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Greater cardiovascular reactivity to a cold pressor test is due to higher cold pain perception in Black Africans: the SABPA study

Short title: cold pain and cardiovascular regulation

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Abstract

Problem: To evaluate the role of pain perception and pain stimulus components for blood pressure responses to stress in the Black African population.

Methods: Cardiovascular regulation of hypertensive Black (n=110) and Caucasian (n=95) Africans was studied during a cold pressor test. Perception of stressfulness of the task which was considered equivalent to a rating of cold pain was assessed on a 7-point Likert scale. Chronic stress level was evaluated by the General Health Questionnaire and the Coping Strategy Indicator was used to assess individual coping behavior.

Results: The cold pressor test elicited significant blood pressure elevations with higher relative increases in the Black Africans. The higher blood pressure reactivity in the Blacks was accompanied by a substantially greater cardiac response as compared to the Caucasians. The Black Africans also reported higher chronic stress levels and rated the task as more painful than the Caucasians. A significant interaction was observed for cardiovascular responses with pain perception but not with chronic stress. A significant smaller proportion of Black than Caucasian Africans used both problem- and emotion-focussed coping.

Conclusions: A steeper rise in heart rate in the Black Africans indicates greater pain-related increments in blood pressure. Ethnic differences in cognitive appraisal of pain may contribute to a higher blood pressure reactivity in Black Africans.

Key words: cardiovascular reactivity; cold pressor test; pain; coping; stress; ethnicity

Introduction

African ethnicity per se is a risk factor for hypertension [1]. Numerous studies have been devoted to elucidate this ethnic phenomenon with several hypotheses arising from it [2]. One has been the stress reactivity hypothesis describing that exaggerated vascular reactivity to stress is antecedent to the development of hypertension [3,4]. It has been proposed that chronic psychosocial stress like perceived discrimination, urbanization or lack of social support act via activation of the sympathetic nervous system as mediator of an increased pressor sensitivity in the Black population [5,6,7]. However, clear-cut evidence for this threefold interaction is scarce as is the pathogenetic role of the autonomic nervous system as stress integrating component in Black hypertension.

Thomas et al reported that low decisional control was related to increased blood pressure reactivity and elevated norepinephrine levels in Black but not in White Americans [8]. Similar results were demonstrated in Black African men with passive coping style [9]. In a recent study the level of psychosocial distress was unrelated to cardiovascular stress reactivity in normotensive Black and Caucasian Africans [10]. In that study the cardiovascular response to physical but not to mental stress was increased in the Blacks. This increased cardiovascular response was related to higher ratings of stress to a cold pressor test (CPT) indicating ethnic differences in pain perception and processing. Although unequivocal evidence exist that pain threshold is elevated in hypertension and in normotensive individuals at high risk for hypertension [11] the role of pain perception for ethnic differences in cardiovascular reactivity and pathogenesis of hypertension remains to be delineated.

To investigate the interrelationship between hypertension, cardiovascular reactivity and pain perception to a cold pressor test we analyzed and compared data of 205 hypertensive

Black and Caucasian Africans from the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study.

Methods

Study population and Ethics

A hypertensive subsample comprising of 110 urban Black and 95 urban Caucasian African teachers was drawn from the SABPA study (n = 409) conducted between February 2008 and May 2009 [12]. Criteria for selection of the subsample are depicted in figure 1. All study participants were working for the Dr. Kenneth Kaunda Education District of the North-West Province, South Africa and thus of comparable social economic background. Exclusion criteria were an oral temperature ≥ 37.5 °C, use of alpha and beta blockers, psychotropic substance dependence or abuse, blood donors and individuals vaccinated in the past 3 months. Participants were fully informed about the objectives and procedures of the study prior to their enrolment. Assistance was available for any participant who requested conveyance of information in their home language. All participants signed an informed consent form and the study was approved by the Ethics Review Board of the North-West University (Potchefstroom Campus). All procedures complied with the guidelines as set in the Helsinki Declaration for investigation of human participants.

Experimental protocol

The experimental procedure for each participant followed a two day protocol. A comprehensive description can be found elsewhere [12]. Before resuming their normal

daily activities on day one, the Cardiotens® ambulatory blood pressure monitor (Meditech, Budapest, Hungary) and the Actical® accelerometer were fitted to each participant in the morning for measurements of 24-h blood pressure and physical activity. Participants also completed validated questionnaires to obtain data on their medical history, medication, socio-demographic and psychosocial status. On the following day anthropometric data and fasting venous blood samples were collected. Thereafter, participants underwent cardiovascular stress testing according to a standardized protocol.

