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Acute myocardial infarction in a patient with anomalous left main coronary artery origin with a hypoplastic left anterior descending artery: A diagnostic and therapeutic challenge

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A Patel



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Creating opportunities for Cardiology training in South Africa



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CURRENT STATE OF AFFAIRS IN SOUTH AFRICAN CARDIOLOGY TRAINING

South Africa continues to see a rise in the prevalence of cardiovascular disease, as is the case for many low- to middle-income countries. This growing cardiovascular disease burden, combined with rapidly evolving treatment modalities, requiring the acquisition of novel skills by practitioners, places an ever-increasing strain on the country's limited number of cardiologists.

Current estimates suggest there are approximately 195 registered cardiologists in South Africa, equating to just 3.3 cardiologists per million people which compares poorly to the situation in other low- to middle-income-, not to mention high-income countries. Of particular concern is that the number of cardiologists has not increased significantly since 2016, while the demand from patients and hospital groups have increased.^(1,2)

The majority of South African cardiologists are based in the private sector (> 85%) (Figure 1), where they endeavour to meet the demands of around 9.8 million people (15.8% of the population) with predominantly mostly private medical insurance.⁽³⁾ A very small proportion of the national pool of cardiologists are based in the public or academic sector, where they face the dual responsibility of providing cardiology services to more than 50 million South Africans, and of training the next generation of cardiologists and allied healthcare workers involved in cardiovascular services. Unsurprisingly, the small number of trainers in the public service, coupled with a small number of national training numbers, have been major stumbling blocks in the drive to successfully address the unmet need to increase the number of cardiologists nationally.

A critical constraint has been the limited number of consultant posts in the public sector (Figure 1). Due to the Health Professions Council of South Africa (HPCSA) regulation that allocates two



Figure 1: Cardiologists and specialist registrars in South Africa

registrar training numbers for every full-time consultant post, the shortage of consultants directly limits training capacity. Furthermore, a number of the currently occupied specialist registrar positions are unfunded by government (supernumerary), instead, relying on external or self-generated revenue streams. Currently we have 34 specialist registrars in training, this would suggest that we can expect the addition of around 10 newly qualified cardiologists per year. If we evaluate the College of Medicine of South Africa's (CMSA) yearly outcome in the certificate examinations, it is clear that we fall well below this mark. The reason for the discrepancy is likely multifactorial, but it highlights the need for quality training opportunities in an environment that is conducive to success at the end of the 3 year training period.

The problems of adequately staffing cardiovascular services are not unique to adult cardiology, extending also to include disciplines such as paediatric cardiology, cardiothoracic surgery and various allied healthcare services including cardiac technologists and perfusionists to name some. Faced with these disheartening statistics, we must ask ourselves how we go about expanding quality training opportunities for future cardiologists in South Africa?

WHAT ARE THE COMPONENTS OF A QUALITY TRAINING PROGRAMME?

A high-quality training programme rests not only on skilled human resources, but on a robust ecosystem comprising adequate infrastructure, sufficient patient volume, and access to research opportunities. Key components include:

- A structured curriculum covering core domains such as clinical cardiology, interventional procedures, imaging, electrophysiology, heart failure, and preventive cardiology.
- Extensive supervised clinical exposure to a broad spectrum of cases and diagnostic modalities.
- Hands-on procedural training in coronary interventions and device implantation.
- Opportunities for academic development and participation in research.
- Access to dedicated mentors who provide consistent guidance, feedback, and support.

The cardiovascular ecosystem, including access to specialist investigations and treatment modalities including catheter laboratories and echocardiography services, are broadly present in the South African public sector, although not necessarily equally distributed. However, where the system is particularly lacking in capacity is perhaps surprisingly, in the category of human resources. A large stumbling block in addressing this constraint remains funding, where the trend over the last 2 – 3 decades has seen funding of infrastructure and primary health, diverting funding away from human resources at sub-specialist level, including cardiology.

WHO SHOULD BE TRAINING FUTURE CARDIOLOGISTS?

At the heart of any training programme is mentorship. Effective training requires supervisors with the skills, time, and passion to guide trainees. Given the limited number of cardiologists in the public sector, we must consider broader inclusion—cardiologists in private practice can help expand training capacity further. Many private cardiologists already contribute to training via teaching forums and part-time affiliation with academic units, often without compensation. Various special interest groups within SA Heart®, supported by industry partners, utilise both sectors to further specialist registrar training and have become an important cog in the training machinery, assisting with cardiology registrar education and training. Strengthening this collaboration is crucial to expanding capacity and improving training quality going forward.

HOW DO WE CREATE MORE TRAINING OPPORTUNITIES?

To create more opportunities, we must expand the ecosystem that includes infrastructure, human resources and research opportunities. First and foremost is the need to increase the number of consultant posts in the public sector, as any increase in capacity should branch from here. Also, we need to ensure that academic careers remain attractive and fulfilling so that high quality trainers choose to remain in the academic/public health training system. Low numbers of consultants in training units create fragile units without redundancy and we have seen several units in the country being severely affected with 1 or 2 core individuals moving on to new opportunities. Cardiology units take a long time to build capacity and without also building redundancy, training centres will not be robust enough to weather temporary change. Currently, the government is the major funder of consultant cardiologist and specialist registrar posts, with universities contributing to a lesser degree. The South African public sector wage bill has attracted significant criticism from various sources. This has led to decisions from healthcare departments to freeze consultant posts, with a subsequent decrease in the number of employed academic/public sector cardiologists. Universities have faced similar financial constraints, so that with both major funders reluctant to increase their human resource expenses, we face an uphill battle. A criticism often levelled at healthcare in South Africa is that it is fragmented, and academic units are certainly not protected from its own form of resource fragmentation where specialists are torn between the different priorities of service delivery, training and research. Increasing post numbers is really the only way to maintain the breadth of academia.

In a system with limited funding, it remains important that all roll players function in harmony and take collective responsibility to maintain physical and human resource infrastructure. The reality is that without service delivery, training and research will always be limited. The other side of this coin is that training and research improves service delivery. Only by investing in research that is locally relevant and adjusting practise through training can we change our local disease landscape. It is important that both universities and government set clear targets for academic units, with incentivising in the form of additional or ongoing funding for systems that achieve targets in infrastructure building and human resource development.

The next step is to address the elephant in the room. Cardiology units in South Africa need more resources if they are to train more cardiologists. Although we, as a community, must continue to lobby government and universities for more funding, it is unlikely that these sources alone will bridge the currently required funding gap. Cardiology training units will have to generate independent (third stream) funds to expand infrastructure and staff. One strategy that has proven successful, is the creation of PhD programmes via grant funding. Although PhD candidates spend the majority of their time conducting research, they do provide important support both in terms of training and research support of specialist registrars, an important component of maintaining the research momentum in a unit. In addition, PhD candidates have the potential to generate significant funding which may assist in developing career paths for cardiologists planning to follow an academic career. Also, private practitioners can play a critical role in supporting academic units on a part time basis through offering time and skills where resources are poorest.

Private sector support is essential to increasing opportunities for training. Industry already contributes significantly to the training of specialist registrars through a number of programmes, and recently, private sector partners and philanthropic organisations have increased funding with a view to improving the manpower shortage at various post levels with a view to expanding training opportunities. It is important that these strategies are supported and that we involve industry further to maximise benefit for all, industry included.

Any cardiology unit can suffer from a rapid succession of manpower losses and may need an increase in support in one or more areas. We need to take collective responsibility as a cardiology

community to ensure that all units remain functional – it is easy to cut down a tree in a day, that has taken years to grow. Healthcare departments, universities and the private sector should work together to prevent the loss of functional training units.

It is important that we provide specialist registrars with quality training and a positive environment during their years of training. This will encourage them to either remain in the public sector after completion or to remain involved in supporting public cardiology systems through training and service delivery within the public sector on a part-time basis for the good of the greater cardiology community. Although private cardiologists already support training of specialist registrars via multiple forums, we do believe this may be an avenue that can be further developed as a lot of expertise resides in our private cardiology corps.

DIFFERENT MODELS

Different models have been considered for training cardiologists. The most common is where training is limited to academic units, as is largely the case in South Africa. Although a purely private training model, similar to the private schools' model, has been considered, it is unlikely to realise soon. A hybrid model, where training in academic units is supported by private cardiologists and where trainees spend some of their training time in private hospitals, are starting to develop. This has been successfully implemented in the training of electrophysiologists and advanced interventional training programmes – particularly in the field of structural heart interventions. Academic units and private practices often have different strengths and by exposing specialist registrars to both environments, we may enhance the quality of training while expanding our training capacity. This hybrid approach may also address the problem of limited caseloads in certain areas of cardiology in the public sector. The hybrid model will require brave leadership to ensure success and mitigate the potential risks.

The time has come to align our goals and our resources to achieve something that will benefit all. Creating additional opportunities for training will require additional investment from government, universities and the private sector. This investment will not only increase training capacity, but will significantly improve the access and quality of care of patients in the public sector.

It is time that we all synchronise our goals, priorities and efforts in the training programmes we develop. If all the segments of our community pull together, in unison, we will have resynchronised our training programme and created a realistic expectation of increasing the output of well-trained cardiologists for South Africa, even given a resource-limited setting.

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Challenges in advancing clinician scientist careers in cardiology in South Africa



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Clinician scientists (CS) are medically trained professionals with advanced expertise in both clinical practice and biomedical research.⁽¹⁾ Their aim is to develop a complete understanding of disease processes, from molecular mechanisms to clinical manifestations and therapeutics, enabling them to play an important role in advancing translational research.⁽¹⁾

It is now well known that only a small fraction of physicians pursue career pathway as CS, declining from approximately 5% in 1985 to just 2% by 2014.⁽¹⁾ Increasingly, CS are being described as an “endangered species”, reflecting concerns about their diminishing presence. Numerous factors have been implicated in this decline, prompting the development of various strategies aimed at revitalising and sustaining this essential professional group.⁽¹⁾



Sliwa, et al. reported 175 registered cardiologists practicing in South Africa in 2016⁽²⁾ However, this number is considered insufficient, with a significant shortage, especially in the public sector. For a population of 52 million, this translates to roughly one cardiologist for every 260 000 people.⁽²⁾ In South Africa there are even fewer CS in cardiology, as of now, there is no publicly available data specifying the exact number of cardiologists in South Africa who hold a PhD. CS in cardiology encounter numerous challenges in South Africa: these in balancing clinical duties with research responsibilities, difficult in securing protected research time and insufficient internal and external support. This results in majority of the clinicians interested in research using after-hours and weekends to do research. Institutions frequently demand that CS meet the expectations of both full-time clinical practitioners and full-time researchers, a standard that is seldom attainable.⁽³⁾ This unrealistic dual burden often results in burnout, diminished job satisfaction, and a departure from research careers.⁽³⁾ Additionally, even with limited healthcare personnel provisions exist for Remunerative Work Outside the Public Service, but none for creating protected research time.

Despite the high clinical demand and complexity associated with cardiology, funding for innovative or flexible roles, such as shared consultant positions or part-time posts, often does not match the remuneration or structural support provided to full-time consultant cardiologists.^(4,5) This is true even within public healthcare systems, where budget allocations and staffing models tend to prioritise traditional, full-time consultant roles.^(4,5) As a result, alternative working arrangements are underfunded or not formally recognised, limiting opportunities for career flexibility, academic engagement, or phased retirement.

Even though South Africa has strong academic institutions, National R&D spending remains below global averages, constraining innovation, and capacity building.⁽⁶⁾ One of the greatest barriers to research in South Africa, particularly in the health and medical sciences, is insufficient and unstable

funding, especially for long-term and collaborative projects. This challenge has been exacerbated by recent cuts to international funding, such as reductions in US support, which have disrupted clinical trials and global health partnerships that rely heavily on South African infrastructure.⁽⁷⁾

The absence of structured training programmes, mentorship, and clear career pathways discourages senior professionals, especially in rural areas, from staying in their roles, leading to a loss of expertise and inadequate training for junior doctors.⁽⁸⁾ This creates a cascading effect: early-career cardiologists are increasingly burdened with clinical, research, teaching, and administrative responsibilities, often without adequate institutional support. As a result, many CS are forced to choose between research and clinical practice, with most opting for the latter due to greater stability and clearer advancement opportunities.^(3,9)

The practice of attributing authorship to individuals who may not fully meet the established criteria can present challenges within the clinician-scientist career pathway.⁽¹⁰⁾ Such practices may inadvertently compromise the integrity of the scientific record, create imbalances in recognition, and potentially affect the advancement of researchers who have made substantial contributions. This concern is particularly relevant for early-career researchers, who might feel obliged to include co-authors with limited involvement.⁽¹¹⁾ By fostering transparent and equitable authorship practices, institutions have an opportunity to uphold scientific integrity, encourage fairness, and support the growth and success of CS.⁽¹⁰⁾

Professional jealousy has been cited as an important hurdle in clinician scientist progression pathway in South Africa.⁽¹²⁾ A recent review highlighted the high prevalence of academic jealousy in South Africa higher education institution characterised by actions such as the sabotage of colleagues' work, spreading false information, and hindrance of academic progress.⁽¹²⁾

Female CS face further challenges in the existing system in Africa. Sliwa, et al. emphasised the urgent need to support and empower women in cardiovascular science across the African continent.⁽¹³⁾ They outline the systemic barriers female CS face, including limited mentorship, funding disparities, and underrepresentation in leadership roles. The piece advocates for building robust, continent-wide networks that foster collaboration, mentorship, and visibility for African women in cardiovascular research.⁽¹³⁾ By strengthening these networks, the article argues, we can create a more inclusive and innovative research environment that addresses Africa's unique cardiovascular health challenges.

Research is essential for shaping effective policy and practice because it provides the evidence needed for informed decision-making, efficient resource use, and equitable outcomes.⁽¹⁴⁾ It supports innovation, accountability, and responsiveness—especially in times of crisis—while also identifying gaps and disparities that need addressing. To strengthen its impact, countries should invest in local research capacity, promote collaboration between researchers and policymakers, ensure findings are accessible, and incentivise studies that directly inform real-world challenges.⁽¹⁴⁾ To strengthen research capacity, a research component has been made compulsory and is now integrated into undergraduate medical curricula at some institutions,^(15,16) as well as into postgraduate registrar training across all South African training programmes.⁽¹⁷⁾ However, these initiatives face significant challenges, including a shortage of research-qualified supervisors, limited protected time for research during demanding clinical rotations, delayed registration with Health Professional Council of South Africa, poor quality research output, and poor retention of research-trained registrars after graduation due to lack of government-funded consultant posts.

We strongly support the establishment of clinician scientist pathways within academic institutions. These tracks should offer flexible, gender-sensitive working environments, protected time for

research, robust core support, and transparent routes for career advancement and succession planning. The work of CS is pivotal in enhancing patient outcomes, informing policy and practice, and driving meaningful, lasting impact across the healthcare landscape—ultimately shaping a legacy of excellence in our profession. Success in clinician scientist pathways can only be achieved by cultivating a genuinely inclusive environment^(18,19)—one that actively confronts toxic leadership,⁽²⁰⁾ favouritism and systematically eliminates bias and exclusionary practices.⁽¹⁹⁾

Drawing from our collective experiences at various stages of our clinician-scientist careers in South Africa, we conclude that—despite considerable challenges such as limited resources and delayed recognition—the role remains deeply rewarding. The opportunity to generate new knowledge, uncover unexpected findings, and foster lasting professional relationships has been invaluable. For those driven by curiosity, research offers a uniquely fulfilling and enduring pursuit.

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The promise and challenges of oral step-down therapy for infective endocarditis in South Africa – Rethinking endocarditis treatment

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INTRODUCTION

IE continues to pose a clinical challenge globally, including in South Africa, where it predominantly affects a younger population.⁽¹⁾ Most IE complications, such as embolic events, heart failure, and uncontrolled infection, usually occur in the initial stages of the disease.⁽²⁾ This highlights the importance of prompt diagnosis and intensive IV therapy during this period. Traditionally, IE was managed exclusively with prolonged courses of parenteral antibiotics, primarily based on historical data and expert opinion.

The longstanding practice of prolonged IV therapy has been increasingly questioned in recent years, particularly following the findings of the POET trial, which contributed to the incorporation of oral step-down therapy in the latest European Society of Cardiology (ESC) endocarditis guidelines.^(3,4) This evidence-based strategy reduces hospitalisation costs, has fewer healthcare-associated complications, and enhances patient comfort without adversely affecting clinical outcomes.⁽⁵⁾

However, oral step-down treatment of IE is not yet widely implemented in South Africa. Given the high burden of

ABSTRACT

Infective endocarditis (IE) remains a complex clinical challenge globally and in South Africa, where it predominantly affects a younger population. Historically, it was managed with prolonged intravenous (IV) antibiotic therapy, an approach mainly based on expert opinion and low-level evidence. However, recent studies, including the landmark Partial Oral Treatment of Endocarditis (POET) trial, have demonstrated that oral step-down therapy is a safe and effective alternative in selected, clinically stable patients. Modern oral antibiotics now exhibit pharmacokinetic profiles comparable to their IV counterparts, and multiple randomised controlled trials (RCT) have confirmed their efficacy in clearing bacteraemia. While oral step-down therapy has been adopted in high-income settings and incorporated into international guidelines, its implementation in South Africa faces significant challenges. These include a high burden of blood culture-negative infective endocarditis (BCNIE), unique pathogens, such as *Bartonella* species (spp.) and *Mycobacterium tuberculosis* (TB), systemic healthcare constraints, limited access to cardiac surgery, and barriers to patient education and follow-up. In South Africa, locally feasible strategies are required to enable the safe and effective use of oral step-down therapy. Continued local research is needed to guide policy and adapt global evidence to the realities of the South African healthcare system.

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prolonged hospital stays, constrained inpatient capacity, and barriers to accessing sustained IV therapy, particularly in rural and resource-limited settings, oral step-down therapy may offer a pragmatic, cost-effective, and clinically safe alternative to conventional IV regimens.

Background on infective endocarditis in South Africa

The high prevalence of rheumatic heart disease in South Africa has historically been a prominent predisposing factor, now compounded by rising rates of IV drug use and a growing number of patients with prosthetic valves and cardiac implantable electronic devices.⁽⁶⁻¹⁰⁾ Previously, the viridans group streptococci were the predominant cause of blood culture-positive infective

endocarditis (BCPIE) in South Africa.^(7,10) However, the pathogen profile has shifted to resemble those observed in high-income countries, where *Staphylococcus aureus* predominates.^(1,11)

This trend was observed across multiple South African studies. De Villiers, et al.⁽¹²⁾ reported that *S. aureus* was the most frequent pathogen in left-sided (19%) and right-sided (73%) IE at Groote Schuur Hospital between 2009 and 2016. Similarly, Meel, et al.⁽⁹⁾ documented *S. aureus* dominance in a Gauteng cohort with a high prevalence of IV drug use, reflecting an epidemiologic shift linked to evolving risk factors. A retrospective analysis from the Western Cape (2017–2018) similarly found *S. aureus* in 43% of culture-positive cases, reflecting a move away from viridans streptococci toward staphylococcal predominance.⁽¹⁾ Consequently, empiric antibiotic regimens for IE now routinely include anti-staphylococcal coverage.⁽¹¹⁾

Prosthetic valve endocarditis (PVE) accounts for approximately 13–16% of IE cases in South Africa and is associated with significantly higher morbidity and mortality than native valve endocarditis (NVE).⁽¹³⁾ Mkoko, et al.⁽¹³⁾ reported that 13.3% of cases were PVE, half of which occurred within 1 year of valve surgery in the Groote Schuur IE registry (2017–2019). Moreover, these patients had notably higher rates of septic shock (22.2% vs. 7%) and heart block (27.8% vs. 12%) compared with NVE. *Staphylococcus* (38.9%) and *Streptococcus* spp. (22.2%) were the most frequent pathogens, with 27.8% being culture negative. In-hospital mortality for PVE was high at 55.6%, compared with 31.6% for NVE. These distinctions highlight the unique microbiological patterns, clinical challenges, and management requirements for PVE in the South African setting.

The high incidence of BCNIE continues to be a problem. Despite this, the addition of routine serological and surgical specimen

analysis has proven to increase the detection of a causative pathogen.⁽¹¹⁾ A recent study conducted in the Western Cape identified *Bartonella* spp. as a common cause of BCNIE, contrasting with developed countries where *Coxiella burnetii* is more common.^(14,15) BCNIE is associated with worse outcomes, but more recent reports found similar mortality rates between BCPIE and BCNIE.⁽¹⁾

ORAL STEP-DOWN ANTIBIOTIC THERAPY: GLOBAL EVIDENCE

Historical context: the rationale for intravenous treatment

Before the discovery of antimicrobial therapy, IE was considered almost universally fatal, with mortality rates approaching 99%.⁽⁵⁾ The introduction of sulphonamides in the mid-1930s marked the beginning of oral antibiotic therapy, followed by the development of oral tetracyclines and macrolides in the late 1940s and early 1950s.⁽¹⁶⁾ Despite initial promise, these early oral agents were ineffective in treating IE.⁽¹⁶⁾ The discovery of IV penicillin in the 1940s was a major therapeutic breakthrough, significantly improving survival and achieving cure rates as high as 85%.⁽¹⁶⁾ Although oral formulations of penicillin soon became available, they were considered unreliable for treating IE due to concerns regarding subtherapeutic blood and tissue concentrations, as well as the poor clinical outcomes associated with other oral antibiotics.⁽⁵⁾ As a result, prolonged IV therapy became the standard of care for IE.

Re-emergence of interest in oral therapy

In retrospect, the limited efficacy observed with early oral regimens was likely attributable to the intrinsic limitations of the antimicrobial agents themselves, rather than the route of administration. Advances in pharmacokinetics have demonstrated

TABLE I: Summary of key clinical studies supporting oral step-down therapy in infective endocarditis.

Study	Design (n)	Population/pathogens	Inclusion criteria for step-down	Oral regimens used	Key findings
Stamboulian, et al. (1991)	RCT (n = 30)	Left-sided streptococcal IE	Completed 2 weeks IV ceftriaxone	Oral amoxicillin × 2 weeks	100% cure in both arms at 3–6 months, reduced length of hospital stay.
Heldman, et al. (1996)	RCT (n = 85)	Right-sided <i>S. aureus</i> IE; IVDU	Febrile, IVDU	Oral ciprofloxacin + rifampicin	Comparable efficacy, reduced adverse drug reactions.
Mzabi, et al. (2016)	Observational (n = 426)	Mixed IE (left/right); <i>Streptococcus</i> , <i>E. faecalis</i> , <i>S. aureus</i>	Completed 7 days IV, stable clinical/lab parameters, negative blood cultures	Amoxicillin, clindamycin, fluoroquinolone, rifampicin	Similar mortality and relapse rate.
Tissot-Dupont, et al. (2019)	Observational (n = 341)	<i>S. aureus</i> IE	Completed 7 days IV co-trimoxazole + clindamycin	High dose co-trimoxazole × 5 weeks	Reduced length of hospital stay and mortality rate.
POET trial (Iversen, et al., [2019])	RCT (n = 400)	Left-sided IE (<i>Streptococcus</i> , <i>S. aureus</i> , <i>E. faecalis</i> , CNS)	≥ 10 days IV, stable, afebrile ≥ 48 hours, CRP ↓, no surgical indication	Amoxicillin, moxifloxacin, fusidic acid, linezolid, rifampin, dicloxacillin (dual therapy)	Oral step-down non-inferior.

CNS: coagulase-negative staphylococci, CRP: C-reactive protein, E. faecalis: Enterococcus faecalis, IE: infective endocarditis, IV: intravenous, IVDU: intravenous drug use, n: number, RCT: randomised controlled trial, S. aureus: Staphylococcus aureus.

that several modern oral antibiotics can achieve blood concentrations comparable to those attained with IV formulations.⁽¹⁷⁾ In keeping with these findings, RCTs have proven that adequate dosing of oral antibiotics can effectively clear bacteraemia in patients with IE.⁽⁵⁾ Oral step-down therapy involves initiating treatment with IV antibiotics until the patient reaches clinical stability, followed by a switch to appropriate oral antibiotics.⁽³⁾

Research supporting oral step-down therapy in infective endocarditis

Spellberg, et al.⁽⁵⁾ identified 21 observational studies and 3 RCTs supporting the use of oral step-down therapy in selected patients with IE (Table I). These studies reported similar cure rates across IV-only and oral step-down regimens, and an overall lower mortality in the oral groups. However, limitations include heterogeneity in lead-in duration (ranging from 0 to 24 days), variations in antibiotic protocols, and underrepresentation of methicillin-resistant *S. aureus* (MRSA) cases and IV drug users.⁽⁵⁾ Among these studies, the retrospective analysis by Mzabi, et al.⁽¹⁸⁾ reviewed 426 IE patients (214 switched to oral vs. 212 managed with IV only). They found similar mortality and relapse rates in the oral step-down cohort.⁽¹⁸⁾ However, as a non-randomised study, differences in baseline comorbidities and illness severity may have influenced their outcomes, and follow-up intervals were not standardised, challenging the reliability of relapse comparisons.

In 2019, Tissot-Dupont, et al.⁽¹⁹⁾ evaluated the efficacy of a switch to oral antibiotics on day 7 in patients with *S. aureus* IE. The study implemented a pre–post design involving 341 consecutive patients with *S. aureus* IE; 170 received standard IV therapy, and a subsequent cohort of 171 were managed with a protocol switch (IV co-trimoxazole and clindamycin for 1 week, followed by 5 weeks of high-dose oral co-trimoxazole).⁽¹⁹⁾ The oral group demonstrated reduced 30-day mortality (7% vs. 14%) and lower long-term mortality (19% vs. 30%). Limitations include its non-randomised design and a lack of MRSA-specific data.

The first RCT evaluating oral step-down therapy in IE was conducted in 1991 by Stamboulian, et al.⁽²⁰⁾ In their trial, 30 patients with penicillin-susceptible streptococcal endocarditis were randomised to receive either 4 weeks of IV ceftriaxone or 2 weeks of IV ceftriaxone followed by 2 weeks of oral amoxicillin. All patients were successfully treated for IE, and most were managed as outpatients, avoiding ~ 380 hospital days in total. Limitations include a small sample size and narrow inclusion criteria (only uncomplicated left-sided streptococcal IE).⁽²⁰⁾

Heldman, et al.⁽²¹⁾ were the first to evaluate exclusive oral antibiotic therapy for IE. In their randomised trial, 85 patients with right-sided *S. aureus* IE were assigned to receive either exclusive IV therapy or an entirely oral antibiotic regimen. Clinical cure rates and mortality were comparable between the two groups, with the oral treatment group experiencing fewer adverse drug reactions.⁽²¹⁾ This trial had limited generalisability due to its exclusive focus on right-sided disease in IV drug users,

lack of allocation concealment or blinding, and limited representation of MRSA or prosthetic valve infections.

The POET trial remains the largest and most influential RCT on oral step-down therapy in patients with IE. Iversen, et al.⁽³⁾ enrolled 400 patients with left-sided endocarditis caused by *Streptococcus*, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci. After 10 days of IV therapy, patients who met clinical stability criteria and had no surgical indications after transoesophageal echocardiography were randomised to continue IV antibiotics or switch to oral treatment. The trial demonstrated the non-inferiority of oral step-down therapy in terms of a composite primary outcome including all-cause mortality, unplanned cardiac surgery, embolic events, or relapse bacteraemia, even in people requiring surgery or with PVE.⁽²²⁾ Furthermore, follow-up data at 3 and 5 years post-randomisation revealed no evidence of delayed treatment failure in the step-down therapy group.⁽²³⁾ Study limitations include a small percentage of MRSA cases and IV drug users, only left-sided IE caused by specific pathogens, need for therapeutic drug monitoring, use of combination, high-dose oral regimens, and intense follow-up that may not be feasible in all settings. This landmark trial has been pivotal in validating oral step-down therapy as a non-inferior alternative to prolonged IV treatment. It has paved the way for its adoption as a potential new standard of care in appropriately selected patients with IE.

Evidence limitations and remaining gaps

The real-world application of the findings above was evaluated in a nationwide Danish observational study, which confirmed that the use of oral step-down therapy was associated with shorter hospital stays and reduced 6-month mortality, thereby supporting the extrapolation of the POET trial results to routine clinical practice in high-income settings.⁽²⁴⁾ However, despite the growing body of evidence supporting oral step-down therapy in high-income countries, a paucity of data exists from low- to middle-income countries, where resource constraints, differing epidemiological patterns, educational barriers, and health system challenges may influence the feasibility and safety of this approach.^(1,11,25-28)

While the clinical rationale and emerging data supporting oral step-down therapy in IE are promising, it is important to recognise the current limitations of the evidence to avoid overstating its generalisability. The POET trial, the key RCT supporting this approach, enrolled a highly selected group of stable patients with left-sided IE who had received at least 10 days of IV therapy, had undergone transoesophageal echocardiography, and were infected with a limited range of pathogens. Patients with right-sided IE, polymicrobial infections, persistent bacteraemia, or complications requiring surgery were excluded. Thus, while the POET trial demonstrated non-inferiority in this narrow group, it does not establish equivalence across all IE cases. Given these gaps, especially in the South African context where pathogen diversity and healthcare resources differ, further local research is essential to confirm the safety and efficacy of oral step-down therapy before widespread implementation.

CURRENT GUIDELINES AND PRACTICES IN SOUTH AFRICA

Due to limited local data on IE, South African healthcare practitioners often rely on guidelines developed in high-income countries for clinical decision-making, even within resource-constrained settings.⁽²⁹⁾ The South African Heart Association (SA Heart®) is an affiliated member of the ESC and endorses the ESC clinical practice guidelines, with adaptations to accommodate local healthcare circumstances.⁽³⁰⁾ However, to date, no South African adaptation of the most recent ESC endocarditis guideline has been developed to support the integration of oral step-down therapy in stable patients. Consequently, patients are often still admitted for 4–6 weeks to complete their IV antibiotic regimens.

