Distinctive Risk Factors and Phenotype of Younger Patients With Resistant Hypertension

Age Is Relevant

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Abstract—Resistant hypertension, defined as blood pressure >140/90 mm Hg despite using ≥3 antihypertensive medications, is a well-recognized clinical entity. Patients with resistant hypertension are at an increased risk of cardiovascular disease compared with those with more easily controlled hypertension. Coronary heart disease mortality rates of younger adults are stagnating or on the rise. The purpose of our study was to characterize the phenotype and risk factors of younger patients with resistant hypertension, given the dearth of data on cardiovascular risk profile in this cohort. We conducted a cross-sectional analysis with predefined age groups of a large, ethnically diverse cohort of 2170 patients referred to the Hypertension Clinic at the University of Alabama at Birmingham. Patients (n=2068) met the inclusion criteria and were classified by age groups, that is, ≤40 years (12.7% of total cohort), 41 to 55 years (32.1%), 56 to 70 years (36.1%), and ≥71 years (19.1%). Patients aged ≤40 years compared with those aged ≥71 years had significantly earlier onset of hypertension (24.7±7.4 versus 55.0±14.1 years; $P<0.0001$), higher rates of obesity (53.4% versus 26.9%; $P<0.0001$), and significantly higher levels of plasma aldosterone (11.3±9.8 versus 8.9±7.4 ng/dL; $P=0.005$), plasma renin activity (4.9±10.2 versus 2.5±5.0 ng/mL per hour; $P=0.001$), 24-hour urinary aldosterone (13.4±10.0 versus 8.2±6.2 µg/24 h; $P<0.0001$), and sodium excretion (195.9±92.0 versus 146.8±67.1 mEq/24 h; $P<0.0001$). Among patients with resistant hypertension, younger individuals have a distinct phenotype characterized by overlapping risk factors and comorbidities, including obesity, high aldosterone, and high dietary sodium intake compared with elderly. **(*Hypertension*. 2017;69: 827-835. DOI: 10.1161/HYPERTENSIONAHA.116.08632.)** • **Online Data Supplement**

Key Words: epidemiology ■ hypertension ■ phenotype ■ risk factors ■ young adult

Resistant hypertension (RHTN) is a well-recognized clinical entity.[1] Patients with RHTN are at an increased risk of cardiovascular disease compared with those with more easily controlled hypertension.[1,2] Risk factors associated with development of RHTN include older age, longer duration of hypertension, higher blood pressure (BP), higher body mass index (BMI) or obesity, diabetes mellitus, target organ damage, including increased arterial stiffness, left ventricular hypertrophy, heart failure, coronary heart disease (CHD), chronic kidney disease (CKD), atrial fibrillation, and stroke.[3–7] Recent evidence has shown the emergence of unfavorable trends in CHD and related mortality in younger individuals (35–55 years). For example, in the United Kingdom, there was an increase in CHD mortality rates among young adults aged 35 to 44 years and a slowing in the decline in CHD mortality rates among 45 to 54-year-old individuals between 1984 and 2002.[8] In Canada, hospitalization risk for acute myocardial infarction in women aged ≤55 years increased between 2000 and 2009.[9] Similarly, in Western Australia among women aged 35 to 54 years, there was an increase in the incidence of acute coronary syndrome.[10] These unfavorable age and sex-specific trends in CHD may be attributable to distinct risk factors and an emerging cardiovascular phenotype of increasing obesity, diabetes mellitus, and sodium consumption rates among young individuals.[11–16] To our knowledge, there are limited data on the cardiovascular disease risk profile of young adults with RHTN.[8,9,17,18] The purpose of this study was to characterize the phenotype of younger patients with RHTN and compare it to the phenotype of middle-aged and elderly patients with RHTN.

Methods

Study Cohort

We conducted a cross-sectional analysis of 2170 patients referred to the University of Alabama at Birmingham Hypertension Clinic for evaluation and treatment of RHTN between the years 2000 and

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2015. RHTN was defined as having BP>140/90 mm Hg despite being treated with ≥3 different antihypertensive medications including a diuretic if tolerated.[1] The primary objective of the study was to determine the prevalence of RHTN according to age groups. The secondary objective was to determine demographics, clinical and biochemical characteristics, risk factors, and comorbidities of individuals within predefined age groups.

