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Chapter 5

COPING AND AUTONOMIC DYSFUNCTION ACT IN TANDEM WITH ALCOHOL-RELATED SUBCLINICAL ATHEROSCLEROSIS: THE SABPA STUDY

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ABSTRACT

Introduction: Alcohol abuse is among the Westernized world's most common lifestyle factors contributing to sensitization of vascular structure and pathology. Gamma glutamyl transferase (γ-GT), as a marker of alcohol abuse, may indicate increased sensitization and vascular disease risk when using chronic defense coping (DefS). DefS was contradicted as a promoter of health, as it was related with dissociation between self-reported behavioral ("in-control") albeit physiological ("loss-of–control") responses. Therefore, we aimed to assess if DefS may

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mask autonomic dysfunction and induce alcohol-related subclinical atherosclerosis.

Methods: A black African male teacher cohort with similar socioeconomic standing and without atrial fibrillation (N=101) from the North-West Province of South Africa, was recruited and investigated. Fasting blood values, 24h ambulatory blood pressure (ABPM) and -ECG, Coping Strategy Indicator (CSI) scores and ultrasound left carotid intima media far wall scanning values, were obtained. The standard deviation between successful R-R intervals (SDNN) was utilized as a marker of time-domain 24h heart rate variability (HRV). Multivariate regression analyses were computed.

Results: A hypertensive state in the men was evident at a much lower ROC γ-GT cut point than the suggested MERCK cut-point of 78 U/L [55.7 U/L, sensitivity/specificity 60%/86% (AUC 0.78; 95% CI: 0.67; 0.88]. Hereafter, males were stratified into low (<55.7 U/l) and high (≥ 55.7 U/l) γ-GT groups. Overall, the high γ-GT group, revealed a poorer lifestyle profile, mean higher 24h ABPM, depressed 24h HRV and more 24h silent ischemic events (14 vs. 2) compared to their low γ-GT counterparts ($P \leq 0.01$). HRV responses were inversely associated with γ-GT when utilizing DefS ($r = -0.28$; $P = 0.015$). Additionally, ABPM predicted 24h silent ischemia (OR 1.11; $P \leq 0.01$) whereas 24h silent ischemia predicted a trend for structural vascular disease in the DefS African men (OR 1.06; $p \leq 0.06$).

*Conclusion***:** DefS revealed behavioral "in-control" responses directly opposing or *masking* physiological "loss-of-control" responses, underpinning a dissociative response. Alcohol, which is a central nervous system depressant, enhanced vasoconstriction in the vasculature. Indeed, alcohol abuse was related to depressed heart rate variability, when utilizing DefS, sensitizing the vasculature, induced silent ischemia and ultimately structural vascular remodeling. The detrimental effects of DefS acting in tandem with autonomic dysfunction augment alcohol-related ischemia and may increase the risk for early sub-clinical atherosclerosis.

Keywords: Africans; gamma glutamyl transferase, alcohol abuse; cardiovascular health; defence coping

INTRODUCTION

Adapting to an urban environment and the stress associated with it lead to lifestyle changes, possibly in an attempt to cope. This includes increased alcohol intake and in some cases misuse thereof. [1] Alcohol abuse is a well-known risk-factor for an array of conditions, including coronary heart disease,

diabetes and hypertension. [2] Contradicting research demonstrated that alcohol can be beneficial for overall cardiovascular health, [3] but the majority of prospective studies demonstrate that these positive effects are only found in low to moderate levels of consumption. [3]

A biomarker for alcohol abuse, γ-glutamyl transferase (γ-GT), has been described as a strong predictor of cardiometabolic disease, vagal-impaired heart rate variability (HRV) responses as well as the development of the metabolic syndrome. [4, 5] The use of γ-GT as marker for alcohol abuse is limited and often questioned, due to the fact that fatty liver disease and oxidative stress cannot be ruled out in elevated γ-GT levels. [6] However, supportive evidence for γ-GT as behavioral adjustment to psychosocial stress in Africans has been demonstrated. [7] It was also found that γ-GT correlated well with other markers for alcohol abuse. [7]

Another important factor in the development of cardiovascular disease (CVD) is the effect of daily stress and how each individual reacts to and copes with such stress. [8] Different coping styles exist, each exhibiting a different psychological stress response. A defensive active coping (DefS) style describes an active problem-solving focused person, who reports to be in control in stressful times [9] which mainly provokes a β-adrenergic cardiac response. [8] An emotional avoidance coping style refers to a person who reports loss of control [10] who will rather avoid the problem than face it head on [9] and which mainly provokes an α-adrenergic vascular response. [11] Whilst social support, another coping style, is mostly known to mediate good cardiovascular health. [9]

Overall poorer health is associated with an emotional avoidance coping style. [12] Conversely, we revealed intensified risk for the development of CVD when using the DefS style. [11, 13] Additionally, studies showed that Africans, when compared to their Caucasian counterparts, had elevated α-adrenergic vascular reactivity responses during exposure to acute mental stress. [11, 14]

They also revealed poorer overall cardiometabolic health, and four times more African than Caucasian males reported that they were under severe stress. [15] Behaviorally, African men reported the use of a DefS style – which should be a health promoter [9], but contradictorily they showed augmented α-adrenergic stress responses, enhanced after- and preload to the heart and ultimately reduced function of the heart. [11] These findings may underpin a mechanism where dissociation between physiological and behavioral stress responses are demonstrated during chronic stress. [15, 16].

