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RESEARCH ARTICLE

Exercise training improves cardiovascular and autonomic profiles in HIV

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Abstract *Objectives* Human immunodeficiency virus (HIV) is associated with cardiovascular (CV) and autonomic dysfunction, however the effects of fitness on vascular and autonomic mechanisms in HIV disease are unknown. *Methods* We studied forty-eight subjects (40.4 ± 4.2 years) in a cross-sectional design matched for age, gender, BMI, and fitness. Participants were assigned to 1 in 4 groups: 1) Healthy Unfit (HU), 2) Healthy Fit (HF), 3) HIV Positive Unfit (HPU), and 4) HIV Positive Fit (HPF). Fitness was assessed via open-circuit spirometry; arterial compliance and autonomic modulations were measured via applanation tonometry and power spectral analysis, respectively, and baroreflex sensitivity was obtained using the alpha index. *Results* Arterial compliance was augmented in HPF vs. HPU [7.4 ± 1.9 mmHg × second vs. 4.4 ± 1.7 mmHg × second ($P = 0.006$)]. Parasympathetic modulation was higher in HPF vs. HPU [2244.5 ± 2997.6 msecond^2 vs. 489.1 ± 552.9 msecond^2 ($P < 0.05$)]. Sympathetic modulation was lower in HPF vs. HU [4.7 ± 5.0 mmHg^2 vs. 12.9 ± 9.7 mmHg^2 ($P < 0.05$)]. Baroreflex sensitivity was higher in HPF vs. HPU [17.3 ± 10.2 msecond/mmHg vs. 7.4 ± 3.8 msecond/mmHg ($P = 0.003$)], and HPF vs. HU [17.3 ± 10.2 msecond/mmHg vs. 6.2 ± 3.0 msecond/mmHg ($P = 0.004$)]. *Conclusions* Augmentations in arterial compliance and baroreflex sensitivity associated with fitness portent an improved CV and autonomic profile for HIV-positive individuals. Physical activity may be an adjuvant method to enhance the overall vascular health in HIV-compromised individuals.

Key words immunodeficiency · HIV · exercise · fitness · baroreflex · autonomic nervous system

Introduction

Cardiac involvement occurs in 45–66% of patients with HIV [16, 37]. Paton et al. [43] reported severe coronary disease in the absence of antiretroviral medications and traditional cardiovascular (CV) risk factors. Although antiretroviral medications reduce the deleterious physiologic effects of HIV, it may be the disease progression itself, not medication, which significantly contributes to coronary artery pathology and higher mortality rates associated with HIV. Highly active antiretroviral therapy (HAART) is

associated with lipodystrophic abnormalities, metabolic dysfunction, and insulin resistance. Myocardial infarct and other vascular insult raise concern that HAART therapy contributes to heart disease in HIV-positive patients [28].

Carotid artery thickness, a potent surrogate marker of future CV events, was studied in HIV-positive patients [11, 35]. Increased carotid intima media thickness, with or without protease inhibitors, exists in a majority of HIV-positive patients and is strongly associated with age, elevated cholesterol, and reduced HDL-C [35]. Data suggest diminished compliance of the arterial system in HIV disease, leading to an increase in atherosclerotic lesions, vessel dysfunction, and myocardial infarction risk and a higher mortality rate.

A diminished autonomic profile is evident in HIV-positive individuals [12, 23, 24, 47, 48, 57]. Although the relevant pathophysiologic mechanisms in HIV-positive patients are not fully elucidated, hyperchronic levels of sympathetic activity is often evident. Vascular insults may be due to a constant surge of sympathetic outflow and persistent stimulation of α-adrenergic receptors. Sympathetic predominance contributes to vessel stiffness, resulting in increased blood pressure and reduced arterial compliance contributing to CV conditions (e.g., atherosclerosis and endothelial damage) seen in HIV-infected patients. Little is known about the extent to which autonomic dysfunction contributes to HIV-associated cardiac dysfunction, morbidity, and mortality. Thus, it is important to explore the preclinical manifestations of autonomic dysfunction in HIV-infected patients.

Many studies investigated exercise capacity in HIV-positive subjects [30, 44, 45, 53], but little is known regarding exercise guidelines in this population. Stringer et al. [53] demonstrated significant improvements in aerobic capacity and quality of life in subjects with AIDS, who performed high-intensity aerobic exercise compared to non-exercise and low-intensity groups; however, immune function showed little change. Conversely, other studies [34, 44] show that exercise training significantly impacts CD4+ cell count and other markers of immune function. It is apparent that regular exercise benefits aerobic capacity in those with HIV [30, 44, 53]. However, exercise capacity in HIV-positive subjects is often lower than HIV-negative, age-matched counterparts [30, 45, 53].

Data relating aerobic fitness to CV and immune profiles in HIV remain sparse and exercise guidelines are general. Thus, the primary aim of this study was to examine the relationship among cardiopulmonary dysfunction, autonomic dysfunction, and functional capacity in HIV disease and to determine the extent to which exercise can modulate these parameters.

