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Cardiac autonomic function and its association with cardiometabolic disease risk factors in Black South African children

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ABSTRACT

Objective: This study evaluated the associations between cardiac autonomic nervous system (ANS) activity and cardiometabolic disease (CMD) risk factors among black South African children.

Design: The participants included 34 black South African children (11.85 ± 0.89 y). CMD risk factors included waist circumference (WC), hip circumference (HC), body mass index z-score (BMI z-score), blood pressure (SBP, DBP), total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), fasting glucose (FG), fasting insulin (FINS), and vessel stiffness index (SI). Heart rate variability was used to quantify cardiac ANS activity.

Results: lnRMSSD, pNN50 and lnSD1 were inversely associated with FINS ($r = -0.33$, $p = 0.05$; $r = -0.36$, $p = 0.03$; $r = -0.41$, $p = 0.01$), WC ($r = -0.45$, $p = 0.01$; $r = -0.39$, $p = 0.02$; $r = -0.45$, $p = 0.01$), and HC ($r = -0.41$, $p = 0.01$; $r = -0.36$, $p = 0.03$; $r = -0.43$, $p = 0.01$). HDL was positively associated with lnRMSSD ($r = 0.37$; $p = 0.03$) and lnSD1 ($r = 0.37$; $p = 0.03$) while, LDL was negatively associated with HF ($r = -0.41$; $p = 0.01$). Regression analysis identified WC as the primary predictor for parasympathetic modulation in time domain (lnRMSSD: $r2 = 0.21$, $p = 0.01$; pNN50: $r2 = 0.18$, $p = 0.01$) and non-linear domain (lnSD1: $r2 = 0.21$, $p = 0.01$).

Conclusion: Elevated resting parasympathetic activity in children is associated with lower CMD risk factors and an elevation in the protective HDL.

1. Introduction

The clustering of cardiometabolic disease (CMD) risk factors is becoming more prevalent in children and may be linked to ethnicity (Crowley et al., 2011). Black adolescents are reported to have higher rates of obesity, insulin-resistance and high blood pressure compared with white adolescents (Cook et al., 2008). Established and emerging CMD risk factors are associated with cardiac autonomic dysfunction and decreased parasympathetic activity (Farah et al., 2014). Cardiac autonomic function refers to the innervation of parasympathetic and sympathetic branches of the autonomic nervous system (ANS) regulating the heart (Malpas, 2010). The influence of the parasympathetic and sympathetic nervous system may be measured using heart rate variability (HRV), a measure which quantifies cardiac ANS activity (Fukuba et al., 2009). Most studies examining associations between CMD risk factors and ANS activity are inconsistent and do not differentiate between different race/ethnicities (Farah et al., 2014; Xie et al., 2013; Mazurak et al., 2016).

Farah et al. (2014) found that higher body mass index (BMI) and systolic blood pressure (SBP) in Brazilian children aged sixteen-years were associated with increased sympathetic activity (LF) and decreased parasympathetic activity (RMSSD, pNN50, HF). Similarly, Paschoal et al. (2009) observed that increased sympathetic activity (LF, LF/HF) was positively related to waist circumference (WC) and triglycerides (TG) and negatively associated with high density lipoprotein cholesterol (HDL), but was not related to either total cholesterol (TC) or low

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density lipoprotein cholesterol (LDL) in Brazilian obese children (9–11 y). Although these studies suggest an association between CMD and sympathetic activity, the concept of the LF component to reflect sympathetic activity is flawed since it is suggested to represent both parasympathetic and sympathetic influences (Parati et al., 2000). Moreover, hypertensive Chinese children demonstrated lower HRV values (SDNN, RMSSD, TP, HF) compared with their normotensive counterparts (Xie et al., 2013). In contrast to these findings, a German study found no significant difference in HRV parameters (SDNN, RMSSD, HF, LF, LF/HF) among healthy weight and obese children (9–17 y) (Mazurak et al., 2016).

Despite the significant volume of literature on CMD, it is unclear which risk factor accounts for the greatest variance in cardiac ANS activity and more specially, it is unclear how risk associations would present in children of black ethnicity. The inconsistent associations between individual risk factors and altered ANS activity have important implications for early ethnic-specific identification of disease risk. To address this gap, this study aimed to profile CMD risk factors among black South African children and their individual associations with ANS activity.

2. Methodology

2.1. Participants

Thirty-four black South African children (14 males and 20 females; 11.85 ± 0.89 y) recruited from a primary school in the province of KwaZulu-Natal participated in this cross sectional study in July 2013. The inclusion criteria included: children of black ethnicity between the ages of 10 and 13 years old (grades 4–7) without any known chronic disease. Approval of this study was obtained from both the institution's Research Ethics Committee (UZREC171110–030) and the KwaZulu-Natal Department of Education Institution (2/4/8/815). Written informed consent was given by the parents and assent was given by the children before participation in this study.

