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Association between muscle strength and the cardiopulmonary status of individuals living with HIV/AIDS

Vagner Raso,[I,II,III] Roy J. Shephard,[IV] Jorge Casseb,[V,VI] Alberto José da Silva Duarte,[V,VI] Paulo Roberto Santos Silva,[VII] Júlia Maria D'Andréa Greve[I,VII]

[I] Faculdade de Medicina da Universidade de São Paulo - (FMUSP), Department of Experimental Pathophysiology, São Paulo/SP, Brazil. [II] Bandeirante University of São Paulo (UNIBAN), Master Program on Body Balance Rehabilitation and Social Inclusion, São Paulo/SP, Brazil. [III] University of Western São Paulo, (UNOESTE), Medicine and Physical Education School, São Paulo/SP, Brazil. [IV] University of Toronto, Faculty of Kinesiology & Physical Education, Toronto, ON/Canada. [V] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - (ADEE 3002-HC-FMUSP), Secondary Immunodeficiency Ambulatory, São Paulo/SP, Brazil. [VI] Faculdade de Medicina da Universidade de São Paulo - (LIM-56-HC-FMUSP), Laboratory of Investigation in Dermatology and Immunodeficiencies, São Paulo/SP, Brazil. [VII] Faculdade de Medicina da Universidade de São Paulo - (LEM-IOT-HC-FMUSP) Movement Studies Laboratory, Orthopedics and Traumatology Institute, São Paulo/SP, Brazil.

OBJECTIVE: The purpose of this study was to compare aerobic function [anaerobic threshold (%$\dot{V}O_2$-AT), respiratory compensation point (%$\dot{V}O_2$-RCP) and peak oxygen uptake ($\dot{V}O_{2peak}$)] between physically active patients with HIV/AIDS and matched controls and to examine associations between disease status, poor muscle strength, depression (as estimated by the profile of mood states questionnaire) and the aerobic performance of patients.

METHODS: Progressive treadmill test data for %$\dot{V}O_2$-AT (V-slope method), RCP and ($\dot{V}O_{2peak}$) were compared between 39 male patients with HIV/AIDS (age 40.6±1.4 years) and 28 male controls (age 44.4±2.1 years) drawn from the same community and matched for habitual physical activity. Within-patient data were also examined in relation to $CD4^+$ counts (nadir and current data) and peak isokinetic knee torque.

RESULTS: AT, RCP and ($\dot{V}O_{2peak}$) values were generally similar for patients and controls. Within the patient sample, binary classification suggested that AT, RCP and ($\dot{V}O_{2peak}$) values were not associated with either the nadir or current $CD4^+$ count, but treadmill test variables were positively associated with peak isokinetic knee torque.

CONCLUSION: The aerobic performance of physically active patients with HIV/AIDS is generally well conserved. Nevertheless, poor muscle strength is observed in some HIV/AIDS patients, which is associated with lower anaerobic power and ($\dot{V}O_{2peak}$), suggesting the possibility of enhancing the aerobic performance of patients with weak muscles through appropriate muscle-strengthening activities.

KEYWORDS: Anaerobic Threshold; Cardiopulmonary Exercise Testing; HIV; Peak Aerobic Power; Muscle Strength.

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E-mail: vraso@usp.br

Tel.: 55 11 2661-6041

INTRODUCTION

The acute phase of HIV/AIDS is frequently marked by a substantial loss of physical fitness. In planning an appropriate course of rehabilitation, it is important to know which aspects of fitness deteriorate and the persistence of this functional loss following treatment. Most studies have pointed to a loss of muscular strength, with little deterioration of cardio-respiratory fitness (1-2). Nevertheless, some reports have also indicated adverse effects of the disease and treatment with non-nucleoside reverse transcriptase inhibitors on various aspects of cardio-respiratory health. Reported changes include delayed heart rate recovery following exercise (3), increased cardiovascular risk factors (particularly the HDL/LDL cholesterol ratio, secondary to decreased plasma adiponectin levels) (4-5), deteriorating endothelial function (6), atherosclerosis progression (7) and increased risk of myocardial infarction (8).

