**%**
Single agent at low dose (adrenaline <0.2 mic/kg/min, dobutamine <5mic/kg/min and dopamine <5mic/kg/min)	66	51.55
Adrenaline at high dose (>0.2mic/kg/min)	30	23.44
Adrenaline at low dose with additional agent	5	3.91
Adrenaline at high dose with additional agent	7	5.47
Adrenaline at high dose with milrinone	20	15.63
Postoperative Intra-Aortic Balloon pump		
No	125	97.66
Yes	3	2.34

Early in-hospital mortality total deaths

The postoperative mortality was 11.50% (13/113); most deaths occurred in the early postoperative phase in the ICU: one patient demised on the surgical table; 11 demised in intensive care unit and one sudden death occurred in the ward after 33 days. Mortality was higher after the second and third reoperations. (Fig 6A and 6B) (table 14)

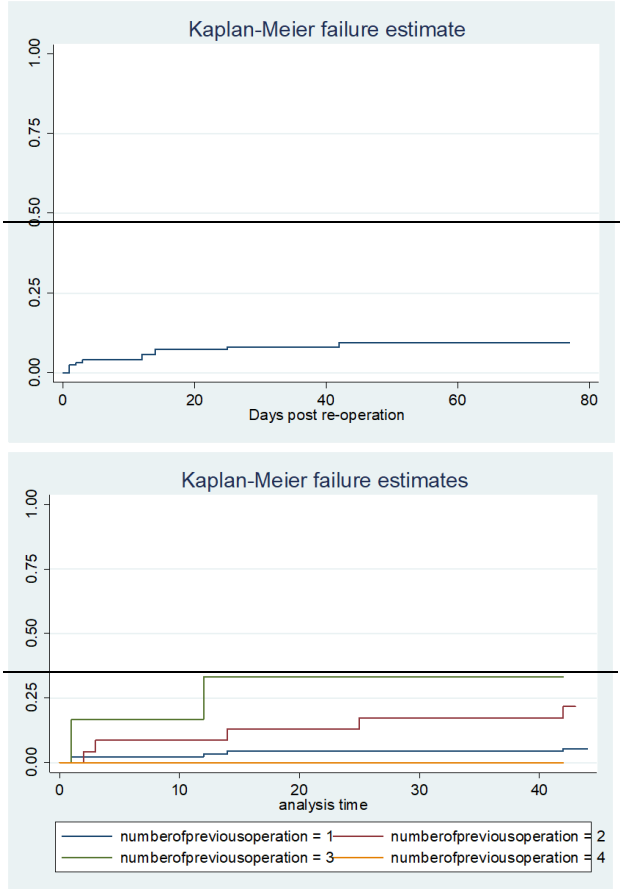

Figure 6A (top) and 6B (below)

The top Kaplan-Meier "failure estimate" graph showed most of the surgical mortality occurred in the early postoperative phase. In the bottom graph early mortality was higher after each subsequent reoperation after the first reoperation.

The median stay in ICU was 4 days (IQR 3-5) and the mean duration of ward stay was 12 days (IQR 9-19.5). (table 14) Of the 12 patients who died early, 8 had cold crystalloid cardioplegic solution and the remaining 4 had cold blood cardioplegic solution as maintenance fluid for myocardial preservation.

Table 14: Postoperative mortality and ICU/ward stay

Early postoperative death (intra-op to ICU)	N=113	%
Total death	13	11.50
1st reoperation (n=94)	7*	6.19
2nd-4th reoperation (n=34)	6*	5.31
Survivors	100	88.50
Duration of ICU stay	**Days**	
Mean (SD)	4.53 (3.34)	
Median (IQR)	4 (3-5)	
Range	1 – 25	
Duration of ward stay	**Days**	
Mean (SD)	16.03 (12.93)	
Median (IQR)	12 (9-19.5)	
Range	3 - 95	

Three factors emerged as significant predictors for postoperative death. These were: cross clamp time greater than 120 minutes (HR 4.84, p=0.024), bypass time more than 3.5 hours (HR 5.58, p=0.024) and the third re-operation (HR 4.26, p=0.022).

(table 15) Ejection fraction did not have a significant impact on postoperative mortality.