2.2. Procedures

All measurements were taken over five consecutive days between 9:00 AM and 12:00 PM in a quiet room at the school. The Suunto t6 monitor system was used to record 5-min interbeat intervals (IBI) in supine position (Suunto Inc.; Vantaa, Finland). IBI measurements were recorded after a 5-min resting period in groups of four, due to equipment availability. Breathing rate was guided with a metronome set at 15 breaths/min (0.25 Hz). Raw IBI were manually screened for artifacts and were replaced with mean values of proceeding and preceding beats (Timonen et al., 2006). Heart rate variability indices were processed using Kubios HRV software and included time, frequency and nonlinear parameters indicative of: overall variability (SDNN, SD2), parasympathetic activity (RMSSD, pNN50, SD1, HF: 0.15–0.4 Hz), baroreflex activity (LF: 0.04–0.15 Hz) and sympathovagal balance (LF/HF) (Biosignal Analysis and Medical Imaging Group, Joensuu, Finland). Power spectral analysis was performed on both autoregressive (AR) and fast Fourier transform (FFT) spectrums.

CMD risk factors included WC, hip circumference (HC), body mass index z-score (BMI z-score), systolic and diastolic blood pressure (SBP, DBP, respectively), fasting TC, HDL, LDL, fasting glucose (FG), fasting insulin (FINS) and vessel stiffness index (SI).

WC and HC were measured in a standing position using a measuring tape. A digital scale measured body weight and was recorded to the nearest 0.1 kg. A portable stadiometer measured height and was recorded to the nearest 0.1 cm. BMI was calculated as body weight divided by height squared (kg/m^2), and BMI z-scores were based on CDC (2005) standards. Resting blood pressure was recorded in a seated position using the Welch Allyn Connex® ProBPTM 3400, a digital automated blood pressure device, after 5-min resting (Skaneateles Falls, NY 13153–0220, USA). Fasting blood samples (TC, HDL, LDL, FG, FINS) were collected by a phlebotomist after a 12-h fasting period and analyzed following standard operation procedures (SOP) of the Lancet Pathology Laboratories (Empangeni, Kwa-Zulu Natal, South Africa). The PulseTrace PCA2® device (Micro Medical, Gillingham, Kent, UK) measured vessel stiffness index (SI) in supine position.

2.3. Statistical analysis

Data are reported as arithmetic means ± standard deviations unless otherwise stated. Normality for HRV variables were assessed by time (pre test and post-test) with the Kolmogorov-Smirnov test. Log-transformation of data was used to normalize variables with skewed distribution (lnRMSSD, lnLF/HF on FFT and AR, lnSD1). Pearson's correlation coefficient was used to measure the association between selected CVD risk factors and cardiac ANS activity parameters. Scatterplots between CVD risk factors and cardiac ANS activity measures were examined to ensure that outliers were not driving the relationships. Linear regression analysis, adjusted for gender and age, arranged the CMD risk factors as independent variables and cardiac ANS activity parameters as the dependent variables. A p-value of ≤ 0.05 was used to indicate statistical significance.

3. Results

From the 34 participants, 20 were female (59%) and 14 male (41%). Participants BMI z-score (0.62 ± 1.19), SBP (105.91 ± 13.52 mm Hg), and DBP (67.24 ± 8.79 mm Hg) were within normal range (Zimmet et al., 2007). Blood lipid levels (TC: 3.88 ± 0.70 mmol/L; LDL: 2.13 ± 0.62 mmol/L; HDL: 1.44 ± 0.30 mmol/L), FINS (8.73 ± 7.14 μUm/L) and FG (4.70 ± 0.53 mmol/L) were within normal limits (Zimmet et al., 2007).

Mean time domain indices were recorded as SDNN 72.97 ± 28.23 ms, RMSSD 61.37 ± 33.83 ms (lnRMSSD: 3.98 ± 0.51 ms), NN50 110.65 ± 59.92, and pNN50 28.51 ± 18.31%. lnLF/HF (0.59 ± 0.65 on FFT; 0.47 ± 0.59 on AR) revealed a high sympathovagal balance due to low HF indicative of parasympathetic withdrawal (LF: 64.43 ± 12.69 nu vs HF: 35.47 ± 12.69 nu) on FFT and on AR (LF: 60.91 ± 13.28 nu vs HF: 38.96 ± 13.19 nu). Regression coefficients (Table 1) showed that WC ($\beta = -0.01$), HC ($\beta = -0.01$), HDL ($\beta = 0.70$) and FINS ($\beta = -0.03$) explained a significant proportion of the variation in lnRMSSD ($p = 0.01$ for all).

