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Front cover:
Cape Recife nature reserve:
The original Portuguese name "Cape Recife" translates to "Cape of the reefs".
Photo: Ruchika Meel

GUEST EDITORIAL

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A contemporary perspective on coronary artery disease in sub-Saharan Africa

Since the turn of the 21st century, death due to non-communicable disease has steadily increased in South Africa. Deaths due to cardiovascular diseases accounted for 12.9% of deaths in 2008 and steadily increased to 17,6% in 2018 with Black Africans having the highest age-standardised mortality rates, followed by Indian / Asian and Coloured population groups, at 170.63 and 168.23 per 100 000, respectively.[1]

Coronary artery disease (CAD) is the leading cause of death globally,[2] and in this issue of the Journal several studies present data that could be useful in understanding the landscape of CAD in South Africa. Naidoo[3] describes ethnic differences in risk factor profiles among patients with coronary artery disease (CAD) at Grey's Hospital in KwaZulu-Natal from 2012 - 2016. In 886 patients with CAD, 60.8% were of Indian ethnicity. African patients with CAD had less clustering of traditional risk factors for CAD, were significantly younger (mean 54.9 years), were more likely to present with ST-elevation myocardial infarction and were more frequently found to have single vessel CAD compared with other ethnic groups. Indian patients had the highest prevalence of dyslipidaemia (97.8%), diabetes (65.9%), family history of CAD (55.1%) and prior history of myocardial infarction (26.7%). The findings in the current study mirror data from Cameroon, Kenya and India, and previous data from the same group in Durban.[4] It is interesting that the rates of dyslipidaemia among Africans from the Pietermaritzburg area were so high (88%) in the current study, suggesting that more screening and primary prevention for traditional risks factors is needed in this population. It would have been interesting to know the HIV rates among younger patients presenting with a first myocardial infarction since this is an important risk factor for CAD in Africa.[5]

From the same group, we learn about CAD among patients presenting with atypical chest pain.[6] Retrospective data was collected from patients presenting to Inkosi Albert Luthuli Central Hospital with stable chest pain. Hospital records of patients with chest pain who did not satisfy the criteria for typical angina but had undergone both nuclear imaging and coronary angiography were evaluated over a 6-year period (2002 - 2008). Nearly 10% of 5 378 patients were deemed to have atypical / non-anginal chest pain and 173 of these underwent both non-invasive ischaemia testing and invasive coronary angiography. Unfortunately, characterisation of the chest pain did not prove helpful in differentiating patients with and without obstructive CAD. These data showed that patients from Durban with obstructive CAD may present with atypical chest symptoms, and it remains important to consider their risk factor profile in deciding whether patients should undergo further invasive testing. The authors highlight diabetes and microvascular

dysfunction as possible reasons for atypical presentations in this population. Non-invasive testing may show ischaemia in patients with microvascular dysfunction but will not necessarily indicate obstructive CAD.[7]

Whether percutaneous coronary intervention (PCI) with second generation drug-eluting stents (DES) can be safely used vs. coronary artery bypass (CABG) surgery remains controversial in the treatment of multi-vessel CAD. Sahue, et al.[8] prospectively followed 2 cohorts of patients with multi-vessel CAD who underwent either PCI (n=30) or CABG (n=30) for 5 years. Although repeat revascularisation was higher among patients who underwent PCI, major adverse cardiovascular and cerebrovascular events were similar between the 2 groups. As this was not a randomised-controlled trial, the decision regarding method of revascularisation was taken by the attending cardiologist and cardiovascular surgeon. Naturally, this results in a selection bias. For example, only 13 of the PCI group compared with 25 of the CABG group had triple vessel disease. Furthermore, few data are presented on the complexity of the CAD in the 2 groups. It would have been interesting to know the SYNTAX and EURO-2 scores to adequately compare the 2 groups. Recent European Society of Cardiology guidelines would certainly support PCI in multi-vessel disease of low-to-intermediate anatomic complexity.[9]

From Stellenbosch, Beyers, et al.[10] evaluated STEMI care within the Tygerberg Hospital referral network. From April - December 2020, 65% of 292 STEMI patients were treated with a protocolised pharmaco-invasive strategy, while 19% were treated by primary PCI. The authors showed that a Hub-and-Spoke model for treatment of STEMI in the Western Cape yields 30-day outcomes comparable with international networks. A significant difference was observed between the pharmaco-invasive group (4.2%) and those not receiving fibrinolysis or primary PCI (22.9%) in terms of both mortality and ACS recurrence. These are important data for South Africa showing that appropriate triage and referral for STEMI patients can result in excellent outcomes. Furthermore, the data from this study can be used by other South African facilities for comparison and as a basis to improve healthcare delivery.

Conflict of interest: none declared.

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EDITOR'S CHOICE

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The Hub and Spoke model: Is it out of reach in South Africa?

Ischaemic heart disease, once thought to be uncommon in sub-Saharan Africa, is now the 8th leading cause of death among both men and women in the region.[1] In South Africa (SA), ischemic heart disease was one of the leading underlying natural causes of death in 2018, accounting for 13 598 deaths, which was 3.0% of all deaths.[2] It ranked as the 8th leading cause of death overall, and was more prevalent among males, ranking 9th among the leading causes of death for males, and 8th for females. The disease was among the top 10 leading causes of death in several provinces, including Western Cape, Northern Cape, KwaZulu-Natal, Gauteng, and Mpumalanga.[2] Data on deaths from acute coronary syndrome (ACS) in South Africa is limited, with a recent study from the Western Cape reporting a 30-day all-cause mortality rate of 6.1% for ACS patients in the region.[3]

In SA, thrombolytic therapy continues to be the main treatment for ST-elevation myocardial infarction (STEMI) due to the limited availability of percutaneous coronary intervention (PCI) in public health facilities, as well as for patients at private health facilities who cannot afford PCI.[4] There is a lack of sufficient data on the use of primary PCI in public health facilities across the country.[4] In this issue of the Journal a study by Beyers, et al. titled "Management and outcomes of patients with ST-segment elevation myocardial infarction in the Western Cape Province of South Africa", evaluated STEMI care within the Tygerberg Hospital (TBH) referral network in the Western Cape province of SA. The objectives included comparing the use of primary PCI vs. the pharmaco-invasive strategy, assessing mortality and ACS recurrence, and investigating reasons for not performing angiography or PCI. This retrospective analysis of STEMI data from the Tygerberg Registry of ACS (TRACS) included 292 patients admitted between April - December 2020. The pharmaco-invasive strategy was used in 65.1% of cases, while 18.5% received primary PCI. In-hospital mortality was 5.5%, and the 30-day mortality rate was 6.9%, with a 3.1% recurrence of ACS. They concluded that despite the healthcare challenges in SA, the pharmaco-invasive strategy, supported by a Hub-and-Spoke outreach model, produced outcomes comparable to those seen in international cohorts.

The study emphasises the importance of administering fibrinolytic therapy promptly at peripheral hospital or out of hospital facility (Spoke) before transferring patients to a PCI-capable centre (Hub). Although the mortality rate was lower in the primary PCI group (1.9%) compared to the pharmaco-invasive group (4.2%), most patients were in the pharmaco-invasive group (65.1%). Further, it was noted that the pharmaco-invasive group had lower mortality and ACS recurrence compared to the group that did not receive fibrinolysis or PCI (16%). The data highlights the importance of early thrombolysis in the SA setting. Meel, et al. and Tickley, et al. conducted similar prospective studies, a decade apart, at 2 large PCI-capable referral centres in Gauteng, focusing on STEMI patients and the time to thrombolysis.[4,5] Both studies concluded that an additional 30 - 32 lives per 1 000 could have been saved if all patients who received thrombolysis had been treated within the first hour. Tickley, et al. observed that half of the participants in their

study received thrombolysis, showing an improvement from the 37% reported by Meel, et al. a decade earlier. However, in both studies, the number of patients receiving thrombolysis within the first hour was extremely low, with only 2 patients in each study.[4,5]

The SA STEMI network conducted an observational study at private health facilities, revealing significant delays for patients needing interfacility transfers.[6] The study found that 70% of patients received reperfusion therapy at PCI-capable facilities, but only 34% received it when an interfacility transfer was necessary.

Stassen, et al. reported a total of 14 public PCI facilities in SA.[7] However, 3 provinces - North West, Northern Cape, and Limpopo - lack any PCI facilities in the public sector. As a result, thrombolysis remains the most commonly used treatment strategy for patients in the public health sector and will continue to be essential, as primary PCI requires a multidisciplinary team of skilled professionals, including an interventional cardiologist, radiographers, specialised nurses, a 24-hour PCI facility, and an efficient emergency medical service (EMS) system.[4] The pharmaco-invasive strategy facilitated by the Hub and Spoke outreach model has showed success in countries like India with resultant improved management of STEMI through a non-profit organisation, STEMI India.[8] Beyers, et al. implemented a similar model in the public health sector with positive results in the Western Cape province of South Africa. However, the question remains whether this model can be replicated in more disadvantaged provinces, which face numerous challenges. These challenges include delays in administering thrombolysis and the absence of PCI facilities in the public sector, further exacerbated by inadequate infrastructure. While South Africa's road network ranks as the 10th longest globally, many of its roads are in poor condition.[9] In the Indian Hub and Spoke model, the government financed the services, while the overall operation was managed by a private organisation.[8]

Data on the challenges in managing STEMI patients has been published by various groups in South Africa for over a decade.[3,4,5,6,7,8,10] It is now time for the government to recognise and address these reported issues by supporting and collaborating with groups such as the SA STEMI network in the development of region-specific Hub and Spoke models. STEMI care can only improve through close public and private partnership as exemplified from STEMI projects in low to middle income countries such as India, China, and Mexico.[8]

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Management and outcomes of patients with ST-segment elevation myocardial infarction in the Western Cape Province of South Africa

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ABSTRACT

Ischaemic heart disease (IHD) is the leading cause of mortality globally and ranking among the top 5 causes of death in South Africa (SA). Acute coronary syndromes (ACS), particularly ST-segment elevation myocardial infarction (STEMI), contribute significantly to this burden. Despite its importance, SA lacks comprehensive ACS data, limiting the detection, estimation of cases, and understanding of patient outcomes. This study aimed to assess STEMI care within the Tygerberg Hospital (TBH) referral network in SA's Western Cape Province. The study objectives were to evaluate the distribution of patients undergoing primary percutaneous coronary intervention (PCI) vs. the pharmacoinvasive strategy, assess mortality and ACS recurrence, and investigate reasons for not performing angiography or PCI.

This retrospective analysis of STEMI data from the Tygerberg Registry of ACS (TRACS) included 292 patients admitted between April - December 2020. The pharmacoinvasive strategy was employed in 65.1% of cases, with 18.5% receiving primary PCI. In-hospital and 30-day mortality rates were 5.5% and 6.9%, respectively, with a 3.1% recurrence of ACS.

The study concluded that despite SA's healthcare limitations, the pharmacoinvasive strategy, facilitated by a hub and spoke outreach model, yields outcomes comparable to international cohorts. This underscores the clinical relevance of protocolised STEMI care in resource-limited settings. SA Heart® 2025;22:6-11

INTRODUCTION

Ischemic heart disease (IHD) is the leading cause of mortality[1] world-wide, surpassing the combined death toll of TB, HIV, and malaria worldwide.[2] In South Africa (SA), while TB, diabetes mellitus (DM), and stroke are the leading causes of death, cardiovascular disease consistently ranks amongst the top 5.[3] Within IHD, acute coronary syndromes (ACS) are the most common cause of death, chiefly attributed to ST-segment elevation myocardial infarction (STEMI). Unfortunately, South African data reporting the incidence and prevalence of ACS are limited.[4] European registries indicate a STEMI incidence ranging from 50 to 60 per 100 000 population[1,5] implying that Tygerberg Hospital (TBH) in SA's Western Cape Province, serving a population of 2 400 000 people,[6,7] should be treating 950 to 1 150 STEMI cases annually. In a retrospective study conducted in TBH in 2018 evaluating STEMI patient care intervals, only 492 cases of STEMI were recorded in a year.[8] A 2020 study by Cilliers, et al., performed in TBH over an 8-month period, identified a total of 284 patients admitted with STEMI, amounting to an extrapolated incidence of 426 patients per annum.[9] The stark contrast between expected and actual cases (1 200 vs. 492 and 426, respectively) remains unexplained. Given the population's risk profile,[10] a considerably lower STEMI incidence seems unlikely. A more plausible reason is under detection due to poor help-seeking behaviour, deficient referral pathways, inaccurate diagnoses, and patients succumbing before accessing healthcare facilities or reaching tertiary facilities.

In SA, healthcare is split between the private and public sectors, highlighting socio-economic gaps in medical access. The private sector serves mainly those with medical insurance, while 84% of South Africans rely on government-funded care.[10] Moreover, SA's expansive land area, 5 times larger than the United Kingdom (UK),[11] leads to longer transport delays in STEMI

care. Additionally, with only a quarter of the nation's catheterisation laboratories in public healthcare centres,[12] access to vital services are limited, further affecting STEMI outcomes.

Two reperfusion strategies can be employed in managing patients with STEMI. Primary percutaneous coronary intervention (PCI), where an occluded coronary artery is mechanically reopened, is the preferred approach, as seen in a UK study where 93.8% of patients presenting with STEMI underwent primary PCI.[13] However, due to the vast geographic spread of referral facilities in SA's Western Cape Province, primary PCI is feasible in only a minority of cases within the recommended 90-minute timeframe.[1] This limitation leads to a reliance on a pharmacoinvasive strategy, involving fibrinolysis at referral centres followed by transfer to a tertiary hospital for further management. The STREAM study demonstrated the pharmacoinvasive strategy's non-inferiority compared to primary PCI.[14]

Within the TBH referral network, healthcare facilities operate on a hub and spoke model, with TBH as the tertiary referral centre (hub). Here, a protocolised STEMI management strategy is enforced, mandated across all referral centres. Due to the province's expansive geography and scarce PCI-capable sites, the pharmacoinvasive strategy is the most common strategy employed within the TBH network. TBH ensures the consistent implementation of this strategy through regular outreach efforts conducted by cardiologists to referral centres, thereby enhancing STEMI care across the network.[15]

Various metrics can assess STEMI management in a referral network. Access to medical care can be gauged by symptom onset-to-diagnosis delay, while reperfusion efficiency can be evaluated by door-to-reperfusion delay. In a 2018 study in TBH, a median door-to-reperfusion delay of 67 minutes was reported.[8] Mortality rates can be measured and compared with other centres or expected rates derived from calculating STEMI-specific Time in Myocardial Infarction (TIMI) scores for each patient.[16] This latter method is particularly applicable to SA, where outcome data for STEMI is scarce. Reports from high income countries suggest 30-day mortality rates after STEMI ranging from 2.5% - 10%,[17,18] indicating better outcomes with improved reperfusion strategies over recent decades. However, findings from low-to-middle income countries suggest poorer STEMI outcomes compared to high-income countries.[19,20]

Our study aims to assess STEMI care within the TBH referral network, by evaluating the different reperfusion strategies implemented, as well as the in-hospital and 30-day mortality rates.

METHODS

The Tygerberg Registry of ACS (TRACS registry) constitutes a repository encompassing patients aged 18 years and above, referred to TBH from facilities within the hub and spoke referral network, presenting with either STEMI or high-risk non-STEMI, defined as the presence of haemodynamic instability, refractory chest pain, life-threatening arrhythmia, acute heart failure, significant ST-segment changes, or markedly elevated cardiac biomarkers.[4] This observational study entails a retrospective analysis of patient data extracted from the TRACS registry, specifically focusing on individuals diagnosed with STEMI between 1 April - 3 December 2020. The data retrieved from the registry was analysed to delineate patient demographics and ascertain cardiovascular risk factors, including HIV status and obesity (defined as a body mass index (BMI) >30kg/m^2). Furthermore, the study evaluated the management strategies employed for patients with STEMI, alongside evaluating mortality rates (both in-hospital and 30 days post-discharge) and the incidence of ACS recurrence within 30 days post-discharge from TBH. Lastly, the study evaluated reasons why angiography and PCI procedures were not performed, sourced from the registry data. Patient outcomes in terms of mortality will be compared to predicted values based on the STEMI specific TIMI score.

STATISTICAL ANALYSIS

The data management process involved the systematic importation of information into the Research Electronic Data Capture (REDCap) system. Subsequently, a statistical analysis was carried out utilising the Strata software platform. Data normality served as the guiding criterion for the chosen method of presentation. For comparative analysis of patient outcomes, a 2-sample proportion z-test was used, with statistical significance set at a p-value of less than 0.05.

ETHICS

This study received approval from the Health Research Ethics Committee (HREC) of the Faculty of Medicine and Health Sciences at Stellenbosch University, under the reference number N20/03/030. It was conducted in adherence to the Declaration of Helsinki (2013 version). Every patient provided written consent to participate. In cases where patients had passed away before providing consent, a waiver was granted.

RESULTS

A total of 292 patients were admitted with STEMI during the study period. Among them, 187 (64.0%) were male, with a median age of 58 years (interquartile range (IQR) 49 to 65

years). The most prevalent cardiovascular risk factors were active or previous cigarette smoking (72.6%) and systemic hypertension (68.5%). The study population included 39 HIV positive patients (13.4%) (Table I).

The pharmacoinvasive strategy was employed in 190 patients (65.1%), with 54 patients (18.5%) receiving primary PCI (Figure 1, Table II). In 48 patients (16.4%), neither primary PCI nor fibrinolysis was administered. Following fibrinolysis at the referral facility, a total of 170 patients (89.5%) underwent angiography, of which 37 patients (19.5%) required rescue PCI. Among the subgroup not receiving fibrinolysis or primary PCI, 23 patients (47.9%) underwent angiography at TBH. In the study population, a total of 45 patients (15.6%) did not undergo angiography, of which 20 patients received fibrinolysis and 25 patients did not receive either fibrinolysis or angiography. Reasons for not performing angiography included renal failure (14 patients) and patient mortality before the procedure could be performed (12 patients). The most common reason for not performing PCI at the time of angiography was patients with an indication for a

TABLE I: Demographics.

Measure	Variable	n=292 n%
Demographic profile	Male gender	187 (64.0)
	Age in years; median (IQR)	58 (49 - 65)
Cardiovascular risk factor prevalence	Pre-existing IHD	10 (3.4)
	Family history of premature IHD	18 (6.2)
	Systemic hypertension	200 (68.5)
	Diabetes mellitus, any type	100 (34.2)
	Obesity	119 (40.8)
	Active or previous cigarette smoking	212 (72.6)
	HIV infection	39 (13.4)

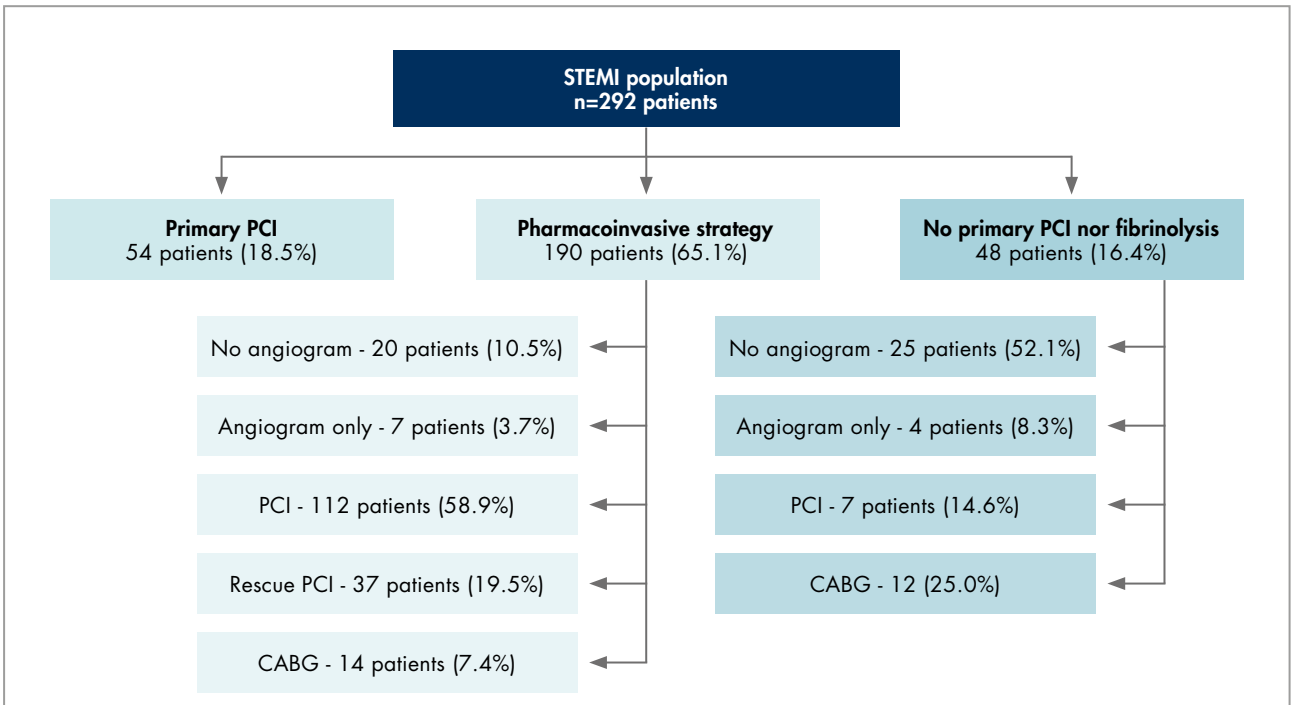

FIGURE 1: Algorithm with management strategies.
CABG: Coronary artery bypass graft, PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction.

TABLE II: Management strategies and outcomes.

Measure	Variable	Population (n)	n (%)
Management strategies	Primary PCI	292	54 (18.5)
	Pharmacoinvasive strategy		190 (65.1)
	No primary PCI or fibrinolysis		48 (16.4)
Reasons for not performing angiography	Renal failure	45	14 (31.1)
	Patient mortality		12 (26.7)
	Other*		19 (42.3)
Reasons for not performing PCI during angiography	Late presentation with occluded artery	37	4 (11.0)
	CABG performed		26 (70.3)
	Indication for CABG, not performed yet		3 (8.1)
	Non-obstructed coronary arteries		2 (5.4)
	Other*		2 (5.4)

*Other reasons include lack of patient consent and the opinion of the attending cardiology consultant.

TABLE III: Outcomes.

Measure	Primary PCI (A) n=54	Pharmaco-invasive strategy (B) n=190	No primary PCI or fibrinolysis (C) n=48	Total n=292	Strategy A vs. B p-value	Strategy B vs. C p-value	Strategy A vs. C p-value
Total mortalities	**1 (1.9)**	**8 (4.2)**	**11 (22.9)**	**20 (6.9)**	**<0.05**	**<0.05**	**<0.05**
Of which in hospital	1 (1.9)	8 (4.2)	7 (14.6)	16 (15.5)	<0.05	<0.05	<0.05
Of which within 30 days of discharge	0 (0.0)	0 (0.0)	4 (8.3)	4 (1.4)	N/A	<0.05	<0.05
Recurrence of ACS within 30 days	**0 (0.0)**	**0 (0.0)**	**9 (18.8)**	**9 (3.1)**	**N/A**	**<0.05**	**<0.05**

coronary artery bypass graft (CABG) (29 patients, of which 26 were performed during the same admission).

A total of 20 patients (6.9%) died within 30 days of hospital discharge, with 16 patients (5.5%) demising during admission and an additional 4 patients (1.4%) succumbing within 30 days of hospital discharge. In-hospital mortality rates were 1.9% in the primary PCI group, 4.2% in the pharmacoinvasive strategy group, and 22.9% in the group of patients not receiving either intervention ($p<0.05$). Moreover, no patients demised within 30 days after discharge in the primary PCI and pharmacoinvasive groups, contrasting with 4 deaths (8.3%) in the group not receiving fibrinolysis nor primary PCI ($p<0.05$). Rescue PCI was performed in 37 patients, with 5 patients (13.5%) demising in hospital and 1 additional death recorded within 30 days of hospital discharge, amounting to an overall mortality rate of 16.2% in this subgroup. Recurrence of ACS within 30 days post-discharge was absent in both the primary PCI and pharmacoinvasive groups, while 9 patients (18.8%) encountered such recurrence in the group not receiving either management strategy ($p<0.05$) (Table III).

The STEMI specific TIMI scores were available for a total of 88 patients in the study population, with a median score of 4 points (IQR 2-5). This amounts to a predicted mortality rate of 7.3%. A total of 6 in-hospital deaths were recorded in this subgroup, amounting to a mortality rate of 6.9%.

DISCUSSION

This study demonstrated a lower than expected in-hospital and 30-day mortality in patients with STEMI when compared to other cohorts from low-to-middle income countries and comparable to those reported from high income countries.[17,18] The mortality rate among patients undergoing primary PCI was the lowest (1.9%), whilst the pharmacoinvasive strategy group demonstrated a comparatively low mortality rate (4.2%), similar to findings from European registries and the STREAM trial.[22] Notably, neither primary PCI nor the pharmacoinvasive strategy led to ACS recurrence within 30 days post-hospital discharge. Conversely, patients with STEMI not undergoing the pharmacoinvasive or primary PCI strategy had less favourable outcomes,

with a 30-day mortality rate of 22.9% ($p<0.05$). The mortality rate was higher in the rescue PCI group when compared to other patients within the pharmacoinvasive group (16.2% vs. 1.3%, $p<0.05$). A significant difference was observed between the pharmacoinvasive group and those not receiving fibrinolysis or primary PCI in terms of both mortality and ACS recurrence. In an analysis involving 88 patients, the predicted 30-day mortality based on the STEMI-specific TIMI score[16] was 7.3%, closely resembling the actual mortality rate of 6.9%. These figures suggest that patients appropriately treated and referred have favourable outcomes and resources should be directed at pre-hospital care, especially patients not offered reperfusion at first medical contact.

Over the 9-month study period, 292 patients were identified, translating to an annual incidence of 389 patients. This figure is lower than that recorded in a 2018 TBH study[8] and significantly lower than the expected incidence based on European data.[1,5] This may be due to several factors, including help-seeking behaviour, prolonged transport delays leading to pre-transfer mortality, as well as the timing of the study overlapping with the COVID-19 pandemic where fewer cases of ACS were seen than during non-pandemic periods.[22]

The median age of patients in our study was younger than the age of STEMI populations in European registries.[23] Prevalence rates of systemic hypertension and DM surpass the rate in the general SA population.[24] Cigarette smoking prevalence among STEMI patients in this study exceeded 65%, contrasting with the 18% prevalence in the general population.[24,25] Although not considered a major cardiovascular risk factor, the HIV prevalence in the study population closely mirrors that of the general population, being 13%.[26]

Most of the patients were treated with a pharmacoinvasive strategy, with the majority successfully reperfused with fibrinolytic therapy (80.5%). High rates of fibrinolysis (65%) were achieved, reflecting on effective management within the referral network (Figure 2). Despite the limited access to PCI-capable facilities within the public healthcare sector, high rates of angiography (86.9%) and PCI (73.2%) were observed in the group of patients receiving successful fibrinolytic therapy. This study demonstrates that a pharmacoinvasive strategy is not only feasible in our setting, but that short-term outcomes are similar to high income countries.

The higher mortality rate of patients undergoing rescue PCI is likely due to a delay to reperfusion. Early recognition of failed reperfusion and improving transport to TBH should improve the outcome of patients in this group. Patients not undergoing a reperfusion strategy had the worst outcome. This supports the strategy of early fibrinolysis at first medical contact, with timeous referral to a PCI-capable facility. In addition, improving patient awareness of STEMI symptoms and improving help-seeking behaviour could shorten patient delays. Furthermore, educating healthcare workers to accurately diagnose and treat STEMI should improve outcomes.

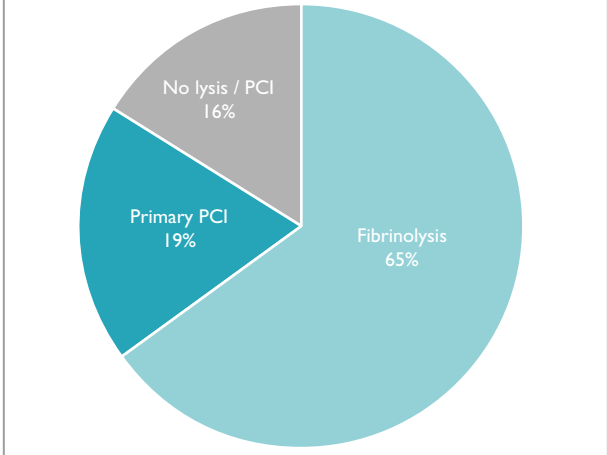

FIGURE 2: Initial management strategy employed.

CONCLUSION

Despite challenges within SA's healthcare system, this study in a region utilising a protocolised pharmacoinvasive strategy demonstrates outcomes similar to published cohorts. The challenges of implementing an efficient pharmacoinvasive strategy were overcome by establishing an outreach system built on a hub and spoke model. Limitations included the exclusion of patients demising prior to referral to TBH and patients not seeking medical attention - although these limitations are similar to that reported in published cohorts. Further investigation into the observed discrepancy between expected and actual numbers of STEMI cases at TBH and SA is warranted.

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Conflict of interest: none declared.

