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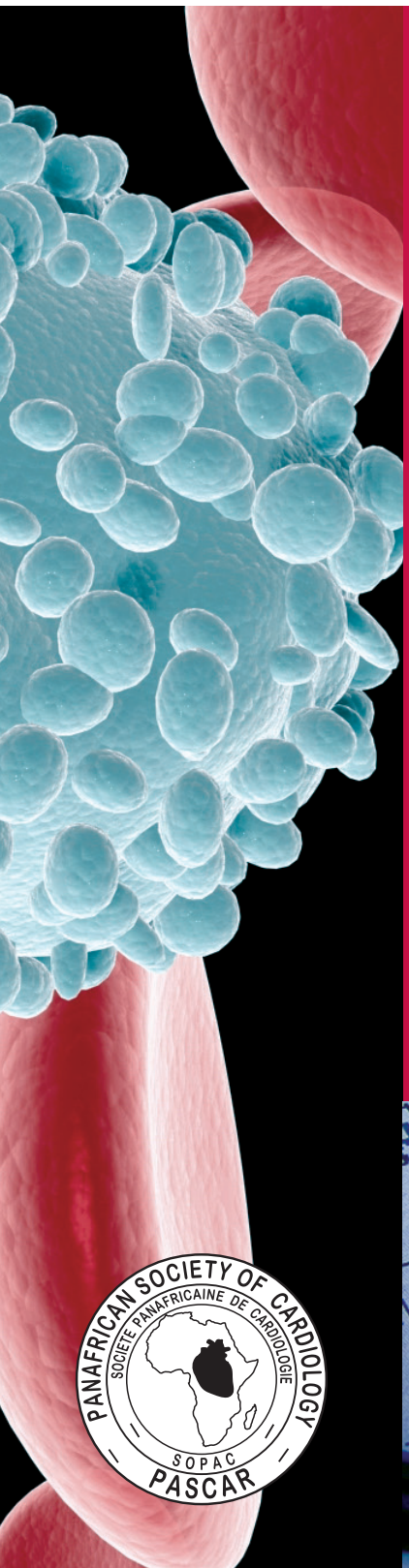

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From the Editor's Desk

Covid-19 and cardiovascular disease

One cannot write an opinion piece or editorial and not address one of the biggest issues facing medicine in 2021, both globally and in Africa. When the current Covid-19 pandemic struck South Africa and Africa in early 2020, I was still in part-time employment in the public academic hospital where I had trained as a medical student and then spent virtually my whole professional life. The hospital administrators took the wise decision that all older staff, in view of their at-risk status, should be excluded from the hospital premises. The result was that I, and many others who were still, after retirement, involved in some measure of patient care and teaching, had to leave the premises. I vacated my office and have never returned. My initial reaction was one of resentment at being excluded from what clearly was going to be a major effort on the part of the many colleagues, at all levels, with whom I had worked for decades.

Currently I am no longer resentful but grateful that that decision was taken and I was spared, involuntarily, exposure both to the disease and the rigors of the changes in practice that my colleagues have experienced when managing it. Despite not being in the hospital, I remain in touch virtually and am aware of the enormous disruption the pandemic has caused in the lives and practices of my erstwhile colleagues. Deployment to providing or supervising care for Covid victims has interrupted their normal provision of specialist cardiology care. I salute those who have interrupted clinical and research careers to care for victims of the pandemic. I am filled with admiration that many have managed to maintain the research enterprise and continue to publish.

Despite the best efforts of universities and departments, the pandemic must have impacted on undergraduate teaching and this will take a considerable time and effort to correct. The impact on post-graduate training may be even more severe. I understand most hospitals, both public and private in South Africa and, I suspect, in the rest of Africa, have had to limit elective admissions. We need to admit that this almost certainly limits the access of trainees in invasive cardiology and cardiac surgery to patients in the treatment of whom they may learn or be taught. There needs to be creative thought given as to how this education gap will be covered. To date I have not heard any suggestions. I would welcome any, and offer the CVJA as a forum to air them.

It is not possible to conclude an editorial such as this without commenting on the views of members of the broader cardiac community, recently aired in a variety of media. I view these with dismay. There are many matters that may block access to vaccines for our patients. The views of high-profile 'medical experts' should not be among them. I have always considered that I should only comment on matters within my area of expertise. Beyond that I believe I should be directed by scientific sources that I trust. Suffice it to say that I and my immediate family are vaccinated.

PJ Commerford
Editor-in-Chief

Cardiovascular Topics

Value of peripheral blood neutrophil-to-lymphocyte ratio for clinical diagnosis and prognosis of elderly patients with chronic heart failure and atrial fibrillation

Chentao Yang, Hua Yang, Sufang Feng, Jie Qin

Abstract

Aim: We aimed to explore the value of peripheral blood neutrophil-to-lymphocyte ratio (NLR) for the clinical diagnosis and prognosis of elderly patients with chronic heart failure (CHF) and atrial fibrillation (AF).

Methods: A total of 248 eligible patients were followed up for five years, and divided into major adverse cardiovascular event (MACE) and non-MACE groups. The independent predictive factors for MACE were explored by multivariate logistic regression analysis. Based on quartile of NLR, they were divided into groups A to D. The duration of MACE was analysed using Kaplan–Meier survival curves. The diagnostic value of NLR for MACE was evaluated by receiver operating characteristic curves.

Results: Higher age, low-density lipoprotein cholesterol and NLR, lower left ventricular ejection fraction, diabetes and NYHA heart function class III and IV were independent predictive factors for MACE. The incidence of MACE rose with increasing NLR. Groups A to D had significantly different rates of acute myocardial infarction, severe arrhythmia and cardiac death ($p < 0.05$). The average duration of MACE in groups A to D were 49.31, 45.27, 43.63 and 40.34 months, respectively.

Conclusion: The sensitivity and specificity of NLR for diagnosis of MACE were 72.39 and 86.18%, respectively. NLR was an independent predictive factor for MACE in these elderly patients with CHF and AF.

Keywords: neutrophil-to-lymphocyte ratio, chronic heart failure, atrial fibrillation, prognosis

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Chronic heart failure (CHF) refers to changes in cardiac structure and function due to various pathogenic factors, leading to ventricular filling, or impairment of the ejection function, pulmonary oedema, cardiogenic shock and other symptoms. Patients are prone to cardiovascular lesions during prognosis.[1] With increasing age, the incidence of cardiovascular disease rises significantly, so elderly people are a high-risk group of HF patients. The incidence of HF in elderly patients above 65 years of age is five to 10 times that in younger adults, therefore seriously threatening the life and health of the elderly.[2]

The incidence of atrial fibrillation (AF) is significantly elevated with increasing severity of HF. AF then further reduces stroke volume and cardiac output in patients with CHF, significantly increasing the risk of major adverse cardiovascular events (MACE). Therefore, early diagnosis and therapeutic measures have important clinical significance for patients with CHF and AF.

Neutrophil-to-lymphocyte ratio (NLR) can directly reflect the inflammatory state and immune level of the patient, and it rises with myocardial ischaemia.[3] In recent years, NLR has been widely used in the diagnosis of cardiovascular diseases, and when it is elevated, it has been confirmed in many studies to be an independent risk factor for coronary heart disease.[4] However, the association between NLR and the prognosis of patients with CHF and AF is rarely reported. Therefore, this study aimed to explore the value of NLR in evaluation of disease risk and prognosis in patients with CHF and AF.

Methods

A total of 248 patients with CHF and AF, admitted to our hospital from October 2013 to June 2014, were selected. According to the New York Heart Association (NYHA) functional classification,[5] there were 58 cases in class I, 62 in class II, 68 in class III, and 60 in class IV. Among the patients, there were 156 males (62.90%) and 92 females (37.10%), aged on average 72.04 ± 10.87 years (65–88).

Inclusion criteria were: (1) patients aged ≥ 65 years, (2) those meeting the relevant criteria in the *Guideline for the Management of Heart Failure* (2014) developed by the Society

of Cardiology, Chinese Medical Association, and (3) those accompanied by paroxysmal, persistent or permanent AF based on the relevant standards in the *Guideline for the Management of Atrial Fibrillation* (2014). All patients gave informed consent to this study, and the study was approved by the hospital ethics committee.

Exclusion criteria were: (1) patients with cardiac dysfunction caused by congenital heart disease, pulmonary heart disease, primary valvular heart disease, or acute myocardial infarction, (2) those with malignant tumours, (3) those with severe hepatic or renal dysfunction, (4) those who failed to complete the study as required due to mental disorders, or (5) those whose condition of disease became stable for less than one week after the acute phase of CHF.

The basic clinical parameters such as gender, age, smoking history, body mass index, blood pressure, diabetes history and hypertension history were collected. In addition, 5 ml of fasting venous blood was drawn from each patient in the morning, the day after percutaneous coronary intervention. It was anticoagulated with EDTA and centrifuged at 3 000 rpm and 4°C for 15 minutes.

The serum was examined using a fully automatic biochemical analyser (Hitachi Labospect 008) to determine creatinine (Cr), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), and blood urea nitrogen (BUN) levels. Neutrophils and lymphocytes were counted using a haematology analyser (Sysmex XE2100). Within 24 hours of admission, left ventricular ejection fraction (LVEF) was determined using a DW-F3 Doppler ultrasonic diagnostic system (DAWEI).

All patients enrolled were followed up for five years through the out-patient clinic, by re-examination, re-hospitalisation and telephone. The occurrence of MACE was taken as the end point of follow up. MACE include acute myocardial infarction, congestive HF, ischaemic stroke, peripheral arterial occlusion, recurrent angina, severe arrhythmia (persistent ventricular tachycardia, ventricular fibrillation, new-onset haemodynamically unstable AF or atrial flutter, high-grade atrioventricular block, excluding reperfusion arrhythmia during PCI), and cardiac death.[6]

Statistical analysis

SPSS20.0 software (SPSS Inc, Chicago, IL, USA, 2011) was used for statistical analysis. Quantitative data in line with normal distribution are expressed as means ± standard deviation, and one-way analysis of variance was performed for comparison between groups. Numerical data are expressed as percentages, and the chi-squared test was performed for intergroup comparison. Factors related to MACE were analysed through multivariate logistic regression models.

The diagnostic value of NLR for MACE was analysed using the receiver operating characteristic (ROC) curves. Survival curves were plotted using GraphPad 5 software, survival analysis was conducted using the Kaplan–Meier method, and the difference in survival curves was detected using the log-rank test. A p-value < 0.05 was considered statistically significant. The corrected test level $\alpha = 0.0206$ was used in the pairwise comparison among groups.

Results

All 248 patients were divided into MACE and non-MACE groups according to whether MACE occurred during the follow-up period. Compared with the non-MACE group, the MACE group had a higher age, higher proportion of cases with a history of smoking and diabetes, LDL-C and FPG level, NLR and NYHA functional class (III + IV), and lower LVEF. The differences were statistically significant ($p < 0.05$) (Table 1).

With the presence or absence of MACE during the follow-up period as the dependent variable, and the statistically significant factors in univariate analysis as the independent variables, multivariate logistic regression analysis was performed. The results showed that higher age, LDL-C level and NLR, and lower LVEF and diabetes, and NYHA class III and IV were independent predictive factors for MACE ($p < 0.05$) (Table 2).

Based on the quartile of NLR, the patients were divided into group A (NLR < 1.98), group B (1.98 ≤ NLR < 2.85), group C (2.85 ≤ NLR < 4.62) and group D (NLR ≥ 4.62). The incidence of MACE during follow up in each group is shown in Table 3. It was found that the incidence of MACE rose with increased NLR and the differences were statistically significant between groups ($p < 0.05$). There were statistically significant differences in the incidence of acute myocardial infarction, severe arrhythmia and cardiac death among the four groups ($p < 0.05$), but the incidence of other MACE showed no statistically significant differences ($p > 0.05$).

According to the Kaplan–Meier curves of patients with CHF and AF, the average duration of MACE was 49.31 months in group A, 45.27 months in group B, 43.63 months in group C and 40.34 months in group D. It was confirmed using the log-rank test that the survival curves of patients with MACE showed statistically significant differences among the four groups ($p < 0.05$; group A vs group B; $p = 0.006$, group A vs group C; $p =$

Table 1. Baseline clinical data of MACE and non-MACE groups [mean ± standard deviation/number (%)]

Index	*Non-MACE group (n = 152)*	*MACE group (n = 96)*	t/χ^2	p-*value*
Age (year)	53.97 ± 10.19	67.24 ± 10.12	10.016	< 0.001
Male	92 (60.53)	64 (66.67)	0.951	0.33
BMI (kg/m²)	24.42 ± 2.11	24.67 ± 2.01	0.926	0.356
Smoking history	70 (46.05)	62 (64.58)	8.116	0.004
Systolic pressure (mmHg)	134.37 ± 12.89	135.18 ± 13.33	0.476	0.635
Diastolic pressure (mmHg)	84.25 ± 7.63	85.34 ± 8.17	1.066	0.287
Diabetes mellitus	60 (39.47)	55 (57.29)	7.512	0.006
Hypertension	87 (57.24)	58 (60.42)	0.245	0.621
LVEF (%)	58.07 ± 6.18	39.42 ± 3.98	26.312	< 0.001
Cr (μmol/l)	75.91 ± 22.54	74.45 ± 20.32	0.516	0.606
TC (mmol/l)	4.21 ± 0.51	4.22 ± 0.49	0.153	0.879
TG (mmol/l)	1.50 ± 0.06	1.51 ± 0.10	0.984	0.326
LDL-C (mmol/l)	2.84 ± 0.12	2.96 ± 0.15	6.953	< 0.001
HDL-C (mmol/l)	1.27 ± 0.19	1.26 ± 0.15	0.437	0.663
FPG (mmol/l)	6.93 ± 0.65	7.63 ± 0.96	6.846	< 0.001
BUN (mmol/l)	5.44 ± 1.39	5.46 ± 1.33	0.112	0.911
NLR	2.38 ± 0.21	4.32 ± 0.38	32.38	< 0.001
NYHA functional class			47.616	< 0.001
I + II	100 (65.79)	20 (20.83)		
III + IV	52 (34.21)	76 (79.17)		

BMI: body mass index; BUN: blood urea nitrogen; Cr: creatinine; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular event; NLR: neutrophil-to-lymphocyte ratio; NYHA: New York Heart Association; TC: total cholesterol; TG: triglycerides.

Table 2. Multivariate logistic regression analysis of independent predictive factors for MACE

	β	*SE*	*Wald*	*p-value*	*OR (95% CI)*
Age					
< 60					1.000
≥ 60	2.304	0.467	22.657	0.008	10.291 (3.789–24.315)
Smoking history					
No					1.000
Yes	2.644	0.854	0.212	0.323	2.32 (0.021–6.544)
Diabetes mellitus					
No					1.000
Yes	0.542	0.343	1.743	0.001	1.622 (1.311–3.245)
LDL-C					
< 2.30 mmol/l					1.000
> 2.30 mmol/l	0.020	0.010	2.6987	0.001	2.022 (1.987–2.056)
NLR					
< 3.50					1.000
> 3.50	1.501	0.341	19.412	< 0.001	4.159 (2.378–8.814)
LVEF					
< 50%					1.000
> 50%	–0.432	0.308	58.802	< 0.001	0.657(0.365–0.802)
FPG					
< 7.1 mmol/l					1.000
> 7.1 mmol/l	0.759	0.218	11.242	0.014	2.142 (1.391–3.132)
NYHA heart function class					
I + II					1.000
III + IV	0.987	0.458	0.102	0.005	1.854 (2.654–4.654)

FPG: fasting plasma glucose; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular event; NLR: neutrophil-to-lymphocyte ratio; NYHA: New York Heart Association.

0.002, group A vs group D; $p = 0.001$, group B vs group C; $p = 0.009$, group B vs group D; $p = 0.011$, group C vs group D; $p = 0.018$) (Fig. 1).

The ROC curves showed that the area under the curve, optimal cut-off value, sensitivity and specificity of NLR for MACE in patients with CHF and AF were 0.879 (95% CI: 0.801–0.978, $p < 0.001$), 3.12, 72.39% and 86.18%, respectively (Fig. 2).

Discussion

CHF is a clinically common and frequently occurring disease. The proportion of patients with HF in the total population is as high as 2–3%, even in developed countries.[7] AF is a common type of arrhythmia and also has a high rate of incidence. HF and

Table 3. Prognosis of patients with different NLR values

	Group A (n = 62)	*Group B (n = 62)*	*Group C (n = 62)*	*Group D (n = 62)*	χ^2	p-*value*
Acute myocardial infarction	1	5	8	10	8.488	0.037
Congestive heart failure	1	3	2	2	1.033	0.793
Ischaemic stroke	1	1	1	1	0.000	1.000
Peripheral artery occlusion	2	2	1	1	0.683	0.877
Recurrent angina	3	3	1	1	2.067	0.559
Severe arrhythmia	2	3	6	10	8.064	0.045
Cardiac death	2	4	8	11	8.674	0.034
Total	12	21	27	36	20.803	< 0.001

NLR: neutrophil-to-lymphocyte ratio.

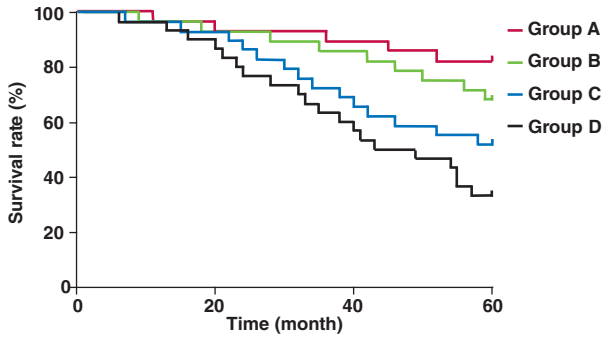

Fig. 1. Survival analysis of patients with different NLR values undergoing MACE. MACE: major adverse cardiovascular event; NLR: neutrophil-to-lymphocyte ratio.

AF often co-exist, and the rate of incidence of AF in patients with HF is up to 54%. There is a positive correlation between the degree of HF and the rate of incidence of AF, and the rate of incidence of AF in HF patients in NYHA class IV is 10 times that in patients in class I.[8]

There has been a consensus in multiple studies that the long-term prognosis of patients with HF and AF is poor. Both chronic diseases seriously affect the quality of life of patients and impose a heavy burden on the medical system.[9] However, there are no reliable methods for predicting the prognosis of patients with CHF and AF. Therefore, we urgently need to find new markers to improve the early identification of adverse prognostic events and improve the quality of life of such patients.

AF leads to a decline and even disappearance of atrial systolic function in patients with HF, it causes irreversible embolism and a systemic inflammatory response, and reduces lymphocyte counts in patients, ultimately resulting in a steady increase in NLR in the blood.[10] It has been confirmed in a large

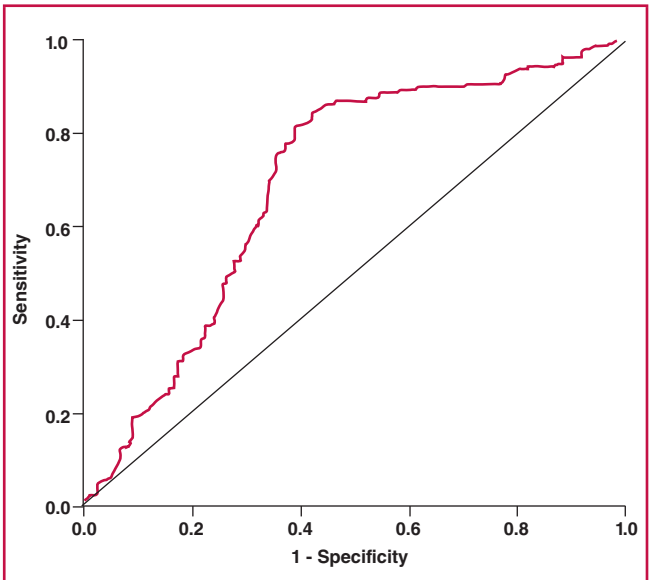

Fig. 2. Predictive value of NLR for MACE. MACE: major adverse cardiovascular event; NLR: neutrophil-to-lymphocyte ratio.

number of studies and clinical practice that NLR serves as an evaluation index for diagnosis and prognosis of patients with cardiac insufficiency.[11] Determining NLR in plasma in patients with CHF and AF has been a subject of study in recent years. It is currently believed that NLR is an ideal marker of myocardial injury, and the level has a significant positive correlation with the degree of myocardial injury.[12]

NLR has predictive value for the prognosis of a variety of cardiovascular diseases.[13] Patients with coronary heart disease have a higher NLR in plasma.[14] Furthermore, NLR in plasma is higher in patients with acute myocardial infarction than that in patients with unstable angina, while it is also higher in the latter than that in patients with stable angina. After correcting for a variety of traditional cardiovascular risk factors, NLR can be used as a predictor for major adverse events of AF.[15] In our study, the results of logistic regression analysis showed that NLR was an independent predictive factor for MACE in patients with CHF and AF.

In our study, the patients were divided into four groups based on the quartile of NLR. It was found that the difference in incidence of MACE was statistically significant between the four groups ($p < 0.05$), manifesting as increased incidence of acute myocardial infarction, severe arrhythmia and cardiac death with increasing NLR. AF raises both resting heart rate and response heart rate, further reducing cardiac output and elevating cardiac filling pressure, which is the internal cause of aggravation of HF by AF and an important factor causing acute myocardial infarction.[16] AF is a common type of arrhythmia, and CHF can further enhance atrial depolarisation and repolarisation dispersion and cause re-entry more easily, thereby leading to severe arrhythmia.[17]

In this study, according to the analysis results of Kaplan–Meier survival curves, the duration of MACE in group D was significantly shorter than that in groups A and B. Yýlmaz *et al*. demonstrated that NLR > 3.08 was an independent predictor of new-onset myocardial infarction and in-hospital death in patients with HF.[18] In our study, the ROC curves showed that the optimal cut-off value and area under the curve of NLR for MACE in patients with CHF and AF were 3.12 and 0.879, respectively, confirming their high diagnostic value.

Conclusion

NLR was an independent predictive factor for MACE in these patients with CHF and AF, and it had high diagnostic value, which is of importance for adopting the appropriate therapeutic regimen and improving prognosis as early as possible.

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Assessing volumetric changes in abdominal aortic aneurysms following endovascular repair

Yalçın Gunerhan, Mehmet Isik, Yüksel Dereli, Omer Tanyeli, Cengiz Kadıyoran, Mehmet Sinan Iyisoy, Niyazi Gormus

Abstract

Objective: Volumetric changes in the aneurysm sac were evaluated following endovascular aortic repair (EVAR) in intact abdominal aortic aneurysm (AAA) patients who underwent EVAR.

Methods: Fifty-two patients, who underwent EVAR from 2015 to 2019, were analysed retrospectively. A total of 158 computed tomography angiography scans was examined by performing reconsctructive volumetric calculations. Total aneurysm volume (TAV), patent lumen volume (PLV) and thrombus-coated aneurysm wall volume (TCAWV) were calculated. The results obtained at six, 12 and 24 months postoperatively were compared with those of the pre-operative period.

Results: Mean TAV had regressed 7% by the sixth month (p = 0.1), 27% by the 12th month (p = 0.0003) and 19% by the 24th month (p = 0.0008). Mean TCAWV had increased 2% by the sixth month (p = 0.3), and regressed 26% by the 12th month (p = 0.3) and 14% by the 24th month (p = 0.8). Mean PLV had regressed by 20% by the sixth month (p = 0.008), 29% by the 12th month (p = 0.0002) and 26% by the 24th month (p = 0.0006). For each individual proximal, middle and distal measurement, regression was observed at six and 12 months; however, an increase was observed at 24 months compared to the previous follow ups.

Conclusion: The expansion measurements of TAV in the 24th month support the doubts on the medium- to long-term results of EVAR. The largest regression in the aneurysm sac was observed in the distal portion, then in the proximal portion, and the least regression was observed in the middle section.

Keywords: endovascular aneurysm repair, abdominal aortic aneurysm, volumetric measurement, endotension, endoleak

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Nowadays, endovascular aortic aneurysm repair (EVAR) is a common method for the treatment of abdominal aortic aneursym (AAA). Lifelong follow up is neccessary for EVAR patients since the aneurysm diameter may increase or an endoleak may develop over time. Changes in aneursym volume are also critically important as they indicate the long-term success of EVAR.[1] Computed tomography angiography (CTA) is commonly used for patient follow up. The status of stent grafts and aneursyms can be evaluated through observing two-dimensional axial sections or three-dimensional volumetric measurements of CTA scans.

Reconstructive volumetric measurement is the process of combining two-dimensional axial sections taken from different reference levels, converting these sections into a three-dimensional image and obtaining volumetric measurements from the newly formed three-dimensional image. Volumetric measurements are considered to be more reliable than measurements obtained from two-dimensional diameter changes.[1,2]

In this study, volumetric changes in the aneursym sac following EVAR were examined in AAA patients. The aim was to investigate to what extent an expected volumetric regression occurred following EVAR, when expansion occurred again, whether the stent graft placed in the patient's lumen changed over time, and in which part of the aneurysm sac the process was more effective.

Methods

In this study, 132 intact infrarenal AAA patients, who had elective EVAR surgery between November 2015 and May 2019 in our clinic, were retrospectively analysed. Fifty-two patients who had had EVAR and CTA scans performed in the sixth, 12th and 24th months postoperatively were included in the study. Retrospective information of the patients was obtained from the hospital software system.

The local ethics committee (2019/1946) approved the study and all patients provided their written informed consent. The study was performed in accordance with the principles of the Helsinki Declaration.

EVAR was performed on patients whose infrarenal aortic diameter was 5.5 cm or more. Patients who had CTA imaging in the postoperative sixth, 12th and 24th months were included in the study. Exlucision criteria were as follows: emergency surgery due to AAA rupture or dissection, and renal function impairment preventing CTA scans in routine control follow ups

(a creatinine value of 1.5 mg/dl or above). Three different stent graft systems were used for EVAR, Medtronic (Endurant II Stent Greft), Jotec (E-vita abdominal Stent Greft) and Lifetech (Ankura AAA Stent Greft) brand devices.

Reconstructive volumetric measurements were performed to assess total aneurysm volume (TAV), patent lumen volume (PLV) and thrombus-coated aneurysm wall volume (TCAWV). In addition, individual measurements were performed at the proximal, distal and middle sections of the aneurysm. The impact of pre-operative thrombus load and the brand of the stent device on volumetric regression were also examined.

The impact of pre-operative thrombus load on TAV change was examined at three different postoperative periods. To do this, the median TCAWV value was measured pre-operatively (131 cm^3) and used as a threshold, and patients who were below or above the threshold were divided into two groups. Postoperative TAV was then measured at three different time points in the two patient groups.

TAV was determined as the total volume of the aortic segment starting from the distal end of the left renal artery to the distal iliac bifurcation. PLV was the open lumen volume through which blood passed. TCAWV was defined as the total thrombus volume smeared on the aneurysm wall between the aneurysm outer wall and the patent lumen (Fig. 1A, B). The measurements were performed with the Syngo.via software (VB20B version; Siemens Health, Erlangen, Germany), which was integrated with the PACS imaging system belonging to the Department of Radiology of our hospital. The measurements were carried out jointly by a radiologist and a cardiovascular surgeon.

Reconstructive volumetric TAV measurements were performed as follows: after the axial section scan was opened and enlarged in 'MM reading' mode, axial sections were taken at 3-mm intervals starting from just below the left renal artery outlet to the beginning of the distal iliac artery bifurcation, and the image borders were drawn manually. Then the software's 'create voi' feature combined semi-automatically drawn segments to make a three-dimensional reconstruction that provided the volume of the three-dimensional structure in cm^3 (Fig. 2A, B).

In some patients, tortuous areas were present in the sagittal and coronal sections. While creating the reconstruction, in areas with aortic tortuousity, measurements were made with 1-mm slices instead of 3 mm in the axial sections. For each TAV measurement, a three-dimensional view was obtained by reconstructing axial sections taken from 30 to 40 different segments, depending on the aneurysm length.

