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CENTRAL ACTIVATION, MUSCLE PERFORMANCE, AND PHYSICAL FUNCTION IN MEN INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

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Abstract

Loss of muscle mass and limitations in activity have been reported in persons infected with human immunodeficiency virus (HIV), even those who are otherwise asymptomatic. The extent to which factors other than muscle atrophy impair muscle performance has not been addressed in depth. The purpose of this study was to determine the extent of neuromuscular activation of the knee extensors and ankle dorsiflexors of 27 men infected with HIV receiving antiretroviral therapy and its relationship to muscle performance. The central activation ratio (CAR) was determined using superimposed electrical stimulation during maximum voluntary contractions. In addition to force and power measurements, muscle cross-sectional area and composition was evaluated using computed tomography. Aerobic capacity was determined from treadmill exercise testing. Eleven of the subjects had an impaired ability to activate the knee extensors ($CAR = 0.72 \pm 0.12$) that was associated with weakness and decreased specific force. The reduced central activation was not associated with muscle area, body composition, aerobic capacity, CD4 count, or medication regimen. Those individuals with low central activation had higher HIV-1 viral loads and were more likely to have a history of AIDS-defining illness. These results suggest the possibility of a different mechanism contributing to muscle impairment in the current treatment era that is associated with impairment of central motor function rather than atrophy. Further investigation is warranted in a larger, more diverse population before more definitive claims are made.

Keywords

central activation; electrical stimulation; HIV infection; muscle cross-sectional area

Loss of skeletal muscle mass has a significant impact on functional performance, independent function, and associated quality of life in persons infected with the human immunodeficiency virus (HIV).^{1,36} Since highly active antiretroviral therapy (HAART) became the standard of care for HIV infection in 1995, the incidence of wasting (involuntary weight loss >10% ideal body weight) has declined, although it is still common.^{29,49} In the era of HAART, recent work indicates that HIV-associated weight loss is primarily due to fat

atrophy, which accounts for approximately two-thirds of the weight loss, while loss of lean body mass accounts for the other third.^{18-29,49} Given the wide-ranging physiological consequences of HIV infection and HAART, mechanisms beyond reduction in muscle mass likely contribute to impaired muscle function.^{3,13} Such additional factors may account for the limitations in vigorous activity that have been reported even in asymptomatic persons infected with HIV.¹¹ It is reductions in the ability to generate force and power that lead to decreases in physical performance and loss of function, rather than loss of muscle per se.^{26,32} Identifying the factors beyond the reduction of muscle mass that contribute to impaired muscle function is required for optimizing the design of rehabilitation strategies to improve muscle strength and functional capacity in this chronically ill patient population.

One factor that can reduce muscle force production in the absence of muscle atrophy is an impairment of central activation (i.e., the ability to activate the available muscle mass). Central activation failure has been shown to contribute significantly to muscle weakness in other clinical populations, e.g., in persons with osteoarthritis, cerebral palsy, or previous knee arthroplasty,¹⁴⁻³¹⁻³⁹ and to negatively influence the relationship between muscle strength and physical function.¹⁴ The role of central activation in muscle performance in persons with HIV has not been evaluated, but such an impairment would be expected to lead to decreased specific force (muscle force per unit cross-sectional area) and potentially limit physical function in persons with HIV, even in the absence of muscle atrophy. Persons with HIV receiving HAART have reduced aerobic capacity, likely due to impaired oxygen extraction/utilization by the working muscle,⁷⁻⁸⁻³⁴⁻³⁵⁻⁴⁵ and when oxidative metabolism is compromised, as with circulatory occlusion, central activation is impaired.³⁷ There is also the possibility that the central nervous system (CNS) effects of HIV may lead to central activation impairments.⁴⁷⁻⁴⁸ Given these observations, it is possible that persons with HIV are particularly likely to exhibit losses of central activation.

In the present study we evaluated middle-aged men infected with HIV who were on HAART. We measured the cross-sectional area, muscle composition, strength, and neuromuscular activation of two muscle groups (knee extensors and ankle dorsiflexors), as physiological changes in muscle associated with systemic processes such as disease or aging can be muscle-specific.²¹ In addition, we measured the subjects' aerobic function and functional status. We hypothesized that specific force in these subjects would be associated with muscle composition, as well as the level of central activation. We further hypothesized that reductions in central activation would be related to aerobic capacity.