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Ethnic differences in risk factor profiles in subjects with coronary disease attending a state hospital in KwaZulu-Natal

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ABSTRACT

Objectives: This study compares the profile of coronary artery disease (CAD) across different ethnic groups at a tertiary referral hospital in KwaZulu-Natal.
Method: We reviewed the clinical records of 1 104 subjects who underwent coronary angiography at Grey's Hospital for suspected CAD over a 5-year period (2012 - 2016). Uni- and multivariable analysis was used to identify associations of risk factors with CAD.
Results: Coronary artery disease was present in 886 subjects, of whom 69.9% were male. The majority were of Indian ethnicity (60.8%). The mean age of Africans was younger (54.9 ± 10.8 years) compared to Indians (58.0 ± 11.0 years), Coloureds (58.6 ± 12.3 years) and Whites (60.0 ± 10.5 years) (p=0.001). The prevalence of premature CAD (PCAD) (<55 years in males and <65 years in females) was 46% of males and 66,7% in females. Most African females (84,6%, p=0.01) and white females (75,6%, p=0.01) presented with PCAD. ST-elevation myocardial infarction was the most frequent presentation among African subjects (n=99, 66.0%), followed by Whites (n=76, 45.2%) and Indians (n=240, 44.5%), and least common among Coloureds (n=11, 37.9%) (p<0.001). The most prevalent risk factors were dyslipidaemia (95.1%), hypertension (70.3%), smoking (67.4%) and diabetes (57.2%). The prevalence of smoking was lowest in the African group (51.3%) compared to about 66% in the other groups (p<0.001) (Table I). About 80% of Indians and Whites had clustering of 3 or more risk factors compared to 39.3% of Africans (p<0.001). A family history of CAD lowest among African (n=13, 8.7%) and Coloured subjects (n=11, 37.9%) (p<0.001) and a history of previous MI was obtained in 5.3% of African subjects compared to >23% in each of the other ethnic groups (p<0.001). Single vessel disease was commoner among Africans (48.7%), while Indians had more triple vessel disease (47.7%), (p<0.001). Univariate analysis identified risk factors and ethnicity (Indians, p=0.02) and Whites, p=0.02) as being associated with CAD, but on multivariable analysis ethnicity fell away. Age (46 - 65 years: OR: 2.2 [1.5 - 3.3], age >65 years: OR: 4.8 [2.8 - 8.2], male gender (OR: 2.7 [1.9 - 3.9]), history of smoking (OR: 2.0 [1.4 - 3.1] (all p<0.001) as well as diabetes (OR: 1.7 [1.2 - 2.4], p=0.005) and atherogenic dyslipidaemia (OR: 1.7 [1.2 - 2.4], p=0.004) were independent cardiovascular risk factors associated with the presence of CAD.
Conclusion: Major risk factors were associated with CAD at a young age across all race groups. Although Africans had a lower risk factor burden, the low prevalence of a family history of MI and near absence of a previous history of MI indicate that recent environmental and / or lifestyle changes that have contributed to the emergence of CAD, often premature, in this group. SA Heart® 2025;22:12-21

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide across various ethnic and racial groups.[1-7] The distribution of CAD displays socioeconomic disparities with an increasing burden of the disease among low income countries.[2,3,8] Almost 3 decades ago Seedat, et al.[9] proposed that Africans were not developing CAD to the same extent as White or Indian subjects due to cardiovascular protective role conferred by the preserved serum levels of both high density lipoprotein and lower total cholesterol. Other observational studies[10-15] have also confirmed that Africans have lower cholesterol levels and are the least likely to be diagnosed with CAD when compared to other ethnic groups. Steyn, et al.[11] further noted that the African subjects were still at the initial phase of epidemiological transition due to urbanisation and changing lifestyle factors, resulting in an increased prevalence of non-communicable diseases, especially cardiovascular disease. However, other local studies have reported an upsurge in the prevalence of cardiovascular risk factors among Africans.[16-19]

Approximately 2 decades ago the INTERHEART study[3] demonstrated that 90% of risk factors for developing acute myocardial infarction (AMI) were attributable to 9 cardiovascular risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity) worldwide. Subsequently, the INTERHEART Africa study[11] showed that 5 of the 9 cardiovascular risk factors (hypertension, diabetes, abdominal obesity, current history of smoking, and apolipoprotein B to apolipoprotein A1 ratio) were accountable for nearly 90% of the risk associated with first time AMI, consistent with that found in the global INTERHEART study. These studies suggest that the spectrum of CAD is changing rapidly in the developing countries.[16,19-23] In South Africa, White and Indian subjects have a higher prevalence of CAD-related deaths compared to Coloured and African subjects.[9,12,19,24] There are few recent studies of subjects with CAD across different ethnic groups.[25-31] In this study we analysed the cardiovascular risk profile of subjects with CAD admitted for coronary angiography to Grey's Hospital in KwaZulu-Natal and related this to the patterns of CAD across 4 ethnicities.

MATERIALS AND METHODOLOGY

The aim of this study was to evaluate the spectrum of CAD over a 5-year period (2012 - 2016) at Grey's Hospital, a tertiary level referral facility in Pietermaritzburg, KwaZulu-Natal, South Africa, servicing the urban and Midlands area of KwaZulu-Natal. This public health care facility provides regional services to lower- and middle-income groups, residing in the uMgungundlovu health district and surrounding areas.

A retrospective chart review of all patients who were referred to Grey's Hospital with a clinical diagnosis of CAD was conducted in order to determine prevalence of atherosclerotic risk factors in adults with CAD, and relate the risk factor profile of to the extent of CAD at angiography. Data extracted from the medical records comprised age, gender, ethnicity, previous medical history for traditional CAD risk factors such as hypertension, diabetes mellitus, dyslipidaemia, previous history of myocardial infarction (MI), family history of premature CAD, and history of smoking. Ethnicity was determined from the admission files and patients were classified accordingly as being of African, Coloured, Indian, and White descent.

Definitions

Coronary artery disease was defined using the criteria from the 2013 American College of Cardiology Foundation / American Heart Association Task Force (ACCF/AHA).[32] Eligible patients were adult males and females, presenting with a diagnosis of stable angina or acute coronary syndrome (ACS). The term ACS as outlined in the Third Universal Classification of Myocardial Infarction encompasses ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), and unstable angina (UA).[33]

Hypertension was defined as blood pressure (BP) ≥140/90mmHg or self-reported use of antihypertensive medication.[34] Diabetes mellitus was diagnosed in patients who were on chronic anti-hyperglycaemic drugs, or self-reported or had documented glycated haemoglobin A1c (HbA1c) ≥6.5%.[35] Dyslipidaemia was diagnosed in patients who were on chronic lipid lowering drugs (e.g. statin), or self-reported, or previously documented diagnosis from medical records or established during the hospital stay by lipogram. The lipid profiles were classified using the criteria from the Third National Cholesterol Education Programme and Adult Treatment Panel III (NCEP-ATP III)[36] guidelines. Total cholesterol (TC) was considered high if >5.17mmol/L, low high-density lipoprotein cholesterol (HDL-C) was defined as <1.3mmol/L for females and <1.03mmol/L for males and hypertriglyceridaemia was defined as triglycerides (TG) >1.7mmol/l. Low-density lipoprotein cholesterol (LDL-C) data was calculated using the Friedewald equation. For TG >4.5mmol/L, the John Hopkins University LDL-C calculator[37] was used to measure LDL (iPhone App Version 1.0.1).

Atherogenic dyslipidaemia was defined in accordance with the criteria used in the NCEP-ATP III[36] guidelines as the combination of elevated levels of triglycerides and low levels of HDL-C. A positive family history of premature CAD[36] was defined as coronary artery disease diagnosed in a first-degree relative before the age of 55 in males and for females before the age of 65. A history of smoking was defined as either current or previous use of tobacco products or cigarettes.

Patient demographic data, past medical history, and presenting diagnosis of CAD were analysed in conjunction with laboratory results and angiographic findings to formulate relevant conclusions about their overall combined contribution to the spectrum of CAD at Grey's Hospital. Data were further analysed according to gender and age groups: (a) those ≤45-years-old, (b) between 46 - 65-years-old, and (c) those >65-years-old. Angiographic obstructive CAD was defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery and multivessel CAD was defined as ≥50% luminal diameter stenosis in ≥2 epicardial coronary arteries. The remaining subjects were classified as normal or non-occlusive coronary disease at coronary angiography. Angiographic findings of obstructive coronary disease were grouped into single-vessel disease (SVD), double-vessel disease (DVD) and triple-vessel disease (TVD). With regards to lesion localisation to a specific coronary artery, patients were further grouped into the left anterior descending coronary artery (LAD), circumflex artery (CxA) and right coronary artery (RCA).

Statistical analysis

Descriptive statistics were used to summarise the clinical and demographic characteristics of the patients. Frequency and percentages were used for categorical variables and means (Standard Deviations [SD]) or medians (interquartile ranges) for numeric variables. Subgroup comparisons of risk factors (diabetes, hypertension, smoking history, family history of CAD, previous MI, and dyslipidaemia) by ethnic group (Africans vs. other ethnic groups) was done using Chi-square tests or Fisher's exact test. The Kruskal-Wallis test was used for comparisons of numeric variables.

A logistic regression model containing cardiovascular risk factors significant at the univariate level was used to identify independent factor differences by gender, ethnic group, age group, cardiovascular risk factors, number of risk factors, and atherogenic dyslipidaemia. Two sets of models were developed: the first model looked at obstructive disease and non-obstructive / normal vessels to determine the predictors of CAD. The second model assessed the severity of CAD, comparing SVD to multivessel disease (DVD and TVD). All data were analysed using Stata V13 and a p-value <0.05 was considered significant.

Ethical considerations

The study protocol was approved by the Bioethics Committee of the Faculty of Health Sciences, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, ethics reference number: BE538/17.

RESULTS

During the 5-year period (January 2012 - December 2016), 1 318 subjects were admitted for evaluation of suspected CAD. Of the 1 318 evaluated subjects, 214 subjects were excluded for reasons of inadequate data (n=202) and declined coronary angiography (n=12). The study population comprised the remaining 1 104 subjects who had undergone coronary angiography. Of these, 886 had angiographically confirmed CAD and comprised the study group, while the remaining 218 subjects had normal angiograms or non-occlusive disease and were used as the comparative group (Table I).

Demographic data

The mean age of the subjects with CAD was 57.9 ± 11.0 years. The youngest were Africans (54.9 ± 10.8 years), followed by Indians (58.0 ± 11.0 years), Coloureds (58.6 ± 12.3 years), and the oldest subjects were Whites (60.0 ± 10.5 years) (p=0.001). There was a predominance of Indian subjects (n=539, 60.8%), followed by Whites (n=168, 19%), Africans (n=150, 16.9%) and Coloureds (n=29, 3.3%) (p=0.001). The majority of the study cohort were male (n=619, 69.9%), with no difference in the male to female ratio across the ethnic groups (p=0.18). One hundred and twenty six subjects (n=126, 14.2%) were under the age of 45; 526 (59.4%) were between 46 - 65-years-old and the remaining 234 (26.4%) subjects were older than 65 (>65) (Table I).

Presenting diagnosis

The commonest diagnosis at presentation was ST-elevation myocardial infarction (STEMI) (n=426, 48.1%) followed by non-ST-elevation myocardial infarction (NSTEMI) (n=243, 27.4%), and the least prevalent were stable (p<0.001) and unstable (p=0.024) angina together making up 24.5% of the CAD subjects. Within the ethnic groups ST-elevation myocardial infarction was most frequent among African subjects (n=99, 66.0%), followed by Whites (n=76, 45.2%) and Indians (n=240, 44.5%), and least common among Coloureds (n=11, 37.9%) (p<0.001). Angina was the least common manifestation among African subjects (n=15, 10.0%) compared to other ethnic groups, Coloureds (n=5, 17.2%), Indians (n=145, 26.9%), and Whites (n=52, 31%). Non-ST-elevation myocardial infarction was equally distributed across all ethnic groups (p=0.089) (Table I).

Premature coronary artery disease (PCAD), defined as CAD in males <55 years and females <65 years, was present in 463 (52.3%) subjects; it was commoner in females (M 46.0%, F 66.7%). There was no difference in males with PCAD across ethnic groups but most of the African females (84.6%, p=0.01) and White females (75.6%, p=0.01) had PCAD. In adults under 45 years, PCAD was commoner among Africans (n=31, 20.7%) and Indians (n=79, 14.7%), compared to Coloureds (n=13, 7.7%) and Whites (n=15, 7.7%) (p<0.001) (Table I).

Risk factor profile

The most prevalent cardiovascular risk factors were dyslipidaemia (n=843, 95.1%), hypertension (n=623, 70.3%), and a history of smoking (n=597, 67.4%) followed by diabetes (n=507, 57.2%) and a family history of CAD (n=410, 46.3%). A history of smoking was present in two thirds of subjects with CAD. About half of the Africans (51.3%) were smokers compared to two-thirds of the Indians (68.1%), and over three quarters of the Whites (77.4%), and Coloureds (79.3%) (p<0.001).

While the majority of all ethnic groups had some form of dyslipidemia, there were significant differences in their risk factor and lipid profiles. Compared to other ethnic groups, Indian subjects had the highest prevalence of dyslipidaemia (97.8%), diabetes (65.9%), a family history of CAD (55.1%) and a history of previous MI (26.7%) (all p<0.001). Almost 80% of Indians and Whites had clustering of 3 or more (≥3) cardiovascular risk factors compared to 39.3% of Africans and 58.6% of Coloureds (p<0.001). The median LDL-C was lowest

TABLE I: Risk factor profile and angiographic findings across ethnic groups.

Variables	All n (%) 886 (100)	African n (%) 150 (16.9)	Coloured n (%) 29 (3.3)	Indian n (%) 539 (60.8)	White n (%) 168 (19.0	p-value
Age (years), mean ± SD	57.9 ± 11.0	54.9 ± 10.8	58.6 ± 12.3	58.0 ± 11.0	60.0 ± 10.5	0.001
Age Group n (%)						
≤45 years	126 (14.2)	31 (20.7)	3 (10.3)	79 (14.7)	13 (7.7)	<0.001
46 - 65 years	526 (59.4)	99 (66.0)	20 (69.0)	304 (56.4)	103 (61.3)	
>65 years	234 (26.4)	20 (13.3)	6 (20.7)	156 (28.9)	52 (31.0)	
Gender n (%)						
Males	619 (69.9)	104 (69.3)	22 (75.9)	365 (67.7)	128 (76.2)	0.18
Females	267 (30.1)	46 (30.7)	7 (24.1)	174 (32.3)	40 (23.8)	
Premature CAD n (% of gender)						
Males (<55 years)	285 (46.0)	54 (51.9)	12 (54.5)	171 (46.8)	48 (37.5)	0.11
Females (<65 years)	178 (66.7)	39 (84.8)	3 (42.9)	107 (61.5)	29 (72.5)	0.01
Risk Factor Profile n (%)						
Hypertension	623 (70.3)	108 (72.0)	19 (65.5)	386 (71.6)	110 (65.5)	0.42
Diabetes	507 (57.2)	75 (50.0)	10 (34.5)	355 (65.9)	67 (39.9)	<0.001
Dyslipidaemia	843 (95.1)	132 (88.0)	27 (93.1)	527 (97.8)	157 (93.5)	<0.001
Family history of CAD	410 (46.3)	13 (8.7)	11 (37.9)	297 (55.1)	89 (53.0)	<0.001
History of smoking	597 (67.4)	77 (51.3)	23 (79.3)	367 (68.1)	130 (77.4)	<0.001
Previous MI	199 (22.5)	8 (5.3)	7 (24.1)	144 (26.7)	40 (23.8)	<0.001
Number of Risk Factors n (%)						
0 - 2	249 (28.1)	91 (60.7)	12 (41.4)	113 (21.0)	33 (19.6)	<0.001
≥3	637 (71.9)	59 (39.3)	17 (58.6)	426 (79.0)	135 (80.4)	
Biochemistry, mmol/L						
Total Cholesterol, median (IQR) - mmol/L	4.9 (4-5.7)	4.2 (3.5-5.3)	5.0 (4.1-5.3)	4.9 (4.0-5.9)	5.0 (4.0-6.0)	<0.001
LDL-C, median (IQR) - mmol/L	2.8 (2.1-3.7)	2.5 (1.9-3.3)	2.8 (2.2-3.4)	2.9 (2.2-3.7)	3.1 (2.2-3.7)	0.004
HDL-C, median (IQR)	1.0 (0.8-1.2)	1.0 (0.8-1.3)	1.0 (0.9-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	0.33
Triglycerides, median (IQR) - mmol/L	1.7 (1.2-2.5)	1.3 (0.8-1.9)	1.9 (1.5-2.5)	1.9 (1.3-2.7)	1.8 (1.2-2.6)	0.001
HbA1c, mean ± SD - %	7.2 ± 2.0	7.4 ± 2.4	6.9 ± 2.1	7.4 ± 2.0	6.5 ± 1.5	0.001
Metabolic syndrome criteria n (%)						
Total cholesterol ≥5.17 mmol/L	338 (38.1)	44 (29.3)	9 (31.0)	208 (38.6)	77 (45.8)	0.02
LDL ≥2.59 mmol/L	507 (57.2)	67 (44.7)	17 (58.6)	318 (59.0)	105 (62.5)	0.006
Triglycerides ≥1.7 mmol/L	445 (50.2)	44 (29.3)	16 (55.2)	298 (55.3)	87 (51.8)	<0.001
HDL-C Male ≤1.03 mmol/L	407 (65.8)	55 (52.9)	15 (68.2)	249 (68.2)	88 (68.8)	0.03
HDL-C Female ≤1.29 mmol/L	188 (70.4)	30 (65.2)	5 (71.4)	131 (75.3)	22 (55.0)	0,07
Glycated haemoglobin A_{1c} ≥6.5%	447 (50.5)	68 (45.3)	10 (34.5)	314 (58.3)	55 (32.7)	<0.001
Blood Pressure ≥130/85 mmHg	169 (19.1)	43 (28.7)	5 (17.2)	94 (17.4)	27 (16.1)	0.01
Atherogenic Dyslipidaemia n (% of gender)						
Males	238 (38.4)	20 (19.2)	10 (45.5)	157 (43.0)	51 (39.8)	<0.001
Females	99 (37.1)	8 (17.4)	4 (57.1)	71 (40.8)	16 (40.0)	0.02
Presenting Diagnosis n (%)						
SA	87 (9.8)	4 (2.7)	0 (0.0)	61 (11.3)	22 (13.1)	<0.001
UA	130 (14.7)	11 (7.3)	5 (17.2)	84 (15.6)	30 (17.9)	0.024
STEMI	426 (48.1)	99 (66.0)	11 (37.9)	240 (44.5)	76 (45.2)	<0.001
NSTEMI	243 (27.4)	36 (24.0)	13 (44.8)	154 (28.6)	40 (23.8)	0.089
Angiographic CAD Findings						
Extent of CAD n (%)						
Single-vessel CAD	260 (29.3)	73 (48.7)	12 (41.4)	116 (21.5)	59 (35.1)	<0.001
Double-vessel CAD	261 (29.5)	38 (25.3)	7 (24.1)	166 (30.8)	50 (29.8)	0.581
Triple-vessel CAD	365 (41.2)	39 (26.0)	10 (34.5)	257 (47.7)	59 (35.1)	<0.001
Epicardial vessel involvement n (%)						
Left anterior descending artery	732 (82.6)	121 (80.7)	19 (65.5)	458 (85.0)	134 (79.8)	0.025
Circumflex artery	521 (58.8)	63 (42.0)	17 (58.6)	360 (66.8)	81 (48.2)	<0.001
Right coronary artery	614 (69.3)	78 (52.0)	20 (69.0)	397 (73.7)	119 (70.8)	<0.001

CAD: coronary artery disease, SD: standard deviation, MI: myocardial infarction, STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST-elevation myocardial infarction, UA: unstable angina, SA: stable angina, HDL-c, high-density lipoprotein cholesterol, LDL, low-density lipoprotein cholesterol, Hypertension: history of hypertension ***OR*** *self-reported use of anti-hypertensive medication* ***OR*** *BP ≥140/90 mmHg, Diabetes: history of diabetes* ***OR*** *self-reported use of anti-hyperglycaemic medication* ***OR*** *HbAc1 ≥6.5%, Dyslipidaemia: history of dyslipidaemia* ***OR*** *TC ≥5.17* ***OR*** *TG >1.7* ***OR*** *HDL-C ≤1.03 in males* ***OR*** *HDL-C ≤1.29 in females.*

among Africans (2.5mmol/L, IQR 1.9 - 3.3), compared to Whites (3.1mmol/L, IQR 2.2 - 3.7, Indians (2.9mmol/L, IQR 2.2 - 3.7), and Coloureds (2.8mmol/L, IQR 2.2 - 3.4) (p=0.004). There was no difference in the median HDL-C (1.0mmol/L, IQR 0.8 - 1.2) across all ethnic groups (p=0.33). The median TG was lowest among the African subjects (1.3mmol/L, IQR 0.8 - 1.9), compared to ≥1.8mmol/L in the other ethnic groups (p=0.001). Atherogenic dyslipidemia was also least frequent in African males (19.2%, p<0.001) and females (17.4%, p=0.02) compared to over 40% for each gender in the other ethnic groups (Table I).

There was a high prevalence of diabetes (52.8%), which increased to 57.2% when we added the diagnostic criteria using the HbA1c >6.5%. Two thirds of the Indian (n=355, 65.9%) and half of the African (n=75, 50.0%) subjects had diabetes compared to over a third of Whites (n=67, 39.9%) and Coloureds (n=10, 34.5%) (p<0.001). Correspondingly, the mean HbA1c was highest among Africans (7.4% ± 2.4%) and Indians 7.4% (SD ± 2.0%), followed by Coloureds 6.9% (SD ± 2.1%), and Whites 6.5% (SD ± 1.5%) (p<0.001).

A family history of CAD was highest among Indians (n=297, 55.1%) and Whites (n=89, 53.0%) whilst it was lowest among African (n=13, 8.7%) and Coloured subjects (n=11, 37.9%) (p<0.001). A history of previous MI was obtained in 5.3% of African subjects compared to >23% in each of the other ethnic groups (p<0.001). (Table I).

In summary, 50% of Africans had diabetes, and they had a lower prevalence of the other major risk factors compared to other ethnic groups. Clustering of 3 or more cardiovascular risk factors was present in 39.3% of Africans compared to almost 80% in Indians and in Whites. Except for HDL-C, the median serum levels of all the remaining lipid subtypes were lower among the African subjects.

Coronary angiography

This showed that single-vessel disease was most common among Africans (48.7%, p<0.001) and triple-vessel disease most common among Indians (47.7%, p<0.001) (Table I). The left anterior descending artery (LAD) was involved in 80% of all ethnic groups except in Coloureds (65.5%) (p=0.025). Africans had less frequent involvement of the right coronary artery (RCA) (52.0%) (p<0.001) and the circumflex artery (CX) lesions (42.0%) (p<0.001).

Predictors of CAD

On univariate analysis age, male gender, ethnicity, diabetes, history of smoking, 3 or more cardiovascular risk factors and atherogenic dyslipidaemia showed significant associations with CAD (Table II). There was a higher risk of CAD amongst Indians (OR: 1.6 [1.1 - 2.3], p=0.02) and Whites: (OR: 1.8 [1.1 - 2.9], p=0.02) which fell away in the adjusted analysis after the risks were controlled for age, gender, ethnicity, number of cardiovascular risk factors and atherogenic dyslipidaemia. Thus, on multivariable analysis age 46 - 65 years (OR: 2.2 [1.5 - 3.3], p<0.001), age >65 years OR: 4.8 [2.8 - 8.2], p<0.001), male gender (OR: 2.7 [1.9 - 3.9], p<0.001), diabetes (OR: 1.7 [1.2 - 2.4], p=0.005), history of smoking (OR: 2.0 [1.4 - 3.1], p=0.001) and atherogenic dyslipidaemia (OR: 1.7 [1.2 - 2.4], p=0.004) remained as independent cardiovascular risk factors associated with the presence of CAD. With regard to extent of disease, multivariate analysis revealed Indian ethnicity (OR: 2.6 [1.6 - 4.0], p<0.001), age (46 - 65 years OR: 1.6 [1.1 - 2.5], p=0.024), age >65 years (OR: 4.1 [2.3 - 7.2], p<0.001), hypertension (OR: 2.1 [1.4 - 3.1], p=0.002), and previous MI (OR: 2.1 [1.3 - 3.4], p=0.002) as independent predictors of multivessel disease (Table III).

DISCUSSION

This study shows a high prevalence of major cardiovascular risk factors in subjects presenting with diagnosis of acute coronary syndrome or stable angina at a tertiary referral centre in KwaZulu-Natal. In keeping with other studies[10,13,14,38] Indians constituted the majority ethnic group and there was a predominance of males[3,5,25,27,28,39-45] with a similar male to female ratio (7:3) across the ethnic groups. The mean age amongst Indians (58 ± 11 years) in our study is similar to that in the Chennai Urban Population Study (58 ± 12 years)[39] and the Kerala ACS Registry (60 ± 12.1 years)(45) in India. The mean age of our African subjects (54.9 ± 10.8 years), is also strikingly similar to reports from Cameroon and Kenya,[41] the INTERHEART Africa study (54.3 ± 11.3 years),[11] as well as study at the Chris Hani Baragwanath Hospital, Soweto (55 [51 - 61] years)[18] and the R.K. Khan Hospital, Durban (54.3 ± 11.0 years).[27] The mean age of African subjects in these studies is about 5 years younger compared to African Americans with CAD.[46]

Most of the subjects in our study were in the age group 45 - 65 years and were male, which we have documented previously at the R.K. Khan Hospital in Durban.[47,48] The age predominance was present across all the ethnic groups, unlike the stepwise increase in CAD prevalence documented in African Americans and Whites from the age of <55 years to >65 years documented by Whittle, et al.[49,50] About half the males and two thirds of the females had PCAD. It has been suggested that the loss of ovarian protection in women may account for the high prevalence of hypertension, diabetes, and dyslipidaemia in females which placed them at a higher risk for cardiovascular events at an earlier stage of their lives.[51] The INTERHEART study[3] showed that men from Africa (10.9%) and South Asia (9.7%) comprised the highest proportion of cases with first AMI

TABLE II: Statistical association of CAD with major risk factors.

Variables	No CAD [x] 218 (%)	CAD [y] 886 (%)	Total 1 104	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Gender							
Female	118 (30.6)	267 (69.4)	385	Reference			
Male	100 (13.9)	619 (86.1)	719	2.7 (2.0 - 3.7)	<0.001	2.7 (1.9 - 3.9)	<0.001
Ethnic Group							
African	52 (25.7)	150 (74.3)	202	Reference			
Coloureds	15 (34.1)	29 (65.9)	44	0.7 (0.3 - 1.3)	0.3	0.5 (0.2 - 1.1)	0.09
Indian	118 (18.0)	539 (82.0)	657	1.6 (1.1 - 2.3)	0.02	1.1 (0.7 - 1.7)	0.68
White	33 (16.4)	168 (83.6)	201	1.8 (1.1 - 2.9)	0.02	1.2 (0.7 - 2.0)	0.61
Age Group							
≤45 years	59 (31.9)	126 (68.1)	185	Reference			
46 - 65 years	124 (19.1)	526 (80.9)	650	2.0 (1.4 - 2.9)	<0.001	2.2 (1.5 - 3.3)	<0.001
>65 years	35 (13.0)	234 (87.0)	269	3.1 (2.0 - 5.0)	<0.001	4.8 (2.8 - 8.2)	<0.001
Hypertension							
No	62 (19.1)	263 (80.9)	325	Reference			
Yes	156 (20.0)	623 (80.0)	779	0.9 (0.7 - 1.3)	0.718		Excluded‡
Diabetes							
No	119 (23.9)	379 (76.1)	498	Reference			
Yes	99 (16.3)	507 (83.7)	606	1.6 (1.2 - 2.2)	0.002	1.7 (1.2 - 2.4)	0.005
Dyslipidaemia							
No	15 (25.9)	43 (74.1)	58	Reference			
Yes	203 (19.4)	843 (80.6)	1 046	1.4 (0.8 - 2.7)	0.232	1.3 (0.7 - 2.7)	0.41
History of Smoking							
No	113 (28.1)	289 (71.9)	402	Reference			
Yes	105 (15.0)	597 (85.0)	702	2.2 (1.6 - 3.0)	<0.001	2.0 (1.4 - 3.1)	0.001
Previous MI							
No	184 (21.1)	687 (78.9)	871	Reference			
Yes	34 (14.6)	199 (85.4)	233	1.6 (1.1 - 2.3)	0.03	1.1 (0.7 - 1.8)	0.63
Family History of CAD							
No	115 (19.5)	476 (80.5)	591	Reference			
Yes	103 (20.1)	410 (79.9)	513	0.90 (0.7 - 1.3)	0.8		Excluded‡
Number of Risk Factors							
0 - 2	96 (27.8)	249 (72.2)	345	Reference			
≥3	122 (16.1)	637 (83.9)	759	2.0 (1.5 - 2.7)	<0.001	0.9 (0.6 - 1.5)	0.77
Atherogenic Dyslipidaemia							
No	161 (22.7)	549 (77.3)	710	Reference			
Yes	57 (14.5)	337 (85.5)	394	1.7 (1.2 - 2.4)	0.001	1.7 (1.2 - 2.4)	0.004

Note: This table shows all patients during the study period who underwent coronary angiography. All percentages add up horizontally to 100%.
No CAD [x]: if normal or non-occlusive coronary disease was identified at coronary angiography. CAD [y]: if any obstructive lesion was identified at coronary angiography.
Excluded‡: if p-value >0.5 under unadjusted column. OR: odds ratio, CI: confidence interval.

under the age of 40 years and the authors[11] suggested that the HIV / AIDS pandemic with shortened life expectancy probably explains the skew towards younger age at presentation.

While the current study shows a high prevalence of cardio-vascular risk factors in subjects with CAD across different ethnic groups, there were significant differences in the prevalence of diabetes, dyslipidaemia, family history of CAD, history of smoking and previous MI which could have accounted for differences in disease severity across ethnic groups.[52] A history of smoking was present in half the African subjects and in over two thirds of the other ethnic groups. This is much higher than

TABLE III: Association of risk factors to extent of disease (single vs. multivessel disease).

