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STRESS APPRAISAL AND RISK MARKERS FOR STRUCTURAL VASCULAR DISEASE

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Stress Appraisal and Risk Markers for Structural Vascular Disease

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Findings from a Sub-Saharan African Cohort

An escalating prevalence of hypertension in black Africans, particularly in males, is causing concern, but the jury is still out on causative factors [1,2]. One possible mechanism is sympathetic nervous system (SNS) hyper-responsivity in urban Africans [1-3], which informed the design of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study (2008- ). In our commentary we will highlight our initial findings on stress appraisal and risk markers for structural vascular disease.

Stress Appraisal and Risk for Structural Vascular Disease

Personality, environment, previous experiences, and perceptions influence our behavioral responses and a person's perception of the stressor as a challenge or threat [4]. Stress appraisal or coping responses include mainly defensive, social support, and emotional avoidance coping responses [5]. Defensive coping responses entails problem solving, being-in-control, acceptance of the stressor as a reality, and endeavoring to actively eliminate the stressor; "seeking social support" implies an active coping process for comfort and advice in stressful times. Emotional avoidance has been associated with denial, defeat, loss of control, and cardiometabolic pathology [5,6]. Stress appraisal or coping responses stimulate intricate sub-cortical pathways including the thalamus, amygdala, prefrontal cortex, paraventricular hypothalamic nuclei, and brainstem areas. We assessed coping responses qualitatively [5] and identified structural vascular risk via high resolution ultrasound imaging [7].

When interactions were examined between defensive coping, ethnicity, and gender, we have consistently observed detrimental effects in black defensive-coping African men for left carotid intima media far wall thickening and silent ischemia. Interestingly, no interaction existed for either seeking social support or emotional avoidance coping strategies [8].

In support of these results, facilitation of structural endothelial changes by defensive coping responses was also evident from ROC curve analyses. The optimal cut points detecting structural endothelial changes, yielding maximum sum of sensitivity and specificity, ranged between 0.57-0.65 mm (ambulatory blood pressure) and 0.71-0.74 mm (ambulatory silent ischemia) in defensive coping ethnic-gender groups. Only HbA1C (> 5.7%) with a sensitivity/specificity 47%/74%, after controlling for confounders, predicted structural alterations at an optimal cut point of 0.69 mm in defensive-coping African men. Behavioral resilience was apparent in defensive-coping African females despite a high prevalence of risk markers. In the defensive-coping males, chronic hyperglycemia facilitated endothelial dysfunction, i.e. a physiological "loss of control" and susceptibility to stroke risk. These findings, however, are contradictory to other data which have
demonstrated an association between emotional avoidance responses ("loss of control") and cardiometabolic pathology [6]. Urban African males seem to be more at risk, since they reported defensive-coping responses indicating behavioral control. On the other hand though, they demonstrated defensive-coping physiological pathology with enhanced (P ≤ 0.05) blood pressure and vascular hyper-responsivity, depressed heart rate variability, down-regulated norepinephrine metabolites, silent ischemia associated ECG structural wall abnormalities, metabolic syndrome markers, and alcohol abuse [1,9-13]. An apparent dissociation evidently occurs between behavioral and physiological stress responses indicating "loss of physiological control" [1,9-13]. These data could further imply that defensive coping responses in an overly challenging urban environment, where chronic stress is experienced [1,9-13], may exhaust "physiological" resources when control cannot be exerted.

**Stress Appraisal May Facilitate Autonomic Dysregulation and Structural Vascular Disease Risk**

The above findings are closely interlinked with abnormalities in sympathetic nervous system (SNS) regulation of the cardiovascular system and impairments in vascular function [14]. Whether autonomic dysregulation is a cause or consequence of the cardiovascular disease process has been strongly debated [14]. The sympatho-excitatory effects of indirect markers of SNS activity such as increased heart rate, 24-hour silent ischemic events, and chronic hyperglycemia, in the Africans could potentiate adrenergic overdrive reinforcing metabolic overdrive and structural alterations [15]. We demonstrated increased SNS with attenuated baroreceptor sensitivity [16], depressed heart rate variability, and down-regulated norepinephrine metabolites in the African males, particularly those utilizing defensive coping [9-13], possibly supporting the adrenergic overdrive notion.

It seems that increased blood pressure levels may 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 vasculature. Indeed, we have previously demonstrated a decreased cardiac output and arterial compliance in defensive-coping African males, implying a possible diminished β-adrenergic responsiveness [14]. Furthermore, a decrease in cardiac output implies an increase in vascular resistance with possible development of vascular hypertrophy [2,14]. When low sympathetic tone and vascular hyper-responsiveness coincide, less sympathetic drive is needed to maintain blood pressure [2,14-15].

The risk for structural vascular disease in defensive-coping Africans was supported by a profile of autonomic dysfunction with frequency-domain disturbed sympathovagal balance. Additionally, time-domain and geometric depressed heart rate variability (HRV) patterns were also apparent in defensive-coping Africans compared to their Caucasian counterparts (P ≤ 0.05). Inverse associations were demonstrated between 24-hour blood pressure and time-domain HRV measures only in the defensive-coping African men. This was supported by inverse associations between subclinical vascular disease risk and depressed HRV and vagal-impaired heart rate. Meta-analysis on HRV and neuro-imaging studies implicated HRV as a marker of stress and health [17]. Our findings complement 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 emotional avoidance and seeking more social support [12].

**Stress Appraisal and SNS Hyperactivity May Facilitate Silent Ischemia and Risk for Structural Vascular Disease**

It remains unknown whether or not silent myocardial ischemia, as a predictor of sub-clinical atherosclerosis, is driven by increased cardiovascular risk markers. A high prevalence of cardiovascular risk markers, including elevated blood glucose, heart rate, hypertension and carotid intima media thickening (CIMT) were evident in African men who demonstrated 24h silent ischemic events [18]. Silent ischemia events in African men were positively associated with CIMT.

Conversely, reduced perfusion of the heart was mostly supported by the high prevalence of silent ischemic events over 24 hours in low testosterone African males (in progress) and defensive-coping African men, i.e. 9.5 events (95% CI, 5.1-14.0) compared to 1.5 (-2.4-5.3) in their Caucasian counterparts [10]. Structural vascular changes could counteract sympathetic vasoconstriction and may contribute to stress-induced ischemia which impairs neuronal re-uptake of norepinephrine.
thereby potentiating sympathetic signaling [14,15]. When essential hypertension and increased SNS activity, i.e. sympathovagal disturbance and depressed HRV prevail, as seen in defensive-coping African men, structural vascular changes may elicit occurrence of ischemic events and thereby reduced perfusion of the heart.

To conclude, vulnerability may emerge in a demanding Westernized society where efforts to take control drain psychophysiological resources pre-empting neural fatigue. Dissociation between behavior and physiological defensive coping responses are apparent in African men. Behaviorally they reported defensive-coping responses aimed at taking control of a stressor, but physiologically they are losing control which may be "masked" before pathology sets in. A possible facilitated defensive pathway and "loss of control" or neural fatigue could therefore potentially increase their risk for atherosclerosis and/or stroke. Prospective data analyses are underway and we will have to confirm if facilitated defensive-coping responses predict structural vascular disease.

Our work highlights the need to consider psychosocial risk factors in preventive cardiology. Some cardiac risk factors cannot be modified (e.g. genetics, age, sex, personality) but stress appraisal can be reduced in lowering sympathetic activity with lifestyle and psychosocial intervention programs. Acquiring healthy coping strategies at a tender age may prove to be more effective as opposed to changing the lifestyle habits of adults.

References