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GUEST
EDITORIAL

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Living with heart failure

Heart failure (HF) remains a global health concern affecting approximately 64.3 million people worldwide.(1) In sub-Saharan Africa the pattern of HF is diverse and different to what is reported by the Global North,(2) such as the relatively young age of participants reported in The Sub-Saharan African Survey of HF (THESUS-HF) study.(3) Despite notable progress over the past 2 decades in advancing the understanding of HF in Africa, important knowledge gaps persist. These include outdated data on access to care and a lack of information regarding the incidence, aetiology, availability, and affordability of HF medications. The THESUS-HF II study, under the umbrella of the Pan African Cardiac Society is currently underway. So far 16 countries participate, and more than 1 400 patients have been recruited (Figure 1). It is expected that the study will provide more understanding into access to care as well as comorbidities, risk factors and outcomes of HF.

This issue of the Journal, which highlights some of the co-morbidities associated with HF and their required management, starts with a large retrospective study conducted by L.C. Mbanga and colleagues. Mbanga highlights the significant impact of HF on receiving renal replacement therapy in the cardiac intensive care unit in South Africa, which results in a high in-hospital and 30-day mortality rate (see article on page 80).

Contrary to this outcome is the extended life expectancy in persons living with human immunodeficiency virus (HIV) (PLWH) since the introduction of antiretroviral therapies (ART). The article on page 86, by Maharaj and Pillay, reviews the relationship between HIV and HF, which is a rising concern of morbidity and mortality. They emphasise the need for regular cardiac monitoring and advanced diagnostic tools in the management of HF in PLWH.

An important cause of myocarditis and cardiomyopathy are viruses. Hanekom, et al. analysed endomyocardial biopsies (EMB) with a focus on the distribution of viruses in dilated cardiomyopathy (DCM) specifically. Parvovirus B19 (B19V) was found to be present in almost all virus-specific EMB samples, promoting the need for further investigation into the pathophysiological role of B19V in the progression of DCM. As described in the article on page 100, a large proportion of DCM remains idiopathic in South Africa, but with better understanding of the causes, scientific management can be improved.

FIGURE 1: The Sub-Saharan African Survey of HF (THESUS-HF) II study sites.

With iron deficiency being the most common nutritional deficiency globally, and associated with poor HF outcomes, HF patients are screened as recommended by the European Cardiac Society (ESC). Gerber, et al. highlight the high prevalence of iron-deficiency despite normal haemoglobin levels in HF patients. The importance of this recommendation is re-emphasised through their cross-sectional study on page 112.

In conclusion, heart failure remains a critical health issue in South Africa, and Africa as a whole, with challenges more diverse than that reported in the past. Ongoing research into the challenges surrounding cardiovascular diseases in sub-Saharan Africa, and enhancing the guideline-directed therapies, accordingly, is essential to improving patient outcome.

Empowering patients to understand and manage HF improves outcomes and contributes to enhanced quality of life. Therefore, healthcare professionals should be aware of (digital) tools that patients and families can access for advice and support when they are not in the healthcare

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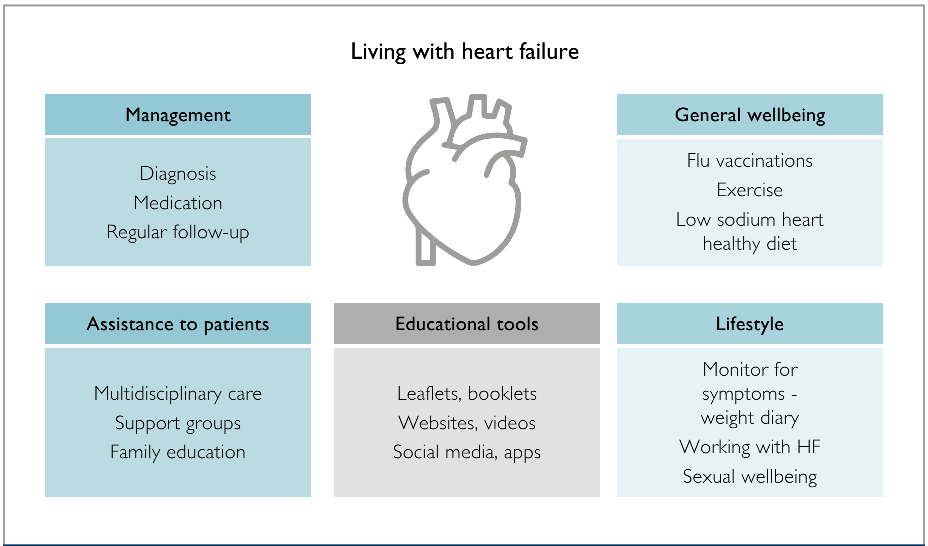

FIGURE 2: Supporting HF patients.

setting. There are a range of tools available to support self-care, including leaflets, booklets, websites, apps, videos, social media pages, and support groups (Figure 2).

Only through concerted efforts can we hope to reduce the substantial burden of heart failure in South Africa and ultimately improve the quality of life and survival rates for those affected.

Conflict of interest: none declared.

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Reflecting on 20 years of collaboration: A tribute to the SA Heart® Journal

As I reflect on the past 20 years with the SA Heart® Journal, it's hard to believe how quickly time has passed. Throughout these 2 decades, I've had the privilege of working alongside an incredible colleague and friend who has been responsible for the design and layout of the journal. Together, we've produced countless editions of this important publication, each with the shared goal of creating a well-designed, error-free journal on time.

My role as the production manager has been deeply intertwined with every step of the journal's journey, from initial submission to final print. For many years, the journal was printed before transitioning to a digital format. I liaised with printers, conducted color proof checks, and arranged for the journals to be delivered to recipients.

I've had the responsibility of liaising with the editor, ensuring that each article was carefully reviewed and refined before it was handed over to me for production. Working closely with the proofreader, we ensured that every issue met the highest standards of quality, accuracy, and clarity. Once the copy was finalised, I passed it along to my layout artist, who transformed it into the beautifully designed journal you see in each edition.

Over the years, I've gained immense respect for the process and the attention to detail required at each stage. From coordinating deadlines and ensuring the smooth flow of content to managing the back-and-forth with the editor and proofreader, every step has been vital to the journal's success. While the technical aspects of production were always challenging, it was the collaboration between all of us that truly made each issue come together seamlessly.

Our layout artist was an exceptional partner in producing a quality academic journal. Her creativity, professionalism, and meticulous attention to detail brought each issue to life in ways I couldn't have imagined. She has an incredible ability to take complex, dense articles and transform them into accessible, well-organised content, always maintaining the journal's high professional standards. I look back at each publication with pride.

The SA Heart® Journal has been more than just a job for me – it has been a passion project, a labour of love, and a vital part of my professional life. It has been incredibly rewarding to know that our work has contributed to the cardiovascular field, helped inform clinicians, and ultimately made a difference in patient care.

As we conclude our involvement with the SA Heart® Journal, I feel a bittersweet sense of pride in what we've accomplished. I am confident that the journal will continue to thrive under the guidance of a dedicated team of specialists and a passionate Editor.

I want to express my heartfelt thanks to everyone who has been part of this journey – I met so many talented and dedicated people who all, in their own way, make a huge difference in the lives of many. The work we've done together has been meaningful, and I'm excited to see the future of the SA Heart® Journal unfold under the guidance of the new team.

Clinical profile and outcomes of patients receiving acute renal replacement therapy in the cardiac intensive care unit at a South African referral centre

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ABSTRACT

Background: At least a quarter of patients admitted to the cardiac intensive care unit (CICU) will develop acute kidney injury (AKI), and some of these patients receive renal replacement therapy (RRT). The clinical profiles and outcomes of CICU patients receiving RRT in resource constraint settings like South Africa are unknown.

Objectives: The objectives of this study were to determine the clinical profiles and outcomes of patients receiving RRT in the CICU in a South African tertiary centre.

Methods: In this retrospective study, we included consecutive patients admitted and receiving RRT at the Groote Schuur Hospital CICU from 1 January 2012 - 31 December 2016.

Results: During the study period, 3 247 patients were admitted to the CICU, and 46 (1.4%) received RRT. The RRT patients had a mean (SD) age of 52 (17) years, 56% were males, and 65% had a background history of systemic hypertension. Heart failure syndromes accounted for 60.9% of CICU admission in the RRT patient group, followed by acute coronary syndromes and arrhythmias, which accounted for 26.1% and 13.0%, respectively. The RRT patient population had in-hospital and 30-day mortality rates of 58.7% and 60.9%, respectively. Baseline use of angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) was associated with a reduced 30-day mortality rate, hazards ratio (HR) 0.43; 95% confidence interval (95% CI) 0.20 - 0.93; p=0.031. In addition, heart failure was associated with an increased 30-day mortality rate, HR 2.52; 95% CI 1.10 - 5.78; p=0.029.

Conclusion: In this single-centre study from an upper middle-income country, a small proportion of CICU patients receive RRT. Heart failure syndrome is associated with most RRT patients admitted to the CICU. Patients receiving RRT in CICU have a high in-hospital and 30-day mortality. SA Heart® 2025;22:82-86

INTRODUCTION

The reported incidence of acute kidney injury (AKI) in patients managed in the cardiac intensive care units (CICU) is increasing.[1-3] This is partly because of the ageing patient population and patients with complex comorbidities treated in the CICU. At least 25% of patients admitted with cardiovascular disease will develop AKI depending on the AKI definition used, including up to 56.1% in patients with acute decompensated heart failure and up to 30% in patients with acute coronary syndromes (ACS).[4-6] AKI complicating cardiovascular disease portends poor outcomes. For example, of the 118 465 patients admitted for acute decompensated heart failure evaluated in the ADHERE (Acute Decompensated Heart Failure National Registry) database, the 56.1% who developed moderate to severe acute renal impairment had a 4-fold increase in in-hospital mortality when compared to those with mild or no renal impairment.[7] Furthermore, a recent systematic review suggested that approximately 3% of patients with ACS, acute decompensated heart failure and / or cardiogenic shock admitted to the CICU received renal replacement therapy (RRT).[8] In this group, the need for RRT conferred a 10-fold increase in the risk of death, and a prolonged length of CICU stay.[8]

In a study conducted by the International Society of Nephrology looking at the availability and accessibility of health services for diagnosis, monitoring, and management of CKD, provision of renal replacement therapies (RRTs), distribution of the nephrologist workforce on a global scale, Qarni and colleagues demonstrated limited access to trained nephrologists, dialysis services and renal transplantation in low- and middle-income countries.[9] In centres where such advanced care is available, there are frequently critical resource-related constraints that limit the number of patients who can access care and require careful selection of patients who are likely to benefit most. The ongoing epidemiological transition and increase in diseases such as coronary artery disease, diabetes and hypertension have led to a rapid rise in the demand for CICUs and advanced renal care.[10] Given the persistently high burden of communicable diseases in South Africa requiring health resources,[11] important decisions about appropriate resource allocation require a thorough understanding of both the burden of non-communicable diseases and their related outcomes. Specifically, in a South African public sector setting where patient demographics and cardiovascular risk factor profiles are different to that found in the Global North,[12] the burden of AKI amongst patients admitted to hospitals with acute cardiac syndromes and their related outcomes would be important to inform appropriate resource allocation and patient care.

OBJECTIVES

The overarching aim of this study was to review the local practice of acute renal replacement therapy in a typical South African tertiary centre CICU regarding the burden, patient profiles, and patient outcomes.

METHODS

Study design and patient population

This was a retrospective folder review of all patients admitted to a 6-bed CICU at a large tertiary centre in Cape Town, South Africa, between 1 January 2012 - 31 December 2016.

After obtaining appropriate regulatory and ethics permissions, ward admission records, renal replacement records and the electronic health information system for public sector hospitals and health care centres in the Western Cape province of South Africa (CLINICOM) were searched for patient data, and related information on all the patients admitted to the CICU during the study period. A standardised data collection form was used to extract and analyse relevant data on those participants receiving RRT from the above hospital records. The study was carried out with the approval UCT Human Subjects Research Ethics Committee (HREC 690/2020).

The conventional indications for renal replacement therapy in acute renal failure are:

- volume overload
- intractable hyperkalaemia
- refractory metabolic acidosis, and / or
- uremic signs or symptoms of progressive azotaemia in the absence of uraemia.[13]

The consultant cardiologist referred patients in the cardiac CICU needing renal replacement therapy to the consultant nephrologist. RRT and the mode of RRT were at the discretion of the treating consultants.

Statistical Analysis

Normally distributed data are presented as means [standard deviation (SD]) and, when highly skewed, as medians [inter-quartile range (IQR)]; discrete variables are presented as numbers (percentages). Continuous data were compared using the t-test or Mann-Whitney test, and categorical data using the Chi-square test or the Fisher exact test. Cox proportional hazard regression models were constructed to identify factors associated with 30-day mortality. All tests were 2-sided, and a p-value <0.05 was considered significant. Collected data were entered and analysed using IBM SPSS Statistical Software.

RESULTS

During the 5-year study period, 3 247 patients were admitted to the CICU, and 46 (1.4%) patients received RRT for AKI. The patients receiving RRT in the CICU had a mean (SD) age of 52.6 (17.1) years, and 56.5% (26/46) were male. The baseline characteristics of RRT in CICU patients are presented in Table I.

Amongst the RRT cohort, the leading indication for CICU admission was acute or decompensated heart failure, 28/46 (60.9%), followed by acute coronary syndromes in 12/46 (26.1%) and unstable cardiac arrhythmias in 6/46 (13.0%) (Figure 1 to Figure 4).

After a median (IQR) of 10 (5; 17) days in the hospital, 27 patients demised, thus representing an in-hospital mortality rate of 58.7%. The 30-day mortality rate was 60.9%. On Cox regression analysis, the baseline use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) was associated with a reduced probability of a 30-day mortality, hazards ratio (HR) of 0.43; 95% confidence interval [95% CI], (0.20 - 0.93); p=0.03. In contrast, admission to the CICU for heart failure was associated with a 2,5-fold increase in the probability of death in 30 days; HR=2.52; 95% CI (1.10 - 5.78), p=0.03 (Table II).

TABLE I: Baseline characteristics of the patients who received renal replacement therapy at the GSH cardiac ICU.

Variable	No = 46
Age, mean (SD) years	52.6 (17.1)
Female, No (%)	20 (43.5)
Hypertension, No (%)	30 (65.2)
Diabetes mellitus, No (%)	18 (39.1)
Dyslipidaemia, No (%)	16 (34.8)
Atrial fibrillation, No (%)	9 (19.5)
Peripheral vascular disease, No (%)	5 (10.9)
Current smoking history, No (%)	15 (32.6)
History of ischaemic heart disease	12 (26.1)
Chronic kidney disease	11 (23.9)
ACE inhibitor / ARB, No (%)	24 (52.2)
Beta blocker, No (%)	14 (30.4)
Loop diuretic, No (%)	16 (34.8)
Thiazide diuretic, No (%)	10 (21.7)
Spironolactone, No (%)	4 (8.7)
Statin, No (%)	20 (43.5)
Sulfonylurea, No (%)	8 (17.4)
Metformin, No (%)	14 (30.4)
Insulin, No (%)	6 (13.0)
Warfarin, No (%)	6 (13.0)

CICU: Cardiac Intensive Care Unit, RRT: Renal Replacement Therapy, PVD: Peripheral Vascular Disease, IHD: Ischaemic Heart Disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, ACS: Acute Coronary Syndrome, SD: Standard Deviation, IQR: Interquartile Range.

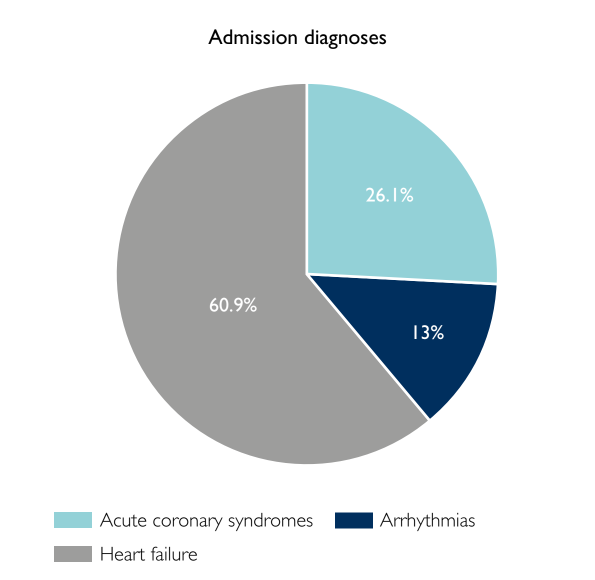

FIGURE 1: Pie chart demonstrating admission diagnoses of patients admitted to the CCU and treated with RRT for AKI. No = 46.

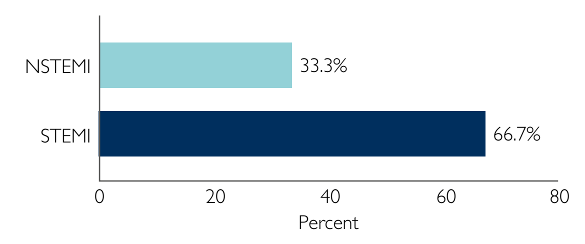

FIGURE 2: Bar chart demonstrating the different types of acute coronary syndromes in patients admitted to the CCU and treated with RRT for AKI. No = 12.

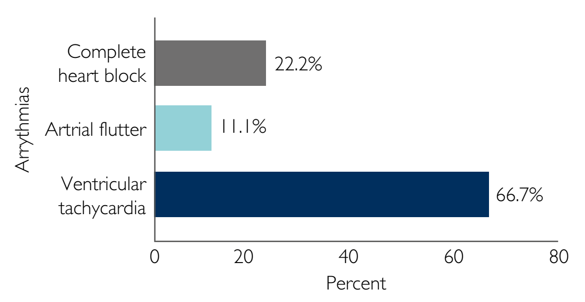

FIGURE 3: Bar chart demonstrating different admission cardiac arrhythmias in patients admitted to the CCU and treated with RRT for AKI. No = 6.

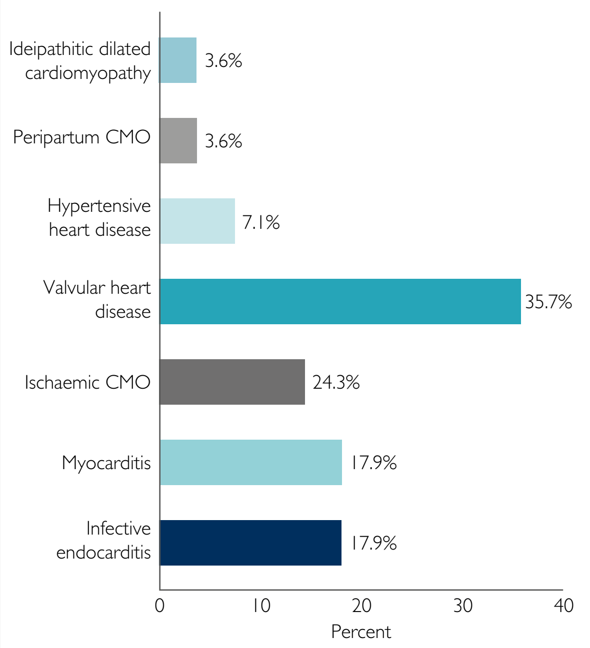

FIGURE 4: Bar chart demonstrating heart failure syndromes diagnosed in patients admitted to the CCU and treated with RRT for AKI. No = 28.

TABLE II: Hazards ratios and 95% confidence intervals for 30-day mortality in patients admitted to CICU and receiving RRT.

Variable	Hazard Ratio	95% CI lower	95% CI upper	P-value
Age in years	1.01	0.98	1.03	0.685
Hypertension	0.65	0.30	1.385	0.262
Diabetes Mellitus	0.62	0.28	1.36	0.232
Atrial fibrillation	1.02	0.35	2.93	0.975
Atrial Flutter	0.64	0.09	4.70	0.659
Dyslipidaemia	1.11	0.51	2.40	0.796
PVD	0.85	0.26	2.81	0.784
Chronic Kidney injury	0.47	0.18	1.24	0.125
IHD	1.17	0.50	2.74	0.727
Metformin	0.56	0.23	1.37	0.204
Sulfonylurea	0.44	0.13	1.47	0.181
Insulin	0.74	0.22	2.46	0.624
ACE inhibitors/ ARB	0.43	0.20	0.93	0.031
Beta blockers	1.94	0.89	4.22	0.095
Atenolol	1.82	0.74	4.52	0.195
Carvedilol	1.15	0.40	3.32	0.795
Spironolactone	0.57	0.13	2.40	0.441
Statins	0.10	0.31	1.45	0.308
Furosemide	0.58	0.27	1.23	0.153
Warfarin	1.15	0.40	3.32	0.798
Hydrochlorothiazide	0.32	0.01	1.06	0.063
Aspirin	0.47	0.21	1.05	0.067
ACS	1.45	0.24	8.72	0.687
Cardiogenic shock	0.85	0.36	1.95	0.702
Heart failure	2.52	1.10	5.78	0.029

CICU: Cardiac Intensive Care Unit, RRT: Renal Replacement Therapy, PVD: Peripheral Vascular Disease, IHD: Ischaemic Heart Disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, ACS: Acute Coronary Syndrome.

DISCUSSION

The main findings of this study are:

- Over the 5 years under review, the proportion of CICU admissions receiving acute RRT for AKI was small, at 1.42 %.
- RRT in our CICU was commonly received by patients with heart failure syndromes.
- CICU patients treated with RRT have a high in-hospital and 30-day mortality.
- Heart failure was associated with an increased probability of 30-day mortality, and baseline use of ACE-inhibitors or ARB were protective.

