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Full Length Research Paper

Autonomic dysfunction as a predictor of heart disease in human immunodeficiency virus (HIV)

Yaser Elnahar[1]*, Mohannad Bisharat[1], Joseph Daoko[1], Ashraf QaQa[1], Anthony Al-Dehneh[1], Vincent A. DeBari[2], Jihad Slim[3] and Fayez Shamoon[1]

[1]Department of Cardiology at St Michael's medical center, USA.
[2]Department of Internal Medicine Seton Hall University, USA.
[3]Department of Infectious disease at St Michael's medical center, USA.

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The purpose of this study was to test the presence of Autonomic Dysfunction (AD) in patients infected with Human Immunodeficiency Virus (HIV). 30 HIV (study) and non HIV (control) patients were prospectively enrolled and underwent five different established methods for detection of autonomic dysfunction. Amongst the five tests employed, there was a statistical difference in 4/5 tests between the two groups. The HIV patients studied had a statistically lower initial resting heart rate than the control group. The data shows that after 15 s, the resting heart rate was still significantly lower in the HIV group ($p = 0.01$) with no significant difference ($p = 0.73$) by 30 s. The ratio of the 30 to 15 s measurements suggests a substantial and highly significant ($p < 0.0001$) difference between the groups. In comparing the two groups with respect to a 2 min standing blood pressure difference, Diastolic blood pressure (DBP) was significantly different between the groups. In the exercise test, both group and the time factors were significant; the former at $p < 0.0001$ and the latter at $p = 0.0001$. There were significant differences of all blood pressure parameters during maximum exercise and recovery, with $p < 0.0001$ for all comparisons of the group factor. In the valsalva maneuver test, there was a statistical difference between the two groups during the longest r-r interval. Moreover, in the HIV group, there were more abnormal responses but these were not statistically significant. The relationship between HIV infection and cardiovascular disease is significant; this study aimed to show that HIV does affect the autonomic nervous system. The study demonstrates the high prevalence of autonomic dysfunction in HIV infected patients and the lack of correlation with markers of disease severity or disease duration. The patients studied showed an abnormal response to most tests employed (4/5).

Key words: Autonomic dysfunction, human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), nervous system, cardiovascular system.

INTRODUCTION

According to current estimates, approximately forty million people worldwide are infected with the Human immunodeficiency virus (HIV). While attention in recent years has focused on the HIV epidemic in Africa and parts of Asia, HIV continues to have a substantial effect in the United States. The Centers for Disease Control (CDC) recently increased the estimated number of HIV infected individuals living in the U.S. to above 1 million persons, and it is estimated that 40,000 individuals acquire HIV infection each year in the U.S (CDC, 2008).

The consequences of the HIV epidemic have been significant in Newark, New Jersey's largest city. The known HIV/AIDS (Acquired immune deficiency syndrome) rate

*Corresponding author. E-mail: yaserelnahar@hotmail.com. Tel: 732 763 1862.

is higher in Newark (2,035 per 100,000 persons) than the entire state of NJ (358 per 100,000), and is among the highest in the United States (CDC, 2008). Now, in the third decade of the HIV epidemic in Newark, the effects have been devastating on the minority populations that inhabit Newark with 1/32 African Americans and 1/86 Latinos living with HIV/AIDS (NJ Department Health, 2004).

Despite a declining rate of HIV related death, proportions of HIV infected patients dying of other causes have increased (Krentz et al., 2005). As an example, a death certificate study in New York City showed that the proportion of deaths among HIV-infected patients due to non-HIV related causes increased from 19.8 to 26.3% between 1999 and 2006, reflecting mortality resulting from cardiovascular disease (CVD), substance abuse, and non-AIDS defining cancers (Sackoff et al., 2006). Among individuals aged 55 years or older, CVD was the leading cause of death. There are several health consequences to patients infected with HIV. The relationship between HIV infection and cardiovascular disease is significant, and has been the subject of several investigations.

There are a number of distinctive neuropathic syndromes which can be classified according to the timing of their appearance during HIV infection, etiology and whether they are primarily axonal or demyelinating (Keswani et al., 2002; Markarian et al., 1998; Brinley et al., 2001; De la Monte et al., 1988; Mcarthur et al., 2005; Verma et al., 2001; Ferrari et al., 2006). These include: distal symmetric polyneuropathy, mononeuropathy multiplex, acquired inflammatory demyelinating polyradiculoneuropathy, cauda equina syndrome (or lumbosacral polyradiculopathy), diffuse infiltrative lymphocytosis syndrome (DILS), autonomic neuropathy, mononeuropathies, herpes zoster radiculitis and sensory ganglioneuritis.

Autonomic dysfunction is one of these relationships, and its serious health hazard of postural hypotension, syncope and pre-syncope as well as cardiopulmonary arrest during invasive procedure has been reported (Prendergast, 2003). Autonomic dysfunction is more pronounced with AIDS patients; however it has been reported in patients with HIV infection without AIDS (Sakhuja et al., 2007; Divine et al., 2002).