Inclusion criteria was RHTN, as defined above. Exclusion criteria were as follows: treatment with <3 antihypertensive medications, missing baseline parameters, nonadherence as reported in medical records, use of mineralocorticoid receptor antagonist at the time of biochemical assessment, incomplete urinary collection evaluated by low 24-hour U-creatinine,[19] CKD stage IV to V,[19,20] and secondary causes of hypertension, other than primary aldosteronism (PA), for example, renal artery stenosis, Cushing disease, or pheochromocytoma (Figure 1). Patients who were treated with a mineralocorticoid receptor antagonist and enrolled in the study had to discontinue the treatment with a mineralocorticoid receptor antagonist for at least 6 weeks before biochemical assessment was done.

Baseline parameters included patient demographics (age, sex, and race), anthropometrics (height, weight, and calculated BMI), clinic BP, duration of hypertension, number and class of antihypertensive medications, risk factors, and comorbidities (dyslipidemia, diabetes mellitus, obesity, obstructive sleep apnea [OSA], CKD, CHD, PA, and stroke). Comorbidities were assessed based on records from previous encounters or our initial clinic evaluation. BMI was calculated utilizing the formula weight (kg)/(height [m^2]). Race was self-reported. All patients underwent assessment of serum potassium, serum creatinine, estimated glomerular filtration rate,[21] plasma aldosterone concentration (PAC), plasma renin activity (PRA), and 24-hour urine collection for analysis of 24-hour urinary aldosterone (U-Aldo), sodium (U-Na^+), volume, and U-creatinine. Aldosterone:renin ratio was calculated by the formula aldosterone:renin ratio=PAC/PRA. PA was defined as PRA<1 ng/mL per hour and 24-hour U-Aldo >12 µg.[22,23]

PAC, PRA, and 24-hour U-Aldo levels were analyzed at Mayo Clinic (Mayo Medical Laboratories, Rochester, MN).[24–28] Estimated glomerular filtration rate was calculated with use of the Modification of Diet in Renal Disease formula.[29] Patients were instructed to bring the 24-hour urine collection to the laboratory early in the morning of the day they completed the collection. A morning blood sample was then collected for measurement of PAC and PRA. Adequacy of the 24-hour urine collection was assessed by measuring 24-hour U-Creatinine by comparing total U-Creatinine in the sample to predicted creatinine.[19]

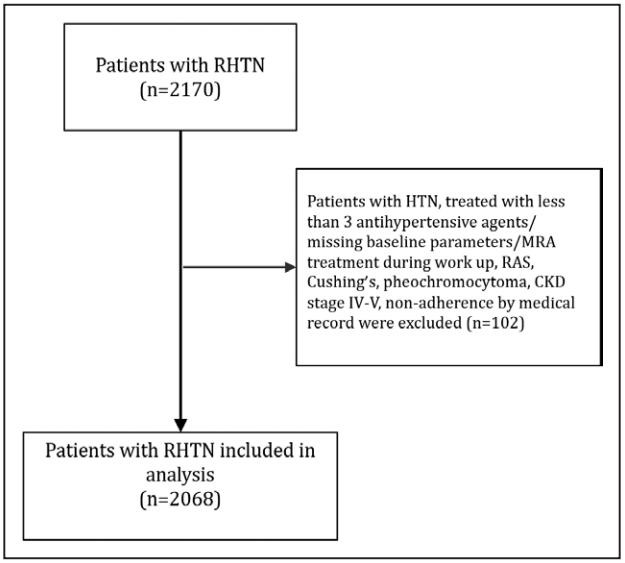

Figure 1. Study flow chart. CKD indicates chronic kidney disease; HTN, hypertension; MRA, mineralocorticoid antagonists; RAS, renal artery stenosis; and RHTN, resistant hypertension.