Assessment of psychological wellbeing and coping styles

The 28-item General Health Questionnaire (GHQ) was used to evaluate perception of psychological wellbeing including signs of depression, anxiety, somatic complaints and social withdrawal [13]. The GHQ has been validated within the Setswana-speaking population with reliability coefficients of subscales ranging between 0.77 and 0.83 [14]. Possible response options for questions like “Have you found everything getting on top of you?” were ‘not at all’, ‘no more than usual’, ‘rather more than usual’ and ‘much more than usual’. The binary scoring method was applied with the two least symptomatic answers scored nil (0) and the two most symptomatic answers given a score of one (1). Total scores exceeding the threshold of four (4) are classified as achieving ‘psychiatric caseness’ [13].

A validated version of coping strategy indicator (CSI)[15] for Africans was used to evaluate the individual habitual coping style. This self-report measure, formulated through a combination of deductive and inductive methodologies, encompasses problem solving and avoidance strategies as well as seeking social support. Participants rated the 33 items of the CSI on a 3-point Likert scale: a lot (3), a little (2), or not at all (1), with a

recent stressful event in mind. Higher scores were indicative for a preference of a specific coping style with cut-off points for problem solving (31), avoidance (23), and seeking social support (28). According to Lazarus and Folkman's proposed classic bipartite classification of coping [16] we classified subjects with a high preference for either avoidance and/or seeking social support as being emotion-focussed and those with a high preference for problem solving as being problem-focussed. While the problem-focussed person alters the situation by instrumental action the emotion-focussed subject does not directly change the situation but based allows it a new meaning being assigned to control emotions associated with the stressful event [16].

Application of the cold pressor test

The cold pressor test (CPT) is an experimental technique for inducing cold pain in humans [17]. It was performed by immersing the participant's right foot in ice water with a temperature of 4°C. The participants were asked to maintain their normal breathing rhythm and to avoid straining. The CPT elicits sympathetically mediated spontaneous vasoconstriction with subsequent increases of total peripheral resistance, afterload and diastolic blood pressure (BP) [18]. Arterial pressure (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) and heart rate (12-lead ECG, Norav NHH1200® Kiryat Bialik, Israel) were monitored continuously throughout the experimental protocol which included 2 min of baseline recordings followed by 1 min of stressor exposure and 5 min of recovery. Immediately after completion of the task, participants reported their overall distress according to the question "How stressful was the task you just completed?" on a 7-point Likert scale ranging from not severe to highly severe [19]. This stress rating was considered equivalent to a rating of cold pain perception.

Multiple Trigonometric Regressive Spectral analyses

Multiple trigonometric spectral analysis (MTRS, ANS Consult, Freital / Dresden, Germany) [20,21,22] was applied to corresponding values of systolic BP and mathematically derived pulse intervals from systolic peaks obtained during stress testing. A non-artifactual global data segment of 1-2 min was analyzed during baseline. The local time window was set at 30 s and was shifted beat by beat for temporal determination of frequency and amplitude. The last 30 s of stressor application were analyzed using a local time window of 15 s. During the 5 min recovery period, the first, third and fifth minute after cessation of the stressor was evaluated using a local time window of 30 s.

Spectral analysis allows for quantification of cardiovascular regulation by assessing spontaneous oscillations in systemic arterial pressure and heart rate. Two main spectral bands are usually considered: High frequency (HF) oscillations (spectral band between 0.15 and 0.4 Hz) of heart rate relate to respiratory sinus arrhythmia and, therefore, to parasympathetic cardiovagal tone [23] while HF oscillations of systolic BP are independent of autonomic activity and not reported here. Low frequency (LF) fluctuations (spectral band between 0.04 and 0.15 Hz) of heart rate are thought to reflect the baroreflex-mediated adjustments to the sinus node encompassing sympathetic and parasympathetic fibres [23]. LF variations of systolic BP are primarily the result of sympathetically mediated fluctuations in peripheral vasomotor tone. The LF/HF ratio of heart rate variability allows for quantification of the relation between the two branches of the autonomic nervous system. Spectral power describes the amount of variability of a signal or stochastic process at a specific frequency. Baroreflex sensitivity was calculated

from coherent oscillation pairs of pulse interval and systolic BP (cross correlation coefficient > 0.7) based on MTRS [22,24].

