Carotid characteristics of black South Africans with five-year sustained hypertension

Melissa Maritz, Carla MT Fourie, Johannes M van Rooyen, Hugo W Huisman, Aletta E Schutte

Abstract

Introduction: An important feature of hypertension is a reduction in large artery distensibility, which may be due to structural and functional adaptations. Black populations are particularly prone to the development of hypertension. We therefore compared the carotid characteristics between five-year sustained hypertensive and normotensive black South Africans, and investigated how carotid characteristics relate to cardiometabolic risk factors, inflammation, endothelial activation and health behaviours.

Methods: We included HIV-free black South Africans who were either consistently hypertensive (n = 351) or normotensive (n = 241) from 2005 to 2010. We assessed carotid characteristics, including intima–media thickness (IMT), distensibility and lumen diameter with B-mode ultrasound, and calculated Young’s elastic modulus, cross-sectional wall area, wall thickness, and beta-stiffness index. We measured the carotid dorsalis pedis pulse-wave velocity, brachial and central systolic blood pressure (cSBP) and determined metabolic, inflammatory and endothelial activation markers from blood samples. Health behaviours were reported in questionnaires.

Results: The hypertensive group presented with higher brachial and central blood pressure, thicker IMT and stiffer carotid arteries (all p < 0.001). However, after adjustment for cSBP but not mean arterial pressure (MAP), all significant differences in carotid characteristics were lost. The carotid thickness measurements did not differ after adjustment for MAP. After adjustment, metabolic, inflammatory and endothelial activation markers did not differ between the two groups.

Conclusion: Our results suggest that besides structural changes, functional adaptations are also involved in deterioration of the carotid wall characteristics of hypertensive black South Africans. These results highlight the importance of proper hypertension control in Africa.

Keywords: ethnicity, large artery, stiffness, distensibility, hypertension, central pressure

Submitted 30/10/15, accepted 5/5/16
Cardiovasc J Afr 2016; 27: 262–269 www.cvja.co.za

DOI: 10.5830/CVJA-2016-059

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Worldwide, cardiovascular disease is the leading cause of death. Arterial stiffness is implicated in the development of cardiovascular disease, which results in stroke, coronary heart disease and heart failure. Arterial stiffness refers to the reduced ability of an artery to expand and recoil with pressure changes, and the arterial distensibility is a measure of vessel stiffness. Decreased distensibility may raise central systolic blood pressure (cSBP) and consequently decrease the amplification of pulse pressure. This results in inadequate coronary perfusion, increased afterload on the heart, as well as an increased pulsatile load on the microcirculation.

The artery is able to resist strain during blood pressure increases via recruitment of collagen fibres in the arterial wall, but sustained high pressure predisposes the vessel to progressive changes in the wall shape and composition, ultimately leading to several clinical complications such as arterial fibrosis and stiffening.

Recently, van Sloten et al. reported that in a European population, carotid artery stiffness independently predicts incident cardiovascular (CV) events and all-cause mortality. The higher incidence of stroke, heart failure and renal failure in black populations are a consequence of the higher prevalence of hypertension and arterial stiffness in black compared to white populations.

Despite the high prevalence of hypertension and stroke among black South Africans, there is limited knowledge on carotid wall properties in this population. We therefore compared the characteristics of the carotid arteries between normotensive and five-year sustained hypertensive black individuals, along with brachial and central blood pressure and conventional cardiometabolic risk factors, markers of inflammation, endothelial activation and health behaviours.

Methods

This sub-study forms part of the South African leg of the multi-national Prospective Urban and Rural Epidemiology (PURE) study. The participants of the PURE-SA study were from urban and rural localities in the North West Province, and baseline data collection took place in 2005 (n = 2 010 participants), while follow-up data was collected five years later, in 2010 (n = 1 288 participants). For this sub-study we included only the HIV-free black participants with two consecutive (2005, 2010) blood pressure measurements in either the hypertensive or normotensive range (n = 592 participants), consisting of a group of five-year sustained normotensive (n = 241participants) and hypertensive (n = 351 participants) black South Africans (Fig. 1).

The Health Research Ethics Committee of the North-West University approved the protocol of the PURE-SA study, as well as this sub-study (ethics number: NWU-00016-10-A1), and it complies with the Declaration of Helsinki. Participants completed structured demographic, lifestyle and physical
activity questionnaires with the assistance of trained African field workers from the communities. Before measurements commenced, all procedures were explained to the participants in their home language. The participants then gave written informed consent.

Height (Invicta stadiometer IP 1465, Leicester, UK), weight (Precision health scale, A & D Company; Tokyo, Japan) and waist circumference (WC) (Holtsain unstretchable metal tape, Apex Tool Group, Apex, USA) were measured using standardised methods and calibrated instruments. Body mass index (BMI) was calculated with the formula: weight (kg)/height (m²).

