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Defensive coping facilitates higher blood pressure and early sub-clinical structural vascular disease via alterations in heart rate variability: the SABPA study.

Running Title: Coping, heart rate variability, structural vascular disease

L Malan[a]; M Hamer[a,b]; MP Schlaich[c]; G Lambert[c]; T Ziemssen[d]; M Reimann[d]; N Frasure-Smith[e]; JH Amirkhan[f]; R Schutte[a]; JM van Rooyen[a]; CM Mels[a], CMT Fourie[a]; AS Uys[a]; NT Malan[a].

[a]Hypertension in Africa Research Team (HART); North-West University; Potchefstroom; South Africa
[b]Department of Epidemiology and Public Health; University College of London; UK
[c]Department of Biological Psychology; Neurovascular Hypertension & Kidney Disease and Human Neurotransmitters Laboratories; Baker IDI Heart and Diabetes Institute; Melbourne; Australia
[d]Department of Neurology, Medical Faculty Carl Gustav Carus; Dresden University of Technology; Germany
[e]Department of Psychiatry and School of Nursing, McGill University; Centre Hospitalier Université de Montréal and Research Centre; Montreal Heart Institute; Canada
[f]Psychology Department, University Long Beach; California State; USA

Corresponding author:

Professor L Malan (RN, PhD)
Hypertension in Africa Research Team (HART)
North-West University (Potchefstroom Campus)
Private Bag x6001
Potchefstroom
2520
South Africa
Email: leone.malan@nwu.ac.za
Tel: +27 18 299 2438
Fax: +27 18 299 1053

Abstract

Objectives: Defensive coping (AC) responses in urban African males have been associated with vascular responsiveness, partly explaining autonomic nervous system dysfunction. We therefore aimed to assess whether AC responses facilitate higher blood pressure and early sub-clinical structural vascular disease via alterations in frequency- and time-domain heart rate variability (HRV) responses.

Methods: We included 355 African and Caucasian men and women without pre-existing atrial fibrillation, aged 45 ± 9 years. Significant interaction on main effects (coping x ethnicity x gender) for left carotid intima media thickness far wall (L-CIMTf) and cross sectional wall area values necessitated selection of AC responders above mean via the Coping Strategy Indicator. We collected B-mode ultrasound L-CIMTf, ambulatory BP and –HRV data. Overnight fasting blood was obtained.

Results: Overall Africans and AC Africans, mostly men, revealed ($P \leq 0.05$) a poorer lifestyle profile, higher prevalence of hypertensive status, disturbed sympathovagal balance and depressed HRV temporal and geometric patterns compared to the Caucasians. Moderately depressed non-linear and time-domain HRV (SDNN <100 ms) was prevalent in 28% of Africans compared to 11% of Caucasians. A similar trend was shown for the AC African participants (32%) compared to Caucasians (16%). Only time-domain depressed HRV (SDNN: adj. R^2=0.34; β=-0.24; p=0.08) and vagal-impaired heart rate responses (RMSSD: adj. R^2=0.28; β=-0.28; p<0.05) were associated with higher blood pressure and early structural vascular changes in AC African men.

Conclusion: Defensive coping facilitated autonomic nervous system dysfunction, which was associated with higher blood pressure and sub-clinical structural vascular disease in an African male cohort.

Keywords: Coping, ethnicity, autonomic function, sub-clinical vascular disease

1. Introduction

Heart rate variability or oscillation in the interval between consecutive heart beats has considerable potential to assess the function of the autonomic nervous system in health, cardiovascular and non-cardiovascular disorders [1-3]. Signs of either increased sympathetic or reduced vagal activity (sympathovagal imbalance) have encouraged the use of frequency- and time-domain 24-hour ambulatory ECG recordings [4]. Depressed heart rate variability (HRV) have been associated with increased sympathetic activity, systemic inflammatory responses, and blunting of circadian patterns [5,6] and are commonly observed in participants with chronic psychosocial stress and depression [7]. Furthermore, increased vascular responsiveness and hypertension have been well documented in urban Africans and have mostly been ascribed to psychosocial stress and associated lifestyle changes [8]. Chronic psychosocial stress in African Americans was also shown to be responsible for a ~40% prevalence of mild to moderate hypertension as well as for cardiovascular disease risk [9,10].

In particular, high defensive problem-solving active coping (AC) and not low AC or avoidance, loss of control (passive coping) responses in urban or city dwelling, African men demonstrated pathology [11]. Dissociation between ß-adrenergic behavioural being-in-control and physiological cardiometabolic responses was observed [8,11]. The physiological responses of AC African males resembled a vascular α-adrenergic “loss of control” and endothelial dysfunction profile [8,11]. Whether similar dissociated AC responses in bi-ethnic gender groups will facilitate alterations in autonomic function and early structural vascular changes in the carotid intima media, still needs to be determined.

A lack of knowledge concerning environmental influences and emotional circumstances such as appraisal of stress in black African and white African (Caucasians) gender groups on HRV also emphasizes the need for an investigation [2]. Therefore the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study is ideally suited and designed for investigating HRV, as participants are drawn from the same occupation with similar working conditions within a well-controlled setting. Our principal aim was to assess whether AC facilitates higher blood pressure and early sub-clinical vascular disease via alterations in frequency- and time-domain heart rate variability in a Black (African) vs. a Caucasian gender cohort from South Africa.

