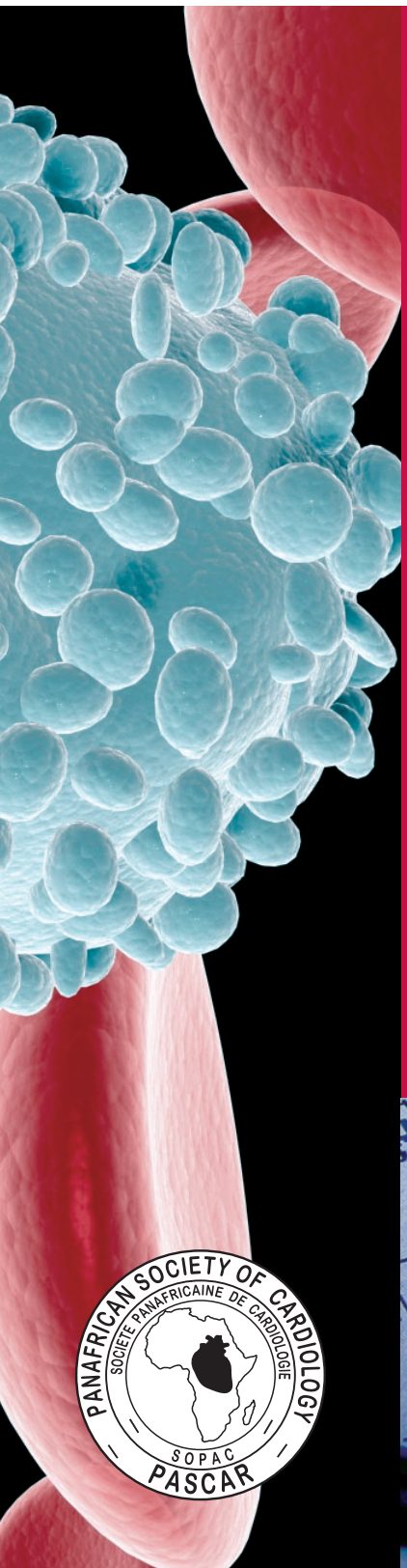
MAY/JUNE 2021
VOL 32 NO 3

CVJ AFRICA

www.cvja.co.za | CardioVascular Journal of Africa (official journal for PASCAR)



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PA1743/05/2021.

ISSN 1995-1892 (print)
ISSN 1680-0745 (online)

CVJ AFRICA

Cardiovascular Journal of Africa | www.cvja.co.za

Vol 32, No 3, MAY/JUNE 2021

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EDITORIAL

CARDIOVASCULAR TOPICS

INDEXED AT SCISEARCH (SCI), PUBMED, PUBMED CENTRAL AND SABINET

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The *Cardiovascular Journal of Africa*, incorporating the *Cardiovascular Journal of South Africa*, is published 10 times a year, the publication date being the third week of the designated month.

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LAYOUT:
Jeanine Fourie – TextWrap

PRINTER:
Tandym Print/Castle Graphics

ONLINE PUBLISHING & CODING SERVICES:
Design Connection & Active-XML.com

All submissions to CVJA are to be made online via www.cvja.co.za

Electronic submission by means of an e-mail attachment may be considered under exceptional circumstances.

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Electronic abstracts available on Pubmed

Audited circulation

Full text articles available on: www.cvja.co.za or via www.sabinet.co.za; for access codes contact elsabe@clinicscardive.com

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South Africa: R490 (incl VAT)
Overseas: $135
Online subscription: R300

Editorial

Costing academic publications: author-pay principle, and manuscript submission and article processing charges

PA Brink

Dataism, an emerging 'religion'! All data should be freely available (explained in *Homo Deus* by Harari). Followers 'believe all good things – including economic growth – depend on the freedom of information.'[1]

So it is with open-access scientific publications – free-to-read medico-scientific research reports on easily accessible sites on the internet. No paywall! With the so-called gold model, which the *Cardiovascular Journal of Africa* (CVJA) incidentally has, this is immediate availability on the day of publication.

The information may be free to the reader. However, there is a cost, one that is born by the author (or institute), the so-called author-pay principle, in contrast to a reader-pay principle. With the traditional reader-pay model, additional means of support are (almost were nowadays) advertising in printed versions (or facsimiles on the journal website), and membership fees of the society that produces a journal. Also, institutional libraries will subscribe to journals. Remember the shelves filled with bound volumes of journals?

In the absence of paper and ink, current web-based publication may be cheaper, but there is still a cost. So, what are authors (or their institutions or benefactors) paying for? Where does the cost lie?[2,3]

A landing site and software is needed to register new manuscripts, track submissions through the review process, allow editors to manage the review process, and maintain a reviewer database: an editorial manager. A system must be in place to take accepted manuscripts and convert them into actual articles that are ready to post. A journal website needs to be maintained and published articles need to be hosted, also for posterity. Servers now replace the shelves in a library to maintain the archives. Lastly, some personnel and utilities, such as electricity and water, need to be paid.

Luckily, with the time-honoured practice where scientists devote free time for reviewing and editing manuscripts, these functions do not add to the costs.

With the author-pay principle, two classes of fees, namely pre- and post-acceptance are of importance. I will discuss one in each class as it pertains to the CVJA, namely, the manuscript-submission fee (MSF, pre-acceptance) and the article-processing charge (APC, post acceptance).

Firstly, it needs to be appreciated that both accepted and rejected manuscripts cost money (excluding time spent by the personnel). The moment the processing is logged with Editorial Manager (EM), the full fee per article is billed by EM, even if it is rejected up front. With a high rejection rate, if only an APC is charged, the cost of publication falls on the small number of accepted manuscripts.

So the MSF decreases competition for review and acceptance[4] where an author may feel the work will not easily be accepted. It also carries some of the cost of the reviewing process. One of the negatives mentioned in the literature is that it may create a bias towards accepting articles, however, the CVJA keeps the fee very modest.

Interestingly, as a model, the take up of open access has been higher in low-income countries, not the developed high-income countries where the concept originated.[5] It may change as major national research agencies and funders from 12 European countries have taken a strong stand with Plan S. This plan mandates that all public-funded research be published in open-access (OA) journals where information is freely available on the date of publication. Even publishing in hybrid journals, journals that are part OA and part propriety, often subscription based, will not be allowed. The reason for maintaining the latter *status quo* is that some highly esteemed journals still attract subscriptions or are supported by membership fees of a society.[3]

This edition sees an increase in the APC to R7 200. The MSF, which is modest, remains the same, at R1 000.

Cost was and always has been an issue, even in the days of Sir Isaac Newton, as recounted in chapter 10 of the most comprehensive biography about him.[6] Realising the explosive importance of Isaac Newton's work on the orbits of planets and the mathematics that goes with it, Edmund Halley, of Halley's comet fame, saw to it and funded one of the most influential publications ever, *Philosophiæ Naturalis Principia Mathematica* (1687).

The Royal Society could not help as it had nearly bankrupted itself publishing a book on fishes, *Historia piscium* (The History of Fishes). This nearly crippled the society and the recently wedded Halley couple. Halley was paid by the Royal Society with 50 exemplars of the *Historia piscium*! But one cannot eat books!

Some consolation, he had a comet named after him! Realising that a particularly bright comet historically kept coming back to earth, he calculated a 76-year cycle using principles expounded by Newton. His prediction of its reappearance in 1758 was correct.

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Cardiovascular Topics

Analysis of risk factors for thrombosis of the left atrium/left atrial appendage in patients with non-valvular atrial fibrillation

He Du, Ke Bi, Lisha Xu, Feng Chen, Wenfeng Xiong, Yin Wang

Abstract

Objectives: Left atrial appendage (LAA) morphology is a powerful predictor of thrombogenesis of the left atrium (LA) in patients with non-valvular atrial fibrillation (NVAF). However, it remains unknown whether LAA morphology is useful for stroke risk stratification in patients with NVAF.

Methods: A total of 555 atrial fibrillation patients were divided into thrombus and non-thrombus groups according to transoesophageal echocardiography. We analysed the correlation between LAA morphology and the $CHADS_2$ score. We determined the L_2CHADS_2 score and compared the ability to predict LA/LAA thrombosis of the $CHADS_2$, L_2CHADS_2 and CHA_2DS_2-VASc scores from the area under the curve (AUC).

Results: The odds ratio of non-chicken wing LAA morphology was 11.48. Non-chicken wing LAA morphology was significantly correlated with LA/LAA thrombosis. We incorporated LAA morphology into the $CHADS_2$ score and named it the L_2CHADS_2 score. The AUC of the L_2CHADS_2 score (0.767) in predicting LA /LAA thrombosis was significantly higher than that of the $CHADS_2$ (0.558) or CHA_2DS_2-VASc scores (0.557). The positive and negative predictive values of the L_2CHADS_2 score (13.1 and 98.7%) were higher than those of the $CHADS_2$ (8.7 and 94.2%) and CHA_2DS_2-VASc scores (6.9 and 6.9%).

Conclusions: Non-chicken wing LAA morphology was a powerful predictor of LA/LAA thrombosis in NVAF patients. The AUC, sensitivity and specificity of the L_2CHADS_2 score were higher than those of the $CHADS_2$ and CHA_2DS_2-VASc scores.

Keywords: atrial fibrillation, thrombus, stroke, left atrial appendage morphology

Submitted 30/6/19, accepted 28/12/19
Published online 16/4/21
Cardiovasc J Afr 2021; **32**: 116–122 www.cvja.co.za

DOI: 10.5830/CVJA-2019-071

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Atrial fibrillation (AF) is one of the most common arrhythmias, which is an independent risk factor for stroke. It is estimated that AF incidence will double by 2035.[1-3] The most valuable evaluation systems for stroke are the $CHADS_2$ and CHA_2DS_2-VASc scores, but the risk factors these scoring systems utilise are relatively limited and less than half of all known possibilities. This means that some important risk factors have not been defined, such as low creatinine clearance rate, increased left atrial (LA) diameter, non-chicken wing left atrial appendages (LAA) and persistent AF.[1,3,4]

As early as 1909, Welch proposed that cardiac stroke associated with AF was mainly caused by emboli originating from a LAA thrombus.[4,5] Previous research has shown that LAA morphology has a close relationship with thrombosis, with the type with obvious bending in the main lobe less likely to form thrombus. In 2010, Wang *et al*. first divided LAA morphology into four types, namely chicken wing, cauliflower, cactus and windsock, in order to guide LAA closure.[6] Di Biase *et al*. then reported that these different LAA morphologies are associated with stroke or transient ischaemic attack (TIA). They also pointed out that the chicken wing LAA morphology (which has an obvious bend in the main lobe) is less likely to form thrombus compared with other LAA morphologies.[7] These discoveries have attracted extensive attention.

In 2013, Kimura *et al*. found that cauliflower LAA was the main predictor of stroke/TIA in non-valvular atrial fibrillation (NVAF) patients with low $CHADS_2$ scores, and the results of multivariable logistic regression analysis suggested that cauliflower LAA was an independent risk factor for stroke or TIA (OR: 3.4; 95% CI: 1.243–9.055; $p = 0.017$).[8] These studies

revealed that LAA morphology has a close relationship with stroke.

The LAA is the main site for thrombosis in NVAF patients, and LAA morphology affects the incidence of stroke. In this study, we sought to determine whether LAA morphology could predict the formation of LA/LAA thrombus in patients with NVAF.

Methods

This study was a retrospective review of transoesophageal echocardiography (TEE) and electronic clinical records.[9] The ethics committee of Changhai Hospital approved the study protocol and written informed consent was obtained from all patients before enrollment.

We searched the TEE databases of Changhai Hospital for patients undergoing consecutive TEE imaging between 2010 and 2016 while in drug-refractory NVAF undergoing catheter ablation or cardioversion. Excluded NVAF patients were those taking warfarin with an international normalised ratio (INR) ≥ 1.5, subjects injecting low-molecular weight heparin subcutaneously, taking heparin intravenously or taking new anticoagulants, and those with chronic kidney disease, malignant tumour, connective tissue disease, valvular heart disease or hyperthyroidism. Patients were also excluded if they had rheumatic valve disease or a history of mitral valve repair or mechanical valve implantation. Finally, 555 patients were selected for analysis in this study.

All NVAF patients were divided into two groups, a thrombus and a non-thrombus group, according to TEE. The thrombus group had a thrombus or a change of 'mud' in the LA/LAA, and the non-thrombus group had no changes in the LA/LAA.

LAA imaging was obtained using 320-channel cardiac CT angiography (Toshiba Aquilion ONE) with volume-rendering post-processing technology (using the Vitrea Enterprise Suite) to reconstruct its three-dimensional structure. The atria were divided into chicken wing, cauliflower, cactus and windsock types[10] by two experienced cardiac CT radiologists blinded to the other clinical data. Each morphological classification represented a consensus decision by both radiologists. No statistically significant bias was detected in the classification of the LAA by the radiologists.

The $CHADS_2$ and CHA_2DS_2-VASc scores were calculated for each patient. The $CHADS_2$ score includes risk factors for the presence of congestive heart failure, hypertension, diabetes, age ≥ 75 years, stroke or TIA. In addition to stroke or TIA (which confers two points), the presence of the other risk factors adds one point to this score. The CHA_2DS_2-VASc score is modified by the addition of further risk factors for stroke such as vascular disease, age 65–74 years and being female.[11]

In order to compare the ability of the two scoring systems ($CHADS_2$ and CHA_2DS_2-VASc) to predict LA/LAA thrombus, we graded and grouped all patients with the three scoring systems. A score of zero, one and two points or more were utilised to define low-, intermediate- and high-risk groups, respectively, and we then compared the intermediate group score to that of the other groups.[12]

Renal dysfunction was defined as a low estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. The eGFR is calculated using the abbreviated Modification of Diet in Renal Disease Study equation:

$$eGFR\ (ml/min/1.73\ m^2) = 186.3 \times [serum\ creatinine\ (mg/dl)]^{-1.154} \times age\ (years)^{-0.203}\ (or\ if\ female \times 0.742).$$[13]

TEE is currently the gold standard for diagnosis of LA/LAA thrombosis.[14] Before a LA/LAA thrombosis develops, the blood in the LA/LAA manifests two dynamic changes, 'smoke' and 'mud'. During the smoke phase, spontaneous ultrasound imaging of the LA reveals dynamic swirling (or smoke-like) echo signals when imaged at optimal gain settings.[15] Mud signals (Fig. 1A) on TEE reveal a mass structure that is relatively clear with a gelatinous appearance.[16] Thromboembolism (Fig. 1B) is visualised through multiple angles as a discrete mass from multiple windows and the mass is independent of the endocardium and pectinate muscles.[17] Generally TEE can identify a thrombosis larger than 2 mm. In our study we categorised mud and thrombosis images as LA/LAA thrombus-positive. Images without LA/LAA mud or thrombus were classified as negative for clots (Fig. 1C).

LAA morphology was classified on the basis of the number of bends in the lobes, the location of origin from the LA and the number of lobes.[18] The radiologists who interpreted the CT images were blinded to the history of the patients, to minimise the risk of bias.

Chicken wing LAA consists of a main lobe and has an obvious bend in the middle or on the base of the main lobe, or the LAA main lobe has an anatomical fold towards the direction of the LAA openings. This LAA morphology usually has secondary lobes or twigs.

In the cauliflower LAA there is usually no main lobe, but there are secondary lobes of varied number among individuals and with limited length. This LAA morphology usually has a complex internal structure. Because of the large variability in morphology, the LAA ostia have less regularity and could be oval or round.

The cactus LAA morphology mainly has a dominant central lobe with secondary lobes extending in both superior and inferior directions. The windsock LAA has a long main lobe with a variety of possible morphologies related to the location and number of secondary or even tertiary lobes (Fig. 2).[10]

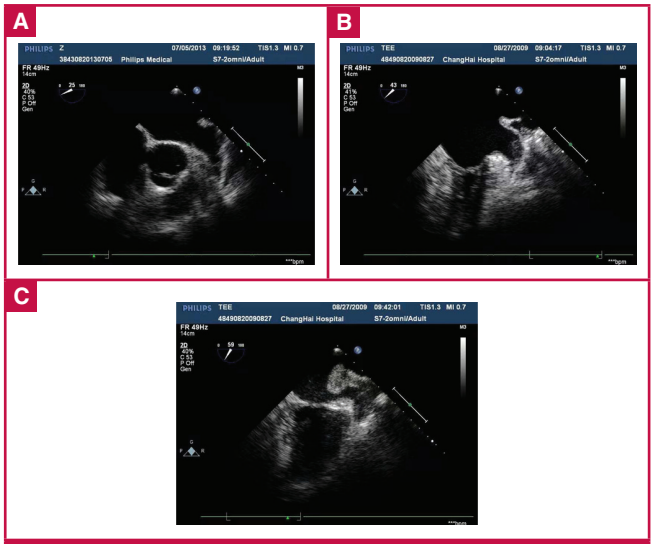

Fig. 1. Spontaneous ultrasound imaging of different changes of blood in the LA/LAA. A: with mud variation in the LAA, B: with thrombus variation in the LAA, C: without mud or thrombus variation in the LAA.

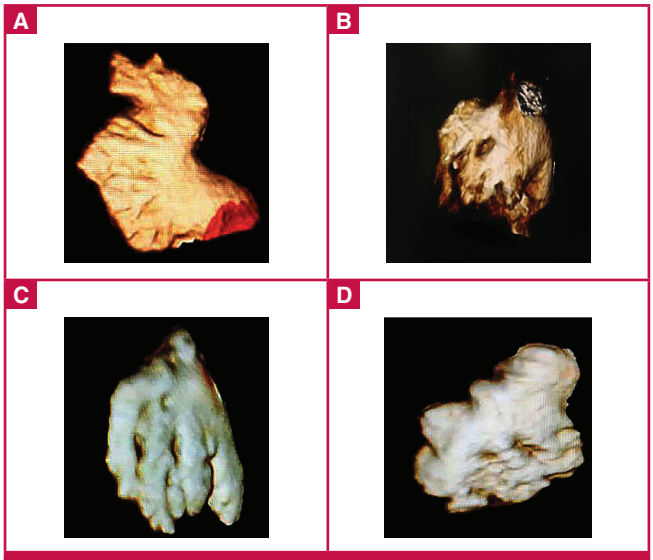

Fig. 2. Four types of LAA morphology. A: chicken wing LAA, B: cauliflower LAA, C: cactus LAA, D: windsock LAA.

Statistical analysis

We used SPSS 17.0 software for data analysis. Continuous variables are expressed as mean (minimum and maximum) values, and if they were normally distributed with homogeneity of variance, the statistical analyses were performed using the Student's *t*-test. If they were not normally distributed, the Wilcoxon rank-sum test was used. Count data are shown with ratios, and were performed with the chi-squared test. Stepwise multivariate logistic regression was used to screen for related risk factors for LA/LAA thrombosis, to devise a new scoring system denoted as the L_2CHADS_2 score, and to calculate a receiver operating characteristic (ROC) curve. This approach was used to contrast this L_2CHADS_2 value with that of the $CHADS_2$ and CHA_2DS_2-VASc scores in predicting LA/LAA thrombosis through the AUC, sensitivity and specificity. A p-value < 0.05 was considered statistically significant.

Results

A total of 555 NVAF patients were recruited, of whom 35 were classified into the thrombus group and 520 into the non-thrombus group. Baseline demographics, clinical characteristics and LAA measurements of patients with and without LA/LAA thrombosis are shown in Table 1. There were no differences in age and gender, $CHADS_2$ and CHA_2DS_2-VASc scores, windsock LAA morphology, prevalence of hypertension, diabetes, stroke/TIA and vascular disease, and lipoprotein(a) levels between the thrombus and non-thrombus groups. There were significant differences between the two groups in brain natriuretic peptide (BNP), D-dimer and fibrinogen levels, eGFR, outside and inside diameter of the LAA, LAA volume, LA diameter, chicken wing, cactus and cauliflower LAA morphology, history of heart failure and renal dysfunction.

Patients with cauliflower or cactus LAA morphology were more likely to have thrombosis (p < 0.001 or < 0.01). In contrast, patients with chicken wing LAA morphology were less likely to have LA/LAA thrombosis (p < 0.001). Eighty and 28.1% of the patients with non-chicken wing LAA were distributed in the thrombus and non-thrombus groups, respectively, and the difference was statistically significant (p < 0.001).

A regression model was built by adding all the covariates listed in Table 1. The results of multivariate logistic regression analysis (Table 2) showed that D-dimer (OR: 1.74; 95% CI: 1.073–2.807; p = 0.025), BNP (OR: 3.00; 95% CI: 1.709–9.677; p = 0.002), LA diameter (OR: 4.07; 95% CI: 1.709–9.677; p = 0.002), non-persistent AF (OR: 5.14; 95% CI: 1.911–13.818; p = 0.001) and non-chicken wing LAA (OR: 11.48; 95% CI: 4.157–31.684; p = 0.000) were independent risk factors for LA/LAA thrombosis.

Table 1. Comparison of general data and related clinical data between the thrombus and non-thrombus groups

Characteristic	*Overall*	*Thrombus group*	*Non-thrombus group*	*c²/t/Z*	*p-value**
No of patients	555	35	520		
Age, years (SD)	59.1 (19–85)	59.8 (34–78)	59.1 (19–85)	0.368	0.713
< 65, *n* (%)	375 (67.6)	24 (68.6)	351 (67.5)	0.017	0.896
65–74, *n* (%)	148 (26.7)	9 (25.7)	139 (26.7)	0.017	0.895
≥ 75, *n* (%)	32 (5.8)	2 (5.7)	30 (5.8)	0.000	0.989
Male/female, *n* (%)	211/344 (38/62)	13/22 (37.1/62.9)	198/322 (38.1/61.9)	0.012	0.912
Hypertension, *n* (%)	265 (47.7)	17 (48.6)	248 (47.7)	0.01	0.92
Diabetes, *n* (%)	66 (11.9)	6 (17.1)	60 (11.5)	0.983	0.321
Heart failure, *n* (%)	33 (5.9)	7 (20)	26 (5)	13.19	0.003
Stroke/TIA, *n* (%)	23 (4.1)	2 (5.7)	21 (4)	0.232	0.63
Vascular disease, *n* (%)	21 (3.8)	2 (5.7)	19 (3.7)	0.382	0.536
Renal dysfunction (eGFR < 60 ml/min/1.73 m²), *n* (%)	21 (3.8)	6 (17.1)	15 (2.9)	18.312	0.000
AF type (persistent AF), *n* (%)	92 (16.6)	20 (57.1)	72 (13.8)	44.45	0.000
$CHADS_2$ score (SD)	0.81 (0–5)	1 (0–3)	0.8 (0–5)	–1.24	0.215
$CHADS_2$ score ≥ 2, *n* (%)	92 (16.6)	8 (22.9)	84 (16.2)	1.07	0.302
CHA_2DS_2-VASc score (SD)	1.52 (0–7)	1.77 (0–5)	1.51 (0–7)	–1.16	0.25
CHA_2DS_2-VASc score ≥ 2, *n* (%)	248 (44.7)	17 (48.6)	231 (44.4)	0.288	0.633
Fibrinogen, g/l (SD)	3.00 (0.07–6.89)	3.47 (2.05–6.17)	2.97 (0.07–6.89)	–2.74	0.006
D-dimer, mg/ml (SD)	0.44 (0.07–6.89)	3.46 (2.05–6.17)	2.97 (0.07–6.89)	–3.02	0.003
eGFR, ml/min/1.73 m² (SD)	98.6 (5–125.2)	86.7 (17.8–125.2)	99.3 (5–125)	–3.62	0.000
Lipoprotein (a), mg/dl (SD)	18.1 (1–96)	18.9 (3–75)	18.1 (1–96)	–0.85	0.39
BNP, pg/ml (SD)	72.9 (4–1560)	235 (27–1560)	62 (4–1070)	–6.86	0.000
LA diameter, mm (SD)	3.11 (1.6–7.5)	4.19 (2.10–7.50)	3.04 (1.60–5.50)	–6.9	0.000
Outside diameter of LAA, mm (SD)	1.67 (0.60–3.90)	1.88 (0.90–3.90)	1.66 (0.60–3.40)	–2.67	0.008
Inside diameter of LAA, mm (SD)	1.94 (0.90–25.00)	2.12 (1.40–4.10)	1.96 (0.90–25.00)	–3.21	0.001
LAA volume, ml (SD)	6.73 (1.00–41.00)	9.49 (3.00–41.00)	6.55 (1.00–26.00)	–3.76	0.000
Chicken wing LAA, *n* (%)	377 (67.9)	7 (20)	370 (71.2)	39.3	0.000
Non-chicken wing LAA					
Windsock LAA, *n* (%)	62 (11.2)	7 (20)	55 (10.6)	2.934	0.096
Cactus LAA, *n* (%)	104 (18.7)	13 (37.1)	91 (17.5)	8.309	0.007
Cauliflower LAA, *n* (%)	12 (2.2)	8 (14.3)	4 (0.8)	37.6	0.000

Values depicted for *n* are mean (minimum and maximum) or percent. TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation; BNP, brain natriuretic peptide; LA, left atrium; LAA, left atrial appendage. *Comparison between thrombus and non-thrombus groups.

Table 2. Multivariate OR for LA/LAA thrombosis

Variable	*Hazard ratio*	*95% CI*	p-*value*
D-dimer	1.735	1.073–2.807	0.025
BNP (pg/ml)	3.002	1.683–5.355	0.000
LA diameter	4.066	1.709–9.677	0.002
Non-persistent AF	5.139	1.911–13.818	0.001
Non-chicken wing LAA	11.476	4.157–31.684	0.000

BNP, brain natriuretic peptide; LA, left atrium; LAA, left atrial appendage.

In multivariable logistic regression analysis (Table 2), non-chicken wing LAA was found to have the highest OR, at 11.48. The $CHADS_2$ risk score is the most popular risk stratification tool used,[19] so we further analysed the correlation between LAA morphology and the $CHADS_2$ score.

Among the thrombus group in subjects with a $CHADS_2$ score of zero or one point, the chicken wing LAA had the lowest prevalence. The non-chicken wing LAA was significantly more prevalent in the thrombus group compared with the chicken wing morphology (85.2 vs 14.8%). In the non-thrombus group with a $CHADS_2$ score of two points or more, the chicken wing LAA had the highest prevalence, which was significantly more prevalent in the non-thrombus group compared with the non-chicken wing morphology (65.5 vs 34.5%). The prevalence of cauliflower LAA was highest (66.7%), followed by cactus and windsock LAA, with the chicken wing LAA the lowest (1.9%) (Table 3).

We hypothesised that LAA morphology might be useful for predicting LA/LAA thrombosis in NVAF patients, especially when incorporating it with the $CHADS_2$ score. We therefore endowed the non-chicken wing LAA morphology with two points (the highest score) and derived the L_2CHADS_2 score based on the $CHADS_2$ score. The L_2CHADS_2 score was composed of a total of six risk factors, namely, congestive heart failure, hypertension, diabetes, age ≥ 75 years, history of stroke or TIA and chicken wing LAA. The chicken wing LAA and a previous stroke/TIA would confer two points and the other four risk factors could each add one point. Therefore the highest possible score was eight points and the lowest was zero.

According to their $CHADS_2$ scores, 12 (34.3%) and 15 (42.9%) subjects were classified as zero and one point, respectively, namely low- and intermediate-risk categories (Fig. 3). The corresponding classification with the CHA_2DS_2-VASc score was four (11.4%) and 14 (40%) subjects. The two scoring systems had a lower prevalence of subjects above two points, namely the high-risk category. It was only with the L_2CHADS_2 score that the percentage of subjects classified in each category increased along with the score and most of the subjects were distributed between two points or more.

Table 3. LAA morphology and risk of LA/LAA thrombus in the thrombus group with a $CHADS_2$ score of zero or one point, in the non-thrombus group with a $CHADS_2$ score of two points or more, and thrombosis ratio of chicken wing and non-chicken wing LAA morphology

		Non-chicken wing (%)		
Variable	*Chicken wing (%)*	*Windsock (%)*	*Cactus (%)*	*Cauliflower (%)*
Thrombus group ($CHADS_2$ score 0 or 1 point)	14.8		85.2	
Non-thrombus group ($CHADS_2$ score 2 points or more)	65.5		34.5	
Thrombosis ratio	1.9	11.4	12.5 15.7	66.7

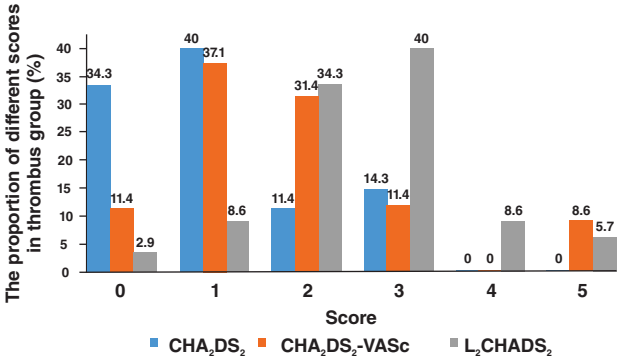

Fig. 3. Prevalence (percentage) of patients classified in each score according to the $CHADS_2$, CHA_2DS_2-VASc and L_2CHADS_2 risk-stratification schemes in the thrombus group.

The incidence of thrombosis in the $CHADS_2$ and CHA_2DS_2-VASc scores showed an increasing trend with the scores increasing gradually (Fig. 4). The L_2CHADS_2 score increased more obviously and the thrombosis incidence was obviously higher than that of the $CHADS_2$ and CHA_2DS_2-VASc scores in the high-risk group.

Using a score ≥ one, one and two as cut-off points for the $CHADS_2$, CHA_2DS_2-VASc and L_2CHADS_2 scores, respectively, their sensitivity and specificity were 0.657 and 0.427, 0.886 and 0.225, and 0.886 and 0.225, respectively; the AUC was 0.558, 0.557 and 0.767, respectively. The AUC of the L_2CHADS_2 score in predicting LA/LAA thrombosis was obviously higher than that of the $CHADS_2$ and CHA_2DS_2-VASc scores, which had similar predictive power.

These results confirmed that the L_2CHADS_2 score was superior to the $CHADS_2$ and CHA_2DS_2-VASC scores for prediction of the development of LA/LAA thrombi. The positive and negative predictive values of the L_2CHADS_2 score (13.1 and 98.7%) were higher than those of the $CHADS_2$ (8.7 and 94.2%) or CHA2DS2-VASc scores (6.9 and 6.9%) (Fig. 5).

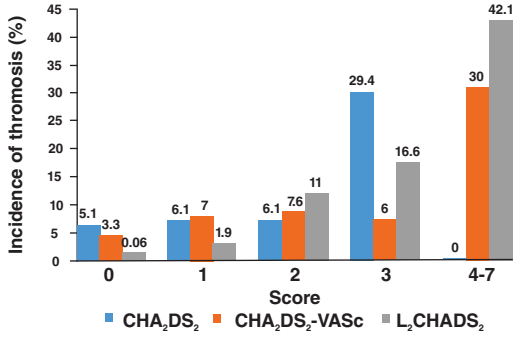

Fig. 4. Prevalence (percentage) of LA/LAA thrombosis in each score according to the $CHADS_2$, CHA_2DS_2-VASc and L_2CHADS_2 risk-stratification schemes.

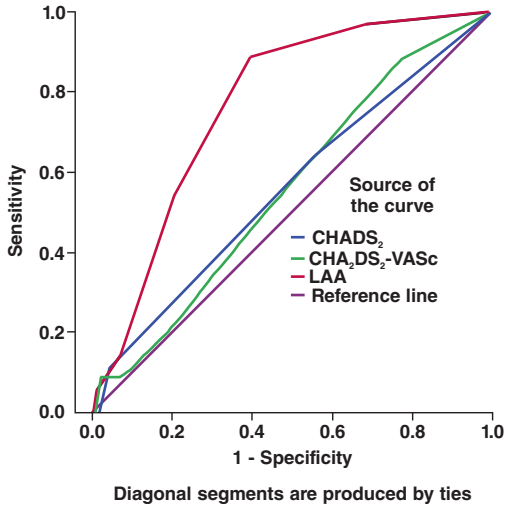

Fig. 5. Receiver operating characteristic (ROC) curves for the prediction of LA/LAA thrombus by the $CHADS_2$, CHA_2DS_2-VASc and L_2CHADS_2 risk-stratification schemes. AUC, area under the curve.

Discussion

To the best of our knowledge, this is the first study to incorporate LAA morphology into a modified $CHADS_2$ score, leading to the L_2CHADS_2 risk score (L with two points). We compared the predictive accuracy of the $CHADS_2$, CHA_2DS_2-VASc and L_2CHADS_2 scores in predicting thromboembolic events in patients with NVAF. The main findings were as follows: (1) LAA morphology was closely related to LA/LAA thrombus; (2) the L_2CHADS_2 score could reliably predict LA/LAA thrombi, and the L_2CHADS_2 score was superior to the $CHADS_2$ and CHA_2DS_2-VASc scores in predicting LA/LAA thrombosis.

AF is an independent risk factor for thromboembolic stroke and peripheral emboli. One of the key steps in preventing stroke associated with AF is effective risk stratification to guide decision making with regard to the need for anticoagulant therapy.[20] The $CHADS_2$ score is commonly used for this risk stratification in patients with AF. The CHA_2DS_2-VASc score was recommended by the European Society of Cardiology and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines in 2012 and 2014, respectively, for stroke risk stratification in NVAF patients.[21-23] However, these two score systems have been criticised.[19]

Yarmohammadi *et al*.[24] reported in a substudy of the ACUTE trial that the $CHADS_2$ score could not reliably predict embolic risk in patients with NVAF because 10% of the patients ranked with zero points had LA thrombi. Fruhauf *et al.*[25] also reported a case involving a NVAF patient who had $CHADS_2$ and CHA_2DS_2-VASc scores of zero points; this patient then developed recurrent LAA thrombi after radiofrequency catheter ablation. Therefore, although the current stroke risk-stratification schemes appear to be practical, they still have some defects and limitations.

