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Research Article

Autonomic Function is Associated with Fitness Level in HIV-Infected Individuals

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Abstract

Background: Cardiovascular fitness can improve autonomic function (AF) in human immunodeficiency virus (HIV)-infected individuals.

Methods: Cross-sectional study investigating relationship between AF and cardiovascular fitness in HIV+ individuals on antiretroviral therapy. Participants' (n=29) maximal oxygen consumption (VO_{2MAX}) were assessed by graded exercise test and scaled allometrically, then divided into tertiles by fitness level (Unfit, Low-fit, and Moderately-fit). Heart rate variability (HRV) and the Autonomic Reflex Screen were used to assess AF.

Results: Median VO_{2MAX} were 104.9, 130.5, and 150.2 $mL \cdot kg^{-.67} \cdot min^{-1}$ for Unfit (n=10), Low-fit (n=10), and Moderately-fit (n=9) groups respectively ($p<0.05$). Positive correlations were found between VO_{2MAX} and HRV (Spearman's rho range 0.383 to 0.553) were found. Quantitative Sudomotor Axon Reflex Test (QSART) Distal Leg volumes was lower in Unfit compared to Low-fit ($p=0.007$) and Moderately-fit groups ($p=0.018$). Unfit QSART total volumes was lower than Moderately-fit ($p=0.014$).

Conclusion: A positive relationship existed between AF and fitness levels. HIV+ individuals could benefit from improved fitness.

Keywords: VO_{2MAX}; Heart Rate Variability; Autonomic Reflex Screen; Autonomic Nervous System; HIV

Abbreviations

HIV: Human Immunodeficiency Virus;

AIDS: Acquired Immunodeficiency Syndrome;

CVD: Cardiovascular Disease;

HRV: Heart Rate Variability;

ART: Antiretroviral Therapy;

HF: High Frequency;

ARS: Autonomic Reflex Screen;

QSART: Quantitative Sudomotor Axon Reflex Test;

HR_{DB}: Heart Rate Deep Breathing;

ACSM: American College of Sports Medicine;

VO_{2MAX}: Maximal Oxygen Uptake;

DEXA: Dual Energy X-Ray Absorptiometry;

HR: Heart Rate;

ECG: Electrocardiogram;

BP: Blood Pressure;

CASS: Composite Autonomic Scoring Scale;

LF: Low Frequency;

SDNN: Standard Deviation of The Normal RR Intervals;

rMSSD: Root of The Mean Squares of Successive Differences;

NN50: Number of RR Intervals Greater Than Fifty Milliseconds Different from its Predecessor;

pNN50: Percentage of RR Intervals Greater Than Fifty Milliseconds Different from its Predecessor

Introduction

Autonomic dysfunction is a common co-morbidity of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) [1,2]. Decreased autonomic function is linked to increased risk of cardiovascular disease (CVD) and all-cause mortality [3,4]. This dysfunction is often characterized by increased sympathetic activity, and decreased parasympathetic activity and heart rate variability (HRV) [5,6].

Cardiovascular fitness has a positive correlation with time- and frequency-domain measures of HRV in healthy populations, regardless of training level [7]. Autonomic function improved with habitual exercise and improved cardiovascular fitness in patients with cardiovascular disease and diabetes [5,7,8]. Autonomic function has been related to physical fitness levels of HIV-positive individuals on ART by Spierer et al. [9], who reported no significant difference in high frequency (HF) power (indicating parasympathetic function) between fit HIV-positive individuals and healthy fit individuals but a significant difference in HF power between fit and unfit HIV-positive individuals. However, the HIV-positive groups investigated by Spierer et al. had a large difference in oxygen uptake between fit and unfit groups (41.4±2.4 vs. 26.9±4.4 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively) [9].

