Evaluation of Mineralocorticoid Receptor Antagonism on Changes in NT-proBNP Among Persons With HIV

Suman Srinivasa,1 Christopher deFilippi,2 Kathleen V. Fitch,1 Sanjna Iyengar,1 Grace Shen,1 Tricia H. Burdo,3 Allie R. Walpert,1 Teresa S. Thomas,1 Gail K. Adler,4 and Steven K. Grinspoon1

1Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA; 2INOVA Heart and Vascular Institute, Falls Church, VA 22042, USA; 3Department of Neuroscience, Lewis Katz School of Medicine at Temple University, Philadelphia, PA 19140, USA; and 4Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115, USA

ORCID numbers: 0000-0003-1950-4770 (S. Srinivasa); 0000-0001-6023-8764 (G. Shen); 0000-0002-6338-000X (S. K. Grinspoon).

Abbreviations: ART, antiretroviral therapy; BP, blood pressure; CV, coefficient of variation; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; MGH, Massachusetts General Hospital; MCP-1, monocyte chemoattractant protein-1; MR, mineralocorticoid receptor; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PWH, persons with HIV; RAAS, renin-angiotensin-aldosterone system.

Received: 6 October 2021; Editorial Decision: 12 November 2021; First Published Online: 19 November 2021; Corrected and Typeset: 10 December 2021.

Abstract

Subclinical myocardial dysfunction is prevalent among well-treated persons with HIV (PWH). We have previously demonstrated unique renin-angiotensin-aldosterone system physiology among PWH with metabolic dysregulation. Mineralocorticoid receptor blockade may be a targeted treatment strategy for subclinical heart disease in PWH. Forty-six PWH were randomized to receive either eplerenone 50 mg daily or placebo in a 6-month randomized, double-blinded, placebo-controlled trial. We assessed changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of cardiac stretch, under controlled posture and dietary conditions. The eplerenone- and placebo-treated groups demonstrated a long duration of HIV with good immunological control. NT-proBNP levels were similar between the groups at baseline (41.1 [20.2, 97.9] vs 48.9 [29.2, 65.4] ng/L, P = .80) and decreased significantly more in the eplerenone- vs placebo-treated groups after 6 months (change NT-proBNP -9.6 [-46.8, 0.3] vs -3.0 [-17.0, 39.9] ng/L, P = .02 for comparison of change between groups). Decreases in NT-proBNP were independent of changes in systolic and diastolic blood pressure, and related to decreases in high-sensitivity C-reactive protein (ρ = 0.32, P = .05) and inversely to increases in serum aldosterone (ρ = -0.33, P = .04) among all participants. Treatment with eplerenone for 6 months vs placebo significantly decreases NT-proBNP levels among PWH, independent
of eplerenone’s known blood pressure-lowering effects. Further studies should elucidate whether lowering NT-proBNP in this at-risk metabolic population with subclinical heart disease will offer cardioprotection.

**Clinical Trial Registration:** NCT01405456

**Key Words:** HIV, renin-angiotensin-aldosterone system, eplerenone, NT-proBNP

The spectrum of cardiovascular disease (CVD) affecting the HIV population has grown to include myocardial dysfunction [1]. Prior studies suggest that approximately 50% to 60% of the HIV population without overt clinical symptoms is expected to have underlying changes in cardiac structure and function [2, 3]. We have previously shown altered renin-angiotensin-aldosterone system (RAAS) physiology in relation to metabolic disease and inflammation among people with HIV (PWH) [4]. Subsequently, in efforts to target this unique hormonal physiology, our group performed the first randomized clinical trial evaluating mineralocorticoid receptor (MR) antagonism in PWH [5]. MR activation may promote changes in the structure and function of the myocardium [6-9], and targeting of the RAAS system may improve critical pathways of inflammation and cardiac function. Few investigations of MR blockade among populations with subclinical myocardial dysfunction have been performed [10-13].

