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Plasma Xanthine Oxidase Activity Is Related to Increased Sodium and Left Ventricular Hypertrophy in Resistant Hypertension

Brittany Butts, PhD[a,b], **David A Calhoun, MD**[a], **Thomas S Denney Jr., PhD**[c], **Steven G Lloyd, MD, PhD**[a], **Himanshu Gupta, MD**[a,h], **Krishna K Gaddam, MD**[a], **Inmaculada Aban, PhD**[d], **Suzanne Oparil, MD**[a], **Paul W Sanders, MD**[e], **Rakesh Patel, PhD**[f], **James F Collawn, PhD**[g], and **Louis J Dell'Italia**[a,h]

[a]Division of Cardiovascular Disease, University of Alabama at Birmingham School of Medicine,

[b]Nell Hodgson Woodruff School of Nursing, Emory University

[c]Department of Electrical and Computer Engineering, Auburn University

[d]Department of Biostatistics, University of Alabama at Birmingham

[e]Division of Nephrology, University of Alabama at Birmingham School of Medicine

[f]Center for Free Radical Biology and Department of Pathology, University of Alabama at Birmingham

[g]Department of Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham

[h]Birmingham Department of Veterans Affairs Medical Center

Abstract

Background: The extra-renal effects of aldosterone on left ventricular (LV) structure and function are exacerbated by increased dietary sodium in persons with hypertension. Previous studies demonstrated endothelial dysfunction and increased oxidative stress with high salt diet in normotensive salt-resistant subjects. We hypothesized that increased xanthine oxidase (XO), a product of endothelial cells, is related to 24-hour urinary sodium and to LV hypertrophy and function in patients with resistant hypertension (RHTN).

Methods: The study group included persons with RHTN (n=91), defined as a blood pressure > 140/90 mmHg on ≥ 3 medications at pharmacologically effective doses. Plasma XO activity and 24-hour urine were collected, and cardiac magnetic resonance imaging (MRI) was performed to assess LV function and morphology. Sixty-seven normotensive persons on no cardiovascular medications served as controls. A subset of RHTN (n=19) received spironolactone without salt restriction for six months with follow-up XO activity measurements and MRI analyses.

Address for correspondence: Louis J. Dell'Italia, M.D., Professor of Medicine and Associate Chief of Staff for Research, Birmingham VA Medical Center, 700 South 19th Street, Birmingham, AL 35294-2180, Telephone: (205) 933-8101 Ext 6792, Fax: (205)-933-4471, louis.dellitalia@va.gov.

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Results: XO activity was increased two-fold in RHTN vs. normal and was positively correlated with LV mass, LV diastolic function, and 24-hour urinary sodium. In RHTN patients receiving spironolactone without salt restriction, LV mass decreased, but LV diastolic function and XO activity did not improve. Baseline urinary sodium was positively associated with rate of change of LV mass to volume ratio and the LV E/A ratio.

Conclusions: These results demonstrate a potential role of endothelium-derived oxidative stress and excess dietary salt in the pathophysiology of LV hypertrophy and diastolic dysfunction in persons with RHTN unaffected by the addition of spironolactone.

Keywords

oxidative stress; left ventricular hypertrophy; dietary sodium; xanthine oxidase

Introduction

An estimated 10% to 20% of hypertensive patients can be considered resistant to treatment, defined as having controlled or uncontrolled blood pressure with the use of ≥ 3 medications that includes a diuretic.[1–3] In persons with hypertension, echocardiographic/Doppler studies provide evidence that elevated serum aldosterone levels are associated with left ventricular (LV) hypertrophy and diastolic dysfunction, independent of changes in BP and intracardiac volume.[4–6]

Studies in rat models with uninephrectomy have long connected aldosterone excess in the presence of high dietary sodium intake to the induction of LV hypertrophy and fibrosis.[7–11] Inflammation and fibrosis also occur in the right ventricle in these models,[8,11] suggesting the changes are not pressure dependent. These adverse effects of aldosterone and high sodium on LV morphology are attenuated during low dietary sodium ingestion.[12] In persons with primary aldosteronism, urinary sodium excretion is an independent predictor of LV mass, [13,14] suggesting that dietary salt interactions with aldosterone excess lead to cardiac damage. Further, Weber and coworkers have demonstrated that the combined infusion of aldosterone and sodium chloride leads to an induction of inflammatory cell infiltration with oxidative stress in the rat heart with subsequent hypertrophy and fibrosis.[11] Although the pathological consequences of excess sodium and aldosterone on the LV have been extensively documented in rats[7–12] and humans,[13,14] the role of oxidative stress in these processes has not been evaluated in humans, especially in persons with RHTN.