Table 15: Factors influencing the surgical outcome

	Hazard ratio	P > | z |	[95% Confidence interval]	
EF Category				
>50	1.511723	0.621	.2932841	7.792129
40-49	2.129827	0.383	.3900921	11.62844
<40	6.22e-15	1.000	0.00	-
Cross clamp time				
<90 minutes	1.01069	0.004	1.003305	1.01813
91-120 minutes	2.106925	0.414	.3520514	12.60933
>120 minutes	4.844377	0.022	1.252295	18.73999
Bypass time				
2.5-3.5 hrs	3.51392	0.085	.8397428	14.70407
>3.5 hrs	5.581668	0.024	1.248538	24.9532
Number of previous operation				
2	4.268935	0.022	1.235402	14.75131
3	5.343637	0.045	1.035719	27.56971
4	1.89e-15	1.000	0	

Postoperatively there were 35/128 complications documented (table 14). The commonest postoperative complication was a low cardiac output (LCOS) with/ without pulmonary oedema or renal failure. Thirteen of the thirty five patients with

LCOS demised (table16) The combined postoperative morbidity and mortality totalled 30.97% (35/113).

Table 16: Immediate postoperative complications

Immediate postoperative complications n=113	survived	demised
LCOS *	5	7*
LCOS, CVA	1	1
LCOS, CVA, renal failure	2	0
LCOS, ARDS, renal failure	0	3
LCOS, pulmonary oedema	4	0
LCOS, Renal failure	1	0
LCOS, postoperative bleeding	0	1
Massive haematemesis	0	1
Systemic embolism with threatened limb **	2 **	0
CVA	1	0
Intra-uterine death	4	0
Compartment syndrome due to drip infiltration	1	0
Emotional instability	1	0
% of total redo cardiac surgery population (n=113)	19.45%	11.50%

Low Cardiac Output Status (LCOS), Cerebral Vascular Accident (CVA),

* on-table death due to LCOS; ** systemic embolism associated with retroviral disease

Early (6week) follow –up

At the initial 6 weeks 9 patients did not return to the cardiology clinic follow up, yielding a follow-up rate of 91%. Table 17 demonstrates the comparison between pre and postoperative NYHA class. Effort tolerance improved from 91.4% (NYHA II-IV) by one or more classes to 96.23% (NYHA class I-II) postoperatively. One patient remained in intractable cardiac failure postoperatively with an EF of 20%.

Table 17: Pre and Postoperative functional class at 6 weeks follow up (NYHA)

NYHA class	Pre-op n=128	%	% hospital mortality	Post-op 6 week n=106	%
I	11	8.59	0	67	63.21
II	45	35.16	8.89	35	33.02
III	44	34.37	13.64	3	2.83
III-IV	28	21.87	10.71	1	0.94

Long term follow up

The surviving 100 patients (n=113 -13 deaths) had a total follow-up of 272.1 patient years over 10 years duration: 53 patients had a complete follow-up (53%), 29 had incomplete follow-up (range 6 months to 8 years) and 18 patients were lost to follow up. Five out of 18 were contacted telephonically and were well. The remaining 13 subjects were not contactable.

Chapter 5: Discussion

1. Reoperation rate and early mortality

This study shows that a 4.9% rate of redo valve surgery for 2618 primary cardiac valve operations over a ten year period. There were 128 events of redo cardiac valvular prosthetic replacement performed in 113 patients. The international data show reoperation rates that range from 12.9-22.48%. Tyers et al. (32) had a reoperation rate of 12.9% (708/5499) over 17 years in Canada and Morishita (46) reported 16% (231/1405) rate from Japan. Higher rates were reported by Rizzoli et al. (26) (1093/4863 22.48%) over a 25 year duration and by Luciani et al. (28) (316/1508, 20.95%) over a six year duration. A probable explanation for our low redo rate is that it does not take into account those patients who did not present to hospital in time for redo surgery. We do not have reoperation rates from the two South African studies in Johannesburg (35) and Stellenbosch (36) for comparison.

Factors influencing operative mortality in reoperations

In our study we have shown an 11.5% operative mortality for reoperations which is much higher than the 3.8% (11/290) and 30 month follow-up mortality of 9.3% reported by Luciani et al. in 2006. (28) Our mortality of 11.50% is in keeping with data mentioned from recent studies. It is similar to the 11% mortality reported by

Rizzoli et al. (25) and Tyers et al. (32) and to the 12.3 % reported in a South African study by Deviri from Johannesburg. Tang et al. from Toronto General Hospital, Canada have also reported an overall hospital mortality rate of 9.4% in 2007 and showed a 5.4% mortality in NYHA class I-III, rising to 14% in NYHA IV. (35) Our corresponding mortality data was 10% for NYHA class I-III and 10.71% for NYHA IV.

