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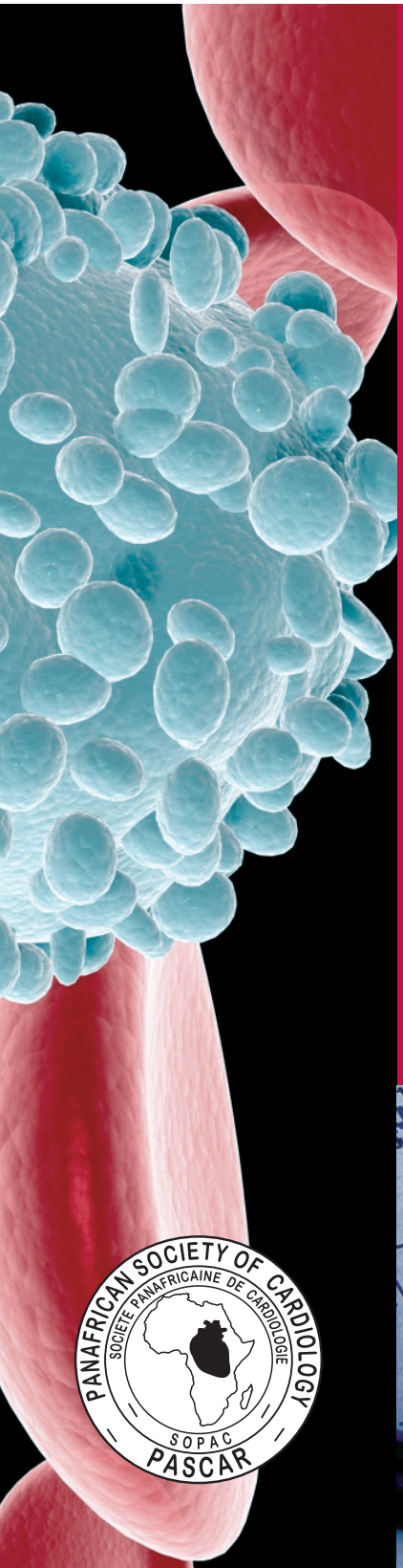

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CASE REPORT

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From the Editor's Desk

What cardiology training and cardiac procedural training does Africa need?

In a letter to the editor, Bonny and co-authors (page 3) offer an appraisal of an article recently published in the *Journal of the American College of Cardiology* (JACC), which describes the feasibility and effectiveness of a proctorship-based approach to the development of African cardiac pacing capabilities, arguing that three missions (median seven days' duration) enrolling 10 to 15 patients were able to efficiently train local teams. The authors of the letter to the *Cardiovascular Journal of Africa* are all experienced cardiologists, knowledgeable in pacing and electrophysiology and, most importantly, they have first-hand experience of the reality of medical and cardiac care in many diverse regions of Africa. They are critical of the content and conclusions of the JACC article. In particular, they do not believe that the training described in the JACC article is adequate. The matter is important and needs further discussion.

There can be no argument that pacemaker implantation for patients with symptomatic (and some asymptomatic) bradyarrhythmias is a most important management tool and should be available for all patients with these conditions. Unfortunately it is not generally available in many parts of Africa. Bonny and colleagues have been involved over several years in ensuring that the admittedly unsatisfactory situation in much of Africa with regard to cardiac pacing be improved. Their letter sets out the details of their efforts and in due course I am sure they will report on the success or otherwise of the project. They are critical of what they consider to be offered in the JACC article to correct the situation. They consider it clinically sub-standard and that it does not meet acceptable international or African standards.

There can be no doubt that the care of patients with heart disease in most of Africa, including its most wealthy countries (except for the lucky few who can afford medical insurance), leaves much to be desired. How do we correct this? Bonny and co-authors point out that training in Africa needs to meet the highest possible standards and we should not 'cut corners' simply because there is nothing else available. We should always be grateful for the help and mentorship received from other countries but never compromise our standards in accepting such help.

My perception is that sometimes we in Africa are prepared to accept a glass half full because the full glass seems too far away. The letter from Bonny and colleagues should be a clarion call to strive for the best solution for our patients and trainees and not to accept second best because that is all that is available. I would welcome input by means of letters or full articles and opinion pieces on this matter, which I consider important.

Pat Commerford
Editor-in-Chief

Letter to the Editor

Cardiac pacing in sub-Saharan Africa

Aimé Bonny, Olujimi A Ajijola, Mohamed Jeilan, Mahmoud Sani, Zaheer Yousef, Matthew F Yuyun, Kamilu Karaye, Mervat Aboulmaaty Nahib, Yazid Aoudia, Loreen Akinyi, Marcus Ngantcha, Saad Subahi, Felix Sogade, Ashley Chin

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We read with interest the report by Jouven *et al*. describing the feasibility and effectiveness of a proctorship-based approach to the development of African cardiac pacing capabilities, arguing that three missions (median seven days) enrolling 10 to 15 patients were able to efficiently train local teams.[1]

The ACC/AHA/HRS has published minimum standards for pacemaker training, which this on-site training approach does not meet for proficiency in pacing.[2] We wonder whether this 'Africa-Pace team' was able to offer comparable training with such limited exposure (30–45 procedures, assuming that the

first implantations were likely observerships) within 21 training days over three years. Careful follow up and troubleshooting of implanted pacemakers appear to be lacking or done remotely from another country, which is not ideal. Implanters are also likely to have an erosion of skills with the infrequent bursts of pacing.

Our recent reports on cardiac arrhythmia services in Africa incorporated most of the 14 countries mentioned in this article and include a survey on training.[3,4] No operator reported training through 'Africa-Pace team' missions. For instance, Dr Ikama, featured in the article, was trained in France. Likewise, Niger is included among 11 countries where cardiac pacing was initiated through the mission. Yet, Niger is one of the 20% of African countries without pacemaker activity.[3] Neither Niger (no existing activity) nor Guinea Conakry (only one mission in 2014) should have been included in this report.

The Pan-African Society of Cardiology (PASCAR) fellowship started in 2016 and has trained pacemaker implanters from three countries at Groote Schuur Hospital in Cape Town through an intense six-month hands-on programme of device implantation and follow up for doctors and technologists.[5] Subsequent on-site proctorship when the implanter returns to his country is mandated.

A French-speaking pacing curriculum has been launched in Dakar (Senegal) since 2017. Over 18 months, fellows must perform 25 and 25 implantations as second- and first-hand operator, respectively, with 100 device follow ups. The College of Medicine of South Africa requires at least 30 and 10 single- and dual-chamber pacemakers, respectively, as first implanter.

We therefore believe that episodic mission-based on-site training is not a model to be recommended. This article[1] may be misleading, as the situation on the ground does not reflect its general message.

African populations need to be treated by well-trained specialists. The message, aiming to maintain Africa outside this standard of care, is devastating. Humanitarian missions are welcomed in Africa but provide a mechanism to support comprehensive training initiatives, which cannot replace conventional curricula. Therefore, the misconceptions conveyed by this article in the long term should be taken into account.

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Cardiovascular Topics

A cross-sectional cohort study with microvascular complications in patients with type 2 diabetes with and without hypothyroidism

Louise Johnson, Brian Rayner

Abstract

Objectives: Previous reports have suggested an association between hypothyroidism and macrovascular complications in type 2 diabetes (T2DM) but the association with microvascular complications is not well documented. This study aimed to determine whether there were significant differences in these complications in patients with T2DM with and without hypothyroidism.

Methods: This was a retrospective, cross-sectional, case–control study from a single centre specialising in diabetes in South Africa. T2DM was defined by American Diabetes Association criteria. The cases were all patients treated for hypothyroidism and the controls were clinically and biochemically confirmed euthyroid, who were under follow up between 1 January and 1 July 2016. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of < 60 ml/min, determined by the CKD-epidemiology collaboration equation (CKD-EPI) and/or albumin/creatinine ratio > 3 mg/mmol. Diabetic retinopathy (DR) was defined as the presence of aneurysms, bleeds, exudates and new vessel formation on the retina examined by an ophthalmologist. Diabetic peripheral neuropathy (DPN) was defined as the presence of symptoms, loss of 128-Hz sensation and abnormal 10-gm monofilament. Cardiovascular disease (CVD) was defined as the presence of major adverse cardiovascular events (MACE).

Results: There were 148 cases and 162 controls. Compared to the controls, the cases were older (65.6 vs 59.4 years, $p < 0.00001$), more likely to be female (67.6 vs 39.5%, $p < 0.0001$) and white (89.2 vs 79.6%, $p = 0.02$), have a lower HbA_{1c} level (7.5 vs 8.2%, $p = 0.0001$), eGFR (64.4 vs 72.7 ml/min, $p = 0.0006$) and triglyceride level (2.18 vs 2.55 mmol/l, $p = 0.04$), have a higher high-density lipoprotein cholesterol level (1.13 vs 1.02 mmol/l, $p = 0.001$), a longer duration of diabetes (14.8 vs 11.6 years, $p = 0.001$) and using fewer antidiabetic agents (1.82 vs 2.19, $p = 0.001$). There was a higher prevalence of CKD (44 vs 57.8%, $p = 0.03$) and CVD (59.3 vs 45.3, $p = 0.06$), and a trend towards higher DR (66.7 vs 47.6, $p = 0.09$). There was no difference in body mass index, hypertension, low-density lipoprotein cholesterol level (all patients received statin therapy), DPN and amputations. After adjusting for confounding factors, there was no association between CKD and DR, and hypothyroidism, but the trend to association with CVD persisted (OR 1.97. $p = 0.07$).

Conclusions: Hypothyroidism in T2DM was not associated with microvascular disease after adjusting for confounding factors. There was a nearly two-fold risk of CVD. The study is limited by the retrospective and observational design.

Keywords: hypothyroidism, type 2 diabetes, microvascular and macrovascular complications

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The National Health and Nutritional Examination Survey III showed a prevalence of overt and subclinical hypothyroidism (SCH) of 0.3 and 4.3%, respectively.[1] Insulin resistance, type 2 diabetes mellitus (T2DM) and hypothyroidism are reported to occur more commonly than by chance, although the exact aetiology is uncertain.[2] Both T2DM and hypothyroidism are associated with cardiovascular disease (CVD), often through complex mechanisms, and the concurrence of hypothyroidism and diabetes may further amplify endothelial dysfunction, insulin resistance, poorer diabetic control and microvascular complications.[3]

In a systematic review and meta-analysis of SCH in T2DM, the prevalence was 10.2%, and T2DM was associated with a 1.93-fold increase in risk for SCH. Furthermore, SCH was associated with an overall odds ratio of 1.74 for diabetic nephropathy, 1.42 for diabetic retinopathy (DR), 1.85 for peripheral arterial disease, and 1.87 for diabetic peripheral neuropathy (DPN).[4] However data from individual studies have not always been consistent with these associations.[5,6]

Given the paucity of data and the contradictory findings of studies, we aimed to investigate the association of T2DM and hypothyroidism with micro- and macrovascular complications in South Africa.

Methods

This was a retrospective, observational, cross-sectional study of patients with T2DM performed in a large private practice

specialising in diabetes. The cases were all patients treated for hypothyroidism including those with SCH, and the controls were clinically and biochemically confirmed euthyroid under follow up between 1 January and 1 July 2016. The aim of the study was to compare the prevalence and severity of micro- and macrovascular complications, and indices of glycaemic control between the cases and controls.

Diabetic kidney disease (DKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min determined by the CKD-epidemiology collaboration equation (CKD-EPI) and/or a urine albumin/creatinine ratio (ACR) > 3 mg/mmol in the absence of other causes of kidney disease. DR was defined as the presence of aneurysms, bleeds, exudates and new vessel formation on retinal examined by an ophthalmologist; DPN as the presence of symptoms, loss of 128-Hz sensation and/or abnormal 10-gm monofilament; and CVD as the presence of major adverse cardiovascular events (MACE: coronary angioplasty, stent, coronary artery bypass grafting, myocardial infarction or cerebrovascular accident) and amputation (surgical removal of any part of a lower limb due to diabetic causes).

SCH was defined as a thyroid stimulating hormone (TSH) level >4 mIU/l with a normal T4 and T3 level, and overt hypothyroidism as a T4 less than the normal range (7.6–16.1 pmol/l) and TSH > 4 mIU/l. Thyroxine was given to all cases to maintain the T4 and TSH level within the normal range. Diabetes was defined according to the American Diabetes Association criteria.[7] Cases were excluded if they were receiving amiodarone or lithium, or had had previous thyroid surgery or ablation therapy.

The study was approved by the University of Cape Town, Research Ethics Committee (331/2017).

Statistical analysis

Descriptive statistics were used to summarise total cohort characteristics. For purposes of analysis, the cohort was divided into black (Africans) and non-black (whites and other race groups). Median with interquartile range was used to summarise continuous variables, and frequency and percentages were used to summarise categorical variables. Differences in continuous variables between cases and control patients were compared using a Wilcoxon rank sum test, while categorical variables were compared using Pearson chi-squared test or Fisher's exact test.

Table 1. Demographics of the total group, cases and controls

Variable	*Total group* (n = *310*)	*Controls* (n = *162*)	*Cases* (n = *148*)	p-*value*
Age (years)	62 (54–71)	58 (52–67)	65 (58–75)	< 0.001
Gender, male (%)	146 (47.1)	98 (60.5)	48 (32.4)	< 0.001
Race, non-black (%)	261 (84.2)	129 (79.6)	132 (89.2)	0.021
Duration of T2DM (years)	11 (7–18)	10 (5–16)	13 (9–19)	0.001
BMI (kg/m^2)	34 (30–41)	34 (29–40)	34 (30–41)	0.370
HbA_{1c} (%)	7.4 (6.3–9.1)	8.0 (6.7–9.6)	6.9 (6.1–8.7)	< 0.001
TSH (mIU/ml)	1.6 (1.0–2.5)	1.6 (1.2–2.2)	1.6 (0.8–3.1)	0.973
T4 (pmol/l)	12.3 (11.–15)	12.0 (10–13)	13.1 (11–16.5)	0.004
Total cholesterol (mmol/l)	4.5 (3.7–5.4)	4.5 (3.7–5.4)	4.4 (3.7–5.3)	0.776
Triglycerides (mmol/l)	2.0 (1.3–2.8)	2.1 (1.4–3.2)	1.9 (1.3–2.6)	0.034
HDL-C (mmol/l)	1.0 (0.9–1.2)	1 (0.8–1.1)	1.1 (0.9–1.3)	0.001
LDL-C (mmol/l)	2.6 (2.0–3.2)	2.7 (1.9–3.3)	2.5 (2.0–3.2)	0.766
eGFR (ml/mim)	71 (55–88)	75 (58–90)	66 (52–82)	0.001
Urine ACR (mgm/mmol)	1.8 (0.7–4.9)	1.6 (0.7–5.2)	2.0 (0.8–4.9)	0.717

Logistic regression was used to determine associations, magnitude and direction between the dichotomous T2DM outcomes (DKD, CVD, DPN and retinopathy) and hypothyroidism, adjusted for *a priori* selection of confounders and covariates. Highly skewed continuous variables were log transformed prior to entering into the model. Linear regression was used to assess associations between eGFR and *a priori* selection of covariates. Goodness-of-fit and influential observations were assessed after fitting each model. All analyses were performed using Stata software (Version 14.2, Stat Corp, College Station, TX).

Results

We identified 310 subjects, of whom 162 were controls and 148 were cases. All the hypothyroid cases were receiving thyroxine. The overall demographics of the population are shown in Table 1. The ethnic breakdown was predominantly white (84%), black (13%) and other races (3%), and hypertension was present in 83% of the hypothyroid group and 79% of the controls.

There were significant differences in the baseline characteristics between the two groups. There were more females in the hypothyroid group (60.8 vs 39.2%, $p = 0.001$) and fewer blacks (10.8 vs 21.4%, $p = 0.021$) compared to controls. In addition the mean age of the patients with hypothyroidism and duration of diabetes was 65 vs 58 years ($p < 0.001$) and 13 vs 10 years ($p = 0.001$), respectively. T4 levels were slightly higher in the cases (12 vs 13.1 pmol/l, $p = 0.004$), but there was no difference in TSH level.

In respect of diabetic control, the cases had better glycated haemoglobin (HbA_{1c}) levels (6.9 vs 8%, $p < 0.001$) and used fewer hypoglycaemic medications ($p = 0.001$) (Table 2). There were differences in use of hypoglycaemic agents with more patients in the control group receiving dipeptidyl peptidase-4 (DPP4) inhibitors (40.1 vs 26.4%, $p = 0.04$), incretin mimetics (GLP agonists) (13 vs 6.1%, $p = 0.01$), and a trend towards more insulin use (51.9 vs 41.9. $p = 0.08$). There were no significant differences in the use of metformin and sulphonylureas.

Regarding components of the metabolic syndrome, waist circumference was not available, but in the cases, high-density lipoprotein (HDL) cholesterol was significantly higher (1.1 vs 1 mmol/l, $p = 0.001$) and triglyceride levels were significantly lower (1.9 vs 2.1 mmol/l, $p = 0.034$). There was no difference in low-density lipoprotein (LDL) cholesterol, but all subjects received statin therapy unless contra-indicated.

Microvascular complications tended to occur more frequently in the hypothyroid group. The eGFR was significantly lower in

Table 2. Use of hypoglycaemic drugs in total group, cases and controls

No. of hypoglycaemic drugs, n *(%)*	*Overall*	*Controls*	*Cases*	p-*value*
1	101 (32.6)	38 (23.5)	63 (42.6)	0.001
2	122 (39.4)	66 (40.7)	56 (37.8)	
3	67 (21.6)	46 (28.4)	21 (14.2)	
4	20 (6.5)	12 (7.4)	8 (5.4)	
Metformin, *n* (%)	254 (81.9)	135 (83.3)	119 (80.4)	0.503
Sulphonylurea, *n* (%)	93 (30.0)	52 (32.1)	41 (27.7)	0.399
GLP agonist, *n* (%)	30 (9.7)	21 (13.0)	9 (6.1)	0.041
DPP4 inhibitor, *n* (%)	104 (33.6)	65 (40.1)	39 (26.4)	0.01
Insulin, *n* (%)	146 (47.1)	84 (51.9)	62 (41.9)	0.08

the cases (66 vs 75 ml/min, $p = 0.001$), but there was no difference in urine ACR. On univariate analysis (Table 3), the odds ratio for DKD was 1.74 ($p = 0.029$), DPN was 0.92 ($p = 0.7$) and DR was 2.2 ($p = 0.1$). Because of baseline differences between the groups, a multivariate analysis was performed to adjust for confounders (Tables 4, 5, 6). The differences between the groups were no longer significant. The most important predictor of microvascular complications was a five-year increase in age, especially for DKD (OR 1.63, $p < 0.001$) and DPN (OR 1.19, $p = 0.008$).

There was a trend towards a higher incidence of CVD in the hypothyroid group (OR 1.76, $p = 0.06$) that was still present in the multivariate analysis (OR 1.97, $p = 0.07$) (Table 7). The most important predictor of CVD was age, and female gender appeared protective. Amputations due to diabetes were 3.1% in the controls and 3.0% in the cases ($p = 0.725$)

Discussion

This was a cross-sectional, retrospective study comparing primarily micro- and macrovascular complications in type 2 diabetes subjects with and without hypothyroidism. It was done in a single-physician practice in South Africa in a predominantly white population, and results must be interpreted in this context.

The major findings of the study were the following: hypothyroid subjects were significantly more likely to be female, older, with a longer duration of diabetes and less likely to be black; diabetic control, defined by HbA_{1c} level, was better in hypothyroid subjects than in the controls despite less use of hypoglycaemic agents; hypothyroid subjects had higher HDL cholesterol and lower triglyceride levels; lower eGFR and greater prevalence of CKD; there was a trend to increased DR with no differences in amputations or DPN; and a trend to increased CV events. However after adjustment for baseline differences, the association of hypothyroidism with DKD and DR was no longer apparent using multivariate analysis. However the trend for CVD remained.

The increased prevalence of hypothyroidism in women in this study probably reflects underlying gender differences, previously reported.[1,8] Similarly, the increased age in the cases probably reflects the higher prevalence in older people.[8] The lower prevalence of hypothyroidism in black people was also reported in previous studies,[1] but our results need to be interpreted with caution in view of the skewed nature of the population.

Hypothyroidism has previously been reported in a systematic review and meta-analysis to be associated with microvascular complications that included DR, DKD and DPN. Although on univariate analysis, an association with DKD was demonstrated, this was not confirmed on multivariate analysis. The most important predictor of microvascular complications in our study was found to be increasing age, especially in relation to DKD and DPN. Unfortunately only 24.2% of our subjects went for formal retinal examination and this could have masked an association between DR due to a type 1 statistical error.

The relationship between hypothyroidism, including SCH and CVD, has been well established,[9] and treatment with thyroxine may reduce this risk.[10] In our study there was a trend for increased CVD in both univariate and multivariate analysis. The reason for not showing a clear association with CVD was probably mitigated by the fact that all the cases received thyroxine and statins to control LDL cholesterol. There was no difference in LDL cholesterol between the cases and controls as a result. Raised LDL cholesterol due to hypothyroidism is probably one of the major mechanisms for CVD.

Table 3. Micro- and macrovascular outcomes between cases and controls on univariate analysis

Outcome (n, *%*)	*Total group* n = *310*	*Controls* n = *162*	*Cases* n = *148*	p-*value*
Amputation,	8 (2.6)	5 (3.1)	3 (2.0)	0.725
CKD (*n* = 297)	90 (30.3)	38 (24.7)	52 (36.4)	0.029
CVD	54 (17.4)	22 (13.6)	32 (21.6)	0.062
Neuropathy	148 (47.7)	79 (48.8)	69 (46.6)	0.706
Retinopathy (*n* = 75)	33/75 (44.0)	11/33 (33.3)	22/42 (52.4)	0.099

Table 4. Associations between DKD and patient characteristics on uni- and multivariate analysis

	Univariate		*Multivariate*	
Variable	*OR (95% CI)*	p-*value*	*OR (95% CI)*	p-*value*
Age, 5-year increase	1.57 (1.37–1.79)	< 0.001	1.63 (1.39–1.91)	< 0.001
Gender, female	1.05 (0.64–1.72)	0.854	0.77 (0.43–1.38)	0.382
Race, non-black	1.16 (0.58–2.33)	0.668	0.67 (0.30–1.48)	0.322
Hypothyroid	1.74 (1.06–2.88)	0.029	1.25 (0.68–2.29)	0.467
HBA_{1c}	0.91 (0.32–2.58)	0.854	2.07 (0.60–7.19)	0.250
Duration of T2DM	1.60 (1.14–2.24)	0.007	0.90 (0.60–1.33)	0.592

Table 5. Associations between DPN and patient characteristics on uni- and multivariate analysis

	Univariate		*Multivariate*	
Variable	*OR (95% CI)*	p-*value*	*OR (95% CI)*	p-*value*
Age, 5-year increase	1.21 (1.10–1.34)	< 0.001	1.19 (1.05–1.35)	0.008
Gender, female	1.10 (0.70–1.71)	0.698	1.07 (0.65–1.77)	0.789
Race, non-black	2.11 (1.11–4.02)	0.023	1.66 (0.83–3.31)	0.152
Hypothyroid	0.92 (0.59–1.43)	0.706	0.63 (0.37–1.08)	0.094
CKD present	1.76 (1.06–2.90)	0.028	1.22 (0.70–2.16)	0.486
HBA_{1c}	1.37 (0.54–3.52)	0.507	1.47 (0.51–4.23)	0.480
Duration of DM	1.63 (1.21–2.20)	0.001	1.37 (0.97–1.93)	0.075

Table 6. Associations between DR and patient characteristics on uni- and multivariate analysis

	Univariate (n = *75*)		*Multivariate* (n = *75*)	
Variable	*OR (95% CI)*	p-*value*	*OR (95% CI)*	p-*value*
Age, 5-year increase	1.26 (1.02–1.54)	0.029	1.19 (0.89–1.60)	0.235
Hypothyroid	2.2 (0.86–5.65)	0.102	1.61 (0.55–4.68)	0.386
CKD present	1.59 (0.62–4.06)	0.334	0.89 (0.29–2.75)	0.838
HBA_{1c}	5.67 (0.64–50.13)	0.118	6.52 (0.56–75.22)	0.133
Duration of DM	1.98 (0.97–4.07)	0.061	1.24 (0.52–2.99)	0.624

Table 7. Associations between CVD and patient characteristics on uni- and multivariate analysis

	Univariate		*Multivariate*	
Variable	*OR (95% CI)*	p-*value*	*OR (95% CI)*	p-*value*
Age, 5-year increase	1.35 (1.18–1.56)	< 0.001	1.41 (1.17–1.70)	< 0.001
Gender, female	0.25 (0.13–0.48)	< 0.001	0.16 (0.07–0.36)	< 0.001
Race, non-black	1.10 (0.48–2.49)	0.826	0.63 (0.24–1.62)	0.336
Obese	0.74 (0.39–1.42)	0.371	0.87 (0.41–1.84)	0.713
Hypothyroid	1.76 (0.97–3.19)	0.064	1.97 (0.94–4.13)	0.073
HBA_{1c}	0.90 (0.26–3.13)	0.872	1.48 (0.33–6.71)	0.613
HDL-C	0.43 (0.15–1.27)	0.127	0.63 (0.18–2.23)	0.472
Duration of T2DM	1.70 (1.11–2.60)	0.014	1.19 (0.71–2.01)	0.512

An interesting finding in this study was that hypothyroid cases had improved glycaemic control, used less hypoglycaemic medication, and had higher HDL cholesterol and lower triglyceride levels. This is suggestive of reduced insulin resistance, which is contrary to reports in the literature.[11] It is possible that because all cases received thyroxine to control T4 and TSH levels, there was reversal of the insulin resistance that contributed to developing T2DM. Improvement in insulin resistance with thyroxine has been reported in experimental models and humans.[12,13]

The major limitation of this study was that it was a single-centre study, and sample size was not calculated. The negative findings may be due to inadequate statistical power of the study. Although we attempted to control for confounders, this does not completely negate the effect of confounders on the micro- and macrovascular outcomes. Furthermore, the patients with hypothyroidism were adequately treated and therefore biochemically euthyroid, thus negating the potential negative micro- and macrovascular consequences of hypothyroidism. The retinopathy group had a limited sample size due to many subjects not attending their ophthalmological examination. This limits the conclusions regarding the association of hypothyroidism and DR.

Conclusions

In this retrospective, observational study, a link between hypothyroidism and SCH and diabetic microvascular complications was not found, but there was a nearly two-fold risk for CVD. Cases also demonstrated improved glycaemic control despite fewer antidiabetic drugs, and indirect evidence for less insulin resistance than the controls with T2DM. These findings warrant further study for confirmation.

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Healthy Heart Africa: a prospective evaluation of programme outcomes on individuals' hypertension awareness, screening, diagnosis and treatment in rural Kenya at 12 months

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Abstract

Objective: To evaluate the impact of Healthy Heart Africa (HHA), a comprehensive hypertension intervention programme, on hypertension awareness, knowledge, screening and diagnosis among rural communities in Kenya.

Methods: Individuals from rural households near intervention and matched control healthcare facilities were randomly surveyed at baseline and the end point (after 12 months). A difference-in-differences analysis estimated the impact of HHA.

Results: This analysis included 838 individuals (intervention, $n = 432$; control, $n = 406$) at baseline and 698 ($n = 364$ and $n = 334$, respectively) at the end point. At baseline, both groups had high hypertension awareness (> 80%) but poor knowledge. After 12 months, healthcare providers were the primary information source for the intervention group only ($p < 0.05$). At the end point, respondents' knowledge of hypertension risk factors, consequences and management trended higher among the intervention versus the control group. Hypertension screening/diagnosis and patient recall of provider recommendations remained unchanged in both groups.

Conclusion: HHA improved hypertension knowledge but screening and diagnosis remained unchanged after 12 months.

Keywords: awareness, Healthy Heart Africa (HHA), hypertension, Kenya, rural

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Hypertension is the leading cause of cardiovascular disease (CVD) worldwide, affecting approximately 31% of the adult population (1.4 billion people) in 2010.[1] The growing prevalence of hypertension is a challenge for developing countries, which already face a high burden of infectious diseases, such as human immunodeficiency virus (HIV), malaria and tuberculosis, and have limited resources to dedicate towards hypertension care and control.[1]

Kenya is one such country facing a growing burden of hypertension, with studies reporting age-standardised prevalence ranging from 18.4 to 22.8%.[2,3] According to the recent Kenya STEPwise survey, the overall national prevalence of raised blood pressure (BP) was 23.8%.[4] Prevalence increased with age, ranging from 13.2% among Kenyans aged 18 to 29 years to 53.2% for those aged 60 to 69 years.[4]

Despite the high prevalence of hypertension, overall awareness and control remain low.[2,5,6] According to the Kenya STEPwise survey, 56% of Kenyans have never been screened for hypertension, and, of those previously diagnosed with hypertension, only 22.3% were currently taking medication prescribed by a healthcare worker.[4] Since hypertension manifests asymptomatically, individuals may not necessarily seek routine BP screening, resulting in late detection and increased risk of stroke, hypertensive heart disease or kidney failure and coronary artery disease.[2] Improving the public's awareness and general knowledge of hypertension may result in positive lifestyle changes and allow for timely detection of hypertension and early prevention of adverse outcomes.

Healthy Heart Africa (HHA), an AstraZeneca-sponsored programme, was designed to provide a model for controlling the growing burden of hypertension in Africa. The HHA programme utilised a collaborative multi-level approach aimed to improve hypertension control through education, BP screening and diagnosis, with longer-term goals of improving retention in care and attainment of treatment goals (Fig. 1). HHA was first initiated in March 2015 across 21 counties in Kenya, including the capital city, Nairobi, and the surrounding areas and parts of western Kenya, and has since expanded across sub-Saharan Africa (Fig. 2).[7]

Here, we report results from a 12-month prospective, controlled evaluation of the impact of HHA intervention on hypertension awareness and knowledge and the frequency of BP screening and hypertension diagnosis among individuals residing in rural Kenya.

