

Excessive Adiposity and Metabolic Dysfunction Relate to Reduced Natriuretic Peptide During RAAS Activation in HIV

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Purpose: Natriuretic peptides (NPs) negatively feedback on the renin-angiotensin-aldosterone system (RAAS) and play a critical role in preserving cardiac structure and maintaining metabolic homeostasis. Well-treated HIV-infected individuals are at risk for fat redistribution and demonstrate evidence of RAAS dysregulation, which relates to metabolic dysfunction. We investigated circulating NPs in relation to RAAS physiology and metrics of body composition in HIV.

Methods: We assessed atrial natriuretic peptide, brain natriuretic peptide (BNP), and amino terminal pro B-type natriuretic peptide (NT-proBNP) during acute activation of the RAAS using a low-sodium controlled diet among 20 HIV-infected and 10 non-HIV-infected individuals well phenotyped for body composition.

Results: BNP was significantly lower [median, 60 (interquartile range, 44, 152) pg/mL vs 196 (91, 251) pg/mL, respectively; $P = 0.04$], and serum aldosterone was higher, among HIV-infected than among non-HIV-infected individuals. BNP was significantly and inversely associated with body composition [waist circumference: $r = -0.46$ ($P = 0.04$); BMI: $r = -0.55$ ($P = 0.01$); body adiposity index: $r = -0.49$ ($P = 0.03$)], metabolic indices [total cholesterol: $r = -0.44$ ($P = 0.05$), insulin resistance calculated by using homeostatic model assessment: $r = -0.44$ ($P = 0.05$); mean arterial pressure: $r = -0.44$ ($P = 0.05$)], and serum aldosterone ($r = -0.49$; $P = 0.03$) among the HIV-infected group. These relationships were not demonstrated in the non-HIV-infected group. In a four-group comparison stratifying by HIV serostatus and above or below a body mass index (BMI) of 25 kg/m², BNP decreased significantly across groups; it was highest in non-HIV-infected patients with a BMI <25 kg/m² and lowest in HIV-infected patients with a BMI ≥25 kg/m² (overall $P = 0.01$).

Conclusion: Relatively reduced NP, particularly BNP, among HIV-infected individuals with excess adiposity may contribute to reduced suppression of aldosterone and potentially drive aldosterone-mediated metabolic complications. Strategies that target RAAS blockade and/or augment NPs may be useful to reduce cardiometabolic disease among HIV-infected individuals in whom these systems are perturbed. (*J Clin Endocrinol Metab* 103: 1558–1565, 2018)

Cardiac natriuretic peptides (NPs) are important neurohormones that serve as negative regulators of the renin-angiotensin-aldosterone system (RAAS). Together, these two hormone systems are integral to maintaining cardiovascular homeostasis. The obese population demonstrates reduced cardiac NPs relative to the nonobese population. This decrease in NPs in the obese population has been attributed to excess adiposity and may provide an underlying mechanism for the demonstrable advanced metabolic risk in this group.

Data suggest that the RAAS has an emerging role in adipose biology and may contribute to insulin resistance, inflammation, and cardiovascular disease (CVD) in states of adipose dysfunction. We have previously reported that HIV-infected individuals with a clinical phenotype of excess adiposity have increased aldosterone during an RAAS-activated state. Furthermore, during conditions of RAAS activation, stimulated with low dietary sodium, increased aldosterone is associated with insulin resistance as well as markers of generalized inflammation and immune activation among the HIV population (1, 2). HIV-infected individuals are at increased risk for fat redistribution and subsequent metabolic consequences, and the exact mechanism linking adipose dysfunction to cardiometabolic disease in HIV remains unclear.

Thus, we hypothesized that, on the basis of known cardiac NP physiology in the obese population, relatively reduced cardiac NPs during a RAAS-activated state

would be associated with unfavorable body composition and metabolic indices among the HIV-infected population, a model of acquired fat redistribution (Fig. 1). No studies to date have used rigorous physiologic techniques to comprehensively evaluate RAAS and NP system feedback in HIV. Indeed, these data expand our knowledge of the interaction between these two relevant hormone systems with respect to HIV status, as well as body composition.

