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*Original Research*

# Body Mass Index but not Physical Activity Level Moderates Lowered Cardiac Baroreflex Sensitivity in People Living with HIV

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ABSTRACT

***International Journal of Exercise Science 16(2): 700-709, 2023.*** Reduced cardiac baroreflex sensitivity (cBRS) is an autonomic marker associated with a worse cardiovascular prognosis. Whether cBRS is lowered in people living with HIV (PLHIV) is yet unclear, as well as potential moderator effects of body mass index (BMI) or physical activity (PA) level. The present study aims to compare the spontaneous cBRS in PLHIV *vs*. HIV-uninfected controls, and to determine among PLHIV the relationship between cBRS *vs.* body mass index (BMI) and PA level. Total, upward (cBRS+), and downward (cBRS-) cBRS gains were assessed using the sequential method from beat-to-beat blood pressure at rest in 16 PLHIV (46.5±8.4 years) under antiretroviral therapy for at least 6 months, and 16 HIV-uninfected controls (CTL; 42.1±8.0 years). PA level was assessed by the Physical Activity Questionnaire (IPAQ short version) overall score. PLHIV showed lower total cBRS (8.7±3.1 *vs*. 15.3±7.7 ms.mmHg$^{-1}$; $p < 0.01$), cBRS+ (9.2±4.9 *vs*. 16.0±6.8 ms.mmHg$^{-1}$; $p < 0.01$) and cBRS- (9.5±4.9 *vs*. 15.3±9.3 ms.mmHg$^{-1}$; $p < 0.01$) *vs*. CTL. No between-group difference was found for BMI (PLHIV: 25.2±2.6 *vs*. CTL: 26.8±3.2 kg.m$^{-2}$; $p > 0.05$) or IPAQ score (PLHIV: 2.4±1.0 *vs*. CTL: 2.0±1.4; $p > 0.05$). In PLHIV, total cBRS was inversely correlated *vs.* BMI ($r = -0.44$; $p = 0.04$), but not *vs.* IPAQ score ($r = 0.17$; $p = 0.26$). HIV infection may reduce spontaneous cBRS, which seemed to be moderated by higher BMI, but not PA level of PLHIV.

KEY WORDS: Cardiac autonomic control, physical activity, baroreflex, acquired immunodeficiency syndrome

## INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV) was first described in the 1980s. The survival of people living with HIV/AIDS (PLHIV) has greatly increased after the introduction of combination antiretroviral therapy (cART) in the mid-1990s (34).

Access to cART has prevented around 12.1 million AIDS-related deaths since 2010 so estimations indicate that 38 million people are now living with HIV (37). Despite this, the longer exposure to the virus infection combined with the cytotoxic side effects of cART harms several organ systems, including the cardiovascular and nervous systems (3). In comparison with uninfected individuals, PLHIV have a higher prevalence of dyslipidemia, hypertension, atherosclerosis, endothelial and autonomic dysfunction (38), and a cardiovascular risk 1.5 to 3 times higher (9). A better understanding of mechanisms underlying the increased cardiovascular risk among PLHIV is therefore important in terms of the prevention of cardiovascular disease.

The baroreflex is one of the components of homeostatic reflexes responsible for cardiovascular autonomic control. It consists of a negative feedback mechanism that permanently adjusts the blood pressure levels, mediating the heart rate and peripheral vasoconstriction (12, 26). The assessment of cardiac baroreflex sensitivity (cBRS) is a well-established tool for evaluating cardiovascular autonomic control (20). Moreover, it is acknowledged as a prognostic marker of cardiovascular events, such as myocardial infarction, stroke, or sudden death (5, 11).

Several factors seem to modulate the cBRS (2, 8, 14). Endukuru et al. (8) reported an inverse correlation between BRS and traditional risk factors, especially body mass index (BMI) in individuals with and without metabolic syndrome. Physical activity levels have also been suggested to influence the cBRS (20, 27). During physical efforts, a reset occurs in the firing threshold of the baroreflex mechanism due to increased blood pressure. It seems that this resetting process has a cumulative effect that leads to increased vagal tonus at rest (30). Although some controversy exists (22), individuals with greater physical activity levels or cardiorespiratory fitness may exhibit more preserved cBRS than physically inactive or unfit counterparts (27, 35).