AKI is common in hospitalised patients. A recent large meta-analysis reported that at least 22% of hospitalised patients will develop AKI.[14] However, there is limited data on the prevalence, management, and outcomes of AKI in patients admitted to the CICU in low- and middle-income countries, particularly in Africa. AKI is particularly common in critically ill patients admitted to the intensive care unit. For example, in a large retrospective study from the Mayo Clinic, 51% of CICU patients developed AKI.[15] AKI in the CICU is associated with an increased risk of in-hospital mortality.[3,6] Further, there is a graded increase in mortality with worsening severity of AKI.[15,16] In a recent retrospective study from the Mayo Clinic reviewing 9 311 CICU patients over 9 years, AKI developed in 50.8% of the CICU admissions.[15] The rate of RRT in the Mayo Clinic study was 14.7%, compared to only 1.4% in our study. Further, the Mayo Clinic cohort was older, with a mean age of 67.5 years and had many more comorbidities, including prior malignancies, lung disease and obesity.[15] These differences between our study and the Mayo Clinic study are partly due to the restricted access to RRT in our setting, therefore the selection of younger patients with fewer comorbidities.[9] The leading admission diagnosis amongst those requiring RRT in the Mayo Clinic study was heart failure (45 %), followed by acute coronary syndromes (44.1%) and shock (13%).[15] Heart failure and acute coronary syndromes were the 2 main cardiac conditions amongst those needing acute RRT in our study cohort, but the proportions differed.

We report an in-hospital rate and 30-day mortality rate of 58.7% and 60.9%, respectively, consistent with those from larger studies from high-income countries.[3,15,17-19] This highlights the complex adverse relationship between the sick heart and the kidneys and vice-versa, the cardio-renal syndrome.[20] In contrast to our findings, where decompensated heart failure was the main predictor of mortality, Van Diepen and colleagues identified shock, cardiac arrest, significant liver disease, and older age as predictors of in-hospital mortality in their CICU patients needing acute RRT.[19]

The significant limitations of this study are its small size, single-centre, retrospective nature of its design and the lack of a comparative group, particularly the group of patients with AKI who are not referred or offered RRT. Further, the data is incomplete; the specific indications for offering RRT were not explicitly clear in the patient files. However, in light of our study findings, a larger, prospective study to confirm the high mortality rate and better evaluate predictors of a poor outcome may be helpful to assist clinicians in similar settings with local evidence-based decision-making.

In conclusion, we set out to determine the clinical profile and outcomes of patients receiving RRT in the CICU at a South African referral centre. We found that acute renal replacement therapy was used sparingly in a relatively young population, most of whom had decompensated heart failure with cardiorenal syndrome. The in-hospital and 30-day mortality was high. These findings highlight the need for more aggressive programmes to screen for cardiovascular risk factors and primary prevention interventions to reduce the burden of the need for both CICU admissions and acute kidney injury needing renal replacement therapy.

Conflict of interest: none declared.

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Heart failure in persons with HIV: A scoping review

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ABSTRACT

Introduction: Human immunodeficiency virus (HIV) infection remains a global health challenge, marked by substantial morbidity and mortality. The introduction of antiretroviral therapy (ART) has dramatically extended life expectancy for people living with HIV (PLWH), but this increased longevity exposes them to long-term conditions such as cardiovascular diseases, particularly HIV associated cardiomyopathy leading to heart failure (HF). HF in PLWH is a rising cause of morbidity and mortality, yet remains poorly understood. This scoping review aims to systematically examine and synthesise the existing literature on the relationship between HIV and heart failure.

Methods: The review followed the Arksey and O'Malley 6-stage methodological framework for scoping reviews. A systematic search was conducted using Boolean search strings across 4 databases: Scopus, Cochrane, PubMed, and ScienceDirect. The search was restricted to studies published between 2019 - 2023. Core articles yielded from data base search total 83. Twenty additional articles included in references do not form part of those yielded from Boolean string search. Total references 103. The results were analysed and synthesised to explore the prevalence, risk factors, and pathophysiology of heart failure in PLWH. Data analysis included descriptive statistics and thematic organisation.

Results: The scoping review highlights a significant association between HIV and heart failure, with PLWH having a 2-fold increased risk of developing HF compared to HIV-negative individuals ($p<0.001$). Studies report a shift from heart failure with reduced ejection fraction (HFrEF) to heart failure with preserved ejection fraction (HFpEF) in aging PLWH populations on ART ($p=0.05$). Additionally, elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) levels were consistently found in PLWH with low CD4 counts, suggesting a persistent inflammatory state affecting the heart ($p=0.02$). Other significant predictors of heart failure include high viral load ($p=0.03$), low CD4 counts ($p=0.01$), and traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia ($p=0.001$). Protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs) were identified as ART classes associated with a higher cardiovascular risk (OR 1.8, 95% CI: 1.5-2.2).

Conclusion: Heart failuare is an emerging clinical entity among PLWH, driven by both HIV-related and traditional cardiovascular risk factors. This review underscores the need for integrated cardiovascular management strategies that encompass regular cardiac monitoring, advanced diagnostic tools, and careful selection of ART regimens. Ongoing research is crucial to develop tailored prevention and management approaches for cardiovascular complications in PLWH, ensuring improved clinical outcomes and quality of life for this vulnerable population. SA Heart® 2025;22:88-101

BACKGROUND

The discovery of human immunodeficiency virus (HIV) in the early 1980s marked a significant challenge for healthcare systems worldwide. Initially, an HIV diagnosis was synonymous with high mortality, primarily due to the vulnerability to opportunistic infections such as tuberculosis. However, the advent and continuous development of antiretroviral therapy (ART) revolutionised the management of HIV, enabling individuals to achieve near-normal life expectancy. Longitudinal studies, including one involving HIV-positive veterans in the United States, have demonstrated a significant increase in the median age of individuals with HIV, underscoring the success of ART in extending life expectancy.(1) With adherence to ART, mortality from opportunistic infections has notably decreased. By 2022, an estimated 39 million people were living with HIV globally, and approximately 29.8 million were receiving ART.(2)

While ART has significantly improved the prognosis for persons living with HIV (PLWH), it has also introduced new healthcare challenges. Non-communicable diseases, particularly cardiovascular diseases, have become increasingly prevalent in this population.[1,3,4] Among these, heart failure is emerging as a major cause of morbidity and mortality in PLWH.[5,6] Heart failure is defined as "a clinical syndrome manifesting symptoms and / or signs caused by structural and/or functional cardiac abnormalities, substantiated by elevated natriuretic peptide levels and / or concrete evidence of pulmonary or systemic congestion".[7] Globally, an estimated 64 million people were affected by heart failure in 2017.[8]

Despite these global trends, there is a significant gap in data documenting the epidemiology of heart failure in low- and middle-income regions, such as Northern and sub-Saharan Africa. This lack of data is concerning, as these regions bear approximately 80% of the global disease burden.[9] The extended lifespan of HIV-positive individuals has revealed a direct association between HIV and an increased risk of heart failure. PLWH are more than twice as likely to develop heart failure compared to their HIV-negative counterparts.[10] However, there remains a scarcity of research exploring the link between HIV and heart failure in countries like South Africa, where the healthcare system is already under considerable strain. This underscores the critical need for further research to identify and support HIV-positive individuals at risk of heart failure within these healthcare settings.

AIM

The aim of this scoping review was to examine the published literature that documents the relationship between HIV and cardiac failure.

METHODS

A scoping review was conducted to examine the available literature on the relationship between HIV and cardiac failure, following the 6-stage framework proposed by Arksey, O'Malley, and Levac, et al.[11,12]

Stage 1 involved formulating a research question, done in collaboration with an expert in the field: "What is currently understood about cardiac failure among people living with HIV?" Following this, a comprehensive search strategy was devised to identify relevant studies from four major databases: Scopus, Cochrane, PubMed, and Science Direct (**Stage 2**). The search employed keywords and Boolean operators (AND / OR / NOT) to form a search string:

(TITLE-ABS-KEY (("heart failure" OR "congestive heart failure" OR "cardiac failure" OR "cardiac insufficiency" OR "HFpEF" OR "heart failure with preserved ejection fraction" OR "HFrEF" OR "heart failure with reduced ejection fraction") AND ("HIV+" OR "HIV positive" OR "HIV infected" OR "human immunodeficiency virus positive" OR "seropositive"))) AND (LIMIT-TO (PUBYEAR, 2023) OR LIMIT-TO (PUBYEAR, 2022) OR LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019)).

The search was applied with necessary filters such as publication year, literature type, and human studies, yielding 1 126 abstracts for initial analysis.

In **Stage 3**, these abstracts were screened based on prede fined inclusion and exclusion criteria. Articles in Chinese (2), French (3), and Spanish (4) were excluded due to translation limitations, while 8 Russian articles were successfully translated using Google Translate. Additionally, 12 letters to the editor and 13 book chapters were excluded. After excluding 991 irrelevant articles and removing 18 duplicates, a total of 83 abstracts remained for further review.

Stage 4 involved critical review and data extraction from the selected publications. The extracted data were thematically organised and summarised (**Stage 5**), leading to the formulation of conclusions in **Stage 6** (Figure 1).

RESULTS

Eighty-three articles were included in this scoping review. A summary of the articles can be found in Appendix 1. Data from the studies has been analysed and thematically categorised below as per the guidelines suggested by Arksy and O'Malley.[12]

Magnitude of the cardiovascular challenges in HIV

The prevalence of cardiovascular disease (CVD) among PLWH has tripled over the past 2 decades, with particularly significant impacts noted in sub-Saharan Africa and the Asia-Pacific regions.[13] Over the same period, the proportion of CVD-related mortalities in the HIV-positive population has risen from 2.5% to 4.6%.[14] The spectrum of cardiovascular disease in HIV is wide however, HIV cardiomyopathy has emerged as the leading cause of mortality within this cohort.[15] The increasing prevalence of heart failure as a result of HIV cardiomyopathy underpins a growing public health concern. Research indicates that individuals with HIV receiving ART face a 2-fold increased risk of developing cardiac failure compared to their HIV-negative counterparts.[16] Moreover, these individuals experience a significantly higher risk of all-cause mortality

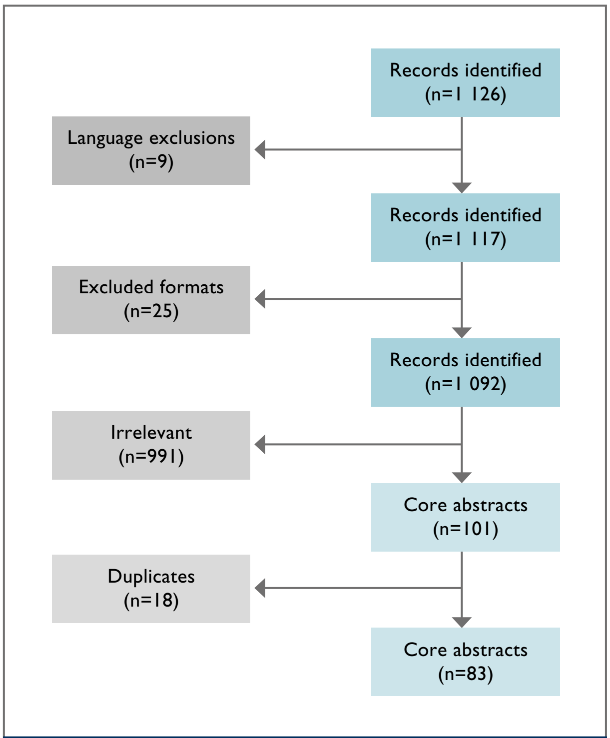

FIGURE 1: Flow diagram showing process of eliminating records for inclusion in scoping review.

when heart failure is present.[17] Elevated levels of N-terminal pro b-type natriuretic peptide (NT-proBNP) among South African PLWH on ART, especially in those with reduced CD4 counts, further highlight the presence of a persistent inflammatory state contributing to myocardial inflammation.[18] This growing body of evidence calls for a critical shift in the clinical management of HIV, placing greater emphasis on addressing cardiovascular complications.

Classification of heart failure in HIV

The aeitology of heart failure is broad with taxonomic classifications including ischemic heart disease, valvular heart disease, hypertensive heart disease, primary cardiomyopathies, secondary cardiomyopathies, congenital heart disease, pericardial disease, and uncategorised causes.[19] Geographical variances in aetiology exist between developed and developing regions. Industrialised countries experience a lower burden of tuberculosis and access to ART is widespread.[20] Thus coronary artery disease presents as the dominant cause of HIV associated heart disease in developed regions. In sub-Saharan Africa, pericardial tuberculosis and cardiomyopathy present as the dominant forms of HIV associated heart disease. HIV cardiomyopathy is characterised by decreased left ventricle ejection fraction (LVEF) or a dilated left ventricle, with or without symptoms of heart failure.[5] Heart failure may be further classified on the basis of echocardiographic assessment: Heart Failure with Reduced Ejection Fraction (HFrEF) and Heart Failure with Preserved Ejection Fraction (HFpEF). Historically, HIV-associated cardiomyopathy predominantly presented as HFrEF, which is characterised by marked left ventricular systolic dysfunction and ventricular dilation.[21] However, with increased ART uptake, an aging HIV-infected population and longer exposure to cardiometabolic risk factors, there has been a shift toward the predominance of HFpEF.[16,22] This shift reflects the intricate interaction between HIV infection, long-term antiretroviral therapy, and conventional cardiovascular risk factors. As a result, clinical management strategies must adapt to the evolving cardiac presentations in this population, addressing both phenotypes and the complex cardiovascular needs of individuals living with HIV.

HIV and heart failure: A significant correlation

A growing body of evidence strongly links HIV infection with an increased risk of cardiovascular disease and heart failure.[1,23-25] People living with HIV who develop heart failure are at a higher risk of hospital readmissions and mortality compared to HIV-negative individuals.[26,27] The progression towards heart failure in HIV-infected individuals is often insidious, with clinical symptoms typically emerging in advanced stages. Studies have revealed a higher incidence of subclinical left ventricular systolic dysfunction (LVSD) in HIV-infected paediatric populations receiving ART compared to non-infected controls,[28] a pattern similarly observed in a Zimbabwean cohort.[29]

An inverse relationship has been established between the age at HIV diagnosis and the prevalence of LVSD.[28] A study in Malawi found an increased rate of left ventricular hypertrophy (LVH) amongst PLWH.[24] HIV-positive veterans with heart failure, for instance, tend to present at a younger age than their HIV-negative peers.[30] Among individuals who have not initiated ART, significant cardiac structural changes have been noted, including increased left ventricular end-diastolic internal diameter (LVEDD), left ventricular mass index (LVMI), and left atrial volume (LAVI), though without significant differences in systolic function.[31,32] HIV seropositivity is associated with increased LVMI, enlargement of left atrial and right ventricular dimensions, and impaired right ventricular function,[22,33] suggesting that HIV directly contributes to cardiac remodelling and the development of left ventricular diastolic dysfunction.[34]

Furthermore, Global Longitudinal Strain (GLS), a key indicator of cardiac systolic function, is reduced in individuals with HIV, reflecting a heightened risk of heart failure in this population.[35,36]

Risk factors for cardiac failure in HIV

Cardiovascular disease risk factors in PLWH encompass both HIV-specific and traditional determinants. HIV infection itself is an independent risk factor for CVD and heart failure,(37-39) with a meta-analysis indicating that HIV increases the risk of heart failure by 48%.(40) The pathogenesis of HIV-associated cardiac failure is multifactorial with multiple risk factors working synergistically to produce a state of persistent myocardial inflammation.(41) Chronic inflammation may occur as a result of direct viral effects, opportunistic infections, ART side effects, and the mode of HIV transmission.(39) By inference, it is appropriate to assume that a reduction in inflammation may result in a reduced risk of HIV associated cardiac failure. Conventional risk factors include type 2 diabetes mellitus, dyslipidaemia, smoking, hypertension, and impaired glucose metabolism. Epidemiological studies have reported varying incidences of these conditions among PLWH, with certain studies highlighting elevated risks of CVD.(42,43)

Notably, hypertension, a well-recognised risk factor for CVD, affects approximately 35% of PLWH on ART(44) and is associated with left ventricular hypertrophy.(24) Additionally, HIV infection accelerates the development of atherosclerosis,(45) with coronary artery disease playing a significant role in the cardiovascular complications linked to HIV.(46,47) Changes in body fat distribution, including increased cardiac adiposity, have been implicated in the development of atherosclerosis and Heart Failure with Preserved Ejection Fraction (HFpEF) in PLWH.(48,49) Furthermore, weight gain, particularly associated with certain ART regimens, is a risk factor for diabetes, dyslipidaemia, hypertension, and CVD.(50,51)

An inverse relationship exists between CD4 cell counts and viral load with CVD risk, with lower CD4 counts, particularly below 200 cells/ml, being associated with more severe heart failure.(52-54) Gender differences also play a crucial role in risk stratification, as women living with HIV experience higher cardiovascular risks compared to men.(55-57) Smoking and polysubstance use further exacerbate cardiovascular risks, with their impact varying across PLWH.(58-60) This multifactorial landscape of HIV-specific and conventional risk factors necessitates a comprehensive approach to cardiovascular risk management in this population.

Pathophysiology of HIV-associated cardiomyopathy

The pathophysiological mechanisms driving HIV-associated cardiomyopathy are complex and multifactorial, involving direct viral effects on the myocardium, immune system dysregulation, systemic inflammation, ischaemic cardiac conditions, pulmonary arterial hypertension, adverse effects of ART, and psychiatric comorbidities.(16,21,61,62) A prevailing hypothesis suggests that the interplay of lifestyle factors, prolonged ART, and chronic immune activation leads to a pro-inflammatory state that promotes atherogenesis, endothelial dysfunction, and myocardial fibrosis.(52) Persistent immune activation is considered a key contributor to the onset and progression of cardiovascular diseases in PLWH.(14,63,64) Systemic inflammation in this population is known to trigger thrombotic events, endothelial damage, and myocardial fibrosis, which are integral to the development of heart failure.(14)

Importantly, myocardial fibrosis, a critical factor in heart failure pathogenesis, is frequently observed in HIV-infected individuals even in the absence of overt cardiovascular disease.(57,65,66) Additionally, myocardial steatosis, which results from metabolic dysregulation, has been implicated in the onset of diastolic dysfunction,(67) with certain metabolites being identified as potential therapeutic targets for intervention.(68,69) HIV-encoded proteins such as NEF and TAT further exacerbate cardiovascular pathology by impairing endothelial function and facilitating atherosclerosis.(58) These mechanisms underscore the complexity of HIV-associated cardiac dysfunction, highlighting the need for targeted therapeutic strategies to mitigate cardiovascular risk in this population.

Impact of antiretroviral therapy on cardiac failure

The advent of ART has significantly improved survivability of HIV. The pathogenesis of cardiac failure amongst PLWH is multifactorial notwithstanding persistent viral replication and immune activation being key role players. Ntusi, et al. found that ART naïve PLWH had lower left ventricular ejection fraction values when compared to those on ART.(70) ART is crucial for achieving virological suppression and improving CD4 cell count, thereby reducing the direct impact of HIV infection on the immune system. ART generally involves a combination of protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (NRTIs). In South Africa, first line ART is provided in the form of a fixed dose combination tablet (TLD) which includes tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and dolutegravir (DTG).(71) Modern ART has improved cardiovascular risk safety profiles. A meta-analysis found that DTG had no significant effect on the risk of adverse cardiac events.(72) Integrase strand transfer inhibitors (INSTIs) and the CCR5 antagonist maraviroc have shown atheroprotective properties, indicating their potential role in mitigating the development of atherosclerosis.[10,73,74] This is corroborated by a Kenyan study which found that ART does not significantly increase the risk of cardiovascular disease in PLWH.[75] In contrast, certain classes such as NRTIs and PIs have been linked to a higher risk of cardiovascular complications.[76-79] The cardiovascular risks associated with ART are thought to arise from a complex interaction of factors, including persistent systemic inflammation, the development of metabolic syndrome, and oxidative DNA damage.[74] These effects underscore the need for a nuanced approach to managing ART, balancing its benefits in controlling HIV with its potential to elevate cardiovascular risk. This highlights the importance of individualised treatment strategies to optimise both virological outcomes and cardiovascular health in people living with HIV.

Management strategies for cardiac failure in PLWH

The management of cardiac failure in PLWH requires a comprehensive strategy that addresses both HIV viral suppression and the reduction of cardiovascular risk factors.[80-82] Ensuring adherence to ART is critical not only for maintaining virological control but also for mitigating the economic burden of cardiovascular complications in this population.[83] The presence of subclinical changes in cardiac morphology and the unique cardiovascular risks associated with PLWH necessitate a personalised approach to risk assessment and management by healthcare providers.[65,84] Despite the increasing burden of cardiac failure amongst PLWH, general risk assessment models may underestimate the cardiac risk this unique group is exposed to.[85] Features suggestive of cardiac failure in PLWH may be detected by imaging before clinical symptoms develop. Thus, basic and advanced imaging modalities are increasingly being used to understand the pathophysiology of subclinical cardiovascular disease. So far they have proven useful in identifying and risk stratifying patients at risk for myocardial dysfunction. While conventional echocardiography provides invaluable insight into cardiac structure and function, 3D speckle-tracking echocardiography (3DSTE) has proven to be more sensitive in detecting early myocardial dysfunction.[86] 3DSTE is able to detect subclinical biventricular dysfunction in PLWH. 3DSTE identified lower left ventricular global longitudinal strain (GLS) and global area strain (GAS) in PLWH when compared to uninfected controls.[87] Increased left ventricular mass index and diastolic dysfunction are also seen in HIV-associated cardiac dysfunction.[88] In addition, weak negative correlation exists between left ventricular GLS and nadir CD4 count.[87] Cardiac magnetic resonance imaging and spectroscopy (CMR) is useful to establish cardiac structure and function. It is also able to detect the presence of HIV-associated cardiac fibrosis, steatosis, diastolic dysfunction, and subclinical systolic dysfunction.[89,90] Subclinical atherosclerosis is a separate disease entity resulting in HIV-associated cardiovascular disease. PLWH are at an increased risk for developing accelerated atherosclerosis which predisposes to cardiovascular disease.[91,92] There have been great strides in using imaging modalities to detect subclinical atherosclerosis. However, this is beyond the scope of this review.