Methods

Study participants

Twenty HIV-infected individuals were recruited from Boston-area HIV clinics and community outreach centers and through local advertisements. In addition, 10 non-HIV-infected persons were recruited from the same Boston-area communities. Study criteria for inclusion and exclusion were identical regardless of serostatus (1). Each group was chosen to be of similar age (18 to 65 years), sex, and waist circumference. HIV-infected individuals were required to be receiving stable anti-retroviral therapy (ART) regimens for 3 months or longer. Individuals with any known history of CVD (including congestive heart failure), hypertension (blood pressure >140/90 mm Hg), or diabetes mellitus were excluded. Additional exclusion criteria were current antihypertensive or antidiabetic medication use; active tobacco use; steroid, estrogen, progesterone, growth hormone, or growth hormone-releasing hormone use within the past 3 months; and pregnancy. Laboratory criteria for exclusion included urine protein >1 g/d and creatinine >1.5 mg/dL, potassium >5.5 mEq/L, and alanine aminotransferase >2.5 times the upper limit of normal. Institutional review board approval was received by the Partners

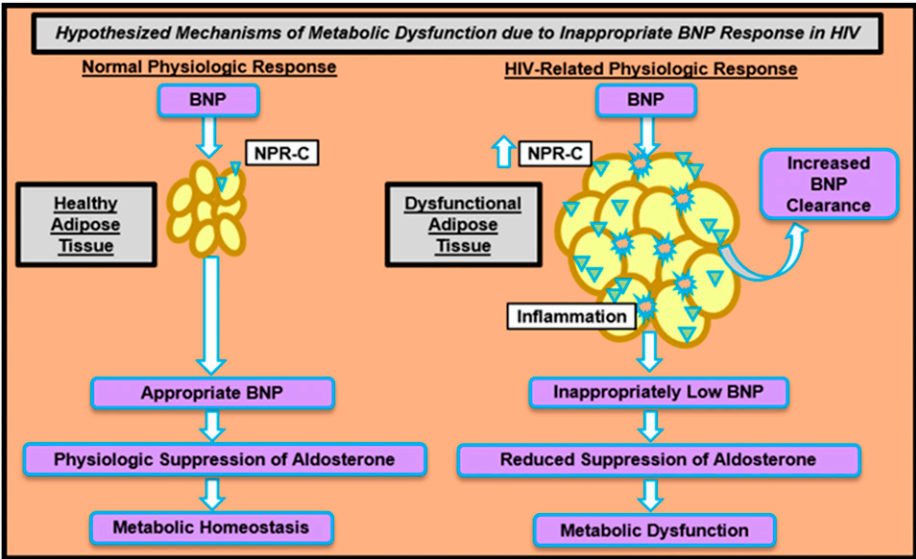


Figure 1. Hypothesized mechanisms of metabolic dysfunction via inappropriate cardiac natriuretic peptide feedback among HIV-infected individuals. HIV-infected individuals with a clinical phenotype of excessive adiposity demonstrate increased aldosterone during an RAAS-activated state. BNP is a negative regulator of RAAS. Dysfunctional adipose tissue is highly inflamed and may be linked to upregulation of NPR-C. When bound to NPR-C, BNP is degraded and cleared. Relatively lower BNP may permit an exaggerated increase in aldosterone and could be detrimental to preventing metabolic dysfunction. Appropriate BNP response among individuals with healthy adipose tissue may contribute to maintenance of metabolic homeostasis through physiologic suppression of aldosterone. Triangular structures represent NPR-C and star-like structures represent the inflammatory milieu.

Human Research Committee to perform this study, and individual informed consent was obtained.

Body composition phenotyping

Body mass index (BMI) was calculated at the time of study enrollment by using height and weight. The iliac crest served as the anatomic reference to standardize waist circumference measurements. Body adiposity index (BAI) was calculated as (hip circumference taken at the broadest location/height^{1.5}) – 18 (3). Magnetic resonance images were acquired by using an axial T1-weighted, fat-suppressed pulse sequence at the L4 vertebral body. Following image acquisition, an offline analysis of tracings was performed by using commercial software (Vitrak; eFilm/Merge, Chicago, IL) to quantitate abdominal visceral adipose tissue and subcutaneous adipose tissue area.

