

**Retrospective Review of Paediatric Rheumatic Mitral Valve Repairs and Replacements Done at Red Cross War Memorial Children's Hospital (RCWMCH) Over a Decade**

by

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## DECLARATION

I, Alfred Mureko, 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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## **Retrospective Review of Paediatric Rheumatic Mitral Valve Repairs and Replacements Done at Red Cross War Memorial Children's Hospital (RCWMCH) Over a Decade**

**Alfred Mureko, Justin Batcheller, Melinda Eller, Martina Northrup-Lyons, Paul Human, Johan Brink, John Hewitson, Peter Zilla**

### **Abstract**

**Objectives:** Rheumatic heart disease remains a significant cause of morbidity and mortality and it is the leading cause of acquired paediatric cardiac disease in the developing world. The aim of this study was to understand the burden of rheumatic heart disease and to review the surgical management of rheumatic mitral valve disease at our institution.

**Methods:** We retrospectively reviewed 76 consecutive patients who underwent mitral valve surgery for rheumatic heart disease between 1998 and 2010. The results and follow-up were reviewed, where death and reoperation were the primary endpoints. The follow up included a review of the latest information from the patients' medical records and telephonic interviews or home visits.

**Results:** A 91% follow up was achieved over a median follow up period of 7.4 years (range 0.1-15.2 years). The mean age at surgery was 10.7 years (SD +/- 2.7 years). The females constituted 66% and males 34%. Mitral valve repairs were performed in 64% of patients and of the 64% repairs, 0.06% only had commissurotomies. Replacements were performed in 36% of patients. All mitral valve replacements were mechanical prostheses. The actuarial freedom from reoperation for repairs was 83% (+2.2) and 66% (+3.4) at 5 and 10 years and for replacements was 87% (+4.8) and 87%(+4.8) respectively (p=0.27). Actuarial freedom from embolic cerebrovascular accidents in the repair group at both 5 and 10 years was 100%, compared to 90.2% (+6.6) and 79% (+12.0) for the replacement group at 5 and 10 years respectively (p=0.02). Actuarial freedom from death at 5 and 10 years for children over 12.8 years was 77.7% (+9.9) and 69.1% (+12.0) respectively, compared to 93.6% (+3.6) and 93.6% (+3.6) for children under 12.8 years (p=0.03). No statistical significant difference was noted in freedom from valve related failure and death between repairs and replacements.

**Conclusions:** There was no significant difference in survival between mitral valve repairs and replacements. There was surprisingly worse survival among children who were above 12.8 years at time of the surgery.

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- Justin Batcheller for assisting with data retrieval and capturing
- Mellinda Eller for the data retrieval and capturing
- Martina Northrup-Lyons for the telephonic follow-up, and tracing of patients

Finally, I would like to thank Paul Human for the statistical analysis of this study.

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## **Abbreviations**

AF- Atrial fibrillation

ARF- Acute Rheumatic fever

CVA- Cerebrovascular Accident

EF- Ejection Fraction

ICU- Intensive Care Unit

INR- International Normalised Ratio

LA- Left Atrium

LV- Left Ventricle

LVESD- Left Ventricular End Systolic Dimension

MAZE- Modified Cox-Maze procedure for atrial fibrillation ablation

MR- Mitral Regurgitation

MS- Mitral Stenosis

MV- Mitral valve

MVR- Mitral valve replacement

MVrep- Mitral valve repair

NHLS- National Health Laboratory Services

OMV- Open mitral valvotomy

On-X- On-X bileaflet mechanical prosthesis

PTFE- Polytetrafluoroethylene

RA- Right Atrium

RCWMCH- Red Cross War Memorial Children's Hospital

REMEDY- Rheumatic Heart Disease Global Registry

RHD- Rheumatic heart disease

RSA- Republic of South Africa

SAPS- South African Police Services

SBE- Subacute bacterial endocarditis

SJM- Saint Jude Medical bileaflet mechanical prosthesis

TA- Tricuspid Annuloplasty

TB- Tuberculosis

TOE- Trans-oesophageal echocardiogram

# Chapter 1

## Introduction and literature review

### Introduction

Acute rheumatic fever is a complication of repeated untreated Group-A streptococcal pharyngitis, which predominantly affect young children and teenagers<sup>1</sup>. Untreated acute rheumatic fever and its repeated attacks results in a chronic inflammatory process, which causes damage to the heart valves and this is referred to as rheumatic heart disease. Rheumatic heart disease is preventable by prolonged penicillin prophylaxis in all patients who had presented with an acute rheumatic fever attack<sup>1-3</sup>. Rheumatic heart disease is still a significant cause of morbidity and mortality among children in the 21<sup>st</sup> century in the developing world<sup>4</sup><sup>5</sup>. In the early part of the last century before widespread antibiotic availability there was a great decline in the incidence and prevalence of acute rheumatic fever in the developed world. However, the same has not been seen in sub-Saharan Africa, where acute rheumatic fever and its dreaded sequelae of rheumatic heart disease still confers a significant burden of disease<sup>2,5</sup>.

### Objectives

- To determine the burden of rheumatic heart disease globally and specifically in the developing world.
- To identify the surgical management of rheumatic mitral valve disease.
- To describe the incidence of rheumatic mitral valve repairs and the success rates.
- To understand the progressive nature of rheumatic heart disease and its impact on mitral valve repair.
- To clarify the role of secondary prophylaxis in prevention of further rheumatic fever infections
- To determine the optimal choice of prosthesis in paediatric mitral valve replacement and associated complications.
- To compare the surgical mitral repair techniques between the developed and developing world.

## **Literature search strategy**

The literature search was undertaken using Pubmed and Google scholar under the following keyword searches: “Rheumatic heart disease”; “Paediatric rheumatic mitral valve surgery”; “Rheumatic mitral valve repair in children”.

The following journal databases were also searched:

- European Journal of Cardiothoracic Surgery
- The Journal of Heart Valve Disease
- The New England Journal of Medicine

Another important source of literature was the reference lists of pertinent journal articles.

## **The literature review**

### **Epidemiology of rheumatic heart disease**

It is estimated that 15 million people are affected by rheumatic heart disease worldwide<sup>6</sup> This estimate is however believed to be a gross under-estimation because a significant number of people in sub-saharan Africa are harbouring subclinical RHD as shown by Remenyi et al and by recent echocardiographic surveys done in Mozambique, Uganda and Senegal<sup>2, 7-10</sup>.

Carapetis et al. in 2005 estimated the global incidence of acute rheumatic fever (ARF) in children between 5-14 years to be more than 336 000 cases. They estimated the annual number of acute rheumatic fever cases in all ages at more than 471 000 cases. They further estimated that over 2·4 million children aged 5–14 years are affected with rheumatic heart disease. Extrapolating this to all age groups, they estimate that there are 15·6–19·6 million people living with rheumatic heart disease. 79% of all rheumatic heart disease cases in the studies came from less developed countries. Their estimates correspond to all age prevalence rates in less developed countries ranging from 2·5 to 3·2 cases per 1000<sup>6</sup>.

Marijon et al.<sup>9</sup> reported that comprehensive echocardiographic screening identified approximately 10 times as many children with rheumatic heart disease as were identified by the traditional strategy of clinical screening with echocardiographic confirmation. In Marijon’s report, rheumatic heart disease was defined by the

presence of any definite evidence of mitral- or aortic-valve regurgitation seen in two planes by Doppler echocardiography, accompanied by at least two of the following three morphologic abnormalities of the regurgitant valve: restricted leaflet mobility, focal or generalized valvular thickening, and abnormal subvalvular thickening. For a definite diagnosis of rheumatic heart disease, these features had to be identified concordantly by each of the echocardiographers, all of whom were experienced in the diagnosis and treatment of rheumatic heart disease <sup>9</sup>.

There has been a decline in the incidence of rheumatic fever in the Western world but this has not been seen in sub-Saharan Africa. The incidence decline in the Western world is not entirely clear but it is probably related to the better socio-economic conditions, such as better sanitation, less overcrowding, and overall better living conditions, all of which result in a reduction in infectious diseases in general and streptococcal infections in particular <sup>5</sup>.

Carapetis et al. described rheumatic fever as a disease of poverty and that it is in many ways the epitome of diseases of poverty and social injustice<sup>11</sup>. There is great underreporting of acute rheumatic fever incidence and prevalence in sub-Saharan Africa. Underreporting has always been a big problem in South Africa despite acute rheumatic fever being declared a notifiable disease in the 1980's. This was shown by Ngudi et al. in 2006 <sup>12</sup>.

As rheumatic heart disease continues to be a major cause of morbidity and mortality in developing nations, particularly in the young economically and socially active sector of the population, the availability of epidemiological data is certain to aid with case finding, delivery of effective primary and secondary prevention, and adequate planning of health services <sup>9</sup>.

## Features of acute rheumatic fever and rheumatic heart disease

Acute rheumatic fever (ARF) is a complication of an untreated Group-A streptococcal pharyngitis, which predominantly affect young children and teenagers<sup>1</sup>. Molecular mimicry explains the triggering of ARF, but an intense and sustained inflammation is needed to cause the sequelae of chronic rheumatic heart disease<sup>13</sup>. This interaction is an autoimmune response, in which genetic factors affect the individual's susceptibility.

