ISSN 1996-6741 (Print)
ISSN 2071-4602 (Online)

SA HEART®

Journal of the South African Heart Association

2024
Volume 21 Number 1

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A view of Cathedral Peak from the Hotel.
Photo: Tony Dalby

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COMMENTARY

Interim Editor, Dr Tony Dalby
Cardiologist, Life Fourways Hospital, Fourways, Johannesburg, South Africa
Chair, SA Heart Board®

Revitalisation of the SA Heart® Journal

The SA Heart® Journal is the academic mouthpiece of cardiology in South Africa and deserves the support of the Association's members.

Circumstances arose during 2023 that led to the failure of publication of the Journal, the exception being the Congress issue edited by Dr Blanche Cupido. The Board is acutely aware of the amount of work involved in preparing a submission and offers its sincere apology to the authors whose work has gone unpublished to date. The former Editor has dealt with the backlog. Accepted articles are expected to be published shortly.

An Interim Editor was appointed by the Board to see to the publication of submissions received this year. Special thanks are due to Drs Stephen Brown, George Comitis, Rob Kinsley, John Lawrenson, Ruchika Meel, Tim Pennell, Mohammed Talle and Andrew Thornton who freely gave of their time and expertise to critically review these papers. The current edition is the product of their joint contribution. I trust you find the content enlightening.

SA Heart® will soon be appointing a new Editor who will be assisted by section sub-Editors to ensure the continued publication of the Journal.

Guest Editor, Professor Eric Klug
Associate Professor, University of the Witwatersrand, Johannesburg, South Africa
President, SA Heart®

SA Heart®: Beating strong for South Africa's cardiovascular health

The South African Heart Association (SA Heart®) stands as a vital pillar in our nation's healthcare landscape. Our not-for-profit organisation, driven by a dedicated team and a resolute mission, serves as the powerful voice of cardiovascular care in South Africa. SA Heart®'s commitment extends far beyond advocacy – it fosters collaboration, propels research, and strives to ensure exceptional care for all South Africans, from the tiniest hearts to the most seasoned.

The strength of SA Heart® lies in its comprehensive structure. An impressive Board of directors sets the strategic course, while the executive committee translates vision into action. Special interest groups, catering to specific areas of cardiovascular medicine, allow for focused expertise. Regional branches ensure a nationwide reach, bringing SA Heart®'s resources and guidance to every corner of the country. Underpinning this impressive framework is a dedicated team. The general manager steers the organisation's day-to-day operations, while the stakeholder manager cultivates vital relationships with healthcare professionals, policymakers and the public.

Presently SA Heart® stands at a crossroad. As the leading voice for cardiovascular care in South Africa, we hold immense power to improve the health of our nation. But the road ahead is not without its challenges.

Firstly, we must solidify SA Heart®'s brand as a unified, coherent force. This means ensuring that our diverse membership – adult and paediatric cardiologists, researchers, and allied health professionals – operates under a single banner. Unity of purpose will amplify our impact and project a clearer image of unwavering support for our members.

Secondly, we need to address the growing pressure from private health funders. We cannot stand idly by when funders attempt to restrict clinical autonomy and limit diagnostic and therapeutic options for our patients. SA Heart® will be a relentless advocate for both patient well-being and the best practices within cardiovascular medicine.

The looming implementation of National Health Insurance (NHI) presents an additional hurdle. While it is admirable to strive for universal healthcare, building it on a fragile public healthcare system with strained finances creates a worrying scenario.

Engaging the next generation of cardiovascular professionals is crucial. We actively encourage younger members to volunteer and participate in SA Heart®'s structures. Their fresh perspectives and enthusiasm are vital to the future of our organisation.

By fostering a patient advisory group, we create a vital communication channel that benefits patients, practitioners, and the entire healthcare landscape. This is a major priority for SA Heart® in 2024. Advocacy efforts will hopefully work to influence policy decisions that prioritise cardiovascular health and improve access to quality care for all. SA Heart® intends to be a proactive voice in the process.

A pivotal tool in our mission is the SA Heart® Journal. However, its viability rests on finding a dedicated editor, securing financial resources, and streamlining administration. This may be the final edition of the Journal, but we cannot afford to lose this valuable platform for knowledge sharing and advancement in cardiac care.

By presenting a unified front, attracting young talent, and securing the future of the SA Heart® Journal, we can overcome obstacles and emerge stronger. SA Heart® is not just an organisation; it is a testament to unwavering dedication. It is the tireless work of the Board, the executive committee, special interest groups, regional branches, the general manager and the stakeholder manager – united by a common purpose - that ensures that every South African heart beats strong and healthy and that its members are supported, protected and secure in their invaluable professional careers.

SA Heart® needs your support to achieve its aims. A cohesive society is a powerful one. This is the moment for making a concerted effort to promote cardiovascular health in South Africa. Join us, our members, and our dedicated staff in reaching that objective. A heart-healthy South Africa will benefit all of us.

NOMOGRAMS FROM NEONATES

Echocardiography nomograms in Black South African neonates

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ABSTRACT

Background: Quantitative estimation of cardiac chambers, valve annulus and great vessel dimensions in paediatric echocardiography is necessary in clinical management. Various studies have already provided normal values in the paediatric population that represent most populations of the world but there is paucity of data originating from sub-Saharan Africa, particularly in neonates. We sought to establish reliable echocardiography nomograms for cardiac chambers, valve annulus, great vessels, and thymus dimensions in the Black South African neonatal population.

Methods: This was a descriptive, cross-sectional study evaluating cardiac chamber, valve annuli, thymus, and great vessel dimensions in Black South African neonates with normal hearts using echocardiography.

Results: This study recruited 386 neonates (51% females, 49% males; Weight range: 2.50 - 4.43kg [mean, 3.180; SD, 0.38]; BSA range: 0.17 - 0.24m^2 [mean, 0.20; SD, 0.01]). After controlling for the effects of confounders, good correlation for most cardiac dimensions were observed. Inter-observer variability revealed a strong correlation (ICC=0.50-0.82) with most measurements. All cardiac dimensions correlated well with body weight and were within ±2 standard deviation with few exceptions.

Conclusion: This study presents nomograms from data acquired from healthy neonates which contributes to the current body of knowledge on cardiac dimensions in the African neonatal age group. SA Heart® 2024;21:6-16

INTRODUCTION

The quantification of cardiac dimensions derived from echocardiography is necessary in assessing cardiac disease in paediatric practice. Evaluation of size and growth of cardiac chambers, valves, and great vessels plays a key role in the diagnosis and management of cardiac disease in children.[1] However, nomograms for these structures are limited in children. Various studies have already provided normal values in the paediatric population that represent most populations throughout the world but there is paucity of data originating from sub-Saharan Africa.[2,3,4] The lack of representative nomograms points to the need for more extensive studies to create reliable, accurate nomograms and reproducible results.[1] Specifically, these studies needed to include larger populations of healthy children and neonates. Other authors have indicated deficiencies in data normalisation according to BSA, and possible differences in normal values related to ethnicity.[1, 5, 6]

The size of cardiovascular structures in neonates is influenced by many elements including growth, gender, race, body composition, basal metabolic rate, haematocrit, exercise, type of delivery, gestational age, and geographical factors.[6] Furthermore, growth of children may be impacted by other influences such as environmental, social, and economic factors of a region; therefore, the development of regional echocardiography nomograms is essential.[4]

This study was undertaken to establish reliable echocardiography nomograms for cardiac chambers, valve annuli, thymus, and great vessels dimensions in Black South African neonatal population at a Southern African tertiary care centre.

METHODOLOGY

Design and population

This was a descriptive, cross-sectional study conducted at Chris Hani Baragwanath Academic Hospital, which evaluated cardiac chambers, valve annuli, the thymus, and great vessel dimensions in Black South African neonates with normal hearts.

Following approval from the "Human Research Ethics Committee (Medical), Ethics Clearance Certificate no. M150721" from the University of the Witwatersrand, a total of 386 participants met the inclusion criteria (healthy Black South African newborns born by normal vertex delivery and by Caesarian section with structural normal hearts, at an age of 12 - 24 hours after birth) were enrolled after informed consent was acquired from all the mothers of participating neonates.

Data acquisition and image post processing

Demographic data was collected from the clinical notes. Echocardiographic measurements were performed in accordance with the guidelines by the American Society of Echocardiography[7], using the GE Healthcare Vivid e Compact Digital Ultrasound system. Scanning was done using a 7.5MHz transducer (S6). Cardiovascular structures were measured in millimetres.

Aortic (AO) and LA diameters were measured using M-mode in the parasternal long axis (PLAX) or parasternal short axis (PSAX) views depending on which view had the better image. The aortic diameter was measured during peak systole using the outer edge to inner edge technique. The LA diameter was measured during end-ventricular systole at its greatest dimension and measured from the leading edge of the posterior aortic wall to the leading edge of the posterior LA wall, following which the LA to AO ratio was calculated. LV dimensions [left ventricle internal diameter (LVID), left ventricular posterior wall (LVPW) and interventricular septum (IVS)] were measured on M-mode during end-diastole and during end-systole using the PSAX view.

Semilunar valve annulus (aortic and pulmonary valve) diameters were measured in the 2D view during peak systole, from hinge point to hinge point. The aortic valve annulus (AV ANN) was measured in the PLAX view and pulmonary valve annulus (PV ANN) in the PSAX view at the level of the aorta. Atrioventricular valve annulus (MV and TV) diameters were measured in diastole at the point of maximal valve excursion and the dimensions were measured from hinge point to hinge point in the apical 4 chamber view. The abdominal aorta (ABD AO), main pulmonary artery (MPA) and pulmonary branches (left and right pulmonary artery) were measured in 2D during systole. The MPA, left pulmonary artery (LPA) and right pulmonary artery (RPA) were measured in the PSAX view at the level of the aorta. The ABD AO was measured in 2D in the subcostal view at the point of maximal systolic dimension at the level of the diaphragm. The thymus was measured in the PSAX view at level of aorta using 2D and was measured from anterior chest wall to the most anterior great artery.

Statistical analysis

Collected data was cleaned and entered onto an Excel spreadsheet, and then analysed using XLSTAT v2019 to obtain baseline demographics such as mean, standard deviation and Z-scores. Data was then exported into STATISTICA (v13.5.0) statistical package for further analyses.

Height, weight, body length (BL), body surface area (BSA), mode of delivery (MOD), and gender were used as independent variables in a regression model to predict the effects of confounding factors. Weight was used to express measurements according to body size and Z-scores were calculated to predict mean values of each echocardiographic measurement. Z-scores were computed using formula:[8]

$$Zscore = \frac{x - \mu}{\sigma}$$

Where x is the measured dimension, μ is the mean of the sample and σ is the standard deviation of the sample. ±2 or 3 standard deviation (SD) was calculated using formula:[9]

$$SD = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$$

Where x is the measured dimension, $\bar{x}$ is the predicted mean, and n is the sample size. Predicted mean values were calculated using linear regression model (y = bx + c). The SD was then multiplied by 2 or 3 and added or subtracted from the predicted mean to obtain ±2 or ±3 SD. The inter-observer variability was tested using intraclass correlation coefficient to detect bias. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic data

A total of 386 patients were studied. There was a slightly higher percentage of females (195, 51%), than males (191, 49%). The study cohort consisted of neonates born both by normal vaginal delivery (NVD) and by Caesarian section (C/S) with equal distribution. Weight ranged from 2.50 - 4.43kg (mean, 3.180; SD, 0.38), BL ranged from 39 - 62cm (mean, 5.6; SD, 3.8), BSA

TABLE I: Effects of confounding factors.

Variable	Weight		MOD		Gender		BSA	
	b	p-value	b	p-value	b	p-value	b	p-value
LA	*1.06	*0.000	0.11	0.499	-0.04	0.807	-7.38	0.257
AO DIA	*1.11	*0.000	0.07	0.512	-0.14	0.219	-4.42	0.331
LVIDd	*1.94	*0.000	-0.37	0.143	-0.19	0.444	-6.97	0.507
LVIDs	*1.19	*0.001	-0.32	0.152	-0.19	0.393	-8.70	0.344
MPA	*1.00	*0.000	*-0.48	*0.000	*-0.30	*0.027	1.16	0.836
RPA	*0.31	*0.002	*-0.17	*0.008	*-0.18	*0.005	2.42	0.360
LPA	*0.37	*0.001	*-0.31	*0.000	-0.04	0.572	-1.15	0.708
MV ANN	*0.74	*0.001	*-0.44	*0.002	-0.11	0.455	*12.84	*0.028
TV ANN	*1.28	*0.000	*-0.50	*0.004	0.10	0.578	-5.65	0.434
AV ANN	*0.50	*0.000	-0.10	0.178	-0.01	0.901	-4.35	0.149
PV ANN	*0.95	*0.000	-0.12	0.372	0.13	0.335	4.92	0.391

*LA: left atrium, AO DIA: aortic diameter, LVIDd: left ventricular internal diameter in diastole, LVIDs: left ventricular internal diameter in diastole, MV ANN: mitral valve annulus, TV ANN: tricuspid valve annulus, AV ANN: aortic valve annulus, PV ANN: pulmonary valve annulus, MPA: main pulmonary artery, RPA: right pulmonary artery, LPA: left pulmonary artery. *: significant values.*

TABLE II: LA and AO diameter M-mode measurements in millimetres.

Cardiac dimensions measurements	Standard deviation	Group 1: 2.50 - 2.99	Group 2: 3.00 - 3.49	Group 3: 3.50 - 4.50
LA	3+	15.42	15.88	16.34
	2+	13.91	14.37	14.83
	MEAN	**10.89**	**11.35**	**11.81**
	2-	7.87	8.33	8.79
	3-	6.37	6.82	7.28
AO diameter	3+	12.04	12.52	13.01
	2+	10.98	11.47	11.95
	MEAN	**8.87**	**9.36**	**9.84**
	2-	6.76	7.25	7.73
	3-	5.71	6.19	6.68
LA/AO ratio	3+	1.96	1.97	1.99
	2+	1.76	1.77	1.78
	MEAN	**1.36**	**1.37**	**1.38**
	2-	0.95	0.96	0.97
	3-	0.75	0.76	0.77

LA: left atrium, AO: aorta.

ranged from 0.17 - 0.24me2 (mean, 0.20; SD, 0.01) and gestational age (GA) ranged from 37 - 42 weeks (mean, 39.0; SD, 1.4).

Effects of confounding factors

Multiple linear regression analysis was used to test the effects of confounding factors (weight, MOD, BSA, BL and GA) on all cardiovascular measurements (Table I). Body weight showed a significant relationship with all cardiovascular dimension

TABLE III: LV M-mode measurements in millimetres.

Cardiac dimensions measurements	Standard deviation	Group 1: 2.50 - 2.99	Group 2: 3.00 - 3.49	Group 3: 3.50 - 4.50
IVSd	3+	7.64	7.80	7.97
	2+	6.59	6.76	6.92
	MEAN	**4.50**	**4.66**	**4.83**
	2-	2.41	2.57	2.73
	3-	1.36	1.52	1.68
IVSs	3+	8.61	8.82	9.02
	2+	7.42	7.62	7.82
	MEAN	**5.02**	**5.22**	**5.43**
	2-	2.63	2.83	3.03
	3-	1.43	1.63	1.83
LVIDd	3+	22.79	23.66	24.53
	2+	20.43	21.30	22.17
	MEAN	**15.73**	**16.59**	**17.46**
	2-	11.02	11.88	12.75
	3-	8.66	9.53	10.40
LVIDs	3+	15.88	16.43	16.98
	2+	13.75	14.30	14.86
	MEAN	**9.50**	**10.05**	**10.60**
	2-	5.24	5.79	6.34
	3-	3.11	3.66	4.21
LVPWDd	3+	5.74	5.93	6.11
	2+	4.88	5.06	5.24
	MEAN	**3.14**	**3.33**	**3.51**
	2-	1.41	1.59	1.78
	3-	0.54	0.73	0.91
LVPWDs	3+	7.52	7.62	7.73
	2+	6.53	6.63	6.74
	MEAN	**4.55**	**4.65**	**4.76**
	2-	2.56	2.67	2.77
	3-	1.57	1.68	1.78

IVSd: interventricular septum in diastole, IVSs: interventricular septum in systole, LVIDd: left ventricle internal diameter in diastole, LVIDs: left ventricle internal diameter, LVPWDd: left ventricle posterior wall diameter in diastole, LVPWDs: left ventricle posterior wall diameter in systole.

TABLE IV: Valve 2D measurements in millimetres.

Cardiac dimensions measurements	Standard deviation	Group 1: 2.50 - 2.99	Group 2: 3.00 - 3.49	Group 3: 3.50 - 4.50
MV ANN	3+	12.38	12.80	13.21
	2+	11.03	11.45	11.87
	MEAN	**8.34**	**8.75**	**9.17**
	2-	5.64	6.06	6.47
	3-	4.29	4.71	5.12
TV ANN	3+	14.06	14.64	15.23
	2+	12.39	12.97	13.55
	MEAN	**9.04**	**9.62**	**10.20**
	2-	5.69	6.27	6.86
	3-	4.02	4.60	5.18
PV ANN	3+	10.78	11.19	11.61
	2+	9.47	9.88	10.30
	MEAN	**6.85**	**7.26**	**7.68**
	2-	4.22	4.64	5.05
	3-	2.91	3.33	3.74
AV ANN	3+	7.69	7.91	8.14
	2+	6.99	7.22	7.44
	MEAN	**5.60**	**5.82**	**6.05**
	2-	4.21	4.43	4.66
	3-	3.51	3.73	3.96

MV ANN: mitral valve annulus, TV ANN: tricuspid valve annulus, PV ANN: pulmonary valve annulus, AV ANN: aortic valve annulus.

measurements (p<0.005). Mode of delivery (MOD) had significant associations with atrioventricular valves (p<0.005), main pulmonary artery, and branch pulmonary artery measurements. There were no significant relationships between all cardiac dimension measurements and body length (BL) or gestational age (GA), (p=0.122 - 0.969), nor for gender and BSA (p=0.149 - 0.836).

Inter-observer variability

The inter-observer variability showed a strong correlation in most measurements, (ICC=0.50 - 0.82). The exceptions included PV and TV annulus, with moderate correlation observed (ICC=0.44 - 0.49) and the LVPWD with weak correlation (ICC=0.30 - 0.35).

Echocardiography measurements

All cardiac dimensions correlated well with body weight. All echocardiographic measurements are presented as mean (shown as bold number) and ±3 standard deviations (SD) (Tables II - V). All cardiac dimensions were within ±2 standard deviations, with a few exceptions-score boundaries which are presented as straight lines with actual values as dots in between the boundary lines. Z-scores for each cardiac dimension are

TABLE V: Arterial and thymus 2D echocardiography measurements in millimetres.

Cardiac dimensions measurements	Standard deviation	Group 1: 2.50 - 2.99	Group 2: 3.00 - 3.49	Group 3: 3.50 - 4.50
MPA	3+	10.76	11.25	11.75
	2+	9.45	9.94	10.44
	MEAN	**6.83**	**7.32**	**7.82**
	2-	4.21	4.71	5.21
	3-	2.90	3.40	3.90
RPA	3+	4.81	4.99	5.17
	2+	4.22	4.39	4.57
	MEAN	**3.03**	**3.21**	**3.38**
	2-	1.84	2.02	2.20
	3-	1.25	1.42	1.60
LPA	3+	5.53	5.70	5.88
	2+	4.84	5.01	5.18
	MEAN	**3.45**	**3.62**	**3.79**
	2-	2.06	2.23	2.40
	3-	1.36	1.54	1.71
THYMUS	3+	24.90	25.63	26.36
	2+	22.11	22.84	23.57
	MEAN	**16.53**	**17.25**	**17.98**
	2-	10.94	11.67	12.40
	3-	8.15	8.88	9.61
ABD AO	3+	7.93	8.21	8.50
	2+	7.13	7.42	7.70
	MEAN	**5.53**	**5.82**	**6.11**
	2-	3.94	4.22	4.51
	3-	3.14	3.42	3.71

MPA: main pulmonary artery, RPA: right pulmonary artery, LPA: left pulmonary artery. ABD AO: abdominal aorta.

shown as dots against weight. Z-scores and Z-score boundaries for all measurements are presented graphically in Figures 1 - 9.

DISCUSSION

Quantitative assessment of the heart is critical for assessments of deviation from the normal but can only be done if there are normative values available against which to make comparisons and to identify abnormalities. Paediatric 2D and M-mode echocardiography nomograms of good quality which are available for chamber size, cardiac valve annulus, and great vessel dimensions have been derived mainly from European and American populations.[6,10,11,12,13,14,15]

This study aimed to establish reliable echocardiography nomograms of Black South African neonates. There were only 2 other studies[4,16] from sub-Saharan Africa found in the literature namely, Majonga, et al.[4] who focused on children and

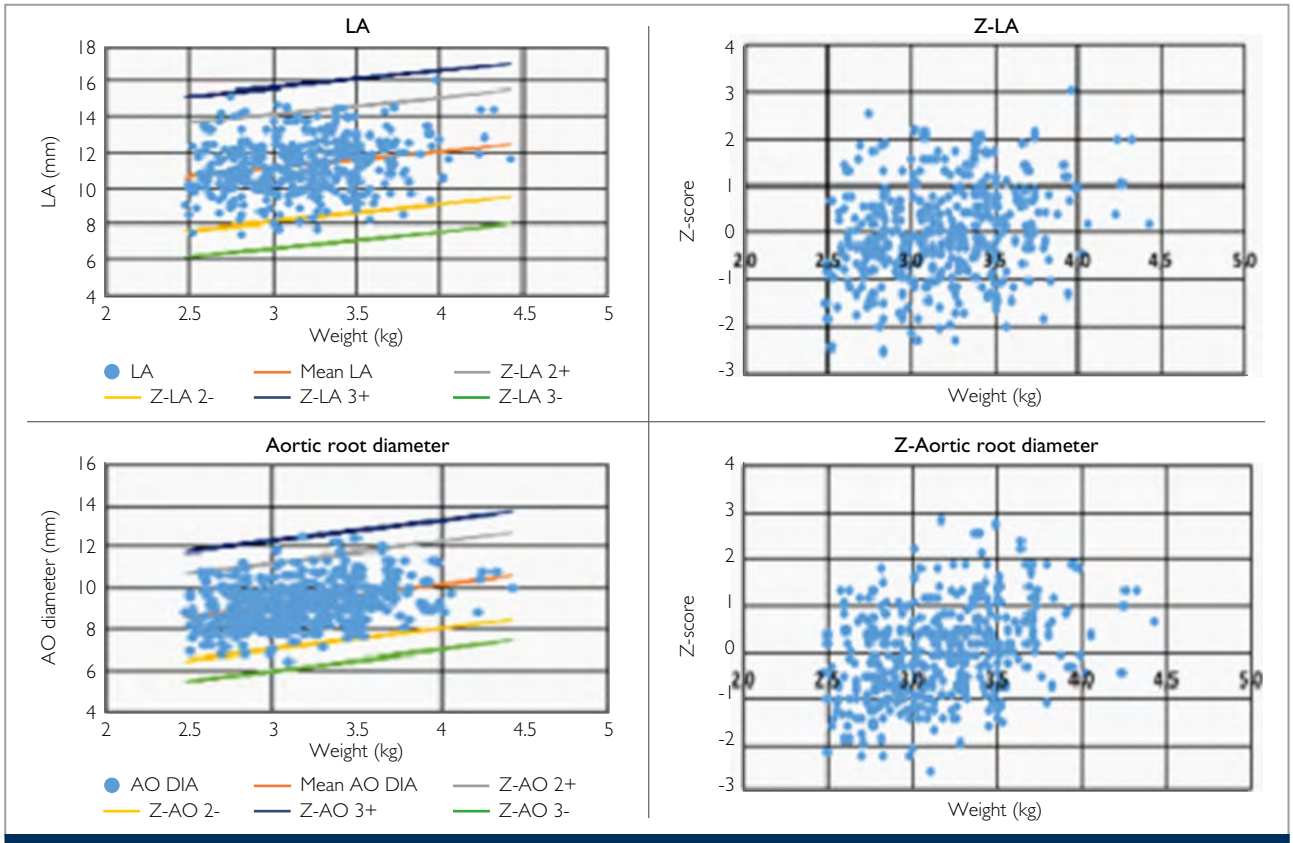

FIGURE 1: Left atrium and aortic root diameter dimension Z-scores and Z-score boundaries by body weight.

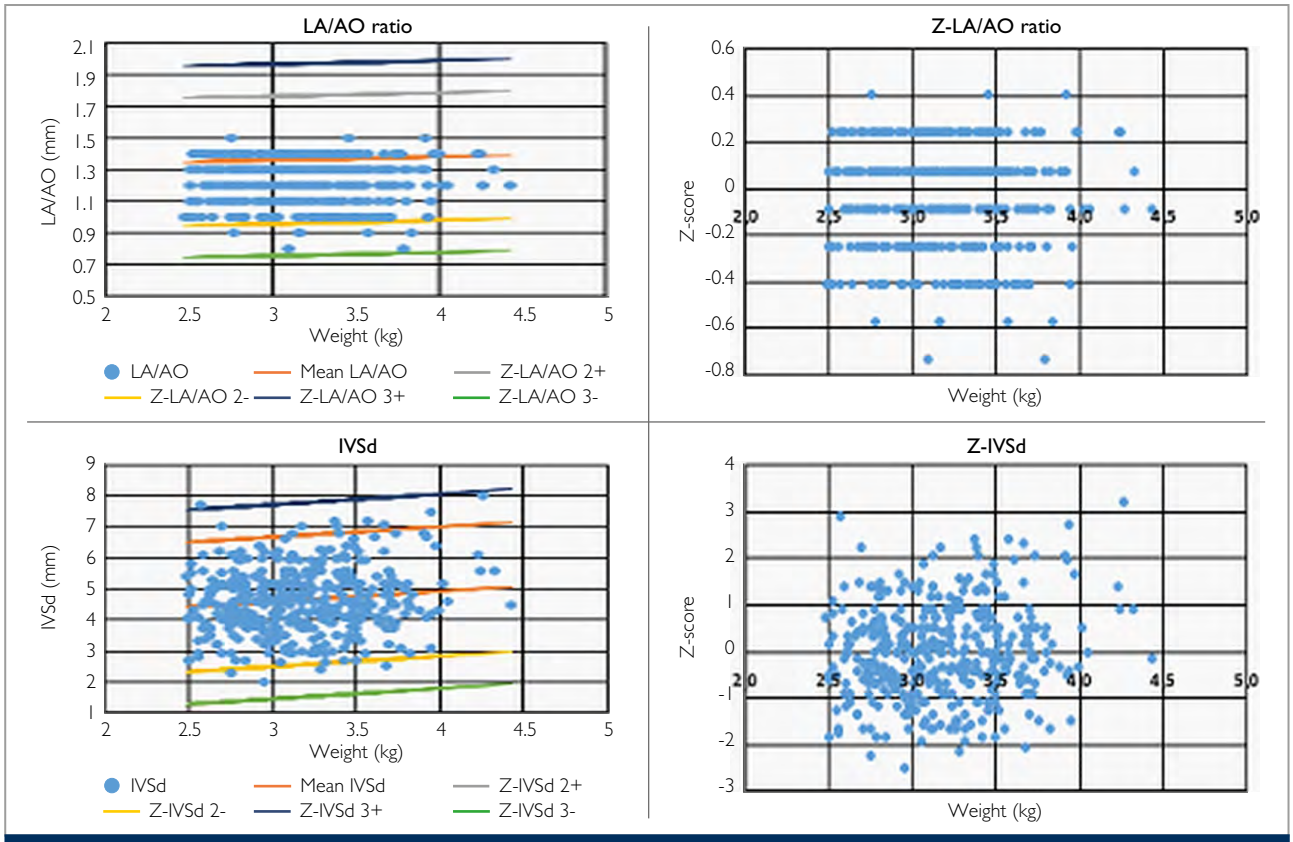

FIGURE 2: LA / AO ratio and IVSd dimension Z-scores and Z-score boundaries by body weight.

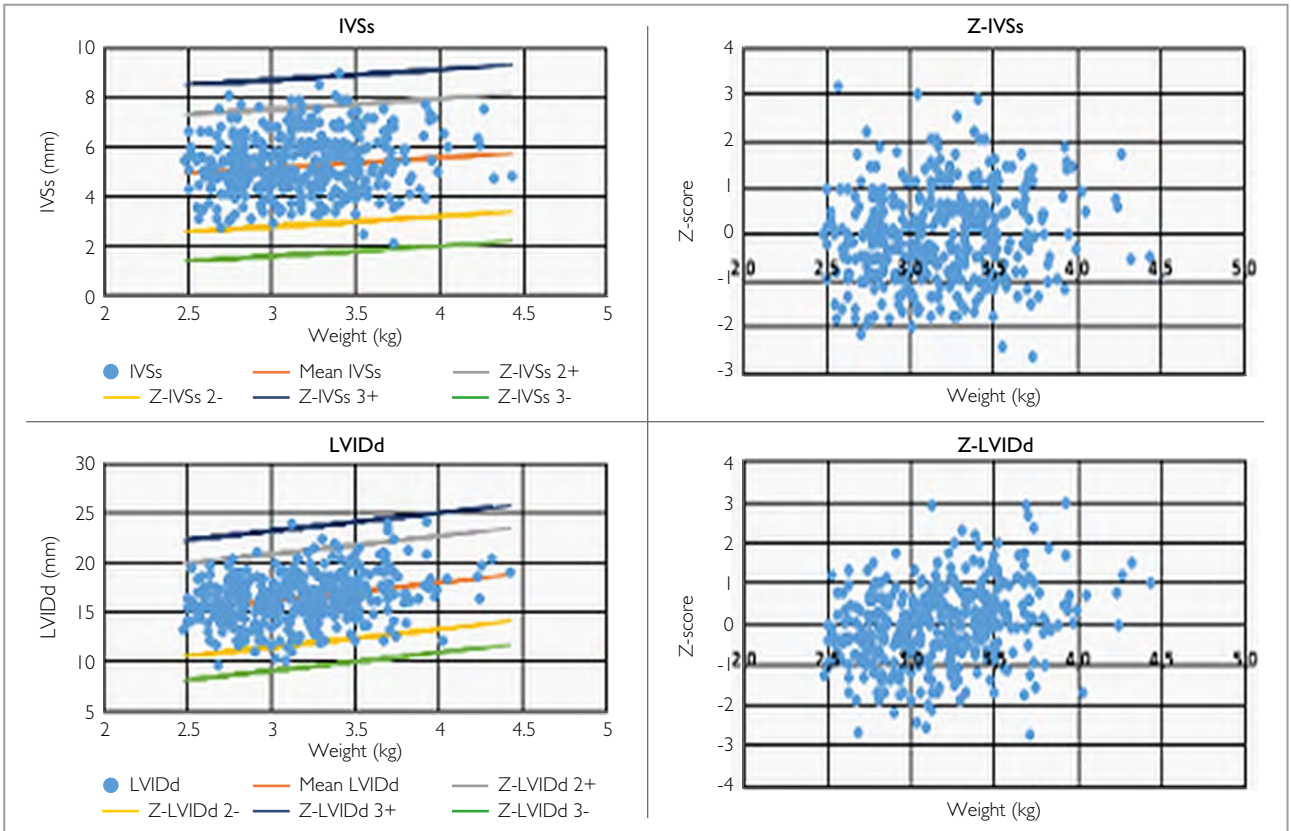

FIGURE 3: IVSs and LVIDd dimension Z-scores and Z-score boundaries by body weight.

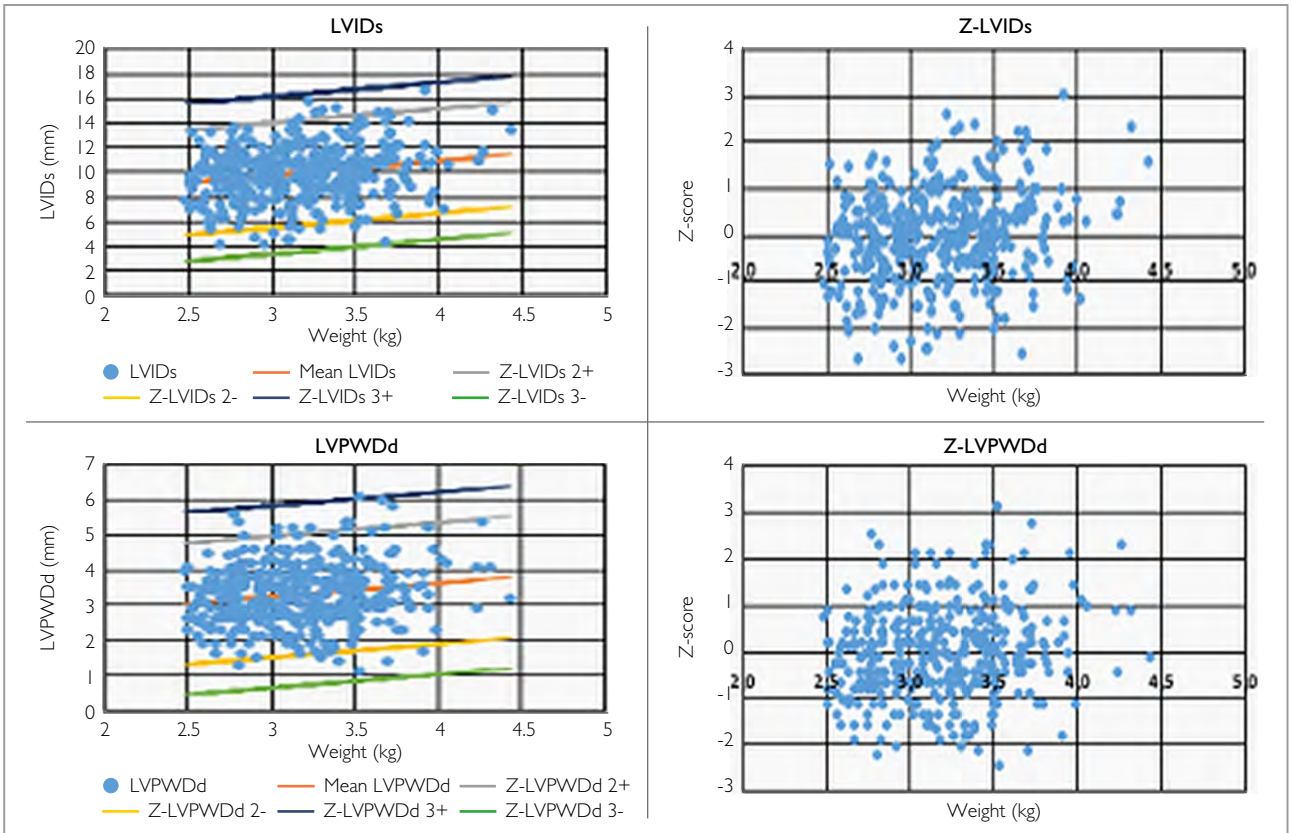

FIGURE 4: LVIDs and LVPWDd dimension Z-scores and Z-score boundaries by body weight.

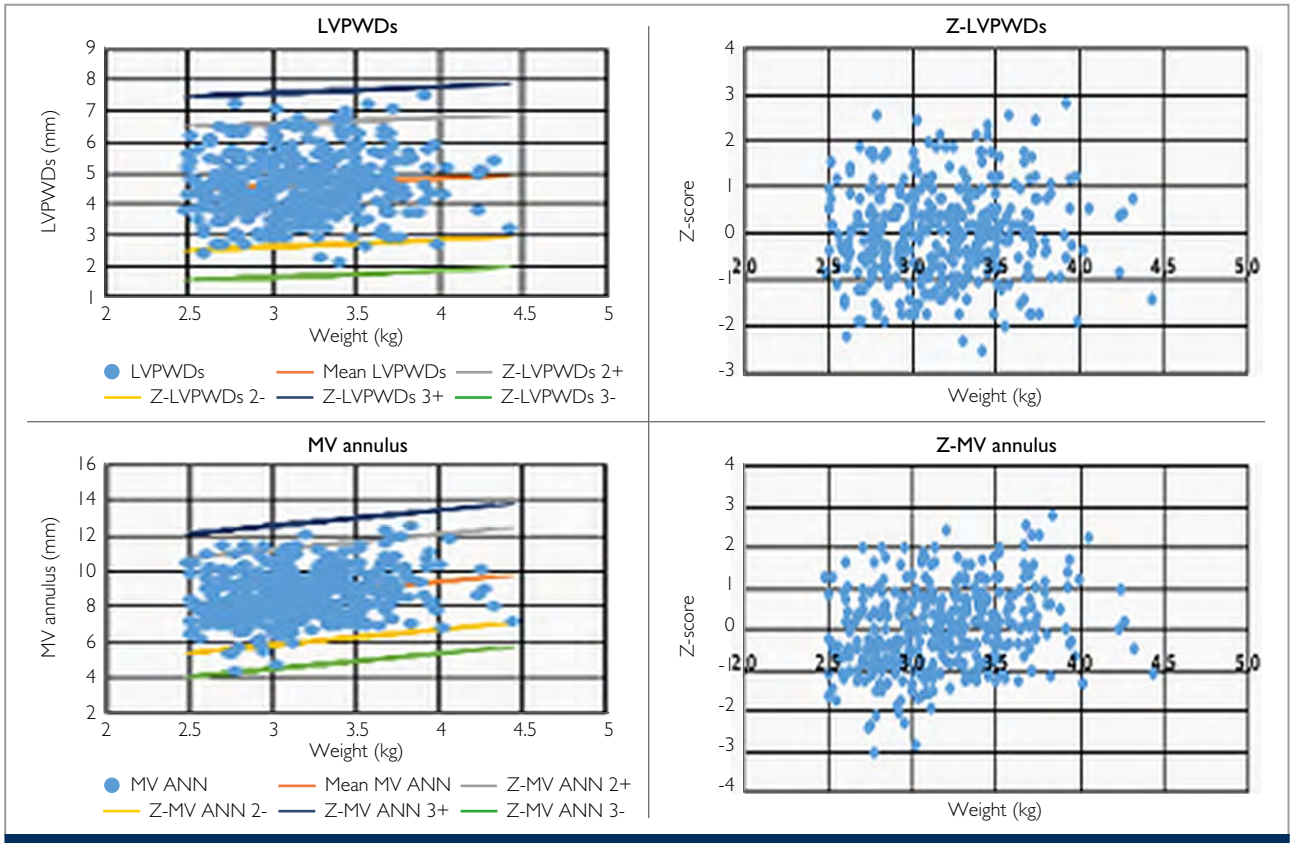

FIGURE 5: LVPWs and MV annulus dimension Z-scores and Z-score boundaries by body weight.

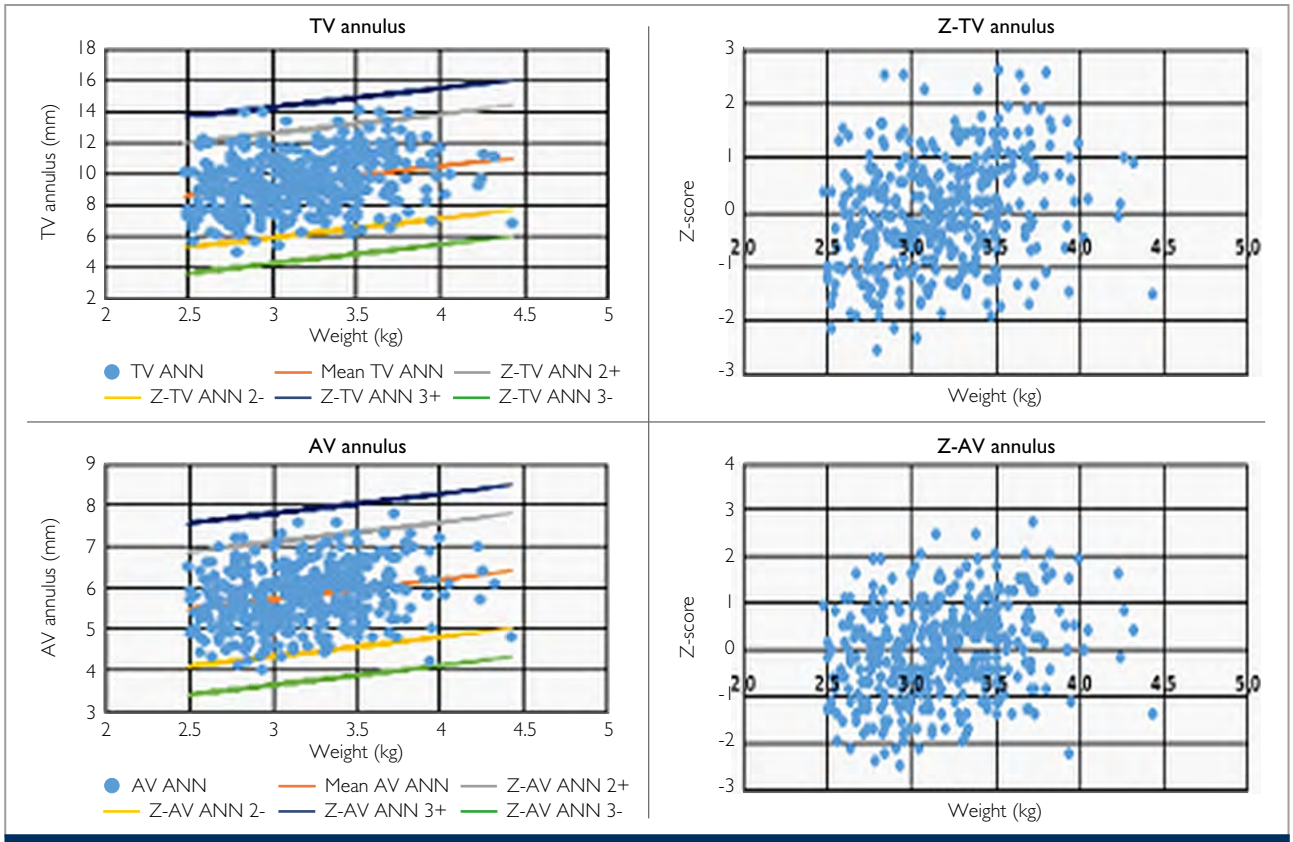

FIGURE 6: TV and AV annulus dimension Z-scores and Z-score boundaries by body weight.