Aerobic exercise has been recommended for patients with HIV/AIDS, both as a possible means of slowing disease progression [with benefits observed by Mustafa et al. (9),

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but not by Stringer et al. (10) or Terry et al. (11)] and also for exercise's potential to reverse the depressed mood that commonly accompanies both HIV/AIDS infection and highly active antiretroviral therapy (HAART) treatment [with elevations of mood state reported by Ciccolo et al. (12), Neidig et al. (13) and Stringer et al. (10), but not by Terry et al. (11)].

In most reports to date, any changes in an individual's muscular strength have been considered independently of peak aerobic power. However, this interpretation is not entirely appropriate. The peak oxygen intake that a patient can attain partially depends upon the muscle mass that is activated by the test exercise (14). Furthermore, if the muscles are weak, perfusion of the active tissues is restricted, and lactate begins to accumulate at a low power output, causing local fatigue and limiting the peak effort that can be developed (15,16).

To shed further light upon these issues, we took a substantial sample of physically active male patients with HIV/AIDS and compared their aerobic performance with matched control subjects from the same milieu. We also compared values for subsets of the patient sample classified in terms of immune status, exposure to retroviral treatment and current peak isokinetic muscle torque. Our primary hypotheses were that aerobic function would generally be well maintained in physically active patients with HIV/AIDS but that even within a sample engaged in regular endurance activity, aerobic performance might nevertheless be impaired in individual patients with substantial muscle weakness.

METHODS

Volunteers

The patient sample consisted of 39 physically active males living with HIV/AIDS. All were volunteers who were recruited from an ambulatory outpatient clinic. The 28 matched controls were drawn from the same city. All subjects were informed about the procedures and risks before giving written consent to participate in the study, which had been approved by the research ethics committee of the São Paulo University Hospital (File reference 768/06). The protocol met all of the ethical standards established for this journal (17).

An initial telephone call was used to invite 56 volunteers with HIV/AIDS for a screening that focused on their current health status, current drug and cigarette consumption and physical activity. This was followed by a hospital visit for a detailed history and physical examination covering previous and current health status and other tests that included a 12-lead electrocardiogram, questionnaires regarding mood state and ability to perform the basic and instrumental activities of daily living, measures of body composition and routine blood and urine tests. Criteria for exclusion included the following: (1) acute or chronic psychological disturbances; (2) central or peripheral nervous system disorders; (3) musculo-skeletal problems; (4) cardiopulmonary or metabolic disorders; (5) cigarette smoking; (6) surgery or bed rest in the previous three months; and (7) any orthopedic conditions that could limit exercise testing or be exacerbated by exercise testing. Thirty-nine of the 56 volunteers met the criteria for the definitive study. Infection had been acquired through homosexual or heterosexual intercourse in 32 of the 39 patients; in the remainder of the patients, the source of infection was intravenous drug use or blood transfusion. The mean duration of diagnosed infection was 6.1 ± 0.8 years, with 20 of the 39 patients developing AIDS within 6.0 ± 0.9 years. HAART had been administered to 18 of the 39 patients for an average of 56.1 ± 7.5 months, with an adherence of 9.2 ± 0.3 on a 0 to 10 scale.

The control group met the same health criteria as the patients, with the exception that the former were HIV-negative. The two groups were also matched in terms of their age, physical activity level and body mass index.

Body composition and habitual physical activity

Height and body mass were determined by standard anthropometric techniques. Adiposity was determined using Harpenden skinfold calipers (Baty International, Burgess Hill, West Sussex, UK); central adiposity was represented by the sum of subscapular, mid-axillary, abdominal and suprailiac skinfolds, and peripheral adiposity was represented by the sum of the biceps, triceps, anterior thigh and mid-calf skinfolds.

A Portuguese version of the international physical activity questionnaire (IPAQ) was used to estimate habitual physical activity (18,19). Subjects reported the frequency and duration of walking (considered light activity) and bouts of moderate and vigorous physical activity. The information was combined to yield an approximate physical activity score, measured in kJ of energy expended per week. For each of the light [3.3 METs], moderate [4.0 METs] and vigorous [8.0 METs] activities, the duration (minutes per day) was multiplied by the reported frequency (days per week) to yield accumulated totals of MET-min $week^{-1}$.