There is evidence that cBRS is impaired in PLHIV (4, 10, 31), which potentially increases their cardiovascular risk. Studies on the determinants of cBRS in this population are scarce, but at least one cross-sectional study showed that unfit PLHIV and healthy controls had worse cBRS than individuals with higher cardiorespiratory fitness, irrespective of HIV status (35). Given the relationship between physical fitness and physical activity, we hypothesized that the cBRS would be more preserved among PLHIV with higher *vs.* lower physical activity levels. However, trials investigating the influence of physical activity level on the cBRS in PLHIV could not be located. Thus, the objectives of this study were to compare the spontaneous cBRS in PLHIV *vs.* HIV-uninfected controls, and to investigate the relationship between BMI and PA level *vs.* spontaneous cBRS in PLHIV under cART.

## METHODS

*Participants*

We enrolled 16 PLHIV aged 35 to 59 years old under cART for at least 6 months, followed up at University Hospital Pedro Ernesto (HUPE) or Federal University of Juiz de Fora (UFJF), and 16 HIV-uninfected controls (CTL) matched for age and sex, randomly recruited from the staff of the same institutions. Exclusion criteria were: a) smoking; b) resting blood pressure ≥ 140/90 mmHg; and c) use of medication influencing cardiovascular responses or autonomic control, or any other substance affecting individual performance (e.g., anti-hypertensives, anticoagulants, non-steroidal anti-inflammatory agents, antidepressants, or herbal supplements). All volunteers provided informed written consent before participation in the study, which complied with recommendations from the Helsinki Declaration. The protocol gained approval from the Ethics Review Board of the HUPE (CCAE 87616418.2.0000.5259) and UFJF (CAAE 91851018.9.0000.5133). This research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (25).

*Protocol*

This cross-sectional study was conducted during a single visit to HUPE or UFJF. Upon arrival at the laboratory, the participants underwent a general medical examination, and when eligible signed the consent form. Body mass and height measurements were made using a calibrated electronic scale (Filizola™, São Paulo, SP, Brazil) and wall stadiometer (Sanny™, São Paulo, SP, Brazil), for further calculation of BMI (body mass.height$^{-2}$). Subsequently, participants responded to the short version of the International Physical Activity Questionnaire (IPAQ), which was validated for this age group in Brazil (23). Finally, they remained for 30 min at rest in the supine position for a beat-to-beat blood pressure evaluation. All participants were instructed to consume only light food up to 1 h before the tests, and not to perform physical exercise or consume alcohol or stimulants up to 48 h before the visit. Assessments occurred always in the morning in a temperature-controlled room (21±1 $^{o}$C, ~60% air humidity).

Blood pressure and cardiac baroreflex sensitivity assessments: Beat-to-beat blood pressure at rest was continuously and non-invasively assessed through digital photoplethysmography (Finometer™ Pro, Finapress Medical System, Amsterdam, Netherlands). A window corresponding to the last 10 min of the 30-min resting period was used to determine the spontaneous cBRS by the sequential method. This approach consists of identifying 3 or more consecutive beats in which there is a spontaneous increase in systolic blood pressure (SBP), followed by a lengthening of RR intervals (RRi) or a decrease in SBP followed by RRi shortening (28).

The upward gain (cBRS+) occurs when there are consecutive increases in SBP, representing activation of the baroreceptors. Consecutive decreases in SBP represent the "turn off" of the baroreceptors, called the downward gain (cBRS-). The normalized gain of all combined variations was considered as the total cBRS gain (cBRS total). Changes equal to or greater than 1 mmHg for SBP and 3 ms for RRi were considered for analysis of the cBRS total, cBRS+, and

cBRS-. Outcomes were obtained by importing the RRi and SBP records into commercially available software (Heart Scope™ II, AMPS, New York, USA).