ARF is mediated by humoral and cellular autoimmune responses that occur as delayed sequelae of *Streptococcus pyogenes* infection. Environmental factors such as poor socio-economic circumstances and limited access to medical care partially explain susceptibility, but individual factors are known to play a role. Only a small proportion of patients develop the full complement of symptoms<sup>13</sup>.

Acute rheumatic fever usually occurs 3 weeks following a group A streptococcal pharyngitis and around half of patients with ARF present with cardiac inflammation mainly involving the valvular endocardium<sup>14</sup>. It usually manifest as a systematic disease, and then cardiac symptoms may become prominent depending on the severity of the carditis. The carditis always present as a pancarditis, affecting all the anatomic layers of the heart; the endocardium, myocardium and pericardium. Valvular incompetence is typically the lesion of acute rheumatic fever with carditis and is the forerunner of the long-term sequelae of this disease, known as rheumatic heart disease<sup>5</sup>. It is worth noting that not all ARF carditis sustain significant valvar damage to progress to MR.

The microscopic hallmark feature of ARF is the Aschoff bodies, which are histiocytes aligned in palisades around fibrinoid necrosis, giving a particular appearance. submiliary nodules located in the myocardium usually in close proximity to small blood vessels. The typical macroscopic characteristics of the ARF endocarditis are very small, warty, firmly adherent vegetations of deposited platelets along the zone of contact of valve cusps.

The intra-operative (macroscopic) findings in acute rheumatic fever associated mitral valve incompetence are usually chordal rupture or elongation and annular dilatation. Often the whole heart is inflamed. On the other hand, the typical intra-operative findings in RHD mitral valve incompetence are; thickened retracted leaflets, elongated or ruptured chordi with associated leaflet prolapsed or

alternatively restricted valve mobility due to chordal tethering (Type 3B according to the Carpentier Classification of mitral leaflet motion). Chronic rheumatic heart disease presenting with predominant mitral stenosis tend to exhibit the following macroscopic features; thickened leaflets with some degree of calcification, immobile leaflets, commissural fusion and shortened sub-mitral apparatus with variable chordal fusion<sup>5 14</sup>.

### **Clinical presentation**

ARF is a systemic illness of few sequelae first time but subsequent attacks cause a much higher incidence of severe carditis and then MR becomes the hallmark. ARF is marked by fever and joint pains, and is diagnosed by the Ducket-Jones criteria. Acute rheumatic fever classically presents as acute mitral incompetence and it is only after repeated acute rheumatic fever attacks and progressive fibrosis and usually in the 3<sup>rd</sup> decade of life when rheumatic mitral stenosis is seen. This has been shown in previous paediatric rheumatic mitral studies by Kalangos et al from Switzerland and by Hillman et al from the USA<sup>3, 15</sup>

However, a recent Ethiopian paediatric (age range 3-15 years) rheumatic mitral study by Tadele et al had shown a significant prevalence of rheumatic mitral stenosis in the paediatric age group<sup>16</sup>. The Ethiopian study observed a high prevalence of mitral stenosis in patients between the ages 6–10 years and the overall prevalence of mitral stenosis in paediatric patients was 34.5% while the overall prevalence of severe mitral stenosis, defined as a valve area of less than 1.0 cm<sup>2</sup>, was 18.1%.<sup>16</sup> This high prevalence of paediatric mitral stenosis in Ethiopia is probably a reflection of the state of the disease in most parts of sub-Saharan Africa, where the epidemiology is not well defined. This unprecedented finding by Tadele et al is certainly related to the persistence of poor socio-economic conditions in sub-Saharan Africa and the associated recurrent acute rheumatic fever attacks coupled with inadequate secondary penicillin prophylaxis. Late presentation to healthcare facilities has been identified as one of the factors that increase the burden of rheumatic heart disease in sub-Saharan Africa. This was clearly shown by Sliwa et al. in the “Heart of Soweto” study, where the majority of patients presented with advanced cardiac disease and where the predominant primary diagnosis was heart failure<sup>17</sup>

## Primary prevention of rheumatic fever

Researchers agree that the reason why there has been a decrease in the incidence of ARF in the developed world is mainly a result of improved socio-economic dynamics. As such, the first emphasis in preventing ARF infections in the high incidence areas is to address the living standards within the poor communities. Addressing overcrowding, poverty, poor sanitation and access to healthcare should form the basis of primary prevention of ARF infections <sup>18, 14</sup>.

It is clearly evident that the socio-economic conditions in the developing world are not about to change drastically within the near future. Looking at RSA, one can appreciate that the poverty gap remains a big problem as the number of informal settlements are still on the rise <sup>19</sup>. With the persistence of the poor socio-economic conditions in our society it is imperative to focus on other means of primary prevention.

This relies on the eradication of group-A streptococcal throat carriage. Early diagnosis and treatment of sore throat with penicillin is widely advocated as an effective means of preventing ARF infections. This mode of primary prevention is often challenging and has been largely neglected in the developing countries <sup>14 18 20</sup>. Clinically, it can be difficult to diagnose group-A streptococcal pharyngitis if the disease is not borne in mind and without microbiological confirmation. The disease should always be part of the differential diagnoses in a patient with fever and a sore throat. Some developing countries do not have the necessary laboratory analysis for confirming the disease <sup>21</sup>. A systematic review by Robertson concluded that giving antibiotics to patients with sore throats and symptoms suggestive of a streptococcal infection reduces the risk of rheumatic fever by 70%. Intramuscular penicillin reduces the risk further, to 80% <sup>22</sup>. Therefore, in communities where ARF is prevalent all young people aged 5-15 years with a sore throat should be considered to have a streptococcal infection and be treated with an antibiotic <sup>23 20</sup>.

With the discovery of a vaccine against measles, the world has seen a massive decline in the incidence of measles. Hence, the development of a vaccine against streptococcal throat infections should be the ultimate weapon in the primary prevention of acute rheumatic fever. One of the constraints hampering the development of the vaccine is the presence of multiple strains of Group A streptococci. The vaccines are developed in the "first world" where the strains are different and as such the vaccines are ineffective where they are needed most. A

number of vaccines are in development, and a safe and effective vaccine may well be available within one or two decades<sup>11</sup>.

### **Secondary prevention of rheumatic heart disease**

It is conceivable that the failure in primary prevention leads to the development of acute rheumatic fever but there is still a chance of preventing the development of chronic rheumatic heart disease. The prevention of further recurrent attacks of acute rheumatic fever is the only way to prevent rheumatic heart disease. This is known as secondary prevention and it is deemed a more cost-effective and attainable goal than primary prevention<sup>23 5</sup>. Penicillin remains the antibiotic of choice. Intramuscular penicillin is preferred over the oral route as it is more effective and results in better compliance<sup>23 21</sup>. The duration of secondary prophylaxis depends on the patients' age, the date of their last attack, and most importantly the presence and severity of rheumatic heart disease<sup>23 14</sup>. The WHO secondary prevention guidelines are as follows<sup>23</sup>:

- **Patients without proven carditis;** *Penicillin for 5 years after the last attack or until 18 years of age (whichever is longer)*
- **Patients with carditis;** *Penicillin for 10 years after the last attack, or at least until 25 years of age (whichever is longer)*
- **Patients with more severe valvular disease;** Lifelong penicillin
- **Patients after valve surgery;** Lifelong penicillin.

For over 20 years, the World Health Organization has recommended secondary prophylaxis to be delivered within a coordinated program using a registry of patients, as the first priority for the control of rheumatic heart disease<sup>11 18</sup>. For a long time most developing countries did not have effective secondary prevention programmes and hopefully with the advent of the Rheumatic Heart Disease Global Registry (REMEDY) programme there will be increased accessibility to secondary prophylaxis in sub-Saharan Africa<sup>2</sup>.

## **Surgical management of rheumatic heart disease**

The surgical options for rheumatic mitral valve disease range from simple closed mitral valvotomy to complex mitral valve repair and finally valve replacement. Mitral valve repair for rheumatic heart disease is commonly believed to yield inferior results in contrast to degenerative aetiology. This is a natural consequence of the progressive nature of the rheumatic process, which continues to distort the valve apparatus even beyond a successful repair<sup>24 25</sup>. This attrition in rheumatic mitral valve repair is further worsened by repeated acute rheumatic fever attacks<sup>10, 15, 24, 26-32</sup>. The WHO now recommends life-long prophylaxis in patients with severe valve disease or who have had valve surgery<sup>23 24</sup>. The choice of the surgical procedure is dictated by the valve lesion, availability of resources and surgical skills.

### *Pure mitral incompetence:*

A. Mitral valve repair: Pure isolated mitral incompetence is often the manifestation of acute rheumatic fever with carditis and it is also the hallmark of chronic rheumatic heart disease. This is the area where Carpentier and others spent a lot of time in the 1970s trying to perfect mitral valve coaptation and abolishing mitral incompetence. Rheumatic mitral valve repair is technically more difficult than degenerative repair and the results are also inferior. It is worth mentioning that in good hands a perfect and durable rheumatic valve repair is possible and has been shown in multiple studies<sup>15 37 38 39 40</sup>. Mitral valve repair is favoured for various reasons; it preserves the LV systolic function through the preservation of the sub-mitral apparatus, it avoids the attendant risks of anticoagulation associated with mechanical mitral valve prostheses, and it also has lower 30-day mortality and better overall survival when compared to replacements.<sup>28, 38, 41, 42</sup>

Modern mitral valve repair is based on the pioneer work of Carpentier<sup>43</sup> and the principles that he described in “the French correction”.