We found that patients with non-chicken wing LAA morphology had a significantly higher risk of LA/LAA thrombosis compared with chicken wing morphology. The chicken wing morphology was the most common LAA form (67.9%) in our population and the least associated with a history of LA thrombosis, which was in accordance with the Di Biase *et al.* studies.[7] To date, there have been no data incorporating LAA morphology into stroke risk stratification.

Our data indicated that LAA morphology remained the most powerful independent predictor of LA/LAA thrombosis with multivariable regression analysis (OR: 11.48; 95% CI: 4.157–31.684; p = 0.000). According to Clark *et al*., the $CHADS_2$ risk score was the most commonly used scoring system for the evaluation of stroke risk.[19] We found that there were 27 subjects (77.1%) with a $CHADS_2$ score of zero or one in the thrombus group but they all developed a LA/LAA thrombus. Of these 27 individuals, 23 (85.2%) had non-chicken wing LAA and only four (14.8%) had chicken wing LAA. Moreover, there were 84 subjects (16.2%) with a $CHADS_2$ score of two points or more in the non-thrombus group. In these 84 cases, 55 (65.5%) had chicken wing LAA and 29 (34.5%) had non-chicken wing LAA. This suggested that LAA morphology might be useful for predicting the risk of thromboembolism in NVAF patients with low and high $CHADS_2$ scores (Tables 1, 3). We therefore incorporated LAA morphology (L with highest points of two) into the $CHADS_2$ score, leading to the L_2CHADS_2 risk score.

The utility of the L_2CHADS_2 score for predicting risk of systemic emboli, as indicated by the results of the AUC calculation, was higher than that of either the $CHADS_2$ or CHA_2DS_2-VASc scores. These results indicated that the L_2CHADS_2 score was superior to either the $CHADS_2$ or the CHA_2DS_2-VASc scores for predicting LA thrombus formation. The $CHADS_2$ score had high specificity but poor sensitivity (Fig. 5). This led to missed opportunities for anticoagulant therapy for a majority of patients with a high risk of stroke. The CHA_2DS_2-VASc score increased the sensitivity at the cost of reducing specificity to 0.225. This observation was in agreement with the USA[26] and Portuguese[27] TEE and European clinical outcomes studies.[11,28-30] On the other hand, compared to the $CHADS_2$ score, the L_2CHADS_2 score had higher sensitivity and specificity (0.427 and 0.606, respectively). These observations suggested that the L_2CHADS_2 score could identify 'truly low-risk' patients without sacrificing overall predictive ability. Therefore the findings were consistent in showing the advantage of the L_2CHADS_2 risk score.

The risk for stroke may be balanced by the risk of bleeding, which can be a deadly complication in patients with NVAF who are treated with anticoagulants.[23] The 2016 AHA/ACC guidelines pointed out that patients with NVAF and a CHA_2DS_2-VASc score of one point, taking aspirin or anticoagulant drugs or not taking any medications (Class IIb, C), had similar outcomes. That is to say, the clinical decision making is still controversial in patients with intermediate risk.[31] The $CHADS_2$ score has been criticised for categorising a great number of patients with NVAF as intermediate risk.[32] Compared with the $CHADS_2$ score, the CHA_2DS_2-VASc and L_2CHADS_2 scores placed a smaller percentage of patients in the intermediate-risk group; there was a reduction to 43 (18.8%) and 73 (31.9%) patients, respectively. Because the L_2CHADS_2 score reduced these percentages to a greater extent, utilising it may reduce uncertainties about the benefits of anticoagulant therapy in patients with intermediate risk.

Our data revealed that for NVAF subjects who had LA thrombus on TEE, more than two-thirds developed these clots despite having a low $CHADS_2$ score of zero or one point. This suggested that a high proportion of patients with high risk of

stroke would not receive anticoagulant therapy. This number was surprisingly high and raised questions about the use of the $CHADS_2$ score as an independent risk-stratification tool. However, with the development of the L_2CHADS_2 scale, only four subjects (11.4%) with a zero or one point score developed a LA/LAA thrombus. There were 231 (44.4%) subjects with a CHA_2DS_2-VASc score of two points or more, but these patients did not have a LA/LAA thrombus. This means that almost half of these patients would have unnecessarily been exposed to oral anticoagulation. In contrast, use of the L_2CHADS_2 score would have minimised this number and reduced the risks of haemorrhage from unnecessary anticoagulant therapy.

Compared to the $CHADS_2$ and CHA_2DS_2-VASc score, the thrombosis incidence in the low- and intermediate-risk subjects, retrospectively identified by the L_2CHADS_2 score, was significantly lower, and in the high-risk group it was significantly higher. This was in accord with the expectations of a thromboembolic risk-stratification system, with higher scores predicting higher incidence of LA/LAA thrombosis. Risk scores based on the $CHADS_2$ and CHA_2DS_2-VASc scales had obvious limitations in our study. It therefore supported the use of modified risk scores and the need for further prospective studies on risk stratification in patients with NVAF.

The R_2CHADS_2 score posits that renal dysfunction is an important predictor of stroke and peripheral embolism in NVAF patients with intermediate and high stroke risk, and is based on the ROCKET-AF and ATRIA stroke risk studies proposed in 2013.[33,34] But in our study, a significant independent effect of renal dysfunction on LA/LAA thrombus was not documented, and so the relationship between them was not explored further. The results of the present study indicated that we could improve the accuracy of LA/LAA thrombus prediction if we simultaneously considered LAA morphology. In addition, renal dysfunction, a significant risk factor for bleeding, was added to the R_2CHADS_2 scoring scheme that is intended to estimate the risk of thromboembolic events and guide antithrombotic therapy, which may not be appropriate.

The causes and mechanisms of atrial thrombi are not completely equivalent for every patient with NVAF, so the benefits of anticoagulant therapy may depend on the potential stroke risks themselves, and therefore the risk/reward ratio of different people may need comprehensive assessment to make optimal decisions regarding anticoagulant therapy. This is one reason why it can be relatively difficult to make decisions about the use of anticoagulation in patients with NVAF. Therefore, if we could develop objective criteria to assess the risk of stroke in NVAF patients and guide the use of anticoagulants in this population, it would be a good step forward.

Study limitations

This was a single-centre retrospective study of a limited number of NVAF patients, with only 35 having LA/LAA thrombus. In addition, the patients with NVAF in the study were refractory to pharmacotherapy. Their general physical condition was relatively good and they could tolerate radiofrequency ablation or cardioversion. Even in those with a history of stroke, the symptoms were mild and prognoses good, so the present results cannot be extrapolated to the overall patient population with NVAF. Because this was a retrospective study, it may have been affected by recall bias and it was difficult to select reasonable controls. Therefore, larger prospective studies would be needed to verify the conclusions. Finally, although TEE has high sensitivity and is the gold-standard test for LA/LAA clots, it cannot discern thrombi less than 2 mm and therefore may produce false negative findings.

Conclusions

This study suggests that LAA morphology is a powerful predictor of thrombus formation and possible subsequent arterial embolic events in patients with NVAF. Compared with the $CHADS_2$ and CHA_2DS_2-VASc schemes, the L_2CHADS_2 score developed here has the advantage of identifying 'truly low-risk' patients without sacrificing overall predictive ability. It can provide insights into the value of the L_2CHADS_2 score for the management of patients with NVAF, which are novel and could prove to be clinically very relevant. Of course, further prospective clinical studies on the relationship of the L_2CHADS_2 score to outcomes in larger populations of NVAF patients will be needed before its widespread adoption in the world.

This work was supported by grants from 2018 Supporting Project of Medical Guidance (Chinese and Western Medicine) of Science and Technology Commission of Shanghai Municipality (18411966700).

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Comparison of the improvement of flow-mediated dilatation in patients with acute coronary syndrome versus stable angina after six-month cardiac rehabilitation

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Abstract

Background: We investigated whether the improvement in endothelial function, measured using flow-mediated dilatation (FMD), an important predictor of cardiovascular outcomes, was comparable in acute coronary syndrome (ACS) versus stable angina patients after percutaneous coronary intervention (PCI) and a six-month cardiac rehabilitation (CR) programme.

Methods: We analysed the results from 119 patients who completed a six-month CR programme after successful PCI for stable angina (n = 50) and ACS (n = 69).

Results: After six months of CR, the results of FMD were significantly improved in both groups. There were no significant between-group differences in the FMD results at the six-month follow up.

Conclusion: After successful PCI and a six-month CR programme, FMD values were equally improved in both stable angina and ACS patients.

Keywords: coronary disease, exercise training, endothelial function

Submitted 8/11/18, accepted 23/6/20
Published online 8/6/21
Cardiovasc J Afr 2021; **32**: 123–128 www.cvja.co.za

DOI: 10.5830/CVJA-2020-022

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Clinical results for cardiac rehabilitation (CR) for secondary prevention indicate that CR can reduce cardiovascular risk and event rates, foster healthy behaviours and promote active lifestyles.[1-5] The recent major evidence-based guidelines from the American Heart Association and the American College of Cardiology Foundation for the management and prevention of coronary heart disease provides a class 1 level recommendation for referral to a CR programme for patients with recent myocardial infarction (MI) or acute coronary syndrome (ACS). Referral to a CR programme is also recommended for patients with chronic stable angina, heart failure, and for patients after coronary artery bypass surgery or percutaneous coronary intervention (PCI).[2]

Impaired endothelium-dependent vasodilatation has been linked to the pathogenesis of atherosclerotic vascular disease. Endothelial dysfunction is an independent predictor of future cardiovascular events in patients with cardiovascular disease. The structural integrity of the endothelium is compromised in patients with atherosclerosis. Endurance exercise training improves nitrous oxide (NO) activity, oxidative stress, inflammation and insulin resistance results.[6-8]

Both invasive and non-invasive methods have been used for the evaluation of endothelial function, and flow-mediated dilatation (FMD) is one of the accepted techniques used to assess endothelial function.[7,9,10] An abnormal FMD result is associated with an increased coronary event risk in patients with established coronary heart disease.[6,8,11] However, only a limited number of studies have been performed that evaluate the effects of CR on the endothelial function of patients after coronary revascularisation, and that compare the improvement in endothelial function in patients with ACS or stable angina.

We investigated whether the improvement in endothelial function, measured using FMD, was comparable in patients with ACS or stable angina after PCI and a six-month CR period.

Methods

This was a single-centre registry study involving 119 patients who had received CR after successful PCI for coronary artery disease from January 2014 to June 2015. Only the patients who had completed the planned CR programme after PCI were enrolled in this study. This study was approved by the local institutional review board.

Patients were excluded from the case series if they dropped out of the CR programme, or if they had a history of prior myocardial revascularisation, high degree of atrioventricular (AV) block, severe aortic stenosis, systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg at rest, left

ventricular ejection fraction 30%, pericarditis, cardiomyopathy, ST-segment depression > 2 mm at rest, uncontrolled tachycardia, exercise-induced malignant ventricular arrhythmia, acute systemic illness, skeletal vascular disease, or acute metabolic disorders. Patients who refused to provide informed consent for the exercise programme were excluded from both groups.

Each patient completed a six-month CR programme that began with an out-patient CR session, which was held within two weeks of the index PCI. The exercise training programme and CR comprised two stages as follows: the first stage consisted of six weeks of prescribed supervised exercise and the second stage of community-based and self-managed exercise for the remaining 28 weeks. Patients were required to visit the cardiac rehabilitation clinic at least twice a month. The second stage could be extended to six months depending on medical judgement or at the patient's request.

Cardiorespiratory capacity was measured twice using a symptom-limited exercise-tolerance treadmill test (ETT). The measurements were performed before the commencement, and at the end of the first six weeks of supervised exercise training. The ETT was conducted on the first day that the patient visited the CR clinic after discharge, using a modified Bruce protocol: we measured oxygen uptake during peak exercise (VO_{2peak}), exercise time, resting heart rate (HR), peak HR, resting blood pressure (BP), peak BP, rate pressure product (RPP), peak respiratory exchange ratio (RER: the ratio of VCO_2 over VO_2; the magnitude of the peak RER roughly reflects the effort expended by the patient at peak exercise), and the rate of perceived exertion (RPE). The exercise test was supervised by experienced physicians.

A real-time recording 12-channel electrocardiograph (Q4500; Quinton Instrument Co, Boston, MA, USA), respiratory gas analyser TrueOne 2400 metabolic measurement system (Parvo Medics Inc, East Sandy, UT, USA), an automatic blood pressure and pulse monitor Model 412 (Quinton Instrument Co), and a treadmill MedTrack ST55 (Quinton Instrument Co) were used for the ETT.

All tests were terminated according to the American Heart Association (AHA) termination criteria and the patients were instructed about the termination of the ETT before the test. When the test was close to the end, patients were encouraged to endure the test and to stop only when experiencing intolerable dyspnoea, unless there was an event that met the ETT termination criteria in the AHA guidelines.

The patients initially participated in six weeks of prescribed, supervised exercise. Exercise intensities of 40 and 85% HR reserve were calculated using the Karvonen formula: [(maximal HR – resting HR × % intensity) + resting HR], based on the results obtained during the first ETT.

The CR programme was composed of 10 minutes of warm up (stretching), 40 minutes of main aerobic exercise, and 10 minutes of cool down, three times a week for six weeks, for a total of 18 sessions. Following the completion of the six-week CR programme, the ETT was performed again. The VO_{2peak}, ETT time, resting HR, peak HR, resting BP, peak BP, RER, RPP and RPE were measured again during the second ETT.

After the six-week supervised exercise period, the community-based, self-managed exercise was performed based on the results of the reassessed cardiorespiratory capacity for the remaining period. The patients were required to exercise at a local fitness centre and maintain aerobic exercise on a treadmill or bicycle ergometer. Every exercise training session was required to be one hour in length and was to be performed three times per week.

The FMD was measured within two weeks of the PCI, and was followed up at six months after the initiation of the CR programme. Endothelial function (endothelium-dependent brachial artery FMD) was measured as previously described.[10,12,13] Briefly, each patient arrived at the laboratory at a similar time of day (8:00–9:00). Patients were required to fast, avoid exercise and smoking, and to avoid consumption of alcohol or anti-oxidant vitamins, for at least 12 hours before the test.

The FMD was measured by a single ultrasonographer who was blinded to the subject's clinical status. After a 10-minute equilibration period, the measurement was taken in the right arm while the patient was in the recumbent position in a temperature-controlled room (22°C). Using an 11–3-MHz linear array (L11-3) transducer connected to a Philips iE33 (Philips Medical Systems, Andover, MA, USA) echocardiography machine, the brachial artery was longitudinally imaged approximately 5 cm proximal to the antecubital crease, at the point at which the clearest image was visible. The skin surface was marked when a reasonable image was obtained. The arm and the ultrasound probe were kept in the same position by the ultrasonographer throughout the study.

A pneumatic cuff was placed distal to the imaged artery, and baseline scans for the assessment of the resting vessel diameter and flow were recorded. The occluding cuff was then inflated to > 50 mm Hg above the systolic blood pressure value for five minutes, and the diameter was measured 30 seconds before cuff deflation. After deflation, the arterial diameter was measured at 60 and 90 seconds in order to determine the maximum post-occlusive reactive hyperaemia diameter. An electrocardiogram was monitored continuously and blood pressure was recorded each minute in the left arm throughout the test.

Statistical analysis

Depending on the distribution, the data are expressed as mean and standard deviation (SD) values or as median values with interquartile ranges. Categorical variables were compared using the χ^2 test. Continuous variable data were compared within groups using the paired Student's *t*-test, and between groups using the unpaired Student's *t*-test. A two-tailed *p*-value < 0.05 was considered to indicate a statistically significant result. All clinical and laboratory data were analysed using SPSS software (version 25.0).

Results

Of the 119 patients, 69 presented with ACS and 50 with stable angina. Table 1 presents a summary of the results of the subjects' clinical characteristics. The mean age of the patients was 54.9 ± 9.1 years, and the patients in the ACS group were slightly younger than those in the stable-angina group (52.9 ± 9.1 vs 57.6 ± 8.5 years, respectively, $p = 0.050$). There were no between-group differences in the distributions of males, hypertension, diabetes, dyslipidaemia or smoking. A greater percentage of patients in the ACS group took angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and beta-blockers, compared to the stable-angina group patients. All the patients in both groups received statin and dual anti-platelet therapy.

Table 1. Baseline characteristics by clinical presentation

Variables	*Total* (n = *119*)	*Stable angina* (n = *50*)	*ACS* (n = *69*)	p-*value*
Age (years)	54. 9 ± 9.1	57.6 ± 8.5	52.9 ± 9.1	0.050
Male, *n* (%)	104 (87.4)	41 (82.0)	63 (91.3)	0.131
BMI (kg/m²)	24.9 ± 2.6	24.9 ± 2.5	24.9 ± 2.7	0.887
Hypertension, *n* (%)	38 (31.9)	19 (16.0)	19 (22.0)	0.227
Diabetes, *n* (%)	36 (30.3)	15 (30.0)	21 (30.4)	0.959
Dyslipidaemia, *n* (%)	39 (32.8)	16(32.0)	23 (33.3)	0.878
Current smoker, *n* (%)	55 (46.2)	18 (36.0)	37 (53.6)	0.057
Medication				
ACEI/ARB, *n* (%)	71 (59.7)	23 (46.0)	48 (69.6)	0.010
β-blockers, *n* (%)	85 (71.4)	29 (58.0)	56 (81.2)	0.006
Calcium antagonist, *n* (%)	21 (17.6)	16 (32.0)	5 (7.2)	< 0.001
Nitrate, *n* (%)	72 (60.5)	27 (54.0)	45 (65.2)	0.086
SBP (mmHg)	119.9 ± 12.1	121.8 ± 10.6	118.5 ± 12.9	0.145
DBP (mmHg)	70.3 ± 13.4	71.8 ± 12.4	69.2 ± 14.2	0.304
Heart rate (beat/min)	65.8 ± 8.9	63.9 ± 8.0	67.1 ± 9.4	0.069

Data are expressed as numbers (%) and means ± SD. ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

The FMD results at baseline and at six months after the initiation of CR are presented in Table 2 and Fig. 1. At baseline, the FMD values were lower in the patients with ACS than in those with stable angina, but the mean difference was not statistically significant (7.6 vs 8.2%, respectively, p = 0.180) (Table 2) (Fig. 1). However, after six months of CR, the FMD was significantly improved in both groups (1.3% increase in the ACS group and 1.0% increase in the stable-angina group, p = 0.002). There were no significant differences in the FMD results at the six-month follow up in the patients with ACS compared to the patients with stable angina (9.2 vs 8.9%, respectively, p = 0.61).

The results for cardiopulmonary exercise testing and the echocardiographic parameters are presented in Table 2. The results for the VO_{2max}, maximal metabolic equivalent (MMET), maximal respiratory exchange ratio (max RER) and exercise duration were similar in both groups. After the six-month CR programme, the VO_{2max} was improved in both groups (Table 2) (Fig. 2); the VO_{2max} increased 2.1 ml/kg/min (0.8–3.4, p = 0.003) more in patients with stable angina and 2.6 ml/kg/min (1.1–4.2, p < 0.001) more in ACS patients at six months compared to the baseline value of each group. The baseline left ventricular (LV) systolic function was better in the stable-angina patients compared to the ACS patients (59.4 ± 10.2 vs 43.6 ± 13.3%, respectively, p < 0.001). Additionally, a greater improvement in LV systolic function occurred in the ACS group compared to the stable-angina group, although the difference was not statistically significant.

The results for the changes in biochemical parameters after the end of the CR programme period are presented in Table 3.

Table 2. Changes in FMD, cardiopulmonary exercise testing and echocardiographic parameter results after a CR programme

	Total		*Stable angina*		*ACS*	
Parameters	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
FMD (%)	7.9 ± 2.6	9.0 ± 2.3**	8.2 ± 2.7	9.2 ± 2.1*	7.6 ± 2.5	8.9 ± 2.4*
Exercise duration (min)	15.3 ± 2.6	16.0 ± 2.7	15.0 ± 2.5	16.3 ± 2.1**	15.4 ± 2.7	15.8 ± 3.0
MMET	8.3 ± 1.9	9.1 ± 2.2**	8.2 ± 2.0	8.8 ± 1.9*	8.5 ± 1.8	9.3 ± 2.4**
Max RER	1.1 ± 0.1	1.2 ± 0.1*	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1*
VO_{2max} (ml/kg/min)	29.2 ± 6.6	31.9 ± 7.9**	28.6 ± 6.9	30.9 ± 6.7**	29.6 ± 6.4	32.5 ± 8.5**
LVEF (%)	48.7 ± 21.1	49.7 ± 19.6	59.4 ± 10.2	59.9 ± 13.7	43.6 ± 13.3‡	46.2 ± 16.3‡

Data are expressed as numbers (%) and means ± SD. ACS, acute coronary syndrome; FMD, flow-mediated dilatation; LVEF, left ventricular ejection fraction; max RER, maximal respiratory exchange ratio; MMET, maximal metabolic equivalent.
Baseline versus six months; *p < 0.05, **p < 0.01, stable angina versus ACS; †p < 0.05, ‡p < 0.01.

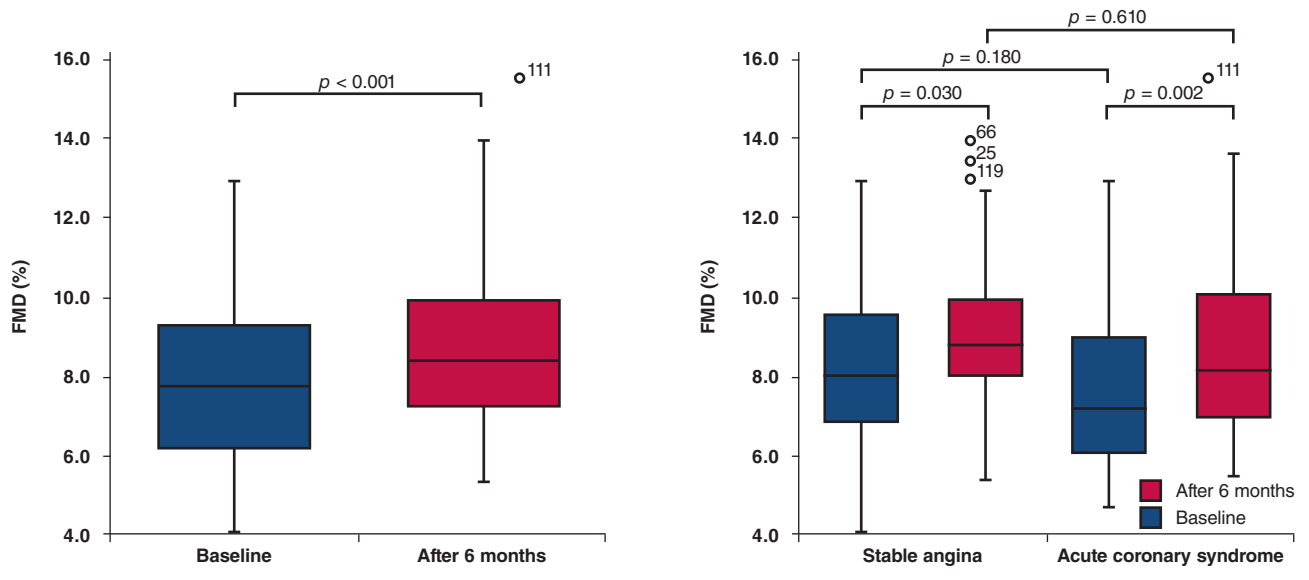

Fig. 1. Changes in FMD before and after a six-month CR programme. A. All patients. B. Patients with stable angina versus ACS.

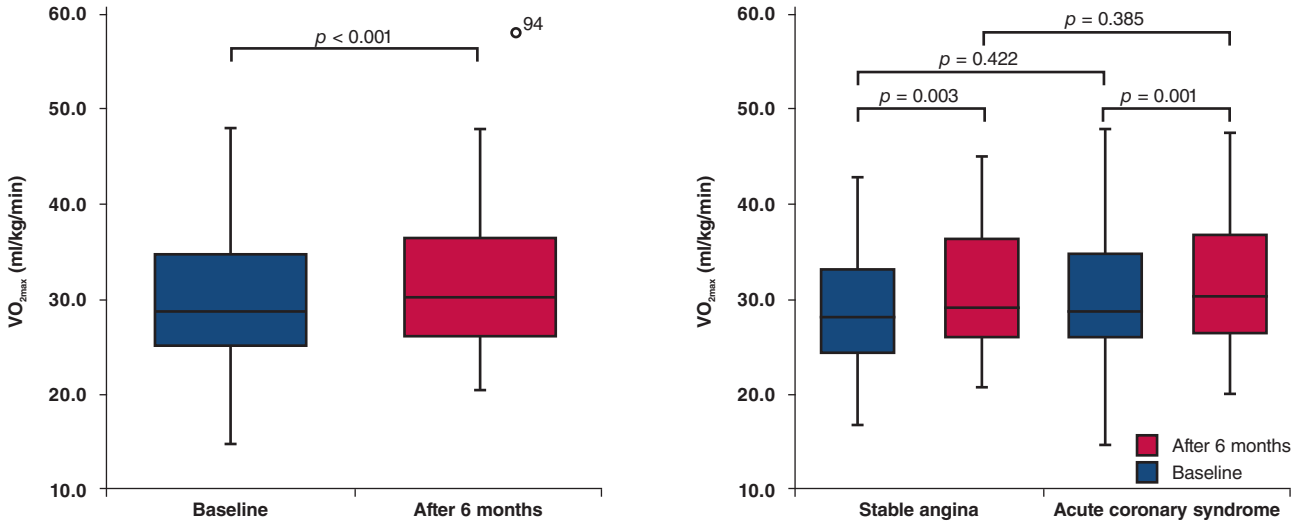

Fig. 2. Changes of VO_{2max} before and after a six-month CR programme. A. All patients. B. Patients with stable angina versus ACS.

The mean concentration of high-sensitivity C-reactive protein (hs-CRP) at baseline was significantly higher in the ACS group than in the stable-angina group (1.21 ± 3.73 vs 0.49 ± 1.46 mg/dl, respectively, $p = 0.023$). However, six months after the initiation of the CR programme, the mean hs-CRP concentration was significantly decreased in both groups and was not significantly different between groups (0.21 ± 0.39 vs 0.24 ± 0.49 mg/dl, respectively, $p = 0.989$). The target goal for the mean low-density lipoprotein (LDL) cholesterol concentration (88.0 ± 28.5 mg/dl; 2.28 ± 0.74 mmol/l) for the ACS group was not reached despite efforts, such as high-intensity statin therapy, used to control it.

Discussion

In this study we showed that endothelial function, measured by FMD, was improved in patients with coronary artery disease who underwent PCI, regardless of ACS or stable angina after a six-month CR programme. However, there was no significant difference in the improvement of the FMD values between the two groups. The ACS patients tended to have lower FMD values before CR, compared to the patients with stable angina.

Endothelial function is an 'excellent barometer' of vascular health and can be used to gauge cardiovascular risk.[9] A pathogenic link between coronary endothelial dysfunction and cardiovascular events was found almost simultaneously by Suwaidi *et al.*[11] and Schächinger *et al.*[8] The FMD result reflects the relaxation of a conduit artery when it is exposed to increased flow and increased shear stress.[14]

Numerous studies have documented the various effects of cardiac rehabilitation on cardiovascular disease. In 2004, Hambrecht *et al.* reported that when patients with stable coronary artery disease participated in a 12-month programme of regular physical exercise, they had superior event-free survival and exercise capacity, and at lower cost, compared to patients treated with PCI.[15] Many investigators have used FMD to evaluate the post-CR improvement in endothelial function in patients with coronary heart disease. Morikawa *et al.* suggested that exercise training improves endothelial dysfunction in patients with coronary spastic angina, and they found a significant correlation between the reduction in attack frequency and the improvement in FMD.[4]

Recently, Ades *et al.* found that there was a dose–response relationship between weight loss and endothelial-dependent FMD in patients with serious coronary heart disease who participated in a CR programme.[1] Weight loss and exercise in overweight patients resulted in a significant improvement in FMD. Their results suggested that the best predictor of the improvement in FMD is weight loss per se, rather than related measures, such as changes in fat mass, visceral fat, waist circumference or insulin sensitivity.[1] The initial mean body mass index (BMI) of their study population was 32.3 ± 4.1 kg/m^2, which was larger than that of our study population (24.9 ± 2.6 kg/m^2). However, we found that there was an improvement in FMD values after exercise training, even though most of the

Table 3. Changes in biochemical parameters after a CR programme

	Total		*Stable angina*		*ACS*	
Parameters	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
hs-CRP	0.87 ± 2.90	0.23 ± 0.44*	0.49 ± 1.46	0.21 ± 0.39*	1.21 ± 3.73†	0.24 ± 0.49*
HDL-C	42.4 ± 8.9	40.4 ± 8.0*	44.7 ± 8.9	41.8 ± 8.3*	40.7 ± 8.6†	39.4 ± 7.8*
LDL-C	116.9 ± 30.7	82.7 ± 24.7**	115.3 ± 31.2	74.3 ± 13.8**	118.2 ± 30.5	88.0 ± 28.5**‡
HbA_{1c} (%)	6.5 ± 1.5	6.5 ± 1.4	6.2 ± 1.1	5.7 ± 0.4	6.6 ± 1.7	6.8 ± 1.6

Data are expressed as numbers (%) and means ± SD. ACS, acute coronary syndrome; hs-CRP, high sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Baseline versus six months; *$p < 0.05$, **$p < 0.01$, stable angina versus ACS; †$p < 0.05$, ‡$p < 0.01$.

patients had a normal-weight BMI value. Therefore, our results are different from those of Ades *et al*. in that the endothelial function could be improved after exercise training, irrespective of the initial BMI value. A similar effect occurred in both of our patient groups.[1]

The high-density lipoprotein (HDL) cholesterol level might have decreased in both groups because we used high-intensity statin treatment to reduce LDL cholesterol levels. The change in the HDL cholesterol level was statistically significant, but decreased only by a small amount (2 mg/dl; 0.05 mmol/l). We do not suggest that this change was clinically significant and we should have applied more effort to reduce the LDL cholesterol level of the ACS group so that the target goal could be achieved.

The VO_{2max}, MMET, exercise duration and FMD results were improved at six months in each group, but there were no statistically significant between-group differences in these parameters. One reason for these results might be that the patients with severe heart failure [left ventricular ejection fraction (LVEF) 30%] were excluded from the ACS group.

Limitations

Our study had several limitations. First of all, we did not perform the comparison analysis between the patients who performed CR versus those who did not. Furthermore, this study was a retrospective study and we analysed registry data that included only patients who had received CR after PCI; therefore, the FMD data of patients who did not receive CR or PCI were unavailable. In addition, there was a significant difference in the patients' age and the use of ARBs or ACEIs; these differences were considered to affect atherosclerosis and endothelial function between the two groups. Despite these differences, the FMD values were improved in both groups when compared to the baseline, and this improvement was similar between the two groups. On the other hand, many previous studies have shown that cardiac rehabilitation has a benefit in improving endothelial function in patients with coronary events, and our study was performed based on these previous results.

Second, we measured FMD while the patients received standard medical treatment for ischaemic heart disease, including ARBs or ACEIs, beta-blockers and statins; these treatments could have affected the FMD results. However, we performed the examination under the same conditions for both groups, at baseline and six months after CR was initiated. Therefore, we suggest that the improvement in FMD after the six-month CR programme was independent of the drugs taken by the patients. Compared to other study populations, patients who had relatively less-serious disease could be enrolled in this study. Therefore, patients with unstable angina might have been included in the stable-angina patient group.

Third, except for seven ST-elevation myocardial infarction (STEMI) patients, PCI was performed via the subject's right arm, followed by measuring the FMD on the right arm within two weeks. In a recent study, Heiss *et al*. suggested that trans-radial catheterisation leads to dysfunction, not only of the radial artery, but also upstream of the brachial artery; they suggest that FMD should be interpreted with caution after trans-radial catheterisation.[16] Therefore, if we had measured FMD using the patients' left arm, we would have been able to see a little more clearly that the FMD improved.

Our study results did not suggest that there were improvements in LVEF as the FMD increased, especially in the ACS group. We also found no beneficial effect with regard to clinical outcome by improving the FMD result. The study duration was six months, which was a relatively short period of time. Patients with less-severe disease and a small number of patients were enrolled in the study. No major adverse cardiac event occurred during the six-month CR period. A long-term follow-up period of one year or more would be required to determine whether the improvements in FMD would affect the LVEF and clinical outcomes.

Conclusion

This study revealed that the FMD was equally improved after a successful PCI and a six-month CR programme for both ACS and stable-angina patients. The ACS patients tended to have a lower FMD before CR, compared to the patients with stable angina. Therefore, it is suggested that the endothelial function might be improved after planned CR in patients who received PCI, irrespective of whether they had ACS or stable angina.

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Telemonitoring may cut heart attack, stroke by 50%: five-year study

People enrolled in a pharmacist-led telemonitoring programme to control high blood pressure were about half as likely to have a heart attack or stroke compared to those who received routine primary care, according to research.

Researchers, led by study author Dr Karen L Margolis, executive director of research at HealthPartners Institute in Minneapolis, found that a heart attack, stroke, stent placement or heart failure hospitalisation occurred in 5.3% of the telemonitoring group versus 10.4% of the routine primary-care group.

'Home blood pressure monitoring linked with treatment actions from the healthcare team delivered remotely (telehealth support) in between office visits has been shown to lower blood pressure more than routine care, and patients really like it,' said Margolis. 'In addition, by avoiding serious cardiovascular events over five years, our results indicate significant cost savings.' Patients reported that they liked having support from a trusted professional, rapid feedback and adjustments to their treatment, and having someone to be accountable to.

