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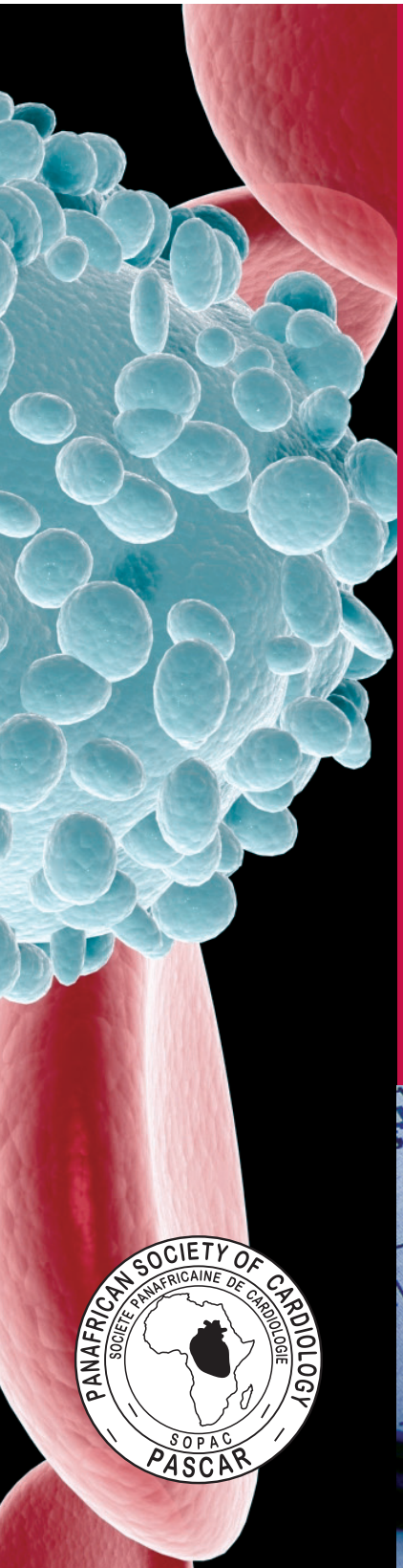

- Safety and efficacy of pharmaco-mechanical thrombolysis in DVT
- NT-proBNP and metabolic risk factors: SABPA study
- Plasma uric acid and risk of stroke in hypertensive populations
- Physical activity and carotid intima–media thickness: SABPA study
- Cut-off values for waist circumference and the metabolic syndrome
- Admission hyperglycaemia in blacks with acute coronary syndrome
- COVID-19 and simultaneous acute anteroseptal and inferior STEMI
- PASCAR commentary on the ISH guidelines 2020: relevance to SSA

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From the Editor's Desk

The authors of the PASCAR commentary (page 325) on the recently published International Society of Hypertension (ISH) global guidelines are to be congratulated on an important, pragmatic and clinically useful commentary that should be read by all who measure and treat the blood pressure of persons in sub-Saharan Africa (SSA). They draw on their extensive clinical experience and personal knowledge of the healthcare situation in SSA to put the ISH guidelines in context for the continent.

They start with a brief but informative discussion for the rationale and usefulness of guidelines and then go on to point out where the guidelines need to be modified or altered by the availability of testing devices and laboratory services. Importantly, they point out that some of the medicines recommended for the treatment of hypertension are not available in much of SSA and those that are, such as intravenous nitrates, may require scarce intensive-care facilities. In each instance the PASCAR commentary offers clinically helpful comments and alternatives. This commentary should be copied and made available to all healthcare practitioners in SSA.

The value of a commentary such as that of PASCAR becomes immediately apparent on reading the contribution of Hu and colleagues (page 298) who measured uric acid (UA) levels in a large cohort of hypertensive patients in China. They concluded that high UA level could significantly increase stroke risk in female hypertensive patients and that these patients may benefit from managing UA at normal levels. The PASCAR commentary offers explicit advice to the contrary. 'The recommendation for treating asymptomatic hyperuricaemia is considered very controversial.'

The importance of establishing norms and values for determination and description of disease states and metabolic disturbance in populations in SSA is further illustrated by the contribution of Tladi and colleagues (page 314). They studied Batswana adults and determined demographic and anthropometric measurements and other risk factors for the metabolic syndrome in 384 men and 416 women in Gaborone and surrounding villages. They concluded that there is a difference between the cut-off values for Europeans and those determined for the Batswana in terms of the definition of abdominal obesity in adults, and inconsistencies in cut-off values used have the potential for undesirable consequences for cardiovascular risk stratification.

From Abidjan, Yao and collaborators (page 319) report that the prevalence of admission hyperglycaemia was 40.6% in a large number of black Africans presenting with an acute coronary syndrome (ACS). This study, carried out in a SSA population, shows that in the acute phase of ACS, admission blood glucose has a powerful prognostic value on mortality rate, in accordance with studies conducted in the West.

The CVJA is privileged to be able to continue publishing these and other articles, documenting and commenting on patterns of cardiovascular disease in Africa.

Pat Commerford
Editor-in-Chief

Cardiovascular Topics

The safety and efficacy of pharmaco-mechanical thrombolysis in lower-extremity deep venous thrombosis

Emced Khalil, Sedat Ozcan

Abstract

Objective: The aim of this study was to investigate the impact of accelerated pharmaco-mechanical thrombolysis (PMT) with low-dose second-generation urokinase for the management of cases with lower-extremity deep venous thrombosis (DVT), and to compare its efficacy in subjects with acute and subacute DVT.

Methods: Thirty-five patients with acute (< 15 days) or subacute (15–30 days) DVT who underwent PMT in a tertiary centre were enrolled in this single-arm, prospective study. Following the placement of a temporary vena cava filter, urokinase (200 000 IU) was administered into the occlusion through a multi-hole catheter for 15 to 20 minutes. Control venography was performed to assess venous flow and the rate of acute recanalisation. Percutaneous balloon dilatation and stent placement were carried out in case of a residual iliac vein stenosis of > 50%. Any residual thrombi were suctioned with an aspiration catheter. The primary outcome measures of this study were the percentages of vessel patency and PTS in the third month after PMT.

Results: Complete recanalisation was noted in 23 (66%) patients, while two (6%) had poor recanalisation. The rate of minor complications was 14%. None of the subjects experienced major complications, such as intracranial haemorrhage or pulmonary embolism. No mortality was recorded during the three months of follow up. Control duplex ultrasonography in the third month revealed that the target vein was patent in all subjects. None of the subjects experienced PTS during follow up. In addition, the percentage of acute complete recanalisation was significantly higher in subjects with acute DVT compared to those with subacute DVT (95 vs 27%, $p < 0.001$).

Conclusion: PMT with an accelerated regimen of low-dose urokinase provided excellent efficacy in the resolution of thrombus and prevented the development of PTS in the mid-term when used for the management of lower-extremity DVT.

Keywords: deep venous thrombosis, catheter-directed thrombolysis, urokinase, outcomes

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Pulmonary embolism and deep-vein thrombosis (DVT) are the most common presentations of venous thromboembolism. DVT, which is common in the lower limbs, is characterised by the formation of thrombus in a deep calf vein. The popliteal vein and those proximal to the popliteal vein are affected in more than 80% of subjects with lower-extremity DVT.[1] Further propagation of thrombus is common and leads to several complications through the embolisation of the thrombus or complete occlusion of the relevant vein. The reported incidence of DVT is about 1.6 per 1 000 individuals per year.[2,3]

While pulmonary embolism is the most common cause of early mortality associated with venous thromboembolism, chronic thrombotic pulmonary hypertension subsequent to pulmonary embolism may result in long-term morbidity and mortality. On the other hand, post-thrombotic syndrome (PTS), a condition characterised by pain, oedema, swelling and pigmentation has been shown to develop in 25 to 38% of patients with DVT, and results in severe morbidity due to the deterioration in skin integrity.[4]

Inflammatory destruction of the venous valves due to venous incompetence caused by venous obstruction has been proposed as the most probable theory for the development of PTS.[5] Early removal of the thrombus and restoration of venous flow through systemic use of thrombolytic agents has been shown to prevent venous dysfunction and subsequent PTS.[6] However, the possibility of major bleeding, especially intracranial haemorrhage, restricts widespread use of systemic thrombolysis in the management of DVT.

It has been shown that three to 6% of subjects treated with intravenous tissue plasminogen activator (TPA) have complications with intracranial haemorrhage.[7] In contrast to systemic thrombolysis, pharmaco-mechanical thrombolysis (PMT) enables administration of the thrombolytic agent directly into the thrombus with a reduced total dose,[8] thereby reducing the possibility of systemic complications.[9] Moreover, systemic thrombolytic agents are delivered to the surface of the thrombus only, whereas PMT enables deep penetration of the thrombolytic agent with relatively low doses.

Our aim was to investigate the impact of accelerated PMT with low-dose, second-generation urokinase for the management

of lower-extremity DVT, and to compare its efficacy in subjects with acute and subacute DVT.

Methods

This single-arm, prospective study was conducted on patients with acute (< 15 days) or subacute (15–30 days) DVT who underwent PMT in a tertiary centre between September 2017 and September 2019. Written informed consent was obtained from all participants. The study was approved by the institutional review board and was performed in accordance with the most recent version of the Helsinki Declaration. The study was prospectively registered at clinicaltrials.gov.

Inclusion criteria were as follows: age between 18 and 75 years, having suffered from an iliofemoral or femoropopliteal DVT within the last 30 days, and receiving duplex ultrasonography imaging. Subjects with any absolute contra-indications for thrombolytics, previous contrast allergy, pregnancy, malignancy requiring chemotherapy, those within less than 14 days of surgery, and those with a creatinine clearance rate < 50 ml/min were also excluded.

DVT of the lower limb was confirmed with duplex ultrasonography. Baseline fibrinogen and D-dimer levels were measured in all subjects. All subjects received anticoagulation with unfractionated heparin from admission to discharge.

With ultrasonographic guidance, a 6F sheath was placed into the contralateral femoral vein under local anaesthesia. Temporary inferior vena cava (IVC) filters (Reya Venocat, Biolas, Ankara, Turkey) to the infrarenal IVC were deployed in all patients under fluoroscopic guidance to prevent the risk of clot-fragment embolisation during the procedure. The patient was then placed in the supine position and ultrasonography was used to enter the popliteal vein on the side of the DVT using a 6F sheath. A pre-interventional venogram was obtained to evaluate the location and severity of the thrombus.

A 0.018-inch hydrophilic guidewire (Terumo glidewire, NJ, USA) was used to traverse the thrombotic lesion, followed by the advancement of a catheter with multiple side holes (UniFuse Infusion Catheter; Angiodynamics, Latham, NY, USA) through the guidewire. Doses of 200 000 IU of urokinase were then administered into the occlusion through the multi-hole catheter for 15 to 20 minutes. Control venography was performed to assess venous flow and rate of recanalisation. Percutaneous balloon dilatation and stent placement (Jaguar, Balton Co, Warsaw, Poland) were carried out in cases with residual iliac vein stenosis of over 50%. An aspiration catheter was used to aspirate any remaining residual thrombus.

The IVC filter was retrieved after thrombolysis under fluoroscopic guidance (Fig. 1). Following thrombolysis, subjects were kept on unfractionated heparin, and rivaroxaban (Xeralto) 20 mg/day was initiated and maintained for 12 months. All study subjects underwent a ventilation–perfusion (VQ) scan for detection of the pulmonary embolism during the follow up. All subjects were recommended to use knee-high, elastic compression stockings for 24 months.

Subjects were categorised according to the degree of post-interventional recanalisation as follows: (1) complete recanalisation if the length of the residual thrombus was < 2

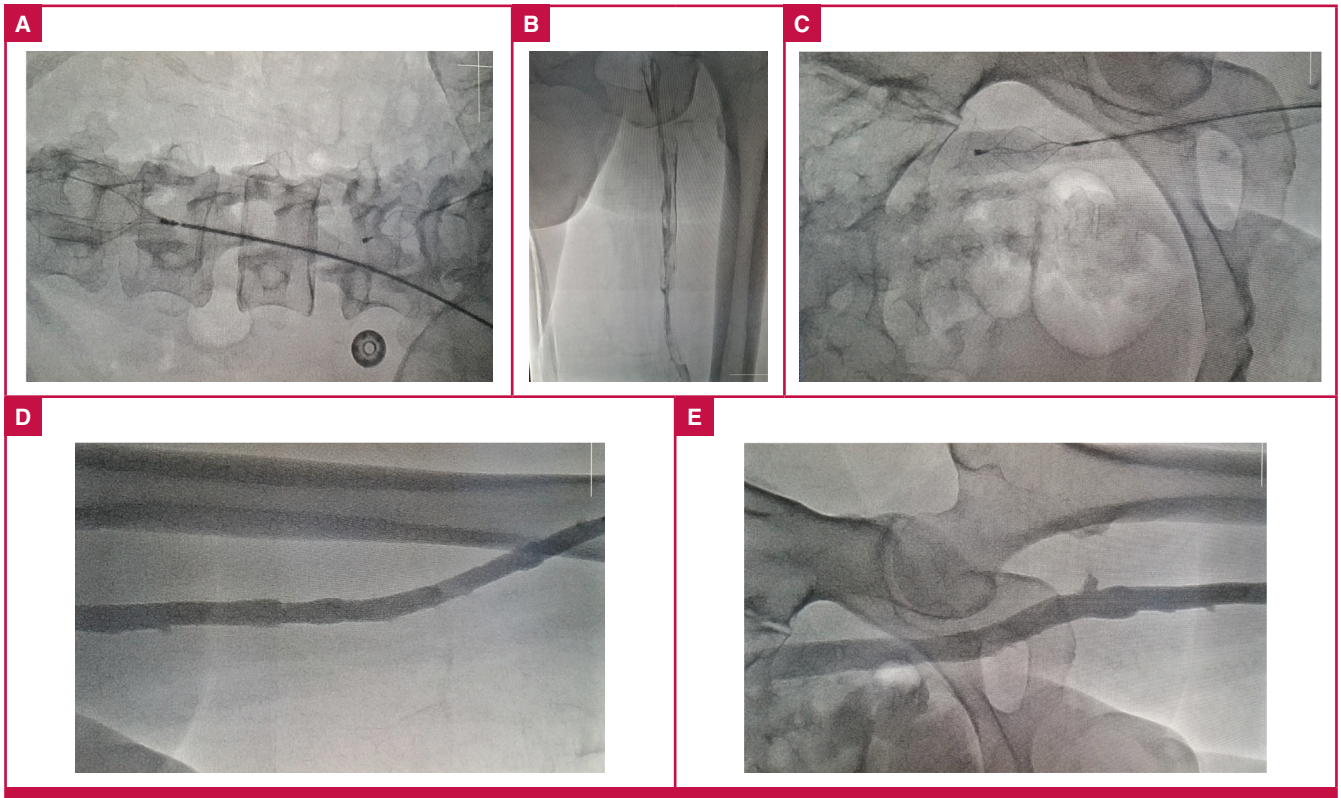

Fig. 1. A: Temporary inferior vena cava (IVC) filters were deployed in all patients to the infrarenal IVC under fluoroscopic guidance to prevent the risk of clot-fragment embolisation during the procedure. B: Entering the popliteal vein on the side with the DVT using a 6F sheath. C: Urokinase was administered into the occlusion through the multi-hole catheter for 15 to 20 minutes. D: Femoropopliteal recanalised venous flow. E: Iliofemoral recanalised venous flow.

cm and venous flow was not limited; (2) partial recanalisation if the length of the residual thrombus was > 2 cm and venous flow was slightly limited by the residual thrombus; (3) poor recanalisation if the venous flow was prominently limited by the residual thrombus. Interventional complications were classified as minor (epistaxis, haematuria, skin ecchymosis) and major complications (pulmonary embolus, intracranial haemorrhage and major bleeding requiring blood transfusion).

All subjects underwent control duplex ultrasonography to evaluate the patency of the relevant vein. Fibrinogen and D-dimer levels were also re-measured. The percentage of vessel patency and PTS development in the third month after PMT were the primary outcome measures of this study.

Statistical analysis

All analyses were performed on SPSS v20 (IBM, Armonk, NY, USA). The Shapiro–Wilk test was used for the normality check. Data are presented as mean ± standard deviation or median (minimum–maximum) for continuous variables, with regard to normality. Comparison of the pre- and post-thrombolysis fibrinogen and D-dimer levels was performed with the paired samples *t*-test. A two-sided $p < 0.05$ was accepted as statistically significant.

Results

A total of 35 subjects (mean age 62 ± 14 years, 57% male) with lower-extremity DVT who underwent PMT were enrolled in this study. Baseline characteristics of the study population are presented in Table 1; 57% of the cases were acute DVT (< 15 days) and 77% were in the femoropopliteal region. More than half of the cases were unprovoked DVT.

Complete recanalisation was noted in 23 subjects (66%), whereas recanalisation was defined as poor in two (6%). Aspiration thrombectomy was performed as adjunctive technique to remove the residual thrombus in two subjects with poor recanalisation and in seven subjects with partial recanalisation after catheter-directed thrombolysis (CDT). Two patients in the subacute DVT group received stents for residual iliac vein stenosis.

Table 1. Demographic features and clinical characteristics of the study population ($n = 35$)

Demographic features	*Number (%)*
Age, years	62 ± 14
Gender, male	20 (57)
Acute DVT	20 (57)
Location	
Iliofemoral	8 (23)
Femoropopliteal	27 (77)
Diabetes	8 (23)
Dyslipidaemia	6 (17)
Smoking	13 (37)
Coronary artery disease	4 (11)
Aetiology	
Major surgery	3 (9)
Obstetric conditions	4 (11)
Prolonged immobilisation	8 (23)
Unprovoked	20 (57)

Data are presented as mean ± standard deviation for continuous variables and frequency (%) for categorical variables.

The rate of minor complications was 14%. None of the subjects experienced major complications such as intracranial haemorrhage or pulmonary embolism. No mortality was recorded during the three months of follow up. Control duplex ultrasonography in the third month revealed that the target veins were patent in all subjects. None of the subjects experienced PTS during the three months of follow up.

Comparison of the subjects with acute and subacute DVT is given in Table 2. Subjects with subacute DVT were older than those with acute DVT (70 ± 11 vs 56 ± 14 years, $p = 0.003$). There were no significant differences between subjects with acute and subacute DVT in terms of risk factors for DVT, aetiology, baseline and third-month fibrinogen and D-dimer levels. Although the frequency of minor complications was slightly higher in those with subacute DVT, the difference did not reach statistical significance. The percentage of patients with acute complete recanalisation was significantly higher in those with acute DVT compared to those with subacute DVT (95 vs 27%, $p < 0.001$).

Discussion

This study aimed to investigate the role of PMT with low-dose urokinase in patients with acute or subacute lower-extremity DVT. Our findings demonstrate that PMT with low-dose urokinase not only provided excellent vessel patency at three months but also enabled safe thrombolysis due to the delivery of lower-dose agents into the thrombus. Notably, with this method, the acute complete recanalisation rate was significantly higher in subjects with acute DVT than those with subacute DVT.

The main therapeutic goals for treating lower-extremity DVT are the preservation of venous valve function and prevention of pulmonary embolism and recurrent DVT. Systemic anticoagulation with low-molecular weight heparin or unfractionated heparin followed by warfarin or new oral

Table 2. Comparison of subjects with acute and subacute DVT

	Acute DVT ($n = 20$) n (%)	*Subacute DVT ($n = 15$) n (%)*	*p-value*
Age, years	56 ± 14	70 ± 11	0.003
Gender, male	11 (55)	9 (60)	0.767
Dyslipidaemia	4 (20)	2 (13)	0.605
Diabetes	3 (15)	5 (33)	0.201
Coronary artery disease	2 (10)	2 (13)	0.759
Smoking	8 (40)	5 (33)	0.686
Aetiology			
Major surgery	3 (15)	0 (0)	
Obstetric conditions	3 (15)	1 (7)	0.254
Prolonged immobilisation	3 (15)	5 (33)	
Unprovoked	11 (55)	9 (60)	
Baseline fibrinogen (mg/dl)	472 ± 114	425 ± 99	0.214
Fibrinogen at 3rd month (mg/dl)	355 ± 85	304 ± 83	0.088
Baseline D-dimer (µg/ml)	3.4 ± 1.2	4.2 ± 2.4	0.287
D-dimer at 3rd month (µg/ml)	1.1 ± 0.6	1.8 ± 1.1	0.232
Complete recanalisation	19 (95)	4 (27)	
Partial recanalisation	1 (5)	9 (60)	< 0.001
Poor recanalisation	0	2 (13)	
Minor complications	1 (5)	4 (27)	0.070
Patency at 3rd month	20 (100)	15 (100)	> 0.999

Data are presented as mean ± standard deviation for continuous variables and frequency (%) for categorical variables.

anticoagulant agents has been accepted as the standard of care for the majority of the subjects with lower-extremity DVT.[10] In addition, the use of elastic compression stockings is recommended in order to support venous valve function and to prevent PTS development.[11] Nevertheless, a considerable number of patients with lower extremity DVT develop PTS and recurrent DVT, despite anticoagulant therapy and the elastic compression stockings.[12]

Theoretically, anticoagulant agents prevent further thrombus propagation but can neither remove the clot nor prevent the sequelae of post-thrombotic alterations.[13] Given the insufficiency of anticoagulant agents in preventing PTS, the consideration of initial thrombolytic therapy in lower-extremity DVT has attracted attention.

Rapid resolution of the thrombus with systemic thrombolysis in DVT provided promising results concerning the prevention of PTS through the preservation of venous valve function.[14-16] Thrombolytic agents may also prevent the organisation of an occlusive thrombus, thus preventing the development of occlusive disease and venous hypertension. The short-term complete resolution rate of the thrombus with systemic thrombolytic agents is 26 to 67%, and the long-term risk of developing PTS ranges between zero and 80%.[17] However, major bleeding, including intracranial haemorrhage and pulmonary embolism are major drawbacks for systemic thrombolytic therapy in DVT.

Pooled analysis of systemic thrombolytic therapy in DVT shows that nine to 13% of subjects receiving streptokinase or TPA for DVT develop major bleeding.[17,18] Moreover, the success of systemic thrombolysis in patients with organised and old thrombus burden is unsatisfactory, most probably due to the limited penetration of the thrombolytic agent into the thrombus.[19]

Although pulmonary embolism resulting from systemic thrombolytic therapy is a theoretical concern, Schweitzer *et al*. reported that 4.5% of their study group, which included patients with leg or pelvic deep venous thrombosis, suffered a pulmonary embolus during systemic thrombolytic therapy.[20] The underlying mechanism associating systemic thrombolytic agents and pulmonary embolism is not clear; however, complete removal of a huge thrombus from the vessel wall with systemic application of a thrombolytic agent may be the cause of such a scenario.

Regional thrombolytic therapy, which allows the delivery of the thrombolytic agent directly into the venous thrombus, has emerged in the last few decades as a potentially superior approach in the management of DVT. With this technique, physicians aspire to overcome the main limitations of systemic thrombolysis, such as the unpredictability of thrombolytic effects and the high risk for major bleeding. PMT relies on the administration of low-dose thrombolytic agents directly into the clot while optimising exposure of the lytic agent to the clot by catheters with multiple side holes. The improved penetration of the thrombolytic agent and additional mechanical fragmentation of the thrombus by the administration of the lytic agent through specialised catheters facilitates the complete resolution of the thrombus. The efficacy of PMT in restoring venous patency and reducing symptoms in the setting of acute DVT has been shown in several studies.[9,21]

Risk for the development of PTE is negatively correlated with the amount of thrombus remaining at the end of CDT. It has been shown that removal of ≥ 90% of the thrombus significantly reduces the risk for PTS.[22] A recent meta-analysis including six trials has reported that compared to CDT, PMT reduced thrombolysis time, length of hospital stay and thrombus score. The meta-analysis also showed that PMT had similar complication rates to CDT.[23] Findings of the recent ATTRACT trial showed that 48% of the patients with lower-extremity DVT who received CDT developed PTS within two years.[24]

Although long-term follow-up data are lacking, our findings demonstrate a higher efficacy of CDT compared to that of the Venous Thrombolysis Registry. Restoration of forward venous flow was achieved in 94% of our study population, despite the enrollment of a considerable number of subjects with subacute DVT. Supporting the findings of the Venous Thrombolysis Registry, which reported complete lysis of the thrombus in 65% of patients with acute (< 10 days) DVT, the complete resolution rate of the thrombus in acute DVT subjects of our study was significantly higher than those with subacute DVT.

The increased success rate noted in complete resolution of the thrombus in this study compared to previous studies might be associated with technical advances and the use of second-generation urokinase, as well as the exclusion of subjects with recurrent DVT. In addition, the vein affected by DVT was patent in all our subjects at mid-term follow up. Moreover, none of the subjects in our study developed PTS, which is closely associated with the forward flow at midterm follow up.

Although head-to-head comparisons of the risk of intracranial bleeding in systemic thrombolysis, PMT and CDT are lacking, it seems to be quite rare with CDT. A pooled analysis of 19 studies revealed a zero to 1% rate of intracranial bleeding following CDT, which is lower than the intracranial bleeding rate reported with systemic thrombolysis.[25] The data regarding intracranial bleeding in PMT are limited. None of the subjects enrolled in our study suffered intracranial haemorrhage during the three months of follow up. We consider that the low-dose administration of urokinase with an accelerated regimen (15 to 20 minutes) in our study was the main cause of the lower frequency of intracranial bleeding, compared to previous studies.

With data from our study and previous studies on this topic, we suggest that accelerated PMT with low-dose urokinase can be used in both acute and subacute lower-extremity DVT with high efficacy and safety. Accelerated PMT with low-dose urokinase may completely prevent the development of PTS, at least until midterm follow up.

This study has some limitations. First, it was a prospective but single-arm study. Therefore, we could not provide data comparing the safety and efficacy of other treatments with either anticoagulant alone or with systemic thrombolysis. However, there is sufficient evidence demonstrating the superiority of PMT in terms of safety and efficacy compared to CDT, systemic thrombolysis or anticoagulants. Second, the follow-up period of the study for the outcomes was three months, which is relatively short to reach a clear conclusion regarding the role of PMT on the development of PTS. Further studies with longer follow up are required to address the role of accelerated PMT with low-dose urokinase in patients with lower-extremity DVT.

Conclusions

This study shows that PMT with an accelerated regimen of low-dose urokinase provides excellent efficacy in the resolution

of thrombus and prevents the development of PTS within three months when used for the management of lower-extremity DVT. Moreover, the safety of PMT with low-dose urokinase was highly satisfactory as none of the subjects enrolled in this study experienced either intracranial bleeding or pulmonary embolism. Nevertheless, further studies with longer follow up are needed to address the role of accelerated PMT with low-dose urokinase in patients with lower-extremity DVT.

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NT-proBNP and metabolic risk factors in a bi-ethnic cohort: the Ambulatory Blood Pressure in African prospective cohort study

Amra Jujić, Olle Melander, Peter M Nilsson, Leoné Malan, Artur Fedorowski, Martin Magnusson

Abstract

Background: We explored the association of N-terminal pro-brain natriuretic peptide (NT-proBNP) with metabolic traits in a bi-ethnic African–Caucasian cohort.

Methods: Baseline examinations of the Sympathetic activity and Ambulatory Blood Pressure in African (SABPA) prospective cohort study were performed between 2008 and 2009, and re-examination after a three-year follow up in South African teachers (black African, n = 194; Caucasian, n = 203).

Results: Each one standard deviation increment of NT-proBNP was significantly inversely associated with body mass index (β –1.01), glycated haemoglobin (β –0.14 %), waist circumference (β –1.82), HOMA-IR (β –0.47), insulin (β –1.66) and triglyceride levels (β –0.04). Each one standard deviation increment of NT-proBNP was also associated with reduced odds of incident diabetes, and subjects within the highest quartile of NT-proBNP were at lowest risk (OR: 0.24; 95% CI: 0.06–0.96; p = 0.041).

Conclusions: In the SABPA cohort, Africans and Caucasians had similar NT-proBNP levels; however, the associations for Africans were stronger. Those findings suggest that BNP may affect the propensity for metabolic disturbances differently in Africans and Caucasians.

Keywords: Africans, bi-ethnic, Caucasians, metabolic, NT-proBNP

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Natriuretic peptides (NPs) are widely recognised as potent vasoactive hormones that play a key role in volume loading and cardiac remodelling.[1] Their gene transcription and secretion increase as a result of cardiac stress, for example, stretching of the cardiac atria or due to ventricular pressure or volume load.[2] Consequently, BNP levels are elevated in conditions such as heart failure, and BNP are also today extensively used as heart failure biomarkers in clinical routine.[3] In addition to cardiac stress, there is also evidence that neurohormonal factors such as angiotensin II, thyroid hormones, inflammatory cytokines interleukin (IL)-1, IL-6 and tumour necrosis factor α (TNF-α) affect and interact with NP secretion.[4,5]

The last two decades of research has also identified NPs as hormones with significant protective metabolic actions, and proposed that genetically predisposed low levels of NPs, the so called 'natriuretic handicap', is a cause, rather than a consequence, of metabolic disorders such as obesity, insulin resistance and diabetes.[6-9] Although NP secretion is greatly influenced by volume load on the heart, there is evidence that as much as 40% of the variation in BNP levels could be explained by genetic factors.[10,11] Other studies demonstrate that African Americans have lower NT-proBNP levels than Caucasians.[12-14] However, higher levels independent of diabetes status were observed in an African cohort compared to Caucasian counterparts.[15]

In this study, we aimed to explore the associations of NT-proBNP with obesity, hypertriglyceridaemia, the metabolic syndrome, insulin resistance and diabetes in an African versus a Caucasian gender-matched cohort from South Africa.

Methods

This study is part of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study of 409 African and Caucasian school teachers (aged 20–62 years), working in the North-West Province, South-Africa.[16] The examination was conducted in 2008 and 2009 and repeated in 2011 and 2012 (mean follow-up time three years), with an 87.8% successful follow-up rate (Fig. 1).

The study sample was selected to ensure homogeneity regarding socio-economic status and working environment. Exclusion criteria for the SABPA study were: the use of alpha- or beta-blockers, use of psychotropic substances, tympanum

temperature > 37.5°C and/or being vaccinated or donating blood within three months prior to participation. Additionally, we excluded participants with missing values of NT-proBNP (n = 12), resulting in 397 participants (194 Africans and 203 Caucasians).

The SABPA study conforms to the principles outlined in the Declaration of Helsinki (revised 2004) (World Medical Association General Assembly 2004) and abided by the institutional guidelines. It was approved by the ethics review board of the North West University, South Africa (0003607S6). All participants provided written informed consent.

The participants were in a semi-recumbent position for at least 30 minutes prior to blood pressure (BP) measurements on the non-dominant arm between 06:15 and 09:00 by a registered nurse and doctor. They used a calibrated sphygmomanometer (Riester CE 0124®) and a 1.3M™ Littman® II SE stethoscope 2205. Two duplicate measures were taken, with a three- to five-minute resting period between each, the second of which was used for statistical analyses.

Body height (stature), weight and waist circumference were measured with calibrated instruments (Invicta Stadiometer, IP 1465, London, UK; Precision Health Scale, A&D Co, Tokyo, Japan; Holtain unstretchable flexible 7-mm-wide metal tape, Crosswell, Wales) while participants were in their underwear. All measurements were done in triplicate by registered anthropometrists according to standard procedures.[17]

A registered nurse obtained fasting blood samples with a sterile winged infusion set from the ante-brachial vein. EDTA whole blood and serum were stored at –80°C. Venous samples for fasting blood glucose were collected in sodium fluoride tubes. All analyses were performed on samples drawn after an overnight fast.