IE diagnosis in South Africa is often hampered by limited access to advanced diagnostics, delayed microbiological confirmation, and a high burden of BCNIE.⁽¹¹⁾ These limitations reduce the sensitivity and specificity of the modified Duke criteria, which form the diagnostic cornerstone in many settings.⁽³¹⁾ In response, the International Society for Cardiovascular Infectious Diseases (ISCVID) proposed a revision of these criteria to enhance diagnostic accuracy.⁽³²⁾ Among the key changes is the reclassification of positive *Bartonella* spp. serology as a major microbiological criterion, reflecting its increasingly recognised role in BCNIE. In contrast, the most recent ESC guidelines still classify positive *Bartonella* spp. serology as a minor diagnostic criterion.⁽⁴⁾ This discrepancy may contribute to the underdiagnosis of definitive IE in South Africa, where *Bartonella* spp. are recognised as a significant cause of BCNIE.⁽¹⁵⁾ Their identification is further complicated by limited access to serological and molecular diagnostic tools.⁽³³⁾

Notably, the management of *Bartonella* endocarditis already incorporates an oral step-down component as patients typically receive an initial 2 weeks' IV gentamicin in combination with oral doxycycline, followed by prolonged doxycycline monotherapy.^(4,15) More broadly, the use of oral antibiotics in IE is not a new concept in South Africa. As early as 1988, a small prospective study of 15 patients with uncomplicated NVE reported an 87% cure rate using high-dose oral amoxicillin alone, highlighting local precedent for alternative treatment strategies in carefully selected cases.⁽³⁴⁾

Potential relevance of oral step-down therapy in South Africa

Oral step-down therapy presents a potentially valuable treatment strategy in the South African context, where prolonged hospitalisation for IV antibiotic therapy places substantial strain on healthcare infrastructure. This approach offers several advantages, including shorter inpatient stays, improved bed availability, reduced healthcare costs, and greater patient autonomy and comfort.^(5,35) In resource-limited settings with high inpatient demand and workforce constraints, transitioning the appropriate patients to oral therapy could help alleviate systemic pressures without compromising clinical outcomes.

In addition to operational benefits, partial oral therapy may align with patient preferences, particularly for individuals from rural or underserved areas who face geographic and financial challenges due to prolonged hospitalisation. Reduced hospitalisation may also lower the risk of nosocomial infections and improve quality of life for stable patients.⁽³⁶⁾ Identifying potential candidates for oral step-down therapy through local implementation research could enable South Africa to safely adopt oral step-down therapy, drawing from international evidence while addressing local health system realities.

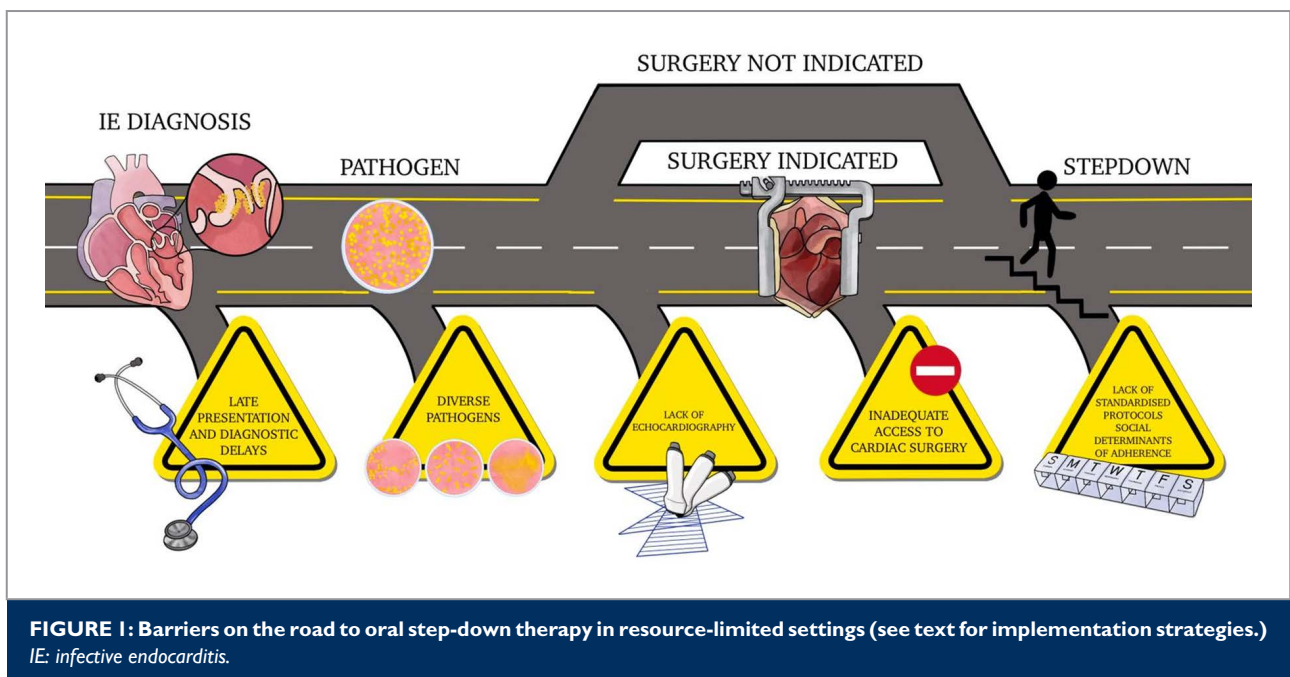


FIGURE 1: Barriers on the road to oral step-down therapy in resource-limited settings (see text for implementation strategies.)
IE: infective endocarditis.

CHALLENGES IN THE SOUTH AFRICAN CONTEXT

Implementing oral step-down therapy in South Africa presents various challenges (Figure 1). The local microbiological landscape is distinct, with a notably high burden of BCNIE, reported to range between 40% and 60% of all IE cases in some South African cohorts.^(8,11) As mentioned, *Bartonella* spp. are among the leading causes of BCNIE in this setting.⁽¹⁴⁾ Although TB is highly prevalent in South Africa, TB endocarditis remains rare.⁽³⁷⁾ Most reported cases are anecdotal or limited to isolated case reports. While TB may occasionally be identified as a cause of BCNIE, it contributes minimally to the overall IE burden in clinical practice. Also, it does not typically fall within the scope of patients considered for oral step-down therapy.

There are currently no reported outbreaks of *Mycoplasma* IE in South Africa. However, the country has experienced significant levels of *Mycoplasma pneumoniae* respiratory infections, particularly among children and individuals living with human immunodeficiency virus (HIV).⁽³⁸⁾ A cluster of IE cases caused by non-toxicogenic *Corynebacterium diphtheriae* was recently reported in the West Coast District of the Western Cape Province.⁽³⁹⁾ Moreover, outbreaks of brucellosis (*Brucella* spp.) have been reported, particularly affecting livestock in the KwaZulu-Natal Province.⁽⁴⁰⁾ While these outbreaks are primarily animal-focused, brucellosis is a recognised cause of IE, particularly in individuals with predisposing factors, such as prosthetic heart valves.⁽⁴¹⁾ These outbreaks highlight the need for heightened awareness and surveillance of these isolates as a potential aetiology of IE, especially in endemic areas and among high-risk populations. The presence of these unique pathogens requires individualised antibiotic regimens, making it difficult to standardise oral step-down therapy protocols.

Access to healthcare services remains a significant barrier to optimal patient management in South Africa, particularly in rural and underserved areas.⁽²⁸⁾ Patients often struggle to attend follow-up appointments at referral facilities due to long distances, insufficient transportation, and financial limitations.^(28,42,43) A study conducted at George Regional Hospital in the Western Cape found that non-attendance rates for outpatient appointments were as high as 40%.⁽⁴⁴⁾ In rural communities, the situation is often more pronounced. A study examining travel burdens for children admitted to hospitals in the Western Cape revealed significant disparities in travel distances to healthcare facilities.⁽⁴⁵⁾ Some communities had to travel up to 4 times the distance compared with others, highlighting the unequal access to healthcare.⁽⁴⁵⁾

Early surgical intervention for IE patients with a surgical indication significantly reduces mortality and the incidence of cerebral embolism, without increasing the risk of peri-operative complications or infection relapse.^(46,47) Despite evidence supporting early surgery, timely access to cardiac surgery remains a significant challenge in South Africa's public healthcare sector, which services more than 80% of the population.^(25,48) This is driven by limited operating theatre availability, a shortage

of theatre staff, and inadequate intensive care unit (ICU) capacity.⁽⁴⁸⁾ These systemic limitations often delay necessary surgeries, making it challenging to adhere to international guidelines.⁽⁴⁷⁾

During these delays, patients are often kept in the hospital on prolonged IV antibiotic therapy. It is important to note that oral step-down therapy is only recommended for clinically stable patients with no surgical indications.⁽³⁾ As such, patients awaiting cardiac surgery are generally excluded from oral step-down therapy, even if they are otherwise stable. While oral antibiotics can technically be administered in a hospital setting, their use in patients with persistent infection or structural complications requiring surgery is not supported by the current evidence. Consequently, delayed surgical access not only prolongs inpatient IV treatment but also limits the feasibility of implementing oral step-down therapy in a significant proportion of patients in the South African context.

In addition to structural barriers, long-term adherence to oral antibiotic regimens requires attention to multiple factors. While educational attainment can influence a patient's ability to understand treatment instructions, adherence is shaped more broadly by socio-economic status, health literacy, trust in the healthcare system, medication access, and the quality of patient-provider communication. In South Africa, 10.5% of adults aged 25–64 have only completed primary education without formal education, and only one-third have completed Grade 12.⁽²⁷⁾ Patient support strategies must extend beyond the educational level. Patients in rural settings may also face frequent medicine stockouts and poor access to follow-up care, both of which undermine adherence, regardless of literacy.⁽²⁶⁾

These multifactorial challenges emphasise the urgent need for locally feasible and evidence-based strategies to implement oral step-down therapy for IE in South Africa. Interventions must go beyond clinical decision-making and address systemic barriers, such as inadequate access to surgical care, limited outpatient follow-up infrastructure, and the social determinants of adherence. Potential strategies include simplified and standardised oral treatment protocols, enhanced patient education through community health workers, integration of follow-up care into existing chronic disease platforms, and the use of digital tools to support care continuity.

In this regard, local research is critical to guide these adaptations, particularly to define appropriate patient selection criteria, measure outcomes, and evaluate the safety, cost-effectiveness, and acceptability of oral step-down regimens in the diverse South African settings. Investing in local data generation will be essential to inform national guidelines and ensure that this promising strategy can be implemented safely and equitably within the realities of South Africa's healthcare system.

OPPORTUNITIES AND FUTURE DIRECTIONS

While current guidelines recommend a treatment duration of 4–6 weeks for IE, this recommendation is based mainly on

historical practice, with supporting evidence drawn from consensus documents, retrospective studies, and case records.⁽⁴⁹⁾ Similarly, the recommendation to treat PVE for 6 weeks is based predominantly on expert opinion.⁽⁴⁾ A retrospective review by Morris, et al.⁽⁵⁰⁾ investigated the outcome of patients with IE following valve surgery concerning the duration of antibiotic treatment. They found no difference in the relapse rate, regardless of whether patients were treated for 2 or 4 weeks post-surgery, suggesting that shorter antibiotic courses may be sufficient in selected cases.⁽⁵⁰⁾ This hypothesis is being tested in ongoing RCTs, such as POET II and SATIE (Shortened Antibiotic Treatment duration for Infective Endocarditis), which aim to evaluate the safety and efficacy of shortened antibiotic regimens in patients with IE.⁽⁵¹⁾

In keeping with the design of the POET trial, current ESC guidelines recommend combination oral antibiotic regimens for step-down therapy, consisting of 2 antibiotics with different mechanisms of action to ensure adequate concentrations of at least 1 antibiotic.⁽⁴⁾ However, there is no evidence that combination oral antibiotic therapy is superior to monotherapy. On the contrary, it may be associated with increased adverse events and cost, and reduced patient adherence.⁽⁵²⁾ Monotherapy is effective in multiple real-world studies, raising questions about the necessity and long-term role of combination oral antibiotic regimens in step-down therapy.^(18,52-55)

Several antibiotics, including linezolid, amoxicillin, rifampicin, moxifloxacin, and fusidic acid, all possess excellent oral bioavailability and tissue penetration, making them well-suited for oral step-down monotherapy in appropriate clinical settings.⁽⁵²⁾ In addition to its potential for drug–drug interactions, rifampicin should be used with caution in TB-endemic areas, where it remains a cornerstone of first-line TB therapy. Its use outside of standard TB regimens should be reserved for situations where no suitable alternatives exist, to mitigate the risk of selecting for rifampicin-resistant TB strains.⁽⁵⁶⁾

Current ESC guidelines recommend step-down therapy exclusively in cases of left-sided IE caused by select Gram-positive organisms.⁽⁴⁾ There is also evidence from small-scale studies supporting oral step-down therapy for uncomplicated right-sided methicillin-sensitive *S. aureus* IE.⁽⁵⁷⁾ However, if one accepts the underlying principle that certain oral antibiotics achieve bioavailability comparable to their IV counterparts, oral step-down therapy could theoretically be considered for IE caused by any pathogen, provided the chosen oral agent achieves adequate blood and tissue concentrations, and the patient meets clinical stability criteria.

To evaluate the safety, feasibility, and clinical outcomes of oral step-down therapy in the South African context, local prospective studies are essential. The Tygerberg Oral Antibiotic Step-down Therapy in Infective Endocarditis (TOAST-IE) study, currently underway, is an important first step in this direction. However, multicentre prospective cohorts across provinces will be critical to capture real-world heterogeneity, including patients

with BCNIE, varying healthcare access, and comorbid conditions, such as HIV and TB.

There is currently no South African guideline on oral step-down therapy for IE. Developing locally relevant consensus statements or position papers, endorsed by national bodies such as SA Heart® or the National Department of Health, would provide a much-needed framework to support clinicians. These guidelines should incorporate patient selection criteria, antibiotic choices, monitoring protocols, and follow-up pathways, informed by local epidemiology and healthcare realities.

Effective implementation will require healthcare provider training, particularly at district and regional hospitals, in the selection, initiation, and monitoring of oral step-down regimens. In parallel, laboratories must be equipped to perform antibiotic susceptibility testing, therapeutic drug monitoring, and pathogen-specific diagnostics (e.g. *Bartonella* spp. serology). Task-sharing with nurses and community health workers, integration into chronic disease follow-up systems, and the use of mobile health platforms could improve care continuity in patients discharged on oral therapy.

CONCLUSION

This review reveals that many aspects of IE management are based on historical practices and outdated evidence. However, a growing body of high-quality pharmacokinetic, observational, and RCT data now support the efficacy of oral step-down therapy. In the South African context, the implementation of oral step-down therapy necessitates developing locally feasible strategies that account for the unique healthcare challenges and resource constraints. These strategies should include simplified step-down protocols, improved access to healthcare and surgical services, enhanced patient education, and better follow-up systems. Further local research is essential to guide policy and practice in this setting.

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Challenges with international normalised ratio control in paediatric patients with rheumatic heart valve replacement surgery in the Eastern Cape Province, South Africa

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INTRODUCTION

ARF is a post-infectious, non-suppurative sequel of pharyngeal infection with group A beta-haemolytic *Streptococcus*.⁽¹⁾ More than one-third of affected patients develop carditis, followed by progressive and permanent valvular heart disease, particularly mitral valve and aortic valve regurgitation and/or stenosis.⁽²⁾ The burden of RHD in developed countries declined drastically at the end of the 20th century, largely due to reduced overcrowding and improved sanitation and living conditions.⁽³⁻⁴⁾

In South Africa, RHD cases declined somewhat since the dawn of democracy in 1994, which was attributed to improved healthcare access.⁽⁵⁾ The earlier improvements in South Africa since 1994 were only demonstrated in certain parts of the country, not its entirety. The previously disadvantaged communities remained poor under the new government of democracy, and, as such, the prevalence of RHD never improved.⁽⁶⁾ The former Transkei region of the Eastern Cape Province remains poor and is overburdened with cases of chronic RHD.

Surgery is indicated for patients with RHD presenting with symptomatic valvular dysfunction.⁽⁷⁾ The surgical options for RHD include closed mitral valvotomy, mitral valve repair, or replacement with a mechanical, bioprosthetic, or autograft valve. Aortic valve disease is usually treated with valve repair or replacement with a mechanical, homograft, or pulmonary autograft valve.⁽⁷⁾ The choice of therapy for young patients is influenced by many factors, such as socio-economic status, access to healthcare, availability of prophylaxis for ARF, and anticoagulation therapy. In these situations, the importance of repair, especially of the mitral valve, is unquestionable.⁽⁸⁾

ABSTRACT

Introduction: Rheumatic heart disease (RHD) is a preventable chronic condition that affects the heart valves. The incidence of acute rheumatic fever (ARF) and RHD has waned in Western countries; however, this is not the case in developing countries. Poor access to healthcare and a lack of adherence to international normalised ratio (INR) monitoring in RHD contribute to thromboembolic complications.

Methods: Records of patients from the Eastern Cape municipal districts with RHD were reviewed over 10 years. Patients who underwent rheumatic valve replacement surgery were isolated and analysed for their INR control.

Results: A total of 30 patients with RHD were reviewed. All patients presented with severe RHD. Of the 30 patients, 20 had mitral valve replacement surgery, and 6 had mitral valve repair surgery. The 6 patients who had mitral valve repair surgery eventually required mitral valve replacement. Those who had mitral valve replacement surgery were started on anticoagulation (warfarin) post-operatively. Two patients died due to mitral valve thrombosis. Four patients were subsequently admitted for anticoagulation due to a thrombosed prosthetic mitral valve. Most of the patients were struggling to maintain a therapeutic range INR with values ranging from 1.1 to 2, and up to 8–10 on rare occasions.

Conclusion: Most chronic RHD patients underwent mitral valve replacement surgery with a prosthetic valve. Most patients who were started on warfarin struggled to maintain a therapeutic range INR post-operatively due to poor healthcare access and adherence.

Keywords: acute rheumatic fever, rheumatic heart disease, valve replacement surgery, international normalised ratio, disease outcomes

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Global survival and survival-free rates from prosthetic valve complications are lower after valve replacement, with either mechanical or biological prostheses, because of higher rates of thromboembolism with mechanical valves and the faster degenerative process with biological prostheses.⁽⁸⁾ Mitral valve repair surgery is preferred in children over valve replacement

surgery; however, the durability of repair of the rheumatic mitral valve is generally poorer than in nonrheumatic valves.⁽⁹⁾

In RHD-endemic regions with limited access to surgery and emerging surgical programmes, the most important considerations may be the risk of needing reoperation, given the limited resources (and low probability of obtaining a second operation) and the surgical team's expertise in valve replacement rather than repair. Consequently, valve replacement is often the practice of choice in many settings, despite the need for lifetime anticoagulation.⁽⁹⁾

For most young patients who undergo replacement valve therapy with mechanical prostheses, reliable anticoagulation management is often unattainable under the prevailing socio-economic circumstances.⁽¹⁰⁾ Cases of patients with clotted valves presenting for emergency surgery due to poor compliance with anticoagulation control are frequent, with INR ranges below the recommended therapeutic ranges (2.5–3.5).

Without trivialising the seriousness of bleeding complications associated with over-anticoagulation, under-coagulation in low- to middle-income countries far exceeds the former.⁽¹¹⁾ In two African studies involving patients with RHD who underwent mechanical valve replacement, most thromboembolic complications, including clotting of the valves, occurred at an INR < 2.⁽¹¹⁾

Risk factors for poor adherence to warfarin are young patient age, lack of formal education, unemployment, and limited access to an immediate healthcare facility.⁽¹²⁾ Unfortunately, these factors are simultaneously the hallmark features of RHD, for which a significant association with low socio-economic circumstances exist.⁽¹³⁾

Our setting, the former Transkei region of the Eastern Cape, is considered one of the poorest provinces in South Africa, characterised by high levels of unemployment and illiteracy.⁽¹⁴⁾ We only have access to 1 cardiothoracic surgeon who performs part-time sessions at the state hospital.⁽¹⁵⁾ We are only able to do 1–2 cases per week, an average of 3–4 cases per month. These cases are prioritised according to which one is deemed an emergency or urgent case at the time.⁽¹⁵⁾ RHD tends to fall behind congenital heart diseases, which are usually more urgent. Therefore, RHD patients tend to suffer the most.

METHODS

This was a retrospective review of paediatric patients treated for rheumatic valvular heart disease at a tertiary hospital in the Eastern Cape Province over 10 years. Demographic data, such as age, sex, and place of origin, were analysed. Patient presentation and type of rheumatic valve disease were analysed. Follow-up echocardiograms were recoded, which were performed immediately post-operatively, at 1 month, 6 months, and 1 year. All patients with prosthetic mitral valves were started on warfarin post-operatively. INR was monitored monthly in all

patients on warfarin, depending on the INR control. The INR therapeutic target range was 2.5–3.5. The INR data were collected from the National Health Laboratory Service (NHLS).

Statistical analysis and ethical clearance

Variables were reported as a mean (standard deviation) or median (interquartile range). Nominal variables were compared using the t-test. Ethical clearance was obtained from the chief executive officer of Dora Nginza Hospital and the Health Research Ethics and Biosafety Committee of Walter Sisulu University.

RESULTS

A total of 30 patients were treated for chronic rheumatic valve disease at a tertiary hospital over 10 years. There were 19 males (63%) and 11 females (36.6%) (Figure 1). Most patients (n = 19, 63%) were from the former Transkei region (OR Tambo District Municipality). The average distance travelled from home to the tertiary hospital was 200 km. The remaining patients were from the Nelson Mandela Bay Metro and Sarah Baartman municipalities. All the patients were between the ages of 5 and 15 at the time of presentation and operation.

Most patients (n = 28) presented with severe mitral valve regurgitation, and only 2 with mixed mitral valve disease. A few patients presented with severe mitral valve regurgitation and mild aortic regurgitation, which did not require any aortic valve repair or replacement.

Most patients (n = 24, 80%) had mitral valve replacement surgery with mechanical prostheses. The rest of the patients initially had mitral valve repair but later required redo surgery for mitral valve replacement due to severe mitral regurgitation post-operatively (Figure 2).

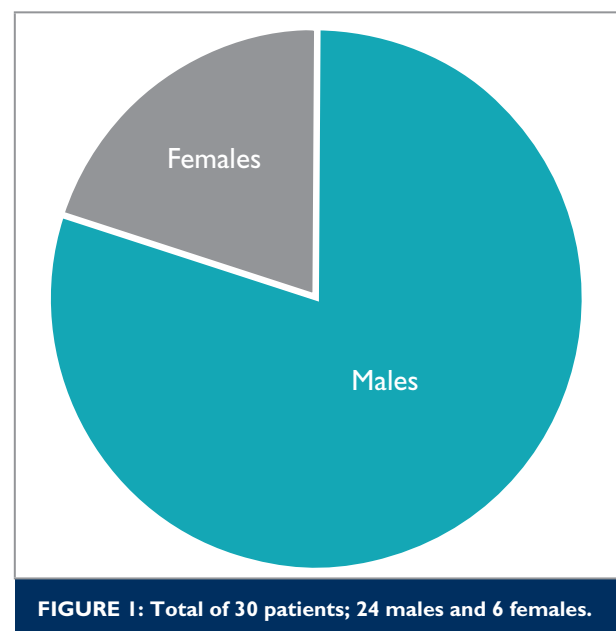
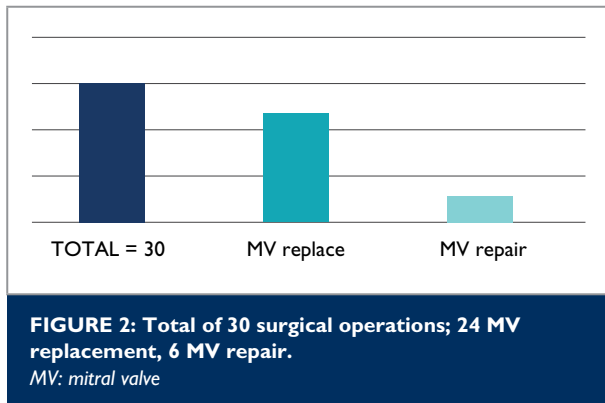


FIGURE 1: Total of 30 patients; 24 males and 6 females.



All the patients with mitral valve replacement were started on anticoagulation therapy with warfarin and were followed up for INR monitoring. Two patients died due to mitral valve thrombosis because of poor anticoagulation adherence. Four patients were admitted to the hospital for intensive anticoagulation for a thrombosed prosthetic valve due to poor anticoagulation adherence. These patients were started on enoxaparin sodium and warfarin in the ward until proper thrombolysis. This was the only option due to the unavailability of cardiothoracic surgical services.

The rest of the patients are currently on anticoagulation with poorly controlled INRs fluctuating between 1 and 2. Most patients (n = 20) have an INR average < 2. The rest of the patients fluctuate between an INR of 2 and 3, and > 3. Only 1 patient was admitted with warfarin toxicity and bleeding.

There are no INR clinics at the district hospitals, and some do not have an on-site laboratory to perform the INR. Therefore, patients must travel for 2 days to access an INR and have their medication adjusted accordingly. Some of the delays in getting the INR contribute to poor control.

DISCUSSION

During the study period, only 30 patients underwent rheumatic valve surgery. There is a long waiting list for some of the patients due for surgery who must wait because of the lack of paediatric cardiothoracic surgeons in the province. Approximately 30 more patients with severe rheumatic valve disease are awaiting surgery.⁽¹⁶⁾ This means, on average, we have only operated on 3 patients per annum. National waiting lists for paediatric cardiac surgery are currently estimated in excess of 3 000 patients, including congenital heart disease and rheumatic valve disease.

There was a male predominance among the patients operated on. Most of these patients were from the former Transkei region of the Eastern Cape, one of the poorest provinces in the country.⁽¹⁴⁾ These patients would travel approximately 200 km from their local district hospitals, which would take an ambulance about 3 hours to reach a tertiary hospital with paediatric cardiologists. After they have been assessed and considered due for surgery, they are referred to another centre with a

cardiothoracic surgeon, approximately 520 km away. There is only 1 part-time cardiothoracic surgeon for the entire Eastern Cape Province. On average, it takes 6–8 hours or more for patients to reach a centre with a surgeon to undergo surgery.^(11,17)

Regarding clinical presentation, most patients had severe mitral regurgitation, with a few cases of mixed mitral valve and aortic valve regurgitation. As such, most patients had mitral valve replacement and repair surgery with no aortic valve surgery.⁽⁶⁾ Most of the patients had mitral valve replacement surgery instead of mitral valve repair, which is the preferred surgical option in children with RHD.^(7,10) Mitral valve repair surgery has the advantage of not requiring anticoagulation post-operatively, thus avoiding the complications of under- or over-anticoagulation.⁽⁷⁾

Due to several reasons, most patients had valve replacement surgery instead of valve repair, which is the preferred surgical option, as a result of the shortage of surgeons, limited skill with rheumatic valve surgery, a long waiting list for paediatric cardiac surgery, and the possibility of redo being required later on in life for patients with valve repair.^(7,8,10,16) Patients who initially underwent mitral valve repair eventually required mitral valve replacement due to severe residual mitral valve regurgitation post-repair.^(8,9)

All patients ultimately received anticoagulation, including those who initially underwent mitral repair surgery. Most patients travel far to access a specialist and other services, such as laboratory testing.^(12,17) The lack of skilled healthcare workers and the unavailability of anticoagulants at their district hospitals and clinics have resulted in patients not receiving their warfarin as prescribed or their INR not being optimised.⁽¹²⁾ Consequently, their INR control was challenging.

Approximately 80% of the patients had an INR average < 2, which is suboptimal. These patients are at risk of valves being blocked by clots.⁽¹²⁾ The other risk was warfarin toxicity because they had to take high doses of anticoagulation to try to achieve INR therapeutic ranges (2.5–3.5). Of the patients on warfarin, 4 were admitted for a thrombosed prosthetic mitral valve, and 2 patients died due to thrombosis of the mitral valves.⁽¹⁰⁾

One of the biggest challenges of INR control is the limited access to medical healthcare services and the scarcity of INR clinics at district hospitals. Due to the unavailability of surgery and long waiting lists for theatre, patients with thrombosed valves were admitted on high-dose anticoagulation and dual anticoagulation therapy to try to dissolve the clots.⁽¹⁸⁾ The 4 patients were picked up early and were treated successfully without any surgery. The two other patients died before their INR could be controlled.

Unfortunately, there are no plans in place by the government to address the situation. Poor patients continue to suffer from a lack of healthcare services and shortages of human resources.

Recommendations

Paediatric cardiac surgical services require a multistakeholder collaboration for success, involving paediatric cardiologists, paediatric cardiothoracic surgeons, the Department of Health, the Colleges of Medicine of South Africa, the Health Professions Council of South Africa, the South African Medical Association, and civil society groups. A collaborative approach is recommended to find solutions to these challenges.

CONCLUSION

Most patients with chronic rheumatic valve disease underwent mitral valve replacement surgery with a prosthetic valve that required anticoagulation post-operatively. Most patients who were started on warfarin had subtherapeutic INR due to poor healthcare access and compliance.

Conflict of interest: none declared.

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ABSTRACT

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INTRODUCTION

Atrial fibrillation (AF) has a worldwide prevalence of 3%–5% in adults above the age of 20 years and is present in 1 out of 10 people over the age of 75 years.^(1,2) The rising prevalence of AF globally can be attributed to ageing populations, an increase in AF-associated co-morbidities and lifestyle-associated risk factors.^(1,2) In addition, as mandated in updated guidelines, improvements in screening and detection of silent or asymptomatic AF in these high-income settings yield higher prevalence rates.⁽²⁾ In low- to middle-income countries such as South Africa (SA), the prevalence of AF ranges from 4%–8%.^(1,2,4,5) The main risk factors for development of AF globally and in sub-Saharan Africa are hypertensive heart disease (HHD), valvular heart disease (VHD) and cardiomyopathy. Prevention through management of comorbidities and strategies to improve lifestyle are lacking globally and locally.^(1,2,4,5) All studies in the low-middle income group reported sub-optimal prophylactic anticoagulation and low uptake of rhythm control strategies.^(1,2,4,5)

Management of AF is aimed at (1) assessing stroke risk and providing appropriate anticoagulation for the prevention of thromboembolic events, (2) rate and rhythm control and

Introduction: The prevalence of atrial fibrillation (AF) in high-income countries is high, with less known about low- to middle-income countries. Information on the patient profile and application of adequate guideline-directed management in this low-middle income setting is lacking. This study aimed to determine the prevalence, clinical profile and management of patients with AF across all disciplines in a tertiary setting, and to compare the management of these patients with current guidelines.

Methods: Electrocardiograms (n = 13 414) recorded at Tygerberg Hospital for patients > 18 years between 1 July 2018 – 30 June 2019 were screened and medical records reviewed.

