

Coping and Cardiac Troponin T – A Risk for Hypertension and Sub-Clinical ECG Left Ventricular Hypertrophy: The SABPA Study



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Background

Defensive coping (DefS) was associated with cardiovascular disease (CVD) susceptibility in Blacks. Whether coping strategies will associate with sub-clinical left ventricular hypertrophy (electrocardiographic-left ventricular hypertrophy [ECG-LVH] or Cornell product), cardiomyocyte injury and blood pressure (BP), is unclear. Therefore, we assessed relationships between ECG-LVH, cardiac troponin T (cTnT) and 24-hour BP in bi-ethnic groups when habitually utilising a certain coping style, and these groups when having a stress-related cTnT cut-point of 4.2 ng/L.

Methods

A target population study included a Black (n = 190) and White (n = 204) teachers' gender cohort (20–65 years) from South Africa. The Coping Strategy Indicator determined DefS, social support and avoidance coping scores. Fasting blood samples, 10-lead ECG, 24-hour BP and ECG data were obtained.

Results

Interaction effects showed no gender, social support and avoidance coping differences. Stratification of groups was done for ethnicity and DefS. Blacks sought more social support, used less avoidance coping and presented with higher CVD susceptibility. Hypertension prevalence and ECG-LVH levels in DefS Blacks (63%) were higher compared to DefS Whites (40%). Multivariate regression analyses showed positive associations between Cornell product, cTnT and BP [$p \leq 0.05$] in DefS Blacks only. Their 24-hour systolic blood pressure (SBP) was associated with time-domain depressed heart-rate-variability and prolonged ST-segment-depression especially when applying an established stress-related cTnT ≥ 4.2 ng/L cut-point.

Conclusions

Defensive coping facilitated autonomic hyperactivity, myocardial injury and subsequent compensatory BP elevations as possible homeostatic reflexes to alleviate myocardial perfusion deficits. The resulting pressure overload increased sub-clinical wall remodelling and ischaemic heart disease risk in Blacks utilising habitual defensiveness. We therefore recommend regular ECG and high sensitivity cTnT screening in asymptomatic patients with emotional stress susceptibility. Longitudinal evidence is needed to confirm causality and progression of cardiomyopathy risk.

Keywords

Coping • Troponin T • ST-segment-depression • ECG-left-ventricular-hypertrophy

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Introduction

Taxing psychological stress has been associated with an increased cardiovascular disease (CVD) risk [1]. Haemodynamic alterations [2] may occur when experiencing emotional stress [3] and supports the notion that stress and cardiovascular disease (CVD) are linked [1–3]. The physiological stress response is not only determined by the type or degree of emotional stress, but also by the individual's unique cognitive appraisal of the stressor, and the ultimate coping strategy used to neutralise the perceived challenge or threat [1,4–5].

Three main, well-recognised coping strategies include active problem solving, seeking social support and avoidance [6]. Active coping is coined defensive coping (DefS), where the perception of control over life stressors is focussed on problem-solving and defence [3,5,7]. Avoidance coping reflects a type of passive or loss-of-control response [3]. Social support coping mainly focusses on the effectiveness of the individual's social support systems and mostly supports DefS [3,5,7]. Prospective analyses showed that a lack of social support from family and friends in Blacks was associated with chronic defensiveness and dysregulated neuroendocrine responses [7–9]. Moreover, chronic defensiveness reflected a novel cardiac troponin T (cTnT) cut-point of 4.2 ng/L [7].

The advent of high sensitivity methodology further allows detection of cTnT at much lower levels as a screening marker for myocyte injury, heart failure and stroke [10]. Indeed, cTnT reflected microvascular perfusion deficits and vascular complications, especially in mentally stressed individuals [7]. In a Black African cohort, enhanced sympathetic responsiveness showed increased pressure overload and associated structural left ventricular hypertrophy (LVH) [3]. In support, Havranek et al. [10] compared ethnic mortality rates for those with electrocardiographic (ECG)-LVH, using data from the Third National Health and Nutrition Examination Survey and the National Death Index in America. They showed that ECG-LVH contributed more to cardiovascular mortality risk in African Americans than in Whites. Whether these findings relate to African Blacks, particularly when habitually utilising a certain coping style, are not clear. Though systolic blood pressure (SBP) [11] and cTnT levels have been associated with LVH [12], the relationship in participants habitually using a specific coping style, is unknown.

We therefore aimed to establish associations between ECG-LVH, cTnT and 24-hour blood pressure (24 h BP) in a bi-ethnic gender cohort using a particular coping style, and to re-assess the latter association in groups when having a stress-related cTnT cut-point of 4.2 ng/L.

