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Racial Differences in XO (Xanthine Oxidase) and Mitochondrial DNA Damage-Associated Molecular Patterns in Resistant Hypertension

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Abstract

Background: We previously reported increased plasma XO (xanthine oxidase) activity in patients with resistant hypertension. Increased XO can cause mitochondrial DNA damage and promote release of fragments called mitochondrial DNA damage-associated molecular patterns (mtDNA DAMPs). Here, we report racial differences in XO activity and mtDNA DAMPs in Black and White adults with resistant hypertension.

Methods: This retrospective study includes 91 resistant hypertension patients (44% Black, 47% female) with blood pressure >140/90 mm Hg on ≥4 medications and 37 normotensive controls (30% Black, 54% female) with plasma XO activity, mtDNA DAMPs, and magnetic resonance imaging of left ventricular morphology and function.

Results: Black-resistant hypertension patients were younger (mean age 52±10 versus 59±10 years; P=0.001), with higher XO activity and left ventricular wall thickness, and worse diastolic dysfunction than White resistant hypertension patients. Urinary sodium excretion (mg/24 hour per kg) was positively related to left ventricular end-diastolic volume (r=0.527, P=0.001) and left ventricular mass (r=0.394, P=0.02) among Black but not White resistant hypertension patients.

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Disclosures

None.

Patients with resistant hypertension had increased mtDNA DAMPs versus controls ($P<0.001$), with Black mtDNA DAMPS greater than Whites ($P<0.001$). Transmission electron microscopy of skeletal muscle biopsies in resistant hypertension patients demonstrates mitochondria cristae lysis, myofibrillar loss, large lipid droplets, and glycogen accumulation.

Conclusions: These data warrant a large study to examine the role of XO and mitochondrial mtDNA DAMPs in cardiac remodeling and heart failure in Black adults with resistant hypertension.

Keywords

biopsy; blood pressure; hypertension; mitochondria; xanthine oxidase

Introduction

Hypertension among Black adults in the United States has one of the highest prevalence rates in the world[1] and is related to major adverse changes in left ventricular (LV) structure and function due, at least in part, to the higher arterial afterload.[2] Hypertension is an underlying factor in >50% of Black adults with heart failure (HF)[3] and is the strongest risk factor for HF in that population.[4] Black adults have a 50% increased incidence of HF, due in large part to the greater prevalence and severity of hypertension,[5] and HF occurs 8 years earlier in Black adults as compared with Whites.[6,7] Further, Black adults with HF have worse quality of life and depressive symptoms[6] and have a 5-year mortality rate that is 34% higher than in White adults.[7,8] Although Black adults have the highest death rate for HF,[9] they are consistently underrepresented in clinical trials.[3,7] The greater HF burden among Black adults calls for further work to discover effective preventive and therapeutic strategies for this higher-risk population.

Arterial afterload is higher in Black adults compared with White adults, associated with known racial differences in arterial stiffness and intravascular volume.[2] This higher arterial afterload is related to more adverse changes in cardiac structure and function, likely related to the increased incidence of HF in this high-risk population.[9] Black adults have higher levels of oxidative stress, even after adjustment for differences in cardiovascular disease risk factors and inflammation.[9] We previously reported significant LV hypertrophy and diastolic dysfunction with normal systolic function in a cohort of persons with resistant hypertension (RHTN).[10]

XO (xanthine oxidase) is a major enzyme in the production of urate during purine catabolism and is widely distributed in the heart, liver, gut, lung, kidney, and brain, as well as in the plasma.[11] In patients with gout, increased urate is linked to RHTN[12] and HF.[13] XO oxidizes hypoxanthine and xanthine to generate hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\bullet-}$) as a byproduct, which damages mitochondria leading to bioenergetic dysfunction and further amplification of oxidant generation. For example, initial damage to mitochondrial proteins by XO-derived oxidants can mediate diminution of ATP as well as enhanced electron leak and further increase the generation of $O_2^{\bullet-}$, which can dismute to peroxide or react rapidly with nitric oxide (NO) to form peroxynitrite ($ONOO^-$) and further propagate the process.

