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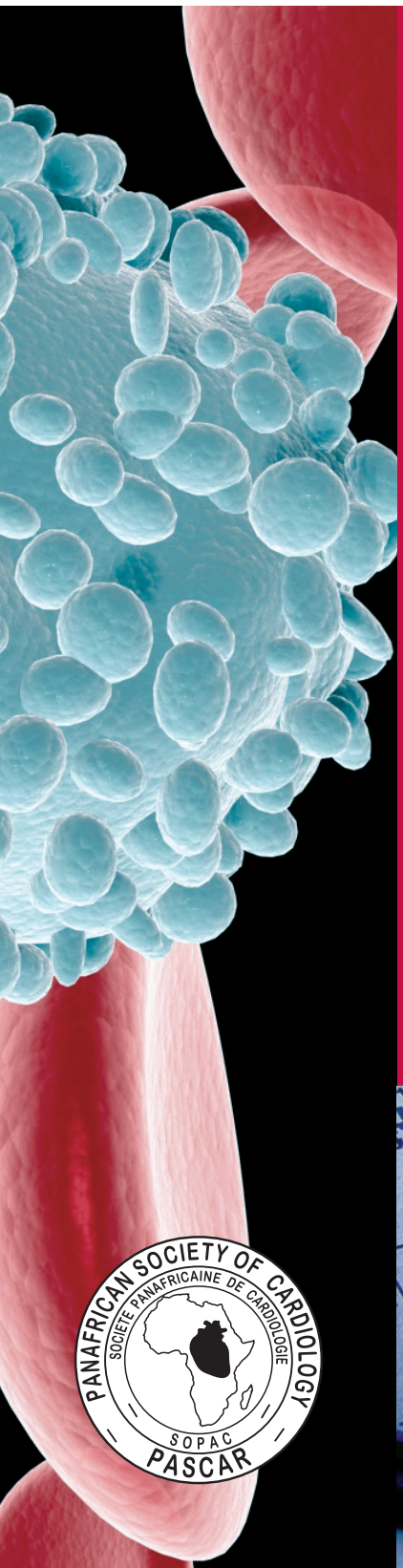

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Editorial

Cardiovascular care in sub-Saharan Africa during the COVID-19 crisis: lessons from the global experience

Kishal Lukhna, Blanche Cupido, Jens Hitzeroth, Ashley Chin, Mpiko Ntsekhe

'by 3 methods we may learn wisdom: first by reflection, which is noblest; second is by imitation, which is easiest; and the third is by experience, which is the most bitter Confucius

Sub-Saharan Africa (SSA) stands on the verge of an unprecedented challenge to its healthcare infrastructure and systems due to a novel infectious disease that has overwhelmed the greatest of healthcare services worldwide. Coronavirus disease 2019 (COVID-19), the clinical disease caused by SARS-CoV-2, was classified by the World Health Organisation (WHO) as an international public health emergency in late January and has increased exponentially to pandemic proportions since then.[1] There are currently over four million confirmed cases and 302 059 deaths documented worldwide.[2] South Africa has become the epicentre of COVID-19 infections in Africa, with approximately 13 524 cases and 247 deaths at the time of writing.[2]

COVID-19 is a viral syndrome with a predilection for the upper respiratory tract and lungs, which can cause severe dysfunction of multiple organs, including the cardiovascular system.[3,4] Analysis of the large number of COVID-19-related fatalities in New York, China and Italy suggests that male patients with advanced age, hypertension, diabetes, obesity and established cardiovascular disease are at highest risk of mortality from COVID-19.[5-9] New and decompensated heart failure, myocarditis, cardiac arrhythmias, pericarditis with or without tamponade, acute pulmonary embolus and acute myocardial infarction (MI) have all been described as the initial presenting manifestation of COVID-19 and as complications in those with established disease.[10,11] Complicating the picture is the fact that biomarkers of cardiac injury and haemodynamic strain are elevated in up to 30% of patients, even where there is no overt evidence of cardiac involvement.[12]

Despite much goodwill and great effort, factors such as overcrowding and limited testing capacity have meant that the continent's goal of prevention, control and containment of the virus has had variable and limited success across countries. As we brace ourselves for the impending COVID-19 medical onslaught, we set out to explore the published experience from geographies that have seen the worst of the pandemic and highlight a few important lessons shared in those reports with relevance for cardiovascular disease clinicians in Africa.

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Lesson 1: 'Don't wait for the rain to prepare the umbrella' *Malaysian proverb*

The preparation and re-organisation of healthcare services to deal adequately and appropriately with the burden of both non-COVID-19 and COVID-19 patients with cardiovascular disease should be prioritised. This will be even more important here in SSA where our healthcare systems are already strained with the current COVID-19-free burden of non-communicable and communicable diseases.

Given the vast diversity and heterogeneity of health infrastructure, resources and disease burden, no single effective plan can be recommended or applied throughout Africa. However, there is little doubt that those countries in Europe, Asia and North America that were best prepared fared much better than those who ignored the writing on the wall, confirming that failure to prepare is almost certainly preparation for failure.

Lesson 2: 'If you hear hooves think horses not zebras'

The vast majority of patients presenting with symptoms and signs of acute cardiac disease will indeed have acute cardiac disease and should be treated as such.

Although the finding that the prevalence of hypertension, diabetes, obesity and cardiovascular disease among those presenting with symptomatic COVID-19 is high, this does not mean that the corollary is also true (that among those presenting with cardiovascular syndromes, COVID-19 is high). In fact, the opposite is true: (1) the vast majority of patients presenting with acute cardiac disorders as their primary presentation will be COVID-19 free, and; (2) the vast majority of patients with COVID-19 do not have cardiovascular complications.[3]

This is important because the temptation to delay the diagnostic work-up and treatment of acute cardiac syndromes until patients have been tested and the disease has been excluded has major consequences and should be avoided. The outcomes of most acute cardiac disorders such as acute MI are time-sensitive and time-dependent. So if you need to test patients for COVID-19, do so, but don't ignore the obvious in front of you.

Lesson 3: 'Treatment deferred is treatment denied'

The public at large should be reminded and encouraged to seek immediate medical attention for symptoms compatible with acute cardiac syndromes. Patients with acute chest-pain syndromes, heart failure and other cardiac emergencies such as life-threatening arrhythmias should be advised to seek help at their nearest emergency healthcare centres with little or no delay.

Following nation-wide shutdowns throughout the globe, there was a dramatic and almost universal drop in acute cardiac syndromes such as MI.[13] While there has been much debate about potential reasons, reports suggest that contributing to this phenomenon was that many patients chose not to go to hospital.[11] Anecdotal reports suggest that for some it was out of fear of contracting COVID-19. For others, it was out of a desire to help by not being an extra burden on healthcare workers. In either case, there is also little doubt that for many it was costly beyond measure. Therefore the public health messages that have helped patients get to hospital promptly and receive timely care around the world in the past should be re-iterated loudly to our communities and society at large.

Lesson 4: 'Practice makes perfect'

Fibrinolytic therapy, pharmaco-invasive therapy and primary percutaneous coronary intervention (PCI) all have pros and cons in this COVID-19 environment. The key to optimal outcomes during COVID-19 is to continue to do what you know how to do best, with appropriate precautions.

There has been much debate about whether patients with acute MI should receive thrombolytic therapy or primary PCI (PPCI). Experience from China, India and Spain suggests that the main potential advantage for a thrombolytic approach is a lower exposure of staff and patients alike to potential COVID-19 transmission.[14] In resource-limited environments where personal protective equipment (PPE) may need to be rationed, thrombolytic therapy may allow for time to test for COVID-19 prior to transfer for pharmaco-invasive therapy, and conservative therapy in low-risk patients, such as those presenting with uncomplicated inferior MI.

Where PPCI is the treatment strategy of choice, the advantages relate to the known superior outcomes compared to fibrinolytic therapy, and the ability to recognise ST-elevation myocardial infarction (STEMI) mimickers such as COVID-19 pseudo-MI and Takotsubo syndrome at the time of angiography.[15] In environments where patients will continue to have access to the laboratory, it is essential that both the laboratory and its staff are fully prepared and trained in the appropriate use of PPE such as caps, masks, gowns, gloves and goggles. What is apparent from the published experience is that changing approach during this period, i.e. from a PPCI service to a fibrinolytic approach or vice versa will not change clinical outcomes.[16] In short, the best strategy is to keep doing what you have been doing.

Lesson 5: 'Treat the patient not the test'

Routine use of troponin and B-type natriuretic peptide (BNP) adds little to diagnostic or treatment decisions in patients with COVID-19 without an overt acute cardiac syndrome. Mild to moderate elevations in troponin and BNP values are found in up to 7% of hospitalised patients and 27% of those requiring admission to the intensive care unit (ICU), in the absence of evidence of overt cardiac abnormalities.[17]

While the mechanisms of these biomarker abnormalities are unclear, their poor prognostic significance is now well established.[18] The American College of Cardiology recently recommended that they should be measured only where there is clinical suspicion of an acute MI or heart failure, after repeated testimony and evidence showed that routine testing triggered a series of additional tests such as echocardiography and angiography, which added little value but exposed additional staff to the virus.[12]

Lesson 6: 'If it ain't broke don't fix it'

Patients on renin–angiotensin–aldosterone system (RAAS) blockers for hypertension, heart failure and diabetic nephropathy should not stop for fear of increased risk of COVID-19.

The combined but unrelated findings that (1) coronavirus attaches to angiotensin converting enzyme-2 (ACE2) receptors for cell entry and infection; and (2) the prevalence of hypertension among hospitalised patients with COVID-19 is high, led to fears that patients on RAAS inhibitors (ACE inhibitors and angiotensin receptor blockers) may be at increased risk of severe infection because of RAAS blocker-induced upregulation of the ACE2 receptor. However, the published evidence is now clear that this hypothesis was incorrect and these first-line therapies do not cause harm and should not be stopped.[4] This is particularly important in Africa in light of the recently published CREOLE trial, which found that the combination of amlodipine and an angiotensin receptor blockers (ARB) offered better control than diuretic-based combination therapy.[19]

Lesson 7: 'First do no harm'

There are currently over 200 treatment options for COVID-19 under investigation. At the time of writing, there remains no proven effective therapy for the treatment of COVID-19. Some drugs under investigation, such as chloroquine and hydroxychloroquine with or without azithromycin can prolong the QT interval and cause harm.[20] These drugs may increase the risk of life-threatening arrhythmias in patients, especially in patients with a prolonged baseline QT interval because of electrolyte abnormalities (such as hypokalaemia) and use of other long QT-prolonging drugs.[21] The judicious use of these drugs should be limited to investigational trials where ECG monitoring is performed until such time as these drugs have been shown to be effective and safe.

Lesson 8: 'Prevention is better than cure'

Given our fragile healthcare infrastructure and limited hospital bed and ICU capacity, the vast majority of African countries will not be able to sustain the massive caseloads experienced elsewhere to date. Therefore, despite the limited success of lockdowns so far, the main self-care tool available to most of society remains to practice social distancing, hand hygiene, wear face masks, practice cough etiquette and avoid crowded spaces where most safe behaviour is near impossible. At the time of writing this article, no drugs have been shown to be effective as prophylaxis

therapy and there are no COVID-19 vaccines. However, if all of us receive and recommend the 'flu vaccine to all, the reduced additional burden of respiratory illness on the healthcare system will make a significant difference on our capacity to treat those with non-COVID-19-related emergencies.[22]

Conclusion

COVID-19 is here to stay. The WHO released a statement predicting approximately 200 000 deaths from COVID-19 in Africa, describing a unique disease profile with slower rates of transmission in lower age groups with severe disease.[23] South Africa is facing community spread of COVID-19. Only time will tell whether the health experts' grim predictions about what is to come can be disproved, but the exponentially growing numbers are not promising. As we acclimatise ourselves to this new normal and learn to live with COVID-19, it will be crucial to heed the lessons of those who have fought the good fight before us.

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Cardiovascular Topics

The effects of aquatic and land exercise on resting blood pressure and post-exercise hypotension response in elderly hypertensives

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Abstract

Objective: This study compared resting blood pressure (BP) using ambulatory BP monitoring (ABPM) responses in two groups of subjects trained in land exercise (LE) and aquatic exercise (AE), and assessed post-exercise hypotension (PEH) using ABPM, after land- and aquatic-based exercises.

Methods: ABPM (24 hours) was used to measure the baseline BP in elderly hypertensive women trained in LE and AE and the PEH induced by exercise. For this, 40 subjects were evaluated at rest and after a land- or aquatic-based exercise session (aerobic: 75% of reserve heart rate combined with resistance exercise).

Results: The daytime BP was lower for AE [systolic BP (SBP) 124 ± 1.0 mmHg, diastolic BP (DBP) 70 ± 1.5 mmHg] than for LE (SBP 134 ± 0.9 mmHg, DBP 76 ± 0.9 mmHg), but there were no differences at night-time. The aquatic exercise-induced PEH in the second hour was maintained at the 24th hour post-exercise. For land exercise-induced PEH, it was maintained at the 12th hour post-exercise. The SBP and DBP were lower at the 24th hour for AE than for LE.

Conclusion: Elderly hypertensive people trained in AE had lower baseline BP during the daytime. SBP and DBP values were lower for individuals trained in AE, and their PEH was more rapid and longer lasting after AE.

Keywords: aquatic exercise, land exercise, hypertension, elderly

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Hypertension (HTN) has been the subject of worldwide study for its clinical aspects or as a health problem. HTN is considered one of the main determinants of cardiovascular morbidity and mortality.[1,2] Among non-pharmacological therapies recommended for HTN treatment, exercise training is essential, with reductions of around –3.5 mmHg for systolic and –3 mmHg for diastolic blood pressure (BP) being reported.[3]

Aerobic exercise for periods of 30 minutes of vigorous or 60 minutes of moderate intensity three to five times a week[4] is universally the most recommended measure to lower BP among those with HTN.[5-7] Resistance training with nine exercises three times a week for 12 weeks, at 75% intensity on one maximal repetition (1RM), with a volume of six to 10 repetitions, promotes a greater nocturnal reduction (> 10%) in diastolic BP (DBP) among older hypertensive subjects than other forms of training.[8]

Individuals can benefit from one session of exercise with immediate or short-term effects that persist for up to 24 hours after an acute exercise bout, a response that is termed post-exercise hypotension (PEH); this effect is considered an important positive factor in HTN treatment.[9-11] Although the modalities of physical exercise (aerobic or resistance exercise) promote different responses in PEH, the magnitudes of PEH that they induce may be distinct. Aerobic exercise seems to promote a higher and longer PEH,[12] and the intensity of the exercise appears to have an influence on PEH.[13] For resistance training there are conflicting data about its effect on PEH due to variance in factors such as the muscle mass involved, the intensity of exercise, and the interval and volume of sets and rest.[13,14]

Aquatic physical exercise (AE) offers advantages over land exercise (LE) for the elderly as it involves lower risk of injury than LE owing to water buoyancy, and guards against joint degradation by decreasing weight-bearing loads[15-17] and reduced joint load.[18] In addition, aquatic-based exercise promotes physiological adjustments resulting from immersion that can affect BP as well as cardiac work, particularly reduction in sympathetic activity and redistribution of blood volume from the lower limbs and abdomen to the upper body.[19,20] Therefore,

excretion of liquids and electrolytes is increased, together with suppression of levels of the fluid-regulating hormones renin, angiotensin II, aldosterone and arginine vasopressin to control plasma volume,[21,22] and peripheral vascular resistance is decreased.[23-25]

Several studies have established the effectiveness of planned interventions using physical exercise in the treatment of HTN with land and aquatic-based exercises,[26-33] but comparisons between the two types of exercise regarding elderly hypertensives trained in different modalities are scarce. In addition, the effects on PEH of land- and aquatic-based exercise during the following 24 hours need further investigation.

In light of the benefits of AE, this study compared resting BP using ambulatory BP monitoring (ABPM), the clinical gold-standard methodology for assessing BP status, in two groups of trained subjects with equivalent cardiorespiratory capacity performing either LE or AE. In addition, using ABPM, we assessed PEH after AE and LE among older women with HTN.

Methods

This was a controlled clinical trial developed at the Exercise Physiology Laboratory (LABFE) of the school of Physical Education of Ouro Preto, Minas Gerais, Brazil. The study protocol was approved by the Research Ethics Committee of the Federal University of Ouro Preto under protocol: 38383314.3.0000.5150.

The study population consisted of 40 elderly hypertensive women, 20 trained in land-based exercise and 20 in aquatic-based exercise. To be included, the subjects had to meet the following criteria: aged over 60 years, hypertensive, female, in regular treatment for BP control, and enrolled in recurrent physical exercise for at least six months before evaluation for a minimum of twice a week. Subjects with symptomatic cardiorespiratory disease or cardiac alterations, the metabolic syndrome, renal or hepatic disease, cognitive impairment, and any other medical contra-indications of physical exercise were excluded.

The participants were divided randomly into four groups:

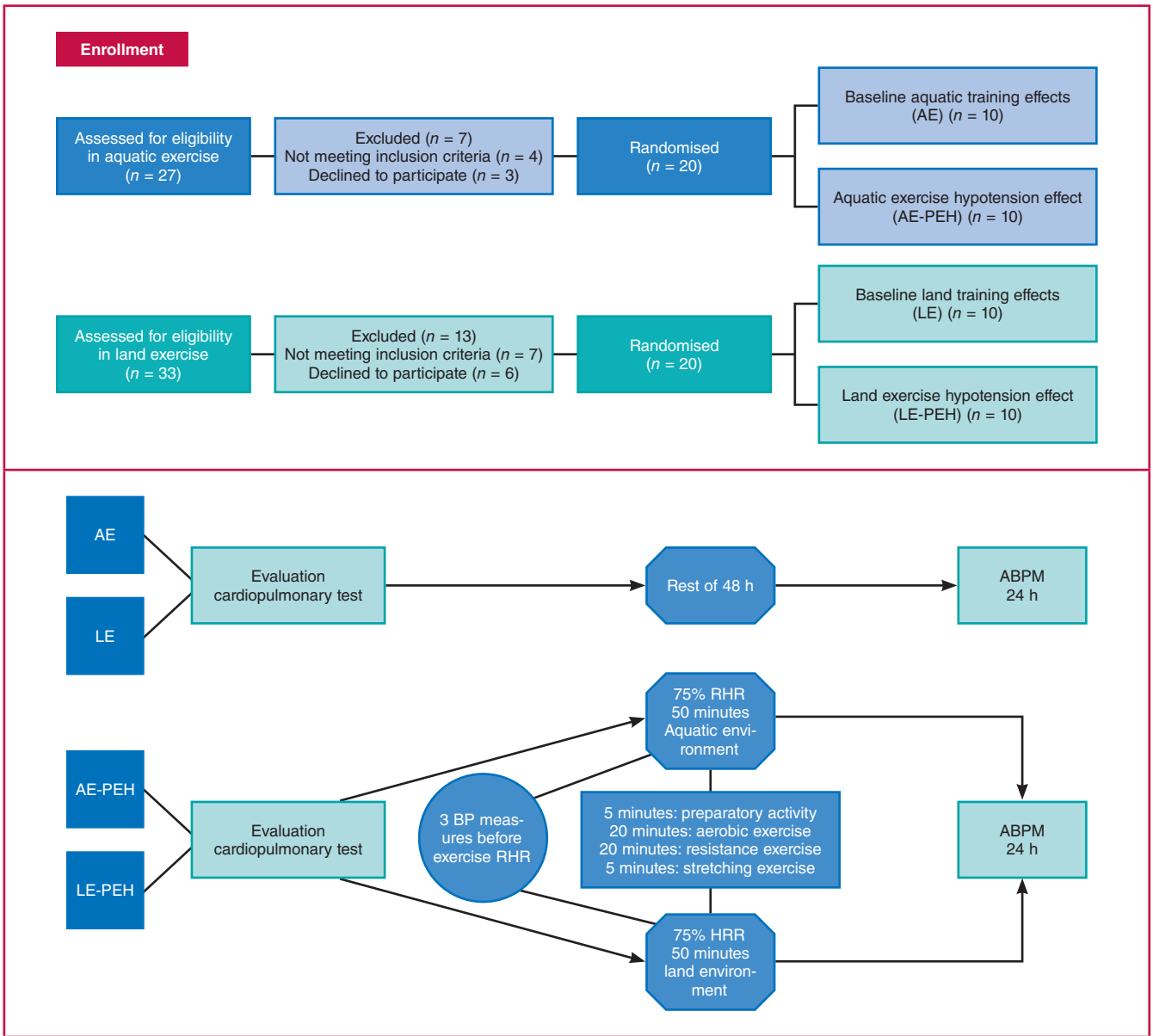

Fig. 1. Study design. RHR: reserve heart rate; ABPM: ambulatory blood pressure measurement.

Table 1. General profile of the two hypertensive groups

	LE-PEH (n = 10)	*AE-PEH (n = 10)*	*LE (n = 10)*	*AE (n = 10)*
Age (years)	67 ± 3	64 ± 3	65 ± 3	70 ± 2
BMI (kg/m²)	26.4 ± 3.4	25.7 ± 2.8	27.3 ± 3.3	26.5 ± 5.2
Peak Vo_2 (ml/kg/min)	23.4 ± 3.4	22.6 ± 2.1	25.7 ± 4.7	24.8 ± 3.4
Resting SBP (mmHg)	140 ± 4.4	153 ± 5.0	130 ± 8.3	128 ± 9.8
Resting DBP (mmHg)	85 ± 4.3	90 ± 5.6	82 ± 4.2	81 ± 8.1
Antihypertensive drugs (*n*)	2 (1–2)	1 (1–2)	2 (2–3)	1 (1–2)
Diuretic (%)	60	50	60	50
ACE inhibitor (%)	20	0	20	0
ARB (%)	80	80	60	80

AE-PEH: aquatic exercise PEH; LE-PEH: land exercise PEH; AE: aquatic exercise; LE: land exercise; PEH: post-exercise hypotension; VO_2: volume of oxygen; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker. Data expressed as mean ± SD.

individuals enrolled in regular AE ($n = 20$), of whom the arterial baseline pressures of 10 were evaluated for 24 hours after 48 hours of rest after their last exercise training; and in the other 10 subjects the PEH induced by an AE session was assessed. The other 20 individuals enrolled in regular LE were randomised and evaluated in the same way (Fig. 1).

Body mass was measured with a digital scale having a capacity of 150 kg and an accuracy of 100 g (EKS® SUPER 9805). Height measurement was performed with a compact stadiometer fixed to the wall, and with a range of 0 to 2.0 m and an accuracy of 1 mm (Coats Corrente® BA1010).

The heart rate (HR) was measured in both groups at rest and after a cardiopulmonary test. For this a cardiac monitor (Polar® model FT1) was used to collect resting HR. The HR recording was made in the seated position for two minutes after a rest of 10 minutes; the lowest HR reached in this period was used. The maximal HR was measured immediately after completion of the cardiopulmonary test.

For evaluation of the maximum aerobic capacity ($VO_{2\ max}$), the progressive treadmill test was applied following the Balke–Ware protocol.[34] The maximal VO_2 was evaluated using an open-circuit spirometry VO2000® ventilometer and an Inbramed® treadmill.[35,36]

BP was measured at rest and after cardiopulmonary tests in both groups. For the former, the BP was assessed three times after 10 minutes of rest in a seated position at intervals of one minute, and the result was taken as the mean value, while for the latter, the BP was assessed immediately after completion of the treadmill test with a stethoscope (Missouri®) and a manual aneroid sphygmomanometer (Missouri®) with a precision of 2 mmHg.

The ABPM was started 48 hours after the last training session to evaluate the baseline BP in the AE and LE groups. To evaluate PEH, the ABPM was started immediately after the exercise session. Three devices of the Meditech KFT® brand, model ABPM-04, were used. The BP cuff was worn on the non-dominant arm. Subjects were instructed to maintain their customary daily activities, not to exercise, and to relax and unbend the arm during the recording interval for daytime ABPM. ABPM data were accepted with more than 75% of the measurements effectively taken. Individual BP measurements were revised for missing and erroneous values.

For comparison purposes, data were distributed across the waking period, which consisted of the mean BP of the

Table 2. Cardiovascular response to maximal effort in the cardiopulmonary test in hypertensive subjects trained in aquatic and land exercise

	AE (n = 10)	*LE (n = 10)*
HR (bpm)	134 (124.9–143.9)	147 (136.5–157.3)*
SBP (mmHg)	160 (150.9–191.7)	162.5 (151.3–177.9)
DBP (mmHg)	80.0 (72.4–89.6)	90.0 (84.1–90.5)*

AE: aquatic exercise; LE: land exercise; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure. *$p < 0.05$ when compared to AE. Mann–Whitney test, data expressed in median and 95% confidence interval.

measurement made every 15 minutes during the periods of the day when the individual was awake (07:00 to 23:00), and the sleep period, during which the BP was measured every 30 minutes and the mean value taken when the individual was asleep (23:00 to 07:00). The result for each hour was then the average of the values recorded during that hour.

For the AE-PEH, each individual remained at rest in a seated position for 15 minutes, then BP was measured three times with a sphygmomanometer and stethoscope. Subsequently the test exercise session was started, which consisted of collective water aerobics with a duration of 50 minutes, comprising five minutes of preparatory activity, 20 minutes of aerobic exercises at 75% of reserve HR (RHR), 20 minutes of strength exercises, and five minutes of stretching. The HR was monitored by a heart rate monitor (POLAR® RS800) during the entire session. After the experimental session, ABPM was used to record BP during the following 24-hour period.

For the LE-PEH, each individual remained at rest in a seated position for 15 minutes, then the BP was measured three times with a sphygmomanometer and stethoscope. Subsequently the test exercise session was started, which consisted of aerobic collective gymnastics with a duration of 50 minutes, including five minutes of preparatory activity, 20 minutes of aerobic exercises at 75% of RHR, 20 minutes of resistance exercises, and five minutes of stretching. HR was monitored by a heart rate monitor (POLAR® RS800). After the experimental session, ABPM was used to record the BP during the following 24-hour period.

Statistical analysis

The Shapiro–Wilk test was used to evaluate the normality of the numerical data. Data are presented as mean ± standard deviation. An unpaired *t*-test with Welch's correction was used to compare the cardiopulmonary response between AE and LE, as well as the magnitude of PEH at the second, 12th and 24th hours after the session.

Two-way ANOVA was used to compare PEH for the sessions by time (second, 12th and 24th hour), as well as determine interaction effects (session and time), followed by Bonferroni's *post hoc* test. A 5% significance level was set. All statistical analyses utilised Graph Pad Prism 7.0

Results

Table 1 shows the characteristics of the experimental groups. There were no differences between the groups by age, body mass index, peak VO_2, or resting systolic BP (SBP) and DBP.

Table 2 shows the HR and BP responses to maximal effort recorded after the cardiopulmonary test. The values of HR and

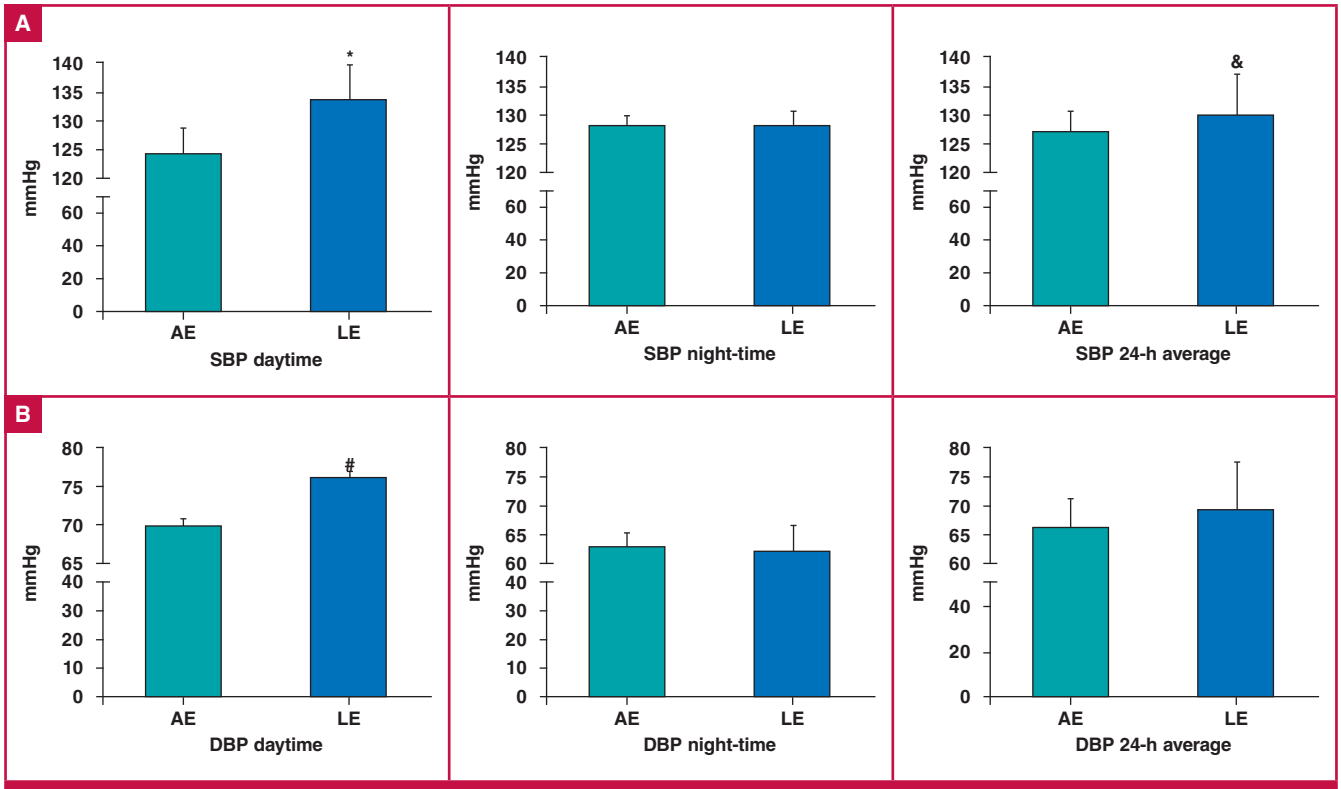

Fig. 2. Average SPB (A) and DBP (B) during the daytime, night-time, and over 24 hours. AE: aquatic exercise; LE: land exercise $^{*}p < 0.0001$ when compared with AE, SPB daytime (AE 124 ± 4 mmHg, LE 134 ± 6 mmHg) ; $^{\#}p < 0.0001$ when compared with AE, DPB daytime (AE 70 ± 3 mmHg vs LE 76 ± 4 mmHg); $^{\&}p < 0.02$ when compared with AE, SPB 24 hours (AE 121 ± 5 mmHg vs LE 125 ± 10 mmHg)

DBP were significantly higher in the LE than the AE group, but there were no differences observed in SBP.

