Refractory Hypertension Is not Attributable to Intravascular Fluid Retention as Determined by Intracardiac Volumes

Alejandro Velasco,* Mohammed Siddiqui,* Eric Kreps, Pavani Kolakalapudi, Tanja Dudenbostel, Garima Arora, Eric K. Judd, Sumanth D. Prabhu, Steven G. Lloyd, Suzanne Oparil, David A. Calhoun

Abstract—Refractory hypertension (RfHTN) is an extreme phenotype of antihypertensive treatment failure defined as lack of blood pressure control with ≥5 medications, including a long-acting thiazide and a mineralocorticoid receptor antagonist. RfHTN is a subgroup of resistant hypertension (RHTN), which is defined as blood pressure >135/85 mm Hg with ≥3 antihypertensive medications, including a diuretic. RHTN is generally attributed to persistent intravascular fluid retention. It is unknown whether alternative mechanisms are operative in RfHTN. Our objective was to determine whether RfHTN is characterized by persistent fluid retention, indexed by greater intracardiac volumes determined by cardiac magnetic resonance when compared with controlled RHTN patients. Consecutive patients evaluated in our institution with RfHTN and controlled RHTN were prospectively enrolled. Exclusion criteria included advanced chronic kidney disease and masked or white coat hypertension. All enrolled patients underwent biochemical testing and cardiac magnetic resonance. The RfHTN group (n=24) was younger (mean age, 51.7±8.9 versus 60.6±11.5 years; P=0.003) and had a greater proportion of women (75.0% versus 43%; P=0.02) compared with the controlled RHTN group (n=30). RfHTN patients had a greater left ventricular mass index (88.3±35.0 versus 54.6±12.5 g/m^2; P<0.001), posterior wall thickness (10.1±3.1 versus 7.7±1.5 mm; P=0.001), and septal wall thickness (14.5±3.8 versus 10.0±2.2 mm; P<0.001). There was no difference in B-type natriuretic peptide levels and left atrial or ventricular volumes. Diastolic dysfunction was noted in RfHTN. Our findings demonstrate greater left ventricular hypertrophy without chamber enlargement in RfHTN, suggesting that antihypertensive treatment failure is not attributable to intravascular volume retention. **(*Hypertension*. 2018;72:343-349. DOI: 10.1161/HYPERTENSIONAHA.118.10965.)** • **Online Data Supplement**

Key Words: blood pressure ■ diuretics ■ hypertension ■ magnetic resonance imaging ■ phenotype

Refractory hypertension (RfHTN), an extreme phenotype of antihypertensive failure, is defined as failure to control blood pressure (BP) with ≥5 antihypertensive agents, including chlorthalidone and a MR (mineralocorticoid receptor) antagonist.[1] This phenotype represents a subgroup of patients with resistant hypertension (RHTN) defined as lack of BP control in spite of the use of ≥3 antihypertensive agents, including a diuretic, or controlled BP with use of ≥4 antihypertensive agents, so-called controlled RHTN.[2]

The prevalence of RfHTN among patients referred to hypertension specialty clinics has been reported to be between 5% and 10%.[3,4] RfHTN patients are more often women and of African ancestry as compared with patients with controlled RHTN.[1] Furthermore, patients with RfHTN have persistent BP elevation by ambulatory monitoring and a low rate of white coat effect.[5] Not surprisingly, large, community-based cohort studies have shown that RfHTN is associated with an increased risk of stroke and coronary heart disease as compared with hypertensive patients in general.[4]

Prior studies have indicated that RHTN is generally attributable to persistent intravascular fluid retention. Taler et al[6] found that thoracic fluid content was increased in patients with uncontrolled RHTN, and intensification of diuretic therapy was necessary to counteract this fluid retention to control BP. In a study by Gaddam et al,[7] patients with uncontrolled RHTN with higher levels of B-type natriuretic peptide (BNP) along with greater left atrial (LA) and left ventricular (LV) volumes had significant improvement in BP, and normalization of intracardiac volumes after diuresis was enhanced using spironolactone.

In contrast, few recent studies have demonstrated that thoracic fluid content is similar in patients with RfHTN and controlled RHTN.[1] However, the RfHTN patients had elevated heart rate and urinary normetanephrine levels as compared

Received February 1, 2018; first decision February 9, 2018; revision accepted May 10, 2018.

From the Division of Cardiovascular Disease (A.V., G.A., S.D.P., S.G.L.), Vascular Biology and Hypertension Program, Division of Cardiovascular Disease (M.S., T.D., S.O., D.A.C.), Division of Nephrology (E.K.J.), and Department of Internal Medicine (E.K.), University of Alabama at Birmingham; and Division of Cardiovascular Disease, University of South Alabama, Mobile (P.K.).

*These authors contributed equally to this work.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.118.10965/-/DC1.

Correspondence to Alejandro Velasco, Division of Cardiovascular Disease, University of Alabama at Birmingham, BDB 201, 1808 7th Ave S, Birmingham, AL 35294. E-mail avelasco-delacuesta@uabmc.edu

with controlled RHTN.[1,8] These differences suggest a potential mechanistic distinction between RfHTN and RHTN in general in that RfHTN may be more neurogenic in cause, that is, secondary to excess sympathetic output, as opposed to being volume dependent, that is, persistent intravascular fluid retention, as is typical of RHTN. If true, such a mechanistic distinction would have important therapeutic implications in that the treatment of RfHTN may require more effective sympatholytic therapies for BP control as opposed to further intensification of diuretic therapy.

