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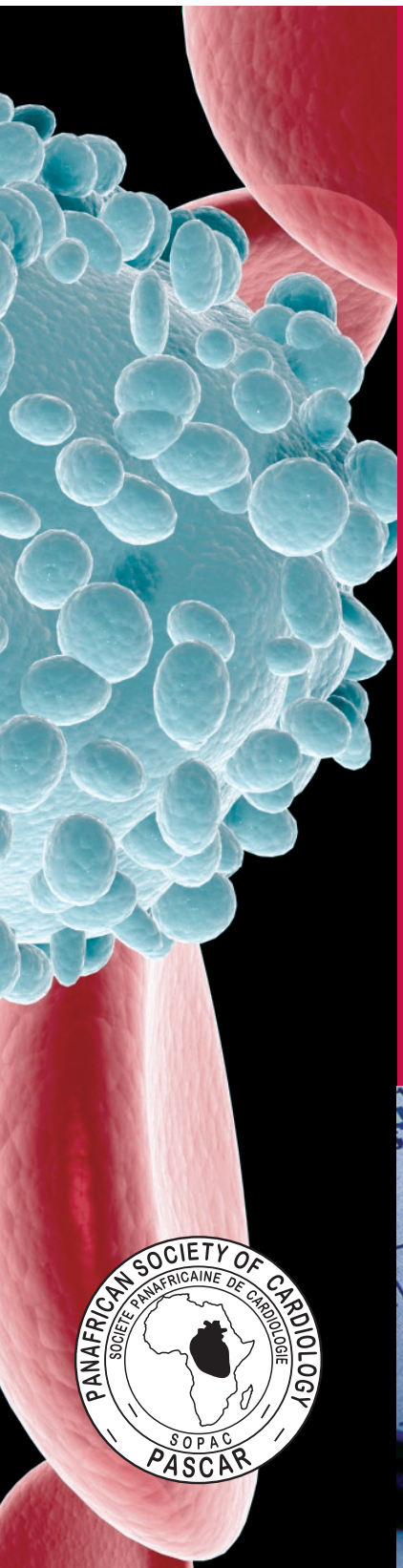

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Editorial

Atrial high-rates episodes: fact or fiction?

Cardiac implantable electronic devices (CIEDs) with atrial-lead sensing afford clinicians a unique opportunity for continuous heart-rhythm monitoring and the detection of atrial high-rate episodes (AHREs). AHREs are recorded as atrial electrograms (EGMs) and stored by CIEDs (date, number and duration of these episodes are recorded). In this issue of the journal, Simu and colleagues (page 102) have written an excellent review to guide physicians and cardiac technologists who are faced with interpreting and managing this relatively new entity.[1] Several aspects of this review need to be highlighted.

Clinicians need to be aware of the definition regarding timing and duration of an AHRE. The current 2020 European Society of Cardiology atrial fibrillation guideline defines AHRE as an atrial rate ≥175 beats per minute with a duration of at least five minutes, while the European Heart Rhythm Association (EHRA) consensus statement refers to higher atrial rates, > 190 beat per minute.[2-4]

While the absolute atrial rate is not important, at these high rates, AHREs are usually due to atrial fibrillation (AF), atrial flutter or other atrial tachyarrhythmias. AHREs are usually clinically silent, brief, and occur without a prior confirmed diagnosis of AF or atrial tachycardia (AT). Paroxysmal episodes of symptomatic AF, previously confirmed on a Holter or electrocardiogram (so-called clinical AF), should not be classified as an AHRE and have different clinical and management implications as these patients are likely to have higher AF burdens. The term subclinical AF can be also be used to describe these AHREs in an asymptomatic patient and the terms can be used interchangeably.

It must be noted that not all AHREs classified by the CIED as AT or AF are due to AF or even an AT. This finding was highlighted from the ASSERT (ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing) trial, which reported 17.3% false positives when 6 000 AHREs were reviewed.[5] These findings highlight the requirement that all EGMs be reviewed to exclude false positives such as far-field oversensing of the T or R waves, myopotentials, premature atrial ectopics, electromagnetic interference on the atrial lead and other supraventricular tachycardias. Examples of AHREs are shown in Figs 1 and 2.

As most patients are asymptomatic during AHREs, episodes are often discovered incidentally at a routine pacemaker clinic. Technologists and clinicians should always perform a detailed CIED interrogation and review CIED diagnostics carefully to classify AHREs. This is important as the incidence of AHREs not due to AF is relatively high. In patients 65 years of age or older without a prior history of AF, AHREs are detected in 10% of subjects by three months of device implantation, in 24% by one year and in 34% by two years.[6,7] If home monitoring is available, downloads of transmissions must be reviewed on a regular basis. It is important to emphasise that AHREs progress to clinical AF in 16% of patients over a 2.5-year period and should prompt closer follow up of these patients, preferably with home monitoring.[6]

There are still many unanswered questions with regard to the clinical implications of AHREs. It is increasingly recognised that AHREs are associated with an increased risk of stroke. However, this finding comes mainly from the ASSERT trial, which was the only trial that did not include patients with a prior history of AF.[6] Therefore the burden of AF may have been higher in all studies where prior clinical AF was recorded, with the finding that AHREs (in the absence of prior clinical AF) increase the risk of stroke, based on a single study. The lower burden of AF in patients with AHRE/subclinical AF can explain the lower absolute thromboembolic risk seen with AHRE compared to clinical AF.

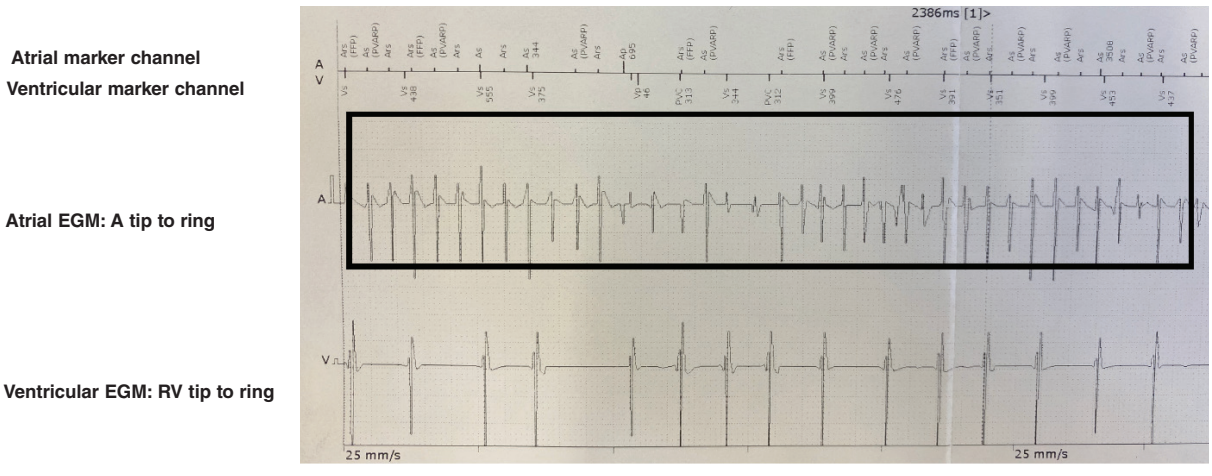

Fig. 1. Intracardiac EGMs and marker channels depicting an AHRE consistent with AF. The box indicates bipolar sensing of the atrial lead with irregular fast atrial EGMs indicative of AF.

The AHRE burden, which takes into account the number and duration of episodes, may be a better description compared to the longest AHRE alone. The absolute burden required to increase thromboembolic risk remains unclear. A re-analysis of ASSERT only demonstrated an increased risk of stroke for AHREs of longer than 24 hours.[8]

The role of anticoagulation in the management of AHREs is still being investigated in randomised, controlled trials. The temporal relationship between AHRE and stroke risk also remains unclear. The finding from the ASSERT and TRENDS (The Relationship between daily atrial tachyarrthymia burdEN from Implantable device Diagnostics and Stroke risk) trials, that only a quarter to a half of patients sustained an AHRE within one month of the stroke, suggests that AHREs may be a marker of increased risk and not directly causative.[9,10]

Until these answers are obtained from ongoing trials, individual practice is likely to vary and be guided by expert opinion. The 2020 European Society of Cardiology atrial fibrillation guidelines recommend a complete cardiovascular examination with an ECG, including risk-factor management and thromboembolic risk assessment, using the CHA_2DS_2VASc [Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female)] score.[2]

Clinicians need to monitor for clinical AF and an increase in burden of AHREs. The most important management decision is whether to treat with anticoagulants. AHREs are classified as short (rare), longer (one to 24 hours) and long episodes (> 24 hours).[2] The guideline recommends consideration for anticoagulation in patients with CHA_2DS_2VASc scores ≥ two for men and ≥ three for women, and patients with long episodes of AHREs (≥ 24 hours) and with a high burden of AHREs.[2] Shared decision making is essential. The 2017 EHRA consensus document on CIED-detected arrythmias recommends initiating lifelong anticoagulation therapy if the episode was longer than 5.5 hours, based on the patient's CHA_2DS_2VASc score (≥ one, male patient; ≥ two, female patients).[3]

In summary, AHREs have emerged as an important cardiovascular condition that is likely a precursor to AF. Recognising this entity as fact needs to trigger the start of a journey with the patient, which includes regular follow up of the

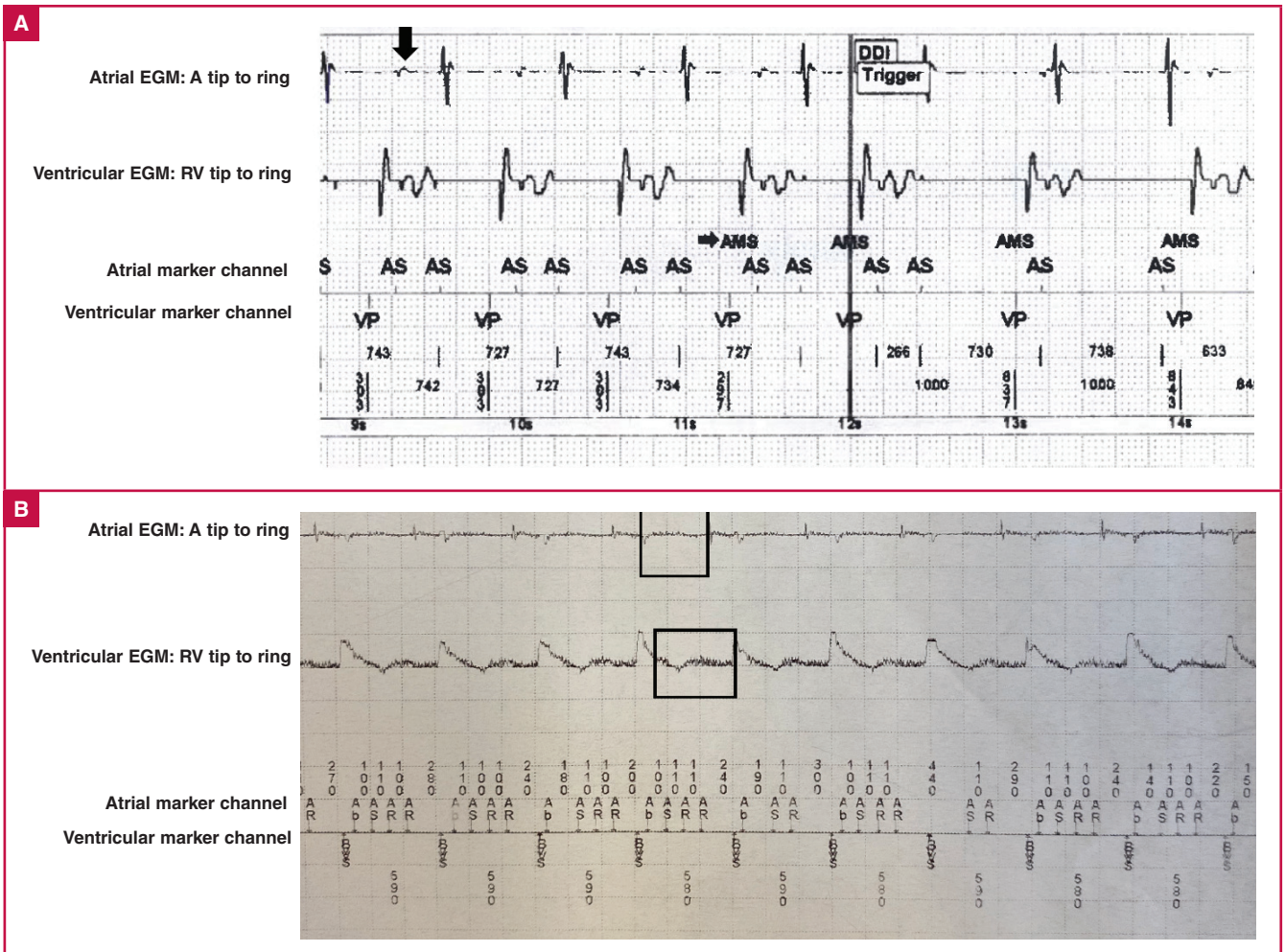

Fig. 2. Intracardiac EGMs and marker channels depicting examples of AHREs consistent with oversensing. A. Far-field R-wave oversensing. The arrow indicates far-field R-wave sensing in the atrial channel (atrial EGM), which results in double counting of the atrial rate. P waves are annotated as AS or atrial sensed, and paced QRS complexes as VP or ventricular paced in the marker channel. B. Oversensing due to electromagnetic interference. The boxes indicate high-frequency electromagnetic noise in both the atrial and ventricular channels. Note the marker channel, which shows very rapid non-physiological intervals (annotated as AS and AR or atrial refractory).

CIED, and which may include the initiation of anticoagulation in higher-risk patients.

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Omega-3 based medicine plus statins may lower stroke risk another 36%

Taking the triglyceride-lowering prescription medicine icosapent ethyl cut the risk of stroke by an additional 36% in people at increased risk of cardiovascular disease who already have their bad cholesterol levels under control using statin medications, according to preliminary research to be presented at the American Stroke Association's International Stroke Conference 2021. The study's results do not apply to supplements available over the counter, stressed the statement released by the American Stroke Association.

'Icosapent ethyl is a new way to further reduce the risk of stroke in patients with atherosclerosis or who are at high risk of stroke, who have elevated triglyceride levels and are already taking statins,' said Dr Deepak L Bhatt, lead author of the study and executive director of interventional cardiovascular programmes at the Brigham and Women's Hospital Heart & Vascular Centre in Boston.

Icosapent ethyl is a prescription medication that is a highly purified form of the omega-3 fatty acid eicosapentaenoic acid. 'It is very different in terms of purity compared to omega-3 fatty acid supplements available over the counter, and these results do not apply to supplements,' said Bhatt, who is also professor of medicine at Harvard Medical School.

Icosapent ethyl was first approved in July 2012 by the US Food and Drug Administration as an adjunct treatment to dietary changes to lower triglycerides in people with extremely high levels of triglycerides (higher than 500 mg/dl = 5.65 mmol/l). Triglycerides are fats from food that are carried in the blood; normal levels for an adult are below 150 mg/dl (1.7 mmol/l).

In late 2018, the REDUCE-IT trial, an 8 000-person multinational study, demonstrated that icosapent ethyl could benefit people with heart disease, diabetes or triglyceride levels above 150 mg/dl and whose low-density lipoprotein (LDL) (bad) cholesterol levels were already under control using statin medication. In the trial, adding icosapent ethyl (compared with a placebo) reduced the risk of serious cardiovascular events (heart attack, heart-related death, stroke, need for an artery-opening procedure or hospitalisation for heart-related chest pain) by 25%.

In December 2019, the FDA approved icosapent ethyl as a secondary treatment to reduce the risk of cardiovascular events among adults with elevated triglyceride levels, and it is now recommended in some professional guidelines. Icosapent ethyl is not included in the American Heart Association's 2018 cholesterol guidelines that were published online prior to the availability of the REDUCE-IT primary results.

In the current analysis, REDUCE-IT Stroke, researchers performed an additional analysis of the impact of icosapent ethyl on stroke in the same 8 000 participants of the original REDUCE-IT trial. They found the risk of a first fatal or non-fatal ischaemic stroke was reduced by 36% for patients treated with icosapent ethyl; for every 1 000 patients treated with icosapent ethyl for five years, about 14 strokes were averted; and the risk of a bleeding stroke was very low, and no difference was found among those taking icosapent ethyl.

'Know your triglyceride levels. If they are elevated, ask your doctor if you should be taking icosapent ethyl to further reduce your risk of heart attack and stroke,' Bhatt said. 'Your doctor may also recommend that you change your diet, exercise, lose weight if needed to lower your triglyceride levels, and may prescribe a statin medication if you need to lower your LDL cholesterol levels.'

'One study limitation is that icosapent ethyl may increase the risk of minor bleeding,' Bhatt added.

Source: Medical Brief 2020

Cardiovascular Topics

The spectrum of rheumatic mitral valve regurgitation presenting to Inkosi Albert Luthuli Central Hospital, KwaZulu-Natal, over a 10-year period

Nomthandazo Lynn Zwane, Somalingum Ponnusamy, Datshana Prakesh Naidoo

Abstract

Background: Recent evidence suggests that there is a change in the profile of rheumatic mitral regurgitation (MR) in South Africa to a pattern of chronic fibrotic valvular disease.

Objective: This study describes the clinical profile of patients with rheumatic MR in the province of KwaZulu-Natal (KZN).

Methods: A retrospective chart review was performed on patients seven years and older with moderate to severe rheumatic MR referred to Inkosi Albert Luthuli Central Hospital from 2006 to 2015.

Results: There were 320 patients meeting the study criteria (mean age 22.2 ± 15.8 years, male:female 1:2). Severe dyspnoea was present in 45.9% of patients, heart failure in 117 (36.6%) and atrial fibrillation in 13.8%. Three patients were diagnosed with active carditis at initial presentation and a further 31 had evidence of carditis during follow up. Of the 216 patients who underwent surgery, over one-third (37%) had prolapse of the anterior mitral leaflet, which was due to chordal elongation (n = 63, 29.2%) and/or ruptured chordae (n = 41, 19%). There were 32 deaths (10%) and of these, 27 (8.4%) patients died prior to surgery.

Conclusion: Rheumatic MR in KZN predominantly affects the young, with concomitant carditis resulting in high morbidity and mortality rates.

Keywords: rheumatic MR, rheumatic carditis, echocardiography, chordal elongation, mitral valve surgery

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The epidemiology of non-communicable diseases in low- and middle-income countries highlights rheumatic heart disease (RHD) as one of the leading causes of death, accounting for up to 1.4 million deaths worldwide per year.[1,2] The gravity of this problem is defined by the degree of complications associated with the disease, such as atrial fibrillation, heart failure, stroke, infective endocarditis and death.[3-7] Recent hospital-based studies in South Africa (SA) reveal an incidence of congestive heart failure secondary to RHD of 25 cases per 100 000 per year.[8,9]

Despite the magnitude of the problem, there is a paucity of data on the disease characteristics, including the demographic pattern, clinical presentations, complications and management in the majority of South African provinces, KwaZulu-Natal (KZN) included.[9] In light of this problem, the World Health Organisation (WHO) has called for a clear documentation of the contemporary clinical characteristics of the disease together with notification of new cases,[10] and has targeted a 25% reduction in mortality rate from RHD and other non-communicable diseases by the year 2025.[10] During the 2016 National Rheumatic Fever week, it was pointed out that SA has the conditions required for successful eradication of RHD, provided detailed characteristics of the disease are well documented and ensuing guidelines implemented.[11]

RHD affects all cardiac valves to varying degrees[12,13] and remains the predominant cause of mitral regurgitation (MR) in geographically low- and middle-income regions, including the South African context.[12] While rheumatic MR has been well documented in some parts of SA,[12,14-16] uncertainty remains about the disease characteristics in the KZN population.

Approximately 30 years ago, Marcus *et al*.[14] published a study on 700 patients with rheumatic valvular heart disease from Chris Hani Baragwanath Academic Hospital (CHBAH) in which he detailed demographic, echocardiographic and surgical data on MR. These data revealed a disease process mainly affecting young individuals with concomitant acute rheumatic carditis.[14] In a study in 1989, Marcus *et al*.[15] performed echocardiographic analyses on 73 young patients (mean age 13 years) with acute rheumatic carditis and severe MR. Here the majority (94%) of the study population had anterior mitral leaflet (AML) prolapse, as noted on the echocardiogram and confirmed at surgery. It was concluded that the mechanism of severe rheumatic MR in acute carditis was mainly due to annular dilatation and chordal elongation.[15]

In a more recent prospective cross-sectional study at the CHBAH, Meel *et al*.[16] described a change in the demographic

profile and echocardiographic findings in 84 subjects with rheumatic MR. In contrast to previous findings,[14,15] Meel and colleagues' subjects with MR were older, with greater associated co-morbidities and less evidence of acute rheumatic fever (ARF).[16] The echocardiographic features revealed signs of chronic disease with leaflet thickening and/or calcification in subjects with isolated rheumatic MR.[16]

Rheumatic MR is an under-studied condition in the KZN population compared to the rest of the country. In this study we examined the clinical profile of subjects with rheumatic MR in KZN and evaluated their surgical findings to determine whether the pattern of disease involvement is similar to that of the rest of the country. Our aim was to document the demographics, clinical presentation and outcomes of patients with rheumatic MR who had presented to our tertiary/quaternary unit over the last 10 years. In order to make a comparison with previous studies, Meel's exclusion criterion was used as part of the sample selection.[16]

Methods

All patients seven years and older with moderate to severe rheumatic MR, confirmed at echocardiography, in the Department of Cardiology at Inkosi Albert Luthuli Central Hospital (IALCH) over a 10-year period (2006–2015) were eligible for inclusion in the study.

Ethical approval was obtained from the Biomedical Research Ethics Committee affiliated to the University of KwaZulu-Natal (BREC No 083/17). HIV status of the patients was obtained from medical records. Informed consent was obtained from all patients when they were admitted for cardiac evaluation with a view to surgery.

Two-dimensional directed m-mode and colour Doppler echocardiography was performed on all patients using a Siemens Sequoia machine (Acuson, Germany) with a phased-array transducer and an emission frequency of 3.0 MHz, with the patient in the left decubitus position. Images were obtained according to a standardised protocol. The left ventricular (LV) end-systolic and end-diastolic dimensions (ESD and EDD), LV wall thickness and left atrial (LA) dimensions were measured according to the American Society of Echocardiography (ASE) chamber guidelines.[17] Ejection fraction (EF) was assessed using the Simpson's method.[17]

The World Heart Federation (WHF) criteria were used to diagnose MR that was rheumatic in aetiology.[18] To describe leaflet motion, the Carpentier classification was used.[19]

The morphological characteristics of the valve were determined using the Wilkins criteria for descriptive purposes,[20] such as leaflet thickening, leaflet mobility, leaflet calcification and subvalvular apparatus involvement. Acute or recurrent rheumatic carditis was diagnosed using the modified Jones and WHO criteria.[21,22]

Clinical evaluation of the severity of MR in this unit was supported by colour Doppler estimation of the regurgitant jet into the LA, the Doppler intensity of the regurgitant envelope, and the LA size using qualitative and semi-quantitative methods as per ASE and European Society of Cardiology (ESC) valvular regurgitation guidelines.[23,24] Calculation of the effective regurgitant orifice using proximal isovelocity surface area (PISA) was not done because in most cases the regurgitant flow into the LA was characterised by an eccentric jet.

The patients' records were identified using the ICD 10 code for rheumatic MR (I05-I09) accessed via the Speedminer software program (Speedminer, Malaysia), which is a Data Warehouse Management software package used at IALCH to record and categorise patients' medical details. Data were extracted from the first visit on the demographics, clinical presentation, co-morbidities, laboratory and echocardiographic findings, as well as the surgical findings on those who underwent surgery. Data were entered into Microsoft excel software and transferred for statistical analyses.

Patients were excluded from the study if they met Meel's exclusion criteria: significant aortic valve disease, concurrent mitral stenosis (MS) with a valve area of less than 2.0 cm^2 (as assessed by planimetry), documented ischaemic heart disease, pre-existing non-valvular cardiomyopathy, prior cardiac surgery, congenital or pericardial disease, pregnancy and severe systemic disorders such as renal failure, uncontrolled hypertension [systolic blood pressure (SBP) > 140 mmHg and diastolic blood pressure (DBP) > 90 mmHg on medication] or severe anaemia (haemoglobin < 10 g/dl).[16]

Statistical analysis

Statistical Package for the Social Sciences (SPSS version 23.0) [International Business Machine (IBM), Los Angeles] was utilised in the analysis of data for the study. A 95% confidence interval (CI) was estimated, and a global significance level of $\alpha = 5\%$ was chosen, to test for the assumptions of the null hypothesis.

Simple descriptive analysis was used to highlight clinical characteristics and results are presented as frequencies, means and percentages. Continuous variables are expressed as means ± standard deviation (SD). The Student's *t*-test and the chi-squared test were used to compare continuous and categorical variables, respectively. A *p*-value of < 0.05 was taken as statistically significant for the variables being measured.

Results

Using the ICD 10 code for rheumatic MR, 2 986 records were retrieved. Patients with mixed mitral valve disease who had dominant MS ($n = 613$) were excluded, as well as those who presented to other medical disciplines ($n = 1\,106$), leaving 1 267 who were referred directly to the Department of Cardiology and underwent a full evaluation. Of these, 947 patients were further excluded based on Meel's exclusion criteria (Fig. 1). We excluded 277 subjects with uncontrolled hypertension so that we could study the rheumatic process unconfounded by the effects of elevated blood pressure on cardiac function and resultant hypertrophy with fibrosis. This left us with 320 patients with isolated rheumatic MR for analysis, approximately 100 subjects in each of the three age groups (Table 1).

The mean patient age was 22.2 ± 15.8 years. The male:female ratio was 1:2 and the ethnic composition was predominantly black African (94.1%), followed by Asian (4.1%), white (0.9%) and coloured (0.3%) subjects. Of the 320 patients, 116 were in the paediatric age group (mean age 9.7 ± 1.7 years) (Fig. 1, Table 1), all of whom were black subjects from rural areas and a poor socio-economic environment characterised by overcrowding and/or single, absent or unemployed parents.

Most patients presented with dyspnoea; effort tolerance was graded as New York Heart Association (NYHA) class II in 54.1%,

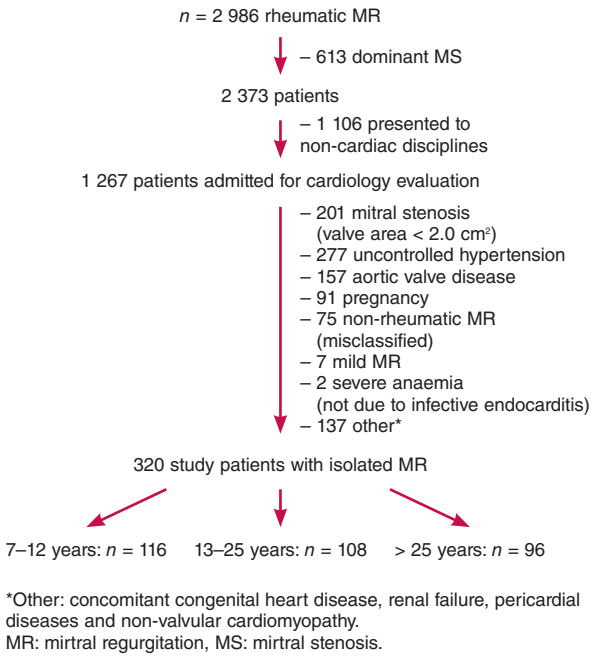

Fig. 1. Selection of the study sample.

followed by class III (37.1%) and class IV (8.8%). Atrial fibrillation was documented in 13.8% of patients. Only three children (0.9%) satisfied the modified Jones criteria for ARF at presentation, with a further 31 subjects (9.7%) satisfying the criteria for active carditis during follow up, yielding a total of 34 subjects with active carditis (10.6%). MR was classified as moderate in 76 (23.8%) and severe in 244 (76.2%) patients, based on clinical assessment and confirmed at echocardiography.

Co-morbidity was encountered in 44 patients (13.75%). The main co-morbidity was HIV infection, which was found in 33 patients (10.3%), all of whom were on antiretroviral therapy. The exclusion of 277 patients with uncontrolled hypertension (SBP > 140 mmHg, DBP > 90 mmHg while on treatment, on two separate visits) resulted in only four patients with hypertension being enrolled into the study.

Overall, heart failure occurred in 117 (36.6%) patients during their illness; of these 23 (19.7%) had heart failure on their initial admission. At the first visit, infective endocarditis was diagnosed clinically in three patients in whom echocardiography showed valve prolapse associated with vegetations. Of these, one patient was subsequently diagnosed as ARF with carditis. In the second patient, the anti-streptolysin O titre (ASOT) was elevated and at surgery, chordal elongation was identified with no evidence of endocarditis. In the last patient, chordal rupture was present at surgery but there was no evidence of endocarditis, and subsequent blood cultures failed to culture an organism.Echocardiographic findings revealed a mean LVEF of 60.6 ± 8.3% with 52.5% of patients having LVEF < 60%. The mean EDD and ESD were 60.0 ± 8.1 and 38.8 ± 7.5 mm, respectively. Pulmonary hypertension was present in the majority (n = 256, 80%) of subjects. Of these, 140 (54.6%) patients had severe pulmonary hypertension; 55 (39.3%) were in the paediatric age group, 37 (26.4%) were adults over 25 years of age and 48 (34.3%) were in the middle age group. Associated tricuspid regurgitation (TR) with pulmonary hypertension was

Table 1. Demographic data

Characteristics	*7–12 years (n = 116)*	*13–25 years (n = 108)*	*> 25 years (n = 96)*	*Overall (n = 320)*
Age (mean ± SD) years	9.7 ± 1.7	17.4 ± 4.0	42.7 ± 12.9	22.2 ± 15.8
Gender (%)				
Male	39.7	34.3	20.8	32.2
Female	60.3	65.7	79.2	67.8
Ethnicity (%)				
Asian	0	0.9	12.5	4.1
Black	100.0	97.2	81.3	94.1
Coloured	0	0	1.0	0.3
Unknown	0	0.9	1.0	0.6
White	0	0	3.1	0.9

present in 172 (53.75%) patients and the severity of TR was classified as mild in 74 (43.0%), moderate in 44 (25.6%) and severe in 54 (31.4%) subjects. It was considered secondary to pulmonary hypertension in most of the patients, except for nine (5.23%) who had organic rheumatic tricuspid valve disease.

MR was classified as moderate in 76 (23.8%) and severe in 244 (76.2%) patients, based on clinical assessment and confirmed at echocardiography. We categorised the echocardiographic findings based on the Carpentier classification of leaflet motion as normal (type 1), excessive (type 2) or restricted motion (type 3A), and recorded the anatomical descriptions of the entire valve apparatus relating to the annulus, leaflet, commissures, chords and papillary muscles. In keeping with the rheumatic aetiology, increased leaflet thickness was reported in all but one patient (99.7%), but commissural fusion was documented in only four (1.2%) patients.

The majority of our patients had Carpentier type 2 leaflet dysfunction with leaflet prolapse present in 196 (61.3%) and chordal rupture identified in 118 (37%) subjects. The posterior mitral leaflet was described as rigid, or having restricted mobility (Carpentier IIIa) in 64 (20%) patients in our study, with thickening of the subvalvular apparatus in 48 (15%) patients. Calcification was found in 27 (8.4%) patients and reported to be severe in one.

A posteriorly directed eccentric jet was present in 97% of cases. The anatomical and functional pattern of regurgitation was quite different from MR due to the rare congenital atrioventricular canal defects associated with mitral valve anomalies such as clefts and bridging leaflets. The commonest pattern of RHD that emerged was that of an eccentric regurgitant directed posteriorly with excessive leaflet motion (Carpentier type 2), due mainly to anterior mitral valve leaflet prolapse as a result of chordal elongation or chordal rupture and associated with increased leaflet thickness. Together with annular dilatation, this was the predominant mechanism of MR in the younger subjects and suggestive of ongoing carditis.