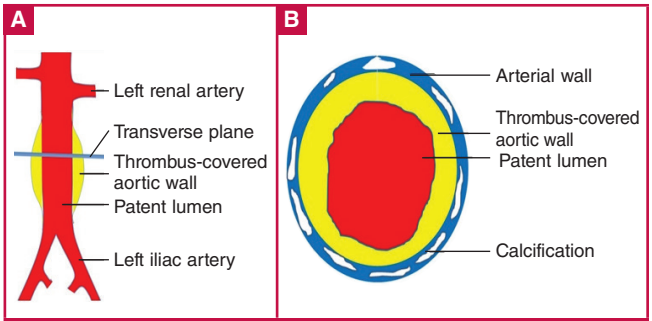

Fig. 1. A. Components of an AAA. B. Transverse plane image of an AAA.

A low molecular-weight heparin (Enoxaparin, 1 mg/kg every 12 hours) was administered to patients for one or two days following the surgery. After hospital discharge, clopidogrel (75 mg/day), acetylsalicylic acid (100 mg/day) and a β-blocker (50–100 mg/day) were prescribed. At the six-month follow up, clopidogrel was terminated and the patients were continued on acetylsalicylic acid and a β-blocker.

Statistical analysis

For continuous variables, mean and standard deviation are used as descriptive statistics. Likewise, for categorical variables, number and percentage are provided. The changes of numerical variables over time were compared using mixed-effects models. Multiple comparisons were performed using Dunnett's adjustments. Analyses were performed using SAS University edition 9.4. A p-value < 0.05 was considered statistically significant.

Results

The mean age of patients was 66.9 years (range 61–73). A total of 158 CTA scans was examined pre-operatively (n = 52), and six (n = 49), 12 (n = 35) and 24 months postoperatively (n = 22). In two patients, a type 1 endoleak was detected and in four, a type 2 endoleak. In nine patients (17%), sac enlargement was observed compared to the pre-operative period. Demographic data of patients are provided in Table 1.

Mean TAV had regressed at six (p = 0.1), 12 (p = 0.0003) and 24 months (p = 0.0008) compared to the pre-operative period (Fig. 3). Mean TCAWV had increased at six months (p = 0.3), while it had regressed at 12 (p = 0.3) and 24 months (p = 0.8) compared to the pre-operative period (Fig. 4). Mean PLV had regressed at six (p = 0.008), 12 (p = 0.0002) and 24 months (p = 0.0006) compared to the pre-operative period (Fig. 5).

Mean proximal measurements suggested a regression at six (p = 0.4), 12 (p = 0.08) and 24 months (p = 0.1) compared to the pre-operative period (Fig. 6). Likewise, mean middle measurements demonstrated a regression at six (p = 0.2), 12 (p = 0.007) and 24 months (p = 0.1) compared to the pre-operative

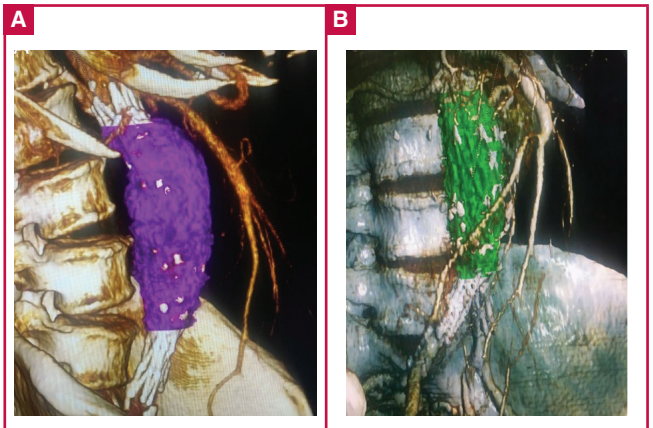

Fig. 2. A. Lateral view of the TAV obtained by reconstructive volumetric measurement in the 12th month postoperatively. B. Oblique view of PLV obtained by reconstructive volumetric measurement in the 12th month postoperatively.

Table 1. Demographic data

Demographic characteristics	*Patient number* (n = 52)	*%*
Gender: female/male	4/48	8/92
Hypertension	23	44
Coronary artery disease	22	42
Cigarette smoking	37	71
Chronic obstructive pulmonary disease	18	34
Peripheral artery disease	10	19
Diabetes	8	15
Cerebrovascular disease	8	15
History of malignancy	6	11
Chronic renal failure	4	7
Body mass index, kg/m²	27.8 (23–39.5)	

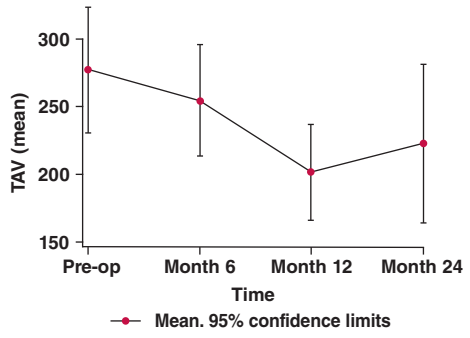

Fig. 3. The change in mean TAV over time.

period (Fig. 7). Mean distal measurements had also regressed at six ($p = 0.3$), 12 ($p = 0.001$) and 24 months ($p = 0.0004$) compared to the pre-operative period (Fig. 8). Volume measurements of patients taken at three different postoperative time points compared to the pre-operative period are provided in Table 2.

In the high pre-operative TCAWV (> 131 cm³) group, postoperative TAV at six ($p = 0.008$), 12 ($p < 0.0001$) and 24 months ($p = 0.0004$) were significantly different. On the other hand, in the low TCAWV group, no significant change was observed (Fig. 9).

Three different stent graft systems were used for EVAR. In 32 patients, Medtronic (Endurant II Stent Greft) was used, eight patients had Jotec (E-vita abdominal Stent Greft) devices, and in 12 patients, Lifetech (Ankura AAA Stent Greft) devices were used. The impact of these three different devices on volumetric regression was investigated, but no significant differences were found.

Table 2. The change in aneursym volume measurement over time

Volume	*Pre-operative, cm³*	*6th month, cm³ (%)*	*12th month, cm³ (%)*	*24th month, cm³ (%)*
TAV	276	254 (7)	201 (27)	222 (19)
TCAWV	158	162 (2)	116 (26)	135 (14)
PLV	118	94 (20)	83 (29)	87 (26)
Proximal	34	32 (6)	24 (27)	25 (24)
Distal	59	53 (10)	42 (28)	47 (21)
Middle	182	168 (7)	131 (27)	149 (18)

TAV: total aneursym volume, TCAWV: thrombus-covered aortic wall volume, PLV: patent lumen volume.

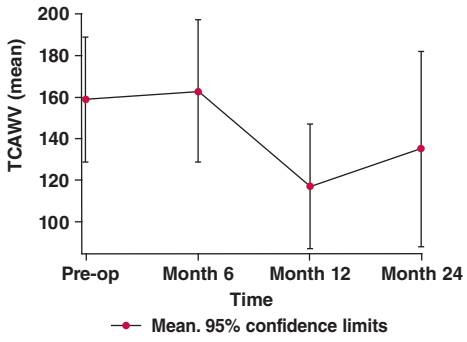

Fig. 4. The change in mean TCAWV over time.

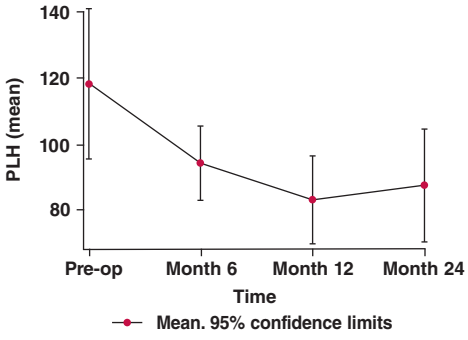

Fig. 5. The change in mean PLV over time.

Five patients died during the study, seven, 10, 12, 13 and 18 months postoperatively. The causes of death were found to be due to co-morbidities. Four patients had hypertension, three had coronary artery disease, three had chronic lung disease, and one had both coronary artery and chronic lung disease.

Discussion

In order to detect potential complications that may develop following EVAR, CTA follow up is suggested at one, six and 12 months postoperatively. In patents without any complications, lifelong annual CTA follow up is recommended.[3-5] Moreover,

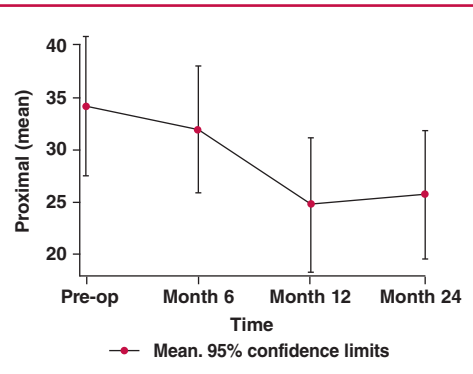

Fig. 6. The change in the proximal 2-cm portion of the mean aneurysm sac volume over time.

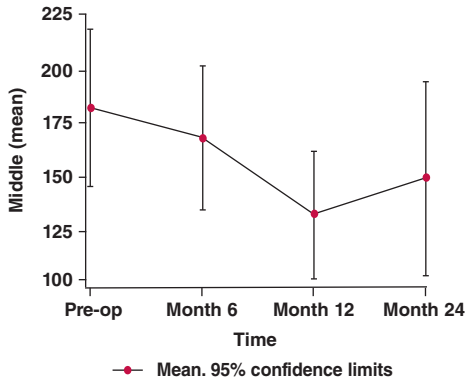

Fig. 7. The change in the middle portion of the mean aneurysm sac volume over time.

assessment of the axial sections of CTA scans or reconstructive volumetric measurements could also be performed.

It has previously been reported that volumetric measurements could more precisely detect the size of the AAA and result in less variation between observers.[2] Since volumetric measurements are three dimenational, they can detect minor changes compared to two-dimensional diameter changes.[1,6] Two-dimensional measurements are inadequate, especially in areas with an irregular aneurysm wall; they can be used for the assessment of a single section instead of examining the whole structure. Therefore, in our study, we preferred assessment of volumetric changes rather than changes in diamter.

When volumetric CTA scans were performed in the third, sixth and 12 months, any increase in the volume more than 2% from the previous examination could be associated with endoleaks.[6] A volume regression of 10% or more within six months and continuous decline over time was considered a successful endovascular repair.[1] In the present study, mean TAV had regressed at six and 12 months, while expansion was observed at 24 months compared to the previous follow-up examination, but this expansion was not comparable to that of the pre-operative period.

A decrease in regression at 24 months, or in other words, restart of the expansion was associated with a TCAWV increase. Since no endoleak was observed, this could have been associated

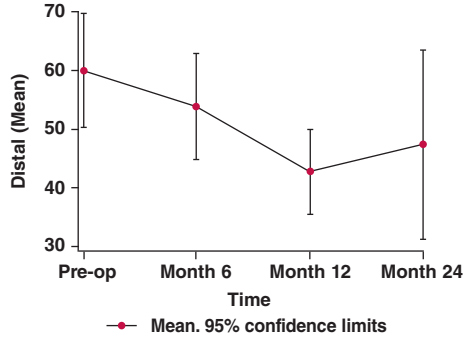

Fig. 8. The change in the distal 2-cm portion of the mean aneurysm sac volume over time.

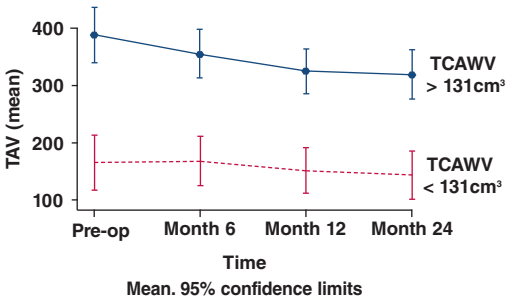

Fig. 9. The change in TAV over TCAWV (below and above 131 cm³).

with endotension, which is defined as persistent pressure in the aneursym and continued expansion of the sac with no endoleak.[7] This may be caused by high hydrostatic pressure in the graft and its associated impact on porosity and transmission. In addition to hydrostatic pressure, recent data suggest that a fluid called 'permeat', which is accumulated inside the sac due to thrombolytic activity but is located outside of the graft, could also be involved in endotension.[8]

Mean TCAWV, which indicates changes in thrombus load, partially increased at six months compared to the pre-operative period, but then started to decline at 12 and 24 months. However, the increase at 24 months was similar to that of the TAV. The increase in the sixth month could have been associated with inferior mesenteric and lumbar artieries causing a type II endoleak. The use of anti-aggregants by the patients could also have caused these results.

Mean PLV was significantly reduced at six months compared to the pre-operative period. Similar mean PLV were obtained from six-, 12- and 24-month measurements. The first measurement showing the internal volume of the stent graft following EVAR was performed at six months, therefore it could be expected that there would be a decline in volume at six months. Similar results obtained at six, 12 and 24 months suggest that there were no major changes in PLV following the stent graft placement.

In order to observe in which region and to what extent the volume change occurred in the aneurysm sac, it was divided into three regions: proximal, middle and distal. The results obtained from these regions were similar to that obtained from the TAV. There was a regression at six and 12 months and an expansion at 24 months compared to the previous follow up. However, the expansion observed at 24 months was not comparable to that of the pre-operative period.

Even though the total regressions were similar, the distal portion displayed the largest regression, followed by the proximal and then the middle portions. The least regression observed in the middle portion could be associated with the weakest aneurysm sac present in this location.

It is known that EVAR reduces mortality rate in the peri-operative period and first six months compared to open surgery.[9,10] Controversial results have been reported regarding long-term effects of EVAR. Similar mortality rates have been reported from six months to eight years. However, after eight years, the EVAR group showed higher mortality rates.[10]

In another study, the first three years' survival rate was significantly higher in EVAR compared to open surgery.

Thereafter, similar survival rates were reported. In the same study, higher complications and interventions were reported in the EVAR group after an eight-year follow-up period. This eight-year follow-up period also revealed that the aneursym rupture rate in the EVAR group was 5.4% compared to 1.4% in the open-surgery group.[11] The EVAR group displayed higher complication rates, secondary interventions, delayed aneursym ruptures, and long-term aneurysm-associated mortality rates compared to the conventional surgery groups.[10]

Endoleaks are the most frequent complications of EVAR and the frequency has been reported to range from 2.4 to 45.5%.[12] The continum of aneursym expansion, rupture development and associated mortalities following EVAR has been reported to be correlated with endoleaks.[13,14] Therefore, endoleaks require a close follow up and the frequency should depend on the endoleak type. The most common endoleaks are types I and II.[15]

In one study, type I and III endoleaks were reported to have higher sac expansion rates. They were suggested to be high-pressure endoleaks and early medical intervention was advised.[16] On the other hand, type II and V endoleaks were considered lower pressure and therefore less urgent for medical intervention.[17] If aneursym volume is not increased significanlty in type II endoleaks, they can be resolved without any medical treatment. Therefore, in such cases a 'wait and see' approach has been suggested.[18]

The importance of pre-operative opening of inferior mesenteric and lumbar arteries has been documented in EVAR-associated type II endoleaks.[2] In the current study, 3.8 and 7.6% of the patients displayed type I and II endoleaks, respectively. Additional interventions were performed in patients who displayed a type I endoleak. In the follow up of patients with type II endoleaks, abnormal sac expansion was not observed, therefore additional interventions were not performed. The reduced endoleak rates in the present study compared to the other published studies in the literaure could be associated with the short follow-up period.

In our study, the impact of the device used on the observed differences in endoleak, graft migration and sac regression following EVAR was also investigated and a potential impact of the device was found.[19] However, opposite results stating no effect of the device has also been reported.[1] The impact of three different devices was investigated on the volumetric regression following EVAR and no significant difference was found. However, irregularities in the number of devices distributed may have impacted on the current results.

The correlation between pre-operative thrombus load and sac regression has been investigated and controversial results have been reported. Some studies report an increased sac expansion with lower thrombus load.[9] Slower regression and higher intervention rates have also been reported in cases of elevated thrombus load.[20] However, there are some studies that do not suggest any association between thrombus load and sac regression.[21] In the present study, volumetric regression of TAV was significantly higher in all three postoperative periods, with a higher thrombus load.

It is well known that development of an aneursym is a chronic condition and may continue after EVAR. Therefore, CTA scans should be performed during the early and late postoperative period in order to determine expansion and the elimination of potential endoleaks. Lifetime CTA monitoring however is a disadvantage.[22] The results of our study suggest the use of three-dimensional reconstructive volumetric measurements that show all surfaces of the aneurysm instead of using two-dimensional longitudinal sections that only allow assessment of diameter.

The main limitations of our study were the retrospective nature of data collection, the relatively small sample size, and lack of long-term follow up. Other limiting factors that could have affected regression or enlargement and were largely unknown were patient-related factors, such as smoking, hypertension and medication used. Also the number of CTA images done decreased, especially by the 24th month postoperatively.

Conclusion

Even though mean TAV displayed volumetric regression for the first 12 months, the re-start of expansion at 24 months supports the long-term doubts about EVAR. PLV measurements demonstrated that six-, 12- and 24-month measurements did not show significant differences after the placement of a stent. However, increased expansion of TAV while PLV were not significantly different at 24 months suggests pathological processes had continued outside the stent graft. The most regression of the aneurysm sac was detected in the distal portion, followed by the proximal and then the middle sections. Future long-term studies are required to determine when sac expansion will reach the pre-operative state and what course this expansion will take in the period after 24 months.

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An epidemiological study to define the recent clinical characteristics and outcomes of infective endocarditis in southern Turkey

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Abstract

Introduction: The aim of this study was to characterise the recent features of patients with infective endocarditis (IE) at one referral centre in southern Turkey, in order to be able to identify the high-risk subgroup and revise preventative measures and management strategies.

Methods: Medical records of patients 18 years and older, who had been diagnosed with IE according to the Duke criteria between January 2009 and October 2019, were retrospectively evaluated in a referral general hospital.

Results: The total of 139 IE cases comprised 59.7% males and 40.3% females, with a mean age of 55 ± 16 years. The most encountered symptom was fever (55.4%) and the mitral valve (54%) was the most frequently involved. The most common causative micro-organisms were coagulase-negative staphylococci (30.2%). The in-hospital mortality rate was 30.2%, with congestive heart failure, chronic renal disease and chronic dialysis found to be significantly associated with in-hospital mortality.

Conclusion: The study results demonstrate the recent epidemiological features of IE in southern Turkey that are important for clinicians to manage diagnostic and therapeutic processes successfully. Older age, the predominance of staphylococci and higher surgery rates are consistent with the changing trends of IE in some parts the world.

Keywords: infective endocarditis, epidemiology, dialysis, mortality

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Infective endocarditis (IE) is an uncommon disease with an annual incidence of three to 10 per 100 000 people, but it remains a serious health problem, causing lengthy hospitalisation with high costs.[1]

Recently there have been some changes in the epidemiology of IE worldwide, with *Staphylococcus aureus* and coagulase-negative staphylococci replacing streptococci as the causative micro-organisms.[2] When the underlying predisposing factors were reviewed, a decrease was seen in the prevalence of rheumatic heart disease (RHD), and an increase in prosthetic heart material, intravenous catheters and immunosupression. IE patients tend to be older now than they were previously.[3] The epidemiology of IE also shows regional variation.

IE has a high mortality rate,[4] possibly because of late or missed diagnosis. Therefore, physicians should be fully aware of recent trends and developments for early diagnosis and optimal management of patients with IE.

This retrospective study was conducted to define recent trends in the epidemiology of IE over a 10-year period at a tertiary-care centre, which is a referral hospital in southern Turkey, and to evaluate clinical outcomes. We aim to guide clinicians in defining the high-risk population and choosing the right empirical antibiotic therapy.

Methods

Medical records of a referral general hospital were scanned to identify patients diagnosed with IE between January 2009 and October 2019. Modified Duke criteria were used to define IE, and definite IE cases were enrolled into the study.[5] The data of 139 IE patients, whose management was completed in our hospital, were included in this research. Patients who were under the age of 18 years or who left the hospital before treatment was completed were excluded from the study.

Basal characteristics (gender, age), symptoms on admission, echocardiographic features (structural heart disease, prosthetic heart valve), laboratory and microbiological examinations (culture results), co-morbidities (hypertension, chronic dialysis, diabetes mellitus), predisposing factors (invasive procedures, intravascular catheters), surgery and mortality outcomes were recorded. Echocardiographic examinations were also screened to identify the valve involved and vegetation size. Possible complications of IE were analysed from clinical course records, and embolic complications were determined from radiological studies.

Approval for the study was granted by the Institutional Ethics Committee (approval code: 43867).

Statistical analysis

Data obtained in the study were analysed statistically using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA) software.

Table 1. Baseline clinical characteristics of the patients

Variables	*Number (%)*
Gender, female	56 (40.3)
Hypertension	57 (41)
Diabetes mellitus	46 (33.1)
Ejection fraction < 55%	29 (20.9)
Chronic kidney disease	45 (32.4)
Immunosupression	5 (3.6)
Chronic dialysis	33 (23.7)
Active smoking	11 (7.9)
Pacemaker	10 (7.2)
Central venous catheter	23 (16.5)
Prior history of endocarditis	1 (0.7)
Intravascular drug abuse	1 (0.7)

Conformity of the data to normal distribution was assessed with the Kolmogorov–Smirnov test. Continuous data are presented as mean ± standard deviation (SD) or median [range, interquartile range (IQR)], and categorical data as number (*n*) and percentage. Categorical parameters were analysed with the chi-squared test, and continuous variables with a normal distribution with the unpaired *t*-test. The Mann–Whitney *U*-test was applied to continuous variables with a non-normal distribution. Multiple linear regression analysis was applied to determine independent determinants of mortality. A value of $p < 0.05$ was accepted as statistically significant.

Results

This retrospective epidemiological research on IE was conducted in a regional referral hospital. Evaluation was made of a total of 139 patients with IE, comprising 59.7% males and 40.3% females, with a mean age of 55 ± 16 years. The basal clinical characteristics of the subjects and predisposing conditions for IE are presented in Tables 1 and 2, respectively.

The primary symptom was fever in 77 (55.4%) patients, coagulase-negative staphylococci (30.2%) were the most frequent causative agents, and the mitral valve was the most commonly affected site (54%) in the study population. The frequency of IE-related symptoms and the site of endocarditis are listed in Table 3, and the causative micro-organisms are presented in Table 4. The median time between hospital admission and diagnosis was three (five) days.

Table 2. Predisposing risk factors of the patients

Underlying heart disease	*Number (%)*
Intracardiac prosthetic material	35 (25.2)
Prosthetic mitral valve	22 (15.8)
Prosthetic aortic valve	9 (6.5)
Prosthetic tricuspid valve	1 (0.7)
Valvular ring	2 (1.4)
Left ventricular assist device	1 (0.7)
Rheumatic valvular disease	5 (3.6)
Rheumatic mitral stenosis	3 (2.2)
Rheumatic mitral regurgitation	2 (1.4)
Mitral valve prolapse	4 (2.9)
Bicuspid aortic valve	7 (5)
Atrial or ventricular septal defect	7 (5)
Hypertrophic cardiomyopathy	4 (2.9)
Other	3 (2.1)
History of invasive procedure	
Percutaneous angiographic procedure	7 (5)
Catheter insertion	6 (4.3)
Valve replacement	3 (2.2)
Dental procedure	3 (2.2)
Endoscopy	2 (1.4)

Table 3. Clinical presentations and site of endocarditis in the study population

Clinical presentation	*Number (%)*
Fever	77 (55.4)
Shortness of breath	11 (7.9)
Weakness	16 (11.5)
Cerebral embolism	10 (7.2)
Back pain	5 (3.6)
Cough	3 (2.2)
Nausea, vomiting	3 (2.2)
Vegetation site	
Mitral	75 (54)
Aortic	36 (25.9)
Tricuspid	11 (7.9)
Pacemaker	3 (2.2)
Catheter tip	2 (1.4)
Pulmonary	1 (0.7)

Transthoracic echocardiography (TTE) displayed a vegetation or related formation (abscess, fistula, dehiscence) in 64.7% of the patients, and this rate increased to 99.3% with the use of transoesophageal echocardiography (TEE). In 44 patients (31.6%) a vegetation was determined on TEE and not on TTE. Echocardiographic examinations displayed moderate to severe mitral regurgitation in 63 patients (45.3%), aortic regurgitation in 40 (28.7%) and tricuspid regurgitation in 33 patients (23.7%).

The surgical treatment ratio was 65.5% in this study population. The most common reason for surgery was persistent infection (28.1%), and the median time between diagnosis and referral for surgery was seven (18) days. Systemic embolism (39.6%) was the most frequent complication encountered during the entire follow-up period in these patients with IE. Other common complications and reasons for surgery are listed in Table 5.

In-hospital mortality was seen in 42 patients (30.2%) with a diagnosis of IE. In logistic regression analyses, chronic renal disease, congestive heart failure and chronic dialysis were found to be associated with an increased mortality risk. A statistically significant correlation was determined between mortality and high C-reactive protein (CRP) and high creatinine levels. The association of mortality with selected variables is shown in Table 6.

Table 4. Micro-organisms isolated from blood cultures in the study

Micro-organisms	*Number (%)*
Coagulase-negative staphylococcus	42 (30.2)
Staphylococcus aureus	22 (15.8)
Viridans streptococcus	4 (2.9)
Streptococcus bovis	1 (0.7)
Other streptococci	15 (10.8)
Enterococci	9 (6.5)
Brucella species	5 (3.6)
Pseudomonas aeruginosa	1 (0.7)
Fungal	1 (0.7)
Culture negative	30 (21.6)

Discussion

In this study, the findings of 139 patients with IE were evaluated to determine recent epidemiological features in southern Turkey during a 10-year period. Compared with previous studies from Turkey, a shift can be seen over the years in terms of patient age, predisposing factors and causative micro-organisms.[6-9]

Consistent with recent trends in IE epidemiology, the median age of our study patients was higher compared with older data.[3,10] The mean age (55 ± 16 years) of this study population is the highest ever reported for IE in Turkey, although it remains below the mean age in European countries.[6-9,11,12] The older age of the IE population can be explained by a decrease in incidence of RHD, an increase in incidence of valvular degenerative disease due to longer life expectancy, and a larger number of patients with intracardiac prosthetic material.

The average diagnosis time of three (five) days was extremely short compared with a previous case series, where a period of 18 days (range, 1–30 days) was reported.[13] This indicates an improved IE diagnostic process.

Supporting previous data, fever was the most frequent symptom in the current study, detected in more than half of the patients.[6-9,14] Conflicting with medical teaching, Roth spots were detected in only one patient and membranoproliferative glomerulonephritis in one patient. However, in 2006, Leblebicioglu *et al.* reported a 50% incidence rate of immunological phenomenona.[11] The low rates in our series may have been due to prompt diagnosis of IE before the emergence of immunological signs.

Diagnostic imaging for IE should begin with TTE. However, in the case of intracardiac devices or prostheses, or unclear results with high clinical suspicion of IE, TEE should be performed. Moreover, even if the diagnosis is clear on TTE, TEE should also be applied to investigate complications such as abscess.[15]

While in the current study, TTE examinations had a sensitivity of 64.7%, which is lower than expected (75%), TEE examinations were more sensitive, supporting the findings of previous studies.[16] This high rate of sensitivity of TEE cannot be attributed to only the presence of prosthetic heart valves in one-third of the study population because 20 of 44 patients who showed a vegetation on TEE and not on TTE had prosthetic heart material. It must be kept in mind that TEE should be the modality of choice in cases with prosthetic heart valves, intracardiac devices, or if there are complications such as a fistula, abscess or leaflet perforation.

Table 5. Complications of IE and indications for surgery

Complications	*Number (%)*
Systemic embolism	
Brain	30 (21.6)
Spleen	22 (15.8)
Lungs	6 (4.3)
Renal	5 (3.5)
Multiple locations	8 (5.7)
Acute renal failure	11 (7.9)
Heart failure	31 (22.3)
Spondylodiscitis	10 (7.2)
Heart block	0
Cause of surgery	
Persistent infection	39 (28.1)
Valvular dysfunction with heart failure	32 (23)
Recurrent embolism on antibiotic therapy	13 (9.4)
Paravalvular invasion or abscess	7 (5)

RHD-related endocarditis was very rare in this study population, with an incidence of 3.5%, which is lower compared to previous reports from Turkey.[7-9,11,17] Elbey *et al.* reported RHD as the most common underlying heart disease, with a prevalence of 28%, in a study from 2005 to 2012 in 13 tertiary-care centres.[7] In a study by Yavuz *et al.* published in 2015, covering the previous 14 years, patients with RHD comprised 33.9% of the IE population.[9] Due to the successful treatment of streptococcal tonsillitis, there has been a decrease in patients with RHD over the years.