The relationship between high salt intake and oxidative stress has been demonstrated in both rats and humans. Boegehold and colleagues have performed a number of studies linking a high sodium diet to increased oxidative stress in the microcirculation of rat skeletal muscle. [15–18] Further, salt resistant normal normotensive persons fed a high salt diet develop endothelial dysfunction and circulating markers of oxidative stress.[19,20] In the Prevention of Renal and Vascular End Stage Disease (PREVEND) study, high salt intake was associated with increases in serum uric acid and urinary albumin excretion.[21] There is now an abundance of evidence linking increased serum uric acid with poor cardiovascular outcomes including hypertension and stroke as well as being causative in the pathobiology of these conditions.[22,23] Xanthine oxidase (XO) is a major enzyme in the production of uric acid

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during purine catabolism but also results in the generation of reactive oxygen species—superoxide and hydrogen peroxide. XO is widely distributed in the heart, liver, gut, lung, kidney, and brain, as well as in the plasma.[24] XO-derived reactive oxygen species production have been implicated in various forms of tissue injury, inflammatory diseases, and chronic heart failure.[25] However, XO has also been shown to contribute to the blood pressure lowering effects of nitrite by reducing it to nitric oxide, thereby providing antioxidant effects in some conditions.[26]

Pertinent to the current study, high salt intake was demonstrated to increase XO activity in the hypertrophied left ventricle of a Dahl salt-sensitive model of hypertension.[27] Sowers et al have also shown that mice fed a Western diet have increased production of uric acid with increased LV XO activity, inflammation, fibrosis, and impaired diastolic relaxation; all results improved with allopurinol treatment.[28] Taken together, these findings, coupled with the well-documented link of a high salt diet and oxidative stress, led us to conduct the current retrospective analysis in which we hypothesize that increased plasma XO activity is related to 24-hour urinary sodium and to LV hypertrophy and diastolic dysfunction in a large cohort of RHTN patients.

Materials and Methods

Study Design and Sample

This study is a retrospective analysis of a cohort of patients with resistant hypertension recruited from our Specialized Centers of Clinically Oriented Research (SCCOR) project [SCCOR in Cardiac Dysfunction and Disease, P50HL077100]. The study group included participants with RHTN (n=91) seen at the University of Alabama at Birmingham Hypertension Clinic, as previously described.[29] Only participants with XO activity measures were included in this study, which excluded 17 participants who were included in the initial study.[29] Normotensive controls on no antihypertensive medications (n=67) were recruited from the greater Birmingham area.

RHTN was defined as having a resting blood pressure ≥ 140/90 mmHg at two clinic visits despite the use of ≥ 3 antihypertensive medications at pharmacologically effective doses. All participants were on a stable antihypertensive regimen for at least one month prior to entering the study, as confirmed by medical records. Exclusion criteria included known or suspected secondary causes of hypertension other than primary aldosteronism (i.e., renal artery stenosis, pheochromocytoma, Cushing's disease), chronic kidney disease (creatinine clearance <60 mL/min), congestive heart failure, use of potassium-sparing diuretic (spironolactone, amiloride, triamterene), cardiovascular event or procedure within 6 months of study enrollment, use of nitric oxide donors (nitroglycerin, minoxidil), and change in medication use that might affect markers of inflammation or oxidative stress (HMG-CoQ reductase inhibitors, metformin, glitazones, vitamins C, E B_6, and B_{12}, hormone replacement therapy). Participants taking uric acid reducers, i.e., allopurinol and febuxostat, were excluded from this analysis. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. All participants provided written informed consent before beginning the study.

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Laboratory Measures

Peripheral venous blood samples were drawn from all participants during early morning clinical assessments; samples were centrifuged at 1500g for 20 minutes at 4ºC and stored at −80ºC until analysis. Following size exclusion chromatography with Sephadex G-25 to remove endogenous purines and low-molecular-weight inhibitors, plasma total XO plus xanthine dehydrogenase (XD) activity was determined by the rate of uric acid production in the presence of xanthine (75 μM) with nicotinamide adenine dinucleotide (NAD^+, 0.5 mM). The activity of XO was measured by the rate of uric acid production in the presence of xanthine (75 μM) without NAD^+. After 60 min of incubation at 37°C, the reaction was terminated by deproteinization with cold acetonitrile. The uric acid content of deproteinized samples was determined using an HPLC-based electrochemical technique.[30] One unit of activity (U) was defined as 1 μmole/min urate formed at 25°C and pH 7.4. Allopurinol (100 μM), an inhibitor of XO and XD, was added to parallel samples to confirm the specificity of the reaction. Total protein concentration was determined prior to and following gel filtration. The XD + XO activity was corrected for the dilution associated with gel filtration and expressed as XO activity per mg total protein. Results were expressed both as a concentration relative to the volume of plasma as well as relative to total protein content of the sample. A 24-hour urine collection was obtained without changes to the participant's usual diet.

Cardiac Magnetic Resonance Imaging (MRI)

All participants underwent cardiovascular MRI to evaluate their cardiac anatomy and function, as previously described.[29,31] Cardiovascular MRI was performed with a 1.5-T clinical scanner optimized for cardiac imaging (Sigma, GE Healthcare) using a 4-element phased-array surface coil and prospective electrocardiographic triggering. Imaging was performed using a steady-state free precession cine sequence to obtain standard (2-,3-, and 4-chamber long-axis and serial-parallel short-axis) views with the following typical parameters: slice thickness of the imaging planes, 8 mm with no inter-slice gap; field of view, 40 cm; scan matrix, 256×128; flip angle, 45°; and repetition/echo times, 3.8/1.6 milliseconds). Cine images were reconstructed into 20 cardiac phases. LV functional parameters were measured from endocardial and epicardial contours manually traced on cine images acquired near the end diastole (ED) and end systole (ES). These contours were propagated throughout the cardiac cycle using in-house software.[32] The LV volume at each time frame was computed by summing the volumes defined by the contours in each short-axis slice multiplied by slice thickness. LV volume–time (V–t) curves, peak ejection rates and volumetric early (E) and late (A) filling rates were calculated as previously described.[32] Peak early and late diastolic mitral annular (MA) velocities were calculated using non-rigid registration to track a manually-selected point on the mitral annulus through the cardiac cycle.