### Elements of the French correction:

#### 1. Functional approach to valve disease based on leaflet mobility

Class I: Normal leaflet mobility, annular dilatation

Class II: Excessive leaflet mobility due to either chordal rupture, elongation, papillary muscle rupture

Class III: Restricted leaflet mobility due to either shortened and thickened chordae or fused chordae or thickened immobile leaflets; or ventricular dilatation with restricted chordal motion.

## 2. Adequate valve exposure

The mitral valve can be approached via different accesses;

- Horizontal left atriotomy; this is the most commonly used incision, it involves developing the inter-atrial groove (Waterston's groove) between the back of the right atrium (RA) and the roof of the left atrium (LA). The LA is then incised in its roof.
- Superior trans-septal approach; this incision is over the roof of the LA and the inter-atrial septum cephalad from the fossa ovalis. It offers excellent exposure in small LA.
- Bi-atrial approach; this approach is uncommon and it involves a vertical right atriotomy and vertical trans-septal incision. It risks damage to the bundle of His, tricuspid annulus and atrioventricular septum.

## 3. Valve analysis

Current valve repair guidelines stipulate the use of intra-operative trans oesophageal echocardiogram (TOE) to assess the valve intra-operatively before and immediately after coming off cardiopulmonary bypass<sup>44</sup>. The pre-operative TOE findings guide the surgeon when performing the surgical valve analysis. The scallops on the posterior mitral valve are used to denote P1-P3 descriptors and the corresponding anterior mitral valve segments are denoted as A1-A3. All the prolapsed components and altered chordae should be identified and as well as fused commissures and retracted leaflets. A saline flush test is performed to test for incompetence prior to commencing the valve repair.

## 4. Ring annuloplasty

It is well described and accepted that some degree of mitral annular dilatation usually accompany mitral valve incompetence. As such, mitral valve repair is usually not complete until an annuloplasty has been performed in order to stabilise the mitral valve complex. The options for mitral annuloplasty are; suture annuloplasty, partial ring annuloplasty and

complete ring annuloplasty. Remodelling of the mitral valve annulus is only possible with moulded rings, which assumes the natural mitral annular configuration. Complete ring annuloplasty is the superior annuloplasty technique. Suture annuloplasty leave a round annulus, which is less functional and has been largely abandoned due to its poor results<sup>29 28 45 42</sup>.

In the modern era, partial rings and suture annuloplasties are only limited to children with diminutive annulus unable to accommodate complete rings.

#### 5. Repair of anterior leaflet prolapse

The options are;

- triangular leaflet resection
- chordal transfer
- chordal transposition
- chordal shortening
- neo-chordal insertion using PTFE (Goretex) suture

#### 6. Repair of posterior leaflet prolapsed

The options are;

- quadrangular leaflet resection
- neo-chordal insertion using PTFE (Goretex) suture

#### 7. Repair of restricted leaflet motion

- Thickened calcified leaflets are decalcified and excessive fibrotic tissue shaved off in order to improve mobility
- Retracted leaflet is addressed by elongation of the leaflet performed with the use of gluteraldehyde treated autologous pericardium

#### 8. Intra-operative evaluation of the repair

- Saline flush test by the surgeon
- Most importantly, TOE assessment has become an essential part of the guidelines for mitral valve repair assessment.

## 9. Repairing all repairable valves

All cases of mitral valve disease should be approached with repair in mind. Indications for mitral valve repair are based upon the lesion rather than the age, cause of the disease and patient condition. However, the younger the patient, the more urgent are the indications for valve reconstruction<sup>43</sup>. According to the latest American Heart Association valve guidelines, it is a class I indication to attempt repair of all valves; mitral valve repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished<sup>44</sup>.

### *Pure mitral stenosis:*

A. Percutaneous balloon mitral valvoplasty: The cardiologists usually assess the valve's favourability for percutaneous valvotomy. The absence of MR, absence of LA clot and a Wilkin's score of less than 8 are all the parameters used in identifying patients favourable for this procedure. The Wilkin's score is a valve assessment score focusing on leaflet mobility, thickness and calcification, and submitral disease<sup>33</sup>. Adequate leaflet mobility, lack of calcification and minimal sub-mitral disease are the favourable elements to look for.

B. Closed mitral valvotomy: This procedure is currently limited to the poor resource constrained units, where balloon valvuloplasty is unavailable. It is performed via a left anterolateral thoracotomy without the use of cardiopulmonary bypass. It involves the use of Tubbs dilators introduced via the left ventricular apex to crack open the stenotic mitral valve to a pre-set diameter while a finger introduced via the left auricle palpates the valve. In other words, this procedure is performed without direct vision of the mitral valve.

C. Open mitral valvotomy: This procedure is performed via a median sternotomy with cardiopulmonary bypass. It is performed under direct vision and it primarily involves commissurotomy of the fused commissures. Surgeons might also opt to shave the thickened leaflets to allow better leaflet mobility. The presence of severe submitral disease, which requires splitting of fused papillary muscles makes valvotomy less successful<sup>34 5 35</sup>.

D. Mitral valve replacement: Pure mitral stenosis is fortunately less common in the paediatric population but certainly more common in sub-Saharan Africa than the developed world <sup>16</sup>. There is a choice between bioprosthetic and mechanical valves. The bioprosthetic valves in the paediatric population degenerate rapidly and as such they are contra-indicated <sup>36</sup>. On the other hand, the implantation of mechanical prostheses in children is complicated by the risk of thrombo-embolism and the attendant drawbacks of anticoagulation, such as catastrophic bleeds with INR toxicity. The developing world is faced with issues of inaccessible health facilities and this means that patients with mechanical valves could go for weeks or longer without their anticoagulants or without surveillance of their INRs. This has been seen time and time again in our setting.

#### *Mixed mitral incompetence and stenosis*

This group of patients have complex disease, which makes mitral valve repair a great challenge<sup>37 46</sup>. Lesions of this nature, call for the application of surgical techniques used in both mitral valvotomy and repair in order to achieve a successful outcome.

#### **Timing of surgery**

The surgical management of rheumatic mitral valve disease is in accordance with the American and European guidelines on valvular heart disease management. The guideline recommendations on surgical intervention are mainly based on the symptoms of the patients and enlarging left ventricular dimensions. Deterioration of the left ventricular function is also an important indicator for surgical management of patients with mitral incompetence. Chronic mitral regurgitation has an insidious course, which results in volume overload of the left ventricle and irreversible systolic dysfunction may occur if surgical correction is delayed too long. Thus, serial echocardiographic follow up is of vital importance in order to identify the tipping point at which the LV function and dimensions deteriorate to meet the indications (LVESD>40mm) for surgical intervention <sup>1 44 47</sup>. Another important indicator for surgery that has been recently added to the general guidelines for mitral valve repair is as follow; mitral valve repair is indicated in asymptomatic patients with moderate to severe mitral incompetence, preserved LV function and dimensions

provided there is a high likelihood (>90%) of a successful repair<sup>44</sup>. This guideline is applicable in patients with degenerative mitral disease but the predictability of mitral repair in rheumatic valve disease is problematic and therefore difficult to recommend in patients with rheumatic mitral incompetence.

### **Challenges in rheumatic MV repair**

Extensive fibrosis and calcification of the sub-valvar apparatus, commissures, and annulus can hamper the success of valve repair<sup>35 27</sup>. Inevitably in mitral valve repair, diseased tissue is left behind, and despite good anatomic valve mobility intraoperatively, some hemodynamic obstruction persists and can progress to clinically important mitral stenosis over time. This phenomenon has been described by Carpentier's group and was related to progressive fibrosis, which usually parallels the degree of preoperative valve fibrosis<sup>48</sup>. The lack of secondary prevention programmes translates into repeated acute rheumatic fever infections and accelerated attrition of repaired mitral valves.

In order to circumvent the progressive nature of the disease, El Oumerie et al.<sup>49</sup>, reported on their series of aggressive excision of the diseased leaflet tissue and of the supporting fused sub-valvular apparatus to remove all valvular tissue that is affected by rheumatic disease. This required an extensive reconstruction using pericardial patches, artificial chordae, tricuspid autograft and or mitral homografts in selected cases<sup>49</sup>. This aggressive approach extends the spectrum of mitral valve repair in RHD<sup>49 50 35</sup>, but a high level of surgical expertise is required.

### **Predictors of poor outcome in mitral valve repair**

The major predictors of outcome can be classified according to timing of surgery, intra-operative findings and repair technique, and lastly the accessibility to secondary prevention. Sometimes, valve surgery is the only management option in children who present with acute rheumatic fever and intractable congestive cardiac failure. The timing of surgery is significant because the presence of active rheumatic carditis at the time of surgery is an important predictor of valve failure and the need for reoperation<sup>51</sup>. Younger age at surgery is also a significant factor because of the prolonged risk of repeated episodes of ARF infections, especially in the developing countries, where secondary prevention is often sub-optimal<sup>46 49 52</sup>.

