CARDIAC BNP DEFICIENCY RELATES TO EXCESS ADIPOSITY AND METABOLIC PERTURBATIONS IN HIV

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Background

•Well-treated persons living with HIV (PLWH) at risk for fat dysfunction demonstrate renin-angiotensin-aldosterone system(RAAS) dysregulation in association with insulin resistance as well markers of generalized inflammation and immune activation.

•Natriuretic peptides (NP) are key neurohormones which serve as negative regulators on the RAAS and play a role in preserving cardiac structure and metabolic homeostasis.

•The obese population demonstrate reduced cardiac NPs relative to the non-obese population. This decrease in NPs in obesity has been attributed to excess adiposity and may provide an underlying mechanism for the demonstrable advanced metabolic risk in this group.

•As NP receptor C (NPR-C) modulates NP metabolism, greater NPR-C receptor expression in the adipose depot may dampen RAAS suppression through NP reduction.

Objectives

We hypothesized based on known cardiac NP physiology in obesity that relatively reduced cardiac NPs during a RAAS activated state would be associated with unfavorable body composition and metabolic indices in HIV, a model of acquired fat redistribution.

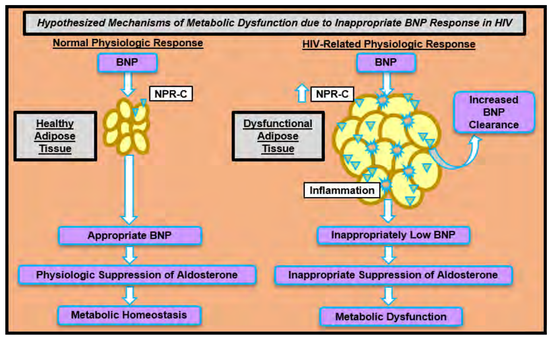


Figure 1. Hypothesized mechanisms of metabolic dysfunction via inappropriate cardiac natriuretic peptide feedback. HIV-infected individuals with a clinical phenotype of excessive adiposity demonstrate increased aldosterone during a RAAS activated state. Brain natriuretic peptide (BNP) is a negative regulator of RAAS. Dysfunctional adipose tissue is highly inflamed and may be linked to upregulation of natriuretic peptide receptor C (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.

Methods

Study Participants and Design

•Inclusion criteria for all individuals: age ≥ 18 and ≤ 65 years
•Inclusion criteria for PLWH: stable ART regimen ≥ 3 months
•Major exclusion criteria for all individuals: history of CVD (including CHF), HTN (>140/90) and DM; 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; urine protein >1 gm/day, Cr >1.5 mg/dL, K > 5.5 mEq/L, and ALT>2xULN

Body Composition Phenotyping

Body mass index (BMI) was calculated using height and weight. The iliac crest served as the anatomic reference to standardize waist circumference. Body adiposity index (BAI) was calculated as [hip circumference taken at the broadest location/(height)$^{1.5}$]-18. MRI images were acquired using an axial T1-weighted fat suppressed pulse sequence at the L4 body to quantitate abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).

Metabolic Evaluation

A standardized 6-day low sodium diet (10±2 mEq Na+, 100±2 mEq K+, and 1000±50 mg Ca2+) was prepared to stimulate RAAS activation. Low sodium balance was achieved if the urine sodium was estimated to be less than 50 mEq/24 hr during the visit.

Laboratory Assessment

Cardiac neurohormones, RAAS parameters, and all other metabolic indices were obtained after individuals 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, individuals were asked to lie supine overnight to standardize posture effects for all laboratories.

Methods (cont.)

Statistical Analysis

Data are presented as mean ± SEM if normally distributed or median [IQR] if not normally distributed. Categorical variables are reported as proportions. Between group comparisons (HIV or non-HIV) were made using the Student's t-test. Non-normally distributed variables were log-transformed to establish a normal distribution. Pearson's 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<or ≥25 kg/m^2) was assessed using ANOVA, after appropriate log transformation, to assess independent effects of HIV status and BMI. For purposes of representing the data in a clinically relevant manner, non-normally distributed variables are reported as values prior to log transformation, and the P value reported is based on the appropriate statistical test applied to the log transformed values. Statistical significance was defined as P<0.05. All statistical analyses were performed using SAS JMP (version 12.0).

Results

Table 1. Baseline Demographics and Clinical Characteristics of Non-HIV and HIV-infected Individuals

	Non-HIV-Infected (n=10)	HIV-Infected (n=20)	P Value
Demographics			
Age (years)	52±2	49±2	0.34
Race (%)			0.27
Caucasian	80	45	
African American	20	35	
Other	0	20	
Male Sex (%)	70	65	0.78
HIV Parameters			
CD4$^+$ T cell count (cells/mL)	N/A	571±73	--
Log HIV RNA Viral Load (copies/mL)	N/A	1.77±0.19	--
Duration HIV (years)	N/A	18±1	--
Duration ART use (years)	N/A	11±1	--
Current PI use (%)	N/A	60	--
Current NRTI use (%)	N/A	90	--
Current NNRTI use (%)	N/A	25	--
History of HCV infection (%)	0	20	0.13
Body Composition and Metabolic Parameters			
Iliac Waist Circumference (cm)	89±4	94±3	0.40
BMI(kg/m^2)	25±1	26±1	0.50
BAI (%fat)	44±3	48±3	0.29
VAT (cm^2)	140 [84,184]	134 [56,188]	0.98
SAT (cm^2)	213 [122,269]	209 [107,342]	0.91
TAT (cm^2)	342 [245, 474]	385 [233, 540]	0.88
Total Cholesterol (mg/dL)	173±11	181±8	0.57
HOMA-IR	0.59 [0.35,1.59]	0.98 [0.58,1.85]	0.21
Creatinine (mg/dL)	0.79±0.04	0.85±0.03	0.27
Potassium (mmol/L)	4.2±0.1	4.1±0.0	0.21