Spironolactone Sub-study

A subset of the RHTN group (n=19) received aldosterone blockade with spironolactone without sodium restriction for six months, as previously described.[29,31] Only participants who had repeated XO activity measures were included in this study, which excluded 15

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participants. Spironolactone was added to current medication regimen at 25 mg per day and increased to 50 mg per day at four weeks. Follow-up cardiac MRI and XO activity measures were collected at three and six months.

Statistical Analysis

Descriptive statistics were calculated for all study variables and data were reviewed for normality assumptions and outliers in preparation for analysis. Data are presented as mean ± standard deviation for continuous variables and counts (percent) for categorical variables. Between-group testing was performed using the Student's t-test for continuous variables and chi-squared tests to compare gender and race distribution. Multiple linear regressions were used to examine linear relationships among continuous outcome variables, controlling for covariates, namely age, gender, and body mass index (BMI). Partial correlations for the variables of interest corrected for covariates were reported. PROC MIXED with Bonferroni adjusted least squares mean analysis was used to compare within group (RHTN) changes across the three time points for participants in the spironolactone sub-study. All data were analyzed using SAS version 9.4 with an alpha set at 0.05.

Results

Demographics and Clinical Measures

The RHTN group was older with a higher mean systolic blood pressure and BMI compared to the normotensive control population (Tables 1 and 2). Among the RHTN group, 57% (n=51) of participants were taking an angiotensin II receptor blocker (ARB), 65% (n=59) were taking an angiotensin-converting enzyme inhibitor (ACEi), 94% (n=86) were taking a diuretic, 74% (n=67) were taking a calcium channel blocker, 74% (n=67) were taking a β-blocker, and 9% (n=8) were taking an α-blocker. There were no significant associations between ACEi/ARB status and measures of aldosterone, sodium, XO activity, or measures of cardiac structure or function. Furthermore, ACEi/ARB status had no significant modifying or moderating effects on relationships between variables.

Daily sodium intake was approximated using 24-hour urinary sodium and dichotomized as high (>3500 mg) and normal (≤ 3500 mg), based on average sodium intake in the United States.[33] Among those with RHTN, 35% (n=32) had normal sodium intake, and 65% had high sodium intake. Further, only 15% (n=14) met the current recommended guidelines <2300 mg of sodium intake for healthy adults.[33]

Left Ventricular Function and Morphology

All indices of LV diastolic dysfunction differed significantly between the RHTN group and the normotensive control group (Table 3). Summated serial short axis magnetic resonance imaging provides a geometry-independent assessment of LV volume and mass. The volume-time curve (Figure 1) demonstrated a representative example of the decrease in the slope of the passive diastolic LV filling phase (normalized peak early diastolic filling rate [E]) and the accentuated slope in the late active phase (normalized peak late diastolic filling rate [A]) that resulted in a decreased E/A in the RHTN compared to normals. This impairment in LV diastolic function was further supported by a decrease in the normalized peak early diastolic

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MA velocity. The higher LV end-diastolic volume, LV end-diastolic volume index, LV mass, LV mass index, and LV wall thickness in RHTN suggested an increased circulating blood volume in addition to greater LV hypertrophy. Cardiac MRI (Figure 2) demonstrated an increased wall thickness and greater LV end-diastolic volume in RHTN as compared to normotensive controls. This adverse myocardial remodeling represented a dilated pattern of LV hypertrophy, manifested by increased mass to volume ratio and decreased radius to wall thickness ratio (Table 3), consistent with a combined volume and pressure overload.

24-hour Urinary Aldosterone and Sodium

Among participants with RHTN, 24-hour urinary aldosterone and urinary sodium were positively associated with LV end-diastolic mass and volume, when controlled for age, gender, and BMI (Figure 3). Further, after controlling for age and gender, urinary sodium (mg/24h/kg) had a positive linear relationship with the mass-volume ratio ($r=.412$, $p=.001$), the hallmark of the combined pressure and volume overload of RHTN.

Plasma Xanthine Oxidase Activity

XO activity was 2-fold higher in the RHTN group compared to normotensive subjects ($p<.001$, Table 2). XO activity, represented as relative to total protein, was positively correlated with 24-hour urinary sodium in persons with RHTN (Figure 4). XO activity had a positive linear relationship with LV end-diastolic mass and a negative linear relationship with normalized peak early diastolic filling rate in RHTN (Figure 4).

Spironolactone Treatment

A subset of RHTN participants (n=19) was given spironolactone treatment for six months.[29,31] XO activity did not decrease with mineralocorticoid receptor blockade at three-month and six-month measures, although the XO activity did increase higher than baseline at 3 months (Table 2). In addition, LV diastolic dysfunction (normalized peak early and late diastolic filling rates, peak early diastolic mitral annular (MA) velocity) did not improve from baseline after six months of spironolactone treatment and remained significantly lower than normotensive controls (Table 3) at all time points ($p<.001$), while E/A ratio worsened from baseline over time (Table 3).