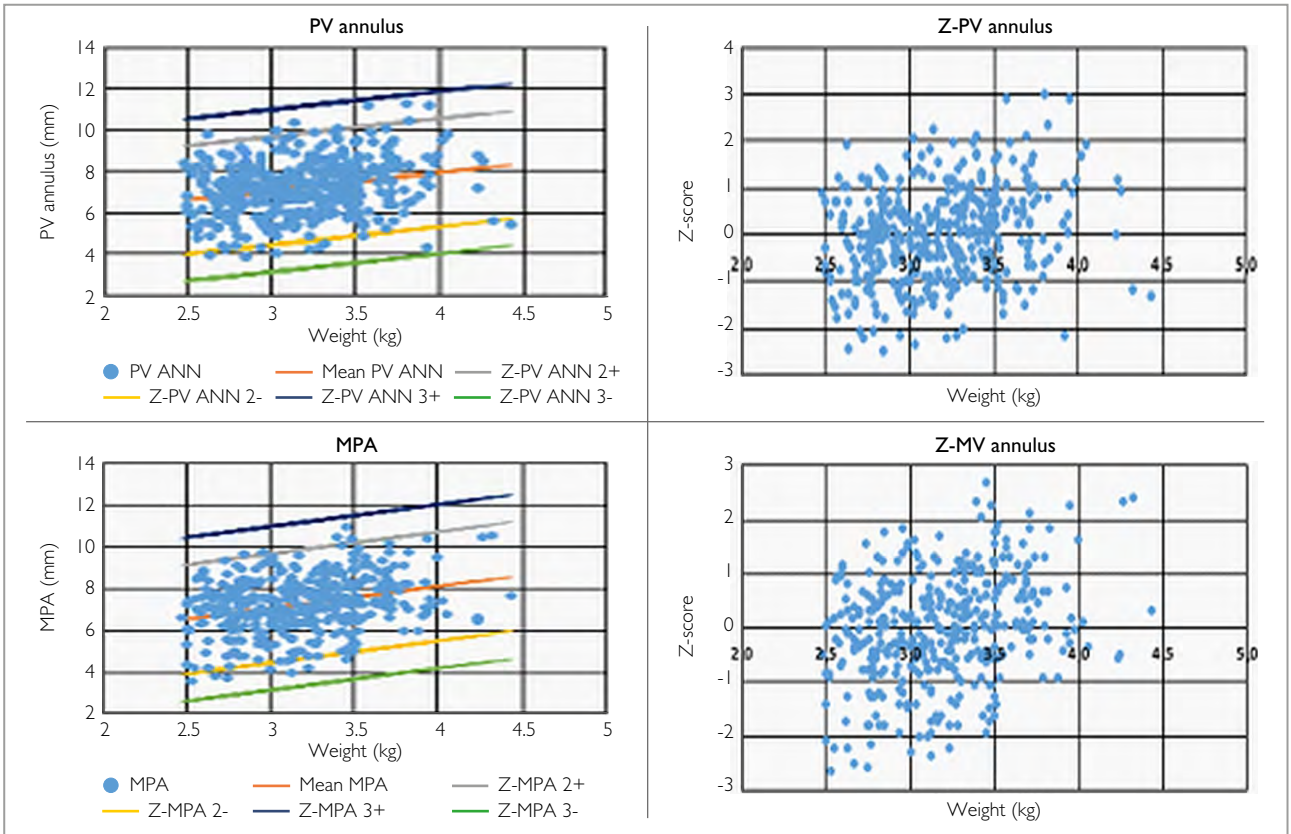

FIGURE 7: PV annulus and MPA dimension Z-scores and Z-score boundaries by body weight.

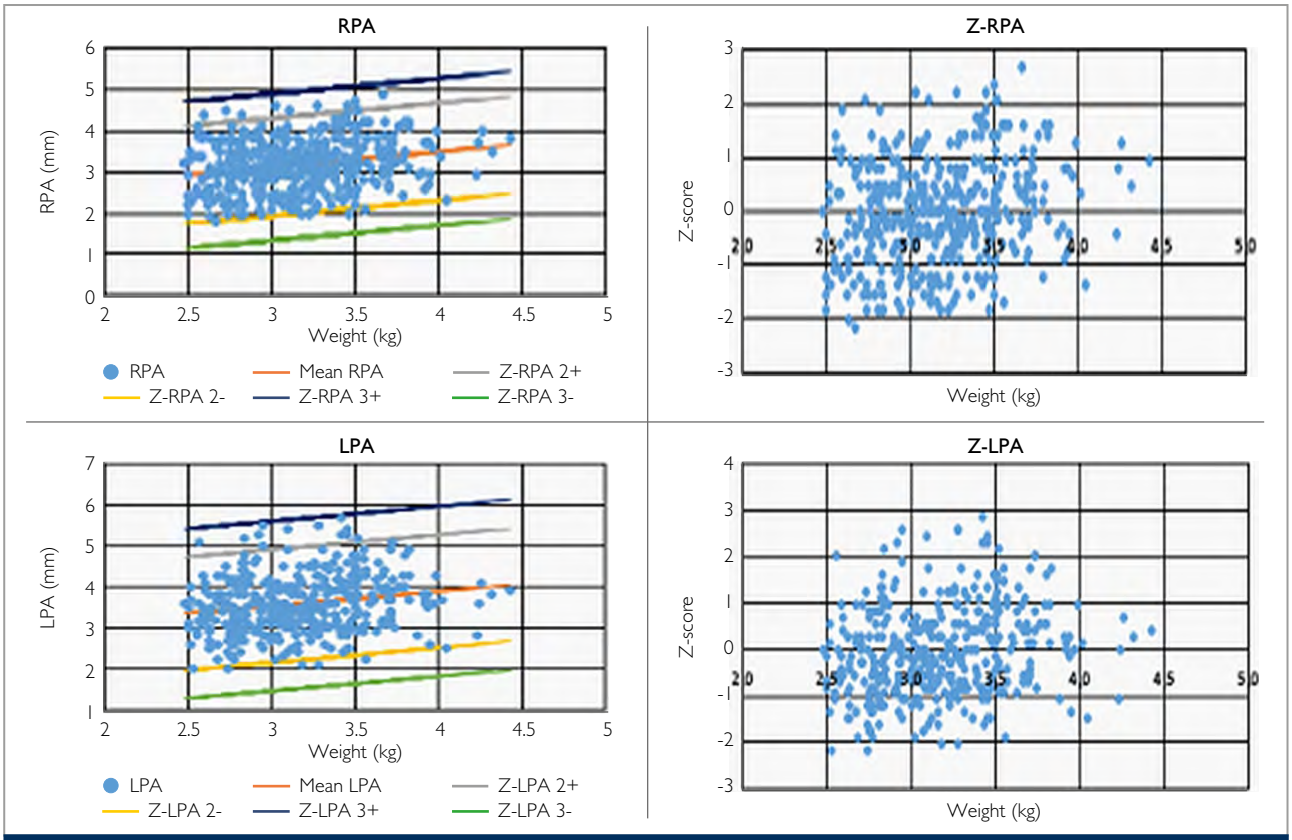

FIGURE 8: RPA and LPA dimension Z-scores and Z-score boundaries by body weight.

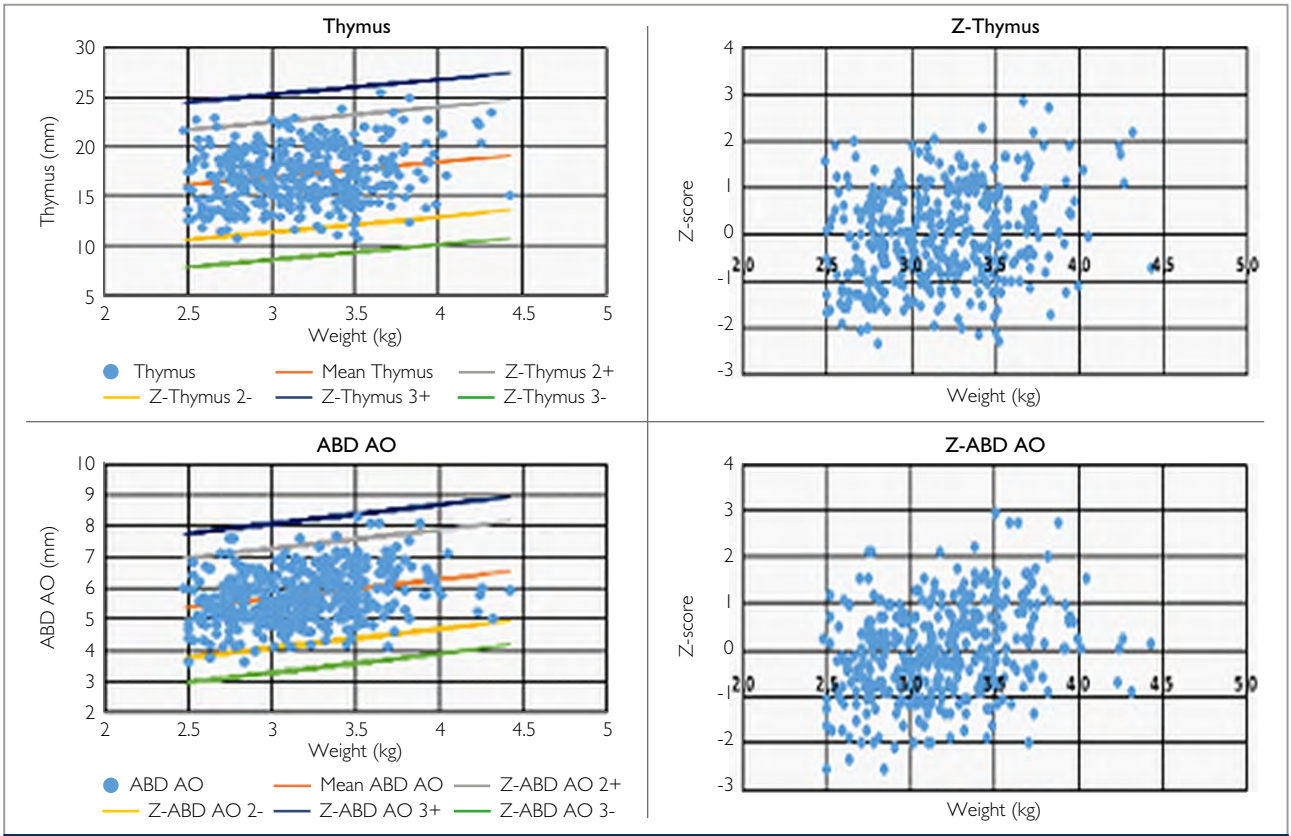

FIGURE 9: Thymus and ABD AO dimension Z-scores and Z-score boundaries by body weight.

adolescents without any neonates with a sample size of 282, and Jacobs[16] who concentrated on preterm neonates with a sample size of 290. Therefore, our study represents the first full-term neonatal echocardiography nomograms from sub-Saharan Africa to date, consisting of the largest sample size compared to previous studies.[4,16]

In this study we showed that body weight had a significant linear relationship with studied cardiovascular structures suggesting a linear relationship between foetal somatic growth and size of cardiovascular structures. Interestingly about 45% of cardiac dimensions showed linear relationship to mode of delivery similarly to a previous study.[6] Smaller dimensions were found in neonates born by C/S. Despite an intensive literature search, there is no known reason to explain this relationship between mode of delivery and cardiovascular dimensions. Gender had a minimal influence on cardiovascular structures, since we found no significant differences between boys and girls with regards to cardiovascular dimensions in accordance with findings from Kammann[10] and Guizeltas and Eroglu.[13] However, 2 studies[5,17] found significant differences between the 2 genders with boys having larger dimensions than girls.

Using interobserver variability we found a strong correlation between measurements done by a senior echocardiographer and junior echocardiographer suggesting that the methods used to measure are reproducible regardless of experience. Of note LVPW dimensions which are M-mode based and PV annulus which is 2D based both failed the interobserver variability testing. Our findings agree with other studies[6,7] which highlighted the issue of overestimation in the leading edge to leading edge measurements, particularly when performed by less the experienced echocardiographer. Furthermore, LV dimension and wall thickness echocardiography measurements are widely used in clinical practice and for research purposes. M-mode ventricular diameter measurements in the paediatric age group is the preferred method for LV quantification but can lead to overestimation of measurements.[6] This lack of accuracy in measurements may explain the poor inter-observer variability calculated for the LVPWd and LVPWDs measurements in our study. Similarly, the reason for the PV annulus measurements having a moderate inter-observer variability correlation may be due to measurements being acquired in the PSAX, which has a relatively low resolution and an oblique orientation resulting in a possible suboptimal measurement accuracy.[7]

We have presented normal cardiovascular dimension reference values that are expressed as Z-scores recommended by the American Society of Echocardiography and other authors.[6,14,18] Our study cohort showed higher dimensional measurements of M-mode cardiac structures compared to those of published literature.[10,13] Majonga, et al.[4] also showed that interventricular septum and left posterior wall dimensions acquired using M-mode were similar to published non-African references. These findings suggest that other factors such as environmental, social, economic, racial, and ethnic factors of the population may influence growth or development and thus account for these minor differences. In generating Z-scores as recommended by the American Society of Echocardiography, our study cohort shows that M-mode based measurements were higher than those of similar studies done in neonates.[10,13,14] Some of the study measurements exceeded Z-scores above +2 and below -2. To accommodate these extremes, Z-scores of +3 and -3 Z-scores were added.

STUDY STRENGTHS AND LIMITATIONS

This study is unique as it represents a homogenous South African population and focuses on an understudied neonatal age group in an African cohort. In addition, structures that have been poorly studied in both African and non-African neonatal subjects, such as the left atrium to aortic root ratio, thymus and abdominal aorta have been included. Interobserver variability was comparable for all measurements.

Limitations of the study include the omission of right ventricle, right atrium, and inferior vena cava dimensions which has been generally understudied.

CONCLUSION

This study has provided echocardiographic nomograms of normal Black South African neonates. Using the same methodology as other studies in the same area, our findings agreed with other published literature. The interobserver variability showed differences between experienced and less experienced echocardiographers for two measurements that used leading edge to leading edge approach. This study therefore contributes valuable data which can be adopted by clinicians for clinical decision making when it comes to interventions for patients with abnormal cardiovascular structures.

ACKNOWLEDGEMENTS

The authors acknowledge Chris Hani Baragwanath Academic Hospital for permission for data collection and equipment in conducting this study, as well as the participants for making this research possible.

AUTHORS' CONTRIBUTION

Ms Hadebe is the principal author of the study. She collected and entered all study data, interpreted data analysis, complied data and is the primary author of the manuscript.

Dr Prakaschandra was the supervisor from the Durban University of Technology. She assisted with guidance, advice, reviewing, and revision of the protocol and manuscript.

Ms Beckerling assisted with data collection, analysis, and interpretation process.

Prof Cilliers was the unit co-supervisor. She conceptualised the study, co-ordinated and assisted with data collection, reviewing and revision of protocol and manuscript.

Prof Ntsinjana was the main unit supervisor. He assisted with development of protocol, supervised data collection and analysis, reviewing and revision of protocol and manuscript.

Conflict of interest: none declared.

REFERENCES

1. Kaski JP, Daubeney PE. Normalisation echocardiographically derived paediatric cardiac dimensions to body surface area: Time for a standardised approach. Eur J. Echocardiogr [internet]. 2008 [cited 2015 Sep 10];1-2. Available from: http://ehjcimaging.oxfordjournals.org/content/ejechocard/early/2008/01/01/ejechocard.jen242.full.pdf. DOI:10.1093/ejechocard/jen242.
2. Lemmer CE, Engel ME, Stanfliet JC, Mayosi BM. Reference Intervals for the echocardiographic measurements of right heart in children and adolescent: A systemic review. Cardiovascular ultrasound [internet]. 2014 [cited 2015 Sep 27];12(3):1-7. Available from: http://www.cardiovascularultrasound.com/content/12/1/3.
3. Roge CL, Silverman NH, Hart PA, Ray RM. Cardiac structure growth patterns by echocardiography. J Am Heart Assoc [internet]. 1978 [cited 2015 Sep 10]; 57(2):285-290. Available from: http://circ.ahajournals.org/content/57/2/285.
4. Majonga ED, Rehman AM, McHugh G, Mujuru HA, Nathoo K, Patel M, et al. Echocardiographic reference ranges in older children and adolescents in sub-Saharan Africa. Int J Cardiol [internet] 2017 Jun [cited 2019 Jan 21];248: 409-413. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28711335.
5. Cantinotti M, Scalese M, Molinaro S, Murzi B, Passino C. Limitations of current echocardiographic nomograms for left ventricular, valvular and arterial dimensions in children: A critical review. J Am Soc Echocardiogr [internet]. 2012 [cited 2015 Sep 10];25:142-152. Available: from: http://www.onlinejase.com/article/S0894-7317(11)00790-5/pdf DOI:10.1016/j.echo.2011.10.016.
6. Cantinotti M, Scalese M, Murzi B, Assanta N, Spadoni I, Festa P, et al. Echocardiographic nomograms for chamber diameters and areas in Caucasian children. J Am Soc Echocardiogr [internet] 2014 [cited 2015 Sep 10];27(12): 1279-1292. Available from: http://www.onlinejase.com/article/S08947317(14)00586-0/pdf DOI:10.1016/j.echo.2014.08.005.
7. Lopez L, Colan SD, Frommelt PC, Ensig G J, Kendall K, Younoszai A K, et al. Recommendations for quantification methods during the performance of a paediatric echocardiogram: A report from the Paediatric Measurements Writing Group of the American Society of Echocardiography Paediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr [internet] 2010 [cited 2015 Sep 27];23:465-495. Available from: http://www.onlinejase.com/article/S0894-7317(10)00266-X/pdf DOI:10.1016/j.echo.2010.03.019.
8. McLeod SA. Z-score: Definition, calculation, and interpretation [internet]. United Kingdom. Creative commons attribution - non-commercial - no derivative works; 2019 [updated 2019 May 17; cited 2019 June 03]. Available from: https://www.simplepsychology.org/z-score.html.
9. Glen S. Standard deviation: Simple definition, step-by-step video [internet]. Florida: Statistics How To. Com; 2019 [cited 2019 June 03]. Available from https://www.statisticshowto.com/probability-and-statistics/standard-deviation/.
10. Kapmann C, Wiethoff CM, Wenzel A, Stolz G, Betancor M, Wippermann CF, et al. Normal values of m-mode echocardiographic measurements of more than 2 000 healthy infants and children in central Europe. Heart [internet] 2000 [cited 2016 Apr 09];83:667-672. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10814626.
11. Overbeek LIH, Kapusta L, Peer PGM, de Korte CL, Thijssen JM, Daniels O. New reference values for echocardiographic dimensions of healthy Dutch children. Eur J Echocardiogr [internet] 2005 [cited 2016 Apr 09];7:113-121. Available from: https://www.ncbi.nlm.gov/m/pubmed/ DOI:10.1016/j.euje.2005.03.012.
12. Neilan TG, Pradhan AD, King ME, Weyman AE. Derivation of a size-independent variable for scaling of cardiac dimensions in a normal paediatric population. Eur J Echocardiogr [internet] 2009 [cited 2016 Apr 09];10:50-55. Available from: https://academic.oup.com/ehjimaging/article/ DOI:10.1093/ejechocard/jen110.
13. Guzeltas A, Eroglu AG. References values for echocardiographic measurements of healthy newborns. Cardiol Young [internet] 2012 [cited 2015 Sep 10];22:152-157. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21933471 DOI: 10.1017/S1047951111001259.
14. Cantinotti M, Scalese M, Murzi B, Assanta N, Spadoni I, Festa P, et al. Echocardiographic nomograms for ventricular, valvular and arterial dimensions in Caucasian children with a special focus on neonates, infants and toddlers. J Am Soc Echocardiogr [internet] 2014 [cited 2015 Sep 10];27: 179-191. Available from: http://www.onlinejase.com/article/S0894-7317(13)00770-0/pdf DOI:10.1016/j.echo.2013.10.001.
15. Cantinotti M, Giordano R, Scalese M, Murzi B, Assanta N, Spadoni I, et al. Nomograms for 2D echocardiography derived valvular and arterial dimensions in Caucasian children. J Cardiol [internet] 2016 [cited 2016 Jun]; 69:208-215. Available at https://www.ncbi.nlm.nih.gov/pubmed/27118699 DOI: 10.1016/j.jjcc.2016.03.010.
16. Jacobs S. Referencing echocardiographic measurements for premature and low-birth weight infants. M. Tech. Central University of Technology [internet] 2016 [cited 2017 May 22]. Available at ir.cut.ac.za> handle.
17. Zilberman MV, Khoury PR, Kimball RT. Two Dimensional echocardiography valve measurements in healthy children: Gender-specific differences. Paediatr Cardiol [internet] 2005 [cited 2016 Apr 09];26(4):356-60. Available at https://pubmed.ncbi.nlm.nih.gov/16374684/ DOI: 10.1007/s00246-004-0736.
18. Mawad W, Drolet C, Dahdah N, and Dallaire F. A review and critique of the statistical methods used to generate reference values in paediatric echocardiography. J Am Soc Echocardiogr [internet] 2013 [cited 2016 Jan 14]; 26:29-37. Available at https://www.ncbi.nlm.nih.gov>pubmed DOI: 10.1016/j.echo.2012.09.021.

Demographic and clinical profile of patients undergoing echocardiography at a tertiary institution in central South Africa

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ABSTRACT

Introduction: Worldwide, cardiovascular disease is associated with substantial economic challenges and profound morbidity and mortality. Considering the dearth of information on cardiovascular disease for the central region of South Africa, this study aimed to assess the profile of patients who were referred to an echocardiography laboratory at a tertiary institution.

Method: A hospital-based, observational, descriptive study was conducted. Demographic, anthropometric, socio-economic, clinical and echocardiographic data were collected. Standard transthoracic echocardiograms were performed.

Results: The study population had a mean age of 51.8 ± 17.38 years, was predominantly black (64%) with a slight female preponderance (55%). The majority of patients were from a low-socioeconomic background (H0 - H2; 91%). Two-thirds of the participants were hypertensive (64%) and 57% had a body mass index exceeding 25kg/m². Sixty-three percent of referrals were for routine echocardiographic assessment. Abnormal echocardiographic findings were reported in 74% of patients. Diastolic dysfunction and left ventricular hypertrophy were detected in almost half of all patients (n=1 034; 41%), followed by cardiomyopathies and systolic dysfunction in about one-third (n=804; 32%).

Conclusion: This is the first study describing the profile of patients referred for echocardiography in central South Africa. A high percentage of patients had underlying cardiac pathology, especially myocardial dysfunction. SA Heart® 2024;21:18-27

INTRODUCTION

The global burden of cardiovascular disease (CVD) is well documented.[1] The impact of CVD has become evident in many countries on different continents, contributing to premature death, increased morbidity and disability, and substantial economic challenges.[1,2] Regardless of continued success in extending life expectancy through ongoing research, CVD remains a prominent cause of death and disability.[3] Listed by the World Health Organisation as one of the most significant causes of death, the worldwide concern is understandable. It is alarming that a third of cardiovascular deaths occur in people younger than 70.[4] Availability of timely diagnostic services and access to treatment may reduce premature deaths caused by CVD.[5,6,7] Several studies were conducted on the African continent to investigate cardiac conditions.[8,9] The "Hearts of Soweto" study evaluated the prevalence of cardiac disorders in residents of Soweto, South Africa.[10] Results revealed that rheumatic heart disease (RHD) and heart failure (HF) were the most common abnormalities found in this predominantly black African population. This and further research also concluded that the burden of heart disease had an immense effect on the health of vulnerable communities consisting of low- to middle-income people.[10,11,12] The increase in CVD in South Africa is a considerable challenge,[5] inflicting economic and social problems on the region.[13] However, diagnosis can be complex in patients with subclinical disease states.[14] Echocardiography is the ultimate tool for early diagnosis of structural and functional cardiovascular conditions.[14] It is a key modality for diagnosis in patients with cardiac symptoms and patients with multiple abnormalities, revealing disease severity, guiding therapy and follow-up of disease state.[15] Various studies highlighted the valuable role of echocardiography in assessing and managing cardiac disease.[15] The effectiveness of prompt diagnosis as

provided by echocardiography should be recognised in central South Africa, as the lack of patient profile data may urge the implementation of prevention and management practices to reduce the economic and social effects of this treatable disease. To date, there is a dearth of information on the frequency and nature of CVD in the central region of South Africa. Investigating trends in patient referrals for echocardiographic evaluation may provide valuable insight into service utilisation and needs. Furthermore, data on referral and disease patterns can provide the scientific platform for redressing inequalities in healthcare delivery in South Africa. This study aimed to assess the profile of patients who were referred to an echocardiography laboratory in the central region of South Africa.

METHOD

Study design

This is a hospital-based, observational, descriptive study. Data were from the time of the patient's first visit to the echocardiography laboratory. Retrospective data were extracted from patient medical records.

Study setting

The study was conducted at the echocardiography laboratory of the Department of Cardiology at the Universitas Academic Hospital (UAH), the only referral centre for echocardiographic examinations for the population of the Free State province, Northern Cape province and neighbouring country, Lesotho.

Inclusion / exclusion criteria

Adult patients aged 18 years and older who presented for echocardiographic evaluation for the first time were included in the study. Patients with suboptimal echocardiographic images were excluded from the study.

Definitions

Suboptimal echocardiographic images were defined as poor acoustic windows that made it impossible to confirm or exclude the presence of cardiac abnormalities.

Inpatients were defined as patients who stayed overnight in the hospital facilities for treatment and special investigations.

Patients from outpatient departments, primary care clinics and district hospitals who did not spend the night in the hospital were classified as outpatients.

Routine echocardiographic evaluations were defined as echocardiograms performed according to the British Society of Echocardiography (BSE) protocol for the minimum dataset[19] for workup of patients prior to administration of chemotherapy, intraoperative risk assessment or before chronic renal replacement therapy commenced.

In this study, systolic dysfunction was defined as a left ventricular ejection fraction (LVEF) of less than 52%. Left ventricular hypertrophy (LVH) included concentric hypertrophy, LV remodelling (abnormal LV geometry) and eccentric hypertrophy. Aortic sclerosis, aneurysm and dissection were defined as aortic abnormalities. In accordance with the 2018 European Society of Cardiology and the European Society of Hypertension guidelines, hypertension was defined as a systolic blood pressure greater than or equal to 140mmHg and / or a diastolic blood pressure greater than or equal to 90mmHg.[16] Renal referrals with hypertension were excluded from the analysis of hypertension. Body mass index (BMI) represented the key index for relating weight to height and was calculated as body weight in kilograms divided by height squared in metres.[17] Myocardial dysfunction refers to ventricular systolic or diastolic dysfunction in the absence of primary valvular heart disease.[18]

Patient enrolment

Patients were recruited prospectively from July 2019 up to the end of December 2020. In addition, retrospective data from September 2018 onward were included to mitigate the impact of the COVID-19 epidemic on referral patterns. Patients were categorised by hospitalisation status as inpatients and outpatients and reason for referral.

Echocardiographic studies

Standard transthoracic echocardiograms (TTE) were performed according to the British Society of Echocardiography protocol for comprehensive adult TTE studies.[19] If abnormal echocardiographic findings were detected, additional views, measurements and calculations were performed as deemed appropriate by the clinical echocardiography professional and then referred to the cardiologist for review and action.

Data collection

Demographic data, including age (years), sex and race / ethnicity, and anthropometric data (height [cm] and weight [kg]) were collected. Patients' BMI was calculated as weight / height^2.[17] The allocated classification of a patient by the Department of Health according to income was used to define the patient's socio-economic status. The different categories were as follows: H0, H1, H2, H3 and H4MA, where H0 indicated full subsidisation of health services, H1 to H3 partial subsidisation and H4MA full paying patients. The place of residence was recorded for all referrals. Referrals were classi-

fied by province, and patients from the Free State were segmented by municipal district. Referrals from specialist health care services were categorised by hospitalisation status. Clinical data included echocardiographic findings and blood pressure measurements. Blood pressure was measured before the echocardiogram investigation using an automatic electronic device.

Data analysis

Data analysis was performed in collaboration with a biostatistician using GraphPad Prism version 5.0 standard Statistical Analysis (GraphPad software, San Diego, California). Raw data were captured on Excel spreadsheets. A t-test was conducted to compare normally distributed data. Nonparametric data were compared using a Mann-Whitney U test. Where required, a Chi-square test or Fisher's exact test was utilised for comparisons. A p-value of less than 0.05 was considered to be statistically significant.

Ethics

Ethical approval (UFS-HSD2019/0353/2506-0003) was obtained from the Health Sciences Research Ethics Committee of the University of the Free State. The Free State Department of Health granted permission for the research to be performed at provincial facilities.

RESULTS

A total of 2 624 patients were referred to the echocardiography laboratory for evaluation over the 28 months from September 2018 - December 2020. Of these, 101 patients were excluded from the study either due to non-consent, poor image quality limiting the accuracy of measurements and diagnosis, or patients younger than 18. One thousand five hundred and sixty-seven patients (62%) were recruited prospectively, and 956 patients were added retrospectively.

Demographics and clinical data

Demographic and anthropometric data of patients at the time of echocardiographic evaluation are presented overall and by hospitalisation status in Table I. Inpatient and outpatient referrals were almost equal (n=1,211; 48% vs. n=1,312; 52%). Overall, the mean age of patients was 51.8 years (SD ± 17.38 years). Echocardiography was performed in slightly more females (n=1,397; 55%) than males (n=1,107; 44%). About two-thirds (n=1,615; 64%) of the study population was black Africans as opposed to Asians (n=23; 1%), who comprised the smallest racial group. Most patients (n=2,298; 91%) were categorised as either H0, H1 or H2; thus, most patients were of low income and presumed to be of low socio-economic status. The mean BMI of patients was 27.34kg/m^2 (SD ± 7.78kg/m^2), and almost half of the patients (n=1,199; 48%) were overweight or obese.

Blood pressure assessments at the time of echocardiographic evaluation are presented overall and by race / ethnicity in Table II. Blood pressure data were recorded for 2 039 patients (81%). Of these, 1 870 patients (92%) were included in the blood pressure assessment analysis set. It was not known whether hypertension was previously diagnosed, treated, or controlled at the time of referral. Two-thirds of patients referred by nephrology specialist services (n=169; 66%) had increased blood pressure at the time of echocardiography and were excluded from data analysis. Results demonstrated that two-thirds of all patients (n=1 202; 64%) were hypertensive and that more than half of patients in each race / ethnicity group, except Asian, were hypertensive. Significantly more black African patients presented with hypertension compared to Caucasian patients (p=0.0466).

Place of residence

The distribution of referrals is presented by geographical location of residence for the total study population in Figure 1. Most referrals were from health facilities in the Free State (n=2 056; 81%), followed by referrals from the Northern Cape (n=345; 14%).

The municipal district in Figure 2A presents referrals within the Free State against the provincial population. Almost half of these referrals (n=938; 46%) were from healthcare facilities in the Mangaung metropolitan municipality, although this district accommodated only 28% of the provincial population (Figure 2B). Considering the relative population of the Thabo Mofutsanyana (27%) and Fezile Dabi (17%) districts, referrals featured only about half of these percentages, 15% and 10%, respectively (Figure 2A).

Echocardiographic referrals from specialist healthcare services

Referrals from specialist health care services are presented by hospitalisation status in Figure 3. Approximately half of all referrals to the echocardiography laboratory were from cardiac services (n=1 245; 49%), followed by referrals from nephrology (n=255; 10%). Almost three-quarters of cardiac referrals were as outpatients (n=903; 73%), whereas almost all referrals from vascular surgery (n=138; 98%) and nephrology (n=241; 95%) were as inpatients. All oncology referrals were marked as outpatients; however, some of these patients were hospitalised in a secondary healthcare facility within the Mangaung metro.

TABLE I: Demographic and anthropometric data at the time of echocardiographic evaluation, overall and by hospitalisation status.

Variable	Overall (n=2 523)	Inpatients (n=1 211) 48%	Outpatients (n=1 312) 52%
Age (years) (mean [SD])	51.8 (17.38)	50.8 (17.69)	52.8 (17.05)
Sex			
Male (n; %)	1 107 (43.9%)	580 (47.9%)	527 (40.2%)
Female (n; %)	1 397 (55.4%)	617 (50.9%)	780 (59.5%)
Unknown (n; %)	19 (0.8%)	14 (1.2%)	5 (0.4%)
Race / ethnicity			
Black African (n; %)	1 615 (64.0%)	814 (67.2%)	801 (61.1%)
Caucasian (n; %)	700 (27.7%)	302 (24.9%)	398 (30.3%)
Mixed race (n; %)	185 (7.3%)	88 (7.3%)	97 (7.4%)
Asian (n; %)	23 (0.9%)	7 (0.6%)	16 (1.2%)
Socio-economic status			
H0 (n; %)	549 (21.8%)	253 (20.9%)	296 (22.6%)
H1 (n; %)	1 630 (64.6%)	804 (66.4%)	826 (63.0%)
H2 (n; %)	119 (4.7%)	51 (4.2%)	68 (5.2%)
H3 (n; %)	26 (1.0%)	15 (1.2%)	11 (0.8%)
H4MA (n; %)	136 (5.4%)	50 (4.1%)	86 (6.6%)
Unknown (n; %)	63 (2.5%)	38 (3.1%)	25 (1.9%)
BMI (kg/m^2) (mean [SD])	27.34 (7.78)		
Underweight (n; %)	185 (7.3%)	97 (8.0%)	88 (6.7%)
Normal (n; %)	733 (29.1%)	357 (29.5%)	376 (28.7%)
Overweight (n; %)	532 (21.1%)	241 (19.9%)	291 (22.2%)
Obese I (n; %)	368 (14.6%)	125 (10.3%)	243 (18.5%)
Obese II (n; %)	163 (6.5%)	57 (4.7%)	106 (8.1%)
Obese III (n; %)	136 (5.4%)	54 (4.5%)	82 (6.3%)
Unknown (n; %)	406 (16.1%)	280 (23.1%)	126 (9.6%)

BMI: Body mass index, overweight BMI ≥25, obese class I BMI ≥30, class II BMI ≥35, class III BMI ≥40; H0 to H4MA: categories by patient income; n: number of patients included in the study; n: number of patients per category; %: n divided by N, multiplied by 100; SD: standard deviation.

TABLE II: Blood pressure assessments at the time of echocardiographic evaluation, overall and by race / ethnicity.

Variable	Overall (n=2 523)	Inpatients (n=1 211) 48%	Outpatients (n=1 312) 52%		
Systolic blood pressure (mmHg) (mean [SD])	158 (17.19)	157.93 (17.51)	157.85 (17.06)	156.09 (15.21)	160.75 (19.62)
Diastolic blood pressure (mmHg) (mean [SD])	99 (9.09)	100.08 (9.43)	98.00 (8.40)	95.49 (5.24)	104.67 (22.03)
Hypertension Yes (n; %) No (n; %)	 1 202 (64.3%) 668 (35.7%)	 754* (66.8%) 374 (33.2%)	 356* (61.9%) 219 (38.1%)	 85 (58.6%) 60 (41.4%)	 7 (31.8%) 15 (68.2%)
P values			Caucasian vs. Black African Caucasian vs. Mixed Race		0.0466* NS

BMI: Body mass index, overweight BMI ≥25, obese class I BMI ≥30, class II BMI ≥35, class III BMI ≥40; H0 to H4MA: categories by patient income; n: number of patients included in the study; n: number of patients per category; %: n divided by N, multiplied by 100; SD: standard deviation, NS: not significant.

Routine echocardiographic evaluation

Requests for routine echocardiographic evaluation accounted for about two-thirds of all referrals (n=1 582; 63%), of these, almost one-third was part of regular pre-operative (n=197; 13%) and pre-chemotherapy (n=238; 15%) protocols. The remaining 941 (37%) patients required emergency echocardiography.

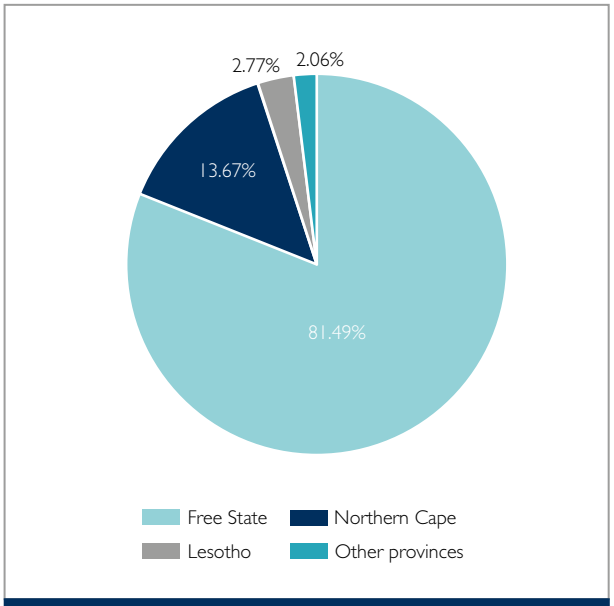

FIGURE 1: Distribution of referrals by geographical location of residence (study population).

Echocardiologic findings

Echocardiographic findings are presented by the referring specialist health care services in Figure 4. Findings were categorised as "normal" or "abnormal". Abnormal echocardiographic findings were observed in three-quarters of all referred patients (n=1 868; 74%). Of these, about half were found in patients referred by cardiac services (n=996; 53%), followed by nephrology (n=211; 11%) and internal medicine and haematology (n=112; 6%).