Fig. 2 shows the values of SBP (A) and DBP (B) during the daytime, night-time and total 24 hours (daytime plus night-time). The AE group showed lower values for daytime SBP (124 ± 4 mmHg) and DBP (70 ± 3 mmHg) than the LE group (SBP: 134 ± 6 mmHg, DBP: 76 ± 4 mmHg), as well as for the 24-hour average for SBP (AE: 121 ± 5 mmHg vs LE: 125 ± 10 mmHg). There was no difference between the groups during the night-time or for the 24-hour average of DBP.

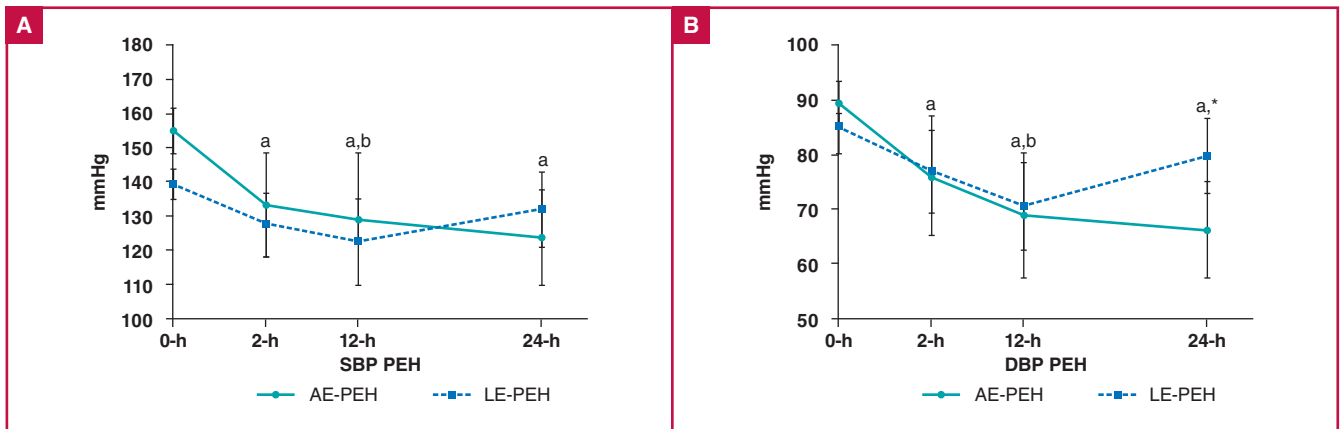

Fig. 3. SBP (A) and DBP (B) PEH in the AE and LE groups at the second-, 12th- and 24th-hour time points. a: represents the difference between AE-PEH baseline and the time points, b: represents the difference between LE-PEH baseline and the time points, *represents the difference between the groups at the same time point. a: $p < 0.001$ when compared to AE-PEH at 0 hours (SBP/DBP AE-PEH: baseline (0 h) 155 ± 7/90 ± 4 mmHg, second hour 133 ± 15/76 ± 11 mmHg, 12th hour 129 ± 19/69 ± 11 mmHg, 24th hour 123 ± 14/66 ± 9 mmHg); b: $p < 0.03$ when compared to LE-PEH at 0 hours (SBP/DPB LE-PEH: baseline (0 h) 139 ± 5/85 ± 2 mmHg, 12th hour 122 ± 9/71 ± 8 mmHg); $^{*}p < 0.01$ when compared with LE-PEH (DBP AE-PEH 66 ± 9 mmHg, LE-PEH 80 ± 7 mmHg). AE: aquatic exercise; LE: land exercise; PEH: post-exercise hypotension. Two-way ANOVA with Bonferroni correction, data expressed as mean ± SD. Interaction for SBP: $p = 0.0544$, DBP: $p = 0.0099$.

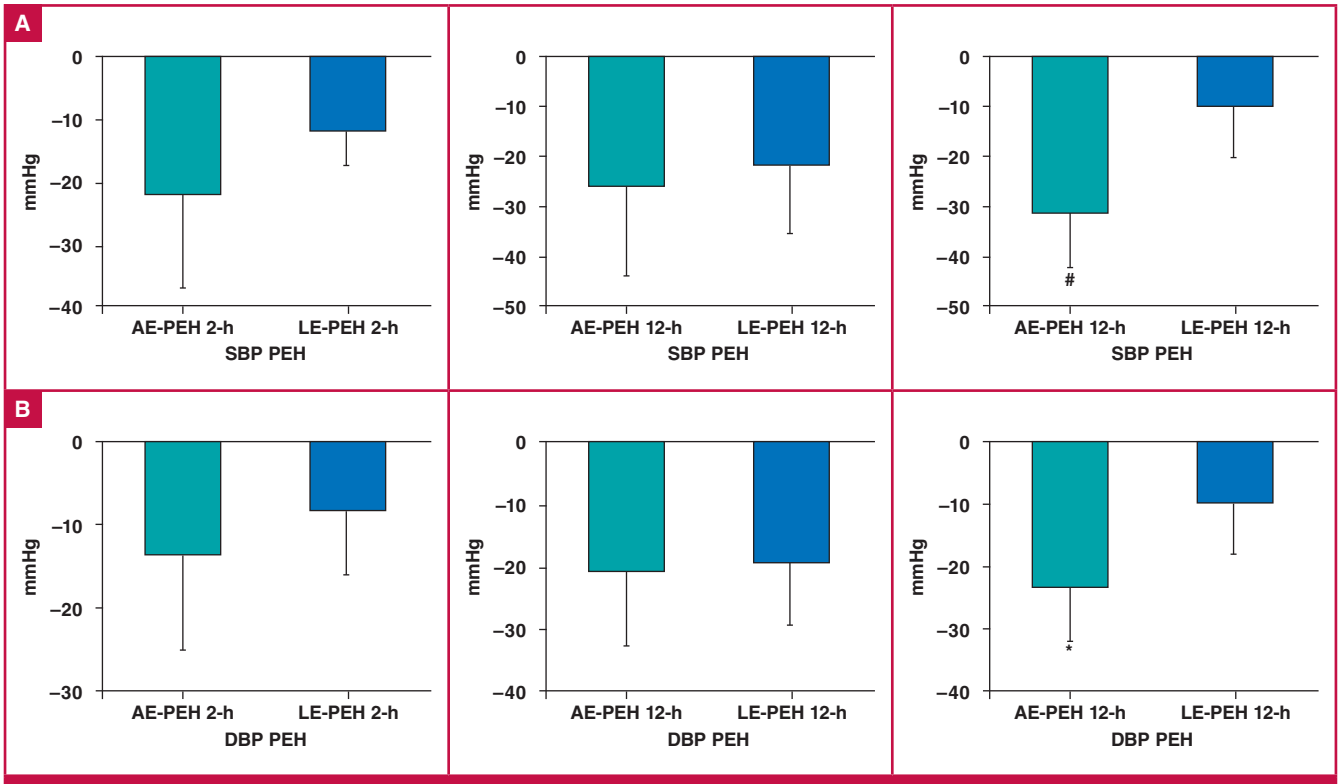

Fig. 4. Magnitude of PEH in the exercise groups AE-PEH and LE-PEH for SBP (A) and DBP (B) at the second, 12th and 24th hour. PEH: post-exercise hypotension. $^{\#}p < 0.001$ when compared with LE-PEH 24th hour (SBP AE-PEH –31 ± 10 mmHg vs LE-PEH –10 ± 10 mmHg); $^{*}p < 0.01$ when compared with LE-PEH 24th hour (DBP AE-PEH –23 ± 9 mmHg vs LE-PEH –10 ± 8 mmHg). Unpaired *t*-test with Welch's correction, data expressed as mean ± SD.

Fig. 3 shows the PEH for SBP (A) and DBP (B) in the AE-PEH and LE-PEH groups at the second, 12th and 24th hours after the exercise session, those times being chosen because the individuals were then awake. The AE-PEH data show that PEH was maintained from the second to the 24th hour, while for the LE group, maintenance of PEH was observed only until the 12th hour. There was no difference in PEH at the second and 12th hour between the groups, but for DBP, at the 24th hour, AE-PEH values were lower (66 ± 9 mmHg) than those of LE-PEH (80 ± 7 mmHg).

Fig. 4 shows SBP (A) and DBP (B) for the groups AE-PEH and LE-PEH. There was no difference in PEH at the second and 12th hours between the groups, but the 24th hour PEH was higher for the AE group (SBP: −31 ± 11 mmHg, DBP: −23 ± 8 mmHg) than for the LE group (SBP: −10 ± 10 mmHg, DBP: −10 ± 8 mmHg).

Discussion

The main finding of this study was that elderly hypertensive subjects trained in AE had different baseline BP responses from land-trained subjects. During the daytime, SBP and DBP values were lower for aquatic-trained hypertensive subjects. In addition, the PEH induced by AE was more rapid and lasted longer than that induced by LE, based on data recorded 24 hours after the exercise session. Another interesting result was the cardiovascular response after a cardiopulmonary test: maximal HR and DBP were higher for land-trained than aquatic-trained subjects.

Both training environments have been shown to be efficacious in reducing BP, but aquatic training caused a more impressive reduction (−10.58 mmHg) than that due to land aerobic training (−3.5 mmHg) or resistance training (−1.8 mmHg).[3] The baseline data show that AE induced lower BP values, an effect appearing during the awake period, which could be due to higher sympathetic tonus activity during the awake period than at night, as data show that in the daytime there is a prevalence of sympathetic tonus.[37]

AE modulates the sympathetic drive differently from that observed for LE. In AE, one should consider the effect of hydrostatic pressure, which induces an increase in blood concentration in the thorax[38] and reflexively decreases the heart rate. Increased venous return during immersion stimulates cardiopulmonary receptors, which decrease sympathetic activity and total peripheral resistance.[39] Bradycardia also occurs during immersion.[40] In addition, data reported in the literature show that aquatic-based exercise induces a different response associated with renal sympathetic nerve activity,[23] as well as higher suppression of the vasopressin and renin–angiotensin systems, from that of physical activities on land.[41,42]

The maximal response to the cardiopulmonary test shows that both groups had the same $VO_{2\ max}$, but, interestingly, hypertensives trained in AE had lower HR and DBP during maximal effort. The chronic effect of AE ameliorates arterial peripheral resistance, and the decrease in levels of epinephrine, norepinephrine and endothelin-1 associated with an increase in nitric oxide levels can improve the BP response during exercise, including DBP.[43] We found that elderly hypertensive subjects had

a better profile of cardiovascular responses during AE. The DBP decreases during aquatic cycle ergometer exercise were greater than in the case of the same exercise intensity on land.[44]

Our data show that PEH for SBP and DBP lasted for 24 hours after AE, which was longer than for LE. Similarly, Ngomane[30] showed that heated AE was more effective in producing PEH for 11–18 hours after a bout of exercise than LE. The higher PEH after AE was observed in reduced SBP and DBP during the daytime, but there was no difference found in any other haemodynamic variable assessed: arterial stiffness, endothelial reactivity or heart rate variability. Our findings likewise corroborate the results of Bocalini,[45] who verified that water ergometric exercise was effective in promoting a higher magnitude of PEH in older hypertensive women with more apparent outcomes in untreated women, than LE.

Concerning the mechanisms associated with PEH, several have been presented in the literature as playing a major role in these effects on BP: reduction in sympathetic activity,[46] attenuation of cardiac adrenergic receptor sensitivity, decreased catecholamine synthesis with changes in renin and angiotensin release as a result,[47] lesser peripheral vascular resistance[48] and stroke volume,[49] and synthesis of vasopressin[21] and endothelins.[50] The mechanism whereby AE creates lasting PEH however needs better elucidation.

Our study used a session of combined aerobic and resistance exercises for AE, and PEH was longer and started earlier (two hours after the exercise session) than for LE. This result is in agreement with Ferrari,[51] who used concurrent training, aerobic plus resistance training, to show a reduction in BP in the first hour after training in hypertensive subjects participating in LE, but such an effect may not last as long as that of aerobic exercise alone. Similarly, Cunha[32] found that moderate-intensity AE elicited PEH for SBP and DBP for over 21 hours. Pinto[52] assessed the effect of concurrent training in water on normotensive subjects to show a similar effect on PEH from resistance and aerobic exercise.

Conclusion

Our study shows that elderly hypertensive individuals who exercised in water had lower SBP and DBP during the day than those trained in land exercise. In addition, hypotension was induced more quickly (two hours) by the exercise session after water-based exercise and lasted longer (24 hours) than that induced by land-based exercise. These data show that water-based exercise has a different pressure control than land-based exercise, such that water-based exercise constitutes a potential clinical approach for the treatment of hypertension.

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Cardiovascular assessment after treatment for retinopathy of prematurity: a comparative study between anti-VEGF agent (aflibercept) and laser

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Abstract

Objective: The aim of this study was to compare the cardiac effects and aortic arterial indices following intravitreal aflibercept treatment or diode laser photocoagulation for the treatment of retinopathy of prematurity (ROP) in infants.

Methods: This single-centre, retrospective study was conducted in infants who were administered laser photocoagulation (LPC) or intravitreal aflibercept (IVA) treatment as initial treatment and had completed at least one year of corrected age. The patients were evaluated in terms of aortic elastic parameters, right and left ventricular systolic and diastolic function using conventional, pulsed Doppler and tissue Doppler imaging (TDI) echocardiographic parameters.

Results: Fifteen infants were in the LPC group, 16 in the IVA group, and 20 in the control group. Although there were some statistically significant differences in terms of pulsed and TDI echocardiographic parameters between the treatment and control groups, these values could not clearly be adopted as a diastolic dysfunction and myocardial performance indices were not influenced. The aortic elastic parameters were impaired in both LPC and IVA groups compared to the control group. Consequently, we observed only minor differences between the treatment groups, which may suggest subtle changes due to the anti-angiogenic treatment.

Conclusion: Although favourable and promising outcomes were obtained with intravitreal injection of anti-vascular endothelial growth factor agents for the treatment of ROP, concerns have been raised about potential systemic side effects, including potential cardiovascular side effects caused by these agents. The small reduction in right ventricular Doppler velocities could probably be explained by the use of anti-angiogenic or laser treatment in infants.

Keywords: Doppler, echocardiography, retinopathy of prematurity, vascular stiffness, ultrasonography

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With the increasing number of premature births in the world, over 15 million preterm neonates (before 37 completed weeks of gestation) are born annually.[1] With improving survival rates of premature babies, more than 50 000 children are blind from retinopathy of prematurity (ROP) in many middle-income countries.[2]

The first option of treatment for ROP has switched from cryotherapy to diode laser photocoagulation (LPC) after randomised clinical studies showed the higher efficacy of LPC therapy.[3] More recent development of novel therapeutic approaches, including the use of anti-vascular endothelial growth factor (VEGF) agents to treat ROP, has been possible with the identification of angiogenesis regulators.[4]

Anti-VEGF therapy may allow posterior retinal and foveal avascular zones to develop better and induce vascular regression promptly in comparison to laser treatment. It has been shown that laser treatment requires general anaesthesia and causes more ocular morbidity (visual field loss, myopia, astigmatism) due to peripheral ablation. Despite the fact that it was iniated in 2007, bevacizumab (Avastin; Genentech, South San Francisco, CA) has not been approved by the US Food and Drug Administration (FDA) for intra-ocular use in the treatment of ocular neovascular diseases in adults. However, the FDA did approve it for only intravenous administration in the treatment of colorectal, breast, lung and renal cell cancer. By contrast, ranibizumab (Lucentis; Genentech) and aflibercept (Eylea; Regeneron) have been approved by the FDA for intra-ocular use in adults.

Despite the lack of studies on the safety of off-label use of intravitreal bevacizumab (IVB), intravitreal ranibizumab (IVR) usage for ROP treatment has increased in the past decade. Although bevacizumab and ranibizumab have been in use for a while in the treatment of ROP and their efficacy has been accurately demonstrated, experience is limited for intravitreal aflibercept (IVA) in neonates, with only a few case series reported in the literature.[5-7]

There is great debate about the use of these anti-VEGF molecules due to their potential systemic complications. After injection of these agents into the eye, they leak into the systemic circulation. As a consequence, a decline in plasma VEGF levels has been demonstrated.[8,9] Because the role of VEGF has been proven in the normal developmental stages of the human brain, lung, heart and kidney, possible adverse effects of VEGF-dependent development should be closely monitored. Previous studies attributed the mechanisms of anti-VEGF-induced hypertension to such action as stimulating arterial vascular remodelling.[10,11]

Abnormal aortic elastic indices affect the relationship between the pulsatile changes in arterial diameter and pressure and play a central role as a strong predictor of cardiovascular

events.[12,13] Therefore, the aim of our study was to compare changes in aortic elastic parameters, using tissue Doppler and conventional echocardiographic measurements for both right and left ventricular systolic and diastolic function after LPC and IVA therapy in infants with ROP.

Methods

This single-centre, retrospective study was performed by evaluating the medical records of infants who were treated for ROP in a tertiary centre for screening and treatment of ROP. The study was carried out between October 2016 and February 2017.

The institutional review board at Adana Numune Training and Research Hospital approved the study. Informed written consent was obtained from all parents or guardians. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

During this period, premature infants who completed the corrected age of one year were evaluated using echocardiography for routine cardiac control. Decision about the treatment option for ROP was made as reported by the indications in the Early Treatment for ROP (ETROP) study.[3] According to the study, infants with type 1 pre-threshold ROP, threshold ROP or aggressive posterior ROP were selected. If infants had treatment-requiring ROP in the posterior zone (zone I and/or zone II), anti-VEGF treatment was recommended for them because laser treatment has low efficacy in posterior disease, along with decreased visual field and high refractive outcomes.

All parents were informed about the treatment effects and systemic concerns of the IVA. They were also informed about LPC treatment regarding its lower efficacy in posterior ROP, and possible side effects such as preventing peripheral retinal vascularisation. The parents were then left with the decision of whether to treat with LPC or IVA. Patients who received laser or aflibercept treatment as monotherapy and primary treatment were included in the study.

Patients who were treated at a different centre, who were administered another treatment option (cryotherapy, surgery and other anti-VEGF agents) or combined therapy (infants who received additional treatment after primary treatment) for ROP and who could not be followed regularly were excluded from the study. Infants with stage 4 and 5 ROP or infants who underwent vitreoretinal surgery were also excluded, as were those who had systemic or ocular disease such as congenital cataract, glaucoma or other ocular anomalies. Further exclusions were infants with congenital heart, lung or other systemic disease and dysrhythmia.

Twenty age- and gender-matched patients were selected from among the patients who were referred for evaluation of an ROP screening and who did not receive any treatment. They were found to have normal intra-cardiac structural anatomy and function.

In this period, 67 medical records were reviewed. Among them, four patients were treated with combined therapy, six received other anti-VEGF agents, two were treated at a different centre, three had ocular or systemic anomaly, and one patient had stage 4 ROP. These 16 patients were excluded from the study (Fig. 1).

Thirty-one infants with a history of prematurity who underwent treatment for ROP were selected for the patient groups, and 20 infants diagnosed with ROP but who did not need any treatment were selected as the control group. Infants with similar demographic features (age, gender, gestational age, birth weight) were involved in this study.

A total of 31 premature infants with ROP and 20 premature infants without ROP were included in this study. They were divided into three groups: the LPC group included 15 infants (mean age: 17 ± 4.4 months) who received diode laser photocoagulation; and the IVA group included 16 infants (mean age: 14.4 ± 4.9 months) who received only a single dose of intravitreal injection of aflibercept (1 mg/0.025 ml) as the primary treatment for ROP; and 20 infants constituted the control group (mean age: 14.5 ± 2.8 months).

Height, weight, birth weight, gestational age and heart rate of the infants were recorded in both patient groups. Ten minutes after calming down in the room and while the infants were held in their parents' laps, a validated oscillometric device (Omron HEM 907; Omron Healthcare, Kyoto, Japan) was used to measure systolic and diastolic blood pressure in the right arm with an appropriate cuff size covering two-thirds of the upper arm.

Laser ablations were performed with an 810-nm diode laser (IRIDEX; Oculight SL, Mountain View, CA, USA) using a 28-day condensing lens. The laser settings were arranged to a power ranging between 150 and 250 mW with a duration of 200 m/s and an interval of 200 s, so that a moderately white laser burn could be achieved. All patients received intravitreal aflibercept (Eylea®, Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA) 1 mg/0.025 ml in the operating room under sterile conditions with topical anaesthesia, using 0.5% proparacaine hydrochloride (Alcaine; SA Alcon-Couvreur NV, Puurs, Belgium) and ketamine sedation. All the treatments were performed by the same specialist (EAS).

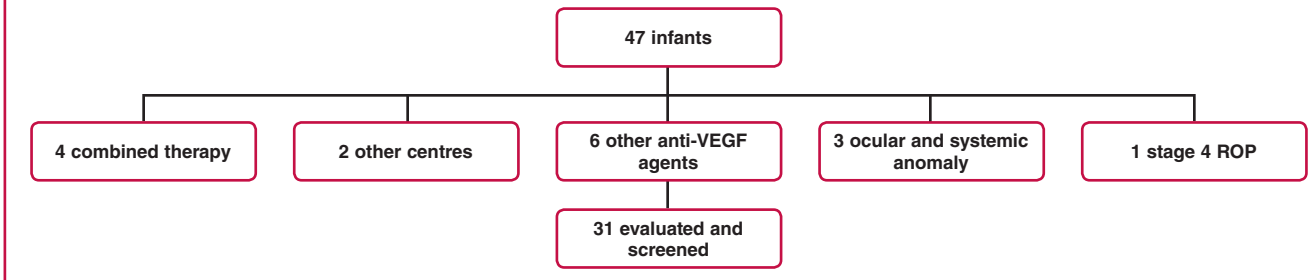

Fig. 1. Flow chart of the study population.

Standard two-dimensional, M-mode, pulsed-Doppler and tissue Doppler echocardiographic examinations were performed with the S5® cardiac ultrasonography system (GE Medical Systems; Horten, Norway) and a 6-MHz transducer. Simultaneous echocardiographic recordings were obtained. One echocardiographer (blinded to the patients' clinical and laboratory data) interpreted each echocardiographic examination independently. All the patients were examined while at rest in the supine position and images were taken from the third or fourth intercostal space. The measurements were recorded according to the American Society of Echocardiography guidelines.[14] Three values were recorded for each examination and the average of the values was used.

The examination consisted of two-dimensional, M-mode and pulsed- and continuous-wave Doppler velocities of the cardiac valves and tissue Doppler imaging (TDI) of the ventricles. Left ventricular (LV) dimensions, shortening fraction, ejection fraction, and mitral (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were measured using the standard M-mode technique. TAPSE and MAPSE were measured in an M-mode examination in the apical four-chamber view during systole, at the junction of the right and left ventricle with the tricuspid and mitral valve, and expressed in mm.

Pulsed Doppler measurements were performed with the transducer from the apical four-chamber view. The LV inflow pattern at the tips of the mitral valve provided peak early (E) and late (A) filling velocities and the E/A ratio was determined. LV and right ventricular (RV) tissue Doppler echocardiographic evaluations were performed from the apical four-chamber position by placing the pulsed-wave Doppler beam on the part of the mitral annulus that was closest to the LV lateral wall and inter-ventricular septum for the left ventricle, and on the part of the tricuspid annulus that was closest to the RV lateral wall for the right ventricle.

Peak systolic (S), early diastolic (E′) and late diastolic (A′) myocardial velocities at the basal segments of the lateral mitral annulus, septal mitral annulus and tricuspid annulus were determined using TDI. The isovolumetric contraction time (interval from the end of the A′ wave to the beginning of the S′ wave) and the isovolumetric relaxation time (interval from the end of the S′ wave to the beginning of the E′ wave) were measured on TDI for the lateral mitral annulus, septal mitral annulus and tricuspid annulus.

The following formula was used with a view to calculating the myocardial performance index (MPI):

$$\text{MPI} = \frac{\text{IVCT} + \text{IVRT}}{\text{ET}}$$

where IVCT = isovolumetric contraction time, IVRT = isovolumetric relaxation time and ET = ejection time (defined as the duration of the S′ wave). All values used for analysis represented the average of three consecutive cardiac cycles, with the exception of patients with dysrhythmia, in whom three-beat averages were obtained.

M mode of the ascending aorta was obtained above 2–3 cm from the aortic valve to calculate arterial wall stiffness indices, and systole (AoS) and diastole (AoD) measurements were averaged from five consecutive heartbeats. Aortic strain (AS), aortic distensibility index (DI) and aortic stiffness index (SI) were calculated from the following formulae:[15]

$$\text{AS (\%)} = \frac{(\text{AoDS}–\text{AoDD})}{\text{AoDD}} \times 100$$

$$\text{SI} = \frac{\ln(\text{SBPDBP})}{(\text{AoDS}–\text{AoDD})/\text{AoDD}}$$

$$\text{DI (cm}^2\text{/dynes} \times 10^{-6}) = \frac{(\text{AoDS}–\text{AoDD}) \times 10^{-3}}{\text{AoDD}/(\text{SBP}–\text{DBP})} \times 2$$

where SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), AoDS = aortic diameter in systole (mm), AoDD = aortic diameter in diastole (mm), ln = natural logarithm.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (version 24.0, SPSS, Inc). Normally distributed data are presented as mean and standard deviation (SD), and non-parametric data are presented as median and ranges. Data obtained by echocardiography were compared between the three groups using one-way analysis of variance (ANOVA) or Kruskal–Wallis tests, depending on the distribution of data. An overall *p*-value of less than 0.05 was considered to show a statistically significant result.

Results

The demographic data of the studied population are presented in Table 1. No significant differences were found between the groups in terms of age at enrollment, gender, gestational age, birth weight and weight at enrollment. There were no statistically significant differences between the patient groups and the control group in terms of systolic or diastolic blood pressure and heart rate.

The mean for gestational age (GA) of the patients was found to be 29.8 ± 2.7 weeks (range 24–35) in the LPC group, 29.3 ± 2.9 weeks (24–34) in the IVA group, and 29.5 ± 2.8 weeks (25–36) in the control group. The mean for birth weight (BW) of the patients was found to be 1 464 ± 451 g (730–2 500) in the LPC group, 1 279 ± 320 g (720–1 950) in the IVA group, and 1 352 ± 394 g (770–2 450) in the control group. The mean age was 17 ± 4.4 months for the patients in the LPC group, 14.4 ± 4.9 months for the patients in the IVA group, and 14.5 ± 2.8 months for the patients in the control group (Table 1). The mean echocardiographic evaluation time was 12.9 ± 2.3 months following the injection of aflibercept, and 13.2 ± 2.8 months after LPC treatment.

All infants in the groups had favourable anatomical outcomes after treatment for ROP.

There were no statistically significant differences between the groups in LV M-mode diameters and function (ejection fraction and fractional shortening). M-mode measurements are shown in Table 2. From the Doppler parameters, tricuspid E-wave values were increased significantly in the treatment groups rather than in the control group ($p = 0.037$), and in comparison between the treatment groups, tricuspid E-wave values were increased significantly in the IVA group ($p = 0019$). Comparison of the other standard trans-mitral and tricuspid Doppler parameters yielded similar E wave, A wave and E/A ratio for the three groups (Table 3). TAPSE measurements were also similar between the patient and control groups. MAPSE values were reduced in the treatment groups but not in the control group ($p = 0.002$); in addition, there were no significant differences between the treatment groups ($p = 0.175$).

Table 1. Clinical features of the study groups

Demographic features	*LPC group (n = 15)*	*IVA group (n = 16)*	*Control (n = 20)*	p-*value*
Age (months)	17 ± 4.4	14.4 ± 4.9	14.5 ± 2.8	0.257
Gender (*n*, %)				
Male	4 (26.7)	9 (56.3)	8 (40)	0.245
Female	11 (73.3)	7 (43.8)	12 (60)	
Weight (kg)	10.1 ± 1.4	9.6 ± 2.1	9.86 ± 0.3	0.743
Height (cm)	78.2 ± 6.1	78.1 ± 10.2	78.3 ± 0.57	0.999
GA (weeks)	29.8 ± 2.7	29.3 ± 2.9	29.5 ± 2.8	0.641
BW (g)	1464 ± 451	1279 ± 320	1352 ± 394	0.196
HR (beats/min)	127.5 ± 14.9	137.7 ± 20.8	139.8 ± 11.9	0.208
SBP (mmHg)	84 ± 9.7 (70–102)	90 ± 6.7 (80–105)	86 ± 9.0 (72–102)	0.971
DBP (mmHg)	48 ± 5.3 (41–60)	48 ± 6.1 (39–65)	49 ± 7.9 (39–63)	0.147
PMA at treatment (weeks)	35.3 ± 1.66 (32–38)	35.5 ± 1.64 (32–37)	–	0.972
Time of echo (months)	13.2 ± 2.8	12.9 ± 2.3		0.125

Data are presented as the mean values ± SD.
Student's *t*-test, Kruskal–Wallis test: $p < 0.05$ considered statistically significant.
GA: gestational age, BW: birth weight, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, LPC: laser photocoagulation, IVA: intravitreal aflibercept, PMA: postmenstrual age, IVI: intravitreal injection.