Similar to the study by Deviri et al. over half of our patients presented with NYHA III-IV dyspnoea and this was associated with eight of the 13 deaths in our study. Taljaard et al. reported only 4 survivors out of 25 patients who presented with NYHA III and IV.(34) Functional class on presenting to hospital at the time of cardiac prosthesis dysfunction has been shown to be one of the predictors of postoperative mortality. In a Cox proportional hazards model Luciani et al. showed that high grade dyspnoea (class NYHA III or IV) was associated with 8.39 fold higher odds ratio of death (95% CI 3.44-10.27, p=0.016).(28) Luciani has also shown that poor left ventricular function (EF<40%) is a predictor of operative mortality (OR 3.21 95% CI 1.48, 7.02, p=0.0079).(28) Although severe left ventricular dysfunction (LVEF<0.4) has been identified as one of the predictors for postoperative mortality (46) we did not show this in our study, probably because only 7.0% of our subjects had markedly depressed left ventricular function. The twelve early in-hospital deaths in our study all had an EF>0.4.

Although over half of our patients underwent emergency surgery this was not associated with increased morbidity or a higher postoperative mortality. The high rate of mitral valve redo surgery (62.50%) compared to aortic valve (21.09%) and double valve redo operations (14.70%) in our study may in part be explained by the high rate of rheumatic valve disease in South Africa with resultant marked atrial enlargement compared to degenerative disease in developed countries.

Similar to Tyres et al. we have shown that our mortality is related to number of reoperations.(32) This may be related to increasing technical difficulty associated with the number of reoperations as well as the clinical condition of the patient at presentation. In our study 15/128 (11.72%) redo valve replacements were performed for valve dysfunction due to prosthetic infective endocarditis yielding an incidence of cardiac prosthetic endocarditis of approximately 0.013% per patient-year. Twelve of our patients demised from a LCOS postoperatively and five with diagnosis of preoperative prosthetic endocarditis succumbed to early in-hospital deaths, yielding a 30.77% (5/13) early in-hospital mortality attributed to infective endocarditis. These patients presented with haemodynamic instability, large vegetations (>10mm) on the valve, unstable prostheses due to annular dehiscence and persistent septicaemia.

Cardiac prosthetic endocarditis carries a high mortality rate ranging from 30 to 50% preoperatively as well as a three-fold higher postoperative mortality.(14, 19, 20, 52) (14, 15, 20, 45, 46) as well as a three-fold higher postoperative mortality. (29, 25) Infection of the prosthetic valve acts as a constant source of systemic infection which activates the inflammatory pathway continuously, leading eventually to prosthetic annular dehiscence with severe regurgitation impairment of myocardial contractility. Reoperative surgery for infective endocarditis is associated with a high mortality (24, 25, 35, 40) ranging from 17% -48%.

The Clinical profile of patients undergoing redo valve surgery

The majority (72.6%) of our patients undergoing redo valve surgery were black African, he majority of whom were female, non-pregnant and HIV negative. Almost two thirds of the patients were under the age of 40 years. None of these subjects had a history of diabetes. Most reoperations were performed in subjects with mechanical valves implanted for previous native mitral valve disease for which they received either mitral or double (aortic+mitral) valve replacement.

Nine females were pregnant at the time of redo cardiac surgery. Two patients had DVR and 7 patients had MVR and their age ranged from 17 to 30 years. The gestational age ranged from 12 to 32/40 weeks. All of the patients had their INR<2 (ranges 0.68-1.9) which accounted for mechanical valve thrombosis in 8 patients. This implies poor obstetric planning and inadequate anticoagulation predisposing to mechanical valve thrombosis. The remaining patient had a biological valve (Glycar bioprosthesis) implanted at age 28 and she returned at age 36 for reoperative valve surgery due to structural valve deterioration of biological prosthesis.

