

ORIGINAL ARTICLE

Blood pressure variability is significantly associated with ECG left ventricular mass in normotensive Africans: The SABPA Study

Aletta E Schutte, Rudolph Schutte, Hugo W Huisman, Johannes M van Rooyen, Carla MT Fourie, Nicolaas T Malan and Leoné Malan

The prognostic significance of blood pressure (BP) variability has lately enjoyed considerable attention. The need for early markers of cardiovascular dysfunction is imperative in black South Africans who have a significant risk for cardiovascular disease. We therefore compared 24-h BP variability with various traditional and advanced BP measurements, regarding their association with sub-clinical organ damage in black and white South Africans. The study included 409 African and Caucasian teachers aged 25–60 yrs. We measured office BP, 1-min continuous (finger) BP, ambulatory BP, BP reactivity and determined weighted 24-h BP variability. Albumin-to-creatinine ratio, Cornell product and carotid cross-sectional wall area (CSWA) were measures of organ damage. Africans had higher 24-h BP, BP variability, BP reactivity and sub-clinical organ damage ($P < 0.001$). Correlations of BP variability with organ damage were overall weak when compared with other BP measurements. In normotensive groups, we found an independent association of 24-h systolic BP (SBP) variability with Cornell product only in Africans ($r = 0.37$; $P = 0.01$), confirmed in multiple regression models, with 24-h SBP included in the model. Only in hypertensive Caucasians, a significant correlation between CSWA and 24-h SBP variability was evident ($r = 0.30$; $P = 0.01$), although CSWA indicated stronger correlations with office or 24-h SBP than 24-h SBP variability. To conclude, 24-h SBP variability could potentially be an effective measure for the early detection of normotensive Africans at increased risk for the development of cardiovascular complications. Its usefulness based on associations with target organ damage in hypertensive groups seems to be less than traditional office or 24-h BP measurements.

Hypertension Research (2011) 34, 1127–1134; doi:10.1038/hr.2011.104; published online 28 July 2011

Keywords: albumin-to-creatinine ratio; ethnicity; intima-media thickness; left ventricular hypertrophy

INTRODUCTION

The prognostic significance of blood pressure (BP) variability has lately enjoyed considerable attention in the literature.^{1–10} Where some papers emphasize the importance of BP variability in prediction of risk of vascular events,^{1,2,6,9} others question its prediction of cardiovascular outcome.^{4,5,10}

Despite this upsurge of recent papers, consistent evidence over the past three decades lends support that both target organ damage and the rate of cardiovascular events of hypertensive patients are significantly and independently related to the degree of BP variability.^{11–15}

A limitation of many of these papers is that either BP variability alone was investigated, or various measures of BP variability (such as s.d. of 24-h BP, average real variability index¹⁶ and weighted 24-h BP s.d.¹⁷) were being compared, regarding the strength of their association with target organ damage.

The question therefore arises how BP variability would benchmark against a comprehensive range of both traditional and advanced

measurements of BP and BP reactivity, regarding their association with target organ damage.

Apart from this question, Hansen *et al.*⁴ recently emphasized that current knowledge regarding the present results of BP variability might not yet be generally applicable, in particular, to Africans of black ancestry, due to limited available data. Our group and others have clearly documented that urban-dwelling black South Africans suffer from alarming increases in hypertension, resulting in soaring rates of hypertensive heart disease and stroke.^{18–20} Importantly, the need for effective and affordable markers of early cardiovascular deterioration as part of a prevention scheme is imperative in this population group, as poverty hinders successful treatment programs.

The aims of this study are therefore to first compare the 24-h BP variability (weighted) with the traditional and advanced BP measurements regarding their association with sub-clinical organ damage in African and Caucasian teachers; and second, to evaluate these relationships in those with normal and elevated BPs.

METHODS

Study population

This study forms part of the SABPA (Sympathetic Activity and Ambulatory Blood Pressure in Africans) Study conducted between February 2008 and May 2009. We recruited 409 urbanized African and Caucasian teachers working in the Dr Kenneth Kuanda Education District in the North West Province, South Africa. The reason for this selection was to obtain a homogenous sample from a similar socio-economic class. We invited all eligible participants between the ages of 25 and 65 years to participate. Exclusion criteria were an elevated ear temperature, psychotropic substance dependence or abuse, blood donors and individuals vaccinated in the past 3 months. For the purposes of the present study, a sub-sample of 166 African and 199 Caucasian participants were selected based on the following exclusion criteria: HIV infected ($N=19$) or hyperglycaemic (fasting glucose >7 mmol l^{-1}) ($N=25$).

Participants were fully informed about the objectives and procedures of the study before their recruitment. All participants signed an informed consent form. The study complied with all applicable requirements of the US and international regulations, in particular the Helsinki declaration of 1975 (as revised in 2008) for investigation of human participants. The Ethics Review Board of the North-West University (Potchefstroom Campus) approved the study.

Organisational procedures

We conducted ambulatory BP measurements (ABPM) during the working week. Each morning at approximately 0800 h, postgraduate students attached an ABPM device on the participants' non-dominant arm at their workplace. In order to assess physical activity, participants wore Actical accelerometers (Mini-Mitter Co., Inc, Montréal, Québec, Canada) around their hip during a normal working day. Participants were transported at 1630 h to the Metabolic Unit Research Facility of the North-West University. This facility consists of 10 bedrooms, two bathrooms, a living room and kitchen. Participants received a standardized dinner and had their last beverages (tea/coffee) and two biscuits at 2030 h. Thereafter, they relaxed by reading, watching television or social interaction, and refrained from consuming alcohol, caffeine, smoking and doing exercise. They were encouraged to go to bed at around 2200 h. At 0545 hours subjects were woken, and after the last ABPM reading was made at 0600 hours, the apparatus was removed and the subsequent measurements were taken. After the collection of a urine sample and anthropometric data, sphygmomanometer and Finometer BP were taken, and nurses obtained a fasting venous blood sample. Thereafter, the continuous BP measurements were performed including mental stress tests.