The objective of our study was to determine whether antihypertensive treatment failure in patients with RfHTN is characterized by persistent intravascular fluid retention as demonstrated by higher LA and LV end-diastolic (LVED) volumes and higher BNP levels. Patients with controlled RHTN served as the comparator group. We performed extensive laboratory testing and cardiac phenotyping of patients with RfHTN to assess ventricular dimensions, ventricular function, and the LV mass/volume ratio as compared with controlled RHTN.

Methods

The authors declare that all supporting data are available within the article.

Study Population

We prospectively enrolled consecutive patients who were referred to the University of Alabama at Birmingham Hypertension Clinic for uncontrolled RHTN (automated office BP [AOBP] >135/85 mm Hg with use of ≥3 antihypertensive medications, including a diuretic) between April 2014 and January 2018. RfHTN was defined as lack of BP control despite the use of ≥5 antihypertensive agents, including chlorthalidone and an MR antagonist, typically spironolactone, after a minimum of 3 follow-up visits. Office BP readings were obtained using AOBP as described below. All patients were evaluated for hyperaldosteronism and pheochromocytoma. Renal artery stenosis was assessed if clinically indicated. Exclusion criteria were nonadherence based on self-report or low medication refill rates; chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 mL/min per 1.73 m^2), or if pregnant or nursing. All patients underwent 24-hour ambulatory BP monitoring (ABPM). RfHTN patients with white coat effect (defined as ambulatory awake BP <135/85 mm Hg and clinic AOBP >135/85 mm Hg) were excluded, as well as controlled RHTN with uncontrolled masked hypertension, (defined as ambulatory awake BP >135/85 mm Hg and clinic AOBP <135/85 mm Hg). The University of Alabama at Birmingham Institutional Review Board approved the study, and written informed consent was obtained from all participants.

Automated Office BP Measurement

The clinic AOBP was measured using the BpTRU device (Coquitlam BC, Canada), after at least 5 minutes of quiet rest in a sitting position with the back supported and the arm supported at heart level.[9] An appropriate sized cuff was used with a cuff bladder encircling at least 80% of the arm.[10,11] The BpTRU AOBP device automatically obtains 6 serial BP readings, 1 minute apart, before displaying the average of the last 5 readings with mean arterial pressure and BP variability. The assessments were unattended, that is, unobserved in clinic.[10,12–15] A BP cutoff of ≥135/85 mm Hg for elevated BP was used based on recent literature validating automated BP devices.[16,17]

Twenty-Four Hours ABPM

Study patients also underwent ABPM using an automated, noninvasive, oscillometric device (Oscar 2; SunTech Medical Inc, Morrisville, NC).[18,19] ABPM measurements were obtained every 20 minutes during the daytime (awake) and every 30 minutes during the night-time (asleep) phases of the 24-hour period. Awake and asleep times were self-reported by the patient. ABPM was determined to be valid if >80% of measurements were successful. Controlled BP by ABPM was defined as mean daytime (awake) BP <135/85 mm Hg.[18,19]

Cardiac Magnetic Resonance Imaging

All patients underwent cardiac magnetic resonance (CMR) to evaluate cardiac and aortic structure and function. CMR was performed with a 1.5-T clinical scanner optimized for cardiac imaging (Signa, GE Healthcare) using a 4-element phased-array surface coil and prospective electrocardiographic triggering as described previously.[20] Imaging was performed using a rapid steady-state free

Table 1. Baseline Characteristics in Refractory and Controlled Resistant Hypertension

Patient Characteristics	Refractory Hypertension (n=24)	Controlled Resistant Hypertension (n=30)	*P* Value
Demographics			
Age, y	51.7±8.9	60.6±11.5	0.003
Women (%)	18 (75.0%)	13 (43.3%)	0.02
Blacks (%)	19 (79.2%)	16 (53.3%)	0.05
Body mass index, kg/m^2	34.6±4.8	31.7±5.7	0.05
Body surface area, m^2	2.00±0.26	2.06±0.26	0.428
Comorbidities, n (%)			
Lifelong nonsmoker	14 (58.3)	20 (66.7)	0.4
Dyslipidemia	11 (45.8)	17 (56.7)	0.43
Congestive heart failure	5 (20.8)	1 (3.3)	0.04
Arrhythmia	2 (8.3)	4 (13.3)	0.56
Coronary artery disease	3 (12.5)	2 (6.7)	0.46
Peripheral vascular disease	4 (16.7)	1 (3.3)	0.09
Diabetes mellitus	12 (50)	7 (23.3)	0.04
Prior stroke/transient ischemic attack	5 (20.8)	2 (6.7)	0.12
Obstructive sleep apnea	12 (50)	11 (36.7)	0.32
Automated office BP			
Systolic BP, mm Hg	164.8±21.5	115.6±12.1	<0.0001
Diastolic BP, mm Hg	95.8±13.0	69.9±8.1	<0.0001
Heart rate, bpm	75.3±13.3	68.0±11.1	0.03
Biochemical testing			
B-type natriuretic peptide, pg/mL*	24.8 (2.0–141.5)	15.4 (2.0–242.2)	0.38
24-hour urine sodium, mmol/d	162.7±76.8	149.4±47.6	0.446
24-hour urine proteinuria, mg	435.2±731.3	170.0±324.5	0.154
24-hour urine creatinine, mg	1601.7±662.9	1686.1±613.0	0.636

BP indicates blood pressure.
*Median (range).

