Sixteen Year Retrospective Analysis of Rheumatic and Non-Rheumatic Heart Disease Patients Undergoing Valve Procedures at Groote Schuur Hospital:

First Incidence Single Aortic and Mitral Valve Replacement

by

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DECLARATION

I, Akinwumi Babatunde Ogunrombi, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION

………. To all sufferers of rheumatic heart disease…………

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Thank you, the Father of Grace. You saw me through!

LIST OF ABBREVIATIONS

GAS – Group A Streptococcus

GSH – Groote Schuur Hospital

ICU – Intensive Care Unit

HDU – High Dependency Unit

MAPE – Major Adverse Prosthetic Events

USD – United States Dollar

WHO – World Health Organization

FDA – Food and Drug Administration

NVE – Native valve endocarditis

PVE – Prosthetic valve endocarditis

INR – International Normalized Ratio

STS – Society of Thoracic Surgeons

NYHA – New York Heart Association

CABG – Coronary Artery Bypass Graft

MVR – Mitral Valve Replacement

AVR – Aortic Valve Replacement

PPM – Prosthetic-patient mismatch

EOA – Effective Orifice Area

EuroSCORE - European System for Cardiac Operative Risk Evaluation

TEE – Transesophageal Echocardiography

PPL – Periprosthetic leak

SVD – Structural Valve Dysfunction

CT – Computerised tomogram

TIA - transient ischemic attacks

RIND - reversible ischemic neurologic deficit

TB – Tuberculosis

HIV – Human Immunodeficiency Virus

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ABSTRACT

Introduction

Rheumatic heart disease is still the most common cause of valvular heart lesions requiring replacement or repair procedures worldwide. In South Africa, where there is an interesting mix of first and third world dynamics, factors sustaining the epidemic of rheumatic disease are still commonplace. The choice of appropriate valve procedure and prosthesis in our setting will depend on an adequate knowledge of short and long term outcomes of valve replacement and repair. The aim of this thesis was to evaluate the demographics and presentation of our rheumatic and non-rheumatic patients and to determine if our current implantation choices could be validated.

Methods

A retrospective data analysis of first incidence, single aortic and mitral valve repair and replacement was carried out over a 16 year period (1993-2008) at the Groote Schuur Hospital, Cape Town, South Africa. As follow-up in indigent patients was not possible, overall failure was deduced from patients returning for re-operation. The possibility of bias due to an oblique mortality in one of the valve-type groups therefore needs to be considered.

Results

Of the 1,449 patients, 770 (53.1%) were rheumatic while 679 (46.9%) were non-rheumatic. Rheumatic heart disease was significantly associated with female gender ($p<0.0001$), black and coloured racial groups ($p<0.0001$), informal housing ($p<0.0001$) and unemployment ($p<0.0001$). The non-rheumatic patients were significantly older with more co-morbidity factors; smoking ($p=0.038$), renal failure ($p=0.005$), hypertension ($p<0.0001$) and diabetes ($p<0.0001$).

Of 1,449 valve procedures (replacement and repair), 801(55.3%) and 648(44.7%) were in the mitral and aortic positions respectively. There were 1210 (83.5%) valve replacements with mechanical valves being the most commonly implanted (60%).

Mitral valve repair was attempted in only 67 (8.7%) of the rheumatic patients, and 123 (18.1%) of the non-rheumatic group ($p<0.0001$).

ICU stay, hospital stay and 30-day mortality figures were significantly better (76.5±113 hours vs 99.3±155.1hours ($p=0.048$); 11.5±10.4 days vs 13.8±27.3 days ($p=0.05$); 2% vs 11% ($p<0.0001$) in the rheumatic group, while time to failure for mechanical valves was significantly earlier in this same group (4.23 vs 6.91years; $p=0.0039$) than in the non-rheumatic group as well as tissue valve failure in 9.54 years.

The ratio of mechanical valves presenting for reoperation was slightly higher than that of tissue valve recipients ($p=0.055$).

Conclusion

Counter-intuitively, mechanical valves which represent our current preferred choice for young, black, rheumatic patients are returning significantly earlier for re-operation than tissue valves. There is an urgent need to investigate this further with prospective studies.

CHAPTER 1. BACKGROUND

1.1 Introduction

Heart valve surgery contributes a significant proportion of cardiac surgical workload worldwide, especially in the developing world where rheumatic heart disease is common and currently the leading etiology associated with valvular heart lesions necessitating valve replacement (1).

Rheumatic heart disease is the chronic sequelae of rheumatic fever, an autoimmune, multi-system inflammatory response following Lancefield group A streptococcus (GAS) pharyngitis (2). Rheumatic fever and rheumatic heart disease are very prevalent in developing countries of Africa, South America and Asia, although pockets of high prevalence are still found in some developed countries (3). South Africa is a unique example of both first and third world dynamics presenting an interesting combination of patients.

Re-operative valve surgery has become an inevitably fast evolving discipline as the number of heart valve replacement surgeries continues to increase. In the past, re-operative surgery has been associated with a considerably higher operative mortality than primary valve surgery. Poor preoperative left ventricular function and duration on cardiopulmonary bypass, but not the number of reoperations, has been correlated with operative mortality (4). It remains to be shown, however, if the current paradigm that re-operative mortality outweighs risks of implanting mechanical valves is unconditionally correct.

It is important to realize that long-term outcome criteria, such as time to re-operation or to Major Adverse Prosthetic Events (MAPE), such as thrombo-embolism, infection or bleeding, offer greater predictive value of valve performance than early (in-hospital) assessment of morbidity and mortality. This was confirmed by Edwards et al. (5) who showed that early failure of valves was largely cardiac, rather than being valve related, suggesting that patient risk factors, rather than prosthesis choice, have greater impact on short term in-hospital outcomes such as intensive care unit (ICU) duration or hospital stay and 30-day mortality.

1.2 Epidemiology of rheumatic heart valve disease

1.2.1 Developing Countries

Rheumatic fever is a disease of the poor (6) and rheumatic heart disease is still widely prevalent in developing countries all over the world but, due to poor facilities for registration of cause of death, reliable statistics are difficult to obtain. In 1995, the World Health Organization (WHO) estimated that 12 million people were affected by rheumatic fever or rheumatic heart disease worldwide, resulting in 400,000 deaths annually (7)**.** It is also estimated that about 282,000 new cases arise every year (8)**.** Unfortunately, most countries where rheumatic fever is prevalent do not have the financial resources nor the sophisticated medical services to treat the long-term sequelae of chronic valvular heart disease **(**Figure 1**).**

Again, there is believed to be continued and unabated prevalence in the countries of Asia and Africa with no change in prevalence in countries like India over a 30 year period, similar to other developing countries (9)**.** A developing (often a euphemism for poor) country is one in which the economy has remained stagnant and the expected benefits of rises in standards of living have not been equitably distributed. Unfortunately, these countries are largely in transition with increasing urbanization and creation of sprawling ghettos. Some are also experiencing massive migrations of large segments of the population into refugee camps due to war.

Padmavati (10), reported a prevalence of rheumatic heart disease from 15 per 1000 in school children in Algeria to 20 per 1000 in Iran while, in other Mediterranean countries such as Cyprus and Egypt, there are varying reports. In other parts of Africa such as Ethiopia, Nigeria and Senegal a high prevalence was also recorded. The actual prevalence of rheumatic heart disease is not known in South Africa (11). However, a reported prevalence of rheumatic fever in Johannesburg among the school children of Soweto in 1996 was 6.9 per 1000 children, and as high as 20 per 1000 among those ages 12-14 year age group (12).

Conflicting reports arise from China with some reports suggesting that rheumatic heart disease is still the most common cause of valvular damage leading to surgery as it had been 40 years ago (13). However, Cheng (14) is of the opinion that there has been a marked reduction of rheumatic heart disease in China as a result of significant improvement in living conditions, better hygiene and good nutrition.

Figure 1: Worldwide prevalence of rheumatic heart disease (15)

1.2.2 Developed Countries

Pharyngeal infection, with the causative organism GAS, is more common in areas of overcrowding and poor socioeconomic conditions. This may explain the decline of cases in the developed world, for example the USA, where the incidence of rheumatic fever has fallen from 100 per 100,000 population at the turn of the century to 45-65 per 100,000 between 1935 and 1960, and still further to 2 per 100,000 currently (9).

Padmavati (10) compared the differences and patterns of rheumatic heart disease in developed and developing countries. Two studies published in the 1960s showed that the presentation of rheumatic heart disease is different in developing countries. These studies reported an increased rate of rheumatic heart disease among individuals younger than 20 years (30%), symptomatic heart disease at younger age of onset, less interval between the onset of symptoms and symptomatic rheumatic fever, and severe mitral stenosis and its complications within a short duration of onset of disease (16) (17). Essop and Nkomo (18) also noted that in developed countries, valvular disease was largely degenerative whilst infectious in developing countries.

Examples of the close inverse relationship between the prevalence of rheumatic heart disease and wealth are provided by the evidence of its diminishing incidence in particular ethnic groups of higher socio-economic status while it remains high in lower socio-economic groups in the same region. There are differences in the incidence of the disease, for example, between Arabs and Jews in Israel, Malaysians, Indians and Chinese in Singapore, Maoris and Whites in New Zealand and Bantus, Asians and Whites in South Africa (19). There may also be variable susceptibility to GAS pharyngitis possibly due to host genetic factors, explaining the observed differences.

While South Africa is a first world country with regard to the diagnosis and treatment of heart disease, it supports a large third world population (20) with an extensive and varied spectrum of valvular heart disease.

1.3 Epidemiology of non-rheumatic heart valve disease.

Unlike rheumatic valve disease, non-rheumatic conditions affecting the heart valve are either congenital or acquired. Congenital conditions most often affect the aortic valve, for example bicuspid aortic valves, or the pulmonary valve, for example pulmonary stenosis.

Infective endocarditis, myxomatous and calcific degeneration are other non-rheumatic lesions. Coronary artery disease leading to ischemia of the papillary muscles is also encountered.

1.4 **Valve pathology**

1.4.1 Mitral Valve

Compared to Western countries, a different clinico-pathological spectrum of valvular heart disease exists in developing countries with rheumatic carditis, infective endocarditis, myxomatous degeneration (prolapse), and calcification occurring amongst others. Of these, rheumatic heart disease is still the leading etiology associated with mitral valve disease requiring valve replacement (Figure 2). Reports from Shanghai, China, indicate that more than three quarters of cases (81%) are rheumatic in origin while restenoses after mitral commissurotomy (4%), congenital heart lesions (5%), endocarditis (3%), Marfans (2%) and miscellaneous (5%) account for the remaining (13)**.**

Figure 2: Mitral valve with stenosis and calcification (21)

In mitral stenosis, when the mitral valve orifice area is <2cm2, a pressure gradient is created, which gradually worsens, preventing atrial blood from filling the ventricle during diastole and ultimately also building pressure within the left atrium leading to pulmonary congestion, left atrial enlargement and atrial fibrillation. When atrial fibrillation develops, the ‘atrial kick’ which contributes blood to the left ventricle during late ventricular diastole is finally lost, leading to a precipitous decrease in cardiac output and congestive cardiac failure.

In mitral regurgitation, the LV volume increases and the contractile function deteriorates and thus leading to dysfunctional LV and a decrease in ejection fraction. Regurgitant volume in mitral regurgitation causes a volume and pressure overload of the left atrium and eventually pulmonary overload.

In general, the ultimate lesions caused by disease in valves produce stenosis, insufficiency (regurgitation or incompetence), or both. The understanding of these lesions is attributed largely to echocardiography as neither postmortem analysis nor observations made intra-operatively in a flaccid non-beating heart are able to appreciate the dimensions and spatial relationships of the valvular and subvalvular components of the mitral valve (18)**.**

Features of severe mitral regurgitation as seen echocardiographically in rheumatic fever include an increase in mitral annular diameter, mainly of the posterior annulus, and elongated chordae to the anterior mitral leaflet but without rupture. Remarkably, leaflet morphology appears normal, at least in the early stages (22)**.** Rheumatic prolapse always involves the anterior leaflet whereas myxomatous prolapse has a predilection for the posterior leaflet. Myxomatous leaflets are thickened, voluminous and redundant with significant systolic bulging or billowing toward the left atrium, contrasting with that in rheumatic carditis (18)**.**

It is important to distinguish rheumatic mitral disease from myxomatous mitral disease as the long term outcomes differ.

Mitral valve prolapse (Barlow's syndrome) is estimated to affect 1-3% or more of adults in the United States. The basis for the changes in these valves is unknown but it is associated with such heritable disorders as Marfans syndrome. Most are asymptomatic. It has only recently been shown that asymptomatic mitral regurgitation is a serious disease with a 33% 5-year incidence of adverse cardiovascular events including death, heart failure and new atrial fibrillation (23)**.**

This underscores the need for these patients to have valve repair or replacement as soon as possible. This is evidently possible in degenerative mitral valve disease which is common in developed populations, but the benefits of repair are questioned in rheumatically damaged valves in which the leaflets may look relatively normal on macroscopic examination but harbor microscopic inflammatory cell infiltration leading to progressive fibrosis and leaflet deformity. The overall freedom from valve failure in one report was only 66% after a mean follow up of 5 years (24) thought to be a result of the rheumatic pathology.

Infective endocarditis usually leads to valvular incompetence by tearing, fraying or perforation of the leaflets. The subvalvar apparatus may also be affected with chordal and papillary muscle rupture. Very rarely, stenosis may occur from huge vegetations. For years, rheumatic heart disease was considered to be the major risk factor for development of endocarditis, accounting for between 20% to 25% in the 1970s but dropped to 7% to 10% in the 1980s in Western countries whilst still responsible for the majority of cases in developing countries. Mitral valve prolapse has emerged as the leading risk factor accounting for between 7-30% of native valve infective endocarditis in Western countries (25).

1.4.2 Aortic Valve

Acquired aortic stenosis results from progressive and advanced age- associated "wear and tear" of either previously anatomically normal aortic valves or congenitally diseased bicuspid valves. The prevalence of aortic stenosis, estimated at 2% in individuals greater than 65 years of age, appears to be increasing with a rising average age of the population. With the decline of rheumatic fever in North America, rheumatic aortic stenosis now accounts for less than 10% of cases of acquired aortic stenosis (26). It is currently thought that degeneration, dystrophy and passive accumulation of hydroxyapatite mineral explain the onset of calcification. However, the body is able to actively regulate this, generating interest in the use of statins to decrease the progression of aortic stenosis (27).

In Africa however, rheumatic aortic stenosis still produces a significant burden of disease. A systolic pressure gradient develops between the left ventricle and aorta, and in order to normalize the left ventricular wall stress, the left ventricle thickens producing concentric hypertrophy. This state may be maintained for several years until left ventricular end diastolic pressure (LVEDP) begins to rise and diastolic dysfunction sets in. Although cardiac output may be sufficient at rest, it is grossly inadequate during exercise. When aortic stenosis is severe enough, atrial filling of the ventricles becomes severely impaired with the development of atrial fibrillation leading to heart failure.

Rheumatic aortic regurgitation on the other hand causes an eccentric left ventricular hypertrophy with a compensatory increase in left ventricular end diastolic volume (LVEDV). The left ventricle becomes larger and more compliant with time until such a time when diastolic pressure begins to rise and cause symptoms.

Other causes of aortic regurgitation include bicuspid aortic valves, which are the most common congenital etiology, infective endocarditis and degenerative aortic valve disease. Abnormalities of the ascending aorta such as may occur with long standing uncontrolled hypertension, Marfans syndrome and Takayasu arteritis may also result in aortic regurgitation.

CHAPTER 2. STATUS OF HEART VALVE SURGERY WORLDWIDE

Over 4 million people worldwide have received a prosthetic heart valve and it is estimated that about 300,000 valves are being implanted annually, which is projected to be 850,000 per year by 2050 because of the high incidence of rheumatic heart disease in developing countries and an increasing burden of degenerative valve disease in the ageing population (28).

2.1 Design trends of valve prosthesis

Ever since the first successful heart valve replacement in 1960 by Dr Dwight Harken using the Starr-Edwards valve (**Error! Reference source not found.**), mechanical valves have undergone much transformation from the days of the 'ball and cage' valves, the monodisc, which were either non-tilting (Table 1) or tilting (Table 2), and now, the bileaflet prostheses with minimal thrombogenicity and hemolysis and improved hemodynamic performance (Table 3). More than 70 different types of mechanical valves and a number of different tissue valves have been implanted throughout the world in the last 50 years.

