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Does Six Minute Walk Test Evoke Significant Cardiovascular Entropy in Persons with Clinical Stage-I HIV? A Case Control Study

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Abstract

Cardiovascular response to exercise is a major prescription criterion for determining suitability and safety of exercise. This study assessed the cardiovascular response to six-minute walk test (6MWT) in Persons Living with HIV/AIDS (PLWH) and their healthy controls. This case-control study involved 74 consenting volunteers (37 PLWH and 37 controls). 6MWT was performed on a 30-meter course level walkway following standardized procedure. Data were obtained on participants' physical characteristics, pre and post-6MWT Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Heart Rate (HR). Rate Pressure Product (RPP) was calculated. Data were analyzed using descriptive statistics of mean and inferential statistics of paired and unpaired t-test at 0.05 Alpha level. PLWH and the controls were comparable in age ($p=0.976$). PLWH had significantly lowered baseline DBP (67.84±10.58 vs. 76.22±10.10mmHg; $p=0.001$) and post-6MWT DBP (84.32±12.59 vs. 92.43±13.00mmHg; $p=0.008$) than healthy controls ($p<0.05$). The post-6MWT cardiovascular parameters were significantly higher than the baseline values for both groups ($p<0.05$). There were no significant differences in groups mean change scores on SBP (24.05±21.01 vs. 22.43±11.16), DBP (16.49±15.31 vs. 16.22±9.82), HR (19.30±12.62 vs.14.35±10.05) and RPP (4174.6±2572.01 vs.3494.9±1951.93) respectively. Baseline cardiovascular parameters of clinical stage 1 PLWH was normal and comparable with that of the healthy controls. However, PLWH had significantly lower baseline and post-6MWT DBP than the controls'. 6MWT led to significant increase in blood pressure, HR and myocardial oxygen demand in PLWH. The magnitude of cardiovascular response to 6MWT in PLWH was comparable with healthy controls'.

Key words: Cardiovascular response, 6MWT, HIV/AIDS, Exercise

Introduction

The human immunodeficiency virus (HIV) infects cells of the immune system, destroying or impairing their function leading to progressive deterioration of the immune system called "immune deficiency" [1]. Acquired immunodeficiency syndrome (AIDS) applies to the most advanced stages of HIV infection, defined by the occurrence of any of more than 20 opportunistic infections or HIV-related cancers [1]. Dube *et al* [2] reported that HIV/AIDS affects the structural and functional structure of the heart. However, there are conflicting reports on cardiovascular status of Persons Living with HIV/AIDS (PLWH). Some studies have reported normal blood pressure in PLWH [3, 4] while others have recorded increased blood pressure in PLWH [5-7]. Additionally, the management of HIV/AIDS with highly active anti-retroviral therapy (HAART) has been reported to have variable effects on the cardiovascular system of PLWH [2, 8-10].

Therapeutic exercise is one of the approaches being explored to help deal with the complication and symptoms of HIV/AIDS [11]. Exercise in PLWH has been shown to improve immunological measures [12-15], physical and mental health [15] and increase functional capacity [13, 15-17]. However, exercise prescription in PLWH is somewhat intricate as it is dependent on the stage of disease of the individual patient, symptoms, medications and functional capacity of the individual patient [15, 18]. Furthermore, the response of an individual to exercise is an indicator of the respiratory, cardiac and metabolic status [19-21].

Exercise has been found to place an increased demand on the cardiovascular system [22]. Variability in cardiovascular response to functional exercise capacity tests and training has been observed among patient with different health conditions [23-25]. Gleim *et al* [26] submitted that it is difficult to define a generalized cardiovascular response to exercise. Consequently, cardiovascular response to exercise is a major prescription criterion for determining suitability and safety of exercise in both the patients and healthy population [27]. Shankar [28] submitted that assessment of systolic and diastolic blood pressure at rest and during the exercise test is important for patient safety and can provide important diagnostic and prognostic information. Additionally, heart rate, stroke volume, cardiac output, blood flow are important aspects of the cardiovascular system to examine. Studies on cardiovascular response to exercise in PLWH are sparse compared with patients with obstructive pulmonary disease [29-31], diabetes [12, 32, 33] and other chronic illnesses. The objective of this study was to assess the cardiovascular response to six minute walk test (6MWT) in PLWH and their age-and-sex matched healthy controls.

Materials and Methods

A total of 74 participants (37 PLWH (15 (40.5%) males and 22 (59.5%) females) and 37 age-and-sex matched apparently healthy controls) volunteered for the study. Consenting PLWH in this study were recruited from the Virology Research Clinic (VRC) of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife, Nigeria. In order to ensure homogeneity of sample, PLWH in clinical stage I of the disease who were 18 years and older and were recruited. Clinical stage I of HIV/AIDS refers to asymptomatic/acute HIV infection, with persistent generalized lymphadenopathy [34, 35]. Participants were excluded if they had a history of unstable angina and myocardial infarction during the previous month. Participants with a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg were also excluded.