Mitochondrial DNA (mtDNA) has been shown to be highly susceptible to oxidative stress and damage in the setting of cardiovascular disease risk factors.[14–20] In this regard, we reasoned that increased XO-derived oxidative stress that causes mtDNA damage should also promote the release of fragments of damaged mtDNA from the mitochondria, producing mtDNA damage-associated molecular patterns (mtDNA DAMPs).[21,22] These mtDNA DAMPs are potent activators of the innate immune response through several pathways including activation of TLR (toll-like receptor) 9 with promotion of proinflammatory cytokine release.[23] Given the higher level of oxidative stress in Black adults,[9] the purpose of this study is to examine racial differences in XO activity and mtDNA DAMPs in patients with RHTN.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Sample

This study is an analysis of a cohort of patients with RHTN 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.[10,24] Control subjects were recruited for the XO and mtDNA DAMP levels. Control subjects were included if they did not have a history of cardiovascular disease or smoking and were not taking any cardiovascular medication, including statins (n=37, 30% Black, 54% female). All control subjects and RHTN patients signed an informed consent form approved by the University of Alabama at Birmingham Institutional Review Board.

Seated clinic blood pressure (BP) was measured manually using a mercury sphygmomanometer and an appropriately sized cuff after 5 minutes of rest. The mean of 2 readings was recorded as the clinic BP. All of the subjects underwent 24-hour ambulatory BP monitoring (SpaceLabs or Suntech Medical). RHTN was defined as having a resting BP≥140/90 mm Hg at 2 clinic visits despite the use of ≥4 antihypertensive medications at pharmacologically effective doses. All participants were on a stable antihypertensive regimen for at least 1 month before entering the study, as confirmed by medical records. Patients were excluded from this study for secondary causes of hypertension other than primary aldosteronism (ie, 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 urate lowering therapy, that is, allopurinol and febuxostat, were excluded from the analysis.

Racial identity was self-reported: Black race included Black, and Afro-Caribbean persons. The 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.

Laboratory Measures

Peripheral venous blood samples were drawn from all participants during early morning clinical assessments. Following size exclusion chromatography with Sephadex G-25 to remove endogenous purines and low-molecular-weight inhibitors, plasma total XO plus XD (xanthine dehydrogenase) activity was determined by the rate of uric acid production in the presence of xanthine (75 μM) with nicotinamide adenine dinucleotide (NAD^+, 0.5 mmol/L).[10] The activity of XO was measured by the rate of uric acid production in the presence of xanthine (75 μM) without NAD^+. After 60 minutes 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. 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 before 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 as a concentration relative to total protein content of the sample.

Uric Acid Levels

Plasma uric acid levels were determined as previously reported.[25] Briefly, following plasma deproteination, drying under nitrogen and resuspension in mobile phase, uric acid was separated via HPLC with a C18 column in an isocratic manner (ThermoFisher Vanquish). Detection and quantification were accomplished electrochemically.[25]

Cardiac Magnetic Resonance Imaging

All participants underwent cardiac magnetic resonance imaging to evaluate their cardiac anatomy and function, as previously described.[10,26] Briefly, cardiac magnetic resonance 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 and end systole. These contours were propagated throughout the cardiac cycle using in-house software.[10,26] 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.[10,26] Peak early and late diastolic mitral annular velocities were calculated using

nonrigid registration to track a manually selected point on the mitral annulus through the cardiac cycle.

Skeletal Muscle Biopsies

Needle muscle biopsies of the vastus lateralis were performed on persons with RHTN. Tissue samples were flash frozen and stored at −80 °C until analysis. Muscle fiber ultrastructure was analyzed using transmission electron microscopy as previously described in our laboratory.[24]

Mitochondrial DNA Damage-Associated Molecular Patterns

mtDNA DAMPs were assessed in cell free plasma collected from participants with RHTN and normotensive volunteers. Briefly, cell-free DNA was extracted from 100 μL of plasma using a MagMax Cell-Free DNA Isolation Kit (Applied Biosystems) following the manufacturer's instructions with minor adaptations (2.5 μL of the MagMax Cell-Free DNA Magnetic Beads per sample was used instead of 5 μL per sample). Cell-free DNA was eluted in 20 μL volumes and aliquots were stored at −80 °C. mtDNA DAMPs were assessed via amplification of DNA within the NADH dehydrogenase subunit 1 and NADH dehydrogenase subunit 6 regions of the mtDNA by real-time polymerase chain reaction as previously described[22,27] with minor modifications using a StepOne Plus Real-Time polymerase chain reaction system (ThermoFisher Scientific). DAMP copies were quantified relative to standard samples of known copies (10–50 000 copies). Data are expressed as mtDNA DAMPs per microliter of plasma.