Standardized low-sodium diets to stimulate RAAS activation

After the baseline visit, a standardized 6-day low-sodium diet (10 ± 2 mEq Na⁺, 100 ± 2 mEq K⁺, and 1000 ± 50 mg Ca²⁺) was prepared by the Brigham and Women's Hospital Center for Clinical Investigation Metabolic Phenotyping Core to stimulate RAAS activation. Low sodium balance was achieved if the urine sodium was estimated to be <50 mEq/24 hours during the visit. A formal 24-hour urine sodium collection was obtained at the visit and paired with measurement of the urine creatinine to assess adequacy of the sampling.

Cardiac NP and RAAS characterization

Serum atrial natriuretic peptide (ANP; sensitivity, 1.02 pg/mL; intraassay variability $<10\%$; interassay variability $<15\%$) and brain natriuretic peptide (BNP; sensitivity, 1.66 pg/mL; intraassay variability $<10\%$; interassay variability $<15\%$) were measured via enzyme-linked immunosorbent assay (Ray Biotech, Norcross, GA). Serum amino terminal pro B-type NP (NT-proBNP), (sensitivity, 5 pg/mL) was measured by using the Cobas electrochemiluminescence immunoassay technique (Roche Diagnostics, Indianapolis, IN) through a clinical diagnostic laboratory. Data evaluating RAAS activation in relation to visceral fat among the same participants were reported in a prior publication (1). Data assessing cardiac neurohormones have not previously been analyzed. Serum aldosterone (sensitivity, 2.5 ng/dL; precision, 4% to 10%) was measured by solid-phase radioimmunoassay by the Coat-A-Count method (Diagnostics Products Corp, Los Angeles, CA). Plasma renin activity (PRA) was assayed by using the GammaCoat (¹²⁵I) radioimmunoassay kit (sensitivity, 0.01 ng/mL/h; precision $<10\%$; DiaSorin, Brea, CA). Blood collection for cardiac neurohormones, RAAS parameters, and all other metabolic indices were obtained after participants underwent a 12-hour fast following the 6-day standardized low-sodium diet. Comparative baseline BNP measures were also obtained during an *ad libitum* sodium diet. In addition, participants were asked to lie supine overnight to standardize posture effects for all laboratories.

Metabolic and HIV-related parameters

Creatinine, potassium, glucose, and total cholesterol were measured using standard techniques. Insulin was assayed with the Access immunoassay system (Beckman Coulter). Insulin resistance was calculated by using the homeostatic model assessment (HOMA-IR) as follows: [fasting glucose (mg/dL) \times fasting insulin

(mU/L)]/405. HIV testing was performed by enzyme-linked immunosorbent assay and confirmed by Western blot. HIV viral load was assessed by ultrasensitive reverse transcriptase polymerase chain reaction (COBAS Amplicor; Roche, Burlington, NC). CD4⁺ T cell counts were determined by flow cytometry.

Statistical analysis

The Shapiro-Wilk test was used to assess the distribution of variables. Data are presented as mean \pm standard error of the mean if normally distributed or median [interquartile range (IQR)] if not normally distributed. Categorical variables are reported as proportions. Between-group comparisons (HIV-infected or non-HIV-infected) were made by using the Student *t* test. Non-normally distributed variables were log-transformed to establish a normal distribution. Pearson correlation coefficient was used to perform linear regression in relation to cardiac NPs by HIV status. A four-group comparison by overweight BMI category (BMI <25 kg/m² or ≥ 25 kg/m²) was assessed by using analysis of variance, after appropriate log transformation, to assess independent effects of HIV status and BMI on cardiac NPs. BMI was selected as the body composition parameter for stratification given its well-established clinical categories. To represent the data in a clinically relevant manner, non-normally distributed variables are reported as values before log transformation, and the *P* value reported is based on the appropriate statistical test applied to the log-transformed values where noted. Determinants of serum aldosterone were evaluated in multivariate regression modeling performed in the HIV group. Statistical significance was defined as $P \leq 0.05$. All statistical analyses were performed by using SAS JMP software, version 12.0 (SAS Institute, Cary, NC).