Therefore, we intend to take it one step further by hypothesizing that alcohol abuse may be a contributing factor to cardiovascular risk in a male cohort when habitually utilizing DefS. Our findings may contradict DefS as a health promoter as associations between alcohol abuse, autonomic dysfunction and sensitization of the vasculature may predict ultimate poorer cardiovascular health in an urban African male cohort.

METHODS

Study Design and Participants

This sub-study forms part of the Sympathetic Activity and ambulatory Blood Pressure in Africans (SABPA) study. The target population study included Caucasian and African teachers from the Dr Kenneth Kaunda Education District of the North West province in South Africa from 2008 to 2009. The participants were selected to ensure similar socio-economic status and professional environments although their cultural characteristics may differ greatly. [16]

All eligible teachers between the age of 20 and 62 years were invited to participate in the study. Original exclusion criteria included users of α- or β-blockers, psychotropic substance abusers, atrial fibrillation, participants with tympanum temperature above 37.5°C, and those who have donated blood or received vaccinations within the 3 months prior to the study. Participants signed informed consent forms prior to the execution of the study. The SABPA study was approved by the Ethics Review Board of the North-West University (Potchefstroom Campus: NWU-0003607S6), and the conducting of the procedures all complied with the guidelines of the Declaration of Helsinki. [17] The total sample size comprised 101 African male participants and females were excluded as a limited sample exceeded the cut point for alcohol abuse.

Cardiovascular Measures

On working days, ambulatory blood pressure- (ABPM), electrocardiogram- (ECG) and accelerometer measurements were recorded (Cardiotens CE120®, Meditech, Budapest, Hungary and Actical®, Mini Mitter, Montreal, Quebec). The apparatuses were fitted respectively onto the

non-dominant arm and the hip of each participant at approximately 07:00. A suitably-sized cuff, be it non-obese or obese, was used for each participant. The Cardiotens CE120® device was programmed to measure the participants' blood pressure (BP) at intervals of 30 minutes between 08:00 and 22:00 and at intervals of 60 minutes from 22:00 until 06:00 the next morning [18] with a successful mean inflation rate of 75.5 %. The silent ischemia/ambulatory ischemic events profile was assessed by two-channel ECG recordings (Cardiotens CE120®) according to a pre-set program for 20 seconds at 5 minute intervals. A silent ischemic event was recorded according to the following criteria (also known as the 1-1-1 rule), namely: horizontal or descending ST-segment depression by 1 mm; duration of the ST-segment episode lasts for 1 minute, and there was a 1 minute interval from the preceding episodes.

Heart rate variability (HRV) responses have been computed to obtain SDNN [4], which is a prognostic tool for cardiovascular outcome and may be 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. [4] SDNN values are closely related to the high frequency (parasympathetic) component of the power spectrum and thus reflect vagus nerve-mediated autonomic control of the heart. [4] The software program automatically filters out ventricular, supraventricular as well as artifacts in RR intervals, and outliers were manually removed.

Participants were instructed to note if they experienced any abnormal disturbances like syncope, nausea or visual impairment on a 24h diary card. After these devices were fitted, the participants carried on with their normal daily activities. At 16:30 they were transported to the North-West University's Metabolic Unit Research Facility for an overnight stay and familiarized with the experimental set-up. Hereafter, they completed a psychosocial battery, supervised by registered clinical psychologists. Later they received a standardized dinner and were requested to go to bed at 22:00, fasting overnight for other clinical measures to be performed the following day.

Participants were woken at 06:00 the next morning and the devices were removed as soon as the last ABPM was recorded. Hypertension was regarded as an average ambulatory BP of ≥ 130 mmHg and/or ≥ 80 mm Hg. [19]

Anthropometric measurements and an eight-hour fasting urine sample were obtained, and lastly blood samples were collected by a registered nurse. A General Socio-demographic and Health Questionnaire was used to gain information regarding the participants' family medical history and lifestyle habits such as smoking and alcohol usage.