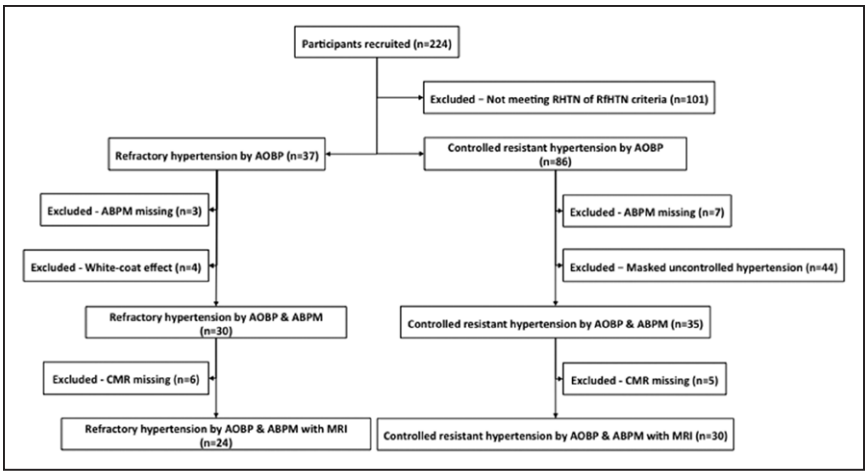


Figure 1. Schematic of enrolled study participants. ABPM indicates ambulatory blood pressure monitoring; AOBP, automated office blood pressure monitoring; CMR, cardiac magnetic resonance; MRI, magnetic resonance imaging; RfHTN, refractory hypertension; and RHTN, resistant hypertension.

precession cine sequence (10 k-space lines per segment). Standard short-axis and 2- and 4-chamber images were obtained from appropriate scout images and used for all the quantitative of right ventricular, LV, and LA volumes. Cine images were reconstructed into 20 cardiac phases.

Slice thickness for the short-axis, 2-chamber, and 4-chamber images was 8 mm without any slice gap. The following parameters were used: matrix size, 256×128; field of view, 40×40 cm; typical repetition time, 3.9 ms; typical echo time, 1.6 ms; flip angle, 45°; bandwidth, 125 Hz per pixel; and typical acquired temporal resolution, 39 ms. CAAS Flow and CAAS MRV software (Pie Medical Imaging, Maastricht, the Netherlands) was used to evaluate ventricular and atrial volume and function. LA contours were manually drawn on 2- and 4-chamber long-axis views at ventricular end systole; this phase corresponds with the largest LA area. The inferior LA border was defined as the plane of the mitral annulus. We excluded the pulmonary veins and the LA appendage as recommended by echocardiographic guidelines.[21] The LA base-to-mitral-valve length was obtained from the middle of the plane of the mitral annulus to the posterior wall. LA volume was calculated by the area-length method $V=8/3\pi$ (A_{2ch} A_{4ch}/L), where A_{2ch} and A_{4ch} represent the LA area acquired from the long-axis 2- and 4-chamber views by planimeter, respectively, and L is the shortest length from basal wall to the mitral valve annulus. Short-axis cine MR imaging (MRI) was performed, and the epicardial and endocardial contours of the ventricles at end systole and end diastole were manually drawn for each slice.[22] Chamber volumes and LV mass were indexed to the body surface area. Ventricular ejection fraction (EF) was calculated as EF=(EDV−ESV)/EDV×100, where EDV stands for end-diastolic volume and ESV for end-systolic volume.

For assessment of diastolic function, segmentation for each short-axis slice was performed across all temporal phases. Volumetric data were used to analyze the LV volume-filling time course.[23,24] The following CMR diastolic parameters were evaluated:

1. Peak filling rate: Maximal LV filling rate defined by maximal change in LV volume between sequential temporal phases (Δ volume/Δ phase). This index was also adjusted for stroke volume to generate normalized peak filling rate.[24]
2. Diastolic volume recovery: Proportion of diastole required for recovery of 80% of stroke volume.[24]

The LV inflow contour was manually traced throughout the cardiac cycle, and velocity encoded, phase contrast MRI was performed to obtain early and late LV filling velocities.[25]

Statistical Analysis

Descriptive statistics are presented as mean±SD, median with range, or frequency number and percentage within the group, as appropriate. Between-group differences were compared by independent Student *t* test or nonparametric Wilcoxon rank-sum test for continuous variables, as appropriate, and by χ^2 test for categorical variables. The *P* values are provided for descriptive purposes. Reported *P* values are 2 sided with $P<0.002$ considered significant after applying a Bonferroni correction for multiple testing of cardiac parameters. Differences in baseline characteristics (Tables 1 and 2) are considered statistically significant for $P<0.05$. Data analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

A total of 224 patients were screened for study participation. After diagnostic testing, 24 patients with RfHTN were enrolled and 30 patients with controlled RHTN were recruited for the

Table 2. Antihypertensive Medications in Patients With Refractory and Controlled Resistant Hypertension