Comparison of TDI parameters measured from the lateral mitral annulus (m) demonstrated similar S′, E′ and A′ velocities; E/E′ ratios; ejection time and isovolumetric contraction time; isovolumetric relaxation time; and myocardial performance index among the three groups (Table 3). The treatment groups (IVA and LPC) had significantly higher ejection time and isovolumetric relaxation time, and lower E′ velocity, measured at the septal part of the mitral annulus, than the control group ($p < 0.001$), whereas S′ and A′ velocity, isovolumetric contraction time and MPI were similar. In addition, A′ velocity derived from the lateral tricuspid annulus was significantly higher in the treatment groups than in the control group ($p = 0.007$), whereas S′ and E′ velocity, ejection time, isovolumetric contraction time, isovolumetric relaxation time and MPI were similar. On the other hand, A′ velocity measured from the lateral tricuspid annulus was not significantly different between the IVA and LPC groups.

Table 2. M-mode echocardiographic parameters of the study groups

M-mode measurements	*LPC group (n = 15)*	*IVA group (n = 16)*	*Control (n = 20)*	p-*value*
IVSd (mm)	0.54 ± 0.09	0.51 ± 0.06	0.52 ± 0.04	0.656
IVSs (mm)	0.56 ± 0.09	0.6 ± 0.08	0.54 ± 0.04	0.192
LVIDd (mm)	2.58 ± 0.25	2.5 ± 0.36	2.57 ± 0.23	0.150
LVIDs (mm)	1.59 ± 0.19	1.5 ± 0.19	1.51 ± 0.13	0.249
LVPWd (mm)	0.43 ± 0.04	0.45 ± 0.06	0.43 ± 0.04	0.584
LVPWs (mm)	0.74 ± 0.08	0.78 ± 0.18	0.75 ± 0.07	0.871
EF (%)	70.9 ± 3.6	71.9 ± 4.2	72.8 ± 3.96	0.466
FS (%)	38.5 ± 3.1	39.6 ± 3.8	40.3 ± 4.1	0.535
MAPSE (cm)	10.0 ± 0.56	10.3 ± 0.99	11.1 ± 1.3	0.020*
TAPSE (cm)	17 ± 1.21	16.3 ± 2.2	16.4 ± 1.58	0.661

Data are presented as the mean values ± SD.
One-way analysis of variance (ANOVA) or Kruskal–Wallis tests: $*p < 0.05$ considered statistically significant.
IVSs: interventricular septum systolic thickness, IVSd: interventricular septum diastolic thickness, LVIDd: left ventricular end-diastolic diameter, LVIDs: left ventricular end-systolic diameter, LVPWd: left ventricle posterior wall diastolic dimension, LWPWs: left ventricle posterior wall systolic dimension, EF: ejection fraction, FS: fractional shortening, MAPSE: mitral annular plane systolic excursion, TAPSE: tricuspid annular plane systolic excursion.

Table 3. Conventional and tissue Doppler echocardiographic parameters of the study groups

'Pulsed' and tissue 'pulsed' Doppler measurements	*Group 1 (LPC) (n = 15)*	*Group 2 (IVA) (n = 16)*	*Controls (n = 20)*	*p-value*
Mitral E (cm/s)	98 ± 8.2	98 ± 14	98 ± 13	0.970
Mitral A (cm/s)	69 ± 11	65 ± 12	60 ± 7.2	0.834
Mitral E/A	1.66 ± 0.31	1.65 ± 0.34	1.65 ± 0.25	0.901
Tricuspid E (cm/s)	74 ± 6.0	78 ± 10	70 ± 16	0.037*#
Tricuspid A (cm/s)	47 ± 8.2	46 ± 11	44 ± 6.6	0.511
Tricuspid E/A	1.55 ± 0.24	1.55 ± 0.24	1.72 ± 0.41	0.428
Sm (cm/s)	7.7 ± 1.9	7.8 ± 1.47	7.4 ± 0.99	0.261
E'm (cm/s)	10.8 ± 1.3	10.4 ± 1.0	12.4 ± 1.4	0.004*
A'm (cm/s)	7.2 ± 1.3	7.2 ± 2.8	7.2 ± 1.06	0.871
ETm (ms)	213.3 ± 16.5	195.6 ± 33.0	185.4 ± 18.3	0.007*
IVCTm (ms)	48.8 ± 7.6	46.1 ± 8.5	47.7 ± 7.1	0.488
IVRTm (ms)	48.3 ± 5.42	44.6 ± 5.88	41.0 ± 4.44	0.002*
MPIm (Tei index)	0.45 ± 0.04	0.49 ± 0.08	0.47 ± 0.03	0.560
E/E′m	8.02 ± 2.03	8.02 ± 2.05	8 ± 1.67	0.900
Ss (cm/s)	6.7 ± 1.9	6.7 ± 1.0	7 ± 0.97	0.766
E′s (cm/s)	11.8 ± 4.8	9.7 ± 3.0	10.6 ± 3.8	0.182
A′s (cm/s)	7.2 ± 1.3	6.6 ± 1.89	7.4 ± 2.2	0.516
ETs (ms)	207.2 ± 27.2	197.3 ± 32.5	193.2 ± 25	0.061
IVCTs (ms)	47 ± 4.6	45 ± 7.6	42.5 ± 7.01	0.174
IVRTs (ms)	43.6 ± 5.4	44.6 ± 5.6	43 ± 6.0	0.236
MPIs (Tei index)	45 ± 4.3	46.1 ± 5.6	44.5 ± 6.21	0.792
E/E′s	9.8 ± 2.05	9.8 ± 2.05	8.8 ± 2.0	0.230
Sr (cm/s)	9 ± 4.4	9.4 ± 4.2	8.7 ± 5.3	0.755
E′r (cm/s)	13.1 ± 3.8	14.6 ± 2.1	14.5 ± 2.03	0.515
A′r (cm/s)	10.1 ± 2.0	11 ± 2.0	8.8 ± 1.0	0.007*
ETr (ms)	210.1 ± 15.8	202.1 ± 27.8	195.8 ± 27.5	0.379
IVCTr (ms)	49.2 ± 5.8	46.3 ± 10	46.8 ± 9.68	0.663
IVRTr (ms)	51.3 ± 5.9	50 ± 8.1	46.5 ± 7.9	0.211
MPIr (Tei index)	45.0 ± 4.3	46.5 ± 6	47.5 ± 5.1	0.815
E/E′r	6.8 ± 1.18	6.8 ± 1.18	6.88 ± 1.09	0.673

Data are presented as the mean values ± SD.
One-way analysis of variance (ANOVA) or Kruskal–Wallis tests: $*p < 0.05$ considered statistically significant, $^{\#}p < 0.05$ (LPC vs IVA, Mann–Whitney *U*-test).
A′: late diastolic myocardial velocity, E′: early diastolic myocardial velocity, S: systolic myocardial velocity, ET: ejection time, IVCT: isovolumetric contraction time, IVRT: isovolumetric relaxation time, MPI: myocardial performance index, m: lateral mitral annulus, r: lateral tricuspid annulus, s: septal mitral annulus.

DI and strain values were significantly lower in the treatment groups (LPC and IVA) than in the control group ($p < 0.05$) (Table 4, Fig. 2). SI values were significantly higher in comparison with the control group ($p < 0.05$) (Table 4). There was no statistically significant difference in aortic elastic parameters between the LPC and IVA groups.

Intra-observer reproducibility of aortic measurements was calculated after the re-evaluation of randomly selected images of 31 patients and 20 controls, and the results were 2.2 and 2.6%, respectively, for AoD, 3.1 and 3.4%, respectively, for AoS, 2.2 and 2.6%, respectively, for DI, and 3.4 and 3.1%, respectively, for SI.

Table 4. Comparison of aortic elasticity parameters of the study groups

Elasticity parameters	*LPC group (n = 15)*	*IVA group (n = 16)*	*Control (n = 20)*	p-*value*
Aortic strain	16.2 ± 4.4	16.7 ± 3.9	22.6 ± 4.5	0.018*
Stiffness index	3.4 ± 0.7	3.6 ± 0.6	2.2 ± 0.3	0.036*
Distensibility index	8.2 ± 1.6	8.0 ± 1.8	11.6 ± 2.4	0.025*

Data are presented as the mean values ± SD
One-way analysis of variance (ANOVA) or Kruskal–Wallis tests: $*p < 0.05$ considered statistically significant.

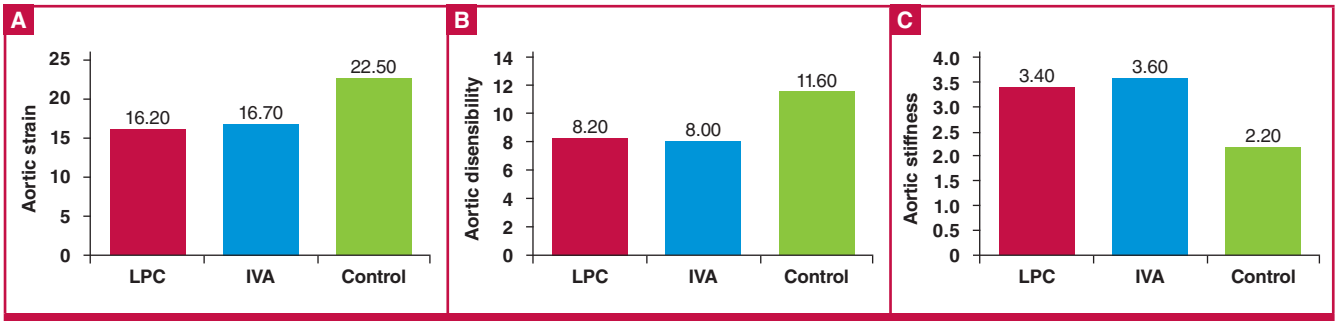

Fig. 2. Comparison of elastic parameters of the ascending aorta of patients and controls.

Discussion

To the best of our knowledge, this is the first study that evaluates cardiac function detected by TDI echocardiography in premature children after ROP treatment with either anti-VEGF or LPC.

There has been great concern about these new agents due to their toxic side effects. There are reports of associated systemic side effects from systemic anti-VEGF agents used in cancer therapy, such as systemic hypertension, thromboembolism and LV dysfunction. They are also reported to have several side effects secondary to intravitreal anti-VEGF therapy, including systemic hypertension, congestive heart failure, proteinuria, arterial thromboembolic events, and systemic haemorrhage, which are linked to cardiovascular toxicities.[16,17] On the other hand, Scott *et al.* published a commentary about anti-VEGF agents and the data suggested no difference in the risk of arteriothrombotic effect or death between anti-VEGF agents.[18] A recent meta-analysis showed 23.6% incidence of all grades and a 7.9% incidence of high-grade hypertension after systemic bevacizumab treatment.[19]

In the present study, systolic and diastolic blood pressure and heart rate values in infants were found to be similar to those in the control group. Development of the blood vessels, vascular growth and organogenesis are extremely VEGF-dependent, as was demonstrated with early embryonic lethality caused by a deletion of the VEGF gene in the signalling pathway.[20] VEGF also has a role in pathological blood vessel growth (macular degeneration), tumoural vasculature growth and normal physiological vasculature growth (menstrual cycle).[21] The endothelium is an active endocrine organ secreting many cytokines and growth factors and interacting with cells that affect the function of many organs such as the heart, kidneys, liver and brain.

After the introduction of intravitreal VEGF treatment, these agents now have a key role in the treatment of ROP. Compared to conventional laser therapy, anti-VEGF agents have some advantages. Although conventional laser therapy led to a persistent destruction of the peripheral retina, it was shown that the development of peripheral retinal vessels continued after the treatment with intravitreal anti-VEGF agents. Due to their ease of use, these agents are preferred above other treatment options. Studies demonstrate that by allowing vasculature to develop further anteriorly and rapidly, intravitreal anti-VGEF treatment causes less visual loss and fewer refractive errors.[22] In contrast to the requirement for general anaesthesia in laser therapy, these agents can be introduced only under topical anaesthesia.[23] They allow the development of the posterior retina and foveal avascular zone and support the more immediate regression of ROP than laser treatment.[24,25]

Belcik *et al.* reported a significant increase in LV wall thickness and mass, a decrease in end-diastolic diameter in accordance with concentric hypertrophy, and they showed a reduction in thickening fraction and stroke volume over the five-week anti-VEEF treatment.[26] In our study, we did not observe any statistically significant differences in LV M-mode measurements, ejection fraction or fractional shortening between the groups.

MAPSE is another useful evaluation parameter and reduced MAPSE implies impaired longitudinal function in patients with various cardiovascular diseases.[27] Our study demonstrated lower MAPSE values in the IVA and LPC groups, and TAPSE values were similar. Advanced imaging techniques such as speckle-tracking methods are needed to prove that reduced MAPSE values show systolic dysfunction, because MAPSE provides only LV long-axis systolic performance, whereas other systolic parameters were in the normal range.

To assess ventricular diastolic function, Doppler data have an important role to depict distinct patterns of abnormality in ventricular filling, abnormal relaxation and restrictive filling. Abnormal relaxation is especially common in disorders producing myocardial hypertrophy. In such cases, atrioventricular early filling velocity is decreased and the atrial component of filling becomes potent.[28]

In our study, we observed statistically significant differences in only both ventricles' 'pulsed' Doppler echocardiography parameters between the groups, except in E velocity derived from RV inflow. The IVA and LPC groups had significantly higher tricuspid E velocity than the control group. It is also known that during inspiration and apnoea, RV inflow velocities are significantly higher. Although the E wave represents the early, rapid-filling period of diastole, higher E-velocity values of tricuspid inflow were more difficult to interpret than the impaired relaxation of the right ventricle alone without the E/A ratio change.[29]

Due to such limitations on load conditions, heart rate and age, which may influence conventional Doppler parameters, TDI has a major potential in the diagnosis of diastolic ventricular dysfunction.[30] When diastolic ventricular relaxation is slowed, prolongation of the isovolumetric relaxation time and a slight increase in the systolic velocity can be observed.

The MPI is a more specific tissue Doppler parameter for diastolic dysfunction. In their animal experiment after the anti-VEGF therapy, using endocardial TDI, Belcik *at al.* reported a mild decrease in S′ and E′ velocities that were not statistically significant.[26] Various paediatric and adult studies have described subclinical impairment of systolic function with changes in MPI, isovolumetric contraction and relaxation time.[31] In our

study, decreased E′ velocity and increased ejection time and isovolumetric relaxation time derived from the septal mitral annulus may indicate a subclinical systolic dysfunction of both ventricles.

Despite the significant differences in these parameters between the three groups, we demonstrated a statistically significant difference of only E velocity of RV inflow values in the comparison between the IVA and LPC groups. Therefore it is also possible that diastolic impairment may be due to retinopathy-related co-morbidities in the treatment groups, rather than to secondary treatment of retinopathy.

Arterial stiffness is an important predictor of cardiovascular events, and non-invasively calculated values showed a powerful correlation with invasive measurements.[32] In a recent study, the relationship with anti-angiogenic drugs and increased aortic stiffness was demonstrated in an adult population with cancer, independent of blood pressure changes.[12] We found that the aortic elastic indices in the treatment group were significantly different from the control group. Moreo *et al*. showed that an increase in arterial stiffness appeared after only two weeks and decreased in the patients whose treatment was ended.[10] On the other hand, there was no significant difference in aortic elastic indices between the LPC and IVA groups; however, higher vascular stiffness values would make it possible to determine whether an increase in this parameter was the direct result of aflibercept or due to hypertension and only indirectly caused by the drug.

Currently, little is known about the systemic effects of intra-ocular anti-VEGF injections. We have limited knowledge and experience, especially in intravitreal aflibercept in ROP treatment, and there are only a few reports with small series in the literature. In the present study, we evaluated both the cardiac effects of aflibercept and laser photocoagulation treatment in infants diagnosed with ROP in comparison to the untreated infant group. Using echocardiography, we demonstrated some differences that point to subtle diastolic dysfunction but we could not show any differences in aortic elastic parameters between IVA and LPC treatment compared with controls.

Limitations

The small sample size of each group and the retrospective, single-centre, cross-sectional design constitute the main limitations of our study. Another limitation is that the patients' echocardiographic assessment should have been done before the treatment because it is important to obtain baseline strain measurements to observe subsequent changes after anti-VEGF treatment. Because the link between the agent and the cardiovascular outcomes could not be confirmed clearly, more observational studies are needed to confirm cardiovascular safety during long-term therapy.

Conclusion

This study assessing ventricular function using TDI demonstrated diminutive diastolic changes in the cardiac parameters measured by echocardiography. The ultimate future goal would be to identify these asymptomatic infants accurately with speckle-tracking echocardiography, using a more sensitive imaging method. Adequately powered, well-designed clinical trials are necessary to clearly define the cardiovascular effects of these anti-VEGF agents in infants.

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A primary aldosteronism-like phenotype identified with the aldosterone-to-angiotensin II ratio in black men: the SABPA study

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Abstract

Introduction: Black populations may be more likely to have primary aldosteronism (PA) due to adrenal hyperplasia or other forms of adrenal hyperactivity, with suppressed renin levels and high levels of aldosterone, which may contribute to the development of hypertension.

Methods: This sub-study involved 35 black men matched for age, gender and race, and aged 20–65 years, living in the North West Province of South Africa. RAAS triple-A analysis was carried out with LC-MS/MS quantification. Blood pressure, electrocardiography and other variables were determined with known methods.

Results: Hypertensive subjects with higher aldosterone levels showed an increased aldosterone–angiotensin II ratio (AA2 ratio) compared to the hypertensive subjects with low aldosterone levels (10.2 vs 3.0 pmol/l; $p = 0.003$). The serum potassium concentration was significantly lower in the high-aldosterone group and the serum sodium–potassium ratio was significantly higher compared to the low-aldosterone group (3.9 vs 4.5, $p = 0.016$, 34.8 vs 31.8, $p = 0.032$, respectively). Furthermore, aldosterone was positively associated with both left ventricular hypertrophy (Cornell product) (Spearman $R = 0.560$; $p = 0.037$) and kidney function [albumin-to-creatinine ratio (ACR)] (Spearman $R = 0.589$, $p = 0.021$) in the hypertensive high-serum aldosterone group.

Conclusions: The AA2 ratio, a novel screening test that is currently being validated for PA case detection, was used to identify a PA-like phenotype in black men. Excess aldosterone was associated with endothelial dysfunction and left ventricular hypertrophy, independent of blood pressure.

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Although the incidence of high blood pressure has decreased worldwide since 1975, a shift is reported from high- to low-income countries, such as those in sub-Saharan Africa.[1,2] In blacks, hypertension is characterised by a greater retention of salt and water by the kidney, with suppressed levels of renin and aldosterone.[3] Black populations may also be more likely to have primary aldosteronism (PA) due to adrenal hyperplasia or other forms of adrenal hyperactivity, with suppressed renin levels and high levels of aldosterone.[3,4]

Furthermore, black populations may also have a greater sensitivity of blood pressure to the increased secretion of aldosterone and are more likely to have hypertension.[5] PA is an overlooked but frequent cause of secondary hypertension. In a recent survey in Italy and Germany, it was found that only 7–8% of general practitioners ordered aldosterone and renin measurements, and the prevalence of diagnosed PA was only 1% of hypertensive patients.[6] The consequence is that only 1% of patients in Italy and 2% in Germany are diagnosed with the disease. From recent studies, a prevalence approaching 5–13% was found.[7-9]

From the literature, it seems that PA is a largely unrecognised and undertreated cause of hypertension. In South Africa, the case may not be different due to the fact that awareness (27%), treatment (18%) and control rates (7%) for hypertension are low.[2] PA is also a common occurrence in resistant hypertension and screening for it may improve hypertension treatment, which is already a challenge in South Africa.

We therefore aimed to evaluate the role of aldosterone as a contributory factor in hypertension in a black cohort by identifying a PA-like phenotype with the use of the novel aldosterone–angiotensin II ratio (AA2 ratio). One parameter obtained in RAAS triple-A testing, the simultaneous LC-MS/MS-based quantification of angiotensin I (Ang I), angiotensin II (Ang II) and aldosterone, was obtained in patient samples. Concerns are raised about the accuracy of renin assays and therefore new mass spectrometric methods were employed for measuring angiotensin II, which are currently being assessed in the clinical setting.

Methods

The baseline Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study was conducted in the North

West Province, South Africa, during 2008 and 2009. The study was a target-population, comparative study and included black teachers aged between 20 and 65 years. All participants were working as teachers for the Department of Education in one of the four Dr Kenneth Kaunda education districts of the North West Province. The study has been well-described elsewhere.[10]

This sub-study forms part of the SABPA study and for this study, 35 black men, matched for age, gender and race, were divided into normotensive (n = 7) and hypertensive participants (n = 27). The hypertensive men were further divided into low- (n = 12) and high- (n = 15) aldosterone groups based on the median value (133.2 pmol/l) of aldosterone observed in the cohort.

The data of one participant was omitted from the analysis because of angiotensin receptor blocker (ARB) therapy, which is known to affect the AA2 ratio. The other participants receiving anti-hypertensive medication potentially interfering with classical PA screening assays were not excluded from this study as recent data suggest that the AA2 ratio is less prone to drug-mediated suppression, as described for the aldosterone-to-renin ratio.[11] Exclusion from the overarching SABPA study was based on the following criteria: ear temperature > 37.5°C, being vaccinated or having donated blood in the three months before the study commenced, clinically confirmed diabetes, and known HIV infection.

All participants signed an informed consent form. The study complied with all applicable regulations, in particular, the Helsinki Declaration of 1975 (as revised in 2008) for investigation of human participants.[12] The Ethics Review Board of the North-West University, Potchefstroom, South Africa, approved the study (NWU-00036-07-A6).

Upon arriving at the North-West University overnight facilities (consisting of 10 bedrooms, two bathrooms, kitchen, dining room and television room), participants were introduced to the experimental set-up to lessen anticipatory stress.[13] They received a standardised dinner and had their last beverages (tea/coffee) and two biscuits at 20:30 hours. The following morning a fasting overnight urine sample was obtained, followed by the anthropometric measurements.

Height and weight of participants were measured using calibrated instruments (Precision Health Scale, A & D Company, Tokyo, Japan; Invicta Stadiometer, IP 1465, UK). Measurements were taken in triplicate using standardised methods,[14] and body mass index (BMI) was calculated. Participants completed a general health questionnaire on family history, diagnosis of hypertension and renal disease, as well as medication use.

Hereafter participants remained in a semi-recumbent position for at least 30 minutes before blood pressure was measured with a sphygmomanometer using appropriate-sized cuffs. Measurements were executed in duplicate with five-minute intervals and the second measurement was used for analysis. This blood pressure reading obtained with the sphygmomanometer was used to classify the participants as hypertensive (≥ 140/90 mmHg).

A resting 12-lead electrocardiogram (ECG) of six cardiac cycles (Norav NHH1200®, Kiryat Bialik, Israel) was determined for each participant. Data from the 12-lead ECG was used to determine the Cornell product [(RaVL + SV3) × QRS duration]. Values > 244 mV/ms are indicative of left ventricular hypertrophy (LVH).

Silent myocardial ischaemic events were assessed by two-channel 24-hour (ECG) recordings (Cardiotens CE120®, Meditech, Budapest, Hungary) for 20 seconds at five-minute intervals. Before the start of the ambulatory investigation, the isoelectric reference point (PQ segment), J point, L point (80 ms after the J point) and an ST-segment detection interval of at least 3 mm as the initial ST level, were calculated individually for each participant.

An ischaemic event was recorded according to the following criteria: horizontal or descending ST-segment depression of at least 1 mm; duration of the ST-segment episode lasting ≥ one minute, and a ≥ one-minute interval from the preceding episode. In case of a horizontal or descending ST depression (1 mm: 1-min duration at a 1-min interval from the preceding episode), an ECG tracing lasting 60 seconds was recorded and an additional blood pressure measurement was automatically initiated by the trigger mechanism of the device. Data were analysed using CardioVisions 1.19 Personal Edition (Meditech, Budapest, Hungary).

Further cardiovascular variables were recorded continuously for five minutes with the Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) device. Finometer measurements were processed with Beatscope 1.1 software (FMS, Finapres Medical Systems, Amsterdam, The Netherlands) from the reconstructed pressure waveform to obtain the stroke volume (SV), total peripheral resistance (TPR) and the Windkessel compliance (C_{wk}). Carotid-dorsalis pedis pulse-wave velocity (c-pPWV) was obtained with the Complior acquisition system (Artech-Medical, Pantin, France).

Hereafter, fasting blood samples were collected from the participants' right arm brachial vein branches with a sterile winged infusion set. The samples were handled and prepared according to standardised procedures. Serum and plasma samples were stored at –80°C until analysis.

For RAAS triple-A testing, serum was allowed to clot for 30 minutes at room temperature before centrifugation (4 700 rpm, 20°C, 15 minutes) on the Hettich 320 centrifuge (Andrew Hettich, GmbH & Co, KG, Germany). The supernatant was then stored at –80°C until analysis.

Following pH-controlled (7.4) *ex vivo* equilibration at 37°C for one hour, serum was stabilised and subjected to LC-MS/MS quantification of equilibrium (eq) angiotensin peptide levels (Attoquant Diagnostics, Vienna, Austria). Briefly, stable isotope-labelled internal standards for Ang I, Ang II and aldosterone were spiked to the samples at a concentration of 500 pg/ml. Following C18-based solid-phase extraction, samples were subjected to LC-MS/MS analysis using a reverse-phase analytical column (Acquity UPLC® C18, Waters) operating in line with a XEVO TQ-S triple quadrupole mass spectrometer (Waters) in MRM mode.

Two different mass transitions were measured per peptide, and angiotensin concentrations were calculated from internal standard-normalised signals under consideration of the corresponding response factors determined by calibration curves prepared in the original sample matrix. A signal-to-noise ratio of 10 was considered as quantification threshold for endogenous peptide signals, resulting in indicated lower levels of quantification.

At 50 pmol/l the inter-assay coefficients of variability (CV) for Ang II and aldosterone were 6.1 and 7.9%, respectively. The intra-assay CVs for Ang II and aldosterone were 4.4 and 5.2%, respectively. The functional sensitivity for Ang II and aldosterone

measurement was > 2.0 and > 14.0 pmol/l, respectively. The angiotensin-based biomarkers AA2 ratio (aldosterone/eq Ang II), PRA-S (eq Ang I + eq Ang II) and ACE-S (eq Ang II/eq Ang I) were calculated from molar concentrations of respective analytes.

Adrenocorticotrophic hormone (ACTH) was analysed with electro-chemiluminescence immunoassay (ECLIA), e411 (Roche, Basel, Switzerland). Inter- and intra-batch variability were 5.4 and 2.9%, respectively. Serum cortisol was analysed using an electro-chemiluminescence immunoassay on the Elecsys 2010 apparatus (Roche, Basel, Switzerland). Both the intra- and inter-assay coefficients of variation for all the assays were less than 10%.

Serum and urinary sodium and potassium concentrations were determined making use of the Konelab TM 20i sequential multiple analyser computer (SMAC) (ThermoScientific, Vantaa, Finland). Gamma-glutamyltransferase (GGT), cotinine and high-sensitivity C-reactive protein (CRP) were analysed using the sequential multiple analyser (Konelab 20i; Thermo Scientific, Vantaa, Finland; Unicel DXC 800 – Beckman and Coulter®, Germany). The intra- and inter-coefficients of variation for all assays were below 10%.