Coping Assessment

The Coping Strategy Indicator (CSI) has a Cronbach reliability index of 0.84 - 0.93 and was used to identify each participant's chronic coping style successfully.[9] The CSI is a self-report measure consisting of 33 items which determine whether a person uses the problem solving, avoidance or seeking social support coping style in difficult times. The 33 items in the questionnaire are divided into three sub-sets of 11 items each. The participant answers each item using a three-point Lickert scale, 3 being "a lot", 2 "a little", and 1 "not at all". They choose 1, 2 or 3 as an answer while keeping in mind a stressful event they have encountered over the last six months. The accumulated score of the answers indicate the use of a certain coping style. A total score of ≥ 26 indicates above mean usage of the problem solving or DefS style, ≥ 23 indicating above mean use of the social support style, and ≥ 19 indicating above mean use of the avoidance style. [9]

Lifestyle Factors and Anthropometric Measurements

Physical activity was measured using the Actical® omnidirectional accelerometer which was fitted on the hip of the participant. Set to 15 second intervals, this device measured movement of the participant whilst they engaged in normal daily activities. The data was then converted into 1-second intervals for analysis. γ-GT levels were measured as marker for alcohol abuse, [7, 20] and for each participant's smoking habits, cotinine was measured.

All anthropometric measurements were obtained by ISAK (International Society for the Advancement of Kinanthropometry) level 2 accredited anthropometrists using calibrated instruments (Precision health scale, A & D Company, Tokyo, Japan; Invicta Stadiometer IP 1465, Invicta, London, UK), with subjects in minimal clothing and without shoes. Measurements were performed with standardized methods and in triplicate to ensure accuracy. Body mass index (BMI) was calculated by dividing the participants' weight

(kg) by their length (m^2). The body surface area (BSA) in m^2 was calculated according to the Mosteller formula. [21] Intra- and inter-observer variability was less than 10%.

Measurements of Target Organ Damage

The left common carotid intima media thickness of the far wall (L-CIMTf) was determined using the SonoSite Micromaxx ultrasound system (SonoSite Inc., Bothell, WA, USA) and utilizing a 6-13 MHz linear array transducer according to the Rudi Meijer protocol. [22] LIMT-f was measured to identify sub-clinical arterial wall thickening. Urinary albumin and creatinine, as an index of kidney function, were determined with the sequential multiple analyzer computer (Konelab 20i TM, Thermo Scientific, Vantaa, Finland).

Biochemical Measures

Fasting blood samples from the antebrachial vein branches were obtained by a registered nurse using a sterile winged infusion set. Liver enzymes were analyzed with the enzyme rate method, C-reactive protein (CRP) levels with the turbidimetric method and the timed-end-point method was used to determine blood glucose, cholesterol, high density lipoprotein (HDL) and triglycerides levels. All the above variables were measured using the Unicel DXC 800 analyzer (Beckman and Coulter, Germany). Serum cotinine levels were measured using the homogeneous immunoassay on the Modular ROCHE automized analyzer (Konelab 20i; Thermo Scientific, Vantaa, Finland). The enzymatic colorimetric test and Cobas® Integra 400 plus (Roche, Basel, Switzerland) were used to determine serum creatinine. Glycated haemoglobin was measured with the Cobas® Integra 400 (Roche, Switzerland), using the turbidimetric inhibition immunoassay method.

Statistical Analyses

Analyses were done using Statistica version 12.0 (Statsoft Inc., Tulsa, USA, 2011). Non–Gaussian distributed variables were logarithmically transformed, after which independent t-tests were computed to describe the

baseline characteristics of the entire group. Together with this, Chi-square (X^2) tests were used to determine prevalence for medications and pathology including ABPM hypertension, diabetes and also the treatment thereof, as well as HIV status.

Thereafter, a non-parametric receiver-operating characteristic (ROC) curve [23] was computed together with the area under the curve (AUC) to explore the association between γ-GT and ambulatory hypertension cut points. [19] Sensitivity and specificity values were computed to determine the cut points that would maximize the sum of the number of true positive and true negative predictions.

The male cohort was stratified according to the suggested cut point for γ-GT. Sensitivity and specificity values were once again calculated to highlight the odds of γ-GT predicting pathological ambulatory hypertension.

Interaction effect analyses were repeated for each of the three dichotomized coping strategies using the following mean cut points: DefS (≥ 26), avoidance (≥19) and social support (≥ 23). Main effects interactions between γ-GT x coping for cardiovascular risk markers were computed. Independent t-tests identified confounders for the two-way analysis of covariance (ANCOVA) tests. The ANCOVA's were adjusted for determined confounders. Multiple linear regression analyses in ethnic-gender groups were performed. Unadjusted linear associations between HRV and γ-GT in Defs groups were computed and presented in scatterplots. Odds ratios (OR's) with 95% Confidence Intervals (CI's) were calculated in several models to highlight the odds of independent risk markers (lifestyle, BP) to predict silent ischemia and structural vascular disease marker, L-CIMTf in high γ-GT as well as in high γ-GT DefS groups. Age, CRP, Cholesterol, BP were added as independent confounders in the L-CIMTf models. Significant values were noted as $p \leq 0.05$..