Antihypertensive Class	Refractory Hypertension (n=24)	Controlled Resistant Hypertension (n=30)	*P* Value
Angiotensin-converting enzyme inhibitors	11 (45.8%)	17 (56.7%)	0.303
Angiotensinogen receptor blockers	13 (54.2%)	12 (40.0%)	0.223
Calcium channel blockers	24 (100.0%)	23 (76.7%)	0.011
Thiazide diuretics	24 (100.0%)	29 (96.7%)	0.556
Loop diuretics	0	1 (3.3%)	0.556
Amiloride	0	1 (3.3%)	0.556
Mineralocorticoid receptor antagonists	24 (100.0%)	20 (66.7%)	0.001
α-Blockers	1 (4.2%)	2 (6.7%)	0.585
β-Blockers	7 (29.2%)	11 (36.7%)	0.387
Combined α-β blockers	12 (50.0%)	5 (16.7%)	0.010
Central acting α2 agonists	17 (70.8%)	6 (20.0%)	<0.001
Nitrate vasodilators	3 (12.5%)	0	0.082
Other vasodilators	6 (25.0%)	0	0.005
Total antihypertensive medications	6 (5–7)	4 (3–7)	<0.001

comparator group (Figure 1). RfHTN patients had a higher clinic heart rate and BP, were younger, and more likely to be women and black (Table 1). By definition, RfHTN patients were on more antihypertensive agents (median [range], 6 [5–7] versus 4 [3–7] medications; $P<0.001$; Table 2). Patients with RfHTN had a higher mean body mass index and a higher prevalence of diabetes mellitus. Notably, the RfHTN group had more patients with a prior heart failure diagnosis, but no difference in known coronary artery disease, prior cerebrovascular events, or confirmed obstructive sleep apnea.

There was no difference in the mean BNP levels between the 2 groups (RfHTN: 24.8 pg/mL [2.0–141.5 pg/mL] versus controlled RHTN: 15.4 pg/mL [2.0–242.2 pg/mL]; $P=0.38$). There was no difference in 24-hour levels of urinary sodium excretion (RfHTN: 162.7±76.8 versus controlled RHTN: 149.4±47.6 mmol/d; $P=0.446$).

CMR-Derived Measurements

Cardiac Morphology

Patients with RfHTN had greater LV mass indexed by body surface area: (88.3±35.0 versus 54.6±12.5 g/m^2; $P<0.0001$), as well as greater interventricular septal thickness (14.5±3.8 versus 10.0±2.2 mm; $P\leq0.0001$) and posterior wall thickness (10.1±3.1 versus 7.7±1.5 mm; $P=0.0005$) than patients with controlled RHTN (Table 3; Figure 2). There was no difference in LA volume indexed by body surface area (RfHTN: 31.8±8.3 versus controlled RHTN: 33.1±13.1 mL/m^2; $P=0.68$) or LVED volume (RfHTN: 142.9±42.8 mL versus controlled RHTN: 138.5±36.3 mL; $P=0.69$) between the 2 groups. Patients with RfHTN had a greater LV mass/LVED volume ratio than patients with controlled RHTN (1.3±0.4 versus 0.8±0.2 g/mL; $P<0.0001$).

A modest linear association within the 2 groups was found between systolic BP and LV mass (Pearson correlation, 0.308; $P=0.023$), along with diastolic BP and LV mass (Pearson correlation, 0.502; $P<0.001$; Figure S1A and S1B in the online-only Data Supplement).

Systolic and Diastolic Functions

Volumetric assessment by MRI did not reveal differences in right ventricular or LV EF among groups. Furthermore, flow assessment across ascending aorta did not reveal differences in cardiac output or stroke volume (Table 4). Although most of the diastolic function parameters were not different between groups, the RfHTN group showed impaired diastolic function evidenced by a lower peak filling rate (normalized by LV stroke volume) compared with the RHTN group (Table 3). RfHTN patients had higher resting heart rates, which was reflected by a trend toward a shorter time in diastole (497.3±95.9 versus 564.7±128.7 ms; $P=0.04$).

Table 3. CMR-Based Cardiac Anatomy of Patients With Refractory and Controlled Resistant Hypertension

Cardiac Parameters	Refractory Hypertension (n=24)	Controlled Resistant Hypertension (n=30)	*P* Value
Left ventricle			
Left ventricular mass, g	179.4±75.0	115.2±37.9	0.0002
Left ventricular mass index, g/m^2	88.3±35.0	54.6±12.5	<0.0001
Left ventricle end-systolic volume, mL	54.5±26.4	52.0±20.8	1.0
Left ventricle end-diastolic volume, mL	142.9±42.8	138.5±36.3	0.69
Left ventricle end-diastolic volume indexed body surface area, mL/m^2	70.7±17.2	67.0±12.5	0.375
Left ventricle end-systolic dimension, mm	32.8±8.6	32.8±6.4	0.99
Left ventricle end-diastolic dimension, mm	47.3±6.7	48.9±5.4	0.34
Left ventricle posterior wall thickness, mm	10.1±3.1	7.7±1.5	0.0005
Inter ventricular septum thickness, mm	14.5±3.8	10.0±2.2	<0.0001
Left ventricular mass/left ventricular end-diastolic volume, g/mL	1.3±0.4	0.8±0.2	<0.0001
Left atrium			
Left atrium volume, mL	65.8±21.6	67.9±29.3	0.77
Left atrium volume indexed by body surface area, mL/m^2	31.8±8.3	33.1±13.1	0.68
Right ventricle			
Right ventricle end-systolic volume, mL	57.4±18.8	65.6±24.1	0.19
Right ventricle end-diastolic volume, mL	135.1±40.6	147.2±37.4	0.27
Right ventricle end-diastolic volume indexed body surface area, mL/m^2	66.8±16.1	71.1±12.1	0.268
Right ventricle end-diastolic dimension, mm	36.5±6.5	40.7±7.1	0.03
Right atrium			
Right atrium dimension, mm	41.1±8.0	48.0±7.3	0.009
Inferior vena cava, mm	18.7±5.5	20.6±4.2	0.52