MATERIALS AND METHODS

Subjects

We recruited 30 community-dwelling patients infected with HIV from the Baltimore VA Medical Center HIV Clinic. All subjects underwent a comprehensive history and physical examination, including blood sampling and electrocardiogram. Subjects had been prescribed HAART for ≥ 6 months prior to the start of the study. Additional exclusion criteria included any acquired immunodeficiency syndrome (AIDS)-defining illness within the previous 6 months, anabolic steroid use or growth hormone replacement, and major comorbidities that would preclude functional testing. Specifically, patients with the following conditions were excluded: myocardial infarction, unstable angina, uncontrolled hypertension (systolic pressure >180 or diastolic pressure >105 mmHg), poorly controlled diabetes mellitus (fasting blood sugar >200 mg/dl, glycosylated hemoglobin level $>10\%$), peripheral vascular disease leading to claudication, endstage liver disease (cirrhosis or decompensated liver disease), renal dialysis, severe anemia (hematocrit $<25\%$), severe pulmonary disease-related disability, other neurological impairments, or use of home oxygen. The study was approved

by the Institutional Review Board of the University of Maryland. All subjects provided written informed consent.

History of AIDS-defining illnesses and HAART therapy were obtained by self-report and confirmed by review of the patient's electronic medical record in the VA Computer Patient Record System. Blood sampling, including a complete blood count and chemistry panel, was performed on the day of enrollment. Immunological/virological measures included CD4 cell count (cells/mm³) and HIV viral load (RNA copies/ml) (Amplicor; Roche Applied Science, Indianapolis, Indiana), a polymerase chain reaction (PCR) assay for the quantification of HIV type 1 (HIV-1).

Functional Status

For the 6-min walk distance (6MWD), subjects were instructed to walk quickly but comfortably on an even surface between two cones.³⁴ The distance walked in 6 min is considered a valid marker of functional status.^{2,19}

Peak Oxygen Consumption

Subjects performed a graded exercise test (GXT) on a treadmill using a modified Bruce protocol¹ and exercised to voluntary exhaustion as described previously.³⁴ Open circuit spirometry was used to measure oxygen consumption (VO₂), CO₂ production, and minute ventilation breath-by-breath with a SensorMedics Vmax 29C series metabolic cart. Continuous 12-lead electrocardiogram was recorded throughout the test. Peak oxygen consumption (VO_{2peak}) and respiratory exchange ratio (RER) were determined from the data averaged over 20-s intervals. In addition, subjects' peak work rates were determined from body mass and treadmill incline and speed, as described elsewhere.⁶

Muscle Imaging

Two 5-mm computed tomography (CT) scans (Siemens Somatom Sensation 16, Malvern, Pennsylvania) of the lower extremities were taken, one at the midpoint between the anterior superior iliac spine and center of the patella, and the other at the midpoint between the tibial tuberosity and medial malleolus. Cross-sectional areas (CSAs) of each muscle group from the right lower extremity were determined by using Medical Imaging Process Analysis and Visualization software (MIPAV, v. 2.7.47; Center for Information Technology, National Institutes of Health, Bethesda, Maryland) to analyze CT scans of the thigh and lower leg. Muscle attenuation of the knee extensor and dorsiflexor muscle groups was also assessed using MIPAV, expressed in Hounsfield units and used as an index of intramuscular fat.¹⁶

Muscle Performance Testing

The ankle dorsiflexors and knee extensors of each subject were tested using a KinCom dynamometer (Chattecx, Chattanooga, Tennessee). For both muscle groups the dynamometer was configured and gravity-corrected according to the manufacturer's guidelines. The order in which the muscle groups were tested was randomly determined for each subject. For the dorsiflexors, a pair of stimulating electrodes was placed roughly longitudinally along the peroneal nerve, just posterior to and ~1 cm distal to the fibular head, taped in place, and further stabilized with a foam pad strapped over the electrodes. EMG recording electrodes (Grass Instruments, Warwick, Rhode Island) were placed as previously described.³⁷ Subjects were positioned supine with the KinCom configured for dorsiflexion testing according to the manufacturer's guidelines. Once the electrodes were in place, subjects lay supine with the trunk supported and foot in the KinCom's dorsiflexion apparatus at a fixed angle of ~120° to the shank. The knee was kept at ~0° flexion and the pelvis, thigh, and foot were secured with nonelastic straps.