Blood pressure measurements

After a 5-min rest in the semi-Fowler's position, duplicate office BP measurements were taken by a registered nurse or medical doctor. The appropriate cuff was placed on the left upper arm, making use of a single-headed stethoscope and mercury sphygmomanometer according to the Riva/Rocci method (Riester CE 0124, No.1010-108 Diplomat-presameter, Jungingen, Germany). Afterwards, the same observer monitored BP continuously by making use of the Finometer device (FMS, Finapres Medical Systems, Amsterdam, Netherlands).^{21,22} This entailed a 5-min recording of each participant's BP under resting, yet awake, conditions. After the first 2 min, the finger pressure was calibrated with the upper arm (brachial) pressure (that is, return-to-flow systolic calibration). This optimized the accuracy of the readings taken. Spontaneous baroreflex sensitivity (BRS) was determined by the validated cross-correlation baroreflex sensitivity (xBRS) method,²³ derived from the continuous BP measurement. It has been suggested that this method be used in clinical and experimental settings because of its lower within-patient variance than other BRS methods.²³

Two behavioral tasks, designed to induce mental stress, were then administered in a random order. The tasks included the Stroop mental stress task and the cold pressor test (immersion of the foot in ice water at 4 °C). Both tests have been used extensively in psychophysiological research.^{24,25} Each task lasted for 1 min, followed by a 15-min recovery. Beat-to-beat BP was continuously assessed throughout psychophysiological testing using the Finometer device. We obtained the average of the last 2 min of the resting recordings and the average of the last 15 s of the stressor recordings.

The ABPM- and 2-lead electrocardiogram apparatus (Meditech CE120 Cardiotsens, Budapest, Hungary) was programmed to measure BP at 30-min intervals during the day (0800–2200 h) and every hour during night time (2200–0600 h). According to a preset program, sequential recording of two-channel electrocardiography (ECG) strips were obtained for 20 s at 5-min intervals. Participants were asked to continue with normal daily activities and record any abnormalities such as headache, nausea and stress on their ambulatory diary cards.

We downloaded the ambulatory BP and ECG data into a database, using the CardioVisions 1.15 Personal Edition (Meditech, Budapest, Hungary). If less than 75% of the ABPM for a particular subject were successful, the ABPM was repeated the next day. Participants were regarded as hypertensive if their 24-h ABPM was ≥ 130 mm Hg and/or 80 mm Hg.²⁶

As a measure of short-term reading-to-reading BP variability, we used the average of the daytime and night time SDs weighted for the duration of the daytime and night time interval (wSD) as proposed by Bilo *et al.*¹⁷ and recommended by Hansen *et al.*⁴

Measurements of sub-clinical target organ damage

In urine, creatinine was determined with a calorimetric method and albumin with the measurement of immunoprecipitation enhanced by polyethylene glycol at 450 nm, with sequential multiple analyzer computer (Konelab 20i TM, Thermo Scientific, Vantaa, Finland) with a coefficient of variation of 1.7–3.3%. Albumin-to-creatinine ratio measured in an 8-h overnight urine sample is highly correlated with 24-hour urine albumin excretion.^{27,28} We calculated the estimated creatinine clearance by using the Cockcroft–Gault formula.²⁹

A standard 12-lead ECG was recorded during resting conditions (PC 1200, v5.030, Norav Medical, Yokneam, Israel). ECG left ventricular mass was determined using the Cornell product.^{30–32}

Pulse wave velocity, a measure of arterial stiffness, was determined using the Complior SP device (Artech-Medical, Pantin, France) over the carotid dorsalis pedis segment.

The carotid intima-media thickness (CIMT) was obtained using a SonoSite Micromax ultrasound system (SonoSite, Bothell, WA, USA) and a 6–13 MHz linear array transducer. Images from at least two optimal angles of the left and right common carotid artery were obtained. Following previous prescribed protocols,³³ these segments were imaged and measured. A single reader conducted measurements using a semi-automated program, namely the Artery Measurement Systems (AMS) II v1.139 (supplied by Professor Tomas Gustavsson, Gothenburg, Sweden). The images were digitized and imported into the AMS automated software for dedicated analyses of CIMT.^{34,35} A maximal 10 mm segment with good image quality was chosen for analysis. The program automatically identifies the borders of the intima-media of the near and far wall, and the inner diameter of the vessel and calculates the CIMT and diameter from around 100 discrete measurements through the 10 mm segment. This automated analysis was capable of being manually corrected if not found appropriate on visual inspection. For the purpose of this study, far wall measurements were used. Intra-observer variability for the far wall was 0.04 mm between two measurements made 4 weeks apart on 10 subjects. We also calculated the cross-sectional wall area (CSWA) to confirm structural and not functional changes in luminal diameter as follows: $CSWA = \pi(d/2 + CIMT)^2 - \pi(d/2)^2$, where d denotes luminal diameter.