CMR indicates cardiac magnetic resonance.

Discussion

There are several key findings of our study. This is the first detailed cardiovascular phenotyping of patients with RfHTN using CMR, a technique considered to be the gold standard for the assessment of cardiac structure and function. Second, we found no difference in LA and LVED volume between the 2 study groups along with similar levels of BNP, suggesting that patients with RfHTN do not have persistent fluid retention as a cause of their antihypertensive treatment failure. Third, our study demonstrated more pronounced cardiac remodeling in RfHTN subjects as evidenced by increased

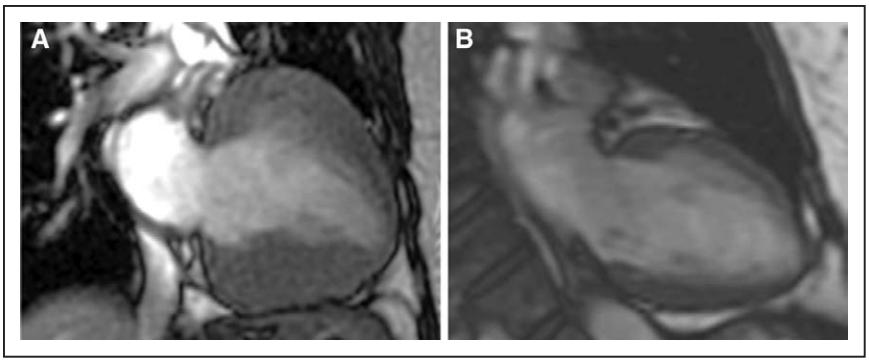


Figure 2. Representative cardiac magnetic resonance images from patients with refractory hypertension (**A**), demonstrating increase ventricular wall thickness with similar end-diastolic volumes when compared with patients with controlled resistant hypertension (**B**).

LV mass and wall thickness, without significant increases in chamber volume as compared with patients with controlled RHTN. Fourth, systolic function was preserved in both groups. However, there was evidence for abnormal diastolic filling in patients with RfHTN as compared with controlled RHTN subjects.

Persistent fluid retention is thought to broadly underlie the development of RHTN. Taler et al[6] reported that RHTN is characterized by intravascular fluid retention, as evidenced by increased thoracic impedance and the observation that intensification of diuretic therapy facilitated better BP control in these patients. Our group previously reported that patients with RHTN have greater end-diastolic volumes and higher BNP levels than control patients without RHTN[7,26] and that this fluid retention could be overcome with use of spironolactone.[7] In the current study, we did not observe any significant differences in cardiac chamber volumes or BNP levels between patients with RfHTN and patients with controlled RHTN, arguing against persistent fluid retention as the cause of the antihypertensive treatment failure. This suggests that alternative mechanisms may be driving the lack of treatment response. The higher resting heart rates and higher urinary metanephrine levels observed in earlier studies suggest heightened sympathetic activity as a potential cause of RfHTN. If so, this carries important clinical implications in that such patients failing maximal or near-maximal antihypertensive treatment may best respond to more effective sympatholytic interventions, either pharmacologic or device-based, as opposed to continued intensification of diuretic therapy, which has been generally recommended for continued lack of BP control in patients with RHTN.

The current study demonstrates that patients with RfHTN have a greater prevalence of LV hypertrophy, characterized by a greater LV mass index and wall thickness as compared with patients with controlled RHTN. Previous studies of patients with RfHTN have likewise reported a high prevalence of LV hypertrophy based on ECG criteria[4] and M-mode echocardiography.[8] The greater LV mass is no doubt attributable, at least in part, to the longstanding, poorly controlled hypertension characteristic of RfHTN.

There were no differences in systolic function between the 2 study groups. However, patients with RfHTN had signs of diastolic dysfunction or subclinical heart failure with preserved EF. First, the LV mass/LVED volume ratio in the RfHTN group was >1 g/mL and greater than in the control group, concordant with findings from prior studies in patients with heart failure with preserved EF.[27] Second, RfHTN subjects showed a delayed LV filling pattern that has been described in patients with diastolic dysfunction,[24] as well as

Table 4. Cardiac Systolic and Diastolic Function Properties Measured With Cardiac MRI in Refractory and Controlled Resistant Hypertension

