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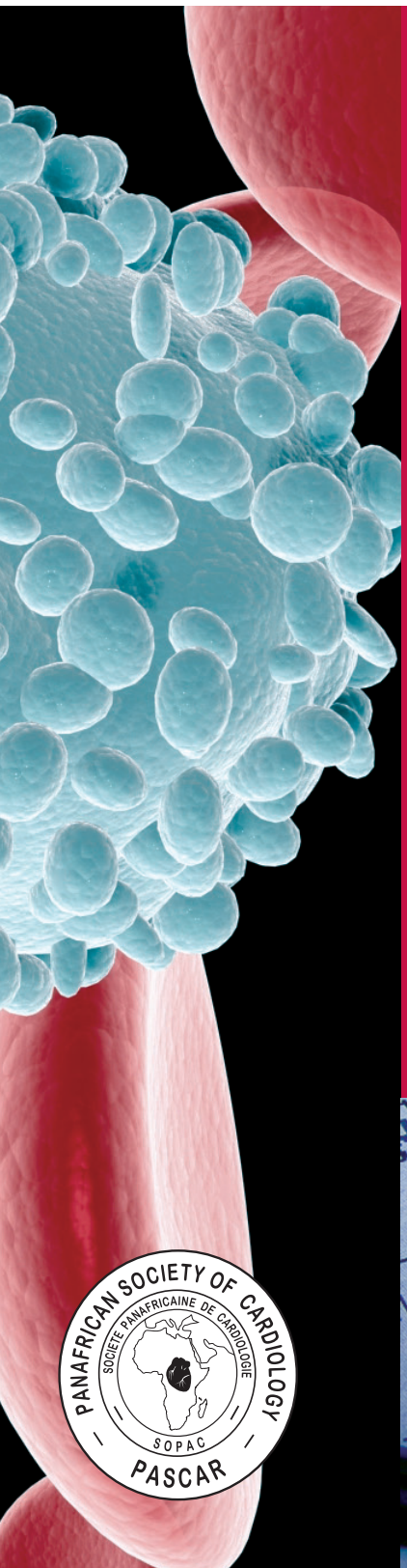

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In Memoriam

Professor Andries Jacob Brink

29 August 1923 – 17 October 2012

It has been my privilege to have known the late Prof Andries Brink for almost 50 years. We first met early on in my career, and I had dinner with him only a few months before he died.

Andries' career has been highly distinguished. Although of a quiet and humble nature, his thinking and actions have always been clear and direct. Born in 1923, he graduated from Medical School at the University of Witwatersrand with a first-class honours MB BCh degree in 1946. Thereafter he worked his way up at Pretoria University to become senior lecturer in Internal Medicine in 1953.

From 1956 to 1961 Andries was head of the Department of Internal Medicine at the University of Stellenbosch and from 1956 to 1969 he was director of the Molecular and Cellular Cardiac Research Unit at the University of Stellenbosch. He was chief physician at the Karl Bremer Hospital from 1956 to 1973. Thereafter he became chief cardiologist at the Tygerberg Hospital from 1973 to 1979. From 1970 to 1976 he was president of the South African Medical Research Council, while from 1971 to 1983 he was dean of the Faculty of Health Sciences. He was the personal cardiologist of John Vorster when Vorster was the president of the Republic of South Africa.

In his lifetime, Andries received more than 30 major awards, including the prestigious Havenga Prize for Medicine from the South African Academy of Arts and Science. He also received gold medals from the University of Stellenbosch, South African Medical Research Council, Wellcome Trust and South African Heart Association.

Andries' many publications are equally meritorious but what caught my eye was a series of seven articles on electrocardiographic studies, published in the *South African Medical Journal* in 1959. He and I had a number of conjoint studies on basic cardiac research, together with Amanda Lochner, all published in top-ranking journals such the *Lancet* in 1964, *Clinical Science* in 1965 and *Circulation Research* in 1967. He was founder and editor in chief of the *Cardiovascular Journal of South Africa*, which later become the *Cardiovascular Journal of Africa*, in keeping with his personal trans-Africa vision.

But how did I meet Andries and what influence did he have on me? My first meeting with this remarkable man was in 1962, over 40 years ago. I was a young research fellow at Harvard Medical School, trained in basic heart research, and wanting to return to South Africa. I was aiming to be a physician–scientist.

During a holiday in Cape Town, I went to sound out the professors of Medicine at Groote Schuur Hospital, Cape Town, and the Karl Bremer Hospital, run by the University of Stellenbosch. Andries Brink was a cardiologist with a vision and he encouraged me. 'Heart metabolism', he said 'is the direction of the future, and that is what you should do'. Accordingly, when I eventually returned to South Africa, he welcomed me to his laboratory at the Karl Bremer Hospital.

Andries had many remarkable talents. In addition to his job as professor of Internal Medicine and head of the hospital medical wards, he was completely at home with laboratory work. He personally oversaw the development of the heart metabolism laboratory and recruited Amanda Lochner, with whom I worked closely for many years.

Apart from undertaking weekly ward rounds on a variety of general medical patients (not just cardiology) and always giving a concise summary and pertinent recommendation for the house staff to carry out, he really loved laboratory work. When I went to climb Kilimanjaro he lent me his rucksack and, what is more, took over the job of perfusing hearts in the laboratory while I was away.

Later, when I came back from further training in London and Oxford, he offered me a job as head of both clinical endocrinology and his heart research laboratory. That was a big challenge. Soon Andries and I came to realise that to really excel, I would need further training in biochemistry. I then went to work with Nobel Prize winner, Sir Hans Krebs at Oxford.

Eventually, after the first Chris Barnard heart transplant, I returned to the University of Cape Town Medical School. When visiting the new Tygerberg Hospital, I had frequent contact with

Andries. By then he had risen to be the dean but despite these many honours, he bore his senior positions with dignity and humility, always keeping a human touch, which warmed him to both his co-workers and visitors.

Andries' hobbies included cycling, walking and, most intriguingly, making boutique wines in his retirement. The initial pressing was achieved literally by his feet pressing the grapes. The brand name of the wines is Galleon and in John Platter's book *South African Wines* (2012) he is, I believe, the only listed cardiologist winemaker, with the intriguing appellation of a 'garagiste winemaker'. Platter quotes Andries as saying that 'the life extension of people who drink wine daily in moderation with food increases by 30%'.

I treasure two cases of Andries' first vintage. His first major distinction in wine making was a Michelangelo Gold for his Cabernet Sauvignon 2005. His 2009 Sauvignon Blanc achieved four stars.

Above all, and despite his major professional commitments, Andries participated actively in a happy and harmonious family life. His wife Rusty was equally remarkable in her personal qualities, and in her devotion to the family and their many friends. Socially, Andries and Rusty were seldom seen apart.

Professionally, Andries also worked with his elder son, Prof Paul Brink, to promote the group PACE Africa (Prevent Arrhythmia Cardiac Events), as part of Paul's flourishing co-operative projects with the renowned Italian electrophysiologist, Prof Peter Schwartz. His younger son, Tinus, is a trained medical specialist in neurology. There are two daughters; Maryna Johnson is a psychologist and has two sons and one daughter. Annaliese Brink has her own school (Natural Learning Academy) and has one daughter and one son. Andries leaves a rich heritage of four children, 10 grandchildren and two great grandchildren.

The last time I had contact with Andries was at the South African Heart Association meeting at Sun City in July 2012. We shared a dinner table and a bottle of good red wine at the social event. As ever, he was sympathetic and alert, and asked me about my work and my latest concepts and publications. He told me he was planning a book to encompass cardiology in Africa. He invited me to write a chapter and only his untimely passing on at the age of 89 halted the development of that unique book.

Lionel Opie

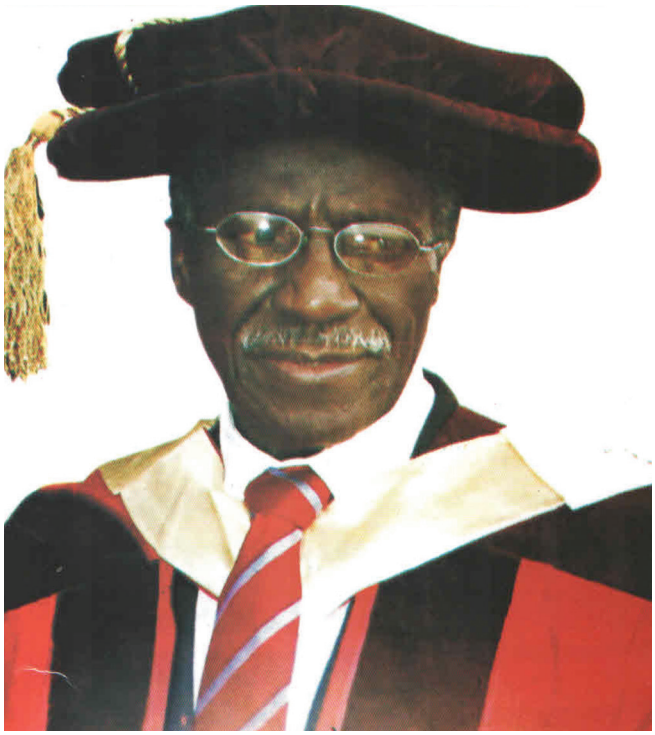
Tribute to the late Professor Oluwole Ademola Adebo

Oluwole Ademola Adebo was born in Lagos on 16 August 1944, the first son to Chief Simeon and Regina Adebo. As his father was the former head of the Civil Service of the old western region of Nigeria and later United Nations Under-Secretary General, he had the opportunity of travelling extensively around the world and had access to the best education in Nigeria, Europe and the USA.

Prof Adebo started at the University of Ibadan staff primary school and at the age of 11 he moved to the UK for further schooling, where he attended Leighton Park School, Reading and lived with English guardians during the holidays. This perhaps contributed to his being 'different' and he was often referred to as 'oyinbo' by others.

Prof Adebo came back home in 1963 for his undergraduate studies in Medicine at the University of Ibadan, graduating with Bachelor of Medicine and Bachelor of Surgery (MB BS) degrees in 1968. He did his internship at the University College Hospital (UCH), Ibadan between 1968 and 1969, after which he preceded to Strong Memorial Hospital, New York where he undertook his residency in general surgery. Thereafter he went to the Providence Rhode Island where he took residency in cardiothoracic surgery. He then became lecturer and director of Emergency Medical Services at Highland Hospital, Rochester, New York.

A turning point in Prof Adebo's life may be traced back to a recent entry from his journal which reads, 'a spiritual rebirth in 1976 altered my life, goals and perspectives. Working for God became the defining motivation for my endeavours. My motivation for diligence, integrity and excellence was to please God, who gave me purpose.'



In 1979 he returned to Nigeria and first took up the position of senior registrar in cardiothoracic surgery at the UCH and later lectureship in cardiothoracic surgery at the College of Medicine of the University of Ibadan and honorary consultant cardiothoracic surgeon to the University College Hospital,

continued on page 23…

Editorial

Impact of HIV on the incidence of pre-eclampsia

J MOODLEY

Pre-eclampsia, a condition unique to human pregnancy, is defined as new-onset hypertension (BP ≥ 140/90 mmHg) in the second half of pregnancy, associated with significant proteinuria (≥ 30 mgms). The aetiology of this condition remains elusive but recent findings suggest that pre-eclampsia is a two-stage disorder. The first stage is thought to be due to failure of the spiral arterioles in the placental bed to undergo vascular remodelling into wide-bore channels. This vascular maladaptation of the placental bed results in a marked reduction in blood flow to the placenta and sets the scene for the second stage.

Reduction in blood flow to the placenta induces cellular hypoxia, which results in the release of trophoblastic debris, necrotic tissue and a variety of anti-angiogenic circulating factors such as soluble fms-like tyrosine kinase 1 and soluble endoglin. It is believed that these excessive anti-angiogenic factors bind with pro-angiogenic factors (vascular endothelial factor and placental growth factors), inhibiting their biological activities and subsequently resulting in widespread endothelial damage and the clinical disorder of pre-eclampsia.[1]

The current view of the pathophysiology of pre-eclampsia as described above is that this pregnancy disorder is a multi-organ endothelial disorder. Therefore it is important to recognise that although hypertension and proteinuria are the dominant clinical signs, pre-eclampsia may present with signs of isolated thrombocytopenia, liver enzyme abnormalities, intra-uterine foetal growth restriction or seizures. The exact cause however remains unknown and management is based on delaying delivery long enough for the foetus to mature, and expediting delivery of the placenta to avoid significant maternal and neonatal morbidity and mortality.[2]

However, what is generally not recognised is that hypertension may get worse following delivery or that women may present with hypertension for the first time in the immediate postpartum period (usually the first 72 hours following delivery). This is thought to reflect mobilisation of fluid accumulated in the extra-vascular space following delivery.

Minimal rises in blood pressure occur in normal pregnancies but more than one-third of pre-eclamptics have sustained high blood pressures in the puerperium and they may also develop pulmonary oedema. The clinical implications of this is that close monitoring of blood pressure levels must continue following delivery and it may be safer to keep all pre-eclamptics in hospital for at least three days to detect any early signs of complications and take timeous measures to prevent maternal morbidity and mortality.[3]

The initiator of the vascular maladaptation is not known but it is believed that immunological abnormalities may be involved. Similarly, HIV is an immune-dysfunction disorder and in the initial stages of this infection, when few symptoms are present, there may be a slight depression in CD_4 T cells.[4] It is plausible that the impaired immunity associated with HIV could lower the risk of pre-eclampsia. The current data on this matter however, are conflicting.[5,6]

Kalumba *et al*. took a different approach from earlier studies to establish whether HIV infection had a protective effect on the incidence of pre-eclampsia.[7] These authors performed a retrospective case–control study by comparing HIV rates in pre-eclamptics and normotensive healthy women. Previous studies have just compared the rate of pre-eclampsia between uninfected and HIV-infected pregnant women.[5,8,9] Kalumba *et al.* found a lower rate of HIV infection in pre-eclamptics in comparison to a control group.[7]

This study suggests that the rates of pre-eclampsia are lower in HIV-positive pregnant women. Because this study was retrospective and CD_4 counts were not available for a large number of the study patients, there is a need for a prospective study involving large numbers of patients to confirm the findings of Kalumba *et al*.[7]

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Cardiovascular Topics

Clinical characteristics and outcomes of atrial fibrillation and flutter at the Aga Khan University Hospital, Nairobi

JAY SHAVADIA, GERALD YONGA, SITNA MWANZI, ASHNA JINAH, ABEDNEGO MORIASI, HARUN OTIENO

Abstract

Introduction: **Scant data exist on the epidemiology and clinical characteristics of atrial fibrillation in Kenya. Traditionally, atrial fibrillation (AF) in sub-Saharan Africa is as a result of rheumatic valve disease. However, with the economic transition in sub-Saharan Africa, risk factors and associated complications of this arrhythmia are likely to change.**

Methods: **A retrospective observational survey was carried out between January 2008 and December 2010. Patients with a discharge diagnosis of either atrial fibrillation or flutter were included for analysis. The data-collection tool included clinical presentation, risk factors and management strategy. Follow-up data were obtained from the patients' medical records six months after the index presentation.**

Results: **One hundred and sixty-two patients were recruited (mean age 67 ± 17 years, males 56%). The distribution was paroxysmal (40%), persistent (20%) and permanent AF (40%). Associated co-morbidities included hypertension (68%), heart failure (38%) diabetes mellitus (33%) and valvular abnormalities (12%). One-third presented with palpitations, dizziness or syncope and 15% with a thromboembolic complication as the index AF presentation. Rate-control strategies were administered to 78% of the patients, with beta-blockers and digoxin more commonly prescribed. Seventy-seven per cent had a CHA_2DS_2VASC score ≥ 2, but one-quarter did not receive any form of oral anticoagulation. At the six-month follow up, 6% had died and 12% had been re-admitted at least once. Of the high-stroke risk patients on anticoagulation, just over one-half were adequately anticoagulated.**

Conclusion: **Hypertension and diabetes mellitus, not rheumatic valve disease were the more common co-morbidities. Stroke risk stratification and prevention needs to be emphasised and appropriately managed.**

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In developed countries, atrial fibrillation is the most common sustained rhythm disorder, with prevalence increasing with age.[1,2] This rhythm disorder is associated with mortality and significant morbidity due to increased stroke risk, heart failure, hospitalisations and reduced quality of life.[3-5] Data from other parts of Africa support the notion of the 'double burden of disease', grappling with increasing cardiovascular disease in addition to the existing maternal and child health problems and infectious disease burden.[6]

Atrial fibrillation, the global arrhythmia epidemic, is proposed to have a more severe epidemiology in Africa, with the incident age being relatively younger and attendant complications more prevalent,[7,8] possibly due to a combination of rheumatic valve disease burden and non-adherence to established clinical guidelines. The purpose of this study was to obtain the epidemiology, predisposing factors, clinical presentation and outcomes of atrial fibrillation (AF) and atrial flutter (AFL) at a private urban referral teaching hospital in East Africa.

Methods

This retrospective survey was performed at the Aga Khan University teaching hospital in Nairobi, Kenya, between January 2008 and December 2010. The Aga Khan University Hospital is a 256-bed hospital serving predominantly an urban middle- to high-income community.

Patients over the age of 18 years, who had an electrocardiographic (ECG) diagnosis of either AF or AFL during their admission were included in the study. The data were collected using a data tool that included patient demographics and clinical presentation, potential risk factors to the development of AF and AFL, management strategy, and anticoagulation status. Follow-up data were from the patients' medical records obtained six months after the index presentation.

Atrial fibrillation was sub-divided into three main classes: paroxysmal (initial or recurrent AF episodes terminating spontaneously within seven days), persistent (non-spontaneously terminating after seven days or requiring electrical or chemical cardioversion), and permanent AF (failed rhythm control with electrical and chemical cardioversion, or cardioversion had never been attempted). 'Lone AF' was defined as an episode in

patients less than 65 years of age, and without structural cardiac abnormalities. Patients who had not completed 12 months since the index AF event at the six-month follow up were classified as having 'incomplete follow up' for the purposes of our study.

We used the $CHADS_2$ scoring system[9] to stratify patients for prediction of thrombo-embolic (TE) and stroke risk. This scheme has been validated, although not in African patients, to provide a predictive value of TE risk. A score of ≥ 2 predicts a significant TE risk, warranting anticoagulation, while a score of 0 or 1 predicts moderate risk, favouring anticoagulation over aspirin.

A comprehensive two-dimensional transthoracic echocardiography with pulsed- and continuous-wave Doppler and colour-flow velocity spectral imaging was performed to determine the severity of valvular heart disease in only patients with clinical signs suggestive of valvular heart disease. Patients with echocardiographic moderate to severe mitral or aortic stenosis, or moderate to severe aortic and mitral regurgitation were classified as having valvular heart disease. Patients with either mitral stenosis, or combined mitral stenosis and aortic regurgitation were labelled as having rheumatic heart disease (RHD).

TABLE 1. BASELINE CHARACTERISTICS

Mean age (years)	67.8 ± 17.1
Incidence by age bracket (years)	
18–30 (%)	3.1
31–50 (%)	13.0
51–70 (%)	26.9
71–100 (%)	57.0
Race	
Native Africans	46.8
Asians	30.7
Caucasians	22.5
AF:AFL	19:1
Male: female	1.27:1
SBP at diagnosis (mmHg)	131 ± 28
DBP at diagnosis (mmHg)	78 ± 16
Heart rate at diagnosis	95 ± 35
BMI	27.2 ± 5.8
AF subtype	
Paroxysmal (%)	40
Persistent (%)	13.5
Permanent (%)	40
Incomplete follow up (%)	6.5
Reason for presentation	
AF/AFL (%)	32.1
Heart failure (%)	17.3
TE event (%)	15.5
Sepsis (%)	13.6
Other (%)	21.5
Risk factors	
Hypertension (%)	68
Heart failure (%)	38
Diabetes mellitus (%)	33
Coronary artery disease (%)	19
Valvular heart disease (%)	12

SBP: systolic blood pressure, DBP: diastolic blood pressure, TE: thrombo-embolic event.

All continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as percentages.

Results

In this survey, 162 patients from 22 144 general hospital medical admissions were recruited over a 36-month period. Their baseline characteristics are given in Table 1. Ninety-five per cent of the patients recruited had AF, with the rest having AFL. The mean age at presentation was 67 years, with incidence increasing with age and peaking at the age bracket 70–100 years, as described in Table 1.

In terms of haemodynamics at presentation, 5% presented with hypotension (systolic blood pressure: SBP ≤ 90 mmHg), and 46% with a rapid heart rate (resting heart rate ≥ 90 beats/min). Thirty-two per cent of the patients presented to hospital due to symptoms related to their rapid heart rate (palpitations, dizziness, syncope and fatigue), 17% had congestive heart failure, 15% thrombo-embolic events (transient ischaemic attack, cerebrovascular accident, other embolic events), 8.3% for other surgical indications, and 1.9% due to acute coronary syndrome and major bleeding, respectively.

Hypertension (68%), heart failure (38%), diabetes mellitus (33%) and coronary artery disease (19%) were the commoner underlying predisposing factors; valvular heart disease (12%), chronic obstructive airway disease (7%), excess alcohol intake (5%) and hyperthyroidism (3%) accounted for the other predisposing risk factors of atrial fibrillation. Only six (32%) of the 19 patients who had valvular heart disease had echocardiographic evidence of rheumatic heart disease.

Rate control was the more preferred strategy for management of arrhythmia (78.4%), while the remainder were managed with a rhythm-control approach. The choice of both rate- and rhythm-control agents is summarised in Table 2. Amiodarone was the only agent used for chemical cardioversion, while direct-current cardioversion was opted for in 37.1% of the patients in the rhythm strategy. AF ablation was not performed in any of the patients, as this modality of rhythm control is not locally available.

For stroke risk categorisation, 18.6, 16.7 and 64.7% of the patients had a $CHADS_2$ score of 0, 1 and ≥ 2, respectively. Of the patients with a $CHADS_2$ score ≥ 2, 21.2% did not receive any form of anticoagulation, with the majority being on aspirin. Of the patients with a $CHADS_2$ score between 0 and 1, 36.4%

TABLE 2. RHYTHM MANAGEMENT STRATEGY

Management strategy	*Rate control (%) (n = 127/162)*	*Rhythm control (%) (n = 35/162)*
Digoxin alone	38 (29.9)	–
BB alone	36 (28.3)	–
BB + digoxin	32 (25.2)	–
CCB	10 (7.8)	–
Amiodarone alone	3 (2.3)	9 (25.8)
BB + amiodarone	4 (3.1)	–
BB + CCB	2 (1.7)	–
CCB + digoxin	2 (1.7)	–
Spontaneous cardioversion	–	13 (37.1)
DC cardioversion	–	13 (37.1)

BB: beta-blockade, CCB: non-dihydropyridine calcium channel blockers, DC: direct current.

TABLE 3. STROKE RISK STRATIFICATION AND MANAGEMENT

$CHADS_2$ score	0	1	≥ 2
Total number	29/156 (18.6)	26/156 (16.7)	101/156 (64.7)
No. on anticoagulation (%)	5 (4.4)	11 (40)	80 (79.8)
No. on ASA (%)	13 (47.8)	7 (40)	17 (17.8)
No. on DAT (%)	0	0	2 (1.6)
No. on no treatment (%)	11 (47.8)	8 (20)	2 (0.8)

ASA: aspirin, DAT: dual antiplatelet therapy.

were on aspirin, 29.1% on oral anticoagulation and 34.5% on no stroke-prevention strategy (Table 3).

Follow-up data six months after the patients' index presentations were available for 124 of the 162 patients (76.5%) recruited to the study. Of these, eight had died, and the cause of death was sepsis related in three, cardiovascular in two and unclear in the rest. Fifteen patients had made at least one hospital revisit, 11 of whom had been re-admitted. Five of these were due to decompensation of heart failure, four due to major bleeding, and one each due to an acute coronary syndrome and an acute ischaemic stroke, respectively. Seven patients had reported an accidental fall at home and this accounted for two of the four patients admitted with a major bleed. At the six-month follow up, 100 of 124 (80.6%) patients were on a rate-control strategy, while the remaining 24 were on a rhythm-control strategy (19 amiodarone, three flecainide, one propafenone, one sotalol).

Discussion

Epidemiologically, the results of this survey were relatively similar to a study from Cameroon,[7] with the mean age of patients being in the mid-sixties. There was a higher preponderance of males in our study. A dominance of native Africans was noted, followed by Asian and Caucasian races. However, the majority of the Asians and Caucasians in our study had been long-term residents in Kenya.

As in the developed countries, AF prevalence in Africa increases with increasing age. Over 80% of our patients were over 50 years of age, and more than 50% of the total study population were in the over-70-year age bracket. This observation was also reflected in the data from the Heart of Soweto study,[8] where a steep increase in case presentation was noted after 50 years of age.

Consistent with existing data, the relationship between hypertension and the development of AF has been traditionally documented, and is thought to be due to changes in myocyte ultrastructure and physiology.[10] In our population, despite the relatively high background prevalence of RHD,[11,12] hypertension was present in over two-thirds of our AF patients. This supports the notion of aggressive screening and treatment for hypertension, as this is singled out as the most common modifiable risk factor driving this arrhythmia epidemic, even in developing countries. Uncontrolled hypertension then progresses to hypertensive heart disease and heart failure, which again was the next most common predisposition, present in over one-third of our patients.

There are no local guidelines and protocols available for the management of AF, and treating physicians would decide on a rate- or rhythm-control approach, based on either their preference or on international guidelines. Due to the pro-arrhythmogenicity of anti-arrhythmic agents, their inappropriate usage may account for an increased mortality rate of AF in our setting.

It was surprising to note that 15% of patients presented with a TE event as the index presentation of AF. It was even more surprising that one in every five patients who needed to be on anticoagulation was on aspirin, an aspirin–clopidogrel combination or no treatment at all. With a five-fold increased stroke risk with AF, our data not only serves to highlight the gravity of the morbidity associated with undiagnosed AF, but more importantly, inappropriate stroke risk stratification by the treating physicians.

Use of the CHA_2DS_2VASC scoring system[13] may improve the predictive index of a TE event, especially in the $CHADS_2$ score 0–1 cohort. However, its non-validation in the native African population currently limits its utility in our study setting.

Prevalence of the disease in the elderly and the risk of major bleeding with oral anticoagulation form a sinister recipe for complications in AF. This was highlighted by accidental falls reported in 5.6% of patients, and re-admissions for major bleeding in 3.2% of patients. In an environment with poor infrastructure and emergency medical services, physician choice of antiplatelets over oral anticoagulants, even in patients needing anticoagulation may be understandable.

The study site, being a private teaching hospital, may have introduced a sampling bias, hence the significantly low proportion of patients with rheumatic valvular disease in our cohort. Additionally, performing echocardiography for only patients who had clinical evidence of RHD may also have accounted for the low numbers of valvular AF in our study, despite a significant background prevalence of RHD.

Our study had several other limitations. (1) Due to the retrospective design, classification of AF subtypes had to be made on available medical records. For patients presenting in the last six months of the study, an inadequate length of follow up prevented appropriate categorisation of these patients. (2) An echocardiographic evaluation was not available for all patients. This would have provided supplementary data on the presence and severity of structural heart disease, and assist in better characterising both valvular and non-valvular AF. (3) A longer follow-up period to assess for hard end-point complications of AF was not possible due to patients returning for medical care only when severely ill.

Conclusion

Clinical characteristics of AF in Kenya are similar to data from other parts of Africa. However, non-valvular AF is more predominant in our setting, with hypertension, heart failure and diabetes being the most common associated co-morbidities. A rate-control modality using digoxin and beta-blockade is the predominant treatment strategy. Stroke risk assessment and stratification is sub-optimally performed in Kenya, with a significant proportion of eligible patients not receiving anticoagulant therapy. Regional data on risk factors and complications of AF should be pooled to generate locally tailored guidelines in an attempt to achieve better adherence to the provision of AF care.

We thank Dr Barbara Karau, Benedict Akoo and the Medical Records Department of the Aga Khan University Hospital. This study complies with the Declaration of Helsinki, and the research protocol was approved by the ethics committee of the Aga Khan University Hospital, Nairobi, and informed consent of the subjects was obtained.

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Cardioprotective and anti-hypertensive effects of *Prosopis glandulosa* in rat models of pre-diabetes

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Abstract

Aim: **Obesity and type 2 diabetes present with two debilitating complications, namely, hypertension and heart disease. The dried and ground pods of *Prosopis glandulosa* (commonly known as the Honey mesquite tree) which is part of the Fabaceae (or legume) family are currently marketed in South Africa as a food supplement with blood glucose-stabilising and anti-hypertensive properties. We previously determined its hypoglycaemic effects, and in the current study we determined the efficacy of *P glandulosa* as anti-hypertensive agent and its myocardial protective ability.**

Methods: **Male Wistar rats were rendered either pre-diabetic (diet-induced obesity: DIO) or hypertensive (high-fat diet: HFD). DIO animals were treated with *P glandulosa* (100 mg/kg/day for the last eight weeks of a 16-week period) and compared to age-matched controls. Hearts were perfused *ex vivo* to determine infarct size. Biometric parameters were determined at the time of sacrifice. Cardiac-specific insulin receptor knock-out (CIRKO) mice were similarly treated with *P glandulosa* and infarct size was determined. HFD animals were treated with *P glandulosa* from the onset of the diet or from weeks 12–16, using captopril (50 mg/kg/day) as the positive control. Blood pressure was monitored weekly.**

Results**: DIO rats and CIRKO mice: *P glandulosa* ingestion significantly reduced infarct size after ischaemia–reperfusion. Proteins of the PI-3-kinase/PKB/Akt survival pathway were affected in a manner supporting cardioprotection. HFD model: *P glandulosa* treatment both prevented and corrected the development of hypertension, which was also reflected in alleviation of water retention.**

Conclusion: ***P glandulosa*** **was cardioprotective and infarct sparing as well as anti-hypertensive without affecting the body weight or the intra-peritoneal fat depots of the animals. Changes in the PI-3-kinase/PKB/Akt pathway may be causal to protection. Results indicated water retention, possibly coupled to vasoconstriction in the HFD animals, while ingestion of *P glandulosa* alleviated both. We concluded that treatment of pre-diabetes, type 2 diabetes or hypertension with *P glandulosa* poses possible beneficial health effects.**

Keywords: *Prosopis glandulosa*, hypertension, cardioprotection, PKB, insulin resistance

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Obesity and type 2 diabetes present with two debilitating complications, namely, hypertension and heart disease. The dried and ground pods of *Prosopis glandulosa* (commonly known as the Honey mesquite tree) which is part of the Fabaceae (or legume) family are currently marketed as a food supplement with blood glucose stabilising and anti-hypertensive properties in South Africa. In the past, the pods of this tree were used as the primary foodstuff for the residents of the south-western regions of the North American deserts and these trees are still widely distributed across a large portion of the south-western United States.[1] The pods are composed of 80% carbohydrate, 13% protein, 25% fibre and 3% fat, and grinding of the plant is thought to improve its use.[2]

Obesity is currently classified as a pandemic and is recognised as the leading cause in the development of the metabolic syndrome. The metabolic syndrome is described as a cluster of pathophysiology outlined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) and the European Group for the Study of Insulin Resistance, to include insulin resistance or glucose intolerance (pre-diabetes), type 2 diabetes, hypertension and atherogenic dyslipidaemia.[3,4] In addition, all of these factors can be considered independent risk factors for the development of cardiovascular disease.[3]

According to the World Health Organisation (WHO), non-communicable diseases such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes are currently (updated June 2011) the leading causes of mortality in the world.[5] This invisible epidemic is an under-appreciated cause of poverty and hinders economic development in many countries. The burden is growing and the number of people, families and communities afflicted is increasing.

The time-line for development of overt type 2 diabetes is described as developing over many years. The cardiovascular consequences of this so-called 'ticking clock' hypothesis, starting from obesity and culminating in type 2 diabetes, is present from the early pre-diabetic stages.[6]

In view of the scarcity and cost of modern oral hypoglycaemic agents, plant-based therapies for the treatment of diabetes are gaining considerable prominence.[7] According to these authors more than 400 plant species have been described as having hypoglycaemic activity. However, not all of these substances have been researched scientifically to validate their efficacy.