Results: An AF prevalence of 3.4% (n = 460) was found, which corresponded to 341 patients and 238 complete medical records. The mean age was 65.4 (±13.9) years and the most prevalent comorbidities reported were hypertension (63.9%, n = 152) and diabetes mellitus (21%, n = 46). Valvular heart disease was found in 31.1% (n = 74). In 80.7% (n = 192) of patients anticoagulation was indicated; however, only 65.1% (n = 125) of those indicated received it, mostly with warfarin. Time in therapeutic range (TTR) was poor (26.5%). Rate control (< 110 bpm), was seen on 80.9% (n = 372) of ECGs and beta blockers were most frequently used for rate control (65.1%, n = 155). No patients had documented information indicating that they received medical or interventional rhythm control management.

Discussion: The AF prevalence and patient profile resemble those of patients in high-income countries. Slightly more than half of patients qualifying for anticoagulation received this with warfarin, with suboptimal TTR. Rate control strategies were somewhat reassuring; however, the lack of early rhythm control may be disadvantageous to our patients.

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(3) managing associated cardiac conditions, comorbidities and lifestyle-associated risk factors.^(1,2,6,7) At the time of the study, the South African Heart Association used the 2020 European Society of Cardiology (ESC) guidelines for the management of AF, developed in collaboration with the European Heart Rhythm Association (EHRA) to guide patient management.^(1,2) The majority of patients treated in the public healthcare sector in SA

come from a lower socio-economic background and this, together with resource limitations within this sector, may challenge the applicability of these international guidelines. Furthermore, little is known about the local adherence to international guidelines across a wide range of disciplines.

The aim of this study was to determine the prevalence, patient clinical profile, and management of patients with AF in a tertiary setting in the Western Cape and to compare this management with current recommended international guidelines.

METHODS

An observational, descriptive study using a retrospective record review was performed. Tygerberg Hospital (TBH) is a tertiary referral hospital with ±1 400 beds situated in the Western Cape, SA. All in- and out-patient ECGs are performed by a central ECG service and recorded on the MUSE® system between 1 July 2018–30 June 2019 were reviewed and adult patients with AF were included. Once an ECG was identified as AF, the medical records were reviewed and demographic and clinical data recorded for each patient. Only medical records corresponding to the date of the ECG captured were included. In the case that an ECG was not associated with a hospital admission, the clinical records closest to the date of the ECG were recorded. Medical records were obtained from the hospital's medical records systems (Enterprise Content Management [ECM®], National Health Laboratory Services [NHLS, Trackcare®] and Echo Pack®). Time in the therapeutic range (TTR) for those patients on vitamin K antagonists, was calculated by the simplistic formula of the total number of INR values in the range over the total number of INR measured as described by Reiffel (2017).⁽⁶⁾ Good rate control was assessed as resting heart rate < 110 bpm.⁽⁴⁾ Ethics approval from Stellenbosch University Health Research Ethics Committee (U19/10/043) as well as institutional approval was obtained.

RESULTS

A total of 13 414 ECGs captured from 1 June 2018 – 30 June 2019 at TBH across all disciplines were screened and 460 were identified as AF, giving an AF prevalence of 3.4%. These 460 ECGs corresponded to 341 patients, as more than one ECG was recorded for some patients. Full medical records were available for 69.7% of these (n = 238). The mean age was 65.4 (±13.9) years. Females made up 52.5% (n = 179) and males 47.5% (n = 162).

All ECGs were standard (25 mm/s, 10 mm/mV, 50 Hz) and the rhythm identified was irregular, in keeping with AF, except for 5.9% (n = 27) that were paced rhythms and 1.4% (n = 5) that had complete heart block. The ECG characteristics of patients with AF are summarised in Table I.

Unfortunately the type or characteristics of AF was not documented accurately in the medical records. Documented symptoms associated with AF included shortness of breath

(8.8%; n = 21), angina (7.6%, n = 18), palpitations (4.6%; n = 11), syncope (3.4%; n = 8), fatigue (2.5%; n = 6), dizziness (1.3%; n = 3) and anxiety (0.4%; n = 1).

The most commonly associated cardiac conditions reported in the medical records or found on echo are presented in Figure 1. Of the patients with VHD, mixed mitral valve disease (MMVD) (7.1%; n = 17) and mitral regurgitation (MR) (6.7%; n = 16) were most common (Figure 2).

Other coexisting cardiovascular conditions not seen in Figure 2 included hypertrophic cardiomyopathy (HCM) (1.3%; n = 3), infective endocarditis (< 0.8%; n = 2), restrictive cardiomyopathy (0.4%; n = 1), and cor pulmonale (0.4%; n = 1).

TABLE I: ECG characteristics of cases with AF (n = 460).

ECG Characteristics	Mean ± SD
Ventricular rate (bpm)	87.30 ± 25.4
QRS duration (mS)	109.1 ± 27.2
QTc duration (mS)	450.5 ± 39.1
	% (n)
QRS axis	
Normal	78.5 (361)
Left axis	16.7 (77)
Right axis	3.00 (14)
North West axis	1.70 (8)
Wide QRS	
LBBB	11.7 (54)
RBBB	8.3 (38)
Non-specific intraventricular conduction delay	1.50 (7)
Complete heart block with ventricular escape	1.40 (5)
Paced rhythm	5.90 (27)
Chamber enlargement	
LVH	11.1 (51)
RVH	0.70 (3)
Pathological Q-waves	22.6 (104)
Location of pathological Q waves	
Inferior	13.7 (63)
Anteroseptal	7.20 (33)
Septal	4.10 (19)
Anterolateral	0.90 (4)
Repolarisation changes	
ST Elevation	26.7 (123)
ST Depression	17.0 (78)
Peaked T waves	33.0 (152)
Inverted T waves	29.1 (134)
Flattened T waves	1.10 (5)

ECG: Electrocardiogram, bpm: beats per minute, mS: milliseconds, LBBB: left bundle branch block, RBBB: right bundle branch block, LVH: left ventricular hypertrophy, RVH: right ventricular hypertrophy.

Comorbidities found in this group included hypertension (63.9%; n = 152), diabetes mellitus (DM) (20.6%; n = 46), obesity (16.0%; n = 38), chronic kidney disease (CKD) (9.2%; n = 22), pulmonary hypertension (8.4%; n = 20), chronic obstructive pulmonary

disease (COPD) 8.0% (n = 19), 3.8%; (n = 9) hypothyroidism and 2.5%; (n = 6) hyperthyroidism, peripheral vascular disease (1.2%; n = 3), gastro-oesophageal reflux disease (0.4%; n = 1), and liver disease (0.4%; n = 1).

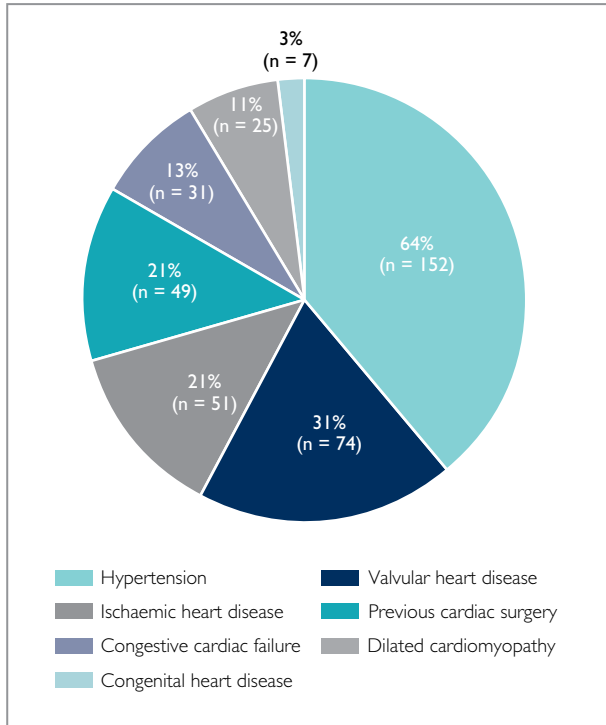


FIGURE 1: Coexisting cardiovascular conditions among patients with AF (n = 238).

Associated lifestyle-related risk factors such as smoking (30.1%; n = 73) and notable alcohol use (> 3 drinks for females and > 4 drinks for males) (8.4%; n = 20) were documented, with obstructive sleep apnea, vigorous exercise and substance abuse not reported in the clinical records.

Echocardiography data was only available for 20.2% (n = 48) of patients and is shown in Table II. Most patients had non-dilated left ventricles with a mean ejection fraction (EF) of 49%. MR was the most common valvular lesion recorded (48.0%; n = 23), followed by aortic regurgitation (AR) (16.7%; n = 8). Stenotic lesions were less prevalent, with aortic stenosis (AS) present in 6.3% (n = 3) and mitral stenosis (MS) in 4.2% (n = 2).

Previous stroke was reported in 5.0% (n = 12) of patients. Information regarding risk and management of thromboembolism is summarised in Table III. Of the 238 patients, 80.7% (n = 192) qualified for oral anticoagulation (OAC) (CHA2DS2-VASc for males > 1 and females > 2). Of these 192 patients qualifying for anticoagulation, 65.1% (n = 125) received vitamin K antagonists (VKA) (warfarin) and only 3 (1.6%) were on a novel oral anticoagulation (NOAC) drug (rivaroxaban). Of these, 49.5% (n = 95) also received concomitant antiplatelet medication and in 18.8% (n = 36) only antiplatelet medication was given even though there was an indication for anticoagulation. Of the patients who received warfarin (n = 125), the mean international normalised ratio (INR) was 2.2 ± 1.3. However, 48.9% (n = 65) had subtherapeutic INR levels (1.4 ± 0.3) and 21.1% (n = 28) INR values >3 (4.1 ± 1.5), while TTR were 0.3 ± 0.2 (26.5%). The HAS-BLED score was approximated using hypertension as a surrogate for absolute blood pressure values and a mean HAS-BLED score of 1.6 ± 0.9 was found. However, 18.1% (n = 43) of patients had a HAS-BLED score > 3.

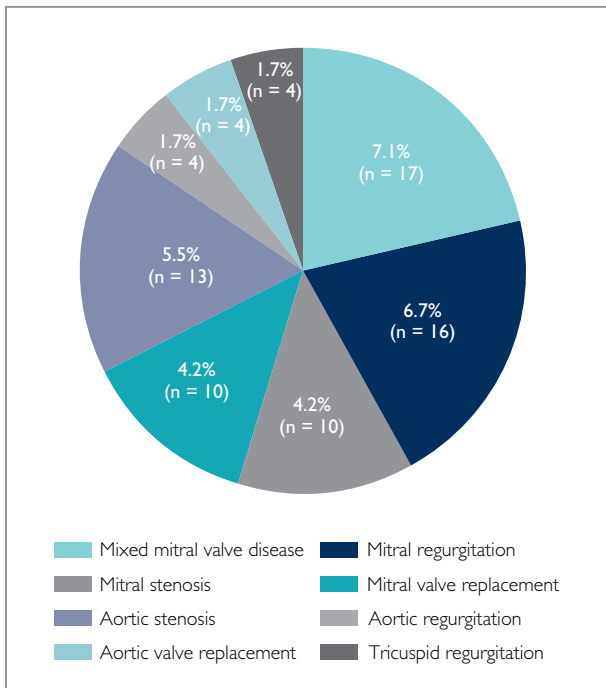


FIGURE 2: Valvular heart lesions among patients with AF (n = 238).

The mean ventricular rate for the cohort was 87bpm (Table I). 80.9% (n = 372) of patients had good rate control (< 110) as read from the ECGs (n = 460). Rate control drugs included beta-1 selective blockers such as atenolol (45.0%; n = 107) and non-selective beta blockers such as carvedilol (20.2%; n = 48). Only 3.8% (n = 9) of patients received antiarrhythmic medication such as amiodarone. Non-antiarrhythmic drugs with antiarrhythmic benefit were commonly used, with drugs such as angiotensin-converting enzyme (ACE) inhibitors (enalapril), HMG-CoA reductase inhibitors (simvastatin) and aldosterone receptor antagonists (spironolactone) being prescribed (Table IV).

Additional medication taken that is not listed in Table IV included tricyclic antidepressants (amitriptyline 6.3%; n = 15), nitrates (isordil 3.8%; n = 9), thyroid medication (levothyroxine 2.9%; n = 7), selective-serotonin reuptake inhibitors (citalopram 1.2%;

TABLE II: Echocardiogram results of patients with atrial fibrillation who underwent echocardiography during their hospital stay (n = 48).

Description	Mean ± SD	Median (25th,75th)	Reference value ¹⁰
IVSd	1.3 ± 1.8	1.0 (0.8;1.0)	0.6 - 1.1 cm
LVIDd	5.2 ± 1.1	5.1 (4.4;6.0)	3.8 - 5.8 cm
LVIDs	4.7 ± 5.0	4.0 (3.2;4.8)	2.0 - 4.0 cm
LVPWd	1.1 ± 1.0	0.9 (0.8;1.0)	0.6 - 1.1 cm
LVEF	49.0 ± 13.2	50.0 (35.0;60.0)	52% - 75%
LA diameter	4.5 ± 0.8	4.4 (4.0;5.1)	3.0 - 4.0 cm
RVOT diameter	4.2 ± 4.7	3.2 (2.7;4.0)	1.0 - 5.0 mm
LA area	28.4 ± 10.5	27.9 (22.1;34.3)	≤ 20.0 cm ²
RA area	23.0 ± 7.1	21.7 (18.7;27.7)	≤ 18.0 cm ²
MV EA	0.9 ± 0.3	0.9 (0.8;1.1)	< 1.3 m/s
E/e'	13.7 ± 8.2	11.8 (8.2;14.7)	< 8.0 normal > 15.0 dysfunction
LVOT VTI	14.7 ± 5.2	14.4 (10.7;17.1)	18.0 - 22.0 cm
TRPG	28.0 ± 12.1	27.8 (22.3;36.6)	17 - 57 mmHg
RAP	9.8 ± 5.6	10.0 (5.0;15.0)	2.0 - 6.0 mmHg
RVSP	40.2 ± 13.1	41.0 (28.0;51.5)	15 - 25 mmHg

IVSd: Interventricular septum thickness at end diastole, LVIDd: left ventricular internal diameter end diastole, LVIDs: left ventricular internal diameter end systole, LVPWd: left ventricular posterior wall end diastole, LVEF: left ventricular ejection fraction, LAD: left atrial diameter, RVOT: right ventricular outflow tract wall thickness, LAA: left atrial area, RAA: right atrial area, MV EA: mitral valve inflow, E/e': E velocity, early mitral inflow velocity to early diastolic mitral annulus velocity ratio, LVOT VTI: left ventricular outflow tract velocity time integral, TRPG: tricuspid regurgitation maximum pressure gradient, RAP: right atrial pressure, RVSP: right ventricular systolic pressure.

TABLE III: Patients qualifying for anticoagulation (n = 191) receiving either anticoagulation / antiplatelet therapy and thromboembolic risk determined by INR.

	CHA2DS2-VASc	Warfarin	Warfarin + Antiplatelet	Antiplatelet only	INR on OAC	INR on OAC	
						mean ± SD	INR < 2 % (n) mean ± 4SD
All	80.3 (192)	65.1 (125)	49.7 (95)	18.8 (36)	2.2 ± 1.3	48.9 (65/133) 1.4 ± 0.3	21.1 (28/133) 4.1 ± 1.5
Males ≥ 1	77.9 (88)	62.3 (55)	59.1 (52)	19.3 (17)	2.2 ± 1.5	57.6 (34/59) 1.4 ± 0.3	20.3 (12/59) 4.4 ± 2.1
Females ≥ 2	83.2 (104)	67.3 (70)	50.9 (53)	18.3 (19)	2.3 ± 1.1	41.2 (31/74) 1.3 ± 0.3	21.6 (16/74) 3.9 ± 1.9

Antiplatelet includes aspirin or clopidogrel only as well as dual antiplatelet (dual AP) with aspirin and clopidogrel, INR: international normalised ratio, OAC: oral anticoagulation included warfarin and rivaroxaban, SD: standard deviation, TTR: time in therapeutic range.

n = 7) and xanthine oxidase inhibitors (allopurinol 2.0%; n = 5).

DISCUSSION

Data analysis yielded an AF prevalence which is in keeping with published international data^(1,2,5,6) but slightly lower than what was found among cardiology admissions in the Heart of Soweto (HoS) study and recent reviews of data from low-middle income countries, including sub-Saharan Africa.⁽⁷⁻⁹⁾ The clinical profile (age, gender distribution) of patients with AF in this cohort is similar to high income populations, where there has been an

increased prevalence among older patients and patients with comorbidities.^(2,5,6) A less pronounced female predominance was seen in this study, compared to other.⁽⁷⁻⁹⁾

Congestive cardiac failure (CCF), cardiomyopathies, and VHD are independently associated with AF and are present in more than a third of patients with AF.^(5,6) VHD specifically is associated with less favorable outcomes and increased stroke risk.^(1,2,5,6) The prevalence of MS and mechanical valves in this cohort was lower than reported in the HoS study.⁽⁷⁾ However, this is not surprising as this study reports on all patients with AF while the HoS study

TABLE IV: Management of patients with AF (n = 238).

Drug category	Drug	% (n)	Dose (mg) Median (min, max)
Anticoagulation	Warfarin	52.5 (125)	5 (5, 10)
	Rivaroxaban	1.30 (3)	15 (15, 20)
	Clexane	2.90 (7)	80 (40, 80)
Antiplatelet	Clopidogrel	9.70 (23)	75 (75, 150)
	Aspirin	31.1 (74)	150 (150, 750)
Rate control	Carvedilol	20.2 (48)	12.5 (3.125, 25)
	Atenolol	45.0 (107)	50 (25, 150)
	Digoxin	7.60 (18)	0.25 (0.125, 0.25)
	Verapamil	1.70 (4)	100 (40, 120)
Antiarrhythmic drugs (AAD)	Flecainide	0	-
	Sotalol	0	-
	Amiodarone	3.80 (9)	200 (200, 200)
Non-AAD with antiarrhythmic benefit	Enalapril	50.4 (120)	10 (2.5, 25)
	Losartan	5.90 (14)	50 (5, 50)
	Simvastatin	47.1 (112)	20 (5, 80)
	Spirolactone	15.1 (36)	25 (25, 80)
Treatment of cardiac risk factors and comorbidities	Hydrochlorothiazide	6.70 (16)	12.5 (12.5, 25)
	Furosemide	45.0 (107)	40 (20, 120)
	Metformin	12.6 (30)	850 (500, 1 000)
	Insulin	2.90 (7)	50 (20, 50)
	Lansoprazole	13.9 (33)	20 (20, 40)
	Amlodipine	15.1 (36)	10 (5, 10)

looked at patients referred to a cardiology service.

Patients in this cohort had similar comorbidities to those seen in high-income countries, and included hypertension, DM, obesity, and CKD. Associated lifestyle risk factors such as notable alcohol use and smoking were also common, highlighting the need for treatment and control of comorbidities as well as lifestyle changes.

The 2020 ESC guidelines, and the more recent 2024 update, provide an excellent framework for the approach to and management of patients with AF. The “CC to ABC” in the 2020 guidelines is a comprehensive approach to better outcomes in patients presenting with AF, including guidelines to confirm and characterise AF, assess the need for and initiate OAC, achieve better symptom control and aggressive management of comorbidities. The importance of a shared decision making process with the patient is also highlighted.⁽²⁾

All the patients in this study had clinical atrial fibrillation diagnosed on a 12 lead ECG. Characterising AF in this cohort was difficult due to reliance on somewhat incomplete patient record keeping.

Patients in this cohort had a significant thromboembolic risk that was not well managed with anticoagulation. Although the prevalence of stroke was lower in this group than what is reported in international literature, especially in high-income countries,^(1,2,5,6) the thromboembolic risk was high based on the calculated CHA2DS2-VASc score. Anticoagulation is recommended irrespective of the type of clinical AF. In addition, the HAS-BLED score should be calculated before commencement of anticoagulation therapy.⁽²⁾ These assessments should be formal, structured and documented and those with increased risk should be assessed and followed up more frequently.⁽²⁾ The assessment and documentation of both these scores were poor in the current study and was calculated by the principal author from the available data.

The mean INR for our cohort falls within the target therapeutic range for patients receiving VKAs. However, almost half had subtherapeutic levels, which increases the risk for stroke and some had levels associated with an increased risk of bleeding. These varied INR levels could be due to the fact that these values may have been taken close to the initiation of treatment, when values are known to still be unstable, or patient factors such as not taking the medication as prescribed, not adhering to dietary guidelines, and poor compliance with regular monitoring of INR levels. Due to this variation in INR values, the TTR was

also calculated. This is a popular way of reporting management of patients on anticoagulation with VKAs and is very useful as a quality indicator at INR clinics. The TTR in this study was significantly lower (26.5%) than reported in bigger trials (65% ENGAGE-AF, 64% RE-LY, 62% ARISTOTLE and 58% ROCKET AF).⁽³⁾ The ESC recommends patients with a TTR < 70% be switched to NOAC therapy, or to improve TTR on VKA with intense counselling and more frequent INR checks.⁽²⁾ In our setting, the low number of patients found to be in the therapeutic range could be overcome by appropriate and timely adjustment of the warfarin dose, patient and physician education, and the possibility of prescribing NOAC medication. NOACs have been shown to be non-inferior to and safer than VKA and are recommended specifically before and after cardioversion.^(1,2) Nevertheless, in this setting, the NOACs remain an expensive alternative, which has precluded their use. A formal cost analysis and evaluation of TTR for patients on warfarin is recommended to further evaluate the cost-effectiveness and potential clinical benefit of making NOACs more readily available to state patients. This is an area that should be researched, especially now that there are generic NOACs available at a lower cost.

Patients in this cohort were still commonly receiving antiplatelet medication and, in many cases, patients received only aspirin or dual antiplatelet therapy when anticoagulation was clearly indicated. A high percentage of patients also received antiplatelet treatment as an adjunct to OAC. In terms of AF management, the use of antiplatelet agents alone is ineffective and is not recommended to prevent thromboembolism. The combination of anticoagulation and antiplatelet agents is not recommended for routine management of AF due to the increased risk of bleeding and intracranial haemorrhage.⁽²⁾ However, it may be required in patients who had a previous stroke or recent myocardial infarction. Due to the retrospective nature of the study and reliance on medical records, there is no certainty whether this was prescribed in the setting of previous CVA on warfarin or due to a recent myocardial infarction or just incorrectly prescribed.

Left atrial (LA) appendage occlusion (LAAO) is an alternative to OAC in patients where these drugs are contraindicated, due to the decreased bleeding risk with this strategy. In our cohort, no patients were referred for LAAO. This may be due to the fact that this remains an expensive intervention which requires trained operators to perform. The procedure has only been offered at TBH since November 2016 and the low number of patients referred may also be due to lack of physician awareness.

The ESC recommends that patients are treated with adequate rate and rhythm control strategies and highlights that patient preference as well as modification of lifestyle factors are paramount in order to improve outcome.⁽²⁾ Although rate control was achieved in half of the patients in this cohort, poor rhythm control efforts were noted. Rate control was achieved with the prescription of mostly beta blockers such as atenolol and carvedilol, achieving target or lenient ventricular rates as described in the RACE II study (< 110 bpm),⁽⁴⁾ well within ranges

reported by studies in other sub-Saharan African countries (65% – 95%).⁽⁸⁾

Rhythm control can be achieved by cardioversion, antiarrhythmic medication or catheter ablation. Antiarrhythmic medication (e.g. amiodarone) may be given for rhythm control in order to improve quality of life^(1,2,5,6) but it was seldom used in this study and other antiarrhythmic drugs such as flecainide and sotalol were not used at all. The low use of these drugs can be improved on in this setting to enhance guideline-directed management.⁽²⁾ Other options when medical treatment fails, such as cardioversion and catheter ablation, were not noted in this study. AF catheter ablation only became available at TBH from October 2020 and would explain why this was not used, but it remains unclear why cardioversion was not documented in a single patient. This data might be inaccurate as we do not have information on what type of AF the patients had or whether they had previously been cardioverted or referred later, outside the window that we evaluated, as such information was limited by the retrospective nature of this study. Cardioversion is safe, easy, and is recommended as first-line treatment for paroxysmal and persistent AF without major cardiac risk factors and after failed or intolerant use of class I/III antiarrhythmic drugs for patients who have had their coagulation risk assessed.⁽²⁾

Non-antiarrhythmic drugs with antiarrhythmic benefit such as enalapril, simvastatin and spironolactone were given frequently. However, most of the patients received these drugs as part of treating other comorbidities and not to improve the treatment of AF, nevertheless providing dual benefit.

The ESC 2020 guidelines focus on risk factor management and lifestyle changes in order to decrease the prevalence of comorbidities in patients with AF.^(1,2) These include guidelines on obesity and weight loss, using alcohol and caffeine in moderation, and regular physical activity.

Documentation of lifestyle counselling was poor, possibly due to the retrospective nature of the study. A strong emphasis on physician education, patient counselling, adherence and inclusion of the multidisciplinary team in management of patients with AF is recommended to achieve a patient-centred, holistic and consistent approach, leading to improved quality of life and longevity in patients with AF.

LIMITATIONS

The authors acknowledge the limitations of a retrospective study design. This includes missing important data that was not captured, and reliance on the accuracy of information in medical notes and reports. Other significant limitations of this study besides those inherent to a retrospective record review include the fact that this record review reflects a “snapshot” in the patients’ clinical course. Further prospective data on the patients’ management and outcome would provide valuable information. The very low number of echocardiograms recorded is also disappointing. The reasons for this remain unclear. It is possible

that these patients may have had echocardiogram performed outside of the study period that were not recorded in the clinical notes or available on Echo Pack®. Although it is a strength of this study that we included all patients admitted to hospital in the time period and not only those admitted to cardiology service, a clear distinction of the number of patients in each department would have provided interesting data and added value.

CONCLUSION

This study showed an AF prevalence which is in keeping with international data. The patient profile in our cohort matched that of high-income countries, with a similar age, gender and comorbidity profiles.

The striking deviation from guideline-directed therapy in our cohort was the poor prescription of OAC in patients where it was clearly indicated, and the low number of patients having INR values within the therapeutic range on VKAs. In addition to this, the wide use of antiplatelet agents deviates significantly from current guidelines and needs to be addressed. While rate and rhythm control are both acceptable strategies to treat AF symptoms and preserve left ventricular function, rhythm control is recommended for improved symptom control and quality of life. The low uptake of rhythm control strategies in this study provides room for improvement in their management. Physician education and early referral to the cardiology service could address both of these problems. It is also standard practice that all newly-diagnosed patients with AF should undergo echocardiography, which was not the case in the present study where only patients admitted to cardiology had echocardiography. Patient preference and inclusion in the management plan should also be addressed as well as improvement in adequate documentation of screening, assessment, risk-factor stratification and management of patients with AF.

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The diastolic inflow and longitudinal movement of the heart in the African full-term newborn infant

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INTRODUCTION

Accurate diagnosis of heart disease using echocardiography depends on establishing normal values of cardiac dimensions.⁽¹⁾

Echocardiography is a cost-effective, non-invasive diagnostic modality for the detection of both structural and functional heart disease in all age groups.^(2,3)

However, there is little information regarding diastolic function of the neonatal heart and even less data about the African newborn infant.

Cantinotti and Lopez, et al. conducted a literature search and discovered there were only 33 published studies evaluating diastolic function in children,⁽⁴⁾ but most have small sample sizes with few neonatal subjects.

The diastolic function patterns that are reproducible in older children cannot be extrapolated to neonates as neonates have much smaller cardiac chambers, a faster heart rate, and a rapidly

ABSTRACT

Introduction: Echocardiography is essential in the assessment of systolic and diastolic left ventricular (LV) function. The diastolic component of the cardiac cycle which is a crucial aspect of cardiac output has been less researched in the neonatal population.

Aim: To determine normal echocardiographic references for diastolic inflow and longitudinal movement of both the left and right heart in healthy full-term Black African neonates.

Methodology: A descriptive, bidirectional study design was undertaken. Healthy African (Black) full-term newborn infants who met inclusion criteria were recruited at the Chris Hani Baragwanath Academic Hospital. Left and right ventricular (RV) systolic and diastolic function were assessed using various echocardiographic M-mode, flow Doppler and tissue Doppler measurements. Statistical analysis was performed using Excel and Statistica version 13.1. Normal ranges were calculated using means \pm standard deviations.

Results: Two hundred and ninety-two neonates (142 males, 152 females; median gestational age 39 weeks, range 37–42 weeks) were included in the study. Most subjects (175/292;60%) were born by caesarean section. Median body surface area was 0.20 m² (range 0.16–0.25 m²). Median weight was 3.12 kg (range, 2.5–4.43 kg). Median post-delivery age at echocardiography was 31 hours (range 12–216 hours). The following measurements (means \pm SD) were documented: LVEF and LVFS were 73.56% (\pm 8.93) and 40.34% (\pm 7.91) respectively. Mitral valve (MV) peak E = 0.58 m/s (\pm 0.113), MV peak A = 0.59 m/s (\pm 0.123), MV peak E/A ratio = 1.01 (\pm 0.21), MV E' = 0.058m/s (\pm 0.012), MV E/E' ratio = 10.38 (\pm 2.65), MV S' = 0.052 m/s (\pm 0.009) and LV Tei = 0.306 (\pm 0.139). Measurements pertaining to the RV function were: TAPSE = 7.51 mm (\pm 1.304), tricuspid valve (TV) peak E = 0.512 m/s (\pm 0.126), TV peak A = 0.616 m/s (\pm 0.127), TV E/A = 0.845 (\pm 0.199), TV E' = 0.079 m/s (\pm 0.021), TV E/E' ratio = 6.78 (\pm 2.02), TV S' = 0.071 m/s (\pm 0.045) and RV Tei = 0.283 (\pm 0.132).

Conclusion: This large study established normal reference values for diastolic function and longitudinal systolic and diastolic movement of the heart in healthy full-term African neonates using echocardiography.

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changing physiological pattern particularly in the early neonatal period.⁽⁴⁾ This lack of diastolic function data in the healthy neonate offers an opportunity to establish normal values that can be used in the evaluation of myocardial function of neonates with heart disease, particularly in the African population.