Other important predictors of poor outcome include; the presence of mixed mitral stenosis and insufficiency, leaflet retraction, severe subvalvar disease and bi-leaflet prolapse<sup>27 53 46 49 37 5 34 40</sup>.

## Summary of the literature

Acute rheumatic fever is a complication of an untreated Group-A streptococcal pharyngitis, which predominantly affects young children and teenagers.<sup>1</sup> Untreated acute rheumatic fever and its repeated attacks results in a chronic inflammatory process, which causes damage to the heart valves and this is referred to as rheumatic heart disease. Rheumatic heart disease is preventable by prolonged penicillin prophylaxis in all patients who had presented with an acute rheumatic fever attack<sup>1-3</sup>. Rheumatic heart disease is still a significant cause of morbidity and mortality among children in the 21<sup>st</sup> century in the developing world<sup>6 5 2</sup>. In the latter part of the last century there has been a great decline in the incidence and prevalence of acute rheumatic fever in the developed world. However, the same has not been demonstrated in sub-Saharan Africa, where acute rheumatic fever and its dreaded sequelae of rheumatic heart disease still confer a significant burden of disease<sup>2,5</sup>. In sub-Saharan Africa and the rest of the developing world there is a persistence of factors, which allow acute rheumatic fever to flourish. These factors are all associated with poverty and include overcrowding, poor sanitation, inaccessible healthcare systems and the erratic availability of secondary prevention measures in the form of penicillin prophylaxis<sup>1,17</sup>. It is projected that 15 million people are affected by rheumatic heart disease worldwide<sup>6</sup>. This projection is however believed to be a gross under-estimation since a significant number of people in sub-saharan Africa harbour subclinical RHD as reported by Remenyi et al and by recent echocardiographic surveys conducted in Mozambique, Uganda and Senegal.<sup>2, 7-10</sup>.

Rheumatic heart disease typically affects the mitral valve before the other heart valves and as a result there is predominantly a higher prevalence of rheumatic mitral valve disease in paediatrics<sup>3</sup>. Acute rheumatic fever classically presents as acute mitral incompetence and it is only after repeated acute rheumatic fever attacks and usually in the 3<sup>rd</sup> decade of life, when rheumatic mitral stenosis is first observed. This has been shown in previous paediatric rheumatic mitral studies by Kalangos et al (2012,Switzerland) and by Hillman et al (2012,USA)<sup>3,15</sup>. However, a

recent Ethiopian paediatric (age range 4-15 years) rheumatic mitral study by Tadele et al. had shown a significant prevalence of rheumatic mitral stenosis in the paediatric age group<sup>16</sup>. The Ethiopian study observed a high prevalence of mitral stenosis in patients between the ages 6–10 years (26.5%) with an overall prevalence of mitral stenosis in paediatrics of 34.5%, while the overall prevalence of severe mitral stenosis, defined as a valve area of less than 1.0 cm<sup>2</sup>, was 18.1%<sup>16</sup>. This high prevalence of paediatric mitral stenosis in Ethiopia is probably a reflection of the state of the disease in most parts of sub-Saharan Africa, where the epidemiology is not well defined. This unprecedented finding by Tadele et al. is certainly related to the persistence of poor socio-economic conditions in sub-Saharan Africa and the associated recurrent acute rheumatic fever attacks coupled with inadequate secondary penicillin prophylaxis. Late presentation to healthcare facilities has been identified as one of the factor, which increases the burden of rheumatic heart disease in sub-Saharan Africa. This was clearly shown by Sliwa et al in the “Heart of Soweto” study, where the majority of patients presented with advanced cardiac disease and where the predominant primary diagnosis was heart failure. Sliwa et al. also showed an increased burden of newly diagnosed rheumatic heart disease but no single case of acute rheumatic fever was diagnosed and this was thought to be a result of under-estimation of acute rheumatic fever by parents and first-line healthcare practitioners<sup>17</sup>.

It is widely accepted that rheumatic mitral valve repair is the procedure of choice in both developed and developing worlds<sup>50, 49, 38, 29, 24, 34, 35, 39</sup>. The attrition in rheumatic mitral valve repair is largely due to the progressive nature of RHD, and due to repeat acute rheumatic fever attacks.<sup>10, 15, 24, 26-32</sup> Mitral valve replacement with mechanical valves in paediatrics will always remain a challenge with regards to anticoagulation monitoring. Antunes’ study on mitral valve replacement in Johannesburg in the 1980’s clearly demonstrated that mechanical valves have a high incidence of thromboembolic complications because of poor anticoagulation adherence. Bioprosthetic mitral valves are a good option for women of childbearing age but they degenerate much faster in the younger active patients and almost always require re-replacement within ten years of the first bioprosthetic replacement

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## Identification of need for further research

It is undisputed that mitral tissue prosthesis in the young deteriorates faster due to the young patient's active haemodynamics<sup>55-57</sup>. As such, it has become common practise at RCWMCH to implant an otherwise undesirable mechanical prosthesis in children. Future research needs to focus on the exact morphology of the repaired mitral valves in order to identify the risk factors associated with poor repair outcomes as has been shown in the adult cohort at Groote Schuur hospital by Geldenhuys et al<sup>59</sup>. The follow up of all paediatric surgery patients registered under the REMEDY database will result in a greater follow up and perhaps a better description of the incidence of rheumatic fever re-infections and its impact on the longevity of the surgical mitral valve repairs.

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# Chapter 2

## Manuscript

### **Retrospective Review of Paediatric Rheumatic Mitral Valve Repairs and Replacements Done at Red Cross War Memorial Children Hospital Over a Decade**

by

Alfred Mureko, Justin Batcheller, Melinda Eller, Martina Northrup-Lyons, Paul  
Human, Johan Brink, John Hewitson, Peter Zilla

## **Retrospective Review of Paediatric Rheumatic Mitral Valve Repairs and Replacements Done at Red Cross War Memorial Children's Hospital (RCWMCH) Over a Decade**

**Alfred Mureko, Justin Batcheller, Melinda Eller, Martina Northrup-Lyons, Paul Human, Johan Brink, John Hewitson, Peter Zilla**

### **Abstract**

**Objectives:** Rheumatic heart disease remains a significant cause of morbidity and mortality and it is the leading cause of acquired paediatric cardiac disease in the developing world. The aim of this study was to understand the burden of rheumatic heart disease and to review the surgical management of rheumatic mitral valve disease at our institution.

**Methods:** We retrospectively reviewed 76 consecutive patients who underwent mitral valve surgery for rheumatic heart disease between 1998 and 2010. The results and follow-up were reviewed, where death and reoperation were the primary endpoints. The follow up included a review of the latest information from the patients' medical records and telephonic interviews or home visits.

**Results:** A 91% follow up was achieved over a median follow up period of 7.4 years (range 0.1-15.2 years). The mean age at surgery was 10.7 years (SD +- 2.7 years). The females constituted 66% and males 34%. Mitral valve repairs were performed in 64% of patients and of the 64% repairs, 0.06% only had commissurotomies. Replacements were performed in 36% of patients. All mitral valve replacements were mechanical prostheses. The actuarial freedom from reoperation for repairs was 83% (+-2.2) and 66% (+-3.4) at 5 and 10 years and for replacements was 87% (+-4.8) and 87%(+-4.8) respectively (p=0.27). Actuarial freedom from embolic cerebrovascular accidents in the repair group at both 5 and 10 years was 100%, compared to 90.2% (+-6.6) and 79% (+-12.0) for the replacement group at 5 and 10 years respectively (p=0.02). Actuarial freedom from death at 5 and 10 years for children over 12.8 years was 77.7% (+-9.9) and 69.1% (+-12.0) respectively, compared to 93.6% (+-3.6) and 93.6% (+-3.6) for children under 12.8 years (p=0.03). No statistical significant difference was noted in freedom from valve related failure and death between repairs and replacements.

**Conclusions:** There was no significant difference in survival between mitral valve repairs and replacements. There was surprisingly worse survival among children who were above 12.8 years at time of the surgery.

## **Introduction**

In South Africa, as seen in other developing nations, we have a significant burden of rheumatic heart disease (RHD) and as such we need to have a good understanding of this disease to enable us manage our patients optimally. This high burden of RHD in South Africa provides an excellent platform for conducting local research, which will be most beneficial to our patient population. The paucity of local research is probably the reason why we are still waiting for the development of an effective vaccine against the local strains of Group- A streptococcus. Having realised the need for local research in RHD, we were inspired to contribute. This study aims to describe the pathology of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Particular attention will be focused on the surgical management options for rheumatic mitral valve disease in our indigent poor population.