We have researched a product from one such plant species, consisting solely of the dried and ground pods of the plant *P glandulosa,* for hypoglycaemic properties.[8] In addition, potent anti-infective and anti-parasitic compounds have also been isolated from this plant.[9]

In view of the hypoglycaemic effects of *P glandulosa*, as well as its ability to partially restore the function of pancreatic tissue and increase cardiomyocyte insulin sensitivity,[7] we set out to determine the cardiovascular effects of treatment, using a well-characterised rat model of obesity and pre-diabetes with known cardiovascular insufficiency and endothelial dysfunction.[10,11] In addition, using a rat model of high-fat feeding known to develop hypertension,[12] we determined whether *P glandulosa* had any effects on the development of high blood pressure.

Models

1. Diet-induced obesity (DIO)

As described previously,[10] Wistar rats (180–200 g) were randomly divided into a control and diet group. The DIO group was fed a diet of normal rat chow supplemented with sucrose and condensed milk for a basic period of eight weeks. From weeks eight to 16 the rats were treated with *P glandulosa* (100 mg/kg/day) set in jelly/gelatine blocks and given to each one individually according to the weight of the animal.[8] This was done to ensure absolute compliance and dose control. The dose of *P glandulosa* was calculated as previously described.[8]

The diet to induce pre-diabetes in the animals was based on hyperphagia.[13] Animals were anaesthetised with sodium pentobarbital (160 mg/kg, intra-peritoneally) before experimentation. At the time of sacrifice, their body weight and the weight of the intra-peritoneal fat were noted and trunk blood was collected for biochemical analyses. For Western blot analyses, the hearts were removed, immediately snap-frozen in liquid nitrogen and stored at –80°C.

2. High-fat diet (HFD)

To induce high blood pressure, the rats were fed a diet containing the following per kg of food: cooking fat 400 g, fructose 100 g, casein 100 g, cholesterol 10 g, and rat chow pellets 390 g. Blood pressure was monitored on a weekly basis over 16 weeks. Treatment with *P glandulosa* (100 mg/kg/day) given in jelly blocks was either started at the onset of the diet to study the effect on prevention of the development of hypertension, or after a period of 12 weeks of the HF diet to study its anti-hypertensive effects. Rats treated with captopril (50 mg/kg/day) from the onset of the diet were included as a positive control. All animals were also placed individually in metabolic cages in order to collect urine samples.

3. CIRKO mice

A mouse model of animals with a cardiac conditional ablation of the insulin receptor was used in conjunction with their C57Bl6 littermates.[14] Mice were fed normal chow and treated with *P glandulosa* at a similar dose to that of the rats for a period of eight weeks before experimentation.

Methods

Animals had free access to food and water and were kept on a 12-hour day/night cycle in the Central Research Facility of the Faculty of Health Sciences of the University of Stellenbosch. The study conformed to the revised South African National Standard for the Care and Use of Animals for Scientific Purposes (South African Bureau of Standards, SANS 10386, 2008) and was registered with the Committee for the use of animals in research of the University of Stellenbosch – numbers P05/11/013 and P07/11/020.

The *P glandulosa* plant material was originally obtained from naturally growing plants. The material was handled according to a patented and standardised procedure[8] and pre-packed in capsules for human consumption, which we emptied and weighed. The voucher specimen was reported previously.[8]

Plasma glucose levels were determined in the fasting state. Blood was obtained via a tail prick and glucose levels were determined using a conventional glucometer (Cipla MedPro). Plasma was stored at –80°C in a Snijders Scientific Ultracool (Tilburg, the Netherlands) and insulin levels were determined using a coat-a-count assay (Diagnostic Products).

Intra-peritoneal glucose tolerance curves (IPGTTs) were generated in the animals after an 18-hour fast. Animals were injected intra-peritoneally with 1 g/kg of a 50% sucrose solution and blood glucose levels were monitored over a 120-min period.

After removal, the hearts were arrested in ice-cold Krebs Henseleit (KH) medium (in mM: NaCl 119, $NaHCO_3$ 25, KCl 4.75, KH_2PO_4 1.2, $MgSO_4.7H_2O$ 0.6, Na_2SO_4 0.6, $CaCl_2.2H_2O$ 1.25, glucose 10) and immediately (within 30 sec) mounted onto the aortic cannula of a perfusion rig. The pulmonary vein was connected to a second cannula in order to perform perfusions in the working-heart mode with a preload of 15 cm H_2O and an afterload of 100 cm H_2O, as described previously.[15] The perfusion medium was continuously gassed with 95% O_2/5% CO_2. Hearts were fitted with a temperature probe and the temperature was kept constant at 36.5–37°C.

After a stabilisation period of 30 min, rat hearts were subjected to 35-min regional ischaemia by coronary artery ligation, followed by reperfusion for one hour, as described previously.[15] Infarct size was determined according to a well-established protocol,[15] followed by planimetry, and expressed as a percentage of the area at risk. Planimetry was performed blind by a third party.

Mouse hearts were perfused retrogradely, meaning via the aorta without a connection to the pulmonary vein. After the 30-min stabilisation period, the hearts were subjected to 20-min normothermic ischaemic cardiac arrest (NICA) by stopping all perfusion. This was followed by one hour of reperfusion, after which the infarct development through the whole heart was determined as described above.

To measure blood pressure, rats were placed in restraining holders with a dark nose cone to calm them. The restrainers were placed on a heating pad (32 ± 2°C) to warm the rat and maintain blood flow to the tail. Animals were placed in the restrainers for at least five minutes before monitoring the blood pressure using a computerised tail-cuff blood pressure monitor (Kent Scientific Corporation, Connecticut, USA). Prior to commencement of the experiment, rats were subjected to the above procedure daily for at least a week to train the animals for the procedure and to avoid stress in the rats during experimental determinations.

Animals were placed individually in metabolic cages and the volume of urine was determined over a period of 24 hours.

TABLE 1. BIOMETRIC DATA – MODEL 1: DIO

	Control	*Control* + P glandulosa	*DIO*	*DIO* + P glandulosa
Weight	433.7 ± 9.3	438.6 ± 9.3	507.7 ± 22.9***	534.3 ± 11.7***
Intra-peritoneal fat	18 ± 2.7	11 ± 1.8	28.0 ± 1.74***	34 ± 1.4***
Blood glucose (mmol/l)	5.42 ± 0.17	5.4 ± 0.18	6.4 ± 0.17*	5.6 ± 0.19
Serum insulin (µU/ml)	17.12 ± 0.8	14.07 ± 1.50	34.33 ± 9.06*	35.93 ± 10.21*
HOMA-IR	4.73 ± 0.71	3.40 ± 0.40	8.96 ± 2.65*	7.88 ± 3.30*

*$p < 0.05$ vs the respective control; ***$p < 0.001$ vs the respective control. Analysis by two-way ANOVA, $n = 6$ per group.

Western blotting

Frozen tissues were pulverised with a liquid nitrogen pre-cooled mortar and pestle and then extracted in lysis buffer containing in mM: Tris-HCl 20 (pH 7.5), EGTA 1, EDTA 1, NaCl 150, Na_2VO_3 1, beta-glycerophosphate 1, sodium-pyrophosphate 2.5, PMSF 0.3, Triton X-100 1% (v/v) plus 10 µg/ml leupeptin and aprotinin, respectively, using a Polytron PT10 homogeniser, 2 × 4 sec, at setting 4. Lysates were cleared from particulate matter by centrifuging for 15 min at 14 000 rpm in a microfuge (Eppendorf Mini-spin plus, Hamburg, Germany) and the protein content was determined by the method of Bradford.[16] Samples were diluted in Laemmli sample buffer, boiled for 5 min and stored at –80°C.

Equal amounts of cytosolic proteins were separated on a SDS poly-acrylamide gel and electro-transferred to Immobilon™-P PVDF membranes. Transfer and equal loading of proteins was determined with Ponceau red reversible stain. The membranes were blocked for two hours in Tris-buffered saline (TBS) containing 0.1% Tween-20 and 5% non-fat milk powder and incubated overnight in the primary antibodies (diluted in TBS–Tween according to the manufacturer's instructions). The following antibodies from cell signalling were used: insulin receptor beta-subunit, phospho-PI3K P85 (Tyr458), total and phospho-PTEN (Ser380/Thr382/383), total and phospho-PKB/Akt (Ser473), Glut 1 and Glut 4.

Blots were stripped using a 5-min incubation in 2% NaOH after washing in distilled water and re-probed with a beta-tubulin antibody to confirm equal loading. Bands were visualised using the ECL detection system and quantified by laser-scanning densitometry with suitable software (Silk Scientific Inc, USA). For comparison purposes, total pixels of bands were expressed as a ratio of the mean of the controls on the same blot.

Statistical analyses

Data are presented as mean ± SEM and were analysed using either a one-way or two-way ANOVA followed by a Bonferroni *post-hoc* test for differences between groups. The blood pressure effects were analysed using a repeated-measures two-way ANOVA. Statistical significance was set at $p < 0.05$.

Results

After the 16-week diet animals from model 1 (DIO) presented with significantly increased body- and intra-peritoneal fat weight (Table 1). As summarised in Table 1, these animals had significantly elevated blood glucose and insulin levels, leading to an increased homeostatic model assessment of insulin resistance index (HOMA-IR), indicative of whole-body insulin resistance.

In neither control nor DIO animals did the treatment with *P glandulosa* have any effect on the body weight or the intra-peritoneal fat weight of the animals. After treatment of the DIO animals with *P glandulosa*, the blood glucose levels were no longer significantly elevated compared to the treated controls but the HOMA-IR was still significantly higher. However, as shown in Fig. 1, the two-hour blood glucose values after intra-peritoneal glucose tolerance analyses were significantly lower in the treated DIO animals, underscoring a slight effect on blood glucose handling, as previously reported.[8]

Infarct size

After 16 weeks of the obesity-inducing diet, the *ex vivo* perfused hearts of the DIO animals presented with significantly larger infarct sizes, calculated as percentage of the area at risk, than the hearts from the control animals (DIO 49.48 ± 3.25 vs control 40.62 ± 2.21%, $p < 0.05$, $n = 17$ per group). The area at risk did not differ between the groups and averaged 54.13 ± 2.21%.

An eight-week treatment regime with *P glandulosa* in conjunction with the diet significantly improved the ability of the hearts to withstand a period of ischaemia, and smaller infarcts developed. There was no significant effect in the hearts from control rats (Fig. 2). Two-way ANOVA indicated a significant effect of the treatment on infarct size ($p < 0.01$).

To confirm these results and rule out any effect of insulin levels on the cardioprotective role of *P glandulosa*, we used a mouse model with a conditional ablation of the insulin receptor in cardiomyocytes.[14] Subjecting these animals and their normal C57Bl6 littermates to *ex vivo* perfusion and NICA, followed by reperfusion, we found that the hearts of both control and CIRKO mice were protected by the *P glandulosa* treatment. This was

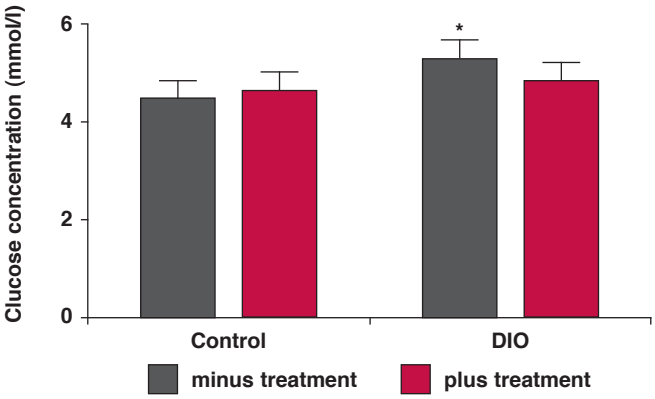

Fig. 1. DIO or control chow-fed rats for 16 weeks with *P glandulosa* treatment for the last eight weeks were subjected to intra-peritoneal glucose-tolerance testing after an 18-hour fast. Blood was collected by tail prick and analysed over a 120-min period using a commercial glucometer. Data given are the 120-min values. *$p < 0.05$ vs control and DIO plus treatment, $n = 6$ per group.

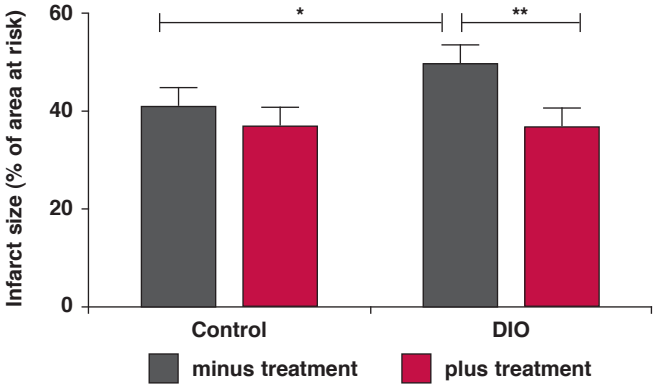

Fig. 2. After the 16-week diet plus *P glandulosa* treatment, isolated hearts from DIO rats were perfused *ex vivo* in the working-heart mode. They were subjected to regional ischaemia as described in Methods. Infarct size was determined as a percentage of the area at risk of infarction. *$p < 0.05$, **$p < 0.01$, $n = 15–17$ per group.

demonstrated by the significantly smaller infarct size observed (Fig. 3). The effect of this treatment was highly significant ($p < 0.001$, $n = 9$ per group) as indicated by two-way ANOVA.

Analyses of proteins forming part of the insulin-signalling cascade

Protection against myocardial damage induced by ischaemia–reperfusion and culminating in the formation of an infarct has been ascribed, among others, to the activity of the phosphatidyl-inositol-3-kinase (PI-3K) pathway. In view of the previously reported improvements in insulin sensitivity of cardiomyocytes, induced by *P glandulosa* treatment,[8] we systematically analysed the proteins involved in this signalling cascade.

As summarised in Table 2 and shown in Fig. 4, hearts from the DIO animals presented with a significantly lower phosphorylated:total ratio of the central protein in this cascade, protein kinase B or Akt. This ratio was significantly improved by treatment. In addition, the expression of the p85 regulatory subunit of the PI-3K enzyme was significantly lower in hearts from the DIO animals, whereas this was not the case after treatment.

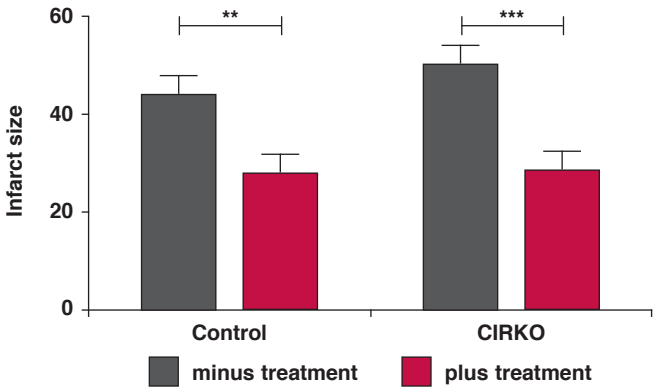

Fig. 3. After the eight weeks of treatment, hearts were removed from the CIRKO mice and perfused *ex vivo* in the Langendorff mode and subjected to NICA as described in Methods. Infarct size was determined throughout the whole heart and expressed as a percentage of the total surface. **$p < 0.01$, ***$p < 0.001$, $n = 9$ per group.

Treatment also resulted in a lower expression of the phosphatase and tensin homologue deleted on chromosome 10 (PTEN) with a higher state of phosphorylation of this enzyme (Fig. 5). Phosphorylation of PTEN further inactivates this enzyme, responsible also for the dephosphorylation of PKB/Akt.[17,18]

Anti-hypertensive effects

As the DIO diet does not cause high blood pressure, we used a modification of a high-fat diet to induce hypertension in the animals.[12] As can be seen in Fig. 5, these animals developed a significant elevation of their blood pressure within four weeks (HFD 135.88 ± 2.0 vs control 125.85 ± 1.9 mmHg, $p < 0.05$, $n = 8$ per group).

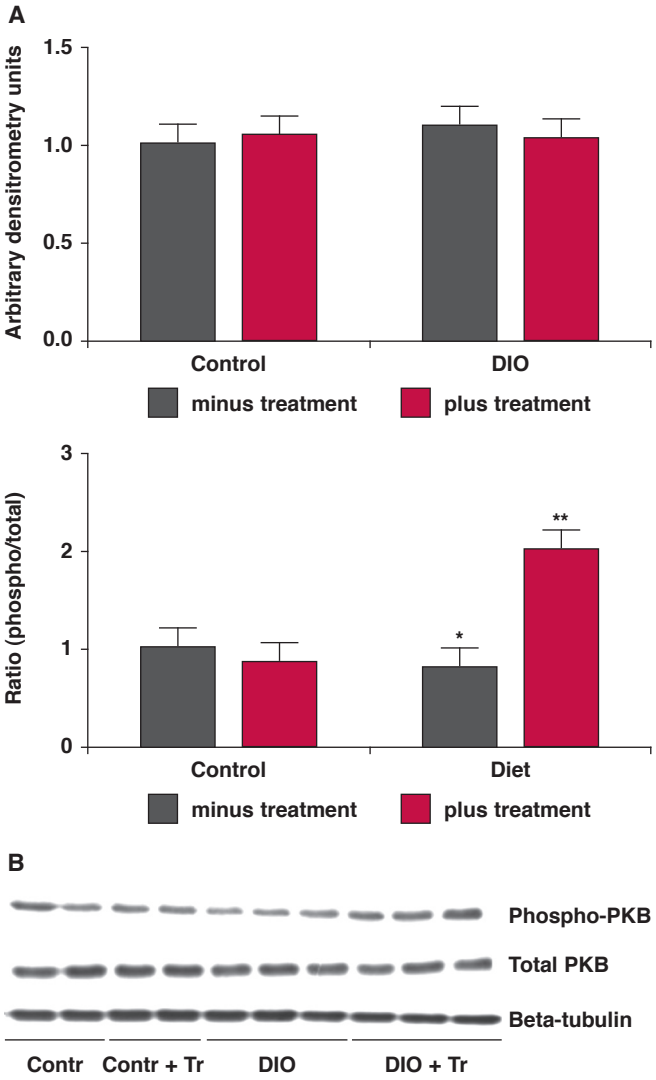

Fig. 4. Hearts from the treated and untreated DIO animals were removed without any intervention and stored in liquid nitrogen. Tissue lysates were prepared and Western blotting was performed as described in Methods. A: bar charts of the expression of PKB protein as well as the ratio of phosphorylated vs total protein. *$p < 0.05$ vs control; **$p < 0.01$ vs untreated DIO, $n = 6$ individual hearts analysed per group. B is a representative blot depicting these proteins and beta-tubulin, used as an indicator of equal loading.

TABLE 2. SUMMARY OF THE WESTERN BLOT ANALYSES OF THE PROTEINS INVOLVED IN THE INSULIN SIGNAL TRANSDUCTION PATHWAY WITH ARROWS INDICATING THE EFFECT INDUCED BY THE DIET ALONE OR THE DIET IN COMBINATION WITH *P GLANDULOSA* TREATMENT. HEARTS WERE FREEZE-CLAMPED IN THE BASAL STATE WITHOUT ANY INTERVENTIONS

Protein	*Effect of diet*	*Effect of treatment*
Glut 1	↔	↔
Glut 4	↔	↔
IR-beta	↔	↔
PKB/Akt	P/T ↓	P/T ↑
p85	↓	↔
PTEN	↔	T ↓ P/T ↑

P = phosphorylated protein, T = total protein; P/T = the ratio of phosphorylated to total protein, $n = 6$ individual hearts per group.

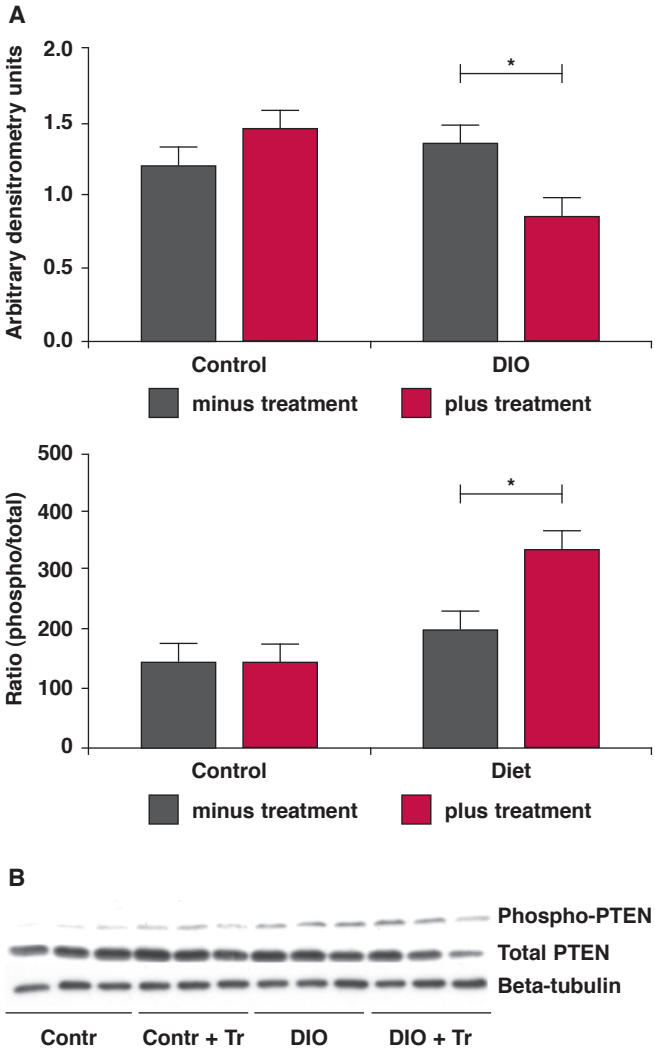

Fig. 5. Hearts from the treated and untreated DIO animals were removed without any intervention and stored in liquid nitrogen. Tissue lysates were prepared and Western blotting was performed as described in Methods. A: bar charts of the expression of the PTEN protein as well as the ratio of phosphorylated vs total protein. *$p < 0.05$, $n = 6$ individual hearts analysed per group. B is a representative blot depicting these proteins and beta-tubulin, used as an indicator of equal loading.

We either pre-treated the animals with *P glandulosa*, starting at the onset of the diet, or we allowed the animals to become severely hypertensive (12 weeks) and then started the treatment. We included a group of animals treated with the angiotensin converting enzyme (ACE) inhibitor captopril from the onset of the diet, as a positive control in this study.

As can be seen in Fig. 6A, captopril prevented the development of hypertension in the animals. Similarly, *P glandulosa* treatment prevented the development of high blood pressure in these animals when given in conjunction with the high-fat diet. *P glandulosa* treatment did not significantly affect the animals on the control diet (Fig. 6B). In addition, treatment of already hypertensive animals (week 12) with *P glandulosa* normalised their blood pressure within two weeks.

Effects on urine production

Measuring the urine output of the animals by keeping them separately in metabolic cages showed that after the 12-week treatment period, the urine output of animals on the control diet was 17.37 ± 0.8 ml while those on the high-fat diet had a significantly lower urine output of 9.8 ± 0.55 ml ($p < 0.001$, $n = 9$ per group).

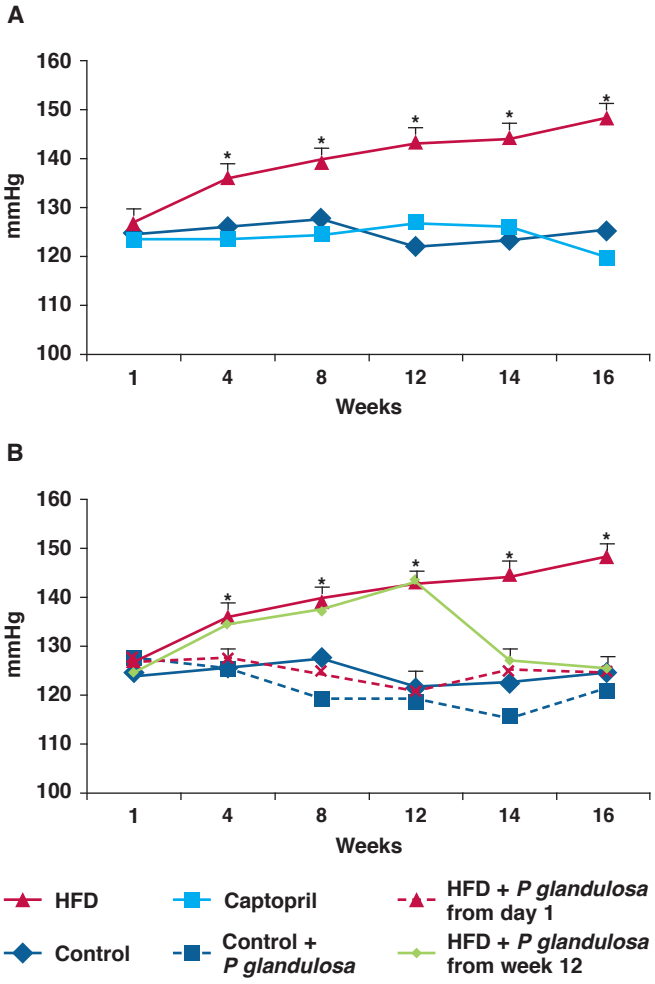

Fig. 6. Rats were fed a high-fat diet for 16 weeks and blood pressure was monitored on a weekly basis as described in Methods. *$p < 0.001$ vs control and captopril, $n = 9$ per group. A: HFD vs captopril, B: HFD vs *P glandulosa* treatment.

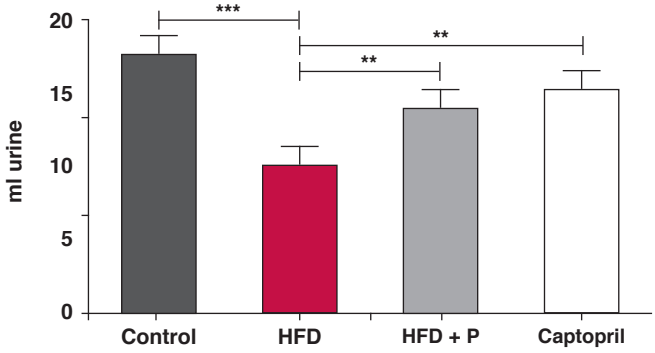

Fig. 7. Rats on the high-fat diet were individually placed in metabolic cages for the collection of urine over a 24-hour period. Data were collected at 12 weeks after the diet was started. **$p < 0.01$, ***$p < 0.001$, $n = 9$ per group.

Captopril treatment elevated the urine output to 15 ± 0.9 ml. Treatment with *P glandulosa* also elevated urine output to 13.68 ± 0.80 ml ($p < 0.01$, $n = 9$ per group) (Fig. 7).

Discussion

Currently, the world is suffering from a silent epidemic starting with obesity and culminating in type 2 diabetes.[3] Two of the most debilitating complications of obesity, especially centrally located obesity, responsible for the high morbidity and mortality associated with such patients are hypertension and heart disease.[19,20] In view of the need for effective medication to supplement lifestyle changes to control these disease states, utilisation of plant-based therapies are currently strongly advocated.[7,21] Such therapies offer potentially cost-effective management but need scientific validation of their effects.

Previous studies from our laboratory demonstrated that the dried and ground pods of the *P glandulosa* tree have a potential benefit in the management of both type 1 and type 2 diabetes.[8] In view of the insulin-sensitising effects on isolated cardiomyocytes from rats treated with *P glandulosa*, we aimed to determine whether this product has any cardioprotective or anti-hypertensive effects.

In this study, we used three different animal models. The first was a model of pre-diabetes (DIO), as also indicated by the biometric data presented in Table 1. These animals were fed an obesity-inducing diet containing only 16% fat.[11,13] DIO animals become insulin resistant but not diabetic, as the blood glucose levels never rose above ~ 6.5 mmol/l. This was however significantly higher than the levels found in the control, chow-fed animals. In order to keep the blood glucose levels low, the animals presented with high plasma insulin concentrations.

Although *P glandulosa* treatment did not significantly alter these parameters, the clinically important two-hour blood glucose values after a glucose tolerance test were significantly higher in the DIO animals and were effectively lowered by the treatment (Fig. 1). This underscores the slight effect on blood glucose handling previously reported.[8]

Determination of infarct size in *ex vivo* perfused rat hearts as a measure of myocardial damage incurred by ischaemia followed by reperfusion, is taken as the gold standard to prove cardioprotection.[15] We previously showed that hearts from the DIO rats developed larger infarct sizes when subjected to regional ischaemia followed by reperfusion.[10]

After eight weeks of treatment of DIO rats or CIRKO mice with *P glandulosa*, it was clearly demonstrated that there was an infarct-sparing effect elicited by ingestion of this plant material (Figs 2, 3). As the CIRKO mice do not possess a myocardial insulin receptor, the protection found in these animals confirmed the results obtained in the rat model and underscores that protection does not occur via the insulin-secretory effects of *P glandulosa*, as previously reported.[8]

One of the best-described and researched mechanisms of protection of the heart against ischaemia–reperfusion injury and infarction is activation of the PI-3K, PKB/Akt pathway, normally activated by various extracellular substances.[22-24] Activation of this pathway has several anti-apoptotic effects, leading to limitation of the development of an infarct after ischaemia.

In addition, activation of PKB/Akt is a pre-requisite for glucose uptake by the heart.[25] Myocardial glucose is taken up via the two transporters Glut 1 and Glut 4. An improved ability to import and utilise glucose is cardioprotective when the heart is subjected to the absence of oxygen, as induced by ischaemia. The heart then uses the energy generated by glycolysis to protect itself.

Measurement of the expression of both Glut 1 and Glut 4 showed no differences between hearts from control and DIO rats. However, the lower ratio of phosphorylated to total protein of PKB/Akt found in hearts from the DIO animals may have been detrimental during an ischaemic incident. In addition, there was lower expression of the p85 subunit of PI-3K documented in these hearts, which may have exacerbated this effect.

Both of these detrimental changes were improved by *P glandulosa* treatment. The changes documented in the phosphatase PTEN will further the positive effects found in both PI-3K and PKB/Akt as the lower expression and elevated phosphorylation of this enzyme will elevate the activity of PKB/Akt when the latter is stimulated.[18] PTEN normally inactivates PKB/Akt.[17] These changes may play a central role in the protection that *P glandulosa* treatment confers on the heart.

The second rat model was aimed at specifically inducing the development of hypertension. A modification of a high-fat diet was used (HFD).[12] These animals, in contrast to the DIO animals, developed severe hypertension within a four-week period, as shown in Fig. 6A and B. Not only was *P glandulosa* treatment able to prevent the development of hypertension when given in conjunction with the high-fat diet, but it normalised elevated blood pressure within two weeks.

The hormonal effects associated with a high-fat diet in rats, namely elevated vasopressin as well as activation of the renin–angiotensin system, leading to elevated aldosterone levels may both be involved in the development of hypertension in these animals.[26-28] Vasopressin, the anti-diuretic hormone leads to water retention and therefore the development of high blood pressure. In addition, it is associated with vasoconstriction.[28] Similar effects can be expected from elevated sympathetic activity, leading to elevated aldosterone levels. Measuring the 24-hour urine output of the HFD animals underscored this, as the HFD animals had a significantly lower urinary output than the controls.

According to Lee and Blaufox,[29] a volume of 16–17 ml urine can be expected from normal animals in the weight range of our experimental rats (control 258.49 ± 15.03 vs HFD 327 ± 12.90 g, $p < 0.05$, $n = 14$ per group) while a high-fat diet will result in concentration of this volume, indicating water retention. It can also be speculated that, in parallel with the latter effect, there will be vasoconstriction, contributing to the observed hypertension.

The treatment with *P glandulosa* was able to alleviate this, thereby adding to the myocardial protection observed. To highlight this argument, in the present study both the ACE inhibitor and *P glandulosa* treatment significantly improved urinary flow of the animals, in conjunction with lowering the blood pressure. Although this was not measured in the current study, we speculate that vasopressin production and aldosterone levels were elevated in the HFD rats. *P glandulosa* treatment may affect the levels of either of these hormones, or it may provide a different, hitherto unrecognised mechanism of lowering blood pressure in the animals.

Conclusion

The present study has confirmed our previous results that the dried and ground pods of the *P glandulosa* tree have anti-hyperglycaemic effects. In addition we have conclusively shown that this treatment was cardioprotective, as determined by the infarct-sparing effects, and anti-hypertensive without affecting the body weight or the intra-peritoneal fat depots of the animals. The results indicated that key proteins involved in the cardioprotective PI-3-kinase/PKB/Akt pathway were affected in a manner that may be causal to this protection.