Systemic immune dysregulation plays a key role in the development of cardiac disease. Certain biomarkers have been associated with cardiac dysfunction in PLWH. HIV infection causes CD4 T cell activation which in turn are recruited to the heart. This is associated with expression of enzymes involved in cardiac calcium regulation. Overexpression of RyR2 and calcium regulatory enzymes induces expression of cardiac foetal genes, MYH6 and MYH7.[93] This results in deterioration of cardiac muscle function. Excessive calcium release in cardiac myocytes is also associated with increased expression of cytokines and chemokines, which portend opportunistic infections.[94] These findings are further supported by the INHALE study which found increased levels of CRP, VCAM-1, TNF alpha, ST2 and GDF-15 in HIV infected children when compared to controls.[95] Furthermore, a 1 unit increase in CRP and GDF-15 was associated with increased odds of cardiac abnormality. N-terminal pro b-type natriuretic peptide (NT-proBNP) levels, offer significant benefits for nuanced risk stratification and targeted therapeutic management of cardiovascular conditions in PLWH.[89,96-97]

Statin therapy is used to lower the risk of cardiovascular disease by reducing LDL cholesterol and hence development of atherosclerosis. In addition, statin therapy also reduces inflammation in PLWH, providing an additional benefit beyond lowering LDL cholesterol.[98,99] A phase 3 randomised control trial demonstrated that taking pitavastatin conferred a lower risk of major adverse cardiovascular events amongst PLWH when compared to placebo.[100] While pharmacological interventions like statins and antithrombotic agents play a crucial role in CVD management, their use must be carefully evaluated to avoid potential drug-drug interactions with ART regimens.[44,101]

Heart transplantation, the ultimate treatment for end-stage heart failure, remains a subject of ongoing investigation in HIV-positive individuals, with its feasibility and outcomes still under review by the medical community.[102,103] This underscores the critical need for further research and the development of tailored clinical protocols to optimise cardiovascular care for PLWH.

CONCLUSION

The management of HIV has undergone transformative advancements, particularly with the development of potent ART, which has significantly extended the life expectancy of PLWH. However, this increased lifespan has introduced complex healthcare challenges, most notably a rising prevalence of cardiovascular diseases (CVD). The intricate interplay between HIV infection, ART, and traditional CVD risk factors necessitates a comprehensive and nuanced approach to managing heart failure and other cardiovascular conditions in this population. The evolving understanding of the pathophysiology of HIV-associated cardiomyopathy characterised by chronic immune activation, myocardial fibrosis, and metabolic disturbances highlights the critical need for continued research and individualised treatment strategies. Advanced imaging modalities show promise in early detection of cardiac failure amongst PLWH. Furthermore the identification of novel biomarkers may assist in developing risk stratification models for myocardial dysfunction.

LIMITATIONS

This scoping review is subject to several limitations. First, the exclusion of non-English language studies may have resulted in the omission of relevant data, particularly from regions where HIV is prevalent, such as sub-Saharan Africa and Latin America. Additionally, the use of Google Translate for some non-English abstracts may introduce translation inaccuracies. Second, the review was restricted to studies published between 2019 - 2023, which may limit insights from earlier research on the topic. The studies included also vary in terms of study design, population size, and geographical distribution, introducing heterogeneity that may affect the generalisability of the findings. Furthermore, the reliance on observational studies for much of the evidence raises concerns about potential bias, including confounding factors that were not accounted for, such as the presence of comorbidities or differences in ART adherence. Finally, there was a paucity of randomised controlled trials (RCTs) specifically examining heart failure in PLWH, limiting the ability to draw strong causal conclusions from the data. These limitations highlight the need for further high-quality, longitudinal research to better understand the relationship between HIV and heart failure across diverse populations and healthcare settings.

Conflict of interest: none declared.

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APPENDIX I: Articles that were included in the scoping review.

Title	Author	Year	Participants	Country of study	Study design	Male (%)	Duration	Age group
Two decade trends in cardiovascular disease outcomes and cardio-vascular risk factors among US veterans living with HIV.[1]	Haji M, et al	2022	50 284	USA	Observational retrospective cohort	96	20 years	Adults
UNAIDS. The path that ends AIDS: UNAIDS Global AIDS Update 2023.[2]	UNAIDS	2023	N/A	N/A	N/A	N/A	N/A	N/A
National trend of heart failure and other cardiovascular diseases in people living with human immunodeficiency virus.[3]	Park DY, et al.	2022	2 483 868	USA	Observational retrospective cohort	65	10 years	Adults
The epidemiology, mechanisms, diagnosis and treatment of cardiovascular disease in adult patients with HIV.[4]	Henning RJ, et al.	2023	N/A	USA	Review article	N/A	N/A	N/A
Heart failure in patients with human immunodeficiency virus infection: Epidemiology, pathophysiology, treatment, and future research.[5]	Remick J, et al.	2014	N/A	USA	Review article	N/A	N/A	Variable
A systematic review exploring the effect of human immunodeficiency virus on cardiac diseases.[6]	Alzubaidee MJ, et al.	2022	12 318 120	USA	Systematic review	N/A	N/A	Adults
Global burden of heart failure: A comprehensive and updated review of epidemiology.[7]	Savarese G, et al.	2023	N/S	Sweden	Systematic review	N/A	N/A	N/A
Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990 - 2017: A systematic analysis for the Global Burden of Disease Study 2017.[8]	James SL, et al.	2018	N/S	195 countries	Systematic review	N/A	27 years	Variable
Cardiovascular risk and events in 17 low-, middle-, and high-income countries.[9]	Yusuf S, et al.	2014	156 424	Bangladesh, India, Pakistan, Zimbabwe, Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Poland, South Africa, Turkey, Canada, Sweden, and the United Arab Emirates	Observational prospective cross sectional	42	4.1	Adults
Adjudicated heart failure in HIV-infected and uninfected men and women.[10]	Feinstein MJ, et al.	2018	8 890	USA	Observational retrospective cohort	82	16 years	Adults
Scoping studies: Advancing the methodology. Implementation science.[11]	Levac D, et al.	2010	N/A	USA	Article	N/A	N/A	N/A
Scoping studies: Towards a methodological framework.[12]	Arksey H, et al.	2005	N/A	N/A	Article	N/A	N/A	N/A
Global burden of atherosclerotic cardiovascular disease in people living with HIV: Systematic review and meta-analysis.[13]	Shah ASV, et al.	2018	793 635	154 countries	Meta-analysis	N/A	25 years	variable
HIV-related myocardial fibrosis: Inflammatory hypothesis and crucial role of immune cells dysregulation.[14]	Teer E, et al.	2022	N/A	N/A	Review article	N/A	N/A	N/A

APPENDIX I: Articles that were included in the scoping review, continued.

Title	Author	Year	Participants	Country of study	Study design	Male (%)	Duration	Age group
Heart health in the age of highly active antiretroviral therapy: A review of HIV cardiomyopathy.[15]	Belkin MN, et al.	2018	N/A	N/A	Review article	N/A	N/A	N/A
Human immunodeficiency virus infection and incident heart failure: A meta-analysis of prospective studies.[16]	Chen Y, et al.	2021	8 848 569	USA, Taiwan, UK, France	Meta-analysis	N/A	1-10	Adults
Human immunodeficiency virus infection and risks of morbidity and death in adults with incident heart failure.[17]	Avula HR, et al.	2021	425 454	USA	Observational cohort	87	16 years	Adults
Elevated N-terminal prohormone of brain natriuretic peptide among persons living with HIV in a South African peri-urban township.[18]	Peterson TE, et al.	2020	224	South Africa	Observational cross sectional		N/A	Adults
Cardiovascular disease among persons living with HIV: New insights into pathogenesis and clinical manifestations in a global context.[19]	M Ntsekhe, et al.	2023	N/A	N/A	Review article		N/A	N/A
High rate of left ventricular hypertrophy on screening echocardiography among adults living with HIV in Malawi.[20]	Hoffman RM, et al.	2022	202	Malawi	Observational cross sectional		N/A	Adults
Cardiac dysfunction among people living with HIV: A systematic review and meta-analysis.[21]	Erqou S, et al.	2019	125 382	India, USA, UK, Iran, Italy, Netherlands, Portugal, Tanzania, Morocco, Germany, Canada, Zimbabwe, Cameroon, Spain, Nigeria, Denmark, Congo, China, Ghana, Rwanda.	Meta-analysis	82	N/A	Adults 47
Risk of death and readmission among individuals with heart failure and HIV: A systematic review and meta-analysis.[22]	Zhou Y, et al.	2024	59 085	China, USA	Systematic review	N/A	N/A	Adults
Heart failure outcomes and associated factors among veterans with human immunodeficiency virus infection.[23]	Erqou S, et al.	2020	39 244	USA	Retrospective cohort	98	19	Adults
Correlate of left ventricular systolic function in children with human immunodeficiency virus infection on combined highly active antiretroviral medications in Aminu Kano Teaching Hospital, Kano State.[24]	Garba NA, et al.	2023	200	Nigeria	Observational cross sectional	49	N/A	Children
Incidence and progression of echocardiographic abnormalities in older children with human immunodeficiency virus and adolescents taking antiretroviral therapy: A prospective cohort study.[25]	Majonga ED, et al.	2019	175	Zimbabwe	Prospective cohort	52	3 years	Children
Age at diagnosis of heart failure in United States veterans with and without HIV infection. Journal of the American Heart Association.[26]	Erqou S, et al.	2021	1 425 897	USA	Retrospective cohort	97	18	Adults

APPENDIX I: Articles that were included in the scoping review, continued.

Title	Author	Year	Participants	Country of study	Study design	Male (%)	Duration	Age group
Echocardiographic assessment of left cardiac structure and function in antiretroviral therapy (ART)-naïve people living with HIV / AIDS.[27]	Hu X, et al.	2023	195	China	Observational cross sectional	84	N/A	Adults
HIV infection is associated with greater left ventricular mass in the multicentre AIDS cohort study. AIDS Research and Human Retroviruses.[28]	Hutchins E, et al.	2019	721	USA	Observational cross sectional	100	N/A	Adults
HIV status, and measures of cardiac stress and fibrosis in Uganda.[29]	Kipke J, et al.	2021	200	Uganda	Observational cross sectional	38	N/A	Adults
Associations between HIV serostatus and cardiac structure and function evaluated by 2-Dimensional echocardiography in the multicentre AIDS cohort study.[30]	Doria d Vasconcellos H, et al.	2021	1 195	USA	Observational cross sectional	100	N/A	Adults
Diastolic dysfunction in patients with human immunodeficiency virus receivng antiretroviral therapy: Results from the CHART Study.[31]	Butler J, et al.	2020	195	USA	Observational cross sectional	70	N/A	Adults
Global longitudinal strain to predict mortality in patients with acute heart failure.[32]	Park JJ, et al.	2018	4172	South Korea	Prospective cohort	53	31,7 months	>18
Cardiac strain is lower among women with HIV in relation to monocyte activation.[33]	Toribio M, et al.	2022	34	USA	Observational cross sectional	0	N/A	Adults
Human immunodeficiency virus infection-associated cardiomyopathy and heart failure.[34]	Papamanoli A, et al.	2022	N/A	USA	Systematic review	N/A	N/A	N/A
Variation in heart failure risk by HIV severity and sex in people with HIV infection.[35]	Lam Jo, et al.	2022	425 437	USA	Observational cross sectional	88	N/A	Adults
Human immunodeficiency virus infection and variation in heart failure risk by age, sex and ethnicity: The HIV HEART Study.[36]	Alan S, et al.	2022	425 454	USA	Observational retrospective cohort	87	16	Adults
Human immunodeficiency virus increases the risk of incident heart failure.[37]	Yen Y-F, et al.	2019	120 765	Taiwan	Observational prospective cohort	N/A	5,85	Adults
HIV infection and risk of heart failure: A meta-analysis and systematic review.[38]	Li X, et al.	2022	303 734	USA, Taiwan	Meta-analysis	N/A	6-17	Adults
Trends of age-related non-communicable diseases in people living with HIV and comparison with uninfected controls: A nationwide population-based study in South Korea.[39]	Kim JH, et al.	2021	296 182	South Korea	Observational cross sectional	91	12	Adults
Incidence of cardiometabolic diseases in people with and without human immunodeficiency virus in the United Kingdom: A population-based matched cohort study.[40]	Gooden TE, et al.	2021	44 954	UK	Observational cross sectional	66	20	Adults
Characteristics, prevention, and management of cardiovascular disease in people living with HIV: A scientific statement from the American Heart Association.[41]	Feinstein MJ, et al	2019	N/A	USA	Review article	N/A	N/A	N/A
Coronary artery disease in patients with human immunodeficiency virus infection.[42]	Mondal P, et al.	2021	N/A	USA	Review article	N/A	N/A	N/A

APPENDIX I: Articles that were included in the scoping review, continued.

Title	Author	Year	Participants	Country of study	Study design	Male (%)	Duration	Age group
Clinical profile, anatomical features and long-term outcome of acute coronary syndromes in human immunodeficiency virus-infected patients.[43]	Postigo A, et al.	2020	92	Spain	Observational retrospective cohort	92	18	Adults
Conceptualising the risks of coronary heart disease and heart failure among people aging with HIV: Sex-specific considerations.[44]	Abelman RA, et al.	2019	N/A	USA	Review article	N/A	N/A	N/A
Cardiac adiposity as a modulator of cardiovascular disease in HIV.[45]	Bonou M, et al.	2021	N/A	Greece	Review article	N/A	N/A	N/A
Myocardial steatosis among antiretroviral therapy–treated people With human immunodeficiency virus participating in the REPRIEVE trial.[46]	Neilan TG, et al.	2020	82	South Africa, USA	Randomised control trial	88	1,5	Adults
Association of concurrent changes in metabolic health and weight on cardiovascular disease risk: A nationally representative cohort study.[47]	Bae YS, et al.	2019	205 394	South Korea	Prospective cohort	59	9	Adults
Association between weight gain and the incidence of cardiometabolic conditions among people living with HIV-1 at high risk of weight gain initiated on antiretroviral therapy.[48]	McComsey GA, et al.	2022	1 252	USA	Retrospective cohort	41	2	Adults
Associations between HIV viremia during antiretroviral therapy and cardiovascular disease.[49]	Elvstam O, et al.	2022	6 562	Sweden	Prospective cohort	N/A	21	>15
Risk factors for the development of severe chronic heart failure in patients infected with human immunodeficiency virus.[50]	Goryacheva OG, et al.	2021	8 848 569	USA, Taiwan, UK, France	Meta-analysis	N/A	1-10	Adults
Heart failure and adverse heart failure outcomes among persons living with HIV in a US tertiary medical centre.[51]	Alvi RM, et al.	2019	2 308	USA	Prospective cohort	54	2 years	Adults
Heart failure with preserved ejection fraction in women living with HIV: Another inflammatory comorbidity?[52]	Moayedi Y, et al.	2019	N/A	Canada	Editorial	N/A	N/A	N/A
Sex- and poverty-specific patterns in cardiovascular disease mortality associated with human immunodeficiency virus, New York City, 2007 – 2017.[53]	Hanna DB, et al.	2020	147 915	USA	Retrospective cohort	73	11	>13
Myocardial fibrosis among antiretroviral therapy-treated persons with human immunodeficiency virus in South Africa.[54]	Shuldiner SR, et al.	2020	229	South Africa	Case-control	35	N/A	>18
HIV infection and pathology of the cardiovascular system. Cardiovascular therapy and prevention.[55]	Shekhovtsova TA, et al.	2023	N/A	Russia	Review article	N/A	N/A	N/A
Association of syndemic unhealthy alcohol use, smoking, and depressive symptoms on incident cardiovascular disease among veterans with and without HIV-infection.[56]	Chichetto NE, et al.	2021	5 621	USA	Prospective cohort	94	12	>18
HIV and drug use: A tale of synergy in pulmonary vascular disease development. Comprehensive physiology.[57]	Cook CM, et al.	2023	N/A	USA	Review article	N/A	N/A	N/A

APPENDIX I: Articles that were included in the scoping review, continued.

Title	Author	Year	Participants	Country of study	Study design	Male (%)	Duration	Age group
Etiology and pathophysiology of heart failure in people with HIV.[58]	Choi H, et al.	2021	N/A	USA	Review article	N/A	N/A	N/A
Mechanisms of cardiovascular disease in the setting of HIV infection.[59]	Hsue Py.	2019	N/A	USA	Review article	N/A	N/A	N/A
HIV and cardiovascular diseases risk: Exploring the interplay between T-cell activation, coagulation, monocyte subsets, and lipid subclass alterations.[60]	Teer E, et al.	2019	80	South Africa	Observational cross sectional	35	N/A	>18
The importance of inflammation in the formation of chronic heart failure in patients infected with human immunodeficiency virus.[61]	Koziolova NA, et al.	2022	100	Russia	Observational cross sectional	60	N/A	>18
Myocardial fibrosis and inflammation by CMR predict cardiovascular outcome in people living with HIV.[62]	De Leuw P, et al.	2021	156	Germany	Prospective cohort	62	19 months	>18
Immune dysregulation in myocardial fibrosis, steatosis, and heart failure: Current insights from HIV and the general population.[63]	Sinha A, et al.	2021	N/A	USA	Review article	N/A	N/A	N/A
Heart failure among people with HIV: Evolving risks, mechanisms, and preventive considerations. [64]	Toribio M, et al.	2019	N/A	USA	Review article	N/A	N/A	N/A
Metabolomic profiling of cardiac fibrosis and steatosis in women with or at risk for HIV.[65]	Shitole SG, et al.	2023	153	USA	Observational cross sectional	0	N/A	N/A
Transmethylamine-N-Oxide is associated with diffuse cardiac fibrosis in people living with HIV.[66]	Colaco NA, et al.	2021	195	USA	Retrospective cohort	71	N/A	>18
Cardiomyopathy and heart failure in patients with HIV infection.[67]	Savvoulidis P, et al.	2019	N/A	USA	Review article	N/A	N/A	N/A
Cardiovascular toxicity of contemporary antiretroviral therapy.[68]	Vos AG, et al.	2021	N/A	South Africa, Netherlands	Review article	N/A	N/A	N/A
HOPX plays a critical role in antiretroviral drugs induced epigenetic modification and cardiac hypertrophy.[69]	Kashyap S, et al.	2021	N/A	USA	Experimental interventional	N/A	N/A	N/A
Incidence of cardiometabolic outcomes among people living with HIV-1 initiated on integrase strand transfer inhibitor versus non-integrase strand transfer inhibitor antiretroviral therapies: A retrospective analysis of insurance claims in the United States.[70]	Rebeiro PF, et al.	2023	14 076	USA	Retrospective cohort	76	2	>18
HIV infection and coronary heart disease: Mechanisms and management.[71]	Hsue PY, et al.	2019	N/A	USA	Review article	N/A	N/A	N/A
Epidemiology, pathophysiology, and prevention of heart failure in people with HIV.[72]	Sinha A, et al.	2020	N/A	USA	Review article	N/A	N/A	N/A
Management of cardiovascular diseases in HIV / AIDS patients.[73]	Ashwitha SK, et al.	2021	N/A	UK	Review article	N/A	N/A	N/A
Prevention of heart failure, tachyarrhythmias and sudden cardiac death in HIV. Current opinion in HIV and AIDS.[74]	Wu KC, et al.	2022	N/A	USA	Review article	N/A	N/A	N/A

APPENDIX I: Articles that were included in the scoping review, continued.

Title	Author	Year	Participants	Country of study	Study design	Male (%)	Duration	Age group
Factors associated with incidence of stroke and heart failure among people living with HIV in Ghana: Evaluating Vascular Event Risk while on Long-Term Antiretroviral Suppressive Therapy (EVERLAST) Study.(75)	Sarfo FS, et al.	2021	255	Ghana	Prospective cohort	17	1	>18
Association of adherence to antiretroviral therapy with economic burden of cardiovascular disease in HIV-infected population.(76)	Liao C-T, et al.	2020	18 071	Taiwan	Retrospective cohort	N/A	11	>18
Getting to the heart of the matter: The need for tailored cardiovascular prevention strategies in patients with HIV.(77)	Fillip I.	2022	N/A	USA	Review article	N/A	N/A	N/A
Myocardial fibrosis and inflammation by CMR predict cardiovascular outcome in people living with HIV.(78)	De Leuw P, et al.	2021	156	Germany	Prospective cohort	62	19 months	>18
Assessment of biventricular function by 3-Dimensional speckle-tracking echocardiography in adolescents and young adults with human immunodeficiency virus infection: A pilot study.(79)	Capototso L, et al.	2019	63	Italy	Retrospective cohort	N/A	N/A	N/A
Imaging modalities for cardiovascular phenotyping in asymptomatic people living with HIV.(80)	Bonou M, et al.	2021	N/A	Greece	Review article	N/A	N/A	N/A
The role of cardiac imaging in the management of non-ischaemic cardiovascular diseases in human immunodeficiency virus infection.(81)	Aljizeeri A, et al.	2020	N/A	Saudi Arabia, Canada, Australia, USA	Review article	N/A	N/A	N/A
Amino-terminal Pro-B-Type natriuretic peptide among patients living with both human immunodeficiency virus and heart failure.(82)	Alvi RM, et al.	2019	2 578	USA	Retrospective cohort	50	1	>18
Cardiovascular disease and risk assessment in people living with HIV: Current practices and novel perspectives.(83)	Fragkou PC, et al.	2023	N/A	Greece	Review article	N/A	N/A	N/A
Guidance for timely and appropriate referral of patients with advanced heart failure: A scientific statement from the American Heart Association.(84)	Morris AA, et al.	2021	N/A	USA	Review article	N/A	N/A	N/A
Heart transplantation survival outcomes of HIV positive and negative recipients.(85)	Doberne JW, et al.	2021	29 923	USA	Retrospective cohort	71	14	>18
Heart transplantation in a well-controlled human immunodeficiency virus infected patient: The first case of Taiwan.(86)	Chen CH, et al.	2022	1	Taiwan	Case report	100	N/A	>18
Advanced heart failure therapies in patients with stable HIV infection.(87)	Brozzi NA, et al.	2020	1	USA	Case report	100	N/A	>18

Viruses identified in endomyocardial biopsy samples in idiopathic dilated cardiomyopathy patients in central South Africa

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ABSTRACT

Background: Heart failure and cardiomyopathy are problematic in South Africa. Viruses are important causes of myocarditis and cardiomyopathy. This study aimed to determine the distribution of viruses in endomyocardial heart biopsy samples in patients with dilated cardiomyopathy.

Methods: Endomyocardial biopsies (EMB) were analysed using histology, immunohistochemical staining, and polymerase chain reaction. The level of fibrosis, presence and type of cellular infiltration, and the prevalence of viral genomes with their replication activity were determined.