Participants that were already involved in an exercise program were also excluded. All the PLWH volunteers were on anti-retroviral therapy (HAART). The apparently controls in this study included patients' relatives and health workers at the VRC. The ethical approval for this study was obtained from the ethical committee of the OAUTHC. The VRC gave permission for the study to be carried out at the centre. Each participant gave informed consent to participate in the study.

Measurements

Anthropometric measurements included height, weight and body mass index (BMI). Height and weight were measured with a stadiometer (Seca: Model number-19066). The participant stood barefooted on the platform of the stadiometer looking straight ahead while the horizontal bar attached to the height meter was adjusted to touch the vertex of the head. The height was read and recorded to the nearest 0.1m. The participants stood barefoot in an erect posture with minimal clothing on the stadiometer, staring straight ahead. The weight was read and recorded to the nearest 0.1kg.

An automatic blood pressure monitor (Medical Llyod pharmacy; model KD-525) was used to assess the pre-walk and post-walk blood pressure and heart rate of the participants respectively. Participants were asked to sit in a relaxed position in a firm armchair for 5 minutes, and the automatic blood pressure monitor's cuffs were placed on the left arm. The cuff width, position, tightness, and deflation rate were controlled in accordance with the manufacturer's instruction. Blood pressure and heart rate were then assessed following the manufacturer's instructions for the use of the sphygmomanometer.

Six-Minute Walk Test

Six-minute Walk Test (6MWT) was used to assess the exercise capacity of the participants in accordance with the American Thoracic Society [36]. A review of functional walk tests concluded that the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than other walk tests [37]. In addition, the test could probably be performed by the elderly, the frail, those with walking difficulties, severely limited patients who cannot be tested with standard and more expensive maximal cycle ergometer or treadmill exercise tests [38, 39]. The 6MWT has been used extensively to determine exercise capacity of various populations [40-42] including HIV/AIDS [43]. This test measures the distance that a participant can quickly walk on a flat, hard surface in a period of 6 minutes referred to as the 6-minute walk distance (6MWD) [36]. A distance of 30m was marked on the hallway with white chalk. The participants were then asked to walk back and forth in the hallway for six minute from one end of the 30 m distance mark to another, pivoting briskly at each end and continue walking without hesitation. Participants that became exhausted were permitted to slow down, to stop, and to rest as necessary. They were allowed to lean against the wall while resting, but resume walking as soon as they were able to. If the participant stopped before the 6 minutes were up and refused to continue, a chair was taken to the participant to sit on, and the walk discontinued. When the test was completed, the spot where the participant stopped was marked and the total distance walked (i.e. 6MWD) in meters was recorded. No encouragement was given during the performance of the test [36]. Data from participants that fail to complete the test were excluded from analysis.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) software (version 16) was used for the data analysis. Data were analyzed using descriptive statistics of mean and standard deviation. Inferential statistics of paired and unpaired t-test were used to compare the baseline and post 6MWT cardiovascular variables within and between groups. Alpha level was set at 0.05.

Computations

BMI (Kgm^{-2}) = Weight (kg) ÷ Height (m^2)

RPP = Systolic Blood Pressure × Heart Rate

Results

The age of the PLWH ranges between 20 and 54 years with a mean age of 35.68 ± 7.71 years. The age of the apparently healthy controls ranges between 20 and 55 years with a mean age of 35.73 ± 7.88 years. The independent t-test comparison between the physical characteristics of the PLWH and the controls are presented in table 1.

Table 1: Independent t-test comparison of the general characteristics of PLWH and control group

Variable	PLWH X±SD	Control group X±SD	t - cal	p-value
Age	35.68 ± 7.71	35.73 ± 7.88	-0.30	0.976
HT	1.67 ± 0.79	1.66 ± 0.08	0.344	0.739
WT	63.49 ± 12.25	67.12 ± 11.35	-1.324	0.190
BMI	22.77 ± 4.17	24.31 ± 4.24	-1.583	0.118

HT = Height, WT = Weight, BMI = Body mass index

The independent t-test comparison of the baseline cardiovascular parameters of the PLWH and control groups is shown in table 2. From the result, the control group had higher systolic blood pressure (SBP) (109.46 ± 11.29 vs. 108.11 ± 15.43; p=0.668), heart rate (HR) (70.38 ± 6.92 vs. 66.84 ±4.26; p=0.100) and rate pressure product (RPP) (7718.1 ± 1204.57 vs. 7250.3 ± 1312.55; p=0.115) than the PLWH. However, this difference was not significant (p>0.05). The baseline diastolic blood pressure (DBP) of the PLWH was significantly lower than the control group (p=0.001).