The validated OMRON HEM-757 (Omron Healthcare, Kyoto, Japan) device was used to measure blood pressure. Each participant was fitted with the correct cuff size. During the measurements, the participant was seated in a relaxed upright position with legs uncrossed. After a resting period of 10 minutes, the brachial systolic (bSBP) and diastolic blood pressure (bDBP) were measured on the right upper arm, followed by a five-minute resting period and a second blood pressure measurement. The value of the second measurement was used for analysis. Participants were classified as hypertensive or normotensive according to standard guidelines.17

The cSBP was measured with the OMRON 9000AI device (Omron Healthcare, Kyoto, Japan), which uses the second systolic peak (reflected wave) as basis for the calculation of cSBP. Diastolic blood pressure is assumed to be consistent throughout the body, therefore the central pulse pressure (cPP) was calculated by subtracting the bDBP from the cSBP.18,19

Pulse-wave velocity (PWV) was measured non-invasively on the left side of each participant while in a supine position. The Complior SP device (Artech-Medical, Pantin, France) uses superficial pulses over the carotid dorsalis pedis (cdPWV) section of the arterial tree to estimate PWV.

The carotid characteristics were measured non-invasively using B-mode ultrasonography with the SonoSite Micromaxx system (SonoSite, Inc., Bothel, WA, USA), using a six- to 13-MHz linear array transducer. A minimum of two optimal angles were used from images of the right and left common carotid arteries. These images were then measured by a single reader according to protocols, and digitised and imported into the automated software of the Artery Measurements System (Gothenburg, Sweden).

The carotid intima–media thickness (IMT) was analysed by a single reader on a good-quality image of a maximum 10-mm segment. The borders of the inner diameter of the blood vessel and the near and far wall of the intima–media were identified by an automated function of the program, but user intervention was possible. Approximately 100 discrete measurement points within a 10-mm segment of the carotid artery were used to obtain the mean IMT and the carotid diameter for each participant.

The carotid cross-sectional wall area (CSWA) was calculated according to the following formula:

\[
\text{CSWA} = ([3.14 \times (\text{LD}^2 + \text{IMTf}^2)] - [3.14 \times (\text{LD}^2 + \text{IMTf}^2)])
\]

where LD = lumen diameter and IMTf = carotid intima–media thickness of the far wall.

A single reader analysed video-clips of the carotid artery in order to determine the maximum and minimum lumen diameters (LD). The carotid distensibility (CD) coefficient was calculated according to the following formula:

\[
\text{CD} = \frac{[2 \times \text{delta LD} \times \text{min LD}] + (\text{delta LD})^2}{cPP \times \text{min LD}}
\]

where LD = lumen diameter, delta LD = maximum LD – minimum LD, min LD = minimum LD, cPP = central pulse pressure.20

Young’s elastic modulus was calculated according to the following formula:

\[
\text{Young’s elastic modulus} = \frac{\text{min LD}}{(\text{IMT} \times \text{distensibility})}
\]

where IMT = carotid intima–media thickness, min LD = minimum lumen diameter.21

The beta-stiffness index was calculated according to the following formula:

\[
\text{Beta-stiffness index} = \frac{\ln (\text{cSBP/dDBP})}{\text{delta LD}/\text{min LD}}
\]

where delta LD = maximum LD – minimum LD, min LD = minimum LD.22

Participants were required to fast for at least eight hours and blood samples were taken from the ante-brachial vein with a sterile winged infusion set and syringes. The preparation of the serum and plasma was done according to standardised methods, snap frozen on dry ice and stored in the laboratory at −80°C. In the case of blood collection in a rural area, serum and plasma were snap frozen and stored at −20°C for no more than five days. The serum was then transported to the laboratory and stored at −80°C for further analysis.

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![Fig. 1. Study population; all participants were HIV-free. BP, blood pressure.](image-url)
The Cobas Integra 400 (Roche® Clinical System, Roche Diagnostics, Indianapolis, IN) was used to assess the quantitative aspect of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), gamma-glutamyltransferase (GGT), creatinine and high-sensitivity C-reactive protein (hsCRP) levels in the serum samples, and glucose levels in fluoride plasma samples. Glycosylated haemoglobin (HbA1c) levels were determined from EDTA whole blood with ion-exchange high-performance liquid chromatography (D-10 haemoglobin testing system, Bio-Rad #220-0101).

The Friedewald formula was used to calculate the quantitative aspect of low-density lipoprotein cholesterol (LDL-C). The estimated creatinine clearance (CrCl) rate was calculated with the Cockcroft–Gault formula.

We determined serum interleukin-6 (IL-6) levels with an electro-chemiluminescence immunoassay (Cobas e411 analyzer, Roche, Basel, Switzerland). Serum intercellular adhesion molecule 1 (sICAM-1) and vascular cell adhesion molecule 1 (sVCAM-1) concentrations were assessed by sandwich ELISAs (human sICAM-1 and human sVCAM-1 assay, IBL, Hamburg, Germany).

### Statistical analysis

Statistical analyses were performed using Statistica® 12 (StatSoft, Inc, Tulsa, OK, USA). Descriptive statistics, including the mean and standard deviation, were performed on data with a normal distribution. If not normally distributed, the data were logistically transformed and presented as the geometric mean and the fifth and 95th percentiles.

We used independent t-tests to determine differences between normotensives and hypertensives or chi-squared tests for categorical variables. We compared the groups using ANCOVA while adjusting for age, gender, WC, GGT, tobacco and anti-hypertensive medication use. We plotted quartiles of cSBP against carotid features, and compared carotid features using ANOVA and ANCOVA while adjusting for cSBP.