ARF is a complication of an untreated Group-A streptococcal pharyngitis, which predominantly affect young children and teenagers.<sup>1</sup> Untreated ARF and its repeated attacks results in a chronic inflammatory process, which causes damage to the heart valves and this is referred to as RHD. Recurrent attacks of ARF, and thus progressive RHD, is preventable by prolonged penicillin prophylaxis in all patients, who have had an ARF attack<sup>1-3</sup>. RHD remains a significant cause of morbidity and mortality among children in the 21<sup>st</sup> century in the developing world<sup>6, 5</sup>. In the early part of the last century before widespread antibiotic availability there was a great decline in the incidence and prevalence of acute rheumatic fever in the developed world<sup>6, 18</sup>. However, the same has not been seen in sub-Saharan Africa, where ARF and its sequelae of RHD still constitute a significant burden of disease<sup>2, 5</sup>. In sub-Saharan Africa and the rest of the developing world there is a persistence of factors, which favours the flourishing of acute rheumatic fever. These factors are all associated with poverty and include malnutrition, overcrowding, poor sanitation, inaccessible healthcare systems and the erratic availability of secondary prevention in the form of penicillin prophylaxis<sup>1, 17</sup>. It is estimated that 15 million people are affected by rheumatic heart disease worldwide<sup>6</sup> This estimate is however believed to be a gross under-estimation because there is insufficient data about underdeveloped areas; Remenyi et al. showed with echocardiographic surveys in Mozambique, Uganda and Senegal that a significant number of people in sub-Saharan Africa are harbouring subclinical RHD<sup>2, 7-10</sup>.

RHD typically affects the mitral valve before the other heart valves and as a result the predominant lesion in children with RHD is mitral valve disease<sup>3</sup>. The general

systemic features of ARF include fever, sore throat, malaise and etc (Ducket-Jones criteria). ARF with significant carditis classically presents as acute mitral incompetence and as fibrosis progresses (RHD), usually in the 3<sup>rd</sup> decade of life we start seeing mitral stenosis. This has been shown in previous paediatric rheumatic mitral studies by Kalangos from Switzerland and by Hillman from the USA.<sup>3, 15</sup> However, a recent Ethiopian paediatric (age range 3-15) rheumatic mitral study by Tadele et al had shown a significant prevalence of rheumatic mitral stenosis in the paediatric age group.<sup>16</sup> The Ethiopian study observed a high prevalence of mitral stenosis in patients between the ages 6–10 years (26.5%) and the overall prevalence of mitral stenosis in paediatrics was 34.5% while the overall prevalence of severe mitral stenosis, defined as a valve area of less than 1.0 cm<sup>2</sup>, was 18.1%.<sup>16</sup> This high prevalence of paediatric mitral stenosis in Ethiopia is probably a reflection of the state of the disease in most parts of sub-Saharan Africa, where the epidemiology is not well defined. This unprecedented finding by Tadele is certainly related to the persistence of poor socio-economic conditions in sub-Saharan Africa and the associated recurrent acute rheumatic fever attacks coupled with inadequate secondary penicillin prophylaxis. Late presentation to healthcare facilities has been identified as one of the factors that increases the burden of rheumatic heart disease in sub-Saharan Africa. This was shown by Sliwa et al in the “heart of Soweto”, where the majority of patients presented with advanced cardiac disease and where the predominant primary diagnosis was heart failure. Sliwa also showed an increased burden of newly diagnosed RHD but no single case of ARF was diagnosed and this was thought to be a result of under-estimation of ARF by parents and first-line healthcare practitioners<sup>17</sup>.

It is widely accepted that rheumatic mitral valve repair is the procedure of choice in both developed and developing worlds<sup>38,24, 29, 39, 43, 45, 50</sup>. The attrition in rheumatic mitral valve repair is largely due to the progressive nature of RHD and repeat ARF attacks.<sup>10, 15, 24, 26-32</sup> Mitral valve replacement with mechanical valves in paediatrics will always remain a challenge with regards to anticoagulation monitoring. Substitute heart valves have major limitations in a third world population. Antunes’ study on mitral valve replacement in Johannesburg in the 1980’s demonstrated that mechanical valves have a high incidence of thromboembolic complications because of poor anticoagulation<sup>36</sup>. Bioprosthetic valves have a high failure rate in the young, although they are still an acceptable alternative in women of childbearing age<sup>36, 61, 62</sup>

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## **Patients and methods**

### **Patients**

The undertaking of the study was approved by the University of Cape Town's Research Committee and by the management of the Red Cross War Memorial Children's Hospital (RCWMCH). Ethical approval was granted by the University's Human Ethics Committee. We retrospectively reviewed 76 consecutive patients who underwent first-time single mitral valve surgery for rheumatic heart disease at the RCWMCH, Chris Barnard Division of Cardiothoracic Surgery, at the University of Cape Town between January 1998 and December 2010. The RCWMCH is one of the major referral centres in South Africa and as such we receive a significant number of patients from other provinces within the country. The majority of our study population (57%) came from within the Western Cape while 41% were referred from the Eastern Cape and a further 2% from the Northern Cape Province. Patients in our study were predominantly black (76%) and the remainder 24% were coloureds (mixed race). This pattern is a reflection of the South African socio-economic distribution and it is illustrative of the fact that RHD is a disease of poverty.

The mean age at surgery was 10.7 years (SD±2.7) with an age range of 4 to 17 years. The females constituted 66% and males 34%. MV repairs (MVrep) were performed in 64% of patients and of the 64% repairs, 0.06% only had commissurotomies. Replacements (MVR) were performed in 36% of the cohort. All the replacements used mechanical prosthesis. The majority of our patients came from poor socio-economic backgrounds associated with malnutrition, overcrowding and poor sanitation.

### **Surgery**

All procedures were performed via a median sternotomy on cardiopulmonary bypass, with aortic and bicaval cannulation at moderate hypothermia (27-32 degrees Celsius). The left atrium (LA) was usually accessed via the Waterstons groove or occasionally trans-septally if a tricuspid annuloplasty (TA) was to be done. Mitral valve procedures ranged from simple open mitral valvotomies to repairs or replacements. All the repairs were performed by two of the authors (JB and JH). Repairs always included the use of an annuloplasty ring, with the exception of one patient in whom a partial suture annuloplasty was done because a suitable ring size was not available. The annuloplasty rings used were mostly Biotek (a rigid ring

made locally and is a copy of the classical Carpentier ring) in the early 2000s but this shifted to the Carpentier/Edwards' Physio rings in the latter 2000s. We employed the various techniques described by Carpentier in achieving competency of the mitral valve, including chordal shortening and transfer, splitting of fused subvalvar apparatus, leaflet resection and/or augmentation with gluteraldehyde-treated autologous pericardium and commissurotomies. Chordal replacement using PTFE was also used as a mitral repair technique. On completion of the mitral valve repair and prior to closing the atrium, competence was tested using a 50ml bulb syringe to inject saline into the left ventricle to observe coaptation and competence of the leaflets. A trans-oesophageal echocardiogram (TOE) was used to assess all the repairs intra-operatively once the heart had resumed beating. If the repair was suboptimal on TOE, the surgeon would re-establish bypass and attempt to improve the repair. If repair was technically unachievable then the valve would be replaced with a prostheses.

All our mitral valve replacements were with mechanical prostheses (either SJM or On-X bileaflet prostheses). The smallest implanted valve was a 21mm SJM and the largest was a 29mm SJM. Concomitant procedures, included in our study were tricuspid annuloplasty (TA) and MAZE procedure. The six TAs performed were DeVega suture annuloplasties. There was a single MAZE procedure performed for Atrial Fibrillation (AF).

### **Data collection and post-operative follow-up**

Ethical approval for the study was granted by the University's Human Ethics Committee. Informed consent was obtained from the parents of minors or directly from the older patients (>18 years at time of the interview). The patient's names were identified from the operating theater record books, the perfusionists' pump sheets and also from our clinical patient database. The patient's medical folders were then retrieved from the hospital's medical records department and all the pertinent information was entered into an electronic spreadsheet (Excel).

All our patients underwent a pre-discharge transthoracic echocardiogram to assess valve function, ventricular contractility and to exclude significant pericardial effusions. The patients, living within the Cape Town Metropolitan District underwent repeat echocardiograms at 6 weeks and 6 months after discharge. However, the patients referred from other provinces were followed-up at their respective referring hospitals where follow up echocardiogram was not always possible. All mitral valve repair patients were placed on 3 months of warfarin therapy in order to allow the

annuloplasty ring to endothelialise. The INR target value was between 2 and 3. Patients having mitral valve replacements were placed on lifelong warfarin therapy with an INR target value of between 2.5 and 3.5. All patients on warfarin therapy were advised to follow up monthly at local clinics for INR control.

The primary endpoints of the study were death and reoperation. The patient follow-up was conducted through review of the medical records, telephonic interviews or through home visits when necessary. For untraceable patients, follow-up data was based on information recorded at the most recent hospital visit, provided that this visit fell within the period in which we started contacting patients. Untraceable patients, whose most visit was prior to our follow up period were considered lost to follow up and were not included in the study.

Patients referred from other centres or provinces were particularly difficult to contact as the majority did not currently valid telephone numbers. This prompted us to travel to the Eastern Cape Province (about 1000km away), our major referring province, where we attended the Cecilia Makiwane and Frere hospitals to examine the patients' medical records for follow-up data and phone numbers. Within the Western Cape Province, we travelled to distant hospitals in George and Mosselbaai (400-500 km away) for the same reason. On one occasion the only link to a patient was their residential address and we successfully reached them when we travelled to their home 400km away. The country's National Health Laboratory Services (NHLS) database, the Clinicom Western Cape Health Database and the South African Police Services (SAPS) were all valuable resources in tracing patients.