Margolis reports that over five years, the savings from reduced cardiovascular disease events exceeded the telemonitoring intervention costs by $1 900 per patient. 'The findings were just short of statistical significance,' said Margolis, 'meaning they could have been due to chance. However, we were surprised that the figures on serious cardiovascular events pointed so strongly to a benefit of the telemonitoring intervention,' she said.

Uncontrolled high blood pressure is the largest modifiable risk factor contributing to death from all causes. Nearly half of US adults have high blood pressure, defined as equal to or greater than 130 mmHg systolic, or 80 mmHg diastolic. However, most adults with high blood pressure don't have their numbers under control.

Four hundred and fifty participants with uncontrolled high blood pressure were enrolled in the study, conducted at 16 primary-care clinics within the HealthPartners system in Minnesota. Participants were blinded and randomised to two groups: 222 patients were in the routine primary-care group, and 228 in the telemonitoring group that also received one year of remote care managed by a pharmacist. In the telemonitoring group, patients were able to measure their blood pressure at home and send it electronically to the pharmacist, who then worked with them to make medication and lifestyle changes in their treatment.

In clinic visits for all participants, researchers monitored blood pressure at enrolment, six months, 12 months, 18 months and five years; kept track of any heart attacks, strokes, coronary stents, heart failure hospitalisations and heart-related deaths that occurred; and counted all the costs of their blood pressure-related care and cardiovascular event care.

They found that in the telemonitoring group, there were 15 serious cardiovascular events (five non-fatal heart attacks, four non-fatal strokes, five heart failure hospitalisations, one cardiovascular death) among 10 patients. This group also had two stent placements, making the total event rate 5.3%.

In the routine primary-care group, there were 26 serious cardiovascular events (11 non-fatal heart attacks, 12 non-fatal strokes, three heart failure hospitalisations) among 19 patients. They also had 10 stent placements, making the total event rate 10.4%.

Based on these findings, 'widespread adoption of the telemonitoring model might help US adults with uncontrolled high blood pressure avoid serious cardiovascular events and reduce healthcare costs,' according to Margolis and colleagues. They recommend future studies to figure out how to increase the number of patients engaged in home blood pressure monitoring over many years, and to measure cardiovascular risk factors and cardiovascular events over that extended period.

The study's limitations are its relatively small size, and it was at a single medical group's urban and suburban primary-care clinics, which may not represent the diversity of patients who receive care in other settings across the country.

Source: *MedicalBrief* 2020

A comparison of two different management plans for patients requiring both carotid endarterectomy and coronary artery bypass grafting

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Abstract

Background: Carotid endarterectomy (CEA) is a prophylactic operation that is used to mitigate the risk of stroke caused by embolism of atherosclerotic plaques in the carotid bifurcation. Previously, the large, multicentre, randomised, controlled GALA study found no significant differences in clinical outcomes between patients treated using general or local anaesthesia. While this study provided important insights into disease outcomes based on treatment modalities, it did not answer questions regarding the safety of CEA under local anaesthesia in patients at high risk for cardiovascular complications. Here, we examined the use of two different management plans in patients requiring both carotid endarterectomy and coronary artery bypass grafting (CABG), in terms of their effects on hospital mortality.

Methods: Thirty-four patients consecutively operated on in our cardiovascular department were included in this analysis. The patients were divided into two groups based on the anaesthetic management plan. The first group consisted of patients who underwent CEA and CABG under general anaesthesia in the same session (GA group); the second group consisted of patients who initially underwent CEA under cervical block anaesthesia followed by CABG under general anaesthesia in a separate session (CB-GA group). These two groups were compared in terms of postoperative complications and hospital mortality.

Results: The incidence of postoperative myocardial infarction was higher in the CB-GA group, with four patients experiencing postoperative myocardial infarction, compared to no patients in the GA group.

Conclusion: For patients requiring CEA and CABG, performing both operations under general anaesthesia in the same session was safer than initially performing CEA under cervical block anaesthesia followed by CABG under general anaesthesia.

Keywords: carotid endarterectomy, cervical block anaesthesia, general anaesthesia, coronary artery bypass grafting

Submitted 15/6/20, accepted 14/9/20
Published online 16/3/21
Cardiovasc J Afr 2021; **32**: 129–132 www.cvja.co.za

DOI: 10.5830/CVJA-2020-042

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Carotid endarterectomy (CEA) is a prophylactic operation that is used to mitigate the risk of stroke caused by embolism of atherosclerotic plaques in the carotid bifurcation.[1,2] In two large studies, the North American Symptomatic Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECTS), CEA was recommended, particularly in symptomatic patients who have more than 70% stenosis of the carotid artery.[3,4] However, the overall mortality rate for CEA was reported to be 1.3–1.8% in two large systematic reviews in which the highest rate was 15%[5,6]

In the GALA study, the largest multicentre, randomised, controlled trial of its kind to date, CEA under general anaesthesia (GA) and local anaesthesia (LA) were compared, with the authors finding no significant differences between the methods in terms of stroke, myocardial infarction (MI), or death in the first 30 days following surgery.[7] However, despite the scope of the trial, the GALA study was not able to answer the questions regarding the safety of CEA performed under LA in patients at high risk for cardiovascular complications.

The aim of this study was to compare two different management plans in patients requiring both CEA and coronary artery bypass grafting (CABG) in terms of their effects on hospital mortality. For the first management plan, patients were initially treated by CEA under cervical block (CB) anaesthesia, followed by CABG administered under GA in a separate session. For the second management plan, both CEA and CABG were performed in the same session under GA.

Methods

This retrospective study was approved by the Selcuk University ethics committee, Konya, Turkey. Over a period of five years (January 2008 to December 2013), 98 CEA operations were performed in our cardiovascular department, of which 73 (74%) were operated under CB anaesthesia and 25 (26%) under GA.

Among the 98 patients who underwent CEA operations, CABG was performed in 34 patients due to coronary artery disease (CAD). In 18 of these 34 patients, CABG was performed in the same session with CEA (GA group). As the skill and experience of our clinic increased in terms of CEA under CB anaesthesia, physicians began performing these procedures in patients scheduled to undergo concomitant CABG for CAD. For these 16 patients, CEA was first performed under CB anaesthesia, followed by CABG performed, as a separate procedure during the same hospital stay, under GA (CB-GA group). The regional anaesthesia technique consisted of a superficial cervical plexus block using 0.25% plain bupivacaine with additional local infiltration as needed during the course of the operation. Heparin was administered before carotid clamping (100 IE/kg).

Patient data were obtained from in-patient charts, out-patient records, operating room notes, and telephone calls. The range of pre-operative symptoms included asymptomatic, non-disabling ischaemic stroke, transient ischaemic attack (TIA) and stroke. Cerebrovascular accident history was investigated by a neurologist through direct interview and medical charts. Non-disabling stroke was defined by a residual deficit, associated with a score of ≤ 2 according to the modified Rankin scale. TIA was defined as an abrupt onset of symptoms and/or signs related to a focal cerebral or visual deficit (amaurosis fugax) attributed to focal loss lasting less than 24 hours. Stroke was defined as an abrupt onset of symptoms and/or signs related to a focal and/or global deficit of cerebral functions lasting more than 24 hours and not attributable to causes other than cerebrovascular accident.[8] Asymptomatic patients had no history of cerebrovascular symptoms.

The following peri-operative variables were considered: demographics (age, gender), presence of current or previous smoking, diabetes mellitus (DM), hypertension (HT), hypercholesterolaemia, presence of peripheral obstructive disease (POD), history of CAD (previous MI, stable or unstable angina, percutaneous or surgical coronary revascularisation), renal dysfunction and obesity.

Duplex ultrasonography (USG) was performed in all patients and findings were confirmed by magnetic resonance angiography (MRA). Indications for surgery were either a stenotic lesion measuring > 50% of the carotid artery together with a neurological event or, for those who were asymptomatic, a stenotic lesion measuring > 70%.

Carotid artery endarterectomy was performed in all patients. After the procedure, heparin was not routinely reversed. Standard heparinisation was used to control the active clotting time during cardiopulmonary bypass. Internal mammary artery and saphenous vein grafts were prepared, and the coronary bypass process was completed. All patients were followed in the intensive care unit postoperatively for at least 24 hours.

In the GA group, patients were intubated. Somatosensory evoked potential (SSEP) monitoring and stump pressure monitoring were routinely used. If SSEP monitoring showed slowing to ≤ 50% of the pre-clamping response or the stump pressure was below 50 mmHg, carotid shunting was performed in the CB-GA group. At the time of carotid clamping, patients were examined neurologically by testing their ability to squeeze a ball that made a sound; shunting was performed using an Inahara-Pruitt outlying shunt if the response was deemed inadequate. CEA was performed using patch closure [saphenous, Dacron or PTFE (polytetrafluoroethylene)] or primary closure.

Bleeding was defined as a need to change postoperative dressings one or more times, a requirement for neutralisation with protamine, or re-operation of the patient because of haematoma. Wound infection was controlled by specialists in infection. For postoperative assessment of cranial nerve damage, the 10th, 11th and 12th cranial nerves were examined. Patients with suspected nerve damage were consulted by a neurologist. All patients were examined by the same neurologist both pre- and postoperatively.

Obstructions identified by Doppler ultrasonography within the first 30 days were interpreted as early restenosis and obstructions identified in the following 30 days were considered late restenosis. All patients who had complaints consistent with symptoms of MI, together with electrocardiograph and troponin changes in the postoperative period were considered to have clinical features of MI.

The primary endpoint was death in the postoperative 30 days. Secondary endpoints were postoperative complications such as bleeding or haematoma, infection, cranial nerve damage, non-disabling ischaemic stroke, TIA, amaurosis fugax, early restenosis, late restenosis and postoperative MI.

Statistical analysis

This was performed using the PASW v.18 software package. For comparisons between groups, independent samples *t*-tests were used for continuous variables and χ^2 or Fisher's exact test were used for categorical variables. In the analysis, p-values < 0.05 were considered statistically significant.

Results

In total, 34 patients treated for both carotid artery disease and CAD were included in this study. Of these 34 patients, 18 (53%) were operated under GA in the same session (GA group). For the other 16 patients (47%), CEA was first performed under CB anaesthesia, followed by CABG performed under GA (CB-GA group). Pre-operative patient data are shown in Table 1.

Intra-operative data of the patient groups are shown in Table 2. The clamping time was shorter in the GA than in the CB-GA group (Table 2). No significant difference in shunting was seen between groups (two patients in the GA group vs three patients in CB-GA group).

No significant differences were found between the groups in terms of postoperative bleeding, infection, cranial nerve damage, early or late restenosis, TIA, stroke or death (Table 3). Postoperative MI occurred in four patients in the CB-GA group, but was not observed in any patient in the GA group ($p = 0.039$) (Table 3). In two of these four patients with postoperative MI, left main coronary artery (LMCA) lesions were observed, while the other two patients exhibited multi-vessel disease. These patients were assessed by a cardiologist and emergency CABG

Table 1. Demographic characteristics and clinical variables of the patient population

Variables	*GA group (n = 18)*	*CB-GA group (n = 16)*	p-*value*
Age	66.39 ± 8.64	67.44 ± 6.34	0.692
Male	14 (77.8)	12 (75.0)	0.999
Asymptomatic	15 (83.3)	13 (81.2)	0.999
Amaurosis fugax	–	–	–
TIA	3 (16.7)	2 (12.5)	0.999
Non-disabling stroke	–	–	–
Stroke	0 (0.0)	1 (6.2)	0.471
Smoking	9 (50.0)	7 (43.8)	0.716
HT	2 (11.1)	7 (43.8)	0.052
DM	2 (11.1)	4 (25.0)	0.387
Hypercholesterolaemia	1 (5.6)	2 (12.5)	0.591
CAD	13 (72.2)	11 (68.8)	0.999
PAD	0 (0.0)	2 (12.5)	0.214
Renal dysfunction	4 (22.2)	2 (12.5)	0.660
Obesity	2 (11.1)	2 (12.5)	0.999

GA: general anaesthesia; CB: cervical block; TIA: transient ischaemic attack; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; PAD: peripheral arterial disease.

surgery was performed. One of the two patients with LMCA lesions could not be saved and died. The other three patients underwent successful CABG operations and were discharged from the hospital.

Discussion

CEA has been shown to reduce the risk of stroke in both asymptomatic and symptomatic patients in several large trials.[3,4,9,10] Current European Society for Vascular Surgery guidelines identify five different indications in patients with carotid artery disease, including neurological symptomatology, degree of carotid stenosis, medical co-morbidities, vascular and local anatomical features and carotid plaque morphology. The last three of these criteria were proposed as a means of differentiating between CEA and carotid artery stenting (CAS).[11] However, in terms of stroke and death, numerous randomised trials did not find any significant difference between CEA and CAS. Stenting may have some possible advantages, such as avoidance of GA and surgical trauma,[12-14] although it has also been identified as an independent predictor of retinal embolisation.[15]

In the 1960s, with the initiation of operations under LA, many surgeons began to prefer it when performing operations.[16] In our clinic, many of the surgeons also prefer LA, resulting in more CEA operations being performed under LA. Previous studies have suggested that use of LA for CEA surgery may change the attitude of many surgeons to the procedure.[17,18] Since it alerts the surgeon for the necessity of a shunt, awake testing of brain function during carotid clamping under LA is more reliable than various indirect techniques that are used under GA. Such an approach may be safer than operations performed under GA, as evidenced by the lower number of shunts used in these procedures. In our study, shunts were used less frequently in patients who underwent CEA under CB anaesthesia; however, this difference was not statistically significant.

Awake testing and cerebral monitoring are regarded as the gold standard for shunting.[19] Although shunts should protect the brain from strokes caused by low cerebral blood flow during carotid clamping, they can damage the arterial wall, causing embolisms in the brain.

LA may have some advantages in terms of MI and pulmonary complication rates, when compared with GA.[17] Furthermore, LA is associated with a better assessment of neurological outcomes.[20,21] The GALA study included 3 526 patients and compared GA versus LA for carotid artery surgery. It found no significant differences in quality of life, length of hospital stay, or primary outcome (stroke, MI, death between randomisation and 30 days after surgery) in the pre-specified subgroups of age (above or below 75 years) or for those considered at higher risk for surgery. While the study provided important insights into disease outcomes based on treatment modalities, it did not answer questions regarding the safety of CEA under LA in patients at high risk for cardiovascular complications.

Table 2. Intra-operative data of the patient groups

Variables	*GA group (n = 18)*	*CB-GA group (n = 16)*	p-*value*
Clamping time	31.06 ± 3.57	41.25 ± 7.39	< 0.001
Contralateral obstruction	2 (11.1)	3 (18.8)	0.648
Shunt	2 (11.1)	3 (18.8)	0.648
Primer closure	6 (33.3)	4 (25.0)	0.715
Saphenous	0 (0.0)	1 (6.2)	0.471
PTFE	–	–	–
Dacron	12 (66.7)	11 (68.8)	0.897

GA: general anaesthetic; CB: central block; PTFE: polytetrafluoroethylene.

Table 3. Comparison of postoperative complications between patient groups

Complications	*GA group (n = 18)*	*CB-GA group (n = 16)*	*p-value*
Bleeding	4 (22.2)	0 (0.0)	0.105
Infection	–	–	–
Cranial nerve damage	1 (5.6)	0 (0.0)	0.999
Early restenosis	–	–	–
Late restenosis	–	–	–
TIA	–	–	–
Stroke	–	–	–
Postoperative MI	0 (0.0)	4 (25.0)	0.039
Death	0 (0.0)	1 (6.2)	0.471

GA: general anaesthetic; CB: central block; TIA: transient ischaemic attack, MI: myocardial infarction.

Conclusion

In our study, the postoperative MI rate was higher in the CB-GA group, with four cases of postoperative MI in the CB-GA group compared to none in the GA group. Based on these observations, for patients requiring CEA and CABG, performing both operations under GA and in the same session was the safer option compared to initially performing CEA under CB anaesthesia followed by CABG under GA.

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The importance of dieticians as healthcare workers

The food we eat is a key contributor to our health. While the phrase 'you are what you eat' is often taken lightly, our food choices play an important role in maintaining a healthy lifestyle. To help with making the right food choices, dieticians are the most equipped healthcare workers whose primary goal is ensuring that you are informed about the importance of a healthy diet. The main concern is the high amount of non-scientific information available on the internet.

Registered dietician and founder of Newtricion Wellness Dieticians, Omy Naidoo, says that 'a registered dietician is an important part of any healthcare team because they provide evidence-based information on, prevention of, and disease-management nutrition-related advice.'

The expertise of dieticians is used in the prevention and treatment of chronic diseases such as diabetes and blood pressure. They also translate complex scientific information into practical advice.

'A dietician's role comes into effect when planning nutritional and food programmes to promote a healthy diet, especially when calculating the nutrients a person needs when creating menus based on a doctor's advice', adds Naidoo.

Registered dieticians can work as nutrition experts for a diabetic patient and help treat diabetes by using medical nutrition therapy that includes counselling and therapy. Dieticians also devise strategies and propose healthy eating habits to reduce blood pressure.

Hospital dieticians play a key role in the journey of a patient in critical care, surgery, oncology, and various other parts of hospitalisation. Dieticians work within a multi-disciplinary team in ensuring the patient meets his/her treatment goals.

Dieticians provide the following important functions:

- Plan individual nutritional therapies to address specific health issues, such as unhealthy weight, diabetes or hypertension.
- Promote public awareness for proper nutritional standards and habits.
- Enhance the accuracy and understanding of food labels.
- Liaise with food manufacturers to improve the nutritional quality of prepared foods.

'Healthcare is void without supplementary nutritional balance, which is why dieticians intervene in the treatment of chronic diseases and prevention thereof', concludes Naidoo.

Vascular health assessment with flow-mediated dilatation and retinal image analysis: a pilot study in an adult population from Cape Town

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Abstract

Aim: Flow-mediated dilatation (FMD) and retinal vascular analysis (RVA) may assist in predicting cardiovascular disease (CVD) but are poorly characterised in South Africa. We recorded baseline FMD and retinal vascular widths in healthy participants, and investigated associations with cardiovascular risk factors.

Methods: Endothelial function (measured with FMD), microvascular structure (evaluated via fundus image analysis) and major CVD risk factors were assessed in 66 participants from Cape Town.

Results: Median FMD% was 9.6%, with higher values in females. Mean retinal arteriolar and venular widths were ~156 and ~250 µm, respectively. FMD was not associated with CVD risk factors. Hypertension was associated with narrower retinal arterioles and venules.

Conclusions: We report novel baseline FMD data in healthy South African adults from the Western Cape, and show that retinal microvascular calibres are associated with blood pressure. Our baseline FMD and RVA data could serve as a reference for future studies in South Africa.

Keywords: vascular health, endothelial function, flow-mediated dilatation, retinal imaging, cardiovascular risk.

Submitted 14/5/20, accepted 2/10/20
Published online 13/11/20
Cardiovasc J Afr 2021; **31**: 133–140 www.cvja.co.za

DOI: 10.5830/CVJA-2020-046

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Cardiovascular disease (CVD) accounts for an estimated 17.7 million deaths globally, of which more than 70% occur in low- and middle-income countries such as South Africa.[1] The prevalence of CVD varies among different regions and populations, and while a steady decline has been noted in many high-income countries, this has not been the case in large parts of sub-Saharan Africa.[2]

In the Western Cape Province of South Africa, where Cape Town is located, cardiovascular and cardiometabolic diseases account for a large proportion of the primary causes of death, including diabetes mellitus, ischaemic heart disease and cerebrovascular disease.[3] According to the South African Medical Research Council (SAMRC) Western Cape Mortality Profile 2013, cardiovascular diseases accounted for 24.3% of all deaths across all age groups in the province (compared to 23% of deaths attributed to infectious diseases).[4] Previous studies have reported a high prevalence of cardiovascular risk factors in Cape Town populations, including type 2 diabetes mellitus, metabolic syndrome, hypertension and smoking.[5,6]

Many traditional cardiovascular risk factors have been implicated in the development of endothelial dysfunction (ED).[7,8] ED, characterised by a loss of vascular homeostasis and reduced nitric oxide (NO) bioavailability, is an early precursor of atherosclerosis and a marker and predictor of CVD.[9-14] Flow-mediated dilatation (FMD) has become the gold-standard non-invasive assessment tool for endothelial function measurement in clinical research.[15] In previous studies, mainly in populations from developed countries, FMD has been shown to be associated with cardiovascular risk factors[11,16,17] and future CVD events.[11,12,14] Yet, despite its potential as a clinical tool that can serve as a surrogate marker of CVD risk, we are not aware of studies utilising FMD in adult South African populations.

Retinal microvascular calibres, measured by non-invasive fundus photography and computerised analysis, are associated with long-term cardiovascular mortality and impaired endothelial function.[18,19] The Multi-Ethnic Study of Atherosclerosis (MESA) reported that smaller retinal arteriolar calibre (central retinal arteriolar equivalent; CRAE) was associated with hypertension, whereas larger arteriolar calibre was associated with diabetes, current cigarette smoking and higher levels of plasma fibrinogen. Larger retinal venular calibre (central retinal venular equivalent; CRVE) has been shown to be associated with diabetes, current cigarette smoking, obesity, dyslipidaemia and systemic markers of inflammation and endothelial dysfunction.[20]

There is a lack of retinal imaging studies in the South African context, particularly in populations of the Western Cape. One Cape Town-based study reported on retinal microvascular calibres in a cohort of HIV-infected participants,[21] however, little is known about the relationship between retinal microvascular

and geometric characteristics and cardiovascular risk in South African populations.

The non-invasive assessment of vascular health with FMD and retinal imaging are deemed useful as a marker of cardiovascular risk and disease, yet there is a paucity of studies utilising these technologies in the South African research context. The growing interest in vascular and endothelial measurements as future diagnostic and screening tools in the clinical setting necessitates that baseline values are established for a variety of populations, including those living in low- to middle-income countries such as South Africa. In South Africa, current evidence suggests that the Western Cape Province has a particularly high prevalence of cardiovascular risk factors.

In view of the above, the present proof-of-concept study was undertaken to record baseline FMD and retinal microvascular and geometric data in a cohort of apparently healthy participants from Cape Town. The study additionally aimed to determine whether a relationship exists between FMD, retinal parameters and traditional cardiovascular risk factors in the study participants.

Methods

For this cross-sectional study, 66 HIV-free and otherwise apparently healthy participants were recruited from the Uitsig community health clinic near Cape Town between September 2014 and July 2015, as a pilot to a larger parent study.[22] Participants were eligible for inclusion if they were adults (18 years or older), willing to give written consent for participation in the study and undergo HIV testing. Screening for HIV infection was performed with a rapid HIV test (SD Bioline HIV 1/2 3.0 immunochromatographic test kit; Standard Diagnostics, Republic of Korea). Participants were excluded if they were pregnant or tested positive for HIV infection.

The study received ethics approval from the Health Research Ethics Committee (HREC) of Stellenbosch University (HREC reference number: N13/05/064) and was conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council of South Africa Ethical Guidelines for Research. All participants supplied written, informed consent for participation in the study, and additionally provided written consent for HIV testing for which appropriate pre- and post-test counselling was provided by a qualified research nurse.

Information regarding participants' medical history, including smoking status, was gathered via a structured interview and health questionnaire. Additionally, participants were weighed and anthropometric measurements recorded to determine body mass index (BMI), waist circumference and waist-to-hip ratio (WHR) according to international guidelines.[23] A return visit was scheduled where participants were required to fast from 22h00 the previous night, and to refrain from smoking, drinking coffee or doing exercise for four to six hours prior to the assessments in order to comply with standard subject preparation recommendations for FMD measurements.[24]

Blood samples were collected and immediately transported to the closest laboratory of the National Health Laboratory Services [a South African National Standard (SANS) accredited laboratory service provider] where the following fasting biochemical measurements were performed: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose and glycated haemoglobin (HbA_{1c}). Appropriate assays were used for quantifying the concentrations of the above markers with a Roche/Hitachi cobas c 311, cobas c 501/502 analyser.

Subsequently, before endothelial function assessments were performed, systolic and diastolic blood pressures were measured in the left arm at three different occasions, two to five minutes apart, with an Omron M6 automatic digital blood pressure monitor (Omron Healthcare, Kyoto, Japan).

The FMD protocol is designed to expose the brachial artery to post-occlusion hyperaemia and the subsequent shear stress-induced release of NO and other pro-vasodilatory factors, resulting in vasodilation that can be imaged and quantified as an index of vasomotor function.[25] In this study, FMD assessment was performed using a MyLab™ Five mobile ultrasound system (Esaote, Italy). The FMD protocol was similar to previously published recommendations.[25,26]

Participants were asked to lie supine on an examination bed, with their right arm abducted and supinated. A blood pressure cuff (deflated) was placed around the proximal part of the forearm. Subsequently, the ultrasound probe was positioned proximal to the cubital fossa (mid to distal humerus), just below the biceps brachii muscle belly, until the brachial artery was located visually on the ultrasound image. The ultrasound probe was secured in this position using a probe holder. Next, cross-sectional still images were captured with the ultrasound probe at three different locations along the designated section of the artery to obtain baseline brachial artery diameter measurements.

Following this, the blood pressure cuff was inflated to 200 mmHg (or 50 mmHg supra-systolic in the case of individuals with a systolic blood pressure greater than 150 mmHg) and blood flow to the forearm was occluded for five minutes. After the blood pressure cuff was deflated, additional cross-sectional ultrasound stills were taken along the same section of artery for a duration of two minutes.

For still analysis, the MyLab™ Five mobile ultrasound system built-in manual measurement tool was used to measure the brachial artery diameter in millimetres, consistently at the end of diastole, in all the stills. The three baseline measurements were used to calculate a mean baseline brachial artery diameter, and the maximum post-occlusion measurement, usually at approximately 60 seconds after blood pressure cuff release, was used to calculate the FMD percentage according the following formula:

$$\text{FMD } \% = \frac{\text{maximum post-occlusion (diameter (mm)} - \text{mean baseline diameter (mm)}}{\text{mean baseline diameter (mm)}} \times 100$$

In order to ensure reliable data collection, the ultrasound operators were subjected to stringent training by experts and multiple practice sessions on student volunteers and colleagues. To keep inter-operator variability to the minimum, only three trained and experienced operators were employed in this study, and only one person independently performed the image analysis and data acquisition.

Retinal images were captured using a Canon CR-2 non-mydriatic digital retinal camera (Canon Europa NV, the Netherlands) based on protocols previously published.[27] Optic disc-centred fundus images of both eyes were obtained. For the static retinal microvascular assessments, images were analysed using MONA REVA™ software version 2.0.2 (Vito, Belgium).

Vessel widths were calculated by measuring the six largest arterioles and six largest venules coursing through a zone between 0.5 and one disc diameter from the optic disc margin. Estimates are summarised as CRAE and CRVE, representing the average diameter (μm) of the arterioles and venules, respectively.[28] Standard procedure was to calculate the CRAE and CRVE values from the optic disc-centred image of the right eye. The left eye was used only when gradable right eye images were not obtained.

The retinal arteriolar–venular ratio (AVR) was calculated separately, which serves as a dimensionless measurement independent of the optical properties of the eye and camera. Additionally, fundus images were analysed by an independent retinal grading expert blinded to the participants' demographic, medical and other study results.

The presence or absence of the following parameters, all associated with possible underlying cardiometabolic disorders, were assessed qualitatively in a binary fashion: retinal tortuosity, cotton wool spots, retinal haemorrhage, telangiectasia and micro-aneurysms. The presence of any cotton wool spots, retinal haemorrhage, teleangiectatic vessels or micro-aneurysms were counted as positive for each parameter, whereas retinal tortuosity was determined according to a pictorial grading scale, as previously published.[29]

Statistical analysis

All data were statistically analysed with Statistica™ version 13.3 (TIBCO Software Inc, CA, USA). Continuous variables with normal distributions are expressed as mean (standard deviation) or mean [95% confidence interval (CI)], and non-parametric data as median (interquartile range). Independent *t*-tests and Mann–Whitney *U*-tests (with continuity correction) were used to compare parametric and non-parametric continuous variables, respectively, among male and female groups, and the Fisher exact (two-tailed) test to compare categorical variables. Correlations between continuous cardiometabolic variables and vascular variables (FMD%, CRAE, CRVE and AVR) were evaluated by Pearson's correlation coefficient (non-parametric data were normalised by logarithmic transformation where indicated). The relationship between categorical cardiovascular risk factor variables (expressed as 'yes' or 'no') and vascular variables was evaluated by analysis of co-variance (ANCOVA) after adjusting for age and/or gender where indicated. Statistical significance was set at $p < 0.05$ for all statistical models.

Results

The study enrolled 66 participants (55% female) with a mean age of 35.4 (10.6) years. Continuous demographic, anthropometric, biochemical and vascular data for the whole cohort are depicted in Table 1, in which additional comparisons are made between the male and female subsets. Mean WHR, median BMI and median waist circumference values for the whole cohort fell well within the normal range. In the male subset in particular, BMI and waist circumference values were in the lower margins of the normal range, and male participants had significantly smaller BMI and WHR values compared to females.

Concerning biochemical variables, female participants had significantly higher triglyceride levels compared to males. For males, baseline brachial artery diameter values were higher, and FMD% values were lower compared to females. Additionally, 38.2% of females and 62.9% of males presented with an FMD% lower than the sample median ($p = 0.05$). Mean retinal vessel diameters were trending higher for CRVE in males, while there were no differences noted for CRAE or AVR.

In a separate set of retinal assessments, qualitative fundus grading and analyses of retinal vessel geometric characteristics showed that retinal tortuosity was present in approximately 18% of the participants, and was predominantly detected in the retinal arterioles. Furthermore, a single micro-aneurysm was identified in one participant, while no cotton wool spots, retinal haemorrhage or telangiectasia were observed in this cohort.

The prevalence of cardiovascular risk factors is shown in Fig. 1. Of the whole cohort, 86.4% of participants indicated that they were current smokers, and 31.8% presented with systolic hypertension, with 40.7% of males being hypertensive. Diastolic hypertension was identified in 23.8% of the study population and in 29.6% of the male subset. Of the female subset, 36.1% were considered overweight or obese and 30.6% presented with central obesity. Reduced HDL-C levels were found in 28.8% of the whole cohort and in 38.9% of females, compared to 16.7% of males.

As expected, an inverse correlation was observed between baseline brachial artery diameter and FMD% (Pearson's correlation coefficient, *r*: –0.33; $p = 0.009$), and a strong positive correlation was noted between the retinal blood vessel equivalents, CRAE and CRVE (Pearson's correlation coefficient, *r*: 0.5; $p < 0.001$).

The correlations between cardiometabolic and vascular (FMD%, CRAE and CRVE) variables in the whole cohort are shown in Table 2. The results indicate that waist circumference showed a positive correlation with FMD%, although there was no correlation with WHR. Both systolic and diastolic blood

Table 1. Population characteristics

Variables	*Whole cohort (n = 66)*	*Females (n = 36)*	*Males (n = 30)*	p-*value (F:M)*
Age (years)	35.4 (10.6)	34.1 (10.6)	36.9 (10.5)	0.29
WHR	0.8 (0.05)	0.8 (0.05)	0.8 (0.04)	0.01
BMI (kg/m^2)	22.1 (19.3–24.7)	23.4 (19.8–27.2)	20.7 (18.8–23.9)	0.03
WC (cm)	75.5 (69–81)	76 (70.5–80.25)	74 (68–81)	0.49
SBP (mmHg)	129.9 (16.9)	127.8 (16.2)	132.9 (17.7)	0.24
DBP (mmHg)	79.6 (14.1)	78.1 (13.9)	81.5 (14.3)	0.33
Total C (mmol/l)	3.8 (3.3–4.4)	4 (3.2–4.7)	3.7 (3.3–4.3)	0.54
HDL-C (mmol/l)	1.25 (1–1.5)	1.3 (1–1.6)	1.2 (1–1.4)	0.38
LDL-C (mmol/l)	2.1 (1.7–2.6)	2.2 (1.7–2.6)	1.9 (1.5–2.6)	0.17
TG (mmol/l)	0.8 (0.6–1)	0.8 (0.6–1)	0.9 (0.7–1.2)	0.04
Fasting glucose (mmol/l)	4.5 (4.2–4.9)	4.45 (4.05–4.7)	4.5 (4.3–4.9)	0.21
HbA_{1c} (%)	5.4 (0.5)	5.4 (0.5)	5.5 (0.4)	0.27
CRAE (μm)	156.2 (14.5)	155.3 (12.9)	157.2 (16.4)	0.61
CRVE (μm)	250.3 (21)	247.4 (18.6)	253.6 (23.5)	0.07
AVR	0.6 (0.06)	0.6 (0.06)	0.6 (0.05)	0.53
Baseline brachial artery diameter (mm)	3.5 (0.6)	3.2 (0.5)	3.9 (0.5)	< 0.001
FMD (%)	9.6 (6.7–14.1)	11.4 (7.7–15.8)	8.6 (3.4 – 12.5)	0.06

Parametric data are expressed as mean (standard deviation) and non-parametric data as median (interquartile range).
WHR, waist-to-hip ratio; BMI, body mass index; WC, waist circumference; SMP, systolic blood pressure; DBP, diastolic blood pressure; Total C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HbA_{1c}, glycated haemoglobin; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, retinal arteriole-to-venule ratio; FMD, flow-mediated dilatation; F:M, female vs male.