The urinary creatinine from an eight-hour overnight fasting urine sample was determined with a calorimetric method. Albumin was determined with the turbidimetric method on a

Table 1. Characteristics of the black men with low and high serum aldosterone levels

Variables	*Normotensive* (n = *7*)	*Hypertensive, aldosterone ≤ 133.2 pmol/l* (n = *12*)	*Hypertensive, aldosterone > 133.2 pmol/l* (n = *15*)	p-*value*[a]
Age (years)	45.0 (45.0–54.0)	50.0 (45.0–53.0)	47.0 (45.0–50.0)	0.373
BMI (kg/m^2)	25.4 (23.5–27.3)	28.8 (23.3–34.4)	28.1 (24.8–30.4)	0.792
Cardiovascular variables				
SBP (mmHg)	132.0 (120.0–138.0)	150.0 (140.0–156.5)	155.0 (130.0–180.0)	0.829
DBP (mmHg)	82.0 (80.0–88.0)	100.0 (95.0–106.5	110.0 (85.0–120.0)	0.548
SV (ml)	92.7 (87.0–142.1)	85.8 (75.8–105.4)	105.9 (83.8–113.5)	0.373
TPR (mmHg/ml/s)	0.96 (0.75–1.02)	1.12 (1.02–1.30)	0.97 (0.88–1.48)	0.516
C_{wk} (ml/mmHg)	1.81 (1.65–2.02)	1.59 (1.33–1.81)	1.84 (1.22–2.02)	0.399
c-pPWV (m/s)	10.2 (8.7–10.3)	9.6(9.4–11.6)	10.5 (9.5–11.0)	0.860
Biochemical variables				
eq Ang I (pmol/l)	10.9 (3.1–23.3)	14.7 (3.5–21.4)	7.6 (3.1–33.4)	0.755
eq Ang II (pmol/l)	33.2 (12.7–58.4)	44.0 (19.0–76.9)	25.7 (10.3–55.2)	0.277
ACE-S (eq AngII/eq AngI) (pmol/l)	2.8 (2.1–4.7)	3.5 (2.4–5.4)	2.30 (0.5–4.9)	0.183
PRA-S (Ang I + Ang II) (pmol/l)	48.8 (15.8–81.7)	53.1 (25.3–102.6)	34.9 (13.4–83.7)	0.373
Aldosterone (pmol/l)	88.4 (71.7–146.0)	101.8 (88.0–126.5)	253.3 (163.9–341.2)	< 0.001
AA2 ratio	2.7 (1.8–10.5)	3.0 (1.2–6.3)	10.2 (4.4–47.6)	0.003
Aldosterone/PRA-S	1.8 (1.3–7.0)	2.3 (0.9–4.4)	5.8 (3.1–22.0)	0.010
sACTH (pg/ml)	11.9 (9.3–33.6)	17.6 (11.8–29.4)	18.4 (12.4–25.9)	0.981
sCortisol (nmol/l	405.2 (255.2–438.0	371.3 (307.1–471.5)	347.3 (276.7–487.6)	0.943
Serum Na^+ (mmol/l)	150.4 (127.3–173.5)	145.7 (125.9–177.2)	126.7 (124.4–132.6)	0.183
Serum K^+ (mmol/l)	5.0 (4.4–5.2)	4.5 (4.0–5.7)	3.9 (3.6–4.4)	0.016
Serum Na^+–K^+ ratio	31.9 (29.4–32.8)	31.8 (29.2–33.0)	34.8 (31.5–35.5)	0.032
Urinary Na^+ (mmol/l)	91.0 (62.0–112.0)	90.0 (66.0–139.0)	86.0 (44.0–107.0)	0.474
Urinary K^+ (mmol/l)	14.0 (8.0–21.0)	18.0 (12.5–22.5)	14.0 (13.0–24.1)	0.867
Urinary Na^+–K^+ ratio	6.5 (5.3–7.8)	6.1 (4.6–7.6)	6.0 (2.5–6.6)	0.470
CRP (mg/l)	3.5 (2.9–4.9)	3.1 (1.7–5.2)	3.3 (2.1–9.3)	0.456
End-organ variables				
Cornell product (> 244 mV/ms)	51.6 (30.2–80.6)	49.9 (40.0–111.9)	93.5 (59.2–141.1)	0.134
Silent 24-h ST events (*n*)	0.0 (0.0–3.0)	12.0 (0.0–25.0)	1.0 (0.0–7.0)	0.507
Est creatinine clearance	111.4 (102.8–127.9)	112.4 (97.3–139.3)	134.7 (113.2–154.1)	0.126
ACR	0.95 (0.72–1.87)	0.99 (0.62–2.77)	1.19 (0.78–1.84)	0.574
Lifestyle variables				
Cotinine (ng/ml)	0.01 (0.01–30.00)	8.51 (0.01–28.01)	0.01 (0.01–61.01)	0.683
GGT (U/l)	53.9 (44.4–130.1)	77.0 (40.5–111.3)	57.4 (42.0–76.3)	0.548
TEE (kcal/day)	2339.9 (2228.7–2559.3)	2119.6 (1818.2–3198.2)	2627.2 (2436.5–3845.1)	0.126
Medication use, *n* (%)				
SNS blocker	–	0 (0)	1 (6.7)	–
ACE inhibitor	–	0 (0)	5 (33.3)	–
Thiazide	–	2 (16.7)	2 (13.3)	–
Calcium antagonist	–	0 (0)	6 (40)	–
Beta-blocker	–	0 (0)	2 (13.3)	–

Data presented as median (lower; upper quartile). [a]2 × 1-sided exact *p*-value between high- and low-aldosterone hypertensives.
BMI: body mass index (kg/m^2); SBP, DBP: systolic and diastolic blood pressure (mmHg), respectively; SV: stroke volume (ml); TPR: total peripheral resistance (mmHg/s/ml); C_{wk}: Windkessel compliance (ml/mmHg); c-pPWV: carotid-pedalis pulse-wave velocity (m/s); eq Ang I and eq Ang II: angiotensin I and angiotensin II (pmol/l); ACE-S: angiotensin-based ACE activity (eq AngII/eq AngI, pmol/l); PRA-S: angiotensin-based renin activity (eq Ang I + eq Ang II, pmol/l); AA2 ratio: aldosterone–angiotensin II ratio; sACTH: serum adrenocorticotrophic hormone (pg/ml); CRP: C-reactive protein (mg/l); ACR: albumin–creatinine ratio; GGT: gamma-glutamyltransferase (U/L); TEE: total energy expenditure (kcal/day); CNS blocker: central nervous system blocker; ACE inhibitor: angiotensin converting enzyme inhibitor.

Unicel DXC 800 apparatus (Beckman and Coulter, Germany) (CV% 1.7–3.3%).

The total energy expenditure (TEE) (kcal) in 24 hours was determined using the Actical® activity monitor (Mini Mitter Co, Inc, Bend, OR; Montreal, Quebec, Canada).

Statistical analysis

Data were analysed with the TIBCO® Statistica™, version 13.3 (Palo Alto, CA, USA). Data are presented as median values with lower and upper quartiles. Due to the small sample size, non-parametric statistics were used. The Mann–Whitney *U*-test was used to determine significance between the hypertensive participants with low and high aldosterone levels. Probability values of $p \leq 0.05$ were regarded as significant. Spearman rank order correlations of aldosterone with the variables were also determined.

Results

The characteristics of the normotensive and hypertensive black men with low and high serum aldosterone levels are described in Table 1. The AA2 ratio, which is currently under evaluation to be used as a novel marker for primary aldosteronism, was significantly higher in the hypertensive high-aldosterone group compared to the hypertensive low-aldosterone group (10.2 vs 3.0; $p = 0.003$). A lower value of 2.7 for the AA2 ratio was encountered in the normotensive participants.

The serum potassium (K^+) was significantly lower and the serum sodium-to-potassium (Na^+–K^+) ratio significantly higher in the hypertensive high-aldosterone group compared to the low-aldosterone group (3.9 vs 4.5, $p = 0.016$, 34.8 vs 31.8, $p = 0.032$ respectively). No differences existed between Ang I, Ang II, PRA-S and ACE-S in the hypertensive low- and high-aldosterone groups although levels appeared non-significantly suppressed in the hypertensive high-aldosterone group (7.6 vs 14.7 pmol/l, $p = 0.755$; 25.7 vs 44.0 pmol/l, $p = 0.277$ and 34.9 vs 53.1 pmol/l, $p = 0.373$, respectively). The medication use is also shown in Table 1.

In Table 2, potassium in the hypertensive high-aldosterone men associated negatively and was borderline significant with aldosterone (Spearman $R = –0.496$, $p = 0.060$). The total peripheral resistance was positively associated with aldosterone only in the hypertensive low-aldosterone group (Spearman $R = 0.699$, $p = 0.011$). Arterial compliance associated negatively and was borderline significant (Spearman $R = –0.511$, $p = 0.052$), and cortisol associated positively with aldosterone in the hypertensive high-aldosterone group (Spearman $R = 0.500$, $p = 0.058$). Ang I was inversely associated with aldosterone in the hypertensive low-aldosterone group (Spearman $R = –0.606$, $p = 0.037$). Aldosterone, in the hypertensive high-aldosterone group associated positively and significantly with both Cornell product (Spearman $R = 0.560$; $p = 0.037$) and ACR (Spearman $R = 0.589$, $p = 0.021$).

Discussion

The primary aim of this sub-study was to evaluate the role of aldosterone as contributory factor of hypertension in a black cohort by making use of the novel AA2 ratio.[11] The main finding of this study was a higher AA2 ratio in the hypertensive high-aldosterone compared to the hypertensive low-aldosterone group, suggesting a PA-like condition represented by Ang II, and independent aldosterone secretion to be a major cause of hypertension in this subgroup.

The serum K^+ concentration was significantly lower in the hypertensive high-aldosterone group and the serum Na^+–K^+ ratio was significantly higher compared to the hypertensive low-aldosterone group. Furthermore, aldosterone was positively associated with both left ventricular hypertrophy (Cornell product) and kidney function (ACR) in the hypertensive high-aldosterone group.

The aldosterone-to-renin ratio (ARR) is the recommended screening test for PA.[15,16] Measurement and interpretation is challenging when using the ARR because several antihypertensive drugs interfere with the RAAS,[15] resulting in an increase in renin concentration and activity, which subsequently suppresses the ARR, resulting in false-negative test results. There is a need for a versatile PA screening assay that does not interfere with anti-hypertensive treatments and therefore allows a more specific identification of PA in hypertensive patients on therapy.

Preliminary data have shown that in contrast to the ARR, the AA2 ratio remains unaffected by angiotensin converting

Table 2. Spearman rank order correlations of aldosterone with independent variables in hypertensive black men with low ($n = 12$) (≤ 133.2 pmol/l) and high ($n = 15$) (> 133.2 pmol/l) aldosterone levels

	Hypertensive, aldosterone ≤ 133.2 pmol/l		*Hypertensive, aldosterone > 133.2 pmol/l*	
Variables	*Spearman* R	p-*value*	*Spearman* R	p-*value*
BMI (kg/m²)	0.007	0.983	–0.014	0.960
Cardiovascular variables				
SBP (mmHg)	0.043	0.896	0.337	0.219
DBP (mmHg)	0.380	0.224	0.259	0.350
TPR (mmHg/ml/s)	0.699	0.011	0.400	0.140
C_{wk} (ml/mmHg)	–0.126	0.697	–0.511	0.052
c-pPWV (m/s)	–0.074	0.820	0.233	0.546
Biochemical variables				
eq Ang I (pmol/l)	–0.606	0.037	–0.084	0.767
eq Ang II (pmol/l)	–0.510	0.090	0.161	0.566
ACE-S (pmol/l)	0.378	0.226	–0.077	0.785
PRA-S (pmol/l)	–0.552	0.063	0.206	0.462
sACTH (pg/ml)	–0.207	0.519	0.218	0.435
sCortisol (nmol/l)	–0.105	0.746	0.500	0.058
Serum Na^+ (mmol/l)	0.287	0.366	–0.204	0.467
Serum K^+ (mmol/l)	–0.196	0.542	–0.496	0.060
Serum Na^+–K^+ ratio	0.559	0.059	0.389	0.152
Urinary Na^+ (mmol/l)	0.400	0.223	0.390	0.150
Urinary K^+ (mmol/l)	–0.193	0.549	–0.058	0.839
Urinary Na^+–K^+ ratio	0.137	0.655	0.478	0.098
End-organ variables				
Cornell product (> 244 mV/ms)	0.001	0.999	0.560	0.037
Silent 24-h ST events (*n*)	–0.233	0.491	0.122	0.664
Est creatinine clearance (ml/min)	0.231	0.471	–0.304	0.271
ACR	–0.100	0.770	0.589	0.021

BMI: body mass index (kg/m²); SBP, DBP: systolic and diastolic blood pressure (mmHg), respectively; SV: stroke volume (ml); TPR: total peripheral resistance (mmHg/s/ml); C_{wk}: Windkessel compliance (ml/mmHg); c-pPWV: carotid-pedalis pulse-wave velocity (m/s); Ang I and Ang II: angiotensin I and angiotensin II (pmol/l); ACE-S: surrogate for angiotensin converting enzyme (AngII/AngI, pmol/l); PRA-S: surrogate for renin activity (Ang I + Ang II, pmol/l); sACTH: serum adrenocorticotrophic hormone (pg/ml); ACR: albumin–creatinine ratio; *p*-values ≤ 0.05 regarded as significant.

enzyme (ACE) inhibitor therapy and may therefore be a valuable alternative to currently employed screening assays.[11] In the current study, due to the small sample size and participants utilising different hypertensive medication, we could not explore the AA2 ratio in full for the diagnosis of PA.

The PA-like phenotype in hypertensive black men was further characterised by a decrease in serum K^+ levels and was associated with higher aldosterone levels, which may aggravate cardiovascular complications.[17] From the literature, it is also evident that the overall prevalence of co-morbidities was higher in hypokalaemic PA patients than in normokalaemic patients.[17] In more than 22 000 Pakistani patients, the risk of sudden cardiac attack or sudden cardiac death and all-cause mortality was associated with hyperkalaemia,[18] however no significant relationship existed between hypokalaemia and outcome.

The association between left ventricular hypertrophy (Cornell product) and aldosterone rather supports cardiac co-morbidities, as excess aldosterone levels might be a risk factor for arrhythmic disorders occurring either via left ventricular hypertrophy or cardiac fibrosis.[19] Furthermore, aldosterone has been associated with endothelial dysfunction,[17] and now also with a lack of arterial compliance, independent of blood pressure.[19] Lower K^+ levels and a lack of compliance concurrently with high aldosterone levels and associated ACR (a marker of kidney and endothelial dysfunction) may be detrimental to the cardiovascular health of hypertensive black men.

Blood pressure control was driven by the TPR and renin–angiotensin system (see Table 2) in the hypertensive low-aldosterone group. Aldosterone is a mineralocorticoid hormone, having 30–50% of its total plasma concentration in free form. Cortisol on the other hand is a glucocorticoid hormone and has 100-fold higher free levels in circulation than aldosterone, with high intrinsic mineralocorticoid activity, although its action is blunted by local conversion to cortisone at the kidney level.[20] Cortisol can bind with the same high affinity as aldosterone to the mineralocorticoid receptor[20] and it may modulate the mineralocorticoid receptor-binding effects of aldosterone.

From the literature, it is evident that the long-term increase in both cortisol and aldosterone reflect changes in risk factors for cardiovascular disease, such as increases in dietary fat, high salt intake, low levels of physical activity and high stress levels, which may lead to the phenotype of aldosterone-associated hypertension.[20] Stress can indeed alter the aldosterone phenotype, as chronic depression was associated with a desensitised renin system and volume-loading hypertension in a black cohort over three years.[21]

Our finding of a positive association between aldosterone and cortisol ($p = 0.058$) in the hypertensive high-aldosterone group further enhances previous findings where hypothalamic–pituitary–adrenal axis dysregulation and compensatory double product (systolic blood pressure × heart rate) increased and acted as a possible defence mechanism to alleviate perfusion deficits, which potentiated ischaemic heart disease risk.[22] The interaction of endogenous levels of aldosterone and cortisol may therefore disrupt blood pressure control and result in an increased proportion of hypertension.

Low-renin hypertension is more common in blacks and is characterised by increased Na^+ retention and suppressed renin and aldosterone levels,[3,21,23] and may be psychosocial in origin.[21, 23] Salt and water retention are greater in blacks, not only because there is an increased likelihood of PA, but also because of genetic variants that affect the function of the renal tubular epithelial sodium channel (ENaC). There are a number of genetic causes of both these phenotypes.[24,25]

PA is an overlooked but frequent cause of secondary hypertension and because only a few hypertensive patients are screened worldwide for PA,[6] mineralocorticoid blockade is also unlikely to be used as treatment for hypertension. It is also worth mentioning that low levels of both aldosterone and angiotensin II would identify patients with a Liddle syndrome phenotype, who would respond best to amiloride.[26,27]

Our data highlight the fact that hypertensive black patients with low K^+ levels should be screened for PA in order to treat them adequately so as to bring the high prevalence of hypertension in sub-Saharan Africa under control. Because PA is also a common occurrence in resistant hypertension, screening for it may further improve hypertension treatment and control in South Africa.

A strength of this sub-study is that use was made of state-of-the-art analysis of the RAAS parameters. A weakness is that follow-up data were not used to determine causality.

Conclusion

The AA2 ratio, which should be explored further to replace the aldosterone-to-renin ratio for the diagnosis of PA, was used to identify the PA-like phenotype in black men. Excess aldosterone was associated with endothelial dysfunction and left ventricular hypertrophy, independent of blood pressure.

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The effect of beta-blockers on foetal birth weight in pregnancies in women with structural heart disease: a prospective cohort study

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Abstract

Objective: To examine whether treatment with beta-blockers (BBs) in pregnant women with structural heart disease (SHD) resulted in a decrease in foetal birth weight (FBW) in a South African cohort.

Methods: This was a prospective cohort study conducted in a tertiary-level hospital in Cape Town from 2010 to 2016. Of the 178 pregnant women with SHD, 24.2% received BBs for a minimum of two weeks. Adverse foetal outcomes and mean FBW were compared between the BB groups and subgroups (congenital, valvular, cardiomyopathy and other). Adverse foetal outcome was defined as: low birth weight (LBW) < 2 500 g, Apgar score < 7, premature birth (< 37 weeks) and small for gestational age (SGA).

Results: BB exposure during pregnancy was found to be associated with a non-significant increased FBW (2 912 vs 2 807 g, $p = 0.347$). A significant decrease ($p = 0.009$) was noted in FBW for valvular SHD pregnancies using BBs, while a significant increase ($p = 0.049$) was observed for the same outcome in the cardiomyopathy subgroup using BBs. A significant increase was observed for SGA ($p = 0.010$) and LBW ($p = 0.003$) pregnancies within the valvular subgroup when exposed to BBs.

Conclusion: BB use in pregnant women with SHD in a South African cohort showed no association with a decrease in FBW or an increase in adverse foetal outcomes when compared to non-BB usage.

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Increasingly, pregnancies worldwide are complicated in women with pre-existing structural heart disease (SHD).[1] Maternal congenital heart disease (CHD) dominates in high-income countries,[2] while rheumatic valvular disease (RVD) represents the most frequent SHD in pregnancies in low- to medium-income countries.[1] Pregnancies in women with SHD exhibit higher-than-average maternal mortality rates,[3] necessitating increased monitoring and medication use during the antenatal period. The most commonly observed maternal complications during pregnancies affected by SHD are congestive heart failure and arrhythmias.[4-6]

SHD also increases the rate of adverse foetal outcomes [preterm delivery, intra-uterine growth retardation (IUGR) and low birth weight (LBW)], with the strongest predictor of these outcomes being maternal cyanosis and reduced cardiac output.[7-11] These adverse events set in motion a cascade of possible foetal neuro- and bronchopulmonary developmental abnormalities,[12,13] resulting in increased healthcare costs[14] and maladaptive programming in adult life.[15,16]

Foetal outcomes, in part, are determined by maternal cardiovascular adaptation during pregnancy. Inadequate adaptation due to SHD leads to reduced utero-placental perfusion, resulting in impaired foetal growth and nutrition.[7] This association is complicated by the use of beta-blockers (BBs) in pregnancies with SHD, as these drugs have been previously associated with small-for-gestational-age (SGA) infants and LBW,[17-19] although some studies show contradictory results.[20-22] BBs have also been associated with neonatal hypoglycaemia and bradycardia in the third trimester, with no increase in congenital defects shown.[21,23]

Studies investigating the effect of BBs on SGA and LBW have focused more on hypertensive pregnancies[19,24-26] than studies regarding SHD pregnancies.[27,28] In addition to the effect on the foetus, BBs can also cause maternal bronchoconstriction, fatigue and sleep disturbances, which further signifies the importance of an interdisciplinary decision regarding the use of BBs in pregnancies with SHD.[23] In this prospective study among patients recruited from a tertiary hospital in South Africa, we aimed to investigate the effect of treatment with oral BBs in woman with SHD on the foetal birth weight (FBW).

Methods

A prospective cohort study was conducted from 2010 to 2016 at a tertiary multidisciplinary maternal care facility in Cape Town, South Africa. This is an analysis of an ongoing cohort for which data on methodology, overall patient characteristics and diagnosis, as well as six- and 12-month outcome has been published recently.[29,30]

All patients gave written informed consent. All principles from the Declaration of Helsinki were adhered to. The study was approved by the ethics committee of the University of Cape Town (HEC ref: 173/2010).

Of 178 consecutive pregnant women with SHD, 24.2% received BBs (n = 43) in pregnancy. Data were manually extracted from both cardiology and obstetric clinical records, after screening for eligibility, and captured in a modified database. Data parameters recorded included gestational age, gender, mode of delivery, birth weight and Apgar scores for all patients. Data on type of BB used, treatment dosage, treatment duration in weeks and trimester of BB initiation were additionally recorded for the BB group. The type of BB available and prescribed in South African public service hospitals was recorded. Atenolol and carvedilol are the only BBs approved for provincial service in South Africa.

SHD pregnancies were sub-divided into congenital, valvular, cardiomyopathy and 'other' for extended analysis. The subgroup 'other' included infiltrative heart disease such as sarcoidosis, ischaemic heart disease and heart disease caused by arrhythmias. Patient exclusion criteria included: (1) essential information regarding birth weight, and gestational age not available, (2) pregnancies not exceeding 24 weeks of gestation, and (3) therapeutic abortions at any gestational period. Adverse foetal outcomes were defined as: perinatal death, LBW defined as birth weight < 2 500 g, Apgar scores < 7 and premature birth (< 37 weeks).

Table 1. Baseline maternal characteristics of study population (n = 178)

Clinical characteristic	*All* (n = *178*)	*BB used* (n = *43*)	*BB not used* (n = *135*)	p-*value*
Age (years)	28 ± 6	30 ± 6	28 ± 6	0.008
Parity, *n* (range)	2 (1–5)	2 (1–4)	1 (1–5)	0.153
BMI (kg/cm^2)	28.1 ± 7.3	28.4 ± 7.0	27.9 ± 7.4	0.664
Systolic blood pressure (mmHg)	121 ± 16	121 ± 17	121 ± 15	0.721
Diastolic blood pressure (mmHg)	74 ± 12	76 ± 13	73 ± 12	0.199
Heart rate (beats/min)	86 ± 17	88 ± 15	85 ± 12	0.176
NYHA functional class, *n* (%)				
I/II	152 (88)	31 (74)	121 (92)	0.001
III/IV	21 (12)	11 (26)	10 (8)	
Haemoglobin (g/dl)	11.6 ± 1.7	11.7 ± 1.5	11.5 ± 1.7	0.340
Echocardiography				
LVEDD (mm)	48.5 ± 7.6	50.1 ± 8.3	48.1 ± 7.3	0.112
LVESD (mm)	33.6 ± 7.6	35.5 ± 9.7	33.0 ± 6.7	0.099
Ejection fraction (%)	58.6 ± 11.8	56.1 ± 13.7	59.6 ± 10.5	0.132
General medical history (%)				
Chronic hypertension	17 (10)	4 (9)	13 (10)	0.949
HIV	38 (21)	9 (21)	29 (21)	0.921
Family history of CVD	31 (17)	7 (16)	24 (17)	0.843
Caesarian section, *n* (%)	90 (51)	25 (58)	65 (48)	0.291

Values are mean ± SD unless otherwise specified. *p*-values based on unpaired *t*-tests, Mann–Whitney *U*-tests or chi-squared tests where appropriate.
BB, beta-blockers; BMI, body mass index; CVD, cardiovascular disease; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NYHA, New York Heart Association; HIV, human immunodeficiency virus.

Statistical analysis

The descriptive statistics are stated as frequency, median and interquartile range or mean value and standard deviations where applicable. Comparison of continuous variables between case and control groups was performed using unpaired Student's *t*-tests for data normally distributed. Otherwise the Mann–Whitney *U*-test was used. To compare categorical variables, the chi-squared or two-tailed Fisher's exact test was used where appropriate; $p < 0.05$ was considered to be significant at the 95% confidence level.

Finally, we correlated the treatment duration of oral BBs with the relative deviation from expected FBW for the 24 patients for whom data were available. Data analysis was performed using SPSS 24 for Windows. Figures were created with GraphPad Prism 7 for Windows, Version 7.03.

Results

Baseline characteristics of all pregnancies are shown in Table 1. Pregnant women exposed to BBs were older than those who were not. No significant differences were noted between the groups for clinical and echocardiographic parameters. When dividing pregnancies into those with New York Heart Association (NYHA) I–II and III–IV physical limitation, a significant increase (p = 0.001) was noted between the number of pregnancies exposed to BBs compared to those not exposed.

Of the 178 patients analysed in this study, 64 (36%) presented with CHD, indicating predominance within this subgroup compared to valvular heart disease (33.1%), cardiomyopathy (20.2%) and 'other' (10.7%) (Fig. 1). Dividing BB use among the four subgroups revealed higher BB usage within the valvular (32.6%) and cardiomyopathy (41.9%) subgroups.

BB exposure during pregnancy was found to be associated with a non-significant increased mean FBW (2 912 vs 2 807 g, p = 0.347) and a similar mean gestational age of delivery (GAD) (37.4 vs 37.5 weeks, p = 0.841) (Fig. 2A, B). The outcomes of mean GAD in weeks and mean FBW among the four subgroups are shown in Table 2. The highest mean GAD and FBW were found in the valvular (37.7 weeks) and cardiomyopathy (2 999 g) subgroups, respectively. Lowest mean FBW was in the 'other' group and lowest mean GAD occurred in the cardiomyopathy group. When comparing the different types of BBs used (atenolol

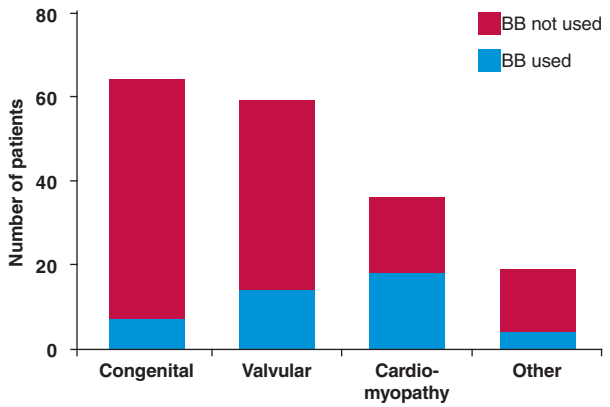

Fig. 1. Distribution of BB groups among the SHD subgroups.

versus carvedilol) with regard to the outcomes of mean GAD and FBW, we found a non-significant increase (2 728 vs 3 138 g, $p = 0.094$) in FBW of 410 g and a similar GAD (37.5 vs 37.3 weeks, $p = 0.51$) associated with the use of carvedilol (Fig. 3).

Data on BB treatment duration and dosage were available for all the treated patients. The median (range) dose used was 12.5 mg (6.25–50) for carvedilol and 50 mg (25–100) for atenolol. The median treatment duration was 98 days with a range of seven to 273 days. No difference in treatment duration was observed between carvedilol [122.5 days (7–273)] and atenolol [63 days (7–273)] ($p = 0.97$). The chi-squared test related to any effects on foetal outcome was not significant ($p = 0.3796$).

Apart from a significant decrease ($p = 0.009$) in FBW for valvular SHD pregnancies and an opposing significant increase ($p = 0.049$) in FBW in the cardiomyopathy subgroup when exposed to BBs, no differences were noted for FBW and GAD between the unexposed and BB-exposed groups in the remaining subgroups.

No significant differences were noted for any adverse foetal outcomes between the SHD pregnancies exposed to BB and those who were not exposed. Apgar scores < 7 occurred in 23 (17%) pregnancies not exposed to BB compared to four (9%) in the BB group ($p = 0.33$). Preterm births were noted in 32 (24%) pregnancies not exposed to BBs, compared to 11 (26%) pregnancies in the BB group ($p = 0.80$). LBWs were noted in 28 (21%) pregnancies not exposed to BB, compared to nine (21%) in the BB group ($p = 0.87$). SGA was documented in 41 (30%) and 12 (28%) pregnancies of the non-exposed and BB-exposed groups, respectively ($p = 0.82$). No significant foetal bradycardia was documented in the hospital records.

When comparing all adverse foetal outcomes between the BB groups for each SHD subgroup separately, we again found no significant differences except for SGA ($p = 0.010$) and LBW ($p = 0.003$) pregnancies within the valvular subgroup when exposed to BB (Table 2).

Severity of maternal SHD at presentation, together with HIV infection, can directly influence foetal outcome independent of BB treatment. We therefore compared women with severe cardiac conditions (NYHA III or IV at presentation) to women with NYHA I or II, for the occurrence of poor foetal events such as preterm birth (< 37 weeks), LBW and Apgar scores < 7. Results in Table 3 show no differences according to the severity of maternal cardiac condition.

In the same way, HIV impact on gestational period, birth weight and Apgar scores was analysed using contingency analyses (Table 3). Despite a trend towards a lower birth weight and abnormal Apgar scores in HIV-positive compared to HIV-negative women, none of the comparisons was statistically significant.

Correlating the duration of BB treatment with the relative deviation from expected FBW as a percentage, we found a non-significant direct correlation ($r = 0.20$; $p = 0.360$; 95% CI: 0.247–0.590) for 24 patients, as seen in Fig. 4.

Discussion

This study, the first of its kind conducted within an African population, assessed whether the use of BBs in pregnant women with SHD decreased FBW and increased adverse foetal outcomes. Surprisingly, considering our status as a low- to middle-income country, the largest percentage of SHD pregnancies had CHD (36.0%) compared to RVD, which predominates in other low- to middle-income countries.[1] This can be ascribed to an effective regional referral system, transferring both new and previously operated CHD cases.

Comparing outcomes between subgroups, we found the highest mean FBW (2 999 g) within the cardiomyopathy subgroup, despite registering the lowest gestational age at delivery in weeks (37.2). Matching these same outcomes to all

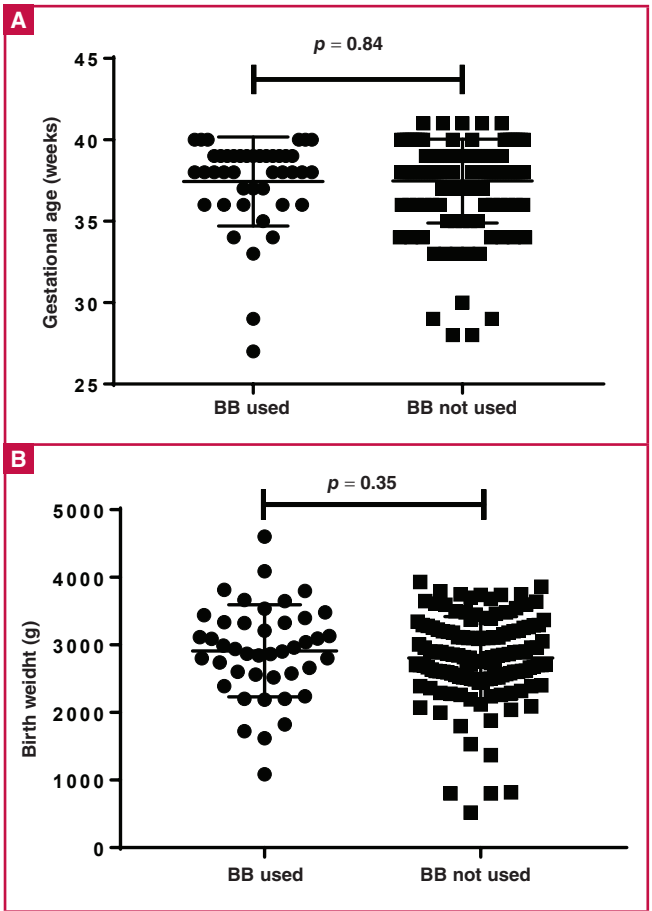

Fig. 2. Comparison between BB groups for mean gestational age and birth weight.