Table 2. Cardiac Natriuretic Peptides during RAAS Activation among Non-HIV and HIV-Infected Individuals

	Non-HIV-Infected (n=10)	HIV-Infected (n=20)	P Value
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/hr)	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/24Hr)	18.2 ± 2.3	23.8 ± 4.5	0.28
MAP (mmHg)	85 ± 2	84 ± 1	0.86

Table 3. Relationship of BNP Among Non-HIV and HIV-Infected Individuals During RAAS Activation

	Non-HIV Infected		HIV-Infected	
	log BNP (pg/dL)		log BNP (pg/dL)	
	r	P	r	P
Body Composition and Metabolic Parameters				
Iliac Waist Circumference (cm)	0.17	0.64	-0.46	0.04
BMI (kg/m^2)	0.21	0.56	-0.55	0.01
BAI (%fat)	0.15	0.68	-0.49	0.03
log VAT (cm^2)	0.04	0.91	-0.26	0.26
log SAT (cm^2)	0.38	0.28	-0.36	0.12
log TAT (cm^2)	0.26	0.46	-0.42	0.06
Total Cholesterol (mg/dL)	0.22	0.54	-0.44	0.05
log HOMA-IR	0.14	0.69	-0.44	0.05
MAP (mmHg)	0.50	0.14	-0.44	0.05
log Serum Aldosterone (ng/dL)	-0.01	0.98	-0.49	0.03

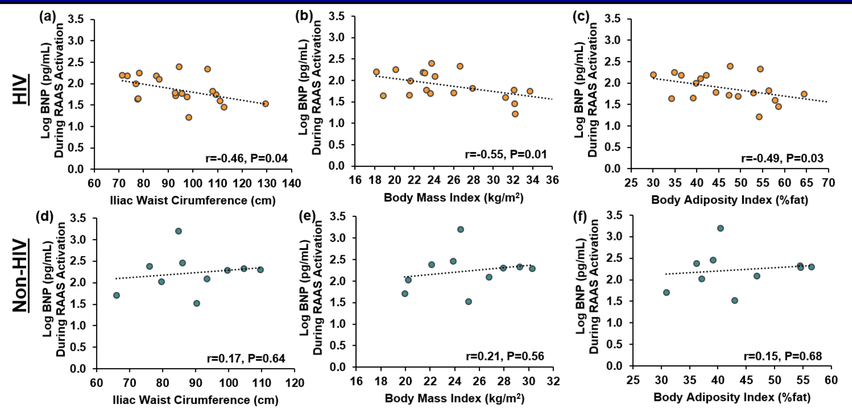


Figure 2. Relationship between BNP (pg/mL) and measures of body composition [iliac waist circumference (cm), body mass index (BMI, kg/m^2), and body adiposity index (BAI, %fat)] among HIV-infected individuals (a-c) and non-HIV-infected individuals (d-f) during the RAAS activated state. Data were analyzed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

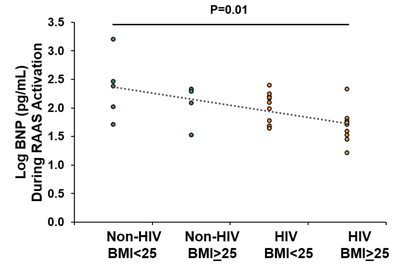


Figure 3. Comparison of BNP (pg/mL) during the RAAS activated state among HIV-infected and non-HIV-infected individuals stratified by above and below overweight BMI. P value reported is based on the appropriate statistical test applied to the log transformed values.

Summary

• During the RAAS activated state, BNP (P=0.04) was significantly lower, and ANP (P=0.07) tended to be lower among HIV vs. non-HIV. In contrast to the biologically active BNP, the biologically inactive prohormone NT-proBNP was not significantly different between groups (P=0.36) during RAAS activation. (Table 2)

•BNP was further characterized during an *ad libitum* sodium diet to confirm this unique physiology in HIV. BNP (108 [88,134] vs. 149 [115,546] pg/mL, P=0.03) was also significantly reduced during baseline physiologic conditions in HIV vs. non-HIV.

•BNP was significantly and inversely related to multiple indices of body composition [iliac waist circumference, BMI, BAI] and metabolic parameters [total cholesterol, HOMA-IR, MAP], as well as RAAS components among the HIV group. (Table 3, Figure 2)

•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[77, 935], 193[78, 206], 125[49, 157], and 52[31, 63] pg/dL in non-HIV/BMI<25 (n=5), non-HIV/BMI>25 (n=5), HIV/BMI<25 (n=11), and HIV/BMI>25 (n=9), respectively (overall P=0.01)). (Figure 3)

•Further stratification among the HIV group into 3 standardized BMI categories, under/normal weight(BMI<25), overweight(25<BMI<30), and obese(BMI>30), was also significant for a reduction in BNP across increasing BMI (P=.01).

Conclusions

Relative BNP deficiency among PLWH with excess adiposity may contribute to RAAS dysregulation and potentially drive metabolic disease, such as insulin resistance. Novel strategies which block aldosterone and augment BNP may be potentially useful to reduce cardiometabolic risk in HIV.

NT-proBNP levels were similar regardless of serostatus, while BNP was reduced in HIV during a RAAS activated state. In this regard, we postulate that the difference in BNP may be due to enhanced clearance in HIV by the NPR-C.

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