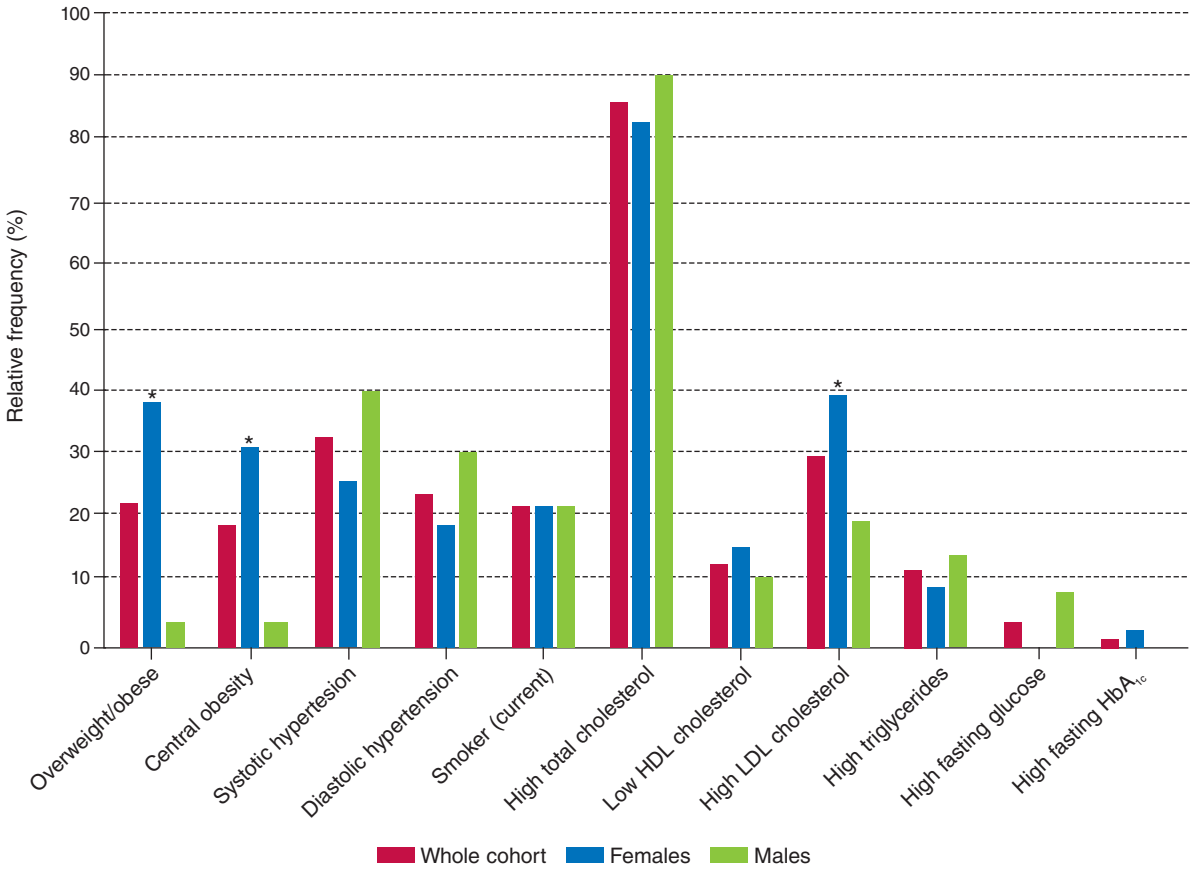

Fig. 1. Relative frequency of cardiovascular risk factors in the whole cohort, and in female and male subsets. Overweight/obese: BMI ≥ 25 kg/m^2; central obesity: waist circumference ≥ 94 cm for males and ≥ 80 cm for females; systolic hypertension: ≥ 140 mmHg; diastolic hypertension: ≥ 90 mmHg; high total cholesterol: > 5.1 mmol/l; low HDL-C: < 1 mmol/l for males and < 1.2 mmol/l for females; high LDL-C: > 3 mmol/l; high triglycerides: ≥ 1.7 mmol/l; high fasting glucose: ≥ 7 mmol/l; high HbA_{1c}: ≥ 6.5%. Cut-off values for the cardiovascular risk factors are from previously published guidelines adapted from the European and International Societies for Hypertension and the International Diabetes Foundation.[30,31] *p < 0.05 females vs males.

pressure correlated inversely with CRAE, while triglycerides correlated positively with CRVE. None of the cardiometabolic variables correlated with AVR. Furthermore, correlation analyses failed to show a relationship between FMD% and the retinal microvascular calibres (not shown). Participants in whom retinal tortuosity was positively identified, had significantly higher diastolic blood pressure values compared to those without retinal tortuosity [data expressed as mean (95% CI): tortuosity present: 85.4 (80.2–90.6) mmHg vs tortuosity absent: 78.3 (76–80.5) mmHg; $p = 0.01$].

Relationships between cardiovascular risk factors and vascular variables were tested with ANCOVA (all models adjusted for age). Overweight or obese participants (BMI ≥ 25 kg/m^2) had significantly higher FMD% compared to normal-weight counterparts [data expressed as mean log FMD% (95% CI): overweight: 1.1 (0.9–1.3) vs normal weight: 0.9 (0.8–0.9); $p = 0.03$]; however the significance disappeared when the model was additionally adjusted for gender. Similarly, participants with high total cholesterol levels (> 5.1 mmol/l) presented with increased FMD% compared to those with normal cholesterol values [mean log FMD% (95 CI): high total cholesterol: 1.2 (0.9–1.5) vs normal total cholesterol: 0.9 (0.8–0.9); $p = 0.03$], but the significance was lost when additionally adjusting for gender. No other cardiovascular risk factors were associated with changes in FMD%.

The presence of systolic hypertension (systolic blood pressure ≥ 140 mmHg) was associated with significantly decreased CRAE (Fig. 2A), which was not affected by additional adjustment for gender, however, the significance was lost when CRVE was added as an adjustor (not shown). CRVE was significantly lower in participants with systolic hypertension (Fig. 2B), even when additionally adjusting for gender, however, the significance disappeared after including CRAE as a covariate in the model (not shown).

Diastolic hypertension (diastolic blood pressure ≥ 90 mmHg) was associated with significantly decreased CRVE, and although significance was not affected when additionally adjusting for gender, the inclusion of CRAE in the model moderated the significance level to $p = 0.057$ (not shown). There were no associations observed between any of the cardiovascular risk factors and AVR.

Discussion

Evidence emanating from both official statistical sources and

Table 2. Correlations between cardiometabolic and vascular variables in the cohort ($n = 66$)

Variables	*FMD%*	*CRAE*	*CRVE*	*AVR*
BMI				
r	0.24	0.04	0.04	0.005
p	0.06	0.76	0.78	0.97
WC				
r	0.27*	0.02	0.15	–0.11
p	0.04	0.84	0.24	0.39
WHR				
r	0.02	–0.04	0.2	–0.22
p	0.87	0.74	0.12	0.09
Systolic BP				
r	0.09	–0.35*	–0.23	–0.16
p	0.48	0.01	0.08	0.22
Diastolic BP				
r	0.1	–0.26*	–0.2	–0.09
p	0.44	0.04	0.13	0.5
Total C				
r	0.12	0.02	0.02	0.007
p	0.34	0.85	0.86	0.95
HDL-C				
r	–0.04	–0.01	–0.05	0.03
p	0.75	0.91	0.68	0.84
LDL-C				
r	0.24	0.01	–0.03	0.04
p	0.06	0.92	0.83	0.72
Triglycerides				
r	–0.21	0.18	0.28*	–0.07
p	0.1	0.16	0.02	0.58
Fasting glucose				
r	–0.22	0.05	0.03	0.03
p	0.09	0.67	0.8	0.81
HbA_{1c}				
r	0.08	0.15	0.17	0.02
p	0.55	0.23	0.19	0.88

The following variables with a skewed distribution were logarithmically transformed: FMD%, BMI, waist circumference, total cholesterol, HDL-C, LDL-C, triglycerides and fasting glucose.
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; BP, blood pressure; Total C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin; FMD, flow-mediated dilatation; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, retinal arteriolar–venular ratio; *r*, Pearson's correlation coefficient; *p*, *p*-value. *Significant.

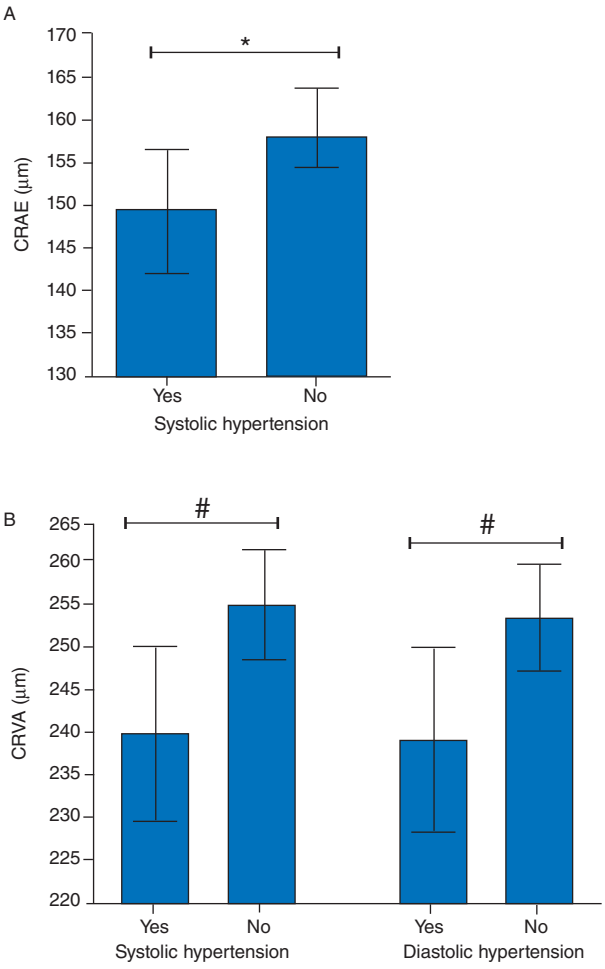

Fig. 2. Relationships between cardiovascular risk factors and retinal vascular variables. A. Effect of systolic hypertension (systolic blood pressure ≥ 140 mmHg) on CRAE; $^{*}p = 0.03$. B. Effects of systolic and diastolic hypertension (diastolic blood pressure ≥ 90 mmHg) on CRVE; $^{\#}p = 0.02$. Data are expressed as mean (95% CI); all ANCOVA models adjusted for age.

research studies is pointing to a high prevalence of cardiometabolic diseases and risk factors in Cape Town and the Western Cape Province of South Africa,[3-6] supporting global trends that low- to middle-income countries carry a high cardiovascular disease burden. The present study collected data from volunteer participants recruited at the Uitsig health clinic, which serves a predominantly low socio-economic status (SES) community outside Cape Town. In recent years, research has increasingly uncovered a link between SES and cardiovascular health, with low-SES individuals being at a greater cardiovascular risk.[32]

Detecting early markers of CVD is critical in the management of the disease burden in high cardiovascular risk populations. The assessment of vascular changes can be particularly useful in this regard, with FMD previously being shown to be a marker of future cardiovascular events,[11,12,14] and the quantitative analysis of retinal microvasculature linked to the development of CVD.[33] Both these non-invasive vascular assessment techniques are new to clinical research in South Africa.

In summary, the results of the present study, conducted in a relatively young adult population with a high smoking prevalence, show that the FMD% and CRAE values were in line with those previously reported in other populations, whereas comparisons of the CRVE values with those from other studies were more varied. Furthermore, as previously shown by others, female participants had increased FMD% and decreased baseline brachial artery diameters compared to their male counterparts. With the exception of modest relationships with waist circumference and elevated BMI, FMD% showed no association with any of the measured cardiometabolic variables. The retinal microvascular calibres in our study cohort were associated with blood pressure, which is in keeping with findings from previous studies, and the presence of retinal tortuosity was associated with increased diastolic blood pressure. There was no relationship between FMD% and the retinal microvascular calibres in this cohort.

Although no internationally standardised cut-off values exist for FMD, the median FMD% recorded in the present cohort

(9.6%) (Table 1) falls within the range of values reported in a systematic review and meta-analysis comprising 23 studies and over 15 000 participants, where the respective FMD values varied between 2.3 and 13.8%.[12] In our study, females had significantly higher FMD% values compared to males (Table 1). This agrees with findings from the Framingham Heart Study, which showed similar trends in their cohort,[34] and emphasises the importance of taking gender differences into account when measuring FMD in study populations. However, this phenomenon may be explained by the significantly larger baseline artery diameters measured in the male participants compared to females, which has also been shown by others.[16,34]

Body weight parameters appeared to be associated with FMD%, as suggested by a modest correlation with waist circumference (Table 2), and observing higher FMD% values in participants with BMI ≥ 25 kg/m^2. However, there was no correlation when waist circumference was expressed as a ratio of hip circumference (WHR) (Table 2) and the age-adjusted association with overweight/obesity was lost when additionally adjusting for gender. Furthermore, the presence of central obesity had no effect on FMD% and no correlation was observed between BMI and FMD%. Taken together, the results show that body weight parameters were not strongly associated with FMD%, likely due to the relatively young mean age of the cohort and the fact that waist circumference, WHR and BMI values were well within the normal ranges.

A previous study by Brook *et al.*[35] also failed to show a significant relationship between BMI and FMD%, while noting that the WHR was inversely associated with FMD%. Although another study showed an inverse association between BMI and FMD%, the study population included subjects with only severe obesity,[34] which was not the case in our cohort. Participants with high total cholesterol levels (> 5.1 mmol/l) had increased FMD% values, however, this age-adjusted relationship disappeared when the model was additionally adjusted for gender, and was therefore unlikely to be of physiological relevance. None of the other lipid and cardiometabolic variables showed relationships with FMD.

In the present study cohort, mean CRAE values corresponded reasonably well with those reported in a systematic review and meta-analysis by Ding *et al.*[36] comprising over 10 000 participants, and studies conducted in the North West Province of South Africa.[37,38] The median CRVE value in our cohort (253.6 µm) (Table 1) was higher than the range of CRVE values (192.3–231.2 µm) reported by Ding *et al.*[36] On the other hand, the present cohort's CRVE compared reasonably well with that of a study in a cohort from the North West Province in South Africa,[38] and tended to be lower than that measured in one of the only other Western Cape Province-based studies investigating retinal microvascular calibres in a Cape Town population.[21]

The apparent inter-study inconsistency may be related to differences in retinal image analysis procedures and methodology, including different software packages used for analysis, as reported previously.[39] In addition, the discrepancy may also be ascribed to our cohort's relatively young mean age of around 35 years, compared to a mean age range of between 50 and 61 years in the meta-analysis study of Ding *et al.*,[36] as previous reports have shown that retinal venular diameters narrow with increasing age.[40] The higher smoking prevalence in our cohort (~86%) (Table 1) compared to the smoking rates in the studies reviewed by Ding *et al.*[36] (11.5–23.7%) may also explain the higher CRVE, since cigarette smoking has been shown to be strongly associated with wider retinal venular calibres.[20]

In our cohort, there was an inverse correlation between CRAE and systolic and diastolic blood pressure (Table 2). In addition, participants with systolic hypertension had lower CRAE values compared to normotensive participants (Fig. 2A), which is in accordance with findings by others, suggesting that narrower retinal arteriolar width may be a marker of hypertension.[20,36,41,42] This finding underscores the potential value of retinal screening in young adults, such as the current cohort, who may not yet clinically present with hypertension. Results also show decreased CRVE values in participants with systolic and diastolic hypertension compared to normotensive participants (Fig. 2B), which is in agreement with observations made in a previous study.[43]

However, the relationship between hypertension and retinal venular narrowing is controversial, with some authors arguing that venular narrowing may be confounded by concomitant arteriolar narrowing.[44] In the present cohort, additional adjustment for CRAE resulted in a loss of significance in the systolic hypertension model, while a borderline significance was maintained in the diastolic hypertension model. Fasting triglyceride levels also showed a significant relationship with wider retinal venules (Table 2), as previously shown by others.[42]

To further investigate the presence of abnormal retinal features and their potential association with cardiometabolic variables, the retinal images of the present cohort were subjected to qualitative fundus grading, which identified retinal tortuosity (mostly arteriolar) in around 18% of the participants. Results showed that participants with retinal tortuosity had increased diastolic blood pressure compared to participants with no signs of tortuosity. Retinal arteriolar tortuosity has previously been associated with increased systolic and diastolic blood pressure.[45,46]

The demonstration of an association between retinal microvascular changes and endothelial dysfunction of systemic arteries has important implications, as it may provide an opportunity to use the retinal microvasculature as a surrogate marker of systemic vascular disease. We could not demonstrate an association between CRAE or CRVE and FMD% in our cohort. In the literature, the relationship between retinal microvascular calibre and FMD% remains generally inconclusive, however, one previous study did demonstrate an independent association between CRVE and systemic endothelial dysfunction as measured by brachial FMD.[33]

Limitations

The study has shortcomings that need to be considered when interpreting the findings. This was intended to be a pilot study to obtain baseline data in a generally disease-free group of participants, hence the relatively small sample size. This placed limitations on some of the statistical analyses, where a number of borderline significant *p*-values (0.05–0.08) were noted. A larger sample size may have generated more significant outcomes and allowed for the inclusion of more sophisticated and robust association analyses such as multiple regression models.

Furthermore, it has to be acknowledged that the cohort was recruited from a relatively restricted geographical location with limited demographic variability, which limits the extent to which the data can be regarded as representative of the wider South

African population. Despite this, it was interesting to note the comparability of our baseline FMD and retinal measurements with those from previously published studies.

The FMD procedure is technically challenging, requires thorough training and may suffer from operator-dependent variability.[24,25,47] We would therefore recommend the use of computerised vessel edge-detecting/wall-tracking software systems for future studies, as computerised analysis has been suggested to improve the reproducibility.[48] Although we have addressed this as far as possible, as described in detail in the methods section, these potential constraints need to be acknowledged.

Conclusion

We present here, for the first time, FMD data in an apparently healthy adult South African cohort from the Western Cape Province. In this cohort, a median FMD of 9.6% was recorded, which compares reasonably well with previously published data in different populations, mainly from Europe and North America. The findings also confirmed previous reports that FMD values appear to be lower in males compared to females. It is proposed that the current FMD values could serve as a starting point of reference for future studies from South Africa and the sub-Saharan African region.

The retinal arteriolar and venular calibre measurements recorded in our cohort are reasonably comparable to those from other studies and will serve to add to a small but growing database of published retinal microvascular data from other South African researchers. In agreement with the literature, narrower retinal microvascular calibres in our cohort were associated with elevated blood pressure, and in a novel finding in the South African context, we showed that participants presenting with retinal tortuosity had increased diastolic blood pressure compared to those without tortuosity. These findings further support the use of non-invasive retinal image analysis in cardiovascular epidemiology research.

We thank the EndoAfrica research team and field workers, in particular the research nursing staff (Charmaine Abrahams, Shirley McAnda and Susan van Zyl) for their contributions towards recruitment and data collection.

This work was funded under the ERAfrica programme of the EU 7th Framework Programme. Funding was disbursed via the Department of Science and Technology in South Africa (contract number DST/CON 0077/2014), the Belgian Science Policy in Belgium (contract number BL/67/eranet03), and Österreichische Agentur für internationale Mobilität und Kooperation in Bildung, Wissenschaft und Forschung, OeAD GmbH (ÖAD) in Austria (grant number: KEF-Projekt P202). HS was supported by the National Research Foundation of South Africa (grant reference: CSUR13082330472). IW was supported by the National Research Foundation (NRF) of South Africa Research Career Advancement (RCA) award.

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Improvement of cardiac ventricular function by magnesium treatment in chronic streptozotocin-induced diabetic rat heart

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Abstract

Objective: Chronic diabetes mellitus is associated with detrimental cardiovascular complications and electrolyte imbalances such as hypomagnesaemia. We investigated the effect of magnesium (Mg^{2+}) on cardiac function and the possible role of histological and electrical alterations in chronic, streptozotocin-induced diabetic rats.

Methods: Wistar rats were treated once intraperitoneally with streptozotocin or citrate, and then daily with $MgSO_4$ or saline for four weeks. Cardiac contractile and electrocardiographic parameters were measured on Langendorff-perfused hearts. Other hearts were histologically stained or immunoblotted for the mitochondrial ATP synthase (ATP5A).

Results: In diabetic hearts, Mg^{2+} prevented a diabetes-induced decrease in left ventricular developed pressure and improved contractility indices, as well as attenuated the reduction in heart rate and prolongation of QT interval, but not the QT interval corrected for heart rate (QTc). Histologically, there were neither differences in cardiomyocyte width nor interstitial collagen. The expression of ATP5A was not different among the treatment groups.

Conclusion: Mg^{2+} supplementation improved cardiac contractile activity in chronic diabetic hearts via mechanisms unrelated to electrocardiographic or histologically detectable myocardial alterations.

Keywords: magnesium, cardiac, diabetes, ventricular function, streptozotocin

Submitted 16/7/20, accepted 11/11/20
Published online 10/12/20
Cardiovasc J Afr 2020; **31**: 141–148 www.cvja.co.za

DOI: 10.5830/CVJA-2020-054

Cardiovascular complications are a major cause of mortality in diabetes mellitus.[1] These complications are a result of the pathological remodelling processes in the heart and blood vessels that are induced by metabolic derangements in diabetes, such as hyperglycaemia, dyslipidaemia, acid–base imbalances and electrolyte disturbances.[2-4] The resultant diabetic cardiomyopathy and coronary artery disease predispose the heart to cardiac contractile dysfunction, ischaemic heart disease and dysrhythmias. In addition, the macrovascular and microvascular angiopathies in diabetes induce target-organ damage in other tissues, such as the brain, kidneys and eyes.[5] Therefore, diabetes mellitus has been proposed to be a cardiovascular disease,[6] and the modulation of pathological cardiovascular remodelling could represent one aspect of diabetic treatment. However, the mechanisms of remodelling are not fully understood.

Hypomagnesaemia is a common and detrimental type of electrolyte disturbance in diabetes, especially in chronic, poorly controlled diabetes.[7,8] In diabetic patients, hypomagnesaemia is associated with cardiovascular conditions such as atherosclerosis,[9] coronary artery disease,[10] and arrhythmias.[11] However, although magnesium (Mg^{2+}) has been shown to modulate insulin receptors and to improve metabolic control in diabetic rats,[12] the role of Mg^{2+} in cardiovascular pathological remodelling remains unclear.

An area of difficulty in determining the role of Mg^{2+} at tissue level is that Mg^{2+} tissue deficits are not readily detectable, given that Mg^{2+} is largely an intracellular ion, binds to cellular components, and has relatively slow shifts across the cell membrane.[13] Furthermore, clinical hypomagnesaemia is indicative of decreased ionised Mg^{2+} in serum and may not necessarily reflect cellular deficits or the degree of imbalance between extracellular and intracellular concentrations. These issues suggest that a possible way to offset the occurrence of subtle, but detrimental Mg^{2+} tissue deficits and imbalances that may be induced by pathological stress conditions such as diabetes would be to prevent subclinical intracellular Mg^{2+} deficiency through Mg^{2+} supplementation.

We previously showed that Mg^{2+} supplementation improved cardiac ventricular compliance and cardiac autonomic function in the early stages of diabetes in rats,[14] but the long-term efficacy of Mg^{2+} in chronic diabetes and the underlying mechanisms remain unknown. In this study, we investigated the long-term effect of Mg^{2+} treatment on cardiac ventricular dysfunction in chronic diabetes and explored the possible role of electrical and myocardial histological alterations.

Methods

The study was approved by the Faculty of Health Sciences Animal Research Ethics Committee of the University of Cape Town (AEC Protocol 014-014). All procedures on animals were performed in compliance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, National Academy Press, 2011). Adult male Wistar rats (~ 275 g) were used in this study. Rats were housed under standardised conditions (12-hour light/dark cycle and temperature of ~ 23°C) and had free access to rat chow and drinking water.

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Unless stated otherwise, drugs and chemicals were obtained from Sigma-Aldrich (SA). Streptozotocin (STZ) was used to induce a moderate form of diabetes mellitus, as previously described.[14] Rats were fasted of food (but not water) for six hours to improve the uptake of STZ before being injected intraperitoneally (i.p.) with STZ (50 mg/kg). The STZ was freshly dissolved in 0.1 M citrate buffer (pH 4.5) before administration.

Blood glucose was measured from tail vein blood samples obtained at similar times of the day using a glucometer (Accu-Chek, Roche, SA).[14] Rats with a random blood glucose concentration ≥ 15 mmol/l were considered diabetic.

Magnesium was administered as $MgSO_4$ (270 mg/kg, i.p.) dissolved in normal saline.[15,16] The i.p. route was chosen for Mg^{2+} to achieve more reliable uptake compared to oral administration in water or food where the uptake may vary in diabetes due to polydipsia and polyphagia.

The rats were randomly divided into four treatment groups, and each rat was identified by a unique label on the tail. The control group was injected i.p. with a single dose of citrate buffer on the first day, and with saline i.p. once daily for 28 consecutive days. The STZ group was injected i.p. with a single dose of STZ 50 mg/kg on the first day, and with saline i.p. once daily for 28 days. The STZ + Mg^{2+} group was injected i.p. with a single dose of STZ 50 mg/kg on the first day, and with $MgSO_4$ 270 mg/kg i.p. once daily for 28 days. The Mg^{2+} group was injected i.p. with a single dose of citrate buffer on the first day, and with $MgSO_4$ 270 mg/kg i.p. once daily for 28 days.

Rat hearts were surgically removed under anaesthesia to euthanise the rats, as previously described.[16] Briefly, rats were anticoagulated with heparin (500 IU/kg, i.p.) and anaesthetised with sodium pentobarbital (70 mg/kg, i.p., Vetserv, SA). Upon loss of the pedal withdrawal reflexes, the hearts were excised via a thoracotomy incision and placed in cold (4°C), filtered (7-µm pore Whatman filter paper, Sigma-Aldrich, SA), modified Krebs-Henseleit (KH) solution containing (in mmol/l): 118.5 NaCl, 4.7 KCl, 25 $NaHCO_3$, 1.2 $MgSO_4$, 1.8 $CaCl_2$, 1.2 KH_2PO_4 and 11 glucose (pH 7.4). $CaCl_2$ was added after the optimisation of pH to prevent precipitation of calcium with phosphate. Some hearts were used for cardiac perfusion studies, whereas the others were either histologically analysed or snap-frozen in liquid nitrogen and stored at –80°C for Western blot analysis.

For perfusion studies, the hearts were retrogradely perfused with K-H solution through an aortic cannula on a constant-pressure (74 mmHg) Langendorff apparatus. To ensure optimal cardiac tissue viability, the time lapse between excision of the heart and commencement of perfusion was limited to three minutes. The K-H solution was gassed with carbogen (95% O_2 and 5% CO_2) and was maintained at 37°C. The coronary flow rate was measured by collecting coronary effluent over time and was normalised to heart weight. Blood samples used for Mg^{2+} assays were collected at the time of removal of the heart and centrifuged at 15 000 *g* (Beckman microfuge, USA) to obtain plasma, which was frozen until further analysis.

Electrocardiographic (ECG) and haemodynamic parameters were measured using the PowerLab data-acquisition system and LabChart Pro 7 software (ADInstruments, Australia), as previously described.[16] ECG was recorded using apex-to-base electrodes via a transducer (ML136) and was analysed using the LabChart Pro ECG module (ADInstruments, Australia). The QT interval, corrected for heart rate (QTc) was calculated using Bazett's formula. Left ventricular (LV) pressure was measured using a water-filled, intraventricular balloon connected to a pressure transducer (MLT1199) and amplifier (ML221, ADInstruments, Australia).

The hearts were stabilised for 20 minutes and the LV end-diastolic pressure (LVEDP) was set at 5–10 mmHg. The LabChart 7 Pro blood pressure module (ADInstruments, Australia) was used to analyse haemodynamic data and to derive the maximal rate of pressure increase ($+dP/dt_{max}$), the maximal rate of pressure decline ($–dP/dt_{max}$), contractility index and the time constant of ventricular relaxation (*tau*). The LV developed pressure (LVDP) was calculated as the difference between LV peak systolic pressure and LVEDP.

Transverse sections of cardiac ventricular tissue were stained with either haematoxylin and eosin (H&E) or Masson's trichrome, as previously described.[16] Histological images were taken using a charge-coupled device camera (Zeiss AxioCam, Germany) attached to an optical microscope (Zeiss AxioSkop, Germany). The cardiomyocyte width on H&E images was analysed using ImageJ software (NIH, USA). The average width of five cells on each of four sections of the heart was calculated for each heart. The degree of interstitial and perivascular fibrosis on Masson's trichrome images was semi-quantitatively scored, as done previously,[16] based on a scoring system described by Buwa *et al*.[17] as follows: none (–), mild (+), moderate (++), and severe (+++).

Frozen LV tissues were homogenised on ice by sonication in a modified radioimmunoprecipitation assay buffer (50 mM Tris-HCl, 150 mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulphate, pH 7.4) containing a protease/phosphatase inhibitor cocktail (Thermo Scientific, USA). Protein concentrations were quantified (Pierce protein assay kit, Thermo Scientific, USA) and protein samples (40 µg) were loaded and electrophoresed on 12% sodium dodecyl sulphate-polyacrylamide gels (Mini-Protean Tetra Cell, BioRad, SA) and transferred to isopropanol-soaked polyvinylidene fluoride membranes (Trans-Blot Turbo, Bio-Rad, SA).

The membranes were blocked with 5% bovine serum albumin (BSA) in 0.1% Tween20 phosphate-buffered saline (PBS-T) for one hour at room temperature, and incubated with anti-ATP5A mouse antibody (1:5000, #136178, Santa Cruz Biotechnology, USA) in 5% BSA in PBS-T overnight at 4°C. The primary antibody was excluded in the negative control in order to rule out non-specific binding of the secondary antibody. The membranes were washed with PBST and incubated with horseradish peroxidase-conjugated secondary antibody (1:10000, #170-6516, Bio-Rad, SA) in 5% BSA in PBS-T for two hours at room temperature.

The membranes were then washed with PBS-T, incubated with enhanced chemiluminescence substrate (Bio-Rad, SA) and exposed to X-ray film in the dark room. The membranes were stripped, blocked and re-probed with anti-β-actin rabbit antibody (1:10000, #16039, Abcam, USA) and goat anti-rabbit secondary antibody (1:10 000, #6721, Abcam, USA). The bands on films were analysed using ImageJ software (NIH, USA) and were normalised to those of the housekeeping protein β-actin.

The Mg^{2+} concentration was measured in the plasma samples prepared at exsanguination, 18–24 hours after the final dose of $MgSO_4$ had been administered. Ionised Mg^{2+} concentration was measured using automated spectrophotometric and

potentiometric analyses (Beckman AU Chemistry Analyzer, PathCare, SA).[14]

Statistical analysis

Data are expressed as mean and standard error of the mean (SEM) or as box plots and the mean, and *n* indicates the number of replicates. Statistical analysis was conducted using Statistica 13. Differences among multiple groups for data with normal distribution (Kolmogorov–Smirnov and Shapiro–Wilk normality tests) were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test. For data without normal distribution, a Kruskal–Wallis test was conducted, followed by Dunn's *post hoc* test. A two-tailed *p* value ≤ 0.05 was considered statistically significant.

Results

In vivo treatment with STZ significantly increased the blood glucose concentration and decreased the rat body weight (Fig. 1), starting from the first week after treatment ($p < 0.05$, STZ vs control for each parameter). Overall, treatment with Mg^{2+} did not prevent STZ-induced hyperglycaemia ($p > 0.05$, STZ + Mg^{2+} vs STZ), except for the transient dips in blood glucose concentration observed in the first and third weeks (Fig. 1A). Mg^{2+} also did not prevent the STZ-induced loss of body weight ($p > 0.05$, STZ + Mg^{2+} vs STZ; Fig. 1B). Mg^{2+} treatment alone had no significant effect on blood glucose concentration or on body weight ($p > 0.05$, Mg^{2+} vs control for each parameter).

STZ induced a significant decrease in the LVDP ($p < 0.05$, STZ vs control), and this STZ-induced hypotensive effect was prevented by Mg^{2+} treatment ($p = 0.03$, STZ + Mg^{2+} vs STZ; Fig. 2A). Mg^{2+} treatment on its own had no significant effect on LVDP ($p > 0.05$, Mg^{2+} vs control; Fig. 2A). STZ-treated hearts also exhibited significant reductions in the indices of LV contraction ($+dP/dt_{max}$) and relaxation ($-dP/dt_{max}$) as well as in the overall contractility index ($p < 0.05$, STZ vs control for each parameter; Fig. 2B–D). Among these changes, Mg^{2+} treatment reversed the STZ-induced reduction of $+dP/dt_{max}$ and contractility index ($p < 0.05$, STZ + Mg^{2+} vs STZ for each parameter; Fig. 2B, C). Mg^{2+} treatment alone had no detrimental effect on $+dP/dt_{max}$, $-dP/dt_{max}$, or the contractility index ($p > 0.05$, Mg^{2+} vs control; Fig. 2B–D).

In addition, there were no significant differences in coronary flow rate or in the ratio of heart weight to body weight among the different treatment groups (Fig. 2E, F). There were also no significant differences in the diastolic time constant of ventricular relaxation (*tau*) among the groups (*tau*: 0.043 ± 0.065 s for control, 0.073 ± 0.030 s for STZ, 0.064 ± 0.023 s for STZ +Mg^{2+}, 0.080 ± 0.033 s for Mg^{2+}; values are mean ± SEM, $p > 0.05$, $n = 6$ per group).

Representative ECG traces recorded on isolated hearts (Fig. 3) showed typical apex-to-base electrical waveforms that resembled lead II tracing on a surface ECG recording. Qualitatively, the traces highlight a reduction in the heart rate of STZ-treated hearts (Fig. 3B) compared to controls (Fig. 3A), but without noticeable alterations of the ECG waveform patterns. Summary data of ECG parameters (Table 1) show that STZ significantly decreased the heart rate and prolonged the QT interval ($p < 0.01$ vs control for each parameter), and both these STZ effects could be prevented by Mg^{2+} treatment. Mg^{2+} treatment alone had no significant effect on heart rate or QT interval. There were no significant differences in the R-, S- or T-wave amplitudes and QRS and QTc intervals among the treatment groups.