2. Methods

2.1 Study Population

The SABPA study has a target population comparative design and was conducted from February 2008 until May 2009. We recruited 409 teachers, aged 25-65 years, working in the Dr Kenneth Kaunda 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. Exclusion criteria included pregnancy, lactation, psychotropic substance users, ear temperature >37.5°C, vaccination or blood donation within 3 months prior to participation. For purposes of our sub-study, we additionally excluded participants with atrial fibrillation (N=16), anxiolytic (N=1) and beta-blocker (N = 6) medication users, HIV positive status (N=19) and clinically diagnosed diabetes (N=13). The final sub-sample comprised 162 Africans and 193 Caucasians.

The SABPA study abided by the institutional guidelines and terms of the Declaration of Helsinki (2008) and was approved by the Ethics Review Board of the North-West University, Potchefstroom Campus (0003607S6). The nature, benefits, and risks of the study were explained to the participants, and their written, informed consent was obtained before participation.

2.2 Research procedure

Ambulatory cardiovascular apparatus and physical activity meters were applied between 0700h to 0800h every morning of the working week. At 1630h participants were transported to the Metabolic Unit Research Facility of the North-West University for an overnight stay in a relaxed, well-controlled setting. They were familiarized with the experimental setup and commenced with the psychosocial battery at 1800h under supervision of registered clinical psychologists. Participants were advised to go to bed at 2200h, fasting overnight. At 0545h they were woken

and the 24-hour apparatuses disconnected and anthropometric measures taken. A battery of clinical assessments followed with participants in semi-recumbent position for the resting 12-lead electrocardiogram (ECG) and venous blood sampling by a registered nurse and medical doctor. General health questionnaires were completed.

2.3 Life style confounders

Anthropometric measurements were taken in triplicate by registered anthropometrists. Body weight was measured with a digital Beurer scale (Model: Typ PS 07, GmBH, Germany) to the nearest 0.1 kg with the participant wearing minimal clothing and with the weight evenly distributed. Height was measured to the nearest 0.1 cm while the participant's head was in the Frankfort plane, heels together and buttocks as well as upper back touching the stadiometer (Invicta Stadiometer, IP 1465, UK). Body surface area (BSA) was calculated with the Mosteller formula. The Actical® (Mini Mitter, Bend OR, Montréal, Québec), an omnidirectional accelerometer monitor, was used to assess physical activity over 24 hours by taking into account the metabolic rate (kcal/h). Serum cotinine levels, a metabolite of nicotine, were used as a marker of smoking status where > 15 µg/L was regarded as being indicative of a smoker [12]. Gamma glutamyl transferase (GGT) was used as a marker of alcohol abuse (≥ 65 u/L for men and ≥ 45 u/L for women) [13].

2.4 Cardiovascular assessment procedures

The validated Cardiotens CE120® (Meditech, Budapest, Hungary) measured 24-hour blood pressure and –ECG. We applied suitable cuffs on the non-dominant arm and the Cardiotens oscillometrically measured blood pressure at 30-min intervals during the day (0800-2200 hours) and 60-min intervals at night (2200–0600 hours) [14]. Successful mean 24h inflation rate was

79.2% and the 24-hour ambulatory ECG was assessed by two channel ECG recordings according to a pre-set program for 20 s at 5-min intervals. Participants were requested to continue with normal daily activities and record on their diary cards any abnormalities such as visual disturbances, headache, nausea, fainting, palpitations and stress. The data was analysed using the CardioVisions 1.19 Personal Edition software (Meditech, Budapest, Hungary).

Frequency- and time-domain analyses were applied to assess spontaneous oscillations resulting from sinus node depolarization obtained from ~3.5 hours of analysable ambulatory ECG data. The software program automatically filtered out ventricular, supraventricular as well as artifacts in RR intervals, and HRV outliers had been manually removed.

Fast Fourier transformation performed frequency-domain analysis identifying the components in absolute (ms^2) and normalized units (nu) for high frequency (HF), low frequency (LF) and the LF/HF ratio. The LF/HF ratio is indicative of sympathovagal balance [2].

Time-domain analyses included measures of SDNN and RMSSD. SDNN is a prognostic tool for cardiovascular outcome and defined as the standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes, which equal the square root of variance. Since variance is mathematically equal to the total power of spectral analysis, the SDNN reflects all cyclic components responsible for variability in the period of recording. SDNN is regarded as the best overall prognostic tool for values <50 ms are indicative of highly depressed HRV, those between 50-100 ms indicate moderately depressed HRV and those >100 ms are classified as normal [1]. RMSSD, the root mean square of successive differences between adjacent RR intervals is closely related to the high frequency (HF) component of the power spectrum [3]. Both SDNN and RMSSD reflect vagus nerve-mediated autonomic control of the heart.

Geometrical analyses included the HRV triangular index (HRVti), which is an index of the pulse variability based on a triangular interpolation method in the given time interval where

cardiovascular risk 0-15 is high; 15-20 is mid; >20 is low. Including only ~3.5 hours of analysable ambulatory ECG data for HRVti might be restrictive and 24h recordings should have been more appropriate [1]. Non-linear analyses were furthermore recorded by plotting each RR interval of a sinus beat as a function of the previous one for a predetermined segment length (Poincaré or Lorenz return maps/plots). Quantitative analyses of these plots are associated with non-linear 5 minutes beat-beat- variability (SD1) and long-term 24h RR-interval variability (SD2) [5,6].