While LV hypertrophy was reduced over baseline after the six-month treatment, LV end-diastolic mass, wall thickness, and mass to volume ratio all remained significantly higher ($p\leq.001$ for all), and LV midwall end-diastolic dimension to wall thickness ratio remained significantly lower ($p<.001$) compared to normotensive controls (Table 3). It is of interest that baseline urinary sodium was positively associated with the rate of change of LV end-diastolic mass to volume ratio ($p=.02$) and the LV E/A ratio ($p=.05$) over the six months of spironolactone treatment.

Discussion

This retrospective study reports that increased plasma XO activity is related to the 24-hour urinary sodium and to LV hypertrophy and function in patients with RHTN. The impetus for analysis of XO activity in our large cohort of RHTN patients emanated from previous

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studies from our laboratory and from the difficulty in treating diastolic dysfunction in the broad syndrome of heart failure preserved ejection fraction (HFpEF) of which the RHTN is a part. As a result, we further connect urinary sodium to increased plasma XO activity and LV diastolic function that are not attenuated by spironolactone treatment in patients with RHTN.

In a three-year study of 182 persons with primary hypertension, LV mass index increased progressively in relation to increasing urinary sodium excretion in the high-aldosterone (> 11.6 ng/L) subjects after three years of treatment with ACE inhibitor or AT_1 receptor blocker.[34] We previously reported that despite a decrease in LV mass and systolic blood pressure, there is no improvement in LV diastolic function in 35 patients with RHTN who remained on a high-salt diet.[29,31] Pimenta et al. have shown that in RHTN patients with high urinary aldosterone, the extent of LV hypertrophy,[13] urinary protein excretion,[35] and severity of sleep apnea [36] increase progressively across urinary sodium groups. Taken together, these human and numerous animal studies highlight the interdependence of aldosterone and dietary sodium in relation to target organ damage.[37] A previous study from our laboratory has shown that rigorous dietary sodium restriction from a mean sodium intake of 195 mmol/24 hours to 50 mmol/24 hours in persons with RHTN resulted in a decrease in 24-hour ambulatory blood pressure (systolic 22.7 mmHg [95% CI 11.8,33.5], diastolic 9.1 mmHg [95% CI 3.1, 15.1]) and the need for antihypertensive medications from four to one.[38]

One stimulus for the increase in XO activity is the stretch stimulus on the left ventricle.[39,40] However, here we found that XO activity persists despite a reduction in the systolic and diastolic blood pressure and LV end-diastolic volume in the spironolactone-treated subset of RHTN patients. We postulate that dietary salt status is a primary stimulus for XO activity in persons with RHTN. This hypothesis is supported by the observation that endothelial dysfunction and oxidative stress are induced by short-term consumption of a high salt diet in salt-resistant normotensive persons.[19,20] In Dahl salt-sensitive rats fed a high salt diet with subsequent development of hypertension, LV hypertrophy, and cardiac fibrosis an XO inhibitor blocked the increase in XO activity and attenuated LV hypertrophy and fibrosis independent of changes in blood pressure.[27] With regard to our 91 RHTN patients, neither ACE inhibitor nor AT_1 receptor blocker alone or in combination affected plasma XO activity. Taken together, the failure of spironolactone therapy to reduce XO activity in the face of an unrestricted salt diet further suggests the effect of salt alone on the induction of oxidative stress in RHTN.

Although there is a major connection of uric acid to cardiovascular disease as well as salt diet,[24] the present study is the first to measure XO activity in a well-defined patient population. Furthermore, an increase in XO activity at the myocardial level has an adverse effect on myofilament calcium sensitivity,[41,42] and thus may in part be responsible for the LV diastolic dysfunction in RHTN patients. In the current report, six months of spironolactone treatment decreased LV volume and hypertrophy but did not alter XO activity or LV diastolic dysfunction. Further, the baseline urinary sodium levels were associated with the response to spironolactone treatment, suggesting a prolonged high sodium diet may have played a role in the underlying LV diastolic dysfunction. Numerous studies in animal models

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have demonstrated that the degree of sodium loading in the presence of aldosterone excess is related to the extent of LV hypertrophy, fibrosis, diastolic dysfunction, and cardiac oxidative stress.[7,11,12,43] Increased expression of aldosterone synthase in transgenic mice made blood pressure more sensitive to a high sodium diet and angiotensin II and increased oxidative stress.[43]

Limitations

This study is correlative in nature, as XO activity was measured in plasma and not in LV. Thus, we are unable to determine if plasma XO activity echoes that of the LV and diastolic dysfunction and for that matter endothelial dysfunction since flow-mediated dilatation was not measured in the current patient population. Nevertheless, previous work demonstrated that flow-mediated dilatation (FMD) was impaired in persons with RHTN and that FMD was improved with a 3-month treatment of spironolactone but not related to a reduction in either systolic or diastolic blood pressure.[44,45] Further, FMD reflects only a small segment of the peripheral vascular bed that may be different in the heart, especially since there is appreciable XO in the human cardiomyocyte.[40] Thus, it is entirely possible that there can be an improvement in flow-mediated, endothelium-dependent vascular reactivity in the spironolactone treatment group despite the lack of improvement in serum XO activity and LV diastolic function.