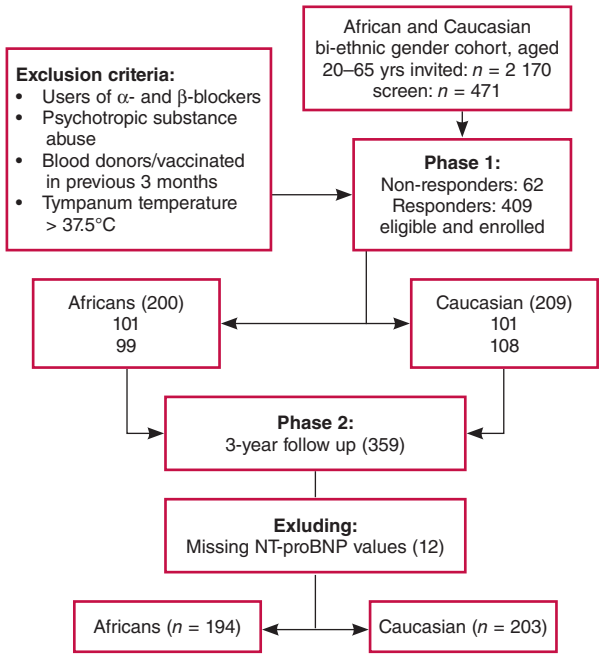

Fig. 1. Design of the bi-ethnic gender cohort of the Sympathetic activity and Ambulatory Blood Pressure in Africans prospective study.

Plasma and serum samples were analysed using two sequential multiple analysers (Konelab 20i; Thermo Scientific, Vantaa, Finland; Unicel DXC 800, Beckman and Coulter®, Germany), doing enzyme-linked immunosorbent assays (Quantikine enzyme-linked immunosorbent assay, R&D Systems, Minneapolis, MN, USA) for serum total and high-density lipoprotein (HDL) cholesterol, serum triglyceride (TG), whole blood glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and serum insulin levels. The intra- and inter-coefficients of variation for all assays were below 10%.

NT-proBNP serum samples were obtained at both baseline and follow-up examinations and frozen at –80°C until analysis in one batch in 2015 (ECLIA method; Roche Diagnostics, Basel, Switzerland) using Cobas e411 automated platform (inter-batch variability: 4.6%; intra-batch variability: 4.2%).

Prevalent impaired glucose tolerance (IGT) at the baseline examination was defined as FPG > 5.6 mmol/l or HbA_{1c} > 5.7%. The metabolic syndrome (MetS) was defined as any three of the following markers exceeding cut-off points: central obesity (waist ≥ 102 cm in men, ≥ 88 cm in women); raised triglycerides [> 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality]; reduced HDL cholesterol level [< 40 mg/dl (1.03 mmol/l) in men, < 50 mg/dl (1.29 mmol/l) in women or specific treatment for this lipid abnormality]; raised BP (systolic BP > 130 or diastolic BP > 85 mmHg, or treatment of previously diagnosed hypertension); raised FPG [> 100 mg/dl (5.6 mmol/l), or previously diagnosed type 2 diabetes mellitus].

Insulin resistance was defined as the upper quartile of homeostatic model assessment of insulin resistance (HOMA-IR), which was calculated according to: (glucose × insulin)/22.5. Prevalent and incident diabetes were defined as clinical diagnosis of diabetes and/or use of anti-diabetic medication. History of kidney disease and cardiovascular disease (defined as diseases affecting the heart or blood vessels) were assessed through questionnaires. Hypertension was defined as systolic BP > 140 mmHg or diastolic BP > 90 mmHg or use of antihypertensive medication.

Overweight was defined according to ethnic cut-off points[18,19] as waist circumference (WC) ≥ 90 cm in African men, and ≥ 98 in African women, together with WC ≥ 94 cm in Caucasian men, and WC ≥ 80 cm in Caucasian women.

Statistical analysis

Variables that were skewed (NT-proBNP, TG and FPG) were log-transformed before analysis. Groups were compared using one-way ANOVA tests. We used linear regression analysis adjusted for age and gender to examine the associations per one standard deviation (SD) increment of log-transformed values of NT-proBNP at baseline with weight, body mass index (BMI), waist circumference, HbA_{1c}, FPG, insulin, HOMA-IR and TG values at baseline and re-examination. In order to get a true perspective of the effect of changes of NT-proBNP in the linear and logistic regression analysis, outcomes were related to one standard deviation of change of the ln-transformed values of NT-proBNP.

Logistic regression models were used to calculate: (1) odds ratios (OR) for prevalent overweight, IGT, hypertriglyceridaemia, the MetS and insulin resistance at baseline examination adjusted for age and gender, and (2) OR for incident diabetes [patients

Table 1. Characteristics of the study sample at baseline

Study sample	*Total*	*Caucasian*	*African*	p-*value*
Number	397	203	194	
Gender (% women)	50.1	50.7	49.5	0.803
Age (years)	44.7 ± 9.6	45.1 ± 10.9	44.4 ± 8.1	0.467
Systolic BP (mmHg)	132.9 ± 17.7	129.4 ± 15.1	136.6 ± 19.5	< 0.001
Diastolic BP (mmHg)	87.3 ± 12.8	84.1 ± 10.3	90.7 ± 14.2	< 0.001
Weight (kg)	82.9 ± 20.0	84.1 ± 21.2	81.7 ± 18.5	0.234
Body mass index (kg/m²)	28.9 ± 6.6	27.6 ± 5.9	30.2 ± 7.1	< 0.001
Waist circumference (cm)	93.5 ± 15.8	93.2 ± 16.1	93.7 ± 15.4	0.717
Triglycerides (mmol/l)	1.05 (0.72–1.53) 1.32 ± 1.06	0.97 (0.69–1.45) 1.21 ± 0.79	1.01 (0.77–1.57) 1.47 ± 1.29	0.023
Plasma glucose (mmol/l)	5.8 (5.4–6.3) 6.2 ±1.8	5.7 (5.4–6.2) 5.9 ± 0.67	5.9 (5.4–6.4) 6.5 ± 2.5	0.002
HbA_{1c} (%)	5.8 ± 0.9	5.5 ± 0.4	6.1 ± 1.2	< 0.001
Insulin (µU/ml)	13.4 ± 9.4	12.1 ± 8.5	14.8 ± 10.2	0.004
HOMA-IR	3.5 ± 3.1	3.2 ± 2.8	3.8 ± 3.4	0.041
NT-proBNP (ng/l)	31.5 (18.1–53.8) 46.3 ± 48.0	34.1 (19.9–55.1) 46.0 ± 47.0	29.9 (16.9–53.6) 46.5 ± 49.2	0.335
Prevalent diabetes, *n* (%)	11 (2.8)	2 (1.0)	9 (4.6)	0.027
CVD, *n* (%)	43 (10.8)	24 (11.8)	19 (9.8)	0.517
Hypertension, *n* (%)	179 (45.1)	63 (31.0)	116 (59.8)	< 0.001
Kidney disease, *n* (%)	9 (2.3%)	5 (2.5)	4 (2.1)	0.789

Values are means (± SD) or median (25–75th interquartile range). AHT = antihypertensive treatment; CVD = cardiovascular disease (coronary events or stroke); HOMA-IR = homeostatic model assessment of insulin resistance; NT-proBNP = N-terminal pro-brain natriuretic peptide

with diabetes (n = 37) at baseline examination excluded] per one SD increment of log-transformed values of NT-proBNP adjusted for age, gender, waist circumference and follow-up time to re-examination. NT-proBNP levels were divided into quartiles to explore the relationship between NT-proBNP and prevalent insulin resistance at baseline (adjusted for age and gender) as well as incident diabetes (adjusted for age, gender, waist circumference and follow-up time to re-examination). All analyses were performed using SPSS Windows version 23.0 and a two-tailed p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the differences between Caucasians and Africans are listed in Table 1. Africans had overall significantly worse metabolic status at baseline compared to Caucasians, with higher systolic and diastolic BP, BMI, and blood glucose, insulin, HOMA-IR and TG levels, and more prevalent diabetes cases. NT-proBNP levels were significantly higher in women compared to men (56.7 and 35.7 ng/l, respectively), however, there were no significant differences between Caucasians and Africans with regard to age, gender or NT-proBNP levels at baseline examination (Table 1). No significant differences between black and white women were observed (p = 0.861).

NT-proBNP and cross-sectional association with continuous metabolic parameters: baseline characteristics of the study samples are listed in Table 1. In cross-sectional linear regression analyses at baseline, each one SD increase in baseline values of NT-proBNP was significantly and inversely associated with body weight (β –2.23; p = 0.042), BMI (β –1.01; p = 0.007), waist circumference (β –1.82; p = 0.033), HbA_{1c} (β –0.14; p = 0.009), insulin (β –1.66; p = 0.002), HOMA-IR (β –0.47; p = 0.006) and TG (β –0.04; p = 0.002) (Table 2).

NT-proBNP and cross-sectional associations with dichotomous metabolic parameters: in cross-sectional gender- and age-adjusted analyses at baseline, each one SD increment of NT-proBNP was associated with reduced odds of prevalent overweight (Caucasians: OR: 0.79; 95% CI: 0.62–1.00; p = 0.045 and Africans: OR: 0.72; 95% CI: 0.57–0.92; p = 0.009), IGT (glucose: OR: 0.77; 95% CI: 0.60–0.99; p = 0.040 and HbA_{1c}: OR: 0.78; 95% CI: 0.62–0.99; p = 0.038), prevalent MetS (OR: 0.76; 95% CI: 0.60–0.96; p = 0.040), hypertriglyceridaemia (OR: 0.64; 95% CI: 0.47–0.87; p = 0.004) and insulin resistance (OR: 0.57; 95% CI: 0.43–0.76; p < 0.001) (Table 3).

The relative risk of insulin resistance at baseline decreased significantly across quartiles of baseline values of NT-proBNP. Compared with the lowest quartile of NT-proBNP, the OR (95% CI) for prevalent IR in subjects belonging to quartiles two, three and four was 0.83 (0.44–1.57), 0.30 (0.14–0.63) and 0.25

Table 3. Associations of one SD increment of NT-proBNP and prevalence of glucometabolic states at baseline

	SABPA baseline		
Dichotomous variables	*OR*	*95% CI*	p-*value*
Waist			
Caucasian cut-off	0.79	0.62–1.00	0.045
African cut-off	0.72	0.57–0.92	0.009
IGT (glucose > 5.6 mmol/l cut-off)	0.77	0.60–0.99	0.040
TG (> 1.7 mmol/l cut-off)	0.64	0.47–0.87	0.004
Prevalent MetS	0.76	0.60–0.96	0.023
IGT (HbA_{1c} > 5.7%)	0.78	0.62–0.99	0.038
Risk of belonging to HOMA-IR Q4	0.57	0.43–0.76	< 0.001

Logistic regressions are adjusted for age and gender. SD = standard deviation; NT-proBNP = N-terminal pro-brain natriuretic peptide; TG = triglycerides; IGT = impaired glucose tolerance; Mets = metabolic syndrome; HOMA-IR = homeostatic model assessment of insulin resistance; Q4 = upper quartile of HOMA-IR. Ethnic waist cut-off points are defined according to Alberti *et al.*[19] and Botha *et al.*[18]

Table 2. Associations of one SD increment of NT-proBNP and glucometabolic traits

	Whole population		*Caucasian*		*African*	
	Beta (SE)	p-*value*	*Beta (SE)*	p-*value*	*Beta (SE)*	p-*value*
Weight (kg)	–2.23 (1.09)	0.042	–0.75 (1.55)	0.628	–3.29 (1.41)	0.021
BMI (kg/m²)	–1.01 (0.37)	0.007	–0.61 (0.50)	0.223	–1.17 (0.50)	0.019
Waist (cm)	–1.82 (0.85)	0.033	–1.68 (1.19)	0.157	–1.92 (1.17)	0.101
HbA_{1c} (%)	–0.14 (0.05)	0.009	–0.01 (0.01)	0.039	–0.03 (0.01)	0.012
Glucose (mmol/l)	–0.01 (0.01)	0.062	–0.02 (0.01)	0.072	–0.03 (0.02)	0.081
Insulin (µU/ml)	–1.66 (0.52)	0.002	–0.11 (0.05)	0.019	–0.15 (0.05)	0.001
HOMA-IR	–0.47 (0.17)	0.006	–0.57 (0.23)	0.014	–0.45 (0.26)	0.082
TG (mmol/l)	–0.04 (0.01)	0.002	–0.07 (0.04)	0.124	–0.13 (0.04)	0.002

Age- and gender-adjusted linear regressions with outcome as a continuous variable. BMI = body mass index; NT-proBNP = N-terminal pro-brain natriuretic peptide; TG = triglycerides; Mets = metabolic syndrome; HOMA-IR = homeostatic model assessment of insulin resistance.

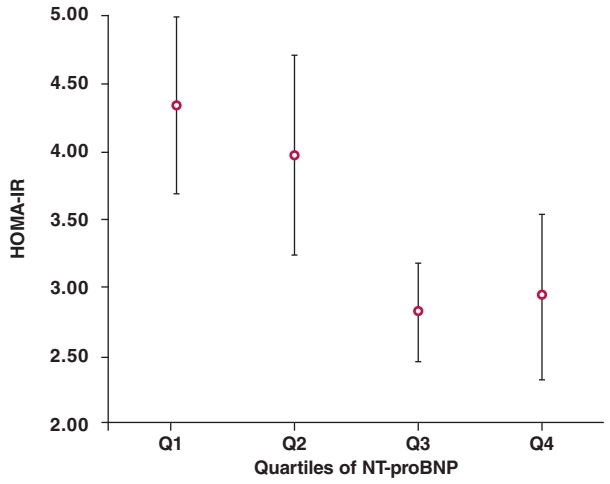

Fig. 2. Distribution of baseline HOMA-IR among quartiles of NT-proBNP. HOMA-IR = homeostatic model assessment of insulin resistance; NT-proBNP = N-terminal pro-brain natriuretic peptide; Q1 = quartile with the lowest NT-proBNP levels; Q4 = quartile with the highest NT-proBNP levels.

(0.11–0.56; p for linear trend < 0.0001), respectively (Table 4). Fig. 2 illustrates the distribution of baseline HOMA-IR among quartiles of NT-proBNP.

NT-proBNP and prospective association with diabetes: the relative risk of incident diabetes at re-examination decreased significantly across quartiles of baseline values of NT-proBNP. Compared with the lowest quartile of NT-proBNP, the OR (95% CI) for incident diabetes in subjects belonging to quartiles two, three and four was 0.54 (0.18–1.61), 0.43 (0.13–1.41) and 0.24 (0.06–0.96, p for linear trend = 0.041), respectively.

Bi-ethnic differences: in cross-sectional linear regression analyses at baseline of the African subjects, each one SD increase in baseline values of NT-proBNP was inversely associated with body weight (β –3.52; p = 0.021), BMI (β –1.25; p = 0.019), HbA_{1c} (β –0.22; p = 0.027), insulin (β –1.76; p = 0.035) and TG (β –0.06; p = 0.002), and borderline associated with FPG (β –0.01; p = 0.062) (Table 5). In the cross-sectional linear regression analyses at baseline of the Caucasian subjects, each one SD increase in baseline values of NT-proBNP was significantly inversely associated only with insulin (β –1.57; p = 0.015) and HOMA-IR (β –0.52; p = 0.014) (Table 5).

In the African study participants, in cross-sectional age- and gender-adjusted analyses at baseline, each one SD increment of NT-proBNP was associated with reduced risk of prevalent IGT (HbA_{1c}: OR: 0.64; 95% CI: 0.44–0.92; p = 0.015), hypertriglyceridaemia (OR: 0.61; 95% CI: 0.40–0.93; p = 0.022) and insulin resistance (OR: 0.52; 95% CI: 0.35–0.77; p = 0.001) (Table 6). In the Caucasian study participants, in cross-sectional age- and gender-adjusted analyses at baseline, each one SD increment of NT-proBNP was associated with reduced risk of prevalent IGT (glucose: OR: 0.62; 95% CI: 0.43–0.89; p = 0.009), the MetS (OR: 0.68; 95% CI: 0.49–0.96; p = 0.028) and insulin resistance (OR: 0.64; 95% CI: 0.42–0.99; p = 0.046) (Table 6).

Table 4. Associations of NT-proBNP quartiles and prevalent insulin resistance

	OR (95% CI)	p-*value*
Continuous NT-proBNP	0.57 (0.43–0.76)	< 0.001
Dichotomous NT-proBNP		
Q1 (lowest values)	Referent	
Q2	0.83 (0.44–1.57)	0.564
Q3	0.30 (0.14–0.64)	0.002
Q4 (highest values)	0.25 (0.11–0.56)	0.001
p for trend < 0.001		

Age and gender adjusted. NT-proBNP = N-terminal pro-brain natriuretic peptide; Q1 = quartile with the lowest NT-proBNP levels; Q4 = quartile with the highest NT-proBNP levels.

Table 5. Bi-ethnic associations of one SD increment of NT-proBNP and glucometabolic traits at baseline examination

	Caucasian (n = 203)		*African (n = 194)*	
	Beta (SE)	p-*value*	*Beta (SE)*	p-*value*
Body weight (kg)	–0.70 (1.44)	0.628	–3.52 (1.20)	0.021
BMI (kg/m²)	–0.57 (0.46)	0.223	–1.25 (0,53)	0.019
Waist (cm)	–1.56 (1.10)	0.157	–2.06 (1.25)	0.101
HbA_{1c} (%)	–0.061 (0.03)	0.052	–0.22 (0.10)	0.027
Glucose (mmol/l)	–0.01 (0.004)	0.072	–0.02 (0.01)	0.081
Insulin (µU/ml)	–1.57 (0.64)	0.015	–1.76 (0.83)	0.035
HOMA-IR	–0.52 (0.21)	0.014	–0.48 (0.27)	0.082
TG (mmol/l)	–0.03 (0.02)	0.124	–0.06 (0.02)	0.002

Linear regressions are adjusted for age and gender. NT-proBNP = N-terminal pro-brain natriuretic peptide; BMI = body mass index; TG = triglycerides; HOMA-IR = homeostatic model assessment of insulin resistance.

Discussion

In the SABPA study, undertaken in a middle-aged, bi-ethnic cohort, we observed that NT-proBNP was inversely associated with metabolic risk factors such as increased waist circumference and BMI, hypertriglyceridaemia, hyperglycaemia and insulin resistance. Moreover, in a prospective analysis, NT-proBNP was inversely associated with incident diabetes, findings in line with previous notions on NPs' involvement in protection against diabetes. Additionally, ethno-stratified analyses revealed that low NT-proBNP levels in Africans were associated with several metabolic conditions such as obesity, IGT, insulin resistance and hypertriglyceridaemia, whereas low NT-proBNP levels in Caucasians were associated with insulin resistance only.

The last two decades of research have demonstrated that NPs play an important role in the control of energy usage,[20] and

Table 6. Bi-ethnic associations of one SD of NT-proBNP increment and glucometabolic states at baseline examination

	Caucasian (n = 203)			*African (n = 194)*		
Dichotomous variables	*OR*	*95% CI*	p-*value*	*OR*	*95% CI*	p-*value*
Waist						
Caucasian cut-off	0.72	0.51–1.02	0.061	0.78	0.56–1.10	0.160
African cut-off	0.72	0.57–0.92	0.061	0.74	0.51–1.08	0.114
IGT (glucose > 5.6 mmol/l cut-off)	0.62	0.43–0.89	0.009	0.85	0.59–1.25	0.412
TG (TG >1.7 mmol/l cut-off)	0.66	0.42–1.04	0.075	0.61	0.40–0.93	0.022
Prevalent MetS	0.68	0.49–0.96	0.028	0.84	0.61–1.17	0.310
IGT (HbA_{1c} > 5.7% cut-off)	0.92	0.64–1.33	0.657	0.64	0.44–0.92	0.015
Risk of belonging to HOMA-IR Q4	0.64	0.42–0.99	0.046	0.52	0.35–0.77	0.001

The results are calculated and presented for each ethnic group separately. Logistic regressions are adjusted for age and gender. SD = standard deviation; NT-proBNP = N-terminal pro-brain natriuretic peptide; IGT = impaired glucose tolerance; TG = triglycerides; MetS = metabolic syndrome; HOMA-IR = homeostatic model assessment of insulin resistance; Q4 = upper quartile of HOMA-IR. Ethnic waist cut-off points are defined according to Alberti *et al.*[19] and Botha *et al.*[18]

have lipolytic properties.[21] Further, atrial NPs exhibit possible favourable effects on chronic inflammation.[22] Cross-sectional studies have demonstrated that NP levels are reduced in subjects with obesity, insulin resistance and type 2 diabetes,[8,23] conditions that are more common in black Africans. Reduced NP response is also associated with the activation of the renin–angiotensin system in experimental studies,[24] an association that could explain the inverse association of NPs and the MetS/insulin resistance. Moreover, several studies have prospectively shown that low levels of NPs are associated with insulin resistance and diabetes.[6,7,9,25]

NP levels were shown to be higher in women and increased with age, therefore all our analyses were age and gender adjusted.[26] Furthermore, a higher variability in NT-proBNP is seen in African Americans than in Caucasians.[27] As for ethno-stratified analyses, we found cross-sectional associations of low NT-proBNP levels and higher BMI, HbA_{1c}, insulin and TG levels in Africans, whereas in Caucasians, low NT-proBNP levels were associated with insulin resistance and higher insulin levels only.

These findings indicate that BNP may affect the propensity for metabolic disturbances differently in Africans and Caucasians, and may play a role in the cause of the higher rates of obesity, insulin resistance, hypertension and diabetes as seen in black Africans.[28,29] There is evidence that African Americans[13,14] but not black Africans have lower NT-proBNP levels than Caucasians, and low BNP levels are associated with higher LDL and TG levels.[30]

Although metabolic risk conditions are more common in blacks, the prevalence of the MetS in black American children and adults is likely underestimated due to the notion that hypertriglyceridaemia, one of the characteristics of the MetS, is observed less frequently in blacks than in whites.[31] Our findings on associations of low NT-proBNP levels and hypertriglyceridaemia in Africans but not Caucasians are therefore somewhat contradictory. The differences might be explained in part by higher intake of alcohol in the Africans in general.[32]

It was shown that subjects with a combination of obesity, diabetes and alcohol excess are prone to develop extremely high TG values.[33] Both the Dallas Heart study and the ARIC study demonstrated that NT-proBNP levels were lower in African Americans than in Caucasians.[11,14] In our study, no significant differences in NT-proBNP levels between Africans and Caucasians were observed, although there was a trend for Africans to have lower NT-proBNP levels (29.9 ng/l) compared with Caucasians (34.1 ng/l). However, NT-proBNP concentration is elevated in hypertension,[34] and a much larger proportion of Africans was hypertensive (n = 116; 59.8%) compared to Caucasians (n = 63; 31.0%), which might have influenced (elevated) NT-proBNP levels in the African population.

Additionally, conditions other than cardiac structural and functional changes influence NT-proBNP levels. Renal dysfunction is known to elevate NT-proBNP levels due to renal clearance of the prohormone.[35] Nonetheless, the proportion of subjects with renal disease in both the Africans and Caucasians was low (2.1 and 2.5%, respectively) and did not differ significantly between the ethnicities. However, prevalence of both cardiovascular and renal disease was assessed through questionnaires, which might be negated by the reporting bias of the participants. It remains to be explored whether the higher diabetes rates in blacks might be, at least partially, explained by genetically predisposed differences in NP levels.[6,7]

Assessment of NT-proBNP is used in clinical routine to identify subjects with heart failure. There is a need to evaluate, and possibly implement, enforced prevention strategies for early identification of subjects with the MetS and increased risk of diabetes development. This type of preventative strategy that could have a great impact on economic aspects of healthcare might include screening for subjects in the lowest quartiles of NT-proBNP. Together with other preventable risk factors, such as a sedentary lifestyle, NT-proBNP deficiency might help to identify individuals at highest risk of the MetS and diabetes development, and focus on prevention efforts.

Study limitations

The data in the SABPA study were collected at a single regional centre and the subjects were matched with regard to age, gender, socio-economic status and ethnicity, which limits the applicability to other populations. Also, as this was a cross-sectional study, it shares the usual limitations of causality and control, as seen for all cross-sectional studies. We had no data on prevalent heart failure, which might have affected the outcome of the analyses.

Furthermore, NPs are unstable hormones that undergo a rapid degradation in plasma. For this reason, immune-assays that target the more stable N-terminal fragments of the prohormones have been developed, and the N-terminal fragments serve as surrogate markers of the biologically active peptides.[36] Nevertheless, one must bear in mind that the measurements of the N-terminal fragments do not necessarily reflect actual levels of the biologically active, mature BNP.

Our samples were stored at –80°C from the baseline examination in 2008–2009 until analysis in 2015, which could be a limitation to our study, considering storage might have affected stability and degradation of NT-proBNP.

Conclusions

In a bi-ethnic cohort, NT-proBNP in the high-normal range was associated with a lower prevalence of metabolic risk factors such as high BMI, increased waist circumference, IGT, high insulin levels and hypertriglyceridaemia, with strongest associations for Africans in spite of similar NT-proBNP concentrations. This indicates that BNP may affect the propensity for metabolic disturbances differently in Africans and Caucasians.

The data that support the findings of this study are available from North-West University, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with the permission of North-West University.

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The contribution of plasma uric acid to the risk of stroke in hypertensive populations

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Abstract

Background: There is limited available evidence of a relationship between uric acid (UA) level and stroke in hypertensive populations worldwide. We aimed to estimate the relationship between UA level and stroke in Chinese hypertensive populations.

Methods: A total of 4 710 essentially hypertensive Chinese patients, including 307 with stroke, were recruited consecutively by cluster sampling from 60 communities in Shenzhen from April 2010 to September 2011. Demographic characteristics, UA level and stroke diagnosis were collected from every participant. Logistic regression analysis was used to estimate the association between UA level and stroke.

Results: The study population comprised 2 361 females and 2 349 males, with a mean age of 58 ± 11.75 years. There were significant associations between UA level and stroke and ischaemic stroke (IS) risk for females in the crude model (M0), model 1 (M1) and model 2 (M2), with increasing odds ratios (OR) as the quartiles (Q) increased. The odds of stroke risk was highest in Q4 in M2 (UA > 396 µmol/l, OR: 3.05, 95% CI: 1.74–5.36 and OR: 3.19, 95% CI: 1.74–5.85), but not for males in M0, M1 and M2. A significant dose–response relationship existed between UA level and stroke, and between UA level and IS for females but not for males. Hyperuricaemia (HU) was also significantly associated with stroke and IS for females but not for males. Taking negative uric acid, homocysteine, triglycerides, total cholesterol and low-density lipoprotein cholesterol (UA-Hcy-TG-TC-LDL-C-) as the reference, the combinations of UA+Hcy+TG-TC-LDL-, UA+Hcy+TG+TC+LDL-C- and UA+Hcy+TG+TC+LDL-C+ were significantly associated with the risk of stroke for females (OR = 2.48, 7.85 and 3.04).

Conclusion: High UA level could significantly increase stroke risk in female hypertensive patients. Female hypertensive patients may benefit from managing UA at normal levels for stroke prevention.

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Stroke is the second commonest cause of death and a major cause of long-term disability worldwide.[1,2] In China, the burden of stroke is increasing,[3] with an increasing annual incidence rate of 8.7%. Stroke has now become the leading cause of death,[4,5] moreover, stroke mortality is projected to double in the next two decades from two to four million deaths.[6]

Ischaemic stroke (IS) is the most common type of stroke, accounting for 63 to 84% of all strokes worldwide.[7] In China, IS has increased by 43.3% from 1990 to 2013,[8] with a 28-day fatality rate of 20%, whereas, haemorrhagic stroke (HS) accounts for 17.1 to 39.4% of all strokes, with the highest 28-day mortality rate of 49.4%.[9] The goal of stroke prevention is to identify high-risk populations and to target the modifiable risk factors.

In a study by Rapsomanik *et al.*, hypertensive patients had a higher lifetime risk of overall cardiovascular disease compared with normotensive patients.[10] From the index age of 30 years, hypertensive populations had higher lifetime risks of IS and HS than normotensive populations. Hypertension was also found to be closely related to uric acid (UA) level.[11-13]

Hypertension often accompanies a UA metabolic disorder, thereby leading to hyperuricaemia (HU). A systematic review from five countries from North America, Asia and Europe showed a significant association between HU and increased risk of hypertension, particularly in young individuals and women.[13] Moreover, a systematic review and meta-analysis indicated that HU may modestly increase the risks of both stroke incidence and mortality.[14] While many studies have shown significant associations between UA level and stroke in the general population,[15-18] few focused on hypertensive populations.[19]

We therefore conducted this cross-sectional study to estimate the association between plasma UA level and the risk of stroke,

including IS and HS, in hypertensive populations, as well as the association between the combination of UA and total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and homocysteine (Hcy) levels and stroke risk.

Methods

We recruited 4 710 consecutive hypertensive patients from the hypertension management information system of 60 community health service centres (CHSCs) in Nanshan District, Shenzhen, from April 2010 to September 2011. Eight sub-districts were selected in Nanshan district, and then six to eight communities were selected from each sub-district using a simple random procedure according to a sequence of computer-generated random numbers.

Written informed consent was obtained from all participants. The study was approved by the ethics committee of the collaborating hospitals and Nanshan Center for Chronic Disease Control.

All the hypertensive patients were diagnosed in one of the collaborating hospitals, according to at least three blood pressure tests at different times, and registered in the electronic information system of CHSC. There were 307 stroke patients among the 4 710 hypertensive patients.

The following information was collected through in-person, standardised questionnaire interviews: age, gender, smoking, alcohol use, leisure and occupational physical activities, detailed history of hypertension and medications used, and family history of IS. Height and weight were measured using standard methods, with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2).

Both leisure and occupational physical activity levels were assessed as in a previous study.[20] Drinking categories were determined according to the content of National Institute on Alcohol Abuse and Alcoholism (NIAAA).[21]

Blood samples were collected from each participant after overnight fasting and centrifuged for 15 minutes at room temperature at 3 000 rpm. Biochemical measurements included fasting glucose, TC, TG, LDL-C, UA, Hcy and creatinine (Cr) levels. TC, TG, LDL-C and glucose levels were measured using enzymatic methods, UA was determined quantitatively with uricase, Cr was detected by the Jaffe method, and Hcy was measured with a circulating enzymatic method. All of these indicators were tested on an automatic biochemical analyser (HITACH 7080). We calculated estimated glomerular filtration rate (eGFR) according to the formula: eGFR (ml/min per 1.73 m^2) = 175 × plasma $creatinine^{-1.234}$ × $age^{-0.179}$ × 0.79 (if female).[22]

Normal values for the serological markers were as follows: TC ≥ 5.18 mmol/l; TG ≥ 1.7 mmol/l; LDL-C ≥ 3.37 mmol/l; HU > 360 µmol/l in females; HU > 416 µmol/l in males; and Hcy > 15 mmol/l.[23-25] Participants were divided into four groups by quartiles (Q1– Q4) of serum UA level: ≤ 274, 274–332, 332–396 and > 396 µmol/l.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a standard mercury sphygmomanometer on the right arm of seated participants after five minutes of rest. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or current use of medication to control blood pressure.[26]

We included cerebral infarction, embolism and small-vessel disease as indicative of IS, and intracerebral haemorrhagic or subarachnoid haemorrhagic stroke as an event of HS. The stroke subtypes (ischaemic, intracerebral haemorrhagic and subarachnoid haemorrhagic) were independently adjudicated retrospectively by two neurologists using a standardised manner based on clinical assessment and neuro-imaging (computed tomography or magnetic resonance imaging). IS and HS diagnoses were also validated through the Stroke Registration system in Shenzhen.

Statistical analysis

Qualitative data are presented as frequency (%) and were analysed using the chi-squared test. Quantitative data are presented as mean [standard deviation (SD)] and were analysed by t-test, or as median [interquartile range (IQR)] and if not normally distributed, were analysed by non-parametric tests.

