SPECTRUM OF CAUSES OF ISOLATED AORTIC REGURGITATION AT A SOUTH AFRICAN PUBLIC SECTOR TERTIARY CARE INSTITUTION

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MSKMAL008

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

FOR THE PARTIAL FULFILLMENT OF THE DEGREE OF MASTER OF MEDICINE (MMED) IN

INTERNAL MEDICINE

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF CAPE TOWN

DATE OF SUBMISSION: 11/07/23

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DECLARATION

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Acknowledgements and Contributions

I am eternally grateful to the following for their immense contribution to my dissertation. Firstly, to my brilliant Supervisors: Prof Mpiko Ntsekhe and Prof Tim Pennel for their continuous mentorship, encouragement, guidance and expertise during thus research. Their overall role as supervisors has been invaluable and would not have been possible without their continued support and vision.

Thus project would not be possible without their input. The process has been a period of considerable growth for me, both personally and academically.

I also wish to acknowledge:

- Department of Cardiothoracic at Groote Schuur Hospital for allowing us to use their database for patients who had aortic valve replacement and information on surgical macro inspection.
- Department of Cardiology for information on clinical presentation and pre-operative echocardiographic data
- Wisdom Basera for his input with statistical analysis.

Finally I would like to acknowledge with gratitude, the support and love of my family- my parents Fanuel and Catherine, my brother Hennings, my sister Pamela, my wife Zamambo and my sons Liam and Caleb. They all kept me going, and this dissertation would not have been possible without them.

The format of the thesis is in the publication ready format to be published in.....

The abstract was presented at the 2022 UCT Department of Medicine Annual Research Symposium.

LISTS OF TABLES AND FIGURES

ABBREVIATIONS

AR – Aortic regurgitation

AoV-Aortic Valve

AVR- Aortic Valve replacement

AOVPG-Aortic Valve peak gradient

BAV- Bicuspid Aortic Valve

GSH- Groote Schuur hospital

HPT-Hypertension

IE-infective endocarditis

LV- Left Ventricle

LVEF-Left Ventricular ejection fraction

MR-Mitral regurgitation

NYHA-New York heart association

MAOVD-Mixed aortic valve disease

Pre-op Echo- Pre-operative Echocardiography

RHD-Rheumatic heart disease

IQR- Interquartile range

SD-Standard Deviation

TEE-Transoesophageal echocardiography

IRAD- International Registry of Acute Aortic Dissection.

HIV-Human Immunodeficiency Virus

HAART-Highly Active Antiretroviral therapy

Redcap-Research Electronic Data Capture

ABSTRACT

BACKGROUND

Aortic Regurgitation (AR) is due to primary abnormalities of the aortic valve, peri-valvular apparatus and/or the aortic root and the ascending aorta. Whereas the etiology and mechanisms of AR are relatively well described in Europe and North America, little information exists about their spectrum and frequency in sub-Saharan and South Africa. Understanding the precise mechanisms of AR informs surgical planning of valve and aorta repair. Reports from local studies suggest that rheumatic heart disease in the commonest cause of valvular heart disease in RSA particularly in population under 40 but whether it's the most common cause of isolated AR is not known. The aims of this study were to report the spectrum of causes of isolated aortic regurgitation and their distribution, including the main mechanisms of aortic regurgitation in our setting. The accuracy of pre-op assessment of etiology by clinical and imaging evaluation was also analyzed along with its concordance to surgical findings.

METHODS

This is a retrospective review of hospital records of patients who had aortic valve replacement (AVR) for isolated AR from Jan 2003 to June 2018 at Groote Schuur Hospital (GSH). Most patients had a presumptive etiological diagnosis determined by pre-operative echocardiography. For this study the etiology and pathological mechanism was confirmed by macroscopic examination at surgery and pathological examination of explanted valves.

RESULTS

There were 141 patient records available over the period. The mean age for the cohort was 43 years (range 29-57) with a male predominance of 63%.
Baseline co-morbid conditions of the participants included hypertension 43.3%, Human immunodeficiency virus (HIV)16.9%, and chronic kidney disease 4.3%.

The mechanistic and etiological diagnosis was available for all 141 study participants. The five predominant mechanisms were:

1- thickening/fibrosis/retraction with commissary fusion in 32.6%.
2- cusp perforation/leaflet destruction in 24.8%.
3- prolapse of the aortic leaflet cusps in 7.1%.
4- aortic root or annular dilatation in 27%.
5- Mixed mechanisms in 8.5%.

The most common diseases which caused aortic regurgitation by affecting the valve leaflets were rheumatic heart disease, infective endocarditis, degenerative valve disease and bicuspid aortic valve. Diseases that affect the root and aorta included hypertension, Marfan' syndrome, syphilitic aortitis, Takayasu's arteritis; and pyogenic aortitis.
Of the 141 patients in the study complete information on the pre-op echo, surgical macroscopic inspection and histological evaluation was available in 92. Of the 92 patients there was consistency in the pre and post of diagnosis in 93.5% (86/92). The most common discrepant diagnosis was rheumatic heart disease at histology or on surgical inspection but having been referred with a pre-operative echo diagnosis of infective endocarditis.

CONCLUSIONS

We show that AR in a South African cohort setting is a disease of young patients, the majority of which is caused by RHD. In our cohort clinical and echocardiographic assessment was able to accurately identify the mechanisms of the AR in 95.7% (135/141) the patients. This information differs from that obtained from the global north where isolated AR is usually a disease of older patients (55-70) that is caused by predominantly by degenerative valve disease and bicuspid valves, further larger studies in an African setting are warranted to validate the findings of this study as our sample size was small.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Aortic regurgitation (AR) occurs when there is a diastolic flow reversal of blood from the aorta into the left ventricle, caused by primary disease of the aortic valve cusps, or abnormalities of the surrounding valve structures such as the aortic root and ascending aorta[1-4] (Table 1). Diseases that affect the aortic valve leaflets and aortic root include congenital bicuspid aortic valve (BAV), aortic valve prolapse, bacterial or nonbacterial endocarditis and rheumatic heart disease. Those involving the aortic root alone include Marfan syndrome, annulo-aortic ectasia, aortic dissection, hypertension, and syphilis. The connective tissue diseases e.g. rheumatoid arthritis, ankylosing spondylitis and other collagen vascular diseases can also result in aortic valve regurgitation.[1, 2, 5, 6]

The abnormal backflow of blood that occurs leads to pathologic changes that are dependent on the severity of AR and rate of disease progression. The resultant volume overload can present acutely as a clinical emergency with hemodynamic instability due to a rapid rise in left ventricular (LV) end-diastolic pressure. The patients typically look unwell, hypotensive, tachycardic, pale, cyanosed and in pulmonary edema. Or more commonly as a chronic progressive disorder with exertional dyspnea, heart failure and angina.[1, 2, 7] In the more insidious presentation, chronic AR develops as a compensatory remodeling of the left ventricle with chamber dilatation and hypertrophy.[4] Eventually symptoms of heart failure develop, and the ultimate treatment is surgical valve replacement. Patients who present with mild chronic AR, are often asymptomatic with good prognosis. However, symptomatic patients who develop LV dysfunction have an annual mortality of up to 25% without surgical intervention.[8] The etiology of AR differs between acute and chronic AR. Acute AR is commonly caused by infective endocarditis (IE), aortic dissection, and trauma. Chronic AR can also be the result of both leaflet abnormalities and aortic root or ascending aorta abnormalities. Causes of chronic AR include rheumatic heart disease, myxomatous degeneration, aortitis, hypertension and BAV.[2, 9, 10]