The purpose of this study was to explore the relationship between unfit, low and moderate aerobic fitness levels and autonomic function in an HIV-positive population receiving stable ART. Time and frequency-domains of HRV were determined; and, unlike previous studies on HIV-positive populations, autonomic function was also assessed using the Autonomic Reflex Screen (ARS), which included the Quantitative Sudomotor Axon Reflex Test (QSART), Heart Rate Deep Breathing (HR_{DB}), and Valsalva tests [10,11]. The ARS is useful in diagnosing autonomic failure and has clinical and prognostic implications.

Methods

Participants were HIV-positive individuals on six months of stable ART medication. Exclusionary criteria were: known cardiac disease, arrhythmia, active substance abuse, pregnancy, and absolute contraindications for exercise testing as outlined by the American College of Sports Medicine (ACSM) [12]. Participants signed a consent form approved by the university's institutional review board, and this protocol was in compliance with the Helsinki Declaration.

Participants completed two separate testing sessions. During the first visit, VO_{2MAX} was measured using a graded cycle ergometer exercise test. Blood samples and anthropomorphic measurements were collected prior to the test, including: height, body mass, and body composition determined by Dual Energy X-ray Absorptiometry (DEXA) (GE Lunar Prodigy Advance, Encore 2004 software version 8.10.027, Waukesha, WI). Training status and current medication were assessed via questionnaire. Autonomic testing was completed separately within one month of the VO_{2MAX} test. Testing was performed in the morning between 8 to 11 am and participants were instructed to fast for at least eight hours, avoid heavy exercise for at least a day prior to testing, not ingest caffeine or nicotine, and avoid taking medication that might affect the results of the tests [7,9,13].

VO_{2MAX} testing

All VO_{2MAX} data were collected in single 90-minute sessions supervised by an attending physician. Participants warmed up on a cycle ergometer (Model 818 E, Monark, Stockholm, Sweden) for five minutes. The initial workload was 50 Watts and increased by 12.5 Watts every minute. Maximal effort was based on ACSM's criteria for maximal exercise testing [12]. Maximal oxygen consumption was assessed with a Max IIa

metabolic cart (AEI technologies, Naperville, IL), using standard open circuit spirometry techniques. Electrocardiogram (ECG) output, blood pressure, heart rate (HR), and ratings of perceived exertion(2) were monitored. Blood lactate concentration was determined pre- and seven minutes post-exercise using a Lactate Plus Lactate Meter (Nova Biomedical Co., Waltham, MA). Absolute maximal oxygen uptake ($L \cdot min^{-1}$) was ratio-scaled using body mass ($mL \cdot kg^{-1} \cdot min^{-1}$) and allometrically-scaled ($mL \cdot kg^{-.67} \cdot min^{-1}$) to eliminate the influence of body mass [14]. Participants were divided into tertiles according to their allometrically-scaled VO_{2MAX}: Unfit (<115 $mL \cdot kg^{-.67} \cdot min^{-1}$), Low-fit (115-140 $mL \cdot kg^{-.67} \cdot min^{-1}$), and Moderately-fit (>140 $mL \cdot kg^{-.67} \cdot min^{-1}$).

Autonomic testing

Three areas of autonomic function were tested using the ARS: sudomotor, cardiovagal, and adrenergic [15]. All three components of the ARS are considered valid and reliable measures of autonomic function [10,13,16]. Additionally, time- and frequency-domain measures of HRV were extrapolated from a resting ECG using Kubios Heart Rate Variability Software Version 2.0 (University of Kuopio, Kuopio, Finland).

Sudomotor Quantitative Sudomotor Axon Reflex Test (QSART)

Four sites on the participant's left side were tested: dorsal surface of the foot, medial surface of the distal leg (5 cm proximal to medial malleoli), lateral surface of proximal leg (5 cm distal to head of fibula), and the two-thirds of the distance down the anterior surface of the forearm. Acetylcholine was administered via iontophoresis for five minutes and data were recorded for an additional five by a Q-Sweat instrument (WR Testworks, Stillwater, MN) [10,11]. The latency period before the sweat response, peak sweat rate, and total sweat volume at the stimulated sites was then determined using WR Testworks Suite 2.1 (WR Testworks, Stillwater, MN).