3.1. Overall variability

SDNN and SD2 indices were reflective of overall variability. SDNN ($r = 0.37$; $p = 0.03$) and SD2 (r = 0.37; $p = 0.03$) were positively associated with HDL. Following regression analysis, adjusted for gender and age, both SDNN ($r^2 = 0.14$; $p = 0.04$) and SD2 ($r^2 = 0.13$; $p = 0.04$) remained associated with HDL.

3.2. Parasympathetic activity

Indices of parasympathetic activity included RMSSD, pNN50, HF and SD1. lnRMSSD was negatively associated with BMI z-score ($r = -0.34$; $p = 0.04$), WC ($r = -0.45$; $p = 0.01$), HC ($r = -0.43$; $p = 0.01$) and FINS ($r = -0.41$; $p = 0.01$) and positively associated with HDL ($r = 0.42$; $p = 0.01$). Regression analysis revealed significant independent associations for lnRMSSD with WC ($r^2 = 0.21$; $p = 0.01$), HC ($r^2 = 0.19$; $p = 0.01$), FINS ($r^2 = 0.17$; $p = 0.02$) and HDL ($r^2 = 0.17$; $p = 0.01$).

pNN50 showed associations with WC ($r = -0.39$; $p = 0.02$), HC ($r = -0.36$; $p = 0.03$) and FINS (r = −0.36, $p = 0.03$). Independent associations were also noted for pNN50 with WC ($r^2 = 0.18$; $p = 0.01$),

Table 1
Multiple regression analysis and Pearson correlation for parasympathetic indicators.

Variables	RMSSD β (SE)	NN50 β (SE)	pNN50 β (SE)	HF β (SE)	SD1 β (SE)
BMI z-score	−6.69 (85.28)	−18.27 (8.72)*	−4.66 (2.72)	−0.02 (2.05)	−4.74 (3.60)
WC (cm)	−0.90 (0.43)*#	−2.14 (0.73)*#	−0.58 (0.23)*#	−0.18 (0.17)	−0.63 (0.30)*#
HC (cm)	−0.96 (0.46)*#	−2.09 (0.80)*#	−0.58 (0.25)*#	−0.20 (0.19)	−0.68 (0.33)*#
SBP z-score	−2.42 (5.42)	−7.57 (9.60)	−1.92 (2.94)	−0.53 (2.13)	−1.71 (3.84)
DBP z-score	9.63 (8.12)	21.22 (14.31)	6.53 (4.37)	4.28 (3.17)	6.83 (5.75)
HDL (mmol/L)	39.63 (19.29)*#	81.68 (33.56)*#	19.98 (10.62)	3.71 (8.06)	28.10 (13.66)*#
LDL (mmol/L)	0.54 (10.25)	−3.17 (18.26)	−0.81 (5.58)	−9.04 (3.67)*#	0.41 (7.26)
TC (mmol/L)	4.23 (8.80)	6.59 (15.70)	1.27 (4.81)	−7.55 (3.18)#	3.02 (6.23)
FINS (μU·mL)	−1.57 (0.86)	−3.73 (1.46)*	−1.03 (0.45)*	−0.16 (0.35)	−1.11 (0.61)
FG (mmol·L)	−6.10 (11.76)	−6.05 (21.03)	−3.34 (6.41)	−3.37 (4.59)	−4.32 (8.33)
SI ($m \cdot s^{-1}$)	0.34 (7.86)	8.77 (13.91)	1.89 (4.27)	−1.03 (3.08)	0.23 (5.56)

Independent variables: BMI: body mass index; WC: waist circumference; HC: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density protein; LDL: low density protein; TC: total cholesterol; FINS: fasting insulin; FG: fasting glucose; SI: vessel stiffness index. Dependent variables: RMSSD: root means square of successive differences; NN50: count of R-R intervals > 50 ms; pNN50: percentage of R-R intervals > 50 ms; HF: high frequency band on AR spectrum; SD1: standard deviation 1 on Poincare plot.

* Multiple regression analysis $p < 0.05$.

Pearson coefficient correlation $p < 0.05$.

HC ($r^2 = 0.16$; $p = 0.02$) and FINS ($r^2 = 0.15$; $p = 0.03$).

HF was significantly associated with LDL ($r = -0.41$; $p = 0.01$) on the AR spectrum. Following regression analysis, HF demonstrated an independent association with LDL ($r^2 = 0.17$; $p = 0.01$) and a dependent association with TC ($r^2 = 0.16$; $p = 0.02$) on the AR spectrum.

lnSD1 was found to be significantly associated with BMI z-score ($r = -0.34$; $p = 0.04$), WC ($r = -0.45$; $p = 0.01$), HC ($r = -0.43$; $p = 0.01$), FINS ($r = -0.41$; $p = 0.01$) and HDL ($r = 0.42$; $p = 0.01$). lnSD1 was independently associated with WC ($r^2 = 0.21$; $p = 0.01$), HC ($r^2 = 0.19$; $p = 0.01$) and HDL ($r^2 = 0.17$; $p = 0.01$).