Rheumatic heart disease (RHD)is the most prevalent form of acquired chronic valvular heart disease presenting to healthcare in low- and middle-income countries. This has been demonstrated in several studies from the global south.[11-13] A review of previous publications shows that the incidence of RHD is on a downward trend in the global north with a profound decline since the 1980s making other causes of AR relatively more important in the developed world.[13-15] A few reasons have been postulated to explain the decrease such as improvement in living standards with better access to medical care, wider use of antibiotics as well as natural changes in the streptococcal strains. The reason for its high prevalence in the low- and middle-income nations is due to its association with poverty, inequality, and overcrowding.[14] It is associated with the presence of congestive heart failure, atrial fibrillation, infective endocarditis and left ventricular dysfunction on presentation as evidenced by the REMEDY registry.[12]

Infective endocarditis is another common cause of AR occurring predominantly in patients with previously damaged valves, RHD or congenital bicuspid aortic valves. In a study on native-valve endocarditis, 12% of the total cases were BAV, highlighting the increased risk of infection associated with this lesion.[16, 17] In another study series on isolated AR conducted in the global north, BAV as a predisposing factor accounted for approximately 33% of the total native valve endocarditis.[18] It is increasing in prevalence in the global north on account of an ageing population, increasing levels of injectable opioid drug abuse and high numbers of patients with intracardiac devices. The irrational use of antibiotics with consequent increase in antibiotic resistance has led to a shift from Streptococcus to more virulent organisms such as Staphylococcus and Enterococcus as the principal organisms causing infective endocarditis.[14, 15, 19] In two retrospective studies performed on

surgically excised valves, IE was the commonest valvular cause with majority of the cases being those of healed IE with perforated cusps and indented margins.[6, 20] Previous studies have also documented that RHD was the underlying disease in a significant proportion of IE cases.[11, 21]

Bicuspid aortic valve disease is the most common adult congenital heart defect and reported to have a prevalence of 1-2% in the general population and a strong male predilection. It is associated with progressive aortic dilatation, aneurysm, acute aortic dissection/rupture and coarctation of the aorta.[22] The occurrence of isolated AR in patients with BAV (with or without associated dilatation of the aorta) severe enough to warrant AVR in the absence of infective endocarditis or aortic dissection is relatively uncommon. Endocarditis complicating BAV is one of the commonest reasons for severe AR in BAV. This has been widely noted in previous published reports.[3, 16, 23, 24] In many cases of BAV-related endocarditis, this complication is usually the first indication for the presence of structural valve disease. Echocardiographic assessment of the bicuspid aortic valve leaflets may signal whether AR is caused by fibrosis and retraction of the commissural margins, cusp prolapse, aortic dilatation or destruction from endocarditis.[17, 25] Information on calcific aortic valve disease is limited in many low-income countries. It is generally associated with risk factors for atherosclerotic disease such as smoking, hypertension and high body mass index.[19]

Aortic root dilatation is another common cause of AR increasing in prevalence as noted in several previous studies on isolated AR.[20, 26, 27] The most common risk factors for aortic dilatation are a history of hypertension, male sex, old age, atherosclerosis, and significant valve disease. Most cases are idiopathic and due to annulo-aortic ectasia but may also be associated with a wide spectrum of other conditions like the inherited aortopathies, aortic dissection and aortitis.[6, 18, 28, 29] The increased stroke volume from the AR results in tension on the diseased aorta and subsequent dilatation. Cumulative clinical evidence favors an association between AR and hypertension through several pathophysiological mechanisms.[30-32] It increases afterload and thus may accelerate progression of AR and causing aortic root dilatation. Hypertension and aging may have been possible contributors to AR in two similar North American studies based on pathological examination of explanted aortas conducted 20 years apart. In these studies, there was a high frequency of idiopathic causes of AR and the resected aortas were histologically normal in patients with dilated aortas. Hypertension and old age were the prevalent comorbidities noted by the investigators.[18, 28] Patients with aortic root dilatation are at increased risk of aortic dissection or rupture which further worsens the AR.

Aortitis is rarely complicated by AR and can be an incidental finding at histological examination. Its epidemiology is poorly studied. It can present as noninfectious or infectious and leads to aortic wall inflammation. Takayasu's arteritis and Giant Cell Arteritis are the commonest causes of noninfectious aortitis. Other inflammatory disorders like Behcet's disease, rheumatoid arthritis, seronegative spondyloarthropathies and systemic lupus erythematosus may cause aortitis. Before the antibiotic era, syphilitic aortitis was the commonest cause of infectious aortitis but has now been superseded by pyogenic aortitis. Staphylococcus, enterococcus as well as streptococcus pneumonia being the most common microorganisms causing infectious aortitis[33]. Cases of cardiovascular syphilis are however still present in developing countries with a prevalence of 6.9% in an autopsy series.[34-36] Nevertheless it can cause life-threatening symptoms and should therefore be diagnosed at an early stage. Inflammation of the aorta can cause AR, aortic dilatation, and dissection and aortic rupture. The clinical presentation is usually nonspecific, and can range from pain, fever, weight loss, rash, arthralgia, and delirium which may mimic other diseases. The diagnosis of syphilis is based on serological and or histological confirmation.[37]

The etiology and mechanisms of AR can be determined pre-operatively via echocardiography and other imaging tools or following pathological examination and surgical inspection. Echocardiography allows visualization of the aortic valve leaflets to detect structural changes, such as commissural

fusion, fibrosis, leaflet destruction, vegetations, flail leaflets and aortic abnormalities like sinus/sino-tubular dilatation and dissection flaps.[38] Following up progression of the AR with consecutive echocardiographic measurements of the LV dimensions identifies patients with severe AR who may need surgery since enlargement of the LV often precedes symptoms or decline in the ejection fraction, both of which are indications for surgery.[2, 5, 39] The precision of transesophageal echocardiography (TEE) in providing a correct evaluation of the etiology and mechanisms of AR was demonstrated in a European study and they found a strong concordance between TEE and the findings on surgical macro inspection. Inconsistencies in the Belgian study between TEE and surgical inspection were noted in a small number of patients identified as aortic root dilatation by echocardiography but noted to be fenestrations on surgical inspection.[40]

Table 1a provides various etiologies of AR and their site.[1-4]

Cusp Disease	**Aortic Disease**
Rheumatic Heart Disease	Syphilis
Infective Endocarditis	Systemic hypertension
Bicuspid Aortic Valve	Marfan's syndrome
Trauma	Aortic dissection
Prolapsing/ Redundant	Collagen vascular disorders
Myxomatous degeneration	Annulo-aortic ectasia
Ventricular Septal defect	Giant cell aortitis
Radiation	Trauma

Mechanisms of aortic regurgitation include cusp abnormalities such as prolapse, fibrous thickening, commissural fusion and retraction by scars, perforation, or indentation of the cusp and calcification.[6, 19, 28, 38] Rheumatic heart disease is typically characterized by diffuse fibrosis of the valve cusps; retraction; calcification and commissural fusion of the cusps. Of which similar mechanisms were demonstrated using echocardiography in previous studies.[6, 11, 41] Infective endocarditis mechanisms causing AR by destruction of the valve leaflets resulting in indentation or perforation or by prolapse of the cusp into the left ventricular outflow tract because of interposition by vegetations.[6, 19] Degenerative calcific aortic valve disease is identified by focal cusp fibrosis with thickening and accumulation of calcium in the sinuses of Valsalva. These changes lead to retraction and shortening of the cusps resulting in incomplete valve closure and subsequent regurgitation. It is distinguished apart from rheumatic heart disease by the absence of commissural fusion.[6, 11, 41]

Those involving the aorta include distortion and dilatation of the annulus or weakening of the aortic wall with focal aneurysms with failure of apposition of the leaflets. In Marfan's syndrome for example there is thinning of the aortic walls because of cystic medial degeneration of the sinus portion of the aorta. Progressive aortic root dilatation in Marfan's syndrome is also thought to be related to mutation of the fibrillin-1 gene and resultant dysregulation of transforming growth factor-beta.[42] Unlike pathologic studies on syphilis which involve the tubular portion of the aorta causing thickening of the wall disrupting the media resulting in aortic dilatation and concomitant secondary valvulitis. [36]

Multiple mechanisms of AR appear to be more common in patients with bicuspid aortic valves as evidenced by previous literature on BAV pathology.[28, 43] A recent Mayo study in which BAV accounted for 44% of the surgical referrals revealed simultaneous dilatation and prolapse in most of the explanted BAV.[28] Bicuspid aortic valves are associated with a primary aortopathy that results in weakening of the aortic wall leading to aneurysm formation and dissection. AR in patients with BAV

can result from prolapse of the larger sized leaflet or from aortic dilatation.[44] BAV leaflets can also undergo accelerated calcific degeneration because of abnormal hemodynamic factors. Calcium deposition and fibrosis of the BAV increases with age.[6, 17] Understanding the precise mechanisms of AR informs surgical planning of valve and aorta repair.