Methods

Study design

This investigation examined healthy subjects defined as HIV negative, and subjects diagnosed with HIV within 24 months of this investigation, defined as HIV positive (n = 48). Groups were categorized as follows:

HIV Healthy Unfit (HU); HIV Healthy Fit (HF);
HIV Positive Unfit (HPU); HIV Positive Fit (HPF).

Subjects

Subjects were nonsmokers between 25 and 45 years of age, normotensive, and had no history of cardiopulmonary disease, kidney disease, or diabetes. Subjects were matched for age, BMI, gender, and fitness level (Table 1). HIV-positive subjects were administered an identical HAART medication regimen and were asymptomatic [55].

HIV-negative individuals were recruited via flyers and word of mouth and were free from any vasoactive drugs or hormone therapy. HIV-positive individuals were recruited from HIV clinics in the New York area and were recommended via physician referral. A questionnaire was used to obtain demographic data and identify significant risk factors. Exercise history and current activity level were assessed using a physical activity questionnaire [42]. Participants were instructed neither to consume caffeine nor to participate in aerobic exercise 24 hours prior to testing.

Informed consent was obtained from all subjects prior to enrollment. This investigation was approved by the institutional review boards of Coler Goldwater Specialty Hospital and Nursing Facility, New York, NY, and Teachers College, Columbia University, New York, NY.

Resting measures were taken in a quiet and dimly lit room. Subjects were instructed to remain in a seated position. Resting heart rate was recorded using a 3-lead configuration. Leads were placed on the left ribcage (V_5 position), right shoulder (AVR position), and the right hip (ground). Resting blood pressure was

Table 1 Subject characteristics

Subjects	HU, n = 9	HF, n = 11	HPU, n = 15	HPF, n = 13	ALL, n = 48	P
Age (years)	40.2 (3.7)	37.8 (4.0)	41.4 (4.6)	41.5 (3.7)	40.4 (4.2)	NS
Height (cm)	172.1 (15.2)	170.8 (12.7)	171.3 (6.7)	171.7 (7.1)	171.5 (10.0)	NS
Weight (kg)	77.0 (19.8)	73 (17.3)	74.2 (7.5)	71.0 (8.7)	73.7 (13.1)	NS
BMI (wt[kg]/ht[m^2])	25.6 (2.6)	24.7 (3.1)	25.3 (2.4)	24.1 (2.3)	24.9 (2.6)	NS

Values are mean ± SD. BMI, body mass index; NS, not significant

Table 2 Hemodynamics

Subjects	HU, $n = 9$	HF, $n = 11$	HPU, $n = 15$	HPF, $n = 13$	ALL, $n = 48$	P
HR (bpm)	79.1 (15.9)	64.3 (9.9)	84.5 (12.3)	66.4 (8.5)	74.0 (14.3)	<0.001
SBP (mm/Hg)	118.3 (17.6)	115.0 (13.5)	113.4 (18.4)	110.7 (15.9)	114.0 (16.2)	NS

Mean values ± SD. HR, heart rate; SBP, systolic blood pressure; NS, not significant

obtained by means of manual auscultation with the use of an aneroid sphygmamonometer. Resting blood pressure was taken and recorded twice, 5 minutes apart by the same technician to ensure less than a 5% variation.

Blood pressures via applanation tonometry were acquired by instructing subjects to sit quietly while placing their left arm on a cushioned table keeping their arm at the level of the atrium. An appropriate sized cuff was placed around the left brachial artery and a tonometer (CDM 7000, Colin Medical, San Antonio, Texas) was fitted over the left radial pulse. Respiratory recordings were acquired with the use of a thermistor (TM 100, Iworx, Inc., Dover, New Hampshire) placed under the left nostril to sense temperature changes as a result of inhalation and exhalation. Subjects were told to breath normally so as not to influence autonomic modulation.

Resting heart rate, resting blood pressure, and respiratory recordings were sampled at 500 Hz. All data were acquired via Labscribe data acquisition software (Iworx Inc., Dover, New Hampshire) and digitized through an IX-114 analog to digital (A/D) board (Iworx Inc., Dover, New Hampshire). The A/D board interfaced with a Pentium IV Dell Inspiron 8200 laptop computer.

Following the recording of resting data, a symptom-limited exercise test was performed using an electronically braked upright cycle ergometer (Lode [Corival], St. Paul, Minnesota). Exercise data (VO_2 [ml/kg/min^{-1}], VCO_2 [ml/minute], and V_E [l/minute]) were acquired using breath-by-breath analysis, and data were saved onto a computer hard drive (Cardio O_2 System, Medical Graphics, St. Paul, Minnesota). The protocol consisted of a 2-minute warm-up against no resistance (freewheel mode), followed by a 25 W/minute ramp at 50–60 revolutions per minute (RPM) [44].

Pulse oximetry (Nonin, Inc., Plymouth, Minnesota), heart rate, and heart rhythm were monitored prior to exercise, every 2 minutes during exercise, and every 2 minutes during a 6-minute recovery period. Blood pressure was recorded prior to exercise, every 2 minutes during exercise, and every 2 minutes for 6 minutes after the test was completed. A cardiologist and exercise physiologist supervised each test. The test was conducted in accordance with published guidelines [26].