Asymptomatic prosthetic dysfunction

Features suggesting an obstructed valve were present in 34.4% of subjects and another 20 % presented either in acute heart failure or in a LCOS. Over 40% of presentations had non-acute low grade dyspnoea or no symptoms indicating the importance of a high index of suspicion and careful follow of these subjects to detect early prosthesis dysfunction. An important finding of this study was the finding of asymptomatic valve dysfunction in 18 subjects (16% of reoperations) detected at the routine transthoracic echocardiographic evaluation during follow up. This is much higher than the 8% reported by Taljaard (34) and by Deviri (30) in a study sample and a clinical setting that was similar to ours. Our higher detection

rate could be attributed to continued long term surveillance of subjects at our tertiary referral centre. Of the 18 asymptomatic patients one had a biological valve and 17 patients had mechanical prostheses. Fourteen of the 17 patients had sub-therapeutic INR levels < 2. Urgent valve replacement surgery was performed in 5/18 patients and rest underwent elective surgery. Although there was no postoperative mortality, operative morbidities included postoperative pulmonary oedema (n=2), intra-uterine foetal death (n=1) and LCOS with CVA and renal failure (n=1).

Factors predisposing to mechanical Prosthetic valve dysfunction

Non-structural valve dysfunction was due to the presence of thrombus, tissue in-growth (pannus) or vegetations ± annular dehiscence arising from prosthetic endocarditis. Of these mechanisms, the single most important factor that contributed to mechanical valve dysfunction was poor adherence to the anticoagulation protocol (in order to maintain therapeutic INR levels) leading to mechanical valve thrombosis. In our study almost two thirds of patients with mechanical prostheses had INR<2. Inadequate anticoagulation contributed to non-structural dysfunction of mechanical valves even in patients with pure pannus ingrowth as well as in those with prosthetic endocarditis.

While control of the INR at therapeutic levels was a critical factor for maintaining anticoagulation, several other factors could have increased the tendency to clotting, valve dysfunction and thromboembolism in our study. These factors include the degree of left atrial enlargement and the presence of AF. Also, the degree of left ventricular dysfunction has now been recognized as an important contributor to stasis and possible valve dysfunction.(13, 41-43, 47) Any foreign material such as the sewing ring in the cardiac chamber may trigger off the coagulation pathway resulting in tissue deposition and endothelialisation of the suture zone. It may be argued that native cardiac valve dysfunction is the primary cause of the entire process, leading to cardiac chamber enlargement and AF which together with the mechanical prosthesis provide the substrate for thrombosis and resultant prosthesis dysfunction. All these factors emphasize the role of full anticoagulation in these patients to decrease the tendency to thrombus formation. (31, 50, 51)

2. Valve position and pattern of native valve involvement

Varying patterns of valve involvement have been reported in reoperative surgery. Both Tang and Bortolotti have reported a high reoperative rate for bioprosthesis in the aortic position, whereas Rizzoli found a high reoperative rate in mitral position for both bioprosthesis and mechanical prosthesis.(24, 25, 31, 35) In our study most reoperations were performed for dysfunctional mitral (62.5%) compared to aortic

(21%) prostheses. Our data are similar to Rizzoli who showed that 52% had mitral lesions and 23.2% had aortic regurgitation.(24, 25) The presence of concomitant AF in 17% of our subjects could explain the development of thrombus formation in the hinge mechanism of the mechanical valve resulting in an obstructed mechanical prosthesis. (41-43, 48) Chesebro et al. reported thromboembolisation in more than 10% of his patients, increasing 18-fold in the presence of concomitant AF.(41) As explained earlier chamber enlargement and the ensuing rhythm disturbance could contribute to higher thrombogenicity predisposing to mechanical prosthesis obstruction.

3. Mechanical vs Biological valves

The very low rate of rheumatic heart disease in developed countries with better access to care and longer lifespan have contributed to a higher usage of biological valves which have a more durable lifespan in the older age group. In Tang et al's study 371 out of 507 biological valves explanted were in aortic position and 175 out of 507 were in mitral position.(35) In contrast, Ruel and co-workers' studied a population of 2348 patients undergoing cardiac prosthesis surgery over a 32 year duration. They showed a similar rate of reoperation in aortic and mitral position for both mechanical (aortic 6.2% vs mitral 5.8%) and biological prosthesis (aortic 40.4% vs mitral 42.4%). There was a higher rate of redo surgery in the bioprosthesis

compared to mechanical prosthesis group. The mean age for reoperation was 61.9±13.6 for the aortic and 59.2 ±12.4 years for the mitral position. (22)