RESULTS

Table 1 demonstrates baseline characteristics of the entire African male cohort. It also shows the prevalence of certain pathology and medications taken by the participants.

Overall, levels exceeding cut points of γ-GT and cardiometabolic values were evident including ambulatory blood pressure (SBP and or DBP 130/80, triglycerides (≥1.7mmol/l), CRP (≥ 3 mg/l), HbA1c (pre-diabetic ≥ 5.7%) and glucose (5.6 mmol/l).

Table 1. Baseline characteristics of African male cohort (mean ± SD)

Variables	African males (N = 101)
Age, (years)	43.18 ± 8.17
Lifestyle factors:	
Body mass index, (kg/m2)	27.72 ± 5.78
Body surface area, (m2)	1.94 ± 0.23
Waist circumference, (cm)	93.56 ± 15.49
Cotinine, (ng/ml)	35.46 ± 65.01
Physical activity, (kcal/24h)	2714.85 ± 800.12
γ-Glutamyl transferase , (U/l)	84.84 ± 91.70
Aspartate aminotransferase : Alanine aminotransferase (AST:ALT)	1.63 ± 1.03
Psychological variables:	
Defensive problem solving score	28.21 ± 4.18
Social support score	24.87 ± 5.37
Avoidance score	21.00 ± 3.62
Biochemical variables:	
HbA1c, (%)	6.24 ± 1.23
C-reactive protein, (mg/l)	5.19 ± 8.23
Triglycerides, (mmol/l)	1.81 ± 1.59
Creatinine, (µmol/l)	77.22 ± 14.22
Total cholesterol, (mmol/l)	4.74 ± 1.17
High density lipoprotein, (mmol/l)	1.05 ± 0.37
Resting glucose, (mmol/l)	5.99 ± 2.02
Albumin:Creatinine (ACR)	1.72 ± 3.25
Cardiovascular variables:	
24hr SBP, (mmHg)	138 ± 16.01
24hr DBP, (mmHg)	88 ± 10.74
24h Heart rate, (beats/minute)	79 ± 11.36
SDNN (ms)	123.72 ± 45.59
Ischemic events, (n)	9.39 ± 20.84
L-CIMTf mean, (mm)	0.72 ± 0.18

Table 1. (Continued)

Variables	African males (N = 101)
Pathology and medications:	
*Hypertensive, n (%)	76 (75)
*Anti-hypertensive drugs, n (%)	20 (19.80)
*Anti-diabetic drugs, n (%)	7 (16.93)
*HIV infected, n (%)	13 (12.87)

Where: HbA1c, glycated haemoglobin; SDNN, standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes; L-CIMTf, left carotid intima media thickness of the far wall. Values presented as arithmetic mean ± SD; *-values, presented as number of observations, n, and percentage of total group, (%).

ROC analysis was used to determine a suggested cut-point for γ-GT levels predicting ambulatory hypertension in 101 African men. Figure 1 illustrates where the AUC was most optimal for ambulatory hypertension, and also shows the cut-points according to the Youden index.

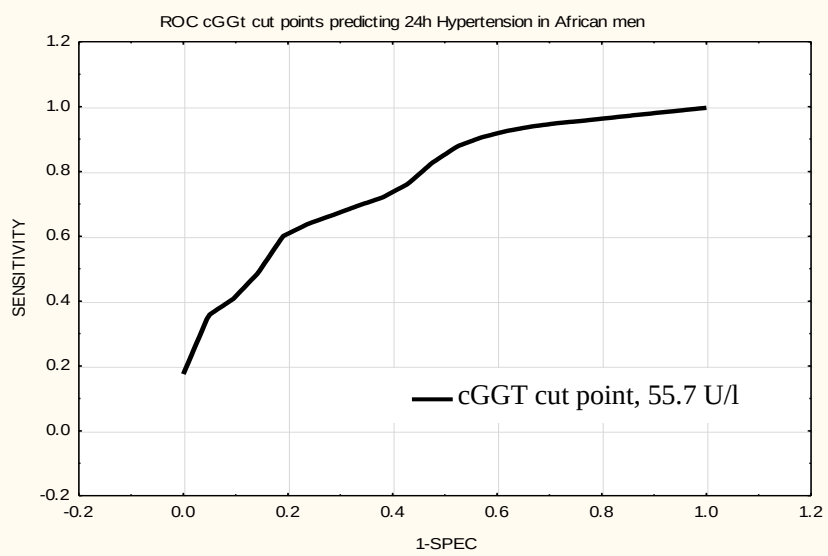


Figure 1. ROC curves depicting cGGT cut points for 24 Hypertension Prevalence in a cohort of 101 African males (AUC ± 95 % CI): 0.78 (0.67; 0.88).

