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Front cover:
A mute Swan in Birds of Eden, Plettenberg Bay.
Photo: Ruchika Meel

GUEST EDITORIAL

Cardiovascular research in South Africa – Past, present, and future

LJ Zühlke[1,2] and E Samodien[1,3]

[1] Office of the Vice-President, South African Medical Research Council, Tygerberg, Cape Town, South Africa
[2] Division of Paediatric Cardiology, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[3] Cochrane South Africa, South African Medical Research Council, Tygerberg, Cape Town, South Africa

Address for correspondence:
Prof Liesl Zühlke
South African Medical Research Council
Tygerberg
7503
Cape Town
South Africa

Email:
liesl.zuhlke@mrc.ac.za

Liesl Zühlke https://orcid.org/0000-0003-3961-2760
Ebrahim Samodien https://orcid.org/0000-0002-8973-7329
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ABSTRACT

Cardiovascular diseases (CVD) remain one of the greatest global health challenges of our time. In the field of cardiology, South Africa (SA) produced several giants and champions whose contributions have been exceptional in their respective spheres. With the complexities required to reduce and prevent such illnesses, we draw inspiration and motivation from our history as we look to overcome future challenges. Here, we share some perspectives on future research priorities, including the usage of several facets of Artificial Intelligence (AI), such as AI-assisted echocardiography, which could unlock pathways to precision medicine, and adopting mobile health (mHealth) technology and wearable instruments for diagnostics, as well as clinical trials investigating the use of polypill interventions. This work echoes calls for health equity, recognising that the future strength of cardiovascular research will require initiatives that promote talent and provide opportunities to grow diverse capabilities within our country. Finally, we highlight the importance of community engagement and co-creation to foster trust and thereby enhance the uptake of interventions, including those aimed at promoting health literacy and education to support positive behaviour change in preventing CVDs and other non-communicable diseases (NCD).
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INTRODUCTION

Cardiovascular health research in SA has made substantial contributions to the field, with a significant global impact. However, research and innovation will need to continue adapting as the burden of CVDs in SA rises. The complexity of SA's CVD burden and the contributing social determinants and risk factors, including the multimorbidity of associated NCDs, makes this task ever more challenging. Multimorbidity can be considered a norm in SA, especially among older adults, with hypertension as the main driver.[1] Such illnesses are now evident not only in adults, but in children too. A recent systematic review and meta-analysis provided updated estimates of paediatric hypertension, suggesting a continued increase in prevalence across the continent, highlighting the potential role of increasing overweight/obesity.[2]

SA's young people also experience a persistent burden of rheumatic heart disease (RHD).[3] This is amidst a legacy of infrastructural disparities in diagnostics and care, with most of these services for CVDs (and others) located mainly in the private sector.[4] Consequently, the vast majority of individuals, especially in rural areas, are unable to access specialised services. There also remain gaps in awareness and education, as well as access to long-term follow-up. These provide opportunities to develop solutions, which will require strengthening multidisciplinary stakeholder engagement.

SA has benefited immensely from the contributions of stalwarts whose exceptional research expertise resulted in significant historical milestones in cardiovascular health, impacting not just our country but the world. If we are to tackle the task ahead, it is best to draw lessons from the past, to remind ourselves of what is possible. Isaac Newton's phrase springs to mind, "If I have seen further, it is by standing on the shoulders of giants." To that we add, "If you don't know where you've come from, how can you hope to know where you are going?" As we look towards the future of CVD research in SA, we offer a moment of reflection on what came before.

FIGURE 1: Cardiovascular research champions of the recent past and unfolding present.
Top, left to right: Prof. Chris Barnard, Prof. Donald Ross, Dr John Barlow, Prof. Lionel Opie, and Prof. Solomon Levin.
Bottom, left to right: Prof. Bongani Mayosi, Prof. Karen Sliwa-Hahnle, Prof. Ntobeko Ntusi, and Dr Martin Mpe.

A history of cardiothoracic surgery in SA has been well detailed by Schewitz.[5] Here we add to it briefly, mentioning some of the giants of the recent past and the unfolding present (Figure 1). These people have massively impacted the field and the current landscape and, to varying degrees, also our personal journeys and careers. As we endeavour to build on the established legacy, we aim to expand the field of cardiovascular research in ways that push scientific boundaries while remaining responsive to society's needs, to ensure the greatest impact for those who require it most. Considering the current cardiovascular research landscape, this work underscores its vital role in shaping the future, particularly in advancing universal health coverage (UHC) and contributing to the National Health Insurance (NHI).

The past – Pioneering foundations

Prof. Chris Barnard is perhaps one of the most notable figures in cardiac surgery in SA, with his special contribution of performing the world's first human heart transplant in 1967 at Groote Schuur Hospital, Cape Town, which caught global attention.[6] Alongside was a colleague, Prof. Donald Ross, an innovator in his own right, developing the Ross procedure, an aortic valve replacement technique that uses the patient's own pulmonary valve.[7] Another sterling contributor was Prof. Lionel Opie, later known as the father of cardiovascular medicine in SA, for pioneering research in heart metabolism and the pharmacological treatment of heart disease, and his advocacy efforts for evidence-based cardiovascular medicine contributed greatly to knowledge building in the field.[8-10] Dr John Barlow, another legend in SA, with his key contribution in linking abnormal heart sounds ("clicks" and murmurs) to mitral valve prolapse, also known as "Barlow syndrome" – a discovery that shaped how doctors worldwide diagnose and understand valve disease.[11] Lastly, though not the least, we remember Prof. Solomon Levin, who published over 120 papers and book chapters and trained hundreds of specialists, leaving an extraordinary legacy in child heart care.[12]

The present – At the heart of the matter

In the free and democratic society of SA, we remember another outstanding clinician, scientist, and teacher, Prof. Bongani Mayosi, whose commitment to academic excellence, collaboration, and social transformation influenced and continues to inspire many. His significant contributions to research, teaching, training, and health policy have deservedly been recognised nationally and internationally with numerous accolades. A champion of research capacity building and health equity, his contributions to the field also included the identification of a novel gene in 2017, which encodes for arrhythmogenic cardiomyopathy. This was recognised as one of the most important medical advances made by a South African scientific team since the first human heart transplant.[13]

Prof. Karen Sliwa-Hahnle is a widely recognised world expert in CVDs, whose efforts have strengthened the CVD research ecosystem in the country, with a special interest in reducing women's mortality, focusing on heart disease in pregnancy and peri-partum cardiomyopathy. She founded the Soweto Cardiovascular Research Unit, advancing knowledge on the intersection of CVDs and maternal health and leads several inter-African and global research projects, with a major impact on creating knowledge and shaping policy on CVDs common in Africa and other low- and middle-income countries (LMIC).[14-16]

FIGURE 2: The board of the South African Medical Research Council (SAMRC) endorsed the adoption of an organisational declaration to raise awareness of persisting health inequities in South Africa, and in particular, their roots in our history of colonisation and apartheid.

Prof. Ntobeko Ntusi is a leading South African cardiologist whose most significant contributions include using advanced imaging and translational clinical research to deepen understanding of heart disease in African populations. He pioneered the use of cardiovascular magnetic resonance (CMR) imaging to characterise and understand heart disease – especially cardiomyopathy, inflammatory heart disease, and human immunodeficiency virus (HIV)-associated CVD.[17-19] Beyond his research, he serves in leadership and mentorship roles, training postgraduate students, supervising research, and is currently the president and chief executive officer of the South African Medical Research Council (SAMRC). His role encompasses influencing health policy, setting research priorities, and capacity building. In 2023, the SAMRC adopted a history and health statement to raise awareness of the persisting health inequities in SA, recognising their roots in our history of colonisation. The declaration acknowledges the organisation's role during apartheid and affirms its active commitment to addressing past injustices while advancing health equity (Figure 2).

Dr Martin Mpe is another noteworthy, distinguished cardiologist known for his leadership in interventional cardiology, cardiac pacing, and heart failure management. He also championed health promotion and education to raise awareness about CVD in under-resourced communities. As the current president of the South African Heart Association, his work combines cutting-edge clinical practice with a strong commitment to public health advocacy.

FUTURE RESEARCH PRIORITIES

SA is experiencing a high prevalence of hypertension, diabetes, and obesity. These are intricately bound to associated risk factors for other NCDs, including cancer and mental health disorders. Such chronic illnesses place an enormous burden on the already strained healthcare system. The consequence is a multimorbid epidemic, a lived experience for many people attempting to manage one or more of these illnesses simultaneously. Any progress to address these NCDs requires an approach that considers social health determinants, aiming to develop interventions that address their common risk factors. In terms of research and innovation, several plausible areas within cardiology can be prioritised. Several of these fields are described below.

Advancing cardiology – Unlocking precision medicine

Going forward, we need both precision and equitable care strategies. There are also calls for the inclusion of underrepresented populations in cardiovascular genetics and epidemiology, with novel genetic risk markers that can expand our current understanding and risk-stratification paradigms.[20] Further research considering genetic, environmental, and social health determinants will be required in developing culturally tailored prevention strategies. This opens the door to more personalised medicine (PM) approaches, which are lacking in SA and broadly across Africa. Adopting policies that incorporate a more PM approach could have a global impact, considering the uniqueness of African genetic diversity.

Furthermore, a study aimed at critically evaluating the current status quo of genetic counselling in SA by uncovering grey areas in their integration within the national healthcare system has highlighted the need for improved genetic education and healthcare inclusiveness to advance genomic medicine and precision healthcare for underserved populations.[21] By analysing policy frameworks, infrastructure, education, and initiatives, genetic counselling could advance patient knowledge and informed decision-making in SA. Despite significant challenges, these can be addressed through targeted research and education, while policy reforms will be critical for integrating genetic-related services into regional healthcare systems, which could be fundamental to improving healthcare strategies and patient outcomes across the continent.[21]

The SAMRC is a partner in the EU-Africa PerMed Consortium, which aims to identify areas of mutual interest and added value for future collaboration and to build sustainable links between Africa and Europe in PM research, development, innovation, and implementation, thereby better integrating the African continent into the global PM agenda. It is also noteworthy to mention the SAMRC's genomics platform and its next-generation sequencing (NGS) technology capability. Starting as a sequencing service with 9 human genomes completed in 2019, it has since developed into a core NGS facility for African genomics, precision medicine, pathogen surveillance, biomarker discovery, clinical trials, and training and mentoring of young scientists. The platform has reached a significant landmark achievement, completing the sequencing of its 10 000th sample, and is well poised to be a leader in advancing the PM agenda on the continent.

AI-assisted echocardiography

Remote interpretation and point-of-care diagnostics in rural areas have the potential to reduce diagnostic delays and human resource burdens. The accuracy of handheld echocardiography

(HAND) has been assessed against that of standard echocardiography (STAND), having the potential to usher in a new age of RHD screening in endemic areas.[22] HAND displayed good accuracy in detecting definite RHD only, and modest accuracy for detecting any RHD; however, it demonstrated poor accuracy in detecting borderline RHD alone. There is also some evidence for the potential of HAND to increase access to echocardiographic screening for RHD in resource-limited and remote settings; nevertheless, further research into the feasibility and cost-effectiveness of wide-scale screening is still required.[22]

Mobile health (mHealth) and wearables

In sub-Saharan Africa (SSA), where there is a high disease burden, a dearth of medical experts, and inadequate healthcare infrastructure, mHealth is particularly advantageous for real-time monitoring and behaviour modification. Behaviour change interventions are increasingly delivered via mHealth, using smartphone applications and wearables. These are believed to support healthy behaviours at the individual level in a low-threshold manner.[23] However, evidence is scarce for LMICs, as well as for people with different socio-economic and cultural backgrounds.

In practice, clinicians and healthcare practitioners could carefully consider the potential benefits, limitations, and evolving research when recommending smartphone applications to overweight or obese adolescents and adults.[23] With the fast adoption of mobile phones and the internet in the SSA region, mHealth technologies are projected to make a substantial contribution to the highly challenged SSA healthcare sector; however, greater efforts are required to integrate wearable sensors into mHealth platforms.[24] The potential impact of this development could be enormous.

Polypill studies

The polypill is a single-pill combination (SPC) therapy for primary and secondary prevention.[25-28] Despite the proven efficacy, safety, and economic benefits of the polypill protocol, pharmaceutical companies remain reluctant to invest in its development and testing. Furthermore, community-based trials to assess uptake and adherence, especially in SA, are still required. Overall, the polypill, combined with advice to improve lifestyles, can facilitate the implementation of worldwide programmes to limit the consequences of CVDs, which is considered the new pandemic of our century.[29]

Currently, there are SPCs for hypertension, which are effective and widely used, but only one formulation is currently licensed for CVD use in SA. Given the tremendous success of SPC antiretrovirals (ARVs) in this country, we have the potential to reduce CVD deaths substantially. According to estimates, only 50% polypill adoption could prevent approximately 2 million CVD deaths and 4 million cardiovascular events per year, which is crucial in attaining the World Health Organization's (WHO) Sustainable Development Goal of reducing global deaths from NCDs by 30% by 2030.[30]

CAPACITY BUILDING, DIVERSITY, AND LEADERSHIP

Increasing evidence suggests that health objectives are best achieved through a multisectoral approach. It requires multiple sectors to consider health and well-being as a central aspect of their policy development and implementation, recognising that numerous health determinants lie outside (or beyond the confines of) the health sector.[31] This needs to be in favour of a "One Health" approach, as opposed to dealing with these illnesses in isolation. Given that several programmes face similar challenges and associated risk factors, efforts aim to target common risk factors for these conditions, such as nutrition and physical inactivity.[32]

Furthermore, infrastructure that benefits a cardiovascular registry may also benefit a cancer registry. With so many people experiencing several of these illnesses, their information and data would likely need to be captured across these registries. As an example, the South African Population Research Infrastructure Network (SAPRIN)-enabled CVD registries/cohorts for real-world evidence and policy feedback loops could be considered.[33] This could facilitate the development of "Big Data" and the generation of standardised national datasets to inform policy and practice. In addition, training and mentoring the next generation of cardiovascular researchers, including strengthening expertise in biostatistics, AI, and implementation science, and investing in research infrastructure, will be necessary. This should include equitable funding mechanisms and initiatives that promote African-led collaborations across the continent.

A diverse workforce is increasingly recognised as paramount in SA's cardiovascular research ecosystem. The critical contributions of women, those from underrepresented groups, universities, and institutions to the cardiovascular research ecosystem in our country are being acknowledged. Of the past five presidents of SA Heart®, three were women, as were the current and recent presidents of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology. Furthermore, increasing African leaders in clinical trials, journal editorships and boards, as well as funding agencies, will ensure a more resilient research landscape, with a focus on LMIC priorities.[34]

We echo calls for partnerships involving various sectors, including robust community engagement, to effectively deliver and sustain health-promoting policies and actions.[31] Regarding health systems research and reform, towards UHC, which is underpinned by cost-effective models for long-term care, decentralised and task-sharing approaches, more public-private academic collaborations are needed. It will be important to conduct policy-relevant research that influences not only CVD research strategies but also the national NCD strategy, given the interconnectedness and associated risks of these illnesses. Chronic condition management increasingly strains health systems, far exceeding acute care needs globally, necessitating adaptation.[35]

In this context, an analysis of clinical interventions targeted at adults aged 15+, with evidence of the direct costs of type 2 diabetes mellitus (T2DM), hypertension, and CVDs in SA, reported primary estimates of in- and out-of-hospital costs from a provider perspective.[36] Drugs and treatment of complications were major cost drivers for hypertension and T2DM, with hospitalisation driving CVD costs. It was found that 39% of identified CVD treatment costs used a private sector perspective, leaving significant research gaps in the public sector and the cheaper to treat hypertension and T2DM.[36]

Furthermore, a systematic review investigating the relationship between socio-economic inequalities and fatal and non-fatal cardiovascular events found that, although not statistically significant, women of low socio-economic status (SES) were at higher CVD risk than men. It was found that CVD risk was more relevant to educational than economic inequality.[37] These results support previous findings, which highlighted that low SES is linked to increased CVD risk in high-income countries, and that women with low SES had a relative risk of 2.24 for angina pectoris (chest pain or discomfort) compared to their high SES counterparts, whereas no significant difference was observed in men.[38,39] Additionally, given the high prevalence of central obesity in children that can ultimately result in cardiovascular risk factors and mental health issues, the need for systems jointly initiated by healthcare providers, policymakers, and general society is highlighted to reduce the burden of central obesity by introducing children and adolescents to health-promoting lifestyles.[40]

Community-level interventions, such as hypertension control, are considered useful for preventing cardiovascular and cerebrovascular events. Unfortunately, systematic evaluation of such community-level interventions among patients living in LMICs is scarce. Thus, community-based strategies are relevant in addressing the burden of hypertension and aid in decentralised hypertension care in LMICs, while confronting the gap in access to care, without diminishing the quality of hypertension control.[41] Thus, a similar approach can be used to ensure that interventions are culturally safe, having been co-designed by the people requiring these services themselves.

CONCLUSION

SA has a long, rich legacy of innovation and multiple global contributions to cardiovascular research. The field is growing with new scientists, basic clinicians, innovators, and trialists – many leading their respective fields. Future research efforts must be diverse, spanning from genetic studies to clinical trials and public health initiatives, with a particular emphasis on the unique challenges faced by our country and region. Addressing the rising burden of CVD requires bridging science, systems, and society. The future lies in equity-driven, data-informed, and technology-enabled solutions. The country needs to prioritise translational research, community and lived-experience partnerships, and the rapid advancement of skilled services, such as cardiac surgery. Overcoming the challenges posed not only by CVDs but by all related illnesses and associated risk factors will require a collective commitment from all of society.

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This work formed the basis for a keynote address at the European Society of Cardiology Conference in Madrid, Spain, in September 2025. Here, we honour several pioneers, champions, and ongoing sterling contributors to South African cardiovascular research, while acknowledging that we were unable to feature many other exceptional researchers. We also acknowledge the academic institutions, funders, and patient communities that have enabled the progress we have witnessed in this field of research specialisation.

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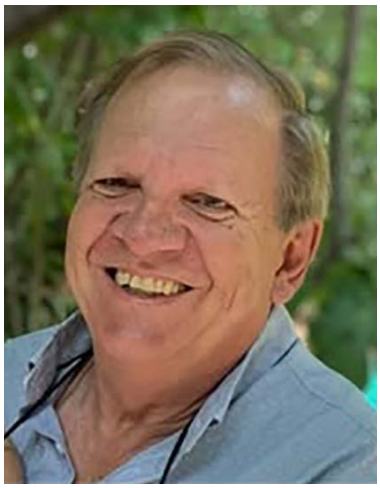
IN MEMORIAM — DR COBUS BADENHORST



Dr Cobus Badenhorst passed away on 27 October 2025 after a short and traumatic illness. It happened too unexpectedly and too soon, leaving his family, friends, colleagues, and patients in deep shock and sorrow.

Born in 1954, Cobus matriculated in Lichtenburg. He went on to study medicine at the University of Pretoria, where he completed his Master of Medicine in Internal Medicine Cum Laude, before pursuing a career in cardiology. In 1989, Cobus entered private practice and became one of the first specialists at Netcare Unitas Hospital, where he built a career defined by excellence and tireless dedication. He chose a field that demands precision and lifelong learning – qualities he fully embodied.

I was privileged to be his partner for 35 years, and in all those years, there was never a single dispute or conflict. Cobus was the epitome of professionalism: a trusted colleague, a loyal friend, and a partner with whom I shared both hardship and immeasurable joy. A gifted cardiologist with exceptional knowledge and technical skill, Cobus was admired for his sound clinical judgment and advice. He was an esteemed member of the cardiology fraternity and served as Treasurer of the South African Heart Association, where his leadership, integrity, and wisdom were widely respected.

We will also remember him for his humility and unwavering commitment. He was a cardiologist whose work was more than a profession; it was a profound calling. Cobus, affectionately known as Dr Badie, was popular, friendly, and accommodating, and his zest for life was infectious. He was the heart and soul of our practice.

Above all, Cobus's greatest pride and joy was his family. His children, Jacques and Elyzka, both followed in his footsteps to become doctors, which brought him immense fulfilment. He embraced life wholeheartedly, was an avid golfer, a lover of the bushveld, an exceptional hunter, and a master storyteller whose company was treasured by all who knew him.

His passing has left an irreplaceable emptiness. Cobus was a remarkable human being who touched countless lives. The legacy of his life and his service will live on in everyone who had the privilege of knowing him.

Dr Jean Vorster
Cardiologist
MBChB (Pret), MMed (Int) (Pret), Cert Cardiology (SA), FESC
South African Society of Cardiovascular Intervention (SASCI) vice-president
Netcare Unitas Hospital
South Africa

Factors associated with deep vein thrombosis recurrence at a cardiology department in sub-Saharan Africa

EH Lengani,[1] WM Nacanabo,[1] A Tall/Thiam,[1] LP Thiombiano,[1] TAA Seghda,[1] IY Tamou-Tabe,[1] M Loya/Abouga,[1] DC Dah,[1] I Sawadogo,[1] SM Dimzouré,[1] GRC Millogo,[2] KK Jonas,[2] Y Kambiré,[3] NV Yaméogo,[2] AK Samadoulougou,[1] and P Zabsonré[2]

[1] Cardiology Department, Bogodogo University Hospital, Burkina Faso
[2] Cardiology Department, Yalgado Ouédraogo University Hospital, Burkina Faso
[3] Cardiology Department, Tengandogo University Hospital, Burkina Faso

Address for correspondence:
Wendlassida Martin Nacanabo
Cardiology Department
Bogodogo University Hospital
Burkina Faso

Email:
nacmartinwend@gmail.com

WM Nacanabo https://orcid.org/0009-0002-2047-1830
A Tall/Thiam https://orcid.org/0009-0009-3437-0003
TAA Seghda https://orcid.org/0000-0003-3840-9322
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ABSTRACT

Objective: Deep vein thrombosis (DVT), once rare, has become increasingly common in Africa. This study aimed to identify factors associated with DVT recurrence.

Methodology: We conducted a descriptive and analytical cross-sectional study from 1 January 2020 to 31 December 2024 at the cardiology department of Bogodogo University Hospital (CHU-B). Patients admitted to the department for DVT on venous echo-Doppler were included. Epidemiological, clinical, and paraclinical parameters were crossed in univariate and multivariate analyses.

Results: During the study period, 164 cases of DVT were recorded out of 2 637 hospitalised patients, with a 6.22% hospital prevalence rate. The mean age was 51.4 years. Women were predominant (90, 55%), with a sex ratio of 0.8. Recurrences occurred in 27.44% of cases (n = 45). A sedentary lifestyle, prior DVT, and obesity were the most frequent thromboembolic risk factors. Multivariate analysis showed that a personal history of DVT (odds ratio [OR] 3; p = 0.03), obesity (OR 3.8; p = 0.005), and the femoral thrombus location (OR 2; p = 0.004) were significantly associated with DVT recurrence.

Conclusion: DVT recurrences are becoming increasingly frequent, and their management requires accurate identification of the risk factors.

Keywords: deep vein thrombosis, recurrence, associated factors, Burkina Faso.

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INTRODUCTION

DVT is the partial obstruction of a deep vein by a thrombus formed in situ.[1] Along with pulmonary embolism (PE), it is the main form of venous thromboembolism (VTE), with an estimated incidence of 115–269 per 100 000 people.[2] DVT can affect the entire venous network, with a preferential location in the veins of the lower limbs.[3] It is often the prelude to PE, can recur in 30% of patients, and 25–40% of cases can develop post-thrombotic syndrome (PTS).[4] Once thought rare in Africa, VTE, and specifically PE, has become one of the leading causes of consultation and hospitalisation in cardiology departments in sub-Saharan Africa, especially in Burkina Faso.[5-7] Isolated DVT has not been well documented, and factors associated with recurrence remain unknown in our context. This study aimed to determine the prevalence of DVT and identify the predictors of recurrence at the cardiology department of CHU-B to promote better curative and prophylactic management.

PATIENTS AND METHODS

Study setting and period

This was a descriptive and analytical cross-sectional study conducted from 1 January 2020 to 31 December 2024 at the cardiology department of CHU-B in Burkina Faso. CHU-B is a third-level hospital in Burkina Faso's health pyramid and receives many patients. The cardiology department is a centre of excellence, with a 24-hour on-duty cardiologist facilitating adequate management of cardiovascular pathologies, particularly thromboembolism.

Inclusion and exclusion criteria

All patients admitted during the study period for DVT of the lower limbs detected by venous Doppler ultrasound were included. Other thrombotic locations and cases with suspected diagnoses not confirmed by Doppler ultrasound were excluded.

Study variables and operational definitions

Recurrent DVT was considered the dependent variable. The subordinate variables were:

- Socio-demographic data, including age and sex.
- Thromboembolic risk factors, such as a sedentary lifestyle, obesity, prolonged immobilisation, recent surgery or trauma, pregnancy or postpartum.
- Clinical variables, particularly the presence of a large painful leg, paraesthesia, fever, tachycardia, Mahler's climbing pulse, and local signs of inflammation (oedema, redness or cyanosis, warmth).
- Homans' sign, reduced calf balloting.
- Ultrasound data, including thrombosis location, extent, etc.
- Therapeutic parameters, evolution, and complications.