Cardiopulmonary parameters

Peak oxygen uptake ($\dot{V}O_{2peak}$) was measured directly using a progressive treadmill protocol (20,21). An automated gas analyzer (CPX/D, Medgraphics, Saint Paul, MN), calibrated against room air and a medically certified gas mixture of 11.9% O_2 and 5.12% CO_2, provided breath-by-breath data on respiratory gas exchange. A 12-lead electrocardiogram was monitored continuously during testing. Exercise began at a walking velocity of 3.6 km h^{-1} and with a 1% gradient. The velocity was increased by 1.2 km h^{-1} in each succeeding minute until volitional exhaustion. $\dot{V}O_{2peak}$ was recorded when one or more of the following criteria were satisfied: 1) respiratory exchange ratio (RER) $\geq$1.10; 2) attainment of the age-predicted maximal heart rate; 3) volitional fatigue; and/or 4) signs of exhaustion (unsteady gait, hyperpnea, sweating, facial flushing and grimacing) (2). The test-retest error of peak oxygen intake determinations was <5%. A computerized regression analysis determined the anaerobic threshold (AT) from a plot of CO_2 intake ($\dot{V}CO_2$) versus O_2 intake ($\dot{V}O_2$) and the onset of excess CO_2 output (V-slope method). The respiratory compensation point (RCP) was detected by plotting respiratory minute ventilation against $\dot{V}CO_2$.

Peak muscle torque

Peak muscle torque was evaluated using an isokinetic dynamometer (Biodex Multi-Joint System, Shirley, NY). This apparatus was calibrated weekly, according to the manufacturer's instructions. After one familiarization test, volunteers performed five definitive maximal extensor movements at an angular velocity of $60^{\circ} \cdot s^{-1}$, with verbal encouragement throughout; a two-minute rest interval was

Table 1 - Characteristics of controls and patients (classified by $CD4^+$ nadir).

	Control (n = 28)	Individuals living with HIV/AIDS		
		$CD4^+$ nadir (cells·mm^{-3})		
		< 200 (n = 17)	≥ 200 (n = 22)	Total (n = 39)
Age (years)	44.4 ± 2.1	41.9 ± 1.9	39.6 ± 2.0	40.6 ± 1.4
Body height (m)	1.74 ± 0.1	1.69 ± 0.2	1.73 ± 0.1	1.71 ± 0.1
Body composition				
Body mass (kg)	80.1 ± 1.2[1]	71.6 ± 2.9	74.0 ± 2.5	72.9 ± 1.9
BMI (kg·m^{-2})	26.4 ± 0.4	24.8 ± 0.8	24.8 ± 0.9	24.8 ± 0.6
CBA (mm)	—	52.2 ± 5.0	71.4 ± 8.0	63.0 ± 5.2
PBA (mm)	—	24.9 ± 2.4	30.8 ± 3.9	28.2 ± 2.4
TBA (mm)	—	77.1 ± 6.9	102.3 ± 11.3	91.2 ± 7.2
HA (MET.min.week^{-1})	1797 ± 56	1589 ± 229	1726 ± 188	1666 ± 144
Immunological parameters				
$CD4^+$ (cells·mm^{-3})		433 ± 67	588 ± 90[2]	521 ± 59
$CD8^+$ (cells·mm^{-3})		1083 ± 111	1086 ± 167	1084 ± 105
$CD4^+$ nadir (cells·mm^{-3})		154 ± 36	344 ± 48[2]	261 ± 34
Viral load (log)		4.1 ± 0.3	4.5 ± 0.2	4.4 ± 0.2

Values are means ± standard errors of mean; BMI: body mass index; CBA: central body adiposity; PBA: peripheral body adiposity; TBA: total body adiposity; HA: habitual activity;
[1]Statistically significant difference between control and HIV/AIDs group with $CD4^+$<200 cells·mm^{-3} (p<0.05); [2]Statistically significant difference between HIV^+ $CD4^+$<200 cells·mm^{-3} and HIV^+ $CD4^+$≥200 cells·mm^{-3} (p<0.05).

allowed between sets. The largest of the five readings was noted as the individual's peak torque [Nm].