For the knee extensors, subjects were tested sitting with the knee in 90° of flexion and the transducer secured around the lower leg ~2 cm superior to the lateral malleolus of the ankle. Large (~4 × 5 in) stimulating electrodes were placed over the rectus femoris and vastus medialis motor points as previously described⁵ and the EMG recording electrodes were placed over the quadriceps as described by McComas et al.³⁰ Subjects were secured to the KinCom with nonelastic straps across the waist and chest.

Electrical stimulation was delivered via an S48 constant-voltage stimulator delivered through an SIU8T stimulation isolation unit (Grass Instruments). Stimulation intensity was determined by monitoring the amplitude of the compound muscle action potential (CMAP) and isometric twitch force in response to single pulses (400 μ s for the dorsiflexors and 600 μ s for the knee extensors). Intensity was increased incrementally until an increase in voltage produced no increase in CMAP amplitude or peak twitch force. The voltage for central activation testing was set ~10% greater than that which produced a maximum response from the muscle.

The dorsiflexor and knee extensor muscles were tested using similar protocols. Subjects performed three maximum voluntary isometric contractions (MVCs), each separated by 2 min or more of rest. Subjects were verbally encouraged to produce a maximum effort during each of the attempts. During the final MVC, a supramaximal, 100-ms, 50-Hz (100-Hz for the knee extensors) stimulation train was delivered to the muscle to measure central activation. Following the isometric testing, dynamic testing was performed to determine peak power. Dynamic testing involved switching the KinCom to isotonic mode, which allowed subjects to produce force against a fixed load. This load was set at 30% of the subjects' MVC because a force-velocity model predicts that maximum power is produced at approximately this load.²⁰ Subjects performed three maximum-effort dynamic contractions, each separated by rest for 2 min. Again, subjects were verbally encouraged to give their best effort. The knee extensors were tested over a 60° range of motion from 90°–30° of knee flexion. The ankle dorsiflexors were tested over a 40° range of motion from 120°–80° of ankle plantarflexion.

All force responses were sampled at 500 Hz with force, velocity, and angle data recorded using customized software. The highest peak force value recorded from either the first two MVCs or during the third MVC prior to delivery of the supramaximal electrical stimulation was used to indicate the maximum voluntary force generated by the subjects. We report the MVC force measure as torque (Newtons × lever arm length in meters). Central activation was determined by calculating a central activation ratio (CAR) as previously described.^{22,37} The CAR equals the maximum voluntary force produced divided by the force produced following the burst during the third MVC. In the absence of any increase in force, CAR equals 1, and any value less than 1 indicates a failure of central activation.^{22,42}

The relationship between the CAR and %MVC is curvilinear rather than linear.^{40,41} Stackhouse and colleagues have determined that the %MVC/CAR relationship is accurately described ($r^2 = 0.98$) by a second-order polynomial.^{39,40,43} We used the measured CAR and the published quadratic equation to generate a corrected CAR value for each subject,^{41,44} and used this as our measure of central activation impairment. Power was calculated as the product of force and velocity during each of the three dynamic contractions. The peak power was recorded for each subject. Each subject's MVC torque and peak power were divided by the CSA of the respective muscles to give a measure of specific torque and specific power.

Data Analysis

Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, North Carolina) with the threshold for statistical significance at $P \leq 0.05$. Except as noted, data are

presented as means $\pm$ SD. Linear regression analyses were performed to determine the strengths of the relationships among the variables of interest. We divided the subjects into two groups post-hoc, based on the quadriceps femoris CAR data (see Fig. 1), and comparisons between these two groups (low and normal CAR) were evaluated by unpaired *t*-tests or Wilcoxon tests for nonparametric data (e.g., CD4 count, log₁₀ viral load). Chi-square tests were used for frequency count data. A viral load below the level of assay detection (<50 copies/ml) was classified as nondetectable. Linear regression analyses were used to investigate the relationship between quadriceps torque and CAR and muscle CSA within the low and high CAR groups. Finally, stepwise regression analyses were used to investigate the amount of quadriceps MVC torque variability explained by the combination of CAR and muscle CSA for all subjects as well as the low and normal CAR groups.