*Statistical Analysis*

An achieved statistical power of 0.86 was obtained by performing post hoc analysis (GPowerTM 3.1; Kiel, University of Kiel, Germany) based on the sample size, predefined p-value, and effect size of 1.12 for a cBRS difference of 6.6 ms.mmHg$^{-1}$. The normality of continuous variables was confirmed using the Shapiro-Wilk test, and therefore data are presented as mean ± standard deviation, except the IPAQ score which is presented as median [interquartile range]. Differences in BRS outcomes between PLHIV and CTL were tested using unpaired t-tests, while sex distribution was tested by the chi-squared test. Correlations between cBRS total *vs.* BMI and IPAQ score in PLHIV were calculated using Pearson and Spearman correlations, respectively. The effect size (ES) of the data was reported using the $r^2$ for the correlations, and expressed by Cohen's d = $(M2 - M1)/\sqrt{((SD1^2 + SD2^2)/2)}$ for the unpaired t-test, considering 0.20 as small, 0.50 as medium, and above 0.80 as a large effect size (7). All tests were performed using the GraphPad Prism version 8 (GraphPad, La Jolla, CA, USA), and statistical significance was set at $p \leq 0.05$.

## RESULTS

The clinical characteristics of the sample are presented in Table 1. No difference was detected between groups for age, sex, height, body mass, BMI, and IPAQ score.

**Table 1.** Clinical characteristics of people living with HIV (PLHIV) and Controls (CTL).

| | PLHIV (n = 16) | CTL (n = 16) | *P-value* |
|---|---|---|---|
| Age (year) | 46.5 (8.4) | 42.1 (8.0) | 0.15 |
| Male (n [%]) | 14 [87.5] | 14 [87.5] | 0.99 |
| Height (cm) | 177.2 (8.5) | 176.4 (5.4) | 0.76 |
| Body Mass (Kg) | 77.9 (10.5) | 83.5 (12.2) | 0.14 |
| Body Mass Index (Kg.m$^{-2}$) | 25.2 (2.6) | 26.8 (3.2) | 0.12 |
| IPAQ score | 2.4 [1.0] | 2.0 [1.4] | 0.27 |

Results are expressed as mean (SD), or median [interquartile range] for nonparametric data. Individual and average spontaneous cBRS data are presented in Figure 1. In comparison with CTL, PLHIV showed lower cBRS total (8.7 ± 3.1 *vs.* 15.3 ± 7.7 ms.mmHg$^{-1}$; $p = 0.001$; ES = 1.11; Panel A), cBRS+ (9.2 ± 4.9 *vs.* 16.0 ± 6.8 ms.mmHg$^{-1}$; $p = 0.003$; ES = 1.13; Panel B), and cBRS- (9.5 ± 4.9 *vs.* 15.3 ± 9.3 ms.mmHg-1; $p = 0.03$; ES = 0.77; Panel C). Figure 2 depicts correlations between cBRS *vs.* BMI and IPAQ among PLHIV. The BMI was inversely correlated with total (Panel A), upward (Panel C), and downward gains of cBRS (Panel E). No correlation was found between cBRS markers and the total IPAQ score (Panels B, D and F).

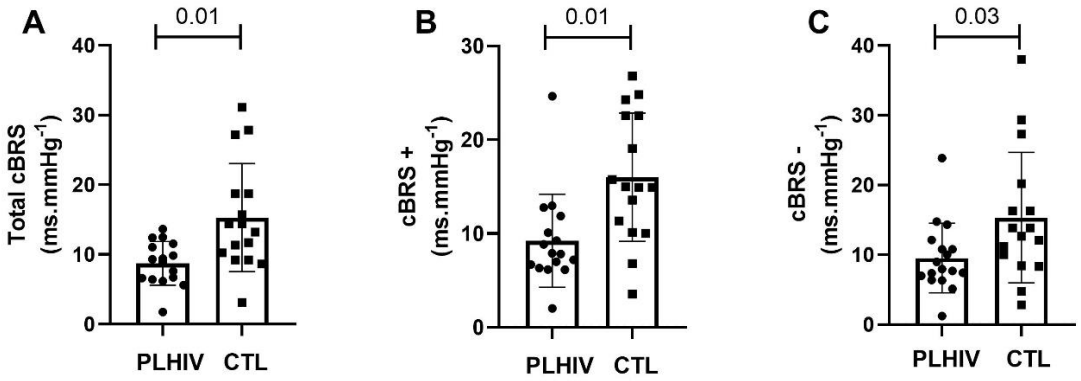


**Figure 1.** Spontaneous cardiac baroreflex sensitivity (cBRS), total gain (A), upward gain (B), and downward gain (C) in people living with HIV (PLHIV) and healthy controls (CTL).