Blood collection, leukocyte counts and flow cytometry

Subjects refrained from ingesting solid or liquid food containing caffeine or chocolate or cola-based products and avoided even moderate physical activity for 48 hours before blood sampling. The subjects arrived at the laboratory at 7:00 a.m., having fasted overnight, and blood was collected from the median antecubital vein after 30 min of seated rest. Differential leukocyte counts were performed using an automated Cell-Dyn 3500 analysis system (Coulter Corp., Miami, FL).

For the flow cytometry, 200 mL of whole blood was incubated with 5 mL of appropriate monoclonal antibodies ($CD4^+$, $CD8^+$ [Becton-Dickinson, Miami, FL]) for 20 minutes in the dark and at room temperature. Samples with isotypic control antibodies (IgG1[FITC]/IgG1[PE]/IgG1[PCy-5]) were run in parallel with each sample. A minimum of 5000 cells was analyzed on the Coulter XL-MCL counter (Coulter Corp., Miami, FL) using XL System II software (Coulter Corporation, Miami, FL). The lowest recorded $CD4^+$ count was considered the $CD4^+$ nadir.

Statistical analysis

All analyses were performed using the Predictive Analytics Software 17.0 for Windows Package (PASW,

Table 2 - Findings during progressive treadmill (TM) test for controls and patients (classified by $CD4^+$ nadir). Shaded areas indicate statistically significant differences.

		Individuals living with HIV/AIDS		
		$CD4^+$ nadir (cells·mm^{-3})		
	Control(a) (n = 28)	< 200(b) (n = 17)	≥200(c) (n = 22)	Total (n = 39)
HR (bpm)	—			
AT	119 ± 3	120 ± 3	122 ± 3	121 ± 2
RCP	140 ± 3	141 ± 4	147 ± 3	144 ± 2
PHR	179 ± 3	178 ± 4	179 ± 2	178 ± 2
RPE	—			
AT	8.5 ± 0.2	8.8 ± ± 0.2	9.2 ± 0.3	9.0 ± 0.2
RCP	11.9 ± 0.3	11.8 ± 0.4	12.2 ± 0.3	12.0 ± 0.3
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})	—			
AT	16.4 ± 0.5	17.4 ± 0.5	17.5 ± 0.6	17.5 ± 0.4
RCP	22.6 ± 0.7	24.3 ± 1.0	23.2 ± 0.9	23.7 ± 0.7
Peak	32.2 ± 0.9	34.6 ± 1.4	33.9 ± 1.2	34.2 ± 0.9
$\dot{V}O_2$ (% peak)	—			
AT	51.3 ± 1.6	50.3 ± 1.5	52.3 ± 2.0	51.4 ± 1.3
RCP	70.5 ± 1.8	70.8 ± 2.0	68.6 ± 2.3	69.6 ± 1.6
TM test duration (min)	6.7 ± 0.2	9.5 ± 0.5	9.6 ± 0.6	9.6 ± 0.4
Peak isokinetic torque (Nm·kg^{-1})	—	242 ± 11	253 ± 11	248 ± 8

p<0.05; Values are means ± standard errors of mean; AT: anaerobic threshold; RCP: respiratory compensation point; $\dot{V}O_2$: oxygen intake; HR: heart rate; PHR: peak heart rate; RPE: rating of perceived exertion; Statistically significant difference between control and HIV^+ subgroups.

Table 3 - Findings during progressive treadmill (TM) test and strength measurements for patients (classified by current $CD4^+$ count, cells·mm^{-3}). Shaded area indicates statistically significant differences.