RESULTS

Subject Characteristics, Functional Status, and VO₂peak Testing

Two subjects who disclosed noncompliance with prescribed HAART at the study exit interview and one transgender subject were excluded. The data presented are from the remaining 27 subjects, of whom 93% were African American, and all of whom were male. The subjects were 48.7 ± 6.5 years of age. Average weight, height, body mass index (BMI), quadriceps muscle attenuation, 6MWD, VO₂peak, maximum heart rate, and RER are summarized in Table 1, along with the peak work rate achieved during the GXT. The subjects' mean CD4 count was 408 ± 293 cells/mm³ and the viral load was 2.18 ± 0.94 log copies/ml (Table 2). All of the subjects were on a nucleoside reverse transcriptase inhibitor-based regimen with 82% receiving a protease inhibitor as a third agent (Table 2).

Muscle Imaging

The average CSA of the knee extensors was 71.6 ± 13.0 cm² and muscle attenuation expressed in Hounsfield units was 56.0 ± 5.5 . The CSA of the ankle dorsiflexors was 11.8 ± 2.7 cm² and the average muscle attenuation in this group was 73.3 ± 11.3 Hounsfield units.

Muscle Performance

For the knee extensors, mean MVC torque was 211 ± 54 Nm, mean peak power was 442 ± 160 watts, and mean CAR was 0.88 ± 0.16 . The average specific torque of the knee extensors was 2.9 ± 0.6 Nm/cm² and the specific power was 6.1 ± 1.8 watts/cm². Regression analysis showed a moderately strong relationship between quadriceps muscle torque and CAR ($R^2 = 0.371$, $P < 0.001$, Fig. 1A) and torque and CSA of the muscle ($R^2 = 0.249$, $P = 0.01$, Fig. 1B). No significant relationship existed between CAR and knee extensor CSA (Fig. 1C). There was, however, a significant, though moderately strong, relationship between knee extensor specific torque and CAR ($R^2 = 0.396$, $P = 0.001$, Fig. 1D). A stepwise regression model was used to explore the amount of variability in quadriceps MVC torque that was explained by the CAR and muscle CSA. The model selected CAR as the variable that accounted for most of the variability in knee extensor MVC torque ($R^2 = 0.371$, $P = 0.001$), and adding CSA to the model accounted for more of the variability in knee extensor torque, improving both the fit and significance of the relationship ($R^2 = 0.582$, $P < 0.001$).

All subjects had a CAR of 1 in the ankle dorsiflexors. The average MVC torque of this muscle group was 39.2 ± 8.8 Nm and the average peak power was 102 ± 33 watts. Specific torque and power were 3.54 ± 0.93 Nm/cm² and 9.1 ± 3.3 watts/cm², respectively.

Normal and Low CAR Groups

Inspection of the quadriceps femoris muscle CAR data revealed two groups of subjects: a normal CAR group ($n = 16$) with CAR values of 1 or only slightly lower (0.99 ± 0.01) and a low CAR group ($n = 11$) with significant impairment in central activation as indicated by CAR values of 0.89 or lower (0.72 ± 0.12) (Fig. 1A). The normal CAR group produced greater MVC torques (233 ± 53 vs. 181 ± 39 Nm, $P = 0.01$, Fig. 2A) but not peak powers (471 ± 182 vs. 402 ± 119 watts, Fig. 2D) than the low CAR group. There was no difference between the CSAs of the quadriceps femoris muscles of the normal and low CAR groups (71.8 ± 13.6 vs. 71.3 ± 12.7 cm², Fig. 2B). Consequently, the low CAR group had a reduced specific torque as compared to the normal CAR group (2.5 ± 0.6 vs. 3.2 ± 0.5 Nm/cm², $P = 0.001$, Fig. 2C), although there was no difference in specific power (5.4 ± 1.5 vs. 6.6 ± 1.8). Dorsiflexor MVC torque (low: 38.56 ± 9.54 ; normal: 39.87 ± 8.38), CSA (low: 11.45 ± 3.48 ; normal: 11.77 ± 2.17), and specific torque (low: 3.41 ± 0.86 ; normal: 3.59 ± 0.99) were not different across groups.

