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Front cover:
Boy on Motorbike street art mural by Lithuanian artist Ernest Zacharevic in George Town, Penang, Malaysia.
Photo: Ruchika Meel

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Valvular heart disease and its growing impact in South Africa

Valvular heart disease (VHD) remains a major health concern worldwide,[1] but in sub-Saharan Africa, it presents a unique and complex challenge.[2-4] VHD encompasses a range of conditions affecting the heart valves, and its impact is felt across a diverse spectrum of patients, from those with congenital defects to those with acquired diseases. A combination of long-standing rheumatic heart disease (RHD), the growing burden of infective endocarditis (IE), and the increasing recognition of secondary tricuspid regurgitation (TR), and congenital heart disease (CHD) highlights the multifaceted nature of valvular disease in the South African setting. The studies featured in the current issue of the Journal highlight the need for a more personalised approach to the diagnosis, treatment, and long-term management of these conditions.

One of the most concerning aspects of VHD in South Africa is the enduring prevalence of RHD, which remains a significant cause of mortality and morbidity, particularly among younger populations.[3,4] A study conducted in KwaZulu-Natal by Naidoo, revealed a strikingly high mortality rate of 20.1%, with younger patients, especially those under 20 years of age, experiencing the worst outcomes. In these patients, heart failure often manifests as a direct result of ongoing carditis, with mitral regurgitation being the most common valve lesion. Despite progress in surgical techniques and valve replacement, managing this condition remains a significant challenge in Africa,[5] with factors such as severe disease in younger patients and the requirement for double valve replacements serving as predictors of mortality, as highlighted by Naidoo.

The high mortality rate linked to IE adds to the already significant burden of valvular disease in South Africa.[6,7,8] In a retrospective study by Poerstamper, et al. comprising a cohort of 75 patients, the 6-month mortality rate was a staggering 34.7%, with cerebral embolism being the most common complication. While the role of RHD as a risk factor for IE persists,[6,8] there is a notable shift towards Staphylococcal infections, resembling trends seen in high-income countries. Additionally, the high incidence of blood culture-negative IE presents a significant diagnostic challenge, potentially contributing to the poor outcomes observed in these patients. These findings highlight the urgent need for improved diagnostic techniques and tailored therapeutic strategies to mitigate the impact of IE on South African patients.

Secondary TR is more prevalent than primary TR, accounting for over 90% of cases in recent studies.[9] Secondary TR is another significant concern, particularly in patients undergoing surgery

for left-sided heart valve disease. Naidoo, et al. evaluated outcomes in 83 patients with mild or greater TR who underwent surgery for left-sided valvopathy found that a multidisciplinary, guideline-directed approach resulted in good short-term outcomes. Sixty seven percent of patients were free from significant TR at 6 months, and 86.7% were alive at follow-up. Despite these positive results, predictors of recurrent TR included female gender, rheumatic valvopathy, and elevated right ventricular systolic pressure. Interestingly, there were no significant differences in primary outcomes between patients who underwent tricuspid valve repair and those managed conservatively.

This study suggests that while tricuspid valve repair may not provide a clear advantage over conservative management in the short term, the management of secondary TR requires careful consideration of individual risk factors and a multidisciplinary approach. Further long-term studies are needed to determine the best treatment strategy for secondary TR, particularly in the context of RHD, which is still prevalent in South Africa.

The occurrence of clinically significant TR in patients undergoing de novo implantation of cardiovascular implantable electronic devices (CIEDs) has been reported to be as high as 39%, and it serves as a predictor for TR progression.[9] The overall prevalence of CIED-related TR remains challenging to determine, with estimates ranging from 0.5% - 5%. In a prospective study by Du Toit, et al. on lead-induced TR following permanent endocardial lead implantation for cardiac pacemakers sheds light on this facet of secondary TR. It included 30 adult patients who underwent pacemaker implantation. TR was evaluated using 2-dimensional echocardiography before implantation, at 6 weeks, and again at 9 - 16 months post-implantation. The study found that TR grade worsened in 46% of patients over the follow-up period. However, despite this progression, the TR did not become clinically significant (moderate or severe). Right ventricular (RV) function, RV dimensions, and right atrial area remained normal, and there was minimal correlation between baseline TR and the post-implantation measurements of RV function and size. This suggests that while the development of TR is a common occur-rence following pacemaker implantation, it does not typically result in clinically significant dis-ease. However, this was a small study and quantitative echocardiographic assessment of TR was not done.

Severe TR is linked to reduced survival rates.[9,10] Secondary TR, especially when associated with underlying heart conditions like left-sided valvular disease or pacemaker implantation, necessitates careful monitoring, long-term follow-up, and management by a heart team.

Severe aortic stenosis (AS) is another important aspect of valvular heart disease in South Africa, where delayed diagnosis often leads to significant myocardial damage. For patients with severe AS, early detection and intervention are critical.[11] Timely aortic valve replacement (AVR) can improve outcomes, but the underlying myocardial changes must be addressed to prevent irreversible damage. A narrative review by Rajah, et al. on the myocardial changes associated with aortic stenosis (AS) emphasised that AS is not merely a valve disorder but a condition that involves maladaptive remodelling of the myocardium. Left ventricular hypertrophy, interstitial fibrosis, and subendocardial fibrosis due to ischemia contribute to the worsening of left ventric-ular systolic dysfunction, even after AVR. The review emphasises the need to differentiate

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between afterload mismatch and true contractile dysfunction to optimise management and improve outcomes. Further research is needed to better understand the molecular mechanisms of maladaptive remodelling and to develop new therapies that could prevent or mitigate these changes before AVR.[11]

Pulmonary stenosis (PS) is predominantly a congenital condition. Isolated PS is rare, affecting about 1 in 2 000 live births globally, and constitutes approximately 8% of all CHD cases.[12] The study at hand by Raphulu, et al. conducted over 3 decades at a tertiary institution, examined patients who underwent percutaneous balloon pulmonary valvuloplasty (PBPV) between 1985 and 2019. It offers valuable insights into the long-term outcomes of PBPV in patients with moderate to severe PS. A total of 68 patients were included in this retrospective, descriptive analysis, all of whom underwent balloon valvuloplasty after meeting specific echocardiographic criteria. The results of the study are promising, with a significant reduction in the peak instantaneous gradient from 79mmHg before the procedure to 33mmHg afterward ($p<0.001$). This marked improvement in haemodynamics speaks to the efficacy of PBPV in relieving the pressure load on the RV and improving overall circulatory function.

The study reports a success rate of 88%, a testament to the high effectiveness of this intervention. However, as with any medical procedure, complications are a consideration. In this cohort, 11.7% of patients experienced complications, with 1 procedural death. While complications were rare, they highlight the importance of a well-planned approach to the procedure and vigilant management of any arising issues. When conducted by skilled practitioners, the risks associated with PBPV are minimal, and the benefits far outweigh the potential drawbacks. As the treatment of congenital PS continues to evolve, PBPV remains a critical intervention in managing valvular heart disease, with promising results for both paediatric and adult populations.

In conclusion, valvular heart disease in South Africa remains a critical health issue, with diverse and complex challenges. A multidisciplinary, guideline-driven approach to the management of valvular disease, coupled with ongoing research, is essential to improve patient outcomes. Only through these efforts can we hope to mitigate the significant burden of valvular heart disease in South Africa and ultimately improve the quality of life and survival rates for affected patients.

Conflict of interest: none declared.

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The profile of rheumatic heart disease at a tertiary hospital in KwaZulu-Natal, South Africa

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ABSTRACT

Background: Rheumatic heart disease (RHD) is a disease of poverty and a significant public health concern in developing countries. There is little data on the profile of RHD in KwaZulu-Natal (KZN), South Africa.

Objectives: To describe the demographic, clinical profile, and outcomes of RHD in patients referred to a tertiary cardiology facility in KwaZulu-Natal.

Methods: This is a 5-year (2012 - 2016) retrospective analysis of all patients with RHD referred to the cardiology department at Inkosi Albert Central Luthuli Hospital (IALCH). A structured format was used to extract demographic, clinical, echocardiographic and outcome data of 981 eligible patients aged >12 years. Descriptive analysis was used to report on quantitative data and logistic regression was used to identify significant associations and independent variables.

Results: The majority of patients were Black (87.9%); the median age was 24 years (IQR 15 - 36 years) and the female to male ratio was 2.3:1. Dyspnoea (92.2%) was the commonest presenting symptom and mitral regurgitation (56.4%) was the commonest valve lesion. The most frequent complications at presentation were atrial fibrillation (AF) (44.9%) followed by heart failure (HF) (28.6%). AF mostly affected the 41 - 60 year age group (OR 2.075, 95% CI 1.22 - 3.52, p=0.007). Compared to the adolescent group (13 -2 0 years), HF was less common in the 21 - 40 years and 41 - 60 years age groups (OR 0.455, 95% CI 0.286 - 0.723, p=001 and OR 0.495, 95% CI 0.288 - 0.852, p=0.011, respectively). Valve replacement was performed in 723 (88.4%) – (mitral valve 62.2%; aortic valve 4.8%; mitral and aortic valves 29%; 3 valve surgeries 4%) – of the 818 patients who had interventional procedures. The mortality rate was high at 20.1%. Mortality was highest in the younger patients (<20 years of age) (p=0.016). Predictors of death were severe disease at a young age (OR 1.268, 95% CI 1.050 - 1.532, p=0.013) and double valve replacement (OR 1.521, 95% CI 1.009 - 2.229, p=0.045).

Conclusion: RHD remains a significant cause of morbidity and mortality in KZN. HF during the teenage years reflects ongoing carditis with haemodynamic failure resulting in death if unoperated.

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INTRODUCTION

Rheumatic heart disease (RHD) is a significant public health problem in low- and middle-income countries.[1,2] It is estimated to affect 30 - 40 million people globally.[3] At least 319 400 deaths were recorded in 2015[1,3] with 60% of the deaths classified as premature (below 70 years of age).[1,3,4]

In Africa, a high prevalence of RHD has been reported from Uganda (15 / 1000 persons),[5] and an even higher prevalence from Mozambique (30.4 / 1 000 cases), when using echocardiographic screening.[6] In the 1980s the prevalence of RHD was reported to be 6.9 per 1 000 persons in South African schoolchildren from Cape Town and Soweto.[7] An even lower prevalence of acute rheumatic fever (ARF) and RHD in children less than 14 years of age has been reported by later studies (1993 - 1995) from Soweto in Gauteng[8] and Limpopo.[9]

There are limited studies on the burden and the outcomes of RHD in KwaZulu-Natal (KZN).[10] Maharaj, et al. reported a much lower prevalence of 1 / 1 000 cases in a school survey from Inanda district of Durban in 1987.[11] This was ascribed to the poor uptake of the survey due to poor school attendance as a result of political turmoil at that time.[11] While there has

been a notable decline in RHD in schoolchildren in Gauteng, Cilliers, et al. recently reported a higher prevalence in the rural parts of KZN and the Eastern Cape[9] but provided very little data on the pattern and severity of the disease. In this study, we describe the clinical profile and outcomes in patients with RHD patients referred for tertiary care in the province of KZN.

OBJECTIVES

The aim of the study was to describe the demographic profile, clinical presentation, complications, management, and treatment outcomes of patients with RHD referred to the cardiology unit at Inkosi Albert Luthuli Central hospital (IALCH) during 2012 - 2016.

METHODS

A retrospective chart review was performed using the hospital SpeedMiner software programme (Speedminer, Malaysia) to extract the relevant patient records. Patients' records were identified using the ICD-10 codes for RHD (I05-I09.8): ARF, mitral stenosis (MS), mitral regurgitation (MR), aortic stenosis (AS), aortic regurgitation (AR), and mixed valve disease (MVD) were used for data abstraction. All adult patients (aged 12 years and over), with an echocardiographically confirmed diagnosis of RHD were included in the study. The diagnosis of RHD on echocardiography was based on the World Heart Federation (WHF) criteria.[12] A structured data collection tool captured demographic characteristics, New York Heart Association (NYHA) functional class, valve involved, clinical findings, complications, comorbidities, echocardiographic findings, and the outcomes of intervention. For patients who were lost to follow-up we attempted to contact the patients and / or their families to determine their outcomes.

Data was analysed using Statistical Package for Social Sciences (SPSS) version 24 (International Business Machine). Simple descriptive analysis was used to document clinical characteristics, and results are presented as frequencies, means, and percentages. Continuous variables are expressed as medians ± interquartile ranges (IQR). The Student's t-tests and the chi-square tests were used to compare continuous variables and categorical variables, respectively. A p-value of <0.05 indicated significant findings for the variables being measured. Logistic regression analysis was used to estimate the association between study variables and the disease severity and outcomes.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee (BREC) of the University of the KwaZulu-Natal (UKZN) (BE 598/17), the KZN provincial Department of Health and from IALCH.

RESULTS

Demographic characteristics

A total of 984 eligible patients were identified and of these 3 records were excluded due to insufficient data. The demographic characteristics of the remaining 981 patients are shown in Table I. The median age was 24 years (IQR 15 - 36 years); most patients were Black African (87.9%) and 70% were women. Over half (52.6%) of the Black African patients were residing in peri- urban areas. Human immunodeficiency virus (HIV) tests were performed in 880 (89%) patients and of these 159 (18.1%) were positive (Table I).

Clinical presentation

Half of the patients (49.5%) presented within 6 months of symptom onset (Table II). Dyspnoea was the commonest presenting symptom (92.2%), especially in the 41 - 60-year age group (OR 3.335, 95% CI 1.39 - 7.98, p=0.007) (Table II). Almost one third of patients (31.3%) presented with heart failure (NYHA class III/IV).

Pattern of valve involvement

A total of 1 337 valve lesions (mitral and aortic valves) were identified in the study population. The mitral valve was the commonest valve involved (71.9%): MR (57.6%), MS (14.5%) and mixed mitral valve disease (MMVD) (27.9%). Aortic valve lesions occurred in 376 (28.1%) cases: AR (72.6%), AS (16.5%) and mixed aortic valve disease (MAVD) (10.9%). Most aortic valve lesions (94.7%) coexisted with MVD. Only 20 (5.3%) patients had isolated aortic valve disease (AR, n=2), (AS, n=3) and (MAVD, n=15) (Table II).

Tricuspid regurgitation (TR) was present in 51.5% of patients and was functional, secondary to pulmonary hypertension in most cases. Almost one third (31.8%) had moderate to severe elevated PAS (Table II). In 18 cases in whom the pulmonary systolic pressure was less than 35mmHg, and echocardiography showed valve thickening with restriction of leaflet motion, tricuspid valve disease was deemed organic, secondary to RHD.

The severity of the mitral and aortic valve lesions stratified by age groups and sex, is shown in Figure 1. Severe MR was the

TABLE I: Demographic data of rheumatic heart disease at IALCH (2012 - 2016).

Characteristics	Total cohort n (%)	Black n (%)	White n (%)	Indian n (%)	Coloured n (%)
Age median (IQR) (years)	24 (15 - 37)	23 (14 - 37)	27 (20 - 49)	24 (15 - 36)	16 (14 - 24)
Age subgroups					
<20	402 (42.2)	390 (97)	0	11 (2.7)	1 (0.3)
20 - 40	355 (37.2)	316 (89)	1 (0.3)	33 (9.3)	5 (1.4)
41 - 60	174 (18.2)	120 (69)	8 (4.6)	45 (25.9)	1 (0.6)
>60	22 (2.3)	14 (63.6)	2 (9.1)	6 (27.3)	0
Area of Residence					
Rural	340 (35.3)	340 (100)	0	0	0
Peri-urban	506 (52.6)	457 (90.3)	0	46 (9.1)	3 (0.6)
Urban	116 (12.1)	47 (40.5)	11 (9.5)	54 (46.6)	4 (3.5)
Type of housing					
Formal	634 (66.3)	345 (36.1)	11 (1.1)	100 (10.4)	7 (0.7)
Informal	323 (33.7)	494 (51.6)			
Referral Hospital					
District Regional	202 (20.7)	197 (97.5)	0	5 (2.5)	0
Tertiary	656 (67.1)	545 (83.1)	11 (1.7)	95 (14.5)	5 (0.8)
No records	110 (11.2)	108 (98)	0	0	2 (2)
Direct admission	11 (1)	10 (91)	0	1 (9)	0
Province					
KwaZulu-Natal	864 (88.3)	748 (86.7)	10 (1.2)	101 (11.7)	5 (0.6)
Eastern Cape	115 (11.8)	112 (97.4)	1 (0.9)	0	2 (1.7)
HIV Positive	159 (18.1)	154 (96.9)	0	4 (2.5)	1 (0.6)

Except where stated all values are expressed as patient numbers (n) with the percentage in brackets.
IALCH: Inkosi Albert Luthuli Central Hospital.

commonest valve lesion in both men (31%) and women (69%), with no statistical significance between the genders (p=0.125) (Figure 1A). In contrast, severe AR was commoner in women (77.8%) than men (22.2%), (p=0.003) (Figure 1A). Severe valve lesions were more frequent in the <20 year and 21 - 40-year age groups, (MS p=0.019, MR p=0.043, AS p=0.002, AR p=0.132) (Figure 1B).

COMPLICATIONS

Over half of the patients (57.4%) presented with complications of RHD (Table II). The commonest complication was atrial fibrillation (AF) (44.9%), followed by heart failure (HF) (28.6%), stroke (14.4%) and infective endocarditis (IE) (12.1%). On univariate analysis AF was significantly less common in the elderly (>60 years age group) (p=0.040) (Table IIIA). On multivariate analysis the risk of AF was 2 times higher in the 41 - 60 year age group compared to the younger population (<20 years) (OR 2.075, 95% CI 1.22 - 3.52, p=0.007) (Table IIIB). No differences were observed in the prevalence of AF (OR 1.181, 95% CI 0.76 - 1.82, p=0.442) or HF (OR 1.06, 95% CI 0.67 - 1.67, p=0.793) between women and men. Infective endocarditis (IE) was less common in men (12.1%) than in women (22.9%), (OR 0.47, 95% CI 0.27 - 0.80, p=0.006). In the multivariate analysis HF was less common in the 21 - 40 year (OR 0.455, 95% CI 0.28 - 0.72, p=0.001) and 41 - 60 year age group (OR 0.495, 95% CI 0.28 - 0.85, p=0.011), compared to the reference age group (<20 years) (Table IIIB). The median ejection fraction (EF) was 53% (IQR 45 - 58). An EF less than 40%, was documented in 12.4%.

MANAGEMENT OF RHEUMATIC HEART DISEASE

A total of 818 patients (83.4%) underwent intervention surgery (88.4%) and percutaneous mitral balloon commissurotomy (PMBC) (11.6%); the remaining 16.6% were managed with medical therapy (Table II). Mitral valve replacement (MVR) was

TABLE II: Clinical characteristics, valve lesions, and outcomes rheumatic heart disease (n=981) at IALCH.

	n (%)
Clinical features	
History of rheumatic fever	138 (14)
Onset of symptoms <6 months	486 (49.5)
Dyspnoea (NYHA I-IV)	905 (92.2)
Dyspnoea (NYHA) III-IV	307 (31.3)
Cough	183 (18.6)
Lower limb oedema	308 (31.3)
Fatigue	357 (36.4)
Valve disease	
Mitral valve lesions	961 (71.9)
Aortic valve lesions	376 (28.1)
Valve lesion distribution	

	Aortic only n	MR n	MS n	MMVD N	Total
Mitral only		362	85	158	605
AR	2	183	21	67	273
AS	3	0	23	36	62
MAVD	15	9	10	7	41
Total	**20**	**554**	**139**	**268**	**981**

	n (%)
Tricuspid valve regurgitation[a]	506 (51.5)
Echo derived pulmonary artery systolic pressure	
Median PASP[b] (mmHg) (IQR)	38 (28 - 45)
Normal <35mmHg	18 (3 .6)
Mild 36 - 45mmHg	327 (64.6)
Moderate 46 - 60mmHg	132 (26.1)
Severe >60mmHg	29 (5.7)
Complications	
Atrial fibrillation	253 (44.9)
Infective endocarditis	68 (12.1)
Stroke	81 (14.4)
Heart failure	161 (28.6)
Ejection Fraction	
Median EF (IQR)	53 (45 - 58)
No data	27 (16.8)
EF <40%	20 (12.4)
EF 41% - 49%	30 (18.6)
EF >50%	84 (52.2)
Treatment modality	
Medical treatment only	163 (16.6)
Interventions	
PMC	95 (11.6))
Surgery	723 (88.4)
MVR	450 (62.2)
AVR	35 (4.8)
DVR	210 (29.0)
More than one intervention[c]	28 (4)
Mortality data	
Total died	197 (20.1)
While awaiting surgery	53 (26.9)
Peri-operative (within 24 hours of surgery)	61 (30.9)
Post-operative	36 (18.3)
Cause not established (death confirmed by telephone)	47 (23.9)

Except where stated all values are expressed as patient numbers (n) with the percentage in brackets.
PMC: Percutaneous mitral commissurotomy, MVR: mitral valve regurgitation, AVR: aortic valve replacement, DVR: double valve replacement, IQR: interquartile range.
[a]detected-on echocardiogram, [b]PASP pulmonary arterial systolic pressure, [c]Details of more than 1 surgical procedure: PMC followed by MVR 19 (68), PMC followed by DVR 6 (21.4%), MVR followed by DVR 2 (7.1%), MVR followed by AVR 1 (3.5%).

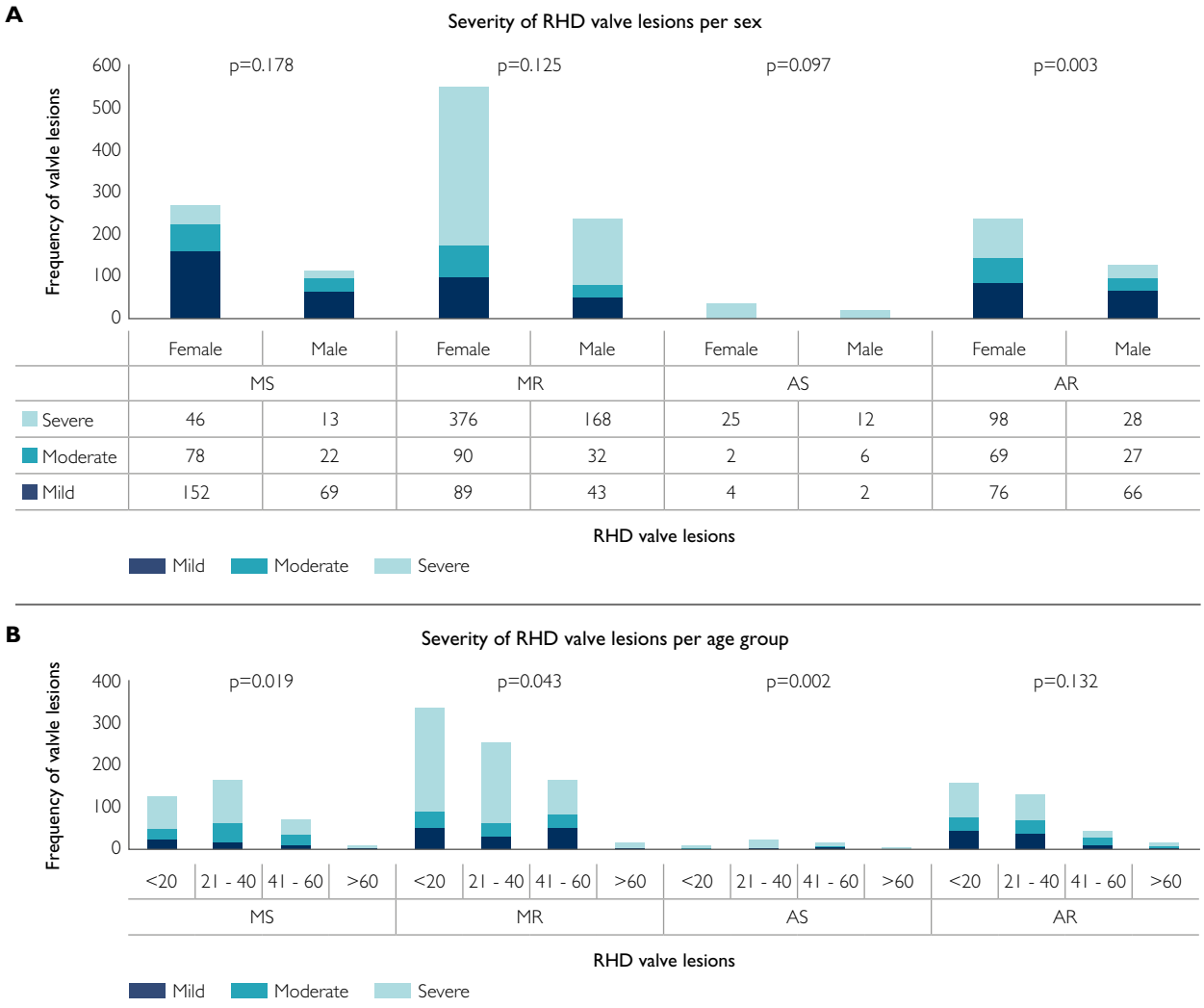

FIGURE 1: Severe MR was the commonest valve lesion in both genders (middle chart). Both mitral and aortic valve lesions were commoner in females (A) and occurred more frequently in the younger age groups (<20 and 20 - 40 years) compared to those over 40 years of age (B). Except for AS, which was the least common valve lesion, all other lesions (MS, MR, and AR) were more severe and occurred more frequently in the younger age groups (<20 years and 21 - 41 years).

the most common surgical procedure performed (62.2%) (Table II); and it was the most frequently performed procedure in the <20 year age group compared to the other age groups (p=0.033) (Table IIIA). Aortic valve replacement (AVR) was more frequently undertaken in the older age groups (41 - 61 year (OR 3.49, 95% CI 1.45 - 8.38, p=0.005) and >60 year (OR 5.17, 95% CI 1.01 - 26.4, p=0.048) compared to the reference group (<20 years) (Table IIIB). After controlling for sex, double valve replacement (DVR) was more commonly performed in the 21 - 40 years age group (OR 1.57, 95% CI 1.09 - 2.25, p=0.013) compared to the other age groups (Table IIIB). Women were more likely than men to have undergone MVR (OR 1.585, 95% CI 0.92 - 2.72, p=0.004) and less likely to have had DVR (OR 0.626, 95% CI 0.44 - 0.8, p=0.007) or AVR (OR 0.389, 95% CI 0.19 - 0.78, p=0.009).

Percutaneous mitral balloon commissurotomy (PMBC) for tight MS was performed in 95 patients. Most procedures (88,2%) were performed in the younger subjects under the age of 40 years [(<20 years n=35, (41.2%) and 21 - 40 years n=40, (47%)]) compared to the older age groups 40 - 60 years (n=10, (11.8%) (Table IIIA). Most of the patients (n=95, 53%) who underwent PMBC subsequently went on to have surgery for MVR due to restenosis of the mitral valve, 2 or more years after the PMBC.

TABLE IIIA: Complications, interventions, and outcomes of RHD stratified by age group and gender.