Variables	SVD 260 (%)	DVD/TVD 626 (%)	Total 886	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Gender							
Female	71 (26.6)	196 (73.4)	267	Reference			
Male	189 (30.5)	430 (69.5)	619	0.8 (0.6 - 1.1)	0.24	1.1 (0.8 - 1.6)	0.61
Ethnic Group							
African	73 (48.7)	77 (51.3)	150	Reference			
Coloureds	12 (41.4)	17 (58.6)	29	1.3 (0.6 - 3.0)	0.5	1.1 (0.5 - 2.7)	0.79
Indian	116 (21.5)	423 (78.5)	539	3.5 (2.4 - 5.1)	<0.001	2.6 (1.6 - 4.0)	<0.001
White	59 (35.1)	109 (64.9)	168	1.8 (1.1 - 2.7)	0.02	1.3 (0.8 - 2.2)	0.37
Age Group							
≤45 years	59 (46.8)	67 (53.2)	126	Reference			
46 - 65 years	168 (31.9)	358 (68.1)	526	1.9 (1.3 - 2.8)	0.002	1.6 (1.1 - 2.5)	0.024
>65 years	33 (14.1)	201 (85.9)	234	5.4 (3.2 - 8.9)	<0.001	4.1 (2.3 - 7.2)	<0.001
Hypertension							
No	113 (43.0)	150 (57.0)	263	Reference			
Yes	147 (23.6)	476 (76.4)	623	2.4 (1.8 - 3.3)	<0.001	2.1 (1.4 - 3.1)	0.002
Diabetes							
No	140 (36.9)	239 (63.1)	379	Reference			
Yes	120 (23.7)	387 (76.3)	507	1.9 (1.4 - 2.5)	<0.001	1.1 (0.8 - 1.7)	0.51
Dyslipidaemia							
No	15 (34.9)	28 (65.1)	43	Reference			
Yes	245 (29.1)	598 (70.9)	843	1.3 (0.7 - 2.5)	0.82		Excluded‡
History of Smoking							
No	76 (26.3)	213 (73.7)	289	Reference			
Yes	184 (30.8)	413 (69.2)	597	0.8 (0.6 - 1.1)	0.2	0.8 (0.5 - 1.3)	0.41
Previous MI							
No	232 (33.8)	455 (66.2)	687	Reference			
Yes	28 (14.1)	171 (85.9)	199	3.1 (2.0 - 4.8)	<0.001	2.1 (1.3 - 3.4)	0.002
Family History of CAD							
No	156 (32.8)	320 (67.2)	476	Reference			
Yes	104 (25.4)	306 (74.6)	410	1.43 (1.1 - 1.9)	0.02	1.1 (0.7 - 1.6)	0.64
Number of Risk Factors							
0 - 2	85 (34.1)	164 (65.9)	249	Reference			
≥3	175 (27.5)	462 (72.5)	637	1.4 (1.0 - 1.9)	0.051	1.2 (0.7 - 2.1)	0.52
Atherogenic Dyslipidaemia							
No	169 (30.8)	380 (69.2)	549	Reference			
Yes	91 (27.0)	246 (73.0)	337	1.2 (0.9 - 1.6)	0.23	1.1 (0.8 - 1.5)	0.60

Note: This table shows all subjects diagnosed with CAD at angiography. Angiographic findings were subdivided into two groups: single vessel disease (SVD) and multivessel disease (DVD and TVD). The varying patient numbers under each characteristic heading (second column) add up vertically to 260 for SVD, 626 for DVD/TVD (third column) and the total adds up to 886 (fourth column). All percentages add up horizontally to 100%.
Excluded‡: if p-value >0.5 under unadjusted column. OR: odds ratio, CI: confidence interval.
Diabetes: history of diabetes ***OR*** *self-reported use of anti-hyperglycaemic medication* ***OR*** *HbAc1 ≥6.5%, Dyslipidaemia: history of dyslipidaemia* ***OR*** *TC ≥5.17* ***OR*** *TG >1.7* ***OR*** *HDL-C ≤1.03 in males* ***OR*** *HDL-C ≤1.29 in females, Hypertension: history of hypertension* ***OR*** *self-reported use of anti-hypertensive medication* ***OR*** *BP ≥140/90 mmHg.*

that reported the Mozambican Africans (13,9%).[13] In contrast to studies showing a higher prevalence of hypertension among African subjects,[3,46,53,54] compared to other ethnic groups, in our study hypertension and diabetes was highly prevalent (70%) across all ethnic groups and predictive of multivessel disease. Compared to the INTERHEART studies[3,11] and other African studies,[27,41] the 2-fold higher prevalence of diabetes in Africans in our study, together with cigarette smoking, point to a rapidly

changing cardiovascular risk factor profile leading to the emergence of CAD, often premature, in this group.[27] Smoking compounded by the sheer stress from hypertension probably served as the trigger for plaque rupture and the premature development of acute cardiovascular events.[55]

Similarly, dyslipidaemia was present in 88% of our African subjects with CAD, quite different from the 10% prevalence reported among Africans in Mozambique 15 years ago.[13] The levels of HDL-cholesterol was similarly low across all ethnic groups, including the African subjects. The low HDL-C levels among the African subjects are very similar to the findings by Nethononda, et al.[10] and Sliwa, et al.[15] among Africans in Soweto, which, coupled with the high prevalence of diabetes in this group may explain the loss of the presumed protective role afforded by higher HDL-C levels against CAD that has been proposed in early studies.[11,15,56,57]

In keeping with previous studies,[25,27,38,44,47,48] STEMI was the most frequent diagnosis at admission. Two thirds of Africans presented with STEMI (about half of the Indian and White subjects), almost all of whom had a first time presentation with myocardial infarction since they had no history of previous MI. Furthermore, we found a positive family history of CAD in under 10% of African subjects with CAD, similar to reports from Cameroon[31] (2.78%) and Kenya[28] (8%). These findings point to recent environmental influences in the last generation that have led to the emergence of CAD among Africans and may explain why triple-vessel disease was least common among Africans, who had more single-vessel disease compared to the other ethnic groups. This pattern is similar to reports from sub-Saharan Africa,[13,31] and is thought to reflect the lower atherogenic burden amongst Africans who had lower levels of smoking, elevated LDL-C and atherogenic dyslipidemia, as well as a lower prevalence of cardiovascular risk factor clustering compared to the other ethnic groups in our study.

Consistent with previous studies[3,5,31,52] multivariable analysis identified male gender, age, diabetes, smoking, and atherogenic dyslipidaemia as independent predictors of CAD in our study. Of note, Table II shows that the unadjusted higher risk of CAD in Indians and Whites compared to the Africans fell away after adjusting for risk factors in the multivariable analysis. With the exception of the family history, the data show that the risk profile of the African group shows characteristics of people who are past the early stages of the epidemiological transition, not dissimilar to the other ethnic groups in our cohort. Age, hypertension, previous MI, and Indian ethnicity were associated with multivessel CAD.[57] Our study confirms the findings of the INTERHEART study and also suggests that variations in risk factor prevalence explains the differences in disease severity across ethnic groups.[11]

LIMITATIONS

Our study had several limitations due to its retrospective nature, affecting the quality and completeness of data collection. Certain factors raise into question the generalisability of the findings. Firstly, the study was conducted at a single urban public referral hospital, so that the sample was limited to subjects from the lower income groups attending state hospitals, and did not include subjects in the private sector. This may also have resulted in subjects with a high risk factor profile being selected out (referral bias). Secondly, we could not determine the true prevalence of the metabolic syndrome across ethnic groups because datasets were not complete for waist circumference and fasting plasma glucose; nor did we analyse clinical characteristics and outcomes of those with CAD. Thirdly, angiographic analysis was limited to the epicardial vessels with obstructive lesions and did not include an estimate of the severity of stenoses using a scoring system. However, a strength of our sample was that it included subjects who underwent both nuclear scans and angiography in order to detect subjects with angiographic stenoses and functional ischaemia. The study sample represents an important segment of the population of subjects with chest pain that has not been adequately studied, and addresses a gap in our knowledge about the relationships between risk factors and CAD among ethnically diverse subjects.

CONCLUSION

This study reaffirms previous reports showing a high prevalence of cardiovascular risk factors in subjects with CAD in KwaZulu-Natal.[11,27,47,48] Across ethnic groups the predictors of CAD were to a large extent, modifiable risk factors, emphasising the importance of these parameters as targets for secondary prevention.[42] While our findings show a lower atherogenic burden amongst the Africans compared to the other ethnic groups, their lipid and glycaemic risk factor profiles clearly show marked changes compared to early studies at the turn of the century. This, together with the near absence of a family history of MI, confirm that environmental influences and lifestyle changes have contributed to emergence of CAD at a younger age in African men and women compared to the other ethnic groups.[21] The observations indicate the need for urgent population interventions to reduce the impact of chronic diseases of lifestyle, which should include intensive educational primary prevention measures at school-going age.

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The profile of subjects with suspected coronary artery disease who have atypical chest pain symptoms

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ABSTRACT

Background: This study describes the risk factor profile of subjects with coronary artery disease (CAD) who present with atypical chest pain.
Method: Hospital records of patients with chest pain who did not satisfy the criteria for typical angina and who underwent both sestamibi nuclear imaging and coronary angiography were evaluated over a 6 year period (2002 - 2008).
Results: Amongst 5 378 subjects referred for evaluation of myocardial ischaemia to a tertiary hospital, the prevalence of atypical / non-anginal pain was 9.9% (531 patients). Of the 173 subjects who underwent both nuclear scans and coronary angiography, 99 (M 66, F 33) (57%) had epicardial CAD at angiography (>50% stenosis) with equal distribution of single, double and triple vessel disease. There was no difference in the pretest probability of CAD in subjects with and without CAD (20.5% vs. 21.9% p=0.891). Neither the number of chest pain criteria nor the individual pain characteristics were associated with the presence of CAD (p>0.05). CAD was more likely in the middle age and older subjects (p<0.001), in males (p<0.001) and in those who smoked (LR 5:2 p=0.001). On multivariate analysis age, smoking, waist circumference and gender emerged as predictors of CAD. Clustering of 3 or more risk factors was associated with the presence of myocardial perfusion deficits (p=0.001).
Conclusion: Characterisation of chest pain symptomatology did not prove to be helpful in the detection of CAD among subjects with a low pretest probability. Decision-making and triage should be supported by a positive smoking history and risk factor clustering.
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INTRODUCTION

Chest pain is a common presenting symptom and raises immediate concerns about coronary artery disease (CAD). In a general practice survey of almost 25 000 subjects presenting with chest pain only 12% of subjects were found to have CAD.[1] The prevalence of "noncardiac" symptoms assessed in the emergency room was 17% in a large registry of 17 737 subjects with acute coronary syndrome.[2] When angina pain is not typical it is not uncommon for subjects to be labelled "atypical chest pain" (ACP) and discharged without a firm diagnosis. Patients with nonspecific chest pain symptoms are not without risk,[3] and continue to seek treatment on a regular basis, imposing a large cost burden for undiagnosed symptoms. In a Mayo Clinic study 49% of subjects who presented to the emergency room were labelled as psychogenic chest pain and during follow up 42% had repeated cardiology evaluations.[4]

Many patients present in a non-acute setting with chest pain symptoms that do not fit the description of typical angina. Typical angina as originally described by the English physician, William Herberden[5] in 1768, comprises distinct criteria that describe a flow of events from onset of pain, its duration and mode of relief. It is characteristically a dull discomfort that is usually brought on by effort and relieved by rest or sublingual nitroglycerine. When evaluating patients presenting with suspected myocardial ischaemia, the clinician's approach is to evaluate the history to assess the typicality of chest pain, and inherently applies conventional risk prediction to estimate the probability (pre-test likelihood) of CAD based on the patient's age, gender and chest pain characteristics.[6,7] However, subjects frequently present with varying symptomatology and severity of chest pain resulting in poor discriminatory power for the diagnosis of coronary disease. While clinicians may appropriately

refer central chest pain with typical angina and avoid referring subjects with musculoskeletal symptoms, they are often faced with the dilemma of unspecified chest pain symptoms with an uncertain diagnosis. In subjects who do not fulfil all the criteria for typical angina the term "atypical chest pain" (ACP) is loosely applied while the subject is being referred or investigated. Chest pain in these subjects should not be disregarded as these symptoms may be associated with a heightened cardiovascular burden. In a Swedish study subjects with nonspecific symptoms were found to have significant morbidity and mortality on long-term follow-up.[3] In this study we describe the clinical and angiographic profile of subjects with atypical chest pain symptoms referred to a tertiary centre for evaluation of suspected ischaemia.

AIMS

We aimed to evaluate whether chest pain categorisation predicts the presence of CAD in a low risk subjects with stable chest pain symptoms. The objectives were to describe the clinical profile of patients who presented to the cardiac clinic with atypical chest pain symptoms, as well as to identify clinical parameters that are likely to suggest the presence of CAD in these subjects.

METHODOLOGY

This was a retrospective study over a 6 year period (2002 - 2008) of subjects with stable chest pain suspected to be of cardiac origin referred to the IALCH cardiac clinic in the Cardiology Department at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa. During this period subjects with atypical symptoms underwent sestamibi scans and coronary angiography. Patients were identified using the Speedminer software programme that was used at the hospital to store data collected on its Medicom database. Data were extracted on age, gender, risk factors, chest pain symptomatology and investigations for CAD (sestamibi, methoxyisobutylisonitrile nuclear scans and coronary angiography). Subjects who did not satisfy the criteria for typical angina were assessed at the cardiac clinic by the senior registrar in consultation with the cardiology consultant. All subjects had stable chest pain symptoms and were initially assessed on history, chest radiograph, electrocardiogram, and exercise stress testing. Troponin estimation was not performed in these subjects as they did not present with acute symptom onset and were stable. Those found to have an extracardiac cause for their symptoms were evaluated and discharged from the clinic. Patients with known established coronary artery disease who underwent coronary artery bypass surgery were excluded. The remaining patients with atypical symptoms constituted the study group.

Typical angina was defined by a set of 3 criteria[8] as follows: (1) onset with effort or emotion, (2) typical nature (retrosternal, crushing, dull), radiation (neck, jaw, left arm, back, epigastrium), duration (2 - 10 minutes) and (3) relief with rest and / or TNT. If all 3 of the criteria for angina were met, the pain was diagnosed as typical angina and the probability for CAD considered high. When 2 criteria were present the pain was classified as "atypical" chest pain and in the presence of only 1 criterion the risk was considered lowest and classified as "non-anginal" chest pain.[8] Exertional dyspnoea and fatigue suspected to be angina equivalents were classified as atypical angina.

Subjects without typical angina (i.e. atypical and non-cardiac pain as defined above) who underwent both coronary angiography and sestamibi scans were selected for study in order to obtain an angiographic as well as a functional assessment of coronary artery disease severity. The end points of this study were obstructive CAD (defined at invasive coronary angiography as >50% reduction in lumen diameter), or inducible myocardial ischaemia on non-invasive stress imaging. The sestamibi study employed a 2-day stress – rest imaging protocol using 15mCi of technetium 99m-sestamibi injected at the peak of stress for stress imaging on the 1st day, and the same dose of technetium 99m-sestamibi for rest imaging study performed at least 24 hours after stress imaging.[9] Single photon emission computed tomography imaging (SPECT) was performed and gated acquisition was done on the stress images. Images were analysed with MPI Siemens Corridor 4DM V501 and the study was interpreted as abnormal if evidence of inducible myocardial ischaemia (reversible defect), and / or infarction (irreversible defect) was present.

Ethical approval for access to the medical records was obtained from the Biomedical Research and Ethics Committee (BREC) - Reference number BR 194/09.

Statistical Package for the Social Sciences (SPSS version 18.0) was used for analysis of data and a 95% level of confidence estimated; a global significance level of $\alpha = 5\%$ was chosen. Chest pain criteria, age and gender were used in a basic model to assess the pretest probability of coronary artery disease.[6, 10] The type of pain as well as the number of criteria were compared with the angiographic findings. The chi-squared test was used for categorical variables and the Student's t-test was used for continuous variables, to assess the significance of any difference in risk between subjects with and without CAD. Binary logistic regression and multivariate analysis was used to control for confounding factors when assessing the independent rela-

tionships between traditional risk factors (age, diabetes, lipid levels, blood pressure and smoking) and the outcome variable (CAD).

RESULTS

During the 7 year study period (2002 - 2008), 5 378 patients were referred to the IALCH cardiac clinic for the evaluation of chest pain of a suspected ischaemic aetiology. Of these, 564 had symptoms that fell short of the classical description of angina (i.e. they satisfied 1 or 2 out of the 3 criteria). Thirty-three patients had previously undergone cardiothoracic surgery and were excluded from the study, leaving 531 subjects for analysis. This yielded a 9.9% (531/5378) prevalence of patients presenting to the clinic for suspected ischaemia in whom chest pain symptoms were not typical for angina. The male to female ratio in this group was 1:1.3 (229/302). The mean pre-test score in these 531 subjects was 20.9%, in keeping with a low risk for ischaemia. After clinical evaluation and non-invasive assessment clinicians attributed the chest pain symptoms to a non-ischaemic cause in 358 subjects, leaving 173 subjects with chest pain symptoms of a possible ischaemic aetiology. These 173 subjects (93M, 80F) had equivocal or negative exercise stress tests and underwent both sestamibi scans and coronary angiography to determine whether there was an ischaemic basis for their symptoms.

The demographic data, clinical and angiographic findings are shown in Table I. The majority of the subjects were of Indian ethnicity (134/173, 77.5%). Subjects with coronary disease were more likely to be male (M:F 2:1) with no racial predisposition. Ninety-one (52.5%) of these 173 subjects presented with a variety of pre-existing conditions which may have contributed to the clinician labelling their symptoms as "atypical" (Table I). The most frequent underlying conditions were gastrointestinal causes, psychiatric conditions and mitral valve prolapse which totalled 49 of the 91 cases. Of the 173 subjects, 22 had atypical chest pain (2 criteria met), 81 had non-cardiac chest pain (1 criterion met) and the remaining 70 subjects met none of the criteria for angina ("zero criteria pain").

Coronary angiography revealed obstructive coronary disease (>50% coronary stenosis) in 99/173 patients with an equal distribution of single, double and triple vessel involvement. This yielded an 18.6% (99/531) prevalence of significant CAD amongst subjects who presented to the clinic with chest pain symptoms that were not typical of angina. There was no difference in the pre-test score (Diamond and Forrester)[6] between those subjects with a normal angiogram and those subjects with coronary CAD (p=0.891) (Table II).

Subjects with a normal angiogram were younger (mean 48 years) than those with CAD (mean 54 years) (p<0.001) and more likely to be of female gender (p<0.001). Obstructive CAD was more likely in middle-aged or older males and smokers (LR 5:2 p=0.001). The number of criteria met (0, 1, or 2) for the diagnosis of angina had no influence on the findings at angiography. Indeed, 42 of the 70 subjects who met none of the criteria for angina ("zero criteria pain") were found to have significant CAD at angiography. Neither the pain characteristics (nature, duration and radiation) nor the relieving factors (rest or sublingual nitroglycerin) showed any association with CAD or with an abnormal sestamibi scan (Table II). Using established cutoff levels,[11] there was a positive association between increased waist circumference (>102cm) and CAD (p<0,001), as well as between obesity (BMI>30kg/m^2) and CAD (p<0,001). After all risk factors were fed into a multivariable predictive model (controlling for age, gender, BMI, waist circumference, hypertension, diabetes, and family history), it was found that only age, gender, smoking and waist circumference emerged as independent predictors of the presence of obstructive CAD (Table III).

There was no difference between the sestamibi and coronary angiographic findings (p=0.127). Smoking (LR 4:1 p=0.028) was the only individual risk factor associated with an abnormal sestamibi scan. Clustering of 3 or more risk factors was present in 78 of the 173 subjects and was significantly associated with the presence of an abnormal sestamibi scan (p=0.001). Of interest, 39 of the 65 subjects with normal angiograms had an abnormal sestamibi findings raising the possibility of micro-vascular disease in these subjects.

TABLE I: Pre-existing disease conditions.

Disease	n=173	%
GIT causes	22	12.7
Psychiatric / Neurological	15	8.7
Valve Disease / ASD	12	6.9
Connective Tissue Diseases	9	5.2
Neck (Joint / bone / muscles) diseases	8	4.6
Thyroid Disease	8	4.6
COPD	7	4.0
HOCM / DCMO	5	2.9
CVA / TIA / PVD	5	2.9
Total	**91**	**52.5**

HOCM / DCOM: hypertrophic / dilated obstructive cardiomyopathy, CVA: cardiovascular accident, TIA: transient ischaemic attack, PVD: peripheral vascular disease.

TABLE II: Clinical features vs. angiographic findings.

Risk parameter	Normal / non-obstructive (n=74) n (%)	CAD on angiogram (n=99) n(%)	Total (n=173)	p-value
Demographic data				
Age (years)	48.5	54.0		<0.001
Female	47 (58.8 %)	33 (41.2 %)	80	<0.001
Male	27 (29.0 %)	66 (71.0 %)	93	
Ethnic Group				
Black	3	4		0.957
Coloured	4	4		
Indian	56	78		
White	11	13		
Clinical characteristics				
Chest pain				
Zero criteria	27 (36)	42	70	
Non-cardiac	35 (247)	46	81	0.415
Atypical	12 (16)	11	22	
Pretest probability*				
Low (0% - 30%)	26 (35)	33	59	0.891
Medium (31% - 70%)	49 (66)	65	114	
Risk Factors				
Diabetes	4 (32)	41	65	0.227
Hypertension	48 (65)	68	116	0.597
Dyslipidemia	45 (60)	71	116	0.131
Family History	43 (58)	50	93	0.321
Smoking**	23 (31)	57	80	0.001
Obesity measures				
Increased WC	54 (73)	48	102	<0.001
BMI >30Kg/m^2	0 (0)	63	63	<0.001
Sestamibi scan				
Smokers**	18/54	61/119	79	0.028

**Pretest probability was calculated using age, gender and number of criteria according to Diamond and Forrester. **Subjects who were smokers were more likely to have CAD on angiogram as well as on the sestamibi scan.*

DISCUSSION

In this study the prevalence of atypical chest pain symptoms in low to intermediate risk subjects referred for evaluation of suspected myocardial ischaemia was 10% (531/5378). Amongst these subjects obstructive CAD (≥50% diameter stenosis in ≥1 vessel on catheter-based coronary angiography) was detected in 18.6% (99/531). Other studies that have examined the lifetime prevalence of chest pain[2,12,13,14] have reported much lower prevalences of CAD of about 9% - 12%. The high prevalence of CAD at catheterisation angiography 57% (99/173) is very similar to that reported in the South African national ACROSS registry[15] in which 1 892 subjects with chest pain underwent angiography after non-invasive stress testing, and in whom a positive test and conventional risk factors were found to be independent predictors of obstructive CAD. In the TOPIC study which evaluated chest pain symptoms in Switzerland in a general practice setting, CAD accounted for 12% of cases of chest pain.[2] The high prevalence of CAD in our study is due to the fact that our patients comprised a select group of subjects referred from secondary level hospitals to our tertiary clinic, often with medical co-morbidities, resulting in a much higher yield of a positive outcome for CAD.

Several factors might have contributed to the atypicality of pain in our subjects found to have obstructive CAD. Firstly, almost two thirds of our subjects with CAD had multivessel disease,

TABLE III: Predictors of coronary artery disease.

Risk factor variables	ANOVA p-value	Univariate p-value	Multivariate p-value
Age*	<0.001	<0.001	<0.001
Gender*	<0.001	0.021	<0.001
Race	0.851	0.571	0.764
Diabetes	0.230	0.241	0.154
Hypertension	0.599	0.859	0.620
Dyslipidaemia	0.133	0.339	0.104
Family History	0.245	0.331	0.280
Smoking*	<0.001	0.070	0.001
Waist Circumference increased > M102cm/F88cm	0.051	0.029	0.036
BMI increased >30Kg/m2	0.029	0.043	0.409

**Multiple analysis of variance showed that age, smoking and gender were associated with angiographic outcomes. The positive association of increased BMI with CAD on univariate analysis fell away after adjustment in the multivariable analysis.*

which might explain symptoms occurring at rest in addition to exertional chest pain. Secondly, the presence of other comorbidities could be a confounding factor. The autonomic neuropathy and microvascular disease in diabetes and the relative ischaemia in hypertension with left ventricular hypertrophy and arterial rarefaction may be associated with altered thresholds in pain perception and symptoms occurring at rest. When there is more than one underlying aetiology for chest pain the subject might perceive pain symptoms as arising from a single organ (and be interpreted by the clinician as such). For instance, smoking-related cough and chest pain may have contributed to the atypicality of symptoms in chronic bronchitis / chronic obstructive pulmonary disease,[16] conditions which are common accompaniments with CAD. Concomitant gastro-intestinal reflux disease may have contributed to the atypicality of chest pain with retrosternal chest symptoms occurring at rest, particularly in many of our subjects who were obese.[17] These considerations have clinical implications in the assessment of stable patients who present with atypical chest pain symptoms.

Several studies have reported that female patients complain more frequently of atypical chest pain symptoms[18,19,20,21,22] that are often unassociated with CAD. In a study performed in the primary care setting, Desiree Lie, et al.[23] examined gender differences and chest pain characteristics in 1 212 patients with chest pain in an attempt to define clinical markers associated with CHD. They found that women were diagnosed more frequently with psychogenic disorders (11.2% vs. 7.3%; p=.02), while men were more likely to have CAD (17.2% vs. 13.0%; p=.04). Although CAD was more common in males in our study, concomitant psychiatric illness was present in 15 subjects, of whom 6 had normal angiographic and nuclear imaging studies; of these 2 were women with anxiety and depression. There is evidence that women could experience chest pain from disease of the coronary arterioles, even in the absence of angiographically evident coronary disease.[24] The finding of myocardial ischaemia on sestamibi scans in subjects without obstructive CAD at angiography suggest the possibility of underlying microvascular disease in these subjects.[25] The constant demand - supply mismatch may account for symptoms occurring at rest, and lend support to the clinician's perception of the atypicality of symptoms in these subjects.[26] Recognition and treatment of microvascular angina are important in addressing the high cost burden associated with persistent symptoms and return visits, and potential for cardiac events associated with this condition.

Unlike previous reports[21,22] we did not show any gender differences in chest pain symptomatology, nor did we show any differences in symptoms between subjects with and without CAD. Using only the type pain, it has been suggested that the more criteria are met, the greater the likelihood of CAD.[27] In contrast, our findings reaffirm the limited ability of atypical symptoms to predict obstructive CAD in subjects with a low–intermediate pretest probability.[10] Indeed we found that many subjects with CAD satisfied none of the criteria for the diagnosis of angina. Older subjects, male gender, and smoking increased the odds of atypical symptoms being due to coronary disease. Our findings are similar to those of Rovai, et al.[27] who showed that age and gender had better predictive ability and this was increased further by the demonstrate on of inducible myocardial ischaemia on the sestamibi scan. Even In studies of subjects who presented in an acute setting[28,29,30] chest pain symptoms alone had limited predictive ability. Swap, et al.[30] found that no single element of the chest pain history increased or decreased the likelihood of an acute coronary syndrome alone or in com-

bination. In that study chest pain characteristics that were stabbing, pleuritic, positional, or reproducible by palpation decrease the likelihood of ACS or AMI (LR 0.2-0.3). Chest pain that radiated to one or both shoulders or arms or is precipitated by exertion was associated with higher likelihood of ACS (LR 2.3-4.7).

All the subjects in our study were of Indian ethnicity. There is evidence that atypical chest pain symptoms are more frequent in South Asians and people of Indian origin.[21,22] Recognising that the Diamond and Forrester model is not adaptable across different populations, and the limitations of chest pain symptoms in risk assessment Genders, et al.[31] developed and validated a new prediction model, based on clinical presentation and cardiovascular risk factors, to improve the estimate for the probability of obstructive coronary artery disease (CAD) in patients with new onset chest pain and guide further diagnostic testing. In an analysis of over 5 000 patients they found that the clinical model using risk factors improved prediction compared to the basic model using the Diamond and Forrester pretest likelihood assessment. We did not apply risk scoring systems such as the HEART score which uses the pain characteristics, age, number of risk factors, electrocardiographic findings, and troponin levels in acute settings of chest pain presenting to the emergency room.[32,33] We determined the pretest likelihood of CAD using the Diamond and Forrester scores[6,7] which have been used in stable subjects with chest pain. The baseline electrocardiograms and exercise stress test were either inconclusive or negative and these subjects underwent sestamibi scanning which was the only non-invasive test available at the hospital during the study period. Many of these subjects were unable to attain their target heart rate because of impaired mobility arising from morbid obesity, highlighting the importance proper pharmacological testing with achievement of target heart rates during sestamibi nuclear testing.

An important finding in our study was that although the major risk factors such as diabetes, hypertension and dyslipidemia were individually not associated with obstructive CAD, we found that clustering of these risk factors was more likely to be associated with myocardial perfusion defects indicative of obstructive coronary disease.[34,35] In the Botnia[34] study of 4 483 subjects the risk for coronary heart disease was increased threefold in subjects with risk factor clustering in the form of the metabolic syndrome ($p<0.001$) and associated with increased cardiovascular mortality (12.0% vs. 2.2%, $p<0.001$). In that study subjects with the metabolic syndrome were more likely to have macrovascular, or even microvascular disease. Detection of CAD in subjects with atypical chest pain has implications for the risk of undetected disease; likewise early exclusion of CAD in the majority of these subjects has health service implications on the cost burden of repeated admissions associated with ongoing symptoms.[36] In subjects with low to intermediate probability chest pain coronary calcium scoring has now been shown to have a better predictive value than the basic clinical model (age and gender plus risk factors) in subjects with stable chest pain.[37,38] Current international guidelines recommend using the CT-based coronary calcium score in patients calculated to be at low to intermediate pretest probability of CAD.

Limitations of our study include its retrospective design and the consequent lack of complete datasets for each patient. Being performed in a tertiary setting introduced a selection bias leaning towards a diagnosis of CAD in a select group of subjects referred to a tertiary centre which probably accounts for the higher prevalence of CAD in our subjects. Subjects with symptoms clearly attributable to non-ischaemic causes e.g. musculoskeletal or respiratory chest symptoms, would have been appropriately triaged, which probably accounts for the higher prevalence of CAD in subjects without typical again. These factors, (together with the fact that we chose subjects who underwent both sestamibi scans and coronary angiography) resulted in a smaller sample size for study. Also, we studied the pain characteristics in low-risk patients presenting with chest pain but did not analyse the effects of associated symptoms such as dyspepsia, dyspnoea and fatigue that have recently been shown to have additive value in the estimation of cardiovascular disease risk in the primary care setting.[39]

CONCLUSION

This study shows that subjects referred for suspected ischaemia without typical anginal symptoms have a wide differential diagnosis which includes CAD in about 10% of cases. It also highlights the limitations of chest pain characteristics in assessing the probability of CAD.[6] The atypicality of chest pain symptoms should alert the clinician to the possibility that existing comorbidities may influence the manifestations of chest pain and may account for the low to intermediate pretest likelihood for CAD. Chest pain characteristics alone were not a powerful enough predictive tool to determine the need for diagnostic testing. In addition to age and gender, smoking history and risk factor clustering influenced the likelihood of CAD and should help triage subjects with a low to intermediate risk of coronary artery disease. These subjects should best undergo non-invasive testing using calcium scoring / CT angiography which has a very high negative predictive value and obviates the need for invasive testing when the calcium score is zero.[40]

Conflict of interest: none declared.