	Individuals living with HIV/AIDS	
	Current $CD4^+$<200 cells mm^{-3} (n = 6)	Current $CD4^+$≥200 cells mm^{-3} (n = 33)
HR (bpm)		
AT	115±2 (107-120)	122±3 (94-156)
RCP	134±5 (122-157)	146±3 (116-178)
PHR	172±8 (136-191)	179±2 (161-203)
RPE		
AT	8.8±0.3 (8.0-10.0)	9.0±0.2 (7.0-12.0)
RCP	11.5±0.9 (9.0-15.0)	12.1±0.3 (9.0-15.0)
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})		
AT	16.5±1.3 (11.4-20.1)	17.6±0.4 (13.4-22.5)
RCP	21.6±1.8 (15.4-28.7)	24.0±0.7 (16.4-31.7)
Peak	32.5±3.3 (20.1-41.7)	34.4±0.9 (25.2-43.4)
$\dot{V}O_2$ (% peak)		
AT	51.7±3.0 (41.0-59.0)	51.5±1.4 (40.9-79.0)
RCP	67.8±4.0 (53.0-77.0)	70.1±1.7 (52.0-92.0)
TM test duration (min)	8.3±0.9 (4.0-10.0)	9.8±0.4 (6.0-20.0)
Peak isokinetic torque (Nm·kg^{-1})	205±13 (151-241)	257±8 (150-349)*

*$p<0.05$; Values are means ± standard errors of mean; AT: anaerobic threshold; RCP: respiratory compensation point; $\dot{V}O_2$: oxygen intake; HR: heart rate; PHR: peak heart rate; RPE: rate of perceived exertion.

Inc., Chicago, IL). Kolmogorov-Smirnov statistics demonstrated that all data were normally distributed. Data are presented as the means ± standard errors of the mean. Unpaired Student t-tests were used to compare patients and control groups and also to compare patient subgroups. Univariate regression analyses also investigated associations of peak isokinetic torque with anaerobic threshold, respiratory compensation point and $\dot{V}O_2$ peak. Statistical significance was set at $p<0.05$ throughout.

We determined that a 10% loss of aerobic performance would have practical and clinical significance. Thus, the sample size of 39 patients and 28 controls provided adequate sample power to detect such an effect at the 95% confidence level. This remained true with binary subdivision of the 39-patient sample.

RESULTS

General characteristics and immunological data for the patients and control subjects are summarized in Table 1. The patients tended to have a slightly lower body mass than the controls, particularly in the subgroup with a lower $CD4^+$ nadir, but the patients did not differ significantly from the controls in terms of age or body mass index. In terms of

Table 4 - Findings during progressive treadmill (TM) test and strength measurements for patients (classified by peak muscle torque at 60°·sec^{-1}). Shaded areas indicate statistically significant differences.

	Peak isokinetic torque (Nm·kg^{-1})	
	<230 (n = 15)	≥230 (n = 24)
TM Velocity (km·h^{-1})		
AT	5.4±0.2 (3.6-7.2)	6.0±0.2 (4.8-7.2)*
RCP	7.3±0.2 (6.0-8.4)	8.3±0.2 (6.0-10.8)*
PEAK	11.3±0.6 (7.2-15.6)	13.4±0.4 (9.6-18.0)*
HR (bpm)		
AT	122±4 (94-145)	120±3 (94-156)
RCP	142±3 (125-159)	145±3 (116-178)
PHR	174±3 (136-195)	180±3 (161-203)
RPE		
AT	9.1±0.3 (7.0-12.0)	9.0±0.2 (7.0-12.0)
RCP	11.9±0.5 (9.0-15.0)	12.0±0.3 (9.0-15.0)
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1})		
AT	15.9±0.7 (11.4-20.0)	18.3±0.4 (15.1-22.5)*
RCP	20.6±0.7 (15.4-23.8)	25.4±0.7 (18.4-31.7)*
Peak	29.8±1.2 (20.1-40.0)	36.6±0.9 (27.7-43.4)*
$\dot{V}O_2$ (% peak)		
AT	54.2±2.7 (41.0-79.0)	49.9±1.2 (40.9-67.0)
RCP	70.0±2.9 (53.0-92.0)	69.6±1.8 (52.0-87.0)
TM test duration (min)	9.0±0.5 (4.0-13.0)	9.9±0.6 (6.2-20.0)
HA (MET.min.$week^{-1}$)	1667±222 (714-3999)	1665±193 (747-3839)
Peak isokinetic torque (Nm·kg^{-1})	203±7 (150-229)	277±7 (231-349)*

*$p<0.05$; values are means ± standard errors of mean; AT: anaerobic threshold; RCP: respiratory compensation point; $\dot{V}O_2$: oxygen intake; HR: heart rate; PHR: peak heart rate; RPE: rating of perceived exertion; HA: habitual activity.