Culture-negative endocarditis was seen in this study at the rate of 21.6%, which is in the expected range of 20.6 to 36.1% in Turkey, and five to 34% worldwide.[3,6-8,18] Culture-negative endocarditis could have been a result of previous antibiotic therapy because 17 (12.2%) patients had been referred to our hospital from other peripheral centres where empirical antibiotic therapy had possibly been given.

It was confirmed in this study that staphylococci seem to have replaced streptococci as the major cause of IE. This could be attributed to the fact that the incidence of dialysis and other intravascular access is increasing, and the number of patients with RHD is decreasing throughout the world.[3,19-21]

In the current series, the surgery rate (65.5%) is higher than previously reported (40–50%).[22] It is also higher than rates (27.8–60%) in previous reports from Turkey.[6-8] This may be a result of the study being done in a tertiary referral centre and the high incidence of prosthetic valve endocarditis in the study population.

Unlike recent data, the most common indication for surgery in the current study population was persistent infection (enlarging vegetation or persistent bacteraemia despite appropriate antibiotic therapy), whereas previous reports have shown valvular dysfunction causing heart failure.[1,23] This may be a result of antibiotic-resistant micro-organisms. Therefore, early surgical management should be kept in mind, because antibiotics alone may not be sufficient to eradicate the disease.[24] Consequently, postponing surgery until after the completion of a course of antibiotics is not recommended.[25]

Tugcu *et al.* reported in 2007 that the median time between diagnosis and surgery was 11 days.[8] In our study population, the median time from diagnosis to surgery was seven (18) days. This trend is consistent with recent recommendations supporting early surgery in IE.[19,22]

In the current study, the most frequent complication was systemic embolism (39.6%), which is in the expected range reported by recent guidelines (20–50%).[5] It should be kept in mind that a cerebral embolic event can be a presenting symptom of IE on admission.

Table 6. Regression analysis of co-morbidities for mortality

Co-morbidities	β	*p-value*
Hypertension	–0.069	0.450
Diabetes mellitus	0.111	0.175
Chronic renal disease	0.239	0.008
Smoking	0.022	0.789
Congestive heart failure	0.198	0.017
Chronic dialysis	0.222	0.009
White blood cell level	0.095	0.266
C-reactive protein	0.222	0.009
Creatinine	0.201	0.018

The mortality rate of IE has been reported to vary between 14 and 37% in various studies, and in Turkey, from 15.3 to 33%.[6,9,26] The mortality rate in our study of 30.2% was higher than the most recently reported rate from Turkey of 27.8%.[9] This may have been due to the high number of dialysis patients and those with prosthetic heart material, and the referral of severely ill patients or those with more complications. However, it is striking that the mortality rate of IE has not decreased over the years.

Consistent with previous reports, this study showed that end-stage renal disease and heart failure were associated with increased risk of death.[9,14] This indicates the high-risk population.

A strength of this research, compared with previous reports from Turkey, is the high number of dialysis patients in the study population. They comprised 23.7% of the series, with a mortality rate of 48.5%. The most encountered micro-organisms in these patients were coagulase-negative staphylococci (39.4%). Our results are also consistent with those of a previous study performed on 52 dialysis patients with IE, which reported a 37% in-hospital mortality rate and a prevalence of 87% gram-positive micro-organisms in the aetiology.[27]

Mostaghim *et al*. reported on a study population of IE that included 26.7% dialysis patients, and the most frequently detected micro-organisms were coagulase-negative staphylococci.[26] Consistent with the current study results, Leblebicioglu *et al*. reported that haemodialysis was a risk factor for mortality.[11] The above data demonstrate that attention must be paid and strategies must be developed to prevent healthcare-related bacteraemia in order to reduce the seriously poor outcomes in dialysis patients. In addition, an arteriovenous fistula should be preferred over vascular catheters.

This study had several limitations, primarily the retrospective design. Previous antibiotic use could not be identified completely, and some statistical analyses according to risk factor and causative organism could not be performed because of the low number of patients. Furthermore, as the study was conducted in a referral centre, there may have been a selection bias towards severely ill patients or those with more complications.

Conclusion

The results of this study are of value for helping in the revision of preventative, diagnostic and management strategies for IE. The important aspects of IE epidemiology in southern Turkey were older age, increased prevalence of staphylococci and high mortality rates. TEE was found to be better than TTE for the diagnosis of IE, even in patients without prosthetic heart valves, and should be performed in all patients with suspected IE.

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Above-normal blood pressure in midlife linked to increased brain damage in later life

Higher-than-normal blood pressure, especially diastolic, is linked to more extensive brain damage in later life, according to a study in the *European Heart Journal*. In particular, the study found that there was a strong association between diastolic blood pressure before the age of 50 years and brain damage in later life, even if the diastolic blood pressure was within what is normally considered to be a healthy range.

The findings come from a study of 37 041 participants enrolled in UK Biobank, a large group of people recruited from the general population aged between 40 and 69 years, and for whom medical information, including MRI brain scans was available.

The research, carried out by Dr Karolina Wartolowska, a clinical research fellow at the Centre for Prevention of Stroke and Dementia, University of Oxford, UK, looked for damage in the brain called 'white matter hyperintensities' (WMH). These show up on MRI brain scans as brighter regions and they indicate damage to the small blood vessels in the brain that increases with age and blood pressure. WMH are associated with an increased risk of stroke, dementia, physical disabilities, depression and a decline in thinking abilities.

Dr Wartolowska said: 'Not all people develop these changes as they age, but they are present in more than 50% of patients over the age of 65 years and most people over the age of 80 years even without high blood pressure, but it is more likely to develop with higher blood pressure and more likely to become severe.'

Information on the participants was collected when they enrolled in UK Biobank between March 2006 and October 2010, and follow-up data, including MRI scans, were acquired between August 2014 and October 2019. The researchers adjusted the information to take account of factors such as age, gender, risk factors such as smoking and diabetes, and diastolic as well as systolic blood pressure. Systolic blood pressure is the maximum blood pressure reached each time the heart beats and is the top number in blood pressure measurements.

'To compare the volume of white matter WMH between people and to adjust the analysis for the fact that people's brains vary slightly in size, we divided the volume of WMH by the total volume of white matter in the brain. In that way, we could analyse the WMH load, which is the proportion of the WMH volume to the total volume of white matter,' said Dr Wartolowska.

The researchers found that a higher load of WMH was strongly associated with current systolic blood pressure, but the strongest association was for past diastolic blood pressure, particularly when under the age of 50 years. Any increase in blood pressure, even below the usual treatment threshold of 140 mmHg for systolic and below 90 mmHg for diastolic, was linked to increased WMH, especially when people were taking medication to treat high blood pressure.

For every 10-mmHg increase in systolic blood pressure above the normal range, the proportion of WMH load increased by an average (median) of 1.126-fold and by 1.106-fold for every 5-mmHg increase in diastolic blood pressure. Among the top 10% of people with the greatest WMH load, 24% of the load could be attributed to having a systolic blood pressure above 120 mmHg, and 7% could be attributed to having diastolic blood pressure above 70 mmHg, which reflects the fact that there is a greater incidence of elevated systolic rather than diastolic blood pressure in older patients.

Dr Wartolowska said: 'We made two important findings. Firstly, the study showed that diastolic blood pressure in people in their 40s and 50s is associated with more extensive brain damage years later. This means that it is not just the systolic blood pressure, the first, higher number, but the

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Experience of cardiac implantable electronic device lead removal from a South African tertiary referral centre

Philasande Mkoko, Nicholus Xolani Mdakane, Glenda Govender, Jacques Scherman, Ashley Chin

Abstract

Background: The rate of cardiac implantable electronic device (CIED) implantation in low- and middle-income countries is increasing. Patients recieving these devices are frequently older and with multiple co-morbidities, which may later lead to complications requiring CIED removal. CIED removals are associated with life-threatening complications. However, high sucesss rates are reported in high-income countries. The purpose of this study was to report on the experience of CIED removal in a resource-constrained setting.

Methods: In this retrospective study, we included consecutive adult patients admitted to Groote Schuur Hospital and the University of Cape Town Private Academic Hospital for CIED removal from 1 January 2008 to 31 December 2019.

Results: During the study period, 53 patients underwent CIED removal (26 extractions and 27 explants). The patients had a mean (standard deviation) age of 59.1 (16.0) years. A history of systemic hypertension was present in 50.9% of patients, diabetes mellitus in 30.2% and dilated cardiomyopathy in 47.2%. Complete heart block was the leading indication for CIED implantation (37.7%), and device infection was the leading indication for removal (69.2%). CIEDs were removed after a median (interquantile range) of 243 (53–831) days. There were 40 leads extracted and 35 explants. Lead extractions were perfomed in the cardiac catheterisation laboratory under general anaesthesia via a percutaneous transvenous superior approach. There was one major and one minor complication related to lead extraction.

Conclusion: CIED infections were the primary indication for CIED removal in a tertiary referral centre in South Africa. Despite being a low-volume centre, we report a high percutaneous transvenous extraction success rate with low complication rate; results which are comparable to high-volume centres.

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Cardiac implantable electronic devices (CIEDs) are a well-established lifesaving technology for the treatment of bradycardias, heart failure and ventricular arrhythmias in susceptible patients.[1-6] Currently, it is estimated that up to 1.4 million CIEDs are implanted globally every year.[7] As the population ages, the rate of CIED implantation also increases.[4,5] Approximately 70% of CIED recipients are older than 65 years of age, often with co-morbidities that may necessitate implantation of more complex CIEDs.[5,8,9] The number of CIED implantations is increasing in low- and middle-income countries.[10] For example, in South Africa there were 54 per million population new pacemaker implants in 2005, which increased to 132 new implants per million population in 2013.[10]

At present the main indications for CIED removal include CIED infection and lead or pacemaker generator malfunction.[7] Percutaneous transvenous lead extraction is now preferred over surgical lead extraction due to its high success rates and low risk of complications. However, percutaneous transvenous lead extraction is associated with a small risk of major complications, including cardiac avulsion, vascular tears and death.[11,12] In high-volume extraction centres, the reported clinical success rates of lead extraction are more than 95%, with low complication rates.[11,13-15] The purpose of this study was to report the experience (indications and outcomes) of lead removal (extraction and explant) from a tertiary South African referral centre.

Methods

We conducted a retrospective review of all patients who underwent percutaneous transvenous CIED lead removal at Groote Schuur Hospital (GSH) and the University of Cape Town Private Academic Hospital (UCTPAH) between 1 January 2008 and 31 December 2019. This study was approved by the University of Cape Town Human Research Ethics Committee (HREC number: 591/2019).

All lead extractions and explants were performed in the cardiac catheterisation laboratory. The extractions were performed under general anaesthesia, with a transoesophageal echocardiogram *in situ* to exclude large vegetations and for monitoring of potential complications. The extraction team consisted of a cardiac electrophysiologist, a cardiothoracic surgeon, a cardiac anaesthetist, a clinical cardiology fellow, a scrub nurse and auxillary catheterisation laboratory staff.

The extractions were all performed via a percutaneous transvenous superior approach. A standard infraclavicular incision was used to extract the pacemaker generator. A stepwise procedure was followed: if the lead could not be removed using a standard stylet and gentle traction, a locking stylet was used to remove the lead. If the locking stylet failed to free the lead with gentle traction, a mechanical extraction sheath (Cook Medical 9–13 French, 40.6 cm Evolution RL controlled-rotation dilator) was used. Occasionally an additional mechanical extraction sheath (Cook Medical 9–11 French, 13.6 cm Evolution Shortie mechanical dilator sheath) was required to free the proximal extent of the lead. Once the lead was successfully extracted, haemostasis of the axillary and subclavian veins was secured using a figure-of-eight suture. In all cases of device infection, an extensive pocket capsulectomy was performed, followed by wound closure with interrupted nylon sutures.

Definitions published in the 2009 and 2017 Heart Rhythm Society (HRS) expert consensus statement on cardiovascular implantable electronic device lead management and extraction and the 2018 European Heart Rhythm Association (EHRA) expert consensus statement on lead extraction were used to define patient outcomes.[7,16,17]

A lead-removal procedure is defined as removal of a pacing or ICD lead using any technique.[7,16] Lead explant is defined as lead removal using simple traction techniques (no locking stylets, telescoping sheaths or femoral extraction tools) or leads implanted for less than one-year duration.[6,7] Lead extraction is defined as the removal of at least one lead that has been implanted for more than one year, or a lead, regardless of duration of implant, requiring the assistance of specialised equipment that is not included as part of the typical implant package, and/or removal of a lead from a route other than the implant vein.[7,16]

Major complications/serious adverse events are defined as any of the outcomes related to the procedure that are life-threatening or result in death (cardiac or non-cardiac).[7,16] Minor complications are defined as any undesired event related to the procedure that requires medical intervention or minor procedural intervention and does not persistently or significantly limit the patient's function, nor does it threaten life or cause death.[7,16]

Complete procedural success is defined as a lead-extraction procedure with removal of all targeted leads and all lead material from the vascular space, with the absence of any permanently disabling complication or procedure-related death.[7,16] Clinical success is defined as lead extraction procedures with removal of all targeted leads and lead material from the vascular space or retention of a small portion of the lead (≤ 0.4 cm) that does not negatively impact on the outcome goals of the procedure.[7,16]

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Macintosh version 24.0 (IBM, USA). Normally distributed continuous variables are reported as means [standard deviations (SD)], and as medians [interquartile ranges (IQR)] when skewed. Discrete data are presented as numbers and percentages. The mortality difference between the extraction group and the explant group was assessed using the chi-squared test; the Kaplan–Meier and log rank tests were used to assess the cumulative survival difference. A p-value < 0.05 represents a statistically significant difference.

Results

A total of 53 patients underwent percutaneous transvenous CIED (lead/s and generator) removal at GSH and UCTPAH between 1 January 2008 and 31 December 2019. Twenty-six (49%) patients required CIED lead extractions and 27 (51%) had their CIED leads explanted.

The baseline characteristics of the patients and the details of their CIEDs are presented in Table 1. The mean age of the patients was 59.1 (16.0) years, 50.9% were male, 50.9% had systemic hypertension, 30.2% had diabetes mellitus and 47.2% had cardiomyopathy. The leading indication for CIED implantation was complete heart block (37.7%). The most common CIED removed was a single-chamber permanent pacemaker (35.8%). The main indication for CIED removal was device infection (69.2%) (Fig. 1A, B). The majority of infected CIEDs removed were for culture-negative endocarditis (Fig. 2) and all patients who had CIED infection had received multiple courses of antibiotics prior to referral.

A total of 75 leads was removed (40 extractions and 35 explants) (Table 2). The CIEDs were removed after a median (IQR) of 243 (53–831) days since the primary implantation. Extraction occurred after a median (IQR) of 831 (359–2546) days from the date of CIED implantation. For CIED extractions, a locking stylet was required in 92.3% and a mechanical extraction sheath was used in 73.1% of patients.

Extraction-related complete procedural success was achieved in 84.6% and clinical success was achieved in 96.2% of patients. One patient who had a lead extraction died a few hours post lead extraction (mortality rate 3.8 %). She had a successful extraction of four leads (two atrial, one right ventricle and one coronary sinus) for CIED infection. She had unexplained ventricular fibrillation and cardiac arrest the morning after the procedure. There were no other major complications.

Minor complications ocourred in one patient (3.8%). This was due to a small lead fragment (< 1 cm) that embolised in the lung without complications and could not be retrieved with

Table 1. Baseline characteristics

Variables	*Removal (extraction and explant)* (n = *53*)	*Extraction* (n = *26*)	*Explant* (n = *27*)
Age, *n* (SD), years	59.1 (16.0)	57.8 (16.3)	60.2 (15.9)
Male gender, *n* (%)	27 (50.9)	17 (65.4)	10 (37)
Systemic hypertension, *n* (%)	27 (50.9)	10 (38.5)	17 (63.0)
Diabetes mellitus, *n* (%)	16 (30.2)	7 (26.9)	9 (33.3)
Dyslipidaemia, *n* (%)	16 (30.2)	10 (38.5)	6 (22.2)
Coronary artery disease, *n* (%)	15 (28.3)	9 (34.6)	6 (22.2)
Chronic kidney disease, *n* (%)	8 (15.1)	6 (23.1)	2 (7.4)
Cardiomyopathy, *n* (%)	25 (47.2)	14 (53.8)	11 (40.7)
Atrial fibrillation, *n* (%)	11 (20.8)	6 (23.1)	5 (18.5)
Chronic obstructive airway disease, *n* (%)	4 (7.5)	2 (7.7)	2 (7.4)
Single-chamber permanent pacemaker	19 (35.8)	5 (19.2)	14 (51.9)
Dual-chamber permanent pacemaker	9 (17.0)	7 (26.9)	2 (7.4)
CRT-P	8 (15.1)	5 (19.2)	3 (11.1)
CRT-D	4 (7.5)	3 (11.5)	1 (3.7)
Dual-chamber ICD	2 (3.8)	1 (3.8)	1 (3.7)
Single-chamber ICD	11 (20.8)	5 (19.2)	6 (22.2)

CRT-P, cardiac resynchronisation therapy pacemaker; CRT-D, cardiac resynchronisation therapy defibrillator; ICD, implantable cardioverter defibrillator.

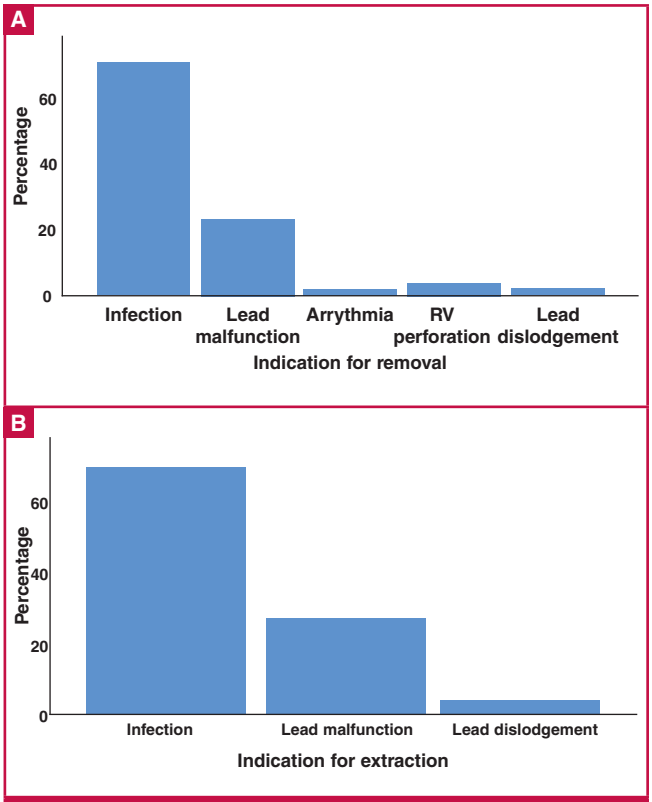

Fig. 1. A. Bar chart depicting indications for CIED removal. B. Bar chart depicting indications for CIED extraction.

a snare. The overall one-year mortality rate after lead removal was 19.1% (19.2% in the extraction group vs 14.8% in the explant group) (p = 0.764). There was no difference in survival rate between patients who had their CIEDs extracted versus explanted (Fig. 3).

Discussion

The key findings of this study are: (1) CIED-related infection was the leading indication for CIED removal (extraction or and explant) at a tertiary referral centre in South Africa; (2) percutaneous tranvenous lead extraction using a locking stylet with or without mechanical extraction sheaths had a high

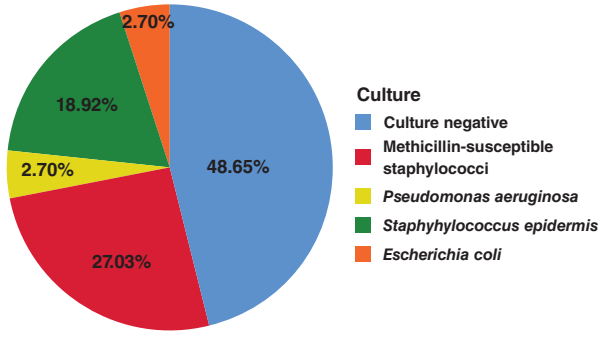

Fig. 2. Pie chart depicting the frequency of causative micro-organisms for CIED infection leading to CIED removal.

Table 2. Lead-removal procedure details and outcomes

Variables	*Removal (extraction and explant)* (n = *53*)	*Extraction* (n = *26*)	*Explant* (n = *27*)
Days since primary implantation, median (IQR)	243 (53–831)	831 (359.5–2546)	57 (36–104)
Total number of removed leads, mean (SD)	75	40	35
Number of removed leads per patient	1.42 (0.69)	1.54 (0.76)	1.3 (0.61)
Locking stylet, *n* (%)	24 (45.3)	24 (92.3)	0
Extraction sheath, *n* (%)	19 (35.8)	19 (73.1)	0
Straight stylet, *n* (%)	27 (50.9)	26 (100)	25 (92.6)
Procedural success, *n* (%)	49 (92.5)	22 (84.6)	27 (100)
Clinical success, *n* (%)	53 (100)	25 (96.2)	27 (100)
Major complications, *n* (%)*	1 (1.9)	1 (3.8)	0
Minor complications, *n* (%)#	1 (1.9)	1 (3.8)	0
In-hospital mortality, *n* (%)	1 (1.9)	1 (3.8)	0

*There was one death, which was recorded as a major complication.
One minor complication was a lead-fragment embolism to the lung without complications.

procedural and clinical success rate; (3) percutaneous lead removal was associated with a low risk of major and minor complications and low mortality rate, which is comparable with high-volume centres in Europe and North America; and (4) the overall one-year mortality rate remained high, similar to previous reports.

The implantation rates of CIEDs are increasing globally and in low- to middle-income countries such as South Africa.[9,10,18] The rates of CIED removal, particularly for CIED infection, have also been on the rise.[8,12] The findings of this study are consistent with the current international standard of extraction procedural success rate of more than 80%, clinical success rate of more than 95% and major complication rate of less than 5%.[11,13]

Although patients who underwent lead extraction in this study had a low in-hospital mortality rate of 3.8%, we found that the one-year mortality rate was 19.2%. These findings are consistent with a study by Maytin *et al.*, who reported a 30-day mortality rate of 2.1%, one-year mortality rate of 8.4% and a 10-year mortality rate of 46.8% in patients who had their leads extracted.[19] Therefore, although the in-hospital mortality rate and minor and major complication rates related to lead

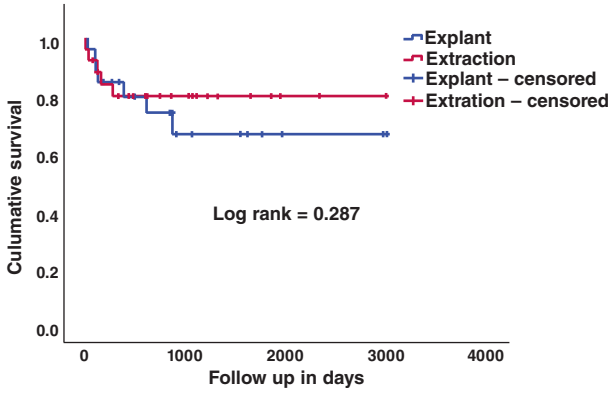

Fig. 3. Kaplan–Meier curves depicting the cumulative survival difference between the extraction and explant group.

extraction were low, the long-term outcomes were poor, a finding that particularly reflects the high-risk population group that frequently has to undergo CIED implantation and extraction.[9]

In our study, CIED infection was the main indication for lead extraction (69.2% of lead extractions, 69.8% of CIED removals). The incidence of infections as the primary indication for lead extraction was almost 20% higher than that from high-income countries. For example, in the European Lead Extraction ConTRolled Registry (ELECTRa), out of 3 555 patients who underwent lead extractions at 73 centres from 19 European countries, infections were the indication for lead extraction in 52.9% of cases.[11] Additionally, in a multicentre study from 13 sites in the USA and Canada that included 1 449 consecutive patients who underwent laser-assisted lead extraction, infections were the indication for extraction in 56%.[13] This probably reflects our current practice of rarely removing redundant or non-functional leads. As our experience with lead extraction grows, removal of non-infected leads is likely to contribute more to the indications for lead extraction.

In this study we present data from a tertiary referral centre serving both public and private patients in the Western Cape province of South Africa. The very low number of patients (26 patients referred for lead extraction procedures over 11 years) referred for extraction raises two points of potential concern:

- The finding of a relatively low number of patients who underwent lead extraction suggests a lack of referral as Groote Schuur Hospital was the only public hospital performing lead extractions over this period in the Western Cape province. This is concerning as patients with CIED are probably inappropriately managed with antibiotics and not referred for lead extraction, which is the only treatment for CIED infection. Non-removal of an infected CIED is associated with a seven-fold increase in 30-day mortality and a three-fold increase in one-year mortality.[20] Furthermore, early removal of infected CIEDs has been associated with reduced in-hospital mortality.[21] In a study by Viganego and colleagues, patients who had their infected CIEDs extracted within three days versus later than three days of hospitalisation had a lower in-hospital mortality rate irrespective of antibiotic use ($p = 0.001$).[21] The rates of CIED implantation in South Africa are increasing,[10,18,22] therefore we expect the rates of CIED infections and extractions or explant to increase in parallel.
- Maintaining competency and procedural skills can be difficult in low-volume centres. Lead-extraction procedural outcomes are reported to be better in high-volume centres.[16,23] In the ELECTRa study, rates of extraction-related major complications and death were significantly lower in high-volume centres (defined as centres performing more than 30 extraction procedures per year) when compared to low-volume centres (less than 30 extraction procedures per year).[11] Furthermore, for maintenance and transfer of skills, knowledge and competence in lead extraction, guidance documents recommend a minimum of 20 extraction procedures on an annual basis.[7] Lead extractions should ideally be conducted in a few highly specialised public and private referral centres in South Africa.

The major limitations of this study are its retrospective nature and small sample size. Data on baseline cardiac function as measured by echocardiography were not available and the duration of symptoms prior to referral for lead extraction and explant was also not available.

Conclusion

CIED infections were the primary indication for CIED removal in a tertiary referral centre in South Africa. Despite being a low-volume centre, we report a high percutaneous transvenous extraction success rate with low complication rate, results which are comparable to high-volume centres. The low number of patients referred for CIED removal probably reflects poor management of device infection at the primary healthcare level.

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diastolic blood pressure, the second, lower number, that is important to prevent brain tissue damage. Many people may think of hypertension and stroke as diseases of older people, but our results suggest that if we would like to keep a healthy brain well into our 60s and 70s, we may have to make sure our blood pressure, including the diastolic blood pressure, stays within a healthy range when we are in our 40s and 50s.

'The second important finding is that any increase in blood pressure beyond the normal range is associated with a higher amount of WMH. This suggests that even slightly elevated blood pressure before it meets the criteria for treating hypertension has a damaging effect on brain tissue.

'Our results suggest that to ensure the best prevention of WMH in later life, control of diastolic blood pressure, in particular, may be required in early midlife, even for diastolic blood pressure below 90 mmHg, while control of systolic blood pressure may be more important in late life. The long time interval between the effects of blood pressure in midlife and the harms in late life emphasises how important it is to control blood pressure long-term, and that research has to adapt to consider the very long-term effects of often asymptomatic problems in midlife.'

Potential mechanisms for the development of WMH include damage to the delicate blood vessels in the brain through sustained elevated pressures over time that directly cause damage to the blood vessels; this leads to the lining of the vessels becoming leaky and results in WMH. Alternatively, diastolic pressure might cause large blood vessels to become stiffer with time, which increases pulsations of blood pressure to the brain. This causes high blood pressure with each heart beat, rapid changes in blood pressure, and blood flow that is too low between heart beats, resulting in damage to white matter.