We used single and linear regression analyses to determine associations between carotid measures and cardiometabolic risk factors, health behaviours, inflammation and endothelial activation. Multiple regression analyses were done to determine independent associations between the carotid characteristics and cardiometabolic risk factors, with the dependent variables including CD and IMT, and CSWA and max LD. The following co-variates were included in the regression model: locality, gender, age, WC, cSBP, heart rate, LDL-C, HbA1c, CrCl, hsCRP, ICAM-1, TG, GGT and self-reported alcohol use were significantly higher in the hypertensive group, anti-hypertensive medication use.

### Results

The characteristics of normotensive and hypertensive black Africans are shown in Table 1. The hypertensives were older, had a higher BMI and WC, and a larger percentage were from an urban area than the normotensives. All the cardiovascular measurements, as well as carotid characteristics, glycaemic and inflammatory markers, ICAM-1, TG, GGT and self-reported alcohol use were significantly higher in the hypertensive group.

After adjustments for age, gender, WC, GGT, tobacco and anti-hypertensive medication use (Table 2), all carotid characteristics except IMT remained significantly different.

| Table 1. Characteristics of normotensive and hypertensive black Africans |
|--------------------------------------------------|
|                                     | Normotensive (n = 241) | Hypertensive (n = 351) | p-value |
|-----------------------------------------------|------------------------|------------------------|---------|
| Men, n (%)                                    | 90 (37.3)              | 129 (36.8)             | 0.88    |
| Urban, n (%)                                  | 78 (32.4)              | 178 (50.7)             | <0.001  |
| Age, years                                    | 52.8 ± 8.9            | 59.0 ± 10.0            | <0.001  |
| Anthropometry                                 |                        |                        |         |
| Waist circumference, cm                       | 78.7 ± 11.9            | 84.7 ± 13.5            | <0.001  |
| Body mass index, kg/m²                        | 24.7 ± 6.87            | 26.6 ± 7.85            | 0.003   |
| Cardiovascular measures                       |                        |                        |         |
| Brachial SBP, mm Hg                           | 119 ± 11.9             | 157 ± 22.4             | <0.001  |
| Brachial DBP, mm Hg                           | 78.9 ± 7.23            | 100 ± 12.5             | <0.001  |
| Heart rate, bpm                               | 61.8 ± 14.7            | 67.8 ± 17.9            | <0.001  |
| Central SBP, mm Hg                            | 116 ± 12.8             | 150 ± 22.2             | <0.001  |
| Central PP, mm Hg                             | 37.4 ± 11.8            | 50.9 ± 20.4            | <0.001  |
| Carotid dorsalis pedis PWV, m/s               | 8.25 ± 1.35            | 10.0 ± 1.89            | <0.001  |
| Carotid characteristics                       |                        |                        |         |
| Distensibility × 10, 1/kPa                    | 4.72 ± 2.00            | 3.02 ± 1.83            | <0.001  |
| Young’s elastic modulus × 10, kPa             | 2.17 ± 1.07            | 3.72 ± 2.20            | <0.001  |
| Beta-stiffness index                          | 7.10 ± 2.62            | 9.37 ± 4.51            | <0.001  |
| Intima-media thickness mm                     | 0.68 ± 0.13            | 0.77 ± 0.27            | <0.001  |
| Cross-sectional wall area, mm²                | 14.2 ± 4.41            | 17.5 ± 5.10            | <0.001  |
| Lumen diameter maximum, mm                    | 6.18 ± 0.77            | 6.60 ± 0.85            | <0.001  |
| Lumen diameter minimum, mm                    | 5.74 ± 0.72            | 6.22 ± 0.83            | <0.001  |
| Lipids                                        |                        |                        |         |
| HDL-C, mmol/l                                 | 1.45 ± 0.65            | 1.51 ± 0.60            | 0.30    |
| LDL-C, mmol/l                                 | 2.86 ± 1.17            | 2.96 ± 1.14            | 0.29    |
| Triglycerides, mmol/l                         | 1.09 (0.57–2.11)       | 1.20 (0.59–2.89)       | 0.039   |
| Glycaemia                                     |                        |                        |         |
| Glucose, mmol/l                               | 4.86 (3.91–6.06)       | 5.27 (3.96–7.90)       | <0.001  |
| HbA1c, (%)                                    | 5.94 (5.30–6.80)       | 6.08 (5.20–7.80)       | 0.038   |
| Inflammatory markers                          |                        |                        |         |
| Interleukin-6, pg/ml                          | 3.39 (0.75–23.5)       | 4.43 (0.75–20.0)       | <0.001  |
| C-reactive protein, mg/l                      | 2.96 (0.21–32.6)       | 3.84 (0.38–28.4)       | 0.022   |
| Adhesion molecules                            |                        |                        |         |
| Intercellular adhesion molecule-1, pg/ml      | 286 ± 92.7             | 321 ± 111              | <0.001  |
| Vascular adhesion molecule-1, pg/ml           | 732 (442–1378)         | 762 (443–1735)         | 0.23    |
| Renal function                                |                        |                        |         |
| Creatinine clearance, ml/min                  | 91.4 (53.7–163)        | 91.6 (47.7–164)        | 0.94    |
| Health behaviours                             |                        |                        |         |
| γ-glutamyltransferase, U/l                    | 33.7 (11.9–167)        | 52.7 (13.6–347)        | <0.001  |
| Self-reported alcohol intake, n, total (%)    | 60/220 (27.3)          | 159/336 (47.3)         | <0.001  |
| Self-reported tobacco use, n, total (%)       | 117/229 (51.1)         | 159/341 (46.6)         | 0.56    |
| Anti-hypertension medication, n, total (%)    | – 124/351 (35.3)       | 172/351 (49.6)         |         |
| Lipid-lowering medication, n, total (%)       | – 5/124 (1.42)         | 5/351 (1.42)           |         |
| Anti-inflammatory medication, n, total (%)    | – 124/351 (35.3)       | 21/351 (5.98)          |         |