With regard to the anti-hypertensive effects, the results indicated water retention, possibly coupled with vasoconstriction in the HFD animals, while ingestion of *P glandulosa* alleviated both water retention and hypertension. Treatment of pre-diabetes, type 2 diabetes or hypertension with *P glandulosa* therefore poses potentially beneficial health effects besides its anti-hyperglycaemic effects.

We declare a contractual agreement between the University of Stellenbosch and Dormell Properties 528 (Pty) Ltd (registration number: 2005/031723/07), the company licensing Conbrio Brands (Pty) Ltd to distribute the dried and ground pods of *Prosopis glandulosa*. We further declare that there was no personal financial gain for the researchers involved in this work.

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Low prevalence of abdominal aortic aneurysm in the Seychelles population aged 50 to 65 years

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Abstract

The prevalence of abdominal aortic aneurysm (AAA) and its risk factors are well known in Western countries but few data are available from low- and middle-income countries. We are not aware of systematically collected population-based data on AAA in the African region. We evaluated the prevalence of AAA in a population-based cardiovascular survey conducted in the Republic of Seychelles in 2004 (Indian Ocean, African region). Among the 353 participants aged 50 to 64 years and screened with ultrasound, the prevalence of AAA was 0.3% (95% CI: 0–0.9) and the prevalence of ectatic dilatations of the abdominal aorta was 1.5% (95% CI: 0.2–2.8). The prevalence of AAA in the general population seemed lower in Seychelles than in Western countries, despite a high prevalence in Seychelles of risk factors of AAA, such as smoking (in men), high blood pressure and hypercholesterolaemia.

Keywords: abdominal aortic aneurysm, screening, ultrasonography, population-based study, African region

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Recent clinical trials have demonstrated a reduction in mortality related to abdominal aortic aneurysm (AAA) in men systematically screened with ultrasound at age 65 to 74 years.[1-4] Risk factors of AAA include male gender, age and smoking, and to a lesser extent hypertension, hypercholesterolaemia and overt atherosclerosis.[5,6] The US Preventive Services task force has recommended the screening of AAA in men aged 65 to 75 years who have ever smoked.[7]

In view of the limited population-based data on AAA available in low- and middle-income countries,[8,9] and none that we are aware of in the African region, we examined the prevalence of AAA in a population-based survey of cardiovascular risk factors conducted in the Republic of Seychelles in 2004. Seychelles is a rapidly developing middle-income island state located in the Indian Ocean approximately 1 800 km east of Kenya (African region).

In 2004, 42.8% of the population was aged less than 25 years and 9.7% was 50 to 64 years old. The majority of the inhabitants is of African descent and a high prevalence of several cardiovascular risk factors was previously demonstrated in the population, particularly high blood pressure.[10,11]

Methods

A random age- and gender-stratified sample of all inhabitants aged 25 to 64 years was drawn using computerised data of a national census carried out in 2002 and thereafter regularly updated by civil status authorities. Methods of the survey have been described previously.[12]

From a total of 1 456 eligible participants (participation rate 80.2%), 566 were aged 50 to 64 years, and 474 took part in the survey (participation rate 83.7%). We restricted the AAA screening to this age range because AAA is rare at younger ages.[13,14]

Ultrasound (General Electric LogiqBook connected to a 2–5-MHz transducer, General Electric Health Care, United Kingdom) was performed in the 353 consecutive individuals who took part in the survey during a 17-week period when a sonographer was available. The abdominal aorta was scanned from its most proximal visualisable segment to the iliac bifurcation, both transversally and longitudinally. Its antero–posterior and transverse diameters were measured at their maximal sizes, and the larger of the two values was recorded.

Results

None of the screened subjects had a history of AAA. The maximal diameter of the aorta could be well visualised in 329 of the 351 eligible participants. AAA, defined as a diameter ≥ 30 mm, was found in only one man (diameter 31 mm, age 59 years, never-smoker, obese, cholesterol 6.7 mmol/l, hypertensive, diabetic). An ectatic dilatation of the aorta (diameter 25–29 mm), which can be regarded as precursor of AAA,[15] was found in four additional participants: three men and one woman (age: 52, 59, 62 and 63; two ex-smokers; all overweight; three with hypertension; two with diabetes; total cholesterol: 5.0, 6.0, 6.3 and 7.4 mmol/l, respectively).

The prevalence of aneurysm or ectasy of the abdominal aorta of all participants aged 50 to 64 years is shown in Table 1. In the same age category, the prevalence was 15% for current smokers (28% in men, 3% in women), 22% for ex-smokers (32% in men and 3% in women), 70% for overweight participants (body mass index ≥ 25 kg/m^2), 33% for obesity (≥ 30 kg/m^2), 70% for high blood pressure (≥ 140/90 mmHg or treatment), 27% for diabetes mellitus and 63% for elevated total cholesterol levels (≥ 5.2 mmol/l).

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TABLE 1. PREVALENCE OF ANEURYSM OR ECTASY OF THE ABDOMINAL AORTA IN THE GENERAL POPULATION OF SEYCHELLES AGED 50–64 YEARS

	Men (n = 151)		*Women* (n = 178)		*Total* (n = 329)	
	%	*95% CI*	*%*	*95% CI*	*%*	*95% CI*
Aneurysm	0.7	0–2.0	0		0.3	0–0.9
Ectasy	2.0	0–4.2	0.6	0–1.7	1.2	0–2.4
Either	2.7	0.1–5.2	0.6	0–1.7	1.5	0.2–2.8

Discussion

The prevalence of AAA in the general population aged 50 to 64 years seemed lower in Seychelles than in North America or Europe. In North America, in participants aged 50–54/55–59/60–64 years, the prevalence of AAA was 0.9/2.5/4.2% in smokers and 0.2/0.5/0.9% in non-smokers, respectively.[4,7] In Norway, the prevalence of AAA in men/women was 1.9/0% and 6.0/1.1% at ages 45–54 and 55–64 years, respectively.[13] In the Netherlands the prevalence of AAA in men/women was 0.9/0.2% and 3.1/0.4% at ages 55–59 and 60–64 years, respectively.[16]

In contrast to what was recently described in a population of mainly symptomatic aortic aneurysm patients in Kenya, we did not find a female predominance for the diagnosis of AAA in Seychelles. This was despite the predominant African descent of the population and the prevalence of high blood pressure in the 50- to 64-year age category, which was the leading risk factor associated with aortic aneurysms in this study.[17] This apparent inconsistency might be due to methodological factors, such as gender differences in health-related habits, since the Kenyan study was based on hospital records and not on population-based data.

A low prevalence of AAA in Seychelles might be consistent with a high prevalence of diabetes and the predominantly African descent of the population, which are two factors reported to be inversely associated with AAA.[6,7] It is however at odds with a high prevalence of smoking (in men), high blood pressure and hypercholesterolaemia in the Seychelles population.

Alternatively, we cannot exclude some imprecision in our estimates in view of the relatively small size of our sample and broad confidence intervals, although the population-based design of the study as well as the high participation rate strengthens the reliability of our epidemiological data. On the other hand, the seemingly higher prevalence of aortic ectatic dilatation could announce increasing rates of AAA in the next decades as the population becomes exposed to high risk-factor levels over long periods of time.

Furthermore, because of a high prevalence of AAA risk factors, such as current smoking (28% in men and 4% in women aged 40–49 years) or high blood pressure (35% in the 40–49-year population) in younger age groups with a lower prevalence of 'protective factors' such as diabetes mellitus (11.7% in the 40–49-year population), ectatic lesions might appear at a younger age in Seychelles than in North America or Europe. However, given the small rate of expansion of small lesions over time, the finding of true AAA in subjects aged less than 50 years is unlikely.[18]

Conclusion

Pending further data on the prevalence of AAA in older age categories, our results do not support routine screening of AAA in the selected population. This is consistent with recommendations for populations in Western countries.[5]

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Comparative evaluation of warfarin utilisation in two primary healthcare clinics in the Cape Town area

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Abstract

Background: **Although warfarin remains the anticoagulant drug of choice in a wide range of patients, its narrow therapeutic window makes patients susceptible to a high risk of bleeding complications or failure to prevent clotting. This has necessitated therapeutic monitoring in warfarinised patients. Factors that could be responsible for the fluctuating responses to warfarin vary from pharmacogenetic to concomitant morbidity, diet and medication. In order to assess the quality of management of warfarin treatment in a local primary-care setting, the current study evaluated warfarin utilisation and monitoring records in two hospitals with different patient groups.**

Methods: **A retrospective study was undertaken in the specialised warfarin clinics at Wesfleur and Gugulethu hospitals (Western Cape, South Africa) covering all warfarin-related therapy records over a 12-month period. Data extracted from the patients' folders included age, gender, race, weight, address, concurrent chronic illnesses, treatment and medication, indication for warfarin and INR history.**

Results: **A total of 119 patients' folders were analysed. Attendance at the clinics reflects the demographics and racial distribution of the host location of the hospitals. While all the patients were maintained above the minimum international normalised ratio (INR) value of 2, about 50% had at least one record of INR above the cut-off value of 3.5. However, over a third of the patients (32.2%) had at least one record of INR greater than 3.5 in Gugulethu Hospital, compared to over half (58.3%) in Wesfleur Hospital.**

In total, atrial fibrillation was the most common indication for warfarinisation while hypertension was the most common concurrent chronic condition in warfarinised patients. All patients who received quinolone antibiotics had INR values above the cut-off point of 3.5 within the same month of the initiation of antibiotic therapy, suggesting drug-induced warfarin potentiation. Other co-medications, including beta-lactam antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-ulcer drugs appeared to alter warfarin responses as measured by recorded INR values.

Conclusion: **The study found inter-individual variability in the response to warfarin therapy, which cut across racial classifications. It also confirms the possible influence of concomitant morbidity on patient response to anticoagulant therapy.**

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Warfarin is a racemic mixture of two optically active (R and S) isomers in roughly equal proportions, which is employed for the prevention and treatment of thrombosis signalled by atrial fibrillation, venous thromboembolism and prosthetic heart valves. Warfarin inhibits vitamin K epoxide reductase complex 1 (VKORC1), preventing the intrahepatic recycling of vitamin K epoxide to vitamin K, thus effectively supressing the vitamin K-dependent activation of clotting factors.[1-4]

In addition, warfarin interferes with the function of two important physiological anticoagulant proteins, C and S. S-warfarin has about five times the potency of the R-isomer with regard to vitamin K antagonism.[5,6] Rapidly absorbed following oral absorption, S-warfarin undergoes CYP2C9-mediated metabolism to form 7-hydroxywarfarin, while the metabolism of the R-isomer is catalysed by CYP1A2 to 6- and 8-hydroxywarfarin, by CYP3A4 to 10-hydroxywarfarin, and by carbonyl reductases to distereo-isomeric alcohols.[7-9]

Warfarin has a narrow therapeutic window and to achieve treatment goals with the lowest risk of treatment failure or bleeding complications, therapeutic anticoagulation, as measured by the international normalised ratio (INR), must be achieved and sustained in patients. The dose response for warfarin is unpredictable in individual patients. It is therefore recommended that the INR is monitored daily during the initiation phase, on alternate days for a week after achieving the desired target, and once stabilised, once a month.[10-12] The importance of therapeutic monitoring of warfarin is further emphasised by the fact that warfarin therapy is contraindicated in cases when INR monitoring is not feasible.[13]

Recommended therapeutic ranges of INR are 2.0–3.0 for most disease indications, and 2.0–3.5 with cardiac valve prostheses.[14] Values outside this range may pose safety concerns. Various factors responsible for fluctuating INR in warfarin therapy include poor compliance, dosage error, concurrent illness, liver and kidney dysfunction, concomitant use of other drugs, dietary interaction, laboratory error, and ageing.[15,16]

Inter-individual responses to warfarin may vary due to genetic factors.[17,18] The effects of concomitantly administered drugs on the pharmacokinetics of warfarin have been extensively investigated.[19-21] The pharmacodynamic activity of warfarin is strongly related to the fractions of free (unbound) drug. Therefore drugs that alter the plasma protein binding of warfarin, including valproic acid and non-steroidal anti-inflammatory drugs (NSAIDs), can potentiate the anticoagulant effects of

warfarin.[22] In addition, drugs such as NSAIDs that possess antiplatelet activity can produce additive anticoagulant effects on concurrent administration with warfarin.[23]

Broad-spectrum antibacterial agents, through their effects on the vitamin K-producing gut flora, increase the effect of warfarin.[24] Competitive substrates, inducers and inhibitors of CYP2C9 and CYP3A4 can alter warfarin plasma levels, with consequent alterations in INR.[25] Therefore studies on utilisation and responses of warfarin in different patient groups are important to assess the causes of differences in its clinical response in a specific environment.

In South Africa, primary healthcare anticoagulation clinics play an essential role in warfarin therapy. These clinics are responsible for the education, optimisation and maintenance of anticoagulant therapy in referred patients. The initiation of anticoagulation is usually performed by the referring doctor following appropriate diagnosis and indications. The anticoagulant clinics are responsible for ensuring there are no contraindications to warfarin therapy (especially the presence of severe bleeding, first and third trimester pregnancy, and severe hepatic disorders) and ascertaining compliance to therapy.

The aim of the present study was therefore to evaluate warfarin utilisation in two primary-care anticoagulation clinics in Cape Town, Western Cape, South Africa. The study aimed at retrospective assessment of INR monitoring with consideration of possible influences of co-medication on therapy.

Methods

A retrospective study was undertaken of all warfarin-related prescriptions in the warfarin clinics of Wesfleur and Gugulethu hospitals, covering a 12-month period between June 2008 and May 2009. Wesfleur Hospital is located in Atlantis, an area under the West Coast district municipality with a population of about 140 000 people, the majority being Coloured [the race classification was based on the national census categories, and described as black (Africans), Coloured, Indian and white]. It is a level-two facility which sees an average of 13 000 patients monthly. It runs a warfarin clinic every Friday, managed by a doctor and supported by specialist physicians at New Somerset Hospital, Cape Town, for referrals.

Gugulethu Hospital is situated in the highly populated Gugulethu Township in the City of Cape Town municipality, and is inhabited primarily by blacks. The hospital takes care of about 6 800 patients per month. The warfarin clinic is mostly managed by a nursing sister or staff nurse, who contacts a doctor if the patient's INR results are abnormal.

Data extracted from the patient folders included age, gender, race, weight, address, concurrent chronic illnesses and medication, INR history (monthly INR levels measured in the 12-month period of the study) and indication for warfarin therapy. For the purpose of this study, a cut-off INR level of 3.5 was chosen. Patients above this limit have an increased risk of toxicity, as discussed above. Patients were assigned to the INR > 3.5 group if they had one or more INR levels above 3.5 during the course of the study.

Medications taken concurrently were pre-classified as potentially relevant or non-relevant for drug–drug interactions with warfarin using the South African Medicines Formulary (SAMF). A list of drugs taken concurrently that could result in drug–drug interactions was compiled.

Ethics approval for the project was obtained from the Health Research Ethics Committee of the University of Stellenbosch, and Wesfleur and Gugulethu Hospital managements approved this project.

MS Excel was used to capture the data and STATISTICA version 8 (data analysis software system, www.statsoft.com) (StatSoft Inc, 2008) was used for data analysis. Summary statistics was used to describe the variables. The Chi-square test was used for statistical comparison between groups. A p-value < 0.05 represented statistical significance in hypothesis testing.

Results

A total of 111 patient folders were retrieved and qualified for this study after the exclusion of eight (four from each hospital) due to incomplete data. The demographic variables are summarised in Table 1. The Wesfleur Hospital had more patients (76) on anticoagulant therapy than Gugulethu (35). The racial distribution of the patients reflected the demography of the inhabitants in the hospital locations; 88.1% of the patients in Wesfleur were Coloured while all patients from Gugulethu were black.

There was a significant variation in INR records in both hospitals. While none of the patient records showed an INR less than 2, over a third of the patients (32.2%) had at least one record of INR greater than 3.5 in Gugulethu Hospital, compared

TABLE 1. DEMOGRAPHIC AND INR VALUES FOR PATIENTS FROM WESFLEUR AND GUGULETHU HOSPITALS

	Wesfleur (n = *76*)	*Gugulethu* (n = *35*)
Gender		
Male	37.5	19.4
Female	62.5	80.6
Race		
Black	5.3	100
White	5.3	0
Coloured	88.1	0
Unspecified race	1.3	0
Co-morbidities		
Diabetes	13	23
Hypertension	61	58
Arthritis	16	14
Chronic obstructive airway disease	11	6
Peptic ulcers	8	3
INR values		
INR > 3.5	58.3	32.2
Gender vs INR		
Male: INR > 3.5	51.9 (n = 27)	50 (n = 6)
Female: INR > 3.5	62.2 (n = 45)	28 (n = 25)
Age vs INR		
Patients > 40 years	86.1	58.1
Patients > 40 years: INR > 3.5	59.7 (n = 62)	33 (n = 18)
Patients < 40 years: INR > 3.5	40 (n = 10)	23 (n = 13)
Weight vs INR		
Patients > 70 kg	33.7	82.4
Patients > 70 kg: INR > 3.5	72 (n = 32)	35.7 (n = 14)
Patients < 70 kg: INR > 3.5	55 (n = 31)	33.3 (n = 3)

to 58.3% for Wesfleur Hospital. INR values above 3.5 generally signify high risks of bleeding. The fact that these high records were present despite monthly monitoring further underscores the importance of monitoring of warfarin therapy. It is an indication that without the hospital facility for monitoring, bleeding complications would have arisen in many of the patients.

More female patients (68%) were enrolled in the clinics than males. Considering gender and INR values, female patients' responses to warfarin in Wesfleur Hospital suggested sensitivity, with 61% of them recording at least one INR above 3.5, compared with 23% in Gugulethu Hospital. While gender-based conclusions cannot be made based merely on this observation, several other unreported factors could account for the higher sensitivity in the female patients. This may include concomitant use of birth-control pills and differences in the use of complementary medicines or diets. Differences in body protein-to-fat ratio may also influence the effective plasma warfarin concentration in men and women, with the resultant differences in sensitivity.

Discussion

There appeared to be differences in INR values along age and racial classification. About 64% of Coloured patients above the age of 40 years had INRs above 3.5 in Wesfleur Hospital, whereas in Gugulethu, only 33% of black patients in same age group had a record of at least one INR above 3.5. Although, no study has reported ethnic/genotype variations in warfarin response between Coloured and black people in South Africa, the body of evidence supporting genetic factors as a key influence on the response to warfarin therapy is increasing.

Scott and co-workers[26] investigated the genetic influence on the inter-individual warfarin dose variability among various racial groups. The results revealed significant variation in the genetic expression of CYP2C9, VKORC1 and CYP4F2 in different ethnic groups. The study identified this variation as a major reason why current genotype-guided warfarin dosing algorithms in America may not yield similar results in all ethnic groups. In another study, age, body size and CYP2C9 genotype were found to be crucial determinants of warfarin dose requirements in different racial and ethnic groups.[27]

Earlier findings have shown evidence of the influence of several genes on the response to warfarin therapy, particularly the polymorphisms in CYP2C9 and VKORC1.[28] These studies have consistently revealed that such genetic influence is less common in African–Americans compared to European–Americans and Asians.[29] The recent report of a new genetic variant in VKORC1 among African–American populations, supported by various other warfarin pharmacogenetic studies, suggests a different warfarin maintenance dosing requirement based on genetic composition.[30-33]

Seventy-two per cent of patients with a body weight above 70 kg and 55% below 70 kg in Wesfleur Hospital had an INR above 3.5. In Gugulethu Hospital, 35.7% of those who weighed more than 70 kg and 33.3% of those who weighed less than 70 kg had records of an INR above 3.5. This underscores the absence of weight as a factor in the fluctuation of INR values.

High body weight is an important risk factor of the indications for warfarin therapy in patients with cardiovascular disorders. The pharmacokinetic disposition and activity of warfarin may be influenced by body weight. The effects of weight may therefore be a necessary consideration in the attainment of a stable INR in warfarinised patients.

When the concurrent chronic diseases of patients attending the warfarin clinics were evaluated, hypertension was the most common disease in both hospitals (57.9% in Wesfleur and 51.4% in Gugulethu Hospital). Hypertension is a chronic lifestyle-related disease with body weight and genetic factors as main risk factors. The maintenance of INR values within an acceptable therapeutic range will be particularly taxing in patients with hypertension and other cardiovascular disorders. In addition to the effects of the cardiovascular medications, fluctuations in cardiac function, such as cardiac output and peripheral vascular resistance may play a significant role in the body distribution of and sensitivity to warfarin.

Hypertension may therefore play a significant role in the warfarin response in these patients. Long-standing hypertension is associated with complications such as atrial fibrillation. This is reflected in the data, as atrial fibrillation was the most common clinical indication for the initiation of warfarin therapy at Wesfleur Hospital (47%), and the second most common indication (39%) in Gugulethu Hospital (Table 2).

Concurrent medications that were commonly prescribed for patients on warfarin therapy were antibiotics, especially fluoroquinolones, beta-lactams and metronidazole; non-steroidal anti-inflammatory drugs; paracetamol; and anti-ulcer drugs (Table 3). Quinolones were prescribed at only Wesfleur Hospital, and an elevated INR above the cut-off value of 3.5 was recorded in all the patients concerned in the month that these drugs were taken concurrently.

A similar occurrence was observed with beta-lactams in both hospitals; 71.4% of patients treated with these antibiotics had INR values above 3.5. The effects of broad-spectrum antibiotics on the vitamin K-producing gastrointestinal microflora can potentiate the anticoagulant effects of warfarin. This may explain the observation of elevated INR in warfarinised patients on concomitant antibiotic therapy. In addition, quinolones are

TABLE 2. INDICATIONS FOR WARFARIN THERAPY FOR PATIENTS FROM WESFLEUR AND GUGULETHU HOSPITALS (SOME PATIENTS HAD MULTIPLE INDICATIONS)

Indication	*Wesfleur (%)*	*Gugulethu (%)*
Myocardial infarction	0.3	0
Valve replacement	31	39
Mixed valve disease	35	42
Atrial fibrillation	47	39
Thrombosis/embolism	24	6

TABLE 3. COMPARISON OF DATA FOR CONCURRENT MEDICATION PRESCRIBED VS INR IN PATIENTS AT FOR PATIENTS FROM WESFLEUR AND GUGULETHU HOSPITALS

	Wesfleur		*Gugulethu*	
Medications	*INR > 3.5*	*INR < 3.5*	*INR > 3.5*	*INR < 3.5*
Quinolones	7	0	0	0
Beta-lactams	9	3	1	1
Metronidazole	3	1	1	1
NSAIDs	1	1	1	0
Paracetamol	6	8	3	0
Anti-ulcer drugs	3	3	0	1

substrates and inhibitors of various CYP isoforms including CYP3A4.[34] Pharmacokinetic interaction at the metabolic level with these antibiotics can inhibit warfarin metabolism, leading to increased INR, as observed in this study.

Various other studies have reported an interaction between warfarin and the quinolones, metronidazole and other antibacterial drugs, leading to bleeding complications. Therefore it is reasonable to infer that drug–drug interactions could have been responsible for the observed increase in INR in the month of concurrent administration with warfarin.

The observations presented in this study reflect the complexity of the many factors to be considered in warfarin therapy. A comprehensive overview of such considerations by McMillin and co-workers[35] concluded that pharmacogenetic testing is important in personalised warfarin therapy. While new anticoagulant drugs are entering the drug market and clinical practice, warfarin will continue to be the reference oral anticoagulant.

This is more so in Africa, where cost and accessibility are important considerations. Therefore, studies that will add to current knowledge and improve warfarin therapy among African populations will benefit clinicians, patients, researchers and policy makers in the health sector.

Conclusions

This study confirmed the variability in patient response to warfarin therapy, with race, gender, weight, and concurrent morbidity and medications as some of the important factors. Over a third of the patients had at least one record of an INR above 3.5 in Gugulethu Hospital, compared to over half in Wesfleur Hospital. Differences in the control of INR values were observed with race, weight and age.

Warfarin remains the oral anticoagulant of choice in South Africa. Its use should be closely monitored. Health practitioners must be aware of the various factors responsible for variations in inter-individual responses to warfarin therapy. INR values should be monitored frequently and closely in high-risk patients, including those on co-medications and with cardiovascular co-morbidities.

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Ibadan. In 1987 he was promoted to professor of Cardiothoracic Surgery and then became head of the Department of Surgery, and dean of the Faculty of Clinical Sciences and Dentistry. He was appointed chairman of the Medical Advisory Committee and director of Clinical Services of the University College Hospital. It will be recalled that as part of his passion for promoting excellence, he initiated the delivery of the faculty lecture, which has persisted till now.

Undaunted by the fact that the facilities available in the country for the most part only permitted palliative intervention for many of the conditions he had spent the better part of his life training to manage through definitive intervention, it was noteworthy that he returned to the country's fledging healthcare delivery services. He resisted the lure to 'check out' and leave for greener pastures in the lean years of our economy.

No wonder he had such a passion for training a critical crop of indigenous cardiothoracic surgeons who will provide the much-needed services to the country. It is to his credit that he was instrumental and to a large measure the driving force for the establishment of a training curriculum for cardiothoracic surgery in both the West African College of Surgeons and the Faculty of Surgery of the National Postgraduate Medical College of Nigeria.

Locally, against many odds, he would unfailingly be in the operating room, 'knife to skin' at 7.30 am. He was part of the team of cardiothoracic surgeons that pioneered open-heart surgery in Ibadan. Others included Profs Grillo, Adebonojo and Osinowo. They spent out-of-pocket funds in organising and training perfusionists and operating room and intensive care nurses, using canine models in collaboration with the veterinary faculty, for performing cardiopulmonary bypass procedures. Between 1979 and 1980 the team went on to perform five cardiopulmonary bypass interventions, four of which were successful.

Other surgeons who had been on the scene earlier included Profs John Weaver, Fabian Udekwu and Michael Bankole. Others who participated included Prof Olufemi Jaiyesimi (paediatric cardiologist), Prof Ayodele Falase (adult cardiologist), Prof Olufunsho Akinyemi (anaesthetist) and Prof Taiwo Kolawole (radiologist). The government of the day unfortunately did not accord this priority attention and it was not possible to sustain this noble venture. Prof Adebo worked with the renowned French cardiac surgeon in Paris, Prof Carpentier in making mitral valve repair a viable option to replacement in the management of patients with mitral valve disease, especially from chronic rheumatic heart disease.

Prof Adebo retired from the University of Ibadan in September 2009 after several years of meritorious service but such was the demand for him that the newly established Bowen University went all out to get him as provost of their College of Health Sciences in Iwo as well as chief medical director of their teaching hospital in Ogbomosho. It is to his credit that the University secured the necessary Nigerian University commission as well as the Medical and Dental Council of Nigeria accreditations for its MB BS programme.

In the 'external cardiovascular healthcare arena' Prof Adebo was one of the delegates from 24 African countries in attendance at the conference in Badagry, Lagos, Nigeria in 1981 when the Pan-African Society of Cardiology (PASCAR) was born. He was therefore a foundation member of PASCAR. Along with Prof Ayodele Falase, Femi Jaiyesimi, Asuquo Antia, Adebonojo, Peter Odiambo and Quarte, to mention but a few, he worked assiduously within the organisation from its infancy to ensure that it took firm roots in as many African countries as possible. This organisation was formed in response to the near total lack of interest in cardiovascular disorders by many health authorities on the continent. The aims and objectives set out in 1981 were to:

- promote activities relating to the prevention and treatment of cardiovascular disease
- promote the education and training of cardiovascular disease personnel
- pursue health education programmes relevant to the field of cardiology
- encourage cardiovascular research by the formation of an African Heart Foundation, which will ultimately fund and coordinate relevant research activities on the continent. These were very much in line with his aspirations and passion for cardiovascular healthcare development on the continent.

When PASCAR suffered some setbacks and was in need of reviving, again he was part of the team that gathered in Accra, Ghana in 2004 to put the organisation back on track. Sometimes self-effacing, he was unlike most surgeons I know, very humble despite his well-known reputation as a meticulously careful and successful surgeon. He was elected Vice President West of PASCAR that year and in 2009 elected president, a position he held until he departed this world on 22 September 2012.

In the conduct of the affairs of PASCAR, his principled and fair approach was well known to all. His wisdom and wealth of experience was often brought to bear in difficult circumstances. He was very down to earth in his approach to practical issues

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Is the prevalence of pre-eclampsia affected by HIV/AIDS? A retrospective case–control study

VMS KALUMBA, J MOODLEY, TD NAIDOO

Abstract

Objective: **To evaluate the rate of HIV/AIDS (and CD_4 levels) in women with pre-eclampsia compared to that of a control group.**

Methods: **This was a retrospective case–control study in a tertiary and regional hospital in South Africa. We reviewed the hospital records of women who had delivered in these hospitals between 1 January 2008 and 30 June 2010. The records of women with pre-eclampsia during the study period were analysed. Their HIV infection rate was compared to that of a control group consisting of normotensive healthy pregnant women.**

Results: **Among 492 cases of pre-eclampsia, 130 (26.4%) were HIV infected. In the control group, 183/500 (36.6%) were HIV infected ($p = 0.001$, OR = 0.62, 95% CI: 0.47–0.82). After adjustment to match the difference in maternal age and parity, the rate of HIV/AIDS was lower in the pre-eclamptic group than in the control group ($p = 0.005$, OR = 0.658).**

Conclusion: **The rate of HIV/AIDS was significantly lower in women with pre-eclampsia than in normotensive healthy pregnant women.**

Keywords: HIV, CD_4 count, pre-eclampsia, eclampsia, pregnancy

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Pre-eclampsia, a condition unique to human pregnancy, clinically presents with hypertension and proteinuria after the 20th week of gestation. It complicates 7–10% of pregnancies worldwide and is a major cause of maternal and perinatal morbidity and mortality.[1,2] The current understanding of the aetiology of pre-eclampsia remains unclear.[1] It has been proposed that placental maladaptation leads to decreased utero-placental blood flow and subsequent intracellular hypoxia, resulting in the release of various substances including trophoblastic debris and apoptotic cells. These cause an imbalance between anti-angiogenic and angiogenic factors, resulting in widespread multi-organ endothelial dysfunction.[2] The end result is generalised vasospasm, hypertension and multiple organ affectation.[3]

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Although much of the pathophysiology of pre-eclampsia is known, the current debate is what causes the placental maladaptation. It is believed that immunological factors may be involved in initiating the cascade of events mentioned above.[2,4] Also, pre-eclampsia has been shown to represent an excessive generalised maternal sterile inflammatory response to pregnancy.[5,6] Further, it has been postulated that the frequency of pre-eclampsia may be affected by immunosuppressive conditions such as HIV/AIDS[4,7-9]

Data on the impact of HIV on the rate of pre-eclampsia are conflicting. There is no consensus as to whether HIV-infected women are at a lower, equal or higher risk of developing pre-eclampsia than the general population. Most studies have included small sample sizes and/or have been retrospective chart reviews.[8]

In South Africa, approximately 30% of antenatal patients are infected with HIV.[10] Also, non-pregnancy related infections (mainly HIV/AIDS) and hypertensive disorders are the commonest causes of maternal mortality and morbidity.[11] Hence, South Africa represents an ideal site for a study involving HIV and pre-eclampsia.

The aim of this study was to evaluate the association between HIV infection and pre-eclampsia. To test the hypothesis that women with pre-eclampsia are less likely to be affected by HIV/AIDS, the rate of HIV in pre-eclamptics was compared to that of a control group without pre-eclampsia. In addition, the CD_4 count levels between the two groups were compared to test the hypothesis that immune-suppression could have a protective effect against pre-eclampsia.

Methods

This was a retrospective case–control study conducted at Grey's and Edendale hospitals (a tertiary and a regional hospital, respectively) in Pietermaritzburg, South Africa. The maternity birth registries in the two study sites were reviewed.

Women who had delivered between January 2008 and June 2010 with a diagnosis of pre-eclampsia were identified and their hospital files were retrieved from the medical registry. Those meeting the inclusion criteria were selected and all relevant data were collected on a structured data sheet until the estimated sample size was reached. The inclusion criteria were a diagnosis of pre-eclampsia, known HIV status, singleton pregnancy and no evidence of other chronic medical conditions, namely hypertension, diabetes, renal disease and connective tissue disease.