Clinic BP Measurements

BP was measured by trained personal after at least 5 minutes of rest in a relaxed sitting position, using the auscultatory method with a manual sphygmomanometer (Welch Allyn, Inc., Skaneateles Falls, NY) according to guidelines.[30] Patients were seated quietly for 5 minutes, both feet on the floor with the arm supported at heart level. A correctly sized cuff with the air bladder encircling at least 80% of the arm was used. BP was measured twice at intervals of 1 minute in each arm, and the average of 2 readings in the arm with the higher BP reading was used for final BP value.[1]

Age Grouping

Patients in our cohort were divided arbitrarily into the following age groups:

≤40, 41 to 55, 56 to 70, and ≥71 years. Individuals aged ≤40 years were identified as youngest, 41 to 55 years as young, 56 to 70 years as older, and ≥71 years as elderly. The study was approved by the University of Alabama at Birmingham Institutional Review Board and conducted according to institutional guidelines.

Statistical Analysis

Demographics and clinical characteristics were summarized using descriptive statistics (mean±SD or frequency [percentage]). χ^2 test (or Fisher exact test) and ANOVA were performed for statistical comparisons of categorical and continuous variables across age groups, respectively. Post hoc tests with Bonferroni corrections were used to examine the pairwise differences between age groups. For any variable that did not meet the assumptions of ANOVA, a nonparametric procedure was applied such as Kruskal–Wallis test followed by a post hoc Dunn test.

To elucidate the associations between age group and clinically relevant phenotypes while accounting for the effects of other covariates, a multivariable logistic regression was used. First, a subset of significant variables, such as sex, race, obesity, OSA, PAC, PRA, PA, 24-hour urinary sodium excretion, and U-Aldo, found in the bivariate analysis was selected. The multivariable logistic regression was fitted using an algorithm as described by Bursac et al.[31] The algorithm is capable of retaining important confounding covariates in addition to significant ones. The *P* values of the inclusion and retention criteria for the model were set to 0.25 and 0.1, respectively, together with a 15% change in parameter estimate indicating confounding. The inclusion criteria for noncandidate was set at a *P* value of 0.15. Multicollinearity was assessed using a variance inflation factor,[32] and all the above-mentioned variables met the variance inflation factor <5 criterion[33,34] before fitting the models. Adjusted odds ratios and 95% confidence intervals were calculated.

To further characterize the age group, conditional inference trees were implemented to discover how the clinical phenotypes mentioned above influence the distribution of age. The conditional inference tree model allows unbiased analysis of multiple variables and is robust to problems in overfitting and selection bias of covariates.[35,36] Then using these variables, conditional inference trees recursively partitioned the subjects into smaller homogenous subgroups by identifying the independent variables that provide the best classification of age group. The variable with the strongest association to age group was chosen at each split based on the smallest *P* value derived from the permutation tests. The recursion continued until no significant association was detected between age group and any of the variables at the Bonferroni-adjusted level of significance. $P<0.05$ was considered statistically significant in 2-tailed statistical tests. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) software and R 3.3.0.

Results

Cohort of Patients With RHTN

The cohort included 2170 patients who were referred to the hypertension Clinic at University of Alabama at Birmingham, of whom 2068 met the inclusion criteria (Figure 1). Characteristics of the patients are shown in Table 1. Patients

Table 1. Characteristics of Patients With Resistant Hypertension as Cohort and by Age