As MRI scans were only available at one time point, the researchers could not quantify the progression of WMH directly. Other limitations include that further analysis is needed to identify differences in different regions of white matter, and that although the researchers showed associations with smoking and diabetes, the potential complex interaction between risk factors, which also include high cholesterol levels, obesity and kidney problems, require further investigation.

Source: Medical Brief 2020

Knowledge, attitude and practice towards therapeutic lifestyle changes in the management of hypertension in Khartoum State

Ahmed Ali Abdalla

Abstract

Background: Hypertension has long been recognised as a major risk factor for coronary artery disease, stroke and kidney disease. Despite a multitude of new pharmacological agents, in the Sudan, a significant proportion of hypertensive patients' blood pressure remains uncontrolled. An important, often underutilised treatment approach is therapeutic lifestyle changes (TLC). This study aimed to assess the knowledge, attitude and practice of patients with regard to TLC in the management of hypertension in a Khartoum locality in 2016.

Methods: The study was cross sectional and descriptive. Data were collected via structured interviews using a questionnaire. Full coverage of patients attending Ahmed Gasim and Al-Shaab hospitals for follow up during August and September 2016 was carried out. Descriptive and inferential statistics were utilised for data analysis.

Results: We identified 112 patients for participation in this study. There was a slight preponderance of females (54.5%) and older age, with 58% in the 55- to 70-year age group. When assessed for knowledge on lifestyle and habits that affect blood pressure, respondents were most familiar with the fact that salt consumption affects blood pressure, 93.8% answering correctly. After knowledge scores were calculated, only 31.3% of participants had above-average knowledge on blood pressure and TLC. The lifestyle change the respondents were least adherent to was regular exercise, with 59.8% of participants struggling with this. Participants' most-cited obstacle was lack of motivation, the same answer being most frequent for each lifestyle change.

Conclusion: This study demonstrated that although the hypertensive patients were generally aware of the importance of TLC in its management, they struggled to implement this. The researcher believes that novel approaches are needed to help motivate patients who are diagnosed with hypertension in a third-world country such as Sudan, and apply their knowledge regarding TLC.

Keywords: hypertension, lifestyle changes, Sudan, exercise, blood pressure

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Hypertension is generally defined as sustained blood pressure at rest above 140/90 mmHg or the need for antihypertensive medication.[1] It has long been recognised as a major risk factor for coronary artery disease, stroke and kidney disease. Responsible for up to 50% of deaths worldwide, the prevalence of hypertension has a large impact on the health economies of both developed and developing countries.[2] Available data suggest that Sudan has one of the highest incidences of hypertension in Africa, with prevalence rates of 20% reported in the general population.[3]

Despite a multitude of new pharmacological agents, a significant proportion of hypertensive patients' blood pressure remains uncontrolled in the Sudan.[4] An important, often underutilised treatment approach is therapeutic lifestyle changes (TLC). This involves the modification of certain aspects of a patient's lifestyle, mainly restricting sodium-rich foods, weight loss, increased physical activity, smoking cessation and moderation of alcohol intake.[5]

Hypertension is a common, treatable disease, with uncontrolled hypertension having serious multisystem sequelae.[6] Considering this and the global and local trends of increasing prevalence of hypertension, ensuring compliance with antihypertensive measures should be a high priority. In addition, given the economic constraints due to the high cost and side-effect profile of antihypertensive drugs, adoption of a healthy lifestyle remains the cornerstone of hypertension management.

Understanding, implementation of and compliance with TLC are challenging aspects in the management of hypertension due to varying socio-economic backgrounds, education levels and time afforded for consultations. This study examined these factors to elucidate their relative association with compliance as well as patients' overall understanding of TLC. Understanding these will allow physicians to emphasise aspects of TLC that are poorly understood by patients, as well as highlighting potential barriers to TLC implementation, in order to advise public health policy.

Methods

This was a cross-sectional, descriptive, analytical study. Hypertension clinics in Ahmed Gasim Hospital and El-Shaab Teaching Hospital were utilised as the study area. The Ahmed Gasim Hospital is a state hospital located in Khartoum North. It has three specialities, paediatrics, renal and cardiology, but no accident and emergency unit. It accepts referrals from other hospitals. It currently has three cardiology wards with a total of 30 beds, and two coronary care units (CCU) with a total of 20 beds. Cardiology referral clinics and echocardiography are carried out every day of the week.

The El-Shaab Teaching Hospital is a government hospital

specialising in cardiology. It is located in the centre of Khartoum. It has three main specialities, cardiology, renal and neurology. There are two cardiology wards for male and female patients with a total of 48 beds, a CCU with six beds and two intermediate-care units attached to the CCU, accommodating 12 beds. Cardiology referral clinics are available every day of the week.

Patients between the ages of 25 and 70 years attending follow up at the cardiology referral clinics in the Ahmed Gasim and El-Shaab hospitals who were previously diagnosed as hypertensive made up the study population. Patients with co-morbidities and those who had had a previous cardiovascular event were included. Patients excluded were those who did not give consent to participate or were admitted to hospital.

There was no sample frame since the sampling was non-probability due to the lack of a registry for hypertension patients. The sample selection method was full coverage of hypertensive patients attending the cardiology referral clinic of El-Shaab Teaching Hospital on Sundays, Tuesdays and Thursdays during the period from 14 August to 1 September 2016 and of all hypertensive patients attending the cardiology referral clinic of Ahmed Gasim Hospital on Sundays, Tuesdays and Thursdays during the period from 4 to 22 September 2016.

Ethical approval for this study was obtained from the ethics review board at the University of Khartoum. Informed verbal consent for participation was obtained from each subject in the study. The author declares no conflict of interest. Information obtained from subjects was held confidentially and used strictly for academic purposes only.

Statistical analysis

A structured interview using an anonymous questionnaire was used for collection of data. Descriptive and inferential statistics were used for data analysis. Software used was SPSS version 21.0.

Independent variables were socio-demographic data of patients, occurrence of previous cardiovascular events, duration of consultations and knowledge level. Dependent variables were different levels of TLC implementation and knowledge level.

Results

We identified 112 hypertensive patients for inclusion in the study, with 100% consenting and completing the study. Of the participants, there was a slight preponderance of females (54.5%) and older age, with 58% in the 55- to 70-year age group, the majority being married (88.4%). Participants were of varying education levels, with primary school education the most frequently attained level of education (27.7%). A high proportion of participants were unemployed (43.8%) and most had not experienced a previous cardiovascular event (67.9%). Table 1 shows the demographics of the study population.

Table 1. Socio-demographic characteristics of the participants

Characteristics	*Number*	*Percentage*
Gender		
Male	51	45.5
Female	51	45.5
Age, years		
25–39	9	8
40–54	38	33.9
55–70	65	58
Marital status		
Single	6	5.4
Married	99	88.4
Widowed	4	3.6
Divorced	3	2.7
Education level		
Primary school	31	27.7
Secondary school	24	21.4
Higher education	15	13.4
Illiterate	23	20.5
Khalwa	19	17
Occupation		
Unemployed	49	43.8
Labourer	3	2.7
Service job	18	16.1
Self employed	24	21.4
Retired	18	16.1
Previous cardiovascular event		
Yes	36	32.1
No	76	67.9

Knowledge

To determine the participants' level of knowledge on blood pressure and therapeutic lifestyle changes, respondents were asked seven questions, five pertaining to lifestyle changes, one question on the ideal blood pressure and one on the general management of hypertension. Respondents were then given a score out of seven depending on their answers, and categorised as 'below average', 'average' or 'above average' in knowledge level.

Regarding ideal blood pressure knowledge, 53.6% of respondents did not know what their ideal blood pressure should be (Fig. 1). When asked what the optimal mode of hypertension management was, most patients (73.2%) answered correctly, stating both antihypertensives and lifestyle changes.

When assessed for knowledge on lifestyle and habits that affect blood pressure, respondents were most familiar with the fact that salt consumption affects blood pressure, 93.8% answering correctly. Alcohol's effect on blood pressure was the least

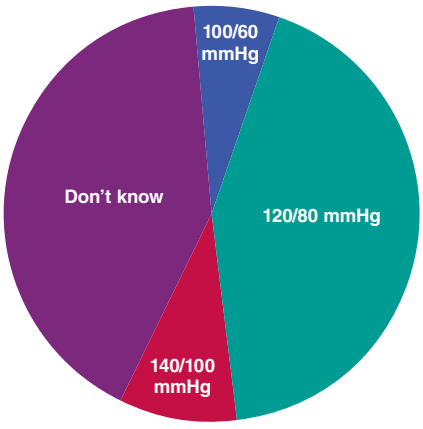

Fig. 1. Knowledge question on ideal blood pressure.

Table 2. Participants' response to knowledge questions

Question	*Answer*	*Number*	*Percentage*
Salt consumption	Yes	105	93.8
	No	7	6.3
Being overweight	Yes	74	66.1
	No	38	33.9
Exercise	Yes	80	71.4
	No	32	28.6
Smoking	Yes	64	57.1
	No	48	42.9
Alcohol consumption	Yes	52	46.4
	No	60	53.6

Table 3. Which lifestyle changes participants received counselling on

Lifestyle change	*Answer*	*Number*	*Percentage*
Salt consumption	Yes	81	72.3
	No	31	27.7
Being overweight	Yes	48	42.9
	No	64	57.1
Exercise	Yes	53	47.3
	No	59	52.7
Smoking	Yes	45	40.2
	No	67	59.8
Alcohol consumption	Yes	24	21.4
	No	88	78.6

familiar to participants, 53.6% answering that alcohol doesn't affect blood pressure. Table 2 shows participants' response to knowledge questions.

Knowledge scores were calculated from the seven questions on knowledge and categorised into below-average (zero to three correct answers), average (four to five correct answers) and above-average (six to seven correct answers) knowledge levels. Only 31.3% of participants had above-average knowledge on blood pressure and TLC, most respondents answering more than two questions incorrectly. Fig. 2 gives overall knowledge scores.

Regarding participants' perception of consultation with doctors, they were asked specifically about each lifestyle change they were counselled upon and the perceived duration they thought they were counselled for on lifestyle changes by a medical professional (Table 3). Seventeen respondents said they were never counselled on lifestyle changes, while of those who were counselled, the most frequent perceived duration of consultation was reported to be 'less than five minutes' (33.9%) (Fig. 3).

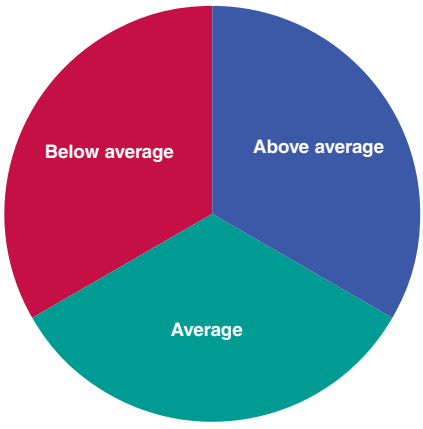

Fig. 2. Overall knowledge score.

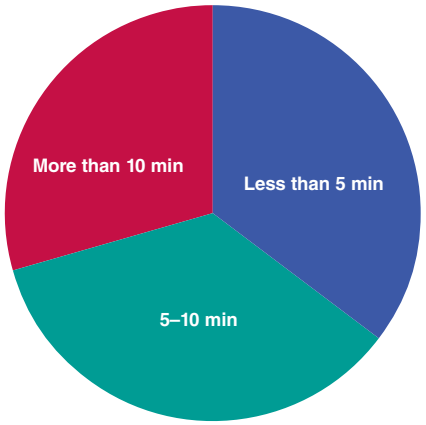

Fig. 3. Participants' perceived consultation time.

Attitude and practice

Participants were asked questions on their adherence to TLC, and the barriers they perceived were preventing them from implementing such changes if they were not adherent. The respondents were then categorised into different groups of level of implementation based on their responses.

Regarding the five questions asked on implementation of therapeutic lifestyle changes, refraining from alcohol consumption was the lifestyle change most frequently adhered to, with 100% of respondents reporting no alcohol consumption, followed by smoking cessation with 96.4% saying they did not smoke. The lifestyle change respondents were least adherent to was regular exercise, with 59.8% of participants admitting to not exercising on most days (Table 4).

After categorising participants' implementation level into 'poor', 'good' or 'full implementation' according to the number of changes adhered to, only 29.5% of respondents were found to be fully implementing TLC, with 25% classified as poor implementation (zero to two changes) and 45.5% classified as good implementation (three or four changes) (Fig 4).

Concerning patients' perceived barriers to implementing TLC, their most frequent response to why they were not implementing a certain change was that they did not feel it mattered enough, the same answer being most frequent for each lifestyle change (Table 5, Figs 5–7).

Table 4. Participants' implementation of TLC

TLC	*Answer*	*Number*	*Percentage*
Minimising salt intake	Yes	95	84.8
	No	17	15.2
Weight-loss plan	Yes	87	77.7
	No	25	22.3
Regular exercise	Yes	45	40.2
	No	67	59.8
Smoking	Yes	4	3.6
	No	108	96.4
Alcohol consumption	Yes	0	0
	No	100	100

Fig. 4. Overall TLC implementation level.

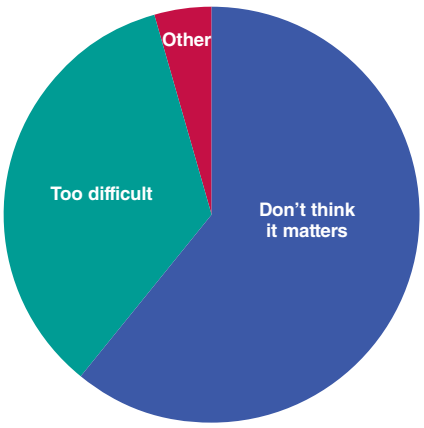

Fig. 6. Barriers to weight loss.

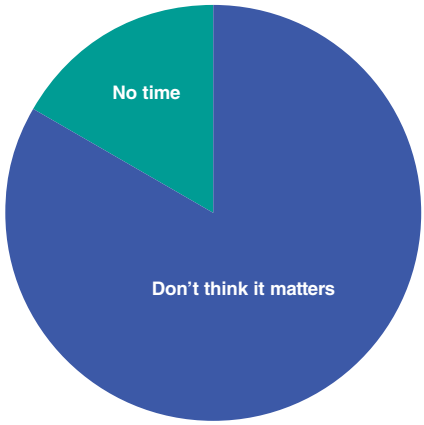

Fig. 5. Perceived barriers to minimising salt intake.

Fig. 7. Barriers to exercise.

Factors affecting knowledge level and TLC implementation

Regarding participants' level of knowledge on hypertension, males were found to be more knowledgeable than females (p = 0.021), and those with a higher education level also had significantly better knowledge scores than other participants of lower educational status (p = 0.001). Also, patients who reported their consultation time to be more than 10 minutes had greater knowledge levels than those who reported their consultation to have taken less time (Fig. 8). No associations were found between age, marital status, occupation, previous cardiovascular events and knowledge level.

Concerning overall TLC implementation level, socio-demographic factors, previous cardiovascular events, consultation times or even knowledge level did not prove to be associated factors, with no statistically significant differences being recorded between the different groups.

Table 5. Patients' perceived barriers to TLC implementation

TLC	*Perceived barrier*	*Number*	*Percentage*
Minimising salt intake	Don't think it matters	14	82.4
	No time	3	17.6
Weight loss	Don't think it matters	16	64
	Too difficult	8	32
	Other	1	4
Regular exercise	Don't think it matters	27	41.5
	No time	19	29.2
	No facilities	6	9.2
	Too difficult	13	20

Discussion

Hypertension is a public health issue of utmost importance, as it is a major reversible risk factor for heart attack, renal failure and stroke. Being a reversible risk factor, the priority in medical research endeavours should be finding new and more effective measures to control hypertension and prevent related complications.

Lifestyle modifications are a suitable primary healthcare measure in the control of hypertension and prevention of its sequelae,[2] as well as a suitable adjunct to medical therapy. The issue with the implementation of TLC is ensuring patients have both adequate knowledge and motivation to adopt these lifestyles. This cross-sectional, descriptive study conducted in Ahmed Gasim Hospital and Al-Shaab Teaching Hospital in Khartoum state aimed to assess patients' level of knowledge,

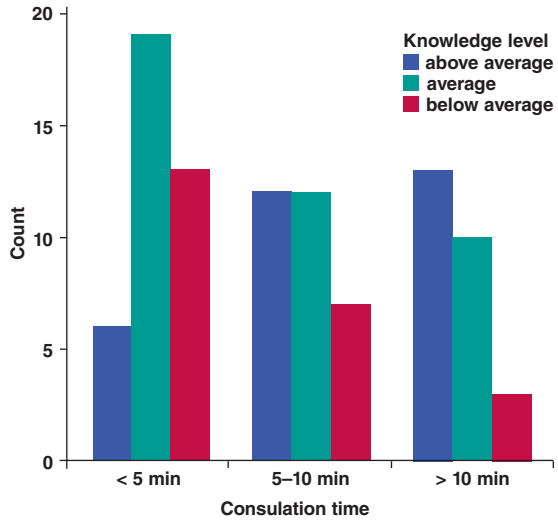

Fig. 8. Association between consultation time and knowledge level.

attitudes and practice towards hypertension and TLC, and the barriers patients perceived to implementing these changes.

The lifestyle changes participants were questioned on were salt reduction, weight loss, regular exercise, smoking cessation and moderation of alcohol intake. Overall, the results of the study showed that hypertensive subjects possessed a good general knowledge regarding TLC and were implementing these modifications to a certain extent.

The lifestyle change found to be most implemented was abstaining from alcohol; none of the respondents reported any alcohol intake, which is most probably due to the cultural and religious beliefs of the area. This was followed by smoking cessation (96.4%), where cultural background probably played a big role. Most respondents were never smokers in their early years. A high percentage of respondents (84.8%) were actively reducing their salt intake since diagnosis with hypertension, which can only be explained by the fact that patients were actively adopting healthier lifestyles. Exercise was the lifestyle modification least adhered to by hypertensive patients, where 60% admitted to not regularly exercising.

The reason reported most often by participants for not implementing each of the lifestyle modifications was 'not thinking it matters' or 'laziness', which could be interpreted as patients not being adequately motivated by health givers to adopt healthier lifestyles and not being educated properly on their importance as adjuncts to pharmacological therapy.

Participants were most knowledgeable on the importance of reducing salt intake in managing hypertension (93.8%), which was reflected in their implementation, as it was the lifestyle change most applied that could not be explained by the cultural background of the study area. More than half of the respondents answered incorrectly to whether alcohol consumption affected blood pressure, suggesting the idea that abstaining from alcohol consumption was more of a cultural issue.

A high percentage of participants (71.4%) answered correctly that regular exercise can help lower blood pressure but it was not reflected in their implementation, exercise being the modification least applied. This implies that other than just being given the knowledge of such lifestyle changes, patients need to be motivated adequately by doctors. Further affirming this view is the fact that no association was found between patients' level of knowledge and their degree of implementation of TLC.

Although duration of consultation was found to be associated with participants' level of knowledge ($p = 0.039$), it did not affect their degree of implementation, which may imply that different methods and skills of motivating patients to adhere to lifestyle changes may be needed and not simply spending more time on each consultation.

Perhaps worryingly, no association was found between previous cardiovascular events and patients' knowledge level, as a previous event would usually stipulate more intense counselling of lifestyle changes. This requires further study, assessing clinicians' practice in this regard.

Upon reviewing the literature in comparison with the results of this study, the general level of knowledge of participants was found to be comparable to most studies on this topic, one such study conducted on attitudes and practice in Cape Coast in Ghana,[7] another one being conducted in South Africa.[8] Salt restriction was the most well-known lifestyle change in both, with both populations having good knowledge on hypertension management.

Results from a Canadian national survey in terms of implementation also partially agreed with the results of this study, with the population having a generally high implementation level.[9] Salt restriction was the lifestyle change most frequently adhered to. It was also comparable with this study with regard to perceived barriers to implementation, as 'not wanting to do so' and 'not feeling it matters' were both frequently reported barriers, similar to that reported in this study. This further confirms the idea that patients were not being adequately motivated by health givers.

Of the studies conducted on awareness of patients of hypertension and its associated risk factors, one such study carried out in Khartoum found uncontrolled hypertension to be associated with a lack of awareness towards lifestyle changes and adherence to medication. As far as the researcher's knowledge is concerned, no other study has been undertaken assessing the knowledge, attitude and practice of hypertensive patients towards TLC specifically.

One of the aspects of this study was to examine whether patients were receiving counselling on lifestyle changes from their doctors and how long they perceived the consultation took. About 85% of participants reported receiving advice on lifestyle change. This proportion is surprisingly high when compared to results reported by a study from Australia,[10] where less than 30% of patients recalled ever receiving advice on lifestyle change. This discrepancy might be explained by the difference in study population as our study recruited from speciality cardiology clinics as opposed to primary practice. The same can be assumed for the generally high level of knowledge and degree of implementation demonstrated by participants in this study.

Limitations

The fact that subjects were selected from referral clinics could be considered a limitation of this study. Other limitations are the small sample size of 112 participants, and that the hospitals selected were from Khartoum and Bahri localities only. Hence

generalisations cannot be drawn to all of Khartoum state, only to populations with characteristics similar to those of the sample.

Since no standardised tool for assessing knowledge and practice of patients towards lifestyle changes exists, the researcher designed the questionnaire based on the literature and what would be applicable to the study population. Hence the comparison of results between different studies is difficult. Another limitation was that implementation of lifestyle changes was assessed by yes/no questions and no varying degrees of implementation were reported, which may have made the results less accurate.

Conclusion

This study demonstrated that hypertensive patients were generally knowledgeable about hypertension and the importance of TLC in its management, particularly the importance of minimising salt intake. Patients implemented regular exercise least often and gave 'don't think it matters' or 'laziness' as their main perceived barrier. Participants gave this reason despite ample knowledge of lifestyle changes and being advised by doctors on these changes. This was deduced since no association was found between patients' level of knowledge or duration of consultation and their degree of implementation of lifestyle change. The researcher believes that novel approaches are needed to help motivate patients diagnosed with hypertension apply their knowledge regarding TLC.

The author recommends more comprehensive research on this topic to accurately ascertain patients' perception of TLC as adjuncts to pharmacological therapy. Once patients' perceived barriers are better understood, novel and more effective approaches to consultation may then be developed and applied.

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Inter-arm difference in blood pressure robustly linked to greater early death risk

Robust evidence from a large meta-analysis published in *Hypertension* confirms that a difference in blood pressure readings between arms is linked to greater risk of heart attack, stroke and death. The study provides a new upper limit of 'normal' for an inter-arm difference in blood pressure, which is significantly lower than the current guidance.

Led by the University of Exeter, the global INTERPRESS-IPD collaboration conducted a meta-analysis of all the available research, then merged data from 24 global studies to create a database of nearly 54 000 people. The data spanned adults from Europe, the USA, Africa and Asia for whom blood pressure readings for both arms were available.

Funded by the National Institute for Health Research (NIHR), the study is the first to conclude that the greater the inter-arm blood pressure difference, the greater the patient's additional health risk.

Currently, international blood pressure guidelines advise health professionals to measure blood pressure in both arms when assessing cardiovascular risk, yet this is widely ignored. This study provides a new upper limit of 'normal' for an inter-arm difference in blood pressure, which is significantly lower than the current guidance. The research could lead to a change in international hypertension guidelines, meaning more at-risk patients could be identified and receive potentially life-saving treatment.

In a methodology that put patients at its heart, working with a patient advisory group at every step of the research, the team analysed data on inter-arm blood pressure difference, and tracked the number of deaths, heart attacks and strokes that occurred in the cohort over 10 years.

Lead author and GP Dr Chris Clark, of the University of Exeter Medical School, said: 'Checking one arm then the other with a routinely used blood pressure monitor is cheap and can be carried out in any healthcare setting, without the need for additional or expensive equipment. While international guidelines currently recommend that this is done, it only happens around half of the time at best, usually due to time constraints. Our research shows that the little extra time it takes to measure both arms could ultimately save lives.'

continued on page 223 …

The discrepancy of aromatase expression in epicardial adipose tissue between CHD and non-CHD patients

Yifan Li, Weiwei Cheng, Bin Zhao, Dongliang Ma, Xing Wei, Shunye Zhang

Abstract

Objectives: Epicardial adipose tissue (EAT) aromatase converts androstenedione and other adrenal androgens into oestrogens. The locally produced oestradiol (E_2) may have cardiovascular protective effects. Little is known about the relationship between EAT aromatase level and coronary heart disease (CHD). Here, we compared EAT aromatase levels in CHD versus non-CHD patients and assessed the relationship between EAT aromatase levels and lesion degree in the coronary arteries.

Methods: EAT and blood specimens were obtained from patients undergoing thoracotomy prior to cardiopulmonary bypass. Serum E_2 levels were obtained from our hospital laboratory. EAT aromatase expression was determined by RT-qPCR and ELISA assays. All patients underwent coronary angiography and the level of coronary lesions was evaluated with the SYNTAX score.

Results: Compared with non-CHD patients, CHD patients had lower EAT aromatase mRNA and protein levels. In the CHD patients, EAT aromatase and oestrogen levels negatively correlated with the severity of coronary artery disease.

Conclusion: Our data revealed that reduced EAT aromatase levels correlated with coronary atherosclerotic lesions. Reduced EAT aromatase protein levels may aggravate the severity of atherosclerosis. Future studies should investigate the mechanisms regulating aromatase expression in epicardial fat.

Keywords: coronary heart disease, epicardial adipose tissue, aromatase, oestrogen

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Due to the close association between obesity and cardiovascular diseases such as coronary heart disease (CHD), heart failure, hypertension, stroke, atrial fibrillation and sudden cardiac death, the roles of adipose tissue have been widely studied. In the past 20 years, adipose tissue, which is regarded as the largest endocrine organ, has been shown to have complex secretory functions with local and systemic effects.[1] As a consequence of maladaptive adipose tissue expansion, adipose tissue cells undergo phenotypic modifications that alter their secretory output.[2]

Adipose tissue can transform steroid precursors into steroid hormones to influence fat distribution and lipid metabolism.[3] This function of adipose tissue depends on aromatase, an enzyme encoded by the cytochrome P450 family 19 subfamily A member 1 (CYP19A1), which catalyses the production of oestrone and oestradiol (oestrogens) from androstenedione and testosterone (androgens), respectively.[4] Even with low levels of aromatase, the abundance of adipose tissue makes it a major source of oestrogen in postmenopausal women and aging men.[5] The oestrogens generated in this way bind to specific receptors to exert cardiovascular protection.[6]

Both epicardial and visceral adipose tissue (EAT and VAT) derive from the splanchnopleuritic mesoderm.[7] EAT is wrapped by the visceral pericardium and directly adheres to the myocardial surface and coronary arteries.[7] In physiological settings, EAT accounts for about 20% of the heart's weight and is mainly distributed along the coronary artery in the atrioventricular sulcus, interventricular sulcus, right ventricular free wall and left ventricular apex, with small amounts around the left and right atria and auricle. There is no fascial structure between EAT and the adjacent myocardial and vascular walls.[8]

EAT releases factors such as adiponectin, interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α and nitric oxide, which directly infiltrate into the myocardium (paracrine) or go through the coronary vasa vasorum (vasocrine) to influence the coronary arteries.[9-11] Currently there is no evidence confirming the relationship between aromatase levels in EAT and CHD. Here, we examined the relationship between EAT aromatase levels and CHD.

Methods

The case group (n = 30) (CHD group) comprised male patients, aged 50 years and older, who underwent coronary artery bypass grafting due to coronary atherosclerotic heart disease, with at least one coronary artery stenosis > 90% as revealed by coronary angiography. The control group (n = 30) comprised non-CHD patients, aged 50 years and older, undergoing thoracotomy due to other cardiac implications, with no significant stenosis on coronary angiography. Patients with severe hepatorenal dysfunction or under treatment with hormones, immunosuppressants, chemotherapy or other special drugs were excluded from the study.

After coronary angiography in our hospital, three researchers with senior attending physicians examined the angiography images and entered the values into the SYNTAX score calculator.

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The patients' data were obtained and the average for each person was calculated.