Methods

HHA collaborated with the Kenyan Ministry of Health and five healthcare service-implementation partners [Academic Model Providing Access to Healthcare (AMPATH); Amref Health Africa, formerly the African Medical and Research Foundation (AMREF); Christian Health Association of Kenya (CHAK);

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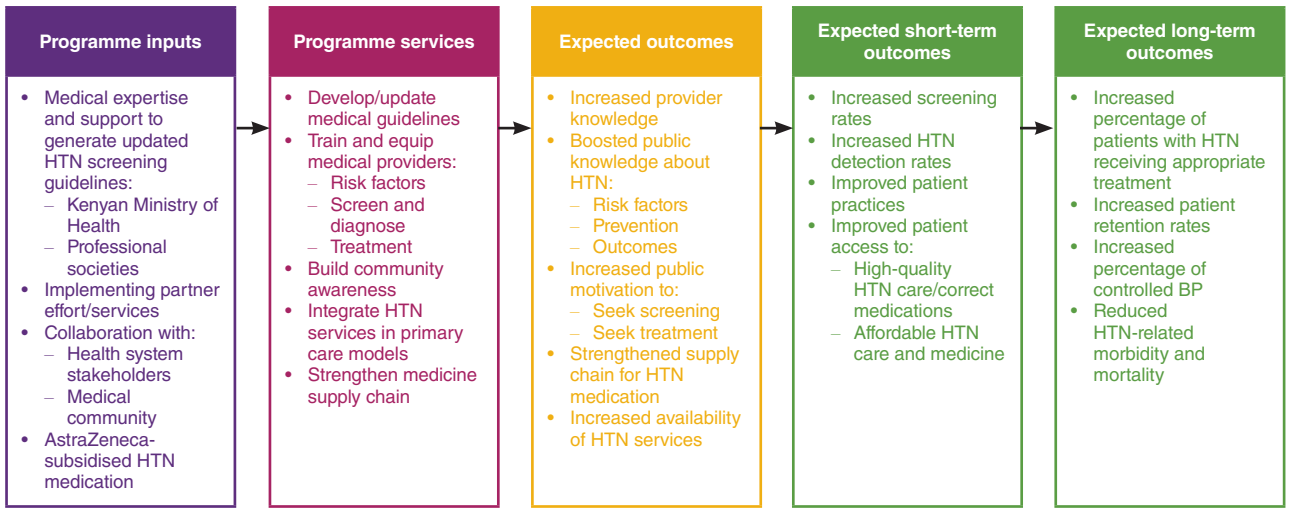

Fig. 1. Logic model for the Healthy Heart Africa programme. BP, blood pressure; HTN: hypertension.

Jhpiego; and Population Services Kenya (PSK)] to improve hypertension education/awareness, screening and primary healthcare services (Table 1). To increase hypertension awareness and knowledge among the public and improve referral to healthcare facilities for hypertension care, the implementing partners conducted education and screening outreach campaigns during market days and at local community events [such as 'barazas' (community meetings), 'chamas' (an informal co-operative society), roadshows and facility outreach events], church gatherings, public transportation stations and home visits.

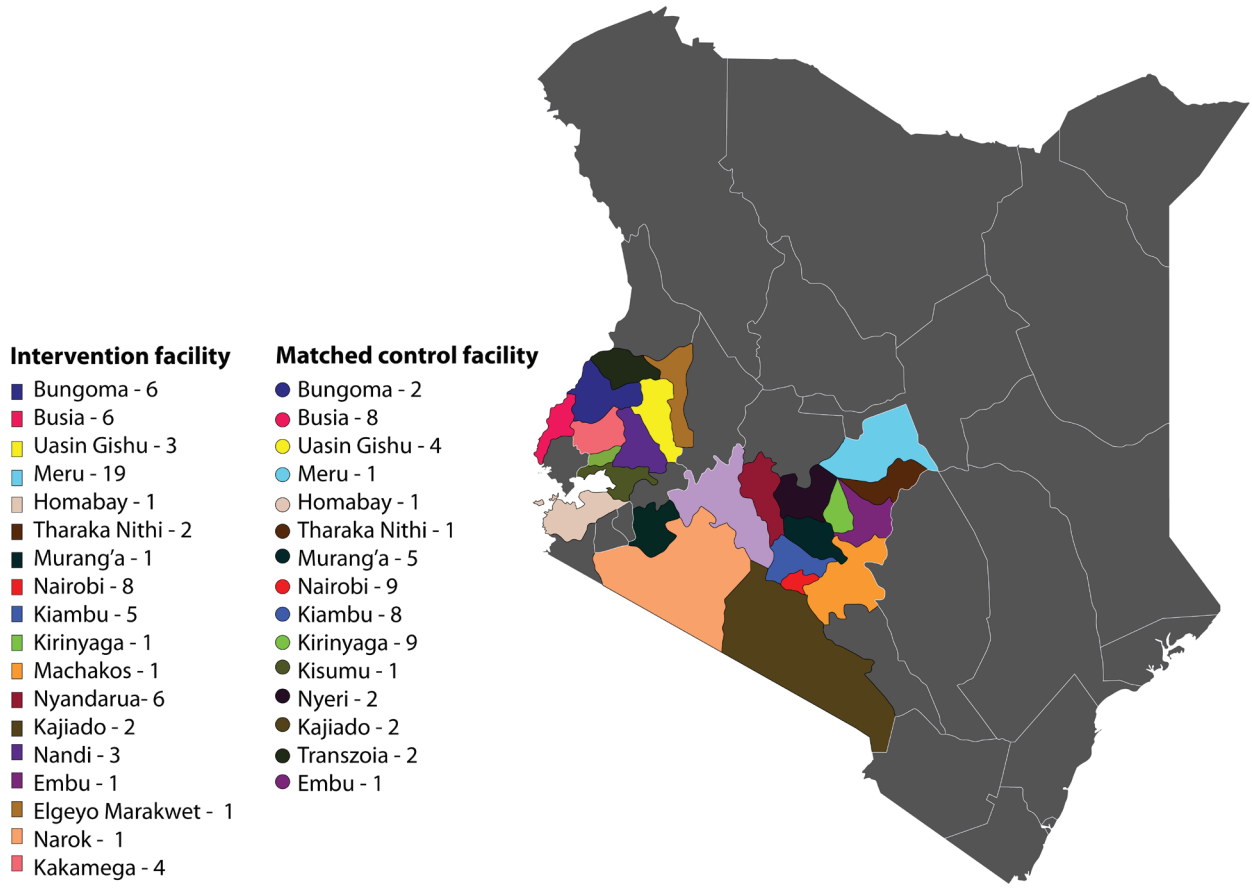

Fig. 2. Map of Kenya showing distribution of intervention facilities and matched control facilities.

Healthcare facilities participating in the HHA programme received educational materials (examples provided in supplementary information) to use at these outreach events. In addition, participating healthcare facilities received access to key hypertension medications, basic resources (equipment and educational and training materials), and a hypertension diagnosis and treatment protocol, which described hypertension risk factors and management methods but not the consequences of hypertension.[7] Of note, during the study period, some healthcare providers who were trained at an intervention facility may have been transferred to either a control or non-participating healthcare facility as part of routine transfer or due to the devolution of the Kenyan government that occurred during the study period.[8]

A 12-month prospective, controlled study evaluated the effect of HHA intervention on facility services for hypertension care, and the knowledge of hypertension among healthcare providers and the general study population. Two separate surveys, the Facility Survey[7] and the Household Survey, were conducted before (baseline) and 12 months after (end point) the implementation of HHA. Initially the Facility Sample included 150 healthcare facilities (75 randomly selected intervention facilities and 75 matched control facilities, paired based on the implementation partner and location) and the Household Sample reflected the catchment areas near 50 facilities (25 intervention facilities chosen at random from the initial 75, and their 25 matched controls). Due to attrition, the final analysis included 132 facilities in the Facility Survey, and the catchment area of 42 facilities in the Household Survey. Sample sizes declined because facilities closed or refused to participate in the end-point survey, or were dropped because their (or their pair's) treatment status was switched after the initial samples were chosen, and they could not be matched to another comparable facility in the other treatment group.

The impact of HHA on facility services and healthcare providers' knowledge of hypertension was evaluated by the Facility Survey and has been reported on by Ogola *et al.*[7] Here, we report the results from the Household Survey, which evaluated the effect of HHA intervention on the knowledge of and attitudes toward hypertension and the frequency of BP screening and hypertension diagnosis among the study population.

The Household Survey (supplementary information) was developed by the investigators to evaluate individuals' awareness and knowledge of hypertension and their attitudes and health-seeking behaviour towards hypertension. The survey was administered to individuals residing near a subset of 25 intervention facilities (randomly selected from the original group of 75 facilities assigned to the intervention) and their matching control facilities at baseline and the end point. The selected facilities were located in rural and urban areas.

The intervention population was defined as individuals residing in the catchment areas of the facilities participating in the HHA programme. The control population was defined as individuals residing in the catchment areas of matched facilities that did not receive HHA intervention. Data for BP screening and hypertension diagnosis were also abstracted from the service delivery registers (used at the point of service) of the selected facilities.

The Household Survey was pilot-tested before fielding by Ipsos Synovate Kenya (Nairobi, Kenya), a contracted survey consulting firm. Trained staff conducted face-to-face interviews with individuals residing in the catchment areas surrounding the participating intervention and control facilities. Each catchment area was divided into four non-overlapping enumeration areas, of which two enumeration areas [one near (1–4 km) and one far (5–7 km) from the facility] were randomly surveyed. For each enumeration area, a random starting point was selected and the right-hand rule (household to the right of the data collector) was used to select every household after 200 metres. The baseline and end-point surveys were conducted at the same enumeration sites; however, different households were randomly surveyed at each time point, resulting in two separate sample populations.

Adults (aged ≥ 18 years) were surveyed if they lived in the same compound, had the same household head and same cooking arrangements, and had lived in the household during the last six months. The surveyors visited each household two additional times to establish contact with adult household members who were not present at the time of the first interview. Households were assigned to the treatment group associated with their local facility (intervention or control); however, the survey did not capture where the survey respondents sought and/or received care (at the facility to which they were assigned or outside the study area or non-traditional medicine).

This study was reviewed and approved by the Kenyatta National Hospital and the University of Nairobi Ethics and Research Committee (KNH/UON-ERC). Written informed consent was obtained from all survey respondents before the start of the study.

Table 1. Healthy Heart Africa implementing partners

	AMPATH	*Amref Health Africa*	*CHAK*	*Jhpiego*	*PSK*
Approach	Extension of existing hypertension programme into Ministry of Health sites in rural West Kenya	Community-based screening clustered around Ministry of Health sites in the Kibera slum area	Initial focus on church/religious leaders and expanding outreach efforts across church, community, facility and workplace	Informal integration of the programme into HIV network in Ministry of Health sites with a significant focus on facility-based screening	Private clinics part of the Tunza Family Health Network, with significant focus on outreach events and *ad hoc* screening at various gatherings of people (e.g. bus stops, parties, funerals and sporting events)
Implementation sites	Public health dispensaries and primary-care facilities	Public health facilities and Ministry of Health sites in the Kibera slum area	Faith-based facilities and community sites (e.g. markets, group meetings, bus stops and workplaces)	Public health facilities	Private clinics, pharmacies, and non-traditional sites (e.g. taxi stands, gyms, market places, primary schools, social halls, roadside, youth bases and women's group)

AMPATH: Academic Model Providing Access to Healthcare; CHAK: Christian Health Association of Kenya; HIV: human immunodeficiency virus; PSK: Population Services Kenya.

Statistical analysis

Since the survey did not capture where individuals sought care, this analysis was limited to the rural population to minimise the possibility of cross-contamination (study participants residing near one facility but receiving treatment from another facility). Because of the sparse distribution of healthcare facilities in rural areas, the likelihood of individuals seeking care from a healthcare facility other than their locally assigned facility was believed to be lower. The analysis was restricted to individuals residing near seven intervention facilities located in rural areas and the seven matched control facilities. Due to difficulties in matching intervention and control facilities supported by the same implementation partner, select rural intervention facilities were matched to control facilities located in more urban areas.

At baseline and end point, statistical differences between the intervention and control groups with regard to demographics and lifestyle characteristics were evaluated using a *t*-test for bimodal variables and a chi-squared test for outcomes with more than two values. The impact of HHA intervention, defined as the treatment effect (TE) on hypertension awareness and knowledge, BP screening and patient recall of provider recommendation was assessed using a difference-in-differences (D-in-D) regression analysis, which minimises bias due to other factors that change over the same time frame.

Results

A total of 838 individuals were surveyed at baseline (intervention, $n = 432$; control, $n = 406$) and 698 at the end point (intervention, $n = 364$; control, $n = 334$). Demographics (age, geographic location and education) were well balanced between the intervention and control groups sampled at baseline and the end point (Table 2). Nevertheless, the two treatment groups at both baseline and end point varied with regard to wealth and lifestyle characteristics. At both baseline and end point, individuals in the intervention group were wealthier and tended to consume one or more servings of fruit per day ($p < 0.05$ for all). In addition, at the end point, a significantly greater proportion of individuals in the intervention group consumed alcohol and one or more servings of vegetables per day ($p < 0.05$ for both).

Hypertension awareness (defined as having heard of hypertension) among the intervention group was high at baseline (91.0%) and increased to 94.9% by the end point (Table 3). In contrast, hypertension awareness was much lower at baseline in the control group (79.1%) but had increased to 96.7% by the end point. Of note, the D-in-D method's underlying assumption of parallel trends could not hold for this outcome, as an increase of 17 percentage points (pp) from an initial level of 91.0% was not feasible in the intervention group.

Family and friends were the primary source of information on hypertension for both the intervention and control groups at baseline and the control group at the end point. However, by the end point, a healthcare provider or facility became the primary source of information for individuals in the intervention group (TE, 19.4 pp; $p < 0.05$; Table 3).

In general, the intervention group experienced an increase in knowledge of individual risk factors for hypertension. Significant improvement was observed in individuals' knowledge of tobacco use as a risk factor for hypertension with intervention (TE, 4.0 pp; $p < 0.05$; Table 3). Within 12 months, individuals' knowledge of three or more hypertension risk factors also showed a trend toward improvement in the intervention group [TE, 3.8 pp; p = not significant (NS)].

A positive improvement in individuals' knowledge of hypertension management was seen in the intervention group. Identification of alcohol reduction as a method for managing hypertension significantly increased four-fold in the intervention group (TE, 8.4 pp; $p < 0.01$). In addition, positive trends were seen in the proportion of individuals who identified salt reduction as a method for hypertension management (TE, 1.0 pp; p = NS) in the intervention group. Individuals' knowledge of three or more or five or more methods for managing hypertension also improved three-fold (TE, 3.7 pp; p = NS) and 17-fold (TE, 1.7 pp; p = NS), respectively, in the intervention group.

Table 2. Characteristics of survey respondents residing in rural areas

	Baseline			*End point*		
	Intervention (n = 432)	*Control (n = 406)*	p-*value*	*Intervention (n = 364)*	*Control (n = 334)*	p-*value*
Geographic region, %						
Central or eastern	63.6	63.6		75.0	72.4	
Nairobi	0.0	0.0		0.0	0.0	
Nyanza	10.1	0.0	0.345	9.8	0.0	0.175
Rift Valley	0.0	10.3		0.0	11.4	
Western	26.4	26.1		15.3	16.2	
Residence location, %						
Rural	93.6	99.4	0.014*	69.3	99.5	0.000**
Urban[a]	6.4	0.6		30.7	0.5	
Age, years, %						
18–24	18.7	20.0		22.4	14.3	
25–29	12.7	8.9		14.2	16.0	
30–34	10.9	12.3		14.0	10.8	
35–39	11.2	13.3	0.647	9.3	7.6	0.128
40–44	11.2	8.7		11.6	9.7	
45–49	6.6	6.9		7.0	8.8	
≥ 50	28.8	30.0		21.6	32.8	
Gender, %						
Male	48.7	46.0	0.269	50.6	55.7	0.448
Female	51.3	54.0		49.4	44.3	
Education, %						
Nursery/kindergarten	1.8	2.0		3.5	2.7	
Primary	47.4	48.7		37.1	48.2	
Post-primary, vocational	4.1	3.5		4.3	5.3	0.310
Secondary, A-level	36.4	32.2	0.834	39.3	30.1	
College (mid-level)	6.0	6.5		11.8	6.4	
University	1.7	1.7		1.4	1.2	
No school attended	2.5	4.8		2.5	6.0	
Wealth quintile, shillings/month, %						
≤ 653	34.3	33.5		25.6	37.9	
654–2 158	17.2	13.6		22.4	20.6	
2 159–2 633	25.8	51.6	0.000**	15.4	38.8	0.000**
2 634–3 631	21.2	0.5		32.4	1.0	
≥ 3 632	1.5	0.8		4.2	1.7	
Lifestyle characteristics, %						
Non-smoker	87.8	91.5	0.392	92.0	86.6	0.104
Does not drink alcohol	78.0	82.8	0.177	80.2	87.4	0.023*
Consumes ≥ 1 fruit serving/day	52.0	26.3	0.001**	60.8	36.0	0.010*
Consumes ≥ 1 vegetable serving/day	68.1	56.5	0.446	84.9	54.1	0.016*

*$p < 0.05$; **$p < 0.01$ vs control.
[a]Select intervention facilities were matched to control facilities.

Similarly, individuals' knowledge of hypertension-related consequences showed a trend toward improvement among the intervention group (Table 3). Knowledge of possible complications during delivery significantly increased among respondents with intervention (TE, 3.3 pp; $p < 0.01$). Similarly, a positive trend was seen in individuals' knowledge of stroke (increased from 19.6% at baseline to 22.4% at the end point), heart failure (from 6.2 to 9.0%, respectively), aneurysm (from 3.8 to 4.1%, respectively) and death (from 43.7 to 52.3%, respectively) with intervention; however, these changes were not significant relative to the control. Individuals' knowledge of three or more consequences of hypertension increased two-fold in the intervention group.

Despite these changes in knowledge surrounding hypertension, the proportion of individuals screened for BP and diagnosed with hypertension slightly decreased from baseline to the end point in the intervention group (Table 4).

Table 3. Impact of Healthy Heart Africa on individuals' knowledge of hypertension

	Baseline		*End point*		*Treatment effect (SE), percentage point*
	Intervention (n = 432)	*Control (n = 406)*	*Intervention (n = 364)*	*Control (n = 334)*	
Awareness of HTN,[a] %	91.0	79.1	94.9	96.7	–15.5 (3.4)**
Sources of HTN education, %					
Television/radio/internet/books/billboard/magazines/newspapers	30.7	28.4	26.8	30.0	–7.7 (5.4)
Friends/family	60.1	56.8	44.1	68.7	–25.6 (6.2)**
Religious leader	1.3	2.1	2.4	4.1	–0.8 (3.3)
CHW/CHEW	5.7	1.0	4.6	2.5	–3.9 (4.2)
Community event	9.6	5.7	6.3	9.6	–7.9 (4.8)
Healthcare provider/facility	28.9	21.7	48.2	20.8	19.4 (8.1)*
School	1.8	2.3	8.7	2.9	2.9 (1.7)
Other	1.4	1.1	1.0	0.5	0.5 (0.6)
Individuals who correctly identified risk factors of HTN, %					
Age	40.3	40.9	46.0	47.5	–0.8 (6.9)
Family history	7.4	5.6	6.5	1.7	0.1 (3.0)
High BMI/obesity/overweight	18.6	19.7	27.8	20.4	4.7 (7.7)
High salt intake	1.7	2.5	4.0	1.9	2.4 (1.5)
Low potassium intake	0.3	0.9	0.9	1.0	–0.4 (0.8)
Use of tobacco products	2.0	3.4	4.4	0.7	4.0 (1.7)*
High alcohol consumption	0.9	3.5	4.4	1.2	5.4 (2.6)
Pregnancy	7.9	5.3	12.1	6.3	1.6 (3.3)
Lack of physical activity	3.4	5.0	7.5	3.6	4.6 (2.6)
≥ 3 risk factors for HTN	4.0	4.5	9.0	3.4	3.8 (2.4)
≥ 5 risk factors for HTN	1.0	0.7	2.2	0.0	1.5 (1.0)
Individuals who correctly identified methods for reducing HTN, %					
Reduce salt	9.4	11.9	15.4	17.5	1.0 (6.2)
Weight loss	7.2	8.6	9.5	8.7	–8.6 (9.8)
Medication	21.6	15.8	20.5	18.1	–2.6 (4.9)
Exercise	14.7	12.7	23.6	21.3	–7.4 (8.7)
Dietary changes	14.0	11.6	19.0	15.7	1.0 (6.9)
Reduce alcohol	2.0	5.3	8.3	1.6	8.4 (1.9)**
Stop use of chemical contraceptives	1.9	1.1	1.0	1.1	–1.4 (1.0)
Reduce smoking	2.3	3.6	2.3	0.9	3.0 (1.8)
≥ 3 methods for managing HTN	3.2	6.5	10.1	7.7	3.7 (2.0)
≥ 5 methods for managing HTN	0.1	0.5	1.7	0.8	1.7 (1.6)
Individuals who correctly identified consequences of HTN, %					
Death	43.7	38.8	52.3	68.1	–23.7 (9.9)*
Heart attack	19.2	10.0	16.4	10.4	–7.4 (6.8)
Stroke	19.6	17.7	22.4	13.4	8.0 (6.1)
Aneurysm	3.8	2.1	4.1	2.7	–2.1 (2.1)
Heart failure	6.2	4.5	9.0	6.0	0.1 (2.9)
Erectile dysfunction	0.6	0.5	1.7	3.8	–2.6 (1.8)
Loss of sight	1.8	1.9	4.5	3.7	1.2 (1.3)
Complications during delivery for pregnant women	0.4	2.2	1.8	0.7	3.3 (0.9)**
Increased risk of miscarriage	1.6	1.5	1.5	1.0	0.7 (1.6)
Renal disease	NA[b]	NA[b]	6.3	0.4	4.9 (2.6)
≥ 3 consequences of HTN	5.0	4.3	11.2	8.5	0.3 (4.8)
≥ 5 consequences of HTN	0.0	0.5	1.0	1.8	0.2 (1.3)

BMI: body mass index; CHEW: community health extension worker; CHW: community healthcare worker; HTN: hypertension; NA: not available; SE: standard error. *$p < 0.05$; **$p < 0.01$ vs control. [a]Defined as having heard of hypertension. [b]Data not captured.

Discussion

Individuals' natural awareness of hypertension may be limited as the disease manifests asymptomatically and care may not be sought until sudden, severe and irreversible consequences occur. Little is known about the optimal method to rapidly educate the general population of a low- to moderate-income developing country about hypertension. The purpose of this 12-month prospective study was to assess the impact of HHA intervention on the status of awareness and knowledge of hypertension among the rural Kenyan population.

General awareness of hypertension among survey respondents was high (approximately 80 to 90%) at baseline; however, the specific knowledge of risk factors and actions was poor, indicating that information from primary sources, namely friends and family, was not necessarily accurate. At baseline, less than 5% of respondents could correctly identify three or more known risk factors for hypertension. Similarly, respondents appeared to be largely unaware that smoking, alcohol consumption and family history of heart disease were possible risk factors for hypertension or associated CVD.

Within 12 months, HHA was successful in conveying information about hypertension to individuals residing in the intervention areas. This is demonstrated by the significant increase in the percentage of respondents in the intervention areas who reported healthcare providers as their primary source of hypertension information compared with the control group.

In general, knowledge of hypertension showed a trend toward improvement among the HHA intervention group. By the end point, more individuals residing in the intervention areas identified tobacco use as a risk factor for hypertension and reducing alcohol consumption as a method for managing hypertension. The observed improvement is of importance because both alcohol and tobacco consumption have been associated with the high prevalence of hypertension in Kenya.[9,10]

According to the 2015 Kenya STEPwise survey, approximately 13.3% of survey respondents, aged 18–69 years, reported current use of a tobacco product (manufactured or hand-rolled cigarettes, pipes or shisha).[4] In addition, 19.3% of respondents reported current alcohol use, with 12.7% consuming alcohol on a daily basis and 12.7% reporting heavy episodic drinking (six or more drinks on a single occasion).[4] Therefore it is believed that improving individuals' awareness of the association between tobacco and alcohol use and hypertension may lead to the adoption of a healthier lifestyle over time.

Table 4. Impact of Healthy Heart Africa on hypertension diagnosis and provider's recommendation

	Baseline		End point		Treatment effect (SE), percentage point
	Intervention (n = 432)	Control (n = 406)	Intervention (n = 364)	Control (n = 334)	
Individuals who reported being screened for BP, %	74.3	62.6	72.9	77.6	–19.9 (7.8)*
Last time BP screening was performed, %					
≤ 6 months	38.7	24.4	37.8	39.4	–15.2 (4.6)**
7–12 months	10.2	8.8	12.1	16.3	7.2 (4.8)
≥ 12 months	24.8	27.8	22.2	21.9	0.7 (4.1)
BP screening location, %					
Public hospital	29.3	29.0	27.1	19.9	8.3 (7.8)
Public health centre or dispensary	40.9	24.1	35.9	44.6	–16.2 (9.0)
Private hospital	5.6	8.9	13.3	18.2	–2.7 (3.4)
Private health centre or dispensary	11.3	6.1	15.5	13.7	–4.6 (6.4)
At screening event	1.2	0.8	2.5	8.1	–7.4 (2.9)
Other	7.7	10.4	15.0	21.1	–2.0 (1.6)
Individuals who reported being diagnosed with hypertension, %	14.9	8.8	12.9	10.3	–0.03 (3.3)
Timing of hypertension diagnosis, %					
≤ 6 months	3.8	2.9	2.7	2.9	–1.2 (3.0)
7–12 months	2.1	1.0	3.8	1.3	2.5 (1.1)
> 12 months	8.8	4.9	5.5	5.1	–1.3 (2.7)
Individuals' recall of healthcare providers' recommendation, %					
≥ 1 healthcare providers' recommendation	13.4	8.8	9.8	9.3	–2.3 (3.5)
≥ 3 healthcare providers' recommendations	0.1	2.1	0.5	1.4	1.2 (0.9)
Medication	13.1	7.1	7.2	8.2	–5.0 (2.5)
Reduction in salt	2.2	3.8	4.0	4.0	2.0 (1.6)
Lose weight	0.1	2.0	0.6	1.3	1.9 (1.7)
Reduce alcohol consumption	0.2	0.7	0.6	0.0	1.3 (0.5)*
Exercise	1.4	2.3	1.3	1.3	1.3 (1.5)
Reduce stress	3.5	2.1	3.8	3.6	0.4 (1.3)
Home remedies	0.3	0.9	0.1	0.7	0.3 (0.7)
Unable to recall	0.9	0.1	1.6	0.6	0.8 (1.5)

*$p < 0.05$; **$p < 0.01$ vs control. BP: blood pressure; SE: standard error.

Individuals' knowledge of hypertension-related consequences remained relatively unchanged. This was expected to a certain extent, as the programme intervention did not educate healthcare providers or the general public on the consequences of hypertension.[7] In addition, HHA intervention areas did not have a significant change in the number of individuals screened for BP or diagnosed with hypertension, emphasising the need for more innovative outreach activities/approaches to identify individuals at high risk for hypertension, including those who may not necessarily visit healthcare facilities.

To the best of our knowledge, this is the first study to characterise and intervene to improve individuals' awareness and knowledge of hypertension among the rural population in Kenya. Previous studies have reported a low degree of awareness among Kenyans, but clinically meaningful comparisons were not possible due to a lack of a standardised definition for hypertension awareness.[2,5,6,11]

However, a recent qualitative study based on a series of focus group discussions with 53 individuals with HIV-1 conducted at the Kenyatta National Referral and Teaching Hospital Comprehensive Care Centre reported a gap between hypertension awareness and knowledge, similar to what was seen in this study.[11] Respondents commonly referred to hypertension as 'pressure' and, although all of the participants had heard of the term, most were unable to adequately describe it. Stress followed by fatty foods, excessive salt intake, and physical inactivity were the most frequently cited causes of hypertension. All respondents demonstrated some knowledge regarding treatment modalities for hypertension; however, most believed that hypertension could not be prevented.

This gap between awareness and knowledge/understanding is not strictly limited to hypertension and extends to individuals' awareness and understanding of CVDs. A systematic review evaluating awareness and knowledge of CVDs in sub-Saharan Africa found that awareness, when reported, was high; however, knowledge and understanding of CVDs and CVD risk factors were poor.[12] Although limited, the data suggest that individuals may benefit from intervention efforts designed to not only raise awareness but also improve general understanding and knowledge of hypertension. The HHA programme's positive impact on knowledge of hypertension may help to address this critical gap in communication, and, when coupled with the previously reported facility-level improvements in provider education and ability to diagnose and treat hypertension,[7] may lead to greater utilisation of hypertension services and, in turn, timely diagnosis and treatment of hypertension.

There are some inherent limitations associated with this analysis. The generalisability of the data is limited, in part, by study design. This study was not designed to collect nationally representative findings and therefore data interpretation is limited to individuals residing near the study sites. In addition, this study did not capture where respondents received care. Potential ramifications of receiving care at distant sites were mitigated by focusing on the rural population, which, due to limited access to healthcare facilities, is more likely to receive care at the local facility. The study design did not the capture frequency and type of study- and non-study-related hypertension awareness/education events conducted within the study area, which may affect programme evaluation.

Furthermore, the short duration of this study may not be sufficient for evaluating the impact of the HHA programme, as significant changes in individuals' behaviours and attitudes towards hypertension care may require a longer period of time in this setting. The impact of the HHA programme may be underestimated as HHA-trained healthcare providers from intervention facilities may have been moved and replaced with untrained healthcare providers, a by-product of routine transfer and the devolution of the Kenyan government,[8] which occurred during the 12-month study period.

Conclusion

Little is known about how to rapidly improve control of hypertension in low- to moderate-income countries. The results from this study may help to develop more realistic expectations on the anticipated rate of improvement in individuals' awareness and knowledge of hypertension and health-seeking behaviour towards hypertension care. In this study, individuals residing in rural Kenya demonstrated a high degree of hypertension awareness; however, their medical knowledge of hypertension was quite poor.

The HHA programme was able to demonstrate an improvement in individuals' knowledge of hypertension within 12 months of programme implementation. These initial improvements may eventually lead to longer-term changes in individuals' attitudes and behaviours, including lifestyle changes and healthcare-seeking practices toward hypertension care. Additional studies are needed to determine realistic time frames for improvements in lifestyle, regular BP screening, adherence to hypertension care and reduction in the negative outcomes of hypertension.

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OPCAB surgery with an alternative retraction method: a single-centre experience

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Abstract

Background: The off-pump coronary artery bypass (OPCAB) technique, which is used in order to avoid the side effects of cardiopulmonary bypass, is often questioned in terms of its efficacy and safety. Also, in this technique, surgeon experience plays a very important role. In this study, we share the results of our 606 OPCAB cases with an alternative retraction technique.

Methods: This study was a retrospective analysis of OPCAB operations performed between January 2014 and December 2018. Patients were evaluated and operated on by a surgical team led by an experienced OPCAB surgeon with over 200 prior OPCAB surgeries.

Results: The study included 606 OPCAB cases, and 21.8% (132) were female and 78.2% (474) were male. Our mortality rate was 1.7% (n = 10) and only two patients suffered a cerebrovascular incident. A statistically significant difference was found between pre-operative and six-month postoperative left ventricular ejection fraction values ($p < 0.01$).

Conclusion: The OPCAB technique can be performed with similar results to on-pump surgery when conducted by an experienced surgeon, as in our study.