Material and Methods

Study Design

The cross-sectional, target population Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) study (n = 409), complied with the Declaration of Helsinki (revised

2004) and has been well described elsewhere [13]. The SABPA study obtained ethical consent (Potchefstroom Campus: NWU-000-36-07-S6).

Participants

Black and White South African teachers of both genders participated (n = 394; aged 20–65 years). Exclusion criteria were pregnancy, lactation, vaccination or blood donation 3 months prior to the study, and abusers or dependants of psychotropic substances. Additional exclusions for this study were tympanum temperature over 37.5 °C (n = 2), α - or β blocker users (n = 7), people with a history of stroke (n = 1) and/or myocardial infarction (n = 3), individuals with the presence of ECG-LVH (n = 1); and a cTnT outlier (237.5 ng/L, committed suicide).

General Procedure of Investigation

Participants were fitted with 24-hour BP and 24-hour physical activity apparatuses at school every working day of the week (Monday to Thursday), between 7:00 and 8:00. Hereafter, participants continued their normal daily activities and extra-curricular activities. They were to report headaches, nausea, palpitations, visual disturbances, hot flushes, acute/chronic stress, syncope episodes, and physical activity on the issued 24-hour BP diary cards. Medical history and medication usage data were obtained.

At 16:30, the participants were transported to the North-West University's Metabolic Unit Research Facility for an overnight stay. They were assigned their own room, were introduced to the experimental set-up and received HIV/AIDS pre-counselling. Hereafter, participants had a standardised dinner and completed a psychosocial battery under supervision of clinical psychologists. The participants fasted overnight, were awoken at 6:00 and then the 24-hour BP and physical activity apparatuses were removed. Anthropometric measurements followed after which the participants remained in a semi-recumbent position for a 30-minute period, before 10-lead ECG and blood sampling commenced. Feedback and referral on immediately available clinical measures were given to the participants in the privacy of their rooms by a registered nurse. Participants had breakfast and were transported back to school.

Coping Strategy Questionnaires

The Coping Strategy Indicator (CSI) questionnaire assessed coping responses to stress and was validated in ethnic groups [6]. Participants had to recall a stressful incident in the last 6 months and had to consider their manner of coping with this particular incident. The questionnaire consisted of 33 items that made use of both inductive and deductive methodologies to unambiguously assess the participant's coping style, used in response to identified stressors. Coping strategies, which form the three subscales of 33 items assessed with the CSI, involved: DefS (active problem solving); avoidance/loss of control; and seeking social support [6]. The 33 items were divided in three sets of 11 questions each (randomly ordered in the questionnaire), to test the

three subscales. Every item was given a numerical value according to the answer, namely: a lot (3 points); a little (2 points); or not at all (1 point). The totals were calculated to give a maximum score of 33 for each sub-scale. According to Amirkhan [6] the above mean coping responses are: DefS (≥ 26), seeking social support (≥ 23) and avoidance (≥ 19). Cronbach- α coefficients were calculated for the SABPA study with 0.83 for DefS, 0.84 for seeking social support and 0.69 for avoidance.

Lifestyle Confounders

Anthropometric measurements were performed in triplicate by level II anthropometrists according to standardised procedures. Intra- and inter-observer variability was less than 10%. Total energy expenditure (TEE) of the participants was determined with the Actical[®] omnidirectional accelerometer (Montreal, Quebec, Canada). Waist circumference (WC) was taken at the midpoint between the lower costal rib and the iliac crest, perpendicular to the long axis of the trunk, and not at the narrowest point. The Mosteller formula [14] was used to determine body surface area (m^2) from body mass and height measurements. Gamma glutamyl transferase (GGT) was used to determine alcohol consumption [15]. Serum cotinine (a nicotine metabolite) values were used to determine smoking status [16].

Biochemical Measurements

A registered nurse used a sterile winged infusion set to collect fasting blood samples from the participants' antebra- chial vein branches. Standardised procedures were followed for preparation and storage of samples at $-80^\circ C$ until analysis. A Modular Roche automised (Switzerland) apparatus was used to measure serum cotinine values with a homoge- neous immunoassay. Serum GGT was analysed with the turbidimetric method (Unicel DXC 800, Beckman and Coul- ter, SYNCHRON System/s, Brea, CA, USA). High-sensitive serum cTnT was analysed with an electrochemiluminescence assay on the Cobas E411[®] (Roche, Basel, Switzerland). One hundred and nine (27.7%) cTnT levels were below detection (< 3 ng/L) and were substituted with lower than detectable values using log-methods. The cTnT inter- and intra-batch variability was 15% and 5.6%.