DVT is defined as thrombotic obstruction (often of fibrinocrural origin) of a deep venous trunk, often located in the lower limbs.[8] DVT recurrence is defined as the occurrence of a new thrombotic event in a subject with a history of DVT.[9] PTS was defined as the presence of chronic venous symptoms and/or signs secondary to DVT of the lower limbs.[10]

Data processing and analysis

All data were entered on a microcomputer and analysed using Epi Info software, French version 7.2.5.0. All patients were divided into 2 groups according to DVT recurrence: "DVT recurrence positive (+)" versus "DVT recurrence negative (-)". Positional parameters were used to characterise the quantitative variables. The chi-square test was used in a univariate analysis to determine which qualitative variables were associated with DVT recurrence. All variables with univariate *p*-values < 0.2 were included in a multivariate logistic regression model to determine independent predictors of DVT recurrence. A *p*-value < 0.05 defined the significance threshold.

Ethical considerations

Data were collected on anonymised, individual survey forms to maintain patient confidentiality. We obtained approval from the CHU-B ethics committee (number 2025-01-35) before patient inclusion. All included patients freely agreed to participate after understanding the rationale of the study. The remainder of the study was conducted in accordance with the principles of good clinical practice.

RESULTS

General characteristics of the study population

During the study period, 2 637 patients were admitted to the department, including 164 patients with DVT. The prevalence of DVT recurrence was 27.43% (*n* = 45). Women accounted for 55% (*n* = 90), with a sex ratio of 0.8. The mean age was 51.4 ± 17.3 years, with extremes of 17 and 94 years. The 41–60 age group was the most represented (*n* = 59, 36%), with a higher recurrence rate in the 61–80 age group (Figure 1). In 2023, there were 38 DVT cases, including 13 patients with at least one previous similar episode. Figure 2 shows the annual distribution of DVT and recurrences.

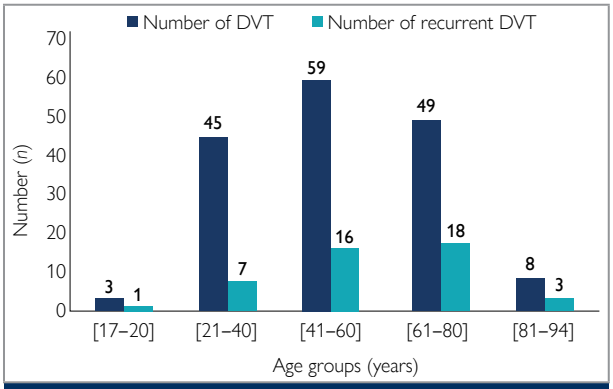

FIGURE 1: Distribution and recurrence of deep vein thrombosis by age group.

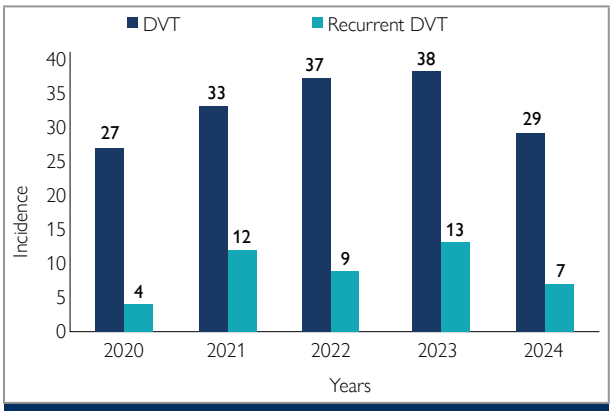

FIGURE 2: Annual distribution and recurrence of deep vein thrombosis.

Comparison of clinical characteristics in univariate analysis

For the univariate comparative analysis of "DVT recurrence +" versus "DVT recurrence -", the thromboembolic risk factors associated with recurrence were bed rest for more than 3 days ($p = 0.18$), a sedentary lifestyle ($p = 0.14$), obesity ($p = 0.02$), infection ($p = 0.006$), age ≥ 65 years ($p = 0.002$), and prior DVT ($p = 0.004$) (Table I). Pelvic limb swelling ($p = 0.003$), decreased calf bouncing ($p = 0.18$), and Homans' sign ($p = 0.15$) were the associated clinical signs in univariate analysis (Table I).

Comparison of paraclinical characteristics in univariate analysis

At the paraclinical level, anaemia ($p = 0.16$), popliteal location ($p = 0.076$), and femoral location ($p = 0.002$) were the parameters associated with DVT recurrence in univariate analysis (Table II).

Therapeutic and evolutionary aspects

In this study, all patients received heparin therapy and venous restraint. Vitamin K antagonists were the most indicated oral

TABLE I: Univariate analysis of clinical parameters.

Variables	General population *n* = 164	DVT recurrence + *n* = 45 (%)	DVT recurrence - *n* = 119 (%)	OR (95% CI)	*p*-value
Recent travel	10	3 (30)	7 (70)	0.9 (0.2 to 3.7)	0.956
Thromboembolic risk factors					
Recent trauma	11	1 (9.1)	10 (90.90)	4.0 (0.5 to 7)	0.730
Postpartum	10	3 (30)	7 (70)	1.6 (0.3 to 7.6)	0.541
Cancer	10	6 (60)	4 (40)	0.4 (0.1 to 1.7)	0.356
Recent surgery	11	1 (9.10)	10 (90.90)	4.0 (0.5 to 34)	0.345
Chemotherapy	4	2 (50)	2 (50)	0.4 (0.1 to 2.8)	0.307
HIV	6	4 (66.70)	2 (33.30)	0.3 (0.1 to 2.0)	0.269
Breastfeeding ≥ 3 days	19	7(36.80)	12 (63.20)	0.6 (0.2 to 1.7)	0.186
Sedentary lifestyle	117	35 (29.90)	82 (70.10)	0.7 (0.3 to 1.7)	0.146
Obesity	43	10 (23.30)	33 (76.70)	4.1 (1.7 to 10)	0.020
Infection	10	7 (70)	**3 (30)**	**7.1 (1.7 to 2.8)**	**0.006**
DVT history	**45**	**45 (100)**	**0 (0)**	**1.7 (1.0 to 2.4)**	**0.004**
General signs					
PGM	17	4 (23.50)	13 (76.50)	1.3 (0.4 to 4.0)	1.00
Tachycardia	30	9 (30.00)	21 (70.00)	0.9 (0.4 to 2.1)	0.722
Fever	33	12 (25.20)	21 (74.80)	0.6 (0.3 to 1.3)	0.244
Swelling of the LP	**147**	**41 (27.90)**	**106 (72.10)**	**0.3 (0.1 to 1.5)**	**0.003**
Physical signs					
Erythematous plaque	14	1 (07.15)	13 (92.85)	1.2 (0.7 to 2.0)	0.860
Satellite adenopathy	73	26 (35.62)	47 (64.38)	0.6 (0.3 to 1.2)	0.706
Local heat	140	10 (07.10)	130 (92.90)	0.5 (0.2 to 1.8)	0.608
Redness	99	31 (31.30)	68 (68.70)	0.8 (0.4 to 1.6)	0.502
Paraesthesia	33	26 (78.79)	7 (21.21)	3.0 (1.1 to 10)	0.430
BC reduction	**125**	**33 (26.40)**	**92 (73.60)**	**1.6 (0.8 to 3.7)**	**0.180**
Homans' sign	**138**	**45 (32.61)**	**93 (63.39)**	**0.4 (0.1 to 1.3)**	**0.156**

CI: confidence interval, DVT: deep vein thrombosis, HIV: human immunodeficiency virus, OR: odds ratio, PGM: Mahler climbing pulse , LP: pelvic limb, BC: Calf bouncing

TABLE II: Univariate analysis of paraclinical parameters.

Variables	General population *n* = 164	DVT recurrence + *n* = 45 (%)	DVT recurrence - *n* = 119 (%)	OR (95% CI)	*p*-value
High D-dimer	88	35 (39.80)	53 (60.20)	1.6 (1.4 to 1.9)	0.860
Sural thrombus	51	28(54.91)	23 (45.09)	1.3 (0.6 to 2.9)	0.777
Leucopaenia	21	7 (33.34)	14 (66.66)	0.7 (0.3 to 1.9)	0.544
Iliac thrombus	83	36 (43.38)	47 (56.62)	0.5 (0.4 to 1.2)	0.476
Elevated CRP	87	29 (33.30)	58 (66.70)	0.8 (0.4 to 1.6)	0.378
Hyperleucocytosis	16	6 (37.50)	10 (62.50)	0.7 (0.1 to 4.1)	0.356
Thrombocytosis	11	1 (90.90)	10 (90.90)	3 (0.5 to 3.0)	0.311
Thrombocytopaenia	16	7 (43.70)	9 (56.30)	0.5 (0.2 to 1.4)	0.205
Anaemia	85	25 (29.40)	60 (70.60)	0.8 (0.4 to 0.8)	0.160
Popliteal thrombus	111	32 (28.29)	79 (71.71)	0.7 (0.3 to 1.5)	0.076
Femoral thrombus	113	37 (32.75)	76 (67.25)	0.5 (0.2 to 1.2)	0.002

CI: confidence interval, DVT: deep vein thrombosis, OR: odds ratio, CRP: C-reactive protein

TABLE III: Results of multivariate analysis of factors associated with DVT recurrence.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sedentary lifestyle	0.7(0.3 to 1.7)	0.146	1.8(0.7 to 3.8)	0.950
Age ≥ 65 years	1.5 (0.2 to 2.1)	0.002	1.8(0.3 to 4.6)	0.687
Age 61–80 years	2 (0.3 to 2.2)	0.004	1 (0.4 to 2.2)	0.634
Bed rest	0.6 (0.2 to 1.7)	0.186	2.6(0.5 to 7.03)	0.410
Homans' sign	0.4 (0.1 to 1.3)	0.156	1.6(0.7 to 3.84)	0.410
Pelvic limb oedema	0.3 (0.1 to 1.5)	0.003	0.4(0.1 to 1.6)	0.329
Popliteal thrombus	0.7 (0.3 to 1.5)	0.076	0.9(0.1 to 3.7)	0.304
Infection	7.1 (1.7 to 2.8)	0.006	1.4(0.7 to 3.5)	0.295
Anaemia	0.8 (0.4 to 0.8)	0.160	1.6(1.0 to 3.5)	0.130
DVT history	1.7 (1.0 to 2.4)	0.004	3 (1.1 to 2.2)	0.030
Obesity	4.1 (1.7 to 10)	0.020	3.8(1.7 to 6.0)	0.005
Femoral thrombus	0.5 (0.2 to 1.2)	0.002	2 (1.1 to 3.7)	0.004

CI: confidence interval, DVT: deep vein thrombosis, OR: odds ratio

anticoagulant in 81.10% of patients (*n* = 133). Complications were noted in 11 patients (6.71%): infection (*n* = 6), venous insufficiency (*n* = 3), and PTS (*n* = 2).

Multivariate analysis of variables associated with thrombosis recurrence

In multivariate logistic regression, the variables significantly associated with DVT recurrence were obesity ($p = 0.005$), prior DVT ($p = 0.03$), and femoral thrombus location ($p = 0.004$). Table III presents the results of the multivariate analysis of factors associated with DVT recurrence.

DISCUSSION

Epidemiological aspects

During the study period, DVT accounted for 6.21% of hospitalisations at the cardiology department of CHU-B. The prevalence of recurrent DVT was 27.43%. In fact, DVT is a real public health problem, with its prevalence increasing markedly in all series. Although this prevalence is higher than in previous Burkina Faso studies (4.71%), it is still lower than Western rates.[3,4,11] Presently, the increasing availability of diagnostics has substantially improved DVT management, even though the disease often recurs. Previous sub-Saharan series reported DVT recurrence rates of 10.2–16.24%.[12,13] This high prevalence is part of a context marked by an outbreak of multiple anticoagulant classes with variable protocols, often making compliance difficult in our population.

Our study shows an average age of 51.4 years, with most DVT recurrences between 61 and 80 years. While it is accepted that the risk of a first VTE event increases with age, the link with recurrence remains controversial.[14,15] It varied between our study and the studies by Soya, et al. in the Ivory Coast and Kaboré, et al. in Burkina Faso.[12,13] This controversy aligns with the increase in thromboembolic risk factors linked to the westernisation of lifestyles, with its corollary of chronic inflammatory and malignant tumours responsible for hypercoagulability.[16,17]

Females predominated in our study, accounting for 55% of DVT cases and 57.77% of recurrences (26/45). These results correspond with most previous series.[12,13] The strong female predominance is not specific to DVT but extends to all venous thromboembolic diseases.[6,18] Women are exposed to an increased risk of thrombosis due to their hormonal physiology, sedentary lifestyle, obesity, and use of oral contraceptives.

Risk factors for DVT recurrence

Although responsible for permanent thrombotic risk, active cancer (*n* = 10) and human immunodeficiency virus (HIV) infection (*n* = 6) did not correlate with DVT recurrence. This contrasts with data in the literature, where the risk of VTE recurrence is multiplied 2–4 times in patients with one of these major thrombotic factors.[14,19] Active research into these factors is not part of routine practice in our context, although it is extremely necessary. Moreover, these patients have not received long-term follow-up. In the presence of these factors, the pathophysiological thrombotic mechanisms are inherent in the secretion of procoagulant factors, certain thrombogenic antitumour and antiretroviral therapies, and the reduction in the levels of physiological anticoagulant proteins.[20,21]

Series studying the link between thrombotic location and recurrence have produced conflicting results. Femoral location was significantly associated with DVT recurrence in this study (OR 2, 95% confidence interval [CI] 1.1 to 3.7; $p = 0.004$). In a study of 738 patients followed up for 3–8 years, Hansson, et al. also found that proximal thrombosis was associated with recurrence (relative risk [RR] 2.40, 95% CI 1.48 to 3.88; $p < 0.001$).[19] In fact, it is clearly established in the literature that the risk of recurrence correlates with the level of DVT and the location of the anterior site.[14] The more proximal a venous thrombosis, the higher the risk of VTE. Proximal DVT doubles

the risk of recurrence compared with distal (sub-popliteal) DVT.[19]

In our series, the recurrence rate was statistically significant in patients with a history of proximal DVT (OR 3, 95% CI 1.1 to 2.2; p = 0.03). This result is consistent with several series in the literature, particularly those by Hansson, et al., who also demonstrated the same association.[19] During the first episode of DVT, valve damage leads to a disturbance in plasma rheology, thus favouring recurrent thrombotic events, especially in the presence of a defect in the coagulation or fibrinolytic system.[22]

Finally, as in most venous thromboembolic disease studies, a sedentary lifestyle and obesity were the most frequent thromboembolic risk factors in patients with thrombotic recurrence in this study. Obesity was also associated with recurrence (OR 3.8, 95% CI 1.7 to 6.0; p = 0.003). Previously considered rare in Africa, obesity is now increasingly becoming a public health problem in our region.[23] In the Ivory Coast, its prevalence was 29% in the study by Soya, et al. in 2019, and was associated with DVT recurrence after 2 years (OR 4.51; p = 0.0012).[12] This physiological state induces chronic inflammation, hypercoagulability, and venous stasis, particularly in the lower limbs, contributing to thrombotic recurrence.

Limitations and future directions

Although our study has many strengths, specifically its analytical and original nature, it may be subject to bias; however, this does not affect its quality. A selection bias could exist in our study due to the organisation of the patient referral system in our country. Peripheral centres, which do not always have qualified staff, often refer patients with venous thrombosis to the central level. The second limitation concerns the study's cross-sectional design. The lack of long-term patient follow-up prevents establishing the necessary duration of curative anticoagulation in black Africans, limiting the recommendations from this study. An information bias is also possible since the investigator was informed of the results of the investigations for DVT diagnosis. Multicentre cohort studies incorporating the risk prediction for recurrence would increase the relevance of these results.

CONCLUSION

DVT is a frequent pathology with significant morbidity and mortality due to the immediate risk of PE. Its incidence is increasing rapidly in Africa, particularly in Burkina Faso. Recurrence was one of the complications encountered and was associated with obesity, prior venous thrombosis, and femoral thrombus location in this study. Larger, more in-depth multicentre studies using prospective cohorts to assess the probability of recurrence using validated scores are needed to confirm and enrich this data.

Conflict of interest: none declared.

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The relationship between clinical parameters and the risk of mortality or requiring the insertion of a pacemaker in patients with bifascicular block

DC Mitchell, AF Doubell and J Moses

Division of Cardiology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

Address for correspondence:
DC Mitchell
6 Weaver Street
Table View
Cape Town
South Africa
7441

Email:
dcmitch1@gmail.com

DC Mitchell https://orcid.org/0009-0008-9645-9495
AF Doubell https://orcid.org/0009-0005-7699-8684
J Moses https://orcid.org/0000-0001-8304-6896
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ABSTRACT

Introduction: Patients with bifascicular block (BFB) are at risk of progressing to high-degree atrioventricular block (AVB) and have a higher mortality risk. This study aimed to identify relationships between clinical parameters in patients with BFB and the risk of mortality and/or requiring permanent pacemaker (PPM) insertion, to better risk-stratify and appropriately investigate patients at the time of diagnosis in a resource-limited setting.

Method: A descriptive study was conducted via retrospective review of all patients who received an electrocardiogram (ECG) during 2014 at Tygerberg Hospital (TBH), South Africa. In total, 16 280 ECGs were assessed, accounting for 11 881 patients (some patients had more than 1 ECG), and those with BFB were identified. Patients' records were assessed at the time of diagnosis and followed for 10 years to identify relationships between clinical parameters in patients with BFB and mortality or requiring a PPM.

Results: Of the 11 881 patient ECGs assessed, 140 patients with BFB were identified. The mean age at diagnosis was 62 ± 17 years. Of these patients, 37 (26%) died, and 9 (6%) required a PPM. The mean age at diagnosis of demised patients was 66 ± 12 years (p = 0.07). Significant relationships with mortality included diabetes mellitus (DM) (p = 0.04) and a reduced left ventricular ejection fraction (LVEF) (p = 0.05), with age and hypertension related at a lower level of significance (p = 0.07 and p = 0.06, respectively). Significant relationships with PPM insertion were symptom presence at diagnosis ($p \leq 0.01$) and PR interval prolongation at a lower level of significance (p = 0.08).

Conclusion: In patients with BFB, DM, hypertension, age, and a reduced LVEF had the most significant relationships with mortality. Symptoms and a prolonged PR interval had the most significant relationships with requiring a PPM. Mortality in patients with BFB is more likely to be related to standard risk factors, such as DM, hypertension, age, and a reduced LVEF, than the conduction defect per se.

Keywords: bifascicular block, mortality, pacemaker.
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INTRODUCTION

The prevalence of bifascicular block (BFB) is estimated at 1–1.5% in the general population.[1] The mortality rate for this population ranges from 2% to 14%, which is higher than that of an age- and sex-matched population without BFB.[1-3] Patients with a bundle branch block have at least a threefold higher mortality risk after 10 years from diagnosis compared with patients who have narrow complexes.[1] BFB is often perceived to be prone to progression to third-degree atrioventricular block (AVB), as it involves 2 of the 3 fascicles in the His-Purkinje System (right bundle branch block [RBBB] with either left anterior or left posterior fascicular block [LAFB/LPFB]), with conduction depending on the remaining fascicle.[4] However, the reason for this higher mortality rate is multifactorial, with intrinsic organic cardiac disease and the risk of developing high-degree AVB and ventricular arrhythmias.[4]

The incidence of progression to high-degree AVB is reportedly low, with previous studies reporting an annual incidence of 1%.[3,5] Symptomatic BFB, defined as unexplained presyncopal symptoms or unexplained syncope, can be effectively managed with permanent pacemaker (PPM) insertion.[6,7] However, according to previous studies, there is no mortality benefit of PPM insertion, suggesting that the cause for mortality in these patients is not related to the development of high-degree AVB, but rather organic cardiac disease and/or ventricular tachyarrhythmias.[4,8] Predictors of mortality or developing high-

degree AVB have been investigated previously; however, these studies were conducted in developed settings with easy access to both electrophysiology study (EPS) and PPM insertion.

Cardiac failure, with an advanced New York Heart Association (NYHA) Functional Classification, hypertension, advanced age, atrial fibrillation (AF), and renal impairment were independent predictors of mortality in patients with chronic BFB.[6,9,10] Factors noted to predict progression to high-degree AVB were indicated by symptom presence, a His-bundle ventricular (HV) interval > 64 ms, a QRS duration > 140 ms, and renal dysfunction.[11] To our knowledge, no studies in Africa have attempted to assess the relationships between clinical parameters and mortality or requiring pacing in patients with BFB.

Current guidelines from the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) for investigating and managing patients with symptomatic BFB require significant expertise, may not be cost-effective, and can therefore be challenging in a resource-limited setting.[12,13] This study aimed to identify relationships between patients with BFB and mortality or progression requiring PPM insertion, to better risk-stratify and appropriately investigate patients at the time of diagnosis in a resource-limited setting.

METHODS

Study design

A descriptive, observational study was conducted via retrospective review. Patients with BFB were identified by screening all electrocardiograms (ECGs) performed at Tygerberg Hospital (TBH) during 1 year, and their clinical data were collected by reviewing hospital records over 10 years. All ECGs were accessed using the MUSE platform and were individually assessed by the investigators for BFB identification. Data analysis was performed to establish relationships between the identified variables and endpoints. The primary endpoints were all-cause mortality or PPM insertion. Ethical approval was obtained from the Health Research Ethics Committee (reference number: N22/07/086).

Patient population

All ECGs performed at TBH and stored on the MUSE system during 2014 (1 January to 31 December) were individually assessed by the investigators to identify patients with BFB. BFB was defined by RBBB with either LAFB or LPFB. RBBB was defined as per the standard definition.[14] LAFB was defined as a mean frontal QRS axis < -45° with a qR pattern in lead aVL, rS pattern in leads II, III, aVF, a R-peak time > 45 ms in lead aVL, and

TABLE I: Descriptive analysis assessing the relationship between variables in patients with bifascicular block and mortality or requiring a pacemaker.

Variables	Total patients (*n* = 140)	Total demised (*n* = 37)	Total survived (*n* = 103)	*p*-value	Required PPM (*n* = 9)	Did not require PPM (*n* = 131)	*p*-value
Age at diagnosis Mean (SD)	62 (17)	66 (12)	60 (18)	**0.07**	63 (18)	62 (17)	0.83
Sex, male *n* (%)	95 (68)	24 (65)	71 (69)	0.68	6 (67)	89 (68)	1.00
Symptomatic at presentation *n* (%)	18 (13)	3 (8)	15 (15)	0.40	5 (56)	13 (10)	**< 0.01**
Smoking *n* (%)	43 (31)	12 (32)	31 (30)	0.84	3 (33)	40 (31)	1.00
Hypertension *n* (%)	95 (68)	30 (81)	65 (63)	**0.06**	4 (44)	91 (70)	0.15
Diabetes mellitus *n* (%)	44 (31)	17 (46)	27 (26)	**0.04**	2 (22)	42 (32)	0.72
Ischaemic heart disease *n* (%)	61 (44)	19 (51)	42 (41)	0.33	2 (22)	59 (45)	0.30
Hypercholesterolaemia *n* (%)	66 (47)	17 (46)	49 (48)	1.00	4 (44)	62 (47)	1.00
eGFR < 60 ml/min/1.73 m^2 *n* (%)	31 (22)	9 (24)	22 (21)	0.82	3 (33)	28 (21)	0.41
PR interval > 200 ms *n* (%)	17 (12)	4 (11)	13 (13)	1.00	3 (33)	14 (11)	**0.08**
Atrial fibrillation *n* (%)	19 (14)	8 (22)	11 (11)	0.16	3 (33)	16 (12)	0.11
Ejection fraction Mean (SD)	51 (14)	46 (14)	53 (13)	**0.05**	55 (11)	51 (14)	0.56

eGFR: estimated glomerular filtration rate, n: number, PPM: permanent pacemaker, SD: standard deviation.

the absence of other causes for left axis deviation (e.g. inferior myocardial infarction [MI]).[15] LPFB was defined as a mean frontal QRS axis > 90° with a rS pattern in leads I and aVL, and a qR pattern in leads III and aVF in the absence of other causes for right axis deviation.[15]

Patients were included in the study if they were older than 18 years and had at least 1 12-lead ECG conducted during the study period. Patients were excluded from the study if they had pre-existing second– or third-degree AVB or a life expectancy < 1 year due to other chronic illnesses. Patients' demographic information and whether they were asymptomatic or symptomatic (any history of unexplained presyncope or syncope), smoking history, chronic comorbidities, coexisting cardiac disease, AF, and left ventricular ejection fraction (LVEF) at the time of diagnosis were documented. All patients who were not documented as having experienced syncope, presyncope, or dizziness were considered asymptomatic.