The association between UA level and stroke was estimated by logistic regression model, with the lowest quartile of UA and normo-uricaemia as the reference. Corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the crude model (M0), multivariable model 1 (M1) adjusted for age and gender, and multivariable model 2 (M2) adjusted for age, gender, BMI, TG, TC, LDL-C, Cr, glucose, Hcy, heart ratio, SBP, DBP, drinking, smoking, sport, heart failure, kidney disease, hypertensive retinopathy, diabetes, family history of stroke and hypertension years.

We selected four serological indicators (TG, TC, LDL-C, Hcy), based on their effect on UA level and stroke,[27-29] in combination with UA level to estimate their associations with stroke risk. The normal values of all four serological markers were used as reference. Statistical analyses were performed with the SAS 9.1 (SAS Inst, Inc, Cary, NC, USA). The forest plot was conducted by R 3.1. All tests were two-sided with a statistical significance level of < 0.05.

Table 1. Demographic and clinical characteristics of the participants

	Stroke			*Total*
Variables	*No (n = 4403)*	*Yes (n = 307)*	p-*value*	*(n = 4710)*
Age	57.68 ± 11.72	62.57 ± 11.16	< 0.0001	58.00 ± 11.75
TG	2.06 ± 1.58	1.87 ± 1.49	0.0449	2.04 ± 1.58
TC	5.18 ± 1.01	5.07 ± 1.07	0.0639	5.17 ± 1.02
LDL-C	3.16 ± 0.79	3.01 ± 0.85	0.0011	3.15 ± 0.80
BMI	24.81 ± 3.03	24.44 ± 3.20	0.0422	24.78 ±3.05
SBP	134.39 ± 14.99	134.20 ± 14.18	0.8233	134.38 ± 14.94
DBP	83.17 ± 10.38	82.21 ± 9.03	0.0760	83.10 ± 10.30
Heart rate	75.26 ± 7.66	75.03 ± 7.84	0.6152	75.24 ± 7.67
Cr	81.90 ± 18.47	81.85 ± 23.92	0.9673	81.90 ± 18.87
Glucose	5.93 ± 1.28	5.78 ± 1.55	0.1202	5.92 ± 1.30
Hcy	14.80 ± 9.81	17.36 ± 14.26	0.0022	14.97 ± 10.18
UA	339.16 ± 94.76	354.66 ± 97.65	0.0057	340.17 ± 95.02
Hypertension years			< 0.0001	
< 2	891 (18.92)	37 (0.79)		928 (19.70)
2+	1288 (27.35)	53 (1.13)		1341 (28.47)
5+	1037 (22.02)	81 (1.72)		1118 (23.74)
> 10	1187 (25.20)	136 (2.89)		1323 (28.09)
eGFR	87.66 ± 27.88	87.87 ± 21.56	0.8408	87.68 ± 27.51

SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; UA, uric acid; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Hcy, homocysteine; BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate.

Table 2. The association between UA level and stroke risk

	UA (μmol/l)					
Variables	*Q1 (UA ≤ 274)*	*Q2 (274 < UA ≤ 332)*	*Q3 (332 < UA ≤ 396)*	*Q4 (UA > 396)*	p-*value*	*Hyperuricaemia vs normo-uricaemia*
Male (stroke/non-stroke)	19/269	27/461	50/663	55/805		151/2198
M0	1	0.83 (0.45–1.52)	1.07 (0.62–1.85)	0.97 (0.56–1.66)	0.7851	1.05 (0.74–1.50)
M1	1	0.87 (0.47–1.60)	1.10 (0.64–1.91)	1.01 (0.59–1.73)	0.8157	1.07 (0.75–1.53)
M2	1	0.89 (0.47–1.67)	1.27 (0.71–2.28)	1.40 (0.76–2.58)	0.3426	1.34 (0.90–2.00)
Female	45/856	40/639	36/429	35/281		156/2205
M0	1	1.19 (0.77–1.845)	1.60 (1.01–2.51)	2.37 (1.49–3.76)	0.0018	1.80 (1.27–2.55)
M1	1	1.14 (0.74–1.773)	1.42 (0.90–2.24)	2.04 (1.27–3.25)	0.0209	1.58 (1.11–2.25)
M2	1	1.26 (0.80–2.008)	1.81 (1.10–2.97)	3.05 (1.74–5.36)	0.0008	1.89 (1.27–2.81)
Total	64/1125	67/1100	86/1092	90/1086		307/4403
M0	1	1.07 (0.75–1.52)	1.38 (0.99–1.93)	1.46 (1.05–2.03)	0.0633	1.36 (1.06–1.75)
M1	1	1.07 (0.75–1.53)	1.36 (0.96–1.93)	1.46 (1.03–2.08)	0.0996	1.30 (1.01–1.67)
M2	1	1.19 (0.82–1.72)	1.69 (1.17–2.45)	2.13 (1.42–3.20)	0.0010	1.58 (1.20–2.09)

M0: crude model not adjusted, M1: model 1 adjusted by age and gender, M2: model 2 adjusted by age, gender, BMI, TG, TC, LDL-C, Cr, glucose, Hcy, heart ratio, SBP, DBP, drinking, smoking, sport, heart failure, kidney disease, hypertensive retinopathy, diabetes, family history of stroke and hypertension years. Q: quartile.

Results

We recruited 4 710 hypertensive patients (male 2 349 and female 2 361) with a mean age of 58 years in this cross-sectional study. The mean age was 63 years in the 307 patients with stroke (male 151 and female 156) and 58 years in the 4 403 patients without stroke (male 2 198 and female 2 205). The characteristics of the 4 710 hypertensive patients are shown in Table 1.

For females, there were significant associations between UA level and stroke risk in M0, M1 and M2, with increasing ORs as the quartiles increased, and the odds of stroke risk was highest at Q4 in M2 (UA > 396 μmol/l, OR: 3.05, 95% CI: 1.74–5.36). However, there were no significant associations between UA level and stroke risk for males in M0, M1 and M2. For all participants, there were significant associations between UA level and stroke risk only in M2, with significantly increasing ORs of stroke risk across the quartiles (the highest OR was 2.13, 95% CI: 1.42–3.20 for Q4).

A significant dose–response relationship between UA level and stroke in all participants ($p = 0.0010$) was mainly driven by females ($p = 0.0008$) but not by males. HU could significantly increase stroke risk comparing with normo-uricaemia in all participants (OR: 1.58, 95% CI: 1.20–2.09) and in females (OR: 1.89, 95% CI: 1.27–2.81) in M2 but not in males. Details are shown in Table 2.

We observed significant associations between UA level and IS for Q4 versus Q1 and Q3 versus Q1 in M2 in all participants (OR: 1.99, 95% CI: 1.29–3.06 and OR: 1.69, 95% CI: 1.15–2.50) and in females (OR: 3.19, 95% CI: 1.74–5.85 and OR: 2.06, 95% CI: 1.22–3.47) but not in males. A significant dose–response relationship between UA level and IS also existed in females and all participants ($p = 0.0007$ and 0.0033) but not in males. Details are shown in Table 3.

We also observed a significant association between HU and IS with OR of 1.55 (95% CI: 1.15–2.08) in M2 (Fig. 1). However, there was no significant association between HU and HS in M0, M1 and M2 (Fig. 2).

As shown in Table 4, taking UA-Hcy-TG-TC-LDL-C- as reference category, none of the combinations was significantly associated with stroke risk for males. Combination UA+Hcy+TG-TC-LDL-C- was significantly associated with

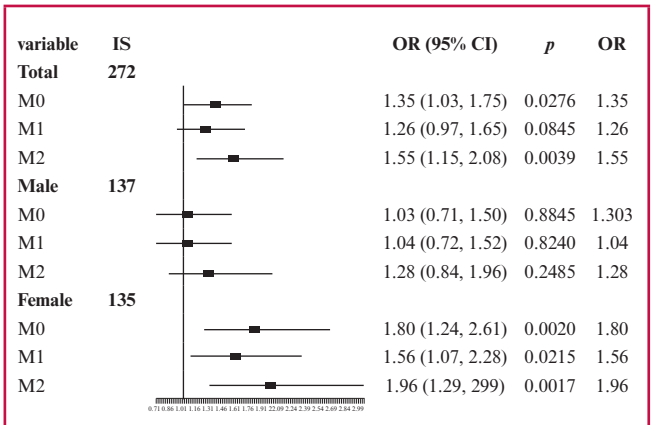

Fig. 1. Forest plot showing associations between UA and IS. M0: crude model not adjusted. M1: model 1 adjusted by age and gender. M2: model 2 adjusted by age, gender, BMI, TG, TC, LDL-C, Cr, glucose, Hcy, heart ratio, SBP, DBP, drinking, smoking, sport, heart failure, kidney disease, hypertensive retinopathy, diabetes, family history of stroke and hypertension years.

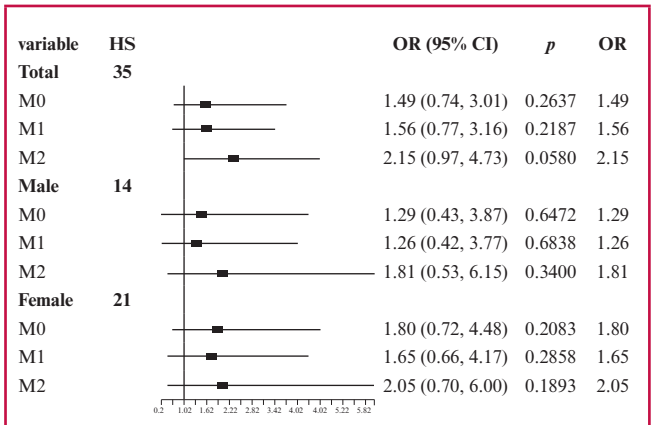

Fig. 2. Forest plot showing associations between HU and HS. M0: crude model not adjusted, M1: model 1 adjusted by age and gender, M2: model 2 adjusted by age, gender, BMI, TG, TC, LDL-C, Cr, glucose, Hcy, heart ratio, SBP, DBP, drinking, smoking, sport, heart failure, kidney disease, hypertensive retinopathy, diabetes, family history of stroke and hypertension years.

Table 3. The association between UA level and IS risk

	UA (μmol/l)				
Variables	*Q1 (UA ≤ 273)*	*Q2 (273 < UA ≤ 332)*	*Q3 (332 < UA ≤ 396)*	*Q4 (UA > 396)*	p-*value*
Male (stroke/non-stroke)	18/261	24/469	46/663	49/805	
M0	1	0.74 (0.40–1.39)	1.01 (0.57–1.77)	0.88 (0.51–1.54)	0.6649
M1	1	0.78 (0.41–1.47)	1.04 (0.59–1.84)	0.92 (0.53–1.61)	0.7239
M2	1	0.77 (0.40–1.48)	1.16 (0.63–2.12)	1.22 (0.65–2.30)	0.3946
Female	39/851	33/644	34/429	29/281	
M0	1	1.12 (0.70–1.80)	1.73 (1.08–2.78)	2.25 (1.37–3.71)	0.0043
M1	1	1.07 (0.66–1.72)	1.53 (0.94–2.46)	1.91 (1.15–3.17)	0.0428
M2	1	1.25 (0.76–2.06)	2.06 (1.22–3.47)	3.19 (1.74–5.85)	0.0007
Total	57/1112	57/1113	80/1092	78/1086	
M0	1	1.00 (0.69–1.46)	1.43 (1.01–2.03)	1.40 (0.99–1.99)	0.0558
M1	1	0.99 (0.67–1.44)	1.37 (0.95–1.97)	1.36 (0.93–1.97)	0.1339
M2	1	1.11 (0.75–1.64)	1.69 (1.15–2.50)	1.99 (1.29–3.06)	0.0033

M0: crude model not adjusted, M1: model 1 adjusted by age and gender, M2: model 2 adjusted by age, gender, BMI, TG, TC, LDL-C, Cr, glucose, Hcy, heart ratio, SBP, DBP, drinking, smoking, sport, heart failure, kidney disease, hypertensive retinopathy, diabetes, family history of stroke and hypertension years, Q: quartile.

stroke risk, with ORs of 2.48 and 4.48 for all participants and females. Combinations UA+Hcy+TG+TC+LDL-C- and UA+Hcy+TG+TC+LDL-C+ were significantly associated with stroke risk, with ORs of 7.85 and 3.04 for females but not for all participants. All other combinations were non-significant.

Discussion

We observed a significant association between UA level and stroke risk in females but not in males. The combinations of UA+Hcy+TG-TC-LDL-C-, UA+Hcy+TG+TC+LDL-C- and UA+Hcy+TG+TC+LDL-C+ could significantly increase the risk of stroke.

We observed significant associations between UA level and stroke risk for females and all participants, which was consistent with the Rotterdam study,[17] but differed from the study of elderly patients with isolated systolic hypertension[30] and a Chinese hypertensive cohort study.[19]

In the general population, two systematic reviews across countries identified consistently significant associations between UA level and stroke for men and women.[31,32] The inconsistent associations between UA level and stroke risk may be explained by the dual characteristics of UA.

UA can exert neuroprotective effects by acting as a free radical scavenger,[33] therefore, UA may reduce the risk of neurological disease, especially vascular and non-vascular dementia.[34] However, as a molecule generated locally in the vessel wall, UA stimulates vascular smooth cell proliferation, which may directly lead to the development of microvascular disease and afferent arteriolopathy. UA also has a pro-inflammatory effect on the vascular cell, with activation of P38, MAPK, NF-KB and AP-1, and increased expression of cyclooxygenase-2 (COX-2) and monocyte chemo-attractant protein-1 (MCP-1).[35]

We identified a significant dose–response relationship between UA level and stroke in female hypertensive patients, which was consistent with the AMORIS study.[36] The gender-specific difference in the association between UA level and stroke may be due to differences in their endocrine profile, because sex steroids play a significant role in UA regulation in biological fluids.[37] Besides, high levels of UA were associated with silent brain infarction, which strongly increased the risk of stroke in females.[38,39] The menopause status in women may also explain the gender-specific difference. UA levels are known to increase in postmenopausal women because oestrogen can increase the renal excretion rate of urate.[40,41]

In the subgroup analyses stratified by stroke subtypes comparing HU with normo-uricaemia, we observed significant associations only between HU and IS. The small sample size of HS and the different pathogenesis of IS and HS may explain the non-significant association between HU and HS because UA could stimulate vascular smooth muscle cell (VSMC) proliferation and oxidative stress[42] and induce IS.

Previous prospective studies focused on the relationship between UA level and stroke in various populations such as in an older general population,[36] and hypertensive participants with different diagnosis criteria.[16,17] Our study was consistent with two studies conducted in China and Australia,[16,36] and was at variance with one study conducted in China.[19]

Table 4. The relationships between different combinations of UA, Hcy, TG, TC and LDL and stroke

Combinations	*Number (non-stroke/stroke)*	*OR*	*95% CI*	p-*value*
Female				
UA-Hcy-TG-TC-LDL-C-	455/29	1	1	1
UA+Hcy-TG-TC-LDL-C-	63/7	1.74	0.73–4.15	0.2087
UA+Hcy+TG-TC-LDL-C-	21/6	4.48	1.68–11.97	0.0027
UA+Hcy+TG+TC-LDL-C-	25/2	1.26	0.28–5.56	0.7647
UA+Hcy+TG+TC+LDL-C-	4/2	7.85	1.38–44.63	0.0202
UA+Hcy+TG+TC+LDL-C+	31/6	3.04	1.17–7.86	0.0221
Male				
UA-Hcy-TG-TC-LDL-C-	332/26	1	1	1
UA+Hcy-TG-TC-LDL-C-	60/6	1.28	0.50–3.23	0.6062
UA+Hcy+TG-TC-LDL-C-	83/12	1.85	0.89–3.81	0.0975
UA+Hcy+TG+TC-LDL-C-	88/6	0.87	0.35–2.18	0.7675
UA+Hcy+TG+TC+LDL-C-	26/3	1.47	0.42–5.19	0.5466
UA+Hcy+TG+TC+LDL-C+	66/5	0.97	0.36–2.61	0.9478
Total				
UA-Hcy-TG-TC-LDL-C-	787/55	1	1	1
UA+Hcy-TG-TC-LDL-C-	123/13	1.51	0.80–2.85	0.2007
UA+Hcy+TG-TC-LDL-C-	104/18	2.48	1.40–4.38	0.0018
UA+Hcy+TG+TC-LDL-C-	113/8	1.01	0.47–2.18	0.9736
UA+Hcy+TG+TC+LDL-C-	30/5	2.39	0.89–6.39	0.0838
UA+Hcy+TG+TC+LDL-C+	97/11	1.62	0.82–3.21	0.1635

Reference: UA-Hcy-TG-TC-LDL-C-

Elevated UA level was significantly associated with the metabolic syndrome and dyslipidaemia, including high LDL-C levels, hypercholesterolaemia and hypertriglyceridaemia.[27] Hypercholesterolaemia was significantly associated with higher cardiovascular disease risk,[28] and hyperhomocysteinaemia was significantly associated with stroke risk.[29] Therefore, we selected TC, TG, Hcy and LDL-C to combine with UA.

The combination of UA+Hcy+TG-TC-LDL-C- could significantly increase the risk of stroke for females and all participants. There were also significant associations between the combinations UA+Hcy+TG+TC+LDL-C- and UA+Hcy+TG+TC+LDL-C+ and the risk of stroke. However, the sample size was relatively small with some of these combinations. More studies with larger sample sizes are needed to shed light on the association between the combinations of UA level and other serological indicators and stroke risk.

As a community-based, cross-sectional study, we must consider the limitations in deriving conclusions. First, based on the characteristics of a cross-sectional study, our results can be used as a preliminary cause hypothesis only and further research is needed to verify the hypothesis. Second, due to the small sample size of HS, we did not explore the association between UA level and HS across quartiles of UA. Finally, in estimating the associations between different combinations of UA, Hcy, TG, TC and LDL-C and stroke, the small sample sizes of different combinations may have limited the statistical power.

Conclusion

We observed significant associations between UA level and stroke as well as IS in females but not in males. Female hypertensive patients may benefit from managing UA at the normal levels for stroke prevention.

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Statins linked to doubled risk of type 2 diabetes

A study of thousands of patients' health records found that those who were prescribed cholesterol-lowering statins had at least double the risk of developing type 2 diabetes. The detailed analysis of health records and other data from patients in a private insurance plan in the Midwest provides a real-world picture of how efforts to reduce heart disease may be contributing to another major medical concern, said Victoria Zigmont, who led the study as a graduate student in public health at The Ohio State University.

Statins are a class of drugs that can lower cholesterol and blood pressure, reducing the risk of heart attack and stroke. More than a quarter of middle-aged adults use a cholesterol-lowering drug, according to recent federal estimates.

Researchers found that statin users had more than double the risk of a diabetes diagnosis compared to those who didn't take the drugs. Those who took the cholesterol-lowering drugs for more than two years had more than three times the risk of diabetes. 'The fact that increased duration of statin use was associated with an increased risk of diabetes – something we call a dose-dependent relationship – makes us think that this is likely a causal relationship, Zigmont said.

'That said, statins are very effective in preventing heart attacks and strokes. I would never recommend that people stop taking the statin they've been prescribed based on this study, but it should open up further discussions about diabetes prevention and patient and provider awareness of the issue.'

Researchers also found that statin users were 6.5% more likely to have a troublingly high HbA1c value – a routine blood test for diabetes that estimates average blood sugar over several months.

The study included 4 683 men and women who did not have diabetes, were candidates for statins based on heart disease risk and had not yet taken the drugs at the start of the study. About 16% of the group – 755 patients – were eventually prescribed statins during the study period, which ran from 2011 until 2014. Participants' average age was 46 years.

Randall Harris, a study co-author and professor of medicine and public health at Ohio State, said that the results suggest that individuals taking statins should be followed closely to detect changes in glucose metabolism and should receive special guidance on diet and exercise for prevention.

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Relationship between physical activity and carotid intima–media thickness among teachers in South Africa: the SABPA study

Tamrin Veldsman, Mariette Swanepoel, Makama A Monyeki, Johanna S Brits, Leoné Malan

Abstract

Objective: To determine the relationship between objectively measured physical activity (PA) and carotid intima–media thickness (CIMT) in teachers in South Africa.

Methods: A cross-sectional study was conducted among 215 teachers aged 25 to 65 years (mean age 49.67 ± 8.43 years) who participated in the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study. Ultrasound CIMT imaging was done using the SonoSite Micromaxx over seven consecutive days. Other measurements obtained included body mass index (BMI), waist circumference, 24-hour ambulatory blood pressure, and C-reactive protein (CRP) and fasting blood total cholesterol levels. Data were analysed using Statistical Package for Social Sciences (SPSS) version 25.

Results: The prevalence of obesity according to BMI and sedentary behaviour was above30%; hypertension was 38.9% and low-grade inflammation (CRP) was 41.1%. Male teachers showed higher mean values for CIMT than female teachers (0.75 ± 0.16 vs 0.66 ± 0.12 mm; $p \leq 0.05$). A borderline negative association existed between CIMT and mean seven-day awake metabolic equivalent of task ($r = –0.19$; $p = 0.08$) in female teachers in the light-PA group. CIMT was inversely associated with total energy expenditure ($r = –0.31$; $p = 0.05$) in sedentary male teachers.

Conclusion: Participation in light PA was associated with lower CIMT values in female teachers. Given the health implications of cardiovascular disease risk among teachers, PA intervention studies are recommended to determine effective interventions to provide information on how to decrease the progression of subclinical atherosclerosis in this population.

Keywords: carotid intima–media thickness, physical activity, South Africa

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Undeniable evidence exists about the protective role of regular physical activity (PA) in the development of chronic diseases;[1-4] however, high levels of physical inactivity continue to be a major public health concern in the 21st century.[5] The global recommendation for adult participation in PA is at least 150 minutes of accumulated moderate-intensity activity per week for at least 10 minutes continuously.[6] One in five adults globally does not meet the PA recommendations.[7] In South Africa, more than one-third (38.2%) of the population does not participate in sufficient PA,[8] and in a 51-country survey, the country was ranked as having the third-highest prevalence of physical inactivity.[9] Physical inactivity, obesity and hypertension are directly associated with the risk of developing cardiovascular disease (CVD) and atherosclerosis.[10-12]

Atherosclerosis is an active inflammatory process involving changes in cell behaviour and lipid accumulation in arteries and can be considered as one of the underlying causes of coronary heart disease events.[13-16] Additionally, C-reactive protein (CRP), as a biomarker for atherosclerosis,[17] has been linked to an increase in carotid intima–media thickness (CIMT) progression.[18] Weingärtner and colleagues[19] also revealed that serum cholesterol was positively associated with CIMT among the healthcare workers at the Saarland University Hospital in Homburg/Saar, Germany. Of concern are the results of a study by Laurence and colleagues[20] in 489 teachers from Cape Town, which reported 18.7% of the teachers to be at a high risk of developing a heart attack or stroke within 10 years.

Using left CIMT, a non-invasive sonographic measurement of atherosclerosis, may enable the prediction of future vascular events such as stroke and myocardial infarction[16] before they happen. Koolhaas *et al.*[21] conducted the population-based Rotterdam Study, including 5 344 adults, and suggested that the beneficial impact of regular PA on CVD might outweigh the negative effect of high body mass index (BMI) among middle-aged and older adults. Conversely, a study by Zulkepli *et al.*[22] using subjective measures of PA revealed no significant correlation between PA level and CVD risk factors. One study found that higher levels of moderate-to-vigorous PA was associated with lower CIMT, and participants who were sedentary had an increased CIMT.[23] A study in Caucasian men and women indicated a positive association between CIMT and time spent sedentary, and a negative association with light PA,[24] while another study in Danish adolescents did not find any

associations between moderate-to-vigorous PA or vigorous PA and CIMT.[25]

Teachers are considered to be in a high-stress profession where sub-optimal facilities, lack of support, unsupportive parents, teaching evaluation and time-management issues, changes in curricula, organisational policies, heavy workload, overcrowded classes, limited resources, high accountability, uncertainties over job security, low salaries, fatigue and parental expectations all contribute to the stress associated with the profession.[26-29] Due to the workload and nature of the occupation, teachers spend a lot of their time sedentary and little time at higher levels of PA.[30] The high job demands together with a lack of PA may lead to high blood pressure, heart disease, stroke, diabetes and cancer.[27,28] Cardiovascular disease and physical inactivity are among the significant causes of mortality and morbidity in both the general population[31,32] and in teachers.[20] We aimed therefore to investigate the relationship between objectively measured PA over seven consecutive days and CIMT among teachers in South Africa.

Methods

This research formed part of the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study, which commenced in 2008/2009 (phase 1) and was followed up in 2011/2012 (phase 2). Phase 2 data were collected similarly to the phase 1 baseline measurements.[33] Given the objective of the study, a cross-sectional study design was followed using the second phase of measurement.

Urban-dwelling South African school teachers residing in the Dr Kenneth Kaunda education district (Potchefstroom and Klerksdorp), North West Province, South Africa, were recruited to participate in the SABPA study (n = 2 170). The study excluded pregnant or lactating female teachers, users of α- and β-blockers, psychotropic substance abusers, blood donors or people vaccinated in the last three months, or individuals with tympanum temperature ≥ 37.5°C. Preliminary screening identified eligible participants (n = 409), all of whom were school teachers (aged 25–65 years) of similar socio-economic standing. Participants who wore the ActiHeart (GBO/67703, CamNtech Ltd, Cambridgeshire, UK) for a full seven days or had less than 40 minutes of 'lost' time (n = 216) in phase 2 were included.

The SABPA study was approved by the Ethics Review Board of the North-West University (Potchefstroom campus: NWU-0036-07-S6) and adhered to the principles outlined in the Declaration of Helsinki (2004). Permission to conduct this study was obtained from the North West Department of Education, as well as the South African Democratic Teachers Union. All participants voluntarily signed an informed consent form before any data were collected.

A 24-hour standardised diet was provided. Each participant's data were collected over eight days. During the first two days, 24-hour ambulatory blood pressure, information on lifestyle risk factors and cardiovascular and biochemical measurements were collected. For the following seven days, an ActiHeart recorded the participant's PA. The participants stayed over at the Metabolic Unit research facility at North-West University where they were introduced to the experimental set-up and were assigned a private bedroom.

Before resuming their normal activities on day 1, the Cardiotens ambulatory blood pressure (BP) monitor (Meditech, Budapest, Hungary) was fitted to measure 24-hour BP. Normal BP, categorised as systolic BP (SBP) and diastolic BP (DBP), was 130/80 mmHg.[34]

On the second day of measurements, body composition and CIMT were measured. Participants' height (cm), body weight (kg) and waist circumference (WC; cm) were measured by two level-two kinanthropometrists in triplicate according to the International Society for the Advancement of Kinanthropometry (ISAK).[35] Waist-to-height ratio (WHtR) of the participants was calculated as weight (kg)/height (m).

BMI was calculated as weight (kg)/height (m)^2 and expressed in kg/m^2.[36] BMI was classified according to the cut-off points of the American College of Sports Medicine (ACSM)[36] as follows: underweight = BMI < 18.5 kg/m^2; normal weight = BMI between 18.5 and 24.9 kg/m^2; overweight = BMI between 25.0 and 29.9 kg/m^2; and obesity = BMI ≥ 30 kg/m^2. Intra- and inter-observer variability were less than 5%.

PA of the participants was measured using a combined heart rate and accelerometer (the ActiHeart) over seven consecutive days. Participants were requested to continue with their daily activities, continuously wearing the ActiHeart monitor while awake or asleep. Individual step test calibration was not performed due to the high cardiovascular risk profiles of various participants[37] and time restrictions during clinical data collection. Therefore, self-reported PA was used to programme the ActiHeart for each participant.[38]

The resting heart rate of the participants was obtained from a resting 12-lead electrocardiogram (NORAV Medical Ltd PC 1200, software v5.030, Kiryat Bialik, Israel), performed by a registered nurse, and was used to calculate the sleeping heart rate required to be entered into the ActiHeart program when the device was being fitted to each participant.

The seven-day recordings for each participant were visually assessed to distinguish between time spent awake (awake time) and time spent asleep. Heart rate, metabolic equivalent of task (METs) and activity levels were used to distinguish between time spent awake and asleep. When the heart rate gradually decreased (throughout 15 or more epochs) in the evening to less than the average heart rate in a selected awake-time sedentary sample period, and the activity level was equal to zero, the participant was considered to be sleeping. The end of sleeping time could clearly be seen by an immediate increase in heart rate of more than 10 to 20 beats per minute, as well as increased METs and increased activity level.

The ActiHeart software was used to derive daily time spent in various MET categories according to activity energy expenditure (AEE). The derived daily time spent in multiple MET categories was grouped according to daily awake time being sedentary (≤ 1.5 METs) and time participating in light-intensity PA (1.5–3 METs).[39] AEE, total energy expenditure (TEE) and PA level (PAL) were also determined by the ActiHeart using inbuilt equations based on a branched model approach, calculated based on the combination of heart rate and accelerometer. PAL was calculated as TEE/resting energy expenditure (REE).

Ultimately, after the data were analysed, participants were allocated to one of two PA groups for analysis purposes, sedentary (≤ 1.5 METs) or light-intensity PA (1.5–3 METs), depending on their total activity levels. Only one participant was classified as moderate-to-high PA (> 3 METs) and, based on

statistical power principles, this individual was excluded from the statistical analyses.

High-resolution ultrasound CIMT scans were used to determine structural changes or subclinical atherosclerosis. CIMT images from two ideal angles of the left and right common carotid artery segments were captured using a SonoSite Micromaxx ultrasound system (SonoSite Inc, Bothell, WA, USA) and a 6–13-MHz linear display transducer, using previously described protocols.[14] Images were digitised and imported to Artery Measurement Systems automated software (AMS, Gothenburg, Sweden, v1.130) for analysing CIMT.[40,41] A maximal 10-cm segment with good-quality imaging was used for analysis. The program automatically detects the borders of the intima–media of the near and far wall, as well as the inner diameter of the vessel, and calculates CIMT. For this study, the far wall left CIMT measurements were used.

Intra-observer variability was 0.04 mm between two measurements taken four weeks apart on the same 10 participants. CIMT of > 0.9 mm was regarded as subclinical atherosclerosis.[42] The images were also examined for the presence of plaque at the right and left bifurcation of the internal carotid artery. Plaque was defined as a focal structure encroaching into the arterial lumen by at least 0.5 mm or by 50% of the surrounding intima–media thickness or demonstrating a thickness > 1.5 mm.[14]

A registered nurse obtained fasting resting blood samples with a winged infusion set from the brachial vein branches of the dominant arm, handled according to standardised methods and stored at –80°C until analysis. Serum high-sensitivity CRP was analysed with a timed, end-point method (UniCel® DxC 800, Beckman and Coulter, Germany). Inter- and intra-variability was less than 5%. CRP ≥ 3 mg/l is regarded as low-grade inflammation as well as a high risk for CVD.[43] Serum cholesterol blood sample analysis was done using the Konelab™ 20i (Thermo Scientific, Vantaa, Finland).

Statistical analysis

Statistical analysis was performed on the data from the 215 participants using SPSS v25 (Inc, Chicago, IL, USA). Normality was assessed using normal QQ plots for visual inspection and the statistical Shapiro–Wilk normality test. Independent *t*-test and ANOVA were used to determine gender and group differences. Additionally, the chi-squared test was used to compare proportions. Analyses for the entire group and specific age groups were also done in the BMI categories. The age groups were determined according to the guidelines suggested by 'Statistics: provisional guidelines on standard international age classification of 1982',[44] with age 25–44 years representing young adulthood, and 45–64 years representing adulthood (further referred to as middle adulthood). Analyses were done according to the two PA categories of sedentary (≤ 1.5 METs) and light-intensity PA (1.5–3 METs) for CIMT, BP, CRP and anthropometric variables.

Pearson correlation coefficient [rho (*r*)] was used to assess the relationship between CIMT and objectively measured PA. Partial correlations followed to determine: (1) the relationship between CIMT, mean seven-day awake METs, AEE, TEE and PAL for both the sedentary and light-PA groups, considering the confounders age, gender, BMI and WC; and (2) associations between CIMT, mean seven-day awake METs, AEE, TEE and PAL for sedentary and light-PA groups in separate male and female groups, controlling for age group, serum cholesterol level, ambulatory 24-hour BP, CRP and WC. The statistical significance was set at $p \leq 0.05$.