Data are arithmetic means ± SD or geometric mean (fifth and 95th percentile intervals) for logistically transformed.

The inflammatory and glycaemic markers, lipids and adhesion molecules did not differ however after the above adjustments.

The carotid characteristics plotted against quartiles of cSBP are shown in Fig. 2. All the carotid characteristics changed significantly with increasing cSBP before and after the adjustments.
We finally adjusted for cSBP when comparing the normotensive and hypertensive groups (Table 3), resulting in no significant differences in the carotid characteristics between the groups. When cSBP was substituted with either brachial SBP (p = 0.029) or mean arterial pressure (MAP) (p = 0.0012), the difference in distensibility remained, but the more physical measures such as IMT, CSWA and LD did not differ.

In sensitivity analysis, we further compared hypertensives who were not using anti-hypertensive therapy (n = 227) with treated hypertensives (n = 124) and normotensives, applying similar adjustments, including cSBP. We found results similar to those in Table 3 (Table 4). Furthermore, excluding participants on anti-hypertensive medication and comparing the normotensive group to the treated hypertensive group did not change the results. The types of medication used by the hypertensive participants are shown in Table 5.

Table 6 reports the forward stepwise multiple regression analyses performed in the normotensive and hypertensive groups with either CD or IMT as dependent variables. As expected, CD associated with cSBP in both groups (p < 0.001), however, IMT associated independently with cSBP in the hypertensive group only (p = 0.016).

Table 2. Adjusted characteristics of normotensive and hypertensive black Africans

| Cardiovascular measures | Normotensive (n = 241) | Hypertensive (n = 351) | p-value |
|-------------------------|------------------------|------------------------|---------|
| Brachial SBP, mm Hg     | 120 ± 20.0             | 155 ± 20.7             | <0.001  |
| Brachial DBP, mm Hg     | 79.2 ± 11.1            | 99.8 ± 11.6            | <0.001  |
| Heart rate, bpm         | 62.7 ± 17.5            | 66.8 ± 18.0            | 0.017   |
| Central SBP, mm Hg      | 117 ± 20.2             | 148 ± 20.9             | <0.001  |
| Central PP, mm Hg       | 38.4 ± 17.9            | 49.4 ± 18.5            | <0.001  |
| Carotid dorsalis pedis PWV, m/s | 8.87 ± 2.06 | 9.37 ± 2.13 | <0.001  |

Carotid characteristics

- Distensibility × 10⁻³, 1/kPa: 4.58 ± 1.98 vs 3.15 ± 2.07 (p < 0.001)
- Young’s elastic modulus × 10¹, kPa: 2.26 ± 1.98 vs 3.59 ± 2.07 (p < 0.001)
- Beta-stiffness index: 7.48 ± 3.98 vs 8.97 ± 4.16 (0.002)
- Intima-media thickness mm: 0.72 ± 0.14 vs 0.73 ± 0.18 (0.42)
- Cross-sectional wall area, mm²: 14.8 ± 4.71 vs 16.7 ± 4.86 (0.001)
- Lumen diameter maximum, mm: 6.24 ± 0.85 vs 6.51 ± 0.92 (0.005)
- Lumen diameter minimum, mm: 5.80 ± 0.85 vs 6.12 ± 0.76 (0.001)

Lipids

- HDL-C, mmol/l: 1.46 ± 0.60 vs 1.50 ± 0.73 (0.47)
- LDL-C, mmol/l: 2.93 ± 1.19 vs 2.90 ± 1.27 (0.81)
- Triglycerides, mmol/l: 1.16 (1.08–1.24) vs 1.11 (1.05–1.19) (0.50)

Glycaemia

- Glucose, mmol/l: 5.01 (4.86–5.16) vs 5.10 (4.97–5.23) (0.43)
- HbA₁c, %: 6.05 (5.93–6.15) vs 5.99 (5.89–6.08) (0.44)

Inflammatory markers

- Interleukin-6, pg/ml: 3.62 (3.19–4.11) vs 4.05 (3.64–4.51) (0.22)
- C-reactive protein, mg/l: 3.41 (2.84–4.08) vs 3.18 (2.72–3.72) (0.62)

Adhesion molecules

- Intracellular adhesion molecule-1, pg/ml: 293 ± 101 vs 308 ± 105 (0.13)
- Vascular adhesion molecule-1, pg/ml: 748 (706–792) vs 747 (711–785) (0.98)

Creatinine clearance, ml/min: 90.8 (87.8–94.0) vs 92.3 (89.8–96.0) (0.54)

Data are arithmetic means ± SD or geometric mean (fifth and 95th percentile intervals) for logarithmically transformed. Data are adjusted for age, gender, waist circumference, γ-glutamyl transferase, tobacco use and anti-hypertensive medication use. Pulse-wave velocity and carotid intima-media thickness additionally adjusted for mean arterial pressure.

