Decreased Peak Arteriovenous Oxygen Difference During Treadmill Exercise Testing in Individuals Infected With the Human Immunodeficiency Virus

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Objective: To determine if arteriovenous oxygen difference was lower in asymptomatic individuals with human immunodeficiency virus (HIV) infection than in sedentary but otherwise healthy controls.

Design: Quasi-experimental cross-sectional.

Setting: Clinical exercise laboratory.

Participants: Fifteen subjects (10 men, 5 women) with HIV and 15 healthy gender- and activity level–matched controls (total N=30).

Intervention: Participants performed an incremental maximal exercise treadmill test to exhaustion. Electrocardiogram, metabolic, and noninvasive cardiac output measurements were evaluated at rest and throughout the tests. Data were analyzed by using analysis of covariance.

Main Outcome Measures: Peak oxygen consumption (VO2), cardiac output, stroke volume, and arteriovenous oxygen difference. The arteriovenous oxygen difference was determined indirectly using the Fick equation.

Results: Peak VO2 was significantly lower (P<.0005) in participants with HIV (24.6±1.2mL·kg–1·min–1) compared with controls (32.0±1.2mL·kg–1·min–1). There were no significant intergroup differences in cardiac output or stroke volume at peak exercise. Peak arteriovenous oxygen difference was significantly lower (P<.04) in those infected with HIV (10.8±0.5 volume %) than in controls (12.4±0.5 volume %).

Conclusion: The observed deficit in aerobic capacity in the participants with HIV appeared to be the result of a peripheral tissue oxygen extraction or utilization limitation. In addition to deconditioning, potential mechanisms for this significant attenuation may include HIV infection and inflammation, highly active antiretroviral therapy medication regimens, or a combination of these factors.

Key Words: Exercise; HIV; Oxygen consumption; Rehabilitation.

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DECREASED AEROBIC CAPACITY has been observed in individuals infected with the human immunodeficiency virus (HIV).1-5 Operationally defined as a measured peak oxygen consumption (VO2) of 73% or less of an individual’s predicted maximum oxygen consumption (VO2max),6,7 functional aerobic impairment has been reported in late adolescents who were in the asymptomatic stages of HIV infection with undetectable to low viral loads.8 Cade et al9 reported that aerobic capacity was reduced in a group of physically inactive adolescents with HIV as well as in a group of age-matched sedentary controls. Although these findings suggest that deconditioning was responsible, at least in part, for the decreased aerobic capacity observed in both groups, functional aerobic impairment was observed only in the group with HIV. Functional aerobic impairment has previously been documented only in groups of individuals who have pathologic conditions known to disrupt oxidative metabolism10-12: it has not been reported in groups of healthy but physically inactive controls. Diminutions of peak VO2 to levels that were 15% to 38% lower than those observed in controls have routinely been reported in groups of adults infected with HIV.1,3,9,10 The degree to which aerobic capacity was diminished in most of these reports appears to have been more severe than diminutions that would have been expected to occur as a result of physiologic deconditioning alone.

Pathologic limitation of oxidative metabolic function generally results from attenuation of central circulatory oxygen delivery, disruption of peripheral muscle tissue oxygen extraction and utilization, or a combination of these factors. Both cardiac dysfunction20-26 and peripheral muscle tissue abnormalities27-43 have been reported in individuals infected with HIV. However, although cardiac dysfunction has often been observed in those with symptomatic HIV infection and acquired immune deficiency syndrome (AIDS),21-26 it has seldom been reported in individuals who have asymptomatic HIV infection or in association with diminished aerobic capacity.20 Skeletal muscle tissue abnormalities that could precipitate an attenuation of tissue oxygen extraction and/or utilization have been observed throughout the course of HIV infection.27-40 After assimilating the available information, the present investigators hypothesized that, in individuals who are in the asymptomatic stages of HIV infection, attenuation of aerobic capacity occurs as a result of attenuated oxygen extraction and utilization by the tissues, rather than impaired central circulatory oxygen delivery. Arteriovenous oxygen difference has been generally accepted as a gross indicator of tissue oxygen extraction and utilization and closely reflects oxidative function of muscle tissue, particularly when measured during strenuous exercise. If oxidative dysfunction of muscle tissue limits aerobic capacity, diminished peak arteriovenous oxygen difference would be expected to occur in conjunction with low peak oxygen consumption. And these diminutions may occur with or without a reduction in peak cardiac output. The aim of the present study was to determine if the arteriovenous oxygen difference and cardiac output responses to maximum exercise treadmill testing...
Physiologic exertion of attaining at least 90% of the predicted therapy (table 3). HIV-infected participants were taking at least 1 nucleoside equal to the mean values of the respective groups, and SD 1 and mean CD4 cell count was 429.8/11006.