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Five-year outcomes of percutaneous coronary intervention using second generation drug-eluting stents for multivessel coronary artery revascularisation

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ABSTRACT

Aim: This report evaluated outcomes of percutaneous coronary intervention (PCI) using drug-eluting stents (DESs) compared to coronary artery bypass grafts (CABG) for multivessel coronary artery disease (CAD).
Methods: Sixty patients (43M, 17F); mean = 64.35 years (SD ± 10.4) who underwent PCI or CABG were followed up for 5 years. Revascularisation included 19 elective and 5 emergency cases. The composite outcome (defined as major adverse cardiac and cerebral events [MACCE]), and rates of repeat revascularisation were compared in each group using survival curves and adjusted Cox pro-portional hazard models.
Results: Nine (15%) patients sustained acute MI and 6 (10%) suffered a stroke during follow-up (PCI n=5, CABG n=4). There were 10 deaths (DVD n=2, TVD n=8) (6 CABG, 4 PCI). There was no difference in treatment effects between the 2 groups for time to MI, stroke, and angina (PCI 40% vs. CABG 23.3%, p=0.194). Adjusted 5-year risk of death (11.7% vs. 17.6%, OR=1.300, CI=0.313 - 5.404, p=1.000) and the composite of death, stroke and MI (51.3% vs. 44% p=0.566) were similar in the 2 groups. There was a higher rate of repeat revascularisation in PCI group (52.8% vs. 29.3%) (p=0.121.)
Conclusions: PCI using DESs for patients with multivessel CAD showed similar outcomes to CABG.
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INTRODUCTION

The selection of appropriate intervention for myocardial revascularisation in the elective setting should be undertaken based upon the outweighing by the expected benefits, in terms of survival or health outcomes to the expected negative consequences of the procedure.[1] Severe multivessel disease (MVD) has traditionally been treated with coronary artery bypass graft (CABG) surgery as the standard revascularisation strategy but this is not without the risks associated with bypass surgery.[2] The advent of percutaneous coronary intervention (PCI) has ushered in an era of comparatively non-invasive coronary revascularisation, but in the early years was limited to balloon angioplasty and the deployment of bare metal stents. These were complicated by significant restenosis rates and acute vessel closure.[3] Recent advances in PCI such as the advent of drug eluting stents (DESs) to maintain vessel patency,[4] as well as advances in CABG techniques[5] have improved the outcomes of revascularisation of patients with MVD, contributing to significant reductions in mortality and morbidity.[6] Optimisation of stent profiles and advances in the drug delivery of DESs have reduced the neointimal response and in-stent stenosis, making it difficult to choose the appropriate revascularisation strategy in patients with multivessel CAD.[7]

Although several studies have shown favourable outcomes of PCI using DESs compared to CABG for multivessel CAD,[8,9] their short duration have not permitted evaluation of late stent stenosis and myocardial infarction (MI) rates in the longer term. Data are still limited on long-term (beyond 5 years) outcomes of PCI or CABG in patients with MVD. In South Africa, the ACCESS (Acute Coronary Events - a Multinational Survey of Current Management Strategies) registry described favourable clinical outcomes (mortality, re-admission rates, and severe bleeding episodes) at 1 year in subjects with ACS, half of whom

received DESs for the culprit lesion.[10] This study examined the safety and outcomes of major adverse cardiovascular and cerebrovascular events (MACCE) at 5 years in patients undergoing PCI using second generation DESs compared to CABG for multivessel CAD.

MATERIALS AND METHODS

Consenting patients between the ages of 30- and 90-years-old with multivessel coronary artery disease undergoing coronary revascularisation with PCI (using second generation DESs) or CABG over a 2-month period (February - March 2013) were recruited for study at the St. Augustine's Hospital Heart Centre, Durban, South Africa. Twenty-one (35%) patients had chronic stable angina and 12 (20%) patients had ACS. Patients who underwent prior CABG or valve surgery, those who had MI within 24 hours and those with cardiogenic shock were excluded (Table I). The choice of revascularisation strategy (PCI or CABG) was made by the attending cardiologist and surgeon. PCI was performed using only the second generation DESs. Dual antiplatelet therapy using aspirin and clopidogrel in standard regimens were prescribed for at least 6 months duration. Surgery was performed using standard bypass techniques and harvesting the internal thoracic artery for revascularisation of the left anterior descending artery and saphenous vein grafts for the remaining vessels. Follow up was performed at 6 monthly intervals in the first year and thereafter yearly for 5 years and endpoint outcomes documented.

Diabetes mellitus was diagnosed according to guidelines published by the American Diabetes Association[11] and hypertension was defined as a blood pressure ≥140/90mmHg on 3 consecutive visits or patients who were on antihypertensive medication.[12] Dyslipidaemia was diagnosed in patients who were on chronic anti-lipid drugs or documented on diagnosis from medical records and classified using the criteria from the Third National Cholesterol Education Programme and Adult Treatment Panel III guidelines (NCEP-ATP III).[13] The BMI was calculated as weight / height^2 and defined as elevated if it was >25.0kg/m.[14] A history of smoking was present if there was previous or current use of cigarettes or tobacco products.

Multivessel disease was defined by the presence of ≥50% diameter stenosis in 2 or more major epicardial coronary arteries and categorised as double vessel disease (DVD) or triple vessel CAD.[15] Total arterial occlusion was defined as the complete obstruction (99%) of a coronary artery, corresponding to the Thrombolysis In Myocardial Infarction (TIMI) flow risk score of TIMI 0 or TIMI 1.[16] The composite endpoints of major cardiac and cerebrovascular adverse events (MACCE) was defined as the composite outcome of death, non-fatal myocardial infarction, stroke, repeat revascularisation, and angina.[17] Cardiac death was described as death due to a cardiovascular event or sudden unexplained death caused by a sudden change in heart rhythm.[15] Myocardial infarction was defined according to the Third Universal Classification of MI which encompasses ST segment elevation (STEMI), non-ST segment elevation (NSTEMI), and unstable angina.[18] Stroke was classified according to the American Stroke Association as either ischaemic or haemorrhagic.[17] Repeat revascularisation was defined as repeat CABG or PCI of the previously stented vessels.[17,18]

TABLE I: Patient selection.

Patient selection	PCI	CABG
Total who underwent coronary angiograms (n=225)	162	63
Exclusions	132	33
Single vessel disease	59	0
Valvular heart disease / surgery	16	17
Prior CABG	0	15
Multivessel disease treated with medication only	47	0
Coronary artery dissection	10	0
Declined procedure	0	1
Patients selected for study	**30**	**30**

STATISTICAL ANALYSIS

Considering a paired t-test for pre- and post-variable comparisons at a 5% level of significance, a sample size of 60 patients was calculated to achieve a power of 80% and to show an effect size of 0.50 for the difference in pre- and post-intervention means.[19] At least 30 subjects undergoing each revascularisation procedure were therefore required for this analysis.

The IBM SPSS software, version 25 was used for statistical analyses. The risk factor profile and baseline characteristics of the patients in the 2 treatment groups were compared with the t-test for continuous variables and with the chi-square statistics or Fisher exact test for categorical variables. Treatment-related differences in the immediate complications and long-term outcomes between the 2 procedures were analysed using G*Power version 3[18] to test the difference between 2 independent group means using a 2-tailed test, a medium effect size (d=.05), and an alpha of .05 in all patients. Differences in the long-term rates of the study outcomes between groups were assessed using Cox regression. Kaplan-Meier curves were constructed for the 5-year outcomes of the composite endpoint

of death, MI and stroke as well as for recurrence of angina. Adjusted covariates included the patients' ages and gender, the presence or absence of clinical parameters and coexisting conditions, left ventricular function, and the number of diseased vessels. All reported p-values are 2-sided, and p-values <0.05 were considered statistically significant.

Full ethical approval was obtained from the Durban University of Technology Institutional Research Ethics Committee (ethical clearance number: IREC 016/19). All patients provided written informed consent before enrolment.

RESULTS

Baseline characteristics

During the 2-month period (February - March 2013), 225 patients underwent coronary angiography at the St. Augustine's Hospital Cardiac Catheterisation Laboratory. Of these 225 patients, 162 patients underwent PCI with DESs (Xience Alpine, Xience Prime, Xience Pro, Xience V, Xience Sierra and Onyx) and 63 patients underwent CABG surgery. There were 165 patients who did not meet the inclusion criteria and were excluded (PCI n=132, CABG n=33). The remaining 60 patients (males n=43 and females n=17) with multivessel coronary artery disease (PCI group n=30 and CABG group n=30) comprised the study group (Figure1). The mean age in these 60 subjects (43 M, 17 F) was 64.35 years (SD ± 10.4) with M:F ratio of 2.53:1. There was no difference in the age distribution between the 2 groups (p=0.531). The majority 39 (65%) of the study sample were Indians, followed by 15 (25%) Whites, 4 (6.6%) Africans and 2 (3.3%) of mixed ethnicity (Coloured). Premature CAD (<55yr in males and <65yr in females) was present in 9 subjects in the PCI group and 7 in the CABG group.

The baseline clinical characteristics showed no difference in the risk profile and comorbid diseases between the 2 groups (Table II). The most common risk factor was hypertension (66.6%) followed by dyslipidaemia (46.6%), cigarette smoking (43.3%) and diabetes mellitus (36.6%). There was also no difference in the mean ejection fraction (55.10% vs. 49.13%; p=0.612) between the PCI and CABG groups prior to revascularisation respectively.

The baseline angiographic characteristics of the study sample are shown in Table III. Double vessel disease was present in 22 subjects (36%) and triple vessel disease in 38 (63%) of the total sample (n=60). The left anterior descending (LAD) artery was the most common major epicardial vessel involved (88.3%).

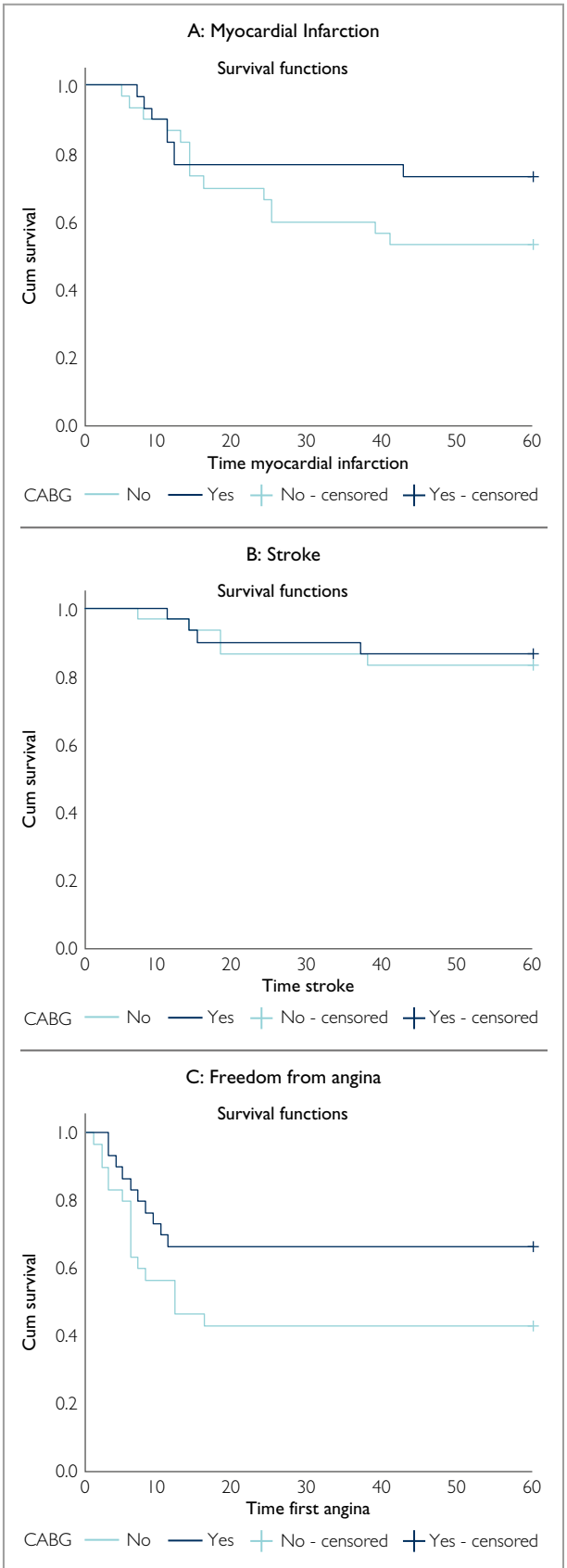

FIGURE 1: Survival curves using Kaplan-Meier estimates for the outcomes of myocardial infarction. (A), stroke, (B) and recurrence of angina, (C) for CABG (blue) vs. PCI (red).

TABLE II: Baseline characteristics of the study sample.

Variable	PCI n (%)	CABG n (%)	Odds ratio*	95% CI	p-value
Mean age, (years)	64.35 ± 10.4			1.000	186
Gender					
Male	17 (56.6)	24 (80)	4.266	0.908 - 4.109	0.798
Female	13 (43.3)	6 (20)	0.259	0.056 - 1.599	0.146
Hypertension	20 (66.6)	20 (66.6)	1.000	0.342 - 2.926	1.000
Diabetes	11 (36.6)	11 (36.6)	1.000	0.350 - 2.858	1.000
Elevated BMI	19 (63.3)	20 (66.6)	0.798	0.216 - 2.819	0.198
Dyslipidaemia	15 (50)	13 (43.3)	0.765	0.277 - 2.114	0.796
Smoker	13 (43.3)	13 (43.3)	1.000	0.360 - 2.777	1.000
Previous heart failure	5 (16.6)	7 (23.3)	1.522	0.423 - 5.472	0.748
Chronic kidney disease	3 (10)	2 (6.6)	0.643	0.100 - 4.153	1.000
Cerebrovascular or carotid artery disease	2 (6.6)	7 (23.3)	4.261	0.806 - 22.532	0.145
Peripheral vascular disease	7 (23.3)	2 (6.6)	0.235	0.044 - 1.241	0.145
Recent MI (1 - 8 days before treatment)	16 (53.3)	17 (56.6)	0.800	0.215 - 2.972	1.000
ECG findings					
Sinus rhythm	21 (70)	25 (83.3)	2.143	0.622 - 7.387	0.360
Atrial fibrillation	6 (20)	4 (13.3)	0.615	0.155 - 2.450	0.731
Paced rhythm	3 (10)	2 (6.6)	0.643	0.100 - 4.153	0.601
Ejection fraction					
<40%	5 (16.6)	8 (26.6)			
40% - 50%	5 (16.6)	5 (16.6)			
≥50%	20 (66.6)	17 (56.6)			
Mean EF (%)	50.10	49.13			0.612

MI: myocardial infarction.
** The ORs and CIs are for the PCI group relative to the CABG. There was no difference in clinical characteristics and comorbid conditions between the 2 groups.*

Seventy two percent of the study sample had lesions in the circumflex (CX) artery and 78.3 percent in the right coronary artery (RCA). There was no difference in proximal LAD involvement (p=0.131) and in left main stem disease between the groups (23.3% vs. 23.3%; p=1.000). Subjects with double vessel disease (DVD) were dominant in the PCI group compared to the CABG group (56.6% vs. 16.6%, p=0.039), while triple vessel disease (TVD) was more common in the CABG group (83.3% vs 43.3%, p=0.129).

Procedural characteristics

There were 81 bypass grafts performed surgically and a total of 73 coronary lesions stented by PCI. Eighty percent of the CABG group underwent off-pump surgery and 93.3% had revascularisation of the left anterior descending artery with the internal mammary artery. During PCI, 111 second generation drug eluting stents were deployed (Xience Alpine, Xience Prime, Xience Pro, Xience V, Xience Sierra and Onyx). Overall, the average lesion length was 24.32 ± 6.67mm. Approximately 33.3% of the study sample had stents implanted for double vessel disease and 36.6% of the study sample had stents implanted for triple vessel disease. Procedural success was obtained in all subjects in both groups with no major in-hospital complications occurring immediately post revascularisation and up to the time of hospital discharge. There were no differences between the groups in the major procedural complications (bleeding, hypotension and worsening renal function requiring dialysis) (Table IV).

Clinical endpoints

The median follow-up was 5.1 years (interquartile range (IQR): 4.1 - 6.2 years) for the overall sample (Figure 1). Complete follow-up was obtained in 88.3% of the overall sample (88.8% for DES and 88% for the CABG group, p=0.16).

Follow-up coronary angiography for chest pain, recurrence of angina and myocardial infarction was performed in 32 patients

TABLE III: Baseline angiographic findings showing lesion location and extent of disease.

CAD vessel characteristics	Total % / 60	PCI n	CABG n	p-value
Affected coronary vessel				
Left anterior descending	88.3*	24	29	0.399
Circumflex	71.7*	19	24	0.126
Right coronary	78.3*	22	25	0.266
Diagonal branch	3.3	1	1	0.075
Ramus branch	11.7	4	3	0.500
Obtuse marginal branch	13.3	3	5	0.353
Posterolateral branch	3.3	1	1	1.000
Left main stem	23.3	7	7	1.000
Extent of coronary artery disease				
Double vessel disease	36.6	17**	5	0.039**
Triple vessel disease	63.3	13	25	0.129
Lesion location in LAD				
With proximal LAD	83.3	22	28	0.131
Without proximal LAD	15	8	1	0.269
Mid LAD	48.3	17	12	0.267
Distal LAD	41.7	16	9	0.128
Total occlusions				
LAD	18	2	9	0.163
Circumflex	13	3	5	
Right coronary	12	4	2	
Ramus branch	3	1	1	
Obtuse marginal branch	2	0	1	

** Most lesions were in the major epicardial vessels and involving the proximal LAD. ** Vessel involvement was similar in both treatment groups but double vessel coronary artery disease was more frequent in the group who underwent PCI.*

TABLE IV: Major procedural complications during revascularisation.

Complication	PCI n (%)	CABG n (%)
Periprocedural death	0 (0)	0 (0)
Periprocedural MI	2 (6.6)	1 (3.3)
Bleeding / haematoma	3 (10)	2 (6.6)
Cardiogenic shock	0 (0)	2 (6.6)
Hypotension	5 (16.6)	7 (23.3)
Requiring dialysis	2 (6.6)	5 (16.6)
Stroke	0 (0)	0 (0)
Procedural failure	0	0

PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, MI: myocardial infarction.
Table IV illustrates the major procedural complications between the 2 revascularisation groups.

(PCI n=19 and CABG n=13). There was no difference in the angina recurrence between the 2 groups (PCI 40% vs. CABG 23.3% p=0.194). In the PCI group in-stent (n=9) and in-segment (n=5) restenosis was managed by repeat PCI with 51 stents deployed in 14 patients. In the CABG group, 27 stents were deployed in 12 patients. Repeat revascularisation was higher in PCI group than in the CABG group (52.8% vs. 29.3% respectively) but this finding was not significant (OR=0.446, CI=0.159-1447, p=0.121).

Nine of the 60 subjects (15%) patients sustained acute MI and 6 patients (10%) suffered a stroke during follow up (PCI n=5, CABG n=4). There was no difference in the rate of MI (p=0.058) or stroke (p=1.000) (Table V) between the PCI and CABG groups. Ten subjects demised (DVD n=2, TVD n=8) and of these 6 underwent CABG and 4 PCI (11.7%).

TABLE V: Endpoint analysis at 5 years.

	PCI n=30 (%)	CABG n=30 (%)	OR	95% CI	p-value
MACCE*	51.3%	44%	0.506		0.566
Death	4 (11.7)	6 (17.6)	1.300	0.313 - 5.404	1.000
Myocardial infarction	5 (14.6)	4 (11.7)	0.348	0.115 - 1.055	0.058
Stroke	3 (8.8)	3 (8.8)	1.000	0.226 - 4.431	1.000
Angina	12 (35.2)	7 (20.5)	0.507	0.180 - 1.422	0.194
Repeat revascularisation	18 (52.8)	10 (29.3)	0.446	0.159 - 1.447	0.121

**MACCE was defined as the composite outcome of death, nonfatal MI, stroke, repeat revascularisation and angina.[24] There was no difference in MACCE or in any of its component endpoints between the 2 groups.*

After adjustment for baseline differences using multivariable-adjusted Cox regression analysis, the 5-year risk of death (11,7 vs. 17.6%, HR=1.300, CI=0.313-5.404, p=1.000) and the composite of death, MI or stroke (51.3% vs. 44% HR 0.506 CI 0.180-1.422, p=0.566) were similar in the 2 groups. (Table IV) The Kaplan-Meier curves showing the time to onset of the major events and to revascularisation are shown in Figure 1.

There was no difference in the treatment outcomes in the high-risk subgroups (diabetes mellitus, ejection fraction <50% and age >65 years) between the PCI and CABG groups. There was also no difference in the rates of death (13.3% vs. 13.3%, p=1.000) and the composite outcome of death, MI, or stroke (40% vs. 26.6%, p=0.785) and the rate of repeat revascularisation (33.3% vs. 20%, p=0.789) among patients with TVD. There were no significant differences between the PCI and CABG groups in the rates of death (13.3% vs. 13.3%, p=1.000) and the composite outcome of death, MI, or stroke (40% vs. 26.6%, p=0.785) and rate of repeat revascularisation (33.3% vs. 20%, p=0.789) among patients with TVD. In subjects with double vessel disease unadjusted rates of death were similar in both groups, whereas the composite of death, MI or stroke (30% vs. 16.6%, p=0.026) and the rate of repeat revascularisation (26.6 vs. 6.6%, p=0.006) was significantly higher in the PCI compared to the CABG group respectively. Among patients with DVD who had proximal LAD involvement, the composite outcome of death, MI and stroke (20% vs. 10%, p=0.024) and rate of repeat revascularisation (16.6% vs. 3.3%, p=0.005) was higher in the PCI group compared to the CABG group.

DISCUSSION

This single centre study showed that PCI using second generation DES for multivessel disease (MVD) could be undertaken safely with low cardiovascular event rates and no immediate post-procedural mortality. The immediate procedural complication rate as well as the long term (5-year) rate for the composite outcome of death, myocardial infarction or stroke were similar in both PCI and CABG groups. These findings are in keeping with that of several large studies such as The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX),[20] Premier of Randomised Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT),[21] and Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL)[22] trials which have shown similar mortality and safety outcomes in the 2 groups. In SYNTAX[20] the composite outcome of safety (death, MI, or stroke) was comparable to CABG at 1 year, but the stroke rate was significantly higher in the CABG group; PCI using first generation DESs was associated with more frequent revascularisation. In our study we showed no increase in stroke in the CABG group, but the rate of repeat revascularisation in our study was lower, though not significant, at 5 years in the CABG group. Our findings are at variance with 2 large recent studies of revascularisation in patients with TVD which found that FFR-guided PCI using the zotarolimus stent was not non-inferior to CABG with respect to the incidence of a composite of death, myocardial infarction, stroke, or repeat revascularisation at 1 year.[23,24]

These findings are in contrast with earlier observational studies comparing PCI using first-[20] and second-generation[21] DES with CABG for multivessel revascularisation which revealed inconsistent findings.[25] While a few studies have indicated that mortality and safety outcomes were similar for PCI and CABG,[22] registries have found a lower rate of survival after PCI with DES than after CABG.[21,22] The effect of unmeasured confounding factors related to case selection may explain some of the discordance in these registry results.[20] Two recent

randomised trials, the EXCEL[25] and Nordic-Baltic-British Left Main Revascularisation (NOBLE)[27] trials have compared PCI using second-generation DES with CABG in patients with unprotected left main stem coronary artery disease. The EXCEL[26] trial showed that PCI with the everolimus DES was non-inferior to CABG for the composite endpoint of death, stroke, or MI at 3 years, whereas the NOBLE[27] trial showed that the 5-year risk of MACCE was higher after PCI. The NOBLE study suggests this could be due to the different stents used in the 2 trials, biolimus DES with biodegradable polymer in the NOBLE trial[27], and Xience durable polymer everolimus-eluting stents (EES) in the EXCEL trial.[26]

In our study the composite outcome of death, MI and stroke (20% vs. 10%, p=0.024) as well as rate of repeat revascularisation was significantly higher among patients with DVD who had proximal LAD involvement who underwent PCI group compared to the CABG. Our study findings are similar to the Bypass Surgery vs. Everolimus Eluting Stent Implantation for Multivessel Coronary Artery Disease (BEST)[3] trial, in which PCI with a second-generation DES (everolimus drug-eluting stent) was associated with increased risk of MI and repeat revascularisation, without any mortality difference when compared with CABG.[28] These findings were confirmed by Bangalore, et al.[4] who found that the outcomes of PCI with the everolimus drug-eluting stent was similar to that associated with CABG. In that study PCI was associated with a higher risk of myocardial infarction (among patients with incomplete revascularisation) but a lower risk of stroke, and a similar risk of death associated with CABG.[4]

In our study we also analysed the relative treatment effects in subsets of patients with major high-risk clinical factors such as diabetes mellitus, abnormal ventricular function, and age >65 years. While there was no difference in the 5-year adjusted rates of the composite of death, MI, or stroke between the 2 groups, the rate of repeat revascularisation appeared to be higher after PCI, but this difference was not significant. This was similar to a recent meta-analysis of 5 trials[29] which reported similar long-term mortality after PCI with DES compared with CABG in patients, with no significant differences in cardiac death, stroke, or MI between these groups. To some extent the risk factor profile of our subjects may partly explain this finding since almost two thirds of our sample in each group were of Asian Indian ancestry with a high prevalence of major cardiovascular risk factors. South Africans Indians are known to have a very high risk for atherosclerotic CAD,[30] related to risk factor clustering and those with established CAD have a very high prevalence of type 2 diabetes.[31] The high prevalence of type 2 diabetes in our sample (36.6%) may explain the need for more frequent revascularisation in our PCI subjects compared to CABG since 3 clinical trials[32,33,34] have established that CABG is the preferred strategy in type 2 diabetes compared to PCI. In a meta-analysis, Bangalore, et al.[4] found a clear long-term survival benefit in choosing CABG over PCI for patients with multivessel coronary artery disease, especially when complicated by diabetes or higher SYNTAX score.[4] The BARI-2D trial[35] aimed to compare 2 major treatment approaches, coronary revascularisation vs. intensive medical therapy, and insulin sensitisation vs. insulin provision strategies. The BARI-2D trials[35,36] reported a significantly lower rate of the composite of all-cause death, myocardial infarction, or stroke between revascularisation and the medical strategy in the CABG group, but not in the PCI group. Similarly, another meta-analysis which sought to compare the effect of PCI and medical therapy with medical therapy alone in patients with stable CAD reported that PCI with medical therapy was not associated with a reduction in death, non-fatal MI, unplanned revascularisation or angina compared with medical therapy alone.[37] Another systematic review showed a clear advantage for CABG in patients with multivessel disease, with lower mortality rates in CABG especially in patients with diabetes and higher SYNTAX scores.[38]

The strength of our study lies in the evaluation of long-term outcomes in a sample of predominantly Asian Indian subjects with a high risk factor prevalence, particularly type 2 diabetes. Among patients with treated diabetes the 10-year follow up of the BARI trial confirmed that CABG conferred long-term survival benefit over PCI with balloon angioplasty,[39] whereas the 2 initial strategies were equivalent regarding survival for patients without diabetes. While it is now well established that diabetics have a more diffuse and complex coronary vasculopathy and appear to have better outcomes after revascularisation with CABG compared to PCI,[39] it is reassuring that the 10-year follow up of diabetic subjects in the SYNTAX study has shown that CABG did not lower the risk of all cause death at 10 years compared to PCI.[40] Our findings suggest that the use of second generation DESs may offer outcomes similar to CABG in diabetic (and non-diabetic) subjects.

LIMITATIONS OF THE STUDY

This study has the limitations inherent to a non-randomised, open label, single-centre analysis. The study was conducted in a select group of subjects and therefore our findings may not be applicable to the general population of subjects with CAD. Twenty seven percent of the subjects undergoing coronary angiography at the centre in the 2-month period were included

in the study, yielding a small sample size of 60 participants which included both participants with recent myocardial infarction and stable CAD. Because the study was not randomised, selection bias probably accounted for more patients with TVD being referred for CABG, while the PCI group had more double vessel disease. Also, we did not examine the stenotic lesion complexity in the 2 groups in this analysis nor were the endpoints adjudicated by an independent committee. The results of our subgroup analysis must also be interpreted with caution because of the smaller number of subjects without adequate power for subgroup analysis. In addition, we did not examine the influence of other confounding parameters such as adherence to lifestyle behaviourial changes and control of risk factors such as diabetes, hypertension and lipid parameters which may have contributed to event rates. Finally, we did not examine outcomes based on risk scores since evaluation of individual patient risk levels prior to intervention using a formal scoring system such as the EUROSCORE or SYNTAX[28] was not performed in this study.

CONCLUSION

This study shows that subjects undergoing revascularisation with PCI using second-generation DESs have immediate and 5-year safety outcomes that were comparable to CABG in terms of the composite endpoint of death, stroke and MI. The higher composite event rate in subjects with DVD with proximal LAD involvement call for a larger, randomised comparison of the 2 revascularisation strategies, adjusting for behavioural factors and risk scores between the 2 groups. This will help clarify the long-term safety and efficacy of PCI using second generation DES compared to CABG for multivessel disease.

Conflict of interest: none declared.

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PATIENTS WITH MECHANICAL HEART VALVE THROMBOSIS

The prevalence, characteristics and outcomes of anomalous left coronary artery from the pulmonary artery at the Chris Hani Baragwanath Academic Hospital over a 28-year period

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ABSTRACT

Background: Anomalous left coronary artery from the pulmonary artery (ALCAPA) accounts for 0.25% - 0.5% of congenital cardiac disease. ALCAPA results in myocardial ischaemia and a dilated left ventricle with impaired systolic function which can be reversed post-surgical correction. We describe the presenting clinical features, diagnostic findings (including classical electrocardiographic findings) and post-operative outcomes, including the improvement in left ventricular function, in patients at a South African tertiary care centre.

Methods: A retrospective analysis of patients with ALCAPA over a 28-year period at the Chris Hani Baragwanath Academic Hospital (CHBAH).

Results: A total of 38 patients were included, with 24 (63.2%) females, and a median age at diagnosis of 4.6 months (IQR: 3.2 - 9.1 months). The clinical presentation was variable and included dyspnoea, poor feeding, and a cough. The majority were diagnosed to have a lower respiratory tract infection (71%). Cardiomegaly on chest X-ray (CXR) was present in 84.2% of patients. Deep Q waves in leads I and aVL was the most prevalent finding on electrocardiography in 96.9% of patients. ST segment depression (8 patients) and T wave inversion (21 patients) was evident in the lateral and inferior diaphragmatic leads. Left ventricular ejection fraction (LVEF) improved significantly from 38.8 ± 6.3% to 57.5 ± 9.1% post-surgical correction (p-value=0.0004) at the first follow up (median of 1.3 months). The early mortality rate was 21.6%.