Cardiac pathology is detailed by referring to specialist healthcare services in Table III. Overall, myocardial dysfunction was the most frequent abnormal echocardiographic finding. Diastolic dysfunction and LVH were detected in almost half of all patients (n=1 034; 41%), followed by cardiomyopathies and systolic dysfunction in about one-third (n=804; 32%). Almost half of the patients from the cardiac services presented with LVH (of all causes) and diastolic dysfunction (n=572; 46%), followed by cardiomyopathy and systolic dysfunction (n=486; 39%), valvular disorders (n=467; 38%) and aortic abnormalities (n=432; 35%) in more than one-third of cases. In nephrology patients, the most frequent abnormal echocardiographic findings were diastolic dysfunction and LVH (n=159; 63%), pulmonary hypertension (n=94; 37%) and systolic dysfunction (n=77; 30%). One-third of oncology referrals presented with myocardial dysfunction (n=56; 33%). Other pathologies such as hypercontrac-

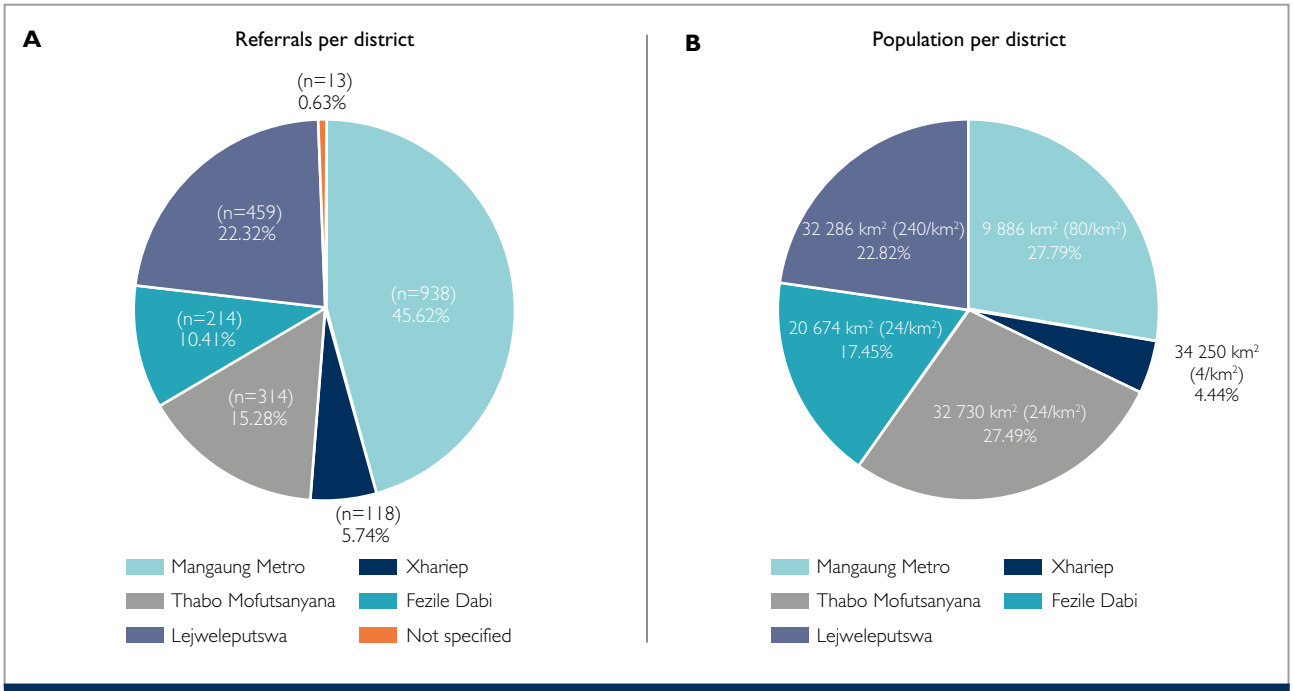

FIGURE 2: Referrals within the Free State (2A) against the provincial population by municipal district (2B).

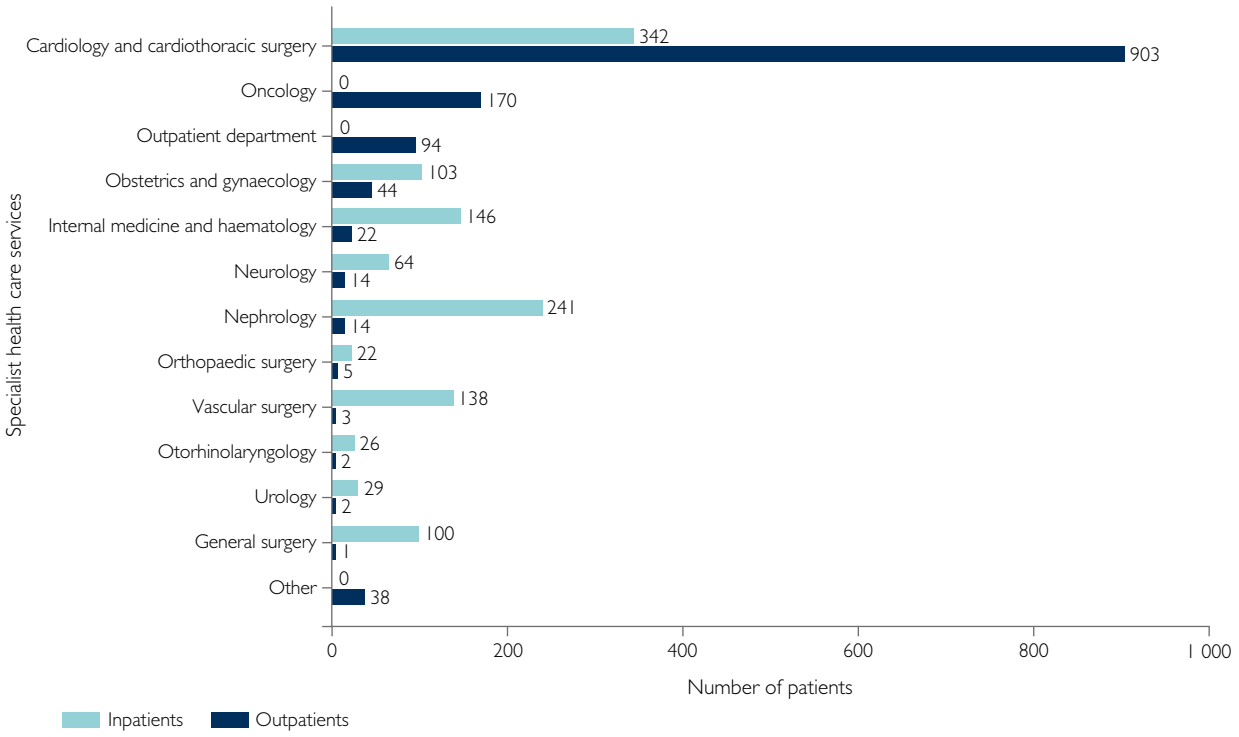

FIGURE 3: Echocardiographic referrals from specialist healthcare services by hospitalisation status.

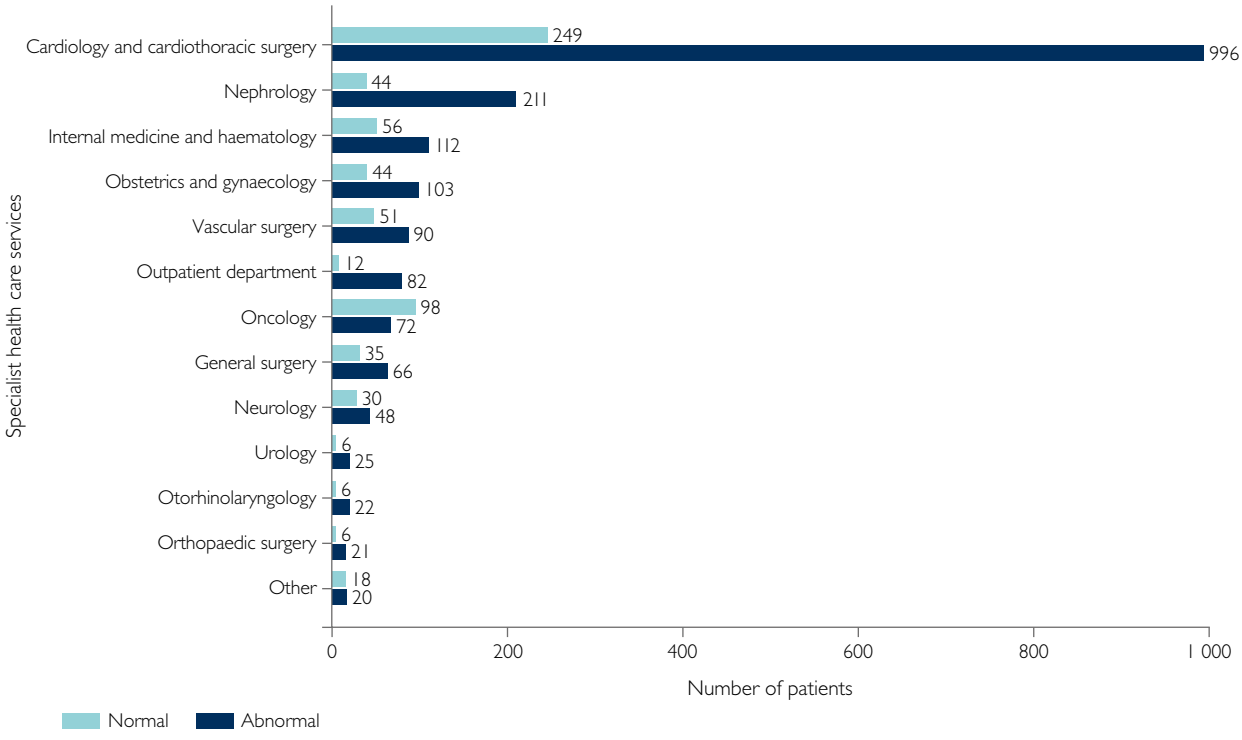

FIGURE 4: Echocardiographic findings.

TABLE III: Cardiac pathology.

Referring services	Valvular disorders (n=679)	Peri-cardial disease (n=37)	IHD (n=151)	Aortic abnor-malities (n=710)	Infective endo-carditis (n=18)	Throm-bus; tumour (n=5)	Systolic dysfunc-tion; cardio-myopathy (n=804)	LVH; diastolic dysfunc-tion (n=1 034)	CHD (n=59)	PHT (n=651)	Other (n=88)
Cardiology and cardiothoracic surgery (n=1245)	467 (68.8%)	15 (40.5%)	107 (70.9%)	432 (60.8%)	10 (55.6%)	3 (60.0%)	486 (60.4%)	572 (55.3%)	38 (64.4%)	341 (52.4%)	38 (43.2%)
Nephrology (n=255)	34 (5.0%)	4 (10.8%)	9 (6.0%)	50 (7.0%)	1 (5.6%)	0	77 (9.6%)	159 (15.4%)	2 (3.4%)	94 (14.4%)	9 (10.2%)
Oncology (n=170)	14 (2.1%)	3 (8.1%)	0	14 (2.0%)	0	1 (20.0%)	30 (3.7%)	26 (2.5%)	1 (1.7%)	18 (2.8%)	9 (10.2%)
Internal medicine and haematology (n=168)	28 (4.1%)	5 (13.5%)	4 (2.6%)	29 (4.1%)	2 (11.1%)	0	42 (5.2%)	4 (0.4%)	0	41 (6.3%)	11 (12.5%)
Obstetrics and gynaecology (n=147)	36 (5.3%)	3 (8.1%)	4 (2.6%)	4 (0.6%)	0	0	31 (3.9%)	49 (4.7%)	9	32 (4.9%)	5 (5.7%)
Vascular surgery (n=141)	11 (1.6%)	2 (5.4%)	7 (4.6%)	61 (8.6%)	0	0	31 (3.9%)	49 (4.7%)	0	32 (4.9%)	5 (5.7%)
General surgery (n=101)	17 (2.5%)	(2.7%)	5 (3.3%)	31 (4.4%)	2 (11.1%)	1 (20.0%)	28 (3.5%)	30 (2.9%)	1 (1.7%)	22 (3.4%)	5 (5.7%)
Neurology (n=78)	9 (1.3%)	0	5 (3.3%)	18 (2.5%)	2 (11.1%)	0	13 (1.6%)	29 (2.8%)	3 (5.1%)	7 (1.2%)	1 (1.1%)
Outpatient referral department (n=94)	39 (5.7%)	2 (5.4%)	6 (4.0%)	25 (3.5%)	0	0	35 (4.4%)	34 (3.3%)	4 (6.8%)	28 (4.3%)	2 (2.3%)
Urology (n=31)	4 90.6%)	0	0	14 (2.0%)	0	0	10 (1.2%)	13 (1.3%)	0	8 (1.2%)	0
Otorhinolaryn-gology (n=28)	10 1.5%)	1 (2.7%)	2 (1.3%)	8 (1.2%)	0	0	9 (1.1%)	8 (0.8%)	0	10 (1.5%)	2 (2.3%)
Orthopaedic surgery (n=27)	6 (0.9%)	1 (2.7%)	2 (1.3%)	10 (1.4%)	1 (5.6%)	0	8 (1.0%)	11 (1.1%)	0	11 (1.7%)	11 (1.7%)
Other (n=38)	4 (0.6%)	0	0	14 (2.0%)	0	0	4 (0.5%)	9 (0.9%)	1 (1.7%)	7 (1.1%)	0

Some patients presented with more than one abnormal finding.
CHD: congenital heart disease, IHD: ischaemic heart disease, LVH: left ventricular hypertrophy, n: number of patients per category, PHT: pulmonary hypertension.

tile left ventricle, interatrial septum aneurysm, lipomatous interatrial septum and mitral valve prolapse were detected in less than 5% of all referrals (n=88; 4%).

DISCUSSION

Demographics and socio-economic status

In our study, two-thirds of all referrals to the echography laboratory at the UAH were black Africans. This corresponded with the demographic profile of the serviced regions. Most of the patients were classified in the low-income categories H0 to H2, which may highlight the plight of the dominantly rural nature of the central region of South Africa. The UAH provided the only public echocardiography service for the entire central region. Many patients had to travel long distances to reach these facilities and could most likely not afford transport if the interhospital commuter services were not available.

Age may impact referral patterns. CVD inflicts early death in young and middle-aged adults. However, other factors such as high blood pressure and increased BMI contribute to mortality besides ageing. Insufficient cognisance regarding cardiovascular health and healthy ageing should be increased across all ages.[20] Considering the current life expectancy of South Africans, the mean age of patients in our study was relatively old (51.8 years [SD ± 17.38 years].[21] This corresponds with the findings of the "Hearts of Soweto" study (mean age 53 years).[14] This is also in agreement with an echocardiographic survey from Nigeria, which revealed a mean age of 54 years.[22] In contrast, a review of confirmed CVD cases from Ethiopia reported a

considerably younger mean age of 32 years. However, the inclusion criteria of the Ethiopian review allowed for the selection of patients from the age of 12 years contrary to our study, where patients 18 years and older were included.[23] Similarly, a study from Cameroon reported a mean age of 48.7 years (SD ± 18 years) in a population with an age range of 5 days and 103 years old.[24] Recent research, with a focus on CVD in a community in rural South Africa, revealed a mean age of 61.7 years. However, the study selected only men and women aged 40 years and older.[25] The distribution of males and females in our study was almost similar, which is in alignment with studies from African countries and the United Kingdom (UK); the latter is considered a high-income country.[10,26,27,28]

Clinical findings

Half of the patients in our study were overweight or obese. This result concurs with findings from 2 South African studies. Gómez-Olivé, et al. recorded high a prevalence of overweight and obesity in 70% of women and 44% of men in a South African community.[25] Similarly, Sartorius, et al. described a high prevalence (38%) of obesity among South African women.[29] The finding is also consistent with results from studies conducted in Tanzania and Sudan and statistics by the American Heart Association, which described the prevalence of obesity in excess of 30% in different populations globally.[30,31,32] It is an important observation as obesity is associated with CVD but is preventable and modifiable. It should be noted that our study was not designed to determine whether obesity is linked to cardiac diseases. Still, the fact that almost 50% of patients were overweight or obese is a cause for concern and emphasises the need for strategies to counter the problem and educate the public of central South Africa.

Two-thirds of patients were hypertensive at the time of echocardiographic evaluation. This is similar to studies in other predominantly black African populations with heart disease.[10,30,33,34] Conversely, a study from Ethiopia reported hypertensive heart disease in 15% of the black African population.[27] As for countries outside of Africa, van Heur, et al. described hypertension as the most frequent cardiovascular abnormality (47%). In a study performed in the Netherlands, Voskuil, et al. reported that a third of adults in the Netherlands suffered from hypertension.[35,36] In our study, blood pressure measurements were collected at the time of echocardiography. The high incidence of hypertension highlights the gravity of the findings and identifies the need for urgent intervention programmes in the central South African population.

Geographical referral patterns

Most referrals were from health facilities within the Free State, with uneven distribution from the different municipal districts. Within the Free State, the Mangaung metro contributed most of the referrals. Although this municipality covered the smallest share of land area, it comprised the largest share of the Free State population. Furthermore, the tertiary institution of concern was located in this district, together with 2 large district hospitals and 1 regional hospital within short travel distances. The lowest number of referrals was from the Xhariep district (6%). Comprising the smallest share of provincial population, this district had only 3 small district hospitals. The Lejweleputswa and Thabo Mofutsanyane districts had 5 and 3 district hospitals and 1 and 2 regional hospitals, respectively. For the Free State, data suggested that more patients were referred for echocardiography evaluation from hospitals located closer to the central referral facility than remote hospitals.

Patients from the Northern Cape accounted for 14% (n=345) of all referrals to the echocardiography laboratory at the UAH. The Northern Cape is the largest province by land area in South Africa, yet it comprises the smallest share of the country's population.[21] At the time of the study, Lesotho had a larger population than the Northern Cape, yet contributed only 3% (n=70) of all referrals. The small number of referrals from distant regions may reflect the impact of travel distances and the access to health services within these regions.

Referral status

Unexpectedly, the number of requests for echocardiography evaluation was almost evenly distributed between inpatient and outpatient referrals. In contrast, many echocardiographic studies showed a predominance of outpatient referrals.[10,22,24,29,37] The dissimilar outcome of our study may be attributed partially to the nature of service delivery at the UAH. This referral facility provided for all tertiary health care services, including complex surgical procedures, nephrology services and other complicated admissions, and held the only public echocardiography laboratory in the region. The referral burden on the centrally-located diagnostic facility may be relieved by delivering basic echocardiography services at the district level to enable the triage of patients.

Referring specialist health care services and reason for referral

Echocardiography referrals were made mainly by 12 different clinical specialities. About half of all referrals were from cardiac services, followed by 10% from nephrology. All other services contributed less than 10% each.

Echocardiographic evaluation before initiation of chemotherapy was requested for 15% of routine referrals, mainly for assessment of left ventricular function. A mean LVEF of 54% was determined for oncology referrals, with LVEFs predominantly within the reference range as anticipated. Although speckle tracking is more appropriate for oncology patients, the modality was not available at the time of this study. Echocardiographic evaluation as part of pre-operative risk assessment comprised 13% of routine referrals. Almost all patients requiring vascular surgery were inpatients, with aortic sclerosis being the most frequent pathology (43%).

Suspected peripartum cardiomyopathy was the main reason for obstetrics and gynaecology referrals. In these patients, diastolic dysfunction and LVH were the most frequent findings (33%), followed by valvular disorders (25%), pulmonary hypertension (22%), cardiomyopathy and systolic dysfunction (21%). In a recent study of pregnant women in the central region of South Africa, Makgato, et al. attributed 48% of cardiac abnormalities found in these patients to RHD.[38] In our study, the relatively high prevalence of valvular disorders is of concern as it too may reflect the ongoing presence of RHD in central parts of the country. Although several referrals from different services indicated suspected embolic sequelae as a reason for referral, intracardiac thrombi were reported in less than 1% of all patients. Although transthoracic echocardiography is used as the first choice to investigate the presence of cardiac thrombi, reduced image quality in some patients may limit the sensitivity; therefore, transoesophageal echocardiography might be better for the detection of intracardiac thrombi.[39]

Our study showed that cardiac abnormalities were present in three-quarters (74%) of referred patients, which is consistent with research results from the African continent. In a study from Tanzania, Raphael, et al. found relevant cardiac abnormalities in 72% of referrals, with normal echocardiography in only 22% of patients.[30] Similarly, cardiac abnormalities in 69% and 75% of patients were reported in studies from Nigeria and Cameroon, respectively.[22,26] An audit of echocardiographic findings prior to non-cardiac surgery revealed abnormal diagnoses in 84% of the Australian population.[40] Contrarily, research from the UK showed abnormalities in only a third (29%) of participants.[27] Echocardiography provides valuable support for the detection of CVD. In view of the prevalence of cardiac abnormalities revealed in our study, basic echocardiography services at district level may expedite the referral and treatment of patients in central South Africa.

LIMITATIONS

Limitations that may affect the interpretation of results include the exclusion of patients with non-diagnostic images and the fact that speckle tracking was not used in the assessment of oncology patients. The exclusion of patients with chronic kidney disease may have led to underestimation of the frequency of LVH. Also, contrast studies and TEE were not used, which might have contributed to the low frequency of thrombus detection Intra / inter-observer variability was not evaluated in this study. LVH may have been underestimated since patients were not asked whether they were on hypertensive medication.

Part of the study data was sourced during the time of COVID-19 restrictions, which affected the number of referrals, bed occupancy, and availability of outpatient services. Furthermore, our study focused on referrals to a single tertiary hospital only. As only first-time referrals were investigated, results may not reflect the full range of CVD presenting at this institution.

CONCLUSION

This study describes the profile of patients referred for echocardiographic evaluation in central South Africa. Patients were mainly of advanced age, of black African descent and held low socio-economic status. Significant comorbidities included hypertension and obesity. Travel distances and obtainability of health services appeared to have impacted referral patterns. Hospitalisation status did not influence referrals. Routine requests provided for more than 60% of the echocardiographic workload. A high prevalence of cardiac abnormalities was detected, with myocardial dysfunction being the dominant pathology.

ACKNOWLEDGMENT

The support of the Robert WM Frater Cardiovascular Research Unit is appreciated.

Conflict of interest: none declared.

REFERENCES

1. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part 1: General considerations, the epidemiologic transition, risk factors, and impact of urbanisation. Circulation 2001;104(22):2746-53.
2. Yadeta D, Guteta S, Alemayehu B, Mekonnen D, Gedlu E, Benti H, et al. Spectrum of cardiovascular diseases in 6 main referral hospitals of Ethiopia. Heart Asia 2017;9(2):e010829.
3. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017;70(1):1-25.
4. Deaton C, Froelicher E Sivarajan, Wu L Har, Ho C, Shishani K, Jaarsma T. The global burden of cardiovascular disease. European Journal of Cardiovascular Nursing. 2011;10(2_suppl):S5-S13.
5. Abdelatif N, Peer N, Manda SO. National prevalence of coronary heart disease and stroke in South Africa from 1990 - 2017: A systematic review and meta-analysis. Cardiovasc J Afr. 2021;32(3):156-160. DOI: 10.5830/CVJA-2020-045.
6. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics - 2012 update: A report from the American Heart Association. Circulation 2012;125(1):188-97.
7. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, et al. European cardiovascular disease statistics 2012. European Heart Network, 2012. https://www.researchgate.net/publication/285685010.
8. Mpe MT. Are we doing enough to prevent a heart disease epidemic? SA Heart J 2010;7(3):146-9.
9. Mocumbi A, Ferreira M. Neglected cardiovascular diseases in Africa: Challenges and opportunities. J Am Coll Cardiol 2010;55(7):680-7.
10. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the "Heart of Soweto" study): A cohort study. Lancet 2008; 371(9616):915-22.
11. Laslett LJ, Alagona P Jr, Clark BA 3rd, Drozda JP Jr, Saldivar F, Wilson SR, et al. The worldwide environment of cardiovascular disease: Prevalence, diagnosis, therapy, and policy issues: A report from the American College of Cardiology. J Am Coll Cardiol 2012;60(25 Suppl):S1-49.
12. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol 2019;74(20):2529-32.
13. Strong K, Mathers C, Leeder S, Beaglehole R. Preventing chronic diseases: How many lives can we save? Lancet. 2005;366:1578-1582.
14. Chan JSK, Tse G, Zhao H, Kam K, Lee APW. Echocardiography update for primary care physicians: A review. Hong Kong Med J 2020;26(1):44-55 | Epub 12 Feb 2020.
15. Potter A, Pearce K, Hilmy N. The benefits of echocardiography in primary care. N.Br J Gen Pract. 2019; 69(684): 358-359. DOI: 10.3399/bjgp19X704513.
16. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018;36(10):1953-2041.
17. Nuttall FQ. Body mass index: Obesity, BMI, and health: A critical review. Nutr Today 2015;50(3):117-28.
18. Jentzer JC, Chonde MD, Dezfulian C. Myocardial dysfunction and shock after cardiac arrest. Biomed Res Int 2015;2015:314796.
19. Wharton G, Steeds R, Allen J, Phillips H, Jones R, Kanagala P, et al. A minimum dataset for a standard adult transthoracic echocardiogram: A guideline protocol from the British Society of Echocardiography. Echo Res Pract 2015;2(1):G9-G24.
20. Roth, G, Mensah, G, Fuster, V. The global burden of cardiovascular diseases and risks: A compass for global action. J Am Coll Cardiol. 2020;76(25) 2980-2981.
21. Statistics South Africa. 60.6 million people in South Africa. Retrieved July 28, 2022, from https://www.statssa.gov.za/?p=15601.
22. Ogah OS, Adegbite GD, Akinyemi RO, Adesina JO, Alabi AA, Udofia OI, et al. Spectrum of heart diseases in a new cardiac service in Nigeria: An echocardiographic study of 1 441 subjects in Abeokuta. BMC Res Notes 2008;1:98.
23. Abdissa SG, Oli K, Feleke Y, Goshu DY, Begna DM, Tafese A. Spectrum of cardiovascular diseases among Ethiopian patients at Tikur Anbessa Specialised University Teaching Hospital, Addis Ababa. Ethiop Med J 2014;52(1):9-17.
24. Jacques Cabral TT, Butera G. Profile of cardiac disease in Cameroon and impact on health care services. Cardiovasc Diagn Ther 2013;3(4):236-43.
25. Gómez-Olivé FX, Montana L, Wagner RG, Kabudula CW, Rohr JK, Kahn K, et al. Cohort profile: Health and ageing in Africa: A longitudinal study of an indepth community in South Africa (HAALSI). Int J Epidemiol 2018; 47(3):689-90j.
26. Akono MN, Simo LP, Agbor VN, Njoyo SL, Mbanya D. The spectrum of heart disease among adults at the Bamenda Regional Hospital, north west Cameroon: A semi urban setting. BMC Res Notes 2019;12(1):761.
27. Tefera YG, Abegaz TM, Abebe TB, Mekuria AB. The changing trend of cardiovascular disease and its clinical characteristics in Ethiopia: Hospital-based observational study. Vasc Health Risk Manag 2017;13:143-51.
28. Chambers J, Kabir S, Cajeat E. Detection of heart disease by open access echocardiography: A retrospective analysis of general practice referrals. Br J Gen Pract 2014;64(619):e105-11.
29. Sartorius B, Veerman LJ, Manyema M, Chola L, Hofman K. Determinants of obesity and associated population attributability, South Africa: Empirical evidence from a national panel survey, 2008-2012. PLoS One 2015; 10(6):e0130218.
30. Raphael DM, Roos L, Myovela V, Mchomvu E, Namamba J, Kilindimo S, et al. Heart diseases and echocardiography in rural Tanzania: Occurrence, characteristics, and etiologies of underappreciated cardiac pathologies. PLoS One 2018;13(12):e0208931.
31. Omar SM, Taha Z, Hassan AA, Al-Wutayd O, Adam I. Prevalence and factors associated with overweight and central obesity among adults in eastern Sudan. PLoS One 2020;15(4):e0232624.
32. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics - 2021 update: A report from the American Heart Association. Circulation. 2021;143(8):e254-e743.
33. Oguanobi NI, Ejim EC, Onwubere BJ, Ike SO, Anisiuba BC, Ikeh VO, et al. Pattern of cardiovascular disease amongst medical admissions in a regional teaching hospital in southeastern Nigeria. Nig J Cardiol 2013;10:77-80
34. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, et al. The causes, treatment, and outcome of acute heart failure in 1 006 Africans from 9 countries. Arch Intern Med 2012;172(18):1386-94.
35. Van Heur LM, Baur LH, Tent M, Lodewijks-van der Bolt CL, Streppel M, Winkens RA, et al. Evaluation of an open access echocardiography service in the Netherlands: A mixed methods study of indications, outcomes, patient management and trends. BMC Health Serv Res 2010;10:37.
36. Voskuil M, Verloop WL, Blankestijn PJ, Agostoni P, Stella PR, Doevendans PA. Percutaneous renal denervation for the treatment of resistant essential hypertension; the first Dutch experience. Neth Heart J 2011;19(7-8):319-23.
37. Habte B, Alemseged F, Tesfaye D. The pattern of cardiac diseases at the cardiac clinic of Jimma University Specialised Hospital, south west Ethiopia. Ethiop J Health Sci 2010;20(2):99-105.
38. Chang P, Xiao J, Hu Z, Kwan AC, Fan Z. Imaging of left heart intracardiac thrombus: Clinical needs, current imaging, and emerging cardiac magnetic resonance techniques. Ther Adv Cardiovasc Dis. 2022;16:17539447221107737.
39. Makgato C, Baloyi SM, Nondabula T. Profile of cardiac patients who delivered at Universitas Academic Hospital (UAH) in Bloemfontein, South Africa: 2012 - 2017. Obstetrics and Gynaecology Forum 2020;30(2): 28-32.
40. Faris JG, Hartley K, Fuller CM, Langston RB, Royse CF, Veltman MG. Audit of cardiac pathology detection using a criteria-based perioperative echocardiography service. Anaesth Intensive Care 2012;40(4):702-9.

The outcome of surgical repair of tetralogy of Fallot in KwaZulu-Natal, South Africa

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ABSTRACT

Background: Surgical repair of tetralogy of Fallot (TOF) is recommended during infancy. Late patient presentation, coupled with limited surgical and intensive care services in our setting results in late repair, potentially worsening patient outcomes.
Objectives: To analyse the clinical characteristics and outcome of patients undergoing complete TOF repair at Inkosi Albert Luthuli Central Hospital (IALCH).
Method: Hospital records of all TOF patients who had complete surgical repair from January 2005 - December 2017 were analysed following ethical approval (BREC/00000476/2019).
Results: Two hundred and ninety-two patients had surgical repair; most (91%) were operated at ≥12 months of age. Preoperatively, 5 patients had infective endocarditis, 1 presented with a brain abscess and 1 suffered a cardiac arrest from a severe hypercyanotic spell. Early mortality occurred in 15 patients (5.1%). These were associated with age at repair <12 months (p=0.017), wasting (p=0.031), prolonged cardiopulmonary bypass (p=0.004), prolonged aortic cross-clamping (p=0.001) and culture proven post-operative infection (p=0.026). Eighteen (6%) suffered major post-operative morbidities, predominantly central nervous system (CNS) complications. One hundred and eighteen (40.4%) children were lost to follow-up.
Conclusion: Most patients at IALCH had late repair and a significant number were lost to follow-up. Age at repair, nutritional status, duration of bypass and infections significantly influenced early mortality.
SA Heart® 2024;21:28-34

BACKGROUND

Tetralogy of Fallot (TOF) is a congenital cyanotic heart disease characterised by a ventricular septal defect (VSD) with an overriding aorta, right ventricular outflow tract (RVOT) obstruction and right ventricular hypertrophy (RVH). In a systematic review and meta-analysis on birth prevalence of congenital heart disease worldwide, TOF was noted to occur in 34 per 100 000 live births.[1]

Though the timing for elective surgical repair of TOF remains controversial, there is a trend towards repair in infancy.[2-4] Due to delays in diagnosis and the limited cardiac surgical and intensive care services in developing countries, surgical interventions for most patients with TOF are done after the age of 1 year.[5,6] The centre under study, Inkosi Albert Luthuli Central Hospital (IALCH), has limited cardiac surgical and intensive care facilities hence there are long delays for patients awaiting surgery. This is further compounded by late presentation and diagnosis resulting in late repairs. In view of these limitations, this review assessed the average age at which the diagnosis and surgical repair of TOF are done at IALCH.

Delayed repair of TOF may result in complications. A chronic cyanotic state as well as persistent exposure of the right ventricle to high pressures may result in poor outcomes in TOF patients who are repaired late.[5,7,8] Increased risk of arrythmias has been reported in patients with TOF who had late repair.[5,9] The study assessed trends in pre-operative characteristics and their effect on outcome.

Post-surgical repair TOF patients may require reoperation in the early post-operative period due to residual RVOT obstruction or significant ventricular septal defect leak. Intra-operative transesophageal echocardiography (TOE) has been shown to be beneficial in detecting residual lesions allowing their correc-

tion before the patient leaves the operating room.[10,11] This study includes populations operated on before and after the availability of intra-operative TOE at IALCH, allowing comparisons between these 2 groups.

Duration of intubation and length of stay (LoS) in the intensive care unit (ICU) may be used as parameters indicating ICU morbidity.[12] Factors that may influence ICU morbidity include duration of cardiopulmonary bypass (CPB) and aortic cross-clamping (AXC) as well as the age and weight of the patient at repair.[12,13]

The mortality in post primary repair of TOF patients was noted to be 1.3% and 2.5% in analysis of two databases.[2,14] In a data analysis in low and medium income countries (LMICs), the mortality after primary repair was 3.3%.[6] This study assessed factors influencing ICU morbidity and mortality in TOF patients post primary surgical repair at IALCH and the factors contributing to it.

METHOD

A retrospective, descriptive, and analytical observational study was done at Inkosi Albert Luthuli Central Hospital (IALCH), a quaternary referral hospital for the province of KwaZulu-Natal in South Africa. Computerised medical records of all patients who had complete TOF repair at the hospital from January 2005 - December 2017 were analysed. Included in the study were all patients who had complete TOF repair during the 13-year period. Patients excluded from the study were those with TOF with pulmonary atresia, absent pulmonary valve and those with TOF who did not undergo complete repair.

Pre-operative data collected included demographic data, nutritional status, neurodevelopment, hypercyanotic spells, haemoglobin, haematocrit, and pre-operative morbidity. Nutritional status was assessed using World Health Organisation Child Growth Standards.[15-17] Children were classified using body mass index (BMI) or weight-for-length / height (normal if ≥-2 to +2, overweight or obese if >+2 and wasted or severely wasted if <-2) and length / height-for-age (normal if ≥-2 to +2, tall if >+2 and stunted or severely stunted if <-2). The relevant growth charts were used for children with Down syndrome.[18]

TOF repairs were done electively or as emergencies. Some patients had initial palliative procedures prior to TOF repair. The TOF repair was valve sparing or non-valve sparing in which case a trans-annular patch (TAP) was used. The ventricular septal defect (VSD) was closed through the right atrium (RA) or the right ventricle (RV). The duration of CPB and AXC was recorded. Intra-operative TOE was available during TOF repair for patients who had repair during the last 6 years of the study (2012 - 2017).

Duration of intubation, LoS in ICU, arrhythmias, infections and major morbidities were noted in the post-operative period. Early mortality and re-operation were defined as mortality or re-operation prior to discharge.

Echocardiographic assessment during the initial post-operative follow-up included assessment for severity of pulmonary regurgitation (PR), RVOT gradient and RV function as assessed with the Tricuspid Annular Plane Systolic Excursion (TAPSE). The number of patients lost to follow-up was also noted.

Data was collected and captured on a Microsoft Excel spreadsheet. The data was analysed with various statistical methods with the assistance of a professional statistician from the School of Public Health, Biostatistics Department at the University of KwaZulu-Natal.

Permission to conduct the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00000476/2019).

RESULTS

Two hundred and ninety-two patients had complete TOF repair from January 2005 - December 2017. Figure 1 shows the number of patients operated each year during the 13-year study period.

One hundred and eighty-six (63.7%) were male and 106 (36.3%) were female. Forty-one (14.0%) patients were wasted or severely wasted while nearly one third (n=93, 31.8%) were stunted or severely stunted. Neurodevelopmental delay was noted in 38 (13.0%) patients. Twenty-four (8.2%) patients had underlying syndromes, the most common syndromes being 22q11 deletion and Trisomy 21 present in 12 and 10 patients respectively. These pre-operative clinical characteristics are shown in Table I.

The median age of presentation and TOF repair was 24 and 42.5 months respectively. The median duration between diagnosis and repair was 4.8 months as shown in Table II. The majority of patients (267, 91.4%) were repaired after infancy with only 8.6% (25) undergoing complete TOF repair below the age of 1 year.

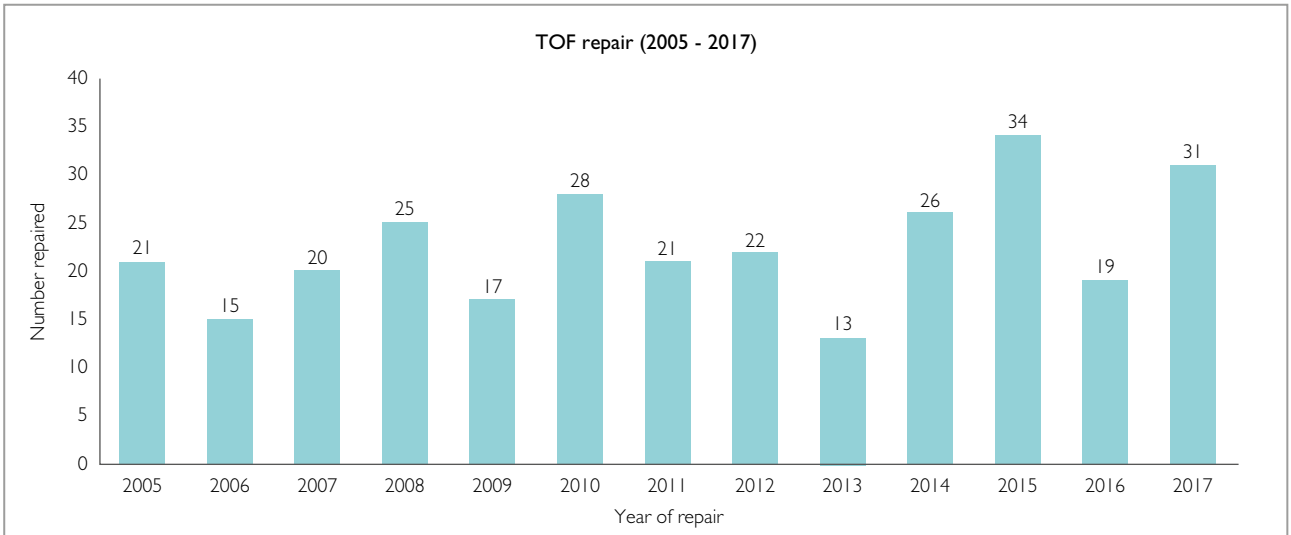

FIGURE 1: Tetralogy of Fallot repair at Inkosi Albert Luthuli Central Hospital from January 2005 - December 2017.

TABLE I: Pre-operative clinical characteristics.

Clinical characteristics	Findings	Number	Percentage
Sex	Male	186	63.7
	Female	106	36.3
Race	African	274	93.8
	Indian	13	4.5
	White	1	0.3
	Mixed race (Coloured)	4	1.4
Nutrition	Normal	230	78.8
	Overweight / Obese	9	3.1
	Wasted / Severely wasted	41	14
	Unknown	12	4.1
Development	Normal	234	80.1
	Delayed	38	13
	Unknown	20	6.8
Syndrome*	Syndromic	24	8.2
	Non-syndromic	253	86.6
	Unknown	15	5.1

**S22q11 deletion: 12, Trisomy 21: 10, Goldenhar syndrome: 1, Fetal Alcohol Spectrum Disorders: 1.*

The mean haemoglobin and haematocrit were 16.3g/dl (range 8.9-30, SD ±3.36) and 49.1% (range 28-80, SD ±9,83) respectively.

The commonest pre-operative morbidity encountered was hypercyanotic spells which occurred in 132 patients (45.2%) with 1 patient complicating with cardiac arrest during a hypercyanotic spell. Figure 2 shows the number of hypercyanotic spells in infancy and older children. Infective endocarditis occurred in 5 (1.7%) patients while brain abscess was noted in 1 patient.

Table III shows the peri-operative management and complications. Initial palliation in the form of a systemic to pulmonary artery shunt was required in 22 patients (7.7%). Twelve (4.1%) patients had emergency TOF repair while 280 (95.9%) had elective repairs. Most patients (n=275, 94.2%) had the VSD closed through a RA approach as opposed to a RV approach. Pulmonary valve sparing surgery was done in 173 (59.2%) patients. Intra-operative TOE was carried out in 118 (40.4%) patients during the last 6 years of the study period. The mean

TABLE II: Age at presentation, age at repair of TOF and time difference between diagnosis and TOF repair.

	n=292	Median	IQR*		Minimum	Maximum
Age at presentation (months)		24	6	58.5	0.04	205
Age at repair (months)		42.5	21	69.5	1.6	210
Diagnosis to repair (months)		4.85	1	16	0.03	103

IQR: Interquartile range.*

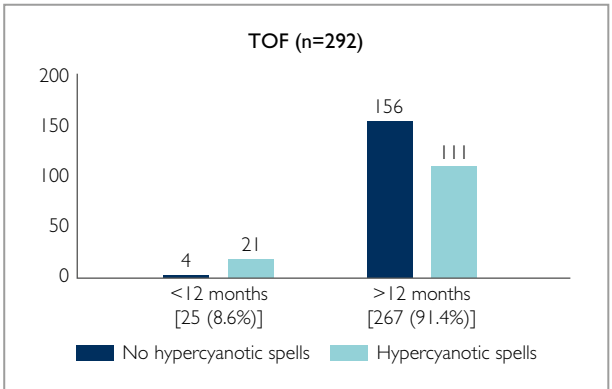

FIGURE 2: Tetralogy of Fallot.