Table 3 reports the forward stepwise regression analyses performed in the normotensive and hypertensive groups with either CSWA or maximum LD as the dependent variables. CSWA associated with cSBP (p < 0.001) in the hypertensive group only, whereas maximum LD associated with cSBP in both the normotensive and hypertensive groups.
Table 3. Carotid characteristics of normotensive and hypertensive black Africans, adjusted for potential confounders

| Carotid characteristics after adjustment for central SBP | Normotensive (n = 241) | Hypertensive (n = 351) | p-value |
|----------------------------------------------------------|------------------------|------------------------|---------|
| Distensibility × 10^11, 1/kPa                            | 3.77 ± 1.98            | 3.95 ± 2.22            | 0.30    |
| Young’s elastic modulus × 10^10, kPa                     | 3.04 ± 1.84            | 2.80 ± 2.05            | 0.34    |
| Beta-stiffness index                                     | 8.43 ± 4.21            | 8.02 ± 4.61            | 0.47    |
| Intima–media thickness, mm                              | 0.71 ± 0.14             | 0.73 ± 0.17             | 0.19    |
| Cross-sectional wall area, mm²                           | 15.2 ± 4.96            | 16.2 ± 5.25            | 0.09    |
| Lumen diameter maximum, mm                              | 6.30 ± 0.82             | 6.41 ± 1.04             | 0.34    |
| Lumen diameter minimum, mm                              | 5.85 ± 0.94             | 6.02 ± 0.89             | 0.12    |
| Data are arithmetic means ± SD.                           |                        |                        |         |

Table 4. Carotid characteristics, untreated and treated hypertensive black Africans, adjusted for potential confounders including central systolic blood pressure

| Carotid characteristics | Untreated Hypertensives (n = 241) | Treated Hypertensives (n = 124) | p-value |
|-------------------------|-----------------------------------|---------------------------------|---------|
| Distensibility × 10^11, 1/kPa | 3.53 ± 2.07                       | 3.70 ± 1.77                    | 0.59    |
| Young’s elastic modulus × 10^10, kPa | 3.28 ± 2.07                       | 3.04 ± 1.79                    | 0.44    |
| Beta-stiffness index | 8.83 ± 4.56                       | 8.42 ± 3.80                    | 0.75    |
| Intima–media thickness, mm | 0.73 ± 0.14                       | 0.75 ± 0.14                    | 0.15    |
| Cross-sectional wall area, mm² | 15.9 ± 5.38                       | 16.8 ± 4.35                    | 0.09    |
| Lumen diameter maximum, mm | 6.34 ± 0.94                       | 6.83 ± 0.83                    | 0.48    |
| Lumen diameter minimum, mm | 5.89 ± 0.94                       | 6.06 ± 0.83                    | 0.17    |
| Data are arithmetic means ± SD.                           |                        |                        |         |

Discussion

As expected, we found that hypertensive black Africans presented with reduced carotid distensibility when compared to normotensives. In fact, we found significant differences for all carotid wall thickness and distensibility measurements between the hypertensives and normotensives prior to adjustments. However, upon adjustment for cSBP, all differences disappeared. The direct physical measures, such as IMT, CSWA and LD, were similar between the hypertensive and normotensive groups after adjustments for both cSBP and MAP. This similarity suggests that the decreased carotid distensibility and increased carotid cross-sectional area of five-year sustained hypertensive Africans are, besides structural changes due to arterial degeneration, also dependent on the distending pressure, and that functional changes in the carotid artery may be more prominent than structural changes in this population.

Our findings are consistent with evidence in white populations that show increased stiffness to be due to the increased distending pressure that accompanies hypertension, suggesting a functional adaptation, and not only structural alterations of the arterial wall.25,26 In contrast to these and our findings, one study found that show increased stiffness to be due to the increased distending pressure that accompanies hypertension, suggesting a functional adaptation, and not only structural alterations of the arterial wall.25,26 In contrast to these and our findings, one study found that the acute reduction in blood pressure by nitroglycerin does not normalise large artery stiffness in essential hypertensives.27

It is expected that sustained high blood pressure, as seen in hypertension, would cause vascular damage by, for instance, altering the collagen–elastin ratio of the arterial wall in favour of collagen.28,29 Indeed, after adjustment for mean arterial pressure, the difference in carotid distensibility between the hypertensives and normotensives remained, therefore suggesting the presence of structural alterations. Nevertheless, in light of the significant