Cardiovascular Measurements

Ambulatory BP was recorded using the Cardiotsens[®] CE120 (Meditech, Budapest, Hungary) [17]. The apparatus was fitted to the non-dominant arm, using appropriate cuff sizes. Blood pressure was recorded every 30 minutes between 8:00 and 22:00 and every 60 minutes between 22:00 and 6:00 [17]. Successful inflation rates in Blacks were $72.8 \pm 11.9\%$ opposed to $84.7 \pm 9.9\%$ in Whites. The CardioVisions 1.19 Personal Edition Software (Meditech, Budapest, Hungary) was used for data analysis. Hypertension status was defined as a mean 24-hour SBP ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 80 mmHg [18]. A 10-lead ECG (Norav 1200 M, Norav Medical, Germany, Software version 5.030) recorded six-cardiac cycles. Electrocardiograph-LVH was

determined with the Cornell product formula: $[RaVL + SV3] \times QRS \text{ duration} \geq 244 \text{ mV.ms}$ [18].

Silent Myocardial Ischaemic Events [19]

Before 24-hour monitoring, the isoelectric reference point (PQ segment), J point, L point (80 ms after the J point), as well as an ST-segment detection interval of at least 3 mm as the initial ST level, were individually calculated for each patient. According to a pre-set program, two-lead 24-hour ECG recordings were obtained for 20 seconds at 5-minute intervals assessing silent ischaemic or ST-segment depres- sion events. Ischaemic events were recorded according to the 1-1-1 rule: 1) 1 mm horizontal or descending ST-segment, 2) the ST-segment event has a duration of at least 1 minute, and 3) two consecutive ST-events must have an in-between inter- val of at least 1 minute to be counted as independent epi- sodes. In case of horizontal or descending ST depression, an ECG tracing lasting 60 seconds was documented, and an additional BP measurement was automatically initiated by the trigger mechanism of the device. The data was analysed using the CardioVisions 1.19 Personal Edition software (Meditech[®], Budapest, Hungary).

Autonomic Function

The software program automatically filtered out ventricular and supraventricular ectopic beats as well as artefacts in RR intervals, while heart-rate-variability (HRV) outliers were manually removed. HRV time domain measures included the standard deviation of the normal-to-normal (NN) inter- vals between adjacent QRS complexes (SDNN). The HRV- SDNN reflects vagus nerve-mediated autonomic control of the heart and is the best overall prognostic tool to detect depressed HRV (< 100 ms) [20], which was also related to endothelial dysfunction and cardiomyocyte damage [7,21,22].

Statistical Analysis

Data analyses were completed using the computer software package Statistica[®] version 13.1 (Dell, Round Rock, TX, USA, 2017). Skewed data were logarithmically transformed. Single three-way analysis of covariance (ANCOVA) determined interaction on main effects (ethnicity \times gender \times coping) for cardiovascular risk markers. Characteristics of the population were compared by using T-tests for independent groups. A *priori* covariates included age, log waist circumference, log GGT, log TEE and cotinine [18]. Chi-square (X^2) test deter- mined proportions and prevalence. One-way ANCOVA's were used to compare differences considering a *priori* covariates. Multivariate regression analyses determined relation- ships in several models between 1) the dependent variable ECG-LVH and independent variables cTnT, HRV-SDNN and either 24-hour SBP or 24-hour DBP and a *priori* covariates; 2) the dependent variable 24-hour SBP and independent variables cTnT, HRV-SDNN and a *priori* covariates; and 3) the dependent variable 24-hour SBP and independent variables HRV-SDNN, 24-hour silent ischaemic events max duration and a *priori* covariates in participants with 24-hour ischaemic events. All

analyses were repeated when having stress-related cTnT \geq 4.2 ng/L [7]. Multiple linear regressions were also repeated after excluding atrial fibrillation ($n = 16$) and clinically diagnosed diabetic cases ($n = 11$). The statistical significance level was set at $p < 0.05$ (two-tailed).

Results

Main interaction analysis showed (ethnicity \times DefS) differences for Cornell product (ECG-LVH) [(F1,338); 5.85; $p = 0.02$] and waist circumference [(F1,389); 5.32; $p = 0.02$]. No such interactions were evident for gender or the other two

coping styles and justified stratification of participants into ethnicity and DefS groups (above scores ≥ 26).