TOF: Tetralogy of Fallot.

TABLE III: Peri-operative management and complications.

		Number (%)
Management	Initial palliation	22 (7.7)
	Emergency	12 (4.1)
	RA approach	275 (94.2)
	Valve sparing surgery	173 (59.2)
	TOE	118 (40.4)
Complications	Arrhythmias	34 (11.6)
	Proven infections	51 (17.5)
	Early mortality	15 (5.1)
	Early re-operation	11 (3.8)

RA: right atrium, TOE: trans-oesophageal echocardiography.

CPB was 119.5 minutes (range 49 - 294) while mean AXC duration was 83.9 minutes, range (23 - 208). Post-operative arrhythmias were noted in 34 (11.6%) patients. Proven infections in the post-operative period occurred in 51 (17.5%) patients. Other major post-operative morbidities included central nervous system complications in 9 patients, upper airway obstruction in 4 patients, combination of upper airway obstruction with a central nervous system complication in 1 patient, complete heart block in 2 patients requiring permanent pacemakers and chylothorax in 2 patients. Eleven (3.8%) patients required reoperation prior to hospital discharge. Early mortality was 5.1%.[15]

The median duration of intubation and LoS in the ICU post-operatively was 1 and 3 days respectively with a range of 1 to 37 days.

Trans-thoracic echocardiographic (TTE) findings on the first post-operative follow-up are noted in Table IV. Severe PR

TABLE IV: First post-operative follow-up trans-thoracic echocardiography.

Follow-up TTE	Severity	Number (%)
Pulmonary regurgitation	<Severe	105 (36.0)
	Severe	127 (43.5)
	Unknown	60 (20.5)
RVOT gradient	<Severe (≤40mmHg)	145 (49.7)
	Severe (>40mmHg)	100 (34.2)
	Unknown	47 (16.1)
TAPSE (2012 - 2017)	Normal to low (≥-3 SD)	51 (35.2)
	Very low (<-3 SD)	72 (49.7)
	Unknown	22 (15.1)

RVOT: Right ventricular outflow tract, SD: Standard deviation, TAPSE: Trans-annular plane systolic excursion, TTE: Transthoracic echocardiography.

was noted in 127 (43.5%) patients while significant residual RVOT gradient was noted in 100 (34.2%). Seventy-two (49.7%) patients had very low right ventricular systolic function as indicated by very low TAPSE. Eighteen (6.2%) patients were lost to follow-up on their first post-operative follow-up visit. Assessment of TAPSE at the study centre started in 2012 prior to which it was not assessed.

Early mortality was found in 15 (5.1%) patients and was significantly associated with age at repair <12 months (p=0.017, 95% CI [1.3 - 15.1]), wasting (p=0.031, 95% CI [1.1 - 11.2]), prolonged CPB (p=0.004), prolonged AXC time (p=0.001) and proven infection (p=0.026, 95% CI [1.2 - 10.0]).

Early re-operation was required in 11 (3.8%) patients. There was no significant association with early repair (p=0.9, 95% CI [0.02 - 8.13]), availability of TOE (p=0.4, 95% CI [0.53 - 5.93]), or surgical technique (p=0.75, 95% CI [0.24 - 2.75] for valve sparing or non-valve sparing surgery (p=0.097, 95% CI [0.05 - 1.28] and for RA or RV approach. The most common indications for re-operation were patch dehiscence due to infective endocarditis in 3 patients, and residual lesions in 2 patients.

Post-operative arrhythmias occurred in 34 (11.6%) patients, 26 (8.9%) of whom had junctional ectopic tachycardia (JET), 2 with complete heart block requiring permanent pacemaker insertion, 2 with transient complete heart block, 2 with ventricular arrhythmias and 2 with tachycardias which were not otherwise specified. There was a statistically significant association between arrhythmias and repair <12 months of age (p=0.051, 95% CI [0.14 - 1.01]).

Early repair was associated with higher mortality (p=0.017, 95% CI 1.3 - 15.1), prolonged intubation (p=0.001), prolonged ICU stay (p=0.003), severe PR (p=0.02 95% CI [1.52 - 92.24]) and higher RVOT gradient (p=0.04, 95% CI [1.0 - 9.4]) on first follow-up. These associations may be due to the patients being more unstable pre-operatively.

A higher post-operative RVOT gradient was associated with a RA approach and early repair, p=0.04 (95% CI [1.1 - 21.9] for RA approach, 95% CI [1.0, 9.4] for early repair). Severe post-operative PR showed a statistically significant association with non-valve sparing surgery (p<0.001, 95% CI [8.9, 37]) and early repair (p=0.02, 95% CI [1.5 - 2.2]). Poor RV function, based on assessment of TAPSE, was associated with non-valve sparing surgery (p=0.03, 95% CI [1.1 - 7.1]) but no significant association with a RA or RV approach, as well as age at repair. Post-operative data may be negatively affected by patients lost to follow-up and missing data. One hundred and eighteen (40.4%) patients were lost to follow-up.

DISCUSSION

Of the 292 patients included in the study, there was a male predominance of 64% which is in keeping with other studies.[4,19,20] The majority of the patients in this study were black African (93.8%), reflecting the demographics of the patients seen at the hospital under study. The majority of our syndromic patients had 22q11 deletion and trisomy 21 which is similar to a retrospective study by Michielon, et al. though their overall number of syndromic patients (27.8%) was higher than in our study (8.2%).[21]

Elective surgical repair of TOF is recommended during infancy though there is still controversy around the optimal timing of repair, especially in the neonatal period.[3-6,19] TOF repair in infancy reduces the risk of morbidities such as hypercyanotic spells and the associated end-organ damage, right ventricular hypertrophy, cardiac fibrosis and dysfunction, late onset post-operative arrhythmias, as well as negative psychosocial effects on the patient and family.[4,5,7,12] Unfortunately, in our setting and in other LMIC, surgical repair is often delayed resulting in some negative outcomes as shown in our study. The median age of repair in our study was 42.5 months which is higher than the recommended age of repair in infancy. In our study, 91.4% were repaired after the age of 12 months. This resulted from several factors including late presentation with the median age of presentation being 24 months. A South African study on repair of TOF also showed delayed repairs with a median age of repair of 39.5 months, while in another study characterising repair of TOF in developing countries, 54% of the patients were repaired after the age of 1 year.[6,20] Limited antenatal diagnostic services and low early neonatal clinical detection contributes to the late presentation and diagnosis. Cardiac, surgical and intensive care services are limited in LMIC, resulting in long surgical waiting lists, further delaying surgery. Reluctance to giving consent for surgery in some of the patients' families also contributed to further delays in surgery in a few of our patients. Due to delayed surgery, some patients in our study presented with pre-operative morbidities, the most common of which were hypercyanotic spells which occurred in 132 (45.2%) patients, 5 (1.7%) patients had infective endocarditis and 1 had a brain abscess with hemiparesis prior to TOF repair. All 6 of them were more than 12 months old. Earlier TOF repair may have prevented these co-morbidities.

Some studies in developed countries reported early mortality of less than 2% in patients post TOF repair.[2,12,22] Sandoval N, et al. reported an early mortality rate of 3.6% in a study assessing TOF repair in LMIC.[6] However, Benbrik, et al. showed no statistically significant difference in mortality between the patients repaired early and those repaired late in their retrospective study.[5] Early mortality in our study was 5.1% which is higher than the aforementioned studies. There was a statistically significant association between early mortality and pre-operative wasting in our study, in keeping with other studies where poor pre-operative nutritional status in patients with congenital heart disease was noted to be associated with poor post-operative outcome.[6,23,24] Lim CYS, et al. showed higher mortality in patients with low weight for age and a longer duration of intubation and hospital stay in patients with low height for age while Marwali EM, et al. showed longer duration of intubation and LoS in ICU in patients with low weight for age.[23,24] These 2 studies included patients with various congenital heart diseases including TOF. In a study characterising repair of TOF in developing countries, malnutrition was also associated with higher mortality.[6] While our study and the others mentioned above used various parameters to define malnutrition, they all show the negative impacts of pre-operative malnutrition on post-operative outcome in congenital heart diseases.

Prolonged CPB and prolonged AXC time were also significantly associated with early mortality in our study. A study by Hashemzadeh K, et al. also showed an association between prolonged CPB and AXC time and mortality.[25]

Proven infection occurred in 17.5% of our patients and this was associated with early mortality as well. In a study by Sandoval N,

et al. assessing TOF repair in developing countries, 5.9% had major infection with an increased risk of mortality.[6] A study by Sen AC, et al. looking at almost 15 000 patients who had cardiac surgeries in various developing countries also showed a significant association between infection and in-hospital mortality.[26] Improved enforcement of infection control measures may help to reduce in-hospital mortality following TOF repair.

The higher mortality found in patients operated under 12 months is a concern and requires further study. This does not imply that patients should be operated on later, but rather suggests to us that patients with more severe disease, who become symptomatic earlier, are not reaching surgical correction. Possible reasons for this include mortality without diagnosis or timeous referral or mortality before corrective surgery is performed.

A study assessing for optimal age for TOF repair noted reoperation in 3%, some of which were due to residual lesions.[3] Unlike in this comparison study, most of the indications for re-operation in our study were secondary to infective endocarditis induced patch dehiscence. Infection has been noted in our study to contribute towards early re-operation and early mortality hence enforcement of infection prevention measures may help improve outcome. There was however no significant association between re-operation and early repair, availability of intra-operative TOE, or surgical technique used.

Post-operative arrhythmias occurred in 11.6%, predominantly junction ectopic tachycardia (JET), which was found in 8.9% of patients. Other studies showed JET to occur in between 7 and 7.9%, similar to our findings.[3,25,27] However, a study which assessed JET in post-TOF repair in children less than 2 years old showed a higher JET incidence of 29.8% with a significant association between JET and younger age.[28]

While patient with some types of surgically corrected congenital cardiac lesions can be discharged from follow-up, TOF is among those that require life-long follow-up due to late complications such as pulmonary regurgitation requiring possible pulmonary valve replacement in adulthood. Unfortunately, 40.5% of our patients were lost to follow-up. A study by Mackie AS, et al. assessing patients with congenital heart disease lost to follow-up to cardiologist services revealed that 28% were lost to cardiology follow-up on the 6th birthday and the number increased as the years progressed.[29] Failure of follow-up may be associated with poorer outcome such as irreversible right ventricular dysfunction, arrhythmias and increased risk of mortality due to lack of an opportunity for timely assessment and intervention.[30,31] Factors contributing to failure to follow-up in our setting includes lack of understanding of the importance of follow-up, poverty resulting in limited funds for follow-up, religious or traditional beliefs, as well as change of caregivers in some patients with no handover of the patient's follow-up plan to the new guardian. The frequent change of phone numbers as well as the unavailability of phones to some of our patients makes follow-up of these patients challenging.

STRENGTH AND LIMITATIONS

The strength of the current study is that it was done over a long period and included a significant number of patients. The study was however limited by the fact that it was retrospective with missing data due to patients lost to follow up or unrecorded information in the patient's file. This could limit some of the conclusions that can be drawn from the study.

CONCLUSION

Most of our patients with TOF were repaired late and a significant number presented with pre-operative morbidities, the commonest of which was hypercyanotic spells. Pre-operative malnutrition and post-operative infection contribute significantly towards early mortality. A significant fraction of our patients are lost to follow-up.

These findings suggest that there is potential for improved outcomes on a number of levels. These include timeous diagnosis, earlier surgery, improvement in peri-operative and post-operative care, prevention of nosocomial infections and improved follow-up. At an institutional level, such improvement can only be achieved by a continuously evaluating outcomes and implementing changes where possible. Additionally, however, development and strengthening of the child health infrastructure within the province as a whole is necessary for sustained progress.

Conflict of interest: none declared.

REFERENCES

1. Van der Linde D, Konings EEM, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: A systemic review and meta-analysis. J Am Coll Cardiol 2011;58(21):2241-7. DOI: 10.1016/j.jacc.2011.08.025.
2. Al Habib HF, Jacobs JP, Mavroudis C, et al. Contemporary patterns of management of tetralogy of Fallot: Data from the Society of Thoracic Surgeons Database. Ann Thorac Surg 2010;90(3):813-9. DOI: 10.1016/j.athoracsur.2010.03.110.
3. Van Arsdell GS, Maharaj GS, Tom J, et al. What is the optimal age for repair of tetralogy of Fallot? Circulation 2000;102(19 Suppl 3):III123-9. DOI: 10.1161/01.CIR.102.suppl_3.III-123.
4. Steiner MB, Tang X, Gossett JM, Malik S, Prodhan P. Timing of complete repair of non-ductal-dependent tetralogy of Fallot and short-term postoperative outcomes: A multicentre analysis. J Thorac Cardiovasc Surg 2014;147(4):1299-305. DOI: 10.1016/j.jtcvs.2013.06.019.
5. Benbrik N, Romefort B, Le Gloan L, et al. Late repair of tetralogy of Fallot during childhood in patients from developing countries. Eur J Cardiothorac Surg 2015;47:e113-7. DOI: 10.1093/ejcts/ezu469.
6. Sandoval N, Carreno M, Novick WM, et al. Tetralogy of Fallot repair in developing countries: International Quality Improvement Collaborative. Ann Thorac Surg 2018;106:1446-51. DOI: 10.1016/j.athoracsur.2018.05.080.
7. Jonas RA. Early primary repair of tetralogy of Fallot. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2009;12:39-47. DOI: 10.1053/j.pcsu.2009.01.021.
8. Marino BS, Lipkin PH, Newburger JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: Evaluation and management: A scientific statement from the American Heart Association. Circulation 2012;126(9):1143-72. DOI: 10.1161/CIR.0b013e318265ee8a.
9. Walsh EP, Rockenmacher S, Keane JF, Hougen TJ, Lock JE, Castaneda AR. Late results in patients with tetralogy of Fallot repaired during infancy. Circulation 1988;77(5):1062-7.
10. Kim SJ, Park SA, Song J, Shim WS, Choi EY, Lee SY. The role of transesophageal echocardiography during surgery for patients with tetralogy of Fallot. Pediatr Cardiol 2013;34(2):240-4. DOI: 10.1007/s00246-012-0423-4.
11. Bezold LI, Pignatelli R, Altman CA, et al. Intra-operative transesophageal echocardiography in congenital heart surgery. The Texas Children's Hospital experience. Tex Heart Inst J 1996;23(2):108-15.
12. Egbe AC, Nguyen K, Mittnacht AJ, Joashi U. Predictors of intensive care unit morbidity and mid-term follow-up after primary repair of tetralogy of Fallot. Korean J Thorac Cardiovasc Surg 2014;47(3):211-9. DOI: 10.5090/kjtcs.2014.47.3.211.
13. Van Dongen EI, Glansdorp AG, Mildner RJ, et al. The influence of perioperative factors on outcomes in children aged less than 18 months after repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2003;126(3):703-10. DOI: 10.1016/S0022-5223(03)00035-7.
14. Sarris GE, Comas JV, Tobota Z, Maruszewski B. Results of reparative surgery for tetralogy of Fallot: Data from the European Association for Cardio-Thoracic Surgery Congenital Database. Eur J Cardiothorac Surg 2012;42(5):766-74. DOI: 10.1093/ejcts/ezs478.
15. World Health Organisation. The WHO Child Growth Standards. http://www.who.int/childgrowth/standards (accessed 18/01/2018).
16. World Health Organisation. Growth reference 5 - 19 years. http://www.who.int/growthref/en (accessed 18/01/2018).
17. World Health Organisation. Training course on child growth assessment. WHO child growth standards. Interpreting growth indicators. http://www.who.int/nutrition/publications/childgrowthstandards_trainingcourse/en/ (accessed 18/01/2018).
18. Growth charts for children with Down syndrome. https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/growth-charts.html (accessed 25/02/2020).
19. Salva JJ, Faerber JA, Haung YV, et al. Two-year outcomes after complete or staged procedure for tetralogy of Fallot in neonates. J Am Coll Cardiol 2019;74(12):1570-1579. DOI: https://doi.org/10.1016/j.jacc.2019.05.057.
20. Ngwezi DP, Vanderdonck K, Levin SE, Cilliers A. An audit of surgical repair of tetralogy of Fallot in an African tertiary care centre. SA Heart 2013;10:520-525 DOI: https://doi.org/10.24170/10-3-1792.
21. Michielon G, Marino B, Formigari R, et al. Genetic syndromes and outcome after surgical correction of tetralogy of Fallot. Ann Thorac Surg 2006;81(3):968-975. DOI: 10.1016/j.athoracsur.2005.09.033.
22. Kim H, Sung SC, Kim SH, et al. Early and late outcomes of total repair of tetralogy of Fallot: Risk factors for late right ventricular dilatation. Interact Cardiovasc Thorac Surg 2013;17(6):956-962. DOI: https://doi.org/10.1093/icvts/ivt361.
23. Lim CYS, Lim JKB, Moorakonda RB, et al. The impact of pre-operative nutritional status on outcomes following congenital heart surgery. Front Pediatr 2019;7:429. DOI: 10.3389/fped.2019.00429.
24. Marwali EM, Darmaputri S, Somasetia DH, Sastroasmoro S, Haas NA, Portman MA. Does malnutrition influence outcome in children undergoing congenital heart surgery in a developing country? Paediatr Indones 2015;55(2):109-116. DOI: https://doi.org/10.14238/pi55.2.2015.109-16.
25. Hashemzadeh K, Hashemzadeh S. Early and late results of total correction of tetralogy of Fallot. Acta Med Iran 2010;48(2):117-22. PMID: 21133005.
26. Sen AC, Morrow D, Balachandran R, et al. Post-operative infection in developing world congenital heart surgery programmes: Data from the International Quality Improvement Collaborative. Circ Cardiovasc Qual Outcomes 2017;10:e002935. DOI: 10.1161/CIRCOUTCOMES.116.002935
27. Ergün S, Genç SB, Yıldız O, et al. Predictors of a complicated course after surgical repair of tetralogy of Fallot. Turk Gogus Kalp Damar Cerrahisi Derg 2020;28(2):264-273. DOI: 10.5606/tgkdc.dergisi.2020.18829.
28. Ismail MF, Arafat AA, Hamouda TE, et al. Junctional ectopic tachycardia following tetralogy of Fallot repair in children under 2 years. J Cardiothorac Surg 2018;13:60. DOI: https://doi.org/10.1186/s13019-018-0749-y.
29. Mackie AS, Ionescu-Ittu R, Therrien J, Pilote L, Abrahamowicz M, Marelli AJ. Children and adults with congenital heart disease lost to follow up: Who and when? Circulation 2009;120(4):302-9. DOI: 10.1161/CIRCULATIONAHA.108.839464.
30. Wray J, Frigiola A, Bull C. Adult Congenital Heart disease Research Network (ACoRN). Loss to specialist follow-up in congenital heart disease: Out of sight, out of mind. Heart 2013;99(7):485-90. DOI: 10.1136/heartjnl-2012-302831.
31. Wren C, O'Sullivan JJ. Loss to follow-up of adults with repaired congenital heart disease. Heart 2013;99(7):440-441. DOI: 10.1136/heartjnl-2012-303121.

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Outcomes of right ventricular outflow tract stenting as a palliative procedure in tetralogy of Fallot patients

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ABSTRACT

Background: Certain patients with tetralogy of Fallot (TOF) require a palliative procedure until their condition permits a full surgical repair. Aorto-pulmonary shunting is the standard palliative procedure but requires a cardiothoracic surgeon in a well-equipped facility. Overwhelming caseloads and limited resources in the public sectors in developing countries frequently restrict access to such treatment. Percutaneous right ventricular outflow tract (RVOT) stenting offers an alternative.

Objectives: To evaluate the safety and effectiveness of RVOT stenting in TOF patients in a resource-limited setting.

Method: A retrospective, cohort observational study at Steve Biko Academic Hospital from January 2014 - March 2021.

Results: Thirty-seven patients required RVOT stent placement. Mean oxygen saturation increased from 65% to 95% post-stent insertion. Mean pulmonary artery (PA) growth, measured by McGoon ratio, increased from 1.36 to 2.05. Average Intensive Care Unit stay was 2 days with zero 30-day mortality. Three stents fractured and required replacement.

Conclusion: Stenting the RVOT in TOF patients presenting beyond the neonatal period, with multiple comorbidities and often in extremis, yielded good results. Significant improvement in oxygen saturations and PA growth permitted the majority of patients to proceed to full TOF surgical repair. This is an especially valuable option to have in resource constrained settings when surgical assistance is not always readily available.

SA Heart® 2024;21:36-44

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CHD) seen at Steve Biko Academic Hospital (SBAH), a tertiary hospital in the Gauteng province of South Africa. The Paediatric Cardiology Department services approximately 15% of the population including the greater part of the provinces of Mpumalanga, Limpopo and Gauteng. It is one of only 6 state cardiothoracic surgery services in South Africa. In 2016, more than 150 cardiothoracic procedures were performed in only 2 of the 6 units.[1] Thus many paediatric patients die while awaiting surgery. Global standards require 1 cardiothoracic surgeon per 800 000 population.[1] In South Africa in 2016 there was 1 cardiothoracic surgeon per 4.5 million population with the majority practising in the private sector.

TOF is defined by 4 congenital heart defects: Right ventricular hypertrophy, ventricular septal defect, aortic override and right ventricular outflow tract (RVOT) obstruction. This report focusses on RVOT obstruction which contributes the majority of the morbidity and mortality in these patients.

The majority of patients with TOF undergo primary complete surgical repair with excellent outcomes.[2] In order for surgery to be successful certain requirements must be fulfilled (Figure 1). An adequate pulmonary artery size is necessary to enable full repair. The McGoon ratio is the ratio of the sum of left and right pulmonary artery diameters to the aortic diameter at the level of the diaphragm (Figure 2). Should the patient weigh less than 2.5kg or there is unfavourable anatomy or medical emergency management of a hypercyanotic spell has failed or the McGoon ratio is less than 2, an interim palliative procedure is indicated before circumstances permit full surgical repair. Dawoud, et al., suggest a McGoon ratio of 1.5 to guide decision making.[3] Our Institution's preference is a ratio of 2.

Aorto-pulmonary shunting is the standard palliative procedure bypassing the RVOT obstruction and supplying blood directly

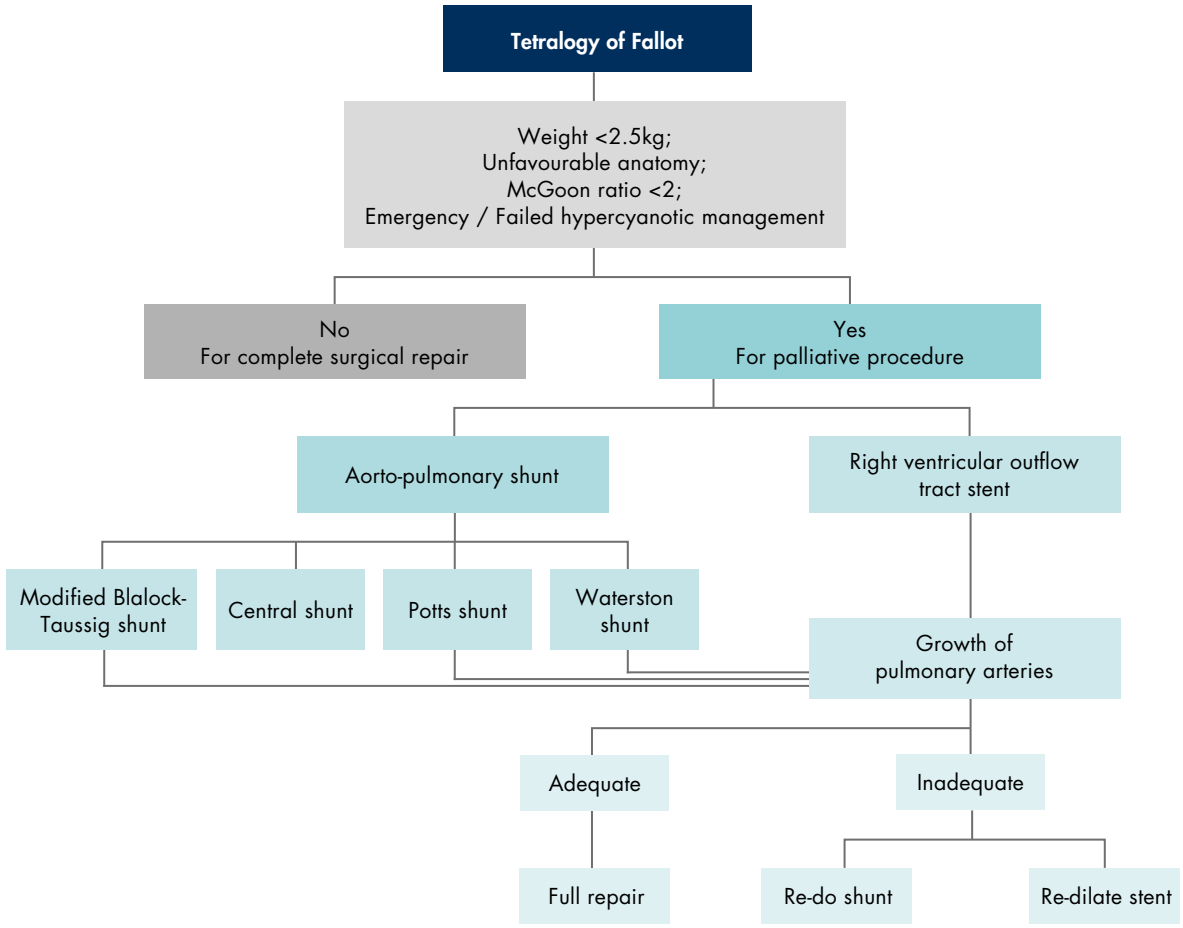


FIGURE 1: Flow diagram depicting the surgical management of tetralogy of Fallot.

to the pulmonary arteries. Amongst the various types of aorto-pulmonary shunts, none provides symmetrical blood flow to the pulmonary arteries resulting in unequal growth of the vessels.[4] Aorto-pulmonary shunting requires a well-equipped cardiothoracic surgical facility with the potential for cardio-pulmonary bypass. The Corona virus disease 2019 (COVID-19) pandemic resulted in the postponement of elective surgeries increasing the burden on a resource-limited system. In this circumstance, a palliative alternative procedure might ensure patient survival and more effectively prepare them for later definitive repair.

Percutaneous RVOT stenting offers such an alternative.[5] It avoids surgery and cardio-pulmonary bypass. Prior studies have shown promising results of the procedure in a neonatal population.[6] In South Africa, many of the TOF patients are diagnosed beyond the neonatal period.[7] Often patients present for the first time in extremis with a hypercyanotic episode. While medical management may be sufficient to treat some patients, others require emergency RVOT stenting as a lifesaving procedure.[8] Given the limited capacity of paediatric intensive care units (PICU) locally, RVOT stenting may offer a shorter post-operative PICU stay and a reduction in hospital stay.

Here we report our experience with RVOT stenting; its benefits and risks and its short- and longer-term outcomes.

METHODS

Aim and objectives

Aim

The aim of this study was to evaluate the safety and effectiveness of RVOT stenting in patients with TOF presenting beyond the neonatal period at SBAH.

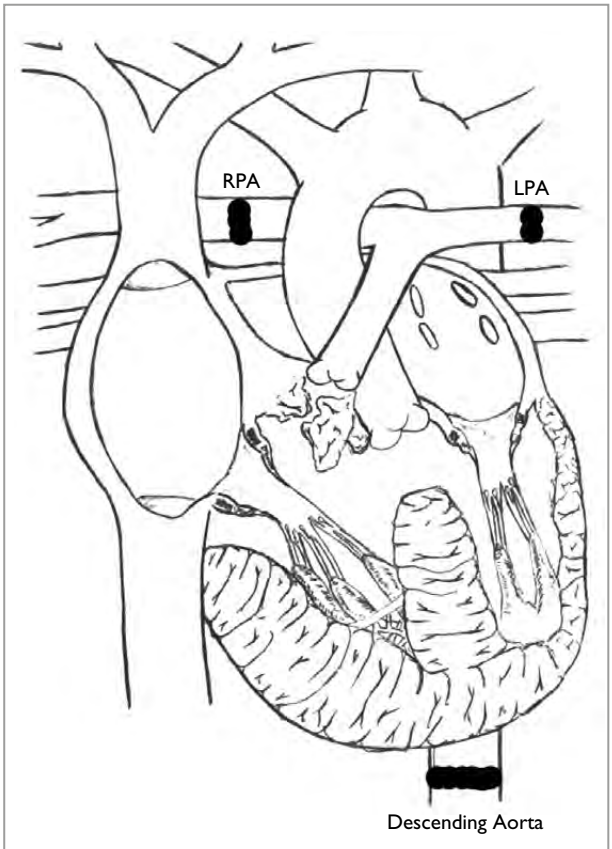


FIGURE 2: McGoon ratio: Relationship between diameters of right pulmonary artery (RPA) and left pulmonary artery (LPA) to diameter of descending aorta.

Primary objectives

- To describe positive clinical outcomes after RVOT stent placement in TOF patients.
- To identify any short- and longer-term negative clinical outcomes after RVOT stent placement in TOF patients.

Secondary objectives

- To describe the clinical and demographic profile of our TOF patients prior to RVOT stent placement.
- To describe the procedure we followed for RVOT stent placement in TOF patients.

Study design

A retrospective cohort observational study was done. All tetralogy of Fallot patients who underwent RVOT placement from 1 January 2014 - 31 March 2021 at SBAH in Pretoria, South Africa, were included. Patients with a prior palliative procedure, i.e. a central shunt, were included. Patients not fulfilling the criteria of TOF anatomy were excluded.

This study received approval from the Research Ethics Committee at the Faculty of Health Sciences at the University of Pretoria (Reference number: 566/2020).

Statistical analysis

The data analysis consisted of frequencies and proportions for short- and long-term negative clinical outcomes and categorical variables. For continuous data such as age, weight, McGoon score, oxygen saturation, the means and standard deviations were calculated to describe the data. The SAS® v.9.4 software (Statistical Analysis Systems Institute Inc., SAS Campus Drive, Cary, NC, USA) was used to perform the analysis and statistical significance was set at $p<0.05$.

Catheterisation technique

- All stent procedures were performed under fluoroscopic visualisation in the cardiac catheterisation laboratory with the patient's arms elevated for biplane views. Patients received a general anaesthetic and a topical local anaesthetic.
- A 5 French short sheath was placed in the femoral vein using the Seldinger technique. Sodium heparin was administered via the sheath at a dosage of 50IU/kg.
- A 5 French catheter was then placed in the right ventricle just below the infundibular stenosis. An angiogram was performed and the McGoon ratio was measured.
- If the pulmonary valve was too small or dysplastic then the valve was to be stented, if not, it was to be spared (Figure 3).
- The Formula stent (Cook® Medical, USA) is available in 2 systems, the 0.018 and 0.035 system.
- Patients can become unstable when crossing the RVOT. To prevent complications, a coaxial system was used, and the stent was prepared prior to deployment.
- The RVOT was crossed using a 5 French right Judkins catheter and a 0.018 Road Runner (Cook® Medical USA) wire placed in the LPA. This provides a straighter line of deployment of the stent.
- Once the wire was in position the long delivery sheath and dilator (Cook® Flexor Ansel) was then advanced over the wire and across the RVOT into the branch pulmonary artery. The sheath was then thoroughly flushed.
- The stent was then advanced to the tip of the long delivery sheath over the wire. Hand injections of contrast confirmed the desired position.

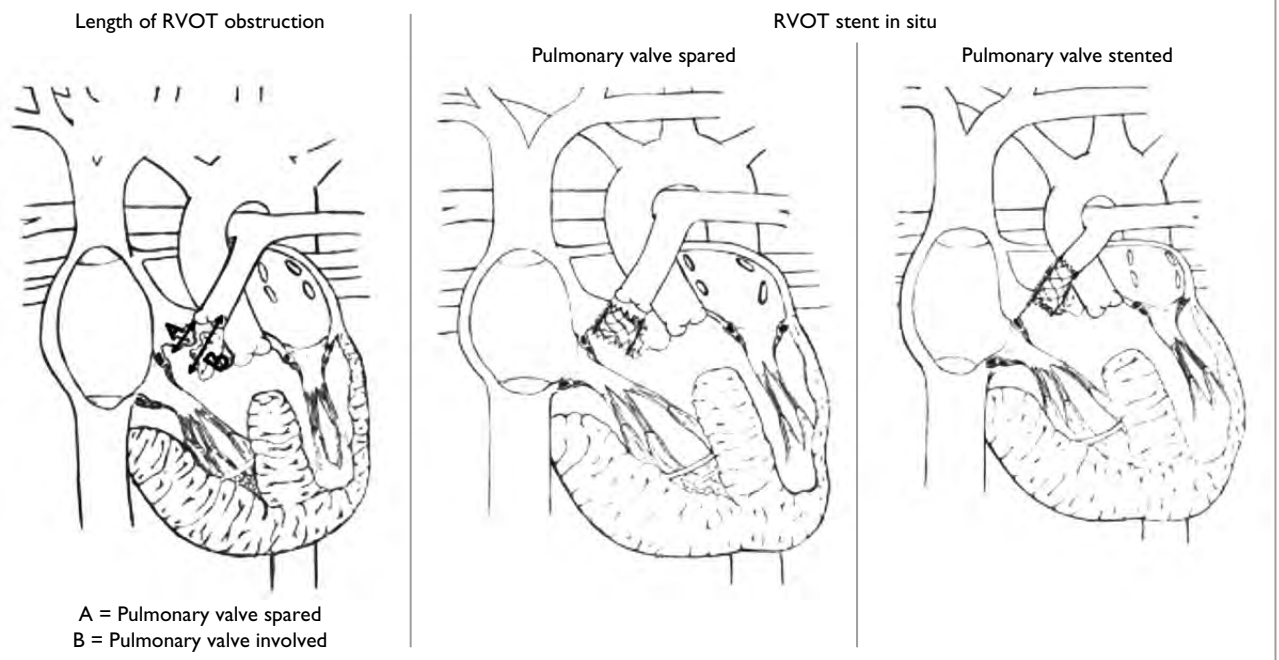


FIGURE 3: Measurement of right ventricular outflow tract obstruction with stent in situ.

- The stent covered the infundibular obstruction completely. The stent balloon was then inflated to the desired atmospheres and then deflated. A pressure injection was then performed, and the area carefully scrutinised to ensure that all of the obstruction was relieved. Any complications of the stent deployment were excluded. These included dissection, rupture and jailing of the branch pulmonary arteries. A dramatic rise in oxygen saturations was noted as the obstruction was relieved.
- If there was some residual obstruction, a second stent was deployed.
- The patient was monitored in PICU for the development of post stent pulmonary oedema which was treated with furosemide. The patient was then initiated on antiplatelet therapy using acetylsalicylic acid 5mg/kg/dose daily.

RESULTS

A total of 37 patients with the prerequisite TOF anatomy required RVOT stent placement at SBAH between 1 January 2014 and 31 March 2021. Of these patients, 4 required reintervention with either a repeat RVOT stent or balloon dilatation.

Demographics

The mean age at presentation was 27.7 months (range 1 - 89 months) with a large variation in age by the time the first stent was implanted: mean age 43.6 months (range 2.4 - 133 months) (Figure 4). Six patients had an occluded central shunt. 46% of patients were female. The average weight was 11kg (range 5 - 26kg) of whom 24% were underweight and 49% were severely underweight (WHO growth charts). The primary cardiac diagnosis was associated with a variety of congenital conditions in 40% of patients (Figure 5). The median haemoglobin level pre-stent placement was 18.2g/dL (range 10.2 - 27.5g/dL).

RVOT stent procedure characteristics

All procedures were done under ketamine-induced general anaesthetic. The Formula stents (Cook® Medical, USA) were used. The majority of the procedures required the placement of only one stent to cover the length of the infundibulum (Table I). 65% of all the procedures spared involvement of the pulmonary valve. The stent and procedural characteristics are shown in Table II.

Positive clinical outcomes post RVOT stent placement

Oxygen saturations improved remarkably (Table III & Figure 6). There was correlation between the pre-stent echocardiographic pulmonary artery (PA) size and the pre-stent angiographic size (Table IV). Echocardiograms were used to measure PA growth at an average of 35 days (1 - 71 days) after the pro-

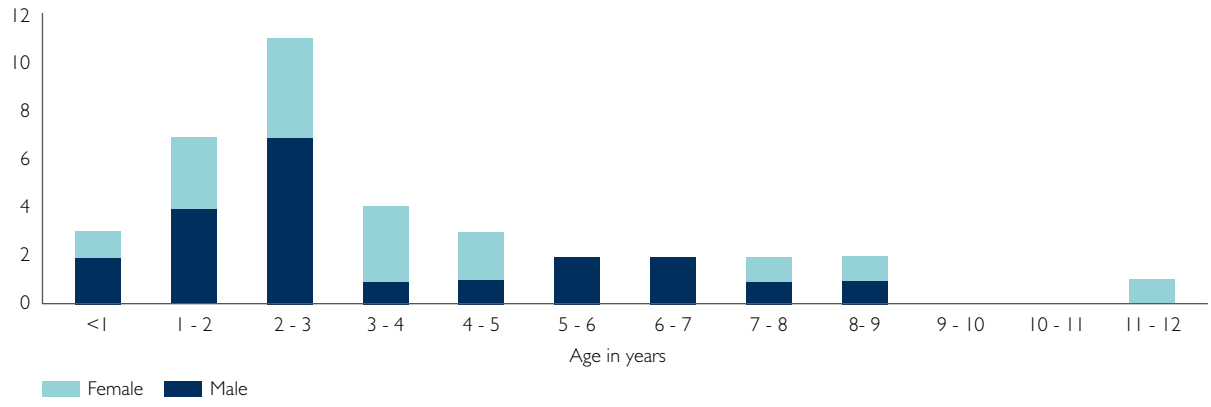


FIGURE 4: Gender and age at time of stent insertion.

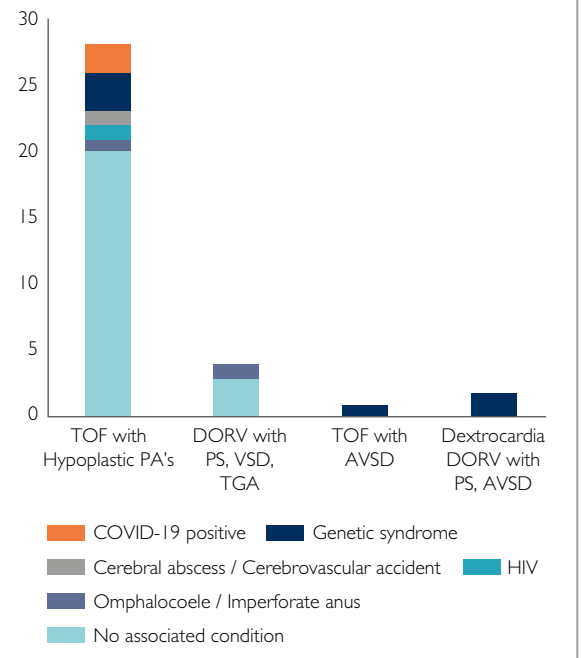


FIGURE 5: Cardiac diagnosis with associated condition.

TOF: Tetralogy of Fallot, PA's: Pulmonary arteries, DORV: Double outlet right ventricle, PS: Pulmonary stenosis, VSD: Ventricular septal defect, TGA: Transposition of the great arteries, AVSD: Atrioventricular septal defect.

TABLE I: Number of stents required per procedure.

Number of stents	Percentage of procedures (n=40)
1	88%
2	10%
3	2%

TABLE II: Stent and procedure characteristics.

	Median	Range
Stent diameter (mm)	8	6 - 10
Stent length (mm)	20	16 - 40
Balloon dilatation (atm)	10	5 - 15
Radiation exposure (min)	44	8.8 - 289
Radiation dose (mGy)	197	42 - 1 556
Contrast dose (ml)	109	30 - 480
Procedural time (min)	110	39 - 420

TABLE III: Oxygen saturations pre- and post-stent procedures.