The low and normal CAR groups did not differ with regard to most of our measures other than CAR (Tables 1 and 2). During the GXT, the low CAR group achieved similar peak VO₂ and maximum heart rate values to those of the normal CAR group. Fewer of the low CAR subjects, however, achieved an RER of ≥ 1.1 (3/11 vs. 11/16; chi-square $P = 0.01$). Interestingly, the low CAR group also attained lower peak work rates (Table 1), despite achieving comparable VO_{2peak} values. There was no significant difference in type or dose of the different HAART medications or cumulative drug class exposure between the low and normal CAR groups in the prior 6 months (Table 2). The low CAR group, however, did have a higher viral load than the normal CAR group (2.54 ± 1.12 vs. 1.93 ± 0.73 log copies/ml, $P = 0.03$), which reflects the finding that the viral load was suppressed in 15 of 16 subjects in the normal CAR group versus 8 of 11 in the low CAR group. A greater proportion of the low CAR group had a history of AIDS-defining illness compared to the normal CAR group (Table 2), but there was no difference in current immune status as measured by CD4 cell count.

For the low CAR group, regression analyses revealed a moderately strong and significant relationship between the quadriceps MVC torque and CAR ($R^2 = 0.599$, $P = 0.005$, Fig. 3A), but not quadriceps CSA (Fig. 3B). Conversely, for the normal CAR group there was a significant relationship between quadriceps MVC torque and CSA ($R^2 = 0.667$, $P < 0.001$, Fig. 3D), with a trend toward significance for a weak relationship between torque and CAR ($R^2 = 0.197$; $P = 0.055$, Fig. 3C). The same stepwise regression procedure was used for all subjects to evaluate the relationship between torque and the combination of CAR, and CSA was employed with the low and normal CAR groups. For the low CAR group, torque was most closely related to CAR and adding CSA did not improve the fit or significance of the model. Conversely, for the normal CAR group, torque was most closely related to CSA and adding CAR only marginally improved the fit ($R^2 = 0.681$, $P = 0.002$).

DISCUSSION

The principal finding of this study was that nearly half (~40%) of subjects with HIV on HAART had an impaired ability to activate their knee extensor muscles that was associated with weakness and decreased specific force, although no deficits in the central activation of the dorsiflexor muscles were observed. The low CAR subjects had higher viral loads and were more likely to have a history of AIDS-defining illness. The inability of the low CAR group to fully activate their knee extensors was unrelated to muscle size or composition, or to VO_{2peak}. However, this group did exhibit what might be termed an “aerobic inefficiency” in that they achieved significantly lower work rates than the normal CAR group, while achieving comparable VO_{2peak} values.

When examined as a whole, the subjects studied had an average CAR that was between those of healthy elderly subjects and healthy younger subjects, as reported by Stevens et al.⁴⁴ Given that our subjects were, for the most part, middle-aged, this was not surprising. Furthermore, the subjects' knee extensor MVCs were comparable to those predicted by the equations of Lindle et al.,²⁸ based on subject age (observed, 619 ± 167 N; predicted, 605 ± 30 N). In contrast, the observed VO_2peak values were substantially lower than established, age-predicted norms (observed, 22.6 ± 5.0 ml/kg/min; predicted, 36.1 ± 2.9 ml/kg/min).¹⁵ Similar impairments in oxygen consumption have been observed previously in HAART-treated individuals with HIV.^{7,8} The subjects in this study also appeared to have a decreased functional status based on their 6MWDs, which were less than the values predicted based on their BMI and age¹² (observed, 593 ± 73 ; predicted, 666 ± 52).

Inspection of the CAR data suggested that our subjects could be divided into two groups, based on their ability to activate their knee extensors (Fig. 1A). In effect, we had two subpopulations, one with normal CAR values in the knee extensors and the other with markedly lower values. Indicative of the concept of two subpopulations, the results of the multivariate regression model incorporating both CAR and CSA produced a much stronger association with MVC torque than either variable alone. This model utilized the major factors for both the low and normal CAR groups (CAR and CSA, respectively), producing the more robust fit.