Anthropometric measurements

Height (stature) and weight of participants were measured while being in their underwear. Measurements were taken in triplicate using standard methods with calibrated instruments (Precision Health Scale, A&D Company, Japan; Invicta Stadiometer, IP 1465, Invicta Plastics Ltd, Leicester, UK).³⁶

Biochemical measurements

A registered nurse obtained a blood sample with a sterile winged infusion set from the antebrachial vein branches. Fasting sodium fluoride (glucose) and serum samples for total and high-density lipoprotein cholesterol, γ -glutamyl transferase and high-sensitivity C-reactive protein were analyzed using two

sequential multiple analyzers (Konelab 20i; Thermo Scientific, Vantaa, Finland; Unicel DXC 800, Beckman and Coulter, Munich, Germany). The intra- and inter-coefficients of variation for all assays were below 10%. Serum cotinine levels were determined with a homogeneous immunoassay (Automated Modular, Roche, Basel, Switzerland).

All biochemical measurements were performed by independent laboratories, blinded to the subjects' cardiovascular profile.

Statistical analyses

We used Statistica version 9 for statistical analyses (StatSoft, Tulsa, OK, USA). Variables with a non-Gaussian distribution were logarithmically transformed and the central tendency and spread represented by the geometric mean and the 5th and 95th percentile intervals. We compared the means and proportions by an independent *t*-test and the χ^2 -test, respectively. We used single and partial regression analyses to determine the associations between measures of sub-clinical end-organ damage and various BP measurements. Cornell product and 24-h systolic BP (SBP) were plotted by tertiles of 24-h SBP variability (wSD) for normotensive groups of each ethnicity. We investigated independent associations between Cornell product or CSWA and 24-h SBP variability, as well as 24-h SBP using multiple linear regressions, and identified covariates by a forward stepwise procedure. Covariates considered for entry in the model were age, gender, body mass index, physical activity, serum cotinine, serum γ -glutamyl transferase and anti-hypertensive medication.

RESULTS

Characteristics of participants

As presented in Table 1, the ages, gender distribution and waist circumferences of the groups were similar, but overall the Africans showed an unfavorable health profile, such as a significantly higher prevalence of hypertension, albumin-to-creatinine ratio, Cornell product and CIMT. The detailed measurements of BP, BP variability and reactivity (Table 2) also reflect this, with significantly elevated values in the African group. When hypertensive African and Caucasian subjects were compared, the SBP (13.3 ± 3.72 vs. 12.5 ± 3.47 mm Hg; $P=0.17$) and diastolic BP variability (10.3 ± 2.16 vs. 9.70 ± 2.90 mm Hg; $P=0.12$), as well as BRS (9.28 ± 6.54 vs. 9.07 ± 5.89 ms per mm Hg; $P=0.82$) were similar. This was also true for the normotensive groups regarding SBP variability (10.7 ± 2.83 vs. 10.8 ± 2.62 mm Hg; $P=0.92$) and BRS (11.9 ± 8.22 vs. 11.7 ± 6.90 ms per mm Hg; $P=0.90$), whereas diastolic BP variability was higher in the normotensive Africans (9.39 ± 3.20 vs. 8.50 ± 2.15 mm Hg; $P=0.02$).

Unadjusted analyses

The single linear regression analyses performed separately in African and Caucasian participants, as shown in Table 3, indicate associations between measures of sub-clinical organ damage and the

Table 1 Characteristics of African and Caucasian participants

| | African | Caucasian | P-values |
|--|-------------------|-------------------|----------|
| <i>N</i> | 166 | 199 | |
| Age, years | 43.9 \pm 8.24 | 44.7 \pm 10.8 | 0.48 |
| Gender, men/women | 76/90 | 92/107 | 0.93 |
| <i>Anthropometric measurements</i> | | | |
| Height, m | 1.64 \pm 0.09 | 1.73 \pm 0.09 | <0.001 |
| Body mass index, kg m ⁻² | 30.3 \pm 7.26 | 27.4 \pm 5.81 | <0.001 |
| Waist circumference, cm | 93.1 \pm 15.6 | 92.1 \pm 15.9 | 0.55 |
| <i>Biochemical measurements</i> | | | |
| Total cholesterol, mmol l ⁻¹ | 4.58 \pm 1.11 | 5.57 \pm 1.29 | <0.001 |
| HDL-cholesterol, mmol l ⁻¹ | 1.16 \pm 0.36 | 1.22 \pm 0.41 | 0.13 |
| Serum glucose, mmol l ⁻¹ | 5.08 (3.92; 6.48) | 5.51 (4.70; 6.60) | <0.001 |
| C-reactive protein, mg l ⁻¹ | 4.61 (0.65; 33.8) | 2.03 (0.99; 9.00) | <0.001 |
| Hypertensive, <i>n</i> (%) | 100 (60.2) | 74 (37.2) | <0.001 |
| Baroreflex sensitivity, ms per mm Hg | 10.3 \pm 7.35 | 10.8 \pm 6.66 | 0.56 |
| <i>Measures of sub-clinical organ damage</i> | | | |
| Albumin-to-creatinine ratio, mg mmol ⁻¹ | 1.02 (0.35; 3.81) | 0.34 (0.09; 1.88) | <0.001 |
| Estimated creatinine clearance, ml min ⁻¹ | 120.8 \pm 36.1 | — | — |
| Cornell product, mV.ms | 66.3 \pm 38.9 | 49.6 \pm 28.3 | <0.001 |
| Pulse wave velocity, m s ⁻¹ | 8.47 \pm 1.58 | 7.96 \pm 1.41 | 0.001 |
| Carotid intima-media thickness, mm | 0.68 \pm 0.14 | 0.64 \pm 0.14 | 0.009 |
| Cross-sectional wall area, mm ² | 13.9 \pm 3.81 | 13.1 \pm 3.87 | 0.046 |
| <i>Lifestyle</i> | | | |
| Physical activity, Kcal d ⁻¹ | 2580 (1702; 4112) | 2903 (1915; 4407) | <0.001 |
| Cotinine, ng ml ⁻¹ | 0.12 (0.01; 149) | 0.04 (0.01; 237) | 0.002 |
| γ -glutamyl transferase, U/L | 45.3 (19.9; 177) | 18.8 (7.00; 76.0) | <0.001 |
| <i>Intake of medications</i> | | | |
| Statins, <i>n</i> (%) | 2 (0.55) | 6 (3.02) | 0.23 |
| Anti-hypertensive medication, <i>n</i> (%) | 33 (19.8) | 16 (8.04) | <0.001 |