The exclusion criteria were women with unknown/unrecorded HIV status, multiple pregnancy and chronic hypertension. Subsequently, an equivalent number of women without pre-eclampsia (control group) were randomly selected to match the case criteria. With the exception of the diagnosis of pre-eclampsia, the inclusion and exclusion criteria of the controls were similar to those of the cases.

The SOMANZ (Society of Obstetric Medicine of Australia and New Zealand) classification and definitions of hypertensive disorders of pregnancy were used.[12] However, for this research purpose, the diagnosis of pre-eclampsia was based only on hypertension and proteinuria from 20 weeks of gestation. Proteinuria was considered as urine dipstick protein of 1+ or more (on two occasions at least) or a 24-hour urine protein of at least 300 mg. In addition, only women whose high blood pressure had returned to normal values within a week of delivery were included in the study to rule out chronic hypertension.

All women are offered counselling and voluntary testing for HIV at these hospital sites as the standard of care. Institutional ethical and hospital regulatory permission was obtained for the study (Biomedical Research Ethics Committee, University of KwaZulu-Natal, South Africa; reference number BE 151/010).

In the province of KwaZulu-Natal, the HIV/AIDS infection rate in pregnant women is 40%.[10] Assuming a reduction in HIV rate from 40% in controls to 25% in cases (pre-eclamptics), 890 women (445 cases and 445 controls) were required to achieve a study power of 80% with statistical significance of $p < 0.05$. This sample size was also estimated by assuming that the proportion of HIV-infected women with a CD_4 cell count < 200 cells/µl (immune-compromised) would be lower among pre-eclamptics.

Statistical analysis

SPSS version 18 was used to analyse the data. A p-value < 0.05 was considered statistically significant. Pearson's Chi-square tests were used to compare categorical variables between cases and controls, while t-tests were used to compare quantitative variables between the two groups if the data were normally distributed. Mann–Whitney tests were used if the data were skewed. Binary logistic regression analysis was conducted in order to assess the adjusted odds ratio for HIV status according to the age and parity difference between the groups.

Results

There was a total of 23 988 deliveries over the study period at the two study sites. Among them, 1 892 women were identified with a diagnosis of pre-eclampsia (including imminent eclampsia, and eclampsia).

Data were collected from 500 cases (pre-eclamptics) and 500 controls (normotensive healthy pregnant women) who met the inclusion criteria. Among the pre-eclamptics, eight cases had information missing from their files (birth weight and/or gestational age at delivery) and were therefore excluded. Finally, 492 cases were used for analysis. The maternal age of the two groups are shown in Table 1.

TABLE 1. MATERNAL AGE DISTRIBUTION IN CASES AND CONTROL GROUP

Age	*< 20 years,* n *(%)*	*20–29 years,* n *(%)*	*30–39 years,* n *(%)*	*≥ 40 years,* n *(%)*	*Mean age (years)*	*Total,* n *(%)*
Controls	147 (29.4)	210 (42.0)	116 (23.2)	27 (5.4)	25.25	500 (100%)
Pre-eclamptics	145 (20.4)	250 (50.6)	93 (18.8)	6 (1.2)	24.09	492 (100%)
Total	292 (29.4)	460 (46.3)	209 (21.9)	33 (3.3)	24.67	992 (100%)

The rate of HIV infection in the pre-eclamptic group was 26.4%. In the control group, the HIV infection rate was 36.6% (OR = 0.62, 95% CI: 0.47–0.82, $p = 0.001$) (Table 2).

Pre-eclamptic women were 38% less likely to be HIV infected than the control group without pre-eclampsia. Because the cases and controls were not exactly age and parity matched, the difference between them in HIV infection rate was adjusted for this confounding factors using logistic regression analysis. The odds ratio of being a case (pre-eclamptic) compared to a control was 0.658 for HIV negative ($p = 0.005$) after adjustment. This means that HIV-infected women were 34.2% less likely to develop pre-eclampsia than women not infected with HIV.

The results of the CD_4 counts were available in only 66 cases (pre-eclamptics) and 75 controls.

In women with pre-eclampsia, the median CD_4 count was 304 cells/µl with a maximum of 906 cells/µl and a minimum of 10 cells/µl, versus 208 cells/µl with a maximum of 725 cells/µl and a minimum of 56 cells/µl in the control group ($p = 0.008$). The proportion of pre-eclamptic women with ≥ 3+ protein was higher in the HIV-negative group (39.2%) than in the HIV-positive group (27.9%) ($p = 0.022$).

Discussion

As far as we know, this is the first study to report the rate of HIV infection in women with pre-eclampsia in comparison with a control group without pre-eclampsia. Most studies on HIV and pre-eclampsia have compared the rate of pre-eclampsia between uninfected and HIV-infected women.[4,7-9]

The rate of HIV/AIDS infection was lower in pre-eclamptic women than in the control group. These findings suggest that women with pre-eclampsia are less likely to be affected by HIV infection than the general population. In other words, HIV infection being the exposure and pre-eclampsia being the outcome variable, HIV-infected women are at a lower risk of developing pre-eclampsia. Our findings also suggest that HIV infection could have a protective effect against the development of pre-eclampsia.

The underlying mechanism of the protective effect of HIV infection is unclear. As postulated in our hypothesis, it is possibly associated with immune suppression in HIV-infected women. To further evaluate this association, the level of immunity (as expressed by the CD_4 count) between the two groups was compared. The CD_4 count result, however, was available in only 66 cases and 75 controls. The median CD_4 count was lower in the control group without pre-eclampsia (median CD_4 count = 208 cells/µl) than in the pre-eclamptic women (median CD_4 count = 304 cells/µl) ($p = 0.008$). This suggests that among HIV-infected women, the immunity was less affected in those who developed pre-eclampsia.

We also found that the proportion of pre-eclamptic women with +3 protein or more in their urine dipstick was higher in

TABLE 2. HIV RATE IN CASES AND CONTROL GROUP

	HIV positive n *(%)*	*HIV negative* n *(%)*	*Total* n *(%)*
Control group	183 (36.6)*	317 (63.4)	500 (100)
Pre-eclamptic group	130 (26.4)*	362 (73.6)	492 (100)
Total	313 (31.6)	679 (68.4)	992 (100)

*$p = 0.001$; OR = 0.62; 95% CI: 0.47–0.82.

the HIV-negative group (39.2%) than in the HIV-positive group (27.9%) (p = 0.022). This correlates with the fact that the mean serum total protein and albumin levels were lower in the HIV-negative than the HIV-positive group ($p < 0.0001$, $p = 0.013$, respectively) and could suggest that immunity plays a role in the pathogenesis of proteinuria in pre-eclampsia.

Our findings are different from those of Frank *et al.* who found no significant association between HIV infection and pre-eclampsia; the rate of pre-eclampsia in their study was not different between HIV-infected (5.7%) and uninfected women (5.2%). In their study the CD_4 count was known in only 13 cases out of 704 HIV-infected women.[7]

The main difference between our study and that of Frank *et al*. is the fact that they included women with underlying medical conditions.[7] This group with underlying medical conditions may have had other independent risk factors for pre-eclampsia and the immune maladaptation was less likely to be the initial event. Underlying medical conditions constituted an exclusion criterion from our study.

Also, the power was estimated assuming a reduction in the rate of pre-eclampsia from 8% (in uninfected women) to 5% in HIV-infected women. This margin was very narrow if we consider the wide variability in the rate of pre-eclampsia from one geographical area to another, and even from one period of time to another in the same area. The findings can easily swing for or against the hypothesis. Our findings are less likely to have been affected by minimal variations in the rate.

Frank *et al*. did raise the fact that the pre-term birth rate is high in HIV-infected women and it is possible that a proportion may have delivered prior to the onset of pre-eclampsia[7] Data on the rate of pre-term births in HIV-infected women is, however, conflicting with some studies showing no differences between HIV-infected and uninfected women.[12,13] This confounding factor is less likely to have affected our results since the mean gestational age at delivery was not significantly different between uninfected and HIV-infected women (34.86 weeks and 33.65 weeks, respectively).

The AmRo study found no difference in pre-eclampsia rate between HIV-positive and HIV-negative women.[12] The incidence of pre-eclampsia was 2.8% among 143 HIV-positive women. This sample size was too small to demonstrate a possible statistical difference and 93 out of 143 women were already on HAART (highly active antiretroviral therapy), hence they were possibly immune competent.[12]

Suy *et al.*[13] found a very low rate of pre-eclampsia among 258 HIV-infected women who were not on HAART. In 140 women on HAART, however, the pre-eclampsia rate was significantly higher (11%). In the same group, the rate of pre-eclampsia in uninfected women was 2.8%. These results suggested that HIV-infected women are at a lower risk of developing pre-eclampsia than uninfected women, but at a higher risk when on HAART.[13]

In our study, we could not evaluate for replication of the rate of pre-eclampsia in women on HAART because of its different approach. However, the findings also suggested that immunosuppression could be protective against pre-eclampsia. Immune reconstitution could alleviate this protection and even possibly increase the risk of developing pre-eclampsia.

Wimalasundera *et al*.[9] also found a low rate of pre-eclampsia in HAART-naïve, HIV-infected women but a higher rate in those on HAART. A retrospective study by Mattar *et al*.[4] found a low rate of pre-eclampsia among 123 HIV-positive women (0.8%) compared to 1 708 controls (10.6%); this was a significant difference. The median CD_4 count in HIV-infected women was 531 cells/µl.

As illustrated above, the results from various studies are conflicting. This is probably due to differences in study design and approach. Some studies included patients with underlying chronic medical conditions.[4,9]

Our approach was unique in comparing the rate of HIV infection in pre-eclamptic women with that in a control group. Because of the high rate of HIV in South Africa, this is the most important study so far on HIV and pre-eclampsia. We excluded women with underlying chronic medical conditions and evaluated the level of immunity as per the CD_4 count level, and correlated proteinuria and other parameters of pre-eclampsia with the HIV status.

There were some limitations to our study and this included the fact that it was a retrospective study. The CD_4 counts were available in only a few cases of both pre-eclamptics and the control group (small sample size). Also, in many cases, these were not recent results; the testing had been carried out up to six months earlier. In these cases, this did not reflect the actual immune status of the women at the time of recruitment.

For the same reason, we could not make a correlation between the severity of proteinuria and the level of immunity as expressed by the CD_4 count. A more accurate quantification of proteinuria (by 24-hour urine protein levels or spot protein:creatinine ratio) and recently obtained CD_4 counts could provide a better evaluation.

Conclusion

Our study revealed a significantly lower rate of HIV/AIDS infection in pre-eclamptic women compared to those without pre-eclampsia. This finding suggests that women with HIV/AIDS are less likely to develop pre-eclampsia.

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generally, and this attribute often found useful application in the conduct of the affairs of PASCAR. In his capacity as PASCAR president he had a seat on the board of the World Heart Federation based in Geneva, Switzerland where he soon became known for his forthrightness, wisdom and candour.

I have had the honour of serving as secretary general of the Nigerian Cardiac Society for two consecutive terms with Prof Adebo as president of the Society, deputy editor with him as editor-in-chief of the *Nigerian Journal of Cardiology*, and until the time of his death, secretary general with him as president of PASCAR. I have also served as executive director with him as chairman of the Board of Trustees of the Save a Child's Heart Foundation of Nigeria, a non-governmental organisation. These close associations, apart from the frequent professional interactions with him in the hospital arena, afforded me the privilege of looking into the life of this great man at close range. He was at the same time president of the Christian Medical and Dental Association of Nigeria.

Prof Adebo combined all these roles very well and never to the detriment of his duties as a teacher, head of department, dean, devoted husband, father, friend and philanthropist. His role as a philanthropist was very much concealed because he believed in the words of the Bible that 'the left hand should not know what the right hand was doing' in that context. He funded many indigent university students through their education. His faith in Christ was never concealed and his dogged pursuit of truth in all matters was a direct result of that commitment.

I can reveal a little more about this rare breed. He lived a Spartan life and was never given to ostentation even though he could easily have afforded some of the luxuries of life. I had the opportunity of travelling with him on a number of occasions for either meetings or conferences. No matter the location, keeping fit was another passion of his. He would be up early ahead of the day's programme of activities and go jogging for at least an hour, then stay with the full day's programme. Such was his level of discipline.

All these other activities never caused him to neglect his much cherished wife of 43 years, Beatrice Taiwo, who he loved very much. He would go to great lengths to find a telephone where none was in the immediate vicinity, to call her, let her know he was alright and affirm her repeatedly. He would do this every day until we returned home. His family commitment also kept him in close contact with his children who were in various parts of the world, accomplished in their own rights.

Prof Adebo was at his best when in multi-tasking mode. With sterling equanimity he took challenges in his stride. He read much and would not be outdone with the use of the latest computerised gadgets, often surfing the web for updates on information. He was always well informed, very often in contemplation but never absent minded. Needless to say he was most articulate, although he would in his self-effacing way, claim he was not given to oratory. He was indeed a man of few words; but those few words were packed with deep wisdom, which I later found, even his opponents were eager to hear. At meetings, after he spoke, it was 'end of discussion'.

He was a teacher whom students, interns and residents were eager to learn from. I never once hesitated to send my patients to him for surgery – in fact he was easily the preferred surgeon to send your patient to. Absolutely meticulous and at great sacrifice to his person, he would often get no sleep, even after the surgery was successfully undertaken, until the patient was stable and 'out of the woods' to use his own words. He was a great mentor, my mentor. He knew how to bring out the best in people.

Just as equally disciplined was his devotional life. His daily communion with Jesus Christ had priority of place in his daily schedules. I could go on, but in essence, he was a living epistle, a living, walking illustration of 2 Cor. 5:17 – 'if any man is in Christ, he is a new creation; old things have passed away and all things have become new'. How he managed to keep such a well-balanced life is again a classic illustration of what the grace of God means in a man's life who is yielded to him. Prof Adebo stood tall among his peers, always playing by the rules. Many far less-deserving men have been robed with accolades and honours here on earth. He did not seek such accolades and the honour of men.

Prof Adebo will be sorely missed in many respects within the cardiovascular healthcare arena and the numerous other bodies he served meritoriously. He must be with the Lord now, whom he loved dearly and to whom he dedicated all his labour. So indeed it should be. Adieu Prof Oluwole Ademola Adebo.

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Presenting features of newly diagnosed rheumatic heart disease patients in Mulago Hospital: a pilot study

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Abstract

Introduction: **Rheumatic heart disease (RHD) continues to cause gross distortions of the heart and the associated complications of heart failure and thromboembolic phenomena in this age of numerous high-efficacy drugs and therapeutic interventions. Due to the lack of contemporary local data, there is no national strategy for the control and eradication of the disease in Uganda. This study aimed to describe the presenting clinical features of newly diagnosed patients with RHD, with particular reference to the frequency of serious complications (atrial fibrillation, systemic embolism, heart failure and pulmonary hypertension) in the study group.**

Methods: **One hundred and thirty consecutive patients who satisfied the inclusion criteria were recruited over a period of eight months from June 2011 to January 2012 at the Mulago Hospital, Uganda. Data on demographic characteristics, disease severity and presence of complications were collected by means of a standardised questionnaire.**

Results: **Seventy-one per cent of the patients were female with a median age of 33 years. The peak age of the study group was 20 to 39 years, with the commonest presenting symptoms being palpitations, fatigue, chest pain and dyspnoea. The majority of the patients presented with moderate-to-severe valvular disease. Pure mitral regurgitation was the commonest valvular disease (40.2%), followed by mitral regurgitation plus aortic regurgitation (29%). Mitral regurgitation plus aortic regurgitation plus mitral stenosis was found in 11% of patients. There was only one case involving the tricuspid valve. The pulmonary valves were not affected in all patients; 45.9% of patients presented in severe heart failure in NYHA class III/IV, 53.3% had pulmonary hypertension, 13.9% had atrial fibrillation and 8.2% had infective endocarditis. All patients presented with dilated atria (> 49 mm).**

Conclusion: **A significant proportion of RHD patients present to hospital with severe disease associated with severe complications of advanced heart failure, pulmonary hypertension, infective endocarditis and atrial fibrillation. There is a need to improve awareness of the disease among the population, and clinical suspicion in primary health workers, so that early referral to specialist management can be done before severe damage to the heart ensues.**

Keywords: rheumatic heart disease, clinical presentation, newly diagnosed

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Rheumatic heart disease (RHD) is the most common acquired cardiovascular disease in children and young adults and remains a major public health problem in developing countries.[1-3] Africa has the largest number of children with the disease; in sub-Saharan Africa, over a million children are estimated to suffer from this debilitating and often fatal condition.[4]

Rheumatic heart disease is the result of damage to the heart valves, which occurs after repeated episodes of acute rheumatic fever (ARF). The valves become stretched and scarred and do not move normally, resulting in regurgitation and/or stenosis. If RHD is not diagnosed and managed early, it may result in heart failure and premature death.[5]

Several factors determine the type of lesion and severity of the disease among affected individuals. Genetic susceptibility and environmental factors (low socio-economic status) are the key determinants of disease pathogenesis.[1-4] The extent to which environmental factors impact on the pathogenesis of the disease varies from population to population and is largely influenced by people's perception of the disease.[6] Hence it is important to identify the common factors within the population that present with RHD. There are no studies in more than 35 years in Uganda to document the characteristics of patients affected by RHD.

The symptoms of RHD depend on the valve lesion and its severity.[5] Symptoms of RHD may not show for many years until valvular disease becomes severe. In general terms, initial symptoms of RHD are the symptoms of early heart failure: breathlessness on exertion, feeling tired and general weakness. As heart failure progresses, other symptoms may develop, including orthopnoea, paroxysmal nocturnal dsypnoea, and peripheral oedema. Palpitations may occur if atrial fibrillation is present (particularly in mitral stenosis). This arrhythmia is associated with increased thromboembolic risk, including stroke. People with aortic valve disease may experience angina and syncope in addition to heart failure symptoms. Clinical examination includes assessment of severity and complications, including signs of heart failure, the presence of atrial fibrillation and any new murmurs.

Early diagnosis of RHD is important as secondary prophylaxis can be started as soon as possible to help prevent the progression

of valve disease.[5] Echocardiography (echo) is essential to confirm the diagnosis and monitor the heart valves to detect any progression of disease.[7,8] The management of RHD is complex and requires careful co-ordination. The main goal is to prevent disease progression and to avoid, or at least delay, valve surgery. Management of RHD depends on the severity of disease.[7,8] The need for surgery is determined by the severity of symptoms, evidence that the heart valves are significantly damaged, the heart chamber size is distorted and cardiac function is significantly impaired.[9]

To our knowledge, there are no systematically collected data on newly diagnosed patients with RHD in the Ugandan setting over the past 30 years. Accordingly, the aim of this study was to describe the presenting features and complications of patients who were newly diagnosed with RHD in the Mulago Hospital.

Methods

Institutional ethics approval was obtained from the School of Medicine Research and Ethics Committee of the College of Health Sciences, Makerere University. We obtained informed consent from all patients and informed assent for those unable to give consent. Patients' initials and study numbers were put on the questionnaires instead of full names to ensure confidentiality.

This was a cross-sectional study describing the clinical and echo features of newly diagnosed RHD patients between June 2011 and January 2012. The study was carried out at Mulago Hospital, the national referral hospital and Makerere University's teaching hospital, located in Kampala, Uganda. Mulago Hospital handles about 25 patients with newly diagnosed RHD a month at different clinics, as follows: (1) Uganda Heart Institute located on ward 1C, Mulago Hospital (in- and out-patient departments) registers on average 10 newly diagnosed RHD patients per month;[10] (2) The adult cardiac clinic in the medical out-patient department (MOPD), Mulago Hospital registers six newly diagnosed RHD patients per month; (3) The paediatric cardiac clinic in the MOPD, Mulago Hospital registers about one newly diagnosed RHD patient per month; (4) The cardiac in-patient firm (ward 4C), Mulago Hospital admits about eight newly diagnosed RHD patients per month.

RHD cases were diagnosed using the WHO and United States National Institutes of Health-recommended echo diagnostic criteria.[11] Complications of RHD were defined as one or more of the following: (1) advanced heart failure (NYHA class III/IV), (2) atrial fibrillation, (3) infective endocarditis (diagnosed using the modified Duke criteria), (4) pulmonary hypertension, (5) atrial thrombus, (6) thromboembolic stroke secondary to atrial fibrillation or infective endocarditis, (7) recurrent ARF (diagnosed using NIH/WHO criteria).[11] The inclusion criteria were age five to 65 years of age in newly diagnosed RHD patients, confirmed by echocardiography (echo) using the above criteria.[11] Patients with prior echo diagnosis of RHD were excluded.

Patients who met the inclusion criteria were consecutively recruited (Fig. 1) over a period of eight months to reach the required sample size of 130 patients. Data on demographic variables (age, gender, tribe, residence, occupation, income level, education level) and clinical variables (history, physical examination, laboratory investigation variables, rest ECG, echo) were recorded on a standardised questionnaire.

Transthoracic echocardiography (TTE)

A commercially available cardiac ultrasound machine, Vivid 7 Dimension, GE Medical Systems (Horten, Norway) with dedicated capabilities for cardiac evaluation, was used to acquire the images. Image acquisition was performed according to the ASE guidelines.[12] Briefly, transthoracic echocardiograms were performed with the subjects at rest in the left lateral decubitus position by the principle investigator, under supervision of an experienced cardiologist. The recorded images were reviewed by two independent experienced cardiologists who did not know the patients. A 3.5-MHz transducer was used for adult (age > 12 years) two-dimensional, M-mode and Doppler examinations, and a 5.0–7.5-MHz transducer was used for children (age 5–12 years).

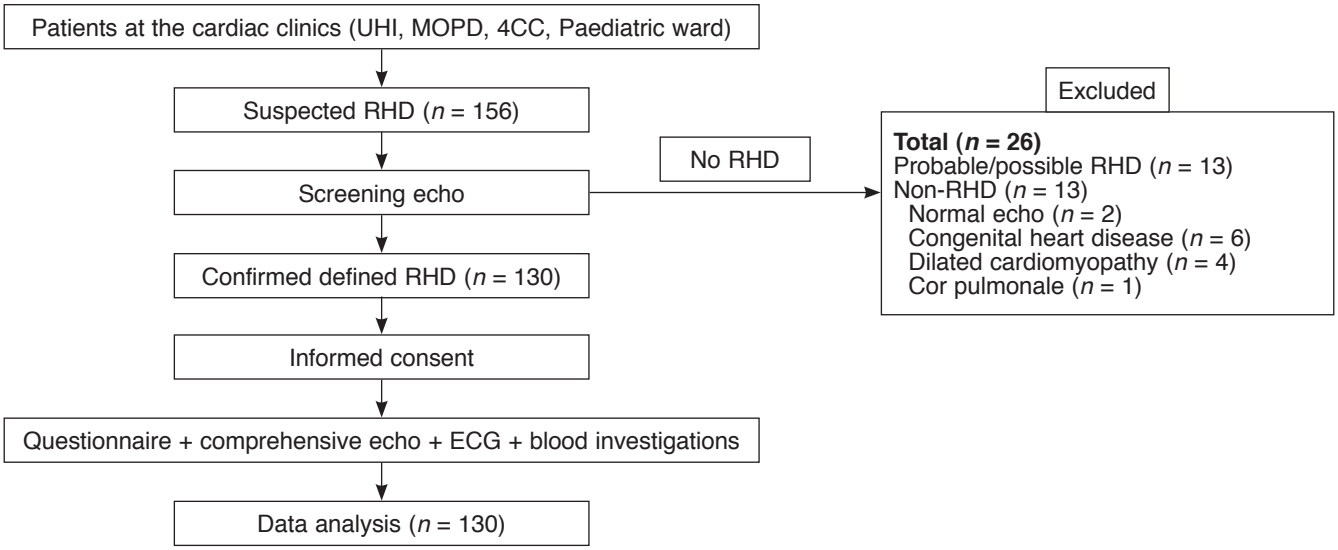

Fig. 1. Patients' flow chart. UHI = Uganda Heart Institute; MOPD = Medical out-patient department; 4C = Ward 4C cardiology

TABLE 1. SOCIO-ECONOMIC DATA OF NEWLY DIAGNOSED RHEUMATIC HEART DISEASE PATIENTS (*n* = 130)

	All (n = *130)*	*Females* (n = *94)*	*Males* (n = *36)*
Gender distribution (%)	100	72.3	27.69
Median age (years)	29.5	33	24
Educational level			
none, *n* (%)	13 (10)	10(10.64)	3(8.33)
primary, *n* (%)	60 (46.15)	41 (43.62)	19 (52.78)
secondary, *n* (%)	42 (32.31)	31 (32.98)	11 (30.56)
college/university, *n* (%)	16 (12.31)	8 (8.51)	8 (22.22)
No formal employment	84 (64.62)	65 (69.15)	19 (52.78)
Temporary housing	42 (32.31)	26 (27.66)	16 (44.44)

M-mode and two-dimensional echocardiography

Simultaneous M-mode and two-dimensional echocardiography was performed. M-mode recordings were made in the parasternal long-axis (PLAX) position during apnea with the cursor at the level of the chordae tendineae and papillary muscles. PLAX, parasternal short-axis (PSAX), apical four-chamber (A4C) and apical two-chamber (A2C) views were taken in ciné-loop format and recorded on DVD discs in both DICOM and MPEGVUE for subsequent evaluation by the independent team. An echocardiography report was written according to the laboratory's protocol and handed to the patient.

Severity of the valvular lesion was classified according to the ACC/AHA.[13] Left ventricular and left atrial dilatation were defined as left ventricular diastolic diameter and left atrial diameter more than 57 and 40 mm, respectively.[13] Left ventricular systolic dysfunction was defined as ejection fraction less than 55%.[13] Pulmonary artery systolic pressure (PASP) was estimated from the peak velocity of the tricuspid regurgitation jet plus the estimated right atrial pressure. Patients with PASP ≥ 30 mmHg were classified into mild (< 50 mmHg), moderate (50–79 mmHg) and severe (≥ 80 mmHg) pulmonary hypertension.[13]

Statistical analysis

Data were captured into EPI-DATA (version 3.1), cleaned and then exported to Stata version 10 for analysis. Continuous variables were summarised as mean (± standard deviation) and median (inter-quartile range), and presented in the tables. Categorical data were analysed using frequency and percentages, and results are presented in frequency tables and bar charts. Test of significance (*p*-value) was determined using the chi-square test. A *p*-value of less than 0.05 was considered significant.

Results

We screened over a period of eight months, 156 patients who were suspected clinically of having RHD, using the echo machine. Twenty-six patients were excluded for the following reasons: probable/possible RHD (13 cases), normal echo findings (two cases), congenital heart disease (six cases), dilated cardiomyopathy (four cases) and cor pulmonale (one case); 130 patients who were confirmed to have definite RHD were recruited and entered in the data analysis (Fig.1).

Table 1 shows the demographic characteristics of the 130 newly diagnosed cases of RHD. Overall, females (72.3%) predominated, with a younger median age of males than females (24 vs 33 years). The majority of the study population's highest education level was primary school (total: 46.2%; male: 52.8%; female: 43.6%), while 10% (male: 8.3%; female: 10.6%) were illiterate. Unemployment rate was as high as 64.6% (male: 52.8%; female: 69.2%) and 32.3% (male: 44.4%; female: 27.7%) lived in temporary houses.

The age distribution of newly diagnosed RHD patients showed a peak in the young adult age group (20–39 years). The disease was lowest in the age group < 12 years (5.4% of RHD cases), increased in the 12–19-year group (15.4%), peaked at 20–39 years (55.4%), followed by a declining number of case presentations in the age group 40–65 years (23.8%). The pattern of case presentation according to age was similar for males and females (Fig. 2).

Fig. 3 shows the frequencies of symptoms with which the study participants presented. Palpitations were the commonest symptom (95.4%), followed by fatigue (89.2%) and dyspnoea (75%). Other symptoms included chest pain (74.6%), syncope (15.4%) and oedema (14.6%). There were no gender-specific statistical differences in most of the symptoms, except females reported more syncope than males (20.2 vs 2.8%) and more males presented with severe heart failure than females.

Table 2 shows the frequency distribution of rheumatic valve lesions by age group. Isolated or multiple valve lesions were observed in the spectrum of RHD. There were eight types of valvular lesions detected according to the valve affected. Pure mitral regurgitation (MR) was the most prevalent lesion (55 cases, 42.3%), followed by MR + aortic regurgitation (AR) (36

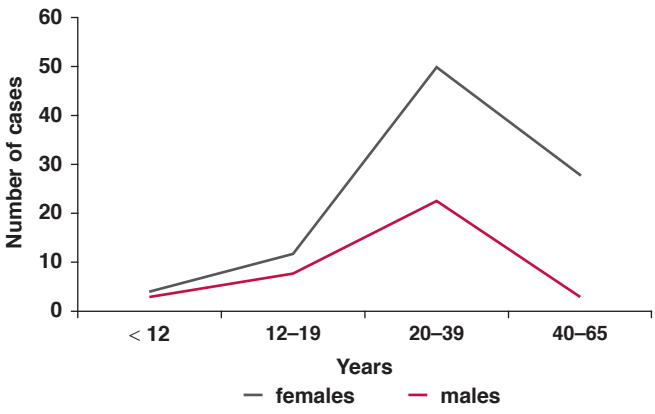

Fig. 2. Age distribution of newly diagnosed RHD.

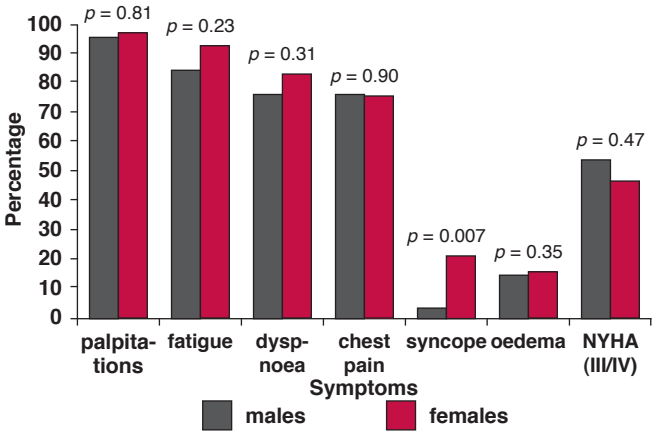

Fig. 3. Frequncy of symptoms in newly dignosed patients.

TABLE 2. DISTRIBUTION OF VALVE LESION BY AGE GROUP

	All	*<12 years*	*12–19 years*	*20–39 years*	*40–65 years*
Valve lesion(s)	130 (100%)	7	20	72	31
MR	55 (42.31)	4 (57.14)	12 (60)	26 (36.11)	12 (38.71)
MS	9 (6.92)	0	0	7 (9.72)	2 (6.45)
MR + MS	9 (6.92)	0	1 (5)	6 (8.33)	2 (6.45)
MR + AR	36 (27.69)	3 (42.86)	5 (25)	20 (27.78)	8 (25.81)
MS + AR	7 (5.38)	0	0	4 (5.56)	3(9.68)
MR + MS + AR	11 (8.46)	0	1 (5)	6 (8.33)	4 (12.90)
MS + AS + AR	1 (0.78)	0	0	1 (1.39)	0
MR + MS + AR + AS	2 (1.54)	0	0	2 (2.78)	0

MR = mitral regurgitation; MS = mitral stenosis; AR = aortic regurgitation; AS = aortic stenosis.

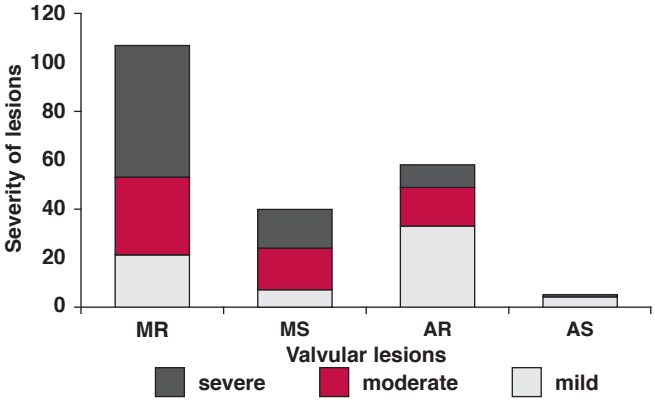

Fig. 4. Severity of valve lesions.

cases, 27.7%). Other lesions included MR + plus mitral stenosis (MS) + AR (11 cases, 8.5%), MR + MS (nine cases, 6.9%), pure MS (nine cases, 6.9%), MS + AR (seven cases, 5.4%), MR + MS + AR + aortic senosis (AS) (two cases, 1.5%) and MS + AS + AR (one case, 0.8%).