Results

The participants were classified according to age groups, consisting of young adulthood (25–44 years) and middle adulthood (45–64 years). Fig. 1 indicates that the prevalence of overweight (34%) and obesity (39%) was high among the entire group of teachers, especially obesity in the young-adult group (46%). Almost half of the young-adult female teachers (48%) were obese.

PA classification according to the mean seven-day awake METs showed that 67 and 33% of the total participants were respectively classified as in the sedentary and light-PA categories (Fig. 2). Fig. 3 shows that 39% of the participants

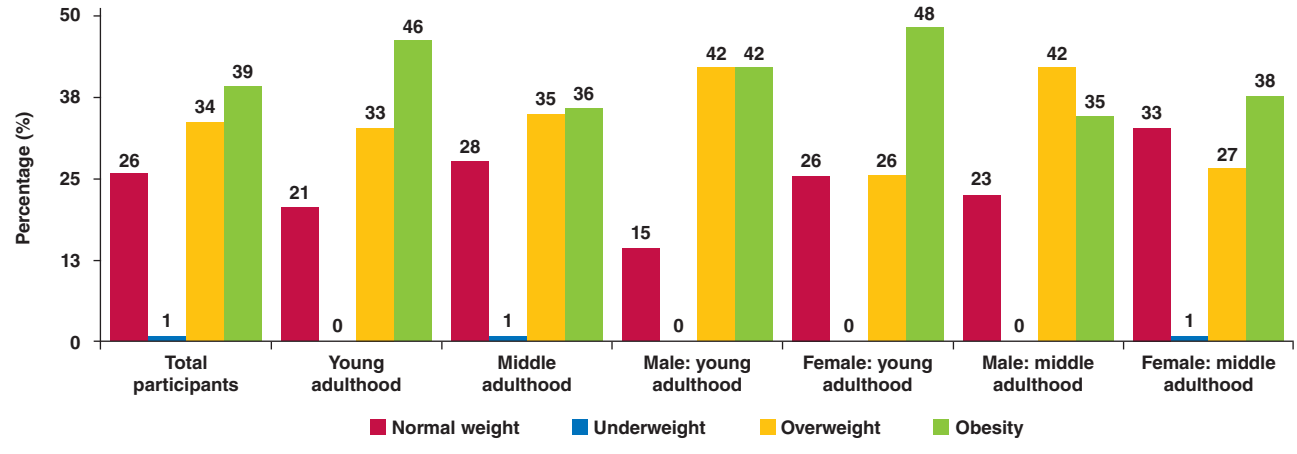

Fig. 1. Percentage of total participants according to BMI categories, age group and gender/age group combined. Young adulthood = 25–44 years, middle adulthood = 45–64 years; normal weight = 18.5–24.9 kg/m², underweight = ≤ 18.5 kg/m², overweight = 25–29.9 kg/m², obesity = ≥ 30 kg/m².

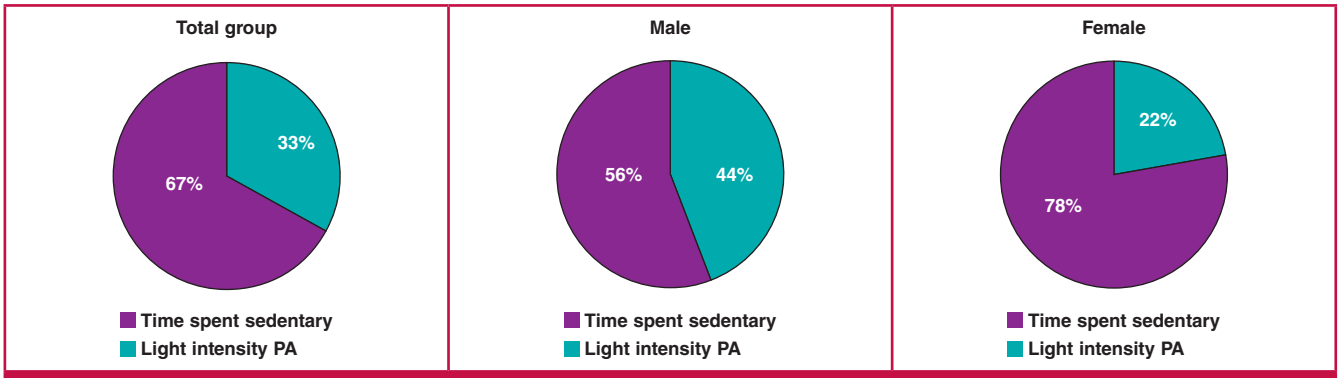

Fig. 2. Activity classification for the entire group and males and females according to mean seven-day awake METs. Time spent sedentary = < 1.5 METs; light PA = 1.5–3 METs.

that were grouped in the sedentary classification were obese and 31% were overweight. Therefore, more than two-thirds of the sedentary participants were overweight or obese. In the light-PA classification, 36% of the participants were overweight and 39% were obese.

In the analysis of CIMT in the two age groups (Table 1), a significantly higher CIMT was found for the middle-adulthood group compared with the young-adult group (0.73 ± 0.14 vs 0.64 ± 0.16 mm; $p < 0.001$). For the total group, male teachers had a significantly higher mean CIMT compared to female teachers ($t = 4.971$; df = 193.82; $p < 0.05$). When male and female teachers were divided into young- and middle-adulthood groups, the middle-adulthood group showed a significantly higher mean CIMT ($t = –3.614$; df = 87.309; $p = 0.001$). Similarly, the young- and middle-adulthood male teachers presented with significantly higher mean CIMT ($t = 3.330$; df = 40.33; $p = 0.002$) compared with the young- and middle-adulthood females ($t = 3.702$; df = 143.21; $p < 0.05$).

In the analysis of CIMT according to gender in the two age groups (Table 1), a significantly higher CIMT ($t = 4.616$; df = 54.81; $p < 0.001$) was found in the middle-adulthood female teachers (0.69 ± 0.11 mm) compared with the young-adult female teachers (0.58 ± 0.11 mm).

Out of 216 participants (Table 2), 38.9% were hypertensive, with middle-aged adults being more affected (39.6%) compared

Table 1. Differences in CIMT between young and middle adulthood, and male and female teachers

Group (n = *215*)	n	*CIMT (mm) Mean ± SD*	t-*test*	*df*	p-*value*
Male	104	0.74 ± 0.16	4.930	193.82	< 0.001*
Female	111	0.66 ± 0.12			
Young adult (total group)	57	0.64 ± 0.16	–3.614	87.309	0.001*
Middle adult (total group)	158	0.73 ± 0.14			
Young adult males	26	0.71 ± 0.18	3.330	40.33	0.002*
Young adult females	31	0.58 ± 0.11			
Middle adult males	78	0.77 ± 0.15	3.702	143.21	< 0.001*
Middle adult females	80	0.69 ± 0.11			
Young adult females	31	0.58 ± 0.11	–4.616	54.81	< 0.001*
Middle adult females	80	0.69 ± 011			
Young adult males	26	0.71 ± 0.18	–1.335	37.09	0.19
Middle adult males	78	0.77 ± 0.15			

Young adult = 25–44 years; middle adult = 45–64 years. CIMT = carotid intima–media thickness; df = degree of freedom; SD = standard deviation; *t*-test of the equality means. *Level of significance was set at $p \leq 0.05$.

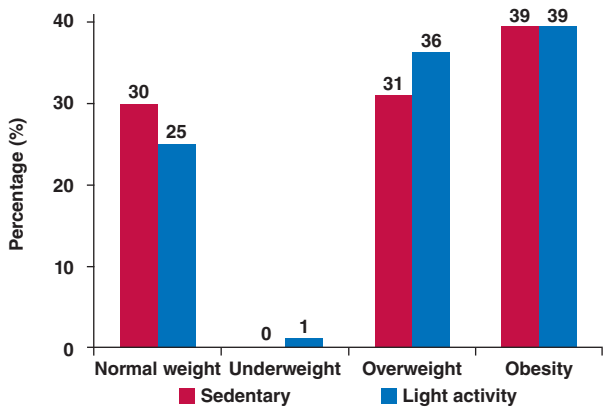

Fig. 3. Percentage of participants in BMI categories according to PA classification. Normal weight = 18.5–24.9 kg/m²; underweight = ≤ 18.5 kg/m²; overweight = 25–29.9 kg/m²; obesity = ≥ 30 kg/m². Sedentary = ≤ 1.5 METs; light PA = 1.5–3 METs.

Table 2. Percentage scores and chi-squared *p*-values for hypertension and CRP for the total group and according to PA and age group categories

Category	*Hypertensive, n (%)*	*Normotensive, n (%)*	*Chi-squared*	*p-value*
Total group (*n* = 216)	84 (38.9)	132 (61.1)	10.667	0.001*
Young adults (*n* = 57)	21 (36.8)	36 (63.2)	3.947	0.05*
Middle adults (*n* = 159)	63 (39.6)	96 (60.4)	6.849	0.01*
Sedentary (*n* = 71)	38 (53.5)	33 (46.5)	0.352	0.55
Light PA (*n* = 145)	46 (31.7)	99 (68.3)	19.372	< 0.001*
Sedentary males (*n* = 46)	30 (65.2)	16 (34.8)	4.261	0.04*
Sedentary females (*n* = 25)	8 (32)	17 (68)	3.240	0.07
Light PA males (*n* = 58)	28 (48.3)	30 (51.7)	0.069	0.80
Light PA females (*n* = 87)	18 (20.7)	69 (79.3)	28.897	< 0.001*
	Increased CRP	*No risk CRP*	*Chi-squared*	*p-value*
Total group (*n* = 214)	88 (41.1)	126 (58.9)	6.748	0.01*
Young adults (*n* = 56)	30 (53.6)	26 (46.4)	0.286	0.59
Middle adults (*n* = 158)	58(36.7)	100 (63.3)	11.165	0.001*
Sedentary (*n* = 71)	34 (47.9)	37 (52.1)	0.127	0.72
Light PA (*n* = 143)	54 (37.8)	89 (62.2)	8.566	0.003*
Sedentary males (*n* = 46)	22 (48)	24 (52)	0.087	0.77
Sedentary females (*n* = 25)	12 (48)	13 (52)	0.040	0.84
Light PA males (*n* = 58)	14 (24)	44 (76)	15.517	< 0.001*
Light PA females (*n* = 87)	40 (47.1)	45 (53)	0.294	0.59

Sedentary = < 1.5METs; light PA =10.5–3 METs. Hypertension = 24-h systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg;[42] low-grade inflammation = CRP ≥ 3 mg/l.[43] *Level of significance was set at $p \leq 0.05$

to the young adults (36.8). Participants who spent more time in sedentary behaviour were more hypertensive compared to the ones who participated in light PA. The results also show that 41.1% of the participants had an increased CRP level with high percentage scores in the sedentary groups.

The characteristics of the participants based on their PA status are presented in Table 3. AEE, TEE, mean seven-day awake METs and PAL differed significantly ($p < 0.001$). Sedentary participants had a borderline significant ($p = 0.06$) larger WC (99.32 ± 17.90 cm) than participants in the light-PA group (94.97 ± 17.71 cm). Sedentary participants had significantly higher ambulatory SBP ($p = 0.02$) and DBP ($p = 0.001$) than those who participated in light PA. No significant CIMT differences ($p = 0.13$) and WHtR ($p = 0.73$) were observed between the sedentary and light-PA groups

Analysis of differences among PA groups (Table 4) in male teachers indicated a significant difference in PA status and AEE ($p > 0.001$), TEE ($p > 0.001$), mean seven-day awake METs ($p > 0.001$) and PAL (p > 0.001). Sedentary male teachers had significantly higher CRP values ($p = 0.01$), ambulatory SBP ($p = 0.01$) and ambulatory DBP ($p = 0.02$) than males who participated in light PA. Among female teachers there was a significant difference in CIMT ($p = 0.01$) between the sedentary and light-PA groups. The PA variables between the sedentary and physically active groups were significantly different.

The value of correlation matrix *rho* indicated that within the sedentary group (Table 5), there was a significant inverse relationship between CIMT and PAL ($r = –0.30$; $p = 0.01$). In the light-PA group, a significant positive relationship between

Table 3. Descriptive statistics of the total group of participants according to PA groups and *p*-value for between groups

Variables	*Activity classification*	n	*Mean ± SD*	p-*value*
Age (years)	Sedentary	71	48.73 ± 9.32	0.26
	Light PA	145	50.12 ± 7.96	
Height (cm)	Sedentary	71	170.04 ± 10.32	0.36
	Light PA	145	168.67 ± 10.12	
Weight (kg)	Sedentary	71	85.96 ± 21.94	0.26
	Light PA	145	82.52 ± 18.36	
BMI (kg/m²)	Sedentary	71	29.58 ± 6.89	0.74
	Light PA	145	29.26 ± 6.30	
WC (cm)	Sedentary	71	99.32 ± 17.90	0.08
	Light PA	145	94.97 ± 14.71	
WHtR	Sedentary	71	0.58 ± 0.10	0.13
	Light PA	145	0.56 ± 0.09	
Cholesterol (mmol/l)	Sedentary	71	4.59 ± 1.13	0.20
	Light PA	144	4.39 ± 0.97	
CRP (mg/l)	Sedentary	71	4.87 ± 6.29	0.16
	Light PA	143	3.69 ± 4.34	
AMBP SBP (mmHg)	Sedentary	71	135.04 ± 19.43	0.02
	Light PA	145	126.62 ± 15.68	
AMBP DBP (mmHg)	Sedentary	71	83.48 ± 11.24	0.001
	Light PA	145	78.07 ± 10.18	
CIMT (mm)	Sedentary	70	0.70 ± 0.17	0.74
	Light PA	145	0.71 ± 0.14	
Mean seven-day awake METs	Sedentary	71	1.32 ± 0.10	< 0.001*
	Light PA	145	2.28 ± 0.62	
AEE (kcal/wk)	Sedentary	71	796.85 ± 722.17	< 0.001*
	Light PA	145	1476.97 ± 1124.39	
TEE (kcal/wk)	Sedentary	71	2814.87 ± 843.07	< 0.001*
	Light PA	145	3482.10 ± 1478.56	
PAL	Sedentary	71	1.49 ± 0.14	< 0.001*
	Light PA	145	2.34 ± 0.62	

AEE = activity energy expenditure; AMBP SBP = ambulatory systolic blood pressure; AMBP DBP = ambulatory diastolic blood pressure; BMI = body mass index; CIMT = carotid intima–media thickness; CRP = C-reactive protein; light PA = light physical activity (1.5–3 METs); METs = metabolic equivalent of task; sedentary = time spent sedentary (< 1.5 METs); TEE = total energy expenditure; PAL= physical activity level; WC = waist circumference; WHtR = waist-to-height ratio. *Level of significance was set at $p \leq 0.05$.

Table 4. Differences in the characteristics of the participants' PA patterns

	Males			*Females*		
Variables	*n*	*Mean ± SD*	*p-value of the differences*	*n*	*Mean ± SD*	*p-value of the differences*
Age (years)						
Sedentary	46	49.22 ± 9.57	0.55	25	47.84 ± 8.98	0.28
Light PA	58	50.24 ± 7.57		87	50.05 ± 8.26	
Height (cm)						
Sedentary	46	175.01 ± 8.69	0.07	25	160.90 ± 5.90	0.25
Light PA	58	177.95 ± 7.02		87	162.49 ± 6.48	
Weight (kg)						
Sedentary	46	90.60 ± 18.82	0.93	25	77.42 ± 24.95	0.93
Light PA	58	90.88 ± 14.60		87	76.95 ± 18.56	
BMI (kg/m²)						
Sedentary	46	29.43 ± 5.52	0.50	25	29.85 ± 9.01	0.89
Light PA	58	28.77 ± 4.11		87	29.58 ± 7.42	
WHtR						
Sedentary	46	0.59 ± 0.08	0.12	25	0.57 ± 0.13	0.73
Light PA	58	0.57 ± 0.06		87	0.56 ± 0.10	
WC (cm)						
Sedentary	46	103.42 ± 14.52	0.37	25	91.78 ± 21.17	0.84
Light PA	58	101.09 ± 11.26		87	90.88 ± 15.37	
Cholesterol (mmol/l)						
Sedentary	46	4.72 ± 1.15	0.10	25	4.36 ± 1.08	0.83
Light PA	58	4.38 ± 0.84		87	4.41 ± 1.04	
CRP (mg/l)						
Sedentary	46	5.25 ± 7.03	0.01*	25	4.18 ± 4.72	0.62
Light PA	58	2.17 ± 2.36		85	4.72 ± 5.04	
AMBP SBP (mmHg)						
Sedentary	46	138.91 ± 17.94	0.01*	25	127.92 ± 20.39	0.42
Light PA	58	130.22 ± 11.99		87	124.22 ± 17.38	
AMBP DBP (mmHg)						
Sedentary	46	86.15 ± 9.90	0.02*	25	78.56 ± 12.09	0.27
Light PA	58	81.81 ± 8.74		87	75.57 ± 10.36	
CIMT (mm)						
Sedentary	46	0.75 ± 0.16	0.99	25	0.59 ± 0.12	0.01*
Light PA	58	0.75 ± 0.16		87	0.68 ± 0.12	
AEE (kcal/wk)						
Sedentary	46	808.39 ± 752.47	< 0.001*	25	775.62 ± 677.33	0.01*
Light PA	58	1839.40 ± 1439.69		87	1235.34 ± 771.65	
TEE (kcal/wk)						
Sedentary	46	2952.07 ± 810.30	< 0.001*	25	2562.43 ± 859.94	0.01*
Light PA	58	4032.46 ± 1722.01		87	3115.20 ± 1163.92	
Mean seven-day awake METs						
Sedentary	46	1.29 ± 0.10	< 0.001*	25	1.36 ± 0.09	< 0.001*
Light PA	58	2.43 ± 0.79		87	2.17 ± 0.47	
PAL						
Sedentary	46	1.46 ± 0.13	< 0.001*	25	1.55 ± 0.14	< 0.001*
Light PA	58	2.47 ± 0.76		87	2.25 ±0.49	

AEE = activity energy expenditure; AMBP SBP = ambulatory systolic blood pressure; AMBP DBP = ambulatory diastolic blood pressure; BMI = body mass index; CIMT = carotid intima–media thickness; CRP = C-reactive protein; METs = metabolic equivalent of task; PAL= physical activity level; TEE = total energy expenditure; WC = waist circumference; WHtR = waist-to-height ratio. *Level of significance was set at $p \leq 0.05$.

Table 5. Correlations matrix *rho* (*r*) for anthropometric measurements, AEE and CIMT by activity group

	Sedentary group				*Light PA group*			
Variables	*CIMT (mm)*	*BMI (kg/m²)*	*WC (cm)*	*WHtR*	*CIMT (mm)*	*BMI (kg/m²)*	*WC (cm)*	*WHtR*
CIMT (mm)								
r	1.00	–0.05	0.14	0.05	1.00	0.09	0.19*	0.12
p	–	0.66	0.25	0.70	–	0.27	0.02	0.14
AEE (kcal/wk)								
r	–0.17	0.02	–0.02	0.04	0.11	–0.01	0.10	–0.05
p	0.15	0.86	0.86	0.75	0.20	0.88	0.24	0.54
Mean seven-day awake METs								
r	–0.20	0.07	–0.06	0.01	–0.02	0.05	0.12	0.04
p	0.11	0.57	0.64	0.93	0.81	0.58	0.16	0.66
TEE (kcal/wk)								
r	–0.05	0.14	0.18	0.14	0.15	0.10	0.24**	0.06
p	0.66	0.23	0.13	0.24	0.08	0.25	<0.001	0.45
PAL								
r	–0.30*	0.13	–0.02	0.14	–0.001	0.20*	0.19*	0.17*
p	0.01	0.30	0.89	0.24	0.99	0.02	0.02	0.04

AEE = activity energy expenditure; BMI = body mass index; CIMT = left carotid intima–media thickness; METs = metabolic equivalent of task; TEE = total energy expenditure; PAL = physical activity level; WC = waist circumference; WHtR = waist-to-height ratio. *Level of significance is set at $p \leq 0.05$. **Level of significance is set at $p \leq 0.001$

WC and CIMT ($r = 0.19$; $p = 0.02$); TEE ($r = 0.24$; $p = 0.00$); and PAL ($r = 0.20$; $p = 0.02$) was found. When partial correlation was performed to control for age, gender, cholesterol, ambulatory 24-hour BP, CRP and WC, a significant inverse relationship was found between CIMT and TEE ($r = –0.31$; $p = 0.05$), and a borderline inverse relationship was found between CIMT and AEE ($r = –0.28$; $p = 0.07$) in sedentary male teachers (Table 6). Furthermore, a borderline significant relationship was found between CIMT and mean seven-day METs ($r = –0.19$; $p = 0.08$), controlled for age, gender, cholesterol, ambulatory 24-hour BP and WC.

When CRP was added among the controlled variables, the borderline significant correlation diminished, therefore CRP was excluded in the analyses. No significant relationships were observed between CIMT and PA for female teachers in the sedentary group.

Discussion

This study aimed to investigate the relationship between objectively measured PA and CIMT among teachers in South Africa. A borderline negative association between CIMT and

Table 6. Partial correlation coefficient (*r*) for the relationship between CIMT and PA, controlled for age group, waist circumference, CRP, 24-h SBP and cholesterol

	Males (n = 41)					*Females (n = 19)*				
Sedentary	*Mean 7-day awake METs*	*AEE (kcal/wk)*	*TEE (kcal/wk)*	*PAL seven days*	*CIMT (mm)*	*Mean 7-day awake METs*	*AEE (kcal/wk)*	*TEE (kcal/wk)*	*PAL seven-day*	*CIMT (mm)*
Mean seven-day awake METs										
r	–	0.06	0.09	0.64	0.09	–	0.43	0.37	0.80	0.21
p	–	0.68	0.55	< 0.001*	0.58	–	0.05*	0.10	< 0.001*	0.35
AEE (kcal/wk)										
r	0.06	–	0.95	0.40	–0.28	0.43	–	0.97	0.55	0.18
p	0.68	–	< 0.001*	0.01*	0.07#	0.05*	–	< 0.001*	0.01*	0.44
TEE (kcal/wk)										
r	0.09	0.95	–	0.28	–0.31	0.37	0.97	–	0.53	0.16
p	0.55	< 0.001*	–	0.06#	0.05*	0.10	< 0.001*	–	0.01*	0.48
PAL seven-day										
r	0.64	0.39	0.28	–	–0.08	0.80	0.55	0.53	–	0.09
p	< 0.001*	0.01*	0.06#	–	0.59	< 0.001*	0.01*	0.01*	–	0.71
CIMT (mm)										
r	0.09	–0.28	–0.31	–0.08	–	0.21	0.18	0.16	0.09	–
p	0.58	0.07#	0.05*	0.59	–	0.35	0.44	0.48	0.71	–
	Males (n = 53)					*Females (n = 82)*				
Light PA	*Mean 7-day awake METs*	*AEE (kcal/wk)*	*TEE (kcal/wk)*	*PAL seven days*	*CIMT (mm)*	*Mean 7-day awake METs*	*AEE (kcal/wk)*	*TEE (kcal/wk)*	*PAL seven-day*	*CIMT (mm)*
Mean seven-day awake METs										
r	–	0.66	0.64	0.95	0.02	–	0.50	0.37	0.88	–0.19
p	–	< 0.001*	< 0.001*	< 0.001*	0.90	–	< 0.001*	< 0.001*	< 0.001*	0.08#
AEE (kcal/wk)										
r	0.66	–	0.99	0.54	0.10	0.50		0.92	0.45	–0.03
p	< 0.001*	–	< 0.001*	< 0.001*	0.44	< 0.001*	–	< 0.001*	< 0.001*	0.75
TEE (kcal/wk)										
r	0.64	0.99	–	0.50	0.12	0.37	0.92	–	0.38	–0.001
p	< 0.001*	< 0.001*	–	< 0.001*	0.38	< 0.001*	< 0.001*	–	< 0.001*	0.99
PAL seven-day										
r	0.95	0.54	0.50	–	0.002	0.88	0.45	0.38	–	–0.16
p	< 0.001*	< 0.001*	< 0.001*	.	0.99	< 0.001*	< 0.001*	< 0.001*	–	0.14
CIMT (mm)										
r	0.08	0.10	0.12	0.01	–	–0.19	–0.03	–0.001	–0.16	–
p	0.90	0.44	0.38	0.99	–	0.08#	0.75	0.99	0.14	–

Sedentary = ≤ 1.5 METs; light PA = 1.5–3 METs. AEE = activity energy expenditure; CIMT = carotid intima–media thickness; CRP = C-reactive protein; METs = metabolic equivalent of task; PAL = physical activity level; SBP; systolic blood pressure; TEE = total energy expenditure. *Level of significance was set at $p \leq 0.05$; #borderline significance.

mean seven-day awake METs in female teachers in the light-PA group was found. The weak relationship between PA and CIMT was also observed in a somewhat similar study.[45]

PA was measured using a combined accelerometer and heart rate monitor, the ActiHeart. One of the main observations of the study was the high level of sedentary behaviour in adults, which is in agreement with other studies.[8,9,46] The participants' occupation might explain the high percentage of teachers being classified as physically inactive or lightly physically active, as most of their working time is spent standing, sitting or walking slowly, which are all forms of sedentary or light energy cost activity.[39] Physical inactivity may lead to the development of cardiovascular disease risk factors, such as overweight and obesity,[47] and this was evident in the present study. The observed high prevalence of overweight and obesity found in this sample of teachers is consistent with the statistics for South Africa noted in the World Health Organisation's 2017 Overweight and Obesity report.[48]

The inverse relationship between CIMT and PA in the sedentary group of teachers is similar to the study by Parsons *et al.*[23] in older males (age 78 years), and the study of Gomez-Marcos *et al.* as assessed by accelerometer and seven-day physical activity recall (PAR)[49] in healthy adults (56 years). The potential beneficial effect of PA and therefore increased energy expenditure on lowering subclinical atherosclerosis levels is apparent.[12] Contrastingly, Ascenso *et al.*[50] indicated that the effect of PA was not observed in sedentary obese adolescents but was present in individuals who were classed as lightly physically active. Conflicting results from Kozàkovà *et al.*[24] indicated a significant positive relationship with a sedentary or light-PA ratio and CIMT in a healthy adult population (44 years).

The relationship between CIMT and PA has not been well established; different studies have reported controversial results about the relationship between CIMT and PA. This controversy may be explained by several influential factors in the relationship, such as age, gender, previous disease, measurement instruments and methods, and PA intensity.[49] Huynh *et al.*[51] indicated that sedentary behaviour and low levels of PA were not associated with carotid distensibility. However, in a systematic review, Kadoglou and colleagues[52] suggested that although the influence of PA on CIMT was inconsistent among healthy individuals, physical inactivity was associated with an increased CIMT.

The association between PAL and CIMT in our cohort may be significant due to the levels of TEE and REE in the equation, taking into account not only the energy expenditure due to AEE and the TEE but also the REE. We can speculate that the observed prevalence of overweight and obesity might be a contributor to the lack of a significant relationship between AEE and CIMT, in the sense that obese individuals' average daily metabolic rate, not non-basal energy expenditure, is positively related to body size.[53]

Westerterp[53] stated that AEE is the energy expenditure associated with muscular contractions involved in performing body postures and movements. We may assume that our study participants with mean BMIs almost equal to 30 kg/m^2 regardless of their PA levels might have struggled to achieve a five- to 20-fold increase in metabolic rate compared with non-obese individuals.[54] Westerterp[53] argued that the ratio of energy cost for low:moderate:high-intensity activity is 1:2:4, and the contribution of high-intensity activity to AEE is about 25%. Most teachers move around or walk when teaching sessions take place,[55] but this might not be enough to reach an AEE equal to or above 25%.

Unfortunately, in our study, only one participant (0.9%), who was not included in the analyses, participated at moderate-to-high intensity, and that could also be a reason for not finding a significant relationship between AEE and CIMT. It should also be noted that sedentary behaviour that is measured at one time point to capture a participant's typical weekly PA might have contributed to the observed associations.[56]

The mean WC values for male and female teachers in our study were above the measurements classified as 'at risk of disease', according to the ACSM (males ≥ 102 cm; females ≥ 88 cm).[36] The non-significant relationship between CIMT and WC in this study is congruent with the findings of one study conducted in apparently healthy adults.[21] Contradictory evidence from Ascenso *et al.*[50] indicates no correlation between sedentary time and WC; however, their study was conducted in obese adolescents, which may explain the reason for the disparity.

In our study, we also found significant gender differences in CIMT, with male teachers in both the sedentary and light-PA groups having higher CIMT than female teachers. This can be explained by risk-factor classification, with males at higher risk of developing CVD at an earlier age.[36] The results can be affirmed by similar studies in young populations; Ried-Larsen *et al.*[57] also found significantly higher CIMT in Danish boys than in girls. Furthermore, Ascenso *et al.*[50] stated similar gender differences in CIMT; however, the results were not significant. This result was similar to Jain *et al.*,[58] who found that males had a significantly higher burden of subclinical disease, measured by non-invasive imaging.

An unexplained significant negative relationship observed in our study between CIMT and TEE was also shown by Walker *et al.*[56] in males who were classified in a sedentary group. The findings might in part be explained by the 56% of participants classified as light PA who presented with overweight and obesity in our study. This finding was inconsistent with findings in obese children and adolescents in other studies; however, they did not focus on adults or teachers and revealed insignificant correlations between sedentary behaviour and CIMT. However, light PA was positively correlated with CIMT.[50]

In a study by Kozàkovà *et al.*[24] among Caucasian males and females, a positive association existed between CIMT and time spent sedentary, whereas an inverse relationship was found between light PA and CIMT. Conversely, Ried-Larsen and colleagues,[25] studying Danish adolescents, reported no associations between CIMT and moderate-to-vigorous PA or vigorous PA. Studies in British adults and young Indian adults have reported inverse associations between CIMT and PA;[23,59] while Ebrahim *et al.*[60] reported no relationship in British adults. Inconsistent findings were most likely due to considerable variation in PA measurement protocols and variability of the study populations, using arbitrary cut-off values.[52,56]

In our study, male teachers had higher AEE, mean seven-day awake METs and PAL than female teachers in the sedentary group, as well as higher TEE than females in the light-PA group. The results are comparable to those of Guthold and colleagues,[9] who reported a higher prevalence of physical inactivity among South African females compared with males. Additionally,

the participants in the current study presented with a high prevalence of hypertension (> 30%) and high CRP levels.

The observed hypertension among the teachers is similar to previous findings in South Africa,[61] and most recently to a study by Muluvhu and colleagues,[62] who reported a 25% prevalence of hypertension among employees of the Vhembe district municipality, Limpopo province. Hypertension in the current study was positively correlated with CRP level (r = 0.27, p < 0.001), and the correlation was relatively strong (r = 0.30, p = 0.01) in the sedentary group compared with those participating in light PA (r = 0.22; p = 0.009). The observed positive relationship between hypertension and CRP is congruent with the US Adults study from 1999 to 2010.[63]

Although our study provides valuable information, it is not without limitations. The cross-sectional design limited data collection to one point in time; future longitudinal studies will need to investigate the progression of CIMT over time. The sample size was relatively small and consisted of teachers in the North West Province only, and this was not representative of teachers in South Africa at large. Individual calibrations of the ActiHeart were not performed for each participant but should be part of a future standard protocol. The South African climate in terms of heat and humidity may have influenced the accuracy of the ActiHeart. Additionally, clear PA cut-off points would have clarified some of the observed relationships between CIMT and PA.

The main strength of the study was that CIMT and PA were objectively measured in an urban South African context. Habitual PA for awake time (over 17 hours) was measured, and only participants who wore the ActiHeart for the full seven days were included in the analysis. Furthermore, adding to the uniqueness of the study was that the analysis was conducted within a South African context among teachers.