### **Statistical analysis**

All inferential statistical analysis was performed using the JMP software application for Apple™ Macintosh (version 10.0.2; SAS Institute, Cary, NC, USA). All normally distributed continuous numerical data (confirmed by Shapiro-Wilk testing) were expressed as Means  $\pm$  Standard Deviation and all nonparametric numerical data as Medians and range. The primary end-point of the study was defined as either valve re-operation or valve-related death in accordance with the guidelines of the Society of Thoracic Surgeons for reporting mortality and morbidity after cardiac valve interventions<sup>58</sup>. Following the identification of patient age as a contributing variable affecting outcome by nominal logistic modelling, reiterative partition modelling was applied to identify an age-related cut point. Product-limit (Kaplan-Meier) survival estimates were calculated at five and ten years postoperatively for both age groups as well as for valve repair and valve replacement groups. A Log Rank statistic was

calculated to test survival homogeneity across the groups. Patients who remained un-reoperated and alive were censored at the end of their respective follow-up periods. A p-value <0.05 was accepted as confirming statistical significance.

## **Results**

### **Early clinical outcome**

There was no intra-operative mortality. 30 day mortality occurred in 2 patients (3%). One was a 15 year old girl, followed up for 1 year at our hospital prior to her surgery. She presented in florid pulmonary oedema due to critical mitral stenosis (valve area of 0.8, peak gradient 50mmHg) and required aggressive pre-op resuscitation following a cardiac arrest in the ICU. Emergent salvage MVR was attempted but she nevertheless died 5 days later without regaining consciousness. The other patient died at the referring hospital in the Eastern Cape Province three weeks following MVrep. The cause of death was cardiac tamponade due to a large pericardial effusion.

### **Late clinical outcome**

#### **Late mortality**

Late mortality occurred in 9 patients (12%). One patient died from severe cardiac tamponade at 6 weeks following MVR shortly after emergent drainage of the pericardial effusion. Another patient died 3 years post surgery after he contracted pulmonary tuberculosis (TB), and defaulted treatment, dying as a result of TB complications. Another patient died from a thromboembolic stroke (CVA) nine years after MVR. The remaining late mortalities were all cardiac-related: three occurred in patients who presented with poor preoperative left ventricular functions (EF less than 40% in the face of severe MR). The other three patients died as a result of structural valve deterioration following repairs and before further surgery could be undertaken.

With statistical partition modelling, an age “cut point” of 12.8 years was identified and the two groups (above and below 12.8 years) were analysed in terms of their differential outcomes. Actuarial freedom from death at 5 and 10 years for children over 12.8 years was 77.7% (+-9.9) and 69.1% (+-12.0) respectively, compared to 93.6% (+-3.6) and 93.6% (+-3.6) for children under 12.8 years (p=0.03) (Figure 1).

## Reoperations

Early reoperations: There were no reoperations within 30-days of surgery.

Late reoperations:

- For the repairs, there were a total of 9 reoperations out of the 45 who underwent repairs (Table 3), giving a reoperation rate of 20% over a mean period of 60.87 months. The earliest reoperation was at 7 weeks in a 13 year old girl, due to dehisced sutures on the mitral annuloplasty ring; she had a MVR. Three out of the nine reoperations had documented new episodes of ARF infections; and two of these patients also had infective endocarditis. Four patients were reoperated due to structural valve deterioration. The remaining patient needed surgery for a persistent prolapse of the A2 segment of the anterior mitral valve leaflet (this is the patient previously mentioned, who had a suture annuloplasty at the first repair). This last patient was the only one in our study, who underwent a second successful repair, at which an annuloplasty ring was used.
- Of the three patients having commissurotomies (OMV) only, one was re-operated after 4 years for restenosis, when a MVR was done, another was reoperated with MVR after 10 months due to severe MR that developed in the months after surgery. The third patient was lost to follow up.
- Of the 28 patients who had MVR, three (10%) had reoperations (Table 3). The earliest reoperation was for a paravalvular leak 90 days after an emergent MVR for MS with pulmonary oedema. At initial surgery, the myocardium was severely inflamed, with the valve histology confirmed acute-on-chronic carditis. The remaining two re-operations were done for clotted valves at one and two years post operatively respectively.

The actuarial freedom from reoperation for repairs was 83% (+-2.2) and 66% (+-3.4) at 5 and 10 years, while it was 87% (+-4.8) and 87% (+-4.8) for replacements (p=0.27)

## Valve-related morbidity

Clotted valves: We had two (7%) clotted valves in the study; one patient was 13 years old at initial MVR and the valve clotted two years later during pregnancy, with a concomitant cerebrovascular accident. The other patient was 8 years old at initial

MVR and clotted the valve one year after surgery due to poor compliance with anticoagulation.

Thromboembolic cerebrovascular accident (CVA): four patients (14%) developed thromboembolic CVA after MVR (Table 3). None in the MVrep group developed a CVA; actuarial freedom from embolic CVA in the MVrep group at both 5 and 10 years was 100%, compared to 90.2% (+-6.6) and 79% (+-12.0) for the MVR group at 5 and 10 years respectively ( $p=0.02$ )(Figure 3).

Paravalvular leaks: There were two paravalvular leaks (Table 3). One patient was reoperated and the other had a trivial leak, managed conservatively.

Infective endocarditis: five patients developed infective endocarditis. Two in the MVrep group, both treated conservatively and three in the MVR group (Table 3), of which two underwent reoperation while the third was treated conservatively.

Anticoagulation related haemorrhage: Only one patient required admission and blood transfusion for anticoagulation related haemorrhage (Table 3).

No statistical significant difference was noted in the freedom from valve related failure and death between repairs and replacements (Fig 4).

### **Demographics, Population Migration and Follow-up**

We achieved a 91% follow up over a median follow up period of 7.41 years (range 0-15 years).The majority (57%) of patients in the study were from within the Western Cape Province, where we are situated. A significant number of patients (41%) were referred from the Eastern Cape Province. A further 2% were referred from the Northern Cape Province. Patients referred from other provinces all returned to their provinces after surgery. The indigent black patients made up 76% of all patients, while the remaining 24% were of mixed race. Females made up 66% of the study population.

## **Discussion**

This study can attest to a previous study from our department by Geldenhuys et al<sup>59</sup> that cellular phone penetration has had a positive impact on the follow up of patients in the developing world. A 91% follow up compares well to studies in developed nations<sup>38 53</sup>, whilst for many studies in the developing world follow-up is particularly difficult. Whilst the official “cut-off” age for treatment at the RCCWMH is 12 years old, because of the particular problems of compliance and follow-up in adolescent patients we prefer to “keep” our patients as long as possible, sometimes even operating on patients as old as 17 years being treated at our paediatric hospital. For this study we included all patients from the ages of birth to 17 years operated at RCWMCH.

One unexpected finding in this study is the poorer outcome of surgery for children over 12.8 years. This is likely due to various factors, particularly late presentation to healthcare facilities, and poor compliance amongst teenagers. Antunes’ South African cohort of 1983 also showed worse for children older than 15 years having mitral annuloplasty for RHD, although it did not reach statistical significance<sup>54</sup>. In our series the majority of children above 12.8 years were referred from distant rural areas of the Eastern Cape Province, where access to health care is poor. African cultural beliefs are also known to play a significant role in delayed presentation to hospital. One family in our study believed their child to be “bewitched” and as a result only sought medical help late in the disease process after consulting various traditional healers. The level of education of the parents has a significant bearing on how they care for their children. To illustrate, the parents of another child, who was failing to thrive with poor effort tolerance labelled her as merely a “weak child” and did not seek medical care until late in the disease process. This cultural impact on healthcare access has been well described by Russel et al<sup>60</sup>.

Thrombo-embolic strokes were seen in 14% of our valve replacement patients but in none of our repairs. The actuarial freedom from embolic CVA in the MVR group (90.2% and 79% at 5 and years respectively) compared to the absence of CVA in the MVrep group (p=0.02) represents a significant morbidity and potential mortality (one of our patients) related to MVR. Thus it is concerning that some of our patients fail to attend follow up visits for anticoagulation control after returning home, especially in the more rural areas. We know of at least two such patients with mechanical valves who have been lost to follow up. This raises a dilemma in the choice of implant for MVR in rural patients. It is well established that bioprosthetic

valves have a high failure rate in the young, although they are still an acceptable alternative in women of childbearing age<sup>36, 61, 62</sup>. In Antunes' study in the 1980's in Johannesburg, South Africa, the survival from degeneration of bioprosthetic valves was only 20% at 6 years in patients younger than 20 years<sup>36</sup>. With this in mind, we have only implanted mechanical valves in children, sometimes opting for a less than perfect repair rather than MVR if a patient is from a rural area.