All biochemistry data were obtained from the South African National Health Laboratory Service, and renal function was assessed using the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated glomerular filtration rate. Valvular heart disease (VHD) was considered significant if the lesion severity was graded at least moderate, per the ACC guidelines for managing patients with VHD, or if the patient had prior valve replacement.[16] Other conduction abnormalities (first-degree AVB, AF, and atrial flutter) were defined as per their standard definitions.[17,18]

Statistical analysis

Normally distributed data were presented as means with standard deviations. Categorical data were presented as percentages. We assessed the relationships between each clinical characteristic and LVEF and each of the 2 endpoints (i.e. mortality and requiring PPM insertion), using analysis of variance (ANOVA), with a least significant difference (LSD) test, chi-squared test, and Fisher's exact test where appropriate. Clinical characteristics were used for comparison when there were more than 10 cases for a specific characteristic or variable. A p-value ≤ 0.05 was considered statistically significant, and a p-value of 0.05–0.1 was significant at a lower level of significance.

RESULTS

A total of 16 280 ECGs were assessed, representing a patient population of 11 881 (some patients had more than 1 ECG in 2014). Of these, 140 patients had BFB, with a prevalence of 1.18% among adults receiving ECGs at TBH in 2014. The mean age was 62 ± 17 years, and 95 patients (68%) were male. RBBB with LAFB was present in 86 patients (61%). At the initial diagnosis, asymptomatic patients accounted for 122 (87%) of the total cohort. AF was identified in 19 (14%) of the cohort, and 17 (12%) had first-degree AVB. Congenital heart disease was noted in 17 patients (12%). Of the total cohort, 95 patients (68%) had hypertension, and 44 (31%) had diabetes mellitus (DM). One patient (1%) in the study population had sarcoidosis, and 2 (1%) had hypertrophic cardiomyopathy (HCM). Echocardiography was performed around the time of diagnosis in 86 patients (61%), with a mean LVEF of 51% ± 14%. A total of 37 patients (26%) demised, and 9 patients (6%) required PPM insertion. The clinical characteristics of the study population are summarised in Table I.

Mortality

The study population's all-cause mortality comprised 37 patients (26%). These patients were older, with a mean age of 66 ± 12 years at the time of initial diagnosis compared with the rest of the cohort, who had a mean age of 60 ± 18 years (p = 0.07). The mean age at the time of demise was 71 ± 13 years (5 years after diagnosis). Of the patients who demised, 24 (65%) were male. This mortality group had a higher prevalence of comorbidities compared with the rest, with 30 (81%) of the mortality group having hypertension versus 65 survivors (63%) (p = 0.06), and 17 (46%) with DM versus 27 survivors (26%) (p = 0.04) (Table I). The mean LVEF in the mortality group was 46% ± 14%, compared with 53% ± 13% in the survivors (p = 0.05). In the mortality cohort, 29% of patients had a LVEF < 35%.

The cause of death could be determined in 35/37 patients who died (Figure 1). Sudden cardiac death (SCD) or death resulting from a documented arrhythmia was not found in any of the 35 cases. The most common causes of death were heart failure (n = 11, 30%) and malignancy (n = 7, 19%). Two patients (5%) had an unknown cause of death; 1 was symptomatic at the time of diagnosis but only demised 5 years thereafter. He was never paced due to the loss of cardiology follow-up while being investigated. None of the other demised patients developed indications for pacing. Statistically significant relationships between patients with BFB and mortality, using the chi-squared test with Fisher's exact test, were DM (p = 0.04) and a reduced LVEF at initial diagnosis (p = 0.05). Due to the small sample size, using a p-value < 0.1 (considered significant at 10%), hypertension (p = 0.06) and age (p = 0.07) may also be considered significant (Table I).

Required pacing

Pacing was required in 9 patients (6%). The only statistically significant relationship between patients with BFB and those who required a PPM was symptom presence ($p \leq 0.01$). Due to the small sample size reaching this endpoint, PR interval prolongation (p = 0.08) may also be considered significant at a lower level of significance ($p < 0.1$) (Table I). The mean age at diagnosis was 63 ± 18 years, compared with 62 ± 17 years in the population that did not require pacing (p = 0.83). The mean age at the time of PPM insertion was 66 ± 18 years (3 years after initial diagnosis, with a range of less than 1 month to 7 years). Regarding comorbidities, there were no statistically significant differences between patients requiring pacing and those not requiring pacing, except for a numerically higher presence of first-degree AVB in those who required pacing (n = 3, 33%) compared with those who did not (n = 14, 11%) (p = 0.08).

VHD was present in 2 patients (22%), with 1 requiring PPM insertion post-valve replacement. Indications for PPM insertion

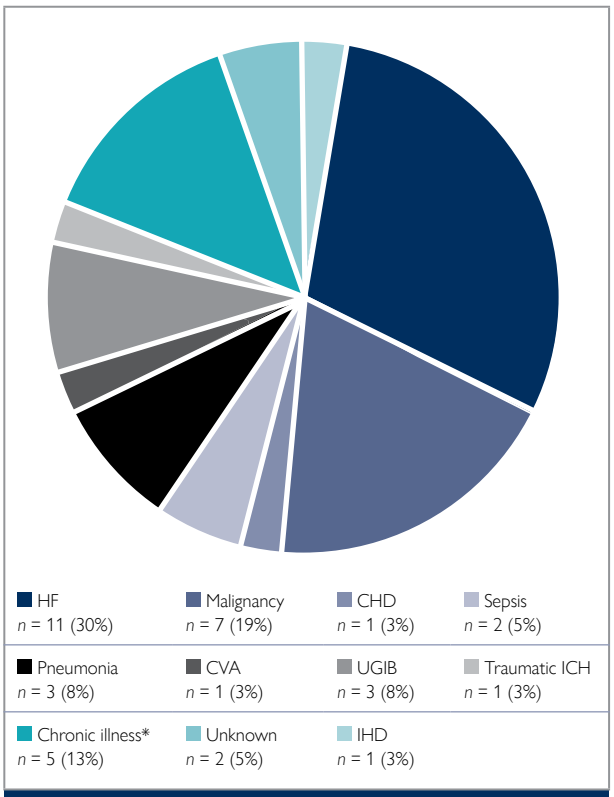

FIGURE 1: Cause of mortality in patients presenting with bifascicular block.
** See Table 1 for chronic illnesses per patient.*

Patient 1: Diabetes mellitus, hypertension, hypothyroidism, previous cerebral vascular accident with scar epilepsy, peripheral vascular disease with previous above-knee amputation, pancreatic insufficiency, and bed-bound prior to death.
Patient 2: Diabetes mellitus, hypertension, hypercholesterolaemia, previous cerebral vascular accident, benign prostatic hyperplasia with a permanent suprapubic catheter in situ, and noted to have poor functional status before death.
Patient 3: Diabetes mellitus, hypertension, intracranial haemorrhage, chronic kidney disease, dementia, and poor functional status (bed-bound), long-standing before death.
Patient 4: Diabetes mellitus, hypertension, intracranial haemorrhage with previous coronary bypass surgery, reduced left ventricular ejection fraction, and previous central retinal artery occlusion (no documented cardioembolic cause).
Patient 5: Hypertension, chronic obstructive airway disease, kidney impairment, left arm axillary artery occlusion requiring embolectomy (no documented cardioembolic cause), and dementia with note of having a poor baseline function.
CHD: congenital heart disease, CVA: cerebral vascular accident, HF: heart failure, ICH: intracranial haemorrhage, IHD: ischaemic heart disease, n: number, UGIB: upper gastrointestinal bleed.

comprised mostly complete AVB (n = 6, 67%), with 1 (11%) developing 2:1 AVB, 1 (11%) developing symptomatic Mobitz type 1 AVB on exertion, and 1 (11%) developing sinus node dysfunction. Five of the 9 patients (55%) who required pacing were symptomatic at the time of diagnosis ($p \leq 0.01$). Of the 4 remaining patients who required pacing, 2 (50%) developed symptoms (1 with 2:1 AVB and the other with complete AVB), and 2 (50%) had higher-grade AVB identified incidentally (post-aortic valve replacement and prior to elective cataract surgery). Therefore, 7 patients (78%) who required pacing were either symptomatic at the time of diagnosis or developed symptoms later.

DISCUSSION

This study indicates that patients with BFB are more likely to die from their comorbidities, which are well-known predictors of mortality in the general population, rather than from the undiagnosed progression of their conduction deficit leading to fatal, complete AVB. The presence or development of symptoms of unexplained presyncope or syncope, and possibly other conduction delays, such as first-degree AVB, may be associated with developing more significant conduction system disease.

Of the mortality group, 35 patients (95%) had an identified cause of death, with no documented SCD or high-degree AVB documented at the time of death. However, the 2 patients (5%) with unknown causes of death may have died because of SCD and possible high-degree AVB. Only 1 of these 2 patients was symptomatic at diagnosis; however, standard ECGs and Holter examination revealed no bradyarrhythmia or ventricular tachycardia, and the patient was lost to cardiology follow-up before further investigations.

Our study's 26% mortality rate is similar to those reported in previous studies by Martí-Almor, et al. (21%), McAnulty, et al. (29%), Tabrizi, et al. (33%), Rivera-López, et al. (33%), and Dhingra, et al. (38%).[3,5,6,10,11] The similar all-cause mortality rates in our study compared with previous studies echo the narrative that the mortality risk in patients with BFB arises from their comorbidities and advancing age rather than conduction disease progression. This was previously reported in studies where PPM insertion did not reduce mortality. Impaired left ventricular function was also a significant contributor to mortality risk, with the mean LVEF being lower in the mortality group. Heart failure accounted for 11 (30%) of the total mortality cohort, and of these patients who had echocardiography around the time of diagnosis, 6 (56%) had a LVEF < 35%.

Therefore, our study's findings align with previous studies that have shown a higher mortality rate in patients with heart failure and BFB. These studies showed that patients with more advanced heart failure and a NYHA functional tolerance classification ≥ 2 with interventricular conduction delays have a higher all-cause mortality than patients with narrow QRS complexes.[19,20] The significance herein may also relate to the rate of possible SCD and to the reason previous studies have not shown improved SCD rates with PPM insertion, as these patients are at high risk for ventricular arrhythmias, which is likely the largest risk factor for SCD rather than high-degree AVB.

The rate of SCD in our study is assumed to be ≤ 5%, as mentioned above, compared with 42% and 14% previously recorded by McAnulty, et al. and Tabrizi, et al., respectively.[3,10] The wide range in these studies' rates can likely be attributed to

the difficulty of documenting such arrhythmias if patients do not present with them or are not on continuous monitoring at the time of death. Therefore, this rate may be higher, as the patients with severely impaired LVEF dying of heart failure may have died of undocumented ventricular arrhythmias. Due to this high mortality rate in such patients, current guidelines indicate implantable cardioverter-defibrillator (ICD) insertion with or without cardiac resynchronisation therapy (CRT) for symptomatic patients with a poor LVEF (< 35%).[21,22]

The presence of symptoms at diagnosis did not have a statistically significant association with mortality. In our study, no patients who required pacing demised. This suggests that progression to high-degree AVB, which may result in SCD, is a gradual process. Patients then present to healthcare facilities with symptomatic progression of disease or high-degree AVB, which is found incidentally with routine follow-up and investigation. However, this finding is influenced by the small cohort size and, therefore, its significance cannot be confidently asserted. The significant difference in the relationships with mortality and requiring pacing suggests that the risk of SCD due to high-degree AVB is low, and that patients with BFB are at higher risk of death due to causes other than high-degree AVB, as described above.

Symptom presence (at the time of diagnosis or later) was the most significant variable for pacing ($p \leq 0.01$). The presence of symptoms is known to be 1 of the most important predictors for requiring pacing, as shown in a study by Martí-Almor, et al.; however, in their study, all patients underwent EPS, and the most significant predictor for requiring pacing was an HV interval > 64 ms.[3,11,22] This was not investigated in our study, as EPS was not available at TBH at the time. Furthermore, 41% of patients in their study required pacing, compared with the 6% in ours.[11] This was likely due to the inclusion of mostly symptomatic patients in their study (87% compared with 13% in our study), as well as EPS being performed in each patient, with lower thresholds for PPM insertion than suggested by guidelines.[22]

Of our total cohort, 18 patients (13%) were symptomatic at diagnosis; 5 received a PPM for the indications described above, and the remaining 13 did not receive a PPM. Of these 13 patients, 7 had a cardiac cause other than high-degree AVB, or other pathological bradycardias (e.g. sinus node dysfunction) for their symptoms, and 2 had symptoms attributed to non-cardiac disease (e.g. neurological). The remaining 4 were regrettably not investigated fully for a cause, but none of them died during the 10-year follow-up. Only 1 of the 13 patients had an implantable loop recorder (ILR) inserted. This patient had known HCM based on cardiac magnetic resonance (CMR) imaging with no outflow obstruction. The ILR showed 1 episode of sinus arrest for 4 seconds, 1 episode of non-sustained ventricular tachycardia, and no high-degree AVB. After further investigation, the patient's symptoms were attributed to an unspecified neurological cause.

According to the ACC and ESC guidelines,[12,13] asymptomatic patients with BFB do not require any specific investigations, but are counselled on danger signs and advised to seek medical attention when experiencing these symptoms. Symptomatic patients, however, require further investigation in order to identify intermittent high degree AVB. If a standard 12-lead ECG and/or Holter does not identify any bradyarrhythmia, the next investigation is echocardiography to assess the patient's LVEF. If the LVEF is < 35%, the recommendation is that the patient receives an ICD/CRT-D due to the high risk of mortality in patients with heart failure and intraventricular conduction deficits as described above (class I evidence). If the LVEF is > 35%, the recommendation is to perform EPS which, if positive (HV interval > 70 msec or second or third degree AVB on incremental atrial pacing or pharmacological challenge), the patient will require a PPM. If EPS is negative, the next step is for ILR insertion and assessment for high degree AVB. If no high degree AVB is captured, clinical follow up is recommended. According to these guidelines, empirical PPM insertion is also reasonable for patients with BFB and unexplained syncope (negative work-up as above and no other identified cause of syncope) or in patients at high risk for traumatic recurrence (e.g. elderly patients). The algorithm for EPS and ILR prior to PPM insertion has been shown to be effective in reducing the rate of syncope recurrence after PPM insertion whereas patients with empirical pacing may undergo an unnecessary procedure and still have recurrent syncopal episodes.[12] Two patients in our cohort received an ILR, one of which had a positive finding of complete AVB and received a PPM. The other eight patients who required pacing had their indication for pacing identified on standard 12-lead ECG's, stress ECG or Holter suggesting that non-invasive investigative methods for symptomatic patients are effective in identifying most patients who require pacing.

In our setting of a low- to middle-income country with resource limitations and the significant relationship of symptoms with requiring pacing, we feel it is reasonable to insert a PPM for symptomatic patients without routinely proceeding to EPS, if no other cause for the symptoms is identified. This strategy may result in some patients receiving an unnecessary PPM and/or higher recurrence rates of syncope or presyncope. Nonetheless, it will assist with effective resource allocation rather than investigating every symptomatic patient with EPS and/or ILR and then possibly inserting a PPM. We agree with current guidelines that asymptomatic patients likely do not require further investigation with EPS and/or ILR, as the risk of developing an indication for pacing is low. Only 4 (3%) of initially asymptomatic patients in our cohort required pacing during the 10-year follow-up, of whom only 2 (2%) remained asymptomatic at the time of requiring pacing. Future studies assessing syncopal recurrence in our setting for symptomatic patients with BFB managed with PPM insertion would be valuable.

This study aimed to identify relationships between clinical variables and mortality and/or progression of the conduction disease leading to PPM insertion in patients with BFB. DM ($p = 0.04$) and a reduced LVEF ($p = 0.05$) at diagnosis had the most significant relationship with mortality. Hypertension and advanced age were also significant contributors. The presence of symptoms ($p \leq 0.01$), either at diagnosis or later, had a significant relationship with requiring pacing, and PR interval prolongation was also associated with requiring pacing at a lower level of

significance. Potential targets for improving mortality outcomes in patients with BFB require further study. PPM insertion for symptomatic patients may be a reasonable management strategy for symptom relief (if no other symptom cause is identified) rather than following the recommended investigative algorithm for every symptomatic patient in a resource-limited setting.

Study limitations

As this was a descriptive, observational study conducted via retrospective review, the main limitation is that of all such studies, including missing data and bias. The long follow-up period of up to 10 years allowed for all patients who reached at least one of the endpoints to likely be captured. The limited cohort size and subsequent small number of patients who reached 1 of the endpoints limit comparisons of variables and the identification of significant relationships. However, to our knowledge, this is the first study in Africa to assess the relationships between clinical parameters and the need for pacing or mortality in patients with BFB. Further studies with larger cohorts are needed to properly assess and corroborate our findings.

CONCLUSION

This study identified DM and a reduced LVEF at diagnosis as the clinical parameters that relate significantly to mortality in patients with BFB, alongside age and hypertension, which were also associated at a lower level of significance. The presence of symptoms and a prolonged PR interval were the only significant variables for requiring pacing. For asymptomatic patients, further investigation is not required due to the low risk of progressive conduction defects. Extensive investigations, as per guidelines, for symptomatic patients with BFB can help reduce unnecessary PPM insertion; however, it may be challenging in resource-limited settings. Therefore, PPM insertion is a feasible alternative if no other cause is identified in such patients. Larger prospective studies with prediction models are needed to identify true predictors of mortality and requiring a PPM in patients with BFB. Further studies should be conducted to identify potential targets for reducing mortality risks.

Conflict of interest: none declared.

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Myocardial fibrosis and sudden cardiac death (SCD) risk factors in mitral valve prolapse patients deemed to be at low SCD risk

J Doubell,[1] A Doubell,[1] J Steyn,[2] M Talle,[1,3] M Rajah[1] and P Herbst[1]

[1] Division of Cardiology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa
[2] Division of Cardiology, Tygerberg Hospital, Cape Town, South Africa
[3] Department of Medicine, Faculty of Clinical Sciences, College of Medical Sciences, University of Maiduguri and University of Maiduguri Teaching Hospital, Maiduguri, Nigeria

Address for correspondence:
Jacques Doubell
Division of Cardiology
Tygerberg Hospital
Francie Van Zijl Drive
Cape Town
7500
South Africa

Email:
jacquesdoubell1@gmail.com

J Doubell https://orcid.org/0000-0002-5440-6917
A Doubell https://orcid.org/0009-0005-7699-8684
J Steyn https://orcid.org/0009-0005-0373-7694
M Talle https://orcid.org/0000-0001-8989-4941
M Rajah https://orcid.org/0000-0001-5599-6608
P Herbst https://orcid.org/0000-0002-7111-1993
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ABSTRACT

Introduction: Mitral valve prolapse (MVP) is associated with risk for sudden cardiac death (SCD); however, there is no consensus regarding risk stratification. Myocardial fibrosis is a substrate for SCD in these patients. Risk markers described for SCD are T wave inversion in the inferior leads and complex ventricular ectopy (ventricular couplets, non-sustained ventricular tachycardia [NSVT], and polymorphic ventricular ectopy), spiked configuration of the lateral annular velocities (Pickelhaube sign), and mitral annular disjunction (MAD).
Purpose: We aimed to investigate the prevalence of these risk factors in our population of MVP patients, a cohort clinically assessed as low risk for SCD. Furthermore, we aimed to investigate the association between these risk factors and myocardial fibrosis and to describe its pattern.
Methods: Our echocardiography database was reviewed from 1 October 2020 to 31 December 2021 for patients with MVP. Patients newly diagnosed from 1 July 2021 to 31 March 2023 were also enrolled. Investigations included a clinical evaluation, assessment for SCD risk markers with electrocardiography (ECG), a 48-hour Holter ECG, a transthoracic echocardiogram, and an assessment for myocardial fibrosis with cardiovascular magnetic resonance (CMR) imaging.
Results: A total of 39 patients, deemed to be at low SCD risk, without prior severe mitral regurgitation, malignant arrhythmias, cardiogenic syncope, or survived SCD, were included for analysis. Of the patients, 66% had areas of replacement fibrosis detected by late gadolinium enhancement (LGE). Segments commonly involved included the basal posterior (39%), basal inferior (39%), and basal lateral (25%). Areas involved were focal, with an average of 1.3 segments involved (± 1.3). No patient had diffuse fibrosis as assessed by extracellular volume (ECV) expansion. Known risk factors in our cohort included inferior T wave inversion (10%), polymorphic ventricular ectopy (18%), NSVT (16%), MAD (49%), and Pickelhaube sign (15%). No correlation was found between replacement fibrosis and any SCD risk marker.
Conclusion: Replacement fibrosis and SCD risk markers were common in this cohort, which was considered low SCD risk. No association was found between fibrosis and risk markers, suggesting poor predictive power for fibrosis. Risk markers for SCD are described in preselected, high-risk MVP populations. The extent to which these risk markers reflect SCD risk in low-risk patients is unclear. Using these risk markers in clinically low-risk patients may over-assess the risk, potentially resulting in medicalising patients and inappropriate therapy.
Keywords: mitral valve prolapse, sudden cardiac death, sudden cardiac arrest, myocardial fibrosis.
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INTRODUCTION

MVP is common, with 1–3% of the world's population being affected.[1] In the absence of severe mitral regurgitation, mitral valve prolapse (MVP) was previously considered a benign condition. However, long-term follow-up studies identified associations with SCD, infective endocarditis, cerebrovascular events, and progressive mitral regurgitation.[2] Since these earlier descriptions, there is a growing body of evidence of MVP's association with sudden cardiac death (SCD).[3]

SCD due to MVP is estimated to occur at a rate of 217 events per 100 000 person-years.[3] While this represents a low

individual risk, the high prevalence of the condition translates to a large total number of patients that may be affected. Identifying which patients with MVP are at higher risk of SCD (so-called malignant or arrhythmogenic MVP), and who would benefit from more intensive investigation, surveillance, and/or intervention to prevent SCD, is an important clinical question yet to be answered and an area of ongoing research. However, given the high prevalence of MVP and the fact that most patients have a low risk of SCD, the risk of over-investigation and medicalising these patients should be guarded against.

Identifying patients at high risk of SCD is challenging, and no reliable risk-stratification tool is currently available. Several risk factors for SCD in patients with MVP have been identified[1,3-5,6-9]:

- Electrocardiographic: T wave inversion in the inferior leads and complex ventricular ectopy [pleomorphic ectopic beats, ectopic couplets, or non-sustained ventricular tahcycardia (NSVT)].
- Echocardiographic: spiked configuration of the lateral annular velocities (Pickelhaube sign).
- Morphological: mitral annular dysjunction (MAD), posterior basal hypertrophy, and bileaflet prolapse.

The mechanisms linking these risk factors to SCD require further investigation, but it is postulated that they serve as risk markers for myocardial fibrosis, a substrate for arrhythmogenesis[10-12]. The identification of risk factors has largely been described in SCD survivors or patients with documented ventricular arrhythmia and has not been properly investigated in low-risk individuals. We aimed to investigate the prevalence of these risk factors in our population of MVP patients, a cohort clinically assessed as low risk for SCD. Furthermore, we aimed to investigate the association between these risk factors and myocardial fibrosis and to describe its pattern.

METHODS

The echocardiography database at Tygerberg Hospital was searched from 1 October 2020 to 31 December 2021 for patients with a MVP diagnosis. Patients identified via this database were contacted for possible enrolment. Patients presenting to Tygerberg Hospital's cardiology unit or surrounding referral centres with newly diagnosed MVP from 1 July 2021 to 31 March 2023 were also enrolled. Informed consent was obtained by the principal investigator. If necessary, an interpreter was provided. The study was approved by the Health Research Ethics Committee of Stellenbosch University (reference number: S21/02/017).

The inclusion criteria were patients with MVP (defined by superior displacement of the mitral leaflets > 2 mm beyond the mitral valve annular plane during systole), as assessed in a para-sternal long-axis view on a transthoracic echocardiogram.[1,13] The exclusion criteria were patients with severe mitral regurgitation, prior valve surgery, ischaemic heart disease, concomitant valvular or myocardial disease, and prior malignant arrhythmic events (ventricular tachycardia, ventricular fibrillation, or survived SCD).

Investigations performed in potential participants included a history and clinical examination, resting 12-lead ECG, 5-day Holter ECG, transthoracic echocardiography, and cardiovascular magnetic resonance (CMR) imaging. Patient demographic data, history, physical examination, and ECG and Holter ECG results were captured on a data collection form. Transthoracic echocardiography and CMR findings were performed using standard protocols (see below), and findings were reported on standard hospital reporting forms. All assessments were completed within 1 week of study enrolment.