N-terminal pro-B-type natriuretic peptide (NT-proBNP), the prohormone of brain natriuretic peptide, is a biomarker of cardiac stretch and strain that can be diagnostic of heart failure and predict CVD mortality [14-16]. Some studies have shown NT-proBNP may be elevated in PWH [17, 18]. The natriuretic peptide hormonal system has critical feedback interactions with the RAAS hormone system to maintain sodium and volume homeostasis. In the current study, we sought to evaluate for the first time the effect of eplerenone on NT-proBNP among PWH, a population with RAAS dysregulation, to begin to understand the potential of MR blockade to improve myocardial dysfunction in PWH.

**Methods**

**Participants**

PWH, representing the general HIV population on antiretroviral therapy (ART), were recruited between January 2012 and May 2017 at Massachusetts General Hospital (MGH) from the greater Boston area to enroll in a 6-month randomized, placebo-controlled trial to investigate the effects of eplerenone on insulin sensitivity [5]. In the current study, we leveraged this cohort to understand treatment effects of eplerenone on NT-proBNP in PWH. Data on NT-proBNP have not previously been published from this study. Participants were required to be 30 to 65 years old and have a history of HIV infection ≥ 5 years treated with continuous ART for at least 12 months before enrollment. Enrollment criteria were designed to ensure patients were on chronic ART, of a relevant age for subclinical CVD, and without a high likelihood of clinical heart disease. Additional inclusion criteria were increased abdominal girth based on National Cholesterol Education Program guidelines for waist circumference (> 102 cm in males and > 88 cm in females) to select for those who may have increased RAAS activation and for evidence of abnormal glucose homeostasis (impaired fasting glucose [glucose > 100 and < 126 mg/dL], impaired glucose tolerance [2-hour glucose > 140 and < 200 mg/dL], or fasting insulin >12 mIU/mL) based on oral glucose tolerance testing. Exclusion criteria included uncontrolled hypertension (systolic blood pressure [BP] ≥ 160 or diastolic blood pressure ≥ 100 mmHg), diabetes, known CVD including cardiomyopathy, and active pregnancy. In addition, current use of other medications targeting the RAAS pathway, potassium supplementation, strong CYP3A4 inhibitors, or St. John’s Wort (a CYP3A4 inducer) were not allowed. Serum potassium > 5.5 mEq/L, alanine aminotransferase > 2.5× the upper limit of normal, hemoglobin < 11 g/dL, creatinine > 1.5 mg/dL, or estimated glomerular filtration rate < 60 mL/min/1.73 m² were exclusionary laboratory values. All participants provided informed consent to participate. This study was approved by the Partners Human Research Committee.

**Standardized Sodium Diets to Normalize Conditions for RAAS at Baseline and 6 Months**

Before baseline studies, a 4-day food record intake was used to assess routine dietary sodium consumption. All participants were instructed by the nutritionist to supplement their usual diet with the appropriate number of broth packets (47.8 mEq Na⁺/packet) for 6 days to achieve a goal dietary sodium intake of 200 mEq/d. Twenty-four hour urine collections were evaluated for adherence to sodium intake.

**Laboratory Assessment at Baseline and 6 Months**

On the evening of day 6 of the sodium diet, participants were admitted to the MGH Translational and Clinical Research Center and instructed to fast for 12 hours and
lie supine overnight. On the following morning, a blood collection was performed. NT-proBNP was measured with the Cobas e602 (Roche Diagnostics, Indianapolis, IN). The measurement range for NT-proBNP was from 5.0 to 35,000 pg/mL; inter-assay coefficients of variance (CVs) ranged from 3.7% to 4.1% at values between 135 pg/mL and 4130 pg/mL. Serum aldosterone was evaluated using solid-phase radioimmunoassay by the Coat-A-Count method (sensitivity 2.5 ng/dL, Diagnostics Products, RRID:AB_2737007). Plasma renin activity was measured using the GammaCoat [\(^{125}\text{I}\)] radioimmunoassay kit (sensitivity 0.01 ng/mL/h, DiaSorin, RRID:AB_2736926). Plasma high-sensitivity C-reactive protein (hsCRP; R&D Systems, RRID:AB_2893119), monocyte chemoattractant protein-1 (MCP-1; R&D Systems, RRID:AB_2894843; https://scicrunch.org/resources/Antibodies/search?q=AB_2894843&l=AB_2894843), and high-sensitivity IL-6 (Invitrogen/Thermo Fisher, RRID:AB_2894844; https://scicrunch.org/resources/Antibodies/search?q=AB_2894844&l=AB_2894844) were quantified by ELISA.