	<20 years n (%)	21 - 40 years n (%)	41 - 60 years n (%)	>60 years n (%)	p-values
Complications					
AF	71 (29.1)	103 (42.2)	64 (26.2)	6 (2.5)	0.040
IE	26 (38.8)	26 (38.8)	13 (19.4)	2 (3)	0.823
HF	68 (44.7)	49 (32.2)	29 (19.1)	6 (4)	0.003
Stroke	24 (30.8)	33 (42.3)	20 (25.6)	1 (1.3)	0.659
Complications in women					
AF	44 (24.3)	82 (45.3)	49 (27.1)	6 (3.3)	0.068
IE	14 (37.8)	12 (32.4)	9 (24.3)	2 (5.5)	0.519
HF	42 (38.5)	38 (34.9)	23 (21.1)	6 (5.5)	0.047
Stroke	10 (19.6)	25 (49)	15 (29.4)	1 (2)	0.279
Complications in men					
AF	27 (42.2)	21 (32.8)	15 (23.4)	1 (1.6)	0.177
IE	12 (40)	14 (46.7)	4 (13.3)	0	0.569
HF	26 (59.1)	11 (25)	6 (13.6)	1 (2.3)	0.056
Stroke	14 (51.9)	8 (29.6)	5 (18.5)	0	0.781
Interventions					
PMC	39 (41)	45 (47.4)	10 (10.5)	1 (1.1)	0.110
MVR	203(46.8)	140 (32.3)	83 (19.1)	8 (1.8)	0.033
AVR	10 (29.4)	10 (29.4)	12 (35.3)	2 (5.9)	0.013
DVR	80 (39.0)	90 (43.6)	31 (15.0)	5 (2.4)	0.009
Outcomes					
Died	68 (34.5)	78 (39.6)	48 (24.4)	3 (1.5)	

AF: atrial fibrillation, IE: infective endocarditis, HF: heart failure, PMC: percutaneous mitral commissurotomy, MVR: mitral valve replacement, AVR: aortic valve replacement, DVR: double valve replacement.

TABLE IIIB: Multivariate analysis stratified by age group at diagnosis.

	21 - 40 years OR	95% CI	p-value	41 - 60 years OR	95% CI	p-value	>60 years OR	95% CI	p-value
Symptoms									
Dyspnoea	2.361	1.32 - 4.22	0.004	3.335	1.39 - 7.98	0.007	2.591	0.32 - 19.06	0.376
PND	1.379	1.00 - 1.89	0.048	2.478	1.70 - 3.60	0.000	2.483	1.04 - 5.92	0.004
Cough	1.534	1.04 - 2.25	0.029	1.955	1.24 - 3.06	0.003	2.271	0.84 - 6.07	0.102
Leg oedema	1.320	0.96 - 1.80	0.082	1.395	0.95 - 2.04	0.088	2.138	0.89 - 5.10	0.087
Surgical procedures									
PMC	1.320	0.81 - 2.15	0.264	0.568	0.26 - 1.21	0.147	0.565	0.72 - 4.42	0.587
MVR	0.592	0.42 - 0.81	0.001	0.924	0.61 - 1.38	0.701	0.656	0.23 - 1.80	0.414
AVR	1.368	0.55 - 3.37	0.496	3.494	1.45 - 8.38	0.005	5.172	1.01 - 26.4	0.048
DVR	1.575	1.09 - 2.25	0.013	0.969	0.60 - 1.55	0.896	1.537	0.51 - 4.58	0.441
Complications of RHD									
AF	1.552	0.99 - 2.41	0.051	2.075	1.22 - 3.52	0.007	1.070	0.32 - 3.47	0.910
HF	0.455	0.28 - 0.72	0.001	0.495	0.28 - 0.85	0.011	1.161	0.35 - 3.76	0.083

Age <20 years is the reference group.
PND: paroxysmal nocturnal dyspnoea, PMC: percutaneous mitral valvulotomy, MVR: mitral valve replacement, AVR: aortic valve replacement, DVR: double valve replacement, AF: atrial fibrillation, HF: heart failure.
Dyspnoea was the commonest presenting symptom in 41 - 60 years and 21 - 40 years. MVR was commonly performed in young patients (<20 and 21 - 40 year). AF was the common complication in patients >20 years old and HF in patients <20 years.

RHEUMATIC HEART DISEASE MORTALITY

One hundred and forty-seven (15%) were referred back to continue follow-up at their base hospitals (Table II). Of these patients 7 had declined surgery and 15 were deemed unfit for surgery due to comorbid illnesses (advanced HIV (CD4 cell count <200cells/mm^3) (n=6), anaemia (n=2), hypothyroidism (n=1), untreated syphilis (n=1), and cardiomyopathy (n=5). A minority of patients (n=58) were lost to follow up.

A fifth of patients (20.1%) died during the 5-year period of the study and the median age at the time of death was 27 years (IQR 18 - 44 years). The 197 deaths comprised those who died: (a) while awaiting surgery (26.9%), (b) during the peri-operative period (49.2%) and (c) those were reported by their families to have died (23.9%) upon telephonic follow-up. Deaths were due to HF / cardiogenic shock (40.6%), AF (48.7%), IE (2.0%) and septic shock (4.6%); and stroke (4.1%).

There was a negative relationship between age and mortality (p=0.016) (Table IV). Most deaths occurred in the 21 - 40 years age group (39.6%), followed by <20 year age group (34.5%), and the 41 - 60 years age group (24.4%), and the least in the >60 years (1.5%). Severe disease at a young age (OR 1.268, 95% CI 1.050 - 1.532, p=0.013) and DVR (OR 1.655, 95% CI 1.109 - 2.472, p=0.014), emerged as independent predictors of death. As expected, surgical intervention was lifesaving (OR 0.471, 95% CI 0.339 - 0.665, p=0.000), with fewer deaths occurring in the patients who underwent single valve surgery (n=122, 16.7%) compared to those who did not have surgery (n=75, 29.3%) (Table IV). Amongst patients who underwent surgical intervention, DVR carried the highest risk of death after surgery (OR 1.521, 95% CI 1.009 - 2.229, p=0.045).

DISCUSSION

This study shows that patients with RHD in KZN present with a full spectrum of advanced chronic manifestations, often occurring at a much younger age. These findings are in keeping with early studies[13,14,15] which described severe valvular damage from recurrent carditis. The peak presenting age in our study was in adolescence and young adults, compared to the third decade in the Heart of Soweto study.[16] A striking finding was that 42.2% of our patients were below 20 years of age at the time of diagnosis and 57.6% of those below 20 years had severe, advanced rheumatic valve disease. Most of our younger patients were referred with severe symptoms of NYHA III / IV dyspnoea, often in decompensated HF with RHD complications. These findings are similar to early reports from the district of Inanda, Durban in 1987,[11] Uganda and Nigeria all of which described severe MR presenting in advanced HF.[17,18,19] Severe disease presenting in early age has been reported in an Australian study[20] which showed a high incidence and rapid progression of RHD within a year after the first episode of ARF. Recently, Okello, et al. reported that suboptimal adherence to benzathine penicillin injections was associated with incident HF and mortality over 1 year from initial presentation.[19,20]

The pattern of severe valve involvement at an early age suggest an accelerated rheumatic process resulting in mitral regurgitation and HF,[25,26] which have recently been described in Cameroon,[27] in Gauteng,[29] and in Uganda.[30] While the frequent coexistence of MVD and AVD at a young age in our study is typical of the natural history of RHD.[21] Severe double valve involvement in our study suggests recurrent carditis with severe valve damage requiring DVR at an early age. This pattern of accelerated valve damage was also seen in the group with tight MS. Forty percent of these subjects that underwent PMBC were under the age of 20 years. Severe MS in the teenage years indicates an accelerated fibrotic process with organisation of valvular tissue resulting in early narrowing of the valve orifice and tight valvular stenosis.[31] Rheumatic involvement of the tricuspid valve is uncommon.[32] In the majority of our patients tricuspid regurgitation was attributed to pulmonary hypertension.[32,33] However, this lesion was also detected at near normal pulmonary artery pressures in subjects with TR who had leaflet thickening and restriction of motion in 3.6% patients, pointing to organic tricuspid valve disease (TVD) secondary to the rheumatic process. This has been described in a cross-sectional study from Nepal[34] and a World Health Organisation (WHO) review by Sultan, et al. who found TVD in 7.7% of cases, with 99.3% of these patients having co-existing MVD.[35]

The majority (88.4%) of our study population underwent valve replacement surgery because patients presented with severe regurgitant lesions and multiple valve involvement. The choice of the intervention modality was informed by the type of valve disease and suitability of the valve morphology, the severity of valve damage[36] and operator skills.[37] PMBC for isolated tight MS was performed in the remaining 11.6% whom the interventionalist judged suitable for the procedure. Although PMBC has been reported to have a favourable short and long-term outcome in carefully chosen candidates,[38,39] recent attention has been drawn to a high rate of restenosis following this procedure.[40] This was borne out in our sample since the majority

TABLE IV: The association of age and valve surgery with mortality in all patients.

	Alive n (%)	Died n (%)	Total n (%)
Age categories			
<20	337 (43)	68 (34.5)	405
21 - 40	277 (35.3)	78 (39.6)	355
41 - 60	126 (16.7)	48 (24.4)	174
>60	44 (5.6)	3 (1.5)	47
Treatment category			
No surgery	106 (65)	57 (35)	163
Surgery	678 (82.9)	140 (17.1)	818
Total	784 (79.9)	197 (20.1)	981

Pearson Chi-square = 10.26, p=0.016. The odds of dying decreased with age.
Surgical procedures were protective against death (Pearson Chi-square = 18.95, pr=0.000).

proceeded to valve replacement 2 years after the procedure, due to valve restenosis, indicating that PMC was being performed in subjects with less than ideal valve morphology.

The mortality related to RHD remains a serious burden affecting young patients from low- to middle- income countries,[41] with a 2-year case fatality rate of 500 deaths (16.9%) in Africa.[41] Our study found a mortality rate of 20.1% which is higher than the case fatality rate of 16.9% described in the Global Rheumatic Heart Disease Registry (REMEDY study).[41] In keeping with other reports[3,41,42] most of the deaths in our study were due to advanced disease with valve destruction resulting in haemodynamic failure, as well as very large atria with atrial fibrillation and clot formation. The median age at the time of death was 27 years (IQR 18 - 44.7 years) was very similar to 28.7 years described in the REMEDY study. In contrast to the REMEDY[41] study, we found that age less than 20 years was a predictor of death. This is explained by the severity of disease observed in this age group, which carried a high mortality risk, especially in subjects undergoing DVR. As expected, valve surgery was life-saving, with fewer deaths observed among those with severe disease who underwent surgery. We found no significant association between mortality and clinical variables such as demographic characteristics, comorbidities, severe symptoms (NYHA class III / IV) and complications.

STUDY LIMITATIONS

The limitations of this study are largely related to its retrospective design. These include missing or incomplete follow up data for analysis, thereby limiting our ability to interrogate data relating to outcomes of complications and mortality. Furthermore, the centralisation of referrals of severe disease to a single state tertiary centre has created an inherent referral bias, so that results may selectively represent severe RHD, as it does not include patients managed at peripheral hospitals and clinics with milder forms of the disease. While the study sample is therefore limited with regards to ethnicity and grades of disease severity, it does reflect the profile of patients in poorer communities and at highest risk of severe RHD. A strength of our study, however, is that echocardiography was used to document the clinical profile of RHD at a tertiary referral hospital in KZN, enabling us to provide a detailed morphology of the underlying rheumatic pathology and its associated complications. Lastly, it must be pointed out that the study portrays a 5-year view and longer-term outcome was not evaluated in this study.

There is evidence that susceptibility to and severity of ARF and RHD differs amongst different ethnic groups.[22] Although we could not assess this in our study, due to small numbers of subjects in the other ethnic groups, the majority (90%) of patients in our study were Black African with over half (52.6%) residing in peri- urban areas. These areas are not only densely populated but also characterised by a rapid rise in informal settlements in KZN where low socioeconomic standing and overcrowding, together with poor access to health care facilities contribute to the development of ARF and RHD.[23,24] In this environment untreated recurrent streptococcal infection and ARF are missed opportunities for primary and secondary prophylaxis measures[2,18,21] and result in ongoing valvular damage[3] requiring surgical intervention at a young age.

CONCLUSION

This study shows that RHD with its sequelae remains a significant cause of cardiovascular morbidity and mortality especially among young Black Africans from disadvantaged communities in KZN. Most patients presented at an advanced stage of the disease requiring urgent valve replacement surgery which was lifesaving. Advanced disease at young age and DVR emerged as significant predictors of mortality. Of note, HIV infection did not appear to adversely influence the disease outcome.

The study highlights the importance of early diagnosis and management of RHD, through continued rheumatic fever surveillance at community level, as well as the availability of point-of-care echocardiographic services to facilitate early diagnosis and referral of patients from peripheral hospitals.[43] These issues have become more imminent in current times and serve to reemphasise the need for effective penicillin prophylaxis to combat streptococcal infection and prevent recurrent carditis and the devastating consequences of this disease. Establishment of a RHD registry in KZN will reflect the true burden of RHD at the community level and inform policies and programmes to increase awareness of RHD in the communities and ensure effective screening and therapeutic measures.

Conflict of interest: none declared.

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Characteristics and outcomes of infective endocarditis in South Africa: A retrospective cohort study

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ABSTRACT

Background: Infective endocarditis (IE) remains a disease with significant morbidity and mortality for a predominantly young group of patients in South Africa. There is a paucity of data assessing contemporary outcomes of IE in South Africa, limiting our ability to institute strategies to improve the outcome of patients with IE in South Africa.

Methods: A retrospective cohort of patients with IE was established from healthcare records for the period of 1 January 2017 - 31 December 2018. A profile of clinical, laboratory, microbiologic, echocardiographic, surgical, and morbidity and mortality data was compiled for each patient.

Results: A total of 75 patients with definite IE were included in this study. The mean age was 39.6 years with a male preponderance (68%). Mortality at 6 months (all cause) was 34.7% and embolic complications were common, especially cerebral embolism (21%). Rheumatic heart disease (RHD) was present in 28% of the cohort. A high rate of blood culture negative IE (BCNIE) was present (62.7%). In patients with a positive blood culture, Staphylococcus aureus (43%) and the viridans group of streptococci (32%) were the most common causative organisms.

Conclusion: IE in South Africa remains a disease with a significant mortality rate despite the young age of the patients affected. The high rate of BCNIE is a likely contributor to the associated adverse outcomes. Some of the features of IE in South Africa have evolved to resemble a profile of disease similar to cohorts from high-income countries with a Staphylococcal predominance and a reduction in underlying RHD as predisposing risk factor. SA Heart® 2024;21:218-224

INTRODUCTION

Infective endocarditis (IE) is an infective process of the endocardial surface of the heart, which may involve native valve structures (native valve endocarditis or NVE), prosthetic valves (prosthetic valve endocarditis or PVE) or implanted cardiac devices (device related IE or DRIE).[1-4] In South Africa, IE carries a significant morbidity and mortality with mechanical valve replacement in more than 40% of cases, reported cerebral embolism rates of 12% - 17% and in-hospital and 6-month mortality of up to 25% and 36% respectively.[5,6] IE in South Africa differs from the pattern of disease observed in high-income countries where in-hospital mortality is 18% - 20% and 6-month mortality 20% - 25%; but similar regarding rates of surgical management (40% - 50%) and embolic complications, particularly cerebral embolism (15% - 20%).[2,7-11]

Infective endocarditis (IE) in high-income countries is predominantly a disease of older patients with normal valves or degenerative valve disease, caused by Staphylococcus aureus and other hospital acquired organisms.[4,12] In contrast, IE in South Africa has been reported to be a disease of predominantly young patients without significant co-morbidities, commonly associated with underlying rheumatic heart disease (RHD) and caused by the viridans group of streptococci.[5]

Previously low rates of Staphylococcus aureus associated IE were reported in South Africa and this led to many local empirical protocols not including specific antimicrobial therapy to target Staphylococcus aureus, an example being the empiric use of ampicillin / penicillin G with gentamicin as standard therapy.[5] Recent reports have shown a more equal distribution with similar rates of Staphylococcus aureus and viridans group of streptococci reported in patients with IE.[6,13] Similar to cohorts from high-income countries, Staphylococcus aureus is the most common cause of right sided IE in South Africa and associated with intravenous drug use.[6,14]

The clinical features of IE have evolved in both low- and middle-income as well as high-income countries. The so-called "classical" features of IE, such as Osler nodes, Janeway lesions and Roth spots, are now rarely encountered in both low- and middle-income as well as high-income countries.[7,15] Clubbing, fever and anaemia with the presence of a regurgitant murmur remains the most common clinical features of IE in both low- and middle as well as high-income countries.[3,5]

We aimed to determine the current morbidity and mortality rates of IE in the Western Cape region of South Africa. In addition, we aimed to describe the clinical features, predisposing heart diseases and common causative organisms associated with IE in a retrospective cohort of patients with IE.

METHODS

Tygerberg Hospital (TBH) is a tertiary referral hospital for a network of 17 hospitals in Cape Town, South Africa, and serves a population of approximately 2.4 million people.[16] All patients presenting to this network of hospitals with suspected IE are referred to TBH.[17] Patients with possible IE were identified by reviewing the echocardiographic database of the Division of Cardiology at Tygerberg Hospital as well as the minutes of the weekly Heart Team meetings for the period January 2017 - December 2018.

The EchoPAC system (GE) is an internal network database of all echocardiograms (transthoracic and transoesophageal) performed by the Division of Cardiology at TBH. All transthoracic echocardiograms were obtained using a standard echocardiography machine (GE, Milwaukee, USA) with a 2- to 3.6MHz transducer probe (GE 3S/4S/5S) and performed by qualified health care professionals according to current guidelines.[18,19] Patient records are identifiable by name, surname, date of birth and a unique hospital number assigned to each patient upon entry into the health care system. This database was reviewed searching for patients either referred for suspected IE as well as all patients whose report mentioned possible vegetation(s) present on imaging.

The Heart Team consists of clinicians from both the Division of Cardiology and the Division of Cardiothoracic Surgery. Meetings are routinely held on a weekly basis. All patients that would potentially require surgery are discussed and reviewed, decisions being documented in minutes of each meeting. The minutes for the time period January 2017 - December 2018 was reviewed and all patients with IE were included.

All patients with suspected IE between 1 January 2017 - December 2018 were identified. Clinical notes, laboratory results, echocardiography images and surgical reports were reviewed and patients with definite or possible IE were included.[20]

Demographic, clinical, laboratory investigation, echocardiographic, surgical and outcome data were collected for all included patients. Demographic data recorded included age, sex and income status categorisation. Clinical data collected was aimed at determining the predisposing conditions (RHD, other history of valvular heart disease, intravenous drug use, previous valve surgery / replacement, history of congenital heart disease), co-morbid diagnoses, general cardiovascular risk factors and specific data such as human immunodeficiency virus (HIV) infection status. All clinical findings were captured including heart rate, blood pressure, measured temperature, presence of clubbing as well as all minor criteria described in the Duke criteria. Laboratory investigations captured included white cell count, haemoglobin concentration, creatinine, C-reactive protein (CRP), complement fraction 3 and 4 (C3 and C4), rheumatoid factor as well as auto-immune serological test results collected during the initial work-up. Echocardiographic data collected included whether TTE or TEE or both were performed, underlying valve characteristics, measurements of vegetations (linear length, circumference, mobility and sites of attachment), peri-annular extension if present and degree of valvular destruction. Surgical data was reviewed to establish the indication for surgery (haemodynamic instability, embolic phenomenon or inability to gain source control), which surgical technique was utilised (valve repair, valve reconstruction or valve replacement), what the calculated EuroSCORE II was and how many days elapsed between diagnosis and surgery. Outcome data collected was sought to confirm whether patients survived to discharge, survival to 6 months, degree of dyspnoea (as measured by the NYHA system) and whether they developed recurrence of IE.

STATISTICAL ANALYSIS

Statistical analysis was done on SPSS v27 for Windows. Descriptive statistics were calculated, nominal data was compared via cross tabulation and Chi-square tests, parametric data was compared using independent-sample T-tests (Cohen's d) and non-parametric data was compared using independent-samples T-test (Mann-Whitney U or Kruskal-Wallis 1-way ANOVA). Where possible, regression modelling was performed on nominal variables for measured outcomes.

ETHICAL CONSIDERATIONS

This study was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (ref S19/10/234) and performed in accordance with the Helsinki Declaration of 1975 (updated in 2013). Waiver of individual consent was obtained from HREC to include data from patient records in this retrospective cohort.

RESULTS

A total of 75 patients were included (Figure 1). The baseline characteristics are summarised in Table I. The mean age was 39.6 years with a male predominance (68%). Thirty-five patients (46.7%) met modified Duke Criteria for definite IE, all the rest having criteria for possible IE. HIV infection was present in 21.5% of patients with a mean absolute CD4 count of 442 cells/µl. The majority of people living with human immuno-deficiency virus (PLHIV) (10/14; 71.4%) were on combination antiretroviral therapy (c-ART). Five patients (6.7%) volunteered a history of intravenous drug use (IVDU).

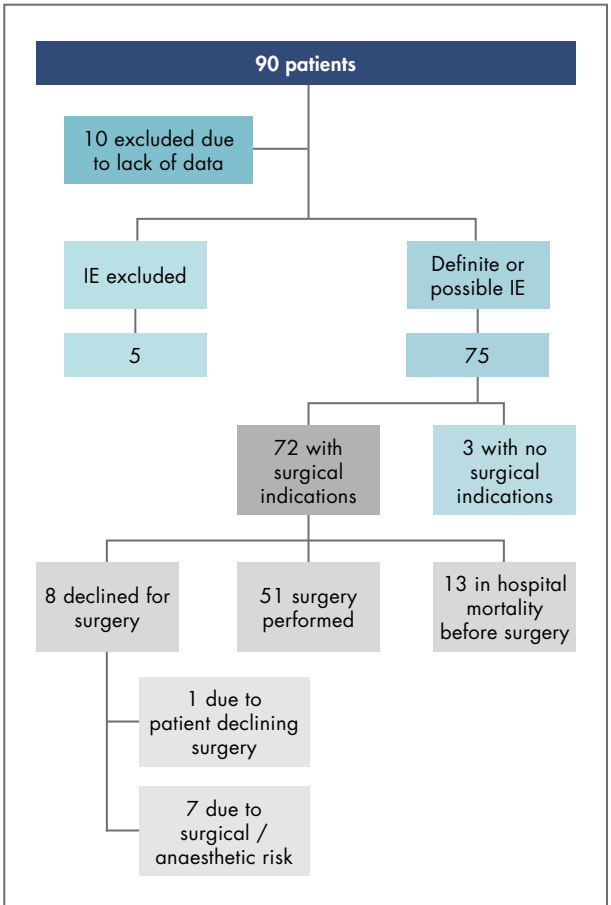

FIGURE 1: Schematic of case selection.

The clinical findings on examination are summarised in Table II. An audible murmur (96%), documented fever >38.3°C (56%), pallor (56%) and clubbing (32/75 or 42.7%) were the most frequently detected findings on examination. Cerebral embolism was the most common embolic complication, present in 16/75 (21%).

Laboratory investigations are summarised in Table III. An elevated CRP was present in 71/75 (94.7%) and a white cell count (WCC) above 11x109 cells/L in 25/75 (33.3%). C3 levels were less than 0.9g/L in 20/65 (30.8%) and C4 less than 0.1g/L in 9/65 (13.8%). Rheumatoid factor was elevated above 10IU/mL in 30/56 (53.6%).

Blood cultures were negative (BCNIE) in 47 of the 75 (62.7%) patients. In patients with positive blood cultures (BCPIE), Staphylococcus aureus was the most common causative organism (12/28; 42.9%) followed by the viridans group of streptococci (9/28; 32.1%). Other organisms identified by blood culture are shown in Figure 2.

Echocardiographic features of vegetations are listed in Table IV. Vegetations were, on average, large with mean vegetation length of 13.7mm on the aortic valve, 14mm on the mitral valve and 18.4mm on the tricuspid valve. Echocardiographic features of underlying rheumatic heart disease were present in 28% of patients.

TABLE I: Baseline characteristics.

	n=75 (%)
Age in years	
Mean (SD)	39.6 (12.3)
Male	51 (68.0)
Income status	
H0-1 (R0-70000 p.a.)	64 (85.3)
H2-4 (R>70000 p.a.)	11 (14.7)
Rheumatic heart disease	
History	15 (20.0)
Echocardiographic evidence	21 (28.0)
IVDU	5 (6.7)
HIV	
PLHIV	14 (18.7)
Unknown	10 (13.3)
On c-ART	10 (13.3)
Previous cardiac surgery	10 (13.3)
Cigarette smoking	27 (36.0)
Hypertension	15 (20.0)
Diabetes	3 (4.0)

SD: standard deviation, IVDU: intravenous drug user, HIV: human immunodeficiency virus, c-ART: combination antiretroviral therapy.

TABLE II: Clinical features.

	n=75 (%)
Dyspnoea present	68 (90.7)
Grade I	2 (2.7)
Grade II	13 (17.3)
Grade III	26 (34.7)
Grade IV	27 (36.0)
Night sweats	25 (33.3)
Weight loss	29 (38.7)
History of valvular heart disease	24 (32.0)
History of congenital heart disease	3 (4.0)
Fever (>38.3˚C)	42 (56.0)
Audible murmur	72 (96.0)
Pallor	42 (56.0)
Clubbing	32 (42.7)
Embolic / vascular phenomenon	
Stroke	16 (21.3)
Septic emboli	6 (8.0)
Major arterial emboli	1 (1.3)
Immunological phenomenon	
Splinter haemorrhages	18 (24.0)
Splenomegaly	6 (8.0)
Janeway lesions	2 (2.7)
Glomerulonephritis*	14 (18.7)
Features of severe AR	29 (38.7)
Features of severe MR	42 (56.0)
Features of severe TR	9 (12.0)
Left heart failure	37 (49.3)
Right heart failure	5 (6.7)
Biventricular failure	16 (21.3)

**Glomerulonephritis based on microscopic haematuria with / without acute kidney injury. Data on presence of haematuria only available in 20 patients. All patients that had microscopic haematuria detected had an elevated creatinine. AR: aortic regurgitation, MR: mitral regurgitation, TR: tricuspid regurgitation.*

Morbidity, mortality rates and surgical characteristics are summarised in Table V. The all-cause mortality rate at 6 months was 34.7%. There was a statistically significant difference in 6-month mortality between patients with an indication for surgery undergoing surgery when compared to patients with an indication for surgery who did not undergo surgery (21.6% vs. 71.4%; p<0.01).

Predictors of mortality at 6 months included failure to undergo surgery when indicated (OR 8.1; p=0.02), left ventricular dysfunction (OR 3.1; p=0.07) and EuroSCORE II more than 12% (OR 4.7; p=0.02) (Table VI).[21]

BCPIE as well as increasing vegetation length in millimetres on the aortic valve were associated with an increased risk for cerebral embolism (Table VII).

TABLE III: Laboratory investigations.

White cell count	<4x10⁹/L	0/75
	4-11x10⁹/L	50/75
	>11x10⁹/L	25/75
Haemoglobin	<10g/dL	31/75
	10-12g/dL	28/75
	>12g/dL	16/75
C-reactive protein	>10mg/L	71/75
Estimated glomerular filtration rate*	>90mL/min/1.73m²	42/75
	61-90mL/min/1.73m²	15/75
	30-60mL/min/1.73m²	15/75
	<30mL/min/1.73m²	3/75
Complement fraction 3	<0.9g/L	20/65
Complement fraction 4	<0.1g/L	9/65
Rheumatoid factor	Positive (>10IU/mL)	30/56
Anti-nuclear antibody	Positive (>1:40)	3/22
Anti-nuclear cytoplasmic antibody	Positive	1/4
Urine dipstick	Haematuria	31/49
	Proteinuria	16/49

**eGFR calculated using CKD-EPI formula; all patients categorised as "not African-American".*

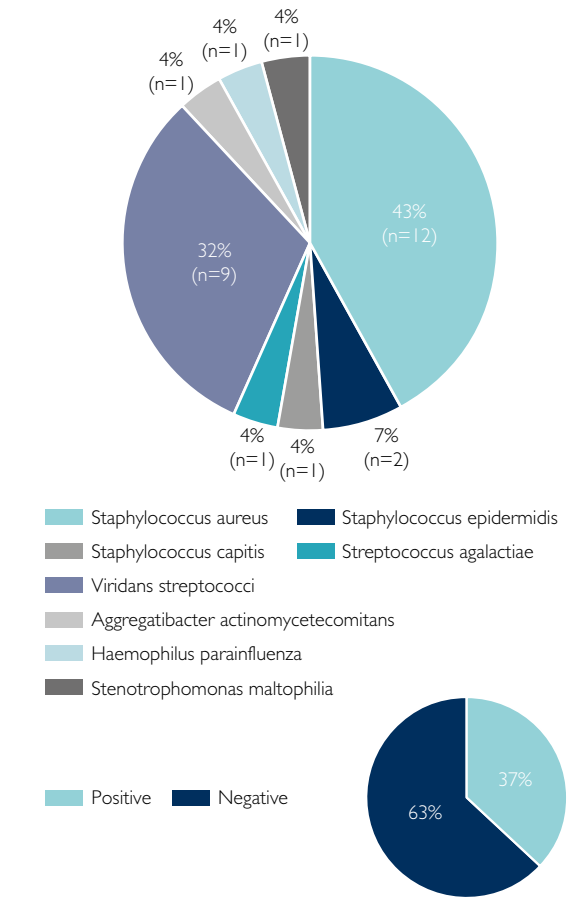

FIGURE 1: Blood culture results.