Several studies have established that ethnicity is a significant determinant of cardiac chamber size and therefore ethnic-specific reference values for echocardiographic interpretations should be considered.⁽⁵⁻⁹⁾ Although when Lopez, et al. compared the paediatric heart network (PHN) database Z-scores to previously published Z-scores found that models based on body surface area (BSA) were not affected by age, sex, race, or ethnicity.⁽¹⁰⁾ The disregard for ethnic differences may have consequences if management decisions hinge on normative values based on other population groups.^(8,9,11)

This study is therefore the first to report on normal values for systolic and diastolic function in healthy Black African neonates.

METHODS

The echocardiographic data were acquired with consent from each mother during the study "Human Research Ethics Committee (Medical)" on 26 May 2017 – Ethics Clearance certificate no. M170524.

Three hundred and twenty-five healthy neonates aged 12 hours or more were recruited in the post-natal wards of Chris Hani Baragwanath Academic Hospital, which is an African tertiary care centre situated on the outskirts of Johannesburg. The hospital serves the indigent population of Soweto, southern Gauteng, and the North West province. The final sample size was reduced to 292, due to some participants not meeting the inclusion criteria. Participant identifiers were omitted and were replaced with a study number to maintain participant anonymity.

Qualifying criteria included healthy African newborn infants delivered by normal vertex (NVD) or caesarean section (C/S) with structurally normal hearts, who were full term, aged 12 hours and older before discharge, and had a birth weight of ≥ 2.5 kg.

Exclusion criteria comprised neonates who were older than 30 days, non-Africans (non-Black), congenital heart disease diagnosed echocardiographically, and a haemodynamically significant patent ductus arteriosus > 2 mm in diameter.

The following demographic data was collected from patient paper records: Date of birth, weight (kg), length (cm), gender (M/F), and gestational age in weeks.

Echocardiographic assessment

Echocardiographic parameters were acquired according to the American Society of Echocardiography Paediatric and Congenital Heart Disease Council guidelines 2010.⁽¹²⁾ Myocardial performance index was acquired according to Tei, et al.⁽¹³⁾

All images were recorded by a MV13-0034 Rev2: GE Healthcare Vivid E compact digital ultrasound console BT12 machine (General Electric, Milwaukee, United States) using a 5–6 MHz transducer.

Ejection fraction (EF) and fraction shortening (FS) was measured using M-mode with the standard leading-edge to leading edge technique.

Tricuspid annular plane systolic excursion (TAPSE), which is a determination of the longitudinal movement of the TV annulus, was measured using M-mode where the cursor was aligned perpendicular to the tricuspid lateral annulus in the apical 4 chamber view. The sample volume in the LV was measured at the tips of the MV leaflets (distal to the annulus) where early diastole / passive filling represented by the peak of the E wave and late filling was represented by the peak of the A wave. The RV measurements were done in the same fashion with the sample volume taken from the TV.

The pulsed wave tissue Doppler imaging (TDI) was measured in the apical 4 chamber view by taking a sample volume from the septal border of the mitral annulus and RV free wall of the tricuspid annulus. The velocities measured included the mitral valve septal E', A' and S' waves, and tricuspid valve lateral E', A' and S' waves and reflected the longitudinal movement of the mitral and tricuspid annuli during diastole and systole.

The myocardial performance index (MPI) of the RV and LV were calculated using measurements taken in the apical 4 chamber view for mitral and tricuspid valve inflow patterns, and the apical 5 chamber view for the aortic valve outflow Doppler envelope in the case of the LV MPI and the parasternal short axis view for the pulmonary valve outflow measurement in the case of RV MPI. The pulsed wave Doppler sample volume was set at 4 mm width. The sample volume was taken at the tips of the mitral valve / tricuspid valve leaflets in diastole, while the second sample volume was taken at the left ventricular outflow tract (LVOT), right below the aortic valve cusps. No angle correction was used.

Statistical analysis

All statistical analysis was performed using Excel and Statistica version 13.1. (TIBCO Statistica 2016). Raw data was captured on Excel. Normal ranges were calculated using means \pm standard deviations. Categorical data were expressed in frequencies and percentages. Confounding factors were fitted to determine the effects on the recorded variables using multiple regression analysis. A p-value of < 0.05 was considered statistically significant. Z-scores were also calculated for the variables. The Shapiro-Wilk test was used to assess the normality of distribution; a probability value of < 0.05 was considered to not be normally distributed. Exploratory statistical testing for normality of the measured data was done using the Breusch-Pagan and White test to check for the presence of heteroscedasticity. Intraclass correlation coefficient (ICC) was used to analyse the reliability between the interraters.

Reproducibility

Inter-observer and intra-observer bias were analysed. Data from 131 echocardiographical studies were re-analysed in a blinded fashion by a second observer. The inter-observer variability was calculated using the ICC.

RESULTS

Demographic data

Two hundred and ninety-two (n = 292) neonates met the inclusion criteria and participated in the research. The gender distribution was almost equal with a slight female preponderance (Table I). There were 142 (49%) male and 150 (51%) female neonates who participated in the study (Table I). The gestational

TABLE I: Baseline demographic and echocardiography characteristics (n=292).

Variable	n	Mean	Median	Minimum	Maximum	Std. Dev
Gender: Male	142					
Female	150					
Gestational age range (weeks)			39	37	42	
Neonatal age range (hours)			31	12	216	
Mode of delivery						
C/S	175					
NVD	117					
Birth weight (kg)		3.2	3.1	2.5	4.4	0.4
Birth length (cm)		50.5	50.0	40.0	60.0	3.1
BSA m ²		0.2	0.2	0.2	0.3	0.0
Age (hrs)		40.1	31.0	12.0	216.0	29.2
Variable	Valid N	Mean	Median	Minimum	Maximum	Std. Dev
Left Ventricle M-Mode						
LV EF%	291	73.6	74.0	51.0	95.0	8.9
LV FS%	291	40.2	40.0	24.0	65.0	7.9
Doppler measurements						
MV PEAK E (m/s)	292	0.583	0.585	0.290	0.900	0.113
MV PEAK A (m/s)	292	0.592	0.580	0.340	1.100	0.123
MV E/A RATIO	292	1.011	1.000	0.455	1.686	0.210
MV E' (m/s)	289	0.058	0.060	0.040	0.110	0.012
MV E/E' ratio	289	10.375	10.000	4.833	18.250	2.653
MV S' (m/s)	289	0.052	0.050	0.030	0.090	0.009
LV Tei	283	0.306	0.300	0.040	0.930	0.139
Right ventricle measurements M-mode						
TAPSE (mm)	152	7.5	7.5	4.8	11.4	1.3
Doppler measurements						
TV PEAK E (m/s)	226	0.512	0.495	0.260	1.060	0.126
TV PEAK A (m/s)	226	0.616	0.615	0.360	1.170	0.127
TV E/A RATIO	226	0.845	0.807	0.480	1.980	0.199
TV E' (m/s)	214	0.079	0.080	0.040	0.190	0.021
TV E/E' RATIO	214	6.783	6.424	2.786	15.800	2.016
TV S' (m/s)	215	0.071	0.070	0.030	0.700	0.045
RV Tei	205	0.283	0.260	0.020	0.730	0.132

n: number of participants, C/S: caesarean section, NVD: normal vertex delivery; KG: kilograms, CM: centimetre, BSA: body surface area; LV EF: left ventricular ejection fraction, LV FS: left ventricular fraction shortening. Std. Dev: standard deviation. MV peak E: mitral valve - early diastolic filling measured by pulsed Doppler, MV Peak A: mitral valve - late diastolic filling measured by pulsed Doppler, MV E/A: mitral valve - early diastolic filling / late diastolic filling ratio, TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI, MV E/E': mitral valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - aystolic wave representing peak myocardial systolic velocity at the septal MV annulus measured by TDI, LV Tei: myocardial performance index. TAPSE: tricuspid annular plane excursion; TDI TV E': tricuspid valve - peak myocardial velocity in early diastole measured by TDI, TV E/E': tricuspid valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus measured by TDI, RV Tei: myocardial performance index.

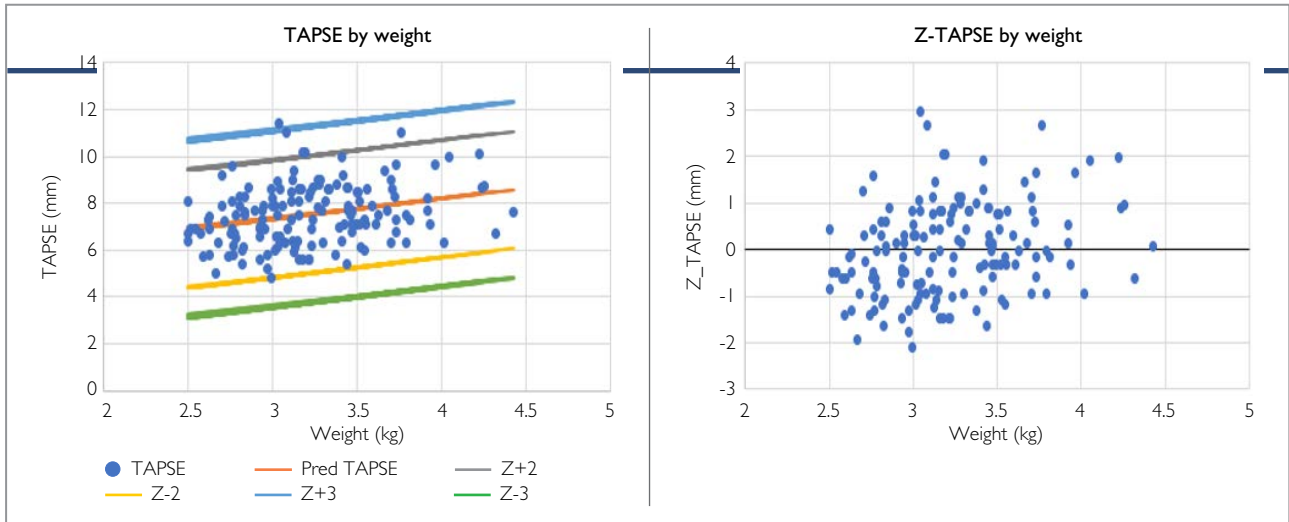


FIGURE 1: TAPSE scatterplots and Z-score boundaries.

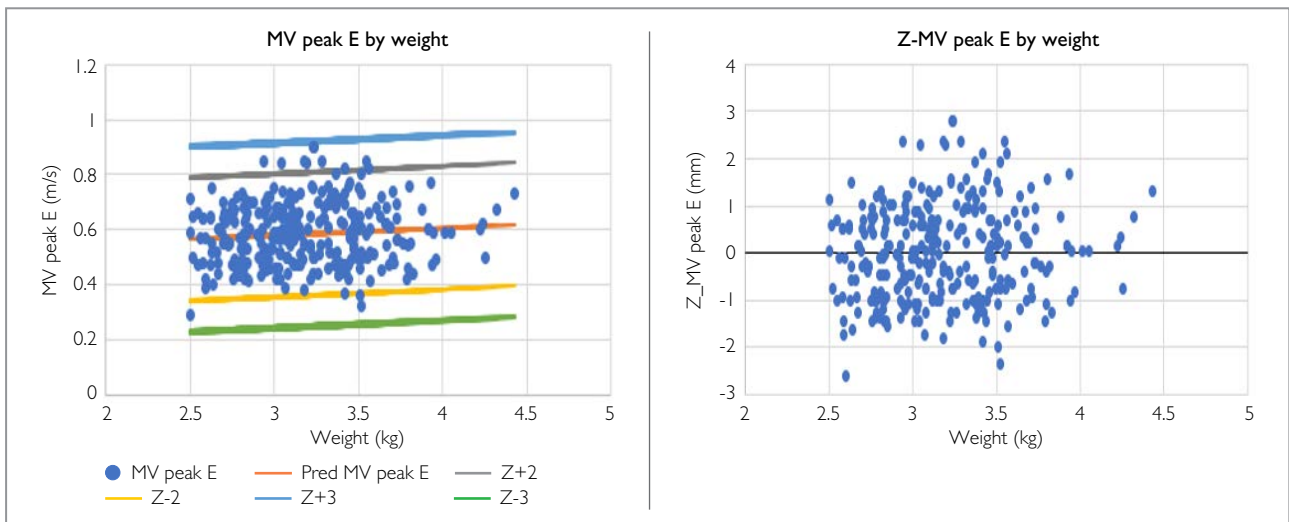


FIGURE 2: MV peak E scatterplot and Z-score boundaries.

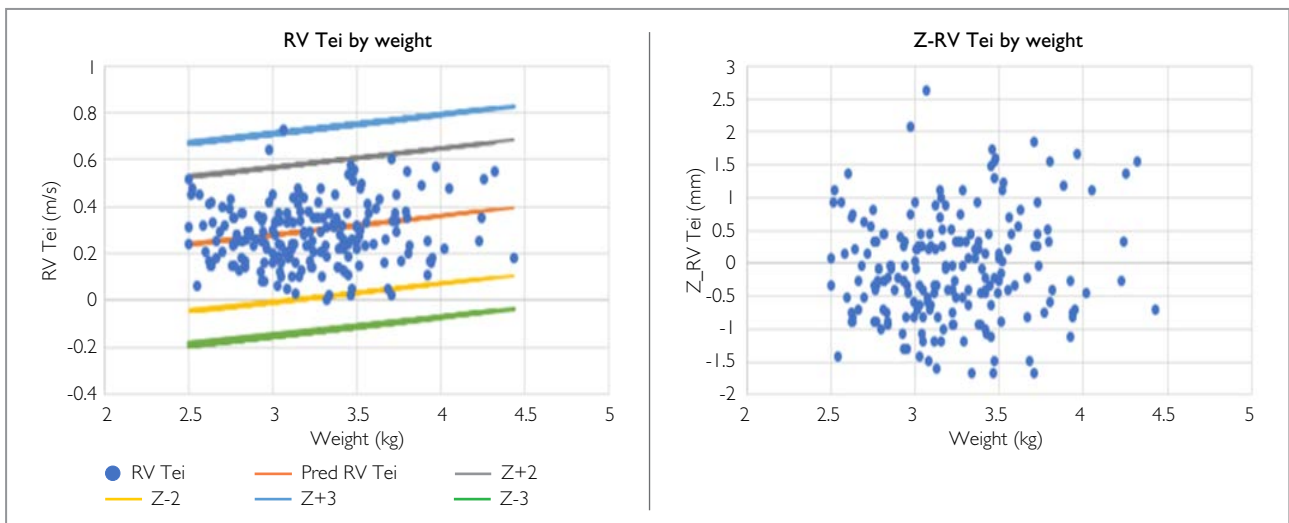


FIGURE 3: RV Tei scatterplot and Z-score boundaries.

TABLE II: Univariate regression analysis of confounding factors.

Variables	BW (kg)		BH (cm)		BSA		GA		MOD		Gender		Age	
	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value
LV EF%	-2.985	0.401	0.124	0.408	129.337	0.266	-0.047	0.912	1.693	0.115	0.407	0.698	0.020	0.275
LV FS%	-2.021	0.521	-0.275	0.383	97.879	0.342	-0.037	0.923	1.401	0.141	0.215	0.817	0.018	0.245
MV PEAK E	0.023	0.610	-0.001	0.888	0.836	0.035	0.007	0.197	0.006	0.663	-0.011	0.420	0.000	0.421
MV PEAK A	0.045	0.014	0.000	0.964	-0.283	0.858	-0.005	0.436	0.019	0.206	-0.023	0.110	0.000	0.489
MV E/A RATIO	-0.210	0.011	-0.008	0.342	5.274	0.052	0.020	0.049	-0.038	0.125	0.029	0.250	0.000	0.728
MV E'	-0.001	0.764	0.000	0.616	0.081	0.619	0.000	0.653	0.000	0.893	-0.002	0.290	0.000	0.675
MV E/E'	-0.034	0.974	0.025	0.812	6.849	0.843	0.067	0.599	-0.107	0.740	-0.105	0.739	0.005	0.339
MV S'	0.002	0.040	0.000	0.537	0.030	0.783	0.001	0.004	0.000	0.745	0.000	0.648	0.000	0.027
LV Tei	0.040	0.474	-0.002	0.722	-0.708	0.697	0.005	0.462	-0.004	0.826	-0.003	0.846	0.000	0.136
TAPSE	0.875	0.001	0.087	0.009	20.879	0.001	0.003	0.973	-0.020	0.930	-0.175	0.414	0.000	0.960
TV PEAK E	-0.037	0.492	-0.010	0.075	2.291	0.194	0.000	0.956	0.040	0.023	0.003	0.835	0.000	0.099
TV PEAK A	-0.005	0.918	-0.010	0.087	1.279	0.471	-0.011	0.096	0.033	0.064	0.003	0.844	0.001	0.017
TV E/A RATIO	-0.065	0.440	-0.002	0.856	2.293	0.417	0.018	0.099	0.022	0.442	0.013	0.636	0.000	0.683
TV E'	0.005	0.593	0.000	0.741	0.142	0.632	-0.002	0.109	-0.003	0.322	-0.003	0.360	0.000	0.405
TV E/E'	-0.912	0.292	-0.116	0.199	27.793	0.331	0.098	0.380	0.481	0.098	0.111	0.687	0.007	0.089
TV S'	-0.013	0.498	-0.001	0.657	0.377	0.562	-0.004	0.159	0.008	0.241	0.004	0.468	0.000	0.821
RV Tei	0.014	0.841	-0.009	0.226	2.540	0.277	0.004	0.706	-0.053	0.031	-0.031	0.178	-0.001	0.007

b: beta coefficient, BW: body weight, BH: birth length, BSA: body surface area, GA: gestational age, MOD: mode of delivery, AGE: age in hours. LV EF: left ventricular ejection fraction, LV FS: left ventricular fraction shortening, MV peak E: mitral valve - early diastolic filling measured by pulsed Doppler, MV Peak A: mitral valve - late diastolic filling measured by pulsed Doppler, MV E/A: mitral valve - early diastolic filling / late diastolic filling ratio, TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI, MV E/E': mitral valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - systolic wave representing peak myocardial systolic velocity at the septal MV annulus measured by TDI, LV Tei: myocardial performance index, TAPSE: tricuspid annular plane excursion, TV peak E: tricuspid valve - early diastolic filling measured by pulsed Doppler, TV peak A: tricuspid valve - late diastolic filling measured by pulsed Doppler, TV E/A: tricuspid valve - early diastolic filling / late diastolic filling ratio, TDI TV E': tricuspid valve - peak myocardial velocity in early diastole measured by TDI, TV E/E': tricuspid valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus measured by TDI, RV Tei: myocardial performance index, Std.Dev: standard deviation.

age ranged between 37–42 weeks (median = 39 weeks) (Table I). The neonatal age at the time of echocardiographical study ranged between 12 hours to 216 hours (median = 31 hours). According to mode of delivery, 175 (59.9%) of the sample was born via C/S, of whom 86 (29.5%) were females and 89 (30.5%) were males. There were 117 (40.1%) neonates who was born via NVD of whom 64 (21.9%) were females and 53 (18.1%) were males (Table I).

Population characteristics

The BSA for the study cohort ranged between a minimum of 0.16 m² and a maximum of 0.25 m² (median = 0.2 m²). The body weight (BW) ranged between a minimum of 2.5kg and a maximum of 4.43 kg (median = 3.12 kg) (Table I). One hundred and seven (36.6%) participants weighed between 2.5 kg–3 kg, 101 (34.6%) weighed between 3.1–3.4 kg and 84 (28.8%) weighed 3.5 kg and more.

Echocardiographic measurements

M-mode measurements

Left ventricular systolic function was assessed using EF and FS derived from M-mode measurements. Out of the 292 participants, 291 (99.65%) had LV EF% and LV FS%

measurements with LV EF% ranging from 51%–95% (mean, 73.56% and median 74%). LV FS% ranged from 24%–65% (mean, 40.3% and median, 40%) (Table I).

There was no correlation between LV EF (r = 0.029), LV FS (r = 0.027) and birth weight. Most (LV EF 96.6%, LV FS 95.5%) of the population clustered within the -2 and +2 Z-Score. TAPSE was used as a measure of right ventricular longitudinal systolic function. The TAPSE was determined in 152 participants, ranging from 4.8 mm–11.4 mm with a mean of 7.5 mm and a median of 7.5 mm (Table I). TAPSE displayed a weak to moderate positive correlation (r = 0,277), with birthweight. A scatterplot and predicted Z-score boundaries are shown in Figure 1.

Doppler measurements

The left heart

Doppler echocardiography was used to determine left ventricular diastolic function (Table I). The majority of the LV measurements showed no correlation with birth weight.

There was no correlation between MV peak E (r = 0.09) and birth weight. Most (96%) of the population plotted between the -2 and +2 Z-score (Figure 2).

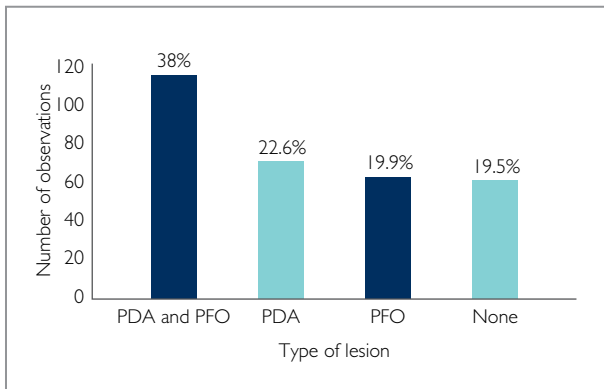


FIGURE 4: Cardiac findings.

The MV peak A ($r = 0.142$) showed a very weak positive correlation with weight. Most (95%) of the population plotted between the -2 and +2 Z-scores.

Most (MV E/A: 95% and MV E/E' 95%) of the population plotted between -2 and +2 Z-scores. LV Tei ($r = 0.035$) showed no correlation with weight.

The right heart

Doppler and tissue Doppler echocardiography were used to assess right ventricular diastolic function (Table I). The majority of the parameters did not show any correlation with birth weight except for TV E' ($r = 0.12$) and RV Tei ($r = 0.113$) which showed weak correlations.

RV Tei ($r = 0.113$) showed a very weak but positive correlation with birth weight. Most (99%) of the population plotted between -2 and +2 Z-scores (Figure 3).

Cardiac findings

A large number (235/80.5%) of neonates were found to have clinically insignificant expected cardiac lesions (Figure 4). The most common findings consisted of the patent ductus arteriosus (PDA) and patent foramen ovale (PFO). There were (111/38%) with PDA and PFO (66/23%) with PDA only and (58/20%) with PFO only. No PDA or PFO was present in the remaining (57/19.5%) patients.

Left and right heart systolic and diastolic parameters displayed for use in the clinical setting.

Left heart and right heart measurements for clinical use are displayed in Table III and Table IV, standard deviation / Z- scores of -3 and +3 are included.

Effects of confounding factors

In the univariate regression analysis, birth weight (BW), birth length (BL), body surface area (BSA), gestational age (GA), mode of delivery (MOD), gender and age in hours were independent variables (predictor variables) as shown in Table I. MV peak A ($p = 0.014$), MV S' ($p = 0.040$) and TAPSE ($p = 0.001$) showed a

significant increase when there was a corresponding increase in birth weight, whereas MV E/A ratio ($p = 0.011$), showed a significant decrease when there was an increase in weight. TAPSE ($p = 0.009$) also showed a significant increase with an increase in BL. MV peak E ($p = 0.035$) and TAPSE ($p = 0.001$) showed a significant increase with an increase in BSA. MV S' showed a significant increase in velocity with an increase in gestational age. TV peak E ($p = 0.023$) showed an increase in the C-section group, whereas RV Tei ($p = 0.031$) showed a significant decrease in the C-section group. Gender did not affect any of the variables. MV S' ($p = 0.027$), TV peak A ($p = 0.017$) and RV Tei ($p = 0.007$) showed a significant increase with an increase in age in hours post-delivery (Table II).

Inter-observer variability

Inter-observer variability was calculated using ICC. Measurements were performed by an independent, experienced paediatric cardiologist and a senior cardiac technologist (the researcher) and compared. Most of the measurements between the observers showed a significant strong similarity / relationship, except for MV E/A ratio, LV Tei, and TV S' which had a R-value of less than moderate similarity / relationship.

DISCUSSION

The study aimed to establish reference values for systolic and diastolic function in term newborn infants of African ethnicity. Normal values are required to interpret the presence of abnormalities. This may indicate pathology or changes that may be positive or negative responses to treatment.⁽¹⁾

The strength and limitations of published paediatric nomograms for echocardiographic functional parameters have not been critically evaluated, especially in the neonatal population⁽⁴⁾ and in particular, the African neonatal population. Regardless of the importance of these measurements in practice, an all-inclusive set of normative data to assist in the evaluation of myocardial function of neonates in the sub-Saharan region has not been established to now.^(14,15)

The definition of what is “normal” varies widely according to age, BSA, gender, and race. These changes may be more apparent in paediatrics as cardiac chamber dimensions change with somatic growth.^(5,15) Therefore, it is imperative to normalise echocardiographic measurements according to body size.

Several echocardiographic references have been published, but the majority are derived from North America and the European populations. In addition, these study cohorts from which most of the current data are obtained are mostly derived from Caucasian and some from Asian populations, which may not apply to other populations. Several studies have established that ethnicity is a significant determinant of cardiac chamber sizes. Therefore, ethnic-specific reference values for echocardiographic interpretations are recommended.^(4-9,15) Furthermore, study methodology varies widely amongst publications. Many studies have small sample sizes, heterogeneous methodologies, and the

TABLE III: Left heart systolic and diastolic measurements for clinical use.

Predicted values (mean ± SD) variables expressed by weight			
Variables	Weight group 1 2.5–3 kg	Weight group 2 3.1–3.4 kg	Weight group 3 = > 3.5 kg
+3 SD	101.881	99.103	100.133
+2 SD	92.354	90.592	91.384
LV EF%	73.300	73.572	73.886
-2 SD	54.246	56.551	56.387
-3 SD	44.720	48.040	47.638
+3 SD	65.099	62.911	63.971
+2 SD	56.742	55.358	56.152
LV FS%	40.028	40.253	40.514
-2 SD	23.314	25.148	24.875
-3 SD	14.957	17.596	17.056
+3 SD	1.994	2.118	1.972
+2 SD	1.781	1.867	1.772
LA/AO RATIO	1.356	1.364	1.373
-2 SD	0.931	0.861	0.974
-3 SD	0.718	0.610	0.775
+3 SD	0.876	0.949	0.940
+2 SD	0.775	0.827	0.826
MV PEAK E (m/s)	0.572	0.583	0.597
-2 SD	0.370	0.340	0.367
-3 SD	0.268	0.218	0.253
+3 SD	0.889	0.970	1.026
+2 SD	0.784	0.844	0.889
MV PEAK A (m/s)	0.574	0.592	0.614
-2 SD	0.364	0.341	0.339
-3 SD	0.259	0.215	0.201
+3 SD	1.672	1.655	1.593
+2 SD	1.455	1.440	1.396
MV PEAK E/A ratio	1.021	1.011	1.000
-2 SD	0.587	0.582	0.604
-3 SD	0.370	0.367	0.406
+3 SD	0.092	0.109	0.098
+2 SD	0.081	0.092	0.085
MV E' (m/s)	0.058	0.058	0.059
-2 SD	0.035	0.025	0.033
-3 SD	0.024	0.008	0.020
+3 SD	17.898	18.373	18.888
+2 SD	15.340	15.709	16.114
MV E/E' ratio	10.222	10.381	10.567
-2 SD	5.104	5.052	5.019
-3 SD	2.546	2.388	2.245
+3 SD	0.079	0.078	0.075
+2 SD	0.069	0.069	0.068
MV S' (m/s)	0.051	0.052	0.053
-2 SD	0.032	0.034	0.039
-3 SD	0.023	0.026	0.031
+3SD	0.697	0.703	0.827
+2 SD	0.565	0.571	0.656
LV Tei	0.301	0.306	0.313
-2 SD	0.037	0.042	-0.031
-3 SD	-0.094	-0.090	-0.202

LV EF: left ventricular ejection fraction (%), LV FS: left ventricular fraction shortening (%), LA/AO ratio: left Atrium / Aorta ratio MV peak E: mitral valve - early diastolic filling, measured by pulsed Doppler (m/s), MV peak A: mitral valve - late diastolic filling, measured by pulsed Doppler (m/s), MV E/A: mitral valve - early diastolic filling/late diastolic filling (ratio), TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI (m/s), MV E/E': mitral valve - early diastolic filling /peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - systolic wave representing peak myocardial systolic velocity at the septal MV annulus, measured by TDI (m/s), LV Tei: myocardial performance index.

TABLE IV: Right heart measurements for clinical use.

Predicted values (mean ± SD) variables expressed by weight			
Variables	Weight group 1 2.5–3 kg	Weight group 2 3.1–3.4 kg	Weight group 3 = > 3.5 kg
+3 SD	10.431	11.870	11.492
+2 SD	9.333	10.405	10.304
TAPSE	7.136	7.475	7.928
-2 SD	4.940	4.544	5.552
-3 SD	3.842	3.079	4.364
+3 SD	0.813	0.903	0.947
+2 SD	0.711	0.772	0.804
TV PEAK E	0.507	0.512	0.518
-2 SD	0.302	0.251	0.232
-3 SD	0.200	0.121	0.089
+3 SD	1.052	1.035	1.147
+2 SD	0.922	0.912	0.988
TV PEAK A	0.663	0.666	0.670
-2 SD	0.403	0.420	0.351
-3 SD	0.273	0.296	0.192
+3 SD	1.435	1.503	1.510
+2 SD	1.257	1.299	1.300
TV PEAK E/A	0.901	0.891	0.879
-2 SD	0.545	0.483	0.459
-3 SD	0.367	0.279	0.248
+3SD	0.136	0.134	0.166
+2 SD	0.116	0.116	0.138
TV E' (m/s)	0.076	0.079	0.082
-2 SD	0.036	0.042	0.026
-3 SD	0.016	0.023	-0.002
+3 SD	14.260	14.667	16.052
+2 SD	12.133	12.430	13.383
TV E/E' ratio	7.880	7.955	8.044
-2 SD	3.626	3.480	2.706
-3 SD	1.499	1.242	0.036
+3 SD	0.112	0.114	0.120
+2 SD	0.285	0.224	0.234
TV S' (m/s)	0.115	0.118	0.122
-2 SD	-0.054	0.012	0.009
-3 SD	0.030	0.029	0.024
+3 SD	0.647	0.789	0.994
+2 SD	0.518	0.624	0.774
RV Tei	0.261	0.294	0.334
-2 SD	0.003	-0.036	-0.106
-3 SD	-0.126	-0.201	-0.326

TAPSE: tricuspid annular plane excursion (mm), TV peak E: tricuspid valve - early diastolic filling measured by pulsed Doppler (m/s), TV peak A: tricuspid valve - late diastolic filling, measured by pulsed Doppler (m/s), TV E/A: tricuspid valve - early diastolic filling / late diastolic filling ratio, TDI TV E': tricuspid valve - peak myocardial velocity in early diastole, measured by TDI (m/s), TV E/E': tricuspid valve - early diastolic filling / peak myocardial velocity in early diastole (ratio) TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus, measured by TDI (m/s), RV Tei: myocardial performance index.

use of variable body size parameters and regression equations, which have resulted in a wide range of Z-scores for a single measurement.^(14,15)

This study aimed to address the gap in the lack of global cardiac function nomograms for neonates in the sub-Saharan African region. To our knowledge, the study represents the first such study from the sub-Saharan region showing normal values for diastolic inflow and longitudinal movement of the full-term neonatal heart. The study population included 292 African (Black) neonatal participants and thus represents the largest studied neonatal population to date.