Statistical methods

The SPSS software package version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical computations. Data are presented as estimated means \pm standard error of the mean (SEM) unless stated otherwise. Normal distribution was evident when SEM of kurtosis and skewness did not exceed the value itself by twofold. Heavily skewed variables were logarithmically transformed (CRP, γ GT, MET, BSA). Smoking status was derived from cotinine levels using a cut off for smoking ≥ 15 ng/ml. Baseline characteristics were compared by student's *t*-test for independent groups or chi-square test. Repeated measures ANCOVA with Huynh-Feldt correction was applied to test for differences in the time course of cardiovascular and autonomic parameters (degrees of freedom $n=4$) and for two- and three-way interactions (time x race, time x GHQ score, time x perception rating, time x race x perception rating). For that purpose, perception rating was converted into a three scale variable encompassing low stress perception (scores 1 and 2), moderate stress perception (scores 3 and 4), and high stress perception (scores 5 to 7). Repeated contrast analysis was used to test the statistical significance of predicted differences on the different levels. Gender, GHQ score, \ln_{γ} GT, \ln_{CRP} , \ln_{BSA} , \ln_{MET} use of antihypertensive medication and smoking status were entered as covariates in all ANCOVA's. P values < 0.05 were considered statistically significant.

Results

Baseline characteristics of hypertensive study participants are presented in table 1. Black and Caucasian Africans are of similar age, gender distribution and BMI. The Black African group had a smaller body surface area (BSA), a lower metabolic equivalent but higher levels of C-reactive protein (CRP) and γ -Glutamyl transferase (γ GT). The proportion of smokers was higher in the Black African group. Despite higher systolic and diastolic BP in the Blacks heart rate, stroke volume, cardiac output and total peripheral resistance did not differ between the groups. Intake of antihypertensive medication was more frequent in the Black Africans.

Stress perception, psychological wellbeing and coping

Black Africans rated higher (4.51 ± 1.74) on the severity of stressors scale for CPT than the Caucasian Africans (3.54 ± 1.58 , $p < 0.001$). The GHQ total score exceeded the threshold for psychological dysfunction of four in both ethnic groups but was double in the Black (8.64 ± 6.46) compared to Caucasian Africans (4.14 ± 4.99 , $p < 0.001$) indicating chronic distress in the former group. More than one third (38.2 %) of Black Africans and 24.2% of Caucasian Africans did not report a significant preference for a coping style. A comparable proportion of Black and Caucasian Africans reported preference for either problem-focussed (13.6 % of Black Africans; 14.7 % of Caucasian Africans) or emotion-focused coping (32.7 % of Black Africans; 31.6 % of Caucasian Africans). A significant higher percentage of Caucasian Africans had a high preference for both coping styles (15.5 % Black Africans, 29.5 % Caucasian Africans, $p < 0.05$)

Influence of cold pressor test on cardiovascular reactivity

Ice water immersion induced significant increases in blood pressure and heart rate and decreases in pulse interval and stroke volume from baseline while changes in cardiac output and total peripheral resistance were only significant in Black Africans (figure 2). Changes of diastolic BP, heart rate/pulse interval and stroke volume upon ice water immersion were more pronounced in Black compared to Caucasian Africans (race by time interaction for diastolic BP $p = 0.023$, heart rate/pulse interval $p = 0.019$, for stroke volume $p = 0.001$). Maximal heart rate was observed at the end of and 1 min after the cold pressor stimulus in Black and Caucasian Africans respectively. Diastolic BP was on average higher in Black African subjects. Baroreflex sensitivity did not significantly change over time.

Influence of cold pressor test on cardiovascular reactivity

High- and low frequency power of pulse interval decreased and increased respectively 60 s after the cold stimulus with a corresponding shift to sympathetic predominance (figure 3). Low frequency power of systolic BP, an indirect marker of vasomotor tone did not change significantly. Autonomic reactivity did not differ between Black and Caucasian Africans. Low frequency oscillations contributed less to the cardiovascular regulation in Black compared to Caucasian Africans.

Influence of stress perception on reactivity

Overall health perception (GHQ score) did not affect cardiovascular reactivity although there was tendency for BP ($p = 0.084$ for diastolic BP x GHQ; $p = 0.095$ for systolic BP x GHQ). A significant interaction was found between high frequency power of pulse

interval, a direct marker of cardiovagal outflow, and the GHQ score ($p = 0.028$), however, the effect size was rather low (0.122). Perception of cold pain was significantly related to BP ($p = 0.012$ for systolic BP; $p < 0.001$ for diastolic BP) and cardiac reactivity ($p < 0.001$ for heart rate/pulse interval, $p = 0.011$ for stroke volume) as well as to autonomic cardiac outflow ($p < 0.001$ for high frequency power; $p = 0.004$ for low frequency power; $p = 0.025$ for HF/LF ratio). High cold pain perception resulted in higher BP and heart rate responses. Autonomic changes were less pronounced in high pain subjects compared to subjects with moderate and low pain perception. While there was a pronounced upregulation in cardiovagal outflow and downregulation of baroreflex-mediated heart rate modulation during the cold stimulus in low and medium pain reactors either no or an opposite change was observed in high pain reactors. Additional adjustment for the CPT perception rating led to loss of significant race x time interaction for diastolic BP and heart rate/pulse interval.