The term autonomic nervous system (ANS) describes nerves that are concerned predominantly with the regulation of bodily functions. It is comprised of sympathetic and parasympathetic nerves, and their function is complementary (Stojanovich et al., 2009). Autonomic failure is a disorder of noradrenergic neurotransmission in which postganglionic sympathetic neurons do not release norepinephrine appropriately. This low norepinephrine release results in impaired vasoconstriction leading to secondary reduced intravascular volume, both of which contribute to orthostatic hypotension. In normal subjects, as the blood pressure falls, there is an appropriate reflex-induced increase in heart rate; however, the presence of a heart rate increase does not exclude autonomic failure. Conversely, heart rate usually decreases during reflex syncope (Kaufmann et al., 1997).

MATERIALS AND METHODS

Over the course of two years, 30 HIV infected patients were prospectively enrolled. Simultaneously, 30 volunteers were matched for age, gender, ethnicity and medical conditions and recruited. Institutional review board approval was obtained for the study. Informed consent was obtained from each subject. The exclusion criteria for enrollment were: Age < 18 and > 80 years, hospitalized patients, patients with the diagnosis of Diabetes mellitus (DM) on or off therapy, patients with fasting blood glucose (FBG) > 120, alcoholic patients, patients in active drug withdrawal (heroin, cocaine, tobacco, active drug use (last 24 h), active tuberculosis (TB) or on TB therapy, adrenal insufficiency, any history of neuropathy and any history of a neurological disorder. In addition, adherence to published recommendation by The American College of Cardiology (ACC) on absolute and relative contra-indication to performing exercise testing was observed: Alcoholic patients, acute myocardial infarction (within 2 days), high-risk unstable angina, uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus or pulmonary infarction, acute myocarditis or pericarditis, acute aortic dissection, left main coronary stenosis, moderate stenotic valvular heart disease, electrolyte abnormalities, severe arterial hypertension, tachyarrhythmias or bradyarrhythmias, hypertrophic cardiomyopathy and other forms of outflow-tract obstruction, mental or physical impairment leading to inability to exercise adequately and high-degree atrioventricular block.

The different baseline characteristics were directly obtained from the study subjects. None of the study subjects consumed caffeine prior to starting the study tests. All of the patients underwent the study in the same room using the same equipment for all of the patients. In addition, the temperature in the room was adequate for the tests and was the same for all of the patients. Individuals who met the study requirements performed an exact sequence of different non invasive maneuvers to evaluate their autonomic system. The sequence of maneuvers performed was as follows:

1. Six breath per minute test;
2. Valsalva maneuver with the subject achieving a 40 mmHg pneumotic pressure for 15 s with subsequent two minute standing and measurement of blood pressure and heart rate;
3. Five minute hand grip test with the subject holding at thirty percent pressure of their maximum hand grip pressure;
4. Exercise stress test performed using the standard Bruce protocol.

Statistical methods

Continuous (interval) data were evaluated for fit-to-normality by the D'Agostino-Pearson omnibus normality test. All data were found to fit normal distributions to a statistically significant degree. Thus, parametric methods were used throughout. Two group-wise comparisons with one independent variable were made by t-tests; when more than one independent variable was to be compared;

Table 1. The base line demographic characteristics between the study (HIV) and control.

Characteristics	HIV group	Control group	P-value
Age	45.4± 8.1	46.6± 10.5	0.585
Gender (m/f)	20/10	20/10	1.000
Race/Ethnicity:			
Black	26	20	
White	1	2	
Hispanic	3	8	
Hypertension (y/n)	3/27	8/22	0.181
Coronary artery disease (y/n)	0/30	0/30	1.000
COPD (y/n)	7/23	1/29	0.052
Neoplasm (y/n)	0/30	0/30	1.000
Neurological disease (y/n)	0/30	0/30	1.000
Smoking (y/n)	15/15	2/28	0.001
Alcohol use (y/n)	11/19	0/30	<0.001
Drug use (y/n)	0/30	0/30	1.000

y = yes, n = no, m = male, f = female

two-way Analysis of variance (ANOVA) was used in a 2 × 4 factor analysis as follows: study groups were treated as an independently assorted variable and clinical maneuver times of measurement (resting, 1, 3 and 5 min for the exercise maneuver, resting and 2 min for the standing maneuver and maximum exercise, 1 and 5 min post exercise for the exercise recovery study) were repeated measures. Categorical variables were compared by contingency table cross-tabulations; 2 × 2 comparisons tested for statistical significance by Fisher's exact test and 2 × 3 comparisons by the chi-square test using Yates' correction. Statistical significance was based on $\alpha = 0.05$, that is $p \leq 0.05$ was considered to be statistically significant. The magnitude of effect is given as the relative risk (RR) with 95% confidence intervals (95% CI) provided. All statistical computations were made with a personal computer using Prism® software (GraphPad Corp., San Diego, CA USA).