The ROC cut point values that showed maximum sensitivity (60%) and specificity (86%) were found at 55.7 U/L with an AUC value of 0.78 (0.67; 0.88). Hereafter, the total group was stratified into low (<55.7U/L) and high (≥55.7 U/L) γ-GT levels.

Interaction effects were only evident for DefS and not for any other coping style. A single main effects (ROC γ-GT x DefS) interaction existed for ambulatory DBP [F (1, 95), 4.72: p=0.03].

Table 2, compares the low and high γ-GT groups, adjusting for the identified confounders, namely BSA and physical activity in the form of total energy expenditure (TEE). Significantly higher levels of triglycerides, aspartate aminotransferase: alanine aminotransferase ratio, ambulatory BP and ischemic events were revealed in the higher γ-GT group compared to the low group. Furthermore, significantly more participants (92%) suffer from hypertension in the high γ-GT group than in the low group (58%).

Table 2. Comparing mean cardiometabolic and coping responses in an African male cohort, stratified into low and high γ-GT levels (±95 % CI)

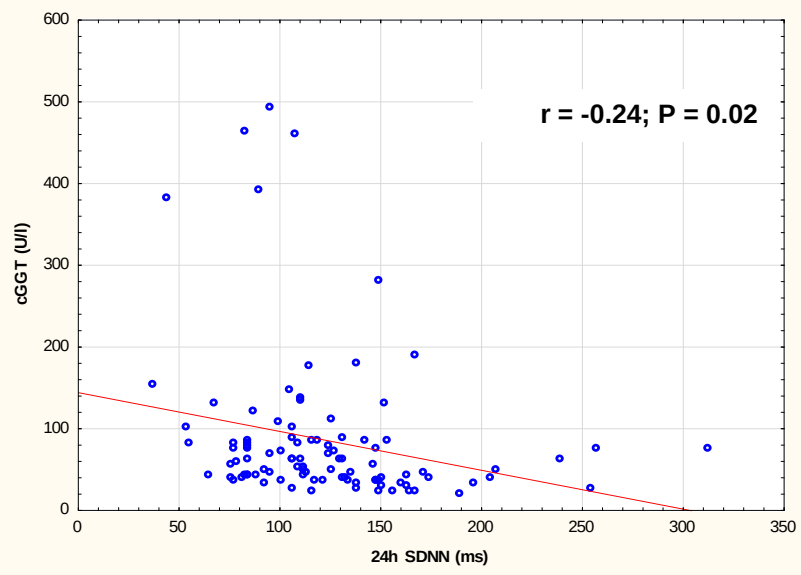
Variables	γ-GT levels (<55.7 u/l) N=50	γ-GT levels (≥55.7 u/l) N=51	P-value
Unadjusted lifestyle factors (mean ± SD):			
Body surface area, (m2)	1.86±1.12	2.00±1.12	0.002
Physical activity, (kcal/24h)	2429±1.28	2794±1.35	0.01
Adjusted for lifestyle factors (Body surface area; Physical activity):			
Age, (years)	42.23 (39.9, 44.4)	44.11 (41.9, 46.4)	0.26
Body mass index, (kg/m2)	26.83 (26.1, 27.6)	27.18 (26.4, 27.9)	0.52
Waist circumference, (cm)	90.84 (88.7, 93.0)	93.73 (91.6, 96.0)	0.07
Cotinine, (ng/ml)	29.13 (10.35, 48.0)	41.66 (23.0, 60.3)	0.36
γ-Glutamyl transferase, (u/l)	35.80 (31.5, 40.7)	108.27 (95.4, 122.9)	<0.001
AST:ALT	1.16 (1.0, 1.8)	1.27 (1.1, 1.5)	0.02
Psychological variables:			
Defensive problem solving score	27.38 (26.1, 28.7)	28.34 (27.0, 29.7)	0.32
Social support score	23.21 (21.6, 24.9)	25.19 (23.5, 27.0)	0.1
Avoidance score	20.38 (19.4, 21.5)	20.97 (20.0, 22.1)	0.45
Biochemical variables:			
HbA1c, (%)	5.97 (5.7, 6.3)	6.32 (6.0, 6.6)	0.10

Table 2. (Continued)