Analysis of arterial compliance was performed using programs written in LABVIEW™. Data was formatted in an ASCII format and was input into a blood pressure "chopping program" allowing the selection of a 1-minute segment of blood pressure waveforms to be analyzed. Blood pressure data were then automatically marked for systolic peaks and diastolic valleys. Blood pressure data detected incorrectly or absent from computation were marked manually. Blood pressure waveforms within the selected 1-minute time period were superimposed onto one another. The resultant waveform was divided into a systolic and diastolic area and was used to determine arterial compliance. Arterial compliance was defined as the area under the diastolic decay curve of the arterial pulse wave [17, 36, 58]. This technique is highly correlated with invasive methods and is valid and reliable in both health and disease [13, 40].

Autonomic modulation of parasympathetic nervous system was determined by power spectral analysis of heart rate variability [2, 7]. After conducting a 5-minute recording, data were saved onto a hard drive and backed up on a rewritable compact disk. The data were converted into text, stored in ASCII format, and input into a LABVIEW™ program. Vertical thresholds (to ensure R waves did not exceed a pre-determined amplitude) and horizontal thresholds (to ensure that two R waves were not detected in close proximity) were automatically chosen before data were analyzed. Data were downloaded into the LABVIEW™ software and R wave peaks were marked. R waves detected incorrectly or R waves absent from detection were marked manually. After R wave detection was complete, a resultant interbeat interval (IBI) was created.

The frequency bands of the power spectrum used in this investigation are in accord with the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [54]. Parasympathetic bands were defined as frequencies between a bandwidth of 0.15 and 0.40 Hz.

Baroreflex sensitivity was analyzed via the alpha index. The alpha index is computed as the square root of the ratio of low-frequency heart rate variability (0.04–0.15 Hz) and corresponding frequency ranges for blood pressure variability. If the coherence of the spectra of R–R interval and the spectra of systolic blood pressure is sufficiently high (i.e., greater than a threshold usually set at 0.5) than the spectra of systolic blood pressure and R–R interval are integrated over the 0.1-Hz peak, reflecting the power of low frequency of R–R interval ($R–R_{LF}$) and the low frequency of systolic blood pressure (SBF_{LF}). The low-frequency modulation of systolic blood pressure was implemented, as opposed to heart rate variability, as it is thought to be more representative of sympathetic activation.

Statistical analysis

A one-way analysis of variance with a Bonferroni post-hoc analysis was implemented. Data are expressed as mean ± SD.

Results

A total of 48 subjects completed this investigation. The gender distribution of subjects was predominantly male (81%). The racial distribution was 75% white (36/48), 19% black (9/48), and 6% Hispanic (3/48). Physical characteristics are presented in Table 1.

Hemodynamics

Resting heart rate (bpm, Table 2) was significantly lower in HF vs. HU (64.3 ± 9.9 bpm vs. 79.1 ± 15.9 bpm, $P < 0.05$), HF vs. HPU (64.3 ± 9.9 bpm vs. 84.5 ± 12.3 bpm, $P < 0.001$), and HPF vs. HPU (66.4 ± 8.5 bpm vs. 84.5 ± 12.3 bpm, $P = 0.001$). No difference was found in heart rate in HF vs. HPF, suggesting HPF subjects who exercise regularly possess a resting heart rate similar to that found in HF subjects. Systolic blood pressure (mmHg) demonstrated no significant difference among the four groups. Respiratory rate was significantly lower in the fit groups vs. the unfit groups; however, the margin of significance does not appear to have clinical applicability.

Arterial compliance

Analysis of arterial compliance (mmHg × second) among groups revealed significant increases (Fig. 1B) in HF vs. HU and HPU (8.4 ± 3.2 mmHg × second vs. 5.5 ± 2.0 mmHg × second and