Statistical Analysis

Descriptive statistics were calculated for all study variables, and data were reviewed for normality assumptions and outliers in preparation for analysis. XO activity was log (LN) transformed to reduce skewness for analyses. The influence of outliers was examined by examining skewness and significant variations between mean and median of each variable. Outliers were minimal and within expected limits; no adjustments for outliers were needed. Data are presented as mean±SD for continuous variables and counts (percent) for categorical variables. Between-group testing was performed using the Student *t* test for continuous variables and chi-squared tests to compare binary variables. Multivariable adjusted linear regressions were used to examine linear relationships among continuous outcome variables, controlling for covariates, namely age, sex, and body mass index. Creatinine was used to control for renal function in uric acid analyses. Partial correlations for the variables of interest corrected for covariates were reported with Bonferroni-corrected *P*. All data were analyzed using SAS version 9.4 with an alpha set at 0.05. MtDNA DAMPs analyses utilized a 2-way ANOVA (group and race), followed by an all pairwise multiple comparison procedure (Holm-Sidak method), using SigmaPlot 12.5.

Results

Demographics and Clinical Measures

Black RHTN patients were significantly younger with a higher diastolic BP (Tables 1 and 2) than White adults with RHTN. There was a higher proportion of diabetes in Black adults

compared with White adults with RHTN. Blood creatinine was significantly higher among Black participants as compared with White participants. There were no differences in sex or measures of body size (body mass index, body surface area). There were no significant differences in measures of aldosterone, sodium, or renin activity. Angiotensin II receptor blocker, angiotensin-converting enzyme inhibitor, diuretic, calcium channel blocker, and β-blocker treatment did not differ between Black and White RHTN patients.

Baseline Left Ventricular Function and Morphology

Black RHTN participants had a higher wall thickness with trends toward a lower mid-wall radius/wall thickness ratio and left ventricle end diastole (LVED) mass/volume ratio (Table 2). Left ventricle ejection fraction and LV fractional shortening did not differ between groups. Black RHTN participants had a higher normalized peak late diastolic filling rate (A, EDV/s), which corresponded to a trend toward a lower E/A ratio.

24-Hour Urinary Aldosterone and Sodium

Plasma aldosterone and renin activity and urinary sodium and aldosterone did not differ between Black and White RHTN patients. However, 24-hour urinary sodium (mg/24 hour per kg) was positively related to left ventricle end diastolic volume (r=0.527, P=0.001), LV mass (r=0.394, P=0.02), and LV wall thickness (r=0.356, P=0.04) among Black but not White RHTN participants, when controlling for sex, body mass index, and age. Urinary aldosterone (μg/24 hour) was positively associated with LVED wall thickness (Black: r=0.561, P<0.001, White: r=0.410, r=0.002), left ventricle end diastolic volume index (Black: r=0.336, P=0.04, White: r=0.359, P=0.007), and LVED mass index (Black: r=0.543, P<0.001, White: r= 0.466, P<0.001) among both Black and White RHTN participants, controlling for sex, body mass index, and age. However, 24-hour urinary aldosterone was associated with LVED mass/volume ratio (r=0.404, P=0.01) among the Black RHTN participants only.

Plasma XO Activity

Plasma XO activity was higher among Black versus White RHTN participants (Table 2). There was a significant relationship between XO activity and uric acid, when controlling for blood creatinine concentration as a measure of kidney function (r=0.442, P=0.001). Diastolic BP, but not systolic BP, was related to XO activity (r=0.705, P<0.001) overall and by group (Black: r=0.800, P<0.001, White: r=0.648, P<0.001). Plasma XO activity had a positive relationship with both LVED wall thickness (r=0.401, P=0.03) and LV mid-wall radius/wall thickness ratio (r=0.427, P=0.02) among the Black but not White RHTN participants.

mtDNA DAMPs

Quantification of mtDNA DAMP levels within the NADH dehydrogenase subunit 1 and NADH dehydrogenase subunit 6 regions indicated that RHTN patients had higher serum DAMP copies than normotensive controls (P<0.001 and P=0.018; Figure 1A and 1B) with no differences between Black and White controls (Figure 1C and 1D). For NADH dehydrogenase subunit 1 (ND1; Figure 1C), White RHTN did not differ (P=0.063) whereas Black RHTN had higher mtDNA DAMPS than race-matched normotensive controls

(P<0.001). Black adults had higher mtDNA DAMPs than Whites with RHTN (P<0.001). For NADH dehydrogenase subunit 6 (Figure 1D), RHTN patients had increased mtDNA DAMP levels compared with Black normotensive controls (P<0.001). However, no differences were observed between White RHTN and race-matched normotensive controls (P=0.664). Black RHTN had increased mtDNA DAMPs compared with White RHTN (P<0.001).