Heart rate $_{\text{deep breathing}}$ (cardiovagal testing)

After completion of the QSART, a five-minute baseline ECG was recorded and participants subsequently followed a visual cue to breathe at six breaths per minute for eight breaths. Mean difference in HR was determined from the five largest consecutive variations between maximum and minimum heart rates. The test was repeated at two-minute intervals until two satisfactory curves were recorded. Chest expansion, HR, and beat-to-beat BP were measured by a Colin Pilot 700 (Colin Medical Instruments Corp., San Antonio, TX) equipped with an Atlas digital to analogue converter box (WR Testworks, Stillwater, MN). Data were recorded on a computer using WR Testworks Suite 2.1 [17,18].

Valsalva test (adrenergic testing)

After a five-minute rest, participants were tilted to a 20 degree head-up angle, and blew a "bugle" maintaining an expiratory pressure of 40 mmHg for 15 seconds followed by a three-minute silent rest. The procedure was repeated until two satisfactory BP curves were obtained. Expiratory pressure, beat-to-beat BP, and HR were recorded [17,18].

Composite autonomic scoring scale

The Composite Autonomic Scoring Scale (CASS) was compiled from the results of the ARS. Autonomic testing data (Valsalva, HR_{DB}, and QSART) were combined to form the CASS [11]. This 10-point scale measures autonomic failure divided into three sections: adrenergic (4 points), cardiovagal (3 points), and sudomotor (3 points). Participants with a score of 1 to 3 have mild autonomic failure, a score of 4 to 6 indicates moderate failure, and a score greater than 7 is indicative of severe autonomic failure [11].

Heart rate variability

Interbeat intervals (RR) were imported into Kubios HRV Software for time- and frequency-domain analysis. Low level artifact correction was applied if necessary and the sample length was set to five minutes. Trend components were removed using a Smooth n Priors method. Interpolation of RR series was set at 4 Hz. Window width for fast Fourier transformation was set at 512 seconds with window overlap set at 50% [13,19].

Parasympathetic and sympathetic modulations of the heart were quantified by assessing the power spectral density of interbeat interval oscillations occurring from 0.04 to 0.40 Hz, thought to originate from autonomic modulations of the sinus node. The low-frequency power (LF; 0.04 to 0.15 Hz) represents both sympathetic and parasympathetic control, and high-frequency power (HF; 0.15 to 0.40 Hz) reflects parasympathetic modulation. The LF/HF power ratio attempts to remove the parasympathetic influences, thereby representing primarily sympathetic activity [13,19].

Time-domain parameters, based on simple statistical measures of variability, address the magnitude of variability and provide information about the vagal (parasympathetic) modulation of the heart, with higher variability generally reflecting greater parasympathetic modulation. Reduced HRV in individuals with symptomatic autonomic neuropathy has prognostic implications for future cardiovascular disease events in the HIV-positive populations [20,21]. Time-domain measures included the standard deviation of the normal RR intervals (SDNN), the root of the mean squares of successive RR differences (rMSSD), the number of RR intervals greater than fifty milliseconds different from its predecessor (NN50) and the percentage of RR intervals greater than fifty milliseconds different from its predecessor (pNN50). Overall HRV is reflected by SDNN and rMSSD measures while pNN50 measures HRV's

short term components, with SDNN being the most representative parameter of HRV [13,19].

Statistical analysis

Data were analyzed using SPSS Statistical Analysis Software Version 20 (IBM, Armonk, New York, USA). Statistical significance was set at a $p<0.05$ probability level. A Kolmogorov-Smirnov test was used to determine that the data were not normally distributed. Spearman's Rank Correlation Coefficients were calculated between measures of fitness, heart rate variability, ARS, and body mass. Kruskal-Wallis One-Way ANOVAs were used to determine the main effects for differences between groups and post-hoc analyses were performed using multiple Mann-Whitney U tests with the Holm's sequential Bonferroni adjustment to determine differences between the Unfit, Low-fit, and Moderately-fit groups.