Randomization and Blinding
A randomization key created by a biostatistician was provided only to the MGH Investigational Drug/Clinical Trials Pharmacy. The randomization was generated using the following strata: sex, age (< 45 or ≥ 45 years), and BP (< 140/90 or ≥ 140/90 mmHg) and used a permuted block algorithm with a random block size of either 2 or 4 with the goal of allocating 1:1 to eplerenone or matching placebo. Identical blinded capsules were created for both the eplerenone and placebo preparations by the pharmacy. Study participants, investigators, and other study staff were all blinded to the randomization.

Following acquisition of baseline data, a dose of 25 mg daily was initiated for 1 week, then titrated to 50 mg daily for the entirety of the study.

Lifestyle Counseling
Participants in both treatment arms received standardized lifestyle counselling over 6 months from a certified nutritionist at the MGH Translational and Clinical Research Center modelled after American Association of Clinical Endocrinologists and National Cholesterol Education Program-Adult Treatment Panel III guidelines and the Diabetes Prevention Program.

Safety Visits
Safety visits were conducted at 1 week, 2 weeks, 4 weeks, 2 months, and 3 months following randomization. Participants were interviewed for interval medical history and side effects. In addition, BP and laboratory values (serum creatinine, potassium, alanine aminotransferase, urine pregnancy test) were obtained. Participants were asked to return their unused study medication at scheduled safety visits and were provided with a new supply. The actual number of pills used was compared with the expected number of pills to be used to assess adherence. A Data and Safety Monitoring Board convened every 3 months for safety monitoring.

Statistical Analysis
Normality of variables was evaluated using the Shapiro-Wilk test. Variables with a normal distribution are reported as mean ± standard error of the mean, and variables with a nonnormal distribution are reported as median (interquartile range). Categorical variables are shown as proportions. Baseline and change between baseline and 6-month NT-proBNP values were compared between randomization groups using the Wilcoxon rank-sum test. Within randomization group changes between baseline and 6 months were assessed using the paired Wilcoxon signed-rank test. One participant was excluded as an outlier for a baseline NT-proBNP > 450 ng/L, diagnostic for pathologic disease. The sample size was calculated initially based on the primary endpoint of the prior study evaluating the effect of eplerenone on insulin sensitivity among PWH [5]. With 46 subjects, the current analysis had 80% power to detect a between-group difference of 0.8 SD in the endpoint of interest, in this case NT-proBNP. Univariate relationships were assessed by Spearman \(\rho\) test. Additional exploratory analyses using linear regression modeling were performed to assess whether treatment effects on NT-proBNP were independent of changes in BP. Statistical significance was determined to a 2-sided \(P < .05\). Analyses were performed using SAS JMP (version 15).

Results

Participant Flow
One hundred and four PWH were recruited for a study to assess the effects of mineralocorticoid receptor blockade on insulin sensitivity. Of those participants screened, 46 PWH were randomized to receive either eplerenone \((n = 25)\) or placebo \((n = 21)\). NT-proBNP values were not available in 4 participants who did not complete the study (eplerenone \(n = 3\) or placebo \(n = 1\)).

Baseline Demographics and Clinical Characteristics
Treatment arms (eplerenone vs placebo) did not differ by age \((49 ± 2 \text{ vs } 52 ± 1 \text{ years})\) or sex \((62 vs 70\% \text{ male})\). Race was similar though the percentage
of participants with Hispanic ethnicity tended to be higher in the eplerenone vs placebo arms (38 vs 15%, \( P = .09 \)). Clinical history of current hypertension (29 vs 35%), dyslipidemia (33 vs 25%), and tobacco use (24 vs 30%) was of similar proportions in the eplerenone- vs placebo-treated groups. The eplerenone- and placebo-treated groups demonstrated a long duration of HIV (19 [10, 24] vs 20 [14, 23] years) and ART therapy use (8 [3, 17] vs 8 [4, 18] years) with good immunological control (CD4\(^+\) T-cell count 624 ± 55 vs 619 ± 51 cells/μL). Diastolic BP tended to be higher among those randomized to placebo vs eplerenone (86 ± 2 vs 80 ± 2 mmHg). Other parameters of RAAS hormones, metabolic indices (systolic BP, lipids, HbA1c, and body composition) and markers of inflammation did not differ by randomization (Table 1).