TABLE IV: Echocardiographic findings.

	n=75 (%)
Total vegetations*	47 (62.7)
Involved valve(s)	
Aortic valve	26 (34.7)
Mitral valve	31 (41.3)
Tricuspid valve	5 (6.7)
Aortic and mitral	8 (10.7)
Aortic and tricuspid	2 (2.7)
Mitral and tricuspid	2 (2.7)
Aortic valve vegetations	36 (48.0)
Mean size linear (SD)	13.7 (6.2)
Mean size circumferential (SD)	34.5 (15.4)
Mitral valve vegetations	41 (54.7)
Mean size linear in mm (SD)	14 (6.6)
Mean size circumferential in mm (SD)	38.6 (16.5)
Tricuspid valve vegetations	9 (12.0)
Mean size linear (SD)	18.4 (6.7)
Mean size circumferential (SD)	46.8 (15.8)

**Forty-seven patients had mobile valvular vegetations, 1 being a windsock deformity of the anterior mitral valve leaflet with submittal aneurysm due to Mycobacterium tuberculosis.*
SD: standard deviation, mm: millimeters.

TABLE V: Surgical characteristics.

	n=51 Surgery indicated, performed (%)	n=21 Surgery indicated, not performed (%)	p
Procedure			
Mechanical valve	34 (66.7)		
Tissue valve	7 (13.7)		
Valve repair	7 (13.7)		
Valve reconstruction*	3 (5.9)		
ICU stay in days (SD)	6.8 (9.9)		
Days from diagnosis to surgery (SD)	42.3 (37.8)		
EuroSCORE II			
Mean (SD)	7.7 (9.6)	15.9 (17.3)	0.01
RHD	15 (29.4)	4 (19.0)	0.36
IVDU	1 (2.0)	4 (19.0)	0.01
Blood culture positive	17 (33.3)	10 (47.6)	0.26
In hospital mortality	4 (7.8)	13 (61.9)	<0.01
Days to in hospital mortality from diagnosis (SD)	45.5 (26.8)	28.9 (17.3)	<0.01
Six 6-month mortality	11 (21.6)	14 (66.7)	<0.01

**Reconstruction defined as use of saphenous vein reconstruction or pericardial patch on mitral valve.*
ICU: intensive care unit, SD: standard deviation, RHD: rheumatic heart disease, IVDU: intravenous drug user. EuroSCORE II.[21]

TABLE VI: Predictors of 6-month mortality.

	OR	95% CI	p
Surgery indicated, not performed	8.1	2.1-30.6	0.02
EuroSCORE II >12%	4.7	1.3-17.8	0.02
Left heart failure	3.1	0.8-12.5	0.07
Weight loss*	1.9	0.6-6.6	0.27

**Variable kept in model due to interaction with subgroup not undergoing surgery – not reaching statistical significance (p=0.16).*

TABLE VII: Factors associated with stroke.

	OR	p
BCPIE	12.3	<0.01
BCPIE – Streptococcus	6.6	0.01
BCPIE – Staphylococcus	2.1	0.15
AV vegetation >10mm in linear length	2.4	0.12
MV vegetation >10mm in linear length	0.12	0.73
TV vegetation >10mm in linear length	0.64	0.43

BCPIE: Blood culture positive infective endocarditis, AV: aortic valve, mm: millimetres, MV: mitral valve, TV: tricuspid valve.

DISCUSSION

The 6-month mortality rate associated with IE (34.7%) recorded in this retrospective study remains higher than published data from high-income countries and similar to previous reports from South Africa.[5,11] In addition, embolic events and cerebral embolism in particular (21.3%) remain a significant contributor to the mortality and morbidity rates associated with IE. The high mortality rate is unexpected given the young age of patients and the low rate of associated comorbidities.

The 6-month mortality rate observed in our cohort (34.7%), is remarkably similar to the 35.6% mortality rate reported 20 years ago, despite advances in diagnostic and treatment strategies.[5] Compared to previous data from our institution, this cohort has a higher rate of PLHIV, PVE and patients reporting intravenous drug use.[5] Although retroviral disease is not considered as a predictor of adverse outcomes, PVE and intravenous drug use associated IE have been validated as predictors of worse outcomes.[22]

We identified various factors associated with mortality at 6 months. In this study failure to undergo surgery when indicated, a EuroSCORE II of more than 12% and left ventricular dysfunction (left ventricular ejection fraction <50%) were associated with 6-month mortality (Table VI).

Mortality at 6 months was significantly lower in patients with a surgical indication who underwent surgical treatment compared to mortality in patients in whom surgery was indicated, but did not undergo surgery (21.6% vs. 66.7%; p<0.01). Failure to undergo surgery when indicated, may be a contributing factor to high mortality rate observed. The group with surgical indications who underwent surgery had a mean EuroSCORE II value of 7.7% which correlated with the observed in-hospital mortality (7.8%).

The majority of patients that underwent surgery had a mechanical valve replacement due to the young age of patients, the prevalence of RHD and the significant valvular destruction observed at presentation. Although there has been a decrease in the prevalence of RHD compared to a previous cohort, a significant proportion of patients (28%) had underlying RHD.[5,14] The decrease in proportion of patients with underlying RHD in this cohort may be due to the change in bacteriological profile as screening studies do not suggest a decrease in the prevalence of subclinical RHD.[23] These subclinical cases may however not progress to severe lesions due to better screening and subsequent prophylactic antibiotic use. It may also reflect the relative increase in other predisposing conditions for the development of IE, such as intravenous drug use and prosthetic valve use.

Cerebral embolism was the most common embolic phenomenon and occurred in 21.3% of patients, which is similar to the reported rates from developed world cohorts in high-income countries.(.[7,11] It has been demonstrated that the presence of large vegetations (>10mm) is an independent risk factor for early cerebral embolism as well as mortality due to IE.[13,23] In this cohort large vegetations (>10mm) was not statistically predictive of cerebral embolism, this is likely due to this study being underpowered. Patients with BCPIE, especially IE caused by the viridans group of streptococci, were associated with an increased risk for cerebral embolism. It should be noted that the average vegetation size in the 9 patients with viridans group streptococcal infections was 17mm and 12.2mm when involving the AV and the MV, respectively. It is therefore possible that it was in fact vegetation size that contributed to cerebral embolism, rather than the specific organism causing infection. These vegetations were not statistically different in size compared to patients with BCPIE with non-streptococcal organisms (p=0.80 and 0.54 for AV and MV respectively) (Table VI).

Staphylococcus aureus was the most common organism detected, in contrast to previous reports identifying the viridans group of streptococci as the most common cause of IE in South Africa.[5] The organism detection rate in our cohort was lower than reported in cohorts from high-income countries, but similar to previously published data from South Africa with a BCNIE rate of 62.7%.[5,14] Even with the addition of serological and surgical specimen analysis, a causative organism could only be detected in 41.3% of patients. It should be noted that no set protocol for organism detection was employed and additional tests were performed on the discretion of the managing physician. The high rates of BCNIE in South Africa has been attributed to antibiotic use prior to blood culture sampling, although a recent publication from an ongoing prospective cohort study at our centre has demonstrated that non-culturable organisms, such as the Bartonella quintana, are an important cause of BCNIE.[24] Although high rates of BCNIE have been associated with worse outcomes, we did not detect a difference when comparing 6 month mortality in patients with BCPIE and BCNIE (37% vs. 31%; p=0.6).

The common clinical features observed in our cohort were similar to previous reports from South Africa and high-income countries.(.[5,14] The most common symptom on presentation was dyspnoea (90.7%), with fever, pallor, and clubbing the most common clinical signs of IE detected. Osler nodes, Janeway lesions, and Roth spots were rarely detected, although still incorporated in the modified Duke / ESC 2015 clinical criteria.[2,15]

LIMITATIONS

This was a retrospective study exposed to the usual limitations associated with it, such as inclusion bias and incomplete data availability. Ten potential cases were excluded due to incomplete data (11.1% or 10/90).

CONCLUSION

The profile of IE in South Africa has evolved to more closely resemble that observed in high income countries with Staphylococcal predominance and a reduction in underlying RHD, the driver for this reduction is not readily apparent. In many other respects it has remained unchanged over the past 2 decades, affecting a younger, otherwise healthy patient population with a high mortality rate and significant morbidity. Cerebral embolism remains the most frequently occurring embolic complication and is common. BCNIE remains a common entity, making directed treatment decisions and compilation of local organism profiles difficult.

Conflict of interest: none declared.

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A case-based narrative review on the structural myocardial changes associated with systolic dysfunction in severe aortic stenosis

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ABSTRACT

Severe aortic stenosis (AS) is not a disease of the valve only, but one involving the myocardium. Left ventricular systolic dysfunction in severe AS is associated with worse outcomes, despite aortic valve replacement (AVR). This case-based narrative review aims to highlight both the macro- and microscopic structural features of the myocardium in severe classic AS, with a particular focus on differentiating the afterload mismatch group from those with true contractile dysfunction. Left ventricular systolic dysfunction is associated with maladaptive patterns of left ventricular hypertrophy, mid-wall interstitial fibrosis, subendocardial replacement fibrosis secondary to ischaemia and possibly, low-grade chronic inflammation, and myocardial oedema. The underlying molecular signals appear to establish an ongoing cycle of maladaptive remodelling, but the initiating triggers remain poorly understood. Furthermore, features that differentiate those with afterload mismatch from those with true contractile dysfunction have been poorly investigated and further prospective research would provide important insight that could translate to earlier detection of those who may benefit from AVR before irreversible myocardial damage ensues, improved decision-making around management of these patients and the development of novel therapeutic strategies. SA Heart® 2024;21:226-236

INTRODUCTION

Aortic stenosis (AS) is a disease of both the aortic valve and myocardium of the left ventricle (LV).[1,2] With a global prevalence of ± 18 million people, AS accounts for roughly 25% of all valvular heart disease and has a significant impact on patients' quality of lives.[2-4] The commonest causes for AS include rheumatic heart disease (RHD), calcific degenerative disease in the elderly and premature degeneration in congenital bicuspid aortic valves. Calcific degenerative disease in higher-income countries, has largely overtaken RHD as a cause for AS. In lower- and middle-income countries, however, RHD still predominates and remains an important cause for AS.[1-4] The only definitive therapy for AS is aortic valve replacement (AVR) which reverses the mechanical obstruction, in turn, reversing some of the adaptive myocardial changes e.g. left ventricular hypertrophy (LVH).[1,2,5] There are no definitive therapies available to address the impact on the myocardium itself and while it is well established that AVR reduces mortality in AS, the procedure itself is costly, invasive, reserved only for severe cases and carries a high surgical risk for those with left ventricular systolic dysfunction.[6-8]

Left ventricular systolic dysfunction is infrequently encountered in the setting of classic, severe AS.[6,9] The 2 described mechanisms underlying the systolic dysfunction include: (i) true myocardial contractile dysfunction, and (ii) afterload mismatch.[10-15] The current understanding is that for the former, there is irreversible myocardial damage that impedes improvement in post-operative systolic recovery while for the latter, intrinsic myocardial contractility is preserved therefore producing an often prompt, and drastic systolic improvement after AVR.[10-15] Understanding the differences between the drivers, morphological characteristics that signal a transition to decompensation / dysfunction, associated molecular pathways and outcomes for these 2 groups is important for predicting post-AVR responses and for the development of novel diagnostic and therapeutic strategies e.g. early biomarkers or gene / other molecular therapies.

This review aims to:

- Describe the existing literature on the macroscopic structural and haemodynamic features that are associated with left ventricular systolic dysfunction in classic severe AS using various cardiac imaging modalities.
- Understand the histological features and molecular pathways underlying these structural characteristics.
- Identify those features capable of differentiating the 2 broad mechanisms (as described) that lead to systolic dysfunction. The paper comprises 3 main sections based on broad themes derived from the literature; namely, LVH, myocardial fibrosis and myocardial inflammation and oedema.

CASE REPORTS

Two cases of severe AS with left ventricular systolic dysfunction are presented as an illustrative aid to the discussion.

Case 1

A 77-year-old woman presented with new onset pre-syncope, exertional dyspnoea (New York Heart Association class III) and exertional angina (Canadian Cardiovascular Society class II). Coronary angiogram showed unobstructed, normal coronary arteries. Severe AS and left ventricular systolic dysfunction was diagnosed on cardiac imaging. Transthoracic echocardiography showed an aortic valve area of 0.4cm^2, mean transvalvular pressure gradient of 60mmHg and a peak velocity of 5.2m/s. Using cardiac magnetic resonance (CMR) imaging, a volumetric assessment demonstrated a dilated, minimally hypertrophied LV with an indexed LV end-diastolic volume (LVEDVi) of 133ml/m^2, a posterior wall thickness (PWT) of 6mm and an indexed left ventricular mass (LVMi) of 96g/m^2 (Figure 1A). The global systolic function was severely impaired with a left ventricular ejection fraction (LVEF) of 21% (Figure 1A). On tissue characterisation, minimal myocardial fibrosis was detected using T1 mapping (Figure 1C) and late gadolinium enhancement (LGE) imaging (Figure 1E).

Case 2

A 62-year-old woman with a background history of hypertension and diabetes mellitus presented with syncopal episodes on exertion. Additionally, she reported a preceding history of worsening dyspnoea from New York Heart Association class I to III, over a 2- year period. Similarly to Case 1, severe AS and left ventricular systolic dysfunction was diagnosed on cardiac imaging. The aortic valve area measured 0.5cm^2 on transthoracic echocardiography, with a mean transvalvular pressure gradient of 69mmHg and a peak velocity of 5m/s. On CMR, the LV was non-dilated and hypertrophied with a LVEDVi of 81ml/m^2, PWT of 11mm and a LVMi of 103g/m^2 (Figure 1B). The global systolic function was mildly impaired with an LVEF of 41% (Figure 1B). The greater degree of LVH was accompanied by a greater degree of myocardial fibrosis (Figure 1D, 1F).

Left ventricular hypertrophy

The natural history of classic aortic stenosis is well described. The myocardial response to a rising afterload is concentric LVH, characterised by the parallel addition of sarcomeres within cardiomyocytes and a thickened LV.[6,7,9-12,14,16-21] In line with the law of Laplace, this thickening normalises wall stress and maintains an adequate LVEF, implying that the hypertrophy is initially adaptive and beneficial.[6,7,9,10,12,17-20] Should patients survive long term, persistence of the pressure overload eventually drives the ventricle into a state of decompensation and left ventricular dilation, which is considered the end-stage morphology of the disease.[17] Associations between LVH and left ventricular systolic dysfunction have been made; more specifically, that dysfunction may be associated with either inadequate LVH or excessive LVH.

Decade-old research has demonstrated an association between inadequate LVH and left ventricular systolic dysfunction.[22,23] This was observed in Case 1 above. Despite severe AS with high mean gradients, the LV wall thickness remained within normal limits with a marginal increase in LVMi (Figure 1A). As the afterload rises in AS, use of the preload reserve and an increase in myocardial contractility are required to maintain adequate pump performance.[19] Two hallmark studies by Carabello, et al. and Grossman, et al. discovered that AS patients with a decreased LVEF, tended to have lower wall thickness, lower left ventricular mass and higher wall tension, implying that there was insufficient LVH and by extension, a failure to normalise wall stress.[22,23] This finding is physiologically and logically supported, as the addition of sarcomeres ultimately translates to the addition of contractile apparatus. Insufficient LVH would fail to improve myocardial contractility and fail to normalise wall stress, and once preload reserve is exhausted, impairment in pump performance is an inevitable consequence. For some, the LVEF recovers once the loading conditions are reversed through AVR, implying that for these patients, the intrinsic myocardial contractility is preserved – a concept now accepted as afterload mismatch, i.e. a mismatch between the degree of afterload increase and compensatory LVH, putatively at fault for the dysfunction.[22,23] For others, the LVEF fails to recover, and this is attributed to irreversible, "true," contractile

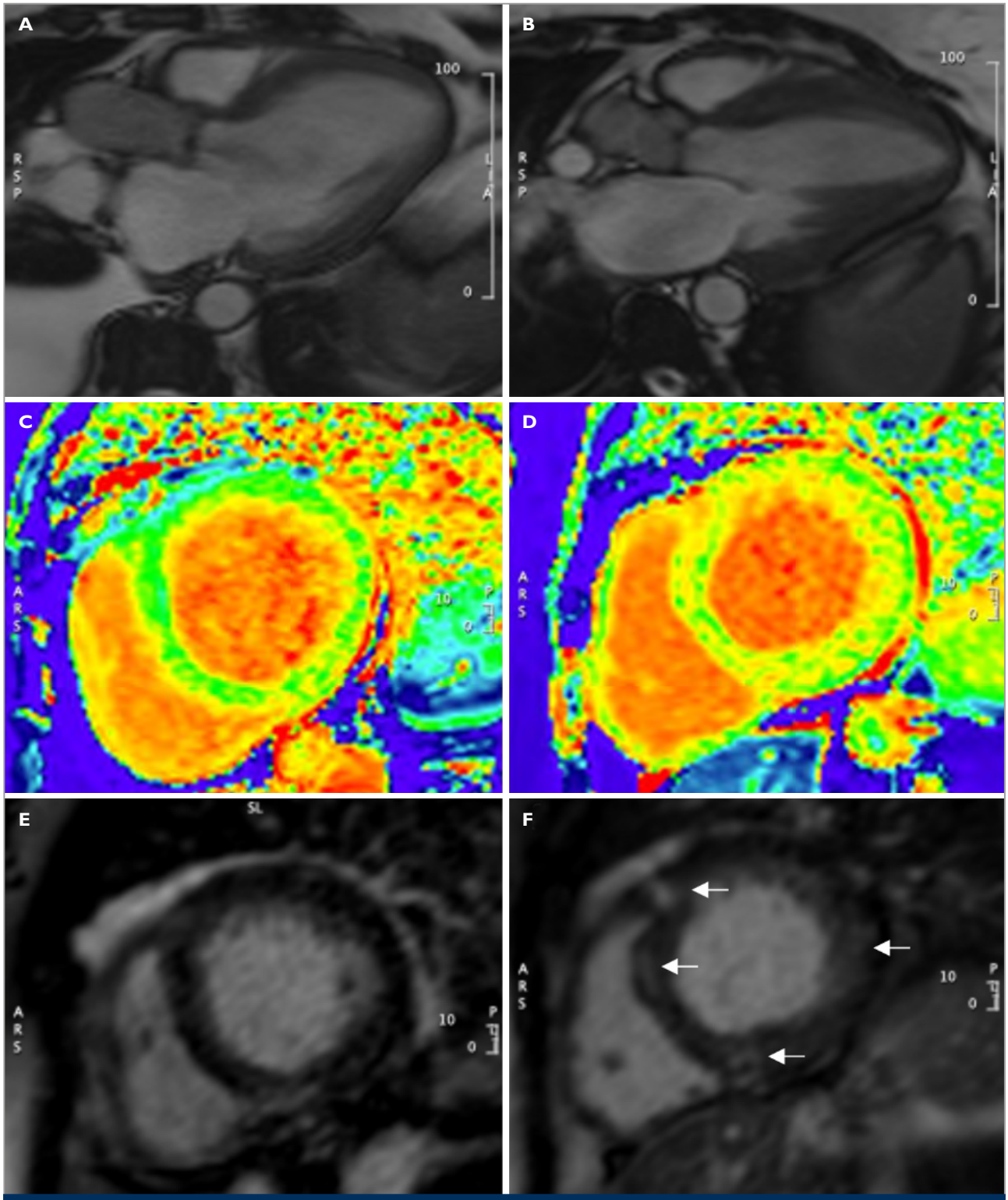

FIGURE 1: CMR images for CASE 1 (left) and CASE 2 (right).
A: End-diastolic cine image (long axis 3 chamber view) of Case 1. LVEF=21%, PWT=6mm, LVMi=96g/m2. B: End-diastolic cine image (long axis 3 chamber view) of Case 2. LVEF=41%, PWT=11mm, LVMi=103g/m^2. C: T1 map (basal short axis view) of Case 1. The global T1 time is within normal range for our magnetic field (1 030ms). D: T1 map (basal short axis view) of Case 2 showing diffuse areas with prolonged T1 time (yellow regions, exceeding 1 100ms). E: LGE image (basal short axis view) of Case 1 demonstrating minimal myocardial fibrosis. F: LGE image (basal short axis view) of Case 2 demonstrating midwall replacement fibrosis in the anterior septum, midwall replacement fibrosis at the RV insertion points and diffuse interstitial fibrosis in the posterolateral wall (indicated by the arrows).

LVEF: left ventricular ejection fraction, PWT: posterior wall thickness, LVMi: left ventricular mass indexed for body surface area, LGE: late gadolinium enhancement, RV: right ventricle.

impairment.[22,23] The factors driving these 2 groups down different pathways was not investigated further at the time, and with advancements in cardiac imaging, the association between left ventricular systolic dysfunction and excessive LVH has since emerged.

A relationship between left ventricular systolic dysfunction and excessive LVH is frequently described in more recent literature. With ongoing pressure-overload, the ventricle continues to hypertrophy. The accepted pathway for how this leads to systolic dysfunction is that the increased muscle mass, together with the increased work required to overcome the high afterload, increases the oxygen demand.[7,9,13,18,24-26] Evidence from perfusion imaging and histology based studies show that endothelial cell damage and capillary loss ensue, leading to impaired myocardial perfusion.[27-29] As the perfusion reserve is depleted, a supply / demand mismatch ensues, leading to ischaemia, cardiomyocyte death, and myocardial fibrosis.[7,9,13,18,24-26] The conclusion that this is the mechanism underlying left ventricular systolic dysfunction is supported by perfusion imaging studies that show an inverse correlation between myocardial perfusion reserve and impaired LV function.[27,29] There are, however, arguments against this theory.

Arguments against this include the observation that excessive LVH in systolic dysfunction is not always accompanied by excess fibrosis or worse function. As illustrated in 2 additional cases below, the degree of LVH is roughly 2-fold higher in Case 4 compared to Case 3, yet the degree of myocardial fibrosis is significantly lower (Figure 2). Secondly, the pattern of fibrosis in those with excessive LVH is not always subendocardial which is expected for ischaemia (Figure 2D). Thirdly, the correlation between the abovementioned histological findings and the degree of LVH was not evaluated in the aforementioned studies, nor the relationship between the degrees of LVH and systolic dysfunction.[27-29] Lastly, whether this theory applies solely to the true contractile dysfunction group, as eluded to in many of these studies, is unclear and cannot be confirmed with the available evidence.

As mentioned, the histological and perfusion imaging studies do not assess the statistical correlation between the degrees of LVH and systolic dysfunction. Similarly, studies using other imaging modalities such as transthoracic echocardiography and / or CMR, infrequently evaluate the correlation and those that do, have collectively, produced conflicting results.[7,13,14,25,30-36] One reason for these conflicting findings may be that most studies capture data that represents a single snapshot of a dynamic process and its evolving structural consequences. Secondly, most of these studies have been designed to evaluate those with severe AS and preserved systolic function. And thirdly, like most processes governed by nature, the underlying molecular pathways leading to LVH are several in number, are complex and dynamic with many signals that have yet to be discovered.

Numerous molecular signals and pathways underlying LVH have been investigated. The molecular milieu clearly differs for those with and without associated left ventricular dysfunction. Beginning at a genetic level, intense genetic reprogramming has been observed in those with left ventricular dysfunction.[37] More specifically, the pattern of gene expression mirrors that of a foetal cardiomyocyte.[37] Downstream of the genetic reprogramming, altered calcium handling, G-protein signalling, reduced capillary density through upregulation of p53 and oxidative stress have been linked to impaired contractility and forward signalling for further LVH, thus establishing a maladaptive cycle.[21,38] Whether some patients are pre-destined for a maladaptive phenotype or whether there is a transition from an initially adaptive phenotype to a maladaptive one, remains unclear. Furthermore, molecular differences between those with afterload mismatch, true contractile dysfunction, and preserved contractile function, and whether one phenotype (afterload mismatch) progresses to another (true contractile dysfunction), have yet to be explored.

Myocardial fibrosis

Myocardial fibrosis, like LVH, is well described in severe AS. The earliest evidence of myocardial fibrosis in AS dates back more than 3 decades, when Krayenbuehl, et al., evaluated myocardial histology on tissue acquired from the anterolateral walls of patients undergoing diagnostic cardiac catheterisation.[39] Since then, several studies have performed similar investigations using basal left ventricular septal biopsies acquired during AVR.[12,14,36,40-47] With the help of Picrosirius Red, Masson Trichrome and Haemotoxylin and Eosin staining techniques, 2 patterns of myocardial fibrosis have been described; namely, diffuse interstitial fibrosis characterised by loose bands of collagen surrounding bundles of cardiomyocytes and replacement fibrosis, identified by dense, focal regions of collagen-containing tissue.[48] The former, has mostly been localised to the myocardial mid-wall and is thought to be a reactive process.[40,44,46,48] The latter, tends to localise within the subendocardium and progressively increases with cardiomyocyte degeneration.[40,43,44,46,48] These histological findings have been corroborated and further characterised through CMR imaging.