In Table 1, Blacks sought more social support with less avoidance coping compared to Whites ($p < 0.05$). Blacks showed increased alcohol consumption, hypertensive 24-hour BP levels, Cornell product, RaVL, lower cTnT levels, depressed HRV-SDNN values, more silent myocardial ischaemic (ST) events and usage of more hypertension medication (32.1% vs. 11.3%) compared to Whites.

In Table 2, adjusted analyses showed similar trends for increased Cornell product, RaVL, lower cTnT levels and 24-hour BP values in DefS Blacks compared to their White counterparts. However, the HRV-SDNN profile in both DefS

Table 1 Clinical characteristics of the bi-ethnic study population.

	Blacks (n = 190)	Whites (n = 204)	P-value
Age (years)	44.07 \pm 8.07	44.80 \pm 10.88	0.452
Men, N (%)	95 (50.00)	98 (48.04)	0.697
Women, N (%)	95 (50.00)	106 (51.96)	0.697
Duration of urban stay (years)	31 \pm 16.43	20 \pm 12.36	≤ 0.001
Coping strategy, scores			
Defensive coping	28.14 \pm 4.10	28.80 \pm 3.88	0.100
Avoidance	21.20 \pm 3.74	23.95 \pm 5.12	≤ 0.001
Seeking social support	25.62 \pm 5.03	18.83 \pm 4.79	≤ 0.001
Lifestyle confounders			
Body surface area (m ²)	1.92 \pm 0.24	2.00 \pm 0.28	0.002
Waist circumference (cm)	93.41 \pm 15.75	92.74 \pm 16.08	0.679
Physical activity (kcal/day)	2582.48 (1616.2–4112.5)	2942.37 (1917.1–4419.4)	≤ 0.001
Cotinine (ng/ml)	26.97 \pm 61.67	23.28 \pm 78.34	0.606
GGT	47.43 (20.07–183.75)	19.19 (7.0–76.0)	≤ 0.001
Cardiac risk markers			
Cornell product (ECG-LVH), (mV.ms)	69.82 \pm 38.67	50.21 \pm 28.47	≤ 0.001
RaVL (mV)	0.35 \pm 0.28	0.20 \pm 0.18	≤ 0.001
cTnT (pg/ml)	4.26 (2.57–8.73)	4.83 (2.6–10.50)	0.006
24 h SBP (mmHg)	132 \pm 14.98	124 \pm 11.76	≤ 0.001
24 h DBP (mmHg)	83 \pm 9.99	77 \pm 8.05	≤ 0.001
24 h Hypertensive, N (%)	123 (64.74)	78 (38.24)	≤ 0.001
24 h PP (mmHg)	49 \pm 8.80	47 \pm 7.03	0.011
24 h PP \geq 50 mmHg; N (%)	81 (42.63)	71 (34.80)	0.111
24 h silent ischaemia events (N)	6 \pm 15.29	3 \pm 5.97	0.004
24 h silent ischaemia events max duration (min)	5.13 (1.00–139.50)	3.27 (1.0–28.50)	0.041
Time domain 24 h HRV-SDNN (ms)	112.53 (59.00–205.00)	142.12 (89.00–219)	≤ 0.001
Medication			
Hypertensive drugs, N (%)	61 (32.11)	23 (11.27)	≤ 0.001
Statins, N (%)	2 (1.05)	8 (3.92)	0.070
ACE inhibitor, N (%)	19 (10.00)	4 (1.96)	≤ 0.001
Ang II blockers, N (%)	0 (0)	2 (0.98)	0.171
Aspirin, N (%)	3 (1.58)	10 (4.90)	0.065

The values are displayed as arithmetic mean \pm standard deviation or geometric mean (5th percentile – 95th percentile) or frequencies (%).

Abbreviations: GGT, gamma glutamyl transferase; Cornell product (ECG-LVH), electrocardiographic left ventricular hypertrophy; RaVL, R-wave of the aVL lead; cTnT, cardiac troponin T; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HRV, heart rate variability; SDNN, standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes; ACE, angiotensin converting enzyme; Ang II, Angiotensin II.

Table 2 Adjusted comparisons between ethnic groups when habitually using defensive or non-defensive coping.