Although annular dilatation was not documented by the echocardiographer, the ESD > 60 mm and EF < 60% in half the subjects suggested that the majority of subjects also had mitral annular dilatation. This was supported by the large size of the prostheses inserted by the surgeon in the cases that proceeded to surgery.

Patients were divided into two age groups based on age (seven to 25 years, and over 25 years) (Table 2) for comparison. Although there was no significant difference in the proportion of individuals having moderate or severe MR, or in the degree of

Table 2. Echocardiographic findings in age groups < 25 vs > 25 years

Variable	*7–25 years (n =224)*	*> 25 years (n = 96)*	*p-value*
EDD, mm*	59.1 ± 7.6	61.9 ± 8.7	0.0041
ESD, mm*	37.8 ± 7.4	41.3 ± 7.1	0.0001
EF, %*	61.4 ± 8.9	59.0 ± 6.3	0.0171
LA, mm*	66.1 ± 8.7	67.8 ± 9.2	0.1164
RV-RA gradient*	48.9 ± 19.0	44.8 ± 17.7	0.0720
↑ Leaflet thickening (%)	100.0	99.0	0.1260
Commissural fusion (%)	1.0	2.1	0.3797
Restricted PML	18.0	25.0	0.1432
Subvalvular thickening (%)	11.4	24.0	0.0033
Leaflet calcification (%)	2.8	21.9	0.0020
Leaflet prolapse (%)	65.1	52.1	0.1321
Ruptured chordae (%)	85.9	25.0	0.0481
MR severity			
Moderate/severe (%)	26.0/74.1	17.7/82.3	0.0964

*Data are presented as mean ± SD
LA: left atrium; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; PML: posterior mitral leaflet; RV-RA: right ventricle – right atrium gradient.
Ruptured chordae and leaflet prolapse were more frequent in the young, while subvalvular damage and valve calcification were frequent findings in older subjects.

elevation of pulmonary pressures between the two age groups ($p > 0.05$), the LV diameters and LVEF showed that the older age group had larger LV chambers ($p < 0.05$) and the younger group had much higher EF ($p < 0.05$). There was no difference in the LA diameters between groups ($p = 0.11$).

Comparative analysis of the morphology of the mitral valve revealed no significant differences in leaflet thickness and commissural fusion ($p > 0.05$) between the two age groups, but subvalvular apparatus thickening and calcification were more frequent in the older group ($p < 0.05$), while chordal rupture was more common in the younger group ($p = 0.04$) (Table 2).

Human immune virus (HIV) was positive in 33 patients, and this subset comprised older patients ($p < 0.05$). Echocardiography revealed no significant difference in terms of the severity of MR ($p = 0.94$) between HIV-positive and -negative subjects. There was also no significant difference in the echocardiographic dimensions of the LV and LA, and the LVEF between the two groups ($p > 0.05$). Apart from the increase in frequency of the leaflet prolapse noted in the HIV-positive group (16.6% in HIV negative vs 38.9 in HIV positive, $p = 0.00$), there were no other significant differences noted in morphological parameters between the two groups. There was also no significant difference observed in pulmonary pressures between the two groups ($p = 0.70$).

Patients were followed up regularly at the cardiology clinic. Overall, complications occurred in 143 (44.7%) patients. Embolic events were diagnosed in 11 patients (3.4%). Infective endocarditis was diagnosed clinically in 34 (10.6%) patients during the course of their illness. In addition to the 23 (7.2%) patients who presented *ab initio* in heart failure, signs of decompensated heart failure developed in a further 94 (29.4%), totalling 117 (36.6%) patients in all with heart failure during the course of their illness.

Eight patients (2.5%) died: seven were young (< 16 years), and the eighth was a 70-year-old female who died in intractable heart failure from poor LV function (Table 3). Three subjects died prior to surgery and the remaining five died during the postoperative period. Four of the patients who died had active carditis and two had infective endocarditis.

Eighty-one patients were lost to follow up. Survival status of the patients lost to follow up was established telephonically as well as by checking the national registry of deaths. In this manner it was established that a further 24 patients had died out of hospital, yielding a total of 32 deaths (10%).

Surgery was performed in 216 patients. Mitral valve replacement was performed in all but 13 subjects who underwent mitral valve repair. A mechanical prosthesis was deployed using the technique of chordal preservation in order to prevent worsening LV function postoperatively. Valve repair was undertaken by one surgeon trained in this procedure and was performed in subjects in sinus rhythm and in those who were not considered to have active carditis. This constituted a minority of subjects with suitable anatomy. Mitral valve repair included chordal shortening and mitral ring annuloplasty.

Evidence of active rheumatic carditis was present in all 34 (10.6%) patients diagnosed clinically; most of these subjects were in the paediatric and teenage groups. Of the 216 patients who underwent surgery, over one-third (37%) had prolapse of the AML, which was due to ruptured chordae in 41 (19%) patients. Furthermore, chordal elongation was present in 63 (29.2%) patients. A chronic rheumatic process characterised by leaflet thickening was found in 135 (62.5%) patients, and evidence of fibrosis with subvalvular thickening in 37 (17%) and leaflet calcification in 19 (8.8%).

There were 34 patients who were clinically diagnosed with infective endocarditis during the course of the illness; of these, 25 (73.5%) patients had echocardiographic features suggestive of vegetations and underwent surgery. At surgery, vegetations were confirmed in 14 (56%) subjects and one had a chordal abscess. In the remaining 10 (40%), there were no findings of infective endocarditis at operation; instead eight (80%) had chordal rupture and two (20%) had chordal elongation. The 15 with

Table 3. Profile of patients who died

Age (years)	*Gender*	*NYHA*	*ESD (mm)*	*EF (%) (admission)*	*EF (%) (late)**	*Complications*	*Surgery*	*Valve findings*
13	F	4	48	65	22	HF	Y	Thickened with elongated chordae
14	F	4	48	55	24	HF	N	Thickened with, subvalvular disease
8	F	4	38	70	34	HF	Y	Chordal elongation
16	F	3	35	65	18	HF	Y	Valve prolapse and chordal rupture
14	M	4	38	56	22	HF	Y	Valve prolapse
11	F	4	35	75	30	HF, IE,	N	Thickened with vegetations
16	M	3	47	52	20	HF	N	Thickened with, subvalvular disease
70	F	2	29	51	38	HF, IE	Y	Calcified with vegetations and subvalvular disease

*EF prior to demise. EF: ejection fraction; ESD: end-systolic diameter; F: female; HF: heart failure; IE: infective endocarditis; M: male; NYHA: York Heart Association. Two patients had infective endocarditis, and of these, one was an elderly woman. Four were young subjects with active carditis.

Table 4. Comparison between echocardiographic and surgical findings

Valve morphology	*Echocardiogram (n = 216) (%)*	*Surgery (n = 216) (%)*	p-*value*
Increased leaflet thickness	215 (99.7)	135 (62.5)	0.0000
Subvalvular apparatus thickness	42 (19.4)	37 (17)	0.3046
Calcification	19 (8.8)	19 (8.8)	1.0000
Prolapse	136 (63)	80 (37)	0.0000
Chordal rupture	77 (36)	41 (19)	0.0001
Chordal elongation	0	63 (29.2)	0.0000
Dilated annulus*	Not assessed	13 (6.0)	0.0003
Vegetations	25 (11.6)	14 (6.5)	0.0003

*Mitral annular measurements were not recorded at echocardiography. Comments on annular dilatation were made in a few cases by the surgeon who performed valve repair and inserted a mitral ring.
Echocardiography over-diagnosed leaflet/subvalvular thickness, chordal rupture, valve prolapse as well as vegetations. About half of the subjects with these diagnoses were confirmed at surgery. Surgery detected chordal elongation in many subjects previously diagnosed with valve prolapse/chordal rupture.

confirmed infective endocarditis at surgery and the nine treated clinically yielded a 7.5% (24/320) complication rate of infective endocarditis in subjects with chronic rheumatic MR.

Using surgery as the gold standard for macroscopic valve morphology, echocardiographic findings were compared with the surgical findings (Table 4). Although formal predictive analysis was not performed, it is apparent that in our subjects with MR, echocardiography over-diagnosed increased valve thickening (99.7 vs 62.5%, $p = 0.00$), prolapse (63 vs 37%, $p = 0.00$) and chordal rupture (36 vs 19%, $p = 0.00$). Most cases of valve prolapse at echocardiography were found to have chordal elongation at surgery ($n = 63$, 29.2%).

To search for any change in the pattern and the severity of valve disease, the clinical profile and echocardiographic findings during the first five years (2006–2010) was compared with the following five years (2011–2015). There was a decline in the percentage of rheumatic MR presenting in the paediatric group (seven to 12 years), from 40.7 to 31.4%, with a corresponding increase in the percentage of new-onset RHD in the adults over 25 years in the latter five years (p = ns).

Of significance was the decline in the number of patients presenting with severe dyspnoea (NYHA III), from 44.9 to 28.8%, with a corresponding increase in NYHA class II symptoms during 2011–2015 ($p = 0.00$). This corresponded with a decrease in the number of patients with severe MR from 85.6 to 66% ($p = 0.00$), with an accompanying decline in heart failure from 46 to 26% ($p = 0.00$).

We also compared the surgical findings over the two five-year periods. While the majority of valve morphology findings remained unchanged, there was a significant increase in leaflet thickening in the latter five years (38 to 97%, $p = 0.00$) and a significant decline in chordal elongation (40.5 to 13%, $p = 0.00$).

Discussion

RHD remains a major public health burden in the province of KZN in southern Africa, despite the previously reported decline in other parts of SA.[25,26] In this study we screened 2 986 patients with rheumatic MR over a 10-year period (2006–2015) and found a 10.7% prevalence of isolated MR in this group. This condition continues to impose an economic burden in our population since the majority of our patients were young, with a mean age of 22.2 ± 15.8 years, and in need of chronic medical and surgical therapies.[27]

In addition, the finding that all 116 (36.3%) patients in the paediatric age group were young black Africans from poor socio-economic circumstances suggests that RHD remains active among those of lower socio-economic class. In contrast, among the Indian race group in our study, there was only a single subject in the 13–25-year age group, and the rest of the Indians were adults above 25 years of age, suggesting that the socio-economic circumstances have improved enough to eradicate rheumatic fever in this group over the last decade. In other provinces in SA, improvement in access to medical care for the general population as well as the introduction of free healthcare to children under the age of six years in 1994[25] has led to a dramatic decline in the number of children younger than 14 years presenting to the paediatric cardiology department with ARF and RHD.[25]

The pattern of disease we describe in KZN most likely relates to the low socio-economic burden in this province. Second to Gauteng, KZN ranked highest in the provincial distribution of population living in SA (Statistics SA between 2002 and 2014),[26] and is the third highest province affected by poverty, following Eastern Cape and Limpopo.[27] Furthermore, the recent census showed that the groups mostly affected by poverty within these provinces were children below the age of 17 years, black Africans, females, people living in rural areas, as well as those with little or no education.[26,27] The relatively higher burden of RHD in KZN affecting the predominantly younger African female population may therefore be attributed to the increased population burden, together with high levels of poverty when compared to the rest of SA.[28]

Although the majority of our patients presented for the first time with RHD, 34 patients (10.6%) satisfied the modified Jones criteria for ARF, and evidence of active rheumatic carditis was confirmed in all at surgery. We postulate that the low rate of ARF in the paediatric age group could be attributed to missed diagnosis of ARF at the primary healthcare level, delayed presentations, or failure to seek medical care at the onset of disease due to socio-economic issues, resulting in patients presenting at a later stage with more established disease. Also, a few patients at our clinic have reported not receiving long-acting penicillin for some time, as it had been out of stock in their base hospitals, which may explain the recurrence of carditis in certain cases. All these factors probably contributed to the failure of implementing early secondary penicillin prophylaxis, which resulted in disease progression. The REMEDY and other studies have provided good clinical evidence that secondary penicillin prophylaxis reduces the chance of recurrent carditis.[1,29-32]

Our findings contrast with those of Meel *et al.*,[16] whose subjects were older than ours (mean age 44 vs 22 years) and had a high prevalence of hypertension (Table 5). Meel *et al.* found only one patient with active carditis, and echocardiography revealed no chordal rupture or elongation, with minimal leaflet prolapse. Instead, they showed marked leaflet thickening, calcification and leaflet retraction with associated chordal thickening.[16]

In contrast, we have shown a high prevalence of anterior leaflet prolapse and chordal rupture, findings that were confirmed in subjects undergoing surgery. This pattern of disease is quite different from that found by Meel *et al.*, who reported restrictive (Carpentier type IIIa) leaflet dysfunction with annular dilatation in the majority (80%) of their subjects, the remainder having a combination of type 2 (excessive leaflet motion) and type IIIa. After excluding uncontrolled hypertension, Meel *et al.*[16] found

Table 5. Comparison of studies by Meel *et al.*[16] and Marcus *et al.*[14] with the current study (Zwane *et al.*)

Variables	*Marcus* et al. (n = *219*)	*Meel* et al. (n = *84*)	*Zwane* et al. (n = *320*)
Age (years), mean ± SD	19 ± 11	44 ± 15.3	22.2 ± 15.8
Females (%)	Not specified	84	67.8
Black African (%)	100	100	93
Functional class (NYHA)	III–IV	II–III	II–IV
Active carditis (%)	14	1.2	10.6
Co-morbidities (%)	0	78	13.7
Mitral valve morphology (%)	Echo/surgery	Echo	Surgery (*n* = 216)
Dilated annulus	95	84.5	6.0**
Thin, pliable leaflets	95	5	37.5
Thickened, non-pliable leaflets	59	41	20 *
Leaflet prolapse	84	20	37
Leaflet calcification (rigid)	5	27	8.8
Elongated chordae	92	0	29.2
Ruptured chordae	25	0	19
Commissural fusion	0	30	0

NYHA: New York Heart Association.
*Rigid posterior leaflet.
**The figure here reflects the comments on annular dilatation by the surgeon who sized the annulus for insertion of a ring during mitral valve repair.
In contrast to the recent findings by Meel *et al.*,[16] our surgical findings (Zwane *et al.*) are similar to the profile of chronic MR described by Marcus *et al.*[15]

extensive fibrosis in isolated MR across her whole cohort, quite different from the pattern in all our younger subjects, who showed little evidence of advanced fibrosis.

It must be pointed out that our age comparisons reflect the natural history of RHD, which is carditis being commoner in the young, followed by a more fibrotic process in older age. Our 96 subjects in the older age group (> 25 years, mean age of 43 years) showed more evidence of a chronic fibrotic process with subvalvular thickening and leaflet calcification, compared to chordal rupture and valve prolapse in subjects under 25 years. Of importance, our findings are suggestive of recent ongoing carditis in young adults, diagnosed clinically and supported by echocardiographic findings, as well as macroscopic surgical findings.

In patients with active rheumatic carditis presenting with overt heart failure, severe MR and its anatomical correlate of annular dilation, chordal elongation and prolapse of the anterior mitral leaflet is regarded as the hallmark of the disease.[12] We feel the age comparison highlights this pattern of disease that is still seen in developing countries and reflects a failure of proper ongoing rheumatic fever prophylaxis.

Our finding of chordal elongation in 29% of subjects at surgery is highly suggestive of ongoing rheumatic carditis in young subjects (mean age 22 years) with isolated MR,[12,15] and it fits the profile of rheumatic MR reported by Marcus *et al.*, who described active carditis in young subjects (mean age 19 years) without any co-morbidities. In Marcus and colleagues' study, patients with pure MR had thin leaflets, elongated chordae, dilated annuli and anterior leaflet prolapse, findings that were corroborated at the time of surgery.[15] The prevalence of clinical carditis in their study was also similar to that of ours (14 vs 10.6%).

Our finding of a 10.6% prevalence of active carditis in patients with isolated MR is probably an underestimate of the true prevalence since, similar to Marcus *et al.*, we also showed a significantly high prevalence of chordal elongation (29%), ruptured chordae (19%) and leaflet prolapse (37%) in the absence of infective endocarditis at surgery. It is clear that the pattern of rheumatic MR in our study reflects the ongoing poor socio-economic environment in many parts of KZN.

Another possible explanation for the discrepancy between our findings and Meel and colleagues' results is that we excluded 277 patients with uncontrolled hypertension because of the confounding effects of hypertension on myocardial function. This excluded a number of the middle-aged patients with RHD, which probably accounted for the effects of co-morbidities on the valve morphology in the study by Meel *et al.*,[16] as well as for Sliwa and co-workers' report on the increase in prevalence of adult cases presenting with RHD in Soweto.[8]

In our study, calcification was found in 8.8% and leaflet thickening in two-thirds of subjects. Comparison of the surgical findings over the two time periods in our study, however, did reveal an increase in leaflet thickness and a decline in chordal elongation in the latter five years of the study period, suggesting that there is a gradual transition towards the pattern of disease currently being seen in Soweto.[16] After the exclusion of those with hypertension, the main co-morbidity encountered in our study was HIV infection. We also compared the echocardiographic and surgical findings of the patients with HIV infection to those who were HIV negative, and found that HIV had no significant influence on the pattern or progression of RHD.

There were 143 patients (44.6%) in our study who suffered 152 complications, in keeping with other hospital-based studies.[7,8] The commonest complication was heart failure, which occurred in 117 patients (36.6%). This is not surprising since over half of the subjects had an EF under 60% and, according to established guidelines, should have undergone surgery at an earlier stage in their illness.[33]

Although we examined the clinical profile of our subjects over the 10-year period and showed there was an improvement in clinical presentation with a decline in heart failure, many patients were lost to follow up and over a third of them had died, according to the deaths registry. Factors that probably contributed to the significant mortality rate in our study included delay in surgical treatment, failure to refer patients with severe MR to surgery, and/or clinician lethargy in referring patients with severe MR to tertiary care until late in the disease.

Limitations and strengths

In addition to its retrospective design, our study has several other limitations. Patients with ARF and MR who were stable and less symptomatic may not have been referred for evaluation. However, we captured the presentation of patients with significant MR since all patients with moderate to severe rheumatic MR managed in the public sector are usually referred for tertiary care to IALCH. Although we have regular cardiac clinics two days a week, long-term patient follow up was often not possible because of difficulty of access to care from rural areas, resulting in over half the patients presenting late with impaired ventricular function (EF < 60%), or being lost to follow up with resultant mortality, as revealed by the examination of the deaths registry.

Second, the retrospective nature of the study and the lack of standardised echocardiographic assessment of patients prior to surgery resulted in an incomplete dataset for analysis. Measurements of the chords and mitral annulus were not

recorded in the echocardiographic reports. Comments on annular dilatation in the 6% at surgery (Tables 4, 5) were recorded by the surgeon who performed mitral valve repair on the few cases and for the limited period that he was in the department. Also it must be pointed out that valve thickness at surgery was based on macroscopic appearances, and formal measurements of valve thickness were not performed by the surgeon. Similarly, both leaflet thickness and chordal thickening were subjectively assessed at echocardiography and may be subject to error if gain settings are not optimal.

Excessive valve echoes and leaflet motion were often misdiagnosed as chordal rupture and shown to be due to chordal lengthening at surgery. Transoesophageal echocardiography would have distinguished between chordal rupture and chordal elongation but this procedure was not routinely performed in patients with severe MR. Furthermore, this procedure would have given a better understanding of the subvalvular apparatus and the degree of chordal elongation prior to surgery.

Despite its limitations, there are important strengths to our study. An important aspect of our study was that we were able to confirm or refute the echocardiographic findings in two-thirds of our patients who underwent valve-replacement surgery. However, the lack of histopathological correlation is a serious limitation of our study since it would have corroborated our contention that ongoing carditis was a major cause of severe regurgitation, particularly in our younger subjects. Nevertheless, the morphological findings of chordal elongation with valve prolapse and chordal rupture at surgery suggested active carditis in many of these patients.[12,15] At surgery, leaflet thickening was not as common and was probably over-diagnosed at echocardiography. We attributed the over-diagnosis of increased leaflet thickness at echocardiography to excessive leaflet motion associated with leaflet prolapse and/or chordal rupture.

Conclusion

In this study, isolated MR occurred in 10% of all patients with rheumatic MR. A significant percentage of these subjects presented with active carditis characterised by chordal elongation, frequent valve prolapse and chordal rupture, associated with a high burden of cardiovascular complications, including death. This pattern of MR with ongoing carditis and valve damage that continues into early adulthood is a reflection of rural populations in KZN, with poorer socio-economic circumstances compounded by difficulty of access to care and lack of availability of antibiotic prophylaxis. This has resulted in recrudescences of carditis well into early adulthood, and emphasises the need for ongoing rheumatic fever prophylaxis at least until the age of 35 years. These findings have serious public health implications in adopting the WHO strategy of targeting a 25% reduction in mortality from RHD by the year 2025.[10]

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The effect of lifestyle modification on depression among myocardial infarction patients after revascularisation

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Abstract

Background: Patients with coronary artery disease (CAD) are prone to depression, and its presence is associated with poor adverse cardiac outcomes. Although lifestyle modification (LSM) has been shown to be beneficial in managing depression in patients with CAD, it is not known whether the mode of cardiac intervention [(coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI)] influences the outcome.

Objectives: We examined the prevalence of depression among myocardial infarction (MI) patients after revascularisation and compared the effect of LSM on incidence of depression in patients who underwent CABG versus PCI.

Methods: We evaluated the risk-factor profile, depression characteristics and lifestyle changes of 100 consecutive participants undergoing coronary revascularisation over a 15-month period (January 2017 to May 2018). The Beck depression inventory II (BDI-II) was used to assess depression and the Goldin leisure-time exercise (GLTE) questionnaire to assess physical activity (PA).

Results: One hundred patients were recruited (mean age: males 60.73 ± 4.52 years, females 60.29 ± 3.64 years) but five dropped out, leaving 95 patients for complete analysis. Most of the patients were low-income earners [53 (53.0%)], and 21 (21.0%) had tertiary-level education. The majority had multiple CAD risk factors and co-morbidities (79.0%). Prior to the LSM programme, 51 patients (51.0%) had depression and depressive traits [CABG 34 (66.7%) vs PCI 17 (33.3%), $p = 0.047$]. After LSM the overall prevalence of depression and depressive traits fell to 33 patients (34.7%) [PCI eight (23.0%) vs CABG 25 patients (72.0%), $p = 0.001$]. The mean depression scores also fell from 21.11 ± 7.75 to 14.98 ± 9.61 ($p = 0.002$). At baseline, PCI patients were more physically active compared to CABG patients [three (60.0%) vs two patients (40.0%), respectively, $p = 0.715$]. After LSM, more PCI patients undertook PA compared to CABG subjects [24 (60.0%) vs 14 patients (35.0%), respectively, $p = 0.012$]. The PA score was also higher among the PCI group compared to the CABG group [14.16 ± 9.73 vs 9.40 ± 10.94, respectively, $p = 0.024$]. In fully compliant subjects, the benefit derived was similar regardless of the mode of intervention [OR 1.10, 95% CI: 0.78–4.23, $p = 0.191$]. Using multivariate analysis, the main predictors of depression and depressive traits were female gender (OR 3.29, 95% CI: 1.51–11.03, $p = 0.008$), CABG (OR 1.86, 95% CI: 1.68–5.77, $p = 0.003$), heart failure (OR 2.65, 95% CI: 5.87–13.62, $p = 0.000$), kidney failure (OR 1.41, 95% CI: 1.30–5.23, $p = 0.041$), atrial fibrillation (OR 1.60, 95% CI: 1.40–4.77, $p = 0.023$), low PA (OR 1.97, 95%, CI: 11.23–33.20, $p = 0.000$), previous history of depression (OR 8.99, 95% CI: 1.90–7.89, $p = 0.002$) and low income (OR 2.21, 95% CI: 1.40–2.85, $p = 0.000$).

Conclusions: Depression and depressive traits are common among subjects undergoing coronary revascularisation, more so among CABG than PCI participants. LSM reduced the prevalence of depression and depressive traits, with fully compliant CABG versus PCI groups deriving nearly the same benefits from the LSM regime. No significant reduction in incidence of depression was recorded among LSM partly compliant patients. This study suggests that failure to implement lifestyle changes and engage in PA are major barriers to managing depression after coronary revascularisation.

Keywords: depression, coronary artery disease, coronary artery bypass graft surgery, percutaneous coronary intervention, lifestyle modification, Beck depression inventory II questionnaire, Goldin leisure-time exercise questionnaire

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Several studies have shown that depression is very common among coronary artery disease (CAD) patients, with a prevalence varying from 10.0 to 65.0%.[1-7] Depression is thought to be a risk factor for CAD as well as being a poor prognostic factor.[8-12] Patients with CAD who have depression have been shown to have worse outcomes and reduced quality of life (QOL).[4,6,7] It is well established that patients with CAD and depression have higher chances for recurrence of myocardial infarction (MI) and increased risk of death.[13-18]

In the Baltimore cohort of the Epidemiologic Catchments Area study follow up, major depression significantly increased the risk of acute MI (OR 4.54, 95% CI: 1.651–12.440).[19] A systematic review by the American Heart Association also found that depressed MI patients had a significant increase in all-cause mortality, cardiac mortality and chance of recurrence, compared to non-depressed patients.[12]

Although the incidence of CAD is increasing globally, morbidity and mortality rates are steadily decreasing in developed countries,[20-23] and this has been attributed principally to better therapy as well as lifestyle modification (LSM), which

has shown promising results in the secondary prevention of CAD, reduction in adverse cardiac outcomes and depression, as well as improvement in QOL.[24-28] In contrast to the developed world, there are few data from developing countries regarding the prevalence of depression and the effect of lifestyle changes on depression among patients with CAD.[21-23] In a recent study, Ranjith *et al*. analysed incidence of depression among MI patients in South Africa and reported a prevalence of 49.0%[29]

To the best of our knowledge, no study has compared the effects of LSM on incidence of depression among patients who undergo coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI). These two modalities of therapy differ greatly in terms of injury severity score, metabolic responses, convalescence time and prognosis.[30,31] Furthermore, studies have shown a causal relationship between depression and post-infarction inflammatory and neurohormonal changes.[32-38] Therefore we hypothesised that the prevalence of depression and response to LSM would differ between the two groups. In this study we analysed the prevalence of depression among MI patients after revascularisation and examined the effect of LSM on incidence of depression between CABG and PCI groups.

Methods

The risk-factor profile, depression characteristics and physical activity (PA) profile were prospectively examined in 100 consecutive participants undergoing coronary revascularisation over a 15-month period (January 2017 to May 2018). The study was conducted in the Department of Cardiology and Cardiothoracic Surgery at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa.

After informed written consent was obtained, patients who met the inclusion criteria were enrolled within two to four weeks after revascularisation. Approval was obtained from the Biomedical Research Ethics Committee (BREC/443/16) of the University of KwaZulu-Natal before starting the study.

Demographic data, anthropometric measurements, vital signs and other clinical data, as well as blood samples, were obtained from the patients at the beginning of the study and thereafter the interview was performed. During the interview, the Beck depression inventory-II (BDI-II) and Goldin leisure-time exercise (GLTE) questionnaires were administered by the researcher (AA) to determine depression status and level of PA.

The GLTE questionnaire is a validated and reliable questionnaire that is used to assess the level of PA.[39] Briefly, the patients indicate the number of times they engage in mild, moderate or strenuous exercise for more than 15 minutes within a week. The level of PA is categorised as: 'sufficiently active' (≥ 24 units/week), 'moderately active' (14–23 units/week), and 'insufficiently active' (< 14 units/week).[39]

For strenuous PA, the GLTE questionnaire demonstrated moderate-to-strong associations with measured indices of PA, particularly maximal oxygen consumption determinations (VO_{2max}), and percentage body fat by hydrostatic weighing (% BF), but a lesser degree of association with the Caltrac accelerometer (CALTRAC) readings. For moderate PA, it was modestly correlated with the above measures, but for mild PA it showed less association with these measures. By and large, it gives a reliable and fairly accurate assessment of PA.[40]

The BDI-II is a simple, reliable and validated 21-item questionnaire, rated on a four-point scale (0–3).[41] It is one of the most widely used psychometric instruments in both research and clinical practice for assessing depression.[42] Based on the total score obtained, a patient is classified as normal (1–10), having mild mood disturbance (11–16), borderline depression (17–20), moderate depression (21–30), severe depression (31–40), and extreme depression (> 40).[41] The BDI-II adequately corresponds to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria and has high reliability and validity.

Based on available psychometric evidence, the BDI-II is considered a cost-effective questionnaire for measuring the severity of depression, with broad applicability for research and clinical practice. Although the questionnaire was originally designed to measure the severity of depression, existing evidence shows that the BDI-II can be effectively used to screen for major depression with a sensitivity of more than 70%. Its major shortcoming is variability of the cut-off score to screen for depression according to the type of sample. Non-clinical samples displayed the lowest range of cut-off points (10–16) to detect major depression, medical samples had an intermediate cut-off point (7–20), and psychiatric samples had the highest cut-off point (19–31). As a self-report measure, there may be reporting bias since the educational level attained, status and gender may affect the respondent's response.[41,42]

Eligible patients were enrolled in a supervised exercise-based LSM programme and after a few sessions, an individualised aerobic exercise regimen was prescribed based on the standard guidelines.[43-45] Psychological counselling, smoking cessation and dietary advice were given as well. At the time of discharge, a referral letter and written instructions about the individualised LSM were given to the patients and they were advised to continue the programme at home. The written instructions included how to monitor the level of exertion manually using their heart rate and the Borg's rating of physical exertion at home. Studies have shown that home-based LSM is safe and not inferior to centre-based LSM.[46-48]

Patients continued the LSM at home, with a monthly follow up at their community clinics. After a 12-week period, the patients underwent a final assessment by the researcher (AA). At the final visit, anthropometric measurement, vital signs, blood samples and clinical evaluation were repeated and documented. The BDI-II and GLTE questionnaires were re-administered and the results were documented.

Inclusion criteria were male or female eligible adult patients over the age of 18 years with a documented acute MI who underwent CABG or PCI in IALCH within the period of the study and consented to participate in the study. Exclusion criteria were any patient with a terminal illness or debilitating co-morbidity, such as incapacitating cerebrovascular accident (CVA), severe arthritis and other severe diseases, which would preclude moderate physical activity.

The primary outcome was depression status before and after LSM as assessed using the BDI-II questionnaire. The secondary outcome was an improvement in physical function and endurance, which is reflected by changes in the level of PA.

Statistical analysis

Data analysis was conducted using SPSS version 25. The demographic, social and clinical characteristics of the patients

were analysed. Descriptive statistics were used to analyse the demographic data, disease characteristics, LSM compliance and incidence of depression. The prevalence of depression was established, and predictors of depression were determined using multivariate analysis.

The results for all the variables were compared before and after initiating LSM. The chi-squared test was used to determine the association between disease characteristics and outcome variables (depression and PA) at baseline and after LSM among CABG and PCI patients. A general linear model was used to evaluate the mean and standard deviation (SD) values, and the differences between the group outcomes (depression severity and number of subjects with depression) at baseline and after three months of LSM, as a function of the main effect (group differences). The changes in study outcome values (depression and LSM compliance) from baseline to the final visit were expressed in both the CABG and PCI groups.

Results

During recruitment, four patients were excluded due to severe congestive cardiac failure (n = 3) and debilitating CVA (n = 1). One hundred patients were recruited (58 males and 42 females), and of these there were five dropouts who did not appear for follow up after the three months of LSM, leaving 95 patients for complete analysis at the end of the study.

The mean age of the participants was 60.56 ± 4.09 years, with males and females having mean ages of 60.73 ± 4.52 and 60.29 ± 3.64 years, respectively. The ages of males and females were normally distributed (p = 0.667 and p = 0.794, respectively) (Shapiro–Wilk score = 0.829). The sample comprised mainly Indians (73.0%), the remaining 27.0% being almost evenly split among the other race groups.