The independent t-test comparison of the post-6MWT cardiovascular parameters of PLWH and control group is shown in table 3. The control group had significantly higher post-6MWT DBP than the PLWH (p=0.008). There was no significant difference between the SBP (p=0.929), HR (p=0.652) and RPP (p=0.702) of PLWH and control group.

Table 2: Independent t-test comparison of the baseline cardiovascular parameters of the PLWH and the control group

Variable	PLWH X±SD	Control group X±SD	t – cal	p-value
SBP	108.11 ± 15.43	109.46 ± 11.29	-0.430	0.668
DBP	67.84 ± 10.58	76.22 ± 10.10	-3.485	0.001*
HR	66.84 ±4.26	70.38 ± 6.92	-2.650	0.100
RPP	7250.3 ± 1312.55	7718.1 ± 1204.57	-1.597	0.115

* Indicates significant difference between groups

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR = Heart rate, RPP = Rate pressure product

Table 3: Independent t-test comparison of the post-6MWT cardiovascular parameters of PLWH and the control group

Variable	PLWH X±SD	Control group X±SD	t - cal	p-value
SBP	132.16 ± 15.66	131.89 ± 9.67	0.89	0.929
DBP	84.32 ± 12.59	92.43 ± 13.00	-0.2725	0.008*
HR	86.14 ± 13.75	84.73 ± 12.92	0.453	0.652
RPP	11425 ± 2547.90	12113 ± 2182.01	0.384	0.702

* Indicates significant difference between groups
SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR = Heart rate, RPP = Rate pressure product

Table 4 shows the paired t-test comparison of the baseline and post-6MWT cardiovascular parameters among the PLWH. The post-6MWT cardiovascular parameters were significantly higher than the baseline cardiovascular parameters at p=0.001 respectively.

Table 4: Paired t-test comparison of the baseline and post-6MWT cardiovascular parameters among PLWH

Variable	Baseline X±SD	Post-walk X±SD	Mean Diff X±SD	t-cal	p-value
SBP	108.11 ± 15.43	132.16 ± 15.66	24.05 ± 21.01 S	6.964	0.001*
DBP	67.8378 ± 10.58	84.32 ± 12.59	16.49 ± 15.32	6.548	0.001*
HR	66.84 ± 4.26	86.14 ± 13.75	19.30 ± 12.63	9.298	0.001*
RPP	7250.3 ± 1312.55	11425 ± 2547.90	4174.59 ± 2572.01	9.873	0.001*

* Indicates significant difference between groups
SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR = Heart rate, RPP = Rate pressure product, Mean Diff = Mean difference

Table 5 shows the result of the paired t-test comparison of the baseline and post-6MWT cardiovascular parameters among the control group. The post-6MWT SBP, DBP, HR and RPP were significantly higher than the baseline cardiovascular parameters at p=0.001 respectively. Independent t-test comparison of cardiovascular response (mean differences) to

6MWT between PLWH and the control group is shown in table 6. The PLWH had greater mean differences in SBP (24.05 ± 21.01 vs. 22.43 ± 11.16; p=0.680), DBP (16.49 ± 15.31 vs. 16.22 ± 9.82; p=0.928), HR (19.30 ± 12.62 vs. 14.35 ± 10.05; p=0.660) and RPP (4174.6 ± 2572.01 vs. 3494.9 ± 1951.93; p=0.204) than the control group. However, the differences were not statistically significant (p>0.05).

Table 5: The paired t test comparison of the baseline and post-6MWT cardiovascular parameters among the control group

Variable	Baseline X±SD	Post-6MWT X±SD	Mean Diff X±SD	t-cal	p-value
SBP	109.46 ± 11.29	131.89 ± 9.67	22.43 ± 11.16	12.230	0.001*
DBP	76.22 ± 10.10	92.43 ± 13.00	16.22 ± 9.82	10.047	0.001*
HR	70.38 ± 6.92	84.73 ± 12.92	14.35 ± 10.05	8.683	0.001*
RPP	7.72 ± 1204.57	11213 ± 2182.01	3494.86 ± 1951.93	10.891	0.001*

* Indicates significant difference between groups
SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR = Heart rate, RPP = Rate pressure product, Mean Diff = Mean difference

Table 6: Independent t-test comparison of cardiovascular response (mean differences) to 6MWT between PLWH and the control group

Variable	PLWH Mean Diff X±SD	Control group Mean Diff X±SD	t-cal	p-value
SBP	24.05 ± 21.01	22.43 ± 11.16	0.415	0.680
DBP	16.49 ± 15.31	16.22 ± 9.82	0.90	0.928
HR	19.30 ± 12.62	14.35 ± 10.05	1.864	0.660
RPP	4174.6 ± 2572.01	3494.9 ± 1951.93	1.281	0.204

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR = Heart rate, RPP = Rate pressure product, Mean Diff = Mean difference