Abbreviation: HDL, high-density lipoprotein
 Values are arithmetic mean \pm s.d., geometric mean (5th to 95th percentile interval), or number of participants (%).

Table 2 Measurements of blood pressure, blood pressure variability and reactivity

| | African | Caucasian | P-values |
|---|--------------|-------------|----------|
| <i>N</i> | 166 | 199 | |
| <i>Office</i> | | | |
| Systolic BP, mm Hg | 133 ± 19.9 | 126 ± 14.4 | <0.001 |
| Diastolic BP, mm Hg | 87.7 ± 12.9 | 81.9 ± 9.50 | <0.001 |
| <i>One-minute continuous</i> | | | |
| Systolic BP, mm Hg | 140 ± 18.3 | 131 ± 13.9 | <0.001 |
| Diastolic BP, mm Hg | 80.1 ± 10.4 | 76.5 ± 8.30 | <0.001 |
| <i>Ambulatory BP measurements</i> | | | |
| 24-h systolic, mm Hg | 132 ± 15.9 | 124 ± 11.8 | <0.001 |
| 24-h diastolic, mm Hg | 82.3 ± 10.6 | 76.2 ± 7.86 | <0.001 |
| Daytime systolic, mm Hg | 137.2 ± 15.9 | 129 ± 11.7 | <0.001 |
| Daytime diastolic, mm Hg | 87.7 ± 11.3 | 81.2 ± 8.52 | <0.001 |
| Nighttime systolic, mm Hg | 122 ± 16.8 | 113 ± 13.6 | <0.001 |
| Nighttime diastolic, mm Hg | 72.8 ± 11.6 | 66.2 ± 8.64 | <0.001 |
| <i>Blood pressure variability (wSD)</i> | | | |
| 24-h systolic variability, mm Hg | 12.3 ± 3.62 | 11.4 ± 3.07 | 0.02 |
| 24-h diastolic variability, mm Hg | 9.94 ± 2.66 | 8.94 ± 2.52 | <0.001 |
| <i>Blood pressure reactivity</i> | | | |
| <i>Cold pressor test</i> | | | |
| Systolic BP during test, mm Hg | 155 ± 22.1 | 148 ± 16.7 | <0.001 |
| Diastolic BP during test, mm Hg | 90.9 ± 12.4 | 83.4 ± 10.2 | <0.001 |
| Systolic BP reactivity, % | 10.8 ± 11.9 | 13.2 ± 9.07 | 0.04 |
| Diastolic BP reactivity, % | 12.8 ± 14.2 | 9.96 ± 10.5 | 0.03 |
| <i>Stroop test</i> | | | |
| Systolic BP during test, mm Hg | 158 ± 22.1 | 150 ± 16.9 | <0.001 |
| Diastolic BP during test, mm Hg | 92.0 ± 12.1 | 85.1 ± 8.99 | <0.001 |
| Systolic BP reactivity, % | 12.8 ± 9.97 | 15.2 ± 10.7 | 0.03 |
| Diastolic BP reactivity, % | 14.2 ± 11.2 | 11.7 ± 10.0 | 0.03 |

Abbreviations: BP, blood pressure; wSD, 24-hour weighted s.d.
Values are arithmetic mean ± s.d.

comprehensive range of BP, BP variability and reactivity measurements. In general, the most prominent correlations observed with sub-clinical organ damage were office BP, ambulatory BP and BP during reactivity tests. Correlations with BP variability were weak overall (although significant in some instances), in comparison to the other measurements.

Both African and Caucasian groups showed significant negative correlations of SBP variability ($r=-0.23$; $P=0.004$ and $r=-0.26$; $P=0.001$) and diastolic BP variability ($r=-0.21$; $P=0.008$ and $r=-0.16$; $P=0.02$) with BRS.

Adjusted analyses

Partial regression analyses were performed separately in normotensive and hypertensive African and Caucasian groups (Figures 1 and 2), with adjustments for age, gender and body mass index. For normotensives, the only significant correlation with BP variability was indicated by the Africans, who showed a strong correlation of Cornell product with 24-h SBP variability ($r=0.37$; $P=0.01$; $N=49$). For hypertensives (Figure 2), the Caucasians showed the only significant correlation of CSWA with 24-h SBP variability ($r=0.30$; $P=0.01$; $N=74$). After additional adjustments for physical activity, cotinine and γ -glutamyl transferase, the correlation weakened slightly ($r=0.29$;

$P=0.02$) and was still non-significant in the African hypertensive group ($r=0.09$; $P=0.39$; $N=97$).