Participants

Fifteen adults with HIV infection and 15 gender- and activity level-matched, healthy controls (total N = 30) were tested (table 1). Power analysis was performed to determine the number of subjects. Based on the results of preliminary work performed in adolescents and adults infected with HIV and controls, we used oxygen consumption as the power criterion variable, because this dependent variable required the largest number of subjects to determine an intergroup difference at α equal to .05 and β equal to .20. The following equation was used to determine the sample size:

\[ N = (\alpha + \beta)^2 (SD_1^2 + SD_2^2)/ (X_2 - X_1)^2, \]

where α was equal to 1.96, β was equal to .84, X_1 and X_2 are equal to the mean values of the respective groups, and SD_1 and SD_2 were the standard deviations of the 2 groups. None of the participants had participated in an exercise program during the past 6 months or routinely engaged in employment or other activity that would cause perspiration on the average of once weekly, discounting the effects of ambience. None of the participants had any known neurologic, orthopedic, pulmonary, hematologic, or cardiorespiratory limitations or were taking any medications that would contraindicate treadmill testing or alter the cardiorespiratory response to exercise. All HIV-infected participants were asymptomatic and never had a CD4 cell count of less than 200 or an opportunistic infection (Centers of Disease Control and Prevention stages A1 or A2). The mean CD4 cell count was 429.8±218.2 cells/mm³ (table 2). All HIV-infected participants were taking at least 1 nucleoside analog and a nonnucleoside analog or a protease inhibitor for a period of at least 6 months and reported good adherence with therapy (table 3).

Participants not reaching 1 of 2 accepted criteria for maximal physiologic exertion of attaining at least 90% of the predicted maximal heart rate (220–age) or a respiratory exchange ratio (RER; RER = volume of expired carbon dioxide \([\text{VCO}_2]/\text{VO}_2\)) of at least 1.10, were excluded from the study. Four of the HIV-infected participants (27%) were cigarette smokers and no smokers were included in the control group. Before participation, the study’s procedure was explained to all participants, and written consent was obtained from each subject, as required by the university’s institutional review board.

Apparatus

All peak exercise tests were conducted on a motor-driven treadmill that interfaced with a microprocessor to control speed and elevation. Measures of cardiorespiratory function were obtained by means of a metabolic cart (CPX/D Breeze). Inspired and expired oxygen concentrations were measured by a zirconium cell oxygen analyzer, and inspired and expired concentrations of carbon dioxide were measured by an infrared cell carbon dioxide analyzer. The metabolic cart was calibrated with gas mixtures of 21% oxygen and 0% carbon dioxide, and 12% oxygen and 5% carbon dioxide, both in nitrogen balances. Inspired and expired pulmonary volumes were determined from flow volume loops obtained from a flow-rate sensitive pneumotachometer interfaced with a microprocessor. The pneumotachometer was calibrated by injecting room air at various flow rates, using a 3-L calibrated syringe. The rebreathing apparatus was comprised of a 98-mL Hans Rudolph slide valve mounted on a headset. The slide valve was attached to a mouthpiece and a 5-L anesthetic bag for the purpose of rebreathing expired air. The rebreathing bag was filled with a volume of gas equal to 1.5 to 2.0 times the participant’s tidal volume (VT) as described by Jones et al. The content of the rebreathing gas was 4.0% carbon dioxide, 35% oxygen, and 61% nitrogen. A 3-way stopcock was connected to the rebreathing bag and to a calibrated 3-L syringe with a graduated volumetric slides. The syringe was also connected to a tank containing the rebreathing gas mixture for the purpose of injecting a controlled volume of gas into the rebreathing bag. When the slide valve was moved to the open position, the participant breathed room air and V\(\text{CO}_2\), V\(\text{CO}_2\), and partial pressure of end-tidal carbon dioxide (PET\(\text{CO}_2\)) were measured by open circuit spirometry. When the slide valve was moved to a closed position, the participant began rebreathing from the bag containing the gas mixture and closed circuit spirometric measurement of partial pressure of carbon dioxide (PCO\(_2\)) was obtained. During the rebreathing procedure, participants were asked to breathe at a rate of 40 breaths per minute in accordance with a metronome, to obtain an optimal number of data collection points for generating exponential plots of expired carbon dioxide. The mixed venous PCO\(_2\) was estimated from the asymptote of the exponential rise in the PET\(\text{CO}_2\) obtained during the rebreathing procedure. This calculation of