	DefS Blacks (n = 143)	DefS Whites (n = 162)	p-value	Non-DefS Blacks (n = 47)	Non-DefS Whites (N = 42)	P-value
Cardiac risk markers						
Cornell product (mV.ms)	68.3 (61.2, 75.3)	53.4 (46.9, 59.9)	0.007	63.2 (53.6, 72.8)	54.4 (44.2, 64.5)	0.256
RaVL (mV)	0.3 (0.3, 0.4)	0.2 (0.2, 0.3)	0.014	0.4 (0.3, 0.4)	0.2 (0.2, 0.3)	0.031
cTnT (pg/ml)	4.2 (3.9, 4.6)	5.0 (4.6, 5.4)	0.011	3.9 (3.4, 4.4)	4.9 (4.3, 5.6)	0.022
24 h SBP (mmHg)	131 (129, 133)	125 (123, 127)	0.001	133 (129, 137)	124 (120, 128)	0.003
24 h DBP (mmHg)	82 (80, 83)	78 (76, 79)	≤0.001	82 (79, 84)	78 (75, 81)	0.130
24 h Hypertensive, N (%)	90 (62.9)	65 (40.1)	≤0.001	33 (70.2)	13 (31.0)	≤0.001
24 h PP (mmHg)	49 (48, 51)	48 (46, 49)	0.232	52 (49, 54)	46 (44, 48)	0.001
24 h PP ≥ 50 mmHg; N (%)	57 (39.7)	60 (37.0)	0.613	24 (51.1)	11 (26.2)	0.017
24 h silent ischaemia events (N)	6 (4.0, 8.0)	2 (0.5, 4.3)	0.025	5 (-0.3, 10.1)	6 (0.5, 11.4)	0.804
24 h silent ischaemia events max duration (min)	4.9 (3.3, 7.5)	2.8 (1.8, 4.3)	0.105	5.9 (2.6, 13.4)	5.8 (2.6, 12.8)	0.963
Time domain 24 h HRV-SDNN (ms)	117.1 (110.1, 124.5)	136.0 (128.3, 144.1)	0.002	112.7 (99.4, 127.8)	142.5 (125.4, 161.9)	0.023

The values are displayed as mean (-95% confidence interval, +95% confidence interval), after the adjustment for *a priori* covariates: age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase and cotinine. 24 h PP was added as covariate for Cornell product (ECG-LVH), RaVL, cTnT, 24 h silent ischaemia events and -duration, as well as 24 h HRV-SDNN comparisons.

Abbreviations: DefS, defensive coping; Cornell product (ECG-LVH), electrocardiographic left ventricular hypertrophy; RaVL, R-wave of the aVL lead. cTnT, cardiac troponin T; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HRV, heart rate variability; SDNN, standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes.

and non-DefS Blacks were lower compared to their White counterparts. In non-DefS Blacks, 24-hour SBP and -pulse pressure (PP) were higher compared to non-DefS Whites. Disturbed sympatho-adrenal dysregulation reflected a stress-related cTnT cut-point of ≥ 4.2 ng/L predictive of 24-hour and clinic BP [7]. Therefore, this cTnT cut-point was used as ischaemic heart disease risk marker [22]. In Figure 1, DefS Blacks with stress-related cTnT ≥ 4.2 ng/L had higher 24-hour BP and ECG-LVH than DefS Whites. Non-DefS differences were not apparent (data not shown).

Unadjusted and adjusted associations were showed between ECG-LVH, cTnT, 24-hour SBP and 24-hour DBP when habitually utilising DefS (Tables S1 and S2). In Table 3, stepwise forward linear regression analyses, showed positive associations ($p \leq 0.05$) in Model 1 between ECG-LVH, cTnT (adjusted $R^2 = 0.16$, $\beta = 0.23$) and 24-hour SBP ($\beta = 0.41$) or 24-hour DBP ($\beta = 0.27$) in DefS Blacks. In DefS Whites, ECG-LVH was associated with 24-hour DBP only (adjusted $R^2 = 0.11$, $\beta = 0.22$). In Model 2 in DefS Blacks, 24-hour SBP was associated with cTnT (adjusted $R^2 = 0.36$, $\beta = 0.23$). In Model 3, in DefS Blacks with