Variables	γ-GT levels (<55.7 u/l) N=50	γ-GT levels (≥55.7 u/l) N=51	P-value
C-reactive protein, (mg/l)	2.37 (1.7, 3.2)	3.19 (2.3, 4.4)	0.20
Triglycerides, (mmol/l)	1.07 (0.9, 1.3)	1.97 (1.7, 2.3)	<0.001
Creatinine, (μmol/l)	75.51 (71.7, 79.5)	76.44 (72.7, 80.4)	0.75
Total cholesterol, (mmol/l)	4.44 (4.2, 4.8)	4.77 (4.5, 5.1)	0.15
High density lipoprotein, (mmol/l)	1.01 (0.9, 1.1)	0.97 (0.9, 1.1)	0.57
Resting glucose, (mmol/l)	5.51 (5.1, 6.0)	6.0 (5.6, 6.5)	0.12
Albumin:Creatinine (ACR)	1.10 (0.9, 1.4)	0.94 (0.7, 1.2)	0.39
Cardiovascular variables:			
24hr SBP, (mmHg)	133 (129, 137)	141 (137, 145)	0.01
24hr DBP, (mmHg)	84 (82, 87)	90 (88, 93)	0.003
24h Heart rate, (beats/minute)	76 (73, 80)	80 (77, 84)	0.77
SDNN, (ms)	132.76 (119.8, 145.7)	115.03 (102.4,127.7)	0.06
Ischemic events, (n)	4.26 (2.22, 8.18)	13.75 (7.59, 24.91)	0.01
L-CIMTf mean, (mm)	0.70 (0.66, 0.76)	0.69 (0.65, 0.74)	0.78
Pathology and medication:			
*Hypertensive, n (%)	29 (58)	47 (92)	<0.01
*Anti-hypertensive drugs, n (%)	4 (8)	16 (31)	0.003
*Anti-diabetic drugs, n (%)	2 (4)	5 (10)	0.25
*HIV infected, n (%)	6 (12)	7 (14)	0.74

Abbreviations: HbA1c, glycated haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; SDNN, standard deviation of the normal-to-normal (NN) intervals between adjacent QRS complexes; ; L-CIMTf, left carotid intima media thickness of the far wall. Values adjusted for body surface area and physical activity. *Values presented as number of observations, n, and percentage of total group.

In Figure 2, unadjusted associations between γ-GT and HRV became stronger when utilizing a DefS. OR's were calculated in Table 3 to determine the probability of high γ-GT levels and utilization of the DefS style predicting silent ischemia and increased structural wall remodelling. 24h SBP mostly predicted silent ischemic events in the high γ-GT as well as the high γ-GT plus DefS utilizing groups.



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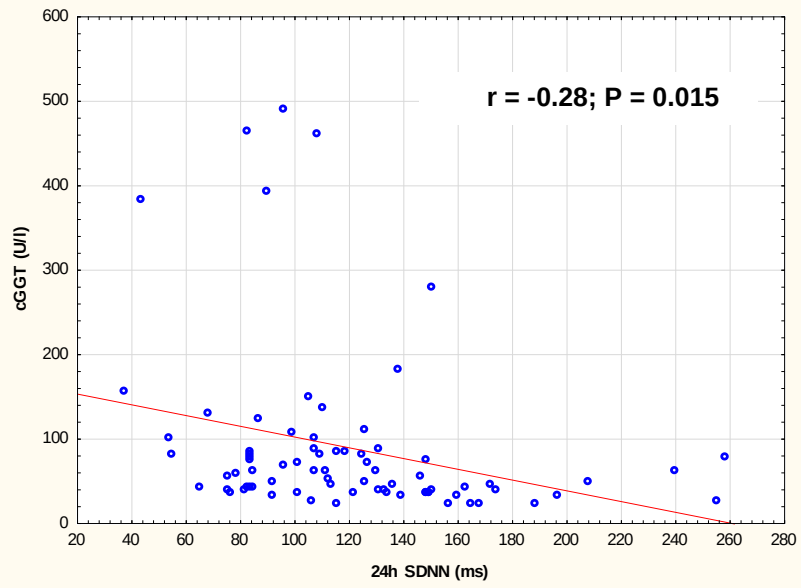

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Figure 2. Unadjusted associations between heart rate variability and alcohol abuse (gamma glutamyl transferase) in all African men (Figure 2a); and (Figure 2b) in Defensive coping African men. Where: (SDNN, standard deviation of each successive R-R interval).

Table 3. Probability of ischemic events and increased structural vascular remodelling (L-CIMTf) in African men

	Prevalence of ischemic events				
Model 1	Nagelkerke R2	Odds Ratio	5th Percentile	95th Percentile	P
African Men – High γ-GT levels (>55.7U\l)					
24h SBP (mmHg)	0.30	1.09	1.03	1.12	<0.01
24h DBP (mmHg)	0.18	1.08	1.01	1.14	0.03
African Men – High γ-GT levels (>55.7U\l) + DefS					
24h SBP (mmHg)	0.36	1.11	1.03	1.18	<0.01
24h DBP (mmHg)	0.16	1.07	1.00	1.15	0.08
Model 2	L-CIMTf ≥ 0.9mm				
	Nagelkerke R2	Odds Ratio	5th Percentile	95th Percentile	P
African Men – High γ-GT levels (>55.7U\l)					
24h SBP (mmHg)	0.14	1.00	0.94	1.05	0.90
24h DBP (mmHg)	0.14	0.99	0.91	1.06	0.69
24h ischemic events (N)	0.14	1.01	0.98	1.04	0.41
African Men – High γ-GT levels (>55.7U\l) + DefS					
24h SBP (mmHg)	0.37	1.06	0.96	1.15	0.25
24h DBP (mmHg)	0.32	1.03	0.90	1.16	0.66
24h ischemic events (N)	0.37	1.06	1.00	1.11	0.06