Ethical approval for the study was granted by the ethics committee of ShanXi Cardiovascular Hospital. All participants gave written informed consent and the study adhered to the Declaration of Helsinki.

Fasting venous blood samples were collected in the ward between 06:00 and 07:00 on the day after hospitalisation. Blood samples were put into the centrifuge tube without anticoagulant and centrifuged at 3 000 rpm for 15 minutes. The serum was separated and the serum oestradiol level was determined with chemiluminescence on a Beckman Coulter unicell DXL 800 immunoassay system.

During thoracotomy, five to 10 g EAT was taken from the initial segment of the right atrioventricular sulcus, close to the right coronary artery, before cardiopulmonary bypass (CPB). The samples were stored in liquid nitrogen for future analysis.

Total RNA was extracted using an RNA extraction kit (Qiagen, 205111) following the manufacturer's instructions. RT-qPCR analysis was done using the SYBR GreenER qPCR kit (Takara, RR820A) following the manufacturer's instructions. Relative gene expression was determined using the $2^{-\Delta\Delta}$Ct method. The results for each gene came from 30 independent repeated measurements (n = 30/group). Primer sequences are shown in Table 1.

To determine the presence of aromatase in EAT and compare its levels in CHD and non-CHD patients, samples were analysed using a human CYP19A1 ELISA kit (Cusabio Biotech, Life Sciences Advanced Technologies). The analysis was done in three independent replicates (n = 30/group).

Statistical analysis

Measurements are presented as mean ± SD and patient proportions as percentages. The Spearman correlation test was used for correlation analysis. The t-test was used for intergroup comparison of measured data and the chi-squared test was used for intergroup comparison of counted data. A p-value ≤ 0.05 indicated statistical significance. Data were analysed on SPSS version 26.

Results

A total of 60 patients were included in this study, with a median age of 59.17 ± 11.66 years in the CHD group and 57 years (52–66) in the control group. Hypertension was more prevalent in the CHD group than in the control group. Low-density lipoprotein cholesterol level and left ventricular ejection fraction were lower in the CHD group relative to the control group ($p \leq 0.05$). Other indicators did not vary significantly between the two groups (Table 2).

Table 1. The primers of related genes for aromatase RT-qPCR

Name	*Sequences (5′→3′)*
Aromatase forward	TGGAAATGCTGAACCCGATAC
Aromatase reverse	AATTCCCATGCAGTAGCCAGG
Internal reference GAPDH forward	CCACCCATGGCAAATTCCAATGGCA
Internal reference GAPDH reverse	TCTAGACGGCAGGTCAGGTCCACC

PCR, polymerase chain reaction; GAPDH, glyceraldehyde 3-phosphate dehydrogenase

Table 2. Basic parameters of the patients

Parameters	*Non-CHD group* (n = *30*)	*CHD group* (n = *30*)	χ^2 / t	p-*value*
Hypertension, *n* (%)	11 (34.4)	21 (65.6)	6.696	0.010
Hyperlipidaemia, *n* (%)	16 (47.1)	18 (52.9)	0.271	0.602
Diabetes, *n* (%)	5 (35.7)	9 (64.3)	1.491	0.222
Smoking, *n* (%)	18 (58.1)	13 (41.9)	1.669	0.196
Age, years	59.03 ± 9.90	59.30 ± 13.36	0.088	0.930
BMI, kg/m^2	26.39 ± 2.62	27.19 ± 2.71	1.163	0.250
SBP, mmHg	126.80 ± 18.09	130.43 ± 18.48	0.770	0.445
LDL-C, mmol/l	3.11 ± 0.85	2.67 ± 0.66	2.202	0.032
HDL-C, mmol/l	1.15 ± 0.31	1.16 ± 0.30	0.042	0.967
Scr, µmol/l	75.22 ± 13.48	78.78 ± 13.97	1.004	0.319
LVEF, %	64.77 ± 5.81	44.10 ± 9.22	10.384	< 0.001
LVEDD, mm	46.47 ± 6.44	47.87 ± 11.92	0.566	0.574

Values are presented as mean ± SD or number (%).
BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Scr, serum creatinine; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

To exclude the effects of serum oestrogen differences on coronary artery lesions, oestrogen levels were measured by chemiluminescence in the blood samples collected before CPB. This analysis did not reveal significant differences in serum oestrogen levels in the two groups (p = 0.7011, Fig. 1A).

RT-qPCR analysis indicated that relative to the non-CHD group, EAT aromatase levels were significantly lower in the CHD group (p < 0.0001, Fig. 1B). ELISA showed that EAT aromatase protein levels were also significantly lower in the CHD group (p < 0.0001, Fig. 1C).

Correlative analysis revealed no correlation between aromatase mRNA and protein levels in the control versus CHD groups ($r_{control}$ = –0.069; $p_{control}$ = 0.717; $r_{CHD\ group}$ = –0.057; $p_{CHD\ group}$ = 0.764) (Fig. 2A, B). There was a negative correlation between aromatase protein content and SYNTAX score in the CHD patients, hence, the higher the SYNTAX score, the lower the aromatase protein content (correlation coefficient = –0.430, p = 0.018, Fig. 2C).

Discussion

Based on clinical and experimental investigation, we report for the first time that aromatase level negatively correlated with CHD severity. Since EAT and VAT have the same embryological origin, EAT can be considered the visceral adipose depot in the heart.[12] There is no fascial structure between EAT, the adjacent myocardium and the vascular walls, and high-density adipose tissue can directly infiltrate into the cardiomyocytes, making contact with the adventitia of the coronary arteries.[13] This offers an important structural basis for the endocrine role of adipose tissue.

Coronary atherosclerotic plaques are reported to mainly occur in arterial segments surrounded by EAT,[14] while intramyocardial coronary artery segments are largely unaffected by atherosclerosis.[15] EAT volume is proposed as a biomarker for subclinical atherosclerosis, independent of other coronary artery disease risk factors.[12] Based on these facts, we hypothesised that EAT plays a critical role in the pathogenesis of coronary artery disease.

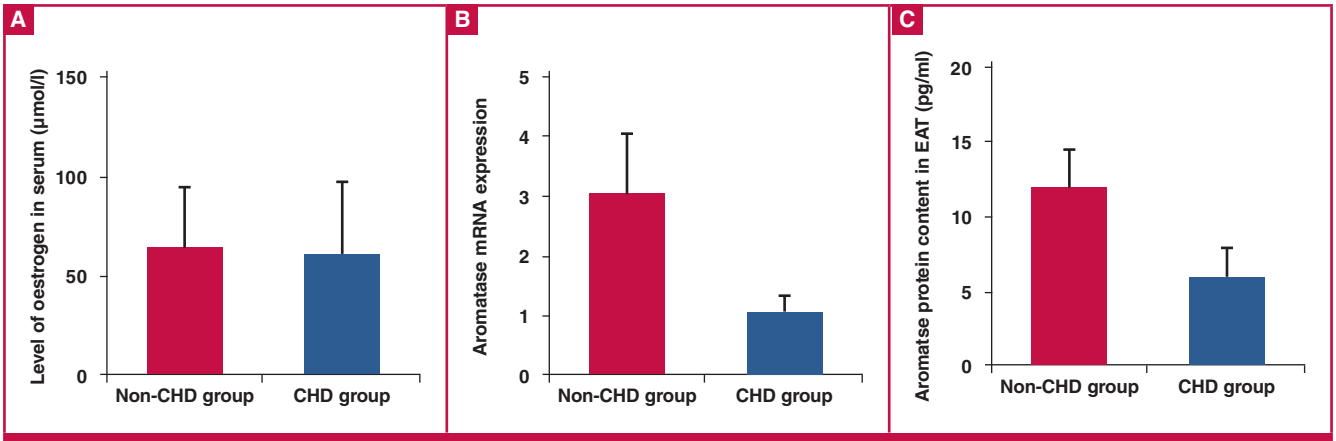

Fig. 1. A. Comparison of oestrogen levels in the serum between the two groups. CHD group: 63.20 ± 32.12 (µmol/l); non-CHD group: 59.79 ± 36.23 (µmol/l). There was no significant difference between the two groups ($p > 0.05$). B. Comparison of the expression of aromatase mRNA in EAT between the two groups. CHD group: 1.0 ± 0.37; non-CHD group: 3.05 ± 0.99. The mRNA expression of aromatase was significantly reduced ($p < 0.05$) in the CHD group. C. Comparison of aromatase protein content in EAT using the *t*-test. CHD group: 5.74 ± 1.97 (pg/ml); non-CHD group: 11.79 ± 2.60 (pg/ml) ($p < 0.0001$). The difference was statistically significant ($p < 0.05$).

CHD incidence in postmenopausal women is almost four times higher than in men.[16] Although adipose tissues has relatively low levels of aromatase and androgens (which are often < 1% in any tissue), their influence on hormone function may be high.[17] For this locally produced oestrogen, especially with gonadal failure, there may be increased cause to exert a cardiovascular protective effect.

Aromatase is involved in sex hormone transformation. Differences in EAT aromatase expression may directly affect local oestrogen levels, the oestrogen/androgen ratio and their biological functions.[18] CYP19 polymorphisms are associated with oestrogen inactivation and CYP19 mutations may alter aromatase protein structure, affecting its activity.[19]

It should be noted that adipose tissue is not homogeneous and control of aromatase expression is tissue specific. For example, while in the ovaries, aromatase expression is regulated by cAMP, and in the breasts it is controlled by prostaglandins.[17] Some studies show that in breast adipose tissue, obesity and low-grade inflammation upregulate aromatase gene expression and oestrogen production.[20-22]

In this study we did not find a correlation between aromatase mRNA and protein levels in the control versus CHD groups. This indicates that there may be other regulatory mechanisms affecting aromatase protein synthesis. The regulatory mechanisms of aromatase expression in EAT have not been studied as yet.

Numerous studies have examined the effects of oestrogen on cardiovascular diseases and found that its protective effects include reduced fibrosis, stimulation of angiogenesis and vasodilation, improved mitochondrial function and reduced oxidative stress.[6] Many of these oestrogen effects have been associated with local EAT aromatase and atherosclerosis, arrhythmia and ischaemia–reperfusion injury.

Some patients with oestrogen-associated breast cancer may require aromatase inhibitor chemotherapy. Cardiovascular events are suggested as primary causes of the low quality of life in breast cancer patients undergoing treatment with aromatase

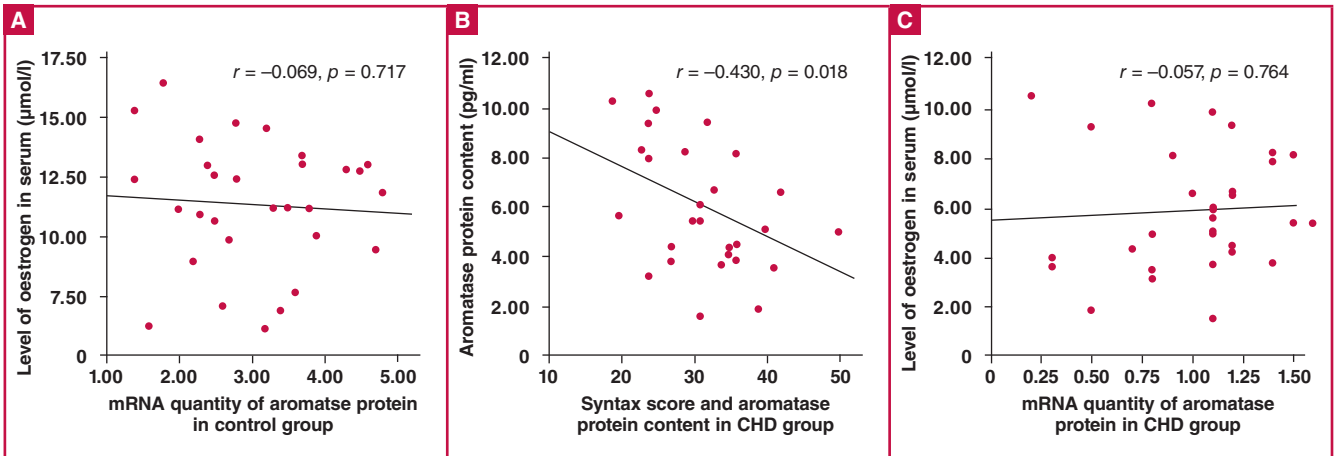

Fig. 2. A. Scatter diagram of aromatase mRNA quantity and aromatase protein content in the control group. B. Scatter diagram of aromatase mRNA quantity and aromatase protein content in the CHD group. C. Scatter diagram of SYNTAX score and aromatase protein content in the CHD group.

inhibitors.[23] This fact is illustrated by findings that elevated EAT aromatase levels may delay or prevent the occurrence of various cardiovascular diseases.

In this study we found a significant negative correlation between severity of coronary artery lesions and level of aromatase protein in the CHD group. However, aromatase activity was not evaluated in this study and the relationship between aromatase protein level, aromatase activity and coronary artery disease needs further study.

Conclusion

Our data show that reduced aromatase expression in EAT correlated with coronary atherosclerotic lesions. Decreased EAT aromatase protein levels may aggravate the severity of atherosclerosis. Future studies should evaluate the mechanisms regulating aromatase transcription and translation in EAT.

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Long-term blood pressure trajectories and associations with age and body mass index among urban women in South Africa

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Abstract

Background: Blood pressure (BP) is known to increase inevitably with age. Understanding the different ages at which great gains could be achieved for intervention to prevent and control BP would be of public health importance.

Methods: Data collected between 2003 and 2014 from 1 969 women aged 22 to 89 years were used in this study. Growth curve models were fitted to describe intra- and inter-individual trajectories. For BP tracking, the intra-class correlation coefficient (ICC) was used to measure dependency of observations from the same individual.

Results: Four patterns were identified: a slow decrease in BP with age before 30 years; a period of gradual increase in midlife up to 60 years; a flattening and slightly declining trend; and another increase in BP in advanced age. These phases persisted but at slightly lower levels after adjustment for body mass index. Three groups of increasing trajectories were identified. The respective number (%) in the low, medium and highly elevated BP groups were 1 386 (70.4%), 482 (24.5%) and 101 (5.1%) for systolic BP; and 1 167 (59.3%), 709 (36.0%) and 93 (4.7%) for diastolic BP. The ICC was strong at 0.71 and 0.79 for systolic and diastolic BP, respectively.

Conclusion: These results show that BP preventative and control measures early in life would be beneficial for control later in life, and since increase in body mass index may worsen hypertension, it should be prevented early and independently.

Keywords: blood pressure, hypertension, body mass index, trajectory, intra-class correlation coefficient

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Hypertension is a major risk factor for non-communicable diseases (NCDs), especially stroke and heart attack,[1] and in South Africa, it was estimated to account for 19.0% of cardiovascular disease deaths in 2016.[2] The prevalence of hypertension in women aged 15 years and older was also estimated at 28.5%,[3] and increased steeply with age, with 84.0% of women aged 65 years and older having hypertension.[4] Urban populations have been shown to have a higher prevalence of hypertension compared with their rural counterparts,[3] and women in such dwellings have also been reported to have higher percentages than men.[5,6]

Accelerated global efforts for the prevention and control of NCDs began during the high-level meeting of heads of state and governments at the 66th session of the United Nations General Assembly in September 2011.[7] Following this, the South African Department of Health developed a strategy in line with the declaration in 2013, of which one of the 10 goals and targets was to 'reduce the prevalence of people with raised blood pressure by 20.0% by 2020 (through lifestyle and medication)'.[8]

Changes in both systolic (SBP) and diastolic blood pressure (DBP) with age are known to show an increasing trajectory that mostly starts between 30 and 40 years.[9-11] However, from approximately 50 years, DBP may plateau and thereafter start to decline.[10,11] An individual's BP trajectory can be used as an indicator for age-related vascular stiffening or for the existence of an underlying disease.[12]

Growth curves (trajectories) play an important role in life-course epidemiology,[13] and can be used in identifying groups of individuals at risk of developing high BP using known risk factors.[14] In addition, population subgroups with different BP trajectories can be useful in selecting people who might benefit most from intervention for the prevention of cardiovascular disease (CVD) risk.[15]

Although age is highly correlated with an increasing BP trajectory, some studies have however reported a decrease in SBP and DBP at the population level, especially for communities in the developed countries of western Europe, Australasia and North America,[16-18] and this decrease is usually attributed to lifestyle and pharmacological interventions.[18]

Understanding how individuals' BPs change and how fast these changes occur (intra-individual change) through their life course, and the patterns for people with different attributes (inter-individual differences in the intra-individual change) could be important in determining best methods for prevention at the

appropriate timing. The aim of this study was therefore to find out the association of age with long-term BP observations. The study had three specific objectives: (1) to identify groups of women with similar SBP and DBP between 22 and 89 years of age; (2) to find out how the trajectories are affected by body mass index (BMI); and (3) identify critical ages when intervention measures would be more appropriate in slowing down a steep upward trajectory.

Methods

Ethical approval (M170866) was granted by the Human Research and Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa.

The study consisted of four measurement time points of data collection on African women dwelling in urban Soweto, Johannesburg, who were care givers of children in the Birth to Twenty Plus cohort study. The majority of the caregivers were the mothers, however a few of the participants included other close relatives such as sisters, aunts and grandmothers.

Data included four waves collected between 2003 and 2014. The four waves provided a sample of 1 969 individuals who had at least one wave of measurements for SBP, DBP, body weight and height, resulting in 4 554 observations. BP measurements were taken in a seated position after 30 minutes of seated rest. The SBP and DBP were measured twice on the right arm using a standard mercury sphygmomanometer and appropriately sized cuff. A final systolic/diastolic BP was calculated by taking the average of the BPs at each time point. Hypertension was defined as systolic/diastolic BP of more than 140/90 mmHg, and BMI was classified according to World Health Organisation as underweight (< 18.5 kg/m^2), normal weight (≥ 18.5– < 25 kg/m^2), overweight (≥ 25– < 30 kg/m^2) and obese (≥ 30 kg/m^2).

Statistical analysis

Multilevel (ML) growth-curve models (a technique to describe and explain an individual's change over time) were used to describe the intra-individual BP trajectories, and the inter-individual differences in the intra-individual changes with age were used as the time metric. Three models were used to describe the patterns of change. The first (model 1) had time effect as the only covariate, model 2 described the changes by adjusting for BMI, and model 3 built on model 2 by allowing effect of BMI to also vary randomly between individuals.

To estimate the mean SBP and DBP trajectories as a function of age, quadratic and cubic non-linear models were used in the analysis, as growth trajectories are known to take a variety of shapes other than linear,[19] mostly characterised by increases or decreases. Age was centred at the minimum age of 22 years to help in the interpretation of the models' intercepts. As BMI is generally known to increase with age, it was included as a time-varying covariate in the second stage of modelling to find out its effect on the BP trajectories. The intra-class correlation coefficient (ICC) was used to measure the degree of dependency among observations within an individual. A group-based trajectory model was used to identify distinct groups for the BPs.

Table 1. Mean and standard deviation for age, SBP, DBP and BMI at the four data-collection time points

Time point	*Number*	*Age (years)*	*SBP (mmHg)*	*DBP (mmHg)*	*BMI (kg/m^2)*
2003	1358	41.1 (7.9)	116.0 (20.1)	76.0 (12.4)	29.9 (6.4)
2005/6	1343	43.4 (8.0)	128.9 (21.6)	80.6 (13.5)	30.7 (7.0)
2007/9	854	45.6 (8.2)	133.5 (21.0)	86.8 (12.9)	30.5 (7.1)
2011/14	999	49.6 (5.7)	134.1 (21.9)	88.7 (12.6)	33.2 (7.2)

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Results

Summary measures for age, BP and BMI at the four time points are shown in Table 1. The mean age at the first occasion (2003) was 41.1 years, and 49.6 years in the fourth occasion. Systolic and diastolic BPs increased from one time point to another, but the increases became smaller with time, and remained almost unchanged, especially for SBP, between the third and fourth occasions. Mean BMI for the four occasions was high, at obesity level, and remained almost constant between the first and third waves, but increased by at least 2.5 kg/m^2 by the fourth occasion. There is an indication of constant variation in BP and BMI across the measurement occasions.

Table 2 shows the percentage of hypertension by BMI category at each data-collection time point. The percentage of subjects who had hypertension in 2003 was 16.7% and by 2014, this had increased to 47.1%. At each time point it was highest for those with an obese BMI, as expected. The greatest percentage increase was between the first and the second occasions (after approximately 2.4 years), where it almost doubled. For those with normal or overweight BMI statuses, the percentage of hypertension almost tripled between the first and fourth occasions. Between the third and fourth time points (approximately 5.3 years), the percentage of those with hypertension among participants in the obese category remained

Table 2. Hypertension percentages by BMI categories at the four data-collection time points

			Blood pressure category		
	BMI		*Non-hypertensive*	*Hyper-tensive*	
Time point	*Category*	n *(%)*	n *(%)*	n *(%)*	*Total* n *(%)*
2003	Underweight	24 (1.8)	22 (91.7)	2 (8.3)	24 (100.0)
	Normal	300 (22.1)	263 (87.7)	37 (12.3)	300 (100.0)
	Overweight	405 (29.8)	349 (86.2)	56 (13.8)	405 (100.0)
	Obese	629 (46.3)	497 (79.0)	132 (21.0)	629 (100.0)
	Total	1358 (100.0)	1131 (83.3)	227 (16.7)	1358 (100.0)
2005/6	Underweight	19 (1.4)	12 (63.2)	7 (36.8)	19 (100.0)
	Normal	269 (20.0)	202 (75.1)	67 (24.9)	269 (100.0)
	Overweight	343 (25.5)	252 (73.5)	91 (26.5)	343 (100.0)
	Obese	712 (53.0)	467 (65.6)	245 (34.4)	712 (100.0)
	Total	1343 (100.0)	933 (69.5)	410 (30.5)	1343 (100.0)
2007/9	Underweight	10 (1.2)	5 (50.0)	5 (50.0)	10 (100.0)
	Normal	188 (22.0)	125 (66.5)	63 (33.5)	188 (100.0)
	Overweight	226 (26.5)	146 (64.6)	80 (35.4)	226 (100.0)
	Obese	430 (50.4)	212 (49.3)	218 (50.7)	430 (100.0)
	Total	854 (100.0)	488 (57.1)	366 (42.9)	854 (100.0)
2011/14	Underweight	7 (0.7)	4 (57.1)	3 (42.9)	7 (100.0)
	Normal	116 (11.6)	77 (66.4)	39 (33.6)	116 (100.0)
	Overweight	217 (21.7)	127 (58.5)	90 (41.5)	217 (100.0)
	Obese	659 (66.0)	320 (48.6)	339 (51.4)	659 (100.0)
	Total	999 (100.0)	528 (52.9)	471 (47.2)	999 (100.0)

BMI, body mass index. Due to approximation to one decimal place, some percentages may fall below or exceed 100% by 0.1.

Table 3. Average BP changes and shifts between categories at the four data-collection time points

Time points	Average years apart	BP category	n	BP category: Non-hypertensive	BP category: Hypertensive	Mean change (SD): SBP	Mean change (SD): DBP
2003 & 2005/6	2.4	Non-hypertensive	824	647 (78.5)	177 (21.5)	11.3 (19.3)	4.1 (12.1)
		Hypertensive	159	53 (33.3)	106 (66.7)		
		Total	983	700 (71.2)	283 (28.8)		
2005/6 & 2007/9	2.0	Non-hypertensive	512	354 (69.1)	158 (30.9)	4.5 (20.4)	6.4 (11.9)
		Hypertensive	237	72 (30.4)	165 (69.6)		
		Total	749	426 (56.9)	323 (43.1)		
2007/9 & 2011/14	5.3	Non-hypertensive	234	162 (69.2)	72 (30.8)	1.7 (19.0)	1.1 (11.2)
		Hypertensive	154	39 (25.3)	115 (74.7)		
		Total	388	201 (51.8)	187 (48.2)		
2003 & 2007/9	4.4	Non-hypertensive	493	303 (61.5)	190 (38.5)	16.4 (20.9)	10.9 (12.6)
		Hypertensive	99	26 (26.3)	73 (73.7)		
		Total	592	329 (55.6)	263 (44.4)		
2005/6 & 2011/14	7.3	Non-hypertensive	460	291 (63.3)	169 (36.7)	8.1 (22.3)	8.1 (12.6)
		Hypertensive	185	49 (26.5)	136 (73.5)		
		Total	645	340 (52.7)	305 (47.3)		
2003 & 2011/14	9.7	Non-hypertensive	549	326 (59.4)	223 (40.6)	19.1 (20.4)	12.6 (12.3)
		Hypertensive	96	15 (15.6)	81 (84.4)		
		Total	645	341 (52.9)	304 (47.1)		

almost unchanged (50.7% in the third occasion and 51.4% in the fourth occasion), even though the percentage of obesity increased by more than 15.6 points (50.4 to 66.0%) between the two occasions.

Table 3 shows the mean change in BP and BMI between two observation periods. Between the first two time points, average SBP and DBP per individual changed by about 11.3 and 4.1 mmHg, respectively but that change decreased substantially between the third and fourth time points to about 1.7 and 1.1 mmHg, respectively. The majority remained in their BP status between observation times but with time (age), the percentage remaining in the hypertension state increased, while the percentage remaining in the normotensive state decreased.

Between the first two occasions when the average age at both times was below 45 years, the percentage of those who were normotensive who transited to the hypertensive state was 21.5%, while the percentage for the counter-transition was 33.3%, or a net recovery of 11.8%. By the fourth occasion when the average age was about 50 years, those initially in the non-hypertensive state who transited to hypertensive state were 40.6%, but the counter-transition (recovery) rate was 15.6%, or a net increase of 25.0% to the hypertensive state.

Fig. 1 and Table 4 show how the progression of BP evolves. A crest (inverted U-shape) marks a negative change (decrease) while a trough (U-shape) marks a positive change (increase). Fig. 1 however shows that the 95% confidence band for ages above 70 years are quite large and therefore the shape in that age group could be spurious. The first crest occurs around 25 years of age and is indicated by negative coefficients (–1.8 for SBP and –1.5 for DBP) for age (Table 4), and the second around 60 years, and is shown by negative coefficients (–0.004 for SBP and –0.003 for DBP) for age cubed. Similarly, the troughs are identifiable around ages 30 and 70 years and marked by the positive coefficients for age squared and age raised to the power of four (Table 4).

Model 1 describes the BP trajectories without accounting for the effect of BMI, while models 2 and 3 show the adjusted

Table 4. Coefficients (95% confidence interval) for the three models predicting SBP and DBP trajectories with standard deviations (SD) for the random effects

BP	Variables	Model 1	Model 2	Model 3
Systolic	Fixed effects			
	Intercept	116.2 (106.7, 125.7)	105.5 (95.7, 115.3)	105.0 (95.1,114.9)
	Age	–1.7 (–3.3, –0.1)	–1.7 (–3.4, –0.1)	–1.8 (–3.4, –0.2)
	Age^2	0.18 (0.08, 0.27)	0.17 (0.08, 0.27)	0.17 (0.08 ,0.27)
	Age^3	–0.004 (–0.006, –0.002)	–0.004 (–0.006, –0.002)	–0.004 (–0.006, –0.002)
	Age^4	0.00003 (0.00001, 0.00005)	0.00003 (0.00001, 0.00005)	0.00003 (0.00001, 0.00005)
	BMI		0.39 (0.29, 0.49)	0.41 (0.30, 0.52)
	Random effects			
	SD (intercept)	14.5 (13.7, 15.2)	14.4 (13.7, 15.1)	24.3 (18.4, 32.2)
	SD (BMI)			0.65 (0.43, 0.96)
	Correlation (BMI, intercept)			–0.82 (–0.91, –0.66)
	SD (residual)	15.5 (15.1, 15.9)	15.4 (15.0, 15.8)	15.2 (14.8, 15.7)
	ICC	0.47 (0.43, 0.50)	0.47 (0.43, 0.50)	0.72 (0.59, 0.82)
Diastolic	Fixed effects			
	Intercept	75.7 (69.8, 81.5)	64.5 (58.5, 70.4)	63.3 (57.2, 69.3)
	Age	–1.4 (–2.4, –0.4)	–1.4 (–2.4, –0.4)	–1.5 (–2.4, –0.5)
	Age^2	0.15 (0.09, 0.21)	0.14 (0.08, 0.20)	0.14 (0.08, 0.20)
	Age^3	–0.004 (–0.005, –0.002)	–0.003 (–0.005, –0.002)	–0.003 (–0.005, –0.002)
	Age^4	0.00003 (0.00001, 0.00004)	0.00002 (0.00001, 0.00004)	0.00002 (0.00001, 0.00004)
	BMI		0.41 (0.35, 0.47)	0.46 (0.39, 0.53)
	Random effects			
	SD (intercept)	9.4 (8.9, 9.9)	9.1 (8.6, 9.5)	17.5 (14.2, 21.7)
	SD (BMI)			0.52 (0.41, 0.67)
	Correlation (BMI, intercept)			–0.87 (–0.92, –0.79)
	SD (residual)	9.4 (9.1, 9.6)	9.3 (9.0, 9.5)	9.0 (8.8, 9.3)
	ICC	0.50 (0.47, 0.53)	0.49 (0.46, 0.52)	0.79 (0.71, 0.85)

SBP, systolic blood pressure; DBP, diastolic blood pressure; ICC, intraclass correlation coefficient.