Keywords: on-pump coronary artery bypass, alternative method

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Coronary artery bypass graft surgery (CABG) is a treatment that improves survival in advanced coronary artery disease. The off-pump coronary artery bypass (OPCAB) technique, which is used in order to avoid the side effects of cardiopulmonary bypass (CPB), is often questioned in terms of its efficacy and safety. Although there are over 100 randomised controlled trials and 60 meta-analyses, the superiority of one technique over the other has not been clearly demonstrated.[1] While some studies did not show any difference between the two techniques,[2,3] one study showed that OPCAB resulted in decreased mortality and morbidity rates and hospitalisation time.[4]

In these studies, another important criterion in determining the effectiveness of OPCAB was the case volume of the institution and the surgeon. In a study by Benedetto *et al.*,[5] five-year follow-up results of 1 260 OPCAB and 1 700 on-pump coronary artery bypass (ONCAB) operations were published. The experience of the surgeons who performed the cases was also evaluated. Surgeons performing sporadic (one to five cases) OPCAB operations had a high conversion rate, low graft count and high mortality rate. OPCAB results of high-volume surgeons were found to be similar to ONCAB surgery.

In our centre, CABG operations are routinely performed by a single team using the off-pump technique. In this study, we share the results of our 606 OPCAB cases and the alternative technique we used for retraction and positioning of the heart.

Methods

This descriptive study is a retrospective analysis of OPCAB operations performed between January 2014 and December 2018. For all patients the OPCAB technique was routinely chosen, and there were no exclusion criteria. Patients were evaluated and operated on by a surgical team led by an experienced OPCAB surgeon (over 200 prior OPCAB surgeries).

All patients were sedated with 2 mg IV midazolam and anaesthesia induction was done with fentanyl 10 µg/kg, midazolam 0.1 mg/kg and rocuronium 1 mg/kg. In order to prevent possible cardiac oedema during the positioning of the heart, 1 mg/kg methylprednisolone was routinely given to all of our patients as well as pheniramine IV in order to prevent possible reactions during protamine administration. Following 100–200 IU/kg heparinisation, the activated clotting time (ACT) was kept between 200 and 400 seconds. In order to benefit from its anti-arrhythmic effects, 1 mg/kg lidocaine 2.5% IV and 10 ml 15% magnesium sulfate were administered during internal thoracic artery harvest. Potassium levels were closely monitored and kept above 4.0 mEq/ml.

After left internal mammary artery (LIMA) harvesting, the pericardium was opened and a deep pericardial suture was placed to elevate the heart. The right pleura was opened in all patients if the circumflex (Cx) coronary artery and its branches were targeted for bypass, thereby preventing haemodynamic deterioration during retraction of the heart. In addition, moistened gauzes were placed through transfer and oblique sinuses. With the placement of these gauzes, the heart could be retracted more efficiently. The retraction gauzes were used to hold the heart until the anastomosis area was determined, as if the operation was done with CPB, and thereafter, the tissue stabilisation system (Octopus® Evolution, Medtronic) was used.

During anastomosis of the left anterior descending (LAD) artery to the LIMA, the gauzes were loosened in order to avoid

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too much compression of the heart and further haemodynamic disturbances, but we still had enough tension to retract the heart and support the stabilisation system. Anastomoses were thus done with direct access and without excess manipulation of the heart (Fig. 1).

During right coronary artery (RCA) anastomosis, the operating table was positioned away from the surgeon and the anastomosis was perfomed with gauzes and the suction system was used to create a more stable state (Fig. 2). When doing bypasses to the circumflex branches [obtuse marginal (OM) or posterolateral (PL) arteries], the operating table was positioned at 20 degrees Trendelenburg and turned to the right side. No apical holder was used in any patient. During anastomosis on the posterolateral surface, the heart was retracted more firmly to the right side with gauzes and the suction system (Fig. 3).

All distal anastomoses were performed using intracoronary shunt, except for total occlusion. After completion of the anastomoses, 50–100 IU/kg protamine (half dose) was administered and the operation was terminated.

The patients were ventilated with high frequency and low tidal volume (350–400 ml) to prevent movement during anastomosis. Tidal volume was increased when there was a problem with saturation in the arterial blood gas values. No patient had an oxygenation problem during the operation.

The patients were monitored and followed closely in the intensive care unit. Low-molecular-weight heparin was given to all patients for four to six hours postoperatively.

In this study, haemodynamic instability, ventricular fibrillation and anastomotic difficulty were the main criteria for conversion to on-pump surgery.

Statistical analysis

SPSS statistics for Windows version 22.0 (SPSS Inc Chicago, IL, USA; released 2008) was used for statistical analysis. The paired-samples *t*-test was used to compare repeated measurements. Since there was only one group of patients, descriptive studies were chosen; p-values < 0.05 were considered to indicate statistical significance.

Results

The study included 606 OPCAB cases performed in a single centre between January 2014 and December 2018, and 21.8% (132) of our patients were female and 78.2% (474) were male. The mean age was 62.25 ± 9.47 (min–max 32–86 years) years.

Table 1 shows the baseline characteristics of our patients. When cardiac function was examined, it was seen that 10.1% (n = 61) of our patients had low left ventricular ejection fraction (LVEF). In these patients, excessive volume overload was avoided in the peri- and postoperative period. Postoperative findings are given in Table 2.

In routine practice in our clinic, when starting inotropic support, dopamine and noradrenaline infusion are the first choice. More than two inotropic supports were not used in our study. The mortality rate was 1.7% (n = 10) in 606 cases and only two patients suffered a cerebrovascular incident (CVI). These patients recovered without neurological sequelae. Two patients (0.3%) were converted to on-pump surgery because of ECG changes (ST elevation) and were haemodynamically affected despite interventions. No additional morbidity and mortality was observed in these patients.

The number of distal anastomoses in our study is shown in Table 3. In Table 4, our six-month postoperative LVEF results

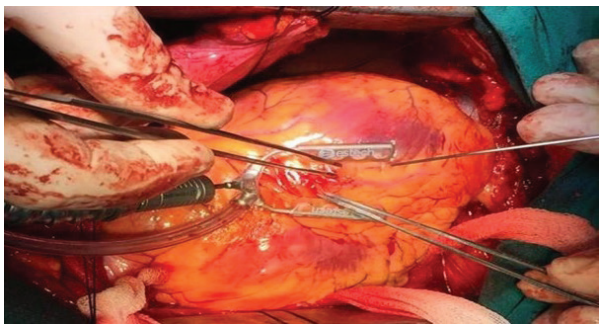

Fig. 1. Anastomosis on the anterior face of the heart with the help of a deep pericardial suture and the Octopus® system.

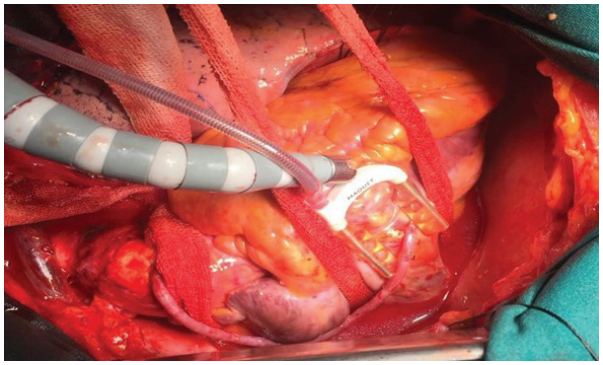

Fig. 2. Anastomosis on the inferior face of the heart with the help of the Octopus® system and moistened gauzes.

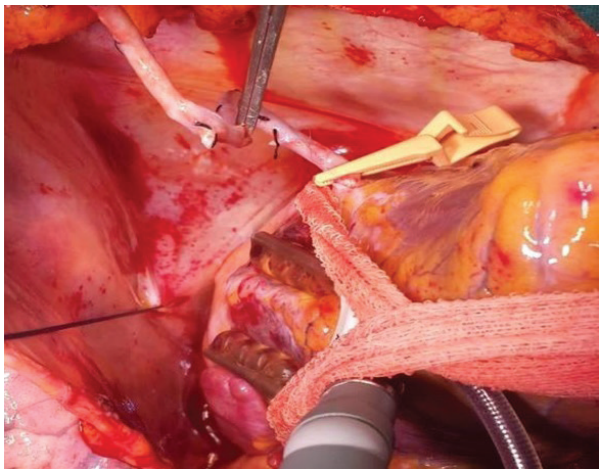

Fig. 3. Sequential anastomoses on the posterolateral face of the heart with the help of the Octopus® system and moistened gauzes.

Table 1. Baseline characteristics of the patients

Variables	n *(%) or mean ± SD*
Female	132 (21.8)
Male	474 (78.2)
Age (years)	62.25 ± 9.47
Body mass index (kg/m²)	29.58 ± 4.98
Recent myocardial infarction	
Yes	362 (59.7)
No	244 (40.3)
Diabetes mellitus	
Yes	329 (54.3)
No	277 (45.7)
Hypertension	
Yes	323 (53.3)
No	283 (46.7)
Chronic obstructive pulmonary disease	
Yes	398 (65.7)
No	208 (34.3)
Smoking history	
Yes	323 (53.3)
No	283 (46.7)
Renal disease	
No renal disease	580 (95.7)
Dialysis dependent	6 (1)
Creatinine > 2.3 mg/dl	20 (3.3)
Ejection fraction	
< 35%	61 (10.1)
35–50%	285 (47.0)
> 50%	260 (42.9)

can be seen. With 10 mortalities among our cases, we compared 596 patients. The paired-samples *t*-test was performed between these two groups and a statistically significant difference was found ($p < 0.01$).

Discussion

In the treatment of coronary artery disease, which is one of the major causes of death worldwide, CABG surgery plays an important role. CABG surgeries are often performed with CPB and most of the time this technique is the major part of residency training.[6] CPB provides great support to the surgeon during distal anastomoses and in the positioning of the heart. Performing an anastomosis on the beating heart is one of the biggest drawbacks in the OPCAB approach. However, OPCAB is an important surgical technique that can be used for prevention of the side effects of cannulation and CPB.[7]

Table 2. Postoperative findings

Variables	*Mean (min–max) or* n *(%)*
Intubation (hours)	6.31 (1–240)
ICU stay (days)	1.22 (0.04–18.75)
Hospital stay (days)	5.62 (3–48)
Intra-aortic balloon pump	
Yes	29 (4.8)
No	577 (95.2)
Inotropes	
None	489 (80.7)
Dopamine	84 (13.9)
Dopamine + noradrenaline	33 (5.4)
Drainage (ml), mean ± SD	683.58 ± 193.52
Revision	
Yes	5 (0.8)
No	601 (99.2)
Postoperative atrial fibrillation	
Yes	36 (5.9)
No	570 (94.1)
Cerebrovascular incident	
Yes	2 (0.3)
No	604 (99.7)

Table 3. Number of distal anastomosis

Number of vessels	n *(%)*
1 vessel	48 (7.9)
2 vessels	232 (38.3)
3 vessels	223 (36.8)
4 or more vessels	103 (17.0)

Table 4. Results of pre- and six-month postoperative LVEF comparison

	Paired-samples statistics	
Variable	*Mean* (n)	*SD*
Pre-operative	50.43 (593)	9.36
Postoperative	51.01 (593)	8.67

*$p < 0.01$.

Although there are more than 100 randomised studies and 60 meta-analyses in which comparison of these two techniques were made, there was no clear superiority of one technique over the other. However the experience of the surgeon was emphasised in all reports.[1] When chosen routinely, OPCAB surgery can be as effective as on-pump bypass surgery.[8] In meta-analyses of randomised studies, one to two years' follow up of low-risk patients showed similar mortality rates, myocardial infarction and need for repeat revascularisation to on-pump surgery.[9,10] Experience of the surgeons participating in the studies increased the success of OPCAB and no significant difference was found between the patients operated with on- and off-pump techniques.[5,11]

The impact of the surgeon's experience in OPCAB success was most strikingly demonstrated in the ROOBY study.[12] The five-year follow up of patients showed a clear superiority of ONCAB over OPCAB (operated on by a minimum of 20 experienced OPCAB surgeons). In the light of these studies and with our dedicated surgical team led by an experienced OPCAB surgeon, OPCAB surgery has became our routine choice for CABG operations.

In Table 2, the morbidities experienced in the postoperative period are shown. We compared our postoperative atrial fibrillation, intra-operative balloon pump (IABP) insertion, cerebrovascular events and postoperative revision numbers with those of the study by Taggart *et al.*[13] with 618 patients in the OPCAB single mammary artery group, and those of the study by Benedetto *et al.*[5] While the number of patients with IABP was similar, the number of cerebrovascular events and revisions was fewer in our study.

One of the major advantages of the OPCAB technique compared to ONCAB is the reduced manipulation of large vessels. During cannulation, embolisation of atheromatous plaque from the aorta, bleeding, iatrogenic dissection and end-organ malperfusion may develop. In addition, cross-clamping can cause injury to the aorta, which can be avoided with the OPCAB technique. However, the risk of CVI is not reduced in OPCAB. The main reason for this is the side-clamp

that is placed during proximal anastomosis. To avoid this, proximal anastomosis devices were developed, but the patency of these grafts was found to be decreased.[7]

The 2018 European Society of Cardiology guideline for myocardial revascularisation recommends OPCAB by experienced operators and preferably no-touch techniques on the ascending aorta.[14] In our study, although we used lateral clamps during proximal anastomosis, CVI was seen in only two patients (0.3%). We speculate that palpation of the aorta and avoiding any palpable plaques before clamp positioning contributed to this result.

In their study, Mack *et al*.[15] initially selected patients for OPCAB surgery who required three or fewer bypasses to the anterior surface of the heart. In the case of unstable patients, re-operations, and the need for bypass to the coronary arteries on the lateral side of the heart, the on-pump technique was preferred. However, as surgical experience increased and stabilisation techniques developed, OPCAB was preferred for all patients. Gauzes, sponges, traction sutures and stabilisation systems are combined to achieve good exploration of the target vessels.[16-18] In our study, with high surgical experience and the support of an alternative retraction method, the anastomoses are performed in a more stable state without haemodynamic impairment. Thus anastomoses could easily be performed to the coronary arteries, especially on the posterior and posterolateral (Cx and RCA field) areas of the heart, and our success rate in revascularising the target vessels increased.

The LVEF, evaluated by two-dimensional echocardiography pre-operatively and at six months after surgery, was analysed in 596 patients and statistically analysed. These data show a statistically significant improvement in LVEF, particularly at six months after surgery. Capuani *et al*.[19] showed a similar result with the comparison of pre- and postoperative LVEF.

In their study, Benedetto *et al*.[5] showed conversion rates around 10%, and this outcome negatively affected five-year follow up. In the same study, the rate of conversion was 12.9% by OPCAB surgeons doing sporadic surgery (one to five cases) and 1.0% by experienced surgeons (> 60 cases). In their study, Angelini *et al*.[20] emphasised that OPCAB results, performed by experienced surgeons who adopted all aspects of the OPCAB technique, were similar to on-pump surgery results. The low conversion rate in our study was attributed to the alternative method of retraction we used and the greater OPCAB experience of the surgeon. In addition, the conversion decision in these cases was done in a timely manner, therefore there was no morbidity or mortality in these patients (data not shown).

Although the ROOBY study showed that OPCAB was associated with increased mortality rates, many other studies do not mention increased mortality rates associated with OPCAB.[7] Kowalewski *et al*.[21] found a mortality rate of 2.04% with no significant difference between the two techniques. Our mortality rate was 1.7% (n = 10), which is similar to the mortality rates of OPCAB surgeries in the literature.

Since only the OPCAB technique is preferred in our centre, this study is presented as a descriptive one.

Conclusion

The OPCAB technique can be performed with similar results to on-pump surgery when performed by experienced surgeons, as in our study. The alternative retraction technique in conjunction with a stabiliser enables good exposure and stability in OPCAB surgery and contributes to the quality of coronary anastomoses, especially of the circumflex and right territory arteries.

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How to deal with the mass killer, hypertension

High blood pressure is the single biggest contributor to the global burden of disease, with hypertension leading to 10.7 million deaths every year.[1] Most worrying is a recent global study showing that on average, more than half of those affected don't know they have it.[2] Because cardiovascular disease affects a third of adults in the world, it is the largest epidemic ever known to mankind.[3]

With mortalities increasing year on year, awareness, and therefore treatment and control rates, have been shown to worsen as the economic status of populations drop.[2] Prof Neil Poulter, immediate past president of the International Society of Hypertension (ISH), says that between the highest-income countries and the lowest, there was an 8.2% drop in awareness, a 15% drop in treatment rates and a 6.3% drop in control. This prompted the ISH to mount an unprecedented global blood pressure (BP) awareness campaign during May last year.[4]

Speaking at the 34th World Congress of Internal Medicine (WCIM) that was held in Cape Town in October, Prof Poulter said an earlier study showed that just 46.5% of 57 840 hypertensive people canvassed knew they had hypertension, followed by a dramatic drop off between those treated (40.6%) and those controlled (13.2%). In the subsequent global ISH screening and awareness initiative, dubbed 'May Measurement Month' (MMM, 2017), volunteers screened over 1.2 million people in 80 countries. They uncovered over 150 000 people with untreated raised BP (17.3% of those untreated) and over 100 000 with treated but uncontrolled BP (46.3% of those treated). The ISH went one better this year, screening over 1.5 million people in 89 countries and detecting over 220 000 with untreated raised BP (18.4% of those untreated) and over 110 000 with treated but uncontrolled BP (just 40.4% of those treated).

He described the MMM campaigns as a major success and a 'heart-warming, fantastic volunteer effort.'

Take-home lessons

'So, we need to put screening in place and provide suitable drugs – most people are not getting enough drug combinations. You need two or more drugs to manage hypertension properly,' said Prof Poulter.

Drug guidelines are confusing, differing in the European Union, America and Britain, with different drug combinations recommended for different race groups. Prof Poulter favours the British combination-drug guidelines.

'Our problem is that world-wide we don't know what the best combinations are. We know that patients need at least two drugs, sometimes three, ideally in a single pill, for the best outcomes. A single (combination-drug) pill gives more effective and rapid BP control than monotherapy and two 'free' drugs. You get reduced side effects, enhanced adherence, improved cardiovascular protection and they're more cost-effective,' said Prof Poulter.

Prof Poulter has just completed a major trial of three different two-drug combinations for lowering BP in black Africans in six sub-Saharan countries (the CREOLE study), with definitive but yet-to-be-released results. He said he hopes to present them 'somewhere prestigious' early next year.

'We now know what works for black Africans. Our primary end-point was to lower ambulatory systolic BP after six months,' he revealed, while keeping tight-lipped about the much-anticipated findings.

Clearing up muddy treatment waters

In two slightly differing presentations to the Cape Town WCIM, Prof Poulter reviewed existing combination-drug trials and decried the American lower treatment threshold BP guideline of 130/80 mmHg. He said that although the SPRINT study, which influenced this lower threshold, had reported lower rates of fatal and non-fatal major cardiovascular events from any cause, at systolic BP targeted to < 120 mmHg, the Americans measured BP 'in a way nobody does in this room – they used a machine with the patient alone in a back room, which gives lower BPs than those measured in your clinics.' He recommends sticking with the higher 140/90 mmHg diagnostic threshold for hypertension.

continued on page 32…

Relationship between clot burden in pulmonary computed tomography angiography and different parameters of right cardiac dysfunction in acute pulmonary embolism

Heba wagih Abdelwahab, Shreif Arafa, Khaled Bondok, Nihal Batouty, Mostafa Bakeer

Abstract

Background: Pulmonary computed tomography angiography (CTA) contains a wealth of information regarding the diagnosis and impact of acute pulmonary embolism (PE). Echocardiography remains the recommended examination to detect signs of right ventricular (RV) dysfunction in patients with shock or hypotension following PE.

Objectives: To detect the relationship between clot volume in pulmonary CTA and different parameters of RV dysfunction assessed by echocardiography and pulmonary CTA in patients with acute PE.

Methods: A cross-sectional study was performed on patients with acute PE from June 2017 to June 2018. Enrolled patients were assessed clinically, radiologically and for cardiac dysfunction. The relationship between clot volume and RV dysfunction was assessed using pulmonary CTA and echocardiography. Data were analysed with SPSS version 16. Correlations were studied using the Spearman and Kruskal–Wallis tests.

Results: There was a significant correlation found between clot volume and parameters of RV dysfunction, assessed by pulmonary CTA, including RV diameter ($p < 0.001$), RV to left ventricular (LV) diameter ratio ($p = 0.01$), pulmonary artery diameter ($p = 0.01$), ratio of main pulmonary artery to ascending aorta diameter ($p = 0.04$), and superior vena cava diameter ($p = 0.01$). On the other hand, there was no significant correlation between clot volume and parameters of RV dysfunction assessed by echocardiography.

Conclusion: In patients with acute PE, the assessment of RV dysfunction using pulmonary CTA showed good correlation with clot burden, unlike the assessment done with echocardiography.

Keywords: acute pulmonary embolism, clot burden, right ventricular dysfunction

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Pulmonary computed tomography angiography (CTA) has been established as the first-line imaging modality for the diagnosis of acute pulmonary embolism (PE) in clinical practice.[1] In addition to its role in diagnosis, pulmonary CTA contains a wealth of information, such as characteristics of the clot, which may be used as biomarkers to improve treatment and clinical management.[2]

Risk stratification for patients with acute PE is important to establish the appropriate management.[3] Patients with PE and preserved right ventricular (RV) function are treated with systemic anticoagulation, while haemodynamically unstable patients are considered to be candidates for thrombolytic therapy.[4]

Echocardiography is recommended as the first-line examination in patients with shock or hypotension following PE to detect signs of RV dysfunction. Pulmonary CTA, on the other hand, is a commonly used technique for diagnosis of PE and assessment of RV dysfunction, which would facilitate risk stratification in all patients.[5] This study was planned to detect the relationship between clot volume and different parameters of RV dysfunction assessed by echocardiography and pulmonary CTA in patients with acute PE.

Methods

A cross-sectional study was performed from June 2017 to June 2018. Seventy patients with acute PE admitted to the Chest Medicine Department, Mansoura University, were enrolled in this study. All patients provided written informed consent prior to participation. The study was approved by the institutional review board. Patients with inadequate pulmonary CTA scans (poor imaging) were excluded. Any decision about treatment was at the discretion of the attending physician.

Enrolled patients in this cross-sectional study were assessed clinically and radiologically, as well as for cardiac dysfunction. The clinical assessment was done using pulmonary embolism severity index score:[6] class I: ≤ 65 points, very low risk; class II: 66–85 points, low risk; class III: 86–105 points, intermediate risk; class IV: 106–125 points, high risk; class V: > 125 points, very high risk.

Assessment of RV dysfunction

For pulmonary CTA, Philips Ingenuity core 128, the Netherlands, and non-ionic iodinated contrast agent Iohexol 350 mgI/ml, Omnipaque, GE Health Care, Ireland, were used. The imaging studies were analysed by a radiologist. PE was assessed on pulmonary CTA images by detecting the presence of an endoluminal central filling defect partially or completely occluding the pulmonary arteries. We used a standard mediastinal

window and a semi-automated segmentation program to segment each clot from pulmonary CTA images and measure clot volume (mm^3). Clot assessment was done with regard to localisation (central, lobar or distal) and clot volume.

Pulmonary CTA signs were used to assess the function of the right side of the heart, including: the ratio of RV to left ventricular diameter (RV/LV ratio), ratio of main pulmonary artery to ascending aorta diameter (PA/AO ratio), and the superior vena cava diameter. The diameters of the right and left ventricles were measured on the axial CTA image of the heart at their widest point (Fig. 1), and the RV/LV ratio was calculated. The diameters of the main PA and the AO were measured on the transverse image at which the right pulmonary artery is in contiguity with the main pulmonary artery. The PA/AO ratio was calculated from this (Fig. 2).

For echocardiography, a Sonoscape A5 portable echocardograph was used. Ideally, multiple parameters should be used to determine RV systolic function.[7] Visual examination is the most commonly used method to quantify RV function (RVF) however it was proved that this method is not accurate if used as a single parameter for evaluation of RVF. Therefore the guidelines suggest using at least one of the following parameters to quantify RVF: fractional area change (FAC), tissue Doppler of the free lateral wall (S′), and tricuspid annular plane systolic excursion (TAPSE) with or without RV index of myocardial performance (RIMP).[8,9]

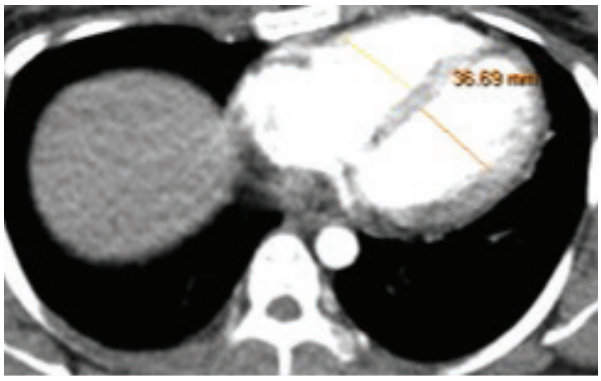

Fig. 1. Measurements of maximal RV and LV diameters in pulmonary CTA.

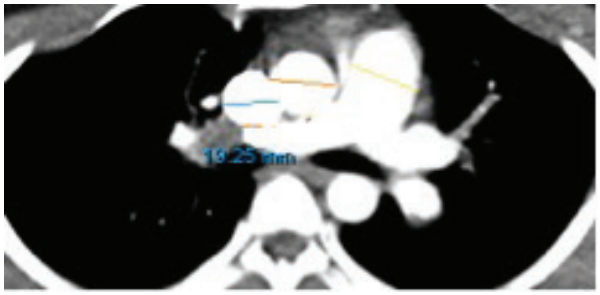

Fig. 2. Measurements of PA, AO and superior vena cava diameters in pulmonary CTA.

In our study, we used the following parameters to assess right cardiac function:

- Assessment of RV dilatation.
- Pulmonary artery systolic pressure.
- TAPSE, which represents a measure of RV longitudinal function. It is measured by M-mode echocardiography with the cursor optimally aligned along the direction of the tricuspid lateral annulus in the apical four-chamber view, measuring the amount of longitudinal motion of the annulus at peak systole (Fig. 3).
- Tissue Doppler imaging (TDI)-derived tricuspid lateral annular systolic velocity (S′), which correlates well with other measures of global RV systolic function.
- The RV myocardial performance index (MPI) or Tei index, which is an index of global RV performance. The isovolumic contraction time, isovolumic relaxation time and ejection time intervals were measured. This reflects both systolic and diastolic RV function. MPI is defined as the sum of isovolumic contraction time (IVCT) and isovolumic relaxation (IVRT) time, divided by the ejection time (ET) of the RV (Fig. 4).

Statistical analysis

SPSS version 16 was used in the analysis of data. Spearman correlation was used to test the association between clot volume and other continuous variables, while the Kruskal–Wallis test was used to test the association between categorical variables and clot volume. The *post hoc* Mann–Whitney *U*-test was applied to indicate which groups had significant associations with clot volume. Linear regression was used to evaluate the contribution of factors found to be significant in bivariate analysis in predicting clot volume.

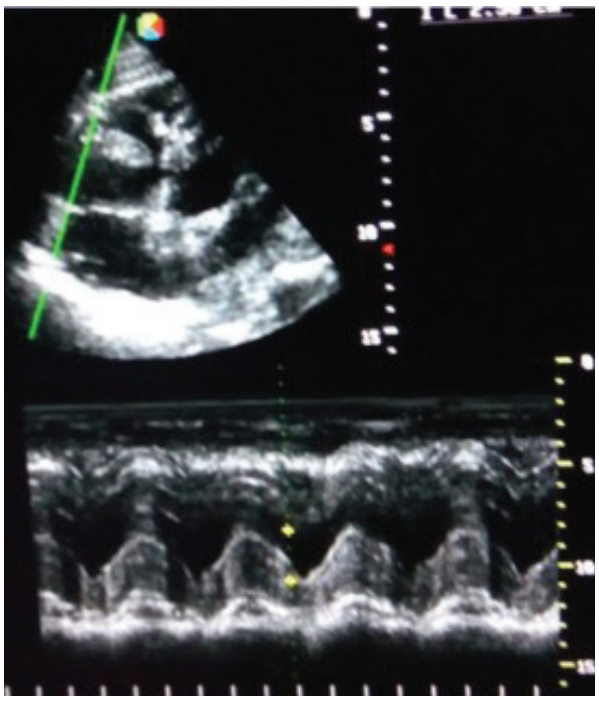

Fig. 3. Echocardiographic measurement of TAPSE.

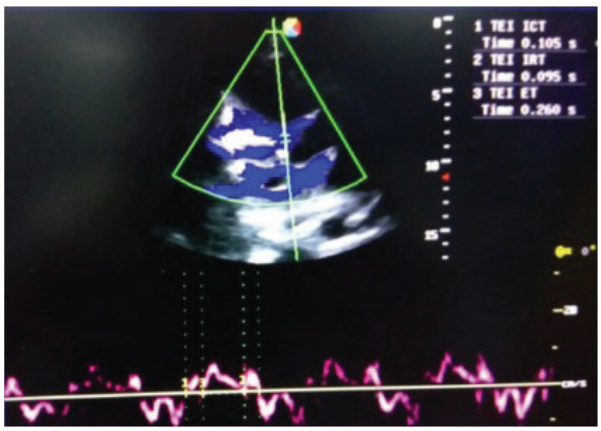

Fig. 4. Echocardiographic measurement of Tei index.

Results

Seventy patients with acute PE were evaluated and 34 (48.6%) were male. Mean age was 43 ± 15 years. Five patients (14.3%) were haemodynamically unstable at admission. Patient characteristics are shown in Table 1.

Localisation of emboli was central in 40 patients (57.14%), lobar in 18 (25.71%) and distal in 12 patients (17.14%). Saddle emboli were observed in eight patients (11.42%).

The median clot volume measured in all patients was 4 285 mm^3 (1 650–11 226) (minimum – maximum). No correlation was found between clot volume and age ($p = 0.24$) or gender ($p = 0.86$). Bivariate analysis using the Kruskal–Wallis test showed that there were significant associations between clot volume and the presence of auto-immune disease ($p = 0.028$) and hypotension ($p = 0.002$).

Regarding pulmonary CTA parameters, a significant correlation was found between clot volume and the following parameters of RV dysfunction: RV diameter ($p < 0.001$), RV/LV ratio ($p = 0.01$), PA diameter ($p = 0.01$), PA/AO ratio ($p = 0.04$) and superior vena cava diameter ($p = 0.01$) (Table 2).

On other hand, regarding echocardiography, there was no significant correlation found between clot volume and the following echocardiographic parameters of RV function: TAPSE ($p = 0.091$), S wave ($p = 0.667$), Tei index ($p = 0.985$), pulmonary artery systolic pressure ($p = 0.173$) and RV diameter ($p = 0.231$) (Table 2).