Discussion

The results of this study demonstrate that among hypertensive Black teachers the greater diastolic pressor responses and higher cardiac reactivity to a cold stimulus were principally related to an increased perception of cold pain rather than to differences in autonomic function.

Since the description of the cold pressor effect by Wolf and Hardy [25] the CPT has been widely used in pain research. Its application was later extended to cardiovascular research for studying stress reactivity. As to early observations by Wolff [26] and others [27,28] it became clear that the cold pressor response is of rather complex nature encompassing

non-pain and pain related components. Previous studies using the CPT as physiological stressor have generally disregarded the pain effect in their consideration which however seems to be critical as BP reactivity is related to the intensity of pain and to pain perception as well as stress appraisal [28,29].

Our results substantiate these findings by showing a positive interaction of cold-induced BP and heart rate responses with the cognitive perception of the task. As the perception of the CPT does primarily relate to the unpleasant feeling of cold pain elicited by local ischemia we therefore regarded the perception of the CPT equivalent to the rating of pain [30]. We demonstrated a higher BP reactivity to stress in Black compared to Caucasian Africans which is consistent with previous results in normotensive subjects [10,31,32]. The prevailing concept of the higher BP reactivity in Blacks alludes to a greater α -adrenergic sensitivity and thus peripheral vasoconstriction [31,32]. With respect to our results we may propose that a stronger stimulation of pain pathways due to lower pain tolerance/higher pain perception in Blacks may also contribute to the greater BP reactivity. As Peckerman and colleagues [28,33] demonstrated the magnitude of the BP response to CPT is determined by activation of both thermo- and nociception. While the non-pain component of cold (i.e. temperature) raises BP mainly through peripheral vasoconstriction (i.e. total peripheral resistance), the induction of cold pain activates both vasomotor and central cardiac mechanisms of BP increase [34]. Due to a reflex reduction of stroke volume and cardiac output non-painful stimuli evoke only moderate BP elevations while painful conditions elicit stronger responses due to concurrent tachycardia. In our study, the greater BP response in Black Africans was accompanied by

a substantial greater cardiac response than in the Caucasians indicating a stronger activation of pain pathways in the Blacks. Another explanation for the greater cardiac reactivity may be a concurrent induction of a fight-and-flight response in the Blacks as to a greater feeling of helplessness during the CPT. This is supported by the fact that a substantially smaller proportion of the Black Africans reported high preferences for both problem- and emotion-focused coping which indicates a less effective coping behavior than in the Caucasians.

It should be noted that Black Africans perceived the CPT as more painful than the Caucasian subjects. The higher pain ratings in Blacks is consistent with the observation by Walsh and colleagues of a lower pain tolerance in individuals of non-Caucasian descent [17]. When BP and cardiac reactivities were adjusted for pain perception the ethnic differences were lost suggesting a major role of pain perception for short-term cardiovascular regulation in Black Africans. The reason for a presumable higher pain perception in Black Africans is not clear but may be explained by the neuromatrix theory of pain proposed by Melzack [35]. This theory alludes to pain as a multidimensional experience generated by a unique matrix of neurons whose output (pain signature) is critically shaped by the individual physical, psychological and cognitive makeup and prior experience rather than by the sensory input. According to this theory long-term exposure to an aversive social environment (i.e. racism and poverty) may impact on the pain-related behavior of Black South Africans. As a matter of fact the Black Africans scored twice as high on the GHQ which constitutes a measure of chronic stress. Higher background stress levels in the Black Africans may have sensitized them to pain- or

stressful situations. In this context it is interesting that the cardiovascular responses to CPT were not significantly related with measures of chronic stress. The literature relating background stress levels with acute psychophysiological responses is mixed, with recent life events being associated with both increased [36] and reduced [37] cardiovascular reactivity. Gump and Matthews [38] reviewed the evidence for the influence of background life stressors on stress reactivity, and found that six studies reported a positive association between ongoing stressors and reactivity, while four reported a negative association. One explanation is that heightened reactivity in the early stages of stress exposure is followed by attenuated reactivity with chronic stress exposure, thus the disparity of findings reflects different stages of stress adaptation. The reason that we have observed no association between GHQ and stress reactivity possibly reflects the fact that the CPT is a novel task that does not have relevance to the types of stressors experienced in real life settings. And unlike mental tasks (i.e. color word conflict test) the effects of the CPT seem to be greatly mediated by the pain component. This would also explain why other non-painful stressors did not have the same effects on BP reactivity in Black Africans [10].