Table 1. Baseline demographics and clinical characteristics of eplerenone- vs placebo-treated groups among persons with HIV

|                                    | Eplerenone-treated (n = 21) | Placebo-treated (n = 20) | \( P \) |
|------------------------------------|-----------------------------|--------------------------|--------|
| **Demographics**                   |                             |                          |        |
| Age, y                             | 49 ± 2                      | 52 ± 1                   | .19    |
| Race, %                            |                             |                          |        |
| Caucasian                          | 57                          | 40                       | .26    |
| African American                   | 38                          | 55                       | --     |
| Other                              | 5                           | 5                        | --     |
| Hispanic ethnicity, %              | 38                          | 15                       | .09    |
| Male, %                            | 62                          | 70                       | .58    |
| Current hypertension, %            | 29                          | 35                       | .66    |
| Current dyslipidemia, %            | 33                          | 25                       | .56    |
| Current tobacco use, %             | 24                          | 30                       | .65    |
| **HIV parameters**                 |                             |                          |        |
| CD4\(^+\) T-cell count, cells/μL  | 624 ± 55                    | 619 ± 51                 | .94    |
| CD8\(^+\) T-cell count, cells/μL  | 846 ± 56                    | 882 ± 80                 | .71    |
| Log HIV viral load, copies/mL      | 1.46 ± 0.06                 | 1.56 ± 0.13              | .51    |
| Undetectable viral load, %         | 81                          | 70                       | .41    |
| Duration HIV, y                    | 19 (10, 24)                 | 20 (14, 23)              | .65    |
| Duration ART use, y                | 8 (3, 17)                   | 8 (4, 18)                | .77    |
| Current PI use, %                  | 48                          | 45                       | .87    |
| Current NRTI use, %                | 95                          | 95                       | .97    |
| Current NNRTI use, %               | 38                          | 60                       | .16    |
| Current integrase inhibitor, %     | 29                          | 20                       | .52    |
| **RAAS parameters**                |                             |                          |        |
| PRA, ng/mL/h                       | 0.3 (0.1, 0.4)              | 0.2 (0.1, 0.4)           | .72    |
| Serum aldosterone, ng/dL           | 3.59 (2.49, 8.77)           | 4.51 (2.49, 6.29)        | .69    |
| **Metabolic parameters**           |                             |                          |        |
| SBP, mmHg                           | 130 ± 4                     | 132 ± 3                  | .68    |
| DBP, mmHg                           | 80 ± 2                      | 86 ± 2                   | .07    |
| Triglycerides, mg/dL               | 172 ± 18                    | 161 ± 15                 | .64    |
| HDL cholesterol, mg/dL             | 42 (32, 51)                 | 43 (35, 51)              | .60    |
| LDL cholesterol, mg/dL             | 98 ± 5                      | 97 ± 7                   | .93    |
| Hemoglobin A1c, %                  | 5.7 (5.5, 6.0)              | 5.8 (5.4, 6.1)           | .96    |
| Body mass index, kg/m\(^2\)       | 32.1 (28.0, 37.0)           | 32.3 (29.0, 34.1)        | .77    |
| Iliac waist circumference, cm      | 110.6 (102.3, 116.5)        | 111.9 (105.1, 121.6)     | .43    |
| **Markers of inflammation and immune activation** | | | |
| IL-6, pg/mL                        | 11.5 (6.9, 19.8)            | 7.8 (6.0, 14.7)          | .34    |
| hsCRP, mg/L                        | 3.3 (1.2, 7.9)              | 3.4 (1.5, 9.0)           | .82    |
| MCP-1, pg/mL                       | 209 ± 18                    | 193 ± 12                 | .46    |

Data reported as mean ± standard error mean, percentage, or median (interquartile range).