Few previous studies included neonatal sex and mode of delivery (Supplementary Table I). Male neonates were predominant in the other studies, whereas in our study, females were dominant.⁽¹⁶⁻¹⁸⁾ Our study also showed a higher number of C/S deliveries than NVDs than the other studies.⁽¹⁶⁻¹⁸⁾ The need for C/S delivery depends on complications experienced by the mother during delivery, parents' choice, or the obstetricians' experience. Another reason could be that Chris Hani Baragwanath Hospital is a tertiary hospital where mothers in labour are admitted following referral from other centres for complications for which a C/S may be required.

Neonatal age varied widely amongst studies; 4 studies enrolled neonates who were 24 hours of age post-delivery,^(16,17,19,20) 2 studies enrolled neonates who were between 1–7 days of age post-delivery,^(18,21) and 4 studies were undertaken between zero days to just less than a month post-delivery. The number of hours post-delivery was not specified.⁽²²⁻²⁴⁾ The majority (an average of 7 studies) of the neonatal studies indicated that a study limitation was the small sample size of the study population.

Our study cohort numbered 292 and enrolled neonates with a mean age of 40.1 hours and a median of 31 hours post-delivery.

Overbeek, et al., Abushaban, et al., and Cantinotti, et al. demonstrated that BSA, body weight, and gestational age correlated well with the cardiac measurements but concluded that it was better to present neonatal measurements in relation to body / birth weight since the neonatal BSA range is small and varies slightly when compared to older and bigger subjects.⁽²⁵⁻²⁷⁾

An increase in birth weight in the current study was associated with a significant increase in certain left heart measurements (MV peak A, MV S'), and a significant increase in TAPSE. Only the MV S' velocity showed a very small but significant increase with gestational age. There was little to no correlation of cardiac function measurements with body size (weight, length, and BSA). The C/S group showed a significant increase in the TV peak E velocity whereas the RV Tei showed a decrease in the C/S group, there was no valid explanation that could be found which could explain the above. Not all studies made a comparison between mode of delivery and cardiac function differences, so it is difficult to compare the similarities.

M-mode

Ejection fraction (EF) and fractional shortening (FS)

Normal values for linear LV function using M-mode have been established in children, with FS reported to be 28%–46%, and EF 56%–78%.^(28,29) This study documented M-mode FS as mean: 40.25% and EF mean: 73.56% in neonates which is similar to previously published normal values (Supplementary Table II).^(18,22)

The disadvantage of M-mode is that one assumes a cylindrical shape of the LV, and if the LV function is reduced the estimation of FS can be under- or over-estimated.⁽³⁰⁾

In addition, if the M-mode cursor is not placed correctly over the myocardium, errors in measurement may also result.⁽²⁹⁾ The LV shape and consequently the calculation of M-mode derived parameters may be skewed in the presence of congenital heart defects (CHD), change in loading conditions (preload and afterload), and may also be affected by RV dysfunction which causes a change in the shape of the LV because of ventricular interdependence.⁽²⁹⁾

Tricuspid annular plane systolic excursion (TAPSE)

While the physiological significance of the right ventricle is often undervalued, it is crucial to assess its function in various diseases such as pulmonary hypertension to predict prognosis.⁽³⁰⁾

TAPSE is an important measurement of the longitudinal function of the right ventricle since the majority of the right ventricle ejection depends on the longitudinal contraction of the right ventricular myocardium.^(24,31,32) Normal ranges of TAPSE have been determined for children.^(24,31,32) However, there are no established reference values for neonates and children in the sub-Saharan Africa. The TAPSE values in our study ranged from 4.8 mm–11.4 mm with a mean of 7.5 mm (Table I); lower than those described in previous studies (Supplementary Table II).^(23,24) There was a significant positive correlation between TAPSE and weight, length, and body surface area, most likely due to an increased excursion of the tricuspid valve annulus in a bigger heart in a bigger neonate.^(23,24)

Pulsed Doppler

Non-invasive pulse Doppler measurements of transmitral flow have been widely used for assessment of left ventricular relaxation abnormalities in all age groups including neonates.⁽¹⁸⁾ In this study the mean mitral valve (MV) peak E velocity (0.583 m/s) was slightly less than the mean MV peak A velocity (0.592 m/s) with a MV E/A ratio of 1.01. The mean tricuspid valve (TV) peak E was 0.51 m/s, the TV peak A was 0.61 m/s, with a TV E/A ratio of 0.845. MV peak E velocity increased with an increase in the body surface area, while the MV peak A velocity seemed to decrease with increasing BSA, although not significant. MV peak E and MV peak A velocities were measured to be marginally higher than other publications (Supplementary Table III).^(17-19,22)

There was some variability regarding the ratio of MV E to A velocities across the various studies (Supplementary Table III) which may be explained by the heterogeneity amongst the studies such as the smaller patient numbers in some studies as well as the differences in the age of the neonates at the time of data acquisition.^(17,18,20-22) The cardiovascular system of the neonate undergoes dramatic changes within the first few hours of birth from a high pulmonary vascular resistant dominance to a systemic vascular resistance dominance which persists throughout life. These haemodynamic changes may explain why⁽²²⁾ the MV E velocity was the dominant velocity compared to the other studies.^(17,18,20-22) This is reflective of a higher systemic vascular resistance state of the neonate at an older age.⁽³³⁾

TV peak E velocity showed a significant positive relationship with delivery by C/S.⁽³⁴⁾ The higher TV E velocity may reflect an element of diastolic dysfunction associated with a less compliant RV. The risk of respiratory distress secondary to transient tachypnea of the newborn, surfactant deficiency and pulmonary hypertension are increased in neonates after delivery by C/S and may explain some of the differences according to the mode of delivery.⁽³³⁾ TV peak A velocity showed a positive significant relationship with age in hours post-delivery. This demonstrates that the compliance of the RV increases with age.⁽³⁵⁾

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is used to analyse longitudinal movement and function as well as diastolic function of both ventricles which is preload independent and which is in contrast to pulse Doppler evaluation.^(21,30,36,37) MV S' showed a correlation with birth weight, gestational age, and age after delivery. MV E' velocity and MV E/E' ratios did not show any association. A possible implication is that the bigger the baby, the bigger the heart and the bigger the excursion of the MV annulus during systole. Adult values for early mitral annular or septal E' wave velocities are higher (< 0.08 m/s) compared to neonates (0.06 m/s \pm 0.01 m/s).^(21,38) In contrast the E/E' ratio, which correlates with invasively measured pulmonary wedge pressure, of a normal adult LV (7.7 ± 3.0) is lower than a neonate (10.38).^(21,29,39,40) This higher value in the neonate is reflective of a sudden higher left ventricular filling pressure of the newborn infant following separation from the placenta which is associated with an abrupt increase in systemic afterload.⁽³³⁾

In our study the mean MV septal S' velocity which represents the mitral annular movement towards the left ventricular apex during systole, was found to be 0.05 m/s, which was slightly higher than Mori, et al. and Taksande (0.04 m/s).^(21,22) These differences demonstrate the heterogeneity amongst the studies where measurements may have been done at different times after delivery.

The TV E' velocities and E/E' ratio showed no correlation with any of the independent variables in contrast to Tao, et al.⁽³⁴⁾ who demonstrated TV E/E' ratio to be significantly higher in the C/S group compared to the NVD group.

The current study showed the mean MV E/E' ratio of 10.38 m/s, to be higher than the mean TV E/E' 6.78 m/s which is similar to the Mori's, et al. study.⁽²¹⁾ This may be attributed to the relatively higher left ventricular filling pressures soon after birth which represents an adaptation of the LV myocardium to the sudden increase in post-natal systemic afterload.⁽³³⁾

The mean TV S' velocity in the study population was noted to be higher than the mean MV S' velocity which is similar to findings by Mori and Taksande (Supplementary Table III).^(21,22) The higher TV S' velocity is a normal finding because the right ventricle is intrinsically more dependent on longitudinal movement against a lower afterload during systole, whereas the left ventricular contraction is more complex and also incorporates twisting and circumferential shortening components.^(21,40)

Myocardial performance index (Tei index)

The Tei index reflects both systolic and diastolic function and can be applied to both the left and the right ventricle and correlates well with invasive measurements of systolic and diastolic function.^(22,41,42) Its value is independent of chamber geometry, heart rate, or age.^(41,43,44)

The RV Tei index showed a moderate, but not significant, positive correlation with birth weight in our study where the RV Tei mean was 0.28 and LV Tei mean was 0.31 at a mean age of 40.13 hours. The study by Bokoniec showed the mean ventricular Tei indexes to be slightly higher (RV Tei mean of 0.42 and the LV Tei index mean of 0.37). However, the neonatal cohort was much younger (≤ 24 hours) post-delivery (Supplementary Table III).⁽¹⁶⁾ The Bokoniec study also showed a decrease in the mean RV Tei index towards the end of the neonatal period, from 0.42 – 0.29 which may reflect the physiological drop in pulmonary artery pressures with age.⁽¹⁶⁾ The LV Tei remained unchanged.^(16,33)

Clinical use table

A unique clinical use table has been compiled with predicted values and Z-scores to be used in an African setting to assist in decision-making regarding the longitudinal systolic function of both ventricles as well as diastolic function of the newborn infant (Table III and IV).

Reproducibility and inter observer variability

ICC was conducted between the 1st and the 2nd observer as a test for reproducibility. The overall ICC average was 71.86% which shows a strong correlation between the 2 observer measurements. Núñez-Gil and Iwashima, Seguchi and Ohzeki with ICCs of 0.74 and 0.91 respectively showed a similar correlation.^(18,24)

Local versus International values

The findings of this study were compared to obtainable international values (Supplementary Table III).

The mean weight of the current study was similar to 2 Asian studies,^(19,20) but the mean age assessment was 40 hours compared to the same Asian study where measurements were done at 24 hours post-delivery. The sample size (n = 292) is much larger than other studies performed on healthy full-term neonates and is therefore highly powered and provides a high level of confidence in the variation of normality in term African neonatal cardiac function.^(21,45)

Study strengths and limitations

This study is one of the largest and most recent undertaken in the neonatal population worldwide. It is also strongly powered in terms of the large sample size, a strong ICC, and the incorporation of other cardiac function parameters (Tei index and tissue Doppler) not included in other studies.^(16,17,19,20,31)

Due to the lack of availability, cardiac speckle-tracking and strain, a measure of tissue deformation, was omitted.⁽⁴⁶⁾

CONCLUSION

This study has established normal reference values for systolic and diastolic function using various echocardiographic modalities in full-term African neonates. It is the first such study to be done in sub-Saharan Africa with a population cohort of 292 subjects, which is the largest worldwide. Comparisons with other studies have confirmed differences between various ethnic groups.

Conflict of interest: none declared.

SUPPLEMENTARY TABLE I: Gender and mode of delivery (Local vs. international values).

	This study 2019 (South Africa) n = 292	Riggs, et al. 1989 (Northern America) n = 22	Iwashima, Seguchi and Ohzeki 2005 (Asia) n = 55	Bokiniec, et al. 2016 (Europe) n = 29
Gender - M/F	142M/150F	-	31M/24F	18M/11F
Mode of delivery - C/S: NVD	175:117	05:17	18/37	11:18

M: male, F: female, C/S: caesarean section, NVD: normal vertex delivery.

SUPPLEMENTARY TABLE II: M-mode measurements (Local vs. international values).

	This study 2019 (Africa) n = 292	Mori, et al. 2004 (Asia) n = 135	Iwashima, Seguchi and Ohzeki 2005 (Asia) n = 55	Núñez-Gil, et al. 2011 (Europe) n=30	Uysal, Boston and Çil 2015 (Europe) n = 22	Taksande 2018 (Asia) n = 15
Mean weight (kg)	3.18	2.95	2.46	-	-	2.56
Mean BSA (m ²)	0.202	-	-	0.23	< 0.25	-
LV EF (%)	73.56 (± 8.93)	-	71.20 (± 6.5)	-	-	-
LV FS (%)	40.25 (± 7.91)	31 (± 0.06)	-	-	-	39.06 (± 3.72)
TAPSE(mm)	7.516 (± 1.30)	-	-	10.56 (± 7.26)	9.09 (± 5.91)	-

n: number of participants in study, BSA: body surface area, m²: metre squared, LV EF: left ventricular ejection fraction, LV FS: left ventricular fraction shortening, TAPSE: tricuspid annular plane systolic excursion. Data is expressed as mean ± standard deviation.

SUPPLEMENTARY TABLE III: Doppler measurements (Local vs. international values).

	This study 2019 (Africa) n = 292	Riggs, et al. 1989 (Northern America) n = 22	Harada, et al. 1994 (Asia) n = 16	Shiota, Harada and Takada 2002 (Asia) n = 45	Mori, et al. 2004 (Asia) n = 135	Iwashima, Seguchi and Ohzeki 2005 (Asia) n = 55	Koesten- erger, et al. 2012 (Europe) n = 83	Bokniecet, et al. 2016 (Europe) n = 29	Taksande 2018 (Asia) n = 15
Mean weight (kg)	3.18	3.44	3.09	3.06	2.95	2.46	-	3.443	2.56
Mean BSA (m ²)	0.20	-	-	-	-	-	0.22	-	-
MV PEAK E	0.58 (± 0.11)	0.50 (± 7.9)	-	0.53 (± 9)	0.52 (± 9.5)	0.54 (± 13.6)	-	-	0.46 (± 0.88)
MV PEAK A	0.59 (± 0.12)	0.49 (± 8.3)	-	0.44 (± 5)	0.48 (± 8.0)	0.48 (± 8.5)	-	-	0.54 (± 0.85)
MV E/A RATIO	1.01 (± 0.21)	1.00 (± 0.25)	-	1.19 (± 0.15)	-	1.14 (± 0.15)	-	-	0.86 (± 0.18)
MV E'	0.06 (± 0.01)	-	-	-	0.05 (± 0.9)	-	-	-	0.03 (± 0.88)
MV E/E'	10.38 (± 2.65)	-	-	-	7.0 (± 1.6)	-	-	-	-
MV S'	0.05 (± 0.00)	-	-	-	0.04 (± 0.7)	-	-	-	0.04 (± 0.75)
LVTei	0.31 (± 0.14)	-	-	-	-	-	-	0.37 (± 0.10)	0.30 (± 4.77)
TV PEAK E	0.51 (± 0.13)	0.47 (± 8.5)	0.42 (± 7.3)	-	0.38 (± 7.1)	-	-	-	-
TV PEAK A	0.62 (± 0.13)	0.53 (± 9.9)	0.49 (± 7.9)	-	0.49 (± 7.5)	-	-	-	-
TV E/A RATIO	0.84 (± 0.20)	0.85 (± 0.23)	0.87 (± 0.17)	-	-	-	-	-	-
TV E'	0.08 (± 0.02)	-	-	-	0.08 (± 1.3)	-	-	-	0.09 (± 0.14)
TV E/E'	6.78 (± 2.01)	-	-	-	5.2 (± 1.2)	-	-	-	-
TV S'	0.07 (± 0.05)	-	-	-	0.07 (± 1.2)	-	0.07 (± 4.75)	-	0.09 (± 0.14)
RVTei	0.28 (± 0.13)	-	-	-	-	-	-	0.42 (± 0.14)	0.40 (± 5.24)

n: number of participants in study, BSA: body surface area, MV peak E: mitral valve - early diastolic filling measured by pulsed Doppler, MV peak A: mitral valve - late diastolic filling measured by pulsed Doppler, MV E/A: mitral valve - early diastolic filling/late diastolic filling ratio, TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI, MV E/E': mitral valve- early diastolic filling / peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - Systolic wave representing peak myocardial systolic velocity at the septal MV annulus measured by TDI, LV Tei: myocardial performance index, TV peak E: tricuspid valve - early diastolic filling measured by pulsed Doppler, TV peak A: tricuspid valve - late diastolic filling measured by pulsed Doppler, TV E/A: tricuspid valve – early diastolic filling / late diastolic filling ratio, TDI TV E': tricuspid valve - peak myocardial velocity in early diastole measured by TDI, TV E/E': tricuspid valve – early diastolic filling / peak myocardial velocity in early diastole ratio, TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus measured by TDI, RV Tei: myocardial performance index.

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Cardioneuroablation for treating refractory vasovagal syncope

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INTRODUCTION

VVS is the most common cause of transient loss of consciousness, accounting for a substantial proportion of syncope referrals.⁽¹⁾ Its underlying mechanism involves a reflex in response to a trigger that causes peripheral vasodilation and/or bradycardia, ultimately compromising cerebral perfusion.⁽²⁾ Although VVS is often considered benign, affected individuals may sustain significant injuries and experience profound impairments in quality of life.⁽³⁾ CNA is a technique that involves endocardial ablation and targets cardiac GP to mitigate excessive vagal activity.⁽⁴⁾ This approach is effective in managing neurocardiogenic reflex syndromes with cardioinhibitory and vasodepressor responses.^(3,5) We present a case that illustrates the successful application of CNA in managing recurrent neurocardiogenic syncope.

BACKGROUND

A 42-year-old female presented with recurrent syncope resulting in severe injuries. Most episodes were preceded by a prodromal phase of dizziness and transient cognitive changes, predominantly occurring upon standing or with postural changes. However, a

ABSTRACT

Vasovagal syncope (VVS), also known as neurocardiogenic syncope, often presents significant management challenges in patients with frequent refractory episodes. Cardioneuroablation (CNA) targets ganglionated plexi (GP) through catheter ablation to mitigate excessive vagal tone. This case report demonstrates the successful application of CNA in a patient with recurrent neurocardiogenic syncope, initially characterised by a mixed response with a minimal cardioinhibitory component and subsequent electrophysiological evaluation, which revealed significant cardioinhibitory and vasodepressor components, prompting a targeted ablation approach. While future studies are required to evaluate the long-term safety and efficacy, this case adds to the growing evidence that supports CNA as a safe and effective intervention for select patients with refractory VVS. Keywords: cardioneuroablation, vasovagal syncope, cardioinhibitory response, mixed response, vasodepressor response

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subset of events arose without any discernible orthostatic triggers. Her symptoms, which began 1 year prior, had persisted despite treatment with midodrine, fludrocortisone, and lifestyle modifications. A loop recorder was implanted, revealing findings suggestive of a mixed response with minimal cardioinhibitory sinus slowing (Figure 1). Given the patient's refractory course, a multidisciplinary discussion was undertaken to explore invasive, catheter-based radiofrequency (RF) ablation of GP to modulate autonomic tone, with a subsequent assessment of procedural efficacy.

PROCEDURE

The procedure was performed under general anaesthesia. Following heparinisation, 2 decapolar steerable catheters (Dynamic XT 6 Fr, Boston Scientific, Marlborough, United States) were advanced from the femoral veins to both internal jugular veins at the base of the cranium, near the jugular foramen, directed medially towards the jugular ganglion of the vagus nerve. High-frequency stimulation (HFS) at 20 Hz, 20 mA, 20 microseconds (μ s) pulse width, with a 4-second duration with Micropace EPS320™ (Micropace EP Inc., Santa Ana, United States) was performed, stimulating the vagus nerve and resulting in immediate hypotension and prolonged asystole from a single pole on the left side (Figures 2 and 3).

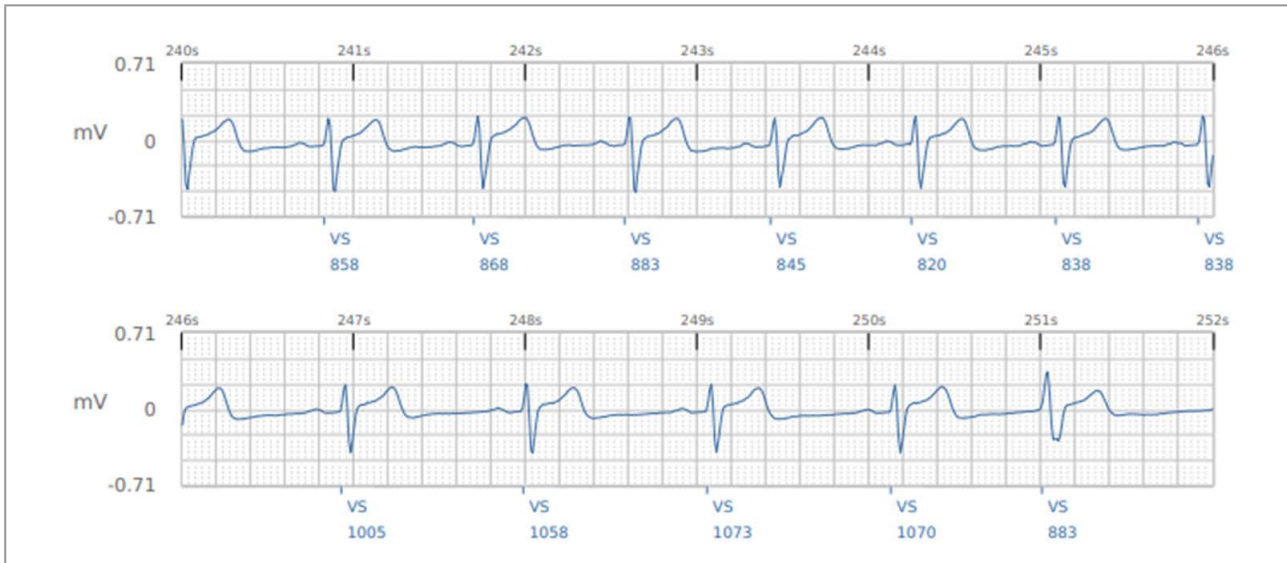


FIGURE 1: Implantable cardiac monitor tracing during a pre-syncope episode, showing progressive sinus slowing without significant bradycardia or pauses consistent with mixed response.

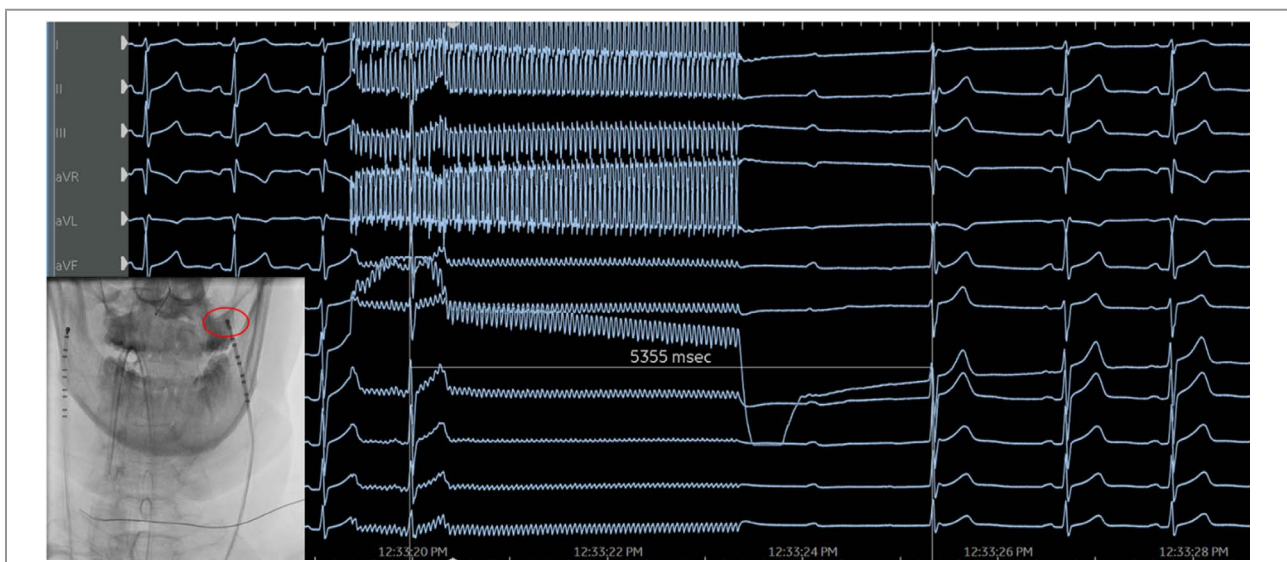


FIGURE 2: Pacing site at left cranial base (red circle) with cardioinhibitory and vasodepressor response.

A multipolar mapping catheter, Advisor HD Grid (Abbott HD, Abbott Park, United States), was utilised for mapping of the right and left atria, identifying areas of fragmentation and high-frequency signals with a bandpass filter set between 300 Hz and 500 Hz (Figure 4). Ablation was performed in all regions with high-frequency/fragmented electrograms, which are hallmarks of GP and targets for CNA. For our patient, this involved the ridge between the left superior pulmonary vein (LSPV) and the appendage, the right superior pulmonary vein, the superior vena cava, and the upper limbus of the interatrial septum (Figures 5, 6, and 7). Notably, ablation near the LSPV ridge elicited a profound bradycardic response with significant vasodepressor effects, necessitating temporary pacing. Pauses exceeding 10 seconds were observed, with each successive lesion resulting in

progressive attenuation of both the cardioinhibitory and vasodepressor responses (Figure 8).

Following ablation of the atrial tissue adjacent to the GP, repeat HFS at the same jugular vein sites no longer elicited significant bradycardia or hypotension, indicating successful autonomic modification (Figure 9). The procedure concluded without complications.

FOLLOW-UP

At the 11-month follow-up, the patient reported 3 syncopal episodes – 2 within the first month and 1 isolated event at 9 months – reflecting a marked reduction from the 4 syncopal



FIGURE 3: Pacing site at right cranial base (red circle) without cardioinhibitory or vasodepressor response.

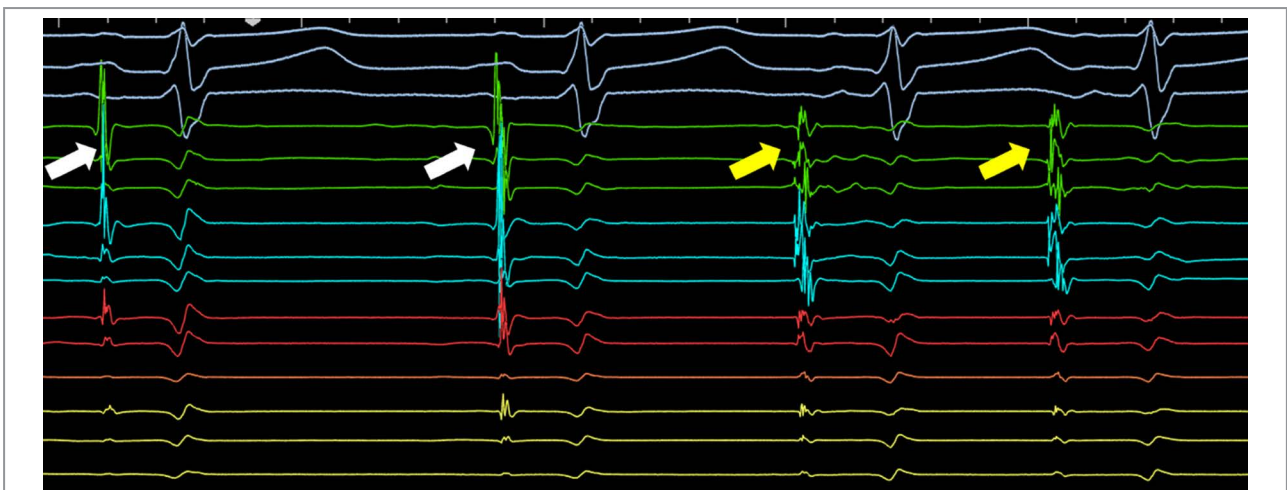


FIGURE 4: Intracardiac atrial electrograms during mapping. Normal electrograms (white arrows) show uniform, discrete deflections, while fragmented electrograms (yellow arrows) exhibit multiple high-frequency components – hallmarks of ganglionated plexi and targets for cardioablation.

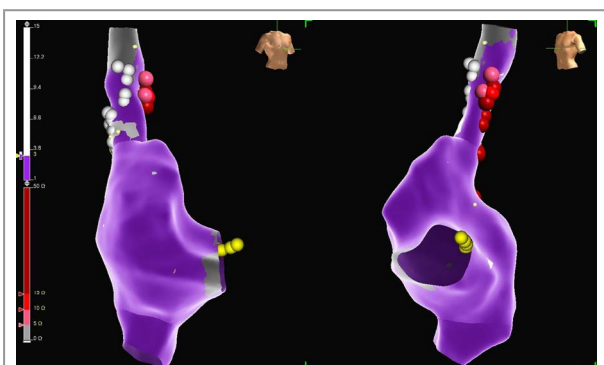


FIGURE 5: Three-dimensional electroanatomic map of the right atrium. Recorded sites of the His bundle are marked in yellow, diaphragm capture in grey, and radiofrequency ablation lesions in red.



FIGURE 6: Three-dimensional electroanatomic map of the left atrium. Sites of diaphragm capture are shown in grey, and radiofrequency ablation lesions are marked in red.