Table 1. Characteristics of the study population

Characteristic	*Value*
Gender	
Male, *n* (%)	34 (48.6)
Female, *n* (%)	36 (51.4)
Age (mean ± SD) years	43 ± 15
Risk factors	
Cancer, *n* (%)	20 (28.5)
Orthopedic surgery, *n* (%)	10 (14.28)
Auto-immune disease, *n* (%)	18 (25.7)
Heart failure, *n* (%)	8 (11.4)
Postpartum, *n* (%)	8 (11.4)
Immobilisation, *n* (%)	6 (8.5)

Discussion

PE is associated with a high risk of morbidity and mortality, mainly resulting from RV dysfunction. The effect of PE on RV function can be evaluated by either transthoracic echocardiography or pulmonary CTA.[10] Echocardiography is less costly than the other techniques available and remains the first-line examination technique for the RV. However, RV evaluation through echocardiography remains difficult because of the complex anatomy of the RV, its retrosternal position, and the interposition of the lungs.[11] In addition, studies comparing severity of clot load with RV burden assessed by echocardiography have reported controversial results.[10]

Pulmonary CTA, on the other hand, is the method of choice for the diagnosis of PE. It can also identify signs of RV dysfunction that may have prognostic significance or implications for treatment, for example, need for the institution of thrombolytic therapy versus conventional anticoagulation alone. Therefore there has been interest in inferring measures of RV dysfunction from pulmonary CTA.[12]

The results of our study showed a good correlation between clot burden and signs of RV dysfunction assessed by pulmonary CTA, but did not demonstrate a good correlation with those commonly used signs assessed by echocardiography. Different echocardiographic and CTA parameters of RV dysfunction were used in previous studies to assess its correlation with clot burden. Rodrigues *et al.*[10] assessed the effect of pulmonary vascular obstruction severity on RV function in patients with acute PE and concluded that no significant correlation was found between clot burden and echocardiographic parameters. These results could support our finding despite the fact that they used quantitative parameters such as fractional area change and pulmonary systolic pressure.

On the hand, another study was performed by Rodrigues *et al.*[13] to evaluate the correlation between a score of angiographic embolic load (Qanadli score, QS) and the parameters of RV dysfunction. They found that a QS > 18 points proved to be an independent predictor of RV dysfunction in acute PE, where echocardiography showed higher pulmonary artery systolic

Table 2. Correlation between clot volume and different imaging parameters

Parameters	*Mean*	*SD*	*Correlation coefficient (rho)*	p-*value*
CT angiography				
RV diameter (mm)	33.8603	6.26018	0.417	< 0.001
RV/LV	0.9331	0.18969	0.304	0.011
PA diameter (mm)	28.4651	5.30013	0.297	0.013
PA/AO	0.9023	0.16398	0.245	0.041
SVC diameter (mm)	18.3343	4.01406	0.287	0.016
Echocardiography				
TAPSE	1.9355	0.45778	–0.258	0.091
S wave	9.3790	1.93405	–0.068	0.667
Tei index	0.3875	0.23753	0.003	0.985
PASP	34.3471	16.31748	0.239	0.173
RV diameter	4.6875	0.86922	0.317	0.231

SD: standard deviation, RV diameter: right ventricular diameter, RV/LV: right ventricular/left ventricular ratio, PA diameter: pulmonary artery diameter, PA/AO: pulmonary artery/aorta ratio, SVC diameter: superior vena cava diameter, TAPSE: tricuspid annular plane systolic excursion, S wave: tissue Doppler imaging (TDI)-derived tricuspid lateral annular systolic velocity, Tei index: RV myocardial performance index, PASP: pulmonary artery systolic pressure.

pressure, and CTA revealed larger RV diameters and higher RV/LV ratio ($p = 0.002$), and greater superior vena cava, azygos vein and coronary sinus diameters. PA diameter and PA/AO ratio were similar.

In addition, the correlation between clot burden and echocardiographic regional RV dysfunction (RRVD) was studied by Tuzovic *et al.*[14] RRVD was defined as normal excursion of the apex, contrasting with hypokinesis of the mid free-wall segment. RV assessment included measurements of ventricular dimensions, fractional area change, free-wall longitudinal strain and TAPSE. The results of that study showed that regional RV dysfunction was associated with an increased clot burden in acute PE and was more prevalent among patients with moderate to severe RV enlargement.

Conclusion

In patients with acute PE, the assessment of right-sided cardiac dysfunction using pulmonary CTA showed a good correlation with clot burden. On the other hand, some commonly used echocardiographic parameters did not show a good correlation between RV dysfunction and clot burden. Despite its essential role in the assessment and diagnosis of acute PE, some common and routinely used echocardiographic parameters should not be used alone to judge the impact of PE with regard to RV dysfunction. It is suggested that pulmonary CTA parameters be used to adequately assess sequela of PE on RV function.

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Salidroside protects the cardiac function of exhausted rats by inducing Nrf2 expression

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Abstract

Objective: To investigate whether salidroside (Sal) protected the rat heart from exhaustive exercise-induced injury by inducing nuclear factor erythroid 2-related factor 2 (Nrf2) expression.

Methods: Forty-eight male Sprague-Dawley rats were divided into four groups (n = 12 rats per group): the control, the exhaustive swimming (ES) group, the low-dose Sal plus acute exhaustive swimming (SLE) group, and the high-dose Sal plus acute exhaustive swimming (SHE) group. In the SLE and SHE groups, 15 and 30 mg/kg Sal were administered, respectively, once a day. The rats in the control and ES groups were administered the same amount of physiological saline, respectively, once a day. On the 14th day, the rats in the ES, SLE and SHE groups underwent exhaustive swimming training once. Then cardiac function parameters and electrocardiograms were recorded. Biomarkers of myocardial injury in the serum and oxidative stress factors in the myocardial tissue were evaluated using ELISA tests. The levels of Nrf2, nuclear Nrf2 and Kelch-like ECH-associated protein 1 (Keap1) messenger RNA and proteins were assessed in the myocardium using q-PCR and Western blotting, respectively.

Results: Compared to the control group, the ES group showed remarkable increases in serum brain natriuretic peptide (BNP), cardiac troponin I (cTnI) and reactive oxygen species levels, but significant decreases in catalase and glutathione levels ($p < 0.05$). Compared to the ES group, the Sal treatment decreased serum BNP and cTnI levels and alleviated the changes in levels of oxidative stress-related factors. After treatment with Sal, nuclear and intracellular levels of Nrf2 protein were increased in the myocardial cells, while the level of Keap1 protein was decreased ($p < 0.05$).

Conclusion: Sal protected the heart from exhaustive exercise-induced injury, and it may improve cardiac function and cardiac bioelectricity in exhausted rats by inducing Nrf2 expression.

Keywords: exhaustive exercise, heart function, nuclear factor erythroid 2-related factor 2, oxidative stress, rats

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High-intensity exercise, such as exhaustive exercise (exercise intensity or duration exceeding the body's limit), not only influences performance in competition but also impairs the physical and mental health of athletes and military personnel.[1] Therefore it is important to explore performance and the pathogenesis of exercise-induced heart injury to improve its treatment.

Exhaustive exercise can cause destruction of the myocardial ultrastructure, abnormal energy metabolism and a reduction in cardiac function and electrocardio-electric changes.[2,3] Exhaustive exercise also increases oxidative stress levels, potentially causing heart damage.[4]

Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a leading role in activating or encoding anti-oxidant enzymes and an important role in regulating the oxidation–anti-oxidation states of cardiac and vascular endothelial cells.[5,6] High-intensity exercise affects Nrf2 levels, but the effect remains controversial. Acute intense exercise increased the messenger RNA (mRNA) transcription of Nrf2 target genes in skeletal muscle and most antioxidant enzyme genes in cardiac myocytes in mice.[7,8] Levels of Nrf2 protein exhibited little change in the skeletal muscle of rats exposed to exhaustive treadmill exercise, and the expression and enzyme activity of its target proteins also exhibited little or decreased change.[9]

Kelch-like ECH-associated protein 1 (Keap1) is a negative regulator of Nrf2. In response to oxidative stress, a conformational change in Keap1 causes Nrf2 to dissociate from Keap1, which is the most common method for activating Nrf2.[10] Upon activation, Nrf2 is transported to the nucleus, then antioxidant enzyme-encoding genes are expressed.[11] The expression of the antioxidant enzymes superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT) is mainly induced by activated Nrf2.

Exhaustive exercise also increases oxidative stress levels. Reactive oxygen species (ROS) activate the stress-response kinases in the MAPK family;[12] many protein kinases, such as the extracellular signal-regulating kinase (ERK) and p38MAPK are located upstream of Nrf2.[13,14] These kinases phosphorylate Nrf2

to regulate Nrf2 transcriptional activity and alter the cellular distribution of Nrf2, while exhaustive exercise alters the levels of p38MAPK and ERK. Therefore we hypothesised that exhaustive exercise may impact on the heart by modulating Nrf2 expression.

Salidroside (Sal) is an effective extract obtained from *Rhodiola rosea* that induces Nrf2 expression.[15,16] The intervention of Sal improved little in normal rats, but Sal increased coronary flow, improved cardiac function, reduced myocardial ischaemia–reperfusion injury, and improved the myocardial ultrastructure and energy metabolism in exhausted rats.[2,3,17] Sal altered myocardial levels of proteins in the MAPK pathway.[18] MAPK activation improved cardiac arrhythmia and other cardiac diseases.[19,20] Therefore we hypothesised that the protective effect of Sal on the exhausted heart was related to Nrf2 expression. In these experiments, we aimed to explore the effects of exhaustive exercise on myocardial levels of Nrf2 and Keap1.

Methods

Forty-eight male Sprague-Dawley rats (385 ± 34 g) were provided by the Academy of Military Medical Sciences (Beijing). National standard rodent dry feed was provided *ad libitum*, the indoor temperature was maintained at 18 to 22°C, and the relative humidity was maintained at 40 to 55%.

All experiments were conducted in compliance with the Guide for the Care and Use of Laboratory Animals and reviewed and approved by the Ethics Committee for the Use of Experimental Animals at No. 252 Hospital of the Chinese People's Liberation Army.

The main reagents used in this study are listed below. The 98% rhodionine powder was purchased from Nanjing Zelang Pharmaceutical Technology Co, Ltd. Solutions containing specific concentrations of Sal were generated by dissolving the Sal powder in sterile normal saline. The cardiac troponin I (cTnI), brain natriuretic peptide (BNP), CAT and GSH enzyme-linked immunoassay kits were obtained from BD Biosciences (New York, USA). The ROS enzyme-linked immunoassay kit was purchased from R&D Systems (USA) and the anti-Nrf2 and anti-Keap1 antibodies were purchased from Abcam (UK). The TRIzol total RNA extraction reagent was purchased from Tiangen Biotech Co, Ltd. The PrimeScript™ RT reagent kit with genome DNA Eraser, SYBR® Premix Ex Taq™ II, DL2 and DNA marker were purchased from TaKaRa Co, Ltd.

The following main instruments were used in this study: a PowerLab signal acquisition and analysis system, MultiscanGO enzyme standard instrument (Thermo, USA), Sigma 3k15 high-speed refrigerated centrifuge (Sigma, Germany), pressure–volume catheter (SPR-838, Millar Company, USA), fluorescence quantitative PCR platform (ABI 7500, Applied Biosystems), vertical electrophoresis system (BIO-TEK, USA), transfer electrophoresis system (BIO-TEK, USA), gel imaging system (BioSpectrum), image analysis system (Image-Pro Plus 4.1), PowerLab data acquisition and analysis system (AD Instruments, Australia), bioelectric amplifier (AD Instruments, Australia) and a needle electrode (AD Instruments, Australia).

Sprague-Dawley rats were randomly divided into four groups (n = 12 rats per group): the control, an acute exhaustive swimming group (ES), a low-dose Sal plus acute exhaustive swimming group (SLE), and a high-dose Sal plus acute exhaustive swimming group (SHE). Six of the 12 animals in each group were used for the pressure–volume catheter detection of cardiac function, which was an invasive experiment. These animals were euthanised after the experiment.

Serum, electrocardiogram and myocardial specimens were collected from the remaining animals (n = 6 rats per group). Each group was administered the Sal solution (15 or 30 mg/kg/d) or the same amount of normal saline for 14 days. The adaptive swimming exercise was performed three times (20 min/time) during the irrigation period. The control group did not exercise.

The rats in the ES, SLE and SHE groups were submitted to one exhaustive swimming training session after the 14-day treatment. Because eating would increase the time an animal would be required to swim to reach exhaustion, rats were fasted for 12 hours before training. The water temperature was maintained at 32°C, and the temperature fluctuated by no more than 1°C. Each rat in the exhaustion groups carried a tin wire (3% body weight) on the tail. The exhaustive swimming exercise was performed until exhaustion was achieved.

The experimental animal model of exhaustive exercise-induced damage was established according to the standards described by Thomas: animals were unable to return to the surface of the water for 10 seconds and when placed upside down, they were unable to complete a righting reflex.[21] Their fur was dried with a heater immediately after exhaustion was reached.

Rats were subjected to abdominal anaesthesia with pentobarbital sodium (40 mg/kg), the chest was opened, and blood was collected from the inferior thoracic vena cava. The blood was centrifuged at 3 000 rpm for 20 minutes and the supernatant was collected and stored in a –80°C freezer until detection of the serum indicators.

The hearts were quickly removed and washed with cold saline. Tissues were stored individually at –80°C until q-PCR and Western blot analysis was done.

Determination of cardiac function parameters with a pressure–volume catheter[22]

Rats were anaesthetised with pentobarbital sodium (40 mg/kg, intraperitoneal), and the closed-chest approach was chosen for catheter insertion. The animal was fixed in the supine position on the operating table. The skin of the neck was disinfected prior to a midline neck incision, and the trachea was separated and intubated. The right carotid artery was separated from the common carotid artery. Two 4-0 silk threads were sewn through the common carotid artery, and one of the silk threads was used to ligate the proximal end of the carotid artery. A cut was made at the end of the heart to complete the knot.

The pressure–volume catheter was inserted through the incision into the left chamber along the inverse blood flow of the carotid artery and calibrated with MPVS control software. The left ventricular pressure–volume waveform of the anaesthetised rats was recorded with Chart7 software in real-time. Vessels and catheters were fixed with another silk thread. Baseline data were recorded for 15 minutes.

The abdominal skin was disinfected, a median incision was made, the inferior vena cava was occluded, and changes in the waveform were recorded. A 20-µl solution of 30% NaCl was rapidly injected into the anterior jugular vein and pressure–volume waveform changes were recorded. The first four holes of a calibration cuvette with known diameters (provided by

the manufacturer) were quickly filled and the catheter tip was submerged in warm, fresh heparinised blood. The conductance changes in the volume channel were recorded and the volume was then calculated.

The heart rate (HR), end-systolic pressure (Pes), end-diastolic pressure (Ped), end-systolic volume (Ves), end-diastolic volume (Ved), stroke volume (SV), ejection fraction (EF), peak rate of the increase in pressure (dP/dt_{max}), peak rate of the decrease in pressure ($-dP/dt_{min}$), slope of the end-systolic pressure volume relationship (ESPVR), relaxation time constant (Tau), and slope of the end-diastolic pressure–volume relationship (EDPVR) were detected. The pressure–volume loop (PV loop) was drawn, with pressure on the *y*-axis and volume on the *x*-axis.

Electrocardiography

Adaptive electrocardiography (ECG) training was performed in all experimental rats. ECGs were recorded from rats in the control group in a quiet state for five minutes after 14 days of intraperitoneal injections of normal saline. In the EE, SLE and SHE groups, ECGs were recorded for five minutes immediately after exhaustive swimming. Wide-awake rats were placed in the rat cage, and both sets of limbs and the right forearm were routinely disinfected. Subcutaneous punctures in the extremities were created to insert the electrodes (the left hind leg was used as the positive electrode, the right foreleg as the negative electrode, and the left foreleg as the grounding electrode), and the electrode needle was fixed.

The dynamic ECG results were recorded using a PowerLab data acquisition and analysis system. The HR, PR interval, QRS interval, QT interval, P amplitude, R amplitude, ST height and T amplitude were obtained.

Enzyme-linked immunoassays for ROS, CAT and GSH levels in the myocardium

The heart was removed from the –80°C freezer and left ventricular myocardial tissue was sheared, weighed and diluted to produce a 10% homogenate in phosphate-buffered saline (PBS) (0.01 mol/l, pH 7.2). All procedures were performed on ice. The mixture was centrifuged at 5 000 rpm for 10 minutes at a low temperature, drained and placed in a new EP tube for storage.

Enzyme-linked immunosorbent assays were performed according to the instructions included in the kits. The optical density (OD) of each sample was measured at 450 nm. The OD value for the standard was measured, and a standard curve was constructed with the OD value on the *y*-axis and concentration on the *x*-axis. The concentration of the indicated marker in each sample was obtained from the standard curve.

q-PCR of mRNA levels in rat myocardial tissues

All gene sequences were obtained from GenBank (http://www.ncbi.nlm.nih.gov) and primers were synthetised by Invitrogen, Beijing. The upstream primer for Keap1 was GTGGAGACAGAGACCTGGACTTTC, its downstream primer was TGTCAAGCGGGTCACTTCACTC, and the product size was 178 bp. The upstream primer for Nrf2 was AAGATGCCTTGTACTTTGAAGACTGT, its downstream primer was GGAAAATAGCTCCTGCCAAACTT, and the product size was 223 bp. The upstream primer for actin was CCTAAGGCCAACCGTGAAAA, its downstream primer was GACCAGAGGCATACAGGGACA, and the product size was 106 bp.

The TRIzol total RNA extraction reagent was used to extract RNA from the samples, and real-time polymerase chain reaction (PCR) was performed according to the instructions for cDNA reverse transcription and PCR. In the reaction system, the fluorescent dye SYBR Green I was added for real-time monitoring, and the relative expression level of the target gene was analysed using the $2^{-\Delta\Delta CT}$ method. The reaction system was: 2X mix, 10 µl; upstream primer (10 µM), 0.5 µl; downstream primer (10 µM), 0.5 µl; template 2, 10 µl; and sterilised distilled water to a 20-µl total volume. The following amplification procedure was used: 95°C for 30 seconds, followed by 45 cycles of 95°C for five seconds and 60°C for 40 seconds.

Western blot analysis of Keap1 and total and nuclear Nrf2 levels in the left ventricular myocardium

The heart was removed from a –80°C freezer, left ventricular myocardial tissue was sheared on ice, minced with fine scissors, and 50 mg was removed and mixed with lysis buffer containing protease inhibitors and a phosphatase inhibitor. The solution was intermittently homogenised with an electric homogenate machine for one minute, incubated on ice for 30 minutes, and centrifuged at 12 000 rpm for 20 minutes at 4°C. The supernatant was then placed in a 0.5-ml centrifuge tube.

The nucleoproteins were extracted according to the manufacturer's instructions. Protein concentrations were determined using the bicinchoninic acid (BCA) method with bovine serum albumin as the standard. Then the protein samples were diluted to the same volume and heated at 100°C for five minutes after the addition of an equal volume of loading buffer. The denatured protein samples were separated by sodium dodecyl sulfate/polyacrylamide gel electrophoresis (SDS-PAGE) at 100 V for two hours and transferred to polyvinylidene fluoride (PVDF) membranes. The membranes were blocked with blocking buffer containing 5% skim milk at room temperature for one hour and then incubated with primary antibodies overnight at 4°C.

After the membranes were washed three times with Tris-buffered saline (TBS) containing Tween, they were incubated with secondary goat anti-mouse IgG antibodies conjugated to horseradish peroxidase for one hour at room temperature, and then exposed to ECL for one to two minutes to detect the bands. A gel imaging system was used to capture images and for the quantitative analysis, and grayscale values were determined.

Statistical analysis

The data are presented as means ± SD. SPSS 17.0 statistical software was used to analyse all experimental data. A single-factor analysis of variance was used for comparisons of multiple means after a one-way ANOVA and homogeneity test were first performed. Comparisons of mean values between two groups were performed using the LSD test if the variance was equal or Dunnett's T3 method if the variance was unequal. A correlation analysis was performed by calculating Pearson's correlation coefficients. A single-factor regression analysis was performed; $p < 0.05$ was considered to indicate a significant difference.

Results

The highest serum BNP (298.15 ± 36.98 ng/l) and cTnI (180.32 ± 19.69 pg/ml) levels were detected in the ES group. Significantly lower levels were detected in the Sal intervention groups.

Compared with the control group, significantly higher myocardial ROS levels were observed in the other groups (ES, SLE and SHE) ($p < 0.05$, $n = 6$). Significantly lower ROS levels were detected in the SLE (6.25 ± 0.36 ng/mg) and SHE (4.91 ± 0.74 ng/mg) groups than in the ES group (7.66 ± 0.81 ng/mg, $p < 0.01$, $n = 6$). Significantly lower ROS levels were observed in the SHE than the SLE group. Myocardial oxidative stress levels were significantly increased by the acute exhaustion produced by swimming, and myocardial ROS levels were reduced by Sal.

Myocardial CAT levels were significantly lower in the SLE, SHE and ES groups than in the control group (0.60 ± 0.04 ng/mg). Compared with the ES group, significantly higher myocardial CAT levels were observed in the SLE and SHE groups ($p < 0.01$, $n = 6$).

Significantly lower myocardial GSH levels were detected in the ES, SLE and SHE groups than in the control group (3.30 ± 0.45 U/mg). A significantly higher GSH level was observed in the SHE than in the ES group ($p < 0.05$, $n = 6$) (Fig. 1).

Compared with the control group, the HR, Pes, dP/dt_{max} and $-dP/dt_{min}$ were lower in the ES group, and the Ved, Ves, Ped, EDPVR and Tau were all higher. The differences in SV, Ved, Ped and Tau were significant between the Sal intervention groups and the control group. The Pes, dP/dt_{max}, $-dP/dt_{min}$, Tau and EDPVR were substantially higher in the SLE and SHE groups than in the ES group. Compared with the control group, a lower HR was recorded in the SLE and ES groups.

Non-significant differences in EF and ESPVR were observed between the groups ($p > 0.05$, $n = 6$). Non-significant differences in EF and ESPVR were also observed between the SLE and SHE groups (Table 1).

HR was increased in the ES group ($p < 0.05$, $n = 6$). The PR and QTc intervals were significantly longer in the ES, SLE and SHE groups than in the control group. A larger R amplitude was observed in the ES group ($p < 0.01$, $n = 6$), but a smaller amplitude was observed in the SLE and SHE groups than in the ES group ($p < 0.01$, $n = 6$). However the QT interval and P amplitude were significantly higher in the ES and SLE groups. The ST-segment of the ES group was changed (Table 2).

Compared with the control group (0.71 ± 0.17), the change in expression of Nrf2 mRNA was not statistically significant. Compared with the ES group (0.57 ± 0.13), a non-significant change in expression of Nrf2 mRNA was observed in the SLE (0.59 ± 0.18) and SHE groups (0.54 ± 0.06) after the application of Sal. A non-significant change in expression of Keap1 mRNA was observed (Fig. 2).

Compared with the control group (0.39 ± 0.07), the level of Nrf2 protein in the ES group (0.43 ± 0.06) did not change significantly. However, significantly higher levels of Nrf2 protein were detected in the myocardium and nuclei of the SLE and SHE groups ($p < 0.01$, $n = 6$). Compared with the SLE group (0.48 ±

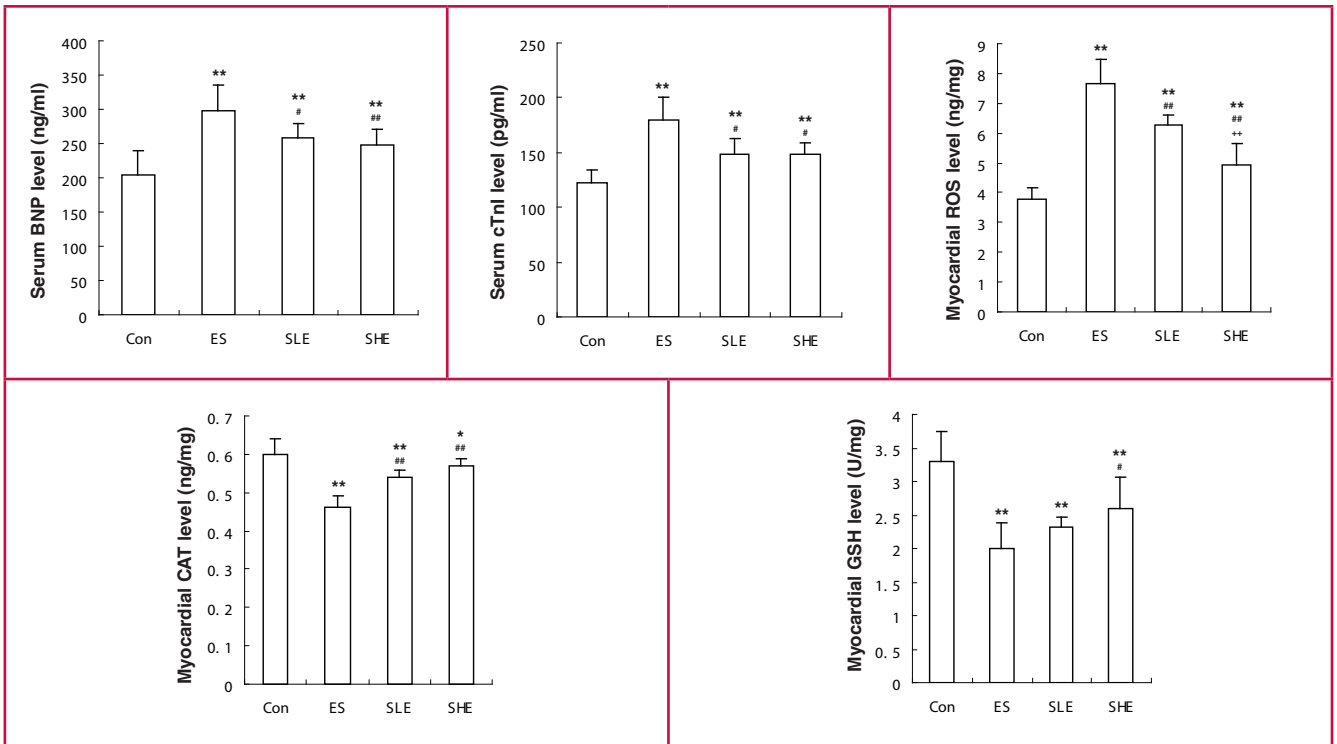

Fig. 1. The effect of Sal on serum BNP, cTnI and ROS levels, CAT and GSH in the myocardium after exhaustive exercise. The data are presented as means ± SD, $n = 6$ animals per group. BNP: brain natriuretic peptide; cTnI: cardiac troponin I; ROS: reactive oxygen species; CAT: catalase; GSH: glutathione; Con: control group; ES: acute exhaustive swimming group; SLE: low-dose salidroside plus exhaustive swimming group; SHE: high-dose salidroside plus exhaustive swimming group. $^{*}p < 0.05$ and $^{**}p < 0.01$ compared with the control group; $^{\#}p < 0.05$ and $^{\#\#}p < 0.01$ compared with the ES group; $^{++}p < 0.01$ compared with the SLE group.

Table 1. The effect of Sal on cardiac function parameters in exhausted rats

Parameter	*Control*	*ES*	*SLE*	*SHE*
SV (μl)	122.10 ± 10.77	166.70 ± 16.71**	176.14 ± 22.69**	183.74 ± 19.34**
Ves (μl)	71.88 ± 6.38	96.21 ± 9.36**	83.22 ± 14.99	85.34 ± 14.80
Ved (μl)	183.60 ± 29.82	249.09 ± 10.46**	257.48 ± 11.45**	262.40 ± 19.12**
Pes (mmHg)	93.05 ± 11.68	71.45 ± 8.93**	92.11 ± 6.04##	99.25 ± 5.57##
Ped (mmHg)	5.05 ± 3.30	7.88 ± 2.04*	6.69 ± 0.86*	6.60 ± 1.2*
HR (bpm)	375 ± 31	298 ± 41**	309 ± 24**	345 ± 12
Systolic indices				
EF (%)	72.17 ± 6.36	69.05 ± 4.00	72.29 ± 4.07	70.02 ± 5.83
dP/dt_{max} (mmHg/s)	7884 ± 1538	4756 ± 627**	7121 ± 1204#	8883 ± 616##
ESPVR	1.28 ± 0.82	1.21 ± 0.27	1.30 ± 0.32	1.32 ± 0.35
Diastolic indices				
$-dP/dt_{min}$ (mmHg/s)	–6336 ± 1643	–3904 ± 826*	–4906 ± 936##	–7361 ± 790##
Tau (ms)	6.06 ± 0.77	14.55 ± 2.36**	11.08 ± 1.36**#	10.69 ± 1.35**#
EDPVR	0.022 ± 0.012	0.036 ± 0.009**	0.025 ± 0.005#	0.020 ± 0.007##

The data are presented as means ± SD, $n = 6$ animals per group.
SV: stroke volume; Ves: end-systolic volume; Ved: end-diastolic volume; Pes: end-systolic pressure; Ped: end-diastolic pressure; HR: heart rate; EF: ejection fraction; dP/dt_{max}: peak rate of the increase in pressure; ESPVR: slope of end-systolic pressure volume relationship; $-dP/dt_{min}$: peak rate of the decrease in pressure; Tau: relaxation time constant; EDPVR: slope of end-diastolic pressure–volume relationship; ES: acute exhaustive swimming group; SLE: low-dose salidroside plus exhaustive swimming group; SHE: high-dose salidroside plus exhaustive swimming group.
*$p < 0.05$ and **$p < 0.01$ compared with the control group; #$p < 0.05$ and ##$p < 0.01$ compared with the ES group.

Table 2. The effect of Sal on changes in ECG parameters in exhausted rats

Parameters	*Control*	*ES*	*SLE*	*SHE*
RR interval (ms)	15.70 ± 0.97	14.04 ± 1.27*	15.49 ± 2.02	15.56 ± 1.14
Heart rate (bpm)	392 ± 21	444 ± 37**	412 ± 33	405 ± 30
PR interval (ms)	4.18 ± 0.28	4.64 ± 0.43*	4.77 ± 0.39**	4.61 ± 0.48*
P duration (ms)	1.64 ± 0.24	1.48 ± 0.24	1.54 ± 0.27	1.65 ± 0.23
QRS interval (ms)	1.96 ± 0.19	1.96 ± 0.18	1.98 ± 0.33	1.84 ± 0.38
QT interval (ms)	5.96 ± 0.55	6.96 ± 0.95*	7.02 ± 0.97*	6.83 ± 0.98
QTc interval (ms)	14.62 ± 1.73	19.70 ± 1.87**	18.07 ± 3.14**	18.42 ± 2.44**
P amplitude (mV)	0.069 ± 0.022	0.120 ± 0.036**	0.112 ± 0.028*	0.096 ± 0.017
R amplitude (mV)	0.514 ± 0.073	0.722 ± 0.107**	0.578 ± 0.088##	0560 ± 0.084##
ST height (mV)	0.033 ± 0.072	0.105 ± 0.050*	0.064 ± 0.067	0.045 ± 0.019
T amplitude (mV)	0.140 ± 0.070	0.174 ± 0.059	0.156 ± 0.053	0.143 ± 0.041

The data are presented as means ± SD, $n = 6$ per group.
ES: acute exhaustive swimming group; SLE: low-dose salidroside plus exhaustive swimming group; SHE: high-dose salidroside plus exhaustive swimming group.
*$p < 0.05$ and **$p < 0.01$ compared with the control group; ##$p < 0.01$ compared with the ES group.