RESULTS

The HIV patients studied had a statistically lower initial resting heart rate than the control group. The HR was also evaluated using measurements of the R-R at 15 s, slight differences were observed with regard to resting blood pressure (BP), with the HIV group having slightly lower systolic blood pressure (SBP). The results of the valsalva maneuver on the R-R interval measured at 15 s of standardized valsalva failed to show statistical significance as a parameter of autonomic dysfunction in the study, the same was also noted upon measuring the blood pressure after five minute of hand grip exercise, the p-value for this test was also insignificant between the HIV group and the control group. Finally, during the stress test recovery phase, 18/30 (60%) had a delayed recovery to baseline heart rate.

In evaluation of background information, there was significant difference observed with regard to alcohol use, with significantly greater respondents in the HIV group (36.7%) claiming alcohol use and none in the control group. The HIV group also had substantially higher prevalence of Chronic obstructive pulmonary disease (COPD) (23.3%) than the control group (3.33%); however this difference did not quite achieve statistical significance (Table 1).

The baseline hemodynamic data [SBP, diastolic blood pressure (DBP) and mean arterial pressure (MAP)] showed a difference between the two groups. The HIV group had a statistically lower initial resting heart rate than the control group. The HR was also evaluated using measurements of the R-R at 15 and 30 s obtained by Electrocardiography (ECG) (Figure 1). These data suggest that after 15 s, the resting heart rate is still significantly lower in the HIV group ($p = 0.01$) with no significant difference ($p = 0.73$) by 30 s. The ratio of the 30 to 15 s measurements suggests a substantial and highly significant ($p < 0.0001$) difference between the groups. Slight differences were observed with regard to resting BP, with the HIV group having slightly lower SBP ($p = 0.32$) and slightly higher DBP ($p = 0.21$). The resultant MAP means were nearly identical ($p = 0.96$) (Figure 2). When comparing the hemodynamic data (SBP, DBP and MAP) with respect to a 2 min standing maneuver, only DBP was significantly different between the groups. There were no significant differences in the time factors for any of the three comparisons (Figure 3).

The results of the means of the HR measurements for the exercise and post-exercise recovery period showed a