Results

Participants

This study included 29 participants (2 female, 27 male) between 22 and 63 years old (median 49.9, Q1 44.1, Q3 52.6 years). Median CD4 count was 500 cells/mm^3 (Q1 333, Q3 681), with only 4 participants (14 %) having a CD4 count <200 cells/mm^3. Viral load was undetectable in the majority of participants (86%). Overall, 20.7% (6 of 29) of participants were current smokers, 30% (3 of 10) in the Unfit group, 10% (1 of 10) in the Low-fit group and 11.1% (2 of 9) in the Moderately-fit group. Six of the non-smoking participants had previously smoked, time since quitting ranged from 1 week to 30 years, median 5.25 years. In the Unfit group, 2 participants (20%) were on statins; in the Low-fit group, 4 participants (40%) were on statins; and in the Moderately-fit group, 3 participants (33.3%) were on statins. Overall, 31% of participants (9 of 29) were on statins. None of the participants had diabetes. Overall body fat percentage was 28% (Q1 21%, Q3 31.5%), the Unfit group was highest at 29% (Q1 23.25 %, Q3 37 %), and the Moderately-fit group was lowest at 20% (Q1 16.5%, Q3 27.5%). The median for the Low-fit group was 28% (Q1 23.5%, Q3 32.25%) (Table 1). Body fat percentage was significantly different between Unfit and Moderately-fit groups (p=0.011) and approached significance between Unfit and Low-fit groups (p=0.057). Fat free mass (Table 1) was significantly different between Moderately-fit and Unfit (p=0.018) and Low-fit groups (p=0.011). According to ACSM normative VO_{2MAX} values for age and gender, the Unfit group was in the 8th percentile, the Low-fit group was in the 29th percentile, and the Moderately-fit group was in the 52nd percentile [12]. All groups had significantly different VO_{2MAX} values using unscaled, ratio-scaled, and allometrically-scaled measures (p<0.0001 for all, see Table 1). Resting HR was significantly different between Unfit and Moderately-fit groups post-exercise (p=0.011).

No participants had a total CASS score over three, indicating no moderate or severe autonomic dysfunction. Low levels of autonomic dysfunction existed in 20% of the Low-fit, 40% of the Moderately-fit, and 60% of the Unfit group. However, there was no correlation between CASS score and HF power (rho=-0.058, p=0.766), or CASS score and LF/HF ratio (rho=-0.176, p=0.360). The QSWEAT results were adjusted using the formulas provided by Sletten et al. [22] in order to compare them to established Mayo Clinic QSART normative means [22,23]. For indices of autonomic function, significant differences were seen in QSART distal leg volume (p=0.008), and total QSART volume (p=0.034). Distal Leg sweat volume was significantly different between Unfit and Low-fit (p=0.007) and Unfit and Moderately-fit groups (p=0.018), but not between Low-fit and Moderately-fit groups (p=0.935). Total Volume was significantly different between Unfit and Moderately-fit groups (p=0.014). These values can be seen in Figure 1. Significant moderate positive correlations were also present between allometrically-scaled VO_{2MAX} and two measures from the QSART: Distal Leg Volume (Spearman's rho=0.553, p=0.002), and Total Volume (rho=0.490, p=0.007).