Most of the patients were low- (53.0%) or moderate-income earners (40.0%). Nine patients (9.0%) had a background history of depression prior to the cardiac event and 55 (55.0%) reported significant alcohol use. All the patients had previously sustained an MI and had angiographically confirmed CAD. Most patients had multiple CAD risk factors and nearly half of the patients [48 (48.0%)] had at least one co-morbidity, the commonest being chronic kidney disease (43.0%) (Table 1).

The overall prevalence of depression and depressive traits in this sample was 51.0%. The main predictors of depression and depressive traits were female gender (OR 3.29, 95% CI: 1.51–11.03, p = 0.008), CABG (OR 1.86, 95% CI: 1.68–5.77, p = 0.003), heart failure (OR 2.65, 95% CI: 5.87–13.62, p = 0.000), kidney failure (OR 1.41, 95% CI: 1.30–5.23, p = 0.041), atrial fibrillation (OR 1.60, 95% CI: 1.40–4.77, p = 0.023), low PA (OR 1.97, 95% CI: 11.23–33.20, p = 0.000), previous history of depression (OR 8.99, 95% CI: 1.90–7.89, p = 0.002) and low income (OR 2.21, 95% CI: 1.40–2.85, p = 0.000). Level of education (OR 0.60, 95% CI: 0.17–2.14, p = 0.430), age (OR 0.56, 95% CI: 0.71–2.00, p = 0.099), chronic obstructive pulmonary disease (OR 1.30, 95% CI: 0.30–2.98, p = 0.327), as well as the other CAD risk factors, complications and co-morbidities did not show any significant influence on the outcome of depression (Table 2).

Prior to initiation of the LSM programme, five participants (5.0%) were already physically active, six (6.0%) had changed their diet on their own to a Mediterranean diet, and 11 (11.0%) had stopped smoking cigarettes; however only three participants (3.0%) were fully compliant with LSM *ab initio*. After three months of the LSM programme, only 32 (33.7%) complied with the protocol. Fifty-eight participants (61.1%) complied with the dietary changes, 72 (75.8%) with cigarette smoking cessation and 38 (40.0%) complied with the minimum accepted PA (Table 3).

After the LSM intervention, the total number of subjects who were physically active increased from five at baseline to 38 (40.0%) three months later and the number who were insufficiently active fell from 95% at baseline to 57 patients (60.0%) (both p = 0.000). The PA score improved from 2.81 ± 4.410 at baseline to 11.65 ± 10.600 (p = 0.000) after LSM (Table 3).

At baseline, 51 participants (51.0%) had depression and depressive traits and 49 (49.0%) were not clinically depressed (36.0% had mild mood disturbance and 13.0% were

Table 1. Demographic data and baseline characteristics

Variables	Mean ± SD	*Percentage (n = 100)*
Age (years)		
Male	60.73 ± 4.52	58.0
Female	60.29 ± 3.64	42.0
Race		
Black		5.0
Coloured		8.0
Indian		78.0
White		9.0
Yearly income		
Low		53.0
High/moderate		47.0
Educational level		
Primary school		11.0
High school/tertiary		89.0
History of depression		
Yes		9.0
No		91.0
CAD diagnosis		
STEMI		89.0
NSTEMI		11.0
CAD risk factors		
Hypercholesterolaemia		84.0
Diabetes		78.0
Hypertension		78.0
Sedentary lifestyle		76.0
Family history of CAD		53.0
Cigarette smoking		70.0
Obesity		45.0
Co-morbidities		
Kidney disease		43.0
Arthritis		19.0
Other vascular diseases*		17.0
Hypothyroidism		7.0
COPD		4.0
Other co-morbidities#		10.0
Complications		
Heart failure		28.0
Atrial fibrillation		8.0

CAD: coronary artery disease; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; COPD: chronic obstructive pulmonary disease.
*Other vascular diseases: 11, peripheral vascular disease; six, cerebrovascular accident.
#Other co-morbidities: two, valvular heart disease; two, renovascular disease; four, psoriasis; two systemic lupus erythematosus.
The sample comprised largely Indian subjects with multiple risk factors and co-morbidities.

Table 2. Predictors of depression

Variables	*Depressed (n = 51)*	*No depression (n = 49)*	*Total*	*OR (95% CI)*	*p-value*
Age (years) mean ± SD	71 ± 1.122	71 ± 2.34		0.56 (0.71–2.00)	0.099
Gender, *n* (%)					
Male	23 (45.1)	35 (71.4)	58	3.29 (1.51–11.03)	0.008
Female	28 (54.9)	14 (28.6)	42		
Income, *n* (%)					
Low	42 (82.4)	11 (22.4)	53	2.21 (1.40–2.85)	0.000
High	9 (17.6)	38 (77.6)	47		
ACS intervention, *n* (%)					
PCI	17 (33.3)	31(63.3)	48	1.86 (1.68–5.77)	0.003
CABG	34 (66.7)	18 (36.7)	52		
History of depression, *n* (%)					
No	42 (82.35)	49 (100)	91	8.99 (1.90–7.89)	0.002
Yes	9 (17.65)	0 (0)	9		
Educational level, *n* (%)					
Low	5 (9.8)	6 (12.2)	11	0.60 (0.17–2.14)	0.430
High	46 (90.2)	43 (87.8)	89		
Physical activity, *n* (%)					
Low	50 (53.0)	45 (47.0)	95	1.97 (11.23–33.20)	0.000
High	1 (20.0)	4 (80.0)	5		
CAD risk factors, *n* (%)					
Cholesterol	43 (84.3)	41 (83.7)	84	1.05 (0.36–3.06)	0.930
Diabetes	43 (84.3)	35 (71.4)	78	1.75 (0.79–5.70)	0.120
Hypertension	43 (84.3)	35 (71.4)	78	1.77 (0.80–4.50)	0.120
Sedentary life	39 (76.5)	37 (75.5)	76	1.05 (0.42–2.64)	0.910
Cigarette smoking	40 (78.4)	30 (61.2)	70	0.30 (0.80–1.60)	0.061
Obesity	27 (52.9)	24 (47.1)	51	0.95 (0.90–7.21)	0.567
Co-morbidities and complications, *n* (%)					
Kidney disease	27 (52.9)	16 (32.7)	43	1.41 (1.30–5.23)	0.041
Heart failure	24 (47.1)	4 (8.2)	28	2.65 (5.87–13.62)	0.000
Arthritis	11 (21.6)	8 (16.3)	19	1.41 (0.51–3.87)	0.504
Other vascular **	10 (19.6)	7 (14.3)	17	1.16 (0.71–4.21)	0.479
Thyroid disease	4 (7.8)	5 (10.2)	9	0.75 (0.19–2.97)	0.679
Atrial fibrillation	1 (2.0)	7 (14.3)	8	1.60 (1.40–4.77)	0.023
COPD	3 (5.9)	1 (2.0)	4	1.30 (0.30–2.98)	0.327

OR: odds ratio, ACS: acute coronary syndrome; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery.
Depression was commoner in women, those with a low income, kidney disease and heart failure, and in those undergoing CABG compared to PCI.

psychologically normal). Among those with depression and depressive traits, 18 (18.0%) had borderline depression, 23 (23.0%) moderate depression, and 10 (10.0%) severe depression at baseline.

After the LSM intervention, the number of participants with depression and depressive traits fell from 51 (51.0%) to 33 (34.7%) ($p = 0.022$) and the number without depression and depressive traits increased from 49 (49.0%) to 62 (65.3%) ($p = 0.022$) (Table 3). Of the latter group, 11 patients (17.7%) had mild mood disturbance and 51 (82.3%) had no psychological disturbance at all. Among the 33 who had depression post LSM, 13 (39.4%) had borderline depression, 13 (39.4%) had moderate, and seven (21.2%) had severe depression. The mean depression scores fell from 21.91 ± 7.747 at baseline to 14.98 ± 9.610 ($p = 0.002$) after LSM, indicating a significant reduction in the severity of depressive symptoms post LSM (Table 3).

Table 3. Effects of LSM on lifestyle parameters and depression

Variables	*Pre LSM (n = 100)*	*Post LSM (n = 95)*	*p-value*
Aerobic exercise compliance, *n* (%)	5 (5.0)	38 (40.0)	0.000
Cessation of smoking, *n* (%)	11 (11.0)	72 (75.8)	0.000
Dietary modification, *n* (%)	6 (6.0)	58 (61.1)	0.004
Total LSM compliance, *n* (%)	3 (3.0)	32 (33.7)	0.000
Aerobic exercise score, mean ± SD	2.81 ± 4.41	11.65 ± 10.60	0.000
Depression score, mean ± SD	21.11 ± 7.75	14.98 ± 9.61	0.002
Depression, *n* (%)	51 (51.0)	33 (34.7)	0.022
No depression, *n* (%)	49 (49.0)	62 (65.3)	0.022

At the beginning, 100 patients were recruited, but there were five dropouts during the study, leaving 95 participants for analysis after the LSM intervention. Lifestyle modification yielded improved aerobic scores and a six-point reduction in the depression scores, with a reduction in the incidence of depression after LSM.

The severity and prevalence of depression and depressive traits after the LSM intervention were compared in compliant and non-compliant subjects. Both the depression severity and the number of subjects with depression were significantly lower in compliant subjects (both $p = 0.000$). Only one (3.0%) fully compliant patient had depression compared to 32 (97.0%) patients in the partly compliant group ($p = 0.000$) (Table 4).

Fifty-two patients underwent CABG [males 27 (51.9%); females 25 (48.1%)], and 48 patients had PCI, [(males 31 (64.6%); females 17, (35.4%)]. The mean ages in these groups were similar and normally distributed ($p = 0.140$)

Most of the 95 (95.0%) participants were insufficiently active at baseline, with only five (5.0%) being physically active. After LSM the number who reached the desired PA level increased from five (5.0%) at baseline to 38 (40.0%) ($p = 0.000$) three months later. The PA score improved from 2.81 ± 4.410 at baseline to 11.65 ± 10.600 ($p = 0.000$) after LSM (Table 3).

The PA scores were low for both the CABG and PCI groups at baseline, although slightly higher for PCI (2.15 ± 4.160 and 3.53 ± 4.603, respectively) ($p = 0.119$). After 12 weeks of the LSM regime, more patients undertook PA in the PCI group compared to the CABG group: 27 (61.1%) versus 15 (33.9%) patients participated often, seven (73.9%) versus two (21.1%) sometimes, and 11 (23.7%) versus 33 (71.3%) rarely ($p = 0.012$). The mean PA scores were also higher in the PCI compared to the CABG group (14.16 ± 9.73 vs 9.40 ± 10.94, respectively) ($p = 0.024$). At the end of the study, 24 (60.0%) subjects in the PCI group and 14 (35.0%) in the CABG group reached a satisfactory level of PA based on the GLTE questionnaire cut-off points ($p = 0.012$).

Table 4. Effects of LSM in compliant and partly compliant groups

Variables	*LSM compliant*	*LSM partly compliant*	*p-value*
Aerobic exercise score post LSM, mean ± SD	15.94 ± 12.00	10.80 ± 9.80	0.018
Depression score post LSM, mean ± SD	10.20 ± 7.00	16.70 ± 10.30	0.000
Depression, *n* (%)	1 (2.9)	32 (92.1)	0.000
No depression, *n* (%)	31 (47.5)	31 (47.5)	0.000

LSM: lifestyle modification yielded improved exercise scores and a fall in depression scores with a reduction in the incidence of depression in compliant subjects.

Table 5. Effect of LSM: CABG vs PCI group

Lifestyle parameters	*CABG (n = 52)*	*PCI (n = 48)*	*p-value*
Aerobic exercise score, mean ± SD			
Pre LSM	2.15 ± 4.16	3.53 ± 4.60	0.119
Post LSM	9.40 ± 10.94	14.16 ± 9.73	0.024
Aerobic exercise compliance, *n* (%)			
Pre LSM	2 (40)	3 (60)	0.715
Post LSM	14 (35.0)	24 (60.0)	0.012
Dietary measures compliance, *n* (%)			
Pre LSM	3 (50.0)	3 (50.0)	0.200
Post LSM	30 (49.1)	28 (45.9)	0.200
Smoking cessation compliance, *n* (%)			
Pre LSM	6 (54.5)	5 (45.5)	0.590
Post LSM	40 (52.8)	32 (42.2)	0.593
Total LSM compliance, *n* (%)			
Pre LSM	1 (33.3)	2 (66.7)	0.217
Post LSM	12 (35.6)	20 (59.4)	0.022
Depression score, *n* (%)			
Pre LSM	22.10±7.60	19.20±7.50	0.049
Post LSM*	17.80±10.60	11.30±6.60	0.000
Depression status pre LSM, *n* (%)			
Depressed	34 (66.7)	17 (33.3)	0.047
Not depressed	18 (36.7)	31 (63.3)	0.047
Depression status post LSM, *n* (%)			
Depressed	25 (72.0)	8 (23.0)	0.001
Not depressed	25 (38.3)	37 (56.7)	0.001

LSM: lifestyle modification; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery.
LSM was more effective after PCI, with lower depression scores and reduced incidence of depression, as well as improved aerobic and dietary compliance in PCI subjects.
The lower participant numbers reflect the changes recorded in 95 participants after LSM because there were five dropouts.

Table 6. Effects of LSM: compliant CABG vs compliant PCI groups

Variables	*Compliant CABG (n =2)*	*Compliant PCI (n = 20)*	*OR (95% CI)*	*p-value*
Total LSM compliance, *n* (%)	12 (35.6)	20 (59.4)	1.70 (2.30–5.67)	0.022
Aerobic exercise score	14.96	18.91	1.10 (1.31–4.82)	0.049
Depression score	10.81	7.62	1.21 (1.12–3.92)	0.046
Depression pre LSM, *n* (%)	5 (41.7)	8 (40.0)	0.91 (0.89–3.97)	0.125
Depression post LSM, *n* (%)	1 (7.9)	0 (0.0)	0.96 (0.80–3.30)	0.063
No depression pre LSM, *n* (%)	7 (58.3)	12 (60.0)	1.0 (0.91–2.94)	0.097
No depression post LSM, *n* (%)	11 (87.1)	20 (95.0)	1.19 (0.75–4.10)	0.113

The prevalence of depression fell from five persons pre LSM to one post LSM (80.0% reduction) among the fully compliant CABG group.
There was no person with depression post LSM, from the initial eight depressed subjects (100.0% reduction), among the fully compliant PCI group.
The differences in reduction between fully compliant CABG and PCI patients were 80.0 vs 100% (OR 1.10, 95% CI: 0.98–4.23, $p = 0.191$), which was not statistically significant.
The number of patients with no depression increased from seven persons pre LSM to 11 post LSM in the fully compliant CABG group (57.1%).
There was a 66.7% increment in the number of subjects with no depression post LSM, from the initial 12 to 20 patients among the fully compliant PCI group.
The difference in increment between the fully compliant CABG and PCI groups was 57.1 vs 66.7% (OR 0.91, 95% CI: 0.97–3.23, $p = 0.210$), which was not statistically significant.

At baseline, there were fewer PCI subjects with depression compared to the CABG group [17 (33.3%) vs 34 (66.3%), respectively ($p = 0.047$)]. The mean depression scores were lower in the PCI group compared to the CABG group (19.20 ± 7.50 vs 22.10 ± 7.60) ($p = 0.049$), respectively, indicating more severe depressive symptoms among CABG subjects at baseline (Table 5).

After three months of LSM, the number of participants with depression and depressive traits fell from 51 (51.0%) to 33 (34.7%) ($p = 0.022$). Fewer cases of depression and depressive traits were seen in the PCI compared with the CABG group [8 (23.0%) vs 25 (72.0%) ($p = 0.001$)], respectively. There was a corresponding increase in the number of non-depressed patients in both groups, with a greater increment among the PCI subjects [37 (56.7%) vs 25 (38.3%) ($p = 0.001$)]. The mean depression scores followed the same pattern, with a greater score reduction in the PCI compared to CABG group (7.90 vs 4.30, respectively) ($p = 0.000$), suggesting that the PCI group derived greater benefit than the CABG group from the LSM regime (Table 5).

After LSM, the prevalence of depression was significantly lower among LSM-compliant subjects, with only one compliant patient being depressed compared to 32 patients in the partly compliant group ($p = 0.001$). Notably, the compliant CABG and PCI patients derived nearly the same benefit from the LSM programme (OR 1.10, 95% CI: 0.78–4.23, $p = 0.191$). There were eight CABG and five PCI patients among the post-LSM fully complaint patients with depressive traits at baseline ($p = 0.125$), which reduced to one CABG and no PCI patient with depressive traits post LSM ($p = 0.063$) (Table 6).

Discussion

In this prospective study we evaluated the prevalence of depression and depressive traits among MI patients after revascularisation and analysed the effect of LSM on depressive symptoms. We found a high prevalence of depression and depressive traits (51.0%) among CAD patients who had sustained an MI and undergone revascularisation. Similarly, several previous studies have shown that depression is common among MI patients, ranging from 10 to 65%.[1-7] Most of these studies were conducted in developed countries, but a recent study by Ranjith *et al.* analysed depression among MI patients in South Africa and reported a prevalence of 49.0%.[29]

In addition to evaluating the prevalence of depression among these patients, we also analysed the effects of LSM on the incidence of depression and compared the findings between CABG and PCI patients. We found that LSM significantly reduced both the incidence and severity of depression among MI patients undergoing revascularisation, with compliant PCI versus CABG patients deriving similar benefits. To the best of our knowledge, no previous study has compared the effect of LSM in these two categories of patients.

Many factors could have contributed to the high prevalence of depression and depressive traits in our study, among them gender, low income, previous history of depression, low PA, as well as the presence of complications and other co-morbidities. Similar to other studies,[16,19,29] we have shown that those participants with a low income, previous history of depression and female gender were more frequently associated with depression. In addition, it appears those participants with more severe CAD requiring CABG and the sicker patients (those with heart and kidney failure) were more likely to experience depressive symptoms. This is in contrast to the study of Pelletier *et al.*, which showed that disease severity did not influence the outcome of depression in MI patients.[14]

The high prevalence of depression in our study could also be related to the fact that all our subjects had sustained a previous MI, resulting in compensatory haemodynamic and neurohormonal consequences of myocardial damage. Factors such as reduced

heart rate variability, caused by autonomic dysregulation, and post-infarction inflammatory and neurohormonal changes are common among MI patients and have been shown to manifest physically as mental and psychological changes of depression and anxiety[33-38] and possibly are the cause of high adverse outcomes reported among these patients.[49]

Patients undergoing CABG probably generate an even greater inflammatory response than PCI subjects since they generally have more severe CAD affecting all three coronary arteries or the left main coronary artery, compared to patients selected for PCI who are more likely to have single- or two-vessel disease. The higher prevalence of depression among CABG compared to PCI subjects in our study could therefore have been related to the severity of myocardial injury and the greater burden of atherosclerotic disease in CABG participants (frequently triple-vessel disease and heart failure compared to single- or double-vessel involvement in the PCI group).

An important finding in our study was that LSM led to a significant reduction in the prevalence of depression, from 51.0% pre LSM to 34.7% post LSM intervention. In addition, we recorded a six-point reduction in the mean depression scores post LSM (Table 3), indicating a reduction in the severity of depressive symptoms with LSM intervention. After LSM, depression was three times more frequent among CABG than PCI patients (Table 5), suggesting that the PCI group benefited more from the anti-depressive effect of LSM.

We attributed the marked difference in depression scores in the PCI compared to the CABG group (7.90 vs 4.30 point reduction, respectively) ($p = 0.000$) to early ambulation with improvement in PA in the PCI group. It is noteworthy that PA scores were similarly low for both CABG and PCI groups at baseline ($p = 0.119$). There was a large increase in the PA scores from a mean of 2.81 at baseline to 11.65 after LSM intervention (Table 3). The PCI group attained higher PA scores compared to the CABG subjects ($p = 0.024$) by the end of the study period because of their more immediate mobility post revascularisation (Table 5).

Although the prevalence of depression in partly compliant participants fell after LSM intervention (51.0% at baseline to 33.7% post LSM), there was a marked reduction recorded in LSM-compliant subjects (51.0% patients at baseline to 1.1% post LSM) ($p = 0.001$). Also, a greater point reduction in depression score was seen for subjects who adhered fully to LSM measures, indicating a better reduction in severity of depressive symptoms with LSM intervention (Table 4). An important finding in our study was that fully compliant CABG and PCI patients derived similar benefit from the LSM programme, emphasising the role of adherence to LSM in reaping maximum benefit after revascularisation, independent of the type of procedure.

The reduction in incidence and severity of depression achieved in partly compliant participants was probably due to modest increments in PA from baseline, without which depressive symptoms may have persisted over time. This has been highlighted by May *et al.* in their ground-breaking study, which showed that depression status may not improve completely after MI and is associated with a two-fold increased risk of death.[16] Our findings are consistent with previous studies, showing that LSM improved mental functioning and reduced depression.[50-53]

In a meta-analysis on mental health treatment and LSM for improving clinical outcomes and incidence and severity of depression among patients with CAD, Rutledge *et al.*[19] demonstrated that not only did LSM reduce depression to the same extent as mental health treatment, but it was also superior in reducing all-cause mortality risk. In another study, Carl *et al.*[13] established that LSM reduced depressive symptoms by 63% and all-cause mortality by 73.0%.

While the adherence to LSM measures showed improvement in dietary changes and cessation of cigarette smoking among the majority of the participants, only 40.0% complied with aerobic exercise recommendations; overall, only one-third of subjects adhered fully to LSM. Poor compliance with LSM recommendations has been reported in previous studies.[54,55]

Similar to these studies, the reasons for non-adherence to LSM measures in our study were mainly lack of motivation, bodily discomfort and fear of an adverse outcome, although no exercise-related adverse effects were reported among the participants. Thoracic cage and lower limb discomfort as well as fear of potentially adverse outcomes after early ambulation post bypass surgery was another possible factor accounting for the lower exercise scores among the CABG subjects. It is therefore not surprising that twice as many PCI subjects participated in frequent PA compared to the CABG group. This may explain the higher prevalence and severity of depression after LSM among the CABG group. This is an important limitation of our study, which to some extent may have been averted if the interview after the LSM intervention had been performed six months after surgery instead of 12 weeks.

Limitations and strengths

Our study has methodological limitations and challenges. Although subjects were prospectively evaluated, the convenient non-random sampling method used in this study limited the ability to generalise our findings to all CAD subjects. Only participants undergoing revascularisation who were able to participate in the LSM recommendations were recruited into the study. Participants recruited were referred by state institutions, so that most participants were from the lower income group. Furthermore, the PA levels were self-reported and were not objectively verified at follow up through stress testing. However, studies have shown that self-reported activity has significant concordance with objectively measured PA using actigraphy-assessed PA.[39,40]

A further important consideration is that the 12-week period after revascularisation might have been too short for assessing the response to LSM in CABG patients since the operation involved mediastinal surgery and lower-limb vein grafts, which may have required a longer period of physical recovery before full PA could be resumed, compared to PCI subjects who were almost immediately ambulant after their procedure. A re-evaluation after six months of LSM would have provided a fairer comparison between the two groups.

The limited time frame of three months for the LSM intervention in our study also does not permit long-term inferences to be made from our findings since persistence of depression over time has been reported by May *et al.*[16] Also, a more informed assessment of the exercise parameters and incidence of depression would have been obtained in subjects matched for ejection fraction and disease severity. A longer-term, randomised, controlled study is needed to verify our findings and to relate these findings to haemodynamic severity of the

underlying disease, and adjust for other confounding factors such as level of income and domestic issues, which we have shown to be predictors of depression.

The main strength of our study lies in its prospective evaluation of the effects of LSM on the incidence of depression after coronary revascularisation and it provides some insight into the varying responses of the intervention among CABG and PCI participants. The findings suggest that LSM changes may safely be implemented without fear of potential adverse cardiovascular events.

Despite its limitations, the study is consistent with previous studies showing that LSM improves mental functioning and reduces depression and depression traits.[50-53]

Clinical implications

Our findings have important clinical applicability, since they emphasise the relationship between mental and physical well-being and suggest a successful outcome, particularly in participants who are able to adhere fully to LSM guidelines regardless of the mode of revascularisation. Lower levels of PA short of the required target also appeared to have had some anti-depressive benefits since a modest benefit accrued in those who were partly compliant with LSM guidelines. These findings suggest that ongoing emphasis on counselling patients to overcome the barriers to engaging in adequate PA, such as lack of motivation and fear of adverse outcomes, are critical to a successful outcome, particularly in CABG subjects. This may well translate into morbidity and mortality benefits in participants who fully adhere to LSM recommendations.

Conclusion

This study confirms a high prevalence of depressive symptoms in MI subjects undergoing coronary revascularisation and showed that participants in the PCI group derived greater benefit from lifestyle intervention than the CABG group, probably because of early ambulation. Although depression is amenable to intervention by LSM measures, the beneficial effect of LSM was seen mainly among LSM-compliant subjects. Fully compliant subjects derived equal benefit, regardless of the mode of revascularisation, emphasising the importance of counselling to overcome the barriers to full participation in LSM and undertaking PA. A long-term, randomised study is needed to verify these findings.

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In Memorium

Somalingum Ponnusamy: 1/9/58 to 10/2/21

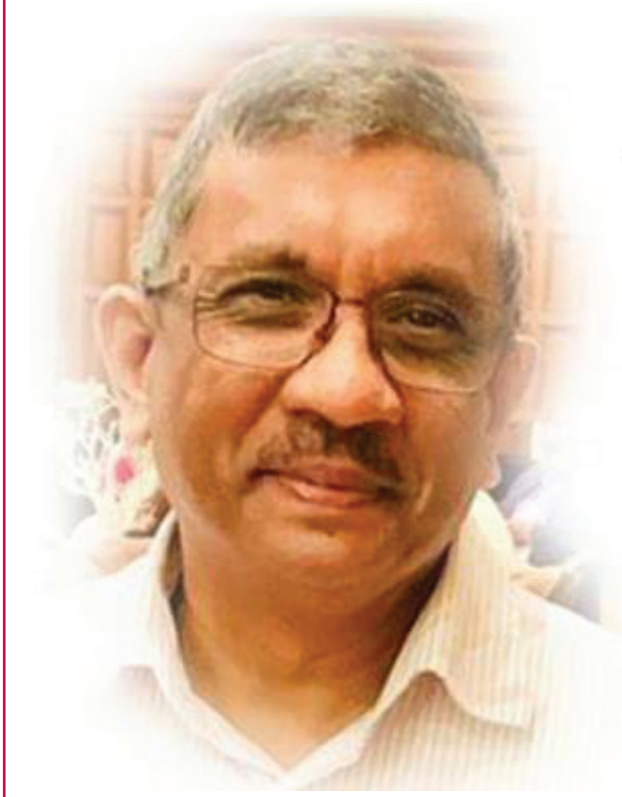
It is with great sadness that I inform the medical fraternity of the untimely passing of Dr Somalingum Ponnusamy at the age of 62 years after a protracted battle with COVID-19 illness. His death is a sad loss to his family, medical colleagues, the military and the community he served. It has left a huge gap in the Department of Cardiology at Inkosi Albert Luthuli Hospital, where he was the head of the clinical unit.

Leslie, as he was affectionately known, was born in the district of Sea Cow Lake, Durban on 1 September 1958. Shortly after he completed schooling, he joined the University of Durban Westville but was targeted by the previous government during the Soweto uprising. He went into exile, leaving for India in 1978, and completed a Bachelor's degree in Veterinary Science with a Government of India scholarship. He returned to Zambia in 1988, won a United Nations scholarship to study medicine and graduated with his MB ChB at Medunsa in 1996. While rotating as a registrar in internal medicine in 2002, he became attracted to cardiology and joined the department in 2004.

From the outset, Leslie dedicated himself wholly to serving the department, to the exclusion of his own social and family life. During this period, Leslie's managerial skills became evident and he became the head of the clinical unit in 2009. Leslie's dedication to duty is unparalleled in the history of the department. He gave selflessly to his patients and his community, sacrificing family time and friends, as well as foregoing his own career development. He worked tirelessly at co-ordinating the cardiology service in KwaZulu-Natal and ensured the smooth running of the department. After work he was usually the last person to leave the department. Often I would see his car in the parking lot late at night and find him still working in his office.

In 2010 he won the RC Fraser International Fellowship in Cardiovascular Intervention at St Thomas Hospital and then developed an interest in electrophysiology. He was responsible for convening the ECG and pacemaker workshops and all of us will remember his enthusiasm for the annual cardiology update, which he organised for 16 years in a row since the third update in 2005.

Leslie touched many lives in his lifetime, both within and outside the department, and his passing leaves a huge void and immense sadness among the staff. In the words of the one of the departmental staff, he was a father to the department. He was a deeply caring, humble and unassuming person who gave fully of himself without expecting anything in return. Many of us will remember the great pains he took to juggle the rosters in order to accommodate often unreasonable leave requests. Through his passion for cardiology, he has produced many cardiology graduates and his legacy will live on in the code of discipline he instilled in the members of the department (which I often mused was a skill that arose from his military training). We have learnt so much from him and he has ensured that the cardiology service will continue in his absence.



Somalingum Ponnusamy

Leslie will be deeply missed and we will always appreciate his contribution to the department. In years to come, we will remember the guard of honour that was held for him the day he left the hospital for the last time, when the whole hospital staff came out in droves to pay their last respects and contributions to a great doctor and colleague. In some way Leslie touched all of us, and in his own inimitable manner, endeared himself to one and all through his strength of character and selfless leadership. Life will not be the same without him. As hard it may seem, Leslie would have wanted us to soldier on together during these difficult times.

We will forever treasure fond memories of him walking the passages of the hospital. May his family and friends find strength and comfort during this time, knowing that he was highly respected and highly valued by his peers.

Prof DP Naidoo (acting head)

Cardiovascular view of intermediate and high-risk COVID-19 patients: single-centre experience with low mortality and intensive care hospitalisation rates

Alpay Medetalibeyoglu, Samim Emet, Naci Senkal, Mehmet Aydogan, Murat Kose, Tufan Tukek

Abstract

Aim: The purpose of this article was to report the low rates of intensive care unit admission and mortality in intermediate- and high-risk COVID-19 patients, and to share our clinical approach with other colleagues. In addition, we sought to reveal the relationship between myocardial injury and clinical outcomes such as death, intensive care unit uptake and hospital stay, and the relationship between inflammatory parameters and cardiac biomarkers in a cardiovascular perspective.

Methods: Patients admitted to the emergency department in the Department of Internal Medicine, Faculty of Medicine, Istanbul University, with laboratory or clinically and radiologically confirmed COVID-19 were included in this retrospective cross-sectional study, which was conducted from 11 March to 10 April 2020. The demographic (age and gender) and clinical (symptoms, co-morbidities, treatments, complications and outcomes) characteristics, laboratory findings, and results of cardiac examinations (cardiac biomarkers and electrocardiography) of patients during hospitalisation were collected from their medical records by two investigators. Data were analysed using SPSS version 25.0 (IBM). A two-sided $p < 0.05$ was considered statistically significant. Analysis began on 11 April 2020.

Results: Mortality and intensive care unit admission rates were statistically significantly higher in patients with cardiac injury than in those without. There was a positive correlation between levels of high-sensitivity TNT and fibrinogen, D-dimer, ferritin, procalcitonin and C-reactive protein ($r = 0.24$, $p < 0.01$; $r = 0.37$, $p < 0.01$; $r = 0.25$, $p < 0.01$, $r = 0.34$, $p < 0.01$; $r = 0.31$, $p < 0.01$).

Conclusion: The first general data of our 309 patients regarding low mortality and intensive care admission rates, and particular treatment algorithms specific to our centre should be helpful in determining better treatment strategies in the future. Our study emphasises the importance and frequency of cardiovascular outcomes, and the significance of some cardiac biomarkers in predicting COVID-19 prognosis.