Abbreviations: ART, antiretroviral therapy; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.
Treatment Effects on NT-proBNP

NT-proBNP levels were not different between the groups at baseline (41.1 [20.2, 97.9] vs 48.9 [29.2, 65.4] ng/L, \( P = .80 \)). NT-proBNP levels decreased significantly more in the eplerenone- vs placebo-treated groups after 6 months (change NT-proBNP -9.6 [-46.8, 0.3] vs -3.0 [-17.0, 39.9] ng/L, \( P = .02 \) for comparison of change between groups) (Fig. 1). Assessing within-group changes, the change within the eplerenone group was highly significant (\( P = .004 \)), whereas the change within the placebo group was not (\( P = .40 \)).

Relationship of Change in NT-proBNP With RAAS, Metabolic, and Inflammatory Parameters

Among all participants, a decrease in the percent change in NT-proBNP over 6 months was associated with a decrease in the percent change in hsCRP (\( \rho = 0.32, P = .05 \)) and an increase in the percent change in serum aldosterone (\( \rho = -0.33, P = .04 \)). Among those randomized to eplerenone, the reduction in NT-proBNP related to a reduction in MCP-1 (\( \rho = 0.47, P = .04 \)) (Table 2).

Multivariate Modeling to Assess Independent Effects of Eplerenone of NT-proBNP

In exploratory models, effects of eplerenone on NT-proBNP (\( \beta \) estimate -24.36, \( P = .008 \); \( \beta \) estimate -24.59, \( P = .008 \)) were independent of changes on either systolic or diastolic BP, respectively (Table 3). We also performed a sensitivity analysis controlling for ethnicity in a multivariate model for eplerenone effects on NT-proBNP. In this model, eplerenone remained highly significantly related to the change in NT-proBNP (\( P = .01 \)), independent of ethnicity, which had no effect in the model (\( P = .99 \)).

Discussion

In the current study, we show for the first time that treatment with an MR blocker significantly reduces NT-proBNP among a population of PWH selected for metabolic dysregulation with no known CVD. The relative median decrease in NT-proBNP levels was approximately 23% of baseline NT-proBNP levels among those treated with eplerenone.

Overall decreases in NT-proBNP appeared to be related to beneficial changes in inflammatory and immune indices, hsCRP, and MCP-1. A majority of well-treated PWH (76%) were recognized to have myocardial inflammation and fibrosis on cardiac magnetic resonance imaging compared well-matched persons without HIV [19]. In a population of individuals without HIV, the Multi-Ethnic Study of Atherosclerosis study showed that among those without known CVD, elevated NT-proBNP correlates with imaging characteristics consistent with myocardial fibrosis [20] and decreased myocardial perfusion [21]. In addition, a greater change in NT-proBNP was linked to CVD events in the Multi-Ethnic Study of Atherosclerosis study, an important finding among participants from the general community without known CVD [22]. We have previously shown that eplerenone may have anti-inflammatory potential in the HIV population, but have not related these changes to the effects of eplerenone on NT-proBNP [5]. Indeed, even well-treated PWH on ART demonstrate chronic inflammation [23] and the risk of heart disease remains increased in PWH after controlling for traditional risk factors [24, 25]. Thus, the chronic inflammatory state in HIV may drive the increased risk of CVD in PWH.

We would expect aldosterone levels to increase with eplerenone because of physiologic feedback from MR blockade, which gives rise to an increase in upstream substrates. As such, we saw that the percent change in NT-proBNP was inversely correlated with the percent change in aldosterone (ie, a decrease in NT-proBNP was related to an increase in aldosterone), consistent with the actions of MR blockade to reduce NT-proBNP and increase aldosterone.