Where: DefS, Defensive active coping; γ-GT, gamma glutamyl transferase and L-CIMTf, left carotid intima media thickness far wall. Confounders for Model 1 included body surface area and physical activity. Model 2 was adjusted for age, log CRP and cholesterol. Significant odds ratios presented where P values ≤ 0.05.

For African men with high γ-GT levels, 24h SBP predicted silent ischemia with an OR of 1.09 (95% CI: 1.03 – 1.12). The prediction is stronger in the group with high γ-GT levels if utilizing DefS, where 24h SBP predicted ischemia with an OR of 1.11 (95% CI: 1.03 - 1.18). 24h DBP also predicted ischemia in the high γ-GT as well as the high γ-GT plus DefS utilizing groups, with OR's of 1.08 (95% CI: 1.01 - 1.14) and 1.07 (95% CI of 1.00 - 1.15)

respectively. Independent of confounders, silent ischemia in these men (high γ-GT + DefS), predicted a trend for structural vascular disease, namely L-CIMTf (OR 1.06; $p \leq 0.06$).

DISCUSSION

The main aim of this study was to assess whether alcohol abuse may be a contributing factor to cardiovascular risk factors in a male cohort when habitually utilizing DefS. The primary finding of our study demonstrated early sensitization of the vasculature in African men where an inverse relationship between autonomic dysfunction and alcohol abuse was demonstrated. High γ-GT levels with a cut point of 55.7 U/L predicted ambulatory hypertension. The significant interaction between γ-GT and DefS for ambulatory DBP enhances the notion of higher vascular responsiveness in the African male cohort. This is further supported by the interaction between alcohol abuse and DefS, where silent ischemia predicted a trend for structural vascular changes in L-CIMTf (≥ 0.90mm). The detrimental effects of DefS and autonomic dysfunction acting in tandem with alcohol-related ischemia seem to aggravate the risk for early sub-clinical atherosclerosis.

It is important to notice that pathology begins to manifest in the chosen group at a lower γ-GT cut point (55.7 U/L) than recommended by the Merck manual (78 U/L). [6] This may indicate early sensitization of the vasculature. Alcohol, which is a central nervous system depressant [6], will enhance vasoconstriction in the vasculature. Indeed, alcohol abuse was related to depressed heart rate variability when utilizing DefS, sensitizing the vasculature and may have induced silent ischemia and structural vascular remodeling. This can clearly be seen where 92% of the high γ-GT group demonstrated hypertension, despite the fact that only 31% of them are taking medication for the treatment thereof. This may suggest ethnic differences in pressor responsiveness and associated cardiometabolic risk. We, therefore, propose an ethnic specific γ-GT cut point indicating early vasculature responsiveness below the recommended cut point of 78 U/L. [6]

We need to mention that controversy exists over the use of γ-GT as marker for long term alcohol abuse, as non-alcoholic liver disease can also contribute to elevated levels thereof. [7] Therefore, we included another marker of liver pathology, namely the AST:ALT ratio. Assessing the ratio, a value <1 indicates liver pathology, which is not alcohol related, such as non-alcoholic fatty liver disease. [24] Thus, the > 1 ratio found in our high γ-GT

group justifies the use of γ-GT as alcohol marker for the purposes of this study. [7]

Independently, both alcohol and DefS responses may be associated with pathology through various mechanisms, such as the well-known vasopressor effect of alcohol, [25] which is further worsened by DefS-induced endothelial dysfunction, especially in African men. [15, 16] The notion of alcohol as coping strategy and vagal-impaired response [16, 26, 27] have been demonstrated in African men, and our current data support alcohol abuse associated with autonomic dysfunction specifically depressed heart rate variability. [16] The current sub study support the above findings as an alcohol abuse ROC cut point predicted subclinical atherosclerosis in an African cohort utilizing DefS. The interaction between alcohol abuse and DefS [26, 27] for ambulatory DBP, underscores cardiac overload and α-adrenergic vascular sensitization and -vulnerability in these males.