Conclusion

Both male and female teachers in the study were overweight/obese, hypertensive, had increased CRP levels and were physically inactive. Male teachers presented with greater CIMT than female teachers, a significant concern given the consequences of elevated CIMT. Among the overweight/obese teachers classified as sedentary, PAL was limited in the benefits of lowering CIMT. However, female teachers who participated in light PA revealed a negative association between CIMT and mean seven-day METs. Therefore participation in light PA may be helpful in the reduction of CIMT. Given the health implications of these findings, in particular the risk of CVD among teachers, critical strategic PA intervention studies are recommended.

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Although statins have clear benefits in appropriate patients, scientists and clinicians should further explore the impact of statins on human metabolism, in particular the interaction between lipid and carbohydrate metabolism, said co-author Steven Clinton, a professor of medicine and member of Ohio State's Comprehensive Cancer Centre.

'In addition, researchers conducting large prospective cohort studies should be considering how statins impact on human health overall. They should consider both risks and benefits, not just the disease that is being treated by the specific drug,' Clinton said.

The study was done retrospectively, meaning that the researchers looked back at existing records from a group of patients to determine if there were any possible connections between statin prescriptions and diabetes. Previous research has suggested a connection, but this study design allowed for a glimpse at what is happening naturally in the clinical setting, rather than what happens in a prospective trial that randomly assigns some people to statins and some people to placebo, said Zigmont, who is now an assistant professor at Southern Connecticut State University.

The study was enriched by the availability of a variety of details on the study population, including data from biometric screenings and a health survey that asked about education, health behaviours and ethnicity, Zigmont said. She also had access to medical claims data and pharmacy claims data.

Zigmont was careful to take a wide variety of confounding factors into account in an effort to better determine if the statins were likely to have caused the diabetes, she said. Those included gender, age, ethnicity, educational level, cholesterol and triglyceride readings, body mass index, waist circumference and the number of visits to the doctor. Programmes that help patients improve their fitness and diets could be considered and discussed when doctors are prescribing statins, so that patients can be proactive about diabetes prevention, she said.

It would also be helpful for future research to better determine which statins and which doses might lead to the greatest risk, Zigmont said. Her study didn't allow for an analysis based on different types of statins.

Limitations of the research include the fact that the majority of statin users were white, and that the research team had no way of knowing how closely patients adhered to their doctors' prescriptions. There also was no way of determining who was at elevated risk of diabetes at the study's onset, Zigmont says.

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Determination of optimal cut-off values for waist circumferences used for the diagnosis of the metabolic syndrome among Batswana adults (ELS 32)

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Abstract

Background: To date, no definitive waist circumference (WC) cut-off values for abdominal obesity (AO) have been established for sub-Saharan Africa, including Botswana. Therefore, the classification of AO among these populations is based on European values. For accurate diagnosis of the metabolic syndrome (MetS), cut-off values reflective of the population investigated must be used.

Objective: The study was an attempt to determine optimal cut-off values for AO among Batswana adults.

Methods: The receiver operating characteristic curve was used to determine the optimal cut-off values for predicting at least two other risk factors of the MetS. Data were used from a descriptive cross-sectional study employing a complex multi-stage cluster sampling. Demographic and anthropometric measurements (weight and height, waist and hip circumferences), blood pressure, and blood glucose, triglycerides, high-density lipoprotein cholesterol and total cholesterol levels were collected from 384 men and 416 women in Gaborone and the surrounding villages.

Results: The ability of waist circumference to predict at least two other risk factors of the MetS gave cut-off values of ≥ 91.0 cm (sensitivity 69.1% and specificity of 90.8%, area under the curve 0.85) for men and ≥ 82.3 cm (sensitivity of 88.6% and specificity of 58.9%, area under the curve of 0.76) for women.

Conclusion: There is a difference between the cut-off values for Europeans with those determined for Batswana adults. Inconsistencies in cut-off values used have the potential for undesirable consequences for cardiovascular risk stratification and prioritisation of preventative strategies for AO and the MetS. The need to determine population-, ethnic- and gender-based cut-off values for AO for Batswana adults has never been more paramount.

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Modernisation and urbanisation of African countries accompanied by sedentary lifestyles and the nutritional transition have resulted in increased obesity among African populations. Obesity is reported to have increased in sub-Saharan African (SSA) countries, with the southern African region being the most affected.[1] A high prevalence of obesity among Batswana adults has also been reported by several groups recently, especially among the women.[2-4]

Abdominal obesity (AO), in particular, is associated with the development of a number of metabolic disorders such as dyslipidaemia and disglyceraemia, some occurring at the same time as the metabolic syndrome (MetS). However, the distribution of fat storage, rather than overall excess body fat, especially visceral body fat, plays an important role in these associations[5,6] and varies between white and black populations.[7,8]

According to the International Diabetes Federation (IDF) definition of the MetS, an individual has to have AO and any two other risk factors, such as low high-density lipoprotein cholesterol (HDL-C), high triglyceride levels (TG), elevated blood pressure (BP) and increased fasting blood glucose (BG) level.[9] The pathogenesis of the MetS and each of its individual components is complex and is not fully understood, however, two components appear to stand out as potential causative factors, namely insulin resistance and AO. The IDF definition has since elevated AO to be the determining factor for the MetS diagnosis, the rationale for this requirement being that AO is more strongly correlated with other MetS features than any other component.[10] Therefore, defining AO accurately is of great importance for a proper diagnosis of the MetS, along with other cardiometabolic risk factors.

AO is generally assessed by measuring waist circumference (WC), which has been found to be ethnic specific,[8,11] suggesting that different cut-off points for different ethnic groups should be used for a proper diagnosis of AO. For example, some ethnic groups, such as Asians, have been reported to be more likely to develop complications of the MetS at a much lower WC compared to Caucasians.[9,12]

Different cut-off points for different ethnic groups have therefore been established. For instance, European cut-off points are ≥ 80 cm for women and ≥ 94 cm for men, South Asians and Chinese are ≥ 80 cm for women and ≥ 90 cm for men, and

Japanese are ≥ 90 cm for women and ≥ 85 cm for men.[9] To date, cut-off points for SSA countries have not been established, with isolated studies from several countries reporting different values.[8,13-17] Hence, the IDF has since recommended the use of the European cut-off points to determine AO for SSA countries, and by extension the MetS, until more specific data are available.[9]

The MetS has been reported to be on the rise in SSA countries, including Botswana. A couple of studies have reported a MetS prevalence of 27 and 34% among Batswana adults[13,15] in different populations. For the MetS to be prevented, it is necessary to ascertain the prevalence rates and also characterise the population most affected. It is vital that the diagnostic tools used are accurate and population specific. Therefore, the primary aim of this study was to determine population-specific optimal cut-off points for AO among Batswana adults. A secondary aim was to evaluate how the prevalence of the MetS was affected when the newly determined cut-off values were used to diagnose AO compared with the IDF-recommended values.

Methods

A cross-sectional study employing a complex, multi-stage, cluster-sampling method was used to recruit 1 000 participants in the city of Gaborone and the surrounding villages of Tlokweng and Mogoditshane. The target population included apparently healthy male and female citizens aged 25 to 65 years residing in Gaborone, Tlokweng and Mogoditshane. Data were collected at shopping malls where people of heterogeneous characteristics converged. There were a total of 37 malls, classified as either super mall or satellite mall, spread across Gaborone, Tlokweng and Mogoditshane. A total of seven malls were randomly selected for the study.

A sampling frame of all shopping malls in Gaborone and surrounding villages of Tlokweng and Mogoditshane was compiled and samples were randomly selected from the list. In the selected malls, shoppers perceived to be eligible were systematically recruited as they passed by the testing area. The recruitment was alternated with a stratifying variable, gender, to ensure a balance between male and female participants. Once eligibility had been established through the use of a national identity card, and consent to participate had been sought, the participants were enrolled into the study. The opportunity was also used to share the results with the participants, to help them appreciate their health parameters and the implications.

Ethical approval was obtained from the institutional review boards of both the University of Botswana (ref no: IRB0005239) and Stellenbosch University (ref no: HREC N13/04/052), and human research office of the Ministry of Health, Botswana. Data were collected from volunteers who agreed to participate in the study after an introduction and briefing on the study intent. After informed consent was obtained, a total of 803 volunteers were recruited, interviewed and assessed.

Data regarding demographic, anthropometric, biochemical and behavioural factors were collected using the standardised methods stipulated in the World Health Organisation (WHO) STEP-wise approach to chronic disease risk-factor surveillance instrument (version 2.0). All procedures as specified by the Health Professions Council of Botswana were strictly adhered to according to good clinical practices.

Demographic data included questions related to gender, age, level of education, marital and work status, number of people above 18 years in the household and average yearly earnings. Medical history included questions related to history of elevated BP, diabetes, total cholesterol (TC) and cardiovascular diseases. Resting BP, height and weight, and waist and hip circumferences were recorded. Biochemical assessments related to BG and blood lipids (TC, TG and HDL-C) were determined. BP measurements were taken using an automated BP monitor (OMRON Intelli Sense M3W) after a five-minute rest following the interview.

Waist and hip circumferences were measured using a SECA measuring tape (201 cm) according to the International Society for the Advancement of Kinanthropometry (ISAK) standard guidelines.[18] Height was measured using a portable SECA stadiometer, using the free-standing method with the head placed in the Frankfort plane, and weight was measured with the SECA Alpha digital scale (model 770). Capillary BG, TG and TC were assessed with a finger-prick test with the Care Sense N BG monitoring system, while blood lipids were measured using the cardio check PA system [Polymer Technology Systems (Pts), IN, USA].

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS version 22). Most of the variables analysed for this output were quantitative, so their means ± standard deviations are reported. All variables tested were contrasted by gender using the Student's *t*-tests. Contrasts for proportions among sub-populations were performed using homogeneity chi-squared tests. A significant difference was accepted if *p*-values were less than 0.05 for both tests.

The MedCalc software was used to generate the receiver operating characteristics (ROC) curves for continuous variables. The area under the curve (AUC) was measured to summarise the ability of WC to detect participants with at least two risk factors for the MetS, as defined by the IDF.[9] The closer the AUC is to one, the higher the ability of the indicator to discriminate among subjects. An AUC value of 0.5 indicated no discriminatory power of the tested indicator. The optimal cut-off values were calculated by plotting the true-positive rate (sensitivity) against the false-positive rate (1-specificity): based on the Yoden Index Parametric method under a normal distribution approach. The optimal cut-off point was calculated by maximising sensitivity and specificity across various cut-off point scenarios.

Results

The participants were mainly residents of Gaborone city and two surrounding villages of Tlokweng and Mogoditshane, who make up about 10% of the Batswana. A total of 800 respondents participated in the study drawn from seven shopping malls, yielding a response rate of 80%. From the 800 participants, 664 were selected from shopping malls in Gaborone, and the remaining 136 from Tlokweng and Mogoditshane. The final results were based on the 756 participants (363 men and 393 women) who had complete WC data.

The men and women were of similar age (36.1 ± 8.9 years) (Table 1). Based on anthropometric and biochemical measurements, no gender differences were noted for WC, diastolic

Table 1. Participants' characteristics by gender

Characteristic	*Number*	*All*	*Men*	*Women*	p-*value*
Number (%)	800		384 (48)	416 (52)	
Age (years)	743	36.1 ± 8.9	36.3 ± 9.2	35.9 ± 8.6	0.583
BMI (kg/m²)	797	26.2 ± 5.7	24.2 ± 4.5	27.9 ± 6.1	< 0.001
WC (cm)	794	85.1 ± 13.9	84.1 ± 13.3	86.0 ± 14.4	0.05
HC (cm)	795	104.2 ± 12.8	99.6 ± 10.5	108.5 ± 13.3	< 0.001
WHR	794	0.82 ± 0.1	0.85 ± 0.11	0.79 ± 0.11	< 0.001
Systolic BP (mmHg)	795	127.5 ± 16.9	130.4 ± 16.7	124.7 ± 16.6	< 0.001
Diastolic BP (mmHg)	795	78.8 ± 10.8	79.2 ± 11.0	78.5 ± 10.7	0.378
BMI (%)					
25 ≤ BMI < 30 kg/m²	232	29.1	15.1	31.0	< 0.001
BMI ≥ 30 kg/m²	192	24.1	13.0	34.4	< 0.001
WC, men/women (%)					
≥ 94/80 cm	380	47.9	24.5	69.6	< 0.001
≥ 102/88 cm	230	29.0	11.0	45.7	< 0.001
WHR > 1.0/0.85	106	13.4	3.7	22.6	< 0.001
Elevated BP, ≥ 130/≥ 85 mmHg (%)	355	44.7	50.3	39.4	0.002
BG, mmol/l (%)	779	5.3 ± 1.3	5.3 ± 1.2	5.4 ± 1.5	0.201
≥ 5.6 mmol/l (%)	251	32.2	29.9	34.2	0.207
TG, mmol/l (%)	785	1.9 ± 2.4	1.8 ± 1.0	2.0 ± 1.1	0.057
≥ 1.7 mmol/l (%)	372	47.4	46.3	48.4	
HDL-C	778	1.2 ± 0.4	1.1 ± 0.4	1.3 ± 0.4	< 0.001
< 1.03/1.29 mmol/l (%)	384	49.4	48.7	50.0	
MetS (%)	787	32.7	20.0	44.5	< 0.001

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist–hip ratie; BP, blood pressure; BG, blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.

BP, BG and TG. However, a significant gender difference was observed for body mass index (BMI) ($p < 0.001$), hip circumference ($p < 0.001$), waist–hip ratio ($p < 0.001$), systolic BP ($p < 0.001$) and HDL-C ($p < 0.001$). The women presented with a higher BMI (34.4 vs 13.0%) and WC (45.5 vs 11.0%) and a lower HDL-C (50.0 vs 48.7%) compared to the men, who presented with a higher systolic BP (50.3 vs 39.4%).

The overall prevalence of AO as determined by WC was estimated at 47.9%, resulting in an estimated prevalence of the MetS of 32.7% (IDF).[9] The prevalence of AO and the MetS was found to be higher among women, at 69 vs 24.5% ($p = 0.05$), than men, at 44.5 vs 20.0% ($p = 0.001$) (Table 1). Overall, low HDL-C identified the highest candidates for the MetS (49.4%), followed by WC (47.9%), TG (47.4%) and elevated BP (44.7%) (Table 1).

The ROC curve was used to determine the optimal cut-off points for AO, predicting at least two other indicators for the MetS in both genders. For men, the ability of WC to predict at least two other indicators of the MetS revealed a sensitivity of 69.1% and specificity of 90.8%, and AUC of 0.85, giving a cut-off point of ≥ 91.0 cm (Fig. 1). Furthermore, the AUC for the women was 0.76, with a sensitivity of 88.6% and specificity of 58.9%, yielding a cut-off point of ≥ 82.3 cm (Fig. 2).

The prevalence of AO, as determined by the two cut-off values of the IDF and the current study, was similar at 47.9 and 47.4%. Differences in the prevalence were observed when the data were further analysed according to gender. When the prevalence of AO was defined by the IDF cut-off values, there was a 5.8% increase in the prevalence of AO among men (from 24.5 to 30.3% when using the new cut-off values) and a 4.6% increase in the prevalence of the MetS (from 19.9 to 24.5% using the new cut-off values) (Table 2). For the women there was a 6.3% decrease in the prevalence of AO (69.6 to 63.3% using the new cut-off values) and a 3.0% decrease in the prevalence of the MetS (from 44.5 to 41.5% using the new cut-off values) (Table 2).

Discussion

The results from this survey indicate a difference between the WC cut-off points used for Europeans for determining AO and the currently determined cut-off points for Batswana adults (≥ 94 cm vs ≥ 91 cm for men and ≥ 80 cm vs ≥ 82 cm for women). Gender differences became more noticeable when data were further analysed by gender, which led to different estimated prevalences

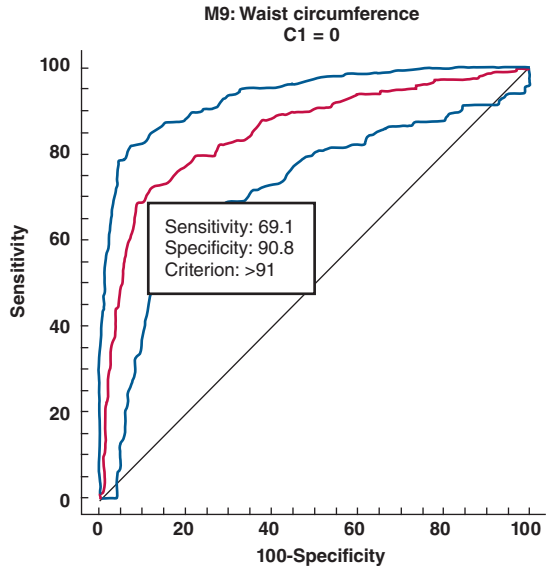

Fig. 1. ROC curve for the WC of males.

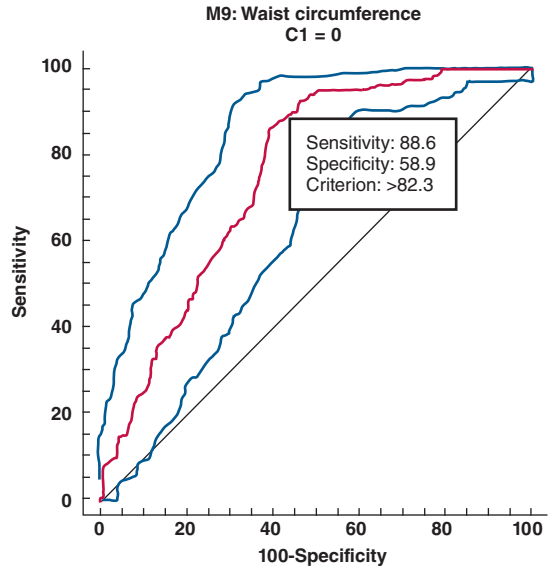

Fig. 2. ROC curve for the WC of females.

of AO and the MetS, with larger differences observed in men compared to women.

The resulting over- or underestimation of AO, leading to the same for the MetS, may have a negative impact on preventative measures or interventions developed. For instance, with overestimation of the prevalence of the MetS, individuals who are at a relatively low risk would be incorrectly identified and targeted for interventions. This in turn might lead to expenditure directed at a cause that is unnecessary, which would be of particular concern to health resource-poor countries such as Botswana. Likewise, if the MetS is underestimated, individuals at a high risk of developing cardiovascular diseases or diabetes would be misdiagnosed or not identified and not targeted by preventative measures aimed at a high-risk population.

It is therefore imperative that population-specific AO cut-off values are determined from large, representative studies, validated and used to determine population-specific risk factors. Further analysis of the results according to gender is necessary as vital information might be overlooked when only considering the sample as a whole. The results from such studies will allow for a more accurate estimation of the ever-changing prevalence levels of the MetS over time, and in response, appropriate and culturally sensitive interventions can be developed.

Table 2. Comparison of the IDF definition criteria with the newly determined optimal cut-off values in determining the prevalence of AO and the MetS

Variables	*IDF values (≥ 94 cm men ≥ 80 cm women)*	*New values (≥ 91 cm men ≥ 8 2cm women)*
AO (%)		
All	47.9	47.4
Men	24.5	30.3
Women	69.6	63.3
MetS (%)		
All	32.6	33.3
Men	19.9	24.5
Women	44.5	41.5

AO, obdominal obesity; MetS, metabolic syndrome.

Table 3. Comparison of this study's determined WC cut-off points with similar studies

Studies	*Ethnicity*	*Men (cm)*	*Women (cm)*
IDF criterion	Europeans	94	80
Current study	Batswana	91	82
Onen *et al.*[15]	Batswana	98	85
Motala *et al.*[18]	South African (Zulus)	86	92
Hoebel *et al.*[19]	South African (urban blacks)	91	84
Magalhaes *et al.*[16]	Angolans	88	81
Ekoru and Murphy[17]	SSA (Benin, Nigeria, Democratic Republic of Congo, Uganda, Kenya, Tanzania, South Africa and Seychelles)	81	81

Evidence from several studies in which the optimal cut-off values for AO were reported in SSA populations showed an emerging trend (Table 3). From the comparisons, the trend is higher WC cut-off values for the men than the women. The WC cut-off points for women seem to be approximately 82 cm, which is similar to the IDF recommendation.[9] It can then be argued that irrespective of the optimal cut-off points for SSA populations, WC for men appears to be higher than for women, and that for women, values are most probably similar to IDF criteria.

This study presented several limitations. Cluster randomisation is the recommended sampling method since the results would be more inferable to the general population. However, targeting malls excluded a portion of the population that does not frequently visit malls, making it impossible to generalise to the population as a whole. The study included only an urban-based population, but only 69.4% of the Botswana population is urbanised according to the 2018 revised United Nations world urbanisation prospects.[20] The relationship between AO and the MetS may be modulated by urbanisation and confounding factors such as dietary habits, physical activity patterns as well as general health.[21]

It would be interesting to conduct a similar study in a rural or peri-urban area and compare the findings to this study. Furthermore, it would be recommended to include additional data collection on diet, physical activity, food security and general health. It is well known that Botswana is burdened with a high HIV prevalence and that this could also influence the prevalence of the MetS in this population.

Conclusion

The results of several studies have indicated that WC cut-off values for AO are ethnic and gender specific.[8,11,18] It is highly probable that the values may be even more variable among different SSA populations. It is therefore imperative to investigate whether this is indeed the case to aid in lowering the burden of the MetS on the public health sectors. It is possible to establish population- and gender-specific cut-off values for different ethnic groups that can be used to classify AO in these ethnic groups. Correctly identifying the MetS will go along way in decreasing disease risk factors.

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this study are those of the authors, and the above-mentioned funding sources do not accept any liability in regard thereto. The authors acknowledge the participants and research assistants for their contribution towards the success of this study. The shopping mall owners are also acknowledged for allowing data collection on their premises.

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Prognostic value of admission hyperglycaemia in black Africans with acute coronary syndromes: a cross-sectional study

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Abstract

Aim: The aim of the study was to determine the relationship between acute hyperglycaemia and in-hospital mortality in black Africans with acute coronary syndromes (ACS).

Methods: From January 2002 to December 2017, 1 168 patients aged ≥ 18 years old, including 332 patients with diabetes (28.4%), consecutively presented to the intensive care unit of the Abidjan Heart Institute for ACS. Baseline data and outcomes were compared in patients with and without hyperglycaemia at admission (> 140 mg/dl; 7.8 mmol/l). Predictors for death were determined by multivariate logistic regression.

Results: The prevalence of admission hyperglycaemia was 40.6%. It was higher in patients with diabetes (55.3%). In multivariate logistic regression, acute hyperglycaemia (hazard ratio = 2.33; 1.44–3.77; $p < 0.001$), heart failure (HR = 2.22; 1.38–3.56; $p = 0.001$), reduced left ventricular ejection fraction (HR = 6.41; 3.72–11.03; $p < 0.001$, sustained ventricular tachycardia or ventricular fibrillation (HR = 3.43; 1.37–8.62; $p = 0.008$) and cardiogenic shock (HR = 8.82; 4.38–17.76; $p < 0.001$) were predictive factors associated with in-hospital death. In sub-group analysis according to the history of diabetes, hyperglycaemia at admission was a predictor for death only in patients without diabetes (HR = 3.12; 1.72–5.68; $p < 0.001$).

Conclusion: In ACS patients and particularly those without a history of diabetes, admission acute hyperglycaemia was a potentially threatening condition. Appropriate management, follow up and screening for glucose metabolism disorders should be implemented in these patients.

Keywords: hyperglycaemia, diabetes, acute coronary syndrome, sub-Saharan Africa

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Studies in the West have shown that elevation of blood glucose is a common condition during the early phase of acute coronary syndrome (ACS), even in the absence of a history of diabetes mellitus (DM).[1-3] There is no uniform definition at present, but the 140 mg/dl (7.8 mmol/l) threshold has often been considered.[4] The prevalence of acute hyperglycaemia > 140 mg/dl ranged from 39 to 58%.[1,2,5]

In addition to established prognostic factors (left ventricular systolic dysfunction, heart failure, ventricular arrhythmias),[6] acute elevation of blood glucose level was associated with an increase in in-hospital stay, and 30-day and long-term mortality rate, and there is evidence that the risk of mortality is higher in patients without a history of DM.[7-10] There is a linear relationship between acute glycaemic levels and outcomes.[2,7] Pathophysiological mechanisms are uncertain, but acute hyperglycaemia may be an epiphenomenon of the stress response, or the trigger of complex underlying mechanisms, leading to severe complications and poor outcomes.[4,5]

In sub-Saharan Africa, data on ACS are scarce,[11,12] particularly on the prevalence and outcomes of patients with acute hyperglycaemia. The aim of this study was to assess the prognostic value of hyperglycaemia at admission in ACS patients in our practice.

Methods

Our study was carried out at the Abidjan Heart Institute (Ivory Coast). We conducted a cross-sectional, observational study between 1 January 2002 and 31 December 2017, including patients aged ≥ 18 years who presented to the intensive care unit (ICU) of Abidjan Heart Institute for ACS. These patients were divided into two groups according to their blood glucose level at admission: admission hyperglycaemia (AH) (blood glucose > 140 mg/dl; 7.8 mmol/l) and absence of admission hyperglycaemia (NAH) (blood glucose ≤ 140 mg/dl).[4] The blood glucose level considered was the first venous plasma glucose level obtained at admission or within the first 24 hours, and before any glucose-lowering therapy was given during hospitalisation.

The exclusion criteria were: ACS patients with incomplete medical records or who declined to participate in the study, patients with suspected ACS in whom the clinical course and

explorations had excluded the diagnosis of ACS, and patients transferred to another department outside the Abidjan Heart Institute during their hospitalisation.

Consent was obtained from each patient participating in this study. Based on our selection criteria, 1 168 patients were included in our study.

Data were collected using a standardised survey form. The parameters investigated were: (1) socio-demographic data (age, gender) as well as clinical data (cardiovascular risk factors and history, clinical presentation); (2) ECG (diagnosis of ACS) and cardiac ultrasound data [left ventricular ejection fraction (LVEF) < 40% or ≥ 40%]; (3) biological data: troponin Ic and cardiac enzymes, (4) coronary angiography findings: number of epicardial vessels affected (one-, two- and three-vessel disease), (5) management: dual antiplatelet therapy (DAPT), percutaneous coronary intervention (PCI), and (6) in-hospital evolution: atrial fibrillation, sustained ventricular tachycardia/ventricular fibrillation, cardiogenic shock, death.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured three times during hospitalisation or treatment of previously diagnosed hypertension. DM was defined according to the American Diabetes Association[13] as one of the following criteria: glycated haemoglobin ≥ 6.5%, fasting plasma glucose ≥ 1.26 g/l (6.99 mmol/l) on two occasions, two-hour plasma glucose ≥ 2 g/l (11.1 mmol/l) after 75-g oral glucose tolerance test (OGTT), random plasma glucose ≥ 2 g/l (11.1 mmol/l), or patients on glucose-lowering therapy on admission. Active smoking was defined as current or interrupted smoking for less than three years.

Dyslipidaemia was defined as total cholesterol concentration > 2.40 g/l (6.22 mmol/l) and/or high-density lipoprotein (HDL) cholesterol < 0.40 g/l (1.04 mmol/l) in males and < 0.50 g/l (1.3 mmol/l) in females and/or low-density lipoprotein (LDL) cholesterol > 1.60 g/l (4.14 mmol/l), or triglyceride levels > 1.5 g/l (1.70 mmol/l). Familial history of coronary artery disease (CAD) was defined as the occurrence of a myocardial infarction or sudden death: before the age of 55 years in the father or in a first-degree male relative; and before the age of 65 years in the mother or in a first-degree female relative. Symptom–admission delay was the time between the onset of symptoms and admission to the Abidjan Heart Institute.

ST-segment elevation myocardial infarction (STEMI) was defined as the presence of symptoms or signs of myocardial ischaemia, persistent ST-segment elevation or newly diagnosed bundle branch block, and an increase in cardiac biomarkers beyond the 99th percentile.[6] Non-ST-elevation ACS (NSTE-ACS) was defined as the presence of symptoms or signs of myocardial ischaemia, absence of persistent ST-segment elevation, and elevation (non-Q-wave myocardial infarction) or no elevation (unstable angina) of cardiac biomarkers beyond the 99th percentile.[14] Left ventricular systolic dysfunction was defined for a LVEF < 40%.[15]

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as numbers and proportions. Statistical comparisons between groups used the Student's *t*-test or Mann–Whitney test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables. A receiver operating characteristics (ROC) curve was performed to determine the admission glycaemic threshold level predictive of death in our population.

Univariate and multivariate backward stepwise logistic regressions were used to assess predictors of in-hospital death, with an inclusion threshold of $p < 0.20$ in the multivariate analysis. The candidate variables considered were selected according to available data in the literature. The Wald (or Fisher) test was used to assess the significance of hazard ratio (HR) and their 95% confidence interval (95% CI). We defined statistical significance using a two-sided *p*-value < 0.05. We used RStudio statistical software version 1.1.383 (Boston, MA, USA).

Results

Table 1 summarises the patients' general characteristics and outcomes according to blood glucose status at admission. Among the 1 168 patients included in our study, 474 had AH, with a prevalence of 40.6%. The average age of our study population was 56.0 ± 11.6 years (range 21–91). Patients in the AH group were significantly older than those in the NAH group (57.9 ± 11.0 vs 54.7 ± 11.8 years, $p < 0.001$). Patients over 60 years old frequently had acute hyperglycaemia (40.7 vs 31.7%, $p = 0.001$). The male gender was predominant (80.7%) with a ratio of male to female of 4.2. Patients in the NAH group were more likely to be female, with no significant difference (Table 1). According to cardiovascular risk factors and history, AH patients had significant increases in hypertension ($p < 0.001$) and DM ($p < 0.001$). Smoking was frequently reported in the NAH group ($p = 0.002$).

The median symptom–admission delay was 19 hours (5–48). There was no difference concerning blood glucose levels at admission ($p = 0.37$). Heart failure often occurred in AH patients (35.4 vs 20.7%, $p < 0.001$). AH patients presented with increased blood pressure and heart rate. In AH patients, peaks in troponin Ic ($p = 0.004$), creatine phosphokinase (CPK) ($p < 0.001$) and creatine kinase-MB (CK-MB) levels ($p < 0.001$) were higher. Coronary angiography was performed in 564 patients (48.3%). Although there was no significant difference ($p = 0.51$), three-vessel disease was more common in AH patients (Table 1). Two hundred and twenty patients underwent PCI (18.8%). Dual antiplatelet therapy (aspirin + clopidogrel) was given to 782 patients (67.0%). No differences were reported between the groups.

Over the study period, 800 STEMI patients out of 1 138 (68.5%) were admitted to ICU. Thrombolysis was performed in 93 patients, in most of the cases with Alteplase (77/93, 82.8%). PCI procedures started on 27 April 2010. One hundred and fifty-one STEMI patients underwent PCI.

Cardiogenic shock occurred significantly in patients with acute hyperglycaemia ($p < 0.002$). Atrial fibrillation and severe ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) were more frequent in the AH group, without significant difference. Overall in-hospital mortality rate was 9.1% (106/1168). It was higher in AH patients (15.2%, $p < 0.001$) (Table 1).

In multivariate analysis, heart failure (HR = 2.22; 1.38–3.56; $p = 0.001$), LVEF < 40% (HR = 6.41; 3.72–11.03; $p < 0.001$), acute hyperglycaemia (HR = 2.33; 1.44–3.77; $p < 0.001$), sustained

ventricular tachycardia or ventricular fibrillation (HR = 3.43; 1.37–8.62; $p = 0.008$) and cardiogenic shock (HR = 8.82; 4.38–17.76; $p < 0.001$) were the risk factors associated with in-hospital death. PCI (HR = 0.35; 0.16–0.79; $p = 0.01$) and dyslipidaemia (HR = 0.48; 0.27–0.84; $p = 0.01$) were identified as protective factors (Tables 2, 3).