Cardiac Parameters	Refractory Hypertension (n=24)	Controlled Resistant Hypertension (n=30)	*P* Value
Flow across ascending aorta			
Cardiac output, L/min	4.8±1.3	4.6±1.5	0.64
Stroke volume, mL/beat	69.6±19.7	68.5±18.0	0.84
Left ventricle			
Left ventricle stroke volume, mL	88.1±24.1	86.1±22.6	0.76
Left ventricle ejection fraction, %	62.9±9.1	63.1±8.2	0.95
Early diastolic mitral inflow maximal velocity (E), cm/s	47.1±8.6	46.2±12.6	0.79
Late diastolic mitral inflow maximal velocity (A), cm/s	48.6±13.8	41.5±12.6	0.10
E/A ratio maximal velocity ratio	1.07±0.55	1.27±0.76	0.12
Total time in diastole (D), ms	497.3±95.9	564.7±128.7	0.04
Time to recover 80% of LV stroke volume (P), ms	457.1±90.2	519.1±118.3	0.04
Left ventricle diastolic volume recovery (P/D)	0.92±0.03	0.92±0.07	0.95
Left ventricle peak filling rate, mL/s	376.5±123.5	422.1±158.3	0.27
Left ventricle peak filling rate normalized by stroke volume	4.5±1.0	5.3±1.3	0.03
Right ventricle			
Right ventricle stroke volume, mL	77.6±24.4	81.5±20.9	0.54
Right ventricle ejection fraction, %	57.6±6.0	56.0±8.4	0.46

LV indicates left ventricle; and MRI, magnetic resonance imaging.

in clinical heart failure, despite no differences in EF among groups.

Although we did not detect differences between the 2 study groups, the small sample size of patients with RfHTN reduces the statistical power of the analysis, increasing risk of a type II error. Study limitations include the small number of patients with RfHTN. Study strengths include the rigorous characterization of the 2 phenotypes based on extensive biochemical testing, ABPM, and cardiac MRI.

In conclusion, the current study demonstrates similar intracardiac chamber volumes and BNP levels in patients with RfHTN and controlled RHTN, suggesting that antihypertensive treatment failure in these patients is not from lack of effective diuresis when treated with chlorthalidone and spironolactone. Instead, it suggests a mechanism of treatment failure separate from persistent fluid retention, such as increased sympathetic tone.[1] Further, patients with RfHTN have evidence of adverse cardiovascular remodeling compared with controlled RHTN, placing them at increased risk for adverse cardiovascular events.[1,28]

Perspectives

Patients with RfHTN represent a subset of individuals with hypertension that remains uncontrolled despite maximal antihypertensive treatment, including use of long-acting thiazide diuretics and MR antagonists. Our detailed cardiac phenotyping analysis using CMR demonstrated greater ventricular wall thickness without chamber enlargement in patients with RfHTN compared with patients with controlled RHTN. These findings are in agreement with prior studies from our group, suggesting that the failure of antihypertensive to control BP in RfHTN is not attributable to persistent fluid retention but instead is mediated by other mechanisms, such as increased sympathetic tone.

Sources of Funding

The National Institutes of Health (NIH R01 HL113004) and the American Heart Association Strategically Focused Research Network (AHA 5SFRN2390002) supported this research.

Disclosures

None.

References

1. Dudenbostel T, Acelajado MC, Pisoni R, Li P, Oparil S, Calhoun DA. Refractory hypertension: evidence of heightened sympathetic activity as a cause of antihypertensive treatment failure. *Hypertension*. 2015;66:126–133. doi: 10.1161/HYPERTENSIONAHA.115.05449.
2. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–e526. doi: 10.1161/CIRCULATIONAHA.108.189141.
3. Acelajado MC, Pisoni R, Dudenbostel T, Dell'Italia LJ, Cartmill F, Zhang B, Cofield SS, Oparil S, Calhoun DA. Refractory hypertension: definition, prevalence, and patient characteristics. *J Clin Hypertens (Greenwich)*. 2012;14:7–12. doi: 10.1111/j.1751-7176.2011.00556.x.
4. Calhoun DA, Booth JN III, Oparil S, Irvin MR, Shimbo D, Lackland DT, Howard G, Safford MM, Muntner P. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. *Hypertension*. 2014;63:451–458. doi: 10.1161/HYPERTENSIONAHA.113.02026.
5. Siddiqui M, Judd EK, Oparil S, Calhoun DA. White coat effect is uncommon in patients with refractory hypertension. *Hypertension*. 2017;70:645–651.
6. Taler SJ, Textor SC, Augustine JE. Resistant hypertension: comparing hemodynamic management to specialist care. *Hypertension*. 2002;39:982–988.
7. Gaddam K, Corros C, Pimenta E, Ahmed M, Denney T, Aban I, Inusah S, Gupta H, Lloyd SG, Oparil S, Husain A, Dell'Italia LJ, Calhoun DA. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism: a prospective clinical study. *Hypertension*. 2010;55:1137–1142. doi: 10.1161/HYPERTENSIONAHA.109.141531.
8. Modolo R, de Faria AP, Sabbatini AR, Barbaro NR, Ritter AM, Moreno H. Refractory and resistant hypertension: characteristics and differences observed in a specialized clinic. *J Am Soc Hypertens*. 2015;9:397–402. doi: 10.1016/j.jash.2015.03.005.
9. Terént A, Breig-Asberg E. Epidemiological perspective of body position and arm level in blood pressure measurement. *Blood Press*. 1994;3:156–163.
10. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111:697–716. doi: 10.1161/01.CIR.0000154900.76284.F6.
11. Manning DM, Kuchirka C, Kaminski J. Miscuffing: inappropriate blood pressure cuff application. *Circulation*. 1983;68:763–766.
12. Beckett L, Godwin M. The BpTRU automatic blood pressure monitor compared to 24 hour ambulatory blood pressure monitoring in the assessment of blood pressure in patients with hypertension. *BMC Cardiovasc Disord*. 2005;5:18. doi: 10.1186/1471-2261-5-18.
13. Wright JM, Mattu GS, Perry TL Jr, Gelferc ME, Strange KD, Zorn A, Chen Y. Validation of a new algorithm for the BPM-100 electronic oscillometric office blood pressure monitor. *Blood Press Monit*. 2001;6:161–165.
14. Mattu GS, Heran BS, Wright JM. Overall accuracy of the BpTRU—an automated electronic blood pressure device. *Blood Press Monit*. 2004;9:47–52.
15. Culleton BF, McKay DW, Campbell NR. Performance of the automated BpTRU measurement device in the assessment of white-coat hypertension and white-coat effect. *Blood Press Monit*. 2006;11:37–42.
16. Myers MG, Kaczorowski J, Paterson JM, Dolovich L, Tu K. Thresholds for diagnosing hypertension based on automated office blood pressure measurements and cardiovascular risk. *Hypertension*. 2015;66:489–495. doi: 10.1161/HYPERTENSIONAHA.115.05782.
17. Wohlfahrt P, Cífková R, Movsisyan N, Kunzová Š, Lešovský J, Homolka M, Soška V, Bauerová H, Lopez-Jimenez F, Sochor O. Threshold for diagnosing hypertension by automated office blood pressure using random sample population data. *J Hypertens*. 2016;34:2180–2186. doi: 10.1097/HJH.0000000000001076.
18. O'Brien E, Parati G, Stergiou G, et al; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31:1731–1768. doi: 10.1097/HJH.0b013e328363e964.
19. Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. *Am J Hypertens*. 1996;9:1–11.
20. Ahmed MI, Desai RV, Gaddam KK, Venkatesh BA, Agarwal S, Inusah S, Lloyd SG, Denney TS Jr, Calhoun D, Dell'italia LJ, Gupta H. Relation of torsion and myocardial strains to LV ejection fraction in hypertension. *JACC Cardiovasc Imaging*. 2012;5:273–281. doi: 10.1016/j.jcmg.2011.11.013.
21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European

Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463. doi: 10.1016/j.echo.2005.10.005.
22. Lawson MA, Blackwell GG, Davis ND, Roney M, Dell'Italia LJ, Pohost GM. Accuracy of biplane long-axis left ventricular volume determined by cine magnetic resonance imaging in patients with regional and global dysfunction. *Am J Cardiol*. 1996;77:1098–1104.
23. Feng W, Nagaraj H, Gupta H, Lloyd SG, Aban I, Perry GJ, Calhoun DA, Dell'Italia LJ, Denney TS Jr. A dual propagation contours technique for semi-automated assessment of systolic and diastolic cardiac function by CMR. *J Cardiovasc Magn Reson*. 2009;11:30. doi: 10.1186/1532-429X-11-30.
24. Kawaji K, Codella NC, Prince MR, Chu CW, Shakoor A, LaBounty TM, Min JK, Swaminathan RV, Devereux RB, Wang Y, Weinsaft JW. Automated segmentation of routine clinical cardiac magnetic resonance imaging for assessment of left ventricular diastolic dysfunction. *Circ Cardiovasc Imaging*. 2009;2:476–484. doi: 10.1161/CIRCIMAGING.109.879304.
25. Daneshvar D, Wei J, Tolstrup K, Thomson LE, Shufelt C, Merz CN. Diastolic dysfunction: improved understanding using emerging imaging techniques. *Am Heart J*. 2010;160:394–404. doi: 10.1016/j.ahj.2010.06.040.
26. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, Pimenta E, Aban I, Oparil S, Calhoun DA. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Arch Intern Med*. 2008;168:1159–1164. doi: 10.1001/archinte.168.11.1159.
27. Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Fu Q, Berk M, Palmer D, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. *Circ Heart Fail*. 2010;3:617–626. doi: 10.1161/CIRCHEARTFAILURE.109.867044.
28. Mancia G, Laurent S, Agabiti-Rosei E, et al; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009;27:2121–2158. doi: 10.1097/HJH.0b013e328333146d.

Novelty and Significance

What Is New?

- Patients with refractory hypertension have increased cardiac damage compared with controlled resistant hypertension.
- Cardiac magnetic resonance imaging showed evidence of increased left ventricular mass and wall thickness without cardiac chamber enlargement in refractory hypertension patients.

What Is Relevant?

- In patients with resistant hypertension, lack of blood pressure control despite multiple medications is associated with adverse cardiovascular remodeling.
- There is no evidence of chamber enlargement in refractory hypertension patients to suggest persistent excess intravascular volume as a cause of antihypertensive treatment failure.

Summary

Patients with refractory hypertension have greater left ventricular mass and adverse vascular remodeling compared with controlled resistant hypertension patients, without evidence of greater intravascular volume to explain their antihypertensive treatment failure.