Skeletal Muscle Transmission Electron Microscopy

Skeletal muscle biopsies were performed in an extra subset of 5 patients with RHTN and 2 normotensive subjects (Table 3). Patients 01, 04, and 05 had no history of diabetes and Patients 08 and 10 were insulin requiring diabetics. Representative transmission electron microscopy images of skeletal muscle biopsies from 5 patients with RHTN and one normal subject at 8000X (left) and 16 000X (right) are shown (Figure 2). All samples from RHTN patients demonstrated numerous subsarcolemmal and interfibrillar large lipid droplets (LD) surrounded by large accumulations of glycogen (Gly) and clusters of small, disorganized mitochondria within glycogen. There was also evidence of glycophagy in RHTN patient HTN04 (Figure 2). Numerous mitochondria had evidence of cristae lysis, which collected in areas of myofibrillar breakdown. Each patient had elevated XO activity, while the 2 normal subjects had no detectable XO activity (Table 3). Taken together, these findings support mitochondrial pathology and a metabolic syndrome with or without insulin-requiring diabetes.

Discussion

This is the first study to show increased plasma XO activity and mtDNA DAMP levels in Black adults with RHTN, compared with White adults with RHTN. Mitochondrial DNA DAMPs activate TLRs, resulting in inflammation, vascular remodeling, and hypertension.[28] Activation of endothelial XO is linked to a major source of oxidative stress and endothelial dysfunction.[29–32] Exposure of mitochondria to peroxide and superoxide, products of XO catabolism, has been shown to increase mtDNA DAMPs and activation of TLR receptors in pulmonary endothelial cells.[33,34] Skeletal muscle biopsies in RHTN patients (n=5) with increased plasma XO activity demonstrated diffuse mitochondrial cristae lysis, small clusters of mitochondria in areas of myofibrillar lysis, and decreased electron density of sarcomeric myofibrils compared with normal controls with undetectable XO activity. Thus, XO activation may set up a feed forward cycle of mitochondrial damage, mitochondrial reactive oxygen species production, mtDNA DAMP release, and inflammation in the pathogenesis of hypertension end organ injury.[28]

We have previously reported that RHTN is associated with increases in LV volume and mass,[10,26] dietary salt intake,[35] and XO activity.[10] Here, we take this scenario one step further with regard to the Black population. When stratified by race, XO activity was positively related to urinary sodium (mg/24 hour per kg), LV end diastolic volume, LV mass, and LV wall thickness among Black but not White RHTN patients. Black patients have a greater propensity to salt sensitivity and suppressed plasma renin, suggesting a predisposition to sodium retention.[36–38] Black adults also have higher levels of oxidative stress even after adjustment for differences in cardiovascular disease risk factors and

inflammation,[9] and greater large artery stiffness.[39] Figure 3 presents a scenario where dietary salt and hypertension produces an increase in XO activity and mtDNA DAMPs in Black adults with RHTN.

The origin of increased plasma XO activity in resistant hypertension is multifactorial. Studies in type II pulmonary alveolar cells show an increase in XO activity in response to stretch and an increase in mitochondrial reactive oxygen species production.[40,41] Cyclical stretch of adult rat cardiomyocytes and induction of volume overload stress results in increased cardiomyocyte XO activity, mitochondrial reactive oxygen species production, mitochondrial cristae lysis, and myofibrillar breakdown—all of which are prevented by allopurinol.[42] Thus, increased XO activity in Black patients could result from a combination of salt sensitivity and increased BP.