Representative images of ventricular slices stained with either H&E or Masson's trichrome are shown in Fig. 4. The H&E images

Table 1. Electrocardiogram parameters

Parameters	*Control*	*STZ*	*STZ+Mg*	*Mg*
Heart rate (bpm)	233 ± 8	178 ± 14*	218 ± 8#	234 ± 13
R-wave amplitude (mV)	5.22 ± 0.79	5.67 ± 1.31	6.24 ± 1.17	6.22 ± 0.85
S-wave amplitude (mV)	1.75 ± 0.27	2.13 ± 0.63	2.35 ± 0.73	0.40 ± 1.38
T-wave amplitude (mV)	2.12 ± 0.53	2.56 ± 0.67	2.73 ± 0.95	1.76 ± 0.46
QRS interval (s)	0.020 ± 0.003	0.024 ± 0.002	0.026 ± 0.006	0.024 ± 0.003
QT interval (s)	0.062 ± 0.002	0.079 ± 0.009*	0.065 ± 0.005#	0.064 ± 0.006
QTc (s)	0.124 ± 0.006	0.137 ± 0.016	0.119 ± 0.007	0.121 ± 0.009

QTc represents QT interval corrected for heart rate. Values are mean ± standard error of the mean; $n = 7–11$ per group; *$p < 0.05$ vs control; #$p < 0.05$ vs STZ.

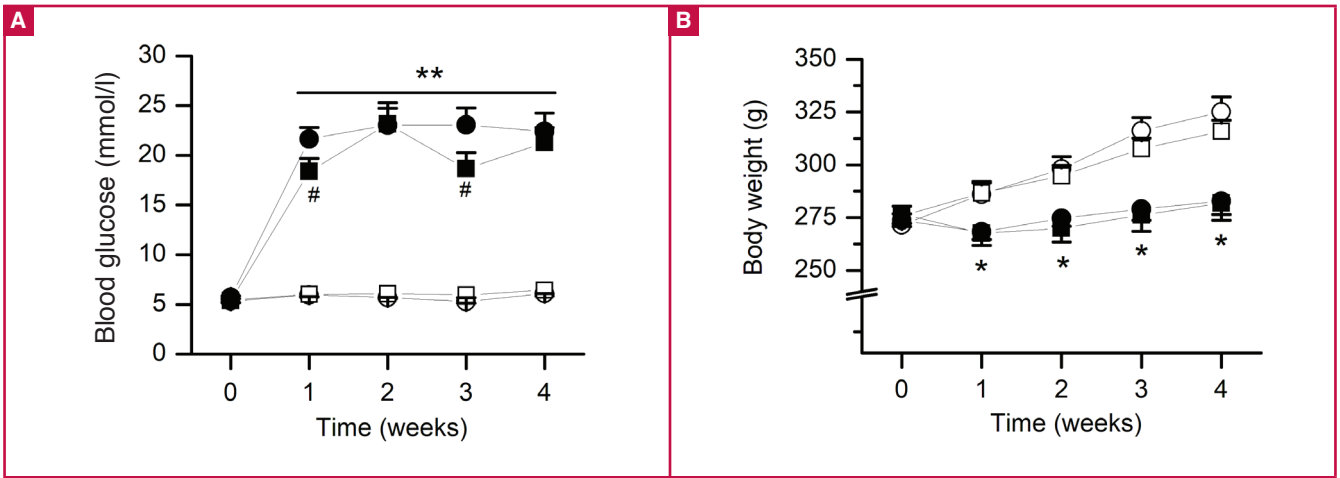

Fig. 1. General parameters. A: Random blood glucose concentration. B: Rat body weight. The parameters were measured weekly in different treatment groups of rats [○, control; ●, streptozotocin (STZ); ■, STZ + Mg^{2+}; □, Mg^{2+}]. Values are mean ± standard error of the mean; $n = 12–15$ per group; *$p < 0.05$, **$p < 0.01$ versus control; #$p < 0.05$ versus STZ.

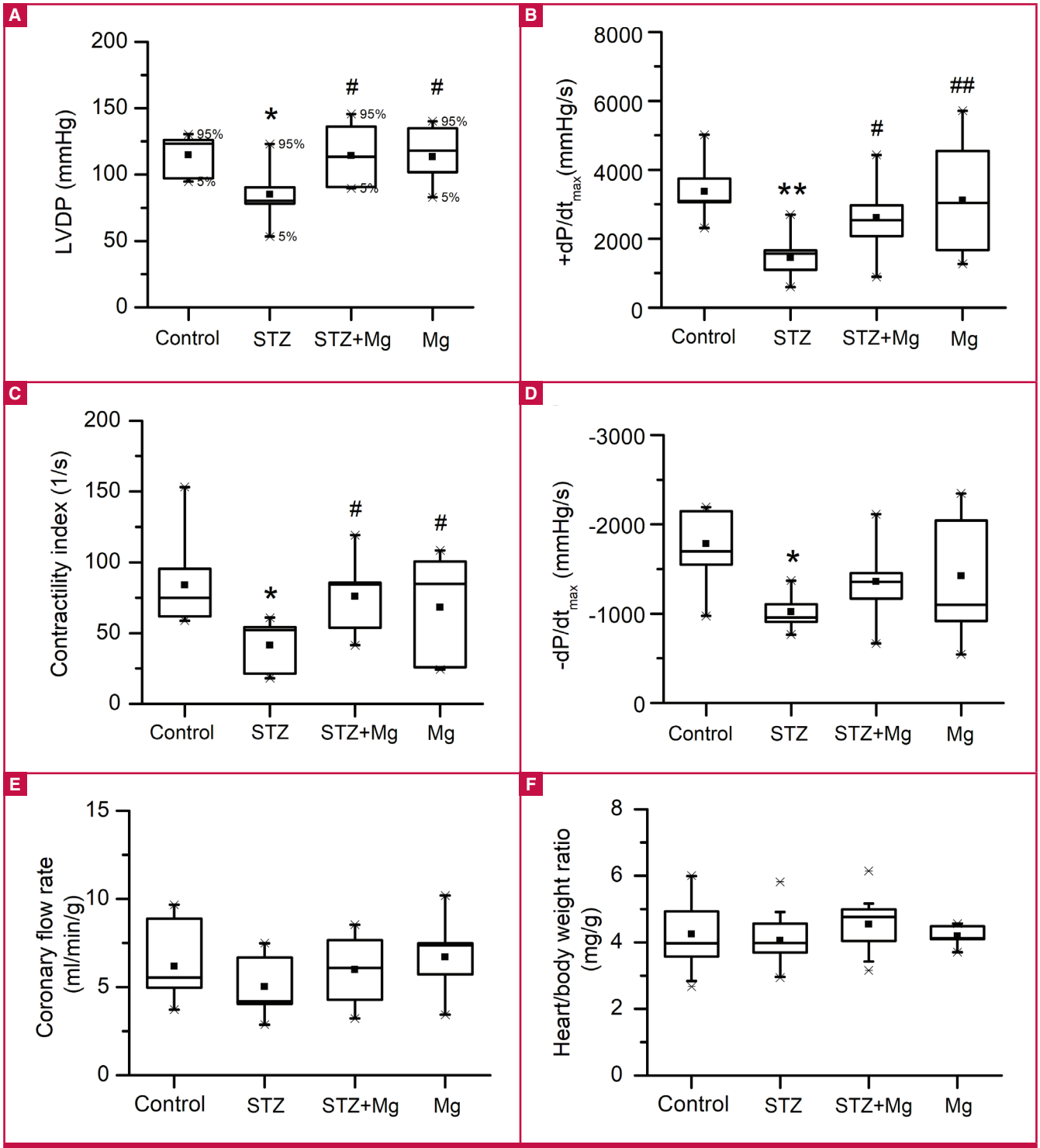

Fig. 2. Effects of treatments on haemodynamic parameters. A: Left ventricular (LV) developed pressure (LVDP). B: Maximal rate of LV pressure increase (+dP/dt$_{max}$). C: Contractility index. D: Maximal rate of LV pressure decline (–dP/dt$_{max}$). E: Coronary flow rate, normalised to heart weight. F: Heart weight to body weight ratio. Data are shown as box plots and the mean (■); n = 6–9 per group; $^{*}p < 0.05$, $^{**}p < 0.01$ versus control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ versus STZ.

showed normal cardiomyocyte structural outlines, separated by extracellular spaces that were relatively free of cellular components or other infiltrates (Fig. 4A). There were also no apparent distortions in the arrangement of the myofibrils. There were no significant differences in cardiomyocyte width among the treatment groups ($p > 0.05$; Fig. 4C). The Masson's trichrome images showed no differences in the interstitial or perivascular fibrosis score among the treatment groups (Fig. 4B, D).

To explore the role of cardiac metabolic stress, Western blot analysis was performed for the mitochondrial ATP synthase (ATP5A), a key component of the mitochondrial respiratory function. Representative images on Western blot films (Fig. 5A)

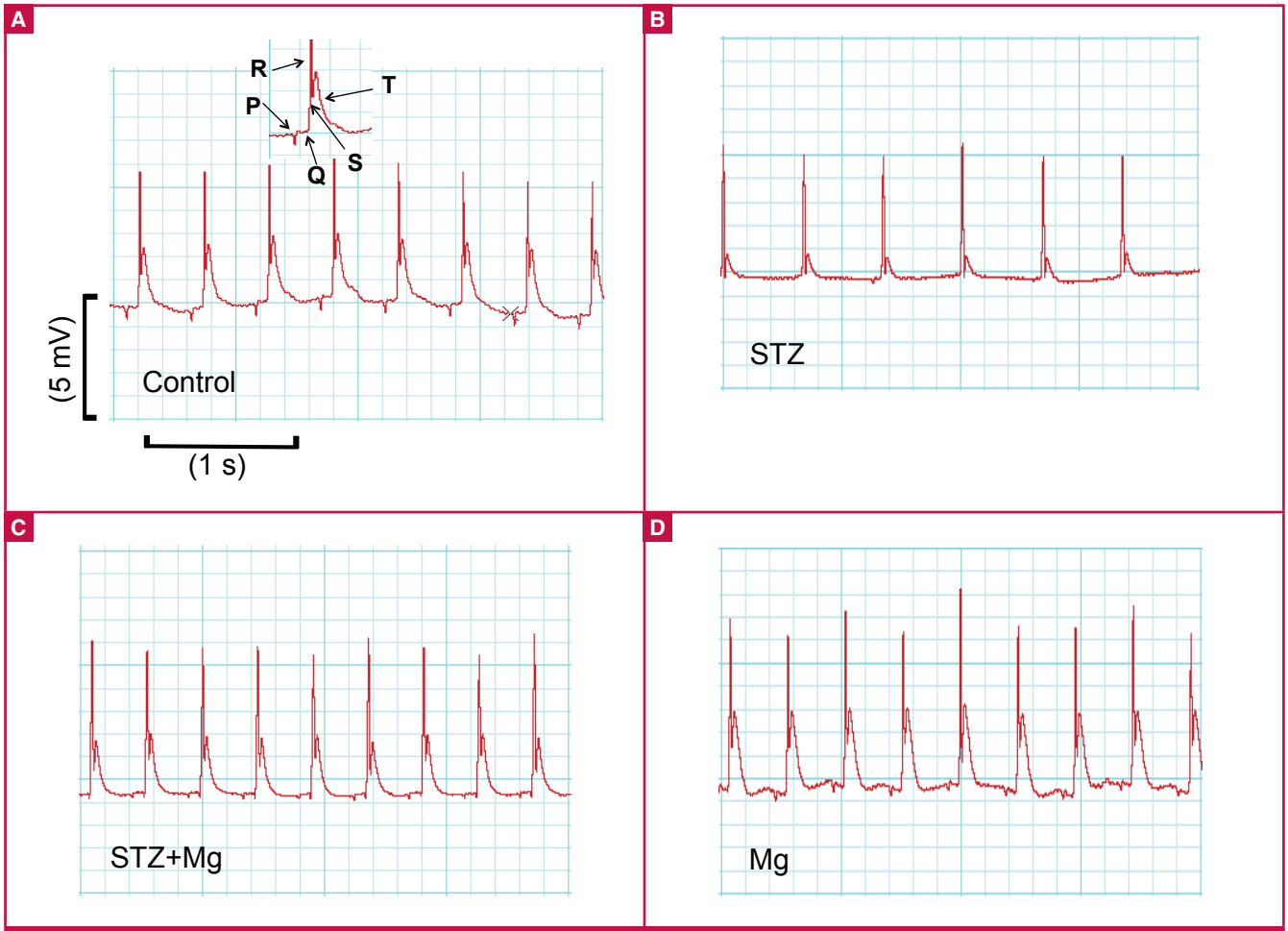

Fig. 3. Electrocardiographic (ECG) traces. A–D: Representative ECG traces recorded from different isolated hearts during Langendorff perfusion. Inset in (A) shows labels of the ECG waves. Notice that the S and T waves in the rat heart are contiguous.

showed bands of ATP5A and β-actin proteins in the ventricles of different hearts. Semi-quantitatively, there were no significant differences in the expression of ATP5A among the treatment groups (Fig. 5B).

There were no significant differences in the plasma Mg^{2+} concentration among the groups (concentration of ionised Mg^{2+}: 0.89 ± 0.01 mmol/l for control, 0.94 ± 0.05 mmol/l for STZ, 0.85 ± 0.04 mmol/l for STZ +Mg^{2+}, 0.83 ± 0.01 mmol/l for Mg^{2+}; values are mean ± SEM, $p > 0.05$, $n = 8$ per group).

Discussion

The onset and severity of cardiovascular complications in poorly controlled diabetes mellitus are time-dependent entities. In this study, we showed that Mg^{2+} treatment induced long-term improvements in LV contractile function and stabilised heart rate in chronic diabetic rats.

Our results indicated the presence of diabetes-induced ventricular systolic dysfunction in chronic diabetes, as was evidenced by the reduction in LVDP, $+dP/dt_{max}$ and the contractility index in diabetic hearts. These findings are consistent with the systolic dysfunction reported in chronic type 1 diabetes patients[18] and in STZ-induced diabetic rats.[19-21] However, the results are in contrast to the lack of systolic impairment that we previously observed in the acute diabetes disease model,[14] where only diastolic dysfunction was observed, suggesting a time-dependent progression of diabetic cardiac complications.[20]

In the present study, except for the unaltered time constant of relaxation (*tau*), diastolic dysfunction was not further evaluated since the LVEDP had to be pre-set to a fixed value in order to measure LVDP. Nonetheless, in this study, the systolic dysfunction in diabetes was reversed by Mg^{2+} treatment. Recently, Mg^{2+} was also shown to improve diastolic function and mitochondrial activity in fat-fed chronic diabetic mice.[22] Given that diabetic diastolic dysfunction is known to precede systolic impairment in type 1 diabetic patients[18] and in STZ-induced diabetic rats,[19,20] and that diastolic dysfunction is a common cause of systolic heart failure in diabetes,[23] the improvement of systolic activity by Mg^{2+} observed in our study could be secondary to the diastolic modulation observed in the acute diabetes disease model.[14]

In the present study, there were no detectable cardiac morphological changes to account for the contractile dysfunction induced by diabetes. The gross heart weight was unaltered, and histologically, there was neither a change in cardiomyocyte size nor interstitial fibrosis. In addition, there was no significant coronary perivascular fibrosis or cellular infiltrates that would have been expected to impair coronary perfusion, a finding that

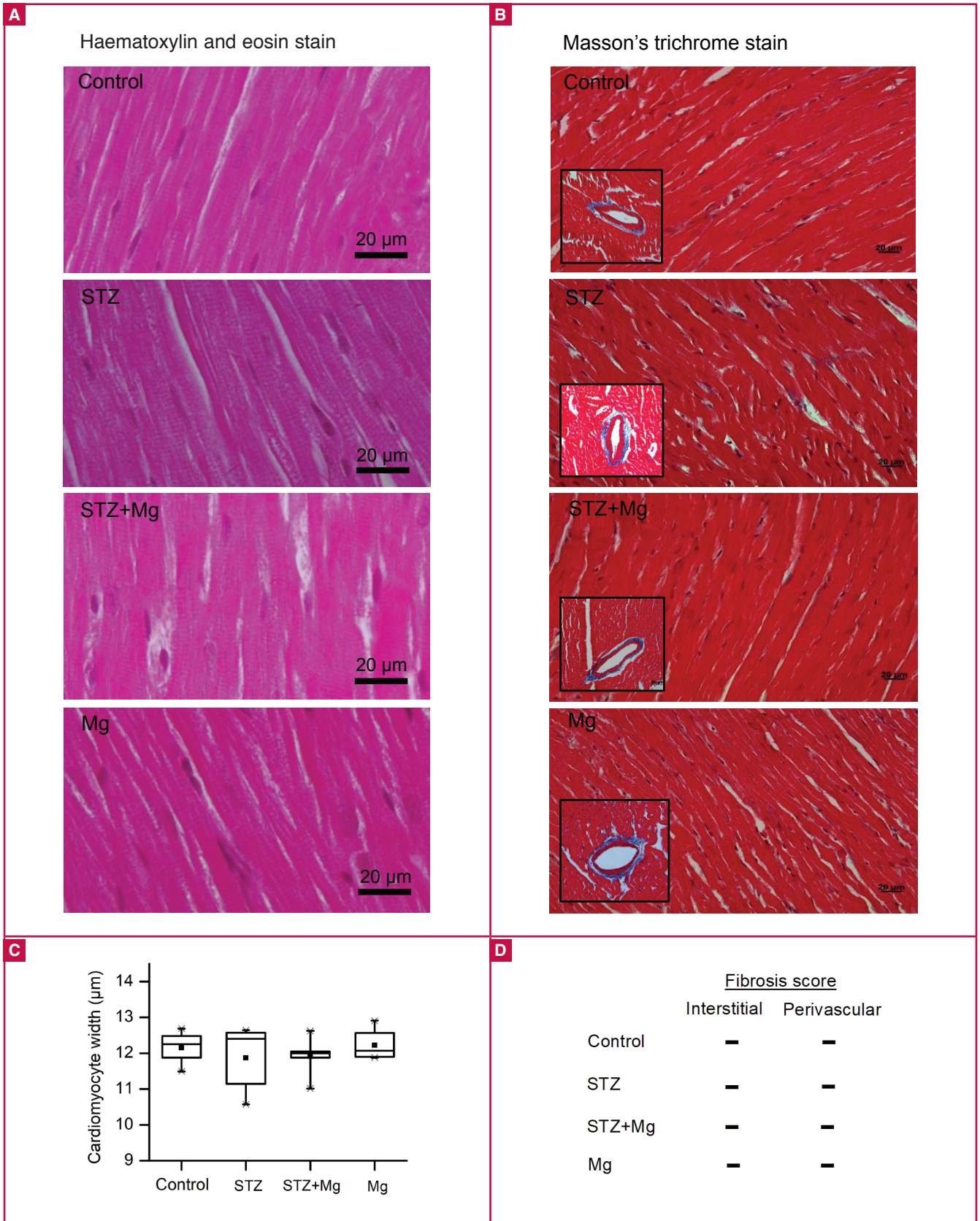

Fig. 4. Histological analyses of ventricular tissue. A: Representative images of different ventricular tissue sections stained with haematoxylin and eosin (H&E). Scale bar = 20 µm (× 40 magnification). B: Representative images of different ventricular tissue sections stained with Masson's trichrome. Insets: Images of perivascular tissue. Scale bar = 20 µm (× 40 magnification). C: Summary data of ventricular cardiomyocyte width. D: Arbitrary score of the degree of interstitial and perivascular fibrosis: –, none; +, mild. Data are shown as box plots and the mean (■); n = 6 per group.

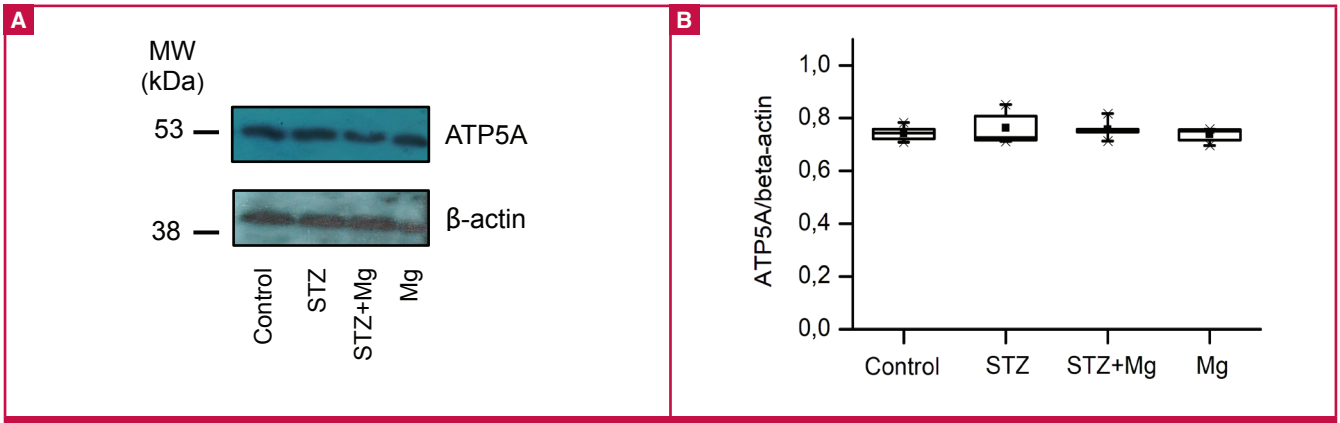

Fig. 5. Western blot analysis of mitochondrial ATP5A protein. A: Representative Western blot film images of ATP5A and the corresponding β-actin in ventricular tissue of different hearts. B: Summary data of the fold-expression of ATP5A, normalised to that of β-actin. Data are shown as box plots and the mean (■); n = 3 per group.

was also consistent with the lack of change in coronary flow rate observed in this study.

These findings are in agreement with those in other studies on chronic STZ-induced diabetic rats in which the cardiac dysfunction was not accompanied by histological evidence of cardiac cellular hypertrophy or fibrosis.[20] In contrast, other studies in chronic STZ-induced diabetic rats showed that there was cardiac dysfunction together with histological evidence of cardiomyocyte hypertrophy and fibrosis.[24] These histological differences are likely to be related to the duration of diabetes, given that in diabetic patients, the deposition of collagen in cardiac tissue only becomes more prominent in the later stages of heart failure when there is a low ejection fraction.[25]

In our study, there were no significant cardiac histological changes to account for the effect of Mg^{2+}. Taken together, the lack of histological alterations in our study supports the concept that the nature of diabetic ventricular dysfunction and the effect of Mg^{2+} were functional, rather than structural.

The STZ-induced decrease in heart rate observed in the present study and its prevention by Mg^{2+} were consistent with our previous findings in the acute-diabetes model where the relative bradycardia was also observed *in vivo*.[14] The bradycardia in STZ-induced diabetic rats has also been reported in other studies,[20,26] and has been attributed to cardiac autonomic synaptic degradation,[26] but the basis of the bradycardia in our study remains unclear. In this study, the bradycardia seemed to be unrelated to the modulation of cardiac electrical activity since there were no significant changes in ECG waves. The prolongation of the QT interval in diabetes was probably related to changes in heart rate because the QT interval, corrected for the heart rate (QTc), was not significantly different among the treatment groups. Taken together, the occurrence of bradycardia both *in vivo* and *ex vivo* and its prevention by Mg^{2+} suggest that these effects were intrinsic to the heart.

Despite the improvements in cardiac function by Mg^{2+}, there were no significant differences in the cardiac expression of ATP5A, a cardiac biomarker that could have accounted for the Mg^{2+} effects at a molecular level. Mg^{2+} is a key co-factor of several co-enzymes that may alter the cardiac metabolic status, it also contributes to cellular energetics via its coupling with ATP to form MgATP,[13] and it may therefore alter mitochondrial function. However, in our study, there were no changes in the metabolic indices, as was indicated by the mitochondrial metabolic component ATP5A. Therefore, further molecular studies such as those evaluating aspects of mitochondrial fusion/fission are required to elucidate the role of Mg^{2+} at the cardiac cellular level.

Limitations of this study include the use of an artificial, STZ-induced diabetic model, in which the Mg^{2+} effects may not be readily translatable to the natural disease. However, the STZ-induced diabetic rat model is known to mimic diabetic complications in humans.[21] We also previously showed the value of this disease model in that, apart from mimicking type 1 diabetes, it also exhibited features of type 2 diabetes, such as dyslipidaemia.[14] Also, the clinical relevance of the Mg^{2+} dose used in this study remains unclear, given that that the dose (270 mg/kg) is higher than that used via the oral route in human supplementation, and is only comparable to the loading intravenous/intramuscular dose used in eclampsia (~ 230 mg/kg).[27] Nonetheless, the peak increases at 3.5 hours of ~ 0.7 mmol/l, achievable under our experimental conditions,[15] are still within the therapeutic ranges of other clinical conditions.[27] Finally, since the experiments were performed at cardiac tissue level, the presence of an intracellular Mg^{2+} deficit cannot be excluded, and therefore requires further investigations at a cellular level.

Conclusion

The results of this study show that Mg^{2+} improved cardiac contractile function and stabilised heart rate in the STZ-induced chronic diabetes rat model, without preventing metabolic derangements such as hyperglycaemia. The mechanisms underlying the attenuation of cardiac dysfunction in chronic diabetes mellitus by Mg^{2+} were unrelated to electrocardiographically or histologically detectable changes, but the exact pathways involved require further investigation.

The study was supported by the South African Medical Research Council (MRC, Grant No 29841) and by the National Research Foundation (NRF) of South Africa (Grant No 91514).

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Effect of mitral valve replacement on left ventricular function in subjects with severe rheumatic mitral regurgitation

Sharen Maharaj, Somalingum Ponnusamy, Datshana Naidoo

Abstract

Introduction: This study describes the effects of mitral valve replacement (MVR) on left ventricular (LV) function in patients with severe rheumatic mitral regurgitation (MR).

Methods: This was a retrospective analysis over a nine-year period (2005–2013). Clinical and echocardiographic parameters were recorded pre-operatively and at two weeks, six weeks to three months and six months following MVR.

Results: Of the 132 patients included in the study, 66% were in New York Heart Association (NYHA) class III–IV and 38% presented with clinical features of heart failure. Pre-operatively, 28% of subjects had impaired LV function [ejection fraction (EF) < 60%] and the majority had advanced chamber dilatation [left ventricular end-diastolic diameter (LVEDD) 60.7 ± 7.9 mm (n = 132), left ventricular end-systolic diameter (LVESD) 39.9 ± 7.2 mm (n = 118) and left atrial size 61.2 ± 12.6 mm (n = 128)]. Paired analysis of 83 patients revealed that the EF was > 55% in 87% (n = 72) pre-operatively, decreasing to 20% (n = 17) of patients at two weeks postoperatively (p < 0.001); thereafter an EF > 55% was recorded in 60% (n = 50) at the six-month follow-up visit (p < 0.001). On multivariate analysis, only LVESD emerged as a significant predictor of postoperative LV dysfunction.

Conclusion: In this study, most patients with severe MR presented late with significant impairment of LV function and chamber dilatation that often did not recover fully after surgery. This study emphasises early comprehensive evaluation of severe MR followed by timeous surgery in order to preserve LV function.

Keywords: mitral regurgitation, mitral valve replacement, left ventricular function, heart failure

Submitted 13/3/20, accepted 1/12/20
Published online 12/2/21
Cardiovasc J Afr 2021; **32**: 149–155 www.cvja.co.za

DOI: 10.5830/CVJA-2020-056

Recent hospital-based studies in South Africa (SA) reveal an incidence of congestive heart failure secondary to rheumatic heart disease (RHD) of 25 cases per 100 000 per year.[1,2] Mitral regurgitation (MR) is one of the commonest causes of heart failure in subjects with RHD. Subjects with MR may remain asymptomatic for several years. Symptoms occur late in the natural history of chronic MR since the left atrium dilates to accommodate large volumes of blood without a significant rise in left atrial (LA) pressure.[3]

As the lesions of MR progress, left ventricular (LV) volume overload ensues as a result of the increase in the regurgitant orifice area.[4] Long-standing severe MR eventually leads to impaired LV function with increasing end-systolic volumes and pulmonary congestion. Although there may be underlying LV dysfunction, ejection fraction (EF) is maintained until late in the disease process.[4]

At the point when the end-systolic diameter (ESD) increases to above 40 mm, the EF falls below 60%.[4] International guidelines therefore recommend surgical intervention when the patient develops dyspnoeic symptoms, and/or echocardiography demonstrates evidence of LV dysfunction (EF < 60%) and/or dilatation (ESD > 45mm).[4,5] However, not much is known about the outcome of surgery in subjects with overt impairment of LV function.[6]

We hypothesised that in these subjects, recovery of contractile function is slow, with persistence of heart-failure symptoms. Since these subjects are known to have a poorer prognosis[7] and reduced survival rates,[8] we examined the early surgical outcome in those with impaired LV function, and evaluated the response of the LV after corrective surgery.

Methods

This retrospective study was conducted in subjects with severe rheumatic MR confirmed by echocardiography in the Department of Cardiology at Inkosi Albert Luthuli Central Hospital (IALCH) over a nine-year period (2005–2013). Patients were selected using the common procedural terminology (CPT) code for mitral valve replacement (33 430) via the Speedminer software program 3 (Speedminer, Malaysia), which is the Data Warehouse Management software package used at IALCH to record and categorise patients' medical details. Patient demographics, HIV status, New York Heart Association (NYHA) classification, presence of atrial fibrillation, chronic medication and echocardiographic parameters were recorded at their most recent pre-operative visit and subsequent to mitral valve replacement (MVR) at two-week, six-week to three-month, and six-month follow-up intervals. Data were collected and grouped according to pre-operative EF in each case: EF < 40%, EF = 40–49%, EF = 50–59% and EF > 60%.

Patients with isolated, pure rheumatic MR were included. Patients with ischaemic and functional MR, concomitant mitral stenosis with mitral valve area (MVA) < 2.5 cm², aortic valve

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disease, congenital heart disease, previous MV surgery or other cardiac surgery were excluded. Surgical operative notes were further scrutinised to determine mitral valve pathology and document cardiopulmonary bypass times (CPBT).

Two-dimensional directed m-mode and colour Doppler echocardiography were 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 LV end-systolic (LVESD) and end-diastolic dimensions (LVEDD), left atrial (LA) size, pulmonary artery systolic pressures (PASP) and the presence and severity of tricuspid regurgitation (TR) were measured according to the American Society of Echocardiography (ASE) chamber guidelines.[9] EF was assessed using the Simpson's method.[9]

MR was considered to be rheumatic in aetiology when the morphology of the valve satisfied the proposed World Heart Federation criteria for the diagnosis of chronic RHD.[10] 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.[9,11] 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 clinical endpoints of this study were cardiovascular mortality and persistent heart failure postoperatively at the six-month assessment. Multivariate analysis of pre-operative EF and other pre-operative echocardiographic parameter/s (LVEDD, LVESD, LA and PASP) was used to predict post-operative LV dysfunction. Comparison between the pre- and postoperative NYHA class was drawn to determine improvement in functional disability and symptoms.

Statistical analysis

The Statistical Package for Social Sciences (SPSS version 23.0) (IBM, Los Angeles) was utilised in the analysis of data for the study. A 95% level of 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 deviations (SD).

The Student's *t*-tests and the chi-squared tests were used to compare continuous and categorical variables, respectively. Paired samples were used to compare changes in echocardiographic variables before and after surgery. A *p*-value of < 0.05 suggested statistically significant findings for the variables being measured. Comparison between the pre- and postoperative NYHA class was drawn to determine change in functional disability. Logistic regression analysis was used to identify pre-operative predictors of impaired LV function (EF < 50%), and included CPBT as a potential factor for post-operative LV dysfunction.

Results

During the nine-year period, 788 subjects underwent surgery for severe MR. Based on the inclusion criteria, a total of 656 patients were excluded, leaving 132 subjects with chronic, severe, isolated MR for analysis. There were 97 females (73%) and 35 males. Eighty three per cent of patients ($n = 109$) were under the age of 25 years. In the 75% of subjects who were tested, 8% ($n = 11$) were HIV infected. Other co-morbid conditions were present in 13% of the sample.

At baseline, 66% ($n = 87$) of patients were in NYHA functional class III–IV (NYHA III, 30%, NYHA IV, 36%). Heart failure with fluid overload was a common mode of presentation and was present in 38% ($n = 50$) of subjects, and 14% ($n = 19$) had atrial fibrillation prior to surgical intervention (Table 1). Medication prescribed to the patients in the study included diuretics (92%), angiotensin converting enzyme (ACE) inhibitors (95%), β-blockers (8%), calcium channel blockers (2%), digoxin (21%) and penicillin (72%).

For the entire group, the median EF was 63% (IQR 58–70%), mean LVEDD 60.7 ± 7.9 mm, LVESD 39.9 ± 7.2 mm, and LA size 61.2 ± 12.6 mm. The median PASP was 59.5 mmHg (IQR 45–80 mmHg). Pre-operatively, 72% ($n = 95$) had an EF > 60% (median EF 65%, IQR 62–70%), 5% ($n = 7$) had an EF between 40 and 49% (median EF 42%, IQR 40–45%) and 23% ($n = 30$) had an EF between 50 and 59% (median EF 56%, IQR 55–57%). The LVEDD and LVESD were significantly higher in both groups with EF < 60% compared to EF > 60% ($p < 0.001$). The LA was grossly enlarged (over 55 mm) across all three EF groups and the PASP was similarly elevated in all three groups. Moderate to severe TR was present in all seven subjects in the EF 40–49% group, 62% of those in the EF 50–59% group and in 58% of those with EF > 60% (Table 2).