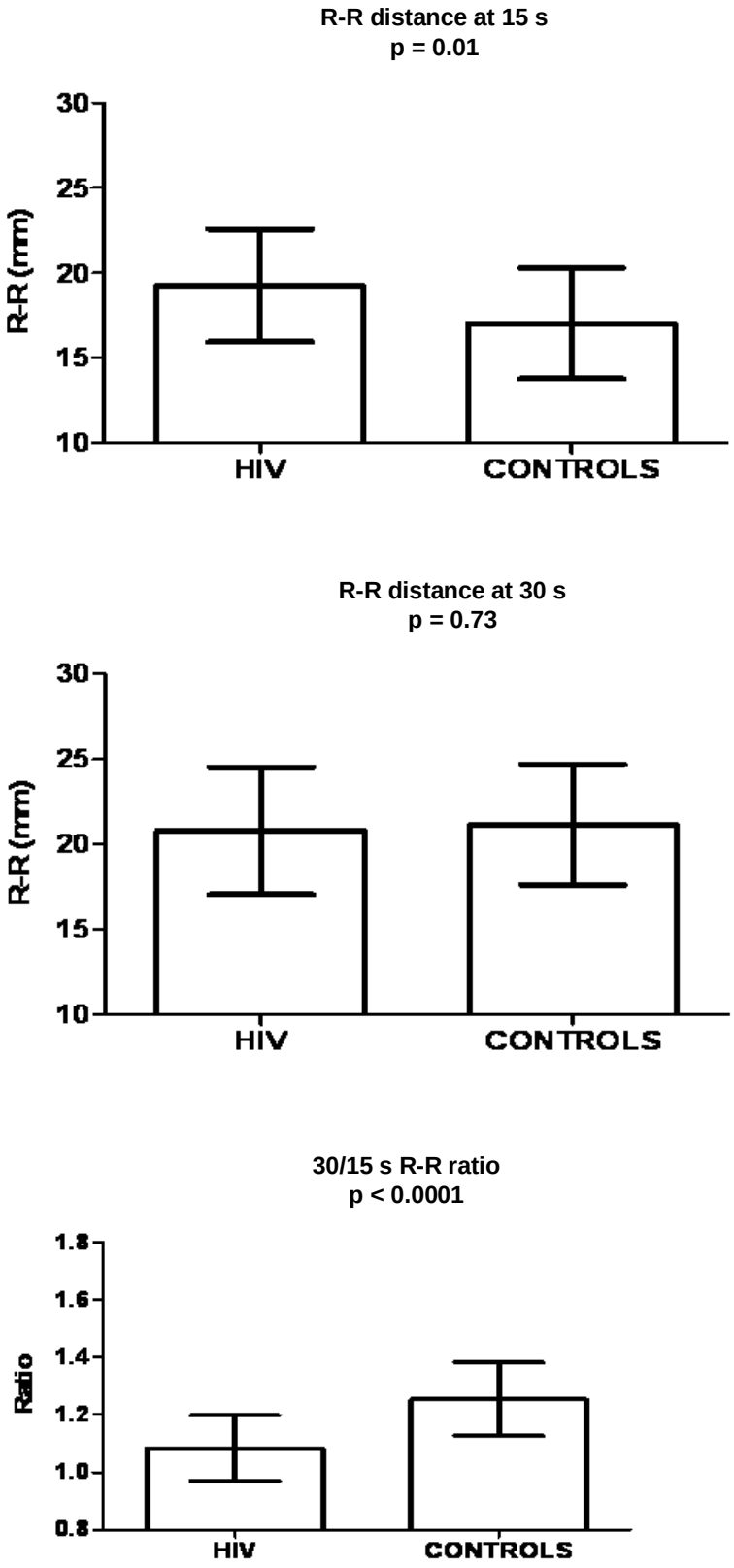

Figure 1. Heart rate (HR) measurements calculated for R-R at 15 s and R-R at 30 s on the electrocardiogram.

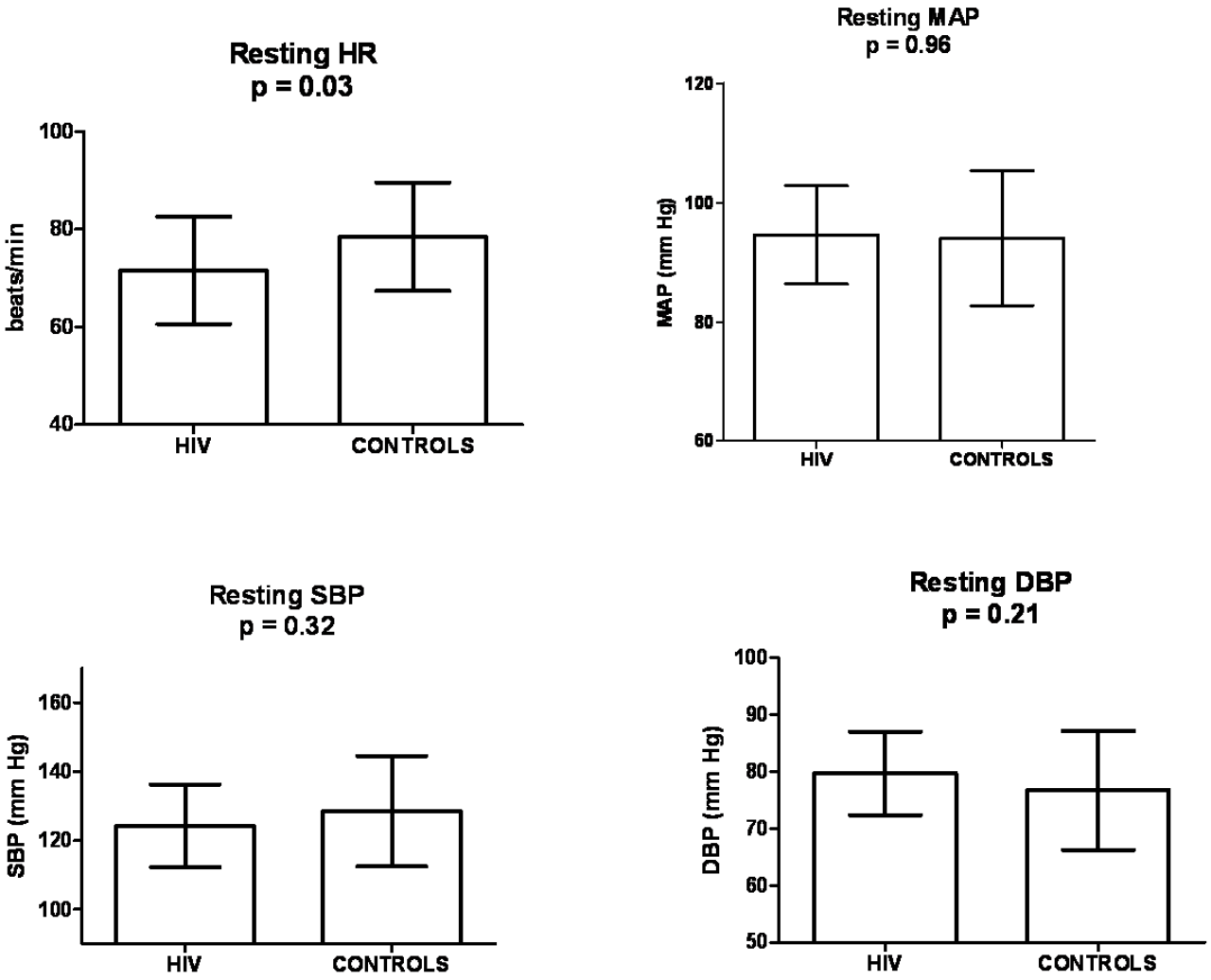

Figure 2. Initial measurements of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

significant difference between the two groups. Both groups and the time factors were significant; the former at $p < 0.0001$ and the latter at $p = 0.0001$. There was also a significant interaction between the two factors with the p-value for interaction of 0.035. There were significant differences of all blood pressure parameters during maximum exercise and recovery. These data are presented in Figure 4, showing highly significant group-wise differences, with $p < 0.0001$ for all comparisons of the group factor. Finally, during the stress test recovery phase, 18/30 (60%) of the HIV had a delayed recovery to baseline heart rate (Figure 5).