In conclusion, our results indicate that ethnic differences in the appraisal of an unpleasant situation (i.e. cold pain) possibly as result of prior experience and/or available resources (i.e. coping) may contribute to the heightened BP reactivity in Black Africans.

Author notes

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Author contributions

Dr Reimann had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analyses. Dr Reimann and Dr Ruediger performed the spectral analyses on the hemodynamic variables. Dr Reimann performed the statistical analyses and wrote the first draft of the manuscript. All other authors contributed to the concept and design of the study, and critical revision of the manuscript.

Conflict of interest

None.

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Table 1. Characteristics of hypertensive study participants

	Black Africans	Caucasian Africans	P value
Age (years)	46 ± 8	48 ± 9	n.s.
Body Mass Index (kg/m ²)	30.8 (21.6-43.4)	29.0 (22.5-44.4)	n.s.
Body Surface Area (m ²)	1.96 (1.60-2.38)	2.12 (1.64-2.62)	<0.001
Smoking (%)	29.4	11.6	0.002
γ-Glutamyl transferase (U/l)	44.9 (20.7-229.6)	22.0 (8.0-119.2)	<0.001
C-reactive protein (mg/l)	5.49 (0.78-34.61)	1.90 (0.99-9.66)	<0.001
MET (kcal/d)	2672 (1682-4324)	3361 (2100-4763)	<0.001
Systolic BP (mmHg)	146 ± 19	138 ± 14	0.001
Diastolic BP (mmHg)	84 ± 10	81 ± 8	0.012
Heart rate (bpm)	70 ± 11	68 ± 11	n.s.
Cardiac output (l/min)	6.9 ± 1.8	6.9 ± 2.3	n.s.
Stroke volume (ml)	101 ± 26	103 ± 29	n.s.
Total peripheral resistance (mmHg/ml/s)	1.0 ± 0.4	1.1 ± 0.7	n.s.
Antihypertensive medication (%)	29.1	16.8	0.047
Beta blocker	4.5	1.1	n.s.
Ca-channel antagonists	11.8	1.1	0.002
Diuretics	17.3	9.5	n.s.
ACE inhibitors	14.5	4.2	0.017

Data are given as mean ± SD or median (5th-95th percentile); MET, metabolic equivalent (total energy cost of an activity/resting energy expenditure)

Figure 1. Selection of the hypertensive study sample

Hypertension was defined according to the European Society of Hypertension 2007 guidelines with average 24-h ambulatory blood pressure being systolic ≥ 125 mmHg and/or diastolic ≥ 80 mmHg.

Figure 2. Time course of hemodynamic parameters during cold pressor test (CPT) in

Black (broken lines) and Caucasian (smooth lines) Africans

Legend: p-values from contrast analysis of repeated measures ANCOVA; vertical brackets indicate univariate differences

Figure 3. Time course of spectral parameters during cold pressor test (CPT) in Black

(broken lines) and Caucasian (smooth lines) Africans

Legend: p-values from contrast analysis of repeated measures ANCOVA; vertical brackets indicate univariate difference

Figure 4. Time course of cardiovascular parameters during cold pressor test (CPT)

according to perceived stressfulness of the task

Legend: grey lines, low stress perception (score 1-2); broken lines, moderate stress perception (score 3-4); black lines, high stress perception (score 5-7); p-values from contrast analysis of repeated measures ANCOVA