Perspectives

There are limited recommendations for sodium restriction in HFpEF except in patients who are prone to volume overload.[46,47] However, the screening procedure for identifying these patients is not well defined. The interaction of excess dietary sodium with aldosterone and XO/uric acid may be an important link that provides the basis for adding restriction to conventional medical therapy in persons with RHTN and LV diastolic dysfunction. The current investigation raises an interesting question and a call for further investigation to determine whether persons with RHTN represent a subset of HFpEF patients who may benefit from sodium restriction in addition to maximal medical therapy.

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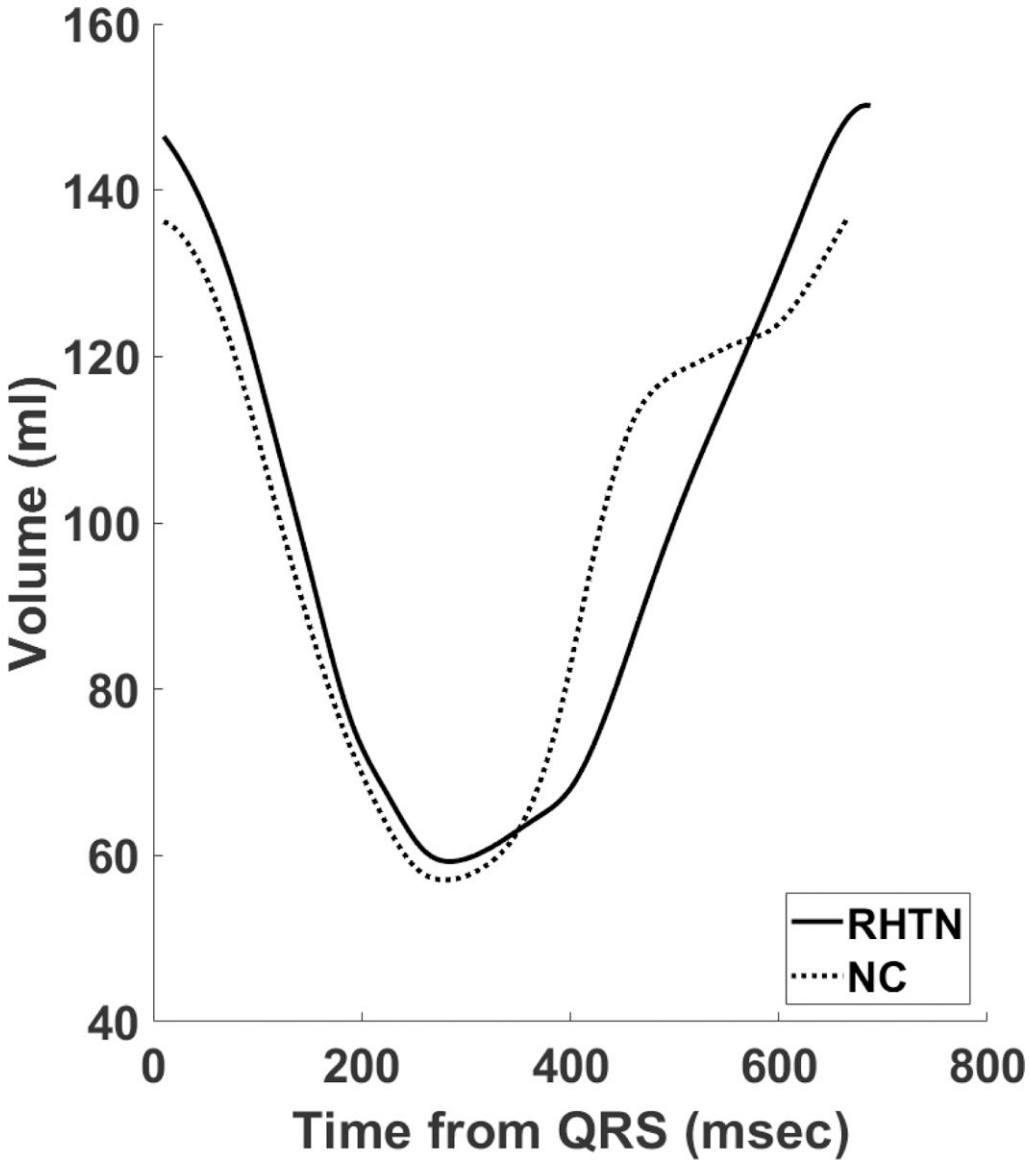

Figure 1.

Representative left ventricular (LV) volume-time curve in resistant hypertension (RHTN) and normotensive control (NC). The decrease in the slope of the passive diastolic LV filling phase and the accentuated slope in the late active phase demonstrate impaired LV diastolic function in RHTN as compared to NC.