The mainstay of surgical treatment is aortic valve replacement. Aortic valve replacement is offered to patients based on the combination of the echocardiographic parameters and the patient's symptoms. Symptom onset which can be in the form of dyspnea on exertion or heart failure are indications for surgery. Surgery is also indicated in asymptomatic patients with reduction in left ventricular function with LVEF<50%, asymptomatic patients with chronic severe AR with impaired systolic function and severe LV dilatation: end-diastolic dimension>70mm or ESD>50mm and in patients who have aortic root disease.[30, 45] In acute AR, surgical intervention is urgent as LV dilatation and other compensatory mechanisms do not develop rapidly enough to avoid hemodynamic impairment.[30] However, if it is due to infective endocarditis the heart failure is stabilized first by medical treatment and a course of antibiotics before planning elective valve replacement.[7, 9]

There is an increasing incidence of AR with age, with a peak incidence in the fourth to sixth decades of life. AR is more common in males more than females.[30] The prevalence of AR was estimated at 4.9% in the general population in a prospective North American study and was noted to vary by geography, age, and other variables.[46]However, the true prevalence in resource poor developing countries is challenging due to limited access to echocardiography. The etiology of AR is relatively well described in Europe and North America. In a recent Mayo study and a prior one 15 years earlier BAV accounted for the most surgical referrals for AVR for AR.[18, 28] Both had a high prevalence of an ageing population. Whereas little information exists about the spectrum and relative frequency of the diseases and abnormalities causing isolated AR in a cohort of patients referred for surgery at a tertiary hospital in the Western Cape. Reports suggest that rheumatic heart disease remains the commonest cause of valvular heart disease Africa and South Africa particularly in the population under 40 years of age.[11, 13] It remains a prominent cardiac cause for presentation and admission to hospitals in the global south. It is associated with the presence of congestive heart failure, atrial fibrillation, infective endocarditis and left ventricular dysfunction on presentation. Whether it is the most common cause of isolated aortic regurgitation is not known.In sub-Saharan Africa and South Africa, RHD still accounts for a significant proportion of patients requiring isolated aortic valve replacement for AR with a bulk of descriptive data on patterns, presentation, and complications.[11, 47] Retrospective registries conducted in Western and Central Africa show a prevalence of 32.1% of isolated AR due to RHD and echocardiographic diagnosis based on morphological changes such as the presence of thickened leaflets, commissural fusion, leaflet retraction and prolapse were noted similar to previous reviews on rheumatic AR .[11, 48, 49] Infective endocarditis in sub-Saharan Africa and SA is strongly associated with RHD and remains a disease of young people with frequent involvement of the aortic valve causing severe AR. Typical findings include valve destruction with peri-annular extension with abscess or fistula formation.[21, 50, 51] However, with the substantial increase in life expectancy in sub-Saharan Africa in the last two decades and more of the population living past the 7th decade, it stands to reason that the etiology of aortic valve disease may also be shifting as has been documented in the global north. Bicuspid aortic valve is relatively rare in Africans and is a strong risk factor for chronic severe AR and aortic wall abnormalities, but scanty information is known about this cause of AR in our setting with few case reports.[52] In a recent series from Cameroon, hypertension as a cause of AR had a prevalence of 17.4% which is lower than that reported in the global north reviews. However like previous studies, the mechanism for AR because of hypertension and aging is a degenerative process leading to aortic root enlargement.[53, 54][50] Less is understood in characterizing the full spectrum of AR in current practice in sub-Saharan Africa and South Africa. Reports on isolated AR in sub-Saharan Africa and SA have used echocardiography to

assess the mechanisms of AR and have lacked pathological description of the valve morphology and AR etiology.[11, 52] There also has been no reports in our setting that have assessed the diagnostic value of pre-operative TEE in defining the mechanisms of AR as determined by surgical inspection. We would like to bring to the forefront, the spectrum and pathology in an urban African setting where there is barely any prior literature recording and investigate if TEE provides a highly accurate anatomic assessment of aortic valve pathology.

Given the lack of any recent information on the epidemiology of isolated aortic regurgitation in South Africa, and its spectrum of causes and their related mechanisms, we set out to use the available data at our tertiary hospital, where people with symptomatic AR are referred for evaluation and treatment. This data includes, several large patient related data resources, that include a surgical data base, patient hospital files, pathology records, imaging (MRI and echocardiography).

The aims of this study were:
1-to describe the spectrum of causes of isolated AR in a cohort of patients referred to surgery in our local setting,
2- to describe the proportional contribution (relative frequency) of each cause.
3- to determine the accuracy of the pre-operative assessment of the mechanisms and etiology of isolated AR as identified by surgical inspection using clinical scenario and echocardiography.

The objectives

1- To determine the causes of AR in the last 151 patients who have undergone aortic valve surgery at Groote Schuur Hospital, Cape Town.
2- To describe the demographic and clinical profile of patients undergoing isolated AR.
3- To report the comorbid conditions of patients undergoing isolated AVR
4- To outline the clinical presentation regarding acute vs chronic, pulmonary edema, blood pressure, duration of symptoms, proportion with dilated ventricles and proportion with LVEF<45%.

We chose January 2003, and June 2018 as our period of interest as the we anticipated that the records during that period were available and relatively complete.

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CHAPTER 2

Publication Ready Manuscript

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SPECTRUM OF CAUSES OF ISOLATED AORTIC REGURGITATION at a South African Tertiary Care Institution

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Background and Rationale

Aortic regurgitation (AR) occurs when there is diastolic flow reversal of blood from the aorta into the left ventricle, caused by primary disease of the aortic valve cusps, or abnormalities of the surrounding valve structures such as the aortic root and ascending aorta[1, 2] (Table 1b).
The resultant volume load can present acutely as a clinical emergency with hemodynamic instability due to a rapid rise in left ventricular (LV) end-diastolic pressure and pulmonary edema, or more commonly as a chronic progressive disorder with exertional dyspnea, heart failure and angina[1, 2, 7].
In this more insidious presentation, chronic AR develops as compensatory remodeling of the left ventricle with chamber dilatation and hypertrophy with resultant heart failure.[1, 4] Patients who present with mild chronic AR, are often asymptomatic with a good prognosis. However, symptomatic patients who develop LV dysfunction have an annual mortality of up to 25 %[8] without surgical intervention. The mainstay of surgical treatment is aortic valve replacement (AVR), and the indications are dependent on both the severity of the AR and its complications such as heart failure symptoms, ventricular remodeling and a reduction in left ventricular function[2-4].

Whereas the prevalence of AR was estimated at 4.9% in the general population in a prospective epidemiological North American study,[46] and the etiology of AR is relatively well described in Europe and North America[3, 18], little information exists about the spectrum and frequency of causes in a South African context. To address this, we set out to describe the spectrum and relative frequency of the main mechanisms and causes of isolated AR in a cohort of patients referred for surgery at a tertiary hospital in the Western Cape. A second aim of the study was to determine the accuracy of the pre-operative assessment of the mechanisms and etiology of isolated AR using clinical scenario and echocardiographic interpretation.