A major contribution to mechanical valves was provided by Jack Bokros who invented a pyrolytic carbon that he called 'Pyrolyte'. This has been used as a component of mechanical valves since 1969 and over the decades has become the principal biomaterial for virtually all new mechanical valves.

The most widely implanted valve so far is the 'St. Jude Medical Bileaflet' valve which has changed very little from the original type implanted in 1977. About 1.5 million had been implanted by 2004. Slight changes have been made in its sewing ring and the 'Regent' valve introduced in 1999 incorporates a housing design that significantly improves the orifice size of smaller aortic prostheses. Other valves in current use include the Starr-Edwards ball valve, the Carbomedics, Omniscience, Omnicarbon, Medtronic-Hall and the Edwards MIRA. The prosthesis most recently approved by the Food and Drug Administration (FDA) is the bileaflet On-X valve made of pure pyrolytic carbon as opposed to its predecessors made of silicon-alloyed pyrolytic carbon, making it stronger and tougher (29).

While it is true that the tilting disc valves and the bileaflet valves that appeared in the 1970s offered hemodynamically superior aortic valve function when compared with the Starr-Edwards prosthesis, the SE#6120 mitral valve still provides quite satisfactory hemodynamic function and continues to be used, particularly in third world countries because of its low cost. Ikizler et al. report on a Starr-Edwards valve implanted 34 years ago in Turkey and still functioning even without anticoagulation (30). Since the first use of homografts was reported in the early 1960s, there was not much use of bioprostheses until the 70s and 80s when they were implanted with increased frequency. The main attraction of these valves was their excellent hemodynamic properties, low thrombogenicity and freedom from substantial structural degeneration during the first years of implantation (31).

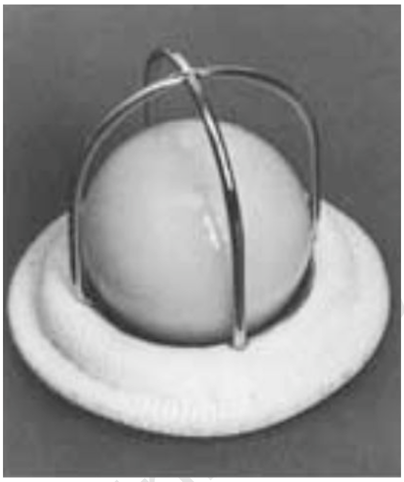


Figure 3: Starr-Edwards Mitral valve (32)

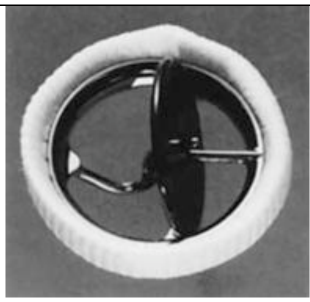
Figure 4: On-X Mitral valve (33)

Table 1: Examples of Non-Tilting Disc Valves

Valve and year of 1st implant		Year production ceased	Information
Kay-Shiley 1965		1980	One of the most widely used mitral valves (1965-1980)
Beall-Surgistool 1967		1985	Discontinued because of fabric wear on disc apron
Cooley-Cutter 1971		1978	Double struts permitted ‘full flow’ orifice

Images from Gott, VL et al. (32)

Table 2: Examples of Tilting Disc Valves

Valve and year of 1st implant		Year production ceased	Information
Bjork-Shiley 1969		1986	Stellite housing with flat Delrin leaflet (disc)
Medtronic-Hall 1977		ongoing	Titanium housing with pyrolytic carbon leaflet; with central hole for guide strut

Images from Gott, VL et al. (32)

Table 3: Examples of Bileaflet Valves

Valve and year of 1st implant		Year production ceased	Information
St Jude (1977)		ongoing	Pyrolytic carbon; first all-carbon valve in clinical use.
Edwards MIRA (1998)		ongoing	Curved leaflet profile; carbofilm-coated titanium alloy
Carbomedics (1986)		ongoing	Pyrolytic carbon coating; housing can be rotated within sewing ring

Images of St Jude and Carbomedics valves from Gott, VL et al. (32); Image of Edwards MIRA valve from Remadi, JP (34)

Biological prostheses have been developed with the principal advantage of avoiding life-long anticoagulation which is the bane of mechanical valves. Despite the improvements in design of these glutaraldehyde treated tissue valves, with ‘new’ concepts such as ‘stentless’ valves, they still fall short with respect to durability, eventually succumbing to tissue degeneration. This resulted in a decline in their use to less than one third of the annual total in the late 80s (35). The legacy of the catastrophic early failure of the Ionescu-Shiley pericardial valve (36) due to a design flaw and resulting in its withdrawal in 1987, only 11 years after its introduction, may have been the tipping point in this decline. Today, however, there is not only a preference for utilization of tissue valves but, compared to their mechanical counterparts, these prostheses are enjoying a more rapid market expansion. This is perhaps also driven by the current interest in transapical or percutaneous valves which are by necessity also tissue valves. Mechanical valves nevertheless remain the preferred prosthesis in young children where the problem of dystrophic calcification limits their use.

2.2 Choice of prostheses

Worldwide, at least 20 different valve designs are implanted annually (37). All clinicians should have access to a national database which reflects the range and performance of individual valves, thereby providing an objective and scientific basis on which to make the choice of valve. The United Kingdom Heart Valve Registry set up in 1986 has been able to show clear trends and changes in the choice of valves. Within a decade, it highlighted a preference for mechanical valves, although recent data suggest that bioprosthetic implants were on the rise. The number of bileaflet implants saw a significant increase with a fall of up to 73% and 76% in single leaflet and ball valves respectively (38). In clinical practice, the choice of a valve is made primarily on the basis of patient age, valve position, patient comorbidity and the risks and benefits of anticoagulation (4). Unfortunately, ultimately the choice of prosthesis model to be implanted has always been at the discretion of the operating surgeon and also dependent on the availability of different brands.

In the mid-nineties, about two-thirds of the approximately 210,000 patients worldwide undergoing valve replacement surgery annually, received mechanical valves (39). The use of bioprosthetic valves saw an increase from 20% to 40% in 2000 and is believed to have reached the 50% mark currently. The majority of these valves, however, are implanted in the geriatric population of Europe, North America and Japan and less so in the developing world, where rheumatic heart disease still remains a huge challenge, anticoagulation is problematic, and a strong indication for bioprosthetic use therefore exists. The proportion of patients receiving heart valves in the Western world are also significantly older (peak age of 60-69) than African patients (peak age of 30-39) and these may have a significant impact on the choice of valve prosthesis (Figure 5) (40).

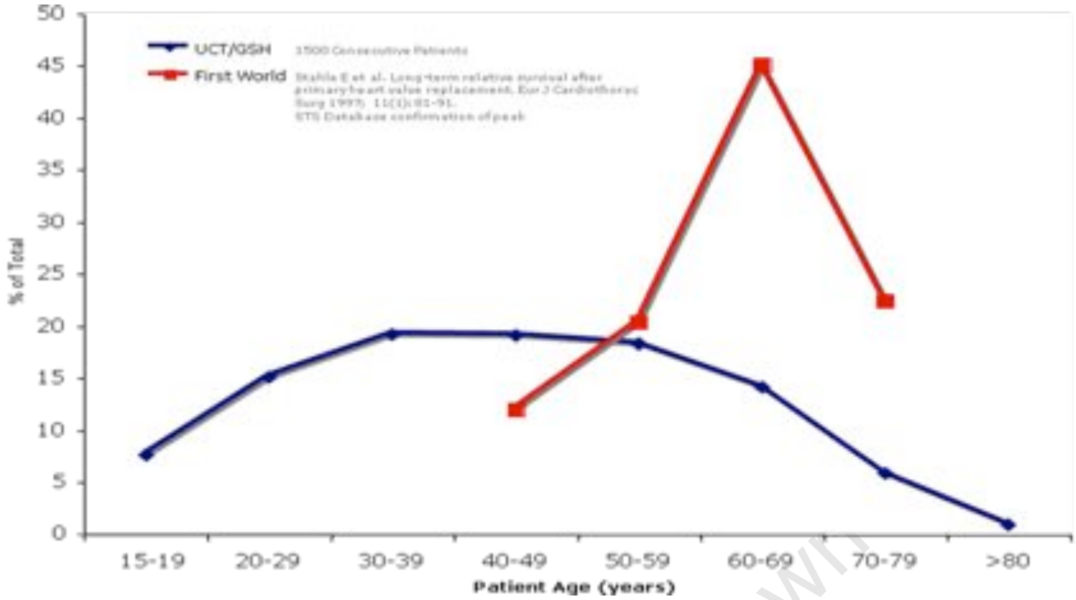


Figure 5: Age distribution of patients undergoing valve surgery at Groote Schuur Hospital (blue) versus that reported for the First World (red) showing a much earlier and more widely distributed age of onset for a developing country such as South Africa compared to the First World (40).

There is currently a bias towards the use of mechanical prostheses in developing countries because of a genuine fear of reoperations due to the expected failure of tissue bioprostheses. The fear of a re-operation is largely the main reason for choosing a mechanical prosthesis because reoperations are fraught with bleeding from release of adhesions during re-entry.

However, some studies have not shown any significant difference in survival between mechanical and bioprosthetic valves despite the known implications and disadvantages of both (41).

The controversy continues as to the choice of prosthesis when reoperations are necessary, and perhaps more importantly in first operations with some series reporting higher mortality in re-replacement of a mechanical valve than with tissue valves (42). It can be argued that the acute and abrupt deterioration in valve function (eg. thrombosis) which is more common with mechanical prostheses produces a severely compromised patient quickly requiring more urgent intervention and therefore increasing the mortality.

Hammermeister and co-workers, reporting for the Department of Veteran Affairs (VA) trial which randomized 575 male patients undergoing single valve replacement in 13 centres between 1977 and 1982, showed significant survival at 15 years for patients who received a Bjork-Shiley prosthesis (79% versus 66%) in the aortic position compared to the Hancock porcine bioprostheses. They also showed a significantly increased risk of re-operation when the Hancock bioprosthesis was inserted in either the aortic or mitral positions (43)**.**

In contrast, the Edinburgh heart valve randomized trial, which was conducted between 1975 and 1979 with a slightly longer follow up of 20 years and reporting on 533 patients, found no difference in patient survival. However, there was also an increased need for reoperation with the Hancock bioprosthesis (44)**.** Peterseim and his colleagues in a large non-randomised series of 841 patients undergoing isolated, first time aortic valve replacement with Carpentier-Edwards or St Jude mechanical prosthesis reported a similar ten year survival in each group (45)**.**

Other studies have however analyzed the risk factors for early and late mortality in reoperations with results showing no difference between mechanical and bioprosthetic valves (46)**.** It is still unclear whether tissue or mechanical valves should be used in a background of native valve (NVE) or prosthetic valve endocarditis (PVE). It may be possible to prevent valve replacement by valve repair if adequate debridement of infected tissue can be guaranteed not to compromise the repair. However, 'simple' valve replacement still remains the procedure of choice in most cases of NVE (47)**.** When the infective process involves the sewing ring or annulus in PVE, re-replacement surgery must be performed. Timing of surgery and incomplete excision of infected tissue may be partly responsible for the poor outcome and mortality of 30% to 80% in cases of early PVE and 20% to 40% in cases of late PVE (48)**.** Infection of a bioprosthetic valve may hasten structural valve degeneration due to injury to the bioprosthetic leaflets. It has been suggested previously though that bioprosthetic valves may be less susceptible to early recurrent endocarditis than mechanical valves but that they may be more susceptible to late endocarditis due to infection of the tissue leaflets. Moon et al. recommend mechanical prostheses for most patients with NVE who are less than 60 years of age while patients older than 60 and younger patients who have limited life expectancy would benefit more from tissue valves (47)**.**

2.3 Anticoagulation

Anticoagulation is mandatory with mechanical valves as it maintains the leaflets of the prostheses free from thrombi as a result of altered blood flow and haemostatic activation caused by vessel-wall disruption during surgery or exposure of artificial surfaces (sutures, sewing ring, occluder and valve housing) to the circulating blood. This is often achieved by short-term parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparin until a therapeutic concentration of an oral vitamin K antagonist, usually warfarin, is reached.

However, based on the socioeconomic circumstances of a significant proportion of these patients, anticoagulation follow-up is often impossible because of proximity to monitoring facilities as well as under dosage due to non-compliance (37). Ogendo reported in Kenyan patients with mechanical valves who attended their anticoagulation clinics once in 59 days that therapeutic International Normalized Ratio levels (INR) could be maintained only 18% of the time (49). Therefore, the ideal heart-valve prosthesis of choice in this setting should be a xenogeneic tissue valve which does not require lifelong anticoagulation because of improved blood flow dynamics resulting in less red cell damage and hence less clot formation. The disadvantage of these prostheses is their relative predictable degeneration and the need for re-replacement, especially in the younger patient who soon outgrows his valve in addition to the problem of mineralization of bioprosthetic valves in the young patient. Until dramatic improvements in the longevity of bioprosthetic valves in the younger population are therefore achieved, there remains a strong bias towards the deployment of mechanical prostheses in the developing world despite the risk of acute thromboembolic events in these patients, mainly because of the trepidation of inevitably having to perform a high percentage of difficult and life-threatening valve reoperation procedures at a later time point. However, the avoidance of anticoagulation especially in females of child-bearing age would remain a reason to choose bioprosthetic valves. Unfortunately, complications arising from imperfect anticoagulation management are often fatal, as opposed to a possibly only perceived higher intra-operative mortality associated with the need for replacing degenerating tissue valves. Therefore, the ability of weighing re-operation risks in tissue-valve recipients against anti-coagulation risks in mechanical valves, constructed of synthetic tilting disks and hinged on a titanium stent may have fundamental consequences for patients needing heart valve replacement from lower socioeconomic circumstances.

In clinical practice, the choice of a valve is made primarily on the basis of patient age, valve position, patient comorbidity and the risks and benefits of anticoagulation (50). In our environment, the perception is that the relatively young age of our patients as well as fear of reoperation informs the choice of mechanical prostheses in spite of the fact that many patients may not have access to proper anticoagulation monitoring. This has prompted some workers in our centre to recommend fixed-dose rather than adjusted-dose anticoagulation regimens (37).

2.4 Valve replacement

As has been indicated above, heart valves can be replaced with either mechanical or tissue prostheses. The current standard mechanical valve commonly implanted is the bileaflet valve. Tissue valves involve either xenografts or allografts (homografts).

Valve replacement was first carried out in 1960 and, with respect to rheumatically damaged valves, is still commonly performed in developing countries where these valves are often irreparable. Valve replacement is performed under cardiopulmonary bypass support on the non-beating heart to provide a bloodless operative field.

2.5 Valve Repair/ Reconstruction

2.5.1 Closed Mitral Commissurotomy

This was one of the earliest forms of repair for the mitral valve with the advantage of avoiding cardiopulmonary bypass which was not widely available in the early 19th century when digital (using a finger) commissurotomy was introduced. It entailed either digitally prising the mitral leaflets apart at the anterolateral and the posteromedial commissures, or with the aid of a Tubbs dilator, without direct visualization. Early reports showed that valuable relief was especially provided to young patients with progressive symptoms of rheumatic mitral stenosis. Figures such as 86%, 75% and 62% symptomatic improvement for the first, third and fifth year were quoted by some workers from China, however prolonged follow up revealed the incidence of re-stenoses as high as 30% - 40% after 10 years (13). Another drawback was the inability to visually assess the mitral valve and make correct diagnoses of the pathology, therefore giving inconsistent results. Another objection to the procedure was the difficulty in obtaining complete relief of the stenosis without producing mitral insufficiency.

With the progress in cardiopulmonary bypass and myocardial protection, closed commissurotomy gave way to open commissurotomy. However, this procedure may still be relevant in developing countries where access to open heart surgery is difficult (51), (52).

2.5.2 Open Mitral Commissurotomy

The era of open commissurotomy commenced in 1956. It has, however, become less popular as mitral valve replacement with durable prosthesis is now preferred. Another procedure which has further reduced the number of patients available for commissurotomy is percutaneous transseptal mitral commissurotomy which was introduced in 1984. Some studies have shown that mitral commissurotomy results in better long-term survival rates and fewer valve-related complications when compared to valve replacement (53).