The valsalva maneuver's effect on the R-R interval between the two groups was also tested as part of the experiment, however, it did not yield a significant difference. The longest/shortest (L/S) R-R distance ratio did not quite achieve statistical significance. In order to demonstrate the actual number of studies falling below the established cut-off of 1.2, the L/S ratio values are shown as dot histogram (means and SD given by lines) with a dotted line at the cut-off. A contingency table analysis comparing those below and above the cut-off for each group suggests that the valsalva maneuver data are not statistically significant with 16.7% of the HIV group and 13.3% of the control group below 1.2 ($p = 1.00$) (Figure 6).

Finally, the hand grip's effect on DDBP was tested and the results did not yield any difference between the two groups. Neither the group-wise differences with DDBP as a continuous variable nor the categorization of the data into those subjects > 16/ ≤ 16 mmHg were statistically significant; the former: $p = 0.55$; the latter: $p = 1.00$

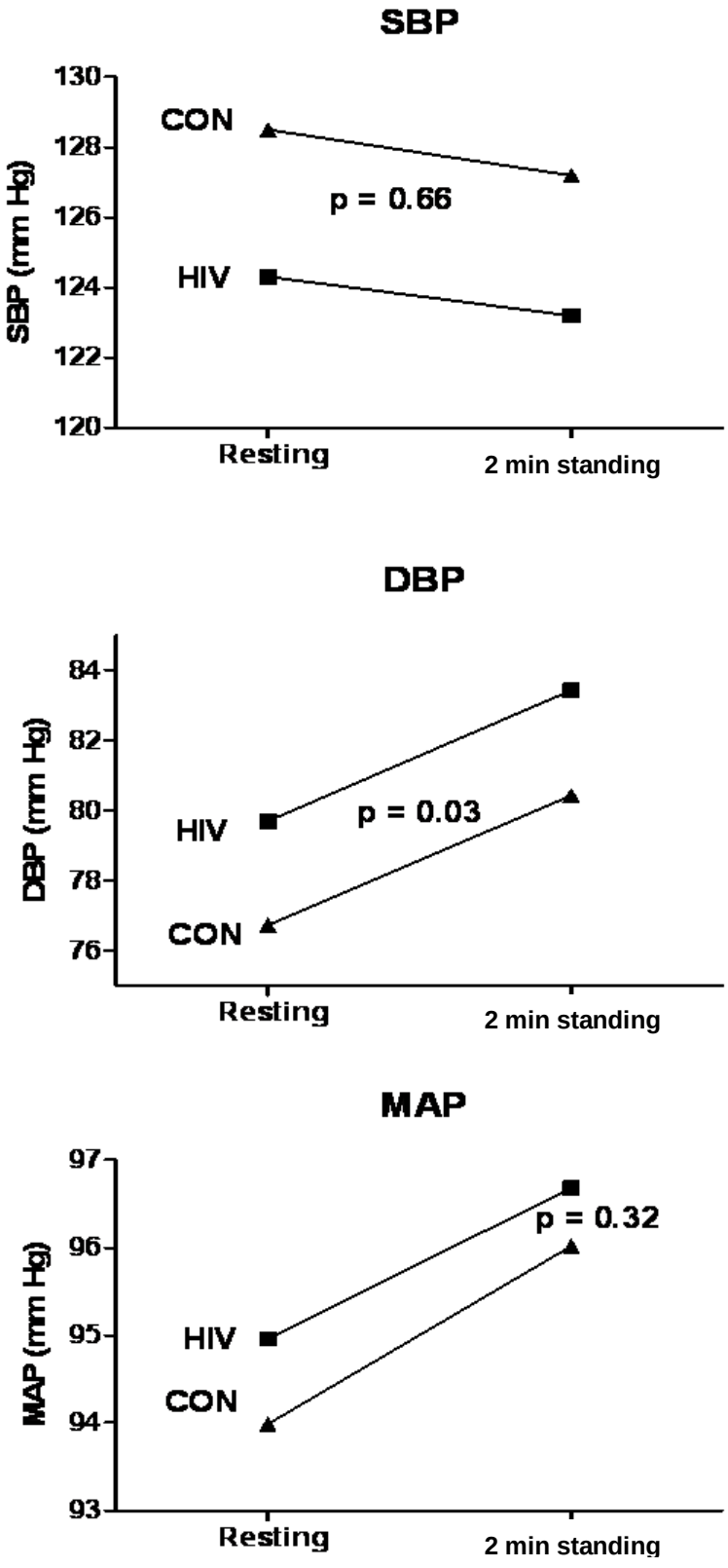

Figure 3. Factorial results of a 2 min standing maneuver upon systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). CON = control.