Results: Viral genomes were found in 73.7% of patients, with parvovirus B19 (B19V) present in 96.4%. No Coxsackievirus was identified, and 2 patients presented with transcriptional intermediates, which indicated active B19V viral replication. Most patients (71.4%) presented with single infections, but some (28.6%) with co-infections. Three patients presented with acute myocardial inflammation and moderate / severe increased lymphocytic infiltration.

Conclusions: This study found B19V predominant and present in almost all virus-positive EMB samples. Our results support the possible virus etiological shift towards B19V. These findings underscore the need to further investigate the pathophysiological role of B19V in the development and progression of DCM.

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INTRODUCTION

Cardiovascular disease remains a leading cause of death. In 2021, it was estimated that 20.5 million (31.8%) of worldwide deaths were due to circulatory and cardiovascular diseases.[(1)] Cardiomyopathies are more frequently observed in poorer societies where pestilence and famine predominate.[(2)] This is exacerbated by nutritional deficiencies and chronic persistent viral infections that render individuals more susceptible.[(3)] Dilated cardiomyopathy (DCM) is defined as contractile dysfunction associated with left ventricular dilation in the absence of coronary artery disease and abnormal loading conditions.[(4,5)] Familial and idiopathic cardiomyopathies and inflammatory myocarditis[(6)] are the most prevalent causes of DCM and are a major contributor to heart failure globally.[(7,8)]

Africa is home to some of the poorest countries and communities in the world,[(9)] and non-communicable diseases are becoming more prominent in Africa compared to the 1990s.[(10)] Cardiovascular disease is a significant health burden in Africa and accounts for 38.3% of non-communicable disease deaths.[(10)] The "Hearts of Soweto" study showed that dilated cardiomyopathy was the most common cause of heart failure in South Africa, responsible for 35% of heart failure cases.[(11)] In the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF), dilated cardiomyopathy was the second most common cause of heart failure in almost a third of patients.[(12)] More recently, the African Cardiomyopathy and Myocarditis Registry Programme (IMHOTEP) reported the largest cardiomyopathy series in South Africa. Dilated cardiomyopathies were the most common cardiomyopathy observed, accounting for 72% of all cases.[(13)]

Determining the etiology of cardiomyopathy is critical as it allows focused and specific treatment.[14,15] Infectious causes such as viruses can lead to myocarditis, which may progress to inflammatory dilated cardiomyopathy.[8,16] The infection may cause chronic or autoinflammatory reactions in the body.[17,18] Patient outcomes depend on the virulence of the virus and the response of the host immune system, which could result in diseases ranging from subclinical to severe heart failure.[19] Performing endomyocardial biopsies (EMB) for suspected inflammatory cardiomyopathies remains the gold standard according to the European Society of Cardiology (ESC) 2023 guidelines.[20]

Enteroviruses have traditionally been regarded as the most common cause of myocarditis, especially until the 1990s.[21-23] In recent years, however, human parvovirus B19 (B19V) has become more prevalent in high-income countries.[24-26] The most frequently detected viruses in biopsies using polymerase chain reaction (PCR) are B19V,[27-31] human herpes virus 6 (HHV-6),[28,30] enterovirus species,[28,30] Epstein-Barr virus (EBV) [28, 30] and adenovirus (ADV).[28,30,32]

The number of studies conducted in sub-Saharan Africa on cardiomyopathies and myocarditis using EMB is limited. The first study that analysed endomyocardial biopsies with molecular testing was conducted in Cape Town in 2013 in patients with and without human immunodeficiency virus (HIV). In the HIV-positive cohort, they reported mostly EBV (64%), herpes simplex virus (HSV), B19V, and cytomegalovirus. In patients without HIV but with idiopathic dilated cardiomyopathy, the majority of patients had CVB3 (56%), followed by EBV, HSV, ADV, and B19V.[33] Almost a decade later, another local study was conducted on 102 myocarditis patients, where viral genomic material was detected in 60 (59%) study subjects. The most frequently detected virus was B19V, which was detected in 76.67% of the positive patients, followed by EBV, HHV-6, and human bocavirus. Co-infections were also identified with 3 double co-infections of B19V / EBV and 1 triple co-infection of B19V / EBV / HHV6.[34] The detection of B19V transcriptional activity in the heart muscle is important in establishing the clinical significance of infection.[35] To distinguish between latent and active parvovirus B19V infection, the detection of novel biomarkers such as ribonucleic acid (RNA) replication intermediates such as nonstructural protein 1 (NS1) and capsid protein (VP1) are used.[36] Active viral replication has been shown to lead to altered cardiac gene expression, cardiac damage, dysfunction, and increased inflammation compared to a control group with latent B19V infection.[37] In patients with acute disease, interferon beta (IFN-ß) can be administered, which has been shown to be very effective in patients with acute dilated cardiomyopathy due to B19V.[15,38,39]

Differences in South African demographics and socioeconomics could also indicate that the viruses frequently associated with cardiomyopathy in South Africa differ from those in high-income countries. South African cardiotropic infections have to be better understood and characterised to determine the true underlying causes of idiopathic dilated cardiomyopathy in sub–Saharan Africa.

The aim of this study was to determine the distribution of viruses in endomyocardial heart biopsy samples in patients with dilated cardiomyopathy.

METHODS

This study was part of a main study that prospectively recruited patients that presented to Universitas Academic Hospital in Bloemfontein, South Africa, between January 2018 - December 2022. The main study recruited HIV-negative patients (≥18 years old) with idiopathic dilated cardiomyopathy, confirmed by the diagnostic criteria as per the ESC guidelines[20] for dilated cardiomyopathy. Only patients in whom endomyocardial biopsies were performed were included in this sub-study. The patients were divided into 2 groups according to whether viruses were detected or not, namely virus-positive and virus-negative.

DATA COLLECTION

Demographic data pertaining to age, ethnicity, and sex were collected. Clinical data (including LVEF%, NYHA classification) and laboratory data (viral PCR and histological and immunohistochemical analysis) were also recorded.

ENDOMYOCARDIAL BIOPSY

Jugular or femoral access was used to perform all the right ventricle septum biopsies using a Cordis (High Tech Medical, Johannesburg, South Africa) 5.5 or 5.4 French Maslanka (Maslanka Chirurgische Instrumente, Tuttlingen, Germany) bioptomes that were guided through 6 or 7 French flexor sheaths under real-time fluoroscopic and transthoracic echocardiogram (TTE) guidance.

A total of 8 specimens were taken from different areas on the septum, as inflammation could have been localised to one or more locations. Three of the specimens were fixed in a 4% buffered formalin solution for histological and immunohistochemical analysis. The remaining samples were fixed in

RNALater® solution (Thermo Fisher Scientific, Waltham, Massachusetts, United States) to ensure the preservation of deoxyribonucleic acid (DNA) and RNA for downstream analysis. The EMB samples were analysed by a specialised cardio-pathology laboratory in Germany, namely the Institut Kardiale Diagnostik und Therapie (IKDT).

VIROLOGICAL ANALYSIS

The total DNA was extracted from patient EMB samples using Gentra Puregene kits (Qiagen, Hilden, Germany) according to standard operating procedures. Total RNA was extracted using QIAzol reagent (Qiagen, Hilden, Germany) treatment with DNAse (Promega, Walldorf, Germany). cDNA synthesis was performed using random hexamer primers and the High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, Waltham, Massachusetts, United States). Nested-PCR and quantitative reverse transcriptase (qRT)-PCR were used for the detection of the cardiotropic viruses, namely enteroviruses (Coxsackievirus B3 and echovirus) EBV, B19V, HHV6, and adenoviruses. To determine whether viruses such as B19V were actively replicating their transcriptional transcriptional activity was determined by testing for transcriptional intermediates such as messenger RNA (mRNA). Only viruses that were not latent would have these transcriptional intermediates present.[40]

HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSIS

Histological examination was performed on formalin-fixed, paraffin-embedded specimens. Several stains were used, such as Azan, Elastika-van-Gieson (EvG), periodic acid-Schiff (PAS), Hematoxylin and Eosin (H&E), and Kryo H&E according to the standard procedures. Immunohistochemical staining was performed on RNAater-fixed cryo-embedded EMBs to allow for the detection and quantification of inflammatory cells. Myocardial inflammation was diagnosed using the European Society of Cardiology (ESC) statement[24] by the detection of ≥14 leukocytes per mm², with the presence of ≥7 clusters of differentiation (CD)3+ T-lymphocytes per mm². In addition, ≥14 lymphocyte function-associated antigen (LFA)-1+ lymphocytes per mm², ≥40 macrophage (MAC)-1+ macrophages per mm², ≥40 CD45R0+ memory T cells per mm², and ≥2.9 perforin+ cytotoxic cells per mm² were also considered pathologic. Endothelial activation was measured by the expression of intercellular adhesion molecule 1 [(ICAM)-1, threshold ≥2 area%)]. The immunohistochemical and histological slides were evaluated with a Leica DMR light transmission microscope and quantified by digital image analysis as described before.[41]

ETHICS AND STATISTICS

Continuous variables were described using the median and interquartile range, and counts and percentages were used to describe categories. The comparison between categories of virus positivity and participants' characteristics was performed using the Mann-Whitney U-test for continuous variables and the Fisher exact test for categories. All statistical tests were 2-tailed, and the type-I error rate was set to 5%.

The SAS software version 9.4 was used to perform the statistical analysis.

The main study and this sub-study were approved by the Health Science Research Ethics Committee of the University of the Free State and the Free State Department of Health with ethical approval numbers (UFS-HSD2017/0320-0008) and (UFS-HSD2017/1398-0002), respectively. Only patients with signed informed consent documents were included.

RESULTS

A total of 38 patients were included in the study. Details and demographics can be viewed in Table I. Patients were fairly young, with a median age of 42 years, and male and female patients were evenly distributed. Almost two-thirds of patients were African (58%), followed by Caucasian (24%) and mixed race (19%). Viral genomic material was detected in more than two-thirds of the study population (virus-positive group). Patients in the virus-negative group were 3 years younger than those in the virus-positive group. The virus-positive group of patients (n=28) presented with more patients who had moderate to severe heart failure (NYHA 3, 4) than those who tested negative for viral genomes. A lower LVEF% was observed in the virus-positive group of patients than in the virus-negative group (p=0.1352).

A breakdown of the positive virological findings for the 28 patients can be viewed in Table II. B19V was found in almost all virus-positive biopsy samples (n=27, 96.4%), followed by HHV-6 and EBV. More than two-thirds of the virus-positive patients had only 1 virus present, whereas 28.3% had co-infections of several viruses. Co-infections consisted of B19V / HHV6 and B19V / EBV. Actively replicating, B19V mRNA was found in 2 patients.

Histological analysis of the EMB indicated that most patients (70%) did not show signs of fibrosis. Mild fibrosis was seen in 19%, severe fibrosis in 8%, and lipomatosis in 3% of patients (Figure 1).

TABLE I: Baseline characteristics.

Demographics	Total n=38	Virus-positive + n=28	Virus-negative – n=10	p-value
Age (year) (median)	42	42.5	39.5	0.3148
Q1;Q3	28, 58	34.5, 60.5	20, 55	
Sex n (%)				
Male	18 (47.4)	15 (53.6)	3 (30)	0.2778
Female	20 (52.6)	13 (46.4)	7 (70)	
Ethnicity n (%)				
Caucasian	9 (23.7)	6 (21.4)	3 (30)	0.4694
African	22 (57.9)	15 (53.6)	7 (70)	0.6731
Mixed	7 (18.4)	7 (25)	0	0.1564
Clinical				
LVEF % (median)	23	22	35.5	0.1352
Q1;Q3	18, 35	17.5, 32	20, 39	
NYHA n (%)				
Class 1	6 (15.8)	2 (7.1)	4 (40)	0.0314*
Class 2	12 (31.6)	10 (35.7)	2 (20)	0.4528
Class 3, 4	20 (52.6)	16 (57.1)	4 (40)	0.4681

**statistically significant, n: number, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, Q1: first quartile, Q3: third quartile.*

TABLE II: Description of the viral genomes detected in endomyocardial tissue.

Viral genomes detected in patients n=28	n (%)
Parvovirus B19 (B19V)	27 (96.4)
Human herpes virus 6 (HHV-6)	6 (21.4)
Epstein-Barr virus (EBV)	3 (10.7)
Adenovirus	0
Enterovirus	0
Replicating (B19V)	2 (7.1)
Single infection	20 (71.4)
Co-infection	8 (28.6)
B19V / HHV-6	5 (62.5)
B19V / EBV	3 (37.5)

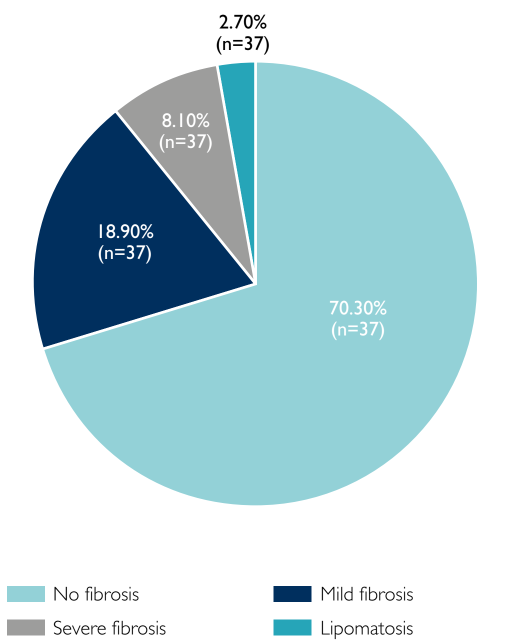

FIGURE 1: Histological analysis of endomyocardial biopsy sample showing the level of fibrosis.

The grade of fibrosis was confirmed with H&E and Kryo H&E histology and presented in Figure 2. No fibrosis was observed, as indicated by the normal endocardium and the normal size and arrangement of cardiomyocytes. Mild fibrosis showed partial fragmentation of myocytes in the interstitial space. Severe fibrosis was indicative of scars and missing cardiomyocytes. Lipomatosis showed fat cells of varying diameters near small vessels.

More than two-thirds of patients (n=25, 71%) had no signs of acute myocardial inflammation, as presented in Figure 3. Increased infiltration was not observed for CD3, CD11b, or CD45 positive lymphocytes. Minor CD11b / Mac-1 cell infiltration was seen but was below the pathological limit.

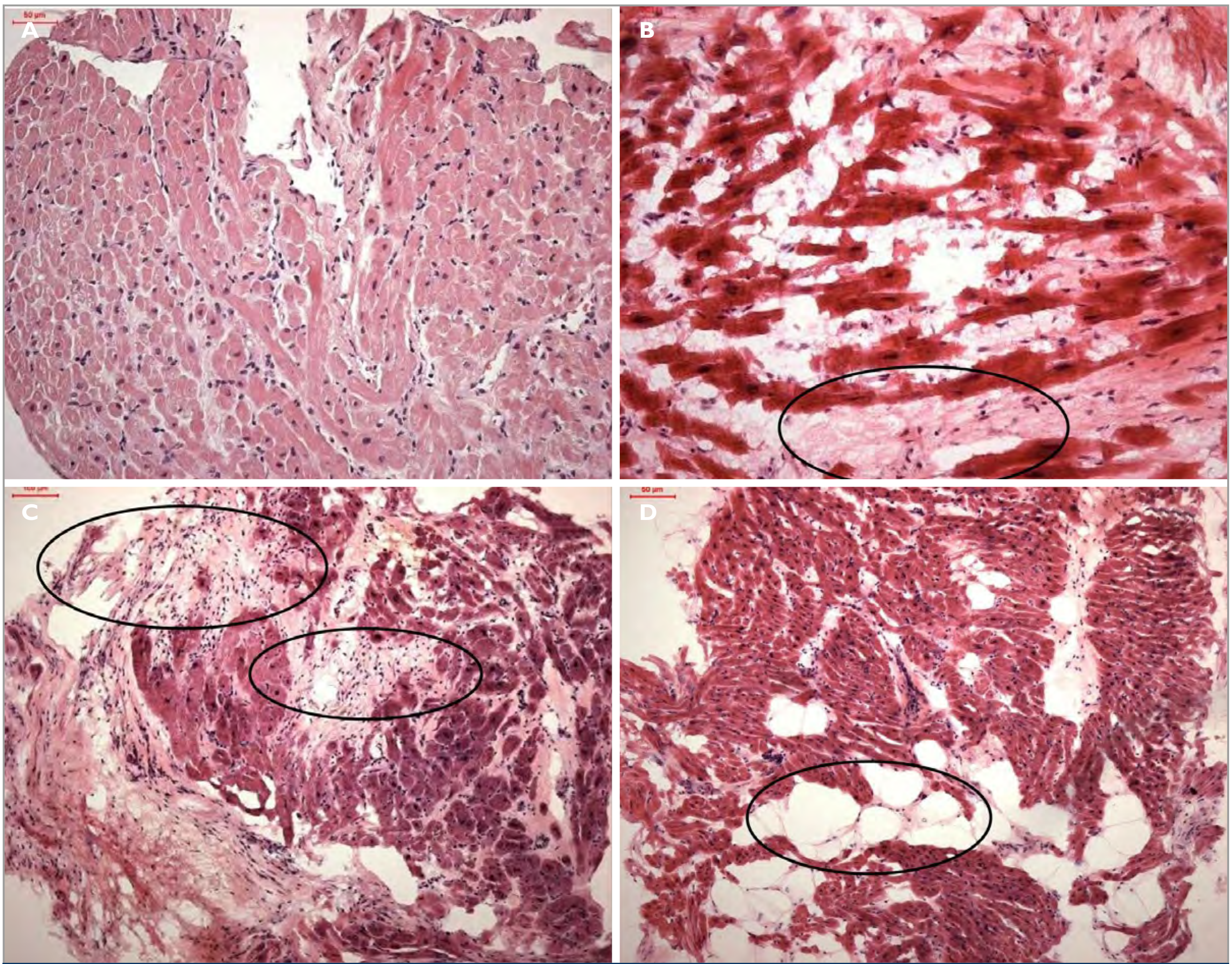

FIGURE 2: Histological presentation of fibrosis.
A. Normal endocardium with no fibrosis (H&E), B. Mild fibrosis (Kryo-H&E), C. Severe fibrosis with scarring (Kryo-H&E), D. Lipomatosis (L).

Mildly increased lymphocytic infiltration was observed in 20% (n=7) of patients and is presented in Figure 4. Mild increases of CD3, CD11a/LFA-1 lymphocytic infiltrates, and enhanced endothelial expression of ICAM-1 were observed.

Only 3 patients (9%) presented with acute myocardial inflammation and moderate / severe increased lymphocytic infiltration (Figure 5). This is indicated by the H&E stain in Figure 5A and the profound infiltration of CD3, CD11a/LFA-1, CD54/ICAM-1, and CD54 positive lymphocytes in Figure 5B - E.

DISCUSSION

Viral infection could be a contributing factor to cardiovascular disease and cardiomyopathy in central South Africa. Results of this study indicated the presence of viral genomes in the myocardium of the vast majority of patients (73.6%). The most prevalent virus was B19V, which was present in 96.4% of positive biopsy samples, with 2 being transcriptionally active, followed by HHV-6 and EBV; no enteroviruses were detected.