<table>
<thead>
<tr>
<th>Group</th>
<th>HIV</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41.9±1.7*</td>
<td>36.1±1.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.6±1.9</td>
<td>178.0±2.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6±4.5</td>
<td>83.5±4.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9±1.2</td>
<td>24.7±0.9</td>
</tr>
<tr>
<td>Men (n)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Women (n)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± standard error (SE) or n. Abbreviation: BMI, body mass index. *Significantly different (P<.02).

Table 1: Descriptive Characteristics of the Group With HIV and the Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>HIV</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6±4.5</td>
<td>83.5±4.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9±1.2</td>
<td>24.7±0.9</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>429.8±56.4</td>
<td></td>
</tr>
<tr>
<td>Leukocyte (×10⁹/μL)</td>
<td>5.4±0.5</td>
<td></td>
</tr>
<tr>
<td>Viral load (copies/cm³)</td>
<td>6012.8±5817.4</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40.0±0.8</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>13.7±0.3</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± SE.

Table 2: Serologic Characteristics of the Group With HIV

<table>
<thead>
<tr>
<th>Medication Regimen for the Group With HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavudine</td>
</tr>
<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Lamivudine</td>
</tr>
<tr>
<td>Zidovudine</td>
</tr>
<tr>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>Duration of HAART (mo)</td>
</tr>
<tr>
<td>Duration of HIV (mo)</td>
</tr>
</tbody>
</table>

NOTE. Values are n or mean ± SE. Abbreviation: HAART, highly active antiretroviral therapy.
PVC0₂ was made by using a noninvasive cardiac output measurement software program (Cardio2) in which an iterative technique was applied to log (PVC0₂ − PETC0₂) to minimize the variance of the value of PVC0₂ around the least squares regression line as described by Heigenhauser and Faulkner.⁴⁶ Arterial carbon dioxide (PAC0₂) was calculated from the PETC0₂ by using the equation by Jones et al.⁴⁸

\[
\text{PAC0}_2 = 5.5 + 90 \cdot \text{PETC0}_2 - 0.221 \cdot V_t
\]

The following equations were used to calculate the venous arterial content difference in carbon dioxide (Cv-aco2) from the partial pressures of PAC0₂ and the PVCO₂ based on the standard carbon dioxide dissociation curve by using log CVCO₂ = (logPVCO₂ × 3.96) + 2.38:

\[
\log \text{Caco}_2 = (\log \text{PCO}_2 × 3.96) + 2.38
\]

Cardiac output (Qt) was then determined⁴⁹ by using Cv-aco2 with the VOC0₂ in the formula:

\[
\text{Pulmonary circulation (Q1) = Qt = VCO}_2/Cv-aco2
\]

Preliminary unpublished work, based on intraclass correlation and conducted in this laboratory, indicated that exponential rise methods identical to those of the present study yield measurements that range from acceptable (R range, .60–.79) to high (R ≥ .80) reliability. Heart rate was determined electrocardiographically. Cardiac stroke volume was determined as the ratio of cardiac output and heart rate. The Aerobic Impairment Index (AII) was determined by the equation:

\[
\text{AII} = \frac{\text{expected VO}_2 - \text{measured VO}_2}{\text{expected VO}_2} \times 100
\]

Ventilatory quotients for peak VO₂ (Ve/VO₂) were compared to determine grossly if ventilatory economy differed between the groups at peak exercise.