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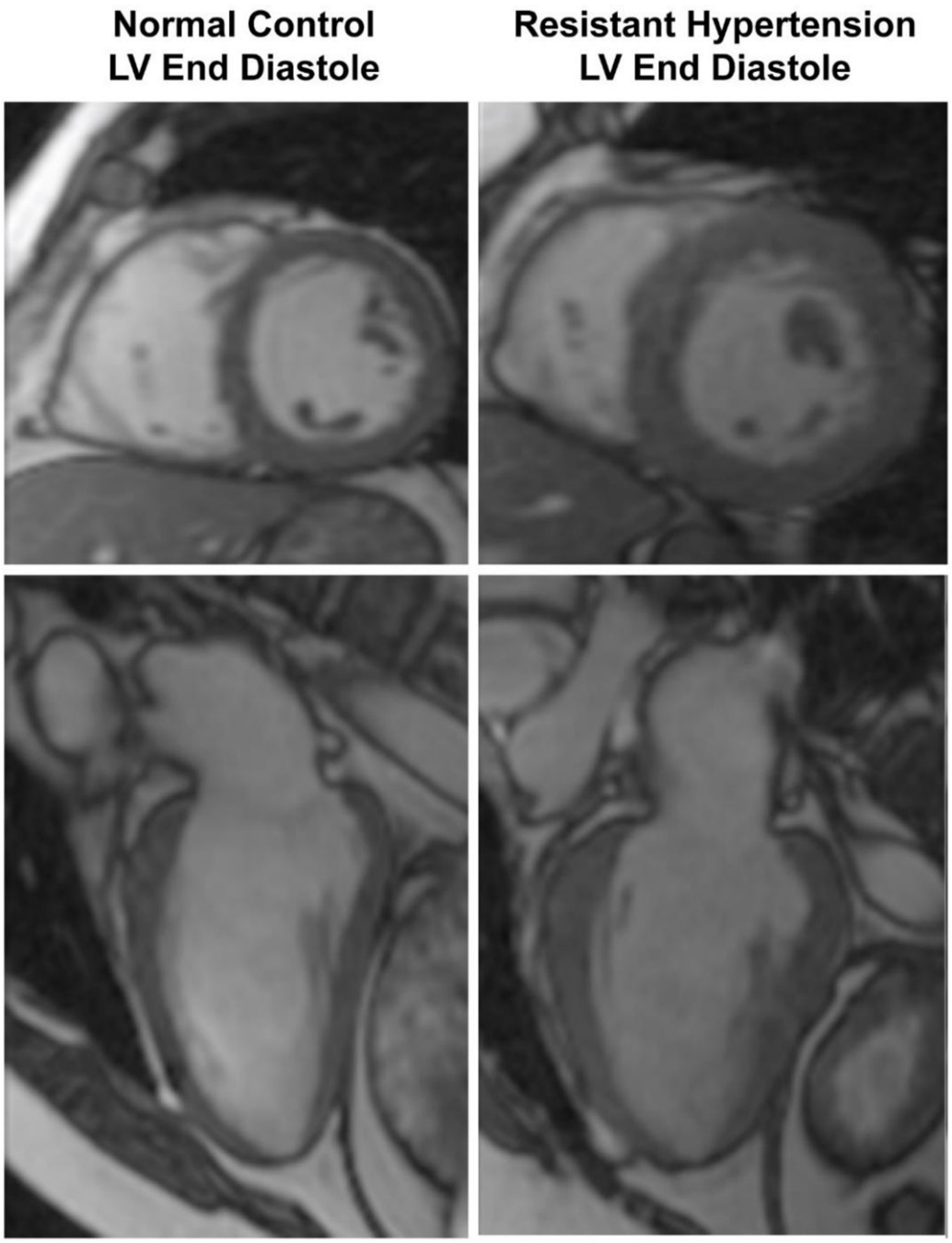

Figure 2.

Cardiac MRI images of a 53-year-old male normotensive control (left column) and a 53-year-old male resistant hypertension (right column). Top row: short-axis view at end diastole. Bottom row: 2-chamber view at end diastole. These images demonstrate the increased wall thickness and end diastolic volume of our patients with resistant hypertension. This represents a dilated concentric pattern of hypertrophy, manifested by increased mass to volume ratio and decreased radius to wall thickness ratio.