0.11), nuclear Nrf2 levels were significantly increased in the SHE group (0.61 ± 0.08) ($p < 0.01$, $n = 6$).

Compared with the control group (0.96 ± 0.03), Keap1 protein was expressed at lower levels in the other groups ($p < 0.01$, $n = 6$). The level of Keap1 protein was significantly reduced in the SLE (0.66 ± 0.06) and SHE groups (0.52 ± 0.03) compared to the ES group (0.72 ± 0.04), and it was expressed at significantly lower levels in the SHE than in the SLE group ($p < 0.01$, $n = 6$) (Fig. 3).

In the control group, Pearson's correlation coefficient between the T amplitude and level of Nrf2 protein was –0.944 ($p < 0.05$), indicating a negative correlation. In the ES group, Pearson's correlation coefficient for dP/dt_{max} with nuclear Nrf2 was 0.836 ($p < 0.05$). Nuclear Nrf2 levels positively correlated with the R amplitude, and Pearson's correlation coefficient was 0.921 ($p < 0.01$). Keap1 level was positively correlated with the QT interval ($r = 0.934$, $p < 0.05$). In the SLE group, nuclear Nrf2 levels were positively correlated with the P amplitude, with a correlation coefficient of $r = 0.875$ ($p < 0.05$). In the SHE group, the P amplitude was negatively correlated with levels of Nrf2 protein ($r = –0.817$, $p < 0.05$) (Table 3).

Expression levels of target proteins were divided by the expression level observed in the control group. Then we obtained the multiples of activated Nrf2 and inhibited Keap1. The effect of Sal on myocardial Nrf2 activation, nuclear translocation of Nrf2 and inhibition of Keap1 were analysed using a single-factor regression analysis ($n = 6$). Myocardial Nrf2 expression increased with increasing Sal concentrations ($y = 0.0429x + 1.112$, $p < 0.05$). Moreover, nuclear translocation of Nrf2 also increased with increasing Sal concentrations ($y = 0.1195x + 1.557$), while the expression of Keap1 decreased ($y = –0.0068x + 0.7592$); however, the differences were not significant ($p > 0.05$) (Fig. 4).

Discussion

In this study, Sal improved cardiac function and electrocardiography in exhausted rats. Regarding the mechanism, for the first time, we revealed that Sal induced Nrf2 expression and increased nuclear translocation of Nrf2. Sal intervention did

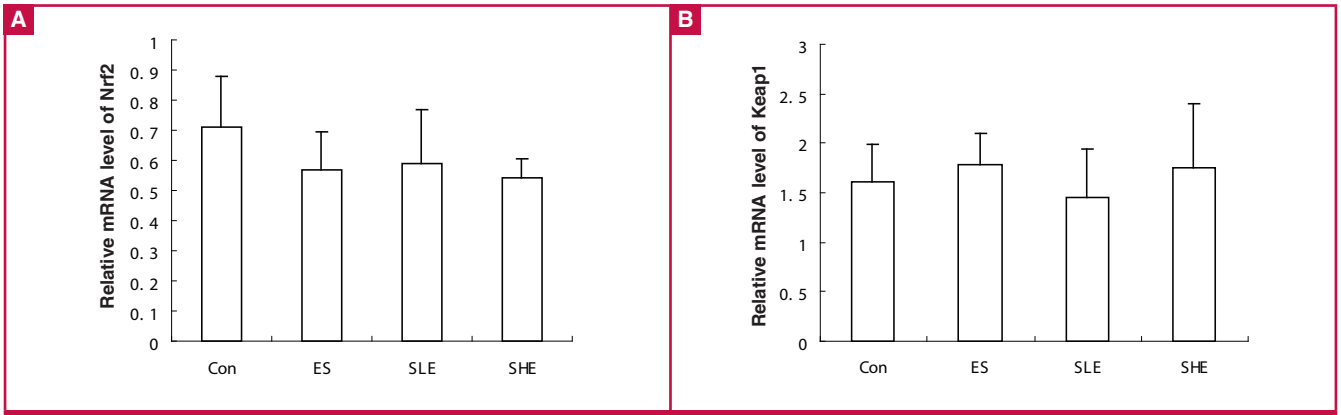

Fig. 2. The effect of Sal on expression of Nrf2 and Keap1 mRNA after exhaustive exercise. The data are presented as means ± SD, $n = 6$ animals per group. A: Relative levels of Nrf2 mRNA in rat myocardium. B: Relative levels of Keap1 mRNA in rat myocardial tissue. Con: control group; ES: acute exhaustive swimming group; SLE: low-dose salidroside plus exhaustive swimming group; SHE: high-dose salidroside plus exhaustive swimming group.

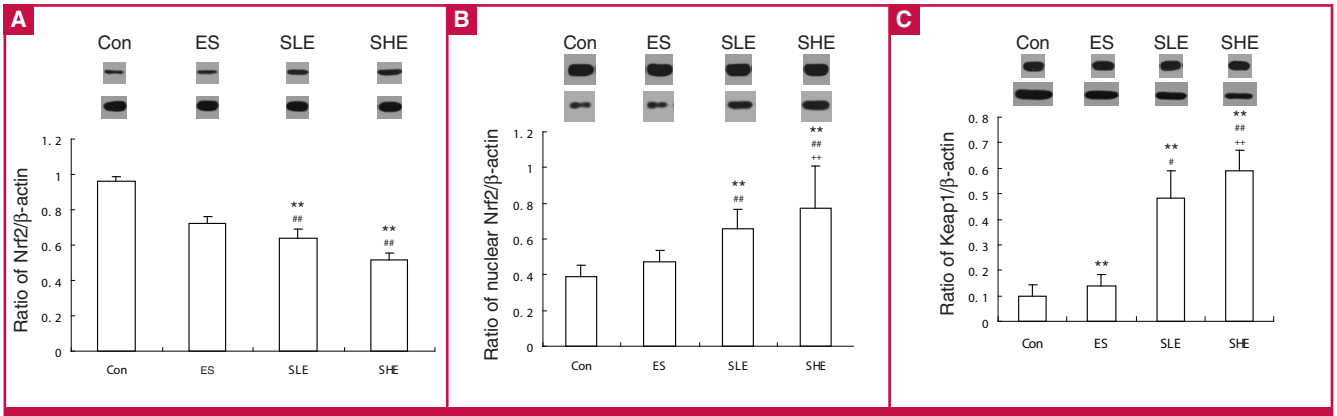

Fig. 3. The effect of Sal on levels of total and nuclear Nrf2 and Keap1 proteins in rat myocardium after exhaustive exercise ($x \pm s$, $n = 6$). A: Ratio of Nrf2/β-actin levels in rat myocardium. B: Ratio of nuclear Nrf2/β-actin levels in rat myocardium. C: Ratio of Keap1/β-actin levels in rat myocardium. Con: control group; ES: acute exhaustive swimming group; SLE: low-dose salidroside plus exhaustive swimming group; SHE: high-dose salidroside plus exhaustive swimming group. $^{**}p < 0.01$ compared with the control group; $^{\#\#}p < 0.01$ compared with the ES group; $^{++}p < 0.01$ compared with the SLE group.

not affect levels of Nrf2 or Keap1 mRNA in the myocardium of exhausted rats. However, it decreased the Keap1 level in the myocardium. Therefore more Nrf2 was transported to the nucleus to induce the expression of antioxidant enzymes in the heart, reduce oxidative stress reactions in the exhausted myocardium, and protect the heart from exhaustion.

Under the high circulatory conditions observed during exhaustive exercise, the strength of cardiac stroke volume must increase to meet the needs of the increased metabolism of organs throughout the body. Ved and Ves increased, ventricular diastolic and systolic load both increased significantly, and the PV loop shifted to the right. Pes and dP/dt_{max} were both markedly reduced, and cardiac systolic function decreased. Stroke volume is always adapted to the Ved phase, and the EF therefore did not show a significant difference. Notably, the $-dP/dt_{min}$ was reduced, while Tau was noticeably longer in the exhaustive exercise groups, suggesting that left ventricular diastolic function was decreased.

The results of this experiment are similar to the findings described in the study by Alexiou.[23] After applying Sal, Ved decreased, Pes increased, dP/dt_{max} and $-dP/dt_{min}$ recovered, and Tau was reduced. Based on these results, Sal improved systolic and diastolic function in exhausted hearts.

On ECG, HR showed a compensatory increase, the RR interval became shorter, and an increase in the ST-segment height caused by myocardial ischaemia was observed during the process of exhaustion. Myocardial ischaemia altered the activity of the heart conduction system, prolonged the PR and QT intervals and increased the risk of arrhythmia. The R amplitude was clearly reduced in the Sal-treated groups. Sal reduced the instability in cardiac electrical activity and conduction dysfunction caused by myocardial ischaemia, and prevented the occurrence of arrhythmias.

As shown in the study by Zhao investigating ECG data, the levels of ST–T changes and arrhythmia differed after exhaustive exercise.[24] In our experiments, the anaesthetised and awake states exerted opposite effects on HR that are potentially related to the inhibitory effect of anesthetic drugs on the exhausted heart.

Exhaustive exercise increased ROS levels, and the accumulation of ROS in myocardial cells leads to structural

Table 3. Pearson's correlation analysis for some parameters (r)

	Control	*ES*			*SLE*	*SHE*
Parameter	*T amplitude (mV)*	*R amplitude (mV)*	*QT interval (ms)*	*dP/dt_{max} (mmHg/s)*	*P amplitude (mV)*	*P amplitude (mV)*
Nrf2	–0.944**	0.041	0.333	–0.362	–0.182	–0.817*
Nuclear Nrf2	0.157	0.921**	0.699	0.836*	0.875*	0.324
Keap1	0.445	0.453	0.934*	0.153	–0.724	–0.250

The data show Pearson's correlation coefficients (r), $n = 6$ animals per group.
$^{*}p < 0.05$ and $^{**}p < 0.01$.
ES: acute exhaustive swimming group; SLE: low-dose salidroside plus exhaustive swimming group; SHE: high-dose salidroside plus exhaustive swimming group; dP/dt_{max}: peak rate of the increase in pressure.

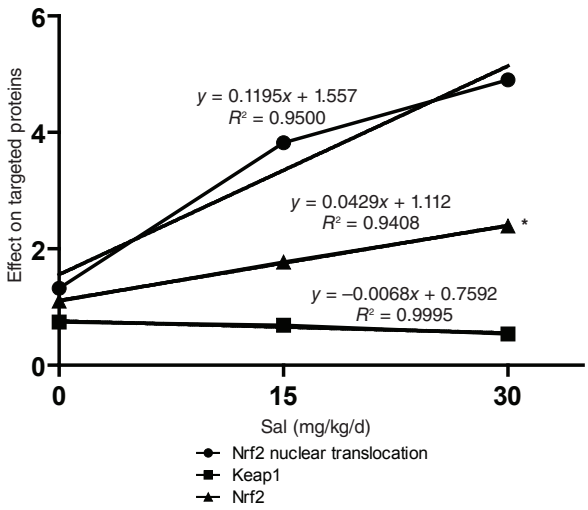

Fig. 4. The effects of different concentrations of Sal on the inhibition of Keap1 and the activation and nuclear translocation of Nrf2 in the myocardium were analysed using a single-factor regression analysis ($n = 6$). The level of target protein was divided by the level observed in the control group, and the multiple of change in inhibition or activation of the target protein was obtained. Sal: salidroside; $^{*}p < 0.05$.

and functional damage in the heart.[2] The accumulation of ROS activated Nrf2 during exhaustive exercise, but did not produce a sufficient level of activation to prevent oxidative damage, and drugs were required to further activate Nrf2. Nrf2 was expressed at significantly higher levels after the Sal treatment. However, the expression of Nrf2 mRNA was not affected by Sal, indicating that Sal did not regulate Nrf2 expression at the transcriptional or translational level, but instead at the post-translational level.

According to Numazawa, inducers rarely promote the biosynthesis of Nrf2.[25] The epigenetic regulation of Nrf2 activity might involve a long-term or basic regulatory mechanism. Sal may either inhibit Keap1 expression or promote its degradation. The abundance of Nrf2 was inhibited and its degradation was reduced, increasing the level of Nrf2 protein. The level of Nrf2 in the nucleus increased significantly as the concentration of Sal increased. Sal induced nuclear translocation of Nrf2.

Devling *et al.* used an siRNA to antagonise the Keap1 mRNA and its expression decreased significantly. The authors observed a significant increase in the level of Nrf2 transported to the nucleus. Moreover, the levels of antioxidant enzymes were also increased significantly.[26,27]

The antioxidant enzyme system downstream of Nrf2 consists of SOD, CAT and GSH and plays a role in preventing cardiac remodelling and cardiac function disorders.[28,29] In the control group, a positive correlation was observed between EDPVR and GSH, while dP/dt_{max} and GSH were positively correlated in the ES group. Therefore GSH exerted a protective effect on the heart and improved cardiac function parameters.

The observed decrease in levels of GSH and other enzymes after exhaustive exercise was due to their function in reversing ROS levels. The levels of SOD, CAT and GSH all increased with increasing concentrations of Sal. Sal induced Nrf2 expression and increased levels of downstream antioxidant enzymes by increasing the amount of Nrf2 protein and activating its nuclear translocation.

Conclusion

Sal protected the heart from exhaustive exercise-induced injury, and it may improve cardiac function and cardiac bioelectricity in exhausted rats. Sal improved the antioxidant capacity by activating Nrf2.

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Meanwhile, reports in the prestigious *Lancet* and *British Medical Journal* differ over the BP targets recommended. What guidelines in the world tend to agree on, he said, was that treating with two drugs as initial therapy was the way to go. Just two drugs in a single tablet has already improved compliance by 21%. If a patient was above a certain level of risk, they should also be on a statin, regardless of cholesterol levels, until at least 80 years of age, he added.

Prof Poulter's conclusions from the ACE inhibitors vs ARB controversy in managing hypertension are that individual trial data and meta-analyses are relatively consistent in showing the superiority of ACE inhibitors. ARBs are better tolerated but do not reduce mortality rate or cardiac events as well as ACE inhibitors and should be used if patients cough on ACE inhibitors. Prof Poulter concluded his presentation with a telling cartoon of an obese man, with a frothy pint of beer in one hand and a cigarette butt in his mouth, sticking his hand through a hole in a wall, on the other side of which, an unseeing doctor measures his BP and puts pills in an outstretched palm.

Session moderator, Prof Sajidah Khan, an interventional cardiologist at the Gateway Private Hospital in Umhlanga, said that in the very country that most funds prevention (North America), the sale of ultra-processed foods this year rose by 2.3% compared to a 71% increase in Africa and Eastern countries. Simultaneously, the revenue growth for the world's biggest tobacco retailer, Philip Morris, rose by 2.8%. It was therefore unsurprising that 80% of all cardiovascular disease occurs in lower- to middle-income countries. The damaging myths about statins paled by comparison with this.

Prof Brian Rayner, head of the Division of Nephrology and Hypertension at the Groote Schuur Hospital and University of Cape Town, said a three-pill regimen would address huge unmet needs in South Africa and the continent. He said up to 90% of hypertensive South African patients remain untreated and agreed with Prof Poulter that the American guidelines, 'have set us back and created confusion in the definition of hypertension – there's a big difference between a target and the definition,' he added.

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Ductal closure in infants under 6 kg including premature infants using Amplatzer™ duct occluder type two additional sizes: a single-centre experience in South Africa

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Abstract

Background: This is a report on percutaneous closure of patent ductus arteriosus (PDA) using Amplatzer Duct Occluder type two additional sizes (ADO II AS) in patients under 6 kg.

Methods: Prospective data were collected and a review of patients' records was conducted. Demographics, and angiographic and clinical outcomes are reported in this article.

Results: During the period June 2011 to June 2017, of the 92 patients who underwent closure of the PDA using the ADO II AS device, 59 were under 6 kg. The median weight of the cohort at closure was 3.6 kg (range: 900 g – 5.8 kg). The median ductal diameter was 1.9 mm (range: 1.0–3.4 mm). Three embolisations in the cohort were all retrieved percutaneously. Two PDAs were closed percutaneously and one surgically. Four premature infants required blood transfusions. The closure rate was 96.6% before discharge.

Conclusion: PDA closure using ADO II AS in small infants is feasible, effective and has few complications.

Keywords: congenital heart disease, paediatric intervention, percutaneous closure

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In the term newborn, patent ductus arteriosus (PDA) accounts for about 5–10% of all congenital heart lesions.[1,2] This incidence is higher in the preterm infant and may be as high as 70% in infants less than 28 weeks' gestation, which could be due to the untoward effect of prematurity on the regulators of ductal tone.[3-5]

Ductal patency in the preterm infant is associated with heart failure and pulmonary oedema, bronchopulmonary dysplasia (BPD) and necrotising enterocolitis (NEC). In addition, ductal patency may lead to intraventricular haemorrhage (IVH), prolonged ventilator or oxygen support, a long stay in hospital and increased mortality rates.[6,7]

Established PDA management methods in small infants include conservative management with supportive therapy, pharmacological therapy with anti-prostaglandins, such as ibuprofen or indomethacin, and surgical ligation.[8-10] Percutaneous closure of a PDA has become standard treatment in older children and adults. Various reports note successful ductal closure using a wide range of available devices on the market, which include the Amplatzer™ duct occluders.[11] However, the Rashkind device is no longer used for PDA closure, and coils are used in appropriately selected patients.[11,12]

There are a growing number of publications on percutaneous ductal closure in small infants, including premature infants.[13-18] The introduction of Amplatzer™ Duct Occluder type two additional sizes (ADO II AS) (Abbott Laboratories, St Jude Medical, St Marks, Minnesota) has revolutionised the management of ducts in the lower-weight infant.[19-22] Routine percutaneous PDA closure in infants under 6 kg using the Amplatzer™ device as standard management is however currently not FDA approved.[23]

Challenges facing a low- and middle-income country (LMIC) such as South Africa include a shortage of congenital heart surgeons and the protracted hospital stay of patients awaiting surgery. These result in increased patient mortality and morbidity rates as well as high hospital costs.[23-26] Therefore the aim of this study was to report on the experience of closing a PDA in infants under 6 kg at a single centre in a LMIC (which is usually faced with the above-mentioned challenges).

Methods

This study reports on percutaneous PDA closure using the ADO II AS device in infants less than 6 kg, including preterm infants, at the Port Elizabeth hospital complex in South Africa. This is a coastal tertiary healthcare centre offering general paediatrics, paediatric cardiology and neonatal healthcare services with fully qualified paediatric cardiologists and neonatologists. As our centre is the only referral site for the diagnosis and management

of congenital heart disease in the province of the Eastern Cape, South Africa, it was used for the study, although the incidence of PDA had not been documented there.

As part of the study protocol, the cohort included all those patients who were under 6 kg at ductal closure, including preterm infants, which included all those who were born before 37 weeks' gestational age. Excluded from the study were patients with other congenital heart diseases requiring surgery and those that had severe congenital abnormalities with redirected overall clinical care.

An echocardiographically haemodynamically significant PDA (hsPDA) was defined as a PDA with a diameter of > 1.4 mm/kg body weight, with or without pulmonary hypertension, and a left atrium:aortic ratio of > 1.4:1.[27-29] Pulmonary hypertension was defined as tricuspid regurgitation velocity of more than 3.4 m/s, with an estimated pulmonary systolic pressure of more than 50 mmHg, with or without additional echocardiographic variables suggestive of pulmonary hypertension.[29]

The criteria for percutaneous closure of the PDA in the premature infants involved in the study included those who were diagnosed with an echocardiographically hsPDA that had failed supportive therapy and medical treatment with anti-prostaglandins (ibuprofen or paracetamol–indomethacin is not used in our unit), and those who were ventilator-dependent and required FiO_2 (fraction of inspired oxygen) of > 60% after failed supportive or medical therapy.

The criteria for ductal closure in other infants included echocardiographic evidence of an hsPDA as above,[30] and signs of left ventricular volume overload. In addition, the criteria included those with severe pulmonary arterial hypertension with pulmonary arterial pressures that were more than two-thirds of systemic pressures or pulmonary vascular resistances that were more than two-thirds of systemic vascular resistances, but still with a left-to-right shunt and with pulmonary vascular reactivity on vaso-reactive testing.[31]

The study was conducted following clearance from the Health Research and Bio-safety Committee of Walter Sisulu University regarding Research in Human Subjects and from the chief executive officer of Dora Nginza Hospital, Port Elizabeth. Moreover, informed consent from patients' parents or guardians was obtained.

Prospective data collection and a review of records of patients who had undergone percutaneous closure of a PDA using the ADO II AS device in a single centre in South Africa was performed. Due note was taken of the manufacturer's recommendation that this device should not be used for the percutaneous closure of the PDA in patients who weigh less than 6 kg. Moreover, the device is not FDA approved for routine use in infants under 6 kg.[23] Parents were therefore informed that, even though these devices are not FDA approved for routine use in this weight group, they possess the Conformité Européenne (CE) mark. This means that they may be utilised for PDA closure in South Africa as per the South African Health Products Regulatory Authority (SAHPRA) guidelines on the use of medical devices in South Africa.[31,32]

The patients' age, gender and weight at the time of closure were documented. Haemodynamic and angiographic data, ductal morphology, device type and size, radiation exposure, complications and outcomes were also recorded. The ductal shape was classified using the Krichenko classification,[33] which classifies ductal morphology according to five types. It is type A if it is conical, B if it is tubular and less than 3 mm in length, type C if it is tubular and more than 3 mm in length, D if it is complex and has more than one constriction, and E if the duct is conical and elongated. The descending aortic diameter was measured in the thoracic aorta just distal to the PDA ampulla. A decision to close a PDA using the ADO II AS was also based on a ductal size of less than 4 mm, as per manufacturer's guidelines. In addition, associated congenital heart defects were documented.

In this study, values are reported as median (range). There were no statistical comparisons that were required for this study.

In all treatment groups, an analysis of all complications including events related to vascular access, sedation, airway and cardiac catheterisation was done as described by Bergersen *et al.*[34] The complications were further classified as being 'major' or 'minor'.[34]

The ADO II AS device is made of a meshwork of self-expandable nitinol wire. A detailed account of various device sizes and guidelines regarding device selection for ductal closure is documented by Kenny *et al.*[19] In brief, the device consists of a central 'lobe', which measures 3–5 mm in diameter, and a retention disk on each side of the lobe (Fig. 1). The disks are 1–1.5 mm more than the central lobe and range from 4–6.5 mm in diameter. The length of the device ranges from 2–6 mm. The devices are delivered using a TorqVue low-profile delivery system (4–5F) (Abbott Laboratories, St Jude Medical, St Marks, Minnesota). ADO II AS transcatheter (percutaneous) delivery protocol was adhered to.[19]

During cardiac catheterisation, patients were sedated using a mixture of intravenous midazolam (at 0.2 mg/kg) and ketamine (at 2 mg/kg) as the initial dose, which was repeated as needed. Femoral arterial and/or venous access was achieved using standard 4–5F vascular access short sheaths. In the premature infants and infants where vascular access using standard vascular access set with a 0.018-inch wire was a challenge, a 0.014-inch wire and a 21- or 23-gauge scalp vein set (Butterfly set) were used. Heparin, at a dose of 50 U/kg, was given following femoral arterial access.

Fig. 1. Amplatzer Duct Occluder type two additional sizes: the device has two retention disks and a central lobe, and is attached to a delivery wire. Published with permission from Abbott Laboratories, St Jude Medical, St Marks, Minnesota.

In premature infants, IVH was diagnosed using cranial ultrasound before cardiac catheterisation. Furthermore, in those infants with IVH, heparin was not given and only venous access was used. However, when there was difficult access through either venous or arterial access, single access was used to close the PDA, as the ADO II AS device is deliverable both anterogradely and retrogradely. Following angiographic assessment and if the PDA was amenable to percutaneous closure, a device thought to be appropriate for PDA closure was selected using the manufacturer's device selection guidelines.

After percutaneous ductal closure, patients received intravenous antibiotics and would receive infective endocarditis prophylaxis for six months. Patients had clinical and echocardiographic follow up. Clinical follow up entailed a general examination, including a check-up of the vascular access site for catheterisation, pedal pulses and the rest of the cardiovascular system. This included the detection of cardiac murmurs, aortic regurgitation and features of congestive cardiac failure. These are known as complications of percutaneous PDA closure (Abbott Laboratories, St Jude Medical, St Marks, Minnesota). The clinical follow up consultations with echocardiography were scheduled in one day, one, three and six months, one year and ultimately two years following PDA occlusion, using this device as per our protocol and as suggested by the manufacturer.

Results

During the period June 2011 to June 2017, 92 patients underwent closure of a PDA using the ADO II AS device in a single centre, and 59 of these had a weight of less then 6 kg at the time of the intervention. There were 15 premature infants who had a PDA with failed medical therapy with either oral ibuprofen or intravenous paracetamol and remained with an echocardiographically hsPDA with FiO_2 requirements of > 60%.

Demographic, haemodynamic and angiographic data are presented in Table 1. There were 32 females and 27 males. The median age of the cohort was four months (range: 23 days to 12 months). The weight ranged from 0.9 to 5.8 kg (median: 3.6 kg) in these infants. There was significant left-to-right shunting across the PDA, with a median pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2.4 in this group. Haemodynamic studies were performed on 96.6% of the patients (57 out of 59). The pulmonary artery mean range was 9–47 mmHg and that of pulmonary vascular resistance was 0.3–7.12 Wood units (Table 1).

There were 16 patients with a type A PDA (Fig. 2A, B), 15 with a type C (Fig. 2C, D), four with a type D (Fig. 2E, F), and 24 with a type E (Fig. 2G, H). There were no patients with a type B PDA. There were no patients with a ductal diameter of > 4 mm across the whole cohort, as the largest ductal diameter was 3.4 mm with the median ductal length was 8.8 mm (Table 1). The descending aortic median was 5.3 mm in the group.

The commonest devices used were the longest devices (n = 52; 88.1%), which included 03x06L (n = 12), 04x06L (n = 16) or 05x06L (n = 24) devices. These were chosen according to manufacturer guidelines.

The device was deployed through the pulmonic side in 41 patients and retrogradely in 18. Difficulty in finding either venous or arterial access dictated the delivery approach of the device since the device could be delivered either in a prograde (anterograde) or retrograde fashion.

There was immediate ductal closure in 43 patients and closure on day one in 13 patients using this device. This excludes those patients who had device embolisation following deployment (see complications below). In total, 57 patients (96.6%) had complete initial (pre-discharge) ductal closure using this device.

The dose–area product (DAP) in microgray units (µGy) × surface area/kg body weight was used to measure patient radiation absorption. The median for this was 251 µGym²/kg (range: 85.5–679.4 µGym²/kg) (Table 1).[35]

With regard to complications, there were no patients who had vascular injury, which might be because vascular access in all infants less than 3 kg was via a size 4F vascular access sheath. There were three patients with device embolisation (a major complication). Two patients had devices (03x06L ADO II AS and 04x06L ADO II AS) embolising into the right pulmonary artery (RPA) and one (04x06L ADO II AS) into the left pulmonary artery (LPA). All devices were retrieved with a size 10-mm (loop) AndraTec Exeter snare through a 4F AndraTec introducer sheath (AndraTec GmbH, Simmernerstr, Koblenz, Germany) (Fig. 3). It was easy to retrieve the device into the sheath as it is a softer device compared to the ADO device.

The defect was closed with a larger ADO II AS device (05x06L ADO II AS device) in one patient, closed with a 3.5 × 5-mm Occlutech duct occluder device in another patient, and surgically closed (off bypass) in the last patient. In addition, there were four patients who required blood transfusion after the procedure. Of these, three patients had haemoglobin levels of 11.7, 12.5 and 11.1 g/dl before the procedure. These levels decreased to 8.9, 9.7 and 10.1 g/dl, respectively, immediately after the procedure. The levels improved to 14.5, 14.1 and 13.6 g/dl, respectively, following blood transfusion. The fourth patient had excessive bleeding at the puncture site following cardiac catheterisation. The haemoglobin levels of this patient were 13.9 g/dl before, 8.2 g/dl immediatetly after the procedure, and 13.2 g/dl following blood transfusion. There were no complications after transfusion in these patients.

Minor complications involved two patients with bleeding at the puncture site, which was managed conservatively. One patient had catheter-induced supraventricular tachycardia before device deployment, which was treated with a single dose of adenosine at 100 µg/kg intravenously.

Concerning co-morbidity, one patient had a secundum atrial septal defect, which measured 10 mm in diameter. It was closed with a size 10.5-mm (waist) Figulla® Flex II Occlutech septal occluder (Occlutech, Helsingborg, Sweden) at the age

Table 1. Demographics, haemodynamic and angiographic data of patients

Demographic, haemodynamic and angiographic data	*Results, median (range)*
Age, months	4 (0.8–7)
Weight at catheterisation, kg	3.6 (0.9–5.8)
Qp:Qs	2.4 (1.1–5.4)
Rp, Wood units	1.7 (0.3–7.12)
PA mean, mmHg	20 (9–47)
PDA narrowest diameter, mm	1.9 (1.0–3.4)
Ductal ampulla, mm	6.1 (2.8–10.6)
PDA length, mm	8.8 (3.7–18.4)
Descending aortic diameter, mm	5.3 (3.6–10.6)
Radiation exposure, µGym²/kg	251 (85.5–679.4)

Number of patients (n) and gender distribution: n = 59, F = 32, M = 27.
F, females; M, males; Qp, pulmonary blood flow; Qs, systemic blood flow; Rp, pulmonary resistance; PA, pulmonary artery; µGym²/kg, microgray × square meter surface area/kilogram body weight.