Conclusion: The clinical presentation is often suggestive of a chest infection and cardiomegaly on CXR is common. Specific electrocardiographic features commonly present in patients with ALCAPA may be a guide to making the diagnosis. Surgical correction is associated with improved left ventricular function.

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INTRODUCTION

Anomalous left coronary artery from the pulmonary artery (ALCAPA) is a result of a poorly understood disruption in the embryological development of the coronary arteries. ALCAPA is a rare congenital cardiac defect accounting for 0.25% - 0.5% of congenital cardiac disease and occurring approximately once per 300 000 live births.[1] An early consideration of the diagnosis of ALCAPA requires the recognition of a constellation of clinical signs and electrocardiogram (ECG) features, and it is thereafter confirmed with echocardiography.

The clinical findings of ALCAPA are nonspecific and thus necessitates a high clinical index of suspicion. The commonest presenting clinical symptoms and signs found in the literature include dyspnoea, feeding intolerance, failure to thrive, irritability, and the presence of a cardiac murmur.[1-4] Patients may initially be asymptomatic due to a high pulmonary artery pressure supplying the myocardium, albeit at a lower oxygen saturation.[3] As the pulmonary resistance decreases, the pulmonary artery pressure decreases and results in a "coronary steal" phenomenon with subsequent myocardial ischaemia.[3] The presence of a collateral blood supply between the right and left coronary arteries is protective and may influence the timing of presentation as well as the presenting clinical manifestations.

While cardiomegaly is frequently evident on chest X-ray (CXR) in patients with ALCAPA,[3,5] a study by Levitas, et al. demonstrated a normal cardiothoracic ratio (CTR) to be a common finding.[6] More importantly, electrocardiographic (ECG) findings may aid in the diagnosis of ALCAPA. A sinus tachycardia,

abnormally deep Q waves (especially in leads I and aVL), ST segment changes (ST segment elevation or depression) T wave inversion, and poor R wave progression may be seen.[1,2,7,8]

The diagnosis of ALCAPA may be confirmed non-invasively by echocardiography whereby the left coronary artery (LCA) can be seen arising from the pulmonary artery. The right coronary artery becomes the dominant coronary artery and may appear larger than the LCA. Colour Doppler is used to assess flow reversal in the left coronary artery reflective of blood flow from the right coronary artery via collateral vessels to the LCA and then into the pulmonary artery (which is the equivalent of a right to left shunt).[9] The consequences of myocardial ischaemia is manifested by the presence of left ventricular dilatation and dysfunction as well as mitral regurgitation.[2,9] An increased echogenicity of the anterolateral papillary muscle and the adjacent myocardium is a common finding and in keeping with fibrosis and infarction.[9]

An ascending aorta angiography can confirm the diagnosis of ALCAPA.[4] A prominent RCA and with an apparent absent LCA may be seen initially followed by retrograde filling of the LCA via the collateral blood flow from the right coronary artery.[1,2,4,10] Other non-invasive diagnostic modalities such as computerised tomography (CT) scans and magnetic resonance imaging (with the added benefit of no ionising radiation exposure) can also be used to confirm the presence of ALCAPA.

Surgical management is the definitive treatment for ALCAPA. Direct reimplantation of the anomalous coronary artery onto the aorta (DIACA) is the most frequent method used.[1,7,10-12] A less common surgical intervention is the Takeuchi procedure which includes a pulmonary arteriotomy, the creation of an aortopulmonary window and the use of the pericardium to reconstruct the pulmonary artery.[10] Excellent postoperative outcomes have been found in patients with ALCAPA across various studies.[10,11,13] Early mortality rates post-surgery range between zero and 16%, while survival rates of 86% - 100%, 10 years post-surgical repair have been reported.[13]

There is a paucity of data regarding the clinical presentation, diagnostic features and outcomes of ALCAPA in the South African paediatric population. South Africa is a low- to middle-income developing country with a large diverse population, many of whom rely on peripheral hospitals for medical services. The recognition of clinical and electrocardiographic features suggestive of ALCAPA in the secondary care hospital setting would assist in the rapid referral of patients to specialist services for appropriate treatment.

MATERIALS AND METHODS

Data collection

A retrospective analysis of all paediatric patients diagnosed with ALCAPA at the Chris Hani Baragwanath Academic Hospital (CHBAH) between January 1991 and December 2018 was conducted. Thirty-eight patients were identified.

The demographic data, presenting symptoms and clinical features, the initial diagnosis and the CXR features were noted. The ECG was analysed according to age-specific norms. Abnormal Q waves were defined as being more than 25% of the R wave height in the same lead or more than 3mm in lead one or more than 2mm in lead aVL, as well as being more than 0.03 seconds in duration.[1,14] ST segment depression was defined as being more than 1mm below the baseline for more than 0.08 seconds duration.[14] T wave inversion and the leads in which the various ECG changes were observed was documented.

Echocardiographic features of ALCAPA such as flow reversal in the LCA, hyperdensity of the papillary muscles and reduced left ventricular function was documented. The left ventricular ejection fraction (LVEF) was defined as normal if between 56% and 78% (mean 66%).[14] The right coronary artery diameter was interpreted based on the mean body surface area-based normal values.[14] Cardiac catheterisation and angiographic data was analysed if available.

Other data such as the method and timing of surgical repair, post operative duration of follow up, the time to being asymptomatic, normalisation of the LVEF, resolution of the mitral regurgitation and outcomes such as death (pre-, intra-, or post-operatively), and the loss to follow up were documented. Early mortality was defined as being within 30 days of the operation.

Data analysis

All data was captured on a Microsoft Excel spreadsheet and analysed using STATA (MP 13) software. Continuous variables were presented as medians and interquartile ranges (IQR) and categorical variables described using frequencies and percentages. These were compared using a Fisher's exact bivariate analysis, dividing the patients into an infant (patients less than 12 months of age) and a non-infant group (patients more than 12 months of age). The associations between multiple variables and the LVEF at presentation were assessed using a univariate regression analysis. A paired samples t-test was used to compare pre- and post-surgical correction LVEFs.

A Fisher's exact test was used to compare the group of patients who survived to those who demised (pre- and post-surgery), as well as to compare the outcomes over 2 decades (the 1990s and the 2000s). A chi-square test analysis was not feasible due

to the small sample size. It became apparent that a multiple of the expected frequencies in the respective categories consisted of values less than 5. A p-value less than 0.05 was considered statistically significant.

Ethical consideration

The University of the Witwatersrand (WITS) Faculty Graduate Studies Committee, the WITS Human Research Ethics Committee (clearance certificate number: M190741) and the necessary medical authorities at the CHBAH all granted permission to access the study data and conduct this study.

RESULTS

A total of 38 patients were diagnosed with ALCAPA between January 1991 and December 2018 at the CHBAH. This constituted 0.45% of the 8 387 patients with congenital cardiac defects seen by the paediatric cardiology unit over this period.

Age at presentation and anthropometry

The median age of diagnosis was 4.6 months (IQR: 3.2 - 9.1 months), with 24 (63.2%) female and 14 (36.8%) male patients. World Health Organisation (WHO) weight-for-length anthropometry charts showed that 16 (51.6%) patients with available anthropometry data plotted values within the normal range, 3 (9.7%) patients were wasted, and 12 (38.7%) patients were severely wasted on presentation. Twenty-five (65.8%) patients presented to CHBAH initially, while the remaining 13 (34.2%) patients were referred from other medical facilities.

Clinical details at presentation

The majority of patients, 31 (81.6%), had no pre-existing medical conditions at the time of presentation. Four patients presented with other cardiac diagnoses (2 patients with a diagnosis of myocarditis, 1 with an anterior mitral valve leaflet prolapse, and 1 patient had Trisomy 21 with a patent ductus arteriosus) who were then subsequently diagnosed to have ALCAPA. Ten patients (26.3%) were human immunodeficiency virus (HIV) exposed, and 2 (5.3%) were HIV positive on treatment. One patient was being treated for tuberculosis at the time of diagnosis.

The most frequent presenting symptoms (Table I) were dyspnoea in 26 (68.4%), a cough in 16 (42.1%), and a history of poor feeding in 7 (18.4%) patients. The most common clinical findings (Table I) were cardiomegaly, with a displaced apex beat, and respiratory distress both occurring in 20 (52.6%) patients, followed by hepatomegaly in 17 (44.7%) patients.

Majority of the patients (n=27, 71.1%) were initially diagnosed to have a lower respiratory tract infection which is reflective of the non-specific presentation of ALCAPA. The next most common initial diagnoses were dilated cardiomyopathy and myocarditis, each diagnosed in 8 (21.1%) patients. Other cardiac defects were suspected in 3 (7.9%) patients, including a congenital cardiac defect for 2 patients and a patent ductus arteriosus (PDA) in the third patient. Sepsis and congestive cardiac failure were diagnosed in 2 (5.3%) and gastroenteritis in 1 (2.6%) of the 38 patients.

CXR findings

The majority of the patients (n=32, 84.2%) were reported to have cardiomegaly on the initial CXR, while 6 (15.8%) had a normal CTR. The median CTR was 70% (IQR: 61% - 70%). The

TABLE I: The presenting symptoms and clinical features in the 38 patients with ALCAPA at the CHBAH (1991 - 2018).

Variable	Number of patients (% of the total number of patients, n=38)	Variable	Number of patients (% of the total number of patients, n=38)
Presenting symptom		**Clinical feature**	
Dyspnoea	26 (68.4)	Displaced apex beat	20 (52.6)
Cough	16 (42.1)	Respiratory distress	19 (50.0)
Poor feeding	7 (18.4)	Hepatomegaly	17 (44.7)
Gastroenteritis	6 (15.8)	Irritability	11 (28.9)
Diaphoresis	4 (10.5)	Cardiac murmur	8 (21.1)
Fever	3 (7.9)	Tachycardia	7 (18.4)
Cyanosis	2 (5.3)	Tachypnoea	7 (18.4)
Inconsolability	2 (5.3)	Hypotension	4 (10.5)
Shortness of breath	2 (5.3)	Crepitations	2 (5.3)
Fatigue	1 (2.6)	Gallop rhythm	2 (5.3)

most prevalent additional CXR findings included pulmonary congestion in 10 (26.3%) patients, followed by biventricular enlargement in 5 (13.2%) and changes suggestive of bronchopneumonia in 4 (10.5%) patients.

ECG findings

Of the 34 patients with available ECGs at diagnosis (Table II), 29 (85.3%) had a normal heart rate for age, 4 (11.8%) had a tachycardia, and 1 (2.9%) patient had a bradycardia. All of the ECGs showed a sinus rhythm. The majority of patients, 24 (70.6%), had a normal axis for age, 7 (20.6%) had a left axis with the remaining 3 (8.8%) having a rightward axis for age. Deep Q waves (fulfilling the defined criteria) were present in 32 (94.1%) of the ECGs.

The abnormally deep Q waves occurred most frequently in both standard leads I and aVL in 31 (96.9%) patients. ST segment depression occurred in 8 (23.5%) of the 34 patients, most frequently in lead aVF in 4 (50.0%) patients, followed by lead II in 3 (37.5%) and lead aVL in 2 (25.0%) patients. Inverted T waves occurred in 21 (61.8%) patients, most frequently in the lateral and inferior diaphragmatic leads. Of the 83 episodes of abnormal T wave inversion across the 34 ECGs analysed, 37 (44.6%) occurred in the lateral leads: I, aVL, V5 and V6, and 32 (38.6%) in the inferior diaphragmatic leads: II, III and aVF. Additional ECG findings included left ventricular hypertrophy in 17 (50.0%) and biventricular hypertrophy in 4 (11.8%) patients.

Echocardiography findings

Of the 37 patients who had echocardiography studies (Table III), the LCA was visualised originating from the pulmonary artery in 32 (86.5%) patients. The LVEF documented in 36 patients was decreased in 33 (91.7%) patients, with a median LVEF of 34.0% (IQR: 23.5% - 43.5%). Mitral regurgitation was present in 27 (73.0%) patients, with majority graded as mild. An increased echogenicity of the papillary muscles and adjacent endocardium was noted in 26 (70.3%) patients.

Measurement of the right coronary artery diameter was documented in 19 (51.4%) patients, with 18 (94.7%) showing enlargement. Collateral blood flow between the right and left coronary arteries was visualised in 2 (5.4%) patients. Retrograde blood flow from the LCA to the pulmonary artery was evident in 16 (43.2%) patients. Other findings on echocardiography included a PDA, a patent foramen ovale, an anterior mitral valve leaflet prolapse and a left coronary ostial stenosis.

Cardiac catheterisation and angiographic findings

There were 19 (50.0%) patients who underwent cardiac catheterisation and angiography (Table IV). All showed an enlarged RCA originating from the ascending aorta. Retrograde

TABLE II: The electrocardiographic manifestations of ALCAPA.

Variable	Number of patients (% of the total number of ECGs analysed, n=34)
Presence of deep Q waves	32 (94.1)
Leads I and aVL	31 (96.9)
ST segment depression	8 (23.5)
Lead aVF	4 (50.0)
Lead III	3 (37.5)
Lead aVL	2 (25.0)
Inverted T waves	21 (61.8)
Left ventricular hypertrophy	17 (50.0)
Biventricular hypertrophy	4 (11.8)

TABLE III: The electrocardiographic manifestations of ALCAPA.

Variable	Number of patients (% of the total number of patients with echocardiographic findings, n=37)
LCA visualised originating from the pulmonary artery	32 (86.5)
LVEF	36 (97.3)
Decreased	33 (91.7)
Normal	3 (8.3)
Median LVEF = 34.0%, IQR: 23.5 - 43.5%	
Mitral regurgitation	27 (73.0)
Mild	14 (51.9)
Mild-moderate	1 (3.7)
Moderate	7 (25.9)
Moderate-severe	4 (14.8)
Severe	1 (3.7)
Increased echogenicity of the papillary muscles and adjacent endocardium	26 (70.3)
Right coronary artery diameter	19 (51.4)
Dilated	18 (94.7)
Normal	1 (5.3)
Other echocardiographic findings	
Presence of collateral blood flow between the right and left coronary arteries	2 (5.4)
Presence of retrograde blood flow from the LCA to the pulmonary artery	16 (43.2)

filling of the LCA into the pulmonary artery was documented in 16 patients, with 10 (52.6%) patients showing visible collateral blood supply via the right coronary artery.

Surgical correction

Thirty (78.9%) of the 38 patients with ALCAPA underwent surgical correction, with 27 (90.0%) patients undergoing DIACA and in the remaining 3 (10.0%) patients a tunnel was created from the LCA to the aorta. The median number of days to repair from the diagnosis of ALCAPA was 27 days (IQR: 12 - 51 days), with a median age of repair of 5.7 months (IQR: 3.7 - 11.6 months).

Post-surgical follow up findings

Follow up findings were available in 19 (63.3%) patients post operatively (Table V). The median first follow up after surgical repair was 1.3 months (IQR: 0.9 - 1.9 months). Eighteen patients (94.7%) were asymptomatic, and 1 (5.3%) patient was tachypnoeic. A cardiac murmur was found in 4 (21.1%) patients. Other complications noted included a right brachial plexus injury in 1 patient and a right hemiplegia secondary to a left cerebral infarct in another. Both patients had a long intensive care unit (ICU) stay post-surgery. The median time to being asymptomatic was 1.4 months (IQR: 0.9 - 2.0 months).

Of the 18 (94.7%) patients with documented echocardiography data at the first post-surgical follow up, 11 (61.1%) showed a normal LVEF. Ten of these patients initially had a decreased LVEF prior to surgery. The other 7 (41.2%) patients had decreased LVEF at the first follow up post-surgery. The median LVEF was 61% (IQR: 39% - 74%) at the first follow up for these 18 patients. The overall LVEF of these patients improved significantly from (38.8 ± 6.3%) pre-surgical correction to (57.5 ± 9.1%) post-surgical correction (p-value=0.0004). Complete normalisation of the LVEF (Figure 1) occurred at a median of 6 months (IQR: 2 - 10 months) post-surgical correction of ALCAPA.

Of the 18 patients with documented echocardiography at the first follow up post-surgery, mitral regurgitation was initially present prior to surgery in 14 (77.8%) patients, with 6 (50.0%) having moderate to severe mitral regurgitation pre-surgical correction. Mild mitral regurgitation was present in 12 (66.7%) of these patients' post-surgery. Mitral regurgitation resolved at a median of 6 months (IQR: 3 - 9.5 months) post-surgical correction. The median number of months of follow up post-surgery was 121.3 months (IQR: 61.1 - 173.9 months).

TABLE IV: The cardiac catheterisation and angiographic findings in patients with ALCAPA.

Variable	Number of patients (% of the total number of patients with cardiac catheterisation and angiography, n=19)
LCA visualised originating from the pulmonary artery	18 (94.7)
Retrograde blood flow evident from the LCA to the pulmonary artery	16 (84.2)
Presence of collateral blood flow from the right coronary artery	10 (52.6)
Additional findings	
Visibly dilated right coronary artery	4 (21.1)
Left ventricular dysfunction	1 (5.3)
Left ventricular hypertrophy	1 (5.3)
PDA and severe pulmonary hypertension	1 (5.3)

TABLE V: Post-surgery follow up findings.

Variable	Number of patients (% of the total number of patients with post-surgical correction follow up findings, n=19)
Symptoms at the first follow up	
Asymptomatic	18 (94.7)
Tachypnoeic	1 (5.3)
Median months until asymptomatic was 1.37 (IQR: 0.9 - 2 months)	
Echocardiographic findings at the first follow up	18 (94.7)
LVEF (median LVEF of 58% (IQR: 39 - 74%))	18 (100)
Normal	11 (61.1)
Decreased	7 (38.9)
Normalisation of LVEF occurred at a median of 6 months (IQR: 2 - 10 months)	
Mitral regurgitation	12 (66.7)
Grade: mild	12 (100)
Resolution of mitral regurgitation occurred at a median of 6 months (IQR: 3 - 9.5 months)	
Other	
Left ventricular dilatation	3 (16.7)
Pericardial effusion	1 (5.6)
Mild pulmonary regurgitation	1 (5.6)
Aortic regurgitation	1 (5.6)
Residual PDA	1 (5.6)

Outcomes

Outcomes are shown in Figures 2 and 3. At the time of data analysis, 12 (31.6%) patients continued to be followed up at the paediatric cardiology clinic and 2 (5.3%) patients had been transferred to the adult cardiology unit. Eleven (28.9%) patients were lost to follow up, and 8 (21.1%) had demised within 30 days. Three patients demised post-operatively on the day of surgery. The median number of days post-surgery to patient demise was 0.5 days (IQR: 0 - 10.5 days). Three (7.9%) patients demised prior to surgery and 2 (5.3%) absconded prior to surgery. A Fisher's Exact test demonstrated no significant difference in outcomes between patients in the infant vs. the non-infant group (p-value=0.383).

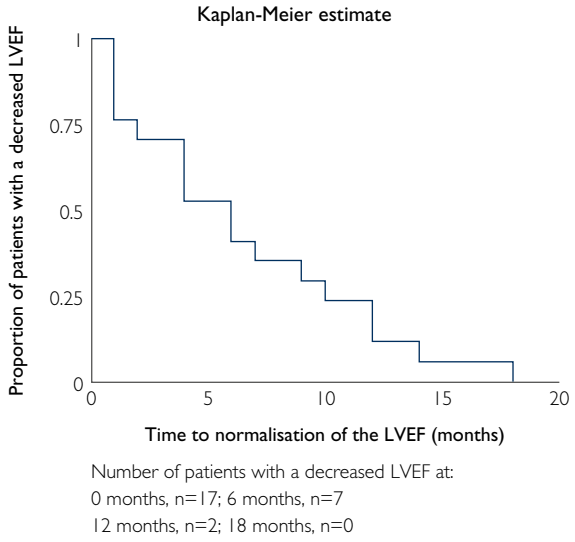

FIGURE 1: Illustrating the time to normalisation of the LVEF following the surgical reimplantation of the LCA.

Additional analysis

Echocardiographic visualisation of the LCA originating from the pulmonary artery and the presence of left ventricular dilatation were statistically significant when comparing the infant and non-infant groups, with p-values of 0.037 and 0.042 respectfully. Analysis of the LVEF and other variables assessed (Table VI) showed that only the presence of anthropometry of the severely wasted category was statistically significant with a p-value of 0.048.

A bivariate analysis of the survival group vs. the non-survival group showed no statistically significant differences with regards to the demographics, diagnostic findings, and the age of repair (Table VII). The median LVEF at diagnosis was 39% (IQR: 30% - 41%) in the survival group versus 31% (IQR: 23% - 40%) in the non-survival group.

A review of the patient cohort over 2 decades – the 1990s and the 2000s - showed no statistically significant differences in the diagnostic modalities between the 2 groups. Mitral regurgitation was diagnosed more frequently in the 2000s group (p-value= 0.001), possibly due to the availability of echocardiographic colour Doppler technology in the more modern echocardiographic machines. The patients in the 2000s group were repaired sooner at a median of 18.5 days (IQR: 9.5 - 46.5 days) vs. the 1990s group which were repaired at a median of 42 days (IQR: 18 - 51 days) post diagnosis. There were no significant differences in outcomes between the 2 groups (p-value=0.126).

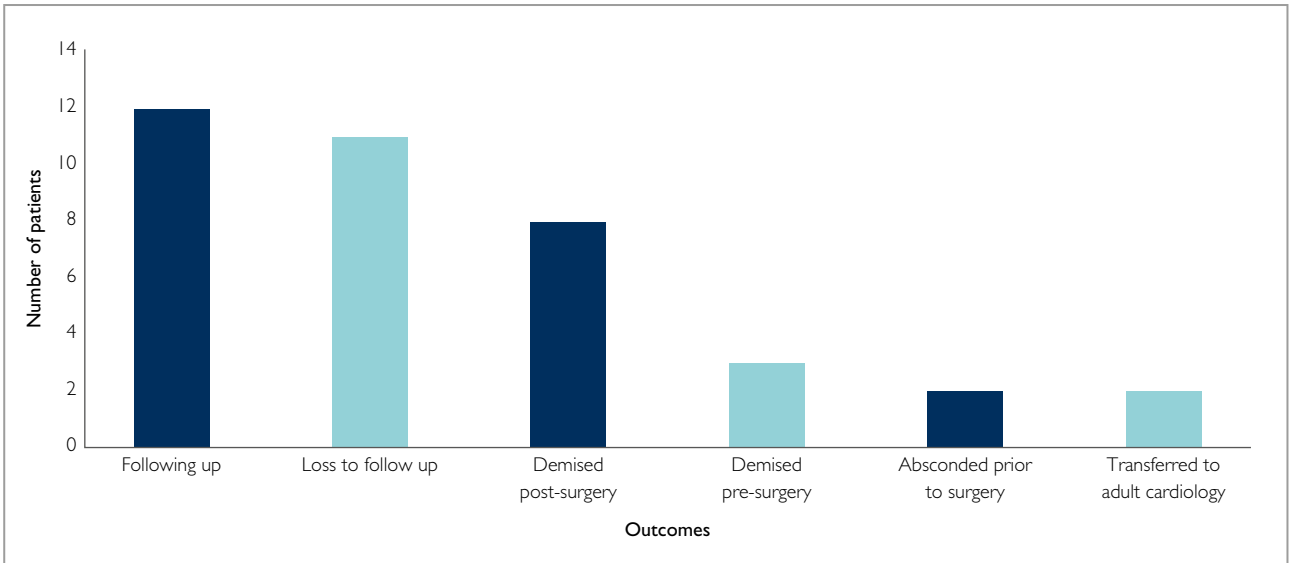

FIGURE 2: Illustrating the outcomes of the patients diagnosed with ALCAPA at the CHBAH from 1991 - 2018.

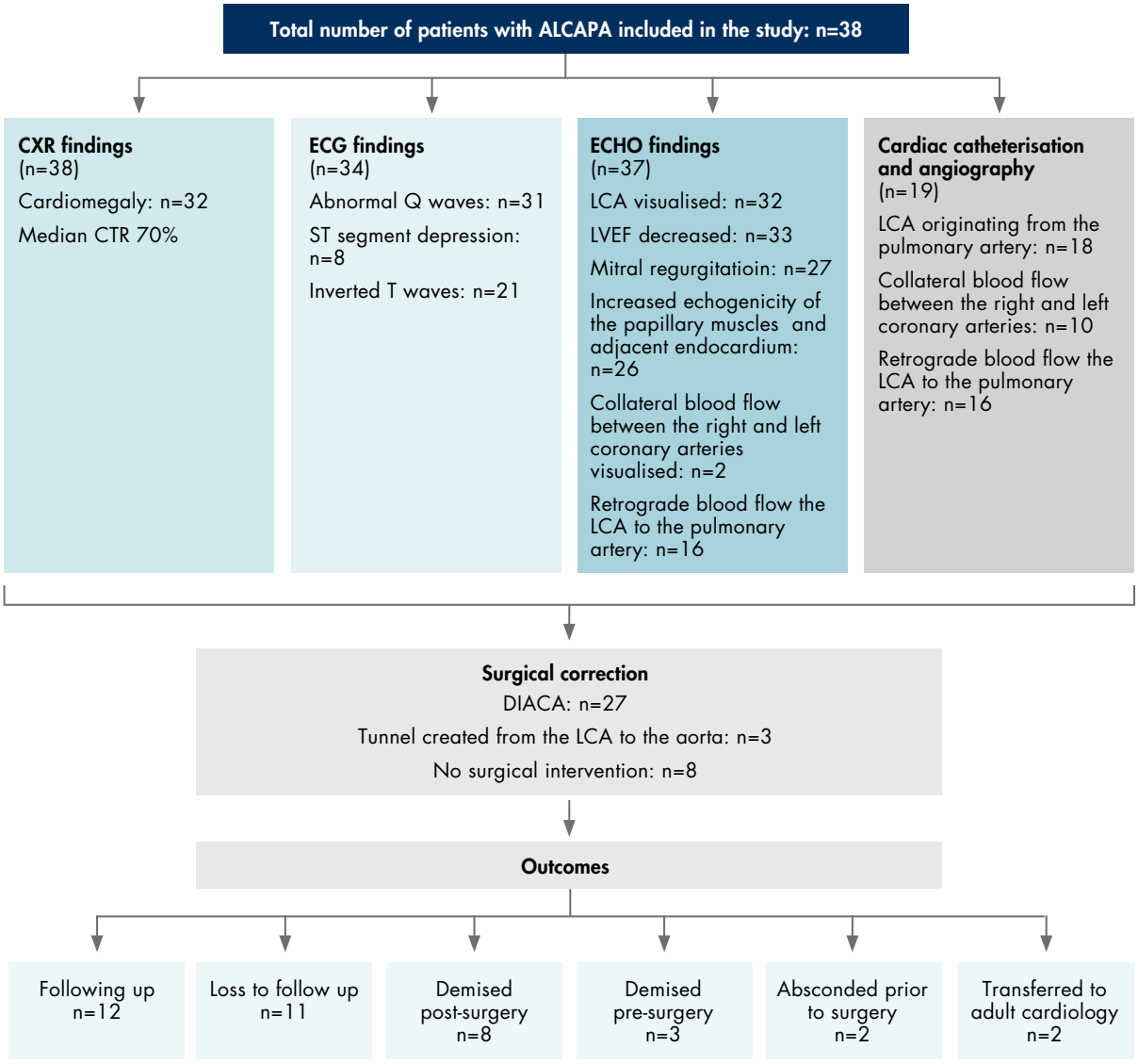

FIGURE 3: Schematic overview of the diagnostic findings and outcomes in the patients included.

DISCUSSION

ALCAPA was found to comprise 0.45% of all congenital cardiac conditions in our study, which is comparable with that of the global incidence. The median age of presentation of the study cohort was 4.3 months, which correlates with the drop in physiological hypertension of the newborn and the consequences thereof. The most frequent symptoms on initial presentation were dyspnoea, cough, and poor feeding, which is comparable with other studies.[1-4] The most common signs occurring in our study cohort at initial presentation were a displaced apex beat, respiratory distress, and hepatomegaly. An initial diagnosis of a lower respiratory tract infection was made in majority of the patients (71.1%).

Previous studies show that most patients have cardiomegaly present on CXR.[3,5] In our study cohort, 84.2% of patients were found to have cardiomegaly on CXR, with a median CTR of 70%. The presence of cardiomegaly is an important red alert to the possibility of an underlying cardiac disease and if it is not present, it may delay the diagnosis. Myocardial ischaemia ensues in the late neonatal and infant period when the pulmonary pressures decline, resulting in ischaemic changes which become evident on the ECG.[3] The majority of the patients, across all age groups (94.1% of the patients with ECGs) showed deep Q waves particularly in standard leads I and aVL which is a classical finding previously reported.[3] Other ischaemic changes such as T wave inversion and ST segment depression were also observed in the lateral and inferior leads.

TABLE VI: A univariate analysis for the variables listed and the LVEF at diagnosis.

Variable	Coefficient (95% Confidence Interval)	p-value
Age in months	0.20 (-0.62 - 0.47)	0.13
Gender	8.81 (-1.35 - 18.97)	0.09
Anthropometry		
Wasted	-12.98 (-32.00 - 6.04)	0.17
Severely wasted	-11.65 (-23.19 - 0.10)	0.05
CTR on CXR	-0.53 (-1.21 - 0.15)	0.12
Abnormal Q waves on ECG	-7.40 (-29.69 - 14.88)	0.50
ST depression on ECG	-1.84 (-14.27 - 10.60)	0.77
Inverted T waves on ECG	-1.32 (-12.18 - 9.53)	0.81
Mitral regurgitation on echocardiography	-5.30 (-17.10 - 6.51)	0.37
Retrograde blood flow from the LCA to the pulmonary artery on cardiac catheterisation and angiography	-4.19 (-30.50 - 22.12)	0.74
Presence of collateral blood flow from the right coronary artery to the LCA on cardiac catheterisation and angiography	-0.63 (-17.32 - 16.07)	0.94

Increased echogenicity of the anterolateral papillary muscle and the adjacent myocardium due to fibrosis and ischaemia, was present in 70% of our study patients. The median LVEF in the study cohort of patients was 34% which is lower compared to other studies.[1,15] This may be attributed to our study having more infant patients (81.6%) who are more likely to present with left ventricular dysfunction.[9,11] There was a high correlation between failure to thrive and wasting and a diminished LVEF. Poor feeding, as a result of heart failure, and a low LVEF could explain why there is a correlation between wasting and a low LVEF.