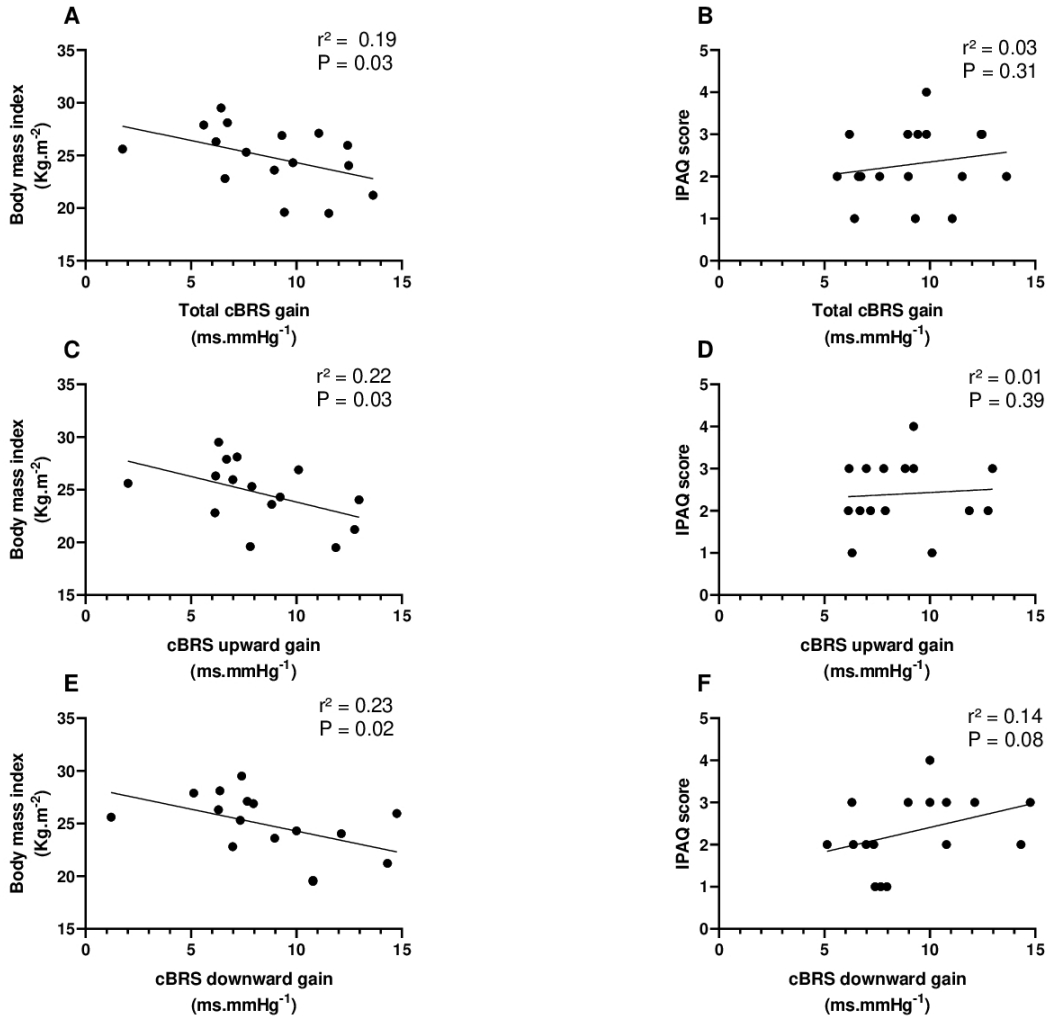


**Figure 2.** Correlations of cardiac baroreflex sensitivity gains (cBRS) *vs.* body mass index (Panels A, C, and E) and IPAQ score (Panels B, D, and F) in people living with HIV (PLHIV).

## DISCUSSION

This study aimed to investigate the spontaneous cBRS in PLHIV under cART and to determine its relationship with BMI and habitual physical activity. The cBRS was reduced in PLHIV *vs*. healthy controls matched for physical activity levels. In addition, the cBRS was inversely correlated with BMI among PLVHIV, while no correlations were found with their self-reported physical activity level.