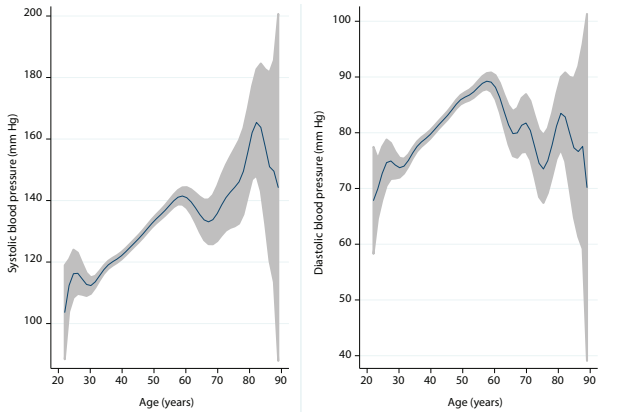

Fig. 1. SBP and DBP trajectories with 95% confidence interval (greyed) by age.

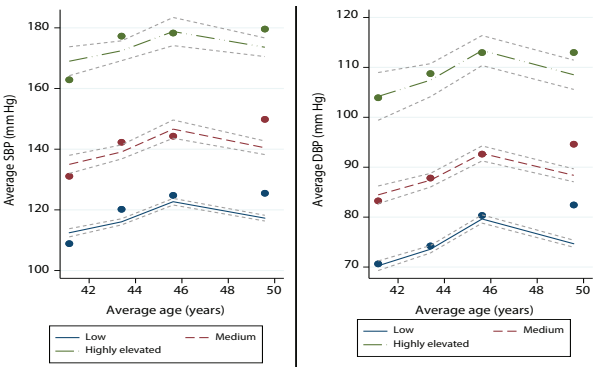

Fig. 2. Observed and BMI-adjusted SBP and DBP trajectories by average age at data-collection time points.

changes. The biggest impact of the BMI adjustment was on the intercepts, shifting each BP's mean trajectory downwards (116.2 to 105.0 mmHg for SBP, and 75.7 to 63.3 mmHg for DBP). Model 2, as shown in Table 4, includes a random effect in the baseline values (intercept) to address the variability in starting point for each individual in the sample. Model 3 in addition to model 2, allowed a random BMI effect (slope) for each individual to explain variability in the slope (change by BMI).

The estimated SBP and DBP for the whole sample at 22 years of age was 105.0 and 63.3 mmHg, respectively, and each individual value varied randomly around these baseline values with 24.3 mmHg standard deviations for SBP and 17.5 mmHg for DBP. Therefore 95% of the estimated individual's BPs at age 22 years lies between $105.0 \pm 1.96 \times 24.3 = (57.4–152.6)$ for SBP and $63.3 \pm 1.96 \times 17.5 = (29.0–96.7)$ for DBP. The estimated increases in BP for every 1 kg/m^2 increase in BMI are 0.41 mmHg for SBP and 0.46 mmHg for DBP for the total sample. But the individual slopes (BMI effect) vary randomly around these values with standard deviations of 0.65 mmHg for SBP and 0.52 mmHg for DBP. Therefore the 95% CI for BMI slopes lie between $0.41 \pm 1.96 \times 0.65 = (–0.86–1.68)$ for SBP and $0.46 \pm 1.96 \times 0.52 = (–0.56–1.48)$ for DBP.

The correlation between the random intercepts and BMI random slopes is strongly inversely proportional (–0.82 for SBP and –0.87 for DBP) implying that higher values of baseline BP at the individual level were associated with a relatively smaller effect of BMI on BP, and vice versa. By including a random BMI effect, the ICC (correlation among observations within an individual) increased from 0.47 (model 2) to 0.72 (model 3) for SBP and from 0.49 to 0.79 for DBP. In addition, the variability in the random intercepts also increased from 14.4 (model 2) to 24.3 (model 3) for SBP, and from 9.1 (model 2) to 17.5 (model 3) for DBP.

There were three distinct groups from the 1 969 individuals (Fig. 2). The low-BP trajectory group comprised the majority of the study participants (70.4% for SBP and 59.3% for DBP), and showed a trajectory that was initially in the normotensive state but gently rose to the pre-hypertensive region. A medium BP trajectory (24.5% for SBP and 36.0% for DBP) had an initial average BP in the pre-hypertensive state that gradually rose to the hypertensive level, while the third group of about 5.0% had highly elevated increasing BPs throughout. Individuals in the medium and highly elevated BP groups were most likely to be aged 40 years and above at baseline, while most of those in the low-BP group were 40 years and below initially.

Discussion

This study examined BP life-course trajectories for a period of approximately 10 years in women from an urban setting in South Africa, and how these trajectories were related to changes in BMI. The trajectories were initially characterised by a short instance of decreasing SBP and DBP with age up to around 30 years (Fig. 1, Table 4). Although our sample for ages below 30 years was small, which could have affected the shape of the trajectories, other studies have shown small downward changes in BP in early adulthood, which could be associated with capacity for vascular repair or adaptations.[20-22] Possible vascular repair could be a reason for our results showing that the percentage of subjects recovering from the hypertensive to the normotensive state was highest (Table 3) in the relatively younger ages.

A second phase of rapid increase in the trajectories began from around 30 up to 60 years. This closely mirrors data from the Framingham Heart Study, which showed that SBP increased continuously between 30 and 84 years, but for DBP the continuous increase was between 30 and 49 years.[23] Increasing SBP and DBP are associated with increased peripheral vascular resistance up to around 50 years, while large arterial stiffness leads to the steeper rise in SBP after 50 years.[24] Studies have shown that younger women have less stiff arteries compared with men of a similar age,[25,26] but increased stiffness occurs after menopause. Attention for control of BP in post-menopausal women would therefore reduce the risk for cerebrovascular and cardiovascular events.[24] Understanding the variation in midlife BP trajectories, and factors associated with this acceleration, may be important in understanding the risk of development and the prevention of CVD, and to implement strategies for lowering BP, as per the National Strategic Plan.[8]

A third phase from around 60 years of age showed a flattening or slightly decreasing trajectory for both BPs (Fig. 1, Table 4). Similar studies have shown a decreasing trend for SBP at ages > 65 years,[27] and for DBP from > 55 years.[28] A decline in BP in old

age has been linked to deteriorating health.[29,30] Decreasing SBP with age has been associated with dementia, depression, polypharmacy (use of a large number of medications) and increased number of co-morbidities.[31,32] A steeper decrease in both SBP and DBP has been associated with a diagnosis of diabetes,[33] and an increase in all-cause and cardiovascular mortality.[34] However, longer-term decreases in BP have also been shown to occur with or without the presence of hypertension, heart failure, atrial fibrillation or stroke,[35] implying that decreasing BP could be due to low cardiac output, a feature of ageing.[36] The deceleration and decline in BP in old age is also associated with use of antihypertensive medication,[22] which we did not account for in this study.

The results of the three group-based trajectories show that the averages for both BPs were either at the pre-hypertensive or hypertensive levels for the medium and highly elevated BP groups. The proportion of women in these two groups of trajectories aged 45 years or above was more than those in the lower BP trajectory group. Persistently elevated BP and hypertension trajectories have been associated with increased incidence of atrial fibrillation, with the associations being stronger in women than men.[37] It has also been associated with a higher risk of subclinical renal damage (SRD) since evidence shows that the higher the levels of SBP in early life, the higher the urinary albumin-to-creatinine ratio and risk of SRD later in life.[38] Some studies have suggested that individuals with high BP, especially SBP in midlife, are at a higher risk of arterial stiffening.[39,40] Evidence has shown that continuously high BP for years is closely correlated with subclinical atherosclerosis,[41] intima–media thickness and left ventricular mass index.[42]

The unadjusted trajectories reflect the added effect of ageing and the influence of other life-course risk factors such as BMI. Generally, the effect of BMI on BP trajectories affected the baseline value (intercept) more than the rate of change (slope). This could be an indication that the effect of BMI on BP is as a result of BMI increases that usually and rapidly take place early in life. Accelerated weight gain and increased BMI in childhood and early adult life increase the risk of elevated BP and the development of hypertension in later life.[43,44]

Surveys in South Africa have shown that the average BMI for women by age 30 years is more than 28.0 kg/m^2,[45-49] which is in the upper range of the overweight level. The majority of the women in this study were at least 30 years old, and the average BMI at the first encounter was 29.9 kg/m^2. An increase in BMI could lead to arterial stiffness, which may cause the development of higher BP levels.[50] Higher SBP levels reflect the stiffening of the arterial walls in areas exposed to increased pressure,[51] while coronary perfusion of the myocardium may be related to DBP.[52]

Allowing the effect of BMI to vary by individual brought about three more important findings. First, the standard deviation of the random intercepts increased, an indication that baseline BPs varied greatly by individual. This was evident from the clear distinction in the group trajectories, which did not interact at any time point. Second, the results showed that the effect of BMI on BP changes was higher in women who initially were in the normotensive status (low BP group), and the effect progressively became less in those initially in the pre-hypertensive (medium BP group) and hypertensive (highly elevated BP) states.

The third issue relates to the correlation between measurements from the same individual, which became more pre-eminent after allowing the effect of BMI to be specific to each individual. A stronger correlation can be helpful in tracking those likely to have persistently high BP. Tracking of a characteristic is the stability of a certain feature over time or its predictability based on earlier measurements.[53,54] Tracking the stability of BPs is of considerable public health interest because those at high risk of developing hypertension could be identified at an early stage,[55] through screening. The influence of change in BMI on BP tracking emphasises the importance of weight control at an early age. Maintenance of normal weight gain in childhood may prevent clustering of hypertension and CVD risk factors in adulthood.[56]

The ideal trajectory for BP is one with minimal fluctuations within the normotensive ranges across all ages. Favourable (less steep trajectory) BP trends are attributed to socially patterned and modifiable BP-related exposures such as lifestyle and diet.[57,58] Few studies from isolated communities such as forager-farmers, have shown minimal age-related BP increases in comparison to Western societies.[59] These communities however have adopted a predominantly vegetarian diet with very low salt content, a physically active lifestyle, and very low or non-existent obesity levels.[59-61] Individuals who undergo an urban migration from one of these isolated communities have been found to adapt quickly to BP profiles of their adopted communities.[60]

The main limitation to the study was that we were unable to account for subjects on antihypertensive medications, which could also have contributed to the decreasing BPs with increasing BMI in higher age groups, and the majority of the women (> 70.0%) having SBP in the lowest of the three trajectory groups. Nonetheless, controlling BMI for this and similar populations should be prioritised as it could be beneficial in many ways and possibly cheaper for BP control than medication alone. Another limitation was that the sample size for women above 60 years at any time point was small and this was the reason for the volatile trajectory in this age range.

Notwithstanding, the major strength was in using repeated BP and anthropometric measurements, which helped in analysing long-term trends in BP changes as they were influenced by age and BMI. This could be useful in guiding clinical practitioners to focus on population segments with particular risk profiles. Another strength was the study result showing that the effect of BMI on elevation of BP was not similar for all individuals, and this could help in clinical practice by designing individualised interventions.

Conclusions

Three subgroups of increasing SBP and DBP trajectories were identified, with the majority of the women in each BP type falling in the lowest group, which on average was initially in the normotensive state. The effect of BMI on the BP trajectory for age was highest in women who initially had relatively lower (mostly in the normotensive state) initial BPs. This BMI effect gradually dropped in tandem with increasing initial BP. The study also showed that steep increasing trajectories could be avoided if preventative interventions are implemented between 30 and 40 years of age from when the BP starts to increase steeply. Follow-up study is required to find out if these trajectories would be similar to findings from a larger and more diverse nationally representative sample.

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Review Article

Dietary intakes of green leafy vegetables and incidence of cardiovascular diseases

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Abstract

Aim: Low- and middle-income countries (LMICs) are currently experiencing increasing cardiovascular disease (CVD) rates. Green leafy vegetables (GLV), which are abundant in these countries, are known to be particularly rich in cardioprotective nutrients. This study sought to determine the specific effect of GLV intake on the incidence of CVD.

Methods: Previously published cohort studies on GLV intake and incidence of CVD were retrieved through a systematic search of Google Scholar, EMBASE, MEDLINE, HINARI and Cochrane Library. A methodological evaluation of studies was carried out using the network of Ottawa scale, and a fixed-effect meta-analysis was applied to estimate pooled relative risk (RR) and 95% confidence interval (CI). Heterogeneity was determined using the I^2 statistic. Sensitivity analysis was done using the leave-one-study-out technique. All statistical analysis was carried out at $p < 0.05$ using RevMan 5.4.

Results: The pooled RR (95% CI) of incident CVD events from 17 studies was 0.93 (0.92–0.95). Specifically, GLV intake was inversely related with incident cerebral infarction (RR: 0.92; 95% CI: 0.88–0.96), heart disease (RR: 0.93; 95% CI: 0.87–0.99) and other CVD events (RR: 0.95; 95% CI: 0.93–0.98).

Conclusion: GLV intake was associated with a lower incidence of CVD, and may be a promising primary-prevention strategy against CVD events. The findings are especially important in LMICs where the burden of CVD remains high.

Keywords: green leafy vegetables, cardiovascular diseases, cerebral infarction, coronary heart disease, heart disease, meta-analysis

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Cardiovascular diseases (CVD) account for about 17.9 million deaths annually[1] and a huge burden of health expenditure worldwide.[2,3] Although CVD rates appear to be declining globally,[1,2,4-6] populations in low- and middle-income countries (LMIC)[6,7] continue to experience increasing CVD rates. CVD are preventable and efforts are currently being mobilised to achieve a 25% reduction in mortality rate attributable to CVD by 2025.[8,9]

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A promising preventative strategy for CVD is diet.[10-13] However, studies on the potential association of diet and CVD events have focused on the effect of red meat,[14,15] salt intake,[16] alcohol,[17] saturated fats/oils and dairy products.[18] Prior reviews and meta-analyses[19-24] investigating the effect of fruit and vegetables on the risk profile for CVD have focused on broad categories of the nutritional modalities. For example, Deng *et al.*[19] and Kwok *et al.*[24] in two reviews of meta-analyses assessed the effect of fruit and vegetable intake, in general, on the burden of diseases and all-cause mortality without providing information on the specific effect(s) of green leafy vegetables (GLV) on the incidence of distinct CVD events.

The information provided by individual studies on the effect of GLV intake remains inconclusive. While some studies reported a reduction in the incidence of CVD events with higher consumption of GLV,[10,25,26] others observed statistically insignificant relationships.[27,28] The pooled effect of GLV intake on incident CVD is currently unknown.

GLV are widely available in LMIC.[29] The vegetables are rich in phytochemicals and micronutrients known to be essential for health.[13,30-32] Also, GLV contain folic acid, vitamins A, C, E and K, as well as high amounts of calcium, iron, potassium, phosphorous and zinc,[33,34] which may be protectively associated with CVD risk.[35] This systematic review and meta-analysis investigated the pooled effect of GLV intake on incident CVD events.

Methods

The systematic review was registered in the international prospective register of systematic reviews and is accessible via https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181050. Google Scholar, EMBASE, MEDLINE, HINARI and Cochrane Library were searched (in December 2020 using specific search terms independent of language and publication dates) for previously published epidemiological reports on consumption of GLV and CVD. The following search terms were used.

EMBASE, Google Scholar and Cochrane Library search terms: 'vegetables' OR 'chlorophyll-containing vegetables' OR 'green leafy vegetables' OR 'broccoli' OR 'cabbage' OR 'celery' OR 'collard green' OR 'green pea' OR 'lettuce' OR 'spinach' OR 'swiss chard' OR 'turnip green' AND 'cardiovascular disease' OR 'cerebrovascular disease' OR 'cerebral infarction' OR 'cerebral haemorrhage' OR 'coronary heart disease' OR 'heart failure' OR 'subarachnoid haemorrhage'.

MEDLINE and HINARI search terms using PubMed interphases: 'vegetables (Title/Abstract)' OR 'green leaves (Title/Abstract)' OR 'edible green leaves (Title/Abstract)' OR 'green vegetables (Title/Abstract)' OR 'leafy vegetables (Title/Abstract)' OR 'green leafy vegetables (Title/Abstract)' OR 'chlorophyll-containing vegetables (Title/Abstract)' OR 'broccoli (Title/Abstract)' OR 'cabbage (Title/Abstract)' OR 'celery (Title/Abstract)' OR 'collard green (Title/Abstract)' OR 'green pea (Title/Abstract)' OR 'lettuce (Title/Abstract)' OR 'spinach (Title/Abstract)' OR 'swiss chard (Title/Abstract)' OR 'turnip green (Title/Abstract)' AND 'stroke (MesH terms)' OR 'transient ischemic attack (MeSH terms)' OR 'haemorrhagic stroke (MeSH terms)' OR 'ischaemic stroke (MeSH terms)' OR 'cardiovascular disease (MeSH terms)' OR 'cerebrovascular disease (MeSH terms)' OR 'cerebral infarction (MeSH terms)' OR 'cerebral haemorrhage (MeSH terms)' OR 'coronary heart disease (MeSH terms)' OR 'heart failure (MeSH terms)' OR 'subarachnoid haemorrhage (MeSH terms)'. Details of the literature search are in the PRISMA flow chart (Fig. 1).

Study assessment for inclusion and exclusion criteria and data extraction were conducted by two independent assessors (AO and APO) based on the descriptions in the original article. Only studies with usable data and appropriate analytical techniques were included in the meta-analysis. The following information was extracted from each included study: first author name, publication year, sample size, average follow-up time, the incidence of CVD, adjusted relative risk (RR)/hazard ratio and 95% confidence interval (CI), etc.

Studies included in this meta-analysis were prospective cohort reports (where the primary exposure was GLV consumption and outcomes were CVD events) only. Where there are significant levels of data overlap among published studies, the study with complete evidence was included in the quantitative synthesis.

A methodological assessment for risk of bias of included studies was conducted (independently by two members of the review team) using the Newcastle–Ottawa scale for quality assessment of observational reports[36] following the Cochrane Collaboration guidelines.[37]

Statistical analysis

Using the RR and 95% CI for highest quintile/category of GLV consumption compared to the lowest quintile/category of GLV

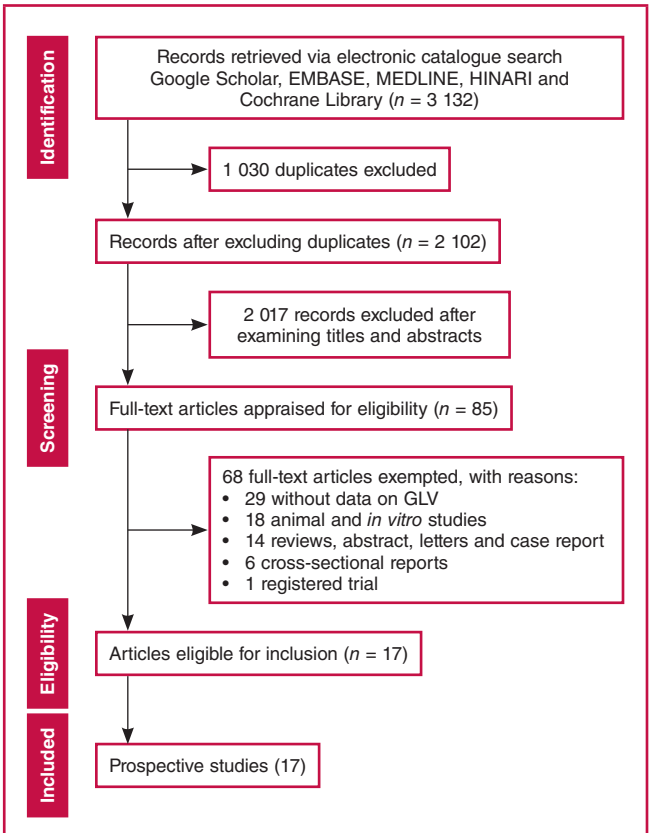

Fig. 1. PRISMA flowchart describing selection of the studies for the meta-analysis

Table 1. Characteristics of prospective reports included in the meta-analysis

	Study characteristics			*Baseline/outcomes evaluation*				
First author	*Year*	*Country*	*GLV intake*	*Incidence*	*Total*	*CVD event(s)*	*Assessment*	*Ascertainment*
Gaziano JM	1995	United States	< 1 s/d* vs ≥ 1 s/d	161	1 299	CVD	Relative-reported deaths[‡†]	Not reported
Joshipura KJ	1999	United States	Increment of 1 s/d[3]	366[W] 204[M]	75 596[W] 38 683[M]	Ischaemic stroke	Self/relative report[‡]	National Stroke Society (NSS) criteria
Joshipura KJ	2001	United States	Increment of 1 s/d[2,3]	1 127[W] 1 063[M]	84 251[W] 42 148[M]	CHD	Self/relative report[‡]	World Health Organisation (WHO) criteria
Johnsen SP	2003	Denmark	1.4 g/d* vs 28.00 g/d	266	54 506	Ischaemic stroke	Self/relative report[‡]	WHO criteria
Sauvaget C	2003	Japan	≤ 1 s/week* vs 1 s/d[2]	1 926	40 349	Stroke	Stroke mortality[‡]	WHO criteria
Hung HC	2004	United States	Increment of 1 s/d[3]	3 864	109 635	CVD	Self/relative report[‡]	NSS criteria
Takachi R	2007	Japan	Not reported	1 386	77 891	CVD	MI or stroke diagnosis using CT scan/MRI[‡]	WHO and NSS criteria
Joshipura KJ	2009	United States	Not reported	1 852[W] 2 040[M]	70 870[W] 38 918[M]	Ischaemic CVD	Self/relative report[‡]	WHO and NSS criteria
Bendinelli B	2010	Italy	≤ 17.60 g/d* vs > 50.80 g/d[1]	144	29 689	CHD	[©]Self/relative report[‡]	Minnesota Code
Oude Griep LM	2011A	Netherlands	34 g/d* vs 105 g/d[2,3]	233	20 069	Stroke	Population and hospital discharge register	Dutch guidelines
Oude Griep LM	2011B	Netherlands	34 g/d* vs 105 g/d[2,3]	245	20 069	CHD	[©]Population and hospital discharge register	WHO criteria
Larsson S	2013	Sweden	< 2.3 s/d* vs > 6.0 s/d[1,2,3]	4 089	74 961	Stroke	Self report[‡]	Not reported
Bhupathiraju SN	2013	United States	0.22 s/d* vs 1.50 s/day[1,2]	6 189	71 141	CHD	Self/relative report[‡]	WHO criteria
Rautiainen S	2015	Sweden	< 0.2 s/d* vs > 1 s/d[1,2,3]	3 051	34 319	Heart failure	Heart failure diagnosis and related deaths[‡]	ESC criteria
Wang JB	2016	China	Increment of twice/week	355	2 445	Stroke	Case, pathology, cytology, X-rays, biochemical, ultrasound, endoscopy and surgery reports	Team of reviewers
Buil-Cosiales P	2016	Spain	32·16 g/d* vs 113.00 g/d[1]	342	7 216	CVD	Self/relative report[‡]	Team of reviewers
Blekkenhorst LC	2017	Australia	Intake per 10 g/d	238	1 226	CHD	CHD diagnosis and related death[‡]	Not reported

*Reference group for comparison; [1]energy-adjusted dietary intakes of GLV; [2]additionally adjusted for other intakes, etc; [3]using median values of quintiles; [M]men; [W]women; [©]MI events, coronary revascularisation, or both not preceded by any other CHD event; [‡]authenticated via vital statistics or medical records or designated registry; [†]validated death certificate.
g/d – grams per day; s/d – servings per day; GLV – green leafy vegetables; ESC – European Society of Cardiology; CVD – cardiovascular disease; CHD – coronary heart disease; CT – computed tomography; MI – myocardial infarction; MRI – magnetic resonance imaging.

consumption (as reference) for the incidence of CVD events reported in the included studies, we computed the log of RR and the matching standard error for the overall pooled RR (95% CI) for the incidence of CVD events and by subgroup stratification [cerebral infarction, cerebral haemorrhage, coronary heart disease (CHD), etc.] using an inverse-of-variance method for weighting in all quantitative estimations for dichotomous outcomes.

The degree of heterogeneity was assessed using I^2 statistics assuming a fixed-effect model (where $I^2 < 50\%$) or a random-effect meta-analysis model if $I^2 > 50\%$. The fixed-effect model presupposes the effect size is likely relatively similar across studies in the meta-analysis.[37,38] However, a random-effect model ideates the difference in effect estimates across studies are valid but follows a normal distribution. Publication bias for the likely effect estimate of GLV intake on CVD events was tested using funnel plots.

The constancy of the pooled RR (95% CI) was tested using the leave-one-study-out method (carrying out the meta-analysis several times, excluding a study at a time). All quantitative analyses were conducted at $p < 0.05$ using the RevMan 5.4 software.[39]

Results

Over 3 000 records were retrieved from the literature search in Google Scholar, EMBASE, MEDLINE, HINARI and Cochrane Library but 1 021 duplicates were excluded. Also, 2 011 records were excluded after screening the titles and abstracts (Fig. 1). On full-text assessment, 65 records were excluded and 17 prospective reports (five reports on composite CVD events,[10,25-27,40] five reports on coronary heart disease,[28,41-44] one report on heart failure[45] and

Table 2. Methodological assessment of prospective studies using the Newcastle–Ottawa scale

		Selection				*Comparability*	*Outcome*			*Total*	*Risk of bias of included studies*
Study	*Year*	*S1*	*S2*	*S3*	*S4*	*C1*	*O1*	*O2*	*O3*	*Scores*	
Gaziano *et al.*	1995	1	1	1		1	1		1	6	High
Joshipura *et al.*	1999	1	1	1	1	2	1	1	1	9	Low
Joshipura *et al.*	2001	1	1	1	1	2		1	1	8	Moderate
Johnsen *et al.*	2003	1	1	1	1	2	1		1	8	Moderate
Sauvaget *et al.*	2003	1	1		1	2	1	1	1	8	Moderate
Hung *et al.*	2004	1	1	1	1	2	1	1	1	9	Low
Takachi *et al.*	2007	1	1	1		2	1		1	7	Moderate
Joshipura *et al.*	2008	1	1	1	1	2		1	1	8	Moderate
Bendinelli *et al.*	2010	1	1	1	1	2	1	1	1	9	Low
Oude *Griep et al.*	2011A	1	1	1	1	2	1	1	1	9	Low
Oude Griep *et al.*	2011B	1	1	1	1	2	1	1	1	9	Low
Larsson *et al.*	2013	1	1	1	1	2	1	1	1	9	Low
Bhupathiraju *et al.*	2013	1	1	1	1	2	1	1	1	9	Low
Rautiainen *et al.*	2014	1	1	1	1	2	1	1	1	9	Low
Buil-Cosiales *et al.*	2016	1	1	1	1	2	1	1	1	9	Low
Wang *et al.*	2016	1	1	1		2	1	1	1	8	Moderate
Blekkenhorst *et al.*	2017	1	1	1	1	2	1	1	1	9	Low

Risk of bias of included studies: high risk of bias: ≤ 6; moderate risk of bias: 7–8; low risk of bias: 9 and empty cells indicate a score of 0.
S1 – representativeness of the exposed cohort; S2 – selection of the non-exposed cohort; S3 – ascertainment of exposure; S4 – demonstration that outcome of interest was absent at the start of the study; C1 – comparability of the cohort based on the design or analysis; O1 – assessment of outcome; O2 – was follow up long enough for outcomes to occur?; O3 – adequacy of follow up of cohorts.

six reports on stroke[46-51]) were included in the meta-analysis.