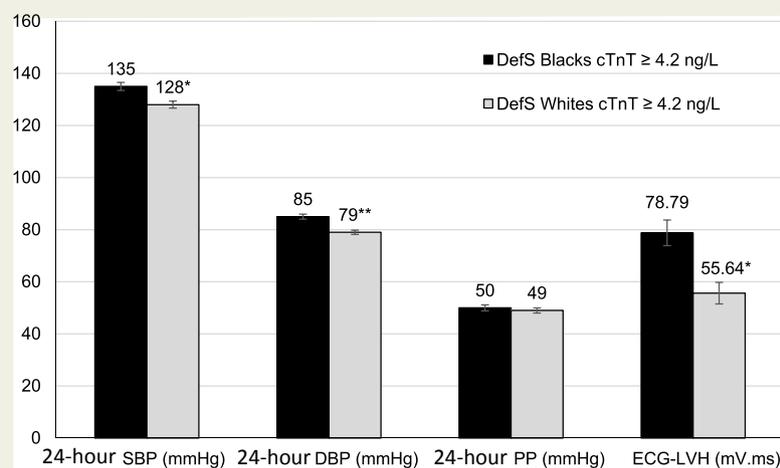


Figure 1 Adjusted comparisons between DefS Black and White groups with cTnT ≥ 4.2 ng/L. *A priori* covariates included age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase and cotinine. 24 h PP was added as covariate for ECG-LVH comparisons.

Abbreviations: DefS, defensive coping; cTnT, cardiac troponin T; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; ECG-LVH, electrocardiographic left ventricular hypertrophy. * $p \leq 0.05$; ** $p \leq 0.001$.

Table 3 Associations between sub-clinical cardiac wall remodelling and cardiac risk markers in a defensive coping bi-ethnic cohort.

	Defensive coping Black participants		
	Model 1: Cornell product (mV.ms) (n = 115) β (95% CI), p	Model 2: 24 h SBP (mmHg) (n = 115) β (95% CI), p	Model 3 (silent ischaemia cases): 24 h SBP (mmHg) (n = 71) β (95% CI), p
Adjusted R ²	0.16	0.36	0.36
Cardiac Troponin T (ng/L)	0.23 (0.04; 0.41), p = 0.019	0.23 (0.06; 0.40), p = 0.008	
HRV SDNN (ms)	NS	NS	-0.23 (-0.43; -0.03) p = 0.027
24 h silent ischaemic events max duration (min)			0.25 (0.05; 0.45) p = 0.020
*24 h SBP (mmHg)	0.41 (0.24; 0.57), p ≤ 0.001		
*24 h DBP (mmHg)	0.27 (0.08; 0.45), p = 0.005		
	Defensive coping White participants		
	Model 1: Cornell product (mV.ms) (n = 140) β (95% CI), p	Model 2: 24 h SBP (mmHg) (n = 140) β (95% CI), p	Model 3 (silent ischaemia cases): 24 h SBP (mmHg) (n = 62) β (95% CI), p
Adjusted R ²	0.11	0.29	0.41
24 h DBP (mmHg)	0.22 (0.05; 0.39), p = 0.013		

Independent variables included, in:

Model 1: age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase, cotinine, cardiac troponin T, HRV-SDNN, and *24 h SBP or 24 h DBP.

Model 2: age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase, cotinine, cardiac troponin T and HRV-SDNN.

Model 3: age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase, cotinine, HRV-SDNN, and 24 h silent ischaemic events max duration in individuals with 24 h ischaemic events.

Abbreviations: HRV-SDNN, heart rate variability standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes; 24 h SBP, 24-hour systolic blood pressure; 24 h DBP, 24-hour diastolic blood pressure.

24-hour silent ischaemic events, 24-hour SBP was associated with HRV-SDNN (adjusted R² = 0.36, β = -0.23) and 24-hour silent ischaemic events max duration (β = 0.25). The small sample sizes for associations in non-DefS groups should be viewed with caution (Table S3).

We then determined ischaemic heart disease risk [22] at cTnT \geq 4.2 ng/L in DefS Blacks with 24-hour silent ischaemic events (Table 4) where ECG-LVH was associated (p ≤ 0.05) with 24-hour SBP (adjusted R² = 0.21, β = 0.47) as well as 24-hour DBP (adjusted R² = 0.21, β = 0.36). Twenty-four hour (24-hour) SBP was associated with HRV-SDNN (adjusted R² = 0.55, β = -0.29) and 24-hour silent ischaemic events max duration (β = 0.29). Findings were not evident in DefS Whites. After excluding atrial fibrillation (n = 16) and clinically diabetic diagnosed cases (n = 11), the outcome did not change.

Figure 2 represents the flow of events where compensatory 24-hour BP elevations followed to combat myocardial perfusion deficits with resultant pressure overload and subclinical cardiac wall remodelling.

Discussion

Overall, habitual DefS in a Black cohort facilitated sympathetic hyperactivity, myocardial injury and compensatory BP

elevations, as homeostatic reflexes, to alleviate myocardial perfusion deficits. Resultant pressure overload contributed to sub-clinical cardiac wall remodelling and potential ischaemic heart disease risk. Similar findings were not found in DefS Whites or non-DefS ethnic groups.