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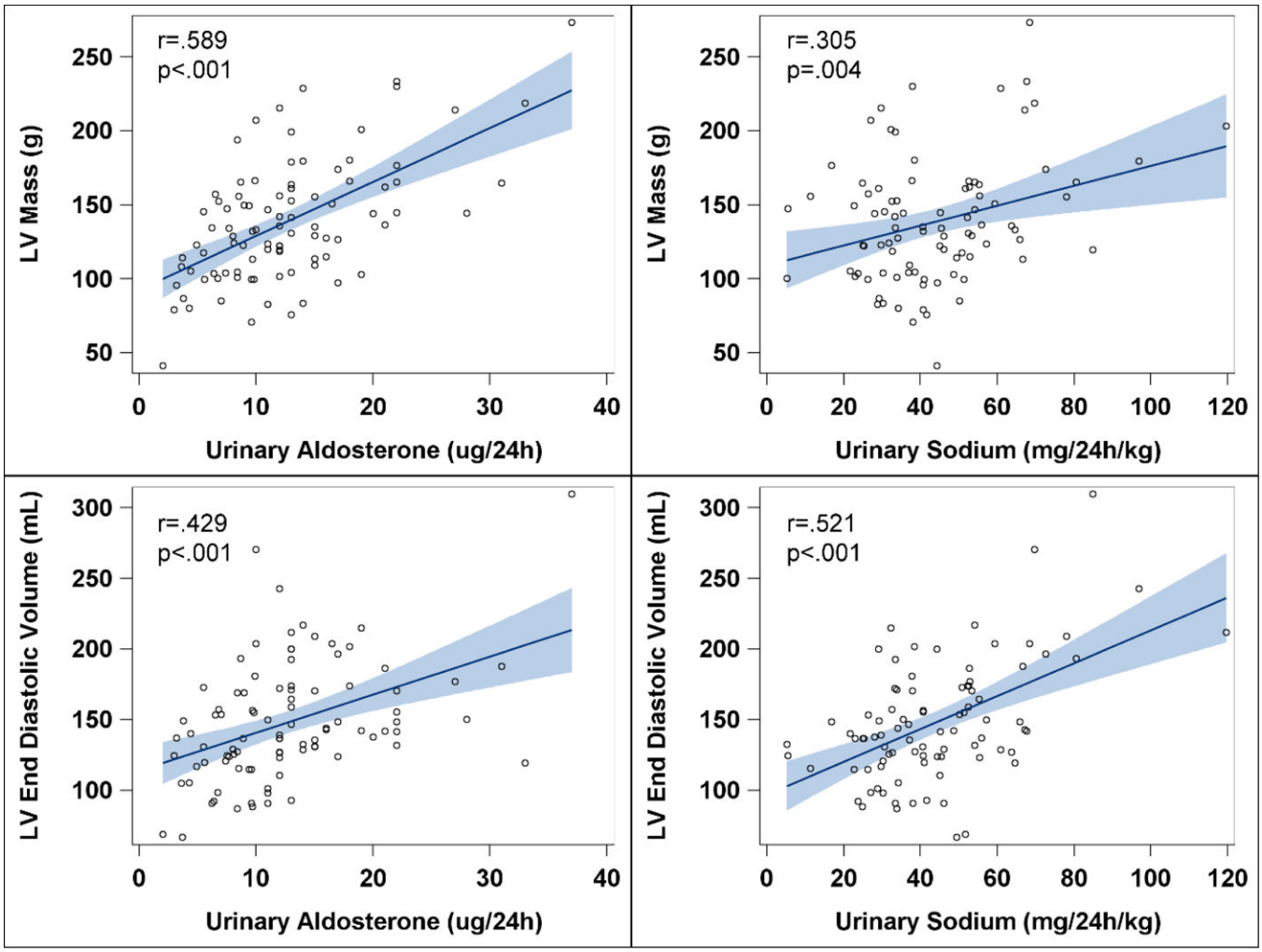

Figure 3.

Linear relationships between left ventricular (LV) diastolic mass and volume and urinary aldosterone and sodium in persons with resistant hypertension (n=91). Partial correlation (r) values are adjusted for age, gender, and BMI. The shaded area represents 95% confidence interval of the mean.

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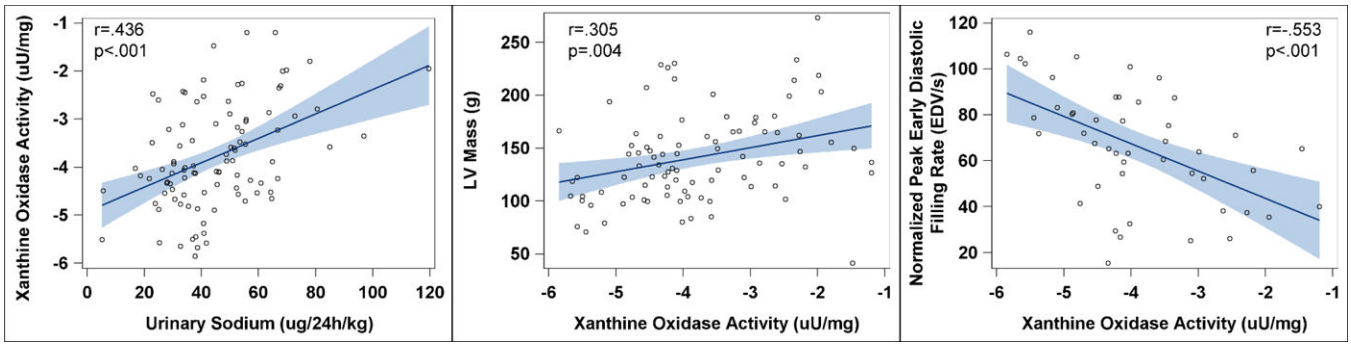

Figure 4.

Plasma xanthine oxidase activity is related to 24-hour urinary sodium, left ventricular end-diastolic mass, and normalized peak early diastolic filling rate in persons with resistant hypertension (n=91). Partial correlation (r) values are adjusted for age, gender, and BMI. Xanthine oxidase values were log transformed for better visualization of the data.

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Table 1.