2.5 Subclinical vascular disease indicators

High resolution ultrasound was applied to determine structural vascular changes as reflected by intima-media thickness in the common carotid artery (CIMT) [15]. Standardized images [16] of the left and the right common carotid artery were obtained, from at least two optimum angles using a Sonosite Micromaxx ultrasound system (SonoSite Inc., Bothell, WA, USA) and 6 - 13 MHz linear array transducer. The images were digitized and imported into the Artery Measurement Systems automated software (AMS) II v1.139 (Gothenburg, Sweden). The far wall of a 10 mm segment, 1 cm distal of the carotid bulb, was chosen for CIMTf analysis [16]. The software automatically identifies the borders of the far wall intima and media by echo tracking and then calculates the CIMT and the inner diameter of the vessel as the mean of 100 discrete measurements throughout the entire segment. The cross sectional wall area (CSWA) measures the luminal diameter and was calculated from CIMT using the following equation: $CSWA = \pi (d/2 + CIMT)^2 - \pi (d/2)^2$, where d denotes luminal diameter. Intra-observer variability was 0.04 mm between two measurements made four weeks apart on 10 participants.

2.6 The Coping Strategy Indicator Questionnaire

The CSI is a 33-item self-report measure of coping responses with construct, convergent and discriminant validity [17] Cronbach's alpha (α) reliability coefficients were determined for the three subscales of 11 items each in each ethnic and gender group and ranged between 0.81- and 0.87 for AC, 0.61- and 0.85 for avoidance and 0.83- and 0.90, for seeking social support. An AC strategy implies actively solving problems, being-in-control and accepting the stressor as reality; seeking social support implies an active process focused on acquiring comfort and advice in stressful times and lastly, emotional avoidance or loss of control implies defeat, with physical and psychological withdrawal. Responses were rated on a three-point Likert scale: a lot (3), a little (2), or not at all (1), with in mind a recent stressful event.

2.7 Biochemical measurements

Fasting plasma and serum samples were prepared according to standardized procedures and stored at - 80°C until analysis. Thyroid stimulating hormone (TSH), cholesterol, γ-GT, cotinine and ultrahigh-sensitivity C-reactive protein (Hs-CRP) were analyzed from serum using two sequential multiple analyzers (Konelab 20i; Thermo Scientific, Vantaa, Finland; Unicel DXC 800 – Beckman and Coulter®, Germany).

2.8 Statistical analyses

Statistical analyses were performed with the software package Statistica 10 (StatSoft, Inc., USA). Normal distribution was evident when standard errors of kurtosis and skewness did not exceed the value itself by twofold. Logarithmical transformation was deemed appropriate for CRP and γ-GT. Data are presented as mean ± standard deviation or percentages unless stated

otherwise. Continuous variables were compared using Student *t* tests for independent samples. Chi-square tests were applied to compare proportions (%). We followed the 2007 guidelines of the European Hypertension Society and adjusted for *a priori* covariates age, BSA and lifestyle factors (log γ-GT, cotinine and physical activity). Analyses of covariance (ANCOVA), adjusted for *a priori* covariates, was performed for HRV and sub-clinical vascular disease risk markers to test significant interaction on main effects between coping, ethnicity and gender. Interaction effect analyses were repeated for each of the three dichotomised coping strategies using the following mean cut points: AC (≥ 26), avoidance (≥19) and social support (≥ 23) [17]. The reason for this approach was to select the most appropriate group for further analyses.

Subsequently, one-way ANCOVAs were applied to compare coping groups by gender and ethnicity, adjusting for *a priori* covariates. Multiple linear regression analyses in AC ethnic-gender groups were performed. Stepwise regression analyses were computed in separate frequency- and time-domain models to avoid co-linearity. Firstly, the best predictors for systolic (SBP) and diastolic blood pressure (DBP) were assessed and included HRV markers, *a priori* covariates and TSH. Secondly, we computed models to assess the association between CIMTf and CSWA including predictor variables, i.e. HRV, *a priori* covariates, log CRP, cholesterol and BP. The models in females were additionally adjusted for TSH and estradiol. We additionally applied a non-linear technique to assess HRV with the so-called Poincaré map (return or Lorenz map) [5] in AC African men and in AC African men with depressed HRV. Statistical significance was defined as a two-sided α level of 0.05 or less.

3. Results

3.1 Baseline characteristics of study participants

In Table 1, Africans demonstrated lower BSA and physical activity (P≤ 0.05). They had lower serum cholesterol and TSH levels albeit higher γ-GT and estradiol levels compared to Caucasians. Furthermore they exhibited a hypertensive ambulatory BP, -HR and higher heart rate profile. The Africans also reported on using less avoidance and more social support coping responses than the Caucasians.

3.2 Comparing cardiovascular risk and HRV in AC Africans and Caucasians

A significant three-way interaction (AC x ethnicity x gender) was revealed for CIMTf (F (1, 355), 4.02; P = 0.05) and CSWA (F (1,317), 5.21; P = 0.02). Furthermore, an interaction only existed between AC x ethnicity for SDNN (F (1,355), 3.86; P = 0.05). No significant interactions existed for avoidance and/or social support coping strategies pertaining to any of the atherosclerotic risk markers. This necessitated selection of only participants above mean (cut off 26) AC, within each ethnic and gender group (Tables 2-3; Figures 1-2). High preference for seeking social support and a low avoidance score were viewed as supportive of AC responses.