Results

Baseline demographic and clinical characteristics

Both HIV-infected and non-HIV-infected groups were of similar age and sex. Most individuals with HIV had a long-term history of exposure (18 ± 1 years) and ART use (11 ± 1 years) and demonstrated stable immunological control; the mean CD4⁺ count was 571 ± 73 cells/ μ L and mean viral load was 1.77 ± 0.19 copies/mL. The most common protease inhibitor and nucleoside/nucleotide reverse transcription inhibitor used were ritonavir and tenofovir, respectively, each by 50% of patients (see Supplemental Table 1 for additional PI and NRTI use). Measures of body composition were overall similar between HIV-infected and non-HIV-infected individuals with respect to iliac waist circumference (94 ± 3 vs 89 ± 4 cm), BMI (26 ± 1 vs 25 ± 1 kg/m²), BAI ($48\% \pm 3\%$ fat vs $44\% \pm 3\%$ fat), visceral adipose tissue [134 (IQR, 56, 188) vs 140 (IQR, 84, 184) cm²], and subcutaneous adipose tissue [209 (IQR, 107, 342) vs 213 (IQR, 122, 269) cm²] (all $P \geq 0.05$). The HIV-infected group appeared to have worse HOMA-IR, but this parameter was not statistically different from that in the non-HIV-infected group. Overall, individuals demonstrated normal renal function and potassium (Supplemental Table 2)

Characterization of cardiac NPs and RAAS among HIV-infected and non-HIV-infected individuals

During the RAAS-activated state, BNP [60 (IQR, 44, 152) vs 196 (IQR, 91, 251) pg/mL; $P = 0.04$] was significantly lower, and ANP [87 (IQR, 54, 138) vs 145 (IQR, 97, 264) pg/mL; $P = 0.07$] tended to be lower among HIV-infected vs non-HIV-infected individuals. In contrast to the biologically active BNP, the biologically inactive prohormone NT-proBNP was not significantly different between groups [10 (IQR, 7, 32) vs 13 (IQR, 4, 19) pg/mL; $P = 0.36$ in HIV-infected vs non-HIV-infected] during RAAS activation. HIV-infected individuals demonstrated increased serum aldosterone [13.8 (IQR, 9.7, 30.9) vs 9.2 (IQR, 7.6, 13.6) ng/dL; $P = 0.03$] compared with non-HIV-infected individuals. Other related parameters of the RAAS, including PRA, 24-hour urine sodium, and mean arterial pressure (MAP), did not differ between groups on the low-sodium controlled diet (Table 1).

Because of its significance during RAAS activation, BNP was further characterized during an *ad libitum* sodium diet to confirm this unique physiology in HIV. BNP [108 (IQR, 88, 134) vs 149 (IQR, 115, 546) pg/mL; $P = 0.03$] was also significantly reduced during baseline physiologic conditions in HIV-infected vs non-HIV-infected groups. Both groups demonstrated similar RAAS parameters, urine sodium, and MAP on the *ad libitum* sodium diet.

Relationships with cardiac NPs among HIV-infected and non-HIV-infected individuals

In the HIV-infected group, BNP was significantly and inversely related to multiple indices of body composition [iliac waist circumference: $r = -0.46$ ($P = 0.04$); BMI: $r = -0.55$ ($P = 0.01$), BAI: $r = -0.49$ ($P = 0.03$)], metabolic parameters [total cholesterol: $r = -0.44$ ($P = 0.05$), HOMA-IR: $r = -0.44$ ($P = 0.05$), MAP: $r = -0.44$ ($P = 0.05$)], and RAAS components [serum aldosterone: $r = -0.49$ ($P = 0.03$)] [Table 2; Fig. 2(a)–2(c)], whereas no relationships with ANP were demonstrated. In

addition, no significant correlations were demonstrated to either cardiac NPs among non-HIV-infected individuals during RAAS-activated conditions [Table 2; Fig. 2(d)–2(f)].

Effects of HIV status and BMI on BNP

A four-group comparison was made after individuals were stratified by HIV status and above and below BMI 25 kg/m² (overweight category). BNP decreased significantly across groups, being highest in non-HIV-infected individuals with BMI <25 kg/m² and lowest in the HIV-infected individuals with BMI ≥25 kg/m² [238 (IQR, 77, 935), 193 (IQR, 78, 206), 125 (IQR, 49, 157), and 52 (IQR, 31, 63)] pg/dL in non-HIV-infected persons with BMI <25 kg/m² ($n = 5$), non-HIV-infected persons with BMI ≥25 kg/m² ($n = 5$), HIV-infected persons with BMI <25 kg/m² ($n = 11$), and HIV-infected persons with BMI ≥25 kg/m² ($n = 9$), respectively (overall $P = 0.01$) (Fig. 3).