Echocardiography

All patients underwent a comprehensive structural and functional two-dimensional (2D) transthoracic echocardiographic analysis performed on a General Electric (GE) machine (E95 scanner, GE HealthCare, Chicago, United States) with a standard 2D transducer (M5Sc 1.7–3.3 MHz) set to 2.5 MHz. A clinician experienced in echocardiography acquired and analysed the images, which the principal investigator then reviewed. All measurements were done in accordance with the British Society of Echocardiography guidelines for the acquisition of a minimum dataset required to define normality.[14] Standard atrial, ventricular, and valvular morphological and functional parameters were reported. In addition, a detailed mitral valve assessment was done with a view to defining MVP, describing the extent of prolapse (utilising Carpentier's segmental mitral valve model), and assessing current known risk predictors of SCD in MVP.[15]

Cardiovascular magnetic resonance imaging

Comprehensive CMR was performed at 1.5 Tesla, in accordance with consensus guidelines.[16-19] Standard long-axis views, as well as a stack of breath-held, retrospectively gated, steady-state free precession short-axis cine images, were obtained. Analysis was carried out using commercially available software (CMR42, Circle Cardiovascular Imaging, Calgary, Canada). Endocardial and epicardial left ventricular borders were traced in the short axis at end-diastole and end-systole to determine left ventricular volume, mass, and functional parameters. Papillary muscles were excluded from the blood pool. Quantitative analysis of short-tau inversion-recovery (STIR) images was performed following endo- and epicardial contouring in the short axis. A skeletal muscle (serratus anterior) region of interest was manually drawn in the same slice. Pre- and post-contrast T1 and pre-contrast T2 mapping images were obtained, the former using a shortened modified Look-Locker inversion sequence.

Late gadolinium enhancement (LGE) images were obtained with a T1-weighted, segmented inversion-recovery sequence at least 12 minutes after contrast administration. The location and distribution of myocardial fibrosis were determined. A standardised 16-segment model of the left ventricle was used to describe the distribution of identified abnormalities, as outlined by the American Heart Association.[20] Participants received Gadovist© contrast at the recommended dose of 0.2 ml/kg. MAD was reported if there was any degree of atrialisation of a mitral valve leaflet's annular hinge point, at any point around the

annulus. The degree and position of maximal disjunction (separation distance between the atrialised hinge point and ventricular myocardium) were then measured and reported.

STATISTICAL ANALYSIS

Statistical analysis was performed in consultation with Stellenbosch University's Division of Epidemiology and Biostatistics. Data were collected and recorded using an Excel spreadsheet and standard hospital reporting forms. The data were then imported into IBM SPSS Statistics version 28.0. (IBM, Armonk, United States) for statistical analysis. Standard descriptive statistics were used to analyse means, standard deviations (SD), medians, proportions, and frequencies. For quantitatively measured, high-risk clinical parameters, the data were tested for normality. Normally distributed data were expressed as mean ± SD. For categorical, high-risk clinical parameters, and to assess the association between myocardial fibrosis and risk factors, chi-squared tests or Fisher's exact two-sided tests were used as appropriate at the 0.05 level of statistical significance.

RESULTS

The initial inclusion criteria for MVP were met by 45 patients. Based on the exclusion criteria, 6 patients were excluded from analysis: 1 did not meet MVP criteria on expert review, 3 had severe mitral regurgitation, 1 had coronary artery disease with a previous myocardial infarct, and 1 withdrew consent due to claustrophobia, precluding CMR performance. The final number of patients included for analysis was 39. Data capture was incomplete for the group as a whole: 3 patients had uninterpretable Holter ECG results due to poor-quality recordings, 3 patients did not have CMR imaging, 2 due to claustrophobia, and 1 due to pregnancy, precluding gadolinium administration.

TABLE I: Patient demographics.

Demographics	***n* (%)**
Female	14 (33)
Age	41 ± 18
Age at diagnosis	31 ± 19
Race	
Caucasian	16 (41)
Black	4 (10)
Mixed race	19 (49)
Asian	0 (0)
Comorbidities	
Hypertension	6 (15)
Dyslipidaemia	5 (13)
Anxiety	7 (15)
Palpitations	26 (66)
Family history of MVP	3 (8)
Family history of SCD	0 (0)

MVP: mitral valve prolapse, SCD: sudden cardiac death.

Of the patients, 14 (33%) were female. The mean patient age was 41 years (± 18 years). Table I shows additional demographic information. Mean left ventricular end-diastolic diameter (LVEDD) was normal, measuring 4.9 cm (± 0.66 cm), and

TABLE II: Morphological and functional parameters assessed on cardiovascular magnetic resonance imaging.

	Mean	**Standard deviation**
Left ventricle		
LVEDD (mm)	48.34	6.45
PWT (mm)	10.41	1.91
IVS (mm)	10.59	1.73
LVEDV (ml)	186.69	63.21
LVEDVi (ml/m^2)	99.49	29.03
LVESV (ml)	75.19	26.47
LVESVi (ml/m^2)	41.10	13.03
LVSV (ml)	108.99	44.37
LVEF (%)	59.88	8.27
LV mass (g)	120.12	33.09
LV mass indexed (g/m^2)	65.33	14.35
Right ventricle		
RVEDD (mm)	43.94	5.19
RVOT (mm)	27.80	6.26
RV base to apex (mm)	86.87	10.67
RVEDV (ml)	179.56	56.80
RVEDVi (ml/m^2)	95.69	27.61
RVESV (ml)	85.10	41.63
RVESVi (ml/m^2)	44.34	21.10
RVSV (ml)	94.50	26.78
RVEF (%)	55.17	8.26
Left atrium		
LA diameter (mm)	31.33	8.50
Biplanar LA volume	85.62	73.75
LAVi (ml/m^2)	44.26	36.94
Right atrium		
Monoplanar RA volume	74.26	33.11
RAVi (ml/m^2)	43.04	20.18
Systolic MV annular diameter (mm)	37.08	6.67
Diastolic MV annular diameter (mm)	29.93	7.36
Mitral regurgitation		
Regurgitant volume (ml)	20.37	22.54
Regurgitant fraction (%)	20.17	17.83

IVS: Interventricular septum, LA: left atrium, LAVi: indexed left atrium volume, LV: left ventricle, LVEDD: left ventricular end-diastolic diameter, LVEDV: left ventricular end-diastolic volume, LVEDVi: indexed left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVESVi: indexed left ventricular end-systolic volume, LVSV: left ventricular systolic volume, MV: mitral valve, PWT: Posterior wall thickness , RA: right atrium, RAVi: indexed right atrium volume, RV: right ventricle, RVEDD: right ventricular end-diastolic diameter, RVEDV: right ventricular end-diastolic volume, RVEDVi: indexed right ventricular end-diastolic volume, RVEF: right ventricular ejection fraction, RVESV: right ventricular end-systolic volume, RVESVi: indexed right ventricular end-systolic volume, RVOT: Right ventricular outflow tract , RVSV: right ventricular systolic volume.

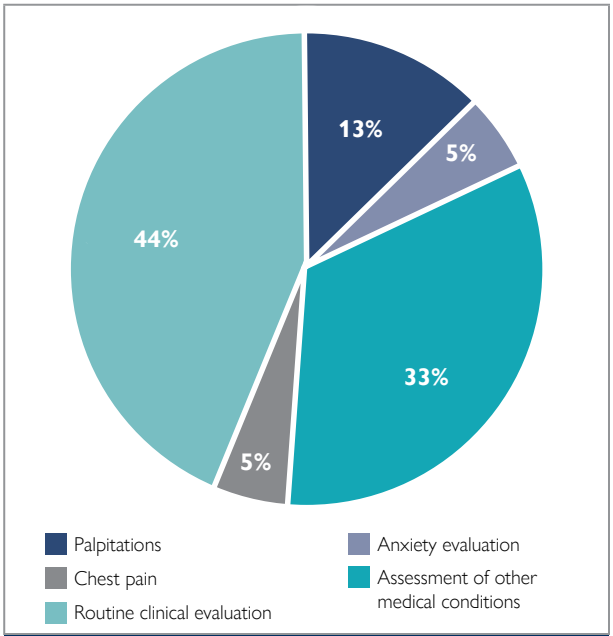

FIGURE 1: Presentations leading to mitral valve prolapse diagnosis.

indexed left ventricular end-diastolic volume (LVEDVi) measured 103 ml/m^2 (± 32 ml/m^2). The mean left ventricular ejection fraction was 60% (± 8%) (Table II).

Bileaflet MVP was present in 26 patients (70%). The frequency of the individual mitral valve segments involved in prolapse included: A1 (29%), P1 (42%), A2 (38%), P2 (86%), A3 (51%), and P3 (58%). Of the patients, 33 (89%) had associated mitral regurgitation, with a mean regurgitant volume of 21 ml (± 23 ml), in keeping with mild-to-moderate mitral regurgitation. Ventricular morphological and functional assessments were all made on CMR imaging.

No patient had documented survived SCD, sustained ventricular arrhythmia, or high-risk cardiac syncope. The MVP diagnosis was often incidental, with benign initial presentations (Figure 1). A history of palpitations was present in 26 patients (66%), and 21 (80%) described frequent palpitations. On further enquiry, 6 patients (15%) spontaneously offered a diagnosis of anxiety.

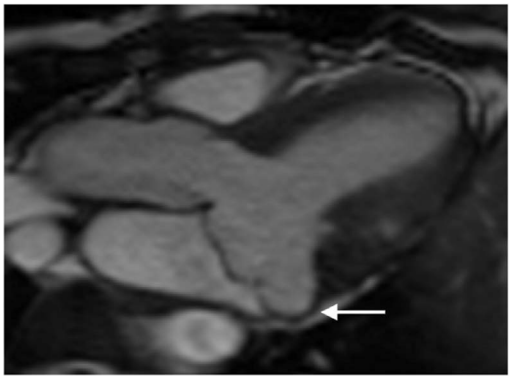

FIGURE 2: Long-axis view demonstrating mitral annular disjunction (arrow) of the posterior mitral valve annulus.

T wave inversion was noted in 4 patients (10%) on standard 12-lead ECG. The 5-day Holter ECG assessment demonstrated ventricular couplets in 22 patients (61%), pleiomorphic ectopic beats in 7 (19%), and NSVT in 6 (17%). Echocardiography demonstrated MAD in 24 patients (62%) (Figure 2) and Pickelhaube sign in 6 patients (15%). MAD was also documented in 24 patients (62%) on CMR, with a 6.6 mm (± 3 mm) mean MAD distance, basal posterior left ventricular hypertrophy (LVH) in 14 patients (38%), and basal lateral LVH in 11 patients (29%).

Myocardial replacement fibrosis was detected on LGE in 24 patients (66%) (Figure 3). The myocardial segments most commonly involved were basal posterior (39%), basal inferior (39%), and basal lateral (25%) (Figure 4). Replacement fibrosis tended to be focal, with an average of 1.3 segments (± 1.3) involved. No patients demonstrated diffuse fibrosis as assessed by ECV expansion (mean 25% ± 2%).

No association was found between any risk factor or combination of risk factors and the presence or absence of LGE (Table III). No association was found between bileaflet prolapse and segmental prolapse or arrhythmic profile.

TABLE III: Association between sudden cardiac death risk factors and late gadolinium enhancement*.

Sudden cardiac death RF	LGE positive		LGE negative		*p*-value
	RF present % (*n*)	RF absent % (*n*)	RF present % (*n*)	RF absent % (*n*)	
TWI	13 (3)	87 (20)	8 (1)	92 (12)	1.000
Ventricular couplets	67 (14)	33 (7)	58 (7)	42 (5)	0.716
Pleomorphic ectopy	19 (4)	81 (17)	25 (3)	75 (9)	0.630
Non-sustained VT	24 (5)	76 (16)	8 (1)	92 (11)	0.379
MAD	65 (15)	35 (8)	69 (9)	31 (4)	1.000
Basal hypertrophy	35 (23)	65 (15)	42 (5)	58 (7)	0.726
Pickelhaube sign	22 (5)	78 (18)	8 (1)	92 (12)	0.385

** Data capture was incomplete for the whole group, as 3 patients had uninterpretable Holter ECG results, and 3 patients did not have a CMR.*

LGE: late gadolinium enhancement, MAD: mitral annular disjunction, RF: risk factor, TWI: T wave inversion, VT: ventricular tachycardia.

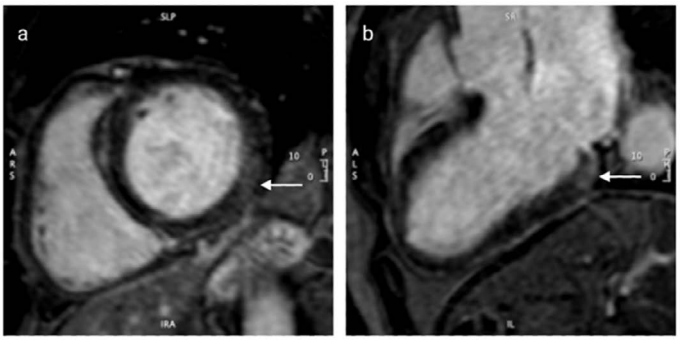

FIGURE 3: Phase-sensitive inversion-recovery images demonstrating late gadolinium enhancement (LGE).
a: Short-axis view at the basal level showing posterior segment LGE (arrow). b: Corresponding long-axis 3-chamber view showing LGE in the basal posterior wall (arrow).

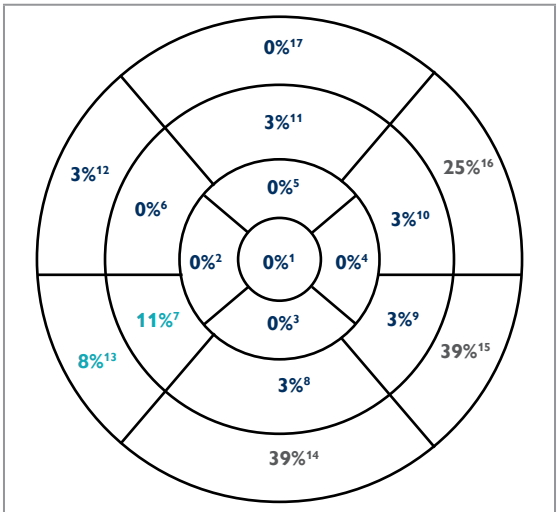

FIGURE 4: Percentage of patients with replacement fibrosis demonstrated on a left ventricular segmental modal.
1: apex 2, 2: apical septal, 3: apical inferior, 4: apical lateral, 5: apical anterior, 6: mid anterior septal, 7: mid inferior septal, 8: mid inferior, 9: mid posterior, 10: mid lateral, 11: mid anterior, 12: basal anterior septal, 13: basal inferior septal, 14: basal inferior, 15: basal posterior, 16: basal lateral, 17: basal anterior.

DISCUSSION

The absolute SCD risk in the general MVP population is considered low. Our cohort of otherwise healthy, community-based patients with no prior arrhythmic events and hitherto benign MVP mirrored the profile of a low SCD risk population. However, risk factors for SCD in MVP, as described in the literature, including focal replacement fibrosis thought to represent the arrhythmogenic substrate for arrhythmia and SCD in MVP, were common in this cohort. No correlation was found between replacement fibrosis and the described SCD risk factors. This highlights the need for further study in low-risk populations and a rational approach to SCD risk evaluation in MVP until more data are available.

Historical SCD cohorts have always attributed a proportion of community-based SCD to MVP.[21] It is important to understand that MVP was diagnosed on post-mortem studies and would therefore be expected to appear in SCD registries at a minimum frequency similar to that found in the background population. Subsequent scrutiny of this data demonstrated rates of SCD attributable to MVP that seemed to track the background prevalence closely, supporting MVP's initial status in the cardiology community as a benign condition.[2] This illustrates the problem of over-assessing risk when the background prevalence is not well known, which was a problem before the definition of MVP was revised, standardised, and incorporated into general echocardiography practice.[3]

Studies performed in high-risk SCD populations have identified an apparently high risk, or so-called malignant MVP cohort, with high SCD risk in a subset of MVP patients, which is supported by several subsequent publications.[1,3] The relatively high background prevalence of MVP appears to have hidden a small but definite incremental SCD risk attributable to MVP itself. Despite identifying a small, high-risk MVP cohort, it is important to remember that the absolute SCD risk in the general MVP population remains very low at an estimated 217 events per 100 000 person-years.[3] Unfortunately, this also means that any risk factor present at a high prevalence in the general low-risk MVP population is unlikely to be a very good predictor of SCD in the individual patient. Our study highlights this point of view.

When approaching SCD risk stratification of an individual with MVP using predefined risk factors, the positive and negative predictive values for SCD, and the pre-test probability for SCD related to the absolute prevalence of SCD in the population are critical metrics to consider. The low pre-test probability of SCD in the general MVP population makes it difficult to predict outcomes using commonly found risk factors.[3] The high baseline prevalence of currently used risk factors in MVP in our otherwise low SCD risk cohort underlines this problem. Furthermore, the identification of a high prevalence of replacement fibrosis, the putative mechanism underlying SCD in this population, and its lack of correlation with risk factors suggest that a more complex interplay of factors would need to be present to increase risk, again making it difficult to ascribe risk to this finding alone. However, the burden of fibrosis in individual patients in the current study was very low.

The pathophysiology of fibrosis, its degree and distribution, its association with MAD, the degree of MAD, and how it relates to annular movement and function may all be important factors to consider when assessing SCD risk attributable to fibrosis. This is an area that requires more study, as minor degrees of fibrosis appear to be a benign finding in most patients. In the current study, no association was found between the presence or absence of any risk factor or combination of risk factors for the presence or absence of LGE on CMR (Table I). Therefore, these risk factors may be markers of risk for SCD unrelated to replacement fibrosis alone, or that the burden of fibrosis needs to be substantially larger to accrue risk.

Given the high population prevalence of MVP, a potentially large absolute number of patients are at risk of SCD. Identifying which

patients with MVP are truly at high risk and would benefit from more intensive investigation, surveillance, and intervention to prevent SCD is a common clinical dilemma. The currently used risk factors derive from high-risk populations, and it is unclear how they should be applied to lower-risk populations for risk stratification. No current consensus guidelines exist to inform management in this scenario.

The risk of medicalising otherwise healthy individuals with associated over-investigation is high in this population. Larger outcome studies are required to follow low-risk MVP cohorts over longer periods to better understand what drives their risk. Overly aggressive investigation with electrophysiological studies, primary prevention intracardiac defibrillators, and investigations and devices with their own associated morbidity and mortality, seems unnecessarily aggressive in this population.

While risk stratification for SCD and the presence of fibrosis and SCD risk is well established for hypertrophic, ischaemic, and dilated cardiomyopathy, we do not currently have the data to support risk-stratification tools with appropriate negative and positive predictive values to implement similar strategies in MVP.[22-24] Our study suggests that the currently described high-risk factors are also common in low-risk patients, with a subsequently poor positive predictive value for SCD. The authors' opinion is that terms such as "malignant" or "arrhythmogenic MVP" should be avoided when assessing patients with MVP who have not had an arrhythmogenic event.

Study limitations

The current study involves a relatively small cohort of patients and has no longitudinal follow-up to assess event rates in this apparently low-risk population. However, the high prevalence of apparently high-risk features for SCD in a healthy, community-based cohort of patients with a common condition, and the low risk of SCD overall in the general MVP population, support the assertion of a poor predictive value of individual risk markers for the general MVP population.

CONCLUSION

This study highlights the need for ongoing investigation in this area, with the hope of accurately risk-stratifying MVP patients for SCD risk in the future. Before this data is available, one should avoid implementing risk stratification tools, especially in patients at an apparent low risk.

Conflict of interest: none declared.

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Case report of a transcatheter tricuspid valve-in-valve replacement

DN Pillay, SC Brown, and DG Buys

Division of Paediatric Cardiology, Department of Paediatrics and Child Health, Faculty of Medicine, University of the Free State, Bloemfontein, South Africa

Address for correspondence:
Paediatric Cardiology Department,
1st Floor
Universitas Academic Hospital
1 Logeman Street
Bloemfontein
Free State
9301

Email:
dhesan.n.pillay@gmail.com

DN Pillay https://orcid.org/0009-0007-8493-7819
SC Brown https://orcid.org/0000-0002-8508-8667
DG Buys https://orcid.org/0009-0001-2795-9276
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ABSTRACT

Transcatheter valve implantations in the tricuspid position are infrequent. We report a case of an Edwards SAPIEN 3 (S3) implantation in the tricuspid position as a transcatheter valve-in-valve procedure in a 12-year-old patient deemed at high risk for surgical reintervention.
Keywords: percutaneous valve, Edwards valve, congenital heart disease, tricuspid replacement, percutaneous intervention.
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INTRODUCTION

Transcatheter valve-in-valve is a growing field of interest, most commonly in the aortic and pulmonary positions. Implantation in the tricuspid position has been limited, especially in children.[1-3] We report a tricuspid transcatheter valve-in-valve replacement of a stenotic bioprosthetic valve in a 12-year-old patient.

CASE REPORT

The patient was a 12-year-old female (39 kg) with a large muscular ventricular septal defect (VSD) and dysplastic tricuspid valve. At 5 weeks of age, due to the complexity of the VSD, a pulmonary artery banding was performed. At 16 months of age, the VSD was closed. During this surgery, it was noted that the tricuspid valve appeared grossly abnormal with sessile chordae tendineae to the anterior leaflet and marked hypertrophy of the anterior papillary muscle. A permanent pacemaker was placed with epicardial leads a month later due to sinus node dysfunction.

The patient's next presentation was at the age of 6 years, with an arrhythmia and hepatomegaly. Her workup identified severe tricuspid insufficiency (TI) that warranted surgical intervention. A tricuspid valve annuloplasty was performed using a 24 mm Edwards spiro ring (Edwards Lifesciences, Irvine, United States). The TI was significantly reduced but still deemed unacceptable; thus, the ring was removed, and a tricuspid valve replacement was performed using a 25 mm Edwards PERIMOUNT Plus stented pericardial valve (Edwards Lifesciences, Irvine, United States), along with a redo of the pacemaker box and leads during the same surgery.

At age 11, a pacemaker pulse generator change was performed. The patient was considered for a repeat valve replacement at age 12 due to tricuspid stenosis (TS) and symptomatic right atrium (RA) enlargement with hepatomegaly. Due to the multiple previous surgeries, a decision was made in agreement with the family to perform the valve replacement as a percutaneous valve-in-valve procedure.

The pre-procedure transthoracic echocardiogram (TTE) showed a congested inferior vena cava (IVC), dilated RA, tricuspid annular plane systolic excursion (TAPSE) of 12 mm, and no dilation of the right ventricle (RV). Doppler evaluation of the Edwards PERIMOUNT valve noted a peak instantaneous gradient (PIG) of 26 mmHg and a mean gradient of 16 mmHg. Mild TI was noted with colour Doppler.

Procedure

The procedure was performed under general anaesthesia with transoesophageal echocardiography (TOE) guidance. The patient was heparinised as per the unit's standard protocol (50 U/kg) and ACT monitoring. Prophylactic antibiotics (cefazolin) were administered. Femoral vascular access was obtained under sonar guidance. A 6 Fr and 5 Fr sheath was inserted in both the left femoral vein and artery, respectively. The right femoral vein was cannulated with a 12 Fr sheath (Cook Medical, Bloomington, United States). Haemodynamic data were collected pre- and post-valve implantation (Table I).

TABLE I: Haemodynamic information from cardiac catheterisation.

	Pressure measurements (mmHg)	
	Pre-valve	Post-valve
Right atrium	23	14
Right ventricle	52/6	47/14
Tricuspid valve gradient	17	0

Pre-implantation TTE and TOE demonstrated a dilated RA, 16 mmHg PIG over the tricuspid valve, and mild TI (Figures 1–3). The tricuspid valve was crossed with a 6 Fr wedge catheter. Using a 0.035-inch Amplatz Super Stiff guide (Boston Scientific, Marlborough, United States), a stable guide wire position was obtained in the distal right pulmonary artery. The 12 Fr sheath was up-dilated to accommodate the Edwards 14 Fr eSheath. A 20 mm × 40 mm Atlas percutaneous transluminal angioplasty (PTA) balloon (Bard Peripheral Vascular Inc., Tempe, United States) was inflated at 16 atmospheres to dilate and size the tricuspid valve (Figure 4). A waist of 16.5 mm was noted, representing a 56% functional area reduction. The delivery system was tracked over the wire, and the valve was aligned with the previous bioprosthetic valve in a coaxial position. An Edwards S3 26 mm valve was placed in the PERIMOUNT ring during rapid pacing at 140 bpm using the patient's pacemaker (Figure 5).

Following valve implantation, haemodynamics improved immediately. TOE post-implantation demonstrated a 10 mmHg PIG over the valve, with no insufficiency, no paravalvular leak, and a well-functioning tricuspid valve (Figure 6). Haemostasis at the right femoral vein access was achieved percutaneously using Perclose™ ProStyle™ (Abbott Laboratories, Chicago, United States). The patient was extubated and transferred to the paediatric intensive care unit (PICU) for high-care monitoring. TTE performed in the PICU after the intervention demonstrated normal left ventricle (LV) function, mild collapse of the IVC with a dilated RA, and good flow over the Edwards valve, with Doppler interrogation noting a 7 mmHg PIG and a mean gradient of 3 mmHg. The patient was discharged on aspirin 100 mg. Endocarditis prophylaxis and good dental and skin hygiene practices were advised.