**Procedure**

Participants who smoked (n = 4) were asked to refrain from smoking for at least 5 hours before the exercise test to minimize the effects of smoking-induced carboxyhemoglobinemia. All participants performed a maximum treadmill exercise test, which was terminated when the participants reached volitional exhaustion. Participants were prepared for testing as follows. After lightly abrading and cleaning the skin with alcohol, Ag/AgCl electrodes were applied in accordance with the Mason-Likar 12-lead electrocardiogram configuration.⁵⁰ The participants next donned the head set apparatus containing the slide valve, mouthpiece, and the rebreathing bag. A nose clip was applied to ensure that the expired air did not escape through the nostrils. Participants then performed a practice session of breathing at the rate of 40 breaths per minute, while breathing in time to a metronome, until adequate performance was attained. Baseline measurements (VO₂, VCO₂, PETC0₂) were taken with the slide valve in the open position during standing rest. The rebreathing bag was then filled with the 4% carbon dioxide and 35% oxygen balanced with nitrogen gas mixture, suitable for closed circuit spirometric measurement of mixed venous PCO₂, by the exponential rise method, at rest and during exercise.⁵¹–⁵⁵ The slide valve was then closed, and the participant rebreathed from the bag containing the gas mixture in accordance with the metronome. The total period of rebreathing was not more than 6 seconds to prevent overestimation of PCO₂ because of recirculation.⁵⁴,⁵⁵ After 6 seconds, the slide valve was opened and the participant again breathed room air. After this baseline procedure, the participant began walking on the treadmill at an initial speed of 1.7mph and 0% inclination. The power output of the treadmill was increased every 3 minutes in accordance with the modified Bruce protocol⁴⁸ until the participants indicated that they could no longer continue. The modified Bruce protocol differs from the regular Bruce protocol in that it had 2 extra stages, each 3-minutes long, added before the first regular stage of the Bruce protocol began. During the first stage of the modified Bruce protocol, subjects walked on the treadmill at a speed of 1.7mph and 0% inclination, and during the second stage the grade was increased to 5% and speed remained the same. Stage 3 of the modified Bruce protocol was identical to stage 1 of the Bruce protocol. The rebreathing procedure was performed at rest, at the beginning of the third minute of every stage, and at peak exercise.

**Statistics**

Analyses of variance (ANOVA) were used to determine if age, height, weight, and body mass index differed significantly between the group with HIV infection and controls. HIV-infected participants were significantly (P < .02) older than controls (see table 1). Calculation of Pearson product-moment correlation coefficients revealed that age was significantly related to peak VO₂ (r = −.41, P < .02) and peak heart rate (r = −.52, P < .003), with variance in age accounting for 16.8% of the variance in peak VO₂ and 27% of the variance in peak heart rate. Because advancing age is known to impose limitations on cardiorespiratory function and aerobic capacity, and because age differed significantly (P < .02) between the groups, it was determined that the relationship between age and the dependent variables was a plausible confounder to the interpretation of the data. In subsequent analyses of covariance (ANCOVAs), the covariate age was determined to have a significant influence on variance associated with most of the measured dependent variables.

Because plateauing of oxygen consumption between the last 2 work stages of an exercise test is an indicator of the attainment of maximal physiologic exertion, separate ANOVAs for both the control group and the group with HIV were used to determine if VO₂ significantly differed during the last 2 work stages. The global cardiorespiratory response patterns during the treadmill tests were next analyzed while controlling the analyses for intergroup variance in age by using 2-way mixed-model ANCOVAs with age as the single covariate. The independent-variable classes were stage (random effect because of nesting of repeated measures within the groups) and group (fixed effect). Dependent variables were oxygen consumption, heart rate, cardiac output, stroke volume, and arteriovenous oxygen difference. Post hoc analyses of the age-adjusted means for the dependent variables were made by using the least square means analyses. Intergroup differences in the dependent variables peak oxygen consumption, peak heart rate, peak cardiac output, peak stroke volume, and peak arteriovenous oxygen difference were determined by 1-way ANCOVA with age as the covariate. Differences in adjusted independent group means were examined post hoc by least squares means analyses. Potential intergroup differences in age-adjusted peak RER and Ve/VO₂ were also assessed by ANCOVA. Pearson product-moment correlation coefficients were calculated to identify expected relationships among the variables.

Significant relationships and differences in the age-adjusted means and the means associated with the secondary analyses were identified when the probability of making a type I error was equal to or less than 5% (P ≤ .05). Throughout the tables and text, data were reported as mean ± 1 standard error (SE).