Relationship of BNP to serum aldosterone among HIV-infected individuals during RAAS activation

In assessing for significant mediators of serum aldosterone (overall model $r^2 = 0.59$; $P = 0.007$) in HIV-infected persons using multivariate modeling, BNP (β estimate = -0.3545 ; $P = 0.04$) remained a negative independent predictor, and PRA (β estimate = 0.4824 ; $P = 0.005$) a positive independent predictor, of serum aldosterone after additionally controlling for 24-hour urine sodium and MAP (Supplemental Table 3). In additional modeling controlling for HOMA-IR and serostatus (overall model $r^2 = 0.22$; $P = 0.03$), HIV serostatus was a significant predictor of reduced BNP (β estimate = -0.1681 ; $P = 0.03$), and in contrast HOMA-IR was not significant in this model (β estimate = -0.2196 ; $P = 0.29$).

Discussion

This study investigated cardiac NPs in HIV by using a well-controlled physiologic protocol to activate the RAAS. Few studies in non-HIV-infected persons have evaluated cardiac NPs under strict physiologic conditions

Table 1. Cardiac NPs During RAAS Activation Among Non-HIV-Infected and HIV-Infected Individuals

| Variable | Non-HIV-Infected (n = 10) | HIV-Infected (n = 20) | P Value ^a |
|---------------------------|---------------------------|-----------------------|----------------------|
| ANP (pg/mL) | 145 (97, 264) | 87 (54, 138) | 0.07 |
| BNP (pg/mL) | 196 (91, 251) | 60 (44, 152) | 0.04 |
| NT-proBNP (pg/mL) | 13 (4, 19) | 10 (7, 32) | 0.36 |
| PRA (ng/mL/h) | 1.8 (1.1, 3.2) | 2.5 (1.4, 3.5) | 0.98 |
| Serum aldosterone (ng/dL) | 9.2 (7.6, 13.6) | 13.8 (9.7, 30.9) | 0.03 |
| Urine sodium (mmol/24 h) | 18.2 ± 2.3 | 23.8 ± 4.5 | 0.28 |
| MAP (mm Hg) | 85 ± 2 | 84 ± 1 | 0.86 |

Unless otherwise noted, data reported as mean ± standard error of the mean or median (interquartile range).

^aTo represent the data in a clinically relevant manner, non-normally distributed variables are reported as values before log transformation, and the P value reported is based on the appropriate statistical test applied to the log-transformed values.

Table 2. Relationships of Cardiac NPs Among Non-HIV-Infected and HIV-Infected Individuals During RAAS Activation

| Body Composition and Metabolic Parameters | Non-HIV-Infected | | | | HIV-Infected | | | |
|---|------------------|----------------|-----------------|----------------|-----------------|----------------|-----------------|----------------|
| | log ANP (pg/dL) | | log BNP (pg/dL) | | log ANP (pg/dL) | | log BNP (pg/dL) | |
| | <i>r</i> | <i>P</i> Value | <i>r</i> | <i>P</i> Value | <i>r</i> | <i>P</i> Value | <i>r</i> | <i>P</i> Value |
| Iliac waist circumference, cm | 0.24 | 0.50 | 0.17 | 0.64 | 0.18 | 0.45 | −0.46 | 0.04 |
| BMI, kg/m ² | 0.03 | 0.93 | 0.21 | 0.56 | 0.14 | 0.56 | −0.55 | 0.01 |
| BAI, % fat | 0.15 | 0.67 | 0.15 | 0.68 | 0.12 | 0.61 | −0.49 | 0.03 |
| log VAT, cm ² | −0.19 | 0.59 | 0.04 | 0.91 | 0.16 | 0.50 | −0.26 | 0.26 |
| log SAT, cm ² | 0.24 | 0.51 | 0.38 | 0.28 | 0.14 | 0.56 | −0.36 | 0.12 |
| log TAT, cm ² | 0.09 | 0.81 | 0.26 | 0.46 | 0.18 | 0.45 | −0.42 | 0.06 |
| Total cholesterol, mg/dL | 0.31 | 0.38 | 0.22 | 0.54 | 0.06 | 0.81 | −0.44 | 0.05 |
| log HOMA-IR | 0.07 | 0.85 | 0.14 | 0.69 | 0.14 | 0.57 | −0.44 | 0.05 |
| MAP, mm Hg | 0.07 | 0.85 | 0.50 | 0.14 | 0.06 | 0.80 | −0.44 | 0.05 |
| log Serum aldosterone, ng/dL | −0.41 | 0.24 | −0.01 | 0.98 | 0.28 | 0.23 | −0.49 | 0.03 |