Table 5. Anti-hypertensive medication use in the hypertensive group

| Type of anti-hypertensive medication | Hypertensive participants using medication | n (n = 124) |
|-------------------------------------|-------------------------------------------|------------|
| Unspecified, n, total (%)           | 61/124 (49.2)                             |            |
| Beta-blockers, n, total (%)         | 12/124 (9.68)                             |            |
| Anti-adrenergics, n, total (%)      | 2/124 (1.61)                              |            |
| Calcium channel blockers, n, total (%) | 30/124 (24.2)                           |            |
| Class 2 ACE inhibitors, n, total (%) | 49/124 (39.5)                            |            |
| Diuretics, n, total (%)             | 54/124 (43.5)                             |            |
| n, number of participants: Unspecified: only indicated as high blood pressure pills or hypertension medication |

Table 6. Forward stepwise multiple regression analyses with carotid distensibility and carotid intima–media thickness as dependent variables

| Distensibility (1/kPa) | β (95% CI) | p-value | Hypertensive (n = 351) | β (95% CI) | p-value |
|------------------------|------------|---------|------------------------|------------|---------|
| Adjusted R²            | 0.27       | 0.37    |                        |            |         |
| Locality (urban)       | -0.16 (-0.31–0.01) | 0.031  |                        |            |         |
| Age, years             | -0.14 (-0.29–0.003) | 0.058  | -0.20 (-0.35–0.05) | 0.009     |         |
| Waist circumference, cm | 0.22 (0.06–0.39) | 0.007  |                        |            |         |
| Central SBP, mm Hg     | -0.44 (-0.59–0.29) | <0.001 | -0.56 (-0.68–0.45) | <0.001    |         |
| Heart rate, bpm         | -0.10 (-0.25–0.04) | 0.16   | -0.12 (-0.23–0.01) | 0.030     |         |
| LDL-C, mmol/l           | 0.08 (0.03–0.19) | 0.18   |                        |            |         |
| HbA1c, (%)              | -0.14 (0.26–0.02) | 0.018  |                        |            |         |
| CrCl, ml/min            | -0.10 (0.28–0.07) | 0.24   |                        |            |         |
| ICAM-1, pg/ml           | 0.11 (0.04–0.25) | 0.16   |                        |            |         |
| Tobacco use (no/yes)    | -0.14 (0.28–0.003) | 0.058  |                        |            |         |
| IMT (mm)                | 0.25       | 0.35    |                        |            |         |
| Adjusted R²            | 0.25       | 0.35    |                        |            |         |
| Locality (urban)       | -0.10 (-0.20–0.01) | 0.030  |                        |            |         |
| Gender (male)           | 0.26 (0.13–0.39) | <0.001 | 0.25 (0.15–0.36) | <0.001    |         |
| Age, years             | 0.33 (0.21–0.46) | <0.001 | 0.44 (0.34–0.54) | <0.001    |         |
| Waist circumference, cm | 0.14 (0.01–0.28) | 0.033  | 0.08 (0.02–0.19) | 0.13      |         |
| Central SBP, mm Hg     | 0.12 (0.02–0.22) | 0.016  |                        |            |         |
| Heart rate, bpm         | -0.08 (-0.20–0.05) | 0.21   |                        |            |         |
| LDL-C, mmol/l           | 0.07 (-0.05–0.19) | 0.29   | 0.15 (0.05–0.25) | 0.005     |         |
| HbA1c, (%)              | 0.07 (0.03–0.18) | 0.17   |                        |            |         |
| C-reactive protein, pg/ml | 0.16 (0.03–0.30) | 0.017  | 0.06 (0.04–0.16) | 0.27      |         |
| ICAM-1, pg/ml           | 0.12 (-0.01–0.24) | 0.079  | -0.08 (-0.18–0.02) | 0.12      |         |
| γ-glutamyl transferase, U/l |                        |         |                        |            |         |
| Tobacco use (no/yes)    | -0.08 (-0.18–0.02) | 0.11   |                        |            |         |
| Anti-hypertension       | -0.10 (-0.19–0.003) | 0.044  |                        |            |         |
| medications (no/yes)    |                        |         |                        |            |         |

Data expressed as beta-values and 95% confidence intervals, p-values obtained with forward stepwise multiple regression analyses. Included in each model: locality, age, gender, waist circumference, heart rate, cSBP, LDL-C, HbA1c, C-reactive protein, ICAM-1, creatinine clearance, γ-glutamyl transferase, tobacco and anti-hypertensive medication use.

IMT, carotid intima–media thickness; CSWA, cross-sectional wall area; Max LD, maximum lumen diameter; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated haemoglobin; ICAM-1, intercellular adhesion molecule-1.
cardiovascular burden that black populations carry, our results suggest that treatment that effectively lowers central pressure may also significantly lower the risk for stroke and other cardiovascular events.

Our results were similar for treated and untreated hypertensives; therefore treatment seems to be largely ineffective in this population. Indeed, the treatment and control of hypertension in low-income countries are largely inadequate despite half of those sampled being aware of their condition.14,30 South Africa has one of the highest hypertension rates (78%) for people over 50 years of age, but only 38% are aware of their hypertensive status and only 7.8% of those treated for hypertension have controlled hypertension.14 It therefore remains to be seen whether effective anti-hypertensive treatment in black Africans will result in improved carotid distensibility.