In our series the actuarial freedom from reoperation for repairs was 83% (+2.2) and 66% (+3.4) at 5 and 10 years. Pomerantzeff in Brazil in 2000 had a 43% freedom from reoperation at 10 years<sup>30</sup>. Skoularigis' rheumatic mitral repair cohort (mean age 18 years) in Johannesburg, South Africa, in 1994 had a 75% freedom from reoperation at 5 years<sup>51</sup>. Choudary in 2001 reported an Indian rheumatic mitral valve repair cohort (mean age 23 years) with a freedom from reoperation at 11 years of 65%<sup>34</sup>. Chauvaud et al. (1986) and Kalangos et al (2008 and 2012) from Europe reported a 10 year freedom from reoperations in excess of 78% up to 93%<sup>15, 39, 53</sup>.

The higher reoperation rate that we experienced among our repair group may in some cases be attributed to repeat episodes of ARF in the post operative period, and to progression of scarring in the valve leaflets. Recrudescence of ARF are due to the poor application of secondary prophylaxis in our setting, where access to healthcare is seriously compromised by socio-economic factors for the majority of our patients<sup>2, 5</sup>.

## **Study limitations**

The retrospective nature of our study was a limitation as for all studies of this nature. We were unable to obtain recent echocardiograms in all the patients at the time of follow-up and this at best only yields a subjective impression of the functional status of the valves as judged from clinical symptoms and effort tolerance of the patients. We run a relatively low volume unit and we could only achieve a follow-up of 91%. It would have been ideal to achieve a follow up of 100% when dealing with small numbers as in our case.

## **Conclusions**

There was no significant difference in survival between the repairs and replacements. There was surprisingly poor survival among children above 12.8 years of age at the time of surgery and this is probably due to late presentation to healthcare facilities, and poor compliance amongst teenagers.

Repair of rheumatic mitral valves should always be attempted if at all possible in order to avoid the complications associated with mechanical valves

- Hopefully with the advent of the REMEDY registry we will see an improvement in secondary prophylaxis with a resultant reduction in the risk of repeated attacks of ARF and also then a reduction in the need for this type of surgery.
- Ensuring timely referral of patients for surgery will be a secondary benefit of improved surveillance through registries.

# Appendix

## Tables

**Table 1. Patient characteristics**

	Overall, n=76	MVrep, n=45(59%)	MVR, n=28(37%)	OMV, n=3(4%)
Females	66%	31	17	2
Males	34%	14	11	1
Age				
Median	11	10.43	11.02	11.14
Range	4-17	5-17	4-15	10-13
Weight (kgs)				
Median	25	26	25	23
range	13-50	14-49	13-50	22-34
Preoperative AF	3	1	2	0
Indication for surgery				
Pure MR	51	34	17	0
Pure MS	5	0	2	3
Mixed MR and MS	20	11	9	0
Follow-up				
Recent	69(91%)	41	26	2
Not recent	7(9%)	4	2	1
Follow up time(years)				
Median	7.41	8	8	7.5
Range	0-15	0-13	0-15	6-9

**Table 2: Concomitant procedures**

Other procedures	MVR	MVRep	OMV
Tricuspid annuloplasty	3	3	0
MAZE	<b>0</b>	1	0

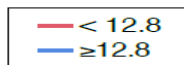
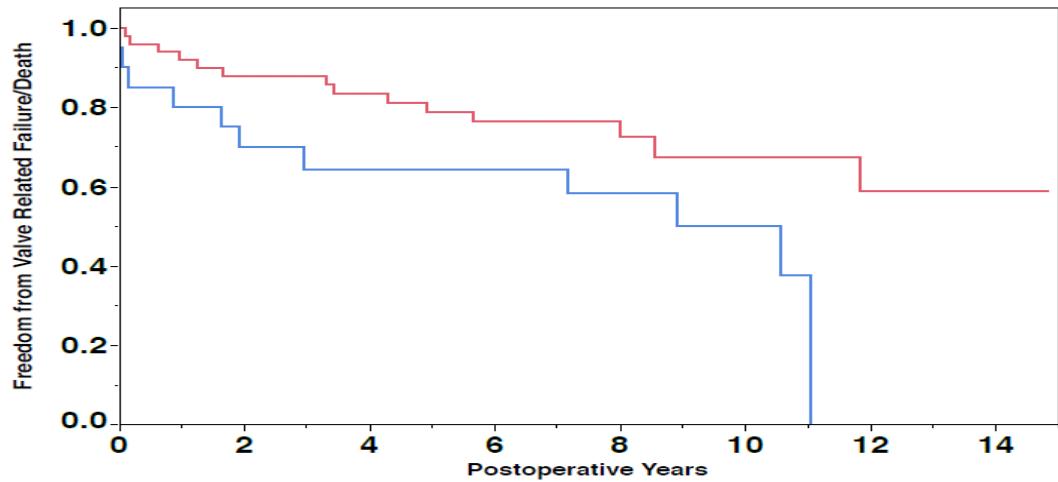
**Table 3. Post-op complications**

**Post-op complications**

	<b>MVrep, n=45(59%)</b>	<b>MVR, n=28(37%)</b>	<b>OMV, n=3(4%)</b>
CVA(stroke)	0	4	0
Prosthetic SBE	2	3	0
Clotted valves	0	2	0
Paravavular leaks	0	2	0
Reoperations	9	3	2
Anticoagulation complication	0	1	0
Pericardial effusion(temponade)	6	2	0

# Figures

**Figure 1.** Freedom from Valve Related Failure/Death as a function of Age Group

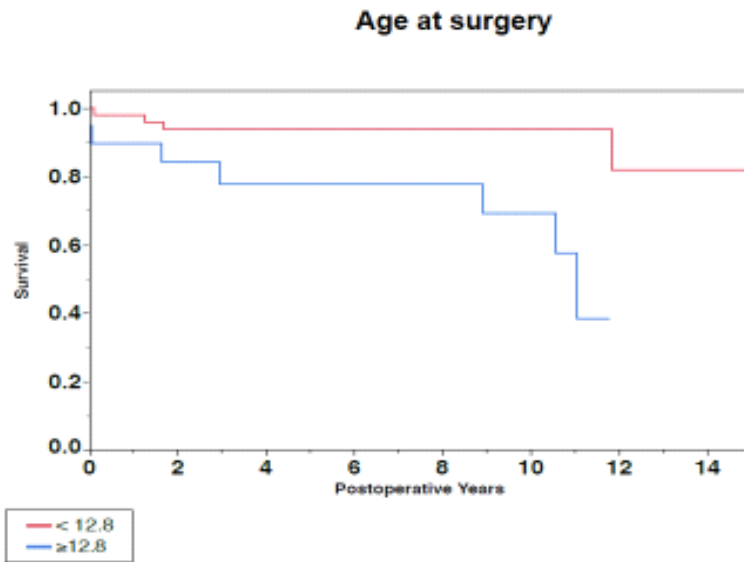


Grouped by Age Cutpoint (based on partition modeling)