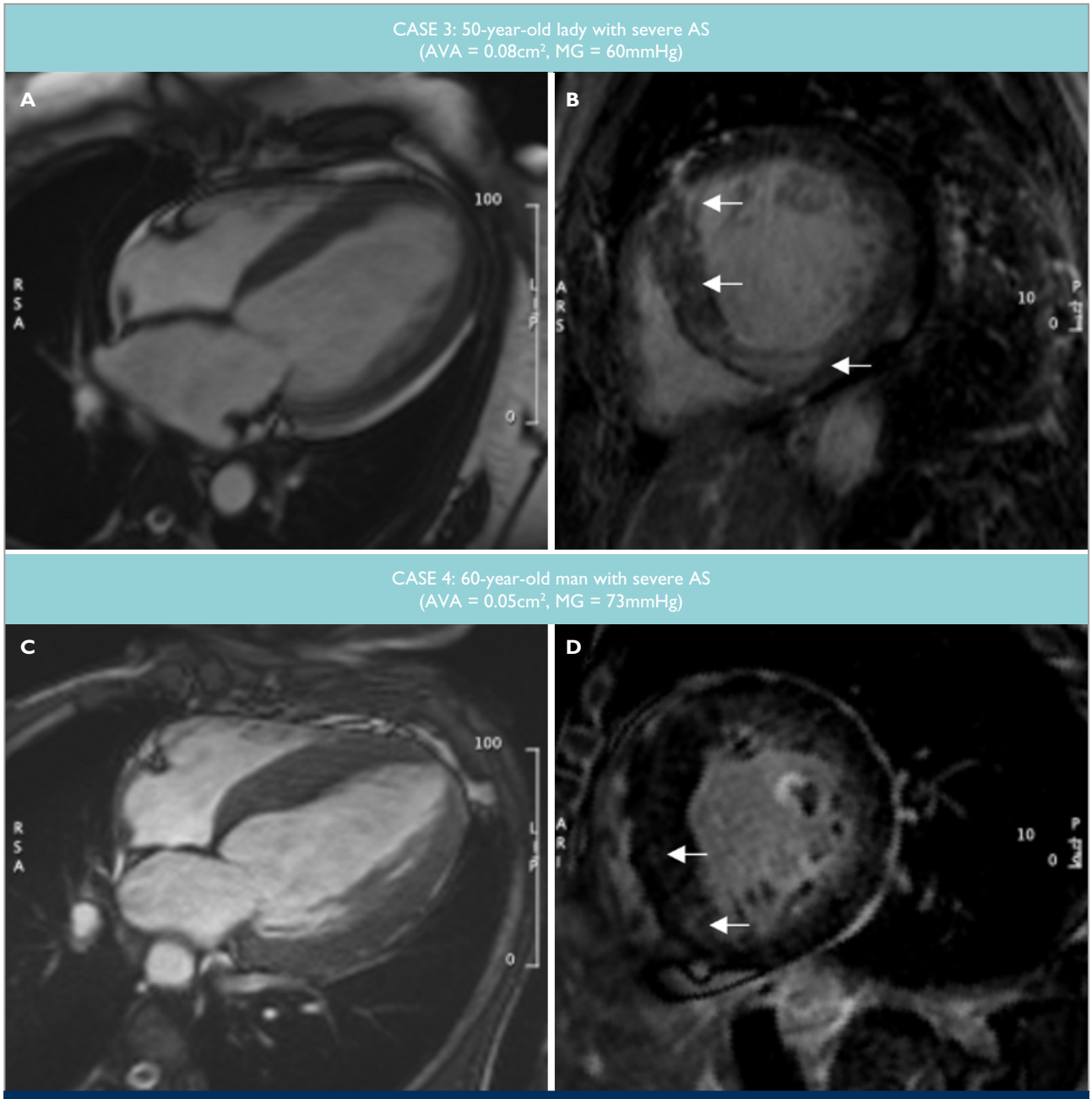

FIGURE 2: CMR images of 2 cases demonstrating variable patterns and degrees of LVH and fibrosis.
A: End-diastolic cine image (long axis 4 chamber view) of Case 3. LVEF=28%, lateral LV wall thickness=6mm, LVMi=125g/m². B: The corresponding LGE image (mid-ventricular short axis view) of Case 3. Arrows indicate midwall replacement fibrosis in the anterior septum and inferior RV insertion point as well as extensive diffuse interstitial fibrosis along the entire septum. C: End-diastolic cine image (long axis 4 chamber view) of Case 4. LVEF=37%, lateral LV wall thickness=14mm, LVMi=237g/m². D: The corresponding LGE image (mid-ventricular short axis view) of Case 4. Arrows indicate a small region of replacement fibrosis in the inferior RV insertion point and diffuse interstitial fibrosis in the septum. The degree of fibrosis, despite excessive LVH, is lower compared to Case 3.

AVA: aortic valve area, MG: mean gradient (transvalvular pressure gradient).

Cardiac magnetic resonance imaging offers a non-invasive approach for the detection of myocardial fibrosis.[49] While endomyocardial biopsy / histopathology remains the gold standard for fibrosis assessment, CMR offers the added benefit of characterising the entire myocardium rather than a single region / segment.[41,43] Delayed contrast imaging / late gadolinium enhancement (LGE) and T1 mapping / extracellular volume (ECV) have been used to identify focal replacement and diffuse interstitial fibrosis respectively.[43,44,47] Using these techniques, a variable pattern of AHA segment involvement has been shown.

Furthermore, there appears to be a predilection for the mid-wall followed by the subendocardium in a non-infarct pattern (spanning different coronary territories and present in those with angiographically proven normal coronary arteries), and a decreasing gradient of fibrosis from base to apex.[32,40,41,43,45,50] Both histology and CMR suggest that a relationship between myocardial fibrosis and left ventricular systolic dysfunction exists.

It is widely accepted that myocardial fibrosis, in classic severe AS, is associated with left ventricular systolic dysfunction and a worse prognosis despite AVR. To our knowledge, no evidence currently exists on how the pattern, distribution and quantity of fibrosis differs between those with afterload mismatch and true contractile dysfunction. Furthermore, no myocardial fibrosis quantity / cut-off exists for predicting left ventricular systolic dysfunction, functional recovery after AVR and / or long-term prognosis. There are several reasons for this. Firstly, most CMR studies exclude those with left ventricular systolic dysfunction. In 2 studies that investigated a wider AS cohort which includes a proportion of cases with left ventricular systolic dysfunction, the fibrotic burden was shown to be higher in those with dysfunction compared to those with normally functioning ventricles.[40,44] Neither of the studies, however, were designed to specifically interrogate those with left ventricular systolic dysfunction therefore limiting their statistical power to detect true differences between those with and without dysfunction. Secondly, while CMR can detect fibrosis, its ability to quantify it proves challenging. Some studies show a good correlation between their CMR based fibrosis quantification and the gold standard technique i.e. biopsy / histology.[40,41,43-47] The techniques used for fibrosis quantification, however, vary. For example, some centres use a manual method for LGE quantification while others use a semi-automated method with varying standard deviations for fibrosis identification and quantification.[32,41] This brings into question the true correlation between CMR based fibrosis quantification and histology. Not only does this hinder the agreement of a quantitative fibrosis cut-off that serves as a reliable predictor of outcomes but also, poses a challenge in terms of comparability across studies.

For myocardial fibrosis to be useful as a predictor of outcomes / prognosis, a quantitative cut-off is necessary for 2 reasons. Firstly, the evidence shows that not all those with left ventricular systolic dysfunction and myocardial fibrosis are destined for a poor prognosis. For example, despite significant diffuse interstitial fibrosis and replacement fibrosis (Figure 1D, 1F) in Case 2, the LVEF recovered to 55% within 3 months after AVR. Secondly, most CMR based studies that identified myocardial fibrosis in severe AS were performed in cohorts with preserved left ventricular systolic function (LVEF >50%). This illustrates the fact that myocardial fibrosis is not a structural feature unique to those with a reduced LVEF or perhaps, highlights the notion that LVEF is a late marker of systolic dysfunction. Speckle-tracking echocardiography and strain analysis show that despite a normal LVEF, there is still a subtle degree of systolic dysfunction in both those with and without myocardial fibrosis.[14,32,42,43] In 2 studies by Hoffman, et al. and Weideman, et al., strain was demonstrably worse in the basal segments where the fibrotic burden was found to be highest thus strengthening the association between myocardial fibrosis and left ventricular systolic dysfunction. In these studies and several others, recovery after AVR tends to be worst in those with the highest fibrotic burden.[31,42]

This contrasts with our local experience where the degree of functional recovery is not always related to the degree of LVH or myocardial fibrosis. For example, in Case 3 where the fibrotic burden was significantly high, the LVEF showed improvement from 28% - 41% after AVR (Figure 2). In Case 4, however, despite a low fibrotic burden, the LVEF failed to recover after AVR (Figure 2). This highlights the fact that the LV response to severe AS and AVR is complex and remains incompletely understood. In addition to these clinical imaging limitations, a knowledge gap also exists in understanding the molecular pathways driving myocardial fibrosis in severe AS.

Signalling from transforming growth factor beta 1 (TGF-ß1) and angiotensin II are considered central components in the development of fibrosis.[51] Their triggering events, however, remain poorly understood. Evidence from stress-perfusion imaging has demonstrated an important inverse association between myocardial perfusion reserve and myocardial fibrosis suggesting a role for ischaemia as a fibrotic trigger.[27,29] The segmental correlation between myocardial hypoperfusion and myocardial fibrosis however, was not reported in these studies and interestingly, a midwall distribution of fibrosis emerged as the predominant pattern.[27,29] This is counter-intuitive as it is well-established that the subendocardial layer of the myocardium remains the most vulnerable to ischaemia-related injury. A limitation highlighted by Steadman, et al., is that this association was illustrated using cross-sectional data thus challenging the true establishment of a temporal relationship between the 2 observations.[29]

An association between AS and cardiac amyloidosis (CA) exists.[52-57] As for the association between myocardial hypo-

perfusion and fibrosis, the temporal or causative relationship between severe AS and CA is unknown.[55] Whether a causative relationship even exists between the 2 conditions remains debatable. The transthyretin (ATTR) subtype accounts for the majority of CA cases in those with severe AS.[52-57] This subtype is known to affect the elderly. Likewise, those with co-existing CA and severe AS are usually over the age of 65.[52-57] Their association therefore, may be an epidemiological chance finding. Nonetheless, it is noteworthy that histological studies consistently show that the extracellular space of the myocardium in CA is shared by both amyloid proteins and fibrosis.[58-60] In a study on CA by Pucci, et al., 100% of endomyocardial biopsies showed interstitial fibrosis as well as subendocardial replacement fibrosis.[58] The prevalence of CA in severe AS varies (4% - 16%) but is exceeded by the prevalence of myocardial fibrosis in AS.[52-57] Therefore, while CA may account for fibrosis in some cases of AS, several other triggers for the fibrosis must also exist.

Other triggers for fibrosis in AS, besides ischaemia and CA, may include haemodynamic / mechanical and / or inflammatory stimuli. The culprit cells responsible for myocardial fibrosis are cardiac fibroblasts; cells that are derived mainly from the epicardium during foetal development and considered quiescent in the healthy adult heart.[51,62,63] During the neonatal period, cardiac fibroblasts undergo population expansion in response to the high left ventricular pressures, a haemodynamic feature that is associated with severe AS and left ventricular systolic dysfunction.[62] This haemodynamic trigger, coupled with TGF-ß1 signalling, may play an important role in inducing fibroblast re-activation and proliferation, and ultimately, promoting fibrosis development. An important source of TGF-ß1 secretion are macrophages and other immune cells.[51] Albeit of low intensity, induction of the inflammatory system through cardiomyocyte signalling, oxidative stress and angiotensin II signalling has been described in several in vivo models of pressure overload.[51] This highlights the importance of considering the impact of inflammation in the development of left ventricular systolic dysfunction in severe AS.

Myocardial inflammation and oedema

Myocardial inflammation and oedema are rarely described in the context of AS pathophysiology. Prior to advanced cardiac imaging, histological studies contributed the most insight into the myocardial structure of AS patients. In addition to cardiomyocyte hypertrophy and myocardial fibrosis, cardiomyocyte degeneration through ubiquitin-related autophagy, oncosis and apoptosis was also observed in cases of left ventricular systolic dysfunction.[39,41,46,47,61] Evidence of myocardial inflammation, on the other hand, was rarely evaluated and / or reported.[39,41,46,47,61] The exception was a study by Hein, et al., where a nearly 3-fold increase in leukocytes, lymphocytes and macrophages was observed in the interstitial space, leading the group to speculate about low grade inflammation potentially contributing towards left ventricular systolic dysfunction.[61] Until recent advancements in CMR techniques that allow for non-invasive myocardial oedema evaluation, this idea was not probed much further in the clinical setting.

Cardiac magnetic resonance imaging, in addition to fibrosis assessment, offers other tools capable of detecting myocardial inflammation and oedema. These include short tau inversion recovery (STIR) imaging and native T1 / T2 mapping techniques.[49,64-66] In 2 tissue characterisation studies that report prolonged native T1 time for severe AS, an inverse relationship between the native T1 and left ventricular systolic function is also demonstrated.[68,69] In both studies, the prolonged T1 time is attributed to the development of myocardial fibrosis.[68,69] Native T1 mapping, however, is not specific to fibrotic detection and may be influenced by increased water content, i.e. oedema.[49,64-66,70] From most papers that report a prolonged native T1 time secondary to fibrosis, information on how oedema is ruled out as a cause for the prolonged T1 is not available.[47,50,68,69] And, for the remainder, fibrosis is concluded as the cause based on concurrent histological evidence of fibrosis from endomyocardial biopsy.[45-47] Amongst these, however, the majority describe a weak or moderate correlation between histology and native T1 and only one demonstrates a strong correlation.[40,45,47] T2 mapping performed in parallel with T1 mapping often serves as a useful arbiter for confirming the presence of oedema in cases where the T1 time is prolonged.

Although T2 mapping is specific for oedema detection, its likelihood of detecting oedema in severe AS may be low. T2 mapping for Cases 1 and 2 showed normal T2 times of 49ms and 50ms, respectively (Figure 3A, 3C). Oedema, in these cases, may not necessarily be ruled out as the sensitivity for oedema detection is lower than its specificity. Additionally, studies showing the high sensitivity of T2 mapping are related to acute inflammation e.g. acute myocarditis or acute myocardial infarction.[66,67] For chronic oedema, on the other hand, the sensitivity of the test decreases to roughly 70% thus introducing the likelihood of missing oedema in the context of severe AS where inflammation is more likely a chronic process.[66] Another consideration for the normal T2 time observed is potential pseudo-normalisation of T2 relaxation by the co-

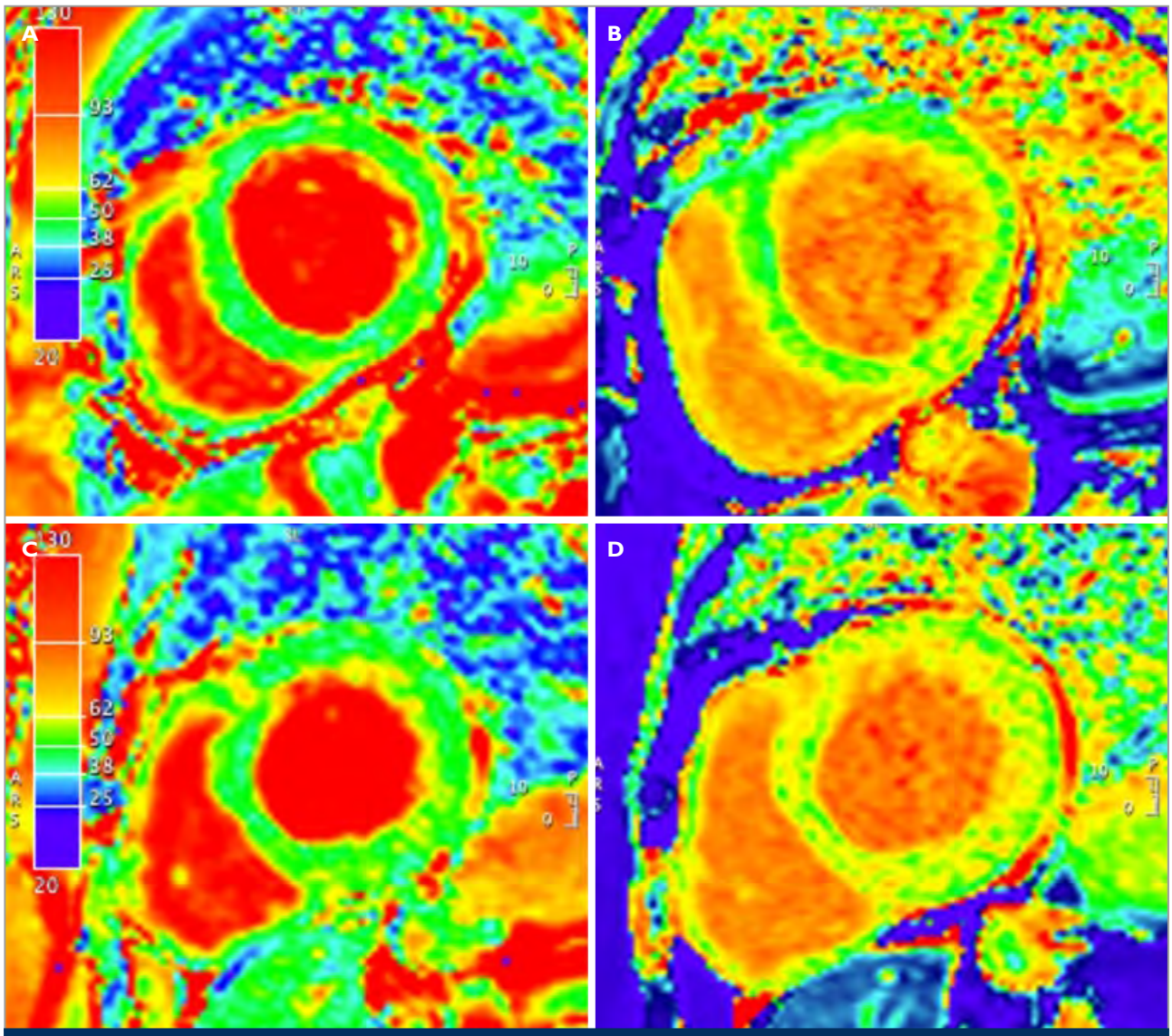

FIGURE 3: T1 and T2 mapping images for CASE 1 (top) and CASE 2 (bottom).
A: T2 map of Case 1 (basal short axis view). Global T2 time is normal (49ms). B: T1 map of Case 1 (basal short axis view). Global T1 time is normal (1 030ms). C: T2 map of Case 2 (basal short axis view). The global T2 time is normal (50ms). D: T1 map of Case 2 (basal short axis view). The global T1 time is markedly prolonged (1 134ms) indicating the presence of diffuse interstitial fibrosis. Despite this finding, the global T2 time remains normal.

existence of myocardial oedema and fibrosis. A recently performed in vivo study by Lee, et al., shows that that myocardial fibrosis in both aged and pressure overloaded mice, is associated with a relative decrease in T2 relaxation compared to their young and healthy counterparts without fibrosis.[71] It is then plausible that the co-existence of myocardial fibrosis and inflammation may falsely normalise the T2 time since it is an averaged measure. This observation has not yet been validated in human studies. Nonetheless, other evidence argues that myocardial inflammation may still form an important component in the pathophysiology of severe AS and LV systolic dysfunction.

The few studies that do report T2 mapping in severe AS, show prolonged T2 relaxation time for AS compared to healthy volunteers.[50,72,73] In one of these studies, prolonged T2 time correlates inversely with the mean transvalvular pressure gradient and in another, with the LVEF.[50,73] These findings suggest that a relationship may exist between inflammation, disease severity and impaired pump performance. This is further consolidated by modern molecular research studies. Tools such as immunohistochemistry and single cell RNA sequencing demonstrate a pro-inflammatory state in patients with severe AS and systolic dysfunction, as well as clusters of immune cells with altered cell signalling in the myocardium.[42,74] While inflammation

and oedema have not been as well characterised as LVH or fibrosis, the existing evidence suggests that further investigation in this regard, is warranted.

Limitations in existing knowledge

Histopathology, cardiac imaging and other basic science investigations have provided valuable insight into the macro- and microscopic myocardial features associated with left ventricular systolic dysfunction in severe AS. In addition, they have allowed for several key areas requiring further investigation, to be identified.

Firstly, most studies have been designed to interrogate the severe AS group with preserved left ventricular systolic function, thus limiting their ability to identify significant clinical characteristics, triggers, thresholds and early features that mark the transition to dysfunction. For example, both inadequate, and excessive LVH have been associated with systolic dysfunction, but a threshold wall thickness or critical left ventricular mass has yet to be investigated, a criterion that might offer clinical use in early decision-making for AVR. Secondly, there is a great paucity in imaging data for the afterload mismatch group and consequently, limited evidence available to understand how this group differs in terms of LVH and / or the type, degree and distribution of myocardial fibrosis. Besides a lack of imaging data for this group, there is also limited evidence on the underlying molecular environment / pathways associated with afterload mismatch. Finally, whether afterload mismatch and true contractile dysfunction are separate entities or form part of a single spectrum has yet to be considered and investigated.

Future prospective longitudinal studies specifically designed to interrogate those with severe AS and systolic dysfunction are needed. Investigating and comparing patients with afterload mismatch to those with true contractile dysfunction would offer important insights into the mechanistic intricacies underlying the dysfunction.

CONCLUSION

Left ventricular systolic dysfunction in severe AS is associated with worse morbidity and mortality both pre- and post-AVR. In this review, evidence from histopathology, cardiac imaging and molecular tools, e.g., enzyme-linked immunoassays for TGF-ß1 detection, was used to understand some of the pathophysiological processes underlying left ventricular systolic dysfunction. The relationship between left ventricular systolic dysfunction and LVH, myocardial fibrosis and myocardial inflammation / oedema has been highlighted. Although this is an important starting point, several gaps in the knowledge remain, including the triggers, structural myocardial features and molecular pathways that differentiate the afterload mismatch group from the true contractile dysfunction group. Furthermore, whether afterload mismatch and true contractile dysfunction are 2 separate scenarios, or whether they fall on a spectrum with one another, remains unknown. Future longitudinal, prospective studies that are better designed to specifically evaluate those with severe AS and left ventricular systolic dysfunction are needed.

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Evaluation of the impact of tricuspid regurgitation on the right ventricle and atrium of the heart caused by pacemaker leads

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ABSTRACT

Introduction: The number of permanent device implantations to treat conduction disorders has dramatically increased over the past decade. The aim of the study was to investigate the development of lead-induced tricuspid regurgitation (TR) after permanent endocardial lead implantation.

Methods: This prospective analytical observational study included 30 adult patients (≥18 years) that qualified for a cardiac pacemaker. Before implantation, demographic and anthropometric data were recorded. A 2D echocardiogram was performed to evaluate TR prior to implantation and at 6-week and 9 - 16-month follow-ups. TAPSE and tissue doppler imaging (RV S') were used to evaluate right ventricular function and basal and mid-right ventricular (RV) diameter and right atrial (RA) area.

Results: The TR grade significantly worsened in 46% of patients from baseline to the 9 - 16-month post-implantation. However, the TR was not clinically significant. RV function, RV dimension and RA area remained within normal reference ranges. There was a negligible correlation between TR at baseline vs. the 9 - 16-month follow-up for TAPSE, RA area, basal and mid-RV diameter.

Conclusion: After long-term follow-up, TR grade worsened after lead implantation, but not to clinically significant (moderate or severe) levels.

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INTRODUCTION

Over the last decade, the number of implantable cardiac devices has increased rapidly. The increased use of pacemaker implantation can be attributed to an ageing population.[1] Therefore, the impact of endocardial implantations on the tricuspid valve is becoming increasingly important. Although tricuspid regurgitation is a common valvular lesion, it typically results from either a physiological functional or structural abnormality.[2] During the 1980s, Gibson was the first to describe the increase in lead-induced TR coincident with the use of implantable devices.[3]

Lead-induced tricuspid regurgitation (TR) is a growing concern worldwide due to the rapid increase in the use of cardiac conduction devices, for example, permanent pacemakers (PPM), implantable cardiac defibrillators (ICD) and biventricular pacemakers (BIV)].[4-6] Lead-induced tricuspid regurgitation is defined as the echocardiographic / clinical situation where tricuspid regurgitation occurs or is aggravated by implantation of a pacemaker / defibrillator lead that transverses the tricuspid valve.[7] PPM or ICD leads can damage the tricuspid valve (TV) and may result in severe symptomatic TR with clinical sequelae, including fatigue and exercise intolerance due to low cardiac output.[8] Moderate and severe TR is associated with a poor prognosis.[6] Some studies found that permanent endocardial lead implantation can lead to TR,[9-11] while others reported that lead-induced TR does not worsen after cardiac device implantation, but may develop or worsen later on during the chronic phase of TR.[1,12-14]

The aim of the study was to investigate whether pacemaker leads implanted in the right side of the heart resulted in lead-induced tricuspid regurgitation, and whether right ventricular size, right atrial size and right ventricular function were affected.

METHODS

This prospective observational study was conducted at a private cardiology practice in the Western Cape, South Africa. Thirty adult patients (≥18 years) that qualified for cardiac pacemaker implantation were included in the study. The indication for

pacemaker implantation was based on the American College of Cardiology / American Heart Association Classifications.[15] Patients with pre-existing TR (moderate to severe), Ebstein anomaly, infective endocarditis, carcinoid syndrome, endomyocardial biopsy, chest trauma, rheumatic fever and congenital heart defects were excluded.

Demographic (age, gender, race, and ethnicity) and anthropometric data (weight, height, and body mass index [BMI]) were recorded before clinical implantation. The indication for implantation, type of leads used, pacemaker type, and programme mode was recorded during implantation.

A 2D echocardiogram was performed to evaluate TR prior to implantation (baseline) and at 6-week and 9 - 16-month follow-up using vena contracta. Echocardiography was performed according to the British Society of Echocardiography guidelines.[16] Right ventricular function was evaluated using tricuspid annular plane systolic excursion (TAPSE) and tissue doppler imaging (right ventricular peak systolic velocity, (RV S'). RV'S were only recorded at 6-week follow-up. Two patients were lost to follow-up at 9 - 16 months.

ETHICS AND STATISTICS

Ethical approval was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State, South Africa (ETOVS nr: HSD2016/1441). All statistical analysis was done using Stata statistical software (Version 13.1; Stata Corp, College Station). Mean with standard deviation (SD) (data normally distributed) or median with interquartile range (IQR) (data not normally distributed) was used to summarise continuous variables. Frequencies and percentages were used to summarise categorical variables. A p-value of less than 0.05 was regarded as statistical significant.

RESULTS

The median age and BMI of the patients were 72 years and 28.9kg/m^2, respectively. Most patients were classified as overweight (n=11, 36.67%), obese grade I (n=11, 36.67%) and obese grade II (n=2, 6.67%). An equal amount of male and female patients were included (n=15) with no statistically significant differences in age, height and BMI. As expected, the mean weight significantly differed between males and females (p=0.037) (Table I).

Sick sinus syndrome (SSS) was the most frequent indication for pacemaker implantation, which included sick sinus syndrome with atrial fibrillation and syncope (n=22; 73%) followed by ventricular tachycardia (n=2; 6.67%) and 3rd degree heart block (n=2; 6.67%). Medtronic pacemakers were predominantly implanted (53.3%), followed by Biotronik (46.7%). The most frequently used leads were 5076-52/5076-58 from Medtronic (30%) and Solia S53 / Solia S60 from Biotronik (30%). All the pacemaker leads were (screw-in) active fixation leads. Ventricular pacing was performed in 93% and atrial pacing in 97% of the study population.

TABLE I: Demographic and anthropometric data.

Variable	n (%)	Median	Q1	Q2	p-value
Age (years)	**30**	**71**	**65.75**	**82**	
Age (Female)	15 (50%)	78	66	83	0.403
Age (Male)	15 (50%)	70	65	79	
Height (cm)	**30**	**170**	**162.75**	**181**	
Female	15 (50%)	168	161	173	0.013
Male	15 (50%)	178	168	184	
Weight (kg)	**30**	**83**	**72.25**	**97**	
Weight (female)	15 (50%)	79	64	84	0.037*
Weight (male)	15 (50%)	92	74	97	
BMI (kg/m^2)	**30**	**28.9**	**25.3**	**32.4**	
BMI (female)	15 (50%)	28.7	23.9	32.5	0.962
BMI (male)	15 (50%)	29.1	25.9	32.3	

*SD: standard deviation, %: percentage, cm: centimetres, kg: kilogram, BMI: body mass index, kg/m^2: kilogram force per square metre. *statistical significance <0.05.*

TRICUSPID REGURGITATION

Fourteen patients (47%) presented with no TR, 15 (50%) with trace TR and 1 (3%) with mild TR at baseline. A significant difference in TR grade was calculated between baseline and 6-week follow-up (n=30; p=0.018) and baseline and 9 - 16-month follow-up (n=28; p=0.002) (Table II).

RIGHT VENTRICULAR FUNCTION

The mean RV ventricular peak systolic velocity (m/s) was normal (≥9cm/s) at baseline and at 6-week follow-up in all patients, indicating normal RV long-axis systolic function.[17] The RV peak systolic function at baseline and 6-week follow-up was comparable (p=0.728) (Table III).

Mean TAPSE was normal at baseline, 6-week and 9 - 16-month follow-up (≥16mm). The mean TAPSE at baseline and 6-week follow-up values were comparable (23.53mm vs. 23.33mm) and did not differ significantly (p=0.527). However, the mean TAPSE differed significantly from baseline to 9 - 16-month follow-up (mean 23.53 vs. 22.68; p=0.023) (Table III).