Characteristics	All	Age Group				*P* Value
Age group, y	16–94n=2068	≤40n=264	41–55n=663	56–70n=747	≥71n=394	
Prevalence, %	N/A	12.7	32.1	36.1	19.1	NA
Demographics						
Age, y	57.0±14.0	32.3±6.5	49.2±4.1	62.7±4.4	76.3±4.6	NA
Women, n (%)	1230 (60)	147 (55.9)	363 (55)	439 (58.8)	281 (71.3)	<0.0001
Black race, n (%)	742 (36.7)	119 (46.5)	312 (48.3)	234 (31.7)	77 (19.9)	<0.0001
Other characteristics						
BMI, kg/m^2	31.0±7.2	31.6±8.1	33.1±7.9	30.7±6.5	27.6±5.0	<0.0001
Age of onset of HTN	41.0±14.5	24.7±7.4	35.1±10.1	44.4±11.4	55.0±14.1	<0.0001
No. of anti-HTN agents	3.9±1.3	3.5±1.5	3.8±1.3	3.9±1.3	4.0±1.4	0.04
Systolic BP, mm Hg	158.9±26.8	149.2±27.0	154.4±26.4	160.6±26.6	168.1±28.3	<0.0001
Diastolic BP, mm Hg	86.7±36.8	93.5±18.2	92.0±15.5	84.7±13.0	76.7±14.2	<0.0001
Comorbidities, n (%)						
Obesity	992 (48.6)	140 (53.4)	388 (59.2)	360 (48.9)	104 (26.9)	<0.0001
Dyslipidemia	1251 (61.7)	100 (38.2)	367 (56.4)	493 (67.6)	291 (75.8)	<0.0001
OSA	561 (27.9)	59 (22.5)	215 (33.4)	235 (31)	62 (16.2)	<0.0001
CKD stage 3	382 (18.8)	29 (11.1)	74 (11.3)	160 (21.9)	119 (30.8)	<0.0001
Diabetes mellitus	567 (27.9)	223 (8.8)	172 (26.4)	249 (34.1)	123 (31.9)	<0.0001
CAD	326 (16.1)	14 (5.4)	79 (12.1)	137 (18.7)	96 (24.9)	<0.0001
Stroke	292 (15)	16 (6.3)	77 (12.4)	124 (17.8)	75 (19.9)	<0.0001
Primary aldosteronism	272 (23.1)	29 (21)	121 (29.9)	100 (22.2)	22 (12.1)	<0.0001
Laboratory measures						
Creatinine, mg/dL	1.0±0.5	1.0±0.3	1.0±0.3	1.1±0.6	1.1±0.4	0.0006
K^+, mEq/dL	4.0±0.5	4.0±0.5	3.9±0.5	4.0±0.5	4.2±0.5	<0.0001
eGFR, mL/min per 1.73 m^2	70.0±21.7	82.1±24.8	73.3±22.0	65.0±17.4	56.5±15.6	<0.0001
PAC, ng/dL	10.6±8.8	11.3±9.8	11.2±8.7	10.7±9.1	8.9±7.4	0.0003
PRA, ng/mL per h	3.5±8.2	4.9±10.2	3.5±7.5	3.5±9.2	2.5±5.0	0.003
ARR (PAC/PRA)	12.6±14.9	10.3±13.4	13.6±15.3	13.2±16.4	12.2±13.9	0.022
U-Aldo, μg/24 h	11.8±9.2	13.4±10.0	12.6±9.7	11.7±8.9	8.2±6.2	<0.0001
U-Na^+, mEq/24 h	180.8±84.6	195.9±92.0	197.6±90.4	172.8±77.0	146.8±67.1	<0.0001
U-Na^+>200 mEq/24 h, %	422 (36.2)	60 (43.8)	171 (43.3)	150 (33.2)	41 (22.5)	<0.0001
U-Vol, mL/24 h	2058.0±895.0	1746.1±852.5	2006.6±922.6	2164.2±871.5	2151.4±878.1	<0.0001
24-h U-Cr, mg/24 h	1638.2±651.2	1905.1±633.9	1839.9±675.4	1545.5±576.7	1205.8±475.7	<0.001

Values are mean±SD or frequency and percentage. *P*<0.05 denotes statistical significance. Primary aldosteronism: urine aldosterone ≥12 μg/24 h and plasma renin activity <1 ng/mL per hour. 24-h U-Cr indicates 24-h urinary creatinine; ARR, aldosterone:renin ratio; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; K^+, serum potassium; U-Na^+>200 mEq/24 h, upper normal limit; OSA, obstructive sleep apnea; PAC, plasma aldosterone concentration; PRA, plasma renin activity; U-Aldo, 24-hour urinary aldosterone; U-Na^+, 24-hour urinary sodium; and U-Vol, urinary volume.

were on average 57.0±14.0 years old, more often women (60.0%), and one third of the cohort was black (36.7%). The mean BMI was 31.0±7.2 kg/m^2. (Table 1). Average age at first diagnosis of hypertension was 41.0±14.5 years in the cohort overall. Patients were treated with a mean of 3.9±1.3 different classes of antihypertensive medications, including angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, diuretics, and other antihypertensive agents such as α-adrenergic blockers and vasodilators. There were no differences across age groups in number or classes of antihypertensive drugs used (Table 2). Cardiovascular disease risk factors and comorbidities of the entire cohort are shown in Table 1. Almost half of the cohort was obese (48.8%), defined as BMI >30 kg/m^2.[37] Two thirds had dyslipidemia; one third had diabetes mellitus or OSA, whereas CHD, CKD, and stroke were less common (Figure 2).