Table 1b provides a comprehensive list of diseases and their mechanism.[3, 18, 28]

	Leaflet Abnormality/Disease	Mechanism
Acute	Infective Endocarditis	Cusp destruction (perforation/indentation) Vegetations
	Trauma	Damage to cusp or leaflet
	Prostheses dysfunction	
Chronic	Degenerative	Aortic valve sclerosis and calcification
	Congenital valvular disease (bicuspid)	Dilated aorta/ cusp prolapse
	Other congenital disease (subaortic membrane; VSD)	Prolapse of cusp
	Rheumatic heart disease	Fibrous thickening Retraction of one or more cusps & commissural fusion

	Aortic/ ascending aorta abnormality	Mechanism
Acute	Aortic Dissection	Cusp attachment to aortic wall torn away
Chronic	Chronic Hypertension	Dilated ascending aorta
	Marfan disease	Dilated aorta/weakened wall with focal aneurysm Redundant/floppy cusps
	Annulo-aortic ectasia	
	Syphilitic aortitis	
	Other systemic inflammatory disorders (Takayasu; Giant cell aortitis, ankylosing spondylitis)	
	Atherosclerotic aneurysm	

METHODS

This study is a retrospective review of hospital records of consecutive adult patients (>18years) who underwent an AVR for isolated AR from Jan 2003 to June 2018 at Groote Schuur Hospital (GSH). The study was approved by the University of Cape Town Human Research Ethics Committee.(HREC No:329/2019). The authors had full access to the data and take full responsibility for its integrity.

Patients were identified from the Cardiothoracic surgery database (Registry Code: R045/2016). Hospital folder review of clinical records included echocardiogram, angiogram, and cardiac MRI reports where necessary. Clinical data including demographic, cardiac symptoms, comorbid conditions was retrieved from institutional health record system. Specific comorbid conditions of interest that were recorded because of their causal or statistical association with AR included hypertension, human immunodeficiency virus infection (HIV), syphilis, and chronic kidney disease. Histological data on the excised valves, aortic wall or roots was obtained from the online laboratory system (NHLS Trakcare). Study data were collected and managed using REDCap electronic data capture tools hosted at Yale University.

In addition to those with isolated severe AR, patients with severe concomitant aortic root disease without pathological cusp disease were also included in the cohort. Exclusion criteria included an aortic valve peak gradient (AOVPG)≥35mmHg, mean gradient ≥ 20mmHg, an aortic valve area<2.0cm^2, concomitant mitral valve replacement, mitral stenosis with mean gradient >5mmHg or MVA <2.0 and previous surgery for structural heart disease,

Table 2 Pre-operative and intraoperative variables collected and their source.
a. Hospital Records, b. Echocardiographic Reports, c. Surgical Database, d. NHLS Database

Variable (Source)	**Variable** (Source)
Demographics [a]	***Clinical Presentation*** [a]
Sex	NYHA
Age	Heart Failure
Smoking	Pulmonary Edema
Substance use	Clinical Signs of AR
Comorbidities	Dyspnea
Hypertension	Arrhythmia
Diabetes Mellitus	Chest pain
Dyslipidemia	Systolic Hypertension
Coronary Artery Disease	Syncope
Chronic Kidney Disease	Stroke
COPD	
Syphilis	
HIV status	
Echocardiography [b]	***Intraoperative Findings*** [c]
Ejection fraction	Surgical macro-inspection report
LVIDD	Type of surgical intervention
LVISD	
Aortic Cusp Morphology	***Histological data*** [d]
Presence of mild/functional MR	Pathology of explanted valve
Presence of mild AS	Microbiology
AOVPG<35mmHg	
Grading of AR	
LVH	
Aortic Root Morphology	

The preoperative etiology and pathological mechanisms were noted from the clinical notes and echocardiographic findings. All the echocardiography reports were either written or reviewed by senior clinicians in the cardiology department prior to surgery and included detailed assessment of AR severity, etiology, and mechanisms. The clinical preoperative etiological diagnosis would then be formulated by the cardiologist based on integration of the clinical and echocardiographic data. The AR was assumed to be chronic AR if there was a history of progressive heart failure symptoms, with evidence of left ventricular remodeling and/or impaired LV systolic function. The Intra operative notes were used to define the gross pathology at surgery. These included the presence of commissural fusion, leaflet thickening and/calcification, vegetations, valve disruption, congenital malformation and translucent or gelatinous leaflets and the excised aortic roots for aneurysms to determine the final causal abnormality/disease and mechanisms. Post operative records were reviewed for pathological examination and histology reports where available. However, the surgeon's description of the macroscopic appearance was mainly used in identifying the etiology and pathological mechanisms for aortic valve dysfunction.

DATA ANALYSIS

All the questionnaire data was exported from the online data management software Redcap into Stata v14.2 (Stata Corp, College Station, TX, USA) for analysis. Categorical data was presented as proportions and comparisons were made using chi square ($\chi 2$) or fisher's exact test with $p < 0.05$ considered significant. Continuous variables were reported as mean ±standard deviation or median (interquartile range) depending on data normality and to test the association in the different etiology groups the Anova test for variance with Bonferroni correction or the Kruskal Wallis test was used. Again, a p-value of less than or equal to 0.05 was used to denote statistical significance.

RESULTS

Over the period under review, 1642 patients underwent Aortic Valve replacement with or without aortic root or ascending aorta surgery. There were 141 patients who met the inclusion/exclusion criteria and whose full patient records were available. The mean age for the cohort was 43 years (29-57). There was a male predominance of 63.1% (89/141.

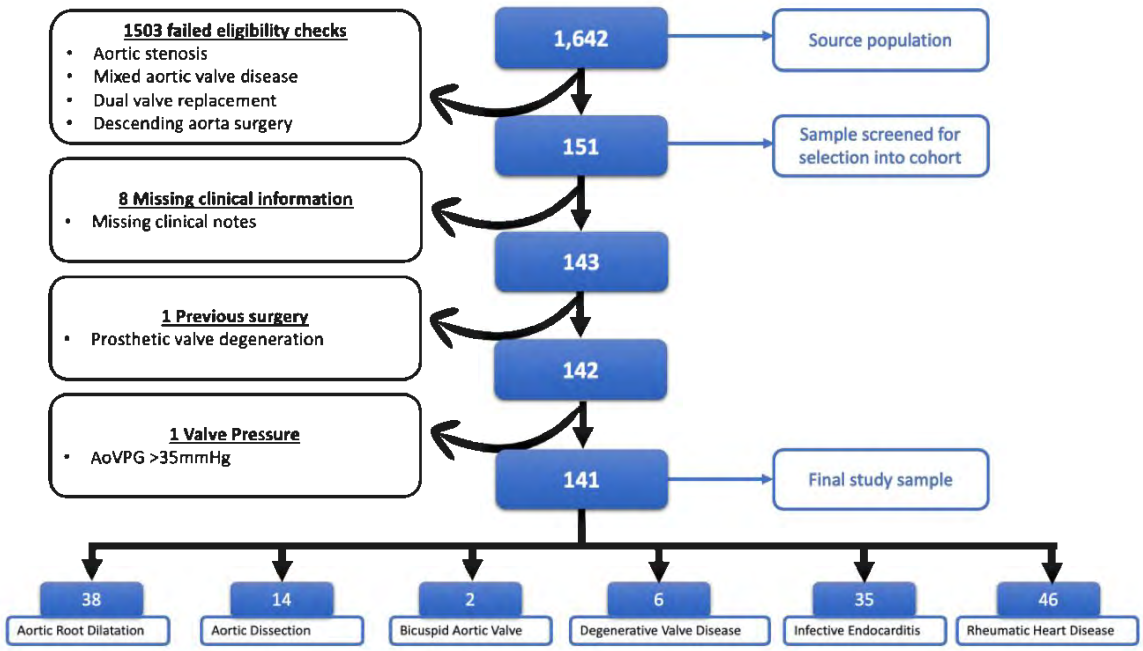

Figure 1: Consort diagram detailing the study cohort.