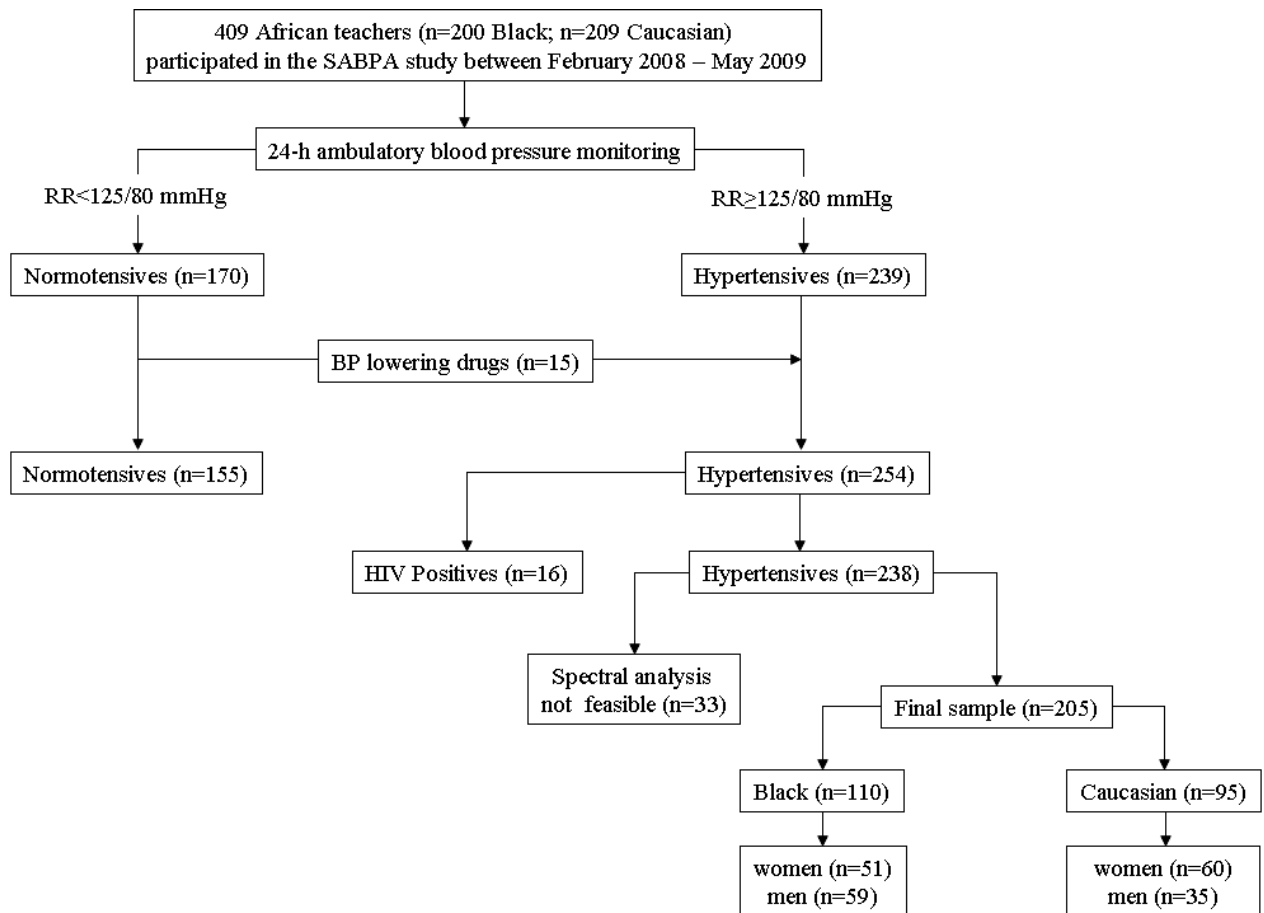


Figure 1