LV diastolic dysfunction in RHTN has been attributed to increased LV stiffness due to interstitial collagen accumulation because of chronic pressure overload.[43] However, XO resides in the human cardiomyocyte along the z-disc[24] in the sarcoplasmic reticulum membrane of the cardiomyocyte near the ryanodine receptor (RyR) and sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase 2 (SERCA2) pump.[44] XO-mediated oxidative modification of RyR and SERCA2 causes increased cytosolic Ca^{2+}, decreases myofilament calcium sensitivity,[45,46] and impairs LV systolic and diastolic function. Thus, in addition to pressure overload–induced collagen accumulation, activation of XO can also contribute to LV diastolic dysfunction in the Black population.

In our RHTN patients, there is a significant relationship between XO activity and uric acid, when controlling for creatinine as a measure for renal function (r=0.442, P=0.001). There is evidence that intracellular uric acid produced by XO also causes oxidative stress by stimulating NADPH oxidase and translocating it to the mitochondria leading to de novo lipogenesis in liver cells.[47] Skeletal muscle biopsies in 5 patients with RHTN demonstrate numerous large lipid droplets surrounded by glycogen and glycophagy in both the subsarcolemmal and interfibrillar regions of the sarcomere. Subsarcolemmal mitochondria provide bioenergetic support of signal transduction, fat oxidation, and substrate transport.

An impairment of electron transport chain activity in this subcellular location has been linked to the pathogenesis of insulin resistance. These findings of metabolic syndrome were present in both insulin requiring diabetic (RHTN 08 and 10) and nondiabetic RHTN patients (RHTN 01, 04, 05). These data suggest an element of metabolic syndrome in patients with RHTN. Additional studies that examine potential racial differences are indicated to determine if metabolic syndrome contributed to the increase in circulating mtDNA DAMPs in RHTN.

There is currently no evidence for genetic control of XO activity per se in Black adults with RHTN. Considering urate levels as a marker of XO activity, there was no genome-wide significant association of the XO locus with serum urate in the largest genome wide associated study performed to date.[48] However, there was a signal approaching significance ($P<10^{-6}$) for association with serum urate levels in people of White European ancestry. The cohort of subjects of self-identified Black ancestry was too small and under-powered to

draw any conclusion.[49] A single candidate gene study of people of White European ancestry reported association of genetic variation in XO with BP and hypertension.[50] In general, there is a dearth of knowledge of genetic control of XO activity, both at the gene itself and other factors controlling expression and activity, most especially in people of sub-Saharan ancestry.

Perspectives

There is greater XO activity and evidence of mitochondrial damage through increased mtDNA DAMPs in Black versus White patients with resistant hypertension. A major limitation of the current study, as with all retrospective studies, is the potential for selection bias in a small number of patients on multiple medications. These results warrant a larger study that includes metabolic syndrome and XO as a potential therapeutic target to reduce mitochondrial damage and attenuate left ventricular diastolic dysfunction in Black adults with resistant hypertension.

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Novelty and Relevance

What Is New?

This is the first study to show increased plasma xanthine oxidase activity and mitochondrial DNA damage-associated molecular pattern levels in Black adults with RHTN, compared with White adults with RHTN.

What Is Relevant?

Mitochondrial DNA DNA damage-associated molecular patterns activate TLRs (toll-like receptors), resulting in inflammation, vascular remodeling, and hypertension.

Clinical/Pathophysiological Implications?

Xanthine oxidase activation may set up a feed forward cycle of mitochondrial damage, mitochondrial reactive oxygen species production, mitochondrial DNA damage-associated molecular pattern release, and inflammation in the pathogenesis of hypertension end organ injury. These data warrant a large study to examine the role of xanthine oxidase and mitochondrial mitochondrial DNA damage-associated molecular patterns in cardiac remodeling and heart failure in Black adults with resistant hypertension.