The patients' operative notes were studied to determine the macroscopic pathology of mitral valve disease as described by

Table 1. Baseline demographic and clinical data

	EF group							
	40–49% (n = 7)		*50–59% (n = 30)*		*> 60% (n = 95)*		*Total (n = 132)*	
Age group (years)	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
< 12	1	14	3	10	39	41	43	33
12–25	4	57	20	67	42	44	66	50
> 25	2	29	7	23	14	15	23	17
Gender								
Male	2	29	7	23	26	27	35	27
Female	5	71	23	77	69	73	97	73
HIV								
Negative	4	57	23	77	61	64	88	67
Positive	1	14	3	10	7	7	11	8
Not known	2	29	4	13	27	28	33	25
NYHA class								
I	0	0	1	3	9	9	10	8
II	1	14	9	30	25	26	35	27
III	2	29	8	27	29	31	39	30
IV	4	57	12	40	32	34	48	36
Heart failure								
Present	5	71	13	43	32	34	50	38
Absent	2	29	17	57	63	66	82	62
AF								
Present	1	14	4	13	14	15	19	14
Absent	6	86	26	87	81	85	113	86

AF, atrial fibrillation; EF, ejection fraction; NYHA, New York Heart Association. Only 23 subjects were over the age of 25 years. The majority was HIV negative.

Table 2. Baseline echocardiographic data across the different EF groups

	EF group			
	40–49% (n = 7)	*50–59% (n = 30)*	*> 60% (n = 95)*	*p-value*
LVEDD (mm)	62.6 ± 6.5	64.3 ± 8.3	59.4 ± 7.6	< 0.001
LVESD (mm)	49.0 ± 6.6	46.4 ± 5.8	37.5 ± 5.9	< 0.001
LA (mm)	56.3 ± 9.7	65.3 ± 13.8	60.2 ± 12.1	0.090
EF (%)*	42 (40–45)	56 (55–57)	65 (62–70)	< 0.001
PASP (mmHg)*	50 (38–53)	61 (35–79)	60 (47–80)	0.200

*Median (IQR). EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PASP, pulmonary artery systolic pressure. Ventricular dimensions were increased in groups with EF < 60%.

the cardiothoracic surgeon. All valves displayed varying degrees of rheumatic involvement as assessed by valve thickness and/or calcification. Fifty two per cent of patients (n = 69) had features of isolated chronic MR with no other findings. In addition to chronic MR, the remaining subjects also had chordal rupture (23%, n = 31), chordal elongation (16%, n = 21), active carditis (1.5%, n = 2), and one subject had both chordal rupture and elongation (1%).

Active carditis was diagnosed in the two patients who had adhesions from fibrinous pericarditis. Chordal elongation was also highly suggestive of ongoing active carditis in 21 patients. Chordal rupture was presumed evidence of active carditis in young subjects in the absence of infective endocarditis. Only two patients had infective endocarditis, both of whom presented in heart failure with EF > 55%. The first patient, a 23-year-old male, was found to have grossly impaired LV function (EF = 18%) at the two-week, and six-week to three-month follow-up visits, and was lost to follow up thereafter. The second, an 18-year-old female, had an EF of 70%, which fell to 40% at two weeks, and she was well (NYHA I) with no clinical features of cardiac failure at two years.

Despite being in heart failure, the majority of patients underwent uneventful surgery with a median CPBT of 77 minutes (n = 111, IQR 64–105 minutes). Most patients experienced significant improvement in NYHA functional class (Table 3) with resolution of heart failure. At six months following MVR (n = 93), 1% of patients were in NYHA III–IV, 1% of patients had heart failure and 7.6% had atrial fibrillation. The one patient who remained in heart failure had a pre-operative EF of 56%, which fell to 30% at two weeks postoperatively, and fell further at the subsequent follow-up visits, with a concomitant increase in left heart chamber dimensions. In total, there were 12 patients with a persistently low EF (< 50%) at the six-month follow-up visit; the median CPBT in this group was not significantly different from the remaining patients (98 minutes, IQR 80–106, p = 0.07).

Table 3. Pre- and postoperative functional class

	Pre-surgery (n = 132)		*6 months postsurgery (n = 93)*	
	n	*%*	*n*	*%*
NYHA				
I	10	7.6	79	84.9
II	35	26.5	13	14.0
III	39	29.5	1	1.1
IV	48	36.4	0	0.0

NYHA, New York Heart Association. Significant improvement was noted in the functional class after surgery.

There were five postoperative deaths, yielding a mortality rate of 4%. These deaths occurred in young patients with advanced NYHA class, grossly dilated LA (n = 2) and PASP > 50 mmHg (n = 3). There was no evidence of infective endocarditis or active rheumatic carditis at surgery. One patient, who had a low pre-operative EF of 40%, was HIV infected and died from lobar pneumonia and cardiac failure two weeks after the operation. Two patients were admitted *in extremis* pre-operatively, required cardioversion in theatre and died from a low-cardiac output state. A 21-year-old male whose EF fell from 68 to 35% at the two-week post-operative visit, died from cardiac tamponade a month later. The last patient was a nine-year-old child who died of massive air embolism following removal of the aortic cross clamp.

Fourteen patients had a marked reduction in EF (to EF < 30%) in the early postoperative period; eight of them had received inotropic support at the end of mitral valve surgery. Pre-operatively, nine of the 14 subjects had an EF < 60%, seven had advanced heart failure (NHYA IV) and five were in atrial fibrillation. The average CPBT in these patients was calculated to be 101 minutes (range 40–180 minutes). The EF recovered to > 50% in five of these 14 patients at the six-month follow up (pre-operative EF 65, IQR 58–67); two patients died and seven were lost to follow up.

Among the seven subjects with a pre-operative EF in the 40–49% range, only three recovered their EF to > 50% (EF: 52, 56 and 59%), with an accompanying fall in LVESD and resolution of TR at the six-month visit (Table 4). In this group there were two HIV-infected subjects: one had a pre-operative EF of 40% and died two weeks after MVR, and the other, who had a pre-operative EF of 55%, made an uneventful recovery. The remaining two groups (EF 50–59% and > 60%) responded similarly with an initial fall in the EF at two weeks and a steady increase thereafter to over 55% in both groups, accompanied by a decline in chamber dimensions and pulmonary artery pressure

Table 4. Follow-up echocardiographic data

		Postsurgery		
	Pre-surgery	*2 weeks*	*6 weeks – 3 months*	*6 months*
Pre-operative EF 40–49%				
LVEDD (mm)	62.6 ± 6.5	57.3 ± 5.9	58.7 ± 15	59 ± 19.8
LVESD (mm)	49.0 ± 6.6	–	35.0 ± 1.4	40.5 ± 13.4
EF (%)*	42 (40–45)	43 (18–48)	52.0 (10–54)	56.0 (52–59)
LA (mm)	56.3 ± 9.7	42.4 ± 6.3	58.0 ± 0	61.5 ± 19
PASP (mmHg)*	50 (38–53)	45 (37–62)	62.0 (40–64)	43.5 (35–52)
Pre-operative EF 50–59%				
LVEDD (mm)	64.3 ± 8.3	56.0 ± 8,7	55.3 ± 10.1	49.0 ± 9.6
LVESD (mm)	46.4 ± 5.8	41.5 ± 6,8	39.8 ± 10.4	36.0 ± 10.9
EF (%)*	56 (55–57)	40 (30–46)	50.0 (28–53)	56.0 (47–59)
LA (mm)	65.3 ± 13.8	51.0 ± 13,4	49.3 ± 11.8	44.6 ± 12.4
PAS (mmHg)*	61 (35–79)	46.5 (35–55)	43.0 (37–46)	34 (28.5–40)
Pre-operative EF > 60%				
LVEDD (mm)	59.4 ± 7.6	51.3 ± 7.7	46.5 ± 7.4	48.2 ± 7.4
LVESD (mm)	37.5 ± 5.9	36.2 ± 9.8	32.5 ± 9.4	31.8 ± 6.4
EF (%)*	65 (62–70)	47.5 (40-57)	56.0 (48.5–60)	57.0 (43–65)
LA (mm)	60.2 ± 12.1	49.0 ± 11.4	43.9 ± 9.1	42.6 ± 8.7
PASP (mmHg)*	60 (47–80)	45 (38–55)	41.5 (36–49)	36.5 (31–41)

*Median (IQR). EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PASP, pulmonary artery systolic pressure. LA size and PA pressure remained elevated in the group EF 40–49%. Most changes were complete at the six-week examination in the group with EF > 60%, while the group with EF 50–59% showed ongoing improvement in echocardiographic parameters until six months.

(Fig. 1). Of significance, most of the recovery in LV function and chamber dimensions was complete at six weeks in the group with a pre-operative EF > 60%, while the PA pressure continued to fall, and normalised at six months (Table 4, Fig. 1).

After feeding all clinical and echocardiographic variables into a predictive model, only ESD emerged as a significant predictor of postoperative LV dysfunction (EF < 50%), both on univariate (OR 0.9, 95% CI: 0.8–0.9, $p = 0.04$) and multivariate analysis (OR 0.8, 95% CI: 0.7–0.9, $p = 0.04$).

Paired analysis was conducted on 83 subjects with complete datasets for all time points. The median pre-operative EF in this paired sample was 63% (IQR 58–70%) (Table 5). At two weeks post MVR, there was a 20% decrease in EF (median 46%, IQR 38–55) ($p < 0.001$), followed by a significant increase at the six-month visit to 57% (IQR 52–63%) ($p < 0.001$). As seen in Table 5, this was accompanied by significant reductions in LVEDD, LVESD, LA and PASP at the six-month follow up. Of note, only 17/83 (20%) subjects who had a pre-operative EF > 55% maintained their EF at two weeks ($p < 0.001$, 95% CI: 0.02–0.09); at the six-month visit, 50/83 (60%) subjects achieved their pre-operative EF > 55% ($p < 0.001$, 95% CI: 0.1–0.5).

Table 5. Paired analysis showing change in echocardiographic parameters ($n = 83$)

	Pre-surgery	*6 months*	*Change*	p-*value*
EF (%)*	63 (58–70)	57 (52–63)	–5	< 0.001
LVEDD (mm)	60.2 ± 7.9	48.6 ± 8.3	–11.6	< 0.001
LVESD (mm)	39.9 ± 6.6	33.2 ± 8.4	–6.7	< 0.001
LA (mm)	61.9 ± 10.1	43.7 ± 10.1	–18.2	< 0.001
PASP (mmHg)	63.9 ± 23.4	37.4 ± 8.8	–26.5	< 0.001

Except for EF showing median (IQR), all other dimensions reflect mean ± SD. LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PASP, pulmonary artery systolic pressure.

Discussion

RHD remains the major cause of cardiac morbidity and mortality in young adults with cardiovascular disease.[12,13] Most of our subjects (83%) undergoing MVR for severe rheumatic MR were under the age of 25 years; two-thirds presented with severe functional disability (NYHA III–IV) and over a third were in advanced heart failure. Despite this, the overall response to surgery was good: among the 70% who returned to follow up at the six-month visit, all but one patient had resolution of their heart failure, with almost complete resolution of TR. The finding of persistent TR in the group with pre-operative EF > 60% suggests the presence of underlying organic tricuspid valve disease in these patients, which was not addressed at surgery.[14]

A sobering finding of this study is that 37 (28%) subjects underwent surgery with an EF < 60% and ESD > 45 mm, which is well beyond the established guidelines recommended for MVR.[5] This pattern is a frequent finding in developing countries where many patients present for the first time with poor prognostic echocardiographic parameters such as an EF < 60% or an ESD > 45 mm.[13] Suri *et al.* demonstrated that the predictors of preserved LV function post-operatively were pre-operative EF > 65% or LVESD < 36 mm.[15] An EF < 60% has been shown to be associated with poorer survival rates after corrective surgery and is likely to indicate contractile dysfunction in MR patients.[7]

Tribouilloy *et al.* showed that LVESD > 40 mm independently predicted higher mortality rates in patients who were medically managed, as well as in those who underwent mitral valve surgery.[8] Our paired analysis of 83 patients revealed that although the

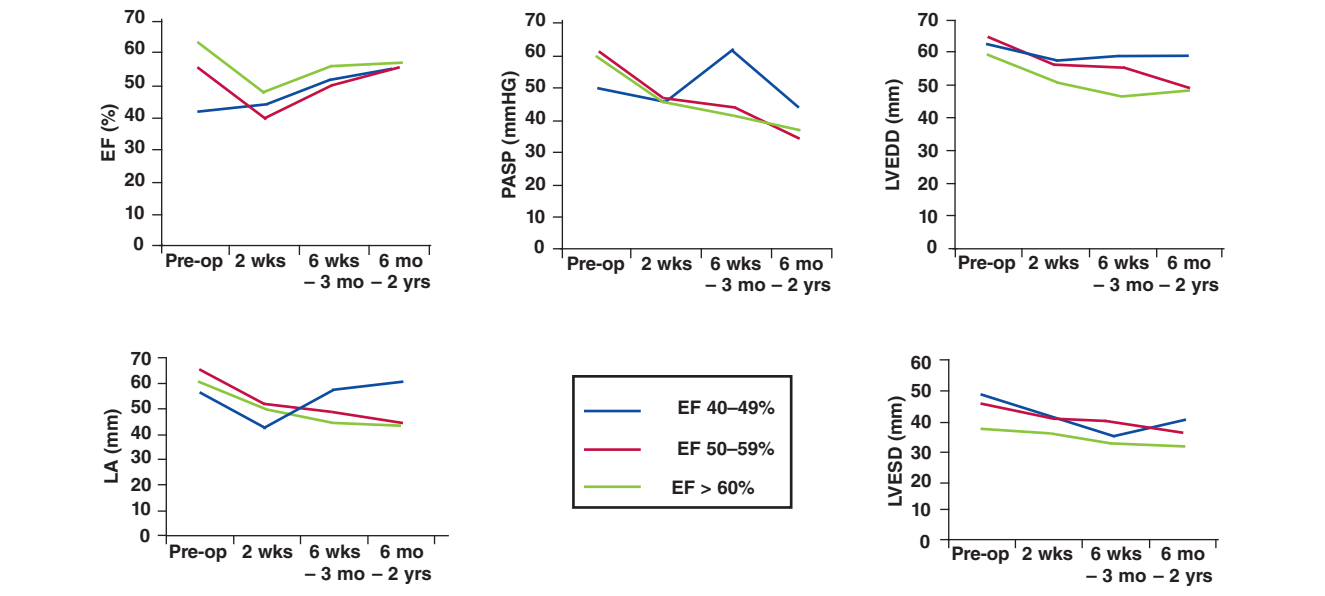

Fig. 1. Trend for pre- and postoperative echocardiographic data at follow up. LVESD, LVEDD, LA, EF and PASP are depicted as per the pre-operative EF groups (40–49%, 50–59%, > 60%) over the follow-up intervals of two weeks, six weeks to three months and six months to two years. EF improved steadily in all groups after an initial decline in the immediate postoperative phase. Only three patients with EF 40–49% reached postoperative EF > 50% at six months. Chamber dimensions, LA size and PASP all decreased after surgery except in the group with EF 40–49%.

majority of subjects had an EF > 55%, only 60% (n = 43) showed improvement in the postoperative EF to pre-operative values (EF > 55%) at six months. This suggests that most subjects had some degree of LV impairment as reflected by the median post-operative EF of 42%, which reflects the true EF upon removal of the low-pressure run-off into the LA following valve replacement.

Nevertheless, the majority of subjects underwent uneventful surgery and postoperative heart failure gradually improved over time. The five documented early deaths in the study occurred in subjects who presented to hospital *in extremis* (n = 2), or suffered postoperative complications (n = 3).

There were significant differences in LVEDD and LVESD values in the respective EF groups, demonstrating an increase in these chamber dimensions as the EF decreased (Table 2). These findings suggest that there are lesser changes in LV configuration when LV function is preserved in the setting of severe MR. Furthermore, the LA was similarly dilated in all EF groups, reflecting both the severity and duration of MR prior to surgery.[16,17]

In our study, the EF decreased significantly from a median of 63% pre-operatively to 45% postoperatively at two weeks. After the initial decline postoperatively, the EF gradually improved while the remaining echocardiographic parameters, LVEDD, LVESD, LA and PASP, decreased steadily at follow-up visits.

Our findings showing an immediate decline in EF following surgery is well described.[18,19] In Enriquez-Sarano's study, the EF showed a significant reduction from 58 ± 13% prior to mitral valve surgery to 50 ± 14% following MVR.[18] Several mechanisms explain the decline in EF following surgery in our patients. As pointed out earlier, in many of these patients, LV dysfunction was masked by the ventricular loading conditions in severe MR, characterised by increased preload and reduced afterload because of the run-off into the low-pressure LA during systole. These loading conditions change immediately after valve surgery when the leak has been corrected, exposing the LV to full systemic pressure and unmasking the true state of LV contractility.[20]

In most cases, the immediate fall in EF that was observed after surgery in our patients improved by six months.[15] Underlying coronary artery disease with ischaemic LV dysfunction was unlikely in our subjects because most of them were young black African patients. The deleterious effect of ischaemic cardioplegic arrest also contributes to the transient decline in early postoperative EF, which must be expected in most subjects with MR.

Among those subjects who had a sharp fall in EF to <30% immediately after the operation, five subjects recovered their EF to > 50% at the six-month follow up and these five had a median pre-operative EF of 65%. It is reassuring that in subjects with mildly impaired LV function (EF 50–59%), the EF improved steadily, albeit more slowly, compared to those with preserved EF (> 60%). These data imply that although impaired LV contractility is encountered in the immediate postoperative period, myocardial function generally improves over time, but reached normality earlier in subjects with preserved pre-operative EF (Fig. 1), emphasising the need for timeous surgical intervention in severe MR. This supports current guidelines recommending surgery in asymptomatic severe MR as soon as the LV begins to dilate (ESD > 40 mm) or the EF approaches 60%.

Among the seven subjects with EF in the 40–49% range, only three recovered their EF to > 50%. The development of contractile dysfunction and its relation to the severity of volume overload in MR is still not clearly understood.[12] It is well recognised that prolonged contractile dysfunction eventually becomes irreversible, even after the MR is corrected, and is predictive of congestive heart failure and death.[7] Under these circumstances, MVR is associated with higher morbidity and mortality rates due to advanced LV impairment.[9] None of our seven patients in the group with EF 40–49% (median EF 42%) underwent mitral valve repair, which is recommended under these circumstances. The choice of surgical procedure was dependent on the available expertise at our centre to carry out mitral valve repair, which is technically more difficult in RHD patients compared to non-rheumatic MR.[12]

The importance of adequate cardioprotection during cardiopulmonary bypass is a critical factor that cannot be underestimated in subjects with already compromised LV function from long-standing, severe MR. Myocardial ischaemia resulting from a longer duration of cardioplegic arrest was reflected in the prolonged CPBT in our subjects with postoperative LV dysfunction, and no doubt contributed to persistent LV dysfunction.[21] Lastly, Essop has emphasised the importance of preserving the chords at surgery since any discontinuity in the chordal–mitral apparatus could lead to further dilatation and impairment of the LV after surgery.[12] Chordal preservation is standard practice during MVR at our centre.

An important consideration is the presence of underlying active carditis in young subjects undergoing MVR. Pure MVR without stenosis causing heart failure is common in the young who have severe active rheumatic carditis.[12,22] Early studies have shown that heart failure is the predominant mode of death in rheumatic carditis, explaining the high early mortality rate among young patients with acute rheumatic carditis.[23,24] Annular dilatation and chordal elongation have been described as the main mechanism leading to mitral valve prolapse and severe regurgitation during active carditis.[23,24] In total, evidence of active carditis characterised by pericardial inflammation, chordal elongation and/or chordal rupture was present in 55 (42%) patients, which may well explain the impairment in LV function in these cases. Early surgery is lifesaving in these patients and the underlying ventricular impairment slowly improves in the majority of cases.[12]

In sub-Saharan Africa, RHD is responsible for the majority of cases of chronic MR. Because of the compensatory haemodynamics in chronic MR, many of these subjects present late in the disease when symptoms are more advanced. This is largely a result of poor socio-economic circumstances affecting both rural and peri-urban communities. Socio-economic challenges prevent timely access to care; these social inequalities coupled with a resource-constrained health sector all contribute to delayed referrals for specialist assessment and intervention. As a result, most of our subjects with severe MR received surgical intervention when their cardiac function had deteriorated beyond the recommended cut-off points for surgical intervention as per international norms. Furthermore, over-burdened, understaffed and under-resourced state health institutions contributed to incorrect and delayed diagnoses.

These factors led to delayed referral to the single tertiary centre in KwaZulu/Natal (IALCH), where bed and theatre constraints resulted in further delays before surgery was undertaken. As a result two-thirds of patients presented with severe functional

disability, often in advanced heart failure, which impacted on postoperative outcomes and contributed to significant morbidity and/or mortality. Wisenbaugh *et al*. have documented that patients in developing countries may present for the first time when EF is < 60% or ESD > 45 mm.[25] These patients tend to suffer poorer outcomes following MVR and would likely benefit from mitral valve repair, even though repair undertaken in RHD is technically more difficult than with degenerative MR.[4]

A more worrying explanation for delayed surgery is that clinicians may not be applying established guidelines in referring patients more timeously for surgery. Patients with moderate-to-severe MR are assessed by more junior staff who may not request an echocardiographic assessment because of the demands of a busy clinic, and because such patients are relatively asymptomatic, they may be given repeated follow-up appointments in the assumption that all is well in stable patients.

Symptoms often occur late in the course of MR since the compliance properties of the LA allow it to accommodate large volumes of blood before a significant rise in pressure is transferred to the pulmonary circulation. With increasing severity of regurgitation, contractile dysfunction may supervene, often preceding the onset of dyspnoeic symptoms.

An EF < 60% has been shown to be associated with poorer survival rates after corrective surgery and is likely to indicate underlying contractile dysfunction in MR patients.[3,8,26] The majority of our patients had markedly enlarged LA sizes (n = 84, 66% with LA > 55 mm) and elevated PASP (n = 66, 50% with PASP > 60 mmHg), indicating that these subjects had severe chronic MR of sufficiently long duration for such advanced changes to have developed. Chronic MR therefore requires careful monitoring by experienced clinicians and repeated echocardiographic assessments, which would reveal the onset of ventricular decompensation and the need for early surgery in such cases.

The timing of surgery in patients with severe MR is a critical factor in the preservation of myocardial function.[27-29] Wisenbaugh *et al*. have shown that pre-operative ESD is the only independent predictor of postoperative death.[25] Whereas a good outcome was predicted at a pre-operative ESD of 40 mm, they showed that the risk of severe heart failure and/or death sharply increased when it reached 51 mm. Taking these observations into account, the recommended optimal time for surgery can be derived at an LVESD between 40 and 50 mm, MV repair being the preferred surgical intervention when LVESD reaches 50 mm.[8,12,15]

Pulmonary hypertension is another independent predictor of postoperative mortality, with the risk of death or occurrence of heart failure being twice as high as in patients without pulmonary hypertension.[30,31,33] The presence of pulmonary hypertension depends on the severity of MR, the functional class of the patient and the presence of LV dysfunction.[32,33] Significant pulmonary hypertension (PAS > 50 mmHg) has been reported in 20 to 30% of patients with severe MR[30] and 64% of patients who are in NYHA functional class III–IV.[31] The pre-operative PASP was elevated beyond 50 mmHg in all EF groups in our study.

The majority of our patients was symptomatic and was receiving heart-failure treatment, including ACE inhibitors. Controlling symptoms in these patients with medical therapy in the belief that LV function and cavity size are stable in such patients is a misinterpretation of the evidence-based guidelines for intervention, which recommend surgery in symptomatic severe MR regardless of chamber dimensions.[5,27] The current paradigm for managing severe MR is to offer early surgery in these patients because of the difficulty in diagnosing underlying LV dysfunction and because the long-term outcome may be poor, even in subjects with good LV function as assessed by EF.

It is well established that pre-operative EF does not predict long-term outcome following MVR.[27,34] Furthermore, surgery may now be accomplished with low morbidity rates since surgical outcomes have improved considerably with better cardioprotection, and also with using the technique of MV repair in subjects with significantly impaired LV function.

Limitations

This study has several limitations, among them being the retrospective design, which resulted in incomplete datasets for analysis, and the use of raw echocardiographic data, which were not indexed to body surface area. Routine HIV testing prior to surgery was not a prerequisite to surgery in the early years when many subjects were not tested. In our study, HIV infection did not explain the impaired LV function in the group with EF 40–49%. Furthermore, the low cardiac-related mortality rate in our study (4%) may not be a true reflection of mortality, as nearly one-quarter of patients failed to return for follow up. The poor follow up after the six-week visit also resulted in reduced numbers of matched pairs for comparison, thereby reducing the total number of patients whose data could be interrogated for statistical purposes. Also, in our study we did not routinely use quantitative measurements such as calculation of the effective orifice area and regurgitant fraction, which are now recommended in both sets of guidelines.[4,5] Lastly, our cohort of MR did not include patients with pre-operative EF < 40% submitted for MVR as per the policy of our surgical unit, and we could not make firm inferences from this small sample with significantly impaired LV function.

Conclusion

In this study, a significant number of subjects with severe MR presented with advanced symptoms and/or decompensated HF with echocardiographic parameters that were well beyond the guidelines recommended for surgical intervention. While it is reassuring that surgical intervention improved cardiac dynamics and LV function in the ensuing three to six months in subjects with mildly impaired LV function, a cohort of patients remained with impaired LV function, in part due to delayed surgery. Several factors accounted for surgery being performed in the very late stages of the natural history of MR in our patients, among them the primary reason being socio-economic challenges associated with lack of access to healthcare as a result of a failing public healthcare system. Pre-operative ESD was the only predictor of postoperative LV dysfunction. Chronic organic MR therefore requires careful clinical surveillance and prompt referral for regular echocardiographic assessment to enable early detection of LV dilatation and timeous surgery in order to preserve ventricular function.

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Review Article

National prevalence of coronary heart disease and stroke in South Africa from 1990–2017: a systematic review and meta-analysis

Nada Abdelatif, Nasheeta Peer, Samuel OM Manda

Abstract

Background: South Africa is experiencing an increasing burden of cardiovascular diseases, including coronary heart disease (CHD) and stroke. We aimed to obtain overall national prevalence estimates of CHD and stroke in South Africa.

Methods: Studies conducted in South Africa were systematically reviewed from PubMed, Scopus and Web of Science from January 1990 to July 2017. Random-effects meta-analyses were conducted on the selected studies to determine the overall prevalence of CHD and stroke.

Results: Out of 2 466 studies, only 12 covering 75 140 participants reported the national prevalence of CHD and stroke. All 12 studies estimated the national prevalence of both diseases based on self-reported disease status. The overall national prevalence was 1.29 (95% CI = 0.83; 1.75) and 4.29 (95% CI = 3.13; 5.45) for CHD and stroke, respectively. Only one study reported incidence rates so we did not perform any meta-analysis of incidence rates.

Conclusions: There are very few studies on national prevalence of CHD and stroke in South Africa. Well-structured registries for CHD and stroke are required to accurately identify the disease burden and enable adequate resources to be allocated for the implementation of appropriate prevention and management programmes.

Keywords: coronary heart disease, stroke, meta-analysis, South Africa

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Submitted 16/10/19, accepted 2/10/20
Published online 26/3/21
Cardiovasc J Afr 2021; **32**: 156–160 www.cvja.co.za

DOI: 10.5830/CVJA-2020-045

Cardiovascular diseases (CVDs) account for 31% of global deaths annually, with more than 80% due to coronary heart disease (CHD) and stroke;[1] this amounts to 15 million deaths.[2] The CVD burden in low- and middle-income countries (LMICs), including those in sub-Saharan Africa (SSA), is more severe and occurs at a younger age, that is, in the working population. This has serious economic and social consequences, not only for the individual but also for their families and the economy. The higher mortality burden in younger individuals in their prime in LMICs is likely attributable to inadequate prevention and management because prevention is not a priority, and effective treatments are not widely available.[3]

In order to address this gap in suboptimal prevention and management, it is vital to have accurate data on the incidence and prevalence of CHD and stroke to adequately manage these conditions. Given that risk factors for CVDs are known and can largely be modified and controlled, 80% of premature heart attacks and strokes could be preventable.[4] This is particularly important for SSA, where there was a 38% increase in CHD from 2000 to 2016, and stroke rose by 25% within the same period, with a projected increase of 21 and 82% by 2030 for CHD and stroke, respectively.[2] This places a great strain on a region that is already highly burdened with HIV and other infections, violent death, and perinatal and maternal diseases.[5]

This is especially true for South Africa where CHD and stroke are among the top 10 leading causes of mortality alongside the high mortality rate attributable to HIV and tuberculosis.[6,7] It is estimated that five and 10 people have a stroke and heart attack, respectively, every hour, 10 of which result in death. Although mortality data are available for CHD and stroke, evidence on the incidence and prevalence of these conditions nationally by gender, urban–rural residence and population group is lacking in South Africa.[9,10]

The available research that focuses on CHD and stroke in the country[11-15] has not been systematically evaluated and described in a manner that summarises the evidence thus far. Accurate and up-to-date information on the incidence and prevalence of these CVDs is crucial to enable appropriate and adequate allocation of healthcare resources for the prevention and management of CHD

and stroke. This requires the appropriate management of CVD risk factors such as hypertension, diabetes and dyslipidaemia, and optimal diagnosis and management of CHD and stroke by adequately trained healthcare professionals.

We are not aware of any nationwide study in South Africa that has assessed and pooled the available evidence on the burden of CHD and stroke. Therefore, this systematic review and meta-analysis aimed to estimate the pooled prevalence of CHD and stroke in South Africa over a period from 1990 to 2017. The findings of this systematic review and meta-analysis provide the depth and quality of evidence, which will support and inform policies and interventions regarding CHD and stroke in South Africa.

Methods

The systematic review of rationale and methods was specified in advance and documented in a protocol, which was published in the PROSPERO register (CRD42017068585). Ethical approval was not required for this study.

We included population-based surveys, modelling, prospective or retrospective cohort studies, case–control studies, and cross-sectional studies with crude or adjusted national prevalence and incidence estimates of CHD or stroke. Our interest was in participants with a diagnosis of CHD, namely acute myocardial infarction (MI), previous MI (ST-segment elevation MI and non-ST-segment elevation MI), unstable or stable angina, and those with a confirmed diagnosis of ischaemic and haemorrhagic stroke. Participants with a self-reported history of CHD or stroke were also included.

A search of the following electronic bibliographic databases was conducted: PubMed, Scopus, and Web of Science. An additional search was carried out on Google Scholar and reference lists of relevant studies were used to identify publications that could have been omitted in the database searches. The search strategy was edited to find epidemiological studies that focused on CHD and stroke. The search terms used are given in Table 1. The study setting was South Africa, and studies that had not been conducted in South Africa were excluded. Only English studies published between January 1990 and July 2017 were eligible for inclusion in the review.

Table 1. Search terms used to find CHD and stroke studies

Search	*Query*
Coronary heart disease	
#1	Search ('Coronary disease' OR 'Myocardial infarction' OR 'Coronary artery disease' OR 'Angina pectoris' OR 'Unstable angina' OR 'Cardiovascular disease' OR 'Coronary heart disease' OR 'Ischaemic heart disease' OR 'Heart attack' OR 'Ischaemic heart disease')
#2	Search (South Africa OR 'South Africa*' OR RSA OR Africa, Southern OR 'Southern Africa')
#3	Search (#1 AND #2)
#4	Search [#3 AND ('1990/01/01' : '2017/07/31') AND Humans]
Stroke	
#1	Search ('Brain infarction' OR 'Brain stem infarctions' OR 'Cerebral infarction' OR 'Lacunar infarction' OR 'Cerebrovascular disease' OR 'Cerebrovascular accident' OR 'Brain ischaemia' OR 'Cerebral haemorrhage' OR 'Cerebral ischaemia' OR 'infarct' OR 'Cerebral ischaemia' OR 'Brain ischaemia')
#2	Search (South Africa OR 'South Africa*' OR RSA OR Africa, Southern OR 'Southern Africa')
#3	Search (#1 AND #2)
#4	Search [#3 AND ('1990/01/01' : '2017/07/31') AND Humans]

Three reviewers (NA, NP and SOMM) independently evaluated the eligibility of the studies obtained from the literature searches. All articles yielded by the database search were initially screened by their titles and abstracts to obtain studies that met our inclusion criteria. In cases of discrepancies, an agreement was reached by discussion.

Data extraction was completed by one reviewer (NA) and comprised study title, author(s), year of study and publication; data source; population characteristics such as age, gender and study setting; and risk of bias criteria. Prevalence and incidence estimates were extracted for studies assessed to have a low or moderate risk of bias.

One reviewer (NA) assessed the risk of bias (ROB) for each study using a framework developed by Pillay-van Wyk *et al*.[16] The framework assesses the external and internal validity of each relevant study and was developed for observational studies. The overall quality score ranges from 1 to 20 (high risk of bias = 1 to 6; moderate risk = 7 to 13 and low risk = 14 to 20). This quality assessment can be evaluated as a source of heterogeneity or in the form of sensitivity analysis in which overall results can be compared with those obtained from studies with defined subsets of quality characteristics.[17] However, this was not done in this study and was only used to assess low- and moderate-risk studies to be included in the meta-analysis.

Statistical analysis

The main parameters of interest were the prevalence and incidence of CHD and stroke. Random-effects meta-analyses were used to pool the prevalence estimates for the two cardiovascular conditions, with 95% confidence intervals (CI) and *p*-values. Incidence estimates were only found in one study (for both CHD and stroke) and could not be pooled to provide an overall estimate. The random-effects model incorporates heterogeneity resulting from variation between studies and assigns greater variability to the estimate of the overall effect.[18,19]

Heterogeneity among study estimates was quantified using Higgins I^2, which computes the proportion of variance between studies due to heterogeneity rather than chance.[20] We considered an I^2 value greater than 50% as indicative of substantial heterogeneity and conducted sensitivity analyses to assess the robustness of the meta-analysis results in outlying effect sizes and studies that looked at subgroups of people. To evaluate possible causes of heterogeneity, subgroup analyses or stratified analyses are recommended; however, if the total number of studies is less than 10, it would not make sense to compare two or more subgroups.[21] Stata 15[22] was used for all analyses.