The sub-group analyses according to the history of DM emphasised cardiogenic shock (HR = 23.75; 7.60–74.27; $p < 0.001$ and HR = 9.05; 3.66–22.33; $p < 0.001$, respectively) in both AH and NAH populations as risk factors (Tables 4, 5). In patients without a history of DM, only hyperglycaemia was associated with in-hospital death (HR = 3.12; 1.72–5.68; $p < 0.001$) (Table 5).

We carried out a second analysis over two periods: 2002–2010 and 2011–2017. Admission hyperglycaemia was a predictive factor only from 2011–2017 (HR = 2.57; 1.52–4.32). (Tables 6, 7).

Table 1. Patient characteristics according to glycaemia status at admission

Characteristics	*AH* n = *474*	*NAH* n = *694*	p-*value*
Age (years), m ± SD	57.9 ± 11.0	54.7 ± 11.8	< 0.001
Age > 60 years	193 (40.7)	220 (31.7)	0.001
Female gender	42 (19.8)	94 (15.1)	0.10
Hypertension	312 (65.8)	377 (54.3)	< 0.001
Diabete mellitus	262 (55.3)	70 (10.1)	< 0.001
Active smoking	113 (23.8)	222 (32.0)	0.002
Dyslipidaemia	149 (31.4)	216 (31.1)	0.91
Familial history of CAD	27 (5.7)	44 (6.3)	0.65
History of MI	42 (8.9)	58 (8.4)	0.76
History of stroke	24 (5.1)	23 (3.3)	0.13
Admission delay (hours), m (IQR)	15 (5–52)	20 (5–48)	0.37
Systolic BP (mmHg), m ± SD	148.8 ± 34.3	143.5 ± 29.1	0.01
Diastolic BP (mmHg), m ± SD	92.1 ± 21.2	88.1 ± 19.0	< 0.001
Heart rate (bpm), m ± SD	89.4 ± 20.9	81.8 ± 18.8	< 0.001
Congestive heart failure	168 (35.4)	144 (20.7)	< 0.001
LVEF < 40%	210 (44.3)	198 (28.5)	< 0.001
ECG findings			0.005
Anterior ACS	274 (57.8)	321 (63.6)	
Inferior ACS	169 (35.7)	315 (45.4)	
Lateral ACS	31 (6.5)	58 (8.4)	
Troponine Ic peak (µg/l), m (IQR)	13.1 (5.2–30.0)	4.9 (1.4–15.0)	0.004
CPK peak (UI/l), m (IQR)	1083 (436–2680)	714 (245–1900)	< 0.001
CKMB peak (UI/l), m (IQR)	91 (40–242)	65 (26–171)	< 0.001
STEMI	369 (77.8)	431 (62.1)	< 0.001
Atrial fibrillation	16 (3.4)	22 (3.2)	0.84
SVT/VF	18 (3.8)	25 (3.6)	0.86
Cardiogenic shock	31 (6.5)	20 (2.9)	0.002
PCI	81 (17.1)	139 (20.1)	0.21
DAPT	455 (65.6)	327 (69.0)	0.22
Death	72 (15.2)	34 (4.9)	< 0.001
Length of stay (days), m ± SD	9.0 ± 5.9	8.4 ± 5.3	0.03
Severity of CAD	*n* = 144	*n* = 420	0.51
Non significant CAD	23 (16.0)	59 (14.0)	
1-vessel CAD	48 (34.0)	162 (38.6)	
2-vessel CAD	44 (30.6)	135 (32.1)	
3-vessel CAD	28 (19.4)	64 (15.2)	

Data are in *n* (%), means ± standard deviation or median (interquartile range). AH: admission hyperglycaemia. NAH: absence of admission hyperglycaemia. CAD: coronary artery disease. BP: blood pressure. MI: myocardial infarction. LVEF: left ventricular ejection fraction. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention.

Table 2. Predictors of in-hospital death. Univariate analysis

Predictors	*Alive at discharge (*n = *1062)*	*Death during hospitalization (*n = *106)*	*HR*	*95% CI*	p-*value*
Age > 60 years	361 (34.0)	52 (49.1)	1.87	1.25–2.79	0.002
Female gender	195 (18.4)	30 (28.3)	1.75	1.12–2.75	0.01
Hypertension	619 (58.3)	70 (66.0)	1.39	0.91–2.12	0.12
Diabete mellitus	288 (27.1)	44 (41.5)	1.91	1.27–2.87	0.002
Active smoking	313 (29.5)	22 (20.8)	0.63	0.38–1.02	0.06
Dyslipidaemia	342 (32.2)	23 (21.7)	0.58	0.36–0.94	0.03
History of MI	92 (8.7)	8 (7.5)	0.86	0.40–1.82	0.69
Admission delay (hours), m (IQR)	18 (5–48)	25 (6–72)	–	–	0.02
Congestive heart failure	249 (23.4)	63 (59.4)	4.78	3.17–7.23	< 0.001
LVEF < 40%	322 (30.3)	86 (81.1)	9.88	5.97–16.36	< 0.001
Anterior ACS	527 (49.6)	68 (64.2)	1.82	1.20–2.75	0.004
Admission hyperglycaemia	402 (37.9)	72 (67.9)	3.48	2.27–5.32	< 0.001
STEMI	707 (66.6)	93 (87.7)	3.59	1.98–6.51	0.01
Atrial fibrillation	35 (3.3)	3 (2.8)	0.85	0.26–2.83	0.54
SVT/VF	33 (3.1)	10 (9.4)	3.24	1.55–6.79	< 0.001
Cardiogenic shock	23 (2.2)	28 (26.4)	16.22	8.92–29.48	< 0.001
DAPT	716 (67.4)	66 (62.3)	0.80	0.53–1.21	0.28
PCI	212 (20.0)	8 (7.5)	0.32	0.16–0.68	0.002

Data are in *n* (%) or median (interquartile range). HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction. LVEF: left ventricular ejection fraction. ACS: acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention.

The blood glucose threshold of 151 mg/dl (8.38 mmol/l) was the one with the best sensitivity and specificity (area under the curve = 0.636; sensitivity 61%, specificity 67%; $p < 0.001$) (Fig. 1). Considering the value of 140 mg/dl (7.8 mmol/l), we found similar sensitivity and specificity (sensitivity 62%, specificity 60%).

Discussion

Whereas estimation of the prevalence of DM in ACS patients is known in sub-Saharan Africa, ranging from 25

Table 3. Predictors of in-hospital death. Multivariate analysis

	Initial model			*Final model*		
Predictors	*HR*	*95% CI*	p-*value*	*HR*	*95% CI*	p-*value*
Age > 60 years	1.60	0.95–2.70	0.07			
Female gender	0.84	0.47–1.51	0.57			
Hypertension	0.88	0.51–1.52	0.65			
Diabetes mellitus	1.50	0.85–2.64	0.15			
Active smoking	0.53	0.27–1.05	0.57			
Dyslipidaemia	0.58	0.32–1.05	0.07	0.48	0.27–0.84	0.01
Admission delay (hours), m (IQR)	1.00	0.99–1.01	0.18			
Congestive heart failure	2.25	1.34–3.75	0.002	2.22	1.38–3.56	0.001
LVEF < 40%	6.02	3.37–10.77	< 0.001	6.41	3.72–11.03	< 0.001
Anterior ACS	1.35	0.78–2.35	0.28			
Admission hyperglycaemia	1.76	1.00–3.09	0.05	2.33	1.44–3.77	< 0.001
STEMI	1.75	0.83–3.69	0.14			
SVT/VF	3.97	1.47–10.74	0.007	3.43	1.37–8.62	0.008
Cardiogenic shock	12.32	5.71–26.58	< 0.001	8.82	4.38–17.76	< 0.001
PCI	0.32	0.13–0.80	0.02	0.35	0.16–0.79	0.01

HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction. LVEF: left ventricular ejection fraction. ACS: acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. PCI: percutaneous coronary intervention.

Table 4. Predictors of in–hospital death in patients with diabetes. Multivariate analysis.

	Initial model			Final model		
Predictors	*HR*	*95% CI*	p-*value*	*HR*	*95% CI*	p–*value*
Dyslipidaemia	0.78	0.28–2.16	0.63			
Congestive heart failure	6.43	2.12–19.54	0.04	5.74	2.68–12.30	< 0.001
LVEF < 40%	1.12	0.42–3.00	0.83			
STEMI	1.40	0.36–5.36	0.63			
SVT/VF	15.11	1.88–121.20	0.01	10.09	1.41–72.27	0.02
Cardiogenic shock	29.24	6.83–125.11	< 0.001	23.75	7.60–74.27	< 0.001
DAPT	0.80	0.26–2.41	0.69			
PCI	1.07	0.29–3.89	0.92			

m (IQR): median (interquartile range). HR: hazard ratio. 95% CI: 95% confidence interval. LVEF: left ventricular ejection fraction. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention.

to 41%,[11,16] to our knowledge this is the first study reporting the prevalence of blood glucose levels at admission and their prognostic value on in-hospital mortality in our practice. The prevalence of admission hyperglycaemia (40.6%) was higher than the prevalence of DM (28.4%). This high rate of acute hyperglycaemia is consistent with available data in the literature in wealthy countries, where the prevalence of hyperglycaemia > 140 mg/dl (7.8 mmol/l) ranges from 39 to 58%.[1,2,5] However, the blood glucose cut-off point differs across studies, and it has been reported that up to 71% of ACS patients had acute hyperglycaemia.[3]

The prognostic impact of hyperglycaemia on admission in patients hospitalised for ACS has been established in numerous studies.[7-10] The Cooperative Cardiovascular Project[7] is the most important registry (n = 141 680) that evaluated the relationship between mortality rate and admission blood glucose after ACS. Mortality at 30 days and one year evolved linearly with blood glucose levels at admission (≤ 110, 110–140, 140–170, 170–240 and ≥ 240 mg/dl) (6.11, 6.11–7.8, 7.8–9.44, 9.44–13.32 and ≥ 13.32 mmol/l). As in our study, the risk of mortality was higher in patients without a history of DM.[7]

Table 5. Predictors of in-hospital death in patients without diabetes. Multivariate analysis

	Initial model			Final model		
Predictors	*HR*	*95% CI*	p-*value*	*HR*	*95% CI*	p-*value*
Age > 60 years	2.39	1.27–4.49	0.007	2.46	1.35–4.49	0.003
Female gender	0.77	0.37–1.6	0.48			
Hypertension	1.17	0.60–2.25	0.65			
Dyslipidaemia	0.53	0.24–1.16	0.11			
History of MI	0.15	0.02–1.32	0.09			
Congestive heart failure	1.44	0.76–2.74	0.27			
LVEF < 40%	8.71	4.05–18.70	0.15	10.18	4.93–21.00	< 0.001
Anterior ACS	1.53	0.78–3.01	0.22			
Admission hyperglycaemia	2.65	1.41–4.99	0.002	3.12	1.72–5.68	< 0.001
STEMI	1.34	0.54–3.30	0.99			
SVT/VF	3.59	1.21–10.64	0.021			
Cardiogenic shock	7.33	2.81–19.08	< 0.001	9.05	3.66–22.33	< 0.001
PCI	0.27	0.09–0.83	0.022	0.29	0.10–0.86	0.02

HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction. ACS: acute coronary syndrome. LVEF: left ventricular ejection fraction. ACS: acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. PCI: percutaneous coronary intervention.

Table 6. Predictors of in-hospital death from 2002–2010. Multivariate analysis

Predictors	*HR*	*95% CI*	p-*value*
Diabetes mellitus	4.79	1.86–12.36	0.001
Congestive heart failure	4.51	1.74–11.70	0.001
Cardiogenic shock	6.10	1.61–23.05	0.008

HR: hazard ratio. 95% CI: 95% confidence interval.

Table 7. Predictors of in-hospital death from 2011–2017. Multivariate analysis

Predictors	*HR*	*95% CI*	p-*value*
Admission hyperglycaemia	2.57	1.52–4.32	< 0.001
Congestive heart failure	3.40	2.05–5.64	< 0.001
Cardiogenic shock	14.41	6.82–30.42	< 0.001

HR: hazard ratio. 95% CI: 95% confidence interval.

In a recent meta-analysis including 214 219 patients, admission hyperglycaemia significantly increased hospital mortality rate (HR = 3.62; $p < 0.0001$), and this impact persisted at 30 days (HR = 4.81, $p < 0.0001$) and long term up to 108 months (HR = 2.02, $p < 0.0001$).[3] In STEMI patients who underwent primary PCI, hyperglycaemia was associated with a higher rate of complications and mortality, including the risk of recurrence of myocardial infarction and heart failure.[17]

In patients without a history of DM, raised blood glucose may correspond to a pre-diabetic state unmasked under a stressful, acute post-ACS phase. In the GAMI trial, OGTT was systematically performed in the follow up of 181 patients with acute myocardial infarction, no history of DM and an admission blood glucose level < 11.0 mmol/l. This study found 67% of new cases of DM and impaired glucose intolerance (IGT).[18]

The potential mechanisms involved with acute hyperglycaemia are still poorly understood, but some hypotheses have been suggested.[4,5] Hyperglycaemia may be a cause or 'marker' of

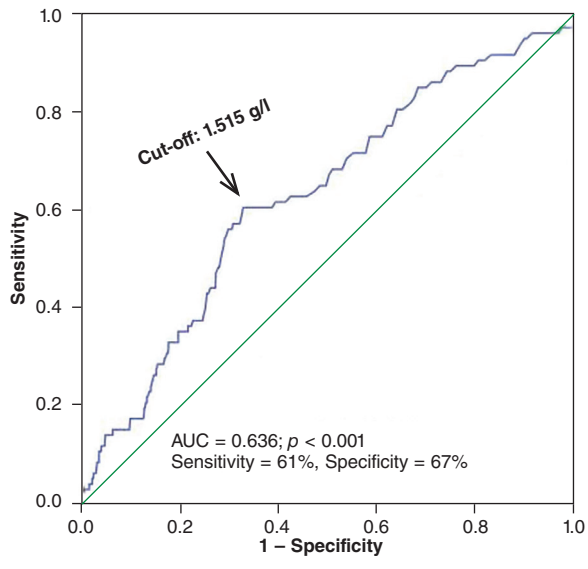

Fig. 1. ROC curve showing glycaemia cut-off value predictive for in-hospital death.

catecholaminergic stress in the post-ACS phase, particularly in relation to the extent of the infarction and the relative alteration of LVEF.[19] Evidence of a reduced mortality rate after lowering blood glucose levels on insulin therapy argues against blood glucose as a simple epiphenomenon of the stress state.[20] Hyperglycaemia is associated with insulin resistance, increased levels of free fatty acids,[21] marked inflammatory response, and endothelial and microvascular dysfunction, leading to myocardial cell vulnerability, ischaemia and hypoxia.[22,23] This may explain why in our study, patients with blood glucose > 140 mg/dl (7.8 mmol/l) had higher peaks of troponin Ic and cardiac enzymes. Recently, a new concept, glycaemic variability, has been described in a few studies. In patients with acute myocardial infarction, glycaemic variability was associated with the severity of CAD[24] and death.[25]

Patients with acute hyperglycaemia and without a history of DM should undergo close follow up and screening for glucose metabolism disorders.[18] Current recommendations emphasise the use of OGTT and glycated haemoglobin as screening tests.[26] In a study conducted in South Africa among patients with CAD, the rate of IGT measured by OGTT was 30% higher than the rate of DM (20%).[27] This study included a small sample of patients, but highlights the need for screening of glucose metabolism disorders in patients with CAD in our practice.

The other predictors for in-hospital death identified in our study (age, heart failure, left ventricular dysfunction, sustained ventricular tachycardia/ventricular fibrillation) are powerful prognostic factors in ACS patients, consistent with studies in developed countries.[6] Dyslipidaemia appeared to be a protective factor, and this observation has already been reported.[28] It is mainly the influence of previous lipid-lowering drugs in patients with high cardiovascular risk that would have a beneficial effect on mortality rate.[28] Previous treatments in our study were not specified.

PCI was a protective factor in our series but remarkably, only in patients without a history of DM in sub-group analyses. First, the low rate of PCI in our patients with ACS[29] is a potential bias. Second, CAD patients with DM frequently have multi-vessel coronary heart disease (28.9%) and complex lesions (39.7%),[30] as in studies conducted in developed countries.[31] Coronary artery bypass graft surgery is often the technique of choice for complete revascularisation in patients with DM,[32] but is of limited practice in sub-Saharan Africa. Finally, DM patients are often high-risk patients in whom an earlier invasive strategy should be implemented. However, the excessive admission delays[11] determine the low rate of PCI, which would weaken its beneficial effect.

Limitations

Our study has some limitations. Incomplete medical records did not allow us to make a thorough analysis. Glycated haemoglobin was not available for all patients and was not included in our analysis, nor was the evolution of blood glucose levels during hospitalisation. The influence of previous treatments (antidiabetic drugs, statins) and glucose-lowering treatments given during hospitalisation (particularly insulin infusion) have not been specified. Finally, the low rate of coronary angiography did not make it possible to assess the link between blood glucose levels and the severity of CAD.

Conclusion

This study, carried out in a sub-Saharan African population, shows that in the acute phase of ACS, admission blood glucose has a powerful prognostic value on mortality rate, in accordance with studies conducted in the West. In association with conventional treatment of ACS, adequate control of blood glucose is an important treatment target, especially in non-diabetic patients. Routine screening for glucose metabolism disorders and follow up after ACS must be implemented, as recommended.[26] It would be interesting to determine the rate of IGT and DM in ACS patients without a history of DM in the post-discharge phase, and assess the long-term impact of glucose-lowering therapy on morbidity and mortality rates.

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Commentary

PASCAR commentary on the International Society of Hypertension global guidelines 2020: relevance to sub-Saharan Africa

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Abstract

Hypertension guidelines have been based on country-specific data until the publication of the International Society of Hypertension (ISH) global guidelines. The major differences between the ISH global guidelines and other international guidelines are the stratified recommendations to accommodate differences in available resources between countries and within countries. This is a key and novel proposal in the new ISH guidelines. There is the separation of optimal versus essential criteria for diagnosis and treatment according to availability of resources. This guideline includes recommendations for sub-Saharan Africa. The Pan-African Society of Cardiology (PASCAR) continues to promote awareness and recommendations on hypertension in Africa. This commentary provides a summary and discussion of the global guidelines in order to clarify the position of PASCAR.

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Most authoritative hypertension guidelines for the diagnosis and management of elevated blood pressure have been developed for specific regions or countries.[1-4] These guidelines have been based on studies that were predominantly performed in high-income countries (HICs), with the vast majority of participants being of non-sub-Saharan African (non-SSA) origin.[2,5,6] No hypertension cardiovascular (CV) outcome study has been performed in SSA. Despite this, these international guidelines have been used to develop management protocols for SSA.

Until 2017, guidelines were unanimous that the cut-off point to diagnose hypertension was 140/90 mmHg, except in the elderly where the systolic blood pressure (SBP) was increased to 150 mmHg.[7-9] Based on this definition, the World Health Organisation (WHO) estimated that Africa had the highest prevalence of hypertension.[10] The Pan-African Society of Cardiology (PASCAR) hypertension roadmap[11] similarly used this diagnostic threshold. However, in 2017, the American College of Cardiology (ACC)/American Heart Association (AHA) revised their hypertension guidelines with radical changes, including lower cut-off points for the diagnosis of hypertension (BP ≥ 130/80 mmHg).

Implications of these changes include an additional 31 million US individuals considered to have hypertension, just because of this change in threshold.[1] The lowering of the threshold of hypertension diagnosis was not replicated in the 2018 guidelines from the European Society of Hypertension (ESH)/European Society of Cardiology (ESC), which maintained the previously set 140/90 mmHg.[2]

In 2018, the International Society of Hypertension (ISH) questioned whether the ACC/AHA high blood pressure guidelines were fit for global purpose, especially in low- and middle-income countries (LMICs).[12] In 2020, the ISH published global hypertension practice guidelines, which have great relevance to SSA. Specific detail for the manner to achieve hypertension control is based on the needs, available resources and practice behaviours of a given population. This commentary aims to clarify the position of PASCAR on these global practice guidelines and their relevance to SSA.

Why do we have guidelines?

Before commenting on the ISH hypertension guidelines, it is important to consider why we need guidelines. The principles were particularly well summarised by Go *et al*.[13] Briefly, they are required to identify people eligible for management; for monitoring at practice and population level; for increasing patient and provider awareness; providing an effective diagnosis and treatment plan; systematic follow up for initiation and

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treatment intensification; clarifying the roles of healthcare providers; and reducing barriers for patients to receive and adhere to treatment and implement lifestyle modifications.

The impact of well-structured hypertension guidelines is typically illustrated by data derived from Lackland *et al.*,[14] which showed that the decline in US population stroke mortality rates coincided with the reduction of population BP, which was consistent with the lowered BP thresholds and targets described in the sequential recommendations from the guidelines. PASCAR identified the creation or adoption of simple and practical clinical evidence-based hypertension management guidelines as one of its 10-point action plan to achieve 25% control of hypertension in Africa by 2025.[11]

Summary of key proposals of the ISH global hypertension guideline and relevance to SSA

Essential versus optimal treatment

The major difference between the ISH global guidelines and other international guidelines is the stratified recommendations to accommodate differences in available resources between countries and within countries. This is a key and novel proposal in the new ISH guidelines. There is the separation of optimal versus essential criteria for diagnosis and treatment according to resource availability in LMICs versus HICs. Even within HICs there are areas with low-resource settings and vice versa.

Optimal care refers to evidence-based standard of care articulated in recent major guidelines (ESH/ESC, ACC/AHA) but it is recognised that implementation of these standards is not always possible in LMICs. Essential standards refer to minimum standards of care for low-resourced settings. However, there was a paucity of evidence supporting this approach and the guideline committee applied expert opinion. The provision of these recommendations is based on the need to develop guidelines that are applicable to all areas of the globe rather than developing country-specific guidelines. This approach makes it possible to develop truly international hypertension guidelines.

However, the committee recognises that it may not be feasible for even the minimum standards to be implemented in many poorer countries in SSA due to lack of health professionals, infrastructure, equipment (ECG and BP machines for example) and finances. No guidance is provided for treating patients under these circumstances. However, it is suggested that the guidelines provide a framework for countries to strive for. Perhaps what is significantly lacking in the essential or minimum standards is their application to non-physician healthcare workers that are critical in providing care to the burgeoning numbers of hypertensive patients in poorer countries in SSA.

This review is not exhaustive and will focus on the essential recommendations of the ISH hypertension guideline and their relevance to SSA.

Definition of hypertension, BP measurement and target BP

The ISH guidelines maintained the traditional definition of hypertension at a level ≥ 140/90 mmHg and have not aligned themselves with ACC/AHA guidelines at ≥ 130/80 mmHg. In SSA more than 90% of hypertensives are not controlled because of lack of awareness (largely attributable to lack of screening), failure to access treatment or persistence with treatment use, and failure of monitoring to ensure control.[15]

By redefining hypertension to a level of 130/80 mmHg, this will significantly increase the prevalence of hypertension. In the US it was estimated that the number of hypertensives will increase by 43% or 31.1 million people, and a similar increase would be expected in SSA, placing an unsustainable additional burden on health facilities.[16] This, in the light of the lack of beneficial evidence for initiating treatment in patients at this lower threshold, does not support these diagnostic criteria for hypertension in SSA.

One weakness of the ISH guidelines is limiting the definition of hypertension into two grades (Table 1), excluding grade 3 hypertension: ≥ 180/110 mmHg. In SSA, grade 3 hypertension is common[17] and usually asymptomatic, but few present with features of hypertensive emergency. This grade of hypertension alerts the healthcare worker to a category of hypertension with a very high risk of adverse outcomes in a short time.

The guidelines make important recommendations regarding the essential requirements for measurement of BP. This has to be done on three separate occasions within a four-week period. Perhaps not completely recognised by the ISH guideline is the limited availability of functioning BP devices and the long distances patients may need to travel to have repeated measurements to establish the diagnosis. While it is ideal to have the BP repeated at different visits, high-risk patients with limited access should be treated based on a single set of readings, possibly if it is > 160/100 mmHg, but especially if > 180/110 mmHg. Similarly, repeated measurements at one clinic visit may enable a diagnosis to be made based on a single visit.

There are slight differences in BP re-evaluation: in those with high-normal BP, the BP should be checked in three years, unless the individual has a higher risk, in which case the BP should be checked in one year. If normal, the ESH/ESC recommends a BP review in five years. However, in SSA it may be more appropriate to make this recommendation three years, due to the high risk of complications.

However, home and 24-hour ambulatory BP monitoring are seen as essential for the diagnosis of hypertension. In the opinion of PASCAR, the latter represents optimal requirement. Even in a LMIC in SSA, such as South Africa, availability of 24-hour and home BP monitoring in the public sector that serves over 80% of the population is extremely limited. There is increasing availability of home-based monitoring devices, however validation of these devices is sub-optimal and needs to be improved. Furthermore, there needs to be training in the use of these devices, both for the patient and home-based carers.

The essential target BP recommended for all hypertensives is < 140/90 mmHg or a 20/10-mmHg reduction in BP by three months. For optimal treatment, it is < 130/80 mmHg if tolerated and not < 120/70 mmHg. In those 65 years old and above or

Table 1. Proposed SSA classification of hypertension, using office blood pressure measurements

	Normal BP	*High-normal*	*Grade 1 hypertension*	*Grade 2 hypertension*	*Grade 3 hypertension*
SBP*	< 130	130–139	140–159	160–179	> 180
DBP*	< 85	85–89	90–99	100–109	> 110

BP, blood pressure; SBP systolic BP; DBP, diastolic BP.
*Classification based on the presence of either or both SBP and DBP.

those with the presence of frailty, the cut-off value is < 140/90 mmHg. This recommendation is particularly applicable to SSA. However, in our view, the 20/10-mmHg reduction needs further comment. Although it is well recognised that this reduction in BP will substantially reduce cardiovascular events, it needs a degree of context. For example, if the initial BP is as high as 190/110 mmHg, a 20/10-mmHg reduction only to 170/100 mmHg would not be appropriate.

Clinical evaluation and diagnostic tests

The ISH guidelines recommend a full medical history addressing previous BP levels, risk factors, co-morbidities, and symptoms of secondary causes, together with a physical examination with a focus on the circulation, heart and signs of secondary causes. Laboratory investigations include Na^+, K^+, creatinine, estimated glomerular filtration rate (eGFR), dipstick urine, lipids and fasting glucose. A 12-lead ECG should be performed to detect left ventricular hypertrophy, atrial fibrillation and ischaemic heart disease. In PASCAR's opinion these basic tests represent an optimal situation to assess hypertension-mediated organ damage (HMOD) and secondary causes at the primary-care level. While these tests are ideal, ECG machine availability and the skills to interpret are lacking in many SSA countries, especially in rural areas.

CV risk stratification

More than 50% of hypertensive patients have additional CV risk factors such as diabetes, the metabolic syndrome, dyslipidaemia and smoking. CV risk assessment is important and should be assessed in all hypertensive patients, and it relies on levels of BP, risk factors, and presence and/or absence of HMOD. The rationale is that patients at highest risk will achieve the greatest absolute reduction in adverse events and allow scarce resources to be optimally used. A simple risk chart is provided and is applicable to SSA. Alongside the chart is QRISK2, an online risk calculator that may be pertinent to SSA due to adjustment for black African race.

Non-pharmacological treatment of hypertension

Non-pharmacological treatment is a fundamental part of the management of hypertension. Healthy lifestyle choices can prevent or delay the onset of high BP and can reduce CV risk, are often the first line of antihypertensive treatment, and enhance the effects of antihypertensive treatment. The recommended changes are provided in Table 2. Briefly, the lifestyle changes include a combination of optimising diet, exercise, weight, alcohol consumption and avoiding precipitants and smoking.

There is no differentiation in the recommendations between optimal and essential. Most of these recommendations are only implementable in HICs due to a variety of reasons. In the poorer communities of SSA, choice of food is determined by affordability and ability to store. Lack of electricity means that cooking and heating is done on open fires in crowded townships and rural villages, causing pollution, and exercise opportunities are limited due to safety concerns and lack of leisure time.

More pragmatic essential recommendations need to be considered for SSA. However, salt and sugar intake can be reduced and should be encouraged as salt is considered a major contributor to poor BP control in SSA. Legislative control of sodium content in processed foods is a feasible means to reduce salt intake at a population level.[18] Further engagement with policy makers needs to address access to freshly grown produce.

Initiation and drug treatment of hypertension

ISH guidelines recommend drug treatment for all patients with established hypertension with BP ≥ 160/100 mmHg, which is certainly in line with PASCAR's viewpoint. However, for patients with stage 1 hypertension, there is differentiation between optimal and essential. Patients at high risk, with HMOD or established CV or renal disease, should receive drug treatment, but those with low to moderate risk without these complications should receive drug treatment under optimal management.

Under essential treatment, if there is limited drug availability, then treatment should be considered for older people, 50–80 years old. In SSA this recommendation is not realistic as the majority of the population is below 50 years of age and hypertension presents at a younger age and is often more progressive (see below). PASCAR recommends treating all patients diagnosed with hypertension, including those with stage 1 hypertension who have not responded to lifestyle modifications.

The ISH guidelines recommend initiation of two drugs, preferably in a single-pill combination (SPC) in the majority of patients. The initial combination is an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in combination with a calcium channel blocker (CCB). According to the ISH guidelines, in African patients an ARB is preferred over an ACE inhibitor due to risk of angioedema, despite the CREOLE study showing a low risk of non-severe angioedema.[19]

ACE inhibitors are generally less costly than ARBs and can be used unless there is a contra-indication. Furthermore, in African patients an initial combination of CCB plus thiazide/thiazide-like diuretic is recommended. In the CREOLE study

Table 2. Recommended lifestyle changes

	Recommended to increase	*Recommended to avoid*
Salt	Reduce salt in food preparation and at the table	High-salt foods (fast foods, processed foods, cereals)
Diet	Eat whole grains, nuts, seeds, legumes, tofu, fruit, vegetables (leafy vegetables, beetroot, avocados), polyunsaturated fats	High-sugar food, saturated and trans fats
Drinks	Coffee, green and black tea, hibiscus tea, pomegranate juice, beetroot juice, cocoa	Excessive (> 2/day) alcohol or binge drinking
Smoking		Smoking
Physical activity	Aerobic and resistance exercise 30 minutes/ day 5–7 days a week, strength training	
Stress	Transcendental meditation/ mindfulness	Chronic stress
Alternative therapies		Complementary, alternative or traditional medicines
Environment		Air pollution and cold temperature

this was more effective than ACE inhibitor-plus-thiazide combination, although potassium needs to be monitored due to risk of hypokalaemia. However, thiazide-like diuretics may not be widely available, in which case a thiazide diuretic would be used.

Importantly, the ISH guidelines stress the importance of controlling the BP, regardless of what drugs are available for use. They have provided alternatives to the standard first-line agents. They have also made it clear that, while it is optimal to use SPC, free combinations can be used in settings where SPC are limited. It is optimal to use agents with longer half-lives that require once-daily dosing. They recommend the use of single agents for BP control in the setting of frail elderly patients only or in the setting of stage 1 hypertension, where lifestyle measures have not improved the BP to target. The long half-life of amlodipine may make it the drug of choice in this setting, making it the preferred choice over a diuretic.

If BP is not controlled, the initial combination must have the dose optimised before adding a diuretic. This is an important difference to other major guidelines. Beta-blockers are only used for treatment of hypertension associated with specific cardiac conditions such as heart failure, ischaemic heart disease and atrial fibrillation.

The ISH guidelines have stressed the importance of ensuring good adherence, as have other international guidelines. They have highlighted means to improve adherence to antihypertensive therapy, both essential and optimal. It is essential that adherence to antihypertensive therapy is improved in whatever ways are available. While it is ideal to be able to monitor adherence, the methods available may not be feasible and have many limitations. However, where possible, it is recommended to monitor adherence using the best tools available/feasible in the particular setting.