A study by Zheng, et al. found that an increased CTR, significant Q waves and T wave inversion, a lower LVEF, and more severe left ventricular dilatation was more prevalent in the infant group.[1] In our study, echocardiographic visualisation of the LCA originating from the pulmonary artery and the presence of left ventricular dilatation in the infant group were the only statistically significant findings when comparing the infant and non-infant groups. Older patients may have poorer echocardiographic acoustic windows that may mitigate against good visualisation of the LCA origin. In addition, older patients at presentation are likely to have developed good collateral blood flow and therefore may have less left ventricular dysfunction and dilatation.

Cardiac catheterisation and angiography confirmed the diagnosis of ALCAPA in several patients where the diagnosis was not clear on echocardiography in the study cohort. The confirmation of the diagnosis using echocardiography alone was possible in 86.5% of patients and improved to 94.7% when angiography was included.

An unusual case from the study cohort illustrating the diversity of the presenting symptoms was that of a patient with Trisomy 21 with a large PDA and severe reversible pulmonary hypertension, who was accepted for surgical ligation. During attempted surgical ligation of the PDA the patient became unstable haemodynamically. Eisenmenger's syndrome was suspected and surgery was abandoned. A subsequent cardiac catheterisation showed reversible pulmonary hypertension again, but a chance observation on review of the pulmonary angiogram showed the LCA originating from the main pulmonary artery. It is likely perfusion of the LCA was dependent on the high pulmonary pressures and following ligation of the PDA, the pulmonary pressures dropped, resulting in reduced perfusion of the LCA with ensuing myocardial ischaemia. The patient subsequently underwent a successful PDA ligation and DIACA of the ALCAPA.

The majority of patients in our study underwent surgical correction using the DIACA approach. Most of our patients showed normalisation of their reduced LVEF within 6 months. Similarly, mitral regurgitation improved from moderate and severe to mild mitral regurgitation with complete resolution at a median of 6 months post-surgery. The majority of patients were asymptomatic by the first follow up visit. An improvement in LVEF post-surgery does not preclude subclinical residual myocardial damage and perfusion deficits, as demonstrated by the late post-surgical MRI findings in a study by Alexi-Meskishvili,

TABLE VII: A Bivariate analysis of the demographic and diagnostic findings in the survival versus the non-survival groups.

Variable	Survival group Number of patients (% of the total number of patients for the variable stated)	Non-survival group Number of patients (% of the total number of patients for the variable stated)	p-value
Demographic	**n=14**	**n=11**	
Age			
Infant	11 (78.6)	11 (100.0)	0.23
Non-infant	3 (21.4)	0 (0.0)	
Gender			
Female	9 (64.3)	8 (72.7)	1.00
Male	5 (35.7)	3 (27.3)	
Anthropometry			
Normal	6 (42.9)	3 (27.3)	1.00
Wasting	5 (35.7)	4 (36.4)	
Severely wasted	1 (7.1)	1 (9.1)	
Radiographic findings	**n=14**	**n=11**	
Presence of cardiomegaly	13 (92.9)	9 (81.8)	0.57
ECG findings	**n=13**	**n=10**	
Rate			
Normal	11 (84.6)	8 (80.0)	1.00
Tachycardic	2 (15.4)	2 (20.0)	
Axis			
Normal	8 (61.5)	9 (90.0)	0.41
Right	2 (15.4)	0 (0.0)	
Left	3 (23.1)	1 (10.0)	
Abnormal Q waves	12 (92.3)	10 (100.0)	1.00
ST segment depression	2 (15.4)	3 (30.0)	0.62
Inverted T waves	9 (69.2)	6 (60.0)	0.69
Echocardiographic findings	**n=13**	**n=11**	
LCA visualised originating from the pulmonary artery	12 (92.3)	10 (90.9)	1.00
Decreased LVEF	13 (100.0)	9 (90.0)	0.44
Presence of left ventricular dilatation	9 (69.2)	7 (63.6)	1.00
Presence of mitral regurgitation	9 (69.2)	6 (54.5)	0.68
Dilated right coronary artery	6 (46.2)	5 (45.5)	1.00
Cardiac catheterisation and angiography	**n=6**	**n=4**	
Retrograde blood flow from the LCA to the pulmonary artery	5 (83.3)	3 (75.0)	1.00
Collateral blood flow from the right coronary artery to the LCA	3 (50.0)	2 (50.0)	1.00

et al.[16] Continued follow up post-surgical correction is therefore required.

In our study, the early mortality rate was 21.6% which is far higher than in other studies.[10,13,17] This may be attributed to various factors including a delay in the initial diagnosis, delays in transfers to a specialist cardiologist due to transport difficulties, delays in surgical correction due to long waiting lists or delays while attempting to optimise patients for open heart surgery.

Anomalous right coronary artery from the pulmonary artery (ARCAPA) is more rare than ALCAPA (incidence of 0.002%) and often an incidental finding.[18] Patients with ARCAPA may occasionally present with symptoms of myocardial ischaemia

when "coronary steal" occurs from the LCA into the right coronary artery.[18] The study cohort included a male child with ARCAPA who presented at 9 months with failure to thrive, dyspnoea, and poor feeding. The CXR showed cardiomegaly and the ECG demonstrated poor right ventricular forces. Echocardiography showed a possible ARCAPA, a decreased LVEF of 46%, and moderate mitral regurgitation. The diagnosis was confirmed on cardiac catheterisation and angiography and the patient underwent surgical reimplantation of the right coronary artery onto the aorta. His left ventricular function normalised 67.4 months after surgery which is considerably longer than the group with ALCAPA.

Our study showed no statistical difference in the diagnosis and outcomes of patients between the first and second decades of the study period, suggesting that despite improvements in diagnostic technologies, the diagnosis of ALCAPA depends more on the awareness of ALCAPA as a possible diagnosis. An early diagnosis can allow for rapid and appropriate surgery and improved patient outcomes.

Limitations

A small sample size was a major limitation of our study; however, similar sample sizes were documented in other studies mainly due to the rarity of this pathology. The retrospective nature of the study contributed to the absence of important data in some patients. In addition, there was a major loss to follow up of patients, which placed a limitation on the post-surgical outcome and survival analysis. The cause of poor follow up is multifactorial in our setting and may be attributed to transport difficulties created by financial constraints, patient demise or patients returning to other provinces or countries of origin.

CONCLUSION

ALCAPA is a rare congenital cardiac condition resulting in left ventricular dysfunction and it is amenable to surgical intervention with good outcomes. Due to the non-specific presenting symptoms and clinical manifestations, a high index of suspicion by clinicians is crucial in prompting further investigations such as an ECG which has features commonly occurring in patients with ALCAPA. An awareness of the classical ECG features by medical staff referring patients from secondary hospitals would contribute to making a diagnosis and then promptly referring the patients to a tertiary centre for confirmation of the diagnosis and management.

Conflict of interest: none declared.

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EFFECT OF NSAID

Endothelial-independent vasorelaxant effect of the non-steroidal anti-inflammatory drugs diclofenac and flufenamic acid on rat isolated aortic vascular rings

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ABSTRACT

Background: Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that is frequently prescribed as an analgesic agent. Most of the NSAIDs' pharmacological effects are attributed to the inhibition of cyclo-oxygenase (COX) enzymes, but they also have COX-independent actions. Notably, diclofenac has substantial cardiovascular side effects, of which the underlying mechanisms are not fully understood.

Aim: We investigated the effect of diclofenac and the structurally-related COX-inhibiting NSAID flufenamic acid on the contractile activity of aortic vascular rings.

Methods: The contractile force of rat aortic rings was measured using a tension transducer coupled to a PowerLab data-acquisition system. Diclofenac or flufenamic acid was applied on phenylephrine pre-contracted aortic rings. Carbachol was used to induce endothelial-dependent relaxation, whereas the endothelial function was eliminated by denudation of the intimal surface.

Results: Diclofenac induced a dose-dependent relaxation of phenylephrine pre-contracted aortic rings (EC_{50}≈10μM), but had no effect on unstimulated rings. The addition of carbachol to diclofenac, significantly induced further relaxation. Similar results were obtained with flufenamic acid. In endothelium-denuded vessels, either diclofenac or flufenamic acid induced a relaxation of phenylephrine pre-contracted aortic rings, and carbachol had no additional effect.

Conclusion: Diclofenac and flufenamic acid induced aortic vascular relaxation through an endothelial-independent mechanism, but the involvement of COX inhibition cannot be ruled out. The results shed novel insights into the potential therapeutic or adverse effects of diclofenac on vascular function.

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INTRODUCTION

Diclofenac [2-(2, 6-dichloranilino) phenyl acetic acid] is a non-steroidal anti-inflammatory drug (NSAID) that is widely used as an analgesic agent.[1] Generally, diclofenac and other structurally-related non-selective NSAIDs used in experimental settings such as flufenamic acid exert their pharmacological effects through the inhibition of cyclo-oxygenase (COX) enzymes such as COX 1 and COX 2, which catalyse the synthesis of bioactive prostanoids.[2,3] The prostanoids include thromboxane A2 and prostaglandins, and mediate various physiological effects at target sites such as the heart, blood vessels, platelets, and kidneys. However, diclofenac also has COX-independent effects such as the modulation of ion channel expression and activity,[4-7] of which the (patho)physiological role is not fully understood.

The known adverse effects of NSAIDs include gastrointestinal mucosal erosion, renal impairment, platelet dysfunction,[2] and the increased risk of cardiovascular disease.[8,9] In particular, a high cardiovascular risk has been associated with COX-2 selective NSAIDs,[10] which in some instances, has led to the withdrawal of drugs such as rofecoxib from the market.[11] Notably, although diclofenac inhibits both COX 1 and COX 2, it is also fairly COX 2 selective,[12] but the implications of that type of COX selectivity profile on the cardiovascular system are still not fully known. Furthermore, diclofenac is reported to have a higher cardiovascular risk score and greater cardiotoxicity compared to other non-selective NSAIDs such as ibuprofen and naproxen.[13-15]

In the vascular system, there is uncertainty regarding the nature of cardiovascular risk associated with the clinical use of diclofenac,[16,17] in part, because several clinical trials evaluate

the vascular effects of multiple NSAIDs at the same time, making it difficult to attribute any of the overall effects to a particular drug.[18] Diclofenac has been implicated in the coronary artery diseases,[1,19] and its accidental intra-arterial injection has been reported to induce severe vasoconstriction.[20] The drug also impairs the development of the vascular structural components in zebrafish,[21] but clinically does not seem to contribute to cardiovascular events related to changes in blood pressure.[22] Therefore, the fundamental vascular effects of diclofenac still remain insufficiently understood to account for either its therapeutic or adverse effects. In the present study, we evaluated the effect of diclofenac or the structurally-related NSAID flufenamic acid on the aortic vascular tone and explored the possible underlying mechanisms.

METHODS

Drugs and chemicals

Analytical-grade chemicals and drugs were purchased from Sigma-Merck (South Africa), unless stated otherwise. Each of the test drugs (diclofenac, flufenamic acid, or carbachol) was dissolved in DMSO (final dilution <0.1% v/v), whereas phenylephrine was dissolved in water.

Animals and tissue harvesting

Seventeen adult male Wistar rats (250 - 300g) were used in this study. The study was approved by the Faculty of Health Sciences Animal Research Ethics Committee of the University of Cape Town (AEC Protocol 014-014). All procedures on animals were performed in compliance with the Guide for the Care and Use of Laboratory Animals (National Research Council, National Academy Press, 2011). The rats were housed under standardised conditions (12 hour light / dark cycle and temperature of 23°C) and had unlimited access to rat chow and water.

Rat tissues were harvested as previously described.[23,24] Briefly, rats were injected intraperitoneally (i.p.) with heparin (500IU/kg) and anaesthetised with sodium pentobarbital (70mg/kg, i.p.; Vetserv, South Africa). Upon the loss of pedal withdrawal reflexes, the heart and aorta were excised through a thoracotomy incision and placed in cold (4°C), oxygenated (95% O_2 and 5% CO_2), and filtered (7-µm pore Whatman filter paper, Sigma-Merck, South Africa) modified Krebs Henseleit solution containing (in mmol/l): 118.5 NaCl, 4.7 KCl, 25 $NaHCO_3$, 1.2 $MgSO_4$, 1.8 $CaCl_2$, 1.2 KH_2PO_4 and 11 glucose (pH 7.4). The descending thoracic aorta was carefully dissected from connective tissues and cut transversely into cylindrical aortic rings (each approximately 4mm long). About 4 aortic rings were obtained from each rat, and each ring was used for a different type of experiment as described below.

Vascular reactivity measurements

Each aortic ring was threaded with 2 stainless steel metal hooks through the lumen (taking care not to damage the endothelial lining) and hanged horizontally in a 30ml water-jacketed, temperature-regulated (37°C) organ bath containing Krebs Henseleit solution (Figure 1A). The Krebs Henseleit solution in the organ bath was bubbled with carbogen (95% O_2 and 5% CO_2) and was renewed at a rate 20ml per hour. The bottom hook was connected to a holder positioned at the base of the organ bath using a surgical string, whereas the top hook was connected, by way of another string, to a tension transducer (MLT050/ST, ADInstruments, Australia), which was coupled to a PowerLab (8/30) data-acquisition system (ADInstruments, Australia). The tension transducer was mounted on an adjustable micro-positioner (MLA41, ADInstruments, Australia). The set up enabled the contractile activity of the aortic ring to be transmitted through the metal hooks and strings to the tension transducer (Figure 1A).

The aortic ring was stabilised for 30 minutes at a pre-tension of 1.5g, achieved by adjusting the micro-positioner. After stabilisation, the transducer tension was calibrated as the zero point (0g), and the aortic ring was contracted using phenylephrine (3µM or 10µM). The test drug doses were added cumulatively as follows: Carbachol (3µM and 100µM), diclofenac (3µM, 10µM, 30µM, and 100µM), and flufenamic acid (3µM, 10µM, 30µM, and 100µM). The test drugs were applied either in the absence of phenylephrine (baseline condition) or during the application of phenylephrine. To evaluate endothelium-independent effects, the aortic ring endothelium was denuded by gently rubbing the vascular intimal surface with the tip of forceps. Data were recorded online via the PowerLab (8/30) data-acquisition system and analysed using the LabChart Pro 7 software (ADInstruments, Australia). Data points of the diclofenac dose-response curve were fitted with a Boltzmann equation using the Origin 6.1 software (OriginLab Corporation, USA) to obtain the effective concentration that produces 50% of maximal activity (EC_{50}).

Data analysis

Data are expressed as mean and standard deviation (SD) or as box plots, and n indicates the number of replicates. Statistical analysis was conducted using the Statistica (Version 13) programme (TIBCO.com). A Shapiro-Wilk test for normality was used to test the distribution of variables. For parametric data, a paired t-test was used to compare measurements before and after drug application, whereas a Wilcoxon test was used for non-parametric data. Parameters measured in each aortic ring under different conditions were compared using repeated-

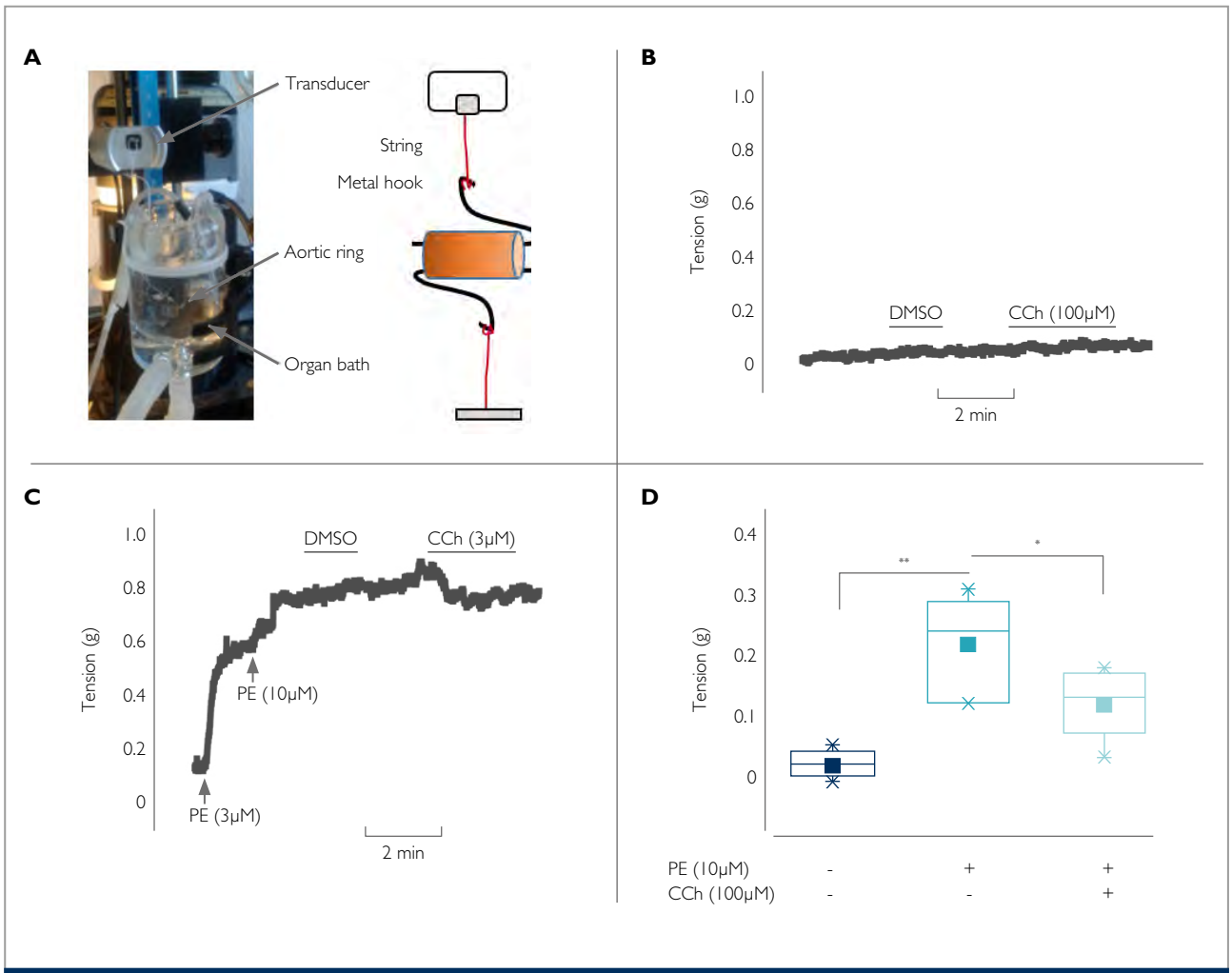

FIGURE 1: Experimental set up and effects of vasoactive drugs.
A: Image of an organ bath and force transducer (left), and schematic of the aortic ring mounting apparatus (right). B and C: Representative tracings of the effects of the vehicle dimethyl sulfoxide (DMSO; 0.1% v/v) and carbachol (CCh) on an unstimulated vessel (B) or on a phenylephrine (PE) pre-contracted vessel (C). D: Quantitative analysis of drug effects on the vascular contractile force (n=6 per group). + or - depicts the presence (+) or absence (-) of a drug. Data are presented as box plot and the mean (filled square). $^{*}p<0.05$; $^{**}p<0.01$.

measures analysis of variance (ANOVA). A 2-tailed p-value <0.05 was considered statistically significant.

RESULTS

Aortic vascular tone and sensitivity to phenylephrine and carbachol

The baseline tension in stabilised aortic vascular rings was relatively steady over time and was altered neither by the vehicle dimethyl sulfoxide (DMSO, 0.1% v/v) nor by 100µM carbachol (Figure 1B). The application of phenylephrine induced an increase in the aortic vascular ring tension with time, until the tension reached a steady-state level (Figure 1C). Carbachol, but not the vehicle DMSO, decreased the tension in phenylephrine pre contracted vascular rings (Figure 1C) by a clinically significant effect size of approximately 50% from 0.21 ± 0.08g [mean (SD)] to 0.11 ± 0.05g [mean (SD)] ($p<0.05$ vs. phenylephrine alone; Figure 1D).

Diclofenac-induced vascular relaxation

In unstimulated aortic vascular rings, the application of diclofenac, on its own, had no effect on the steady-state baseline tension (Figure 2A). However, in phenylephrine pre-contracted aortic rings, diclofenac induced a dose-dependent vascular relaxation, with an effective concentration that produces 50% of maximal activity (EC_{50}) of approximately 10µM (Figure 2B and 2C). The addition of carbachol to the previously applied diclofenac on phenylephrine pre-contracted aortic vascular

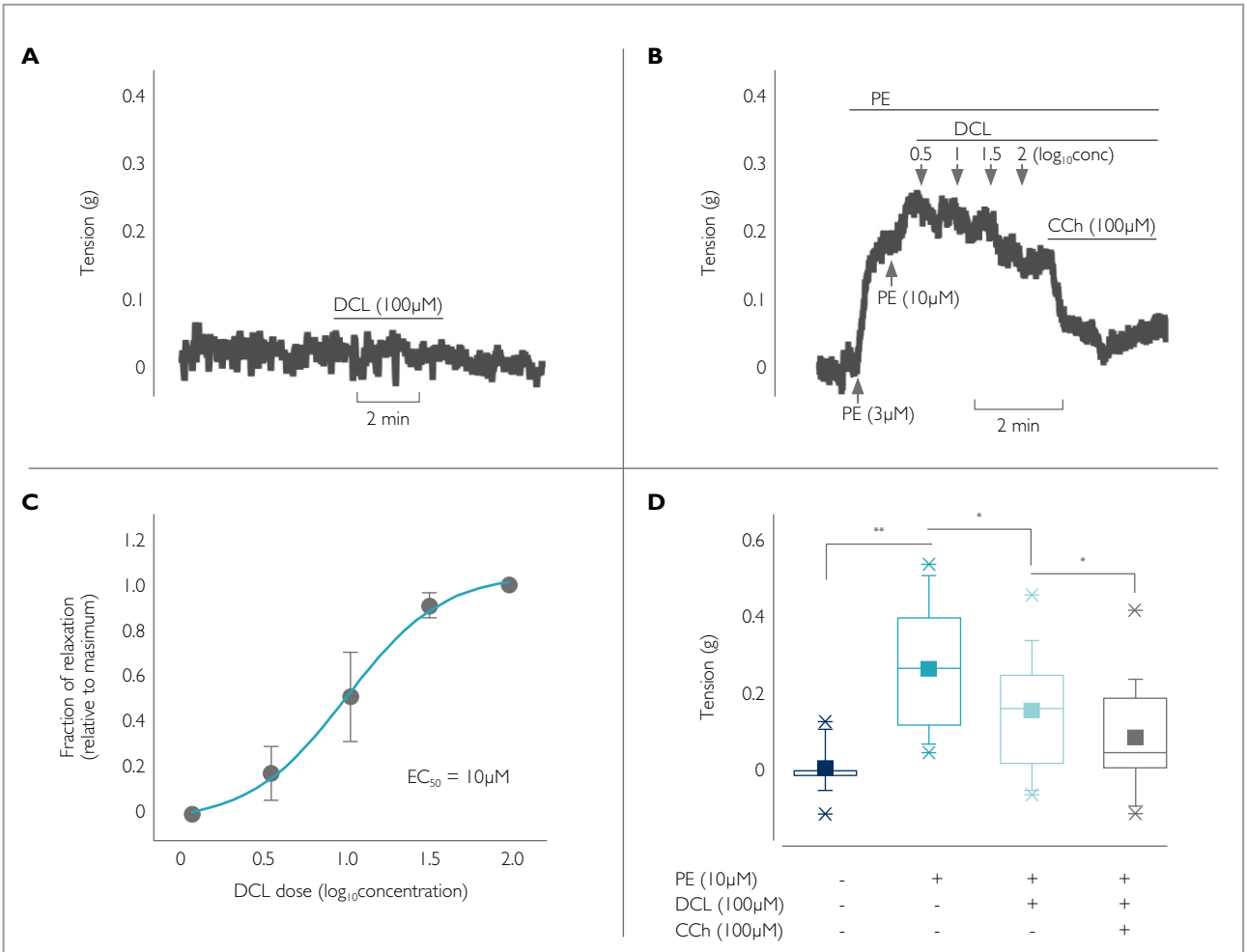

FIGURE 2: Diclofenac-induced vascular relaxation.
A and B: Representative tracings of the effect of diclofenac (DCL) on an unstimulated vessel (A) or on a phenylephrine (PE) pre-contracted vessel (B). The DCL dose is shown as log10 of the concentration. CCh, carbachol. C: The dose-response curve of DCL, with data fitted using a Boltzmann equation (n=12 aortic rings per each data point). Data are presented as mean (SD). EC50, effective concentration that produces 50% of maximal activity. D: Quantitative analysis of drug effects on the vascular contractile force (n=17 per group). + or - depicts the presence (+) or absence (-) of a drug. Data are presented as box plot and the mean (filled square). *p<0.05; **p<0.01.

rings caused a further decrease in tension, beyond the initial effect of diclofenac alone (Figure 2B). As such, the tension after the addition of carbachol to diclofenac was significantly lower than that before carbachol (p<0.05 for before vs. after carbachol; Figure 2D).

Effect of flufenamic acid on the aortic vascular ring tension

To evaluate whether a vasorelaxant effect similar to that of diclofenac could also be produced by another COX-inhibiting NSAID, a non-selective COX inhibitor flufenamic acid was tested. Structurally, both flufenamic acid and diclofenac contain a core phenyl-amino-phenyl ring (Figure 3A). Flufenamic acid had no effect on the baseline tension in unstimulated vessels (Figure 3B), but decreased the tension in phenylephrine pre contracted aortic vascular rings (p<0.05 vs. phenylephrine alone; Figure 3C and 3D). The addition of carbachol to the previously applied flufenamic acid on phenylephrine pre-contracted aortic vascular rings caused a further decrease in tension that was significantly lower than that before the carbachol application (p<0.05 for before vs. after carbachol; Figure 3D).

Effect of endothelial denudation on diclofenac-induced vascular response

To evaluate the contribution of endothelium-dependent activity to the effect of diclofenac, endothelium-denuded vessels were used. The application of phenylephrine induced an increase in the aortic vascular ring tension (p<0.05 vs. baseline; Figure 4A), but as would be expected in endothelium-denuded vessels,

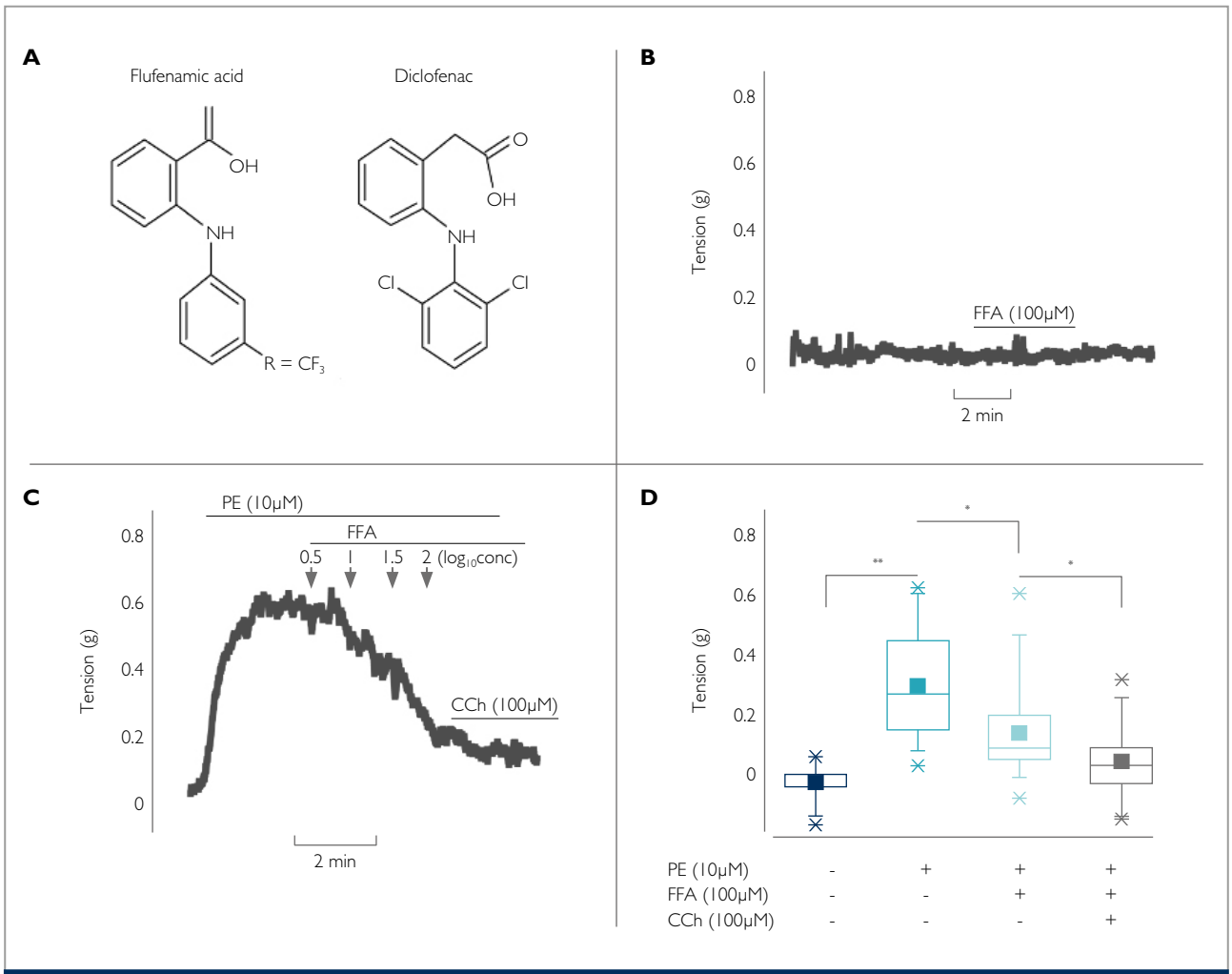

FIGURE 3: Effect of flufenamic acid on aortic vascular reactivity.
A: Chemical structures of flufenamic acid (FFA) and diclofenac (DCL). B and C: Representative tracings of the effects of FFA on an unstimulated vessel (B) and on a phenylephrine (PE) pre-contracted vessel (C). The FFA dose is shown as $\log_{10}$ of the concentration. CCh, carbachol. D: Quantitative analysis of drug effects on the vascular contractile force (n=17 per group). + or - depicts the presence (+) or absence (-) of a drug. Data are presented as box plot and the mean (filled square). $^{*}p<0.05$; $^{**}p<0.01$.

carbachol had no effect on the phenylephrine pre contracted aortic vascular ring (Figure 4A). Diclofenac decreased the vascular tension of the phenylephrine pre contracted, endothelium-denuded aortic vascular rings ($p<0.05$ vs. phenylephrine alone; Figure 4B and 4C). The addition of carbachol to the pre existing diclofenac did not induce further vascular relaxation ($p>0.05$ for before vs. after carbachol; Figure 4B and 4C). Similarly, flufenamic acid decreased the vascular tension in phenylephrine pre contracted endothelium-denuded vessels, whereas the addition of carbachol on top of flufenamic acid had no further effect (Figure 4D).