When Cornell product was plotted against tertiles of 24-h SBP variability (Figure 3), again only the normotensive Africans showed a significant increase in Cornell product after adjustment for age, gender, body mass index, physical activity, cotinine and γ -glutamyl transferase. Africans within the highest tertile of SBP variability also had higher Cornell product than Caucasians from the same tertile ($P=0.02$), which was not evident for the lower tertiles. It is noteworthy that the 24-h SBP of the ethnic groups of the highest tertile did not differ significantly ($P=0.68$; Figure 3b). With similar adjustments applied to BRS against tertiles of 24-h SBP variability in the same normotensive groups (not shown), BRS of Africans did not show a significant trend ($P=0.12$), whereas Caucasians indicated a significant decrease in BRS with increasing 24-h SBP variability tertiles ($P=0.035$).

The independent associations between Cornell product and SBP variability in normotensive Africans and Caucasians are shown in multivariate analyses (Table 4a). The relationship between Cornell product and SBP variability was confirmed in normotensive Africans ($\beta=0.39$; $P=0.006$), when also including 24-h SBP into the model. When similar analyses were repeated in either hypertensives or the whole group (normotensives and hypertensives) for each ethnicity, SBP variability did not enter significantly into any of the models. In both the whole groups and hypertensive groups, 24-h SBP was included significantly into the models. When investigating the independent associations between CSWA and SBP variability in the hypertensive groups (Table 4b), SBP variability was not included into the model in neither of the ethnic groups, but 24-h SBP was included in both instances.

DISCUSSION

We attempted to benchmark weighted 24-h BP variability against a range of traditional and advanced measurements of BP in African and Caucasian teachers, regarding its association with target organ damage. At first glance, 24-h BP variability indicated much weaker relationships with sub-clinical organ damage than traditional office or ambulatory BP. However, division of our study population into normotensive and hypertensive groups yielded novel results.

A prominent result from our study was a significant independent relationship between carotid CSWA and 24-h SBP variability only in hypertensive Caucasians. This result confirms previous findings in European,³⁷ American³⁸ and Japanese hypertensive populations.³⁹ However, in our multiple regression analyses that included 24-h SBP in the model, 24-h SBP variability did not enter the final model in neither the Caucasian or African groups, whereas 24-h SBP did. Although this significant association between CSWA and 24-h SBP variability was shown in our study, it is important to mention that other measures of BP, such as office SBP, 24-h SBP, daytime and night time SBP, as well as SBP during the Stroop reactivity test, yielded stronger relationships with carotid artery alteration than 24-h SBP variability.

Another key finding of our study was that Cornell product was significantly related to 24-h SBP variability of normotensive Africans, independent of 24-h SBP. This relationship was absent in the Caucasian normotensive group, despite having similar 24-h SBP variability, 24-h SBP and baroreflex sensitivities.

African populations are known to have increased left ventricular mass and a two- to three-fold higher prevalence of left ventricular hypertrophy in the general population,⁴⁰ with increased left ventricular mass already originating from late childhood.⁴¹ Furthermore,

Table 3 Associations with measures of sub-clinical organ damage in single regression analyses