Relationships were assessed by Pearson correlation coefficient.
Abbreviations: SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

(4, 5) and to our knowledge have not performed a comprehensive evaluation to assess the interaction between NP and aldosterone hormone physiology, controlling for diet and posture.

Under conditions stimulating RAAS activation, we would expect BNP to increase in response to the rise in aldosterone levels, functioning as a negative regulator of RAAS. Indeed, acute infusions of BNP in human physiology studies have suppressed aldosterone (6). This normal physiology was clearly demonstrated among the non-HIV-infected individuals, who overall had increased BNP during the RAAS-activated state. Instead, we demonstrate contrasting physiology among the HIV-infected individuals, such that BNP was relatively decreased among HIV-infected individuals compared with non-HIV-infected individuals during the RAAS-activated state. These data suggest dysfunctional feedback between aldosterone and the cardiac NP system in HIV, leading to an exaggerated rise in aldosterone. This pathophysiology, which reflects an inability of cardiac NPs to counterregulate when perturbed in a state of RAAS activation, may be detrimental to the prevention of long-term cardiac and metabolic complications in HIV (Fig. 1).

Few studies in HIV have evaluated NPs. We measured the mature forms of BNP and ANP, which are the active forms of the hormone, rather than the inactive forms of the hormone specific to the *n*-terminal fragments. Results from the SMART study demonstrated that HIV-infected individuals with a CVD event had higher levels of NT-proBNP than did HIV-infected individuals without a CVD event (7). Our data differ from findings of the SMART study, in which NPs were not measured under strict controlled RAAS conditions, in comparison with a

non-HIV-infected population, or stratified by body composition as in our current study. In addition, we studied only a well-treated population receiving continuous ART. A prior study from our group comparing NT-proBNP among HIV-infected and non-HIV-infected individuals demonstrated no difference between groups when measured during uncontrolled physiologic conditions (8). The SATURN-HIV study did show an increase in NT-proBNP in HIV-infected compared with non-HIV-infected persons, which was attenuated with statin use. Interestingly, the attenuation in NT-proBNP was associated with worsening HOMA-IR and increased peripheral fat (9), similar to our data, and also suggest that relatively lower NT-proBNP could have metabolic detriment in HIV.

ANP and BNP exert their action by primarily binding to NP receptor (NPR)-A and have lower affinity for NP receptor B. In addition, there are NP clearance receptors (NPR-C), which when bound to ANP and BNP result in NP internalization and degradation. In contrast, the biologically inactive prohormone NT-proBNP is not cleared by the NPR-C. NP receptors are well known to be expressed abundantly in the adipose depot (10), and NPR-C may be more widely upregulated in obesity and in the presence of insulin, presumably because of excess adipose depots (11, 12). As such, an imbalance between the ratio of NPR-A and NPR-C in obesity has been described (13) and is specifically localized to the adipose depot and associated with inflammation (14). In support of this, NPR-C is downregulated with weight reduction (15).

We took advantage of the unique interaction between BNP and NT-proBNP with NPR-C to understand whether reduced BNP in HIV might be related to