The mitral valve was involved in all cases, while 73 cases (56.2%) had isolated mitral valve lesions. All patients who had aortic valve disease had associated mitral valve disease (57 cases, 43.8%). Only one case was found to have abnormal morphology (thickening) of the tricuspid valve. Isolated MR or in association with AR was the most common finding detected among children and adolescents (100% of age group < 12 years and 85% of 12–19 years). MS was less frequent in these age groups. Although MS, AS and multiple valve lesions appeared in adolescents, their frequency increased in young adult patients.

Fig. 4 shows the degree of severity of RHD according to valvular lesion. The four types of valvular lesions were found in mild, moderate and severe forms; 72.9% of the lesions fell into the moderate and severe degree. Moreover, in mild-degree lesions, AR prevailed, while in the severe form, MR was predominant.

Table 3 shows the echo features and complications of the study population according to the predominant rheumatic valvular lesion. Patients having haemodynamically significant valvular disease affecting two valves were counted twice. Presentation with an impaired systolic function of a left ventricular ejection fraction < 55% was not uncommon; 20 of 112 cases (17.9%) presenting with mitral regurgitation and five of 28 cases (17.9%) presenting with aortic regurgitation.

Chamber dilatations were much more frequent findings than systolic dysfunction; left ventricular dilatation was seen in 60 (46.2%) cases, with a predominant proportion with MR (53.6%) and AR (56.2%). Prevalence of left atrial dilatation in the study group was as high as 75.4%. Pulmonary hypertension (53.3%) was the most detected complication by echo and more related to mitral lesions (both MR and MS). Other complications were less frequent. Atrial fibrillation (13.9%) was the characteristic complication of MS. Infective endocarditis was found in 10 (7.7%) cases, and was mainly associated with MR and AR.

Although no patient presented with a history of stroke or left atrial thrombus in our study group, three of the patients had echo findings of left atrial spontaneous echo contrast, which carries a very high risk of left atrial thrombus formation and cardiovascular accident (stroke). Almost half of the patients presented with clinical heart failure in NYHA class III and IV. This was more prevalent in patients with mitral valve lesions. Eight (6.2%) patients had evidence of recurrent ARF and 93 cases (71.5%) required valvular surgery, according to the NHFA/CSANZ 2006 guidelines of management of RHD.[9]

TABLE 3. ECHOCARDIOGRAPHIC FEATURES AND COMPLICATIONS ACCORDING TO PREDOMINANT VALVULAR LESION

Total cases	*Total 130 (100%)*	*MS 30 (23.08%)*	*MR 112 (86.15%)*	*AS 1 (0.77%)*	*AR 28 (21.15%)*
Echo features					
Mean LVEF	61.15	63.96	59.85	67	48.76
Systolic dysfunction	27 (20.77)	2 (6.67)	20 (17.86)	0	5 (17.86)
Mean LVIDD	55.89	43.9	57.57	55	62.69
LV dilatation	60 (46.15)	3 (10)	60 (53.57)	0	15 (53.57)
Mean LA	50.48	52.02	49.35	50	50.46
LA dilatation	98 (75.38)	25 (83.33)	78 (69.64)	1 (100)	24 (85.71)
Spontaneous echo contrast	3 (2.31)	1 (3.33)	2 (1.79)	0	2 (7.14)
Complications					
PHT	73 (56.15)	16 (53.33)	56 (50)	0	13 (46.43)
IE	10 (7.69)	1 (3.33)	8 (7.14)	0	3 (10.71)
AF	18 (13.85)	7 (23.33)	11 (9.82)	0	2 (7.14)
NYHA class III/IV	56 (43.08)	13 (43.33)	42 (37.5)	0	9 (32.14)
Definite recurrent ARF	4 (3.08)	1 (3.33)	3 (2.68)	0	0
Probable recurrent ARF	4 (3.08)	0	4 (3.57)	0	0

LV = left ventricle; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diameter in diastole; LA = left atrium; PHT = pulmonary hypertension; IE = infective endocarditis; AF = atrial fibrillation; NYHA = New York Heart Association; ARF = acute rheumatic fever.

Discussion

In this small, tertiary hospital-based study, we described the presenting features and complications of newly diagnosed RHD patients in a Ugandan population. All participants were indigenous blacks and 72.3% of the study participants were female, which concurs with the Soweto study where 68% were female.[14] It contrasts with the Pakistan study were only 46% were female.[15] More males had formal education than females. Lack of formal employment was more prevalent in females than males. The rates of living in temporary housing were similar in both genders.

Although this study did not evaluate the association between socio-economic status and RHD presentation, the finding that low levels of formal education, high levels of unemployment and poor housing conditions underscored their role in determining disease incidence.[16] On the other hand, the nature of the heart disease will have an impact on an individual's education and employment opportunities. Hence, there might be a vicious circle between socio-economic status and RHD in the population. This reminds us that control of the disease needs a dual effort from both the economic sector and health service systems.

The higher prevalence of disease in females than males correlated with their illiteracy and unemployment status. However, this could have been attributed to factors such as genetic predisposition, hormonal factors and poor health-seeking behaviours among males. This needs to be studied further.

Fatigue and palpitations were the most common presenting symptoms, followed by difficulty in breathing and chest pain. Given that fatigue and palpitations are non-specific symptoms of many physiological and pathological conditions, including early heart failure,[5] it is proposed that health workers do not overlook these symptoms. Improvement in disease awareness at the community level is needed in order to diagnose the disease as early as possible. The finding that over 40% of patients presented in NYHA class III/IV indicates the poor quality of life, delayed diagnosis and low level of knowledge of the disease in the population, among both patients and health workers.[17,18]

We found that the most common lesions seen in patients with newly diagnosed RHD were pure MR, followed by MR + AR. Tricuspid valve involvement was extremely rare. Regurgitation was more common than stenotic lesions. Stenotic lesions were understandably rare in children and adolescents, as time is required for fibrosis and re-organisation to develop. Multiple valvular lesions were mainly seen in young adults. This finding is very important. For example, the finding that the most common multi-valve lesion was MR + AR, and it was most prevalent in the age group 20–39 years supports available evidence that repeated attacks of ARF in RHD patients are responsible for disease progression, thus underscoring the importance of prophylaxis against repeated ARF.

Most valvular lesions in the patients were in the moderate-to-severe form, which is consistent with previously reported data from different countries.[17-20] Beaton and colleagues have previously reported 4.9 cases of mild RHD per 1 000 asymptomatic school children in Uganda.[21] This finding, combined with the finding that predominant disease in the hospital was moderate to severe, again reinforces the importance of screening and regular echocardiographic checks for high-risk populations. Early intervention with prophylaxis would protect other valves from infection and also control the progression of the affected valve(s).

There were 6.9% of patients who had pure MS, and 6.9% had MS + AR. The majority of these patients were in the age group 20–39 years. These patients could benefit from percutanous mitral valvoplasty, which has been available at the Uganda Heart Institute since December 2012. Optimal benefit depends on early presentation before calcification and development of other complications,[22] such as gross atrial dilatation, atrial fibrillation and severe CCF, further emphasising the need for early disease detection.

Almost half (43.1%) of the patients presented in NYHA class III/IV heart failure, but 20.8% of patients had a calculated ejection fraction (EF) of less than 55%. The lowest mean EF in AR cases was related to the finding that AR was associated with the most dilated left ventricles, understandably due to volume overload and compensatory left ventricular (LV) wall stretch (Table 3). All disease categories presented with significant dilatation of the left atrium (LA). This frequency of LA dilatation could partly explain the high prevalence of pulmonary hypertension (PHT). Atrial fibrillation was more frequent in MS and MR.

The presence of these complications heavily influences the method and outcome of treatment, including surgery where possible.[23] Patients with gross distortions of the heart, notably grossly dilated atria will require chamber resection during valve replacement.[23] This makes the operation more expensive but also increases the risk of postoperative complications. Patients with atrial fibrillation will need warfarin for prophylaxis against thromboembolism. This however is associated with a high risk of bleeding due to difficulty in INR monitoring and control, as most patients are too poor to afford the cost of the test.

The data from this study showed a predominant proportion of young adults with advanced forms of RHD, which is in agreement with findings from other studies in Africa.[14,18] We also noticed a 6.2% of recurrent ARF among our study group, which was similar to that described in the Fiji study,[22] however none of the study population could recall a clear history of past ARF. This reaffirms the importance of meticulous secondary prophylaxis. That the majority of patients were in the age group 20–39 years reflects the adolescent nature of ARF/RHD. The presentation by the majority with moderate-to-severe disease confirms the poor/low diagnostic rate of ARF in this population.

The findings of this study indicate that the majority of patients with RHD present with palpitations, fatigue, dyspnoea and chest pain. Given that these are not specific symptoms for RHD, it is important for general practitioners and other lower-cardre health professionals who see the majority of these patients to suspect RHD and refer these patients for specialist evaluation using echocardiography. This would facilitate early confirmatory diagnosis of cases and hence aid in early intervention, so preventing complications.

Our study had a number of limitations. First, this study population reflects those who were fortunate enough (or sick enough) to seek specialist care at the hospital and was always likely to describe those with more advanced forms of RHD. Second, unfortunately, there are no gold-standard diagnostic criteria for RHD. We applied a clinically orientated approach based on published criteria and acknowledge that there may be inherent biases in our classification of cases. For example, according to the NIH/WHO RHD echo-diagnosing criteria,[11] an

isolated aortic valvular lesion is not considered a definite RHD case. That is why there was no patient with isolated aortic vulvlar lesion seen in our study.

Conclusion

Rheumatic heart disease continues to be a major health problem in cardiac patients presenting to Mulago Hospital. It accounts for a large percentage of cardiovascular disease-related admissions and is an important indication for cardiac surgery in Uganda. Patients with newly diagnosed RHD in Mulago present with an advanced disease pattern of clinically severe symptoms associated with poor quality of life, moderate-to-severe form of valvular lesions and high frequency of complications. All these reflect a high burden of RHD in this country, a delayed diagnosis and delayed seeking of medical services. Young females accounted for the majority of the study population. The majority of the newly diagnosed RHD patients required valvular heart surgery, which is not yet available locally.

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Review Article

Epidemiology of ischaemic heart disease in sub-Saharan Africa

CHURCHILL LUKWIYA ONEN

Abstract

Background: **The epidemiology of ischaemic heart disease (IHD) in sub-Saharan Africa (SSA) remains largely enigmatic. Major obstacles to our understanding of the condition include lack of reliable health statistics, particularly cause-specific mortality data, inadequate diagnostic capabilities, shortage of physicians and cardiologists, and misguided opinions.**

Methods: **This review of the epidemiology of ischaemic heart disease in sub-Saharan Africa involved a systematic bibliographic MEDLINE search of published data on IHD in SSA over the past century. Search words included epidemiology, ischaemic (coronary) heart disease, myocardial infarction, cardiovascular risk factors and sub-Saharan Africa. Selected data are presented on the prevalence of cardiovascular risk factors and mortality from ischaemic heart disease from different countries representing the main regions of the continent.**

Results: **Although IHD in SSA remains relatively uncommon, its prevalence is predicted to rise in the next two decades due to the rising prevalence of risk factors, especially hypertension, diabetes, overweight and obesity, physical inactivity, increased tobacco use and dyslipidaemia. It is estimated that age-standardised mortality rates for IHD will rise by 27% in African men and 25% in women by 2015, and by 70 and 74%, respectively by 2030.**

Conclusion: **Ischaemic heart disease remains relatively uncommon in SSA, despite an increasing prevalence of risk factors, but its incidence is rising. The pace and direction of economic development, rates of urbanisation, and changes in life expectancy resulting from the impact of pre-transitional diseases and violence will be major determinants of the IHD epidemic in SSA. The best window of opportunity for prevention of the emerging epidemic of ischaemic heart disease in sub-Saharan Africa is now.**

Keywords: epidemiology, ischaemic heart disease, sub-Saharan Africa

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'a riddle wrapped in a mystery inside an enigma'
1 October, 1939
Sir Winston Churchill, British orator, author and Prime Minister (1874–1965)

Over a century ago, Sir Winston Churchill, a renowned British statesman and leader during the Second World War (WWII), made a celebrated visit to Uganda, where he was so moved as to describe it as 'the Pearl of Africa'. Sir Winston, referring to the quality of intelligence gathered by Western allies during WWII, called Russia a 'riddle wrapped in a mystery inside an enigma'.

While the same phrase could be used today to describe the epidemiology of ischaemic heart disease (IHD) in sub-Saharan Africa (SSA) because of many puzzles and lingering myths, what is enigmatic is the contempt with which the potential threat of IHD has been treated at various levels of health sectors, governments and international agencies. A recent change in posture by World Health Organisation (WHO) Regional Office for Africa, with greater focus on non-communicable disease (NCD), and the United Nations high-level meeting on NCD prevention and control in New York on 19–20 September 2011 are good indicators of the recognition of the importance of NCDs and the rapidly unfolding epidemiological landscape catalysed by the birth of conjoined twins, infectious diseases and non-communicable diseases.

The 30th anniversary of the Pan-African Society of Cardiology (PASCAR) conference along with the Third All-Africa Conference on Heart Disease, Diabetes and Stroke took place at Munyonyo Speke Resort in Kampala on the shores of Lake Victoria in May 2011. The warmth of the land, the gentle tropical rain showers interspersed with bright sunshine, and above all, the friendliness of Ugandans must have pervaded the hearts of most foreign delegates to the conference.

This review article will focus on some of the obstacles to our understanding of IHD in SSA. A synopsis of cardiovascular risk factors and their role in IHD in SSA, and selected mortality data on IHD from various countries across the continent are presented in this article. A plea for urgent and concerted action to avert the impending epidemic of IHD in SSA is made.

Obstacles to our understanding of IHD in SSA

Major obstacles to our understanding of IHD in SSA include lack of reliable statistics on health, life expectancy and disease incidence, and the absence of cause-specific mortality data. This is confounded by lack of diagnostic capabilities in most of SSA, emanating from a shortage of physicians, particularly cardiologists, and lack of appropriate investigations, such as

resting 12-lead electrocardiographs (ECGs), exercise ECGs, cardiac biomarkers (troponins, CKMB) and cardiac imaging such as echocardiography, coronary angiography, computed tomography (CT) angiography, intravascular ultrasound scans (IVUS) and radionuclide myocardial perfusion studies.

Resting 12-lead ECGs, although generally more widely available and relatively inexpensive, have limited sensitivity and specificity for the diagnosis of acute coronary syndromes. Furthermore, there are high rates of non-specific ST-segment and T-wave changes suggestive of myocardial ischaemia in up to 10% of asymptomatic African men and 20% of women over the age of 40 years.[1]

Physiologically or pharmacologically induced stress tests are helpful to differentiate cardiac from non-cardiac aetiology of chest pain in patients with inducible ischaemia due to obstructive coronary artery disease. The safe performance of provocative stress testing and IVUS requires appropriate professional competence, careful selection of patients and availability of resuscitation equipment in cases of adverse events during testing. Low autopsy rates often coupled with uncertified deaths outside health facilities exacerbate the situation.

This lack of evidence on IHD in SSA is erroneously reinforced by beliefs that IHD affects only the wealthy and elderly, that it arises from freely acquired risks and that its management is expensive, ineffective and of a lower priority than infectious diseases such as HIV/AIDS, tuberculosis, malaria, and a number of neglected tropical diseases. Moreover, there are strong opinions that IHD in SSA affects mainly small Westernised populations and that it is a less serious cause of morbidity and mortality.[2] Some of these authorities are of the opinion that cardiovascular risk factors in groups of older Africans, including obesity, diabetes and metabolic disorders are virtually non-existent and that IHD is bound to be a less serious threat, as there are very few black populations in the older age category.[2]

Others have expressed disbelief of the potential epidemic of IHD in SSA in the next few decades and contend that resources should be appropriated to the current threats, particularly rheumatic heart disease and cardiomyopathies.[3] Additional setbacks accrue from lack of appropriate resources and skills to guide and direct epidemiological studies of ischaemic heart disease; crisis management often focused on acute conditions and infectious diseases; and perpetual uncoordinated approaches to health issues that are often reactionary, leading to neglect of NCDs.

The majority of the 57 countries in the world with critical shortages of health workers are in SSA. The total health workforce density in SSA is the lowest in the world with just 2.3 per 1 000 population, compared to 18.9 and 24.8 per 1 000 population in Europe and the Americas, respectively. In fact, SSA has only 4% of the global number of health workers but 25% of the global burden of disease.[4]

Sadly, some of the myths regarding IHD in SSA are fuelled by the notion that the various cardiovascular disease (CVD) risk factors, although prevalent in urban black Africans, appear to exert their influence in a far less noxious manner than is the case in most Western populations. Also that lipid profiles are generally less atherogenic, leading to suggestions of the 'genetic resistance' of black Africans to IHD.

The view that IHD is rare in SSA is rooted in old beliefs arising from earlier authors such as Cook[5] and Donnison,[6] and needs to be effectively demystified. Firstly, atherothrombotic cardiovascular disease is a global problem that afflicts every community regardless of region, ethnicity or gender. The burden of cardiovascular disease is increasing rapidly in Africa and it is now a public health problem throughout the African region, particularly hypertension, stroke, cardiomyopathies, and not least, ischaemic heart disease. Rheumatic heart disease is still a major concern.

Scarcity of data on IHD and the non-existence of epidemiological surveillance systems for cardiovascular diseases in most of SSA should not be construed to mean rarity of the disorder. INTERHEART, a global case–control study of acute myocardial infarction (AMI) of 28 000 subjects in 52 countries showed that nine risk factors accounted for 90% of population-attributable risk (PAR) in all regions.[7] These risk factors included hypertension, diabetes, central obesity, dyslipidaemia, physical inactivity, psychological stress, tobacco use, inadequate intake of fruits and vegetables, and inadequate or no alcohol intake.

Although the results of the INTERHEART study have been challenged on account of it being a case–control study rather than a prospective study, the major contributing individual risk factors for acute myocardial infarction are generally consistent across the globe and reminiscent of the conclusions of the original Framingham Heart study several decades ago, as well as its 30-year follow-up study.[8,9] Some have questioned the reliability of information on some of the cardiovascular risk factors used in the INTERHEART study, for example history of hypertension and diabetes mellitus, and have raised concerns about recall bias regarding diet and psychosocial factors in the setting of devastating effects of index acute myocardial infarction on a person's mental state. In some parts of SSA, haemoglobinopathies such as haemoglobin S or haemoglobin C might contribute to ischaemic heart disease due to vaso-occlussive crises.

Secondly, despite variations in genetic susceptibilities to IHD in different ethnic groups, the common environmental and traditional coronary heart disease risk factors pathogenetically play their roles through a common final pathway in the development of clinical atherosclerotic heart disease in all ethnic groups. Marked regional differences in the impact of CVDs merely reflect a myriad of factors, among them the level of care, quality of health statistics, and differences in stages of socio-economic, nutritional and epidemiological transition between countries, communities and even between individuals.

Thirdly, as societies undergo 'urbanisation', risk-factor levels for CVDs including IHD increase. For instance, only about 5% of Africans were urbanised by 1900. At the start of independence in the 1950s, 14.7% of inhabitants of Africa were urban. In 2000, the urbanisation rate had risen to 37.2%, and by 2015 the rate is expected to hit 45.3% with continually high rates of rural–urban migrations across Africa.[10]

The burden of cardiovascular risk factors in SSA

Hypertension

Systemic arterial hypertension poses a special challenge in SSA, with immense socio-economic implications because of its high prevalence, especially in urban dwellers. Hypertension is arguably the most powerful cardiovascular risk factor in the

African context and has been declared by the African Union as one of the greatest health challenges to the continent other than HIV/AIDS. The problem is compounded by lack of awareness, frequent under-diagnosis, low levels of control and the severity of its complications.[11-13]

Despite the dearth of data and marked variation between and within studies, hypertension is estimated to affect 10 to 30% of Africans, virtually one in six people. In West Africa, hypertension affects 30 to 40% of people aged 65 years or older in rural areas, and approximately 50% of semi-urban dwellers. In the mixed population (Coloureds) of South Africa, 50 to 60% of people over the age of 65 years have hypertension. These figures approximate the 60 to 70% prevalence of hypertension in African-Americans over 65 years of age.[14] An estimated 75 to 80 million Africans, more than twice the global estimate of people with HIV/AIDS, had hypertension in 2000. The number of Africans with hypertension will escalate to 150 million by 2025.[15]

The rising prevalence of hypertension in rural settings is of great concern and probably relates to the rapid 'urbanisation' of rural dwellers.[15,16] About 40% of Africans with hypertension are undiagnosed, less than 30% of those who are diagnosed with hypertension are on treatment, and less than 20% of those on treatment have optimal blood pressure control (< 140/< 90 mmHg).[13,17-21]

Diabetes mellitus and impaired glucose tolerance

In 2010, an estimated 12.1 million people with diabetes mellitus (4.2% of the global estimate of 285 million) were in sub-Saharan Africa.[22] The following year, diabetes prevalence rose to 14.7 million (4.02% of the global 366 million). By the year 2030, there will be a 90% projected increase in diabetes prevalence in SSA, bringing the number of Africans with diabetes to 28 million.[23]

Nearly 78% of people with diabetes in sub-Saharan Africa are undiagnosed. Heavily populated countries such as Nigeria have three million diabetics, followed by South Africa with 1.9 million.

Fuelling the diabetes epidemic is a large pool of people with impaired glucose tolerance (IGT), totalling an estimated 26.9 million in 2010, and expected to rise to 47.3 million by 2030. Diabetes is associated with a pro-coagulant state, compounding the commonly accompanying insulin resistance and hyperinsulinaemia, and thus contributing to accelerated atherogenesis.

Although diabetes mellitus and pre-diabetes are important cardiovascular risk factors globally, their roles in populations undergoing rapid epidemiological transition are unclear. Atherosclerotic complications of diabetes are likely determined by the pace and degree of affluence, genetic factors, phenotypic heterogeneity of type 2 diabetes, changes in life expectancy, and burden, duration and contribution of other cardiovascular risk factors such as hypertension, dyslipidaemia and tobacco use. In many parts of SSA, micro-angiopathies are the dominant chronic complications of diabetes,[24-30] unlike in the Western world, where macrovascular complications (MAC) predominate.

Overweight and obesity

Estimates of the prevalence of overweight and obesity vary widely across SSA, but it is generally higher in females than in males and particularly in southern Africa, Mauritius and Seychelles, compared to the rest of the continent. In East and Central Africa the prevalence of overweight (body mass index from > 25 to < 30 kg/m^2) in women is two to three times higher than in men (Table 1). In Ghana, males appear to be more overweight than women. However, in much of West Africa, southern Africa and in the islands off the east coast of Africa, the prevalence of overweight in men is approximating that of females. This trend towards parity indicates that overweight is now a widespread continental problem in populations of SSA above the age of 15 years.

However obesity still has relatively low prevalence rates throughout SSA, ranging between 1.1 and 43.2% in females and 0.1 and 21.3% in males. Populations of southern Africa and the islands of Mauritius and Seychelles exhibit a greater prevalence of obesity, particularly among the women.

Physical inactivity

There are scant data on the prevalence of physical inactivity in SSA. A WHO report of national surveys in both urban and rural settings in five African countries (Ethiopia, Republic of Congo, Ghana, South Africa and Zimbabwe) in 2003, involving a total of 14 725 individuals aged 18 to 69 years revealed a mean prevalence of physical inactivity in 19.6% of men and 22.9% of women.[31]

Physical inactivity was defined using the International Physical Activity Questionnaire (IPAQ). IPAQ inactive is defined as not meeting any of the following three criteria: three or more days of vigorous activity of at least 20 minutes per day, accumulating at least 1 500 MET-min per week, OR five or more days of moderate-intensity activity or walking of at least 30 minutes per day, OR five or more days of any combination of walking, moderate-intensity or vigorous-intensity activities, achieving a minimum of at least 600 MET-min per week.

Across the continent, low levels of physical activity are reported in women compared to men. According to the WHO survey, a greater number of lazy people are found in southern

TABLE 1. PREVALENCE OF OVERWEIGHT AND OBESITY IN FEMALES AND MALES AGED 15 YEARS AND OLDER IN SELECTED AFRICAN COUNTRIES BY REGION, 2011

	Overweight (BMI > 25 kg/m^2, < 30 kg/m^2)		*Obesity (BMI > 30 kg/m^2)*	
Region/country	*Females (%)*	*Males (%)*	*Females (%)*	*Males (%)*
Eastern Africa				
Uganda	23.9	8.2	1.9	0.1
UR Tanzania	28.7	16.8	3.6	0.8
Central Africa				
DR Congo	15.8	5.7	1.1	0.1
Rwanda	20.7	8.1	1.6	0.1
Western Africa				
Nigeria	36.8	26.0	8.1	3.0
Ghana	32.5	35.6	5.9	4.8
Southern Africa				
Botswana	53.5	41.6	17.7	6.9
South Africa	68.5	41.3	36.8	7.6
Islands				
Mauritius	56.8	44.8	22.3	8.0
Seychelles	73.8	63.8	43.2	21.3

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.
World Health Organisation: WHO Global Infobase: https://apps.who.int/infobase/Comparisons.aspx (Accessed 28 December 2011). Database updated 20/01/2011. Accessed 28 December 2011.

TABLE 2. PREVALENCE OF PHYSICAL INACTIVITY IN SELECTED SSA COUNTRIES, WHO 2003

Country N/U/R (18–69 years)	*Males (%) [95% CI]*	*Females (%) [95% CI]*	*Both genders (%) [95% CI]*
Congo (n = 1 335) M:F = 623:712	23.5 [16.5–30.5]	30.2 [21.8–38.51]	27.2 [20.5–33.9]
Ethiopia (n = 4 430) M:F = 2 171:2 259	9.4 [7.1–11.8]	16.0 [13.9–18.2]	12.7 [11.0–14.4]
Ghana (n = 3 362) M:F = 1 532:1 830	7.9 [5.9–9.8]	15.1 [12.7–17.5]	11.5 [9.7–13.3]
South Africa (n = 2 028) M:F = 957:1071	43.0 [37.4–48.6]	46.6 [41.4–51.9]	44.9 [40.4–49.4]
Zimbabwe (n = 3 570) M:F = 1 296:2 274	14.1 [11.6–16.6]	22.0 [19.6–24.5]	18.1 [16.4–19.8]

N/U/R = National Urban and Rural Survey.
Source: http://infobase.who.int. Accessed 28 December 2011.

Africa, Mauritius and Seychelles, while those in the Horn of Africa and in West Africa are relatively more physically active (Table 2, Fig. 1). This observation closely mirrors the reported prevalence of overweight and obesity. There are no consistent national (rural and urban) surveys for similar years or later from other SSA countries.

The Seychelles Heart study of 2004, reported by Bovet and colleagues in 2007, revealed a disparate prevalence of physical inactivity, ranging from 28 to 58.6% in both genders aged 25 to 64 years, because of variable and subjective operational definitions of physical inactivity using a modification of the WHO STEPS survey questionnaire, which was not identical to the IPAQ.[32] More surveys are therefore required in many SSA countries using standard questionnaires to provide better insight of the emergence of this cardiovascular risk factor in the continent. There are likely to be wide variations of the levels of physical activities, determined by culture, gender, age, occupation, socio-economic status and levels of education.

Tobacco use in SSA

Most estimates of tobacco use in SSA vary in their operational definitions. For instance, some surveys have used different age ranges for men and women and between countries. Also, while some surveys considered current tobacco use including smoked and non-smoked tobacco, others have used only daily cigarette smoking. Moreover, these studies were performed in different years, making comparison of prevalence of tobacco use across most African countries problematic.

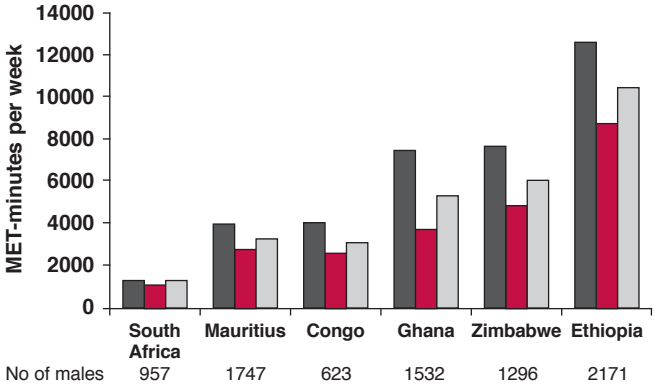

Fig. 1. Physical activity in men and women aged 18 to 69 years in selected countries.

According to WHO-Afro,[33] tobacco-smoking rates were considerably lower (< 10%) in countries such as Democratic Republic of Congo, Congo, Ethiopia, Nigeria, Ghana, Swaziland and Lesotho. Countries in Central, West and East Africa had smoking prevalence rates ranging between 10 and 19%. High rates of tobacco use (> 20%) were found mainly in southern Africa, Guinea, Guinea Bissau, Niger, Seychelles and Mauritius. There were no data from certain countries such as Angola, Central African Republic, Gabon and Equatorial Guinea.

It is widely known that some countries on the continent are major tobacco growers. For instance, tobacco accounts for 61 and 23% of export earnings in Malawi and Zimbabwe, respectively. South Africa, Tanzania, Kenya and Nigeria rank closely behind Malawi and Zimbabwe. Continual commercial pressures, price incentives and other subsidies provided by transnational cigarette companies to African farmers, coupled with aggressive marketing and advertisements will drive the prevalence of tobacco use in SSA. It is therefore not surprising that very few African countries have been signatories to the Framework Convention on Tobacco Control Ratification, with countries such as Zimbabwe, Malawi and Eritrea declining to sign the convention altogether.

Table 3 shows age-standardised prevalence estimates for current smokers in males and females aged 25 years or older in 2006 in selected countries. In general, smoking prevalence remains quite low among African women, although increased trends are emerging in young urban women. The prevalence of smoking is 20 to 50 times higher in men than in women across Africa, with estimates of below 2% in women in most SSA

TABLE 3. AGE-STANDARDISED PREVALENCE ESTIMATES FOR TOBACCO SMOKING (CURRENT USERS) IN MALES AND FEMALES AGED 15 YEARS AND OLDER IN SELECTED SUB-SAHARAN AFRICAN COUNTRIES BY REGION, 2006

Region/country	*Current smoking prevalence in males aged 15 + years (%)*	*Current smoking prevalence in females aged 15 + years (%)*
Eastern Africa		
Uganda	19.0	2.0
UR Tanzania	24.0	2.0
Central Africa		
DR Congo	13.0	0.6
Malawi	21.0	2.0
Western Africa		
Nigeria	12.0	0.2
Ghana	10.0	0.5
Southern Africa		
Zimbabwe	33.0	2.0
South Africa	29.0	8.0
Islands		
Mauritius	34.0	0.9
Seychelles	32.0	3.0

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.
Source: https://apps.who.int/infobase/Comparisons.aspx Accessed on 31 December 2011.
The figures represent age-standardised prevalence rates, using the standard WHO world population for age, for current tobacco smokers. These figures should be used only to draw comparisons of prevalence between countries and between men and women within a country. These figures are different from the crude data reported in country surveys in Infobase.

countries except in South Africa and Namibia, where smoking prevalence among women was 5.5 and 5.9%, respectively.[34]

Various estimates of smoking prevalence in African men between 1976 and 2005 revealed rates below 10% in many African countries. But in Tanzania, Mozambique, South Africa, Mauritius and Seychelles, smoking prevalence rates ranged between 15 and 30%. Smoking prevalence rates in adults increased substantially across SSA by 2009, especially in Mauritius where a third of adults smoked, closely followed by South Africa, Tanzania, Burkina Faso and Senegal with smoking rates of 27.5, 27.1, 22.0 and 19.8%, respectively. Even in Nigeria and Ghana, where smoking rates were relatively low before 2003, estimated at 6.1% in Nigerian men, 0.1% in Nigerian women, 4.6% in Ghanaian men and 0.2% among Ghanaian women, overall smoking prevalence more than doubled in men to 13 and 10.2% in Nigeria and Ghana, respectively in 2009 but remained quite low in women.