RIGHT VENTRICLE LINEAR DIMENSION

Basal (RVD1) and mid-cavity right ventricle linear dimension measurement (RVD2)

The mean RVD1 at baseline, 6-week and 9 - 16-month follow-up was within the normal reference range (females ≤43mm; males ≤47mm).[16] The RVD1 increased significantly from baseline to 6-week follow-up (p=0.002) and from baseline to 9 - 16-month follow-up (p=<0.001). The RVD1 in female and male patients increased significantly from baseline to 6-week follow-up (p=0.018 and 0.030). However, the RVD1 significantly increased from baseline to 9 - 16-month follow-up in male patients (p=0.002) (Table IV).

The mean RVD2 at baseline, 6-week and 9 - 16-month follow-up for the female and male patients were within normal limits (females ≤35mm; males ≤ 42mm).[16] The mean RVD2 increased significantly from baseline to 6-week and 9 - 16-month follow-up in both groups (p<0.05).

RIGHT ATRIUM AREA

The mean right atrial area for female and male patients was within the normal range (females ≤19cm^2; males ≤22cm^2)[16] (Table V). The RA area increased significantly from baseline to 6-week follow-up (p=0.004) and from baseline to 9 - 16-month follow-up (p=0.002). The male patients showed a significant increase in the RA area from baseline to 6-week follow-up (p=0.026) and from baseline to 9 - 16-month follow-up (p=0.012), but the female patients not (p>0.05).

Correlation of TR with RV peak systolic velocity, TAPSE, right atrium area, RVD1 and RVD2

TR progressed from none or trace (baseline) to mild (9 - 16-month follow-up) in 7 (23%) patients (Table VI). The increase in TR severity was correlated with TAPSE, right atrium area, RVD1 and RVD2 at the 9 - 16-month follow-up.

There was a negligible correlation (0.00 to 0.30; 0.00 to -0.30) between TR baseline vs. the 9 - 16-month follow-up for TAPSE, RA area, RVD1 and RVD2 (<0.3; <-0.3) (Table VII).

DISCUSSION

The study aimed to investigate the development of lead-induced TR after permanent pacemaker implantation. The primary indication for pacemaker implantation was SSS and most patients were either overweight or obese. TR progressed from baseline to 6-week and 9 - 16-months in 13 patients, but no patients demonstrated moderate to severe TR after follow-up.

The study population was of advanced age (71 years), with females slightly older than males at presentation. The BMI of 80% of patients was classified as either overweight or obese I and II. Obesity is a modifiable risk factor for the development of cardiac disease and is a rapidly growing problem seen in modern-day societies.[18] Excessive amounts of adipose tissue contribute to haemodynamic and metabolic changes. The total blood volume and cardiac output increase with a higher body mass index and are associated with altered cardiac morphology and function, including the development of right ventricular (RV) dilation and dysfunction.[18]

Niazi, et al. (2020)[19] studied 153 patients receiving permanent pacemaker implantations and 15.8% of patients that presented with TR had a BMI >30kg/m^2. In this study, 13 patients (43%) had a BMI >30kg/m^2, of which 3 patients (4.3%) had increased TR after a 6-week follow-up and 6 patients (21.4%%) had increased TR after a 9 - 16-month follow-up. However, according to Attanasio, et al. (2017),[20] CIED implantation can be safely achieved in obese patients with a BMI >30kg/m^2.

CLINICAL INDICATION FOR PACEMAKER IMPLANTATION

SSS, including those with atrial fibrillation and syncope, was the most frequent indication for pacemaker implantation. In a study

TABLE II: Tricuspid regurgitation (TR) grade at baseline, 6-week and 9 - 16-month follow-up.

TR	n (%)	None	Trace	Mild	p-value
Baseline	30 (100%)	14 (46.7%)	15 (50%)	1 (3.3%)	
6-week follow-up	30 (100%)	9 (30%)	17 (56.6%)	4 (13.3%)	0.018*
9 - 16-month follow-up	28 (93%)	6 (21.4%)	14 (50%)	8 (28.6%)	0.002*

*mild TR: <0.3cm, trace TR: mild TR not met, but subjectively present. *statistical significance <0.05.*

TABLE III: RV peak systolic velocity and TAPSE at baseline, 6-week and 9 - 16-month follow-up.

Parameter	Mean ± SD	Range (Min-max)	p-value
RV peak systolic velocity (m/s)			
Baseline (n=30)	0.12 ± 0.02	0.1 - 0.19	0.728
6-weeks follow-up (n=30)	0.12 ± 0.02	0.1 - 0.17	
TAPSE (mm)			
Baseline (n=30)	23.53 ± 2.45	19 - 32	-
6-week follow-up (n=30)	23.33 ± 2.71	18 - 32	0.527
9 - 16 months follow-up (n=28)	22.68 ± 3.04	17 - 32	0.023*

*SD: standard deviation, min: minimum, max: maximum, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion. *statistical significance <0.05.*

TABLE IV: RVD1 and RVD2 per study group and for male and female patients.

Parameter	n	Mean ± SD	Range (min-max)	p-value
RVD1 (mm) (study group)				
Baseline	30	34.97 ± 3.71	27 - 44	-
6-week follow-up	30	36.5 ± 3.21	30 - 44	0.002*
9 - 16-month follow-up	28	37 ± 3.40	30 - 44	<0.001*
Female				
Baseline	15	35.20 ± 4.25	30 - 44	-
6-week follow-up	15	36.47 ± 3.64	30 - 44	0.018*
9 - 16-month follow-up	14	36.14 ± 3.84	30 - 44	0.088
Male				
Baseline	15	34.73 ± 3.22	27 - 40	
6-week follow-up	15	36.53 ± 2.85	32 - 42	0.030*
9 - 16-month follow-up	14	37.85 ± 2.77	33 - 43	0.002*
RVD2 (mm) (study group)				
Baseline	30	30.1 ± 4.20	22 - 37	-
6-week follow-up	30	32.23 ± 2.86	26 - 38	<0.001*
9 - 16-month follow-up	28	32.39 ± 2.75	26 - 37	<0.001*
Female				
Baseline	15	30.20 ± 4.70	22 - 37	-
6-week follow-up	15	32.47 ± 3.00	28 - 38	0.021*
9 - 16-month follow-up	14	32.29 ± 2.55	29 - 37	0.011*
Male				
Baseline	15	30.00 ± 3.82	24 - 37	-
6-week follow-up	15	32.00 ± 2.80	26 - 37	0.006*
9 - 16-month follow-up	14	32.50 ± 3.03	26 - 37	0.003*

*SD: standard deviation, min: minimum, max: maximum, RVD1: Basal right ventricular dimension, RVD2: Mid-cavity right ventricular dimension. *statistical significance <0.05.*

TABLE V: RA area per study group and for male and female patients.

Parameter	n	Mean ± SD	Range (min-max)	p-value
RA area (cm²)				
Baseline	30	15.43 ± 2.42	10.4 - 20	-
6-week follow-up	30	16.65 ± 2.79	12 - 25	0.004*
9 - 16-month follow-up	28	16.86 ± 2.81	12 - 24	0.002*
Female				
Baseline	15	14.97 ± 2.05	12 - 20	-
6-week follow-up	15	16.21 ± 3.04	12.9 - 25	0.072
9 - 16-month follow-up	14	16.28 ± 3.35	12.4 - 24	0.685
Male				
Baseline	15	15.9 ± 2.73	10.4 - 19.7	-
6-week follow-up	15	17.09 ± 2.55	12 - 20.8	0.026*
9 - 16-month follow-up	14	17.44 ± 2.11	12 - 20.1	0.012*

*SD: standard deviation, min: minimum, max: maximum, RA: right atrium. *statistical significance <0.05.*

TABLE VI: Patients demonstrating worsening TR from baseline to 9 - 16-month follow-up and corresponding TAPSE, RA area, RVD1 and RVD2.

Patient number	TR baseline	TR 9 - 16-month follow-up	TAPSE baseline	TAPSE 9 - 16- month follow-up	RA area base-line	RA area 9 - 16-month follow-up	RVD1 baseline	RVD1 9 - 16-month follow-up	RVD2 baseline	RVD2 9 - 16-month follow-up
4	Trace	Mild	23.0	23.0	16.1	15.8	37.0	37.0	34.0	33.0
5	Trace	Mild	23.0	23.0	20.0	20.4	44.0	44.0	37.0	37.0
7	Trace	Mild	24.0	24.0	14.1	17.6	34.0	43.0	24.0	31.0
9	Trace	Mild	25.0	25.0	19.2	18.5	40.0	40.0	37.0	37.0
22	Trace	Mild	23.0	23.0	16.0	16.0	36.0	36.0	31.0	31.0
23	Trace	Mild	20.0	19.0	12.0	12.0	27.0	33.0	26.0	29.0
24	None	Mild	24.0	17.0	15.5	24.0	32.0	35.0	29.0	33.0
Mean			**23.14**	**22.00**	**16.13**	**17.76**	**35.71**	**38.29**	**31.14**	**33.00**

TR: tricuspid regurgitation, TAPSE: tricuspid annular plane systolic excursion, RA: right atrium, RVD1: Basal right ventricular dimension, RVD2: Mid-cavity right ventricular dimension.

TABLE VII: Summary of correlation coefficients for 7 patients demonstrating worsening TR from baseline to 9 - 16-month follow-up for TAPSE, RA area, RVD1 and RVD2.

	TAPSE	RA Area	RVD1	RVD2
TR baseline versus 9 - 16-month follow-up	-0.2566	0.2558	0.2741	0.2306

Correlation coefficients of zero and near to zero indicate no correlation between the 2 variables.

conducted by Dalia, et al. (2020), sinus node dysfunction (SND) and high-grade atrioventricular (AV) block were the most common indications for permanent pacemaker implantation.[21]

LEAD-INDUCED TRICUSPID REGURGITATION

Most patients' TR grade at baseline was either none or trace (97%). Mild TR was reported in 13.3% of patients after 6-week follow-up and in 28.6% of patients after 9 - 16-month follow-up. Although the TR grade progressed significantly from baseline to 6-week and 9 - 16-month follow-up, none of the patients' TR grading progressed to clinically relevant moderate or severe TR. These results concur with other studies that also reported worsening of TR after pacemaker implantation.[5,11,12] In 2020, Nadar and co-workers reported a progression in TR at 12-

month follow-up after patients received a pacing lead across the tricuspid valve (TV).[6] The patients also demonstrated an increase in the incidence of right heart failure. The most likely explanation for the progression of TR is the mechanical effect of the lead as it crosses the TV, leading to mal-coaptation and interference with valve function. Fibrosis and adhesions also contribute to valve dysfunction, which can occur as early as 5 days after implantation because of the body's reaction to a foreign object.[6]

Discussions on lead-induced TR development and progression after pacemaker implantation remain controversial. The current body of evidence regarding symptomatic TR after lead implantation seems to be based mainly on case reports and observational studies.[2] Some reports confirm the development of lead-induced TR after pacemaker implantation,[6,9,11,19,22,23] while other do not.[1,12-14]

Anvardeen, et al. (2019) documented a 30% increase in TR after 1-year follow-up and reported that endocardial lead interference of the tricuspid leaflet was a predictor for new or progressive TR.[24] They also indicated that the lead position, nature of the lead, patient factors such as age and gender, atrial fibrillation, and RV dyssynchrony, measured by the percentage of RV pacing, were not associated with TR development.

None of the patients in this study developed moderate or severe TR after 9 - 16-month follow-up.

Right ventricular peak systolic velocity

The RV peak systolic velocity did not differ significantly between baseline and 6-week follow-up (p=0.728). All the measurements were within the normal reference limit and concluded that RV function (RV S') was not negatively influenced by pacemaker-lead implantation. These findings are in keeping with other Silva, et al. (2007),[25] Agarwal, et al. (2009),[5] Núñez-Gil, et al. (2011)[26] and Chen et al. (2013).[27]

In 2011, Núñez-Gil and co-workers included 85 patients in a study using standard pacemaker indications. After pacemaker implantation, echocardiography was used to evaluate RV function. RV apical pacing did not affect RV systolic function, despite induction of electromechanical dyssynchrony.[26]

Tricuspid annular plane systolic excursion (TAPSE)

TAPSE was used to evaluate RV systolic function. The results confirmed that RV function was not influenced by pacemaker lead implantation after a 6-week and 9 -16 -month follow-up. All TAPSE measurements (baseline, 6-week and 9 - 16-month follow-ups) were within the normal reference range of ≥16mm[17] and no RV systolic dysfunction was documented. The mean baseline and 6-week follow-up TAPSE values were comparable and did not significantly differ (p=0.527). However, when comparing the mean baseline TAPSE with that of the 9 - 16-month follow-up, a significant decrease in TAPSE was noted (within normal reference range, p=0.023). These results concur with results reported in literature.[9,28,29]

In 2012, Porapakkham, et al. reported that RV dysfunction is not commonly seen after pacemaker implantation.[30] They used 2D echocardiography to analyse RV function (TAPSE and S' velocity) with a mean follow-up of 6.4 years. They documented that only 4% of patients had RV dysfunction (normal TAPSE ≥16mm and S' velocity ≥9cm/s). The site of pacing, pacing mode and percentage of ventricular pacing did not influence right ventricular function.[30]

However, in 2020, Nadar, et al. reported a decline in TAPSE from baseline to late follow-up. They reported that the presence of a pacemaker lead across the TV led to the development of new TR or the worsening of pre-existing TR and was associated with an increase in RV size, deterioration of RV function, and an increase in PA pressure. TAPSE (mm) decreased from 1.87 ± 0.44 to 1.68 ± 0.42 over a period of 12 - 24 months.[9]

RV dimensions and right atrial size

The RVD1 measurement increased significantly from baseline to 6-week follow up in the female patients and from baseline to 6-week and 9 - 16-month follow-up in the male patients. Both males and females demonstrated a significant increase in RVD2 size from baseline to 6-week and from baseline to 9 - 16-month follow-up. Only the male patients showed a significant increase in the RA area from baseline to 6-week follow-up and from baseline to 9 - 16-month follow-up. However, it is still important to note that all mean RVD1 and RVD2 measurements were within the normal reference limits (sex-specific ranges used).

Sinkar, et al. (2021) documented no increase in RV parameters (e.g. RV length, basal-diameter and mid-diameter) and RA size after a 6-month follow-up after the insertion after PM implantation. According to the authors, a follow-up period of 6 months may be too short to reveal changes in RV and RA dimensions.[29]

In 2015, Arabi, et al. prospectively assessed the effect of trans-tricuspid placement of PPM, ICD and CRT leads in 41 patients.[31] The RV diameter showed a progressive increase after cardiac device implantation after a 12-month follow-up when compared to baseline measurements. Both the RVD1 and RVD2 also increased from baseline to the 9 - 16-month follow-up reported a significant increase in the RA minimum diameter from baseline to the 12-month follow-up (40.4 ± 8.7cm vs. 43.1 ± 7.6cm, $p<0.05$). The RA diameter also increased in this particular study from baseline to the 9 - 16-month follow-up (15.4 ± 2.4cm^2 vs. 16.9 ± 2.8cm^2) and showed a significant difference ($p<0.05$). None of the patients in the Arabi, et al. (2015) study showed deterioration in the development of clinical right-sided heart failure after cardiac device implantation. According to Arabi, et al. (2015) the follow-up period of 12 months was too short to observe significant changes in the echocardiographic parameters, which concur with the results of this specific study.

Nemoto, et al. (2015) raised an important point that mild TR comprises early tricuspid annular dilation and right / left atrial enlargement.[32] Atrial volume and tricuspid annular dilation are early and sensitive indicators of tricuspid regurgitation significance. RV enlargement occurs in the later stages with lead-induced TR. However, each of these effects occur in conjunction with TR severity. None of the patients that presented with TR warranted clinical treatment after lead-induced implantation in our study. At most, after 9 - 16 months, patients presented with only mild TR. The fact that the TR was not moderate to severe after 9 - 16-month implantation could explain why the RV and RA did not increase to abnormal clinical values.

The increase in TR severity was compared with TAPSE, right atrium area, RVD1 and RVD2 at the 9 - 16-month follow-up. There was a negligible correlation (0.00 to 0.30; 0.00 to -0.30) between TR baseline vs. the 9 - 16-month follow-up for TAPSE, RA area, RVD1 and RVD2 (<0.3; <-0.3).

STUDY LIMITATIONS

A small sample size limits the study. A follow-up time of 9 - 16 months may not be adequate to evaluate the impact of pacemaker lead-induced tricuspid regurgitation. An adequately powered prospective study with a longer follow-up period will contribute much to the knowledge base of this topic.

CONCLUSION

Lead-induced TR is a growing concern worldwide, as can be seen in the rapid increase in the usage of implantable devices to treat cardiac conduction disorders. The TR grade deteriorated in almost half of the patients from baseline to long-term follow-up. None of the patients developed clinically significant moderate or severe TR after pacemaker implantation. After long-term follow-up, RV function, RV dimensions, and RA area remained within the normal reference limits. This study provided baseline information within the South African context on the development of lead-induced TR.

Conflict of interest: none declared.

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Short-term outcomes of secondary tricuspid regurgitation after left-sided heart valve surgery

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BACKGROUND

Secondary tricuspid regurgitation (TR) is a common manifestation of valvular heart disease, often co-existing with left-sided valvopathies.[1] Historically, a conservative strategy was recommended for the majority of secondary TR as it was believed that most cases would resolve with treatment of the left-sided disease, when followed by decrease in pulmonary arterial systolic pressure.[2-5] Recent evidence suggests that this may indeed be the case with recurrent or progressive TR being uncommon after isolated mitral valve (MV) surgery for degenerative disease.[6] Furthermore, this is not limited to isolated MV surgery as 20% of patients undergoing combined mitral and aortic valve (AV) surgery will experience spontaneous improvement of TR within 6 months.[7] However, there is evidence that secondary TR does not always resolve. It can be a progressive disease that may worsen over time and is associated with morbidity, mortality, and poor functional status.[1,3-5,8-11] In particular, higher grades of TR (moderate or severe) correlate with worse clinical and functional outcomes.[12] The poorer outcomes associated with worsening TR severity have been demonstrated to be independent of pulmonary artery pressure or right ventricular (RV) dysfunction.[13]

ABSTRACT

Background: Secondary tricuspid regurgitation (TR) is a common finding in patients undergoing surgery for left-sided heart valve disease. The indications for concomitant tricuspid valve (TV) repair have been progressively expanded based on data suggesting adverse sequelae for patients in whom secondary TR is not treated.

Method: This was a prospective observational study of patients undergoing left-sided valve surgery with at least mild TR. Eighty-three patients were enrolled between July 2019 - April 2021. Patients received either conservative management (no TV repair) or concomitant TV repair (TV repair) based upon a guideline-directed, multidisciplinary team approach. Primary outcomes were freedom from recurrent TR, poor functional status, and mortality at 6 months. The secondary outcomes were to identify predictors of recurrent TR and compare no TV repair vs. TV repair outcomes in patients with moderate or severe pre-operative TR.

Results: The mean age was 49 ± 15.5 years and 51.8% (43 of 83) were female. Thirty-seven (44.6%) had rheumatic heart disease. The most common procedures involved the mitral (50.6%) and aortic (28.9%) valves in isolation. Additional procedures were performed in 33 (39.8%) patients, including resection of the left atrial appendage in 21 (63.6%). Pre-operative moderate or severe TR was present in 34 (40.9%) patients, and TV repair was performed in 9 (10.8%) patients who all received rigid ring annuloplasty. At 6 months the 56 patients (67.5%) were free of significant TR, 14 (16.9%) were in a poor functional state and 72 (86.7%) were alive. Suggested predictors of recurrent TR at 6 months were female gender (OR 9.9, p=0.04), rheumatic left-sided valvopathy (OR 14.4, p=0.02), and elevated right ventricular systolic pressure (OR 1.1, p<0.01). An exploratory sub-group analysis did not reveal any primary outcomes differences between no TV repair vs. TV repair at 6 months, despite the latter group demonstrating more high-risk features.

Conclusion: Guideline-directed, multidisciplinary team approach for the management of secondary TR associated with left-sided valve disease produced good overall short-term outcomes that appeared similar whether or not the TV was repaired. Prospective studies with long-term outcomes are required to determine the optimal treatment strategy for secondary TR in patients undergoing left-sided valve surgery.

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Regardless of the severity, untreated pre-operative TR may either fail to improve or progress after left-sided valve surgery in a significant number of patients.[7,10] Current guidelines reflect this reality, and have adopted a more aggressive management approach toward secondary TR.[14,15] These guidelines suggest treating both severe and less-than-severe TR, and incorporate symptomatology and tricuspid valve (TV) morphology into the algorithm. The treatment of less-than-severe grades of TR with concurrent TV repair is supported by evidence that suggests improved RV reverse remodeling and reduced heart failure symptoms, without increasing operative risk.[3]

Despite these factors, only 80% and 40% of severe and less-than-severe cases of secondary TR are repaired according to the Society for Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD).[16] The reason for this may be that the evidence for long term benefit after concomitant TV repair is relatively limited.[17] It remains uncertain whether concomitant TV repair imparts a meaningful improvement to functional class or survival.[9,18,19] Furthermore, significant TR after TV repair is not uncommon with up to 9% of patients experiencing early moderate or severe TR.[20] Given these factors it is not surprising that many surgeons do not concomitantly repair the TV during left-sided valve surgery.[21] We aimed to determine the short-term outcomes of patients with secondary TR undergoing left-sided valve surgery by prospectively enrolling patients scheduled for surgery.

METHOD

Study design

This was a prospective observational cohort study of consecutive patients undergoing left-sided valve surgery at Tygerberg Hospital in Cape Town, South Africa. Eighty-three patients were enrolled between July 2019 - April 2021. Inclusion criteria included all patients older than 13 years who received repair or replacement of the MV and or the AV or aortic root, with at least mild TR. Exclusion criteria included none or trace TR, primary TV disease (based on clinical features and echocardiography), tricuspid stenosis, presence of pacemaker leads through the tricuspid valve, and redo surgery. Patients who had conservative management of TR formed the no TV repair group, whereas those who had concomitant repair of the TV formed the TV repair group.

Study procedures

Treatment approach

Patients were referred for surgery utilising the weekly heart team meeting. Members of the team included 2 cardiothoracic surgeons, 1 of whom was fellowship trained in structural heart disease, 4 cardiologists with both imaging and structural heart expertise, and 1 electrophysiologist. Patients who were accepted for left-sided valve surgery had routine assessment of the TV performed. The decision to recommend conservative treatment of the TV vs. concomitant TV repair was based upon a combination of internationally accepted guidelines and expert opinion at our centre. In summary these included severe TR (Class I); or less-than-severe TR with dilated tricuspid annulus (TA) (≥40mm or ≥21mm/m^2), or previous right heart failure (RHF), or RV dilatation (Class IIa).[14,15] Other features of TV morphology that were assessed included tenting height (distance between the coaptation point and the annular plane), and tenting area (area contained within the TV leaflets and the annular plane). Once a consensus was reached for each case, a recommendation was made and documented in the clinical notes. If the surgery differed from this initial recommendation the reasons for this were documented in the operative notes. There were no such cases in this study.

Operative approach

The operative approach was median sternotomy with cardiopulmonary bypass (CPB), mild systemic hypothermia and cold blood cardioplegia. For MV replacement part of the contractile apparatus was preserved where feasible. AV replacement was done through a standard aortotomy incision. For valve replacement the sizing and orientation of the prostheses was performed according to manufacturer's guidelines. Braided 2-0 sutures with pledgets were used to secure both the mitral and aortic prostheses. Mitral annuloplasty ring size was determined by the surface area of the anterior leaflet. The implanted left-sided prosthesis included: St. Jude Mechanical / Regent (SJM/SJR) (St. Jude Medical, St. Paul, MN, USA), Carpentier Edwards (CE) Perimount (Edwards Lifesciences, Irvine, CA, USA), and Medtronic CG Future Ring (Medtronic, Minneapolis, MN, USA). These were selected according to the patient's informed preferences. TV repair was performed on the arrested heart, through an oblique right atriotomy and always involved ring annuloplasty with the Medtronic Contour 3D Ring (Medtronic, Minneapolis, MN, USA) using non-pledgeted braided 2-0 sutures. Sizing was performed according to the length of the attachment of the tricuspid septal leaflet. No other TV repair techniques were employed.

Post-operative care and follow-up

Post-operative care occurred in the specialised cardiothoracic surgery unit at Tygerberg Hospital. Follow-up was carried out at the outpatient cardiac surgery clinic 6 months after discharge. This approach was tailored to each patient, and closer follow-up occurred as required. Clinic visits consisted of a thorough clinical assessment, and further tests if indicated. Additional testing including laboratory, chest radiography, electrocardiogram, and echocardiogram were available if required. Poor

functional status was defined as New York Heart Association (NYHA) class III or IV. Features of RHF included raised jugular venous pressure (JVP), liver congestion, ascites, or pedal edema. Adverse events and the cause of death was determined by hospital chart review or information from the physician on duty at the time of the event. Clinical follow-up was complete for 76 of 83 patients (91.6%) and echocardiographic follow-up was complete for 66 of 83 patients (79.5%).

Echocardiographic assessment

All patients underwent standard transthoracic echocardiography pre-operatively and at 6 months after surgery employing the current techniques recommended by the American Society of Echocardiography.[22] Only patients with an indication for trans-esophageal echocardiography (TEE) underwent TEE. Specific parameters evaluated included chamber dimensions, ventricular function, valvular morphology and function, and pulmonary artery pressure estimation derived from TR Vmax. The RV focused apical 4 chamber views used to measure the TA diameter in diastole, the tenting height and area. Leaflet tethering was considered significant when the tenting height was more than 8mm or the tenting area was more than 1 6mm^2.[23] Moderate or severe TR at the 6-month follow-up was considered significant and accordingly termed "recurrent TR".

Outcomes

The objective of the study was to assess the short-term clinical and echocardiographic outcomes of secondary TR after left-sided valve surgery. Primary outcomes were freedom from recurrent TR, poor functional status, and mortality at 6 months. The secondary objectives were to determine predictors of recurrent TR and a sub-group analysis comparing no TV repair vs. TV repair in patients with moderate or severe TR pre-operatively.

Data collection

Demographic, clinical, and echocardiographic data were collected at 2 time points during the study. The first data collection point was at enrollment and during the course of the index hospitalisation. The second collection point was at the 6-month post-operative clinic visit.

Statistical analysis

Continuous variables are expressed as mean and standard deviation, or median and interquartile range as appropriate. Categorical variables are expressed as counts and percentages. Echocardiography data was analysed using McNemar's test and the paired t-test where appropriate. Predictors of recurrent TR were assessed by univariate logistic regression analysis using chi-squared analysis or Fisher's exact test for categorical variables, and Student's t-test or Mann-Whitney U-test for continuous variables. A p-value=0.05 was considered statistically significant. However, emphasis was placed on results reporting 95% confidence intervals and clinical significance, over the p-value results. All analysis was conducted using Statistical Package for the Social Sciences, version 28 (SPSS Inc, Chicago, Ill). Data was analysed with the support of the Division of Epidemiology and Biostatistics at the Faculty of Medicine and Health Sciences, University of Stellenbosch.

Ethical considerations

The study was approved by Stellenbosch University Health Research Ethics Committee (HREC Reference Number S18/10/251).

RESULTS

Pre-operative characteristics

Pre-operative characteristics are summarised in Table I. Patients were a mean age of 49.3 ± 15.5 years (range, 17.3 - 79.2 years) and 51.8% (43 of 83) were female. Atrial fibrillation (AF) was present in 23 (27.7%) patients. Most patients were in NYHA functional class II (38.6%) or III (54.2%). Features of RHF were

TABLE I: Pre-operative characteristics.