The full list of baseline co-morbid conditions is presented in table 3. 43.3% (61/141) of the cohort had hypertension, HIV was present in 14.9% (21/141) and 4.3% (6/141) had CKD. Incidental coronary artery disease (CAD) requiring revascularization at the time of AVR was noted in 4.3% (6/141). 92.2% (130/141) of the participants had tricuspid aortic valves while the remainder were bicuspid.

Most participants 70.2% (99/141) presented with chronic AR and heart failure while 29.8% (42/141) had acute AR. In both acute and chronic AR TEE was the primary imaging modality for diagnosis. Chronic AR was caused by several diseases affecting either the leaflets or aorta (i.e RHD,

degenerative valve disease for the former and aortic root dilatation as the latter and in a few instances both components e.g bicuspid aortic valve disease. Rheumatic heart disease was the prevalent cause of chronic AR and was identified in 32.6% (46/141). Thickening, cusp calcification. and restriction of leaflet motion was noted at echocardiography. Degenerative valve disease in 4.2% (6/141) and BAV disease were the other common causes of chronic isolated AR. They were prevalent in older age group cohort. Prolapse or flail leaflets were seen at TEE in both patient groups. Aortic root dilatation was the second commonest cause of chronic AR making up 27% (38/141). The spectrum of causes of aortic root abnormalities in these 38 patients included hypertension in 36.8% (14/38), Marfan's in 23.7% (9/38), syphilitic aortitis in 18.4% (7/38), Takayasu's in 5.3% (2/38), pyogenic aortitis in 2.6% (1/38) and of unknown etiology in the remaining 13.2% (5/38).

Patients with acute AR presented with fever,tachycardia, shortness of breath, peripheral signs of hypoperfusion or with acute chest pain. Pulmonary congestion was less pronounced compared to chronic severe AR. Supportive findings of severe chronic AR on TEE noted by cardiologists were the presence of flail leaflets, wide coaptation gap and dilated LV. Acute AR was noted in 42 patients. The most common cause of acute AR was acute infective endocarditis in 19.9% (28/141). Preoperative echocardiography demonstrated vegetations and leaflet destruction in all 28 patients. The second commonest cause of acute AR was acute aortic dissection in 8.5% (12/141), with preoperative echo findings of dissection flap involving the ascending aorta with enlargement of the aortic root and normal cusps. Acute aortitis was noted in 1.4% (2/141) and aneurysm of the ascending aorta or root was seen at TEE in these patients.

The mechanistic and etiological diagnosis was available for all 141 study participants. Five predominant categories of mechanisms were found, three of which involved the valve leaflets. The main mechanisms were:
- thickening, fibrosis, restricted opening, and retraction of the leaflets with commissary fusion. This was noted in 32.6% (46/141) of participants.
- cusp perforation and/or leaflet destruction. This was noted in 24.8% (35/141).
- prolapse/flail or thinning the aortic leaflet cusps in 7.1% (10/141) of participants.
- primary abnormalities of the aortic root or annular dilatation with normal cusps was seen in 27% (38/141) as the mechanism.
- Mixed mechanisms involving abnormalities of both the leaflets and either the aortic root or wall were noticed in 8.5% (12/141).

In in 65.2% (92/141) of participants, the pre-op echocardiograms, surgical macroscopic inspection, and histological evaluation were all available allowing a comparison of the pre-op diagnosis with intra-operative and post operative findings. (table 3) Of these there was consistency in the diagnosis in all 3 parameters in 93.5% (86/92). Aortic dilatation 34.8% (32/92) had the most consistency among the chronic AR causes and infective endocarditis 23.9% (22/92) had the most consistency among the acute AR causes. RHD was confirmed in only 18.5% (17/92) despite being the most prevalent overall cause of AR and chronic AR because not all rheumatic looking valves were sent for histology.

The sensitivity of pre-operative clinical and echocardiographic assessment for predicting histological diagnosis of surgical specimens was 95.9% with a positive predictive value of 93.4% and specificity of 87.5%. Discrepancy between the histological diagnosis and the pre-op echo diagnosis occurred in 6.5% (6/92). The most common discrepant diagnosis was rheumatic heart disease confirmed at histology or suspected surgical inspection but having been referred with a pre-op diagnosis of IE.

Table 3 Patients with surgical and histological data

Etiology	Primary site of abnormality	Echo findings	Pathology at surgery	Histology
RHD (n=17)	Leaflet	-thickened and nodular AoV -calcified and restricted motion	-fibrotic and thickened	-chronic rheumatic valvulitis
IE (n=22)	Leaflet	-pliable leaflets with torn commisure. - dysmorphic and perforated with vegetations -±root abscess	- destroyed AoV leaflets -vegetations	-consistent with SBE - consistent with SBE with background chronic rheumatic valvulitis -positive blood culture
Degenerative valve disease (n=3)	-leaflet	-thinned AoV cusps	-prolapse of cusp leaflets with poor coaptation	-calcified leaflets - myxomatous degeneration
Aortic Dilatation (n=32)	-aorta/root± leaflet	- dilated aortic root and ascending aorta -thin walled aorta	- ascending aortic aneurysm	- cystic medial degeneration (CMD) -atherosclerosis
Aortic dissection (n=12)	-aorta/root ± leaflet	-dilated root with dissection flap	- dilated root with dissection flap	-suggestive of dissecting aneurysm -CMD

DISCUSSION

The etiology of isolated AR is known to be complex and diverse with a long list of causes. that include congenital deformities (i.e., BAV), RHD, IE, myxomatous degeneration, HPT, Marfan's, syphilis, connective tissue disorders (e.g., ankylosing spondylitis, lupus, rheumatoid arthritis, and other collagen vascular diseases) and aortic dissection. Its etiology and mechanisms can be ascertained pre-operatively via clinical scenario and signs; echocardiography and other imaging tools or post operatively following pathological examination and surgical inspection of the explanted valve apparatus.[3, 18] Mechanisms of aortic regurgitation include cusp prolapse, cusp retraction or restriction by scars and perforation of the cusp or distortion and dilation of the annulus with normal cusps. These mechanisms can be defined pre-operatively by echocardiography to describe leaflet motion abnormalities using the Carpentier classification or post operatively using surgical inspection or histology.[19, 28] Understanding the precise mechanisms of AR informs surgical planning of valve replacement or repair. There are few sources of data from sub-Saharan Africa which describe the predominant causes of isolated aortic regurgitation.