In Table 2, cardiovascular risk was more pronounced in AC Africans than in AC Caucasians. Africans demonstrated increased prevalence of elevated CRP (>3 mg/L) and BP (>125 and/or 80 mmHg), indicating risk [15], coupled with higher HR. Their cardiovascular risk is further supported by a profile of autonomic dysfunction with frequency-domain disturbed sympathovagal balance (LF/HF), i.e. lower LF and higher HF. Additionally, time-domain (SDNN, RMSSD) and geometric (HRVti) depressed HRV patterns were also apparent in the AC Africans compared to their counterparts (P ≤ 0.05).

AC African females demonstrated higher CIMTf and CSWA values compared to their Caucasian counterparts (P ≤ 0.01) albeit lower than seen in the AC men. Both AC African gender groups reported using less avoidance coupled with higher social support coping strategies (P ≤ 0.01).

In Figure 1, 27.72% of all Africans, (32.34% of AC African men and 31.17% of AC African women) demonstrated moderately depressed HRV prevalence (SDNN, 50-100 ms) compared to 10.89, 15.85 and 9.52% of their Caucasian counterparts respectively. Figure 2 demonstrates a dispersed complex-like Lorenz map (SD2) in moderately depressed AC African males (Figure 2a) despite SD1 not being demonstrated. In Figure 2b, HRVti risk is revealed in an AC African male with moderately depressed HRV (84 ms) [5]. Partial correlations showed inverse associations (P ≤ 0.05) between HRV responses and γ-GT in AC Africans (r = -0.28, P ≤ 0.05) (*data not shown*).

3.3 Autonomic dysfunction, BP and subclinical structural vascular disease risk in AC Africans

In Table 3, frequency-domain HRV markers did not enter any of the regression analyses models. Inverse associations were demonstrated between 24-hour BP and time-domain HRV measures (SDNN and RMSSD) only in the AC African men. This was supported by inverse associations between subclinical vascular disease risk and depressed HRV (ß = -0.24, 95% CI, -0.51 to -0.03; p = 0.08) and vagal-impaired heart rate, RMSSD [CIMT (ß = -0.27, 95% CI, -0.56 to -0.02; p = 0.07) and CSWA (ß = -0.28, 95% CI, -0.55 to –0.01; p = 0.05)] in these men.

4. Discussion

Our aim was to assess whether AC facilitates higher BP and early sub-clinical vascular disease via alterations in temporal-, frequency-, geometric and non-linear HRV patterns in Africans compared with Caucasians from South Africa. The main finding revealed a more vulnerable cardiovascular risk profile in Africans, especially in AC men. Furthermore, depressed HRV and a vagal-impaired HR were associated with ambulatory BP as well as early sub-clinical structural vascular disease risk in AC African men only.

4.1 A vulnerable cardiovascular profile in Africans

The Africans demonstrated a higher prevalence of hypertensive status [mean 24-hour SBP and DBP] compared to Caucasians. These levels may be linked to abnormalities in sympathetic nervous system (SNS) regulation of the cardiovascular system and impairments in vascular function [18,19]. Whether autonomic dysregulation is a cause or consequence of cardiovascular disease process, is strongly debated [20] as an increased SNS hyperactivity has previously been demonstrated in Africans [8] as well as in African Americans [9].

4.2 Coping responses facilitate autonomic dysregulation

When coping responses were taken into consideration the depressed HRV profile was more obvious in the African groups, and particularly in the men. A possible autonomic dysregulation in the current investigation in urban Africans was substantiated by a smaller frequency-domain LF/HF ratio, depressed temporal (SDNN, RMSSD), geometric (HRVti) and non-linear (Poincaré: SD2 plot) HRV measures in the AC Africans. Their increased blood pressure could facilitate a shift from a predominant cardiac output-driven hemodynamic pattern to a high vascular resistance pattern, with alterations in the structure and responsiveness of the heart and blood

vessels. Indeed, we have previously demonstrated a decreased cardiac output and arterial compliance in AC African males, implying a possible diminished ß-adrenergic responsiveness [19]. Furthermore, a decrease of cardiac output implies an increase in vascular resistance with possible development of vascular hypertrophy [10]. When low sympathetic tone and vascular hyperresponsiveness coincide, less sympathetic drive is needed to maintain blood pressure [18]. This mechanism seems to support recent findings in the SABPA study where attenuated resting baroreceptor sensitivity and decreased arterial compliance predicted elevated ambulatory SBP and DBP in African men [21]. In these African men, α-adrenergic cardiovascular responses to stress predicted ECG structural left wall abnormalities [21].

In the current study, depressed HRV was associated with increased parasympathetic dominance albeit cardiac contractility (24-hour HR and SBP) in the AC African men rather suggesting ß-adrenergic receptor activation [18]. Conversely, increased SNS activity and a possible vagal-impaired HR profile may contribute to disturbed endothelial function, possibly because of activation of ß-adrenergic receptors [22]. When α-adrenergic responsiveness though prevails, [8,18,21] dysregulation or desensitisation of ß-adrenergic receptors may occur. The clustering of increased SBP, HR and depressed HRV values may indicate a possible diminished ß-adrenergic responsiveness and vagal-impaired response. A plausible explanation may be that depressed HRV as a reflection of α-adrenergic sympathetic overdrive could also be due to poor ventricular performance as observed in African men [21].