Although correlations were noted between allometrically-scaled VO_{2MAX} and time-domain measures of HRV, no differences were seen between fitness level groups in time- and frequency-domains. Group medians (Q1, Q3), and p values for all autonomic variables (both time- and frequency-domains) can be seen in Table 2. All participants fell within two standard deviations of the HR_{DB} normative values for HIV-positive participants established by the Mayo Clinic and WR Medical. Allometrically-scaled VO_{2MAX} had significant moderate positive correlations with the time-domain measures of SDNN (rho=0.383, p=0.041), rMSSD (rho=.403, p=0.030), NN50 (rho=.387, p=0.038), and pNN50 (rho =0.412, p=0.026). No significant correlations between frequency-domain measures of HRV and allometrically-scaled VO_{2MAX} were found. Significant moderate positive correlations were present between allometrically-scaled VO_{2MAX} and two QSART measures: Distal Leg Volume (rho=0.553, p=0.002), and Total Volume (rho=.490, p=0.007). A significant positive correlation existed between HF power and HR_{DB} differences (rho=0.395, p=0.034) and Valsalva percentile rank (rho=0.472, p=0.010); and a significant negative correlation between HF power and the adrenergic portion of the CASS (rho=-0.447, p=0.015). Significant correlations were also found between total cholesterol and LF and HF power, as well as LF/HF ratio (rho=-0.681, 0.681, and -0.686 respectively, p<0.001 for all). The only significant correlations between the CASS composites and time domain measures of HRV were significant negative correlations between the Adrenergic portion of the CASS and SDNN and RMSSD (rho=-0.376, p=0.044 for both).

	Unfit Group (n=10)	Low-fit Group (n=10)	Moderately Fit Group (n=9)	Sig. 2-Tailed (*p*)
Age, years	49.7 (44.4, 52.4)	48.7 (44.2, 54.7)	49.9 (42.8, 52.6)	0.253
Sedentary, n, %	7, 70	8, 80	5, 56	-
Body Mass, kg	79.5 (67.5, 89.75)	81.5 (74.5, 89.25)	76 (69, 85.5)	0.287
Body Fat, %	29 (23.25, 37)†	28 (23.5, 32.25)	20 (16.5, 27.5)†	0.030*
Fat Free Mass, kg	53.35 (48.88, 60)†	58.75 (52.33, 63.43)	59.8 (53.75, 65.1)†	0.031*
BMI, kg/m^2	25.7 (23.8, 29.5)	27.1 (23.4, 30.0)	24.3 (23.7, 25.8)	0.419
CD4 count, $cells/mm^3$	192.5 (161.3, 205.8)	156 (148.8, 177)	170 (166, 213)	0.473
Years HIV+	16.5 (7.5, 19.3)	15.5 (6.8, 20.3)	16.0 (10.0, 21.0)	0.700
Undetectable Viral Load <48$cells/mm^3$ n, %	9 (90)	8 (80)	7(78)	-
Cholesterol, mg/dL	192.5 (161.3, 205.8)	156.0 (149.8, 177.0)	170.0 (166.0, 213.0)	0.530
Resting HR, BPM	66.5 (59.25, 68.25)	58.5 (53.5, 66)	58 (48, 60.5)	0.214
Resting SBP, mmHG	119 (110, 138.5)	112.5 (103.5, 133.3)	125 (115, 140)	0.672
Resting DBP, mmHG	75 (69, 81.5)	67.5 (64.5, 79.5)	76 (72.5, 79)	.864
Estimated Max HR, BPM	174.2 (172.2, 177.7)	174.9 (170.5, 177.8)	174.1 (172.1, 178.7)	0.310
Absolute VO_{2MAX}, $L \cdot min^{-1}$	2.1 (1.7, 2.2)†	2.4 (2.1, 2.6)†	3.0 (2.4, 3.1)†	<0.001*
Ratio-scaled VO_{2MAX}, $mL \cdot kg^{-1} \cdot min^{-1}$	24 (23.5, 30)†	29.5 (28.0, 32.3)†	36.0 (34.0, 39.0)†	<0.001*
Allometrically-scaled VO_{2MAX}, $mL \cdot kg^{-.67} \cdot min^{-1}$	104.9 (98.3, 117.0)†	130.5 (117.4, 135.3)†	150.2 (141.4, 161)†	<0.001*
RER max	1.06 (0.99, 1.14)	1.14 (1.06, 1.23)	1.15 (1.03, 1.23)	0.097
Peak HR, BPM	173.6 (171.8, 177.7)	174.3 (170.3, 177.3)	173.5 (171.7, 178.2)	0.099
Post exercise Lactate, mmol/L	8.5 (5.75, 9)	9.5 (7.8, 12.5)	9 (6, 11.5)	0.279
Sedentary (n,%)	7, 70	8, 80	5, 56	-