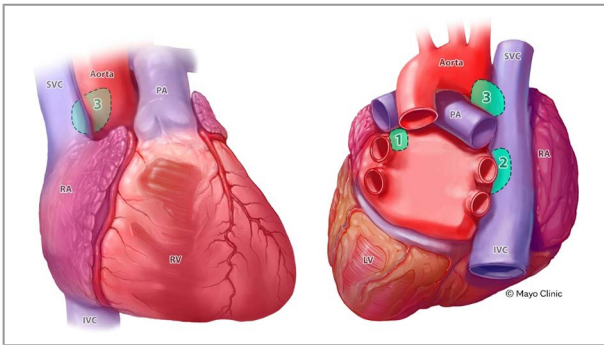


FIGURE 7: Schematic illustration of the ganglionated plexi targeted during cardioneuroablation. 1 – ridge between the left superior pulmonary vein and left atrial appendage, 2 – right superior pulmonary vein and upper limb of the interatrial septum, 3 – superior vena cava region. RA – Right Atrium, PA – Pulmonary Artery, SVC – Superior Vena Cava, IVC – Inferior Vena Cava, RV – Right Ventricle, LV – Left Ventricle

events recorded in the 3 months before CNA. She also noted substantial improvements in her energy, mood, and overall well-being, stating that she “finally got her life back”.

DISCUSSION

VVS arises from 2 primary pathophysiological mechanisms: vasodepression, manifested by vasodilation and resultant hypotension, and cardioinhibition, in which excessive parasympathetic activation leads to sinus bradycardia or pauses. When both responses are involved, the condition is classified as “mixed”.⁽⁶⁾ Clinical presentations often include dizziness or syncope secondary to hypotension, vagally mediated sinus node slowing or arrest, and/or atrioventricular block.⁽⁷⁾ VVS predominantly affects younger individuals without underlying structural cardiac or neurological disorders.⁽⁸⁾

In more severe forms of VVS, where episodes of syncope are frequent and often occur with little or no prodrome, treatment can be particularly challenging.⁽³⁾ Traditional VVS management includes counterpressure manoeuvres and the use of pharmacologic agents, like midodrine and fludrocortisone.⁽⁶⁾ In cardioinhibitory VVS, permanent pacing may be considered, especially in individuals over 40 with documented asystolic episodes.⁽⁹⁾ Importantly, pacemakers have limited sustained benefit as they do not address the vasodepressor reflex and have a risk for short- and long-term complications.^(6,7)

CNA has emerged as a promising alternative treatment for VVS, using RF ablation to target cardiac vagal ganglia, effectively reducing excessive vagal activity.⁽³⁾ Several observational studies and 1 randomised controlled study reported excellent short- and long-term outcomes for patients with VVS, functional atrioventricular block, and sick sinus syndrome treated with CNA.⁽¹⁰⁾

CNA is performed with RF energy and irrigated catheters to deliver current into the tissue to induce resistive and conductive heating.⁽¹¹⁾ Ablation parameters commonly include 25–35 W for 40–60 seconds, with shorter durations (< 20 seconds) for the

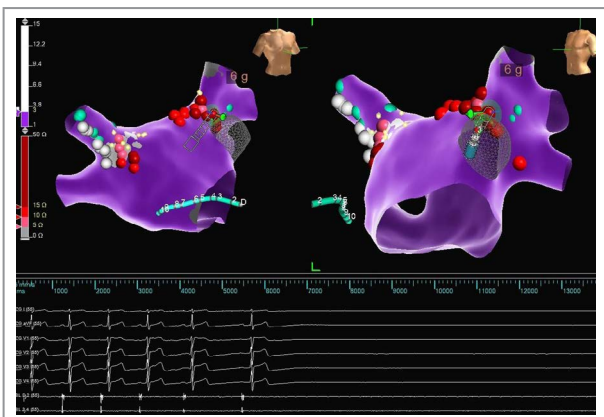


FIGURE 8: Radiofrequency ablation anterior to the left superior pulmonary vein eliciting a profound vagal response, evidenced by transient sinus arrest on intracardiac electrograms (bottom panel). The electroanatomic map demonstrates the ablation catheter position and the lesion set near the left superior pulmonary vein ridge.

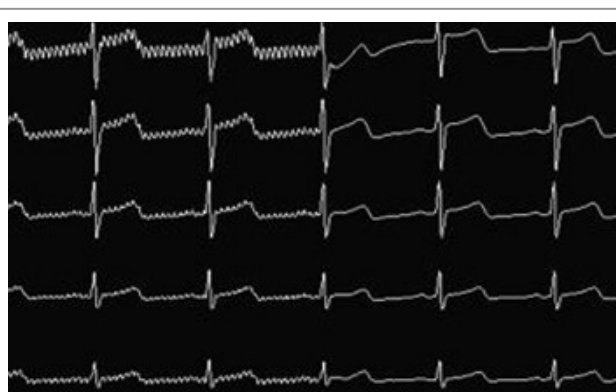


FIGURE 9: High-frequency stimulation at the left cranial base before (left) and after (right) cardioneuroablation. Pre-ablation stimulation induced a significant vagal response with bradycardia and hypotension, while post-ablation stimulation failed to elicit any notable autonomic effect, indicating successful parasympathetic modulation.

posterior wall, and avoiding lesion stacking while monitoring the oesophageal temperature.⁽¹²⁾ Procedural endpoints vary but generally fall into three categories: (1) elimination of vagal response to HFS, (2) targeting of high-frequency or fractionated atrial electrograms, and (3) empiric anatomical ablation at established GP sites.⁽¹³⁾ In this case, we used a physiology-guided approach incorporating both HFS and electrogram mapping to guide targeted ablation.

Emerging technologies, such as pulsed field ablation (PFA), are also being explored for CNA in atrial fibrillation, as autonomic input from GP can abbreviate atrial refractoriness and promote re-entry.⁽¹⁴⁾ In pre-clinical studies, PFA selectively ablated cardiomyocytes via electroporation while preserving myelinated structures, such as the phrenic and sciatic nerves.⁽¹⁵⁻¹⁷⁾ GP ablation with PFA was initially shown to be safe and feasible from an epicardial approach via substernal access in canine models.⁽¹⁸⁾ While human data are limited for epicardial ablation, a trial of epicardial RF GP ablation during thoracoscopic pulmonary vein isolation showed no benefit in atrial fibrillation suppression and was associated with increased adverse events.⁽¹⁹⁾

Outcomes of CNA for VVS are encouraging. However, there have been concerns, including attenuation of vagal tone, resting tachycardia, exercise intolerance, atrial arrhythmias, and, in animal models, increased susceptibility to ventricular arrhythmias.^(13,20) Intra-procedural risks are similar to those of left atrial ablation and include oesophageal injury and thromboembolic events.⁽¹²⁾

While CNA is gaining traction in patients with cardioinhibitory VVS, its role in vasodepressor-predominant syncope remains controversial, as cardiac parasympathetic denervation is believed to improve bradycardia without directly affecting vasodepressor response.⁽⁹⁾ However, a recent case series compared 13 patients with vasodepressor VVS and 19 with mixed-type VVS who underwent CNA, and found no significant difference in syncope recurrence at 11 months.⁽²¹⁾ Another study reported similar benefits in patients with vasodepressor responses on tilt table testing.⁽²²⁾

CONCLUSION

This case adds to the emerging literature by highlighting a patient with minimal cardioinhibitory findings on a loop recorder that demonstrated both cardioinhibitory and vasodepressor responses with HFS and benefited from CNA. This vagal response to HFS was eliminated after ablation, suggesting the effective modulation of autonomic tone.⁽²³⁾ This finding aligns with anatomical studies showing that GP contain both afferent and efferent parasympathetic neurons, which have mechanoreceptors and chemoreceptors.⁽²⁴⁾ Efferent signals drive bradycardia, while afferent GP activation may provoke a vasodepressor reflex. This duality may explain how CNA benefits patients who have mixed syncope with a minimal cardioinhibitory component. Further study is warranted in this subset of patients.

DISCLOSURES

The authors do not have any funding to disclose.

Conflict of interests: none declared.

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Acute myocardial infarction in a patient with anomalous left main coronary artery origin with a hypoplastic left anterior descending artery: A diagnostic and therapeutic challenge

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INTRODUCTION

Coronary artery anomalies are rare congenital abnormalities, with a reported prevalence of 0.15–0.84%, often discovered incidentally or at autopsy.^(1,2) While many anomalies are benign and asymptomatic, certain types – particularly those involving an anomalous origin or course of coronary artery – are associated with myocardial ischaemia, arrhythmias, and sudden cardiac death, especially in younger individuals or during exertion.⁽²⁾ Their clinical relevance becomes particularly significant in the setting of acute coronary syndromes, where they may contribute directly to ischaemia or complicate diagnosis, risk stratification, and revascularisation planning.⁽³⁾ In such cases, the presence of an anomalous artery may obscure the identification of the culprit lesion, delay timely reperfusion, or alter the choice of intervention.

We report an exceptionally rare case of STEMI involving two vascular territories in a patient with coexisting congenital coronary anomalies and multiple cardiovascular risk factors. Initial ECG showed ST-segment elevation in the inferior and anterolateral leads, raising suspicion for multivessel involvement.

ABSTRACT

Congenital coronary artery anomalies are rare but clinically significant. We present a 41-year-old Caucasian male who presented with acute ST-elevation myocardial infarction (STEMI) involving two distinct vascular territories. Initial electrocardiogram (ECG) findings showed ST-segment elevation in the inferior and anterolateral leads, raising suspicion of multivessel involvement. Delayed access to a cardiac catheterisation laboratory warranted thrombolysis as the primary reperfusion strategy; however, this was unsuccessful. Emergent coronary angiography revealed an anomalous left main coronary artery (LMCA) originating from the right coronary cusp, sharing a common ostium with the right coronary artery (RCA). A critical stenosis of the mid-RCA was identified, attenuated proximally by a thrombolysis in myocardial infarction (TIMI) 3 thrombus burden and complete occlusion of its distal branches. Coronary computed tomography angiography (CCTA) further revealed a hypoplastic left anterior descending artery (LAD). The patient was initially managed with medical therapy alone, and subsequent percutaneous coronary intervention (PCI) was performed for ongoing stable angina, resulting in complete coronary revascularisation. This case highlights the importance of considering coronary anomalies in patients with atypical clinical presentations and the need for individualised treatment approaches. The coexistence of congenital and atherosclerotic coronary artery disease poses significant challenges, and further studies are needed to refine screening and management guidelines.

Keywords: congenital coronary artery anomal, anomalous left main coronary artery origin, anomaly, hypoplastic left anterior descending artery, myocardial infarction, coronary computed tomography angiography

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Despite thrombolysis, failed reperfusion necessitated coronary angiography, which revealed an anomalous LMCA originating from the right coronary cusp and suspected chronic total occlusion (CTO) of the LAD. The RCA demonstrated severe mid-vessel stenosis with a high thrombus burden and was initially

managed medically. CCTA excluded the presence of a CTO and instead identified a rudimentary, hypoplastic LAD, while also confirming a prepulmonic course of the anomalous LMCA originating from a common ostium with the RCA.

The coexistence of an anomalous LMCA originating from the right coronary cusp and a hypoplastic LAD is extremely rare, with no reported cases in living patients. This combination not only complicates diagnosis and clinical decision-making but also poses challenges in selecting an appropriate management strategy. Current guidelines support an individualised approach, including medical therapy, PCI, or surgical correction, depending on the anatomical course, presence of ischaemia, and patient-specific factors. This case underscores the importance of recognising coronary anomalies in atypical STEMI presentations and highlights the diagnostic and therapeutic complexities posed by the coexistence of congenital and atherosclerotic coronary disease. Further research is needed to refine screening protocols, improve early recognition, and optimise treatment strategies in this patient population.

CASE REPORT

A 41-year-old Caucasian male presented to the emergency department of a peripheral hospital 10 hours after the initial onset of acute retrosternal chest pain radiating to the left jaw associated with nausea and diaphoresis. Relevant medical history and cardiovascular risk factors included untreated diabetes

mellitus, active cigarette smoking, and a family history of ischaemic heart disease.

The initial ECG findings (Figure 1) were those of ST-segment elevation in the inferior and anterolateral leads with reciprocal ST-depression, raising suspicion for thrombosis in two distinct vascular territories. Laboratory investigations revealed a high-sensitivity troponin T of 824 ng/L (World Health Organization rule-in criteria > 100 ng/L) and a haemoglobin A1c (HbA1c) of 7.9% (above the 7.0% therapeutic target). Serum chemistry, inflammatory markers, lipogram, and coagulation studies were all within normal range. Initial mortality risk stratification was low: Global Registry of Acute Coronary Events (GRACE) score of 76, TIMI score of 2, and Killip Class I.

Presentation within the 12-hour thrombolysis window and the absence of contraindications warranted fibrinolytic therapy as the primary reperfusion strategy, as prolonged transfer time to a PCI-capable facility precluded timely intervention. Tissue plasminogen activator, alteplase, was administered without any electrical or mechanical cardiac complications. ECG 90 minutes post-thrombolysis showed persistent ST-segment elevation with < 50% reduction in initial ST-segment elevation, suggestive of failed thrombolysis by ECG criteria. Loading doses of aspirin 300 mg, clopidogrel 300 mg, and atorvastatin 80 mg were administered, followed by maintenance doses and therapeutic enoxaparin.

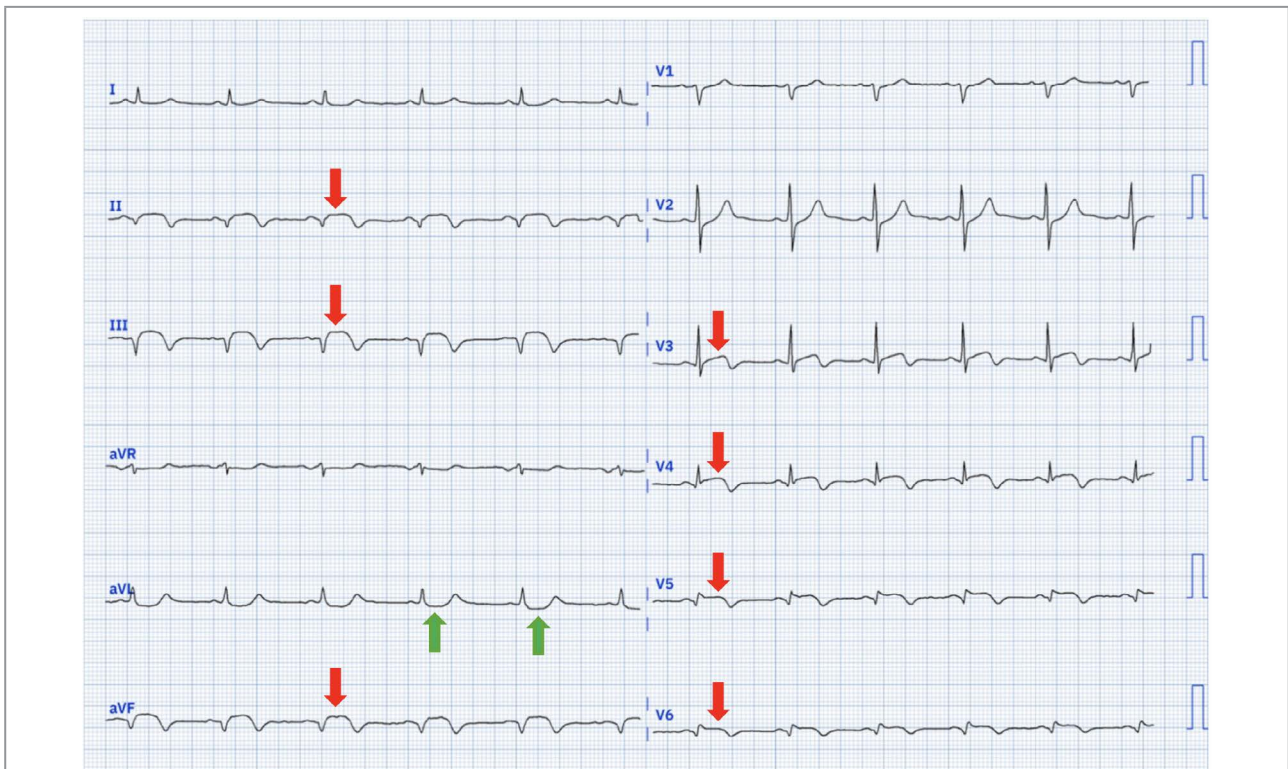


FIGURE 1: Electrocardiogram on initial presentation; 12-lead electrocardiogram showing ST-segment elevation (red arrows) in inferior (II, III, aVF) and anterolateral leads (V3–V6), with reciprocal ST-segment depression in lead aVL (green arrows).

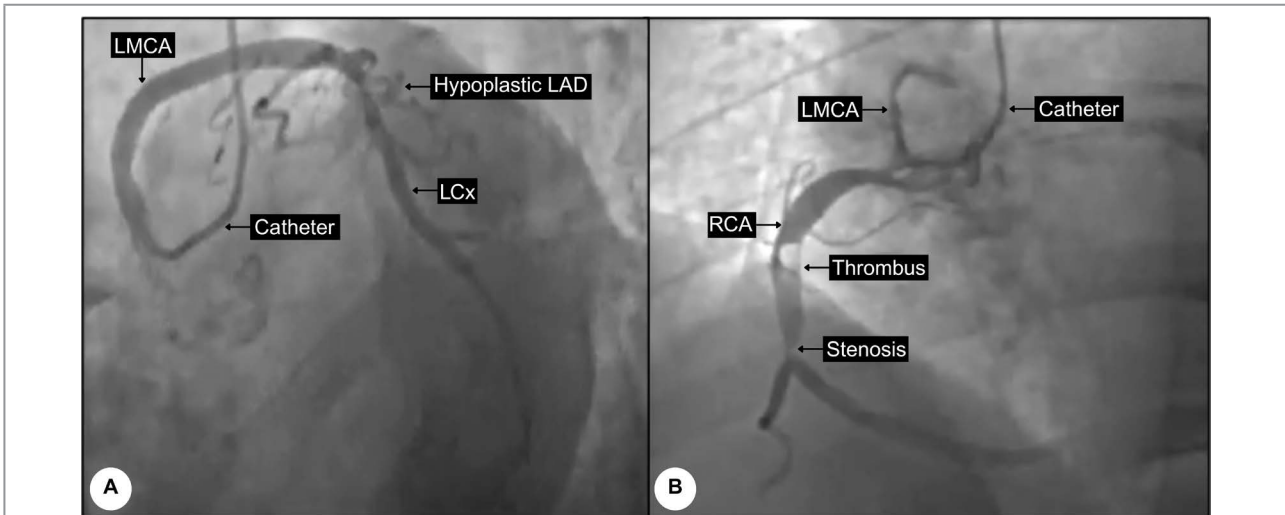


FIGURE 2: Angiogram of the right and left coronary arteries.

A: Invasive coronary angiography LAO caudal "spider view" revealing the LMCA arising from the right coronary cusp, a hypoplastic LAD, and the LCx. B: LAO cranial view showing that both the LMCA and RCA originate from a common ostium in the right coronary cusp. A subtotal stenosis of the RCA with complete occlusion of its distal branches – the PDA and posterolateral branches. Proximal to the stenosis, a persistent filling defect was visualised in multiple projections throughout the cardiac cycle and on repeat contrast injections, characterised by haziness and contrast staining. The defect was consistent with an intraluminal thrombus, thereby excluding an air bubble.

LAD: left anterior descending artery, LCx: left circumflex artery, LMCA: left main coronary artery, LOA: left anterior oblique, PDA: posterior descending artery, RCA: right coronary artery.

Upon arrival at our institution, the patient underwent emergent coronary angiography (Figure 2), revealing a LMCA arising from the right coronary cusp. Proximally, the left circumflex artery (LCx) was of adequate calibre, with a mid-type A lesion and 40% stenosis. A CTO of the LAD was suspected, as the vessel was not clearly visualised; instead, several rudimentary, short vessels extending anteriorly to the mid-ventricle were observed, supplying portions of the expected LAD territory. No definitive proximal cap or abrupt cut-off was identified, and there was no evidence of calcification. Interrogation of the right cardiac circulation showed a RCA of normal origin with a tight 90% mid-RCA stenosis, accentuated by a TIMI 3 thrombus burden proximal to the lesion, suggestive of an acute thrombotic event superimposed on a high-grade chronic lesion. The posterior descending artery (PDA) and posterolateral branches were poorly visualised, suggesting complete occlusion of these vessels. Ventriculography of the left ventricle demonstrated reduced ventricular contractility and inferior wall hypokinesia. This finding supports designating the RCA as the infarct-related artery, consistent with the clinical presentation and ECG changes, because the RCA potentially subtended both the inferior wall and anterior segments through collateral vessels.

The patient was transferred to the cardiac intensive care unit (CCU) for a 24-hour tirofiban infusion. Post-infusion transthoracic echocardiogram confirmed a reduced ejection fraction of 40–45% and inferior wall hypokinesia. CCTA (Figure 3) was requested to further study the anatomy of the LAD and the course of the anomalous LMCA. Imaging confirmed an anomalous origin of the LMCA arising from the RCA ostium with a prepulmonic course. This anomalous vessel gave rise to a

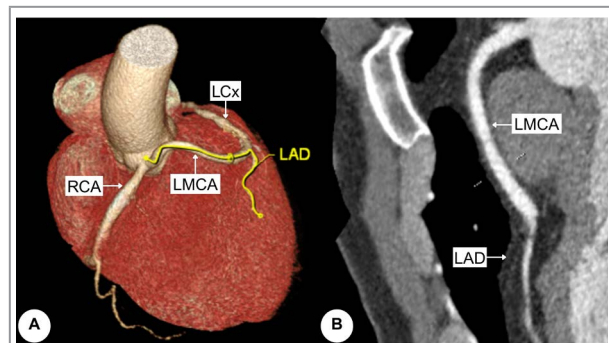


FIGURE 3: Coronary computed tomography angiography with reconstructed views (LMCA and LAD course is highlighted in yellow).

A: Three-dimensional reconstruction of the heart and coronary vessels showing the RCA, LMCA originating from the right coronary cusp, with a prepulmonic course, the LCx, and hypoplastic LAD.

B: Multiplanar reconstruction of the hypoplastic LAD originating from an anomalous LMCA.

LAD: left anterior descending artery, LCx: left circumflex artery, LMCA: left main coronary artery, RCA: right coronary artery.

diminutive LAD that coursed in the anterior interventricular groove but terminated mid-ventricle – findings that refuted the initially suspected CTO – and demonstrated collateral branches from the RCA supplying the LAD territory.

The remainder of the hospital admission was uneventful. The patient was discharged home on dual antiplatelet therapy, high-dose statin, and oral antihyperglycaemic therapy. At the routine 1-month follow-up, the patient reported ongoing angina,

prompting initiation of atenolol 25 mg daily. Due to persistent symptoms despite up-titration of medical therapy, the patient was scheduled for an elective coronary angiogram, which demonstrated a persistent mid-RCA stenosis exceeding 75%. The RCA was successfully engaged, dilated, and stented. The final angiogram confirmed successful revascularisation.

DISCUSSION

We report a rare case of two concurrent coronary anomalies confirmed by ECG, coronary angiography, and CCTA findings. Unusually, the patient's initial ECG showed ST-segment elevation in both the LAD and RCA territories. Angiography revealed an anomalous LMCA arising from the right coronary cusp, sharing a common ostium with the RCA. CCTA further demonstrated a rudimentary, hypoplastic LAD, refuting the initial suspicion of CTO. Failure to recognise an anomalous coronary origin or branching pattern can lead to misinterpretation during angiography, potentially resulting in an incorrect diagnosis or suboptimal management strategy. It also poses a risk of iatrogenic injury during cardiac interventions. Multiple cardiac risk factors accelerated coronary atherosclerosis, leading to mid-RCA and LCx stenosis, and eventual STEMI of the RCA territory. As the RCA supplied portions of the anterior and anterolateral walls via small collateral branches (typically supplied by the LAD), these regions were also affected.

Literature review

STEMI typically results from single-vessel occlusion, with simultaneous involvement of two arteries being exceptionally rare and associated with a poor prognosis.⁽⁴⁾ Known risk factors include dyslipidaemia, diabetes, hypertension, tobacco use, and a family history of coronary artery disease. The mechanism behind dual-vessel STEMI remains unclear but is often linked to vasospasm, thrombophilia, or cocaine use.⁽⁴⁾ To our knowledge, no prior reports describe ST-segment elevation in two vascular territories in a patient with dual congenital coronary anomalies, highlighting the rarity of our findings.

The prevalence of anomalous coronary arteries originating from the opposite coronary cusp ranges from 0.15% to 0.84%, with LMCA arising from the right cusp in only 0.03–0.28% of cases.^(1,2) Hypoplastic coronary artery disease (HCAD) is a rare congenital underdevelopment of a major epicardial artery – a rudimentary vessel with a shortened course or luminal diameter < 1.5 mm, reported in fewer than 35 cases, with only 10 involving the LAD.^(1,2,5,6) HCAD increases the risk of myocardial ischaemia and sudden cardiac death. The coexistence of two coronary anomalies is extremely rare, given their usual isolation in congenital cases.⁽⁶⁾

While both anomalous coronary origins and hypoplastic coronary arteries have been described independently, their coexistence remains exceptionally rare. One case report described a hypoplastic left coronary artery with an anomalous origin from the left ventricular outflow tract, emphasising the role of advanced imaging in defining complex congenital

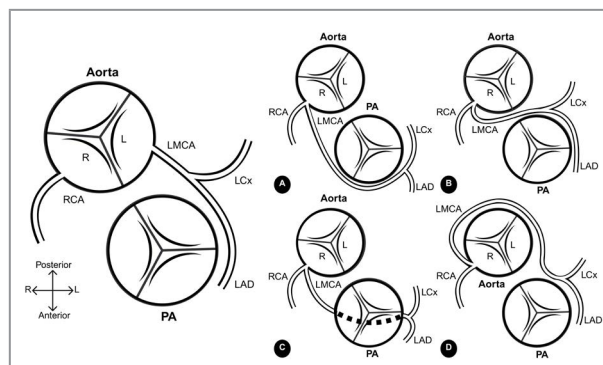


FIGURE 4: Schematic illustration of LMCA pathways.

Left panel: Normal LMCA originates from the left coronary cusp and its bifurcation into the LAD and LCx.

Right panel: Anomalous LMCA arising from the right coronary cusp with four potential courses: (A) prepulmonic, (B) interarterial, (C) subpulmonic, and (D) retroaortic.⁽⁹⁾ In our patient, the anomalous LMCA followed the prepulmonic course (A).

L: left, LAD: left anterior descending artery, LCx: left circumflex artery, LMCA: left main coronary artery, PA: pulmonary artery, R: right, RCA: right coronary artery.

anatomy.⁽⁷⁾ Another report documented a single coronary artery arising from the right sinus of Valsalva, in which the LAD was hypoplastic.⁽⁸⁾ However, to our knowledge, no published cases to date have described an anomalous LMCA arising from the right coronary cusp in conjunction with a hypoplastic LAD in a living patient presenting with acute STEMI. This highlights the clinical novelty of the case and expands on the limited literature regarding dual congenital coronary anomalies.

Pathophysiological considerations

Coronary artery embryonic development begins with intramural vessels within the primordial myocardium joining a subepicardial vascular network, forming the right and left coronary arteries by day 14 of embryonic growth. Congenital coronary anomalies result from abnormal ingrowth of the initially formed subepicardial vascular plexus into the aortic root during embryonic development and include those arising from aberrant sinus origins, intrinsic arterial anatomical abnormalities, or termination defects.⁽⁹⁾ In most instances, these anomalies support foetal myocardial development to ensure post-natal function.⁽⁹⁾ Approximately 26% of coronary artery anomalies are associated with abnormalities of the aortic root, including bicuspid aortic valve or asymmetry in the size and morphology of the aortic valve leaflets.⁽¹⁰⁾ In this patient, the coexistence of a bicuspid aortic valve was excluded using both transthoracic echocardiography and CCTA.

Anomalous LMCA from the right cusp can follow four potential courses (Figure 4): prepulmonic (anterior to the right ventricular outflow tract), interarterial (between the aorta and pulmonary artery), subpulmonic (intramyocardial within the interventricular septum), or retroaortic (posterior to the aortic root).⁽⁹⁾ The prepulmonic course, as identified in this patient, is typically considered haemodynamically benign and is less likely to

predispose to myocardial ischaemia and sudden cardiac death. Unlike the interarterial course – where the artery passes between the aorta and pulmonary artery and may be subjected to lateral compression during systole, a phenomenon that can be exacerbated by physical activity due to increased great vessel wall stress – the prepulmonic course avoids external compression by major vascular structures.⁽²⁾

Clinical presentation and diagnostic challenges

Congenital coronary artery anomalies present variably, with symptoms in ~20% of cases.⁽¹¹⁾ Sudden cardiac death is often due to ventricular arrhythmia following exertion-induced myocardial ischaemia. In an anomalous LMCA, ischaemia may result from slit-like or stenotic ostial abnormalities or interarterial compression by major arteries.⁽²⁾ The anomalous origin of the LMCA from the right coronary sinus is consistently associated with sudden cardiac death in 59% of reported cases, with 81% of these events triggered by physical activity.⁽¹²⁾

HCAD-related ischaemia arises from thrombosis, coronary spasm, or physical exertion, further restricting blood flow to an already narrowed arterial lumen.⁽⁶⁾ Whether coronary anomalies independently contribute to obstructive atherosclerosis remains debated.⁽¹¹⁾ Though most anomalies are asymptomatic, clinical features include exertional dyspnoea, chest pain, syncope, palpitations, or dizziness.⁽⁶⁾ The high prevalence of asymptomatic cases before critical events highlights the challenge of risk assessment and the lack of screening guidelines.

Management and therapeutic implications

Due to the complex pathophysiology, treatment must be individualised based on anatomy, coexisting disease, and imaging findings. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend beta-blockade, angioplasty with stenting, or surgical repair for an anomalous LMCA originating from the right coronary cusp.⁽¹³⁾ Surgical intervention is a 2018 AHA/ACC class I recommendation for symptoms or diagnostic evidence of ischaemia and a class IIa recommendation for asymptomatic cases without ischaemia.⁽¹³⁾ Though rare, coronary artery bypass grafting has been employed in single-vessel hypoplasia, with its feasibility largely dependent on anatomical considerations and disease distribution.⁽⁵⁾ HCAD treatment is limited due to its diffuse nature. Implantable cardioverter-defibrillator placement is recommended for secondary prevention of arrhythmia and sudden cardiac death.^(5,6)

The management of this patient highlights significant challenges faced within the public healthcare system in Johannesburg. The patient presented late to a peripheral hospital and was initially managed medically with fibrinolysis, given the anticipated delays in transfer to a PCI-capable facility. This reflects the ongoing difficulty in securing timely ICU ambulance transport. Despite failed thrombolysis, rescue PCI could not be performed due to logistical constraints. At our facility, coronary angiography was performed 78 hours after symptom onset. A relook angiogram following tirofiban infusion was not done, given high patient

volumes and the absence of ongoing symptoms more than a week after presentation. Further delays were encountered in obtaining a CCTA scan, which was only available at an external site at the time.