| | African | | | | | | Caucasian | | | | |
|--------------------------------|-------------------|-------|-------------------|-------------------|-------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|
| | ACR | eCcr | Cornell P | CIMT | CSWA | PWV | ACR | Cornell P | CIMT | CSWA | PWV |
| Age | 0.12 | 0.08 | 0.03 | 0.47 [‡] | 0.39 [‡] | 0.35 [‡] | 0.29 [‡] | 0.05 | 0.53 [‡] | 0.48 [‡] | 0.43 [‡] |
| Body mass index | 0.01 | -0.06 | 0.07 | 0.09 | 0.04 | 0.12 | -0.02 | 0.07 | 0.24 [†] | 0.30 [‡] | 0.15* |
| Physical activity | -0.12 | -0.05 | 0.13 | 0.09 | 0.12 | 0.14 | -0.22 [†] | 0.28 [‡] | 0.19 [‡] | 0.30 [‡] | 0.26 [‡] |
| Cotinine | -0.06 | 0.12 | 0.04 | 0.19* | 0.17* | 0.11 | -0.07 | 0.01 | 0.07 | 0.11 | -0.05 |
| γ-glutamyl transferase | -0.03 | -0.03 | 0.13 | 0.13 | 0.23 [†] | 0.20* | -0.16* | 0.26 [†] | 0.30 [‡] | 0.38 [‡] | 0.33 [‡] |
| <i>Blood pressure measures</i> | | | | | | | | | | | |
| <i>Office</i> | | | | | | | | | | | |
| Systolic BP | 0.23 [†] | -0.05 | 0.40 [‡] | 0.22 [†] | 0.34 [‡] | 0.42 [‡] | 0.05 | 0.18* | 0.49 [‡] | 0.55 [‡] | 0.46 [‡] |
| Diastolic BP | 0.14 | -0.03 | 0.35 [‡] | 0.11 | 0.22 [†] | 0.40 [‡] | -0.06 | 0.22 | 0.36 [‡] | 0.43 [‡] | 0.43 [‡] |
| <i>One-minute continuous</i> | | | | | | | | | | | |
| Systolic BP | 0.26 [†] | -0.07 | 0.45 [‡] | 0.27 [‡] | 0.38 [‡] | 0.46 [‡] | 0.06 | 0.10 | 0.40 [‡] | 0.44 [‡] | 0.43 [‡] |
| Diastolic BP | 0.17* | -0.06 | 0.42 [‡] | 0.05 | 0.21 [†] | 0.35 [‡] | -0.20 [†] | 0.21 [†] | 0.34 [‡] | 0.41 [‡] | 0.38 [‡] |
| <i>Ambulatory BP</i> | | | | | | | | | | | |
| 24-h systolic | 0.14 | -0.06 | 0.43 [‡] | 0.29 [‡] | 0.39 [‡] | 0.43 [‡] | 0.02 | 0.24 [†] | 0.41 [‡] | 0.50 [‡] | 0.37 [‡] |
| 24-h diastolic | 0.15 | -0.01 | 0.37 [‡] | 0.18* | 0.33 [‡] | 0.47 [‡] | -0.05 | 0.31 [‡] | 0.40 [‡] | 0.47 [‡] | 0.43 [‡] |
| Daytime systolic | 0.11 | -0.04 | 0.38 [‡] | 0.32 [‡] | 0.40 [‡] | 0.42 [‡] | 0.01 | 0.20 [†] | 0.41 [‡] | 0.49 [‡] | 0.39 [‡] |
| Daytime diastolic | 0.06 | 0.02 | 0.27 [†] | 0.22 [†] | 0.34 [‡] | 0.46 [‡] | -0.07 | 0.28 [‡] | 0.37 [‡] | 0.44 [‡] | 0.46 [‡] |
| Night time systolic | 0.20 [†] | -0.09 | 0.44 [‡] | 0.25 [†] | 0.35 [‡] | 0.42 [‡] | 0.04 | 0.24 [†] | 0.35 [‡] | 0.44 [‡] | 0.28 [‡] |
| Night time diastolic | 0.22 [†] | -0.04 | 0.38 [‡] | 0.17* | 0.30 [‡] | 0.46 [‡] | 0.01 | 0.27 [‡] | 0.37 [‡] | 0.43 [‡] | 0.33 [‡] |
| <i>BP variability (wSD)</i> | | | | | | | | | | | |
| 24-h systolic variability | 0.06 | -0.15 | 0.24 [†] | 0.21 [†] | 0.18* | 0.21 [†] | 0.07 | 0.08 | 0.25 [‡] | 0.27 [‡] | 0.19 [†] |
| 24-h diastolic variability | -0.03 | -0.10 | 0.13 | 0.13 | 0.11 | 0.08 | 0.04 | 0.11 | 0.12 | 0.14* | 0.10 |
| <i>BP reactivity</i> | | | | | | | | | | | |
| <i>Cold pressor test</i> | | | | | | | | | | | |
| Systolic BP during test | 0.32 [‡] | -0.03 | 0.42 [‡] | 0.23 [†] | 0.27 [†] | 0.26 [†] | 0.06 | 0.01 | 0.36 [‡] | 0.37 [‡] | 0.39 [‡] |
| Diastolic BP during test | 0.21 [†] | 0.01 | 0.40 [‡] | 0.10 | 0.18* | 0.19* | -0.18 | 0.08 | 0.18 [†] | 0.26 [‡] | 0.35 [‡] |
| Systolic BP reactivity | 0.12 | -0.01 | 0.01 | -0.05 | -0.11 | -0.19* | 0.01 | 0.16 | -0.04 | -0.07 | -0.03 |
| Diastolic BP reactivity | 0.03 | 0.05 | -0.03 | 0.06 | -0.01 | -0.17* | -0.02 | 0.12 | -0.13 | -0.11 | 0.02 |
| <i>Stroop test</i> | | | | | | | | | | | |
| Systolic BP during test | 0.20* | 0.03 | 0.42 [‡] | 0.25 [†] | 0.37 [‡] | 0.43 [‡] | 0.01 | 0.14 | 0.43 [‡] | 0.46 [‡] | 0.44 [‡] |
| Diastolic BP during test | 0.14 | 0.07 | 0.39 [‡] | 0.03 | 0.18* | 0.34 [‡] | -0.17 [†] | 0.21 [†] | 0.34 [‡] | 0.42 [‡] | 0.37 [‡] |
| Systolic BP reactivity | -0.09 | 0.13 | -0.04 | -0.03 | -0.01 | -0.03 | -0.05 | 0.04 | 0.04 | 0.04 | 0.03 |
| Diastolic BP reactivity | -0.05 | 0.16* | -0.08 | -0.03 | -0.02 | -0.01 | 0.04 | -0.01 | -0.04 | -0.02 | -0.05 |

Abbreviations: ACR, albumin-to-creatinine ratio; BP, blood pressure; CIMT, carotid intima-media thickness; Cornell P, Cornell product; CSWA, cross-sectional wall area; eCcr, estimated creatinine clearance; PWV, pulse wave velocity; wSD, 24-hour weighted s.d.
 * $P < 0.05$; [†] $P < 0.01$; [‡] $P < 0.001$.

Havranek *et al.*⁴² indicated that ECG left ventricular hypertrophy contributes more to the risk of cardiovascular mortality in African Americans than in Caucasians. They also suggested that left ventricular hypertrophy should be a target of therapy to reduce ethnic differences in cardiovascular mortality. In poverty-stricken countries, there are major challenges in diagnosing and especially treating those with increased cardiovascular risk, such as left ventricular hypertrophy. A more ideal solution would be to identify those at increased risk before the development of organ damage. On the basis of our results, SBP variability in normotensive African individuals may be a better predictor of increased left ventricular mass than any office, 1-minute continuous, 24-h, daytime or night time BP measurement.

Conversely, in hypertensive Africans, left ventricular mass was significantly associated with office, 1-minute, 24-h, daytime and night time BP, as well as BP reactivity measurements, but there was

a complete absence regarding the relationship with 24-h SBP variability. Schillaci *et al.*³⁸ and Roman *et al.*⁴³ also observed this lack of association in Caucasians with essential hypertension. Contradictory results have been provided over the years regarding the predictive value of BP variability,^{4,8,10,14} which might be due to differences in methods, too few events or different indexes of BP variability. Interestingly, most of these studies focused on the general population or hypertensive groups, excluding the possibility that BP variability might be an effective measurement for the early identification of those at risk when focusing on normotensive groups exclusively.