Table 1. Continuous variables are displayed as medians (Q1,Q3); HR=Heart Rate; BPM=Beats Per Minute; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; mmHG=millimeters of mercury of pressure; M=meter; kg=kilogram; BMI=Body Mass Index; HIV=Human Immunodeficiency Virus; Undetectable Viral Load <48 $cells \cdot mm^{-3}$; mL=milliliter; min=minute; RER=Respiratory Exchange Ratio; mmol=millimole; L=Liter; *Main effect significant at p=0.05 level; †Post-hoc effect significant at p=0.05 level.

	Unfit Group (n=10)	Low-fit Group (n=10)	Moderately Fit Group (n=9)	Sig. 2-Tailed (*p*)
Autonomic Reflex Screen				
HR_{DB} Average Difference, BPM	13.0 (8.0, 15.5)	12.5 (10.0, 15.8)	15.0 (8.0, 20.0)	0.318
HR_{DB} Percentile Rank, %	20.5 (9.0, 49.0)	21.5 (11.8, 53.3)	25.0 (11.5, 67.0)	0.875
Valsalva Test Greatest HR Ratio, BPM	2.0 (2.0, 2.3)	2.0 (1.8, 2.0)	2.0 (2.0, 2.5)	0.514
Valsalva Test Percentile Rank, %	57.5 (31.8, 85.3)	38.5 (27, 51.3)	70.0 (49.0, 94.0)	0.763
Time-Domain Measures				
SDNN, ms	34.5 (31.5, 42.3)	30.0 (18.3, 52.5)	40.0 (29.5, 52.0)	0.223
rMSSD, ms	28.5 (21.5, 39.5)	27.5 (12.8, 48.8)	43.0 (27.5, 58.0)	0.283
NN50, count	22.5 (7.8, 69.3)	23.0 (1.8, 75.5)	39.0 (24.0, 105.0)	0.283
pNN50, %	7.0 (2.8, 21.3)	8.0 (0.8, 27.5)	16.0 (8.0, 45.0)	0.240
Frequency-Domain Measures				
Total Power, ms^2	907.5 (694.8, 1371.8)	791.0 (310.8, 2102.0)	1718.0 (744.0, 2724.0)	0.153
LF Power, ms^2	478.5 (252.0, 1073.3)	348.5 (186.3, 849.3)	955.0 (291.5, 1934.5)	0.427
LF Power, nu	56.5 (45.5, 81.5)	65.5 (51.3, 82.3)	70.0 (55.0, 78.5)	0.244
HF Power, ms^2	336.5 (185.8, 488.3)	125.0 (51.0, 736.0)	387.0 (207.0, 913.5)	0.483
HF Power, nu	43.5 (18.5, 54.8)	34.0 (17.8, 48.8)	30.0 (21.5, 45.0)	0.244
LF/HF Power Ratio	1.0 (1.0, 4.3)	2.0 (1.0, 5.0)	2.0 (1.0, 3.5)	0.342

Table 2. Continuous variables are displayed as medians (Q1,Q3); µL=Microliters; QSART=Quantitative Sudomotor Axon Reflex Test; HR_{DB}=Heart Rate Deep Breathing; HR=Heart Rate; BPM=Beats Per Minute; SDNN=Standard Deviation of Beat to Beat Intervals; rMSSD=Root Mean Squares of Standard Deviation; NN50=Number of Beats Varying More Than 50 Milliseconds from Previous Beat; pNN50=Percentage of Total Beats Varying More Than 50 Milliseconds from Previous Beat; RR Triangular Index=Geometric Measure of Heart Rate Variability; ms=Milliseconds; LF=Low Frequency; HF=High Frequency; ms^2=milliseconds squared; nu=normalized units; * Main effect significant at p=0.05 level.