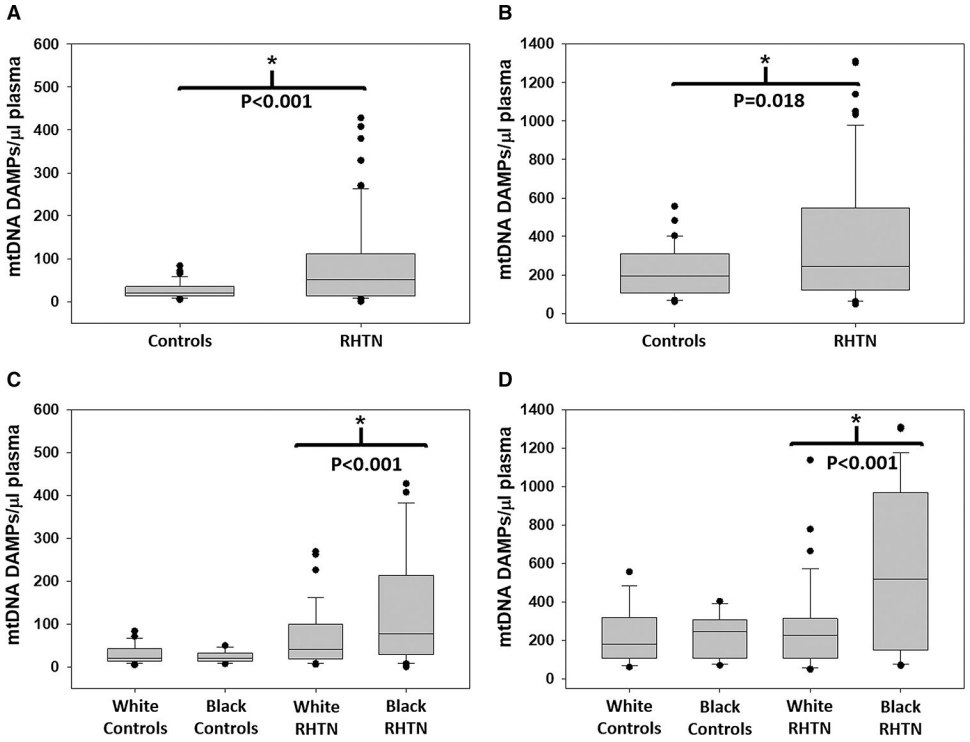

Figure 1. Box plots presenting quantitative mitochondrial DNA damage-associated molecular patterns (mtDNA DAMP) levels in plasma samples from control and resistant hypertension (RHTN) patients.

Cell-free DNA was extracted from plasma samples, and levels of mtDNA DAMPs from the NADH dehydrogenase subunit 1 (ND1) and NADH dehydrogenase subunit 1 (ND6) regions of the mtDNA were quantitatively determined. **A** and **B**, mtDNA DAMP levels of controls and RHTN patients from the ND1 and ND6 regions, respectively. **C** and **D**, mtDNA DAMP levels of controls and RHTN patients segregated by race for the ND1 and ND6 regions, respectively.