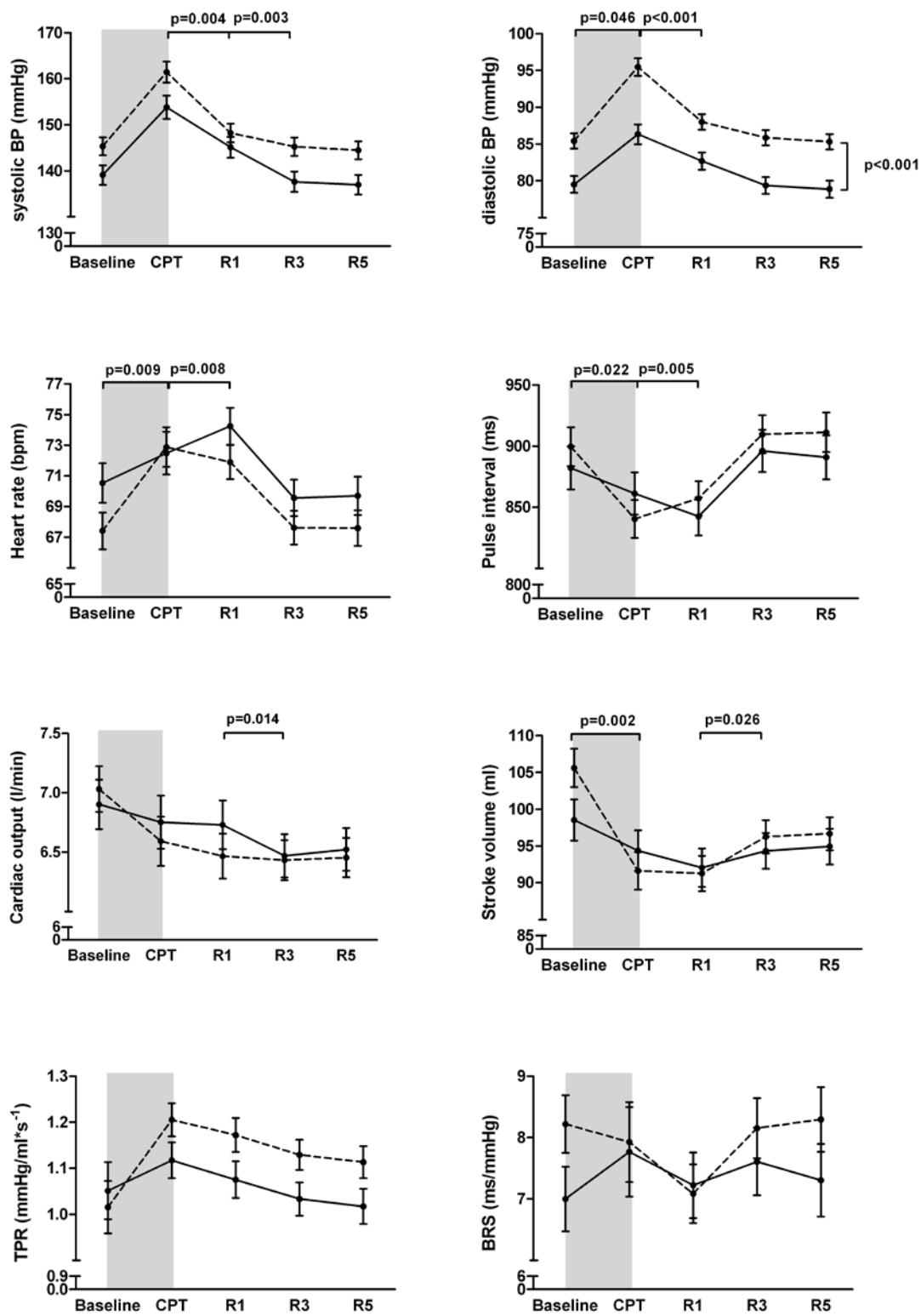


Figure 2

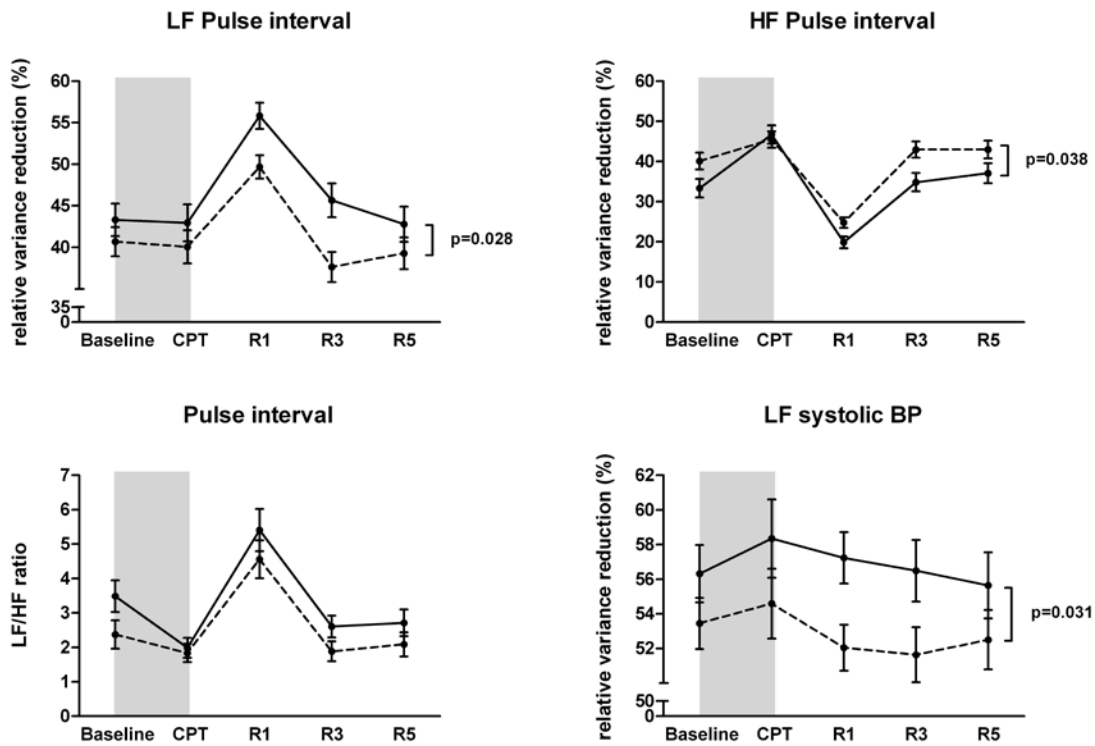