Given eplerenone’s known mechanism of action as an antihypertensive and the direct influence of volume status on NT-proBNP levels, we further investigated whether changes in NT-proBNP were dependent on measures of BP. Similar to prior studies in those without HIV, eplerenone’s actions on NT-proBNP consistently appeared to be independent of BP-lowering effects. In comparison to these prior studies investigating MR antagonism on NT-proBNP, our study had the advantage of collecting the NT-proBNP under standardized controlled dietary and posture conditions. Sodium intake and posture are critical stimuli for changes in the natriuretic peptide and RAAS hormones.
Few medications have been tested for their effects on NT-proBNP in PWH. To our knowledge, the current study of eplerenone is the first study to evaluate MR blockade on NT-proBNP in the HIV population. In this regard, MR blockade may have complementary anti-inflammatory properties [5] desirable to treat the HIV population with subclinical CVD and chronic inflammation compared to other strategies such as statins [26-28]. Although all our participants reported ART use and the majority had an undetectable viral load, some may have not been adherent. We did not formally assess ART compliance or specifically include a noncompliant group to determine whether differences in NT-proBNP responses to eplerenone would be seen between these groups.

This study had strengths as well as limitations. Data on eplerenone effects were determined in a placebo-controlled trial under careful conditions of sodium intake, in a highly relevant population with known RAAS dysfunction. Though we evaluated changes in NT-proBNP, a surrogate measure of cardiac stretch and assessed inflammatory indices, we did not correlate these findings with pathologic changes in the heart. The Effects of Eplerenone on Cardiovascular Disease in HIV study (NCT02740179), an ongoing 12-month randomized double-blinded, placebo-controlled trial, will allow us to investigate the effect of eplerenone on cardiac structure and function using coronary positron emission tomography and cardiac magnetic resonance imaging among PWH to further associate changes in the myocardium and

| Table 2. Correlations between change in NT-proBNP and RAAS, metabolic, and inflammatory parameters from baseline to 6 months among persons with HIV |
| --- | --- | --- |
| All participants | Eplerenone-treated | Placebo-treated |
| (n = 41) | (n = 21) | (n = 20) |
| %Δ NT-proBNP | %Δ NT-proBNP | %Δ NT-proBNP |
| ρ | P | ρ | P | ρ | P |
| RAAS parameters | | | | | |
| %Δ PRA | -0.20 | .21 | -0.24 | .30 | 0.12 | .62 |
| %Δ Serum aldosterone | -0.33 | .04 | -0.38 | .09 | -0.14 | .57 |
| Metabolic parameters | | | | | |
| %Δ SBP | -0.03 | .84 | -0.08 | .72 | -0.02 | .95 |
| %Δ DBP | -0.13 | .42 | -0.02 | .94 | -0.15 | .53 |
| %Δ BMI | -0.07 | .69 | -0.11 | .64 | -0.12 | .63 |
| %Δ Iliac WC | 0.02 | .91 | -0.21 | .37 | 0.21 | .38 |
| Inflammatory parameters | | | | | |
| %Δ IL-6 | 0.13 | .45 | 0.12 | .61 | 0.06 | .83 |
| %Δ hsCRP | 0.32 | .05 | 0.25 | .29 | 0.25 | .33 |
| %Δ MCP-1 | 0.27 | .10 | 0.47 | .04 | -0.06 | .82 |

Relationships determined by Spearman correlation coefficient.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; hsCRP, high sensitivity C-reactive protein; MCP-1, monocyte chemoattractant protein-1; NT-proBNP, N-terminal pro B-type natriuretic peptide; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; WC, waist circumference.

| Table 3. Linear regression model to assess blood pressures determinants of NT-proBNP among persons with HIV |
| --- | --- |
| Δ NT-proBNP (ng/L) | Model 1 | Model 2 |
| β Estimate (95% CI) | P | β Estimate (95% CI) | P |
| Eplerenone arm | (R² = 0.19; P = .02) | .008 | (R² = 0.17; P = .03) |
| Δ SBP (mmHg) | -24.36 (-41.96 to -6.76) | .48 | -24.59 (-42.48 to -6.69) | .008 |
| Δ DBP (mmHg) | 0.391 (-0.71 to 1.49) | NA | NA | NA |
| Δ DBP (mmHg) | NA | 0.13 (-1.57 to 1.83) | .88 |