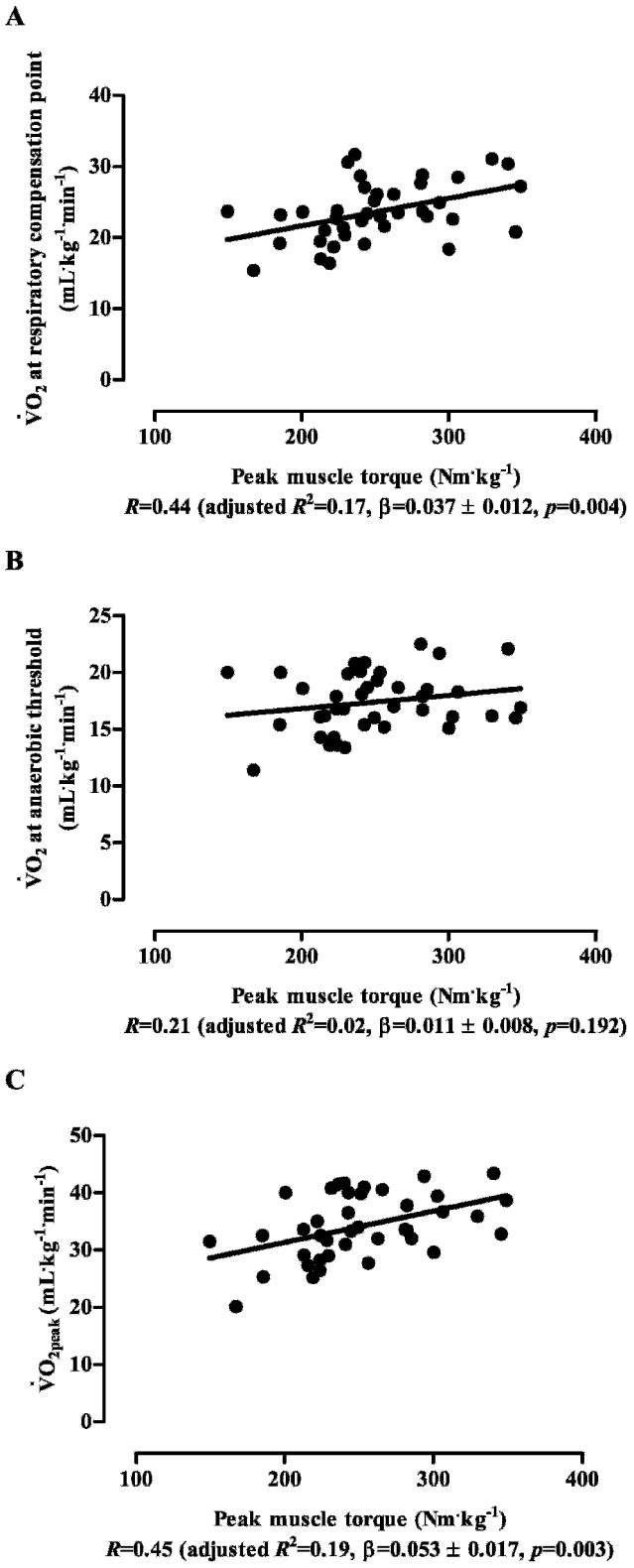

Figure 1 - Relationship between peak muscle torque (Nm·kg^{-1}) and $\dot{V}O_2$ at (A) the anaerobic threshold, (B) the respiratory compensation point and (C) the peak oxygen intake (mL·kg·$^{-1}$min^{-1}).

reported activity, both groups were quite active, undertaking the equivalent of 60 minutes or more of moderate activity (4 METS) per day. The average peak isokinetic extensor torque of the patients (248 ± 8 Nm) was similar to previously reported values for healthy subjects in this age group (21-27).

Findings during the progressive treadmill test are summarized in Table 2. Patients and control subjects reached similar peak heart rates, which were relatively high for their age, but the peak oxygen intake values were not outstanding in either group. There was no evidence that the AT, RCP or ($\dot{V}O_{2peak}$) was any lower in the patients than in the control subjects, irrespective of the patients' $CD4^+$ nadir. A similar analysis in terms of whether the patients had received HAART revealed no differences in this subgroup (data not shown).