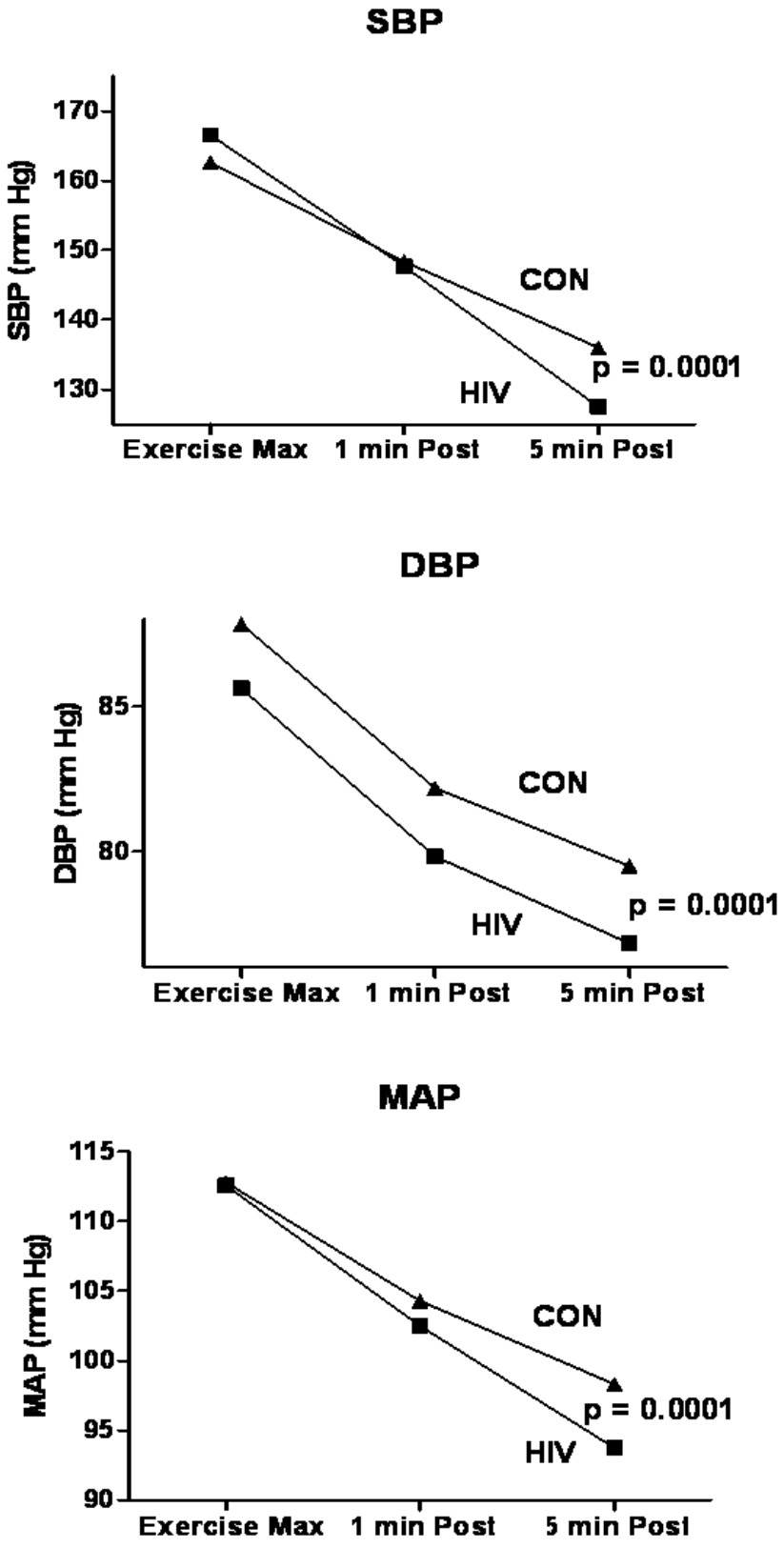

Figure 4. The maximum exercise and recovery systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). CON = control.

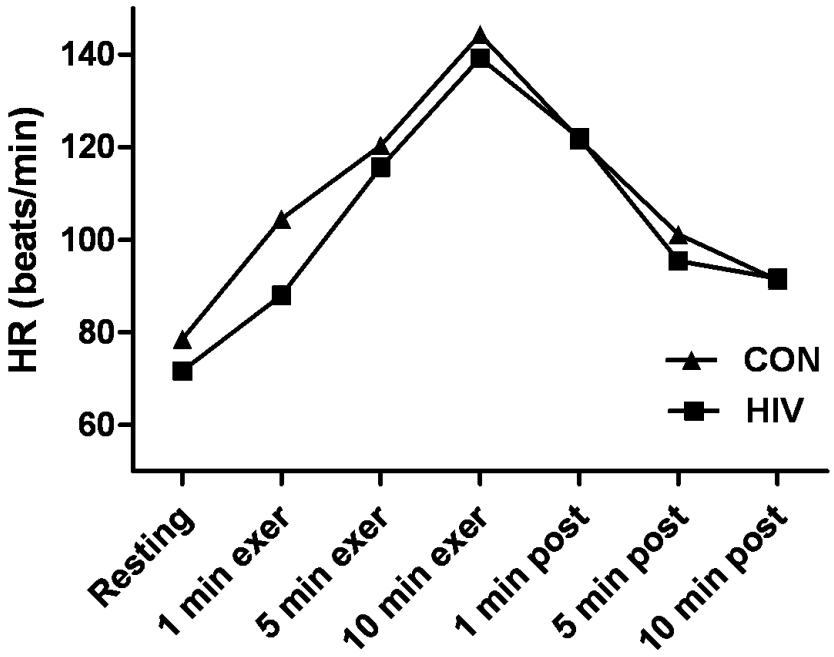

Figure 5. Means of the heart rate (HR) measurement for exercise and for the post exercise recovery period. CON = control.