Surprisingly, the IMT was similar between the two groups after adjustments, suggesting a lack of visible structural changes in the hypertensive blacks. IMT is an important marker of the atherosclerotic burden of the carotid artery, but it may also indicate non-atherosclerotic compensatory remodelling of the arterial wall in response to hypertension. However, neither of these possibilities seems to be the case in this black population. On the other hand, IMT was independently associated with cSBP in the hypertensive group only, therefore suggesting that the continued high pulsatile load of uncontrolled hypertension may eventually mediate structural changes in the carotid artery. This result shows a similar trend to the findings of Wang et al., confirming the relevance of central blood pressure to IMT.

We observed no differences in the inflammatory and endothelial activation markers, lipid levels and glycaemic status between the normotensives and hypertensives. Africans are generally not prone to atherosclerosis and coronary heart disease, and exhibit a favourable lipid profile, possibly explaining the similar lipid levels between the two groups. However, our results confirm the commonly found association between IMT and LDL-C level, and an association between CD and HbA1c level in the hypertensive group only.

Although we did not observe structural differences after adjustment for cSBP, these results suggest glucose metabolism and lipid abnormalities may play a role in the arterial changes, although these are not yet detectable with ultrasound. Inflammation and endothelial activation (as indicated by the adhesion molecules) may not play a major role in the mediation of central arterial stiffness at this stage of disease progression. These results are unexpected in the light of previous findings, which indicate that acute and chronic inflammation are associated with stiffness of the large arteries, and that endothelial activation may be an important mediator of hypertensive vascular injury.

The findings of this study should be interpreted in the context of its limitations and strengths. Our study population consisted of individuals from specific urban and rural areas in the North West Province of South Africa, and may not be representative of the whole population. We were not able to use echo-tracking techniques to determine local arterial stiffness in our field study; however, the procedures of ultrasound assessment are standardised and were performed by a single reader in a large study population. Carotid distensibility was calculated with a formula that includes cSBP, and we adjusted for cSBP. However, neither direct measurements such as IMT nor indirect variables such as carotid distensibility differed after adjustments for cSBP. Due to the cross-sectional study design, causality cannot be inferred. Although the results were consistent after several adjustments, we cannot exclude residual confounding.

### Conclusion

Although differences existed in terms of carotid structure and function between the normotensive and hypertensive Africans, it seemed to be partially accounted for by the increased distending pressure of the hypertensive group. Despite their hypertensive status, structural adaptations, such as IMT thickening, were not detectable in this African population after adjustment for potential confounders, and even before cSBP or MAP were taken into account. The classic cardiometabolic risk factors, markers of inflammation, endothelial activation and health behaviour seemed to play only a minor role in the mediation of carotid distensibility in this population at this stage of disease.

### Table 7. Forward stepwise multiple regression analyses with CSWA and max LD as dependent variables

|                        | Normotensives (n = 241) | Hypertensives (n = 331) |
|------------------------|-------------------------|-------------------------|
|                         | β (95% CI) p-value       | β (95% CI) p-value       |
| CSWA (mm^2)            | 0.23                    | 0.32                    |
| Adjusted RF            |                         |                         |
| Locality (urban)       | -0.11 (-0.21 – -0.01)   | 0.022                   |
| Gender (male)          | 0.29 (0.15–0.42)        | <0.001                  |
| Age, years             | 0.29 (0.17–0.42)        | <0.001                  |
| Waist circumference, cm| 0.18 (0.05–0.31)        | 0.008                   |
| Central SBP, mm Hg     | 0.18 (0.08–0.28)        | <0.001                  |
| LDL-C, mmol/l          | 0.12 (0.01–0.23)        | 0.026                   |
| HbA1c (%)              | 0.08 (-0.03–0.19)       | 0.13                    |
| Creatinine clearance, ml/min | 0.11 (-0.05–0.26)     | 0.18                    |
| C-reactive protein, pg/ml | 0.16 (0.02–0.29)      | 0.025                   |
| γ-glutamyl transferase, U/l | 0.11 (-0.22–0.24)  | 0.10                    |
| Anti-hypertension medication (yes) | -0.12 (-0.22–0.02) | 0.013                   |
| Max LD (mm)            | 0.27                    | 0.10                    |
| Adjusted RF            |                         |                         |
| Locality (urban)       | -0.08 (-0.21–0.05)      | 0.21                    |
| Gender (male)          | 0.26 (0.10–0.42)        | 0.001                   |
| Age, years             | 0.13 (-0.03–0.29)       | 0.12                    |
| Waist circumference, cm| 0.14 (-0.005–0.28)      | 0.061                   |
| Central SBP, mm Hg     | 0.19 (0.05–0.35)        | 0.010                   |
| Heart rate, bpm         | -0.09 (-0.24–0.06)      | 0.22                    |
| LDL-C, mmol/l          | -0.16 (-0.30–0.02)      | 0.027                   |
| Creatinine clearance, ml/min | 0.21 (0.05–0.37)   | 0.011                   |
| C-reactive protein, pg/ml | 0.16 (0.01–0.30)    | 0.037                   |
| ICAM-1, pg/ml          | 0.16 (0.01–0.30)        | 0.037                   |
| γ-glutamyl transferase, U/l | 0.17 (0.03–0.32)  | 0.023                   |

Data expressed as β-values and 95% confidence intervals, p-values obtained with forward stepwise regression analyses. Included in each model: locality, age, gender, WC, HR, cSBP, LDL-C, HbA1c, C-reactive protein, ICAM-1, creatinine clearance, γ-glutamyl transferase, tobacco and anti-hypertensive medication use. CSWA, cross-sectional wall area; Max LD, maximum lumen diameter; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated haemoglobin; ICAM-1, intracellular adhesion molecule-1.
development. These results suggest that interventional strategies and the use of medication targeted at effectively lowering blood pressure may also lower the risk for adverse cardiovascular events in black South Africans.