Rheumatic heart disease remains the most prevalent form of chronic valvular heart disease primarily encountered in middle- and low-income countries and certain indigenous groups or tribes in high income countries due to its association with poverty, inequality, overcrowding, lack of healthcare facilities including access to treatment.[14, 15] Reports from local studies suggest that RHD remains the commonest cause of valvular heart disease in South Africa and the rest of the global south particularly in the population under 40 years.[11, 13, 21] It remains a prominent cardiac cause for presentation and admission to hospital.[13, 14, 55]
In the present study, RHD was the commonest cause of isolated AR with a prevalence of 32.6% (46/141). The finding of RHD was not unexpected given the geography and demography of South Africa. We had a male predominance 19.1% (27/141) of patients with RHD which was inconsistent with the literature which states RHD tends to be more common in females. The similarities between the REMEDY registry and the patients in our study with RHD were the presence of congestive heart failure 78.3% (36/46); infective endocarditis 26.1% (12/46); arrhythmias mainly atrial fibrillation and left ventricular dysfunction in our cohort. RHD of the aortic valve (AoV) in our study was characterized by fibrous thickening, retraction, calcification of one or more cusps with commissural fusion being the macroscopic hallmark. These findings were in keeping with RHD from previous isolated AR studies.[3, 6, 11, 20]

Infective endocarditis was the second most prevalent valvular cause of AR in our study with a prevalence of 24.8% (35/141) Our study was consistent with more recently published literature with a predominance of Staphylococcal aureus as the leading cause of IE. It was characterized by cusp perforation and destruction of valve tissue as a result of the inflammatory process and associated with interference of proper leaflet coaptation by vegetations.[6, 9, 28] In a similar study of surgically excised valves, IE was the commonest cause with majority of cases being healed IE with perforated valve cusps or indented margins.[6]Previous studies documented that RHD was the underlying heart disease in a significant proportion of IE cases.[11, 13]In our study cohort we demonstrated similar findings at histology or echocardiography with 8.5% (12/141) showing endocarditis on the background of chronic rheumatic valvulitis. Unlike in the global north where IE is increasing in prevalence because of an ageing population, we had a younger population with an average age of 41.5 with the only similarity being the association with increasing levels of opioid drug usage with 20% (7/35) actively using substances.[14, 15]

Degenerative valve disease 4.3% (6/141) and bicuspid aortic valves (BAV), 1.4% (2/141) were not as common as in high income countries in our cohort as causes of AR even though we had 7.8% (11/141) of the patients identified with bicuspid aortic valve morphology at pre-op echo. In studies from the global north BAV was the commonest cause of surgical referrals for isolated AR in adults.[18, 28, 56] In these studies there was a high prevalence of BAV in ageing populations. BAV is most frequently associated with dilation of the proximal ascending aorta secondary to abnormalities of the aortic media that results in weakening of the aortic wall leading to aneurysm formation and dissection resulting in AR. Pure AR in BAV disease patients can result from redundant and prolapsing cusps alone.[22, 56] Furthermore BAV leaflets can undergo accelerated calcific degeneration because of abnormal hemodynamic factors. Our study cohort had similar findings consistent with the literature. The number of patients in our series with both aortic root dilatation and BAV is small 2.1% (3/141) that no firm conclusion can be drawn whether there is simply a chance association or whether there is a genetic link between BAV and aortic medial degeneration. Many of our patients with BAV had RHD as the etiology of AR and were associated with restricted opening of the AoV or thickened, calcified, and retracted cusps at pre-op echo.

Aortic root dilatation was the second most common cause of isolated AR in our cohort, 27% (38/141). Our finding that aortic root dilation was a common cause of AR agrees with the increasing incidence noted in previous studies on pure AR.[3, 18, 20, 26] This change in prevalence of the disease is undoubtedly contributed to by the older population with degenerative disease , including aortic root dilation becoming increasingly common. Out of the 38 patients with abnormal dilatation of the aorta, the spectrum of causes included hypertension (14/38), Marfan's (9/38), syphilitic aortitis (7/38), Takayasu's (2/38), pyogenic aortitis (1/38) and idiopathic in the remainder. Even though hypertension was a prevalent comorbidity 40,4% (57/141); we did not declare it as the AR etiology for patients without an identifiable cause as the association between HPT and AR is inconclusive.[31, 53] Unlike in previous studies[18, 28] in which there was a high frequency of idiopathic causes of AR and the resected aortas were histologically normal in patients with dilated aortas. HPT and aging may have been possible contributors to the AR in these patients as they were prevalent comorbidities. Cumulative clinical evidence favors an association between AR and HPT through several pathophysiological mechanisms. It increases afterload per se and thus may accelerate progression of AR and it also causes aortic root dilation. Hypertension was considered causal in patients with dilated root and/or annulus if there was a history of moderate to severe hypertension and no alternative explanation was found.

Marfan syndrome and its forme frustes with dissecting aneurysms, aortic root dilatation as the main mechanisms of AR was found in 9.9% (14/141) of our cohort. The patients with Marfan syndrome were diagnosed based upon a positive family history or the presence of Marfanoid features (high arched palate, joint laxity and hyperextension of the wrists, arachynodactyly and dociocephalic head). The aortopathy in Marfan syndrome is thought to be related to mutation of the fibrillin-1 gene and resultant dysregulation of transforming growth factor – beta.This leads to progressive aortic root dilatation and development of AR beyond the increased risk of aortic dissection. Available histology reports from our study described atherosclerosis, myxoid degeneration with increased mucopolysaccharides and cystic medial degeneration consistent with previous studies.[26, 27, 42]

Aortic Regurgitation due to Syphilitic Aortis was found in 5% (7/141), a prevalence that was in line with that described in literature from the global north. The steady decline in recent decades owing to early recognition of the disease and widespread use of penicillin [36, 37] Syphilitic aortitis is now a relatively rare type of cardiovascular syphilis especially in the antibiotic era. However, an increase in sexual promiscuity and drug abuse has led to a re-emergence of syphilis worldwide and may mean that the delayed cardiovascular complications of late syphilis will be seen with increasing frequency.

Like studies in the global north[34, 36, 37] the predominant cardiovascular complications of syphilis in our present study involved the aorta leading to formation of aneurysms and aortic regurgitation, both requiring surgical treatment. The mechanism of the AR in syphilitic aneurysm is because of concomitant secondary valvulitis and aortic dilatation. The diagnosis of syphilis was based on serological and or histological confirmation. Characteristic gross morphological features involving the ascending aorta such as thickening of the aortic wall with the typical "tree bark" appearance of the intima was a constant feature also noted at histology in our present study which was in keeping with similar studies on syphilitic aortitis.[34, 36]

Aortic dissection AR in 9.9% (14/141) of out surgical cohort. Population-based studies from elsewhere suggest that it has an incidence of 3 per 100 000 people per year and a registry on acute aortic dissection reported a mean age of 63 years with a male predominance.[57-59] The mean age for dissection in our study was lower at 46 years. Marfan's syndrome, was noted in 28.6% (4/14) of the patients with dissection related AR. Other common predisposing factors for dissection were HPT, atherosclerosis, and presence of aortic root dilation.

Aortic regurgitation mechanisms were described in all patients. These included a defect of the aortic cusps characterized by cusp fibrosis, thickening and retraction 32.6% (46/141), infectious with cusp perforation and tears 24.8% (35/141) and cusp prolapse 5% (7/141) seen in patients with degenerative valvular disease and BAV. The mechanisms in patients with aortic root pathology were functional aortic dilatation 26.2% (37/141) and mixed mechanisms 11.3% (16/141) Mechanisms were determined by echocardiography[3, 38] or surgical macro-inspection of the explanted valve or aortic root. Multiple mechanisms of AR appeared to be more common in patients with BAV relative to those with tri-leaflet valves.[28] The most common mixed mechanism combination was aortic root dilatation with prolapse. This was consistent with recent similar study which explained that mechanisms of AR are complex and that BAV-AR patients exhibit a high prevalence of mixed mechanisms involving cusp prolapse and aortic annulus/Sino-tubular junction dilation while TAV patients exhibit more isolated AR mechanisms .[28] In this study of the 141 patients with documented mechanisms; 68.8% (97/141) had mechanical prostheses; 19.1% (27/141) bio prosthesis and 12.1% (17/141) had valve-sparing root replacement. The choice of valves among other factors depends on the patient's age and well-being.