Clinical course

At the 6-month follow-up, the patient reported improved effort tolerance and no adverse events following the percutaneous valve implantation. TTE showed the IVC and RA were not dilated, with good flow across the tricuspid valve, PIG of 9 mmHg and a mean gradient of 6 mmHg, good RV function with TAPSE of 18 mm, and good LV function.

DISCUSSION

Transcatheter valve-in-valve procedures are a growing area of interest in the literature, offering a viable, low-risk alternative to high-risk repeated surgical interventions. Percutaneous tricuspid valve-in-valve (TVIV) via a transjugular approach was first described by Van Garsse, et al. in 2011, and via a transfemoral approach by Calvert, et al. in 2012.[4,5] At present, the available percutaneous valve devices are used off-label when in the tricuspid position.[3] TVIV has thus far been accomplished using

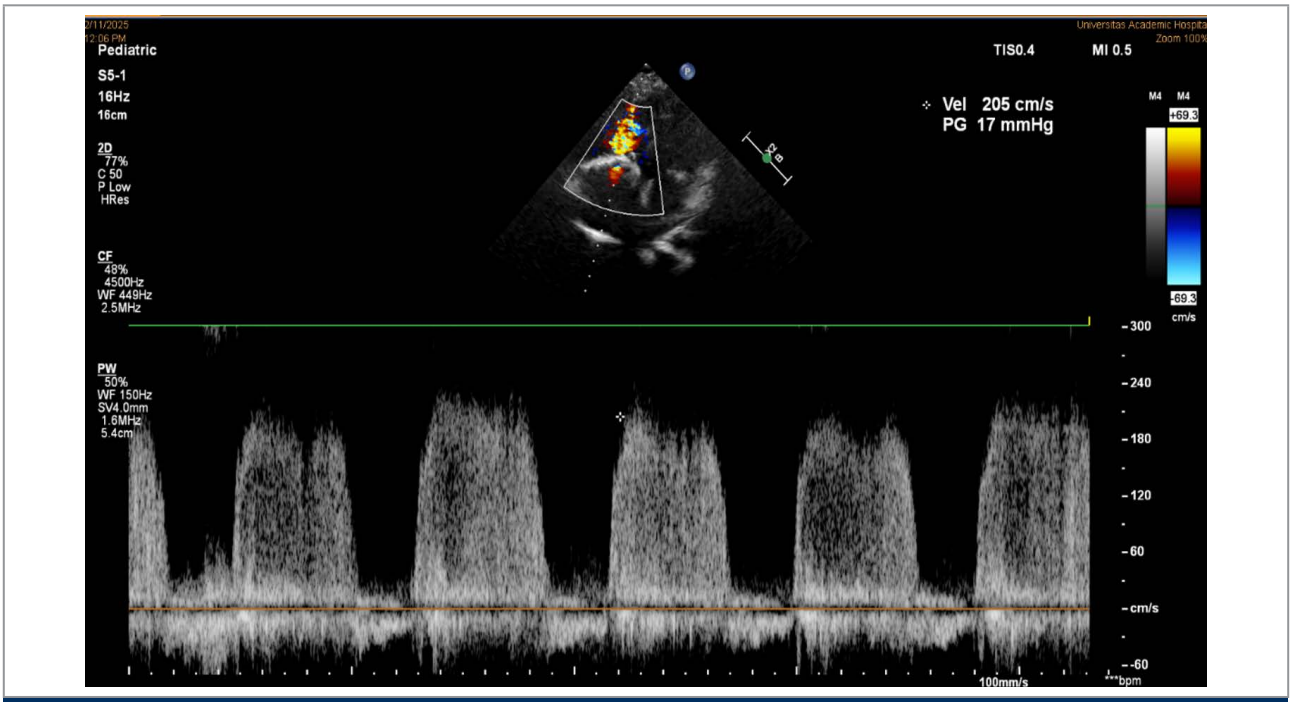

FIGURE 1: Transthoracic echocardiogram showing pulsed wave Doppler tracing of tricuspid stenosis, with loss of E wave and A wave differentiation.

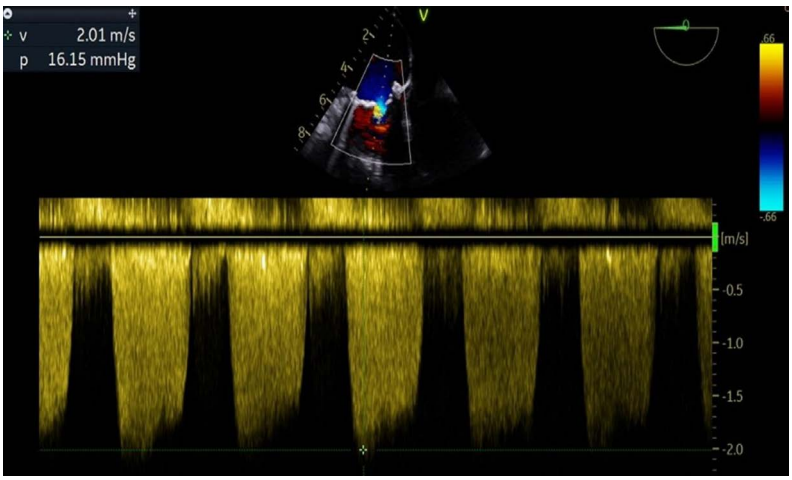

FIGURE 2: Transoesophageal echocardiography showing tricuspid stenosis with Doppler pre-implantation.

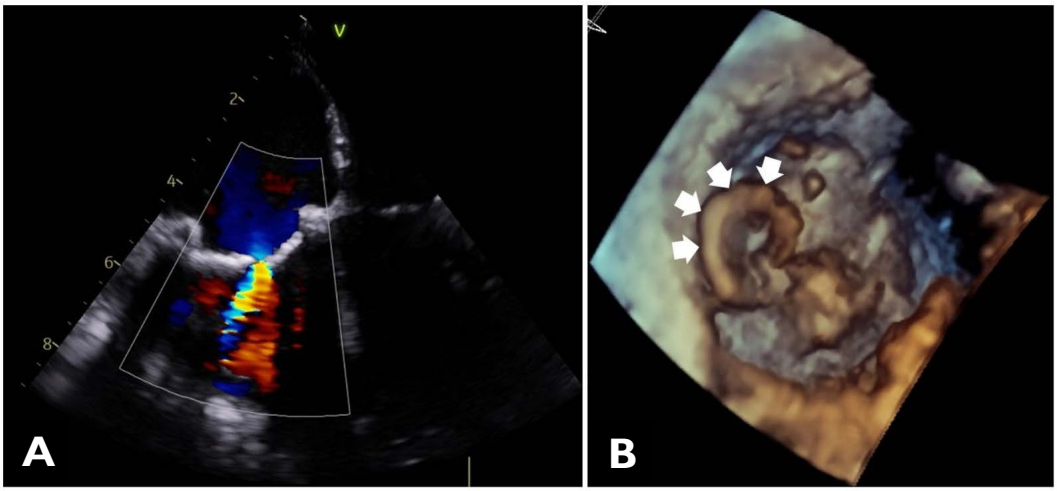

FIGURE 3: Transoesophageal echocardiography showing tricuspid stenosis with colour Doppler (A) and a 3-dimensional rendering of the bioprosthetic tricuspid valve (B) showing the thickened leaflets with a stenotic orifice (white arrows).

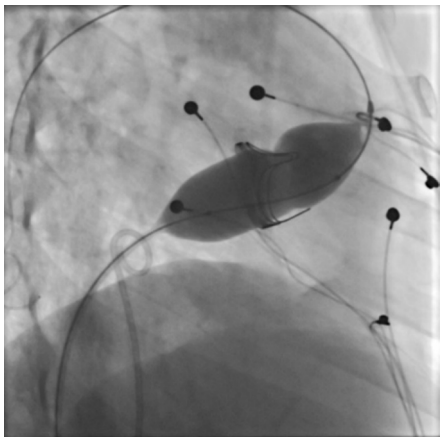

FIGURE 4: Balloon interrogation of the bioprosthetic tricuspid valve showing severe stenosis with a prominent waist.

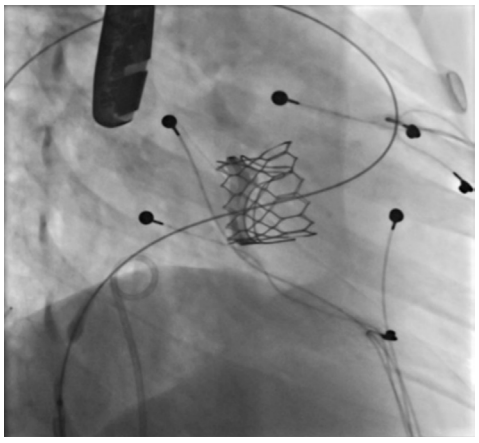

FIGURE 5: The Edwards valve is implanted with a good apposition to the walls of the bioprosthetic valve.

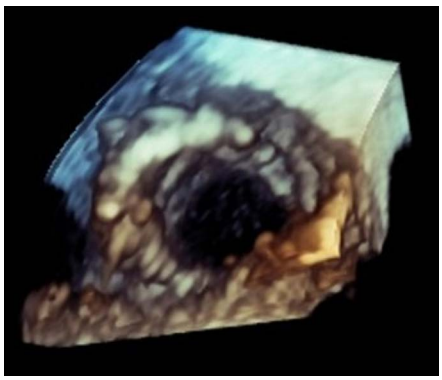

FIGURE 6: Transoesophageal echocardiography with 3-dimensional rendering post-implantation showing a functional valve and no orifice stenosis.

the Melody (Medtronic, Minneapolis, United States) and the Edwards SAPIEN XT and S3 valves.

Prosthetic tricuspid valves have been reported to have shorter longevity than their systemic counterparts, leading to TS, TI, or mixed tricuspid valve disease, all of which may necessitate valve replacement.[2,3] However, surgical replacement of dysfunctional tricuspid prostheses has been noted to confer a higher risk, especially in the setting of concomitant RV dysfunction.[2,6] Due to the off-label use of percutaneous valves in the tricuspid position, there are currently no formal indications for TVIV. Through the Valve-in-Valve International Data (VIVID) registry, McElhinney, et al. described indications for reintervention with TVIV as significant TI, which is moderate or greater in severity according to standard definitions, or TI warranting reintervention. TS for reintervention was deemed significant if there was a mean Doppler gradient ≥ 10 mmHg or if the degree of TS warranted reintervention. However, in both studies using the VIVID registry, the indication was determined by the treating physician.[3,7]

Valve selection is determined by the size of the previously surgically implanted valve. Consequently, the internal and external diameters are needed for device selection.[2] The surgical notes serve as a crucial starting point to identify the true internal diameter of the prosthesis. However, detailed computed tomography (CT) imaging may be needed in cases with uncommon or unknown rings or valves.[6] Valve-in-valve apps may be a useful adjunct, but ultimately, the decision would be informed by a review of the CT images.[6,8] The current recommendation in the literature is to use a Melody or SAPIEN valve if the bioprosthesis' outer diameter is ≤ 25 mm or ≥ 29 mm, respectively.[6] The current comparative data show no difference in the short- and medium-term between the two valve types.[7,9] Due to the pathophysiological mechanisms causing bioprosthetic TS, the inner diameter may be irregularly distorted.[2] Thus, use of a sizing balloon helps to identify the constrictive points within the prosthesis that will serve as a landing zone, and provide information on how the prosthesis may deform during deployment of the percutaneous valve.[2,9]

The youngest reported patient to receive a TVIV was 5 years old, weighing 17.1 kg.[9] Tzifa, et al. previously reported on a successful TVIV in a 6-year-old patient, weighing 13 kg, in addition to successful implantation in an 11- and 12-year-old during their early experience.[2] To the authors' knowledge, our case is the youngest TVIV in South Africa.

Safety considerations

Similar to percutaneous pulmonary valve implantation (PPVI), establishing a safe landing zone is paramount for a stable valve implantation and a lower risk of embolisation. Previous case reports described the use of pre-stenting bioprosthetic valves that have a short landing zone, especially when implanting the Edwards valve due to its short stent length.[2] However, Eicken, et al. suggested that pre-stenting may lead to a smaller orifice area, which could lead to long-term complications.[9] It is also advised that if pre-stenting is not performed, rapid pacing may assist with the accurate positioning of the valve. Rapid pacing may be performed via the coronary sinus, LV, or pericardial approach. In our case, we utilised the patient's pacemaker.

Long-term outcomes

The clinical and haemodynamic outcomes for TVIV have been promising thus far. Most studies report improvement in New York Heart Association functional classification from class III or IV to class I or II post-TVIV.[2,3,7,9] Reported complications include third-degree heart block, mild-to-moderate TI due to over-dilation of the implanted valve, and endocarditis.[2] However, due to the limited case reports, incidence rates for these complications are not widely available. Presently, long-term outcomes for TVIV are unavailable, while the largest medium-term outcome data set is by McElhinney, et al., reporting on the VIVID registry. Key findings reported from this study included a 3-year incidence of death (17%), reintervention (12%), and valve-related adverse outcomes (8%).[7] The annualised incidence rate of endocarditis in TVIV was 1.5% per patient-year, similar to that reported for PPVI in a systematic review.[10] It is also suspected that there may be no significant difference in endocarditis incidence between surgical tricuspid valve replacement and TVIV.[7] The time to diagnosis of endocarditis post-TVIV ranged between 2 and 29 months.[7] Valve thrombosis was noted to occur with a cumulative incidence of 3.3% over the 3 years. A higher post-TVIV inflow gradient was associated with a higher risk of valve thrombosis and need for reintervention.

CONCLUSION

Transcatheter TVIV replacement is a safe alternative approach for patients who may be at higher risk for surgical revalvulation. The current case adds to the growing literature, demonstrating procedural safety and good efficacy in young patients with post-operative tricuspid pathology.

Conflict of interest: none declared.

ETHICAL CONSIDERATIONS

This article followed all ethical standards for research. The patient provided signed informed consent to the publication of a personal medical report in an impersonal form. Ethics approval was obtained from the University of the Free State Health Sciences Research Ethics Committee (UFS-HSD2025/1225/3009).

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Cardiac dysfunction in patients treated for cancer: a challenge to cardiologists

AJ Dalby

Address for correspondence:
Cardiologist,
D46 Life Fourways Hospital
Cedar Avenue West
Fourways
Randburg
South Africa
2121

Email:
ajd@drdalby.co.za

AJ Dalby https://orcid.org/0000-0002-4174-0940
DOI: https://doi.org/10.24170/23-1-7813

INTRODUCTION

The rapid and extensive development of numerous cancer therapies has led to greatly improved patient survival. In parallel with greater survivorship, the incidence of cancer therapy-related cardiac disease (CTRCD) has increased. Therefore, it behoves cardiologists to anticipate the many manifestations of CTRCD, requiring awareness of the nature and extent of the cancer, its genetic type, detailed insight into the treatment to be applied or already given, its possible side effects, and the intrinsic risk to the patient's cardiovascular health at baseline.

A common scenario

The cardiologist's problem is illustrated by the case of an 80-year-old woman. She had been treated successfully for heart failure for 15 years on a beta blocker, an angiotensin receptor blocker, and a loop diuretic. At age 78, she was diagnosed with a moderately differentiated colon carcinoma and commenced continuous chemotherapy following a partial colectomy. In the 3 years before chemotherapy, her left ventricular ejection fraction (LVEF) averaged 0.63. Before treatment, her estimated glomerular filtration rate (eGFR) was 51, and a year later it was 36. Despite continuous treatment with a beta blocker, sodium-glucose transport 2 (SGLT2) inhibitor and furosemide, she developed increasing dyspnoea. Her symptoms raised the possibility of CTRCD; its likelihood depending on the nature of her cancer treatment.

The patient was unable to provide any details beyond taking 6 tablets a day for 2 out of every 3 weeks and a "drip" once every 3 weeks. In the absence of any prior communication from her oncologist to the treating cardiologist, she learned from the clinic that she had been receiving capecitabine and bevacizumab. By referencing the literature, it was established that capecitabine is an antimetabolite, a 5-fluorouracil prodrug, the side effects of which include leukopaenia, bleeding (especially when combined with a vitamin K antagonist), coronary vasospasm, stress cardiomyopathy (takotsubo), proteinuria, hepatic impairment, venous thromboembolism, hypertension, and palmar-plantar erythrodysesthaesia (hand-foot syndrome). Bevacizumab is a monoclonal antibody that blocks vascular endothelial growth factor (VEGF). Its use is associated with hypertension, heart failure, QT prolongation, acute vascular events, such as dissection or stroke, and venous thromboembolism.[1]

Transthoracic echocardiography established her current ejection fraction at 0.51, a fall of 12 percentage points. The QT interval was unchanged. Considering the moderate reduction in her left ventricular function, her treatment was intensified by adding sacubitril/valsartan.[1]

The nature of CTRCD

CTRCD has been sub-classified as causing cardiac dysfunction (an adverse impact on cardiac structure and function in cancer patients, presenting either as asymptomatic cardiac dysfunction or symptomatic heart failure resulting from the therapy received) and that resulting in cardiac toxicity (including myocarditis, vasculitis, arterial and venous thrombosis, hypertension, prolongation of the QT interval, and/or arrhythmia).[2] Indeed, CTRCD may involve cardiac dysfunction, heart failure, coronary artery disease, valvular heart disease, arrhythmia, autonomic dysfunction, arterial hypertension, dyslipidaemia, metabolic syndrome, thromboembolism, peripheral arterial disease, stroke, pulmonary hypertension, and pericardial disease.[1]

In 2022, the European Society of Cardiology (ESC) issued a guideline on cardio-oncology outlining commonly encountered scenarios in cancer treatment. The guideline is extremely complex, describing 17 treatment protocols associated with the risk of CTRCD, and detailing 11 categories of potential cardiac complications, each of which may or may not be associated with a specific protocol.[1] Cancer may affect multiple organs, and their genetic subtype will dictate the particular therapy or combination of therapies to be used. An example is breast cancer with its HER2-positive and BRCA-positive subtypes, for which any suitable agent or a combination of agents could be selected from a list of 21.[3] Each of these agents may affect

cardiovascular function differently. Thus, cancer treatment and its ensuing CTRCD cannot be considered as a "one size fits all" situation.

The proposed pathophysiologic mechanisms underlying CTRCD include oxidative stress, inflammation, calcium overload, VEGF, pyroptosis, and fibrosis.[4] The incidence of developing CTRCD is influenced by the baseline cardiovascular risk profile/pre-existing cardiovascular disease, which increases during the treatment period and diminishes somewhat during long-term follow-up.[2] Fluoropyrimidines (such as 5-fluorouracil) are commonly used in the treatment of gastrointestinal cancers and are the second most common cause of CTRCD.[5] Not only do these agents cause direct cellular damage, but they may also provoke coronary vasospasm, resulting in angina pectoris, acute coronary syndromes, atrial fibrillation, myocarditis, pericarditis, and consequent heart failure.

The most frequent cancers encountered in South Africa are breast (most frequent in females), prostate (most frequent in males), cervix (leading cause of cancer deaths in females), lung (overall leading cause of cancer deaths), and colorectal. Examples of the commonly used therapies among these cancers, their main cardiovascular toxicities, and their appropriate monitoring and treatment are shown in Table I.[4-6]

The role of the cardiologist

The cardiologist's role in CTRCD encompasses the patient's entire journey.[1] At baseline, before treatment starts, the cardiovascular risk factors should be assessed, and any pre-existing cardiovascular disease should be treated effectively. Accurate knowledge of the intended cancer treatment is needed to anticipate and promptly treat potential cardiovascular complications. After treatment cessation, long-term surveillance is necessary to detect cardiovascular complications that may emerge.[1]

Predicting CTRCD

To predict cardiovascular risk during treatment, the patient's individual characteristics (genetics, lifestyle, environment, and their social determinants of health) should be weighed alongside the classical cardiovascular risk factors (smoking, diabetes, hypertension, and dyslipidaemia). Furthermore, the potential cardiotoxicity of the planned treatment, with consideration of its pharmacokinetic and epigenetic factors, should be considered.[7]

Risk prediction combined with standard risk factor algorithms, such as the ESC Cardiovascular Disease Risk Score (SCORE2 or SCORE2-OP, easily accessible on the ESC CVD Risk smartphone application), and the Heart Failure Association of the ESC, and the International Cardio-Oncology Society (HFA-ICOS) score, have proved useful in predicting which patients are more likely to develop CTRCD.[8] Risk assessment enables more frequent monitoring in high-risk patients and reduces the need for more frequent re-evaluation in those at low risk. The application of the HFA-ICOS score is complex, as a non-uniform set of risk factors is applied to individual treatments, and similar risk factors

TABLE I: Commonly encountered cancers in South Africa, illustrating the variety of possible treatments, the main cardiovascular toxicities that may be encountered, and the monitoring and prevention measures that may be applied.[4-6]

Cancer	Agent/s	Main cardiovascular toxicities	Monitor & treat
Breast	Anthracyclines	Cardiomyopathy, heart failure	LVEF, GLS GDMT, including SGLT2 inhibitor
	Human EGFR2 targeting: • Trastuzumab	Reduction in ejection fraction, heart failure	LVEF
	Cyclin independent kinase 4/6 inhibitor	QT prolongation, venous & arterial thrombosis	ECG monitoring
Prostate	Androgen deprivation therapy: • Degarelix • Abiraterone • Enzalutamide	QT prolongation, hypertension, cardiovascular events, arrhythmia	ECG monitoring, BP monitoring
Cervix	Pembrolizumab	Hypertension, arrhythmia	BP monitoring
	5-fluorouracil	Cardiac ischaemia, ACS, MI	hs-troponin T
	Paclitaxel	Cardiomyopathy, tachyarrhythmia, heart block	Transthoracic echo monitoring, ECG monitoring
	Topotecan	Heart failure: low risk	NT-proBNP
Lung	Immune checkpoint inhibitors	Myocarditis, pericarditis, pericardial effusion & tamponade, MI, arrhythmias	Cardiac markers, echo, stop treatment, high-dose steroids, immune modulators
Colorectal	VEGF: • Monoclonal antibodies • Tyrosine kinase inhibitors	Hypertension, myocardial ischaemia, systolic dysfunction, arterial thrombosis, QT prolongation	Frequent BP monitoring, RAASi & DHP CCB

ACS: acute coronary syndrome, BP: blood pressure, DHP CCB: dihydropyridine calcium channel blockers, ECG: electrocardiogram, echo: echocardiogram, eGFR: estimated glomerular filtration rate, GDMT: guideline-directed medical therapy, GLS: global longitudinal shortening, hs-troponin T: high-sensitivity troponin T, LVEF: left ventricular ejection fraction, MI: myocardial infarction, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, RAASi: renin-angiotensin-aldosterone system inhibition, SGLT2: sodium-glucose transport 2, VEGF: vascular endothelial growth factor

are variously treated as indicating very high, high, or moderate risk, based on the specific agent.[9]

Although there is no perfect risk assessment strategy, precise risk calculation should be attempted, as the greatest impact will be among medium- and high-risk individuals, whereas identifying low-risk patients offers potential savings in health costs.[10] For instance, a progressive increase in the occurrence of CTRCD and heart failure was observed in patients rated at baseline as low, medium, or high risk when treated either with trastuzumab or trastuzumab with an anthracycline.[6]

Monitoring for CTRCD

At any stage, monitoring for CTRCD requires meticulous clinical assessment, with evaluation for cardiovascular risk factors and the presence of underlying cardiovascular disease. Electrocardiography is appropriate to exclude cardiac ischaemia and to measure the QT interval. The markers of cardiac injury (high-sensitivity [hs]-troponin T/I and N-terminal prohormone of brain natriuretic peptide [NT-proBNP]) may facilitate CTRCD detection, but do not necessarily constitute standard monitoring.[1] False positive values may be encountered, particularly in the case of hs-troponin I, due to the presence of immunoglobulin-troponin complexes (so-called macrotroponin), which should be suspected when the result is incongruous with the clinical picture and imaging.[1] In this instance, a troponin measurement before treatment initiation may provide important information. Macrotroponin can be identified by specific testing.[11]

The LVEF should be measured before starting treatment by transthoracic echocardiography. Measurement of global longitudinal strain is proposed as a useful parameter, though its superiority to LVEF has been questioned. Serial estimations of LVEF should employ the same methodology on each occasion. A fall in LVEF of 15% or more on treatment is considered significant.[1] Magnetic resonance imaging may be required when the acoustic window does not allow for accurate assessment of the LVEF by transthoracic echo.[5]

Preventing CTRCD

CTRCD prevention includes ensuring patients' adherence to a healthy lifestyle, i.e. smoking cessation, weight control, regular exercise, and a healthy diet. Stringent control of the classical risk factors is important. Attempts to ameliorate CTRCD with beta blockers (carvedilol, metoprolol), renin-angiotensin-aldosterone system inhibitors (enalapril, candesartan), and statins have not yielded convincing results.[12] SGLT2 inhibition has an anticancer effect, as well as being cardioprotective.[13] Recent observational studies of SGLT2 inhibition (dapagliflozin, empagliflozin) demonstrated encouraging improvements in overall survival, cardiac dysfunction, heart failure incidence, and heart failure hospitalisation.[14-16] In a study of 83 women with breast cancer, treatment with spironolactone, a mineralocorticoid receptor antagonist, was associated with lesser rises in troponin I and NT-proBNP, and a smaller impact on LVEF compared with a placebo.[17]

Managing CTRCD

When CTRCD emerges, the risks and benefits of continued treatment should be carefully considered. Whether dose reduction, reduction in the frequency of treatment, temporary interruption, or treatment alteration is indicated depends on balancing the cardiovascular prognosis with that of the cancer.[18] For example, despite the cardiovascular risks of fluoropyrimidine chemotherapy noted above, experience has shown that the overall survival benefit of treatment outweighs the risk.[18]

Atrial fibrillation is among the common arrhythmias encountered in CTRCD. Its occurrence may influence cancer therapy and adversely affect survival. Various cancer drugs have been shown to double or quadruple the risk of atrial fibrillation. The true incidence of atrial fibrillation in cancer therapy is uncertain, as the condition is frequently asymptomatic and is not routinely recorded in trials of anticancer treatment. Most trials only record atrial fibrillation when it arises as a serious complication.[19] Aside from the usual complications of atrial fibrillation, attention should be focused on the anticoagulation strategies in patients who frequently have thrombocytopaenia and are prone to serious bleeding.[19]

Arterial and venous thrombosis and embolism are encountered in up to 55% of cancer patients. The high frequency is accounted for by increases in life expectancy, the use of thrombogenic anticancer treatments, extensive use of central venous catheterisation, and heightened awareness of cancer-associated thrombosis. Deep venous thrombosis and pulmonary embolism are 4–7 times more frequent in cancer patients.[20] The reported mortality rate of venous and arterial thromboembolism is 8.4%, and it is the leading cause of death outside cancer-related deaths.