Subsequent comparisons of the low and normal CAR groups revealed that the low CAR group was weaker, despite comparable knee extensor muscle CSA, resulting in reduced specific force (Fig. 2). Our index of muscle attenuation was similar in both groups (Table 1), suggesting that the lower specific forces were not the result of increased intramuscular fat and less contractile tissue in the low CAR group. When we calculated the age-predicted MVC forces for the two groups as we did for the entire subject pool (see above), the low-CAR group was below its predicted values (observed, 549 ± 115 N; predicted, 608 ± 30 N), whereas the normal CAR group was actually stronger than predicted (observed, 701 ± 174 N; predicted, 602 ± 30 N). The study that provided the equations for these predictions²⁸ did not include CSA, and so it is possible that our subjects had larger average muscle areas, which would account for the higher MVC values in the normal CAR group. The impaired activation in the low CAR group would explain why the MVC forces in this group were lower than predicted, despite having CSAs similar to the normal CAR group.

Decreased central activation contributing to weakness has been reported in other patient populations. For example, inhibition of quadriceps activation has been reported in orthopedic conditions of the knee, including osteoarthritis^{14,27,43} and joint replacement surgery.^{31,43} Pain has been shown to account for at least some of the central activation failure in these populations.⁴³ Although we did not screen for knee pain during our testing of the quadriceps muscles, no subject reported pain or appeared to have knee discomfort during or after the burst test. Kent-Braun and colleagues^{23,33} have shown central activation impairment of the ankle dorsiflexors in patients with either multiple sclerosis or amyotrophic lateral sclerosis, likely mediated by upper motor neuron dysfunction associated with these diseases. Interestingly, a clinical syndrome mimicking amyotrophic lateral sclerosis in many respects has been reported, although infrequently, in patients infected with HIV.⁴⁷

The inability of the subjects in the low CAR group to activate fully their quadriceps muscle was not related to our measure of functional performance (6MWD). However, the 6MWD test does not place a significant demand on the force-generating capacity of the knee extensors, and is more likely to be influenced by aerobic capacity than maximum force-producing ability. Consistent with this position, both the low and normal CAR groups failed

to achieve their predicted 6MWD and had VO_2peak values substantially lower than established norms, which were calculated as described above. It is possible that if we had chosen a more demanding task as a measure of functional performance, such as a timed stair climb, we would have observed a decreased functional performance associated with the low CAR.

Although the low and normal groups did not differ with regard to VO_2peak , the mean RER of the low CAR group was less than that of the normal CAR group, indicative of the fact that fewer of the subjects in the low CAR group reached an RER of 1.1 or more. In isolation, these data might be taken to indicate that the low CAR group was simply poorly motivated and that this lack of drive accounted for the low CAR values. Had the low CAR group exhibited comparable maximum work rates to those of the normal CAR group, while not attaining the higher RERs, we would be inclined to accept this interpretation. However, the low CAR group actually achieved lower maximum work rates than the normal group, despite producing comparable VO_2peak values at exhaustion. Essentially, the low CAR subjects had to utilize comparable aerobic metabolism to achieve less work, an observation that we feel makes it unlikely that the subjects were simply not trying. Perhaps this finding is related to the impaired oxygen on-kinetics that have been previously associated with HIV infection, but not HAART.⁹

Given the comparable ages, aerobic capacities, muscle attenuation values, and body compositions of the two groups, none of these factors is likely to account for the difference in central activation. Furthermore, both groups were on comparable HAART medication regimens and had similar median CD4 cell counts, making it unlikely that drug effects or immune suppression were contributing to the differences. The reduced aerobic capacity in all the subjects reflects the previously shown association of lower oxygen consumption with HAART.⁸ Since there was no difference in aerobic capacity between the CAR groups, it seems unlikely that the same mechanism of drug toxicity is contributing to the difference in central activation.