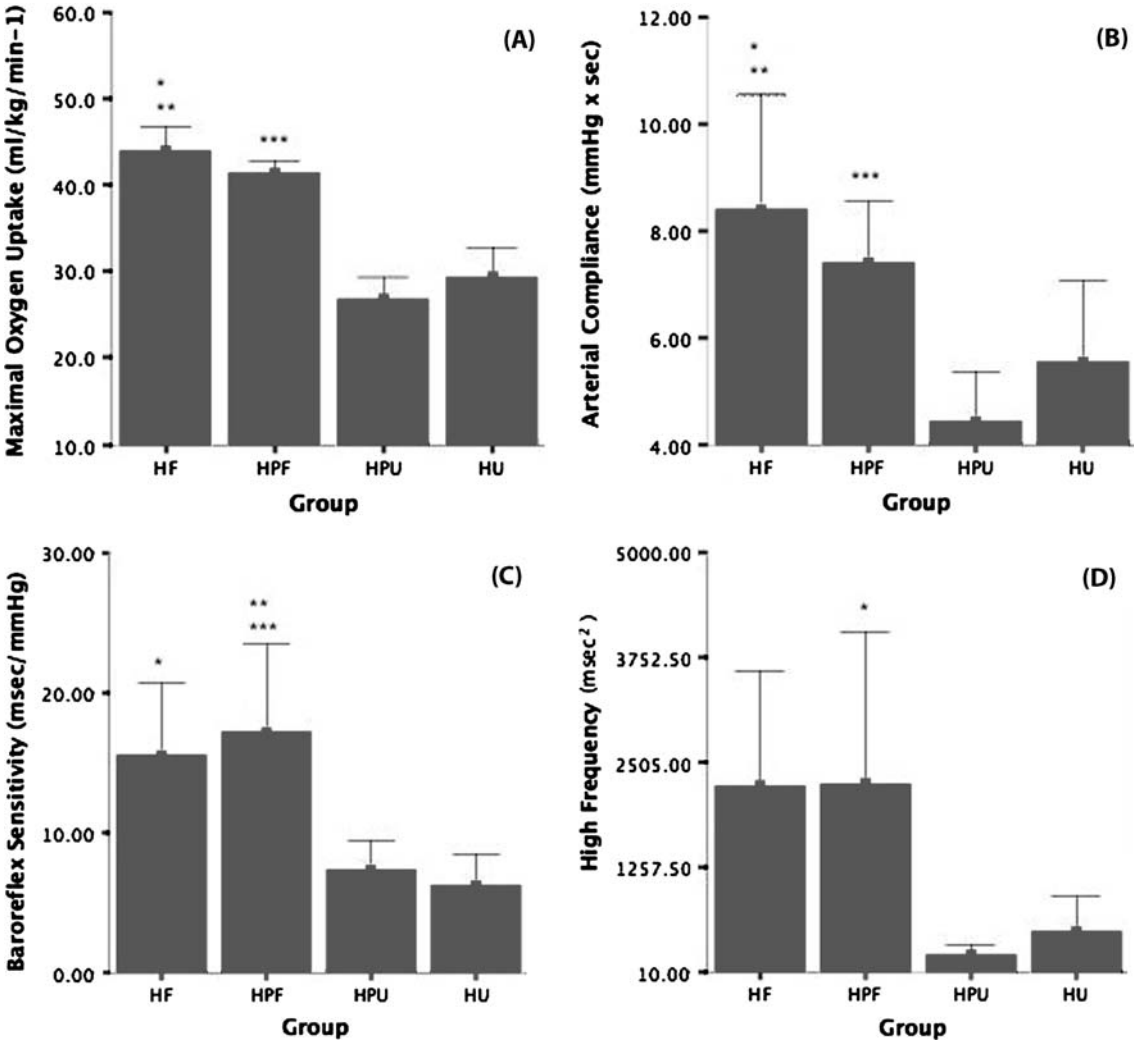

Fig. 1 (**A**) Maximal oxygen uptake (ml/kg/minute) for all groups (mean ± SD). Healthy Fit (HF), HIV Positive Fit (HPF), HIV Positive Unfit (HPU), and Healthy Unfit (HU). Maximal oxygen uptake was significantly higher in HF vs. HU and HPU, HPF vs. HPU and HU. *,**,***Indicate differences between groups ($P < 0.01$, $n = 48$). (**B**) Arterial compliance (mmHg × second) for all groups (mean ± SD). Healthy Fit (HF), HIV Positive Fit (HPF), HIV Positive Unfit (HPU), and Healthy Unfit (HU). Mean arterial compliance was significantly higher in HF vs. HU and HPU, HPF vs. HU and HPU. *,**,***Indicate differences between groups ($P < 0.05$, $P < 0.01$, $P < 0.10$, $n = 48$). (**C**) Baroreflex sensitivity (msecond/mmHg) for all groups (mean ± SD). Healthy Fit (HF), HIV Positive Fit (HPF), HIV Positive Unfit (HPU), and Healthy Unfit (HU). Mean baroreflex sensitivity is significantly higher in HF vs. HU and HPU, HPF vs. HU and HPU. *,**,***Indicate differences between groups ($P < 0.05$, $P = 0.04$, $P = 0.03$, $n = 48$). (**D**) High frequency (msecond^2) for all groups (mean ± SD). Healthy Fit (HF), HIV Positive Fit (HPF), HIV Positive Unfit (HPU), and Healthy Unfit (HU). Mean high frequency is significantly higher in HPF vs. HPU. *Indicates differences between groups ($P < 0.05$, $n = 48$)

4.4 ± 1.7 mmHg × second, respectively, $P < 0.05$ and $P < 0.001$). There were also significant findings in HPF vs. HPU and HU (7.4 ± 1.9 mmHg vs. 4.4 ± 1.7 mmHg × second and 5.5 ± 2.0 mmHg × second, respectively, $P < 0.010$ for both).