Cancer patients have a higher risk of bleeding and recurrent venous thromboembolism.[20] Low-molecular-weight heparin treatment has not been successful in countering thrombotic complications. Direct oral anticoagulants are associated with lower recurrence rates and reduced major bleeding. Compared with standard doses, a lower dose of apixaban (2.5 mg bd) was effective in preventing recurrent venous thromboembolism and was coupled with a lower bleeding risk.[21]

Aftercare

Cancer patients' aftercare should ideally be a collaborative effort, providing social support to the patient, family, and caregiver by the primary physician, oncologist, and cardiologist. Allied professionals, such as dieticians, rehabilitation experts, and social workers, should also be involved.[7] Encouraging moderate-to-vigorous exercise in recovered patients should not be overlooked, as it benefits anxiety–depression, physical functioning, cardiac health, and cardiovascular disease, as well as cancer-specific and overall survival.[22]

CONCLUSION

As illustrated by the case presented, communication among the physician or surgeon who made the diagnosis, the treating

oncologist, and the cardiologist responsible for detecting and treating CTRCD is often lacking in the local setting. The increasing number of patients at risk of CTRCD demands closer cooperation and communication between the professionals treating them, acquiring a deeper understanding of their treatment protocols, accurate assessment of their intrinsic risk, appreciation of the potential adverse side effects to which they may be exposed, early detection and management of cardiac complications, and assurance of sustained follow-up once treatment is completed.

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STATISTICS MADE EASY

The new frontier of statistics: Modern machine learning approaches as alternatives to traditional statistical tests in biological, clinical, and epidemiological research with a focus on cardiac event prediction

A Wentzel[1,2] and M Blignaut[3]

[1] Hypertension in Africa Research Team, North-West University, Potchefstroom, South Africa
[2] South African Medical Research Council, Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa
[3] Centre for Cardio-Metabolic Research in Africa, Division of Medical Physiology, Department of Biomedical Sciences, Stellenbosch University, Tygerberg, South Africa

Address for correspondence:
M Blignaut
Division of Medical Physiology
Centre for Cardio-Metabolic Research in Africa (CARMA)
Biomedical Research Institute
Faculty of Medicine and Health Sciences
Level 3, Room 3023
Tygerberg Campus
Stellenbosch University
Stellenbosch
South Africa
7599

Email:
mblignaut@sun.ac.za

A Wentzel https://orcid.org/0000-0002-3765-2040
M Blignaut https://orcid.org/0000-0001-7645-9780
DOI: https://doi.org/10.24170/23-1-7883

ABSTRACT

As the complexity and volume of biological and clinical data increase, traditional statistical methods, such as logistic regression, discriminant analysis, analysis of variance (ANOVA), and multivariate analysis, often fall short of capturing the intricate patterns needed for accurate prediction and classification. Here, we explore alternative analytical frameworks rooted in modern machine learning (ML) techniques that offer enhanced capabilities for diverse biomedical applications. For example, these frameworks demonstrate superior predictive performance for cardiac events compared with classical logistic regression. However, challenges, interpretability, and future directions are important considerations when facing this new frontier. Moreover, systematically integrating these advanced computational tools into routine clinical and epidemiological research is imperative. This co-authored column forms part of the "Statistics Series" and builds on *A simple guide to analyse data* by Prof. Libhaber.[1]
Keywords: machine learning, neural networks, deep learning, high-dimensional biological data
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WHAT ARE THE CHANCES?

At the heart of statistics lies the need to accurately estimate the probability that a given event, feature, or phenotype falls within or outside the expected range. Normality in biomedicine is traditionally defined as the likelihood that an observation falls within an expected range, based on sample data and probability models.[2] For example, the effect of a new treatment or therapy applied to the general population can be inferred by measuring the outcomes in a small subset of the population, and testing the null hypothesis that there will be no effect in the population. This hypothesis is tested with mathematical models based on certain features of the dataset that quantify the probability (if the study were repeated many times) that the same treatment or therapy effect observed in the study sample will be detected to the same extent in the larger, general population.

Herein lies the key difference between traditional statistical methods and ML: both inference and probability are based on mathematical models, whilst ML uses algorithms to identify patterns within existing data to make predictions about other datasets. Although traditional statistical tools, such as t-tests, simple correlations, and standard regression, remain essential for hypothesis-driven analyses, effect estimation, and transparent inference, they often assume linear relationships (never the case in biology), limited interactions, and relatively simple datasets with few features or attributes (referred to as low-dimensional datasets in ML).[3,4]

However, contemporary biological and clinical datasets are often large and high-dimensional, with numerous variables or features, where each feature becomes a dimension. These datasets can also be heterogeneous, combining omics, imaging, continuous physiological monitoring, and longitudinal electronic health

record data, where the true relationships are likely nonlinear, interactive, and highly context-dependent.[5] ML methods, including neural networks (NN), tree-based ensembles, and kernel methods (see "Definitions"), are specifically designed to model such complex structures, leading to more accurate predictions and enabling the discovery of clinically relevant patterns that may not be apparent using traditional methods alone.[5,6]

DEFINITIONS OF MACHINE LEARNING (ML)

ML is a set of computational methods that actively learn and identify patterns from data to make predictions, connections, or uncover structure, without explicitly programmed, fixed decision rules. These models are trained on clinical data, including laboratory results, imaging, waveforms, and health records, to predict outcomes like disease presence, deterioration risk, and treatment response.[6] Unlike the classical inferential statistics discussed in the previous section, ML emphasises predictive performance and flexibility, allowing correlated variables and complex, multidirectional relationships to be considered simultaneously.[7]

Neural networks and deep learning

Artificial NNs are a widely used subset of ML methods inspired by how biological neurons process signals, consisting of layers of interconnected "nodes" that transform input data using learned weights and nonlinear activation functions.[8,9] When many layers are stacked, the resulting deep NNs (deep learning) can automatically learn increasingly abstract, multidirectional representations and relationships from complex, raw data without manual feature engineering.[7,10] Consequently, deep learning has exceeded expert-level performance in tasks such as medical image classification, disease detection on radiographs, and protein structure prediction, demonstrating its capacity to handle high-dimensional, unstructured biomedical data.

WHEN AND HOW TO APPLY MACHINE LEARNING IN BIOMEDICINE

ML is particularly appropriate when the primary goal is prediction, pattern recognition, or classification (predicting disease risk, identifying biological marker patterns, stratifying patients, or detecting pathology in images), especially in the presence of many predictors, potential nonlinearities, and interactions.[7,8] It is well-suited to high-dimensional omics data, medical imaging, waveform data (electrocardiography [ECG], electroencephalogram, continuous blood pressure), and rich electronic health record datasets, where traditional models may overfit or fail to capture structure, provided that sufficient sample size, careful validation, and appropriate regularisation are used.

However, when the main objective is to estimate interpretable effect sizes, test specific mechanistic hypotheses, or communicate simple associations, conventional regression and related statistical models remain preferable. In these cases, ML can be used as a complementary tool, applied initially to optimise traditional methods, rather than as a replacement. Table I provides an extensive summary of traditional statistical methods, their uses, the ML alternative, and examples in biomedical applications. For instance, a systematic review of the application of different ML approaches to analyse ECG data found that ECG deep-learning models are increasingly clinically relevant; however, their reporting is highly variable, and few publications provide sufficient detail for methodological reproduction or model validation by external groups.[11]

TYPES OF MACHINE LEARNING TASKS AND DATA

Most biomedical ML applications fall into 3 broad paradigms: (1) supervised learning, where models are trained on labelled outcomes (e.g. disease vs. no disease) to perform prediction or classification; (2) unsupervised learning, which discovers structure, such as clusters or latent patterns in unlabelled data; and (3) semi- or self-supervised approaches that leverage both labelled and unlabelled data.[8] Supervised methods are widely used for diagnostic and prognostic models, mortality risk prediction, and treatment response modelling, while unsupervised methods underpin patient subtyping, endotype discovery, and exploratory analysis of high-dimensional biological measurements.[5,6] Deep learning extends these paradigms to unstructured data, such as images, free text, and raw signals, allowing direct modelling from pixels, narrative notes, dimensional data, or waveforms when sufficient data and computational resources are available.

INTEGRATING MACHINE LEARNING IN CLINICAL PRACTICE AND CLASSIC STATISTICS

For clinical researchers and clinicians, the key is not to abandon traditional statistics, but to integrate ML and NN methods where they add clear value, such as improving risk stratification, automating image interpretation, or identifying novel patient subgroups. Rigour remains essential; model development should include careful preprocessing, transparent variable selection, appropriate cross-validation or external validation, and attention to calibration, fairness, and interpretability, particularly when models influence patient care.[6,10] As biomedical data become more complex and abundant, ML and NNs provide a powerful, complementary, informative toolkit that can augment and provide richness, rather than replace established statistical approaches, setting the stage for more precise, data-driven, and individualised medicine. There are already many easily accessible tools available, many of which are free and open source (such as Python-based libraries). However, their use depends on experience, coding capabilities, dataset type, and available hardware (Figure 1 illustrates a broad overview of the different ML tools and their applications).

Nonetheless, it is important to note that traditional statistical adjustments are often required when using ML and NNs to ensure reliable performance, generalisation, and interpretability, particularly in biomedicine. Moreover, incorporating more traditional statistical techniques may also address ML's sensitivity to data quality by focusing on issues such as overfitting through

TABLE I: Comparing traditional statistics to machine learning alternatives.[13-20]

Traditional method and aim	Typical biomedical use	ML/NN alternative for a similar aim	When the ML alternative is useful	Example biomedical application*
Two-sample t-test (continuous outcome, 2 groups for univariate analysis), multiple linear regression for continuous outcomes (if normally distributed)	Compare the mean of a biomarker or physiological measure between 2 groups (biomarker levels in cases vs. controls).	**Regularised regression (e.g. Lasso/ridge), tree-based models (e.g. random forest, gradient boosting), including group indicator plus additional covariates.**	When there are many correlated biomarkers or covariates, and the goal is to predict group membership or an outcome (rather than only test the mean difference), and to capture nonlinear relationships.	Predicting tuberculosis treatment failure using multiple clinical and demographic variables where simple mean differences are insufficient; random forest or NNs can model complex risk patterns.
One-way ANOVA (continuous outcome, multiple groups)	Compare mean outcome across several treatment or exposure groups (e.g. comparing mean blood pressure across 3 drug regimens).	**Supervised learning models with categorical group variables plus covariates (e.g. gradient-boosted trees, random forest, NNs) predicting continuous outcomes.**	When interest is in predicting the outcome under different treatment or exposure conditions, while incorporating many patient-level features, and when interactions and nonlinear dose–response relationships may exist.	Modelling systolic blood pressure response to different antihypertensive regimens using numerous baseline characteristics with gradient boosting to identify subgroups with the largest benefit.
Pearson/Spearman correlation (pairwise association) or a partial correlation	Quantify the association between 2 continuous variables (e.g. CRP and disease severity score) but does not account for the bidirectionality of biological systems.	**Nonlinear regression, kernel methods (e.g. support vector regression), or flexible feature importance measures from tree-based models.**	When relationships are suspected to be nonlinear or involve interactions with other features, ML models can estimate variable importance and partial dependence instead of a single correlation coefficient.	Exploring complex associations between continuous glucose monitor metrics and cardiovascular risk markers, using random forest to capture nonlinear effects rather than a single correlation per pair.
Simple/multiple linear regression (continuous outcome)	Model a continuous clinical outcome (e.g. lung function, ejection fraction) as a function of several predictors with interpretable coefficients.	**Regularised regression (Lasso, elastic net), random forest regression, gradient boosting machines, or feedforward NNs.**	When there are many predictors, multicollinearity, or nonlinear effects and interactions, ML can improve prediction and automatically select or weight variables while controlling overfitting.	Predicting heart disease severity or exercise capacity from numerous clinical, lab, and imaging features with random forest regression often achieves better predictive performance than standard linear models.
Logistic regression (binary outcome)	Model probability of an event (e.g. disease presence, treatment failure) as a function of predictors, with odds ratios for interpretability.	**Tree-based classifiers (random forest, gradient boosting), support vector machines, or deep NNs.**	When accurate classification or risk stratification is prioritised, particularly with many variables, nonlinear interactions, or complex feature sets (e.g. combined clinical and laboratory data).	Predicting risk of treatment failure in tuberculosis or cardiovascular disease using multiple demographic, clinical, and lab features; studies show that random forests or gradient boosting can outperform logistic regression in some datasets for discrimination metrics.
Multinomial/ordinal logistic regression (multi-class outcomes)	Model categorical outcomes with more than 2 levels (e.g. disease stage I–IV, NYHA class).	**Multi-class random forests, gradient-boosted trees (e.g. XGBoost), multi-class support vector machines, or multi-class NNs.**	When there are high-dimensional predictors and complex decision boundaries between classes, or when using heterogeneous inputs (e.g. imaging plus tabular data).	Classifying heart failure stage or severity class from combined EHR data using gradient-boosted trees to optimise multi-class discrimination beyond a parametric ordinal model.
Cox proportional hazards regression (time-to-event outcome)	Model hazard of events (e.g. time to death, time to readmission) using covariates, providing hazard ratios and survival curves.	**Random survival forests, gradient boosting for survival (e.g. survival XGBoost), and survival NNs (e.g. DeepSurv).**	When proportional hazards or linear effects may be violated, when many predictors and nonlinearities are present, or when prediction of individualised risk trajectories is prioritised over simple hazard ratios.	Predicting breast cancer survival or lung cancer prognosis using high-dimensional clinical and molecular predictors with random survival forests or survival gradient boosting, sometimes outperforming classical Cox models in discrimination.

TABLE I: Continued

Chi-squared test/Fisher's exact test (categorical association)	Test association between 2 categorical variables (e.g. genotype vs. disease status, treatment vs. response categories) in contingency tables.	**Supervised classifiers (e.g. random forest, gradient boosting, naive Bayes) using categorical predictors to model outcome probabilities directly.**	When there are multiple categorical predictors and their interactions matter for outcome prediction, rather than simply testing the independence of a single pair.	Predicting antibiotic resistance profile or treatment response category from multiple categorical predictors (e.g. pathogen type, prior exposure, comorbidities) using gradient boosting rather than separate chi-squared tests.
Principal components analysis for dimension reduction	Reduce dimensionality of correlated continuous variables (e.g. many metabolic markers) to a smaller set of uncorrelated components for visualisation or downstream modelling.	**Nonlinear dimension reduction, such as autoencoders (NNs), t-SNE, or UMAP (although not all are predictive models).**	When the underlying structure is believed to be nonlinear or manifold-like, and the aim is to discover latent patterns or clusters in high-dimensional data (e.g. omics, imaging-derived features).	Discovering patient subtypes in multi-omics cancer data using autoencoders to learn low-dimensional representations, then clustering patients to identify molecularly distinct disease phenotypes.
Cluster analysis (k-means, hierarchical clustering)	Unsupervised grouping of patients or features based on similarity, often to identify phenotypes or subgroups without outcome labels.	**Model-based clustering (Gaussian mixture models), density-based clustering (DBSCAN), or deep clustering approaches (IDEC) that couple NNs (auto-encoders) with clustering objectives.**	When clusters may be non-spherical, overlapping, or embedded in high-dimensional nonlinear spaces, a richer structure is expected than can be captured by distance-based methods alone.	Phenomapping in heart failure or sepsis, using high-dimensional clinical and biomarker data with advanced ML clustering methods to identify clinically meaningful subgroups that differ in prognosis or treatment response.
Repeated-measures ANOVA/linear mixed models (longitudinal continuous outcomes)	Analyse trajectories over time (e.g. repeated blood pressure or biomarker measures) and test group or time effects with random effects for subjects.	**Recurrent NNs, temporal convolutional networks, or sequence models (e.g. transformers) for time series; random forest or boosting with engineered longitudinal features.**	When temporal patterns are complex, sampling is irregular, or large-scale time series from wearables or ICUs are available, and the aim is to predict future events or detect deterioration rather than only test mean trajectory differences.	Early prediction of sepsis or decompensation in ICU patients using multichannel vital sign time series with recurrent or convolutional NNs, enabling continuous risk scoring beyond traditional mixed-model analyses.

** Artificial intelligence (Perplexity) was used to identify biomedical application examples (listed in the last column) in literature (cited at the top).*
ANOVA: analysis of variance, CRP: C-reactive protein, DBSCAN: Density-Based Spatial Clustering of Applications with Noise, EHR: electronic health record, ICU: intensive care unit, IDEC: Improved Deep Embedded Clustering, ML: machine learning, NN: neural network, NYHA: New York Heart Association Functional Classification, t-SNE: t-distributed stochastic neighbour embedding, UMAP: uniform manifold approximation and projection.

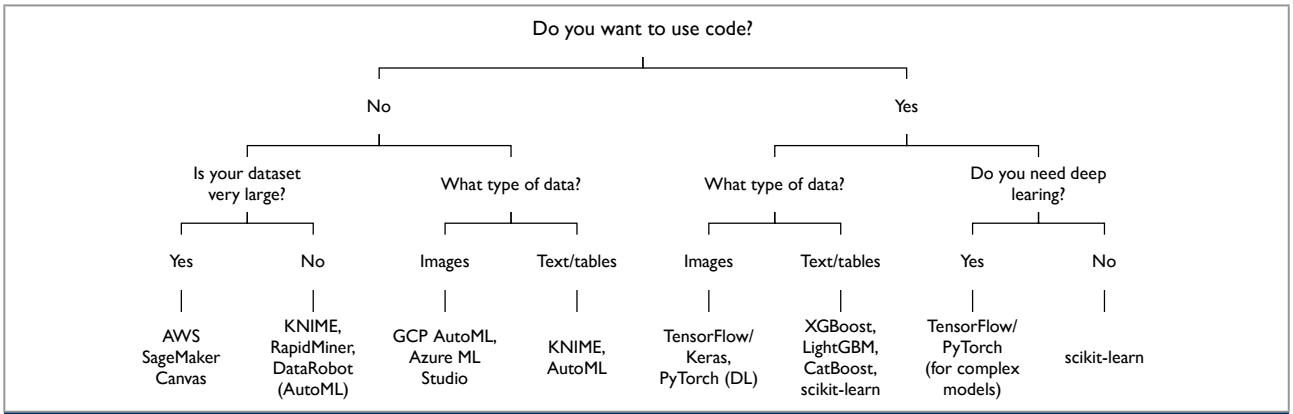

FIGURE 1: This schematic (generated with ChatGPT using specific prompts to identify the most used AI tools, followed by a prompt to organise the data according to the ability to code) shows the types of ML tools that can be used based on data type and coding experience. Amazon (AWS) SageMaker Canvas is a no-code ML service for data processing and model building. Scikit-learn works very well for tabular biomedical data (e.g. clinical variables, lab tests, biomarker panels), whilst XGBoost/ LightGBM is best for high-performance models on structured biomedical datasets. For DL purposes, TensorFlow with Keras is very good, with a user-friendly interface. PyTorch offers greater flexibility and is most commonly used in academic environments to build custom biomedical DL architectures. KNIME is often used as a data analytics, reporting, and integration platform, integrating various components for ML and data mining through its modular data pipeline.
AutoML: automated machine learning, AI: artificial intelligence, DL: deep learning, ML: machine learning.

TABLE II: Pros and cons of machine learning in biomedical research.[13,15,18-20]

Dimension	Pros (advantages)	Cons (limitations/risks)
Data complexity and scale	Can handle high-dimensional, heterogeneous data (imaging, omics, waveforms, EHR) without requiring simple, prespecified linear relationships, making it well-suited to modern, multimodal biomedical datasets that are complex, nonlinear, and often contain many correlated predictors.	Strongly dependent on data quality, completeness, and representativeness; noisy labels, missingness, site effects, and small or biased samples can severely degrade performance and undermine external validity, especially when training data do not reflect the target population.
Prediction and pattern recognition	Often achieves superior performance to traditional models for tasks such as disease risk prediction, image-based diagnosis, and outcome forecasting when datasets are sufficiently large and well-curated, detecting subtle patterns (e.g. in retinal or radiology images) that are difficult for humans or simple models to capture.	Prone to overfitting if model complexity is high relative to the effective sample size, if feature engineering is careless, or if validation is weak; internal metrics can appear excellent while true generalisation to new settings or hospitals is poor, leading to overly optimistic published results.
Personalisation and precision	Enables more granular risk stratification, identification of high-risk subgroups, and personalised treatment strategies by integrating many clinical, biological, and behavioural predictors, supporting precision medicine and biomarker-based trial design or response prediction.	Personalisation can exacerbate bias if subgroup models are derived from small or unbalanced strata; models may encode and amplify structural inequities (e.g. underrepresented ethnic groups or sexes) unless fairness and subgroup performance are explicitly evaluated and corrected.
Efficiency and automation	Once trained and validated, models can process large data volumes rapidly, automating repetitive tasks such as image triage, signal screening, or EHR-based early warning scores, potentially freeing clinicians and researchers to focus on interpretation, study design, and patient-facing decisions.	Automation can encourage over-reliance on algorithmic outputs, with the risk that clinicians or researchers defer to model predictions without adequate scrutiny; poorly integrated tools can increase workload or alert fatigue rather than reduce it, and errors may propagate at scale.
Discovery and hypothesis generation	Facilitates data-driven discovery of new patterns, phenotypes, and interactions (e.g. phenomapping, unsupervised clustering of omics or imaging), suggesting novel hypotheses, biomarkers, or mechanistic leads that can be tested with targeted experiments or classical statistical models.	Data-driven discoveries can be difficult to interpret mechanistically, and spurious clusters or associations are common when multiple testing and validation issues are not handled rigorously; there is a risk of "pattern hunting" without sufficient biological grounding or prespecified questions.
Interpretability and transparency	Some ML methods (e.g. regularised linear models, shallow trees, generalised additive models, or post-hoc explainability tools) can provide variable importance, partial dependence, and other insights that complement traditional effect estimates, aiding understanding of complex relationships.	Many high-performing models, especially deep NNs, behave as "black boxes" with limited transparency about how predictions are generated, which complicates mechanistic understanding, communication with clinicians and regulators, and formal adoption into guidelines or decision pathways.
Data access, privacy, and governance	Can encourage the development of high-quality, well-curated research datasets and data infrastructures, and motivate federated or privacy-preserving methods that analyse distributed data without centralising identifiable information.	Requires access to large, often linked patient-level datasets, raising substantial issues around consent, privacy, re-identification risk, data ownership, and security; regulatory and ethical constraints may limit data sharing and multicentre validation, reducing reproducibility and generalisability.
Technical and resource demands	Stimulates multidisciplinary collaboration between clinicians, statisticians, computer scientists, and engineers; open-source tools and pre-trained models (e.g. for imaging or NLP) can lower entry barriers for research groups.	Robust model development and deployment demand specialised expertise in data engineering, ML, and software practices; deep learning can be computationally expensive, requiring substantial hardware, maintenance, and monitoring infrastructure that not all groups possess.
Evaluation, validation, and reproducibility	When done well, rigorous cross-validation, temporal validation, and external validation across sites can yield models with strong, well-characterised generalisation performance and well-calibrated risk estimates that stand up to prospective testing.	Many published biomedical ML studies use small datasets, weak validation, optimistic performance metrics, and incomplete reporting, hindering reproducibility and inflating expectations; code, trained models, and data are often not fully shared, limiting independent verification and re-use.
Workflow and culture	Offers potential to streamline research pipelines (e.g. automated feature extraction from images, structured data from free text) and clinical workflows (e.g. triage, prioritisation), and can augment human expertise in a complementary way.	Integration into existing research and clinical workflows can be challenging, requiring changes in processes, training, and culture; scepticism from clinicians, concerns about medico-legal liability, and misalignment with clinical priorities can slow or block adoption, even for technically strong models.