Keywords: cardiovascular outcomes, myocardial injury, troponin, COVID-19, mortality, intensive care hospitalisation

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In December 2019, in Wuhan city of Hubei province in China, a novel coronavirus [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] emerged with cases of treatment-resistant pneumonia, and subsequently spread rapidly, causing the first pandemic of the 21st century.[1-3] After it was officially detected in our country on 11 March 2020, the number of cases has increased rapidly.

The main cause of death in coronavirus disease 2019 (COVID-19) is severe acute respiratory failure.[1,4-6] In published patient series, 40% of patients hospitalised due to COVID-19 positivity had cardiovascular or cerebrovascular disease, 17% had arrhythmia and 7% had acute cardiac damage. In some case reports, COVID-19 has been reported in the form of the first acute onset of heart failure, acute myocardial infarction (MI), myocarditis or sudden cardiac arrest.[1,4,5]

The four main effects of COVID-19 on the cardiovascular system are listed below:[7]

- The risk of serious illness and death increases with COVID-19 in the presence of accompanying cardiovascular disease.
- COVID-19 is responsible for a large number of direct or indirect cardiovascular complications such as myocarditis, myocardial damage, arrhythmia and venous thromboembolism.
- Drugs that are in research and/or development phase for COVID-19 have various cardiovascular side effects.
- Healthcare professionals providing cardiovascular care services play a role as host or carrier in COVID-19 spread.

The purpose of this article was to report the low intensive care unit (ICU) admission and mortality rates in intermediate- and high-risk COVID-19 patients and to share our clinical approach with other colleagues. In addition, we reveal the relationship between myocardial injury and clinical outcomes such as death, ICU admission and hospital stay, and the relationship between inflammatory parameters and cardiac biomarkers in a cardiovascular perspective.

Methods

Patients admitted to the emergency department in the Department of Internal Medicine at Istanbul University Faculty of Medicine, with laboratory or clinically and radiologically confirmed COVID-19 were included in this retrospective, cross-sectional study, which was conducted from 11 March to 10 April 2020. The patients with COVID-19 enrolled in this study were diagnosed according to World Health Organisation interim

guidance.[8] Patients who had mild pneumonia and/or mild illness such as uncomplicated upper respiratory tract viral infection, had non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnoea, nasal congestion or headache and rarely presented with diarrhoea, nausea and vomiting, were followed without hospitalisation.

Patients were hospitalised if they had one of these listed below:

- patients with mild pneumonia (unilateral infiltration) but with age older than 60 years and/or existence of co-morbidities such as diabetes, hypertension, cardiovascular disease, cerebrovascular disease, chronic renal disease, chronic obstructive pulmonary disease and immune incompetence (for exclusion: active malignancy, ongoing chemotherapy or radiotherapy, HIV infection)
- patients with moderate/severe pneumonia (bilateral infiltration and/or multiple mottling and ground-glass opacity)
- patients with hypotension (< 90/60 mmHg) or tachypnoea or hypoxaemia [arterial oxygen (O_2) saturation below 93% without O_2 supply]
- patients with mild pneumonia (unilateral infiltration) but having severe biochemical or haematological parameters such as ferritin value above 1 000 ng/ml or high-sensitivity C-reactive protein (hs-CRP) level above 40 mg/dl or lymphopaenia.

Patients were taken to the ICU if the following clinical and laboratory parameters were involved:

- respiratory rate ≥ 30 breaths/minute
- dyspnoea
- SpO_2 < 90% and PaO_2 < 70 mmHg despite > 5 l/min nasal oxygen supply
- $PaO_2/FiO_2 \leq 300$
- lactate > 2 mmol/l
- hypotension (systolic blood pressure < 90 mmHg or drop > 40 mmHg in usual systolic blood pressure or mean arterial pressure < 65 mmHg), tachycardia (> 100 beats/min)
- findings showing renal, hepatic, haematological (thrombocytopaenia) or cerebral (confusion) dysfunction (sepsis or septic shock)
- skin findings of capillary return disorder such as cutis marmaratus.

The demographic (age and gender) and clinical (symptoms, co-morbidities, treatments, complications and outcomes) characteristics, laboratory findings, and results of cardiac examinations (cardiac biomarkers and electrocardiography) of patients during hospitalisation were collected from their medical records by two investigators (NS and AA). Cardiac biomarkers measured on admission were collected, including high-sensitivity troponin T (hs-TNT) and N-terminal proB-type natriuretic peptide (NT-proBNP). The radiological assessments included radiography, computed tomography or magnetic resonance imaging. All data were independently reviewed and entered into the computer database by two analysts (HK and GD).

To confirm COVID-19, the SARS-CoV-2 (2019-nCoV) polymerase chain reaction (qPC) detection kit (Bio-Speedy®) was used for detecting the epidemic virus SARS-CoV-2 (2019-nCoV) causing COVID-19. The kit was applied to nucleic aid isolates from nasopharyngeal aspirate/lavage, broncho-alveolar lavage, nasopharyngeal swab, oropharyngeal swab and sputum samples. Rapid diagnosis with the kit was achieved via one-step reverse transcription (RT) and real-time qPCR (RT-qPCR) targeting the SARS-CoV-2 (2019-nCoV)-specific RdRp (RNA-dependent RNA polymerase) gene fragment.

Arterial and/or venous thrombosis were defined as documented thrombosis with imagining modalities such as magnetic resonance imaging, computed tomography or Doppler ultrasound. Malignant arrhythmia was defined as rapid ventricular tachycardia lasting more than 30 seconds, inducing haemodynamic instability and/or ventricular fibrillation.

Patients were considered to have acute myocardial injury if serum levels of TNT were above the 99th percentile upper reference limit (hs-TNT ≥ 14 pg/ml).[9] Acute coronary syndrome was defined as the presence of chest pain or ischaemic equivalent at rest, lasting longer than 20 minutes, associated with one of the following conditions: ECG showing ST-segment elevation or depression ≥ 1.0 mm in two or more contiguous leads; elevated biomarkers of myocardial necrosis (i.e. CK-MB > once the upper limit of normal of the local laboratory, or hs-TNT ≥ 14 pg/ml). Cerebrovascular accident was defined as the presence of neurological symptoms and proven ischaemic and/or haemorrhagic focus by imaging modalities. The clinical outcomes (discharges, mortality and length of stay) were monitored up to 10 April 2020, the final date of follow up.

Treatment algorithms in hospitalised patients

Infection-specific treatment

- Hydroxychloroquine + oseltamivir (if influenza could not be excluded) + azithromycin were initiated in patients with pneumonia including normal blood values [leukocyte, lymphocyte, lactate dehydrogenase (LDH), ferritin, troponin] and patients with CRP < 20 mg/l.
- In cases of moderate (bilateral infiltration) pneumonia:
  - Hydroxychloroquine was given for 7–10 days.
  - Conditions for addition of favipravir were examined (clinical deterioration under hydroxychloroquine or progression of pneumonia).
  - A patient-based decision was made about anti-inflammatory treatments.
  - High-flow nasal oxygen therapy (SpO_2 < 93% or PaO_2/FiO_2 < 300 or respiratory rate > 24 breaths/min) was given.
- Patients with severe pneumonia (multiple mottling and ground-glass opacity), including those who developed acute respiratory distress syndrome, sepsis or myocarditis, and those at risk of developing shock:
  - Hydroxychloroquine and/or favipravir + azithromycin (should be evaluated for its contra-indications) + oseltamivir (if influenza could not be excluded).
  - Patients who developed myocarditis were treated like patients with severe pneumonia.

Other specific treatments and prophylaxis regimens

Antithrombotic and anticoagulant therapy/prophylaxis were initiated unless contra-indicated, to all patients admitted to the hospital, with a regimen of subcutaneous enoxaparin 4 000 IU once a day and oral dipyridamole 75 mg twice a day.

In patients with severe pneumonia, enoxaparin 100 IU/kg twice a day (at the treatment dose) was used subcutaneously if serum ferritin levels were > 1 000 ng/ml (or nearly two-fold increase in follow up) or serum LDH levels were > 400 U/l (or increase in follow up) or serum D-dimer levels were > 2 000 µg/l.

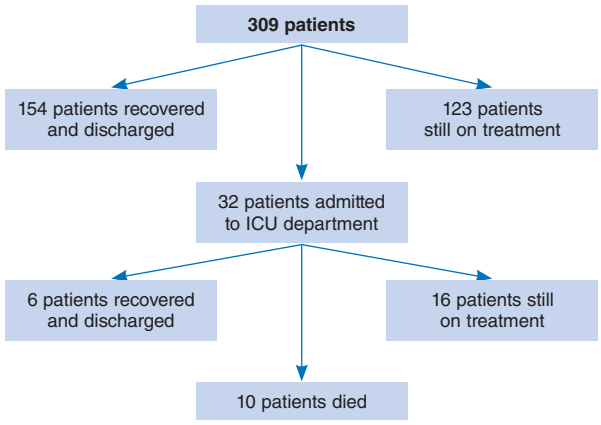

Fig. 1. Flowchart of the patients admitted to the COVID-19 wards (309 patients) between 11 March and 10 April 2020 and included in the study.

Tosilizumab, an IL-6 antagonist, was added in addition to other treatments in patients who developed macrophage activation syndrome findings with worsening of pneumonia and acute-phase response.

Tosilizumab was used in patients with severe pneumonia and serum CRP level > 70 mg/l and serum ferritin level > 1 000 ng/ml, and also if there were at least two of the following criteria:

- fever (≥ 38.5°C)
- hepato/splenomegaly
- bicytopaenia /pancytopaenia
- triglycerides > 350 mg/dl (3.96 mmol/l)
- fibrinogen < 250 mg/dl
- aspartate aminotransferase > 42 U/l
- haemophagocytosis in the bone marrow
- immunosuppression.

Statistical analysis

Descriptive statistics were obtained for all study data. Categorical variables were compared for the study outcome using the Fisher exact test or χ^2 test, and continuous variables were compared using the *t*-test or the Mann–Whitney *U*-test, as appropriate. Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Simirnov/Shapiro–Wilk's test) to determine whether they were normally distributed. Continuous data are expressed as mean (SD) or median [interquartile range (IQR)] values. Categorical data are expressed as proportions.

The Pearson correlation coefficient and Spearman rank correlation coefficient were used for linear correlation analysis. The ANOVA test was used to compare laboratory findings of patients grouped according to thorax computerised tomography (CT) scans. The Bonferroni test was used for *post hoc* analysis of the multiple comparisons. Data were analysed using SPSS version 25.0 (IBM). A two-sided $p < 0.05$ was considered statistically significant. Analysis began on 11 April 2020.

Results

Patients admitted to the COVID wards (309 patients) between 11 March and 10 April were included in the study. During this period, a total of 32 patients were taken to the ICU. Ten of these ICU patients died and six were discharged. The intensive care treatments of the remaining 16 patients were ongoing. Our mortality rate was 3%. A total of 154 patients hospitalised in the COVID wards were discharged. Treatment of the remaining 123 patients is ongoing (Fig. 1).

Table 1. Baseline characteristics, signs, symptoms, accompanying chronic diseases and drug usage of the patients

	Patients, n (%)			
		Cardiac injury		
Characteristics	*All (n = 309)*	*With (n = 78)*	*Without (n = 231)*	*p-value*
Age, median (range), years	57 (23–94)	70 (32–94)	52 (23–93)	< 0.001
Males	190 (61)	46 (59)	144 (62)	> 0.05
Smoking	49 (16)	4 (5)	45 (19)	< 0.01
Signs and symptoms at admission				
Fever	241 (78)	48 (61)	193 (83)	> 0.05
Cough	279 (90)	68 (87)	211 (91)	> 0.05
Sputum production	12 (3)	3 (3)	9 (3)	> 0.05
Shortness of breath	111 (36)	45 (58)	66 (28)	< 0.001
Fatigue	298 (91)	73 (93)	225 (97)	> 0.05
Nausea	47 (15)	10 (12)	37 (16)	> 0.05
Diarrhoea	21 (6)	3 (3)	18 (7)	> 0.05
Anosmia	14 (4)	1 (1)	13 (5)	> 0.05
Saturation, median (range), %	94 (79–99)	91 (79–98)	95 (82–99)	< 0.001
SBP, median (range), mmHg	130 (80–200)	132 (80–200)	128 (80–180)	> 0.05
DBP, median (range), mmHg	75 (50–120)	75 (50–120)	76 (50–110)	> 0.05
Pulse, median (range), bpm	94 (50–123)	94 (50–123)	94 (52–122)	> 0.05
RR, median (range), breaths/min	18 (14–34)	23 (14–34)	19 (14–32)	< 0.001
Chronic disease/ACEI/ARB usage				
Hypertension	122 (39)	53 (67)	69(30)	< 0.001
CAD	33 (11)	21 (27)	12 (5)	< 0.001
CHF	18 (6)	15 (19)	3 (1)	< 0.001
COPD	32 (10)	15 (19)	17 (7)	< 0.01
Diabetes	69 (22)	24 (31)	45 (19)	0.02
CKD	43 (14)	26 (33)	17 (7)	< 0.001
ACEI/ARB usage	78 (25)	30 (38)	48 (21)	> 0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Baseline characteristics, signs, symptoms, accompanying chronic diseases and drug usage of the patients are shown in Table 1. The median age of the study population was 57 years (23–94). There was a statistically significant difference between the median ages of patients with and without cardiac injury ($p < 0.001$) (Table 1). The study population was slightly male predominant (61%) but it was not statistically significant ($p > 0.05$) (Table 1).

Unpredictably, the proportion of smokers was statistically significantly lower in patients with myocardial injury than in those without injury ($p < 0.01$) (Table 1).

It was only shortness of breath that reached statistical significance in terms of the symptoms of patients with and without cardiac damage at the time of hospitalisation ($p < 0.001$) (Table 1).

Saturations and respiratory rates were statistically significantly different when patients with and without cardiac damage were compared in terms of vital signs at the time of admission ($p < 0.001$) (Table 1).

Hypertension was the lead chronic medical illness, with a rate of 39% of the total patients that had COVID-19. Diabetes was second, with a rate of 22% of all patients. Chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease and chronic heart failure were the other most common diseases, respectively. The incidences of all chronic diseases were statistically different in patients with and without cardiac injury (Table 1). However, there was no statistically significant difference in angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) usage in patients with and without cardiac injury (Table 1).

Baseline laboratory findings, blood gas analysis and chest CT of the patients with and without cardiac injury are shown in Table 2. Serum creatinine, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), LDH, CRP, ferritin, D-dimer, hs-TNT, NT-proBNP and fibrinogen levels were statistically significantly different in patients with and without cardiac injury (Table 2).

The appearance of severe pneumonia (multiple mottling and ground-glass opacity) in thorax CT scans was statistically significantly higher in patients with cardiac injury than in those without ($p < 0.01$) (Table 2). In addition, mortality, hospital discharge and ICU admission rates were statistically significantly higher in patients with cardiac injury than in those without (Table 2).

Cardiovascular outcomes of hospitalised patients were acute myocardial injury, with a rate of 25% (78 patients), acute coronary syndrome, with a rate of 0.6% (two patients), myocarditis, with a rate of 0.6% (two patients), arterial thrombosis, with a rate of 0.3% (one patient), venous thrombosis, with a rate of 0.9% (three patients), stroke, with a rate of 0.3% (one patient), and malignant ventricular arrhythmia, with a rate of 0.3% (one patient) (Table 3).

Correlations between hs-TNT, inflammatory markers and NT-proBNP are shown in Table 4. There was a strong correlation

Table 2. Baseline laboratory findings, blood gas analysis and chest computed tomography of the patients

	Patients, n (%)			
Variables		*Cardiac injury*		
Laboratory findings, median (range)	*All (n = 309)*	*With (n = 78)*	*Without (n = 231)*	*p-value*
WBC, cells/µl	7284 (280–97110)	9175 (280–97110)	6643 (1470–58330)	0.005
Lymphocytes, cells/µl	1384 (110–81150)	1927 (110–81150)	1200 (350–2800)	> 0.05
Platelets, $\times 10^3$ cells/µl	216 (10.5–552)	223 (10.5–518)	213 (42.5–552)	> 0.05
Haemoglobin, g/dl	13 (6.1–17.7)	12 (6.1–16.1)	13.4 (6.2–17.7)	< 0.001
ALT, U/l	31 (4–508)	33 (7–508)	31 (4–170)	> 0.05
AST, U/l	36 (9.8–302)	42 (10–362)	34 (12–159)	> 0.05
Albumin, g/dl	3.9 (1.9–5.1)	3.6 (1.9–4.7)	4 (2.1–5.1)	> 0.05
Creatinine, mg/dl	1.09 (0.4–18)	1.6 (0.6–18)	0.92 (0.4–2.5)	< 0.001
Potassium, mEq/l	4.2 (2.9–6)	4.3 (3–6)	4.2 (2.9–5.7)	> 0.05
Sodium, mEq/l	137 (124–151)	136 (124–151)	137 (128–147)	> 0.05
Glucose, mg/dl	134 (73–633)	149 (75–633)	129 (73–399)	> 0.05
GGT, U/l	48 (5–718)	65 (6–718)	42 (5–711)	0.02
ALP, U/l	74 (28–381)	93 (38–381)	68 (28–266)	< 0.001
LDH, U/l	14 (131–1135)	353 (136–1135)	280 (131–706)	< 0.001
C-reactive protein, mg/l	73 (1–460)	113 (1–460)	60 (1–359)	< 0.001
Procalcitonin, ng/ml	0.6 (0–57)	1.2 (0–57)	0.4 (0–48)	> 0.05
Ferritin, ng/ml	603 (14–5812)	790 (21–5083)	537 (14–5812)	0.01
D-dimer, µg/l	1310 (230–19440)	2157 (270–10850)	1022 (230–19440)	< 0.001
hs-TNT, pg/ml	38 (3–3417)	137 (14–3417)	5 (3–13)	< 0.001
NT Pro-BNP, pg/ml	714 (5–35000)	2522 (17–35000)	120 (5–2977)	< 0.001
Fibrinogen, mg/dl	549 (146–1028)	588 (146–1028)	535 (278–792)	0.004
aPTT, s	30 (14–65)	32 (22–65)	29 (14–58)	> 0.05
Blood gas analysis				
PaO_2, mmHg	62 (36–132)	60.5 (36–132)	62.8 (36–102)	> 0.05
$PaCO_2$, mmHg	40 (22–66)	37.2 (23–66)	41.7 (22–60)	> 0.05
Lactic acid, mmol/l	1.7 (0.7–6.2)	1.8 (0.8–6.2)	1.7 (0.7–4.1)	> 0.05
HCO_3, mEq/l	24 (10–33)	22.7 (10–33)	25 (17–33)	> 0.05
Chest radiography and CT findings				
Pneumonia				
Mild (unilateral)	158 (51)	31 (40)	127 (55)	> 0.05
Moderate (bilateral)	84 (27)	19 (24)	65 (28)	> 0.05
Severe (multiple mottling and ground-glass opacity)	67 (22)	28 (36)	39 (17)	< 0.01
Clinical outcomes				
Mortality	10 (3)	6 (7.7)	4 (1.7)	0.01
Discharge	160 (52)	22 (28)	138 (60)	< 0.001
Hospital duration (days)	8 (2–20)	8 (4–20)	7 (2–11)	> 0.05
ICU admission	32 (10)	19 (24)	13 (6)	< 0.001

WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; hs-TNT, high-sensitivity troponin T; NT-proBNP, N-terminal proB-type natriuretic peptide; aPTT, activated partial thromboplastin time; CT, computed tomography; ICU; intensive care unit.

Table 3. Cardiovascular outcomes of the patients

Cardiovascular outcomes	*Patients, n (%)*
Acute myocardial injury	78 (25)
Acute coronary syndrome	2 (0.6)
Myocarditis	2 (0.6)
Arterial thrombosis	1 (0.3)
Venous thrombosis	3 (0.9)
Stroke	1 (0.3)
Malignant ventricular arrhythmia	1 (0.3)

Table 4. Correlations between hs-TNT, inflammatory markers and NT-proBNP

		Fibrinogen	*NT-proBNP*	*D-dimer*	*Ferritin*	*Procalcitonin*	*CRP*
hs-TNT	Correlation co-efficient (*r*)	0.24	0.65	0.37	0.25	0.34	0.31
	p-value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

hs-TNT, high-sensitivity troponin T; NT-proBNP, N-terminal proB-type natriuretic peptide; CRP, C-reactive protein.

between hs-TNT and NT-proBNP ($r = 0.65$, $p < 0.01$) (Table 4). Also, there was a positive correlation between levels of hs-TNT and fibrinogen, D-dimer, ferritin, procalcitonin and CRP ($r = 0.24$, $p < 0.01$; $r = 0.37$, $p < 0.01$; $r = 0.25$, $p < 0.01$; $r = 0.34$, $p < 0.01$; $r = 0.31$, $p < 0.01$) (Table 4).

Serum levels of hs-TNT, NT-proBNP, ferritin, D-dimer, procalcitonin, CRP, fibrinogen, and neutrophil and lymphocyte counts are shown in Table 5 and compared with each patient grouped according to thorax CT scans, which were divided into three categories: 1, mild pneumonia; 2, moderate pneumonia; and 3, severe pneumonia (Table 5). Mean plots of the comparisons according to thorax CT scans are shown in Figs 2–5.

Discussion

By 19 April 2020, the COVID-19 pandemic had reached 2 241 359 cases and 152 551 deaths worldwide, according to the data of the religious health organisation. In Turkey, there were 82 329 cases and 1 890 deaths by 18 April 2020.

This study reflects a general and cardiovascular perspective on the current data of Istanbul University Medical Faculty Hospital, where original treatment protocols and advanced intensive care services are provided. In addition, our study demonstrates the prognostic significance of cardiovascular biomarkers in the follow up of COVID-19.

In general, our mortality rates and ICU admission rates were lower than reported in other previous studies. We linked this lower mortality and ICU admission rates to certain specific applications in our treatment protocol. Favipravir treatment was started in all patients with severe pneumonia and in those whose treatment was unresponsive to the routine treatment protocol, and/or in those with clinical deterioration of moderate pneumonia. In addition, due to the increased tendency to thrombosis in COVID-19 patients, antithrombotic and anticoagulant therapy/prophylaxis was initiated unless contraindicated in all patients admitted to the hospital, with a regimen of subcutaneous enoxaparin 4 000 IU once a day and oral dipyridamole 75 mg twice a day.

In patients with severe pneumonia, enoxaparin 100 IU/kg twice a day (at the treatment dose) was used subcutaneously if serum ferritin levels were > 1 000 ng/ml (or nearly two-fold increase in follow up) or serum LDH levels were > 400 U/l (or increase in follow up) or serum D-dimer levels were > 2 000 µg/l. We believe that these treatment protocols (early favipravir usage and routine anticoagulant/antiplatelet use) might have played a role in our favourable treatment results.

A recent report on 138 patients hospitalised with COVID-19 has shown that 7.2% had acute cardiac injury, and patients admitted to ICU were more likely to have cardiac injury (22.2%) than non-ICU patients.[1] This observation suggests that cardiac injury is possibly associated with worse clinical outcomes of COVID-19. In addition, another study also found 19.7% of

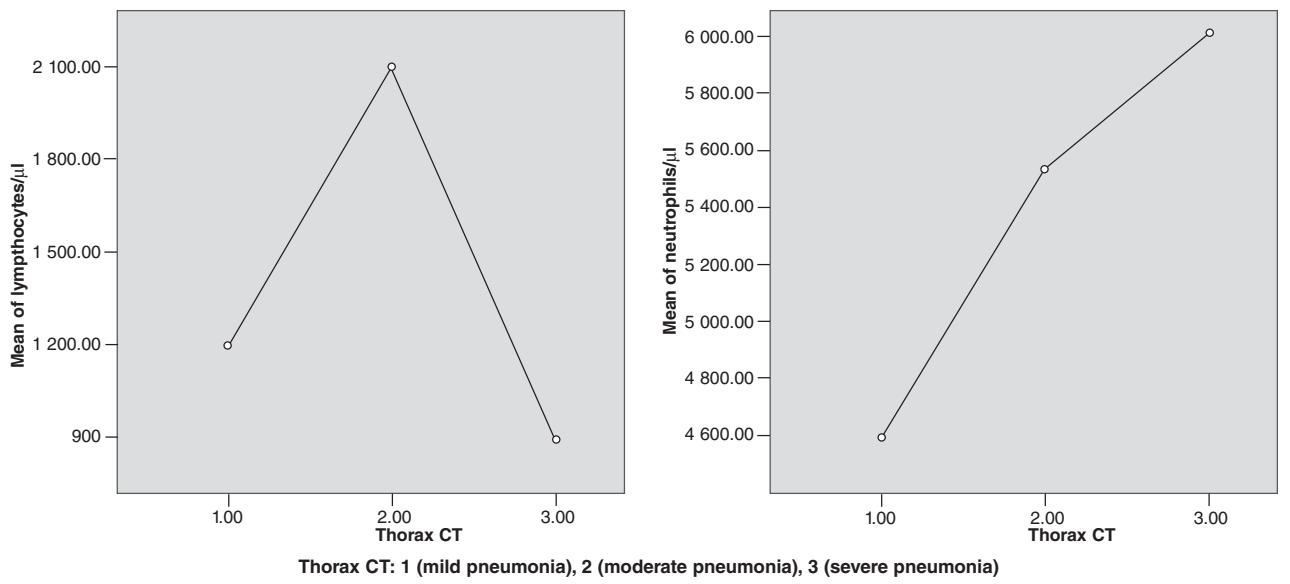

Fig. 2. Mean plots of neutrophil and lymphocyte counts compared with patients grouped according to thorax CT scans, which were divided into three categories: 1, mild pneumonia; 2, moderate pneumonia; and 3, severe pneumonia.

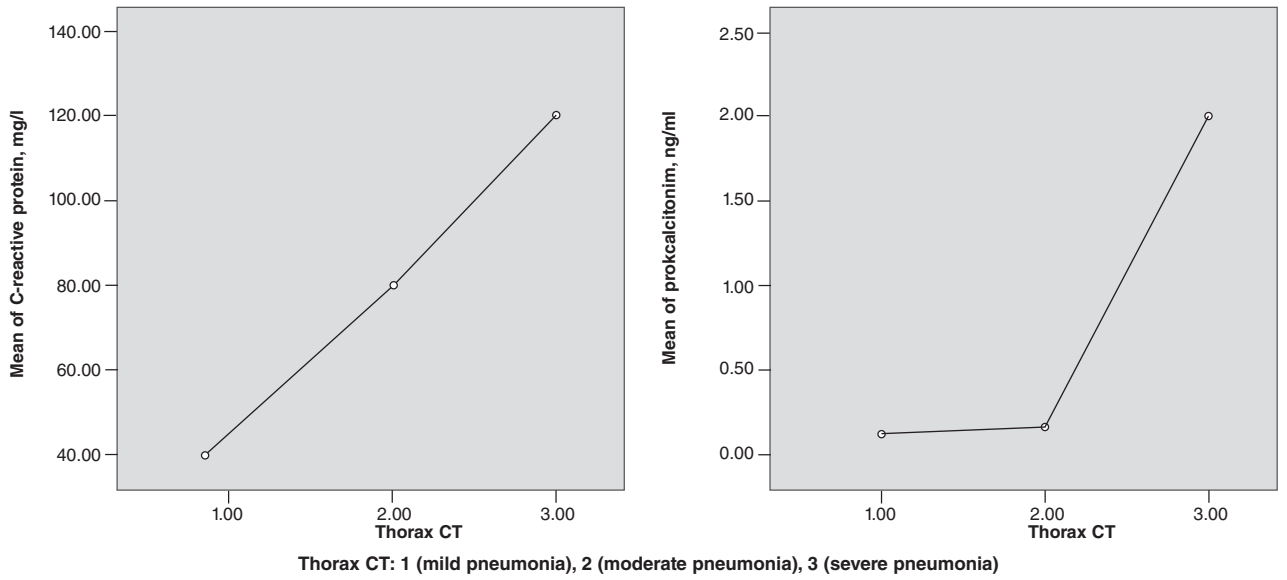

Fig. 3. Mean plots of serum levels of C-reactive protein and procalcitonin compared with patients grouped according to thorax CT scans, which were divided into three categories: 1, mild pneumonia; 2, moderate pneumonia; and 3, severe pneumonia.

patients had cardiac injury and first demonstrated that cardiac injury was independently associated with an increased risk of mortality in patients with COVID-19.[10]

Compared with patients without cardiac injury, those with cardiac injury presented with more severe disease, manifested by abnormal laboratory and radiographic findings, such as higher levels of CRP, NT-proBNP and creatinine, more severe pneumonia, and a greater proportion required mechanical ventilation.

Consistently, our study demonstrated that cardiac biomarkers such as hs-TNT and NT-proBNP were associated with clinical outcomes in COVID-19 and had correlations with other inflammatory markers such as fibrinogen, D-dimer, ferritin, procalcitonin and CRP. Higher mortality and ICU admission rates were seen in patients with cardiac injury.

Severe respiratory distress is mostly considered the leading cause of COVID-19-induced death. According to a published study of the largest clinical trial in China,[11] severe pneumonia was independently associated with admission to an ICU, mechanical ventilation or death.

The laboratory results of patients who were classified in thorax CT scans according to severity of infiltration were compared, and as the severity of infiltration increased, an increase in level of cardiac biomarkers and inflammatory markers was shown in our study and in the literature.

This study shows that patients with co-morbid conditions were more predisposed to experience myocardial injury during the progression of COVID-19. For patients with underlying chronic illness, including hypertension, coronary heart disease and cardiomyopathy, the viral disease can further damage myocardial cells through several mechanisms, including direct damage by the virus, cytokine storm damage by systemic inflammatory responses, destabilised coronary plaque leading to MI, and aggravated hypoxia leading to myocardial ischaemia and infarction.

Although the accurate pathophysiological mechanism underlying myocardial injury caused by COVID-19 is not fully understood, a previous report showed that in 35% of patients with severe acute respiratory syndrome coronavirus (SARS-CoV) infection, the SARS-CoV genome was positively detected in the heart. This raises the possibility of direct damage of the cardiomyocytes by the virus.[12] SARS-CoV-2 may share the same

Table 5. Laboratory findings of patients grouped according to thorax CT scans

Biomarker	*Thorax CT group*	*Median (range)*	*Multiple comparison (Bonferroni)*	*p-value*
hsTNT, pg/ml	1	15 (3–228)	Thorax CT (1–2)	0.55
	2	53 (3–3417)	Thorax CT (1–3)	0.42
	3	61 (3–1249)	Thorax CT (2–3)	1.0
NT-proBNP, pg/ml	1	512 (5–25826)	Thorax CT (1–2)	1.0
	2	556 (5–10054)	Thorax CT (1–3)	0.12
	3	1398 (8–35000)	Thorax CT (2–3)	0.25
Ferritin, ng/ml	1	463 (14–5812)	Thorax CT (1–2)	0.23
	2	659 (39–2797)	Thorax CT (1–3)	0.006
	3	827 (21–3882)	Thorax CT (2–3)	0.59
D-dimer, µg/l	1	1034 (230–10850)	Thorax CT (1–2)	0.66
	2	1349 (270–8970)	Thorax CT (1–3)	0.005
	3	1918 (370–19440)	Thorax CT (2–3)	0.20
Procalcitonin, ng/ml	1	0.21 (0–5.9)	Thorax CT (1–2)	1.0
	2	0.25 (0–7.35)	Thorax CT (1–3)	0.01
	3	2.03 (0–57)	Thorax CT (2–3)	0.03
CRP, mg/l	1	47 (1–300)	Thorax CT (1–2)	< 0.01
	2	84 (3–353)	Thorax CT (1–3)	< 0.01
	3	124 (8–460)	Thorax CT (2–3)	< 0.01
Fibrinogen, mg/dl	1	502 (146–1020)	Thorax CT (1–2)	< 0.01
	2	600 (414–1028)	Thorax CT (1–3)	< 0.01
	3	593 (294–896)	Thorax CT (2–3)	1.0
Neutrophil, cells/µl	1	4571 (20–27490)	Thorax CT (1–2)	0.11
	2	5525 (620–15340)	Thorax CT (1–3)	0.01
	3	5949 (870–18100)	Thorax CT (2–3)	1.0
Lymphocyte, cells/µl	1	1209 (200–2800)	Thorax CT (1–2)	0.48
	2	2090 (350–81150)	Thorax CT (1–3)	1.0
	3	911 (110–3480)	Thorax CT (2–3)	0.36

hs-TNT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein.