Although deaths from tobacco-related causes probably accounted for only 5 to 7% in African men and 1 to 2% in African women in the year 2000,[34] by 2030, tobacco is expected to be the greatest contributor of deaths in SSA. Most victims will die 20 to 25 years prematurely of various cancers, respiratory diseases, IHD and other circulatory disorders.

Regrettably, most governments in African countries have avoided action to control smoking for fear of harmful economic consequences on their fragile economies. Without effective tobacco-control measures, SSA risks becoming the biggest global ashtray as many transnational tobacco companies shift their targets to middle- and low-income countries.

Dyslipidaemia

There is overwhelming epidemiological evidence implicating cholesterol as a cause of atherosclerosis. Most black Africans reportedly have low levels of total cholesterol associated with high high-density lipoprotein (HDL) cholesterol levels.[35] Higher cholesterol levels however, have been found in diabetic patients from Zimbabwe and Tanzania. The total serum cholesterol was also significantly higher in women than men. Reports from West Africa indicate a worrying trend of dyslipidaemia among patients with either type 1 or type 2 diabetes mellitus.[36] Data from the Transition of Health during Urbanisation of South Africa (THUSA) study indicate that black South Africans may be protected from IHD because of favourable lipid profiles characterised by low total cholesterol and high HDL cholesterol levels.[37]

In Nigeria, IHD contributes very little to mortality rates in middle-aged men and women, partly because of particularly low mean cholesterol levels.[38] Different black African communities may be at different stages of their epidemiological transition, as shown in an epidemiological study of coronary heart disease risk factors in the Orange Free State in South Africa.[39] Table 4 illustrates this point quite vividly. Selected countries representing the different regions of SSA show wide differences in mean total cholesterol levels with a tendency to higher cholesterol levels in females in some countries.

The cardiovascular impact of HIV/AIDS

SSA bears a disproportionate share of the global HIV burden. The interaction between HIV infection, acquired immunodeficiency syndrome (AIDS), its treatment with highly active antiretroviral drugs (HAART), and cardiovascular disorders is complex and incompletely understood.

The transformation of HIV/AIDS into a chronic disorder with the advent of antiretroviral drugs is associated with the emergence of certain characteristic cardiovascular risk factors, and raises apprehension about the potential increase in prevalence of cardiovascular diseases, including IHD, in SSA. In Botswana, for instance, where antiretroviral therapy coverage exceeds 90%, AIDS-related deaths declined by approximately 50% between 2002 and 2009.[40]

The repertoire of immunological responses associated with acute and chronic HIV infection is quite complex and will be only highlighted here. Perturbations of cytokine expression, cellular dysfunctions, redistribution of lymphocyte sub-populations, increased cellular turnover and apoptosis are some of the features of general activation of the host's immune system that characterise chronic HIV infection.[41] Chronic HIV infection, and not its pharmacological treatment, induces changes in markers of endothelial function.[42] Untreated HIV infection is also associated with impaired elasticity of both large and small arteries.[43]

Some authors have suggested that HIV infection accelerates atherosclerosis via a pro-inflammatory effect on the endothelial cells through the effects of various cytokines, especially interleukin-6 and D-dimers.[44,45] Other mechanisms of arteriopathy include the direct toxic effects of HIV-associated g1p20 and tat proteins on vascular or cardiac cells. There is also evidence of a hypercoagulable state, which inversely correlates with CD_4 count.[46]

Although traditional risk factors for cardiovascular diseases might overshadow the role of non-traditional risk factors, there is increasing evidence that young, asymptomatic, HIV-infected men with long-standing HIV disease demonstrate an increased prevalence and degree of coronary atherosclerosis compared with non-HIV-infected patients.[47] Furthermore, HIV-infected patients tend to develop perturbations in lipid metabolism, characterised by decreased HDL cholesterol and low-density lipoprotein (LDL) cholesterol levels, followed by an increase in

TABLE 4. ESTIMATED MEAN TOTAL CHOLESTEROL IN SELECTED AFRICAN COUNTRIES BY REGION IN FEMALES AND MALES AGED 15 YEARS AND OLDER, 2011

Region/country	*Females mean total cholesterol (mmol/l)*	*Males mean total cholesterol (mmol/l)*
Eastern Africa		
Uganda	4.4	4.7
UR Tanzania	5.2	4.4
Central Africa		
DR Congo	4.3	4.3
Rwanda	4.3	4.3
Western Africa		
Nigeria	3.7	3.6
Ghana	5.9	4.4
Southern Africa		
Botswana	4.7	4.7
South Africa	4.4	4.4
Islands		
Mauritius	5.2	5.2
Seychelles	5.9	5.8

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.
Source: https://apps.who.int/infobase/Comparisons.aspx Accessed on 31 December 2011.

plasma triglyceride levels pre-HAART and prior to developing AIDS.[48]

Both traditional and non-traditional risk factors therefore appear to contribute to atherosclerotic disease in HIV-infected patients. Those on HAART, particularly protease inhibitors, develop a myriad of class- and non-class-specific metabolic effects on lipid profiles, glucose levels, insulin sensitivity and anthropometric body changes characteristic of lipodystrophy. Untreated HIV infection may also have a paradoxical overall effect on cardiovascular disease and thereby reduce the risk of ischaemic heart disease because of severe and progressive weight loss, wasting syndrome, hypotension resulting from chronic gastroenteritis, hypoadrenalism and shortened life expectancy associated with advanced AIDS.

Despite the scarcity of data from SSA, there are some indications of overall excess CVD risk factors in HIV-infected patients. Situation analysis in 2008 of 501 HIV-infected patients from Botswana using the database of the Botswana Medical Aid Scheme combined with data from the Centre for Chronic Diseases revealed impressive clustering of hypertension, dyslipidaemia, obesity, dysglycaemia and smoking (Fig. 2). The peak age range for the occurrence of CVD risk factors was about a decade after the peak age for HIV infection in Botswana.

Given the difficulty of determining whether the observed increase in CVD risks were due to HIV itself, treatment with HAART or merely a factor of improved longevity, it would be ideal to perform case–control studies on the prevalence of CVD risk factors and the prevalence of arteriosclerotic cardiovascular endpoints such as IHD, stroke, and peripheral arterial disease in HIV-infected versus age- and gender-matched non-HIV-infected individuals. Also, a comparison of pre-HAART and on-HAART HIV-infected patients would shed light on this grey area. It is important to remember that the enormous impact of HIV/AIDS does not appear to have diminished the impact of chronic cardiovascular diseases on mortality in SSA.[49]

Reports on IHD in SSA

There are a few scattered reports of IHD in SSA. Kengne and colleagues[50] collated a total of 356 cases of SSA patients with coronary heart disease (CHD) from four selected countries (Ghana, Cameroon, Senegal and Kenya). They reported a high prevalence of CHD risk factors, which was not surprising in this selected population of patients with established CHD. Males outnumbered females by ratios ranging from 1.3:1 to 6:1, with hypertension in up to two-thirds of the patients. The report highlighted the fact that IHD was by no means rare in these African populations.

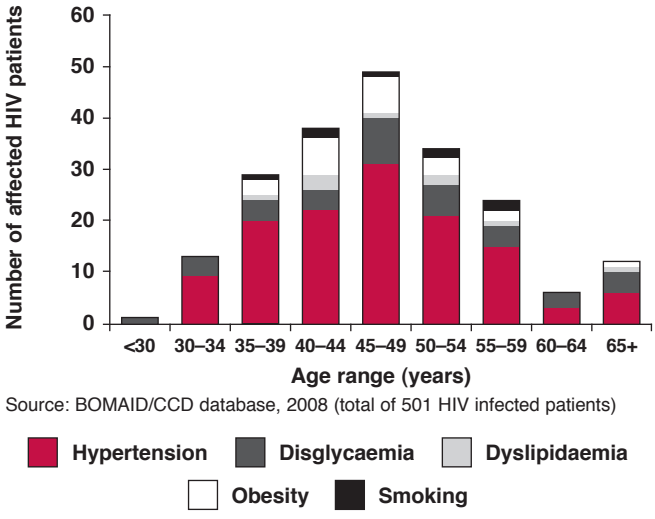

Fig. 2. Cardiovascular disease risk factors in HIV-infected patients in Botswana.

The African arm of the INTERHEART study showed that dyslipidaemia, abdominal obesity and tobacco use accounted for greater population-attributable risk in the overall African population, whereas hypertension and diabetes were less prominent risk factors.[51] However, in black Africans, dyslipidaemia was followed by hypertension, abdominal obesity, diabetes and then tobacco use.

The INTERHEART African study cast doubt on the notion of protective lipid profiles in blacks, as one reason for implicitly low IHD prevalence in Africa. High HDL cholesterol levels in black Africans might be dysfunctional and less protective than generally believed. However, the findings of the INTERHEART African study were at slight variance with reports by Ezzati and colleagues who showed that hypertension, low intake of fruits and vegetables and physical inactivity accounted for population-attributable fractions for ischaemic heart disease mortality of 43, 25 and 20%, respectively, in the Africa region. These were all above the population-attributable fraction of 15% for high cholesterol.[52]

Limitations in diagnostic evaluation of patients with possible IHD might explain, at least in part, the apparent rarity of IHD in SSA. This is illustrated by the study on black South Africans by Joubert and colleagues using data from the Medical University of South Africa (MEDUNSA) stroke data bank. The study showed increased prevalence of CHD with improved diagnostic tools.[53]

History of angina pectoris or myocardial infarction using the Rose questionnaire yielded a prevalence of only 0.7% in 741 black patients with stroke, 71% of whom had cerebral infarction. Resting 12-lead electrocardiography was analysed for the presence of poor R-wave progression in the precordial leads, the presence of pathological Q waves and ST–T wave changes using the Minnesota code in 555 stroke patients, 72% of whom had cerebral infarctions confirmed on computed tomography. Ninety-three of the 555 patients (16.8%) had evidence of coronary artery disease, of whom 81 had features of myocardial ischaemia, eight had pathological Q waves and four patients had features of acute myocardial infarction. There has been long-standing controversy regarding ECG diagnosis of myocardial ischaemia in black Africans.[53-57]

Ignoring ECG features of ‘ischaemia’ and ascribing such changes to ‘normal variation’ poses the potential danger of under-diagnosis or misdiagnosis of myocardial ischaemia in black Africans. Rather, future work should attempt to unravel the genetic mechanisms behind abnormal ECG patterns in black Africans.

The combination of clinical assessment, chest radiograph, resting electrocardiography, transthoracic echocardiography and MUGA scanning showed features of CHD in 18 patients (17.6%) in the MEDUNSA study. Scintigraphy with or without dipyridamole infusion in 60 stroke patients in this study revealed features of coronary heart disease in 45% of the patients. Macroscopic and microscopic pathological examinations of the

TABLE 5. TOP 10 CAUSES OF MORTALITY IN SOUTH AFRICAN MEN AND WOMEN > 60 YEARS IN 2000

Cause of death	*Percentage (%) in males aged > 60 years [n = 71 641]*	*Cause of death*	*Percentage (%) in females aged > 60 years [n = 73 474]*
Ischaemic heart disease	17.2	Stroke	17.7
Stroke	12.2	Ischaemic heart disease	16.0
COPD	8.0	Hypertensive heart disease	9.8
Tuberculosis	6.4	Diabetes mellitus	7.3
Lower respiratory tract infection	5.1	Lower respiratory tract infection	5.3
Hypertensive heart disease	4.2	COPD	4.4
Cancer of airways	4.1	Nephritis	2.8
Diabetes mellitus	4.0	Tuberculosis	2.7
Cancer of prostate	3.1	Asthma	2.4
Cancer of oesophagus	2.8	Cancer of the breast	1.9

COPD = chronic obstructive pulmonary disease.

heart and coronary arteries for evidence of infarction in 23 stroke patients in the study revealed the highest rate of myocardial infarction (17.4%).

Observed differential mortality rates in different ethnic groups in multiracial African communities such as South Africans have been at least partly ascribed to different stages of the epidemiological transition. For instance, Norman and colleagues[58] found that black Africans had approximately 60, 70 and 82% less CHD mortality rates compared to South African Coloureds, whites and Asians, respectively.

Part of the reason for relatively high IHD mortality rates in South African Asians is due to their high prevalence of diabetes mellitus.[59-61] By contrast, mortality from stroke in black Africans exceeds the rates for Coloureds, whites and Asians by 2, 96 and 19%, respectively. However, mortality from hypertensive heart disease in black South Africans was 2.5, nine and three times higher than rates in Coloureds, whites and Asians, respectively.

Bradshaw and colleagues[62] demonstrated that IHD was the leading cause of death among 71 641 South African men over 60 years, while it was the second most common cause of death among the top causes of deaths in 73 474 women in the year 2000 (Table 5). In South African men aged 15 to 45 years in the same study, IHD was ninth among the top 10 causes of death (1.1%), although it did not feature among the top 10 causes of death in women. HIV/AIDS was the predominant cause of mortality in younger age groups, accounting for 40.7% of deaths in men and 64.4% in women.

In 2005, the WHO estimated 188 000 and 173 000 deaths from IHD in men and women, respectively in SSA.[63] These age-standardised mortality rates (ASMR) will rise by 27 and 25% in men and women, respectively by the year 2015, and by 70 and 74%, respectively by the year 2030.

Table 6 represents ASMR from IHD in selected countries from the main regions of SSA. Despite higher ASMR in men in mainland Africa, rates in females were close to those in men (Table 6). In Seychelles, ASMR in men was three-fold higher than rates in women, while Mauritius shows the highest ASMR for IHD in both genders, with a male preponderance.

TABLE 6. AGE-STANDARDISED MORTALITY RATES FOR ISCHAEMIC HEART DISEASE IN THE WHO AFRICA REGION, BY SELECTED COUNTRIES AND GENDER, 2002

Region/country	*Estimated population (millions)*	*Age-standardised mortality rates for IHD (per 100 000)*	
		Males	*Females*
Eastern Africa			
Uganda	25.00	150	120
Tanzania	36.28	147	128
Ethiopia	6.90	149	127
Central Africa			
DR Congo	51.20	166	132
Rwanda	8.27	149	122
Malawi	11.87	152	125
Southern Africa			
Botswana	1.77	142	102
South Africa	44.76	159	99
Mozambique	18.54	124	107
Western Africa			
Nigeria	120.91	160	127
Ghana	20.47	143	114
Cameroon	15.73	154	124
Islands			
Mauritius	1.21	277	161
Seychelles	0.80	151	49

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.

TABLE 7. COMPARISON OF AGE-STANDARDISED MORTALITY RATES FOR ISCHAEMIC HEART DISEASE AND HIV/AIDS IN THE WHO AFRICA REGION IN SELECTED COUNTRIES IN 2002

Region/country	*Estimated population (millions)*	*ASMR (per 100 000)*		*ASMR HIV/AIDS: IHD ratio*
		IHD	*HIV/AIDS*	
Eastern Africa				
Uganda	25.00	270	555.6	2.06
UR Tanzania	36.28	275	593.2	2.16
Central Africa				
DR Congo	51.20	298	277.7	0.93
Malawi	8.27	271	345.4	1.27
Western Africa				
Nigeria	120.91	287	316.8	1.10
Ghana	20.47	257	174.6	0.66
Southern Africa				
Botswana	1.77	244	2,243.1	9.19
South Africa	44.76	258	840.3	3.26
Islands				
Mauritius	1.21	438	1.6	0.004
Seychelles	0.80	200	5.5	0.03

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania, ASMR = age-standardised mortality rates.
Sources: WHO Global InfoBase http://infobase.who.int; WHO Statistical Information System http://www.who.int/whosis ; Mackay J, Mensah GA. *The Atlas of Heart Disease and Stroke*. Geneva: World Health Organization. 2004. http://www.who.int/cardiovascular_diseases/resources/atlas/en.

Some caveats against current and future projections of mortality data for IHD in SSA include the use of approximations that often embrace substantial uncertainties, especially in the estimation of cause-specific deaths. This huge degree of uncertainty has been attributed to a meagre database on IHD as a specific cause of death in Africa and to the overall low coverage of vital registration.

Despite the heavy toll inflicted by HIV/AIDS in SSA, comparative ASMR across the continent indicate that mortality from IHD matches and already exceeds those from HIV/AIDS in some regions of SSA,[48,64-65] except in southern Africa, the epicentre of the HIV/AIDS epidemic (Table 7). In Botswana and South Africa, respectively, there were nine- and three-fold more deaths from HIV/AIDS compared to deaths from IHD. In Mauritius, ASMR for IHD was 274-fold higher than rates from HIV/AIDS, and in Seychelles, the difference was 36-fold. In Ghana, ASMR for IHD was 1.5 times that of HIV/AIDS between 2002 and 2004.

Conclusion

Nearly 40 years ago, Bradlow and colleagues[66] stated that Africa provided a vast natural laboratory for the study of the aetiology and epidemiology of heart disease. Little appears to have changed in terms of the epidemiology of IHD in SSA. The scarcity of cause-specific data makes a mockery of the case for agitating for greater action plans to combat IHD in SSA amidst a storm of infectious diseases such as HIV/AIDS, tuberculosis and malaria.

We need epidemiological data to make IHD less tentative and unconvincing to sceptics, healthcare providers and policy makers. An important starting point is the establishment of cardiac registries in multiple centres across the continent.

Various tertiary centres of excellence already exist in parts of sub-Saharan Africa for care of acute coronary syndromes and cardiac rehabilitations. However, these facilities are few and far between and are not within the reach or affordability of all of those who need them. As with HIV/AIDS, the fight against the pandemic of cardiovascular diseases must concentrate on primary prevention. Novel approaches must be developed that effectively connect community resources with organised healthcare systems and must integrate both behavioural and biomedical approaches.

IHD remains relatively uncommon in SSA despite an increasing prevalence of risk factors but its incidence is rising. The pace and direction of economic development, rates of urbanisation and changes in life expectancy resulting from the impact of pre-transitional diseases and violence will be major determinants of the IHD epidemic in SSA. The best window of opportunity for concerted action to tackle the emerging epidemic of IHD in SSA is currently shrouded by the lingering burden of infectious diseases.

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6th World Congress
Paediatric Cardiology and Cardiac Surgery
Cape Town, February 2013

Satellite symposium

Consequences of underlying infection complicate CVD management in Africa

Patients in Africa with a high risk of coronary artery disease (CAD) often have elevated levels of C-reactive protein due to inflammation caused by infections. Additionally, this underlying inflammation produces significant platelet dysfunction in people who have the added complication of diabetes. Each of these complications and their therapeutic consequences were discussed by a distinguished faculty at a symposium titled: *Unmasking cardiovascular complications: what are we missing?*

'Any infection creates a risk of myocardial infarction (MI) because bursts of inflammation destabilise arterial plaques. A high rate of infectious diseases resulting in high prevailing C-reactive protein (CRP) levels in Africa, together with social deprivation, hypertension, diabetes and renal disease add to the coronary artery disease (CAD) risk in these individuals.' This view was expressed by Prof Thomas F Lüscher, head of Cardiology, University of Zurich and current editor-in-chief of the *European Heart Journal*.

'Supportive evidence for this view on infections comes from studies in patients with long-term rheumatoid arthritis,[1] where treating these patients with simvastatin improved vascular function considerably. This vascular benefit can also be attributable to reduced levels of CRP and other inflammatory cytokines', Prof Lüscher pointed out.

Low-density lipoprotein (LDL) cholesterol is the main target for addressing the lipid-related risk of cardiovascular events, with added benefit to be derived from also addressing CRP levels. 'The potential benefit of targeting high-density lipoprotein (HDL) cholesterol has also been investigated in many trials; most of them have however been negative', Prof Lüscher said.

By contrast, the evidence for lowering LDL cholesterol is consistent, and the message for both primary and secondary prevention is 'the lower the LDL level, the better the outcome'.

'Also at the level of the coronary plaque, lowering LDL cholesterol levels as far as possible achieves better results. This was clearly shown in the ASTEROID trial with rosuvastatin where intensive therapy led to an actual regression of atherosclerosis', he explained.

JUPITER, the most important trial of lipids in primary prevention, also highlighted the value of lowering LDL cholesterol and CRP levels. In this trial, 17 000 men and women were randomly assigned to rosuvastatin 20 mg or placebo and followed up for up to five years until the occurrence of a myocardial infarction, stroke, cardiovascular-related hospital admission or cardiovascular death. Participants in the trial had low-to-normal LDL cholesterol levels (3.4 mmol/l) and raised CRP levels of 2 mg/l or higher.[2]

'There was a marked reduction in cardiovascular events in patients receiving rosuvastatin therapy and the size of this reduction was more than expected from the statistical modelling', Prof Luscher said (Fig. 1).

'The JUPITER data have also proved to be invaluable in the interpretation of the recent finding that statin therapy can increase patient's overall risk of diabetes', Prof Luscher said, referring to the recently published evaluation which showed that among the primary-prevention patients included in the JUPITER study, the cardiovascular and mortality benefits of statin therapy far exceeded the diabetes hazard, even in study participants who were at high risk of developing diabetes.[3] Nevertheless, plasma glucose level needs to be monitored in patients on statin treatment.

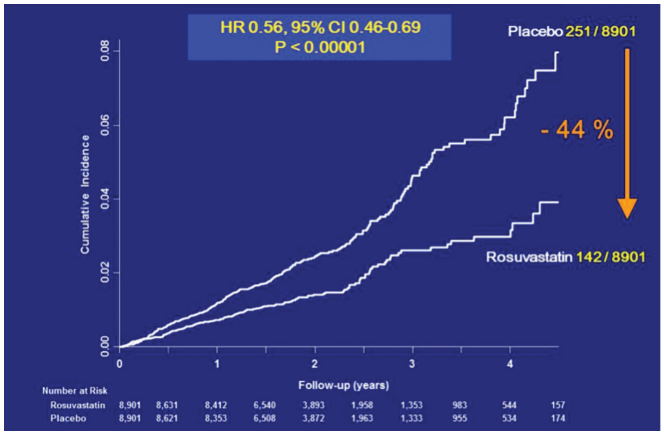

Fig. 1. JUPITER trial endpoint: myocardial infarction, stroke, UA/revascularisation, cardiovascular death.

> **"JUPITER . . . highlighted the value of lowering LDL cholesterol and CRP levels"**

New era in antiplatelet therapy

Is clopidogrel adequate in 2013?

In reviewing oral anti-platelet therapy for acute coronary syndromes today, clinicians would most likely demand that any acceptable therapy meet at least three criteria and provide:

- rapid onset of action
- reproducible and reliable inhibition of platelet activation
- acceptable risk of bleeding.

Adhering to today's standard, Dr Stephen Wheatcroft, consultant interventional cardiologist at the University of Leeds noted that his Unit now uses ticagrelor across the board for acute coronary syndrome (ACS) patients, both STEMI and NSTEMI patients. 'There is no doubt that clopidogrel is a good drug, as shown in the CURE study. However, there is also a good evidence base for the new agents, prasugrel and ticagrelor, and the latter offers significant advantages over clopidogrel', he noted.

In terms of today's criteria, ticagrelor has a faster onset of action than the other agents, as it is direct acting and does not require *in vivo* biotransformation. An active metabolite is also formed which contributes in part to ticagrelor's clinical effect.

Reproducible and reliable platelet inhibition is not a characteristic of the clinical experience with clopidogrel. 'Low responders are exposed to a doubled risk of adverse events compared to those ACS patients who respond well to clopidogrel', Dr Wheatcroft pointed out.

One of the reasons for the heterogeneity of platelet inhibition is that

Dr Stephen Wheatcroft

clopidogrel requires a two-step biotransformation in the liver to its active metabolite, thereby allowing genetic polymorphisms to influence the reliability of the antiplatelet response. Ticagrelor is direct acting and its effect is independent of genetic polymorphisms, ensuring a consistent inhibition of platelet activity.

Ticagrelor also produces a greater inhibition of platelet aggregation than clopidogrel. The more reliable platelet inhibition with ticagrelor (180 mg loading dose, then 90 mg bid) was seen in the PLATO results where ticagrelor significantly reduced the combined endpoints of cardiovascular death, myocardial infarction and stroke.

'Importantly, the overall risk reduction was not only driven by a myocardial infarction rate reduction as was the experience in the CURE study, but also by a reduction in cardiovascular death and all-cause mortality (Fig. 2). 'While the overall risk of experiencing an event was higher in medically managed patients who formed 36% of the total PLATO cohort, ticagrelor treatment also reduced the composite endpoints in this important group of patients', Dr Wheatcroft noted.

Finally, in terms of today's third criteria of safety, the additional benefits of ticagrelor did not come at the price of increased bleeding, as there was no significant difference in major bleeding rates between the clopidogrel- and ticagrelor-treated patients in the PLATO study (Fig. 2). Non-coronary artery bypass graft (CABG)-related major bleeds were more common in ticagrelor-treated patients, while CABG-related bleeding rates were similar with both agents.

While dyspnoea is an important side effect, it is typically mild, resulting in a less than 1% discontinuation rate in the PLATO study. 'In our own clinical experience, this dyspnoea is certainly mild and transient and, with appropriate reassurance, patients can continue with the medication', Dr Wheatcroft concluded.

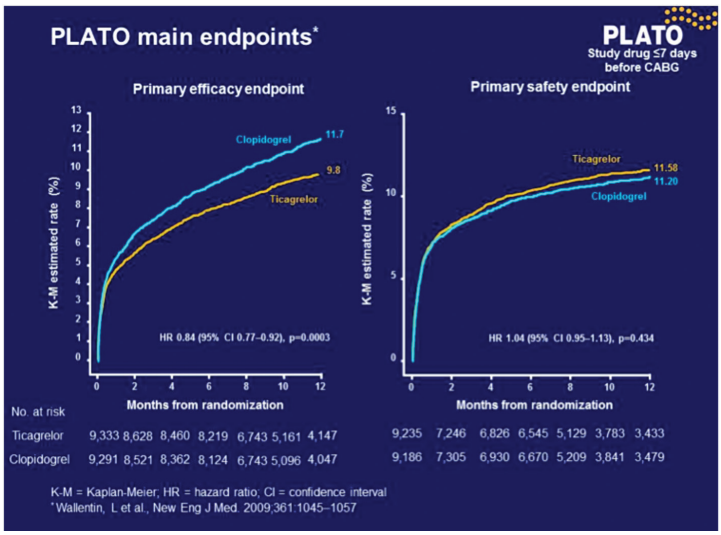

Fig. 2. PLATO main endpoints.

"There is a good evidence base . . . that ticagrelor offers significant advantages over clopidogrel"

Achieving glycaemic control

Incretins: cardiovascular safety and rationale for use

The majority of type 2 diabetes patients die from cardiovascular events with MI and stroke being responsible for 75% of the increased mortality seen in diabetic patients. 'One of the most important interpretations of the UKPDS trial[4] of newly diagnosed patients and that of the STENO II trial[5] of recently diagnosed type 2 diabetes patients is that the earlier you can treat the patient, the better the outcome, and then you can achieve a reduction in MI events over time', Dr Adri Kok, Johannesburg physician noted.

'The failure of our current diabetes treatment is that we do not achieve adequate glycaemic control. The incretins, with their weight-loss or weight-neutral effects are able to add to our HbA_{1c}-lowering efficiency without causing hypoglycaemia or further side effects in patients who are already taking multiple therapies', she said.

Dr Adri Kok

Giving a snapshot view of the GLP-1 agonist injectables, exenatide and liraglutide, followed by the oral DPP-4s (vildagliptin, sitagliptin and saxagliptin), Dr Kok noted that their usefulness has been shown in a wide range of type 2 diabetes patients on both oral and insulin therapy. 'While we do not yet have clinical trials designed to show effects on cardiovascular outcomes, there have been studies on all the incretins that indicate a cardiovascular risk reduction',[6] Dr Kok said. This finding has led to a study-generating hypothesis which is currently being evaluated in the SAVOR-TIMI53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes-thrombolysis in Myocardial Infarction).

Dr Kok noted that the 2012 SEMDSA guidelines for type 2 diabetes management support the early use of the oral DPP-4 inhibitors in combination with metformin.

'It is important to discuss with your diabetic patients their cardiovascular risk, explaining the important benefits and advantages of these incretin-based therapies as alternative to other agents such as the sulphonylurea and thiazolidinedione groups of drugs. The total cardiovascular risk of the patient with type 2 diabetes must be addressed with strict glucose control early in the course of the disease to avoid micro- and macrovascular complications later on', Dr Kok concluded.

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"The failure of our current diabetes treatment is that we do not achieve adequate glycaemic control"

6th World Congress Paediatric Cardiology and Cardiac Surgery Cape Town, February 2013

Philips hosts breakfast symposia to drive experience-sharing on minimally invasive cardiology procedures

The burden of acquired heart disease in adults and children presents a very real healthcare challenge across the world. Philips Healthcare's commitment to improving access to healthcare infrastructure in Africa was emphasised through the hosting of and participation in dialogues, discussions and workshops at the sixth World Congress on Paediatric Cardiology and Cardiac Surgery that recently took place in Cape Town, South Africa.

'Philips is committed to providing innovative solutions to the challenges that the African continent currently faces in the management of cardiology diagnoses and treatment', commented Jose Fernandes, district manager, Philips Healthcare, Southern Africa. 'At the World Congress, we e our extensive portfolio of products and solutions for cardiology. These will provide clinicians a continuum of solutions for 21st-century cardiac care, customised for them and the needs of their community.'

Discussions centred on how innovations in interventional radiology treatment are helping to transform the future of patient care. These were a platform for experience-sharing on minimally invasive cardiology procedures.

Structural heart disease interventions: the growing wave of new therapies

The standard imaging procedure for endovascular interventions is invasive biplane (2D) angiography. Three-dimensional reconstructions from pre-procedural computed tomography (CT)/magnetic resonance (MR) angiography are regarded as major advances in non-invasive cardiac imaging.

However, with the advent of three-dimensional rotational angiography (3DRA) and real-time tomographic reconstruction of the acquired images, a volumetric view of the vascular anatomy can be created. This may optimise decision making for treatment planning and may provide improved guidance during the intervention.

At one of the Philips breakfast symposia, Dr Thomas Fagan, Children's Hospital Colorado in Denver, shared his experience with multi-modal cardiac imaging in trans-catheter interventional paediatric cardiology. He performed 3DRA with the 3DRA Philips Healthcare system, employing a 4.1-second rotation of the C-arm. From his experience with more than 100 patients, he concluded that in the majority of cases, 3DRA provides additional clinically useful information compared with planar biplane angiography.

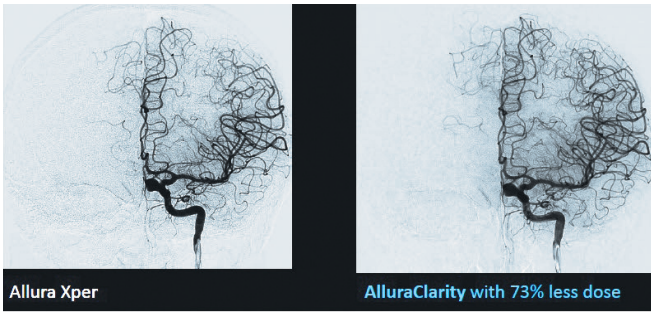
Dr Fagan also reported on the use of the Philips HeartNavigator, an interventional planning tool. With this tool he was able to segment the anatomy of interest and plan the procedure with measurements, optimal view selection and landmarks. He then registered this dataset to the live fluoroscopy in order to obtain live overlays of the anatomy, enabling him to perform the procedure under guidance.

Contrast volume could be reduced and a decrease in need for additional angiography was observed. This modality also appeared to improve confidence in the guidance of catheters. It is envisaged that 3DRA availability will become of increasing importance in paediatric cardiology and that these tools will afford virtual training in endovascular procedures.

Finally, Dr Fagan presented his recent experience with EchoNavigator, the new Philips platform, which for the first time 'makes fluoroscopy smart' by combining two live imaging modalities: fluoroscopy and transoesophageal echocardiography (TEE). The platform registers the two modalities and re-orients the live 3D echocardiographic view to match the fluoroscopic projection angle.

It also gives control to the interventionalist of the 3D TEE display, using a tableside mouse to interrogate the anatomy, rotate and crop the 3D volume, as well as place markers on the soft tissue, which then appear on the fluoroscopy screen. The tool facilitates communication between interventionalist and echocardiographer, increases interventional confidence and enables the placement of targets and reference anatomy directly on the fluoroscopy screen.