In our study, the median age for the mechanical valve was 32 years (mean 31.4 years 95% CI 28.7-34) and the median for biological group was 54 years (mean 52.8, 95%CI 44.9-60.6), showing that our redo cardiac valve subjects were much younger in keeping with the profile of rheumatic valvular disease in a developing country. We have shown varying intervals from previous valve surgery to reoperation for the different types of valve prostheses implanted. The biological prostheses in our series had a surgical interval to redo surgery ranging between 2 to 35 years compared to 1-40 years for the mechanical valve. (total median time to dysfunction for all prostheses was 5 years). In our study the Carpentier-Edward biological valve had a longer surgical interval to reoperation of 17.5 years compared to the Edward Perimount which had a two year interval. The mortality for the biological prosthesis group was 3/25 (12%) and for the mechanical prosthesis 10/101 (9.9%), which is very similar. Biological valve structural failure occurred more frequently in the age group <65 years (aortic 26% and mitral 44%) compared to those over 65 years (aortic 9% and mitral 6%); no mechanical structural failure was shown for the mechanical prosthesis in both age groups and for both positions. This is quite different from the Veterans Affairs group who showed that the all-

cause mortality after aortic valve replacement was 13% lower for the mechanical compared to bioprosthetic valve. They did not demonstrate this for the mitral position.(30, 49) Similarly, Ruel et al. demonstrated a much higher rate of reoperation in the bioprosthetic group versus mechanical valve group and this was due to structural valve deterioration of the biological prosthesis. The age group of their study population ranged from 46 to 76 years of age. Freedom from all-cause reoperation at 10, 15 and 20 years was 96.2, 94.1 and 93.8% for aortic mechanical valves, 76.1, 61.4 and 59.6% for aortic bio-prosthetic valves. Similar rates to the aortic were shown for the mitral mechanical valves (96.4, 94.8 and 94.2%) and mitral bioprosthetic valves (79.8, 63.3 and 57.6%).(22)

In our mechanical prosthesis group, the commonest valve explanted for non-structural valve failure was Cryolife ON-X mechanical (38/2151) and this were due to poor anticoagulation with INR level<2 in 62.18% of cases. Although this amounted to 1.8% of the total number of On-X valves implanted during the ten year period the time to surgical intervention was one year with the On-X valve compared to the St. Jude valve which had a 9.5 year interval to reoperation. The mechanical prosthesis group had high rate of poorly controlled levels of anticoagulation (INR<2) at 68/110 (61.81%), the mean INR of the group being 2.36 compared to the reference INR≥2 (95% CI 1.93-2.79, p<0.0001). The diagnosis of a thrombosed

mechanical valve was identified intraoperatively in 78.95% of patients with the Cryolife ON-X valve, 50% of the Carbomedics Sorin and 30% of the St. Jude valves. The latter valves had a 9.5 year and 8 year interval to reoperation in keeping with pannus ingrowth leading to non-structural dysfunction of the valve. The pathology described by the operating surgeon revealed the mechanism of prosthesis failure. Obstruction of single mechanical prosthetic leaflet regardless the aetiology made up 56.25% of all the reoperations. The combination of a short surgical interval to reoperation, coupled with low levels of anticoagulation and fresh clot on the explanted valve suggest that Cryolife On-X mechanical valves may require a higher level of anticoagulation to prevent the valve thromboses in our study population.

Whereas no structural valve deterioration was identified in the mechanical valve group, our study has documented structural valve deterioration of the biological prostheses, accounting for 11.72% of the reoperations. Surgical findings revealed calcification and/or stiffening; leaflet perforation with/without paravalvular leaks and root abscess were found in subjects with infective endocarditis. Two patients developed marked calcification of their bioprostheses. The first was a young patient who received the Edward Perimount pericardial valve at age of 16 and returned two year later for a redo cardiac prosthetic replacement due to calcification of the bioprosthetic leaflets. The second patient aged 36 years returned 8 years later with

severe calcification of the leaflets and paraprosthetic leaks. Such rapid structural valve deterioration has been well described in biological valves implanted in younger age groups (14, 19, 22, 23) and for this reason younger patients receive mechanical valves.