p=0.028

	5y	10y
Age < 12.8	78.8±6.0	67.3±8.2
Age ≥ 12.8	64.2±10.9	50.0±12.4

**Figure 2.** Freedom from Death as a function of Age Group

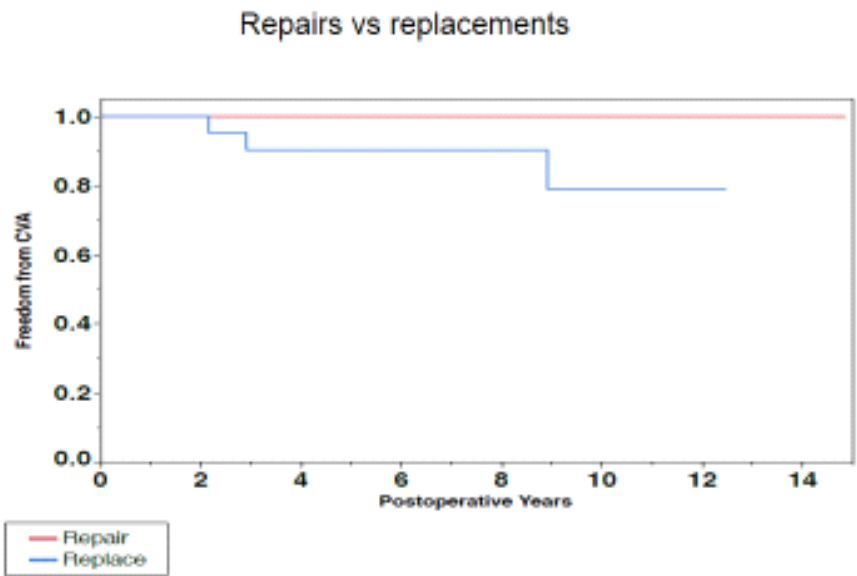


p=0.003

	5y	10y
Age < 12.8	93.6±3.6	93.6±3.6
Age ≥ 12.8	77.7±9.9	69.1±12.0



**Figure 3.** Freedom from CVA as a function of Mitral Valve Procedure

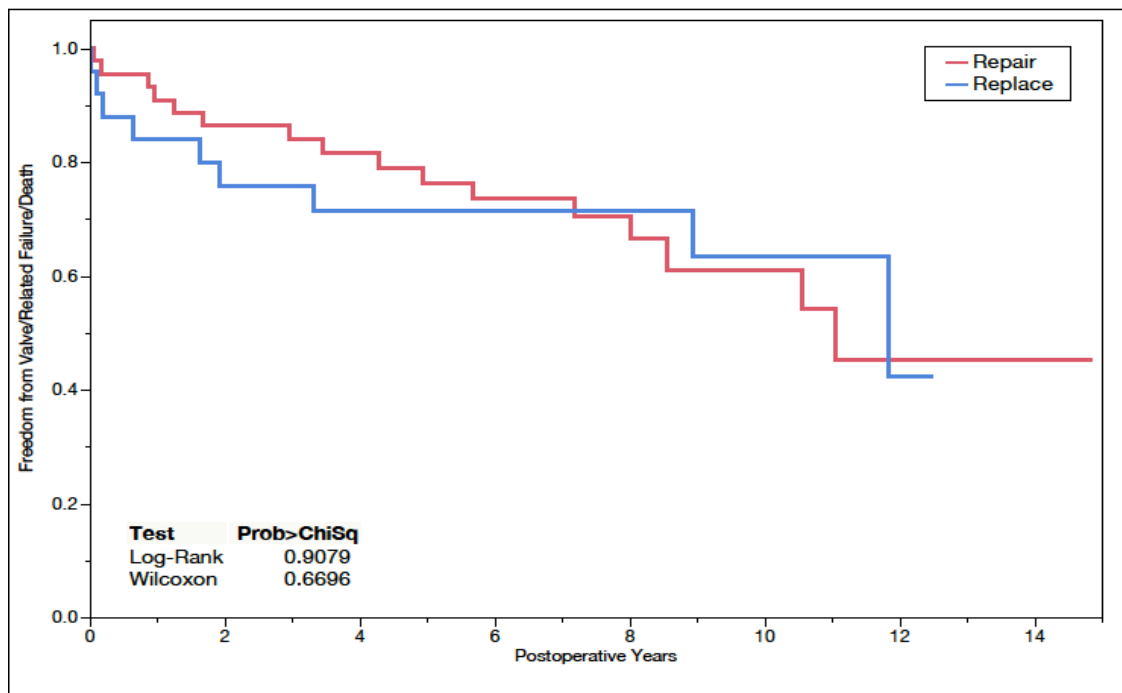


p=0.020

	5y	10y
Repair	100±0	100±0
Replace	90.2±6.6	79.0±12.0



**Figure 4.** Freedom from Valve Related Failure/Death as a function of Mitral Valve Procedure



# Ethics approval

 UNIVERSITY OF CAPE TOWN

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Faculty of Health Sciences  
Faculty of Health Sciences Research Ethics Committee  
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Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
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29 February 2012

HREC REF: 076/2012

Dr A Mureko  
Cardiothoracic Surgery  
Ward D-24  
NGSH

Dear Dr Mureko

**PROJECT TITLE: RETROSPECTIVE REVIEW OF PAEDIATRIC RHEUMATIC MITRAL VALVE REPAIRS AND REPLACEMENTS DONE AT RED CROSS WAR MEMORIAL CHILDREN (RCWMC) HOSPITAL OVER THE PAST DECADE**

Thank you for addressing the issues raised by the committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

**Approval is granted for one year till the 15 March 2013.**

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the REC. REF in all your correspondence.**

Yours sincerely

  
**Signed**

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, HSE HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), *sAricklee*

# University research department approval



UNIVERSITY OF CAPE TOWN

## Department of Surgery

Departmental Research Committee  
Professor Anwar Suleman Mall  
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13<sup>th</sup> January 2011

Dr A Mureko  
Department of Surgery  
Division of Cardiothoracic Surgery  
Grootte Schuur Hospital  
University of Cape Town

Dear Dr Mureko

**RE: PROJECT 2012/009**

**PROJECT TITLE:** Retrospective review of paediatric rheumatic mitral valve repairs and replacements done at Red Cross War Memorial Children (CWMC) hospital over the past decade

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

**Signed**

**PROFESSOR ANWAR S MALL  
CHAIRMAN: RESEARCH COMMITTEE**

"OUR MISSION is to be an outstanding teaching and research university,  
educating for life and addressing the challenges facing our society."

# RCWMCH authorisation letter



Dr TA Blake  
Manager: Medical Services  
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Dr A Mureko  
Cardiothoracic Surgery  
Ward D-24  
GSH

Dear Dr Mureko

#### APPROVAL OF RESEARCH

**PROJECT:** Retrospective review of paediatric rheumatic mitral valve repairs and replacements done at Red Cross War Memorial Children's Hospital (RCWMCH) over the past decade

I am pleased to inform you that approval has been granted to conduct the above-mentioned study at RCWMCH.

Yours faithfully,

**Signed**

Dr Thomas Blake  
Manager: Medical Services

Date: 09 March 2012

[www.westerncape.gov.za](http://www.westerncape.gov.za)

## Journal instructions to authors

# European Journal of Cardio-Thoracic Surgery

The manuscript should be organized as follows:

### **Title page (1st page)**

**Title:** should be brief and descriptive (100 characters) - no abbreviations are allowed, even if well known.

**Authors:** list all authors by full first name, initial of or full middle name and family name. Qualifications are not required. Ensure the author names correspond (in spelling and order of appearance) with the metadata of the system.

**Institution(s):** include the name of all institutions with the location (department, institution, city, country) to which the work should be attributed (in English). Use superscript numbers to connect authors and their department or institution.

**Corresponding author:** The full name, full postal address, telephone/fax numbers and the e-mail address should be typed at the bottom of the title page.

**Meeting presentation:** If the manuscript was (or will be) presented at a meeting, include the meeting name, venue, and the date on which it was (or will be) read; also indicate if you have submitted an Abstract of this manuscript for the EACTS or ESTS annual meeting and whether it has been accepted (if known).

**Word count:** The total number of words of the whole article (including title page, abstract, main text, legends, tables and references) must be specified on the title page.

**Clinical registration number:** for the registration number of Clinical Trials please see the [section above](#).

### **Abstract (2nd page)**

An abstract should be a concise summary of the manuscript. Reference citations are not allowed. The abstract should be factual and free of abbreviations, except for SI units of measurement. A structured abstract must have four sections:

- (1) Objectives: should describe the problem addressed in the study and its purpose.
- (2) Methods: should explain how the study was performed (basic procedures with study materials and observational and analytical methods).
- (3) Results: should describe the main findings with specific data and their statistical significance, if possible.
- (4) Conclusions: should contain the main conclusion of the study.

### **Keywords**

Following the abstract, 3-6 keywords should be given for subject indexing.

## **Main text (3rd page and following)**

### **Introduction**

Should state the purpose of the investigation and give a short review of pertinent literature.

### **Materials and methods**

Should be described in detail with appropriate information about patients or experimental animals. Use of abbreviations renders the text difficult to read; abbreviations should be limited to SI units of measurement and to those most commonly used, e.g. VSD, ASD, CABG (abbreviations should not be included in headings and extensions should be included at first mention). Generic names of drugs and equipment should be used throughout the manuscript, with brand names (proprietary name) and the name and location (city, state, country) of the manufacturer in brackets when first mentioned in the text.

### **Results**

Results should be reported concisely and regarded as an important part of the manuscript. They should be presented either in tables and figures, and briefly commented on in the text, or in the text alone. Repetition of results should be avoided! For statistical analysis, follow the 'Statistical and data reporting guidelines' ([Eur J Cardiothorac 2015](#)).

The full set of raw data must be available at any time should reviewers or editors request these for more in-depth review during the review process and/or after publication.

### **Discussion**

The discussion is an interpretation of the results and their significance with reference to pertinent work by other authors. It should be clear and concise. The importance of the study and its limitations should be discussed.

### **Acknowledgement**

Acknowledgements and details of non-financial support must be included at the end of the text before the references and not in footnotes. Personal acknowledgements should precede those of institutions or agencies.

### **Funding statement**

See [Funding and conflict of interest section](#) below.

### **Conflict of interest statement**

See Funding and conflict of interest section below.

### **Figure (and video) legends**

A list with legends for each figure (and each video) must be included.

### **Tables**

All tables must be included in the manuscript file, should start on separate pages and be accompanied by a title, and footnotes where necessary. The tables should be numbered consecutively using Arabic numerals. Units in which results are expressed should be given in parentheses at the top of each column and not repeated in each

line of the table. Ditto signs are not used. Avoid overcrowding the tables and the excessive use of words. The format of tables should be in keeping with that normally used by the journal; in particular, vertical lines, coloured text and shading should not be used. Please be certain that the data given in tables are correct. All tables must be cited in the text.

### **References**

Authors are responsible for checking the accuracy of all references. If you use EndNote or Reference Manager to facilitate referencing citations (not required for submission), this journal's style is available for use.

References should be numbered in order of appearance in the text (in Arabic numerals in parentheses) and must be listed numerically in the reference list. Journal titles and author initials should be properly abbreviated and punctuated. See list of abbreviated journals in [Index Medicus](#). If an automatic referencing system has been used in the preparation of the paper, the references must not be left embedded in the final text file submitted. The citation of journals, books, multi-author books and articles published online should conform to the following examples:

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