Variable	Value (n=83)
Age (years), mean (SD)	49.3 (15.5)
Female, n (%)	43 (51.8)
Comorbidities, n (%)	50 (60.2)
Hypertension	34 (41.0)
Diabetes Mellitus	8 (9.6)
Dyslipidemia	9 (10.8)
HIV	9 (10.8)
AF, n (%)	23 (27.7)
NYHA, n (%)	
I	1 (1.2)
II	32 (38.6)
III	45 (54.2)
IV	5 (6.0)
Previous RHF, n (%)	48 (57.8)
Current RHF, n (%)	59 (71.1)
Etiology, n (%)	
Rheumatic	37 (44.6)
Infective	22 (26.5)
Degenerative	19 (22.9)
Ischaemic	3 (3.6)
Congenital	2 (2.4)
EuroScore II,[36] median (IQR)	2.2 (1.5; 3.5)

HIV: Human Immunodeficiency Virus, AF: atrial fibrillation, NYHA: New York Heart Association, RHF: right heart failure.

present in 59 patients (71.1%) at the time of surgery and 48 (57.8%) had been in RHF previously. Thirty-seven patients (44.6%) had rheumatic heart disease, 22 (26.5%) had infective endocarditis, and 19 (22.9%) had degenerative valve disease. The median EuroScore II was 2.2 (IQR: 1.5; 3.5).

Operative data and outcomes

Forty-two (50.6%) left-sided valve procedures were performed that involved the MV in isolation vs. 24 (28.9%) that involved the AV in isolation (Table II). Combined MV / AV procedures accounted for 13 (15.7%) cases, of which 11 were dual-valve replacements and 2 were MV repair with AV replacement. Thirty-three (39.8%) patients received additional procedures, and most of these were for resection of the left atrial appendage (LAA) (63.6%) and coronary artery bypass grafting (CABG) (27.3%). TV repair was performed in 9 (10.8%) patients who all received Medtronic 3D contour ring annuloplasty. No other TV repair techniques were employed. CPB time was 163.3 ± 53.4 minutes and the aortic cross clamp time was 121.2 ± 43.1 minutes. The length of hospital stay from surgery to discharge was 18 (IQR 12.0; 28.0) days for the entire group vs. 15 (IQR 10.0; 19.5) days excluding those with infective endocarditis.

TABLE II: Operative data and peri-operative outcomes.

Variable	Value (n=83)
Left-Sided Valve Procedure, n (%)	
MV Replacement	25 (30.1)
MV Repair	17 (20.5)
AV Replacement	24 (28.9)
Combined MV / AV	13 (15.7)
Aortic Root Repair or Replacement	4 (4.8)
Additional Procedure, n (%)	33 (39.8)
LAA Resection	21 (63.6)
CABG	9 (27.3)
Other	3 (9.1)
Concomitant TV Repair, n (%)	9 (10.8)
Procedural Time (min)	
CPB, mean ± SD	163.3 ± 53.4
AOC, mean ± SD	121.2 ± 43.1
LOS (days), median (IQR)	18.0 (12.0; 28.0)
Excluding Infective Endocarditis	15.0 (10.0; 19.5)
Morbidities, n (%)	24 (28.9)
POAF	10 (12.0)
Pneumonia or Prolonged Intubation	6 (7.2)
Wound Infection	7 (8.4)
Relook for Bleeding	5 (6.0)
Permanent Pacemaker	1 (1.2)
UTI	3 (3.6)
MACCE	3 (3.6)
Mortality (30-Day), n (%)	
Cardiac	1 (1.3)
Non-Cardiac	0

MV: mitral valve, AV: aortic valve, LAA: left atrial appendage, CABG: coronary artery bypass grafting, TV: tricuspid valve, CPB: cardiopulmonary bypass, AOC: aortic cross clamp, LOS: length of stay, POAF: post-operative atrial fibrillation, UTI: urinary tract infection, MACCE: major adverse cardiac or cerebrovascular event.

Operative outcomes are listed in Table II. One (1.2%) patient required a permanent pacemaker (PPM) for complete heart block following a double valve procedure (MV repair and AV replacement) with no TV repair. Major adverse cardiac and cerebral events (MACCE) occurred in 3 (3.6%) patients who had low cardiac output syndrome due to severe RV failure. There were no cases of cerebrovascular accident or myocardial infarction. There was 1 (1.3%) operative death that occurred due to a complication of AV replacement on post-operative day one.

We defined this in the methods under post-operative care and follow up section: "Clinical follow-up was complete for 76 of 83 patients (91.6%) and echocardiographic follow-up was complete for 66 of 83 patients (79.5%)".

At this point (i.e. operative and preoperative data we had a complete dataset, and there was no loss to follow up yet - therefore n=83).

Clinical outcomes

At 6 months the freedom from recurrent TR, poor functional status, and mortality was 56 (84.8%), 69 (90.8%), and 72 (94.7%) respectively (Table III). The numerator for recurrent TR is 66 (available echo data), and for poor functional status and mortality it was 76 (available clinical follow-up data). At 6 months there were 4 (5.3%) readmissions for heart failure, and 3 of these patients ultimately demised. The remaining readmission was due to left ventricular (LV) failure from rapid ventricular response and inadequate rate control in the setting of chronic AF. At 6 months, 4 (5.3%) patients had died from cardiac causes. There were no non-cardiac deaths. Two patients demised due to RV failure. Both patients had poor pre-operative RV function (TAPSE 13mm and 14mm respectively), with significant pre-operative TR being present in 1 patient. The third mortality at 6 months was due to LV failure from a thrombosed MV prosthesis due to subtherapeutic anticoagulation. The fourth death was classified as an operative or early death within 30 days and was described in the preceding paragraph: "There was 1 (1.3%) operative death that occurred due to a complication of AV replacement on postoperative day one".

Echocardiographic data of the entire cohort

Pre-operative moderate or severe TR was present in 34 (41.0%) patients (Table IV). The proportion of patients with moderate or severe TR decreased significantly over the study period (41% vs. 13.6%, OR 0.3, p<0.01). The chamber dimensions, including LV end-systolic diameter (LVIDs 41.9 ± 9.9mm, 95% CI: 39.8 - 44.0 vs. 36.1 ± 8.9mm, 95% CI: 34.1 - 38.1, p<0.01), left atrial (LA) area (32.5 ± 13.0mm^2, 95% CI: 29.7 - 35.3 vs. 23.7 ± 8.7mm^2, 95% CI: 21.7 - 25.7, p<0.01), and right atrial (RA) area (20.5 ± 7.6mm^2, 95% CI: 18.8 - 22.2 vs. 17.6 ± 5.4mm^2, 95% CI: 16.4 - 18.8, p<0.01) improved significantly between the pre-operative and follow-up studies. The RV systolic function worsened over the study period (TAPSE 18.5 ± 5.3mm, 95% CI: 17.4 - 19.6 vs. 15.5 ± 3.5mm, 95% CI: 14.7 - 16.3, p<0.01) even though the RV systolic pressure (RVSP) improved (53.3 ± 19.1mmHg, 95% CI: 49.2 - 57.4 vs. 32.7 ± 14.7mmHg, 95% CI 29.3 - 36.1, p<0.01). Measurements of pre-operative TV morphology revealed TA diameter (42.5 ± 7.3mm, 95% CI: 40.9 - 44.1), tenting height (9.1 ± 2.7mm, 95% CI: 8.5 - 9.7), and tenting area (14.6 ± 5.7mm^2, 95% CI: 13.4 - 15.8).

TABLE III: Clinical outcomes of the entire cohort.

Variable	Patients (n=76)
NYHA	
I	51 (67.1)
II	18 (23.7)
III	4 (5.3)
IV	1 (1.3)
Mortality (6-month)	
Cardiac	4 (5.3)
Non-Cardiac	0
Readmission for Heart Failure	4 (5.3)
Freedom from	
Recurrent TR (n=66)	56 (84.8)
Poor Functional Status	69 (90.8)
Mortality	72 (94.7)

NYHA: New York Heart Association, Recurrent TR: moderate or severe tricuspid regurgitation at 6 months, Poor Functional Status: NYHA class III or IV at 6 months, Freedom from Mortality: overall at 6 months.

Predictors of recurrent TR

Logistic regression was restricted to univariate analysis due to the limited study power. Variables that appeared to be significant were female gender (OR 9.9, 95% CI: 1.2 - 84.7, p=0.04), rheumatic left-sided valve (OR 14.4, 95% CI: 1.7 - 123.6, p=0.02), and RVSP (OR 1.1, 95% CI: 1.0 - 1.1, p<0.01) (Table V). AF (OR 3.8, 95% CI: 0.9 - 15.9, p=0.07), RHF (OR

TABLE IV: Echocardiographic data of the entire cohort pre-operatively and at 6 months.

Variable	Pre-operative value (n=83)	6-month value (n=66)	p-value
Left Heart, mean ± SD (95% CI)			
LVEF (%)	48.3 ± 13.4 (45.4 - 51.2)	49.1 ± 11.3 (46.5 - 51.7)	p=0.47
LVIDs (mm)	41.9 ± 9.9 (39.8 - 44.0)	36.1 ± 8.9 (34.1 - 38.1)	p<0.01
LA Area (cm^2)	32.5 ± 13.0 (29.7 - 35.3)	23.7 ± 8.7 (21.7 - 25.7)	p<0.01
Right Heart, n (%) or mean ± SD (95% CI)			
TR			
None	0	28 (43.1)	p<0.01
Mild	49 (59.0)	28 (43.1)	p=0.06
Moderate	24 (28.9)	8 (12.3)	p=0.01
Severe	10 (12.0)	1 (1.5)	p=0.03
RA Area (cm^2)	20.5 ± 7.6 (18.8 - 22.2)	17.6 ± 5.4 (16.4 - 18.8)	p<0.01
TAPSE (mm)	18.5 ± 5.3 (17.4 - 19.6)	15.5 ± 3.5 (14.7 - 16.3)	p<0.01
RVSP (mmHg)	53.3 ± 19.1 (49.2 - 57.4)	32.7 ± 14.7 (29.3 - 36.1)	p<0.01
TA Diameter (mm)	42.5 ± 7.3 (40.9 - 44.1)	-	-
Mild TR (mm)	41.1 ± 6.4 (39.21 - 42.79)		
TV Tenting Height (mm)	9.1 ± 2.7 (8.5 - 9.7)	-	-
TV Tenting Area (mm^2)	14.6 ± 5.7 (13.4 - 15.8)	-	-

LVEF: left ventricle ejection fraction, LVIDs: left ventricle internal dimension in systole, LA: left atrium, TR: tricuspid regurgitation, RA: right atrium, TAPSE: tricuspid annular plane systolic excursion, RVSP: right ventricle systolic pressure, TA: tricuspid annulus, TV: tricuspid valve.

TABLE V: Predictors of recurrent TR.

Variable	Univariable OR (95% CI) (n=83)	p-value
Demographic		
Age	1.0 (0.9 - 1.0)	p=0.55
Female Gender	9.9 (1.2 - 84.7)	p=0.04
Left-Sided Rheumatic Etiology	14.4 (1.7 - 123.6)	p=0.02
AF	3.8 (0.9 - 15.9)	p=0.07
RHF	2.2 (0.3 - 19.2)	p=0.48
NYHA Class (III/IV)	0.4 (0.1 - 1.7)	p=0.22
Operative		
TVA	0.2 (0.1 - 12.4)	p=0.83
Concomitant Procedure	3.6 (0.8 - 16.0)	p=0.09
Echocardiographic		
TA Diameter (mm)	1.1 (1.0 - 1.2)	p=0.35
TV Tenting Height (mm)	1.1 (0.8 - 1.5)	p=0.52
TV Tenting Area (mm^2)	1.0 (0.9 - 1.2)	p=0.87
Moderate or Severe Preoperative TR	3.6 (0.8 - 16.0)	p=0.09
RVSP (mmHg)	1.1 (1.0 - 1.1)	p<0.01
TAPSE (mm)	1.0 (0.8 - 1.1)	p=0.65
LVEF (%)	1.1 (1.0 - 1.1)	p=0.08
LA Area (mm^2)	1.0 (1.0 - 1.1)	p=0.11
RA Area (mm^2)	1.1 (1.0 - 1.2)	p=0.12

AF: atrial fibrillation, TVA: tricuspid valve annuloplasty, RHF: right heart failure, NYHA: New York Heart Association, TA: tricuspid annulus, TV: tricuspid valve, TR: tricuspid regurgitation, RVSP: right ventricle systolic pressure, TAPSE: tricuspid annular plane systolic excursion, LVEF: left ventricle ejection fraction, LA: left atrium, RA: right atrium.

2.2, 95% CI: 0.3 - 19.2, p=0.48), concomitant procedure (OR 3.6, 95% CI: 0.8 - 16.0, p=0.09), and significant pre-operative TR (OR 3.6, 95% CI: 0.8 - 16.0, p=0.09) trended towards an increased risk for recurrent TR at 6 months. We were unable to demonstrate an association of TA diameter, TV tenting height or area, TAPSE, LVEF, or atrial size with recurrent TR at 6 months.

Sub-group analysis of no TV repair vs. TV repair in patients with moderate or severe pre-operative TR

Pre-operative characteristics and echocardiographic data between the groups are summarised in Table VI. There were 25 patients with moderate or severe pre-operative TR that did not receive TV repair, which included 20 (80%) with moderate TR and 5 (20%) with severe TR. The TV repair group had larger pre-operative TA diameter than no TV repair for patients with moderate TR (42.4 ± 5.1mm, 95% CI: 40.4 - 44.4 vs. 48.3 ± 6.9mm, 95% CI: 43.8 - 52.8, p=0.03), although not for severe TR. Pre-operative TV tenting distance (9.3 ± 2.0mm, 95% CI: 8.5 - 10.1 vs. 13.1 ± 2.3mm, 95% CI: 11.6 - 14.6, p<0.01) and TV tenting area (15.1 ± 5.1mm, 95% CI: 13.1 - 17.1 vs. 21.8 ± 4.1mm, 95% CI: 19.1 - 24.5, p=0.01) were larger in TV repair compared with no TV repair. At 6 months patients with TV repair had worse LVEF (52.7 ± 10.7%, 95% CI: 48.0 - 57.4 vs. 41.5 ± 8.7%, 95% CI: 34.5 - 48.5, p=0.03) than those with no TV repair, yet the remaining echocardiographic outcomes between the groups were comparable. Patients in the TV repair group had either no change (n=2), or improvement by 1 (n=3) or 2 grades (n=2) of TR at 6 months. Table VII summarises the operative data and outcomes between the groups. Resection of the LAA occurred more frequently in the TV repair group (28.0% vs. 66.7% p=0.04). Cardiopulmonary bypass and cross clamp times were numerically greater in the TV repair group. Operative morbidity and mortality between the groups were similar, although pneumonia or prolonged ventilation was more frequent in the TV repair group (0% vs. 22.2% p=0.02). The groups had comparable (2.7% vs. 11.1% p=0.20) MACCE. There was no difference in functional status, mortality, readmission, or recurrent TR at 6 months between the no TV repair and TV repair sub-groups.

DISCUSSION

We found good short-term outcomes in a heterogenous group of patients with secondary TR undergoing left-sided valve surgery employing a guideline-directed, multidisciplinary team approach. The primary outcomes for the entire cohort were characterised by high rates of freedom from recurrent TR (86.2%), poor functional class (90.8%), and mortality (94.7%) at 6 months after surgery.

There are limited and often conflicting data to inform whether these results can be sustained over the medium and long term, especially among patients with no TV repair.[24] The natural history and outcomes of secondary TR depend on numerous factors, including etiology of the left-sided valvopathy, degree of pulmonary hypertension, pre-operative TR grade, TA dimension, RV function, and tenting height and tenting area making it difficult to generalise and create a uniform approach.[1] There is conflicting evidence surrounding the notion that progression of TR and deterioration of functional status occurs over time when secondary TR is managed conservatively. At 4.8 years after MV repair for degenerative MV disease, in patients with significant TA dilatation and varying degrees of TR, recurrent TR and worse NYHA functional status was more frequent in those without TV repair than those who had TV repair, yet their mortality rates were similar.[25] At 4 years significant recurrent TR was more common in patients who did not undergo TV repair in a cohort of patients undergoing MV replacement

TABLE VI: Pre-operative characteristics and echocardiographic data of no TV repair vs. TV repair in patients with moderate or severe pre-operative TR.

Variable	No TV Repair	TV Repair	p-value
Pre-operative	**(n=25)**	**(n=9)**	
Age (years), mean (SD)	47.2 (14.7)	42.9 (14.2)	p=0.45
Female, n (%)	13 (52.0)	5 (55.6)	p=0.86
Comorbidities, n (%)	15 (60.0)	7 (77.8)	p=0.34
AF, n (%)	7 (28.0)	5 (55.6)	p=0.14
NYHA, n (%)			
I	0	0	-
II	8 (32.0)	4 (44.4)	p=0.50
III	16 (64.0)	4 (44.4)	p=0.31
IV	1 (4.0)	1 (11.1)	p=0.44
Previous RHF, n (%)	16 (64.0)	7 (77.8)	p=0.45
With Pre-operative Moderate TR Severe TR	 11 (55.0) (n=20) 5 (100.0) (n=5)	 2 (50.0) (n=4) 5 (100.0) (n=5)	 p=0.86 -
Etiology, n (%)			
Rheumatic	14 (56.0)	9 (100.0)	p=0.03
EuroScore II,[36] median (IQR)	2.8 (2.0)	2.9 (1.4)	p=0.75
Echocardiographic Pre-operative Six-month	 (n=25) (n=20)	 (n=9) (n=6)	
Left Heart, mean ± SD (95% CI)			
LVEF (%) Pre-operative Six-month	 46.4 ± 14.3 (40.8 - 52.0) 52.7 ± 10.7 (48.0 - 57.4)	 43.2 ± 7.4 (38.4 - 48.0) 41.5 ± 8.7 (34.5 - 48.5)	 p=0.41 p=0.03
LVIDs (mm) Pre-operative Six-month	 41.6 ± 9.7 (37.8 - 45.4) 34.0 ± 7.5 (30.7 - 37.3)	 41.3 ± 8.2 (35.9 - 46.7) 40.2 ± 2.4 (38.3 - 42.1)	 p=0.93 p=0.06
LA Area (cm^2) Pre-operative Six-month	 35.7 ± 15.5 (28.9 - 42.5) 23.4 ± 6.9 (20.4 - 26.4)	 36.5 ± 8.4 (30.7 - 42.3) 26.5 ± 7.1 (20.8 - 32.2)	 p=0.89 p=0.35
Right Heart, n (%) or mean ± SD (95% CI)			
TR (Moderate or Severe) Pre-operative Moderate Severe	25 (100.0) 20 (80.0) 5 (20.0)	9 (100.0) 4 (44.4) 5 (55.6)	-
Six-month Moderate Severe	8 (40.0) 7 (87.5) 1 (12.5)	1 (16.7) 1 (100.0) 0	p=0.29
RA Area (cm^2) Pre-operative Six-month	 20.6 ± 7.0 (17.9 - 23.3) 17.7 ± 5.0 (15.5 - 19.9)	 28.5 ± 8.3 (22.8 - 34.3) 20.7 ± 7.2 (14.9 - 26.5)	 p=0.01 p=0.24
TA Diameter (mm) With Pre-operative Moderate TR Severe TR	42.2 ± 6.0 (39.9 - 44.6) 42.4 ± 5.1 (40.4 - 44.4) 41.6 ± 9.4 (37.9 - 45.3)	49.1 ± 10.2 (42.4 - 55.8) 48.3 ± 6.9 (43.8 - 52.8) 49.8 ± 13.0 (41.3 - 58.3)	p=0.08 p=0.03 p=0.14
TV Tenting Height (mm) With Pre-operative Moderate TR Severe TR	9.3 ± 2.0 (8.5 - 10.1) 9.5 ± 2.0 (8.7 - 10.3) 8.6 ± 1.8 (7.9 - 9.3)	13.1 ± 2.3 (11.6 - 14.6) 13.3 ± 2.5 (11.7 - 14.9) 13.0 ± 2.4 (11.4 - 14.6)	p<0.01 p<0.01 p<0.01
TV Tenting Area (mm^2) With Pre-operative Moderate TR Severe TR	15.1 ± 5.1 (13.1 - 17.1) 15.5 ± 5.1 (13.5 - 17.5) 13.4 ± 5.5 (11.2 - 15.6)	21.8 ± 4.1 (19.1 - 24.5) 21.3 ± 3.8 (18.8 - 23.8) 22.2 ± 4.7 (19.1 - 25.3)	p=0.01 p=0.02 p=0.01
TAPSE (mm) Pre-operative Six-month	 17.6 ± 5.3 (15.5 - 19.7) 15.4 ± 3.8 (13.7 - 17.1)	 15.6 ± 6.3 (11.2 - 20.0) 13.8 ± 3.5 (11.0 - 16.6)	 p=0.39 p=0.39
RVSP (mmHg) Pre-operative Six-month	 62.4 ± 22.1 (53.7 - 71.1) 34.5 ± 19.6 (25.9 - 43.1)	 57.4 ± 22.8 (42.5 - 72.3) 38.5 ± 6.1 (33.6 - 43.4)	 p=0.57 p=0.63

TV: tricuspid valve, AF: atrial fibrillation, NYHA: New York Heart Association, RHF: right heart failure, TA: tricuspid annulus, TR: tricuspid regurgitation, RVSP: right ventricle systolic pressure, TAPSE: tricuspid annular plane systolic excursion, LVEF: left ventricle ejection fraction, LVIDs: left ventricle internal dimension in systole, LA: left atrium, RA: right atrium.

TABLE VII: Operative data and outcomes of no TV repair vs. TV repair in patients with moderate or severe pre-operative TR.

Variable	No TV Repair	TV Repair	p-value
Operative data	**(n=25)**	**(n=9)**	
Left-Sided Valve Procedure, n (%)			
MV Replacement	10 (40.0)	8 (88.9)	p=0.01
MV Repair	9 (36.0)	0	p=0.20
AV Replacement	10 (40.0)	1 (11.1)	p=0.16
Additional Procedure, n (%)			
LAA Resection	7 (28.0)	6 (66.7)	p=0.04
CABG	3 (12.0)	0	p=0.28
Procedural Time (min)			
CPB, mean ± SD (95% CI)	150.4 ± 34.8 (136.8 – 164.0)	200.9 ± 74.5 (152.2 – 249.6)	p=0.08
AOC, mean ± SD (95% CI)	112.2 ± 31.7 (99.8 – 124.6)	141.1 ± 58.3 (103.0 – 179.2)	p=0.07
Operative outcomes	**(n=25)**	**(n=9)**	
Morbidities, n (%)			
POAF	5 (20.0)	1 (11.1)	p=0.55
Pneumonia or Prolonged Intubation	0	2 (22.2)	p=0.02
Wound Infection	3 (12.0)	1 (11.1)	p=0.94
Relook for Bleeding	4 (16.0)	0	p=0.20
Permanent Pacemaker	0	0	-
UTI	1 (4.0)	0	p=0.70
MACCE	2 (2.7)	1 (11.1)	p=0.78
Mortality (30-day), n (%)			
Cardiac	0	0	-
Non-Cardiac	0	0	
Six-month outcomes	**(n=23)**	**(n=7)**	
NYHA			
I	15 (65.2)	5 (71.4)	p=0.76
II	6 (26.1)	1 (14.3)	p=0.52
III	2 (8.7)	1 (14.3)	p=0.78
IV	0	0	-
Mortality			
Cardiac	1 (4.3)	1 (14.3)	p=0.36
Non-Cardiac	0	0	
Readmission for Heart Failure	1 (4.3)	1 (14.3)	P=0.36
Freedom from			
Recurrent TR	15 (75.0) (n=20)	5 (83.3) (n=6)	p=0.67
Poor Functional Status	21 (91.3)	6 (85.7)	p=0.67
Mortality	22 (95.7)	6 (85.7)	p=0.36

TVA: tricuspid valve annuloplasty, MV: mitral valve, AV: aortic valve, LAA: left atrial appendage, CABG: coronary artery bypass grafting, TV: tricuspid valve, CPB: cardiopulmonary bypass, AOC: aortic cross clamp, POAF: post-operative atrial fibrillation, UTI: urinary tract infection, MACCE: major adverse cardiac or cerebrovascular event, NHYA: New York Heart Association, Recurrent TR: moderate or severe tricuspid regurgitation at 6 months, Poor Functional Status: NYHA class III or IV at 6 months, Freedom from mortality: overall at 6 months.

for rheumatic disease, despite both groups having less than moderate TR pre-operatively.[26] A third study found that 5 years after MV repair for secondary MR, patients with pre-operative moderate or more TR who did not have TV repair had a significantly higher risk of recurrent TR, poor functional status, and mortality.[27] In contrast, another study showed that at 5.5 years TR progression was unusual in patients undergoing repair of degenerative MV disease without TV repair.[28] Our practice was generally characterised by selective treatment of severe TR associated with various left-sided valvopathies, yet

mostly conservative treatment of less-than-severe TR, where other factors like RHF and TV morphology were considered to reach a treatment decision.

The effect that various left-sided valvopathies had on secondary TR outcomes after conservative TV management was summarised by Song, et al.[29] who reported that rates of recurrent moderate or severe TR at 8.5 years in 638 patients with pre-operative mild TR, was 8% - 26% for rheumatic MV disease, 5% for degenerative MV disease, and 3% for mixed aortic valve disease. Our study included a significant proportion of patients with rheumatic valve disease (44.6%) associated with mild (66.2%) and moderate or more (33.8%) pre-operative TR who did not undergo TV repair. The long-term outcomes of this cohort are difficult to predict, however it is likely that these patients remain at risk of recurrent TR. Longer follow-up is required to clarify the risk.

Despite these long-term concerns, this study demonstrated that our multidisciplinary team used an individualised, evidence-based approach to achieve good short-term results in this cohort of patients. We performed TV repair for those who had class I indications (i.e. severe TR). In contrast, patients with class II indications for concomitant TV repair (i.e. less-than-severe TR with TA dilatation or previous RHF) were generally treated more conservatively unless compelling indications for surgery existed such as severely enlarged TA or significant TV tethering. This study had a high proportion of patients with mild pre-operative TR (59.0%) who had TA measurement exceeding 40mm (mean=41.1mm). None of these patients received TV repair despite the guidelines suggesting a class II indication for concomitant repair in these circumstances. The 6-month outcomes in this group remained satisfactory in the vast majority of patients. For patients who had moderate TR with TA dilatation (mean=42.4mm), it could be argued that we should have pursued a more aggressive approach as 7 patients had moderate TR at 6 months. Our approach yielded good short-term outcomes and these patients (especially the group with moderate TR) should be followed in the medium and long term to monitor the evolution of TR. A recent trial supported this cautious approach to less-than-severe secondary TR.[19] That trial demonstrated that even though recurrent TR was more common in the no TV repair group at 2 years, the risk of major adverse outcomes, poor functional status, and death were the same in the 2 groups, whereas the PPM rate was almost 6 times higher in the TV repair group. Based on these results, Chikwe and colleagues suggest these seemingly benign medium-term consequences of recurrent TR, together with the significantly increased risk for PPM mean that an aggressive approach to TV repair is probably not warranted – especially not for high risk patients.[30] None of the patients in this study undergoing TV repair required PPM implantation post-operatively.

Reported predictors of recurrent TR after left-sided valve surgery include age, female gender, rheumatic left-sided valvopathy, increased pulmonary artery (PA) pressure or RVSP, AF, RHF, pre-operative TR severity, TV morphology, impaired ventricular function, and increased atrial size.[5,9,19,21,31,32] This study demonstrated similar findings, with female gender, left-sided rheumatic valve disease, and increased RVSP being significant risk factors for recurrent TR. Although AF, RHF, and pre-operative TR severity did not reach statistical significance, there was a trend to an increased risk of recurrent TR. True differences between the groups were probably underestimated due to the small numbers in our study. Considering that recurrent TR has not been conclusively linked with poorer clinical outcomes in the long term, some authors[17] believe that it may actually be these underlying pre-operative risk factors that are more important for the long-term outcomes of patients with secondary TR. However, they emphasise that 5-year follow-up may not be long enough to assess the true effect of significant TR, which may have a long latent period before significant effects on the heart are observed.