Philips Healthcare then introduced their revolutionary new interventional X-ray system: AlluraClarity. The system, built upon an unprecedented



Same image quality at 73% less X-ray dose.

A well attended breakfast symposium – Dr Greil

Prof Greil, with Lee Roering from Philips.

breakthrough in image acquisition and processing called ClarityIQ Technology, enables 75% reduction in radiation dose in neuro-interventions without compromising image quality. For the first time, reduction in dose on such a large scale is substantiated by clinical studies aiming to prove non-inferiority in image quality, as assessed by blind reviewers.

Philips also gave a presentation of the top 10 best practices to reduce dose in the cardiac catheterisation laboratory. These 10 commandments of dose management are listed below:

- Take an integrated approach to dose management, from patient management to system configuration, e.g. by using the AlluraClarity system.
- Maintain acute awareness of dose-related behaviour and exposure track records, e.g. by using Philips DoseAware, a solution which provides individual live feedback of scatter radiation dose, enabling monitoring and adjustment of behaviour.
- Reduce the source–image distance and increase the table height.
- Use shutters and wedges.
- Reduce radiation exposure per run.
- Optimise projection angles.
- Remove the anti-scatter grid.
- Use low magnification.
- Increase the distance from the radiation beam and use protective equipment.
- Use advanced imaging solutions, such as the solutions presented by Dr Fagan: 3DRA, HeartNavigator and EchoNavigator, all potentially contributing to reduced exposures.

Multi-dimensional imaging in children with congenital heart disease: an end to neonatal catheterisation?

Another breakfast symposium hosted by Prof Gerald Greil, consultant paediatric cardiologist and director of the Congenital Cardiac Magnetic Imaging Service at Evelina Children's Hospital in London. Prof Greil considered the application of multidimensional imaging in children with congenital heart disease. The thrust of his discussion centred on how magnetic resonance imaging (MRI) is replacing invasive X-ray-dependent cardiac catheterisation as a diagnostic tool, providing valuable clinical information regarding cardiovascular anatomy and physiology.

Retrospective analysis of paediatric data from elective diagnostic cardiac catheterisation or MRI in the Cardiology Department of the Evelina Children's Hospital indicates that replacing catheterisation with cardiovascular MRI results in reduced rates of complication and shorter hospital stays, without a significant impact on surgical outcome. These conclusions were based on the outcome measures of indication, length of stay and incidence of complication. In cases where the procedures were used to plan surgery, 30-day survival following the procedure was recorded. Surgical outcomes were compared between the two groups, and those using MRI were compared with national outcomes from the Congenital Cardiac Audit Database.

MRI imaging for delineating extracardiac vasculature in newborns with congenital heart disease is not widely used. Current MR angiographic techniques lack the temporal resolution to assess complex cardiac anatomy within a single breath-hold, due to fast circulation times. Prof Griel shared his experiences of four-dimensional time-resolved keyhole angiography (4D TRAK) to confirm diagnoses not fully resolved by echocardiography in newborns.

MR keyhole angiography permits rapid acquisition of three-dimensional datasets with high temporal resolution. Within a single breath-hold, the sequential

Philips team with Dr Fagan, 3rd from left.

filling of arterial and venous vessels can be visualised, overcoming the limitations of temporal resolution that existing MR angiography presents.

A retrospective review of nine neonates (< 28 days old) undergoing cardiac MR imaging with 4D TRAK performed on a commercial Philips Achieva 1.5-T scannerT assessed indication for referral, diagnosis made from the MRI scans and correlation with surgical findings. Seven patients proceeded to surgery based on the MRI, where findings were confirmed. One required no further interventions and one required diagnostic catheterisation to assess multiple aorto-pulmonary collateral arteries.

The use of 4D TRAK confers high diagnostic accuracy vital for surgical planning. 4D TRAK is appropriate where diagnostic uncertainty remains following echocardiographic assessment and should be considered in place of invasive diagnostic cardiac catheterisation or X-ray-dependent computed tomography.

Prof Greil summarised, 'We combine X-ray, MRI and echocardiography within one procedure for each patient, depending on the complexity of the cardiovascular condition. This provides tremendous benefit due to availability of more comprehensive clinical data. Therefore, replacing catheterisation with cardiovascular MRI has resulted in reduced rates of complication and shorter hospital stays, without a significant impact on surgical outcome. It also reduces costs for healthcare systems.'

R Delport, G Hardy

Case Report

ST–T-wave alternans in Brugada electrocardiogram type I pattern during the resolution of febrile states

YIFENG ZHOU, JIALI WANG, XIANLUN LI, YONG WANG

Abstract

Brugada syndrome is often electrocardiographically characterised by ST-segment elevation in the right precordial leads. The characteristic Brugada electrocardiogram pattern is often dynamic and concealed, and may be revealed during febrile states or under the challenge of drugs that have a sodium channel-blocking effect. In this report, we describe two cases of exposure of the Brugada electrocardiogram pattern during febrile states. When the patients' body temperature decreased and before the ST-elevation disappeared, ST-segment and T-wave alternans in the right precordial leads were observed, especially in lead V2.

Keywords: ST-segment elevation, body temperature, right precordial leads

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Brugada syndrome, an inherited cardiac disease causing life-threatening ventricular tachyarrhythmias in patients with a structurally normal heart, is often electrocardiographically characterised by ST-segment elevation in the right precordial leads. The characteristic Brugada electrocardiogram pattern is often dynamic and concealed, and may be revealed during febrile states or under the challenge of drugs that have a sodium channel-blocking effect.[1]

In this report, we describe two cases of exposure of the Brugada electrocardiogram pattern during febrile states. Furthermore, ST-segment and T-wave alternans in the Brugada electrocardiogram were observed when the body temperature decreased.

Case report

Case 1 was a 45-year-old man with fever due to pulmonary infection, who was admitted to our hospital. Two hours before admission, he experienced two episodes of syncopal polymorphic ventricular tachycardia in a local hospital, which were terminated by electric cardioversion. Case 2 was a 33-year-old man with fever due to a common cold. He presented to the emergency room with chest pain; no syncopal episode occurred.

Both patients' temperatures were above 38.5°C on arrival, and the electrocardiograms showed the characteristic Brugada pattern in leads V1–V3, characterised by a J wave and coved-type ST-segment elevation of 2 mm or more, followed by a negative T wave.[2] The haematological and biochemical tests, including cardiac enzymes and electrolytes, were within normal limits.

There was no evidence of structural heart disease on echocardiographic examination. Neither of the patients had a history of palpitations, syncope, febrile seizures, or a family history of sudden cardiac death. Coronary angiography revealed normal findings in patient 1.

The two patients were treated with intravenous antibiotics on the following days, and their temperature returned to normal. Repeat electrocardiogram tracings showed regression of the Brugada pattern to normal, and syncope and chest pain did not recur.

When the body temperature decreased but before the ST-elevation disappeared, ST-segment and T-wave alternans in the right precordial leads were observed, especially in lead V2. The ST-segment alternans were characterised by beat-to-beat alteration in the coved and saddle-back type of morphology. The T-wave alternans were characterised by beat-to-beat alteration in the amplitude and polarity (Figs 1, 2).

The patients were discharged without surgery. During a follow up of 10 months, neither experienced sudden cardiac death.

Discussion

ST-segment elevation in Brugada syndrome is caused by a shift in the balance of ionic current and the creation of a voltage gradient between the epicardium and the endocardium. Mutations in the cardiac sodium channel gene SCN5A, the gene encoding for the alpha subunit of the cardiac sodium channel, have been identified in 15 to 30% of patients with Brugada syndrome.

The ionic mechanism of Brugada syndrome has been shown to be temperature dependent. Febrile states may accelerate the decay of the sodium current and be associated with syncopal malignant ventricular tachyarrythmias.[3,4] Unmasking of a concealed Brugada syndrome by fever suggests that some patients may be more at risk during febrile states, such as patient 1.[5]

T-wave alternans are considered a sign of electrical instability and can be a mode of risk stratification for ventricular arrhythmia. T-wave alternans in the setting of Brugada syndrome, particularly

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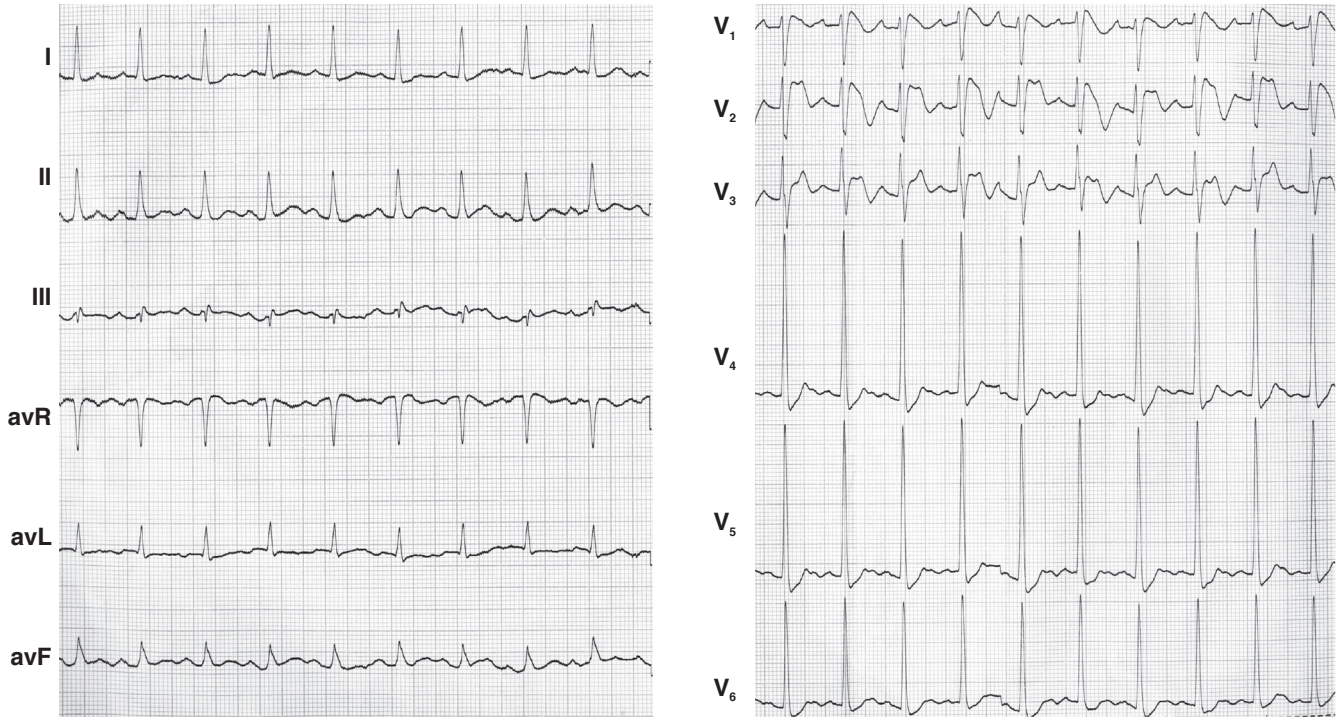

Fig. 1. Case 1: Brugada electrocardiogram pattern with ST-segment and T-wave alternans in the right precordial leads (body temperature 37.5°C).

following exposure to sodium channel blockers, is thought to be associated with an increased risk for the development of ventricular tachycardia/ventricular fibrillation.[6,7] Little is known about the occurrence of T-wave alternans in patients with Brugada syndrome.

An experimental model of Brugada syndrome showed that T-wave alternans may be due to alternating loss of the epicardial action potential dome and/or concealed phase 2 re-entry, both serving to increase transmural dispersion of repolarisation and creating the substrate for the development of ventricular tachycardia/fibrillation.[8] Similar cases of Brugada electrocardiogram patterns associated with T-wave alternans during febrile states have been described in several clinical reports.[9,10]

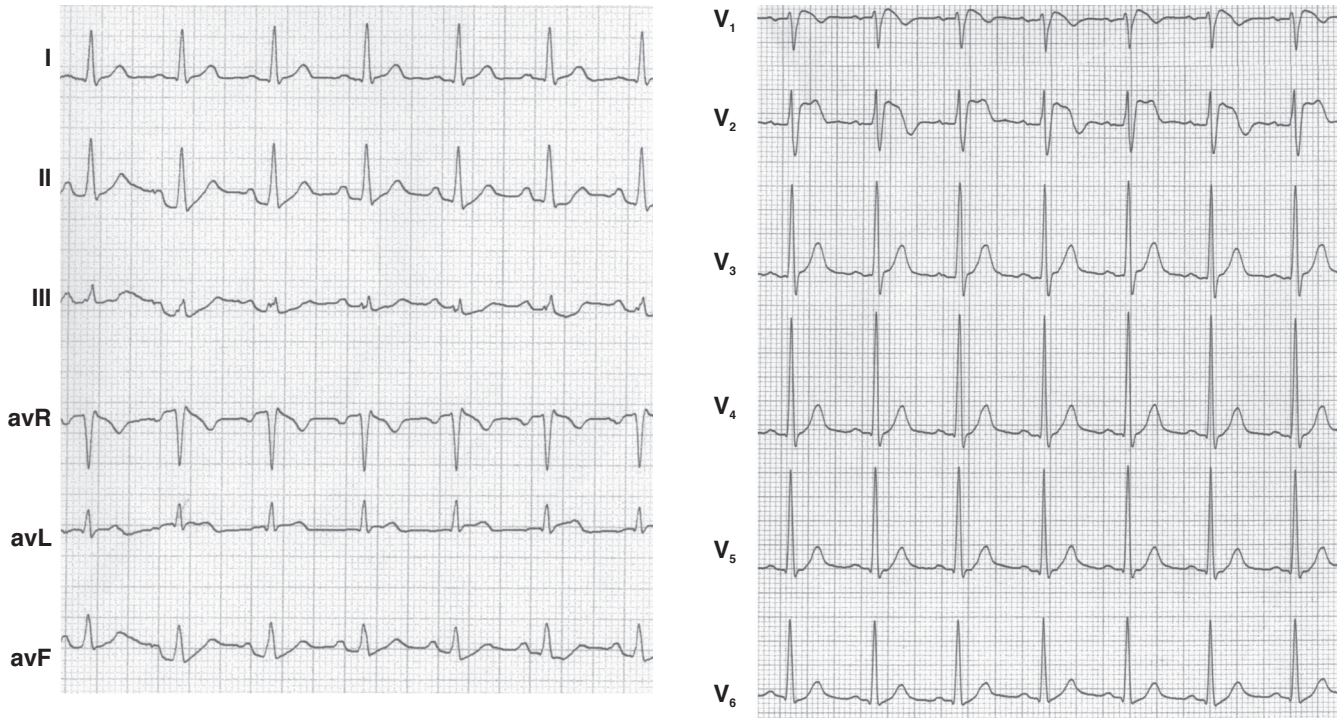

Fig. 2. Case 2: Brugada electrocardiogram pattern with ST-segment and T-wave alternans in lead V2 (body temperature 37.6°C).

In these two cases, the occurrence of both ST-segment and T-wave alternans in the right precordial leads was observed during the recovery phase from febrile states, rather than at peak hyperthermia, without associated ventricular arrhythmias. In this regard, the cellular mechanism of ST–T-wave alternans may be related to incomplete recovery of the ionic current balance, and these kinds of alternans in Brugada electrocardiogram may be regarded as normal during the recovery phase from febrile states.

Electrophysiology may be useful for the diagnosis of Brugada syndrome and risk stratification of individuals with a Brugada electrocardiogram. This was not done in these two cases.

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Case Report

Is a drug-challenge test with propafenone adequate to exclude Brugada syndrome?

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Abstract

Brugada syndrome is associated with sudden cardiac death in patients with a structurally normal heart. The electrocardiogram (ECG) pattern of Brugada syndrome is characterised by complete or incomplete right bundle branch block and ST-segment elevation in the right precordial leads. These ECG signs may not always be apparent but can be unmasked with certain anti-arrhythmia agents. We report here a case of a 26-year-old woman without detectable structural heart disease but with a history of syncope, cardiac arrest, intubation and defibrillation for ventricular fibrillation. We performed challenge tests with propafenone and ajmaline. After infusion of propafenone, there were minimal ECG changes which were not diagnostic for Brugada syndrome. One week later the provocation test was repeated with ajmaline. During infusion of ajmaline, prominent J waves and ST-segment elevation appeared in the right precordial leads (V1–3). Premature ventricular complexes were seen on a 12-lead ECG. The patient's ECG showed Brugada type 1 pattern. She received an internal cardioverter/defibrillator and was discharged with a beta-blocker.

Keywords: Brugada syndrome, propafenone, ventricular fibrillation

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Brugada syndrome (BS) is characterised by complete or incomplete right bundle branch block (RBBB) pattern with ST-segment elevation in leads V1–3 and a propensity for episodes of sudden cardiac death or syncope caused by life-threatening cardiac arrhythmias in a structurally normal heart.[1,2] The clinical presentation is distinguished by a male predominance and the appearance of arrhythmic events at an average age of 40 years.[3] The syndrome is usually identified by a characteristic Brugada-type ECG that consists of ST elevation of a coved type in precordial leads V1 to V3, although affected individuals may have a normal ECG.[4,5] Because patients with BS usually become symptomatic at a relatively young age, early diagnosis is crucial to prevent sudden cardiac death (SCD) due to a higher risk of developing an arrhythmic event.[6]

Case report

A 26-year-old woman was admitted to the Department of Cardiology for dizziness, history of syncope, cardiac arrest and cardiopulmonary resuscitation (CPR). There was no family history of sudden death. The patient had a history of syncope eight years previously while walking, without prodromal signs. The syncope attack was repeated three weeks prior to admission. She had had palpitations before the syncope but no chest pain. She had CPR for 15 minutes and had been intubated. In the ambulance she had been defibrillated twice with 360 Joules because of ventricular fibrillation, and was admitted to the emergency department.

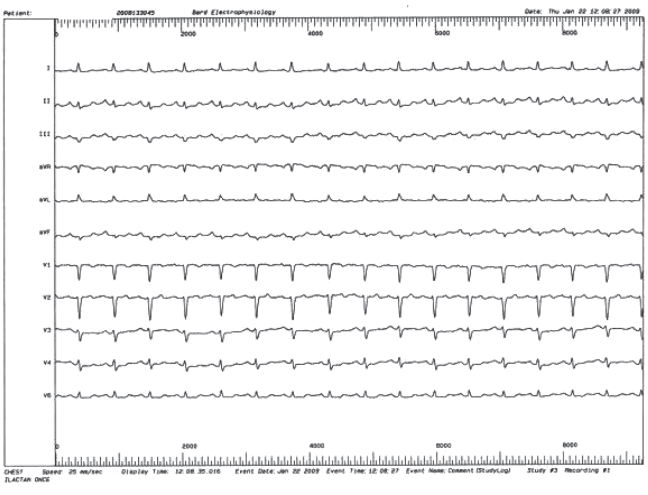

Fig. 1. Basal ECG.

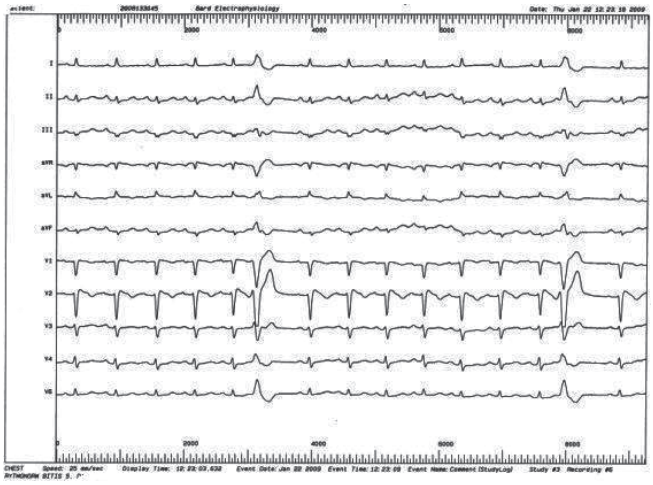

Fig. 2. Minimal ST changes after administration of propafenone and rarely premature ventricular contraction (PVC).

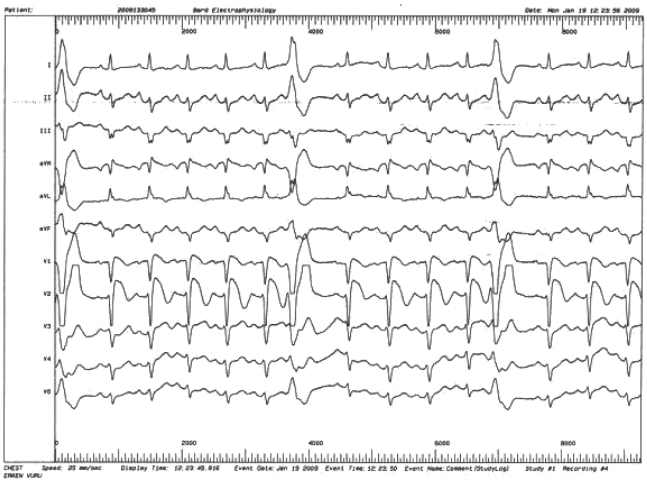

Fig. 3. New gigantic coved-type, down-sloping ST-segment elevation and J waves seen in leads V1–3 and PVCs in pairs after administration of ajmaline.

The patient's cranial CT scan was normal. There was no bleeding or cerebral infarction. She had generalised tonic, clonic seizures once due to post-CPR hypoxic encephalopathy. She had a normal EEG and laboratory analyses, chest X-rays and 12-lead ECG were normal. She had been in the anaesthesiology intensive care unit for 15 days.

After the patient was discharged, she was referred to the Cardiology Department. On physical examination she had paraparesis and spasticity on the lower extremities. She had no history of using psychotropic and class I anti-arrhythmic drugs, cocaine or insulin. The 12-lead ECG showed a sinus rate of 96 beats/min with a suspicious type 1 pattern of Brugada syndrome. The PR, QRS and corrected QT intervals were 142, 88 and 422 ms, respectively (Fig. 1).

Her blood pressure was 110/70 mmHg. Chest X-ray and routine laboratory examinations, including serum electrolytes were normal. The thyroid-function test at the time of evaluation was also within normal limits.

Echocardiography showed normal cardiac structure and function. There were no thoracic abnormalities on magnetic resonance imagining (MRI). The 24- and 72-hour Holter ECG showed a total of 25 premature ventricular, non-repetitive complexes and the heart rate variability parameters were normal.

Blood pressure recorded over 24 hours was within normal limits. Exercise-stress testing was negative for the induction of either transient acute myocardial ischaemia or arrhythmias.

The patient was also sent to the neurology department. The EEG was normal and cranial MRI was consistent with hypoxic encephalopathy (small demyelinated areas) but showed no haemorrhagia or infarction.

Informed consent was obtained from the patient and she was taken to the electrophysiology laboratory with a suspected diagnosis of BS. The drug-challenge test was performed by intravenous administration of propafenone (2 mg/kg/10 min = 90 mg for 10 min) but she had no documented spontaneous polymorphic ventricular tachycardia (VT). Minimal ST-segment changes were seen compared with the basal ECG (Fig. 2) but it was inadequate to describe BS because of minimal changes seen in the patient's basal ECGs from day to day.

The provocation test was performed one week later with intravenous ajmaline (1.2 mg/kg/5 min), during which she was continuously monitored (12-lead ECG and blood pressure). From the first minute of the test a new gigantic coved type, down-slopping ST-segment elevation and J waves were seen in leads V1–3, and premature ventricular complexes (PVCs) developed in pairs (Fig. 3). These changes reverted to the same as those in the original ECG 25 minutes after administration of ajmaline.

The patient was treated with an implantable cardioverter defibrillator (ICD) for cardiac arrest and VF. She was discharged with a diagnosis of BS.

Discussion

Due to the prognostic implications for the affected individual, it is important to recognise the suspect ECG pattern, which is the cornerstone for diagnosis of BS.[7] However, there are certain circumstances mimicking the Brugada ECG that should be ruled out. Transient normalisation of the ECG signature of this syndrome may lead to failure to recognise it. This could have negative consequences on the management of these patients at high risk for recurrence of lethal arrhythmias.

In this regard, inspection of previous ECGs and performance of a baseline and follow-up ECG in all patients to whom class I anti-arrhythmic drugs are prescribed, and carefully reviewing it for the appearance of a typical pattern of right bundle branch block and ST elevation seems good clinical practice, as it could unmask the disease in patients with occult or borderline ECG patterns. Furthermore, pharmacological interventions may facilitate development of polymorphic VT/VF. The correct diagnosis of a suspicious ECG pattern is of great importance in saving a patient's life and avoiding medico-legal consequences. Suspicion of BS should therefore lead to the performance of a pharmacological challenge.

A number of substances facilitate the elevation of the ST segment by either reducing the inward sodium current or increasing the outward potassium current. As the transient outward current is better represented on the right than the left ventricular epicardium, the transmural (epicardium–endocardium) voltage gradient is amplified in the right precordial leads where the typical ECG repolarisation abnormalities are usually displayed. Sodium

channel blockers, cocaine, antidepressants and antihistamines are known to facilitate a Brugada-type ECG by reducing the inward current.

Hyperkalaemia, vagatonic agents and IKatp activators augment the outward current, which is also transduced in the ECG as the typical Brugada pattern.[8,9] The syndrome has autosomal dominant transmission. Mutation of the SCN5A gene, which encodes for cardiac sodium channels, causes loss of cardiac sodium channel function,[10] resulting in a shortening of the action potential duration in the right ventricular epicardium. This causes a transmural voltage gradient, seen as ST elevation and re-excitation on the ECG. This voltage gradient creates a vulnerable window for extra-systoles or premature impulses to initiate phase 2 re-entry, triggering VF.

Class IA (ajmaline, procainamide) and class IC (propafenone, flecainide) anti-arrhythmia agents and heightened parasympathetic tone increase ST-segment elevation and may precipitate VF. Sympathetic activation, stress testing, isoproterenol and dobutamine may decrease ST-segment elevation and result in transient normalisation of the ECG.[11,12] The VF frequently seen during sleep in patients with BS is probably due to a decrease in sympathetic tone.

Our case underlines the ability of ajmaline to confirm an ECG pattern compatible with BS in individuals in whom the disease is suspected due to a positive family history of Brugada syndrome, syncope or sudden cardiac death, previous syncope, documented VT or a suspicious but non-diagnostic ECG.[11] Class IC and IA anti-arrhythmia drugs (flecainide, propafenone, ajmaline, disopryramide, procainamide) accentuate ST-segment elevation and are capable of unmasking concealed forms of the disease.[10-14] Class IC anti-arrhythmia drugs tend to induce ST-segment changes in BS more reliably than class IA drugs.[10,11] This was considered to be caused by the differences in the strength of the sodium channel blocking effect of class IA and IC drugs.[15]

Ajmaline, which is available only for intravenous application due to its poor oral bioavailability, seems to be the best drug to unmask BS, possibly because of its kinetics and strength of rate-dependent sodium channel-blocking effects. Additionally, a short half-life and the brief duration of its electrophysiological effects (minutes) render it superior to the other anti-arrhythmia drugs.[16] Mortality from BS is approximately 30% at two years following diagnosis.[4] An ICD implant is the only effective treatment option for prevention of sudden cardiac death in patients with BS.

Conclusion

Early recognition of BS may contribute to a decrease in the frequency of VF. Therefore, patients who have a history of syncope or sudden cardiac death in relatives, or a suspicious but non-diagnostic ECG must be evaluated carefully. If the provocation test, which is done with propafenone is negative, BS should not be excluded. The challenge test should be repeated with ajmaline.

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Case Report

Acute arterial thrombosis following chemotherapy in a patient with a gastric carcinoma

SUAT DOGANCI, MURAT KADAN, ERKAN KAYA, GOKHAN EROL, CELALETTIN GUNAY, UFUK DEMIRKILIC

Abstract

The pathogenesis of *in situ* thrombosis in cancer patients is not well known. Possible factors include endothelial damage, decreasing levels of anticoagulant factors and increasing levels of pro-coagulants. In the literature, the incidence of arterial thrombosis in cancer patients is reported to be 3.8%; 5-fluorouracil is mentioned as a rare causative agent, whereas cisplatin is thought to be the most common agent responsible for *in situ* thrombosis. In this report we present a 43-year-old male patient with bilateral popliteal artery embolism after 5-fluorouracil/cisplatin/taxotare combination chemotheraphy for gastric carcinoma. He had no additional risk factors such as smoking or any persistent organic arterial disease. He had sinus cardiac rhythm on electrocardiography and there were no abnormalities on echocardiography that could have been source of emboli. Surgical thrombectomy was performed with effective anticoagulation. After the operation, our medical oncologist discontinued 5-fluorouracil. At follow up, there was no evidence of thrombosis, with normal vascular flow rate.

Keywords: acute arterial ischaemia, malignancy, chemotherapy, surgical intervention

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Thrombotic episodes are one of the most common causes of morbidity and mortality in patients with malignancies, with or without concomitant chemotherapy. The exact pathogenesis of thrombosis is poorly understood and most likely multifactorial.[1] Chemotherapy is a recognised risk factor for thrombosis in patients with malignancy.[2] The majority of thrombotic events associated with malignancy occur in the venous system and the rate of arterial thrombosis is much lower.[3]

Despite the serious consequences of more invasive treatment modalities, and the higher rates of morbidity and mortality, the association between arterial thrombosis, malignancy and chemotherapy has not been well studied. In this report we present a case of a patient with newly diagnosed gastric carcinoma in whom bilateral femoral artery thrombosis developed after the first round of chemotherapy treatment.

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Case report

A 43-year-old male patient was admitted to our department with bilateral lower limb paresthesia, pallor and pulselessness. He had had a diagnosis of gastric carcinoma one month previously, and he had started treatment with a chemotherapy protocol of 5-fluorouracil 750 mg/day for three days, cisplatin 40 mg/day for three days, and taxotare 120 g/day for the initial day. After one day of the first treatment, his symptoms began.

Physical examination showed intact sensory and motor functions but no palpable pulses below the popliteal artery. On Doppler ultrasonography, there were three-phasic flow patterns on both femoral arteries, however from both popliteal arteries there were no flow signals. In order to identify the source of the thrombi, echocardiography was performed. There was no intra-cardiac thrombus, wall motion disorder or arrhythmia. Furthermore, the patient did not have a history of smoking or

Fig. 1. Thrombus material derived from surgical thrombectomy.

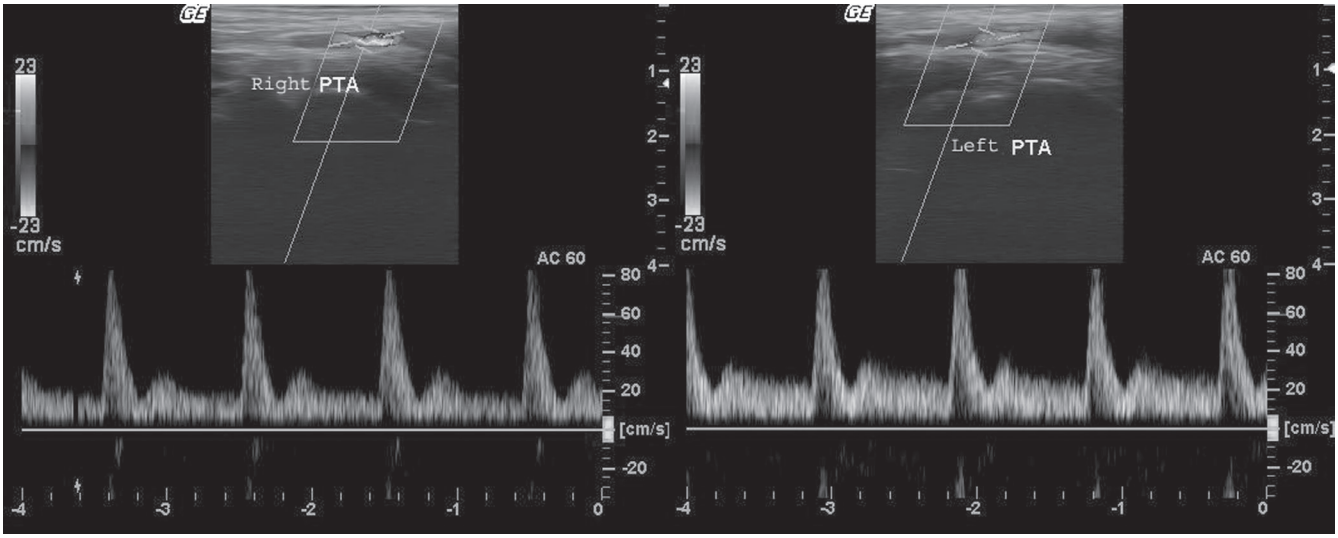

Fig. 2. Doppler ultrasonographic data of the patient's first month of follow up.

evidence of peripheral artery disease.