3.3. Baroreflex activity

LF is considered an indicator of baroreflex activity modulated by both the parasympathetic and sympathetic nervous system. On the AR spectrum, LF showed a significant association with LDL ($r = 0.41$; $p = 0.02$) and remained independently associated ($r^2 = 0.17$; $p = 0.02$). TC ($r^2 = 0.16$; $p = 0.02$) revealed a significant association with LF following regression analysis despite not being significantly associated with Pearson's correlation, indicating a dependent association.

3.4. Sympathovagal balance

lnLF/HF, an indicator of sympathovagal balance, had significant associations with LDL ($r = 0.40$; $p = 0.01$) and TC ($r = 0.39$; $p = 0.02$) on the AR spectrum. LDL ($r^2 = 0.16$; $p = 0.02$) and TC ($r^2 = 0.15$; $p = 0.02$) remained significant following regression analysis on the AR spectrum.

An additional dependent association with WC ($r^2 = 0.17$; $p = 0.02$) on the FFT spectrum was noted.

4. Discussion

This study is the first to report on the individual associations between CMD risk factors and ANS activity among black South African children. The primary findings of this study indicate that: overall variability (SDNN, SD2) is independently associated with HDL; parasympathetic activity (lnRMSSD, pNN50, HF, lnSD1) is independently associated with WC, HC, HDL, LDL and FINS; baroreflex activity (LF) is independently associated with LDL; and higher lnLF/HF ratio due to lower HF is independently associated with higher levels of TC and LDL.

Chinese and Brazilian studies have reported associations between parasympathetic activity and CMD risk factors in children (Zhou et al., 2012; Farah et al., 2013). A cross sectional study of 180 Chinese children (9–11 y) found a decrease in parasympathetic activity (RMSSD, HF) with increasing BMI and WC (Zhou et al., 2012). Similarly, Farah et al. (2013) reported reduced parasympathetic activity (RMSSD, pNN50) in 74 Brazilian obese normotensive adolescents (13–18 y) that had higher WC (RMSSD: $r^2 = 0.15$, $p = 0.039$; pNN50: $r^2 = 0.16$, $p = 0.033$), however, in contrast to Zhou et al. (2012), BMI was not significantly associated with any HRV indices (Farah et al., 2013). The authors proposed that parasympathetic modulation is related to central obesity rather than general obesity in obese normotensive adolescents. In 2014, Farah et al. revealed the same correlation between WC and pNN50 but opposing results for BMI that negatively correlated with HF among 1152 Brazilian adolescent boys (16 y). The results from the latter study indicated an additional association between parasympathetic activity (RMSSD, pNN50, HF) and blood pressure (SBP, DBP). Elevated SBP also correlated with lower parasympathetic activity (RMSSD, HF) in 101 Chinese children (10 y) (Xie et al., 2013). This is in contrast with the present study's findings that had observed no association between blood pressure and any HRV parameter. The conflicting results reported for blood pressure may be explained by the different age groups examined by Farah et al. (2014) who reported on adolescents (16 y) and Xie et al. (2013) findings were based on hypertensive children (9–11 y). Tanaka et al. (2000) support this notion with results demonstrating significant correlation between resting arterial pressure and sympathovagal balance (LF/HF) among 56 adolescents (13–16 y), but not among 71 preadolescents (6–12 y). The authors proposed that blood pressure levels may only be associated with cardiac ANS activity during and after puberty and not during preadolescence. This is consistent with the present study's findings that revealed no association between blood pressure and LF suggested to reflect baroreflex activity.

Finally, regression analysis, adjusted for age and gender, from the current study's findings identified WC as the primary predictor for parasympathetic modulation in time domain (lnRMSSD: $r^2 = 0.21$, $p = 0.01$; pNN50: $r^2 = 0.18$, $p = 0.01$) and non-linear domain (lnSD1: $r^2 = 0.21$, $p = 0.01$) HRV indices, while LDL revealed to be the major determinant in frequency domain (HF: $r^2 = 0.17$, $p = 0.01$). Furthermore, regression coefficients indicated that a 1 mmol/L increment in HDL is associated with an increase of 0.70 ms lnRMSSD and 0.71 ms lnSD1.

5. Conclusion

The findings from this study suggest that obesity indicators (WC,

HC), lipid profile (LDL, HDL) and insulin concentrations relate to parasympathetic activity in black South African children. This may have important implications for the prognosis of CMD in this population. Efforts to eliminate ethnic-disparities in CMD ought to include interventions specially aimed at reducing these risk markers. The lack of a control group and another racial group may be a limitation of the current study. This study is the first to provide normative values for HRV in black South African children. Further pediatric studies are required in order to differentiate HRV indices among ethnicity, gender and their associations with the more commonly reported CMD risk factors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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