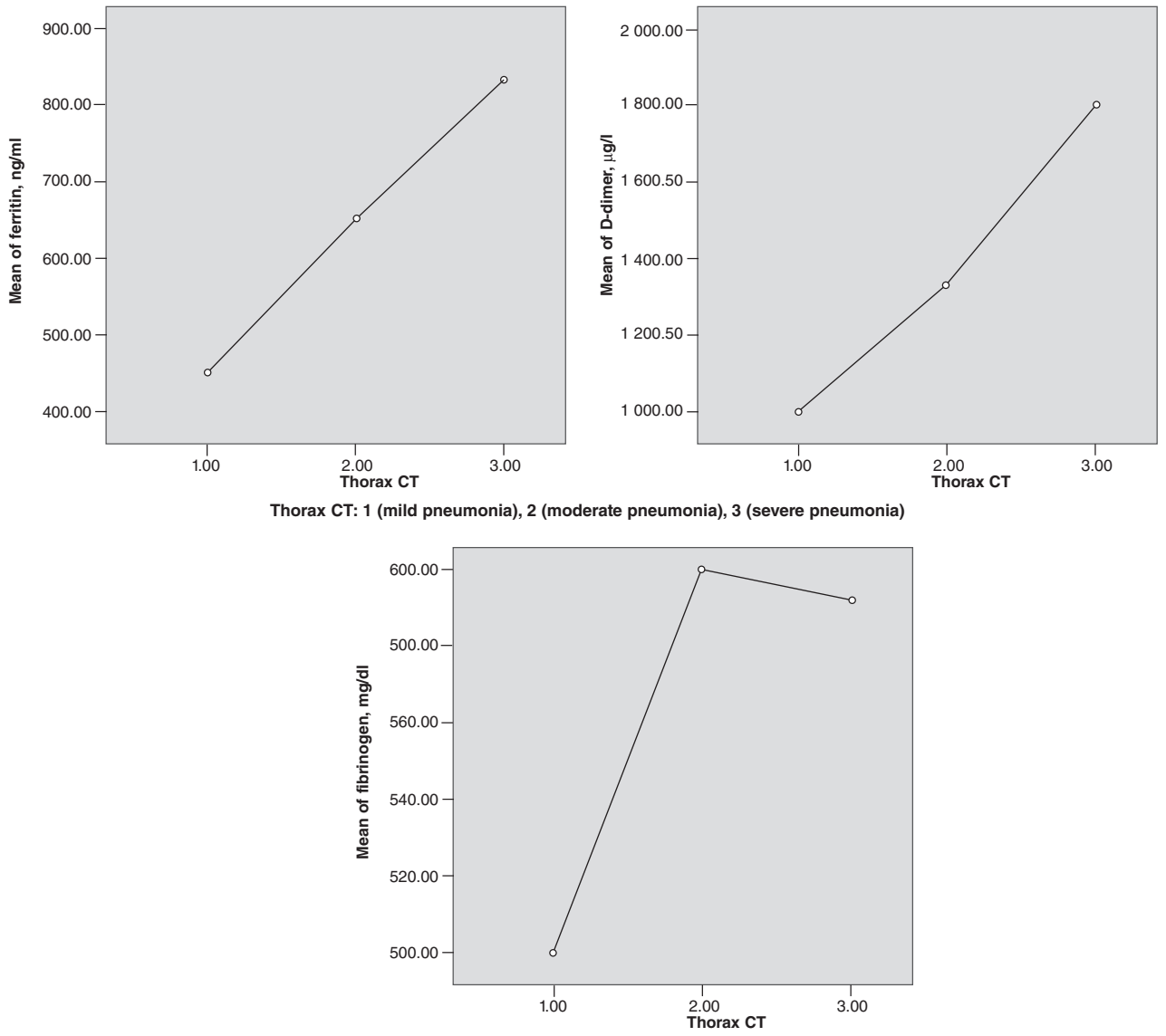

Fig. 4. Mean plots of serum levels of ferritin, D-dimer and fibrinogen compared with patients grouped according to thorax CT scans, which were divided into three categories: 1, mild pneumonia; 2, moderate pneumonia; and 3, severe pneumonia.

mechanism with SARS-COV because the two viruses are highly homologous in the genome.[13,14]

In our study, plasma TnT levels were significantly positively correlated with other plasma inflammatory markers such as fibrinogen, D-dimer, ferritin, procalcitonin and CRP, indicating that myocardial injury may be closely related to inflammatory pathogenesis during the evolution of the disease.

Viral particles could precipitate a cytokine storm and a series of immune responses. Huang *et al.*[4] emphasised that in patients with COVID-19, an imbalance of T-helper 1 and T-helper 2 responses developed in a cytokine storm, which may have contributed to myocardial injury. The release of inflammatory cytokines after infection may cause a reduction in coronary blood flow, decrease in oxygen supply, destabilisation of coronary plaque and microcirculatory thrombogenesis.

Unpredictably, the proportion of smokers was statistically significantly lower in patients with myocardial injury than in those without injury ($p < 0.01$) (Table 1).

In a recently published article, Guo *et al.*[15] found 11 of 18 patients who were in the smoking group had normal TnT levels and seven had elevated troponin levels. However, it was not statistically significant. In another trial, researchers found no link between cigarette smoking and the severity of COVID-19 among cases in China, according to results of a preliminary meta-analysis published in the *European Journal of Internal Medicine*.[16]

Although there are articles showing no relationship between smoking and the severity of COVID-19, there are also articles showing the opposite. Therefore, this situation remains uncertain and more studies are needed to clarify it.

Study limitations

First, as a retrospective study, information regarding cardiovascular complications, such as from echocardiography, and other inflammatory markers, such as cytokine levels, including IL-6, are not presented in this study because the data were incomplete owing

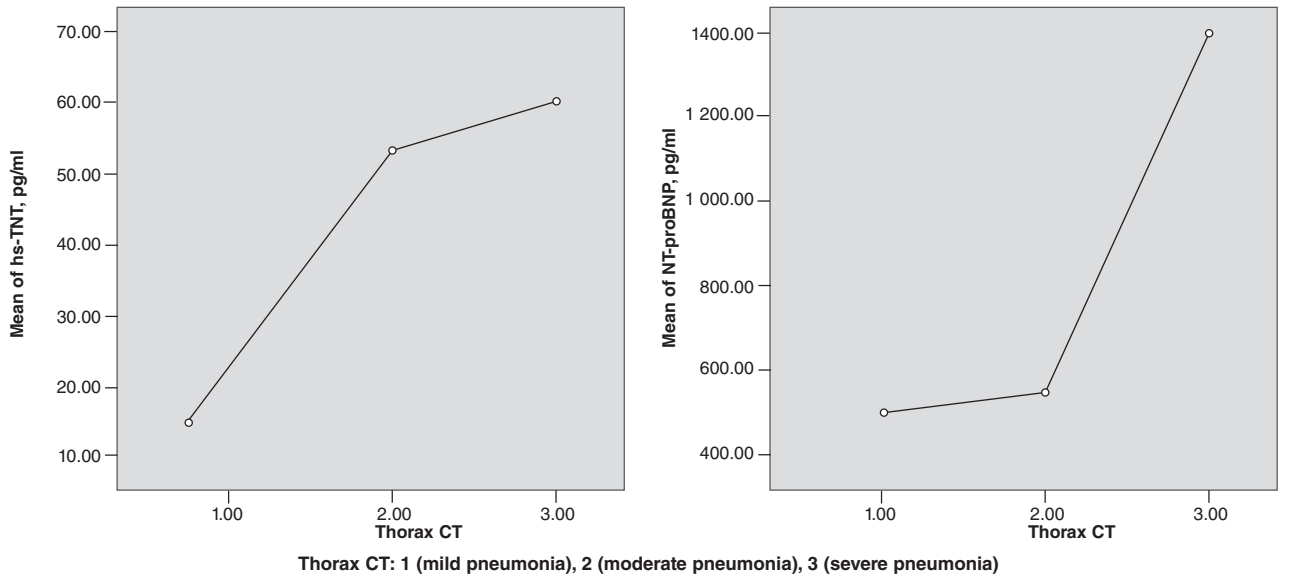

Fig. 5. Mean plots of serum levels of high-sensitivity troponin T and NT-proBNP compared with patients grouped according to thorax CT scans, which were divided into three categories: 1, mild pneumonia; 2, moderate pneumonia; and 3, severe pneumonia.

to the limiting conditions in the COVID isolation wards. Second, the cause of death may have included multiple organ dysfunction in most cases, and it was difficult to identify myocardial injury as the main and direct cause in individual cases. Long-term observations and prospective studies are needed.

Conclusion

The first general data of our 309 COVID-19 patients regarding low mortality and ICU admision rates, and detailed treatment algorithms specific to our centre should be helpful in determining better treatment strategies in the future. Our study emphasises the importance and frequency of cardiovascular outcomes, and the importance of certain cardiac biomarkers in predicting COVID-19 prognosis.

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The modulating effects of green rooibos (*Aspalathus linearis*) extract on vascular function and antioxidant status in obese Wistar rats

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Abstract

Purpose: Obesity is associated with the development of risk factors for cardiovascular disease (CVD) and polyphenols have been shown to possess ameliorative effects against obesity-induced CVD risk factors. Rooibos (*Aspalathus linearis*) is rich in polyphenols, therefore we investigated the cardioprotective effects of aspalathin-rich green rooibos (GRT) on obesity-induced CVD risk factors in obese Wistar rats.

Methods: Adult male Wistar rats (n = 20 per group) were fed a control or a high-fat diet (HFD) for 16 weeks and treated with GRT (60 mg/kg/day) for six weeks. Blood pressure was monitored throughout. Vascular reactivity was measured and Western blots of cell-signalling proteins (eNOS, AMPK and PKB) were performed in aortic tissues. Effects on oxidative stress were determined by measuring antioxidant enzyme activity and thiobarbituric reactive substance (TBARS) levels in the liver.

Results: HFD animals had (1) increased blood pressure, (2) impaired vasodilation, (3) attenuated PKB and AMPK expression, (4) decreased antioxidant enzyme activity, (5) increased malondialdehyde (MDA) levels, and (6) increased phosphorylated eNOS levels. Treatment with GRT extract significantly alleviated these obesity-induced CVD risk factors.

Conclusion: Supplementation with GRT extract alleviated cardiovascular risk factors in the HFD animals, suggesting a therapeutic potential for GRT in obesity-induced cardiovascular risk.

Keywords: obesity, blood pressure, vascular reactivity, oxidative stress, glucose homeostasis, Afriplex GRT™ extract

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Cardiovascular disease (CVD), the leading cause of death globally, accounted for 17.7 million deaths in 2016, and is mostly prevalent in low- to middle-income countries.[1] Behavioural risk factors for CVD include a sedentary lifestyle, tobacco smoking and alcohol abuse, which manifest as obesity, hypertension, type 2 diabetes, dyslipidaemia and raised blood glucose levels in individuals.[2]

Obesity is a major global health problem and is on the rise, especially in developing countries where it is mostly prevalent in the adult population.[2] It results when there is an energy imbalance between caloric intake and caloric expenditure,[3] and is associated with development of the metabolic syndrome (MetS), a conglomerate of cardiometabolic risk factors that elevate CVD risk.[4,5] The MetS is characterised by insulin resistance, elevated blood pressure, impaired glucose homeostasis, atherogenic dyslipidaemia and systemic inflammation.[4,5] Obesity is also associated with the development of endothelial dysfunction[6] and oxidative stress.[7]

Rooibos (*Aspalathus linearis*), a leguminous shrub indigenous to the Cederberg Mountains of the Western Cape in South Africa, has numerous health-promoting properties, such as anti-hypertensive,[8] antidiabetic,[9,10] anti-hyperglycaemic,[9-12] anti-inflammatory,[13] antioxidant,[14] anti-cancer[15] and anti-obesity effects.[16] This is mainly attributed to its polyphenolic composition, particularly aspalathin, a unique major active flavonoid compound, and nothofagin, a 3-dehydroxydihydrochalcone glucoside.[12]

When the rooibos plant is harvested, it is processed into fermented (oxidised) and unfermented (un-oxidised) products, which may be used to make herbal infusions and extracts.[17,18] The unfermented 'green' rooibos is commonly used to prepare aspalathin-rich extracts due to the preservation of its polyphenolic content.[9] Afriplex GRT™ (GRT) extract, a spray-dried powder with a high aspalathin content, used in this study, was prepared from unfermented rooibos.

To date, no studies have been performed investigating the relationship between the ameliorative effects of this GRT extract on obesity-induced CVD risk factors. Therefore, in view of the known health benefits of rooibos, we set out to determine whether GRT extract could improve obesity-induced CVD risk factors in an animal model.

Methods

Adult male Wistar rats weighing between 150 and 210 g and approximately seven to eight weeks old were obtained from the central animal facility of the Faculty of Medicine and Health Sciences at Stellenbosch University. They were housed in cages containing four rats per cage and maintained under a 12-hour day/night cycle at 24–25°C. Animals had *ad libitum* access to food and water.

Animals were randomly divided into five experimental groups (n = 8–10 per group) and fed either a control or high-fat diet (HFD) for a period of 16 weeks. The age-matched control group received standard Epol™ [Epol (Pty) Ltd, Worcester, Western Cape, RSA] rat chow composed of: fat 4.8 g/100 g, protein 17.1%, carbohydrates 34.6%, sugar 6.6 g/100 g and energy 1 272 kJ/100 g. The HFD group however received a diet composed of: fat 27.9 g/100 g, cholesterol 6.4 mg/100 g, protein 14.6%, carbohydrates 29.5%, sugar 13.3 g/100 g, fructose 11 g/100 g and energy 1 823 kJ/100 g. The HFD diet was specifically adapted to induce high blood pressure together with obesity.[19] The rat chow and HFD compositions were analysed by Microchem Laboratory (Pty) Ltd in Maitland, Cape Town. Food and fluid intake were measured three times weekly and the animals were weighed once a week.

The good manufacturing practice (GMP)-certified GRT extract was prepared by Afriplex (Pty) Ltd (Paarl, South Africa) and it was kindly given as a donation. It was supplied with the total polyphenolic composition analysis[19] (Table 1).

A total of 10 rats per group in both the HFD and control groups were treated with 60 mg/kg/day of GRT extract from week 11 to week 16 of the diet period. An additional HFD group was included, which served as a positive control (n = 8) for blood pressure effects and these rats were treated with captopril (50 mg/kg/day), a well-known ACE inhibitor and anti-hypertensive drug.

The administered GRT extract dose was deduced from available literature on similar extracts[9,20] as there is currently no evidence on the exact recommended dosage of this specific product. The captopril dosage was previously used in our laboratory as a positive control in the same rat model.[21] The GRT extract and captopril treatments were prepared in the form of strawberry jelly/gelatine blocks and were given to each animal individually according to their body weight. The untreated groups (without GRT extract or captopril supplementation) were given jelly/gelatine blocks to normalise for the effect the additional sugar content present in the jelly/gelatine might have.

An oral sucrose tolerance test (OSTT) were performed in the week before commencement of treatment (week 10) and again a week before sacrifice (week 15) in both the controls and HFD groups. The animals were fasted overnight with free access to drinking water. Blood glucose levels were determined, using a handheld Glucoplus™ glucometer, from a drop of blood collected after a tail prick with a lancet at the tail tip. Following measurement of baseline (0 minutes, fasting level) glucose levels, the animals were gavaged with 50% sucrose solution (1 g/kg) and the disappearance of glucose in the blood was monitored for two hours. After the OSTT procedure, the animals were left to recover for a week from this metabolic insult, prior to sacrifice.

Table 1. High-performance liquid chromatography (HPLC) analysis of the GRT extract used in the study

Compound (g compound/100 g soluble solids)	*HPLC analysis*
Phenylpyruvic acid-2-*O*-glucoside (PPAG)	0.423265
Aspalathin	12.78348
Nothofagin	1.974419
Isoorientin	1.427281
Orientin	1.255839
Ferulic acid	nq
Vitexin	0.338513
Isovitexin	0.298022
Quercetin-3-robinobioside	1.040565
Hyperoside	0.398773
Rutin	0.496034
Isoquercitin	0.572251852

Nq, not quantifiable.

The blood pressure of each animal was measured using a CODA® non-invasive blood pressure acquisition system (Kent Scientific), which utilises a volume pressure-recording (VPR) tail-cuff system to measure the blood volume of the tail. Prior to the actual study, the animals were acclimatised to the apparatus for a period of two weeks. Blood pressure was then monitored on a weekly basis for 16 weeks, and baseline levels were determined for two weeks prior to treatment.

Glucose present in the urine was determined in weeks 10 and 16 of the study. Animals were individually placed in metabolic cages for a 24-hour period while having *ad libitum* access to food and water. Urine was collected in a plastic measuring cylinder attached to each cage. Glucose levels were determined using a Test-it™ 10 dipstick.

At the time of sacrifice, the animals were weighed and euthanised with an overdose of sodium pentobarbital (Euthanaze 160 mg/kg, intra-peritoneally). Following this, fasting or non-fasting blood was collected from all the animals, transferred to vacutainer tubes (SGVac) and allowed to clot at room temperature (25°C). After 30 minutes, the blood was centrifuged at 1 200 × g for 10 minutes at 4°C. Thereafter, the serum was collected and stored at –80°C for biochemical analysis.

The liver and the intra-peritoneal (IP) fat were removed, rinsed, weighed, snap-frozen in liquid nitrogen and stored at –80°C for downstream experimental procedures. Additionally, the thoracic aorta was gently excised from the thoracic cavity with the perivascular adipose tissue (PVAT) intact. Then one aortic ring per animal was cut in half and one piece was immediately used for vascular contraction/relaxation experimentation, while the rest of the tissue was stored in liquid nitrogen for Western blot analyses.

Vascular contraction/relaxation of the aortic rings was performed to determine the endothelial function of the animals. A total of 10 aortae were used for each experimental group, except for the captopril group (n = 8). The noradrenergic agonist phenylephrine (1 mM; 0.002g Phe in 10 ml 0.9% saline) and the endothelium-dependant nitrogen oxide (NO)-releasing agent acetylcholine (10 mM; 0.0182 g in 10 ml 0.9% saline) stocks were prepared. Acetylcholine (10 mM), labelled stock A, was serially diluted to make stock B (1 mM; 1 ml stock A in 9 ml 0.9% saline), and finally stock C (100 µM; 1 ml stock B in 9 ml 0.9% saline).

The aortic ring (3–4 mm) was mounted onto two stainless steel hooks and slowly submerged in the organ bath (AD Instruments, Bella Vista, New South Wales, Australia) filled with Krebs-Henseleit buffer (KHB composition in mM: 119 NaCl, 25 $NaHCO_3$, 4.75 KCl, 1.2 KH_2PO_4, 0.6 $MgSO_4.7H_2O$, 0.6 Na_2SO_4, 1.25 $CaCl_2.H_2O$ and 10 glucose) at 37°C and gassed with 95% O_2 and 5% CO_2. The tension was slowly adjusted to 0.2 g and the preparation was initially stabilised for a period of 40 minutes, changing the buffer after every 10 minutes while gradually increasing the tension to 1.5 g. After 40 minutes, the KHB was changed and adjusted to exactly 25 ml.

Thereafter, 100 nM phenylephrine (2.5 µl of 1 mM stock) was added to induce maximal contraction, followed by 10 µM acetylcholine (25 µl of stock A) to induce at least 70% relaxation. The organ bath was rinsed three times with pre-warmed KHB to

flush out the drugs and refilled to 25 ml. After another 30 minutes of stabilisation, cumulative concentrations of phenylephrine (to maximal vasocontraction), followed by titration with acetylcholine (to induce vasorelaxation) were added. Thereafter, the organ bath, string and steel hooks were thoroughly rinsed with boiled distilled water.

Western blot analysis was used to determine the expression and activation of selected proteins involved in endothelial function, such as AMPK, PKB and eNOS. Frozen sections of the aortic tissue (40–50 mg, n = 5 per group) were pulverised in a liquid nitrogen pre-cooled mortar and pestle and then transferred into a microcentrifuge tube [Scientific Group (Pty) Ltd, Milnerton, Western Cape, RSA] filled with 600 µl of lysis buffer [composition in mM: 20 Tris-HCl (pH 7.5), 1 EGTA, 1 EDTA, 150 NaCl, 1 β-glycerophosphate, 2.5 sodium pyrophosphate, 1 Na_3VO_4, 50 nM NaF, 10 µg/µl leupeptin, 10 µg/ml aprotinin, 0.1% SDS, 1% Triton X-100 and 50 µg/ml PMSF, which was added last]. Samples were homogenised in a bullet blender® 24 (Next Advance, Inc, New York) using 1.6-mm stainless steel beads at speed 8 for one minute at 4°C, for a total period of three minutes, with five-minute rests in-between cycles. Samples were allowed to stand on ice for 15 minutes and centrifuged at 15 000 rpm for 20 minutes at 4°C.

Protein concentration was determined using the Bradford method.[22] The samples were diluted in Laemmli sample buffer, boiled for five minutes and stored at –80°C. Equal amounts of protein were separated using 26-well Bio-Rad TGX stain-free™ 5–20% gradient precast gels and transferred to polyvinylidene fluoride (PVDF) membranes using a Bio-Rad midi-transfer system. Proteins that were successfully transferred onto the membrane were visualised utilising the Bio-Rad ChemiDoc™ MP system and a record thereof was stored.

The non-specific sites on all the membranes were blocked with 5% fat-free milk in TBS-Tween (Tris-buffered saline and 0.1% Tween® 20). Membranes were incubated overnight at 4°C in a 7.5-µl polyclonal primary antibody solution, diluted in 5 ml TBS-Tween or in primary SignalBoost™. Thereafter, the membranes were incubated for one hour in 2.5 µl horse radish peroxidase-coupled secondary antibody (Amersham Life Science, Buckinghamshire, UK) in 5 ml TBS-Tween or in secondary SignalBoost™ immunoreaction enhancer (Sigma-Aldrich, St Louis, MO, USA), diluted in 5 ml TBS-Tween. The primary and secondary SignalBoost™ were specifically used for the incubation of the eNOS antibody.

The following antibodies from Cell Signaling Technologies® were used: total [catalogue number (cat #): 2532] and phospho-AMPK (Thr172; cat # 2531), total (cat # 9272) and phospho-PKB/Akt (Ser473; cat # 9271) and total (cat # 9572) and phospho-eNOS (Ser1177; cat # 9571). The proteins were visualised by incubating the membrane with enhanced chemiluminescence (ECL) (AEC Amersham, Buckinghamshire, UK) and exposed in the Bio-Rad ChemiDoc™ MP system. The band pixels from the exposed bands of the blot were normalised towards the total protein per lane that was transferred to the PDVF membrane for equal protein loading.

Antioxidant enzyme analysis

For the lysate preparation, the liver tissue samples were homogenised in 0.05 mM sodium phosphate buffer (pH 7.5) in a Bullet blender® 24 (Next Advance, Inc, New York) using 1.6-mm stainless steel beads, in a coldroom, at speed 8 for three minutes and speed 9 for four minutes, with one-minute rest periods in-between cycles. Samples were then allowed to stand on ice for 30 minutes and centrifuged at 15 000 rpm for 20 minutes at 4°C. Protein concentration was determined by means of a Bicinchoninic acid (BCA) protein assay kit (BCA1, Sigma Aldrich), using bovine serum albumin (BSA) (1 mg/ml) used as a standard, as supplied in the kit. The lysates were then frozen at –80°C and used for the downstream antioxidant enzyme assays and for the determination of lipid peroxidation.

Catalase (CAT) [enzyme commission number (EC) 1.11.1.6] catalyses the conversion of two H_2O_2 molecules into oxygen and two water molecules mostly in aerobic cells[23] Liver tissue homogenates were diluted to 0.1 µg/µl protein in assay buffer (50 mM potassium phosphate, 0.5% Triton X-100, pH 7.0). From the diluted tissue lysate, 5 µl was assayed in triplicate in a 96-well ultraviolet (UV) plate, followed by 170 µl of assay buffer. To initiate the reaction, 50 µl of H_2O_2 stock solution was added to all the wells and the absorbance was measured over five minutes to measure the linear decrease over time at 240 nm in a FLUOstar® Omega microplate reader. The molar extinction coefficient of H_2O_2 (43.6 M/cm), adjusted for the well path length, was used to determine catalase activity (µmole H_2O_2 consumed/min/µg protein).

Superoxide dismutase (SOD) (EC 1.15.1.1) catalyses the dismutation of the reactive superoxide radical (O_2^-) into H_2O_2 and oxygen. Activity was determined according to the method modified from Ellerby and Bredesen.[23] Liver tissue homogenates were diluted to 0.1 ug/µl of protein in SOD assay buffer (50 mM sodium phosphate, pH 7.4). 6-hydroxydopamine (6-OHD) 1.6 mM was freshly prepared as follows: a volume of 50 µl of concentrated (70%) perchloric acid ($HClO_4$) was added to 10 ml deionised water (deiH_2O) and purged with nitrogen for 15 minutes to displace the oxygen. Thereafter, 4 mg of 6-OHD was added to this solution, wrapped in foil and kept on ice.

The samples (10 µl) and the blank (15 µl SOD assay buffer) were assayed in triplicate and 170 µl of 0.1 mM diethylenetriaminepentaacetic acid (DETAPAC), prepared in SOD assay buffer (1 mg in 25 ml), was added to all the wells. SOD assay buffer (5 µl) was added to all the sample wells, excluding the blank well and the reaction was initiated by adding 15 µl of 6-OHD to each well of the 96-well plate. The kinetics of the auto-oxidation of 6-OHD was monitored at 490 nm for five minutes at 25°C, using the FLUOstar Omega® microplate reader, and the results are expressed as units/mg protein.

Glutathione peroxidase (GPx) (EC 1.11.1.9) catalyses the dismutation of lipids and hydroperoxides, including H_2O_2, by reduced glutathione, and the activity was determined according to Ellerby and Bredesen.[23] Liver tissue homogenates were diluted using a 2.5 × dilution (40 µl sample: 60 µl assay buffer) so that the protein concentration fell between the required range (5–10 mg/ml). A cocktail solution consisting of 210 µl assay buffer [50 mM potassium phosphate, 1 mM of ethylenediaminetetraacetic acid (EDTA), pH 7.0], 2.5 µl glutathione (GSH) solution (30.7 mg/ml, in deiH_2O), 2.5 µl glutathione reductase (1.6 mg/ml, diluted in assay buffer), 2.5 µl of 0.1 M sodium azide to inhibit catalase and lastly, 2.5 µl of nicotinamide adenine dinucleotide phosphate (NADPH) [5 mg dissolved in 0.1% of sodium bicarbonate ($NaHCO_3$)] was prepared.

Following this, 5 µl of the sample and blank (assay buffer: 50 mM potassium phosphate, 1 mM EDTA, pH 7.0) were assayed in triplicate, followed by the addition of 215 µl of the cocktail solution to the wells. The absorbance of NADPH oxidation in the absence of H_2O_2 was measured for three minutes with 30-second intervals, at 340 nm. To initiate the reaction, 25 µl of 1.5 mM H_2O_2 (3.4 µl of 30% stock solution in 20 ml assay buffer) was added immediately after the first absorbance measurement. The hydroperoxide-dependent linear NADPH oxidation was recorded for two to five minutes at 30-second intervals at the same wavelength. The GPx activity was expressed as µmol NADPH oxidised/min/mg protein.

Thiobarbituric acid reactive substances (TBARS) assay

Measurement of TBARS is a widely used assay for the determination of lipid peroxidation in tissue homogenates and serves as an indicator of oxidative stress. The assay was performed according to the modified method of Esterbauer and Cheeseman.[24] Liver tissue was homogenised in 0.01 mM sodium phosphate buffer (pH 7.5) containing 1.15% KCl in a Bullet blender® 24 (Next Advance, NYC, USA) using 1.6-mm stainless steel beads, at speed 8 for three minutes and speed 9 for four minutes, with one-minute rest cycles in-between.

Protein concentrations of the samples were determined using a BCA assay kit (Sigma Aldrich). The MDA standard solution (500 µM) was prepared by diluting 1.23 µl of the MDA stock (125 µM) solution in 10 ml of deiH_2O and it was serially diluted in MDA diluent (nmol/ml MDA: 0, 0.322, 0.625, 1.25, 2.5, 5, 10, 25 and 30). Samples and standards (100 µl) were added to glass test tubes, followed by 100 µl of SDS solution (2%), 2 ml of trichloroacetic acid (TCA) reagent {composition: 10% TCA, BHT [12.5 mM butylated hydroxytoluene (BHT)/10 ml TCA solution]} and 2 ml thiobarbituric acid (TBA) (0.67% w/v) solution on the side of each tube, and the glass tubes were capped with marbles.

Test tubes were incubated in a water bath at 95°C for one hour and cooled at room temperature for 10 minutes. Thereafter, the samples were centrifuged at 3 000 rpm for 15 minutes and the supernatant was plated (150 µl) in triplicate. The absorbance was measured at 530 nm using the FLUOstar Omega® microplate reader. The MDA concentration in the liver was determined using an MDA standard curve. Thereafter, the results were normalised using the previously determined protein concentrations and expressed in µmole MDA equivalents/mg protein.

Statistical analysis

All the results were analysed using GraphPad Prism® 6. Statistical analysis was performed using one- or two-way analysis of variance (ANOVA), followed by the Bonferroni *post hoc* test for comparison within the groups. The results are expressed as the mean ± standard error of mean (SEM). A probability of $p < 0.05$ was considered significant.

Results

Food and water intake were measured three times weekly and body weight was measured once a week during the 10-week period (Table 2). The HFD group showed a significant increase in food intake and a significant decrease in mean water intake relative to the control group. Furthermore, the HFD group showed a significant increase in mean body weight when compared to the control group. Blood pressure was measured from week eight to 10 and the HFD group showed a significant increase in the mean systolic, diastolic and arterial blood pressure when compared to the control group. The mean arterial pressure (MAP) was calculated as follows:

$$\text{MAP} = \text{mean DBP} + \frac{1}{3}(\text{mean SBP} - \text{mean DBP})$$

where DBP is diastolic blood pressure and SBP is systolic blood pressure.

In week 10, quantitative blood glucose measurements were obtained in both the control and HFD group after an overnight fast. At baseline (Fig. 1A), the HFD group showed a significant increase in blood glucose levels compared to the control (5.56 ± 0.220 vs 4.66 ± 0.113 mmol/l; $p < 0.01$, $n = 7–8$ per group). After oral administration of the 50% sucrose solution, the HFD group showed a significant increase in plasma glucose levels at three (6.13 ± 0.219 vs 4.84 ± 0.341 mmol/l), five (6.59 ± 0.108 vs 5.06 ± 0.229 mmol/l), 10 (7.31 ± 0.437 vs 5.89 ± 0.245 mmol/l), 15 (7.63 ± 0.359 vs 5.51 ± 0.362 mmol/l), 20 (7.44 ± 0.270 vs 6.40 ± 0.229 mmol/l) and 25 minutes (7.04 ± 0.248 vs 6.31 ± 0.212 mmol/l; $p < 0.05$, $n = 7–8$ per group), compared to the control group (Fig. 1A). No significant differences were observed between the control and HFD groups from 30 to 120 minutes.