**RESULTS**

Three HIV-infected participants and 1 control (n = 4) were excluded from the study because they did not meet 1 of the
criteria for maximal physiologic exertion. All remaining participants reached at least stage 5 of the modified Bruce protocol (stage 2 of the standard Bruce protocol), and several in each group attained higher work stages; all stopped exercise voluntarily despite strong encouragement to continue by the investigational staff. Participants met at least 1 of 2 physiologic criteria for identifying maximal exertion on a treadmill exercise test. The 2 criteria were reaching or exceeding 90% of the subject’s predicted peak heart rate and attaining an RER of at least 1.10. On average, HIV-infected participants reached 93% of their predicted peak heart rate (220 beats per minute − age in years), whereas controls reached 99.5% of their age-predicted peak heart rate. Mean peak RER was 1.21 ± 0.02 in the HIV-infected participants and 1.29 ± 0.02 in the controls. Peak V̇O₂ did not differ between the final 2 work stages either in the HIV group or in the controls. Collectively, these data indicated that both the HIV-infected and non–HIV-infected participants reached maximal levels of oxygen consumption and that lack of motivation or other nonphysiologic reasons for stopping exercise did not exert a noticeable influence on measurements of peak aerobic capacity.

The overall direction of cardiorespiratory responses was similar to that generally expected for treadmill exercise testing in both the HIV-infected group and controls (figs 1 and 2). With both groups combined, V̇O₂ during all exercise stages correlated with cardiac output (r=0.90, P<.0001), stroke volume (r=0.53, P<.0001), arteriovenous oxygen difference (r=0.82, P<.0001), and heart rate (r=0.75, P<.0001). When the HIV-infected and noninfected groups were independently examined, the results were similar: V̇O₂ during all exercise stages correlated with cardiac output (r=0.91, P<.0001), stroke volume (r=0.68, P<.0001), arteriovenous oxygen difference (r=0.72, P<.0001), and heart rate (r=0.72, P<.0001), in the HIV-infected group and with cardiac output (r=0.92, P<.0001), stroke volume (r=0.42, P<.0001), arteriovenous oxygen difference (r=0.88, P<.0001), and heart rate (r=0.78, P<.0001) in the noninfected group. Viral load, CD4 count, white blood cell count, the duration (months) of HIV infection and antiretroviral therapy, hematocrit, and hemoglobin levels (see table 3) were not significantly related to peak V̇O₂, heart rate, cardiac output, stroke volume, or arteriovenous oxygen difference. V̇O₂ increased with workload throughout the tests in both groups (P<.05) (figs 1 and 2), but age-adjusted peak V̇O₂ was significantly diminished (P<.0005) in the group with HIV compared with controls (table 4). Functional aerobic impairment was observed in the HIV-infected participants (AII=30.1% ± 12.0%) but not in controls (AII=13.1% ± 12.2%). Cardiac output and heart rate rose throughout the test in both groups (P<.05), whereas stroke volume plateaued after the initial work stages. Significant differences in age-adjusted peak cardiac output and stroke volume were not observed between the group with HIV and controls. Although it exceeded 90% of the age-predicted maximum heart rate, age-adjusted peak heart rate was significantly (P<.02) lower in the group with HIV than in the controls. The arteriovenous oxygen difference widened during the submaximal exercise stages in both groups (P<.05) (fig 3), but the age-adjusted peak arteriovenous oxygen difference was significantly lower (P<.04) in the HIV-infected participants.
than in the controls. The unaffected peak stroke volume combined with the decreased peak heart rate and peak arteriovenous oxygen difference indicated that the diminished aerobic capacity observed in those with HIV was the result of attenuation of peripheral muscle oxygen extraction and utilization. This attenuation further resulted in decreased physical work capacity in the HIV-infected participants compared with controls (table 5).

**DISCUSSION**

Decreased aerobic capacity has been previously reported in both adolescents and adults infected with HIV. Results of the current study were in agreement with these previous reports. Keyser et al previously identified functional aerobic impairment in a group of late adolescents with HIV. The present study has expanded this knowledge to include adults in the asymptomatic stage of HIV infection. Because functional aerobic impairment was observed in the subjects with HIV but not in controls, the degree to which aerobic capacity was diminished in those with HIV may have been because of mechanisms that were in addition to those associated with physiologic deconditioning. The ventilatory quotient for oxygen consumption was similar in the HIV-infected participants, indicating that smoking-mediated carboxyhemoglobinemia or other abnormalities of blood oxygenation did not limit peak aerobic capacity in the HIV-infected participants in the present study. Central circulatory function did not appear to differ for those with HIV and controls, whereas muscle tissue oxygen extraction and utilization was determined to be lower in those with HIV.