The exploratory analysis between no TV repair and TV repair should be interpreted with caution and is meant to be purely hypothesis generating due to the limited numbers in the groups. No differences in the 6-month outcomes between these sub-groups were detected. The early operative outcomes between the groups were also similar. These seemingly comparable results between the no TV repair and TV repair groups occurred despite the latter demonstrating a higher risk profile including more rheumatic heart valve disease, mitral valve replacement, and LAA resection. There was 1 (1.4%) operative death due to a complication of AV replacement that occurred in the no TV repair group. The observed operative mortality for this diverse group of patients compares favorably with rates of 4% as reported by other authors.[20,33]

The implantation of 1 (1.4%) PPM was required for complete heart block which occurred following a dual-valve procedure in the no TV repair group. Although this tentative analysis did not demonstrate a higher risk of PPM implantation in the TV repair group, there is conflicting data regarding the risk of PPM after TV repair. Even though a systematic review of mostly observational data failed to demonstrate an association between TV repair and need for early PPM implantation,[20] a recent trial revealed that the incidence of pacemaker implantation was significantly higher in the concomitant TV repair group.[19]

It is not unexpected that even with low rates of recurrent TR and significantly improved RVSP, RV dysfunction (as measured by diminished TAPSE) was still present at 6 months. There is evidence that irrespective of TV repair status, early RV dysfunction tends to worsen for all patients undergoing surgical repair of MV disease, except in those with pre-operative severe TR and significant RV dysfunction, who often demonstrate transient early improvement in RV function.[34] The reasons for early RV dysfunction are uncertain, but may include post-surgical changes from sub-optimal intra-operative myocardial protection of the RV, or could reflect the effect of various loading conditions on the heart (e.g. post-operative changes in pre- and afterload).[34] Additionally, we demonstrated that LV dysfunction (measured by LVEF) at 6 months appeared to be more pronounced in the TV repair group. In light of the preceding discussion about RV dysfunction, this is not surprising as it is well established that the function of both ventricles is intimately linked.[35] Reassuringly, others have found that medium- to long-term outcomes at 3 - 5 years demonstrated that RV dysfunction resolved, and the improvement of RV function and TAPSE occurred sooner in patients with TV repair vs. no TV repair.[13,34] In our study, longer follow-up is required to confirm whether or not this subsequent improvement of RV and LV function occurs. It would also be valuable to have additional parameters to assess RV function, including echocardiography based myocardial performance index and RV fractional area change, and cardiovascular magnetic resonance assessments of chamber volume and function.[4]

In conclusion, this study has shown that careful and individualised application of secondary TR guidelines produced good short-term results. Overall, the cohort demonstrated low rates of recurrent TR that were associated with good functional status and low mortality at 6 months. The similar results between the sub-groups are encouraging considering that the TV repair group had more pre-operative and operative risk features than the no TV repair group. It was also reassuring to note that PPM rates were low. Although we have demonstrated good short-term outcomes, longer follow-up is required to assess the long-term outcomes of patients undergoing left-sided valve surgery with associated secondary TR in order to clarify indications for concomitant TV repair.

LIMITATIONS

This study had a number of limitations. It was a single centre study and therefore the results may not be generalisable. Observational studies are also open to treatment allocation bias and hidden confounders. Furthermore, the inclusion of various types of left-sided heart valve disease may have a confounding effect on TR outcomes. The study duration was relatively short and further follow-up is necessary to determine the long-term effects on clinical and echocardiographic outcomes of secondary TR. The small sample size was underpowered to allow adequate comparisons between no TV repair and TV repair or inferences about predictors of TR. Inclusion of patients with rheumatic heart disease may confound the etiology of TR (histopathological testing was not uniformly performed), and lead to the erroneous inclusion of patients with primary rheumatic TV involvement. To mitigate this TV morphology was carefully interrogated to ensure that only cases of secondary TR were included.

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Balloon valvuloplasty for valvar pulmonary stenosis: A 34-year experience at a large tertiary-level hospital, Southern Africa

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ABSTRACT

Background: Congenital pulmonary valve stenosis (PS) is one of the most common congenital cardiac defects, accounting for 8% - 12% of all congenital cardiac defects. Percutaneous balloon pulmonary valvuloplasty (PBPV) has been the preferred treatment since its introduction in 1982.
Aim: To evaluate the efficacy and safety of PBPV over the last 3 decades at a single institution.
Method: A retrospective, descriptive analysis was conducted at a tertiary-level hospital in Southern Africa to evaluate patients who underwent PBPV between 1985 and 2019.
Results: During the study period, 68 patients underwent balloon valvuloplasty for moderate to severe pulmonary stenosis. Patients were selected using echocardiographic criteria. The mean pulmonary valve annulus measured on angiography was 11.2mm (SD 3.9) with a mean balloon size of 13.1mm (SD 4.4). The balloon size to pulmonary valve annulus ratio was 1.169:1. The median peak instantaneous gradient (PIG) before balloon valvuloplasty was 79mmHg (IQR 64 - 102mmHg) which decreased to 33mmHg (IQR 23 - 40mmHg) after balloon valvuloplasty (p<0.001). There was an 88% success rate. Complications occurred in 8/68 (11.7%) patients, with 1 procedural death reported.
Conclusion: Our study shows that PBPV is a safe and effective treatment of moderate and severe PS with a good outcome. Complications are rare if the procedure is well planned and managed promptly if they arise.
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INTRODUCTION

Congenital pulmonary valve stenosis (PS) is one of the most common congenital cardiac defects, accounting for 8% - 12% of all defects.[1] PS can occur as an isolated defect or in association with other cardiac defects.[1] The associated cardiac defects include atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus arteriosus (PDA).[1] Congenital PS may be found in association with genetic syndromes including Noonan, Holt-Oram, Leopard, William, and Allagile Syndromes.[1] Acquired PS is rare in the paediatric population.[1] The pathologic features of the stenotic pulmonary valve vary, with the most common variety being a dome-shaped pulmonary valve.[2] The fused pulmonary valve leaflets protrude from their attachment into the pulmonary artery as a conical, windsock-like structure.[2] Pulmonary valve ring hypoplasia and dysplastic pulmonary valves where the leaflets are not fused but are thickened, may be present in a small percentage of patients.[2] The diagnosis can be made on clinical cardiac examination by the presence of a murmur and confirmed by echocardiography.[3]

The severity of the PS is classified as mild to severe using an echocardiographically derived Doppler flow gradient.[1,3] Critical PS is associated with very poor pulmonary blood flow and may be confused with cyanotic heart disease because there is usually right-to-left shunting through the patent foramen ovale (PFO) or an atrial septal defect (ASD) and survival is dependent on the patency of a ductus arteriosus.[1,3]

Surgery was the treatment of choice for valvar pulmonary stenosis in the past.[4] However, percutaneous balloon pulmonary valvuloplasty (PBPV) has become the preferred alternative treatment since its introduction in 1982 by Kan, et al.[4] Success rates of approximately 75% - 88% have been reported with PBPV.[4,5] The first attempt to relieve pulmonary valve obstruction by transcatheter methodology was in the early 1950s by Rubio-Alverez, et al.[2,6,7] where they used a ureteral

catheter percutaneously with a wire to cut open a stenotic pulmonary valve.[2,6,7] More recently, Kan and associates applied the technique of Gruentzig, et al. to relieve pulmonary valve obstruction by using an inflated balloon catheter positioned across the pulmonary valve.[2] Initial recommendations were to use balloon sizes 20% - 40% larger than the pulmonary valve annulus, with a balloon to pulmonary valve annulus ratio of 1.2 – 1.4.[4] The use of balloon sizes 20% - 40% larger than the pulmonary valve annulus was associated with the development of pulmonary insufficiency at late follow up.[4] In subsequent years, the use of balloon size 1.1-1.2 larger than the pulmonary valve annulus has been recommended to prevent the development of significant pulmonary insufficiency at late follow-up.[4] A good response is achieved using PBPV in patients with moderate to severe pulmonary valve stenosis, however, dysplastic pulmonary valves may not respond to balloon dilatation and frequently require surgical treatment.[8]

Immediate-, short-, and mid-term outcomes of balloon pulmonary valvuloplasty are well documented, but there is limited information on long-term results.[9,10,11,12] Pulmonary oedema complicating balloon dilatation of the pulmonary valve is rare and usually associated with treatment of severe stenosis.[13] This complication was described by Shrivastava, et al. where they reported 2 children who developed pulmonary oedema following PBPV.[13] Management includes administration of diuretics, inotropes, and ventilatory support. One of the 2 cases of pulmonary oedema reported by Shrivastava, et al. proved to be fatal despite treatment.[13] Right ventricular outflow tract obstruction or hypercontractile infundibular obstruction, otherwise known as "suicide right ventricle", may appear after balloon valvuloplasty, particularly in those patients with severe pulmonary valve obstruction.[14] Relief of the infundibular obstruction can be treated with administration of b-blockers.[14, 15] Additional treatments include fluid administration combined with beta-blockers or calcium channel blockers.[15] A sudden decompensation of the patient post BPV or surgery, therefore, should alert one to the possibility of infundibular obstruction particularly in patients with supra-systemic right ventricular pressure.[15] Pre-procedure administration of a beta-blocker may be helpful as a prevention strategy.[15]

A successful PBPV is labelled as successful if the peak-to-peak angiographic pressure gradient (PG) is reduced to less than 50% of its initial value.[16] A suboptimal result is regarded as a PG reduced by 25% - 49% and unsuccessful result if the PG is reduced by less than 25%.[16] Restenosis has been described in 10% of children who undergo PBPV particularly in instances where a balloon / annulus ratio <1.2 was used.[17,18] Redilatation of the pulmonary valve in patients who develop restenosis following previous PBPV has been associated with good results and is the procedure of choice in this group of patients.[17,18] Results of late follow up of PBPV are excellent, with some patients having mild residual pulmonary regurgitation.[18,19] The use of large balloon sizes, complex valvular morphology due to a previous surgical valvotomy, or the presence of dysplastic valves have been associated with the development of significant pulmonary regurgitation following PBPV.[20,21,23,24]

METHODS AND MATERIALS

Study design

We conducted a retrospective, descriptive analysis at a tertiary-level hospital in Southern Africa to evaluate patients who underwent percutaneous balloon pulmonary valvuloplasty (PBPV) between February 1985 - May 2019.

Statistical analysis

Data was extracted from the electronic paediatric cardiology database at CHBAH, and hospital records were interrogated.

Descriptive statistics presented continuous variables as means and standard deviations (SD) for normally distributed data, and as medians with interquartile ranges (IQR) for skewed data. The Shapiro-Wilk test was used to test for normality of the pressure gradients. The Mann-Whitney U test was used to compare medians. P-values <0.05 were considered significant. Data were analysed using Stata.

Definitions

Severity of PS based on echocardiographic derived Doppler gradients.[1]

- **Mild PS** is defined as a Doppler flow gradient less than 36mmHg.[1]
- **Moderate PS** is defined as a Doppler flow gradient between 36 and 64mmHg.[1]
- **Severe PS** is defined as a Doppler gradient greater than 64mmHg.[1]
- **Successful PBPV** is defined as a reduction of the pressure gradient across the pulmonary valve to less than 50% of its initial value.[16]
- A **suboptimal result** is defined as a reduction of the pressure gradient by 25% - 49%.[16]
- **Unsuccessful PBPV** is defined as a reduction of the pressure gradient by less than 25%.[16]

RESULTS

During the study period from February 1985 - May 2019, 68 patients underwent balloon valvuloplasty at CHBAH. Patients were selected using echocardiographic derived Doppler gradients.

Echocardiographic derived Doppler gradients before PBPV, balloon sizes, pulmonary valve annulus, patient demographics, and complications were documented for all 68 patients. Patient selection for balloon valvuloplasty was based on echocardiographic derived Doppler gradients and not symptomatology. When record review was conducted, immediate pressure gradients after PBPV were documented for 60/68 patients; however the echocardiographically derived Doppler gradients at 3 month follow-up were documented for all 68/68 patients. Descriptive analysis (Median, IQR) to assess the statistical significance in the reduction of the pressure gradients after PBPV was done on the 60/68 patients who had documentation of the immediate post-PBPV pressure gradients. On analysis of the outcome of patients who underwent PBPV, the 3 month follow-up echocardiographically derived Doppler gradients were included.

Characteristics of patients

Of the 68 patients, 5/68 (7%) were less than 1 month of age, and 63/68 (93%) were older than 1 month of age. There was a male:female ratio of 1.1:1. The indication for PBPV was moderate PS in 14/68 (21%) patients and severe PS in 54/68 (79%) patients (Table I).

Echocardiography and catheterisation data

The mean pulmonary valve annulus measured on angiography (Figure IA) was 11.2mm (SD 3.9) and the mean balloon size was 13.1mm (SD 4.4). The balloon size (Figure IB) to pulmonary valve annulus ratio was 1.169:1 (SD 1.1) (Table II).

TABLE I: Characteristics of patients (n=68).

Age stratification	
<1 month	5/68 (7.4%)
>1 month	63/68 (93%)
Gender	
Male	35/68 (51%)
Female	33/68 (49%)
Indications	
Moderate PS	
(PIG 36 – 64mmHg)	14/68 (21%)
Severe PS	
(PIG >64mmHg)	54/68 (79%)

PS: Pulmonary stenosis, PIG: Peak instantaneous gradient.

Outcomes

There was an 88% success rate. A suboptimal reduction was found in 5/68 (7.4%) of patients due to the presence of dysplastic valves. One of the patients had a co-morbid sinus venosus ASD which required surgery (Table III).

TABLE II: Echocardiography and catheterisation data.

Parameter	Mean (SD)
Pulmonary valve annulus (mm)	11.2 (3.9)
Balloon size (mm)	13.1 (4.4)
Balloon / PV size ratio	1.169:1

SD: Standard deviation, PIG: Peak instantaneous gradient, PV: Pulmonary valve, BV: Balloon valvuloplasty.

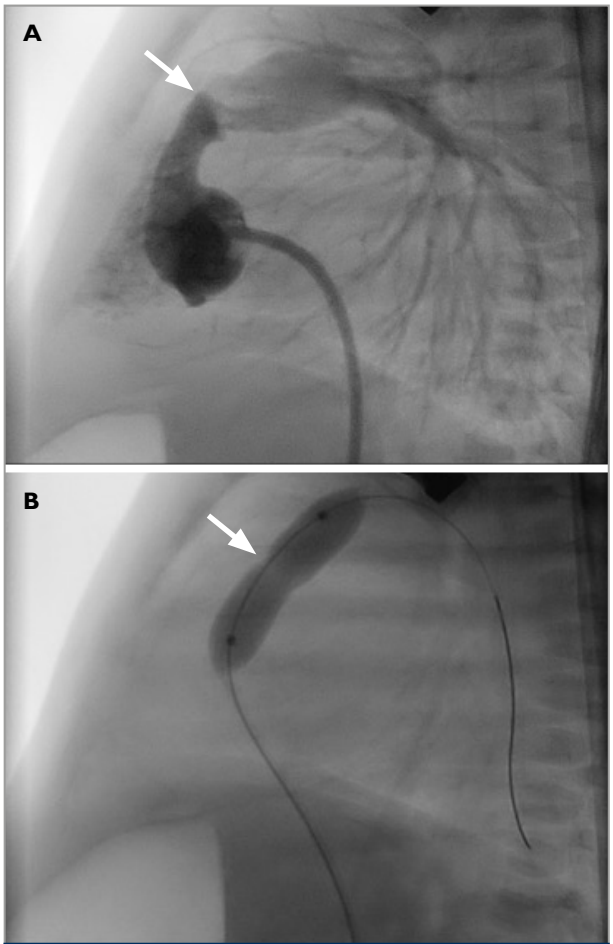

FIGURE 1: Angiography and fluoroscopy during PBPV.
A: RV angiogram in lateral view showing a doming pulmonary valve (arrow).
B: Balloon catheter with wire and inflated balloon showing a "waist" caused by the stenotic pulmonary valve (arrow).
RV: Right ventricle, PBPV: Percutaneous balloon pulmonary valvuloplasty.

Descriptive and analytical statistics for pre- and post-balloon dilatation gradients

We tested for normality of the peak instantaneous gradient (PIG) pre- and post-balloon dilatation (BD) using the Shapiro-Wilk test (p-value=0.015 and 0.016, respectively). Both were not normally distributed hence the medians and inter-quartile ranges (IQR) are reported. The median pre-BD PIG was higher than the post-BD PIG (79mmHg vs. 33mmHg). We tested whether there was a statistically significant difference pre-BD PIG and post-BD PIG using the Wilcoxon signed-rank test and found strong evidence that the pre- and post-PIG were significantly different (Table IV).

Complications

Complications occurred in 8/68 (11.7%) patients, with 1 death reported. An iatrogenic "suicide right ventricle" or hyper-contractile infundibular obstruction was observed in 2 patients, while 1 patient developed reperfusion pulmonary oedema. One patient developed sudden severe tricuspid regurgitation during the procedure caused by ruptured tricuspid valve chordae due to a sudden downward movement of the balloon across the tricuspid valve during balloon inflation, and 2 patients developed severe pulmonary regurgitation. Both patients who developed severe pulmonary regurgitation had dysplastic pulmonary valves. One of the patients who developed severe pulmonary regurgitation required serial balloon dilatations; however, the balloon / PV ratio of the biggest balloon used was 1.1:1, which is acceptable. The other patient who developed severe pulmonary regurgitation also had appropriate balloon sizing, with a balloon / PV ratio of 1.2:1. One patient had a cardiac arrest during the procedure during cannulation of the PV with the balloon and developed cerebral palsy. One patient had perforation of the right ventricular outflow tract with a wire, and subsequently died. The patient who had perforation of the right ventricular outflow tract was a neonate with critical pulmonary stenosis. This happened during the first decade of the study (Table V).

TABLE III: Immediate outcomes.

Outcome (n=68)	
Good outcome	60/68 (88.2%)
Suboptimal pressure reduction	5/68 (7.4%)
Procedure not undertaken due to complications	3/68 (4.4%)
Reasons for suboptimal reduction (n=5)	
Dysplastic pulmonary valve	5/5 (100%)

ASD:Atrial septal defect, PV: Pulmonary valve, RVOT: Right ventricular outflow tract.

TABLE IV: Descriptive and analytical statistics for pre- and post-balloon dilatation gradients.

	Shapiro-Wilk test for normality p-value	Median (IQR) PIG, mmHg	Wilcoxon signed rank test p-value
PIG pre-BD, n=60	0.015	79 (64 - 102)	<0.001
PIG post-BD, n=60	0.016	33 (23 - 40)	<0.001

TABLE V: Complications.

Complications (n=68)	
Suicide right ventricle	2/68 (2.9%)
Reperfusion pulmonary oedema	1/68 (1.5%)
Severe pulmonary regurgitation	2/68 (2.9%)
Ruptured TV chordae	1/68 (1.5%)
Cerebral palsy	1/68 (1.5%)
RVOT perforation with a wire	1/68 (1.5%)
Mortality	1/68 (1.5%)

TV: Tricuspid valve, RVOT: Right ventricular outflow tract.

Follow up at 3 months

Patients with dysplastic pulmonary valves

Three out of the 5 patients who had dysplastic valves had no change in the immediate post-balloon dilatation gradient; however, they were monitored clinically and were noted to have a further reduction in the pulmonary valve gradient at 3 months, which required no further intervention. One out of the 5 patients went on to have a surgery in the form of a transannular patch. One out of the 5 patients was unfortunately lost to follow-up.

Patients with severe pulmonary regurgitation

The 2 patients who developed severe pulmonary regurgitation are currently asymptomatic and being monitored clinically.

DISCUSSION

Congenital pulmonary valve stenosis (PS) is one of the most common congenital cardiac defects with a good outcome if treated correctly.[1,4] PS can occur in isolation or in association with other cardiac defects or syndromes, most commonly Noonan Syndrome.[1] The pathologic features of PS vary, with the dome-shaped pulmonary valve being the most common type.[2] In our cohort of patients, the majority of patients, 92.6% (60/68), had the fused pulmonary valve leaflet and a doming pulmonary valve variety with a minority of patients having dysplastic leaflets, 7.4% (5/68).[2] The findings of majority of patients having fused pulmonary valve leaflets with a doming

pulmonary valve and a minority with dysplastic valves in our study is similar to the findings of a study done by Rao PS.[2]

The indications for PBPV in our cohort were moderate PS (21%) and severe PS (79%), based on the echocardiographically derived Doppler gradient, similar to other studies where PBPV was done in patients with moderate and severe PS.[2,8,11,18]

The mean pulmonary valve annulus measured on angiography was 11.2mm (SD 3.9) and the mean balloon size was 13.1mm (SD 4.4), with a balloon to PVA ratio of 1.169:1. A slightly smaller balloon / PVA of 1.125 ratio was documented by Maostafa, et al. where the mean pulmonary valve annulus was 14.23mm (SD2.7) and the mean balloon size was 16.02mm (SD 3.00).[4] The majority of the patients in the latter study were infants and older children, with no reference made to neonates. Smaller balloon / PVA ratios of 1.1 were used in neonates in a study conducted by Loureiro P, et al. and the recommendation is to use balloon sizes not exceeding a balloon / PVA ratio of 1.1 in this age group.[23]

The success rate of PBPV in our cohort was 88%, which is similar to what has been reported by studies done in Iran and Spain, with reported success rates ranging from 75% - 88%.[4,5] The median peak instantaneous (PIG) before balloon valvuloplasty was 79mmHg (IQR 64 - 102mmHg) which decreased to 33mmHg (IQR 23 - 40mmgHg) after balloon valvuloplasty. There was a poor response to PBPV in the minority of the study patients (7.4%, n=5) due to the presence of dysplastic valves which are poorly responsive to balloon valvuloplasty. Similarly, 6.7% (n=4) of the cohort reported by Maostafa, et al. had dysplastic pulmonary valves.[4]

Although PBPV has a good success rate a small number have complications that the interventionalist needs to be aware of, in particular pulmonary oedema and infundibular obstruction.[13,14] Shrivastava, et al. from Escorts Heart Institute and Research Centre, New Delhi, India, described 2 cases of pulmonary oedema soon after balloon dilatation of the pulmonary valve.[13] These patients were treated with diuretics, inotropes, and ventilatory support.(13) Only 1/68 (1.47%) patients in our study developed pulmonary oedema following PBPV. This patient showed a good response to diuretics and ventilatory support. Although our patient who developed pulmonary oedema responded to treatment, some cases have been reported to be fatal despite treatment, as reported by Shrivastava, et al.[13] Due to the risk of fatality associated with pulmonary oedema following PBPV, this complication needs to be anticipated prior to starting the procedure.

Infundibular obstruction after PBPV, also referred to as a "suicide right ventricle", may be related to the severity of pulmonary valve obstruction and a hypercontractile infundibulum.[14,15] This complication is rare, and normally results in cases where the RV pressure is suprasystemic before the procedure.[15] Chinawa, et al. did a systematic review from 1987 - 2016, published in the Nigerian Journal of Cardiology, looking at suicidal right ventricle in children and adults following PBPV.[15] The review showed that this complication is rare, which is similar to the findings from our study where this complication was seen in 2/68 (2.9%) patients. Relief of the infundibular obstruction can be treated with administration of b-blockers.[14,15] The patients in our cohort were treated with beta-blockers, with both showing a good response. Suicide right ventricle should be anticipated particularly in patients who have suprasystemic RV pressure prior to the procedure, and pre-procedure administration of a beta-blocker may be helpful as a prevention strategy.[15]

Another complication described is the development of pulmonary regurgitation. Most studies report a low incidence of significant pulmonary regurgitation following PBPV in the paediatric population.[4,20,21] Studies done by Maostafa, et al. in Iran and Al Balushi, et al. in Muscat reported a low incidence of significant pulmonary regurgitation.[4,21] Maostafa, et al. reported an incidence of 18% for moderate pulmonary regurgitation and 6% for severe regurgitation.[4] Al Balushi reported an incidence of 3.8% for moderate pulmonary regurgitation. The low incidence of significant pulmonary regurgitation reported was similar to the findings in our study, with only 2/68 (2.9%) developing severe pulmonary regurgitation in our study. The use of large balloon sizes, complex valvular morphology due to a previous surgical valvotomy or the presence of dysplastic valves have been associated with the development of significant pulmonary regurgitation following PBPV.[24]

The 2 patients who developed severe pulmonary regurgitation in our cohort had balloon to PVA ratios of 1.1 and 1.2 respectively used, which is within the recommended range. One patient had serial balloon dilatations done; however, the biggest balloon used had a balloon to PVA ratio of 1.2. Both patients who developed severe pulmonary regurgitation had dysplastic valves. It appears that in our cohort the development of pulmonary regurgitation was observed in some patients with dysplastic valves and was not related to the balloon sizing as both patients had adequate balloon sizing. The presence of complex valvular morphology, which includes dysplastic valves has also been associated with the development of significant pulmonary regurgitation as reported in a study done by Hatem, et al. which may have been the risk factor associated with severe pulmonary regurgitation in our patients.[24] In addition

to adequate balloon sizing as a precaution to prevent the development of severe pulmonary regurgitation, patients with complex valvular morphology should be monitored closely for the development of this complication. The 2 patients who developed severe pulmonary regurgitation in our study have remained asymptomatic and are currently being monitored clinically.

In our cohort, 1 patient died during PBPV following perforation of the RVOT with a wire. The patient who died was a neonate with critical pulmonary stenosis. This complication of RVOT perforation has been described by Maostafa, et al. where they also encountered a death in a neonate with critical pulmonary stenosis following perforation of the RVOT.[4]

Over the 3 decades of our study, the procedure of PBPV has evolved. During the first decade of the study, a balloon to PVA ratio of 1.3 was used, which changed over the years to a ratio of 1.2, with more research done around the procedure. The technique of PBPV and patient selection have remained the same over the 3 decades of the study. Furthermore, there has been an increase in awareness and anticipation of immediate complications described, such as pulmonary oedema and suicidal right ventricle, resulting in prompt treatment of such complications when they arise.

CONCLUSION

PBPV is a safe and effective treatment of moderate and severe PS with a good outcome and should continue to be the treatment of choice for moderate and severe PS. Complications are infrequent if procedural guidelines are followed. Rare complications such as infundibular obstruction and pulmonary oedema following PBPV should be anticipated and managed quickly. Appropriate sizing of the balloon is important to avoid the development of significant pulmonary regurgitation.

LIMITATIONS

The retrospective nature of the study and the small sample size are limitations of our study.

FUTURE RESEARCH

Most studies have looked at short- and medium-term complications of PBPV, but there are few studies that focus on the long-term complications. An area for future research would be to look at the long-term complications of PBPV.

Conflict of interest: none declared.