Conversely, the higher prevalence of hypertension and usage of anti-hypertensive drugs in the high γ-GT African male group were confirmed in previous studies. This undercores that alcohol is a great risk factor in the development and progression of hypertension, and we recommend the restriction of alcohol in the treatment of hypertension. [5, 19, 28] High concentrations of alcohol are generally known to cause vasoconstriction of blood vessels. This can be due to the fact that alcohol inhibits endothelial-dependent vasodilation, and as previously mentioned – endothelial dysfunction. [29, 30] The higher number of ischemic events found in the high γ-GT group emphasizes higher central demand and compensatory increased autonomic activity, resulting in enhanced vasoconstrictive responsiveness, [29, 30] Ultimately reduced oxygen supply to the heart may increase the risk for coronary artery disease. [31, 32] It is however, also true that low to moderate consumption of alcohol leads to vasodilation, rather than vasoconstriction. [33] Therefore, recommended ethnic-culturally different cut points are needed as it seems that alcohol effects may vary considerably depending on the amount consumed and ethnicity of the user.

It seems clear that the majority of studies confirmed the alcohol-induced increased BP responses. It was demonstrated that arterial stiffening was significantly associated with consumption of large amounts of alcohol. [34] Subsequent pressor responses may induce elevated coronary artery disease risk. [35] Indeed, Hamer et al. computed odds ratios in African males of the SABPA study, where γ-GT was shown to indicate a risk of 3.1 (95% CI 0.6 - 15.5, independent of other confounders, predicting early structural vascular changes. [1] We take it one step further by demonstrating that an OR of 1.11

(95% CI 1.03 - 1.18) for silent ischemia may induce early structural vascular changes in high γ-GT, DefS African men.

Regarding the metabolic profile, it was evident that the high γ-GT group showed significantly increased levels of triglycerides, which confirm the findings of other studies where alcohol was directly linked to hypertriglyceridemia. [36, 37] Alcohol abuse is known to up-regulate hepatic fatty acid absorption, associated with the development of steatosis. [38] Triglycerides are then deposited into the liver and accumulate in the hepatocytes, which may also be evident in our own African group as significantly elevated levels of triglycerides were found in the high γ-GT group. This may be linked to central obesity and other cardiovascular risk factors. [39, 40] Literature describing the effects of alcohol usage on waist circumference shows that high consumption of alcohol shows an increase in weight gain, and as a result, an expansion of waist circumference or central obesity. [41] Cautiously, we want to speculate that the central obesity tendency (93%) in the high γ-GT group might also be stress related. Indeed, Björntorp & Rosmond confirmed this phenomenon in participants adapting to, or coping with psychosocial stress. [42] They demonstrated an association between psychosocial stress and increased corticoid receptor binding in abdominal adipose tissue that reflected increased cortisol and central obesity. [42] We cannot, however, declare the actual extent of alcohol abuse, as self-reporting alcohol intake may not always reflect actual intake.

What our result do show is that the high γ-GT group had significantly more silent ischemia, which are in line with previous fndings. It was suggested that dissociation between behavioral and physiological responses in DefS African men facilitates vascular hyper-responsiveness and sensitivity to even the smallest of challenges. [43] Indeed, DefS facilitated autonomic nervous system dysfunction, which was associated with higher blood pressure and sub-clinical structural vascular disease. This may further attribute to the vulnerable cardiovascular profile in the African male cohort, partly explaining why the prevalence of CVD amongst urban Africans is escalating at an alarming rate. It is suggested that this may be enforcing adaptation of their African collectivistic cultural lifestyles to a Westernized lifestyle and behavior. It may be that they turn to, amongst other things, alcohol as coping mechanism in order to cope with this transition or challenges in an individualistic westernized environment. [1] Limitations in the study included the controversial use of γ-GT as true marker of alcohol abuse. Another limitation is the absence of another group to compare the data with, for example their Caucasian counterparts. The motivation behind this limitation is the fact that

too few Caucasian males showed levels of γ-GT ≥ 55.7 U/L. Expanding analyses to other ethnic-cultural groups in prospective studies may confirm the detrimental effect of alcohol abuse on the vascular system and subsequent CVD's or events.

In conclusion, alcohol abuse directly causes myocardial damage [43] due to the toxic effects it has on myocytes, and has been associated with an increased incidence of atherosclerotic coronary artery disease. [1] Our findings thus underscores a vulnerable cardiometabolic and vagal-impaired profile in an African male cohort. It emphasizes a mechanism of defense coping and sensitized autonomic responses during chronic or taxing circumstances. The detrimental effect of excessive alcohol usage subsequently induces reduced perfusion and early structural vascular remodeling. Our data support previous findings where DefS revealed self-reported behavioral "in-control" responses directly opposing or *masking* physiological "loss-of-control" responses, underpinning a dissociative response. Thus, an ethnic cultural specific cut point of 55.7U/L of γ-GT is suggested to reveal the level at which alcohol intake may drive increased risk for silent ischemia and a tendency for early structural vascular pathology.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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