R² represents the coefficient of determination and the proportion of variance explained by the model. Overall P value represents significance by the whole model ANOVA test.
Abbreviations: DBP, diastolic blood pressure; NA, not assessed in model; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure.
vasculature with changes in NT-proBNP. In addition, it would be important for studies to assess for myocardial changes with MR blockade using transthoracic echocardiogram. A further limitation of the study was the minimum age criteria of 30 years, which does not allow for assessment of this class of medication among a younger population with HIV infection. We did not formally analyze our results by HIV type. Although HIV-1 is the most common subtype of HIV, studies have shown that HIV-2 may have similar immunologic dysregulation to HIV-1 [29], and HIV-related mortality has been shown to relate to CD4 count regardless of type of HIV [30]. As such, we would hypothesize similar results in both subtypes of HIV provided both groups had similar baseline immunological control [31].

In conclusion, these initial data suggest some benefit of eplerenone to reduce NT-proBNP in the ART-treated HIV population, which is independent of the well-recognized mechanism of action of MR antagonism as an antihypertensive. Changes in NT-proBNP related to improved inflammatory indices. MR antagonism may have independent cardioprotective and anti-inflammatory properties that could be leveraged by targeting distinct RAAS physiology and an increased prevalence of inflammatory-driven subclinical CVD in PWH—a population for which no current CVD treatment strategy exists.

Acknowledgments

The investigators thank the nursing staff on the Massachusetts General Hospital Translational and Clinical Research for their dedicated patient care as well as the volunteers who participated in this study.

Funding: Funding was provided by National Institutes of Health (NIH) RO1 DK49302 to S.K.G.; Harvard cMeRIT, NIH K23 HL136262, NIH RO1 HL151293 to S.S.; NIH K24 HL103845 to G.K.A.; NIH UL1 TR000170, NIH UL1 RR025758, and NIH UL1 TR001102 to the Harvard Catalyst/Harvard Clinical and Translational Science Center from the National Center for Research Resources and National Center for Advancing Translational Sciences; and NIH P30 DK040561, Nutrition and Obesity Research Center at Harvard. Funding sources had no role in the design of the study, data analysis, or writing of the manuscript.

Additional Information

Correspondence: Steven K. Grinspoon, MD, Metabolism Unit, Massachusetts General Hospital, 55 Fruit St, SLO207, Boston, MA 02114, USA. Email: sgrinspoon@mgh.harvard.edu.

Disclosures: C.D., K.V.F., S.I., G.S., T.H.B., T.S.T., and A.R.W. have nothing to declare. S.S. was the recipient of a Gilead Sciences Research Scholars award. G.K.A has received consulting fees from Pfizer. S.K.G. has received research funding from KOWA, Gilead, ViiV, and Theratechnologies, and received consulting fees from Theratechnologies and ViiV. All disclosures are unrelated to this manuscript.

Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Sinha A, Feinstein MJ. Immune dysregulation in myocardial fibrosis, steatosis, and heart failure: current insights from HIV and the general population. *Curr HIV/AIDS Rep*. 2021;18(1):63-72.
2. Hsue PY, Hunt PW, Ho JE, et al. Impact of HIV infection on diastolic function and left ventricular mass. *Circ Heart Fail*. 2010;3(1):132-139.
3. Savoulidis P, Butler J, Kalogeropoulos A. Cardiomyopathy and heart failure in patients with HIV infection. *Can J Cardiol*. 2019;35(3):299-309.
4. Srinivasa S, Fitch KV, Wong K, et al. RAAS activation is associated with visceral adiposity and insulin resistance among HIV-infected patients. *J Clin Endocrinol Metab*. 2015;100(8):2873-2882.
5. Srinivasa S, Fitch KV, Wong K, et al. Randomized, placebo-controlled trial to evaluate effects of eplerenone on metabolic and inflammatory indices in HIV. *J Clin Endocrinol Metab*. 2018;103(6):2376-2384.
6. Oestreicher EM, Martinez-Vasquez D, Stone JR, et al. Aldosterone and not plasmogen activator inhibitor-1 is a critical mediator of early angiotensin II/NG-nitro-L-arginine methyl ester-induced myocardial injury. *Circulation*. 2003;108(20):2517-2523.
7. Rao AD, Shah RV, Garg R, et al. Aldosterone and myocardial extracellular matrix expansion in type 2 diabetes mellitus. *Am J Cardiol*. 2013;112(1):73-78.
8. Rocha R, Stier CT Jr, Kifor I, et al. Aldosterone: a mediator of myocardial necrosis and renal arteriopathy. *Endocrinology*. 2000;141(10):3871-3878.
9. Young M, Head G, Funder J. Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. *Am J Physiol*. 1995;269(4 Pt 1):E657-E662.
10. Pitt B, Pfeffer MA, Assmann SF, et al.; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383-1392.
11. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131(1):34-42.
12. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic importance of changes in cardiac structure and function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circ Heart Fail*. 2015;8(6):1052-1058.
13. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). *J Card Fail*. 2011;17(8):634-642.
14. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med*. 2004;350(7):655-663.
15. McKie PM, Cataliotti A, Sangaralingham SJ, et al. Predictive utility of atrial, N-terminal pro-atrial, and N-terminal pro-B-type natriuretic peptides for mortality and cardiovascular events in the general community: a 9-year follow-up study. *Mayo Clin Proc*. 2011;86(12):1154-1160.
16. Geng Z, Huang L, Song M, Song Y. N-terminal pro-brain natriuretic peptide and cardiovascular or all-cause mortality in the general population: a meta-analysis. *Sci Rep.* 2017;7:41504.

17. Berg T, Zdunek D, Stalke J, et al. N-terminal pro-B-type natriuretic peptide (NT-proBNP) in HIV-1 infected individuals on HAART. *Eur J Med Res.* 2007;12(4):152-160.

18. Mansoor A, Althoff K, Gange S, et al. Elevated NT-pro-BNP levels are associated with comorbidities among HIV-infected women. *AIDS Res Hum Retroviruses.* 2009;25(10):997-1004.

19. Holloway CJ, Ntusi N, Suttie J, et al. Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. *Circulation.* 2013;128(8):814-822.

20. Liu CY, Heckbert SR, Lai S, et al. Association of elevated NT-proBNP with myocardial fibrosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol.* 2017;70(25):3102-3109.

21. Mitchell A, Misialek JR, Folsom AR, et al. Usefulness of N-terminal Pro-brain natriuretic peptide and myocardial perfusion in asymptomatic adults (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol.* 2015;115(10):1341-1345.

22. Daniels LB, Clopton P, deFilippi CR, et al. Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J.* 2015;170(6):1170-1183.

23. Hunt PW, Sinclair E, Rodriguez B, et al. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. *J Infect Dis.* 2014;210(8):1228-1238.

24. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab.* 2007;92(7):2506-2512.

25. Freiberg MS, Chang CC, Kulier LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173(8):614-622.

26. Eckard AR, Jiang Y, Debanne SM, Funderburg NT, McComsey GA. Effect of 24 weeks of statin therapy on systemic and vascular inflammation in HIV-infected subjects receiving antiretroviral therapy. *J Infect Dis.* 2014;209(8):1156-1164.

27. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis.* 2014;58(4):588-595.

28. Dirajlal-Fargo S, Kinley B, Jiang Y, et al. Statin therapy decreases N-terminal pro-B-type natriuretic peptide in HIV: randomized placebo-controlled trial. *AIDS.* 2015;29(3):313-321.

29. Gottlieb GS, Sow PS, Hawes SE, et al. Equal plasma viral loads predict a similar rate of CD4+ T cell decline in human immunodeficiency virus (HIV) type 1- and HIV-2-infected individuals from Senegal, West Africa. *J Infect Dis.* 2002;185(7):905-914.

30. Martinez-Steele E, Awasana AA, Corrah T, et al. Is HIV-2 induced AIDS different from HIV-1-associated AIDS? Data from a West African clinic. *Aids.* 2007;21(3):317-324.

31. Cardoso JS, Miranda AM, Moura B, et al. Cardiac morbidity in the human immunodeficiency virus infection. *Rev Port Cardiol.* 1994;13(12):901-911.