Discussion

The significant positive correlations between VO_{2MAX} and the time-domain variables of HRV (Spearman's rho range 0.383 to 0.412, $p<0.05$) indicate that even low or moderate increases in aerobic fitness contribute to increased HRV. The correlation between HF power and allometrically-scaled VO_{2MAX} approached significance (rho=0.348, $p=0.055$), indicating a positive trend in the relationship between VO_{2MAX} and parasympathetic tone. However, there were no significant differences between groups for time- or frequency-domain measures of HRV. Allometrically-scaled VO_{2MAX} was significantly correlated with both Distal Leg sweat volume and Total volume, which increased significantly with increased fitness in HIV-positive participants ($p=0.050$**).** When viewed with the correlations between fitness level and HRV time-domain measures, this difference in sweat volumes support a relationship between autonomic function and cardiovascular fitness levels for a largely sedentary cohort of HIV-positive participants on ART. The lack of correlation between CASS and HF and LF/HF power suggest that the two methods measure different aspects of autonomic function.

Overall, parasympathetic function in the current study was lower and sympathetic function was higher compared to Buchheit and Gindre's fit participants, who defined "fit" as having a VO_{2MAX} above 50 $mL \cdot kg^{-1} \cdot min^{-1}$; greater than all but one participant in the current study [7,15]. The distribution of VO_{2MAX} scores in the current study was fairly narrow, with approximately half of participants falling below the 20th percentile of ACSM norms for a healthy population [15]. The indicators of HRV from the current study predominately fall below the values for the fit groups from the aforementioned studies, but are similar to values from their unfit groups [7,9].

Unlike HRV, sweat production is regulated predominately by the sympathetic nervous system and QSART dysfunction is often indicative of small nerve fiber neuropathy [10]. Total Volume and Distal Leg QSART volume differed significantly between groups. Most sample sites, including Total Volume, had higher percentiles of Mayo Clinic norms in the Moderately-fit group and decreased percentiles in the Unfit group (Figure 1). Therefore, greater physical fitness levels in sedentary HIV-positive participants were associated with improved sweat responses and peripheral autonomic function. It should be noted that the participants were acclimatized to a tropical environment, which may make comparisons against the Mayo Clinic norms problematic. Although not measured in the present study, this could be an indicator of impaired glucose tolerance in the Unfit group as compared to the Moderately-fit group [24].

Spierer et al.'s study of unfit and fit HIV-positive and -negative groups revealed a relationship between fitness level and cardiovascular/autonomic health [9]. All three fitness groups from the current study had lower HF power than the HIV-positive fit group from Spierer et al. and displayed reduced parasympathetic function compared to Spierer et al.'s fit HIV-positive group [9]. Although the results from the current study span a smaller range of oxygen uptake values clustered at lower fitness levels, the positive correlation between VO_{2MAX}, time-domain HRV measures, and sweat responses supports their findings that physical fitness is associated with improved autonomic function, even at lower fitness levels.

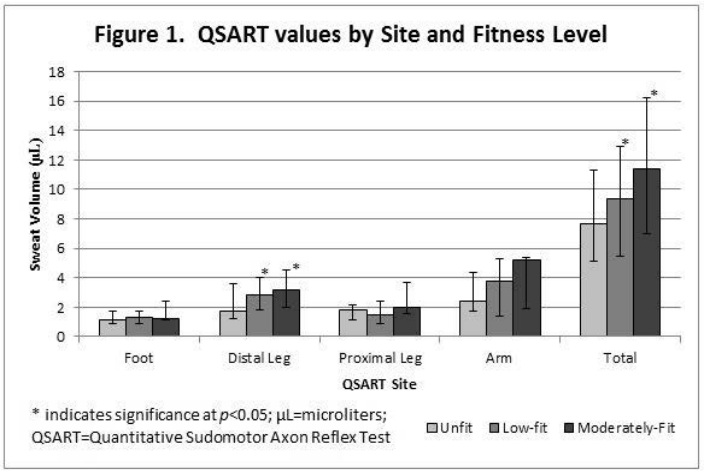

Figure 1. Quantitative Sudomotor Axon Reflex Test according to_Fitness Level groups.
* indicates significance compared to the unfit group ($p<0.05$), sweat volumes by microliters.