Results

The PRISMA flow diagram displays the process of selecting the studies[23] (Fig. 1). The literature search returned 2 959 publications (2 705 for CHD and 254 for stroke) from PubMed, Scopus and Web of Science. After removing duplicates, 2 466 publications remained. After the screening of titles and abstracts, 2 343 publications were excluded, giving a total of 123 full-text articles that were assessed. A total of 12 studies were retained for the final review (five for CHD and seven for stroke).

The 12 studies retained provided population-level prevalence and only one study provided incidence estimates of CHD and

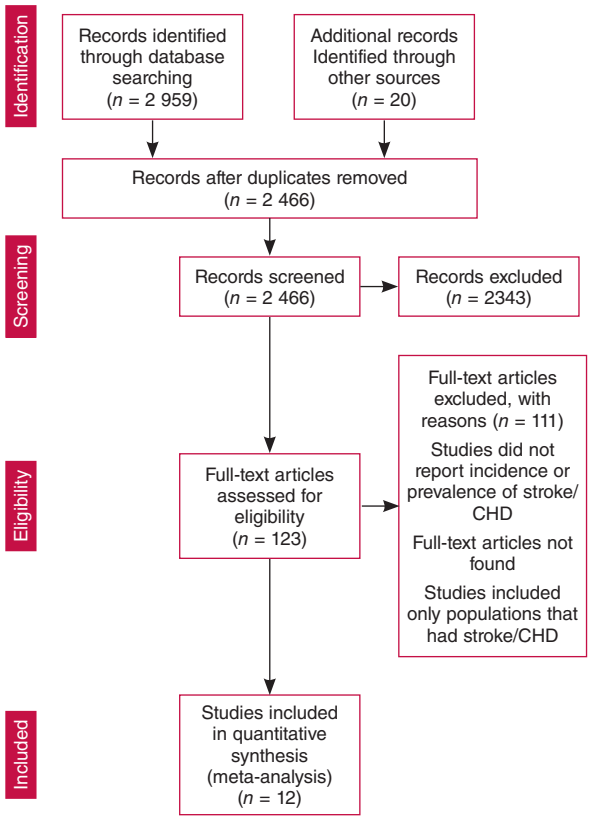

Fig. 1. Study-selection process using the PRISMA flow diagram.

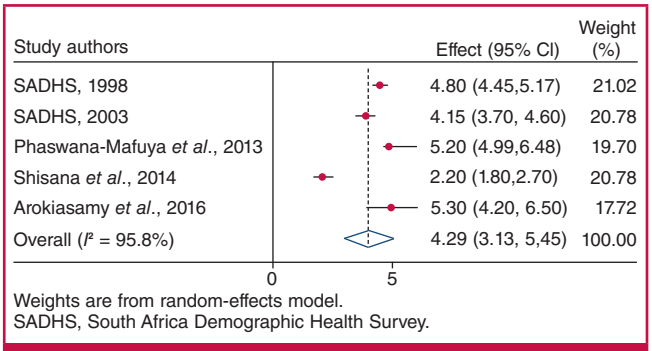

Fig. 2. Pooled prevalence rates of CHD.

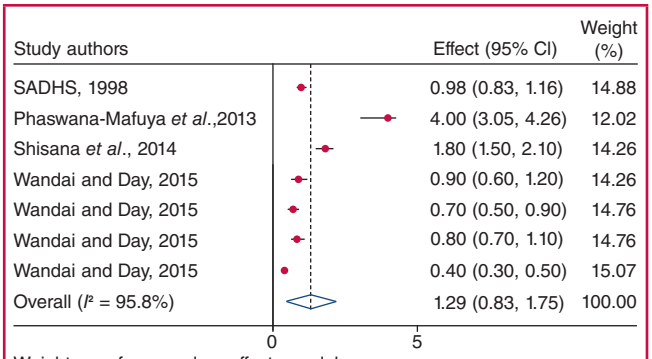

Fig. 3. Pooled prevalence rates of stroke.

stroke (Table 2). All the estimates were self-reported conditions. The total sample size of the studies that were included was 75 140 (41 168 for CHD and 33 972 for stroke).

Only a pooled estimate for prevalence was calculated, since there were insufficient studies found that reported incidence rates. The pooled overall prevalence for stroke was 1.29% (95% CI = 0.83; 1.75, I^2 = 97.2%, p-value = 0.000), and for CHD it was 4.29% (95% CI = 3.13; 5.45, I^2 = 95.8%, p-value = 0.000). The I^2 statistic showed high between-study heterogeneity, greater than 90% for both CHD and stroke (Figs 2, 3).

As a sensitivity analysis, outlying studies were excluded to assess whether the effect estimate was greatly influenced (Table 3). For stroke, Phaswana-Mufaya *et al.*[26] and Shisana *et al.*[27] were individually removed, and then both were removed at the same time. The overall effect estimate was reduced from 1.29 to 0.92 when Phaswana-Mufaya *et al.* was excluded, and went down slightly to 1.20 when Shisana *et al.* was excluded. The heterogeneity was smallest (I^2 = 90.7%), although still quite large, when both studies were removed and therefore had the most profound influence on the overall prevalence effect estimate.

Table 2. Final CHD and stroke studies included in the meta-analysis

Author, year	*Study period*	*Case definition*
Coronary heart disease		
South African Demographic Health Survey, 1998[24]	1998	Self-reported CHD
South African Demographic Health Survey, 2003[25]	2003	Self-reported CHD
Phaswana-Mafuya *et al.*, 2013[26]	2008	Self-reported angina
Shisana *et al.*, 2014[27]	2012	Self-reported heart disease (heart attack, angina or chest pain)
Arokiasamy *et al.*, 2016[28]	2007–2010	Self-reported angina
Stroke		
South African Demographic Health Survey, 1998[24]	1998	Self-reported stroke
Phaswana-Mafuya *et al.*, 2013[26]	2008	Self-reported stroke
Shisana *et al.*, 2014[27]	2012	Self-reported stroke
Wandai and Day, 2015[29]	2008	Self-reported stroke
Wandai and Day, 2015[29]	2010	Self-reported stroke
Wandai and Day, 2015[29]	2012	Self-reported stroke
Wandai and Day, 2015[29]	2013	Self-reported stroke

Table 3. Sensitivity analysis with outlying studies and those with gender breakdowns excluded

Condition	*Meta-analysis*	*Number of studies*	*Esti-mate*	*95% CI*		*Higgins I^2 (%)*
Without outlying studies						
CHD	All studies	5	4.29	3.13	5.45	95.8
	Excluding Shisana *et al.*[26]	4	4.75	4.25	5.25	65.6
Stroke	All studies	7	1.29	0.83	1.75	97.2
	Excluding Phaswana-Mufa-ya *et al.*[26]	6	0.92	0.58	1.26	95.0
	Excluding Shisana *et al.*[27]	6	1.20	0.74	1.65	96.9
	Excluding both	5	0.75	0.49	1.01	90.7
Without those with gender breakdowns						
CHD	All studies	5	4.29	3.13	5.45	95.8
	Excluding Arokiasamy *et al.*;[29] SADHS;[24] Shisana *et al.*[27]	2	4.63	3.61	5.66	82.1
Stroke	All studies	7	1.29	0.83	1.75	97.2
	Excluding SADHS;[24] Shisa-na *et al.*[27]	5	1.26	0.70	1.83	97.3

For CHD, the exclusion of Shisana *et al*. from the meta-analysis resulted in a slightly higher effect estimate, from 4.3 to 4.8. Removing Shisana *et al.* also resulted in a significant reduction in the level of heterogeneity, from 96 to 66%, which is a moderate level of heterogeneity.

To assess whether excluding studies that assessed gender-specific prevalence affected the overall prevalence effect estimate, the South African Demographic Health Survey (SADHS)[24] and Shisana *et al*.[27] were excluded for stroke, and Arokiasamy *et al*.,[28] SADHS[24] and Shisana *et al*.[27] were excluded for CHD. The overall prevalence effect estimate went down slightly for stroke from 1.29 to 1.26, and went up for CHD, from 4.29 to 4.63. The heterogeneity improved to 82% for CHD by removing those studies. For stroke, heterogeneity did not change much, indicating that the inclusion of these two studies did not make a significant difference.

Only SADHS 1998 reported a national incidence rate of CHD and stroke for men and women. For men, the incidence rates were 135 and 795 per 100 000 people for CHD and stroke respectively, and 234 and 1 744 for women. No other studies looked at incidence rates for either disease at a national level.

Discussion

The overall national prevalence of CHD and stroke in South Africa between 1990 and 2017, determined from five and seven studies, respectively, was low. This was also low compared to the crude prevalence rate of stroke of 387.93 per 100 000 in Africa.[30] The crude prevalence of stroke was 243 cases per 100 000 population in those aged 15 years or more, and 300 cases per 100 000 population in a rural community in north-east South Africa.[10] Another report estimated that 842 incident cases of stroke occurred in South Africa from 2007 to 2011.[10]

Our research has highlighted only one study on incidence and very few studies on the prevalence of CHD and stroke in South Africa. Given the high mortality burden, we would have expected a larger body of literature on these topics. Furthermore, there were insufficient data to estimate the prevalence of CHD or stroke by urban–rural residence.

Differential exposures to CVD risk factors by urban–rural residence, among other factors, is likely to influence the development of CHD and stroke. For example, poorer diets with higher caloric intake, greater sedentary behaviour and lower physical activity levels in urban compared with rural residents lead to higher rates of obesity, diabetes and hypertension in urban subjects. The uptake of these unhealthy lifestyle behaviours, together with the above cardiometabolic conditions, contribute to a greater risk for developing CHD and stroke in urban versus rural residents. Therefore, more epidemiological research needs to be conducted in both urban and rural areas, by gender and across population groups, because differential exposures to risk factors is likely to influence the burden of CHD and stroke.[31] Detailed and accurate information across these subgroups on the incidence and prevalence of CHD and stroke is essential for the prevention and management of CVDs.[32]

Although some studies have found that self-reported estimates were congruent with clinically measured estimates of disease,[33,34] others found that there were major differences between self-reported measures and actual clinical measurements.[35,36] There is also evidence that even though rates may seem low for CHD and stroke, this may be due to poor ascertainment or because it is under-diagnosed.[37,38] This could be a contributory factor to the low rates found in this study. There is, therefore, a need to determine prevalence estimates based on clinical assessments rather than relying on self-reported estimates, as this will likely provide a more accurate picture.

Although resting 12-lead electrocardiographs (ECGs) are available and inexpensive diagnostic tools for CHD, they have limited sensitivity and specificity for the diagnosis of acute coronary syndromes.[39] ECGs are inadequate screening tests in research settings where reproducibility is of paramount importance.[40] A standardised system, for example, the Minnesota coding system, is required when conducting epidemiological studies to ensure uniformity of interpretation. However, this has its disadvantages and may lead to over-reading.[40]

To determine the true burden of stroke, community-based studies that include brain imaging for accurate classification of stroke would be optimal, but such studies are expensive and challenging to conduct, particularly in low-resource settings.[31,41] A possible solution may be to establish well-structured CHD and stroke registries nationally. However, such an undertaking requires much effort and infrastructure costs to ensure good co-ordination and communication across centres.[42] Furthermore, there needs to be continuous monitoring and quality control to optimise data capturing.

The limitations of this review are that the 12 included studies were based on self-reported conditions and only one study was found that estimated incidence rates in CHD and stroke. Also, due to the small number of studies found, we were unable to conduct meaningful subgroup analyses. Only English language studies were included in this review. Grey literature, pre-prints and theses were also not included. The strength of this study was that we were able to provide pooled prevalence estimates of CHD and stroke in South Africa, which to date has not been done.

Conclusions

The findings of this review quantify the overall national prevalence of CHD and stroke, which was found to be low and may be due to the absence of the relevant evidence in the literature. This highlights the need for reliable and nationally representative data, as well as data by urban–rural residence, population group and gender, to identify high-risk, vulnerable communities. This can be achieved by the introduction of well-structured registries to correctly identify the burden of CHD and stroke in South Africa, which in turn could inform health policies and the delivery of appropriate healthcare services.

This study was funded by the South African Medical Research Council (SAMRC) with funds from the National Treasury under the SAMRC Computative Intramural Research Fund (SAMRC-RFA-IFF-02-2016).

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Kenya Country Report

PASCAR and WHF Cardiovascular Diseases Scorecard project

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Abstract

Data collected for the World Heart Federation's Scorecard project regarding the current state of cardiovascular disease prevention, control and management, along with related non-communicable diseases in Kenya are presented. Furthermore, the strengths, threats, weaknesses and priorities identified from these data are highlighted in concurrence with related sections in the accompanying infographic. Information was collected using open-source data sets from the World Bank, the World Health Organization, the Institute for Health Metrics and Evaluation, the International Diabetes Federation and relevant government publications.

Cardiovasc J Afr 2021; **32**: 161–167

DOI: 10.5830/CVJA-2021-022

On behalf of the World Heart Federation (WHF), the Pan-African Society of Cardiology (PASCAR) co-ordinated data collection and reporting for the country-level Cardiovascular Diseases Scorecard to be used in Africa.[1-4] In 2018, Kenya participated in the pilot study to develop the scorecard that was used to inform some of the discussions at the roundtable held together with the Kenya Cardiac Society (KCS) (OS, pers commun). Therefore, it was decided to include Kenya's data within the present project, which were updated with assistance from the KCS and Ministry of Health (MoH). In this report, we summarise Kenya's strengths, threats, weaknesses and priorities identified from the collected data, along with needs to be considered in conjunction with the associated sections in the accompanying infographic. Data sets that were used included open-source data from the World Bank, the World Health Organization (WHO), Institute for Health Metrics and Evaluation, the International Diabetes Federation (IDF) and government publications.

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Part A: Demographics

Kenya is a lower-middle income country, as indicated by the World Bank (2018), with 72.5% of its people living in rural areas.[5] In 2015, about 37% of the population was living below the US$1.9-a-day ratio. Life expectancy at birth in 2019 was 64 and 69 years for men and women, respectively.[5] The general government health expenditure was 2.1% of the gross domestic product (GDP), while the country's GDP per capita was US$1 816.5 in 2019.[5,6]

Part B: National cardiovascular disease epidemic

The national burden of cardiovascular diseases and non-communicable disease risk factors

Kenya had a premature (30–70 years old) cardiovascular disease (CVD) mortality rate of 8%, while the total CVD mortality rate was 13.8% in 2019.[7] The percentage of disability-adjusted life years (DALYs) resulting from CVD was 6.3%. The prevalence of atrial fibrillation (AF) and atrial flutter was 0.1%, while that of rheumatic heart disease (RHD) was 1.2%.[7] The total RHD mortality rate was 0.14% of all deaths (Table 1).[7]

Tobacco and alcohol

The prevalence of tobacco use in adult men 15 years and older was 18.8% in 2018, while adult women (2.3%) hardly smoked.[6] However, STEPS (Step-wise survey for NCD risk factors) data reported in 2015 indicated 23% of Kenyan men and 4.1% of women aged 18–69 years used tobacco.[8] Data available for the young smokers, 13–15 years old, revealed 12.8 and 6.7% of boys and girls, respectively, smoked tobacco in 2013.[9] The estimated annual direct cost of tobacco use was not available. The premature CVD mortality rate attributable to tobacco is 2% of the total deaths, which is much lower than the global 10%.[10] The three-year (2016–18) average recorded alcohol consumption per capita (≥ 15 years) was 1.7 litres, which is lower than most neighbouring countries, except Ethiopia with 0.9 litres (Table 1).[6]

Raised blood pressure and cholesterol

In 2015 the percentage of men and women with raised blood pressure (BP) [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg] was 25.1 and 22.6%, respectively.[8] Country data for raised total cholesterol level (≥ 5.0 mmol/l) in 2015 was 7.3% for men and 12.8% for women.[8] The percentage of DALYs lost because of hypertension was 4.0%,[11] whereas mortality rate caused by hypertensive heart disease was 1.7% in 2019,[7] which was lower than the global figure of 2.05% (Table 1).

Physical activity

In a study among adolescents, 86.8% were found to be insufficiently active [< 60 minutes of moderate to vigorous-intensity physical activity (PA) daily].[12] In 2015, the age-standardised estimate for adults who were insufficiently active (< 150 minutes of moderate-intensity PA per week, or < 75 minutes of vigorous-intensity PA per week) was 6.5%, which was much lower than that of the global data at 27.5% (Table 1).[8]

Overweight and obesity

In 2015, adults aged 18 to 69 years had a prevalence of overweight [body mass index (BMI) ≥ 25–< 30 kg/m^2] and obesity (BMI ≥ 30 kg/m^2) that was 19 and 8.9%, respectively.[8] More women were respectively overweight or obese (24.9, 13.7%) than men (13.2, 4.3%) (Table 1).[8]

Diabetes

The percentage of the population aged between 18 and 69 years old, defined with a fasting glucose of ≥ 7.0 mmol/l or on medication for raised blood glucose (age-standardised) in 2015, was 1.5% for men and 2.3% for women.[8] In 2019, the prevalence of age-adjusted (adults 20–79 years) diabetes was 3.1%,[13] which is lower than the global prevalence of 9.3% (Table 1).[13]

Part C: Clinical practice and guidelines

Health system capacity and guidelines for NCD risk factors

Kenya had an average of 1.6 physicians and 10 nurses per 10 000 of the population in 2018/19. The number of hospital beds was 13.3 and reported as 'The national average in-patient bed density' by the health facility assessment in 2018/19.[14]

In 2018, a locally relevant clinical tool was developed to assess CVD risk, which included locally relevant clinical guidelines for CVD prevention and detecting and managing AF.[15] Guidelines for managing pharyngitis were reported in 2009.[16] Locally relevant clinical guidelines for the management of acute rheumatic fever (ARF) and RHD have also been implemented, as have those for the treatment of tobacco dependence and its detection.[15] However, no clinical registers of people with a history of ARF and RHD were available. In 2010, national clinical guidelines for managing diabetes were developed based on local and international best practices and updated in 2018.[17,18]

Table 1. Cardiovascular disease indicators for Kenya

Indicators	*Male*	*Female*	*Total*	*Year*
Status of the national CVD epidemic				
Premature CVD mortality (30–70 years old) (% deaths)	-	-	8	2012
Total CVD mortality (% of deaths)	12.9	15.0	13.8 (31.8)[7]	2019
Total RHD mortality (% of deaths)	0.11	0.17	0.14 (.5)[7]	2019
DALYs attributable to CVD (%)	6.5	6.04	6.29 (14.7)[7]	2019
AF and atrial flutter (%)	0.1	0.07	0.09 (.5)[7]	2019
Prevalence of RHD (%)	1.11	1.22	1.17 (.5)[7]	2019
Tobacco and alcohol				
Prevalence of adult tobacco use (≥ 15 years old) (%)[8]	23 (36.1)[6]	4.1 (6.8)[6]	-	2015
Prevalence of youth (13–15-year-olds) tobacco use (%)[8]	12.8 (18.4)[6]	6.7 (8.3)[6]	-	2013
Estimated direct (healthcare-related) cost of tobacco use in your population (current US$)	-	-	-	
Proportion of premature CVD mortality attributable to tobacco (%)	-	-	2 (10)[7]	2004
Recorded alcohol consumption per capita (≥ 15 years) (litres of pure alcohol) (three-year average)			1.7	2016-18
Raised blood pressure and cholesterol				
Population (15–64 years old) with raised BP (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) (%)[8]	25.1 (24.1)[6]	22.6 (20.1)[6]	-	2015
Population with raised TC (≥ 5.0 mmol/l) (%)[8]	7.3	12.8	10.1 (38.9)[6]	2015
DALYs attributable to hypertension (%)	4.05	3.95	4.0 (9.3)[7]	2019
Mortality caused by hypertensive heart disease (% of deaths)	1.12	2.46	1.73 (2.05)[7]	2019
Physical activity				
Adolescents (11–17 years old) who are insufficiently active (< 60 minutes of moderate- to vigorous-intensity PA daily) (%)[12]	84.9	88.9	86.8 (80.7)[6]	2015
Adults (age-standardised estimate) who are insufficiently active (< 150 minutes of moderate-intensity PA per week, or < 75 minutes of vigorous-intensity PA per week) (%)[8]	6.3	6.8	6.5 (27.5)[6]	2015
Overweight and obesity				
Adults (18−64 years old) who are overweight (BMI ≥ 25–< 30 kg/m^2) (%)[8]	13.2	24.9	19 (38.9)[6]	2015
Prevalence of obesity (BMI ≥ 30 kg/m^2) (adults 25−64 years old) (%)[8]	4.3	13.7	8.9 (13.1)[6]	2015
Diabetes				
Defined population with fasting glucose ≥ 126 mg/dl (7.0 mmol/l) or on medication for raised blood glucose (age-standardised) (%)[8]	1.5 (9)[6]	2.3 (8)[6]	1.9	2015
Prevalence of diabetes (20−79 years old) (%)	-	-	3.1 (9.3)[13]	2019

CVD, cardiovascular disease; RHD, rheumatic heart disease; DALYs, disability-adjusted life years; AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; PA, physical activity; BMI, body mass index.
[7]IHME global data exchange; [8]STEPS 2015; [6]WHO GHO data; [12]Guthold *et al.*; [13]*IDF diabetes Atlas.*

However, no system to measure the quality of care provided to people who have suffered acute cardiac events has been noted.

Essential medicines and interventions

Most of the essential medicines were generally available in primary-care facilities except for warfarin and clopidogrel.[6] In 2015, total cholesterol measurement was generally available at the primary healthcare level, while CVD risk stratification or secondary prevention of rheumatic fever and RHD were not prioritised at this level.[6] However, in the new NCD strategic plan 2021–25, CVD risk stratification has been prioritised and should be available later in 2021.

Secondary prevention and management

The STEP survey revealed that 7% of hypertensive persons received medical treatment in 2015,[8] whereas no data were available on high-risk patients with AF being treated with oral anticoagulants or those with a history of CVD who were taking aspirin, statin and at least one antihypertensive agent.

Part D: Cardiovascular disease governance

Kenya does not have a national strategy or plan that specifically addresses CVD and their risk factors or RHD prevention and control as a priority. However, there is one that focuses on non-communicable diseases (NCDs) and related risk factors.[6,19] A national surveillance system that includes CVD and their risk factors has been set up.[8,20]

A national tobacco-control strategic plan and a multi-sectoral co-ordination mechanism have respectively been launched and implemented.[21,22] Collaborative projects for NCD interventions, including CVD, have been implemented between the MoH and non-health ministries and civil societies in Kenya.[23,24]

In a report by the World Bank Group and MoH, the benefits of CVD prevention and control for population health and the economy have been modelled using the United Nation's interagency OneHealth Tool. This software-based health-modelling tool is used to assess the costs and health benefits of interventions.[25]

Assessment of policy response

There is no legislation mandating health financing for CVD, essential CVD medicines at affordable prices or any court orders protecting patients' rights and mandating improved CVD interventions, facilities, health-system procedures or resources. Legislation is employed in areas where smoking is banned, as are visible warnings on tobacco packs, advertising, and measures to protect tobacco control policies from tobacco industry interference.[21] Through the solatium fund, that is from taxation of tobacco or other 'sin' products, sustainable funding for CVD is partially available.[26]

Policies that ensure equitable nationwide access to healthcare professionals and facilities are also present.[23] Furthermore, policy interventions that promote a diet that reduces CVD risk are available.[15] Kenya's Health Act of 2017 mandates implementing policies to reduce NCDs, including CVD.[27] No other legislation is available or in place.

Stakeholder action

Non-governmental organisation advocacy for CVD policies and programmes,[28] along with active involvement of patients' organisations in advocacy for CVD/NCD prevention and management, are in place.[24] Advocacy champions along with patient engagement groups for RHD have been implemented.

Civil society is involved in the development and implementation of a national tobacco-control plan.[21] There is a technical working group that draws multi-sectoral participation for NCDs/CVD.[24,29] These societies include the Kenya Association for Prevention of Tuberculosis and Lung Diseases, KCS, Kenya Diabetes Association, Kenya Society for Haemato-Oncology and the Non-Communicable Disease Alliance, Kenya.[24]

Specific activities by cardiology professional associations aimed at 25% reduction in premature CVD mortality by 2025 have been developed,[19] while no hypertension screening by businesses at workplaces was reported.

Forthcoming from these data, we summarise Kenya's strengths, weaknesses, threats and priorities.

Strengths

National guidelines for most CVD and NCD risk factors have been developed.[15,17] Through Kenya's national NCD strategic plan 2015–20 (the NCD strategic plan 2021–25 will be launched by May/June 2021), the MoH has envisioned to:

- establish mechanisms to integrate NCD prevention and control at national and county level into policies across all government sectors
- formulate and strengthen legislations, policies and plans for preventing and controlling NCDs at county and national government level
- promote healthy lifestyles and implement interventions to reduce the modifiable risk factors for NCDs, which include unhealthy diets, physical inactivity, harmful use of alcohol, tobacco use and exposure to tobacco smoke
- promote and conduct research and surveillance for the prevention and control of NCDs, which include CVD
- promote sustainable local and international partnerships for preventing and controlling NCDs
- establish and strengthen effective monitoring and evaluation systems for NCDs and their determinants
- strengthen health systems for NCD prevention and control across all levels of the health sector
- promote and strengthen advocacy, communication and social mobilisation for NCD prevention and control.

The Kenya Health Policy 2014–30[23] outlines the direction the health sector has taken to ensure that the overall status of health is not only in line with the Constitution of Kenya 2010 but is also significantly improved.[14] Furthermore, the policy identifies key areas of focus, which include reducing the burden of NCDs through strengthening primary healthcare, among other strategies.[23] Kenya reported having a nutritional strategy to control unhealthy diets, by promoting healthy diets.[19] Since 2013, free maternity services have been introduced, leading the way for increased access to healthcare by reducing household expenditure on health.[30]

Cardiovascular Disease Scorecards – Africa

KENYA – APRIL 2021

Status of Cardiovascular Disease (CVD) and Non-communicable diseases (NCD)

Country Demographics

World Bank Classification

Low-Middle income

72.5%

of population living in rural areas

60% (Sub-Sahara Africa)

KENYA

0.14%

of total mortality caused by **RHD**

Global data: **0.51%**

1.17%

Prevalence of rheumatic heart disease **(RHD)**

Global data: **0.53%**

2%

of premature CVD mortality attributable to **tobacco**

Global data: **10%**

MALE **18.8%** **2.3** FEMALE

Prevalence of **tobacco** use **age ≥15**

Global data: **36.1%** (male) **6.8%** (female)

1.73%

of deaths caused by **hypertensive heart disease**

Global data: **1.65%**

25.1% **22.6%**

MALE FEMALE

of population with raised **blood pressure** (SBP ≥140 or DBP ≥90)

Global data: **24.1%** (male) **20.1%** (female)

8.9%

Prevalence of obese adults (BMI of ≥30 kg/m²)

Global data: **13.1%**

13.82%

of **deaths** caused by CVD

Global data: **31.8%**

10.1%

of population with raised total **cholesterol** (≥5.0 mmol/L)

Global data: **38.9%**

3.1%

Prevalence of diabetes **(ages 20-79)**

3.9% (Africa)

WORLD HEART FEDERATION

www.worldheart.org
www.pascar.org
www.kenyacardiacs.org

KENYA

Health System Capacity

1.6
Number of physicians (per 10,000 population)

10
Number of nurses (per 10,000 population)

13.3
Number of hospital beds (per 10,000 population)

KEY: No data | Not in place | In process/ partially implemented | In place

Clinical Practice and Guidelines

Locally-relevant (national or subnational level):

- Clinical tool to assess CVD risk
- Guidelines for treatment of tobacco dependence

Clinical Guidelines for:

- The detection and management of atrial fibrillation
- The detection and management of acute rheumatic fever
- The detection and management of rheumatic heart disease
- The detection and management of diabetes
- CVD prevention (within the last 5 years)
- A system to measure the quality of care provided to people who have suffered acute cardiac events

KENYA

Cardiovascular Disease Governance

A national strategy or plan that addresses:

- CVDs and their specific risk factors
- NCD and their risk factors
- Rheumatic heart disease prevention and control as a priority
- A national surveillance system that includes CVDs and their risk factors

Stakeholder action

- Non-governmental organizations' advocacy for CVD policies and programmes
- Civil society involved in developing and implementing of national CVD prevention and control plan

For more information, please email info@worldheart.org info@pascar.org

Source References: Global Health Data Exchange; WHO Global Health Observatory data repository; WHO NCD Document repository; Country specific publications.

Weaknesses

Kenya does not have a national strategy or plan that specifically addresses CVD and their risk factors or RHD prevention and control as a priority. Although the country's Poverty Reduction Strategy Paper and National Development Plan, *Vision 2030*, include health under the social pillar, NCDs are not mentioned. Furthermore, implementation of the nutritional strategy is weak.[24]

Threats

Raised BP levels among Kenyans are a matter of concern, as in the other countries under investigation, except Ethiopia and Rwanda that had levels below 20% among men and women. A project by Abt Associates was done to find the best approach to addressing NCDs in Kenya.[31] Heart disease and diabetes were increasing, with hypertension being the leading cause of CVD. The Healthy Heart Africa programme was established with the main barriers being a lack of awareness, insufficient screening and inadequate access to affordable medication for hypertension.[31]

Kenya's total CVD mortality rate (13.8%) is higher than most of the other African countries participating in the CVD Scorecard project; those with a higher rate are South Africa (16.1%), Namibia (17.7%), Sudan (33%) and Tunisia (51.5%). Although the prevalence of RHD (1.2%) is higher than most of these countries, the mortality rate, in comparison, is similar or lower, with only Namibia having a lower rate at 0.11 versus 0.14%.

Tobacco use among young men is high at almost 13%, while more young women (6.7%) were found to make use of this habit than adult women (4.1%). Almost 90% of adolescents are not physically active according to the daily 60 minutes of moderate- to vigorous-intensity PA recommended by the WHO.

Priorities and achievements

To achieve global and national health goals highlighted in the Sustainable Development Goals, strengthening the health workforce through policy, adequate financing, planning, recruitment, training and retention will ensure improved access to healthcare and health systems.[30]

In a study on the determinants of CVD mortality, it was suggested that prevention and adherence to treatment for CVD be addressed at the policy, population and individual level, along with socio-economic factors.[32]

Dissemination of the National CVD guidelines launched by the MoH in 2018 to improve heart health outcomes of Kenyans has commenced at various workshops throughout the country. CVD prevention, hypertension control, heart failure and RHD are top-listed to receive attention by health professionals and related officials.[33] KCS, through the WHF's World Heart Grant Programme, initiated a campaign, 'Meet your Heart Doctor'.[34] The main objectives are to:

- increase awareness of heart diseases and the link between COVID-19 and CVD
- educate people to manage their condition and prevent COVID-19 infection
- build up the capacity for KCS to interact more effectively with patients and develop a strategy for meaningful engagement with this population.

The country is continually training healthcare workers on hypertension and heart failure. So far 1 500 health workers have been trained in Kenya and we plan to train more (GG, pers commun). Improvement of routine data systems for CVD is a priority in the MoH in Kenya.

This publication was reviewed by the PASCAR Governing Council and approved by the president of the Kenya Cardiac Society.

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Omega-3 supplementation linked with atrial fibrillation risk: a meta-analysis

Omega-3 supplements are associated with an increased likelihood of developing atrial fibrillation in people with high blood lipids, a meta-analysis of randomised control trials published in the *European Heart Journal* found.

'Currently, fish oil supplements are indicated for patients with elevated plasma triglycerides to reduce cardiovascular risk,' said study author Dr Salvatore Carbone of Virginia Commonwealth University, USA. 'Due to the high prevalence of elevated triglycerides in the population, they can be commonly prescribed. Of note, low-dose omega-3 fatty acids are available over the counter, without the need for a prescription.'

Some clinical trials have suggested that omega-3 fatty acids may be associated with an increased risk for atrial fibrillation, the most common heart rhythm disorder. People with the disorder have a five times greater likelihood of having a stroke.

These studies tested different formulations of omega-3 fatty acids at different doses. The authors therefore performed a comprehensive meta-analysis of randomised controlled trials to answer the question of whether fish oils were consistently related to a raised risk for atrial fibrillation.

The analysis included five randomised controlled trials investigating the effects of omega-3 fatty acid supplementation on cardiovascular outcomes. Participants had elevated triglycerides and were either at high risk for cardiovascular disease or had established cardiovascular disease. A total of 50 277 patients received fish oils or placebo and were followed up for between two and 7.4 years. The dose of fish oils varied from 0.84 to 4 g per day.

The researchers found that omega-3 fatty acid supplementation was associated with a significantly increased risk for atrial fibrillation compared to placebo, with an incidence rate ratio of 1.37 (95% confidence interval 1.22–1.54; $p < 0.001$).

Carbone said: 'Our study suggests that fish oil supplements are associated with a significantly greater risk of atrial fibrillation in patients at elevated cardiovascular risk. Although one clinical trial indicated beneficial cardiovascular effects of supplementation, the risk for atrial fibrillation should be considered when such agents are prescribed or purchased over the counter, especially in individuals susceptible to developing the heart rhythm disorder.'

Source: *European Heart Journal* 2021

Case Reports

Exacerbation of severe constrictive pericarditis after prior inadequate pericardiectomy

Yoshinori Kuroda, Tetsuro Uchida, Masahiro Mizumoto, Kentaro Akabane, Mitsuaki Sadahiro

Abstract

Pericardiectomy is commonly used to treat constrictive pericarditis (CP); however, persistent calcification can complicate recovery. An 82-year-old man presented with CP following an inadequate pericardiectomy at another hospital two years earlier. He was referred to our hospital with a diagnosis of recurrent CP. Pre-operative computed tomography revealed that the pericardium was not calcified on the anterior of the heart, while the inferior, posterior and lateral surfaces exhibited calcification. Notably, calcification along the inferior portion of the heart formed a calcium envelope structure. Pericardiectomy via re-sternotomy without cardiopulmonary bypass was performed. While dissecting the calcium envelope, a paste-like substance was exuded. Cardiac function improved after pericardiectomy, although the postoperative recovery from heart failure was prolonged. Calcified pericardium should be removed to the extent possible to enhance the efficacy of pericardiectomy, which contributes to improved early surgical results and prevents CP recurrence.