Additional support for reduced perfusion of the heart could be the high prevalence of silent ischemic events over 24 hours in the AC African men i.e., 9.5 events (95% CI, 5.1 – 14.0) compared to 1.5 (-2.4 – 5.3) in AC Caucasian men [8]. Structural vascular changes could counteract sympathetic vasoconstriction and may contribute to stress-induced ischemia which

impairs neuronal re-uptake of norepinephrine thereby potentiating sympathetic signalling [23-25]. When essential hypertension and increased SNS activity, i.e. sympathovagal disturbance and depressed HRV prevail, as seen in AC African men, structural vascular changes may elicit occurrence of ischemic events [8] and thereby reduced perfusion of the heart. The dispersed complex Poincaré plot pattern of moderately depressed AC African men may support above findings. Excessive fluctuations in the HRV intervals were apparent, which have been directly related with cardiovascular risk [1,2,6].

Meta-analysis on HRV and neuro-imaging studies implicated HRV as a marker of stress and health [3]. Our findings compliment this notion as depressed HRV and early structural vascular changes in African men seem to be facilitated by a defensive coping pathway, supported by less avoidance and more social support seeking coping responses. Facilitated defensive coping in rodents and humans have been implicated in maladaptive amygdala-striatal interactions [24], vascular hyperresponsiveness, metabolic dysregulation and the development of essential hypertension [8,18,25]. It is also assumed that the pathways subserving the defense responses become markedly facilitated in essential hypertensives and hyperresponsiveness of the SNS becomes greater than in normotensives [24,25].

4.3 Contributing factors to autonomic dysregulation in urban Africans

Previous findings revealed that a demanding individualistic urban environment may contribute to chronic stress [8,11,23] where an ethnic group with a collectivistic orientation [11] may not be able to exert control [26-29]. Conversely, it is also not clear why depressed HRV predicted SBP only in the AC African men and not in the AC African women as the same argument holds pertaining to a collectivistic nature [26]. Maybe two other important factors can indirectly address

this issue, namely γ-GT and estradiol. Firstly, the effect of alcohol to induce depressed HRV has been demonstrated [28] and was evident in partial regressions ($r = -0.28$; $P \leq 0.05$). The apparent abuse of alcohol in our AC African males revealed γ-GT levels of 77.58 ± 79.10 u/L thereby exceeding upper normal limits > 65 u/L [13]. By using γ-GT as measure of alcohol abuse may be limiting, seeing that e.g. fatty liver disease and oxidative stress cannot be ruled out [13]. Supportive evidence for γ-GT as behavioural adjustment to psychosocial stress in Africans was demonstrated ($P \leq 0.05$) [7]. Hamer et al. [7] showed that the odds of early structural vascular changes (≥ 0.9 mm CIMT) based on high γ-GT levels were 3.1 (95% CI; 0.6 – 15.5) in the African men, independent of other confounders. It is possible that alcohol abuse is utilized as a coping strategy in the African male [27-29]. Secondly, estradiol levels were significantly increased in AC African men compared to their Caucasian counterparts. Estradiol has a vasodilatory and cardiovascular protective function [30] and could possibly explain the resilience in the AC African females who are still relatively young. In the AC African men, α-adrenergic vascular hyperreponsiveness and depressed HRV may up-regulate estradiol as a homeostatic protective factor in emotional demanding situations [3] attenuating the central stress responses in the thalamus, amygdala, prefrontal cortex, paraventricular hypothalamic nuclei and brainstem areas.

4.4 Limitations and recommendations

The cross sectional design of the study cannot infer causality. Non-linear advanced neural network analyses [31] may support non-linear beat-beat- variability (SD1) and long-term RR-interval variability (SD2) measures in larger prospective cohort samples. In addition, as we did not compare participants from urban and non-urban environments in the present study, it is difficult to firmly conclude that inadequate coping behaviours in African men are entirely explained by the urban environment. Nevertheless, our previous findings [7,8,11] that compared

rural vs. urban environments did demonstrate pathology related to AC behaviour in an urban environment. Since the study population consisted of teachers from the Dr Kenneth Kaunda Education District using a target comparative sample, the present results might not be representative of all urbanised black Africans.

In conclusion, experiencing emotional stress is assumed to create strong demands on a central control system. Sufficient mental energy for the processing of thought and actions is lacking under stress, resulting in possible distorted reasoning and a breakdown of control [23]. Seemingly, AC African men may experience this in a too demanding individualistic urban environment where control cannot be exerted. Subsequently, an AC behavioural ability fails with apparent loss of physiological control or *neural fatigue*, emphasizing previous findings on dissociation between behavioural and physiological control [8,11,23]. Ultimately, defensive responses facilitated autonomic dysfunction acting as a hyperkinetic driving force for increased ambulatory blood pressure, early sub-clinical vascular changes and an emerging pathway for structural vascular disease risk in African men.

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Author contributions

Prof Malan (Principal Investigator) had full access to the data and takes responsibility for the integrity of the data and accuracy of the statistical analyses. All authors contributed to the concept and design of the study, drafting and critical revision of the manuscript.

Conflict of interest

None

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Table 1

Baseline characteristics (mean ± SD) by ethnic status.