A unique aspect in the current study was allometrically-scaling fitness levels to remove the confounding influence of body mass on the scaled variable (VO_{2MAX}), which resulted in five participants being assigned to a different group than if ratio-scaled. Nevill [25] stated that "simple ratio standards 'over-scale' by converting the positive correlation between the physiological performance variable and the body size variable to a negative one." In the current study ratio scaling resulted in a significant negative correlation with body mass (rho=-0.41, $p=0.022$), overcorrecting for body mass and failing to eliminate the influence of body mass on VO_{2MAX}. It has been previously shown that when comparing fitness levels, if VO_2 is left unscaled ($L \cdot min^{-1}$), larger individuals will have a higher VO_{2MAX} (as seen in the present study with a correlation with body mass rho=0.511, $p=0.003$) [26]. Allometric scaling ($mL \cdot kg^{-.67} \cdot min^{-1}$) helps correct for these influences. The allometric exponent validated by Heil et al. (0.67) was used in the current study to remove the confounding effects of body mass on VO_{2MAX} [14]. Vanderburgh has previously suggested that the "litmus test" for controlling for body mass using different scaling methods is that the scaled variable should have a correlation with body mass that approaches zero [27]. The efficacy of allometric scaling can be seen by the reduced correlation between body mass and VO_{2MAX}, which approached zero (rho=-0.08, $p=0.653$), thus supporting the use of allometric scaling.

The relationship between allometrically-scaled VO_{2MAX} ,

time-domain measures and sweat volumes existed despite the fact that the majority of the participants were sedentary (less than 30 minutes of moderate physical activity three times a week for the past 3 months). Buchheit and Gindre previously reported a positive relationship between indices of HRV and VO_{2MAX} in a healthy population, but that training load had a limited effect on HRV [7]. A sedentary lifestyle has been reported to desensitize the baroreflex response, resulting in a decrease in vagal tone and a shift towards sympathetic activity [9]. Since an active lifestyle is related to increased levels of physical fitness, HIV-positive individuals would likely improve autonomic function by adopting an active lifestyle.

Askgaard et al. reported a significant inverse correlations of total cholesterol with multiple time-domain measures (rMSSD r =-0.26, pNN50 r=-0.24) [28]. The authors speculated that "hypercholesterolemia causes more damage to the autonomic nervous system in HIV-positive patients than in controls." In contrast, the current study found significant correlation between total cholesterol and HF power, and an inverse relationship with LF/HF ratio (rho=0.681, and -0.686 respectively, $p<0.001$ for all), but not with time-domain measures of HRV. These findings suggest a need for future study as suggested by Askgaard et al [1].

Limitations to the current study included the cross-sectional design (which didn't allow for comparison of autonomic function and fitness levels over time), the lack of control group or controlling for lipodystriphy and dyslipidemia, and the small range of fitness levels. This narrow range of fitness levels or the HRV measures used may have contributed to the lack of differences in HRV found between groups. Despite these limitations, significant differences in QSART volumes were found between groups.

Conclusion

Positive correlations between fitness levels and time-domain measures of HRV coupled with differences in the total sweat volume from the QSART indicate a relationship between aerobic fitness and autonomic function in low to moderately fit HIV-positive individuals on a stable ART regimen. An active lifestyle that increase or maintain aerobic fitness could potentially ameliorate symptoms of autonomic dysfunction in HIV-positive individuals.

Conflicts of Interest

There were no conflicts of interests with any of the authors.

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