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ECG Quiz 66

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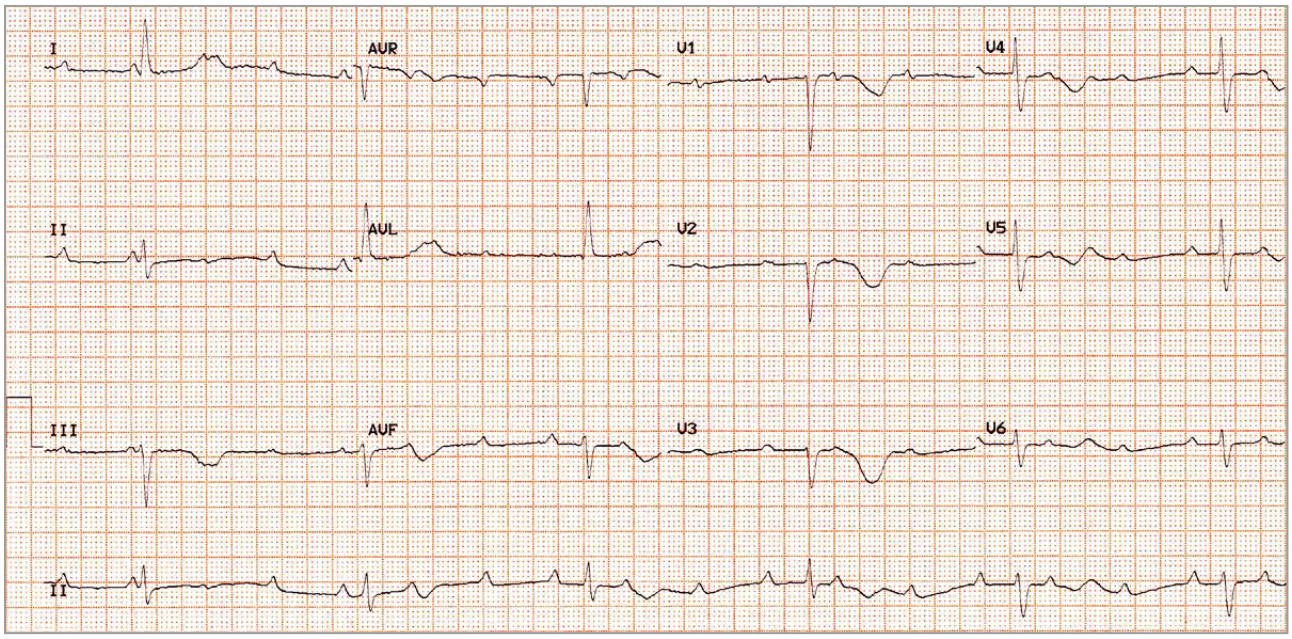

An 80-year-old woman complains of feeling very tired and short of breath on minimal exertion.

QUESTION 1: Which of the following diagnoses are compatible with this ECG?

a. Complete heart block
b. High grade AV block
c. Mobitz II AV block
d. Isorhythmic AV dissociation

QUESTION 2: She is being monitored in ICU. Would you insert a temporary pacing lead?

a. Yes
b. No
c. Maybe

Please analyse the ECG carefully and commit yourself to an answer before checking the explanation.

ANSWER on page 265

1. OVERVIEW OF THE ECG

Marked bradycardia (mean 36/min), regular until the last 2 QRS complexes which are slightly faster. The QRS complexes are wide (140ms). There are non-conducted P waves.

MORE DETAILED ANALYSIS OF THE ECG

The atrial rate is 106/min, with variable PR interval, so there is AV dissociation. The QT interval is markedly prolonged at 720ms (QTc 557ms). The last 2 complexes have a different morphology to those preceding.

High grade AV block (3:1 and higher ratios of Ps to QRS complexes) requires the presence of at least 1 conducted QRS. The last 2 QRS complexes are preceded by P waves, but the PR intervals differ. This indicates that the escape rhythm has changed to a different focus and is not conducted.

Mobitz II AV block requires at least 2 consecutively conducted P waves before the block occurs, which is clearly not the case here (Figure 1).

Isorhythmic AV dissociation only occurs when the atrial and ventricular rates are very close (Figure 2).

The criteria for complete heart block are met:

- More P waves then QRS complexes.
- AV dissociation.
- Slow ventricular escape rhythm (usually regular).

The correct answer is therefore (a): Complete heart block.

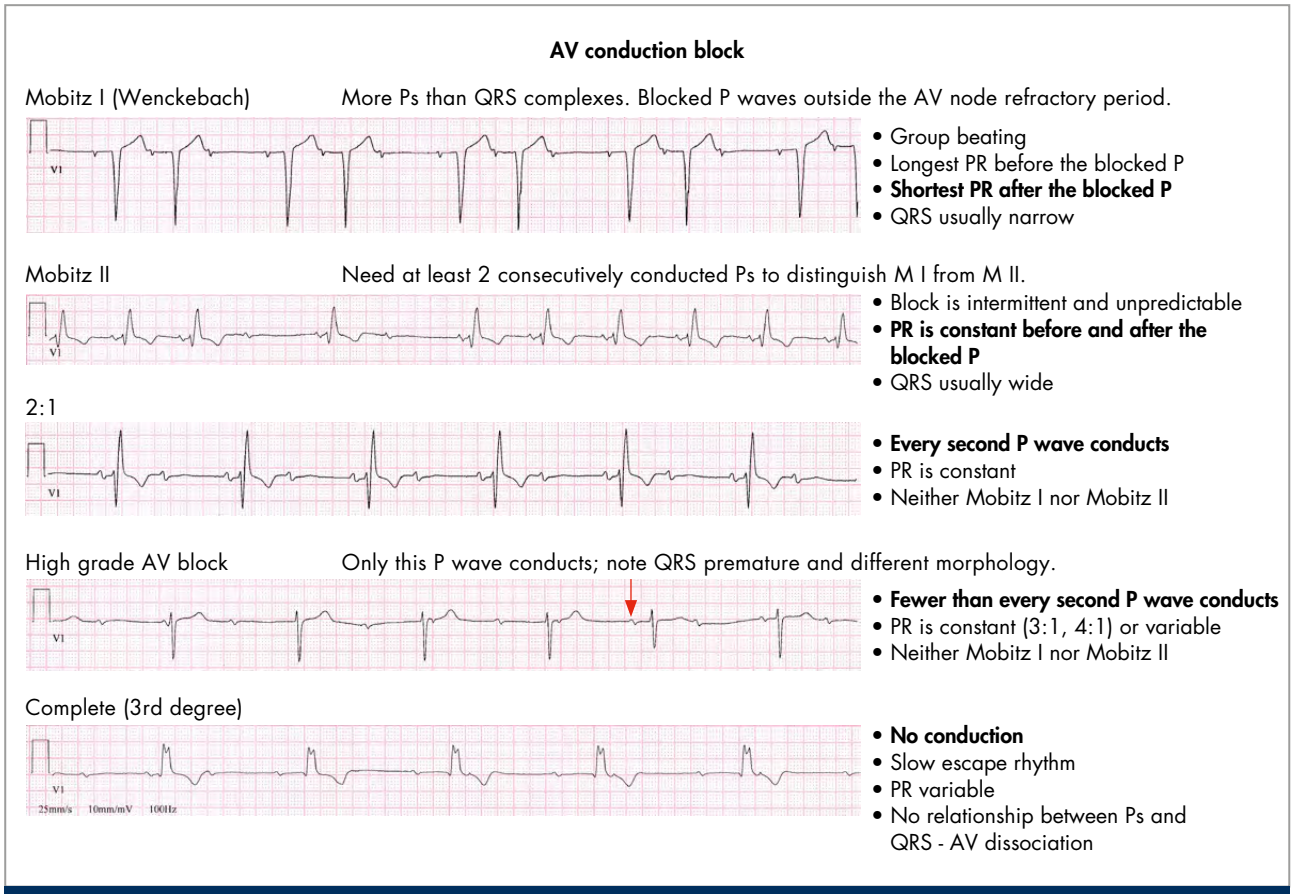

FIGURE 1: AV Conduction Block.

FIGURE 2: Isorhythmic AV dissociation.

2. SHE IS BEING MONITORED IN ICU;WOULD YOU INSERT A TEMPORARY PACING LEAD?

Temporary pacing leads have potential complications and are better avoided, if possible.

However, there are features of this ECG which strongly suggest that she should have a temporary pacing lead inserted, even though she has not had syncope. The sinus tachycardia of 106/min indicates that the heart is under stress and there has been catecholamine activation.

The last 2 complexes differ in morphology to those preceding and are slightly faster, indicating a change in the escape rhythm focus. An unstable escape rhythm indicates a risk of asystole (Figure 3).

The markedly prolonged QT interval is a strong reason to start temporary pacing without delay. A QT over about 600ms indicates a high likelihood of developing torsade de pointes ventricular tachycardia which can quickly degenerate into ventricular fibrillation or be followed by ventricular asystole. The pacing wire can be inserted via the femoral vein, where it will not interfere with the permanent pacemaker implantation, which should be done as soon as possible.

A temporary pacer had not been instituted and she developed a run of torsade de pointes, followed by asystole (Figure 4). Fortunately, an escape rhythm kicked in.

Increasing the heart rate by pacing will shorten the QT and reduce the dispersion of depolarisation that precipitates this arrhythmia (Figure 5) and removes the risk of asystole.

The answer is (a): Yes.

DISCUSSION

Complete heart block is a lethal arrhythmia (Figure 6) and is an indication for urgent admission to a centre where a permanent pacemaker can be inserted. Exceptions include conditions in which the AV block is reversable, e.g. acute inferior wall myocardial infarction.

We don't know how many people die with their first Stokes-Adams attack. A natural history study, published in 1964[1]

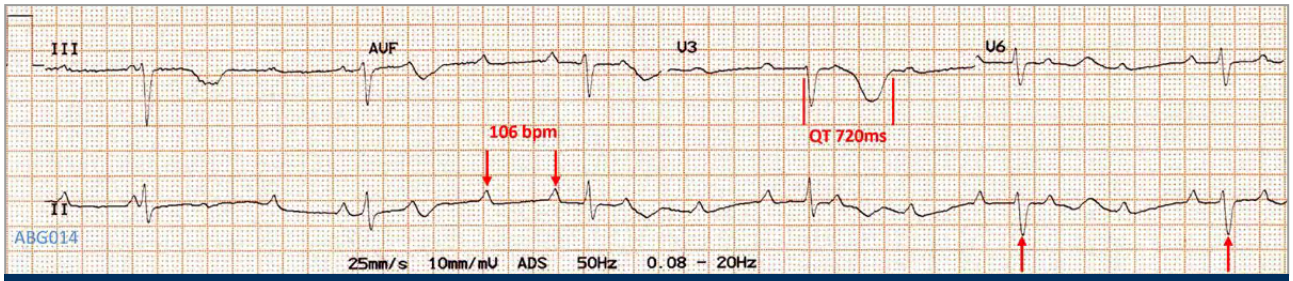

FIGURE 3: Sinus tachycardia, prolonged QT interval and change in escape focus.

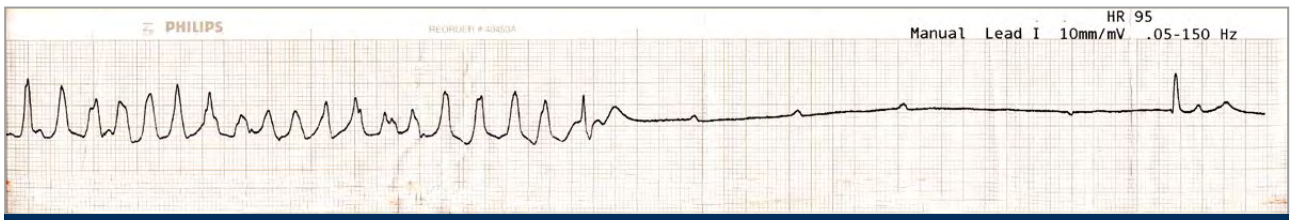

FIGURE 4: Torsade de Pointes, followed by asystole.

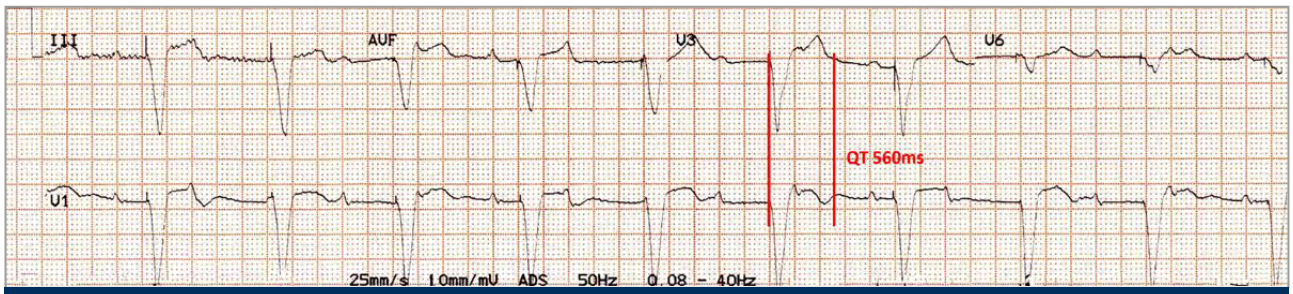

FIGURE 5: Shortened QT after temporary pacing.

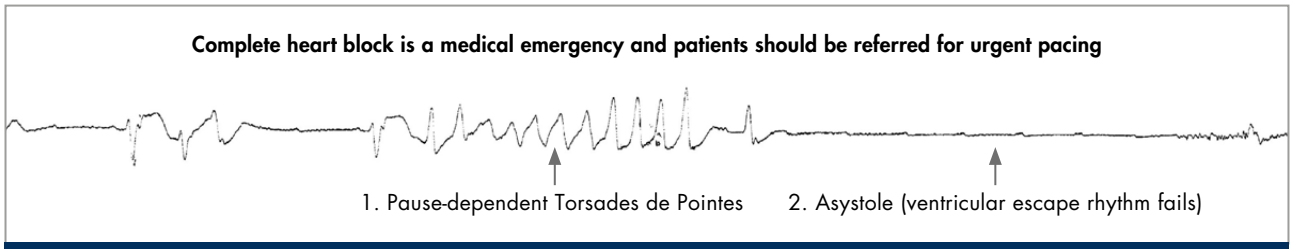

FIGURE 6: Mechanisms of death in complete heart block.

followed 100 patients for up to 5 years. Fifty percent died within a year, but only 37 were known to be alive (Figure 7). The fall off was slower after that but only 20 were known to be alive at 5 years. Five studies, including one from Johannesburg, of patients with early pacemakers (mostly VOO), showed 1 year survival of 80% -90% and 5 year survival of 60% - 70%. The study by Monty Zion, Paul Marchand and Pro Obel[2] compared the survival to an age-matched insured population and showed no significant difference in survival between the paced patients and the controls. There are few interventions in medicine that compare with this dramatic improvement, both in longevity and relief of symptoms. The artificial cardiac pacemaker has been acknowledged as one of the great inventions of the 20th century.

Most patients who develop heart block are over the age of 65. In most cases, no cause is evident. Idiopathic age-related degeneration of the conducting system is the most likely pathology

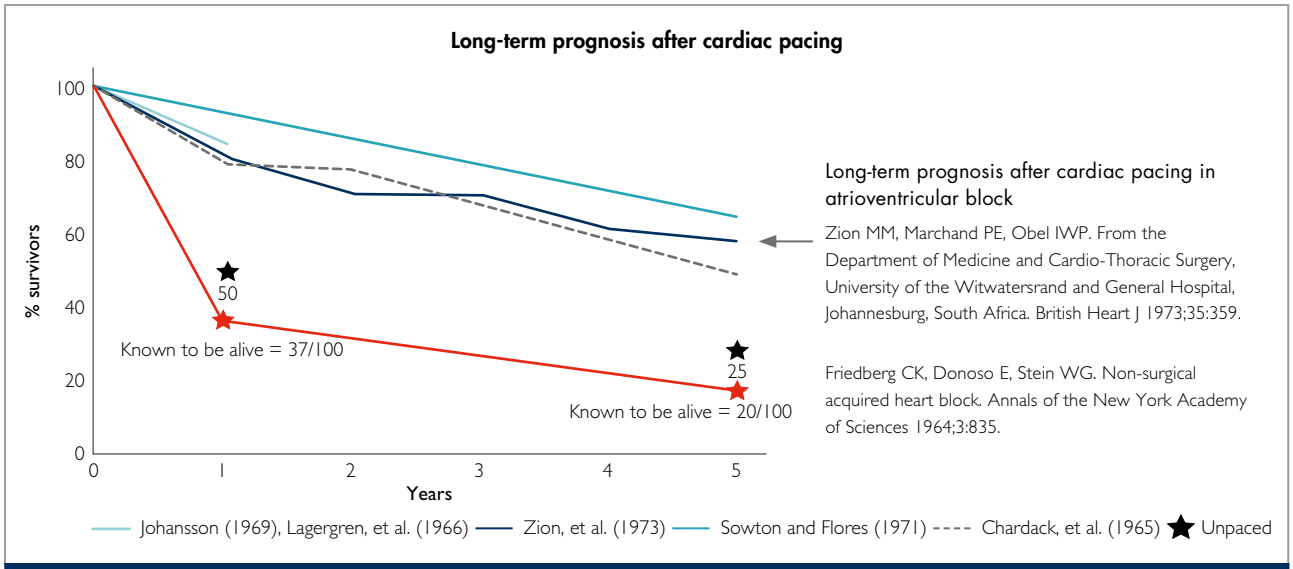

FIGURE 7: Effect of pacing on long term prognosis.

FIGURE 7: Survival curves in this and in previously reported series, compared with the natural history for atrioventricular block.

(Lenegre's disease). They will often be otherwise fit and well for their age and will benefit from pacing, even into their 90s. However, heart block can occur at any age from in utero onwards. Consider the long list of conditions that can cause heart block (Table I) and perform the necessary investigations, particularly in younger patients. Some cases, such as AV block complicating acute inferior wall STEMI, are reversable and permanent pacing may not be necessary.

If a patient presents with a heart rate under 40/min, an ECG is obviously necessary for a definitive diagnosis. However, clinical signs of AV dissociation will point to the diagnosis:

- A regular, slow pulse but varying pulse volume.
- Irregular canon waves in the jugular venous pulse.
- Varying intensity of the first heart sound.

In an older person, the pulse pressure tends to be high. A typical BP would be 170/70mmHg. Left ventricular function is usually normal and compensates for the slow rate by increasing stroke volume. This higher stroke volume is being ejected into a non-compliant arterial tree, causing a high systolic pressure. Lack of elastic recoil and long diastolic time contribute to a lower diastolic pressure. If the BP is low, suspect an acute cause, such as myocardial infarction or myocarditis.

A patient who develops heart block in South Africa has to have access to a doctor who will do an ECG and recognise the condition and act appropriately by referring him or her directly and urgently to a practitioner or hospital that can implant a pacemaker. A survey of GP's ability to recognise important arrhythmias showed that only 1% were able to diagnose complete heart block.[3] This is a shocking statistic, given the seriousness of the condition and the effectiveness of treatment. Prof Chin tells me that they are still getting referrals of patients with heart block to Groote Schuur hospital, correctly diagnosed, to an outpatient clinic instead of to the emergency room for urgent admission.

Access to diagnosis and treatment, particularly in rural areas, is poor. It is reflected in the unequal distribution of pacemaker implants in White vs. Black South Africans.[4] More recent comparisons are not available, but the 2001 survey of cardiac pacing in South Africa showed large discrepancies in implant rates between the insured (mostly White) with the uninsured (mostly Black) population, with a ratio around 8.5:1.[4] Implant

TABLE I: Causes of heart block

Older age The risk increases with advancing age, due to idiopathic age-related degeneration of the conducting system. These are the majority of cases.	**Chronic infiltrative / inflammatory myocardial disease** • Sarcoidosis • Other granulomas (e.g. Wegener's) • Amyloid • Connective tissue disorders • Tuberculosis • Chaga's disease (South America)
Idiopathic Can occur at any age. Some of these cases are probably due to undiagnosed infiltrative conditions, such as sarcoidosis.	**Aortitis** • Ankylosing spondylitis • Syphilis
Acute myocardial damage **Infarction.** Second or third degree AV block is most common after inferior ST elevation myocardial infarction (STEMI). This is usually transient, especially after successful reperfusion, and does not require a permanent pacemaker. AV block after anterior STEMI is more serious. It tends to occur with large infarcts destroying the interventricular septum. Survivors should be paced. **Myocarditis** • Heart block is common in myocarditis from a variety of causes – viral, Lyme disease, typhoid, and others **Trauma** (e.g. stab)	**Genetic** • Muscular dystrophies - Kearn-Sayers - Myotonic dystrophy • Inherited conduction disease - E.g. Progressive familial heart block
Chronic myocardial disease • Ischaemic • Cardiomyopathy	**Drugs** (usually in overdose or combination) • Digoxin • Calcium channel blockers • Beta blockers – usually in combination with digoxin or calcium blocker • Sodium channel blockers – e.g. Class II antiarrhythmics, antidepressants
Post surgical • Valve repair / replacement • Following surgery for congenital heart disease • Following trans-cutaneous aortic valve implantation	**Other** • Hyperkalaemia – usually causes sinus slowing, PR prolongation and P wave flattening, but may cause complete heart block • Hyperthyroidism is a rare cause of heart block, usually precipitated by an intercurrent infection
Infective endocarditis	

rates among Whites approximated the average in Europe. This may be partly explained by the relative youth of the Black population, but it is unlikely to account for so large a difference. Heart block accounted for more than 80% of implants in the public sector, as opposed to 45% in the private sector, typical of a resource poor environment. While there is likely to be shift over the last 23 years with growth in the number of insured Black people, there is no reason to believe that this life-saving treatment has become more accessible to indigent, mostly rural people, given the poor state of peripheral health services, many of which do not even have an ECG machine. The overall implant rate has, however, increased significantly from 39/m in 1998[5] to 132/m in 2013.[6]

The situation is even worse in the rest of sub-Saharan Africa, with only a few countries providing pacemakers, usually only in the private sector. Attempts are being made to improve this, by providing training in pacemaker implantation in South Africa to doctors from other African countries, and trying to secure donations of resterilised explanted units for indigent patients.

LESSONS AND CONCLUSIONS

- **A heart rate below 40/min is heart block until proven otherwise** – 40 to 50 is suspicious.
  - A bradycardia in which there are more P waves than QRS complexes = heart block.
  - Heart block + AV dissociation (no relationship of Ps to QRS complexes) = complete heart block.
  - The escape rhythm is usually wide (ventricular) and regular but may be narrow (junctional).
  - Escape rhythms are often unreliable, as in the case presented.
  - A QT interval over 600ms increases the risk of torsade de pointes, which may degenerate into VF.
  - The mechanism of syncope is either torsade de pointes or asystole.
  - The mechanism of sudden death is either ventricular fibrillation or asystole.
- **Heart block is a medical emergency.** Refer urgently for pacing, even if asymptomatic.
- **Pacemakers save lives.**

Conflict of interest: none declared.

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ECG and **QUESTION** on page 264

CARDIAC IMAGING QUIZ

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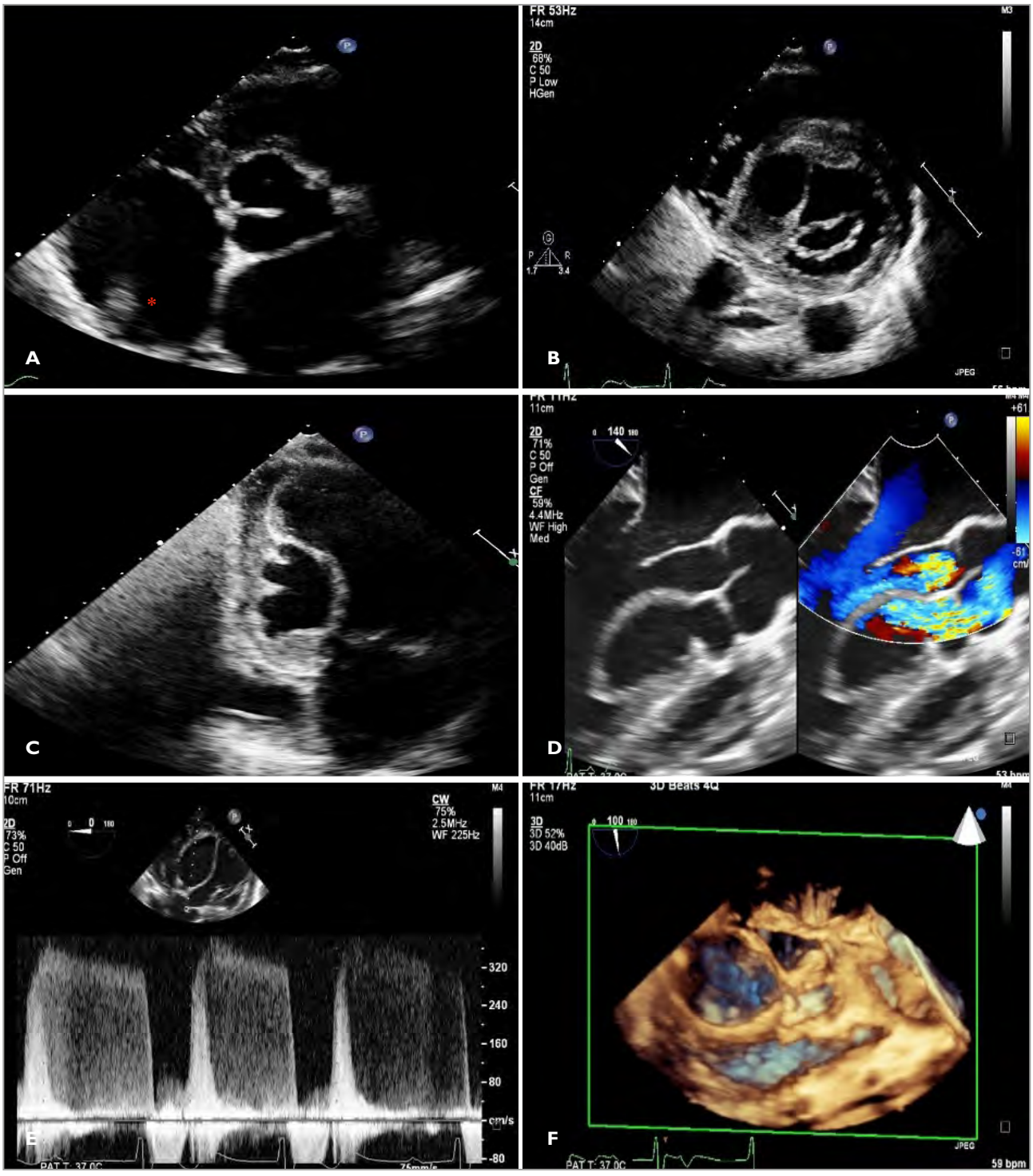

QUESTION: What is the diagnosis?

A. Infective endocarditis B. Aortic aneurysm C. Sinus of Valsalva aneurysm D. Coronary arterial-venous fistula

ANSWER

C. Sinus of Valsalva aneurysm involving the right coronary sinus (A, short axis view) complicated by aortic regurgitation (D, E), erosion into the interventricular septum (B, short axis view and C, 2 chamber view; D, long axis view and F, 3D reconstruction) and complete heart block (A, right atrial / ventricular lead marked with asterisks).

These images belong to a 50-year-old male who presented in heart failure and complete heart block.

A sinus of Valsalva aneurysm (SVA) results from a weakness in the elastic lamina at the junction between the aortic media and the annulus fibrosus. Although the true prevalence is unclear, autopsy studies suggest that SVAs occur in less than 0.1% of the general population. These aneurysms can be congenital, and may be linked to connective tissue disorders such as Marfan syndrome, or acquired due to conditions like syphilis or atherosclerosis. They most frequently develop from the right coronary sinus (in 70% of cases), and less frequently from the non-coronary sinus (in 25%). If rupture occurs, the resulting shunt typically leads to the right ventricle or right atrium. Complications such as right ventricular outflow obstruction, coronary artery compression with infarction, conduction disturbances, endocarditis, and thrombus formation within the aneurysmal cavity have also been reported. While many patients remain asymptomatic, some may experience chest pain, shortness of breath, or heart failure. Rupture is a serious complication that can result in life-threatening conditions, including shock or the formation of an aortic fistula. Diagnosis is usually confirmed through echocardiography, CT, or MRI, and surgical repair is the standard treatment, particularly for large or symptomatic aneurysms. Without treatment, rupture can be fatal, but early detection and surgical intervention typically result in a favourable prognosis.

Conflict of interest: none declared.

SUGGESTED READING

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