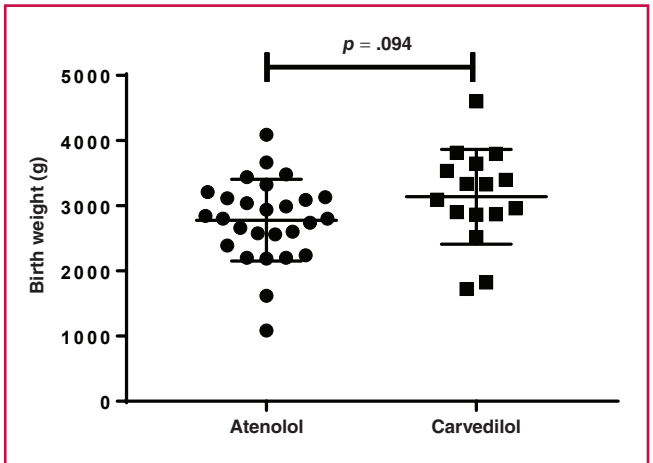

Fig. 3. Comparison between the two types of BB with regard to mean birth weight.

Table 2. Foetal outcomes for structural heart disease pregnancies on BB compared to non-BB usage per subgroup

	Congenital			*Valvular*			*Cardiomyopathy*			*Other*		
Variables	*BB not used (n = 57)*	*BB used (n = 7)*	p-*value*	*BB not used (n = 45)*	*BB used (n = 14)*	p-*value*	*BB not used (n = 18)*	*BB used (n = 18)*	p-*value*	*BB not used (n = 15)*	*BB used (n = 4)*	p-*value*
Apgar score < 7	10 (17)	1 (14)	1.00	9 (20)	3 (21)	0.938	2 (11)	0 (0)	0.486	2 (13)	0 (0)	0.582
Preterm birth < 37 weeks	15 (26)	1 (14)	0.669	10 (22)	4 (28)	0.722	5 (28)	5 (28)	1.00	2 (13)	1 (25)	0.530
LBW < 2 500 g	17 (30)	0 (0)	0.175	4 (9)	6 (43)	0.003	3 (17)	2 (11)	0.630	4 (27)	1 (25)	0.946
SGA	19 (33)	0 (0)	0.094	12 (27)	9 (64)	0.010	3 (17)	2 (11)	0.679	7 (47)	1 (25)	0.435
Gestational age (weeks)	37.4 ± 0.387 [38 (28–41)]	37.6 ± 0.782 [38 (33–39)]	0.720	37.6 ± 0.293 [38 (33–41)]	37.9 ± 0.430 [38 (35–40)]	0.715	36.9 ± 0.527 [37.5 (30–41)]	37.4 ± 764 [39 (27–40)]	0.152	37.9 ± 0.813 [38 (29–41)]	35.8 ± 2.29 [37.5 (29–39)]	0.221
Birth weight (g)	2755 ± 93.7 [2750 (520–3930)]	2994 ± 103 [3040 (2560–3440)]	0.319	2906 ± 60.9 [2900 (1880–3640)]	2561 ± 121 [2618 (1620–3322)]	0.009	2774 ± 139 [2670 (1370–3740)]	3225 ± 171 [3325 (1725–4600)]	0.049	2743 ± 199 [2863 (820–3600)]	2594 ± 536 [2905 (1085–3480)]	0.754

Values are mean ± SD [median (range)] unless otherwise specified. *p*-values based on unpaired *t*-tests with Welch's correction, Mann–Whitney *U*-tests or Fisher's exact tests where appropriate. BB, beta-blocker; SGA, small for gestational age; LBW, low birth weight.

subgroups combined, we established that SHD pregnancies exposed to BBs showed an increase in mean FBW, although this was not significant. Further analysis of foetal outcomes between BB-exposed and non-exposed groups within subgroups revealed significant outcomes for FBW in the cardiomyopathy and valvular subgroups.

BB usage in the valvular subgroup resulted in a significant decrease in FBW due, in part, to the predominant use of atenolol in this subgroup, and given that the use of BB generally accompanies advanced cardiac disease. Conversely, BB usage in cardiomyopathy resulted in a non-significant increase in mean FBW, possibly due to the later mean gestational delivery age. A second potential causative factor could be the predominant use of carvedilol in this group.

Most pregnancies within the congenital and valvular subgroups were prescribed atenolol, which has previously been shown to decrease FBW.[31] The largest proportion of BB use occurred within the valvular and cardiomyopathy subgroups with carvedilol predominantly used as a first-line BB. The variation in BB prescribing practice can be attributed to patients having treatment initiated at different sites, which follow different prescribing protocols. Atenolol is the only BB available in most primary healthcare facilities in South Africa and is, therefore, commonly used in patients with valvular heart disease. Conversely, cardiomyopathy patients are usually referred to a tertiary hospital for initiation of treatment where carvedilol is more readily available.

Further dividing the BB-exposed group ($n = 43$) between the different BBs used, we found an increase in mean FBW trending toward significance ($p = 0.094$) for pregnancies exposed to carvedilol ($n = 16$). The difference in FBW found between SHD pregnancies on atenolol versus those on carvedilol strengthens the previously mentioned hypothesis that a combined α- and non-selective β-receptor blocker (carvedilol) impairs placental vascular perfusion to a lesser degree than a β1-selective blocker (atenolol).[32]

This hypothesis is based on the opposing placental vascular adrenergic innervation, β2-receptor stimulation causing vasodilation and α-receptor stimulation producing vasoconstriction, which in turn leads to foetal growth retardation. Although classified as a β1-selective blocker, atenolol usage at increased doses causes β2-receptor blockade and therefore vasoconstriction.[33] Conversely, the vasoconstriction caused by carvedilol's non-selective β-blockade is opposed by its concomitant α-receptor stimulation and therefore reduces the possibility of foetal growth retardation.[33] Interestingly, based on small reports, both drugs were shown to cross the placental barrier.[34,35]

Additionally, higher NYHA functional classes, a clinical indicator of moderate/severe cardiac impairment, have been shown to increase adverse foetal outcomes, including SGA.[36] This association, independent of BB usage, may similarly result from impaired placental perfusion. Atenolol was mostly used in the valvular subgroup while carvedilol was predominately used in the cardiomyopathy subgroup. Although underpowered, our results should encourage re-examination of BB prescribing

Table 3. Impact of maternal SHD severity and HIV on foetal outcome

	NYHA I/II (n = 148–152)	*NYHA III/IV (n = 19–21)*	p-*value*	*HIV negative (n = 134–139)*	*HIV positive (n = 38)*	p-*value*
Variables						
Preterm birth < 37 weeks	40 (26)	3 (16)	0.409	38 (27)	7 (18)	0.301
Low birth weight < 2 500 g	46 (31)	6 (29)	0.999	38 (28)	15 (39)	0.169
Apgar score at 1 min < 7	25 (17)	2 (10)	0.750	19 (14)	8 (21)	0.317
Apgar score at 5 min < 7	6 (4)	1 (5)	0.590	4 (3)	3 (8)	0.182

Values are *n* (%). *p*-values based on Fisher's exact tests.
NYHA, New York Heart Association functional class.

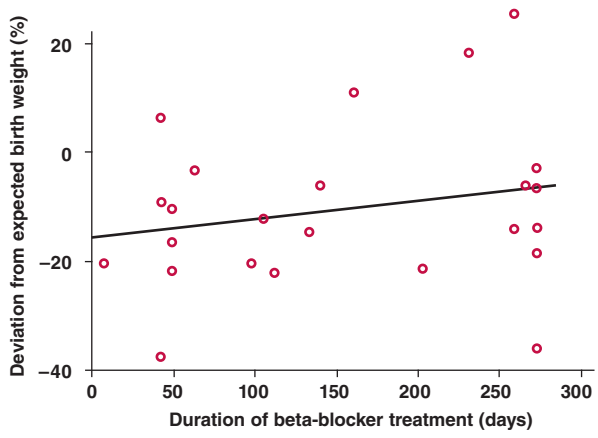

Fig. 4. Scatter plot of duration of BB treatment versus relative deviation from expected birthweight.

practices within SHD pregnancies at Groote Schuur Hospital. Predominant use of a BB type within a subgroup prohibited analysis of BB subtype effects within each SHD subgroup.

Adverse foetal outcomes that were compared between the BB-exposed and non-exposed groups included Apgar score, preterm delivery (< 37 weeks), LBW (< 2 500 g) and SGA. SGA was defined as birth weight under 10% of expected weight for that gestational age. Variables such as the presence of IUGR and maternal parameters such as weight gain during pregnancy were not available for all pregnancies. They were therefore not incorporated in deciding whether to classify a delivery as SGA, as this may have affected interpretation of the results, especially when comparing them with other studies.

No significant differences were noted for all adverse foetal outcomes when comparing all SHD pregnancies exposed to BB and those not exposed to BB. Repeating the comparison between the different subgroups, we found a significant increase in SGA ($p = 0.01$) and LBW ($p = 0.003$) pregnancies in the BB-exposed group in the valvular subgroup only. As mentioned before, this most likely results from the predominant atenolol use within this subgroup, as well as the principle of confounding by indication. No bradycardia in foetuses or newborns was documented in the hospital records of women who had received BB therapy.

Previous studies have shown a significant inverse correlation between the duration of BB treatment (days) versus the relative deviation from expected FBW. We had detailed information regarding days of treatment with BB for 24 patients within our cohort. For these 24 pregnancies, we found a non-significant direct correlation ($r = 0.20$), showing that increased duration of treatment in pregnancy did not significantly correlate with an increase or decrease in deviation from expected FBW.

It has been previously described that HIV[37] or severity of cardiac condition[38] in pregnant women may influence foetal outcome. Despite some interesting tendencies towards an impact of HIV on LBW or abnormal Apgar scores, non-significant differences were observed in our cohort. It would appear that NYHA was not associated with poor foetal outcome.

Limitations and strengths

Limitations for this study include sample size, particularly in the BB group. Secondly, the principle of confounding by indication complicates interpretation of results, as pregnancies with more severe disease are more likely to receive BBs and thereby increase the probability of an adverse foetal outcome. Multivariate analysis was not performed and hence we could not delineate the contribution of several maternal variables to the outcome of FBW and adverse foetal outcomes. Comparison between studies is also limited due to the variation in inclusion criteria for the different SHD subgroups in different studies. Results concerning BB subtype are mainly applicable in low- to middle-income countries were atenolol is regularly used.

Despite these limitations, this study addresses a clinically relevant topic and the information could be very helpful to obstetricians and cardiology care providers. Indeed, the topic of BB use in pregnancy in these women deserves attention, and prospective data are required in this field. Furthermore, most data about pregnancy in structural heart disease come from high-income countries, while this is a relatively large cohort from an (upper) middle-income country.

Conclusion

Use of BBs in a South African cohort of pregnancies complicated with SHD was found to have no significant effect on the outcomes of mean FBW and adverse foetal outcomes. The use of carvedilol, an α- and β-receptor blocker resulted in a notable although not significant increase in mean FBW, compared to SHD pregnancies using atenolol. The results of this study reiterate the importance of making clinical decisions on an individual patient basis with careful consideration of both type of BB and subgroup of SHD being treated.

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Prevalence of hypertension and selected cardiovascular risk factors among adolescents in selected rural and urban secondary schools in Botswana

Matshidiso Mokgwathi, Julius Chacha Mwita

Abstract

Background: Adolescent hypertension and other cardiovascular risk factors tend to track into adulthood. Consequently, there is a need to determine the prevalence of hypertension and pre-hypertension, and its co-existence with glycaemia, obesity, tobacco and alcohol use among senior secondary school students in Botswana.

Methods: A cross-sectional study was undertaken between December 2015 and March 2016 among students in selected rural and urban senior secondary schools in Botswana. Data were collected through a self-administered questionnaire, measurements and fasting blood glucose testing. Participants were asked about cigarette smoking, alcohol use and levels of physical activity. Body weight, height, waist circumference, blood pressure and fasting blood glucose levels were measured. Hypertension, pre-hypertension, overweight and obesity were defined based on gender, age and height from normative tables.

Results: A total of 252 students with a mean age (standard deviation) of 17.1 (0.9) years participated in the study. Rural students were older than urban students (17.5 vs 16.7 years; $p < 0.001$). The prevalence of hypertension and pre-hypertension were 13.1 and 15.5%, respectively. Physical inactivity (37.7%), overweight/obesity (10.3%) and alcohol intake (9.1%) were also prevalent. Cigarette smoking was rare (2.0%). Impaired fasting glucose levels were found in 1.6% of participants, and none had diabetes mellitus. Hypertension ($p < 0.001$) and cigarette smoking ($p = 0.019$) were more prevalent among male than female participants. Female students were more likely to be overweight or obese than male students ($p < 0.001$). There were no urban–rural differences in hypertension, pre-hypertension and smoking. Urban students were more likely to drink alcohol than rural students ($p = 0.008$)

Conclusion: Hypertension, overweight/obesity and alcohol intake were common among these adolescents in Botswana. Strategies to reduce the risk factors of cardiovascular diseases should be urgently developed and implemented to prevent cardiovascular disease-related morbidity and mortality in the future.

Keywords: hypertension, cardiovascular risk factors, adolescents, Botswana

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Demographic and epidemiological changes in sub-Saharan Africa (SSA) have resulted in an increase in non-communicable diseases, including hypertension, leading to concerns and activities to reduce rising rates.[1-4] In children and adolescents, hypertension is often underdiagnosed and may progress into adulthood.[5-8] The prevalence of hypertension among children in developed countries is 1–5%.[9] By contrast, the prevalence of hypertension in SSA paediatric populations is 0–12.5 and 0–21.5% for boys and girls, respectively.[10]

Hypertension is usually found in constellation with obesity, smoking, alcohol intake and physical inactivity.[10] All these may track from childhood to adulthood and are predictive of cardiovascular risk later in adult life.[10] The prevalence of all the above risk factors has been increasing among children, mainly as a consequence of urbanisation and changes in lifestyle.[11-13] Urbanisation has led to an increase in the use of tobacco and alcohol, poor diet and physical inactivity.[14-16]

For a country with a high burden of HIV/AIDS, the increase in non-communicable diseases, including cardiovascular disease (CVD) and diabetes, poses a challenge for health policymakers and providers to the already stretched health system and progress towards the development of millennium goals.[17-19] This is particularly important in Botswana with its high rate of HIV/AIDS, alongside the wish to maintain universal healthcare.

There is evidence that early identification and modification of risk factors during childhood decreases the occurrence and magnitude of associated complications due to CVD.[10,20] However, data on the burden of hypertension and other cardiovascular risk factors among adolescents in Botswana are currently scarce. Consequently, the objective of this study was to determine the prevalence of hypertension and co-existing selected cardiovascular risk factors among secondary school students in Botswana and to use the findings, if pertinent, to guide future strategies in Botswana.

Methods

This cross-sectional study was conducted from December 2015 to March 2016 among students in the rural Shakawe senior secondary school and the urban St Joseph's College in Botswana. Shakawe is the only senior secondary school in the Okavango, a sub-district with a population of 2 529 inhabitants, mostly subsistent farmers and pastoralists.[21] St Joseph's College is located in Gaborone, the capital city, with a population of 231 592.[21]

The two schools were conveniently selected based on their ease of accessibility and to provide widely different populations. There were 36 and 42 classes at St Joseph's College and Shakawe senior secondary school, respectively. Four classes were selected from each school using a simple random-sampling technique.

All students in the selected classes were invited to participate in the study and were provided with a written description of

the study, and informed consent forms to take to their parents/guardians (written in both English and Setswana). If willing to allow their child to participate, parents/guardians were then asked to sign the consent form. Students agreeing to participate signed assent forms.

Ethical approval for this study was obtained from the Ministry of Health institutional review board [HPDME: 13/18/1 Vol. X (152)]. Permits were obtained from the Ministry of Education and Skills Development, local authorities in Okavango and Gaborone and from each school administration.

Information on date of birth, gender, alcohol intake and tobacco use, and the level of physical activity was obtained using self-administered questionnaires. Personal and family history of heart disease, hypertension, kidney disease, diabetes mellitus, dyslipidaemia and stroke were also documented. Height was measured in all participants without footwear to the nearest 0.1 cm using a stadiometer. Weight was measured using a digital scale to the nearest 0.1 kg in light clothing and without footwear.

We used WHO AnthroPlus version 1.0.4 software to calculate body mass index (BMI) for all participants aged below 18 years.[22] BMI *z*-scores according to age, gender and height were recorded for each participant and designated as underweight [*z*-score < –2 standard deviations (SD)]; normal weight (*z*-score –2 SD – +1 SD); overweight (*z*-score +1 SD – +2 SD); and obese (*z*-score > +2 SD). For participants ≥ 18 years, adult BMI reference values were used for underweight (≤ 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–30 kg/m^2) and obesity (≥ 30 kg/m^2).[23]

Waist circumference (WC) was measured to the nearest centimetre in light clothing at the level of the umbilicus using a non-distensible measuring tape. Using the Canadian percentile charts for WC based on gender and age, WC > 90th percentile was categorised as overweight for students < 18 years.[24] For students ≥ 18 years, adult cut-offs of 94 cm and 80 cm were used for males for females, respectively.[23]

After five minutes of rest, two seated blood pressure (BP) measurements were taken from the participants' right arms using portable sphygmomanometers (BPCB0A–2H, China). The second measurement was taken after a five-minute interval and the average of the two BP readings was recorded. An average systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥ 95th percentile for age, gender and height was used to define hypertension. Pre-hypertension was defined as SBP and/or DBP ≥ 90th percentile but < 95th percentile.

A repeat blood pressure measurement was done after one week for participants whose readings were consistent with pre-hypertension and hypertension during the initial measurement. Participants whose average SBP and/or DBP remained high in the second visit were categorised as hypertensive and pre-hypertensive as appropriate.[25,26] We also defined hypertension among participants who self-reported current antihypertensive medication use.

Fasting blood glucose (FBG) level was measured in mmol/l on capillary blood from a finger-prick test using the Accu-check Performa system (Roche Diagnostics, Mannheim, Germany) following a minimum fasting period of eight hours in participants not known to have diabetes mellitus. Using the American Diabetes Association diagnostic criteria, participants were classified as having normal fasting glucose levels (< 5.6 mmol/l), impaired fasting glucose (5.6–6.9 mmol/l) or diabetes mellitus (≥ 7.0 mmol/l).[27]

Alcohol use was defined as any reported alcohol consumption in the previous year, while cigarette smokers were current smokers. We assessed self-reported physical exercise duration and intensity in the previous week (both at school and during leisure time) to three levels of physical activity: inactive, minimally active and health-enhancing physical activity.[28]

Statistical analysis

The prevalence of hypertension and selected risk factors among adolescents is unknown in Botswana. Consequently, the sample size was calculated from the assumption that the prevalence of hypertension in Botswana was 20%, similar to that found in South Africa.[29] We needed 250 participants to determine the true prevalence of hypertension with a margin of error of ± 5%.

Data were entered and analysed using SPSS for Windows, version 23.0 (IBM Corporation). Continuous variables (fasting blood glucose, height, weight, WC, SBP, DBP and age) were summarised by means (± SD). Counts and percentages summarised categorical variables. A Pearson's chi-squared test was used to compare the prevalence of selected cardiovascular risk factors (hypertension, diabetes mellitus, smoking, obesity/overweight, level of physical activity and alcohol use) between urban and rural students.

For univariate analysis of continuous variables (fasting blood glucose, height, weight, WC, age), the Student's *t*-test was used. A *p*-value less than 0.05 was considered statistically significant. Variables that were variables with $p < 0.25$ in the univariate analysis were included as independent variables for the multivariable logistic regression.

Results

A total of 252 students (132 from Shakawe senior secondary school and 120 from St Joseph's College) participated in the study (Table 1). Of these, 172 (68.3%) were females, and the mean (SD) age was 17.1 (0.9) years. Students from the rural school were older than those from the urban school (17.5 vs 16.7 years; $p < 0.001$). None of the participants had a history of diabetes mellitus, stroke or dyslipidaemia.

Overall, obesity or overweight was observed in 10.3% of students (12.5% in the urban school and 8.3% in the rural school). Female students were more likely to be overweight or obese than male students (Table 2). Underweight was found in 25 (9.9%) students, and was more prevalent in male than in female students. There were no urban–rural differences in the prevalence of underweight.

None of the study participants had diabetes mellitus. Impaired fasting glucose was found in 1.6% of participants (all females), 1.7 and 1.5% among urban and rural school participants, respectively.

Twenty-three (9.1%) participants reported drinking alcohol. Urban students were more likely to drink alcohol than rural students (14.2 vs 4.5%; $p = 0.008$). Smoking was rare in both schools. However, male students were more likely to report cigarette smoking than female students (0.6 vs 5%; $p = 0.019$).

There were 37.7% inactive students, and inactivity was more common in Shakawe senior secondary school students than those at St Joseph's College. Physical activity did not vary with gender in the two schools.

Table 1. Characteristics of student participants at St Joseph's and Shakawe senior secondary schools (*n* = 252)

Characteristics	*All* (n = *252*)	*St Joseph's* (n = *120*)	*Shakawe* (n = *132*)	p-*value*
Mean age (SD), years	17.4 ± 0.9	16.74 ± 0.74	17.49 ± 0.9	< 0.001
Age groups, years				
< 18 years, *n* (%)	182 (72.2)	104 (86.7)	78 (59.1)	< 0.001
≥ 18 years, *n* (%)	70 (27.8)	16 (13.3)	54 (40.9)	
Gender				
Girls, *n* (%)	172 (68.3)	83 (69.2)	89 (67.4)	0.767
Boys, *n* (%)	80 (31.7)	37 (30.8)	43 (32.6)	
Height, mean (SD), cm	164.9 ± 8	163.42 ± 7.8	166.19 ± 8	0.006
Mean WC (SD), cm	69.3 ± 7.1	68.00 ± 7.8	70.49 ± 6.3	0.006
Mean weight (SD) kg	55.6 ± 9.9	55.3 ± 11.4	55.88 ± 8.7	0.670
Mean HC (SD), cm	91.3 ± 9.5	90.45 ± 11.2	92.0 ±7.5	0.208
Mean FBG (SD), mmol/l	4.70 ± 0.5	4.70 ± 0.44	4.71 ± 0.47	0.788
Mean SBP (SD), mmHg	118 ± 13.2	112.39 ± 12.6	122.62 ± 12.7	< 0.001
Mean DBP (SD), mmHg	71.8 ± 9.5	68.5 ± 9.5	74.8 ± 8.4	< 0.001
Mean pulse (SD), bpm	80.3 ± 13.3	79.1 ± 11.7	81.4 ± 14.6	0.164
Family history of HPT, *n* (%)	75 (29.8)	42 (35)	33 (25)	0.083
Family history of DM, *n* (%)	15 (6)	10 (8.3)	5 (3.8)	0.128
Family history of stroke, *n* (%)	16 (6.3)	2 (1.7)	16 (10.6)	0.004

HPT: hypertension; DM: diabetes mellitus; FBG: fasting blood glucose; WC: waist circumference; HC: hip circumference; BMI: body mass index; SBP; systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute, SD: standard deviation.

The mean (SD) SBP and DBP was 118 (13.2) and 71.8 (9.5) mmHg, respectively, and BP was significantly higher among students in the rural school than those in the urban school (Table 1). Overall, the prevalence of hypertension and pre-hypertension was 13.1 and 15.5%, respectively (Table 2). There were no urban–rural differences in hypertension and pre-hypertension. Hypertension was more prevalent among male (OR = 4.3) than female participants (Table 3).

Table 2. Table showing the distribution of cardiovascular risk factors among students at St Joseph's and Shakawe senior secondary schools (*n* = 252)

		School			*Gender*		
Parameters	*All* (n = *252*)	*St Joseph's* (n = *120*)	*Shakawe* (n = *132*)	p-*value*	*Female* (n = *172*)	*Male* (n = *80*)	p-*value*
Hypertension, *n* (%)							
Normal	180 (71.4)	89 (74.2)	91 (68.9)	0.380	138 (80.2)	42 (52.5)	< 0.001
PreHPT	39 (15.5)	19 (15.8)	20 (15.2)		20 (11.6)	19 (23.8)	
Hypertension	33 (13.1)	12 (10)	21 (15.9)		14 (8.1)	19 (23.8)	
Overweight or obesity, *n* (%)							
Underweight	25 (9.9)	11 (9.2)	14 (10.6)	0.536	9 (5.2)	16 (20)	< 0.001
Normal weight	201 (79.8)	94 (78.3)	107 (81.1)		141 (82)	60 (75)	
Overweight/ obese	26 (10.3)	15 (12.5)	11 (8.3)		22 (12.8)	4 (5.0)	
WC, cm							
Normal	229 (90.9)	108 (90)	121 (91.7)	0.109	162 (94.2)	77 (96.3)	0.491
Increased	23 (9.1)	12 (10)	11 (8.3)		10 (5.8)	3 (3.8)	
Fasting blood glucose, mmol/l							
Normal	248 (98.4)	118 (98.3)	130 (98.5)	0.923	168 (97.7)	80 (100)	0.169
IFG	4 (1.6)	2 (1.7)	2 (1.5)		4 (2.3)	0 (0.00)	
Level of physical activity, *n* (%)							
Inactive	95 (37.7)	32 (26.7)	63 (47.7)	0.002	70 (40.7)	25 (31.3)	0.164
Minimal	76 (30.2)	45 (37.5)	31 (23.5)		53 (30.8)	23 (28.8)	
Highly active	81 (32.1)	43 (35.8)	38 (28.8)		49 (28.5)	32 (40)	
Smoking, *n* (%)	5 (2)	3 (2.5)	2 (1.5)	0.567	1 (0.6)	4 (5.0)	0.019
Alcohol intake, *n* (%)	23 (9.1)	17 (14.2)	6 (4.5)	0.008	14 (8.1)	9 (11.3)	0.425

PreHPT: pre-hypertension; HPT: hypertension; BMI: body mass index; WC: waist circumference; IFG: impaired fasting glucose.

Table 3. Factors associated with hypertension among students at Shakawe and St Joseph's senior secondary schools (*n* = 252)

	Bivariate analysis			*Multivariate analysis*		
Variable	*Crude OR*	*95% CI*	p-*value*	*Adjusted*	*95% CI*	p-*value*
Gender						
Female	1 (ref)	1 (ref)		1 (ref)	1 (ref)	1 (ref)
Male	3.5	1.66–7.44	0.001*	4.31	1.83–10.13	< 0.001
School						
Shakawe (rural)	1					
St Joseph's (urban)	0.59	0.28–1.25	0.168*	0.62	0.26–1.44	0.263
Age	0.98	0.66–1.46	0.923			
Alcohol intake						
No	1 (ref)	1 (ref)				
Yes	3.57	0.47–27.44	0.221	4.86	0.44–54.0	0.198
Smoking						
No	1 (ref)	1 (ref)				
Yes	4.65	0.75–28.91	0.1	7.47	0.544–102.59	0.132
BMI category						
Normal weight	1 (ref)	1 (ref)				
Underweight	0.64	1.03–7.13	0.563	0.457	0.089–2.345	0.348
Overweight/ obese	2.72	1.03–7.13	0.043*	2.998	0.716–12.56	0.133
WC	1.07	1.02–1.13	0.005			
Fasting blood glucose	1.32	0.59–2.93	0.496			
Physical activity						
Inactive	1.19	0.51–2.77	0.681	–	–	–
Minimally active	0.65	0.24–1.76	0.393	–	–	–
Highly active	1 (ref)	1 (ref)		–	–	–
Family history of hypertension	0.73	0.31–1.69	0.458	–	–	–
Family history of diabetes	1.022	0.22–4.75	0.980	–	–	–
Family history of stroke	0.425	005–3.33	0.415	–	–	–

OR: odds ratio; CI: confidence interval; WC: waist circumference; BMI: body mass index.

Discussion

In this study, conducted among adolescents in a rural and urban setting in Botswana, a high burden of hypertension was found in constellation with obesity, tobacco use, alcohol use, obesity and physical inactivity. All these may track from childhood to adulthood and are predictive of increased cardiovascular morbidity and mortality later in adult life.[10] For a country with a high burden of HIV/AIDS, the increase in non-communicable diseases is a challenge to the already stretched health system.[17,18]

The prevalence of all the above risk factors has been increasing among children, mainly as a consequence of urbanisation and change in lifestyle,[11-13] with urbanisation leading to an increase in the use of tobacco and alcohol, poor diet and physical inactivity.[14-16] The prevalence of hypertension found in this study was within the prevalence of 0.2 to 24.8% reported in the recent meta-analysis of hypertension studies among African children and adolescents.[30]

Although our findings are consistent with previous studies, we recognise that comparing the prevalence of paediatric hypertension is a challenge due to differences in the definition of hypertension, the age groups of the studied populations and the blood measurement methodology. Nonetheless, the burden of hypertension among our participants was appreciably higher than the prevalence of 3 to 5% among adolescents in the developed world.[31] We also observed a high prevalence of pre-hypertension in our adolescents.

This is a cause for concern in Botswana where about a third of adults are hypertensive.[32,33] As childhood hypertension progresses

to adulthood, the findings suggest that a significant proportion of our participants are at high risk of becoming hypertensive in adulthood.[34] We did not observe an urban–rural difference in the prevalence of hypertension. However, our participants from the rural school were significantly older than their urban counterparts, making it difficult to compare the two populations.

Both hypertension and pre-hypertension were more common in the male students than the females in our study. Our finding may be explained by the fact that male students were significantly older than their female colleagues. Results from the most recent meta-analysis on hypertension in adolescents in Africa however showed no difference between boys and girls in the prevalence of hypertension.[30,35-37]

Similar to other studies, overweight/obesity was associated with up to a four-fold increased risk of hypertension among our participants.[5, 29,35,36,38-41] A similar link between obesity and CVD has been established among adults.[42] Overweight/obesity and hypertension are some of the components of the metabolic syndrome, an indicator of high risk for CVD as well as type 2 diabetes.[43]

The burden of overweight and obesity among our participants is consistent with reports from other SSA countries where between 2.5 and 10.6% of adolescents are overweight or obese.[2,39,41,44] There is evidence that the increase in overweight/obesity is associated with urbanisation.[2] Although we did not see a rural–urban difference in the prevalence of overweight/obesity, earlier data from urban students in Botswana reported a higher proportion of overweight and obesity.[45] Consistent with other studies, overweight/obesity affected more girls than boys.[29]

Although none of the students was found to have diabetes mellitus, 1.6% of participants had IFG. As for the other components of the metabolic syndrome, IFG is a cardiovascular risk factor.[43] This is in contrast to findings from Cote d'Ivoire where 0.4 and 14.5% of adolescents had diabetes mellitus and IFG, respectively.[46] The reasons for this discrepancy are not clear.