Refractory Hypertension Is not Attributable to Intravascular Fluid Retention as Determined by Intracardiac Volumes

Alejandro Velasco, Mohammed Siddiqui, Eric Kreps, Pavani Kolakalapudi, Tanja Dudenbostel, Garima Arora, Eric K. Judd, Sumanth D. Prabhu, Steven G. Lloyd, Suzanne Oparil and David A. Calhoun

Hypertension. 2018;72:343-349; originally published online June 4, 2018;
doi: 10.1161/HYPERTENSIONAHA.118.10965
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Online Supplement

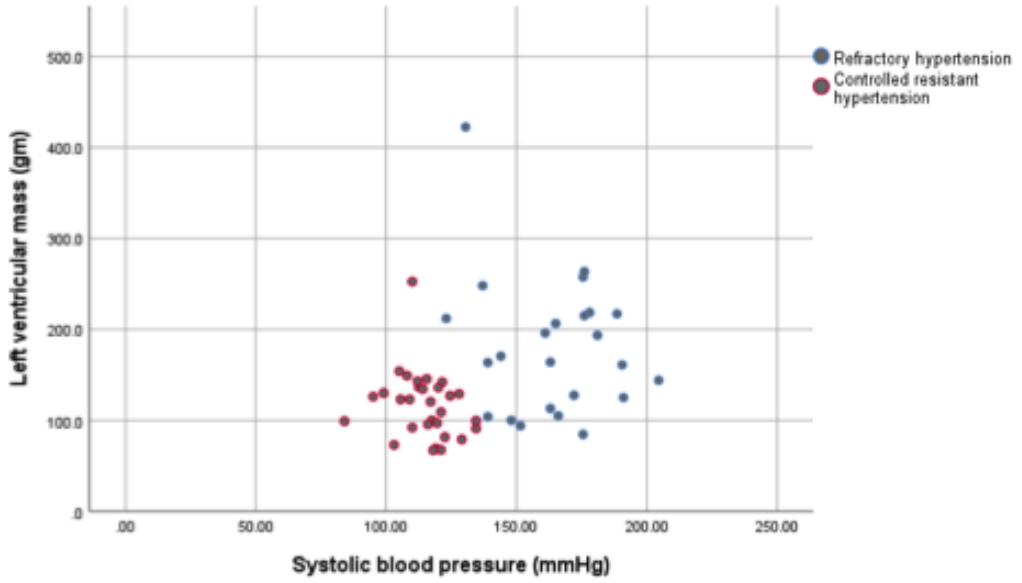
Supplement to: **Refractory Hypertension is not Attributable to Intravascular Fluid Retention as Determined by Intracardiac Volumes**

Alejandro Velasco[1*], Mohammed Siddiqui[2*], Eric Kreps[3], Pavani Kolakalapudi[4], Tanja Dudenbostel[2], Garima Arora[1], Eric K Judd[5], Sumanth D. Prabhu[1], Steven G. Lloyd[1], Suzanne Oparil[2], David A. Calhoun[2]

1. Division of Cardiovascular Disease, University of Alabama at Birmingham. Birmingham, AL, USA
2. Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, University of Alabama at Birmingham. Birmingham, AL, USA
3. Department of Internal Medicine, University of Alabama at Birmingham. Birmingham, AL, USA
4. Division of Cardiovascular Disease, University of South Alabama. Mobile, AL, USA.
5. Division of Nephrology, University of Alabama at Birmingham. Birmingham, AL, USA

Supplemental figures:

S1A



S1B

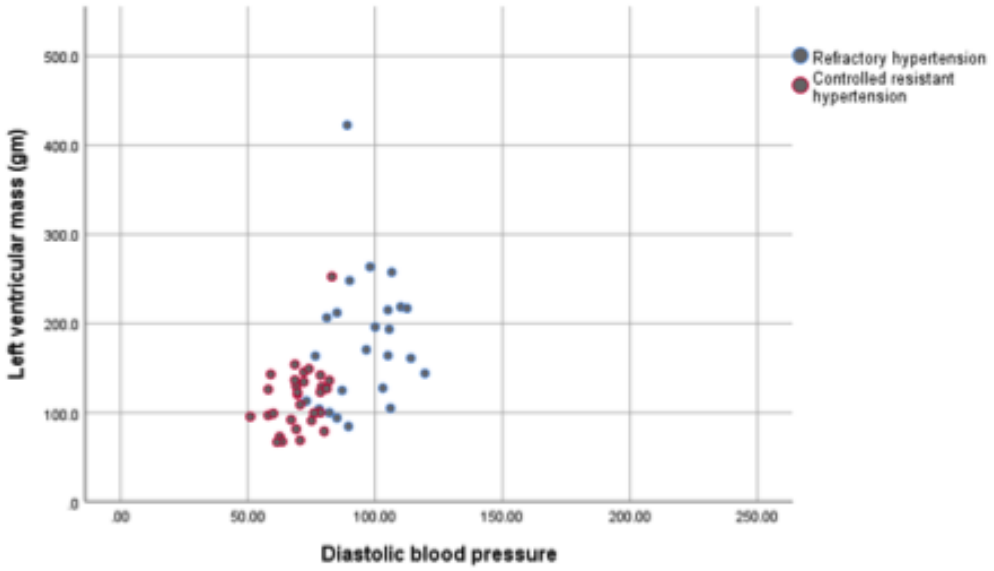


Figure S1: Plot graph showing linear correlation between SBP and LV mass (S1A) and DBP and LV mass (S1B).