The defence response is evoked by changes in the environment, which are perceived as a threat or challenge by limbic structures, i.e. the thalamus, hippocampus and amygdala. Cognitive appraisal of the stressor in the prefrontal cortex will stimulate the insula and hypothalamic paraventricular nuclei for appropriate autonomic pathway activity [3,7,9]. Usually an in-control habitual DefS response elicits a β -adrenergic central cardiac response [6,13], with increases in myocardial contractility, SBP and cardiac output [23,24]. However, DefS Blacks previously exhibited physiological loss-of-control α -adrenergic vascular responses and a perception of emotional distress [8,21,25]. We take it one step further by suggesting that habitual defensiveness enhances sympathetic hyperactivity [7] and vascular responsiveness or β -hyporesponsivity [21,25], as the current DefS Black cohort also presented a more depressed HRV profile. It will enforce microvascular coronary perfusion deficits (ischaemia), as well as stroke risk [26]. With no apparent evidence of a vasodilatory β 2-Adrenoceptor polymorphism in African Caribbeans [27] or in Black women [28], we cautiously

Table 4 Associations between sub-clinical cardiac remodelling and cardiac risk markers in defensive coping Blacks with stress-related cardiac Troponin T (cTnT) values ≥ 4.2 ng/L.

	Defensive coping Black participants with cTnT ≥ 4.2 ng/L (n = 55)	
	Model 1: Cornell product (mV.ms) (n = 55) β (95% CI)	Model 2: 24 h SBP (mmHg) in silent ischaemia cases: (n = 36) β (95% CI)
Adjusted R ²	0.21	0.55
HRV-SDNN (ms)	NS	-0.29 (-0.52; -0.05) p = 0.023
24 h silent ischaemic events max duration (min)		0.29 (0.05; 0.53) p = 0.024
*24 h SBP (mmHg)	0.47 (0.23; 0.71); p \leq 0.001	-
*24 h DBP (mmHg)	0.36 (0.11; 0.62); p = 0.008	-

Covariates included, in:

Model 1: age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase, cotinine, cardiac troponin T, HRV-SDNN, and *24 h SBP or 24 h DBP.

Model 2: age, log waist circumference, log physical activity (GGT), log gamma glutamyl transferase, cotinine, HRV-SDNN and 24 h silent ischaemic events max duration in individuals with 24 h ischaemic events.

Abbreviations: HRV-SDNN, heart rate standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes; 24 h SBP, 24-hour systolic blood pressure; 24 h DBP, 24-hour diastolic blood pressure.

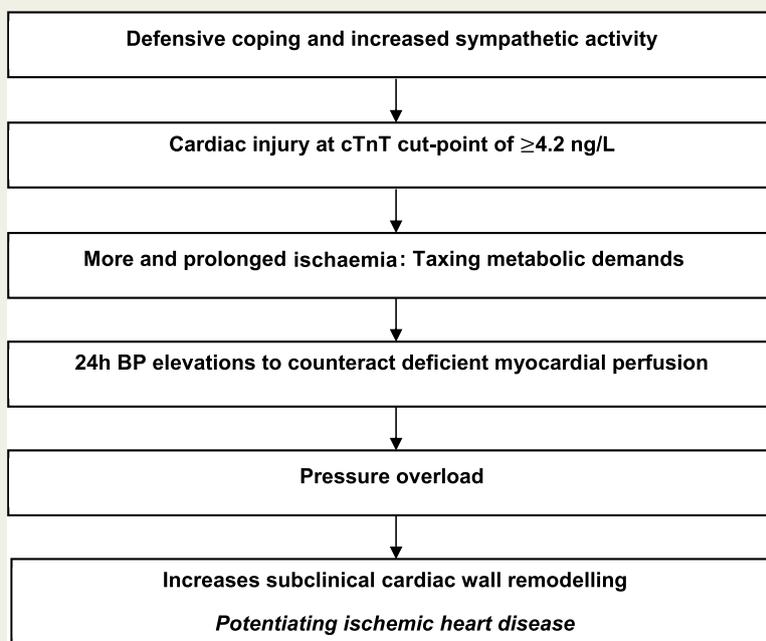


Figure 2 The proposed mechanism of a DefS pathway in Blacks. Habitual defensiveness increases sympathetic activity and stress-related cardiomyocyte injury (4.2 ng/L). Subsequently, increasing myocardial metabolic demands, compensatory BP increases, and the risk for sub-clinical cardiac wall remodelling and ischaemia heart disease.

suggest that DefS responses and emotional distress might rather induce α -adrenergic responsiveness, volume overload and cTnT release.