DISCUSSION

The present study showed a dose-dependent vasorelaxant effect of diclofenac and flufenamic acid on isolated aortic rings as was evidenced by a decrease in phenylephrine-induced contraction. Although the experiments in the present study were performed on isolated vessels, the diclofenac vasorelaxant effect, with an $EC_{50}\approx10\mu M$, occurred at a dose that is clinically relevant, given that the peak plasma level of diclofenac at 2 hours after oral (50mg) dose is 1 µg/ml.[25] Such a dose translates to approximately 3.4µM plasma concentration in an average adult person, which is in the same order of magnitude as the diclofenac EC_{50} observed in the present study. However, as reported in another study on renal vessels, diclofenac had no effect on the contractile force, but instead, decreased the luminal area of phenylephrine-stimulated vessels,[26] probably indicating the tissue-specificity of the NSAID effects. Nevertheless, the vasorelaxant effect of diclofenac observed in the

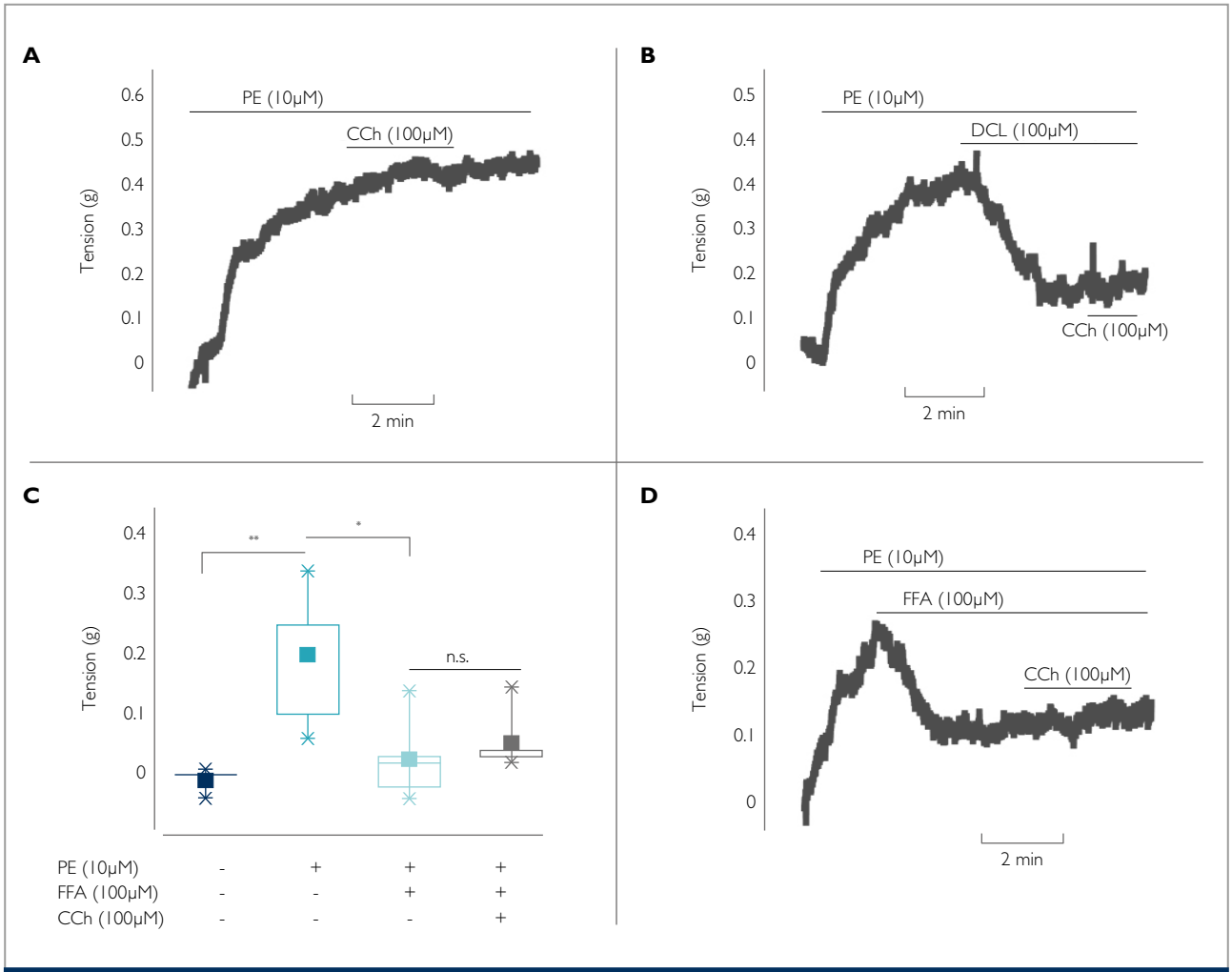

FIGURE 4: Effect of endothelial denudation on the NSAID vascular action.
A and B: Representative tracings of the effects of phenylephrine (PE), carbachol (CCh), and diclofenac (DCL) on the contractile force of endothelium-denuded vessels. C: Quantitative analysis of drug effects on the vascular contractile force (n=5 per group). + or - depicts the presence (+) or absence (-) of a drug. Data are presented as box plot and the mean (filled square). *p<0.05; **p<0.01; n.s., non significant. D: Representative tracing of the effects of phenylephrine (PE) and flufenamic acid (FFA) on the contractile force of an endothelium-denuded vessel (n=4 replicates).

present study is novel in that the generally expected effect of the NSAID inhibition of the constitutively active COX-1 in blood vessels would be to suppress the production of the physiological vasodilatory prostaglandins such as prostacyclin,[2,3] and thereby induce vasoconstriction. As such, this present finding contrasts with the proposed pro-hypertensive effects occurring via COX inhibition in vascular endothelial cells and smooth muscle cells.[12] The reasons behind these opposed vascular effects are not clear and the overall impact of diclofenac treatment on blood pressure has also remained doubtful.[22] However, given the acute application of NSAIDs in the present study, the vasorelaxant effects may reflect short term effects, whereas the pro-hypertensive effects reported in other studies could reflect long-term effects. In addition, since most clinical trial studies have evaluated multiple NSAIDs concurrently,[18] the specific contribution of an individual drug at a given dose may remain unknown. Therefore, the clinical implications of the observed diclofenac effect remain unclear, but depending on the specific tissue involved and the timing of drug application, the vasorelaxant effect could be beneficial through short term improvements in regional blood flow, but could also become detrimental if severe hypotension is induced.

Mechanistically, the vascular effect of diclofenac observed in the present study appears to be independent of the endothelium, since the diclofenac-induced relaxation was still present in endothelial-denuded vessels, whereas, in intact vessels, the carbachol-induced relaxation was still present, despite the

diclofenac effect. A mechanism involving the inhibition of COX by diclofenac could possibly play a role, given that the effect of diclofenac in the present study could be mimicked by another non-selective COX inhibitor flufenamic acid. However, although, like flufenamic acid, diclofenac is considered a non-selective COX inhibitor (i.e., inhibits both COX 1 and COX 2), it also has a unique profile in that it is fairly COX 2 selective.[12] Therefore, although COX inhibition cannot be ruled out as a possible underlying mechanism, it may not fully account for the vasorelaxant effects of diclofenac and flufenamic acid.

Diclofenac and several other NSAIDs also have COX-independent effects such as the modulation of the expression and activity of cardiovascular ion channels,[4,5] which could account for diclofenac and flufenamic acid effects seen in the present study. Both diclofenac and flufenamic acid have stuctural similarities in that they contain a core phenyl-amino-phenyl ring (Figure 3A), a feature that may contribute to unique mode of actions unrelated to COX inhibition. For diclofenac, such COX-independent effects include the blockade the L type $Ca2^{+}$ channel by diclofenac in cardiomyocytes, an effect which, if it were to occur in vascular smooth muscle cells (though not yet known), could produce a vasodilatory effect that is consistent with the findings in the present study. However, there are some key differences between the effects of diclofenac and flufenamic acid in that flufenamic acid (but not diclofenac) induces a non-selective cation current[27] and blocks $Ca2^{+}$-activated chloride currents.[28] So, the role of ion channel modulation in the effects of NSAIDs on blood vessels remains uncertain. As such, there remains a key limitation of the study in that the mechanisms underlying the endothelial-independent vasorelaxant action of diclofenac remain unclear. In addition, since only 2 NSAIDs were tested in the present study, there was a limited scope to evaluate a broad spectrum of COX inhibition.

The present study showed that diclofenac (at a clinically relevant concentration) and flufenamic acid dose-dependently induced the relaxation of aortic vascular rings. The results suggest that the NSAIDs acted via an endothelial-independent mechanism, but a COX-mediated action cannot be ruled out. The findings provide new insights into the potential therapeutic or adverse short-term vascular effects of diclofenac in clinical practice.

ACKNOWLEDGEMENTS

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Conflict of interest: none declared.

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The initial experience and outcomes of patent ductus arteriosus closure at Nelson Mandela Academic Hospital, Mthatha, Eastern Cape

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ABSTRACT

Background: Transcatheter closure of the patent ductus arteriosus (PDA) is a common intervention worldwide. An initial experience and outcomes in percutaneous closure of patent ductus arteriosus in a new catheterisation laboratory at Nelson Mandela Academic Hospital (NMAH) in Mthatha was reviewed.

Methods: Data regarding ductal closure using the Amplatzer Duct Occluder type I (ADO1) and Amplatzer Vascular Plug II (AVP II) were reviewed and prospectively collected. Demographics, haemodynamics, angiographic patent ductus arteriosus type, complications and outcomes were documented.

Results: A total of 26 patients underwent percutaneous patent ductus arteriosus closure from September 2019 - August 2021(1year 11 months). There were 17 females and 9 males. The median age of the patients was 23 months (range 3 - 60 months) and the median weight was 8.3kg (range 3.6 - 14kg). The mean pulmonary vascular resistance was 4 Wood unit (WU).

Seven patients had Krichenko Type C Duct (27%) and 15 (58%) patients had Type A Duct. The ductal size (narrowest diameter at the pulmonic end) mean was 6mm for the Type C Ducts and 3.5mm for the Type A Ducts. Fluoroscopy time was mean was 18 minutes and the radiation dose was about 450 microGreys.

Out of the 26 patients that were done catheterisation, 4 patients were not done patent ductus arteriosus closure. Of the 4 patients, 2 patients had tiny PDAs that could not be closed percutaneously, and the other 2 patients had associated coarctation of the aorta.

Six of the 7 patients with Type C Duct were closed successfully with Amplatzer Vascular Plug, and 1 patient had device embolisation. Fifteen patients with Type A Duct were closed successfully with Amplatzer Ductal Occluder 1 with no complications. Complete ductal occlusion was achieved in 21 patients on day 1 and only 1 patient had residual ductal flow following the ductal closure.

Conclusion: Percutaneous ductal closure with Amplatzer Duct Occluder at Nelson Mandela Academic Hospital is comparable to other centres in South Africa in terms of safety and outcomes. SA Heart® 2025;22:56-60

INTRODUCTION

Nelson Mandela Academic Hospital is situated in the former Transkei region of the Eastern Cape. The hospital services around 6 million people and is the only referral hospital for the former Transkei region. For the longest time it had no paediatric cardiologist until 2019. There is a new catheterisation lab with a Phillips machine that was bought previously and was never used because there were no cardiologists at the time. Since September 2019, we started using the catheterisation lab to do diagnostic and intervention catherisations.

Percutaneous closure of the patent ductus arteriosus (PDA) is the main therapy for this congenital heart defect. The PDA incidence is around 11.9% - 15.6% of all congenital heart defects.[1-2] Over 2 decades, a wide range of devices have been employed for transcatheter closure of the PDA from small infants to adult patients.[3-15]

The Amplatzer Duct Occluder (ADO 1) has proven to be an elegant device that allows moderate and large sized ducts (up to 11mm in diameter) to be successfully occluded by the percutaneous approach. It combines ease of implantation with a high occlusion rate and a low rate of procedure related complications.[16-17] The procedure can be safely carried out in infants >3.5kg in weight with symptomatic PDA.

METHODS

The data of patients who have undergone patent ductus arteriosus closure was collected. Patients' age, sex and weight were documented during the time of PDA closure. Haemo-

dynamic characteristics were documented and included quantification of the left to right shunting, Qp/Qs, and pulmonary vascular resistance (PVR) before ductal closure. Angiographic data including ductal size (narrowest diameter at the pulmonary end), aortic ampulla, ductal length, and the shape or type of the PDA were recorded.

The duct was defined as small if the narrowest diameter was <2mm; moderate size, if the narrowest diameter was 2 - 3.5mm in patients with symptomatic heart failure; and large if it was >3.5mm in symptomatic patients or >4mm in asymptomatic patients.[18]

The ductal shape was classified using the Krichenko angiographic morphological classification.[19] Device type and size, screening time, including complications and outcomes were noted. Presence of other congenital heart disease was also documented. Values were reported as mean and range.

The follow-up plan involved review at 7 days post PDA closure, 1, 3, 6, 12 months and finally 2 years following percutaneous ductal closure.

DEVICE DESCRIPTION

Amplatzer Duct Occluder

The Amplatzer Duct Occluder (AGA Medical Corporation, Golden Valley, MN) is a self-expanding and self-centering device, made from 0.0004 to 0.0005-inch Nitinol wire mesh. It is mushroom-shaped with a low profile and consists of a flat retention disc and a cylindrical main body, into which polyester fibers are sewn. Platinum marker bands are laser welded to each end and a steel sleeve with a female thread is welded into the marker band (Figure 1).

The retention disc is 4mm larger than the main body, which itself has a conical structure. The delivery system consists of a delivery cable, a Mullins-type sheath, loader, and a pin vice. The device comes in different sizes, requiring sheath sizes from 5-7F for delivery. The size of the device chosen is generally such that the diameter of the pulmonary end of the device is at least 2mm larger than the narrowest diameter of the duct.

The device sizes are categorised according to the diameters of the aortic and pulmonary ends of the device. The standard device sizes are 6/4, 8/6, 10/8, 12/10, 14/12, and 16/14mm respectively, where the first number refers to diameter of the aortic end and the second number to the pulmonary end of the conical shaped device. The devices are all 7mm long. They can be delivered through sheath sizes ranging from 5F (for devices up to 8/6mm) to 7F for devices larger.

The AmplatzerTM Vascular Plug II (AVP II)

The AVP II is a multi-layered mesh designed to increase density and flow disturbance. It has 6 planes of cross-sectional coverage resulting in rapid occlusion of the vessel (Figure 2). When you preparing to close the duct, you must select a device that is 30% - 50% larger in diameter than the diameter of the vessel.

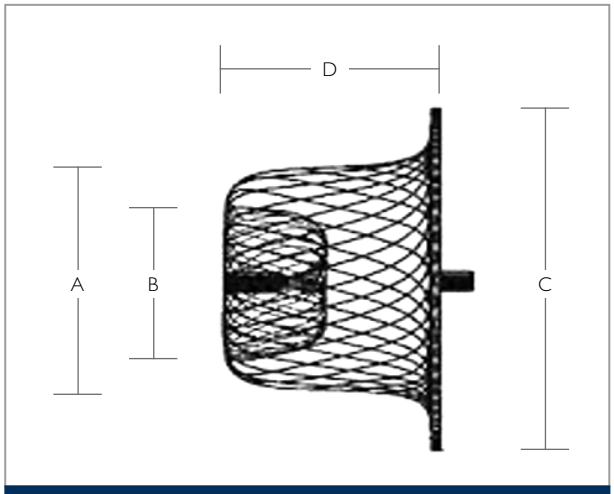

FIGURE 1: A: Device diameter at descending aorta. B: Diameter at pulmonary artery. C: Retention skirt diameter. D: Device length. (Figure used with permission from Abbott Cardiovascular, 5050 Nathan Lane, North Plymouth, MN 55442).

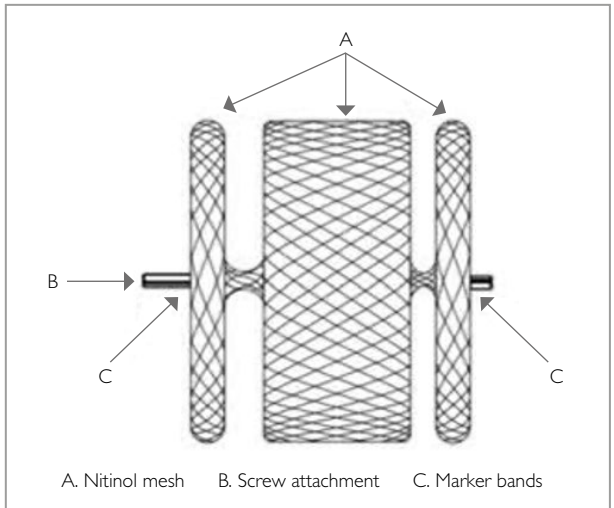

FIGURE 2: Amplatzer Vascular Plug. (Figure used with permission from Abbott Cardiovascular, 5050 Nathan Lane, North Plymouth, MN 55442).

PATENT DUCTUS ARTERIOSUS OCCLUSION PROCEDURE

The patient is usually prepared for routine cardiac catheterisation. Under sedation, the patient is scrubbed and draped. Femoral arterial and venous access is achieved, using standard vascular access short sheaths. About 50IU/kg of heparin is given. Descending aortography in the straight lateral view is performed. The size and the shape (type) of the PDA are then determined and classified using the Krichenko classification. The ductal anatomy information is used to select the device size compared to ductal size and device length (long shank vs. short shank).

Approximately, 1 - 3mm larger device than ductal size is chosen to occlude the duct. Standard left and right cardiac catheterisation procedure is performed. Calculations to ascertain the extent of left-to-right (or right-to-left) shunting and pulmonary vascular with systemic vascular resistances are done. Following angiography and haemodynamic data, the decision to or not to close the PDA is made. If the PDA is amenable to percutaneous closure based on the size and length of the duct, an appropriate device is selected using the manufacturer's device selection table as a guide.

The delivery system is flushed using heparinised saline. A 0.035" guide wire is passed across the PDA using an end-hole catheter. A size 6F - 9F Cook's Mullins long sheath is used as a delivery system and this sheath is passed across the PDA over the guide wire. Blood is allowed to flow through the side connector, to purge all air from the system. The delivery wire is passed through the loader. The device is attached to the delivery wire using a screw mechanism. Under water, the device is retrieved into the loader so that its distal radiopaque end is at the tip of the loader. The loader is then firmly introduced into the delivery sheath. Under fluoroscopy, the device is advanced into the sheath using the delivery wire until it reaches the tip of the delivery sheath. At this stage, the whole assembly is repositioned until the operator is satisfied to deploy the distal (aortic) disk. Once the distal disk is well positioned and conforms to the vessel wall, the shank is deployed.

Angiography may be performed at any stage of device deployment using the Cook's side connector and an angiographic catheter to check for device positioning in the duct, pulmonary, and aortic positioning. The device is released, repositioned, or retrieved as the operator deems fit. The patient receives an intravenous antibiotic and may receive infective endocarditis prophylaxis for 6 months. The patient is followed up at 1 day, 1, 3, and 6 months, 1 year, and 2 years following transcatheter closure of the PDA using this device, to look for complications that may arise from the catheterisation procedure or the device itself.

RESULTS

Over a period of 1 year and 11 months (September 2019 - August 2021), 26 patients underwent PDA percutaneous closure using Amplatzer Duct Occluder (ADO 1) and Amplatzer Vascular Plug (AVP II). Of the 26 patients that were taken for PDA closure, 4 of them were not closed. Two patients had small PDA of 1mm and could not be closed. The other 2 patients had associated coarctation of the aorta with the large PDA and were refereed for surgical closure of the PDA and coarctation repair.

Patient basic characteristics are presented in Table I.

The angiographic data, basic haemodynamics, device selection and outcomes are presented in Table II.

The smallest device used was a 6/4mm ADO, and the largest device was a 14mm AVP. The average device size was 8/6mm ADO and a 12mm AVP. Only 2 patients required upsizing of the device due to severe residual flow on angiogram prior to release of the device.

There was only 1 patient who had a PDA and a restrictive perimembranous ventricular septal defect (VSD) which was treated conservatively.

Only 1 patient had a device embolisation on day 5 of device closure. This was a 12-month-old baby with a large 5mm tubular duct. The baby weight was 6kg. Due to the size of the PDA on angiogram measurements, we opted for the 10mm AVP for closure of the duct. Post device release there was a significant residual left to right shunting of the contrast on angiogram and echocardiogram. We opted to observe the patient because the device was holding well despite some leak that was seen. Five days later we discovered that the device had embolised into the left pulmonary artery with a good pulmonary blood flow into the lung. The device embolised due to under-sizing of the duct.

TABLE I: Patient basic characteristics / demographics.

Number of patients	Sex	Age	Weight
26	Male - 9	Median - 23/12	Median - 8.3kg
	Female - 17	Range - 3 - 60/12	Range - 3.6 - 14kg

TABLE II: Angiographic data, basic haemodynamics, PDA sizes, device used and outcomes.

PDA Type	Number	Diameter	QP / QS	PAP	PVR	Device used	Outcome
Type A	15	Mean - 3.5mm	Mean - 1 - 2: 1	Mean - 30mmhg	Mean- 4WU	ADO I	100% limmediate closure
Type C	7	Mean - 6mm				AVP II	1 device embolisation 6 successful closures

All the patients had complete ductal occlusion on day 1 of the procedure and on discharge. Patients were followed up on day 7, 1, 3, 6, 12 months and some are due for the 2 years follow-up soon.

DISCUSSION

In the period of the study, which is September 2019 - August 2021, we managed to successfully close 22 PDA with only one complication. This is for the first in Mthatha, Nelson Mandela Academic Hospital, Walter Sisulu University, that we have done this intervention.

So far, the unit has been using the Amplatzer devices because of the consignment that we have with the company. We were unable to use other devices due to unavailability of the agreement between the hospital and the other companies. Also due to the lock-down levels 3 - 5 that we had in 2020 during the outbreak of the COVID-19 in South Africa, our Cath lab was closed, and we could not do any cases for a period of 6 - 8 months and that has affected the number of cases that we did in 2020.

The average age at ductal closure was 23 months. The youngest patient was 3 months old. This shows that most of the patients were diagnosed very late with the PDA and therefore could only be closed at almost 2 years of age. This data is almost like what Prof L. Pepeta, et al. described in their study of the ductal closure using Occlutech Duct Occluder in Port Elizabeth.[20] Due to the late presentation of the patients to the cardiology clinic and delayed ductal closure, most of the patients had high pulmonary artery pressures and a high PVR at the time of closure.[20]

In terms of the weight at the time of closure, the smallest patient was 3.6kg and the biggest was 14kg. The 3.6kg baby was the youngest of the cohort with symptomatic PDA. The average weight at closure was 8.3kg. Therefore, most of our patients presented late with advanced age compared to some of the other studies of PDA closure in small babies. This was partly because previously the cardiac clinic at NMAH was run by junior non-cardiologist doctors and sometimes the patients are missed in the district hospital.

Most of the patients had Type A Duct, and few had a tubular duct. There were no patients with Type D and E Ducts in our cohort.

The Amplatzer Duct Occlude device is known to have a high occlusion rate of about 99% within 6 months of device deployment with minimal complications.[16-17] This was also the case in our cohort, 100% of our patients had complete occlusion of the duct on discharge and 6 months later the duct was still closed. There were no significant complications on the Amplatzer Duct Occluder group of patients.

The determinants of success with the Amplatzer Duct Occlude in our cohort was multifactorial:

- Correct diagnosis and measurement of the PDA.
- Correct selection of the device type and the device sizes based on the type and size of the PDA.
- Doing the procedure of PDA closure following all the steps as described in the manuals.

The Amplatzer Vascular Plug 11 has been used for the closure of selected patent ductus arteriosus types more especially Type C Tubular Duct with good outcomes. The device can also be used in other morphological types of the duct and in small patients. It is a low profile, easily repositioned, and has excellent results.[21]

Out of the 22 patients that were occluded with Amplatzer Duct Ocluder and Vascular plug, there was only one device embolisation and 21 successful PDA closures with no complications. There was a 100% ductal closure on day 1 of ductal occlusion and on follow up until 6 months.[22]

The only patient that had a device embolisation was a 1-year-old child with failure to thrive weighing 6kg. The patient had a large tubular duct of 5mm on angiographic measurements. The decision was to use size 10mm AVP to close the duct based on

the angiographic measurements that were repeated more than twice. Following the placement of the device in the duct, there was a good closure on the first angiogram before the device was released. The device was eventually released completely, and a follow up angiogram was done. There was a shift in the positioning of the device following release and there was a residual left to right shunt about 2.5mm in size. The echo-cardiogram was done which also confirmed a 2.5mm residual duct and the device was in situ. The decision was to observe the patient and see if the leak will get better overtime or not.

The patient was kept in the ward and the follow up echos done to confirm the positioning of the device and to monitor the leak. On day 5 post device deployment, the echo was done which showed significant PDA flow and the decision was to take the child for repeat Cath and device retrieval and to upsize and use a bigger device. The device had embolised into the left pulmonary artery at the time. The positioning of the device in the pulmonary artery made it difficult for the device to be retrieved in Cath lab because the screw was against the wall of the LPA and facing towards the branch pulmonary artery. The patient was referred for surgery removal of the device.[20]

CONCLUSION

The Amplatzer Duct Occluder can be used successfully in patients as small as 3.5kg and above in carefully selected patients with minimal complications. The initial experience and outcomes in PDA closure in the new Cath lab in Mthatha are satisfactory.

Conflict of interest: none declared.

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The skeletonised right gastroepiploic artery for coronary artery bypass grafting: A case report

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ABSTRACT

Coronary artery bypass grafting (CABG) has been the mainstay for treating multivessel coronary artery disease for many decades. Various conduits have been studied to optimise surgical outcomes of CABG. The gastroepiploic artery (GEA) has been used as an in situ graft for over 30 years. Multi- and total arterial revascularisation using the internal thoracic artery, radial artery, and GEA grafts are an option for better outcomes.

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INTRODUCTION

Coronary artery bypass grafting (CABG) has been the mainstay for treating coronary artery disease (CAD). Multiple conduit options exist, with each having its benefits and complications. The saphenous vein graft is prone to atherosclerotic changes and is therefore inferior in long-term patency rates than internal mammary artery (IMA) grafts. The gastroepiploic artery was described in the late 1960s in Vineberg's procedure performed by Bailey, et al., where indirect myocardial revascularisation was done using the right gastroepiploic artery (GEA).[1] Anastomosis of the GEA to the right coronary artery was attempted by Sterling Edwards, et al. in the 1970s.[2] The GEA graft has since been utilised as an alternative conduit in numerous landmark procedures by Pym, et al. in Canada and Suma, et al. in Japan.[3,4] Instead of harvesting the artery with its surrounding omentum, the skeletonised GEA allows for a longer conduit, better blood flow, and a larger calibre vessel for distal coronary anastomosis.

CASE PRESENTATION

A 52-year-old male with a history of coronary artery disease sustained a non-st segment elevation myocardial infarction in 2018. His current symptoms were angina and dyspnoea. The coronary angiogram revealed severe proximal stenosis of the left anterior descending (LAD) coronary artery, an occluded mid-circumflex coronary artery with late filling of the obtuse marginal branch (OM), and an occluded mid-right coronary artery. In addition, the posterior descending coronary artery (PDA) received collaterals from the left coronary artery circulation. The ejection fraction was 52%. He was referred for coronary artery bypass grafts. He had severe psoriasis of the lower limbs which precluded harvesting an extended length of saphenous vein for multiple grafts. In addition the Allen test was abnormal which prevented harvesting the radial artery. Triple vessel coronary artery bypass grafts were undertaken with the left internal thoracic artery anastomosed to the LAD, the right gastroepiploic artery anastomosed to the PDA, and a reverse saphenous vein graft anastomosed to the OM. The postoperative course was uneventful, and he was discharged on day 6.

Surgical procedure

The midline incision was made about 5cm longer than the usual sternotomy incision. Following a pericardiotomy, the peritoneum was opened, and the stomach was extracted to the surgical field. The GEA was detected by palpation to determine adequate size and length. It is essential to touch the GEA softly because it readily contracts under mechanical stimulation. The GEA was mobilised from the greater curvature of the stomach using electric cautery and an ultrasonic scalpel in a skeletonised fashion without any surrounding tissue (Figure 1). The skeletonised GEA can be used as a free graft if required. The skeletonised GEA produces a more extended graft and is easier for sequential anastomoses. Also, Y- or I-composite grafts using

a free GEA graft in combination with the in situ left or right IMA graft further increase the possibility of total arterial myocardial revascularisation. The distal end was cut after mobilising the GEA from the pylorus to more than half of the greater curvature. The GEA and coronary artery anastomosis can be performed using cardioplegic arrest or off-pump beating heart surgery. Finally, kinking or twisting is prevented by fixing the GEA to the epicardium (Figure 2).