Almost two-thirds of the patients in our study population were African, corresponding to our region's demographic profile. The study population was relatively young at 42 years compared to the "Hearts of Soweto" study, which reported a 53-year-old mean age, and the Bloemfontein group, which reported a 51.8-year-old mean age.[11,42] Our results concur with the recent largest cardiomyopathy study (IMHOTEP) conducted in South Africa and published in 2024, which reported an overall median age of 35 years.[13] We found our LVEF% to be quite low, similar to the IMHOTEP study that reported an LVEF of 26%. Another local study in 2024 reported an LVEF of <30%.[13,43] There was a difference between the virus-positive group, which had an LVEF% of 13.5% lower than the virus-negative group, although not statistically significant. More patients in the virus-positive

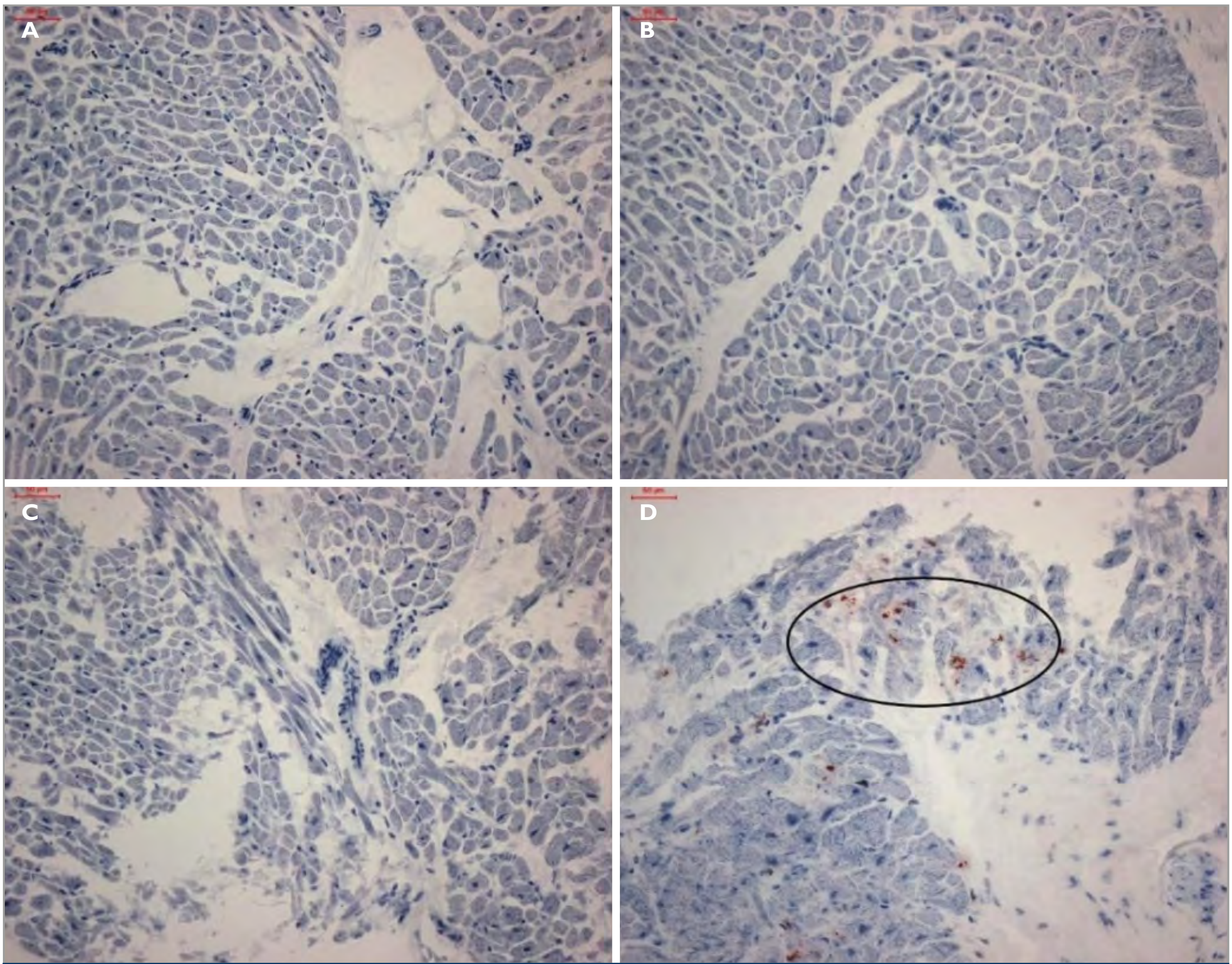

FIGURE 3: No myocardial inflammation.
A. No CD3 positive lymphocytes, B. CD11b positive cells, C. CD45RO, D. CD11b/Mac-1 cells.

group presented with moderate to severe heart failure (NYHA 3/4), although this difference was also not significant. Overall, patients in our study presented in a late stage of the disease, which is not uncommon in our public sector.[13,43]

Although we found a high positivity of viral genomes in our study population, with BV19 being the most prevalent, its significance still needs to be determined. Even though B19V viral genomes are commonly detected in endomyocardial biopsies of patients with heart failure, the clinical relevance is difficult to determine since viral genomes are detected in both symptomatic and asymptomatic patients.[30,44,45] Only 2 of the viral-positive patients had actively replicating B19V, confirmed by the detection of B19V mRNA. A German study in 2021 evaluated the clinical outcomes in a large cohort of 871 patients with positive parvovirus B19 DNA in their EMB samples. Patients were compared with and without parvovirus mRNA replicative intermediates, and those with replicating viruses had worse clinical outcomes. It demonstrated for the first time that transcriptionally active parvovirus B19 was pathologically and clinically relevant and not something that should just be dismissed.[40] It should be noted that there is still a debate on the significance of the contribution of B19V to DCM or whether it is only an innocent bystander and it has to be further investigated. Several authors consider B19V to be an innocent bystander.[35,45] Further studies would be required to determine the significance of active viral infection and its contribution to cardiovascular disease in our local populations.

Limited studies have been performed in sub-Saharan Africa that analysed EMB samples. In 2013, Shaboodien conducted the first study in South Africa on EMB samples that were tested for viral genomes. In contrast to our results, they showed that enteroviruses were important and present in 56% of patients with idiopathic dilated cardiomyopathy, and limited B19V was detected.[33] Several global studies have found that enteroviruses

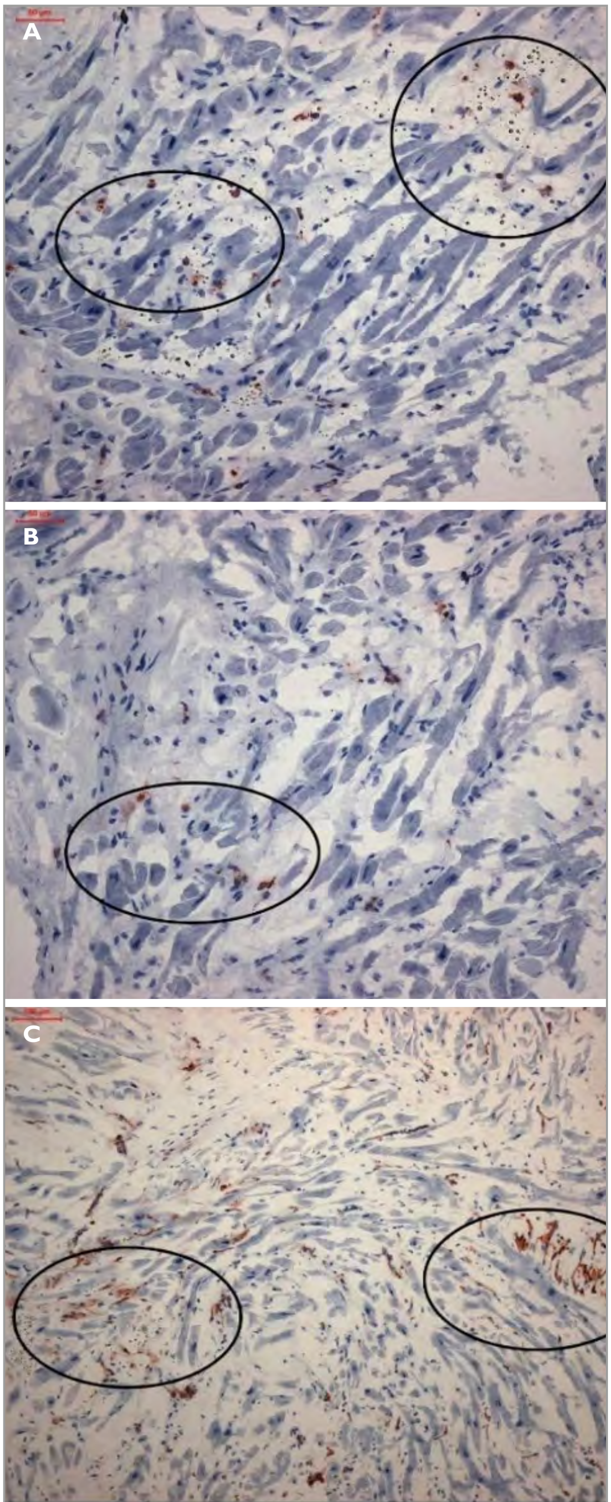

FIGURE 4 : Mild increased infiltration.
A. CD3 positive cells marked brown, B. CD11a/LFA-1 marked brown, C. Enhanced endothelial expression of ICAM-1.

were the most common virus associated with cardiomyopathy / myocarditis until the 1990s.(21-23) However, this seems to have started to shift, with B19V becoming the most frequently associated cardiotropic virus.(18,24-26,28-31) In 2022, a group in Stellenbosch, South Africa, evaluated myocarditis patients who were tested for cardiotropic viruses. Their findings support our results, as no enteroviruses were found. Most of their patients also had B19V, followed by HHV-6 and EBV.(34) Our findings and the findings of Hassan, et al. concur with the global trend of a declining involvement of enteroviruses and the overwhelming presence of B19V.(25,28-30,34)

Immunohistochemical analysis, which allows the differentiation and quantification of infiltrative inflammatory cells, remains an invaluable tool for identifying cardiac inflammation.(20,27) Our study found that only a third of our patients had mild to severely increased infiltrates and inflammation. This, combined with the limited number of patients with actively replicating viruses, meant that few patients in our cohort had acute cardiac inflammation and disease. This supports the concept of late presentation, which is seen in our clinical units and other similar ones.

Understanding and finding the cause of heart disease is important for improved scientific management. In South Africa, the proportion of dilated cardiomyopathy that remains idiopathic is very large.(11,12) Endomyocardial biopsy plays a role in allowing further investigation and testing. In South Africa, EMB is not routinely performed due to cost implications, and the role of EMB in advanced disease needs to be defined. This leads to a high percentage of dilated cardiomyopathy patients who keep the diagnosis of "idiopathic cardiomyopathy". Patients are only being managed and treated for their symptoms and not the underlying cause of the disease. It is important to keep investigating the use of non-invasive testing to filter through patients. Newer, less invasive diagnostic techniques have to be considered to guide which patients would require an EMB. This includes cardiac magnetic resonance imaging (CMR), taking blood samples, and testing for elevated levels of microribonucleic acid (miRNA) such as miR-133a and miR-155 in blood, which have been shown to have a positive correlation with viral myocarditis and inflammatory cell counts.(27,46) These could be explored further in the future, but currently, limited hospitals in our setting offer CMR services. The viability and usefulness of miRNA testing are promising, but the assays for the analysis of miRNAs would have to be developed, optimised, and standardised before they can be used routinely for patient screening.

LIMITATIONS

Our sample size was limited. It should be noted that the main study included patients with dilated cardiomyopathy based on the ESC criteria; the emphasis of this sub-study was on the histology and virology of EMB samples, and therefore, clinical correlations were not investigated. Cardiac MRIs were unavail-

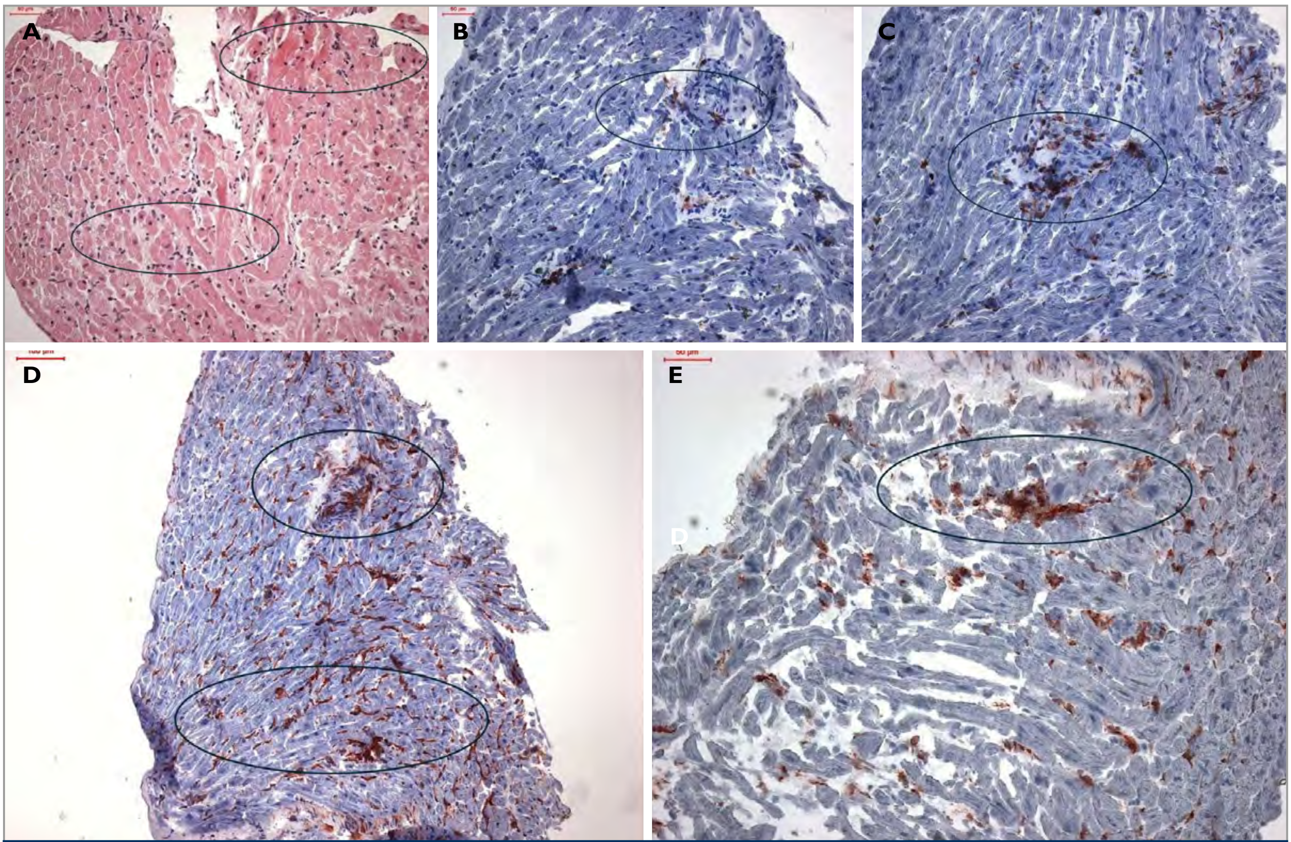

FIGURE 5: Moderate to severe increased infiltrates.
A. H&E stain, B. CD3, C. CD11a/LFA-1, D. CD54/ICAM-1, E. CD54.

able in our public sector facility at the time of the study. Minimal acute infections were detected - this can be ascribed to patients presenting late once advanced symptoms have already appeared. Only the viruses most commonly found were tested for. However, it still remains to be proven whether B19V is an innocent bystander or plays a role in the underlying pathophysiology. Further studies are warranted. It should be emphasised that the role of EMB in advanced disease should be investigated, especially in resource-limited environments.

RECOMMENDATIONS

Further studies should be undertaken to investigate a larger sample size. HIV-positive patients should also be considered to investigate the effect of HIV on myocardial disease and the viruses associated with the EMB in central South Africa. Techniques such as next-generation sequencing could be invaluable in enabling the non-targeted detection of viruses that might be important in the developing world.

CONCLUSION

Our findings indicate that B19V is the predominant virus detected in virus-positive endomyocardial biopsy (EMB) samples (96.4%), with no enteroviruses identified, suggesting a potential etiological shift toward B19V in the context of dilated cardiomyopathy (DCM). These findings underscore the need to further investigate the pathophysiological role of B19V in the development and progression of DCM. Of particular concern is the observation that severe cardiac inflammation was present in only a small subset of patients, indicating that many patients only presented at an advanced stage of the disease.

SUPPLEMTARY DATA

A supplementary table with the raw data endomyocardial biopsy analysis is provided in Supplementary Table 1 to provide an overview of the biopsy results per patient.

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Conflict of interest: none declared.

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SUPPLEMENTARY TABLE I: Raw data endomyocardial biopsy analysis.

Patient Nr	Histology	Cardiomyocytes	Immunohistological	Diagnosis as per pathology report	Virus Detection	Replicating virus	Copies / µg DNA	Virus type
1	Not done - sample issue	Not done	Not done	No diagnosis given	+	N	1 669 copies	B19V
2	Mild fibrosis	Hypertrophied	No increased infiltrates	DCM	+	N	31 copies	B19V
3	Normal, without fibrosis	Normal	No increased infiltrates	DCM	+	N	4 copies B19V, 6 copies HHV6	HHV6, B19V
4	Normal, without fibrosis	Mild atrophied	Mild increased infiltrates	Inflammatory cardiomyopathy	+	N	54 copies	B19V
5	Endocardium thickened and fibrotic	Normal	No increased infiltrates	DCM	+	N	881 copies	B19V
6	Mild perivascular, interstitial fibrosis	Mild atrophied	Increased lymphocytic infiltrates, enhanced expression of ICAM- 1	Borderline myocarditis	+	N	304 copies	B19V
7	Normal, without fibrosis	Mild atrophied	No increased infiltrates	DCM	+	Y	2 copies mRNA B19V	B19V mRNA
8	Normal, without fibrosis	Normal	Mild increased infiltrates	iDCM, low grade inflammation	+	Y	942 copies / 2 mRNA	B19V mRNA
9	Normal, without fibrosis, pronounced myocyte atrophy	Moderate atrophied	No increased infiltrates	No diagnosis given	+	N	<LOD	B19V
10	Normal, without fibrosis	Normal	Moderate to severe increased infiltrates	Inflammatory cardiomyopathy	+	N	<LOD	B19V
11	Normal, without fibrosis	Mild atrophied	No increased infiltrates	No diagnosis given	+	N	<LOD	B19V, EBV
12	Normal, without fibrosis	Moderate atrophied	Moderate increased infiltrates	Borderline myocarditis / inflammatory cardiomyopathy	+	N	16 copies	HHV6, B19V
13	Normal, without fibrosis	Mild atrophied	No increased infiltrates	No diagnosis given	-	N	None	None detected
14	Normal, without fibrosis	Mild atrophied	No increased infiltrates	No diagnosis given	+	N	<LOD EBV and B19V	B19V, EBV
15	Normal, without fibrosis	Normal	No increased infiltrates	No diagnosis given	+	N	<LOD	B19V
16	Normal, without fibrosis	Mild atrophied	No increased infiltrates	No diagnosis given	+	N	694 copies	B19V
17	Normal, without fibrosis	Normal	No increased infiltrates	No diagnosis given	-	N	None	None detected
18	Normal, without fibrosis	Normal	No increased infiltrates	No diagnosis given	+	N	<LOD	B19V
19	Normal, without fibrosis	Normal	No increased infiltrates	No diagnosis given	-	N	None	None detected
20	Normal, without fibrosis	Moderate atrophied	No increased infiltrates	DCM	-	N	None	None detected
21	Normal, without fibrosis	Normal	No increased infiltrates	DCM	+	N	30 copies	B19V

SUPPLEMENTARY TABLE I: Raw data endomyocardial biopsy analysis - continued.

Patient Nr	Histology	Cardiomyocytes	Immunohistological	Diagnosis as per pathology report	Virus Detection	Replicating virus	Copies / µg DNA	Virus type
22	Normal, without fibrosis	Hypertrophied	No increased infiltrates	Due to moderate lipomatisis, biopsy results compatible with ARVC or toxic myocardial damage	+	N	<LOD	B19V
23	Moderate lipomatisis	Normal	No increased infiltrates	Mild inflammatory cardiomyopathy	-	N	None	None detected
24	Normal, without fibrosis	Normal	No myocardial tissue, only fatty tissue	No diagnosis given	+	N	<LOD	B19V
25	Normal, without fibrosis	Normal	No increased infiltrates	Cardio-myopathy	+	N	410 copies	B19V
26	Normal, without fibrosis	Normal	No increased infiltrates	No diagnosis given	-	N	None	None detected
27	Mild fibrosis, atrophied cardiomyocytes	Hypertrophied	No increased infiltrates	Low intramyocardial inflammation / DD postinfectious	+	N	<LOD	B19V
28	Fibrosis with amyloid	Normal	Mild increased infiltrates	Mild inflammatory cardiomyopathy	+	N	506 copies B19V, HHV6 77 copies	B19V, HHV6
29	Mild fibrosis	Mild atrophied	Mild increased infiltrates	No diagnosis given	-	N	None	None detected
30	Normal, without fibrosis. Mild lipomatosis	Normal	Mild increased infiltrates	Borderline myocarditis / inflammatory cardiomyopathy	-	N	None	None detected
31	Mild perivascular fibrosis, mild cardiomyocyte hypertrophy	Mild atrophied	No increased infiltrates	Cardio-myopathy	+	N	<LOD EBV and B19V	B19V, EBV
32	Mild fibrosis	Normal	Quality sample not good	Cardio-myopathy	+	N	1 493 copies	B19V
33	Normal, without fibrosis.	Normal	Mild increased infiltrates	Borderline myocarditis / inflammatory cardiomyopathy	+	N	132 copies	HHV6
34	Normal, without fibrosis.	Normal	No increased infiltrates	No signs of myocarditis or inflammatory cardiomyopathy	-	N	None	None detected
35	Mild fibrosis	Normal	Massive infiltration	Massive inflammatory cardiomyopathy	+	N	7 copies B19V, <LOD HHV6	B19V, HHV6
36	Normal, without fibrosis	Normal	No increased infiltrates	No diagnosis given	-	N	None	None detected
37	Normal, without fibrosis	Normal	No increased infiltrates	DCM	+	N	23 copies B19Vand 77 copies HHV6	B19V, HHV6
38	Fibrosis with amyloid	Normal	No increased infiltrates	DCM	+	N	57 copies	B19V

DCM: dilated cardiomyopathy, EBV: Epstein Barr virus, HHV6: human herpes virus 6, iDCM: inflammatory dilated cardiomyopathy, LOD: limit of detection, N: no, B19V: Parvovirus B19, Y: yes.

Ironing out the iron profile in heart failure patients: A single centre, outpatient-based cross-sectional study in South Africa

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ABSTRACT

Background: Iron deficiency is the most common nutritional deficiency globally, affecting up to 55% of patients with heart failure. Iron deficiency is an independent predictor of poor outcomes in heart failure patients. Screening for iron deficiency is recommended by the European Society of Cardiology (ESC) and adopted locally.
Objectives: To provide insight into the burden of iron deficiency in patients with heart failure in South Africa by measuring the iron profile and analysing differences in the iron profile between sexes and subgroups of heart failure.
Methods: A single-centre descriptive cross-sectional study was performed. Demographic, clinical, echocardiographic and laboratory data of patients with heart failure attending Universitas Academic Hospital in Bloemfontein for 3 months in 2023 were collected and analysed.
Results: We included 147 patients, 127 of whom had iron profile results. Over half (60.6%, 77/127) had iron deficiency, while the majority (74.0%, 57/77) had non-anaemic iron deficiency. Iron deficiency was more prevalent in females than males (p-value = 0.0006).
Conclusion: A high prevalence of iron deficiency in heart failure was noted. Even though their haemoglobin levels were normal, most patients were iron deficient. Routine screening of heart failure patients, as adopted from the ESC Guidelines 2021, is recommended.
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INTRODUCTION

Heart failure is a complex, multifactorial syndrome resulting from impaired heart function due to a structural or functional abnormality of the heart.[(1)] Globally, heart failure affects 64.3 million people, of whom 29.5 million are males and 34.8 million are females.[(2)] Iron deficiency was recently recognised as a heart failure-associated comorbidity, and its presence independently predicts a poor outcome in acute and chronic heart failure patients.[(1)]

The heart has the highest energy expenditure of all organs, and cardiomyocytes depend highly on effective mitochondrial function. Iron deficiency leads to mitochondrial damage by altering the mitochondrial morphology, as well as functioning. Dysfunctional mitochondria lead to decreased ATP production, damage to mitochondrial DNA, increased gluconeogenesis, increased lactic acid production, impaired mitophagy, increased apoptosis and oxidative stress. Cardiomyocytes, deprived of iron, lead to decreased contractility and structural changes in the heart. Iron deficiency further alters calcium handling with a shift towards lactic acid-producing glycolytic metabolism.[(3)]

Iron deficiency leads to a deterioration in exercise capacity, precipitates circulatory decompensation and promotes skeletal muscle dysfunction in an already failing heart, leading to an increase in hospitalisations and death.[(1)]

The impact of iron deficiency in patients with heart failure is so profound that the ESC, in their 2021 guideline, recommended that all patients with heart failure are periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin and transferrin saturation.[4-7] Screening for iron deficiency has thus become the standard of care.