Complete information on pre-operative echo, surgical macroscopic inspection and histological evaluation was available in 65.7% (92/141) with histology not available as some of the explanted valve or root wall specimens were not sent to the laboratory at the surgeon's discretion. Consistency in diagnosis in all three parameters was seen in 93.5% (86/92). This finding was compatible with a previous report demonstrating the precision of transesophageal echocardiography (TEE) in providing a correct evaluation of the etiology and mechanisms of AR which found a strong concordance between TEE and the findings on surgical macro inspection of 93%. Inconsistencies in the Belgian study between TEE and surgical inspection were noted in a small number of patients identified as aortic root dilatation by echocardiography but noted to be fenestrations on surgical inspection.[40] In our series however RHD was the most common discrepant diagnosis confirmed in the 6.5% (6/92) on surgical inspection, for patients referred with a pre-op echo diagnosis of IE. IE was suspected pre-op based on presence of clinical signs of fever, embolic phenomenon and suspicious mobile lesions mistaken for vegetations on echocardiography, likely nodules from rheumatic carditis. Histology in these patients was consistent with acute rheumatic valvulitis.

LIMITATIONS

The relatively small size of our sample could have confounded our results. Rheumatic valves and degenerative valves were distinguished by surgeons and pathologists based on macroscopic appearance of the explanted valve and because of this there exists a possibility that some of the severely calcified degenerative valves might have been classified as rheumatic valves because of an apparently fused commissure. Due to the retrospective nature of our study, it is possible that some discrepancies of mechanisms between echocardiography and macroscopic findings at surgery and histology was due to incomplete recording of data. Another reason to account for this is that surgical inspection may have been difficult however due to cross clamping of the aorta resulting in internal inspection of the AoV and root being performed under non-physiologic conditions. Furthermore the surgeons were not blinded to the results of the preoperative TEE and we therefore cannot exclude the possibility that this might have somehow influenced their judgement. In addition, our study being a retrospective study depended on data being entered into a clinical database and in some of the patients not all variables were recorded which may potentially have affected the study outcome and led to statistical bias in the present study. Current valvular assessment requires an integration of echocardiographic leaflet morphology, direction of the colour jet and leaflet mechanism (Carpentier adaptation) to infer pathology for primary leaflet disorders. For aortic abnormality with secondary leaflet dysfunction a similar approach is utilized in addition to clinical signs of relevant genetic and systemic disorders in combination with the relevant laboratory tests. Thus, the preoperative prediction is based on the clinical (scenario, clinical signs, lab data) and echocardiographic integration to formulate a preoperative diagnosis. A limitation of this report maybe that preoperative echocardiography from an earlier period e.g., prior to 2012 may not have included/ reported the contemporary echocardiographic approaches in current practice. Not all the patients that had AVR had histological reports; hence our sample size in analyzing the mechanisms was limited and the etiologies of isolated AR was less comprehensive. However, despite these limitations, our present study is worthwhile in the that it showed a general trend of the etiology of isolated aortic valve disease in our setting. There is therefore a pressing need to better understand the contemporary clinical and epidemiological characteristics of AR, particularly in developing countries. Previous studies have been hospital based or retrospective in design like the present study and thus subject to selection biases. There are no contemporary prospective large-scale population-based studies specific to AR in developing countries. Reliable contemporary data demonstrating the prevalence of AR are essential requirements for researchers and clinicians to improve understanding of its underlying pathophysiology, risk factors and natural history.

CONCLUSION

We show that AR in a South African cohort setting is a disease of young patients, the majority of which is caused by RHD. It is the commonest cause of chronic AR and primary leaflet abnormality. Acute IE is the commonest cause of acute AR in our setting and RHD is the principal risk factor for IE with the majority of endocarditis cases occurring on a background of chronic rheumatic valvulitis. In our cohort clinical and echocardiographic assessment was able to accurately identify the mechanisms of the AR in 95.7% (135/141) the patients. Our data also demonstrates that pre-operative clinical and TEE assessment of functional anatomy for AR is excellent and has a strong concordance with surgical andnhistological findings. This information differs from that obtained from the global north where isolated AR is usually a disease of older patients (55-70) that is caused by predominantly by degenerative valve disease and bicuspid valves, further larger studies in an African setting are warranted to validate the findings of this study as our sample size was small. The Carpentier classification was created by surgeons in the operating theatre to help direct AV repair. Embracing this schema in the echocardiography lab for AR could help unify the way we report causes of AR and advance the way we think about AR. For the foreseeable future, preoperative TEE with morphologic and functional classification of leaflet motion with surgical anatomic inspection will likely be the primary tools for following and determining the timing and type of surgical intervention.

Disclosure Statement

The authors have declared that no competing or conflicts of interest exist.

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APPENDIX

Ethics Approval: Ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town. HREC 329/2019. Attached

CONSENT FOR PUBLICATION- to be published in the SAMJ.

AVAILABILITY OF DATA & MATERIAL

Data sets are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare they have no competing interests.

FUNDING

The study required no funding.

AUTHOR CONTRIBUTIONS

MN provided the research idea. MN and TP provided the study design. MM wrote the proposal under the guidance of MN & TP. MM performed data collection. MM, MN, TP, and WB were involved in the data analysis and interpretation.MM, MN, and TP were involved in the manuscript preparation and writing the paper. Each author contributed important intellectual content during manuscript writing and accepts accountability for the overall work.

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UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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30 May 2019

HREC REF: 329/2019

Prof Mpiko Ntsekhe
Cardiology
E17, NGSH

Dear Prof Ntsekhe

PROJECT TITLE: SPECTRUM OF CAUSES OF ISOLATED (PURE) AORTIC REGURGITATION AT A SOUTH AFRICAN PUBLIC SECTOR TERTIARY CARE INSTITUTION (MMED CANDIDATE - DR M MASIKATI)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

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

Approval is granted for one year until 30 May 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Malcolm Masikati will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human 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), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 329/2019

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	25/02/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	7/2/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown

HUMAN RESEARCH ETHICS COMMITTEE
FEB 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Comments to PI	Thank you for your Study Deviation
HREC Chair Signature	
Date:	9/2/2023

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	07/02/23		
HREC REF Number	329/2019	Current Ethics Approval was granted until	30/5/20 -30/5/21
Protocol title	SPECTRUM OF CAUSES OF ISOLATED (PURE) AORTIC REGURGITATION AT A SOUTH AFRICAN PUBLIC TERTIARY CARE HOSPITAL.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐x No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Mpiko Ntsekhe		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Department / Office Internet Mail Address	molko.ntsekhe@uct.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	☐x No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)

For invoicing purposes, please provide:

Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

2. List of documentation for approval

n/a

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐x	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Number of participants enrolled to date	n/a
Number of participants enrolled, since last HREC Progress report (continuing review)	n/a
Additional number of participants still required	n/a

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	n/a

6. Cumulative summary of participants

Total number of participants who provided consent	n/a
Number of participants determined to be ineligible (i.e. after screening)	n/a
Number of participants currently active on the study	n/a
Number of participants completed study (without events leading to withdrawal)	n/a
Number of participants withdrawn at participants' request (i.e. changed their mind)	n/a
Number of participants withdrawn by PI due to toxicity or adverse events	n/a
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	n/a
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	n/a
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	n/a

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
A descriptive study of the spectrum of causes of isolated (pure) aortic regurgitation at a South African Public Sector Tertiary Care institution with subsequent analysis of the demographic and clinical profile of the patients undergoing isolated AVR. To determine the causes of AR in 100 patients who have undergone Aortic Valve surgery at Groote Schuur Hospital. The study will review existing data information captured from buffs in the Cardiac clinic and adult cardiac database in the department of cardiothoracic surgery. To date we have reviewed and collected data of a 141 patients spread from 2003-2018. We have transposed the data captured thus far to the RedCap database and analyzed it using a research assistant. We requesting an extension so as to allow us ample time to host a database on the UCT RedCap space and complete t the current phase of write up of our manuscript.