Consequently, the patient was managed as having chronic coronary syndrome. Recurrent anginal episodes despite optimal medical therapy necessitated PCI, directed at the atherosclerotic RCA stenosis, considered the primary culprit lesion, with a favourable outcome. Although surgical repair remains the recommended intervention for anomalous coronary arteries associated with ischaemia, treatment options for HCAD are limited due to its diffuse nature. In this patient, surgical revascularisation was not feasible, as the LAD was a rudimentary vessel and the distal RCA branches supplying the anterior left ventricle were too small to serve as suitable graft targets.

Though the patient's ischaemic symptoms were attributed to atherosclerotic RCA and LCx stenosis, surgery remains the recommended treatment for anomalous coronary arteries with ischaemia. In the limited literature describing similar anomalies, surgical or conservative strategies were typically pursued depending on anatomical feasibility and the presence of ischaemia. This case contributes to existing reports by demonstrating the feasibility of a non-surgical management pathway in the context of complex dual coronary anomalies with concomitant atherosclerotic coronary artery disease.

The lifetime risk associated with anomalous coronary arteries remains unclear, highlighting the need for multicentre registry data to inform evidence-based guidelines. Currently, there is no consensus on diagnostic or management strategies for congenital coronary variants. Further longitudinal studies are needed to guide patient selection for revascularisation versus conservative management.⁽¹⁴⁾

CONCLUSION

This case report highlights the rare coexistence of two distinct congenital coronary artery anomalies in a patient presenting with STEMI. Although the acute presentation was primarily attributed to atherosclerotic coronary artery disease and thrombosis, the incidental discovery of these anomalies complicated clinical decision-making by influencing both diagnostic interpretation and the timing of intervention. The case underscores the importance of recognising coronary anomalies, particularly in patients with atypical electrocardiographic findings. Furthermore, it emphasises the challenges in evaluating individuals at risk for sudden cardiac events, given the often asymptomatic nature of these anomalies.

Management should be individualised based on anatomical characteristics, coexisting coronary disease, and functional imaging. While surgical correction remains the definitive treatment for high-risk coronary anomalies, medical management and percutaneous interventions may be appropriate in select cases.

Moreover, this case reinforces the need for long-term follow-up and surveillance in patients with coronary artery anomalies, especially those involving the LMCA, due to the potential risk of sudden cardiac death – even in the context of a haemodynamically benign course. The rarity of this dual anomaly, with associated acute coronary syndrome, highlights the need for further research to better understand its clinical implications, guide management strategies, and clarify long-term outcomes.

DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest.

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Current status of acute rheumatic fever and heart disease in South Africa: Is it on fire, dead, or smouldering?



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INTRODUCTION

Rheumatic heart disease (RHD) is the most common acquired heart disease in people aged under 25 years. It affects an estimated 55 million people worldwide and claims approximately 360 000 lives each year, mostly from low- to middle-income countries.⁽¹⁾

RHD results from damage to heart valves caused by one or several episodes of acute rheumatic fever (ARF), which is a complex autoimmune inflammatory reaction to a throat infection caused by the group A β -haemolytic *Streptococcus* (GAS) organism in genetically susceptible individuals, most often during childhood. It is preventable through controlling the spread of GAS by addressing poverty and overcrowding, and prompt treatment of streptococcal throat infections with antibiotics.⁽¹⁾

Despite RHD's eradication in many parts of the world, it remains prevalent in sub-Saharan Africa, the Middle East, Central and South Asia, the South Pacific, and among immigrants and older adults in high-income countries (HIC), especially indigenous peoples.⁽¹⁾ RHD epidemiology in Africa, where it remains an important health problem, is largely unknown and poorly documented. Prevalence rates vary in relation to poverty, limited education, awareness, and inadequate healthcare infrastructure.⁽²⁾

PREVALENCE OF RHD IN SOUTH AFRICA

The prevalence of RHD in South Africa (SA) was first documented by McLaren, et al. in the 1970s, who reported an overall prevalence rate of 6 - 9 / 1 000, based on clinical examinations among children in Soweto, Johannesburg.⁽³⁾ Studies done in the last 2 decades show an echocardiography-based prevalence rate of 4.9 / 1 000 in Grade 10 - 12 learners in central SA (Bloemfontein, Kimberley, Welkom, Brandfort), while a similar study in Cape Town showed a 8.1 / 1 000 prevalence rate in the 15 - 19 year age group in Bonteheuwel and 32 / 1 000 in Langa, both socio-economically disadvantaged population groups with Langa being the most affected.^(4,5) These studies indicate a clear regional variation in the prevalence of RHD in SA.

NOTIFICATION OF ARF

Although ARF was declared a notifiable disease by the Department of Health in 1989, a study in 2006 showed that very few physicians were aware that rheumatic fever is a notifiable condition and that the notification system was dysfunctional in SA.^(6,7) Consequently, without proper reporting, far less is known about ARF than RHD.

DECLINE OF ARF/RHD IN SA

An indication of the status of ARF in SA is shown in a report documenting a substantial decline in the frequency of both ARF and RHD in children over a 17-year period (1993 - 2010) at the Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg. CHBAH is a tertiary care institution serving the population of Soweto and southern Gauteng, which are mainly peri-urban areas, with a smaller rural population originating from the North West Province. An improved socio-economic environment and better primary healthcare availability were thought to contribute to the decline.⁽²⁾ Another report showed a similar downward trend in the prevalence of RHD among children in the Limpopo Province.⁽⁸⁾

A hospital-based study conducted in Soweto in 2006 / 2007 revealed a high incidence of new RHD cases among patients older than 14 years, with an average of 24 cases / 100 000 / year. There was a high frequency of complications documented, with 26% being treated for bacterial endocarditis and 22% needing heart valve replacement or repair within 30 months of their initial diagnosis.⁽⁹⁾ Severe rheumatic valve disease and heart failure have a devastating impact on the potential economically active young adults and pregnancy outcomes in young women. With the promise of a possible downward trend in the frequency of ARF / RHD in children in some parts of SA, a reduction in the frequency of RHD in adults is likely to follow.^(2,8)

HISTORY OF ARF/RHD

A historical timeline reveals a substantial decline in research interest and funding for ARF / RHD worldwide between 1970 and 2000, following the decline in incidence in HICs after the 1960s.⁽¹⁰⁾ The World Health Organization (WHO), although attempting to introduce preventive measures against ARF / RHD during this period, was more focused on the oversight of other infectious diseases, such as malaria, tuberculosis, human immunodeficiency virus (HIV), and acquired immunodeficiency syndrome (AIDS).

A subsequent resurgence of interest in ARF / RHD in Africa between 2000 and 2010 was driven by publications such as the Drakensberg Declaration and the Mosi-o-Tunya call to action.^(11,12) Between 2015 and 2020, there was a proliferation of school screening and secondary prophylaxis, as well as attempts to understand the genetic predisposition to ARF, and an improvement in diagnostic strategies for GAS pharyngitis worldwide. In addition, there has been a push for polyvalent vaccine development; however, this endeavour has been stalled because of the heterogeneity of the GAS organism.⁽¹⁰⁾

CURRENT STATUS OF ARF/RHD IN SA

The current status of ARF / RHD in SA is largely unknown. Anecdotally, there has been no substantial change in the observed frequency of children presenting with ARF / RHD to large tertiary referral hospitals across various provinces between 2014 and 2024.⁽¹³⁾ An email survey sent to the Paediatric

Cardiology Unit heads at the major academic institutions still show higher numbers of ARF / RHD in the Eastern Cape, Steve Biko Academic Hospital (referrals from Limpopo, Mpumalanga, North West Province), and KwaZulu-Natal (personal communications with Prof Masonwabe Makrexeni, Prof Belinda Mitchell, and Dr Ebrahim Hoosen, respectively) than CHBAH (Prof Antoinette Cilliers) and the Free State (Prof Stephen Brown). Children with ARF / RHD admitted to CHBAH are so infrequent that few medical students are exposed to the clinical presentation and management of the disease. This information suggests that ARF / RHD has died in southern Gauteng but is smouldering in some provinces and regions with higher levels of poverty, such as the Eastern Cape, Limpopo, and KwaZulu-Natal.

REGIONAL SOCIO-ECONOMIC DIFFERENCES

The variations in frequencies of ARF / RHD in SA may be explained by regional wealth differences reflected in the Gross Domestic Product (GDP) and larger rural populations in some provinces. A provincial breakdown of GDP in 2023 showed that the Northern Cape, Free State, North West Province, Limpopo, and Eastern Cape had lower GDPs than the better-performing provinces, such as Gauteng, KwaZulu-Natal, and Western Cape.⁽¹⁴⁾ The Eastern Cape, KwaZulu-Natal, and Limpopo provinces also have the largest proportions of rural populations, with over 70% of the country's rural children residing there.^(15,16)

TREATMENT

No proven treatment alters the natural history of ARF. Therefore, prevention is the key to reducing the burden of disease, which, apart from eradicating poverty and overcrowding, includes detection of GAS sore throats in susceptible individuals and treatment with oral or parenteral penicillin. Provision of secondary prophylaxis in the form of monthly intramuscular or oral penicillin to patients who have had previous ARF or RHD reduces the risk of recurrences and relies on patient compliance; however, it does not reduce the development of chronic RHD or mortality due to RHD.⁽¹⁷⁾

SUMMARY

The continuation of healthcare challenges in SA and the persistence of preventable diseases such as ARF / RHD are fuelled by severe socio-economic challenges and increasing unemployment.⁽¹⁸⁾ In addition, the COVID-19 pandemic that gripped the world and SA from 2020 to 2023 shifted the focus on health priorities away from common diseases such as HIV, tuberculosis, and ARF.⁽¹⁹⁾ It is possible that a resurgence in the prevalence of ARF / RHD, as well as other preventable infectious diseases, may occur in the foreseeable future.

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A simple guide to analyse data: Descriptive statistics in quantitative research

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STATISTICAL ANALYSIS

Statistical data analysis can be divided into two big domains: descriptive statistics and inferential statistics. The process of statistical inference in drawing conclusions about the entire population is based on the information from a sample.⁽¹⁾ Notably, “the inferential statistics process fails if the sample is not representative of the population”.⁽²⁾ To achieve statistical inference, the first step of data analysis before hypothesis testing is descriptive statistics, which is directly linked to the research questions or the study objectives. This guide assumes that sampling and sample size were adequately considered before data analysis. The various steps involved in the analysis of descriptive data are discussed below.

EARLY STAGE: COLLECTING DATA

REDCap (Research Electronic Data Capture) is a tool used to build and manage online surveys and databases.⁽³⁾ This software is widely applied in clinical research scenarios and basic sciences, reducing data entry errors. The data captured with REDCap can be exported directly to Excel or any statistical package (SPSS, STATA, SAS, R, etc.). For simple data entry and quick data management, an Excel spreadsheet serves its purpose, and it can perform primary statistical analyses. Data saved in Excel can also be exported to any statistical software (Statistica, SPSS, STATA, SAS, R, GraphPad, etc.).

All variables for each participant should be stored in a single, merged dataset to ensure compatibility in analysis. A frequent hurdle in inferential statistics arises when demographic and clinical data are captured in different formats and/or placed on different sheets. Consequently, the demographic data cannot be analysed together with the rest of the data. An example is a comparison between male and female patients with idiopathic cardiomyopathy, or predicting ischaemia in patients with severe hypertension by adjusting for age and sex, which cannot be performed unless the clinical and demographic data are merged.

It is advised not to use a statistical programme to capture data initially. The decision of which statistical software to use depends on the nature of the analysis.

DETECTING MISSING DATA

Missing data is a frequent problem in medical research. Excluding individuals with missing observations can yield substantial bias in the results and reduce statistical power. Different methods have been introduced to handle missing data. The most recommended method is multiple imputation (MI).⁽⁴⁾ This method is already included in standard statistical programmes, such as STATA, SPSS, and R. However, the primary approach to identifying missing data is to run a descriptive analysis.

All outputs of descriptive statistics, regardless of the statistical software used, will show the number of observations per variable (n). Thus, a first reading of the results should be to check the size of the study sample (N) and n per group if more than one group is included. The purpose is to verify if the numbers concur with the initial sample size calculations, stated as such in the methods section of the protocol.

An easy way to detect missing data is to examine the number of observations; whether key variables, such as age and sex, have consistent numbers of observations, which may reveal missing data patterns, e.g. age (n = 135), sex (n = 135), heart rate (HR) (n = 132), body mass index (BMI) (n = 123), and ejection fraction (EF) (n = 132). Subsequently, the identification of patients who exhibit missing observations may assist with the retrieval of the omitted data. If variables such as sex and age are missing, those participants will have to be excluded from the analysis, unless MI techniques are applied.

REPORTING DATA

In the description of the summarised data in the results, variables must be classified according to the scale in which they were measured: nominal (categorical and ordinal) or numerical (discrete [integer], continuous) (Figure 1).⁽⁵⁾ Categorical variables are presented as frequencies (n) and percentages (%). Continuous data following an approximately normal distribution (symmetric) are summarised as the mean and standard deviation (SD) (e.g. age (SD) 29(6)), otherwise median and interquartile range (IQR) (75%–25% quartile) (e.g. BMI 26 [17–52]).⁽⁶⁾

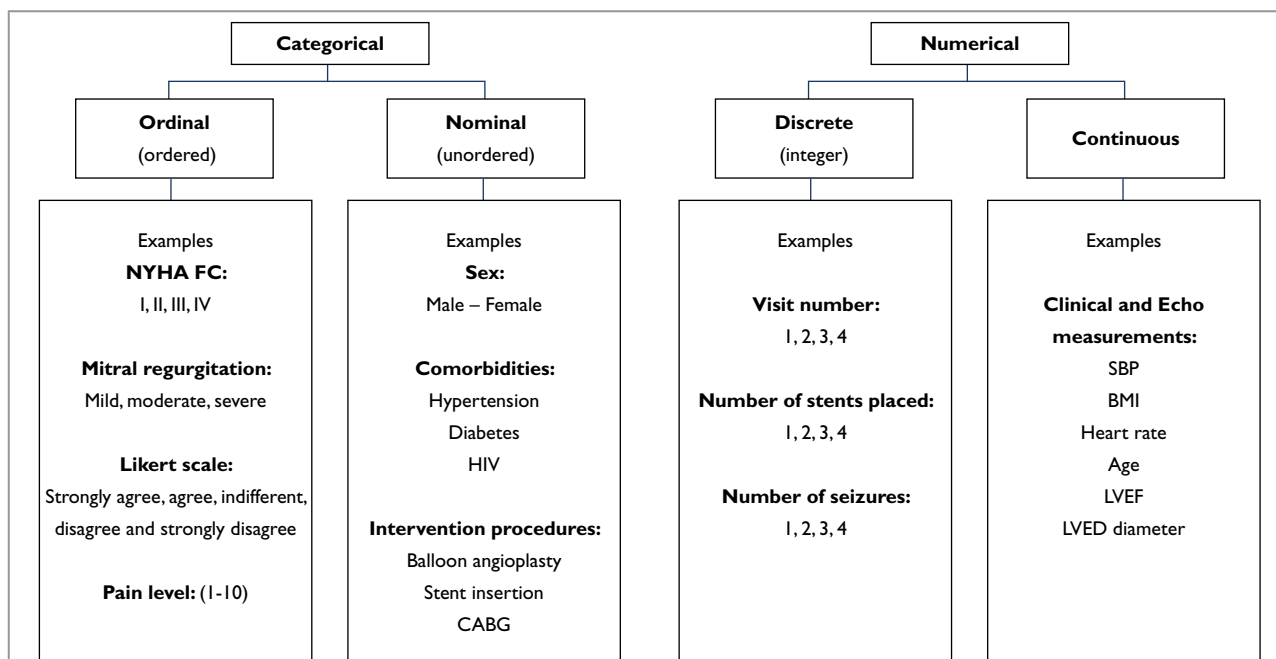


Figure 1: Variable types according to the scale of measurement

Modified and adapted from "Petrie and Sabin, Medical biostatistics at glance"⁽⁶⁾

It is essential to depict data graphically to better guide one with the inferential statistics (e.g. by detecting skewness to the right or left, outliers, etc.). Graphic methods, such as histograms, box plots, normality plots, and/or a statistical test (e.g. the Shapiro–Wilk test), can be used to assess normality. The conventional summary statistics of reporting discrete data (e.g. number of stents) are frequency and percentages, or median and IQR (e.g. parity 2 [1–4]).⁽⁶⁾

PRESENTING DATA IN A TABLE

Descriptive tables are usually sufficient to summarise sample characteristics; there is no need to supplement the information with a pie chart or bar graph. There are cases where a figure highlighting a particular variable, such as “multiple comorbidities”, could better visually summarise data than a table.

Herewith, some recommendations to draw up a comprehensive table (examples provided in Tables 1a and 1b):

- Identify the type of variables (categorical or numerical) to select the summary statistics adequately.
- Ensure that the information in the table supports the objectives of the study.
- Always display the “N” for the total sample and the “n” for each group (if more than one group) in the title of the table, on the first row, or the second row.
- Always write the units of the variables.
- Always clarify if continuous variables are expressed as means (SD) or median (IQR) next to the variables’ name or in the footnotes.

- Do not display percentages without frequencies if the sample/group size is not shown in the table, especially when the sample size is small or varies between groups.
- Ensure that percentages in columns add up to 100%; otherwise, include a sentence in the footnotes of the table (e.g. “Column percentages do not add to 100% as patients can have more than one condition.”).
- Write out abbreviations with the full wording. If the name of a variable is too long and there is not enough space for full words, list the abbreviations in the footnote.
- If the study design is cross-sectional and includes more than one group of patients p-values of comparisons (t-tests or chi-square tests) between the characteristics can be added as an extra column.
- If the study design is longitudinal (e.g. EF measurements at baseline, 6 months, and 1 year), the table should include only baseline data (see Table 1a).
- Symbols indicating the significant differences could be placed next to the results and the p-value in the footnotes (see Table 1b).
- It is not advisable to collapse categorical data before inferential analysis.
- Never duplicate results in figures and tables; it is redundant.

Printing out the table will help to visualise the data and guide the researcher for subsequent analyses. A thorough descriptive analysis will lead to the selection of appropriate statistical tests, such as an independent or paired t-test, chi-square test, ANOVA, Mann–Whitney U test, and Kruskal–Wallis in inferential statistics.

TABLE Ia: Baseline clinical and echocardiographic characteristics.*

Variables	Total (n = 120)
Age (years)	38.7 ± 12.8
Sex, female, n (%)	60 (50)
Body mass index (kg/m ²)	27.9 ± 5.8
Systolic blood pressure (mmHg)	122 ± 17
Diastolic blood pressure (mmHg)	77 ± 10
Heart rate (bpm)	77.2 ± 12.6
Ejection fraction (%)	62.5 ± 8.1
LV mass index (g/m ²)	61.1 ± 18.0
Left atrial volumes	
Max-LAVi (ml/m ²)	19.7 ± 5.9
Min-LAVi (ml/m ²)	7.7 ± 3.2

Data reported as mean ± standard deviation, unless otherwise noted.

LV: left ventricular, max-LAVi: maximum left atrial volume index, min-LAVi: minimum left atrial volume index.

* Table extracted partially and adapted from Meel, et al.⁽⁷⁾

TABLE Ib: Clinical and demographic characteristics of hypertensive patients with normal and low ejection fraction.*

Variable	HTNEF group	HTLEF group
Number of patients	41	41
Age (years)	55.5 ± 8.4	55.1 ± 9.0
Women/men (n)	22/19	22/19
Body mass index (kg/m ²)	30.2 ± 4.9	28.9 ± 4.5
NYHA functional capacity		
I	26 (63%)	12 (29%)**
II	15 (37%)	14 (34%)
III		15 (37%)
Duration of hypertension (years)	15.6 ± 8.4	12.2 ± 6.4
Duration of heart failure (years)	1.8 ± 1.0	3.3 ± 1.6**
Systolic blood pressure (mmHg)	141 ± 14	156 ± 8
Diastolic blood pressure (mmHg)	84 ± 12	89 ± 11
Heart rate (bpm)	75 ± 12	81 ± 10**
Medications		
Furosemide	41 (100%)	41 (100%)
ACE inhibitors or ARBs	41 (100%)	41 (100%)
β-blockers	28 (68%)	41 (100%)

Data are expressed as mean ± standard deviation or number (percentage).

HTNEF: hypertensive with normal ejection fraction, HTLEF: hypertensive with low ejection fraction, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, NYHA: New York Heart Association.

* Table extracted partially and adapted from Maharaj, et al.⁽⁸⁾

** p-value < 0.05.

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SASCI-Mayo Clinic Fellows webinar: Managing bleeding complications in acute coronary syndrome

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Discussants are three fellows from different Universities in South Africa.

AM: Case presentation

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Mr E.W. is a 67-year-old gentleman who, aside from a history of tobacco use, is otherwise healthy. He presented to his local clinic with a two-hour history of ischaemic chest pain and was diagnosed with an acute inferior ST-segment elevation myocardial infarction (STEMI) – Figure 1.

ABSTRACT

Education remains a core purpose of the South African Society of Cardiovascular Intervention (SASCI), with an emphasis on engaging cardiology fellows in training through regular, structured educational initiatives. In support of this mission, SASCI has partnered with two of our past "Visiting Professors", David Holmes and Gregory Barsness of the Mayo Clinic in Rochester Minnesota, to host quarterly, case-based Fellows Webinars. The webinars are designed to foster critical thinking and clinical decision-making through interactive, case-based discussions and have thus far been very well received, with an average of 70 participants across Southern Africa and beyond.

Specific topics are selected by the SASCI faculty in collaboration with the Mayo cardiologists. Each webinar session has a structured agenda, starting with a clinical case presentation by a cardiology fellow. This is followed by a concise, focused lecture by a Mayo Clinic expert, to provide context and evidence-based guidance. A robust discussion then follows, moderated jointly by the SASCI and Mayo faculty, where active participation by fellows is encouraged. The session concludes with the case presenter sharing a brief follow-up, detailing patient outcomes and the rationale behind management decisions.

All cases are anonymised to protect patient confidentiality. Each webinar is recorded and made available online at <https://form.jotform.com/251685088627570>. Access is restricted to verified healthcare professionals.

In line with our commitment to ongoing academic contribution, each webinar is intended to culminate in a peer-reviewed manuscript for publication in the *South African Heart Journal*. As part of the webinar series, the current manuscript focuses on uncommon bleeding complications in patients with acute coronary syndromes, a clinically relevant yet often under-appreciated challenge in contemporary interventional cardiology.

SA Heart® 2025;22:191-195

On admission, his pulse rate was recorded as 41 beats per minute and his blood pressure at 118/71 mmHg. He was given stat doses of oral Aspirin 300 mg, Clopidogrel 300 mg and subcutaneous Enoxaparin of 80 mg. After excluding any major contraindications, systemic thrombolysis with 100 mg Alteplase was administered. Laboratory investigations showed no major

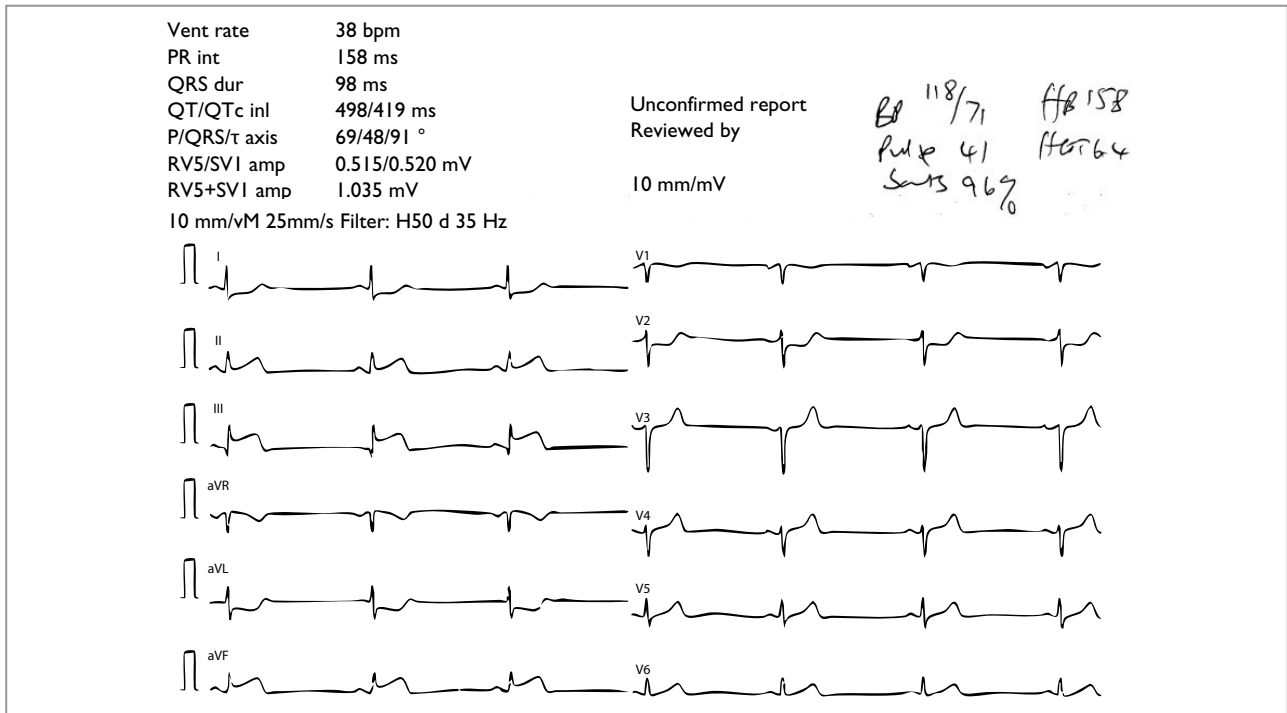


FIGURE 1. A 12-lead ECG showing an acute inferior STEMI.

abnormalities. There was a good clinical response with resolution of his chest pain and ST-segment elevation. As part of the local clinical practice, he was referred to Tygerberg Hospital on the Friday evening to await angiography the following Monday.

Twelve hours after arrival, he developed a right hemiplegia with expressive aphasia. An urgent CT brain scan demonstrated a left occipito-parietal haematoma. Instructions for immediate cessation of all antiplatelet and anticoagulant therapy were issued and an urgent neurosurgical opinion was sought. The initial plan was for conservative management but a follow-up CT brain scan done after 24 hours showed expansion of the haematoma volume from 40 ml to 68 ml – Figure 2.

He subsequently underwent emergency evacuation of the haematoma with platelet and cryoprecipitate transfusions. He was referred for intense inpatient rehabilitation, and he had no recurrence of chest pain within the first week of his admission. In summary, we had a patient who presented with a high-risk acute coronary syndrome, without any clear risk factors for life-threatening bleeding complications. He had clinically successful thrombolysis but unfortunately this was complicated by an intracranial haemorrhage. The next options are of major importance and include the questions

- At this point, would he still need invasive coronary angiography, and if so, when?
- Or should we let sleeping dogs lie because of any bleeding risk that comes with coronary intervention?
- Do we need to know his LV function?



FIGURE 2. A CT brain image showing the large intracerebral haematoma.

Discussant 1: The patient had a BARC 3C bleed which is significant and will impact post intervention antiplatelet therapy. I would let the neurosurgical management take preference and let them decide when coronary intervention is safe.

Discussant 2: The patient has had a life-threatening cerebral bleed, and the infarct is 2 days old with established Q-waves on the ECG so I think there is little need for angiography at this stage.

HW: What about just doing a diagnostic angiogram with no intervention? Could that not help your decision-making?

Discussant 2: I don't see much benefit in that. One can consider non-invasive ischaemia testing but unless he becomes haemodynamically compromised or has ongoing angina, I would prefer to let him recover from his intracranial bleed first.

GB: Excellent case. Although strokes and bleeds are rare (< 1%), they are uniformly fatal so it's rare that we get a chance to discuss a case like this. I agree with your management plan and ultimately, we are going to want to see his coronary anatomy, but not at this stage. He has preserved left ventricular function, so there appears to be viability in the inferior wall. So, what if he has a sudden re-occlusion? Or develops acute ischaemic mitral regurgitation or haemodynamic compromise? How would you manage that?

Discussant 1: I think very short-term dual antiplatelet therapy may be an option but at high risk but I'm not sure what I would do.

Discussant 3: If we really have a life-threatening coronary event, one can have a look and try only ballooning to buy time but I would prefer not to stent.

Discussant 2: I think lytic is out of the question, but I would discuss risks with the patient to make an informed decision.

GB: Just so I'm clear, he just had an evacuation procedure to clear blood and not a vascular intervention, so the risk of bleeding is still there. Even if you just balloon a coronary, you will need to give anticoagulants for the intervention which would place him at risk of additional bleeding. It was a trick question really because I don't think there is a good answer. You'll only know the right answer retrospectively.

MG: Those are all good points and I agree that the time sensitivity of angiography has passed and I think the patient has reperfused and the only indication to go to the lab would be clinical. My first question to the surgeons would be when I can start low dose aspirin. I would wait on the idea of interrogating the coronaries.

HW: I would like to sketch the opposite scenario to what Greg did: if the patient remains stable, is it necessary, let's say in two weeks, to do an angiogram at all.

Discussant 1: Although CT coronary angiography is rarely indicated in infarcts, it may be useful to non-invasively exclude left main and significant proximal disease. This may be useful to plan further management without the risk of blood thinners.

SK: Valid point. May I ask what blood thinning therapy he was placed on?

AM: Nothing. What would your plan be in terms of recommencing antiplatelet therapy?

Discussant 2: I would be guided by the neurosurgeons, and they will likely prefer two weeks. I would then only start low dose aspirin.