Anticoagulation was started immediately with unfractionated heparin (UFH), and the patient underwent surgical thrombectomy. Fresh thrombi were obtained from both popliteal arteries at the level of bifurcation via a femoral arterial incision (Fig. 1). Anticoagulant therapy was continued with UFH for three days and with low-molecular weight heparin (LMWH) at a dosage of 6 000 IU twice daily throughout his hospital stay.

He was discharged uneventfully on the fifth postoperative day with LMWH treatment (enoxaparin 8 000 IU/day). He was doing well at the first month's postoperative follow up, with palpable distal pulses, warm feet and three-phasic flow characteristics on the Doppler control (Fig. 2).

Discussion

The incidence of thrombosis in malignancy is rapidly increasing. Furthermore, malignancy is the second most common cause of death in patients with peripheral arterial disease. In one study, the incidence of clinical thrombosis in patients with cancer was 5–17% compared with 0.1% in the general population, most of which are venous thrombosis.[4] In a recent study, Tsang *et al.* reported a 3.8% incidence of arterial thrombosis in cancer patients. Of the 419 patients with acute limb ischaemia, 16 had associated cancer.[5]

Despite many shared risk factors, the association between arterial thrombosis and malignancies, and the pathogenesis of thrombosis are not well understood. Goldenberg *et al*. reported an increase in plasma levels of the thrombin–antithrombin complex and prothrombin fragments 1 and 2, together with a significant decrease in protein C activity in cancer patients.[6] Contributing factors to thrombosis in malignancy include pro-coagulant and cytokine release from damaged tumour cells, endothelial damage caused by cytotoxic agents, and decreasing levels of anticoagulants due to hepatotoxic effects of the chemotherapy agents.[5]

Up to 30 years ago, acute arterial embolism was usually caused by atrial fibrillation or mural thrombosis. The atherosclerotic process is the most common cause of this phenomenon today.[7]

However, Tsang *et al*. found that the development of arterial thrombosis in cancer patients depended mainly on spontaneous *in situ* thrombosis in vessels without any pre-existing vascular disease, rather than atherosclerosis or other structural vascular problems.[5] They reported that histological examination of the thromboembolic material derived from their subjects was consistent with thromboembolism, and no tumour cells were identified.[5] They concluded that nearly all acute ischaemic events, as in our case, are the result of thromboembolus rather than tumour emboli.

Arterial thrombosis is an uncommon adverse event following chemotherapy with 5-fluorouracil. In the literature however, cisplatin was reported as the most common agent of thromboembolism (8.4–17.6%).[5,8] In some individual case series, different aetiological agents were referred to, such as bleomicin,[9] cyclophosphamide[4] or methotrexate.[5] When we examined these studies, we noted that most used multiple chemotherapeutic agents in combination, rather than one agent.

Heinrich *et al*. reported an aorto-bifemoral embolism in an 18-year-old patient after cisplatin and 5-fluorouracil chemotherapy, and treated it with discontinuation of the cisplatin regimen.[8] However, in our patient, although he had been taking both 5-fluorouracil and cisplatin, the oncologist considered 5-fluorouracil to be the causative agent of the thrombogenesis and discontinued this agent. On LMWH treatment, there was no evidence of thrombosis, and our patient had an almost totally undamaged vascular wall and normal vascular flow rate on Doppler ultrasonography. The exact mechanism of the thrombosis triggered by 5-fluorouracil, however, is unclear.

Optimal management of cancer patients requires a strong suspicion of an ischaemic event, concurrent with immediate anticoagulation and surgical intervention. On the other hand, in patients with acute arterial thrombosis without any history of or risk factors for peripheral arterial disorder, screening for occult malignancy should be considered.[5]

Conclusion

We present an unusual case on the relationship between combined chemotherapy and arterial thrombosis. Although there are conflicting reports in the literature on the origins of thrombi, combined chemotherapy regimens may be the causative factors. However tumour-related release of pro-coagulants may also

contribute to *in situ* thrombosis. It is therefore difficult to make a distinction between causative factors. In patients with arterial thrombus we should not only change the chemotherapeutic regimen but also put them on a strong anticoagulant in order to prevent future thrombotic events.

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Case Report

Kounis syndrome secondary to simultaneous oral amoxicillin and parenteral ampicillin use in a young man

TAHIR BEZGIN, ÇETIN GEÇMEN, BIROL ÖZKAN, GÖKHAN ALICI, MEHMET EMIN KALKAN, RAMAZAN KARGIN, ALI METIN ESEN

Abstract

The concurrence of acute coronary syndrome with allergy or hypersensitivity as well as with anaphylactic or anaphylactoid reactions is increasingly encountered in daily clinical practice. There are several reports associating mast cell activation with acute cardiovascular events in adults. This was first described by Kounis as 'allergic angina syndrome', progressing to 'allergic myocardial infarction'. The main mechanism proposed is the vasospasm of coronary arteries. We present a case of a 28-year-old man who was admitted to our hospital with thoracic pain and dyspnoea. The symptoms recurred after simultaneous use of 1 g amoxicillin/clavulanic acid orally and 1 g ampicillin/sulbactam parenterally for tonsillitis the night before presentation and on the morning of admission.

Keywords: Kounis syndrome, allergic MI, penicilline-induced acute coronary syndrome

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Allergic angina and allergic myocardial infarction, referred as Kounis syndrome (KS), have gained acceptance as a cause of coronary artery spasm. Kounis and Zavras[1] described the 'syndrome of allergic angina' as the coincidental occurrence of chest pain and allergic reactions, accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult.

Causes of KS[2] include drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants), various conditions (angio-oedema, bronchial asthma, urticaria, food allergy, exercise-induced allergy, mastocytosis, serum sickness) and environmental exposure (stings of ants, bees, wasps and jellyfish, grass cuttings, millet allergy, poison ivy, latex contact, eating shellfish, viper venom poisoning).

KS due to penicillin use is rare in adults. Its appearance, caused by the simultaneous use of these agents both parenterally and orally, may be even rarer, and it has not been reported before. Such was the case in a young man, to be described below.

Case report

A 29-year-old male patient was admitted to the emergency department with symptoms of dyspnoea and severe squeezing chest pain. The symptoms had occurred the night before presentation and had recurred that morning. The patient had had an intramuscular injection of 1 g ampicillin sulbactam and 1 g oral amoxicillin clavulanate 30 min before each episode, for an upper respiratory tract infection.

His history was unremarkable for any allergic reaction, hypertension, diabetes mellitus or dyslipidaemia. He was a non-smoker. Lung sounds were clear, and no murmurs, rubs or extra sounds were found on cardiac auscultation.

The physical examination revealed blood pressure of 110/80 mmHg, a regular pulse of 81 beats/min, and oxygen saturation of 92%. He did not have pruritus or a rash. Initial and subsequent ECGs showed sinus rhythm and slight ST-segment elevation in the inferior leads (Fig. 1).

The patient's laboratory findings, taken in the emergency room, were as follows: haemoglobin 12.7 g/dl, leukocytes 11 700/µl, eosinophil count 0.04 (in the normal range), troponin I: 29 ng/ml, creatinine kinase (CK) 2 116 U/l, and CK-MB isoenzyme 101 U/l). Serum tryptase and IgE levels were not determined.

He was given 5 mg morphine sulfate, 25 mg prednisolone, 50 mg of diphenydramine and 50 mg of ranitidine intravenously. On this treatment the retrosternal pain and dyspnoea started to improve. Transthoracic echocardiography revealed normal left ventricular systolic functions and no segmentary wall-motion abnormality. An emergency coronary angiogram was performed and showed normal coronary arteries (Fig. 2 A-B, Movie 1-2).

His recovery was uneventful and he was discharged on his third day of hospitalisation. On prick-skin testing for B-lactams, a strongly positive result to penicillin was noted after discharge.

Discussion

Development of acute coronary syndrome after exposure to an allergic insult is an unexpected and rarely reported phenomenon.

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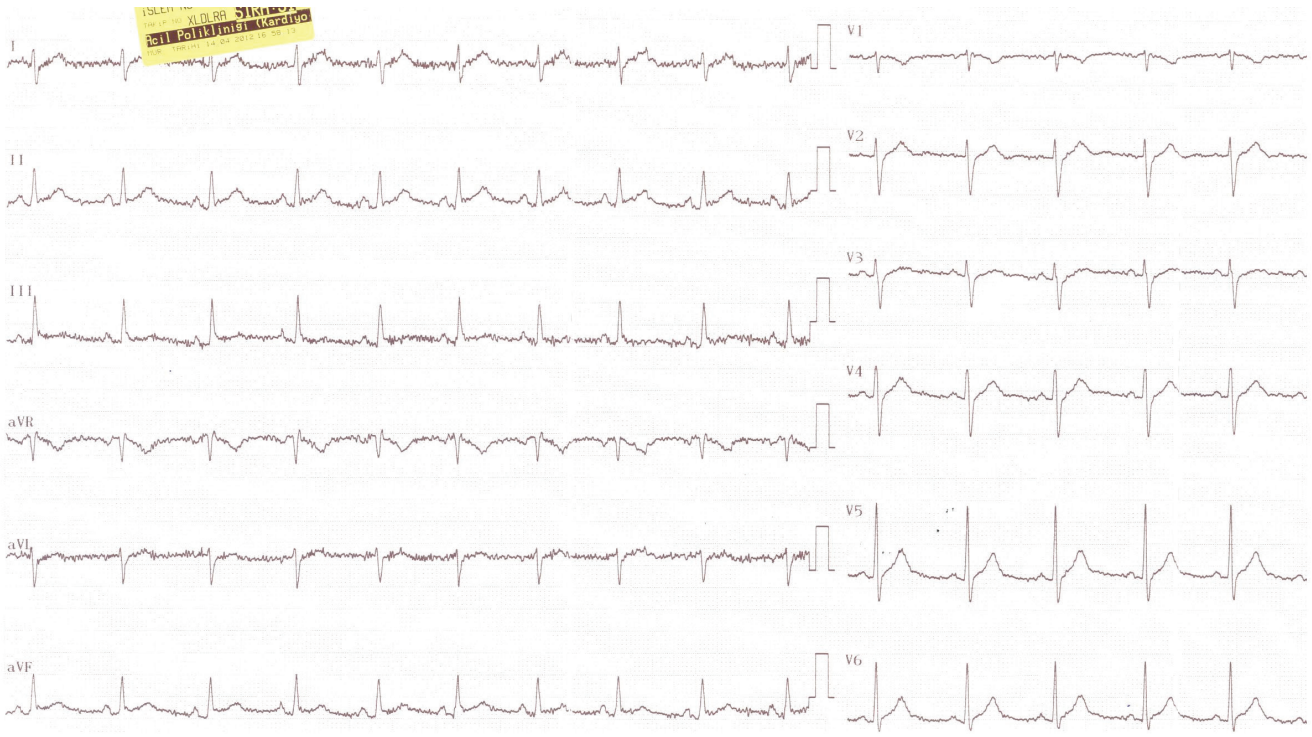

Fig. 1. The electrocardiogram shows slight ST-segment elevation in the inferior leads.

This concept of 'the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of angina pectoris' was first described in 1991 and is known as the Kounis syndrome.[1]

On recognition of this clinical entity, a number of hypotheses have been proposed to explain the causal relationship between allergic reactions and acute coronary syndromes. Of these, a mast cell-driven vasospastic and inflammatory response acting on the coronary endothelium has gained acceptance as the main causative mechanism.

Mast cells are present in numerous parts of the human body, including the heart and blood vessels. During an acute allergic reaction, activated mast cells degranulate and release large amounts of mediators, such as histamine, tryptase, platelet activating factor, leukotrienes and thromboxane. These have been experimentally shown to cause coronary artery spasm or plaque rupture.

Two types of KS have been described. The type I variant (coronary spasm), which may represent a manifestation of endothelial dysfunction or microvascular angina, includes

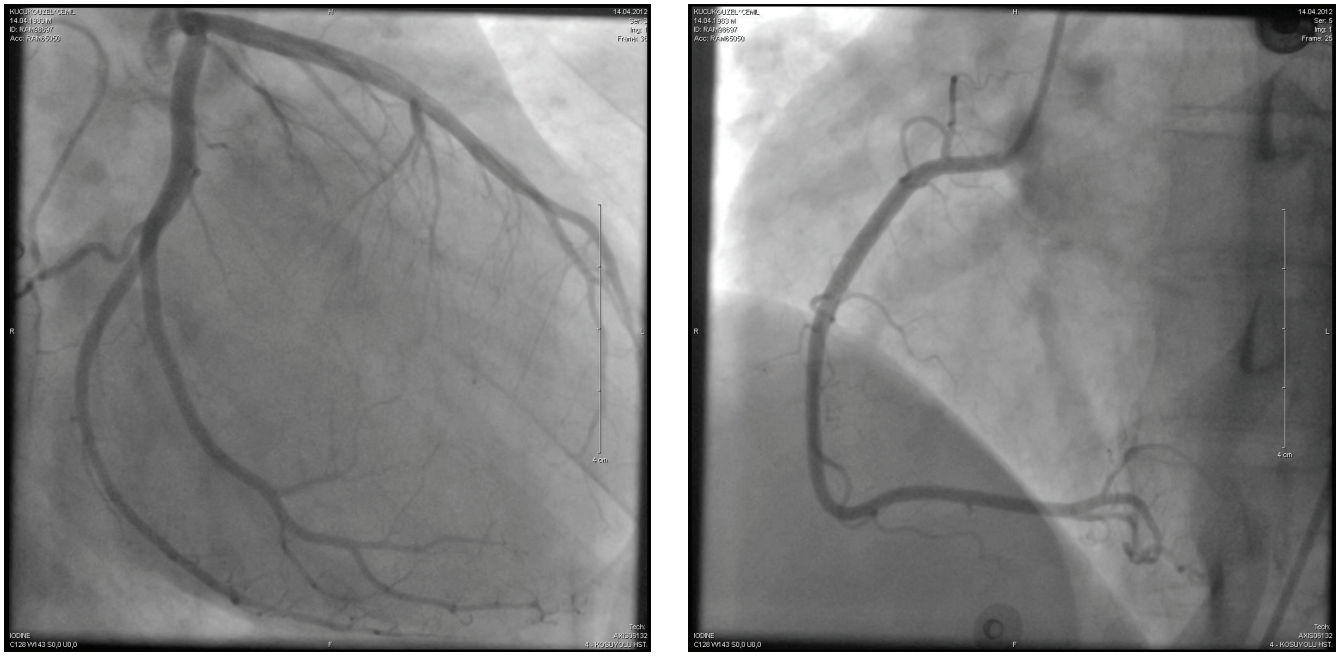

Fig. 2. The patient's left (A) and right coronary arteries (B) were normal on coronary angiography.

patients with normal coronary arteries without predisposing factors for coronary artery disease. In these patients, the acute release of inflammatory mediators can induce either coronary artery spasm without an increase in levels of cardiac enzymes and troponins, or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins.

The type II variant (coronary thrombosis) includes patients with culprite but quiescent pre-existing atheromatous disease. In these patients, the acute release of inflammatory mediators can induce coronary artery spasm with normal levels of cardiac enzymes and troponins, plaque erosion, or rupture, manifesting as acute myocardial infarction.[2]

Until now, KS was found to be related to poisons, venoms, drugs and contrast agents. Among these, antibiotic-related acute coronary syndrome is rare. It has been reported commonly only with penicillins in the course of an anaphylactic shock where coronary hypoperfusion and epinephrine-induced vasospasm were strongly proposed to explain the underlying mechanism of myocardial injury.[3,4]

However, allergy-induced acute coronary events in the absence of anaphylaxis are increasingly encountered in clinical practice, suggesting mast cell-based vasospasm as the principal mechanism.[5] It is also hypothesised that there is a threshold level of mast cell content above which it could provoke coronary artery spasm and plaque rupture. This threshold level is closely associated with the allergen concentration, the patient's sensitivity and the route of antigen entrance.[3,6]

There are studies reporting that IgE antibodies with different specificities can have an additive effect, and corresponding antigens can trigger mediator release when the patient is simultaneously exposed to them. This suggests that atopic individuals are more vulnerable to coronary artery spasm than normal people.[3,5]

The management of KS may be challenging for clinicians, and unfortunately guidelines have not been established yet. Patients with KS need treatment with steroids, antihistamines, fluid resuscitation, possibly epinephrine, oxygen and antithrombotics before transfer to the cardiac catheterisation laboratory.

The treatment should both dilate coronary vessels and suppress the allergic reaction. Vasodilator drugs, including nitrates and calcium channel blockers, should be considered as first-line therapy in young and previously healthy individuals, since vasospasm is the primary mechanism.

Acute coronary syndrome protocol should be followed in patients with the type II variant. These patients should be followed up in cardiology and allergy clinics following hospital discharge. A full cardiology work-up, including a 12-lead ECG, echocardiogram and cardiac risk-factor modification is necessary.[7]

In our patient, myocardial injury occurred in the absence of an anaphylactic reaction, strengthening the suspicion of mast cell-based pathophysiology. On the other hand, his chest pain developed suddenly without any apparent allergic reaction, suggesting a possible local effect of ampicillin and amoxicillin, individually or in combination, directly on the coronary mast cells. This sole cardiac involvement may represent another aspect of allergic reactions, ranging from urticaria to anaphylaxis.

Reasons for the variability in clinical manifestations of this syndrome are currently under research. The absence of coronary lesions on the angiogram and a positive skin-prick test for B-lactams indicated coronary spasm and type 1 variant of KS in our case.

To the best of our knowledge, this is the first case in the literature describing the association between this syndrome and penicillin simultaneously administered orally and parenterally. This report, as well as others,[8] show that this unique disease should be entertained when acute-onset chest pain is accompanied by allergic symptoms, electrocardiographic changes, and increased levels of markers of myocardial damage.

Conclusion

All patients admitted to emergency departments with chest pain, ST-segment changes on electrocardiography and/or increased markers of myocardial necrosis should be investigated for allergic insults.

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Case Report

Localised bullous eruptions after extravasation of normal saline in the forearm during left ventricular device-assisted surgery

CHIH-HSIEN LEE, CHENG-HSI CHANG, CHING-WEN WU, JENG WEI, YI-TING TSAI

Abstract

Peripheral infusion of intravenous agents is a daily routine in hospitals. Extravasation is an unintended complication associated with intravenous infusion where accidental injection or leakage of fluid occurs into the perivascular or subcutaneous space. Extravasation is fairly common but is usually without serious consequences. This has led clinicians to underestimate the potentially serious consequences of extravasation. Extravasation injury results from a combination of factors, including cytotoxicity of the solution, osmolality, vasoconstrictor effects, infusion pressure and other factors. We describe a case of upper extremity localised bullous eruptions resulting from the pressurised infusion of crystalloid solutions through an intravenous catheter, placed in the operating room during left ventricular device-assisted surgery. Peri-operative management of acute localised bullous eruptions requires surveillance for unforeseen consequences. Early recognition, diagnosis and intervention averted potential complications and morbidity.

Keywords: bullous eruptions, extravasation, ventricular assisted device

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Extravasation is defined as the unintentional leakage of solutions from the vein. This may cause damage to the surrounding tissue during intravenous infusions. Subcutaneous extravasation is a known complication of intravenous infusion of iodinated contrast solutions or cancer chemotherapy.[1,2] We describe a case of upper extremity localised bullous eruptions resulting from pressurised infusion of crystalloid solutions through an intravenous catheter, placed in the operation room during left ventricular device-assisted surgery.

Emergency peri-operative management of unstable surgical patients frequently departs from the routine of elective anaesthesia. In the operating room, however, on-going assessment and management of potential complications are the responsibility of the anaesthesiologist. He/she may also rely on colleagues in the cardiovascular team for patient care. Extravasation is fairly common but is usually without serious consequences. This has led clinicians to underestimate the potentially serious consequences of extravasation.

Case report

A 51-year-old man had a history of dilated cardiomyopathy, with regular out-patient follow up since 2008. He had suffered from sudden-onset dyspnoea and chest tightness. Because of his persistent symptoms, the patient visited our hospital for evaluation and treatment.

On the second day after admission, the patient complained of progressive dyspnoea and echocardiography showed an ejection fraction of 7%. Cardiogenic shock was diagnosed and a large dose of dopamine and norepinephrine was administrated. Emergency extracorporeal membrane oxygenation (ECMO) was set up.

He received a left ventricular assistance device on the second day after ECMO. On arrival in the operation room, routine monitors were attached and general anaesthesia was maintained, with a non-invasive blood pressure (NIBP) cuff positioned on the upper right arm. A right antecubital 16-gauge intravenous catheter was inserted. The operative procedure was performed without any problems.

Unstable vital signs were noted after cardiopulmonary bypass was stopped. His blood pressure (BP) decreased rapidly from 100/60 to 60/40 mmHg, as determined by the NIBP device. Approximately 2 000 ml of normal saline was infused into the right antecubital vein using pressure bags inflated to 150 mmHg. Dopamine, norepinephrine and blood products were added to the

central vein catheter over the next five minutes, with subsequent stabilisation of his BP.

After the operation, we noted the localised bullous eruptions on the right forearm (Fig. 1). Further examination revealed red, swollen blisters over the right forearm (Fig. 2). This condition had not been noticed earlier. Digital capillary refill was noted to be delayed compared to the contralateral extremity. The NIBP cuff and right antecubital catheter were removed and the cardiovascular team was alerted. Doppler monitoring detected diminished right radial and ulnar pulses.

Extravasation of the fluids infused under pressure was the apparent aetiology. Initially, conservative treatment was chosen with needle aspiration of the fluid in the localised eruptions. We then sent the patient to the intensive care unit with protective gauze covering the right forearm. The right upper extremity was closely monitored during the initial postoperative period. Neurological and vascular functions remained intact.

Seven days after the operation, the forearm oedema gradually decreased and the wound was clean. He underwent heart transplantation one month later. Follow up at six months identified no long-term sequelae of his upper extremity injury.

Discussion

Peripheral intravenous infusion of agents is a daily routine in hospitals. Extravasation injury is defined as damage caused by leakage of fluid from a vein into the surrounding tissue spaces during intravenous infusion. Extravasation of intravenous infusions is one of the iatrogenic complications frequently encountered in hospitals.

For central venous catheters, extravasation is less frequent but potentially more dangerous because the anatomical structures escape attention. Depending on the insertion depth, the extravasal position of the proximal port can occur when the catheter is inadvertently withdrawn just a few centimetres.[1] Extravasation may also go unnoticed in peripheral lines when the area is covered by drapes during surgery. This has led clinicians to underestimate the potentially serious consequences of extravasation.

Common sites of injury are the dorsum of the hand (extension crease to the metacarpophalangeal joint) and the antecubital fossa, where there is little soft-tissue coverage.[3,4] Venous extravasation is caused by escape of the needle or cannula tip from the vessel lumen through accidental pull out, penetration of the counter vessel wall, or injection of large volumes or at a fast rate through the infusion pump with the needle still inside the vein.[2,3] However, in most cases, the tip of the cannula remains in the lumen and extravasation is through the hole made by the cannula or needle entering the vein.[3,4]

Extravasation is relatively more common in elderly or cachetic patients, whose veins are more fragile, and the puncture hole from the cannula is easier to enlarge, which may cause a leak. Our patient was a typical example. The vascular supply to the skin has been described as segmental perforator systems. Extravasation of fluid stretches the vessels, leading to partial venous occlusion, followed by arterial occlusion.[4] The resulting increase in intraluminal pressure leads to leakage of fluid from the puncture site.[3]

In the peri-operative period, the mechanism of tissue necrosis can include solution cytotoxicity, osmolality, vasoconstrictor effects, infusion pressure, regional anatomical peculiarities, and other factors.[1,4] If this continues for an extended period of time, cellular death and skin breakdown follow.

In our case, blistering was a sign of serious skin injury, possibly resulting from oedema. The depth and extent of tissue injury depend on factors such as the volume of fluid extravasated, composition of the fluid, location of the leak, passage of time before the accident is discovered, and the measures taken after discovery of the incident.

Given this situation, intra-operative attention and on-going patient assessment by the anaesthesiologist is important. In our case, a swollen forearm and diminished radial pulse were the only findings that prompted further investigation. Prompt

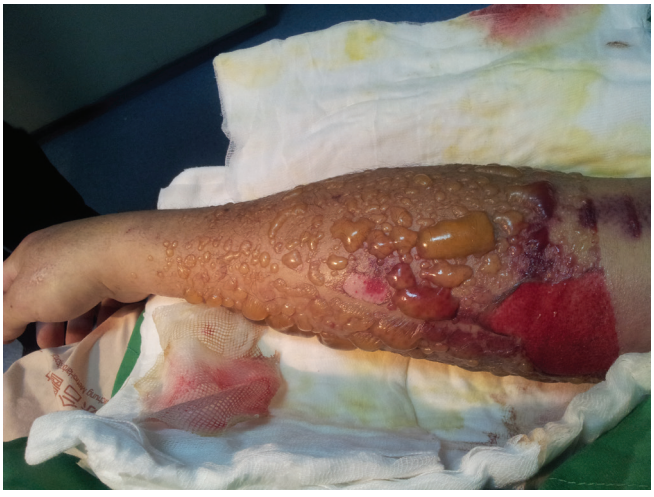

Fig. 1. Localised bullous eruptions on the right forearm.

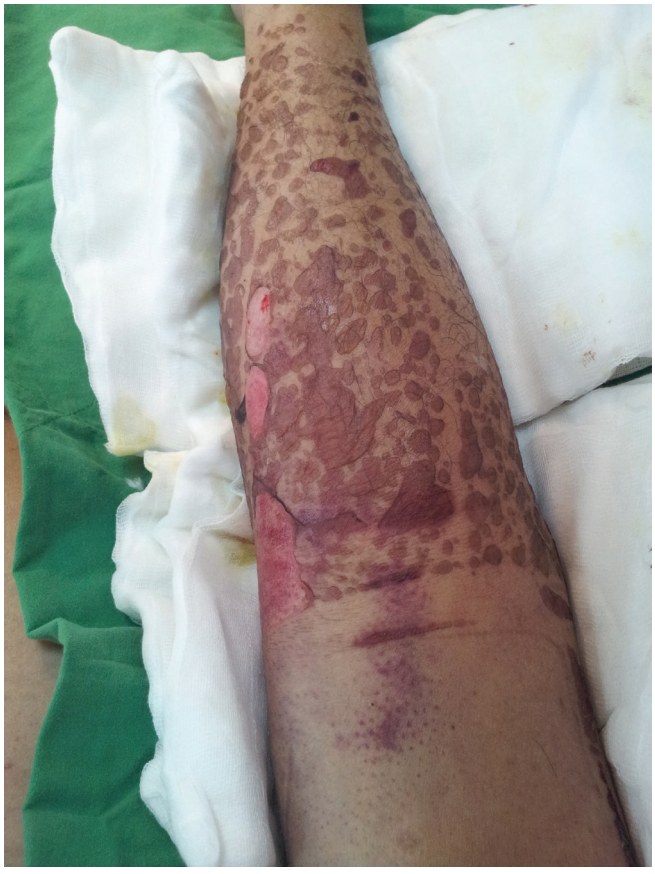

Fig. 2. Red, swollen blisters over the right forearm.

evaluation and diagnosis can avoid potential complications and morbidity.

The clinical manifestations of extravasation of solutions can range from mild redness and swelling of the tissue to necrosis associated with progressive oedema of the skin.[2] Pain, swelling or local hyperthermia are not reliable predictors of the degree of tissue damage.[1,2] Furthermore, agents that cause pain during intravascular injection may not necessarily cause tissue injury upon extravasation.

Tissue damage after extravasation may be slight and may involve a limited local inflammatory response or may be large and involve necrosis of the skin and underlying soft tissues.[1] The degree of damage depends on the localisation of the extravasation, the physicochemical characteristics of the agent administered, and the duration of soft tissue exposure to the agent.[1] In some cases, extravasation accidents have caused injuries ranging from painful swelling to deep necrotic lesions with damage to nerves, tendons and vessel. Local skin necrosis after extravasation of chemotherapy drugs is responsible for 0.5–6% of extravasation cases.[1]

Most cases of subcutaneous extravasastion occur due to small volumes of extravasation of contrast, causing pain, minimum swelling and localised erythema, which rapidly subsides.[2] If larger volumes are extravasated, extensive tissue and skin necrosis may occur.[2] Although extravasation is a frequent but usually benign injury, one should carefully evaluate the patient for the classic 5Ps: pain, paresthesias, paresis, pallor and pulses.

There is no general agreement regarding the best approach for the management of extravasation. Most surgeons believe that a large proportion of injuries caused by extravasation heal without surgery and recommend a conservative approach.[2] In the face of the devastating consequences of tissue destruction, flushing and drainage of the affected area should be strongly considered.[1] Once a harmful extravasation is noticed, the infusion should be stopped immediately and aspiration of the extravasated solution with a syringe should be attempted before the wandering needle is removed.

The most important measure to minimise complications caused by extravasation is not to insert intravenous catheters outside the visual area and observation limits of the anaesthesiologist. Multiple punctures of the same vein, high infusion pressure, tourniquet effect, and peripheral access sites in close proximity to tendons, nerves or arterial vessels should be avoided.[1]

Larger veins in the forearm without a blood pressure cuff are recommended sites for intravenous access. All venous accesses should be visible and checked regularly, and nurses should be educated to recognise abnormalities with venous-access cannulas to allow early treatment of extravasation during surgery.

After an extravasation has occurred and been recognised, an immediate systematic approach may help to prevent extensive tissue injury.[1] Most (86%) of the patients reported by Schummer and colleagues healed without any soft tissue loss.[1]

Elevation of the limb is often useful to reduce oedema, and cooling the injection site with ice packs is useful to limit inflammation.[2] Corticosteroids, vasodilators and a variety of other drugs have also been proposed for the treatment of extravasation, but most studies have not shown their efficacy.[2] There are contradictory reports on the efficacy of treating extravasations with topically applied drugs.[1]

Even when extravasation is recognised, underestimation of the risk for subsequent tissue damage is common.[1] This often results in inadequate management. In addition, to evaluate the extent of deep-tissue damage, magnetic resonance imaging is advised.[1]

The risk of extravasation can be reduced. Prompt and appropriate intervention is important to avoid or minimise extensive tissue injury. Treatment options are outlined and emphasis is made on prevention of this iatrogenic complication.[2] Clear information to patients and prompt recognition of the complication can allow for other non-surgical treatment options.

Conclusion

Infusion sites should be inspected regularly where possible in patients under general anaesthesia. Medical personnel should be made aware of the possibility of extravasation incidents so that early diagnosis and treatment can be carried out. However, the best way of treating an extravasation injury is to prevent it.

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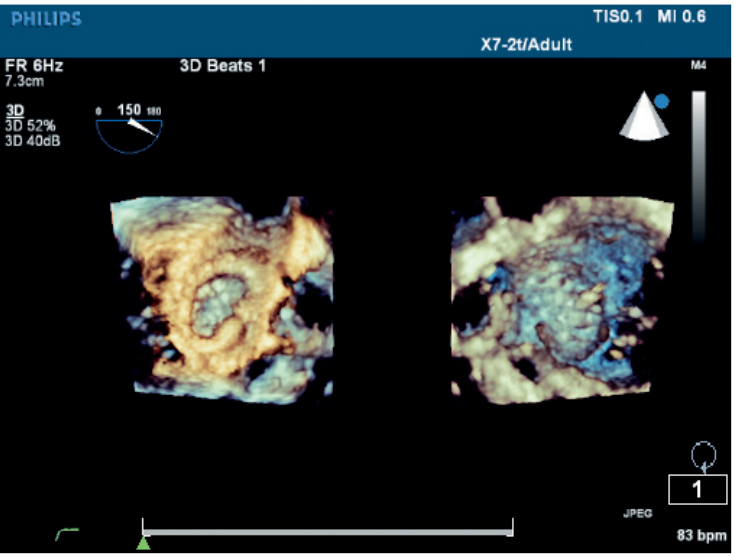

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