Heart failure patients are at risk of developing iron deficiency as they gradually decrease iron stores due to many factors, including loss of appetite, poor nutrition, and decreased gastrointestinal absorption of iron from intestinal oedema and chronic inflammation.[8] Gastrointestinal bleeding, secondary to medications such as antithrombotics and anticoagulants, is another proposed mechanism for developing iron deficiency.[8]

The European Society of Cardiologists classify heart failure according to the left ventricular ejection fraction (LVEF).[1] There are three distinct groups, namely heart failure with a reduced ejection fraction (HFrEF, LVEF ≤40%), heart failure with a midrange ejection fraction (HFmrEF, LVEF 41% - 49%), and heart failure with a preserved ejection fraction (HFpEF, LVEF ≥50% with objective evidence of cardiac abnormalities). Intravenous iron supplementation is recommended in symptomatic iron-deficient heart failure patients with a reduced or midrange ejection fraction to alleviate symptoms and improve quality of life.[9] Intravenous ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic iron-deficient heart failure patients with a reduced or midrange ejection fraction to reduce the risk of hospitalisation.[9] No iron supplementation is currently recommended in heart failure patients with a preserved ejection fraction,[1,9] and therefore, we did not include this group in our study.

According to European studies, iron deficiency is present in up to 36% - 55% of chronic heart failure patients.[5,6,10,11] A similar prevalence of 49% - 60% is seen in sub-Saharan heart failure patients.[12,13] However, to our knowledge, minimal data to date describes the iron profile of heart failure patients in South Africa. The prevalence and characteristics of iron deficiency in our context are unknown.

This study, therefore, aims to explore the iron profile of patients with heart failure (HFrEF and HFmrEF) attending the Cardiology Clinic at Universitas Academic Hospital. The study's objectives are firstly to measure the iron profile in patients with heart failure and determine the prevalence of iron deficiency in this population. Secondly, we aim to analyse iron profile differences between sexes and subgroups of heart failure and explore associations between CRP, nT-proBNP and iron deficiency. We hope to provide knowledge and insight into the burden of iron deficiency in heart failure in a South African setting, as limited data on this topical topic exist.

METHODS

Study design

We conducted a single-centre descriptive cross-sectional study that enrolled heart failure patients with a reduced or midrange ejection fraction to measure their iron profile. We reviewed their clinical, echocardiographic and laboratory data.

Setting

The study was performed at the Cardiology Clinic at Universitas Academic Hospital (UAH) in Bloemfontein, South Africa. UAH is a 636-bed hospital. It is the only centre providing specialist cardiology services for patients primarily from the Free State, Northern Cape Province, and Lesotho.

Study size

The study size was determined by the time set out to do the study, i.e. 3 months. On average, 20 patients are seen in the Cardiology Clinic per day. About a quarter of these patients have heart failure. Our estimated study size was 240 patients for the 3 months.

Participants

The study population consisted of all patients 18 years and older with a confirmed diagnosis of heart failure who attended the clinic during the data collection period of 3 months (1 March - 31 May 2023). We defined heart failure as a clinical syndrome with symptoms of dyspnoea, lower limb swelling and fatigue, and signs of raised jugular venous pressure, pulmonary congestion, and peripheral oedema with echocardiographical evidence of a decreased left ventricular ejection fraction (LVEF).

A field worker screened patients according to the inclusion criteria, obtained informed consent from eligible patients, and completed the data forms. We included all consenting heart failure patients with an LVEF of 49% or less. We divided heart failure into subgroups based on the LVEF, namely, heart failure with a reduced ejection fraction (LVEF ≤40%) and heart failure with a midrange ejection fraction (LVEF 41% - 49%).

Definitions

Heart failure was graded according to LVEF, as found on the echocardiographic report. Heart failure with a reduced ejection fraction is defined as an LVEF ≤40%, and heart failure with a mildly reduced ejection fraction is defined as an LVEF between 41% - 49%.

Heart failure symptoms were classified according to the NYHA Functional Classification.[1] Class I patients have no limitations of physical activity and are asymptomatic. Class II patients have slight limitations in physical activity. Class III patients have marked limitations in physical activity. Class IV patients cannot continue physical activity without discomfort and have symptoms at rest.

Iron deficiency was defined as either a serum ferritin concentration of less than <100ng/mL or 100 - 299ng/mL with transferrin saturation of less than 20%.[1] Anaemia was defined as a haemoglobin of <12g/dL in females and <13g/dL in males.[14]

Variables

Categorical and numerical data were collected. Age, sex, LVEF, haemoglobin, mean corpuscular volume and haemoglobin, ferritin, transferrin saturation, C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (nT-proBNP) were collected as numerical variables. Each participant's home province, New York Heart Association (NYHA) functional classification, and concomitant medications were captured as categorical variables. Preceding iron studies and iron supplementation were captured as categorical data.

Sources / measurement

An electronic data form was created to capture data. The researcher collected clinical data from participant files. Echocardiography data were collected from relevant records in patient files, and laboratory data were collected from the National Health Laboratory (NHLS) Trakcare. Research Electronic Data Capture (REDCap) facility hosted by the University of the Free State (UFS) was used to process all data. REDCap is a secure, web-based software platform that supports data capture for research studies.[15] A p-value of less than 0.05 was considered statistically significant.

Data analysis

Numerical variables were summarised by medians, ranges, or percentiles. Categorical variables were summarised by frequencies and percentages. Differences between groups were evaluated using the Chi-Square test. The Department of Biostatistics, Faculty of Health Sciences, UFS, analysed the data using SAS version 9.4.

Ethical considerations

The Health Sciences Research Ethics Committee of the University of Free State provided ethical approval to conduct the study. (Reference no. UFS-HSD2022/1969/2802) The head of the Department of Internal Medicine, School of Clinical Medicine, UFS. The Free State Province Department of Health granted permission to conduct the research at a provincial facility.

Participation in the study was voluntary, and written consent was obtained before inclusion. No identifiable data was used, and a number was allocated to each patient in the study to ensure anonymisation.

Data management

This study adhered to ethical data management practices. REDCap employs access controls to restrict access to raw data to authorised members only. Only the research team was granted access to the project. De-identified data will be securely stored on REDCap for at least 5 years, after which it will be securely deleted.

RESULTS

Description of the study population

We pre-screened 156 patients during the 3-month period that fulfilled our study's inclusion criteria. We enrolled 144 patients, as 12 did not sign informed consent to participate in the study. A further 17 patients were excluded from the study because of incomplete blood results. We studied the iron profile in 127 patients (Figure 1).

Of the 127 patients, 60.6% (77/127) had iron deficiency as defined by the ESC definition of iron deficiency in heart failure. Table 1 compares the baseline characteristics of the iron-

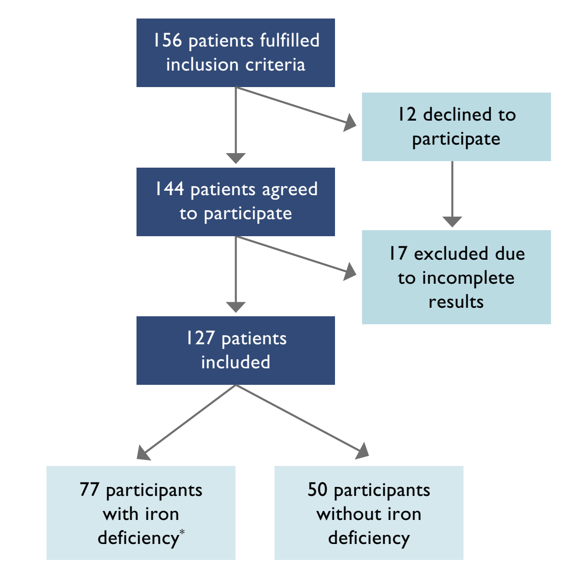

FIGURE 1: Scheme for determining the study population.
*as defined by Ferritin <100ng/mL or Ferritin 100 - 299ng/mL with Transferrin Saturation of <20%.

TABLE I: Baseline characteristics of iron-deficient and non-iron-deficient heart failure patients.

Variable	Iron-deficient n=77	Non-iron-deficient n=50
Age		
20 - 29 (freq; %)	7 (9.1%)	0 (0%)
30 - 39 (freq; %)	10 (12.9%)	4 (8.0%)
40 - 49 (freq; %)	14 (18.2%)	11 (22.0%)
50 - 59 (freq; %)	21 (27.3%)	10 (20.0%)
60 - 69 (freq; %)	13 (16.9%)	18 (36.0%)
70 - 79 (freq; %)	11 (14.3%)	6 (12.0%)
80 - 89 (freq; %)	1 (1.3%)	1 (2.0%)
Sex		
Male (freq; %)	27 (35.1%)	33 (66.0%)
Female (freq; %)	50 (64.9%)	17 (34.0%)
Home province		
Free State (freq; %)	70 (90.9%)	43 (86.0%)
Northern Cape (freq; %)	7 (9.1%)	6 (12.0%)
Eastern Cape (freq; %)	0 (0%)	1 (2.0%)
Iron studies performed in the last 6 months		
Yes (freq; %)	3 (3.9%)	6 (12.0%)
No (freq; %)	71 (92.2%)	44 (88.0%)
Unsure (freq; %)	3 (3.9%)	0 (0%)
Taking iron supplementation		
Yes (freq; %)	3 (3.9%)	1 (2.0%)
No (freq; %)	72 (93.5%)	48 (96.0%)
Unsure (freq; %)	2 (2.6%)	1 (2.0%)
NYHA functional classification		
Class I (freq; %)	19 (24.7%)	15 (30.0%)
Class II (freq; %)	40 (51.9%)	27 (54.0%)
Class III (freq; %)	16 (20.8%)	8 (16.0%)
Class IV (freq; %)	2 (2.6%)	0 (0%)
Heart failure classification		
HFrEF (freq; %)	48 (62.3%)	33 (66.0%)
HFmrEF (freq; %)	29 (37.7%)	17 (34.0%)

deficient and non-iron-deficient patients. More females (64.9%, 50/77) were affected than males (35.1%, 27/77). Iron deficiency was most prevalent in the 50 - 59 age group, with 27.3% (21/77) of the iron-deficient patients falling into this age category.

Most iron-deficient patients (92.2%, 71/77) had no iron studies performed before the index clinic visit. Of the iron-deficient patients, only 4.2% (3/77) took iron supplementation at the time of the clinic visit. These patients were all taking oral ferrous sulphate.

TABLE II: Presence of concomitant anaemia in iron-deficient heart failure patients.

Variable	Males n=27	Females n=50	Total n=77
Anaemic (freq; %)	6 (22.2%)	14 (28.0%)	20 (26.0%)
Non-anaemic (freq; %)	21 (77.8%)	36 (72.0%)	57 (74.0%)

Of the 77 patients, 24.7% (n=19) had NYHA Functional Class I heart failure, 51.9% (n=40) Class II, 20.8% (n=16) Class III, and 2.6% (n=2) Class IV. Heart failure with a reduced ejection fraction was present in 62.3% (48/77) of iron-deficient patients. The rest of the iron-deficient patients had heart failure with a midrange ejection fraction.

Almost three-quarters (74%, 57/77) of iron-deficient patients had a normal haemoglobin level, as previously defined. Concomitant anaemia was present in 26% (20/77) of iron-deficient patients; therefore, most iron-deficient patients with heart failure had normal haemoglobin (Table II).

Iron deficiency and sex

Iron deficiency was more prevalent in females than males (p-value = 0.0006). There was no statistically significant difference in the median MCV between males and females (p-value = 0.0945). We also found that ferritin and transferrin saturation were lower in females than males (p-value = 0.0015 and p-value = 0.0032, respectively).

Iron deficiency and left ventricular ejection fraction

We explored differences within the iron profile in the subgroups of heart failure (Table III). Females were more affected by iron deficiency than males in both subgroups. The median ages of the patients within the subgroups ranged from 48.5 - 59 years. Most of the patients had NYHA functional class II heart failure.

In both groups, the females' MCV were lower than the males' MCV. The median transferrin saturation ranged between 13.5% - 15%, with median ferritin of 46.5 - 56.5µg/L in the females, as opposed to 13% - 14.5% and 68.5 - 69µg/L in the males. Females' ferritin was lower than their male counterparts. The median CRP was low in both subgroups.

There was no association between the left ventricular ejection fraction and iron deficiency (p-value = 0.6748). No association was noted between NYHA functional class and anaemia (p-value = 0.5926) or NYHA functional class and iron deficiency (p-value = 0.5703).

TABLE III: Differences in iron profile within subgroups of heart failure patients, based on the left ventricular ejection fraction.

	LVEF ≤40%		LVEF 41% - 49%	
	Males n=20	Females n=28	Males n=7	Females n=22
Age (mean; range)	54.5 (50.0 - 62.5)	48.5 (33.5 - 60.0)	59.0 (40.0 - 70.0)	54.5 (41.0 - 68.0)
NYHA Functional Class				
I (freq; %)	3 (15.0%)	7 (25.0%)	3 (42.9%)	6 (27.3%)
II (freq; %)	12 (60.0%)	13 (46.4%)	3 (42.9%)	12 (54.6%)
III (freq; %)	4 (20.0%)	8 (28.6%)	1 (14.3%)	3 (13.6%)
IV (freq; %)	1 (5.0%)	0 (0%)	0 (0%)	1 (4.6%)
MCV (mean; range)	94.5 (92.1 - 100.6)	91.6 (84.4 - 95.2)	96.9 (86.8 - 99.5)	93.2 (88.4 - 94.3)†
MCH (mean; range)	29.6 (29.1 - 32.2)	29.1 (26.4 - 30.3)	30.4 (27.3 - 33.4)	28.4 (27.7 - 29.8)†
TSAT (mean; range)	13.0 (10.5 - 18.5)	15.0 (12.0 - 17.0)*	14.5 (13.0 - 19.0)†	13.5 (10.0 - 17.0)
Ferritin (mean; range)	68.5 (37.0 - 139.5)	56.5 (33.5 - 96.0)	69.0 (38.0 - 126.0)	46.5 (20.0 - 88.0)
CRP (mean; range)	6 (4 - 13)***	5 (2 - 9)**	5 (2 - 7)†	1 (1 - 3)^

**2 patients' results missing, **6 patients' results missing, ***3 patients' results missing, †1 patient's results missing, ^3 patients' results missing.*
LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, TSAT: Transferrin saturation, CRP: C-reactive protein.

Iron deficiency and C-reactive protein

We found that the CRP does not affect the iron profile in heart failure patients. The median CRP in the iron-deficient group was 4 and 3.5mg/L in the non-iron-deficient group. We could not find any statistical association between CRP and iron deficiency (p-value = 0.8475).

Iron deficiency and N-terminal prohormone of brain natriuretic peptide

Only 4 patients in our study had nT-proBNP done. These patients' results were 1028, 3935, 5046 and 560ng/L, respectively. Three patients with positive nT-proBNP results had iron deficiency. We could not assess any association between nT-proBNP and iron deficiency as the results were incomplete.

Iron deficiency and concomitant anticoagulants

Most patients with iron deficiency were on warfarin (31.2%, 24/77), aspirin (29.9%, 23/77) and rivaroxaban (9.1%, 7/77). Only 3 patients were taking clopidogrel, and only 2 were on enoxaparin. There was no difference between the iron-deficient and non-iron-deficient groups related to the use of these medications (p=0.1704, p=0.6245, p=0.7131, p=0.055, p=0.7024, respectively).

DISCUSSION

Our study found that more than half of our heart failure patients had iron deficiency, as defined by the ESC definition for iron deficiency in heart failure.[1] Iron deficiency was missed in most of these patients, as most had no previous iron studies before the clinic visit. Nearly three-quarters of heart failure patients with iron deficiency had normal haemoglobin values. These results are important because iron deficiency is common in heart failure patients, and normal haemoglobin should not exclude heart failure patients from having their iron studies checked, as patients with iron deficiency are eligible for intravenous iron supplementation as per ESC guidelines.[1] There is a need for further studies to determine the optimal treatment of iron deficiency considering conflicting results regarding improvements in symptoms, functional capacity and safety.[16-17] Side effects and alternatives to intravenous iron repletion warrant careful consideration.

Iron deficiency is common in heart failure patients and is associated with adverse cardiovascular outcomes.[18-19] Our study is one of the first studies in South Africa to report on the iron profile in heart failure patients. Our finding is in keeping with European data, which suggest a 36% - 55% prevalence of iron deficiency in heart failure patients.[5,6,10,11] Our findings were also comparable to data from sub-Saharan Africa, which found a prevalence of 49% in Tanzania and 60% in Nigeria, respectively.[12,13]

We found that iron deficiency is often missed in heart failure patients as they often have a normal haemoglobin count despite being iron deficient. Possible reasons why routine iron studies are not done might be because doctors are not familiar with the new ESC Guidelines or that doctors feel no need to investigate the iron profile as the patient might have had normal haemoglobin at the time of consultation. Cost constraints may also influence the uptake of laboratory tests in smaller institutions; however, as the study site is an academic hospital, this is not likely a factor. Our study highlights the need for routine iron studies in all South African heart failure patients.

It is important to note that iron deficiency and anaemia do not necessarily need to coexist. One may be anaemic without ID, but also and perhaps more importantly, one may have ID without anaemia. It has been noted that in heart failure ID does not correlate closely with anaemia.[20]

There was a statistically significant association between iron deficiency and sex, consistent with European data, showing that females are more likely to develop iron deficiency.[5,6] Our findings failed to show statistically significant associations between iron deficiency and left ventricular ejection fraction, NYHA functional class and CRP. Literature,[1,5,6] however, suggests that these associations exist, and our relatively small study population might be a possible reason we could not prove the existence of these associations. Because of incomplete data, we could not assess the association between iron deficiency and nT-proBNP.

Strengths and limitations

The study's strengths include that it is one of the first studies reporting on the prevalence and characteristics of iron deficiency in heart failure patients in South Africa. We recruited heart failure patients with a confirmed echocardiographic diagnosis of heart failure and used validated assays for our laboratory data. These measures ensured good quality data. However, several limitations should be highlighted. One limitation is that our study was conducted in a single-centre outpatient department for 3 months. Our results only give a 3-month glimpse of the burden of iron deficiency in heart failure patients and do not represent South Africa or the Free State as a whole, as not all patients with heart failure are referred to Universitas Cardiology. Our relatively small study population is another limitation, as patients were excluded from the study because of incomplete results and not agreeing to participate.

CONCLUSION

We conclude that iron deficiency is common in heart failure patients in the South African context. Furthermore, iron deficiency can occur in patients with normal haemoglobin; therefore, the diagnosis is often missed. A normal haemoglobin should not exclude patients from having their iron status routinely checked. Iron deficiency is treatable, and by diagnosing these patients, treatment can be offered, improving symptoms and quality of life in these patients. We support the adoption of ESC Guidelines 2021, which advocate for routine screening for iron deficiency in heart failure with treatment thereof in managing South African heart failure patients, and we appeal to South African doctors to screen for iron deficiency in heart failure patients. This recommendation is particularly important to female patients with heart failure given the higher prevalence of ID in that population.

Further research is needed on iron deficiency in heart failure patients in South Africa. This can be done by conducting bigger, multicentre studies for longer periods to ensure the generalisability of results. We believe that larger numbers will provide more insight into the prevalence and characteristics of iron deficiency in South African heart failure patients, leading to the development of our own guidelines on screening and managing iron-deficient heart failure patients.

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DISCLOSURES

The views and opinions expressed in this article are those of the authors and are the product of professional research. It does not necessarily reflect the official policy or position of the University of the Free State. The authors are responsible for this article's results, findings, and content.

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Common atrium with single ventricle in a newborn: A case report

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ABSTRACT

The presence of a common atrium, a common atrio-ventricular valve in combination with a single ventricle, occurs very rarely, accounting for 1% - 2% of all congenital heart malformations.

We report a rare case of a 21-day old male neonate diagnosed with a common atrium, single ventricle, a common atrioventricular valve and a patent ductus arteriosus. High index of suspicion and early diagnosis is vital for appropriate management and timely surgical interventions as required. SA Heart® 2025;22:122-123

INTRODUCTION

Common atrium (CA) is defined as complete or near complete absence of the interatrial septum, and has clinical and haemodynamic similarities with large-size atrial septal defect of fossa ovalis type.[1-3] Common atrium is very rarely seen in patients with single ventricle (SV) accounting for 1% - 2% of all congenital heart malformations.[4,5] In patients with common atrium and SV, there is mixing of arterial and venous blood in the common cardiac chamber which causes severe cyanosis and hypoxia in these patients.[5,6]

CASE PRESENTATION

We report the case of a 21-day-old male newborn of non-consanguineous parents; that was referred to our facility with complaints of central cyanosis and feeding difficulties observed since birth, and he subsequently developed cough and dyspnoea by the 14th day of life. He was delivered via spontaneous vaginal delivery at 38 weeks of gestation, and had good extrauterine transition with a birth weight of 3 300 grams. His mother reported a positive history of febrile illness without rashes during early pregnancy, but there was no exposure to ionising radiation, no history suggestive of gestational diabetes, and she received only prescribed medications.

On examination he was cyanosed, not febrile, with no dysmorphic features or external malformations. Cardiovascular system examination revealed bounding peripheral arterial pulses, with a capillary refill time of <3 seconds and oxygen saturation of 77% in room air. The auscultatory findings included tachycardia, first and second heart sounds with a grade III/VI continuous murmur loudest in the second intercostals space, left upper parasternal border. He was dyspnoiec and tachypnoiec on respiratory examination with vesicular breath sounds. His abdominal examination demonstrated a palpable liver 4cm below the right costal margin that was soft, tender with a smooth surface.

An initial working diagnosis of a complex cyanotic congenital heart disease with patent ductus arteriosus in heart failure was considered. Chest radiography showed cardiomegaly with a cardiothoracic ratio of 0.69, increased intrapulmonary vascular markings and widened cardiac pedicle (Figure 1).