2.5.3 Mitral Valve Repair

Surgical valve repair for mitral regurgitation has significant advantages over valve replacement. This is especially crucial in patients from developing countries since it obviates the problems of anticoagulant monitoring and bleeding complications. Furthermore, coumarin is largely contraindicated in women of child-bearing age. This advantage is evidenced in degenerative mitral valve disease common in developed populations, but the benefits of repair are questioned in rheumatically damaged valves in which the leaflets may look relatively normal on macroscopic examination but harbor microscopic inflammatory cell infiltration leading to progressive fibrosis and leaflet deformity. The overall freedom from valve failure after repair in one report was only 66% and thought to be the result of rheumatic pathology after a mean follow up of 5 years (24)**.**

In the setting of endocarditis, controversy still exists as to the success of mitral valve repair, but more and more studies are beginning to show better early and late mortality as well as event-free survival when compared with replacement (54)**.** This has been possible with the advancement of complex repair techniques including leaflet and commissural reconstructions. The key to success remains adequate debridement of all infected or devitalized tissue.

2.5.4 Balloon valvuloplasty

Percutaneous mitral balloon valvotomy was introduced in 1985 for the treatment of selected patients with isolated mitral stenosis. This procedure is ideal for patients who are candidates for surgical commissurotomy, especially those with non-calcified pliable mitral valves and no left atrial thrombus. It avoids thoracotomy for closed commissurotomy which is still performed in some developing nations where cost and lack of balloon catheters are continuing problems.

Some studies report 10 year continued good functional results in patients who had immediate procedural success (55).

2.6. Outcome of primary valve surgery

Outcome of valve replacement depends on many factors including patient profile, pathology and, probably, geography. It must, however, be stated that much morbidity and mortality is a direct consequence of the interaction between the patient and operated valve(s), although patient variables may be more responsible for outcomes than an operated valve.

It has been difficult to understand the role that various patient variables exert on operative mortality for a multitude of reasons. Many studies have reported on small numbers in specific subgroups of patients thereby having incomprehensive analyses, while some have been reluctant to publish high-mortality data from complex procedures. Again, there has been a lot of confusion from patient classification and changing results over time as a result of evolution of prognosis.

Traditional predictors of operative morbidity and mortality may no longer have as important an impact on clinical outcomes as they used to have. Therefore, periodic assessment of a surgical population is necessary to identify a changing demographic profile.

2.6.1 Determinants of Operative Mortality

The Society of Thoracic Surgeons (STS) database which records more than 70% of US adult cardiac surgical procedures is typically used to generate a simple but comprehensive risk factor analysis of operative mortality (56).

2.6.1.1 Acute Presentation

The most striking factor observed was acute presentation, associated with a 2-fold increase in operative mortality. One disappointing trend noted was a 42% increase in acute presentation over the decade studied. The reason for this is not clear. Cardiac clinicians, however, need to intensify efforts to emphasize earlier surgical referral for all types of severe valve lesions before urgent or emergency intervention is required.

Although some patients are obligatory acute presenters such as in the case of aortic dissections and endocarditis, many more have already been evaluated for surgery for a while and then are suddenly hospitalized with pulmonary edema requiring surgery. Obviously, these patients should have been operated much earlier.

In populations with low socioeconomic status, presentations are usually late and patients are frequently in grave hemodynamic condition. Surgeons then often have no choice but to attempt to salvage these patients as they virtually have no prospect for successful medical treatment or survival without operation. Kinsley et al. from

South Africa reported a 77% early salvage rate and a 52% 3-year actuarial survival in a series of 170 patients over a 4½-year period. Among the five subgroups studied, including infective endocarditis, acute rheumatic carditis, previous valve operation, acute-on-chronic disease and miscellaneous disease, excellent survival of patients was noted in the infective endocarditis group (91% at 3years). The 3-year actuarial survival of hospital survivors in patients with acute rheumatic carditis and previous valve operation was only 51% and 65% respectively (57)**.**

Even though there is reluctance to operate on acute rheumatic carditis because of concomitant myocarditis, it may become imperative as there is frequently a mechanical valvular impediment.

al Kasab et al. reported on six patients with acute rheumatic carditis and intractable left ventricular failure, all in class IV New York Heart Association (NYHA) classification, from the Kingdom of Saudi Arabia. They attributed the severe hemodynamic deterioration in their patients to be due to valvular structural insufficiency as opposed to those patients in which severe congestive heart failure was as a result of poor left ventricular function with minimal valvular insufficiency in which valvular surgery may be of no value. Their results showed that over a mean follow-up period of two years, no mortality was recorded and all six patients had improved to NYHA class I-II (58)**.**

There is a direct relationship between timing of surgery and risk of primary and re-operative valve replacement, making determination of optimal timing an important issue. Patients with no or minimal symptoms in NYHA class I-II prior to surgery, show excellent results both short- and long- term, leading to a tendency to perform surgery earlier (59)**.**

2.6.1.2 Tricuspid valve procedures

Many of the patients requiring this procedure are usually very ill with chronic systemic venous hypertension leading to hepatic and renal failure. Post-operative management is also usually challenging.

2.6.1.3 Re-operation

Reoperation has been identified as another important preoperative variable but is thought to become only significant when more complex lesions are to be tackled. The factors influencing outcome of re-operations are further highlighted later.

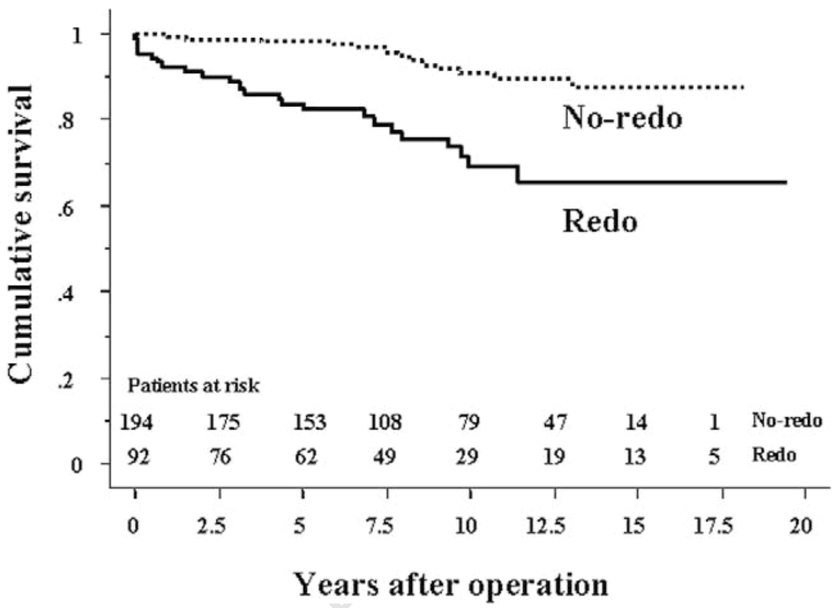


Figure 6: Survival following re-operation in a study of 92 patients (60).

In a study of 92 patients who underwent re-operation **(**Figure 6**)**, the survival rate was significantly lower compared with that of patients who had not required reoperation during the same period (p<0.0001) (60).

2.6.1.4 Age

In the last decade there have been complex changes in the patient population with more patients with advanced valvular disease being submitted for surgery. The demand for cardiac surgical procedures in the very elderly is also expected to increase with time as life expectancy increases. Elderly patients with significant co-morbid conditions are increasingly being offered surgery.

Advancing age subjects the heart to fibrosis and calcification such that senile aortic stenosis is one of the most prevalent valvular lesions in the elderly but this may be relatively well tolerated in patients despite their years, unlike mitral valve disease which is less well tolerated. The successes recorded are a testimony to the improved medical and surgical care of the cardiac patient. Guyton and coworkers prospectively examined the profile of 2,972 patients undergoing heart valve replacement over a ten year period and showed that, although older and sicker patients were managed, outcome remained constant with significantly reduced length of hospital stay (61).

Similarly, improved early results following heart valve surgery have been reported by Hellgren et al. in a ten year period involving 2327 patients (62).

In contrast, Grunkemeier (63) found that the older the patient at the time of prosthetic heart valve implantation, the lower the 10- to 20-year survival rate (Figure 7), a phenomenon most likely due to a greater incidence of significant associated comorbidities.

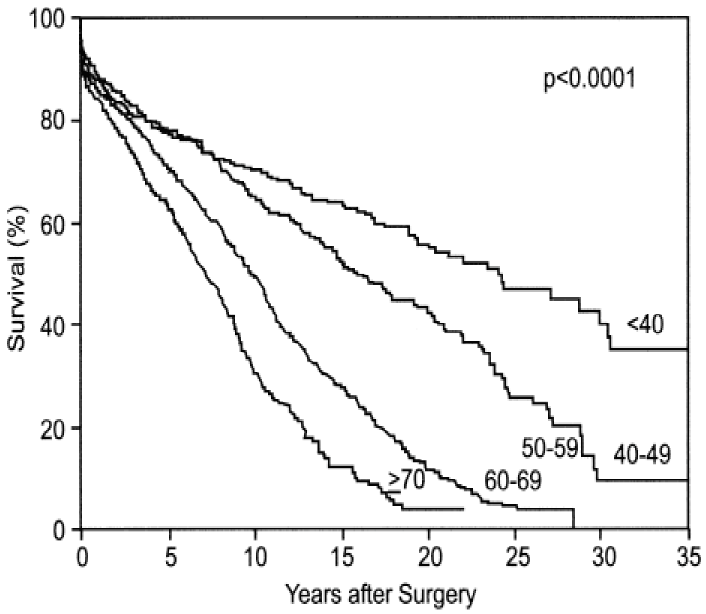


Figure 7: Survival after PHV replacement by patient's age at time of implantation (63).

2.6.1.5 Gender

It is known that gender differences affect the pathophysiology of valvular heart disease, with women having a 5% to 10% higher cardiac output at any level of submaximal oxygen uptake than men. This is attributed to lower hemoglobin in women. The higher cardiac output implies a higher valve gradient, which is important when calculating valve area. This becomes even more important when one realizes that normal pregnancy is associated with a 30% to 50% increase in blood volume and cardiac output. Also, because women are on average smaller than men, it is best to index for body size when performing valve calculations (19).

- Mitral stenosis has a 3:1 preponderance among females, and calcification of the valves tends to occur later in women providing a longer time window in which balloon valvuloplasty can be performed (19).
- Aortic valve disease, such as bicuspid valves and non-rheumatic aortic stenosis have nearly a 3:1 male predominance in clinical and autopsy studies (64).

2.6.1.6 Race

Previous studies had shown the black race to be an independent predictor of increased mortality after coronary artery bypass graft (CABG) surgery (65). However, based on STS data, Bridges and co-authors found that there was no significant difference in risk-adjusted mortality between white and black patients studied for either mitral valve replacement (MVR) or aortic valve replacement (AVR). Black patients, however, were more likely to suffer certain complications, including renal failure and prolonged ventilation. Postoperative stay greater than 14 days and reoperation for bleeding were also significantly increased among the black race (66). In a symposium focused on 'Understanding Disparities in Cardiovascular and Thoracic Surgical Outcomes in African Americans', Bridges noted that there has not been a study specifically investigating the role of race as an independent predictor of mortality. He did however note that racial bias on the part of the referring physician may be implicated, as evidence suggesting that neither disease severity, availability of health insurance nor socioeconomic status could explain the observed differences compared to whites (65).

2.6.1.7 Demographics of the Western Cape

The Chris Barnard Division of Cardiothoracic Surgery at GSH, one of five other referral centres, is a tertiary hospital unit serving a large indigent population of the Western Cape. This province probably has the greatest mix of first and third world dynamics.

According to 2001 census figures (67), of the 4.5 million estimated population, more than half of the Western cape population were of the Coloured racial group (Figure 8) with 17% of population aged 15-65 being unemployed. The largest age group falls between 25-44 years (33%). This is traditionally the most active age bracket. Very few are older than 65 years (5%).

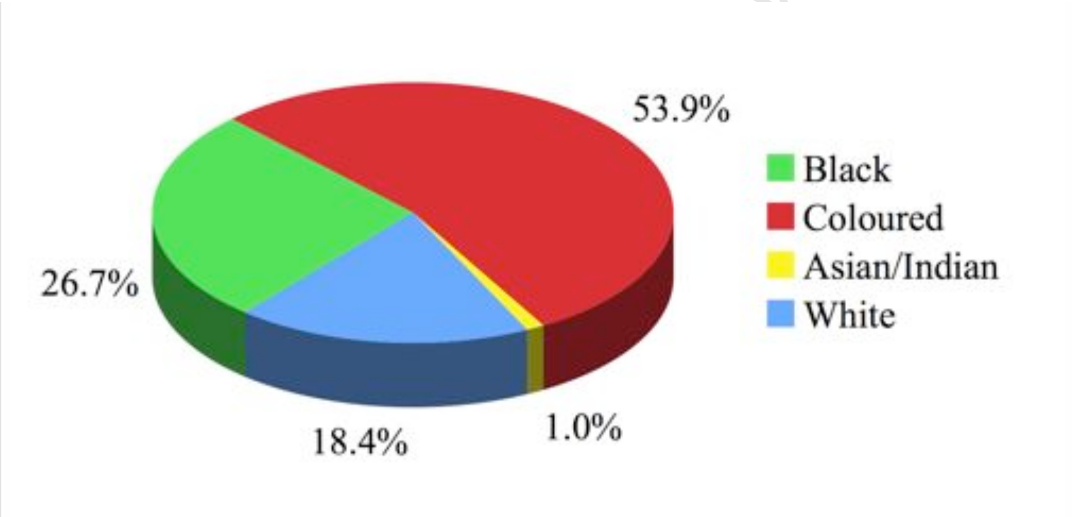


Figure 8: Racial distribution of the Western Cape (67)

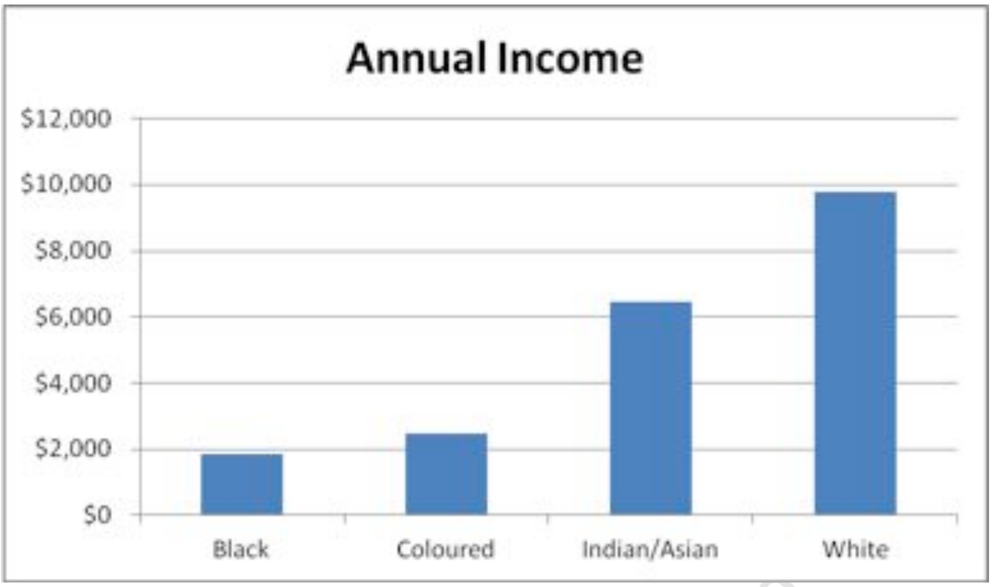


Figure 9: Average annual income of Western Cape racial groups (67)

The majority of the population represented by blacks and coloureds (80%) also fall into the lower income bracket **(**Figure 9**).**

Educational Level

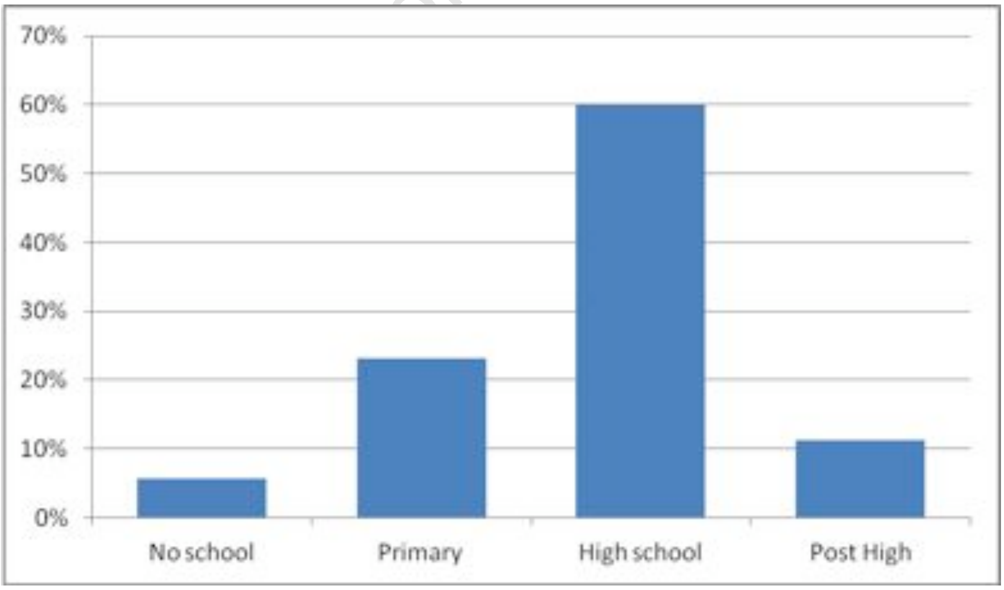


Figure 10: Educational levels in the Western Cape (67)

There is a high level of educational attainment in the Western Cape with < 5% remaining unschooled (Figure 10).