Aerobic capacity

Maximal oxygen consumption (ml/kg/minute) was increased significantly between groups (Fig. 1A). A statistical difference was found in HF vs. HU and HPU (43.9 ± 4.2 ml/kg/minute vs. 29.4 ± 4.3 ml/kg/minute and 26.9 ± 4.4 ml/kg/minute, respectively, $P < 0.001$ for both). Statistical differences were reported in the HPF vs. HU and HPU groups (41.4 ± 2.4 ml/kg/minute vs. 29.4 ± 4.3 ml/kg/minute and 26.9 ± 4.4 ml/kg/minute, respectively, $P < 0.001$ for both). Non-significant findings in HF vs. HPF confirm our finding that fit individuals with HIV can achieve aerobic capacities similar to that of fit individuals without disease.

Autonomic modulation

Baroreflex sensitivity (msecond/mmHg) was higher in the HF vs. HU and HPU groups (15.5 ± 7.7 msecond/mmHg vs. 6.2 ± 3.0 msecond/mmHg and 7.4 ± 3.8 msecond/mmHg, respectively, $P < 0.05$ for both). Results of baroreflex are depicted in

Fig. 1C. Baroreflex was highest in the HPF group and was significantly different from the HU and HPU groups (17.3 ± 10.2 msecond/mmHg vs. 6.2 ± 3.0 msecond/mmHg and 7.4 ± 3.8 msecond/mmHg, $P < 0.004$ and $P < 0.003$, respectively). Parasympathetic modulation (msecond^2) was significantly higher in HPF vs. HPU (2244.5 ± 2997.6 msecond^2 vs. 199.6 ± 232.7 msecond^2, $P < 0.05$) as shown in Fig. 1D. Low frequency of systolic blood pressure (mmHg^2) was significantly lower in the HPF and HPU vs. HU (4.7 ± 5.0 mmHg^2 and 5.2 ± 4.0 mmHg^2 vs. 12.9 ± 9.7 mmHg^2, respectively, $P < 0.05$ for both).

Discussion

The prevalence of CV disease in HIV patients is a major concern. Our data suggest that higher fitness levels in those with HIV disease may attenuate arterial stiffness. Prior studies on the effect of habitual physical activity on the age-associated decline in large artery compliance supports this notion [50]. One possible mechanism for enhanced arterial compliance seen in the trained HIV-positive subjects in response to physical activity is the preservation of compliant components of the artery. This is supported in studies of animals [56] as well as in humans [20]. Thomas et al. [56] reported that habitual physical activity is associated with increased elastin content and less cross-linking of collagen (<50%) in the left ventricle of rats. In addition, physical activity in humans is shown to preserve vascular endothelial tissue content and enhance nitric oxide bioavailability [20].

Augmentation of nitric oxide results in attenuated vascular smooth muscle tone, a strong determinant of arterial compliance. Further, suppression of vascular smooth muscle may be strongly influenced by α-adrenergic stimulation. The lower hemodynamic values in the fit HIV-positive group (Table 2) suggest attenuated α-adrenergic stimulation manifest as lower heart rates, possibly augmenting arterial compliance.

Other mechanisms include alterations in cardiac function. Greater stroke volume and preservation of elastic recoil may have caused increased arterial compliance in the fit HIV-positive subjects. Less impedance to blood flow and greater diastolic filling time reduce pulse pressure and pulse wave velocity. Thus, augmented arterial compliance reported in the fit vs. unfit HIV-positive subjects may exist because of reduced turbulence in the vessel and less endothelial damage. Although endothelial function was not examined in this study, endothelial response to physical activity in fit and unfit HIV-positive populations should be examined further.

Reduced baroreflex sensitivity is linked to cardiac disease, including impaired blood pressure regulation [52], myocardial ischemia, and sudden cardiac death [5, 10]. Little is known about the impact of HIV disease on baroreceptor sensitivity. Freeman et al. [24] examined autonomic function in HIV and noted a trend toward reduced systolic blood pressure in response to postural challenge. Brownley et al. [9] reported that HIV-infected men ($n = 83$) possessed an inability to sustain a blood pressure response during prolonged postural challenge and demonstrated a disruption of the normal relationship between stroke volume and baroreceptor vagal responsiveness compared to healthy male controls ($n = 55$).

Baroreflex sensitivity is enhanced in endurance-trained individuals [18, 19, 25, 38, 39]. Regular aerobic exercise positively modulates autonomic function and increases baroreflex sensitivity. Greater baroreceptor sensitivity is demonstrated in those with enhanced arterial compliance [3, 50]. Thus, increased compliance may lead to a greater ability of baroreceptors to fire signals in response to alterations in blood pressure.

The predominance of parasympathetic modulation, reflected in the high frequency of heart rate variability, is apparent in fit HIV-positive subjects. This view is echoed in other populations, such as endurance-trained male athletes [21, 27], physically active middle-aged and older men [19, 51], and physically active postmenopausal women [15]. Possible mechanisms may be a reduction in the intrinsic sinoatrial node rate, an elevation of parasympathetic drive, or a blunting of sympathetic drive.

Since vessel wall alterations influence arterial pressure, it may be hypothesized that greater arterial compliance leads to normal baroreflex functioning. A sensitive baroreflex results in appropriate responses to spontaneous changes in pressure and greater stimulation of parasympathetic nerve fibers. Thus, profound changes in autonomic modulation in the fit HIV-positive subjects in response to aerobic fitness are likely related to an augmented arterial compliance.