4. Other Factors influencing postoperative outcome

Emergency reoperative cardiac valve surgery

In our study over half the subjects with valve dysfunction underwent emergency surgery with an overall *early* in-hospital mortality rate of 11.50% (13/113) compared to no deaths in asymptomatic subjects undergoing elective surgery. The urgency of surgery was related to the mechanism of valve dysfunction and the severity of presenting symptoms. Acute obstruction of a mechanical prosthesis resulted in an acute presentation with high level dyspnea with/without pulmonary oedema and/or cardiogenic shock necessitating emergency surgery. Our 10.71% mortality for patients presenting with NYHA IV symptoms (cf 17.5% reported by Deviri et al.) suggests that emergency surgery for acute mechanical valve obstruction was associated with a lower surgical mortality and morbidity. Deviri concluded that early surgery in patient with acute symptoms is associated with a better outcome.(35)

Compared to elective valve operations emergency surgery is associated with increased morbidity and mortality.(18, 25, 32, 40, 49) In a multivariate analysis Rizzoli et al. showed that emergent and urgent surgery was associated with a hazard ratio of 5.8 and 2.1, respectively.(24) Similarly, Tang et al. examined 743 patients who underwent reoperative surgery in Toronto and showed that the urgency of the operation was an independent predictor of hospital death after redo mitral valve surgery. Patient who underwent urgent or emergent reoperation carried a 3.8-fold increased risk of hospital death with a 19% mortality in urgent and 33% mortality in emergent operations.(35)

Myocardial protection strategy is an important factor that can influence the postoperative mortality and morbidity, as well as short and long term survival. (45-47) The mean aortic cross clamp time in our study was 107 minutes (range 36-360 minutes). This is longer than the 90 minute cut-off shown by Morishita et al. to be associated with a 98% of one year survival rate and a 96% of 5-years survival rate. He showed that cross-clamp time >121 minutes was associated with lower one and five year survival rate, respectively. He also showed that the cardiopulmonary bypass time less than 150 minutes had 95% of 1-years survival and 81% of 5-years survival rate and a time longer than 211 minutes led to a decrease in both one and five year survival rate to 91% and 77% respectively.(46) In our study the mean

bypass time was 158 minutes and aortic cross clamp time was 107 minutes, which probably accounted for the favourable response to inotropes since a longer pump time is associated with some degree of ventricular dysfunction before the patient's heart is able to maintain a cardiac output.

Since most of our reoperations were performed using Crystalloid St. Thomas II solution, we are unable to comment on whether the choice of cardioplegia used had an influence on postoperative outcome. Morishita et al. showed crystalloid vs cold blood cardioplegia in patients with redo cardiac prosthetic valve surgery had better one year survival rate (89% vs 95%) but this survival difference decreased at 5 years (83% vs 85%).(46) There is conflicting evidence as to which type of cardioplegia is superior since studies show a lower incidence of LCOS with blood cardioplegia,(50) while other workers show no difference between cold blood or crystalloid cardioplegia. (45,50,51)

Limitations of the study

Being a retrospective, largely descriptive analysis, this study is limited by lack of complete datasets and complete records of anticoagulant status. Furthermore, this study examines only those patients who were referred by the cardiologist for surgical intervention. These were subjects who presented to the referring hospital

with symptoms and were referred the cardiac unit, or were detected during their annual follow-up at the cardiology clinic. Our data is therefore limited by the lack of a centralized cardiac valve replacement registry to adequately follow up patients who demised at home or shortly after presenting to their local rural clinic or hospital, nor does it include those subjects who arrived *in extremis* and demised without a diagnosis. This was not measurable due to poor medical resources and poor accessibility to care in rural regions. Furthermore, the focus on the large communicable disease burden from tuberculosis and HIV infection might have compromised subjects who failed to reach the tertiary care due to misdiagnosis of the cause for dyspnoea, delay in referral, and lack of formalised anticoagulation treatment and monitoring program.

Chapter 6: Conclusion

In this study we have documented the clinical profile and surgical outcome of patients presenting for redo valve surgery over a ten year period to a referral tertiary center. The majority of our patients undergoing redo valve surgery were young black African women of childbearing age, some of whom were pregnant, who had mechanical prostheses that were obstructed in the mitral position.