It should also be kept in mind that in our study, the ECG left ventricular mass-SBP variability relationship was also absent in normotensive Caucasians, indicating that the proposed strategy to use BP variability to identify normotensive individuals at increased risk may not be viable in all populations. The question therefore arises

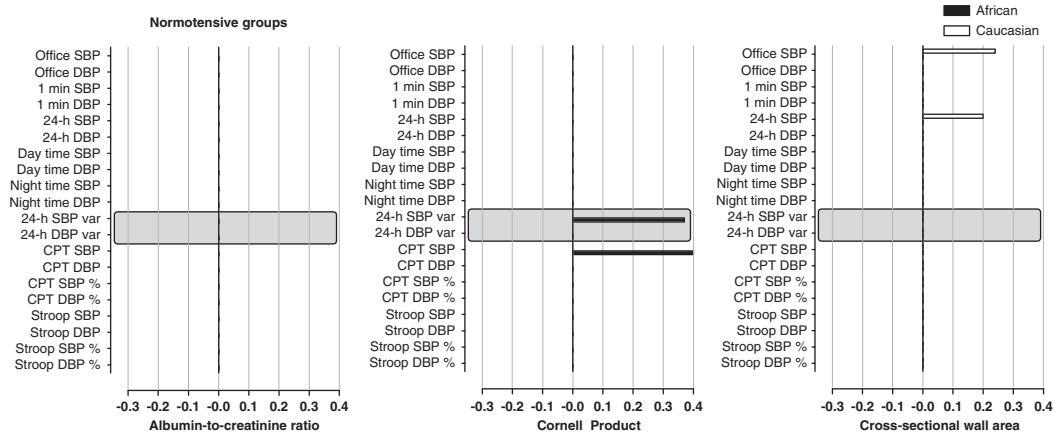


Figure 1 Comparing 24-h blood pressure (BP) variability to traditional and advanced measurements of BP regarding their association with markers of sub-clinical organ damage in normotensive groups. Only correlations with $P < 0.05$ are shown. Correlations are adjusted for age, gender and body mass index. CPT, cold pressor test; DBP, diastolic BP; SBP, systolic BP; %, reactivity.

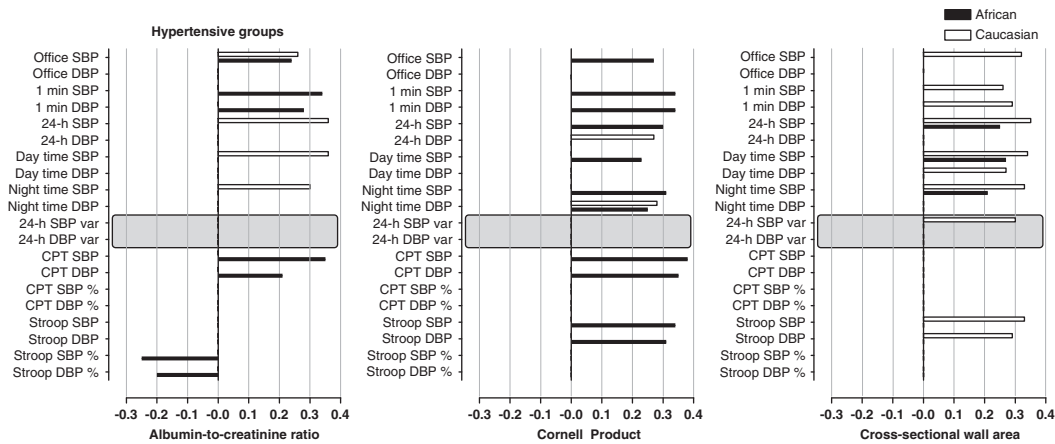


Figure 2 Comparing 24-h blood pressure (BP) variability to traditional and advanced measurements of BP regarding their association with markers of sub-clinical organ damage in hypertensive groups. Only correlations with $P < 0.05$ are shown. Correlations are adjusted for age, gender and body mass index. CPT, cold pressor test; DBP, diastolic BP; SBP, systolic BP; %, reactivity.

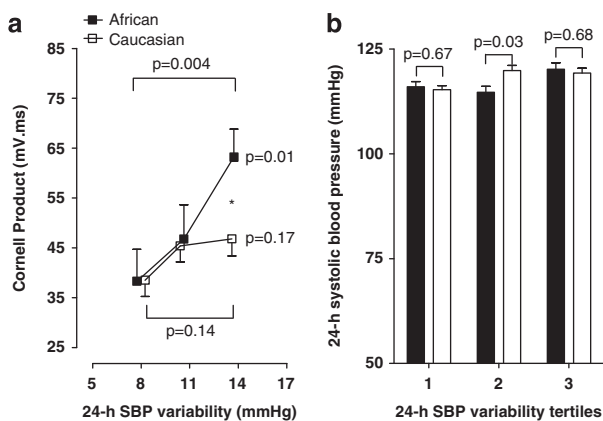


Figure 3 A comparison of normotensive African and Caucasian groups: (a) Cornell product by tertiles of systolic blood pressure variability (SBP wSD); and (b) ambulatory SBP within each SBP wSD tertile. Adjusted for age, gender, body mass index, physical activity, cotinine and γ -glutamyl transferase. * $P < 0.05$.

why ethnic differences are observed, and whether it could be merely due to the early development of left ventricular hypertrophy in the African population?^{40,41}

Apart from increased left ventricular mass in Africans, Li *et al.*⁴⁴ indicated recently that African Americans have higher BP variability than European Americans, contradicting a small study performed in England ($N=26$) that indicated no ethnic differences.⁴⁵ Li *et al.*⁴⁴ argue that the higher BP variability values of Africans are consistent with the prognostic value of BP variability, and the higher incidence and mortality of cardiovascular disease in Africans. Our study indicates contrasting results. Although our general group of African school teachers had significantly higher BP variability than the Caucasian group, comparisons of hypertensive ethnic or normotensive ethnic groups indicated no differences in BP variability (except for diastolic BP variability in normotensives). This result suggests that BP variability is independent of ethnicity, but dependent on BP, as 60.2% of Africans were hypertensive compared with 37.2% of Caucasians.