Demographic and Clinical Characteristics

	RHTN N=91	Normotensive Controls (n=67)	p-value
Age, years	56 ± 1.1	41 ± 1.5	<.001
Female, n/%	43/47%	31/46%	ns
AA/Black, %	39/43%	15/23%	ns
BMI, kg/m^2	32.64 ± 0.7	22.48 ± 0.8	<.001
Body Surface Area, m^2	2.09 ± 0.2	1.87 ± 0.2	<.001
Aldosterone, plasma, ng/dL	10.20 ± 0.6	--	
Renin activity, plasma, ng/mL per h	3.3 ± 0.7	--	
Aldosterone, urine, μg/24h	12.63 ± 1.1	--	
Sodium, urine, mg/24h/kg	43.82 ± 1.8	--	

RHTN – resistant hypertension

AA – African American

BMI – body mass index

BP – blood pressure

ns – not significant

Values are listed as mean ± SD

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Table 2.

Blood Pressure and Xanthine Oxidase Measures over Time

	Normotensive Controls n=67	**RHTN - All Baseline n=91**	**RHTN[a] Baseline n=19**	**RHTN[a] 3 Months n=19**	**RHTN[a] 6 Months n=19**
Systolic BP, mmHg	117 ± 1.7	148 ± 2.2 *	137 ± 3.9 *	125 ± 3.5 *†	122 ± 3.9 *†
Diastolic BP, mmHg	74 ± 1.3	87 ± 1.5 *	85 ± 2.6 *	78 ± 2.5 †	74 ± 2.2 †
Xanthine oxidase activity, μU/mL	1.68 ± 0.4	2.98 ± 0.4 *	3.23 ± 1.6 *	4.30 ± 0.8 *†	3.56 ± 0.9 *
Xanthine oxidase activity, μU/mg	0.017 ± 0.004	0.037 ± 0.006 *	0.04 ± 0.002 *	0.06 ± 0.01 *†	0.05 ± 0.01 *

*p<.01 vs normotensive controls

†p<.01 vs Spironolactone subset of RHTN at baseline

[a]Spironolactone subset of resistant hypertension group

RHTN – resistant hypertension

BP – blood pressure

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Table 3.

Differences in Left Ventricular Function and Morphology at Baseline and Over Time

	Normotensive Controls n=67	RHTN - All Baseline n=91	RHTN[a] Baseline n=19	RHTN[a] 3 Months n=19	RHTN[a] 6 Months n=19
Normalized peak early diastolic filling rate (E), EDV/sec	2.93 ± 0.1	2.37 ± 0.1 *	2.27 ± 0.1 *	2.53 ± 0.2 *	2.30 ± 0.1 *
Normalized peak late diastolic filling rate (A), EDV/sec	1.45 ± 0.1	2.32 ± 0.1 *	1.83 ± 0.2 *	1.99 ± 0.2 *	1.84 ± 0.2 *
E/A ratio	2.74 ± 0.4	1.61 ± 0.07 *	2.07 ± 0.6 *	1.61 ± 0.3 *†	1.52 ± 0.3 *†
Peak early diastolic MA velocity (e'), mm/sec	76.61 ± 3.1	54.64 ± 2.5 *	55.27 ± 5.2 *	56.58 ± 3.0 *	58.57 ± 4.3 *
Normalized peak early diastolic MA velocity, % long axis length/sec	81.80 ± 3.6	63.72 ± 2.8 *	61.00 ± 4.9 *	66.40 ± 4.4 *	69.08 ± 5.1 *
LV End-Diastolic Volume, ml	139.53 ± 4.5	147.75 ± 4.3	170.43 ± 6.6 *	153.48 ± 5.9 *†	158.91 ± 5.5 *†
LV End-Diastolic Volume Index, ml/m2	74.77 ± 2.1	70.75 ± 1.9 *	77.38 ± 4.1 *	70.05 ± 3.5 †	73.35 ± 4.5 †
LV End-Diastolic Mass, g	103.54 ± 3.6	139.67 ± 4.3 *	147.15 ± 9.6 *	133.63 ± 8.0 *†	126.12 ± 9.3 *†
LV End-Diastolic Mass Index, g/m2	55.38 ± 1.6	65.84 ± 2.0 *	66.62 ± 3.1 *	60.12 ± 2.8 †	58.67 ± 3.6 †
LV End-Diastolic wall thickness, cm	0.78 ± 0.02	1.02 ± 0.02 *	1.00 ± 0.03 *	0.95 ± 0.04 *†	0.92 ± 0.4 *†
LV End-Diastolic Mid-wall Radius to Wall Thickness Ratio	3.89 ± 0.1	3.08 ± 0.1 *	3.29 ± 0.09 *	3.36 ± 0.2 *†	3.55 ± 0.2 *†
LV End-Diastolic Mass to Volume Ratio	0.75 ± 0.02	0.97 ± 0.03 *	0.87 ± 0.02 *	0.88 ± 0.04 *†	0.82 ± 0.06 *†
LVEF, %	63.41 ± 0.8	68.19 ± 0.8	71.64 ± 1.6	66.66 ± 1.6	64.57 ± 2.3

[a]Spironolactone subset of resistant hypertension group

*p<.01 vs normotensive controls

†p<.05 vs Spironolactone subset of RHTN at baseline

EDV, end diastolic volume

MA, mitral annular

LV, left ventricular

EF, ejection fraction

NRHTN, non-resistant hypertension

RHTN, resistant hypertension

Values are listed as mean ± SD

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