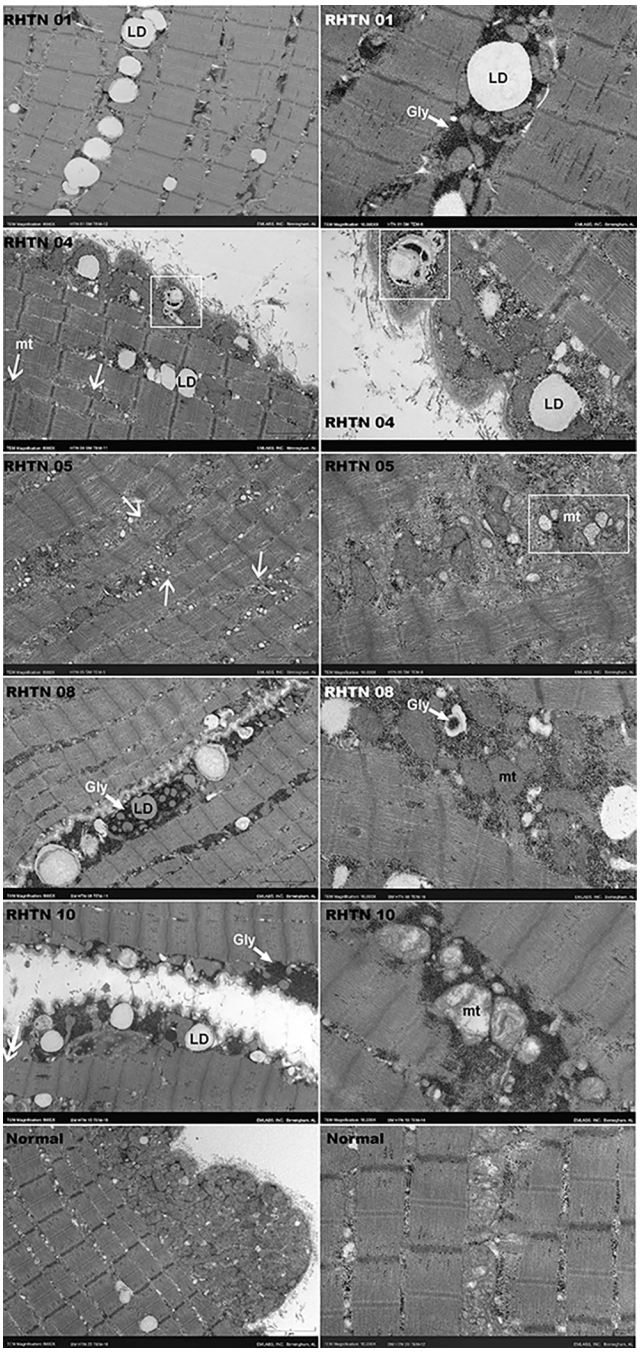

Figure 2. Transmission electron microscopy images of skeletal muscle biopsies from 5 patients with resistant hypertension and one normal subject at 8000X (left) and 16 000X (right).

RHTN Patient 01: 35-y-old Black female with numerous interfibrillar large lipid droplets (LDs) surrounded by large accumulations of glycogen (Gly) and clusters of small, disorganized mitochondria within glycogen. RHTN Patient 04: 48-y-old Black male with large subsarcolemmal lipid droplets and evidence of glycophagy (white box). RHTN Patient 05: 74-y-old White female with myofibrillar breakdown (arrows) and multiple small mitochondria (mt) in disarray with lysis of cristae (box). RHTN Patient 08: 70-y-old Black female with large increases in glycogen (Gly) amidst numerous LDs and many

multiple sized mitochondria (mt) in areas of myofibril lysis. RHTN Patient 10 has large accumulations of subsarcolemmal glycogen and large lipid droplets. Interfibrillar areas have numerous mitochondria (mt) with cristae lysis. The skeletal muscle biopsy from the Normotensive control subject (HTN20), a 35-y-old White female showed none of these pathological changes.

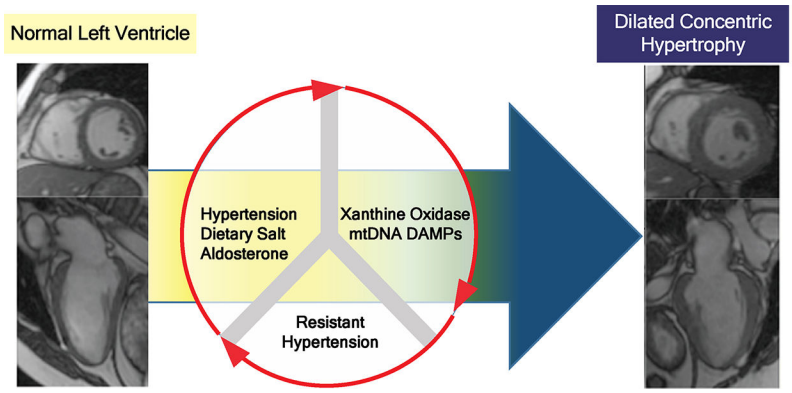

Figure 3. Scenario that connects hypertension, dietary salt indiscretion, and aldosterone to a combined pressure and volume overload as demonstrated by a dilated concentric hypertrophy.
However, in Black adults, stretch on the heart and vascular endothelium perpetuates a more aggressive vicious cycle of XO (xanthine oxidase), and mitochondrial DNA damage-associated molecular patterns (mtDNA DAMPs).

Table 1.

Demographic and Clinical Characteristics in RHTN Patients

	Black (n=40)	White (n=51)	*P* value
Age, y	52±10	59±10	0.001
Female, n/%	20 (50%)	23 (45%)	0.834
Body mass index, kg/m^2	33.6±7.1	32.1±6.0	0.260
Body surface area, m^2	2.17±0.04	2.08±0.3	0.105
Diabetes, n/%	14 (35%)	8 (16%)	0.033
ACE inhibitor	24 (60%)	33 (65%)	0.176
Ang II receptor blocker	22 (57%)	28 (56%)	0.530
Diuretic	38 (95%)	49 (96%)	0.580
Beta blocker	28 (70%)	37 (73%)	0.356
Calcium channel blocker	31 (78%)	37 (73%)	0.606
Plasma aldosterone, ng/dL	11±1	9±1	0.507
Plasma renin activity, ng/mL per h	25±15	43±20	0.549
Plasma creatinine, mg/dL	1.14±0.3	1.04±0.3	0.036
Urine aldosterone, μg/24 h	12±1	13±2	0.519
Urine sodium, mg/24 h per kg	48±4	50±3	0.934

ACE indicates angiotensin-converting enzyme; and RHTN, resistant hypertension.