A small proportion of both rural and urban students reported using tobacco. This is lower than earlier data from Botswana, in which 10% of the students were current tobacco smokers, and up to 29% reported having tried smoking.[47] Our findings are also inconsistent with the Global Youth Tobacco Survey (GYTS), which reported a prevalence of 10–33% among 13–15-year-olds.[48] Tobacco use was more common among males than females, consistent with a previous study in Botswana.[32] The lower prevalence of tobacco use among our participants was possibly due to under-reporting of tobacco use because of its prohibited use within schools in Botswana.

Only about 9% of our students reported using alcohol. The figure is lower than what would be expected in a country where nearly half (48.4%) of adults are said to consume alcohol regularly,[32] and again may be due to under-reporting. Similar to a study in Australia, our urban students were more likely to use alcohol than their rural counterparts.[49] It is possible that urban students have more access to alcohol than those in the rural setting, contributing to these findings.

We observed a lower level of physical activity among rural than urban students. This finding was unexpected, most likely explained by the fact that rural students were in a boarding school therefore had minimal travelling distance to their classes.[45]

There are some limitations. The study had a small sample size and relied on some self-reported variables that were prone to recall bias. We measured blood pressure on only two visits. More than two readings would have been needed to provide the best estimate of blood pressure.

Conclusion

This study has shown that hypertension, overweight/obesity and alcohol intake were common among these senior secondary school students in Botswana. Strategies to prevent the risk factors of CVD should be developed and implemented to avoid CVD-related morbidity and mortality in the future. These strategies are being advanced and will be the subject of future research.

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Association between galectin-3 levels and isolated coronary artery ectasia

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Abstract

Background: Coronary artery ectasia (CAE) is a well-recognised disorder characterised by abnormal dilation of the coronary arteries. Underlying mechanisms associated with abnormal luminal dilation in CAE remain to be elucidated. However, histopathological features resemble those of coronary atherosclerosis. Galectin-3 (Gal-3) is a valuable biomarker for both progression and destabilisation of atherosclerotic lesions. To the best of our knowledge, there is no study in the literature examining serum Gal-3 levels in patients with isolated CAE. In the present study, therefore, we aimed to investigate the possible relationship between serum Gal-3 levels and isolated CAE.

Methods: Between March 2016 and March 2017 this prospective, case-controlled study included a total of 49 consecutive isolated CAE patients (31 males, 18 females) diagnosed with CAE by coronary angiography at the catheter laboratory of Medeniyet University, Goztepe Training and Research Hospital, and 43 individuals (19 males, 24 females) with normal coronary arteries. Physical examination, medical history, blood biochemistry and transthoracic echocardiography were performed in both groups. Serum concentrations of Gal-3 were measured using blood samples.

Results: Median Gal-3 levels were significantly higher in isolated CAE patients than in the controls [23.2 (23.9 ± 7.1) vs 16.8 ng/ml (17.8 ± 7.3); $p < 0.001$]. According to the Markis classification, the extent of CAE was not correlated with Gal-3 levels ($p = 0.41$). Multivariate regression analysis revealed that Gal-3 concentration was an independent predictor of isolated CAE.

Conclusion: Our study results suggest that Gal-3 serum concentrations significantly increased in patients with isolated CAE, indicating that Gal-3 may be involved in the pathogenesis of isolated CAE.

Keywords: isolated coronary artery ectasia, galectin-3, atherosclerosis

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Coronary artery ectasia (CAE) is defined as the dilatation of coronary arteries to a diameter of 1.5 times or greater than that of the adjacent normal coronary artery.[1,2] Among patients undergoing coronary angiography, 0.3 to 4.9% have been reported to have CAE.[1,3] Isolated CAE, which is an uncommon angiographic finding with varying presentation patterns, is defined as pure ectasia without significant coronary artery stenosis, accounting for 0.1 to 0.79% of all cases with CAE.[1] More than half of the patients with CAE have coronary atherosclerosis, although concomitant connective tissue disorder or vasculitis may present in certain patients.[4,5]

Histopathological examination of the ectatic segments reveals extensive atherosclerotic alterations as well as disruption of the media layer of the vessel wall. Risk factors for atherosclerosis have also been found to be pertinent to patients with CAE.[6] These findings have suggested that, despite having a varying aetiology, CAE may be considered a variant of coronary atherosclerosis.[7] On the other hand, underlying mechanisms associated with abnormal luminal dilation in CAE patients remain to be elucidated. In addition, CAE may lead to increased cardiac morbidity and mortality through a number of mechanisms, including low coronary flow, coronary vasospasm and dissection formation.[4]

Galectin-3 (Gal-3) is a galactoside-binding lectin, also known as Mac-2 antigen, which is expressed by macrophages, fibroblasts, activated T-lymphocytes and endothelial cells.[8,9] It is involved in a number of biological processes, including cell growth, adhesion,

apoptosis and phagocytosis, as well as in pathological processes such as inflammation, fibrosis and atherosclerosis.[10-13] It has been suggested that it plays a key role in atherogenesis through increased phagocytosis and induction of the proliferation of vascular smooth muscle cells (VSMCs).[14,15]

In addition, Gal-3 has been shown to play a central pathophysiological role in the development of cardiovascular diseases by enhancing cardiac hypertrophy, fibrosis, arterial stiffness, inflammation and oxidative stress during cardiovascular remodelling.[8] Recent studies have demonstrated not only the potential role of Gal-3 in atherogenesis, but also an association between increased Gal-3 expression and the development of atherogenesis.[15]

In the literature, there are several studies carried out in animal and human models. In an animal model, inhibition of Gal-3 was found to be associated with decreased atherosclerotic plaque volume in mice with apolipoprotein E deficiency.[16] In a recent study, the utility of Gal-3 as a diagnostic and prognostic marker for cardiovascular conditions was reported.[17] In the light of these data, Gal-3, which is associated with inflammation and atherosclerosis, may play a major role in coronary artery disease (CAD) as well as in CAE, which is considered to represent a variant of CAD and to have a similar aetiopathology and clinical course.[18]

To the best of our knowledge, there is no study in the literature examining serum Gal-3 levels in patients with isolated CAE. In this study therefore we aimed to investigate the possible relationship between serum Gal-3 levels and isolated CAE.

Methods

In this prospective, case-controlled study, we included a total of 49 consecutive isolated CAE patients diagnosed with CAE by coronary angiography at the catheter laboratory of Medeniyet University, Goztepe Training and Research Hospital between March 2016 and March 2017. The control group consisted of a total of 43 individuals with normal coronary arteries. Detailed demographic data were obtained from each patient. Physical examination, medical history, blood biochemistry and transthoracic echocardiography were performed in both groups to rule out systemic conditions.

Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg or current use of hypertensive agents. Diabetes was defined as fasting blood glucose of > 126 mg/dl (6.99 mmol/l) or current use of a diet or oral antidiabetic agents to lower blood glucose levels. The use of anti-hyperlipidaemic agents or a fasting plasma total cholesterol of > 200 mg/dl (5.18 mmol/l) or a low-density lipoprotein cholesterol (LDL-C) of > 130 mg/dl (3.37 mmol/l) were considered to denote hyperlipidaemia.

Exclusion criteria were as follows: the presence of acute coronary syndrome, left ventricular dysfunction (ejection fraction < 50%), left ventricular hypertrophy, valvular heart disease, peripheral vascular disease, congenital cardiac disease, hepatic, renal, inflammatory or connective tissue, infectious or autoimmune disorders and malignancy.

A written informed consent was obtained from each participant. The study protocol was approved by the local ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Morning venous blood samples were obtained after 12 hours of fasting. Serum glucose, creatinine, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured using standard laboratory methods. Additional blood sampling was performed to measure serum Gal-3 concentrations.

Blood samples were immediately centrifuged at 1 000 µg for 15 minutes and sera were separated and stored at –80°C until Gal-3 assays. Serum Gal-3 concentrations were analysed in a blinded manner using a commercial enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions (eBioscience, CA, USA). The values were normalised to the standard curve. Intra-assay and inter-assay variance for Gal-3 at a Gal-3 concentration of 1.5 ng/ml were 6.4 and 11.4%, respectively.

Indications for coronary angiography were the presence of typical angina pectoris symptoms or suspicious or positive test results in non-invasive methods to assess coronary ischaemia (dobutamine stress echocardiography, treadmill test or myocardial perfusion scintigraphy). Coronary angiography was performed using the Judkins technique with left heart catheterisation and without the use of nitroglycerine (Siemens, Medical Solutions 2007, Munich, Germany). The angiography results were based on agreement between two experienced angiography specialists blinded to the study groups. Isolated CAE was defined as the dilatation of coronary arteries with a diameter of 1.5 times or greater than that of the adjacent normal coronary artery without significant stenotic lesions.[1,2]

In the absence of an identifiable adjacent normal segment, the mean diameter of the corresponding coronary segment in the control group was accepted as the normal value. The severity of ectasia was defined according to the Markis classification on the basis of the extent of ectatic involvement, as follows, in decreasing order of severity: diffuse ectasia in two or three vessels (type 1); diffuse involvement in one vessel and segmental involvement in another vessel (type 2); diffuse involvement in a single vessel (type 3); and segmental or localised involvement (type 4).[7]

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 software (IBM Corp, Armonk, NY, USA). Descriptive data are expressed as mean ± standard deviation (SD), median (min–max) or number and frequency. The distribution of variables was analysed using the Kolmogorov–Smirnov test. The Mann–Whitney *U*-test and independent samples *t*-test were used for the analysis of quantitative data. The chi-squared test was used for analysis of qualitative data, and Fisher's exact test was used when the chi-squared test was not suitable. The impact level and cut-off values were assessed using receiver operating characteristic (ROC) curves. The impact level was examined using univariate and multivariate logistic regression analyses. A p-value of < 0.05 was considered statistically significant.

Results

In the study population there were 31 males and 18 females in the isolated CAE group and 19 males and 24 females in the control

Table 1. Baseline demographic, clinical and laboratory characteristics of the study population

	Control group (n = 43)	*Patient group (n = 49)*	
	Mean ± SD, n *(%)*	*Mean ± SD,* n *(%)*	p-*value*
Age, years	57.2 ± 8.3	60.6 ± 8.2	0.057[t]
Gender			
Female	24 (55.8)	18 (36.7)	0.067[*]
Male	19 (44.2)	31 (63.3)	0.067[*]
BMI (kg/m^2)	31.9 ± 6.2	29.9 ± 0.0	0.084[t]
Smoking	12 (27.9)	19 (38.8)	0.271[*]
Alcohol	2 (4.7)	1 (2.0)	0.597[*]
Hypertension	21 (48.8)	31 (63.3)	0.164[*]
Diabetes	7 (16.3)	11 (22.4)	0.457[*]
Hyperlipidaemia	13 (46.7)	22 (53.3)	0.148*
Family history	3 (7.0)	9 (18.4)	0.106*
SBP (mmHg)	117.9 ± 14.3	117.5 ± 13.5	0.933[m]
DBP (mmHg)	68.9 ± 7.9	68.3 ± 7 .8	0.745[m]
Fasting glucose (mg/dl)	110.1 ± 38.3	110.5 ± 34.5	
(mmol/l)	(6.11 ± 2.13)	(6.13 ± 1.91)	0.488[m]
Creatinine (mg/dl)	0.7 ± 0.2	1.1 ± 2.5	
(µmol/l)	(61.88 ± 17.68)	(97.24 ± 221)	0.415[m]
Total cholesterol (mg/dl)	200.4 ± 42.5	192.5 ± 60.7	0.790[m]
(mmol/l)	(5.19 ± 1.10)	(4.99 ± 1.57)	
LDL-C (mg/dl)	120.3 ± 38.0	129.1 ± 41.1	0.360[m]
(mmol/l)	(3.12 ± 0.98)	(3.34 ± 1.06)	
Triglycerides (mg/dl)	160.8 ± 80.4	143.9 ± 71.2	0.305[m]
(mmol/l)	(1.82 ± 0.91)	(1.63 ± 0.80)	
hs-CRP (mg/dl)	1.8 ± 1.5	3.2 ± 6.5	0.461[m]
Fibrinogen (mg/dl)	305.8 ± 36.5	307.2 ± 76.8	0.554[m]
WBC (× 10^3)	8.1 ± 2.2	7.6 ± 1.8	0.158[m]
HDL-C (mg/dl)	47.1 ± 11.8	43.5 ± 9	0.109[t]
(mmol/l)	(1.22 ± 0.31)	(1.13 ± 0.23)	
HbA_{1c} (%)	6.0 ± 1.1	6.1 ± 0.9	0.044[m]
Galectin-3 (ng/ml)	17.8 ±7.3	23.9 ±7.1	0.000[t]

[t]: *t*-test; [m]: Mann–Whitney *U*-test; *chi-squared test (Fisher's exact test).
SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell count; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin.

group. There was no significant difference in age, gender, systolic arterial pressure, diastolic arterial pressure, body mass index, hypertension, hyperlipidaemia, cigarette and alcohol use and family history between the groups ($p > 0.05$). However, median glycated haemoglobin (HbA_{1c}) and Gal-3 levels were significantly higher in patients with isolated CAE compared to the controls ($p < 0.05$). Demographic, clinical and laboratory characteristics of the study population are shown in Table 1.

Table 2 shows frequency of distribution of ectatic coronary arteries and the Markis classification in isolated CAE patients. Ectasia occurred most frequently in the left anterior descending artery (32%), followed by the circumflex artery (30%), right coronary artery (26%) and left main coronary artery (15%). Type 4 was the most common type of ectasia according to the Markis classification in 36% of patients. Median Gal-3 levels were significantly higher in isolated CAE patients than in the controls [23.2 (23.9 ± 7.1) vs 16.8 ng/ml (17.8 ± 7.3); $p < 0.001$) (Table 1, Fig. 1).

In patients with isolated CAE, there was no significant association between Gal-3 levels and Markis classification or the number of involved vessels ($p = 0.41$ and 0.093, respectively; Table 3). In univariate analysis, natural log (ln) Gal-3 was found to

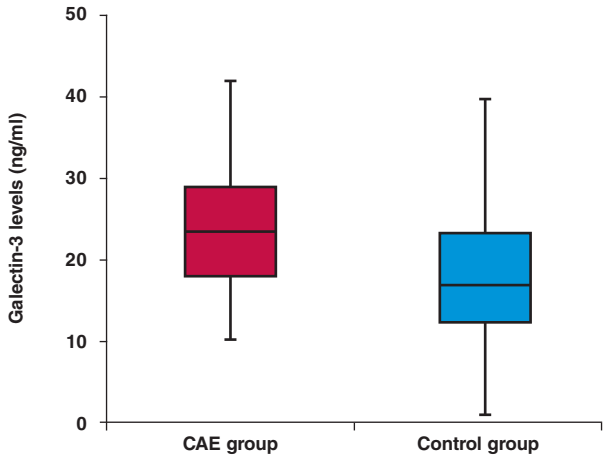

Fig. 1. Comparison of galectin-3 levels of patients with CAE and the control group ($p < 0.001$). CAE, coronary artery ectasia.

have a significant impact for differentiating controls and patients ($p < 0.05$). Multivariate logistic regression analysis demonstrated that concentrations of ln Gal-3 were an independent predictor of isolated CAE (Table 4). In ROC curve analysis, area under the curve was 0.692 (0.581–0.803) for 16 ng/ml serum Gal-3 cut-off value (91.8% sensitivity and 46.5% specificity) ($p < 0.05$) (Fig. 2).

Discussion

In this study, we investigated the relationship between serum Gal-3 levels and isolated CAE. Our results showed significantly increased Gal-3 levels as a novel cardiac biomarker among isolated CAE patients, compared to controls. However, there was no significant association between serum Gal-3 levels and the extent of isolated CAE.

Despite uncertainties regarding the pathophysiological mechanisms of CAE, the frequent occurrence of concurrent CAD and the presence of atheromatous ulcerations in ectatic segments suggest an important role for atherosclerosis in the development of CAE.[19] Degeneration in the media layer of the coronary artery, a common denominator of all conditions resulting in coronary ectasia, has been reported to be associated with advanced atherosclerosis.[7,20]

Table 2. Distribution frequency of CAE and Markis classification

	Number	*Percent*
CAE		
LMCA	15	30.6
LAD	32	65.3
Cx	30	61.2
RCA	26	53.1
Markis classification		
Type I	16	32.7
Type II	9	18.4
Type III	6	12.2
Type IV	18	36.7

CAE, coronary artery ectasia; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; RCA, right coronary artery.

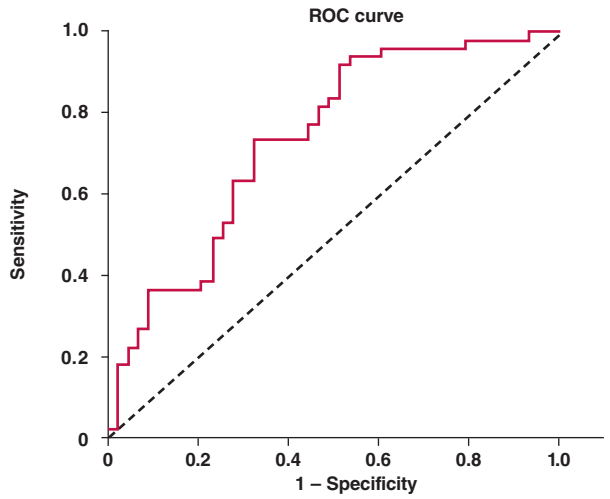

Fig. 2. Receiver operating characteristic (ROC) curve analysis of serum galectin-3 levels in predicting CAE. CAE, coronary artery ectasia.

Atherosclerosis typically presents itself as a narrowing of the vessel lumen. However, post mortem and intravascular ultrasound (IVUS) studies have demonstrated that atherosclerotic plaque may also advance into the medial layer and external elastic membrane (EEM) without a marked narrowing in the vessel lumen, indicating that the vessel wall may react to atherosclerosis in two different ways.[21] While negative remodelling results in reduced vessel lumen diameter, positive remodelling is associated with the propagation of plaque towards the EEM. The latter may result in dilation without significant lumen narrowing and obstructive CAD.[22]

Formation of foam cells is directly linked to the weakened connective tissue of the arterial wall. Macrophages secrete elastase in response to endocytosis of modified LDL-C. Weakening of the coronary artery, particularly caused by protease activity, may lead to positive remodelling.[23,24] It has been proposed that CAE may represent an exaggeration of positive remodelling. Other studies examining the pathogenesis of CAE have shown that endothelial injury due to atherosclerosis may lead to degeneration in the media layer of the vessel via activation of macrophages and inflammatory mediators such as metalloproteins and that these structural changes may result in segmental vessel dilation through the release of nitric oxide and other vasodilator agents from the endothelium.[25] In a post mortem case report by Markis *et al.*,[26] diffuse hyalinisation, fatty accumulation, disrupted intima and media layers, focal calcification and fibrosis, cholesterol crystals and intramural haemorrhage were found, while CAE was not present in areas where the media layer was grossly intact.

Gal-3 belongs to the family of soluble β-galactoside-binding lectins. Although Gal-3 is primarily released by activated macrophages, it can be also synthesised by T-lymphocytes, endothelial cells and fibroblasts.[8,9] Gal-3 also plays a role in the conversion of monocytes to macrophages and macrophages to foam cells. It has been found to be expressed in foam cells and macrophages in atherosclerotic lesions.[14,27,28] It also enhances entry of this cell into the arterial wall, resulting in intracellular cholesterol deposition through augmentation of the internalisation of advanced glycation end-products and endocytotic uptake of modified lipoproteins.[29,30] Furthermore, Gal-3 aggravates vascular inflammation, leading to the expression of a series of chemokines and other pro-inflammatory molecules from macrophages.[31]

In addition, an important process that contributes to plaque instability and the progression of atherosclerotic lesions is the phenotypic switch of VSMCs from a differentiated state to a de-differentiated state. *In vitro* experiments have shown that Gal-3 plays a role in the phenotypic switch of VSMCs.[32] Due to the aforementioned mechanisms, Gal-3 is recommended as a biomarker for the progression and imbalance of atherosclerotic plaques.[33,34]

The impact of Gal-3 on both atherosclerotic plaque formation and destabilisation has been confirmed in several studies.[28,35,36] In one study, MacKinnon *et al.*[16] reported that pharmacological inhibition of Gal-3 in a well-characterised mouse model of atherosclerosis reduced plaque development. In another study, Tsai *et al.*[37] found a significant increase in serum Gal-3 levels in patients with ST-segment elevation myocardial infarction (STEMI). In addition, patients with STEMI undergoing primary percutaneous coronary intervention had higher Gal-3 levels compared to healthy controls, and Gal-3 levels were found to have a predictive value for major adverse cardiac events on day 30. Furthermore, Falcone *et al.*[38] found higher serum Gal-3 levels in patients with unstable angina pectoris compared to those with stable angina pectoris, with a significant correlation between Gal-3 levels and the number of diseased vessels.

In another study, type 2 diabetes mellitus patients were found to have higher Gal-3 levels compared to type 2 diabetics without CAD. The authors also found a significant correlation between serum Gal-3 levels and the total number of diseased vessels and plaques, as well as the type of calcified plaques.[39] A cross-

Table 3. Galectin-3 levels according to the number of affected ectatic arteries and Markis classification

	Galectin-3			
	Mean ± SD	*Median*	*Min–Max*	p-*value*
1-vessel disease	25.6 ± 7.3	23.9	15–42	0.093[k]
2-vessel disease	25.4 ± 7.2	25.1	18–39	
3-vessel disease	19.5 ± 6.4	18.2	10–34	
4-vessel disease	24.3 ± 4.4	25.0	18–31	
Markis classification				
Type I	22.4 ± 5.5	22.7	12–34	0.418[k]
Type II	25.4 ± 5.8	23.9	18–34	
Type III	28.7 ± 10.5	33.3	15–39	
Type IV	22.9 ± 7.3	21.8	10–42	

[k]Kruskal–Wallis test, SD: standard deviation.

Table 4. Variables associated with CAE according to univariate and multivariate logistic regression analysis

	Univariate model			*Multivariate model*		
	OR	*95% CI*	p-*value*	*OR*	*95% CI*	p-*value*
Ln age	1.05	1.00–1.11	0.061			
Ln gender	2.18	0.94–5.02	0.069			
Ln HbA_{1c}[a]	1.13	0.74–1.74	0.566			
Ln Gal-3[a]	1.13	1.06–1.21	0.000	1.12	1.03–1.21	0.005

[a]ORs for continuous variables are expressed in per one standard deviation change in the natural log-transformed variables; Ln, natural log; CI, confidence interval; OR, odds ratio; HbA_{1c}, glycated haemoglobin; Gal-3, galectin-3.

sectional study also demonstrated higher plasma Gal-3 levels in patients with carotid atherosclerosis than in those without.[33] These findings indicate the role of Gal-3 in atherosclerotic plaque instability, macrophage activation and increased monocyte recruitment. Furthermore, studies involving long-term follow up have suggested that Gal-3 levels may represent an independent predictor of cardiovascular events and mortality in patients with CAD.[40] Finally Gal-3 plays a key role in vascular inflammation and fibrosis induced by aldosterone.[8]

In light of these data, it appears reasonable to assume a cause-and-effect relationship between elevated serum Gal-3 levels in isolated CAE patients and the development of ectasia through weakening of the arterial wall as a result of a number of mechanisms including atherosclerosis, vascular inflammation and oxidative stress.

Furthermore, in our study, patients with isolated CAE were further classified into four groups based on the extent of ectasia. Serum Gal-3 levels did not differ significantly among these four groups, suggesting that Gal-3 may be associated with the atherosclerotic process rather than the severity of ectasia. However, the number of patients in each subgroup was too low to draw a firm conclusion. Considering several studies examining the physiopathology of CAE and showing a more intense inflammatory process compared to those with CAD, similar fibrinogen and hs-CRP levels in our study as biomarkers of inflammation may be explained on the basis of a subtler inflammatory process.

There are some limitations to this study. Its small sample size and single-centre design are the main limitations. Another limitation involves the fact that normal coronary arteries were defined on the basis of contrast angiography of the lumen without using IVUS. Therefore, the presence of underlying atherosclerotic plaques might have been overlooked. In addition, normal epicardial arteries in the control group were not able to be evaluated for vasospasm or microvascular dysfunction with an independent method, which can be deemed another limitation.

Conclusion

This study is the first to show a significant increase in serum Gal-3 levels in patients with isolated CAE, indicating that Gal-3 may play a role in the pathogenesis of CAE, similar to CAD. Based on our study results, we suggest that increased Gal-3 levels may affect coronary remodelling in a way that favours the development of ectasia. However, further studies at a cellular level in larger series are warranted to gain a better understanding of the role of Gal-3 in patients with isolated CAE.

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Review Article

Treatment of atrial fibrillation: a comprehensive review and practice guide

Jianhua Li, Mei Gao, Minwei Zhang, Donglu Liu, Zhan Li, Juanjuan Du, Yinglong Hou

Abstract

Atrial fibrillation (AF) is an ectopic rhythm originating in the atrium. AF is the most common sustained cardiac arrhythmia in clinical practice and it is an enormous burden worldwide because of the high rates of morbidity, disability and mortality. Treatment of AF has become a hot spot in the field of cardiovascular medicine. Recently, increasing evidence and advancements in medical technology have helped us gain a better understanding of AF. As a result, management of AF has evolved in the past few years, so that we can better prevent and control AF. Current therapy for AF mainly includes drug therapy, catheter ablation, cryoballoon ablation, left atrial appendage closure and the maze procedure. The goal of this article is to update current treatment options for AF. We hope that this article will help deliver good care to AF patients based on the current state-of-the-art evidence.

Keywords: atrial fibrillation, drug therapy, catheter ablation, cryoballoon ablation, left atrial appendage closure, maze procedure

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Atrial fibrillation (AF) is an ectopic rhythm originating in the atrium. An electrocardiogram (ECG) of AF shows the normal sinus P waves are replaced by f waves (350 to 600 beats per min) and the ventricular rate is often irregular, which is characterised by an uneven R-R interval.[1,2] The prevalence of AF is higher in men than in women and it has increased rapidly due to the ageing population.[3,4] AF is associated with an increased risk of stroke,[5] heart failure,[6] myocardial infarction[7] and chronic kidney disease,[8] which increases the burden on healthcare systems around the world. Treatment of AF has become a huge challenge in the field of cardiovascular diseases.

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Risk factors and upstream treatment of AF

Previous studies have confirmed that initiation and maintenance of AF result from atrial remodelling, including electrical and structural remodelling, atrial energy metabolic remodelling and autonomic neural remodelling,[9-11] which are associated with a variety of risk factors,[2,12] such as valvular diseases, hypertension, ischaemic heart diseases, heart failure, hyperthyroidism, lung diseases, diabetes, obstructive sleep apnoea syndrome and atrial fibrosis. In addition, obesity, smoking, alcohol abuse and negative emotions (anger, stress, impatience and anxiety) are also risk factors for AF. Potential reversible causes of AF should be identified and treated where possible. Identification, prevention and proper management of these risk factors could effectively reduce the incidence of AF.

Upstream therapy refers to the use of non-anti-arrhythmic drugs that target the mechanisms of AF to prevent or reduce the occurrence of AF.[13] Recent research has highlighted the beneficial effects of lifestyle and risk-factor management for AF as upstream therapy. Treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) will delay or even reverse atrial remodelling of individuals with hypertension or left ventricular dysfunction, resulting in a reduction in new-onset AF.[14] Patients with cardiac surgery will achieve clinical benefits from preventing the occurrence of AF by using statins.[15] Long-chain 3-polyunsaturated fatty acids (n-3 PUFA) are considered to be able to prevent AF because of their multiple effects on cardiac electrophysiology, such as membrane stabilisation in the myocardial cell, and antifibrotic, anti-inflammatory and antioxidant characteristics, which may influence the mechanisms involved in the initiation and maintenance of AF.[16]

Prevention or treatment of AF-related risk factors and upstream treatment can effectively reduce the prevalence of AF and hospital admissions of AF patients.

Drug therapy for AF

The three major drug treatment strategies for AF are rhythm control, rate control and prevention of stroke. A guiding principle of therapy is to eliminate reversible conditions, such as hyperthyroidism or alcohol consumption, before treatment.

Table 1. Anti-arrhythmic drugs for the maintenance of sinus rhythm

Drug	*Route*	*Typical dose*	*Contra-indications*	*References*
Flecainide	Oral	50–150 mg, BID	Ischaemic or structural heart disease; sinus node dysfunction, second- or third-degree atrioventricular block or bundle branch disease without a pacemaker	20, 21
	IV	1.5–2.0 mg/ kg, over 10 min		
Propafenone	Oral	150–300 mg, TID	Ischaemic or structural heart disease; asthma; sinus node dysfunction, second- or third-degree atrioventricular block or bundle branch disease without a pacemaker	20, 21
	IV	1.5–2.0 mg/ kg, over 10 min		
Sotalol	Oral	80–160 mg, BID	Asthma; creatinine clearance < 40 ml/min; left ventricular dysfunction; QTc > 450 ms; sinus bradycardia < 50 bpm, second- or third-degree atrioventricular block without a pacemaker	20
Amiodarone	Oral	200 mg, TID for 1 week; 200 mg, BID for 1 week; then maintenance dose of 200 mg QD	Avoid in those with advanced lung disease, severe hepatic impairment, thyroid dysfunction	21
	IV	5.0–7.0 mg/kg		
Ibutilide	IV	1.0 mg over 10 min, the same dose after waiting for 10 min	Avoid in patients with QT prolongation, hypokalaemia, severe left ventricular hypertrophy or low ejection fraction	21
Dronedarone	Oral	400 mg, BID	Permanent atrial fibrillation; severe heart failure (NYHA class III–IV); QTc > 500 ms; severe hepatic impairment	17, 20

QD, once daily; BID, twice daily; TID, three times a day; IV, intravenous.