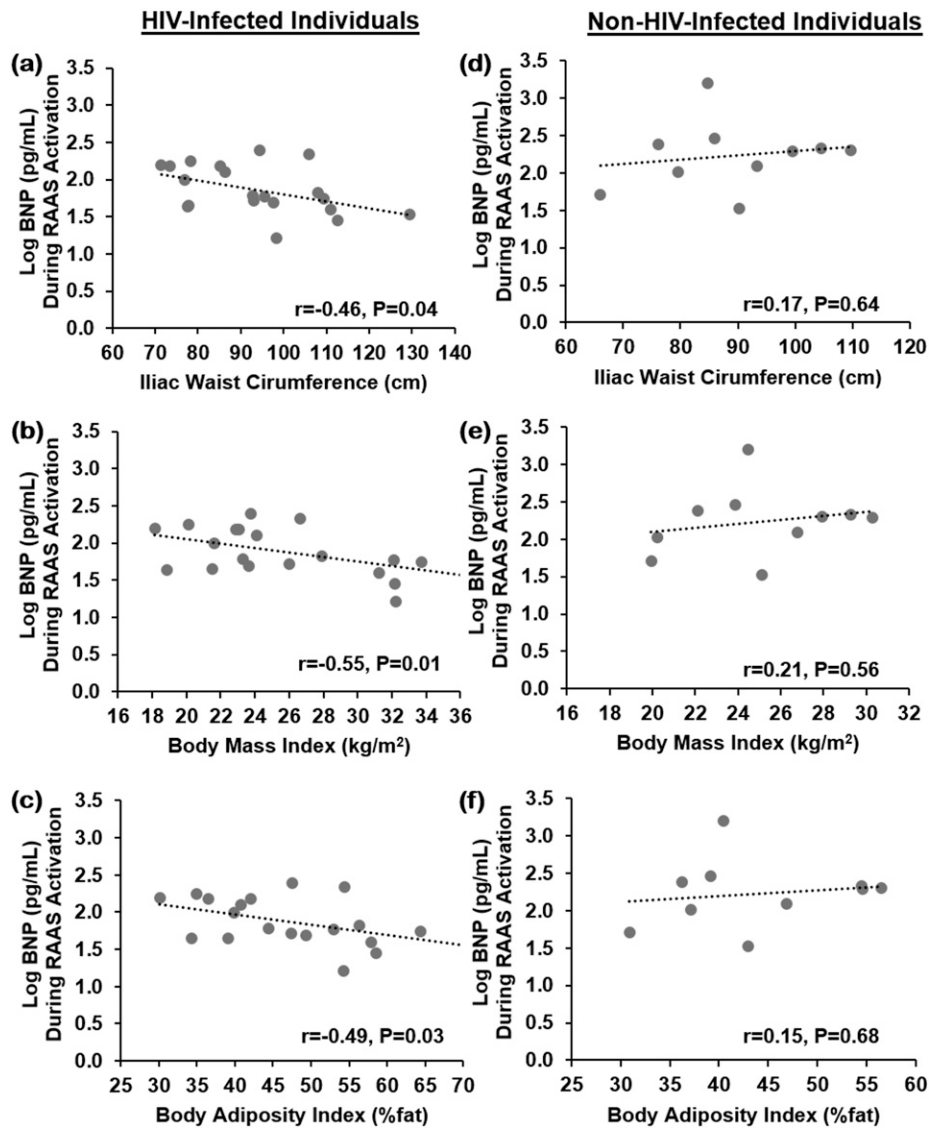


Figure 2. Relationship between BNP (pg/mL) and measures of body composition [iliac waist circumference (cm), BMI (kg/m²), and BAI (%fat)] among HIV-infected individuals (a–c) and non-HIV-infected individuals (d–f) during the RAAS-activated state. Data were analyzed by using Pearson correlation coefficient and are represented here as linear regression.

enhanced clearance or reduced hormone secretion. If we were to attribute the mechanism to reduced hormone secretion, we would expect that both BNP and NT-proBNP would be reduced in HIV. In contrast, we demonstrate similar NT-proBNP levels regardless of serostatus, whereas BNP is reduced in HIV during an RAAS-activated state. In this regard, we postulate that the difference in BNP may be due to enhanced clearance in HIV. As NPR-C modulates NP metabolism, greater NPR-C receptor expression in the adipose depot may dampen RAAS suppression through NP reduction, thereby permitting a type of aldosterone escape. By this mechanism, it is conceivable that a maladaptive interplay between the RAAS and NP in states of excess adiposity may contribute to metabolic burden in HIV.