Studies on this subject (Table 1) were published over 12 years (1995–2017). Most reports assessed GLV intakes using the food-frequency questionnaire, but limited studies[42,45,50] adjusted for

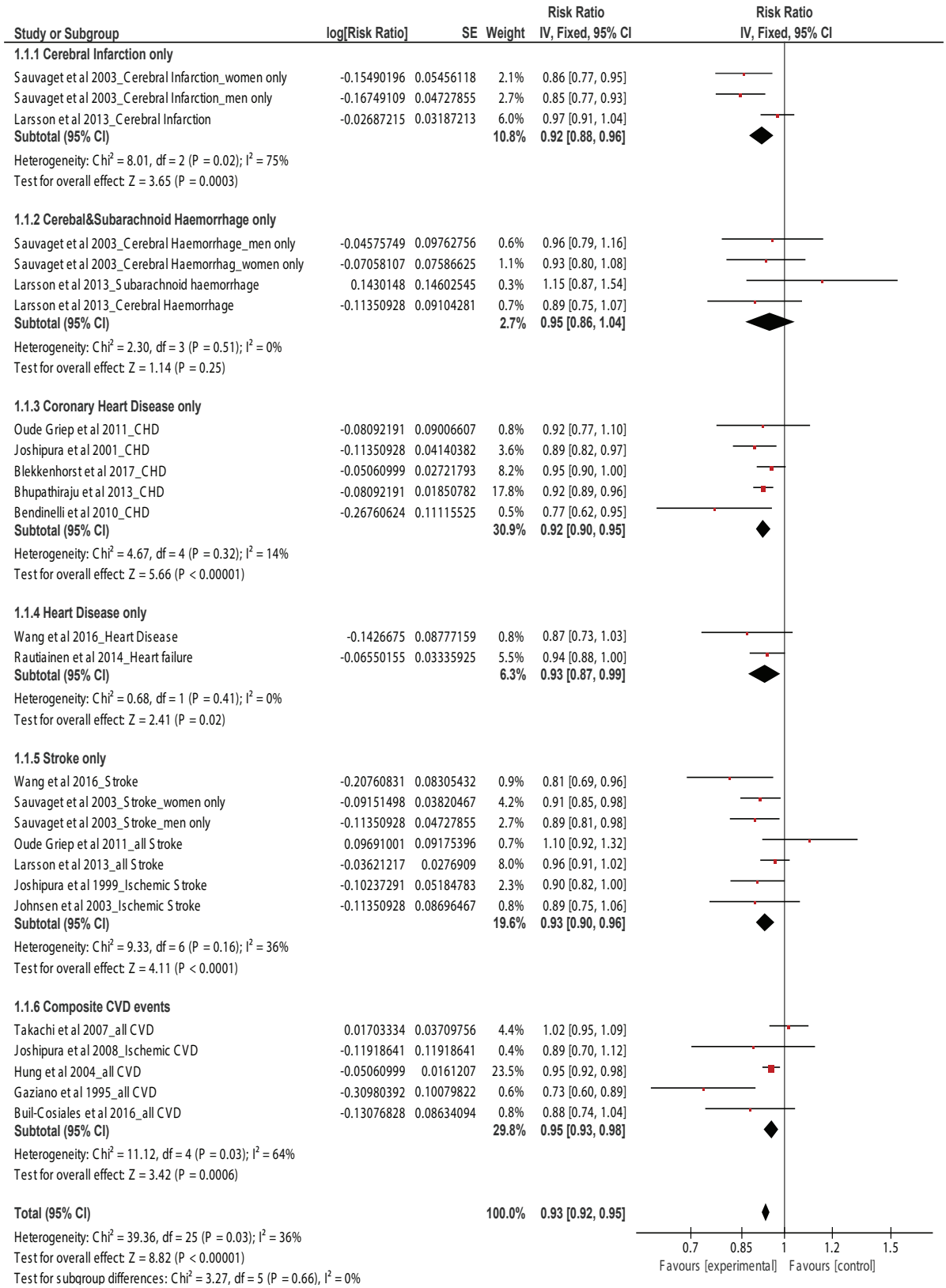

Fig. 2. Relative risk, 95% CI and *p*-value of incidence of all CVD events in the meta-analysis.

total energy intakes (and other dietary confounding factors) in the multivariate analysis of GLV and CVD outcomes.

More than half of the studies included in this report presented a low risk of bias (Table 2). In all, methodological assessment of included reports revealed no evidence of high risk of bias in most studies included in the meta-analysis.

Overall, higher intake of GLV (Fig. 2) was associated with reduced incidence of all CVD events by 7% (RR: 0.93; 95% CI: 0.92–0.95; $p < 0.00001$). Similarly, higher GLV intake was inversely related to the incidence of cerebral infarction (RR: 0.92; 95% CI: 0.88–0.96; $p = 0.0003$), CHD (RR: 0.92; 95% CI: 0.90–0.95; $p < 0.00001$), heart disease (RR: 0.93; 95% CI: 0.87–0.99; $p = 0.02$) and stroke (RR: 0.93; 95% CI: 0.90–0.96; $p < 0.0001$). The result remained unchanged after stratifying the studies by gender of respondents (Fig. 3A); men (RR: 0.92; 95% CI: 0.88–0.96; $p < 0.0001$) and women (RR: 0.92; 95% CI:

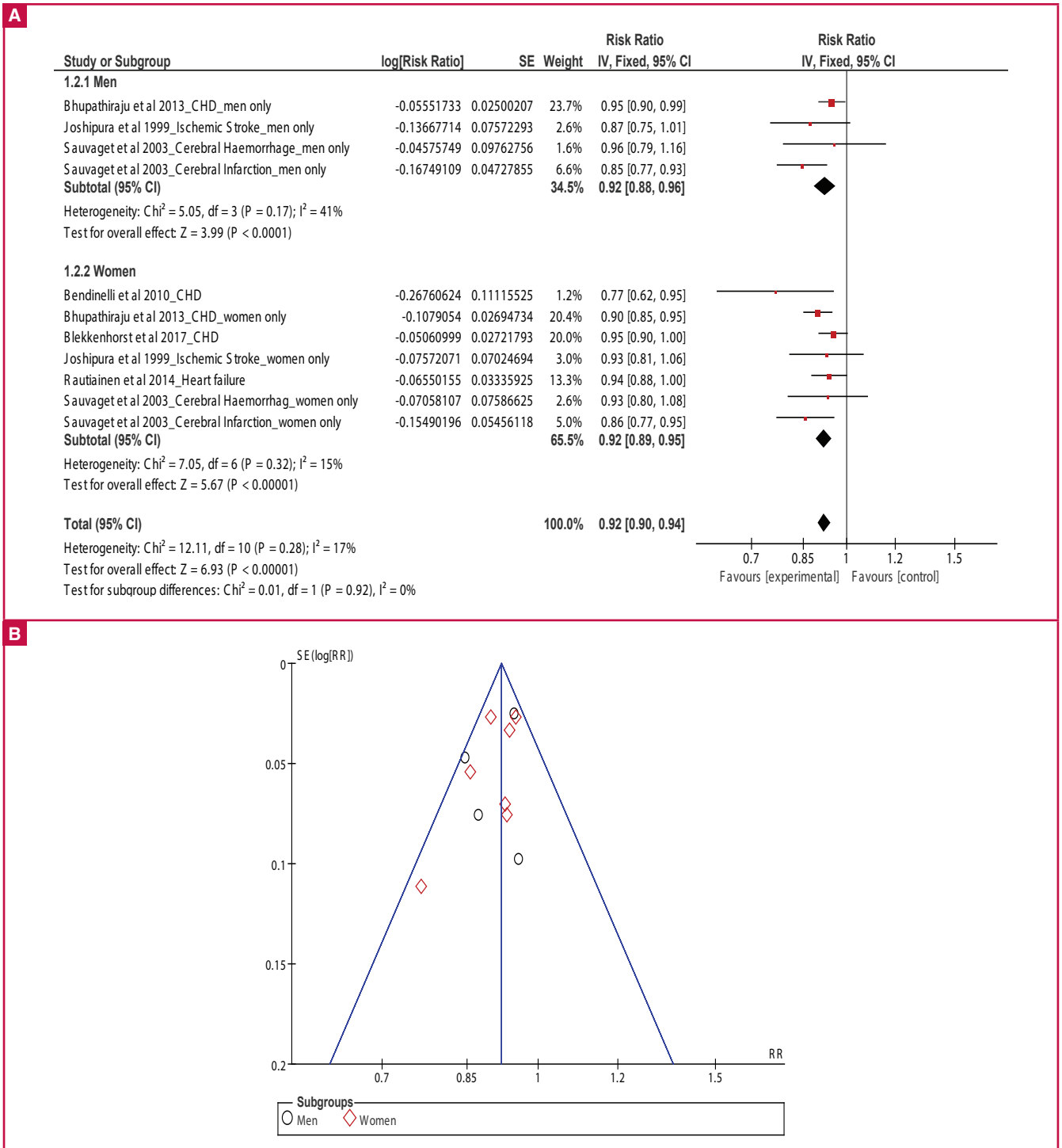

Fig. 3. Relative risk, 95% CI and *p*-value of incidence (A) and funnel plot (B) of all CVD events stratified by gender in the meta-analysis.

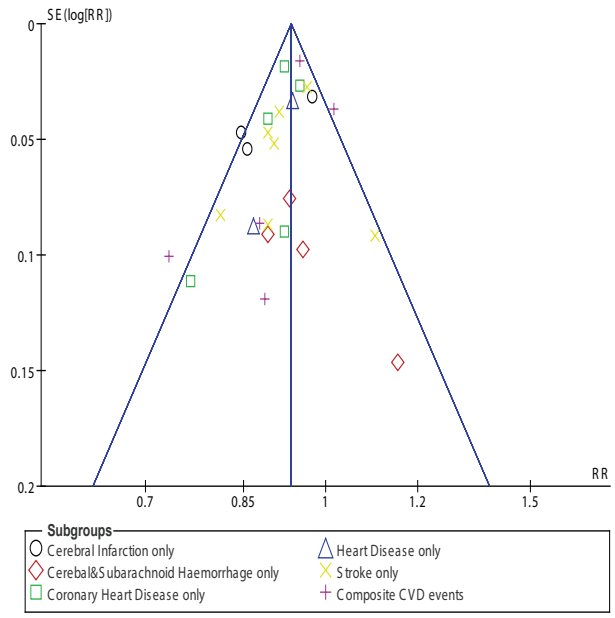

Fig. 4. Funnel plots assessing publication bias in the meta-analysis.

Table 3. Sensitivity analysis of pooled RR stratified by categories of CVD events in the meta-analysis

Studies in the meta-analysis	I^2 *(%)*	*Pooled RR (95% CI)*	p-*value*
All studies	36	0.93 (0.92–0.95)	< 0.00001
Cerebral infarction only	28	0.94 (0.92–0.95)	< 0.00001
Cerebal and subarachnoid haemorrhage only	43	0.93 (0.92–0.95)	< 0.00001
Coronary heart disease only	41	0.94 (0.92–0.96)	< 0.00001
Heart disease only	40	0.93 (0.92–0.95)	< 0.00001
Stroke only	40	0.93 (0.92–0.95)	< 0.00001
Composite CVD events	22	0.93 (0.91–0.94)	< 0.00001

0.89–0.95; $p < 0.00001$).

Statistical heterogeneity (Fig. 1) was low for studies on heart disease only ($I^2 = 0\%$), CHD only ($I^2 = 14\%$), and stroke only ($I^2 = 36\%$) but not among studies on cerebral infarction only ($I^2 = 75\%$).

Funnel plots (Figs 3B, 4) suggested no evidence of publication bias and no sole study exerted a significant effect on the sensitivity of the overall findings of the meta-analysis (Tables 3, 4).

Table 4. Sensitivity analysis of pooled RR of all cohort studies included in the meta-analysis

Studies in the meta-analysis	I^2 *(%)*	*Pooled RR (95% CI)*	p-*value*
Cerebral infarction only			
All studies	75	0.92 (0.88–0.96)	0.0003
Larsson *et al.* 2013_Cerebral infarction	0	0.85 (0.79–0.91)	< 0.00001
Sauvaget *et al.* 2003_Cerebral infarction_men only	76	0.94 (0.89–0.99)	0.03
Sauvaget *et al.* 2003_Cerebral infarction_women only	84	0.93 (0.88–0.98)	0.007
Cerebal and subarachnoid haemorrhage only			
All studies	0	0.95 (0.86–1.04)	0.25
Larsson *et al.* 2013_Cerebral haemorrhage	0	0.97 (0.87–1.08)	0.57
Larsson *et al.* 2013_Subarachnoid haemorrhage	0	0.93 (0.84–1.02)	0.12
Sauvaget *et al.* 2003_Cerebral haemorrhage_women only	0	0.96 (0.85–1.08)	0.48
Sauvaget *et al.* 2003_Cerebral haemorrhage_men only	13	0.95 (0.85–1.05)	0.30
Coronary heart disease only			
All studies	14	0.92 (0.90–0.95)	< 0.00001
Bendinelli *et al.* 2010_CHD	0	0.93 (0.90–0.95)	< 0.00001
Bhupathiraju *et al.* 2013_CHD	36	0.93 (0.89–0.97)	0.0003
Blekkenhorst *et al.* 2017_CHD	4	0.91 (0.88–0.94)	< 0.00001
Joshipura *et al.* 2001_CHD	23	0.93 (0.90–0.96)	< 0.00001
Oude Griep *et al.* 2011_CHD	36	0.92 (0.90–0.95)	< 0.00001
Heart disease only			
All studies	0	0.93 (0.87–0.99)	0.02
Rautiainen *et al.* 2014_Heart failure	–	0.87 (0.73–1.03)	0.10
Wang *et al.* 2016_Heart disease	–	0.94 (0.88–1.00)	0.05
Stroke only			
All studies	36	0.93 (0.90–0.96)	< 0.0001
Johnsen *et al.* 2003_Ischemic stroke	45	0.93 (0.90–0.97)	< 0.0001
Joshipura *et al.* 1999_Ischemic stroke	44	0.93 (0.90–0.97)	0.0003
Larsson *et al.* 2013_all stroke	22	0.91 (0.87–0.95)	< 0.0001
Oude Griep *et al.* 2011_all stroke	14	0.92 (0.89–0.96)	< 0.0001
Sauvaget *et al.* 2003_Stroke_men only	41	0.94 (0.90–0.97)	0.0005
Sauvaget *et al.* 2003_Stroke_women only	45	0.93 (0.90–0.97)	0.0007
Wang *et al.* 2016_Stroke	24	0.94 (0.90–0.97)	0.0003
Composite CVD events			
All studies	64	0.95 (0.93–0.98)	0.0006
Buil-Cosiales *et al.* 2016_all CVD	75	0.95 (0.93–0.98)	0.001
Gaziano *et al.* 1995_all CVD	30	0.96 (0.93–0.98)	0.003
Hung *et al.* 2004_all CVD	73	0.96 (0.90–1.02)	0.17
Joshipura *et al.* 2008_Ischemic CVD	72	0.95 (0.93–0.98)	0.0009
Takachi *et al.* 2007_all CVD	59	0.94 (0.91–0.97)	< 0.0001

Discussion

In this study, higher intake of GLV was linked to reduced incidence of all CVD events by 7% and, in particular, it was inversely related to the incidence of cerebral infarction, CHD, heart disease and stroke. These findings may suggest a potential role of GLV intake as a primary-prevention strategy in the management of CVD.

Similar to our findings, the largest study on stroke among Africans [the Stroke Investigative Research and Educational Network (SIREN) study] reported a strong protective dose–response association such that daily consumption of GLV was more protective against stroke [odds ratio (OR): 0.27; 95% CI: 0.19–0.38] than weekly consumption (OR: 0.70; 95% CI: 0.52–0.95), compared to no consumption.[52] Earlier systematic reviews and meta-analyses were broadly focused and generally combined fruit and vegetables in investigating the effect of these nutritional modalities on incident CVD events.[11,19,20,22,53-58] The uniqueness of our study is therefore in the deconstruction of the specific contribution of GLV on CVD. Also, our approach offered vital insights into the potential roles of GLV in the occurrence of CVD subtypes.

Although the exact mechanism of the protective effect of GLV is not well understood, some constituents of GLV are likely to confer small-to-moderate but clinically important protection against CVD.[25] For example, Vitamin B_9, micronutrients and other

constituents of GLV are known to promote optimal health and protect against several diseases.[29,59] The fibre component of GLV is also known for its cholesterol-lowering effects.[60] Similarly, folic acid (a constituent of GLV) intake is inversely associated with homocysteinaemia,[61,62] a known risk factor for atherosclerosis and ischaemic stroke.[63-65] Furthermore, micronutrients in GLV may promote cardiovascular integrity, haemostasis (Vitamin K content), neuronal transmission (calcium content), antioxidant activity (vitamins C and E content)[32,66] and vasodilatory effects (nitrates content).[67,68]

There are existing gaps in the literature on the effect of GLV on CVD outcomes not covered by the present systematic review and meta-analysis. For example, the mode of preparation and preservation of GLV on CVD outcomes remains unclear. Similarly, the underlying molecular mechanisms mediating the protective effect of GLV remains incomplete. These gaps in our understanding of the relationship between GLV and CVD could be the basis of future cohort studies and clinical trials.

Limitations, strengths and recommendations

GLV are not consumed singly in diets. Similarly, higher GLV consumption in the presence of exposure to traditional risk factors of CVD (such as smoking, alcohol intake, low physical activity) does not imply less CVD risk. Our study considered populations exposed to higher GLV intakes in their overall diet only, independent of the magnitude of consumption of other food items.

This systematic review and meta-analysis has other limitations. First, this meta-analysis did not investigate the relationship between GLV and CVD outcomes according to ethnic background and country of study due to the limited number of studies on the subject. Most studies were from the United States. There were limited studies from populations of African and Asian ancestry. This hindered us from performing subgroup analyses by region and ethnicity as indicated in the study protocol.

Second, there were methodological differences in the estimation of GLV intake among studies included in this systematic review and meta-analysis. However, these differences are likely insignificant given the consistent direction and strength of the relationship in our reported pooled-effect estimate after stratifying the meta-analysis across several subgroups. However, it is necessary to establish models that can uniformly quantitate GLV consumption across different populations.

Third, our search for grey literature was limited to informal requests for unpublished data and reports on the effect of GLV on CVD from local specialists in human nutritional research. This strategy did not result in the retrieval of additional primary data suitable for our meta-analysis objectives.

A key strength of our study is that it may be the first to summarise data on the association between GLV intake and not only incident CVD events in general but also subtypes of these outcomes.

Conclusion

Our meta-analysis demonstrated that a higher intake of GLV was associated with a lower incidence of CVD events, independent of subtypes of CVD manifestation. Promoting the consumption of GLV may be useful for the management and prevention of CVD. Also, dietary strategies that incorporate GLV consumption may be encouraged and promoted. Further studies are necessary to determine the underlying mechanism(s) and the significance of duration of exposure on the magnitude of the effect of GLV on CVD events. In particular, a future multicentre cohort study with uniform quantification of GLV consumption and duration between exposure and CVD events would be desirable to confirm these findings.

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'We've long known that a difference in blood pressure between the two arms is linked to poorer health outcomes. The large numbers involved in the INTERPRESS-IPD study help us to understand this in more detail. It tells us that the higher the difference in blood pressure between arms, the greater the cardiovascular risk, so it really is critical to measure both arms to establish which patients may be at significantly increased risk. Patients who require a blood pressure check should now expect that it's checked in both arms, at least once.'

Blood pressure rises and falls in a cycle with each pulse. It is measured in units of millimetres of mercury (mmHg), and the reading is always given as two numbers: the upper (systolic) reading represents the maximum blood pressure and the lower (diastolic) value is the minimum blood pressure. A high systolic blood pressure indicates hypertension. This affects one third of the adult population and is the single leading cause globally of preventable heart attacks, strokes and deaths. A significant difference between the systolic blood pressure measurements in the two arms could be indicative of a narrowing, or a stiffening, of the arteries, which can affect blood flow. These arterial changes are recognised as a further risk marker for subsequent heart attack, stroke or early death, and should be investigated for treatment.

The researchers concluded that each mmHg difference found between the two arms elevated predicted 10-year risk of one of the following occurring by one percent: new angina, a heart attack or stroke.

At the moment, both UK and European guidelines recognise a systolic difference of 15 mmHg or more between the two arms as the threshold indicative of additional cardiovascular risk. This study found that a lower threshold of 10 mmHg was clearly indicative of additional risk, which would mean that far more people should be considered for treatment if such a difference between arms is present. To this end, the research team has created a tool that is easy for clinicians to use, to establish who should be considered for treatment based on their risk, incorporating the blood pressure reading in both arms.

Research co-author Professor Victor Aboyans, head of the department of cardiology at the Dupuytren University Hospital in Limoges, France, said 'We believe that a 10-mmHg difference can now reasonably be regarded as an upper limit of normal for systolic inter-arm blood pressure, when both arms are measured in sequence during routine clinical appointments. This information should be incorporated into future guidelines and clinical practice in assessing cardiovascular risk. It would mean many more people were considered for treatment that could reduce their risk of heart attack, stroke and death.'

Source: Medical Brief 2020

Case Reports

Caseous calcification of the mitral annulus mimicking benign cardiac tumour of the mitral valve

Huanhuan Gao, Lei Yao, Yan Cheng, Chao Wu, Xiaoli Mei, Yun Mou, Lijun Jiang, Zhelan Zheng

Abstract

Caseous calcification of the mitral annulus (CCMA) is a rare subtype of mitral annular calcification. It usually appears as a large, round, mass-like calcification with an echolucent core, which may be misdiagnosed as an intracardiac mass, cyst, thrombus or abscess of the mitral valve.

We present a case report of CCMA that was misdiagnosed by echocardiography as a benign tumour due to its atypical imaging. The mitral valve mass was resected and it was pathologically confirmed to be a myxoid change with calcification.

Echocardiography is the preferred initial diagnostic tool. Myocardial contrast echocardiography (MCE) is used to evaluate the vascularity of intracardiac masses or mass-like lesions, but neither echocardiography nor MCE is reliable for identifying atypical lesions. Cardiac computed tomography is helpful in establishing a diagnosis by showing dense calcifications, while cardiac magnetic resonance imaging is used primarily as a credible tool. We therefore recommend that a diagnosis should be made based on various imaging modalities, if necessary, and operators should be skilled to avoid misdiagnosis.

Keywords: caseous calcification, mitral annulus, masses, case report

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Mitral annular calcification is a common echocardiographic finding in our daily work, and is considered chronic degeneration of the mitral valve fibrous ring, involving mainly the posterior leaflet of the annulus. Caseous calcification of the mitral annulus (CCMA) is a rare variant of mitral annular calcification, which tends to occur in the elderly, with female, hypertensive individuals and patients with chronic renal failure or calcium metabolism abnormalities being the most vulnerable.[1]

This disorder usually appears as a large, round, mass-like hyperechoic lesion that may cause diagnostic mistakes. We present a case of CCMA that was misdiagnosed by echocardiography as a benign tumour located in the base of the posterior leaflet of the mitral valve, accompanied by secondary mitral stenosis.

The study was approved by the Institutional Review Board at the First Affiliated Hospital, College of Medicine, Zhejiang University. The procedures were conducted according to the principles of the Helsinki Declaration. Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Case report

A 64-year-old Chinese female with a suspicious-looking tumour at the posterior leaflet of the mitral valve was referred to our hospital for further diagnosis. She had no chest pain or dyspnoea. The physical examination, electrocardiogram and chest X-ray were unremarkable. Her vital signs were normal with a heart rate of 94 beats/minute, a respiratory rate of 20 breaths/minute, a body temperature of 37°C and a blood pressure of 134/80 mmHg. No cardiac murmur or thrill was present. Initial laboratory tests, including serum creatinine (51 μmol/l), sodium (136 mmol/l), chlorinum (97 mmol/l), potassium (4.89 mmol/l), calcium (2.04 mmol/l) and magnesium (0.98 mmol/l) were all in the normal range.

Four years earlier, the patient underwent a routine echocardiography examination and a hyperechoic lesion in the posterior leaflet of the mitral valve was discovered (Fig. 1A). It was 15 × 9 × 8 mm with no significant mitral regurgitation or stenosis. On presentation, echocardiography revealed that the hyperechoic lesion had increased to 22 × 20 × 16 mm and was attached to the posterior leaflet of the mitral valve (Fig. 1B). It caused moderate mitral stenosis.

Myocardial contrast echocardiography (MCE) was further performed to evaluate the vascularity of the mass and it was found that it was a ring-enhancement mass with distinct borders (Fig. 2A). Quantitative analysis revealed that when compared to ventricle myocardium, the intensity of the mass was higher,

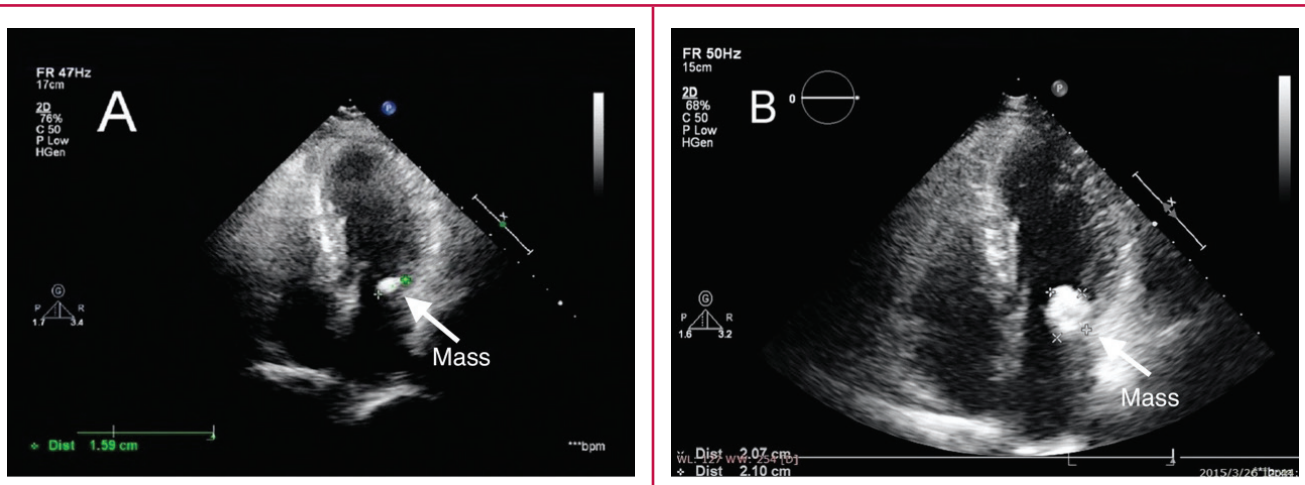

Fig. 1. Echocardiographic images revealing the progression of the lesion. A. The mass was first incidentally detected by echocardiography four years earlier. The small, strong echo was limited to the mitral annulus like a calcified plaque. The size was 15 × 9 × 8 mm. B. Echocardiographic image taken on admission to our hospital. Compared with the image four years earlier, the mass had enlarged to 22 × 20 × 16 mm, occupied the mitral valve orifice, and was accompanied by a secondary mitral stenosis.

which meant that the lesion had a greater microvascular blood volume (Fig. 2B). Based on its location, appearance and microperfusion, the diagnosis of a benign cardiac tumour (most probably papillary fibroelastoma) was made.

Surgery was performed and it showed that a solid, mixed cystic mass, originating from the posterior leaflet of the mitral valve, approximately 20 mm in length, protruded into the left atrium. The mitral valve mass was resected, while further intraoperative transoesophageal echocardiography revealed severe mitral regurgitation. An Edward bioprosthetic valve (25#) was imbedded. The patient's recovery was uneventful.