Peak arteriovenous oxygen difference has been reported to range from 14% to 15% in sedentary young (age range, 20–30 y) men and from 12% to 14% in sedentary older (age range, 60–70 y) men. Arteriovenous oxygen difference has been reported to range from 12% to 14% in sedentary young women and from 11% to 13% in sedentary older women. In the present study, arteriovenous oxygen difference for the control group was similar to these previously reported ranges and was lower in participants with HIV infection than in controls. Mechanisms for this attenuation of arteriovenous oxygen dif-

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**Table 4: Peak Cardiorespiratory Variables Adjusted for Age Differences**

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 peak (mL·kg⁻¹·min⁻¹)</td>
<td>24.6±1.2*</td>
<td>32.0±1.2</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>17.8±1.3</td>
<td>19.7±1.3</td>
</tr>
<tr>
<td>Stroke volume (mL/beat)</td>
<td>107.0±7.2</td>
<td>107.5±7.2</td>
</tr>
<tr>
<td>a-VO2 (vol%)</td>
<td>10.8±0.5†</td>
<td>12.4±0.5</td>
</tr>
<tr>
<td>RER</td>
<td>1.2±0.02‡</td>
<td>1.3±0.02</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>167.8±3.5†</td>
<td>180.1±3.5</td>
</tr>
<tr>
<td>VE peak (L/min)</td>
<td>77.7±6.9†</td>
<td>103.2±6.9</td>
</tr>
</tbody>
</table>

**NOTE.** Values are mean ± SE adjusted for age (ANCOVA).

* P<.001.
† P<.05.
‡ P<.005.
ference could not be determined by the methods of the present study. In general, muscle abnormalities associated with HIV infection have included necrosis, rod bodies, inflammation, vacuolitis, microvesiculation, and loss of thick filaments.37 Muscle mitochondrial abnormalities including abnormal size, shape, cristae structure, and the presence of intramitochondrial paracrystalline inclusions have been reported.38 Evidence of direct HIV infection and HIV-mediated inflammation in muscle has also been presented,37,39,58-61 including macrophages containing HIV antigens and cytokine expression (specifically interleukin-1 and tumor necrosis factor-α) that were found in muscle tissue of individuals infected with HIV.37,38,59 Clinical evidence of HIV-mediated myopathy has also been reported.39,60,61 HIV-infected monocytic invasion of vascular basement membrane62,63 and other endothelial dysfunction64 may have resulted in tissue oxygenation limitations that contribute to the attenuation of arteriovenous oxygen difference in persons infected with HIV. Besides the direct effects of HIV infection, it is also plausible that the highly active antiretroviral therapy (HAART) medication regimen used by the subjects in the present study (see Table 3) may have disrupted oxidative metabolic function, possibly resulting in functional aerobic impairment.

The HAART regimen regularly consists of at least 1 nucleoside analog, a nonnucleoside reverse transcriptase inhibitor, and/or a protease inhibitor. In particular, nucleoside analog medication may have resulted in mitochondrial toxicity. Zidovudine, the oldest and most widely studied nucleoside analog medication, has been reported to attenuate expression of cytochrome-c oxidase34,38,40,43,60 and has resulted in other mitochondrial alterations, including damaged and decreased mitochondrial deoxyribonucleic acid (DNA) and ribonucleic acid35,41,64-66 and pathologic changes in the mitochondrial structure. When muscle metabolism was measured in vivo by P31 magnetic resonance spectroscopy, there was a greater decrease in phosphocreatine during muscular exercise in individuals treated with zidovudine than in those not treated, indicating oxidative pathway dysfunction of the muscle. Treatment with zidovudine has been reported to decrease the rate of muscle adenosine triphosphate production, possibly because of an inhibitory effect on mitochondrial DNA synthesis.33,69 All HIV-infected participants in the present study were taking a nucleoside analog. The decreased arteriovenous oxygen difference and aerobic capacity in the HIV-infected participants could have been, at least in part, mediated by HAART, specifically nucleoside analog toxicity.