Additionally, according to the area under the curve (AUC, Fig. 1B) analysis, the HFD group presented with a significant increase in blood glucose levels when compared to the control group (716 ± 15.4 vs 635 ± 31.2 arbitrary units, $p < 0.05$, $n = 7–8$ per group). The untreated control and HFD animals showed normal urinary glucose levels during the 16-week period ($n = 8$ per group, Table 2).

The results in Table 3 represent biometric and blood pressure measurements during and after the 16-week period. The HFD animals showed a significant increase in food intake and a significant decrease in water intake compared to the control animals. Furthermore, the HFD animals showed a significant increase in leptin levels, and IP fat, liver and absolute body weight when compared to the control animals. Additionally, the HFD group showed a significant increase in the mean systolic, diastolic and arterial blood pressure compared to the control group,

Table 2. Mean food and water intake per rat per day together with the mean body weight, and systolic, diastolic and arterial blood pressure of the HFD versus control groups before treatment with the GRT extract

Parameters	*Control*	*HFD*	*Sample size (n/group)*
Mean food intake (g)	17.18 ± 0.272	20.58 ± 0.429****	20–28
Mean water intake (ml)	20.48 ± 0.445	13.60 ± 0.229****	20–28
Mean body weight (g)	246.00 ± 4.404	274.10 ± 4.886***	20–28
Mean systolic blood pressure (mmHg)	125.00 ± 1.720	139.00± 2.460****	10
Mean diastolic blood pressure (mmHg)	84.48 ± 1.171	93.95 ± 1.226****	10
Mean arterial pressure (mmHg)	99.94 ± 1.480	111.70 ± 2.240****	10
Urinary glucose (mmol/l)	Normal	Normal	10

All data are expressed as mean ± SEM, ****$p < 0.0001$ HFD versus control, ***$p < 0.001$ HFD versus control, $n = 20–28$ per group, except urinary glucose, mean systolic and diastolic blood pressure and mean arterial pressure, $n = 10$ per group.

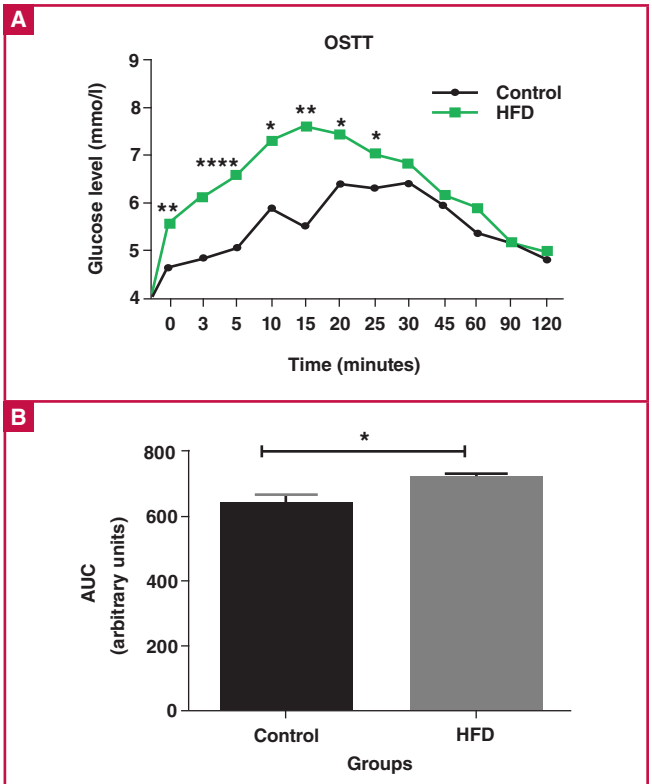

Fig. 1. OSTT results and AUC representation of the HFD and control animals measured in week 10, n = 7–8 per group. (A) Plasma blood glucose levels (mmol/l) of the HFD versus control animals; $^{*}p < 0.05$; $^{**}p < 0.01$ and $^{****}p < 0.0001$, HFD versus control. (B) AUC representation of the effect of the diet on glucose tolerance of the HFD versus control groups; $^{*}p < 0.05$, HFD versus control group.

measured over the last six weeks of the 16-week diet regime.

Treatment with the GRT extract showed no effect on food intake. However, control animals treated with the GRT extract showed a significant increase in water intake when compared to the untreated control animals. HFD animals treated with the GRT extract presented with a decrease in leptin levels, and IP fat, liver and absolute body weight when compared to the untreated HFD animals. Additionally, treatment with the GRT extract and captopril in the HFD animals significantly decreased the mean systolic, diastolic and arterial blood pressure compared to the untreated HFD group. Lastly, GRT treatment did not affect the blood pressure, leptin levels, and IP fat, liver and absolute body weight of the control animals.

In week 15, the blood glucose levels (Fig. 2A) of the HFD and control (GRT treated and untreated) animals were determined after an overnight fast. According to the AUC analysis (Fig. 2B), the HFD rats showed a significant increase in blood glucose levels when compared to the control animals (741.1 ± 16.20 vs 671.5 ± 23.93 arbitrary units; $p < 0.05$, n = 6–8 per group). Treatment with the GRT extract significantly decreased blood glucose levels in the treated HFD animals when compared to the untreated HFD animals (657.2 ± 32.02 vs 741.1 ± 16.20 arbitrary units; $p < 0.05$, n = 6–8 per group). Furthermore, treatment with GRT extract also significantly decreased the blood glucose levels in the treated control animals, relative to the untreated controls (555.9 ± 56.45 vs 688.9 ± 19.02 arbitrary units, n = 6–8 per group). Interestingly, 100% of the untreated control and HFD animals presented with normal glucose excretion in their urine, whereas 50% of the GRT extract-treated control and HFD animals presented with increased glucose excretion in their urine (n = 6–8 per group, Table 3).

As shown in Fig. 3A, the HFD animals presented with a decrease in vascular contractility compared to the control group (p = 0.0011), and the HFD animals treated with GRT extract showed a significant reduction in vascular contractility compared to the untreated HFD animals (p = 0.0107). Additionally, supplementation with the GRT extract significantly increased vascular relaxation in the HFD group compared to the untreated HFD group (Fig. 3B, p = 0.0001). The same effect was observed in the HFD captopril-treated group compared to the untreated HFD group (p = 0.0123) (Fig. 3B).

To elucidate the possible mechanisms behind the vascular effects observed in the GRT extract-treated groups, the signalling proteins involved in endothelial function were analysed with Western blot analysis. The data in Fig. 4 reflect the total (T) expression, phosphorylated (P) protein levels and phosphorylated:total (P:T) ratio of each protein. The HFD animals presented with a significantly lower T-AMPK expression and P-AMPK level, respectively, when compared to the control animals (Fig 4A, B). Treatment of the HFD rats with the GRT extract upregulated the P:T AMPK ratio (Fig. 4C) but had no significant effect on T-AMPK and P-AMPK levels. Additionally, captopril upregulated P-AMPK levels and the P:T AMPK ratio.

Table 3. Summary of the biometric and blood pressure measurements during and after the 16-week treatment period

Parameters	*Control*	*HFD*	*Control + GRT extract*	*HFD + GRT extract*	*HFD + captopril*
Food intake (g)	17.11 ± 0.529	20.64 ± 0.631***	17.45 ± 0.468	21.11 ± 0.622	nd
Water intake (ml)	23.38 ± 0.442	17.01 ± 0.647****	26.66 ± 0.859$^{\#\#\#}$	14.76 ± 1.324	nd
Body weight (g)	339.50 ± 6.870	396.20 ± 13.660**	324.30 ± 7.460	344.50 ± 11.740$^{@}$	nd
IP fat weight (g)	7.32 ± 0.995	23.79 ± 3.481***	8.27 ± 0.596	13.90 ± 1.315$^{@}$	nd
Liver weight (g)	10.30 ± 0.392	15.23 ± 0.803****	10.20 ± 0.411	11.70 ± 0.541	nd
Leptin assay (pg/ml)	2858 ± 210.80	5477 ± 791.50*	2948 ± 185.70	2431 ± 608.70	nd
Mean systolic blood pressure (mmHg)	122.30 ± 1.317	134.00 ± 1.770***	119.90 ± 1.252	120.60 ± 1.531$^{@@@@}$	115.40 ± 1.381$^{\$\$\$\$}$
Mean diastolic blood pressure (mmHg)	81.270 ± 1.645	91.64 ± 1.477****	79.22 ± 1.428	81.02 ± 1.482$^{\#\#\#\#}$	78.96 ± 0.739$^{@@@@}$
Mean arterial pressure (mmHg)	94.94 ± 1.417	105.80 ± 1.415****	92.80 ± 1.283	94.22 ± 1.431$^{\#\#\#\#}$	91.09 ± 0.8434$^{@@@@}$
Urinary glucose (mmol/l)	Normal in 100% of animals	Normal in 100% of animals	Glucose present in 50% of animals	Glucose present in 50% of animals	nd

All data are expressed as mean ± SEM, two-way ANOVA was used for result analysis. nd, not determined.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ HFD versus control; $^{\#\#\#}p < 0.001$ control + GRT versus control; $^{@}p < 0.05$, $^{@@@@}p < 0.0001$ HFD + GRT versus HFD, $^{\$\$\$\$}p < 0.0001$ HFD + captopril versus HFD, n = 10 per group.

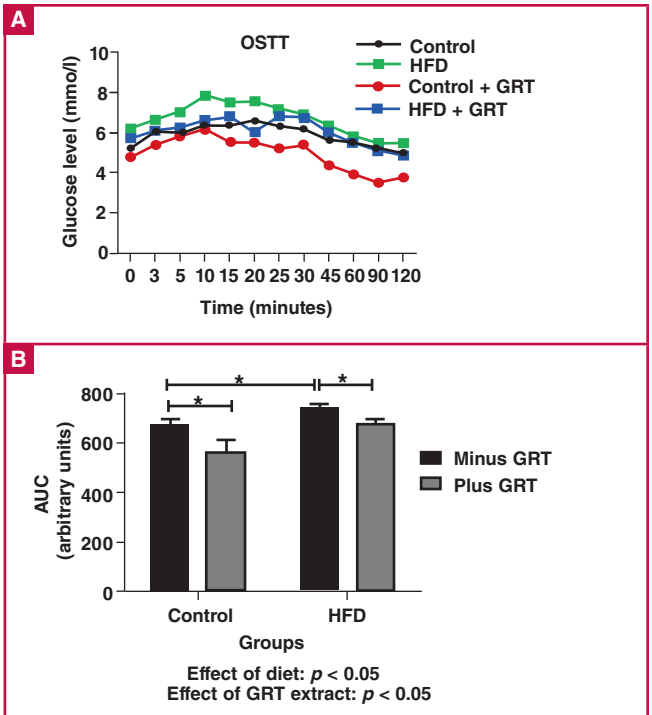

Fig. 2. OSTT results and AUC representation of the HFD and control animals (GRT treated and untreated) measured in week 15, n = 6–8 per group. All data are expressed as SEM. (A) Plasma blood glucose levels (mmol/l) of the HFD versus control groups (GRT treated and untreated). (B) AUC representation of the effect of diet and GRT extract on glucose tolerance of the HFD versus control groups (GRT treated and untreated); $^{*}p < 0.05$, HFD versus control group and $^{*}p < 0.05$, HFD + GRT versus HFD group. According to a two-way ANOVA, the HFD resulted in a significant ($p < 0.05$) increase in blood glucose levels in the HFD animals relative to the control animals. Additionally, the GRT extract significantly ($p < 0.05$) attenuated the increase in glucose levels in the HFD group.

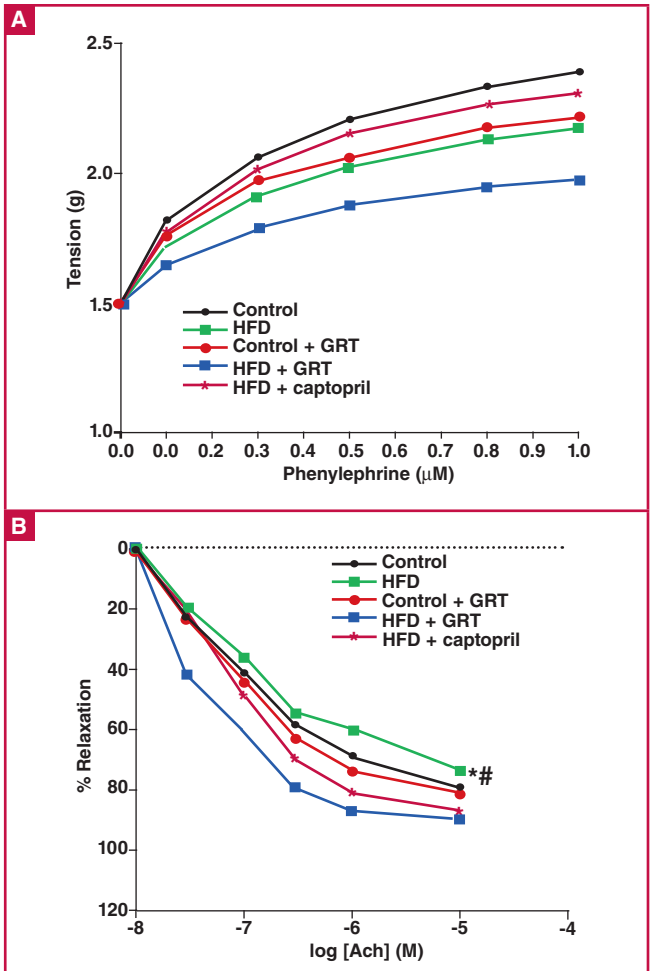

Fig. 3. Vascular contraction and relaxation measured in the aortic tissue of the HFD versus control groups (treated and untreated), including the HFD + captopril groups, n = 8–10 per group. (A) Cumulative phenylephrine-induced vascular contraction in the HFD versus control groups (GRT treated and untreated), including the HFD + captopril groups; $^{*}p < 0.001$, HFD versus control and $^{\#}p < 0.05$, HFD + GRT versus HFD. (B) Cumulative acetylcholine-induced vascular relaxation in the HFD versus control groups (GRT treated and untreated), including the HFD + captopril groups; $^{*}p < 0.0001$, HFD versus HFD + GRT and $^{\#}p < 0.05$, HFD versus captopril groups.

The HFD animals showed a significant decrease in the T-PKB expression and P-PKB levels when compared to the control group (Fig. 5A, B). Treatment with captopril significantly increased P-PKB levels and treatment with GRT extract showed no significant effect. Furthermore, no significant differences were observed in the PKB P:T ratio in all the groups assessed (Fig. 5C). HFD animals presented with an increase in P-eNOS (Fig. 6B) and P:T eNOS (Fig. 6C) ratio when compared to the control animals. The GRT extract significantly increased T-eNOS expression (Fig. 6A) with no significant effect on P-eNOS and P:T eNOS levels.

Activities of the primary antioxidant enzymes were determined in the liver (Table 4). The HFD animals had significantly lower SOD, CAT and GPx activity and increased MDA levels when compared to the control animals. Supplementation with GRT extract in the HFD animals significantly increased SOD and CAT activity and decreased MDA levels when compared to the untreated HFD animals. Additionally, the GRT extract in the treated control animals significantly increased GPx activity and decreased MDA levels when compared to the untreated control animals.

Discussion

Obesity, especially visceral obesity, results in enlargement of the adipose tissue, a major storage site for excess energy, which is also considered a secretion site for pro- and anti-inflammatory cytokines.[5] Therefore in an obese state, there is upregulation in the release of pro-inflammatory cytokines, downregulation of anti-inflammatory cytokines and increased free fatty acid (FFA) release into the circulation.[5] The released FFA and pro-inflammatory cytokines enter the liver and skeletal muscle cells and induce modifications in lipid and glucose homeostasis in these metabolic tissues, including modification in the inflammatory responses. As a result, this imbalance greatly contributes to the development of insulin resistance,

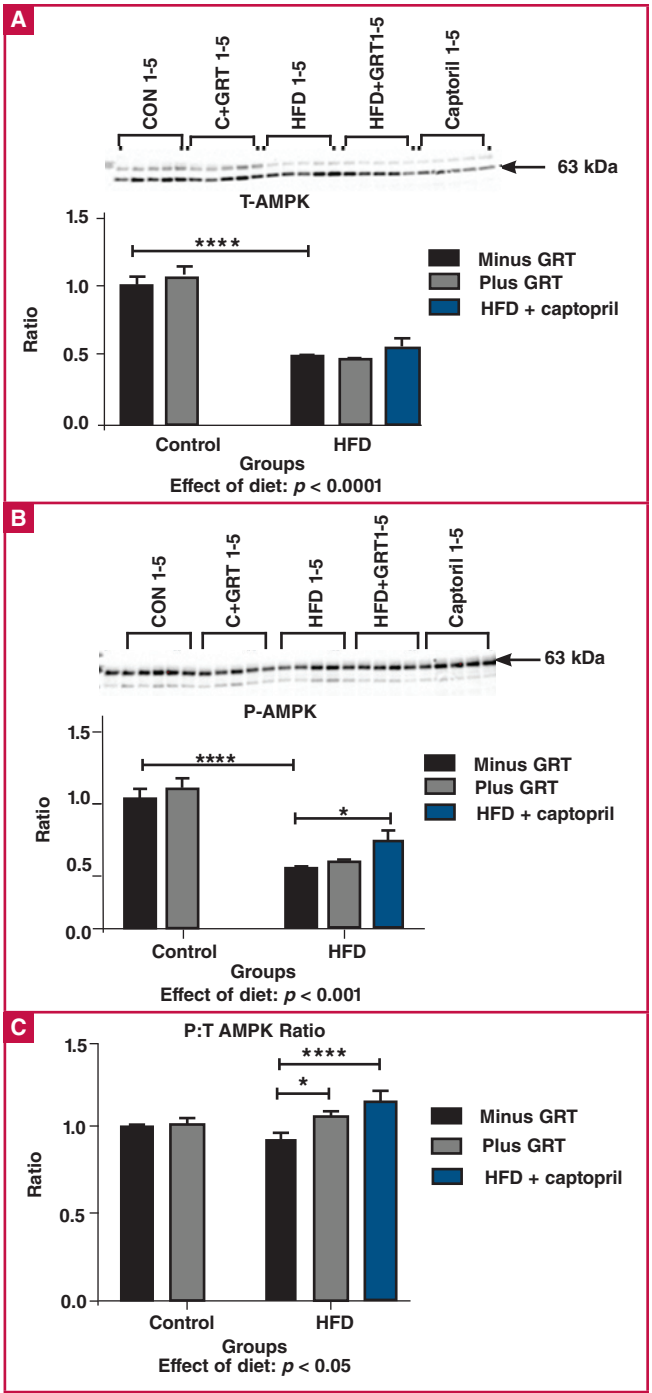

Fig. 4. AMPK expression in the aortic rings of the HFD versus control groups (GRT treated and untreated), including the HFD animals treated with captopril. (A) T-AMPK expression; ****$p < 0.0001$, HFD versus control groups. According to two-way ANOVA, the HFD had a significant effect ($p < 0.0001$) on the T-AMPK expression (n = 5 per group). (B) P-AMPK expression; ****$p < 0.0001$, HFD versus control groups; *$p < 0.05$, HFD + captopril versus HFD + GRT groups. According to two-way ANOVA, the HFD had a significant effect ($p < 0.001$) on the P-AMPK levels (n = 5 per group). (C) P:T AMPK ratio; *$p < 0.05$, HFD + GRT versus HFD groups; ****p < HFD + captopril versus HFD group. According to two-way ANOVA, the GRT extract had a significant effect ($p < 0.05$) on the P:T AMPK ratio (n = 5 per group).

Table 4. Summary of primary antioxidant enzyme activity in the liver of the HFD versus control groups (GRT treated and untreated), n = 9–10 per group

Parameters	*Control*	*Control + GRT extract*	*HFD*	*HFD + GRT extract*
SOD (units/mg)	281.90 ± 10.640	320.60 ± 19.260	227.60 ± 5.631***	335.60 ± 37.310@@
CAT (µmole/min/µg)	91.88 ± 6.507	101.3 ± 5.252	63.59 ± 2.801***	76.88 ± 3.900@
GPx (µmole/min/mg protein)	0.01848 ± 0.00164	0.03535 ± 0.00612#	0.003563 ± 0.000889****	0.007414 ± 0.0007801@@
Malondialdehyde (µmol/mg) protein)	3.60 ± 0.276	2.51 ± 0.226##	5.12 ± 0.347**	3.10 ± 0.284@@

All data are expressed as mean ± SEM, **$p < 0.01$, ***$p < 0.001$, ****$p <$ 0.0001 HFD versus control; #$p < 0.05$, ##$p < 0.001$ control + GRT versus control; @$p < 0.05$, @@$p < 0.01$ HFD + GRT versus HFD.

hyperglycaemia, dyslipidaemia, hypertension, endothelial dysfunction (ED) and oxidative stress.[5]

Leptin and angiotensinogen serve as examples of pro-inflammatory adipokines, which contribute to the dysregulation in adipocyte metabolism. A number of studies have shown the ameliorative effects of unfermented rooibos against the above obesity-induced CVD risk factors,[8,9,11-13,16-18] resulting from adipocyte hypertrophy. Fermented rooibos has been shown to inhibit adipogenesis and intracellular lipid accumulation, and it attenuates leptin secretion.[25] This was mainly attributed to its polyphenolic content, with aspalathin and nothofagin as active and the most abundant compounds.

The HFD used in this study successfully induced obesity in the Wistar rats,[19,26] and excess consumption of a high-fat, high-sugar diet has been previously shown as a contributing factor to obesity.[27,28] The increase in food intake by the HFD animals contributed to their higher body weight, leptin levels, and IP fat and liver mass (Tables 2, 3), which has been previously shown in obese rats fed a HFD.[28-32] Increased liver weight may be attributed to the increase in FFA release from the enlarged adipose tissue and increased lipid synthesis in the liver.[5] Additionally, the HFD animals had impaired glucose homeostasis (Figs 1, 2), as was previously documented by studies that used a similar diet.[19,26] Increased leptin levels and excessive accumulation of triglycerides in the liver have also been associated with dysregulation in glucose homeostasis.[30] The impairment in glucose homeostasis observed in the HFD animals was also supported by downregulation in the expression of AMPK in the vascular system (Fig. 4), an insulin-independent signalling protein. This protein is responsible for glucose uptake and NO production via the phosphorylation of eNOS.[33,34]

Furthermore, the HFD animals had increased blood pressure (Tables 2, 3), and decreased vasocontraction (Fig. 3A) and vasorelaxation (Fig. 3B). Increased blood pressure is as a result of an impairment in vasodilation, due to reduction in NO availability or production in the endothelial cells, a condition defined as ED.[35,36] Interestingly, the HFD animals presented with an upregulation in eNOS phosphorylation (Fig. 6B) despite the increased blood pressure and decrease in vasodilation. We speculate that this could be as a result of the decrease in SOD enzyme activity (Table 4), which contributes to a reduction in NO bioavailability via the eNOS uncoupling process. This process occurs when NO binds with superoxide radical-producing peroxynitrite, a highly reactive free radical, in the absence of the SOD enzyme.[36]

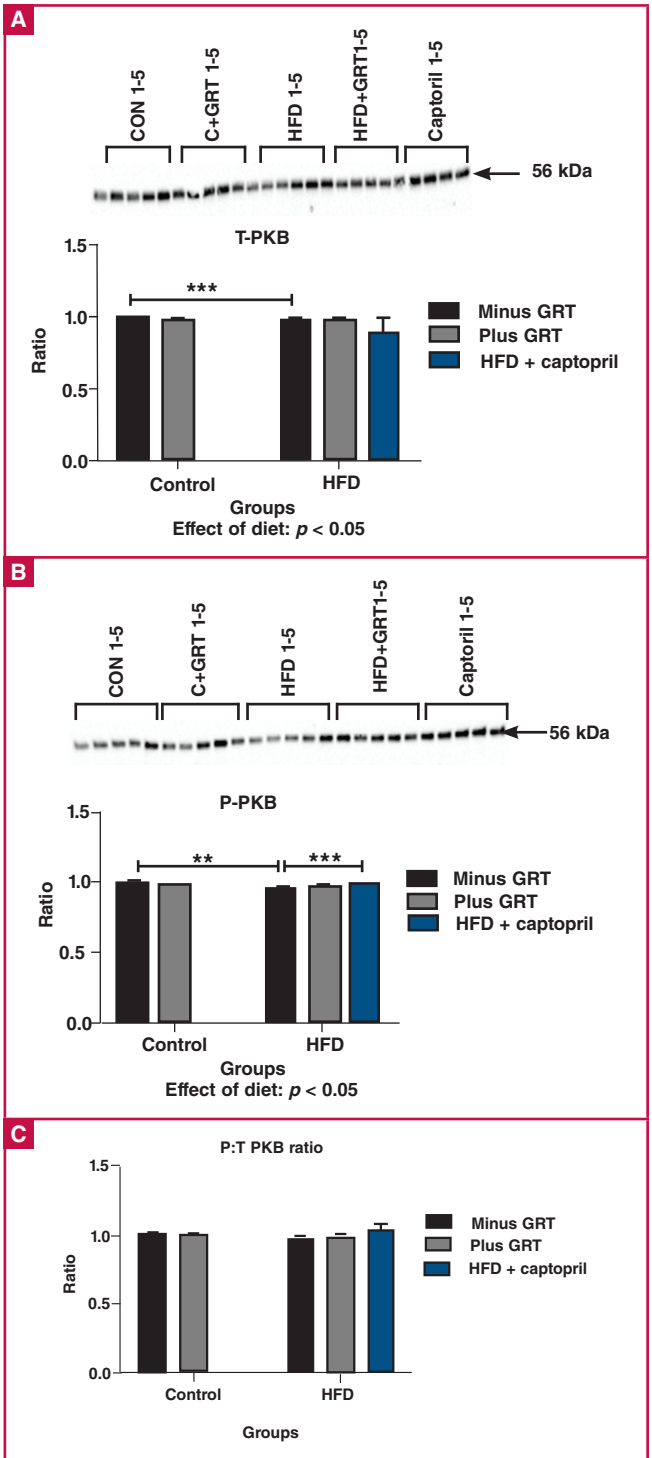

Fig. 5. PKB expression in the aortic rings of the HFD versus control groups (GRT treated and untreated), including the HFD animals treated with captopril. (A) T-PKB; ***p < 0.001, HFD versus control groups (n = 5 per group). According to two-way ANOVA, the HFD had a significant effect (p < 0.05) on T-PKB expression (n = 5 per group). (B) P-PKB; **p < 0.01, HFD versus control groups; ***p < 0.001, HFD + captopril versus HFD groups. According to two-way ANOVA, the HFD had a significant effect (p < 0.01) on P-PKB levels (n = 5 per group). (C) P:T PKB ratio; no significant differences between the groups

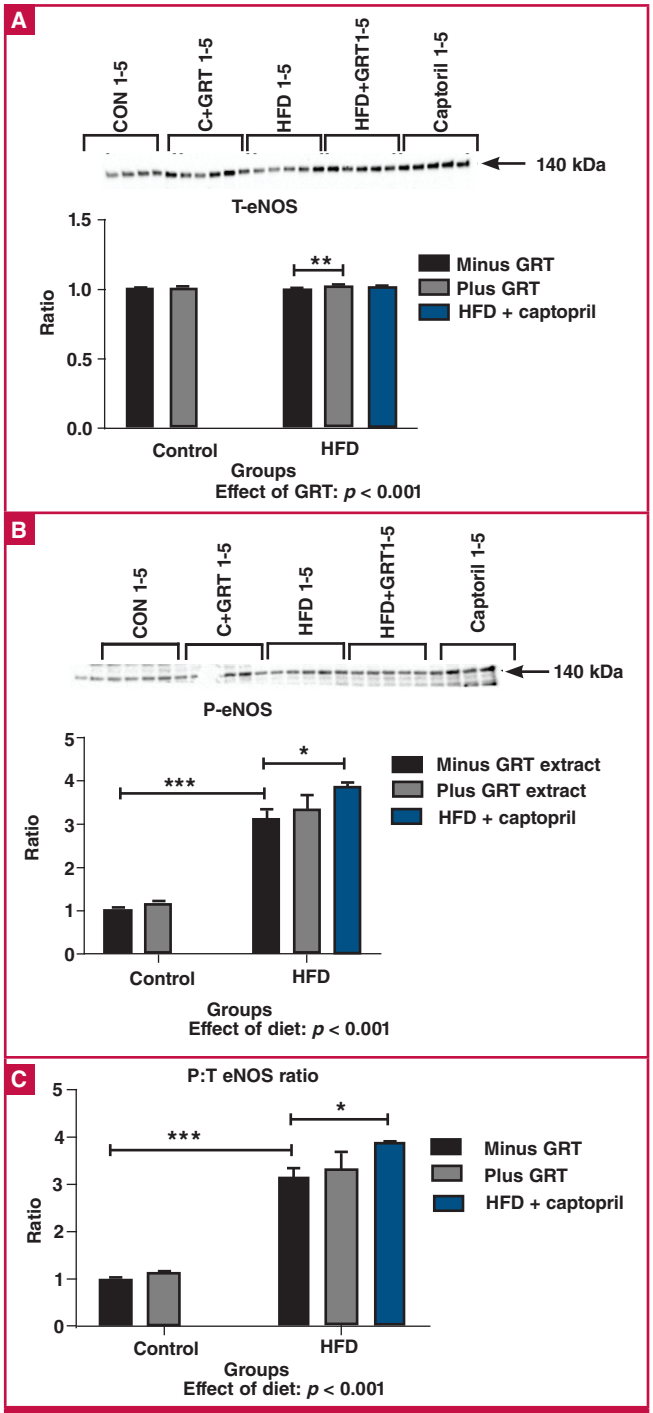

Fig. 6. eNOS expression in the aortic rings of the HFD versus control groups (GRT treated and untreated), including the HFD animals treated with captopril. (A) T-eNOS; **p < 0.01, HFD + GRT versus HFD groups. According to two-way ANOVA, the GRT had a significant effect (p < 0.01) on T-eNOS expression (n = 5 per group). (B) P-eNOS; ***p < 0.001, HFD versus control groups; *p < 0.05, HFD + captopril versus HFD groups. According to two-way ANOVA, the HFD had a significant effect (p < 0.001) on the P-eNOS levels (n = 5 per group). (C) P:T eNOS; ***p < 0.001 HFD versus control groups; HFD + captopril versus HFD groups. According to two-way ANOVA, the HFD had a significant effect (p < 0.001) on P:T eNOS levels (n = 5 per group).

The elevated blood pressure observed in the HFD animals could potentially be as a result of physical compression of the kidneys due to the accumulation of fat in and around the kidneys, and stimulation of the sympathetic nervous system as a result of increased leptin levels,[37,38] since leptin has been shown to be one of the factors that mediates increased blood pressure in obesity.[39,40] The HFD animals also presented with an increase in oxidative stress, reflected by an increase in lipid peroxidation and downregulation of CAT, GPx and SOD activity in the liver (Table 4). HFD has previously been documented to induce oxidative stress in obese Wistar rats.[28]

Treatment with GRT extract resulted in less weight gain, a decrease in IP fat mass, leptin levels, liver mass and blood pressure, as observed in the treated HFD animals. It also decreased vasocontraction (Fig. 3A) and improved vasorelaxation (Fig. 3B). Additionally, the GRT extract did not affect the body weight of the control animals. This corresponds with previous studies done in mice that used unfermented rooibos and green rooibos extract (GRE).[14,41]

It is believed that these herbal substances bring about the anti-obesity effects by inhibiting adipocyte differentiation and downregulate mRNA expression of the transcription factors responsible for the adipocyte differentiation, such as peroxisome proliferator-activated receptor-gamma (γ) (PPAR-γ).[25] This further results in reduction in leptin levels, AMPK activation, an increase in glucose uptake and a decrease in lipolysis and lipogenesis. Rooibos extracts have been shown to decrease the size and number of adipocytes.[25] These changes may also have resulted in decreased liver weight, as fat accumulation inside the liver primarily contributes to an increase in liver weight.