DISCUSSION

Anatomy

The right GEA is the largest terminal branch of the gastroduodenal artery, a hepatic artery branch. Occasionally, it arises from the left hepatic artery or the celiac trunk or rarely from the superior mesenteric artery. Suppose a cardiologist was unaware of this, hepatic or selective gastroduodenal angiography to seek the GEA graft patency after CABG could fail to find a patent GEA graft. The right GEA reaches approximately half to two-thirds of the greater curvature of the stomach and terminates in a varying fashion with or without communication with the left GEA.[5,6]

Various properties render the GEA an ideal conduit option for CABG. Atherosclerosis of the GEA was found to be less frequent than in the coronary artery.[7] The diameter of the right GEA renders it suitable for CABG as the diameter is about 3mm or greater at its origin and 1.5 - 2mm at the middle of the greater curvature of the stomach. Histologically, the GEA contains many smooth muscle cells in the media, whereas the IMA has rich elastic fibres. Therefore, the GEA is considered a muscular artery, and the IMA is an elastic artery.[7] The GEA contracts more powerfully in response to vasoactive drugs, including phenylephrine and noradrenaline, than the IMA. Hence, it is essential to prevent spasm of the GEA caused by adrenergic agents or platelet aggregators.[8,9] Histamine causes dilation of the GEA, and its blood supply is shown to increase after a meal.[10]

Indications for gastroepiploic artery grafting

The American College of Cardiology Foundation / American Heart Association guideline for CABG stated that arterial grafting of the right coronary artery is contraindicated for patients with less than 90% stenosis of the native vessel.[11] The GEA is most suitable for grafting the distal right coronary artery and

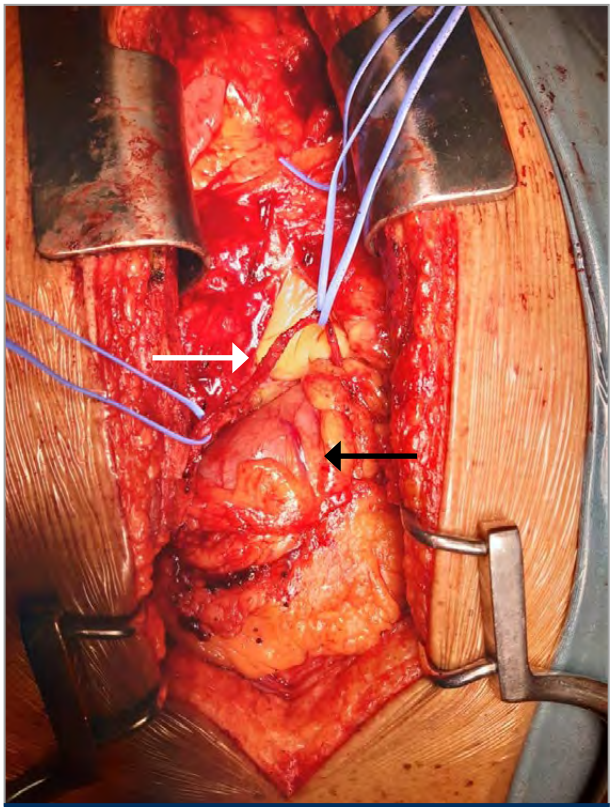

FIGURE 1: Skeletonised right gastroepiploic artery.
Black Arrow: Stomach.
White Arrow: Skeletonised right gastroepiploic artery.

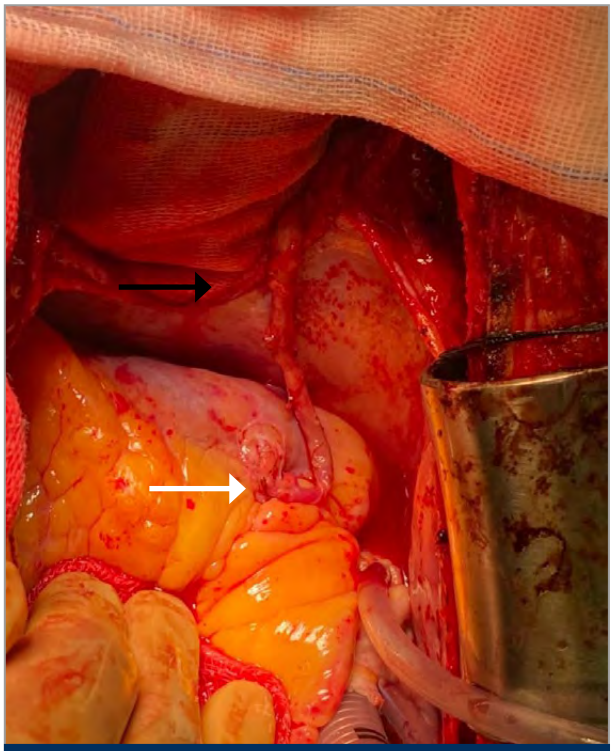

FIGURE 2: Gastroepiploic artery anastomosis to the posterior descending artery..
White arrow: Right gastroepiploic artery anastomosed to posterior descending coronary artery.
Black Arrow: Incision in the diaphragm.

the posterior descending artery because these areas are nearest to the in situ GEA graft and most distant to the right IMA graft. The left anterior descending artery may be a target for the GEA when the LIMA is unavailable. In addition, the distal circumflex artery is also a possible target for the GEA graft. The in situ GEA graft may be utilised during aortic no-touch CABG surgery.[12] The GEA is also helpful in re-do CABG cases as the GEA can be mobilised from the abdomen before re-do sternotomy. GEA grafts are not recommended in very elderly patients or obese patients. In addition, future abdominal operations and unstable haemodynamics during emergency surgery are contraindications to utilising the GEA graft.

Complications

Intraoperative complications include haemorrhage / haematoma formation from gastric and omental branches of the GEA. In addition, kinking and twisting can occur during its course through the diaphragm and at the peri-anastomotic site.

Postoperative complications such as peri-op myocardial infarction, graft occlusion, low cardiac output, vasodilatory shock, arrhythmias, pericarditis, myocarditis, pericardial effusion, and tamponade are rare.

CONCLUSION

The right GEA is an excellent arterial conduit for CABG. It does not induce gastric ischaemia after harvesting and has survival and patency rates comparable to the internal mammary artery (IMA) grafts.[13]

ETHICS

Written informed consent was obtained from the patient.

Conflict of interest: none declared.

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ECG Quiz 67

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

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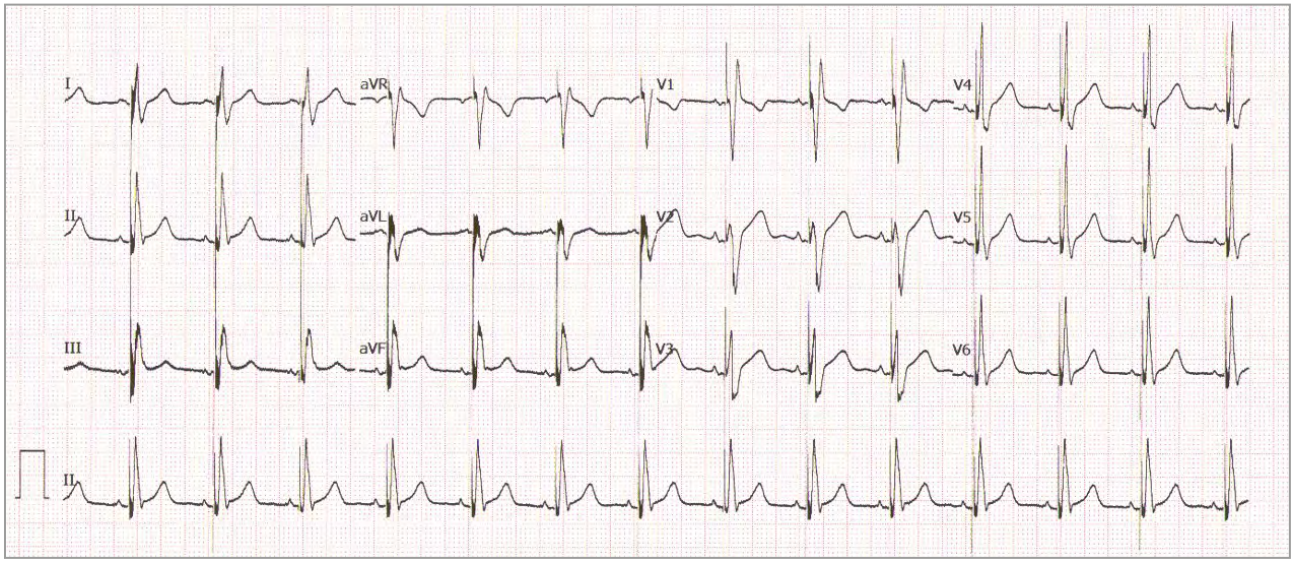

A 32-year-old man received a pacemaker for idiopathic complete heart block (presenting ECG showed a junctional escape with left bundle branch block at 42bpm). He now presents to the device clinic for a routine visit 6 weeks post implant.

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

a. Biventricular pacing (cardiac resynchronisation therapy)
b. Conduction system pacing – His bundle pacing
c. Conduction system pacing – left bundle branch pacing
d. Epicardial left ventricular / coronary sinus pacing
e. Right ventricular outflow tract pacing

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

ANSWER on page 67

OVERVIEW OF THE ECG

This ECG shows a regular, wide complex paced rhythm (QRS 132ms) with a ventricular rate of 84bpm. This patient has a dual chamber pacemaker with sensed P waves followed by paced QRS complexes.

MORE DETAILED ANALYSIS OF THE ECG

The paced QRS morphology and QRS axis are the keys to determine the type of ventricular pacing (Figure 1).

This paced QRS morphology has a rSR' pattern in V1 and a qR pattern in V6 (resembling an atypical right bundle branch block (RBBB) pattern). The QRS duration is wide (132ms) with rapid initial activation. The rapid r wave in V1 and q wave in V6 suggests rapid conduction towards the left ventricular (LV) apex and R' in V1 suggests delayed activation to the right ventricle (RV). The paced QRS axis has an inferior axis (75 degrees).

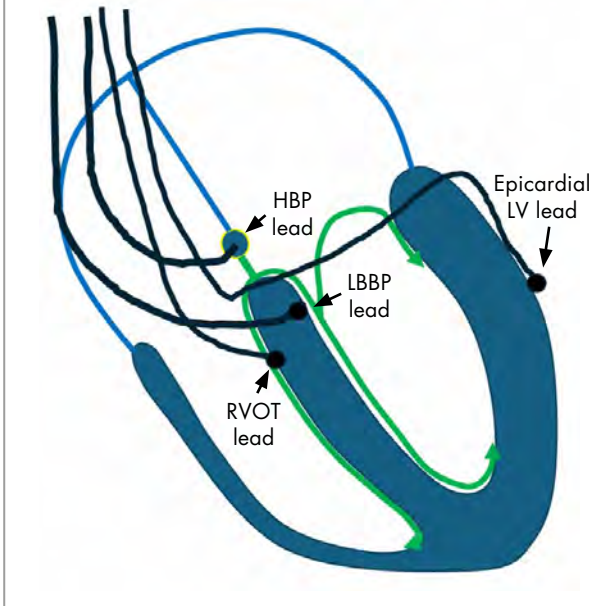

FIGURE 1: Different lead positions for different types of ventricular pacing. HBP = His bundle pacing, RVOT = right ventricular outflow tract, LBBP = left bundle branch pacing, LV = left ventricular. Cardiac resynchronisation therapy = biventricular pacing (pacing from both right ventricular lead and epicardial LV lead simultaneously).

Right ventricular outflow tract (RVOT) pacing usually causes a wider QS or rS pattern in V1 and V2 (atypical left bundle branch block (LBBB) morphology) because depolarisation is moving away from V1 and V2 with an inferior QRS axis. The activation is delayed throughout the QRS complex because of slow cell-to-cell depolarisation.

Biventricular pacing / cardiac resynchronisation therapy (CRT) results in simultaneous RV and LV pacing following a sensed or paced P wave (with a short PR interval). CRT-paced morphology can be highly variable between patients because of different positions of the RV and LV leads. A qR or Qr pattern in lead I is usually indicative of CRT pacing with a QRS duration between 120ms and 200ms (typically narrower than either RV or LV pacing) with a north-west axis.

Epicardial / coronary sinus pacing usually causes a very wide QRS morphology (epicardial pacing results in very wide QRS complexes because impulses proceed from the outer LV) with a dominant R wave in V1 with usually right axis deviation when pacing the lateral LV wall.

RV outflow tract pacing, biventricular pacing and epicardial / coronary sinus pacing can therefore be excluded based on the QRS morphology and axis.

His bundle pacing (HBP) involves pacing the His bundle only (selective His capture) or His bundle and local myocardium (non-selective His capture). Selective His capture usually produces a narrow QRS (similar to the conducted QRS) in the absence of bundle branch block with a normal QRS axis. Non-selective His capture produces a pseudo delta wave (due to local myocardial capture) with an initial widening of the QRS with a normal axis. While non-selective His capture is possible in this ECG because of the lack of an isolelectric baseline after the pacing spike, we are told that the presenting ECG showing complete heart block with a LBBB junctional escape, this would not explain the atypical RBBB pattern in V1.

Left bundle branch area pacing (LBBAP) refers to capture of the left subendocardial area of the interventricular septum and comprises:

- Left bundle branch pacing (LBBP) where there is capture of the left bundle branch (LBB) i.e. conduction system capture occurs.

- Left ventricular septal pacing (LVSP) where there is capture of ventricular muscle on the left interventricular septum without capture of the LBB i.e. no conduction system capture occurs.

LBBP, like HBP, therefore provides a form of physiological pacing. Growing evidence suggests that LBBP may reduce the risk of pacing-induced cardiomyopathy and heart failure admissions compared to RV pacing.[1] LBPP may also be a suitable alternative to CRT.[2]

Both LBBP and LVSP can cause an atypical RBBB pattern (qR or Qr pattern) with a normal axis. However, differentiating between LBBP and LVSP can be challenging as the pacing morphology can appear similar on a 12 lead ECG. Detailed measurements are often needed on a faster paper speed with the use of digital callipers in the cath lab at the time of implant. In general, LBBP results in a narrower QRS complex and more rapid QRS activation compared to LVSP. These changes are best seen and measurements made in the cath lab on an EP recording system.

There have been numerous proposed criteria to help differentiate LBBP from LVSP.[3] The best evidence for LBBP includes morphology changes in V1 and V6 when transition occurs between LBBP and LVSP during threshold testing. The speed of activation from pacing to apical lead V6 measured as the R wave peak time (RWPT) from pacing spike to R wave in V6 is a useful measurement (see Figure 2). The RWPT typically prolongs in V6 by >15ms when LBBP transitions to LVSP (this occurs because activation to the apex is faster with LBBP because of conduction system capture). A RWPT <75ms has also been shown to be accurate for confirming LBBP. In this case the RWPT was 45ms confirming LBBP (Figure 3). Another useful measurement is the V6-V1 inter R wave peak interval with longer intervals confirming LBBP (as RWPT is typically short resulting in longer V6-V1 times). A V6-V1 interval >44ms is specific for LBBP. The V6-V1 interval was measured as 46ms (91ms - 45ms) confirming LBBP (Figure 4).

The correct answer is (c) Conduction system pacing – left bundle branch pacing.

DISCUSSION

Conduction system pacing, which includes HBP and LBBP, is a physiological alternative to RV pacing for bradycardia pacing for the prevention of pacing-induced cardiomyopathy and as an alternative to traditional CRT for heart failure with left LBBB.

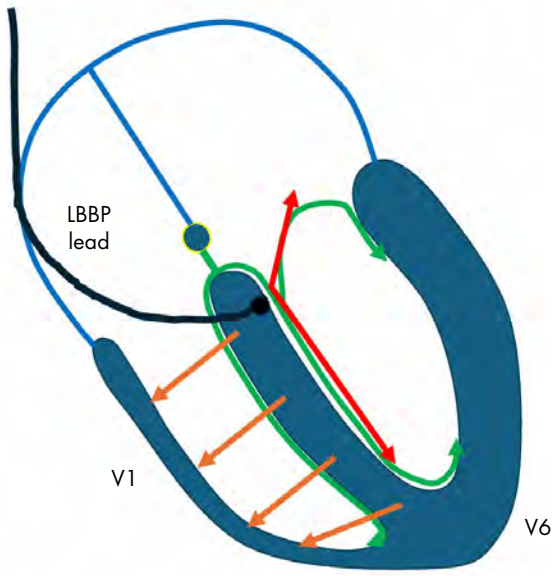

FIGURE 2: With left bundle branch pacing (LBBP), conduction capture occurs which causes rapid activation down both fascicles to the apical lead V6 (red arrows) resulting in a very short R wave peak time (RWPT). Right ventricular depolarisation follows later (orange arrows), resulting in a qR wave in V1 with a delayed R wave peak time. In LVSP, no conduction capture occurs which results in a longer RPWT in V6 with similar R wave peak time in V1 which results in a longer V6-V1 interval.

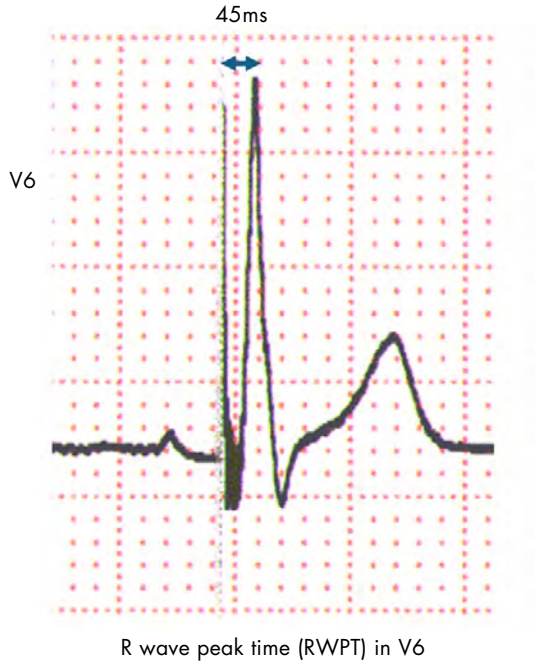

FIGURE 3: R wave peak time (RWPT) in V6 is measured from the pacing spike to the R wave. A RWPT <75ms is specific for LBBP. RWPT = 45ms in this patient confirming LBBP.

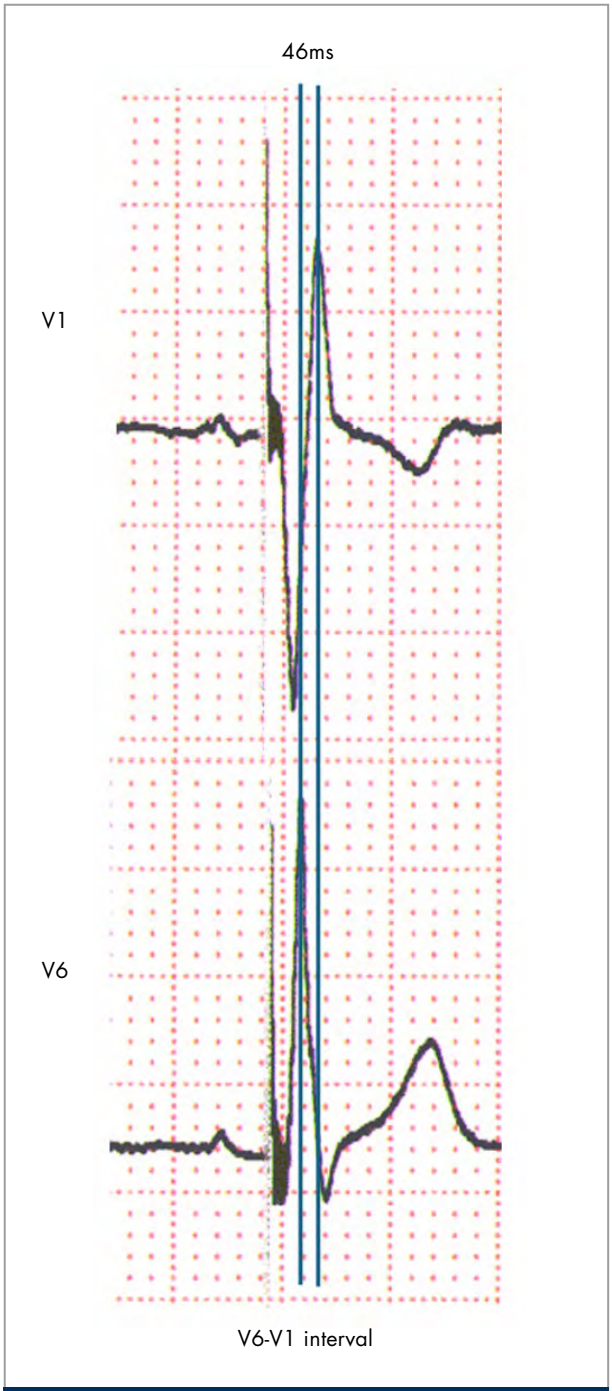

FIGURE 4: The V6-V1 interval is the interval between the R wave in V6 and the R' wave in V1. A V6-V1 interval >44ms is specific for LBBP. V6-V1 interval = 46ms in this case confirming LBBP.

Disadvantages of HBP include high capture thresholds, lead stability with a high risk for lead repositioning. LBBP has gained popularity over HBP due to several advantages. LBBP has low capture thresholds and leads tend to be more stable with a larger target area and has the ability to correct distal conduction disease.

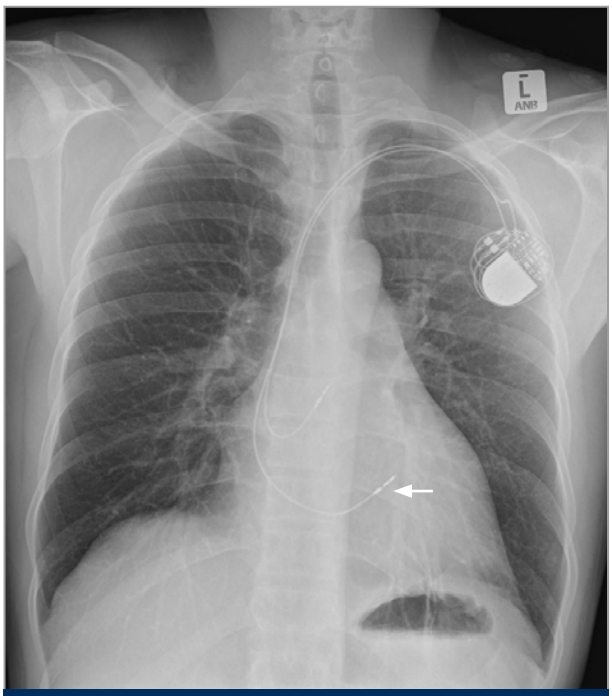

FIGURE 5: A PA chest X-ray showing position of the right atrial lead and the left bundle pacing (LBBP) lead. The LBBP is fixed in the high interventricular septum using an active fixation lead (white arrow).

LBBP is performed by advancing a guiding catheter into the RV 1.5 - 2cm from the His bundle towards the apex. The lead is then rapidly rotated and advanced into the interventricular septum. The lead is advanced until LBBP is achieved before perforation into the LV occurs. LBBP must be distinguished from LVSP before the sheath is slit and the lead secured. An X-ray showing lead positions is shown in Figure 5.

While the indications for LBBP are evolving, the strongest indications for LBBP include the following:

- LBBP may be considered for the treatment of heart failure as a bailout or alternative to conventional CRT.
- LBBP may also be considered for bradycardia pacing for AV block when the anticipated high burden of ventricular pacing and LV dysfunction is present.
- LBBP may also be considered as part of a pace and ablate strategy for rate control for atrial fibrillation and AF with heart block with a high percentage anticipated RV pacing.

Pacemaker follow-up is very important to ensure persistent LBBP. A 12 lead ECG is important and should be compared to the post implant ECG. It is not uncommon for a patient to return with LVSP and lack of LBBP at follow-up visits. Careful

pacemaker interrogation should be performed to confirm both LBBP and LVSP thresholds.

This patient had good LBBP thresholds at the 6 week visit.

CONCLUSION

LBBP is a relatively new form of physiological pacing which is gaining popularity worldwide and in South Africa as an alternative to conventional CRT and for some bradycardia indications.

Careful analysis of the ECG is essential to confirm LBBP and careful threshold testing confirming LBBP is mandatory at every device follow-up visit.

The classic ECG of LBBP is an atypical RBBB morphology with a rapid RWPT in V6. Careful analysis is required at the time of implant to distinguish LBBP vs. LVSP.

Implanters need to be able to differentiate LBBP from LVSP as LVSP appears not to have the same benefits of LBBP.

Conflict of interest: none declared.

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ECG and **QUESTION** on page 66

SA HEART

CARDIAC IMAGING QUIZ

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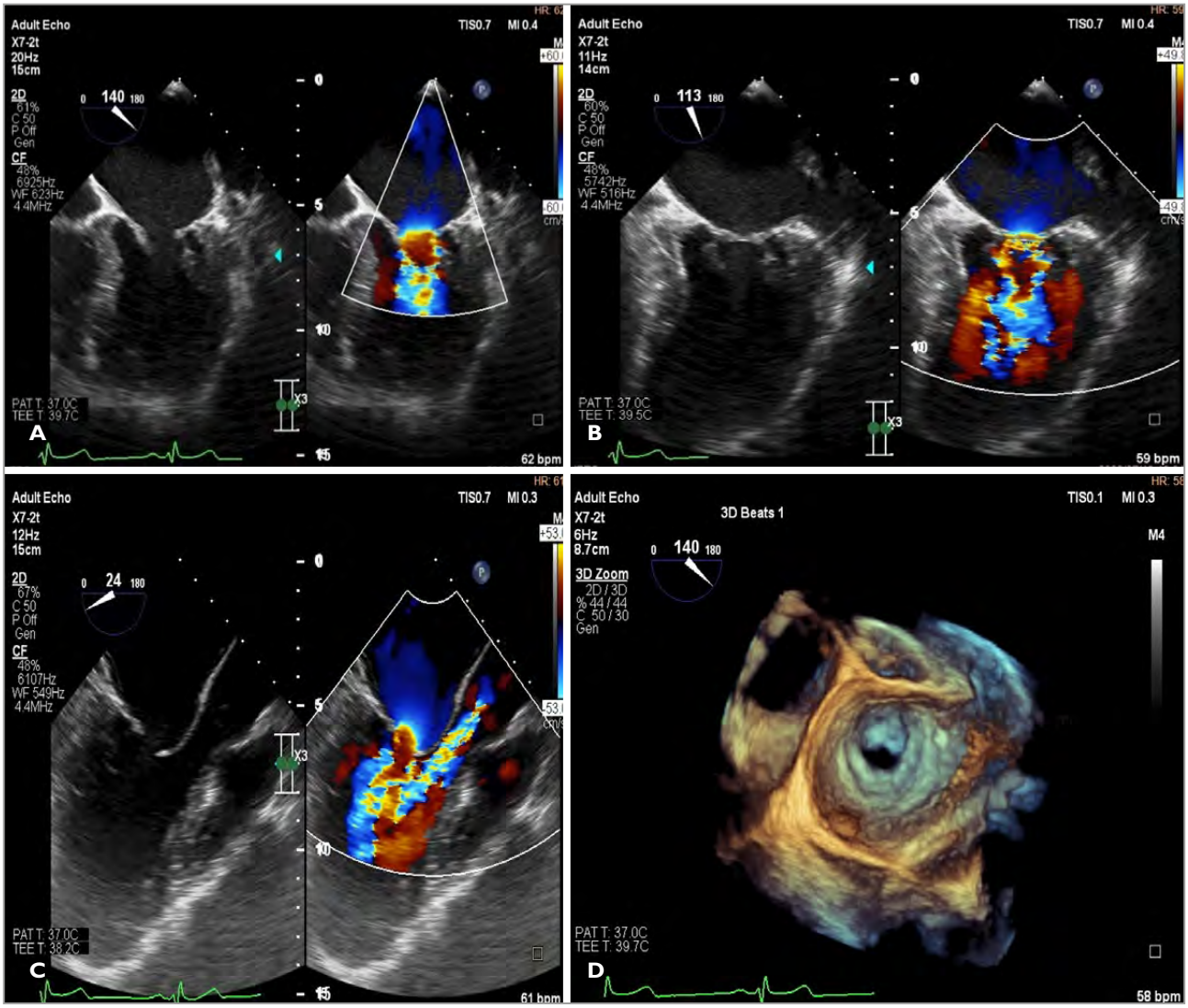

QUESTION: What is the diagnosis?

a. Dextroversion with rheumatic valvular disease.

b. Dextrocardia with rheumatic valvular disease.

c. Dextroposition with rheumatic valvular disease.

d. Mixed rheumatic valve disease.

ANSWER

(B) Dextrocardia with rheumatic valvular disease.

These transoesophageal (TEE) echocardiographic images were obtained from a 20-year-old male who presented with shortness of breath. Cardiac positional changes and abnormal cardiac looping during foetal development can result in dextrocardia, with a mirror-image loop, where the morphologic right ventricle is on the left of the morphologic left ventricle. Specific manipulations of the TEE probe and transducer are necessary to obtain the required views, as seen in the images above. Standard mid-oesophageal TEE views are: 4-chamber (0-10°); 2-chamber view (45-60°), 3-chamber or long axis view (135-150°). In this case 4-chamber view obtained at 140°, 2-chamber view at 113° and long axis or 3-chamber view at 24°, a mirror-image of normal views. Additionally, the typical appearance of rheumatic mitral valve stenosis is evident in the 2-dimensional (top and bottom panels) and 3-dimensional enface views (bottom panel) with thickened tips, diastolic restriction and a fish-mouth appearance visualised respectively in these views. Additionally aortic regurgitation is also noted on the 3-chamber view.

Dextrocardia is a rare cardiac positional anomaly where the heart is positioned in the right hemithorax, with its base-to-apex axis directed rightward and downward. It is generally discovered incidentally and may be associated with other congenital abnormalities. The prevalence of dextrocardia is reported to be less than 1%. It must be distinguished from cardiac dextroversion which is a congenital condition that results from the heart malrotating around its long axis, with left ventricle lying anterior to the right ventricle. Additionally it must be differentiated from cardiac dextroposition, which occurs when the heart is displaced to the right due to extracardiac factors such as right lung hypoplasia, right pneumonectomy, or diaphragmatic hernia.

Individuals with dextrocardia exhibit variant intracardiac anatomy and may have congenital conditions such as discordant atrioventricular connection, univentricular atrioventricular connection, ventricular septal defect, and pulmonary artery anomalies. Extracardiac anomalies are also common in these patients. Dextrocardia can be categorised into 4 types. The isolated form, as seen in our patient. Other types of dextrocardia include dextrocardia situs inversus, where the liver and spleen are located on the opposite side of the body, dextrocardia situs inversus totalis, where all vital organs in the chest and abdomen are reversed, and dextrocardia with heterotaxy, where some or all vital organs are misplaced or absent.

Diagnosis is based on clinical evaluation, chest X-ray, which reveals the right-sided location of the cardiac apex and aortic arch, and electrocardiogram findings such as inverted or reversed electrical waves, right-axis deviation of the P wave, and the QRS complex, which are indicative of dextrocardia. Cardiac imaging, including echocardiography, cardiac CT, and MRI, is used to assess structural and functional abnormalities. The management and prognosis of dextrocardia depend on the specific type and whether there are associated congenital defects.

This case is notable due to the presence of acquired rheumatic heart disease with predominant mitral valve stenosis. No other cardiac or extracardiac defects were observed in this patient.

Conflict of interest: none declared.

SUGGESTED READING

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

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