2.6.1.7 Prosthesis-patient mismatch

Ever since Rahimtoola in 1978 proposed the term ‘prosthetic-patient mismatch’ (PPM) to describe high postoperative transprosthetic gradients despite normally functioning prostheses, it has become a more frequent problem than originally believed and it may have a significant impact on the long term results of valve surgery.

It has been demonstrated that to avoid any significant gradient at rest or during exercise, the indexed Effective Orifice Area (EOA) should ideally be no less than 0.85 to $0.90cm^2/m^2$.

PPM has been recognized by the American STS and has been identified as a nonstructural hemodynamic abnormality rather than being due to an intrinsic defect of the prosthesis.

The incidence of PPM is estimated to be about 52% of patients with a stented bioprosthesis (68)**.** The consequences of PPM include excessive resting residual transvalvular gradients which double during exercise, and are associated with persistent left ventricular hypertrophy. This leads to left ventricular diastolic dysfunction with heart failure and arrhythmias.

2.6.2. The EuroSCORE Scoring System

Many scoring systems have been developed in the past to aid in predicting mortality following cardiac surgery. These include Parsonnet, The Cleveland Clinic coronary scoring system and the UK Society of Cardiothoracic Surgeons Risk score. These older systems were developed from institutional and national databases and have given way to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) introduced in 1999 which is based on a 20,000 patient database drawn across eight European countries and has been developed for the prediction of in-hospital mortality after adult cardiac surgery.

The standard EuroSCORE system consists of three risk groups: low risk (0-2) with an expected mortality under 2%; medium risk (3-5) with an expected mortality under 5%; and high risk (>6) with an expected mortality greater than 10%. EuroSCORE is effective for both early and long-term mortality prediction after cardiac surgery (69). Two different scoring systems exist for the EuroSCORE namely the additive model - a score that can be calculated by simple arithmetic - and the logistic model - which is more extensive and requires computer based calculations. It has been observed that the additive model tends to underestimate risk in very high risk patients while conversely overestimating risk in low and moderate risk patients.

The EuroSCORE system has been tested with good correlation in several local populations around the world including Europe, Japan, Scandinavia and the USA. In a validation study in Australia, using the database from the Australian Society of Cardiac and Thoracic Surgeons (ASCTS), the additive and logistic EuroSCORE were unable to accurately predict outcomes (70). It is therefore used with caution for risk-adjustment or risk-prediction in Australia.

Unfortunately, this system is yet to be validated in Africa with its unique spectrum of cardiovascular disease. It may be necessary to modify the EuroSCORE to suit the African population which is clearly distinct from European or American populations. It is interesting to note that the EuroSCORE was developed because of the inappropriateness of extrapolating North American patient population figures which 'may' not apply to European practice (71).

While validating the EuroSCORE in North America, it was observed that there were important differences between the European and American populations. American patients were older, with proportionately more females. American patients were also associated with a higher incidence of comorbidity (respiratory, vascular, neurological and renal). Endocarditis had a higher incidence in Europe. All these differences were highly significant (72).

To facilitate an African modification of the EuroSCORE, the establishment of a South African, that is a national, Cardiac and Thoracic Surgery database is certainly long overdue. The creation of a national database is crucial to the proper assessment of outcome. This ought to be the cornerstone of developments in cardiac surgery as it allows quality assessment and meaningful comparison and improvement of outcome.

2.6.3 Outcome

The consequences of these morbid events include reoperation, valve-related mortality, sudden unexplained death and permanent valve-related impairment which includes neurologic or other functional deficits.

In assessing outcome of valve replacements, the term 'major adverse prosthesis-related event' (MAPE) has been developed, defined as the composite outcome of any reoperation, major bleeding, thromboembolic event, or endocarditis during the late follow-up. In the last decade there have been complex changes in patient make-up with more patients with advanced valvular disease being submitted for surgery. Elderly patients with significant co-morbid conditions are increasingly being offered surgery. The successes recorded are a testimony to the improved medical and surgical care of the cardiac patient. Guyton and coworkers prospectively examined the profile of 2,972 patients undergoing heart valve replacement over a ten year period and showed that although older and sicker patients were managed, outcome remained constant with significantly reduced length of hospital stay (61). Similarly, improved early results following heart valve surgery have been reported by Hellgren et al. in a ten-year period analyzing 2,327 patients (62). This group also recommended surgery in the early stages of valvular disease to improve long-term outcome.

There is a direct relationship between timing of surgery and risk of primary and re-operative valve replacement, making determination of optimal timing an important issue. Patients with no or minimal symptoms, NYHA class I-II, prior to surgery show excellent results both short and long term, leading to a tendency to perform surgery earlier (10).

2.7 Reoperative valve surgery

In the early years of cardiac surgery, most reoperations were carried out for structural valve dysfunctions, including fabric fatigue in fabric reinforced prostheses, and lipid absorption and poppet swelling in the early Starr-Edwards valve models. This often happened acutely with resultant emergency conditions and high mortality. In the mid-70s, prophylactic replacement of the Braunwald-Cutter valve and other cloth covered valves for hemolysis or cloth wear were accompanied by extremely low mortality. Most reoperations today are due to paravalvular leaks, prosthetic valve thrombosis, prosthetic valve endocarditis and lately, structural degeneration of bioprosthetic valves implanted from the late 70s and 80s (73)**.** These prosthetic valve complications are further discussed below.

2.7.1 Prosthetic Valve Complications

2.7.1.1 Prosthetic valve thrombosis

Mechanical prosthetic valves are particularly prone to acute prosthetic thrombosis, usually as a result of failure of anticoagulation (74)**.** The incidence of prosthetic valve thrombosis can be as high as 13% in the first year in any position and as high as 20% in the tricuspid position. There is still a risk of thrombosis even with adequate anticoagulation of between 1% to 4% per year (75)**.**

In developing economies like South Africa, where there is a lack in certain areas of proper follow-up and anticoagulation monitoring, this is not uncommon as many patients are unable to access INR facilities near where they live. This has prompted some workers to recommend fixed-dose rather than adjusted-dose anticoagulation regimens (37)**.**

Emergency or urgent surgery has been the mainstay of management, with replacement of the prosthesis, but thrombolysis has gained ground, although there are no randomised trials evaluating surgery with thrombolysis (75)**.** Bioprosthetic or homograft valves on the other hand do not require long-term anticoagulation unless the patient has a significant risk of thromboembolism or has had a thromboembolic event with their prosthesis. In the first three months however, the current American College of Cardiology / American Heart Association guidelines recommend anticoagulation with warfarin because of the increased risk of thromboembolism before the exposed surfaces of stented bioprosthesis endothelialize (76)**.**

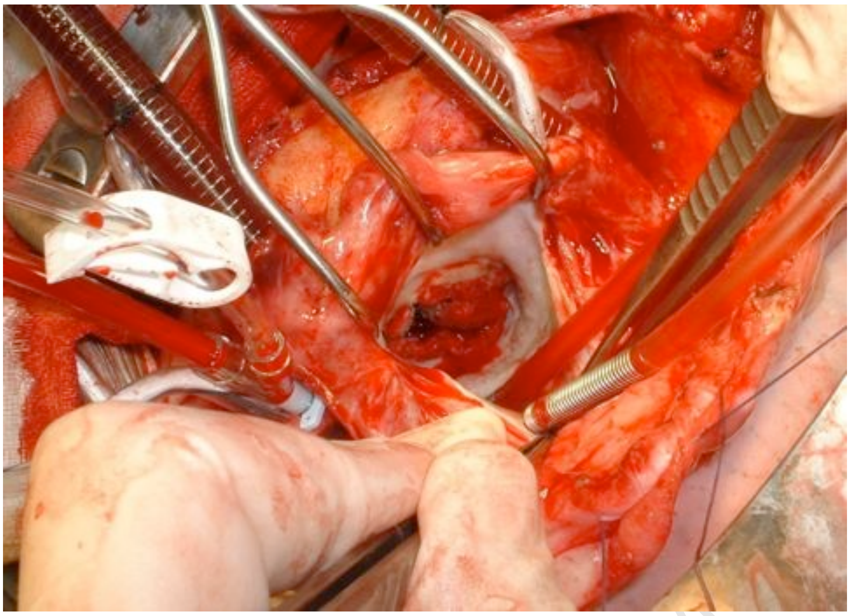


Figure 11: Prosthetic valve thrombosis (77)

2.7.1.2 Pannus

Pannus is a membrane of granulation tissue as a response to healing that often causes prosthetic valve obstruction. It is very difficult to differentiate it from thrombus but duration of symptoms and adequacy of anticoagulation are helpful in differentiating thrombus from pannus formation. The use of transesophageal echo (TEE) can assess the mechanism and etiology of obstruction. Thrombus is overall larger than pannus and often extends into the left atrium in prosthetic mitral valves. The best TEE parameter that differentiates the two entities is the ultrasound intensity of the mass. A videointensity ratio of <0.7 had the best negative predictive value for thrombi. A high negative predictive value for thrombus would allow detection of most thrombi and therefore identify patients with pannus formation and in whom one can forgo attempts at thrombolytic therapy and instead initiate immediate valve surgery, particularly when presenting with hemodynamic instability.

The combination of clinical parameters and ultrasound density of the mass by TEE further strengthens the differentiation of thrombi from pannus formation and may therefore be of value in refining the selection of patients for thrombolysis (78).

2.7.1.3. Prosthetic valve endocarditis

This is a catastrophic complication following valve replacement with an incidence of about 0.3% to 1.2% per patient year and cumulative risk of 5% at 10 years (79). Despite improvements in antibiotic prophylaxis, the incidence does not seem to be declining with a mortality of between 2% and 60% in different reports (80).

2.7.1.4. Structural Failure (Structural valve dysfunction – SVD)

Mechanical Valves: It is very uncommon for mechanical prostheses to undergo structural failure. For example, there have been no failures reported with the original Medtronic-Hall valve in approximately 130,000 implants while the D16 variation reported 4 disc fractures in approximately 80,000 implants and has since been removed from the market (81). In the event of structural failure of a valve, this is reported to the manufacturers for appropriate actions.

The latest occurence of structural failure was with the TRI Technologies (TT) valve, a low-profile bileaflet prosthesis commercialised in Brazil. After three valve-related deaths occured between 2002 and 2004, the valve was promptly removed from the market. Patients who had received the valve underwent a prophylactic replacement program with St Jude valves (82).

Freedom from reoperation for currently available mechanical valves is greater than 95% at 10 years and greater than 90% at 15 years (43).

Tissue Valves: Bioprosthetic valves on the other hand will inevitably undergo structural degeneration which is the leading cause and most frequent indication for reoperation in patients with bioprosthetic valves (83), (84).

The mechanism of degeneration is mainly due to increased calcification in the cuspal commissures and basal attachments extending later into the center of the leaflet, largely because these parts receive the greatest hemodynamic stress and become stenosed and incompetent. Currently, glutaraldehyde is the standard fixative in the processing of tissue valves with no alternative yet in sight. There is some contention on the role of glutaraldehyde in the calcification process, with some workers suggesting that glutaraldehyde itself is partly responsible for calcification of xenograft tissue (85). However, recently, Zilla et al. showed increased glutaraldehyde concentrations conversely significantly mitigated bioprosthetic tissue calcium levels in the sheep and the rat. Contemporary valves may therefore be using suboptimal glutaraldehyde concentrations rendering them more immunogenic and thus proinflammatory (86). Prolonging the lifespan of these valves will require inhibition of this mineralization process through the use of different chemical anticalcification agents (31). Such anticalcification agents such as surfactants, biphosphonates and alpha-amino oleic acid have been extensively studied. Recently, Zilla et al. showed even further augmentation of anticalcification properties of alpha-amino oleic acid combined with carbodiimide (87), suggesting that much research is still required in this field.

Both mechanical and tissue valves are, however, not immune from endocarditis, dehiscence, perivalvular leak and pannus formation, amongst other complications. It is therefore difficult to adequately compare the two different valves because of differences in the mechanism of failure.

With the availability of new stentless valves and homografts, more aortic bioprosthesis are being implanted in progressively younger age groups (88) with the knowledge that these valves would only last between 12 to 15 years (89). The decision to use a bioprosthesis for primary isolated AVR requires the lowest possible reoperative mortality to improve the long-term outcome in these patients.

The cryopreserved allograft (homograft) is believed to be superior to the xenograft and 4˚C-stored allograft valves in patients younger than 60 years while there is no difference for all three in patients older than 60 years. Allograft valve failure appears to be a complex interplay between mechanisms such as leaflet degeneration, geometric distortion, changing mechanical properties of the leaflet tissue, and aortic root dilatation (90). Furthermore, the allograft valve has an additional advantage over both xenograft and mechanical valves for aortic valve replacement in the setting of endocarditis with a lower probability of recurrent endocarditis (91).

2.7.1.5. Periprosthetic leak (PPL)

Periprosthetic leak (PPL) occurs in 1% to 3.5% of patients after aortic valve replacement while in the mitral valve, the incidence is as high as 13%. Factors known to predispose to this problem include prosthetic valve endocarditis, dilated cardiomyopathy, ischemic mitral regurgitation and of course suture or surgeon related technique.

The role of anatomical factors in the occurence of periprosthetic leak in both the aortic and mitral positions has not been properly studied. The current thinking is that the role of anatomical predisposition is much more than previously thought. G. DeCicco et al. have suggested in two different reports (92), (93) that the majority of PPL in the mitral area occur at the anterolateral and posteromedial segments of the mitral valve annulus, whereas the area of the aortic annulus between the middle of the right coronary sinus and the middle of the non-coronary sinus were more at risk of developing PPL.

2.7.2. Factors influencing mortality

It was to this end that the National Cardiac Surgery Database of the STS which contains records of 86,580 patients was created. In the analysis of the ten year data with 51 preoperative variables, Jamieson and colleagues report that re-operative mortality rates are only significant when first operations were elective or urgent but not with emergent and emergent-salvage operations (94)**.** Ideally, the hospital mortality after valve re-replacement should be identical to that of the equivalent primary valve procedure to improve the long term outcome especially with bioprostheses (88)**.**

The beauty of the STS Database is that institutions can enter their patient population data and obtain direct risk-adjusted comparisons with the national standard (94). Many workers will agree that the overall mortality for first reoperations is about 10% (42). However, the risk reduces to about 3% in patients who had initial reparative procedures, for example mitral valve repairs, or who underwent surgery for new native valve disease. This encourages the use of valve repair where possible because the risk at reoperation is not increased (42)**.** In the past, reoperative surgery has been associated with a considerably higher operative mortality than primary valve surgery. Poor preoperative left ventricular function and duration on cardiopulmonary bypass, but not the number of reoperations has been correlated with operative mortality (4). Another important predictor of hospital mortality is the NYHA classification. This has led some workers to suggest that patients with structural dysfunction of bioprostheses may be operated on, even when oligosymptomatic (73).

Vogt et al. agrees that emergency surgery is the most important factor responsible for high early mortality and that early reoperation of failing bioprosthesis is advised to reduce the incidence of emergency surgery (86). They therefore emphasize proper timing of the reoperation with early reoperation improving the long-term outcome of patients with tissue valves.

SVD can be identified two to three years before the patient becomes symptomatic and needs reoperation. Regular Doppler echocardiographic follow-up examinations should be carried out starting no later than six to seven years after implantation (31).