Variables	Africans (N = 162)	Caucasians (N = 193)	P values
Confounders			
Age, years	44.28 ± 8.01	44.92 ± 10.86	0.49
Sex (males %)	162 (46.51)	193 (47.76)	0.83
Body surface area, m^2	1.92 ± 0.23	2.11 ± 0.28	<0.001
Body mass index, kg/m^2	30.13 ± 7.01	27.61 ± 5.94	<0.001
Physical activity, kcal/h	2682.37 ± 795.41	3112 ± 1596.54	<0.001
Cotinine, ng/mL	27.24 ± 60.94	22.71 ± 77.47	0.51
γ-Gluthamyl transferase, u/L	66.34 ± 82.39	26.91 ± 33.91	<0.001
Coping responses, scores			
Defensive active coping	28.15 ± 4.09	28.83 ± 3.87	0.08
Social support	25.67 ± 5.01	18.76 ± 4.79	<0.001
Avoidance	21.07 ± 3.78	24.00 ± 5.16	<0.001
Cardiovascular measures			
Estradiol, pmol/l	207.48 ± 314.35	162.64 ± 260.16	0.36
C-reactive protein, mg/L	8.51 ± 10.51	3.09 ± 3.88	<0.001
Cholesterol, mmol/L	4.60 ± 1.19	5.54 ± 1.28	<0.001
24h SBP, mmHg	133 ± 16.18	124 ± 12.04	<0.001
24h DBP, mmHg	84 ± 10.70	77 ± 8.04	<0.001
24h Heart rate (HR), bpm	80 ± 10.73	74 ± 10.17	<0.001
12-lead ECG HR, bpm	67.86 ± 12.9	65.51 ± 11.2	0.05

TSH, µIU/mL	2.12 ± 2.22	2.71 ± 2.98	0.05
Hypertensive, N (%)	137 (84.57)	102 (52.85)	<0.001
Medications			
Hypercholesterolemia, N (%)	2 (1.23)	9 (4.67)	0.05
Hypertension, N (%)	43 (26.54)	18 (9.33)	<0.001

1 Data are presented as mean ± SD or number of participants (%). Abbreviations: TSH - Thyroid
2 stimulating hormone.

Table 2

Defensive active coping (AC) cardiovascular and heart rate variability (HRV) responses in African vs. Caucasian gender groups.

	AC African Males (N = 61)	**AC Caucasian Males (N = 79)**	**AC African Females (N = 60)**	**AC Caucasian Females (N = 77)**
Unadjusted cardiovascular markers potentially affecting the endothelium				
γ-GT, u/L	77.58 ± 79.10	29.95 ± 21.85**	47.73 ± 79.72	21.35 ± 42.02**
Estradiol, pmol/l	95.33 (85.1,105.6)	71.76 (63.0,80.5)**	318.85 (232.4,404.3)	203.16 (127.6,278.7)
Cholesterol, mmol/L	4.77 (4.5,5.1)	5.53 (5.3,5.8)†	4.46 (4.1,4.8)	5.43 (5.2,5.7)**
C-reactive protein, mg/L	5.80 (4.1,7.5)	1.59 (0.1,3.1)†	12.29 (10.2,14.4)	4.47 (2.6,6.3)**
Adjusted cardiovascular and coping markers				
24h SBP, mmHg	139 (135,142)	126 (123,129)**	126 (123,129)	120 (117,123)**
24h DBP, mmHg	89 (86,91)	78 (76,80)†	77 (76,79)	74 (73,76)*
24h Heart rate, bpm	79 (76,82)	71 (69,74)†	78 (76,81)	75 (73,77)
12-lead ECG HR, bpm	69.33 (65.5,73.2)	61.19 (57.9,64.5)**	66.27 (63.6,68.9)	67.76 (65.4,70.1)
TSH, µIU/mL	2.45 (2.1,2.8)	2.12 (1.8,2.4)	2.01 (1.1,2.9)	3.41 (2.6,4.2)*
CIMTf, mm	0.70 (0.66,0.74)	0.68 (0.64,0.71)	0.66 (0.6,0.7)	0.60 (0.58,0.63)**
CSWA, mm^2	15.59 (14.5,16.7)	14.74 (13.8,15.7)	12.94 (12.3,13.6)	11.61 (11.0,12.2)**

Time domain HRV markers				
SDNN, ms	114.93 (101.8,128.1)	165.51 (154.4,176.7)***	115.27 (104.4,126.2)	137.15 (125.2,149.1)*
RSSD, ms	27.67 (22.6,32.7)	42.21 (37.9,46.5)**	35.71 (30.8,40.6)	33.86 (29.7,38.0)***
HRVti	28.18 (25.0,31.3)	40.71 (38.0,43.4)***	32.10 (29.6,34.6)	36.23 (34.1,38.4)*
Frequency domain HRV markers				
LF, ms^2	663.29 (425.7,900.9)	1757.14 (1558.6,1956.7)***	715.91 (575.6,856.3)	872.48 (753.3,991.7)
LF, n.u.	69.94 (66.9,72,9)	77.56 (75.0,80.1)***	60.65 (57.8,63.5),	69.85 (67.5,72.2)***
HF, ms^2	363.81 (222.3,505.3)	363.81 (222.3,505.4)	433.25 (341.3,525.2)	387.69 (309.6,465.7)
HF, n.u.	27.68(25.1,30.4)	20.39 (18.1,22.7)***	35.18 (32.6,37.8)	27.83 (25.6,30.0)***
LF/HF ratio	3.06 (2.4,3.7)	4.59 (4.07,5.1)***	1.95 (1.6,2.3)	2.96 (2.7,3.3)***
Coping Strategy Indicator				
Defensive active coping	30.06 (29.4,30.8)	30.53 (30.1,31.1)	30.21 (29.7,30.8)	30.07 (29.6,30.6)
Social support	25.56 (24.1,27.0)	17.43 (16.2,18.7)**	26.52 (25.3,27.7)	19.17 (18.1,20.2)**
Avoidance	20.84 (19.6,22.1)	24.60 (23.6,25.7)**	20.88 (19.6,22.2)	25.06 (23.8,26.0)**

Values depicted as mean (95% confidence interval) and proportions as N (%) and adjusted for *a priori* covariates including age, body surface area (BSA), physical activity, log γ-GT and cotinine. Abbreviations: CIMTf - carotid intima media thickness far wall; CSWA – cross sectional wall area; SDNN - standard deviation of normal RR intervals; RSSD - root mean square of successive differences; HRVti - Heart rate variability triangular index: pulse variability based on the triangular interpolation geometrical method in a given time

interval; LF – low frequency; HF – high frequency. Superscript symbol denotes significance for: *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.