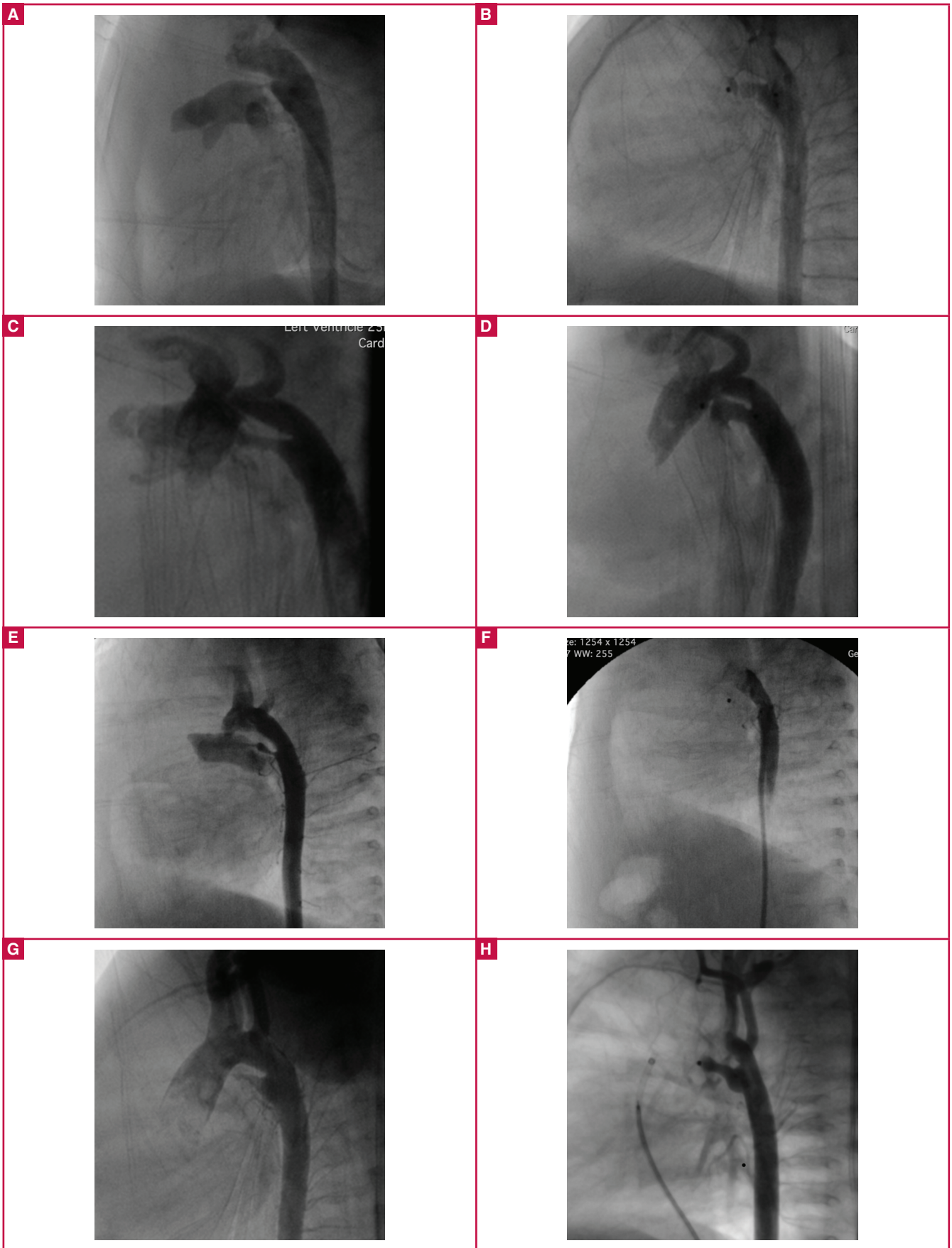

Fig. 2. Descending aortograms in straight lateral views demonstrating PDAs pre- and post-closure with the Amplatzer Duct Occluder type two additional sizes device and classified as Krichenko type A (A, B), C (C, D), D (E, F) and E (G, H).

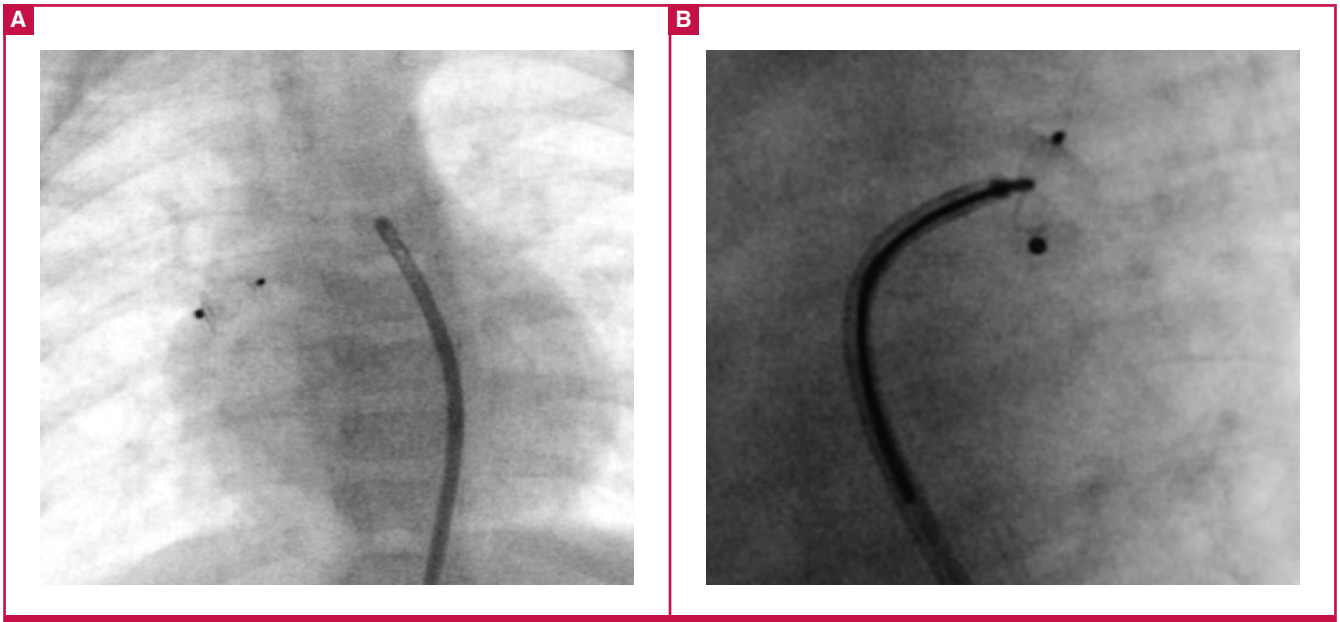

Fig. 3. Embolised device into the right pulmonary artery (A). The device is being retrieved using a 10-mm (loop) AndraTec Exeter snare (AndraTec GmbH, Simmernerstr, Koblenz, Germany) (B).

of four years nine months and four years seven months after percutaneous PDA closure.

The duration of the follow up with regard to our cohort ranged from 15 months to two years (median: two years). Of note, there was no device-induced coarctation of the aorta, left pulmonary artery stenosis, procedure-induced aortic regurgitation or left ventricular dysfunction. Forty-nine patients had already been discharged from follow up at the time of writing this article, as they had completed the two-year follow-up duration as per the study protocol.

Discussion

Morbidity and mortality associated with the PDA in preterm infants is well documented.[6,7] In this group, failed medical therapy with ibuprofen is reported to be around 22–24%, which is comparable to failed treatment with oral paracetamol, at 18–31%.[36] Therefore this group was subjected to percutaneous closure of the PDA in our unit.

Both medical treatment and surgery are fraught with complications. Devices other than the ADO II AS are also being explored and have been successfully utilised in percutaneous closure of the PDA in this challenging group with lower body weight. These include the Amplatzer vascular plug and the Medtronic micro vascular plug.[17,37-39] Challenges faced by this lower-weight group include, among others, difficult vascular access, vascular access injury, excessive bleeding in relation to body mass index, haemodynamic instability, metabolic acidosis, hypothermia and death.[40]

There have been attempts to close PDAs percutaneously using echocardiography in the neonatal unit in preterm infants who have haemodynamically significant PDAs.[18,19] This approach was prompted by listed poor outcomes experienced in the cardiac catheterisation of small infants in the catheterisation laboratory. However, this bedside technique has not been translated into routine clinical practice.

In our study, there was successful closure of the PDA in 57 patients (96.6%). This is comparable with the results reported by Kang *et al.* in their multicentre study of 408 lower-weight patients,[18] where there was also a 95% closure rate recorded in the last recorded patient follow up. Kenny *et al.* reported on the successful ductal closure in 16 of 17 patients, and there was only one embolisation in this cohort.[19] The device was surgically retrieved with the ligation of the duct. Of note, nine patients weighed less than 6 kg, and the smallest patient was 1.7 kg in this cohort.

In another study, the ADO II AS device was used in 60 patients to close the PDA, and 26 of these patients weighed less than 6 kg.[22] Moreover, there was successful PDA closure in 96.6% of patients without major complications, except for one embolisation.

Recently, the Medtronic micro vascular plug has been used to close a PDA in eight patients weighing less than 6 kg.[37] In fact, half of the patients in this recent study were infants weighing less than 2.5 kg. Furthermore, there was one embolisation in this cohort. The embolised device was retrieved transcutaneously and an Amplatzer type II device was successfully deployed to close the PDA.

Although, there is little data on PDA closure in premature infants weighing less than 1 000 g, the Amplatzer vascular plug II has been successfully used for ductal closure in this group.[38] Moreover, in our cohort, we had one preterm infant weighing less than 1 000 g (900 g) at the time of ductal closure. In this patient, the PDA measured 3.4 mm in diameter and was 9.3 mm long. A 05x06L device was used to close the PDA in an anterograde approach. The patient was discharged without any complications.

The ducts in preterm infants are usually large and tubular and need either medical or surgical intervention.[41] All the patients in the study cohort had ducts that were long and the majority of these PDAs were longer than the recommended maximum length for closure using the ADO II AS. Despite this, owing to the shape of the device and the small diameter of the retention disks, it was

possible to manoeuvre the device so that it was pulled into the duct, and the central lobe was snuggly placed over the narrowest diameter of the PDA. However, further research is needed into ductal length and ductal closure outcomes using the ADO II AS, as there is a lack of data in the literature in this regard.

In this study, we also examined the aortic diameter and ductal closure outcomes. None of the study patients were documented to have device-induced coarctation, which has previously been defined by Kang *et al.* as a descending aorta catheterisation gradient of more than 10 mmHg or a velocity of > 2 m/s during echochardiography.[18] In their cohort, there were 10 patients with device-induced coarctation of the aorta immediately following cardiac catheterisation.

On follow up, the velocity was reported to have normalised in seven patients and there was only one patient that remained with a high velocity but without a diastolic tail. In the remaining two patients, the follow-up data were incomplete. This finding may imply that device-induced coarctation of the aorta may resolve with vessel growth and somatic growth of the patient.

One advantage of this device is that it can be delivered using a delivery sheath of 4–5F. This avoids complications, such as vascular access and injury. To reduce the risk of vascular injury, we utilised a 0.014-inch wire and scalp vein needle (Butterfly) sets for vascular access, particularly in preterm infants, although this approach has not been reported in the literature. Another advantage of the ADO II AS device is that it can be delivered in both anterograde (pulmonic) and retrograde (arterial) approaches. The anterograde approach is usually the preferred approach in lower-weight infants as it eliminates femoral arterial injury if this access is avoided.[40] Therefore the majority of our patients (about 70%) had closure of the PDA through the pulmonic route.

Regarding radiation exposure, our patients were exposed to higher doses of radiation than reported by Kobayashi *et al.*[35] Their reference value at the 90th percentile was 130 μGym^2/kg for percutaneous PDA closure in their multicentre study. This finding suggests that in our unit, we need to be more meticulous and limit radiation exposure to the absolute minimum during cardiac catheterisation.

Complications reported in our cohort have been documented elsewhere when dealing with lower-weight infants, particularly those that are premature.[18,37-40] The one common complication in this group was the need for blood transfusion.[18,40] However, this complication was well managed in our cohort.

In addition, there were three embolisations in this cohort owing to the under-sizing of the device. Our 5% embolisation rate is comparable to that reported by Kang *et al.* in their study of 408 low-weight patients.[18] With regard to embolisation of the device, the learning curve in the use of this device in our unit was a contributing factor. All the embolised devices were retrieved percutaneously, two ducts were closed with larger alternative devices, and one duct was surgically closed.

When it comes to outcomes, there were no medium- and long-term complications noted in our study. In particular, there was no LPA stenosis. To prevent LPA stenosis when using the ADO II AS device, we positioned the device in such a way that the pulmonary disk was against the roof of the main pulmonary artery, with some tenting of the disk. In addition, the central lobe and in some patients the aortic disk of the device were placed in the duct (Fig. 2B).

With regard to limitations of the study, a clinical trial comparing percutaneous PDA closure to surgical closure in lower-weight infants would be a more robust study. A recent study, which compared surgical ligation to percutaneous ductal closure using this device, has shown that percutaneous closure is feasible and safe.[42] However, patient numbers that underwent percutaneous closure were very small in this study (25 subjects).

Conclusion

The Amplatzer Duct Occluder type two additional sizes is practical, effective and has few complications in patients less than 6 kg with a duct that is less than 4 mm in diameter, even though the infant is from a from a LMIC with reduced resources, such as South Africa. Owing to the small retention disks of the device compared to the central lobe, the device may be deployed in ducts that are longer than 8 mm, and there is a low risk for device-induced coarctation of the aorta. More studies are needed to examine the safety and efficacy of this device in ductal closure in patients weighing less than 1 000 g.

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Echocardiographic left atrial remodelling and determinants of left atrial size in the early phase of high blood pressure: a comparative cross-sectional study in Douala, Cameroon

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Abstract

Background: Left atrial remodelling (LAR) has been described in Western populations with chronic hypertension and is associated with a higher risk of adverse cardiovascular events. Although hypertension tends to occur earlier and is more severe in sub-Saharan Africa than in more developed nations, LAR and its associated factors in these African hypertensive subjects have been poorly elucidated.

Objectives: To assess left atrial structural remodelling in black hypertensive patients and determine factors associated with left atrial size.

Methods: This was a cross-sectional, comparative study carried out in two tertiary hospitals in Douala, Cameroon over a period of three months. Fifty-two patients, either newly diagnosed with hypertension or known hypertensives treated for less than a year, were consecutively recruited. These patients were matched (unpaired matching) for age and gender to 40 randomly selected healthy subjects. The posterior–anterior diameter indexed to body surface area (BSA), volume indexed to BSA, and longitudinal and transverse diameters of the left atrium (LA) were measured using transthoracic echocardiography, in accordance with the American Society of Echocardiography guidelines. LAR was defined as increase in LA size, characterised by LA volume ≥ 34 ml/m^2. Early morning urine was analysed for microalbuminuria using urine strips to obtain spot albumin/creatinine ratio. Data were analysed using SPSS version 23 and statistical significance was set at $p < 0.05$.

Results: The gender distribution and mean age were similar between the two groups. Hypertensive patients had significantly higher mean body mass index, left ventricular mass and an altered diastolic function. They also had significantly higher LA longitudinal diameter (50.0 vs 47.4 mm; $p = 0.045$), surface area (17.9 vs 15.5 cm^2; $p = 0.003$) and volume (52.4 vs 43.8 ml; $p = 0.002$) compared to the non-hypertensive counterparts. Fourteen patients (26.9%) had LA enlargement compared to one (2.5%) in the non-hypertensive group (odds ratio = 9.78, CI: 2.67–35.8, $p < 0.0001$). Diastolic dysfunction ($p = 0.008$) was the only independent predictor of LA size in the hypertensive subjects. Microalbuminuria did not significantly correlate with LA size.

Conclusion: Our study shows evidence of LAR in newly diagnosed black African patients with hypertension, characterised by an increase in the LA length, surface area and volume. Future studies are warranted to better elucidate the biological mechanisms underlying the link between the early phase of hypertension and LAR, as well as its prognostic implications in our population.

Keywords: hypertension, left atrium, remodelling, SSA

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Hypertension is an important public health challenge worldwide.[1] In sub-Saharan African populations, hypertension tends to occur at an earlier age than in more developed nations, is frequently under-diagnosed, and is often severe and complicated at the time of diagnosis.[2-4]

Systemic hypertension causes well-recognised structural and functional changes in the heart, which are known as cardiac remodelling. The spectrum of hypertensive heart disease is characterised by left ventricular hypertrophy (LVH), atrial remodelling and heterogeneity of atrial conduction, and fibrosis, all of which can result in atrial fibrillation.[5] Although the effect of hypertension on the left ventricle has been extensively studied, its effect on the left atrium is less well defined.[6]

Left atrial (LA) size has rapidly gained interest over the years as some studies have shown its role in predicting cardiovascular events.[7] Evidence suggests that LA remodelling (LAR) occurs even before the development and detection of LVH and is therefore an early sign of hypertensive heart disease.[8] LA remodelling, characterised by LA enlargement, has been associated with an increased risk of developing atrial fibrillation and stroke.[9] Variables known to affect LA size are age, obesity, race, body surface area and left ventricular mass.[10,11] The burden of chronically elevated blood pressure on LA size, as demonstrated by an increasing size, has been shown in studies on Caucasians and Asians.[12,13] Few studies have been conducted in black hypertensive patients in sub-Saharan Africa.

The paucity of studies on LAR in black hypertensive patients in the early phase of hypertension is a real concern. The objectives of our study were three-fold: first, to determine the difference in LA size between hypertensive and non-hypertensive individuals, second, to determine the proportion of hypertensive patients with LA enlargement, and third, to determine the predictors of LA size in hypertensive patients.

Methods

This study was a cross-sectional, comparative study conducted at the out-patient cardiology units of two hospitals in Douala, Cameroon, namely the Douala General Hospital (DGH) and Deido District Hospital (DDH), over a period of three months from January to March 2017. These hospitals are among the busiest hospitals in Douala, the economic capital of Cameroon, which has a population of about three million people. Each of these hospitals has a cardiology unit with an equipped examination room and expert cardiologists.

Hypertensive patients (cases) were enrolled consecutively while a non-hypertensive group (controls) was enrolled conveniently and consisted of volunteers from hospital staff and patient carers attending the DGH and DDH (all native Africans). Cases were matched by age and gender to non-hypertensive control subjects.

Hypertensive patients were native African adults who fulfilled the following inclusion criteria: aged 18 years and above, diagnosed with hypertension for less than a year to the period of recruitment (drug naïve or treated), and with mild to moderate hypertension. Patients with evidence (medical records) of coronary heart disease, heart failure, valvular heart disease, diabetes mellitus, co-existing cardiomyopathy or arrhythmia were excluded. Controls were non-hypertensive patients with no cardiovascular or renal diseases.

Ethical approval was obtained from the institutional review board of the Faculty of Health Sciences of the University of Buea. Written informed consent was obtained from all study participants before their enrolment into the study. The study was carried out in conformity to the Declaration of Helsinki.

Basic and clinical variables of all the subjects were collected. These included age, gender, height and weight. Blood pressure was measured with an appropriate-sized cuff on the right arm of the patient after the subject had been seated quietly for at least five minutes. Hypertension was diagnosed in subjects having a systolic blood pressure (SBP) of more than 140 mmHg and diastolic blood pressure (DBP) of more than 90 mmHg on at least two separate occasions, or on anti-hypertensive therapy. Files were reviewed to obtain recent laboratory results (less than three months).

The procedure for urine collection was explained to each participant and 5 ml of midstream urine of the first morning void was used for each patient. Patients were asked to avoid exercise or exertion at least 24 hours prior to urine collection. The urine samples were analysed for microalbuminuria using a microalbumin strip (microalbuPHAN®).

Two-dimensional Doppler and M-mode echocardiography was performed using a commercially available machine (Vivid3® Sonoscape, as seen in Fig. 1) with a 3.5-MHz probe. Cardiac echography was done by two experienced cardiologists with subjects lying in the left lateral decubitus position. A one-lead electrode was placed continuously during the course of the examination. All cardiologists were given a protocol with standard operating procedures for each measurement, which was done according to previously published guidelines.[14] Measurements from at least three different cardiac cycles were averaged and used in the analyses.

The LA anteroposterior linear dimension was obtained from the parasternal long-axis view, from the trailing edge of the posterior aortic wall to the leading edge of the posterior LA

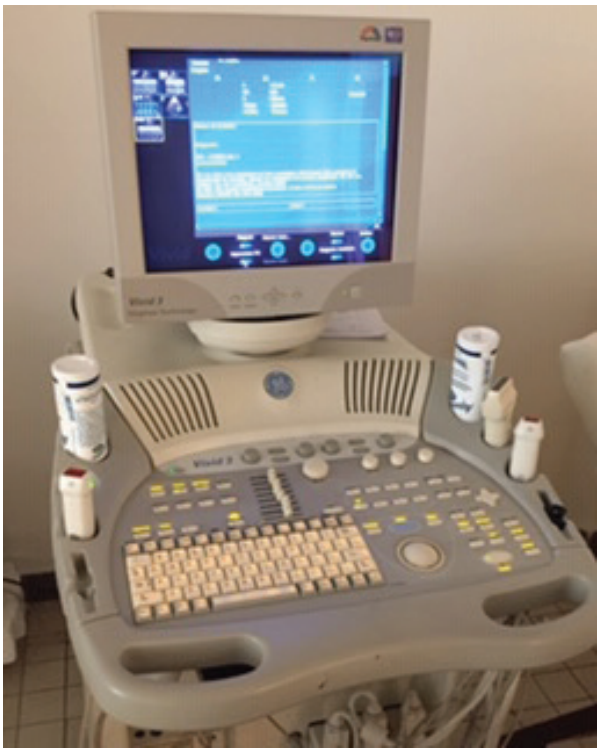

Fig. 1. A Vivid3® Sonoscape was used for two-dimensional Doppler and M-mode echocardiography.

wall at the end-ventricular systole (just before the opening of the mitral valve) when the LA chamber is at its greatest dimension. Measurements were indexed to body surface area (BSA).

LA surface and volume were obtained on an apical four-chamber view at end-systole. The inner border of the LA, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins was traced, giving the LA a shape roughly like a square. The LA volume was calculated using the biplane area–length method and the formula is given by

$$0.85(A1 \times A2)/L.$$[15]

where A1 and A2 are the areas of the LA in four- and two-chamber views and L is the shortest of the lengths obtained from the orthogonal views and indexed to BSA (Fig. 2).

The LA length (major axis) and width (minor axis) were also measured in the apical four-chamber view. The length was measured from the plane of the mitral annulus to the roof of the atrium and the width was defined as the distance between the lateral LA wall and inter-atrial septum, at the mid-atrial level, defined by half of the LA long axis.

In the parasternal long-axis view, left ventricular (LV) parameters were measured using the leading edge-to-leading edge convention of the recommendations by the American Society of Echocardiography. End-diastolic and end-systolic LV internal diameters, interventricular septum thickness and posterior wall thickness were measured from two-dimensionally guided M-mode tracings recorded at 50 to 100 cm/s speed during three or more consecutive cycles, according the American Society of Echocardiography guidelines.[14]

Relative wall thickness was defined by the ratio of posterior wall plus interventricular septum thickness to LV internal diastolic diameter. Left ventricular mass (LVM) was calculated using the Devereux-modified Penn formula[16] and was indexed to BSA (calculated using the formula of Dubois).

$$0.8\ \{1.04[(LVEDD + PWTd + IVSTd)3 - (LVEDD)3]\} + 0.6$$

where LVEDD is left ventricular end-diastolic diameter, PWTd is posterior wall thickness in diastole, IVSTd is interventricular septal thickness in diastole.

Left ventricular ejection fraction (LVEF) was calculated using the Teichholz formula. Fractional shortening was calculated from LV internal dimensions in diastole and systole:

$$\frac{LVIDd - LVIDs}{LVID} \times 100$$

where LVIDd is left ventricular internal diameter in diastole and LVIDs is left ventricular internal diameter in systole.

Diastolic function parameters

From the apical four-chamber view, trans-mitral echo-Doppler velocity flow profile was recorded in all patients, positioning the sample volume at the level of the leaflet tips; the highest discernible signal was determined as velocity. The diastolic filling indices were measured: peak flow velocity of early (peak E) and late (peak A) diastole, E/A ratio and deceleration time (DT), defined as the time interval required for the E velocity to decline from its peak to the baseline. The isovolumetric relaxation time (IVRT) was also considered, measured from the aortic valve closure to the beginning of trans-mitral flow.

The pulsed-wave Doppler tissue imaging (DTI) sample volume was placed on the mitral annuli at the apical four-chamber view. The spectral longitudinal velocity of the myocardium, normally consisting of a positive systolic wave and two diastolic peaks, notably the S′, E′ and A′, respectively, were measured in the lateral and septal mitral annuli.

LAR was defined as changes in LA structure (as evidenced by increased anterior–posterior diameter, surface or volume) or function (increased atrial contraction measured from the late diastolic wave velocity, A) induced by hypertension. Left structural changes were defined as increase in LA volume index (LAVI > 34 ml/m^2). Mild LA enlargement was 35–41 ml/m^2,

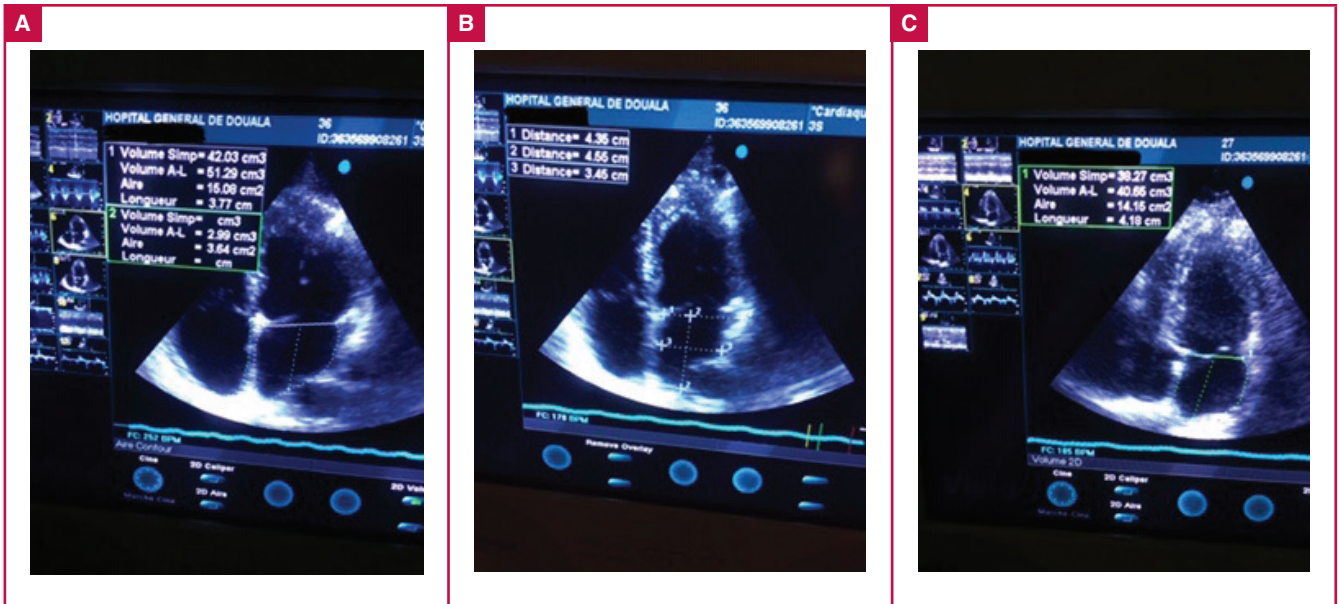

Fig. 2. Measurement of LA volume from the biplane area–length method, using apical four- and two-chamber views to obtain A1, A2 and the longitudinal diameter (L) (distance 2 in B) (courtesy of Doula General Hospital).

moderate LA enlargement was 42–48 ml/m², and severe LA enlargement was > 48 ml/m².[14]

LVH was defined as left ventricular mass index > 114 g/m² in men and > 99 g/m² in women.[14] Ventricular remodelling was defined based on the relative wall thickness (RWT) and LVM; concentric remodelling was increased RWT and LVM, eccentric remodelling was decreased RWT and normal LVM. Diastolic dysfunction (impaired relaxation) was defined as an E/A ratio < 1 and deceleration time > 220 ms.[14]

ECG criteria for determining LVH was defined by the Sokolow–Lyon index: the sum of the largest R wave of the V5 or V6 derivation with wave S of the V1 ≥ 3.5 mV (35 mm) and/or R wave in aVL ≥ 1.1 mV (11 mm). ECG criteria for LA hypertrophy included: P-wave duration in lead I, II or III > 110 ms; P-wave notching in lead I, II or III with inter-peak duration > 40 ms (P mitrale); any current or former smokers; impaired fasting glucose level of 100–125 mg/dl (5.55–6.94 mmol/l); an abnormal high-density lipoprotein cholesterol < 40 mg/dl (1.04 mmol/l), low-density lipoprotein cholesterol > 110 mg/dl (2.85 mmol/l) and total cholesterol ≥ 200 mg/dl (5.18 mmol/l).

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences version 23 (IBM SPSS, Atlanta). Data are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Medians were compared using the Mann–Whitney *U*-test.

Pearson's correlation was used to assess the individual relationship between LA size with age, body mass index (BMI), SBP, DBP, pulse pressure, LVM, LVH and other echocardiographic parameters. Variables that had significant associations on bivariate analysis were tested in a step-wise linear regression model and adjusted for age and gender.

Results

A total of 52 patients were enrolled along with 40 control subjects. The median age was 49 years. The age ranged between 33 and 75 years with a similar male-to-female ratio between the two groups. There was a significant difference in blood pressure variables (SBP, DBP, mean atrial pressure and pulse pressure) between the two groups. Table 1 shows the clinical characteristics of patients.

Table 1. Clinical characteristics of the study population

Variable	*Hypertensives* (n = *52*)	*Controls* (n = *40*)	p-*value*
Age (years)	49.0 (43.2–59.7)	49.0 (43.0–57.7)	0.93
Male, *n* (%)	22 (42.3)	18 (45)	0.834⁺
BMI (kg/m²)	29.2 (26.9–32.4)	27.7 (24.6–31.0)	0.04
SBP (mmHg)	150.0 (142.0–159.0)	125 (115.0–130.0)	< 0.0001*
DBP (mmHg)	95.0 (89.0–100.0)	79.0 (68.5–89.0)	< 0.0001*
Heart rate (beats/min)	75.5 (69.0–88.7)	75.5 (68.0–82.7)	0.34
Pulse pressure (mmHg)	56.0 (48.2–65.0)	42.0 (35.5–54.0)	< 0.0001*
MAP (mmHg)	113.8 (105.7–118.5)	93.8 (87.5–101.0)	< 0.0001*

Values are presented as median (interquartile range) or number (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
⁺*p*-value from Fisher's exact test; **p*-value from Mann–Whitney *U*-test.

The median duration of hypertension was one month and 15% of the patients were not yet treated. Monotherapy with calcium channel blocker (34.6%), followed by combination therapy of thiazide diuretic and angiotensin converting enzyme inhibitors (13.4%) were the most frequently used medication. Table 2 shows characteristics specific to the hypertensive patients.

The LV mass was significantly higher in hypertensive patients compared to the control group. Similarly, the diastolic function assessed by the E/A ratio was significantly impaired in hypertensive patients. These findings are shown in Table 3.

The LA longitudinal diameter ($p = 0.045$), surface area ($p = 0.003$) and biplane volume ($p = 0.002$) were significantly higher in the patients with hypertension. Table 4 shows the difference in LA sizes between hypertensive patients and controls.

LA structural changes, defined by LA enlargement, was found in 14 (26.9%) hypertensive patients versus one (2.5%) control individual ($p < 0.0001$). Among these patients, 64.3% had mild LA enlargement, 21.4% moderate and 14.3% severe LA enlargement, as shown in Figs 3 and 4.