	Oxygen saturations (mean, 95% CI)	
Procedure	**Pre-stent**	**Post-stent**
Procedure 1 (n=37)	65% (62 - 68)	95% (93 - 96)
Procedure 2 (n=4)	80% (79 - 81)	92% (85 - 99)
Procedure 3 (n=1)	71%	93%
Procedure 4 (n=1)	70%	90%

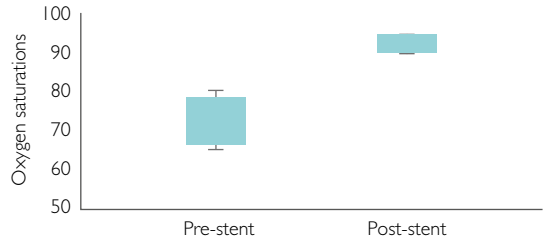


FIGURE 6: Boxplot illustrating oxygen saturations pre- and post-stent procedures.

TABLE IV: Pulmonary artery growth post procedure one.

	Pre-stent		Post-stent	
	Angiographic measurement	Echocardiographic measurement	First echocardiographic measurement	Second echocardiographic measurement
LPA diameter mm (median, range)	5 (3 - 9.6)	7 (5 - 10)	9 (7 - 13)	11 (7 - 15)
LPA diameter z-score (median, range)	-0.06 (-1.76 - 3.83)	-0.22 (-1.72 - 2.03)	0.07 (-1.33 - 2.87)	0.08 (-2.23 - 2.38)
RPA diameter mm (median, range)	6 (3 - 8)	5 (3 - 7)	7 (5 - 8)	8 (6 - 10)
RPA diameter z-score (median, range)	0.31 (-2.06 - 1.89)	-0.06 (-2.27 - 2.13)	0.37 (-1.64 - 1.37)	-0.23 (-2.34 - 1.88)
McGoon ratio (median, range)	1.35 (0.55 - 1.86)	1.36 (0.55 - 1.86)	1.71 (1 - 2.29)	2.05 (1.4 - 2.67)

TABLE V: Pulmonary artery growth post final procedure.

	Echo - Pre-stent			Echo - Post final procedure			Percentage increase %		
Patient	LPA (mm)	RPA (mm)	McGoon ratio	LPA (mm)	RPA (mm)	McGoon ratio	LPA	RPA	McGoon ratio
5	3	3	0.55	9	8	1.55	67	63	65
13	6	7	1.86	10	10	2.00	40	30	7
16	6	6	1.50	9	10	1.90	33	40	21
19	4	5	1.29	5	6	1.57	20	17	18

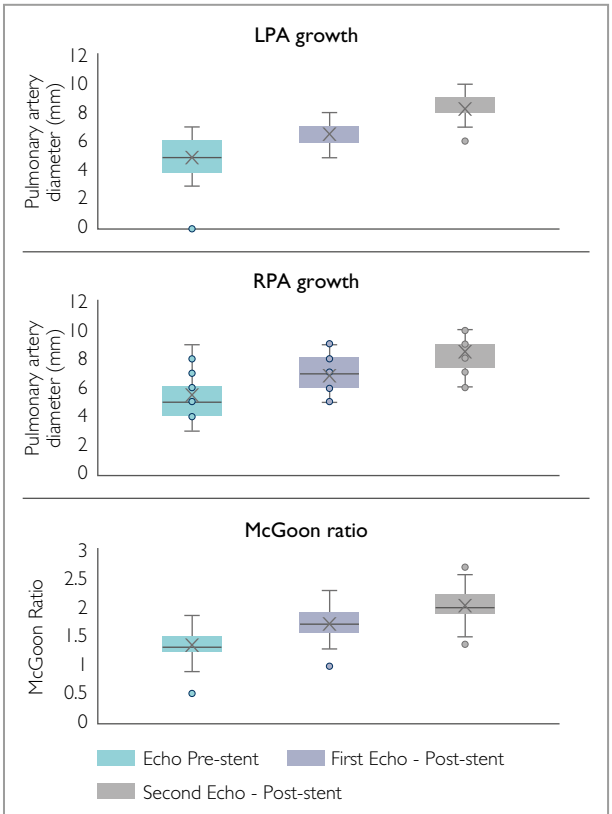


FIGURE 7: Boxplot diagrams illustrating the echocardiographic measurement of the LPA and RPA in millimetres and McGoon ratio pre-stent, 1 month post-stent, and approximately 7 months post-stent placement.

cedure and again after approximately 7 months (5 - 9 months) (Table V & Figure 7). Twenty six of 37 patients (70%) achieved a McGoon ratio of 2 or greater at the 7-month post-stent echo (Figure 8).

Short-term negative clinical outcomes post RVOT stent placement

The 30-day mortality rate was zero after stent placement. Two patients had severe hypercyanotic episodes and demised on the operating table prior to induction of anaesthesia or stent placement. The stent embolised into the aortic arch in 1 patient and a small pericardial effusion arising from guidewire perforation developed in another. There was no report of tricuspid valve damage, RVOT obstruction, stent dislodgement or branch pulmonary artery jailing. Patients spent an average of 2 days in PICU (range 0 - 10 days). The median length of hospital stay was 6.5 days (range 2 - 80 days).

Long-term negative clinical outcomes post RVOT stent placement

Stent fracture occurred in 3 patients (Figure 9) resulting in replacement in all. There has been no report of infective endocarditis nor arrythmia 6 months after the enrolment period.

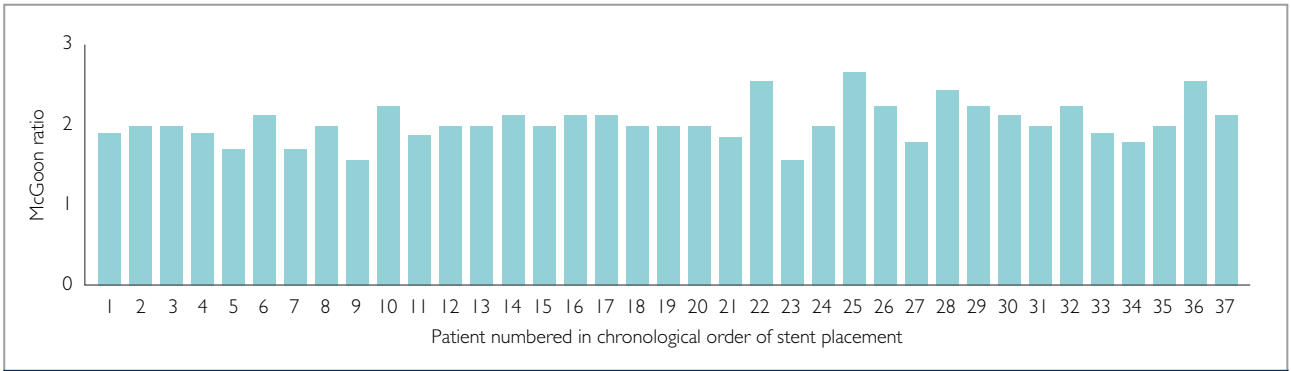


FIGURE 8: McGoon ratio post final procedure.

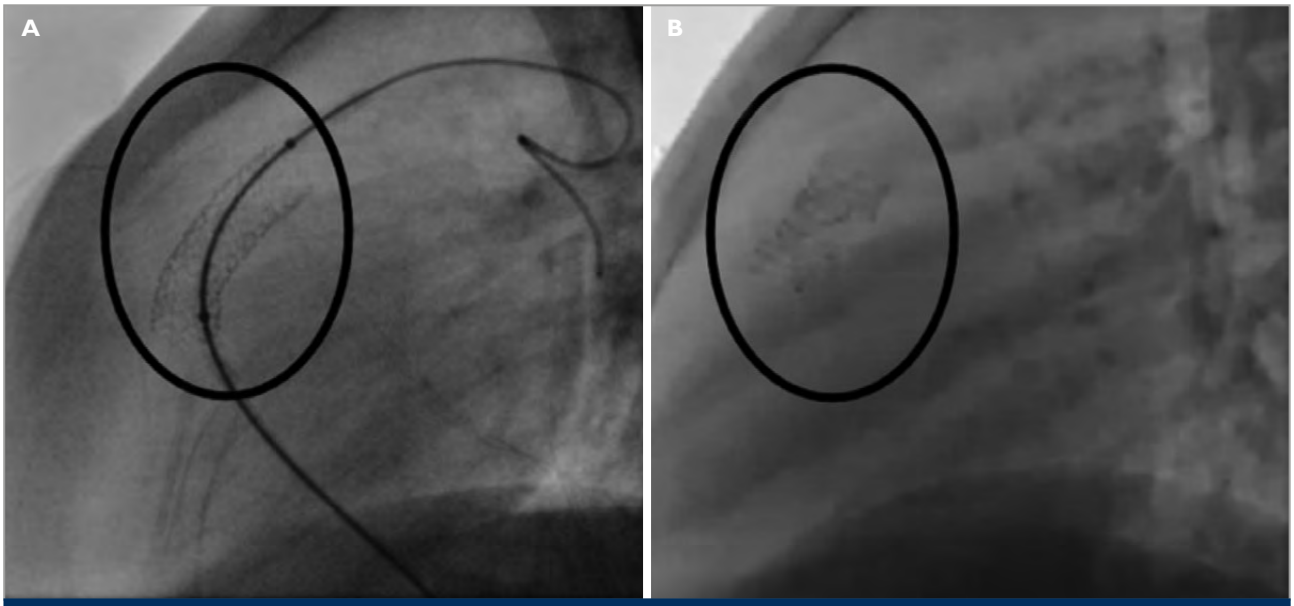


FIGURE 9: Lateral chest radiographs with right ventricular outflow tract stents in situ.
A - RVOT stent intact. B - RVOT stent fracture

DISCUSSION

We found that stenting of the RVOT is an effective and safe initial palliative procedure in patients with TOF. The pulsatile forward flow of systemic venous blood into the pulmonary arteries allows symmetrical growth and potentially permits patients to progress to complete surgical repair.

This finding is in keeping with reports in neonatal populations.[6,9-11] Despite advances in medicine, the diagnosis of many congenital conditions is delayed beyond the neonatal period in developing countries such as South Africa. In our study, the average age of diagnosis of TOF was 2 years and 4 months. Factors contributing to the delay range from poor primary healthcare, social factors and the inconsistent use of Western medicine. Furthermore there was an average delay of 15 months between the time of diagnosis and the first placement of a stent. Inadequate resources played a significant role in this delay magnified by the postponement of elective procedures after onset of the COVID-19 pandemic. Delay in referral to a tertiary centre after diagnosis, missed follow-up visits and 6 patients with occluded central shunts contributed to the longer time interval between initial diagnosis and stent placement.

Delayed diagnosis and treatment in a patient with cyanotic CHD increases the risk of complications. Two patients had a cerebrovascular accident, 1 had a cerebral abscess, 27 were malnourished, and 8 presented with refractory hypercyanotic spells requiring emergent stent placement. Two of these 8

patients tested positive for COVID-19. Neither responded to medical management of the hypercyanotic episode, and one had a brief cardiac arrest requiring cardio-pulmonary resuscitation.

During the study, there was a significant increment in operator experience and evolution in the materials employed.[12] The placement of the first stent involved the longest procedural time (420min), used the greatest amount of contrast (480ml) and required a repeat procedure following stent fracture that resulted in the largest radiation dose (1556.17mGy). Four patients required further intervention for stent replacement or balloon dilatation. These 4 patients were the first 4 participants in the study, 3 of whom had stent fractures. Though the same type of stent was used throughout the study, there were progressive improvements in design.[12] The Formula stent (Cook® Medical, USA) allows significant over-dilatation with virtually no shortening. Despite 5 patients requiring more than 1 stent to cover the infundibular stenosis, this did not contribute to stent dislodgement or jailing of the branch arteries. The use of the long sheaths or guide catheters prevented stent dislodgement or tricuspid valve damage.[5] Only 1 patient developed a small pericardial effusion due to guidewire perforation and was discharged in 5 days after conservative management. Despite the steep learning curve, no mortalities were recorded within 30 days of stenting.

A general anaesthetic was used for each of these procedures. Our study specifically made use of ketamine-induced anaesthesia, given that systemic vasoconstriction is beneficial in patients with a right-to-left shunt. The majority of patients were extubated in theatre. Seventy one percent of patients required post-operative PICU care of whom 45% were admitted for more than 3 days. Reasons for prolonged PICU admission included pulmonary oedema, convulsions secondary to electrolyte derangements, nosocomial sepsis and a patient who deteriorated and required emergency surgical repair. The total length of hospital stay exceeded that of international experience averaging 12.8 days.[13] This was influenced by the 4 patients that were admitted for more than 48 days. One developed a cerebral abscess that required drainage, while another developed a chylothorax and multiple episodes of nosocomial sepsis. Two patients developed multiple cerebral infarcts which required stabilisation prior to stenting.

A known consequence of cyanotic CHD is polycythaemia. Our patients had an average haemoglobin level of 18.4g/dL, increasing the threshold for visible cyanosis to an oxygen saturation of approximately 85%.[14] Our study participants were deeply cyanosed with an average saturation level of 65% prior to stent insertion which improved to 95% after stent insertion. We do not report on the potential improvement in polycythaemia due to the retrospective nature of the study.

In order to quantify growth, multiple assessments of the branch PA sizes were required. As in other studies, this could only be done by serial echo's as serial catheter pulmonary angiograms were not feasible nor acceptable due to the significant radiation exposure.[15] Despite the first echo being only about a month after stent placement, growth could be appreciated with the McGoon ratio increasing from 1.36 to 1.71. At this stage, 18% of the patients had a McGoon ratio greater than 2 therefore potentially qualifying them for a complete surgical repair. After the final echo, approximately 7 months post stent placement, the average McGoon ratio was 2.05 thereby potentially already qualifying 70% of the patients to a full surgical repair. As of December 2023, 9 of the patients have undergone a full surgical repair.

The pulmonary valve was spared in two thirds of patients. Not covering the pulmonary valve with a stent potentially avoids the need for a transannular patch at the time of corrective surgery.[5]

Stenting of the RVOT as the initial palliative procedure in TOF patients that present beyond the neonatal period enables effective growth of the pulmonary arteries with marked improvement in oxygen saturations and minimal post-operative complications. Further prospective studies analysing the longer-term effects of stent placement in TOF, a comparison with other palliative procedures, and outcomes in patients subsequently undergoing complete surgical repair are needed.

STUDY LIMITATIONS

This was a single centre, retrospective, non-randomised study in patients with TOF. Our 37 patients excluded the 2 who demised on the operating table prior to placement of the stent. PA growth was measured by various paediatric cardiologists allowing inter-observer variability, likely pertaining to the minimal change of the Z score measurement. The timing of the various measurements varied due to erratic patient follow-up. Observation for long-term complications was limited to 6 months post-stent placement.

CONCLUSION

Our experience of stenting the RVOT in TOF patients who present at an older age, with multiple comorbidities and often a poor prognosis, has yielded good results. In the absence of freely available access to cardiothoracic surgery and surgical ICU beds when these patients present in extremis with hypercyanotic spells, RVOT stenting can be a lifesaving procedure. The procedure has the potential to save children's lives in resource-limited hospitals throughout developing countries. Significant improvement in oxygen saturations and PA growth permitted majority of our patients to undergo a full TOF surgical repair.

ACKNOWLEDGEMENTS

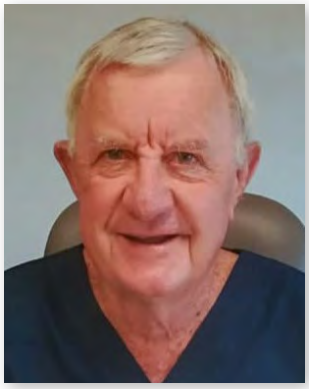
Dr Pickup thanks Dr Joshi for his leadership and advice, Mr Masenge for data analysis and Mr Mahlangu for artwork.

Conflict of interest: none declared.

REFERENCES

1. Sliwa K, Lecour S, Zühlke L, et al. Cardiology-cardiothoracic subspeciality training in South Africa: A position paper of the South Africa Heart Association. Cardiovasc J Afr. 2016;27(3):188-193. DOI:10.5830/CVJA-2016-063.
2. Barron DJF, Jegatheeswaran AMDP. How and when should tetralogy of Fallot be palliated prior to complete repair? Seminars in thoracic and cardiovascular surgery: Pediatr Card Surg Annu. 2021;24:77-84. DOI:10.1053/j.pcsu.2021.02.002.
3. Dawoud MA, Abd Al Jawad MN, Hikal T, et al. Single-stage complete repair versus multistage repair of tetralogy of Fallot with borderline pulmonary arteries. JSM Heart Surg. 2018;21(6):466-471. DOI:10.1532/hsf.2075.
4. Luxford JC, Adams PE, Roberts PA, et al. Right ventricular outflow tract stenting is a safe and effective bridge to definitive repair in symptomatic infants with tetralogy of Fallot. Heart Lung Circ. 2023;32(5):638-644. DOI:10.1016/j.hlc.2023.02.010.
5. Quandt D, Penford G, Ramchandani B, et al. Stenting of the right ventricular outflow tract as primary palliation for Fallot-type lesions. J Congenit Cardiol. 2017;10(17):1774-1784. DOI:10.1016/j.jcin.2017.06.023.
6. Castleberry CD, Gudausky TM, Berger S, et al. Stenting of the right ventricular outflow tract in the high-risk infant with cyanotic teratology of Fallot. Pediatr Cardiol. 2014;35(3):423-430. DOI:10.1007/s00246-013-0796-z.
7. Ngwezi DP, Vanderdonck K, Levin SE, et al. An audit of surgical repair of tetralogy of Fallot in an African tertiary care centre. SA Heart®. 2013;10(3):520-525. DOI:https://doi.org/10.24170/10-3-1792.
8. Sasikumar N, Mohanty S, Balaji S, et al. Rescue right ventricular outflow tract stenting for refractory hypoxic spells. Catheter Cardiovasc Interv. 2023;101(2). DOI:https://doi.org/10.1002/ccd.30522.
9. Barron DJ. Tetralogy of Fallot: Controversies in early management. World J Pediatr and Congenit Heart Surg. 2013;4(2):186-191. DOI: 10.1177/2150135112471352.
10. Dryżek P, Moszura T, Góreczny S, et al. Stenting of the right ventricular outflow tract in a symptomatic newborn with tetralogy of Fallot. Postępy Kardiol Interwencyjnej. 2015;11(1):44-47. DOI: 10.5114/pwki.2015.49184.
11. Korbmacher B, Heusch A, Sunderdiek U, et al. Evidence for palliative enlargement of the right ventricular outflow tract in severe tetralogy of Fallot. Eur J Cardiothorac Surg. 2005;27(6):945-948. DOI: 10.1016/j.ejcts.2005.02.010.
12. Beshchasna N, Saqib M, Kraskiewicz H, et al. Recent advances in manufacturing innovative stents. Pharmaceutics. 2020;12(4):349. DOI: 10.3390/pharmaceutics12040349.
13. Quandt D, Ramchandani B, Penford G, et al. Right ventricular outflow tract stent vs. bt shunt palliation in tetralogy of Fallot. Heart. 2017;103(24):1985-1991. DOI: 10.1136/heartjnl-2016-310620.
14. Park MK, Salamat M. Park's paediatric cardiology for practitioners e-book: Elsevier Health Sciences. 2020;7:378-390.
15. Quandt D, Ramchandani B, Stickley J, et al. Stenting of the right ventricular outflow tract promotes better pulmonary arterial growth compared with modified Blalock-Taussig shunt palliation in tetralogy of Fallot–type lesions. JACC Cardiovasc Interv. 2017;11(10):1774-1784. DOI: 10.1016/j.jcin.2017.06.023.

COMMENTARY



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Management of tetralogy of Fallot in South Africa

This issue of the Journal contains 2 papers on the local management of tetralogy of Fallot (TOF). The first comprehensively and frankly reviews the surgical repair of TOF in a state hospital. The detailed text is well complemented by excellent tables and figures. Particularly noteworthy is the complete (100%) early postoperative studies of the severity of pulmonary regurgitation, right ventricular outflow gradients and trans-annular plane systolic excursion (TAPSE), by transthoracic echocardiogram. Under the circumstances, the surgery itself was satisfactory.

There are important lessons for all who are considering paediatric cardiac surgery in developing countries. Presentation, and hence operations, were delayed to an older age and 40% of patients were lost to follow-up. Major limitations were encountered in the quality and quantity of intensive care, malnutrition was common and postoperative infection was frequent. There was a high incidence of hypercyanotic spells in the older patients with a relatively high frequency of polycythaemia. Almost half the early survivors were lost to follow-up. These are the challenging conditions in which surgery is performed in this environment.

I commend the author for a frank and detailed analysis. No doubt similar circumstances prevail for the repair of all paediatric congenital heart defects in developing countries. As the author states, improved management is imperative and will only be achieved by "timeous diagnosis, earlier surgery, improvement in perioperative care, prevention of nosocomial infections and improved follow-up." Sound advice. These obstacles confront all surgical teams working in this environment. It is testimony to the obvious. Paediatric cardiac surgery is not "a one surgeon show" but involves the coordinated action of a multitude of disciplines, with a complete follow-up and accurate data analysis. No component can fail without jeopardising the early and long term outlook.

With almost half of patients lost to follow-up. I am reminded of the biblical adage "forgive them Lord for they know not what they are doing. "

The second publication is a report on right ventricular outflow tract (RVOT) stenting as a palliative procedure in patients with TOF. Because of a significant operative mortality, there is no doubt interventional cardiological procedures, including RVOT stenting, have had a major beneficial effect on outcomes in the rescuing neonates and infants with TOF. However a pre-

requisite of this strategy is that patients should subsequently undergo surgical repair when stabilised, older and bigger and when the risk of open heart surgery and cardiopulmonary bypass is lower.

In the series from the Steve Biko Hospital, 37 patients had RVOT stenting. Oxygen saturation increased and the pulmonary arteries enlarged. The zero procedural mortality is commendable; less commendable is mean age of the patients (43.6 months) that is uniquely greater than that in published literature and that less than 25% of patients subsequently underwent surgical repair without their outcomes being reported. The application of expensive, limited resources to provide temporary benefit is concerning.

These reports sadly reflect the deficiencies in paediatric cardiac surgery in South Africa and hopefully will provide strong motivation for future improvement.

Subclinical cardiovascular remodelling in HIV-infection: A multimodal case study of 2 serodiscordant, monozygotic twins

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ABSTRACT

Cardiovascular abnormalities are increasingly recognised among people newly diagnosed with HIV, but subclinical pathology may be challenging to diagnose. We present a case study of subtle cardiovascular changes in identical twins, one without HIV-infection and the other recently diagnosed with HIV (serodiscordant). We hypothesise that cardiovascular parameters would be similar between the twins, unless non-genetic (environmental) factors are at play. These differences likely represent occult pathology secondary to the effects of early HIV-infection.

A 25-year-old female incidentally diagnosed with HIV, and her HIV-uninfected identical twin, living with her since birth, underwent comprehensive cardiovascular assessments. The HIV-positive twin exhibited a globular left ventricle (LV), larger LV volumes, decreased LV strain, peak atrial longitudinal strain (PALS) and higher native T1 and T2 mapping values compared to her sister. Cardiac biomarkers high sensitivity cardiac troponin T and N-terminal proBNP, as well as the novel markers of fibrosis and remodelling, galectin-3 and soluble-ST2, were higher in the HIV-infected twin. Given the twins' shared environment and genetic makeup, these differences likely stem from HIV-infection.

Our study supports previous findings and suggests potential screening markers for HIV-associated cardiovascular disease, including PALS. Further research is warranted to explore PALS' utility in this context.

SA Heart® 2024;21:48-57

INTRODUCTION

The link between human immunodeficiency virus (HIV) infection and cardiovascular dysfunction and mortality is well established.[1,2] With the advent of modern antiretroviral treatment (ART), the profile of cardiovascular disease has largely shifted to atherosclerotic cardiovascular disease in high income countries, but this has not been consistently demonstrated in low- and middle-income countries. In these regions, HIV-associated cardiomyopathy still contributes significantly to the burden of HIV-associated cardiovascular disease,[3-5] with HIV-infection seen to almost double the risk of heart failure.[6] HIV-associated cardiomyopathy remains a poorly understood entity due to numerous contributing factors.[5,7] Of these factors, data on the genetic susceptibility of HIV-associated cardiomyopathy in individuals is especially sparse.[8-10]

Cardiovascular research from both high- and low- to middle-income countries has demonstrated the presence of subclinical structural, functional, and biochemical abnormalities in newly diagnosed people living with HIV (PLWH), before the influence of ART.[11-16] However, some controversy remains regarding the finding of systolic dysfunction in asymptomatic PLWH, as this finding has not been consistently observed in contemporary studies.[17] ART may improve subclinical HIV-related alterations in cardiovascular structure and biochemical signals of cardiac disease[16,18] and cardiovascular magnetic resonance imaging (CMR) research has demonstrated improvements

in LV tissue characteristics after the initiation of ART.[19] There are limited prospective studies that track cardiovascular changes after the initiation of ART, and comparisons are usually made between mixed groups of treated and untreated individuals. This heterogeneity may explain the conflicting results, as subclinical abnormalities may be subtle, and observations between matched control groups may be masked by unknown genetic or environmental factors. Many knowledge gaps remain on early myocardial disease in asymptomatic PLWH, and further research is needed to adequately characterise these functional, structural and tissue characterisation abnormalities to better inform research in the ART-era and aid in establishing evidence-based screening and treatment strategies.

Multimodal cardiovascular assessment combines several modalities, employing each of their unique strengths in evaluating various aspects of the cardiovascular system. CMR is the non-invasive gold standard for volumetric examination of the heart and boasts excellent inter- and intra-observer variability.[20,21] Echocardiography with Doppler is a well-validated tool to interrogate diastolic function.[22] Speckle tracking echocardiography (STE) and CMR feature tracking are modalities that may be used to analyse myocardial deformation.[23] STE, however, has the distinct advantage of almost 2 decades of research and its clinical use is supported by treatment guidelines.[24] Peak atrial longitudinal strain (PALS) of the left atrium (LA) is increasingly used to assess atrial reservoir function and mirrors elevation in LA filling pressures,[25] serving as a sensitive tool to assess early cardiac dysfunction. Relatively few studies on this topic have been carried out, but there is emerging evidence to suggest its utility in the diagnosis of subclinical HIV-associated cardiovascular disease.[26,27] Biochemical cardiac markers are integral to the diagnosis and management of cardiovascular conditions. High sensitivity cardiac troponin T (hs-cTnT) and N-terminal proBNP (NT-proBNP) are well established markers that provide information on cardiac injury and myocardial stretch respectively. Various novel cardiac markers, including soluble ST-2 (sST-2) and galectin-3 are associated with specific pathophysiological processes per se, rather than the sequalae of disease. sST-2 is involved in cardiac remodelling, hypertrophy and fibrosis,[28] whereas galectin-3 may be directly involved in the process of ventricular remodelling through tissue repair and fibrosis.[29]

In this article we describe known and novel multimodal cardiovascular findings in the rare scenario of HIV-serodiscordance (1 twin with HIV and the other without) in identical female twins. As monozygotic twins have identical genetic makeup and cardiac heritability has been shown to be high,[30-33] the influence of environmental factors can be evaluated in the absence of genetic confounders. We hypothesised that a difference in cardiovascular parameters would not be demonstrable between the twins, unless non-genetic (environmental) factors were influencing the cardiovascular system. Secondly, we hypothesised that such a difference would represent occult pathology secondary to the direct or indirect effect of early HIV-infection, before the initiation of ART.

METHODS

Study design

This case study was nested within a larger prospective cohort study in the Western Cape, South Africa evaluating newly diagnosed PLWH without known cardiovascular disease.[13] The study was approved by the Stellenbosch Human Research Ethics Committee (Ref: S19/07/137) and all volunteers provided written informed consent for data collection and publication.

Clinical information

A 25-year-old, asymptomatic, African female (twin 1) incidentally tested positive for HIV at a local non-profit organisation's public service and was referred to her local clinic for ART. Her HIV-status was serologically confirmed prior to enrolment in the study, and her identical twin sister volunteered as a HIV-uninfected control (twin 2). Twin 1's last confirmed negative HIV test was 14 months prior. The clinical history and contact tracing estimate her time from HIV-seroconversion to enrolment as 7 months. The twins have shared a household in a low-income neighbourhood since their uncomplicated births. They have both excelled academically, participated in organised sport, and have shared similar lifestyles in terms of physical activity and diet. The twins give a history of equal levels of fitness over the years, frequently walking and exercising together. Both twins have attained a tertiary level qualification. They have never smoked or used illicit drugs and have negligible alcohol intake. There is no significant family history of cardiovascular disease, no comorbidities, no history of COVID-19, or any past illness requiring hospitalisation. The clinical examination was unremarkable, other than the finding of palpable, small axillary and cervical lymph nodes in twin 1. The twins share almost identical physical features. Twin 1 was not overtly wasted but could be described as leaner than her sister. Twin 2 was marginally taller than her sister, although this is not readily apparent without a side-by-side comparison.

Data collection

Detailed description of data collection and methodology has been published previously.[12,13,34] In short, a comprehensive cardiovascular evaluation including anthropometric, biochemical, immunological, virological, pulse wave velocity, and electrocardiogram (ECG) investigations were performed on both twins. Fasting blood for a full lipogram, blood glucose, creatinine, HIV-viral load, CD4 count, hs-cTnT and NT-proBNP was collected and analysed by the on-site National Health Laboratory Service (ISO 15189 accredited laboratory).[35] Additional laboratory work on novel cardiac biomarkers, soluble ST-2 and galectin-3, was performed by the Stellenbosch University Immunology Research Group (ISO 15189 accredited laboratory). Serum concentrations of soluble ST-2 and galectin-3 were determined using multiplexed immunometric assays (Human magnetic Luminex screening assay, R&D Systems, Minneapolis, United States of America). Glomerular filtration rate was estimated using the CKD-EPI equation.[36]

Cardiovascular magnetic resonance

Both CMR studies were performed on a 1.5T magnetic resonance scanning system (Magnetom Avanto, Siemens Healthcare, Germany) with commercially available cardiac sequences as described previously.[12,13] Images included cine imaging for LV function and morphology, as well as native T1, T2, extracellular volume (ECV) mapping and late gadolinium enhancement imaging for myocardial tissue characterisation. The studies were post-processed and analysed by 2 independent observers blinded to the clinical information, using CVI[42] (version 5.11.2, Circle Cardiovascular Imaging, Calgary, Alberta, Canada).[12,13] Quantitative mapping values are reported as the mean basal values.

Echocardiography

Structural and functional 2D echocardiographic studies were acquired using a 2.5 mHz 4Cv probe on a Vivid E95 unit (GE Medical Systems, Norway. Software: EchoPAC PC, version 204, GE Healthcare, United Kingdom). Images were acquired in the left lateral decubitus position by a cardiac physiologist who was blinded to the clinical information. Echocardiographic parameters were acquired using standardised methodology.[37-40] The frame rate and image gain were continuously adjusted to optimise image quality and the cardiac cycle with the best image quality, and free from artefact, was selected for analysis.

Speckle tracking echocardiography derived ventricular strain

Endocardial contours were manually traced at end systole and a concentric region of interest, including the LV myocardial wall, was automatically traced by the EchoPAC software. The myocardial tracking was manually verified and where necessary the region of interest width was adjusted to optimise tracking. Peak systolic longitudinal strain was calculated by averaging the peak systolic values of the 16 LV segments,[41] derived from the apical 2-, 4-, and 3-chamber views.

Speckle tracking echocardiography derived atrial strain

To assess the atrial reservoir function, PALS was obtained using dedicated apical 2- and 4-chamber views to ensure visualisation of the LA throughout the cardiac cycle.[42] The LA endocardial border was contoured in both views, starting at the annulus and tracing along the atrial wall, crossing the pulmonary vein orifices and the LA appendage, stopping at the opposite mitral annulus. Accurate bi-plane tracking of the atrial endocardial border during the cardiac cycle was manually verified and adjusted on the EchoPAC software when necessary.

RESULTS

Clinical data

The twins were well matched in terms of anthropometry, blood pressure, and biochemistry (see Table I). Although twin

TABLE I: Clinical data.

Parameter	Twin 1 HIV-infected	Twin 2 HIV-uninfected
Weight (kg)	64	70
Height (cm)	167	169
Body mass index (kg/m^2)	23	25
Waist circumference (cm)	77	80
Systolic blood pressure (mmHg)	96	98
Diastolic blood pressure (mmHg)	78	68
6-minute walk test distance (m)	623	746
Biochemistry		
Creatinine (µmol/l)	66	65
eGFR (ml/min/1.73m^2)	111	114
Fasting glucose (mmol/l)	4.8	4.9
Fasting blood lipids		
Total cholesterol (mmol/l)	5.12	4.43
HDL cholesterol (mmol/l)	1.62	1.5
LDL cholesterol (mmol/l)	3.35	2.79
Triglycerides (mmol/l)	0.32	0.3
Virological and immunological markers		
WHO clinical stage	1	-
HIV viral load (copies/ml)	4096	-
HIV viral load (log copies/ml)	3.61	-
CD4 count (cells/µl)	513	673
CD8 count (cells/µl)	941	770

eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, WHO: World Health Organisation.

I had no cardiac symptoms, her sister outperformed her in the 6-minute walk test and walked almost 20% further during the assessment.

Electrocardiogram and heart rate

Both twins were in sinus rhythm, with normal heart rates of 60 and 66 beats per minute, respectively. Both sisters had non-specific T-wave inversion of standard lead III, with otherwise normal ECGs.

Cardiac morphology

For both cases, the cardiac morphology measured within normal CMR reference ranges,[43] but differed when compared to one another (see Table II). The most prominent difference between the twins' cardiac morphology was the globular geometry of twin 1's LV. This globular LV geometry was most appreciable in the three-chamber view and verified by the quantitative CMR measurements (Figure 1, Table II). Both the sphericity index and the midventricular LV end-diastolic dimension of twin 1 was higher than twin 2, confirming the observation of a more globular LV in twin 1. Furthermore, the LV end-diastolic volume was higher in twin 1 compared with twin 2. The other cardiac chambers of twin 1 demonstrated a similar trend of being larger than her (slightly taller) twin sister. The LA, right atrium and right ventricle were all larger in twin 1. A sliver of pericardial fluid was present in both twins, respectively measuring 4mm and 2mm at the base of the heart.

Systolic function

Visually, the systolic function of the ventricles in both twins were within normal range, although side-by-side CMR evaluation placed the LV ejection fraction (EF) of twin 1 about 5% lower than twin 2. This finding was confirmed with a blinded, quantitative CMR analysis that showed a 2% difference between twin 1 and twin 2. A notable difference was also present in the GLS of twin 1, which measured 3% lower than her sister.

Diastolic function

The diastolic function of both the twins was normal with the E:E' measuring <8 respectively (see Table II). Twin 1's transmitral inflow velocity and the E:E' were noted to be marginally higher than her sister.

Atrial reservoir function

Atrial strain curves are shown in Figure 2. The PALS of the LA was 56% lower in twin 1 compared with her sister and her atrial reservoir function is decreased for a female of her age (2.5th percentile is 29%).[44]

TABLE II: Cardiac parameters.

Parameter	Twin 1 HIV-infected	Twin 2 HIV-uninfected
Diastology of the LV		
E (cm/s)	114	50
E' septal (cm/s)	16	22
E' lateral (cm/s)	18	14
Averaged E' (cm/s)	17	18
E: E'	6.7	2.8
Speckle tracking echocardiography		
GLS (%)	-18	-21
PALS of the LA (%)	24	55
Cardiovascular magnetic resonance		
LA area (cm^2)	22	20
LA volume (ml)	68	58
RA area (cm^2)	20	20
RA volume (ml)	74	68
Basal LVEDD (mm)	50	47
LVEDD at midventricle (mm)	55	43
Sphericity index	0.56	0.48
LV EDV (ml)	146	138
LV mass (g/m^2)	57	55
LVEF (%)	68	70
RV EDV (ml)	153	140
RVEF (%)	62	62
Septal native T1 (ms) Mean basal native T1 (ms)	1 020 1 002	995 992
Mean basal T2 (ms)	48	47
Basal T2 myocardial: skeletal muscle ratio	1.4	1.4
Mean basal ECV (%)	23	23
LGE of myocardium or atria	Absent	Absent
Cardiac biomarkers		
hs-cTnT (ng/l)	5	<3
NT-proBNP (ng/l)	84	60
Galectin-3 (ng/ml)	8.6	5.5
sST-2 (ng/ml)	23.8	9.3
Aortic stiffness		
Carotid-femoral pulse wave velocity (m/s)	4.6	4.4

MV: mitral valve, GLS: global longitudinal strain, BLS: basal longitudinal strain, PALS: peak atrial longitudinal strain, LA: left atrium, RA: right atrium, LV: left ventricular, EDD: end-diastolic dimension, EDV: end-diastolic volume, EF: ejection fraction, RV: right ventricle, ECV: extracellular volume, LGE: late gadolinium enhancement, hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, sST-2: soluble ST2. Normal local reference ranges for myocardial mapping: Native T1: 950-1040 ms, T2: 44-52 ms

Multiparametric mapping and late gadolinium enhancement

The native T1 and T2 mapping, ECV and the T2 myocardial to skeletal muscle ratio were comparable between the sisters and were within the normal reference ranges (see Table II). How-

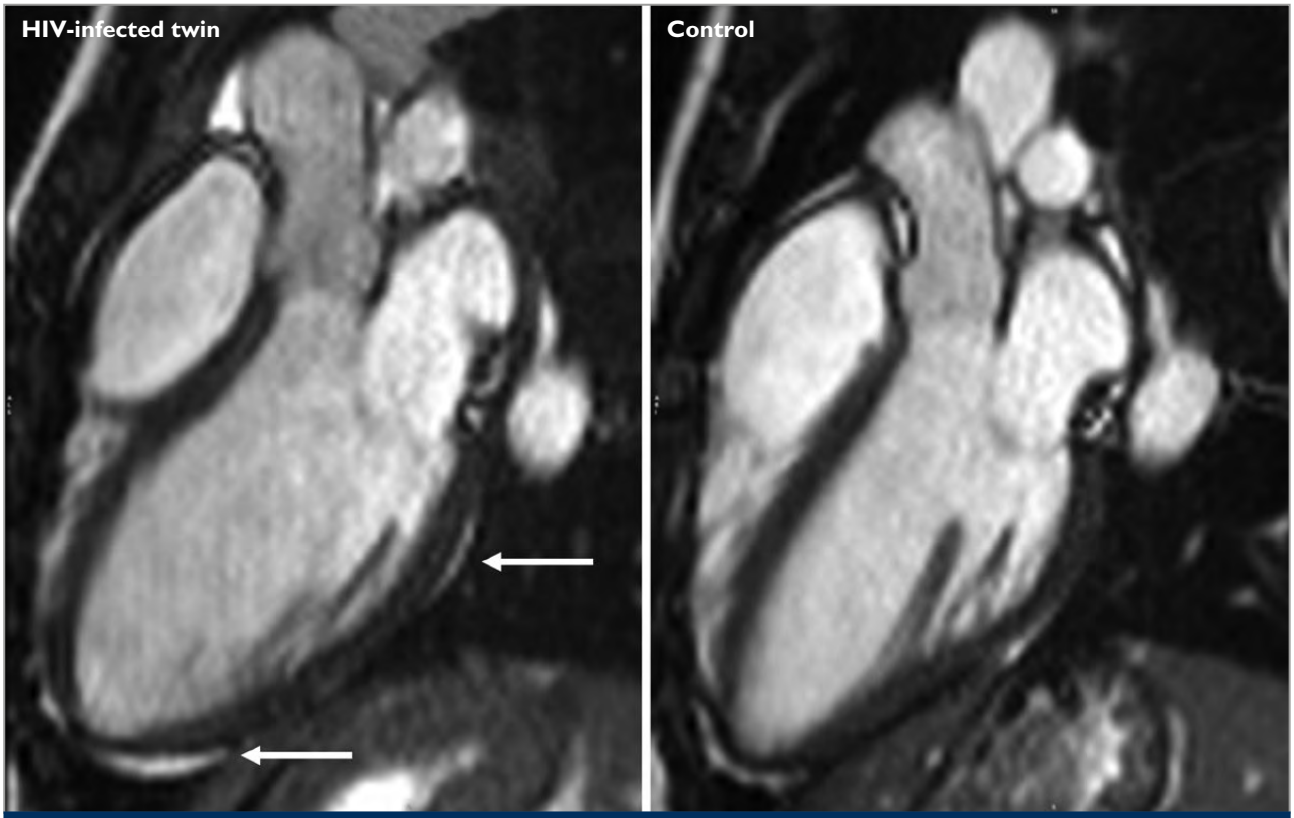

FIGURE 1: Cardiovascular magnetic resonance imaging (balanced steady state free precession image), end-diastole freeze frame of an HIV-infected female (left) and her HIV-uninfected, identical twin sister (right). The left ventricle of the HIV-infected twin appears globular and remodelled compared with her sister, with midventricular end-diastolic diameters of 50 and 47mm respectively. Note the small pericardial effusion in the HIV-infected twin (white arrows).

ever, both the native T1 and T2 were higher in twin 1. No late gadolinium enhancement of the myocardium or atrial walls were present in either twin.