The low CAR group, however, did have higher median viral loads and a greater prevalence of past AIDS-defining illness than the normal CAR group. The higher median viral load in the low CAR group is driven by the finding that only 73% of these subjects had nondetectable viral loads compared to 93% of subjects with normal CAR. This is an interesting finding, given that all the subjects were receiving standardized HAART regimens at established doses, which should have uniformly led to low or nondetectable viral loads. Since noncompliance with these potent regimens is associated with poor immunological and virological outcomes, subjects with poor adherence by chart review or self-report (two patients) were initially excluded. Therefore, considering the similar HAART regimens and CD4 cell counts between the CAR groups, compliance or current access to care are unlikely to explain the difference in viral loads. Length of HIV infection and chronic viral load control are factors that need to be considered but are beyond the scope of this study. However, the fact that the low CAR group had a two-fold increased risk of prior AIDS illness implies that these subjects have been infected with HIV for longer than the normal CAR group. These findings suggest the possibility, although highly speculative, that some sort of long-term viral-associated CNS dysfunction that impairs central activation is operating.

In addition to the sporadic syndrome resembling amyotrophic lateral sclerosis mentioned earlier, other CNS disorders have been associated with HIV.^{4,48} Although HIV is not thought to routinely infect motor neurons, it is well established that the virus does enter the CNS and infect glial cells, and can lead to neurological impairment via inflammation, neurotoxic viral proteins, or both.⁴⁷ Because of the blood-brain barrier, both the infection

and the inflammation may be difficult to treat. Although our findings are consistent with an infection-mediated as opposed to a HAART-mediated impairment of central motor function, the present study is limited by a small homogeneous patient sample and less than 1 year of HAART data. Further research is clearly needed to establish any sort of definitive link. Nevertheless, it appears that a significant proportion of individuals with HIV (40% in the present study) may have muscle activation deficits that are not related to medication regimen or muscle atrophy.

We examined the dorsiflexors as well as the knee extensors and observed no central activation deficits in this muscle group, as all subjects appeared to be able to maximally activate their ankle dorsiflexor muscles (i.e., CAR = 1). Although it is not unusual to see uniformly high CAR values in this muscle group,^{10,24,38} even in elderly individuals,^{24,25} we were surprised by the lack of impairment in the low CAR group, given the marked reductions observed in knee extensor activation. One potential concern is that dysfunction of the peripheral nervous system may be present. Our assessment of CAR uses electrical stimulation to activate muscles via their peripheral nerves. Detection of central activation failure could be hindered in the distal dorsiflexor muscles if they are affected by some peripheral nerve disorder to a greater extent than the proximal knee extensors. Several peripheral neuropathic syndromes have been described in patients with HIV, including distal symmetric polyneuropathy, inflammatory demyelinating polyneuropathy, and multineuropathy multiplex.^{13,46,50} Distal symmetric polyneuropathy is the most common neurological disorder associated with HIV infection and has greater impact distally than proximally because longer motor neurons are more affected than shorter ones.¹³ Unfortunately, the subjects did not undergo neurological examination to determine whether it was present.

Overall, the results of this study indicate that impaired central activation may be a problem in a significant proportion of individuals with HIV, although perhaps not in all muscle groups. The subjects with impaired central activation were weaker than those without impairment, but their muscles were of similar sizes. Consequently, impaired central activation was associated with reduced specific force, although mechanisms other than the loss of central activation may well have been at work. Contrary to our hypothesis of a link between aerobic capacity and CAR, the two groups did not differ with regard to VO_{2peak}, although some form of aerobic impairment may have been present in the low CAR group. These subjects attained similar VO_{2peak} values to the normal CAR group, while performing at lower work rates. In these subjects the central activation deficit appeared to be more closely linked to viral loads and past history of AIDS-defining illnesses than to HAART medications, suggesting that this impairment is related to the progression of the disease itself. While such a mechanism would be consistent with existing reports of impaired motor function in HIV-positive individuals, further research is needed to examine this possibility.

Abbreviations

6MWD	6-minute walk distance
AIDS	acquired immunodeficiency syndrome
CAR	central activation ratio
CMAP	compound muscle action potential
CNS	central nervous system
CSA	cross-sectional area
CT	computed tomography

GXT	graded exercise treadmill test
HAART	highly-active antiretroviral therapy
HIV	human immunodeficiency virus
MVC	maximum voluntary isometric contraction
PCR	polymerase chain reaction
RER	respiratory exchange ratio
VO₂peak	peak oxygen consumption

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Figure 1.