A special category of 'high risk' patients undergoing reoperation are the octogenarians. The population >80 years is expected to rise to 25 million in America, that is one in twelve Americans, by 2050. In a study by Kirsch et al. the indication for reoperation in this group as a result of degeneration of previously implanted bioprostheses accounted for 50% of the study population. Twenty seven percent had new valvular diseases while 18% had progression of rheumatic valvular heart disease. Five percent (1 patient) had prosthetic valve endocarditis. The mortality in octogenarians from their study was as high as 38% (95). Ghosh and co-workers (96) advocate very careful screening in this high risk group to achieve a beneficial outcome. It will be necessary to identify contraindications to surgery, a practise amounting to rationing of medical care in this vulnerable aged subset, but which promises to ensure definitive benefits in reoperative candidates.

2.7.3 Surgical Technique

2.7.3.1 Resternotomy

Resternotomy is technically demanding, and careful attention to not go beyond the posterior table of the bone with the oscillating saw is essential to avoid complications. Most authors recommend dividing the posterior table using a combination of scissors and lateral retraction. Preoperative computerised tomogram (CT) scans to detect aortic and right ventricular adhesions to the sternum have significantly dropped the incidence of sternotomy-related injuries (97)**.** The exact incidence of this dreaded complication is unknown due to lack of consistent definition and partly due to underreporting as it may imply a technical error (98)**.** Analysing 552 patients who underwent reoperative valvular surgery, Husebye et al. had a 4% complication rate directly related to sternal opening with two operative deaths from coronary artery graft laceration and laceration of the aorta with subsequent exanguination (73)**.** Attempts at resternotomy should be abandoned once major hemorrhage occurs and peripheral cannulation using the femoral vessels should be immediately carried out.

Alternative perfusion sites using the groin and the axillary routes have been developed and preparations for emergency cardiopulmonary bypass should be completed prior to beginning the resternotomy. Proper use of deep hypothermic cardiac arrest and improved myocardial protection. have also contributed significantly (99)**.**

Minimally invasive valve procedures have gradually become more acceptable in the setting of reoperations. Partial upper resternotomy using an inverted-T incision has been refined since it was first used in 1996 (100)**.** There has been an evolution of techniques in reoperative valve surgery. This has contributed significantly to the reduction of mortality. Major advances include the development of alternative incisional approaches to minimize injury to adherent cardiac structures. Right anterolateral thoracotomy is a safe alternative to resternotomy for mitral valve replacement. It provides excellent exposure of the mitral and tricuspid valves and avoids the dissection of the pericardium.

CHAPTER 3: PATIENTS AND METHODS

3.1. Introduction

This study is a retrospective analysis of valve and valve redo-procedures performed at Groote Schuur Hospital (GSH) within the University of Cape Town's Chris Barnard Division of Cardiothoracic Surgery during a 16 year period in order to examine short term outcomes of valve surgery as well as factors that may influence the time to failure of these valves.

The main thrust of this study was to determine the demographics and presentation of patients and to assess whether the currently preferred choice of prostheses could be validated by retrospective examination of longer term outcomes.

From 1993 to 2008, consecutive patients who underwent heart valve procedures were captured by our 'Summit' database which commenced in 1993 and subsequently by a database developed in-house which replaced it in 2003. We did not include patients prior to 1993 because there was no database in existence during that period and complete records were infrequent. Even in the original Summit database, demographic and comorbidity data or type of valve implanted, for example, was incomplete although core data, that is relating to the etiology, the surgical procedure performed and short-term outcome, were nevertheless available. In some cases though, patients operated from 1993 but prior to 2003 (the capture period for the Summit database) were excluded from the study when even these core parameters were unavailable.

In order to better identify the differences between patients with rheumatic heart disease and those without, patients who had only single valve procedures were selected for analysis to remove the complex interactions of double or triple valve procedures with various combinations of incidence of operation and disease etiology.

During the 16 year period (1993-2008), 1,449 patients were thus defined for the purposes of this study who underwent first incidence single valve procedures out of a total of 2,939 patients who had 4,145 valve procedures at GSH which included single, double and triple valve surgeries.

Of the 1,449 (study population), 770 (53.1%) patients were identified with rheumatic etiology while 679 (46.9%) were non-rheumatic.

3.2. Variables

The following demographics were analyzed in this study: age, sex, race, educational status, employment status, housing type and preoperative NYHA class. Other intra operative variables include implant type and position, repair or replacement procedure and short term outcomes such as ICU stay, hospital stay and 30-day mortality. The time to reoperation was assessed as a long term outcome, but was severely limited by loss to follow-up of patients not presenting for redo procedures.

3.3. Guidelines for definitions

The following definitions, as established by the Society of Thoracic Surgery (http://www.sts.org), were applied in part in this analysis:

3.3.1 Mortality

Thirty-day mortality (sometimes termed operative mortality) referred to death within 30 days of operation regardless of the patient's geographical location.

Hospital mortality referred to death within any time interval after operation if the patient was not discharged from the hospital. Note that hospital to hospital transfer was not considered discharge. In-hospital mortality is one of the most widely used measures of outcome for determining the risks/benefits of cardiac surgery (5), (101).

3.3.2 Morbidity

SVD is any change in function (a decrease of one New York Heart Association functional class or more) of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. These are changes intrinsic to the valve such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components (e.g., leaflets, chordae) of an operated valve.

Nonstructural dysfunction refers to any abnormality which resulted in stenosis or regurgitation, exclusive of thrombosis and infection, not intrinsic to the valve itself. Examples include entrapment by pannus, tissue, or suture, paravalvular leak, inappropriate sizing or positioning, residual leak or obstruction from valve implantation or repair, and clinically important hemolytic anaemia.

Valve thrombosis refers to any thrombus, in the absence of infection, attached to or near an operated valve that occluded or interfered with valve function.

Embolism - any embolic event that occurred after the immediate perioperative period i.e. when anesthesia-induced unconsciousness was completely reversed. A neurologic event included any new, temporary or permanent, focal or global neurologic deficit. These included transient ischemic attacks (TIA), reversible ischemic neurologic deficit (RIND), stroke or permanent neurologic event.

Bleeding event - any episode of internal or external bleeding that caused death, hospitalization or necessitated transfusion.

Operated valvular endocarditis - any infection which involved an operated valve.

3.4 Statistical Analysis

Values of continuous data were presented as means ± sample standard deviation (SD) or as medians plus range, when appropriate. Categorical variables were displayed as frequency distributions (n) and simple percentages (%). Univariate comparison between the groups for categorical variables was made using the chi-square and the Fisher's exact tests when appropriate. Logistic regression was used to examine the relationship between the short and long term outcome variables and potential risk factors. Statistical significance was accepted when $p < 0.05$.

All statistical analyses were performed using the JMP6.0.2 (SAS,Inc, Cary, NC) application on an Apple PowerPC-based Macintosh computer (Apple, Cupertino,CA).

3.5 Challenges (Limitations)

This study is particularly challenging because it is difficult to provide medical services and conduct research in a disadvantaged population where patient follow-up is hampered by an indigent and especially migrant population. Many of our primary valve operated patients are lost to follow-up and may undergo re-operation in other centers and *vice versa*, either for prosthesis-related complications or for progression of native valve disease, thereby complicating the process of data collation.

A further challenge is the sifting of retrospective data generated from a 4-valved organ with various combinations of etiologies, procedures differing from valve to valve and even within the same valve, for example repair followed by replacement, one or more reoperations on the same valve and a host of other confounding factors. Technically speaking for example, a replacement of a previously repaired valve is a reoperation but also a first time replacement. So whilst there was no 'explant', it could easily be coded in a database as a reoperation … without an explant. There are countless examples of this kind of 'impure' data. To minimize this effect, patients who had single valve procedure only were selected for analysis.

Retrospective analyses too are however flawed because although capable of showing association, they cannot reliably determine causation and hence its value is not as strong as adequately controlled studies. It is also less likely to suffer the problem of 'missing data' which will also affect the power of the analysis.

Many patients in South Africa still do not have funds to promptly access medical attention resulting in poor patient clinical presentation with advanced disease states when and if they finally arrive. This unfortunately translates to very little surgical activity, and where it exists, fluctuating numbers of patients benefiting per year. This makes it impossible to plan any meaningful service or research.

This is similar in other sub-saharan countries which are often plagued by inadequate human and material resources. In Nigeria, for example, it has been very difficult to sustain cardiothoracic services in the few hospitals that have been able to offer them since 1974, largely because of the current severe devaluation of the Nigerian Naira (currency), making it difficult to procure consumables and other necessary equipment. Very few patients in Nigeria are able to afford cardiac surgery whilst insurance scheme cover for cardiac surgery is lacking (102). The story is no different in Uganda, where the health care budget is less than USD $ 15 per person per year (103).

It is hoped that future prospective studies will be undertaken at GSH which caters for a significant percentage of patients from poor backgrounds to distinguish between virtual and real risks in the context of the indigent patient.

We also hope that this study may eventually stimulate the development of a multi-centre study with the aim of establishing a regional database with large numbers, allowing inferences that will be useful in the practice of heart valve surgery across the African continent.

CHAPTER 4. RESULTS

Examination of the two cohorts of patients demonstrated a higher female prevalence in the rheumatic group (female:male ratio = 1.7) but a more equal distribution, albeit with a slight male prevalence, between the sexes in the non-rheumatic group (female:male = 0.86; p<0.0001) (Figure 14). The non-rheumatic patients were also significantly older by 17 years (Table 4).

Apart from female gender, rheumatic heart disease was significantly associated with black and coloured racial groups (p<0.0001), informal housing (p<0.0001) and unemployment (p<0.0001) (Table 4). Patient demographic data is displayed in Table 4 and in Figure 12 through Figure 16.

Whilst the coloured racial group accounted for the majority of patients in both rheumatic and non-rheumatic groups, there was a distinct black majority compared to whites (32.7% - black vs. 5.8% - white) in the rheumatic group and a distinct white majority compared to blacks (27.1% - white vs. 17.7% - black) in the non-rheumatic group (p<0.0001) (Figure 13).

The median age irrespective of race in the rheumatic group at the time of valve surgery is 42.2 years, compared to 59.6 years in the non-rheumatic group (Table 4) with a significant difference existing between racial classes in the rheumatic group (36.5yrs amongst Blacks compared to 51.6yrs amongst Whites; p<0.0001) (Figure 13). Both groups presented largely in poor NYHA class (III & IV) (p<0.0001) (Figure 17 and Figure 18).

Non-rheumatic patients were associated with significantly more co-morbidity factors such as smoking (p=0.038), renal failure (p=0.005), hypertension (p<0.0001) and diabetes (p<0.0001) as highlighted in Table 5.

Table 4: Patient Demographics

	RHD (n=770)	**Non-RHD (n=679)**	**P value**
SEX(M/F)	287/483	366/313	<0.0001
AGE Median (range) yrs	42.2 (16-81.3)	59.6 (16-85.2)	<0.0001
RACE			
Black (%)	252 (32.7%)	120 (17.7%)	
Coloured (%)	463 (60.2%)	366 (53.9%)	<0.0001
White (%)	45 (5.8%)	184 (27.1%)	
Asian (%)	10 (1.3%)	9 (1.3%)	
NYHA			
I	35 (4.6%)	42 (6.2%)	
II	279 (36.2%)	203 (29.9%)	<0.0001
III	401 (52.1%)	324 (47.7%)	
IV	55 (7.1%)	110 (16.2%)	
HOUSING	n = 539	n = 540	
Formal	439 (81.5%)	491 (90.9%)	<0.0001
Informal	100 (18.6%)	49 (9.1%)	
EDUCATION	n = 518	n = 529	
Matric	102 (19.7%)	126 (23.8%)	N.S.
No matric	416 (80.3%)	403 (76.2%)	
EMPLOYMENT	n = 531	n = 536	
Employed	275 (51.8%)	380 (70.9%)	<0.0001
Unemployed	256 (48.2%)	156 (29.1%)	

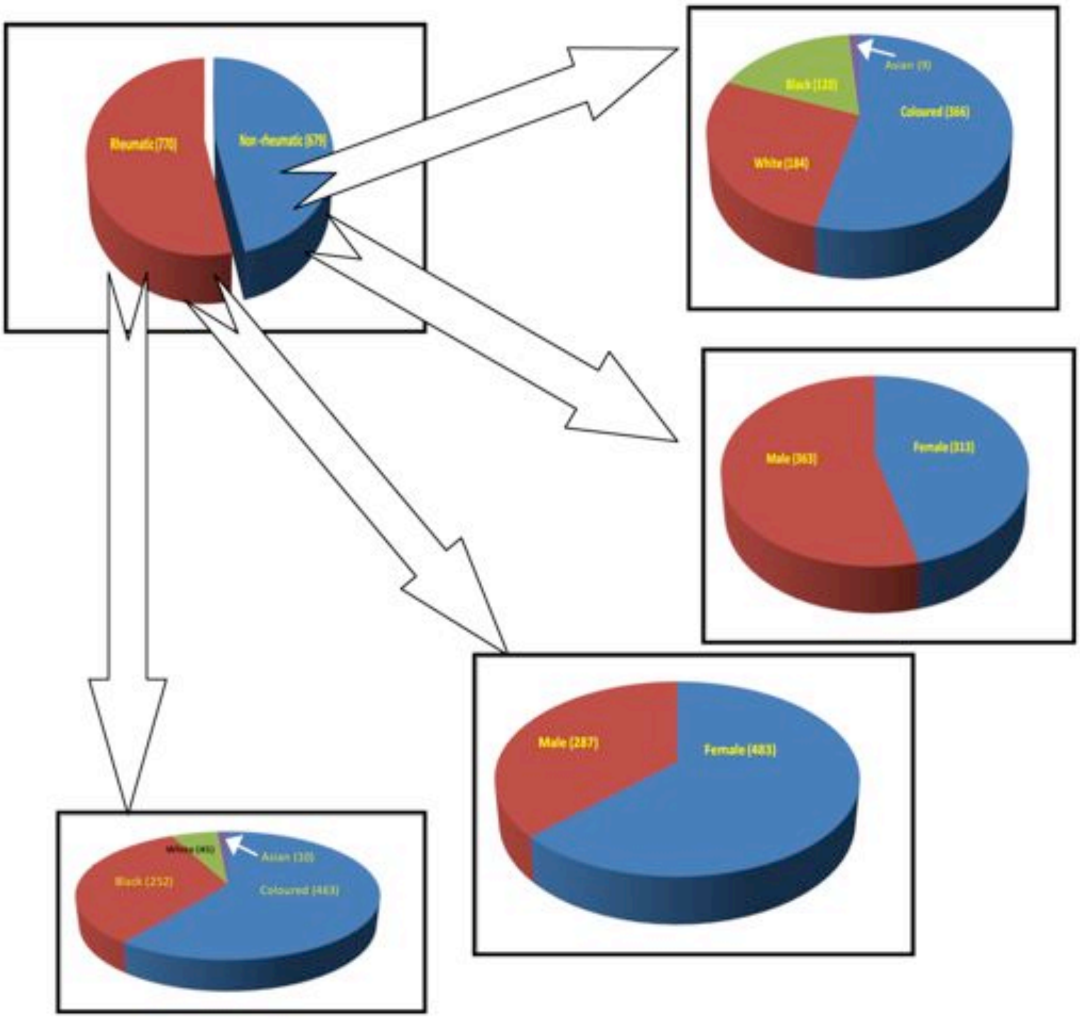


Figure 12: Demographics of gender and racial class between non-rheumatic and rheumatic patients

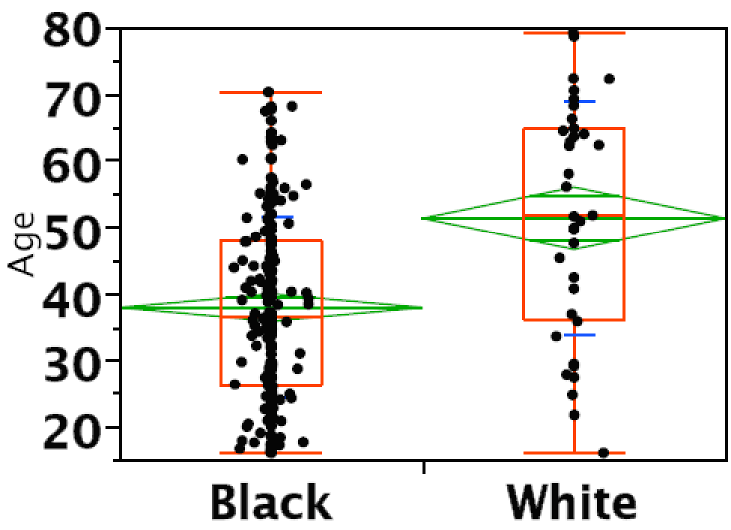
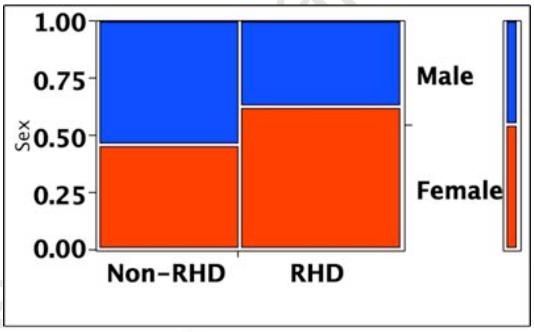
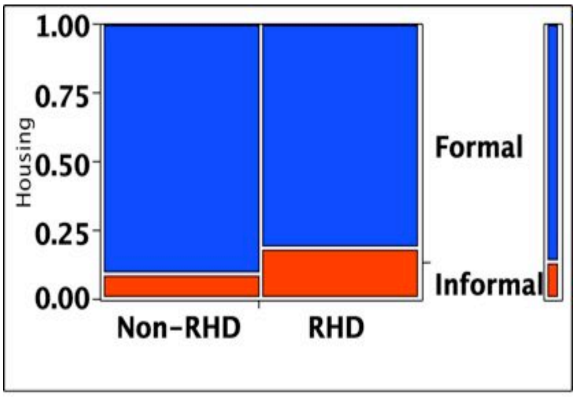


Figure 13: Age distribution of black and white racial groups.