A postoperative pathological examination revealed that the mass was a mitral valve myxoid change with calcification (Fig. 3).

Discussion

CCMA, also called liquefaction necrosis,[2] is a rare type of mitral annular calcification that describes chronic degenerative changes of the cardiac fibrous skeleton, and mainly involves the area between the crest of the posterior left ventricular muscle and the posterior mitral annulus.[3,4] The elderly female population is the most vulnerable although no clinical significance has been found at present.[5,6]

CCMA comprises a calcified rim and surrounding caseous material that is composed of calcium, fatty acids and cholesterol, with a toothpaste-like texture. Under the microscope, the CCMA manifested as an amorphous, acellular, basophilic and calcific structure, with a chronic inflammatory response with macrophages as the most numerous cell type.[7] CCMA usually

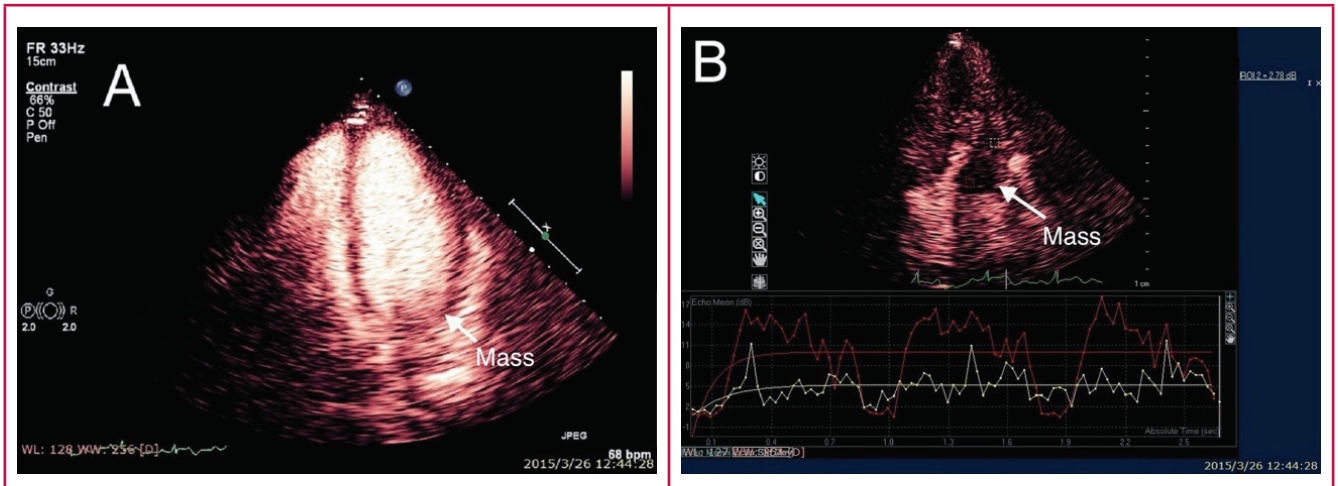

Fig. 2. Perfusion of the mass evaluated by myocardial contrast echocardiography. A. The image revealed a ring-enhancement mass with distinct borders that was attached to the posterior leaflet of the mitral valve. B. Quantitative analysis was performed, with a time–intensity curve obtained by the software attached to the equipment. The red line is the perfusion curve of the mass membrane above the yellow line, which is the perfusion curve of the normal myocardium. Compared with the surrounding normal ventricular myocardium, the mass represented a greater microvascular blood volume.

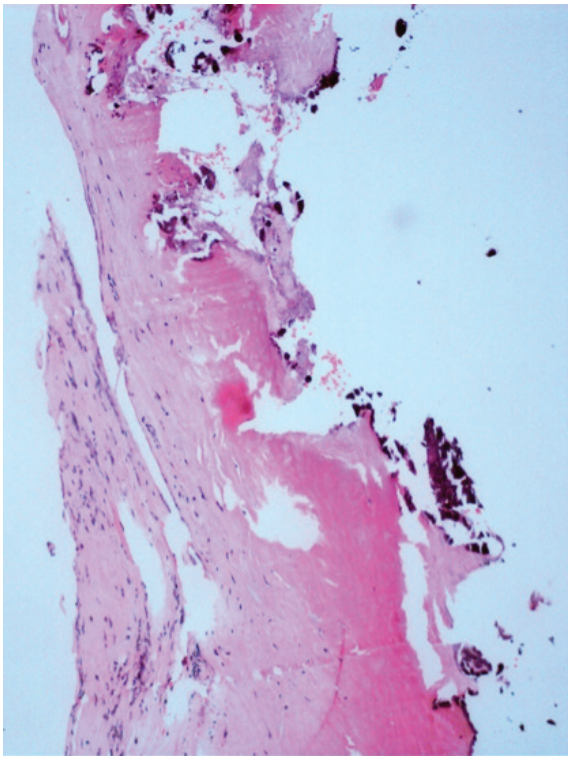

Fig. 3. Pathological examination of the resected tissue revealed hyperplasia of the tissue (mitral valve) with myxoid and calcific degeneration, and it also had some scattered chronic inflammatory cell infiltrate into the tissue.

behaves as a benign and asymptomatic lesion and is easily confused with other intracardiac masses, cysts, thrombus or abscess.

Under this condition, an association between the CCMA and a medical history of hypertension, chronic renal failure or haemodialysis, and abnormal calcium metabolism should be checked.[3] No related medical history was found in our patient, which was one of the reasons for the misdiagnosis.

Another reason that led to misdiagnosis may have been the relatively small size and atypical imaging of the mass. CCMA is usually large, round, calcified and enveloped in a echolucent core, typically located at the base of the posterior leaflet, and can be misdiagnosed as a cardiac tumour or abscess on echocardiography. The posterior leaflet becomes thickened, stretched and arched over the mass.

Secondary to these anatomical changes, mitral valve dysfunction (either stenosis or regurgitation) can be detected. Since the mass was mimicking a benign cardiac tumour that had increased in size and could not be differentiated from the degenerative valves and with significant valvular dysfunction, surgery was performed on the patient.

MCE may provide much more information about the location, border and perfusion of the CCMA, however no report has been published on the details. According to its pathological findings, the authors concluded that a ring-enhancement mass with a no-perfusion core should be detected by MCE. However, the present case did not seem to fit the characteristics.

The CCMA had a small volume and edge with abundant neovascularisation, which was misleading since the mass was vascular. Another potential contributing factor was the 'bleeding' effect, which means the blood of the surrounding left ventricular cavity was moving into the regions of interest as the mass was rapidly oscillating in and out of the imaging plane. We therefore suggest that when MCE is used to evaluate the vascularity of an intracardiac mass, operators need to be aware of these potential pitfalls.

Cardiac computed tomography (CT) and magnetic resonance imaging (MRI) also can be helpful in confirming or establishing diagnosis. Non-contrast CT showed a large calcified mass at the base of the posterior mitral annulus, extending to the adjacent mitral valve and myocardium.[6] On contrast-enhanced CT, the central part appeared less hypodense due to the caseous toothpaste-like material contained within the denser calcified peripheral rim.[8-10] MRI has shown low signal on both T1- and T2-weighted images due to calcification but was inferior in showing the calcification directly.[9]

Surgical intervention is not only the definitive treatment to remove the potential obstacle of obstruction or embolisation the mass brings about, but also a way to accurate diagnosis and therapy. Therefore our patient had the mass resected and the valve replaced. She is now in a good general condition and undergoing out-patient care with follow up and further management.

Conclusion

CCMA is an exceedingly rare valvular lesion with an excellent outcome following complete surgical removal. Histopathological findings of an amorphous, acellular, basophilic and calcific structure, with a chronic inflammatory response, is the gold standard for diagnosis. Although it was difficult to differentiate from other cardiac masses via echocardiography, diagnosis could be made based on combined imaging modalities. This incidental lesion may be encountered in clinical practice now and then, and cardiac imaging interpretation experts should be familiar with it in order to avoid misdiagnosis.

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Eating fish associated with significant health benefits: pooled analysis

There is a significant protective benefit of fish consumption in people with cardiovascular disease, as well as with significant improvements in multiple other health outcomes.

An umbrella review of meta-analyses found that increased fish consumption also improved rates of cardiovascular and all-cause mortality. However, fish consumption had no significant effects on rates of hypertension, atrial fibrillation, or type 2 diabetes.

Although not directly reflected in the findings, modest fish consumption also appears to be was associated with significant improvements in multiple health outcomes, including the risks for myocardial infarction, stroke and heart failure to have cardiac benefits, according to a *Journal of the American Medical Association* commentary.

Medscape Medical News reports that researchers Jayedi and Shab-Bidar examined 34 meta-analyses of prospective observational studies, which featured a total of 40 different outcomes. Greater fish consumption of 100 g/day was associated with significant improvements in multiple health outcomes, including the risks for myocardial infarction, stroke and heart failure.

Medscape Medical News comments that there is a lack of large studies that have differentiated the effects of fish consumption among adults with and without a history of cardiovascular disease (CVD). The current study addresses this gap.

People with CVD who regularly ate fish had significantly fewer major CVD events and there were fewer total deaths compared with similar individuals who did not eat fish, but there was no beneficial link from eating fish among the general population in prospective data collected from more than 191 000 people from 58 countries.

Despite the neutral finding among people without CVD, the finding that eating fish was associated with significant benefit for those with CVD or who were at high risk for CVD confirms the public health importance of regular fish or fish oil consumption, says one expert.

A little more than a quarter of those included in the new study had a history of CVD or were at high risk for CVD. In this subgroup of more than 51 000 people, those who consumed on average at least two servings of fish weekly (at least 175 g, or about 6.2 ounces per week) had a significant 16% lower rate of major CVD events during a median follow up of about 7.5 years.

The rate of all-cause death was a significant 18% lower among people who ate two or more fish portions weekly compared with those who did not, say Dr Deepa Mohan and associates. The researchers saw no additional benefit when people regularly ate greater amounts of fish.

'There is a significant protective benefit of fish consumption in people with cardiovascular disease,' summed up Dr Andrew Mente, a senior investigator on the study and an epidemiologist at McMaster University in Hamilton, Canada. 'This study has important implications for guidelines on fish intake globally. It indicates that increasing fish consumption, and particularly oily fish, in vascular patients may produce a modest cardiovascular benefit,' he said in a statement released by McMaster.

The neutral finding of no significant benefit (as well as no harm) regarding either CVD events or total mortality among people without CVD 'does not alter the large body of prior observational evidence supporting the cardiac benefits of fish intake in general populations,' notes Dr Dariush Mozaffarian, in a commentary that accompanies the report.

Although the new analysis failed to show a significant association between regular fish consumption and fewer CVD events for people without established CVD or CVD risk, 'based on the cumulative evidence from prospective observational studies, randomised clinical trials, and mechanistic and experimental studies, modest fish consumption appears to have some cardiac benefits,' he adds.

'Adults should aim to consume about two servings of fish per week, and larger benefits may accrue from non-fried oily (dark meat) fish,' writes Mozaffarian, a professor of medicine and nutrition at Tufts University School of Medicine, Boston, Massachusetts. Oily, dark fishes include salmon, tuna steak, mackerel, herring and sardines. Species such as these contain the highest levels of long-chain omega-3 fatty acids, eicosapentanoic and docosapentanoic acid; these nutrients likely underlie the CVD benefits from fish, Mozaffarian says.

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Prosthetic heart valve thrombosis in pregnancy: a case series on acute management

S Foolchand, H Ramnarain

Abstract

Rheumatic heart disease is one of the leading causes of valve dysfunction, resulting in prosthetic valve implantation. Changes in physiology and the haemodynamics of pregnancy increase the susceptibility of thrombosis to the prosthetic valve in the pregnant woman. Valve redo surgery carries a considerable risk of maternal and perinatal morbidity and mortality. Women of reproductive age should be well counselled regarding compliance with anticoagulation, contraception and pre-pregnancy planning.

Keywords: thrombosis, prosthetic valves, pregnancy, cardiac surgery, cardiopulmonary bypass pregnancy

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Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide,[1] and remains one of the top five causes of maternal death in South Africa.[2] Cardiac disease accounted for 34.3% of maternal deaths in the sub-category of medical and surgical conditions as a cause of maternal mortality in the Sixth Triennial report.[2] The burden of rheumatic heart disease and its sequelae contribute to a large proportion of women presenting with CVD in low- and middle-income countries (LMIC) such as South Africa.[1] The increased risk of heart failure secondary to valve degeneration may be abrogated by valve-replacement surgery,[1] resulting in a marked improvement of an individual's quality of life as well as life expectancy.[3]

Mechanical and biological prosthetic (bio) heart valves are used in replacement surgery depending on clinical presentation, preference of the patient and availability of the various types of prosthetic valves.[3] However, bio prosthetic valves often result in re-operation due to dysfunction, especially when implanted in younger patients.[3] Mechanical valve prostheses are more commonly used in South Africa. These operations are generally performed on younger women in the reproductive age group and the implications of surgery and especially the use of warfarin (an oral anticoagulant) and its potential problems associated with pregnancy are often poorly understood.

The use of warfarin is lifelong, which poses the risk of teratogenicity in pregnancy, particularly in the first trimester, and foetal wastage later in the pregnancy.[3,4] The use of unfractionated heparin is associated with adverse effects on the mother.[4] Reports also include the risk of postpartum haemorrhage at delivery in patients who have been anticoagulated.[5]

Cardiac surgical intervention in pregnancy historically carries a greater risk to both mother and foetus. A recent meta-analysis, assessing maternal and foetal outcomes after cardiac surgeries during pregnancy involving cardiopulmonary bypass (CPB), found the following in women: per 100 pregnancies, the pooled unadjusted estimate of maternal mortality was 11.2 (95% CI: 6.8–17.8), pregnancy loss was 33.1 (95% CI: 25.2–41.2), maternal complications were 8.8 (95% CI: 2.8–24.2) and neonatal complications were 10.8 (95% CI: 4.2–25.2).[6]

Thrombosis of prosthetic valves is a medical/surgical emergency and all healthcare workers attending to pregnant women with prosthetic valves should have a high index of suspicion for valve thrombosis and resultant valve dysfunction. It can be life-threatening and appropriate management reduces maternal and foetal adverse outcomes.[7] Pregnant women are at greater risk for valve thrombosis due to poor compliance secondary to risk of possible foetal affectation, poor knowledge of healthcare workers in counselling patients on the different anticoagulation regimes in pregnancy, resource limitations in terms of assessments and monitoring, poor access to healthcare, nausea and vomiting during pregnancy, and a reduction in fibrinolysis and anti-thrombin III, contributing to the prothrombotic nature of pregnancy.[5]

Open-heart surgery carries considerable risk, especially in early pregnancy.[8] Therefore, CVD is considered a significant non-obstetric cause of maternal mortality.[9] In resource-limited countries such as South Africa, the management of such patients is challenging due to the obstetric risks and complications of anticoagulant therapy.[9]

The following are six cases of pregnant patients on anticoagulant therapy with malfunctioning prosthetic mitral valves, seen during the period of a year at two tertiary institutions in KwaZulu-Natal, requiring emergent valve replacement.

Case reports

Patient 1

A 30-year-old patient, P3G4, presented at 15 weeks' gestation. She had a routine echocardiography, which revealed dysfunction of a single mitral leaflet. This was confirmed by fluoroscopy. The patient had defaulted on multiple follow-up appointments and obtained warfarin from her local clinic. She had utilised an

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intra-uterine contraceptive device for contraception, which was removed due to abnormal bleeding, and no further contraception was offered to the patient. She was discussed in a multi-disciplinary team (MDT) involving cardiothoracic surgery/cardiology/maternal–foetal medicine/high-risk obstetrics.

The patient elected to have a valve redo and a 25-mm ON-X valve was inserted. The patient recommenced oral anticoagulation after a period of intravenous heparin post operatively and the foetal heart was confirmed. She had an uneventful vaginal delivery of a 3-kg female neonate with good apgars.

Patient 2

A 20-year-old P0G1 presented at 21 weeks' gestation to her local hospital with a history of mitral valve prosthesis at age six years. She had defaulted on follow up at cardiology since 2017 and had stopped taking warfarin at least eight months previously. Screening of her valves confirmed that one leaflet was stuck. She was counselled in a MDT about valve redo surgery and the complications to her herself and the foetus.

At surgery, a thrombus and pannus were noted, which were impeding the valve leaflet movement. Her valve was replaced with a 25-mm ON-X prosthesis. She had an uneventful postoperative course and the foetal heart was confirmed on ultrasound pre- and post surgery. She went into spontaneous labour and delivered a 2.75-kg female with good apgars.

Patient 3

A 26-year-old primigravida was referred in active labour with hypertension and cardiac failure. Her warfarin was stopped by her local clinic mid-second trimester and the patient was not referred for tertiary care. The patient rapidly progressed and delivered vaginally. Valve screening showed suspicion of a stuck valve. She was assessed by the MDT and counselled for an emergent redo valve surgery.

The intra-operative findings included the mitral valve leaflet stuck in an open position with thrombus formation around the valve hinge. The valve was replaced with a 25-mm ON-X prosthetic valve. She recovered well post operation and was discharged to her referral centre for follow up, with counselling on contraception, compliance with anticoagulation therapy and pre-pregnancy assessment should she contemplate future pregnancies.

Patient 4

A 24-year-old patient, P1G2, presented with an anembryonic pregnancy. She had had a previous stillbirth at 28 weeks' gestation, most likely due to warfarin exposure. Screening of her valves revealed a stuck mitral valve leaflet.

The patient agreed to a suction curettage and valve-redo surgery. On day seven post evacuation, she had her mitral valve explanted and replaced with a 27/29-mm ON-X mechanical prosthesis as the mitral valve prosthesis was thrombosed with a large clot on both the left atrial and ventricle sides. The aortic valve was inspected and found to be incompetent and a 21-mm ON-X mechanical aortic prosthesis was implanted. The patient had an uneventful recovery and was counselled on compliance, contraception and booking at the pre-pregnancy clinic when planning her next pregnancy.

Patient 5

A 19-year-old primigravida in her first pregnancy presented to cardiology with a stuck mitral valve and poor compliance with warfarin. She was counselled and admitted for intravenous heparin and review by cardiothoracic surgery for possible mitral valve-redo surgery.

At surgery, the mitral valve leaflet was seen to be thrombosed at the hinge. She had her mitral valve prosthesis replaced with a 27/29-mm ON-X prosthesis and her native aortic valve replaced with a 21-mm ON-X mechanical valve due to severe aortic valve disease. She made an uneventful postoperative recovery.

The high-risk obstetrics unit was consulted immediately post operation as there was now a suspicion that she was pregnant. Subsequent ultrasound assessment revealed an 18-week intra-uterine gestation with an absent foetal heart pulsation. She was counselled and had a termination of pregnancy with misoprostol. The patient was counselled on contraception and the importance of a pre-pregnancy planning for the future. She was returned to the care of the cardiothoracic team.

Patient 6

A 27-year-old patient, P2G3, was referred at 29 weeks' gestation. She had a history of poor compliance. Although asymptomatic, screening revealed a stuck mitral valve leaflet. She was extensively counselled by a MDT and consented to valve-redo surgery.

The patient had her mitral valve prosthesis redone with the foetus *in utero*. At surgery the leaflet was noted to be thrombosed and the valve was replaced with a 27/29-mm ON-X mechanical prosthetic valve. The patient did not consent to foetal monitoring during surgery and an intra-uterine foetal death was noted post procedure. She underwent induction while still on intravenous heparin and delivered a 1.2-kg stillbirth vaginally. She was bridged onto oral anticoagulation and discharged via the cardiothoracic ward on optimal oral anticoagulation and contraception.

Discussion

The cases outlined above reinforce the areas of concern in the management of pregnant women with cardiac prosthetic valves. Maternal mortality as a result of valve thrombosis ranges between two and 15%, even on heparin therapy.[8] Pregnant women are at increased risk for valve thrombosis, which may be exacerbated by the physiological changes of pregnancy.[8]

Pregnancy is a hypercoagulable state due to the increase in factors VII, VIII and X.[7] The formation of a thrombus or pannus at the valve impacts on its functionality, leading to stenosis or regurgitation.[10] Management of patients with thromboses is complex due to the risk of perinatal morbidity and mortality. Poor compliance and follow up contributed significantly to the presentation of the above patients. Compliance failure is a well-known problem to all healthcare workers in our country and reasons include lack of insight into the need for anticoagulation, poor follow up, the reluctance or failure of medical professionals outside of obstetrics and gynaecology to actively advocate contraceptive use in women of reproductive age, lack of resources and knowledge regarding the management of anticoagulation in pregnancy, as well as financial constraints on the part of the patient.

The use of subcutaneous low-molecular weight heparin in pregnant women with mechanical prosthetic valves without meticulous anti-Xa monitoring is not an option and cannot be emphasised enough. The administration of anticoagulants and thrombolytic agents during pregnancy increases the risk of sub-placental bleeding and embolism.[8]

The index of suspicion for valve thrombosis must be high for all pregnant women with mechanical heart valves. Patients may present with worsening dyspnoea, palpitations or cardiac failure, new murmurs, and new symptoms of cardiac or respiratory compromise.

A detailed clinical examination and transthoracic echocardiography (TTE) should be the basic assessment for all pregnant women with mechanical prosthetic valves,[11] irrespective of symptoms, as some may be asymptomatic, similar to our second patient. TTE should be the imaging used as first line, as a normal prosthetic heart valve function seen on TTE is reassuring.

The echocardiographic signs of obstructive valve thrombosis include reduced valve mobility, presence of thrombus, abnormal trans-prosthetic flow, central prosthetic regurgitation, elevated trans-prosthetic gradients, and reduced effective prosthetic area (as seen in patient 2).[12] The 2017 guidelines from the American Heart Association recommends urgent multimodality imaging in patients with suspected mechanical heart valve thrombosis to assess valvar function, leaflet motility and the presence and extent of thrombus.

Surgery is considered in the presence of a thrombus.[7] CPB surgery has implications for both the patient and her foetus. Surgery carries a risk of up to 30% for foetal mortality. Over the years, techniques have been introduced to decrease the risk to the foetus, such as avoiding hypothermia during bypass,[13] maintenance of a high flow rate (> 2.5 l/min/m^2), mean arterial pressure > 70–75 mmHg,[14] maintenance of the haematocrit above 28%, avoiding maternal hypoglycaemia and hypoxia, as well as by placing the patient in the left lateral recumbent position during CPB to avoid inferior vena cava compression by the uterus.[15,16]

Pulsatile flow has been suggested as being more beneficial in pregnant women than in non-pregnant women as it decreases vasoconstriction (in foetal lamb studies) by decreasing the activation of the foetal renin–angiotensin–aldosterone axis, which may reduce uterine contractions.[17] CPB can induce uterine contractions, especially during the cooling and rewarming phases.[18]

In the above case series, the patients were assessed, managed and counselled for valve-redo surgery, which was carried out successfully. The implications for both the mother and foetus were also discussed as surgical mortality rates are between five and 36%.[19] Therefore, the prosthetic type, and imaging and surgical risks (co-morbidities, age) are considered.[19] Follow up is imperative after prosthetic heart valve-replacement surgery.[20]

Conclusion

Women of reproductive age with prosthetic valves should be counselled adequately for potential risks. Prosthetic valve dysfunction in pregnancy increases the risk of adverse outcomes for both mother and foetus. Therefore, careful management is warranted to ensure positive outcomes and improvement in quality of life.

Clinicians taking care of reproductive-age women should enquire on a menstrual history and fertility desires. Patients with medical or surgical disorders should be referred for pre-pregnancy counselling and assessment. All women with mechanical prosthetic cardiac valves should be counselled on the various anticoagulant regimes available, with advantages and disadvantages discussed in detail, preferably prior to stopping contraception or planning a pregnancy. The options should include oral anticoagulants, unfractionated heparin or low-molecular weight heparin. Pregnant women with mitral valve prostheses should have a detailed history/examination and a TTE at the first antenatal consultation. The frequency of TTE depends on symptoms and available resources.

These women should also be managed in a tertiary institution. There should be a high index of suspicion for valve dysfunction. Those with a suspicion of valve malfunction should be urgently seen by a MDT consisting of cardiology/cardiothoracic/high-risk obstetrics/neonatology (if relevant) and anaesthetics. Patients requiring urgent valve-redo surgery should be counselled extensively on the surgery and possible foetal and maternal outcomes. Measures to decrease foetal loss at CPB should be instituted in all pregnant women.

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'Fish oil lowers heart rate, blood pressure and triglycerides (at high dosages), increases adiponectin, improves endothelial function, and in some studies improves oxygen consumption in myocardium. If there is benefit from fish, it's from the omega-3s, and all in all the evidence supports this,' but because the evidence is primarily observational, it can only show linkage and cannot prove causation, he explains.

Given the potential benefit and limited risk: 'I think everyone should aim to eat two servings of fish each week, preferentially oily fish. That's very solid,' says Mozaffarian, who is also a cardiologist and dean of the Gerald J and Dorothy R Friedman School of Nutrition Science and Policy, Boston, Massachusetts. The investigators did not have adequate data to compare the associations between outcomes and a diet with oily fish versus less oily fish.

For people who either can't consume two fish meals a week or want to ensure their omega-3 intake is adequate, 'it's very reasonable for the average person to take one [over-the-counter] fish oil capsule a day,' Mozaffarian adds.

He acknowledges that several studies of fish-oil supplements failed to show benefit, but several others have. 'It's a confusing field, but the evidence supports benefit from omega-3s,' he concludes.

He discounts the new finding that only people with established CVD or who are at high risk benefit. ''m not sure we should make too much of this, because many prior studies showed a lower CVD risk in fish-eating people without prevalent CVD,' he said. The new study 'provides important information, given its worldwide breadth,' he added.

The new report used data regarding 191 558 people enrolled prospectively in any of four studies. The average age of the participants was 54 years, and 52% were women.

During follow up, death from any cause occurred in 6% of those without CVD or CVD risk and in 13% of those with these factors. Major CVD events occurred in 5 and 17% of these two subgroups, respectively. To calculate the relative risks between those who ate fish and those who did not, the investigators used standard multivariate adjustment for potential confounders and adjusted for several dietary variables, Mente says.

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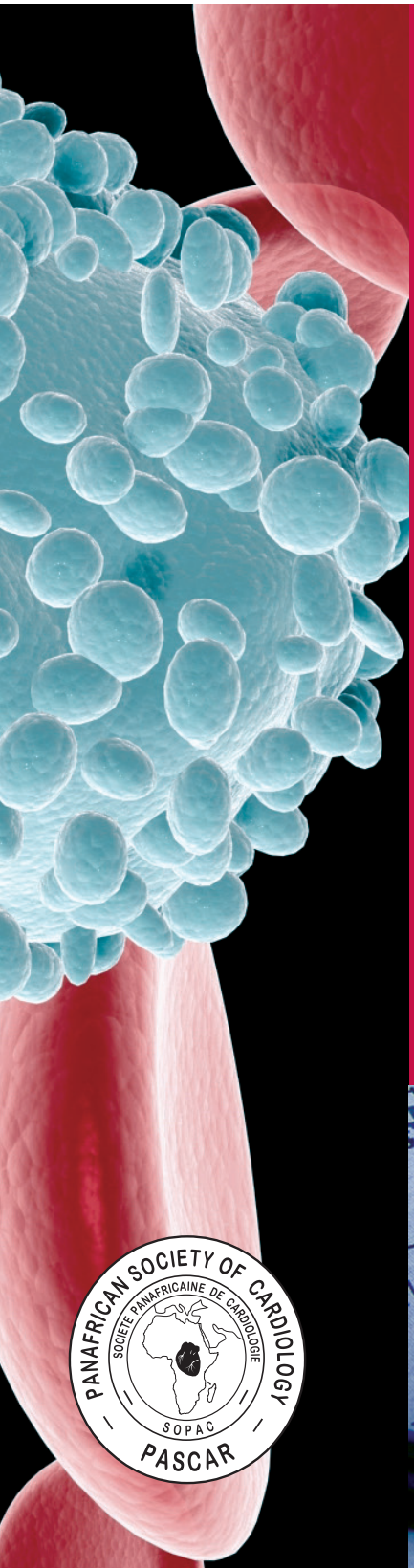

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