Echocardiogram revealed a patent ductus arteriosus, with a common atrium, common atrio-ventricular valve and a single ventricle of left ventricular morphology with a normal aorta and pulmonary artery arising from the single ventricle (Figure 2).

Patient was treated conservatively with furosemide, spironolactone, and captopril. His cardiac symptoms improved and was discharged on same care plan to the cardiology clinic. He remained clinically and haemodynamically stable on follow up visits, and awaits surgical evaluation due to financial constraints.

DISCUSSION

The single ventricle or univentricular heart occurs in ~5 in 100 000 newborns.[7] In most cases, both atria empty into a

FIGURE 1: Chest radiography showing cardiomegaly, increased intrapulmonary vascular markings and widened cardiac pedicle.

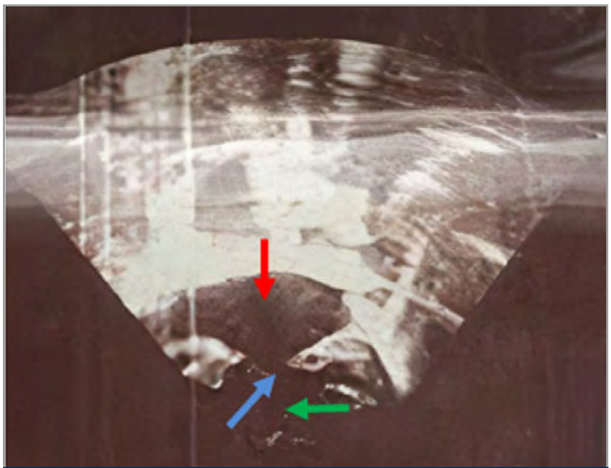

FIGURE 2: Transthoracic echocardiogram showing common atrium (red arrow), single ventricle (green arrow) and a common atrioventricular valve (blue arrow).

common ventricle through a separate atrioventricular valve. The presence of a common atrium, a common atrioventricular valve in combination with a single ventricle as in our case, occurs very rarely, accounting for 1% - 2% of all congenital heart malformations and was first described in 1842.[4,8]

The clinical presentation and long-term outlook depends on the presence or absence of obstruction to pulmonary blood flow, pulmonary vascular resistance, morphology and function of the ventricle and atrioventricular valve, and the degree of obstruction to aortic flow.[9] The median age of survival in a patient with right ventricle morphology is 4 years, while that of a left ventricle morphology is 14 years.[5,10,11]

Review of patients with long survival demonstrate that patients with univentricular heart and well-balanced pulmonary perfusion might survive into late adulthood with good quality of life and functional capacity, without major symptoms or depression of cardiac function.[12]

Patients however having decreased pulmonary blood flow would need a modified Blalock-Taussig shunt while those with increased blood flow may require a pulmonary artery banding procedure. This is usually followed up by a bidirectional Glenn operation as the second-stage after 3 - 6 months and a subsequent Fontan procedure at 2 - 3 years.[10] The surgical mortality of each case depends on the complexity of the lesion and the type of surgery planned at each stage of presentation and may range from 5% - 10% at each stage.[10]

CONCLUSION

We presented a case of a common atrium, a single ventricle with a common atrio-ventricular valve and patent ductus arteriosus, in a neonate. High index of suspicion and early diagnosis is vital for appropriate management and timely surgical interventions as required.

Conflict of interest: none declared.

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ECG Quiz 68

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

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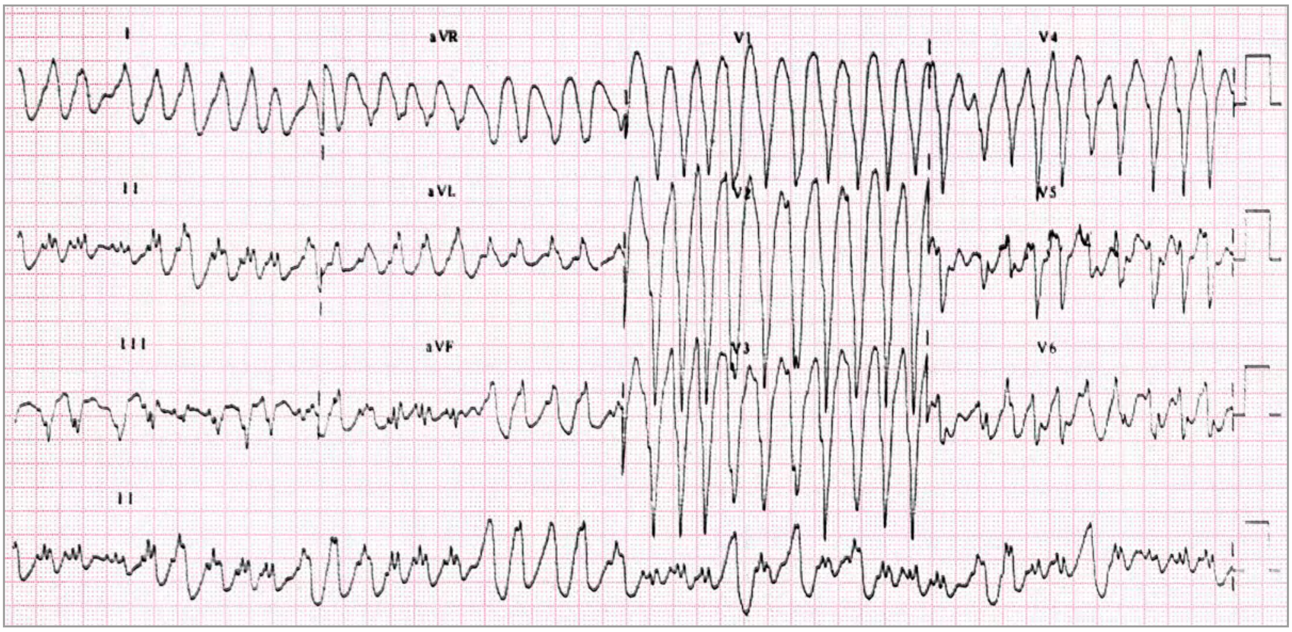

QUESTION: Which ONE of the following is the best ECG diagnosis?

a. Torsade de pointes
b. Artefact
c. Pre-excited atrial fibrillation
d. Atrial fibrillation with left bundle branch block
e. Polymorphic ventricular tachycardia
f. Bidirectional ventricular tachycardia

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

ANSWER on page 125

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OVERVIEW OF THE ECG

The tracing shows what appears to be a very fast (232bpm), wide QRS (±200ms), irregular rhythm with at least 2 QRS morphologies. No clinical information is given.

MORE DETAILED ANALYSIS OF THE ECG

When confronted with a bizarre, rapid ECG tracing which looks like ventricular tachycardia or fibrillation, particularly in the setting of a patient on a monitor, always consider the possibility of artefact. Careful inspection of an artefactual recording in all available leads will almost always reveal normal QRS complexes superimposed on the false ones (Figure 1). Their origin can be confirmed by their regularity and similarity to the R-R intervals before or after the event and the lack of a reactive sinus tachycardia following the abnormal tracing. The artefact is usually short-lived. The patient will not have any symptoms related to the event.

There is no evidence of normal QRS complexes on this ECG. In addition, it would be unusual for artefact to persist long enough to be recorded on a 12 lead ECG. Artefact can therefore be excluded.

The differential diagnosis is therefore that of an irregular wide QRS tachycardia, which includes all the other possibilities given. In contrast to a regular wide QRS tachycardia, atrial fibrillation is usually the underlying mechanism, not ventricular tachycardia (VT) (Figure 2).

All the QRS complexes are negative in the mid-chest leads and positive in V6. However, AF with left bundle branch block

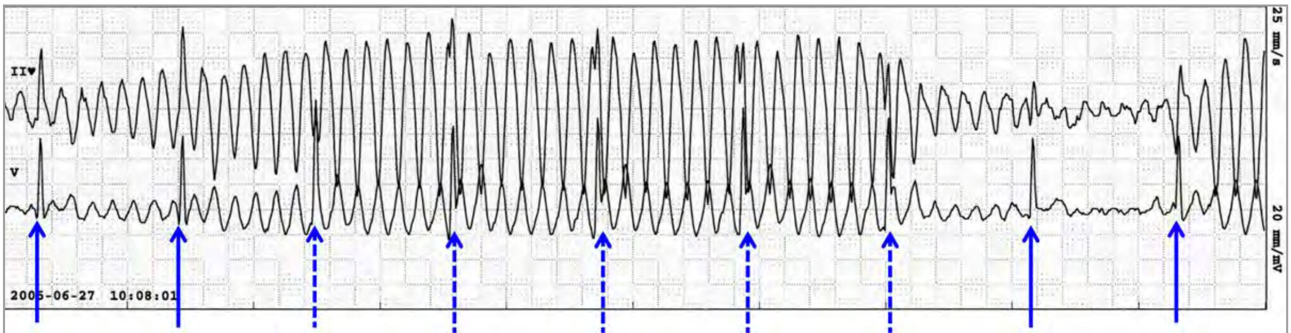

FIGURE 1: Monitor strip showing movement artefact. The arrows indicate the normal QRS complexes hidden by the artefact.

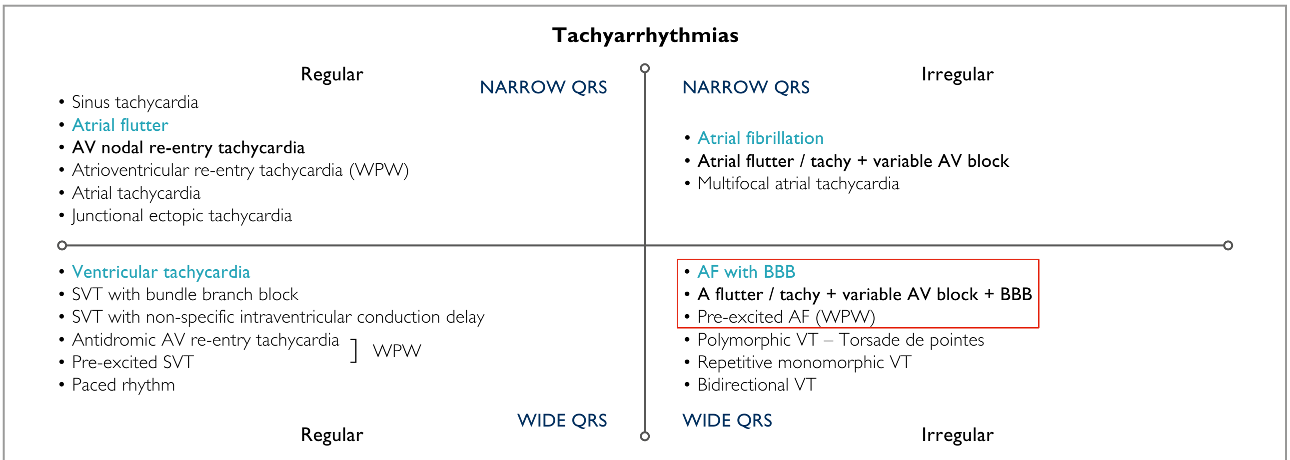

FIGURE 2: Tachyarrhythmias can be divided into 4 quadrants, depending on whether the rhythm is regular or irregular, and whether the QRS is narrow (= <100ms) or wide (= >120ms). Most irregular, wide QRS tachycardias are due to atrial fibrillation, with QRS morphology dependent on the presence of bundle branch block or pre-excitation.

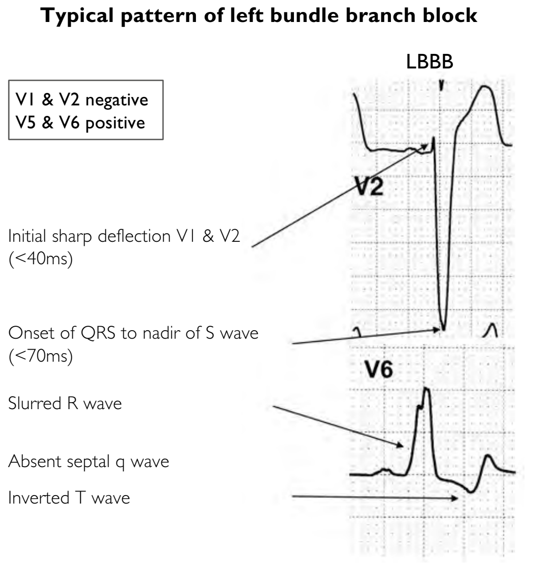

FIGURE 3: Left bundle branch block is best characterised by the pattern in V1 - V2, by the small, narrow r wave and relatively sharp descent of the S wave. V6 can be misleading as many ventricular tachycardias and pre-excited rhythms can mimic the "M" pattern, which is not always present in otherwise typical LBBB.

(LBBB) is excluded by the time from the onset of the QRS in V2 to the nadir of the S wave = 95ms (LBBB <70ms) (Figure 3).

While the varying QRS morphology superficially resembles torsade de pointes (TDP), there is no twisting from negative to positive in any of the leads. Torsade de pointes usually starts with a short-long-short sequence (R on T phenomenon). It is unusual to record TDP on a 12 lead ECG as it is usually transient, or else degenerates into ventricular fibrillation (Figure 4).

Bidirectional VT is characterised by a regular alternation of QRS axis, usually best seen in the limb leads (Figure 5). This is not bidirectional VT.

We are therefore left with polymorphic VT or pre-excited AF, conducted rapidly via an accessory pathway in a patient with WPW syndrome.

Polymorphic VT occurs most commonly in the setting of an acute coronary syndrome, particularly a STEMI. It tends to be non-sustained (last less than 30 seconds), but may rapidly degenerate into ventricular fibrillation (VF) (Figure 6). Like TDP, it is unusual to record it on all 12 leads of an ECG. The mor-

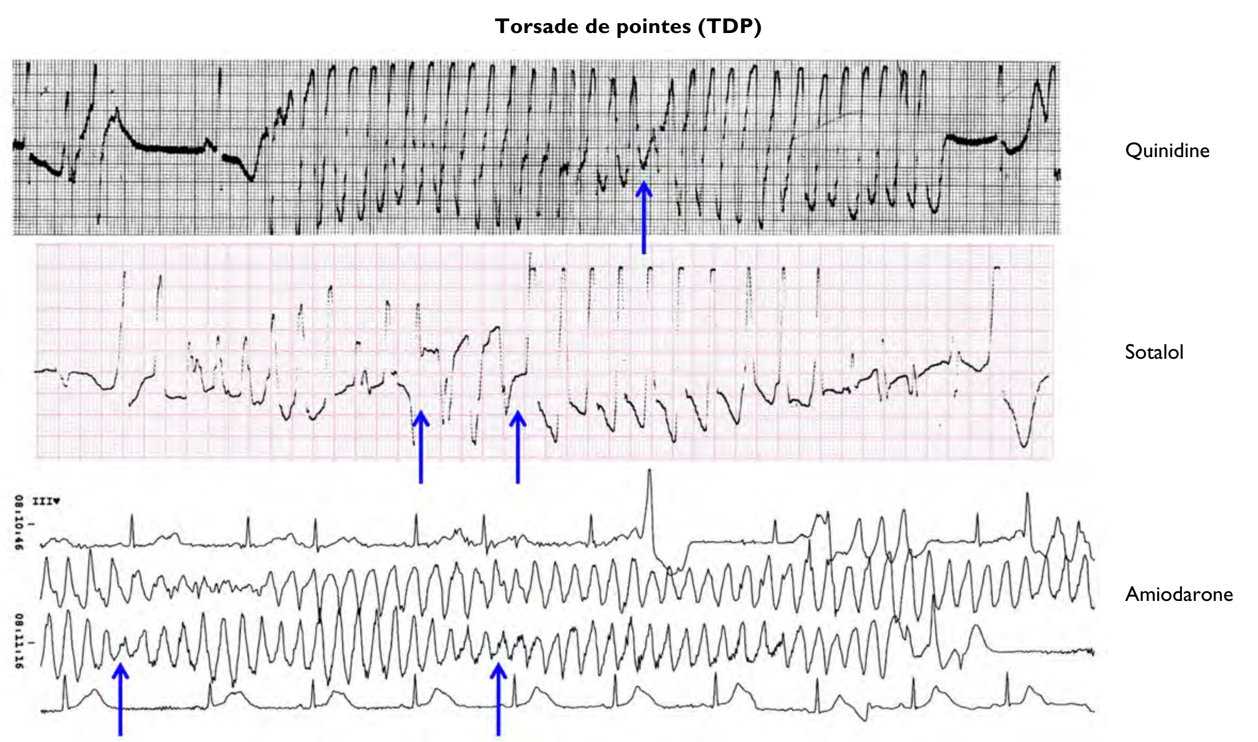

FIGURE 4: Torsade de pointes was first described by Dessertenne in 1966, based on the twisting pattern of the QRS complexes. The term is now reserved for rhythms with this pattern associated with QT prolongation. TDP is most commonly induced by the wide variety of drugs which prolong repolarisation, usually by blocking the I_{Kr} channel. It is usually initiated by a pause following a premature beat. TDP also occurs in the congenital long QT syndromes.

The arrows in these 3 examples, induced by antiarrhythmic drugs, indicate the points of reversal of the QRS axis.

Bidirectional VT

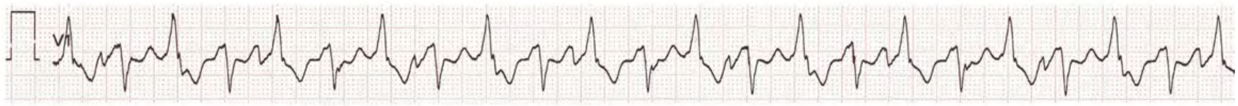

FIGURE 5: Bidirectional ventricular tachycardia in a patient with catecholaminergic polymorphic VT.

Polymorphic VT & VF

FIGURE 6: Ischaemia-induced polymorphic VT which may be self-limiting or degenerate into ventricular fibrillation (VF). While it may resemble TDP, the axis does not necessarily rotate (arrow). VF is an extremely rapid, chaotic rhythm, not commonly recorded on a 12 lead ECG.

phology of the complexes also tends to vary more than in the case of this ECG.

The most likely diagnosis is therefore (c): Pre-excited atrial fibrillation.

The patient was a 30-year-old woman, working in the Winelands. She was previously well apart from intermittent palpitations. She developed rapid palpitations, dizziness and near-syncope and was admitted to Paarl Hospital where the ECG was recorded before cardioversion. After cardioversion, her sinus rhythm ECG was diagnostic for WPW syndrome (Figure 7). The PR interval is extremely short (60ms); the end of the P wave merges with the beginning of the QRS. The QRS is very wide, at least 200ms. The pattern resembles LBBB, particularly in V6. However, the initial r wave in V1-2 is 70ms (LBBB = <40ms) and the time from the onset to the nadir of the QRS is 115ms (LBBB = <70ms). The slurred onset of the QRS is due to delta waves with a high degree of pre-excitation. The pseudo LBBB pattern with a late QRS transition suggests a right free wall AP.

Subtle changes in QRS morphology are often present in patients with pre-excited AF due to varying degrees of fusion between AP and AV nodal conduction. In this ECG, there are 2 distinct QRS morphologies; they are both wide and pre-excited with similar axes in all the leads. This suggests a strong possibility that there are 2 distinct APs, both on the right side, in close proximity to one another. Their refractory periods are similar, in that the shortest R-R interval of the larger complexes is 230ms and the smaller 210ms during atrial fibrillation. This indicates a risk of degeneration into VF[1] (Figure 8). Ablation of the pathways was therefore mandatory.

Two right free wall APs were successfully ablated (Figure 9).

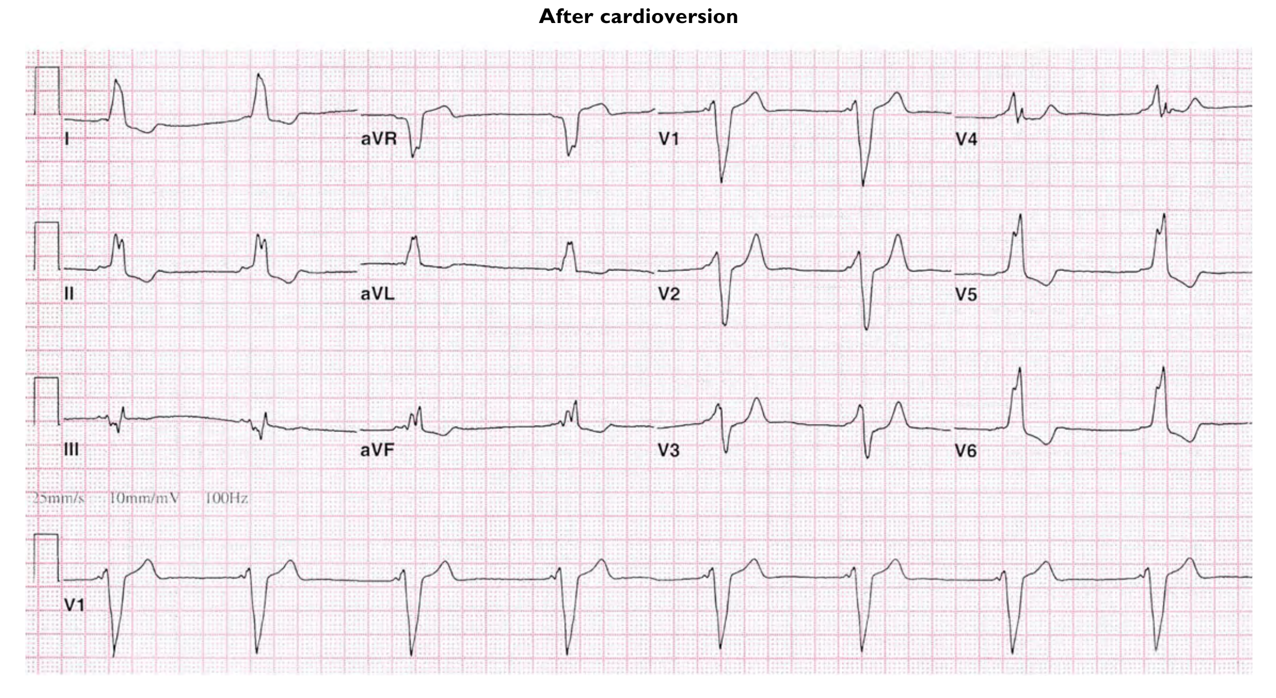

FIGURE 7: The ECG in sinus rhythm after cardioversion shows a clear-cut Wolff-Parkinson-White pattern (see text).