Rhythm-control therapy in AF

Maintenance of sinus rhythm is the primary goal, especially for patients younger than 65 years with severe symptoms or first-diagnosed AF.[17,18] For these individuals, restoration and maintenance of sinus rhythm may alleviate symptoms and improve the quality of life. Selection of the anti-arrhythmic drug for maintenance of sinus rhythm is based on the drug's safety and efficacy. Generally, class Ic and IIIc anti-arrhythmic drugs are mainly used for maintenance of sinus rhythm (Table 1).

Class Ic treatment with flecainide or propafenone is often preferred, which exerts its effects by blocking sodium channels to reduce the rate of rise of the action potential and reduce excitation of the cardiac tissue. Class Ic drugs are recommended for paroxysmal AF, but their use is contra-indicated for AF patients with underlying structural heart diseases due to increased risk of ventricular arrhythmias and atrial flutter.[19]

Class IIIc treatment with sotalol, amiodarone, ibutilide or dofetilide is often preferred, which exerts its effects by potassium channel blockade and prolonging action potential duration to delay conduction. Class IIIc drugs are recommended for persistent AF, and also benefit AF patients with structural heart diseases.[19,20]

For patients with infrequent episodes of AF (less than one per month), oral flecainide or propafenone can be self-administered by the patient at home ('pill in the pocket' therapy). In those patients with frequent episodes of AF, daily maintenance anti-arrhythmic drug therapy with propafenone, flecainide or sotalol is preferred as first line. Amiodarone is used for those patients with low left ventricular ejection fraction (LVEF) ischaemic heart disease. Interventional therapies or surgical treatments should be taken into consideration when anti-arrhythmic drugs are contra-indicated, have been ineffective, or cannot be tolerated.[18]

Rate-control therapy in AF

Rate-control therapy has been demonstrated to improve symptoms and reduce hospital admissions, which benefit patients older than 65 years with minimal symptoms.[17,19] According to the latest European Society of Cardiology (ESC) guidelines for the management of AF,[21] AF patients should target a resting heart rate of < 110 beats per minute (bpm); it can be reduced to 80 to 100 bpm if symptoms call for stricter rate control. Commonly used drugs to control ventricular rate are β-adrenergic receptor

Table 2. Drugs for rate control

Drug	*Route*	*Typical dose*	*Contra-indications*	*References*
β-blockers				
Metoprolol (tartrate)	Oral	25–100 mg, BID	Acute pulmonary oedema, heart failure, asthma, severe atrioventricular block and severely depressed patients	17, 28
Metoprolol (succinate)	Oral	50–400 mg, QD		
Bisoprolol	Oral	2.5–10 mg, QD		
Atenolol	Oral	25–100 mg, QD		
ND-CCBs				
Diltiazem	Oral	120–360 mg QD	Severe hypotension, cardiogenic shock, second- or third-degree atrioventricular block or sick sinus syndrome without a pacemaker, patients with left ventricular systolic dysfunction and decompensated heart failure owing to their negative inotropic effects	17, 21, 28
	IV	0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h		
Verapamil	Oral	120–480 mg QD		
	IV	(0.075–0.15 mg/kg) IV bolus over 2 min, then 0.005 mg/kg/min infusion		
Digitalis glycosides				
Digoxin	Oral	0.125–0.25 mg QD	Ventricular tachycardia, hypertrophic obstructive cardiomyopathy and pre-excitation syndrome combined with AF	17, 21, 28
	IV	0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h		
Specific indications				
Amiodarone	Oral	100–200 mg QD	Severe sinus node dysfunction, second- or third-degree atrioventricular block or bundle branch disease, syncope caused by bradycardia and diffuse interstitial pulmonary fibrosis	21, 28
	IV	300 mg IV over 1 h, then 10–50 mg/h over 24 h		

QD, once daily; BID, twice daily; IV, intravenous.

blockers (β-blockers), non-dihydropyridine calcium channel blockers (ND-CCBs), digitalis and amiodarone (Table 2).

The choice of these drugs should be based on individual characteristics and a patient's preferences. β-blockers are the preferred first-line agents for rate control during AF owing to the efficacy (lower heart rates) as well as potential survival advantage.[18] The most commonly used β-blockers are metoprolol, bisoprolol and atenolol. Contra-indications should be considered before we use β-blockers; briefly, acute pulmonary oedema, heart failure, asthma, severe atrioventricular block and severely depressed patients cannot choose β-blockers.

Commonly used ND-CCBs include diltiazem and verapamil, which are recommended for AF combined with chronic obstructive pulmonary disease or asthma. Digitalis can slow ventricular rate through increasing vagus nerve tension, so it is a reasonable alternative for those patients in whom other treatments are ineffective or contra-indicated, especially in heart failure and hypotension. Amiodarone can reduce ventricular rate due to its short-term effect in blocking calcium channels and the sympathetic nervous system, but it is not used for long-term ventricular rate control. Amiodarone can be useful for rate control when other drugs are ineffective or contra-indicated and for acute symptoms.

The latest ESC guidelines[21] use LVEF = 40% as the dividing line. Patients with LVEF ≥ 40% can use β-blockers, ND-CCBs and digitalis to control ventricular rate (Class I, level of evidence B), while β-blockers should start from a low dose for patients with LVEF < 40%, and ND-CCBs should be avoided (Class I, level of evidence B).

Prevention of stroke

Patients with AF are five times more likely to have a stroke,[22] which has long attracted the attention of clinicians. Besides, cognitive impairment, silent cerebral infarcts, memory impairment, hippocampal atrophy, Alzheimer's disease and other forms of dementia have been demonstrated at a higher prevalence in AF compared with non-AF.[23]

Anticoagulant therapy is highly recommended in preventing strokes for AF patients. CHA_2DS_2-VASc (Table 3) and HAS-BLED (Table 4) scoring systems are recommended to be used before anticoagulant therapy. There is strong evidence that patients with a CHA_2DS_2-VASc risk score of two or more in men, and three or more in women, benefit from oral anticoagulants (Class I, level of evidence A). Oral anticoagulants should be considered for men with a CHA_2DS_2-VASc score of one and women with a score of two, balancing the expected stroke reduction, bleeding risk, and patient preference (Class IIa, level of evidence B). No antiplatelet or anticoagulant therapy is recommended for men with a CHA_2DS_2-VASc score of zero and women with a score of one (Class III, level of evidence B).[21]

Low bleeding risk refers to a HAS-BLED score of two or less, while a score of three or more puts the patient at high bleeding risk. HAS-BLED score is a tool for clinicians to objectively assess the risk of bleeding in AF patients, aiming to treat reversible risk factors, especially for high-risk bleeding patients. Choices of anticoagulant drugs are new oral anticoagulants (NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban) and oral anticoagulants (OACs, such as warfarin).

According to the latest ESC guidelines,[21] NOACs are the preferred therapy unless contra-indications exist in patients, and OACs are secondary choices (Class I, level of evidence A). A meta-analysis[24] of NOACs versus warfarin included 42 411 participants receiving NOACs and 29 272 participants receiving warfarin. It demonstrated that NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; $p < 0.0001$). NOACs also reduced all-cause mortality by 10% (0.90, 0.85–0.95; $p < 0.0001$), while gastrointestinal bleeding events were more frequent (1.25, 1.01–1.55; $p = 0.04$). NOACs had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage and mortality rates, and with similar major bleeding events to warfarin. The efficacy and safety of NOACs over warfarin seem to be even greater in East Asians compared with non-Asians.[25] But in the latest ESC guidelines,[21] warfarin is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves (Class I, level of evidence B).

Combinations of OACs and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition (Class III, level of evidence B). Aspirin is neither effective nor safe as thromboprophylaxis for AF patients, even possibly increasing stroke risk in elderly patients.[26,27] During anticoagulant therapy, monitoring the coagulation function is necessary to ensure the efficacy and safety of anticoagulants.

Direct-current cardioversion (DCC)

DCC is an effective therapy for AF patients or AF with rapid ventricular response to restore sinus rhythm. If unsuccessful, repeat DCC attempts should be made after applying pressure over the electrodes or adjusting the location of the electrodes or combining with anti-arrhythmic drugs.[28] DCC is recommended for AF patients who do not respond to pharmacological therapies, combined with heart failure or haemodynamic instability.[21,28] A study of the effect of early DCC on the recurrence of AF

Table 3. CHA_2DS_2-VASc scoring system

Risk factor	*Score*
Chronic heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Previous stroke/transient ischaemic attack	2
Vascular disease	1
Age 65–74 years	1
Gender category (female)	1

Table 4. HAS-BLED scoring system

Risk factor	*Score*
Hypertension	1
Abnormal renal function	1
Abnormal liver function	1
Stroke	1
Bleeding history or predisposition	1
Labile INR	1
Elderly (> 65 years)	1
Drugs concomitantly	1
Alcohol concomitantly	1

demonstrated that patients with persistent AF for less than 60 days who received early DCC had a significant reduction in AF recurrence risk, while in those with persistent AF for more than 60 days, there was no benefit of early DCC.[29]

Conversion of AF to sinus rhythm is associated with an increased risk of stroke. Two strategies of anticoagulation are available for reducing thromboembolic risk. The first is warfarin for three weeks prior to DCC and continues for four weeks after cardioversion. The second is transoesophageal echocardiography and combination treatment with an anticoagulant using heparin, enoxaparin or one of the NOACs immediately before DCC and followed by warfarin or NOACs for four weeks after cardioversion.

Radiofrequency catheter ablation (RFCA)

An important mechanism of AF is abnormal electrical activity surrounding the vestibule of the pulmonary veins (PVs). RFCA is primarily a treatment outcome achieved through isolation of the PVs. A long-term follow up showed the rate of freedom from atrial arrhythmia with a single procedure was 54.1% in paroxysmal AF patients and 41.8% in patients with non-paroxysmal AF. With multiple procedures, the long-term success rate improved to 79.8%.[30] Collective data from a number of randomised clinical trials had demonstrated the superiority of RFCA over drug therapies in maintaining sinus rhythm, reducing cardiovascular events, and improving quality of life.[31,32]

RFCA is highly recommended for symptomatic paroxysmal AF patients aiming to prevent recurrent AF and improve symptoms, especially when anti-arrhythmic drug therapy is unsuccessful. It is also a reasonable alternative for those symptomatic AF patients with heart failure, low ejection fraction or AF-related bradycardia.

A worldwide survey of 85 institutions indicated a 4.5% rate of major complications of RFCA. Specifically, the rate of procedure-related deaths was 0.15%, stroke or transient ischaemic attack were 0.94%, cardiac tamponade was 1.31% and atrial–oesophageal fistula was 0.04%.[33] RFCA is a therapy that highly depends on clinicians' experience and skill, which are related to the success rate and incidence of complications. Individual characteristics, patient preferences, as well as experience and skill of the clinician should be taken into consideration before making a decision.

Cryoballoon ablation

Catheter ablation using technical requirements with three-dimensional mapping systems with a point-by-point ablation strategy is time-consuming, and clinical outcomes and complications depend on the operator's experience and skill. To overcome these limitations, cryoballoon ablation was developed.[34] As a single-shot device, cryoballoon ablation markedly simplifies the ablation procedure and shortens the procedure time.[35]

Cryoablation systems work by delivering liquid nitrous oxide under pressure through the catheter to its tip or within the balloon, where it changes to gas, resulting in cooling and damage to the surrounding tissue, thus resulting in a reduction in the risk of AF.[36] A first-generation cryoballoon (CB-1) was released in 2010 and the more developed second-generation cryoballoon (CB-2) was developed in 2012. The one-year success rate of CB-2 was improved from CB-1, and the complication rates decreased in the former.[36]

Data from recent studies have demonstrated the clinical benefit of cryoballoon ablation for paroxysmal AF patients.[35,37] It is a promising, effective and safe alternative technique for paroxysmal AF patients. However, cryoablation is specially designed for dissection of the pulmonary artery. Pulmonary vein isolation is the cornerstone of cryoablation and other treatments should be considered for AF that does not originate in the pulmonary veins.

Left atrial appendage closure (LAAC)

Studies have shown that 91% of strokes occur in the left atrial appendage of non-rheumatic AF patients and 57% in rheumatic AF patients.[38] This understanding has prompted the development of novel percutaneous strategies for LAAC as an alternative to anticoagulation therapy for AF patients. Briefly, LAAC is recommended for elderly patients and those who can tolerate short-term anticoagulation but are not optimal candidates for long-term anticoagulation.[39]

A meta-analysis that compared LAAC with warfarin for stroke prevention in AF included 2 406 patients with a mean follow up of 2.69 years. It found that Watchman LAAC had significantly fewer haemorrhagic strokes and better clinical outcomes compared with warfarin therapy.[40] A network meta-analysis found that Watchman LAAC and NOAC therapy were both superior to warfarin for preventing haemorrhagic strokes, and that there were no significant differences in clinical outcomes between Watchman LAAC and NOACs.[41] According to the latest ESC guidelines, LAAC is a good alternative for AF patients with contra-indications to OAC (Class IIB, level of evidence B).

Surgical management

The Cox maze I procedure, introduced by James Cox in 1987, interrupted the aberrant re-entrant circuits in the atrium by 'cutting and sewing'. After iterative improvements, Cox maze I was modified into the Cox maze III procedure.[42] But the Cox maze III did not gain widespread acceptance due to its complexity and technical demand. It is mainly used in AF patients undergoing open-heart surgical procedures. Development in technology led to shortening and simplification of the operation to the Cox maze IV, which utilises new ablation technologies to replace the 'cut-and-sew' technique, and has decreased morbidity and mortality rates.[43] Cox maze IV is currently the gold-standard surgical treatment for AF, with a 93% freedom from AF at one year, and a 78% freedom from AF at five years.[44]

The totally thoracoscopic maze procedure (TT-maze) was developed in 2003. It was a minimally invasive alternative for treating AF with limited complications and high success rates.[45] Future studies are needed to determine whether the high success rates after TT-maze are stable over time.

Conclusions

Management of AF has evolved greatly in the past few years and there have been substantial advances and developments, which help clinicians to deliver better care to AF patients (Fig. 1). Treatment of AF is an individual therapy and the characteristics

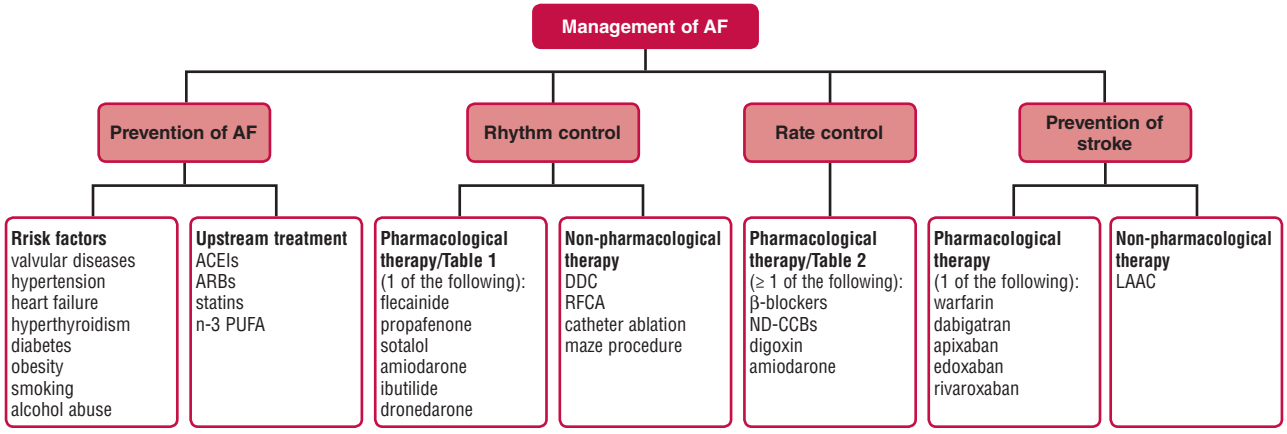

Fig. 1. Overview of management of AF.

and willingness of patients, as well as the experience and skill of the clinician should be taken into consideration before making a decision.

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J Li, M Gao, M Zhang and D Liu contributed equally to the work.

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Perspective

The acute coronary syndrome revisited: effects and therapeutic modulation of excess metabolic fuel supply

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Our proposal is that that metabolic perturbations occurring during and after the onset of the acute coronary syndrome (ACS) require careful management from the moment patients with this diagnosis are admitted to the intensive care unit (ICU). We advocate that insulin treatment should be initiated when blood glucose levels rise to above 11 mM (or 200 mg/dl), thereby providing additional therapeutic benefits. The reasons are as follows.

Metabolic substrate alterations in ACS

Physiologically the heart relies on a mixture of exogenously supplied substrates (predominantly long-chain fatty acids) for ATP production and for muscle contraction. The main source for the heart's high demand for ATP is oxidative phosphorylation of ADP in the respiratory chain. Metabolism of energy-providing substrates produces the reducing equivalents for the proton gradient across the inner mitochondrial membrane. The collapse of this proton gradient transfers energy to ATP.

Neurohumoral stress alters substrate supply and utilisation in the heart

Increased sympathetic nervous system (SNS) activation during the ACS triggers the stimulation of sympathetic fibres within the myocardium, leading to greater norepinephrine/epinephrine discharge. This 'fight or flight' response has profound metabolic consequences. The adrenal medulla simultaneously releases epinephrine that suppresses pancreatic β-cell insulin secretion and in parallel elevates hepatic gluconeogenesis and myocardial glycogenolysis. In addition, higher SNS activation enhances cortisol production (adrenal cortex) that results in downstream stimulation of hepatic gluconeogenesis. Therefore high circulating catecholamine levels associated with the ACS elicit a robust increase in both blood free fatty acids (FFA) and glucose concentrations and a concomitant decrease in insulin levels that may persist for several hours, resulting in detrimental effects on the ischaemic heart.

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Damaging effects of high FFA levels

The concept that high circulating plasma FFA damage the ischaemic myocardium is well established. For example, isolated hearts perfused with high FFA levels display abnormal contractility and heart rhythm,[1] and also increased myocardial oxygen uptake. This effect can be explained by FFA-mediated uncoupling of mitochondrial respiration, leading to oxygen 'wastage' and attenuated ATP production.[2-4] Excess FFA availability and myocardial uptake also influences glucose–fatty acid interactions, whereby elevated β-oxidation of fatty acids lowers mitochondrial glucose utilisation (at the pyruvate dehydrogenase step), and, to a lesser extent, attenuates glucose uptake. Such FFA-induced metabolic abnormalities can be lessened by the promotion of glucose metabolism when both glucose and insulin are added to the perfusate (see Fig. 1).[5] These observations are particularly relevant to the heart in diabetes, which is already exposed to high systemic FFA and glucose levels.

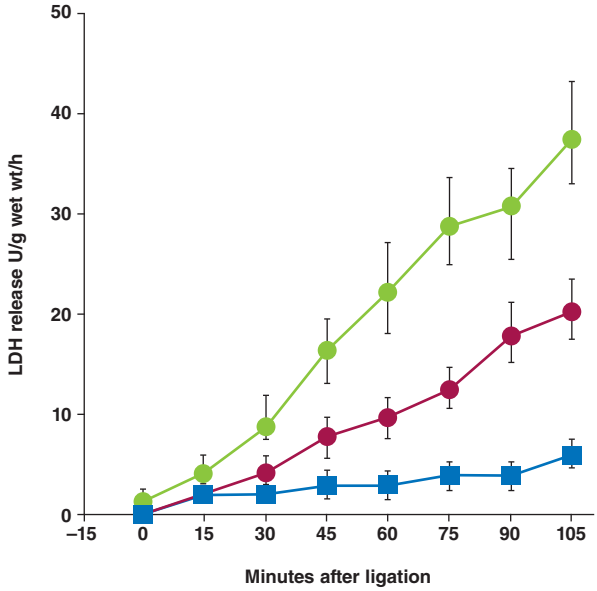

Fig. 1. In experimental regional ischaemia, the addition of high free fatty acids (FFA) (as 5:1 molar ratio for palmitate:albumin) increased enzymatic release as lactate dehydrogenase (LDH) release (top line) versus lower FFA (palmitate:albumin ratio of 1:1) (middle line).[5] This release indicated the extent of tissue damage, which was reduced by added glucose and/or insulin ($p < 0.004$) (bottom line).

Consequences of elevated blood glucose levels

ACS-induced hyperglycaemia is associated with increased risk for in-hospital deaths, congestive heart failure and cardiogenic shock.[6] The relative risk of in-hospital deaths for non-diabetic ACS hyperglycaemic patients [admission blood glucose ≥ 110 mg/dl (6.11 mmol/l)] is several fold higher versus matched normoglycaemic counterparts.[6] This hyperglycaemia in non-diabetic individuals is likely a combination of three factors: previously undiagnosed diabetes, impaired glucose tolerance and the acute stress response.

Whether elevated glucose levels are markers or direct mediators of damaging outcomes following an acute myocardial infarction (AMI) remains unresolved, although pre-clinical and clinical data suggest harmful effects. For example, clinical trials and epidemiological studies support a causative role because intensive glycaemic control with insulin lowers the incidence of cardiovascular complications.[7] High blood glucose availability may also lead to 'glucotoxic' effects in cardiac endothelial cells, to a much greater extent than in cardiomyocytes where increased uptake is more dependent on the insulin-responsive glucose transporter, GLUT-4. However, enhanced glycolytic flux also has potential benefits: first, the membrane protection afforded by increased flux and production of glycolytic ATP, and, second, the enhanced oxidation of pyruvate with a decreased production of harmful protons.

Here we propose that glucose–fatty acid interactions in the ischaemic heart (FFA-induced lowering of glucose metabolism) would not be restricted to only cardiomyocytes in this instance. In support of this hypothesis, hyperglycaemia is associated with impaired microvascular function, leukocyte capillary plugging, enhanced platelet activation, larger infarct sizes and worse functional recovery in AMI patients.[7] Key molecular mechanisms whereby hyperglycaemia exerts such toxic effects include higher intracellular oxidative stress, downstream metabolic perturbations and activation of inflammatory pathways.

Clinical management

It is our viewpoint that one should routinely determine the metabolic status (FFA, glucose, insulin) of suspected and confirmed AMI patients (non-diabetic and diabetic) at the time of admission, and thereafter monitor this in the ICU (for example, to check for persistent hyperglycaemia). Which easily available metabolic therapeutic options would be most appropriate under such circumstances? The selection of a metabolically favourable β-blocker may be useful as in conjunction to its well-known effects on haemodynamic parameters, β-blockers also inhibit adipose lipolysis and limit subsequent FFA-mediated damaging effects.

Modulating blood glucose levels is another therapeutic option by employing the glucose–insulin–potassium (GIK) cocktail originally proposed by Sodi-Pallares in 1969.[8] Indeed, pharmacodynamic doses of insulin improve cardiac pump function without increasing myocardial oxygen consumption in acute ischaemic heart failure.[9] Lastly, FFA reduction and stimulation of glucose metabolism in the ischaemic myocardium by GIK treatment is able to blunt metabolic derangements.[7] However, such treatment must be initiated early, within the first hours of symptom onset, because the relatively weak benefit of most prior GIK studies is attributed to delayed infusion when the ischaemic heart has already undergone substantial damage.[10]

The major protective component of this cocktail is likely to be insulin, which is known to lower FFA mobilisation, to decrease circulating FFA levels and to promote glucose uptake, thereby alternating dangerously high circulating blood glucose levels. Insulin administration is also linked to additional cardioprotective actions, independent of its ability to lower systemic blood glucose levels.[7] Interestingly, when insulin was infused at doses high enough to overcome stress-induced insulin resistance, the subsequent lowering of FFA levels and restoration of normoglycaemia were associated with cardioprotection in patients undergoing coronary bypass grafting.[11] However, among patients with suspected ACS, out-of-hospital administration of intravenous GIK did not reduce progression to myocardial infarction.[12] This study requires independent confirmation.

We agree with the American Heart Association (AHA) that insulin treatment be initiated for ACS patients as soon as blood glucose levels exceed 180 mg/dl (10 mmol/l), regardless of prior diabetes history.[13] This option may easily be overlooked in ACS patients with no history of diabetes in the ICU. The AHA also recommends that ACS patients without diabetes should be further evaluated at the time of hospitalisation (fasting blood glucose and HbA_{1c} levels) to assess a persistent severity of metabolic derangements. However, clinicians must also be mindful of hypoglycaemia and the associated adverse prognosis with intensive insulin treatment, and frequent blood sugar testing is required.[14]

Conclusion

Metabolic dysregulation is a frequent and actionable event in ACS. Modulation of hyperglycaemia and increased circulatory FFA levels call for diverse pharmacological interventions. Additional studies and further refinement of current guidelines are needed.

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Significant financial stress associated with 13-fold higher odds of having a heart attack

Significant financial stress is associated with a 13-fold higher odds of having a heart attack, according to research presented at the 18th Annual Congress of the South African Heart Association.

'The role of psychosocial factors in causing disease is a neglected area of study in South Africa, perhaps because there are so many other pressing health challenges such as tuberculosis and HIV,' said lead author Dr Denishan Govender, associate lecturer, University of the Witwatersrand, Johannesburg.

'The INTERHEART study showed that psychosocial factors are independently associated with acute myocardial infarction (heart attack) in Africa but as far as we are aware there are no other published local data,' said last author Professor Pravin Manga, professor of cardiology, University of the Witwatersrand.

This study included 106 patients with acute myocardial infarction who presented to a large public hospital in Johannesburg. A control group of 106 patients without cardiac disease was matched for age, gender and race. All participants completed a questionnaire about depression, anxiety, stress, work stress and financial stress in the previous month. The Likert scale was used to grade the experience of each condition.

Regarding financial stress, patients were graded with no financial stress if they were coping financially; mild financial stress if they were coping financially but needed added support; moderate financial stress if they had an income but were in financial distress; and significant financial stress if they had no income and at times struggled to meet basic needs. Levels of psychosocial conditions were compared between groups and used to calculate associations with having a heart attack.

Self-reported stress levels were common, with 96% of heart attack patients reporting any level of stress, and 40% reporting severe stress levels. There was a three-fold increased risk of myocardial infarction if a patient had experienced any level of depression (from mild to extremely severe) in the previous month compared to those with no depression.

Both work stress and financial stress were associated with a higher risk of acute myocardial infarction. The odds of myocardial infarction was 5.6 times higher in patients with moderate or severe work stress compared to those with minimal or no stress. Patients with significant financial stress had a 13-fold higher odds of having a myocardial infarction.

Dr Govender said: 'Our study suggests that psychosocial aspects are important risk factors for acute myocardial infarction. Often patients are counselled about stress after a heart attack but there needs to be more emphasis prior to an event. Few doctors ask about stress, depression or anxiety during a general physical and this should become routine practice, like asking about smoking. Just as we provide advice on how to quit smoking, patients need information on how to fight stress.'

Professor Manga said: 'There is growing recognition that many developing countries are experiencing an increasing prevalence of chronic diseases of lifestyle such as myocardial infarction, and South Africa is no exception. Our study shows that psychosocial aspects are an area of cardiovascular prevention that deserves more attention.'

Dr David Jankelow, chairman of the SA Heart 2017 congress, commented: 'We know that the depressed cardiac patient is at greater risk. We as clinicians need to identify them much earlier, so that they can be referred for appropriate intervention. Cardiac rehabilitation together with counselling and reassurance will play an important role as well.'

Professor Fausto Pinto, ESC immediate past president and course director of the ESC programme in South Africa, said: 'Psychosocial factors including stress at work, depression and anxiety contribute to the risk of developing cardiovascular disease and having a worse prognosis. European prevention guidelines say that psychosocial risk-factor assessment should be considered in people with, or at high risk of, cardiovascular disease to identify possible barriers to lifestyle change or adherence to medication.'

Source: European Society of Cardiology Press Office

Cardiorhythm Africa 2020 report

The inaugural meeting of the Africa Heart Rhythm Association (AFHRA)

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Abstract

Cardiorhythm Africa, the inaugural conference of AFHRA, was conceived during the biennial PASCAR congress held in Johannesburg in November 2019, with the ambition to be the largest ever pan-African conference focused purely on arrhythmia. Significant aims were to (1) bring together arrhythmia specialists from across Africa and from the diaspora; and (2) announce the newly formed African Heart Rhythm Association (AFHRA), an affiliate organisation of PASCAR formed from the amalgamation of the Cardiac Pacing and Arrhythmias taskforces. The meeting held in Nairobi (29–31 January 2020) was organised to provide a focus on resource-constrained arrhythmia management within the African context and novel/advanced and potentially home-grown solutions. There was full representation from all five PASCAR regions (North, East, West, Central and Southern Africa). This report summarises the scope and perspective of the first Cardiorhythm Africa meeting and presents the future directions for this annual meeting.

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Cardiorhythm Africa, the inaugural conference of the African Heart Rhythm Association (AFHRA) was conceived during the biennial Pan-African Society of Cardiology (PASCAR) congress held in Johannesburg in November 2019 with the ambition of being the largest ever pan-African conference focused purely on arrhythmia. Significant aims were to (1) bring together arrhythmia specialists from across Africa and from the diaspora; and (2) announce the newly formed AFHRA, an affiliate organisation of PASCAR, formed from the amalgamation of the Cardiac Pacing and Arrhythmias taskforces.

Surveys conducted by PASCAR over the last decade have indicated a significant problem with access to expertise and technology in the field of arrhythmia care in Africa and an unmet gap in training.[1-3] The meeting programme was organised to provide a focus on resource-constrained arrhythmia

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management within the African context and novel/advanced and potentially home-grown solutions. Presentations at the conference were invited to focus on contemporary management of arrhythmias with emphasis on setting up and sustaining service provision in Africa. This report summarises the scope of the first annual Cardiorhythm Africa meeting held in Nairobi from 29–31 January 2020 and summarily presents the future directions.

Purpose of the meeting

The main scope of the first Cardiorhythm Africa meeting was to (1) raise the profile of cardiac arrhythmia in Africa and form an executive committee to advise and promote healthcare professional education as well as public awareness, (2) develop within African healthcare specialists a network to advance arrhythmia management along clinical, advocacy, research and training lines, (3) initiate a pan-African conversation on improving access to arrhythmia services involving clinicians, funders, industry partners and patients, (4) form a network to demonstrate expertise and referral opportunities within the region and appraise the existing skill and mentorship models that already exist within Africa, (5) provide a connection with the diaspora and specialists from other networks, including Europe and North America, and (6) engage with the specialists in a detailed survey on arrhythmia care among different African nations.