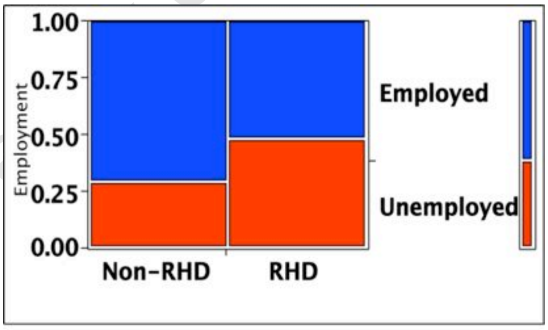
Count Total % Col % Row %	Sex Female	Male	
Non-RHD	313 21.60 39.32 46.10	366 25.26 56.05 53.90	679 46.86
RHD	483 33.33 60.68 62.73	287 19.81 43.95 37.27	770 53.14
	796 54.93	653 45.07	1449

Figure 14: Relationship between RHD and gender



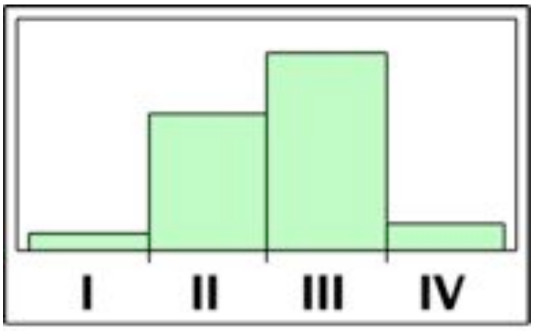
Count Total % Col % Row %	Informal	Formal	
Non-RHD	49 4.54 32.89 9.07	491 45.51 52.80 90.93	540 50.05
RHD	100 9.27 67.11 18.55	439 40.69 47.20 81.45	539 49.95
	149 13.81	930 86.19	1079

Figure 15: Housing and RHD



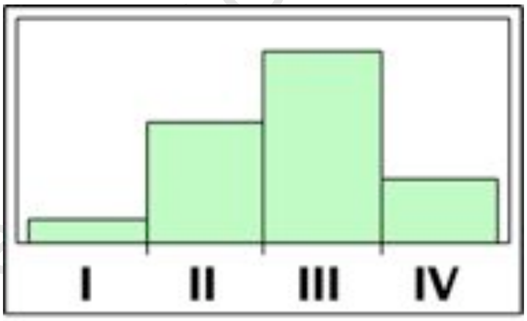
Count Total % Col % Row %	Unemployed	Employed	
Non-RHD	156 14.62 37.86 29.10	380 35.61 58.02 70.90	536 50.23
RHD	256 23.99 62.14 48.21	275 25.77 41.98 51.79	531 49.77
	412 38.61	655 61.39	1067

Figure 16: Employment and RHD



Level	Count	Prob
I	33	0.04609
II	259	0.36173
III	373	0.52095
IV	51	0.07123
Total	716	1.00000

Figure 17: NYHA classification of rheumatic patients



Level	Count	Prob
I	39	0.06200
II	188	0.29889
III	300	0.47695
IV	102	0.16216
Total	629	1.00000

Figure 18: NYHA classification of non-rheumatic patients

Table 5: Associated co-morbidity factors

Factor	RHD		Non-RHD		P-value
Diabetes	n= 42/528	(8.0%)	n= 80/496	(16.1%)	< 0.0001
Smoking	n= 258/515	(50.1%)	n= 283/500	(56.6%)	0.038
Renal failure	n= 10/533	(1.9%)	n= 25/497	(5.0%)	0.005
Obesity	n= 59/295	(20.0%)	n= 88/372	(23.7%)	0.260
Hypertension	n= 101/518	(20.0%)	n= 203/515	(39.4%)	< 0.0001
Ischaemic Heart Disease	n= 60/765	(7.8%)	n= 240/659	(36.4%)	< 0.0001

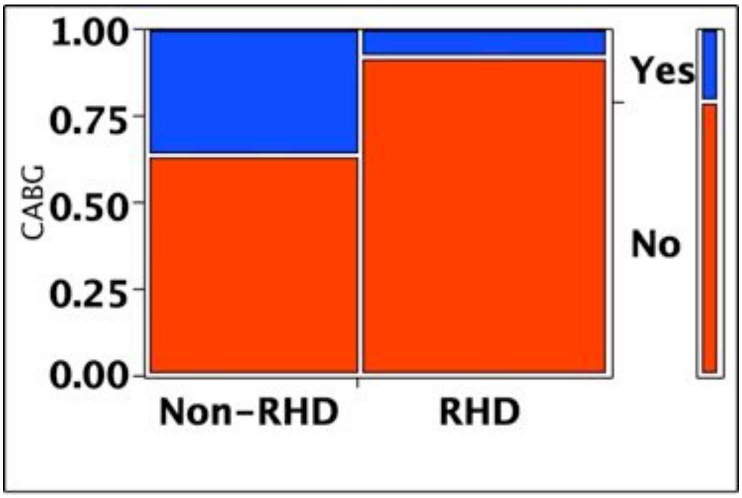
The etiology of non-rheumatic disease included calcific degeneration (38.4%), ischemic heart disease (14.4%) and myxoma (9.8%). Native valve endocarditis accounted for 8% of cases.

Table 7 highlights the procedural characteristics with 801 mitral (55.3%) and 648 aortic procedures. There were 190 (23.7%) repairs to the mitral valve. In only 67 (8.7%) of the rheumatic patients was repair attempted, while 123 (18.1%) of the non-rheumatic group had mitral valve repair (p<0.0001).

Valve replacement was the more common surgical procedure (83.5%) with 864 (60%) being mechanical. The majority of rheumatic patients (72%) had a mechanical prosthesis implanted. There were significantly larger numbers of concomitant CABG procedures in the non-rheumatic group (36%) than rheumatic (8%); (p<0.0001) (Figure 19).

From the study cohort of 1,449 patients (valves), there were 216 re-operations giving a presentation rate for reoperation of 15%. During the 16 year period, 163 (21.2%) of the rheumatic patients presented for reoperation while only 53 (7.8%) of the non-rheumatic group returned for re-intervention (Table 6). Most (70%) of implanted valves in both primary and redo surgeries were mechanical. Of the patients who received mechanical valves, 15.6% returned compared to 11.5% in the case of tissue valve patients (p=0.055).

The major reasons accounting for patients presenting for reoperation in the rheumatic group were progression of the rheumatic process in 36%, prosthetic valve thrombus in 26% and endocarditis in 8%. In the non-rheumatic group, degeneration of tissue valve accounted for 23% of reoperations, thrombus in 15%, pannus in 11% and endocarditis in 8%.



Count Total % Col % Row %	No	Yes	
Non-RHD	419 29.42 37.28 63.58	240 16.85 80.00 36.42	659 46.28
RHD	705 49.51 62.72 92.16	60 4.21 20.00 7.84	765 53.72
	1124 78.93	300 21.07	1424

Figure 19: CABG performed in RHD

Table 6: Original procedure in those patients undergoing reoperation

Ratios	RHD	Non-RHD	P-value
Aortic:Mitral	42:121	38:15	<0.0001
Mechanical:Tissue*	79:38	25:11	N.S.
Repair:Replace	19:144	11:42	N.S.

* (data was not available for all replacement patients)

Table 7: Operative Procedures

	RHD (n=770)	Non-RHD (n=679)	P value
Repair			
Mitral	**67**	**123**	**<0.0001**
Aortic	**1**	**48**	**<0.0001**
Replace			
Mitral	**465**	**146**	
Aortic	**237**	**362**	
Valve type*			
Mechanical	**458 (72.2%)**	**209 (45.4%)**	**<0.0001**
Tissue	**176 (27.8%)**	**251 (54.6%)**	
Reoperations	**163 (21.1%)**	**53 (7.8%)**	
Simultaneous CABG	**60 (8%)**	**240 (36%)**	**<0.0001**

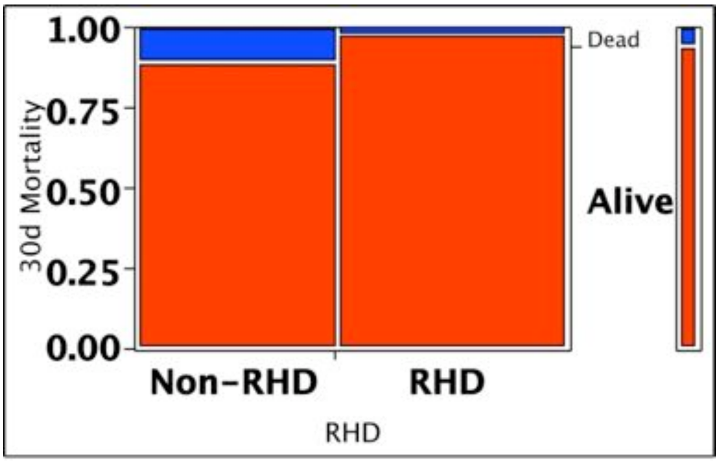
* (data was not available for all replacement patients)

Analysis of short and long-term outcome is shown in Table 8 and Table 9 respectively.

The mean ICU stay in the rheumatic patients was shorter (76.5±113 hours) than in non-rheumatic patients (99.3±155.1hours) (p=0.048). However, this was independent of the valve type or position. Patients with rheumatic disease had hospital stays of 11.5±10.4 days in hospital compared to 13.8±27.3 days for non-rheumatic patients (p=0.05). Thirty-day mortality occurred in 15 (2%) rheumatic patients and 72 non-rheumatic patients (11%) (p<0.0001) (Figure 20).

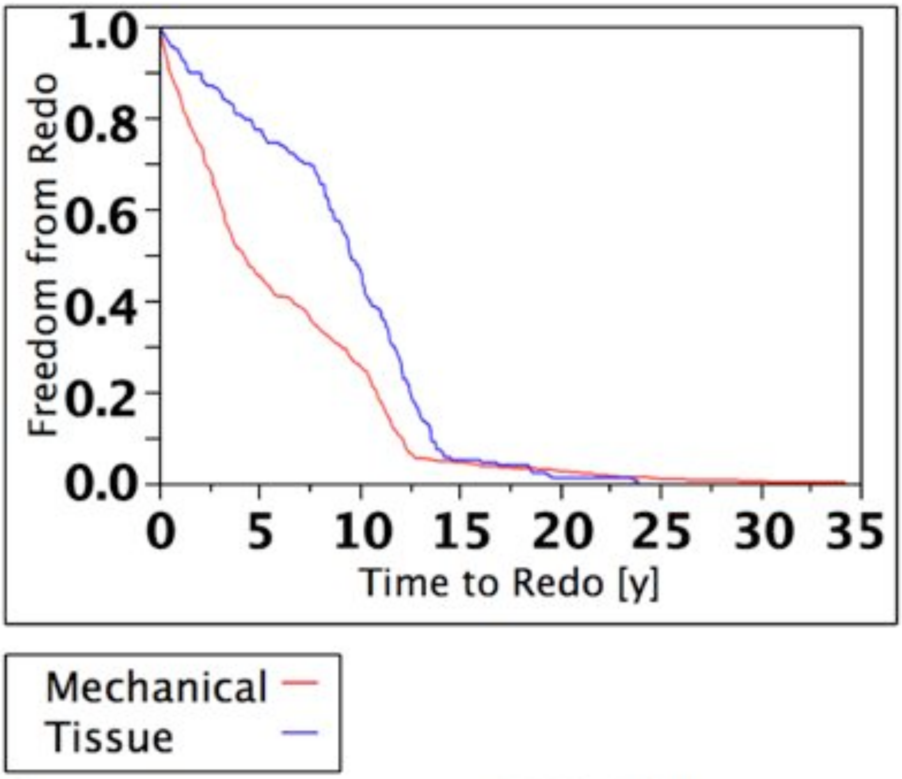
Mortality in rheumatic patients was dependent on valve type (tissue > mechanical) (p=0.0015), and presence of renal failure (p=0.019).

Patients presenting with failed mechanical valves did so significantly earlier [4.23 (0.003-34.3) years] in rheumatic patients compared to non-rheumatic patients [6.91 (0.01-24.4) years] (p=0.0039) as well as earlier than tissue valves in rheumatic patients, which presented with failure after 9.54 (0.11-23.89) years **(**Figure 21**).**



Count Total % Col % Row %	Alive	Dead	
Non-RHD	607 41.89 44.57 89.40	72 4.97 82.76 10.60	679 46.86
RHD	755 52.10 55.43 98.05	15 1.04 17.24 1.95	770 53.14
	1362 94.00	87 6.00	1449

Figure 20: 30-day mortality in RHD



Group	Median Time
Mechanical	4.2327
Tissue	9.5797
Combined	6.2505

Figure 21: Time to reoperation of valve prostheses used for rheumatic patients

Table 8: Early Outcome Analysis

ICU stay (hrs)	RHD	Non RHD	P value
Overall	**76.5±113**	**99.3±155**	**0.048**
Repair	**66.9±59.6**	**113.2±218.7**	**0.200**
Replace	**77.5±119.3**	**94±122.9**	**0.170**
Aortic	**65.9±84.1**	**81±82.8**	**0.180**
Mitral	**80.9±122.8**	**128.2±224**	**0.018**
Renal Failure	**125.9±170.2**	**119.8±23.1**	**0.907**
No renal failure	**71.1±97.5**	**101±166.9**	**0.013**
First incidence	**45(5.9-1127)**	**55.7(0.3-1415.3)**	**0.0003**
Reop	**64.5(39.5-1410.8)**	**65.9(38.4-309)**	**0.850**
Hypertensive	**59.1±18.2**	**126.0±15.9**	**0.006**
Normotensive	**75.5±7.3**	**82.6±11.6**	**0.594**
Diabetes	**102.1±23.9**	**176.9±47.3**	**0.169**
No Diabetes	**68.8±5.8**	**91.1±10.9**	**0.050**
Smoker	**69.6±7.8**	**105.4±10.0**	**0.037**
Non-Smoker	**74.6±8.8**	**98.1±16.0**	**0.161**
Obese	**59.4±5.3**	**113.2±18.3**	**0.031**
Non-obese	**88.0±9.6**	**97.5±12.2**	**0.534**
IHD	**117.8±30.2**	**143.8±29.6**	**0.592**
Non-IHD	**72.6±6.3**	**83.4±9.0**	**0.317**
Repair			
Aortic	**-**	**71.6±23.0**	**-**
Mitral	**69.9±9.0**	**127.7±36.5**	**0.136**
Replace			
Aortic	**65.9±8.7**	**82.2±7.4**	**0.153**
Mitral	**83.6±10.0**	**128.8±30.8**	**0.078**
Replace			
Mechanical	**72.7±7.8**	**92.6±12.9**	**0.187**
Tissue	**90.8±19.2**	**98.1±13.8**	**0.757**

Table 8 (continued)