Findings of augmented arterial compliance and improved baroreflex sensitivity with a concomitant parasympathetic modulation in relation to improved aerobic fitness may portend cardioprotection in humans and animals [6, 39] due to a favorable shift in vasomotor tone and autonomic balance. Findings in this investigation emphasize that aerobic exercise may decrease the incidence of CV dysfunction prevalent in HIV disease.

A sedentary lifestyle is associated with reduced arterial distensibility and downregulation of baroreceptors. Reduced arterial compliance challenges the baroreceptors, which, over time, lose their sensitivity to pressure changes. Decreased sensitivity of the baroreflex causes a decrease in efferent vagal outflow to the heart, and a shift toward sympathetic activity. This reflexive decrease is highly correlated with CV disease, including myocardial infarction [4, 22, 32, 33], hypertension [8], congestive heart failure [41, 49], and sudden cardiac death [46].

Immunosuppression also contributes to a poor autonomic profile. HIV is known to reside in lymphoid tissue and attacks CD4+ cells as they migrate. Lymphoid tissue is innervated by the sympathetic nervous system and is, therefore, a direct path of communication for rapid autonomic modulation. Lymphocytes express β-adrenergic receptors, making them responsive to sympathetic transmissions (i.e., norepinephrine and epinephrine) able to immediately up or downregulate, depending upon the stimulus.

Lymphocytes also express receptors for cortisol and adrenocorticotrophic hormone (ACTH). Receptor binding may result in the inhibition of cell responsiveness altering DNA and RNA synthesis. These peripheral catecholamines and corticosteroids influence immune function by blunting or modifying T-lymphocyte and natural killer cell activity [14]. Thus, communication between the nervous system and the immune system is dynamic and bi-directional, having a substantial impact on the sympathetic nervous system.

The medications in this study temper the results. Although fit and unfit HIV-positive subjects were taking HAART, individual responses may vary. Although certain nucleoside analogue antiretroviral drugs in HAART (i.e., stavudine, didanosine) are associated with peripheral neuropathies, a multicenter trial [31] reported adverse effects may be caused by high doses typically administered in Phase 1 clinical trials, rather than in therapeutic doses similar to those prescribed for subjects in this study. In addition, HIV subjects who possess a CD4+ cell count less than 50 cells/mm^3 are more likely to present with drug-induced peripheral neuropathy. Our data provide no evidence that the low-normal response in autonomic function in the unfit HIV-positive subjects was associated with antiretroviral drug use. Potential selection bias exists for all subjects. However, control for age, body mass index, and fitness level; the use of open-circuit spirometry; and the overall non-invasive, non-pharmacologic nature of this investigation seem to be adequate to overcome any confounding issues.

This is the first clinical investigation to monitor changes in arterial compliance and autonomic modulation in relation to aerobic fitness level in an HIV-positive population. Enhanced arterial compliance as a consequence of improved aerobic capacity may be a key factor influencing the relationship between baroreflex sensitivity and parasympathetic activity in HIV disease.

Greater arterial compliance in fit HIV-positive subjects in response to activity may have important consequences for treatment modalities and CV risk prevention. An enhanced baroreflex in relation to aerobic fitness speaks to the importance of regular exercise in HIV. Altering the baroreflex to augment parasympathetic modulation may play a large role in preventing CV complications. Further, non-invasive and convenient methods, such as those used in this investigation, may allow physicians to further explore the pathophysiology of HIV patients.

Our findings should prompt others to look at cellular functioning and physical activity response in HIV-positive subjects. Normal endothelial cell function and vascular preservation in response to physical activity in those with HIV disease may lead to the development of medications and other treatments designed to enhance the beneficial effects of exercise therapy in this population. Although exercise is known to be beneficial, specific exercise guidelines for those with HIV disease are lacking. Thus, an investigation of a dose–response relationship of exercise training and HIV disease pathologies is needed.

The findings of parasympathetic modulation in response to improved aerobic fitness may shed light on the relationship between one's autonomic profile and their immune status. Natural killer cells are associated with the prevention of malignant cell development and progression, and relate to chronic viral syndromes (including AIDS) and certain autoimmune diseases [59]. However, natural killer cell number and function in HIV in response to physical activity still remains unknown. Future studies may examine natural killer cell subpopulations and their response to physical activity.

Conclusion

Exercise is associated with improvements in immune function [44, 53], and long-term survival [29] in HIV. However, the mechanistic effects of aerobic fitness on vascular and autonomic function in HIV are not known. Given the prevalence of autonomic dysfunction in an HIV-positive population may be associated with a risk for developing cardiac and vascular pathology, an assessment of arterial compliance and autonomic modulation should be performed and interpreted during comprehensive clinical evaluations of those with HIV disease. Although much still needs to be learned regarding the most effective and comprehensive treatment for HIV-positive patients, the implementation of aerobic training and specific exercise guidelines may go a long way toward promoting CV and autonomic health in those with HIV.