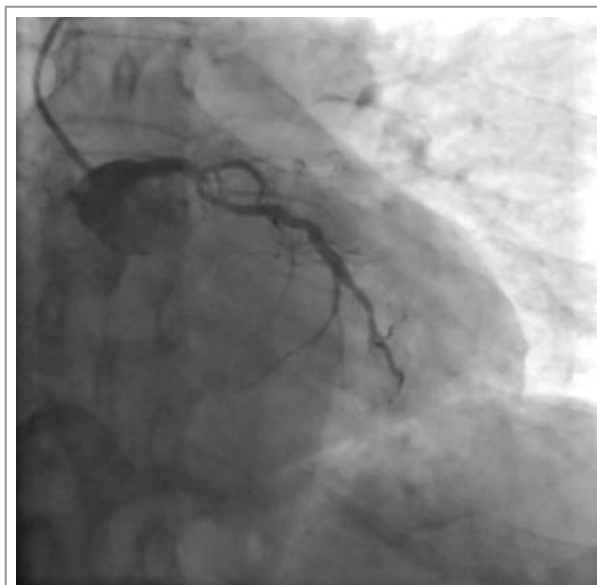


FIGURE 3. Angiographic view of the left coronary system showing an occluded LAD and diffusely diseased left circumflex artery.

MG: To come back to the CT angiogram, although it is very unlikely to be normal, I think this is a great option to exclude proximal disease, although I think in this country, somebody who has had successful lysis, resolution of ST-elevation and no symptoms may be best treated by a functional test for ischaemia. It doesn't have to be angiography.

HW: That's an interesting thought, but ischaemia testing will not identify an angiographic unstable lesion in a proximal vessel if it is not flow limiting so one might combine the 2 to decide. Arlene, shall we proceed to your management of the case?

AM: The neurosurgeons were happy to say that it would probably be safe to reinstate antiplatelet therapy after 2 weeks. His neurological fallout showed mild improvement, and we decided to proceed with coronary angiography, with a plan to define the coronary anatomy.

In the first injection, we now see that the LAD is occluded – Figure 3. The circumflex is also diffusely diseased and one of the obtuse marginals is occluded. The right coronary artery is a very large system, and it is collateralising the left system – Figure 4. The culprit from the acute event is probably in the mid-right coronary artery and the patient has normal left ventricular systolic function.

We now had a patient 2 weeks post-infarct with evidence of triple vessel coronary artery disease, but with a culprit lesion that is actually a very important vessel as it is collateralising the LAD. Now that we've seen the coronary anatomy, we'll get some more opinions from the panel about what to do.

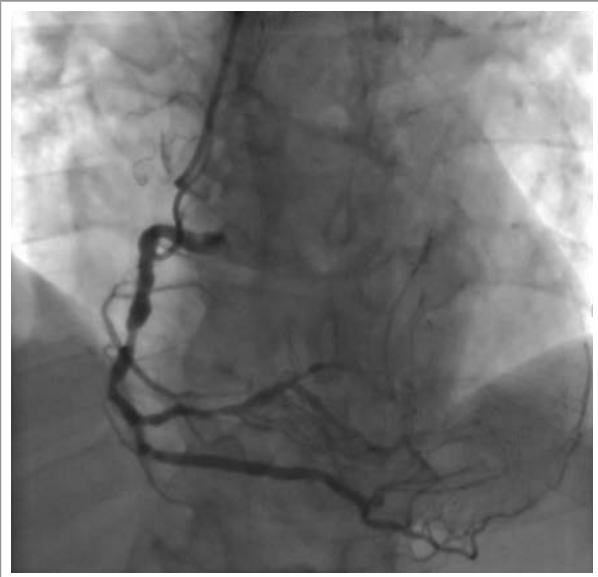


FIGURE 4. The right coronary artery is a large vessel collateralising the left. There is a midvessel lesion which we deemed to be the culprit.

Discussant 1: It's a very tricky case because even if you must do a bypass on him, unless you're going to do it off-pump, he's going to need heparinisation. An off-pump bypass may be an option, but it would be quite difficult, I suppose. I think he would get mortality benefit from revascularisation, but the risk is also very high. So, I think you'd have to put it to the patient, speak to his family. Also depending on what his recovery was like following his neurosurgical intervention, what his level of functioning is, was he mobile, was he bed bound?

Discussant 2: In my centre, this patient would be offered bypass surgery because he has triple vessel disease. Waiting time for bypass surgery in my hospital is about 3 to 6 months. This would give his brain time to heal, and you can control his risk factors. The LAD and RCA are both good targets.

HW: Two questions:

- The lesion in the RCA looks unstable, and I'm not sure we can trust it to settle over the next 3 months and if it does re-occlude, it may not be well tolerated.
- What if you work in the private sector and the surgeons say they can do the bypass tomorrow?

Discussant 2: The current guidelines also recommend a hybrid approach so one could stent the RCA now and do a bypass to the LAD at a later stage. I would target the RCA because this is the simpler lesion to treat and can explain his presentation.

MG: I guess the question fundamentally is, do you think the RCA is stable? If you think the RCA is stable, you could nurse this patient along medically until they're more neurologically out of the woods. I think a recent head bleed is a no-go for many

surgeons. So, the idea that this patient's going to go for CABG anytime soon is probably not correct. Maybe, ultimately, CABG would be a good idea, but you've got to get that patient through the next several months. So really, is there anything here that could help us decide whether to just do the mid-right in that positively remodelled, ectatic vessel? Or do we just walk away and treat medically? And I think it's a tough decision. I think there's equipoise.

GB: I think it could go either way. I think some sort of hybrid procedure is probably worthwhile to consider in the very distant future. But I like the idea of stabilising the mid-right vessel. We have data that, in general, this single vessel intervention is likely going to be safe and effective at reducing reinfarction and improving prognosis. So, I think limited stenting of the mid-right certainly seems reasonable to me. I would avoid balloon angioplasty alone. I wouldn't over-treat, but I think managing what appears to be the offending lesion or lesions in the mid-right would be reasonable. Imaging might play a role here, although, again, with the caution that you want to mitigate risk by trying to avoid doing too much. Arlene, we are dying to hear what you did.

AM: There was a question of whether the LAD could be at play, so we opted to first wire interrogate the LAD and we were quite happy it was a CTO. We then proceeded to treat the mid-right and achieved a good result with no complications. We then offered the patient 1 month of dual antiplatelet therapy. See Figure 5.

He continued inpatient rehabilitation, and we aimed to address future revascularisation options once his neurological state stabilises. Depending on his symptoms and degree of neurological recovery, it would either be a LIMA to the LAD or a formal CTO procedure percutaneously.

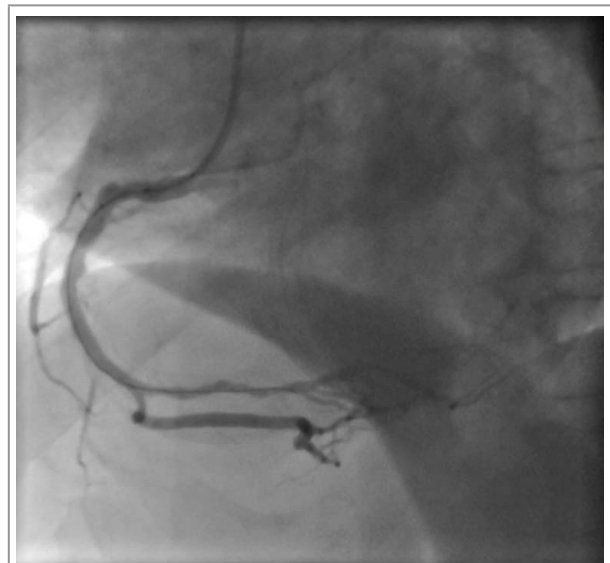


FIGURE 5. Right coronary artery after stenting the mid vessel lesion.

GB: That was great, great, great management. Fantastic. Just amazing that the patient survived all of that. I mean, that's, that's really, really, really remarkable.

HW: Who thinks he's going have symptoms? Are we going to end up treating this LAD?

GB: So I think in answer to your question, it depends on his neurologic state. If he has improved neurologic status, then he may well have some symptoms. I think, especially with the LAD residual territory, if his prognosis is reasonable, there's going to be some sort of benefit to complete revascularisation, survival benefit even. But it depends on his wishes and his underlying state. But yeah, fascinating.

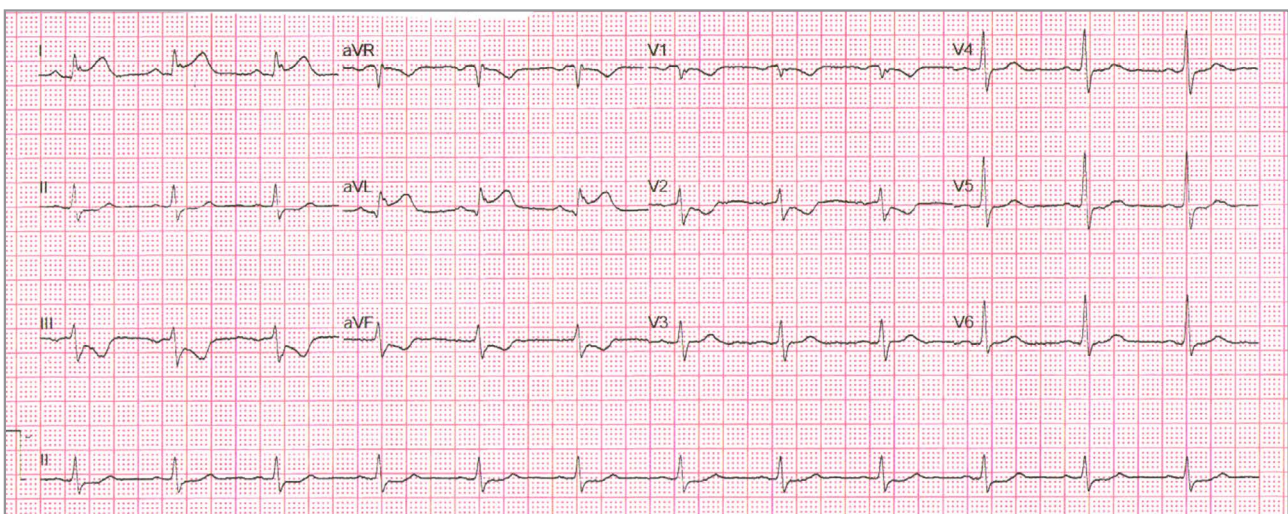
MG: Great case. I agree that time will tell for this case, I think, which way it's going to go. He may never really do very much to have angina, to have a lot of ischaemia. He may do well with this and medical therapy. If the patient becomes more active, he's a young person, then dealing with the LAD may become an issue. Although with some of these images, it's hard to tell how diffuse the disease is in the LAD. You know, he's probably going to come back to the cath lab at some point in the future

SK: Well, that was a fantastic discussion. Thanks everybody for participating and I look forward to seeing you soon for the next one.

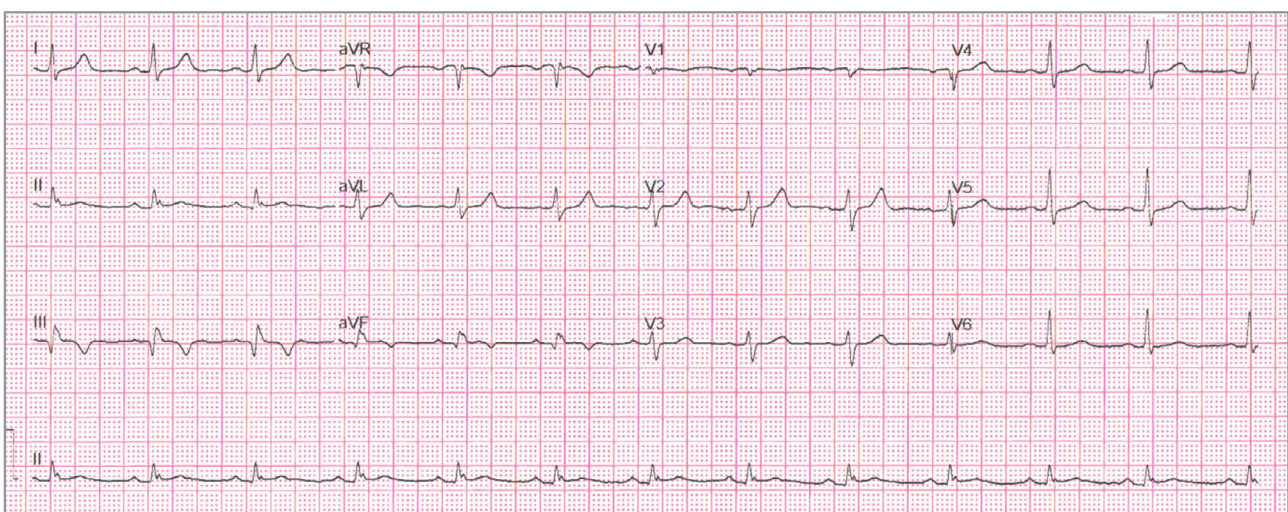


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A 64-year-old man presents to the emergency room with an acute episode of chest pain.



A 90-minute electrocardiogram (ECG) is performed post-thrombolytic therapy.



QUESTION: What is the diagnosis?

- a. Acute high lateral ST-segment elevation myocardial infarction (STEMI).
- b. Acute high lateral STEMI and inferior/posterior STEMI.
- c. Acute inferior/posterior STEMI.

QUESTION: What is the best explanation for the findings?

- a. The patient had 2 STEMIs in 2 coronary territories.
- b. Coronary anomaly.
- c. Lead reversal.

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

ANSWER on page 198



OVERVIEW OF THE ECGS

The presenting ECG shows a regular rhythm, with a rate of 72 bpm. The P wave axis is at 0 degrees. There is 1.5–2 mm ST-segment elevation in leads I and aVL, and a 1–2 mm ST-segment depression in leads III, aVF, V1, and V2. The 90-minute ECG shows a regular rhythm, with a rate of 78 bpm. The P wave axis is +45 degrees. The ST-segment elevation and depression have resolved. Q waves are visible in leads III and aVF, with T wave inversion.

MORE DETAILED ANALYSIS OF THE ECGS

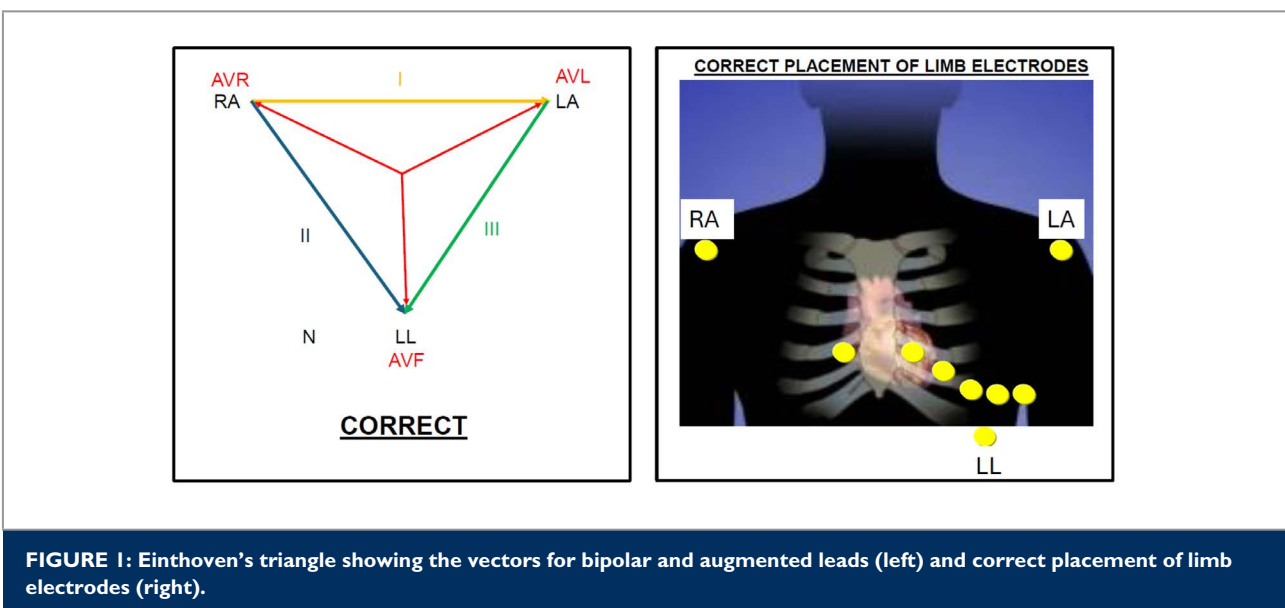
The presenting ECG shows features of an acute high lateral STEMI with ST-segment elevation in leads I and aVL. ST-segment depression in leads III and aVF may be due to reciprocal change. The P wave axis is not compatible with a sinus rhythm and suggests an ectopic atrial rhythm. An acute high lateral STEMI may have isolated ST-segment elevation in V2 (the so-called “South African flag sign”).⁽¹⁾ In this ECG, ST depression is present in V1 and V2, which cannot be explained by reciprocal change alone. A concomitant posterior STEMI in the absence of an acute inferior STEMI is a possible explanation; however, it is unusual with an acute high lateral STEMI. Posterior leads were not performed in the acute setting and would have been useful.

The 90-minute ECG post-lytic therapy shows apparent resolution of ST-segment elevation in leads I and aVL. The ST-segment depression in leads III, aVF, V1, and V2 have also

resolved. Notably, there are now pathological Q waves present in leads III and aVF, with T wave inversion, suggesting an evolved acute inferior STEMI. There is also a change in the P wave axis to 45 degrees (now compatible with a sinus rhythm). No Q waves are seen in leads I and aVL to suggest an evolved high lateral STEMI. A dominant R wave in V1 is not present to suggest an evolved posterior STEMI.

In summary, this patient appears to have ST-segment elevation and depression compatible with high lateral STEMI (presenting ECG), inferior STEMI (90-minute ECG), and a possible posterior STEMI (presenting ECG). While an inferior and posterior STEMI can occur together, usually due to an occlusion in a dominant right coronary artery, a high lateral STEMI is usually due to an occlusion in the first diagonal branch artery, implying concomitant occlusions in 2 different coronary arteries, which is highly unlikely. A coronary anomaly or collateral supplying both these territories is also very unlikely.

So, did this patient have a high lateral STEMI and/or an inferior/posterior STEMI? A big clue is the change in the P wave axis and the unchanged aVR in both ECGs. Incorrect placement of the limb lead electrodes can account for the change in the P wave axis. It can result in the apparent change in ST-segment elevation/depression in different territories. The abnormal P wave axis suggests that an incorrect lead placement occurred on the presenting ECG.



In this case, the left arm (LA) and left leg (LL) electrodes have been swapped on the presenting ECG (incorrect lead placement). The right arm (RA) electrode is in the same place for both ECGs, as aVR is unchanged. To understand how these changes can take place, an understanding of the normal lead electrode placements and Einthoven's triangle is needed (Figure 1).

The 3 bipolar leads are leads I, II, and III:

- Lead I is the voltage difference between the LA and RA electrodes directed towards the LA at 0 degrees.
- Lead II is the voltage difference between the LL and RA electrodes directed towards the LL at +60 degrees.
- Lead III is the voltage difference between the LL and LA electrodes directed towards the LL at +120 degrees.

The 3 augmented unipolar leads are leads aVL, aVF, and aVR (directed from Wilson's central terminus):

- Lead aVL is directed towards the LA electrode (-30 degrees).
- Lead aVF is directed towards the LL electrode (+90 degrees).
- Lead aVR is directed towards the RA electrode (-150 degrees).

When the LA and LL lead electrodes are swapped (LA/LL reversal), Einthoven's triangle changes (Figure 2):

- aVR remains unchanged.
- Leads I and II are swapped.
- Leads aVL and aVF are swapped.
- Lead III becomes inverted.

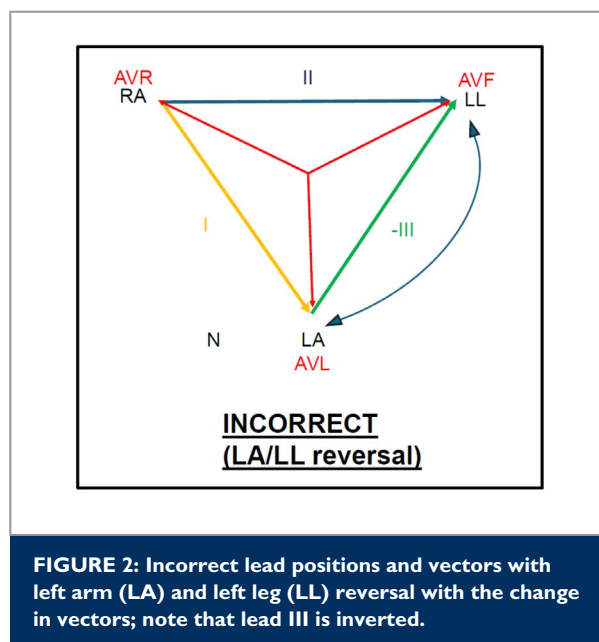


FIGURE 2: Incorrect lead positions and vectors with left arm (LA) and left leg (LL) reversal with the change in vectors; note that lead III is inverted.

We can now look at the presenting ECG where the lead swap occurred and compare it with the “corrected” lead positions (Figure 3). It becomes clear when the leads are corrected that the patient has an acute inferior/posterior STEMI with ST-segment elevation in II, III, and aVF, with reciprocal ST-segment depression in aVL.

Therefore, the answers are c) acute inferior/posterior STEMI, and c) lead reversal. An occlusion in a coronary anomaly (e.g. a “wrap-around” LAD [left anterior descending] that supplies the anterior and inferior wall of the left ventricle) can produce an acute anterior/inferior STEMI with ST-segment elevation in V1–V3, II, III, and aVF. This patient had a coronary angiogram the

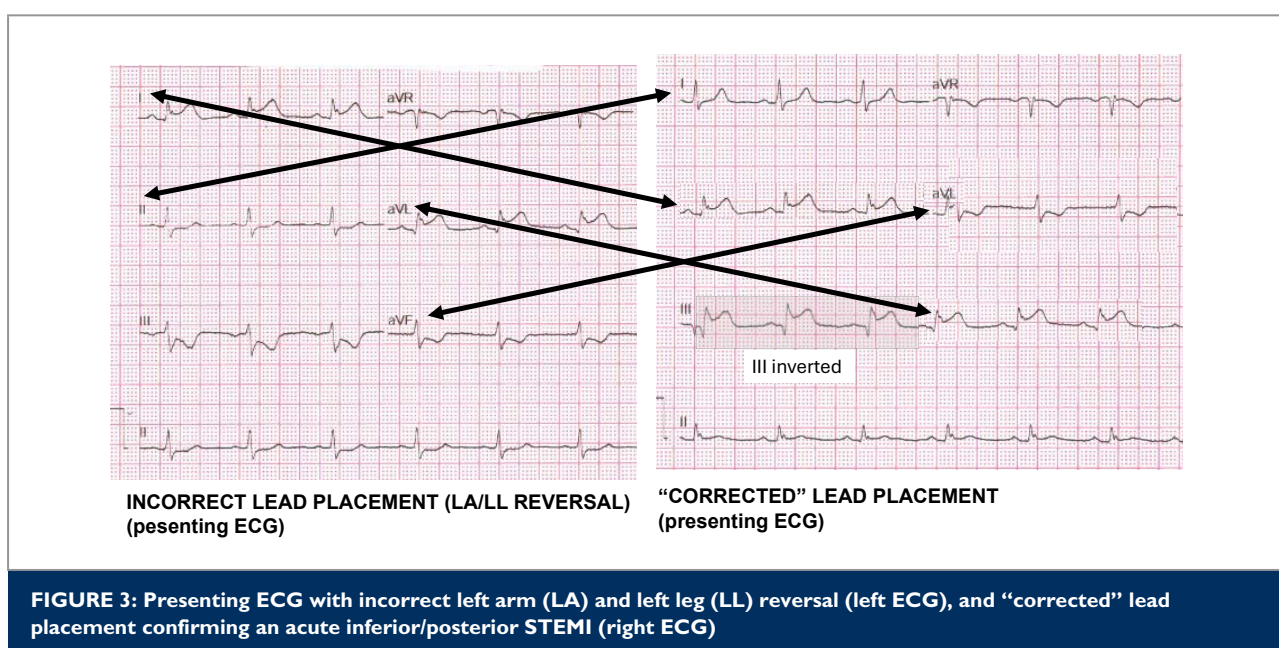


FIGURE 3: Presenting ECG with incorrect left arm (LA) and left leg (LL) reversal (left ECG), and “corrected” lead placement confirming an acute inferior/posterior STEMI (right ECG)

following day, which confirmed a severe stenosis in the proximal right coronary artery, which was stented.

DISCUSSION

Many different combinations of limb lead reversal can occur (including LA/RA, LA/LL, and RA/LL). In addition, clockwise rotation of leads (RA becomes LA, LA becomes LL, and LL becomes RA) or anticlockwise rotation of leads can occur (RA becomes LL, LL becomes LA, and LA becomes RA) – which can be quite confusing! Obviously, the chest leads will not change with limb lead reversal.

The most common lead reversal is RA/LA reversal. With RA/LA reversal:

- aVF remains unchanged.
- Leads II and III are swapped.
- Leads aVL and aVR are swapped.
- Lead I becomes inverted.

Think of lead reversal when an abnormal P wave axis is present on an ECG, and whenever there are unexplained changes in QRS/ST or T wave morphologies between ECGs performed at different times.

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CARDIAC IMAGING QUIZ

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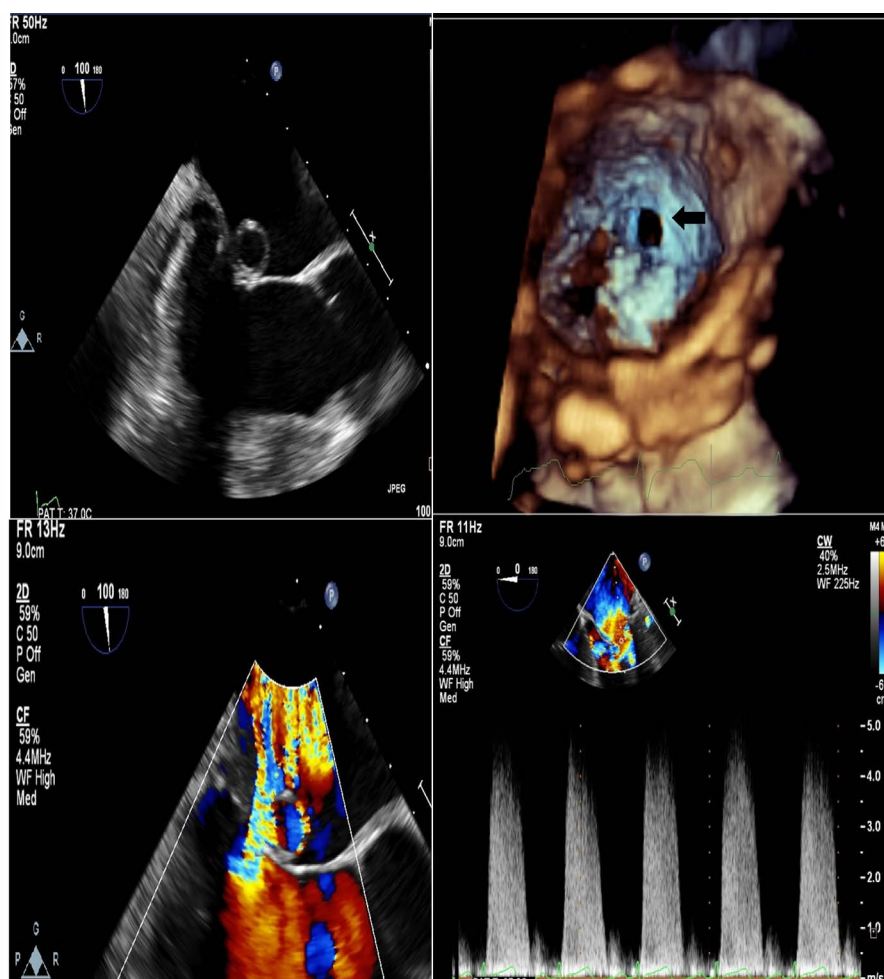
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QUESTION: What is the diagnosis?

- A. Infective endocarditis.
- B. Marantic endocarditis.
- C. Mitral valve prolapse.
- D. Mitral valve blood cyst.

ANSWER

(A) Infective endocarditis.

These echocardiographic images belong to a 30-year-old male who presented with heart failure. No relevant past medical history was noted. No clinical features of infective endocarditis (IE) were noted.

Transoesophageal echocardiogram at mid-oesophageal level shows anterior (A3 scallop) mitral leaflet perforation with no obvious vegetation (top left image). This was confirmed on a three-dimensional enface view of the mitral valve (top right image). The leaflet perforation is characterised by a defect in the leaflet tissue through which flow is observed (bottom left image). Additionally, diffuse thickening of the posterior mitral leaflet is noted (top left image). There is concurrent mitral regurgitation (bottom left and right images). Blood culture was negative for IE, which was suspected.

Echocardiographic characteristics of IE form part of the Duke's major diagnostic criteria. Echocardiography is the primary imaging modality for diagnosing IE and evaluating the structural and functional damage to cardiac tissues. Key echocardiographic findings for diagnosing and assessing local complications of IE include the characteristics and size of vegetations, evidence of valvular destruction (leaflet perforation in this case), and perivalvular complications, such as abscesses and/or pseudoaneurysms – often accompanied by a pericardial effusion.

In certain clinical situations, additional imaging techniques, such as computed tomography, magnetic resonance imaging, and nuclear imaging, are necessary to confirm or rule out IE, assess the extent of cardiac involvement, and identify extracardiac complications. These modalities can also offer valuable insights for optimising patient management.

Each imaging technique has its strengths and limitations. The choice of the most appropriate strategy depends on the availability of resources and expertise. However, when clinically indicated, a multimodality imaging approach is crucial and should be actively promoted by the endocarditis team for patients with suspected IE.

Microbiology consultation is essential in cases of suspected IE (with negative blood cultures after 48 hours). A structured diagnostic approach includes targeted blood cultures followed by serological testing for specific pathogens and autoimmune markers based on clinical context and local epidemiology. Surgical specimens should undergo culture, histology, and molecular analysis (16S/18S rRNA sequencing) to detect pathogens.

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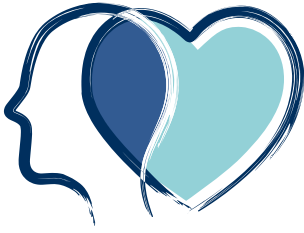
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