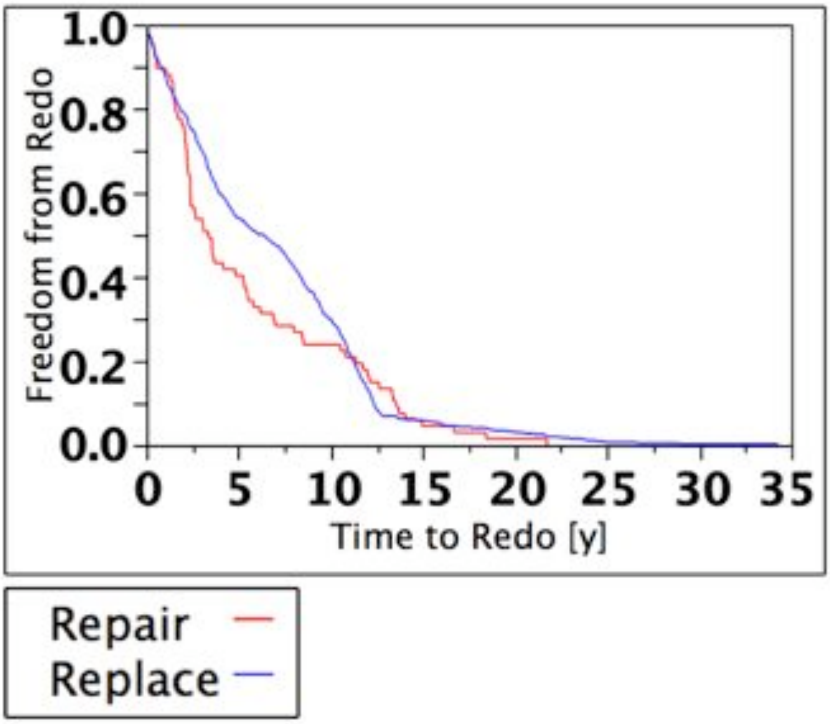
Hospital Stay (days)	RHD	Non RHD	P value
Overall	11.5±10.4	13.8±7.3	0.050
Repair	12.06±9	15.0±41.6	0.620
Replace	11.5±10.6	13.4±19.9	0.052
Aortic	11.3±7.5	12.5±21.0	0.430
Mitral	11.6±11.6	15.7±34.5	0.028
Renal Failure	16.8±14.7	12.6±11.1	0.380
No renal failure	11.7±10.9	14.3±30.8	0.065
First incidence	11(1-334)	11(1-91)	0.600
Reop	12(1-66)	10(1-75)	0.086
Hypertensive	12.2±1.0	12.0±0.7	0.826
Normotensive	11.5±0.4	12.7±0.6	0.085
Diabetes	15.7±2.0	12.5±1.1	0.144
No Diabetes	11.4±0.5	12.5±0.5	0.150
Smoker	11.3±0.8	11.8±0.6	0.594
Non-Smoker	11.5±0.6	12.5±0.6	0.237
Obese	12.5±1.4	15.3±2.0	0.230
Non-obese	12.1±0.6	14.6±0.9	0.020
IHD	11.9±0.6	11.3±0.6	0.598
Non-IHD	11.4±0.5	12.9±0.5	0.041
Repair			
Aortic	-	9.8±1.0	-
Mitral	12.2±1.3	12.6±0.9	0.804
Replace			
Aortic	11.3±0.5	11.7±0.5	0.607
Mitral	11.6±0.6	14.7±1.1	0.011
Replace			
Mechanical	11.5±0.6	14.3±0.8	0.007
Tissue	11.6±0.9	11.8±0.7	0.836

Table 8 (continued)

30-day mortality	RHD	Non RHD	P value
Overall	2.0%	10.6%	<0.0001
Repair	0%	14%	< 0.0001
Replace	2.14%	9.45%	< 0.0001
Aortic	3.36%	9.76%	0.002
Mitral	1.32%	11.9%	<0.0001
Renal Failure	20%	36%	0.340
No renal failure	2.1%	9.96%	< 0.0001
First incidence			
Reop			
Hypertensive	2.0%	12.8%	0.001
Normotensive	2.6%	9.9%	<0.0001
Diabetes	9.5%	18.8%	0.293
No Diabetes	1.9%	9.9%	<0.0001
Smoker	1.2%	9.5%	<0.0001
Non-Smoker	2.7%	10.1%	0.001
Obese	1.5%	10.3%	0.049
Non-obese	2.0%	11.1%	0.0003
IHD	3.3%	17.9%	0.004
Non-IHD	1.8%	6.0%	0.001
Repair			
Aortic	-	16.7%	-
Mitral	0.0%	13.0%	0.0008
Replace			
Aortic	3.4%	8.8%	0.011
Mitral	1.5%	11.0%	<0.0001
Replace			
Mechanical	1.1%	7.2%	<0.0001
Tissue	5.7%	11.6%	0.041

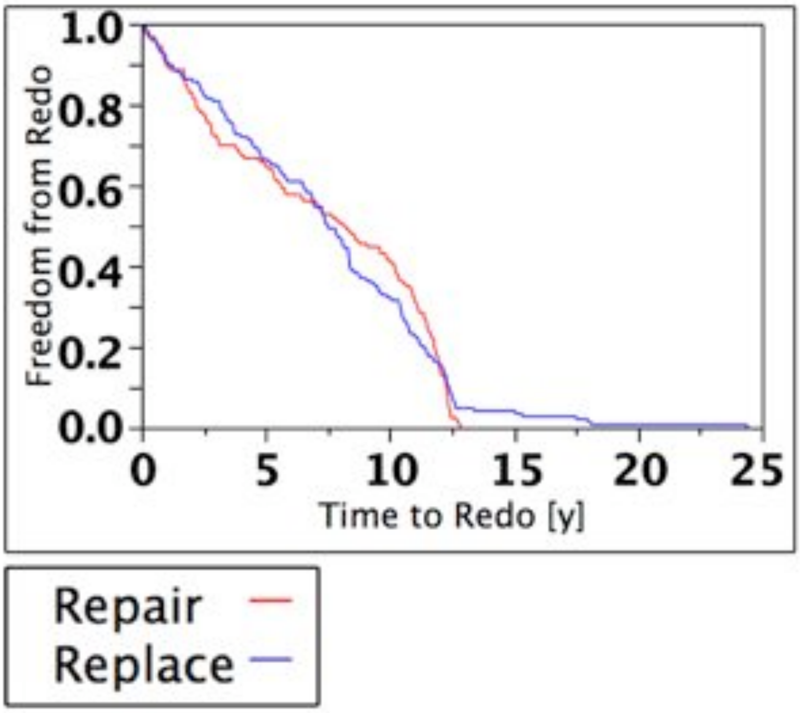
Table 9: Late Outcome

Median time to redo (range) yrs	RHD	Non RHD	P value
Mechanical	**4.23 (0.003-34.3)**	**6.91 (0.01-24.4)**	**0.0039 (Wilcoxon)**
Tissue	**9.54 (0.11-23.9)**	**7.69 (0.07-17.1)**	**<0.0001 (Wilcoxon)**



Group	Median Time
Repair	3.3703
Replace	6.3409
Combined	5.4976

Figure 22: Repair vs replacement in rheumatic mitral valves



Group	Median Time
Repair	8.178
Replace	7.4743
Combined	7.8166

Figure 23: Repair vs replacement in non-rheumatic mitral valve

CHAPTER 5. DISCUSSION

The practice of heart valve surgery in a threshold country such as South Africa clearly reveals differences in patient characteristics as there is a complex mix between the different population groups. There is a similar challenge in areas in Australia and New Zealand with similar population dynamics, that is a mix of both first and third world patients (18). There are therefore obvious challenges in performing such surgery in this environment and care should therefore be taken to tailor procedure to patient and not vice versa.

Interestingly, though, many of the studies available on heart valve surgery in rheumatic heart disease come from countries where incidence of rheumatic heart disease has drastically declined (104). In developing countries, where the bulk of cases arise, it is very difficult to publish definitive conclusions as a result of poor data collation and therefore analysis (22).

More than 80% of the population of the Western Cape, the home of GSH, are members of the Coloured and Black racial groups. These same groups form the majority that live in poor housing, overcrowded situations and poor socio-economic circumstances which are risk factors for the development of rheumatic fever (23). In fact, the racial distribution of rheumatic patients seen in our unit during this period is an accurate reflection of the 2001 census population figures of the Western Cape (105).

The significantly younger age of the Black patient at the time of surgery underscores the grave economic impact of valvular heart disease in this developing country. This fact also underlines many issues for urgent attention, including rheumatic fever prevention and choice of heart valve prosthesis which have been previously highlighted by others (9). It is clear that much more needs to be achieved in the area of prevention.

The onset of rheumatic fever, which is about 10 - 15 years earlier than the development of established rheumatic heart disease (6), should stimulate concerted attempts at disease prevention. Rheumatic heart disease continues to be the leading etiology associated with valvular heart disease requiring valve replacement (4) corroborated by our study which showed that 53.1% of the patients (valves) operated had a rheumatic etiology**.**

Rheumatic fever is a disease of poverty (23) and rheumatic heart disease is still widely prevalent in developing countries all over the world but, due to poor facilities for registration of cause of death, reliable statistics are difficult to obtain. In 1995, the WHO estimated that 12 million people were affected by rheumatic fever or rheumatic heart disease worldwide, resulting in 400,000 deaths annually (106). It is also estimated that about 282,000 new cases arise every year (26)**.** Unfortunately, most countries where rheumatic fever is prevalent do not have the financial resources nor the sophisticated medical services to treat the long term sequelae of chronic valvular heart disease.

Pharyngeal infection with its causative organism, GAS, is more common in the areas of overcrowding and poor socioeconomic conditions. Our study surprisingly showed a predominance of formal housing in both subsets although a significantly stronger association of informal housing was seen in the rheumatic subset ($p<0.0001$). It must be emphasized that exposure to rheumatic fever occurs about 10 to 15 years before established valve disease (6) during which time there may be a change of living standards, as may have occurred in South Africa since 1994. This change in living standards may explain the decline of cases in the developed world in the USA for example, where the incidence of rheumatic fever has fallen from 100 per 100,000 population at the turn of the century, to 45-65 per 100,000 between 1935 and 1960, and further to 2 per 100,000 currently (106)**.**

Irrespective of racial background, 62% of our study population presented in poor clinical state of NYHA III and IV. This high figure brings to question the access of the population to prompt and effective medical care which becomes even more pertinent after insertion of mechanical prostheses which tend to fail acutely resulting in significant morbidity and mortality if intervention is delayed.

Surgery for rheumatic heart disease in the young in developing countries such as South Africa has been aptly described as ‘attempting to mop up the water on the floor while leaving the faucet open’ (9) as many of these patients return to living conditions at high risk for rheumatic fever.

The scourge of tuberculosis (TB) and human immunodeficiency virus (HIV) throws more complexities at this same group of individuals.

Rheumatic heart disease was significantly associated with female gender, black and coloured racial groups, informal housing and unemployment. Previous studies have highlighted gender differences in valvular heart disease (107), (108) with a 3:1 female predominance in mitral stenosis and a reversed 3:1 male preponderance in bicuspid aortic valve and-non rheumatic aortic stenosis (108).

We found an almost 2:1 female predominance in rheumatic disease patients and a reversal of this trend in non-rheumatic patients which parallels the findings of the previous authors. These studies on gender differences have implicated hormonal imbalances in pathophysiology and outcome (107), but further studies need to be done to understand the exact relationship that exists between gender and pathogenesis.

Pregnancy is also known to accelerate the deterioration in clinical presentation because of significant increases in the blood volume and cardiac output in an already compromised heart (108) contributing to early presentation in pregnancy.

There was also a significant relationship between rheumatic patients and unemployment, presumably as this was directly linked to poverty.

It is known that the rheumatic process affects the mitral valve more commonly than the aortic, with the tricuspid much less and the pulmonary valve hardly at all (109)**,** (110)**.** The pathology of the mitral valve in most cases is that of pure mitral stenosis, mitral insufficiency or both, with mitral regurgitation being predominant in the young patient but mitral stenosis becoming progressively more common with age (104)**.** Aortic stenosis from chronic rheumatic heart disease is typically associated with aortic insufficiency. Our study showed almost equal percentages of aortic and mitral valve replacements, together forming the bulk of our replacement program.

Our prostheses of choice in the young rheumatic patient is the mechanical valve because of the notion that insertion of mechanical prostheses can avoid the reoperation due to degeneration of bioprosthetic valves which almost always will occur in the young patient (7)**.** Unfortunately, however, re-operations cannot be completely eliminated, due to thrombotic and infective complications of mechanical valves which, if they occur, can be rapidly fatal especially in indigent patients who are non-compliant with respect to anticoagulation and easily lost to follow-up. The choice is therefore difficult to make in the absence of both short- and long-term outcome data.

An overall rheumatic mitral repair rate of about 8.7% is rather low compared to 25% as reported by Yau et al. in a Canadian study (111) and the greater than 50% reported in other studies (14). This may not be very surprising with the large number of badly damaged and irreparable valves as a result of the rheumatic process. The success of mitral valve repair will depend on variable factors including proper patient selection and a steep learning curve which ultimately depends on volume of suitable cases and therefore development of expertise. There is consensus on the advantages of mitral valve repair over replacement in patients with non-ischemic mitral valve disease, although in ischemic mitral repair, a lower 30-day mortality did not achieve statistical significance (10). Results of repair of rheumatic mitral valves remain inconsistent, as there is a wide spectrum of the disease process as well as significant variability in the technical feasibility of repair (112). In our study, there was no significant difference in the median time to redo between repair and replacement of rheumatic mitral valves although it took twice as long for replaced valves to fail. However, although there was a slight advantage of repair over replacement in non-rheumatic valves, this was not statistically significant.

There was a significantly higher proportion of concomitant coronary artery bypass grafting with procedures in non-rheumatic patients, as a large proportion of non-rheumatic cases may be of ischemic etiology. This may explain the slightly longer, albeit not statistically significant, time to redo of mitral repairs in non-rheumatics as there is revascularization of the valve apparatus. However, other confounding or co-morbidity factors such as the more advanced age of the non-rheumatic patients may eliminate this advantage. Most of the valve repairs were performed by a single surgeon, hence eliminating the learning curve and standardizing the surgical outcome. Most of the techniques of repair were valvular elongation and sliding plasty. All the repairs were supported with ring annuloplasty and assessed with intraoperative TEE. There was also better 30-day mortality in repair of rheumatic versus non-rheumatic valve. However, there was no observed advantage in ICU stay.

Repairs avoid the lifelong anticoagulation necessary for mechanical prostheses and the degeneration of tissue valves and hence should play a more prominent role in the armamentarium of cardiac surgeons, especially in developing economies. Another important advantage of mitral repair is the preservation of intrinsic mitral apparatus which allows for improvement of post-operative ventricular function. Unfortunately, it is more time consuming and requires patience but efforts must be made to develop these skills in the next generation of surgeons. Early referral for surgical intervention will increase the number of valves amenable for valve repair. This is often a difficult decision on the part of the cardiologists and constant interaction of physicians and surgeons may reduce the time to surgery. In this study, we did not evaluate for long-term follow up.

The success of mitral valve repair is noticed to be dependent on the mitral valve pathology and anatomy though there is no consensus on what anatomy exclusively precludes attempt at repair. Therefore, surgeons' experience will ultimately determine what gets repaired or replaced. The development of a 'scale of distortion' of the mitral valve will be necessary as a guide for those involved in the art of valve repair because, often, considerable time and effort is put into the repair attempt, only for it to fail 'on table' and then a replacement is inevitable.

The success of mitral valve repair in rheumatic patients is improved significantly when aggressive tissue resection is performed to remove all diseased tissue whilst leaving behind as much unaffected tissue as possible and using techniques not classically described for rheumatic mitral valve repair, such as resuspension of leaflets using polytetrafluoroethylene neochordae, use of a tricuspid autograft or a mitral homograft (16)**.**

In the developing world, there is still a place for other techniques of valve 'repair' that have all but disappeared from the practice in more developed countries. Procedures such as closed mitral valvulotomy and commissurotomy which, if successful, could delay the insertion of bioprostheses and lifelong anticoagulation, especially in the young rheumatic patient.

In our environment, it is very difficult to conduct research on outcome analysis of long term factors for obvious reasons. Many of our patients are indigent and often travel great distances for medical attention. For this reason, we have decided to analyze only three early outcome variables, namely ICU stay, hospital stay and 30-day mortality. Time to reoperation was analyzed as a late outcome for patients with available and reliable data.

a. <u>ICU Stay</u>

It has become very important in the field of cardiac surgery to predict the length of ICU stay by developing risk scoring systems to determine preoperative mortality risks. ICU stay is expensive and personnel consuming, especially in developing countries and so this information becomes vital in the preparation of valve surgery programs. Unfortunately, many of the existing systems do not allow for variables such as etiology of valve lesions, therefore highlighting the need to have a scoring system appropriate to our environment where rheumatic disease will continue to play an important role. At GSH, the Cardiothoracic ICU is a six bedded unit that caters for our immediate post-operative needs.