The decrease in leptin levels may also have resulted in lowering of blood pressure, subsequently improving vascular function. However, further mechanisms need to be explored, such as measuring endothelial-derived vasorelaxation and vasocontraction factors, as well as the renin–angiotensin system intermediates. The anti-hypertensive effects of unfermented rooibos have previously been documented.[8,42,43] Effects on the expression and phosphorylation state of the main proteins involved in the activation of eNOS were affected by the ingestion of GRT observed in this study. This could be one of the mechanisms that potentially contributed to the reduction in blood pressure, as observed in the HFD animals treated with the GRT extract. Previously, treatment with rooibos and aspalathin have been shown to activate AMPK.[25,44] Captopril possibly also resulted in upregulation of the production of NO by improved phosphorylation of AMPK, PKB and eNOS, decreasing blood pressure. Captopril is a well-known inhibitor of the angiotensin converting enzyme, thereby lowering the activity of the renin–angiotensin–aldosterone system.[45]

Treatment with GRT extract improved glucose metabolism (Fig. 2) in the treated HFD animals. Previously, it was reported that GRE extract and aspalathin improved glucose uptake *in vivo* via phosphorylation of AMPK and PKB signalling proteins and lipid metabolism.[12] Furthermore, aspalathin decreased fasting blood glucose levels and improved glucose intolerance in a diabetic rat model, confirming the effects of aspalathin on glucose homeostasis.[11] Interestingly, in the current study, the GRT extract showed no significant effect on phosphorylation of AMPK and PKB (Figs 4, 5), respectively, in the aorta. However, according to the P:T AMPK ratio, GRT extract increased the AMPK phosphorylation state in the treated HFD group (Fig. 4). This could mean that the GRT extract may have induced upregulation of glucose uptake in the tissues via the AMPK pathway.

In half of the control animals and in all the HFD animals, GRT interestingly increased urinary glucose levels (Table 3). The excretion of glucose in the urine is closely associated with inhibition of the sodium/glucose co-transporter 2 (SGLT2), thereby speculating that GRT might act as an SGLT2 inhibitor. Confirming this suggestion, a previous study reported that aspalathin can inhibit SGLT2.[46] SGLT2 is predominantly expressed in the renal proximal tubules of the kidneys, and to a lesser extent in the liver, muscle, heart[47] and pancreatic α-cells.[48] Since glucose is mainly reabsorbed by the kidney via SGLT2, inhibition of SGLT2 offers an insulin-independent novel mechanism for the treatment of type 2 diabetes. We speculate that the improved glucose clearance in the HFD animals could be ascribed to the inhibition of SGLT2 by the GRT extract. Further studies are needed to explore the postulated mechanism at the level of this transporter. Lastly, the GRT extract restored the oxidant–antioxidant imbalance in the treated HFD animals, thus restoring the antioxidant defence system (Table 4).

Conclusion

There is a strong correlation between visceral obesity and the pathogenesis of CVD risk factors. The use of natural, safe and affordable therapeutics may be useful in alleviating these pathologies. As demonstrated in the HFD rats in this study, obesity was strongly associated with impaired glucose homeostasis, increased blood pressure, ED, dyslipidaemia and oxidative stress, synergistically increasing cardiovascular risk. These were, however, attenuated by treatment with GRT extract, but the mechanisms need to be explored to further elucidate some of the findings. Therefore, GRT extract may be a potential therapeutic agent against obesity-related vascular dysfunction, impaired glucose homeostasis, elevated blood pressure, oxidative stress, leptin resistance and weight gain.

We thank Afriplex (Pty) Ltd and the South African Medical Research Council (SAMRC) for provision of the Afriplex GRT™ extract and HPLC analysis, Harry Crossley Foundation for financial support and Mr LDM Bennie for performing the glutathione peroxidase and lipid peroxidation assays. We declare that the rats received humane care in compliance with the revised South African National Standard for the Animal Care and Use for Scientific Purposes (South African Bureau of Standards, SANS 10386, 2008) and the protocol was approved by Stellenbosch University Animal Ethics Committee, Tygerberg, South Africa (ethics number: SU-ACUM15-00102).

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Sex differences in 'normal' blood pressure and associated CVD risk

Women have a lower 'normal' blood pressure range compared to men and this is linked to risk for each specific cardiovascular disease (CVD) type, including heart attack, heart failure, and stroke, a large study from the Smidt Heart Institute at Cedars-Sinai Medical Centre found.

Currently, established blood pressure guidelines state that women and men have the same normal healthy range of blood pressure. But this research shows there are differences in normal blood pressure between the sexes.

'Our latest findings suggest that this one-size-fits-all approach to considering blood pressure may be detrimental to a woman's health,' said Dr Susan Cheng, associate professor of cardiology and director of the Institute for Research on Healthy Aging in the Department of Cardiology at the Smidt Heart Institute and senior author of the study. 'Based on our research results, we recommend that the medical community reassess blood pressure guidelines that do not account for sex differences.'

For years, 120 mmHg has been considered the normal upper limit for systolic blood pressure in adults. Persistent elevations above this limit amount to hypertension, which is well known as the key risk factor for common cardiovascular diseases, such as heart attack, heart failure, and stroke.

In their newest study, Cheng and her research team examined blood pressure measurements conducted across four community-based cohort studies, comprising more than 27 000 participants, 54% of whom were women.

In doing so, the research team identified that while 120 mmHg was the threshold of risk in men, 110 mmHg or lower was the threshold of risk in women. Systolic blood pressure levels that were higher than these thresholds were associated with risk for developing any type of cardiovascular disease, including heart attack, heart failure and strokes.

Investigators also found that women had a lower blood pressure threshold than men for risk of each specific cardiovascular disease type, including heart attack, heart failure and stroke. 'We are now pushed to rethink what we thought was a normal blood pressure that might keep a woman or a man safe from developing heart disease or stroke,' added Cheng, who also serves as director of cardiovascular population sciences at the Barbra Streisand Women's Heart Centre and is the Erika J Glazer chair in women's cardiovascular health and population science.

These findings build on past research led by Cheng suggesting women's blood vessels age faster than those of men. Cheng's research, published last year, confirmed that women have different biology and physiology from men and also explained why women may be more susceptible of developing certain types of cardiovascular disease and at different points in life.

With both the 2020 study and in their latest work, Cheng and her team compared women to women and men to men, rather than the common model of comparing women to men.

'If the ideal physiological range of blood pressure truly is lower for females than males, current approaches to using sex-agnostic targets for lowering elevated blood pressure need to be reassessed,' said Dr Christine Albert, chair of the Department of Cardiology at the Smidt Heart Institute. 'This important work is far reaching and has numerous clinical implications.'

As a next step, researchers plan to study whether women should be treated for hypertension when their systolic blood pressure is higher than 110 mmHg, but still lower than the systolic measurement of 120 mmHg for men.

Source: Medical Brief 2021

Analysis of the vascular access service for patients on haemodialysis in Livingstone Hospital

Ian R Grant, Robert J Freercks, Eduard J Honiball, Bhekifa Dube

Abstract

Background: Reliable vascular access is key to sustainable haemodialysis treatment. Guidelines recommend an arteriovenous fistula (AVF) as the preferred modality in preference to arteriovenous grafts (AVGs) or central venous catheters (CVCs). There are limited data on vascular access in sub-Saharan Africa. This study aimed to evaluate the vascular access used in a South African tertiary hospital and identify problems with achieving the recommended access goals.

Methods: A cross-sectional analysis was performed of the haemodialysis programme at Livingstone Tertiary Hospital. Current and initial vascular access used, timing until the creation of permanent access, and any complications experienced were recorded.

Results: CVCs were used in 56% of subjects, 38% were using an AVF and 5% were using an AVG. Only 12% of the group had no AVF attempt. The overwhelming majority (95%) had dialysis initiated with a CVC. The rate of pre-emptive AVF creation was low and a delay in AVF creation was seen in 63% of patients. Central venous stenosis or occlusion was present in 26% of patients and likely due to prior or current CVC use.

Conclusions: The prevalence of CVC use was high and there were significant delays to AVF creation. High rates of central venous stenosis compromise future AVF use and are likely due to prolonged CVC use. Changes needed to improve the vascular access service include a multidisciplinary access clinic, dedicated theatre list, vascular access co-ordinator and further data collection to continually evaluate the vascular access service.

Keywords: arteriovenous fistula, haemodialysis access, arteriovenous graft, tunnelled central venous catheter

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Haemodialysis offers life-saving therapy to patients with advanced chronic kidney disease (CKD). Unfortunately, access to haemodialysis is limited by cost, availability and reliable vascular access.[1] Optimal management of this limited resource is therefore of key importance in reducing the high burden placed on the healthcare system.[2-4]

Currently, vascular access options are limited to an autogenous arteriovenous fistula (AVF), a prosthetic arteriovenous graft (AVG) and a central venous catheter (CVC). It is well established that the autogenous AVF is superior to the other modalities in terms of patency rates and infection risk. This is reflected in local and international guidelines where it is recommended as the primary option for all patients on haemodialysis.[5-7] The Fistula First Breakthrough Initiative and the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in 2006 set in motion a drive to create more AVFs and limit the use of CVCs.[7] This saw a change in practice in high-income countries as more fistulae were created and fewer AVGs and CVCs were used.[6]

Access complications contribute to ineffective dialysis and interruptions in treatment, which further contribute to the cost of care. Significant problems with AVFs include non-maturation and early thrombosis. Some studies have shown an early failure rate as high as 46%.[6] If no suitable vessels are available, or when all vessels in the arm are exhausted, a prosthetic AVG can be placed.[8] The risk of infection is increased for an AVG compared to an autogenous AVF but primary patency may be higher.[7] The most common problem with an AVG is stenosis due to an abnormal turbulent flow pattern, which causes focal shear stress in the native blood vessel and neo-intimal hyperplasia, which ultimately leads to narrowing and thrombosis of the graft.[9]

CVCs are the least-preferred modality and not recommended for permanent access.[5] They have a high infection risk and also cause permanent damage to the native vessels, which can lead to central venous stenosis and occlusion, eventually limiting future access modalities. They do have some benefits however, since they can reliably be used as soon as they are placed when urgent dialysis is required. CVCs also cause less haemodynamic change and no increase in blood flow to the heart, which may be important in patients with congestive cardiac failure.[10]

The choice of vascular access should be individualised according to the specific patient characteristics. The primary goal should be a distal autogenous AVF in the non-dominant arm, created three to six months prior to the expected start of haemodialysis.[5,6] This would allow time for maturation and even intervention in the event the fistula fails to mature adequately, which will decrease the need for CVC use. A recent study suggested that the benefit of an autogenous fistula is lost when a patient is started on a CVC and then has an AVF created.[11] The use of CVCs, even for a short period, should be discouraged. This practice relies on the timeous identification and referral of patients with CKD.

Reports from middle- and low-income countries show a common theme: a high rate of AVF creation but typically only

after initiating dialysis with a CVC (90 to 95%).[12,13] Factors associated with improved outcomes in these countries include early referral and a multidisciplinary approach.[14,15] Late referral, conduit damage by venepuncture and a lack of secondary intervention for failing fistulae contributes to high failure rates.[16]

Another strategy proven to improve outcomes includes pre-operative ultrasound to evaluate the size and quality of the vein to be used.[6,17] A structured pre-dialysis care programme allows the patient to be adequately prepared with counselling and training, as well as early referral to the vascular access surgeon.[17] Regular multidisciplinary meetings are useful to refer new patients, discuss patients with early concerns about access complications and deal with problematic vascular access.[17] Having a dedicated vascular access co-ordinator with a pre-operative ultrasound protocol was shown to be the most important factor in improving haemodialysis access outcomes.[18]

There is currently no database for vascular access in South Africa, and high-quality data in low- and middle-income countries are limited.[4] The South African Renal Registry was the only active African registry until the establishment of the African Renal Registry in 2015.[19] Unfortunately, they do not yet record vascular access data. Having data in registries helps to inform future planning, guides practice, assists in future research and helps decide on resource allocation.[19] In order to improve access utilisation in the haemodialysis population, one needs to evaluate the current practice.[19]

The aim of this study was therefore to examine the current and past use of AVFs, AVGs and CVCs in our unit, in light of national and international recommendations. This was done by performing an audit of all patients enrolled in the haemodialysis programme at our hospital. The objective was to identify any factors preventing this unit from achieving guideline targets and to propose changes that could be implemented to achieve a better haemodialysis access service.

Methods

Ethical clearance was obtained from the Faculty of Health Sciences Postgraduate Education, Training, Research and Ethics Unit of the Walter Sisulu University.

We performed an audit on the vascular access for chronic haemodialysis patients in Livingstone Tertiary Hospital in Port Elizabeth, South Africa. A retrospective folder review was done to identify demographic data and full vascular access history. The data were used to calculate the time from commencement of haemodialysis until the first attempt at the creation of a permanent vascular access. Each modality of haemodialysis access was then evaluated in the patient's records. The date of insertion or creation of each modality was recorded. Where available, the complications associated with each were also recorded.

All patients enrolled in the haemodialysis programme at Livingstone Hospital on 1 June 2018, who had adequate records, were included in the study. Patients requiring temporary dialysis or awaiting transfer to peritoneal dialysis were excluded.

Table 1. Demographic data of the 66 patients

Demographics	*Values*
Mean age, years (95% CI)	44 (42–46.8)
Gender, *n* (%)	
Male	35 (53)
Female	31 (47)
Race, *n* (%)	
Black	43 (65)
Coloured	17 (23)
White	6 (9)
Aetiology of renal failure, *n* (%)	
Hypertension	50 (76)
Unknown	6 (9)
Polycystic kidney disease	3 (5)
Systemic lupus erythematosus	3 (5)
Vesico–ureteric reflux	2 (3)
Sepsis	1 (2)
Glomerulonephritis	1 (2)
Mean BMI, kg/m^2 (95% CI)	24.4 (22.6–25.3)

BMI, body mass index.

Results

Sixty-six patients formed the study sample, with age ranging from 21 to 67 years and a mean age of 44 years (95% CI: 42–46.8). Demographic details are shown in Table 1.

The majority of subjects [37 (56%)] were using a tunnelled CVC as their permanent vascular access, an autogenous AVF was used in 25 (38%) and an AVG in three (5%) patients. One patient was using a temporary CVC while awaiting a more definitive access modality (Table 2). Within the group that was using a CVC as permanent access, three subgroups were identified: those who had no AVF created or AVG inserted (12%), those with one previous failed AVF or AVG (21%), and those who had had more than one previous attempt at an AVF or AVG (23%).

Central venous catheters were used in 95% of the studied patients as the initial modality. This included 38 patients (58%) who started with a temporary CVC and 25 (38%) who started with a tunnelled CVC. Only six (10%) patients had pre-emptive creation of permanent access, of which three were successfully used. The other three had a primary failure and had to have dialysis initiated using a CVC (Table 2).

The timing from initiation of haemodialysis until the first attempt at AVF creation was also investigated (Fig. 1). In total, 101 AVFs were created in the study group. The number of access creation attempts and the complications experienced are shown in Table 2. There was no recorded episode of significant dialysis access-associated steal syndrome. The data were inadequate to calculate primary and secondary patency rates.

Discussion

Despite the young age of this population receiving haemodialysis in our unit, there was a high rate of CVC use and a very high rate of serious complications, such as clinically apparent central venous stenosis. The target for AVF use in any unit, as set by the Fistula First Breakthrough Initiative, is 65%. Several high-income countries are reporting AVF prevalence this high.[7] Only 38% of our study population were using an AVF. The high rate of CVC use in this study is therefore not in keeping with guideline recommendations. However, on further investigation, it is clear that CVC use was not the primary strategy, since most of these patients had had prior AVFs that failed.

While only 12% of the entire group had never had, or was not then using an AVF, unfortunately 95% of the patients started dialysis using a CVC, with only 5% having a successful pre-emptive fistula. This reliance on CVCs increases the failure rate of AVFs created in the future as prior CVC use decreases the benefit of an AVF.[11]

Table 2. History of vascular access creation and complications

History	*Number*	*Percentage of study populations*
Current access		
Tunnelled CVC	37	56
AVF	25	38
AVG	3	5
Temporary CVC	1	2
CVC group sub-analysis		
Patients using a CVC at present	37	56
With no previous AVG or AVF	8	12
With 1 previous AVG or AVF	14	21
With > 1 previous AVG or AVF	15	23
Initial vascular access		
CVC	63	95
Non-tunnelled CVC	38	58
Tunnelled CVC	25	38
Pre-emptive AVF	3	5
Number of AVF or AVG attempts		
No previous AVF or AVG	8	12
1 AVF or AVG	29	44
2 AVF or AVG	15	23
3 AVF or AVG	13	20
4 AVF or AVG	1	2
Complications		
Central venous stenosis or occlusion (of 66 patients)	17	26
Aneurysmal dilatation (of 101 AVFs)	15	15
Aneurysmal and still in use (of 15)	9	60
Aneurysmal and abandoned (of 15)	6	40
Dialysis access-associated steal syndrome	0	0

CVC, central venous catheter; AVF, arteriovenous fistula; AVG, arteriovenous graft.

While late presentation with advanced kidney disease is a common occurrence in our unit, necessitating the use of CVCs, long delays to creation of permanent access after starting dialysis prolongs exposure to the harmful effects of CVCs.[11,20] Almost a third of patients in this study waited more than 12 months prior to the first AVF attempt. This most likely contributed to the high failure rate when an AVF was eventually created. Pre-emptive fistulae should ideally be fashioned three to six months before the first haemodialysis session to allow for maturation and re-intervention if necessary.[5-7]

These findings are similar to reports from sub-Saharan Africa as well as other low- and middle-income countries, where most patients will start dialysis on an emergency basis and cannot wait for a fistula to mature.[16,21] This perpetuates the cycle, as higher rates of CVC use lead to poorer outcomes with AVFs, which lead to more CVC use. Except for the high primary failure rate, a lack of secondary intervention also decreases the long-term patency rates of the AVFs. Whenever failing fistulae are identified, rapid referral for intervention prior to a complete occlusion is required. Interventions done to maintain the fistula prior to complete occlusion are more likely to be successful.[22] The access surgeon also requires available theatre time to be able to attempt salvage. When urgent secondary interventions are not available, the fistulae will simply be abandoned when they occlude.[16]

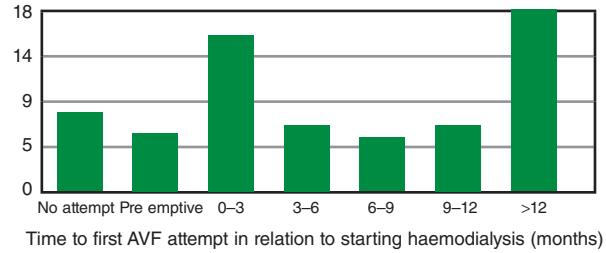

Fig. 1. Time to first fistula attempt (months).

The documented complication rates may have been underestimated in this retrospective study as it relied on the adequacy of the patient records. Central venous stenosis or occlusion was recorded in a quarter of the patients. This may even be an underestimation, since patients are not routinely screened for evidence of central venous obstruction and only clinically apparent central venous obstruction was recorded. The damage caused by long-term CVC use leads to central venous stenosis and can compromise future access options.[23]

Recommendations for improving current practice

Early detection of CKD and timely referral: many patients present late with end-stage kidney disease. Ongoing education of healthcare providers is needed to promote early referral. Early detection of CKD may avoid the need for urgent dialysis and therefore CVC use, allowing time for pre-emptive access creation.[24]

Dedicated vascular access clinic: a specialised multidisciplinary clinic should be formed that deals primarily with new and problematic vascular access cases.[18] This multidisciplinary team should include a vascular access surgeon, a nephrologist, dialysis nursing staff and supporting staff. All new referrals can be seen and access planning started prior to the first dialysis session. Ultrasound evaluation can be done at the initial visit to map out potential access sites and look for problematic areas such as prior vein injury by cannulation. When there are concerns regarding early AVF failure, intervention can then be planned and the patient prioritised for surgical revision from this clinic. In this format there will be open communication between the different members of the haemodialysis team. It will also allow time for patient education in a neutral environment with all the different team members available.

Availability of a dedicated vascular access theatre list: without access to theatre it would not be possible to run an effective vascular access service. The best way to optimise the timing to AVF creation and deal with failing fistulae or complications would be to allocate a dedicated vascular access theatre list. This list should ideally be in a hybrid theatre or a theatre with fluoroscopy available so that both open surgical and endovascular interventions can be performed as needed. The haemodialysis patients can then be prioritised and would not need to compete for theatre time with all the other emergency and elective surgical patients.

A dedicated access co-ordinator: it would be valuable to appoint a dedicated vascular access co-ordinator. This should be a trained nurse experienced in haemodialysis and vascular surgery. Ideally one of the experienced nurses currently in the unit could fulfil this role. The co-ordinator will be the link between the patient, dialysis staff, nephrologist and access surgeon. This strategy has been shown to be very effective in improving haemodialysis outcomes.[18]

Prospective data collection and interval evaluation: having a registry of vascular access data can help to plan resource allocation, guide the design of future clinical trials and monitor the local vascular access practice. There is currently no prospective registry for vascular access in South Africa, although the South African Renal Registry does collect data on haemodialysis across South Africa.[25] The newly established registry of the African Association of Nephrology will collect valuable data on CKD management across Africa but lacks data collection on vascular access.[26] Adding vascular access data to these registries would be beneficial to the African dialysis population.

Conclusion

It is a great privilege to be able to offer chronic haemodialysis to our patients. To make the most use of this service we need to optimise their vascular access. Our current practice falls short of local and international guidelines in terms of AVF and CVC use. The overwhelming majority of patients start dialysis with a CVC rather than a recommended pre-emptive AVF and there are significant delays prior to the first AVF creation. This translates to a longer time using a CVC and increased complications as well as limiting future access options. Recommendations to improve the service would be to create a multidisciplinary vascular access clinic, establish a dedicated vascular access theatre list and assign an access co-ordinator. Ongoing education of healthcare practitioners on the earlier identification and referral of kidney disease will facilitate pre-emptive creation of vascular access.[24] Finally, there is also a need for a South African vascular access registry to identify the local practices of each haemodialysis unit.

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Review Article

Atrial high-rate episodes: a comprehensive review

Gelu Simu, Radu Rosu, Gabriel Cismaru, Mihai Puiu, Gabriel Gusetu, Ioan Minciuna, Sabina Istratoaie, Raluca Tomoaia, Dumitru Zdrenghea, Dana Pop

Abstract

Cardiac electronic implantable devices (CIEDs) have the ability to monitor, store and interpret complex arrhythmias, which has generated a new arrhythmic entity: atrial high-rate episodes (AHRE). AHRE are atrial tachyarrhythmias, detected only by CIEDs. They are widely considered a precursor to atrial fibrillation (AF) but can also be represented by other kinds of supraventricular arrhythmias such as atrial flutter or atrial tachycardia. CIED-detected AHRE are associated with an increased risk of stroke, but the risk is significantly lower than the stroke risk of clinical AF. Moreover, there seems to be no temporal correlation between AHRE and thromboembolic events. Because of the current gaps in evidence, the appropriate management of this arrythmia can be challenging. In this review we take into account the epidemiology behind AHRE, predictive factors, clinical impact and management of this arrhythmia.

Keywords: atrial high-rate episodes, anticoagulant agents, atrial fibrillation, stroke, pacemaker

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Atrial fibrillation (AF) is the most common sustained tachyarrhythmia encountered in clinical practice. Because of its high impact on morbidity and mortality, it is also the most studied tachyarrhythmia.[1] Despite the latest progress achieved in managing AF, it still is one of the major causes of stroke, heart failure, sudden death and cardiovascular morbidity.[1-4] Its incidence and prevalence are expected to rise steeply in the following years because of population ageing and the progress achieved in diagnosing asymptomatic episodes.

The recent development of devices capable of long-term continuous monitoring of cardiac rhythm revealed that asymptomatic AF is more frequent than symptomatic AF.[5-8] Despite the obvious difference in quality of life, there is currently no evidence that these two entities have a different risk profile. There are however several prospective ongoing trials that focus on this subject.[9-11]

Different options in long-term monitoring of the cardiac rhythm are currently used: handheld electrocardiograph (ECG) monitoring devices, long-term Holter ECG, subcutaneous implantable cardiac monitors (ICM), cardiac implantable electronic devices (CIEDs) and even smartphone ECG applications. A significant advantage of CIEDs when compared to other long-term rhythm-monitoring devices is their ability to continuously monitor cardiac rhythm. Due to their complex algorithms, modern CIEDs are able to store and interpret complex arrythmias, which has resulted in a new arrhythmic entity: atrial high-rate episodes (AHRE).

Definitions

The European Heart Rhythm Association (EHRA) consensus for device-detected subclinical atrial tachyarrhythmias defines AHRE as follows: atrial tachyarrhythmia episodes with an atrial rate of > 190 beats/min (bpm) detected only by CIEDs.[12]

The various definitions used in the literature have generated confusion between AHRE and subclinical atrial tachyarrhythmias (AT). Subclinical (asymptomatic) AT can be detected by a variety of different methods, including external surface-monitoring methods (standard ECGs, Holter monitors or event monitors) and CIEDs [pacemakers, implantable cardioverter defibrillators (ICDs)], while AHRE are detected only by CIEDs. Furthermore, AHRE are widely considered a precursor to AF but can also be represented by other kinds of supraventricular arrythmias such as atrial flutter or atrial tachycardia.[12]

While the impact of AHRE on morbidity and mortality has been proven, there are certain differences when compared to AF. CIED-detected AHRE are associated with a two-fold increase in stroke risk when compared to patients with no AHRE, but the risk is significantly lower than the stroke risk of clinical AF.[13,14] This is the main reason why AHRE must be distinguished from asymptomatic paroxysmal AF diagnosed by surface ECG

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methods, which usually identify patients with higher burdens of AT. Moreover, several studies have shown that AHRE do not seem to be temporally associated with stroke.[15,16] These two main differences support the idea of two distinct clinical entities.

Incidence and prevalence

The reported incidence of AHRE varies with the definition of AHRE, study design, indication for CIED, presence of AF history, following period and type of device.

Because many CIED-recorded arrhythmias have proven to be inaccurate, the diagnosis of AHRE requires several criteria as well as manual reviewing of the electrogram (EGM). Therefore, a > 190-bpm threshold has been chosen to increase the specificity of CIED-diagnosed AHRE. While this threshold increased the specificity of the AHRE diagnosis, one study reported that almost 20% of the CIED-detected AHRE were not accurate when reviewed by an expert.[17]

There are a number of different issues why a CIED can misdiagnose an AHRE episode, which can be classified into false-negative detection (true atrial undersensing because of small EGM signals, functional atrial undersensing because of the EGM signals coinciding with blanking times) and false-positive detection (myopotential oversensing, electromagnetic interference and lead failure) (Fig. 1).[12]

The specificity of the diagnosis also depends on the type of device and the duration of the arrhythmic episode. Therefore, a temporal threshold of five to six minutes was established for several reasons. First of all, to increase the specificity of the diagnosis (decrease the number of false-positive detected episodes).[13,18] Second, episodes longer than five minutes have been shown to increase the risk of stroke.[13,18] Furthermore, certain devices were programmed to only record and classify events longer than a pre-established temporal threshold.

The overall incidence of AHRE in unselected patients is approximately 50%.[13,19-22] However, the studies that excluded patients with a history of AF reported an incidence of approximately 30%.[23-25] The patient population included in most of the above-mentioned studies consisted of elderly patients (mean age > 70 years) with multiple thromboembolic risk factors (mean CHA_2DS_2-VASc score > 2).[13,19-25] An atrial lead is necessary for the CIED in order to accurately diagnose an atrial arrhythmia, which is why single-chamber CIEDs with a ventricular lead have not been included in most studies.

Predictive factors

While AF is still a matter of great interest, the underlying mechanisms that cause and maintain this arrythmia have not been fully understood. Numerous clinical, biological and paraclinical factors have been associated with AF but there are only a handful of studies that examined the role of predictive factors in AHRE.

False-positive AHRE	Myopotential oversensing
	Electromognetic interference
	Lead failure
	Ineffective atrial pacing (non-re-entrant VA synhrony)

Fig. 1. Causes for incorrect AHRE detection by the CIED.

In the TRENDS study, the incidence of newly detected AHRE did not vary with the $CHADS_2$ score ($CHADS_2$ score of 1: 30%, $CHADS_2$ = 2: 31%, $CHADS_2$ = 3: 31%) but episodes longer than six hours were associated with an increased $CHADS_2$ score.[24] One study, which included patients with a prior history of AF, showed that older age and increased left atrial volumes were predictors for pacemaker-detected AF.[20]

An increased percentage of ventricular (VVI) pacing has been associated with an increased risk of developing AF.[26] However, even in patients with dual-chamber pacemakers, where atrioventricular synchrony is preserved, an increased percentage of ventricular pacing has been associated with a higher risk of developing AF.[27-35] The most likely explanation is that ventricular pacing causes paradoxical septal motion, which alters interventricular synchrony, lowers ejection fraction and increases filling pressures in the heart chambers. This leads to electric remodelling of the left atrium.

Cumulative ventricular pacing of > 50% has been associated with an increased risk of developing AHRE in patients with no prior history of AF.[23,36] However, one study showed that a high percentage of atrial pacing can also be detrimental. In this study, conducted on patients with no prior history of AF, cumulative atrial pacing > 50% was associated with a three-fold increase in risk of developing AHRE.[37]

Tekkesin *et al*. demonstrated that inter-atrial block (IAB) was a predictive factor of AHRE occurrence; 30.1% of the 367 pacemakers implanted for sinus node dysfunction presented AHRE six months after the implantation, at device interrogation. Only 67 patients (27%) in the AHRE-negative group presented with IAB compared to 48 (44.9%) patients in the AHRE-positive group.[38] Another study conducted by Rubio Campal *et al.* also found IAB to be a strong predictor for developing AHRE.[39]

Although inflammation has been proven to play a certain role in developing and maintaining AF, the underlying mechanism is not fully understood.[40-42,43] Pastori *et al.* were the first to associate inflammation with an increased risk of developing AHRE.[44] The results showed that high C-reactive protein and white blood cell count were independently associated with AHRE occurrence. These results suggest a common pathogenetic pathway between AF and AHRE. Another interesting finding of this study was that there was no association between anti-arrhythmic treatment and AHRE incidence, which implies that an optimal level for the management of this arrythmia has not yet been reached.[44]

AF can be a marker of underlying vascular disease because of the direct and indirect mechanisms leading to electrical and anatomical atrial remodelling, which lead to atrial fibrosis.[42,45] The prevalence of CAD in patients with AF ranges from 17 to 46.5%.[46-48] The relationship between vascular disease and AHRE has not been sufficiently investigated. More studies are necessary to investigate the underlying mechanisms and predictive factors of AHRE.