On univariate analysis the following factors were tested for relationship with LA volume: age, gender, systolic and diastolic blood pressures, BMI, LV wall thickness [left ventricular end-systolic diameter (LVESD), interventricular septal diameter at diastole (IVSD), posterior wall diameter at diastole (PWDD)], LVM, and diastolic function (E/A, E/E′). Significant correlations were found with BMI ($r = 0.30$; $p = 0.004$), DBP ($r = –0.30$; $p = 0.02$), LVEDD ($r = 0.367$; $p = 0.009$) and E/A ($r = 0.368$; $p = 0.009$) among the hypertensive patients (See Table 5).

Variables with significant correlation and a p-value < 0.05 were entered in a step-wise multiple linear regression model and adjusted for age and gender. Diastolic function (E/A < 1) was the only independent predictor of LA volume in hypertensive patients ($p = 0.006$). This is shown in Table 6.

Discussion

Our study showed that there was a significant increase in the LA longitudinal diameter, surface area and volume among

Table 2. Characteristics of the hypertensive patients

Variable	*Number (%)*	*Overall,* n
Duration of hypertension (months)	1 (0–6)	52
Alcohol intake	18 (34.6)	52
Former smoker	1 (2)	52
Current smoker	2 (4)	52
Sedentary	32 (61.5)	52
Family history of hypertension	25 (48)	52
ECG LV hypertrophy	8 (15.3)	52
ECG LA hypertrophy	5 (9.6)	52
Elevated LDL-C	5 (19.6)	26
Low HDL-C	7 (26.9)	26
Elevated cholesterol	8 (30.7)	26
Abnormal creatinine	0 (0)	38
Elevated uric acid	2 (12.5)	16
Impaired fasting glucose	2 (5.2)	38
CCB	18 (34.6)	52
ACEI/ARB + thiazides	7 (13.4)	52

Values are presented as median (interquartile range) or number (%). LV, left ventricular; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor, ARB, aldosterone receptor blocker.

Table 3. Echocardiography parameters

Variable	*Hypertensives (n = 52)*	*Controls (n = 40)*	p-*value*
AOD (mm)	28.8 (26.6–31.0)	28.8 (26.5–31.4)	0.79
IVSD (mm)	9.2 (7.5–10.4)	8.4 (7.1–9.8)	0.28
IVSS (mm)	13.6 (12.7–15.3)	13.8 (12.1–15.0)	0.61
LVEDD (mm)	49.1 (45.0–54.0)	46.8 (43.1–51.0)	0.11
LVEDS (mm)	30.0 (25.9–34.7)	28.5 (25.5–32.6)	0.20
PWDD (mm)	9.4 (8.3–11.1)	8.6 (7.5–9.8)	0.89
PWDS (mm)	15.7 (13.8–17.3)	14.4 (12.7–15.9)	0.19
FS (%)	37.0 (34.2–42.0)	0.35 (0.31–0.40)	0.91
EF (%)	68.0 (61.2–74.0)	83.3 (66.7–76.0)	0.17
LVMI (g/m^2)	86.0 (72.7–101.7)	73.3 (58.4–88.7)	0.01*
RWT	0.35 (0.32–0.44)	0.35 (0.31–0.35)	0.11
Peak E (cm/s)	75.3 (58.8–92.5)	80.0 (67.0–90.0)	0.43
Peak A (cm/s)	83.0 (62.2–96.0)	63.5 (51.0–83.7)	0.001*
E dec (ms)	199.0 (179.0–219.0)	189.0 (165.0–209.0)	0.23
IVRT (ms)	96.0 (83.5–105.0)	90.0 (78.0–101.0)	0.31
E/A ratio	0.89 (0.70–1.2)	1.24 (0.94–1.49)	< 0.0001*
S′ lateral (m/s)	10.0 (7.0–12.0)	9.0 (8.0–12.0)	0.88
Lateral E′ (m/s)	9.0 (7.0–11.0)	11.0 (9.0-15.0)	0.009*
Lateral A′ (m/s)	11.0 (9.0–2.8)	9.0 (7.01–0.0)	0.002*
E/E′ ratio	9.0 (6.9–10.7)	7.25 (5.7–8.8)	0.001*

Values are presented as median (interquartile range). *Statistically significant. AOD, aortic root diameter; IVSD, interventricular septal diameter at diastole; IVSS, interventricular septal diameter at systole; LVEDD, left ventricular end-diastolic diameter; LVEDS, left ventricular end-systolic diameter; PWDD, posterior wall diameter at diastole; PWDS, posterior wall diameter at systole; EF, ejection fraction; FS, fractional shortening; LVMI, left ventricular mass index; RWT, relative wall thickness; E, early mitral flow velocity; A, atrial contraction velocity; dec, E wave deceleration time; IVRT, isovolumetric relaxation time; S′, systolic myocardial velocity at lateral annulus; A′, myocardial velocity associated with atrial contraction; E′, early diastolic myocardial velocity.

Table 4. Comparison of left atrial size between hypertensives and controls

Variable	*Hypertensives (n = 52)*	*Controls (n = 40)*	p-*value*
LA anteroposterior diameter (mm)	38.1 (34.6–38.0)	36.7 (34.1–39.6)	0.064*
LA anteroposterior diameter indexed BSA	19.8 (17.8–19.8)	19.1 (18.0–21.0)	0.148
LA transverse diameter (mm)	37.0 (32.7–49.8)	39.3 (34.6–42.8)	0.097*
LA longitudinal diameter (mm)	50.0 (45.0–55.0)	47.4 (44.0–51.8)	0.045
LA surface area (cm^2)	17.9 (13.3–21.2)	15.5 (13.6–17.4)	0.003
LA volume, biplane (ml)	52.4 (38.9–65.7)	43.8 (35.2–48.5)	0.002
LA volume, biplane indexed BSA (ml/m^2)	28.1 (19.9–34.5)	22.9 (18.8–26.6)	0.003

*Statistically significant. LA, left atrial; BSA, body surface area.

Table 5. Pearson correlation for covariates of left atrial size (volume) in hypertensive patients

Variable	*Correlation coefficient,* r	p-*value (n = 52)*
Age	0.008	0.544
BMI	0.402	0.004*
SBP	–0.040	0.782
DBP	–0.300	0.019*
IVSD	–0.022	0.880
LEVDD	0.360	0.009
PWDD	1.310	0.366
LVM/BSA	0.055	0.704
E/E	0.351	0.013*
E/A	0.368	0.009
RWT	0.073	0.621
Microalbuminuria (mg/g)	0.130	0.350

*Statistically significant. BMI, body mass index; SBD, systolic blood pressure; DBP, diastolic blood pressure; IVSD, interventricular septal diameter at diastole; LVMI, left ventricular mass index; LVEDD, left ventricular end-diastolic diameter; PWDD, posterior wall diameter at diastole; RWT, relative wall thickness.

hypertensive participants compared to the reference group (non-hypertensive). About a quarter (26.9%) of hypertensive patients had an increase in LA volume. Determinants of LA volume were BMI, BSA, DBP, and LV septal thickness at diastole in hypertension. Diastolic dysfunction was the only independent predictor of LAR in hypertensive patients. Also, we found no correlation between microalbuminuria and LA size (volume) among hypertensive patients.

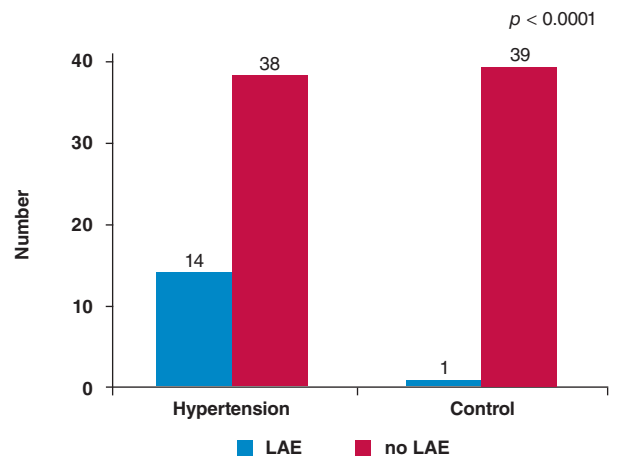

Fig. 3. Proportion of patients with LA enlargement in hypertensive subjects and controls. LAE, left atrial enlargement.

The LA length, surface area and volume were significantly increased in patients with hypertension compared to the controls. This finding was consistent with several reports that showed that there is an increase in LA length and volume in hypertension.[13,17,184,25] Contrary to the findings by Sun *et al.* in China, changes in anterior–posterior and transverse diameters were not significant.[12] There are possible explanations to these differences, which include LA anatomical variations and severity

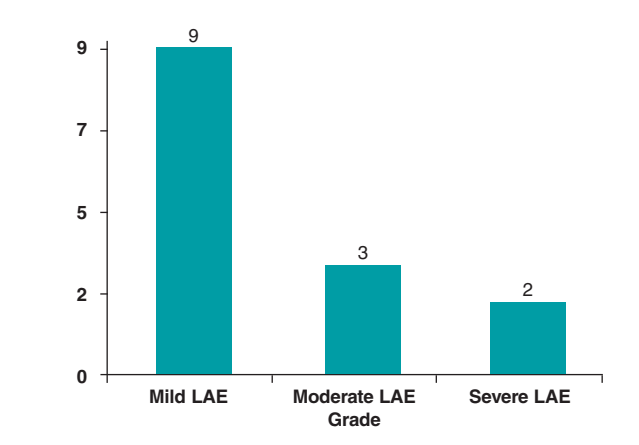

Fig. 4. Classification of severity of LA enlargement according to the American Society of Echocardiography. LAE, left atrial enlargement.

Table 6. Multivariate linear regression analysis for independent predictors of left atrial size

Variable	*B*	*95% CI of the difference*	p-*value*
BMI	0.300	–0.026 to 0.041	0.300
DBP	–0.280	–0.001 to 0.007	0.330
LVEDD	–0.110	–0.013 to 0.020	0.630
E/A	0.370	0.328 to 1.832	0.003*
E/E′	0.150	–0.016 to 0.080	0.290

R^2= 38.3%. *Statistically significant. B, coefficient of regression; CI, confidence interval, BMI, body mass index, BSA, body surface area; SBP, systolic blood pressure, DBP, diastolic blood pressure, LVEDD, left ventricular end-diastolic diameter.

of hypertension. Results from the study by Dewland *et al.* suggest that LA diameter is significantly greater in whites than blacks.[19] Severe hypertension in hospitalised patients recruited by Sun *et al.* would have had a greater effect on LA size compared to patients with mild hypertension in this study.

It should be noted that the LA is not shaped symmetrically and LA enlargement does not occur uniformly. Expansion of the LA is constrained by the thoracic cavity, aortic root, right ventricular outflow tract and the rigid trachea bifurcation. With the above in mind, changes in LA size therefore preferentially occur in the superior–inferior axis (longitudinal diameter).[20]

Consequently, all the morphological changes in LA size only become prominent with age and duration of hypertension. Therefore, the aforementioned anatomical factors, coupled with severity of hypertension accounted for the differences observed between our findings and those of Sun *et al.*[12] Our analysis supports the fact that estimation of LA changes by surface and volume will be more relevant and accurate in the clinical setting than anterior–posterior and transverse dimensions.

Up to a quarter of the hypertensive patients in our study had LA enlargement. This is considerable and is a call for concern, given the fact that LA enlargement increases the risk of stroke and is associated with poor cardiovascular outcomes. Our findings are in agreement with of those of Cuspidi *et al.* in Italy.[21] However, we had a lower proportion of participants with LA enlargement relative to those found by Chen *et al.*[22] in Japan and Milan *et al.* in Italy.[23]

Possible explanations for the variations lie in differences in study designs, presence of concomitant pathologies in their subjects, and different diagnostic cut-off values used to define LA enlargement. In these studies, co-morbidities included atrial fibrillation, diabetes mellitus and obesity, among others. In the study by Chen *et al.,* mean age was 69 ± 10 years and diagnostic cut-off for LA enlargement was LAVI > 32 ml/m^2. In the study by Milan *et al.,*[23] the mean age was 50.7 ± 12.2 years with duration of hypertension ranging from 11–120 months and diagnostic cut-off for LA enlargement was LAVI > 22 ml/m^2. Finally, in the study by Cuspidi *et al.*,[21] mean age was 58.3 ± 16 years, with the elderly patients above 65 years making up 41% of patients.

The observation that a large proportion of hypertensive patients had LA changes in the early phase of high blood pressure has important prognostic and diagnostic implications. This highlights the fact that structural changes may occur early in these patients therefore early screening for diagnosis may prevent future cardiovascular events.

Factors that correlated with LA volume were BMI, DBP and diastolic dysfunction. An association between increasing body mass and LA volume has been shown in previous studies by Adebayo *et al.*[18] Although the mechanism is not well understood, obesity is linked with increased stoke volume, which causes cardiac alterations.

Contrary to previous studies, ours did not show any relationship between LAR and LVM and age. Our patients were mostly newly diagnosed and relatively young hypertensive patients, which could explain the differences. In our final analysis, LV diastolic dysfunction was the only predictor of LA size. A clear relationship has been reported by Matsuda *et al.*[24] This strengthens the fact that, in the absence of other pathological disease, hypertension leads to impaired LV relaxation and reduced expandability of the left ventricle. The end result is increased atrial filling pressures and subsequent LA enlargement.

Our study was limited in that we had a small sample size and therefore the resultant loss of power could lead to decreased chances of finding associations (type II error). Second, we worked on both treated and untreated hypertensive patients, which could have modulated changes in LA size. However, there was a significant number of hypertensive patients with increase in LA size compared to the controls, indicating that the blood pressure medication had very little or no effect on LA size. We also believe that the short duration of treatment might have had little or no effect on LA size. Lastly, the case–control design limited this study with regard to establishing a temporal relationship.

The strength of this study is based on the fact that we used newly diagnosed hypertensive patients and/or those with a short duration of hypertension from diagnosis. This makes our finding more relevant in enhancing management.

Conclusion

This study shows that that there was a significant proportion of patients with hypertension who had LA remodelling, even early at diagnosis, and hence there could be early cardiac morphological modifications in these patients. Also, LA size increased disproportionately with a significant increase in the length, surface area and volume.

LA volume measurements should be assessed routinely in order to identify early morphological changes in hypertensive heart disease, and not lay emphasis only on traditional parameters of the left ventricle. Future studies are warranted to better elucidate the biological mechanisms underlying linking of the early phase of hypertension with LAR as well as its prognostic implications in our population.

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Geographical influence on the distribution of the prevalence of hypertension in South Africa: a multilevel analysis

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Abstract

Background: As a response to the growing burden of non-communicable diseases, the South African government has set targets to reduce the prevalence of people with raised blood pressure, through lifestyle changes and medication, by 20% by the year 2020. It has also recognised that the prevalence varies at local administrative level. The study aim was to determine the geographical variation by district of the prevalence of hypertension among South African adults aged 15 years and above.

Methods: Data from all five waves of the National income Dynamics Study, a panel survey, were used for estimation by both design-based and multilevel analysis methods. In the multilevel analysis, a three-level hierarchy was used with panel participants in the first level, repeated measurements on patients in the second level, and districts in the third level.

Results: After accounting for demographic, behavioural, socio-economic and environmental factors, significant variation remained in the prevalence of hypertension at the district level. Districts with higher-than-average prevalence were found mostly in the south-western part of the country, while those with a prevalence below average were found in the northern area. Age, body mass index and race were the individual factors found to have a strong effect on hypertension prevalence for this sample.

Conclusions: There were significant differences in hypertension prevalence between districts and therefore the method of analysis and the results could be useful for more targeted preventative and control programmes.

Keywords: hypertension prevalence, district variability, random effects, multilevel analysis

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Hypertension is a major risk factor and consistent predictor for cardiovascular diseases, such as coronary heart disease, stroke, transient ischaemic attack and congestive heart failure.[1,2] A study based on data from the 36-year follow-up Framingham study pointed out the urgent need for primary prevention of hypertension by addressing associated risk factors through weight control, exercise and reduced salt and alcohol intake.[3]

In 2015, global age-standardised prevalence of raised blood pressure was estimated to be 24.1% (21.4–27.1) of men and 20.1% (17.8–22.5) of women. The number of adults with raised blood pressure has increased from 594 million in 1975 to 1.13 billion in 2015, with the increase largely in low- and middle-income countries (LMICs).[4] According to the 2012 South African National Health and Nutritional and Health Examination Survey (SANHANES), the prevalence of hypertension was approximately 26.0%,[5] and the 2016 Demographic Health Survey estimated the prevalence to be 46.0 and 44.0% for women and men, respectively.[6] A number of studies have reported higher-than-global average prevalence in LMICs,[7-9] and this has been attributed to non-compliance with treatment, urbanisation, population ageing and behavioural risk factors, including tobacco and alcohol use, poor diet and physical inactivity.[7,9,10]

In 2013, the South African National Department of Health developed a strategic plan for the prevention and control of non-communicable diseases, which targets reducing the prevalence of people with raised blood pressure by 20% by the year 2020, through lifestyle change and medication.[11] While prevalence has been estimated at both provincial and national levels, little is known on the prevalence of hypertension at levels below the province due to limited data that can reliably be used for estimation.

In South Africa, existing surveillance and estimation of hypertension and other non-communicable disease (NCD)-related risk factors are overwhelmingly focused at the first (national) or second (provincial) level geographies,[5,12-14] but gaining a better understanding of variations at the finer resolutions (district level in particular) could be important in decision making for improving the effectiveness and efficiency in the response to hypertension.

While efforts have been made to estimate hypertension prevalence at the district level, the method used has fallen short as it does not account for factors that are known to be associated with prevalence. In one study, district-based prevalence of

cardiovascular co-morbidities, including hypertension, were estimated using an outdated data set (1998 South African Demographic Health Survey).[15] National prevalence of disease can conceal important differences in prevalence in sub-national areas.[16] In most high-income countries where data are available to finer geographies such as counties, NCD-related studies have shown substantial heterogeneity in the prevalence of these diseases and associated risk factors between sub-regions within a country.[17-19]

The aim of this study was therefore to profile the variations in hypertension prevalence between districts in South Africa after controlling for the individual's demographic, social, economic, behavioural and environmental variables.

Methods

The 2008, 2010/11, 2012, 2014/15 and 2017 samples for adults aged 15 years and above from the National income Dynamics Study (NiDS) panel survey were used in the study. The survey provides a large nationally representative sample that is stratified by the country's 52 districts.

The target population was adult (15+ years) individuals in private households and residents in workers' hostels, convents and monasteries, but excluded other living quarters such as students' hostels, old-age homes, hospitals, prisons and military barracks. The sampling technique employed in the panel study is exhaustively discussed elsewhere.[20] The sample retained for the study includes respondents who had at least two blood pressure (BP) measurements taken at the time of the survey.

The outcome of interest was hypertension prevalence for individuals with systolic/diastolic BP of more than 140/90 mmHg or on medication for hypertension. BP measurements for each panel were taken twice from each survey respondent. Valid BP measurements were determined according to previously applied criteria[13,21] as follows: (1) if the second systolic or diastolic BP differed by more than 5 mmHg, the first BP reading was excluded; and (2) a set of BP readings (systolic and diastolic) was retained in the data set if the systolic BP was 80 mmHg or higher AND if the systolic BP was at least 15 mmHg higher than the diastolic BP level. A final systolic/diastolic blood pressure was calculated as the average of the valid BP measurements (Table 1).

Several risk factors known to be associated with hypertension and recorded in the NiDS data were adjusted for in estimating the prevalence of hypertension, using multilevel logistic regression. Important factors at the individual level were (1) demographic factors: age, gender and race (self-identification as African, Coloured, white, Asian/Indian); (2) biological factors: specifically body mass index (BMI); (3) behavioural factors: alcohol use (never used and past/current user), smoking status (never and past/current) and physical exercise (none or some exercise); (4) social and economic factors: education level (≤ primary school, high school, and post high school), employment status (employed, unemployed or economically inactive), medical cover status (membership subscription to a registered medical aid provider), residency type (urban and traditional/farms), and income tertile calculated from equivalised per-capita household income (household income divided by square root of number of people in household); and (5) one environmental factor: the season (summer, autumn, winter and spring) when the BP measurements were taken.

Subjects self-identifying as whites or Indians/Asians were combined in the analysis as they had relatively smaller sample sizes. The alcohol use variable was not available for wave 5 (2017), and so the last observed status (from previous waves) was used, or indicated as unknown if the subject was not in previous waves.

Ethics approval was granted by the Human Research and Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa

Statistical analysis

The prevalence of hypertension was estimated using the following two statistical methods reporting results at the district level.

Design-based estimates used the survey's post-stratification weights. This first step of the analysis was to estimate the prevalence of hypertension nationally and by the levels of each explanatory variable on univariate basis, followed by the estimation of the prevalence by districts.

A three-level analysis model was used where periodic (survey waves or the repeated measurements) hypertension statuses (first level) are nested in individual respondents (second level), nested within districts (third level). The risk factors listed above were adjusted for in the model.

- Level-specific distribution of hypertension variance. This step aimed at estimating the distribution of the hypertension prevalence variance between the three levels, and the proportion of variance explained by the individual-level demographic, behavioural and socio-economic risk factors. This involved first fitting a multilevel model without the covariates (a null model), which allowed partitioning the variance between the hierarchical levels. This was followed by constructing a full model that adjusted for the risk factors (covariates) stated above. The variance structure was described by the variance partition coefficient (VPC) and the level-specific change in variance ($\Delta\sigma^2$). The VPC measures the proportion of variance explained by each level within the model, and the $\Delta\sigma^2$ measures the proportion of change in variance for each level between the null and the adjusted model. Together, these two measures describe how much of the variation is explained by the variables included in the model.
- Association of hypertension prevalence with individual-level risk factors. Using the fully adjusted model, odds ratios (OR) and *p*-values were calculated for each risk factor in the model.
- Estimation of adjusted hypertension prevalence at the district units involved using the predicted individual probability for hypertension in estimating the prevalence at district level. The estimated prevalences and 95% confidence intervals (CI) were graphically presented to profile districts. This procedure allowed a visualisation of which units were significantly different from the national prevalence. Further analysis was

Table 1. Sample by wave for participants 15 years and above

Wave	*Valid hypertension data*	*Total sample*	*Percentage valid*
2008	14 135	18 617	75.9
2010/11	15 128	21 943	68.9
2012	18 393	25 228	72.9
2014/15	22 526	28 460	79.1
2017	23 605	32 123	73.5
Total	93 787	126 371	74.2

done allowing for hypertension prevalence to vary by age and BMI at the geographic (district) level. This analysis was used to graphically identify units with relatively steeper slopes by age and BMI.

All analyses were performed using Stata version 15. For design-based prevalence estimate, the 'svy: tab' command for two-way tabulation was used, while the mixed-effect logit (melogit) command was used for multilevel analysis.

Results

Design-based (unadjusted) prevalence of hypertension: the univariate (weighted) analysis (Table 2) shows a decreased trend in hypertension prevalence, except for a slight increase in the 2012 period. On a period-by-period basis, the prevalence of hypertension in females was higher than that of males. Age, BMI status and educational level had the highest differentials, with those relatively older (40+ years) having a prevalence that was about four times that of the younger adults (< 40 years), and those whose BMI was 25 kg/m^2 or above (overweight or obese) having a prevalence almost double that of those with a BMI less than 25 kg/m^2 (normal weight).

Subjects who had primary-level education or no education had a significantly higher prevalence compared to those with relatively higher educational levels, and those who were unemployed had lower prevalence compared with the employed and economically

Table 2. Percentage (95% CI) of hypertension prevalence in South Africa by covariate and period

Characteristic	*2008*	*2010/11*	*2012*	*2014/15*	*2017*	*Average (all)*
Gender						
Female	33.7 (31.7–35.7)	31.9 (30.2–33.7)	33.5 (31.8–35.2)	29.4 (27.8–31.0)	28.5 (27.1–29.9)	31.2 (30.1–32.4)
Male	28.7 (26.5–30.9)	27.8 (25.5–30.2)	30.4 (28.0–32.9)	26.8 (24.7–28.9)	27.3 (25.6–29.1)	28.1 (26.5–29.8)
Age group						
≤ 40 years	16.4 (14.8–18.1)	16.0 (14.6–17.5)	17.3 (15.8–18.9)	13.8 (12.4–15.4)	13.9 (12.8–15.0)	15.3 (14.4–16.3)
> 40 years	58.0 (55.5–60.4)	55.0 (52.6–57.3)	57.2 (54.8–59.5)	53.0 (51.0–55.0)	52.7 (50.6–54.7)	55.0 (53.5–56.4)
Race						
African	29.2 (27.5–30.9)	28.2 (26.8–29.6)	30.0 (28.3–31.7)	25.6 (24.4–26.9)	25.4 (24.3–26.6)	27.5 (26.5–28.5)
Mixed race	41.7 (37.4–46.1)	41.1 (35.1–47.3)	40.2 (34.7–45.9)	39.3 (35.8–42.8)	38.3 (34.3–42.5)	39.9 (36.2–43.7)
Asian/Caucasian	40.6 (35.8–45.7)	35.7 (29.0–43.1)	40.1 (35.1–45.4)	36.5 (29.5–44.2)	39.9 (35.7–44.3)	38.6 (34.7–42.6)
Residency						
Urban	33.4 (31.2–35.6)	32.6 (30.6–34.7)	33.0 (30.8–35.2)	29.5 (27.5–31.6)	29.3 (27.8–30.9)	31.3 (29.9–32.7)
Traditional/farms	28.8 (26.8–30.9)	26.2 (24.6–27.9)	30.6 (28.6–32.7)	25.9 (24.5–27.3)	25.2 (23.8–26.7)	27.3 (26.2–28.5)
Education level						
≤ Primary	46.1 (43.4–48.8)	45.3 (43.1–47.6)	48.9 (46.3–51.4)	48.1 (45.9–50.3)	47.9 (45.5–50.4)	47.2 (45.4–49.0)
High school	24.7 (22.6–26.8)	23.4 (21.6–25.3)	25.6 (23.6–27.8)	21.5 (19.7–23.4)	21.5 (20.1–23.0)	23.2 (21.8–24.7)
Certificate/diploma/bachelors'+	28.1 (24.6–31.9)	28.3 (24.1–32.9)	31.0 (27.8–34.5)	26.8 (24.0–29.9)	29.4 (27.1–31.8)	28.7 (26.8–30.7)
Income tertile						
Low	29.1 (27.3–31.0)	27.3 (25.7–28.9)	28.7 (26.5–30.9)	24.4 (22.5–26.4)	23.5 (20.6–26.7)	27.3 (26.1–28.5)
Medium	33.3 (30.7–36.0)	31.8 (29.4–34.3)	32.4 (30.4–34.4)	27.7 (25.9–29.6)	26.1 (24.6–27.6)	29.9 (28.6–31.2)
High	34.3 (31.3–37.4)	32.0 (29.1–35.0)	34.4 (31.8–37.1)	29.8 (27.7–32.0)	29.8 (28.3–31.3)	31.4 (29.9–32.9)
Employment status						
Employed	32.8 (30.6–35.1)	31.4 (28.8–34.2)	32.9 (30.7–35.2)	28.6 (26.6–30.7)	27.8 (26.2–29.4)	30.3 (29.0–31.8)
Unemployed	24.4 (21.8–27.1)	23.1 (19.9–26.7)	23.4 (20.6–26.5)	19.8 (16.8–23.1)	19.9 (17.4–22.7)	22.2 (20.6–23.9)
Economically inactive	33.8 (31.3–36.3)	31.2 (29.5–33.0)	34.6 (32.5–36.7)	30.3 (28.5–32.1)	30.4 (28.8–32.1)	31.9 (30.5–33.3)
Medical aid						
Yes	35.7 (31.3–40.4)	31.7 (26.7–37.2)	36.8 (32.7–41.0)	33.2 (28.9–37.9)	33.3 (30.0–36.7)	29.0 (28.0–30.1)
No	30.8 (29.2–32.5)	29.7 (28.3–31.2)	31.3 (29.7–32.9)	27.2 (25.9–28.6)	26.9 (25.7–28.2)	34.1 (31.4–36.9)
Body mass index						
Below overweight	21.5 (19.7–23.3)	20.1 (18.5–21.7)	21.2 (19.4–23.1)	16.8 (15.4–18.2)	17.1 (15.8–18.5)	19.1 (18.1–20.2)
Overweight/obese	40.7 (38.5–42.9)	38.7 (36.7–40.8)	41.9 (39.7–44.0)	38.6 (36.6–40.7)	38.2 (36.6–39.7)	39.5 (38.2–40.9)
Exercise						
Never exercise	34.2 (32.5–36.0)	32.2 (30.5–33.9)	34.0 (32.3–35.8)	31.1 (29.5–32.6)	30.7 (29.4–32.1)	32.3 (31.3–33.4)
Some exercise	26.7 (24.0–29.5)	25.4 (22.7–28.4)	27.8 (24.9–30.8)	23.1 (20.8–25.6)	22.8 (21.1–24.5)	24.9 (23.2–26.7)
Alcohol use						
Yes	34.1 (31.5–36.9)	30.5 (27.4–33.8)	33.3 (30.7–36.0)	29.8 (27.4–32.3)	30.3 (27.7–33.0)	29.5 (28.3–30.8)
No	30.6 (28.8–32.4)	29.9 (28.3–31.5)	31.6 (29.9–33.3)	27.3 (25.9–28.9)	28.4 (27.0–29.8)	31.4 (29.7–33.2)
Unknown	–	–	–	–	23.5 (21.2–26.0)	23.5 (21.2–26.0)
Smoking status						
Never smoked	30.6 (29.0–32.3)	29.2 (27.7–30.8)	31.0 (29.3–32.7)	26.7 (25.3–28.2)	26.9 (25.7–28.1)	28.7 (27.7–29.8)
Ever smoked	33.9 (31.2–36.7)	33.2 (29.8–36.9)	35.9 (32.2–39.8)	32.3 (29.2–35.6)	30.9 (28.6–33.4)	33.1 (31.0–35.3)
Season of BP measurement						
Summer	29.3 (26.8–31.8)	24.4 (21.3–27.8)	25.3 (20.4–30.9)	25.4 (24.0–26.9)	24.7 (23.0–26.5)	26.1 (25.0–27.3)
Winter	35.8 (32.8–39.0)	31.9 (29.8–34.1)	32.9 (30.7–35.2)	32.2 (27.9–36.8)	31.3 (29.2–33.4)	32.5 (31.2–33.9)
Autumn/spring	32.2 (29.7–34.9)	28.8 (26.6–31.2)	31.6 (29.4–33.9)	30.5 (27.9–33.3)	29.0 (27.1–30.9)	30.4 (29.0–31.8)
All	31.5 (29.9–33.1)	30.0 (28.6–31.5)	32.1 (30.5–33.8)	28.2 (26.8–29.6)	27.9 (26.7–29.1)	29.8 (28.7–30.9)

inactive. The African race had a lower prevalence compared with the other races. Urban dwellers, and those who had a medical aid, or engaged in no physical exercise, or had ever smoked, or had ever used alcohol, or whose BP measurements were taken in winter had hypertension prevalences higher than their respective counterparts. Those who were higher in the income band had prevalences significantly higher than those in the lower income level.