Another explanation regarding these ethnic differences may be sought in sympathetic drive. The sensitivity of the arterial baroreflex

Table 4 Forward stepwise multiple regression analyses (a) with Cornell product as dependent variable performed in normotensive African and Caucasian participants; (b) with cross-sectional wall area as dependent variable performed in hypertensive African and Caucasian participants

| | Cornell product | | | |
|--------------------------------|---------------------------|---------|-------------------|---------|
| | African (N=46) | | Caucasian (N=104) | |
| | R^2 | P-value | R^2 | P-value |
| (a) Normotensive groups | 0.17 | | 0.43 | |
| | β (s.e.) | P-value | β (s.e.) | P-value |
| Gender (men/women) | | | -0.60 (0.09) | <0.001 |
| Body mass index | 0.25 (0.14) | 0.08 | -0.30 (0.09) | <0.001 |
| Physical activity | | | 0.17 (0.10) | 0.09 |
| γ -glutamyl transferase | 0.21 (0.14) | 0.14 | | |
| Anti-hypertensive medication | | | -0.15 (0.07) | 0.04 |
| SBP variability (wSD) | 0.39 (0.14) | 0.006 | | |
| (b) Hypertensive groups | Cross-sectional wall area | | | |
| | African (N=97) | | Caucasian (N=74) | |
| | R^2 | P-value | R^2 | P-value |
| | 0.23 | | 0.33 | |
| | β (s.e.) | P-value | β (s.e.) | P-value |
| Age | 0.37 (0.09) | <0.001 | 0.43 (0.10) | <0.001 |
| Gender (men/women) | -0.28 (0.09) | 0.003 | -0.32 (0.10) | 0.002 |
| 24-h systolic blood pressure | 0.22 (0.09) | 0.02 | 0.34 (0.10) | <0.001 |

Abbreviations: SBP, systolic blood pressure; wSD, weighted s.d. Independent variables included in model: age, gender, body mass index, cotinine, γ -glutamyl transferase, physical activity, 24-h systolic blood pressure, 24-h weighted systolic blood pressure variability, anti-hypertensive medication.

and 24-h BP variability are linked by an inverse relationship, that is, the greater the BP variability, the lower the ability of the arterial baroreceptors to modulate BP and heart rate.⁴⁶ This negative relationship was demonstrated by the total African and Caucasian groups. Although the BRS of the African and Caucasian normotensive groups were similar, only the normotensive Caucasians showed a significant negative trend in BRS, with increasing 24-h SBP variability tertiles (Caucasians $P=0.035$ vs. Africans $P=0.118$), thereby excluding sympathetic drive as the explanation for the ethnic difference.

Perhaps this ethnic-specific relationship of BP variability with left ventricular mass should be viewed from another perspective. Due to the discrepant findings in the literature, the question is still open whether BP variability has a pathogenetic role (direct causality), or whether it is simply a secondary phenomenon of subclinical vascular changes.⁴⁷ Our results suggest that 24-h SBP variability may lead to sub-clinical organ damage, independently of 24-h SBP, in asymptomatic African individuals who may have a genetic predisposition for the development of hypertension.^{48,49}

This result also needs to be confirmed by other studies in Africans. If our results are applicable to other African populations, it could have far-reaching implications regarding preventive strategies, involving 24-h BP measurements in more affluent countries. In poor countries, the record-keeping of visit-to-visit BP variability in local clinics might prove as effective, as it has been indicated as a strong independent predictor of stroke.²

Notwithstanding the highly controlled study environment, comprehensive range of cardiovascular measurements and first results on BP variability in a black South African cohort, our study has potential limitations. Due to the cross-sectional design, we could not infer

causality. Ambulatory BP monitoring techniques has a limited reproducibility, and the discontinuous low-frequency BP sampling limits their accuracy in assessing BP variability.⁵⁰ Nonetheless, the weighted SD_{ln} technique used in the present study was suggested as an accurate and useful measure.^{4,10} Lastly, echocardiography was not used for determination of left ventricular mass, but we used a validated electrocardiographic method (Cornell product).

In conclusion, our results indicate that weighted BP variability compares poorly with traditional and advanced measurements of BP in hypertensive Africans and Caucasians, regarding their relationship with target organ damage. However, in Africans with normal BPs, 24-h SBP variability was significantly associated with ECG left ventricular mass. From a clinical point of view, the applicability of BP variability may be useful as an early marker in identifying Africans at increased risk for the development of left ventricular hypertrophy.

ACKNOWLEDGEMENTS

The Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) Study would not have been possible without the voluntary collaboration of the participants and the Department of Education, North-West Province, South Africa. We gratefully acknowledge the technical assistance of Mrs Tina Scholtz, Dr Szabolcs Péter and Sr Chrissie Lessing. This study was supported by the National Research Foundation, South Africa; the North-West University, Potchefstroom, South Africa; and the Metabolic Syndrome Institute, France.

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