Biomarkers

All measured cardiac biomarkers were higher in twin 1 than in twin 2 (see Table II). hs-cTnT was undetectable in twin 2, whereas it was detectable at normal levels in twin 1. Notably, s-ST2 was 2.6 times higher in twin 1 compared with her sister. The high sensitivity C-reactive protein in twin 1 and twin 2 measured 1.6mg/l and 9.7mg/l respectively.

DISCUSSION

The multimodal cardiovascular data from this set of identical twins supports the hypothesis that the hearts of the serodiscordant twins are different. Given that the twins have an identical genome and live in the same environment, this also supports the hypothesis that these differences suggest subclinical pathology and likely represent manifestations of HIV-infection or its secondary effects. Furthermore, we describe the novel finding of unexplained, early atrial dysfunction in an otherwise healthy, HIV-infected patient before the initiation of ART: A finding that should be explored further in larger cohorts as a potentially sensitive marker of early cardiovascular alteration.

In prior work from our research group, we demonstrated that at population level, there are subtle morphological, functional, and tissue characterisation abnormalities present at the time of HIV diagnosis, before the initiation of ART.[12,13] CMR and biochemical studies emanating from both high and low- to middle-income countries have made similar observations.[11,14,15] In our twin case study, we observed cardiovascular differences that bear a striking resemblance to what was observed in our larger research cohort.[12,13] Notably, the subtle difference in LVEF of 2% in the twins mirrors a difference of 3% in our larger cohort. These findings are comparable to research from other groups. Menacho, et. al and Ntusi, et al. demonstrated a 3% and 4% difference respectively, in the LVEF of PLWH compared to controls.[14,15] This further increases the likelihood that the observed differences in the twins are primarily due to HIV rather than a chance occurrence or measurement error. Although most parameters fall within normal reference ranges and the

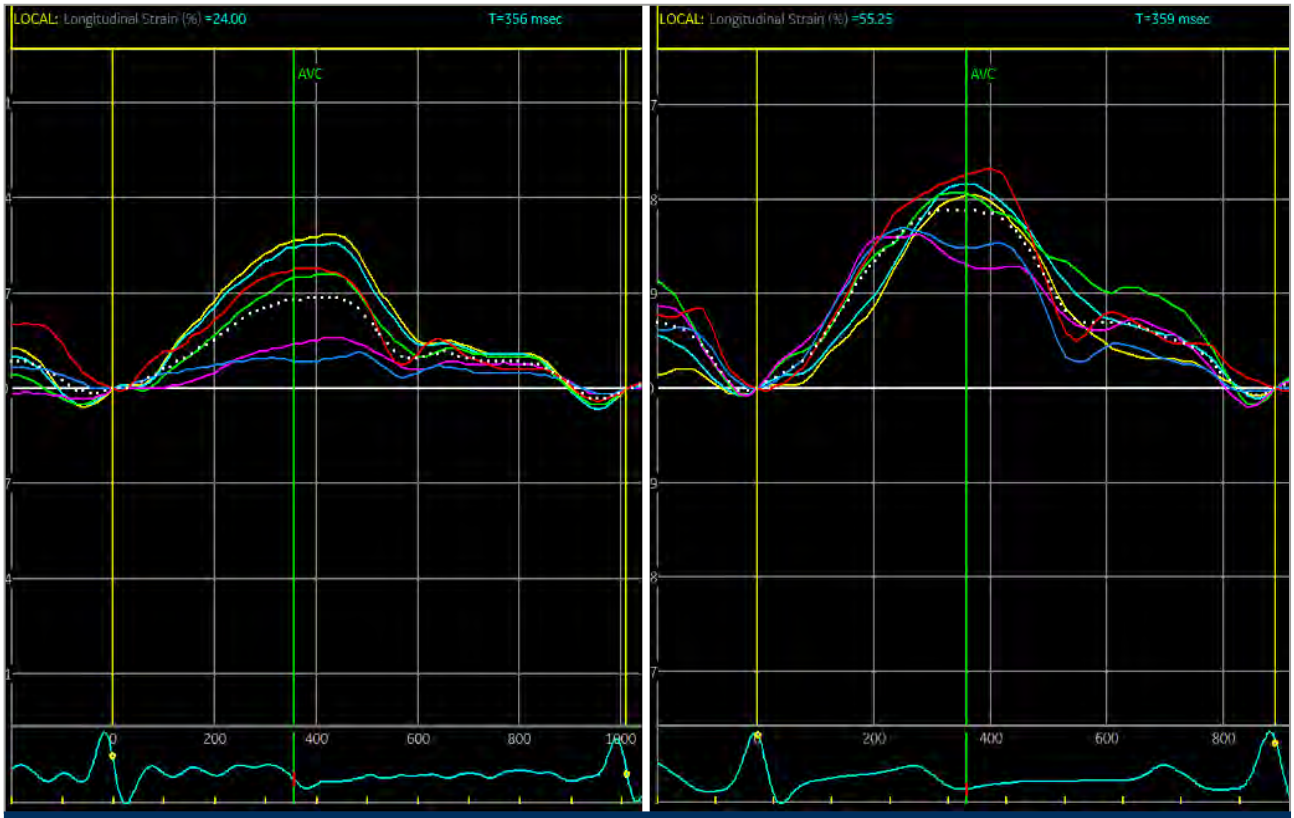

FIGURE 2: Bi-plane peak atrial longitudinal strain (PALS) of the left atrium (LA) demonstrating decreased atrial reservoir function in a 25-year-old HIV-infected female (left). Her HIV-uninfected, identical twin sister's normal PALS of the LA is shown for comparison (right). These findings suggest HIV-related atrial abnormalities and may form part of an HIV-related atriopathy.
AVC: aortic valve closure.

differences are small, it should be noted that these blinded measurements all tended toward abnormality in the HIV-infected twin. The exception was the abnormal PALS measurement that will be discussed later. By using an HIV-uninfected, genetically identical control, we were able to demonstrate subtle cardiovascular pathology in an HIV-infected individual. Demonstrating this would otherwise be extremely challenging, if not impossible, when pathology is only starting to manifest. This descriptive work contributes to our understanding of HIV's early effect on the cardiovascular system, as occult pathology may later manifest as symptomatic heart disease if these underlying pathophysiological mechanisms are not adequately addressed.

Our study's observations are consistent with the view that multiple pathophysiological processes work in synergy to initiate and maintain a chronic state of myocardial inflammation[7] that may be improved, but not completely halted, by ART.[13] These chronic pathological processes likely lead to the cardiac remodelling, fibrosis and disproportionate risk of cardiovascular disease seen in PLWH.[45] The level of systemic inflammation as measured by the high sensitivity C-reactive protein in twin 1 was not elevated in this case study and suggests that systemic inflammation and inflammation at the tissue level may be discrepant.

Strategies to prevent these complications in the ART era are largely understudied. The use of statin therapy has shown promise in preventing HIV-related myocardial infarctions, stroke and peripheral artery disease.[46] A limitation of this trial is that myocardial disease and heart failure were not specifically studied as outcomes and, when evaluating the individual components of major adverse cardiovascular events in this landmark study, no benefit was evident for death from any cardiovascular cause. This highlights the need for additional preventative research in this understudied group of patients.

Nature vs. Nurture: Determinants of cardiac morphology and function

Our participants' hearts demonstrated clear morphological differences. Whether these differences are due to genetic influences on cardiac morphology or due to the HIV-infection and /

or its secondary effects, must be determined. Since our participants are identical twins, we argue that their cardiac morphology should not differ considerably due to genetic influences, and we discuss key findings in the literature to support this. Heritability is the degree (usually reported as a percentage) to which a specific personal trait may be explained by an individual's genetics. Echocardiographic research suggests that the heritability of cardiac morphology is high.[31] Adams, et al. showed high cardiac similarity (predominantly chamber dimensions) between twins (monozygotic and dizygotic), as well as siblings when compared to random subjects. Furthermore, their data show that familial influences, which include common environmental and genetic factors, are important determinants of cardiac size. A cardiovascular study on a large twin cohort observed that LV mass has a significant genetic basis.[47] Contemporary research utilising CMR substantially exceeds the heritability estimates of cardiac structures in monozygotic twins compared to echocardiography, and provides additional evidence of a strong genetic basis for cardiac morphology.[30] High heritability of structural and functional cardiovascular parameters has been demonstrated across 3 South African generations.[33] This provides good evidence that genetics have a significant influence on cardiovascular structure and function in the African context too. Lastly, it has been shown that longitudinal strain has increased heritability in persons with African ancestry, compared to Caucasians.[32] Available data on twins and siblings support the notion that the structure and function of our study's twins should be almost identical, especially considering that they have shared the same environment since birth. However, this was not what was observed in our study. Given that, without exception, our quantitative values consistently trend toward abnormality, the likelihood that these differences are due to measurement error or chance is low. Notably our study employed different modalities and diagnostic techniques that demonstrated the same tendency of subtle abnormality in the HIV-infected twin. This supports the contention that the differences identified are not due to chance or measurement error and are rather, related to the only apparent difference between our twins: their discordant HIV status.

Ventricular dysfunction and remodelling in early HIV-infection

Our dataset suggests that the difference in the twin's LV size and geometry may be due to subclinical cardiac remodelling from HIV-infection or its secondary effects. Using CMR, we demonstrated larger LV dimensions and volumes in twin 1, findings that are corroborated by our biochemical observation of increased NT-proBNP, indicative of myocardial stretch.[29] Although the novel biomarkers sST-2 and galectin-3 are less studied compared to NT-proBNP, increases in these markers are associated with the processes of LV hypertrophy, fibrosis, and remodelling.[28,29] sST-2 has been shown to be useful in predicting cardiac dysfunction, even in otherwise healthy persons,[48] and its use to predict future heart failure in the HIV milieu warrants further study. Importantly, the sST-2 measurement of twin 1 was more than double that of twin 2. This biochemical evidence is in keeping with the imaging findings of an underlying process of remodelling and fibrosis, as sST-2 is believed to reflect cardiovascular stress and fibrosis with the ability to predict cardiovascular outcomes in heart failure.[28]

Employing aortic stiffness as a surrogate marker for risk, it has been shown that cardiovascular risk is higher in asymptomatic, HIV-infected persons compared to age- and sex-matched controls.[34] This difference was observed between twin 1 and twin 2 as well, although the difference was subtle at 0.2m/s.

The underlying cause of the cardiac remodelling in twin 1 is thought to be due to the direct or indirect cause of HIV-infection. Unfortunately, the pathophysiology of HIV-associated cardiovascular disease remains incompletely understood with numerous possible aetiologies.[7] As twin 1 was yet to be placed on ART at the time of study, these findings provide evidence of early cardiac remodelling in the absence of ART; an aetiological consideration frequently explored in contemporary literature. Chronic cardiovascular inflammation (before and despite ART) is thought to play an integral role in the development of a variety of HIV-associated cardiovascular diseases.[6,7,14,49,50] Mirroring the observations from our greater cohort, we measured a higher LV mass, native T1 and T2 in twin 1 compared to twin 2,[13] as well as higher levels of hs-cTnT in twin 1. These findings are in keeping with underlying myocardial oedema with / without concurrent myocardial fibrosis. One should be careful not to overcall pathology based on these subtle findings in the twins, but the clustering of our observations across different modalities is in keeping with the current inflammatory hypothesis of HIV, and in this case, likely represents myocardial inflammation in the HIV-infected twin. We hypothesise that HIV-related inflammation leads to low-grade myocardial injury and oedema, and manifests as structural and functional myocardial changes over time that are detectable with imaging and cardiac biomarkers. The long-term implication of these morphological and functional changes at the time of HIV diagnosis is not known. If underlying inflammation is closely associated with myocardial injury and remodelling, the persistence of inflammation, despite ART,[13,14] could lead to cumulative myocardial dysfunction and ultimately, symptomatic cardiac disease. This plausibly explains the excess cardiovascular

risk that is seen in PLWH, despite modern ART. Prospective research evaluating the cardiac outcomes of HIV-infected patients with subclinical cardiac remodelling is required to better understand the true clinical implication of these findings. This may ultimately lead to improvements in our ability to detect early manifestations of cardiac disease in PLWH using a combination of imaging and / or biochemical modalities.

HIV-associated atriopathy

We demonstrated that twin 1's LA was larger compared to her sister, although still within the normal range. However, we found distinct differences in twin 1's PALS of the LA, falling outside accepted reference ranges. The role of the LA in the modulation of ventricular filling and cardiac output is frequently overlooked. Pathology of the LA in HIV-infection has not been well researched, but there is evidence to suggest that the LA is not excluded from the detrimental effects of HIV, as seen with almost all other components of the cardiovascular system.[51] LA reservoir function is determined by the inherent stiffness of the atrium and the descent of the cardiac base.[52] Given the presence of ventricular function well within the normal range and normal diastolic function, we considered raised atrial stiffness in twin 1 as an explanation for our observations. The decrease in LA reservoir function in twin 1 may represent an early HIV-associated atriopathy. There are alternative explanations for this dysfunction, but given the presence of subclinical fibrosis in the ventricles of PLWH,[13,14] it is reasonable to speculate that the abnormal reservoir function is due to stiffening of the atrium from fibrosis. Although the native T1 of twin 1 was marginally higher than her sister, we do not have compelling evidence of myocardial fibrosis in the twins. Without comparing the PALS to her HIV-uninfected sister, the PALS measurement in twin 1 was already in the abnormal range. Since LA function is frequently employed by clinicians as a sensitive marker for early cardiac disease, the use of atrial strain may prove useful to screen for early HIV-associated cardiovascular dysfunction and merits dedicated future research.

LIMITATIONS

Despite the rare opportunity to compare a set of serodiscordant, monozygotic twins that are well matched and otherwise healthy, it remains possible that unknown environmental factors may have confounded our observations. Although twin 1 was an above average historian, the calculated 7-month duration of HIV-infection is not known with absolute certainty. The possibility remains that the duration may be as long as 14 months. However, examination, clinical staging, and immunological findings correlate with the clinical history and are in keeping with early HIV-infection. Our findings are thought-provoking and support the current thinking of HIV-associated cardiovascular disease. However, our study remains a descriptive case study of subtle findings in 2 (albeit well matched) subjects and should not be interpreted as conclusive, but rather as hypothesis generating to guide future research avenues.

CONCLUSIONS

The morphological, functional, and biochemical cardiovascular differences in our set of identical twins fall outside anticipated genetic variation and likely represent subclinical cardiovascular dysfunction and remodelling secondary to HIV-infection. These observations, in a genetically matched pair, mirror observations from matched, population-based studies and supports the thinking that the cardiovascular system is affected early during HIV-infection, and is most likely secondary to cardiovascular inflammation. Furthermore, atrial strain may be a useful parameter to detect early cardiac dysfunction in this setting and warrants further investigation. More research is required to evaluate the mid- to long-term significance of subclinical cardiac remodelling and dysfunction in PLWH.

Conflict of interest: none declared.

REFERENCES

1. Hsue PY, Waters DD. Time to recognise HIV infection as a major cardiovascular risk factor. Circulation. 2018;138(11):1113-1115.
2. Shah ASV, Stelzle D, Lee KK, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV. Circulation. 2018; 138(11):1100-1112.
3. Agbor VN, Essouma M, Ntusi NAB, Nyaga UF, Bigna JJ, Noubiap JJ. Heart failure in sub-Saharan Africa: A contemporaneous systematic review and meta-analysis. Int J Cardiol. 2018;257:207-215.
4. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus / acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto study cohort. Eur Heart J. 2012;33(7):866-874.
5. Hsue PY, Waters DD. Heart failure in persons living with HIV infection. Curr Opin HIV AIDS. 2017;12(6):534-539.
6. Bloomfield GS, Alenezi F, Barasa FA, Lumsden RBS, Mayosi BM VE. Human immunodeficiency virus and heart failure in low- and middle-income countries. JACC Heart Fail. 2016;15(5):477-491.
7. Robbertse PS, Doubell AF, Nachega JB, Herbst PG. The hidden continuum of HIV-associated cardiomyopathy : A focussed review with case reports. SA Heart® J. 2021;18(2):126-135.
8. Shaboodien G, Engel ME, Syed FF, Poulton J, Badri M, Mayosi BM. The mitochondrial DNA T16189C polymorphism and HIV-associated cardiomyopathy: A genotype-phenotype association study. BMC Med Genet. 2009;10(1):37.
9. Teer E, Joseph DE, Driescher N, et al. HIV and cardiovascular diseases risk: Exploring the interplay between T-cell activation, coagulation, monocyte subsets, and lipid subclass alterations. Am J Phys Heart Circ. 2019; 316(5):H1146-H1157.
10. Simon MA, Lacomis CD, George MP, et al. Isolated right ventricular dysfunction in patients with human immunodeficiency virus. J Card Fail. 2014;20(6):414-421.
11. Schuster C, Mayer FJ, Wohlfahrt C, et al. Acute HIV infection results in subclinical inflammatory cardiomyopathy. J Infect Dis. 2018;218(3):466-470.
12. Robbertse PS, Doubell AF, Steyn J, Lombard CJ, Talle MA, Herbst PG. Altered cardiac structure and function in newly-diagnosed people living with HIV: A prospective cardiovascular magnetic resonance study after the initiation of antiretroviral treatment. Int J Cardiovasc Imaging. 2023; 39(1):169-182.
13. Robbertse PS, Doubell AF, Lombard CJ, Talle MA, Herbst PG. Evolution of myocardial oedema and fibrosis in HIV infected persons after the initiation of antiretroviral therapy: A prospective cardiovascular magnetic resonance study. JCMR. 2022;24(1):72.
14. Ntusi N, O'Dwyer E, Dorrell L, et al. HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. Circ Cardiovasc Imaging. 2016;9(3):1-8.
15. Menacho K, Seraphim A, Ramirez S, et al. Myocardial inflammation and edema in people living with human immunodeficiency virus. JACC Cardiovasc Imaging. 2020;13(5):1278-1280.
16. Robbertse PS, Doubell AF, Esterhuizen TM, Herbst PG. Antiretroviral therapy and HIV-associated cardiovascular disease: A prospective cardiac biomarker and CMR tissue characterisation study. ESC Heart Fail. 2024; 11(2):748-758.
17. Hoy JF, Lee SJ, Trevillyan JM, et al. Asymptomatic people with well-controlled HIV do not have abnormal left ventricular global longitudinal strain. Front Cardiovasc Med. 2023;10:1-9.
18. Menacho Medina KD, Seraphim A, Ramirez S, et al. Cardiac magnetic resonance detects early cardiac involvement in HIV patients: Oedema and inflammation, which may be reversible with therapy. Eur Heart J Cardiovasc Imaging. 2019;20:411-412.
19. Robbertse PS, Doubell AF, Lombard CJ, Talle MA, Herbst PG. Evolution of myocardial oedema and fibrosis in HIV-infected persons after the initiation of antiretroviral therapy: A prospective cardiovascular magnetic resonance study. JCMR. 2022;24(1):72.
20. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J. 2004;147(2):218-223.
21. Grothues F, Smith GC, Moon JCC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with 2-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90(1):29-34.
22. Dugo C, Rigolli M, Rossi A, Whalley GA. Assessment and impact of diastolic function by echocardiography in elderly patients. J Geriatr Cardiol. 2016; 13(3):252-60.
23. Pedrizzetti G, Claus P, Kilner PJ, Nagel E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. JCMR. 2016;18(1):51.
24. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-3726.
25. Tan TS, Akbulut IM, Demirtola AI, et al. LA reservoir strain: A sensitive parameter for estimating LV filling pressure in patients with preserved EF. Int J Cardiovasc Imaging. 2021;37(9):2707-2716.
26. Berg C, Patel B, Reynolds M, et al. Left atrial strain and diastolic dysfunction amongst HIV-positive individuals: Insights from the Veterans Aging Cohort Study. J Am Coll Cardiol. 2021;77(18):1422.
27. Mirea O, Donoiu I, Manescu M, Dumitrescu F, Istratoaie O, Militaru C. Left atrial dysfunction by speckle tracking echocardiography in young subjects with HIV infection. Ultrasound Med Biol. 2022;48:S4-S5.
28. Villacorta H, Maisel AS. Soluble ST2 Testing: A promising biomarker in the management of heart failure. Arq Bras Cardiol. 2015;106(2):145-152.
29. Gaggin HK, Januzzi JL. Cardiac biomarkers and heart failure. Am Coll Cardiol. 2023 [Online] https://www.acc.org/Latest-in-Cardiology Articles/2015/02/09/13/00/Cardiac-Biomarkers-and-Heart-Failure. Accessed 22 Jan 2024.
30. Busjahn CA, Schulz-Menger J, Abdel-Aty H, et al. Heritability of left ventricular and papillary muscle heart size: A twin study with cardiac magnetic resonance imaging. Eur Heart J. 2009;30(13):1643-1647.
31. Adams TD, Yanowitz FG, Fisher AG, et al. Heritability of cardiac size: An echocardiographic and electrocardiographic study of monozygotic and dizygotic twins. Circulation. 1985;71(1):39-44.
32. Khan SS, Kim K-YA, Peng J, et al. Clinical correlates and heritability of cardiac mechanics: The HyperGEN study. Int J Cardiol. 2019;274:208-213.
33. Ware LJ, Maposa I, Kolkenbeck-Ruh A, et al. Are cardiovascular health measures heritable across three generations of families in Soweto, South Africa? A cross-sectional analysis using the random family method. BMJ Open. 2022;12(9):1-10.
34. Robbertse PS, Doubell AF, Innes S, Lombard CJ, Herbst PG. Pulse wave velocity demonstrates increased aortic stiffness in newly diagnosed, antiretroviral naïve HIV infected adults: A case-control study. Medicine. 2022; 101(34):e29721.
35. Sciacovelli L, Aita A, Padoan A, Antonelli G, Plebani M. ISO 15189 accreditation and competence: A new opportunity for laboratory medicine. J Lab Precis Med. 2017;2:79-79.
36. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604.
37. Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: Basic principles. Heart. 2010;96(9):716-722.
38. Masani N, Wharton G, Allen J, et al. Echocardiography: Guidelines for Chamber Quantification British Society of Echocardiography Education Committee. [Online] https://www.bhf.org.uk/-/media/files/information-and-support/publications/g407_echocardiography_guidelines_for_chamber_quantification_poster_0411.pdf?rev=bf9f180d83904e03870af2a82317fb92. Accessed 22 Jan 2024.
39. Geyer H, Caracciolo G, Abe H, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: Fundamentals and clinical applications. J Am Soc Echocardiogr. 2010;23(4):351-369.

40. Lang RM, Bierig M, Devereux R, et al. Recommendations for Chamber Quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiograph. J Am Soc Echocardiogr. 2005;18(12):1440-1463.
41. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardised myocardial segmentation and nomenclature for tomographic imaging of the heart. Circulation. 2002;105(4):539-542.
42. Badano LP, Kolias TJ, Muraru D, et al. Standardisation of left atrial, right ventricular, and right atrial deformation imaging using 2-dimensional speckle tracking echocardiography: A consensus document of the EACVI/ASE/ Industry Task Force to standardise deformation imaging. Eur Heart J Cardiovasc Imaging. 2018;19(6):591-600.
43. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, et al. Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. JCMR. 2020;22(1):87.
44. Nielsen AB, Skaarup KG, Hauser R, et al. Normal values and reference ranges for left atrial strain by speckle-tracking echocardiography: The Copenhagen City Heart Study. Eur Heart J Cardiovasc Imaging. 2022;23(1):42-51.
45. Henning RJ, Greene JN. The epidemiology, mechanisms, diagnosis and treatment of cardiovascular disease in adult patients with HIV. Am J Cardiovasc Dis. 2023;13(2):101-121.
46. Grinspoon SK, Fitch K V, Zanni M V, et al. Pitavastatin to prevent cardiovascular disease in HIV infection. NEJM. 2023;1-13.
47. Sharma P, Middelberg RP, Andrew T, Johnson MR, Christley H, Brown MJ. Heritability of left ventricular mass in a large cohort of twins. J Hypertens. 2006;24(2):321-324.
48. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress. Circulation. 2012;126(13):1596-1604.
49. Luetkens JA, Doerner J, Schwarze-Zander C, et al. Cardiac magnetic resonance reveals signs of subclinical myocardial inflammation in asymptomatic HIV-infected patients. Circ Cardiovasc Imaging. 2016;9(3):1-8.
50. Sood V, Jermy S, Saad H, Samuels P, Moosa S, Ntusi N. Review of cardiovascular magnetic resonance in human immunodeficiency virus-associated cardiovascular disease. S Afr J Radiol. 2017;21(2):1-10.
51. Pastori D, Mezzaroma I, Pignatelli P, Violi F, Lip GYH. Atrial fibrillation and human immunodeficiency virus type-1 infection: A systematic review. Implications for anticoagulant and antiarrhythmic therapy. Br J Clin Pharmacol. 2019;85(3):508-515.
52. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. Circulation. 1999;100(4):427-436.

Atrial arrhythmias arising from the superior vena cava presenting as paroxysmal atrial fibrillation, flutter and focal atrial tachycardia

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ABSTRACT

The superior vena cava (SVC) harbours about 25% - 40% of the non-pulmonary vein foci in atrial fibrillation (AF) and could manifest itself as paroxysmal atrial tachycardia (AT). AF ablation focusing on pulmonary vein isolation alone could miss SVC ectopy and result in failure of the procedure. Successful ablation is usually curative in SVC ectopy-induced AT / AF, however, potential complications include injury to the phrenic nerve, vagus nerve or the sino-atrial node. A focal ablation approach or SVC isolation are both proven options in the management of SVC tachycardia. In this article, we report SVC ectopy with variable conduction into the right atrium mimicking sinus rhythm, AT, atrial flutter (AFL) or AF. SA Heart® 2024;21:58-65

INTRODUCTION

Pulmonary vein (PV) isolation has been proven to be a useful strategy for paroxysmal atrial fibrillation (AF) with origin in the PVs worldwide. However, non-PV foci play an important role in initiating and maintaining AF in about 20% of patients. Non-PV foci are located at sites including the superior vena cava (SVC), left atrial (LA) posterior wall, the crista terminalis, the coronary sinus, the ligament of Marshall, the inter-atrial septum, the left atrial appendage.[1,2] In particular, the SVC harbours 25% - 40% of the non-PV foci for AF and is the most common non-PV source.[3] Atrial myocardial sleeves into the superior vena cava (SVC) are well known to cause focal ectopy which can induce AT / AF. We report our experience with SVC ablation performed as a stand-alone procedure for patients demonstrated to have focal ectopy from the SVC and presenting with focal AT / AFL / AF.

METHOD

A total of 323 patients who underwent ablation for atrial tachycardia and atrial fibrillation were analysed retrospectively and 3 patients with SVC-origin ectopy-induced AT / AFL / AF encountered between 2009 and 2023 in Christian Medical College, Vellore, India, were included in the study. All 3 patients presented with AT / AFL or AF were proven to be SVC ectopy initiated at cardiac electrophysiological study (EPS) and followed up after successful RFA. St Jude Medical EnSite NavX 3D mapping system was used for the creation of geometry, activation mapping and RFA.

CASES

Case 1:

A 52-year-old male presented to us with chief complaints of paroxysmal palpitations and chest pain for 3 months. The 12 lead ECG obtained during symptoms showed narrow QRS complex regular tachycardia which was initially diagnosed as AFL with 2:1 atrio-ventricular (AV) conduction (Figure 1). The patient was taken for an electrophysiological study (EPS) followed by radio-frequency ablation as appropriate. At EPS, the diagnostic EP catheters (Dua-Decapolar around the tricuspid annulus, Decapolar in the CS, 2 quadri-polar catheters in the right atrium – RA and the right ventricle – RV respectively) and a mapping and ablation catheter (St Jude Medical 8mm tip non-irrigation catheter) were utilised. The initial electrograms deceptively suggested an atrial flutter (AFL) rhythm with 2:1 A-V conduction and demonstrated a sequential activation around the lateral RA. The His-channel "A", however, was earlier, compared to the "A" in the CS 9/10 channels (Figure 2) unlike what is expected in typical cavo-tricuspid isthmus (CTI) dependent macro-re-entrant counter-clockwise right atrial flutter. The CS atrial activation progressed in a proximal to distal sequence. Catheter-induced RBBB was evident at this stage. The rhythm spontaneously degenerated into AF which

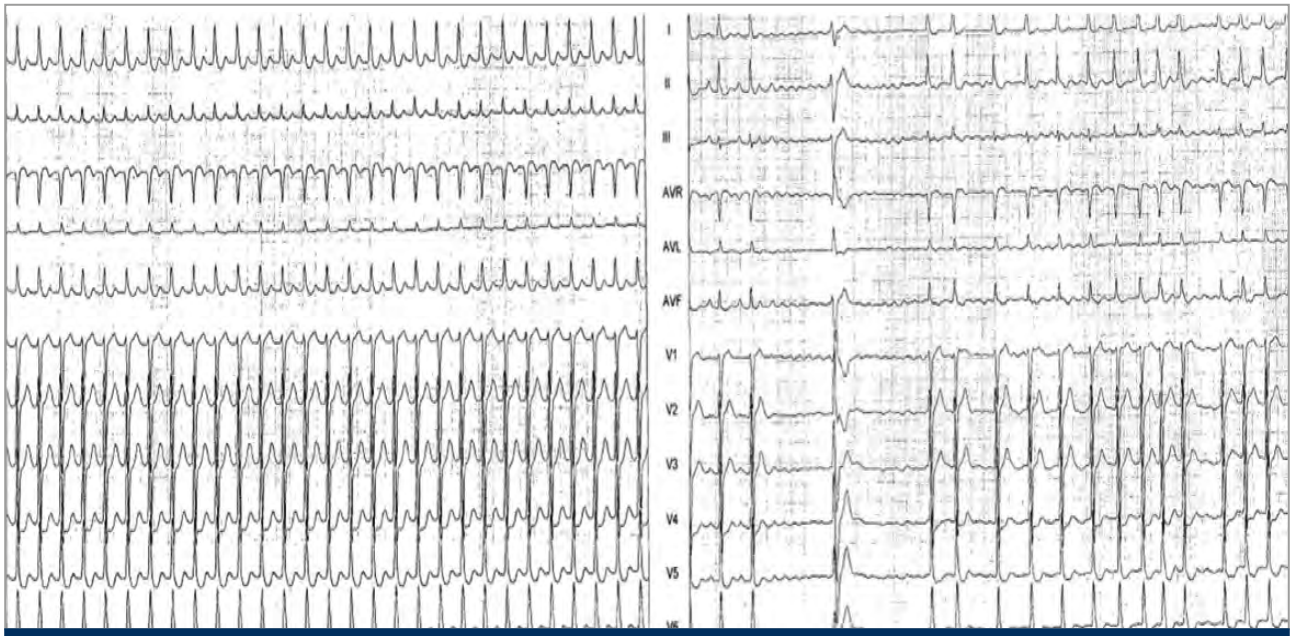

FIGURE 1: On the left side ECG shows narrowing complex short RP tachycardia on the left side which frequently degenerates into atrial fibrillation on adenosine administration as seen on the right side ECG.

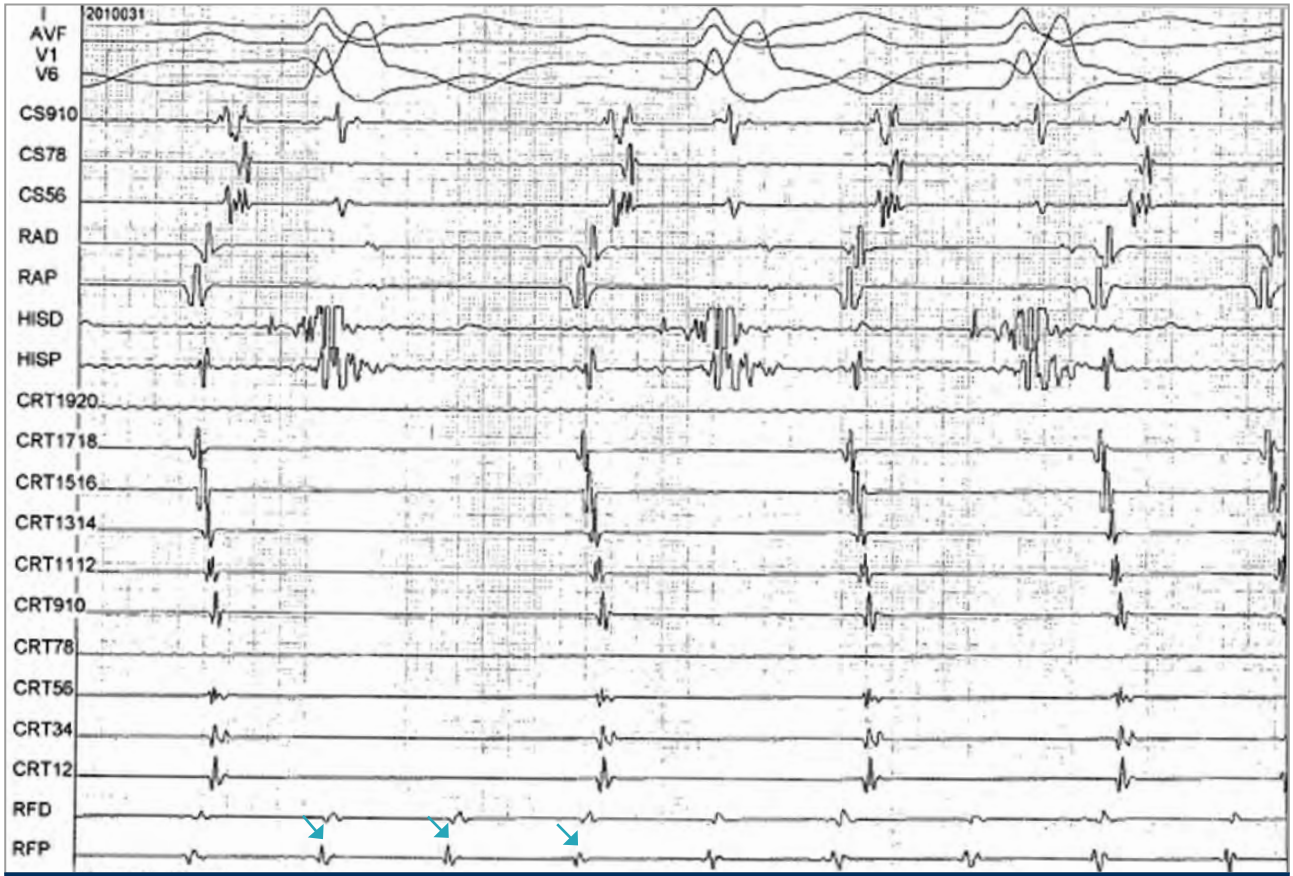

FIGURE 2: Shows superior to inferior activation of the lateral RA and bidirectional activation wavefront in coronary sinus with ablation catheter in SVC showing continuous firing of SVC (blue arrows) with variable conduction into RA and LA. Also, note the "A" signal on the His channel (HisD and HisP) was earlier than the "A" signal on the proximal coronary sinus (CS910) suggesting against typical Cavo-tricuspid dependent flutter.

then terminated to demonstrate sinus tachycardia-like P waves. Repeatedly the rhythm abruptly accelerated to AF before switching back to 1:1, 2:1 or variable A-V node conduction with AT / AFL pattern on ECG, however, the intracardiac EGMs during the AF and AT were consistently showing organised and regular firing from the SVC indicating a focal mechanism for the tachycardia during all the different manifestations on ECG described above (Figure 3 & 4). The earliest atrial EGMs were evident in the high RA (RA proximal) and the Dua-Decapolar catheter was exchanged for a Crista 2-2-2 spacing catheter and a superior to inferior activation pattern was evident straight-away. The ablation catheter was also exchanged for a Biosense Webster 4mm non-irrigated mapping and ablation catheter and was positioned in the SVC. High up in the SVC, rapid regular potentials were evident, present all the time with variable degrees of decrement sequentially, at the SVC-RA junction, and variably, at the A-V node (Figure 3). The beats originating high up from SVC also showed rapid firing with a cycle length of 145 - 170ms with a fairly constant rate and a variable SVC to RA exit block. These potentials were mapped to the postero-lateral SVC and RF energy application was initiated at this site, without termination of the tachycardia. At this stage, a linear RF lesion set was attempted to connect to the SVC-RA junction and the adjoining superior RA. As this lesion set progressed, dissociation was noted between the distal to proximal RF channels and slowing of the CL resulted in termination. No further tachycardia occurred on testing with atrial burst pacing, decrementing up to 200ms CL. The patient developed symptoms of vagus nerve dysfunction in the form of oesophageal and gastric symptoms which subsided gradually over the course of 2 years after the procedure. The patient complained of symptom recurrence after 2 weeks without any documented arrhythmia and he was taken back for EPS which however did not reveal any SVC firing. SVC isolation was attempted due to the recurrence of the symptoms, although no potential could be demonstrated in SVC (no demonstration of SVC isolation possible). At his last visit the patient had been free of symptomatic arrhythmia for 12 years.

Case 2:

A 31-year-old male who underwent a successful radiofrequency ablation procedure for a left-sided accessory pathway in a different centre 5 years prior and presented to us with chief complaints of recurrent palpitations and 1 episode of syncope. Each episode of palpitations was sudden in onset and offset, increasing with exertion. The ECG taken immediately after the syncope demonstrated focal AT with no pre-excitation (Figure 5). Exercise stress test (EST) showed bursts of narrow complex tachycardia with a 1:1 A-V relationship. The bursts occurred at about 200bpm and progressed to a sustained tachycardia demonstrating slowing of the tachycardia before termination. The tachycardia P waves were almost identical (in

FIGURE 3: Shows the continuous firing as detected by the ablation catheter (RFD) in the SVC with a decrement in RA. Note the highlighted ECG (blue colour) suggesting an AT with 1:1 AV node conduction. The ECG varied markedly and could be read as AT or AF while the intracardiac EGMs showed persistent firing from SVC.

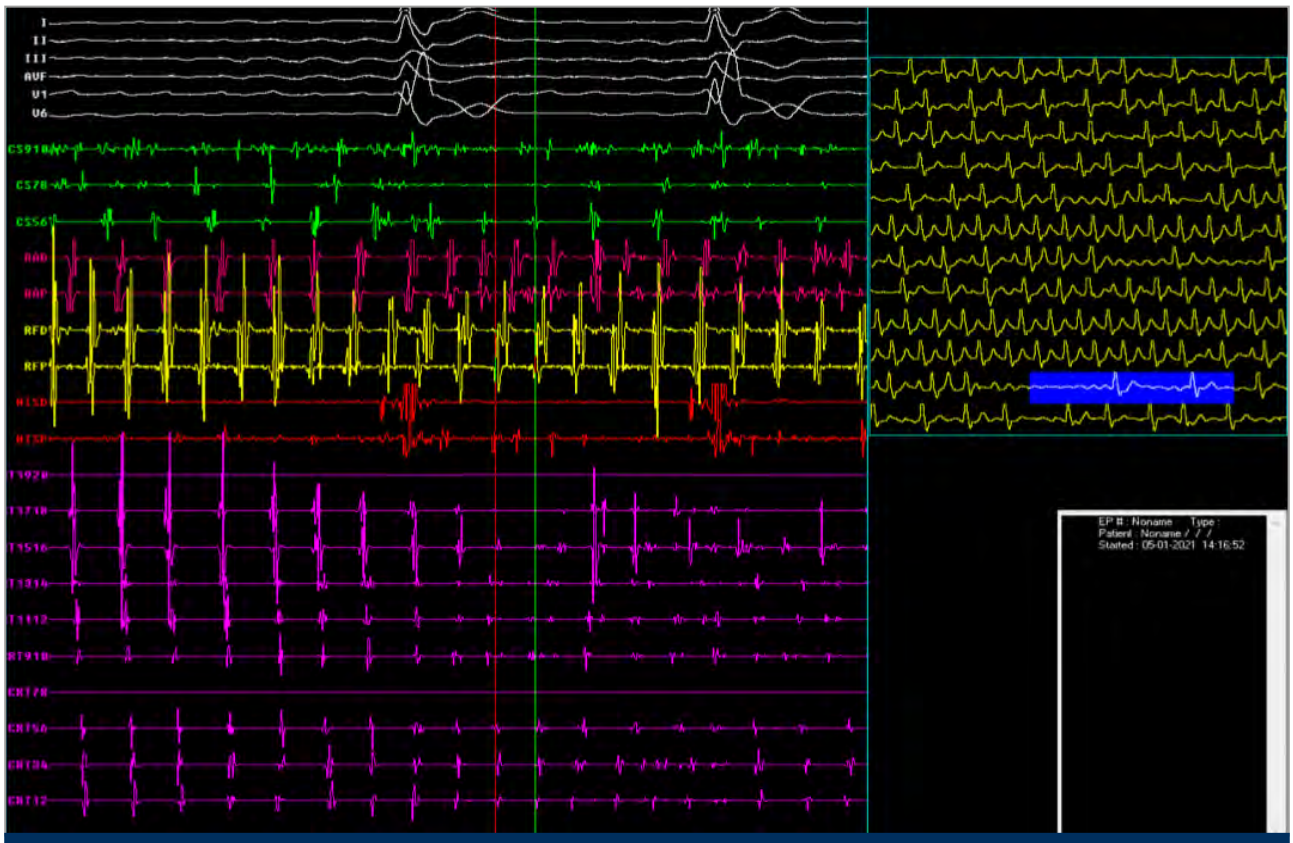

FIGURE 4: The Holter on the right side shows ECG suggestive of atrial fibrillation (see the closest showing highlighted ECG (in blue) and the corresponding EGMs show sharp EGMs (bright yellow colour) arising from SVC (ablation catheter in SVC).