(Figure 7).

DISCUSSION

The interest of this project was to study the autonomic dysfunction (AD) in HIV infected patients. Although there are multiple studies that have shown that HIV infected patients have AD, none have utilized the exercise stress test. There are several methods that can be employed for defining AD in HIV. These include but are not limited to blood pressure response and heart rate variability (Divine et al., 2002). The presence of AD was prospectively studied in thirty HIV infected patients using the previous reported methods (Divine et al., 2002). The results of this group were compared to a matched control group of non HIV patients.

This study investigated the presence of autonomic dysfunction in HIV infected patients in comparison to non HIV infected patients. The data shows that in evaluation of base line heart rate, the HIV group had a statistically lower initial resting heart rate than the control group. Secondly, the HR was also evaluated using measurements of the R-R at 15 and 30 s as obtained by ECG (Figure 1). These data suggest that after 15 s, the resting heart rate is still significantly lower in the HIV group ($p = 0.01$) with no significant difference ($p = 0.73$) by 30 s. The ratio of the 30 to 15 s measurements suggests a substantial and highly significant ($p < 0.0001$) difference between the groups. In comparing the two groups with respect to a 2 min standing blood pressure difference, DBP was significantly different between the groups.

In the exercise test, both group and the time factors were significant; the former at $p < 0.0001$ and the latter at $p = 0.0001$. There was also a significant interaction between the two factors with the p- value for interaction of 0.035. There were significant differences of all blood pressure parameters during maximum exercise and recovery. These data are presented in Figure 4, showing highly significant group-wise differences, with $p < 0.0001$ for all comparisons of the group factor. In the valsalva maneuver test, there was a statistical difference between the two groups during the longest R-R interval. Moreover, in the HIV group there were more abnormal responses but they were not statistically significant. The lack of statistical significance on this test may be a result of a small sample size. Overall, in comparing HIV versus non HIV infected patients, there was a significant difference between the two groups on 4 out of the 5 tests employed.

The data supports the notion that there exists a difference in autonomic function between HIV patients and controls. The positivity to multiple autonomic parameters in patients that have a low CD4 count as well as in patients with a good CD4 count indicates that the autonomic dysfunction exists independent of disease