Keywords: constrictive pericarditis, recurrent pericarditis, pericardiectomy

Submitted 2/10/19, accepted 14/7/20
Published online 22/7/20
Cardiovasc J Afr 2021; **32**: 168–170 www.cvja.co.za

DOI: 10.5830/CVJA-2020-027

Constrictive pericarditis (CP) is a clinical condition of the heart in which the myocardium is enveloped in a calcified and fibrotic pericardium. CP induces diastolic and systolic dysfunction of the heart, thereby greatly reducing cardiac function. Pericardiectomy is an effective surgical technique for improving cardiac function. Herein, we describe a surgical case of re-pericardiectomy for recurrent CP with an atypically calcified pericardium after prior inadequate pericardiectomy.

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Case report

An 82-year-old man with CP underwent pericardiectomy at another hospital to resect only the anterior portion of the calcified pericardium, which did not satisfactorily resolve the condition. Two years after the operation, the patient again experienced heart failure, and he was referred to our hospital with a diagnosis of recurrent CP.

Computed tomography before the previous operation had shown a single layer of calcified pericardium enveloping the entire surface of the heart (Fig. 1A, B). Computed tomography before the operation described herein revealed that the pericardium was not calcified on the anterior of the heart, while the inferior, posterior and lateral surfaces exhibited calcification. Notably, calcification along the inferior portion of the heart formed a calcium envelope structure (Fig. 2A, B). Echocardiography revealed that the wall motion was globally reduced and that the ejection fraction was 43%. Pre-operative coronary angiography indicated no significant coronary artery stenosis. The causes of heart failure were believed to be diastolic dysfunction due to calcified pericardium and compression by the inferior calcified mass.

The patient was diagnosed with exacerbated CP. The right femoral artery and vein were exposed, and although cardiopulmonary bypass (CPB) was kept on standby, re-sternotomy for pericardiectomy was performed without CPB being required. The pericardiectomy was started at the anterior surface of the right ventricle. Although it was difficult to locate the border between the calcified tissue and the heart, we identified the edge of the calcium plate at the lower anterior margin of the right ventricle. The calcified pericardium was gently removed from the heart using an electric knife and ultrasonic scalpel (Fig. 3). While cutting into the calcified mass enveloping the inferior portion of the heart, a paste-like substance was exuded. The calcified pericardium and the inferior mass were removed completely.

Cardiac contraction improved as resection of the pericardium progressed. The cardiac index increased from 1.2 l/min/m^2 at the time of anaesthesia induction to 3.2 l/min/m^2 after the pericardiectomy. Total pericardiectomy was also completed without CPB being required.

The pathological diagnosis was recurrent idiopathic CP, while the paste-like substance inside the calcium envelope was determined to be haematoma. We found no evidence of infection. The postoperative course was uneventful, although the duration of recovery from heart failure was prolonged.

Discussion

CP is a type of pericardial disease whose causes could be idiopathic

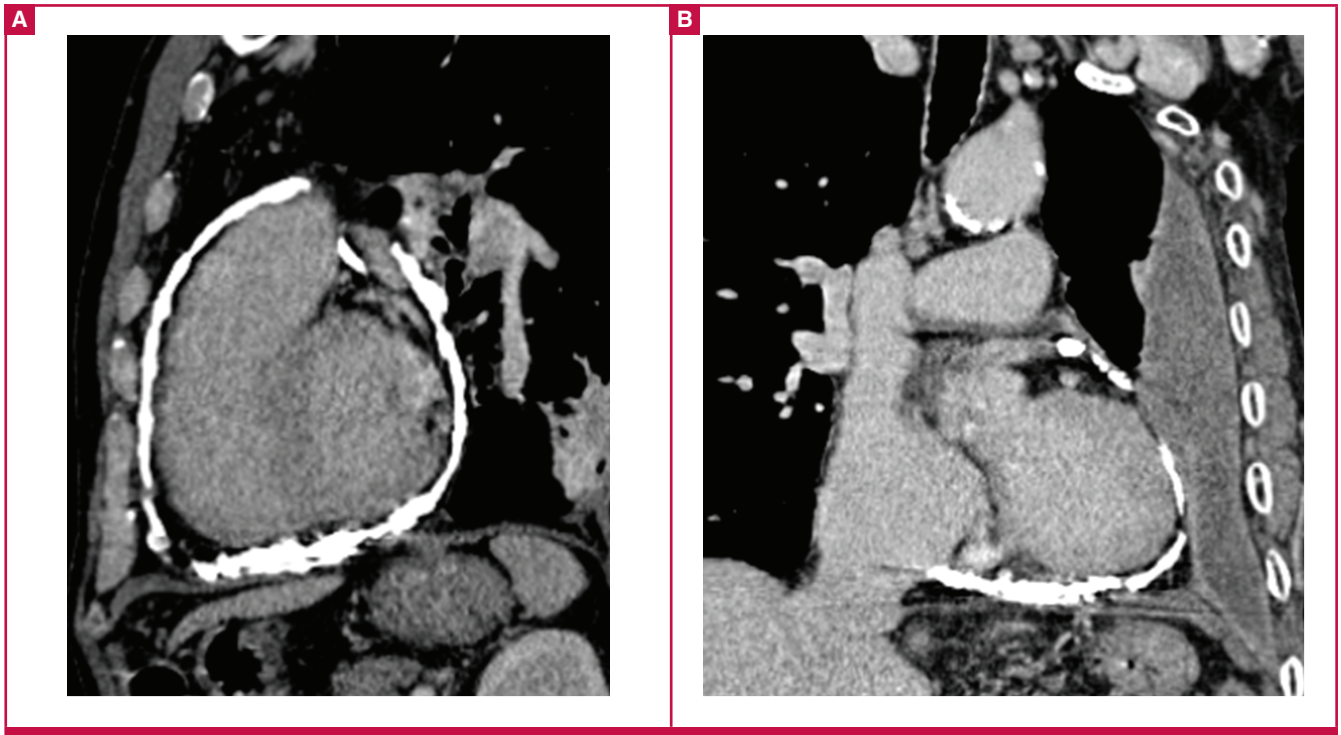

Fig. 1. The pre-operative computed tomography scans acquired before the previous operation show a single layer of calcified pericardium enveloping the whole surface of the heart (A: sagittal plane; B: coronal plane).

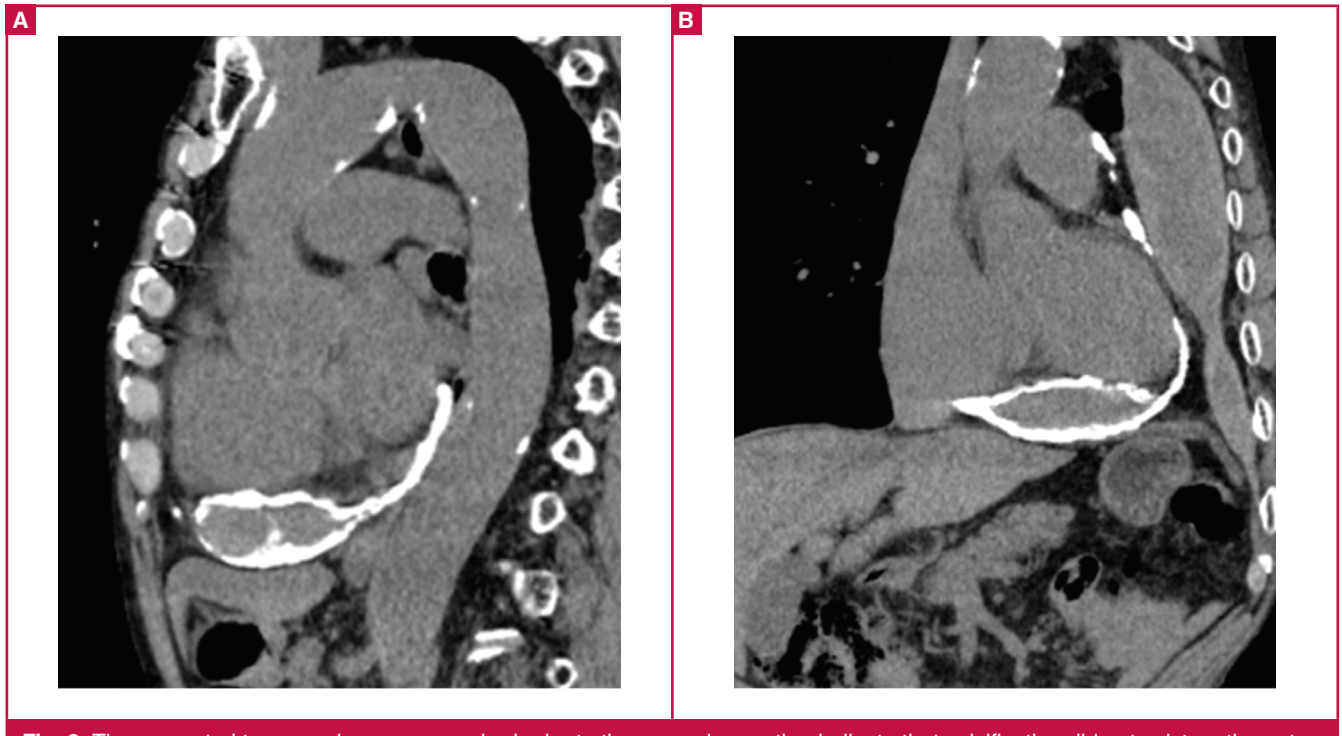

Fig. 2. The computed tomography scans acquired prior to the second operation indicate that calcification did not exist on the anterior pericardium, but instead was present on the inferior, posterior, and lateral portion of the pericardium. Notably, calcification along the inferior portions of the heart formed a calcium envelope structure between the heart and the diaphragm (A: sagittal plane; B: coronal plane).

or due to tuberculosis, prior cardiac surgery, post-mediastinal radiation therapy, connective tissue disease, infection, uraemia and sarcoidosis.[1] Fibrotic and calcified pericardium restricts diastolic function, thereby reducing cardiac output. The surgical result of CP is unfavourable, with an early mortality rate of 6–7.6%. Furthermore, the commonly observed postoperative low-output syndrome is aggravated because of degeneration of the myocardium due to poor cardiac function after inadequate pericardiectomy.[2,3]

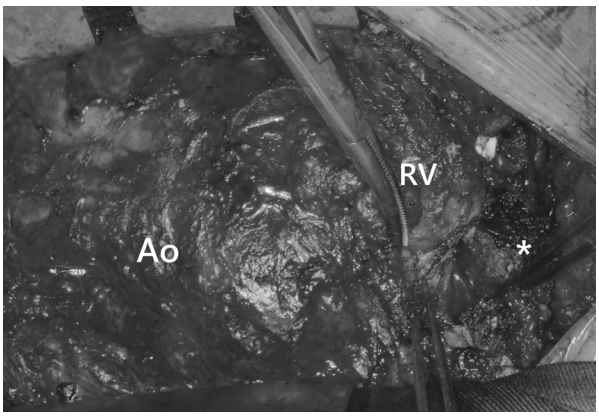

Fig. 3. The calcified pericardium strongly fixed on the heart surface is gently removed from the heart using an electric knife and ultrasonic scalpel. Ao: aorta; RV: right ventricle; *thick calcified pericardium on the inferior portion of the heart.

Since the standard treatment of CP is pericardiectomy, fibrotic and calcified pericardium should be removed to the extent of enhancing the efficacy of treatment. Furthermore, calcified pericardium effectively grows into the cardiac surface, thereby increasing the risk of heart injury when attempting to remove the pericardium.

The complications of pericardiectomy are as follows: bleeding due to myocardial injury, coronary artery injury and phrenic nerve injury, therefore, when conducting a pericardiectomy, an ultrasonic scalpel should be used due to its safety and compatibility with minor tissue damage.[4] Total pericardiectomy is defined as radical phrenic-to-phrenic excision of the pericardium, from the great arteries superiorly to the diaphragmatic surface inferiorly,[5] and in case of fibrotic and calcified pericardium, total pericardiectomy is advisable to prevent future exacerbation. Although good surgical outcome of left anterolateral thoracotomy for recurrent CP has been reported in a previous study, total pericardiectomy using this approach is difficult and the article does not mention total pericardiectomy.[6]

Recurrence or exacerbation of CP following previous partial pericardiectomy is common. Interestingly, a previous report described a case involving re-pericardiectomy 43 years after a previous pericardiectomy had been performed.[7] The authors of that report indicated that the cause of CP recurrence was the inadequate removal of calcified pericardium. Therefore, inadequate pericardiectomy renders the early surgical results unfavourable and increases the risk of recurrent CP.

The patient in our case had undergone prior pericardiectomy to treat only anterior calcified pericardium. However, during postoperative follow up, heart failure occurred due to the recurrence of CP two years later. Furthermore, the calcified pericardium had changed over time; however, a haematoma was found to have developed prior to the second operation, which contributed to the development of the atypical calcification. As a result, the enveloped haematoma occupied the space between the heart and the diaphragm. We conclude that the calcified tissue not only perturbed diastolic function, but also physically compressed the heart.

Conclusion

It is important to remove as much fibrotic and calcified pericardium as possible since effective pericardiectomy contributes to improved early surgical results and prevents the recurrence of CP. Inadequate pericardiectomy can result in an unfavourable postoperative course and prognosis; therefore, total pericardiectomy should be performed for CP.

We thank Editage (www.editage.jp) for English language editing.

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Basal Takotsubo syndrome induced by pheochromocytoma rupture

Shanshan Yuan, Tao He, Lijia Yang, Qiang Chu, Weiqing Huang, Hongyan Dai

Abstract

Takotsubo syndrome (TTS), characterised by transient left ventricular systolic dysfunction, is divided into five types: (1) apical ballooning, (2) mid-ventricular, (3) basal or inverted, (4) and focal wall-motion patterns, and (5) other types, including biventricular type, isolated right ventricular and global type. The common clinical features of TTS are similar to acute coronary syndrome, which makes them indistinguishable in the early stages. TTS has a wide spectrum of emotional or physical triggers. Pheochromocytoma has been widely recognised as a distinct physical trigger of TTS. Alhough reports of pheochromocytoma causing TTS are not uncommon, spontaneous rupture of pheochromocytoma causing TTS is extremely rare because of the low incidence of tumour rupture. Here we report on a case of a 31-year-old man with adrenal pheochromocytoma rupture developing basal TTS.

Keywords: Takotsubo syndrome, pheochromocytoma, spontaneous rupture, cardiogenic shock, heart failure

Submitted 16/2/20, accepted 30/8/20
Published online 5/10/20
Cardiovasc J Afr 2020; **31**: 171–174 www.cvja.co.za

DOI: 10.5830/CVJA-2020-039

Since its first description in Japan in 1990, Takotsubo syndrome (TTS), also known as broken-heart syndrome, stress cardiomyopathy or apical ballooning syndrome, has emerged as an important form of acute reversible myocardial injury characterised by transient left ventricular (LV) systolic dysfunction.

The common clinical features of TTS are cardiac symptoms (acute chest pain, dyspnoea or syncope), new ECG abnormalities (ST-segment elevation, ST-segment depression, T-wave inversion and QTc prolongation) and elevated levels of cardiac biomarkers (troponin and creatine kinase), which make it indistinguishable from acute coronary syndrome (ACS) in the early stages. Recently, it has been shown that TTS has a comparable in-hospital mortality rate with ST-segment elevation myocardial infarction (STEMI) and non-STEMI.

Based on the distribution of regional wall-motion abnormalities, five types of TTS can be differentiated: (1) apical ballooning (81.7%), (2) mid-ventricular (14.6%), (3) basal or inverted type (2.2%), (4) and focal wall-motion patterns (1.5%), and (5) other types, including biventricular type (apical type and right ventricular involvement), isolated right ventricular and global type.[1,2]

TTS has a wide spectrum of emotional or physical triggers, the former including grief, interpersonal conflict, fear and panic, anger, anxiety, financial or employment problems and even some happy emotions. The physical triggers include acute respiratory failure, pancreatitis, cholecystitis, traumatic injury, sepsis, malignancy, thyrotoxicosis, and nervous system diseases such as stroke, head trauma, migraine, intracerebral haemorrhage and seizure.[1,2]

Pheochromocytoma, a catecholamine-secreting tumour, has been widely recognised as a distinct physical trigger of TTS. The prevalence of TTS in patients with pheochromocytoma may be up to 3%.[3] Although reports of pheochromocytoma causing TTS are not uncommon, spontaneous rupture of pheochromocytoma causing TTS is extremely rare because of the low incidence of tumour rupture.[4] Here we report on a case of a 31-year-old man with adrenal pheochromocytoma rupture developing basal TTS and pheochromocytoma crisis.

Case report

A 31-year-old man was admitted to hospital due to sudden severe abdominal pain. Prior to this event, he had experienced intermittent abdominal pain, headache and palpitations for two years without any treatment. On arrival at a local hospital, his blood pressure (BP) was 206/115 mmHg and heart rate was 120 bpm. Plain computed tomography (CT) showed a 3.7-cm mass of uneven density in the left adrenal gland (Fig. 1A). An ECG showed ST-segment elevation on the precordial leads V3–V6 and limb leads I and aVL, and ST-segment depression on limb leads II, III and aVF. Troponin I (TnI) and creatine kinase isoenzyme MB (CK-MB) levels were normal at that time.

In less than 12 hours, his abdominal pain progressively intensified, and BP dropped to 90/60 mmHg. He was transferred to our hospital. The repeat CT scan revealed the mass had expanded to 6.5 cm in diameter, with accumulation of fluid surrounding the left pararenal and parapancreatic space (Fig. 1B).

Haemoglobin and red blood cell counts were in the normal range. Levels of serum and urine epinephrine (E), serum and urine norepinephrine (NE), serum metanephrine (MN) and normetanephrine (NMN), and urine vanillylmandelic acid (VMN) were found to be markedly elevated (serum E: 767.66 pg/ml, reference range 0–100 pg/ml; serum NE: 2148.52 pg/ml,

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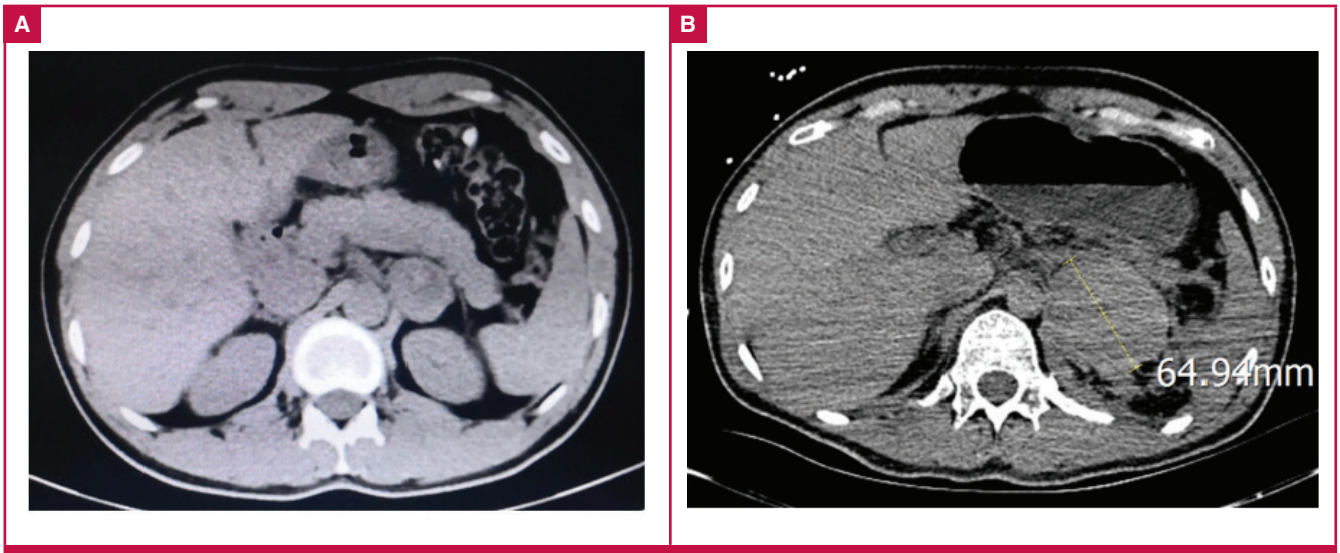

Fig. 1. A. The first computed tomography (CT) on admission showed a 3.7-cm mass of uneven density in the left adrenal gland. B. The second CT revealed the mass had expanded to 6.5 cm in diameter, with accumulation of fluid surrounding the left pararenal and parapancreatic space.

reference range 0–600 pg/ml; urine E: 66.74 µg/day, reference range 0–20 µg/day; urine NE: 240.15 µg/day, reference range 0–90 µg/day; serum MN: > 20.56 nmol/l, reference range ≤ 0.5 nmol/l; serum NMN: > 20.56 nmol/l, reference range ≤ 0.9 nmol/l; urine VMN 46.7 mg/day, reference range ≤ 12 mg/day).

Repeat ECG showed elevated/depressed ST-segments somewhat recovered, but retest of cardiac biomarkers showed a TnI level of 12.4 ng/ml (reference range 0–1 ng/ml) and CK-MB of 29.5 ng/ml (reference range 0–4.3 ng/ml). A transthoracic echocardiogram (TTE) showed severely impaired LV systolic function [ejection fraction (EF) 27%] with akinesis/hypokinesis of the basal and middle LV segments and hyperkinesis of the apical segments (Fig. 2A, B).

The patient soon developed heart failure and shock. He was transferred to the intensive care unit (ICU) for life support, utilising vasoactive drugs (noradrenaline), intra-aortic balloon pump (IABP) and ventilator assistance. During treatment, the TnI level, which peaked within 24 hours, began to drop from the fourth day, and returned to normal in one week. CK-MB, which peaked within 24 hours, began to drop from the third day, and returned to normal on the 10th day.

During his hospitalisation, we paid close attention to the change in cardiac function and checked his heart regularly with TTE. TTE showed a distinct improvement in wall motion of the LV basal and middle segments on the 12th day with an EF of 36%, so the IABP and ventilator were withdrawn on the 13th and 14th days, respectively. On TTE, the wall motion of the LV returned to almost normal after 17 days.

After discharge from hospital, the patient received adrenergic alpha-receptor blockers. Three months later he had a repeat TTE and the results were normal.

He thereafter underwent a left adrenalectomy. The pathology examination revealed adrenal pheochromocytoma with haemorrhage and rupture (Fig. 3A, B). After the patient was

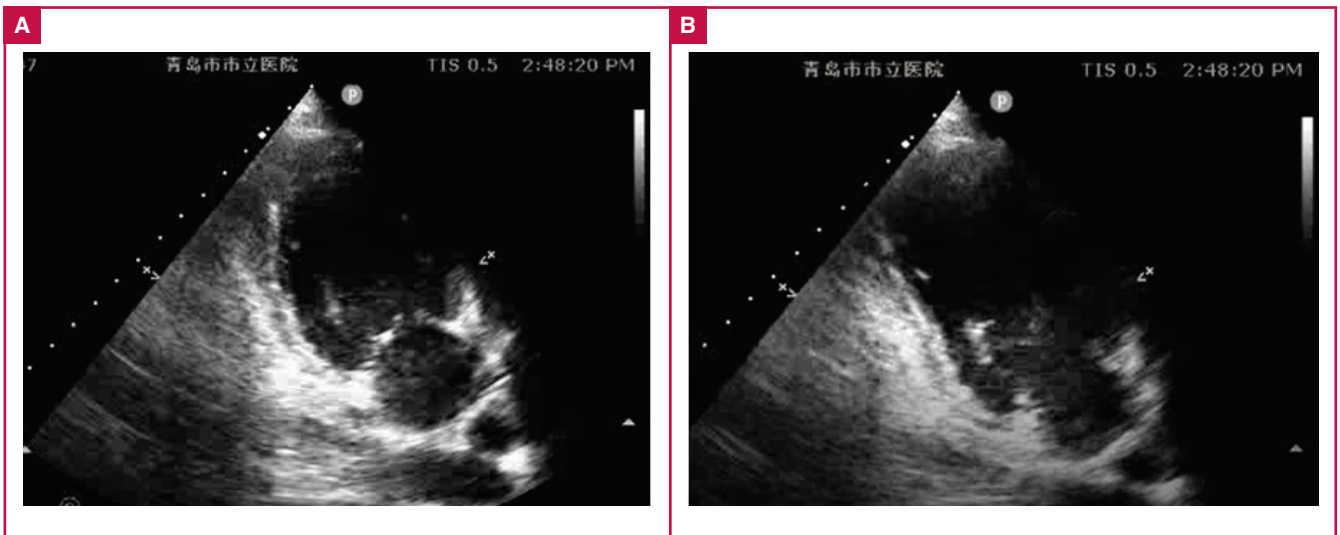

Fig. 2. Transthoracic echocardiogram (TTE) showing severely impaired left ventricular systolic function with akinesis/hypokinesis of the basal and middle left ventricular segments and hyperkinesis of the apical segments. A. Systolic phase. B. Diastolic phase.

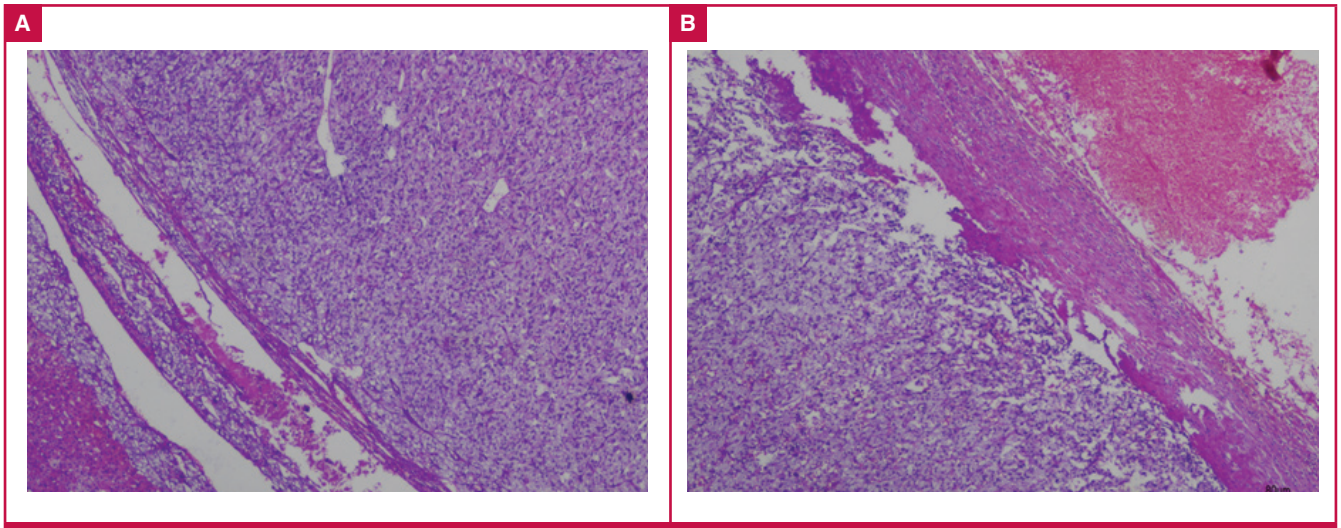

Fig. 3. A. The pathology examination revealed an adrenal pheochromocytoma. B. Haemorrhage and rupture of the pheochromocytoma.

discharged, he took no beta-blockers or angiotensin converting enzyme inhibitors (ACEIs). His BP was in the normal range and activity tolerance returned to normal levels. TTS did not recur after the tumour was removed during follow up of a year.

Discussion

Pheochromocytomas are uncommon catecholamine-secreting tumours. Intractable hypertension is one of the most common symptoms, accompanied by headache, palpitations and perspiration. Pheochromocytoma crisis, with an occurrence rate of about 10%, induced by sudden release of large amounts of catecholamines, is a dreaded and potentially lethal complication of pheochromocytoma. Clinical manifestation consists of severe hyper- and/or hypotension, high fever, encephalopathy and multiple organ system failure.[5]

Haemodynamic abnormality of pheochromocytoma crisis has a variety of causes such as cardiomyopathy, myocardial infarction, arrhythmia, pulmonary oedema, cerebrovascular accident, encephalopathy, liver and kidney failure, adrenal haemorrhage and others. Spontaneous rupture of adrenal pheochromocytoma, one cause of pheochromocytoma crisis, is rare, and most of such rare cases present as haemorrhagic shock.[4] Here we discuss a case of a young man with adrenal pheochromocytoma rupture developing pheochromocytoma crisis, which presented with basal TTS and cardiogenic shock.

Pheochromocytoma serves as a distinct physical trigger of TTS, and TTS may be found in up to 3% of patients with pheochromocytoma and paraganglioma.[3] The types of pheochromocytoma-induced TTS (pheo-TTS) differ significantly in all patients with TTS (all-TTS), with the basal type in almost 30% of pheo-TTS and the global type in 20% of pheo-TTS. Both types are rare in all-TTS, with the basal type only accounting for 2.2% of all-TTS and the global type even less. Patients with pheo-TTS are significantly younger than all-TTS, with a relatively high proportion of men. In addition, pheo-TTS is characterised by a dramatic clinical presentation with high complication rates, especially in patients under 50 years, and a relatively high recurrence rate.

Common complications are heart failure (occurrence rate 51%), pulmonary oedema (45%) and cardiogenic shock (34.6%), which occurs more frequently in the global and basal patterns of pheo-TTS than the apical type.[6] As reported in most previous cases, levels of cardiac biomarkers are slightly or moderately elevated,[7] but were significantly increased in our patient.

In this case, the patient presented as acute myocardial infarction initially, with ECG changes presenting as ST-segment elevation and depression, cardiac biomarkers significantly elevated, and wall-motion abnormality of the LV on TTE. However, this young man had no chest pain, no history of hypertension, diabetes mellitus, smoking, or family history of early-onset coronary heart disease. TTE showed akinesis/hypokinesis of the entire basal and middle LV segments, which extended beyond a single epicardial vascular distribution. These features and the presence of physical stress of pheochromocytoma rupture pointed to the basal type of TTS. Regular TTE showed LV wall motion distinctly improved on the 12th day and almost recovered after 17 days, which indicated LV dysfunction was transient and confirmed the diagnosis of TTS.

A coronary CT angiogram should be performed to exclude coronary artery diseases, but at that critical time, with life support of IABP and ventilator, the patient had no chance of getting a CT angiogram. In this patient, severely impaired LV systolic function with an EF of 27% caused by TTS was one of the main causes of shock. His haemoglobin and red blood cell count were in the normal range, so haemorrhagic shock was excluded.

The precise pathophysiological mechanisms of TTS are incompletely understood, but there is considerable evidence that catecholamine excess and sympathetic stimulation is central to its pathogenesis.[8,9] Catecholamine levels of this patient were significantly elevated. We supposed that the sudden release of large amounts of catecholamines from the ruptured pheochromocytoma played an important role in the pathogenesis of TTS in this patient. However, the reason why the basal type of TTS has a high incidence in pheo-TTS remains unclear.

Alhough reports of pheochromocytoma causing TTS are not uncommon, spontaneous rupture of pheochromocytoma causing TTS is extremely rare because of the low incidence of tumour rupture. So far, only one case diagnosed with apical TTS caused by pheochromocytoma rupture has been reported around

the world.[10] This case of pheochromocytoma rupture-induced basal TTS is the first explicit report in the literature.

Conclusion

This case provides us with three insights: (1) young patients with abdominal pain and clinical evidence of ACS should be checked for pheochromocytoma; (2) the impaired LV systolic function recovered in two to three weeks with timely mechanically assisted therapy; (3) TTS did not re-occur even without taking any beta-blockers or ACEIs after the tumour was removed.

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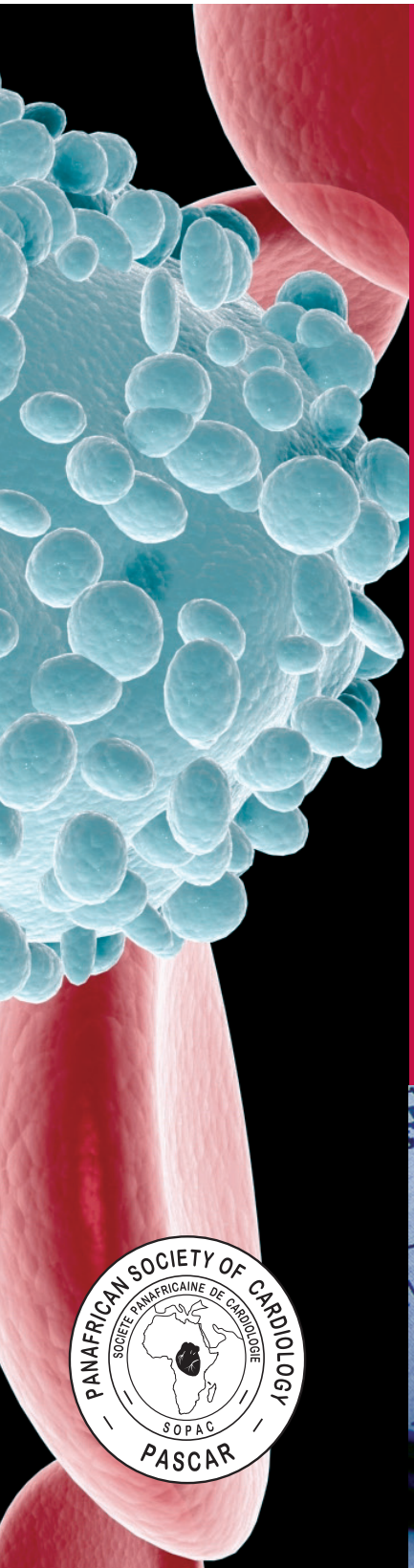

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