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References

1. Akselrod S, et al. (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science 213:220–222.
2. Avolio A, Chen S, Wang R, Zhang C, Li M, O'Rourke M, et al. (1983) Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 68:50–58.
3. Bigger J, Fleiss J, Steinman R, Rolintzky L, Kleiger R, Rottman JN, et al. (1992) Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 85:164–171.
4. Billman GE, Schwartz PJ, Stone HL (1982) Barroreceptor control of heart rate: a predictor of sudden cardiac death. Circulation 66:874–879.
5. Billman G, Schwartz P, Stone L, et al. (1984) The effects of daily exercise on susceptibility to sudden cardiac death. Ciculation 69:1182–1189.
6. Bloomfield P (1976) Fourier analysis of time series: an introduction. John Wiley Publishing, New York.
7. Bonaduce D, Petretta M, Betocchi S, Lanniciello A, Marciano F, Apicella C, et al. (1997) Heart rate variability in patients with hypertrophic cardiomyopathy: association with clinical and echocardiographic features. Am Heart J 134:165–172.
8. Brownley K, Milanovich J, Motivala S, Schneiderman N, Fillion L, Graves JA, et al. (2001) Autonomic and cardiovascular function in HIV spectrum disease: early indications of cardiac pathophysiology. Clin Auton Res 11:319–326.
9. Cerati D, Schwartz PJ (1991) Single cardiac vagal fiber activity, acute myocardial ischemia, and risk for sudden death. Circ Res 69:1389–1401.
10. Cheminot N, Gariepy J, Chironi G, et al. (2000) Diagnosis and determinants of sub-clinical arterial disease in HIV-1 infected patients on HAART. In: 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA.
11. Cohen J, Laudenslager M (1989) Autonomic nervous system involvement in patients with HIV infection. Neurology 39:1111–1112.
12. Cohn J, Finkelstein S, McVeigh G, Morgan D, Le May L, et al. (1995) Noninvasive pulse wave analysis for the early detection of vascular disease. Hypertension 26:503–508.
13. Cupps T, Fauci A (1982) Corticosteroid-mediated immmunoregulation in man. Immunol Rev 65:133–155.
14. Davey K, Miniciler N, Taylor A, et al. (1996) Elevated heart rate variability in physically active postmenopausal women: a cardioprotective effect? Am J Physiol 271:H455–H460.
15. De Castro S, et al. (1992) Heart involvement in AIDS: a prospective study during various stages of the disease. Eur Heart J 11:1452–1459.
16. DeMeersman R (1989) New noninvasive computerized method for the area measurement of the dicrotic notch. Comp Biol Med 9:189–195.
17. DeMeersman R (1992) Respiratory sinus arrhythmia alteration following training in endurance athletes. Eur J Appl Physiol 64:434–436.
18. DeMeersman R (1993) Heart rate variability and aerobic fitness. Am Heart J 125:726–731.
19. De Souza C, Shapiro L, Clevenger C, et al. (2000) Regular aerobic exercise prevents/restores the age related decline in endothelium-dependent vasodilation in healthy men. Circulation 102:1351–1357.
20. Dixon E, Kamath M, McCartney N, et al. (1992) Neural regulation of heart rate variability in endurance athletes and sedentary controls. Cardiovasc Res 26:713–719.
21. Farrell T, Paul V, Crippe T, Malik M, et al. (1991) Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. Circulation 83:945–952.
22. Freeman R (1997) Autonomic failure and AIDS. In: Low PA (ed) Clinical autonomic disorders, 2nd edn. Lippincott-Raven, Philadelphia, pp 727–735.
23. Freeman R, Roberts M, Friedman L, Broadbridge C, et al. (1990) Autonomic function and human immunodeficiency virus infection. Neurology 40(4):575–580.
24. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. (1997) ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 30(1):260–311.
25. Goldsmith RL, Bigger JT, Steinman RC, et al. (1992) Comparison of 24-hour parasympathetic activity in endurance-trained and untrained young men. J Am Coll Cardiol 20:552–558.
26. Goldsmith R, Bigger J, Bloomfield D, Steinmann R, et al. (1997) Physical fitness as a determinant of vagal modualtion. Med Sci Sports Exerc 29(6):812–817.
27. Hoffman C, Jaeger H (2001) Cardiology and AIDS: HAART and the consequences Ann NY Acad Sci 946:130–144.
28. Ironson G, Friedman A, Klimas N, et al. (1994) Distress, denial, and low adherence to behavioral interventions predict faster disease progression in gay men infected with human immunodeficiency virus. Int J Behav Med 1:90–105.
29. Johnson J, Anders G, Blanton H, et al. (1990) Exercise dysfunction in patients seropositive for the human immunodeficiency virus-1. Am Rev Respir Dis 141:618–622.
30. Kelleher T, Cross A, Dunkle L (1999) Relation of peripheral neuropathy to HIV treatment in four randomized clinical trials including didanosine. Clin Ther 21:1182–1192.
31. Kleiger RE, Miller JP, Bigger JT, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59:256–262.
32. La Rovere MT, Bigger JT, Marcus Fl, Mortara A, Schwartz PJ, et al. (1998) Baroreflex sensitivity and heart period variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 14:478–484.
33. Laperriere A, Klimas N, Fletcher MA, et al. (1997) Change in CD4+ cell enumeration following aerobic exercise in HIV disease: possible mechanisms and practical applications. Int J Sports Med 18:S56–S61.
34. Lenormand-Welckenaer C, Cazaubon M, Joly V, et al. (2000) Carotid intima media thickness in protease inhibitors-treated HIV-1 infected patients with hyperlipidemia. In: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario.
35. Liang Y, Teede H, Kotsopoulos D, et al. (1998) Non-invasive measurements of arterial structure and function: repeatability, interrelationships, and trial sample size. Clin Sci 95:669–679.
36. Milei J, Grana D, Alonso GF, Matturi L, et al. (1998) Cardiac involvement in the acquired immune deficiency syndrome—a review to push action. Committee for the Study of Cardiac Involvement in AIDS. Clin Cardiol 21:465–472.
37. Monahan KD, Dinenno FA, Tanaka H, et al. (2000) Regular aerobic exercise modulates age-associated declines in cardiovagal baroreflex sensitivity in healthy men. J Physiol 529(pt1):263–271.