Discussion

This study assessed the cardiovascular entropy to 6MWT in PLWH and their age-and-sex matched healthy controls. From the results of this study, the baseline cardiovascular parameters of PLWH and their controls were comparable, except for diastolic blood pressure (DBP) that was significantly higher among the controls. The finding on comparable systolic blood pressure (SBP) among PLWH and healthy controls is consistent with findings of Mattana *et al* [3] and Bergersen *et al* [4]. However, the study's finding on significantly lower DBP among PLWH could not be compared with any previous study. Nonetheless, previous studies have reported isolated SBP and DBP hypertension in PLWH [5-7]. The normal baseline SBP, HR and RPP among the PLWH comparable with that of the controls observed in this study may be attributed to younger age of the sample, asymptomatic stage of the HIV infection (clinical stage I) and the effect of the HAART medications. Conversely, Seaberg *et al* [9] carried out a study on the blood pressure of PLWH in a multi-centre AIDS Cohort Study and found that, a longer duration on HAART has a significant risk of systolic blood pressure. Palacios *et al* [10] discovered increased SBP in PLWH after receiving 48weeks of HAART.

This study's finding on lower baseline DBP compared to the healthy controls may be as a result of atherosclerotic changes that take place in HIV infection. Endothelial change is a common complication in HIV/AIDS [4, 44] and it is one of the causative factors of atherosclerosis [45]. Endothelial dysfunction is associated with the clinical signs of atherosclerosis [45], a condition associated with high systolic blood pressure and low diastolic blood pressure [46]. Meng *et al* [47] found associated coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in persons living with HIV-1. Bots *et al* [48] found an association between low DBP and increased carotid atherosclerosis. Nonetheless, the reason adduced for the finding of this study should be taken with caution as atherosclerosis is known to be related with low DBP with advancing age [48].

From this study, the pattern of cardiovascular response of PLWH and the controls to 6MWT were similar. Cardiovascular response to 6MWT among both groups revealed a significant increase in SBP, DBP, HR and RPP. This pattern is consistent with previous studies that found significant increase in the cardiovascular parameters of participants after performing the 6MWT [49-51]. The cardiovascular system is one component of an integrated mechanism that functions to compensate for the increased metabolic demands of exercise, and the performance of each component is influenced by the action of the others [26]. During exercise oxygen demand by the muscles increases sharply, metabolic processes speed up with the creation of more waste, more nutrients being used up as body temperature rises and thus to perform as efficiently as possible the cardiovascular system must regulate these changes and meet the body's increasing demands [22]. Anigbogu *et al* [51] assessed the cardiovascular status of 15 patients with chronic heart failure before and after the 6MWT. They discovered 9% and 8.5% increase in HR in male and female participants respectively, while male and female controls had 13.4% and 9% increase in HR respectively. There were also significant increases in the DBP of male patients, male control subjects and female control subjects. The pattern of cardiovascular response to 6MWT observed among PLWH and the controls in this study is akin to trends reported for general exercise which include increased HR, increased SBP, unchanged or decreased DBP, increased stroke volume and increased ejection fraction [52]. The result of this study showed that 6MWT in PLWH had a significant effect on the blood pressure (systolic and diastolic), heart rate and RPP which is a predictor of oxygen consumption of the heart [53-55] as should be expected in normal individuals.

The results of this study indicate that the comparison of cardiovascular response to both 6MWT between PLWH and healthy controls were comparable. Specific studies on cardiovascular response of PLWH to 6MWT are scarce. However an available study by Dolan *et al* [56] found no significant difference in the change in SBP and DBP for both PLWH and apparently healthy controls following 16 weeks of aerobic exercises. Nonetheless, significantly lower post-6MWT DBP was observed among the PLWH compared with the controls. This difference can be attributed to the baseline difference in DBP that exist between the groups.

Owing to the importance of objective evaluation of functional exercise capacity in patients with chronic illnesses, the 6MWT was adopted to assess the cardiovascular fitness of PLWH in this study. The test assesses not only the response of pulmonary, cardiovascular and circulatory systems, but also motor control, functional neuromuscular units and muscle [57]. The 6MWT permits clinicians to monitor exercise capacity, and also encourage selfmanagement by enabling individuals to monitor changes in their functional capacity [58]. However, the outcome of this study cannot be generalized to PLWH in other clinical stages. This is because symptoms and the stage of disease of the individual patient are important factors to be considered in the assessment of functional capacity in PLWH [15].

Conclusion

Baseline cardiovascular parameters of clinical stage 1 PLWH was normal and comparable with that of the healthy controls. However, PLWH had significantly lower baseline and post-6MWT DBP than the controls'. 6MWT led to significant increase in blood pressure, HR and myocardial oxygen demand in PLWH. The magnitude of cardiovascular response to 6MWT in PLWH was comparable with healthy controls'.

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