8. Protocol violations and exceptions (tick ✓ all that apply)

☐x	No prior violations or exceptions have occurred since the original approval

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐x	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
n/a

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☐x Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	☐ x Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☐x Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☐ x No
If yes, please explain:	

12. Level of risk (tick ✓)

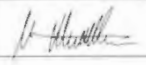
12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☐	Shown no change
If there has been a change, please explain:	
n/a	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
n/a

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☐x No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	07/02/2023

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	9/2/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf. file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

RESEARCH ETHICS COMMITTEE
09 FEB 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	8/2/23
HREC REF Number	HREC329/2019
Project Title	SPECTRUM OF CAUSES OF ISOLATED AORTIC REGURGITATION AT A SA PUBLIC TERTIARY HOSPITAL : THE GSH EXPERIENCE
Protocol number (if applicable)	
Principal Investigator	PROF M NTSEKHE
Department / Office Internal Mail Address	Department of Cardiology/ mpiko.ntsekhe@uct.ac.za

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.

Failure to submit protocol extension by MMED student from 2021 to 2022. Student was preparing for his final FCP 2 certificate exams coupled with added pressures of work in the COVID -19 pandemic and in error forgot to fill in an fhs016 form last year

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.

Ethics etiquette discussed with student.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	9/2/2023

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Please clarify your plan for research-related activities during COVID-19 lockdown

RESEARCH ETHICS COMMITTEE
09 FEB 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol information

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Principal Investigator	PROF M NTSEKHE
Department / Office Internal Mail Address	Department of Cardiology/ mpiko.ntsekhe@uct.ac.za

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3. Follow-up actions

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Ethics etiquette discussed with student.

Table 4

Demographics, comorbidities, clinical presentation, echocardiographic findings and causes of AR

Variable	Total (N=141)	Aortic Root Dilatation (N=38)	Aortic Dissection (N=14)	Bicuspid Aortic Valve (N=2)	Degenerative Valve Disease (N=6)	Infective Endocarditis (N=35)	Rheumatic Heart Disease (N=46)	p-value
Demographics								
Sex								
Male	89 (63.1)	23 (60.5)	8 (57.1)	0	4 (66.7)	27 (77.1)	27 (58.7)	0.22
Female	52 (36.9)	15 (39.5)	6 (42.9)	2 (100)	2 (33.3)	8 (22.9)	19 (41.3)	
Age (years)	43.1 (±14)	45.0 (±15)	44.9 (±13)	44.0 (±17)	43.1 (±19)	41.8 (±12)	42.0 (±15)	0.91
Medical history								
Hypertension	61 (43.3)	20 (52.6)	8 (57.1)L	1 (50.0)	2 (33.3)	8 (22.9)	22 (47.8)	0.09
Diabetes mellitus	2 (1.4)	0	0	0	1 (16.7)	1 (2.9)	0	0.17
Dyslipidaemia	13 (9.2)	5 (13.2)	2 (14.3)	1 (50.0)	1 (16.7)	2 (5.7)	2 (4.4)	0.17
Coronary Heart Disease	6 (4.3)	3 (7.9)	0	1 (50.0)	0	0	2 (4.4)	0.15
CKD	7 (5.0)	2 (5.3)	0	0	1 (16.7)	2 (5.7)	1 (2.2)	0.26
COPD	8 (5.7)	4 (10.5)	0	0	1 (16.7)	2 (5.7)	1 (2.2)	0.11
HIV positive	21 (16.9)	5 (15.6)	1 (8.3)	1 (50.0)	0	7 (21.9)	7 (17.5)	0.59
On HAART	13 (61.9)	3 (60.0)	1 (100)	1 (100)	-	3 (42.9)	5 (71.4)	0.94
CD4 count	344 (259-545)	173 (96-357)	490 (490)	239 (239)	-	340 (312-578)	442 (279-839)	0.23
Syphilis reactive	12 (8.5)	4 (10.5)	1 (7.1)	0	1 (16.7)	2 (5.7)	4 (8.7)	0.50
Clinical presentation								
NYHA								
I	15 (10.8)	5 (13.9)	2 (14.3)	0	0	4 (11.4)	4 (8.7)	***0.03***
II	45 (32.4)	14 (38.9)	5 (35.7)	2 (100)	2 (33.3)	6 (17.1)	16 (34.8)	
III	65 (46.8)	15 (41.7)	7 (50.0)	0	1 (16.7)	18 (51.4)	24 (52.2)	
IV	14 (10.1)	2 (5.6)	0	0	3 (50.0)	7 (20.0)	2 (4.4)	

Heart failure	104 (73.8)	25 (65.8)	9 (64.3)	1 (50.0)	6 (100)	27 (77.1)	36 (78.3)	0.35
Pulmonary Oedema	33 (23.4)	6 (15.8)	3 (21.4)	0	4 (66.7)	14 (40.0)	6 (13.0)	***0.01***
Aortic valve morphology								
Bicuspid	11 (7.9)	2 (5.4)	1 (7.7)	1 (50.0)	1 (16.7)	1 (2.9)	5 (10.9)	0.16
Tricuspid	128 (92.1)	35 (94.6)	12 (92.3)	1 (50.0)	5 (83.3)	34 (97.1)	41 (89.1)	
Presence of minimal/functional MR	97 (71.9)	29 (80.6)	6 (50.0)	1 (50.0)	5 (83.3)	25 (73.5)	31 (68.9)	0.35
Presence of mild AS	12 (8.8)	4 (11.1)	1 (8.3)	0	1 (16.7)	3 (8.6)	3 (6.5)	0.83
AoVPG <35 mmHg	91 (64.5)	23 (60.5)	4 (28.6)	2 (100)	4 (66.7)	25 (71.4)	33 (71.7)	***0.05***
Grading of AR								
Mild	2 (1.4)	0	1 (7.1)	0	0	0	1 (2.2)	***0.04***
Moderate	18 (12.8)	8 (21.1)	1 (7.1)	1 (50.0)	2 (33.3)	1 (2.9)	5 (10.9)	
Severe	121 (85.8)	30 (79.0)	12 (85.7)	1 (50.0)	4 (66.7)	34 (97.1)	40 (87.0)	
Surgical Intervention								
Mechanical prosthesis	88 (68.2)	21 (58.3)	6 (46.2)	1 (50.0)	2 (40.0)	25 (73.5)	33 (84.6)	***<0.001***
Bioprosthesis	24 (18.6)	5 (13.9)	1 (7.7)	1 (50.0)	2 (40.0)	9 (26.5)	6 (15.4)	
David's procedure	17 (13.2)	10 (27.8)	6 (46.2)	0	1 (20.0)	0	0	

Table 5

Pathology at surgery								
Consistency with ECHO n1=125; n2=35; n3=10; n4=2; n5=0; n6=34; n7=39	115 (92.0)	33 (94.3)	10 (100)	1 (50.0)	5 (100)	30 (88.2)	36 (92.3)	0.34
Consistency with NHLS n1=76; n2=26; n3=1; n4=0; n5=1; n6=27; n7=13	55 (72.4)	22 (84.6)	8 (88.9)	-	1 (100)	16 (59.3)	8 (61.5)	0.15

Table 6

NHLS Histology								
NHLS histology n1=107; n2=34; n3=13; n4=0; n5=4; n6=30; n7=26	84 (78.5)	31 (91.2)	10 (76.9)	-	2 (50.0)	28 (93.3)	13 (50.0)	***<0.001***
Consistent with ECHO n1=83; n2=31; n3=8; n4=0; n5=2; n6=29; n7=13	59 (71.1)	23 (74.2)	7 (87.5)	-	2 (100)	17 (58.6)	10 (76.9)	0.44
Consistent with surgical findings n1=85; n2=31; n3=10; n4=0; n5=2; n6=29; n7=13	67 (78.8)	27 (87.1)	9 (90.0)	-	2 (100)	18 (62.1)	11 (84.6)	0.15

Instructions to Authors
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Research
Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:

o **Background:** why the study is being done and how it relates to other published work.
o **Objectives:** what the study intends to find out
o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
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- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.