Table 2.

Differences in Left Ventricular Function and Morphology, Xanthine Oxidase Activity, and Blood Pressure at Baseline in RHTN

		RHTN	*P* value*
		Mean±SD	
Normalized peak early diastolic filling rate (E), EDV/s	Black	2.50±0.8	0.9
	White	2.26±0.7	
Normalized peak late diastolic filling rate (A), EDV/s	Black	2.65±0.9	0.035
	White	2.10±0.8	
E/A ratio	Black	1.05±0.5	0.7
	White	1.40±1.3	
Normalized peak early diastolic MA velocity, % long axis length/s	Black	65.73±26.7	0.9
	White	61.59±24.2	
LV end-diastolic volume index, mL/m^2	Black	70.94±18.7	0.9
	White	68.84±14.6	
LV end-diastolic mass index, g/m^2	Black	70.19±18.5	0.8
	White	62.68±16.8	
LV end-diastolic wall thickness, cm	Black	1.09±0.22	0.4
	White	0.99±0.19	
LV end-diastolic mid-wall radius to wall thickness ratio	Black	2.86±0.7	0.07
	White	3.24±0.8	
LV end-diastolic mass to volume ratio	Black	1.04±0.26	0.2
	White	0.93±0.28	
LV end-diastolic fractional shortening, %	Black	32.42±7.6	0.3
	White	33.21±7.9	
LV ejection fraction, %	Black	67±8	0.2
	White	70±7	
Xanthine oxidase activity, μU/mgNormal: 0.017±0.004[10]	Black	0.06±0.08	0.02
	White	0.03±0.03	
Uric acid, mg/dLNormal: 3.21±1.09	Black	4.25±1.6	0.03
	White	3.53±1.4	
MT-ND1, mtDNA DAMPs/μLNormal: 27±19	Black	133±130	0.02
	White	67±69	
MT-ND6, mtDNA DAMPs/μLNormal: 224±131	Black	568±422	0.003
	White	259±232	
Systolic blood pressure, mm Hg	Black	150±24	0.2
	White	146±18	
Diastolic blood pressure, mm Hg	Black	90±14	0.02
	White	84±13	

RHTN: Black n=40, White n=51;

[10]—Values taken from reference 10.

LV indicates left ventricular;

MA, mitral annular;

MT-ND1, mitochondrial genome for NADH-ubiquinone oxidoreductase chain 1; and

MT-ND6, mitochondrial genome for NADH-ubiquinone oxidoreductase chain 6.

[*]Bonferroni-adjusted *P* Value for Black vs White RHTN.

Table 3.

RHTN With Skeletal Muscle Biopsies for TEM

	Age	Sex	Race	BMI, kg/m^2	BSA, m^2	Diabetes	Medications	LVEF, %	LVED Wall thickness, mm	XO activity, μU/mg
RHTN										
HTN01	35	F	Black	40.9	2.27	No	ARB, HB, CCB, diuretic	N/A	N/A	0.150
HTN04	48	M	Black	29.7	2.26	No	ACEi, BB, diuretic	65	4.9	0.369
HTN05	74	F	White	28.3	1.85	No	ARB, BB, CCB, diuretic	61.6	4.4	0.064
HTN08	70	F	Black	33.0	1.97	Yes	ACEi, BB, CCB, insulin	64.7	5.6	0.035
HTN10	55	F	Black	32.2	1.72	Yes	ARB, CCB, HBP, diuretic, insulin	65	4.3	NM
Normal										
HTN20	35	F	White	18.2	1.65	No	None	N/A	N/A	Undetectable
HTN21	50	M	White	24	1.77	No	None	N/A	N/A	Undetectable

Medications:

ACEi indicates angiotensin II converting enzyme inhibitor;

ARB, angiotensin II receptor blocker;

BB, beta blocker;

CCB, calcium channel blocker;

HB, other high blood pressure medication;

LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; NM, not measured; and

XO, xanthine oxidase.