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Chronic defensiveness and neuroendocrine dysfunction reflect a novel cardiac troponin T cut point: The SABPA study

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ABSTRACT

Background: Sympatho-adrenal responses are activated as an innate defense coping (DefS) mechanism during emotional stress. Whether these sympatho-adrenal responses drive cardiac troponin T (cTnT) increases are unknown. Therefore, associations between cTnT and sympatho-adrenal responses were assessed.

Methods: A prospective bi-ethnic cohort, excluding atrial fibrillation, myocardial infarction and stroke cases, was followed for 3 years (N = 342; 45.6 ± 9.0 years). We obtained serum high-sensitive cTnT and exposure measures [Coping-Strategy-Indicator, depression/Patient-Health-Questionnarie-9, 24 h BP, 24 h heart-rate-variability (HRV) and 24 h urinary catecholamines].

Results: Blacks showed moderate depression (45% vs. 16%) and 24 h hypertension (67% vs. 42%) prevalence compared to Whites. A receiver-operating-characteristics cTnT cut-point 4.2 ng/L predicting hypertension in Blacks was used as binary outcome measure in relation to exposure measures [AUC 0.68 (95% CI 0.60-0.76); sensitivity/specificity 63/70%; P ≤ 0.001]. Bi-ethnic cTnT-incidence was similar (25-27%) with cTnT-recovery better in Blacks (9%) compared to Whites (5%), P = 0.001. In cross-sectional analyses, elevated cTnT was related to DefS [OR 1.08 (95% CI 0.99–1.16); P = 0.06]; 24 h BP [OR 1.03–1.04 (95% CI 1.01–1.08); P ≤ 0.02] and depressed HRV [OR 2.19 (95% CI 1.09–4.41); P = 0.03] in Blacks, but not in Whites. At 3 year follow-up, elevated cTnT was related to attenuated urine norepinephrine:creatinine ratio in Blacks [OR 1.46 (95% CI 1.01–2.10); P = 0.04]. In Whites, a cut point of 5.6 ng/L cTnT predicting hypertension was not associated with exposure measures.

Conclusion: Central neural control systems exemplified a brain-heart stress pathway. Desensitization of sympatho-adrenal responses occurred with initial neural- (HRV) followed by neuroendocrine dysfunction (norepinephrine:creatinine) in relation to elevated cTnT. Chronic defensiveness may thus drive the desensitization or *physiological depression*, reflecting ischemic heart disease risk at a novel 4.2 ng/L cTnT cut-point in Blacks.

1. Introduction

Coping with everyday stressors (Amirkhan, 1990) may disturb sympatho-adrenal activity and cardiac rhythmicity as indicated by changes in catecholamine turnover (De Kock et al., 2012) as well as heart-rate variability (HRV) (Malan et al., 2013). Particularly, defensive coping (DefS) or the *fight-flight response* encompassing perception of control and active problem solving, has been suggested as a promoter of health (Amirkhan, 1990). In spite of this view, DefS outcomes have also been linked with pathology and emotional distress related alterations (De Kock et al., 2012; Malan et al., 2008; Malan et al., 2013), in that attenuated sympatho-adrenal responses to acute mental stress in a cross-sectional analysis were associated with wall remodeling and silent myocardial ischemia in a Black male cohort (Malan and Malan, 2017). Therefore, it seems plausible that chronic defensiveness, reflecting emotional distress, may drive direct relationships between sympatho-

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adrenal activation and markers of cardiac injury (Lazzarino et al., 2013) such as elevated cardiac troponin (cTnT) levels.

A subunit of the troponin complex, namely cTnT is released in response to sympathetic activation or catecholamine overload and myocyte necrosis (Muthu et al., 2014). A decrease in the metabolic supply to the myocardial tissue results in ischemia and resultant cardiomyocyte necrosis of the myocardium (Muthu et al., 2014). Reduced metabolic supply when accompanied by catecholamine vascular responsiveness may further increase myocardial ischemia and cTnT-related damage (Mazzeo et al., 2014; Muthu et al., 2014). Resultant changes in cardiac autonomic modulation and blood pressure may therefore occur to counteract myocardial ischemia, in order to improve perfusion. Accumulative effects of higher chronic metabolic demands may also be taxing if emotional distress is present (Malan et al., 2016). To maintain metabolic homeostasis, central neural control and downstream adrenergic-related signaling will be apparent with either sensitization/up-regulation in acute or desensitization/downregulation in chronic situations (Guilliams and Edwards, 2010). Therefore, we aimed to assess sympatho-adrenal exposure measures, including 24 h urinary catecholamines, 24 h heart-rate-variability (HRV), blood pressure and levels of coping and depression in a bi-ethnic cohort from South Africa. Sympatho-adrenal responses resembling emotional distress might translate to cTnT activity at a certain cut point indicative of future ischemic heart disease risk. Thus, the main aim was to examine prospective associations between binary outcome cTnT and sympatho-adrenal exposure measures.