The mean age for reoperative cardiac valve prosthetic surgery of 35 years is much younger compared to the literature. Luciani et al. (28) from Rome, and Ruel et al. (22) from Ontario, Canada have both documented the mean age at reoperation of about 60 years. Not only were our patients much younger, but a significant percentage (13%) had comorbidities such as HIV infection with/without HAART. This is a marked increase compared to the single HIV case reported by Taljaard.(34) Also the differences during redo surgery compared to previous surgery may be related to the higher prevalence of underlying rheumatic valvular disease in our African population. In contrast to western series where the patients were older and had more degenerative disease and to other South African studies (Deviri and Taljaard) our patients were much younger, and 13% suffered from significant comorbidities such as HIV infection with/without HAART. The low subtherapeutic

INR (INR<2) in the majority of patients supports the Funderburg hypothesis that HIV infection activates a chronic inflammatory response that leads to changes in vascular function and damage to endothelial cells, a process that initiates the coagulation cascade.(51, 52) More research is needed to determine whether HIV infected subjects need higher levels of anticoagulation to prevent future mechanical prosthetic valve thrombosis in susceptible subjects.

Worldwide it is well established that mechanical prostheses have a longer durability compared to bioprostheses which are prone to structural deterioration. Bioprosthetic valve dysfunction develops within 10 years of implantation and requires reoperation in at least 50 to 60% of patients after replacement (22). In our study we found that bioprosthesis dysfunction over time was due to valve deterioration and leaflet calcification and less commonly to tearing and perforation of the leaflets from infective endocarditis. Our findings of thickened, calcified leaflets within restricted leaflet motion in the biological prostheses has important clinical implications since the patients prone to such deterioration are younger and these subjects should therefore receive mechanical valves. The interval to reoperation ranged from 10 to 17.5 years for the Medtronic Hancock and Carpentier Edward pericardial valves. In our study the interval to redo cardiac valve replacement was shorter in the mechanical cardiac prosthetic group due to non-

structural dysfunction commonly caused by obstructed valve leaflet/s as a result of inadequate anticoagulation, even in subjects with pure pannus ingrowth.

The three commonest explanted mechanical valve types were the St. Jude medical, Carbomedics Sorin and Cryolife On-X. The shortest interval to reoperation was one year with the On-X valve. This is a purely observational finding since all three valve types were obstructed as a result of inadequate anticoagulation (subtherapeutic INR <2.0). One might be tempted to infer that the On-X valve requires higher levels of anticoagulation to prevent valve thrombosis but this needs to be shown in a prospective study.

Current literature shows that the incidence of left-sided mechanical valve obstruction ranges between 0.5 to 6% per patient years. Whereas it is commonly caused by the pannus formation of the mechanical valve in the developed world (26,27,44), it is due to thrombosis of the mechanical valve due to inadequate anticoagulation in developing countries.(2, 3, 53, 54) In our study 50% of our mechanical valve dysfunction group was due to leaflet obstruction from fresh clot or organized thrombus and about 18% had pannus ingrowth. Of interest was that 19% had a mixed aetiology for prosthetic dysfunction characterised by fresh clot, organized thrombus and pannus ingrowth. The majority of subjects with valve

dysfunction had subtherapeutic INRs raising the question of whether pannus ingrowth is a consequence of ongoing inadequate or borderline levels of anticoagulation.

Although prosthetic dysfunction has been well studied the finding of mechanical valve dysfunction with low grade symptoms has not been well documented. A significant finding of our study is that we identified a group of 18/128 (14.06%) totally asymptomatic patients with prosthetic valve dysfunction (17 mechanical and one biological valve) that was detected during echocardiography performed at our routine follow up clinic. These patients were identified by an increasing gradient across the prosthetic valve and/or leaflet immobility which was easily detected at transthoracic echocardiography. This technique has a potential role for distant screening of subjects in rural areas who are unable to gain access to the tertiary level care. This modality is eminently feasible in a province like KZN where noninvasive cardiac imaging is available in at least six secondary level hospitals in the province. Echocardiography will also enable evaluation of left ventricular function and the pulmonary pressure in these subjects; this technique facilitates closer monitoring of patients with significant left ventricular dysfunction which may contribute to valve dysfunction as a result of blood stasis within the left ventricle and left atrium and predispose to thrombosis around the hinge of the prosthesis.

In addition, the province of KwaZulu-Natal has a large communicable and non-communicable disease burden. The mixture of rheumatic cardiac valvular disease, valvular disease associated with retroviral disease and co-existent HIV infection with/without HAART poses several challenges in the evaluation of these patients. Many of these patients who present with dyspnea are a diagnostic conundrum for the medical practitioner who may readily attribute chest symptoms to HIV infection when in fact the symptoms may point to valve dysfunction. A low index of suspicion for valve dysfunction is required in such circumstances prompting referral for evaluation and imaging. Furthermore, the rapidly changing the landscape following the HAART roll out program has converted HIV into a chronic infection; such patients may benefit from surgery with prolongation of life expectancy. This subset of patients in the study may require further investigations and analysis to determine the effects of HAART after valve replacement.