The scientific programme was organised in sessions, aligning with clinical syndromes related to conduction and/or arrhythmia, including (1) heart failure and device therapy, (2) heart block and bradycardia, (3) syncope and sudden cardiac death, (4) drugs and devices, (5) atrial fibrillation in Africa with a focus on rate versus rhythm control and stroke prevention, (6) ventricular arrhythmia, and (7) acute and long-term narrow-complex tachycardia. A session with shared African cases and abstracts allowed clinical discussions of common and unusual arrhythmia presentations from around Africa and beyond. The programme was completed with 'The big ECG challenge' a quiz organised by the Egyptian Cardiac Rhythm Association.

The programme narrative was delivered through case scenarios, live-in-box demonstrations and live cases, and allowed showcasing of technology that many were not aware was available in Africa. The scientific programme of the meeting sandwiched three sessions focusing on the critical initiatives of the newly birthed AFHRA. A detailed report of the AFHRA vision, mission, strategies, current activities and future directions is beyond the scope of this article and will be published separately.

Highlights from the scientific sessions

The scientific programme included 10 sessions with over 25 regional and international speakers covering a wide range of topics in cardiac pacing and electrophysiology. Highlights included (1) a live cardiac resynchronisation therapy (CRT-D) implant from Nairobi, Kenya, with tips and tricks on implantation, patient selection, responders and super-responders to optimal CRT; (2) optimising drug therapy in heart failure, including the role and place of novel agents such as sacubitril/valsartan and dapagliflozin, and (3) an overview of conventional pacing indications followed by a pre-recorded demonstration of His bundle pacing with clear guidance on how to insert a His bundle lead.

Also discussed were sudden cardiac death in Africa, challenges with making a diagnosis, challenges with risk stratification and the current lack of data. There was a demonstration on both transvenous and subcutaneous implantable cardioverter defibrillator (ICD) implantation, as well as guidance on selection of patients where this mode of treatment is indicated.

This was followed by an interactive live pre-recorded atrial fibrillation (AF) ablation case, presentation of complications of AF ablation and a heated discussion whether single-shot technologies to ablate AF could be safely employed by non-electrophysiologists. There was a presentation and discussion on the eagerly awaited INVICTUS trial (a randomised trial of rivaroxaban versus warfarin in patients with rheumatic AF), which may have important implications in the management of patients with rheumatic mitral valve disease in both AF and sinus rhythm. Simplified coagulation pathways were presented to assist clinicians in making decisions in the face of the expanding number of locally available anticoagulants.

A masterclass was conducted on ventricular arrhythmia, including case-based discussion around a patient with ischaemic cardiomyopathy and ventricular tachycardia, focusing on work-up and management options with drugs and catheter ablation. The fellows-in-training were treated to a practical workshop on pacemaker implantation and the basics of cardiac electrophysiology.

The Fellows course wetlab

PASCAR president and CEO with newly appointed interim AFHRA president

Congress group photo

Following presentations on supraventricular tachycardia management based on current international guidelines, Dr Mohamed Salim (Kenya) presented a pre-recorded case from the only electrophysiology laboratory with three-dimensional mapping capabilities in East and Central Africa (Mombasa, Kenya) where a patient with a manifest right-sided accessory pathway underwent successful ablation with a mapping system without fluoroscopy.

The birth of AFHRA

The opening ceremony of the meeting served as the official launch of AFHRA and was officiated by PASCAR president Saad Subahi, executive officer George Nel and interim president of AFHRA, Aimé Bonny. This session invited an open discussion between clinicians, industry players, funders and healthcare advocates on multidimensional and collaborative strategies to improve access to arrhythmia care in Africa in alignment with the vision of AFHRA. Emphasis was placed on success stories of trans-national cardiology training under PASCAR's training network. Dr Akwanalo, the first fellow to train under the PASCAR fellowship programme in South Africa, has subsequently implanted more than 120 pacemakers in rural Kenya in three years and gave his perspectives on the opportunities and challenges of establishing a pacemaker programme outside the capital of Kenya.

The meeting was attended by 217 specialists with an audience of healthcare practitioners of diverse cadres, including arrhythmologists from the five PASCAR regions, including Egypt (10), Algeria (one), Sudan (four), Nigeria (three), Ghana (one), Cameroon (three), Democratic Republic of Congo (one), Ethiopia (three), Rwanda (one), Tanzania (three), Uganda (two), Kenya (> 100), South Africa (four), Mauritius (one), and from North America, Europe and Asia. Although the majority of attendees were cardiologists, a substantial minority were nurses and allied healthcare professionals. Fellows-in-training comprised 15 attendees, mostly from Egypt, Kenya and Tanzania.

Perspective, opportunities and future directions

PASCAR-affiliated societies are the future of accessible, extensive and specialised cardiology services across Africa. They have great potential to foster training and advocacy, and to levy support from local and international stakeholders. Annual or other interval societal meetings are an invaluable forum to teach, connect, review performance and strategise for the future. AFHRA has determined to plan an annual Cardiorhythm Africa congress with expectations of increased visibility and successive increases in delegate numbers and representation of all African countries. The cardiorhythm meetings will serve as fora for annual review and evaluation of AFHRA's activities, annual general meetings and for setting of key milestones and strategies.

The next Cardiorhythm Africa meeting will be held in 2021, with the venue to be announced in August 2020. The AFHRA scientific board agreed to maintain the current programme format of a syndrome-based approach but will introduce sessions for allied health professionals and non-cardiologists, and broaden workshops to provide a focus on diagnostic strategies for arrhythmia care in underserved parts of Africa and to build a referral network.

Conclusion

Cardiorhythm Africa 2020, the first meeting of AFHRA, was an ambitious project that met its objectives. Specifically, it created a pan-African conversation on access to arrhythmia care in Africa; allowed the creation of a pan-African arrhythmia network; facilitated the formation of the AFHRA executive council; and provided physicians with information on regional and international expertise with a view to developing referral links for both patient care and training. During the meeting we were able to conduct a more detailed and up-to-date survey of arrhythmia practice from all participating countries. Scientific sessions spanning resource-constrained arrhythmia management through to novel and advanced techniques created a framework for all of these successes. The programme design and objectives of Cardiorhythm Africa as an AFHRA launch meeting may provide a blueprint for other affiliate groups of PASCAR.

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Case Report

Early Supera stent fracture in the femoropopliteal artery

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Abstract

The Supera peripheral stent has been designed to resist stent fracture, which can develop from the torsion and compressive forces in the femoropopliteal artery. We report on a case of Supera peripheral stent fracture in the early period after the index procedure in a patient with femoropopliteal artery disease. An individualised approach, considering the lesion location, patient's age and exercise capacity is important for the treatment of femoropopliteal artery disease.

Keywords: peripheral artery disease, popliteal artery occlusion, Supera interwoven nitinol stent, stent fracture

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The Supera peripheral artery stent (Abbott, CA, USA) has an interwoven nitinol design that allows it to mimic the natural movement of the anatomy and supports the vessel with minimal chronic outward force. Therefore, Supera stents can be effective when treating the dynamic environment of the superficial femoral artery and proximal popliteal artery. While observational data has supported its use, some complications have been reported.[1-3] Here we present a case with a Supera peripheral stent fracture 12 days after stent implantation in the femoropopliteal artery.

Case report

A 73-year-old male patient visited our hospital complaining of right leg claudication (Fontaine stage IIb, Rutherford category 3) over three months. His past medical history and laboratory results were non-specific. Non-invasive studies of ankle–brachial index (ABI) and lower extremity computed tomography (CT) angiography showed right femoropopliteral artery total occlusion (Fig. 1).

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The patient underwent percutaneous transluminal angiography (PTA) through the ipsilateral femoral artery (6 French, Ansel® sheath, Cook Medical, IN, USA) (Fig. 2A) using microcatheter support (CXI®, Cook Medical, IN, USA). A 0.014 wire (Command ES®, Abbott, CA, USA) was used for lesion crossing. As required by the Supera stent instructions for use,[3] sequential predilatation of the femoropopliteal lesion was performed (Admiral Xtreme® 5 × 80 mm, Medtronic, MN, USA) and the Supera 5 × 80-mm stent was implanted. A final angiogram showed good patency of the right popliteal artery with no residual disease (Fig. 2B) and post-PTA ABI was 1.07.

However, 12 days later, he visited our hospital and complained of claudication again. ABI was 0.62 and lower extremity CT angiography showed stent fracture with right popliteal artery total occlusion (Fig. 3A). We performed secondary PTA. The angiogram showed stent fracture (type V),[4] with a large amount of thrombus in the area of the Supera stent (Fig. 3B, C).

Thrombus aspiration was done and a 0.035 wire (Terumo®, Terumo Medical Corporation, Tokyo, Japan) was passed through the back-up of the guiding catheter (Glide®, Terumo Medical Corporation, Tokyo, Japan). After popliteal filter deployment, balloon angioplasty (Admiral Xtreme® 5 × 60 mm, Medtronic, MN, USA) was performed and drug-coated balloon angioplasty (Lutonix® 5 × 120 mm, Bard, AZ, USA) was applied. The final angiogram showed good patency of the stent (Fig. 3D) and post-PTA ABI was 0.9.

Unfortunately, claudication developed again three days after repeated PTA. We transferred the patient to the vascular surgeons and bypass surgery between the superficial femoral artery and

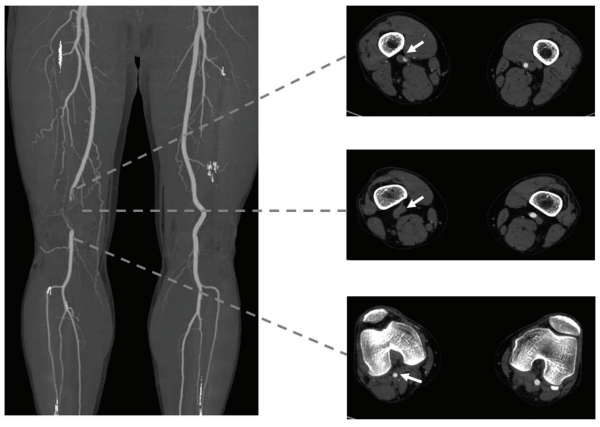

Fig. 1. Lower extremity with computed tomography. White arrows indicate the right femoropopliteal artery with total occlusion in the P2 segment.

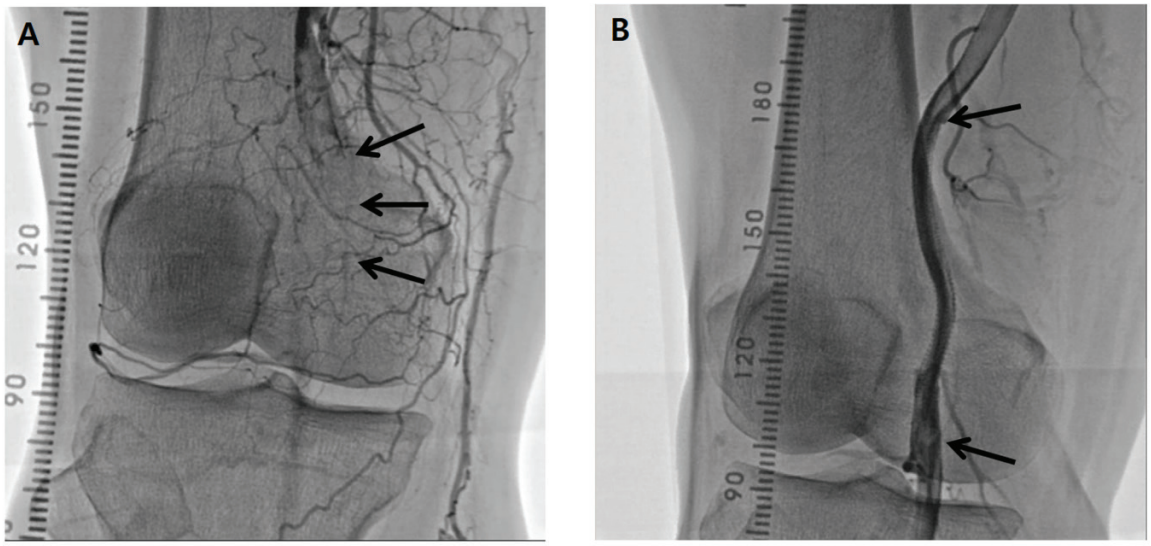

Fig. 2. Percutaneous transluminal angiography at the initial index procedure. A shows the initial angiogram with total occlusion of the right femoropopliteal artery (black arrows) and B depicts the well-positioned Supera stent (between black arrows) without residual stenosis.

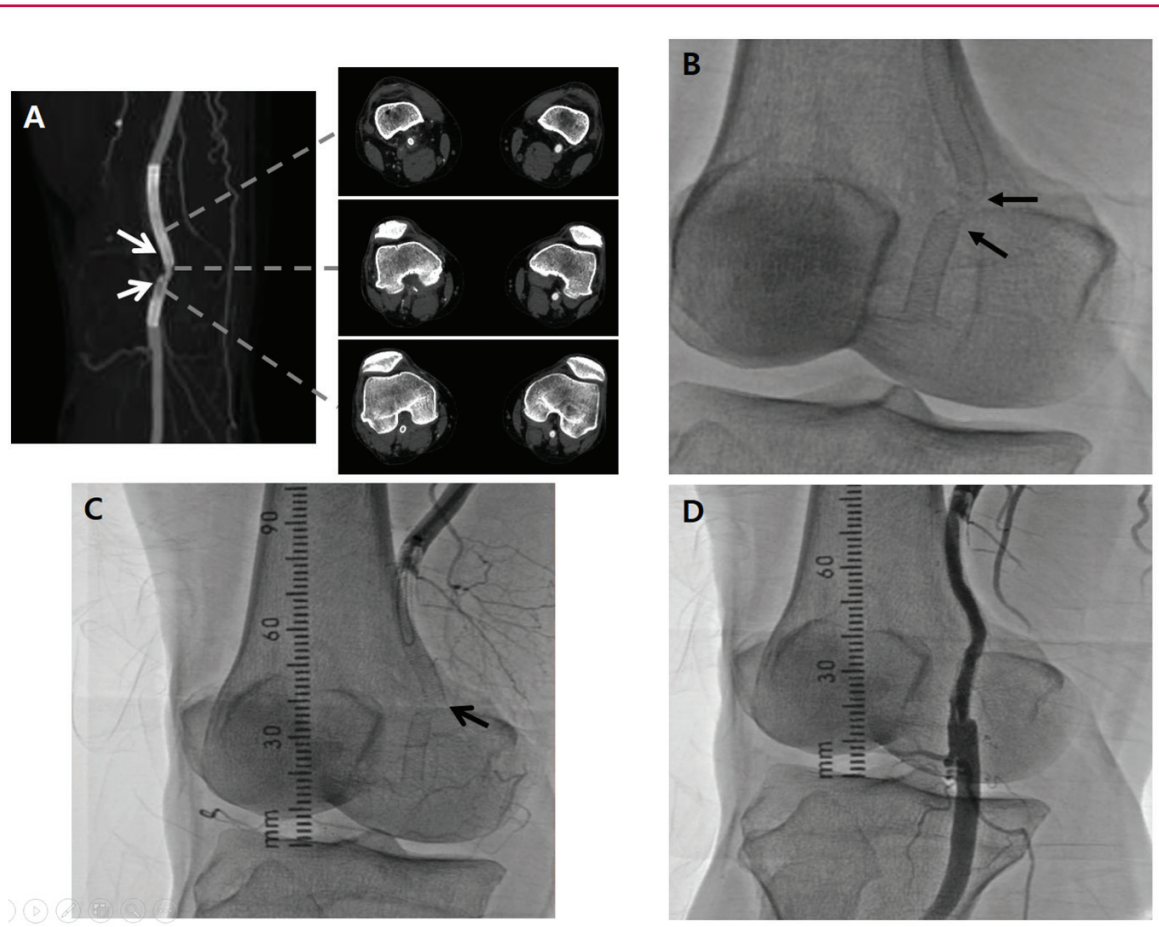

Fig. 3 Supera stent fracture. There is a definite stent fracture observed on computed tomography (A, between white arrows) and fluoroscopy (B, between black arrows). The percutaneous transluminal angiography is performed (C, right popliteal artery is completely occluded and black arrow demonstrates a stent fracture) and successful revascularisation is shown (D).

popliteal artery was performed. ABI after the operation was 1.27 and the patient was discharged without complications.

Discussion

Femoropopliteal artery disease accounts for a significant proportion of endovascular interventions in patients suffering from disabling claudication or chronic limb ischaemia. The femoropopliteal artery descends along the hip and knee joints and passes through the muscular adductor canal of the thigh, which places the artery at increased biomechanical stress.[5] Stents in the femoropopliteal lesion have historically been associated with increased rates of stent fracture. The cumulative incidence of stent fractures ranged from 2 to 65%,[6] and stent fracture is associated with increased risk of in-stent restenosis and re-occlusion of the target vessel.[7]

The self-expanding wire-interwoven nitinol stent (Supera stent) was designed to withstand the unique stressors along the course of the femoropopliteal artery.[8,9] In the prospective, multicentre, non-randomised, single-arm trial (SUPERB trial), 264 patients with symptomatic peripheral artery disease undergoing endovascular treatment of *de novo* or restenosis lesions of the superficial femoral or proximal popliteal artery were enrolled. In this study, absence of stent fracture was observed by independent core laboratory analysis in the 243 stents evaluated at 12 months.[1] In the final three-year outcomes of the SUPERB trial, only one stent fracture (0.6% event rate) was noted in a patient with restenosis who underwent multiple atherectomy procedures within the stent.[2]

Since then, four cases of Supera peripheral stent fracture have been reported. All cases were detected three months after the Supera stent implantation and three cases were type V and one was type III. One case was treated with only balloon angioplasty and another with an additional Supera peripheral stent. Two cases were treated with bypass surgery.[10-13]

The occurrence of stent fractures is not only determined by the stent architecture and length but also by the technique of implantation. In a *post hoc* analysis of the DURABILITY I study, stent elongation occurred during implantation in 90% of all fractured stents, which was associated with continuous strain exerted on the stent struts.[14] Additionally the implantation of multiple overlapping stents may increase the axial stiffness of the stent segment.[15] Vigorous exercise by the patient can adversely affect stent fracture.[16]

Our Supera stent fracture case was detected 12 days after stent implantation. The exact fracture mechanism in our case could not be postulated; however, because of the premature time of fracture after implantation, we assumed that it might not be associated with a fatigue fracture, as seen in the above cases. We can assume that the most important risk factor for stent fracture is the lesion location in femoropopliteal arterial disease. Moreover, our patient was 73 years old but had a very active lifestyle. So, together with the lesion location, an individualised approach, considering the patient's daily activity according to his age, is needed for better clinical outcomes.

Conclusion

Femoropopliteal artery stenting, especially the Supera stent, is a promising option for the treatment of claudication. However, the Supera stent is not fracture-proof. Careful observation after Supera peripheral stent implantation and an individualised approach for treatment of femoropopliteal artery disease, considering the lesion location, patient's age and exercise capacity is warranted.

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Short Communication

Feasibility and effect of community health worker support and home monitoring for blood pressure control in Nigeria: a randomised pilot trial

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Abstract

In a three-arm, randomised, controlled trial among 60 Nigerian adults with hypertension, community health worker support and home blood pressure monitoring led to greater reductions in systolic blood pressure at four weeks compared to the usual care.

Keywords: measures, blood pressure, control, Nigeria

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Raised blood pressure (BP) is a leading modifiable risk factor for global cardiovascular disease morbidity and mortality.[1] Among Nigerian adults, the prevalence of hypertension, defined as blood pressure > 140/90 mmHg or patients taking blood pressure medications has been estimated to be 28.9% (95% CI: 25.1–32.8) based on a 2015 systematic review and meta-analysis of 27 studies (n = 27 122 participants).[2] In addition, there is a high burden of complications from hypertension in Nigeria, including hypertensive left ventricular hypertrophy,[3] hypertensive heart failure,[4,5] chronic kidney disease,[6,7] and strokes.[8,9]

Randomised trials have shown that a multi-level intervention strategy at patient, provider and health-system levels is a more effective approach for hypertension control than a strategy that focuses on a single level. For example, in the Hypertension Improvement Project, the greatest BP control was seen in the group with both provider- and patient-level interventions.[10] Furthermore, while self-monitoring of BP has been associated with better BP control among higher-risk patients, its effects are greatest when coupled with system- or provider-level co-interventions that provide individually tailored support.[11]

Despite the high burden of hypertension in Nigeria and the benefits of such multi-level strategies, no such multi-level interventions have been tested in Nigeria. To address this gap, we performed a pilot, three-arm, randomised trial to evaluate the feasibility and effect of community health worker support and self-home BP monitoring compared with usual care on BP treatment and control at four weeks with the long-term goal of testing these interventions in combination in the context of a large-scale, system-level hypertension-control programme.

Methods

Between November and December 2017 we recruited eligible adults between 30 and 79 years old from two primary care centres in Abuja, Nigeria. Participants were eligible if they had a previous diagnosis of hypertension and a systolic blood pressure (SBP) ≥ 140 mmHg and < 180 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and < 110 mmHg who were either untreated or on monotherapy. The study was approved by the University of Abuja Human Research Ethical Committee and all participants provided written, informed consent.

Blood pressures were measured by the community health worker using an automated BP machine (Omron M3; HEM-7131-E). BP measurements were taken after each

participant had been sitting for five minutes. SBP and DBP were measured three times at one- to two-minute intervals with the average of the last two readings taken as the mean clinic reading. Participants were randomly assigned in a 1:1:1 fashion (to receive community health worker support, home blood pressure monitoring or usual care) by simple ballot conducted by health records officers in each of the two health centres.

Study personnel were instructed to treat participants with SBP ≥ 140 mmHg and < 159 mmHg and/or DBP ≥ 90 mmHg and < 100 mmHg who had not previously been on blood pressure-lowering therapy with amlodipine 5 mg. All other patients were recommended to be treated with fixed-dose combinations of amlodipine 5 mg/ ramipril 5 mg or amlodipine 5 mg/losartan 50 mg for those intolerant of ramipril, according to local practice.

Community health worker support consisted of four structural education sessions and eight home visits over four weeks for tailored counselling related to health behaviours, medication adherence and clinic follow up. Home blood pressure monitoring included training and provision of an automated home blood pressure-monitoring device for daily monitoring.

At baseline, we collected data on demographics, medical and social history, anthropometry and laboratory studies. Four weeks after randomisation, participants returned to the clinical site for an evaluation of change in SBP and hypertension control (co-primary outcomes). Secondary outcomes included self-reported blood pressure-lowering medication adherence and side effects.

Statistical analysis

We reported baseline data using means (standard deviation) or medians (interquartile range) as appropriate for continuous variables, and proportions for categorical variables. We used analysis of variance (ANOVA) and Pearson's chi-squared test to compare baseline continuous and categorical data. We calculated the mean change in SBP from baseline to follow up and compared these results across groups using analysis of covariance (ANCOVA), adjusting for baseline SBP. We defined statistical significance as a two-sided $p < 0.05$ and used SAS v9.4 (Cary, North Carolina) for analyses.

Results

Table 1 summarises the baseline data and co-primary and secondary results. Among the 60 participants recruited, mean (SD) age was 41 (11), 46 (8) and 42 (7) years in the community health worker-supported, home blood pressure-monitoring, and usual-care groups, respectively ($p = 0.18$). Overall, 35% of participants were male with a higher proportion in the home blood pressure-monitoring group (65%) compared with other groups.

Most (75%) participants had been diagnosed with hypertension for five to 10 years. Baseline mean (SD) SBP were 159 (11), 151 (13) and 155 (12) mmHg in the community health worker-supported, home blood pressure-monitoring and usual-care groups, respectively ($p = 0.12$). Baseline mean (SD) DBP were 99 (11), 91 (8) and 98 (8) mmHg in the same groups, respectively ($p = 0.86$).

At the four-week follow up, the mean SBP differences were –31 (12), –27 (14) and –21 (8) mmHg in the community health worker-supported, home blood pressure-monitoring and usual-care groups, respectively ($p = 0.02$). There were no differences in DBP at the four-week follow up. Only one adverse event (dizziness) occurred in one participant in the home blood pressure-monitoring group and no adverse events occurred in the other groups. Self-reported use of two BP-lowering drugs at the four-week follow up was higher in the community health worker-supported (80%) and home blood pressure-monitoring (70%) groups compared with the usual-care group (65%), but these differences were not statistically significant ($p = 0.12$).

Discussion

Our study demonstrates that community health worker support and home blood pressure monitoring are feasible and may be effective in primary care settings in Nigeria. However,

Table 1. Baseline characteristics and outomes of participants by intervention group

Parameters	*Community health worker support (n = 20)*	*Home blood pressure monitoring (n = 20)*	*Usual care (n = 20)*	p-*value*[a]
Baseline characteristics				
Age, mean (SD), years	42 (11)	46 (8)	42 (7)	0.18
Male, *n* (%)	5 (25)	13 (65)	3 (15)	< 0.01
Height, mean (SD), cm	161 (12)	168 (12)	163 (10)	0.17
Weight, mean (SD), kg	73 (13)	77 (11)	69 (9)	0.06
Duration of hypertension, *n* (%)				0.86
< 5 years	14 (70)	15 (75)	16 (80)	
5–10 years	5 (25)	4 (20)	4 (20)	
> 10 years	1 (5)	1 (5)	0 (0)	
Occupation, *n* (%)				0.04
Caterer	1 (5)	0 (0)	0 (0)	
Clergy	0 (0)	1 (5)	0 (0)	
Driver	0 (0)	0 (0)	1 (5)	
Farming	1 (5)	0 (0)	1 (5)	
Housewife	1 (5)	0 (0)	2 (10)	
Lecturer	0 (0)	1 (5)	0 (0)	
Public servant	1 (5)	11 (55)	3 (15)	
Retired	1 (5)	0 (0)	0 (0)	
Trader	15 (75)	7 (35)	13 (65)	
Baseline medication, *n* (%)				0.29
None	5 (25)	5 (25)	11 (55)	
CCB	7 (35)	7 (35)	6 (30)	
ACE-I	6 (30)	6 (30)	1 (5)	
BB	2 (10)	2 (10)	2 (10)	
Baseline SBP, mean (SD), mmHg	159 (11)	151 (13)	155 (12)	0.12
Baseline DBP, mean (SD), mmHg	99 (11)	97 (8)	98 (8)	0.86
Follow up characteristics				
Follow up medication, *n* (%)				0.12
CCB	4 (20)	6 (30)	7 (35)	
CCB and ACE-I	6 (30)	3 (15)	0 (0)	
CCB and ARB	10 (50)	11 (55)	13 (65)	
4-week SBP, mean (SD), mmHg	128 (5)	125 (5)	133 (11)	< 0.01
4-week DBP, mean (SD), mmHg	81 (8)	80 (5)	82 (6)	0.51
Decrease in SBP, mean (SD), mmHg[b]	31 (12)	27 (14)	21 (8)	0.02
Decrease in DBP, mean (SD), mmHg[b]	18 (9)	17 (9)	16 (6)	0.88
Adverse events, *n* (%)	0 (0)	1 (5)	0 (0)	0.36
Non-adherence to study medication, *n* (%)	0 (0)	1 (5)	1 (5)	0.60

CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD standard deviation; [a] ANOVA or chi-squared test; [b] Decrease = baseline – 4-week follow up.

our study also has limitations, including: lack of prospective registration, small study size, unconventional randomisation approach and open study design. However, the primary purpose of our study was to demonstrate feasibility, which we were able to accomplish. Furthermore, our co-primary outcome assessment was objectively measured and defined and therefore less susceptible to detection bias.

We aim to use these data to catalyse a large-scale, multi-level interventional study in Nigeria that tests the effects of community health worker support and home blood pressure monitoring together, rather than separately, to improve hypertension treatment and control rates and reduce the burden of hypertension-related diseases in Nigeria.

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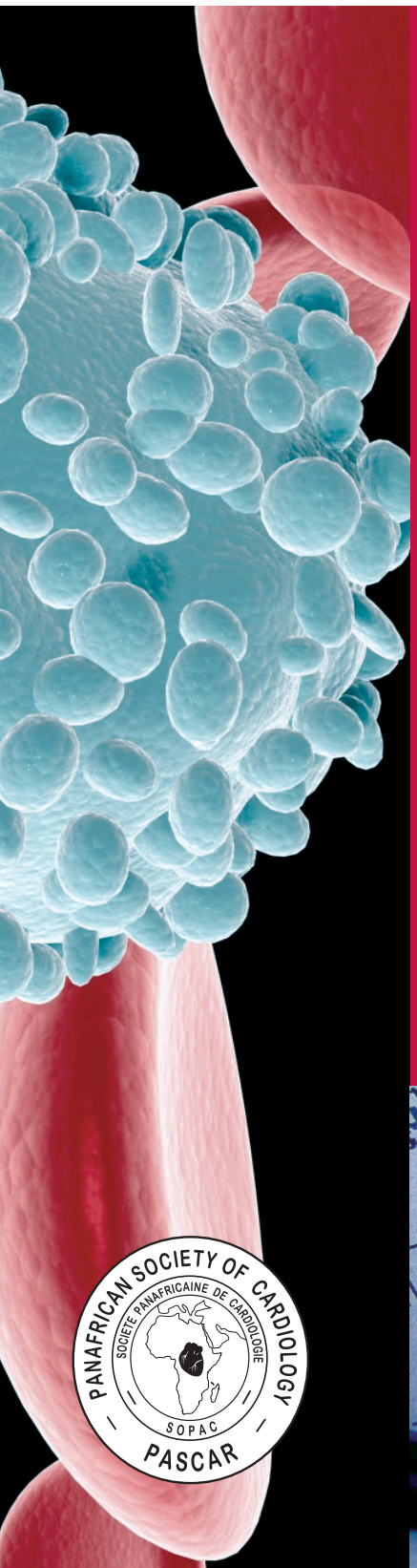

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