Our results regarding cBRS were consistent with the current evidence. Freeman et al. (16) observed impaired blood pressure control in PLHIV, reflected by poor adjustments to autonomic reflex tests (i.e.; Valsalva maneuver, orthostatic challenge, and cold pressor test). Brownley et al. (18) reported that PLHIV had difficulties sustaining the sympathetic drive during handgrip, with reductions in DBP and stroke volume. More recently, Robinson-Papp et al. (31) evaluated the adrenergic component of BRS (αBRS) among 47 PLHIV. This component is a marker of α adrenergic receptors (24) that mediate sympathetic increases in total peripheral resistance. In 30% of individuals with HIV-associated autonomic dysfunction the αBRS was lowered, which was directly related to several inflammatory cytokines, including IL-6. This finding corroborates previous evidence from pre-clinical studies indicating that higher cardiovascular risk in PLHIV may be linked to greater chronic inflammation (17, 18).

The present study was the first to investigate the correlation between spontaneous cBRS and BMI among PLHIV. Interestingly, we found that cBRS was moderately correlated with BMI in this population. This is consistent with previous data in older people (16) and patients with metabolic syndrome (8). The reasons explaining the relationship between increased BMI and poor cBRS are not fully understood, but at least in part, this may be due to the greater insulin resistance and sympathetic overactivity often found in individuals with excess weight (16). This possibility is reinforced by the fact that 56% of participants in the PLHIV group were classified as overweight (BMI ≥ 25 kg/m$^2$). This is suggestive that weight management in PLHIV would be important to prevent autonomic dysfunction, including cBRS preservation (15). This is particularly relevant when considering that PLHIV frequently develops dyslipidemia and lipodystrophy (33).

Regarding the association between cBRS and physical activity, studies are scarce. However, evidence indicates that physical training improves cBRS irrespective of the health condition (13, 21, 36), and cross-sectional studies suggest that age-related declines in baroreflex may be prevented by habitual physical activity (19, 27). Climie *et al.* (6) evaluated 8,649 adults for spontaneous BRS and habitual physical activity through the Baecke Questionnaire (occupational, leisure, and sports activities). The BRS was inversely associated with occupational and directly associated with sports activities. In the present study, cBRS did not correlate with self-reported physical activity, but the IPAQ does not allow stratified analysis according to the physical activity domain.

Cardiorespiratory fitness may be considered a surrogate of the physical activity level. Spierer et al. (35) compared the cBRS between 28 PLHIV and 20 healthy controls with different cardiorespiratory fitness and found no difference when groups were matched for physical fitness. However, it is worth noticing that unfit PLHIV and healthy controls showed similar cBRS and autonomic function. Methodological differences, such as the method and posture used for cBRS assessment may account for these controversial findings *vs.* studies that compared PLHIV and healthy samples. A spectral method based on blood pressure recordings via applanation tonometry was applied, which is disputable to assess the cBRS in individuals with depressed blood pressure variability, such as PLHIV (20). Furthermore, evaluations were performed with participants seated, which might have influenced the autonomic response (32). Previous studies showing differences between PLHIV and healthy controls adopted the supine position (1).

Our study has strengths and limitations. A major strength is the application of the sequential method through spontaneous oscillations of SBP and iRR to assess the cBRS in PLHIV. This is a clinically relevant approach (29) that has not been previously used in research with this population. In addition, we are the first to show the relationship between cBRS *vs.* BMI. The major limitation refers to the use of IPAQ as a marker of physical activity level. Moreover, the sample consisted mostly of men (87.5%). Although groups were matched for sex, this limits the external validity of our data.

In conclusion, the present study added to the current knowledge by demonstrating that PLHIV under cART exhibit lower cBRS *vs.* healthy controls. It is noteworthy that the difference between the groups showed a large ES, which can be considered a relevant finding. Moreover, PLHIV with greater BMI showed poorer cBRS, suggesting that being overweight could be a moderator of autonomic control among PLHIV. On the other hand, at least in our sample with homogeneously low physical activity levels, this outcome did not correlate with cBRS. Further studies including larger and more heterogeneous samples and applying objective assessments of physical activity and body composition are warranted to ratify those findings.

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