Defensive coping responses and emotional distress may explain why Blacks sought more social support from family and friends in an attempt to cope with stress, but habitual defensiveness rather shows physiological inability to exert control. Similarly, in 13,686 men and women from the

Atherosclerosis Risk in Communities study a small social network was associated with an increased risk of incident stroke compared to participants with a large social network [29].

DefS Whites showed higher cTnT levels compared to DefS Blacks. However, when the chronic stress-related cTnT cut-point of ≥ 4.2 ng/L [7] was considered, DefS Blacks showed increased BP and ECG-LVH levels compared to DefS Whites.

Cardiomyocyte injury in the Black population may thus be reflected at a lower cTnT level with habitual DefS. Importantly, the effectiveness and timing of prefrontal cortex modulation of limbic-mediated emotional reactivity may thus have important health consequences, including the ability to regulate neuroendocrine stress hormones [7] and cardiac response patterns through cognitive appraisal. Emotional dysregulation or habitual DefS may thus affect tolerance and increase ischaemic heart disease risk at lower cTnT thresholds in Blacks. Indeed, habitual DefS in Blacks, were accompanied with sympathetic hyperactivity (depressed HRV) and prolonged silent myocardial ischaemia, which increased cardiac metabolic demands. It might also sensitise cTnT at lower levels and explain the compensatory blood pressure increases to alleviate myocardial perfusion deficits. If the situation is chronic, sub-clinical cardiac wall remodelling may progress faster. Electrocardiograph-obtained silent myocardial ischaemic events may, therefore, seem to be a more sensitive method to evaluate initial injury of the myocardium at lower cTnT point levels, when ST-segment depression is apparent.

Habitual DefS and depression can influence cardiac health resiliency [7] with associated changes in the astroglia of the amygdala, hippocampus and prefrontal cortex [30]. Indeed, recent functional magnetic resonance imaging (fMRI) findings from a prospective cohort showed associations between CVD risk, perceived stress and increased amygdalar activity [31]. The reason why DefS Whites did not reveal the same degree of ECG-LVH risk at cTnT ≥ 4.2 ng/L, may be ascribed to the fact that they reflected cardiac β -adrenergic (in-control) DefS responses [13]. Previous findings support this notion as a cTnT cut-point of ≥ 5.6 ng/L in Whites was not associated with incident 24-hour hypertension, silent myocardial ischaemia events or duration [32] nor neuroendocrine dysregulation [7].

Furthermore, DefS facilitated an enhanced risk for LV structural changes in Blacks compared to Whites. The Dallas Heart study reported similar increased LVH prevalence in African Americans, compared to other ethnic groups [29]. These results relate to our current findings, where positive associations existed between ECG-LVH, cTnT and 24-hour BP in the DefS Blacks. The presence of a 24-hour hypertensive status in DefS Blacks will evidently increase afterload; ventricular stress and potentiate cardiomyocyte hypertrophy [30]. Hypertrophic growth, therefore acts as a compensatory mechanism, because it counteracts increases in systolic wall stress and oxygen demand [33,34]. In the long-term, maladaptive growth can progress to systolic dysfunction, unresponsive and dilated ventricles, with ECG changes, which can manifest as ventricular arrhythmia and eventually heart failure [35,36]. Higher ECG-LVH and pressure overload may independently be explained by dysfunctional DefS. Indeed, when coping disability prevails, the sympathetic nervous system became hyperactive and resultant catecholamine overload will have a direct trophic effect on the myocardium, regardless of BP levels [3,7,37].

The findings from our study might have been strengthened by a larger sample size and a longitudinal rather than a

cross-sectional design. However, the homogeneity of our ethnic samples, rigorous selection criteria, and well-designed and controlled protocols may contribute meaningfully to the literature.

Conclusions

As ischaemic heart disease precedes heart failure [38], susceptibility for heart failure increases in Blacks when habitually utilising DefS. Defensive coping facilitated sympathetic hyperactivity, myocardial metabolic demands and injury at stress-related cTnT ≥ 4.2 ng/L. Compensatory 24-hour BP elevations followed to combat myocardial perfusion deficits with resultant pressure overload and subclinical cardiac wall remodelling. We, therefore, recommend regular ECG and high sensitivity cTnT screening in asymptomatic patients with emotional stress susceptibility. Longitudinal evidence is needed to confirm causality and progression of cardiomyopathy risk.

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Declarations of Interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.hlc.2018.05.101>.

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