Fig. 1 shows the unadjusted weighted hypertension prevalence and 95% CI for South African districts. The average national prevalence was 29.8% (95% CI: 28.7–30.9%: green band). Approximately eight districts showed a prevalence that was lower than that of the national level, while about 16 districts showed a prevalence that was significantly higher than that of the national level. However these estimates are imprecise as characterised by the large confidence intervals.

Except for A Nzo and OR Tambo (both in the Eastern Cape Province), the districts with a lower-than-average prevalence were found in the north-eastern provinces of Limpopo and Mpumalanga. By contrast, the districts with a higher prevalence than average were from the Western and Northern Cape provinces. In between these two extremes lay the majority of the districts whose prevalence was approximately equal to the average. These districts were mostly found in KwaZulu-Natal, Gauteng, parts of the Free State and Eastern Cape, and North West provinces.

Fig. 1. Design-based hypertension prevalence rates by districts in South Africa.

Factors associated with hypertension: after accounting for other factors, the greatest effect on hypertension was shown to be basically from the demographic factors of age and race, where the OR was approximately 5.5 times more for every five years increase in age, while the Coloured and black African populations, respectively, were about 2.5 and 1.5 times more likely to be hypertensive compared with the combined races of whites and Asians.

Other factors associated with hypertension prevalence were BMI (OR = 2.29, $p = 0.001$ for those with BMI at least 25.0 kg/m^2), alcohol use (OR = 1.25, $p < 0.001$), season (OR = 1.33, $p < 0.001$ for winter vs autumn/spring) and residence (urban vs traditional/farm, OR = 1.12, $p \leq 0.011$). Adjusted prevalence was more likely to be lower for females compared with males and decreased with level of education. Medical aid and smoking status were not found to be significant predictors of hypertension prevalence for these samples.

Hypertension variance: Table 3 presents the distribution of hypertension variance at the individual and district levels. Most

Table 3. Fixed and random effects associated with hypertension prevalence in South Africa

Factor	*Odds ratio (95% CI)*	*p-value*
Period/year (vs 2008)		
2010/11	0.72 (0.66–0.78)	0.000
2012	0.81 (0.75–0.88)	0.000
2014/15	0.75 (0.70–0.81)	0.000
2017	0.64 (0.59–0.70)	0.000
Gender (vs male)		
Female	0.86 (0.80–0.92)	0.000
Age	1.11 (1.10–1.11)	0.000
Race (vs Asian/Caucasian)		
African	1.52 (1.30–1.78)	0.000
Mixed race	2.56 (2.13–3.07)	0.000
Residency (vs traditional/farms)		
Urban	1.12 (1.03–1.22)	0.011
Education level (vs pry and below)		
High school	0.86 (0.80–0.93)	0.000
Certificate/diploma/Bachelors'+	0.76 (0.68–0.84)	0.000
Income tertile (vs low)		
Medium	0.90 (0.85–0.96)	0.001
High	0.96 (0.89–1.03)	0.231
Employment status (vs employed)		
Unemployed	0.97 (0.90–1.04)	0.375
Economically inactive	0.93 (0.87–0.99)	0.014
Has medical aid	1.01 (0.91–1.11)	0.861
BMI (vs ≤ normal weight)		
Overweight/obesity (≥ 25 kg/m^2)	2.29 (2.16–2.42)	0.000
Physical exercise (vs no exercise)		
Some exercise	0.98 (0.92–1.03)	0.438
Alcohol use (vs never used)		
Yes	1.25 (1.17–1.33)	0.000
Unknown	1.06 (0.93–1.20)	0.384
Smoking status (vs never smoked)		
Ever smoked	1.00 (0.93–1.08)	0.920
Season (vs autumn/spring)		
Summer	0.80 (0.76–0.85)	0.000
Winter	1.33 (1.26–1.40)	0.000
Random effects		
District	0.11 (0.07–0.18)	
Repeated observations	3.32 (3.13–3.51)	

of the variance for both the unadjusted and adjusted models was at the individual level. The VPC shows the proportion of hypertension prevalence variation at the district level to be 3.5%. When adjusting for the explanatory variables, about 1.9% (3.5–1.6) of the variance in the higher level (district) is explained by the geographic distribution of demographic, behavioural, socio-economic and environmental factors (Table 4). Level 1 variance (within individuals' observation) is the fixed value 3.29 ($\pi^2/3$), which is the value assigned for a multilevel logistic regression.

Adjusted prevalence at the district level: the risk-factor adjusted prevalence estimates, unlike the unadjusted (weighted) prevalence, had narrower confidence intervals, and only about 10 districts had a prevalence approximately equal to the average prevalence. A common scenario under both estimation methods was that most of the districts with a lower-than-average prevalence were found in the northern and north-eastern part of the country, while those with a higher-than-average prevalence were mostly in the south and south-western parts of the country (the 'Cape' provinces). All the districts in the Western Cape, except Cape Town, and all the provinces in Northern Cape except Frances Baard had prevalences above average. All districts in Limpopo, Mpumalanga and Gauteng had prevalences below average (Fig 2).

Random district slopes for age and BMI: the effect of age for some districts was lower (districts whose slopes were below the red horizontal line in Fig. 3) than its overall effect. These districts included all from the Limpopo Province, and most of those in Kwa-Zulu Natal and Eastern Cape. The effect of BMI was relatively stronger in most of the districts in Limpopo, Free State, Northern Cape and Kwa-Zulu Natal, and least for most districts in the Eastern Cape.

Discussion

The purpose of this study was to analyse the degree of hypertension prevalence variation for adults aged 15 years and above at the district level before and after adjusting for risk factors associated with hypertension. According to the results of the multilevel model, factors that explained variation in hypertension status in this study were found to be consistent in certain aspects with previous research. For example, age and BMI were the two strongest factors affecting hypertension prevalence in this study, which is in agreement with other studies.[22-26]

The effect of gender on hypertension has been conflicting, with some studies showing a weak association, with females having a lower prevalence of hypertension than males,[25-27] while other studies have showed no association.[23,24,28] The results of the multivariate analysis in this study showed that females had a lower hypertension prevalence compared with males.

Table 4. Variance partition and specific-level change in variance between the null and the adjusted model

Variance component	*Null model: variance (SE)*	*Adjusted model: variance (SE)*	*Change in variance (%) (Ds^2)*
Individual	8.47 (0.224)	3.32 (0.0963)	–60.8
District	0.430 (0.082)	0.110 (0.026)	–74.4
Individual VPC (%)	69.4	49.4	
Geographic VPC (%)	3.5	1.6	

VPC: variance partition coefficient.

Alcohol use (past or current) has also been found to increase the risk of hypertension in some studies,[24,29,30] while in another study no relationship was found.[25] Smoking status, education, and employment status have also yielded conflicting results from various studies.[23,25]

The mixed race and Africans were found in the multilevel logistic regression to have increased prevalence of hypertension compared with Asians/Caucasians. This is consistent with a study done in the United States of America where there are such mixed races.[31]

Univariate analysis showed that prevalence of hypertension for those who had subscription to a medical aid provider was higher compared to those without medical aid, but multivariate analysis showed no association. This is possibly because its confounding effect was reduced by income level and education. The percentage of those subscribed to a medical aid cover increased with higher income and educational level.

The study also found seasonal effects with the odds of increased hypertension prevalence being higher in the winter months compared with summer. This is consistent with other studies that have shown cold ambient temperatures to be associated with elevated blood pressure,[32-35] and therefore the effect has also been found to be larger in winter than in summer.[36-38]

Analyses of variance at the individual and district level showed differences in the hypertension prevalence variance

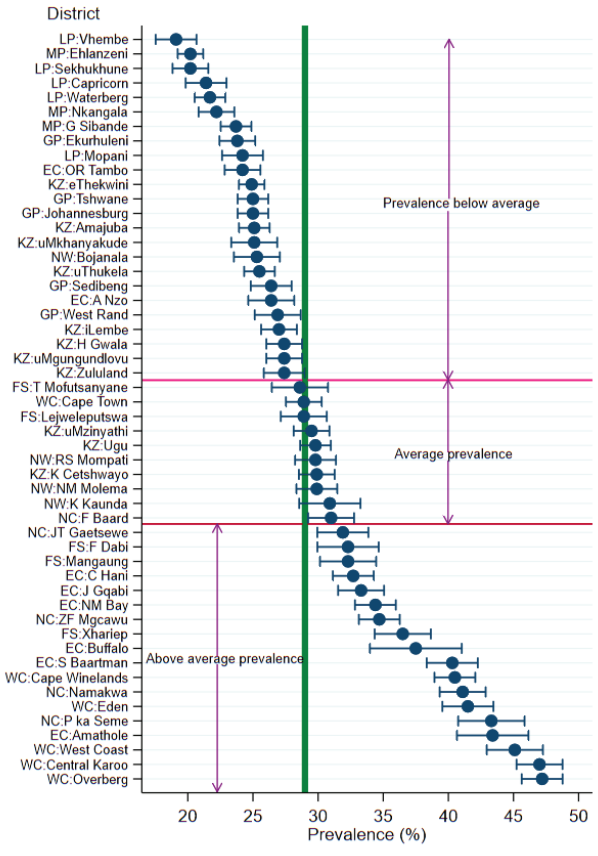

Fig. 2. Mean difference in hypertension prevalence and 95% CI for South African districts (adjusted model).

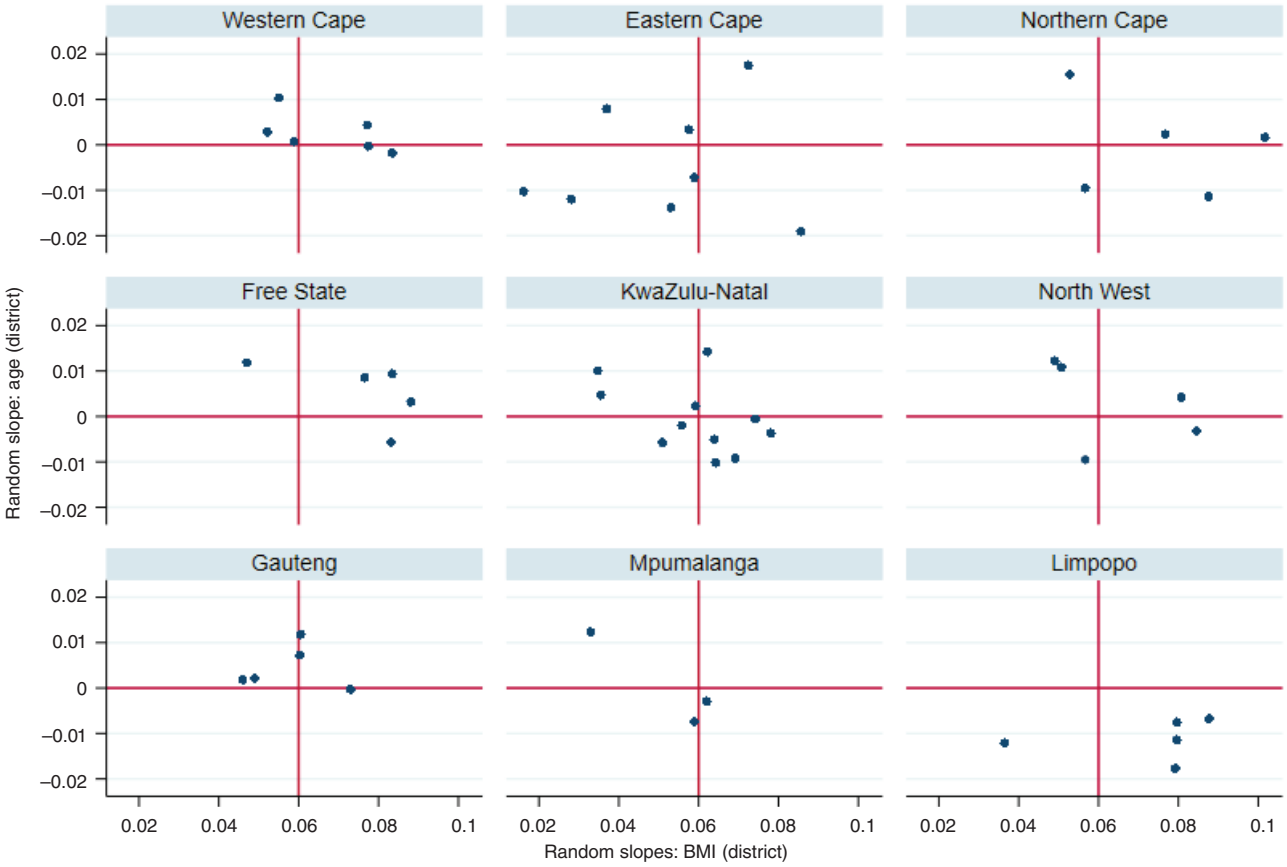

Fig. 3. Scatter plot for districts' random slopes for age and BMI.

distribution at the higher level (district), with a VPC of 3.8 and 2.1% for the null and the risk-factor-adjusted models, respectively. After adjusting for the effect of risk factors, the level-specific change in variance (Ds^2) was equally important at both the individual and district level.

This implies that the risk factors were unequally distributed between individuals and between districts. This could possibly be the reason for the difference in race-wise results between the unadjusted and adjusted estimates. The unadjusted prevalence showed that prevalence was highest in Asian/Caucasians, followed by the mixed race, and lowest in Africans, while the adjusted estimates showed lower chances of hypertension in Asians/Caucasians. This most likely was due to the reduced confounding effect of age, whose average was highest in Asians/Caucasians, followed by the mixed race and lowest for Africans. A previous study found age-standardised self-reported hypertension to be highest in mixed-race women followed by African women.[39]

There were important geographic variations in hypertension prevalence between districts in South Africa, even after controlling for socio-demographic and behavioural background factors. Districts with a lower-than-average prevalence were mostly in the north-eastern part of the country (Limpopo, Mpumalanga and Gauteng provinces) while those with a higher-than-average prevalence were mostly found in the Western, Eastern and Northern Cape provinces. Most of these districts are coastal districts in close vicinity to the Atlantic Ocean. A previous study that limited geographic variation of hypertension to the provincial level found similar clustering of hypertension prevalence.[22]

Identifying districts (sub-units) with high and low hypertension prevalence could be useful in programming public health interventions. Districts with a high hypertension burden could be considered for targeted prevention and control programmes, rather than one national intervention programme. As governments, especially in LMICs, are faced with multiple needs and limited resources, their role of ensuring that all people have equitable access to preventative, curative and rehabilitative health services involves preventing them from developing hypertension and its complications.[40-42] Our study has shown that, although the majority of South African districts had approximately the same burden of hypertension, some had a heavier burden than others, even after accounting for risk factors documented to have a strong influence on hypertension prevalence.

The effects of age and BMI on hypertension prevalence were found to vary from district to district, showing their slopes were higher in some districts relative to others. Health services that address the risks of hypertension, for example body mass, should target such areas.

Strengths and limitations

To the best of our knowledge this is the only study to have estimated the prevalence of hypertension at the district level,

taking into consideration the associated risk factors. The study, however, has a few limitations. First, while the study sample was large enough to allow credible estimates of hypertension at the national level, the samples at the district level were not large enough and this resulted in wide confidence intervals for the estimated prevalence rates. Second, although we adjusted for seasonal variation when BP measurements were taken for each subject, it was not possible to fully adjust for ambient temperatures since these measurements were not available in our data set.

Third, although we adjusted for race in the analysis, it is possible that there could be differences within the same race, especially for black South Africans, who are also characterised by different ethnicities/tribes. The data set did not have details on ethnicity or tribe. A few studies in sub-Saharan Africa have shown variability of hypertension by ethnicity. In Nigeria, prevalence of hypertension was found to differ significantly by ethnicity after adjusting for age, gender, place of residence and socio-economic status.[43] Similarly, some evidence of ethnic variation has been reported in Kenya where statistically significant differences between ethnic groups were reported after adjusting for sociodemographic and other cardiovascular risk factors,[44] but a study from Nigeria and Cameroon did not find any association of hypertension with ethnicity.[45] It may be interesting to analyse other aspects of diet and cultural differences in food intake, such as salt and sugar consumption, both of which were not available in our data set, and are known for their strong influence on hypertension.

Conclusions

The results from this study show that there were significant differences in the prevalence of hypertension at the district level. Districts with a higher-than-average prevalence appeared to be clustered together, as were those with a lower-than-average prevalence. An implication of these results is that there could have been other risk factors not captured in the data that were associated with hypertension prevalence and were also distributed unequally between the districts.

It could also mean that there were differentials in the clusters of districts in prevention, management and control of hypertension. Effective management without complete control could imply people living longer with the condition, thereby increasing the prevalence of hypertension. On the other hand, districts with a low prevalence could indicate poor management, which could result in hypertension-related deaths. Alternatively, low prevalence could be a result of either low incidence or effective prevention and control interventions. These could be issues for further related research and in particular an examination of the impact of district-level covariates/factors.

The data sets analysed during the current study are available in the NiDS DataFirst repository: https://www.datafirst.uct.ac.za/dataportal/index.php/catalog/NIDS. We acknowledge the NiDS for providing access to data used for this study.

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Case Report

A giant aneurysm of the left anterior descending coronary artery in the setting of Behcet's disease

Mejdi Ben Messaoud, Nidhal Bouchahda, Ayoub Belfekih, Fadwa Omri, Mezri Maatouk, Walid Mnari, Habib Gamra

Abstract

Behcet's disease is a chronic inflammatory syndrome that can affect arteries and veins of all sizes and is an unusual cause of myocardial infarction. We report a case of a 42-year-old male with no cardiovascular risk factors who was referred to our department for a spontaneously resolving anterior ST-elevation myocardial infarction. Clinical and biological investigations revealed a high probability for Behcet's disease. The coronary angiogram showed severe left main artery stenosis with a huge coronary aneurysm of the proximal left anterior descending coronary artery, which was treated by aneurysm resection and coronary artery bypass grafting. Inflammatory arteritis should be considered in young patients with low cardiovascular risk presenting with acute coronary syndrome.

Keywords: Behcet syndrome, coronary aneurysm, acute coronary syndrome

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Acute coronary syndrome in young patients with low cardiovascular risk is rare but it can reveal non-atherosclerotic aetiologies such as systemic inflammatory syndromes. In this article we report on the case of a giant coronary artery aneurysm in a young man with no cardiovascular risk factors, who was admitted for acute coronary syndrome.

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Case report

A 42-year-old male with no cardiovascular risk factors was admitted in our department for a spontaneously resolving anterior ST-elevation myocardial infarction. The initial physical examination revealed a fever of 38.5°C with mouth and genital aphthous ulcers.

Laboratory tests showed a marked elevation of white blood cells at 17 800 cells/µl (normal range: 4 000–11 000 cells/µl), C-reactive protein at 252 mg/l (normal value < 6 mg/l) and erythrocyte sedimentation rate of 95 mm/h (normal value < 15 mm/h) with positive pathergy test and negative antinuclear antibodies. Based on these findings, Behcet's disease was strongly suspected, and other inflammatory systemic diseases such as systemic lupus erythematous were much less likely.

Echocardiography showed a preserved left ventricular ejection fraction and a vascular mass between the aorta and pulmonary trunk with an accelerated continuous-wave Doppler flow inside the mass (Fig. 1). The coronary angiogram showed severe left main artery stenosis, a huge aneurysm (43 × 33 mm) of the proximal left anterior descending artery causing slow flow, and another smaller (10 × 8 mm) aneurysm of the distal right coronary artery (Fig. 2). A coronary computed tomography scan confirmed the above findings and showed a partial thrombosis of the left anterior descending artery aneurysm that was compressing the pulmonary trunk (Fig. 3).

The patient was given corticosteroids and immunosuppressive therapy (cyclophosphamid), with a favourable outcome. One month later, he underwent successful cardiac surgery consisting of a resection of the huge aneurysm and bypass of the left anterior descending and circumflex arteries.

Follow up at six months with a clinical and echocardiographic evaluation was unremarkable. Because the patient was asymptomatic, no other tests for myocardial ischaemia, such as stress test were performed. Inflammatory markers including C-reactive protein were negative.

Discussion

Behcet's disease is a multisystem vasculitis that can involve vessels of all sizes and is characterised by recurrent oral and genital ulcers, with variable manifestations affecting the skin, eyes, central nervous and musculoskeletal systems.[1] Venous and arterial involvement and aneurysm formation of the vascular tree may be seen. First described by Schiff *et al*.[2] as a myocardial infarction, coronary involvement in Behcet's disease is very rare (0.5%).[3]

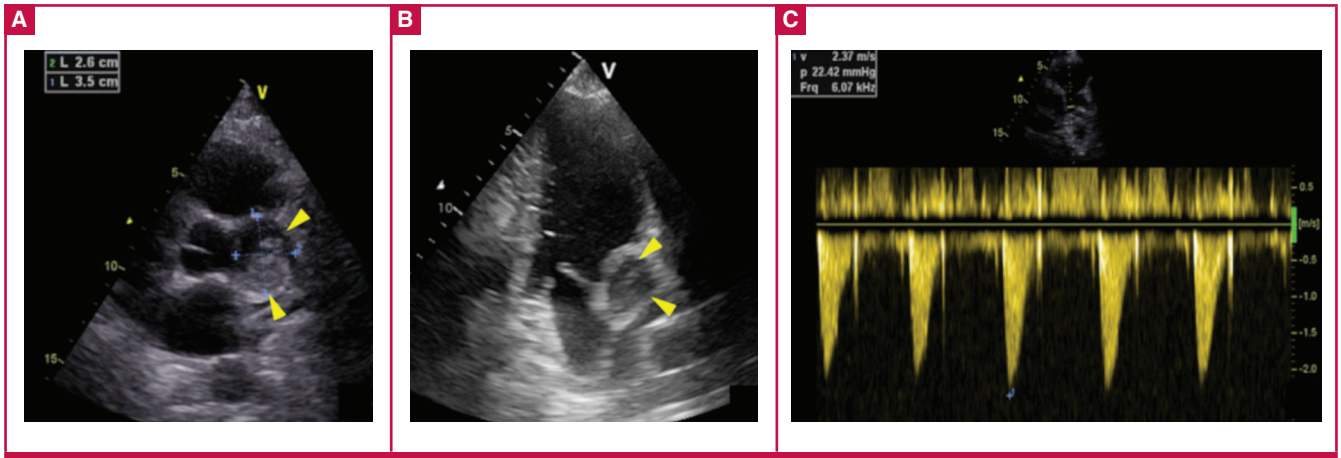

Fig. 1. Echocardiographic images. A and B show the giant aneurysm of the left anterior descending artery (arrowhead). C shows accelerated flow inside the aneurysm by continuous-wave Doppler.

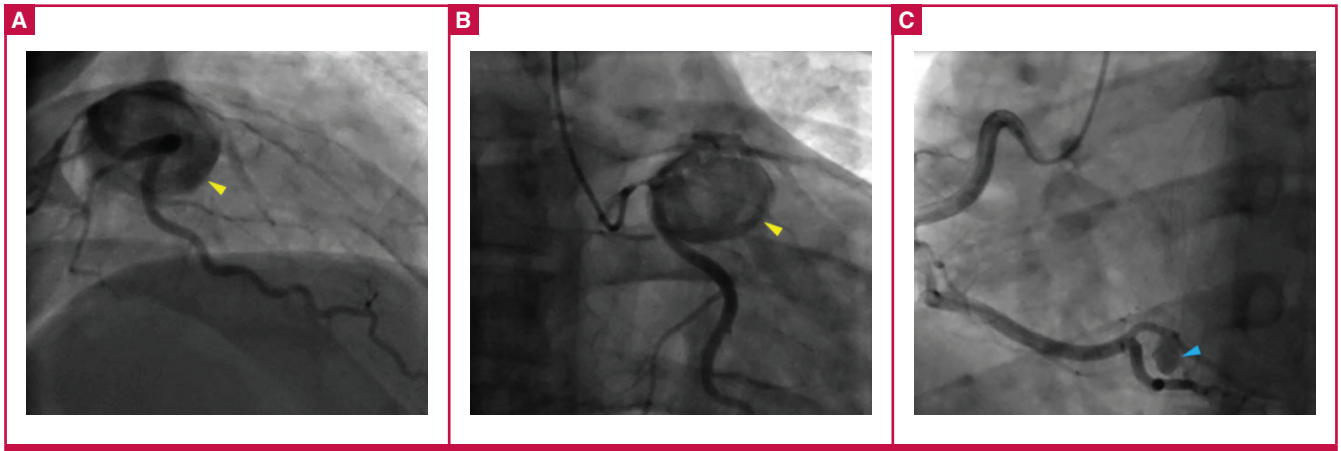

Fig. 2. Coronary angiogram images. A and B show severe stenosis of the left main artery and a giant aneurysm (arrowhead) of the proximal left anterior descending artery with a slow TIMI flow. C shows a small aneurysm (arrowhead) of the distal right coronary artery.

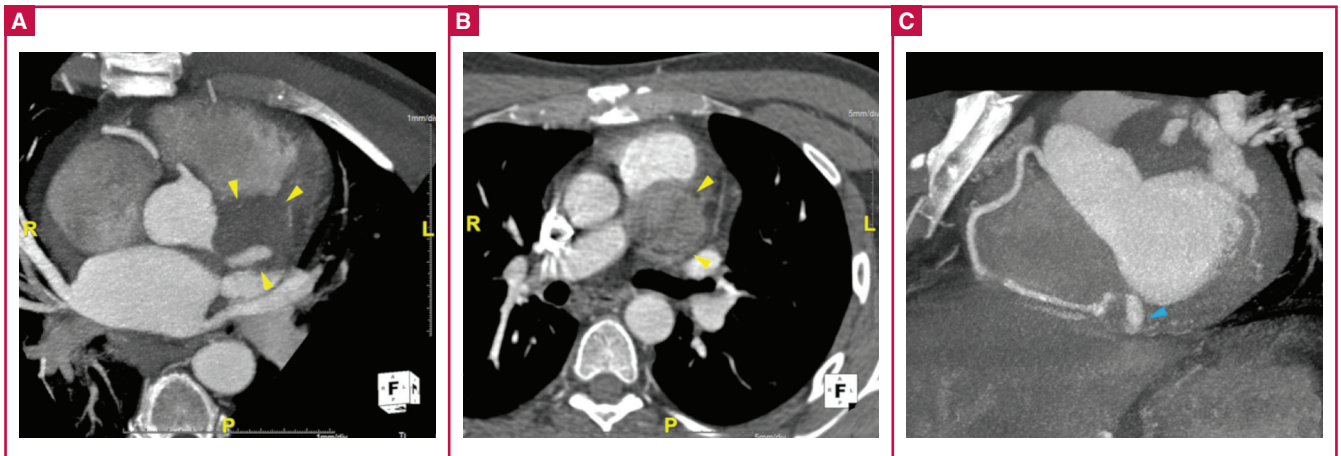

Fig. 3. Coronary computed tomography scan images. A shows a giant aneurysm of the left anterior descending artery (arrowhead). B shows the left anterior descending artery aneurysm compressing the pulmonary trunk (arrowhead). C shows a small aneurysm of the distal right coronary artery (arrowhead).

Angiographically, coronary artery aneurysms and stenosis are the most frequently detected lesions. Local coronary vasculitis causing fibrous intimal thickening may result in coronary occlusion with subsequent development of acute coronary syndromes. The left anterior descending coronary artery is affected in most cases and aneurysm rupture is the most common

cause of death in Behcet's disease. Other complications such as thrombosis and dissection have also been reported.[4]

In the majority of cases, patients develop coronary events several months or years after having been diagnosed and treated for Behcet's disease. Less commonly, coronary complications may occur as the first manifestation of the disease, such as in this case.[5]

Early initiation of immunosuppressive therapy is recommended for the management of coronary artery aneurysms due to Behcet's disease. Corticosteroids, colchicin, azathioprine and cyclophosphamid were the most commonly used agents in previous reports.[6]

Management of these patients might be challenging because of the increased risk of bleeding, scar thinning and myocardial rupture on the combination of antithrombotic therapy and corticosteroids. Radical treatment is mostly surgical, including aneurysm resection or ligation with coronary artery reconstruction or coronary artery bypass grafting.[4] In some cases, percutaneous interventions are performed using covered stents.[7] These interventions are usually indicated after clinical remission on corticosteroids and immunosuppressive therapy because coronary manipulation in the active phase may expose patients to complications.[6]

Conclusion

Although coronary artery aneurysm is a rare manifestation of Behcet's disease, it should be suspected in cases of acute coronary syndrome in young patients with no cardiovascular risk factors. As the presence of cardiac involvement worsens the prognosis of Behcet's disease, prompt diagnosis and initiation of immunosuppressive therapy are of paramount importance before surgical or percutaneous management of the aneurysm.

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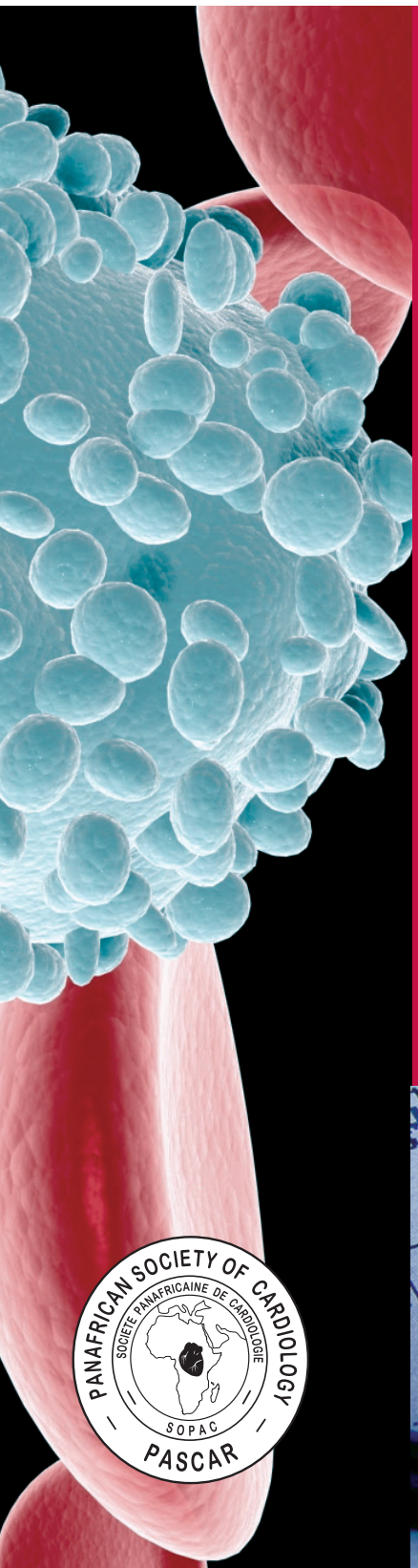

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