EHR: electronic health record, ML: machine learning, NN: neural network.

TABLE III: When to use traditional methods versus machine learning.

Aspect	Traditional statistical methods (e.g. t-test, linear/logistic/Cox regression, correlations)	ML/NNs (including deep learning)
Primary goal	Estimate and test associations or effects (e.g. exposure–outcome relationships, hazard ratios), with emphasis on inference and interpretability.	Maximise predictive accuracy or pattern recognition (e.g. classify, risk-stratify, detect structure), often with less emphasis on explicit parameter interpretation.
Typical assumptions	Prespecified model form (often linear), limited interactions, relatively low number of predictors versus sample size, and structured noise assumptions (e.g. normality, proportional hazards).	Flexible, data-driven function classes that can capture nonlinearity and complex interactions, with fewer parametric assumptions but a stronger need for regularisation and validation.
Data size and dimensionality	Best when the number of observations is much larger than the number of predictors, and variables are carefully selected a priori (e.g. classical cohort studies, public health surveys).	Particularly advantageous for high-dimensional data (e.g. genomics, radiomics, multi-omics, rich EHR data) where the number of predictors can rival or exceed the sample size.
Data type	Structured, tabular data with clearly defined variables (e.g. age, blood pressure, lab values, questionnaire scores).	Can handle both structured and unstructured data, such as images, free text, waveforms, and sensor streams, often directly from raw inputs (pixels, time series).
Example: prognosis/risk prediction	Cox regression model to estimate hazard ratios for mortality in a cardiovascular cohort using a small panel of risk factors (age, blood pressure, cholesterol, smoking) and to quantify their independent effects.	Gradient boosting or deep learning model using dozens to hundreds of variables from EHRs to predict in-hospital deterioration or 30-day mortality, focusing on accurate risk stratification rather than individual effect sizes.
Example: diagnostic classification (tabular data)	Logistic regression using a limited set of clinical variables (e.g. body mass index, fasting glucose, blood pressure) to estimate odds of metabolic syndrome and test specific risk factor hypotheses.	Random forest or support vector machine using a richer set of features (e.g. labs, vitals, comorbidities, medication history) to classify patients at high risk of developing diabetes or metabolic syndrome, optimised for sensitivity/specificity.
Example: medical imaging	Linear measurements and simple thresholds (e.g. lesion size, ejection fraction) analysed with standard statistics to compare groups or assess associations with outcomes.	Convolutional NN trained on large sets of labelled computed tomography, magnetic resonance imaging, or X-ray images to detect lung nodules or classify tumours, often achieving radiologist-level accuracy in identifying malignancy.
Example: omics/ high-throughput biology	Multiple regression or univariate testing with correction for multiple comparisons to relate a small subset of preselected genes or proteins to an outcome, mainly for hypothesis-driven analysis.	Regularised models, tree-based ensembles, or deep learning applied to genome-wide or proteomic profiles to predict drug response or discover molecular subtypes of cancer or other diseases.
Example: longitudinal/ monitoring data	Mixed-effects models or repeated-measures ANOVA to test average trajectories over time (e.g. HbA1c or blood pressure trends) and assess group differences with interpretable coefficients.	Recurrent or temporal convolutional NNs trained on continuous wearables or ICU monitoring data (e.g. heart rate, rhythm, glucose sensors) to detect early signs of sepsis, arrhythmia, or decompensation in real time.
Strengths	Transparent modelling, explicit effect estimates (odds ratios, hazard ratios), strong theory for inference and uncertainty quantification, easier to audit and communicate to clinicians and regulators.	Captures complex nonlinear patterns and interactions, scales to large and heterogeneous datasets, excels at prediction and pattern discovery, and can directly ingest raw or minimally processed data.
Limitations	May underperform when relationships are nonlinear or highly interactive, or when many correlated predictors are present; performance can degrade in very high-dimensional settings.	Models can be less interpretable, prone to overfitting without rigorous validation, and resource-intensive; performance advantages over well-specified traditional models are not guaranteed in small or simple datasets.
When to prefer	Hypothesis-driven work where quantifying and testing specific associations is primary, datasets are moderate in size and dimensionality, and interpretability is paramount (e.g. guideline development, mechanistic research).	Prediction- or classification-focused problems with complex, high-dimensional, or unstructured data, where improving accuracy, risk stratification, or pattern discovery is central (e.g. imaging artificial intelligence, multi-omics risk scores, EHR-based early warning systems).

ANOVA: analysis of variance, EHR: electronic health record, ICU: intensive care unit, ML: machine learning, NN: neural network.

regularisation, where all variables are taken into account, even though they might not have the same effect (which is accounted for with Lasso and ridge regression in traditional statistics and adjusted R^2 metrics to penalise unnecessary complexity).[11] Similarly, cross-validation and bootstrapping used in traditional statistics provide confidence intervals for model predictions, mitigating variance in high-dimensional biological data, like multi-omics. At the same time, feature selection via principal component analysis or elastic nets reduces noise in heterogeneous datasets, thereby improving representativeness before NN training. For example, batch effect correction using variance analysis is essential to adjust for technical heterogeneity in large sequencing datasets, enabling accurate cell clustering with deep learning models.

PRACTICAL IMPLICATION FOR BIOMEDICAL RESEARCH

When grounded in high-quality data, rigorous validation, and well-posed clinical or biological questions, ML can markedly improve discovery, prediction, and personalisation in biomedicine. Simultaneously, it must be integrated with domain expertise and conventional statistical reasoning, rather than treated as a stand-alone solution. ML excels at modelling complex, high-dimensional heterogeneous data and can enhance disease prediction, image-based diagnosis, patient stratification, and biomarker discovery. Yet, its performance is highly dependent on data quality and representativeness, and many powerful models are opaque, limiting mechanistic insight and trust.[12] For example, the data quality of cross-sectional dataset tests used for drug efficacy prediction is of utmost importance, as batch effects and heterogeneity can decrease accuracy during training and affect real-world biomedical data.

Opaque models, like NNs, limit mechanistic insight. For instance, "black box" predictions in genomics data hinder trust and biological interpretability, prompting "visible ML" that incorporates pathways for transparency. Thus, as with traditional statistics, ensuring excellent initial data quality through rigorous preprocessing, batch effect correction, and representative sampling is paramount when applying NNs or ML techniques in biomedicine, as it directly bolsters model accuracy, generalisation to real-world scenarios, and overall trustworthiness beyond opaque predictions.

Biomedical ML also raises challenges around bias, generalisability, privacy, consent, and secure data infrastructure, and often requires specialist expertise in data engineering and model development. Without careful validation and governance, models are vulnerable to overfitting and overly optimistic performance claims, which remain major concerns in the current literature. Table II summarises the advantages and the limitations/risks of ML in biomedical research.

CONCLUSION

It is important to know when to use ML, and when traditional methods will suffice (summarised in Table III), while including the type of analysis that will be performed in the planning stages of the study, ensuring that the data complies with the analysis requirements, and improving the outcome and applications of biomedical studies, overall.

Conflict of interest: none declared.

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SASCI-MAYO CLINIC FELLOWS WEBINAR

SASCI-Mayo Clinic Fellows webinar: Lifelong management of adults with repaired tetralogy of Fallot

H Weich,[1] A Engelbrecht,[1] S Khan,[2] J Anderson,[3] GW Barsness[3] and DR Holmes[3]

1 Division of Cardiology, Tygerberg Hospital and Stellenbosch University, Cape Town, South Africa
2 Department of Cardiology, School of Clinical Medicine, Inkosi Albert Luthuli Central Hospital, University of KwaZulu-Natal, Durban, South Africa
3 Department of Cardiovascular Medicine, Mayo Clinic, Rochester, United States

Address for correspondence:
Prof Hellmuth Weich
Division of Cardiology
Tygerberg Hospital and Stellenbosch University
Tygerberg
7505
Cape Town
South Africa

Email:
hweich@sun.ac.za

H Weich https://orcid.org/0000-0002-4283-0198
A Engelbrecht https://orcid.org/0000-0001-7482-5791
S Khan https://orcid.org/0000-0003-2206-8658
J Anderson https://orcid.org/0000-0002-3941-0707
GW Barsness https://orcid.org/0000-0002-6353-6780
DR Holmes https://orcid.org/0000-0002-0037-0373
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ABSTRACT

This is the second in our series of South African Society of Cardiovascular Intervention (SASCI)-Mayo Clinic summit webinars to be published. This webinar was hosted by the regular faculty, with Dr Anderson, a congenital heart disease expert from the Mayo Clinic, in attendance. He provides background on the lifetime management of repaired tetralogy of Fallot (rToF), followed by a clinical case (presented by Dr Engelbrecht) spanning 3 distinct phases in the patient's lifetime. The discussants are cardiology fellows from South African universities.

Objective: This manuscript, arising from the webinar series, summarises a multidisciplinary discussion on the lifelong management of rToF.

Design: Edited transcript of an expert webinar jointly hosted by SASCI and the Mayo Clinic faculty.

Case: The management of a female patient is discused in three stages at different age points of the patient's lifetime. The patient received a surgical rToF as a 1-year-old girl. She was then followed longitudinally into adulthood. At 19 years old, she was asymptomatic at presentation with severe pulmonary regurgitation (PR), progressive right ventricle (RV) remodelling, and borderline functional capacity. The discussion explored thresholds for intervention, imaging strategies where cardiac magnetic resonance imaging (CMR) access is limited, and surgical versus transcatheter valve replacement options. The patient ultimately underwent surgical pulmonary valve replacement (PVR) with a 27 mm bioprosthetic valve. At phase 3, she presented at the age of 29 with degeneration of her bioprosthetic valve. She was evaluated and received a transcatheter valve.

Key messages: (1) Understanding embryology and surgical history informs lifelong surveillance; (2) PR-driven RV remodelling is central to management; (3) objective imaging and functional markers (RV volumes, QRS, cardiopulmonary exercise test [CPET], arrhythmia burden) guide timing more reliably than symptoms alone; (4) procedural choice balances anatomy, concomitant lesions, device availability, and lifetime reintervention planning; and (5) lifelong exercise and structured follow-up are essential.

Online resource: Recorded SASCI fellows webinars (restricted to verified healthcare professionals) are available from: https://www.sasci.co.za/content/page/sasci-educational-videos1.

Keywords: tetralogy of Fallot, adult congenital heart disease, pulmonary regurgitation, right ventricle, pulmonary valve replacement, cardiology education, SASCI fellows webinar.

SA Heart® 2026;23:42-46

INTRODUCTION

Moderators (Weich and Khan): Welcome, everyone. Tonight's topic is the lifetime management of adults with rToF. Adults now comprise most congenital heart disease survivors; most have had childhood repair and require lifelong surveillance. We'll focus on pathophysiology, what to monitor, imaging choices, indications, and timing for intervention – especially PVR – and how we decide between surgical and transcatheter options.

Why tetralogy of Fallot (ToF) looks the way it looks (Anderson)

Rather than memorising "ventricular septal defect (VSD), overriding aorta, pulmonary stenosis (PS), right ventricular hypertrophy", start with embryology: malalignment/rotation of the conotruncal septum shifts anteriorly, narrowing the right ventricular outflow tract (RVOT), creating a VSD and overriding

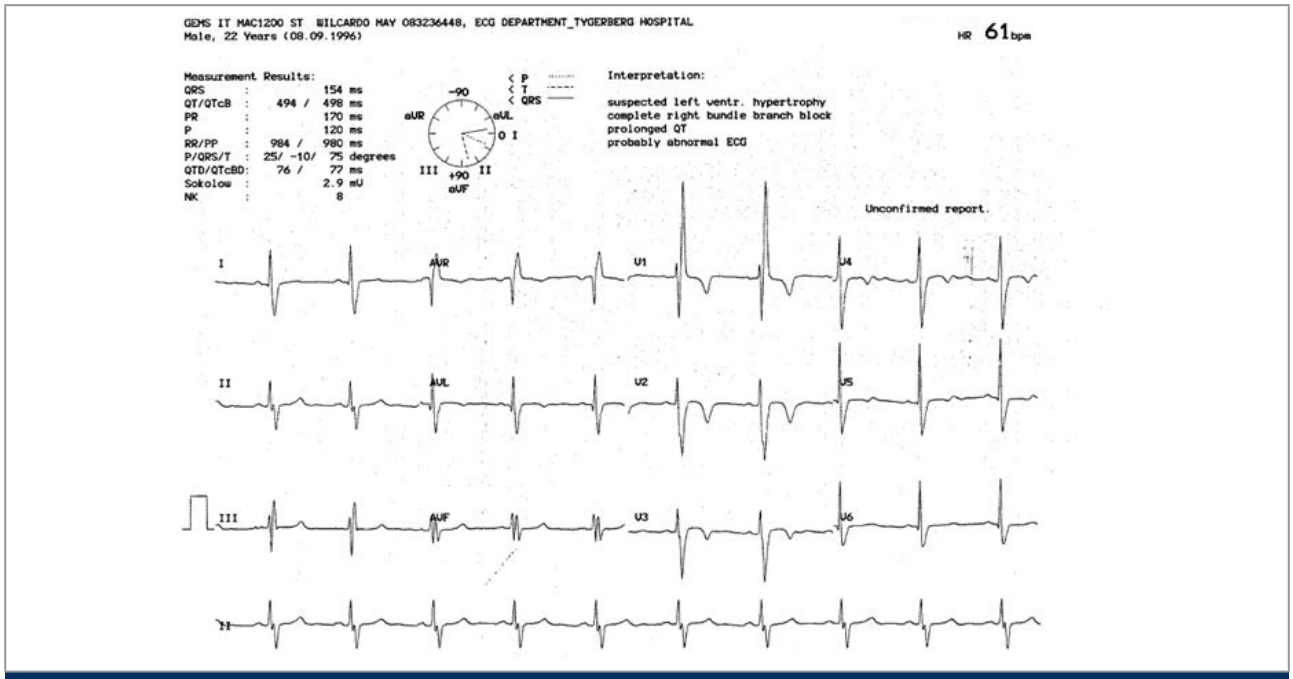

FIGURE 1: Electrocardiogram showing right bundle branch block and a QRS duration of 154 ms.

aorta. This spectrum explains variability – from classic ToF to ToF with pulmonary atresia – and why coronary variants crossing the RVOT matter surgically. Historically, ToF shaped paediatric cardiac surgery and modern transcatheter valves. The first transcatheter heart valve was deployed in the pulmonary position, and native/anastomotic RVOT anatomy still dictates strategy today.

Key pearl: Stenosis is poorly tolerated across the lifespan. Isolated PR is often well tolerated until RV remodelling accrues.

Residual lesions after childhood repair

- Common sequelae: Free PR after transannular patch, mixed PS/PR after valve-sparing repair, branch pulmonary artery (PA) issues at shunt sites, unexpected residual VSD, tricuspid regurgitation (TR) from RV dilation, left ventricular (LV) dysfunction from ventricular interaction, aortic root changes, and ventricular arrhythmias due to scar and dilation.
- RV remodelling matters: Progressive PR results in RV dilation leading to electromechanical dyssyncrony and LV dysfunction through ventritular interdependence. Our current practice focuses less on mortality (evidence limited) and more on how far remodelling can go, yet still reverse after PVR.
- Risk markers: LV systolic/diastolic dysfunction, non-sustained ventricular tachycardia (VT), QRS duration ≥ 180 ms, extensive RV scar, inducible VT.

CLINICAL CASE

Phase 1, age 1 year (Engelbrecht)

The patient was born with ToF and received a repair at Red Cross War Memorial Children's Hospital at the age of 1. She did very well after this and enjoyed a good quality of life throughout childhood.

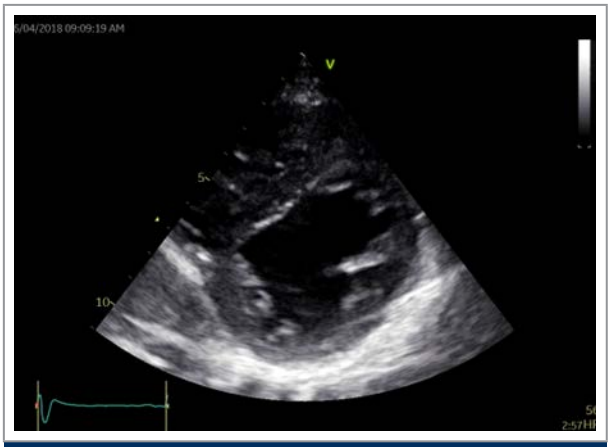

FIGURE 2: Echo showing D-shaping of the interventricular septum.

Phase 2, age 19 years

The patient presented for routine follow-up at her paediatrician. She continues to enjoy a good quality of life with no symptoms.

- Electrocardiogram: Sinus rhythm, right bundle branch block (RBBB), QRS 154 ms (Figure 1).
- Echo: Dilated proximal RVOT (45 mm), akinetic RVOT segment (likely secondary to a transannular/patch), paradoxical septal motion (Figure 2), severe PR with dense diastolic jet and brief PR pressure half-time (Figure 3),

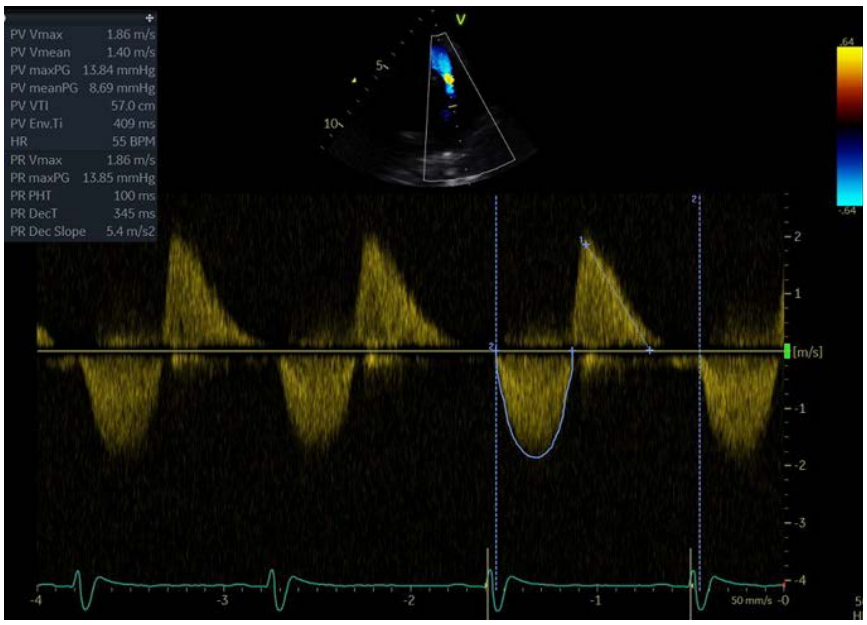

FIGURE 3: Continuous wave Doppler over the pulmonary valve showing a low systolic gradient over the valve (8 mmHg) but severe pulmonary regurgitation with a pressure half-time of 100 ms.

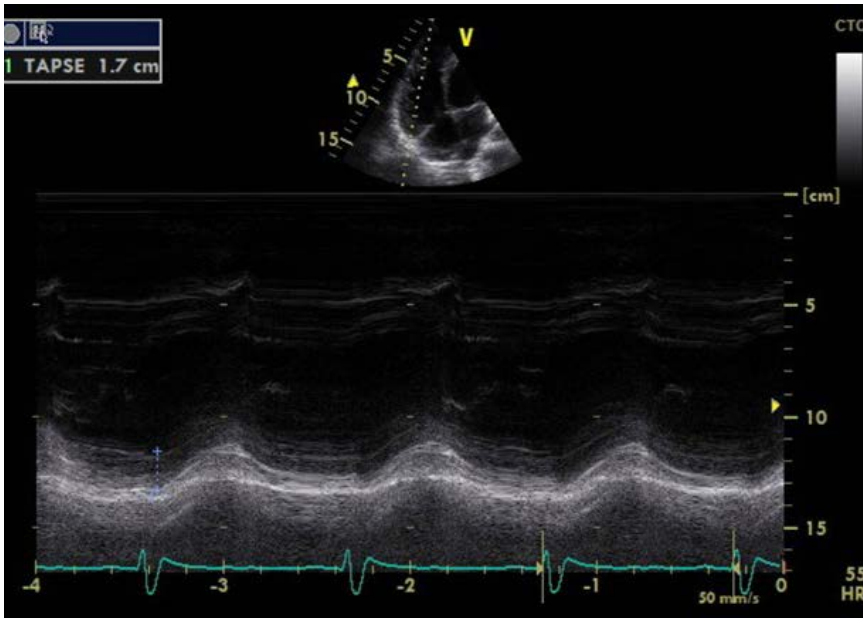

FIGURE 4: Echocardiography showing tricuspid annular plane systolic excursion (TAPSE) of 17 mm.

mildly reduced LV systolic function, tricuspid annular plane systolic excursion (TAPSE) of 17 mm, and S' 7 cm/s (suggesting mild RV systolic impairment in a volume-loaded RV) (Figures 4 and 5).

- CPET: VO_2 max 28 ml/kg/min (63% predicted), respiratory exchange ratio of 1.09 indicating adequate effort.
- CMR: Free PR, regurgitant fraction 58%, indexed RV end-diastolic volume (RVEDVi) 208 ml/m^2, indexed RV end-systolic volume (RVESVi) 97 ml/m^2, RV mildly to moderately impaired (right ventricular ejection fraction [RVEF] ≈ 40%), no branch PA stenosis. Apparent native annular remnant with post-stenotic main pulmonary artery (MPA) dilation – suggesting valve-sparing childhood repair.

Discussant 1: The central dilemma is an asymptomatic patient with severe PR and RV dilation/dysfunction. CPET shows reduced capacity, though not profoundly. Objective measures (volumes, function) guide us more than symptoms.

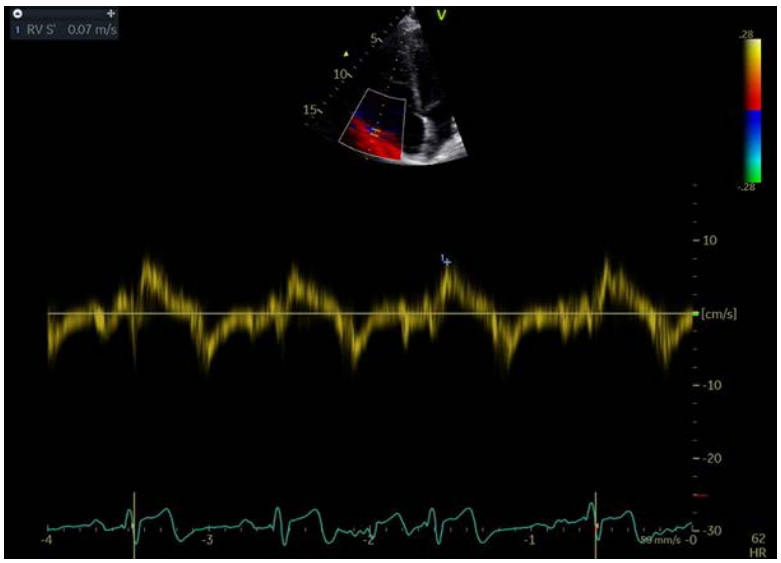

FIGURE 5: Echocardiography tissue Doppler showing a right ventricular S'- wave of 7 cm/s indicating right ventricle systolic dysfunction.

Discussant 2: CMR is the gold standard for RV volumes (notably the RVEDVi), but access is limited in many centres. Where CMR isn't feasible, serial echo (including RV:LV ratio on parasternal short-axis [PSAX]) and, if possible, computed tomography (CT) angiography with systolic/diastolic phases can help.

Weich (to panel): The QRS is 154 ms. Why mention it?

Anderson: It tracks with remodelling and arrhythmic risk. QRS ≥ 180 ms is a recognised risk threshold; watching the QRS trajectory helps frame timing even before symptoms declare themselves.

Echo pearls

On PSAX, RV is enlarged but not "2:1" versus LV. Septal flattening appears in diastole (volume load) rather than systole (pressure load). The Doppler profile shows early diastolic PR deceleration heading towards baseline – features compatible with significant PR. In volume-loaded physiology without restrictive RV features, the LV appears relatively preserved here.

Exercise and lifestyle

Aerobic conditioning improves outcomes across adult congenital heart disease (ACHD). We used to restrict exercise, but now encourage regular, structured exercise. Interpreting CPET needs context: 63% predicted in a sedentary person is not the same as 63% in a trained runner.

How do we decide on management at this stage?