38. Monahan KD, Tanaka H, Dinenno FA, Seals DR (2001) Central arterial compliance is associated with age- and habitual exercise-related differences in cardiovagal barroreflex sensitivity. Circulation 104:1627–1632.
39. Morris JN, Everett MG, Pollard R, Chave SPW, AMS (1980) Vigorous exercise in leisure time: protection against coronary heart disease. Lancet 2:1207–1210.
40. Nichols WW, O'Rourke MF (1998) McDonald's blood flow in arteries, 4th edn. Arnold, London.
41. Nolan J, Flapan AD, Capewell S, MacDonald TM, Neilson JM, Ewing DJ, et al. (1992) Decreased cardiac sympathetic activity in chronic heart failure. Br Heart J 67:482–485.
42. Paffenbarger RS Jr, Blair SN, Lee IM, Hyde RT (1993) Measurement of physical activity to assess health effects in free-living populations. Med Sci Sports Exerc 25:60–70.
43. Paton P, Tabib A, Loire R, Tete R (1993) Coronary artery lesions and human immunodeficiency virus infection. Res Virol 144(3):225–231.
44. Perna FM, Laperriere NG, Klimas N, et al. (1999) Cardiopulmonary and CD4 changes in response to exercise training in early symptomatic HIV infection. Med Sci Sports Exerc 31:973–979.
45. Pothoff G, Wasserman K, Ostmann H (1994) Impairment of exercise capacity in various groups of HIV-infected patients. Respiration 61:80–85.
46. Raab W, Silva PP, Machet H, Kimura E, YK S (1960) Cardiac adrenergic preponderence due to lack of physical exercise and its pathogenic complications Am J Cardiol 5:300–320.
47. Rogstad KE, Shah R, Tesfaladet G, Abdullah M, Ahmed-Jushuf I, et al. (1999) Cardiovascular autonomic neuropathy in HIV infected patients. Sex Transm Infect 75(4):264–267.
48. Sakhuja A, Goyal A, Jaryal AK, Wig N, Vajpayee M, Kumar A, et al. (2007) Heart rate variability and autonomic function tests in HIV positive individuals in India. Clin Auton Res 17:193–196.
49. Saul JP, Yutaka A, Berger RD, Lilly LS, Colucci WS, Cohen RJ, et al. (1988) Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. Am J Cardiol 61:1292–1299.
50. Seals DR (2003) Habitual exercise and the age-associated decline in larger artery compliance. Med Sci Sports Exerc 31(2):68–72.
51. Seals DR, Chase PB (1989) Influence on physical training on heart rate variability and barroreceptor circulatory control. J Appl Physiol 66:1886–1895.
52. Shi X, Walter DW, Formes KJ, et al. (2000) Orthostatic hypotension in aging humans. Am J Physiol 279:H1548–H1554.
53. Stringer WW, Berezovskaya M, O'brien WA, Beck CK, Casburi R, et al. (1998) The effect of exercise training on aerobic fitness, immune idices, and quality of life in HIV+ patients. Med Sci Sports Exerc 30:11–16.
54. TaskForce of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use Circulation 93(5):1043–1065.
55. The different stages of HIV infection. Avert 2002 June 26.
56. Thomas D, Zimmerman S, Hansen T, et al. (2000) Collagen gene expression in rat left ventricle: interactive effect of age and exercise training. J Appl Physiol 89:1462–1468.
57. Villa A, Foresti V, Confalonieri F (1987) Autonomic neuropathy and HIV infection. Lancet 1:915.
58. Watt TB, Burrus C (1976) Arterial pressure contour analysis for estimating human vascular properties. J Appl Physiol 40:171–176.
59. Whiteside TL, Herberman RB (1989) Short analytical review. The role of natural killer cells in human diseases. Clin Immunol Immunopathol 53:1–23.