Table 3

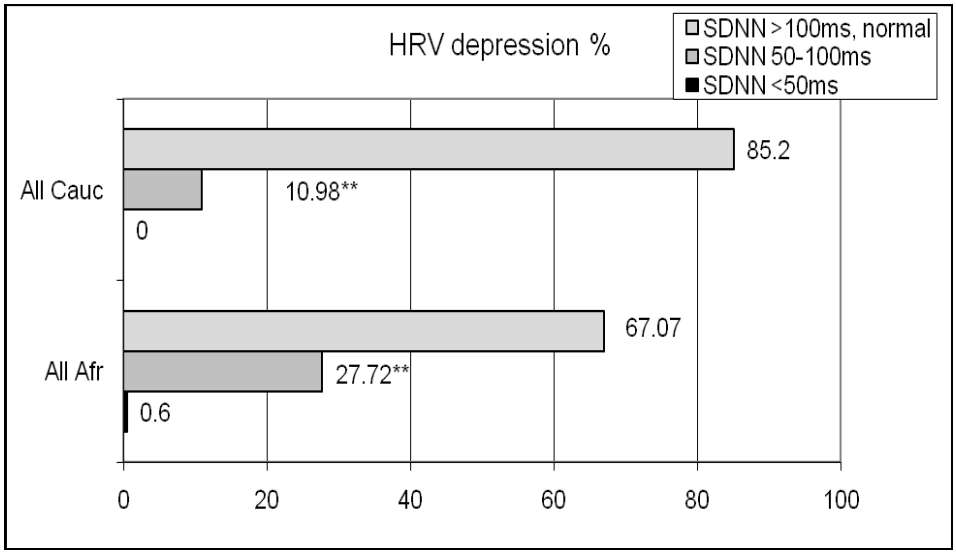
Forward stepwise associations between dependent variables ambulatory BP, structural vascular disease and HRV measures in Africans, as well as defensive active coping (AC) African men.

		All Africans (N = 157)			
		24h SBP (mmHg)	**24h DBP (mmHg)**	**CIMTf (mm)**	**CSWA (mm)**
	Adjusted R^2	**0.20**	**0.13**	**0.26**	**0.30**
		β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
SDNN		NS	NS	NS	NS
	Adjusted R^2	**0.19**	**0.13**	**0.21**	**0.20**
RSSD		NS	**0.17 (0.14,0.31)***	NS	NS
		AC African males (N=59)			
	Adjusted R^2	**0.41**	**0.35**	**0.34**	**0.36**
SDNN		**-0.26 (-0.5, -0.02)***	**-0.27 (-0.51, -0.03)***	**-0.24 (-0.51, 0.03)††**	NS
	Adjusted R^2	**0.36**	**0.34**	**0.21**	**0.28**
RSSD		**-0.33 (-0.60, -0.11)***	**-0.27 (-0.49, -0.05)***	**-0.27 (-0.56, 0.02)†**	**-0.28 (-0.55,-0.01)***

ß denotes standardized regression coefficient. Covariates for models included age, BSA, physical activity, cotinine, log γ-GT and TSH. Structural vascular disease models were additionally adjusted for log CRP, cholesterol and mean 24h blood pressure.

Abbreviations: SDNN - standard deviation of normal RR intervals; RSSD - root mean square of successive differences. Superscript symbol denotes significance for: *p ≤ 0.05; †p ≤ 0.07; ††p ≤ 0.08.