Patients with rheumatic valve lesions generally spent significantly less time (76.5hours) than non-rheumatics (99.3 hours) in the ICU irrespective of procedure performed. The younger average age of the rheumatic patient may have contributed to reduce the incidence of co-morbidity, which is more common with the older, non-rheumatic patients. This may explain the finding of rheumatic mitral valve patients having stayed significantly shorter periods in the ICU compared to non-rheumatic mitral patients, although this was not observed in the case of aortic procedures.

It appears that the short-term advantage that repair gives over replacement was pronounced in the rheumatic group with repair of rheumatic valves correlating with a shorter ICU stay than in the case of replacements (66.9 hours vs 77.5 hours), whilst the converse was true in non-rheumatic valves (113.2 hours vs 94 hours). This difference was however not statistically significant. It has however been proposed that as a result of a perceived progression of the disease process and inferior durability of reconstruction, repair of rheumatic valves may become redundant in the long-term, despite its short-term advantages. The repair of rheumatic valves, though controversial, should however be encouraged whenever possible in the developing world, therefore accepting the risk of reoperation (17)**.** In the setting of non-rheumatic mitral valve disease, repair is generally believed to be superior to replacement in the long term with better preservation of LV function, improved late survival and a lower likelihood of valve-related complications (19).

However, there is a trend for the average ICU stay of patients who have undergone a first procedure to be shorter than that following redo operations (p=0.08). Patients presenting for redo procedures are usually acutely ill and in a worse NYHA class. Reoperations are technically more demanding as a result of severe mediastinal and pericardial adhesions and often subsequent bleeding from inadvertent lacerations. It is no surprise, therefore, that the ICU stay may be more prolonged in these cases. The lack of a high dependency unit (HDU) in our hospital also prolongs ICU stay in patients who cannot yet be transferred to the regular ward as they still require close monitoring.

Of all the co-morbidities, hypertension (p=0.006), smoking (p=0.037) and obesity (p=0.031) significantly increased ICU stay among the non-RHD patients. Ventilatory requirements are usually increased in smokers, hence the need to advise patients to stop smoking well ahead of their elective surgeries.

b. <u>Hospital Stay</u>

Rheumatic patients generally also had a shorter period in hospital than non-rheumatics (11.5 days vs 13.8 days; p=0.05) and this was particularly evident in mitral procedures, with hospital stay between rheumatic and non-rheumatic aortic procedure patients being similar. This may suggest that patient characteristics in aortic procedures were similar whether rheumatic or not, whilst being different in mitral disease.

c. **30-day mortality**

One of the important outcome variables in cardiac surgery is the 30, 60 or 90-day mortality which is defined as 'all cause' mortality at 30, 60, or 90 days. This refers to all deaths from any cause after a valve intervention.

This information is especially valuable to cardiologists and surgeons as they discuss the possible potential risks and benefits with the intended patient. Even though some workers have challenged the usefulness of these figures and have proposed that a longer term outcome may be more informative for the discerning patient (20)**,** it nevertheless continues to remain a very useful tool. We decided to utilize the 30-day mortality figures as this would be the most reliable in patients who are prone to poor follow-up compliance. Edwards et al. (5) also found that 30-day mortality correlated well with 1 year mortality figures after valve replacement.

Patients with no or minimal symptoms (NYHA Class I &II) tend to do very well after heart surgery while the results in patients in advanced NYHA classes show excessive morbidity and mortality. This has led to the recommendation to perform surgery at an earlier stage of the disease process. Unfortunately, the majority of our patients still present in advanced NYHA Class III.

The overall 30-day mortality rate in the non-rheumatic patients was 10.6% (72) and 2% (15) in the rheumatic patients. This significant difference was likely the contribution of the older, sicker, patients in the non-rheumatic group. The overall 30-day mortality rate for the primary operation was 3.7% compared to 7.9% for the first reoperation. This compares favorably with other centers in developing countries (56) where the 30-day mortality of redo procedures is about double the mortality of first procedures. Although our study did not particularly investigate differences, if any, between patients having a redo as a result of a failed mechanical or tissue valve, it is generally known that bioprosthetic valves usually fail chronically whereas, mechanical valves instead fail acutely and with a higher mortality. The 30-day mortality figures following valve repair or replacement in rheumatic patients were not statistically different in our analysis, and a similar observation was seen in non-rheumatic patients. However, there was a trend towards lower mortality in repairs than in replacement of rheumatic valves, while a reversed trend of lower mortality following replacement was seen in non-rheumatic patients. Rheumatic patients had better 30-day mortality rates of repair (0%) than in non-rheumatic patients (14%) and a similar advantage in replacement (2.14%) compared with 9.45% in non rheumatics. The younger, rheumatic patient with less co-morbidities will have a better chance of survival following these procedures.

The same co-morbidities that were significantly associated with ICU stay were also noted to increase 30-day mortality, namely hypertension (p=0.001), smoking (p<0.0001) and obesity (p=0.049). Ischemic heart disease (p=0.004) was an additional risk factor associated with early mortality. Clearly, there is a need to address these factors to mitigate the incidence of early mortality.

d. <u>Time to Re-operation</u>

There is always a risk of reoperation no matter the type of prosthesis. Unfortunately, no single prosthesis type has completely eliminated this risk. Though the reasons and pattern of failure differ, reoperation is necessary when the patient outlives his valve. Consequently, the younger the patient, the more likely the chances of a possible re-replacement. With a background of rheumatic disease, returning patients with failing mechanical valves did so much earlier in our series compared to tissue valves (4.3 years vs. 9.6 years; p<0.0001).

The most common reason for failure of mechanical valves was acute thrombosis usually as a result of poor anticoagulation. This is contrary to what occurs in Ghana where strict anticoagulation control has almost completely addressed this mode of failure to the extent that mechanical valves are used exclusively with very good results. Tissue valves are hardly used, for example, in the Cardiothoracic Centre in Accra – personal communication (113).

The intention of implanting mechanical valves is the benefit of longevity and avoidance of a redo operation. With the median time to redo of the mechanical prosthesis is this study cohort of about 4 years and 9.6 years for tissue valves, this objective has clearly not been realized. These figures are only representative of the patients who returned for a reoperation at our center and it is possible that there may be others who failed acutely and presented at other centers in the country or died before reaching hospital.

Is the mechanical prosthesis therefore more of a ‘disease’ than a ‘cure’ in limited resource countries?

Other studies will need to look into anticoagulation monitoring, especially in this environment, as this may hold the answers to the reason of the failure of these valves.

Our results suggest that it may be more expedient to insert tissue valves which will ultimately fail but in a more predictable way, therefore making it a priority to conduct research geared towards improving the longevity of tissue valves currently in use.

Until then, concerted efforts at proper patient anticoagulation education and follow-up, provision of INR facilities in rural areas and better coordination of heart valve services in referral hospitals in South Africa may reduce the incidence of acutely obstructed mechanical valves.

We also therefore need to overcome the mindset of fear of re-operations, because re-operations become inevitable whether a tissue or mechanical valve is implanted in our environment as most of our patients will outlive their prosthesis.

Time to re-operation of rheumatic mitral valves that have been repaired (3.4 years), is shorter but not significantly so from those that were replaced (6.3 years). This is disappointing in our setting, because repair whenever possible, will obviate the need for anticoagulation and avoid the catastrophes thereof.

Our analysis showed that time to re-operation was only significantly different between rheumatic and non-rheumatic patients in the 40-50 year age group ($p=0.0185$). This appears therefore to be the age group around which prospective studies could be designed to understand the differences in outcome between rheumatic and non-rheumatic patients.

CHAPTER 6. CONCLUSIONS

Valve replacement continues to occupy a large proportion of our cardiac surgical workload at the GSH, primarily because of the huge burden of rheumatic heart disease whose incidence in South Africa appears unabated.

In order to stem the potential of prosthesis-related disasters, the traditional practice of inserting mechanical prostheses in young rheumatic patients is challenged by the lack of evidence of mechanical valve longevity shown in this study.

While progression of the rheumatic process and prosthetic valve thrombus were responsible for the majority of re-operations, it is virtually impossible to halt the chronic rheumatic process with other valve sites subsequently succumbing to the destructive process. Although technically, this is not a 'failed' prosthetic valve, the patient is subjected to a re-operation for a valve procedure at another site. On the other hand, rigorous INR control policies including better patient follow-up, availability of self-test INR kits and fixed Warfarin dosing regimes may reduce the risk of prosthetic valve thrombosis that will occur with sub-therapeutic Warfarin doses.

A more aggressive approach to valve repair needs to be adopted as repair rates are still low. This may entail earlier referrals for surgery, before the valves become irreparably damaged as well as overcoming the steep learning curve for these difficult procedures. Furthermore, research geared towards improving the durability of bioprosthestic valves should continue to be encouraged.

Prospective studies in the 40-50 year age bracket of patients is needed, since this was the only group where mechanical valves failed significantly earlier in the rheumatic patient compared to the non-rheumatic patient (5.3 versus 7.4 years; $p=0.018$). This may better facilitate an understanding of the reasons leading to prosthetic valve failure.

South Africa is a dynamic environment where major social changes have occurred in the last two decades. As was noted earlier, rheumatic heart disease is distanced from its early beginnings as rheumatic fever by a gap of 10 to 15 years, and it may come as no surprise that analysis of the now improved social demographics such as housing and employment belie the contribution of a lifelong history of poverty.

Conversely, though, once an individual has missed a chance at education, this may not be so easily undone, even though he or she now lives in a better house.

There remains, however, a higher percentage of informally housed patients in the RHD group compared to non-RHD one and, although there are reasonably high percentages of formal housing and employment in this same group of patients, these numbers are significantly lower than is the case in the non-RHD patients. It is important to realize that this is what has been specifically compared. The analysis has not compared, for example, formal versus informal housing in the context of RHD alone, but rather informal housing amongst RHD patients versus informal housing in non-RHD ones.

The observation that mechanical valves appear to 'fail' earlier than tissue valves clearly does not follow what is known about mechanical valves in first world countries. However, this is exactly the point that needs to be emphasized here. Could it be that the 'right' valve is being placed in the 'wrong' patient? Mechanical valves need more rigorous follow-up than tissue valves. Could the low standard of education of our patients affect their understanding of the requisites for mechanical valves, that is anticoagulant drug compliance? The problem therefore lies clearly with the patient, or does it? Could the problem be one of apathy related to the expectations these patients have in a country where social equality is only now undergoing positive change, but where crime fueled by problems of unemployment and drug abuse is rife? Is it simply a problem related to access to clinics for routine INR tests? Could new anticoagulants such as Dabigatran, which requires less frequent INR testing, improve the outcome following replacement of diseased valves with mechanical prostheses? Could it be that we are not doing enough in terms of follow-up?

Perhaps all of these hold a modicum of truth. A more definitive answer will certainly require carefully controlled prospective studies and, of course, time.

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November 17, 2011

Professor Risenga Frank Chauke
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Dear Professor Chauke

Response to Thesis Review of Dr Akinwumi Ogunrombi

Thank you for your thorough review of Dr Ogunrombi's thesis entitled "Sixteen Year Retrospective Analysis of Rheumatic and Non-Rheumatic Heart Disease Patients Undergoing Valve Procedures at Groote Schuur Hospital: First Incidence Single Aortic and Mitral Valve Replacement".

Dr Ogunrombi has hopefully addressed your questions satisfactorily and I include a summary of his changes below. Additional to this are the mostly typographical changes required by the second reviewer.

While both Dr Ogunrombi and myself appreciate the limitations of a retrospective study, that is, in terms of demonstrating at most an association between a variety of risk factors and eventual outcome, he had, I believe, recognised this shortcoming and not hidden that from view. He is a co-author on a subsequent study which addressed the problem more precisely by performing propensity matching between cohorts of mitral valve repair and replacement patients, thereby controlling for extraneous variables. This was in my mind beyond the scope of this Masters degree study but I also believe he has performed a valuable and long overdue analysis of the outcomes of indigent rheumatic patients undergoing valve surgery, thereby paving the way for more definitive studies.

Yours sincerely

Dr PAUL HUMAN

SUMMARY OF CHANGES

CHAPTER 1

1 Source of figures and tables: These have now been appropriately acknowledged.
2 Formatting in bold/regular: This has now been corrected throughout
3 Discussion under valve pathology: This has been added and the text under "Aortic Valve" which was misplaced has been moved to "Mitral Valve".

CHAPTER 2

1 Source of figures and tables: These have now been appropriately acknowledged.
2 Spacing on p17 corrected
3 Style of writing: made same for tables and figures
4 Reference 35 in bold: made regular
5 Figure 5: The legend which refers to survival is a reference embedded in the figure in the original publication. The chart correctly indicates numbers of patients across the age groups.
6 References 15/16 incorrect: This has been corrected.

CHAPTER 3

1 No discussion on methods: I would agree that, for a prospective study, methods pertaining to the surgical aspect of such a study would need to be included. Since this is a retrospective study, the methodology refers purely to the statistical analysis performed. I believe that Dr Ogunrombi has discussed the cohort of patients in reasonable detail and indeed the challenges of the study, as well as the statistical methods used.
2 Core data/data crucial to analysis: An improved definition of these terms has been provided:
"Even in the original Summit database, demographic and comorbidity data or type of valve implanted, for example, was incomplete although core data, that is relating to the etiology, the surgical procedure performed and short-term outcome, were nevertheless available. In some cases though, patients operated from 1993 but prior to 2003 (the capture period for the Summit database) were excluded from the study when even these core parameters were unavailable."
3 How many of 1449 patients excluded? What are host of confounding factors? Were patients with "impure" data included?: The confusion in this regard was due to typographical errors in Table 6 (now Table 7) as well as the lack of a definition of what was meant by the above mentioned terms. All of the 1449 patients were in fact included in the study (see next point).

CHAPTER 4

1&2 TABLE 6 (Now Table 7): The numbers of patients receiving either a mechanical or tissue valve was reported in error in this table, although the relative percentages given were correct. The numbers have been corrected to 458 and 176 respectively for RHD patients and 209 and 251 for Non-RHD patients. A footnote has also been added to the table indicating that these figures were dependent on availability of data since, in 136 RHD patients (10.7%) undergoing replacement and in 219 Non-RHD patients (9.4%) undergoing replacement, this information was not available. The total number of repaired plus replaced RHD patients is 770 and the total number of repaired plus replaced Non-RHD patients is 679. Together these make up the 1,449 patients of the cohort.

3 Reoperation breakdown: This has now been included as Table 6.

4 IHD not included in Table 5, but included in Table 6: IHD has now been included in Table 5 and as "Simultaneous CABG" in Table 7 (previously Table 6).

5 Other co-morbidity factors in Table 7: Hypertension, diabetes, smoking, obesity and IHD have now been included in Table 8 (previously Table 7). Additional comments have been added in this regard in Chapter 5.

CHAPTER 5

1&2 We agree that the findings are controversial but most of what is known relates to First World scenarios. The problems of compliance, both in terms of performing regular INR tests and with respect to taking anticoagulative drugs, may well be appreciably large in an indigent, albeit urban, population and Dr Ogunrombi has added discussion on this as well as the social dynamics and its potential impact in a country such as ours.
You are correct that much of the discussion is based on assumption. Unfortunately, such a study, as is the case with most retrospective studies, serves little purpose other than to identify potential hypotheses where causation needs to be unambiguously tested. Again, this was outside the scope of the thesis for practical reasons.
Nevertheless, I feel that Dr Ogunrombi has extracted as much as was possible from the available data and gained significant insight and understanding which would assist him immeasurably in future research in this field.

3&4 In Chapter 6, Dr Ogunrombi has added commentary (again an assumption) hypothesizing the disparity between education and housing and why improvement in the one does not immediately imply the other.

5 Is the valve the problem or the patient?: Dr Ogunrombi has added thoughts on this in Chapter 6.

6 Table 8 (previously Table 7) now includes a breakdown of valve, prosthesis type and repairs.

7 Reoperation surgery adds a further dimension of complexity since this could refer to reoperation of the same valve or of the patient, where alternative valves are compromised. Also, sometimes, an original tissue bioprosthesis could of course be replaced with a mechanical prosthesis. Whereas I agree that an analysis of reoperations would be of particular interest, our restriction of Dr Ogunrombi's study to single valve, first time procedures avoided these complexities in an already variable-rich data set.

CHAPTER 6

1-3 These points are now briefly discussed.