2. Methods

2.1. Study design

The Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective study (Fig. 1) was conducted in 2008/9 and 2011/12 and included 409 Black and White teachers (Malan et al., 2015). For the current sub-study, we only included teachers participating in both phases and additionally excluded individuals with atrial fibrillation (N = 10), history of or current myocardial infarction or stroke (N = 3) and missing cTnT data at baseline (N = 4). The final study sample comprised of 342 participants who were fully informed about the objectives and procedures prior to recruitment. All participants provided written, informed consent. The study conformed to the Helsinki Declaration (revised 2004) and was approved by the Ethics Review Board of the North-West University, Potchefstroom Campus, South Africa: Approval number 0003607S6.

The three-year follow up investigation was performed using a similar methodology to the baseline evaluation with clinical assessments done over a 36 h period. During the working week, 24 h ambulatory blood pressure, -ECG and 24 h physical activity devices were fitted to the participants at their working place after which they resumed normal daily activities. After 15:00, participants were transported to the North-West University overnight facilities, where they were introduced to the experimental set-up. Afterwards they enjoyed a standardized dinner, and completed a battery of psychosocial questionnaires under supervision of registered clinical psychologists. The next morning, anthropometric (*E-component*) and sphygmomanometer blood pressure measurements were obtained and registered nursing staff collected overnight fasting blood samples after 07:00.

2.2. Cardiovascular risk measures

2.2.1. Ambulatory BP and ECG monitoring (ABPM)

ABPM devices were attached to participants' non-dominant arm (Cardiotens CE120® Meditech, Budapest, Hungary) by trained cardiovascular research personnel. The Cardiotens® was programmed to

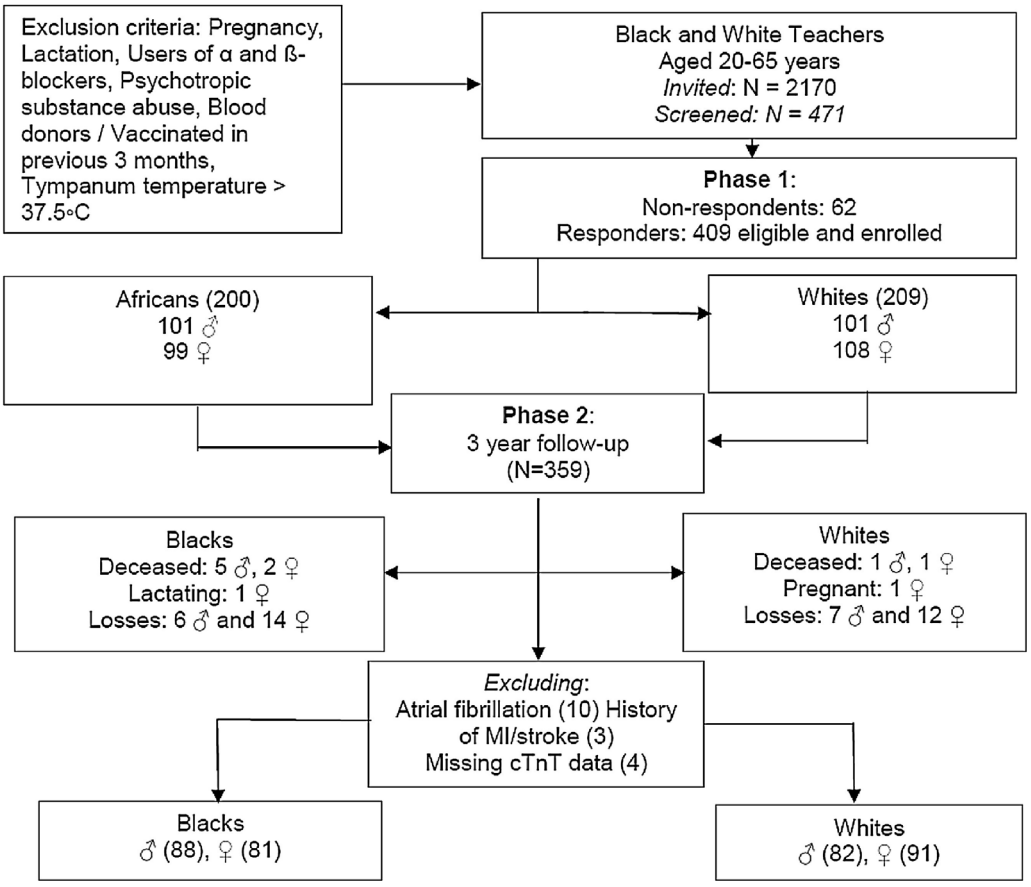

Fig. 1. Design of the bi-ethnic gender cohort of the Sympathetic Activity and Ambulatory Blood Pressure in Africans prospective study. Where: cTnT = cardiac troponin T at baseline.