1a



1b

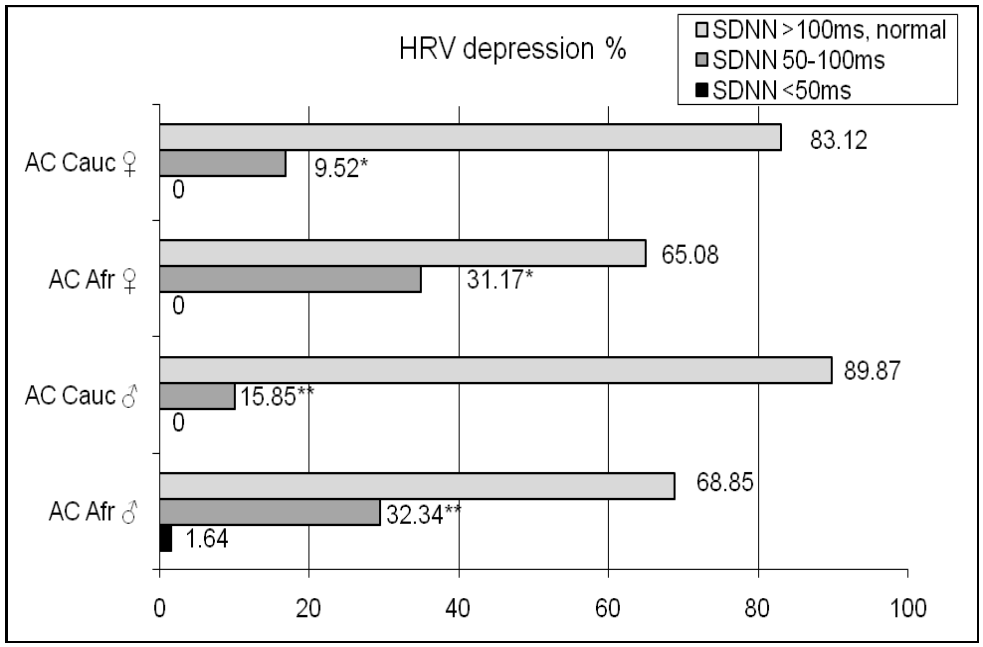


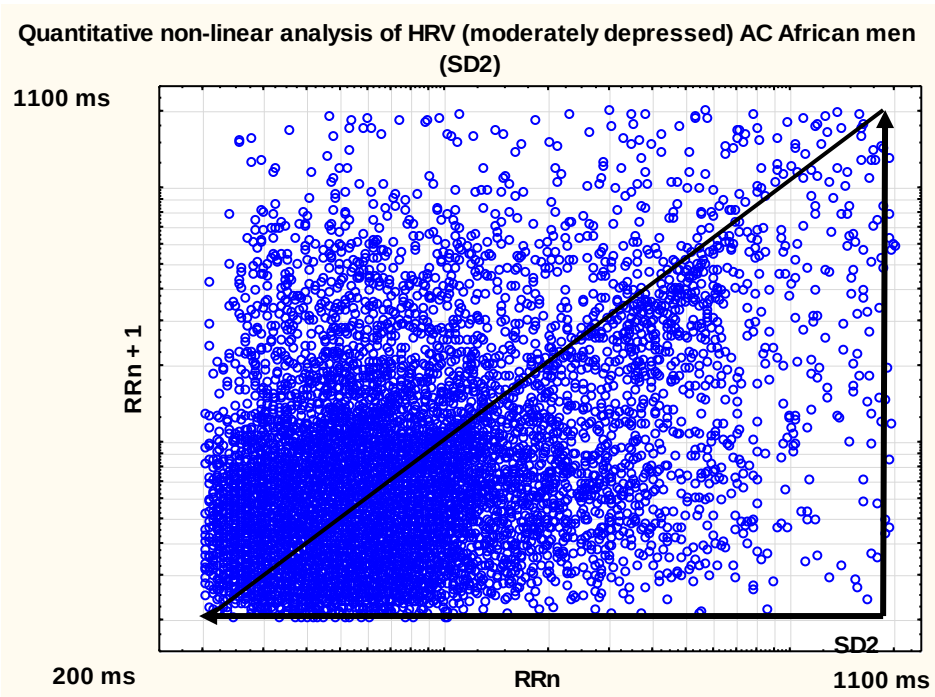
Figure 1

Comparing HRV depression prevalence in Africans and Caucasians (Fig 1a) and in Defensive coping ethnic-gender groups (Fig 1b). Abbreviations: SDDN - standard deviation of the normal-

to-normal (NN) intervals between adjacent QRS complexes. Superscript symbol denotes significance for: *p ≤ 0.05; **p ≤ 0.01.

1

2a



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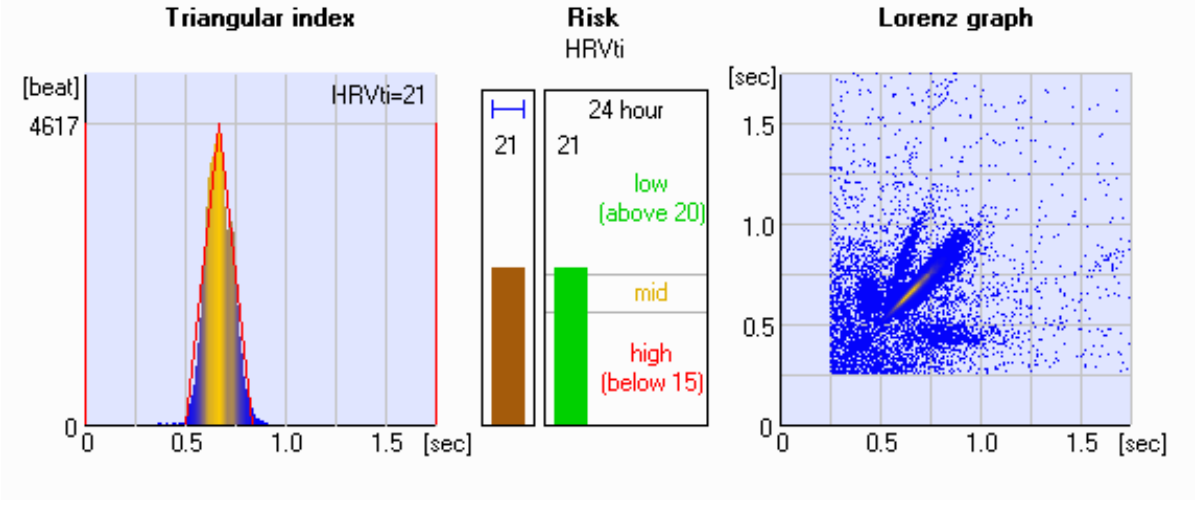

2

3 **Figure 2**

4 Poincaré plot non-linear analysis (SD2) in a) moderately depressed HRV (SDNN, 50-100 ms)
5 AC African men (N=19), and b) an example of an AC African male revealing moderate
6 cardiovascular risk (HRVti 15-20) (N=1).

1