These caveats aside, it should be noted that 68% of our reoperations had poor levels of anticoagulation control with INR<2 in the mechanical prosthetic group. Anticoagulation is the most crucial factor to prevent prosthetic valve thrombosis, making adherence to the anticoagulation regime an absolute essential in the management of the patient after valve replacement. We need to think an innovative

way to create awareness and an understanding of the importance of anticoagulation. Such an innovation must be able to overcome the hurdle of the space, time and access to health care in some geographically inaccessible regions. An example of this is the concept of cloud-based technology where people can gain access to information at any time and anywhere. Cellphone technology and the network coverage has also improved over time to include smartphone with instantaneous access to medical information on the need of valve replacement, type of mechanical valves and finally the need of anticoagulation. The patient who stays in a remote rural area where he or she does not have adequate access to health care service may benefit as long as one has access to a network. This modality may also be used to educate the patient as well as provide a service to newly qualified medical professionals.

Recommendations

There is an urgent need to install measures to prevent valve dysfunction and to improve the detection rates for valve dysfunction.

1. The solution to the problem of anticoagulation lies in basic medical education prior to discharge from hospital after valve surgery, implementing a successful outreach program to rural communities and setting up INR

clinics that are accessible for INR regular checks and monitoring of the dose of warfarin properly.

2. Measures to prevent valve dysfunction and to improve the detection rates for valve dysfunction include the wide dissemination of knowledge on anticoagulation, education of doctors and patients, improved organization of care and the institution of checklists, as well as strong policies and guidelines on anticoagulation.

3. Close collaboration between departments of medicine, cardiology and cardiothoracic surgery departments, is important not only for rapid triage of symptomatic patients, but also for the implementation of an outreach program comprising a team comprising of a nurse, physician, cardiologist and cardiothoracic surgeon, to provide support to regional as well as rural hospitals in each region. Health education presentations by the team, as well as clinic visits to review the INR protocols, policy and examination of programs monitoring the INR levels will help raise awareness of the seriousness of monthly INR checks to maintain therapeutic levels of the INR.

4. An ongoing prospective study of anticoagulation by such a team, possibly funded by industry, would go a long way to incentivise staff to join the team to outreach areas and participate in the project to determine the predictors of valve dysfunction after surgery. Such a team would also serve as a bridge

between the rural hospital and the tertiary hospital, facilitating ease of access to tertiary health care.

5. An important aspect of the cardiac evaluation is the availability of imaging by trained technologists at regional centres who may be the first to detect asymptomatic valve dysfunction. The concept of technological support has already been implemented in KwaZulu-Natal for the last fifteen years by the Department of Cardiology but has been poorly supported by the Health authorities. Trained cardiac technologists have been placed at regional centres throughout KZN but have not been supported with imaging equipment. Such skills should be harnessed and technologists retrained on the features of new valves and their appearance on imaging so that any changes on imaging may be detected early and the patient referred to the tertiary centre. Although our finding of a 6.0% rate of redo valve surgery is much lower the 12.9% reported by Tyers et al. (32) in Canada, ours is likely an underestimate of the true prevalence of valve dysfunction for the logistical reasons of early access to secondary and tertiary care in a developing world setting. Had the resources that have already been put in place been supported by the health authorities many more cases of prosthetic valve dysfunction may have been detected early by routine INR monitoring and

echocardiography with avoidance of the catastrophes that have already occurred.

Conclusion

This study has documented a high rate of prosthetic valve dysfunction due to obstructed mechanical valve prostheses in the mitral position, in young African women as a result of inadequate anticoagulation. While about half the patients may be detected more easily because of an acute presentation, a substantial number have milder or no symptoms and may be suspected only by a change in their symptomatology coupled with low levels of anticoagulation. Patients undergoing mechanical prosthetic valve replacement in developing world settings therefore need careful ongoing surveillance and reinforcement of the importance of regular INR monitoring through structured educational programs. Reoperation for valve dysfunction is associated with significant morbidity and mortality related to technical factors and the preoperative clinical status of the patient.

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