Resistant hypertension

Resistant hypertension should be suspected if office BP is > 140/90 mmHg on treatment with at least three antihypertensives (in maximal or maximally tolerated doses), including a diuretic. It is essential to exclude pseudo-resistance (white-coat effect, non-adherence to treatment, incorrect BP measurements, errors in antihypertensive therapy) and substance-induced hypertension, such as non-steroidal anti-inflammatories (NSAIDs) as contributors. Health behaviours and lifestyle also need to be optimised.

If truly resistant, low-dose spironolactone is recommended, especially if K^+ is < 4.5 mmol/l and eGFR is > 45 ml/min. If this fails, then referral to a specialist or the investigation of secondary causes is recommended under the optimal approach. Under the essential approach, addition of other antihypertensive medication is recommended and a screen for secondary causes with a history, examination and basic tests, for example, thyroid-stimulating hormone, electrolytes, creatinine and eGFR, and dipstick urine.

Ethnic differences

In populations of African descent, hypertension and HMOD occur at younger ages. There is greater resistance to treatment, more nocturnal hypertension, and increased risk of kidney disease, stroke, heart failure and mortality.[20] This may be related to physiological differences in the renin–angiotensin–aldosterone system, altered renal sodium handling, CV reactivity and early vascular aging. These are important considerations when treating patients from SSA. Studies done in SSA suggest amiloride is a useful agent in controlling BP in patients with resistant hypertension,[21] but amiloride is not mentioned in the ISH guideline.

Hypertensive emergencies/urgencies

Hypertensive emergency is a severely elevated BP associated with acute HMOD and requires immediate BP lowering, usually with intravenous therapy. Urgency refers to severely elevated BP without acute HMOD and can be managed with oral antihypertensive agents. In SSA these complications of hypertension are relatively common, but an evidence-based approach to management is lacking.

The essential requirements are a clinical examination, evaluation of HMOD, including fundoscopy, and the following investigations: haemoglobin, platelets, creatinine, sodium, potassium, lactate dehydrogenase, haptoglobin, urinalysis for protein, urine sediment and ECG. In SSA, access to ECG and urinary sediment is limited, and measurement of lactate dehydrogenase and haptoglobin is unnecessary. A simple dipstick and creatinine will alert the clinician to kidney damage, which is the most common complication of a hypertensive emergency.

Hypertensive emergencies require immediate BP lowering to prevent or limit further HMOD, but unfortunately there is sparse evidence to guide management, and recommendations are largely consensus based. The time to lower BP and the magnitude of BP reduction depends on the clinical context, but in general a 25% immediate reduction is recommended. Large drops in BP can precipitate stroke due to loss of cerebral autoregulation.

The ISH guidelines recommend intravenous labetalol and nicardipine, which are generally safe to use in all hypertensive emergencies. However, intravenous labetalol has limited availability in SSA and nicardipine is not listed on the WHO essential drugs list and in 2010 was only available in Cameroon and Senegal.[22] Nitroglycerine is an option, however, access to high-care and intensive-care units is very limited. In the absence of the above, an oral long-acting CCB[23] or oral labetolol is probably the safest choice and a loop diuretic is an option in the setting of pulmonary oedema. All patients should be followed up and should achieve optimal BP control.

Hypertension and co-morbidities

A detailed analysis of this section is beyond the scope of the review. In addition to BP control under optimal and essential recommendations, effective treatment of the other risk factors to reduce the residual cardiovascular risk is essential. Low-density lipoprotein (LDL) cholesterol should be reduced according to risk profile: (1) > 50% and < 1.8 mmol/l in hypertension and cardiovascular disease (CVD), chronic kidney disease, diabetes mellitus or no CVD and high risk; (2) > 50% and < 2.6 mmol/l in high-risk patients; (3) < 3 mmol/l in moderate-risk patients. The fasting serum glucose levels should be reduced below 7 mmol/l or glycated haemoglobin (HbA_{1c}) below 7%. Serum urate should be maintained below 0.387 mmol/l, and < 0.357 mmol/l in patients

with gout. Antiplatelet therapy should be considered in patients with CVD (secondary prevention only).

From the PASCAR perspective, the lipid guidelines are too complex and rely on web-based risk charts for implementation, and the recommendation for treating asymptomatic hyperuricaemia is considered very controversial. In addition, aspirin should be used in all patients with established atherosclerotic CVD, unless there is a contra-indication.

Other

In SSA, where there is the highest prevalence of people living with HIV and, with around one of every four of them having hypertension, it is important to be aware of the drug interactions between CCB and antiretroviral therapies. Amlodipine dose should be reduced when used in combination with protease inhibitors due to the risk of prolonging the PR interval.[24] Other antihypertensives that are affected by various anti-retrovirals are detailed by van Zoest *et al*.[25] Otherwise the treatment of hypertension remains the same as in general hypertensives.

Rationale for creating this commentary

The ISH guidelines were developed in order to create a uniform platform that is accessible and usable to all environments, both high and low income. In order to improve accessibility, they were published in two major hypertension journals. The aim was to create recommendations that can be adopted in different settings but that are accepted international standards of care.

The guidelines provide a tool to promote the improvement of BP control to 25% in Africa as developed by the PASCAR task force.[11] Adopting the ISH guidelines will provide a standard of care for African hypertension groups to lobby healthcare providers and governments to develop basic standards of care for the diagnosis and treatment of hypertension. However, this commentary serves to underline that some of the recommendations are not realisable in SSA at the current time. There is also a need to develop a guideline to enable nurse practitioners to treat hypertension and provide greater access to basic care for patients.

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Elderly may benefit from more invasive treatment: large seven-year study

Elderly patients suffering the most common type of heart attack may benefit from more invasive treatment, research has shown. The study draws on data captured over seven years from 1 500 patients aged 80 years or over. It was conducted by researchers from the National Institute of Health Research Health Informatics Collaborative (NIHR-HIC), led by Imperial College Healthcare NHS Trust and Imperial College London.

The research looks at elderly patients admitted to hospital with a non-ST-segment elevated myocardial infarction (NSTEMI). It found patients who underwent invasive treatment with a coronary angiogram, followed up with bypass surgery or coronary stenting as appropriate, had higher survival rates than those who were treated with medication alone. Patients who had coronary angiograms were also less likely to be re-admitted to hospital with a second heart attack or heart failure.

Coronary angiograms are specialist X-rays to identify blockages in the blood supply to the heart. They can help a clinician determine the cause of an NSTEMI and decide on effective treatment, such as increasing blood flow through a coronary stent or bypass grafting.

Previous trials have shown increased survival rates in younger patients with NSTEMI following invasive treatment, but there has been conflicting evidence as to whether these benefits extend into patients over 80 years. Only 38% of NSTEMI patients in this older age group currently receive invasive treatment, compared to 78% of the under 60 years.

Dr Amit Kaura, lead author of the research, British Heart Foundation clinical research fellow and NIHR clinical research fellow with the National Heart and Lung Institute at Imperial College London explained: 'Because there has been no clear consensus on how best to manage elderly patients with this type of heart attack, many doctors have erred on the side of caution, not wanting to risk complications in their more vulnerable patients. These results show they can now be more confident of the benefits that invasive treatment can bring for this group.'

The study, funded by the NIHR Imperial Biomedical Research Centre, identified just under 2 000 patients aged over 80 years who were diagnosed with an NSTEMI at five hospitals between 2010 and 2017. To ensure the robustness of the study, the researchers used sophisticated statistical techniques to apply the kind of criteria used in a clinical trial, to determine which of these patients would be included in the analysis. In total, 1 500 patients were included, with just over half having invasive treatment. After five years, 31% of those in the invasive treatment group had died, compared to 61% in the non-invasive group.

The team estimates that if all patients had received invasive treatment, just 36% would have died, compared to 55% if all had received non-invasive treatment. These figures take into account over 70 variables that might have affected prognosis, such as other medical conditions.

The analysis also showed that patients were at no greater risk of stroke or bleeding if they received invasive treatment, as there were similar rates across both groups. Patients who had invasive treatment were also a third less likely to be re-admitted to hospital for heart failure or heart attack.

Kaura said: 'The gold standard is to base treatment decisions on evidence from randomised control trials, but that doesn't yet exist for this group of patients. In the interim, we've done the next best thing, by looking at retrospective data gathered from these five large hospitals and using it like a clinical trial. The results are clear: clinicians should positively consider invasive management for any patients over 80 diagnosed with an NSTEMI.'

The data used in the study was gathered through the National Institute for Health Research Health Informatics Collaborative (NIHR-HIC), which involves: Imperial College Healthcare NHS Trust, Oxford University Hospitals NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, King's College Hospital NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust.

Source: Medical Brief 2020

ECG Series

Posterior infarction: a STEMI easily missed

Lina Hähnle, Charle Viljoen, Julian Hoevelmann, Robert Gill, Ashley Chin

Abstract

Anterior ST-segment depression encompasses important differential diagnoses, including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and pulmonary embolism. Diagnostic accuracy is crucial, as this has important therapeutic implications. This ECG case report reviews the electrocardiographic changes seen in patients with chest pain and anterior ST-segment depression.

Keywords: ECG, STEMI, NSTEMI, pulmonary embolism

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A 65-year-old woman with a 30 pack-year smoking history, hypertension, dyslipidaemia and type 2 diabetes mellitus woke up with severe central crushing chest pain and autonomic symptoms. She was rushed to her nearest emergency centre where a 12-lead electrocardiogram (ECG) was performed (Fig. 1). This showed a sinus tachycardia, with narrow QRS complexes and no Q waves. The ST-segment depression in the anterior leads (V1 to V4) prompted the attending physician to acquire another ECG, which extended the recording to include posterior leads (V7, V8 and V9) (Fig. 2). This showed ST-segment elevation in V7 to V9, confirming the diagnosis of an acute posterior ST-segment elevation myocardial infarction (STEMI).

The patient was given loading doses of dual antiplatelet therapy and taken for primary percutaneous coronary intervention (PCI). Coronary angiography showed an acute occlusion of the proximal circumflex artery (LCx), which was the culprit lesion. The patient also had severe coronary artery disease in both the right coronary artery and the left anterior descending artery (LAD). (Fig. 3A, B). A drug-eluting stent (DES) was inserted in the LCx to treat the culprit lesion, resulting in good reflow. The patient was stabilised in the coronary care unit and discharged on guideline-directed medical therapy. Percutaneous intervention of the non-culprit lesions was planned as an elective procedure.

Discussion

All patients who present with chest pain should have a 12-lead ECG.[1] The ECG should be scrutinised for any features that might suggest myocardial ischaemia, infarction or pulmonary embolism (Table 1). Prompt recognition of these life-threatening conditions will aid in the institution of timeous and appropriate revascularisation therapy.[1,2]

Table 1. ECG features of acute posterior STEMI, NSTEMI and acute PE

	Acute posterior STEMI	*NSTEMI*	*Acute PE*
Q wave in III	Only present if inferior STEMI involvement	Should not be present	May be present as part of $S_IQ_{III}T_{III}$
Dominant R in V1	Usually present and develops over days	Should not be present	Only present if RVH developed from chronic pulmonary thromboembolic disease. Severe PE may cause incomplete or complete RBBB.
S wave in I	Should not be present	Should not be present	May be present as part of $S_IQ_{III}T_{III}$
ST-segment depression V1–V3	Usually present	May be present	May be present
ST-segment elevation V7–V9	Usually present	Should not be present	Should not be present
ST-segment elevation elsewhere	Inferior ST-segment elevation may be present	Should not be present	Should not be present
T-wave inversion in V1–V3	May be present in the acute setting, followed by upright T wave in V1	May be present (Wellens' pattern)	May be present
T-wave inversion in III	May be present	May be present	May be present as part of $S_IQ_{III}T_{III}$

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PE, pulmonary embolism; RBBB, right bundle branch block; RVH, right ventricular hypertrophy;.

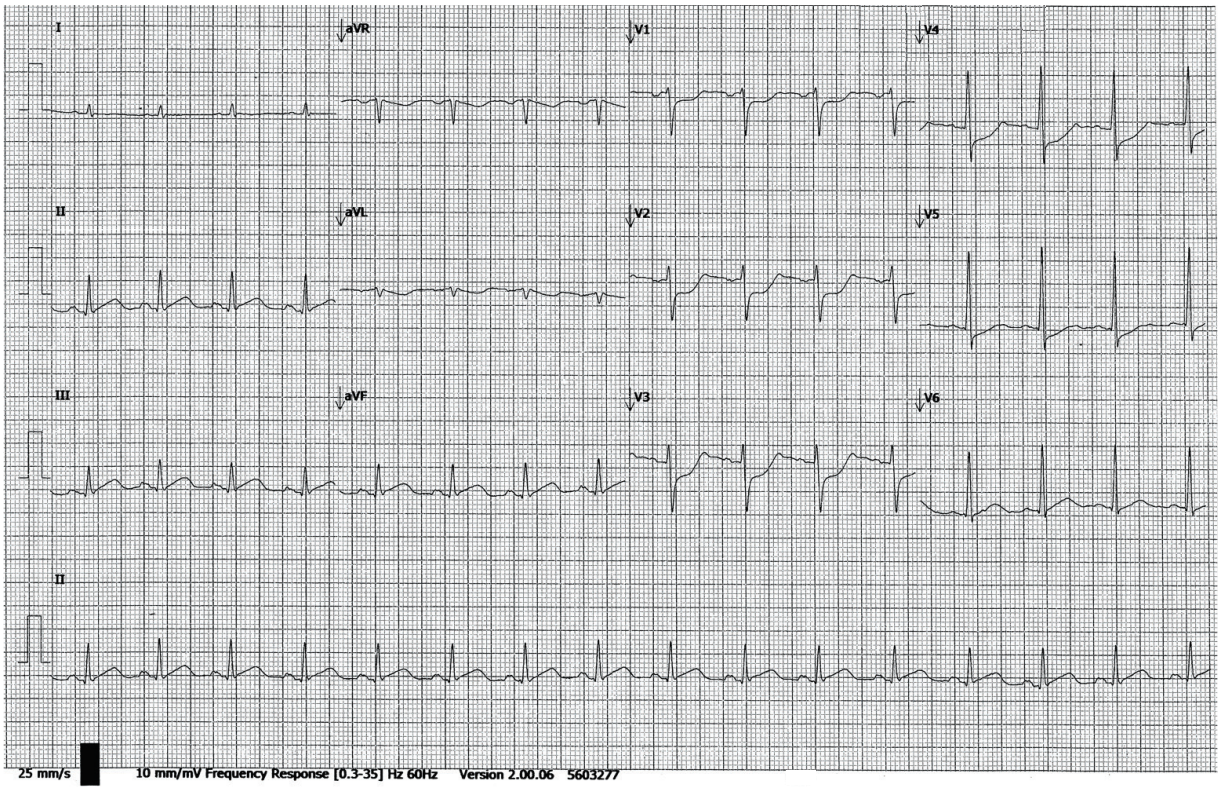

Fig. 1. A 12-lead ECG showing ST-segment depression in the anterior leads (V1 to V4).

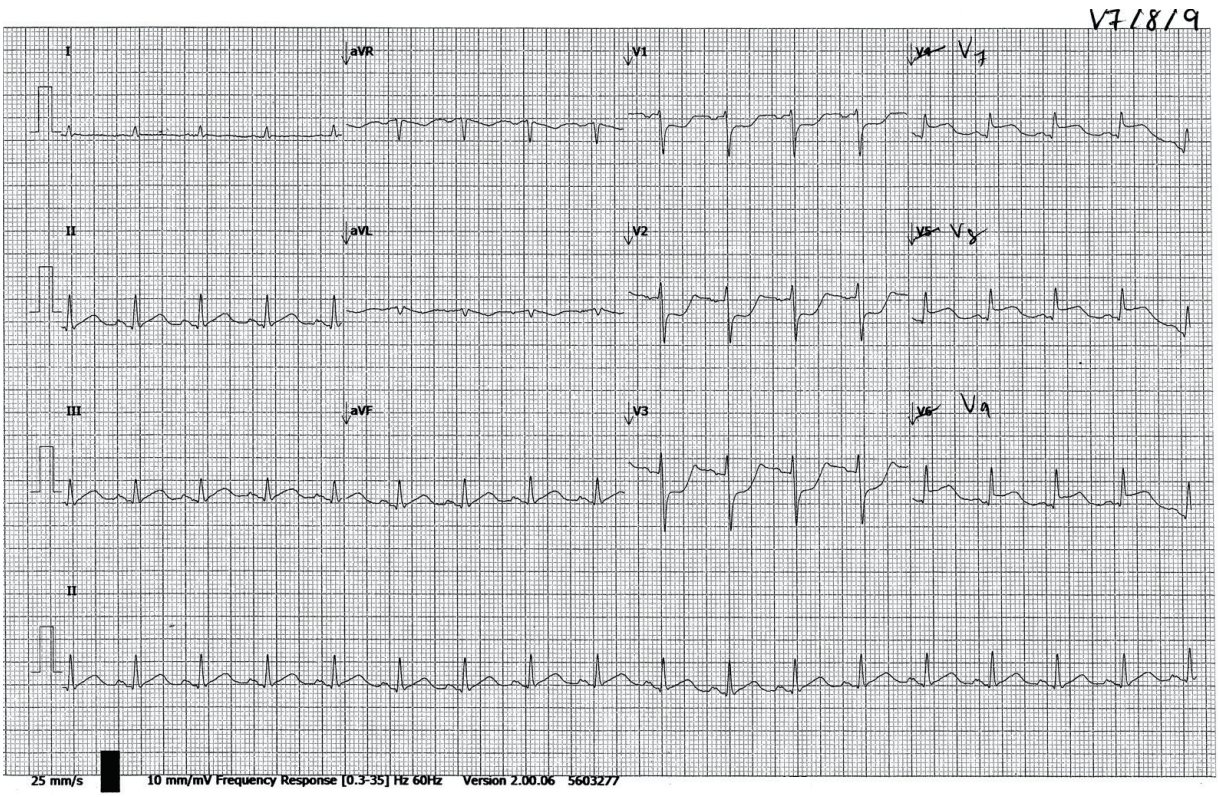

Fig. 2. ST-segment elevation demonstrated in the posterior leads (V7, V8 and V9).

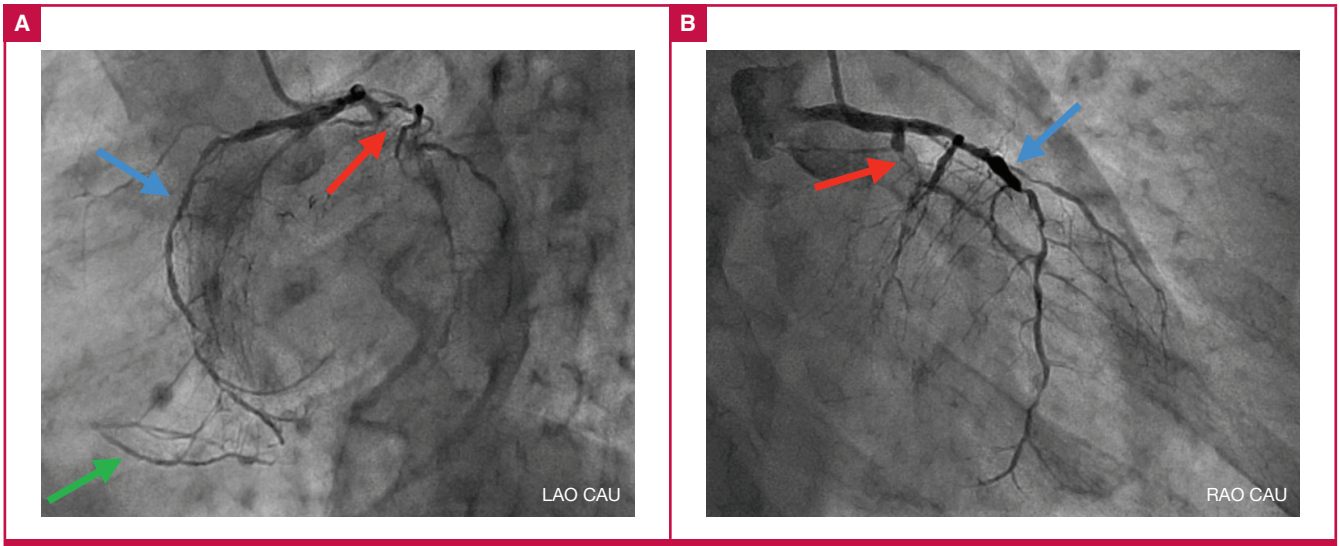

Fig. 3. A. Left anterior oblique (LAO) caudal view demonstrated extensive coronary artery disease. The proximal left circumflex artery (LCx) was totally occluded (culprit lesion) (red arrow), and the left anterior descending artery (LAD) was severely diseased (blue arrow). The posterior descending artery (PDA) filled competitively from left to right collaterals (green arrow). B. The culprit lesion was the proximal occlusion of the left circumflex artery (LCx), as shown in this right anterior oblique (RAO) caudal view (red arrow). There was a long segment of severe disease in the left anterior descending artery (LAD) (blue arrow).

In normal physiology, the vectors at the end of depolarisation and the beginning of repolarisation neutralise each other. On the ECG, this manifests as a J point (start of ST-segment), which is not deviated from the isoelectric line.[3] This balance of charge is maintained by Na^+/K^+ ATPase channels, which are dependent on glucose. In coronary artery occlusion, the lack of glucose supply causes malfunctioning of these ion-gated channels, resulting in an imbalance of electrical charge across the myocardial cell membrane. This imbalance in electrical charge manifests as ST-segment deviation. Transmural ischaemia leads to ST-segment elevation in leads overlying the ischaemia, whereas sub-endocardial ischaemia can manifest as ST-segment depression or T-wave inversion.[4] However, in some cases, ischaemia can be electrocardiographically silent.[5]

ST-segment depression can represent reciprocal changes of ST-segment elevation recorded by leads opposite those overlying the acute infarction (Table 1). Because the standard 12-lead ECG does not include leads that overlie the posterior aspect of the heart, ST-segment depression in the anterior leads should prompt the acquisition of posterior leads (V7, V8 and V9) to rule out posterior ST-segment elevation (Fig. 4).[6,7] ST-segment elevation in the posterior leads confirms the diagnosis of posterior STEMI. If no ST-segment elevation is recorded in the posterior leads, non-ST-segment elevation myocardial infarction (NSTEMI) (Fig. 5) or pulmonary embolism (PE) (Fig. 6) should be considered as alternative diagnoses.

Acute posterior STEMI can be accompanied with inferior STEMI if the culprit lesion is proximal to the posterior

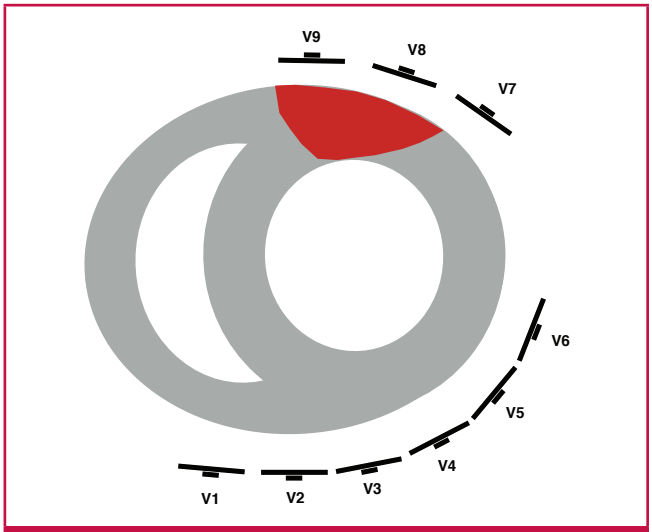

Fig. 4. Posterior transmural myocardial infarction (STEMI) would cause ST-segment elevation in the posterior leads, which in the anterior leads will manifest as ST-segment depression (reciprocal changes).

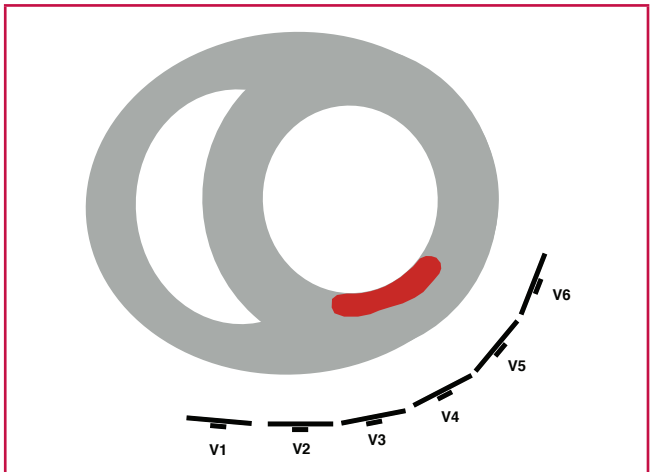

Fig. 5. Sub-endocardial ischaemia (NSTEMI) can manifest as ST-segment depression in the anterior leads.

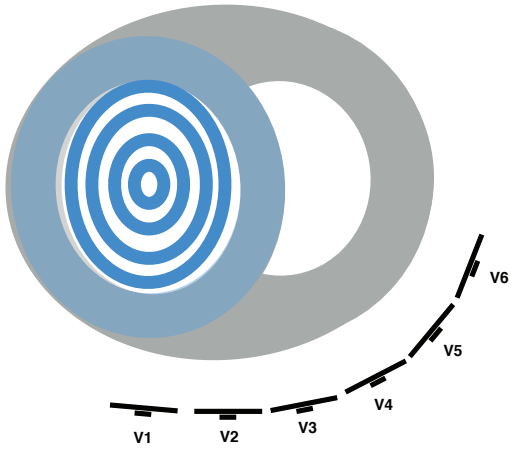

Fig. 6. Acute pulmonary embolism causing right ventricular strain, which translates to ST-segment depression in the anterior leads.

descending artery of the right coronary artery. However, isolated posterior STEMI can occur if the culprit occlusion is in a posterior lateral wall branch of the right coronary artery or in the circumflex artery (as in this case). In a posterior STEMI, the evolution of changes over days includes the development of a dominant R wave in V1 (a reciprocal Q wave) or Q waves in V7 to V9 with a T wave that is usually upright in V1 (Table 1).

PE is an important differential diagnosis to be excluded in the patient presenting with chest pain. This life-threatening condition can be clinically indistinguishable from MI, as both conditions may present with chest pain and/or dyspnoea. In addition, a further confounder is that a massive PE can mimic a MI on the ECG. Both posterior MI and PE could be associated with a dominant R wave in V1 and ST and/or T-wave changes in the anterior leads (Table 1).

Chronic pulmonary thromboembolic disease can cause right ventricular hypertrophy (RVH) with a dominant R wave in V1, but in acute PE the right ventricle has not had time to hypertrophy. Severe cases of PE may cause incomplete or complete right bundle branch block (RBBB).[8] However, RBBB could also be caused by MI.

Occasionally, patients present with the pathognomonic $S_IQ_{III}T_{III}$ (S wave in lead I, Q wave in lead III, T-wave inversion in lead III), ST-segment changes and/or widespread T-wave inversion. The mechanism for the ST-segment deviation and T-wave inversion in the anterior leads seen in PE could be explained by the strain on the right ventricle caused by the sudden rise in pulmonary artery pressure.[9] Whenever suspected, compacted tomography pulmonary angiography (CTPA) would be the diagnostic modality of choice for PE.[2] As sinus tachycardia is the most common ECG feature of acute PE, its absence makes the diagnosis less likely.[8]

Because biomarkers such as troponins and CK-MB could be elevated in STEMI, NSTEMI and PE, they should not be relied on as the sole diagnostic modality. In this setting, imaging such as coronary angiography and/or CTPA should be performed. [10]

Accurate diagnosis of STEMI, NSTEMI or acute PE allows for the timely institution of appropriate therapy. STEMI requires emergency revascularisation in the form of PCI, or thrombolysis if a PCI centre cannot be accessed within two hours of diagnosis,[1] whereas angiography is indicated within 24 hours after presenting with a NSTEMI.[4]

Pain management and appropriate antiplatelet therapy form part of the mainstay of therapy in both STEMI and NSTEMI.[1,4] PE, however, requires anticoagulation. Systemic thrombolytic therapy is recommended for PE with haemodynamic instability. In centres with the necessary skill, percutaneous catheter-directed therapy or surgical embolectomy could be considered in high-risk PE when thrombolysis has failed or is contra-indicated.[2]

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Case Report

Coronavirus disease 2019 (COVID-19) and simultaneous acute anteroseptal and inferior ST-segment elevation myocardial infarction

Mustafa Yolcu, Fusun Gunesdogdu, Metin Bektas, Derya Turan Bayirli, Kivanc Serefhanoglu

Abstract

Coronavirus disease 2019 (COVID-19) is a recently recognised pandemic spreading rapidly from Wuhan, Hubei, to other provinces in China and to many countries around the world. The number of COVID-19-related deaths is steadily increasing. Acute ST-segment elevation myocardial infarction (STEMI) is a disease with high morbidity and mortality rates, and primary percutaneous coronary intervention is usually recommended for the treatment. A patient with diabetes mellitus and hypertension for five years was admitted to the emergency unit with symptoms of fever, cough and dyspnoea. These symptoms were consistent with viral pneumonia and a COVID PCR test was performed, which tested positive three days later. The patient had chest pain on the eighth day of hospitalisation. On electrocardiography, simultaneous acute inferior and anterior STEMI were identified. High levels of stress and increased metabolic demand in these patients may lead to concomitant thrombosis of different coronary arteries, presenting with two different STEMIs.

Keywords: COVID-19, acute anterior wall myocardial infarction, acute inferior wall myocardial infarction

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Coronavirus disease 2019 (COVID-19) is a recently recognised pandemic spreading rapidly from Wuhan, Hubei, to other provinces in China and to several countries throughout the world.[1] The number of COVID-19-related deaths is steadily increasing.[1] Acute ST-segment elevation myocardial infarction (STEMI) is a disease with high morbidity and mortality rates, and primary percutaneous coronary intervention (PPCI) is usually recommended for the treatment.[2] Co-existence of cardiovascular disease (CVD) is common in patients with COVID-19 and is related to an increased mortality rate. In this case report, we present a patient who was diagnosed with simultaneous acute anteroseptal and inferior STEMI while he was receiving treatment for COVID-19.

Case report

Our patient (a 55-year-old male, body mass index 26 kg/m^2) with diabetes mellitus (DM) and hypertension (HT) for five years was admitted to the emergency unit on 25 March 2020 with symptoms of fever, cough and dyspnoea. He had a history of stable angina pectoris and 2.5 years earlier had had a stent implantation in his left anterior descending (LAD) artery. He had no chest pain on admission.

He was pre-diagnosed with COVID-19 after a thorough physical examination and work-up, including a thoracic computed tomography (CT) scan. There was ground-glass opacity on the CT scan. Azithromycin and oseltamivir treatment were started for COVID-19. His COVID PCR test was positive on 28 March and he was diagnosed with COVID-19. Hydroxychloroquine was added to the treatment regime.

On the morning of 2 April, he experienced chest pain with an increase in dyspnoea. As the level of oxygen saturation decreased, he was intubated. On electrocardiography (ECG), simultaneous acute inferior and anterior STEMI were identified (Fig. 1). It was decided to proceed with the PPCI.