In the present study, all subjects reached or exceeded an RER of 1.15 and/or at least 90% of their predicted heart rate, indicating that a maximum volitional effort was obtained.45 Participants with HIV infection were able to reach only 93% of their predicted maximum heart rate, whereas controls were able to reach 99.5% of their predicted maximum heart rate. To determine if this difference indicated that the participants stopped exercising because of nonmetabolic factors such as an earlier or more intense perception of fatigue or, possibly malingering, we examined the difference in oxygen consumption during the peak or final exercise stage and the stage before it. Failure to observe significant differences between the oxygen consumption at peak exercise and the preceding work stage indicated that a plateau in oxygen consumption had occurred in both groups and that volitional exhaustion occurred in conjunction with maximal exertion.45 By identifying these 3 factors—the oxygen consumption plateau, group attainment of a peak RER that well exceeded 1.15, and group attainment of a peak heart rate that exceeded 90% of the age-predicted maximum heart rate—we learned that neither malingering nor differences in perception of fatigue were likely reasons for the intergroup differences in attained percentage of predicted maximum heart rate.

Autonomic dysfunction, including both sympathetic and parasympathetic systems, has been reported in individuals infected with HIV.70-79 and its prevalence has been reported to range from 5% to 77%.77 However, abnormal autonomic function appears to be more frequent in those with AIDS than in those with HIV infection but without AIDS.72 Autonomic function tests were not performed in the current study. Although we found no reports of peak heart rate abnormalities in the literature, wide variation exists among the results of studies examining peak heart rate in individuals with HIV. Findings include peak heart rates ranging from well below to above 90% of the age-predicted maximum heart rate.5,35 Our present results were similar to those of Johnson et al3 and Perna et al1 in

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**Table 5: Exercise Test Variables Adjusted for Age Differences**

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT (mL·kg⁻¹·min⁻¹)</td>
<td>13.1±0.7</td>
<td>14.7±0.7</td>
</tr>
<tr>
<td>Test duration (min)</td>
<td>16.4±0.9*</td>
<td>19.3±0.8</td>
</tr>
<tr>
<td>Power output (W)</td>
<td>207.1±22.0*</td>
<td>278.4±22.0</td>
</tr>
</tbody>
</table>

**NOTE.** Values are means ± SE adjusted for age (ANCOVA).

*P<.001.
that the group with asymptomatic HIV attained a peak heart rate that exceeded 90% of their predicted heart rate. Cardiac output and stroke volume varied from rest throughout exercise in trends that were similar among participants with asymptomatic HIV infection and controls, whereas the arteriovenous oxygen difference response appeared to be blunted in the group with HIV. The rapid increase in heart rate with increasing exercise intensity indicated 2 things: (1) peak heart rate was not attenuated by autonomic dysfunction in those with HIV and (2) local muscle fatigue most likely resulted in exercise cessation before the HIV-infected participants could attain peak heart rates that were closer to their age-predicted values.

Fatigue in adults infected with HIV has been associated with patient self-reports of physical and functional limitations in activities of daily living such as housework, climbing stairs, and walking, as well as activities required for employment, thus leading to disability in this population.80-82 Future studies are warranted. Moreover, studies to determine whether regular aerobic exercise training can attenuate or reverse decreases in peak oxygen extraction and utilization may also be valuable. Such studies could help in developing complementary therapies to use in conjunction with current regimens for the aggressive treatment of HIV infection.

**CONCLUSION**

Peak aerobic capacity was diminished in HIV-infected participants compared with controls. Aerobic capacity in HIV-infected participants was decreased to levels associated with functional aerobic impairment and therefore may have been as a result of pathologic processes. The current findings of similarity in age-adjusted peak cardiac output and stroke volume among those with HIV and controls and the observation of diminished arteriovenous oxygen difference supported the hypothesis that aerobic capacity in asymptomatic HIV-infected participants was limited by muscle tissue oxygen extraction and utilization abnormalities rather than by central circulatory oxygen delivery deficits. Potential mechanisms for the observed attenuation of oxygen extraction and utilization may have included HIV infection and inflammation, HAART medication regimens, or a combination of these factors. Further studies aiming to determine specific mechanisms for attenuated arteriovenous oxygen difference and aerobic capacity are warranted.

**References**


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