With regard to body composition, an inverse correlation of BNP was demonstrated among the HIV population

in this study. We did not see any relationships to ANP. In a large community sampling, aldosterone correlated with central obesity, and aldosterone levels in the highest tertile, although within normal range, were associated with lower cardiac NPs and greater mortality (5). Results from a clinical study investigating peptide physiology following intervention with gastric bypass surgery show that weight loss was related to increased cardiac NPs (4). Although we did not see a relationship specifically between BNP and the visceral depot, other similar measures, such as BMI, waist circumference, and BAI, were inversely related to BNP in the HIV-infected group and serve as clinical surrogates for excess adipose and likely fat redistribution. In contrast, we saw no relationship between BNP and body composition among the non-HIV-infected group.

Cardiac NPs also have a critical role in mediating lipolysis in the adipose depot aside from suppressing

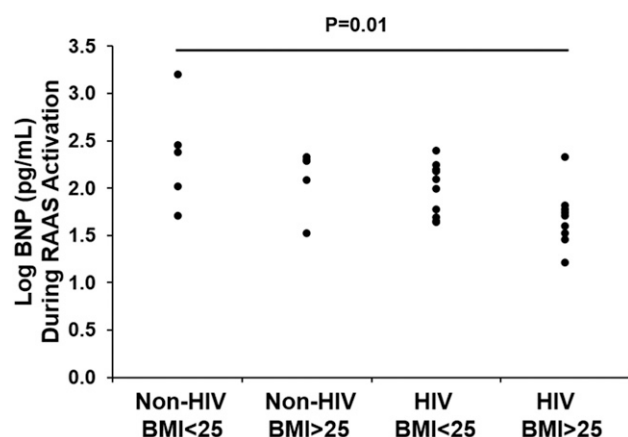


Figure 3. Comparison of BNP (pg/mL) during the RAAS-activated state among HIV-infected and non-HIV-infected individuals stratified by above and below overweight BMI. *P* value reported is based on the appropriate statistical test applied to the log-transformed values.

aldosterone. In this regard, adipose-tissue specific knock-out murine models of the NPR-C show that these mice develop resistance to obesity and ectopic fat accumulation and benefit from greater insulin sensitivity (16, 17). We did see an inverse correlation of BNP to HOMA-IR in the HIV-infected group during the RAAS-activated state. In our study, BNP remained different in HIV-infected and non-HIV-infected persons, after controlling for HOMA-IR. These data suggest that differences in BNP were not due to any differences in insulin sensitivity between the groups.

Our data suggest a mechanism of increased aldosterone in HIV via reduced BNP and prompt the question of whether RAAS blockade may be of use in this population. Studies in non-HIV settings suggest maximal cardiovascular benefits of spironolactone and angiotensin-receptor blockade in populations with the lowest BNP (18, 19). In our study, we stratified non-HIV-infected and HIV-infected individuals across the weight spectrum and demonstrate that BNP is lowest in the HIV-infected/overweight category and increases gradually to the non-HIV-infected/normal-weight category. Taken together, these data suggest that the HIV population, especially those with excessive adiposity, may be a subgroup that could benefit from RAAS blockade.

Limitations of this study include the small sample size. Nonetheless, we demonstrate reduced NP in the context of RAAS activation in HIV. Moreover, we show that several adverse measures of body composition were inversely related to NP. Although on the basis of the current data we can only hypothesize that the adipose depot is dysfunctional, future investigations should evaluate tissue-specific expression of adipocyte NPR-C to reveal a potential mechanism for reduced NP among HIV-infected individuals. Moreover, detailed phenotyping of the subcutaneous and visceral adipose depots in a

larger cohort will permit us to discern whether this physiology is distinct to fat redistribution or compounded by generalized obesity, which is increasing in prevalence in the HIV population.

In summary, these data provide further insight into a potential mechanism for RAAS activation in HIV, which could be driven by enhanced NP clearance from the adipose depot. Studies have investigated neprilysin inhibition, which blocks degradation of NPs, along with angiotensin-receptor blockade in heart failure (20–22), and few studies evaluating this therapeutic strategy in obesity have demonstrated improved glucose and lipid metabolism (23). As such, a dual strategy that targets RAAS blockade and augments the cardiac NP system may have synergistic effects to reduce cardiometabolic disease in HIV. In this regard, an ongoing study will begin to evaluate the effects on mineralocorticoid receptor blockade on cardiac NPs (the MIRACLE HIV study, NCT02740179) among HIV-infected individuals with excess visceral adiposity.

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