This work was financially supported by the SANPAD (South Africa–Netherlands Research Programme on Alternatives in Development), PHRI (Population Health Research Institute), Medical Research Council of South Africa, South African National Research Foundation (NRF) (GUN numbers 2069139 and FA2006407000010), North-West University and Roche Diagnostics. Any opinion, findings and conclusions or recommendations expressed in this material are those of the authors, and therefore the NRF do not accept any liability in regard thereto.

The authors thank all supporting staff and the participants of the PURE study and in particular:

PURE-South Africa: the PURE-NWP-SA research team, field workers and office staff in the Africa Unit for Transdisciplinary Health Research (AUTHHeR) and the Hypertension in Africa Research Team (HART), Faculty of Health Sciences. North-West University, South Africa;

PURE International: Dr S Yusuf and the PURE project office staff at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, ON, Canada.

References

1. World Health O. Global status report on noncommunicable diseases. Report. 2010.
2. Laurent S, Cockcroft J, van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588–2605.
3. Van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RMA, et al. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality. J Am Coll Cardiol 2014; 63: 1739–1747.
4. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. J R Soc Med Cardiovasc Dis 2012; 1: 11–21.
5. Avolio AP, van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protegerou AD, et al. Role of pulse pressure amplification in arterial hypertension. Experts’ opinion and review of data. Hypertension 2009; 54: 375–383.
6. Nichols WW, O’Rourke MF. McDonald’s Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. London: Edward Arnold, 2005.
7. Sáez P, Peño E, Martínez MA. A structural approach including the use of medication targeted at effectively lowering blood pressure. Hypertension 2009; 54: 404–410.
8. Humphrey JD. Mehanisms of arterial remodelling in hypertension. Hypertension 2008; 52: 195–200.
9. Wagensie JEM, Mechem RP. Elastin in large artery stiffness and hypertension. J Cardiovasc Transl Res 2012; 5: 264–273.
10. Damasceno A, Azevedo A, Silva-Matos C, Prista A, Diogo D, Lunet N. Hypertension prevalence, awareness, treatment and control in Mozambique: Urban/rural gap during epidemiological transition. Hypertension 2009; 54: 77–83.
32. Spence JD. Carotid plaque measurement is superior to IMT: Invited editorial comment on: Carotid plaque, compared with carotid intima–media thickness, more accurately predicts coronary artery disease events: A meta-analysis. Inaba Y, Chen JA, Bergmann SR. Atherosclerosis 2012; 220: 34–35.

33. Wang KL, Cheng HM, Chuang SY, Spurgeon HA, Ting C, Lakatta EG, et al. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? J Hypertens 2009; 27: 461–467.

34. Sliwa K, Wilkinson D, Hansen C, Niyyintye L, Tibazarwa K, Becker A, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (The Heart of Soweto study): a cohort study. Lancet 2008; 371: 915–922.

35. Fowkes FGR, Thorogood M, Connor MP, Lewando-Hundt G, Tzoulaki I, et al. Blood pressure, LDL cholesterol, and intima–media thickness: A test of the “Response to injury” hypothesis of atherosclerosis. Arterioscler Thromb Vasc Biol 2006; 26: 2005–2010.

36. Vorster HH. The emergence of cardiovascular disease during urbanisation of Africans. Public Health Nutr 2002; 5: 239–243.

37. Sun P, Dwyer KM, Merz CNB, Sun W, Johnson CA, Shirocore AM, et al. Blood pressure, LDL cholesterol, and intima–media thickness: A test of the “Response to injury” hypothesis of atherosclerosis. Arterioscler Thromb Vasc Biol 2006; 26: 2005–2010.

38. Yang C, Sun Z, Li Y, Ai J, Sun Q, Tian Y. The correlation between serum lipid profile with carotid intima-media thickness and plaque. BMC Cardiovasc Disord 2014; 14: 181.

39. McEniery CM, Wilkinson IB. Large artery stiffness and inflammation. J Hum Hypertens 2009; 23: 507–509.

40. Preston RA, Jy W, Jimenez JJ, Mauro LM, Horstman LL, Valle M, et al. Effects of severe hypertension on endothelial and platelet microparticles. Hypertension 2003; 41: 211–217.

41. Caviezel S, Dratva J, Schaffner E, Schindler C, Zemp Stutz E, de Groot E, et al. Sex-specific associations of cardiovascular risk factors with carotid stiffness – Results from the SAPALDIA Cohort Study. Atherosclerosis 2014; 235: 576–584.