Figure 3

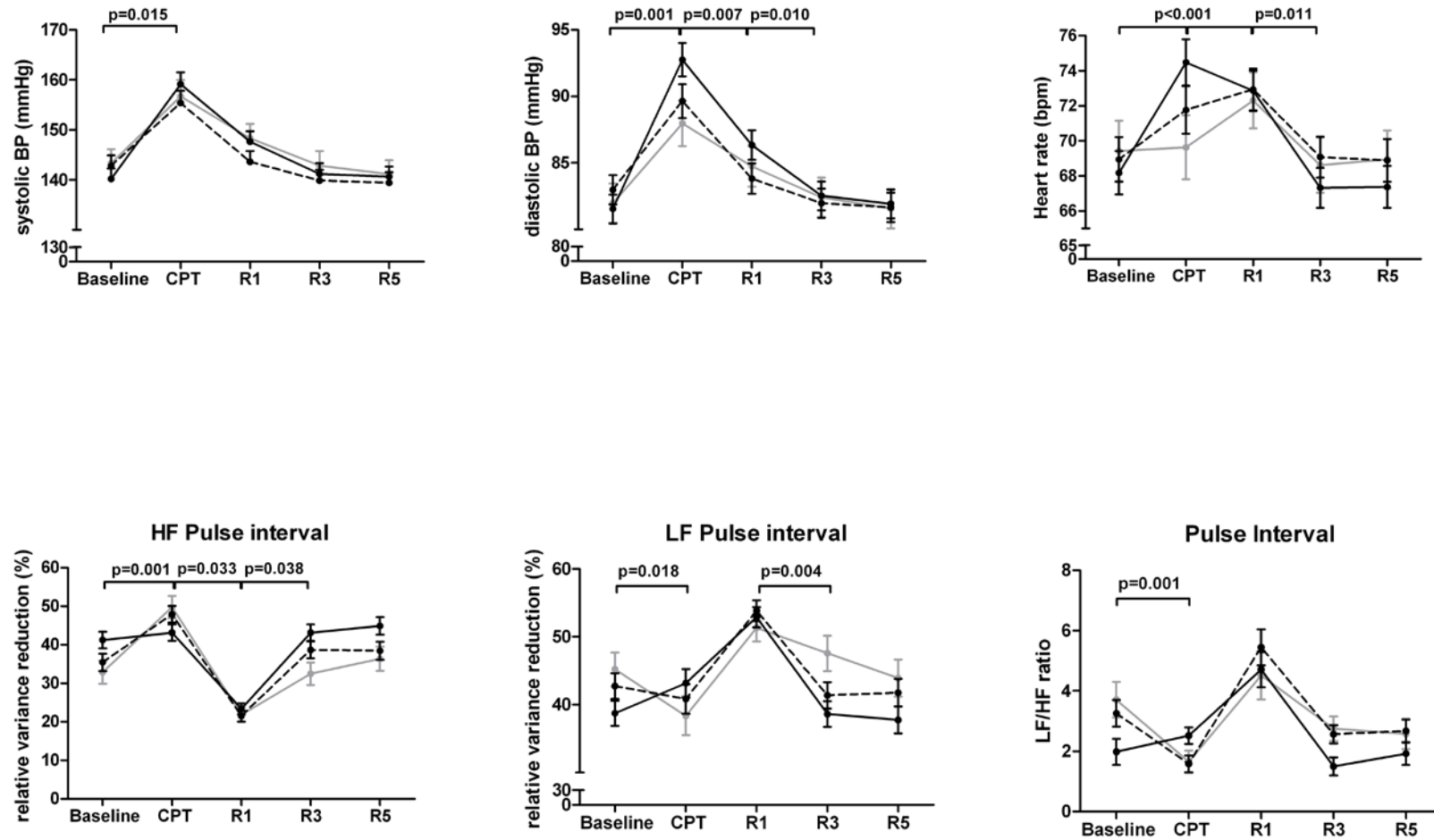


Figure 4