Classification of patients based on their current $CD4^+$ counts (Table 3) again revealed no statistically significant differences, with the exception of peak isokinetic torque, which was approximately 20% less in those individuals with a count <200 cells.mm^{-3}.

However, when patients were classified in terms of their peak isokinetic torque (Table 4), the AT, RCP and peak aerobic power were all significantly greater in those individuals with well-preserved muscular strength; stronger subjects were able to progress to a significantly greater treadmill velocity. Linear regression analysis revealed parallel trends among individual subjects (Figure 1); AT and RCP exhibited statistically positive associations with peak isokinetic torque.

DISCUSSION

Our data confirm our initial hypothesis: on average, the ($\dot{V}O_{2peak}$) of physically active individuals with HIV/AIDS does not differ from that of control subjects of similar age and with similar physical activity patterns. This is in agreement with previous reports, which have also suggested that after treatment, the cardio-respiratory fitness of physically active individuals with HIV/AIDS generally shows little deterioration (1-2). Nevertheless, our findings also underline that within this apparent normality of aerobic function, individual patients who have substantial muscle strength deficiency also exhibit substantial deficiency of aerobic performance, averaging around 20%, relative to equally active but stronger peers.

Because our analysis was cross-sectional, it might be argued that the individuals who developed a low peak isokinetic torque had engaged in less habitual activity during their leisure time or were simply less motivated during exercise testing. The first of these explanations can be largely discounted because the reported activity levels of the two subgroups were equal. The small and statistically non-significant trend to a lower peak heart rate (Table 4) and some association between a poor aerobic performance and high depression scores, as measured by the profile of mood states questionnaire (data not shown), may signal somewhat poorer motivation in those who were depressed. Nevertheless, it seems of importance that lower muscle strength was also linked to a lower current $CD4^+$ count (Table 2). Moreover, although differences in motivation might have influenced the peak oxygen intake, it is not as easy to explain the lower ATs of the weaker individuals (Table 4) simply in terms of differences in individual motivation. A direct effect of local muscle strength upon perfusion of the limbs and, thus, peak oxygen transport offers a more plausible explanation (14). Therefore, we

conclude that an HIV/AIDS-induced reduction in muscle mass and the resultant loss of muscle strength appears to impair both anaerobic effort (by causing lactate to accumulate at a lower fraction of maximal oxygen intake) (15) and ($\dot{V}O_{2peak}$) (because of both earlier fatigue and the lower volume of muscle that is available for activation during treadmill testing) (14).

There are a number of limitations to our data. Unfortunately, we were unable to obtain strength data for the control subjects, but the average values observed in the patients were not much lower than those reported in previous normal studies (22-27). It could also be objected that with greater opportunity to practice procedures, higher test scores might have been obtained on both the treadmill and the dynamometer tests; however, this in no way invalidates the differences we have observed between patients with high and low muscular strength values. It should also be emphasized that our patient sample was male, and the sample was deliberately selected in terms of a number of criteria for good health; the sample represented approximately one-sixth of patients attending the HIV/AIDS clinic. It would be interesting to extend our observations by assessing the effects of muscle weakening upon aerobic function in an unselected group of HIV/AIDS patients, including women and men.

The practical clinical implications of our findings point to the following: to ensure good aerobic power in patients with HIV/AIDS, rehabilitation should include a program of progressive muscle strengthening exercises, and such rehabilitation should be continued until the strength of the major muscle groups has been normalized. This proposal now needs to be tested with a group of HIV/AIDS patients with aerobic impairment secondary to poor muscle strength by evaluating how far the patients' aerobic power can indeed be enhanced by a program that normalizes muscular function.

AUTHOR CONTRIBUTIONS

Casseb J, Duarte AJ, DGreve JM and Raso V had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. DGreve JM, Raso V and Shephard RJ were responsible for the study concept and design and provided critical revision of the manuscript for important intellectual content. DGreve JM, Raso V and Silva PRS were responsible for data acquisition. Raso V was responsible for data analysis and interpretation and performed the statistical analysis. DGreve JM and Raso V drafted the manuscript. Duarte AJS was responsible for administrative, technical or material support and study supervision.

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