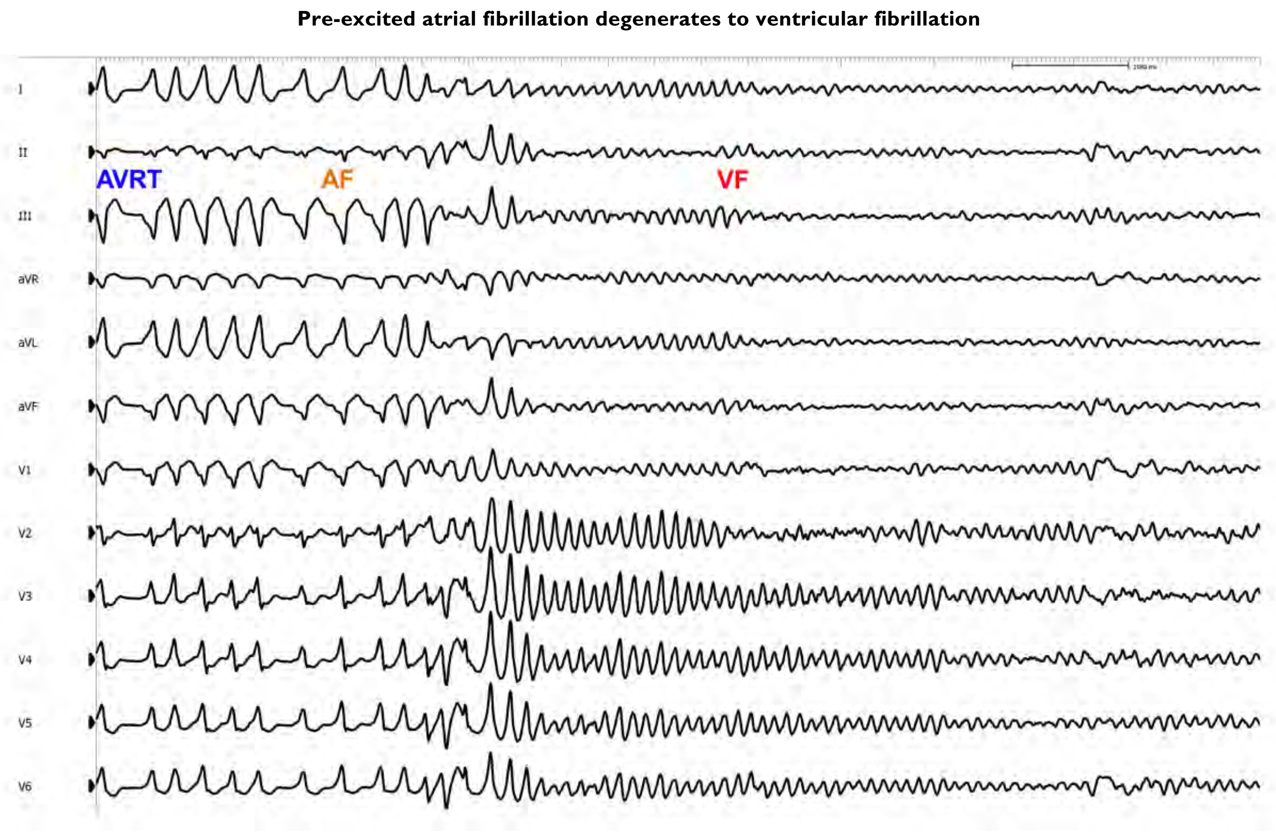

FIGURE 8: Twelve lead ECG of a patient with WPW recorded in the EP lab. Atrioventricular re-entry tachycardia (AVRT) was induced, which triggered pre-excited atrial fibrillation. The AF rapidly degenerated into ventricular fibrillation.

APPROACH TO THE DIAGNOSIS OF IRREGULAR, WIDE QRS TACHYCARDIAS (Table 1)

Unlike regular, wide QRS tachycardias, in which the default diagnosis is ventricular tachycardia, the most common mechanism for an irregular, wide QRS rhythm is AF. The QRS morphology is determined by the characteristics of the conduction pathway(s) from the atria to the ventricles. Left or right bundle branch block, usually pre-existing, can be diagnosed from the QRS morphology. If one or more accessory pathways is functional, the QRS will differ from typical LBBB or RBBB. Depending on the balance of refractory periods between the accessory pathway (AP) and the AV node, the QRS may exhibit varying degrees of fusion or an occasional narrow QRS (Figure 10).

Pre-excited AF may occur in up to 20% of patients with WPW syndrome, in the absence of structural heart disease, even in children as young as 10 years. It is often triggered by rapid atrioventricular re-entry tachycardia and does not usually recur after ablation of the accessory pathway. Multiple APs are not uncommon and can occur in 10% of WPW patients. Pre-excited AF accounts for the approximately 0.25% annual risk of sudden cardiac death in symptomatic patients with WPW and all patients should be referred for an ablation.[2,3] The risk of sudden death in asymptomatic WPW patients is lower and routine invasive management in most asymptomatic patients with the Wolff-Parkinson-White ECG pattern is not required.[3]

TABLE 1: Irregular wide QRS tachycardias.

ECG features
Sustained tachycardia, typical bundle branch block – favours AF + BBB
Sustained tachycardia, not typical bundle branch block – favours pre-excited AF
Occasional narrower beats and slight variation in QRS favour pre-excited AF
Sustained tachycardia over 180bpm – favours pre-excited AF
Polymorphic VT usually non-sustained (unless > VF)
Torsade de pointes – twisting pattern and non-sustained (unless > VF)
Alternating axis – > bidirectional VT (catecholaminergic, digoxin)
Clinical context
History suggesting current or past MI – > polymorphic VT
Age – Youth favours pre-excited AF, but VT can occur from infancy to senility
Prior cardiac symptoms
Episodes of rapid palpitations, regular or irregular, favour AF
SOB, chest pain – > polymorphic VT
QT prolonging drug – > torsade de pointes
Signs of structural heart disease or heart failure – polymorphic VT
ECG in sinus rhythm
Delta waves confirm WPW
Pathological Q waves of old MI suggest VT, but beware pseudo-infarct patterns in WPW
Other: E.g. ARVC patterns, conduction problems (sarcoid), HOCM
Other tachycardia ECGs
Orthodromic or antidromic AVRT – WPW
AV dissociation
Different QRS pattern favours VT

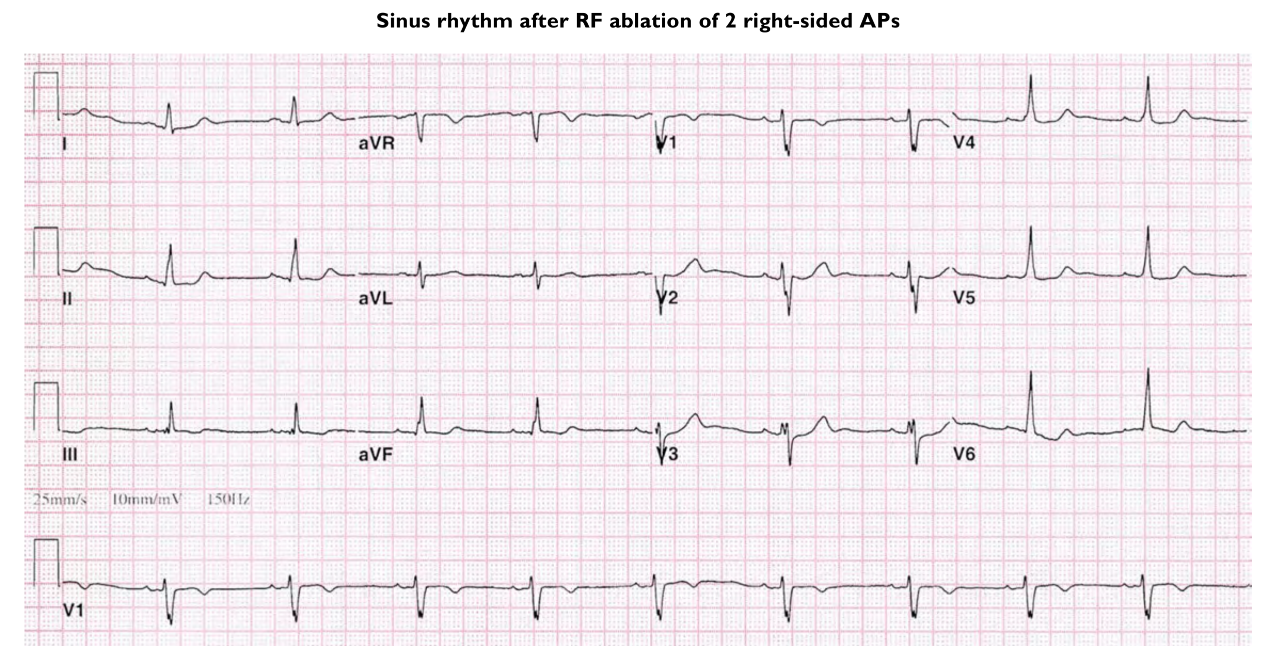

FIGURE 9: The patient was referred to Groote Schuur Hospital. Mapping confirmed 2 right free wall accessory pathways which were successfully ablated.

Pre-excited atrial fibrillation

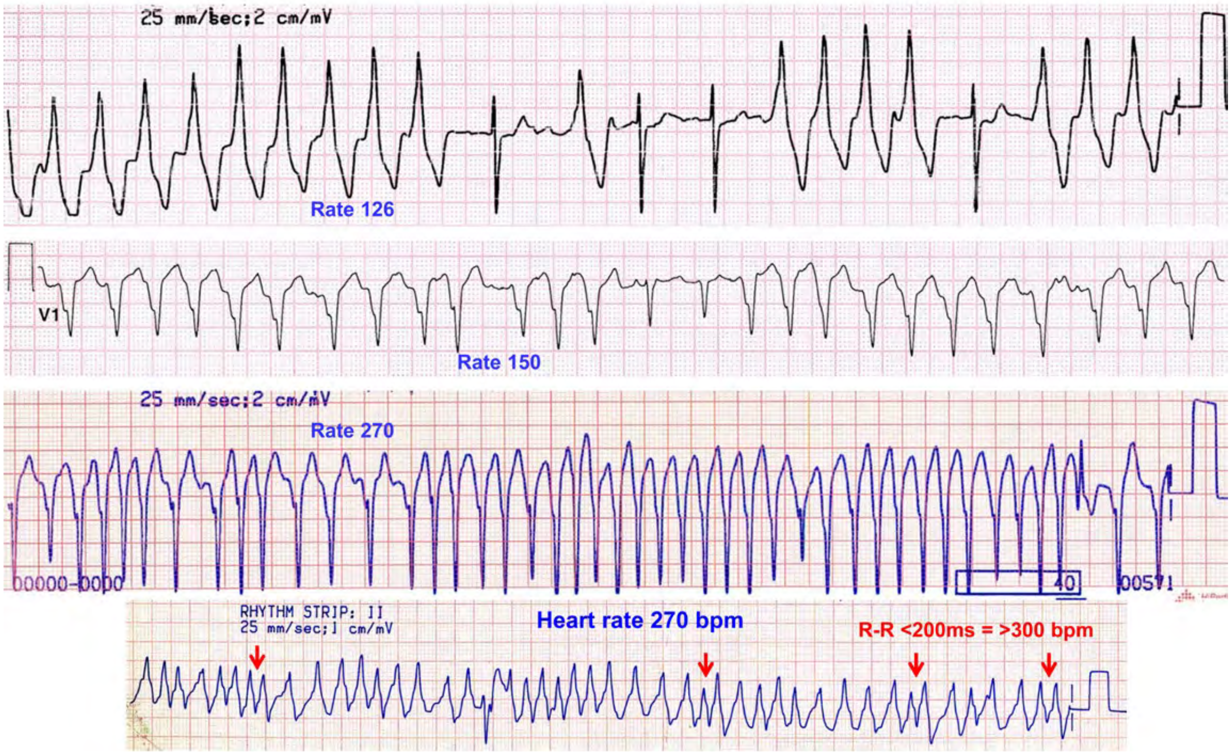

FIGURE 10: Pre-excited AF is not always rapidly conducted. The top panel shows pre-excited AF with a minimum R-R interval of 380ms, indicating a relatively safe accessory pathway refractory period. The pre-excited beats are interspersed with others conducted via the normal conducting system.

The second panel is from another patient with a relatively long AP refractory period, whereas the lower 2 are from patients with short refractory periods (<240ms), very rapid ventricular responses and a risk of degeneration into VF.

All the traces show the characteristic QRS variability due to variable degrees of fusion between conduction via the His-Purkinje system versus the accessory pathway(s).

CONCLUSIONS

- AF is the most common mechanism for sustained irregular wide QRS tachycardias, but other atrial arrhythmias, such as atrial flutter may be responsible.
- The QRS morphology is determined by pre-existing or rate-related bundle branch block, or accessory pathway(s).
- Polymorphic VT and torsade de pointes are usually non-sustained (<30 seconds), unless they degenerate into VF.
- Bidirectional VT is uncommon. It may be due to catecholaminergic VT[4] or digoxin toxicity.

Conflict of interest: none declared.

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CARDIAC IMAGING QUIZ

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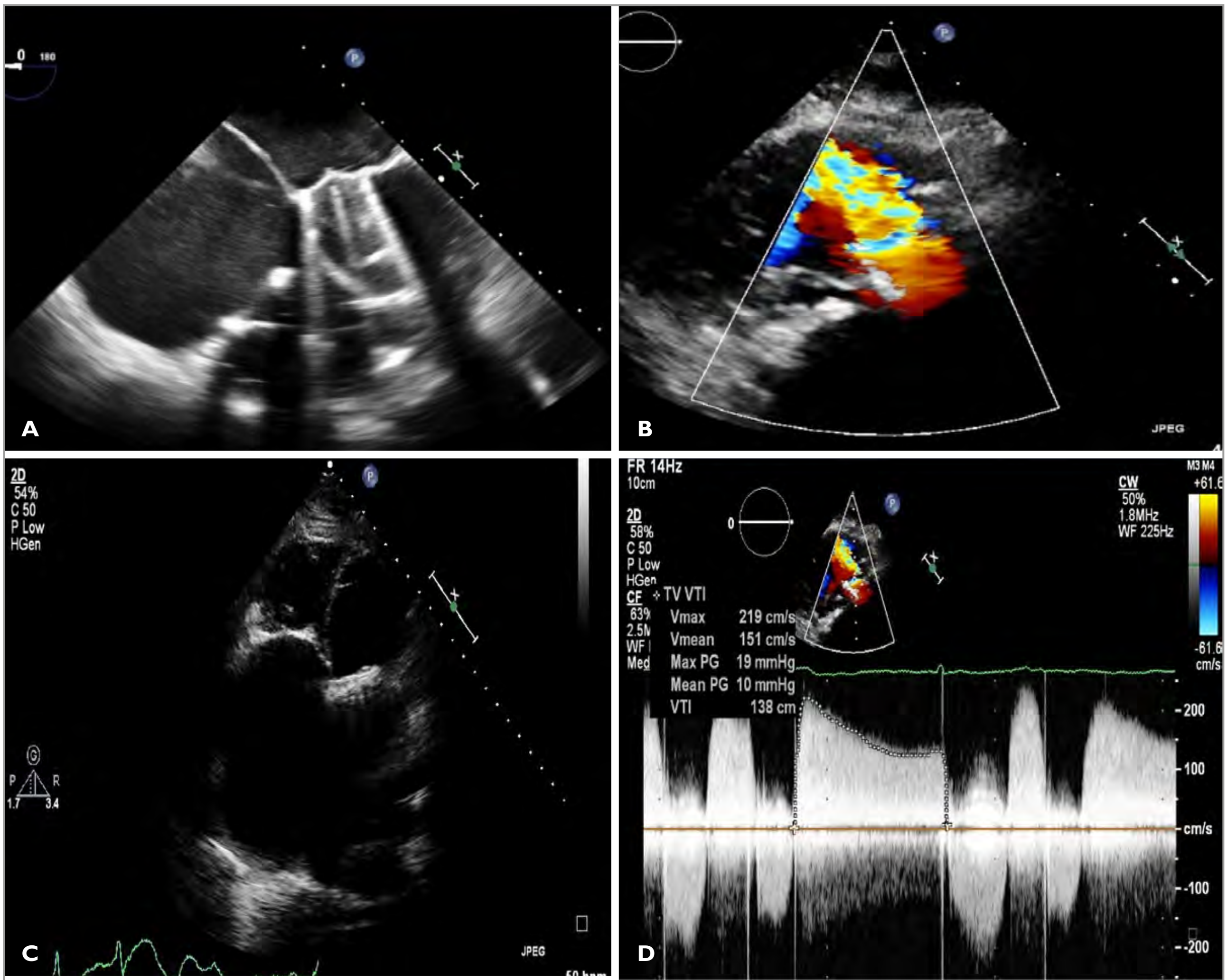

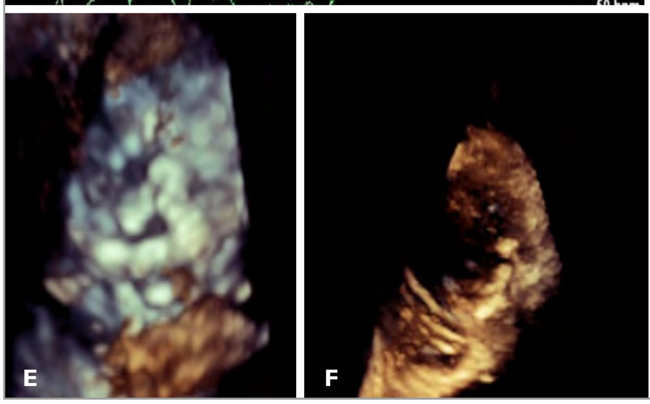

QUESTION: What is the diagnosis?

a. Infective endocarditis of the tricuspid valve

b. Carcinoid heart disease

c. Rheumatic tricuspid valve disease

d. Degenerated tricuspid valve bio-prosthesis

e. Ebstein's anomaly

ANSWER

D. Degenerated tricuspid valve bio-prosthesis.

These images belong to a 57-year-old female who had previous mitral valve replacement (MVR) and tricuspid valve (TV) replacement for rheumatic heart disease (RHD). She presented with signs and symptoms suggestive of right heart failure and atrial fibrillation.

The top panel on the left (mid trans-oesophageal view) shows a markedly enlarged right atrium (RA) with bioprosthetic tricuspid valve (prominent ring visible) and metallic bi-leaflet mitral valve (Image A). The image on the right is the right ventricle (RV) inflow view depicting convergence zone across the TV on colour flow imaging suggestive of significant stenosis (Image B). The middle panel shows the markedly enlarged RA in the apical 4-chamber view with echo drop out of the interatrial septum due to presence of metallic mitral valve prosthesis (Image C). The continuous wave Doppler shows a significant gradient of 10mmHg across the TV prosthesis and presence of tricuspid regurgitation (Image D). The bottom panel shows three-dimensional (3D) imaging of the TV bio-prosthesis, the valve is severely calcified with limited opening (Image E). The 3D image on the right emphasises the thickened chordae secondary to RHD of the TV in the RV inflow view (Image F).

TV replacement (TVR) is a relatively rare surgical procedure, typically performed on patients with severe structural or advanced functional problems in their tricuspid valve.[1] As a result, those undergoing TVR often have a high-risk profile, with many having previously undergone TV repair and facing complications such as RV dysfunction. TVR is linked to high mortality and morbidity rates, with operative mortality ranging from 5% - 50%. A systematic review and meta-analysis compared the clinical outcomes of mechanical vs. biological prostheses for TVR.[1] The study found that mechanical valves had a higher risk of thrombotic events but showed a non-significant trend towards lower 30-day mortality. Bioprosthetic valves, on the other hand, demonstrated better durability and a lower risk of thrombotic complications. Another study compared the long-term results of mechanical and biological prostheses in patients who underwent isolated or combined TVR.[2] The findings suggested that biological prostheses might be a better choice for patients without Ebstein's anomaly, especially in isolated TVR, due to a lower incidence of valve thrombosis and bleeding.

On echocardiography, differentiating a native tricuspid valve with annuloplasty from a bioprosthetic valve primarily involves visual inspection of the valve structure and surrounding tissue, noting the presence of a ring or prosthesis, and assessing valve motion and regurgitation patterns.[3] Assessment of prosthetic valve is much more complex than native valve.[4] Differentiating native valves from prosthetic valves can be challenging as often just an annular ring may be present in native valve repair as well as bioprosthetic implanted valves. Acoustic shadowing may obscure clear differentiation and hide important information. Native tricuspid valves have characteristically unequal leaflet areas whereas bioprosthetic valves often have uniform leaflets. Disease processes may make this distinction difficult with leaflet size and excursion variability. A mean gradient of >5mmHg across a bioprosthetic TV is suggestive of significant stenosis.[5] Current guidelines support the use of multimodality imaging in assessment of prosthetic valve.[6]

Degeneration of a structural valve is an irreversible process characterised by gradual degenerative changes in the prosthesis, such as growth of pannus, fibrosis of leaflets and calcification, disintegration of the connective tissue, and appearance of perforations and rupture.[7] Structural valve deterioration is a result of multiple complex and poorly understood mechanisms such as immune rejection and valve tissue remodeling as in atherosclerosis.

Due to the problem of TV bio-prosthesis degeneration and high risk associated with repeat surgery, the Edwards SAPIEN valve has been successfully used for valve-in-valve implantation in the tricuspid position. This procedure is considered feasible and safe, with good mid-term outcomes.[8] The Edwards SAPIEN valve may become the preferred prosthesis for such procedures in the future. Percutaneous tricuspid valve balloon valvuloplasty has been performed in patients deemed high risk for surgery with severe tricuspid bio-prosthesis stenosis with variable success in limited case studies.[9]

Conflict of interest: none declared.

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