Clinical impact

Atrial high-rate episodes must be distinguished from clinical AF, which is diagnosed by surface ECG and identifies patients with a higher burden of AF. The ancillary MOST analysis was the first study to prove that in CIED patients, AHRE of more

than five to six minutes were associated with an increased risk of developing clinical AF.[18] Similar results were reported later by the ASSERT study, where 16% of patients with AHRE longer than six minutes developed clinical AF. These findings suggest a pathogenic connection between these two arrhythmic entities.[49]

In CIED patients, AHRE was associated with a two- to 2.5-fold increase in stroke risk when compared to patients without AHRE.[13,49,50] However, the risk of stroke was smaller than in patients with clinical AF.[14] Kazuo Miyazawa *et al.* also showed that patients with AHRE had higher mortality rates when compared to patients without AHRE.[50] However, the West Birmingham Atrial Fibrillation project showed that AHRE did not increase the thromboembolic risk, while the baseline CHA_2DS_2-VASc score was independently associated with thromboembolic events.[25]

Several burden thresholds have been investigated, ranging from five minutes to 24 hours, to establish a minimum threshold that increases stroke risk. A minimum burden of five minutes has been proven to increase the risk of stroke.[17,18] Pastori *et al.* showed that AHRE ≥ five minutes were associated with a 1.7-fold increase in major adverse cardiovascular events (MACE) while episodes of more than 24 hours showed a 2.3-fold increase in MACE.[51] However, a re-analysis of the ASSERT study found that only episodes longer than 24 hours were associated with an increased risk of stroke.[52]

In the SOS AF project, a dichotomised analysis was performed in order to investigate the risk of stroke when comparing different cut-off thresholds (five minutes, one, six, 12 and 23 hours). The one-hour threshold was associated with a hazard ratio of 2.11.[53] Data from the RATE registry, a multicentre, prospective, observational study, which investigated outcomes of over 5 000 patients with device-detected AF, showed that short episodes of AF terminating within a single adjudicated EGM recording (up to 20 seconds) did not increase the risk of a composite outcome of stroke, TIA, hospitalisation or mortality. However, approximately 50% of these patients did go on to develop longer episodes of AF over two years of follow up.[22]

While the association between AHRE and stroke or systemic thromboembolism has been proven, the minimum duration of an AHRE that increases the thromboembolic risk remains uncertain. Despite the contradictory data, a minimum threshold of five to six minutes is widely considered to increase the risk of thromboembolic events (Table 1).

Despite the temporal relationship between AF and stroke, proven first by the Framingham study and later by the AFFIRM study, there seems to be a temporal discordance between AHRE and stroke.[15,16,54,55] AHRE was diagnosed in only half of the patients with stroke or systemic embolism in an analysis of the TRENDS study.[15] Moreover, 73% of the patients did not present with an AHRE in the preceding month. A similar analysis performed on the ASSERT study identified an AHRE in 51% of the patients with stroke.[16] The cause for this temporal discordance between AHRE and stroke is not completely understood.

AHRE and anticoagulation

Initiation of anticoagulant therapy is difficult in these patients. The threshold of AHRE duration leading to an elevated stroke risk is one of the major knowledge gaps in the EHRA consensus for device-detected subclinical AT.[12] Selecting the most efficient antithrombotic therapy for patients with AHRE was one of the gaps in evidence identified by the European Society of Cardiology (ESC) taskforce for the 2016 guidelines on the management of AF.[56] There are however ongoing trials that compare oral anticoagulation with aspirin in patients with AHRE[9,10] (Table 2).

There are no randomised controlled trials published to date to guide anticoagulant therapy in patients with AHRE. All

Table 1. Relationship between CIED-detected AHRE and systemic embolism

Trial	*Number of patients*	*Follow-up duration*	*AHRE duration cut-off*	*Atrial cut-off rate (bpm)*	*Hazard ratio for TE event (p-value)*
Ancillary MOST[18]	312	27 months (median)	> 5 min	> 220	6.7 (0.020)
Italian AT500 registry[59]	725	22 months (median)	> 24 h	> 174	3.1 (0.044)
Botto *et al.*[60]	568	1 year (mean)	$CHADS_2$ and AF burden ≥ 5 min in a day or > 24 h	> 174	NA
TRENDS[13]	2486	1.4 years (mean)	≥ 5.5 h	> 175	2.2 (0.060)
Home Monitor CRT[61]	560	370 days (median)	≥ 3.8 h	> 180	9.4 (0.006)
ASSERT[49]	2580	2.5 years (mean)	≥ 6 min	> 190	2.5 (0.007)
SOS AF[53]	10016	2 years (median)	≥ 1 h	> 175	2.11 (0.008)
RATE REGISTRY[22]	5379	22.9 months (median)	NA	NA	0.87 (0.51)

Table 2. Comparison of ARTESIA and NOAH trials

Study	*Identifier*	*Inclusion criteria*	*Number of patients*	*Design*	*Endpoint*	*Current status*	*Estimated completion date*
ARTESIA[9]	Clinicaltrials.gov NCT01938248	Patients without clinical AF Pacemaker, ICD or CRT Age ≥ 65 years CHA_2DS_2-VASc score ≥ 4 ≥ 1 episode of symptomatic AF ≥ 6 min, atrial rate > 175 bpm no single episode > 24 h in duration	4000	Randomised, double-blind, double-dummy Randomised to Apixaban 2 × 5 mg or 2 × 2.5 mg vs aspirin 1 × 81 mg	Composite of stroke and SSE Major bleeding	Recruiting	2022
NOAH AFNET 6[10]	Clinicaltrials.gov NCT02618577	Only patients without overt AF Pacemaker or ICD Age ≥ 65 years CHA_2DS_2-VASc ≥ 2 ≥ 1 episode of AHRE ≥ 6 min, atrial rate > 180 bpm, no single episode > 24 h	2686	Randomised, double-blind double-dummy Edoxaban 1 × 60 mg or 1 × 30 mg vs 1 × aspirin 100 mg or placebo	Composite of time to first stroke, SSE or CV death	Recruiting	2022

AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronisation therapy; SSE, systemic embolism.

Table 3. Society guideline recommendations

Guideline	*Subclinical AF duration*	*CHA_2DS_2-VASc score*	*Class of recommendation*
Device-detected subclinical atrial tachyarrhythmias: definition, implications and management; a European Heart Rhythm Association (EHRA) consensus document[12]	≥ 5.5 h*	≥ 2	Recommended/indicated
	≥ 5.5 h*	1 (men) or 2 (women)	May be used or recommended
ESC 2016 guidelines for the management of atrial fibrillation[57]	> 5–6 min	≥ 1 in male patients or 2 in female patients	IA

*Data suggests risk is similarly increased by a mere five minutes. AF, atrial fibrillation.

recommendations regarding anticoagulant therapy initiation in these patients are expert recommendations only. Therefore, patient choice regarding this matter is an important consideration.[12,57]

The CHA_2DS_2-VASc score seems to also be suitable to assess the stroke risk in patients who present with AHRE.[21,25,58] A recent study, performed on over 21 000 non-anticoagulated patients with CIEDs, showed that the annualised risk of systemic embolism (SSE) was associated with increasing CHA_2DS_2-VASc score and increasing AF duration.

In this study, in patients with a CHA_2DS_2-VASc score of 0 to 1, SSE rates were low, regardless of the duration of the device-detected AF. However, the stroke risk increased, crossing an actionable threshold, defined as > 1% per year, in patients with CHA_2DS_2-VASc score of 2 with > 23.5 hours of AF, patients with CHA_2DS_2-VASc score of 3–4 and > six minutes of AF, and patients with a CHA_2DS_2-VASc score ≥ 5 even if they presented with no AF.[58] More studies are necessary to assess if the usual strategies for stroke risk stratification and bleeding risk apply to these patients.

Both the ESC taskforce for the 2016 guidelines on the management of AF and the EHRA consensus for device-detected subclinical AT recommend using the CHA_2DS_2-VASc score in order to initiate anticoagulation treatment, with similar indications as in AF. Therefore, the ESC taskforce for the 2016 guidelines on the management of AF recommends initiating oral anticoagulation when an AHRE is detected with a duration of more than five to six minutes and an atrial rate of over 180 bpm in male patients with a CHA_2DS_2-VASc score ≥ 1 or in female patients ≥ 2.[57]

The EHRA consensus for device-detected subclinical AT proposes oral anticoagulation based on the same CHA_2DS_2-VASc values in episodes that are ≥ 5.5 hours.[12] However, the same consensus mentions that an AHRE episode of only minutes has a similar stroke risk as one of > 5.5 hours. The question that arises is whether continuous anticoagulation in these patients is necessary. The 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS)-focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with AF recommends further evaluation in patients with AHRE to document clinically relevant AF in order to guide the treatment[56] (Table 3).

Our approach

In CIED patients we interrogate the device at six weeks after a successful implantation procedure to assess the functioning parameters. Afterwards, we interrogate the devices once a year. If an AHRE episode is observed, we ask for an expert opinion (rhythmology specialist) to confirm that the recorded episode is an AHRE instead of an inaccurately labelled (false-positive) recording. Before considering anti-coagulation therapy, we try to verify the presence of AF by one of the following: resting ECG, Holter ECG recording, patient-operated devices or by reviewing the EGM (if available) to determine if the AHRE was AF. We sometimes use external ECG monitoring devices in CIED patients where the data recorded by the device are uncertain.

After we confirm that the recorded episode is in fact AF, we follow the recommendations of the EHRA consensus for CIED-detected arrythmias and initiate lifelong anticoagulation therapy if the episode was longer than 5.5 hours, based on the patient's CHA_2DS_2-VASc score (≥ 1 for male patients, ≥ 2 for female patients).[12]

In patients presenting with multiple short episodes of AHRE (≥ five minutes) we follow the same indication, even though the thromboembolic risk is not as high as in the previous group. We therefore initiate anticoagulation therapy based on the CHA_2DS_2-VASc score (≥ 1 for male patients, ≥ 2 for female patients).[12]

In patients with a single short episode of ≥ five minutes, we follow individualised treatment and patient choice based on the thromboembolic risk (CHA_2DS_2-VASc score) and bleeding risk (HASBLED score). We follow the recommendations of the same consensus and observe the AF burden of the patient on multiple follow ups, usually every three to six months, before initiating lifelong anticoagulation. We initiate anticoagulant therapy in this group, only in patients with a high/very high risk of stroke (CHA_2DS_2-VASc score > 4) and low bleeding risk, in which a clear clinical benefit can be anticipated. We do not usually initiate anticoagulant therapy in patients with AHRE < five minutes, because of the lack of data in the literature regarding this duration. Anticoagulant therapy is initiated in these patients on a case-by-case basis.[12] Our strategy always takes into consideration patient choice and wishes.

Conclusion

AHRE represent a complex arrhythmic entity that significantly increases the thromboembolic risk. Further studies are necessary to understand the underlying pathogenic mechanisms behind AHRE and to guide the management of this arrythmia and its complications.

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Case Report

Severe bradycardia caused by diabetic ketoacidosis

João Ferreira, João Martins, Lino Gonçalves

Abstract

Atrial standstill is an uncommon but serious clinical entity that is often unrecognised in the clinical setting. Its diagnosis and treatment should be swift as malignant arrhythmias and thromboembolic complications can arise. We present a 79-year-old man brought to our emergency department with acute confusion, heart failure and severe bradycardia in the context of diabetic ketoacidosis, and discuss the diagnosis and management of this arrhythmic condition.

Keywords: atrial standstill, electrocardiogram, transthoracic echocardiogram, emergency, bradycardia, diabetic ketoacidosis, medical education

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Case report

A 79-year-old man with a history of hypertension, type 2 diabetes mellitus and known poor therapeutic compliance was brought to our emergency department with acute confusion. A physical examination revealed normal blood pressure (144/65 mmHg), a heart rate of 30 beats/min and tachypnoea on ambient air with normal peripheral oxygen saturation (95%). Lung auscultation showed bilateral basal crackles with concomitant jugular venous distention.

Arterial blood gas analysis showed partially compensated metabolic acidosis (pH 7.312, Pa_{CO_2} 21.5 mmHg and HCO_3 10.6 mmol/l), severe hyperkalaemia (7.89 mmol/l), high serum lactate level (2.5 mmol/l) and hyperglycaemia (849 mg/dl; 47.12 mmol/l). High-sensitivity cardiac troponin was negative (27.9 ng/l). Blood tests also showed acute kidney injury (serum creatinine 3.89 mg/dl).

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The initial electrocardiogram (ECG) revealed no discernible P waves with a slightly irregular bradycardic junctional rhythm (Fig. 1A). Bedside transthoracic echocardiography revealed a preserved left ventricular ejection fraction, moderate mitral regurgitation, mild left atrial enlargement and confirmed absent atrial contraction as there were no A waves on transmitral pulsed-wave Doppler flow (Fig. 2). These findings were suggestive of atrial standstill (AS).

The patient was quickly started on calcium gluconate, furosemide, inhaled salbutamol, intravenous saline and insulin perfusion, restoring normal glycaemic levels. While the metabolic and electrolyte changes were being corrected, and because he had a supra-hissian escape rhythm, the patient was put on isoproterenol infusion in order to treat acute heart failure, mainly caused by new severe bradycardia. The patient successfully returned to sinus rhythm 82 minutes after the first ECG (Fig. 1B).

After the emergency presentation, the patient was hospitalised in the endocrinology ward, where treatment was continued and antidiabetic drugs were optimised. He was discharged symptom free and referred for a cardiology and endocrinology consultation, where he has been followed up with good glycaemic control and no further rhythm disturbances.

Discussion

AS was first described in 1946 by Chavez *et al*.,[1] and is characterised by the complete absence of electrical and mechanical atrial activity. Therefore, the most common ECG pattern associated with this entity is the absence of atrial depolarisation with bradycardic regular junctional or ventricular escape rhythm[2,3] (Fig. 1A). Recognising this ECG pattern is important because secondary causes must be excluded, avoiding unnecessary interventions and non-priority therapies.[4]

AS is usually transient, occurring with digitalis or quinidine intoxication, hypoxia, hyperkalaemia or myocardial infarction. Persistent AS is rare, being reported in association with some types of muscular dystrophies, cardiomyopathies, valvular diseases, congenital heart diseases, Ebstein's anomaly, amyloidosis, acute myocarditis, following open cardiac surgery or after longstanding atrial fibrillation.[4] In this specific case, as the patient did not present any other major causes of AS, severe hyperkalaemia was most likely responsible for the transient AS.

The mainstay of diagnosis of this entity is an electrophysiological study, capable of proving the bilateral absence of atrial electrical activation, and transthoracic echocardiography, through spectral Doppler, showing lack of atrial contraction by the absence of an A wave in transmitral or transtricuspid flow, the absence of atrial contraction in tissue Doppler imaging or the absence of telediastolic mitral valve opening.[5] Also, the lack of an A wave during jugular venous pulse when jugular distension

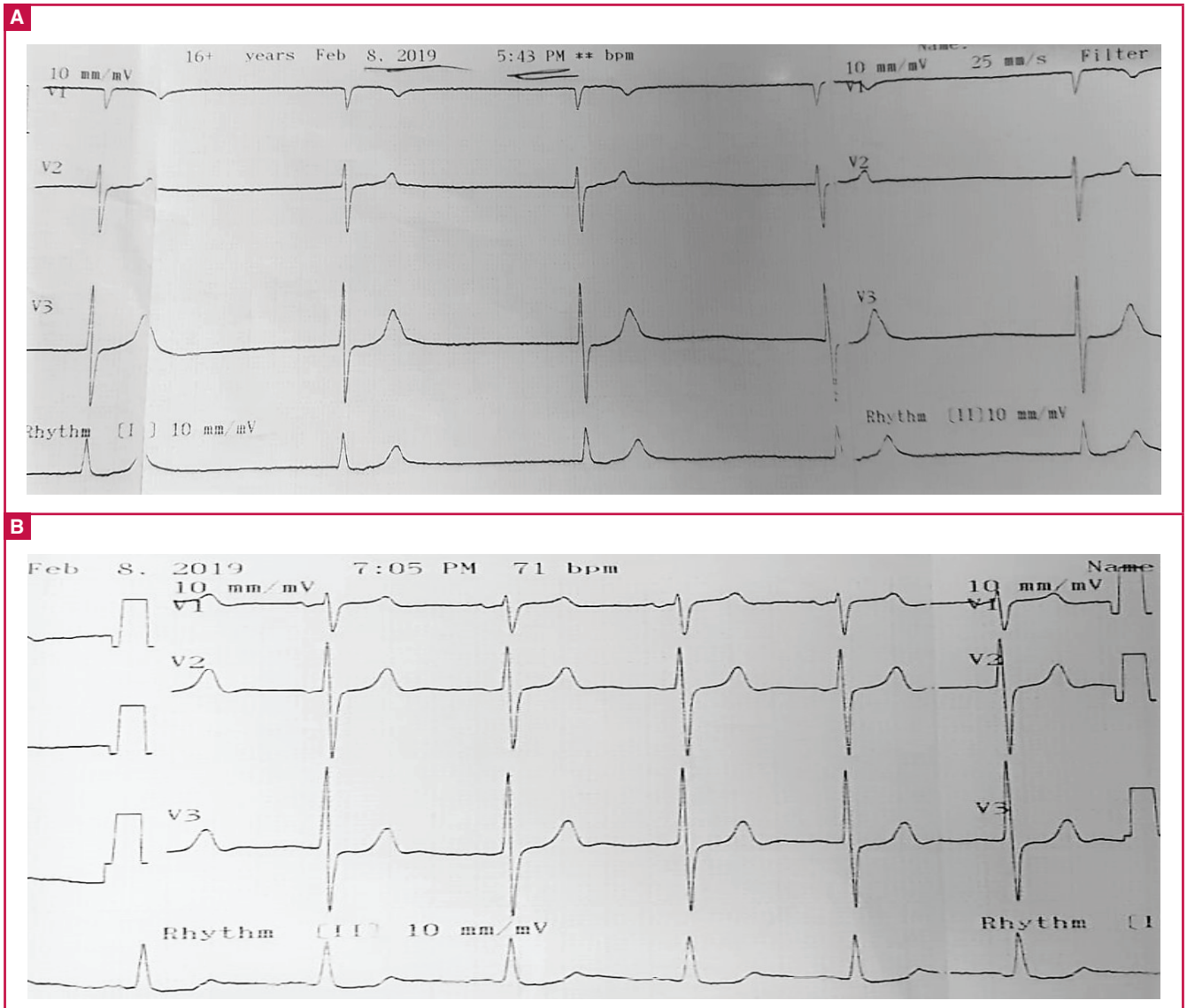

Fig. 1. A: Initial ECG showing slightly irregular junctional rhythm and absence of atrial electrical activity. B: ECG showing sinus rhythm after metabolic and electrolyte correction.

is present, a sign nowadays rarely searched for, is also proof of absent atrial contraction. However, in the emergency setting, a rapid approach to this patient is needed, and diagnosis must be confirmed with ECG, jugular venous pulse observation and transthoracic echocardiography, tools readily available in the majority of emergency departments.

AS can be a serious condition as the loss of active atrial contraction and profound bradycardia can lead to markedly decreased cardiac output. Cardiac arrest can also occur, not only because the escape mechanism can be unstable but also because the bradycardia can be extreme, and pause-related ventricular arrhythmias such as polymorphic ventricular tachycardia can arise.[6] Moreover, blood stasis, originating with no atrial activity, can cause thromboembolic events, as would happen with other arrhythmias such as atrial fibrillation.[2,6]

Treatment of AS depends on clinical consequences and the underlying cause. If the patient shows important signs of heart failure, treatment with diuretics and vasodilators is indicated, as well as positive chronotropic drug infusion, such as isoproterenol, for a limited time as a supportive measure while the underlying condition that gave rise to the AS is corrected.

Temporary transvenous pacing should be deferred and only used as a last resort if chronotropic drugs are insufficient, in cases of a high-degree atrioventricular block without escape rhythm, and for pacing in cases of pause-related ventricular arrhythmias. Temporary transcutaneous pacing should be avoided, as pacing provided by patches and an external defibrillator does not provide reliable ventricular stimulation and should only be used under strict monitoring when no other option is available.[7]

Conclusion

Severe hyperkalaemia in the context of acute kidney injury was the most likely cause of AS in this case. We highlight three learning points: (1) AS is an uncommon but potentially hazardous condition, which can present as a complication of diabetic ketoacidosis; (2) diagnosis of AS can be made with readily available tools in any emergency room, such as ECG and

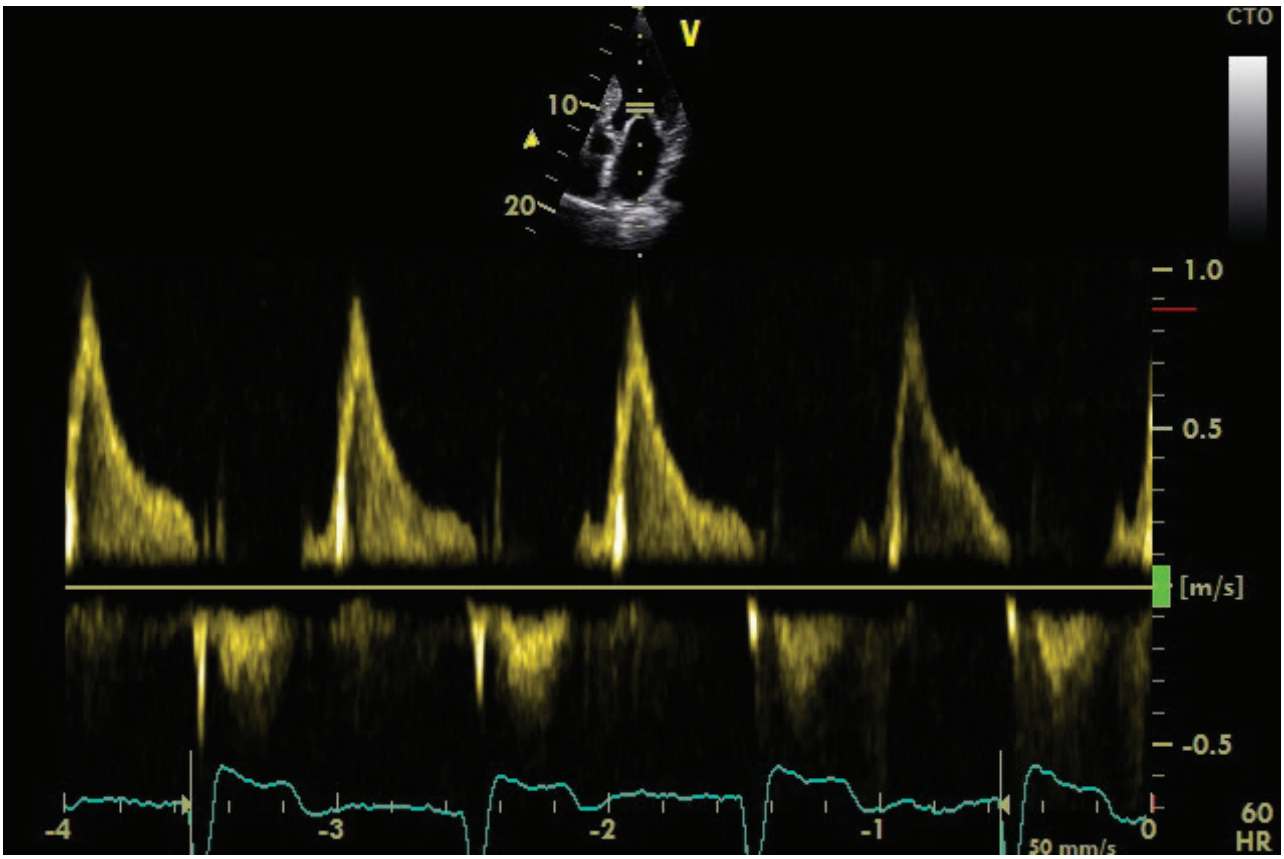

Fig. 2. Transmitral pulsed-wave Doppler imaging after isoproterenol infusion, showing the absence of A waves.

echocardiography; (3) treatment should be prompt and depends on the aetiology of AS, resorting to transvenous pacing only in refractory cases, as AS is usually transient.

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Letter to the Editor

Melatonin against pulmonary arterial hypertension: is it ready for testing in patients?

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Abstract

Pulmonary arterial hypertension (PAH) is a fatal disease defined as a mean pulmonary artery pressure exceeding 25 mmHg when diagnosed with right heart catheterisation. Its pathophysiology involves multiple molecular pathways, including key components leading to an inflammatory and oxidative stress environment that ultimately causes right ventricular hypertrophy and failure. Compared to the developed world, the overall PAH prevalence is higher in developing countries, including Africa, where it is mostly associated with left heart disease, obstructive/restrictive pulmonary disease, HIV and rheumatic heart disease. Current targeted PAH treatments are expensive, not always available in developing countries, and have a limited impact on PAH progression and mortality rate. Therefore, there is an urgent need for effective and affordable medications that can be used as adjunct therapy against PAH in developing countries. Recently, there have been mounting pre-clinical and clinical data suggesting that melatonin may provide health benefits against PAH.

Keywords: pulmonary arterial hypertension, melatonin, adjunctive therapy

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Melatonin (N-acetyl-5-methoxytryptamine) is a hormone present in vertebrates and produced mainly by the pineal gland. Its production is dependent on the day–night cycle, and serum physiological melatonin levels range from 10 to 180 pg/ml, with a peak observed between 02:00 and 04:00.[1] Melatonin exerts multiple cardiovascular benefits that are mediated, at least in part, via its strong anti-oxidant, anti-inflammatory and vasodilatory properties.[2] In patients with pulmonary arterial hypertension (PAH), levels of melatonin are lower than in healthy patients and this negatively correlates with an increase in cytokine levels.[3] Of greater importance, lower levels of melatonin correlate with a worse long-term survival rate of PAH patients.[4]

Pre-clinical data from our group and others have demonstrated that melatonin inhibits PAH progression and ameliorates right ventricular dysfunction.[5-7] It reduces inflammation, pulmonary oedema, structural pulmonary damage, interstitial fibrosis and oxidative stress, pulmonary vascular remodelling and pulmonary vasoconstriction.[5-7] Taken together, pre-clinical and clinical studies advocate a role for melatonin as a safe, affordable, adjunct therapy that may improve PAH and confer cardioprotection in patients.

However, before melatonin is tested in the clinical setting for patients with PAH, we strongly believe that lessons should be learned from previous clinical testing of melatonin in patients with ischaemic heart disease. The MARIA trial showed no effects after melatonin administration, while smaller trials have suggested benefits.[8,9] These inconsistent findings have been attributed to disputable study design and translational errors in the treatment regimen.[10] Nevertheless, we do believe that a clinical study to test melatonin in PAH is feasible and can be effective if properly designed.

Of concern is the high dose of melatonin that is commonly used in both clinical and pre-clinical studies without any rationale for the selection of this dose. These doses (given in the range of 10 mg of melatonin orally or intravenously) increase blood melatonin levels up to 5 000 times higher than physiological concentrations.[11] It is therefore possible that these supraphysiological concentrations may negatively disturb the physiological inflammatory and anti-oxidant balances, thus resulting in the lack of protection.

Interestingly, melatonin is also present in foodstuffs, including fruit, vegetables and wine. Regular and moderate consumption of wine, pineapple, orange or banana all increase serum melatonin levels to physiological values and offer anti-oxidant properties (see review).[12] In a pre-clinical setting, we have been able to demonstrate that chronic oral consumption of melatonin, given at a concentration similar to the amount obtained via the diet by drinking two to three glasses of wine (75 ng/ml given in drinking water), confers cardioprotective benefits against PAH by reducing cardiac interstitial fibrosis, right ventricular hypertrophy and function, and reducing plasma oxidative stress.[7] Most importantly, this protective effect was observed whether melatonin was given prior to the development of the disease or after the PAH was established. This suggests that dietary melatonin may benefit PAH patients whether it is given as a preventative or a curative treatment.[7]

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Although research is still needed to delineate the time of day when melatonin therapy should be given, pre-clinical findings, strengthened by the findings that melatonin levels are lower in patients suffering from PAH, strongly suggest that melatonin, given via a diet rich in melatonin, is worth testing as a safe, simple and inexpensive therapy that could benefit PAH patients, especially in resource-limited settings where patients cannot receive expensive, targeted PAH therapies.

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Even low-dose steroid treatments substantially increase cardiovascular disease risk

While high doses of steroids are known to increase the risk of cardiovascular disease (CVD), the impact of lower doses is unknown. A Leeds University study in *PLOS Medicine* suggests that even low doses of glucocorticoid may increase the risk of CVD.

Why was this study done?

- Glucocorticoids (steroids) are widely used to reduce disease activity and inflammation in patients with a range of immune-mediated inflammatory diseases, such as rheumatoid arthritis, polymyalgia rheumatica, giant cell arteritis and inflammatory bowel disease.
- Adequate assessment of cost-effectiveness of new steroid-sparing treatments for immune and inflammatory diseases requires modelling of estimates of risk and cost of the main treatment complications of steroids.
- It is widely recognised that high-dose steroids may increase the risk of CVD (heart disease, stroke, or other vascular diseases), but it is debated whether this increase also applies to lower steroid doses.
- Earlier studies of CVD risk associated with glucocorticoid therapy failed to account for changes in dose over time and for use of non-oral steroids and other potentially confounding therapies.

What did the researchers do and find?

- In 87 794 adults with immune-mediated inflammatory diseases and no prior CVD (five-year median follow up), we studied the risk of six common CVDs associated with the steroid dose prescribed, quantified either as current or as cumulative dose.
- We found strong dose-dependent risks of all CVDs, including myocardial infarction, heart failure, atrial fibrillation and cerebrovascular disease, in patients diagnosed with the six inflammatory diseases studied.
- After one year, the overall absolute risk of CVD doubled for individuals using less than 5 mg prednisolone per day and was six times higher for users of 25 mg or greater.
- Many individuals had known modifiable cardiovascular risk factors, including current smoking (24%), obesity (25%) or hypertension (25%).

What do these findings mean?

- We have provided evidence that individuals receiving steroids have an increased risk of developing a broad spectrum of fatal and non-fatal CVDs and that this risk increases with the dose of steroids and with the duration of steroid treatment.
- It was previously believed that less than 5 mg of prednisolone was safe long term, but even at this 'low dose' patients with immune-mediated inflammatory diseases have a doubling of their underlying risk of CVD.
- New treatment approaches that avoid the need for long-term steroid treatment and have better cardiovascular safety profile are required for immune-mediated inflammatory diseases.
- All patients requiring long-term steroid treatment should be prescribed the lowest effective steroid dose and have a personalised CVD risk-prevention plan that takes into account current and prior steroid use.

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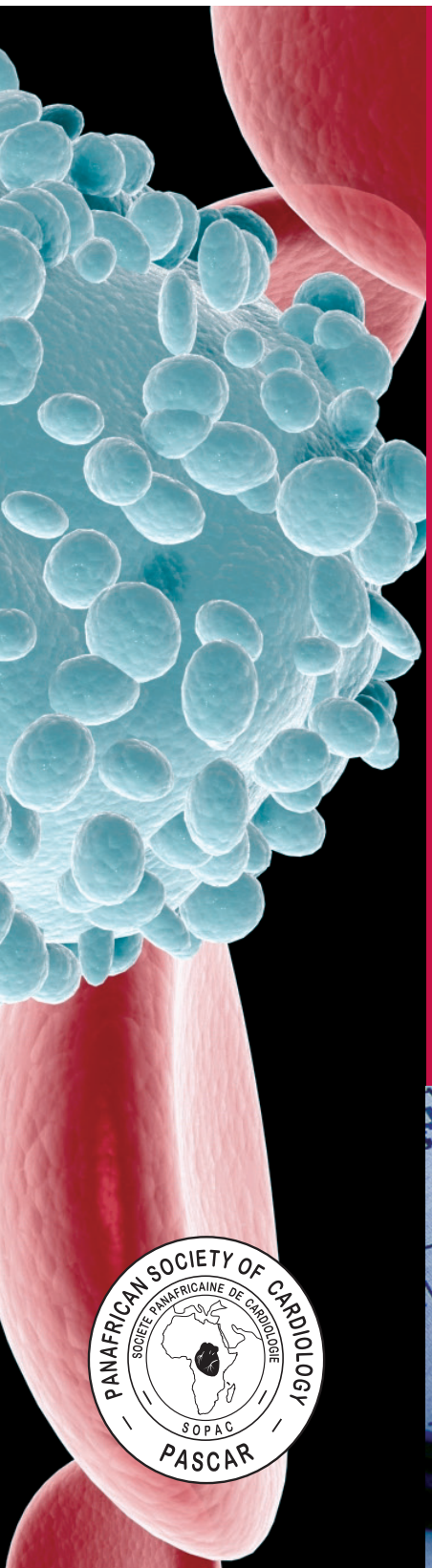

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