All necessary precautions were taken for viral protection. All laboratory staff wore N95 masks and protective goggles with single-use coveralls with an opening for the face. Additionally,

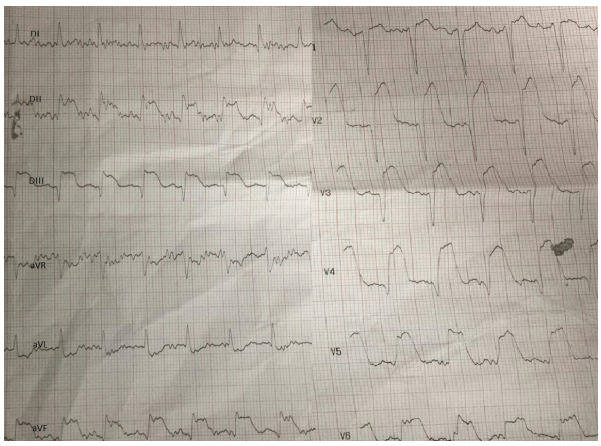

Fig. 1. Electrocardiography of the patient showing inferior and anteroseptal myocardial infarction.

the performing physician and the technician wore sterile single-use laboratory coats.

On coronary angiography, the stent in the mid LAD was found to be patent, however it was occluded totally after the stent, and the right coronary artery (RCA) had subtotal occlusion. Initially, a Partner sirolimus-eluting stent of 2.75 × 15 mm was placed in the mid LAD (Fig. 2). After stent implantation, some blood flow was observed beyond the occlusion, however, a thrombotic total occlusion occurred in the distal LAD. Repeated dilatations were performed on this site, however no blood flow was observed. Two Boston Scientific Rebel bare-metal stents of 4.0 × 24 mm and 4.0 × 16 mm were directly implanted (Fig. 2) into the RCA.

In our hospital we have two catheterisation units. The laboratory used for the intervention was sterilised with disinfectant solutions and ultraviolet light and closed for 48

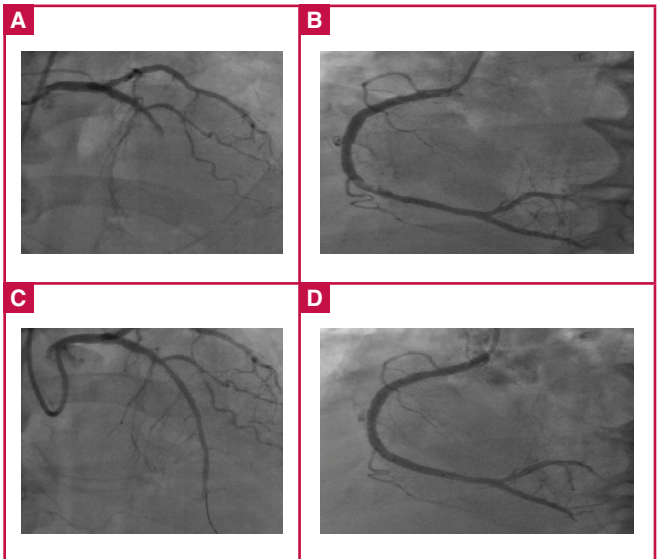

Fig. 2. A, C. Angiographic views of the left anterior descending artery before and after primary percutaneous coronary intervention. B, D. Angiographic views of the right coronary artery before and after primary percutaneous coronary intervention.

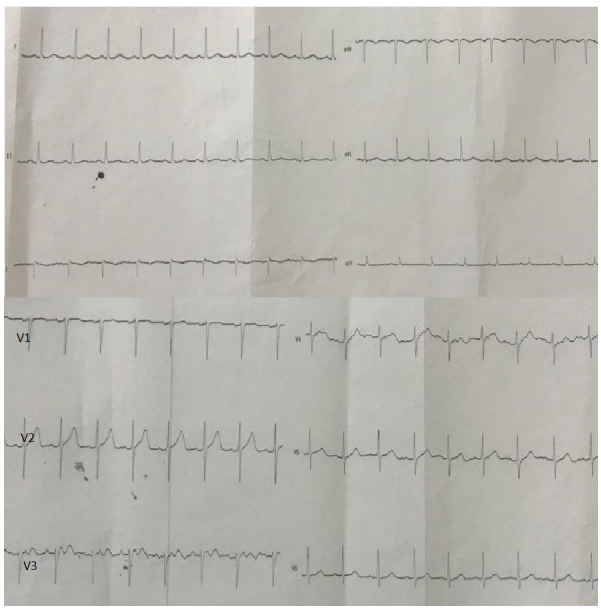

Fig. 3. Electrocardiography of the patient after primary percutaneous coronary intervention.

hours. The patient was taken into the intensive care unit. After the intervention, we observed resolution of ST-segment elevations on his ECG (Fig. 3). On a transthoracic echocardiogram (TTE), the ejection fraction was observed at 45% with apical akinesia. In his control TTE performed on 6 April, we observed similar findings after the intervention. The patient was discharged as healthy on 21 April.

Discussion

COVID-19 is a pandemic spreading over approximately 208 countries/regions. By 6 April 2020, more than 1 287 742 patients had become infected worldwide and it had caused the death of more than 70 000 people.

The prevalence of CVD is higher among those with COVID-19, and myocardial injury occurs in more than 7% of patients due to the infection (22% of them critically ill).[3] COVID-19 infection can directly affect the cardiovascular system and the presence of CVD also facilitates COVID-19 infection.[4] The Chinese Centre for Disease Control and Prevention reported in the recently published largest case series in mainland China that the overall mortality rate was 2.3% (1 023 deaths in 44 672 confirmed cases); however, the mortality rate increased up to 10.5% in patients with a history of CVD.[5]

STEMI is still a significant underlying factor for increased morbidity and mortality rates all around the world, although there has been a decrease in incidence and an increase in survival rates recently.[6] Thrombotic occlusion occurs in a coronary artery at the site of a ruptured or eroded plaque and it leads to STEMI.[6] Characteristic symptoms, and changes in the ECG are the basis for diagnosis, and elevated cardiac enzymes subsequently confirm the diagnosis.[6] If it is performed by experienced specialists timeously, mechanical reperfusion via PPCI is superior to fibrinolytic therapy.[6]

For patients with COVID-19, there are two possible pathophysiological mechanisms: (1) type-I MI caused by anxiety-induced catecholamine discharge, prothrombotic system activation triggered by severe inflammatory activation, and plaque rupture, and (2) type-II MI caused by decreased oxygen delivery due to acute inflammation, respiratory failure and hypoxia.[7,8]

Moreover, Huang *et al*. stated that high concentrations of interleukin-1β, interferon-γ (IFN- γ), IFN-γ-inducible protein 10 and monocyte chemoattractant protein-1 could be observed in COVID-19 patients, thereby leading to activated T-helper-1 cell responses.[9,10] It was also suggested that invasion by the virus of angiotensin converting enzyme-II, which is abundantly present in myocytes and vascular endothelial cells and is also the binding site of the coronavirus, may be the direct cause of cardiac involvement.[9]

In a published study, it was reported that a total of 40% of patients with positive test results for COVID-19 had cardiovascular or cerebrovascular disease and 7% had the possibility to develop acute cardiac injury. In case reports, on the other hand, the first causes of admission to hospital due to COVID-19 were heart failure, acute MI, myocarditis and sudden cardiac arrest.[10-12] Shi *et al.* found that 19.7% of patients experienced cardiac injury, and the report showed for the first time that cardiac injury was independently related to an increased risk of mortality in patients with COVID-19 infection.[13]

It was also reported that in a significant number of patients with COVID-19 infection, levels of high-sensitivity cardiac troponin were increased.[14] In a retrospective analysis of 191 patients hospitalised due to COVID-19, it was observed that levels of troponin were increased in more than 50% of patients who died.[14] In other words, increasing levels of troponin in patients presenting with COVID-19 infection is an important indicator of mortality.[14]

Li *et al*. reported in a meta-analysis of six studies including 1 527 patients that the prevalence of CVD in patients with COVID-19 was 16.4%.[15] The prevalence of CVD was higher in patients who required intensive care than those who did not require it.[15] It was also reported that at least 8% of the patients were troponin positive.[15]

In their analysis, Guo *et al*. showed that while in-hospital mortality rates of intensive care patients who were without CVD and had normal troponin levels was 7.62%, it was 69.44% in patients with known CVD and high troponin levels.[1] In a study evaluating 187 patients, troponin elevation, which is an indication of myocardial injury, was observed in 52 (27.8%) patients, and while the mortality rate was 59.6% in patients with high troponin levels, it was 8.9% in those with normal troponin levels.[1]

For the first time, acute MI was identified at the autopsy of a 53-year-old woman with chronic renal failure in Jinyintan Hospital (data not published; obtained via personal communication with a pathologist from the Chinese Academy of Science).[14]

In this study, we present a case of MI with anterior and inferior ST elevation on ECG, with the sudden onset of chest pain and increasing dyspnoea while receiving treatment for COVID-19. These patients may be hypoxic due to pneumonia, and both catecholaminergic discharge due to stress and plaque rupture with prothrombotic system activation induced by inflammatory activation related to COVID-19 may develop and result in STEMI. Moreover, in these patients, increased thrombophilia and arterial and venous embolisms are observed.

Our case presented with HT and DM, however, there was no history of chest pain or dyspnoea. On the fourth day of hospitalisation, sudden onset of chest pain with ST-segment elevation in the anteroseptal and inferior leads on ECG were observed. The Turkish Society of Cardiology (TSC), in its recently published expert opinion report, recommended thrombolytic therapy as the first option during STEMI.[4] They also recommended PPCI in cases of wide anterior wall infarcts.[4] We considered PPCI in our patient because of ST elevations in the V1-6 and inferior leads on ECG, in agreement with the recommendations of the TSC. PPCI was performed with coronary angiography for the LAD and right coronary arteries.

In COVID-19 patients, the incidence of CVD together with multiple cardiovascular risk factors is high. It is difficult to evaluate chest pain in these patients as they are isolated in intensive care units and the number of intubated patients is high. Moreover, ECG and TTE are performed less often due to strict isolation of these patients. In retrospective analysis, troponin was determined to be positive in approximately half of the deceased patients. With co-morbid coronary artery disease and positive troponin results, these patients were identified as a group with a significantly higher mortality rate.

Conclusion

Serial ECG monitoring and performing echocardiography as required in these patients in the intensive care unit could help to diagnose STEMI or non-STEMI accurately. A true diagnosis of MI may lead to the administration of appropriate treatment and lowering of mortality rates. On the other hand, a diagnosis of MI during an autopsy suggests that the reported rate of MI diagnosis is lower than the actual rate. High levels of stress and increased metabolism in these patients may lead to thrombosis of several coronary arteries with the concurrent occurrence of two different STEMIs.

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Aspirin use best for those with high coronary calcium, low risk of bleeding

An X-ray test, commonly used to assess hardening of the arteries, could help doctors decide whether the benefits of taking aspirin to prevent a first heart attack or stroke outweigh the risks of bleeding from its use, UT Southwestern research suggests. The findings could give doctors and patients more concrete guidelines for making this important decision.

Due to its anti-clotting properties, aspirin is widely prescribed as a preventative measure to patients who have already had cardiovascular events, such as a heart attack or ischaemic stroke. However, aspirin's role in primary prevention – averting first heart attacks and strokes – has been unclear, explains study leader Dr Amit Khera, professor of internal medicine.

After decades of commonly prescribing aspirin for primary prevention, recent guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) recommend more select use for those with the highest risk of cardiac events due to the increased risk of bleeding.

'We used to say for aspirin, generally yes, occasionally no,' Khera says. 'With these new guidelines, we've flipped that on its head and are saying that we should not use aspirin for most people in primary prevention.'

However, he adds, 'it's been unclear how to select which patients might still benefit most from aspirin therapy, taking into account the risk of bleeding. We need tools to find that sweet spot where aspirin is most beneficial and offsets the associated risks,' he says. In the study, Khera and his colleagues looked to a diagnostic test – coronary artery calcium (CAC) scanning – to see if it could help doctors make this important decision. CAC scanning, a CT scan that scores the amount of calcium that lines the heart's arteries, is commonly performed to detect hardening of the arteries and risk of a heart attack or stroke.

The researchers gathered data from the Dallas Heart Study, an ongoing study that tracks the development of cardiovascular disease in more than 6 000 adults in Dallas County. Initially, participants were invited to three visits for the collection of health and demographic information, laboratory samples and various imaging studies, including CAC scanning. These volunteers were then followed for 12 years on average to track those who had heart attacks, died from heart disease, or had a non-fatal or fatal stroke – medical problems collectively called atherosclerotic cardiovascular disease – and/or who had a bleeding event that caused hospitalisation or death.

The researchers used data from 2 191 participants with a mean age of 44 years who had CAC scans and follow-up information available. About 57% were female and 47% were black.

Overall, about half of the participants had a CAC score of 0, suggesting little to no calcium build-up in their arteries. About 7% had a CAC score of more than 100, suggesting heavy calcium build-up. The rest had values in the middle (1–99).

When Khera and his colleagues examined the rates of atherosclerotic cardiovascular disease (ASCVD) and bleeding in the study group, they found that both events increased in a graded fashion as CAC scores rose. However, when they used statistical modelling to see how many of the ASCVD events may have been prevented by aspirin use – based on values gleaned from a recent meta-analysis that informed the AHA and ACC guidelines – they found that aspirin's benefits only outweighed its risks for those with CAC scores above 100. For this group, the risk of ASCVD was about 15-fold and the bleeding risk about three-fold of those with a CAC score of 0.

Yet, this effect only held true for those whose inherent risk for bleeding was already low, Khera says, meaning that in practice, as mentioned in the guidelines, if someone has had prior significant bleeding episodes, risk factors for bleeding, or was on medications that increase bleeding, they should not take aspirin for primary prevention regardless of their CAC score.

Together, Khera says, the findings reinforce new guidelines suggesting that aspirin for primary prevention is only appropriate for select patients and that CAC scanning can help doctors and patients make that decision.

'Aspirin use is not a one-size-fits-all therapy,' says Khera, who holds the Dallas Heart Ball chair in hypertension and heart disease. 'CAC scanning can be a valuable tool to help us tailor care to help more patients avoid a first heart attack or stroke.'

Source: Medical Brief 2020

Case Report

Persistent cardiac arrest caused by profound hypokalaemia after large-dose insulin injection in a young man with type 1 diabetes mellitus: successful rescue with extracorporeal membrane oxygenation and subsequent ventricular assist device

Ying-Hsiang Wang, Chien-Sung Tsai, Yi-Ting Tsai, Chih-Yuan Lin, Hsiang-Yu Yang, Jia-Lin Chen, Po-Shun Hsu

Abstract

A 28-year-old man who had a history of type 1 diabetes mellitus with poor medication compliance was referred to the emergency department of our institute with suspected diabetic ketoacidosis. The patient developed sudden cardiac arrest following continuous insulin administration. Laboratory data revealed severe hypokalaemia. Cardiopulmonary resuscitation was performed immediately for 63 minutes. Although his spontaneous circulation resumed, the haemodynamics remained unstable. Peripheral extracorporeal membrane oxygenation was therefore employed for mechanical circulatory support. Echocardiography under these conditions revealed generalised hypokinesia of the bilateral ventricles. The left ventricular ejection fraction was only 10–15%. The chest film revealed bilateral pulmonary congestion. The patient developed multiple organ dysfunction, including acute kidney injury, liver congestion and persistent pulmonary oedema, although the hypokalaemia resolved. A temporary bilateral ventricular assist device (Bi-VAD) was used for superior systemic perfusion and unloading of the bilateral ventricles after 16 hours of extracorporeal membrane oxygenation support. After the start of maintenance using the Bi-VAD, extracorporeal membrane oxygenation was discontinued and the inotropic agents were tapered down immediately. Subsequently, the haemodynamics stabilised. All the visceral organs were well perfused with Bi-VAD support. Subsequent echocardiography demonstrated recovery from the myocardial stunning, with the left ventricular ejection fraction returning to 50–60%. The Bi-VAD was gradually weaned and successfully removed 12 days after implantation. The patient had an uneventful recovery and was discharged without organ injury. Over one year of follow up in our out-patient clinic, adequate cardiac function and improved diabetes control were found.

Keywords: hypokalaemia, cardiac arrest, cardiogenic shock, ventricular assist device

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Profound hypokalaemia (< 2.5 mmol/l), a severe complication following subcutaneous administration of insulin, is reported in 5–10% of patients with type 1 diabetes mellitus,[1] and can easily be resolved through potassium infusion. Clinical manifestations of hypokalaemia vary in severity, depending on the acuteness and degree of the hypokalaemia. Although mild degrees of hypokalaemia are usually asymptomatic, severe degrees can lead to marked muscle weakness, ileus, and lethal arrhythmia, including cardiac arrest, ventricular tachycardia (VT) and ventricular fibrillation (Vf). The incidence of Vf has been found to be three- to five-fold higher in patients with low serum potassium compared with patients with high serum potassium concentrations.[2,3]

Although the mortality rate for hypokalaemia-related VT/Vf has not been reported, the mortality rate for cardiogenic shock following cardiopulmonary resuscitation (CPR) is 50–80%.[4] Herein, we report on a young man who developed refractory hypokalaemia-induced VT/Vf and cardiogenic shock following CPR. We performed emergent veno-arterial (VA)-mode extracorporeal membrane oxygenation (ECMO)

in the emergency room; thereafter, a bilateral ventricular assist device (Bi-VAD) was implanted to provide cardiogenic shock after CPR.

Case report

A 28-year-old man with a history of type 1 diabetes mellitus and inadequate compliance with insulin administration was referred to our emergency department due to general weakness with impaired consciousness lasting one day. Laboratory data revealed hyperketonaemia (blood ketone level 7.6 mmol/l), hyperglycaemia [glucose level 1 091 mg/dl (60.55 mmol/l)] and diabetic ketoacidosis (serum bicarbonate level 6.8 mmol/l). Additionally, leukocytosis (white blood cell count 20.90 × 10^3 cells/µl) and hyperkalaemia (K^+ 5.3 mmol/l) were noted.

Under suspicion of diabetic ketoacidosis, an insulin pump (insulin actrapid 50 units usage in 500 ml normal saline) was immediately administered at a rate of 60 ml/h. However, cardiac arrest occurred abruptly. An electrocardiogram revealed pulseless VT (Fig. 1) and CPR was immediately performed with sequential defibrillation, which was repeated five times. Laboratory data revealed severe hypokalaemia (K^+ 1.6 mmol/l). Large-dose inotropes including dopamine (17.3 mcg/kg/min) and norepinephrine (26.5 mcg/kg/min) were administered. Simultaneously, continuous KCl infusion was performed. However, the haemodynamic status remained inadequate with refractory VT and low cardiac output.

Peripheral VA-ECMO implantation was therefore performed through the right femoral vein and artery at a pump speed of 3 000 rpm and flow rate of 3.3 l/min. A Glasgow coma scale result of E2M2Vt was observed. Blood pressure was approximately 70/60 mmHg irrespective of the high doses of inotropes, and occasional VT was noted despite anti-arrhythmia medication. Moreover, echocardiography revealed generalised hypokinesia of the bilateral ventricles with left ventricular ejection fraction of 10–15%. However, despite the VA-ECMO support, the patient developed multiple organ dysfunction, including acute kidney injury, congestive liver and severe pulmonary oedema.

We therefore changed the VA-ECMO to a temporary continuous-flow Bi-VAD (Levitronix® CentriMag) for better systemic perfusion (Fig. 2). Using a sternotomy and under the guidance of transoesophageal echocardiography, the left ventricular assist device (L-VAD) inflow tube was inserted from the right superior pulmonary vein into the left ventricular apex, whereas the outflow tube was cannulated on the ascending aorta. The right VAD (R-VAD) inflow tube was inserted into the right atrium, and the outflow tube was inserted into the pulmonary artery. The operation time was approximately two hours. The initial L-VAD pump speed was 3 700 rpm and flow rate was 4.74 l/min. The R-VAD pump speed was 3 000 rpm and flow rate was 4.87 l/min (Table 1).

For severe hypoxaemia resulting from pulmonary oedema, an oxygenator was inserted into the L-VAD outflow to optimise systemic oxygenation. Mean arterial pressure (MAP) was maintained at 75–80 mmHg with low-dose norepinephrine (4.3 mcg/kg/min). Potassium level was maintained within the range 4.2–4.7 mmol/l and serum glucose level within 180–220 mg/dl (9.99–12.21 mmol/l).

At the time of maintaining support with Bi-VAD, the ventilator was set at 40% FiO_2 with positive end-expiratory pressure at 8 cmH_2O to prevent alveolar collapse. The support pressure was set at 12–15 cmH_2O to achieve an optimal tidal volume status (6–8 ml/kg), and the plateau pressure was controlled under 24 cmH_2O. During the time of support with VAD, the patient's MAP was closely monitored and both VAD and inotropic agents were gradually tapered down to prevent vasoconstriction in the vital visceral organs.

Systemic heparinisation was performed to maintain an active clotting time of 140–160 seconds to prevent thromboembolism. Additionally, a broad-spectrum antibiotic was prophylactically prescribed following the Bi-VAD implantation. On day three of Bi-VAD implantation, the pulmonary oedema was completely resolved; subsequently, the oxygenator was taken down from the L-VAD outflow. Although renal function did not recover immediately, it recovered completely after hospitalisation with temporary haemodialysis (post-VAD implantation days one to nine). Following 12-day support with the Bi-VAD, the

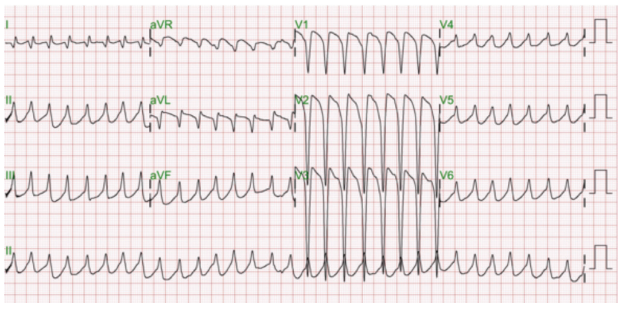

Fig. 1. Electrocardiogram demonstrating refractory ventricular tachycardia despite correction for profound hypokalaemia.

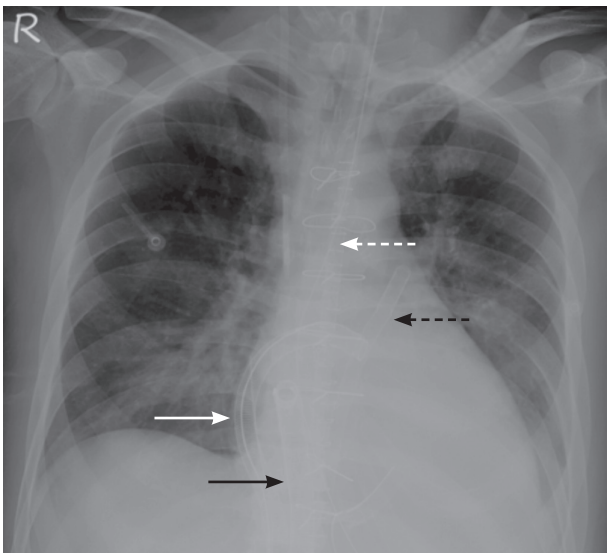

Fig. 2. The chest plain film demonstrates the L-VAD inflow tube from the right superior pulmonary vein (solid white arrow), outflow tube into the ascending aorta (dotted white arrow), R-VAD inflow tube from the right atrium (solid black arrow), and outflow tube into the pulmonary artery (dotted black arrow).

Table 1. Biochemistry data, inotrope dosage and echocardiography presentation during the VAD course

	Before VAD	*POD1*	*POD2*	*POD3*	*POD4*	*POD5*	*POD7*	*POD11*	*Day 3 after removal*
K^+ (mmol/l)	1.6	4.2	4.7	3.7	3.5	3.5	3.3	3.5	3.1
BNP (pg/ml)	176								
CK (U/l)	4862	> 10000	> 10000	> 10000			3292		
Tro-I (ng/ml)	8.28	7.11	5.765	3.813			1.516		
BUN (mg/dl)	60		26		28		31	61	78
Cr (mg/dl)	4.2		2.5		2.6		2.1	3.7	3.0
Urine output (ml/day)	170	995 (haemodyalysis)	1720 (haemodyalysis)	1620 (haemodyalysis)	3060 (haemodyalysis)	3420 (haemodyalysis)	4160 (haemodyalysis)	1480	2295
Norepinephrine (mcg/kg/min)	26.5	14.4	12.8	2.65	–	–	–	–	–
Dopamine (mcg/kg/min)	17.3	9.4	9.35	8.7	8.65	8.65	8.65	8.65	–
Epinephrine (mcg/kg/min)	16.7	13.3	13	2.7	–	–	–	–	–
L-VAD (rpm/flow)		3700/4.74	3700/5.07	3700/4.86	3600/4.5	3500/4.14	3400/3.81	2100/1.30	–
R-VAD (rpm/flow)		3000/4.87	3000/5.02	2700/4.4	2600/4.2	2400/3.75	2200/3.31	1200/0.91	–
MAP (mmHg)	65	65–75	65–75	80–90	78–86	88–100	97–105	72–82	95–100
Echocardiography									
LVEF (%)	10–15			30–35			51		

POD = post-operative day; L-VAD = left ventricular assist device; R-VAD = right ventricular assist device, BUN = blood urea nitrogen; CK = creatinine kinase.

myocardial stunning was adequately improved; eventually, the Bi-VAD was removed successfully.

Table 1 presents the biochemistry data, inotrope dosages and echocardiography presentation during the VAD course. The patient was weaned off the ventilator, and extubation was performed three days after VAD removal. The day after extubation, the patient was transferred to an ordinary ward and discharged one week later. Out-patient follow up revealed normal cardiac and renal function and cognition, and adequate control of diabetes.

Discussion

Hypokalaemia is a common electrolyte imbalance present in 20% of hospitalised patients,[5] and some of these patients require immediate pharmacological treatment. Insulin-induced hypokalaemia results in a decrease in serum potassium level due to intracellular potassium shifts and, potentially, the aldosterone-like effect of insulin on the renal tubule further increases urinary potassium losses.

The goal of the treatment for insulin-induced hypokalaemia ($K^+ < 2.5$ mmol/l) is to replenish potassium stores through slow intravenous infusion of KCl,[6] with insulin therapy delayed until serum potassium levels are corrected back to > 2.5 mmol/l.[7] The most severe complication of hypokalaemia is lethal arrhythmia, such as VT/Vf. Potassium replenishment and cardioversion defibrillation should be performed immediately.

In our case, the patient experienced in-hospital cardiac arrest (IHCA) resulting from hypokalaemia-induced VT/Vf. Extracorporeal CPR (ECPR) restored tissue and end-organ perfusion to allow stabilisation and recovery of function. ECPR can be defined as the implantation of VA-ECMO in a patient who has experienced a sudden and unexpected pulseless condition attributable to cessation of cardiac mechanical activity.[8] Many prospective and retrospective studies have demonstrated the superiority of ECPR over conventional CPR regarding the odds of survival and neurological outcome.[9–11] ECPR can be viewed as a late intervention in a moribund patient, possibly a candidate for an earlier circulatory support system in case of IHCA.

Compared with ECMO, which provides both cardiac and pulmonary support, a Bi-VAD usually provides cardiac support only. However, a Bi-VAD can be implemented long term with more cardiac support than ECMO, especially when the ECMO is set up peripherally. Moreover, patients on ECMO support usually require large doses of inotropes, which cause extreme vasoconstriction and lead to malperfusion of the visceral organs. In patients with refractory cardiogenic shock, a VAD has been reported to provide a better survival rate than VA-ECMO.[12]

In the current case, although VA-ECMO was instituted for mechanical circulatory support and the potassium level was corrected back to the normal range, the patient experienced cardiogenic shock with multiple organ dysfunction and exacerbations. Therefore, ECMO was substituted with Bi-VAD implantation for optimal systemic perfusion. More importantly, the Bi-VAD completely unloaded the bilateral ventricle, maximising the likelihood of recovery from myocardial stunning.[13] Based on our experience, the indications for VAD intervention can be defined for these critical patients with ECMO support (Table 2).

In our case, following Bi-VAD implantation, we were able to immediately withdraw the inotropes and all the visceral organs were preserved. Bedside echocardiography showed no distention of the bilateral ventricle. Initially, the pulse pressure was narrowed but returned three days later, which implied that the myocardial stunning was completely resolved.

The CentriMag VAD (Levitronix LLC) was chosen for several reasons. First, it has continuous flow, which is reported to have better outcomes than pulsatile flow, especially for

Table 2. Indications of VAD intervention after ECMO support

1	ECMO flow insufficiency; ECMO complications
2	Any organ dysfunction with ECMO maximal flow
3	Three or more inotropes or large dose
4	Narrow pulse pressure, ≥ 10 mmHg
5	Sustained VT resulted from LV distension
6	Echocardiography: No opening of aortic valve LV thrombus formation Blood stasis in LV, presented as smoke swirl sign

lower incidence of bleeding and thromboembolism.[14,15] Second, Levitronix CentriMag VAD was used as a temporary short-term VAD as a bridge towards recovery and transplantation, if not the destination. Unlike with a long-term VAD, it is easy to implant the device without extensively damaging the myocardium. More crucially, repairing the cannulation sites during explanation of the VAD is simple. Third, from the economic perspective, it is much cheaper than a permanent long-term VAD such as the HeartMate and HeartWare devices. Fourth, after CPR, most patients develop pulmonary oedema and poor oxygenation, and an oxygenator is always required for optimal oxygenation. The Levitronix CentriMag VAD, categorised as an extracorporeal VAD, can be easily integrated with an oxygenator, which is not possible with an intracorporeal VAD.

Conclusion

The Levitronix® CentriMag VAD was able to temporarily provide satisfactory mechanical circulatory support in acute decompensated heart failure. It can provide better circulatory support than ECMO. Additionally, it is easy to set up and repair without causing considerable damage to the myocardium if a bridge to recovery is expected. In this case, the Levitronix® CentriMag VAD was successfully implemented to save the life of a young patient who had experienced hypokalaemia-related cardiac arrest resulting from iatrogenic insulin infusion.

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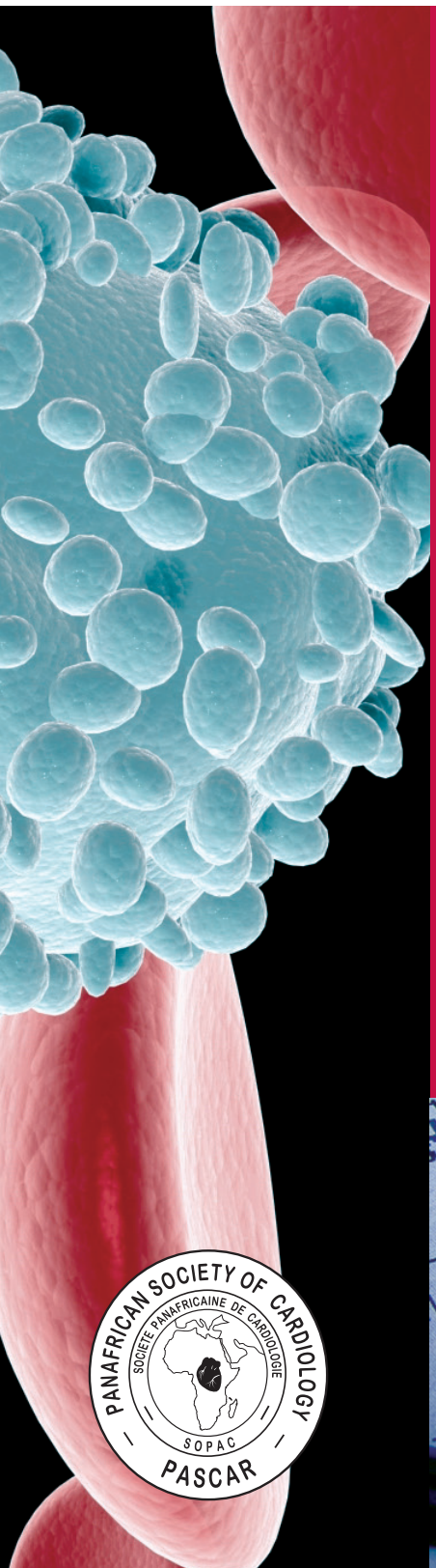

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