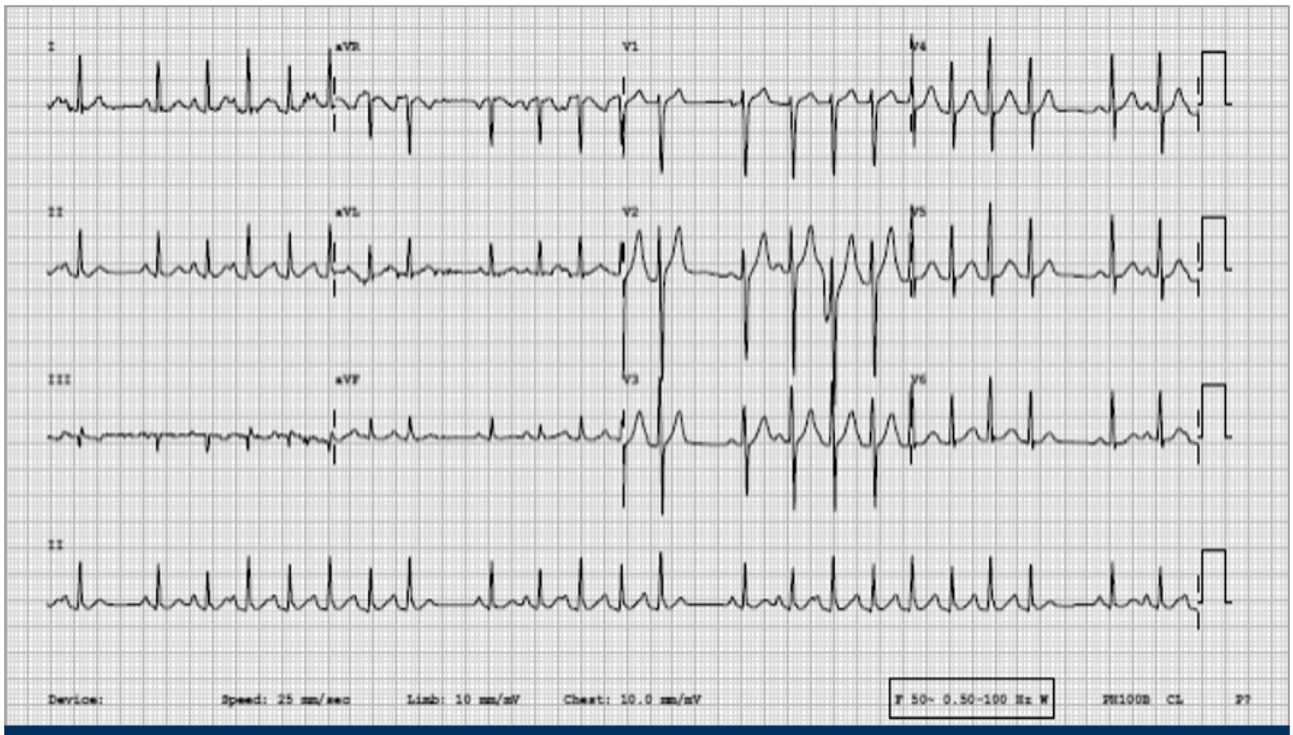

FIGURE 5: Shows bursts of focal AT with P waves positive in limb leads LI and LII, and negative in lead aVR suggestive of origin from the high right atrium.

morphology and axis) to the sinus P waves except that they were slightly larger with a sharper peak in lead II. He underwent EPS and radio-frequency ablation with 3D mapping (St Jude Medical Ensite NavX). At EPS frequent focal atrial premature contractions (APC) in the form of atrial bigeminy occurred with isoproterenol infusion. The earliest atrial activation was in the HRA catheter. Within 2 - 3 minutes of the appearance of APCs, repeatedly, runs of long RP narrow complex tachycardia (variable conduction) were induced with intermittent termination and re-initiation after 2 - 3 sinus beats. Tachycardia could not be entrained, and all the atrial EGMs fell within a narrow window suggesting a focal AT with the earliest atrial activation mapped to the postero-medial aspect of SVC, 1 - 2cm superior to the SVC- RA junction. This was 100ms earlier compared to the proximal CS reference EGM (CS 9-10), but just 40ms earlier compared to the right upper PV. The tachycardia terminated spontaneously and was no longer inducible, hence the early site in the SVC obtained from the activation map on the 3D mapping system was used for successful RFA lesion delivery (Figure 6) on the same day. Exercise stress testing 2 days after did not show any tachycardia and there was no recurrence on follow-up after 5 years.

Case 3:

A 46-year-old female presented with a history of recurrent episodic palpitations associated with pre-syncope for one year. Her ECG and trans-thoracic echocardiogram were normal and the Holter study showed multiple runs of very rapid atrial tachycardia with P waves very similar to the sinus morphology. She underwent EPS which revealed fast AT with the origin from SVC with SVC potentials and this was confirmed with a 15 - 25mm variable loop multi-polar Lasso catheter. Pacing from high up in the SVC at a low voltage output captured the RA myocardium indicating the connection of the SVC muscle sleeves with the RA (Figure 7). A 3D mapping system (St Jude Ensite NavX) was used for creating RA geometry and activation mapping of frequent APCs which revealed a focal origin in the SVC with the EGMs in SVC preceding P wave by 47ms

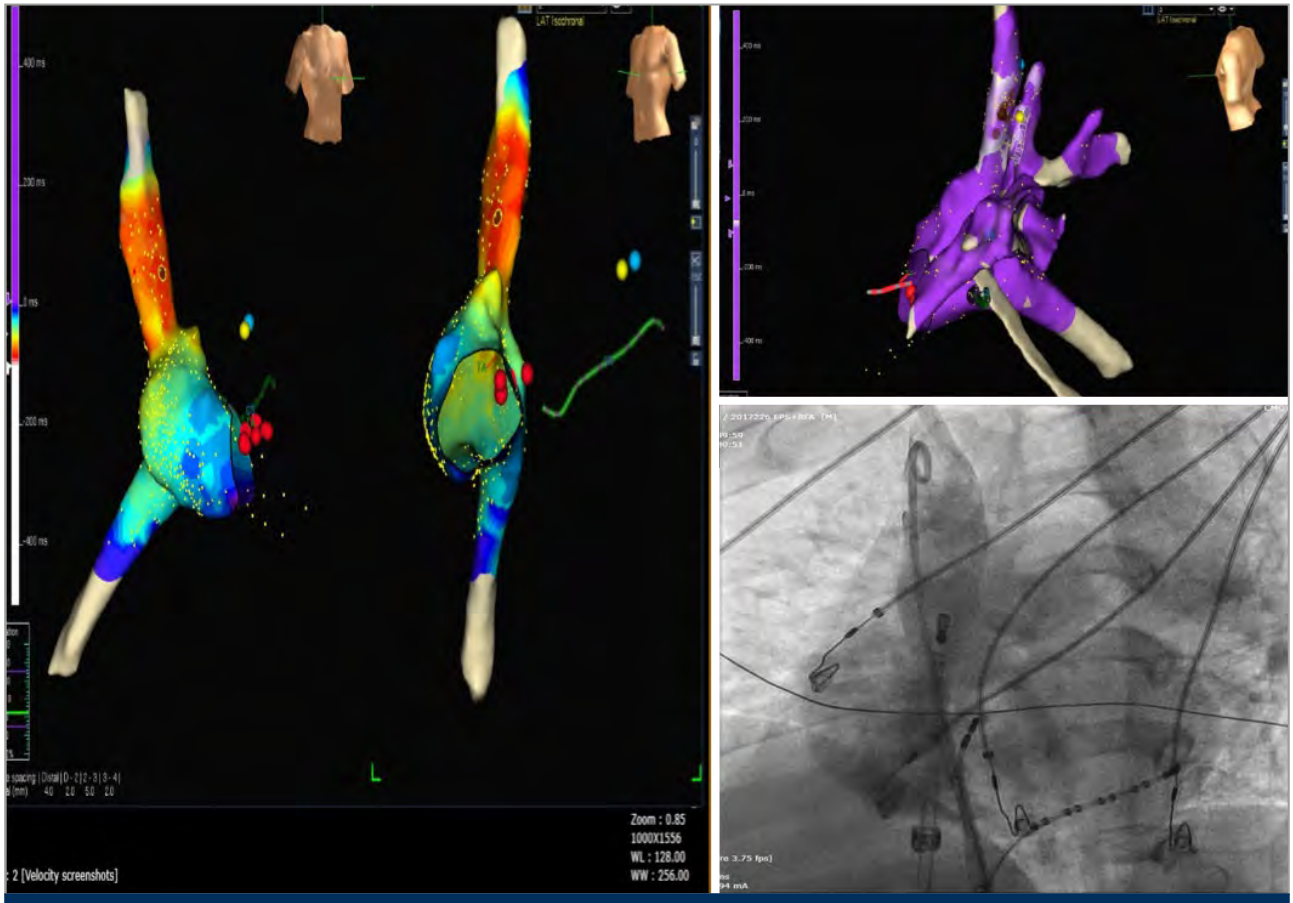

FIGURE 6: Shows on activation mapping the earliest signals were noted in SVC with late activation of the right upper and lower pulmonary veins (left and upper right). SVC EGMs preceded the P wave by 30ms. In the right lower part of the figure, the angiogram shows a pigtail catheter in high up in SVC with an ablation catheter in SVC antrum. Also seen in the Figure are His catheter and Decapolar catheter in the coronary sinus.

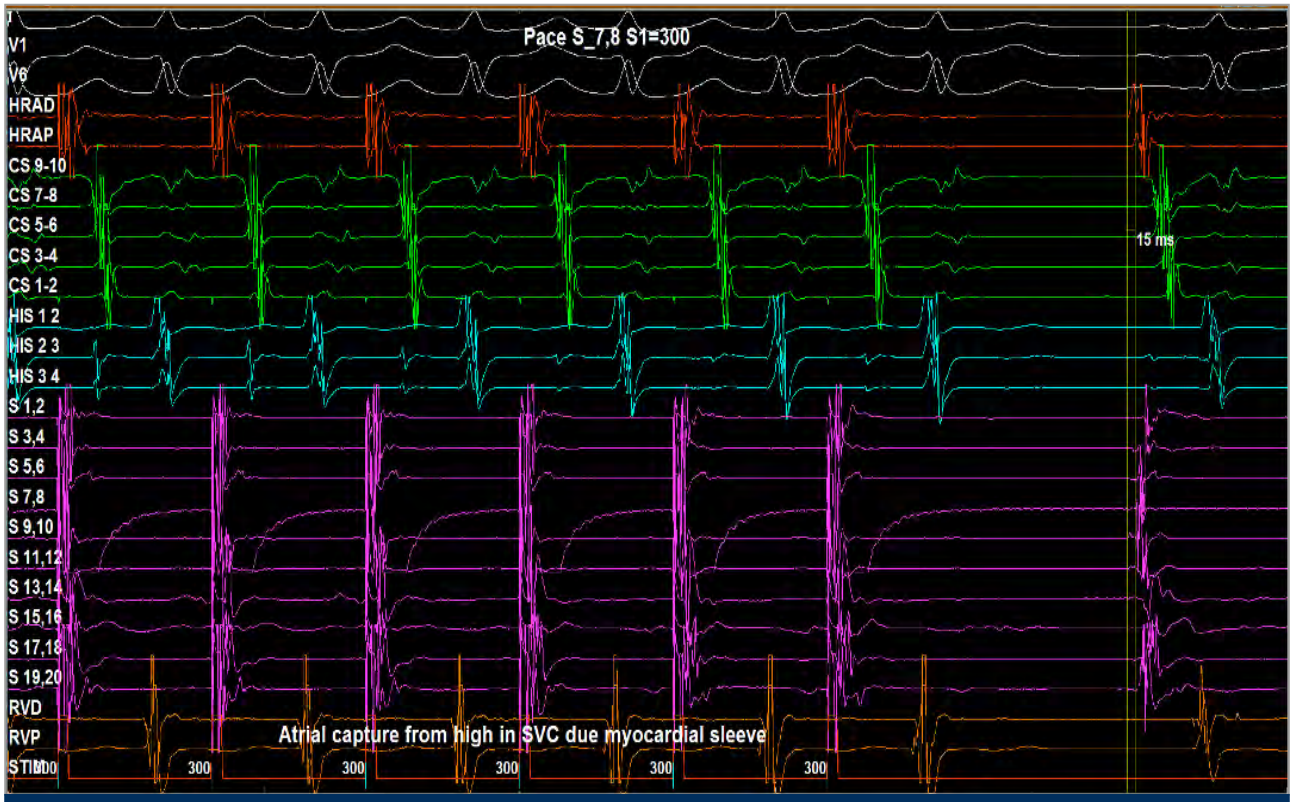

FIGURE 7: Shows atrial capture on pacing at low output from a Lasso catheter placed high up in SVC indicating SVC myocardial capture with connection with RA.

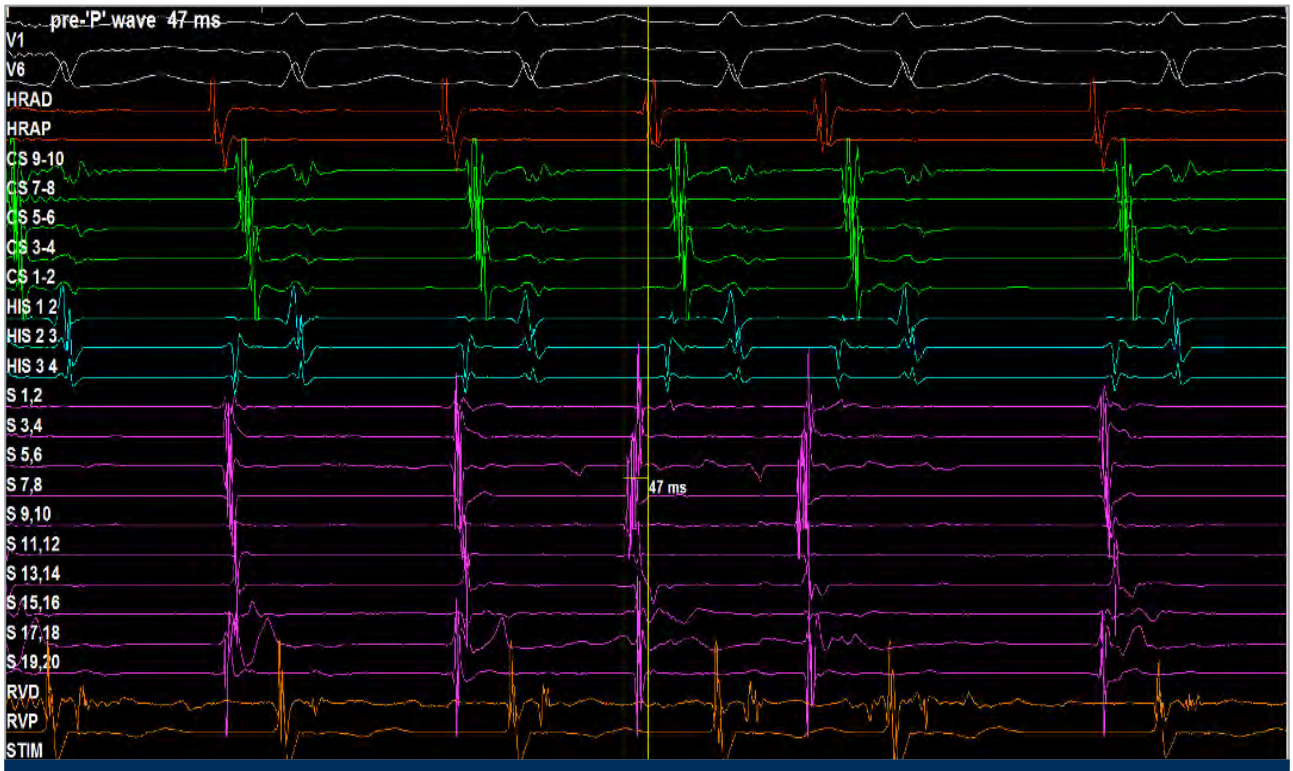

FIGURE 8: Shows activation mapping during APCs with the earliest signal from SVC preceding P wave by about 47ms. Note that the Duo-Decapolar catheter shows activation in the lateral RA.

(Figure 8). SVC tachycardia was spontaneously induced during isoprenaline infusion and the reversal of atrial activation on the St Jude Medical Tacticath Quartz catheter ablation catheter (i.e. proximal to distal in sinus rhythm, distal to proximal during tachycardia) indicating the origin for the respective rhythm. Focal ablation targeting the earliest signal in the postero-superior SVC was not successful. Progressive RF applications proceeding from a superior to the inferior direction for eliminating all potentials guided by the Lasso were attempted with no success. Finally, in the SVC / RA junction, a segmental approach was used, guided by the Lasso catheter channel EGMs and RF applications in the multiple RF applications were required linearly towards the SVC-RA junction anterolaterally for the termination of the tachycardia. After the procedure, the patient developed asymptomatic sinus bradycardia due to inadvertent sinus nodal damage. The patient was asymptomatic on follow-up at 4 years with a peak exercise heart rate of 118 beats per minute on the treadmill test

RESULTS

All 3 patients found to have SVC-origin atrial tachycardia in our series had successful ablation of SVC-origin tachycardia. One of these patients presented with paroxysmal AF and atrial tachycardia at other times and the AF was proven to have a trigger from SVC and the other 2 patients presented with focal atrial tachycardia. During follow-up no patient had recurrent symptoms after SVC ablation. One of the patients in our series developed gastroparetic symptoms which resolved gradually over 2 years, quite likely due to reversible right Vagal nerve damage and another patient developed asymptomatic Sinus Node dysfunction. Our study shows the curative ablation of paroxysmal AF initiated by SVC ectopy. For focal AT with P wave morphology like the sinus P wave and the importance of SVC mapping as well as the long-term success of ablation in SVC alone was also demonstrated. The possibility of damage to the adjacent structures like the phrenic nerve, sinus node and vagal inputs to the oesophagus are potential complications while ablating in SVC.

DISCUSSION

The incidence of tachycardia of SVC origin has been reported variedly and in 1 series SVC induced AF has been reported as 5% in patients with paroxysmal AF by Miyazaki, et al.[4] The mechanism of AF originating from the SVC is thought to be similar to typical PV-related muscle sleeve firing triggered AF. Pulmonary veins are the commonest triggers of AF and the isolation of pulmonary veins is well established in the treatment of AF.[3,5] The role of SVC triggers have not been studied as well as those of the pulmonary veins. However, it has been reported in some cases by various authors.[6] Interestingly in our series of 3 patients, 2 patients presented with focal AT and 1 patient presented with paroxysmal AFL / AF which was proved to be triggered by SVC ectopy. The SVC ectopy was very rapid, conducting with variable decrement into the RA and at times it induced AF. During AF, the fast regular and organised activity in SVC was characteristic of triggered AF. In 1 of our patients, a long muscle sleeve was demonstrated, and the atrium could be captured from this relatively remote site from the atrium. Interestingly the superior extent of such muscle sleeves could be quite long, as demonstrated in our patients. Tsai, et al.[7] reported SVC muscle sleeve extensions of 33 ± 7mm above the SCV-RA junction.

SVC ectopy may present clinically as AT / AFL or AF. The fast ectopy usually conducts very rapidly in the atrium and the patient may present with paroxysmal AF due to fibrillatory conduction in the atria. Hence a high clinical suspicion of SVC ectopy is pivotal in such cases so that appropriate ablation strategies can be formulated in the management of paroxysmal AF rather than a conventional pulmonary vein isolation.[7] In our series, finding a P wave morphology similar to the sinus rhythm P wave morphology was a useful clue to SCV ectopy while there was variable ECG presentation of the arrhythmia as was seen in our first case. When Atrial activation progresses in a supero-inferior direction in the Atria, looking for the most superior extent of origin is necessary, followed up with ruling out activation potentials in the SVC using catheters such as the variable loop Lasso catheters. For mapping these SVC potentials, the direction of the activation on the EGM's obtained from any straight EP catheter in the SVC during the tachycardia, looking for a distal to proximal activation, with the catheter placed deep in the SVC and gradually withdrawn into the RA will be helpful as well. A deflectable multi-polar EP catheter may also help ensure better contact with the SVC. Just rotating it completely round at the same level while maintaining gentle flexion to ensure contact gives an estimate of the possible location of the muscle sleeve extension. Further, if left-atrial mapping in the right-sided PVs, especially the right inferior PV is pivotal to rule out earlier activation from those sites, in which case achieving PV Isolation would be the ablation strategy. Once SVC triggers are identified as the triggers of AT / AFL / AF, one could use either a focal, a segmental or a complete SVC-RA junction Isolation approach depending on the extent of clear SVC potentials. Thick or wide muscle sleeves would require more RF energy applications. Usually, there is a single breakthrough site from SVC into RA and a focal ablation may be undertaken.[8] SVC Isolation will be required if multiple or

wide sleeves are considered possible and during total isolation or a wide segmental approach (guided by potentials recorded using a Lasso catheter or similar such catheters, to avoid a complete encircling lesion set in the SVC-RA junction) potential damage to the SA node and the phrenic nerve in the immediate vicinity should be considered. Damage to the right vagus nerve is also a potential complication and at present there is no specific easy-to-use technology available for locating the right vagus nerve (which lies posteromedial to the SVC). The phrenic nerve (which lies in the lateral aspect of the SVC) however is easily located by pacing close to it in the SVC.[4] One of our patients developed vagal nerve damage symptoms that improved gradually over 2 years.

CONCLUSION

SVC-triggered AT / AFL / AF is a well-known entity and a high clinical suspicion is required to diagnose it. SVC ablation is safe and effective, however, the risk to the sino-atrial node, phrenic nerve and right vagus nerve needs to be borne in mind. The monitoring of phrenic nerve function and sinus nodal function in the form of sinus rhythm cycle length during RF application would help reduce the complications.

CLINICAL IMPLICATIONS

While dealing with focal AT / AFL or AF, SVC ectopy triggers should be considered and ruled out in the appropriate setting. Ablation in SVC alone could suffice in such situations saving the patient the risks of more complex procedures.

Conflict of interest: none declared.

REFERENCES

1. Katritsis D, Loannidis JP, Anagnostopoulos CE, et al. Identification and catheter ablation of extracardiac and intracardiac components of ligament of marshall tissue for treatment of paroxysmal atrial fibrillation - Journal of Cardiovascular Electrophysiology - Wiley Online Library. https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1540-8167.2001.00750.x
2. Liu H, Lim KT, Murray C, Weerasooriya R. Electrogram-guided isolation of the left superior vena cava for treatment of atrial fibrillation. EP Eur. 2007;9(9):775-780. DOI:10.1093/europace/eum118.
3. Lin WS, Tai CT, Hsieh MH, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non–pulmonary vein ectopy. Circulation. 2003;107(25):3176-3183. DOI:10.1161/01.CIR.0000074206.52056.2D.
4. Miyazaki S, Taniguchi H, Kusa S, et al. Factors predicting an arrhythmogenic superior vena cava in atrial fibrillation ablation: Insight into the mechanism. Heart Rhythm. 2014;11(9):1560-1566. DOI:10.1016/j.hrthm.2014.06.016.
5. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659-666. DOI:10.1056/NEJM199809033391003.
6. Higuchi K, Yamauchi Y, Hirao K, et al. Superior vena cava as initiator of atrial fibrillation: Factors related to its arrhythmogenicity. Heart Rhythm. 2010;7(9):1186-1191. DOI:10.1016/j.hrthm.2010.05.017.
7. Tsai CF, Tai CT, Hsieh MH, et al. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava. Circulation. 2000;102(1):67-74. DOI:10.1161/01.CIR.102.1.67.
8. Goya M, Ouyang F, Ernst S, Volkmer M, Antz M, Kuck KH. Electroanatomic mapping and catheter ablation of breakthroughs from the right atrium to the superior vena cava in patients with atrial fibrillation. Circulation. 2002;106(11):1317-1320. DOI:10.1161/01.CIR.0000033115.92612.F4.

The incidence of head and neck cancer in interventional cardiologists

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ABSTRACT

The occupational risk to interventional cardiologists related to using X-rays in the catheterisation laboratory (cath lab) includes a range of radiation-induced effects. The primary concern is the possibility of developing head and neck malignancies. A literature review of reports on developing head and neck malignancies among interventional cardiologists was conducted. Several individual cases of head and neck malignancies have been reported, predominantly on the left side. However, these studies do not have a sufficient sample size to generalise the results. Based on the available reports, it is concluded that head and neck malignancies are unlikely to constitute an occupational risk for interventional cardiologists. More research is required to establish whether head and neck malignancies are more prevalent among interventional cardiologists.

SA Heart® 2024;21:66-69

INTRODUCTION

It is well known that ionising radiation, such as X-rays, is used as a noninvasive modality to diagnose various diseases, including cancer. However, ionising radiation for interventional procedures has become increasingly popular in recent decades due to its minimal invasiveness. As therapeutic techniques advance, interventional cardiologists utilise catheter-based diagnostics and treatments more frequently using fluoroscopy, a real-time X-ray imaging modality, resulting in an exponential increase in their exposure to radiation,[1] predominantly to the head and neck regions not protected by lead aprons or leaded glasses.[1-4]

The growing concern over radiation-induced diseases among physicians performing interventional procedures, especially in interventional cardiology, highlights the need for stringent protective measures.[5,6] Experienced interventional cardiologists working in high-volume catheterisation laboratories close to the X-ray source have some of the highest occupational exposure rates to ionising radiation, with an annual exposure equivalent to 200 - 250 chest X-rays.[7] As the field advances with longer and more complex procedures, addressing both deterministic and stochastic effects becomes pivotal, acknowledging the need for advancements in safety protocols and technologies to minimise the potential risks associated with the increased duration of exposure.[8]

Radiation has both stochastic and deterministic effects. The stochastic effects of radiation suggest that cancer is indeed a random side-effect of radiation exposure, which can occur at any level of exposure. The deterministic effect of radiation exposure implies that a side-effect can be anticipated after exceeding a threshold dose. Reports have indicated an asymmetrical risk of brain tumours on the left side, possibly due to higher radiation exposure, underscoring the importance of awareness and taking appropriate precautions.[8,9] This review analyses studies concerning the occupational exposure of interventional cardiologists to X-rays and evaluates the effects of radiation on head and neck tumours associated with these exposures.

METHODS

The diverse sampling techniques described in the literature highlight the comprehensive approach to data collection for tumour induction research.[10] Methods included slit camera examinations, retrospective estimation of cumulative eye lens doses, interviews, medical record analysis, family input, and tele-

phone surveys. Additionally, some studies incorporated clinical eye examinations, dose rate testing, and blood sample analysis to assess the long-term effects of low-dose radiation exposure.[11-13]

A literature search was conducted. Articles were collected using the EBSCOhost network, which included Academic Search, Africa-wide, Scopus, and Medline databases, as shown in Figure 1. Keywords used were "cancer risk", "radiation effects", "brain tumours", "radiation exposure", "cath lab", "occupational dose", and "interventional cardiology", and their synonyms. Articles published from 2010 - 2023 and selected based on their title and abstracts were included for review. Selected articles had to contain information about interventional cardiologists performing interventional procedures and their occupational dose, radiation effects, or cancer development. The information analysed included the sample size and the location of effects. Articles that did not mention head and neck cancers, interventional cardiologists, or a catheterisation laboratory and did not perform original research were excluded. The resulting helpful articles are shown in Table I.

RESULTS

Several cases of radiation-induced head and neck malignancies among interventional cardiologists have been reported in the literature, as shown in Table I. In the Italian study by Andreassi, et al., data collection took place during the Annual Scientific meetings of the Italian Society of Interventional Cardiologists in 2011 and 2012, where a structured questionnaire was completed by participants.[14] The study revealed a median lifetime dose of 21 mSv (quartile: 12-71 mSv); however, it is unknown whether it was a whole-body- or head dose; therefore, the assumption was made that it was a whole-body dose. The median working time was 10 years.

The research study by Roguin, et al.[15] provided a list of several of these cases. The types of tumours identified were mainly glioblastoma multiforme, which accounted for 78% of all tumours and occurred on the left-hand side 74% of the time. The other interesting fact of the study was the average working years of 20 and distribution over North America, the Middle East and Europe.

The multi-centre study in Pakistan reported a 2% prevalence of head and neck malignancy in a sample of 50 interventional cardiologists who had worked for more than 10 years.[16] The side involved in the identified head and neck tumour was not specified. The doses recorded by personal radiation monitoring devices (PRMD) were not mentioned as part of the data collection.

DISCUSSION

Most reported cases were left-sided, the side closest to the X-ray source. The development of cataracts is also considered a potential risk in catheterisation laboratories as the eyes are susceptible to ionising radiation.[10,17,18] Cases of multiple left-sided cutaneous malignancies have also been reported.[10,19]

Due to the small sample sizes in the reported studies, there is no conclusive evidence that occupational exposure in catheterisation laboratories causes the appearance of head and neck malignancies.[20] References to cases without conducting a new study further limit establishing direct correlation.[21] Acknowledging these constraints, there is a need to evaluate larger cohorts of subjects.

Case-control design and case studies in small populations[19] limit the precision and generalisability of findings. Broad confidence intervals contribute to the uncertainty.[6] Inadequate sample sizes and outdated data may affect the relevance of the findings in a contemporary setting.[22] It is crucial to address

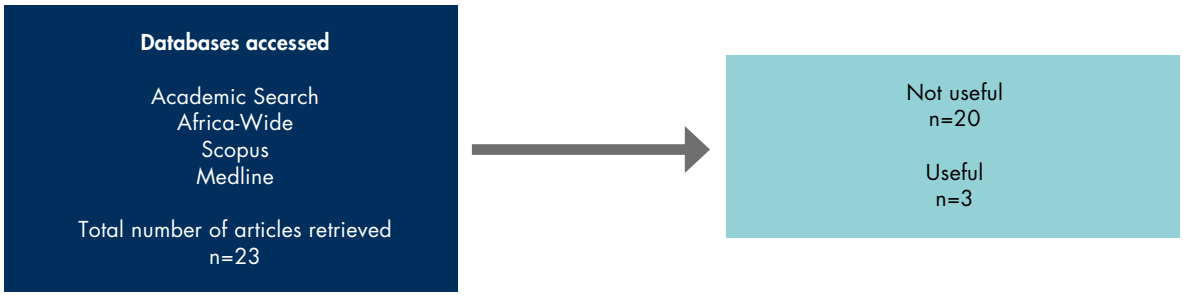

FIGURE 1: Databases accessed and the number of articles retrieved and included for review.

TABLE I: Summary of articles with the study type, sample size and findings on head and neck effects due to radiation to interventional cardiologists.

Authors	Country / Region	Study type	Population used	Sample size	Findings
Andreassi, et al.[14]	Italy	Structured self-administered questionnaire	Interventionalists	45	Tumours occurred in 5. Tumours identified: 2 basal cell carcinomas, 1 melanoma, 1 seminoma, 1 prostate adenocarcinoma. Side involved: 2 left-sided and 3 unspecified.
Roguin[15]	Europe & North America	Reports	Interventionalists	23	Tumours occurred in 23. Tumours identified: 13 GBM, 3 meningiomas, 2 parotids, 2 astrocytoma, 1 neck lymphoma 1 tonsillar tumour. Side involved: 18 were left-side, 1 midline, 2 right-sided and 2 unspecified.
Tariq, et al.[16]	Pakistan	Interviews	Interventionalists	50	Tumours occurred in 1. Tumours identified: 1 head and neck neoplasms. Side involved: Not specified.

GBM: glioblastoma multiforme.

these limitations in future studies to accurately determine the validity and applicability of their findings in the context of evolving radiation protection practices. The studies quoted (Table I) either did not require or did not report dosimeter-measured occupational radiation doses to the heads of interventional cardiologists. Knowing the distribution of the radiation dose an individual had received when a head or neck tumour is discovered may indicate the dose threshold for the induction of neoplastic changes.

Understanding the dual nature of cellular changes due to low-dose radiation is essential.[21] While some modifications may be advantageous, the associated risks, such as increased DNA damage and oxidative stress, highlight potentially harmful consequences. Given these uncertainties, acknowledging limitations in research becomes crucial for a comprehensive assessment of the long-term implications and to guide further studies in this complex field.[21]

Various aspects of radiation exposure in interventional cardiology have been highlighted, addressing factors such as occupational conditions, protective measures like lead-free caps, variations in operator doses, and the impact of ClarityIQ (low-dose high-quality imaging) technology on reducing radiation exposure. Additionally, the studies emphasised the importance of minimising radiation risks through techniques such as reducing fluoroscopy time, using radiation reduction technology, and optimising imaging-chain geometry.[4,11]

CONCLUSION

Head and neck malignancies are uncommon among interventional cardiologists. The small sample sizes and the limited number of reports available do not allow an accurate risk assessment. Further studies are needed to clarify the incidence. This review article highlights the importance of sufficient radiation protection knowledge and implementation by interventional cardiologists. In addition, improved radiation protection training and awareness may have significant long-term benefits.

ACKNOWLEDGEMENTS

We thank Ms A.M. Mophoso (Library and Information Services) and Dr Daleen Struwig (Medical editor) of the University of the Free State for their assistance with journal articles and manuscript editing, respectively.

Conflict of interest: none declared.

REFERENCES

1. Biso SMR, Vidovich MI. Radiation protection in the cardiac catheterisation laboratory. J. Thorac. Dis. 2020;12:1648-1655.
2. Anselmino M, Marcantonib L, Agrestac A, et al. Interventional cardiology and X-ray exposure of the head: Overview of clinical evidence and practical implications. J. Cardiovasc. Med. 2022;23:353.
3. Bärenfänger F, Walbersloh J, El Mouden R, Goerg F, Block A, Rohde S. Clinical evaluation of a novel head protection system for interventional radiologists. Eur. J. Radiol. 2022;147:110-114.
4. Faroux L. Blanpain T, Nazeyrollas P, et al. Effect of modern dose-reduction technology on the exposure of interventional cardiologists to radiation in the catheterisation laboratory. JACC Cardiovasc. Interv. 2018;11:222-223.
5. Ciraj-Bjelac O, Rehani MM, Sim KH, Liew HB, Vano E, Kleiman NJ. Risk for radiation-induced cataract for staff in interventional cardiology: Is there reason for concern? Catheter. Cardiovasc. Interv. Off. J. Soc. Card. Angiogr. Interv. 2010;76:826-834.
6. Finkelstein MM. Is brain cancer an occupational disease of cardiologists? Can. J. Cardiol. 1998;14:1385-1388.
7. Russo GL, Picano E. The effects of radiation exposure on interventional cardiologists. Eur. Heart J. 2012;33:423-424.
8. Reeves RR, Ang L, Bahadorani J, et al. Invasive cardiologists are exposed to greater left-sided cranial radiation: The BRAIN Study (Brain radiation exposure and attenuation during invasive cardiology procedures). JACC Cardiovasc. Interv. 2015;8:1197-1206.
9. Vaño E, Gonzalez L, Fernandez JM, Alfonso F, Macaya C. Occupational radiation doses in interventional cardiology: A 15-year follow-up. Br. J. Radiol. 2006;79:383-388.
10. Purohit E, Karimipour D, Madder RD. Multiple cutaneous cancers in an interventional cardiologist: Predominance in unprotected skin nearest the radiation source. Cardiovasc. Revascularisation Med. Mol. Interv. 2021;28S: 206-207.
11. Grabowicz W, Masiarek K, Górnik T, et al. The effect of lead-free cap on the doses of ionising radiation to the head of interventional cardiologists working in haemodynamic room. Int. J. Occup. Med. Environ. Health 2022;35: 549-560.
12. Mayr NP, Wiesner G, Kretschmer A, et al. Assessing the level of radiation experienced by anesthesiologists during transfemoral transcatheter aortic valve implantation and protection by a lead cap. PLOS ONE 2019; 14:e0210872.
13. Steelman, C. Unique occupational health risks in cardiac catheterisation laboratory workers. J. Med. Imaging Radiat. Sci. 2022;53:S7.
14. Andreassi MG, Piccaluga E, Guagliumi G, Del Greco M, Gaita F, Picano E. Occupational health risks in cardiac catheterisation laboratory workers. Circ. Cardiovasc. Interv. 2016;9:e003273.
15. Roguin A, Goldstein J, Bar O, Goldstein JA. Brain and neck tumours among physicians performing interventional procedures. Am. J. Cardiol. 2013;111: 1368-1372.
16. Tariq MN, Samore NA, Rashid MH, et al. Prevalence of brain and neck neoplasms among interventional cardiologists: A multicentre study. Pak. Armed Forces Med. J. 2022;72:S467-71.
17. Picano E, Vano E, Domenici L, Bottai M, Thierry-Chef I. Cancer and non-cancer brain and eye effects of chronic low-dose ionising radiation exposure. BMC Cancer. 2012;12:157.
18. Richardson RB, Ainsbury EA, Prescott CR, Lovicu FJ. Etiology of posterior subcapsular cataracts based on a review of risk factors including aging, diabetes, and ionising radiation. Int. J. Radiat. Biol. 2020;96:1339-1361.
19. Eagan JT, Jones CT, Roubin GS. Interventional cardiologists: Beware and be aware: An updated report of radiation-induced cutaneous cancers. Catheter. Cardiovasc. Interv. Off. J. Soc. Card. Angiogr. Interv. 2018;91:475-477.
20. NRC (National Research Council). Health risks from exposure to low levels of ionising radiation: BEIR VII Phase 2. National Academies Press, Washington, D.C., Occupational Radiation Studies. 2006;189-206. DOI:10.17226/11340.
21. Lin MJ, Chen CY, Lin HD, Wu HP. Impact of diabetes and hypertension on cardiovascular outcomes in patients with coronary artery disease receiving percutaneous coronary intervention. BMC Cardiovasc. Disord. 2017;17:12.
22. Ainsbury EA, Barnard S, Bright S, et al. Ionising radiation induced cataracts: Recent biological and mechanistic developments and perspectives for future research. Mutat. Res. Rev. Mutat. Res. 2016;770:238-261.

SA HEART® IS AN OFFICIAL JOURNAL OF THE SOUTH AFRICAN HEART ASSOCIATION AND APPEARS ON A QUARTERLY BASIS

Instructions for authors

SA Heart® publishes peer reviewed articles dealing with cardiovascular disease, including original research, topical reviews, state-of-the-art papers and viewpoints. Regular features include an ECG quiz, image in cardiology and local guidelines. Case reports are considered for publication only if the case or cases are truly unique, incorporates a relevant review of the literature and makes a contribution to improved future patient management.

Publication policy

Articles must be the original, unpublished work of the stated authors. Written permission from the author or copyright holder must be submitted with previously published material including text, figures or tables. Articles under consideration elsewhere or previously published (except as abstracts not exceeding 400 words) may not be submitted for publication in SA Heart®. On acceptance transfer of copyright to the South African Heart Association will be required. No material published in SA Heart® may be reproduced without written permission. Permission may be sought from the Editor (Email: ntobeko.ntusi@uct.ac.za).

Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects) and the South African MRC ethics guidelines (https://www.samrc.ac.za/research/ethics/guideline-documents). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
5. All articles are to be in English.
6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial.[13]

The following format should be used for references:

Articles
Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. Clin Orthop 1993;294:73-8. (If there are more than six authors, list only the first three followed by et al.).

Chapter in a book
Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. Philadelphia: JB Lippincott; 1991:377-94.

Online media
Perreault, L. (2019). Obesity in adults: Role of physical activity and exercise. UpToDate. Retrieved January 12, 2020, from https://www.uptodate.com/contents/obesity-in-adults-role-of-physical-activity-and-exercise

9. Articles are to be submitted on the online SA Heart® platform https://tinyurl.com/y9prlopt. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.
10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.
12. Include 3 challenging questions on the content of the manuscript relating to the key messages. The questions will be included in a questionnaire for CPD accreditation purposes. Please supply each question with a choice of 4 - 5 possible answers of which only one is correct (multiple correct answers not allowed) and highlight the correct answer. Please do not supply questions with a simple yes/no option.

Submission of manuscripts

The manuscript should be submitted online on the SA Heart® Journal open access platform https://tinyurl.com/y9prlopt. Follow further instructions on this website.

SA HEART®
Newsletter of the
South African Heart Association

2024
Volume 21
Number 1

LETTER FROM THE PRESIDENT

SA HEART®: BEATING STRONG FOR SOUTH AFRICA'S CARDIOVASCULAR HEALTH

The South African Heart Association (SA Heart®) stands as a vital pillar in our nation's healthcare landscape. Our not-for-profit organisation, driven by a dedicated team and a resolute mission, serves as the powerful voice of cardiovascular care in South Africa. SA Heart®'s commitment extends far beyond advocacy – it fosters collaboration, propels research, and strives to ensure exceptional care for all South Africans, from the tiniest hearts to the most seasoned.

The strength of SA Heart® lies in its comprehensive structure. An impressive Board of directors sets the strategic course, while the executive committee translates vision into action. Special interest groups, catering to specific areas of cardiovascular medicine, allow for focused expertise. Regional branches ensure a nationwide reach, bringing SA Heart®'s resources and guidance to every corner of the country. Underpinning this impressive framework is a dedicated team. The general manager steers the organisation's day-to-day operations, while the stakeholder manager cultivates vital relationships with healthcare professionals, policymakers and the public.

Presently SA Heart® stands at a crossroad. As the leading voice for cardiovascular care in South Africa, we hold immense power to improve the health of our nation. But the road ahead is not without its challenges.

Firstly, we must solidify SA Heart®'s brand as a unified, coherent force. This means ensuring that our diverse membership – adult and paediatric cardiologists, researchers, and allied health professionals – operates under a single banner. Unity of purpose will amplify our impact and project a clearer image of unwavering support for our members.

Secondly, we need to address the growing pressure from private health funders. We cannot stand idly by when funders attempt to restrict clinical autonomy and limit diagnostic and therapeutic options for our patients. SA Heart® will be a relentless advocate for both patient well-being and the best practices within cardiovascular medicine.

Prof Eric Klug.

The looming implementation of National Health Insurance (NHI) presents an additional hurdle. While it is admirable to strive for universal healthcare, building it on a fragile public healthcare system with strained finances creates a worrying scenario.

Engaging the next generation of cardiovascular professionals is crucial. We actively encourage younger members to volunteer and participate in SA Heart®'s structures. Their fresh perspectives and enthusiasm are vital to the future of our organisation.

By fostering a patient advisory group, we create a vital communication channel that benefits patients, practitioners, and the entire healthcare landscape. This is a major priority for SA Heart® in 2024. Advocacy efforts will hopefully work to influence policy decisions that prioritise cardiovascular health and improve access to quality care for all. SA Heart® intends to be a proactive voice in the process.

Continued on page 72

LETTER FROM THE PRESIDENT continued

A pivotal tool in our mission is the SA Heart® Journal. However, its viability rests on finding a dedicated editor, securing financial resources, and streamlining administration. This may be the final edition of the Journal, but we cannot afford to lose this valuable platform for knowledge sharing and advancement in cardiac care.

By presenting a unified front, attracting young talent, and securing the future of the SA Heart® Journal, we can overcome obstacles and emerge stronger. SA Heart® is not just an organisation; it is a testament to unwavering dedication. It is the tireless work of the Board, the executive committee, special interest groups, regional branches, the general manager and the stakeholder manager – united by a common purpose - that ensures that every South African heart beats strong and healthy and that its members are supported, protected and secure in their invaluable professional careers.

SA Heart® needs your support to achieve its aims. A cohesive society is a powerful one. This is the moment for making a concerted effort to promote cardiovascular health in South Africa. Join us, our members, and our dedicated staff in reaching that objective. A heart-healthy South Africa will benefit all of us.

Warm regards

Eric Klug
SA Heart® President

SA HEART® BOARD: CHANGING OF THE GUARD

Following the AGM, there have been several changes in the Board's membership. Prof Blanche Cupido left the Board when her term as President ended in 2022. Dr Martin Mpe, Prof Alfonso Pecoraro, Mr François Mintoor and Mrs Robyn MacMhaoinigh indicated their unavailabilty for another term and Dr Thomas Mabin and Dr Tawanda Butau resigned from the Board for personal reasons.

SA Heart® is deeply indebted to all these individuals who gave freely of their time, expertise and knowledge to bring the Association closer to its vision of developing cardiovascular healthcare for all South Africans, while at the same time protecting members' interests, serving the best interests of the company, complying with governance requirements and managing the funds, contracts and communications responsibly.

The Board was augmented in May by recruiting Dr Tim Pennel (cardiothoracic surgery), Dr Anthony Dalby (cardiologist) and Ms Mandi Fine (marketing). They have joined Prof Eric Klug, current President, to serve during the new Board cycle. Following the SA Heart® AGM the Board also includes Prof Nqoba Tsabedze, Prof Ruan Kruger and 2 independent Board members, Mrs Roanleigh Thambiran (finance) and Mrs Maryna Wiesner (legal).

You can meet the current Board at:
https://www.saheart.org/menu/board_directors

New Board members were inducted on 6 November 2023. New Board Committees and their Chairs were appointed and Dr Dalby was elected Chair of the Board.

Dr Martin Mpe has been appointed president-elect of SA Heart®.

The Board will need strength and insight to steer SA Heart® through the challenges facing cardiovascular care in the country. To achieve its aims the Board will need the backing of volunteers on the Board Committees, the Standing & Project Committees, the Special Interest Groups, the Branches and the members at large who must all contribute to ensuring SA Heart®'s position as the leading professional opinion on South Africa's cardiovascular health.

Tony Dalby
SA Heart® Chair of the Board

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ACC	www.acc.org
ESC	www.escardio.org
World Heart	www.world-heart-federation.org

POPULAR CONGRESSES FOR 2024

CONGRESS	DATE	PLATFORM	HOST
SA HEART® JOURNAL CLUB - hosted by SASCI Check your email for registration code	08 May 2024	Virtual	South Africa
ESC HEART FAILURE CONGRESS https://www.escardio.org/Congresses-Events/Heart-Failure	11 - 14 May 2024	Lisbon	Portugal
EUROPCR https://www.pcronline.com/Courses/EuroPCR	14 - 17 May 2024	Paris	France
SUNECHO COURSE https://consultus.eventsair.com/sunecho-2024	20 - 24 May 2024	Stellenbosch/ Tygerberg	South Africa
SA HEART® JOURNAL CLUB - hosted by Johannesburg Branch Check your email for registration code	05 June 2024	Virtual	South Africa
SA HEART® FELLOW EXAM PREPARATION COURSE By invitation	07 - 09 June 2024	Johannesburg	South Africa
HeFFSA SPECIALIST SYMPOSIUM For information contact info@hefssa.org	07 - 08 June 2024	Sandton	South Africa
CARDIO ALEX https://cardio-alex.com	11 - 14 June 2024	Alexandria	Eygpt
ORIENTAL CONGRESS OF CARDIOLOGY TOGETHER WITH THE WORLD CONGRESS OF CARDIOLOGY https://world-heart-federation.org/world-congress-of-cardiology	27 - 30 June 2024	Shanghai	China
SA HEART® JOURNAL CLUB - hosted by PCSSA Check your email for registration code	03 July 2024	Virtual	South Africa
M & M MEETING By invitation	19 - 20 July 2024	Irene	South Africa
SA HEART® JOURNAL CLUB - hosted by ISCAP Check your email for registration code	07 August 2024	Virtual	South Africa
ESC CONGRESS 2024 https://www.escardio.org/Congresses-Events/ESC-Congress	30 August - 02 September 2024	London	Great Britain
SA HEART® JOURNAL CLUB - hosted by KZN branch Check your email for registration code	04 September 2024	Virtual	South Africa
SA HEART® JOURNAL CLUB - hosted by CASSA Check your email for registration code	02 October 2024	Virtual	South Africa
24TH ANNUAL CONGRESS OF THE SOUTH AFRICAN HEART ASSOCIATION **https://www.saheart.org/congress**	**8 - 10 November 2024**	**Sandton Convention Centre**	**South Africa**

Check SA Heart® online calendar for updates and training events across the country.
https://www.saheart.org/calendar

SA HEART® CONGRESS 2023

As we are preparing for SA Heart® Congress 2024 (see convenor note), we want to hold a short review of Congress 2023 and express our sincerest thanks to all who made it such a huge success:

- Dr Farouk Mamdoo, convenor, who spent many days, nights and weeks putting together a sterling programme, engaging with speakers, funders, committees and congress organiser with vision, patience, and dedication.
- All those who contributed to the programme, as congress committee member, as faculty, presenter and chair, as abstract presenter and judge.
- To our supporting industry who gave generously to make this all happen.
- Event Options, the professional congress organiser with Larna and Sue at the helm and many efficient members of staff, who didn't tire to give their best to put the congress together and ensure smooth running, administration, accounting, and reporting.
- The AV and Tech team supporting the show ensuring smooth broadcast in each venue, and all those working in the background from registration desk to cleaning staff, from ushers to catering contingent and security personnel.
- And the Bokke, who lifted the spirit with their win!
- Last not but not least, all the delegates who attended the congress.

Here are some impressions from the SA Heart® Congress 2023. We are looking forward to welcoming you in Sandton for SA Heart® Congress 2024.

Drs Farouk Mamdoo, Convenor 2022 - 2023 congresses and Ahmed Vachiat, convenor 2024 - 2025 congresses.

SA HEART® BOOTH AT THE SA HEART® CONGRESS IN 2023

During the SA Heart® Congress 2023, SA Heart® had a welcoming booth in the Foyer, inviting delegates to meet Board and Committee members, to sign up to SA Heart®, to engage and discuss. Here are some impressions from the booth, well used by delegates to interact or just rest a bit, and most of all proudly find their name on the member board, hidden in the big Thank You to our members.

Make sure to keep your membership current to find your name on the board this year at SA Heart® Congress 2024. We are looking forward to improved engagement and interaction. You don't have to wait until the congress, comment, discussion and questions are invited throughout the year. Please contact info@saheart.org.

SA HEART® JOURNAL CLUB NEWS

In 2021, SA Heart® proudly launched the National Monthly Journal Club, an online educational platform accredited for Continuing Professional Development (CPD) to enrich our members' learning experience. This monthly event, hosted and presented by our esteemed special interest groups or regional branches in rotation, has quickly become a cornerstone of our educational calendar. We are grateful for the generous support of our industry partners, which has contributed significantly to the success and impact of this initiative.

In October 2023 ISACP hosted the October edition of our Journal Club. We are grateful for the sponsorship provided by Vertice, allowing us to execute the series successfully. We had an array of esteemed Speakers for the night with Ms Rajoo opening, closing and managing the Q & A. Thank you to our colleagues for covering the following topics during the course of the evening; Dr K Moodley (LBB pacing- journal article / case presentation), Dr N Hadebe (Tausig Bing- Case presentation), Dr Bissetty (Cath lab Gremlins and superstitions) and Dr A Horak (Chronic ischaemic heart disease).

The Heart Failure Society of South Africa (HeFSSA) hosted the last edition of 2023, with their current president Prof Tsabedze as the host and Speaker. Thank you to CIPLA for sponsoring the November event. Prof discussed "HFrEF/AF: A Sub-Saharan African Perspective", a topic that our members found interesting and engaging. This was shortly followed by Dr Viljoen's compelling discussion and analysis on the study "Point-of-care NT-proBNP for the screening of PREGnancy-related Heart Failure: the PREG-HF".

Post summer break, the Pretoria branch commenced our 2024 series with an engaging presentation by Dr Shuping Mokgosi, who is currently in the third-year rotation of cardiology sub-specialty at Sefako Makgatho Health Science University / Dr George Mukhari Hospital. Dr Mokgosi covered a variety of topics, including Tachycardia and Atrial Fibrillation-Related Cardiomyopathies: Potential Mechanisms and Current Therapies, https://www.jacc.org/doi/abs/10.1016/j.jchf.2023.11.016. Peripartum Cardiomyopathy, and Mitral Annular Calcification https://www.jacc.org/doi/abs/10.1016/j.jcin.2023.06.044 https://www.jacc.org/doi/epdf/10.1016/j.jacc.2022.06.009. These presentations were well-received, and attendees participated in an interactive Q & A session before concluding the evening.

Wrapping up the first quarter, The Lipid and Atherosclerosis Society of South Africa (LASSA), led by Professor David Marais, presented the March Journal Club in partnership with the EAS Lipid Clinic Network. Professor Dirk Blom commenced the evening by delving into the topic of "Lp(a), an EAS consensus paper." Later, Professor Raal redirected the focus to the local context, discussing the "Applicability of the guidelines to the Black African population."

We extend our heartfelt gratitude to all programme organisers, hosts, and presenters for generously dedicating their time and effort for the benefit of our members. We also want to express our appreciation to the Virtual Options team for their exceptional technical support and to our industry sponsors for their invaluable contributions, which have made these educational endeavours possible. We urge our current members to join us at our next Journal Club which will be hosted by CISSA Imaging on 3 April 2024.

SA Heart® is looking to expand the monthly national journal club, to date a member-only event to non-members against a nominal fee in the near future.

Thobile Ziqubu
SA Heart®'s Stakeholder Relationship Manager

THE ANNUAL 2024 CASSA SYMPOSIUM

CASSA
CARDIAC ARRHYTHMIA SOCIETY OF SOUTHERN AFRICA
A SPECIAL INTEREST GROUP OF SA HEART®

Thank you to all who contributed to the success of the 2024 CASSA Symposium.

Your dedication, expertise, and collaborative spirit made this event an unforgettable triumph.

The Symposium served as a dynamic platform where thought leaders, innovators, and professionals converged for insightful discussions on the latest developments in Cardiac Arrhythmia.

We commend our esteemed speakers for their thought-provoking presentations.

We also thank all who attended - your engagement was pivotal in creating an environment conducive to learning, networking, and collaboration.

Together, we are driving positive change and contributing to the advancement of Cardiac Arrhythmia understanding.

Adèle Greyling
CASSA President

Drs Ruan Louw and Adèle Greyling.

Drs Len Steingo, Mervin Sender and Les Osrin.

SA HEART® CONGRESS 2024

On behalf of the Organising Committee of the SA Heart® Congress, we would like to invite all our colleagues in the Cardiovascular field and those interested to join us for the 24th Annual SA Heart® Congress at the Sandton Convention Centre in Johannesburg from 8 - 10 November 2024.

The theme for this year's Congress is **"Cardiology Connections"** representing Cardiologists, Cardiothoracic Surgeons, General Practitioners and other Subspecialists, Nurses, Technicians, Radiographers, Basic Scientists, and students in South Africa.

This year we intend to **"Connect"** various special interest groups namely the Society of Cardiovascular Interventions (SASCI), Cardiovascular Imaging Society of South Africa (CISSA), Cardiovascular Arrhythmia Society of South Africa (CASSA), Heart Failure Association of South Africa (HEFFSA), Interventional Society of Cathlab Allied Professionals (ISCAP) and the South African Society of Cardiovascular Research (SASCAR) as well as the Paediatric Cardiac Society of South Africa (PCSSA). We intend to have Joint sessions where we can work together to discuss cardiovascular themes to further improve healthcare for people of South Africa. Besides these established interest groups, we look forward to incorporating our cardiacthoracic surgeon colleagues and other subspecialists in an all-encompassing interdisciplinary programme.

We anticipate with excitement a vibrant Local and International Faculty. A Cardiovascular Team from the Mayo Clinic includes Prof Vuyi Nkomo (Imaging Cardiologist), Prof Soron Pislaru (Chair, Structural Heart Disease), Dr Juan Crestanello (Chair, Cardiothoracic Surgery) which will be conducting an Echocardiography workshop alongside other specialist workshops taking place on Friday morning, 8 November. We will be incorporating new innovative ways to learn, share and grow during our workshops and scientific sessions.

Dr Thomas Alexander from India will be enlightening us on creating STEMI (ST elevation networks) in South Africa. Dr Raman Krishna Kumar, also from India, with a diverse clinical and research interest will be joining the International Faculty team for the Paediatric programme. The programme is enhanced with great national support from our local experts who have proven time and again to deliver quality presentations of international standard. We look forward to seeing many colleagues in Johannesburg.

Connecting colleagues and role players, whether it may be private-public, industry, government, research, mentors or students, will be the aim of this congress, speaking to the vision of the SA Heart® which is to improve the Cardiovascular Care for all living in South Africa.

Ahmed Vachiat
SA Heart® Convenor

CARDIOLOGY
CONNECTIONS

24th Annual SA Heart® Congress 2024
Sandton Convention Centre
8 - 10 November 2024

SA HEART® RESEARCH SCHOLARSHIP 2024

Understanding the pathophysiology involved in the development of doxorubicin-induced cardiotoxicity in breast cancer patients is key to identify novel cardioprotective strategies and early biomarkers. In this regard, our recent unpublished data identify high-density lipoprotein (HDL) particles as a potential key role player in the development of doxorubicin-induced cardiotoxicity. In both breast cancer patients and tumour bearing mice receiving a doxorubicin treatment, we observe an association between a shift in the HDL subclasses and cardiac abnormalities. Most importantly, HDL particles isolated from tumour bearing mice receiving doxorubicin have lost their cardioprotective properties.

HDL particles are composed of numerous functional proteins and lipids that may be altered by doxorubicin and breast cancer, causing these particles to become dysfunctional. Therefore, the aim of our current research is to characterise the composition of HDL particles in cancer mice treated with doxorubicin using a multiomics approach as this will enable us to better understand the pathophysiological mechanisms involved in the development of doxorubicin-induced cardiotoxicity and to hopefully delineate sensitive novel biomarkers that can detect early cardiotoxicity in breast cancer patients.

Carmelita Abrahams and Prof Eric Klug.

We would like to congratulate Carmelita Abrahams for her outstanding hard work. She is the receiver of the SA Heart® Research Scholarship 22024.

"Well done Carmelita!!"

PROUDLY SA HEART® MEMBER

The SA Heart® membership system now issues membership certificates for your current membership which you can print and display in your rooms.

Either login to your membership account, navigate to the My Membership tab and click on the relevant icon in the "edit" column, or when renewing membership, the certificate will be emailed together with your invoice.

THE SOUTH AFRICAN HEART ASSOCIATION RESEARCH SCHOLARSHIP

This scholarship is available to all members of the SA Heart® Association. It is primarily intended to assist colleagues involved in much-needed research to enhance their research programmes.

REQUIREMENTS

- Applicants need to be fully paid-up members in good standing for at least 1 year.
- Applications must include:
  - The applicant's abbreviated CV
  - A breakdown of the anticipated expenses
  - Ethics approval
  - Full details of the research
  - The completed application form - please request a fillable MS Word document from erika@saheart.org
  - Contact details of Head of Department or supervisor/mentor
- The research for which funding support is sought has to have direct relevance to South Africa.

RECOMMENDATIONS

- Preference will be given to early and mid-career applicants (<5 years post-qualification as specialist and/or <5 years post-PhD qualification).

CONDITIONS

- Applicants may only submit 1 application every second year. Preference is given to those who have not had previous scholarships awarded.
- Awards are granted for one specific research project. Should that specific project be cancelled or the full amount allocated not be utilised for any reason, then the funds must revert to SA Heart®.

APPLICATIONS MUST BE EMAILED TO:

erika@saheart.org

THE SELECTION PANEL WILL REVIEW APPLICATIONS ANNUALLY AND THE CLOSING DATE IS 30 SEPTEMBER 2024.

One scholarship to a maximum amount of R80 000 will be awarded annually.

SA Heart® commits to inclusive excellence by advancing equity and diversity.

We particularly encourage applications from members of historically under represented racial/ethnic groups, women and individuals with disabilities.

INTRODUCING THOBILE ZIQUBU

SA Heart® is pleased to announce that Thobile Ziqubu has joined SA Heart® in the newly created Stakeholder Relations Manager (SRM) position. She brings with her over a decade of experience in the healthcare industry, mainly in the pharmaceutical space. As an SRM, she will work alongside General Manager, Erika Dau as well as our President Prof Eric Klug and other Board and committee members in executing a number of the organisations objectives and exciting projects going forward.

"Welcome Thobile."

Thobile Ziqubu.

EXCEPTIONAL SERVICE TO SA HEART®

We extend our gratitude to Marlize Stander for her exceptional service to SA Heart® over the past 2 years. Marlize has consistently demonstrated the utmost professionalism in managing our Facebook, LinkedIn, and Twitter accounts, contributing significantly to our online presence and engagement. As Marlize moves on to new endeavours, we wish her the very best in all her future pursuits. Her dedication and contributions will be fondly remembered, and we thank her for her invaluable contributions to our organisation.

"Wishing her the very best for the future."

Marlize Stander.

NEW SOCIAL MEDIA PARTNER

We are pleased to announce the addition of our new social media partner, Doclink, to the SA Heart® team. They will be instrumental in shaping our branding, design, and digital marketing strategies throughout 2024. With their wealth of industry experience, we anticipate significant enhancements to our member experience and a strengthened SA Heart® brand presence. We are excited to embark on this journey with Doclink and explore new avenues for growth and engagement.

Welcome aboard!

SA HEART® TRAVEL SCHOLARSHIP 2024

I am writing to express my heartfelt gratitude to the South African Heart Association for awarding me with a local travel scholarship which allowed me to attend the 23rd annual SA Heart® Congress, which was held in Sandton, from 27 - 29 October 2023. This was my first time attending the Congress and it was an honour and a privilege to attend such an esteemed event. As a 5th-year medical student and having recently graduated with an MSc degree, this event presented an invaluable opportunity for me to present the findings of my research, to network and learn from esteemed professionals. I could gain insights into the ever-evolving landscape of cardiovascular medicine and research.

The Congress, aptly titled "The Cardiac Collaboration" provided a platform for a wide range of cardiovascular researchers both from South Africa and all around the world to come together, share valuable insights and engage in discussions on the latest advancements and challenges within the field. Furthermore, the Congress was filled with national pride and excitement because it was the weekend of the Rugby World Cup final. It was great to see attendees in their Springbok shirts, people predicting the final score and the joy on Sunday morning after our national team won a much-deserved fourth World Cup.

There were a remarkable array of workshops, presentations and interactive sessions that covered a broad spectrum of topics ranging from novel basic sciences research to preventive cardiology strategies. One of the highlights of the Congress for me was the CVD – IMIBIZO workshop which was an interactive seminar aimed at young researchers within the cardiovascular field. I was honored to learn from renowned international and local speakers and to hear about their research journey of how they got to where they are today.

The South African Society for Cardiovascular Research (SASCAR) is a special interest group of the SA Heart® Association. They hosted 2 abstract sessions where researchers had the opportunity to give a short presentation of an abstract which they submitted to the Congress. It was in 1 of these sessions that I presented the findings of my MSc thesis, titled, "Investigating high-density lipoprotein (HDL) subfractions, composition and functionality in people living with HIV". Other interesting abstract presentations

Dr Peter Hudson together with Prof Sandrine Lecour and Carmelita Abrahams.

included discussions on how doxorubicin-induced is associated with dysfunctional HDL particles (by Ms Carmelita Abrahams) and how antiretroviral therapy reduces aortic stiffness in newly diagnosed HIV-infected patients after just 9 months (by Dr Pieter-Paul Robbertse) to name a few.

The organisation and logistics of the Congress were commendable, ensuring a seamless experience for all participants. From registration to session management, everything was efficiently handled, allowing attendees to focus entirely on the content and discussions. Moreover, the networking opportunities facilitated fruitful discussions and collaborations among attendees, fostering a sense of camaraderie and shared purpose in advancing cardiovascular health.

In conclusion, I extend my deepest appreciation to the SA Heart® Committee for their generosity and dedication in organising such an enlightening and enriching congress. Thank you once again for the honour of the local travel scholarship. I look forward to continuing to contribute to the field and hope it was the first of many SA Heart® Congresses that I can attend.

Peter Hudson
Cape Heart Institute

LOUIS VOGELPOEL TRAVELLING SCHOLARSHIP

Applications are invited for the annual Louis Vogelpoel Travelling Scholarship for 2025. An amount of up to R20 000 towards the travel and accommodation costs of a local or international congress will be offered annually by the Western Cape branch of the South African Heart Association in memory of one of South Africa's outstanding cardiologists, Dr Louis Vogelpoel.

Louis Vogelpoel was a pioneer of cardiology in South Africa who died in April 2005. He was one of the founding members of the Cardiac Clinic at Groote Schuur Hospital and the University of Cape Town. He had an exceptional career of more than 5 decades as a distinguished general physician, cardiologist and horticultural scientist. Dr Vogelpoel's commitment to patient-care, teaching and personal education is remembered by his many students, colleagues and patients. Medical students, house officers, registrars and consultants benefited from exposure to his unique blend of clinical expertise, extensive knowledge, enthusiasm and gracious style.

A gifted and enthusiastic teacher, he was instrumental in the training of generations of undergraduates by regular bedside tutorials. He served as an outstanding role model for postgraduates and many who have achieved prominence nationally and internationally acknowledged his contribution to the development of their careers.

All applications for the scholarship will be reviewed by the executive committee of the Western Cape branch of the South African Heart Association. Preference will be given to practitioners or researchers in the field of cardiovascular medicine who are members of the South African Heart Association and are resident in the Western Cape.

Applications should include: (i) A brief synopsis of the work the applicant wishes to present at the congress; and (ii) A brief letter of what the applicant hopes to gain by attending the relevant congress. The applicant should submit an abstract for presentation at the relevant national or international meeting. Should such an abstract not be accepted by the relevant congress organising committee, the applicant will forfeit his or her sponsorship towards the congress. (Application can however be made well in advance of the relevant congress but will only be awarded on acceptance of the abstract.) A written report on the relevant congress attended will need to be submitted by the successful applicant within 6 weeks of attending the congress. The congress report will be published in the South African Heart Association Newsletter.

> "A gifted and enthusiastic teacher, he was instrumental in the training of generations of undergraduates."

Applications should be sent to Dr Alfonso Pecoraro, President of the Western Cape branch of the South African Heart Association, Division of Cardiology, Tygerberg Hospital, Francie van Zijl Drive, Tygerberg 7505; or alternatively email: pecoraro@sun.ac.za.

Previous recipients of this prestigious award include Sandrine Lecour, Roisin Kelle, Liesl Zühlke and Prof Hans Strijdom.

Applications close on 31 January 2025.

TRAVEL SCHOLARSHIPS OF THE SOUTH AFRICAN HEART ASSOCIATION

Applications for the SA Heart® Travel Scholarship for the second term in 2023 are invited to reach the SA Heart® Office by 31 May 2024.

The scholarship is for the value of up to R35 000.00 for international meetings and R15 000.00 for local meetings.

This scholarship is available to all members of the SA Heart® Association. It is primarily intended to assist junior colleagues to ensure continued participation in local or international scientific meetings or workshops.

REQUIREMENTS

- Applicants must be fully paid-up members for at least 1 year.
- The research presented at the congress for which funding is sought, needs to be relevant to South Africa.

RECOMMENDATIONS

- Early and mid-career applicants (<5 years post-qualification as specialist and/or <5 years post-PhD qualification).
- Acceptance of an abstract/poster presentation at the scientific meeting to be attended.

CONDITIONS

- Awards will not be made for conferences or workshops retrospective to the application submission deadline. If the conference is taking place within 6 (six) weeks following the submission deadline, please indicate this in the appropriate place on the application form.
- It is not a requirement for the abstract to be accepted by the conference travel application closing date. Should the acceptance of the paper, including proof of registration, not be available at the time of submission of the application, then a provisional award may be made pending receipt of the acceptance of the paper.
- Please ensure that applications are made as well in advance as possible **(preferably at least 6 months prior to the conference date)**.
- Applicants may only submit 1 application every second year. The scholarship is for the value of up to R30 000.00 for international meetings and R9 500.00 for local meetings.
- Awards are only made in the event that a paper or a poster is being presented or in the event of a workshop attendance, if the reviewers deem the workshop attendance to be of high impact and consequently of benefit to the SA Heart® community.
- The applicant must ensure that the application is fully completed including the requirements as detailed in the checklist section. Applicants are asked to be concise and to only include applicable and relevant information.
- Awards are granted for 1 specific conference. Should that specific conference be cancelled or the full amount allocated not utilised for any reason, then the funds must revert to SA Heart®; and
- A written report on the relevant congress attended will need to be submitted by the successful applicant within 6 weeks of attending the congress. The congress report will be published in the South African Heart Association Newsletter.

SUBMISSION REQUIREMENTS

- For more information and application forms, please visit https://www.saheart.org/cms-home/category/39.

LASSA REPORT

LASSA
LIPID AND ATHEROSCLEROSIS SOCIETY OF SOUTHERN AFRICA
A SPECIAL INTEREST GROUP OF SA HEART®

The difficulties in sustaining lipidology expertise in South Africa persist. Attempts to remedy the lack of exposure to lipid disorders during training of specialists treating patients with high cardiovascular risk have not been successful. The meeting about noncommunicable disease held in November 2022 failed to attract the attendance of the Minister of Health. The priming of the head of the department of internal medicine ahead of the meeting and input by Prof D. Blom who represented LASSA, failed to make an impact. The "Johannesburg Declaration" stated that noncommunicable disease would receive increased attention from the Department of Health. LASSA is unaware of progress. In January 2023, SA Heart® indicated that it could not assist in conserving lipidology. Subsequently LASSA has twice submitted documents about the plight of lipidology to the Minister of Health and the national committee of deans of the health science faculties as we hope expertise in lipidology will be strengthened by better training at health science faculties.

The guide from council for medical schemes about prescribed minimum benefit conditions was published in early 2023. (Hyperlipidaemia. PMB-X Guidelines 2023. Pages 53-56. Editor, McMillan CR. https://medicalacademic.co.za/issues/2023/pmbx2023/Accessed 2023.04.18). In the opinion of the LASSA committee the PMB-X did not appropriately deal with the wide range of disorders of lipid and lipoprotein metabolism and did not prioritise the most serious conditions, was somewhat dated about treatment recommendations and did not suggest referral criteria for patients requiring special attention. A letter was submitted to the South African Medical Journal, but this has been delayed for publication.

LASSA regrets the endless dealings around the National Health Insurance while patients with serious lipid and lipoprotein disorders in the public and private sectors of healthcare are not receiving best clinical assessment, diagnostic investigation and optimal treatment. Under these circumstances it is difficult to obtain appropriate information and to research locally relevant problems. Nevertheless, LASSA has embarked on an observational study evaluating patients with very severe hypercholesterolaemia.

The aim of the TC 12+ study (total cholesterol > 12mmol/L and triglyceride <5mmol/L) initiated by LASSA is to obtain information on the most severe cases of hypercholesterolaemia that most likely will need additional management beyond treatment with statins and ezetimibe. This may not necessarily be PCSK9 neutralising treatment for all as some rare sterol disorders may respond dramatically to diet. The study assesses hypercholesterolaemia following referral by the medical practitioner and involves combining the information the medical practitioner provides and a phone call to the patient to check on details. Subsequently, a blood sample is submitted for electrophoresis to characterise apolipoprotein B- containing lipoproteins and the most common LDL receptor mutations are sought by genetic testing where relevant. Armed with such information LASSA will be able to assess the management of severe dyslipidaemia in South Africa and make recommendations.

LASSA is experiencing some problems in common with the SASCI experience discussed in the communication on the 9th February 2024 by Prof E. Klug and Dr H. Weich concerning " ...the clinical autonomy in therapeutic decision making of our members.... We appeal to funders to respect cardiologists' clinical judgement in selecting either of these modalities or indeed other non-invasive ischaemia tests recommended by the guidelines." The difference, however, is that there are very few experienced and knowledgeable medical practitioners to deal with dyslipidaemia. Patients do not have ready access to expertise and in addition decisions about management are made by persons without full insight into the complex set of derangements. The severe dyslipidaemias in the broadest context involve about 500 000 persons in South Africa and the category for which high expertise is necessary will number at least 50 000.

The hope is that LASSA will find support for providing service, teaching and research in 2024 and beyond and that the developments that improve the well-being of people with severe derangements in lipid and lipoprotein metabolism will receive the best care under the current constraints in healthcare in South Africa.

David Marais
LASSA Chairperson

RETIRING STEWARDS

We would like to wish 2 hard working gentlemen, Dr Anthony Stanley and Dr Adriaan Snyders, huge congratulations on their retirement. Dr Stanley retired at the end of February 2024, and Dr Snyders retired at the end of March 2024. Thank you very much for dedicating your time and energy into Cardiology.

We hope you get to enjoy your future with lots of time to enjoy your hobbies, friends and family. Most importantly, we wish you good health and delight.

Dr Anthony Stanley.

Dr Adriaan Snyders.

"Congratulations on their retirement."

IN MEMORY OF PROFESSOR VLADIMIR GRIGOROV

13 June 1965 - 14 February 2024

When Prof Vladimir Grigorov joined Team Arwyp 2 decades ago, he brought not only his expertise as a cardiologist but also his remarkable spirit, becoming an integral and cherished member of our team. His leadership, mentorship, and unwavering commitment to excellence have guided us all. May we honour his legacy by continuing the important work to which he dedicated his life. Prof Grigorov will forever remain in our hearts, a shining example of humanity and excellence.

"Forever in our hearts."

CONTRIBUTION TO LITERATURE

The LIBerate-HR trial demonstrated that lerodalcibep reduces LDL-C levels in addition to statin therapy.

DESCRIPTION

The goal of the trial was to evaluate lerodalcibep compared with placebo among patients with increased risk of cardiovascular disease (CVD). Lerodalcibep blocks proprotein convertase subtilisin/kexin type 9 (PCSK9) binding to low-density lipoprotein (LDL)-receptors, thus preventing receptor degradation, which enhances LDL-C clearance and lowering of LDL-C levels.

PRINCIPAL FINDINGS

The primary outcome, change in LDL-C at 52 weeks, was -56.3% in the lerodalcibep group vs. -0.14% in the placebo group ($p<0.001$).

REFERENCES

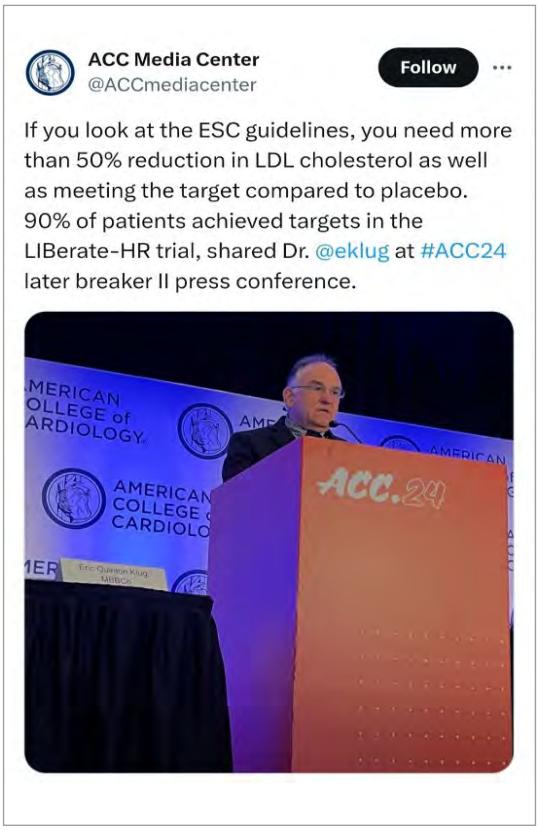
Presented by Prof Eric Klug at the American College of Cardiology Annual Scientific Session (ACC.24), Atlanta, GA, 7 April 2024.

ACC CONGRESS

SA Heart® President, Prof Eric Klug travelled to the US for the 73rd Annual American College of Cardiology (ACC) congress in Atlanta Georgia where he got to represent the organisation as well as present the LIBerate-HR trial for a globally represented cardiovascular care community.

Prof Eric Klug representing SA Heart® at the Convocation of the ACC together with mace bearer Dr Nicole L. Lohr – Chair of the Board of Governors of the ACC.

TWEET OF PROF ERIC KLUG AFTER HIS PRESENTATION

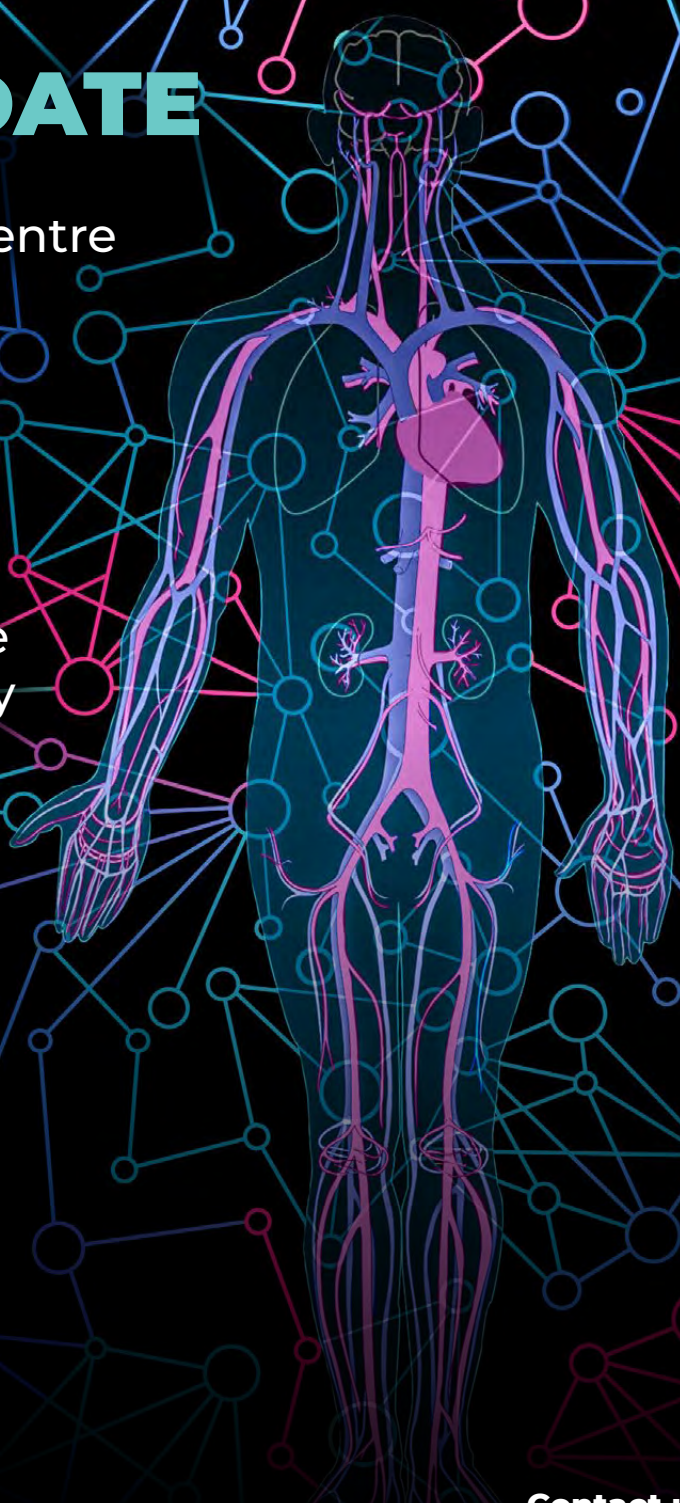


CARDIOLOGY CONNECTIONS

24th Annual SA Heart® Congress 2024

SAVE THE DATE

8 - 10 November 2024
Sandton Convention Centre



Join us in an Innovative Approach to Cardiology Connections

Registration Opens
May 2024
Watch this space for further updates

SA HEART®

Contact us at
saheartcongress@shiftideas.co.za