Symptoms alone are unreliable in slow, insidious PR remodelling. Objective triggers discussed:

- Function: RV and/or LV systolic dysfunction (≥ mild-to-moderate) in ≥ moderate PR.
- Remodelling: RV enlargement (e.g. magnetic resonance imaging measured RVEDVi > 160 ml/m^2 and/or RV:LV end-diastolic volume ≈ 2:1).
- Haemodynamics: Significant RVOT obstruction (PS), elevated right ventricular systolic pressure (RVSP) (context-dependent) may indicate the need for surgery, although this was not a problem for the patient.
- Exercise capacity: Objective fall in exercise performance (e.g. CPET).
- Arrhythmias: non-sustained VT, inducible VT, or progressive QRS prolongation are potential indicators for intervention.

Choose surgery when concomitant work is needed (e.g. residual shunt, aortic work), complex arrhythmias requiring surgical ablation, small fixed surgical rings (e.g. small prosthetic heart valves) that will not accommodate dilation, high risk of coronary compression, or endocarditis. Choose a transcatheter for isolated RVOT disease, favourable anatomy, or high surgical risk – keeping in mind this is the first step in a lifetime sequence (valve-in-valve strategies, frame fracture, over-expansion planning).

Is there a place for medical therapy to prevent remodelling?

Evidence supports guideline-directed medical therapy for LV dysfunction in ACHD, but we lack convincing data that medical therapy alters RV volume-overload remodelling from PR. This may evolve with ongoing research.

What about pregnancy?

PR is generally tolerated in pregnancy; PS is more problematic. For a planned pregnancy with advanced remodelling, optimising physiology (e.g. timely PVR) may support maternal and foetal outcomes.

Case management

A multidisciplinary team weighed the substantial RVEDVi (208 ml/m^2), PR fraction 58%, QRS 154 ms, mildly reduced RVEF, and reduced CPET. Given the anatomy and local device availability, the team recommended a surgical bioprosthetic pulmonary valve replacement (27 mm Edwards PERIMOUNT [Edwards Lifesciences, Irvine, United States]). Post-operative echo showed a well-functioning valve with relief of PR.

Phase 3, age 29

At 29 years old, now a fitness instructor, the patient re-presented with reduced effort tolerance and near-syncope at high intensity.

- Echo: Mixed disease with severe PS (peak ~ 66 mmHg, mean ~ 37 mmHg) plus severe PR, markedly enlarged RV, and septal D-shaping. Invasive peak-to-peak RV-PA gradient 38 mmHg, RVSP ~ 65 mmHg.
- Doppler learning point (Discussant 1): PR backflow that equalises well before the next systole indicates severe regurgitation. In the presence of PS, derived RVSP largely reflects the stenotic gradient rather than true PA pressure.

Discussant 2 (strategy): Given prior surgeries and increasing risk with re-do surgery, transcatheter valve-in-valve is attractive when anatomy and frame size permits the use of locally available device options and when there is suitable expertise. In some settings, native anatomy can be tricky for transcatheter options, and device availability varies.

PRACTICAL TOOLBOX (FROM THE DISCUSSION)

Imaging when CMR is limited

- Serial transthoracic echo with RV:LV size ratio on PSAX, RVOT dimensions, PR Doppler contour, tricuspid regurgitation velocity context, and qualitative RV function.
- Consider CT angiography with systolic/diastolic reconstructions for volumetric estimates and RVOT geometry when CMR is unavailable. However, this will expose the patient to significant radiation.

Objective triggers used by the panel

- Worsening RV volumes (e.g. markedly elevated RVEDVi) or RV ≈ 2 × LV end-diastolic volume.
- Decline in RVEF and/or left ventricular ejection fraction, electromechanical dyssynchrony.
- CPET reduction versus expected training status.
- Arrhythmic markers: NSVT, progressive QRS prolongation, especially toward ≥ 180 ms.
- Development of PS (haemodynamically significant) or rising RV pressures.

Choosing surgical versus transcatheter PVR

- Surgery: Concomitant lesions (residual VSD, aorta), complex arrhythmias requiring surgical ablation, small nonfracturable ring, coronary compression risk, or active endocarditis (after acute phase).
- Transcatheter: Isolated RVOT disease, suitable landing zone (stented valve, conduit, or native RVOT, where dedicated systems are available), and a plan for lifetime valve-in-valve expansions.

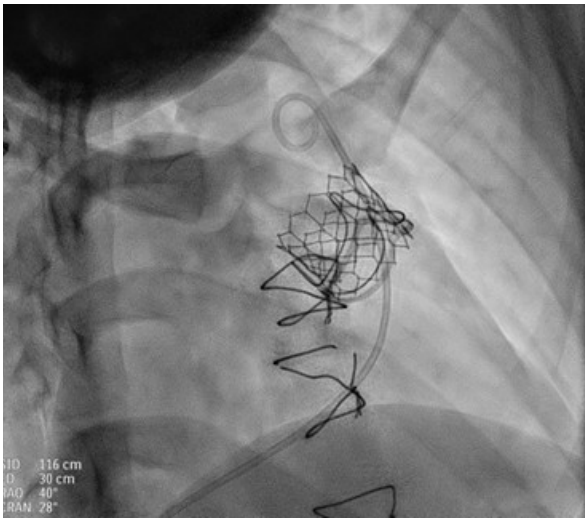

FIGURE 6: An Edwards SAPIEN 3 valve implanted within the degenerated bioprosthetic valve.

MANAGEMENT (Weich)

Because of the haemodynamic measurements and her symptoms, it was decided to perform a transcatheter pulmonary valve implant. Pre-operative CT scan excluded significant branch stenoses of her pulmonary arteries, and no hostile features at the landing zone. The Edwards PERIMOUNT valve has a true inner diameter of 25 mm, so we elected to implant a 29 mm Edwards SAPIEN 3 valve as recommended by the manufacturer. It is possible to perform a fracture of the bioprosthetic valve, but the very large fracture balloon required was unavailable. The SAPIEN 3 valve was implanted uneventfully under sedation, and she was discharged the next morning (Figure 6). At follow-up, she was asymptomatic and able to perform rigorous physical exercise.

Lifestyle and follow-up

- Encourage structured aerobic training across the lifespan.
- Regular electrocardiogram (QRS tracking), periodic CPET, and imaging keyed to prior findings.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Case presentation and drafting: Engelbrecht. Conceptual content and editing: Anderson/Weich/Barsness/Holmes/Khan. All authors reviewed and approved the manuscript.

ECG Quiz 71

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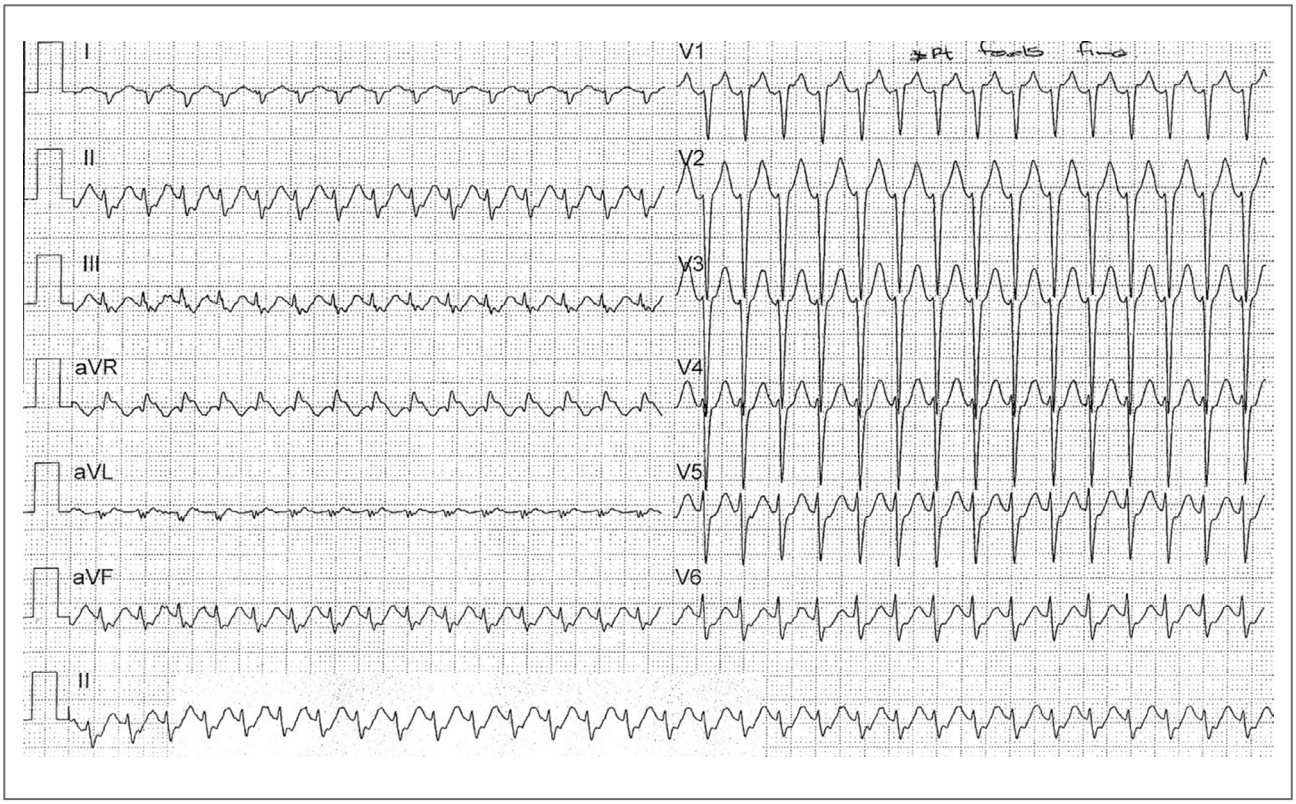
A Chin and RS Millar
Cardiac Clinic, University of Cape Town / Groote Schuur Hospital
Cardiac Arrhythmia Society of Southern Africa (CASSA)

Email:
ashley.chin1@uct.ac.za

A Chin https://orcid.org/0000-0001-6930-3673
RS Millar https://orcid.org/0000-0002-5608-0623
DOI: https://doi.org/10.24170/22-4-7878 | https://doi.org/10.24170/22-4-7948

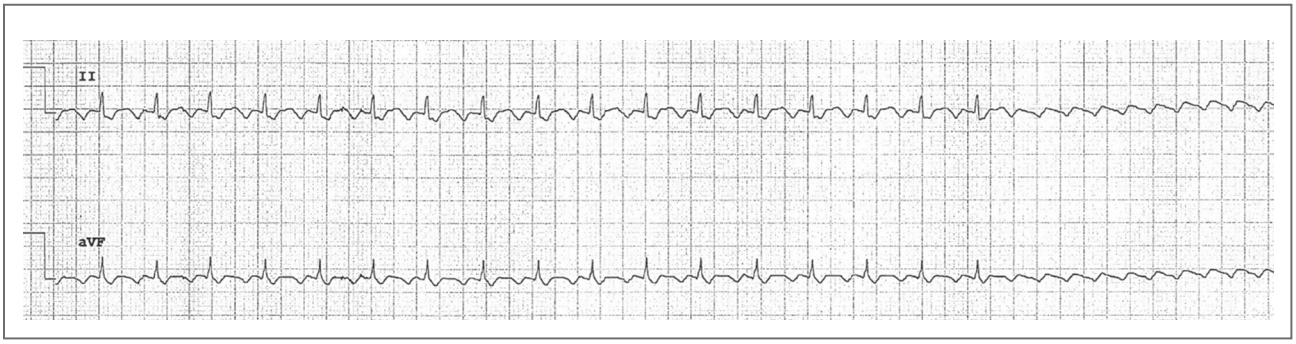
A 68-year-old man has an electrocardiogram (ECG) performed in the emergency room for an acute episode of palpitations. The patient received an oral antiarrhythmic drug before this ECG.



QUESTION: Which one of the following is the best diagnosis?

1. Atrioventricular-nodal re-entrant tachycardia (AVNRT).
2. Atrial flutter.
3. Atrial tachycardia.
4. Atrioventricular re-entrant tachycardia (AVRT).
5. All the above are possible.

You find the rhythm strip of the presenting arrhythmia (before administration of the antiarrhythmic drug) with carotid sinus massage:



QUESTION: What is the final diagnosis? What antiarrhythmic drug did the patient most likely receive?

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

ANSWER on page 49

ECG Quiz 71

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ANSWER

OVERVIEW OF THE ECG

This is a regular narrow complex tachycardia with a ventricular rate of 186 bpm. P waves are visible in II, III, and aVF that distort the ST segment (Figure 1). This is a 1:1 short RP tachycardia (RP time ~ 90 ms). The QRS duration is borderline wide (100 ms). AVNRT, atrial tachycardia, and AVRT are possibilities. The ventricular rate of 186 bpm in the setting of a 1:1 short RP tachycardia is unusual for an atrial flutter with 1:1 conduction, unless the patient has a markedly enlarged right atrium, or if the atrial flutter has been slowed by an antiarrhythmic drug. In this case, an antiarrhythmic drug was given, so a 1:1 atrial flutter must also be included in the differential diagnosis.

ANSWER

The correct answer is: 5. All the above are possible.

The rhythm strip with carotid sinus massage (before antiarrhythmic drug administration) shows atrial flutter with 2:1 atrioventricular (AV) block with an atrial rate of 250 bpm (ventricular rate 125 bpm). The typical sawtooth pattern of right atrial counterclockwise flutter can be seen in II and aVF. Carotid sinus massage induces AV block, which reveals continuous atrial flutter waves. The antiarrhythmic drug, therefore, slowed the atrial rate from 250 bpm (in 2:1 atrial flutter) to 186 bpm (in 1:1 atrial flutter). This resulted in a paradoxical increase in the ventricular rate from 125 bpm to 186 bpm.

The final diagnosis is 1:1 atrial flutter.

The most likely oral antiarrhythmic drug the patient received slows the atrial flutter rate but has minimal effect on the AV node. Class Ic antiarrhythmic drugs, like flecainide and propafenone, are likely culprits. Disopyramide, a class Ia antiarrhythmic drug, can also slow the atrial flutter rate and has vagolytic effects, which may increase AV node conduction and cause the same. This patient received oral flecainide without an AV nodal blocker. Another clue that the patient received flecainide is the mild QRS prolongation of 100 ms in the 12-lead ECG. A wider QRS duration is seen in II and aVF on the ECG compared with the rhythm strip performed before flecainide administration.

DISCUSSION

Flecainide, a class Ic antiarrhythmic drug, blocks cardiac sodium (Na) channels and slows atrial conduction (by prolonging the atrial action potential) with minimal effect on AV node conduction. Flecainide, taken with an AV nodal blocker, is commonly used in the acute setting to terminate atrial fibrillation ("pill in the pocket" or intravenous infusion) and in the chronic setting to prevent atrial fibrillation episodes. However, flecainide should NOT be used in the acute or chronic management of atrial flutter.[1]

Atrial flutter is a macro-re-entrant atrial tachycardia, which usually depolarises the atria at a rate between 240 bpm and 360 bpm. Atrial flutter usually occurs with 2:1 AV block, resulting in a ventricular rate of 120–180 bpm (usually ~ 150 bpm). Flecainide slows atrial conduction and can reduce the atrial rate by about one-third.[2] A reduction in atrial rate can facilitate 1:1 AV conduction, resulting in a very fast ventricular rate (as flecainide has a minimal effect on the AV node). A 1:1 atrial flutter is therefore a serious complication of flecainide and has no role in the acute or chronic treatment of atrial flutter. Occasionally, 1:1 atrial flutter can conduct with a rate-related bundle branch block, which can be misdiagnosed as ventricular tachycardia. Flecainide may convert atrial fibrillation into atrial flutter; it is therefore advised to prescribe flecainide with an AV nodal blocker (like a beta blocker), which reduces the likelihood of 1:1 AV conduction with atrial flutter.

Clinicians need to be aware of the other pro-arrhythmic effects of flecainide. Flecainide can cause monomorphic ventricular tachycardia and is associated with increased mortality, heart failure, and cardiac arrest in patients with prior myocardial infarction and impaired left ventricular function. It is advised to avoid flecainide in patients with ischaemic or structural heart disease, including significant left ventricular hypertrophy.[1] In the Cardiac Arrhythmia Suppression Trial (CAST), flecainide was

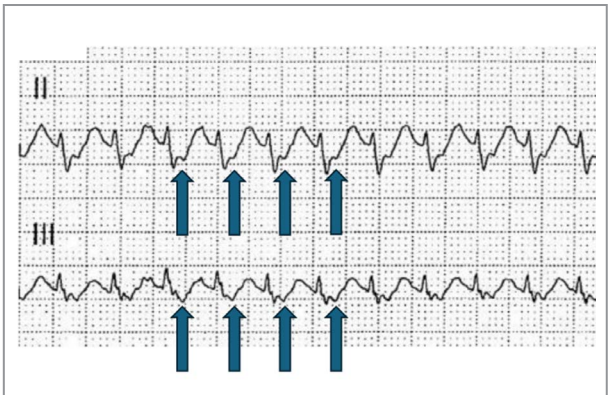

FIGURE 1: Arrows show P waves in II and III; this is a 1:1 short RP tachycardia with a wide differential diagnosis that includes atrioventricular-nodal re-entrant tachycardia, atrioventricular re-entrant tachycardia, atrial tachycardia, and 1:1 atrial flutter.

associated with an increased risk of death due to arrhythmias when given to suppress ventricular ectopy post-acute myocardial infarction.[3]

Flecainide also prolongs the action potential duration of ventricular muscle and, therefore, prolongs QRS duration. If the QRS widens by > 25% from baseline, it is advised to reduce the dose or to discontinue the drug. These drugs are not advised for patients with a baseline QRS > 120 ms due to the risk of excessive conduction delay, especially in those with left bundle branch block (LBBB) or bifascicular block. Flecainide must not be prescribed to patients with congenital long QT syndrome because of the risk of torsade de pointes. Flecainide may also unmask the Brugada ECG pattern and should be avoided in patients with the Brugada syndrome.

CONCLUSION

Flecainide without an AV nodal blocker may convert atrial fibrillation to atrial flutter with 1:1 AV conduction, which can be a life-threatening complication. Flecainide should also be avoided in the acute and chronic treatment of atrial flutter because of the dangers of 1:1 AV conduction. Atrial flutter with 1:1 AV conduction can cause very fast ventricular rates > 200 bpm, which can be difficult to distinguish from AVNRT, AVRT, or atrial tachycardia. Clinicians need to be aware of the potential pro-arrhythmic effects of flecainide, which can be fatal.

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CARDIAC IMAGING QUIZ

R Meel[1] and M Matshela[2,3,4]

[1] Faculty of Health Sciences, Department of Internal Medicine, University of the Witwatersrand and Mediclinic Sandton Hospital, Johannesburg, South Africa
[2] Joint Medical Holdings, City Hospital, Cardiology, Durban, South Africa
[3] University of Minnesota, Minneapolis, United States
[4] Robert Kennedy College, Zürich, Switzerland

Email: ruchikameel@gmail.com
R Meel https://orcid.org/0000-0002-1405-4259
M Matshela https://orcid.org/0000-0002-5043-2122
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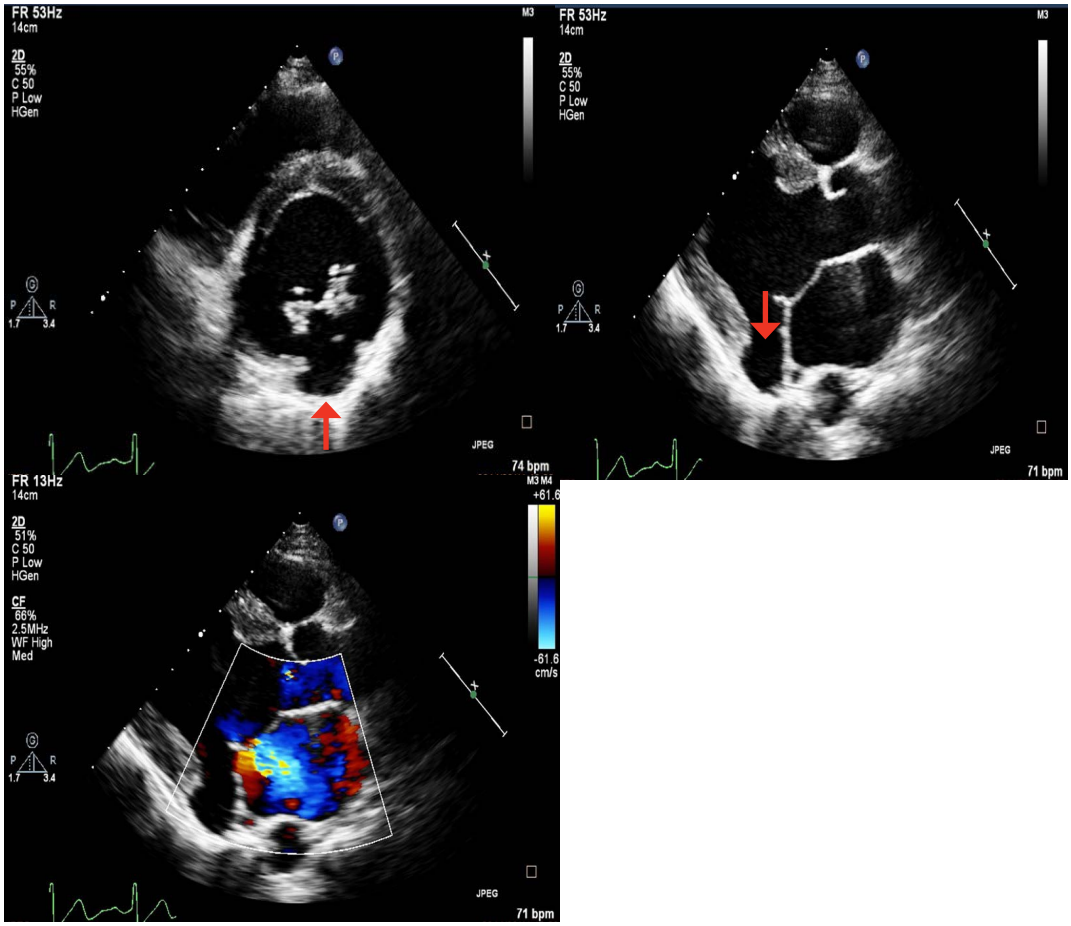

QUESTION: What is the diagnosis?

A Rheumatic heart disease

B Infective endocarditis

C Submitral aneurysm

D Coronary artery disease

ANSWER

Correct answer: C. Submitral aneurysm

CASE PRESENTATION

The images are from a 29-year-old woman of mixed ancestry who presented with atypical chest pain and exertional dyspnoea. She had a history of human immunodeficiency virus (HIV) infection treated with antiretroviral therapy. She had no history of rheumatic fever or tuberculosis.

On examination, the patient was clinically not in heart failure, euvolaemic, with a grade 3/6 pansystolic murmur radiating to the axilla, consistent with mitral regurgitation. Transthoracic echocardiography demonstrated significant mitral regurgitation (bottom panel) and an inferobasal left ventricular aneurysm (top panel, arrows), consistent with a submitral aneurysm (SMA). The aneurysm caused displacement of the posterior mitral leaflet, resulting in the failure of leaflet coaptation. No thrombus was identified within the aneurysm. Additional findings included left atrial enlargement and left ventricular systolic dysfunction, with an ejection fraction of 42%.

There were no clinical or laboratory features of infective endocarditis, with normal inflammatory and septic markers. Screening for autoimmune and connective tissue disease was negative. A 12-lead electrocardiogram showed sinus rhythm with features of left ventricular hypertrophy. Coronary angiography was normal, excluding obstructive coronary artery disease. A diagnosis of congenital SMA complicated by severe mitral regurgitation was established.

DISCUSSION

SMAs are rare cardiac abnormalities, and most are considered congenital; however, genetic susceptibility and acquired inflammatory or infective causes, including tuberculosis, have been described. SMAs occur predominantly in individuals of African descent, making recognition particularly relevant in the southern African context.

Congenital SMAs arise from a defect in the fibrous portion of the posterior mitral annulus, resulting in aneurysmal outpouching of the adjacent left ventricular myocardium. Its clinical presentation is heterogeneous and includes arrhythmias, heart failure, thromboembolism, circumflex coronary artery compression, and mitral regurgitation. The latter results from mechanical distortion or displacement of the posterior mitral leaflet.

Echocardiography is the diagnostic modality of choice, typically demonstrating a left ventricular outpouching adjacent to the posterior mitral leaflet, best visualised in the parasternal long-axis (right, top panel image) and basal short-axis views (left, top panel image), as illustrated in this case. Multimodality imaging, including cardiac computed tomography or cardiac magnetic resonance imaging, may be useful to further define aneurysm anatomy, assess its relationship to adjacent structures, and exclude thrombus.

Management is guided by symptomatology, aneurysm size, and associated complications. Treatment options include medical therapy for heart failure, anticoagulation when indicated, and surgical repair in selected patients, particularly those with severe mitral regurgitation or progressive ventricular dysfunction.

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