Data from all subjects showing relationship of quadriceps MVC torque to (A) CAR and (B) quadriceps CSA, and of CAR to (C) CSA and (D) quadriceps specific torque. In (A) the thin oval encloses the subjects that were classified as belonging to the low-CAR group and the thick oval encloses subjects in the high-CAR group. Coefficients of determination and *P*-values from linear regression analysis are presented on each plot. Using a bivariate regression model that incorporated both CSA and CAR explained a greater percentage of MVC torque variance than either CSA or CAR alone (see text for details).

Figure 2. Comparisons of quadriceps MVC torque (**A**), quadriceps cross-sectional area (**B**), quadriceps-specific torque (**C**), and quadriceps peak power between the low (filled bars) and normal CAR (open bars) groups (**D**). Asterisk indicates significant difference between groups.

Figure 3.

Data from low (**A,B**) and normal CAR (**C,D**) groups, showing the relationships between quadriceps MVC torque and CAR (**A,C**) and quadriceps MVC torque and quadriceps cross-sectional area (**B,D**). Coefficients of determination and *P*-values from linear regression analysis are presented on each plot. Stepwise multiple regression analyses were also performed for both groups to determine the combined effects of cross-sectional area and CAR on MVC torque (see text for details).

Table 1

Physical characteristics and performance.

Variables mean $\pm$ SD	All subjects (n = 27)	Low CAR group (n = 11)	Normal CAR group (n = 16)	P-value *
Age (yr)	48.7 $\pm$ 6.5	48.1 $\pm$ 6.8	49.1 $\pm$ 6.4	0.70
Weight (kg)	75.7 $\pm$ 14.9	72.8 $\pm$ 11.3	77.6 $\pm$ 16.9	0.44
Height (m)	1.77 $\pm$ .08	1.76 $\pm$ .08	1.78 $\pm$ .08	0.41
BMI (kg/m ²)	24.2 $\pm$ 4.1	24.1 $\pm$ 4.4	24.2 $\pm$ 4.0	0.92
Quadriceps femoris muscle attenuation (Hounsfield units)	56.0 $\pm$ 5.5	57.0 $\pm$ 4.8	55.6 $\pm$ 6.0	0.51
VO ₂ peak (ml/kg/min)	22.6 $\pm$ 5.0	21.4 $\pm$ 4.4	23.4 $\pm$ 5.4	0.30
Maximum heart rate (beats/min)	142 $\pm$ 20	148 $\pm$ 18	134 $\pm$ 21	0.09
RER	1.08 $\pm$ 0.10	1.02 $\pm$ 0.1	1.12 $\pm$ 0.08	0.01
Treadmill max work rate (W)	125 $\pm$ 46	98 $\pm$ 31	143 $\pm$ 46	0.01
6MWD (m)	593 $\pm$ 73	584 $\pm$ 83	599 $\pm$ 67	0.61

Data presented as means $\pm$ SD.* Comparison of low and normal CAR group with unpaired *t*-tests.

Table 2

HIV blood tests and history.

Variables	All subjects (<i>n</i> = 27)	Low CAR group (<i>n</i> = 11)	Normal CAR group (<i>n</i> = 16)	<i>P</i> -value *
CD4 count (cells/mm ³) median (range)	398 (18–1401)	426 (101–950)	359 (18–1401)	0.7
HIV-1 viral load (log copies/ml) median (range)	1.7 (1.7–4.6)	1.9 (1.7–4.6)	1.7 (1.7–4.5)	0.03
Detectable viral load, [†] >50 copies/ml, <i>n</i> (%)	4 (14.8)	3 (27.3)	1 (6.3)	0.2
History of AIDS-defining illness, <i>n</i> (%)	13 (48.1)	8 (72.7)	5 (31.3)	0.04
Cumulative months HAART in prior 6 months				
NRTI, median (range)	10.3 (3–20.1)	8.4 (3–17.8)	11.0 (4–20.1)	0.4
PI, median (range)	5.9 (0–16.4)	6.9 (0–11.4)	5.7 (0–16.4)	0.9
NNRTI, median (range)	0 (0–4.9)	0 (0–4.9)	0 (0–4.8)	0.7
Thymidine analog	0 (0–5.9)	0 (0–5.9)	0 (0–5.7)	0.4

NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor

* Comparison of low and normal CAR group with chi-square, Fisher's Exact or Wilcoxon rank-sum test

[†] Lower limit of PCR assay, 50 c/ml, used to calculate log value for nondetectable values.