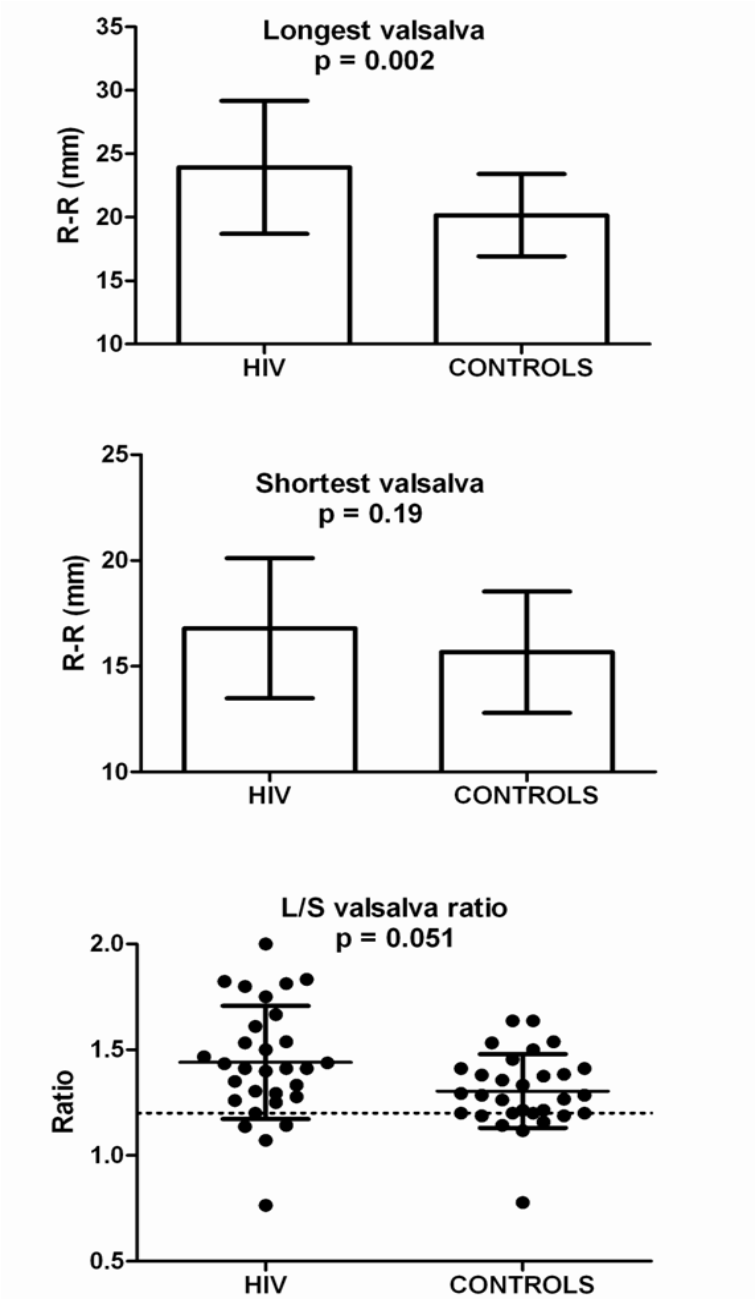

Figure 6. The results of the valsalva maneuver on the R-R interval are shown with the bar histograms giving the longest and the shortest R-R intervals.

severity. However, most of the patients (87%) in the study did not have AIDS, and thus this may have limited drawing a proportionality relationship between CD4 count and test response. There was no correlation between the number of positive tests and the CD4 count viral load for years, since diagnosis or the use of antiretroviral therapy.

Amongst the parameters tested, beat-to-beat heart rate variation seems to have yielded the greatest number of abnormal responses, while measuring systolic blood pressure in response to standing yielded the least number of abnormal responses. The limitation to the study is the small sample size in both groups; however, the data supports the presence of an abnormal autonomic response to the multiple tests employed. In

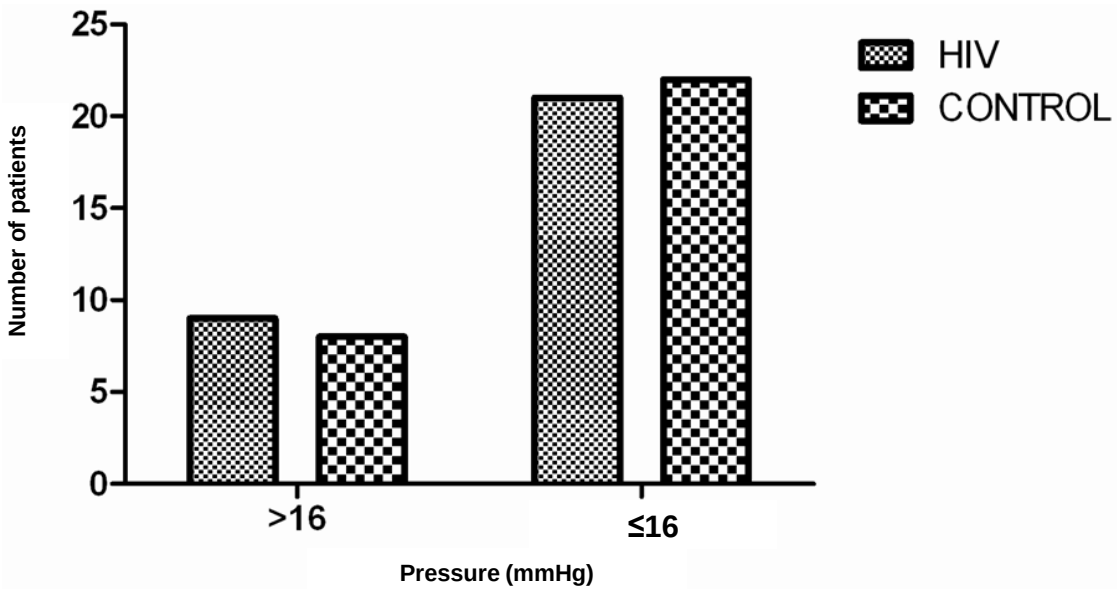

Figure 7. The results of the hand grip contigency data are given as ΔDBP.

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comparing this study with other published data, these results are comparable but show that AD can exist in the absence of AIDS. The utility of multiple tests for detection of AD is essential in showing its presence.

The limitation to the study is the small sample size in both the control and the study group. However, despite the limited number of patients, the results were significant for showing autonomic dysfunction in the HIV patients when compared to non-HIV matched controls. As such, we recommend a larger study which can employ other tests for autonomic dysfunction and a correlation with CD4 count, viral load and duration of infection.

Conclusion

The relationship between HIV infection and cardiovascular disease is significant; this study aimed to show that HIV does affect the autonomic nervous system. The study demonstrates the high prevalence of autonomic dysfunction in HIV infected patients and the lack of correlation with markers of disease severity or disease duration. This study is a testimony that HIV may have asymptomatic autonomic dysfunction and unless sought after, it may be missed. The patients studied showed an abnormal response to most tests employed (4/5). These results indicate that despite acceptable CD4 counts in HIV patients, autonomic dysfunction is present.

ACKNOWLEDGMENTS

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