Table 2. Distribution of Antihypertensive Agents Across Age Groups

	Age Distribution, y				
%	≤40	41–55	56–70	≥71	*P* Values
α-1 Blocker	7.58	10.3	9.92	9.92	0.65
β-Blocker	22	22.3	21.7	21.1	0.97
ACEi	14.4	15.8	16.2	14.7	0.86
ARB	12.1	12.2	11.5	12	0.98
CCB	19.8	21.3	21.5	20.9	0.95
Diuretic	19.3	22.6	22.8	20.6	0.58
Other	7.2	8.45	7.77	7.12	0.86

ACEi indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; other include vasodilators, α-2 agonist.

Prevalence, Biochemical, and Clinical Characteristics by Age Groups

Of the entire cohort, approximately half was <55 years old indicating that patients with RHTN evaluated in a specialty clinic are not predominantly old. In detail, 12.7% were ≤40 years, 32.1% were 41 to 55 years, 36.1% were 56 to 70 years, and 19.1% were ≥71 years old. Table 1 shows the comparison of characteristics among the different age groups. There was a higher proportion of women than men in all groups and a higher percentage of blacks in the youngest group compared with the elderly age group (46.5% versus 19.9%, respectively; *P*<0.0001). The average age at first diagnosis of hypertension was reported as 24.7±7.4 years in the youngest group and 55.0±14.1 year in the elderly group (Tables 1 and 3). Thus, there were large disparities between the youngest and the elderly group in both, age at onset of hypertension, and in the interval between time of first diagnosis and presentation at our clinic with RHTN. These important disparities suggest the possibility of different pathophysiologic mechanisms and contributory factors to treatment resistance in the 2 patient populations.

Obesity was the most prevalent comorbidity among the youngest patients (53.4% versus 26.9% in the elderly; *P*<0.0001). The majority of elderly (73.1%) were normal weight (Tables 1 and 3). Similarly, the youngest patients were on average obese, whereas elderly patients had on average normal BMI (31.6±8.1 versus 27.6±5.0 kg/m^2; *P*<0.0001; Tables 1 and 3). Age remained significantly associated with obesity (*P*=0.002) in the multivariable analysis with an odds ratio of 2.33 (95% confidence interval, 1.37–3.95) for comparing youngest age group to the elderly (Tables 4–6), suggesting that obesity plays a more important role in the pathogenesis of treatment resistance in younger patients with RHTN than in the elderly.

OSA was significantly more prevalent in the youngest than in the elderly groups (22.5% versus 16.2%; *P*<0.0001) and roughly twice as prevalent in the younger group (41–55 years), which was also the group with the highest BMI (33.1±7.9 kg/m^2). Other cardiovascular risk factors associated with OSA, such as obesity and aldosteronism, were also more prevalent in younger patients (Tables 1 and 3). In contrast, diabetes mellitus, dyslipidemia, and cardiovascular disease, including CHD, stroke, and CKD, became significantly more prevalent with increasing age and were most common in the elderly.

Biochemical assessment showed that PAC, PRA, and 24-hour U-Aldo levels were highest in the youngest patient group and decreased across age groups with the lowest levels in elderly patients (Table 3). Mean 24-hour U-Aldo, a more integrated marker than PAC, was highest in the youngest group at 13.4+10.0 μg compared with 8.2±6.2 μg (*P*<0.0001) in the elderly (Table 1). Prevalence of PA was highest in the youngest and younger groups and less prevalent in the elderly (21% versus 12.1%; *P*=0.27; 29.9% versus 12.1%; *P*<0.001, respectively). Age was significantly predictive of OSA, PRA, and 24-hour U-Aldo in the multivariable logistic regressions (*P*<0.05) except for PAC (*P*=0.57), all demonstrated higher odds ratios when comparing the youngest age group to the elderly.

Further biochemical analysis showed that the youngest patients had significantly higher 24-hour U-Na$^+$ excretion compared with elderly patients (195.9±92.0 versus 146.8±67.1 mEq, respectively; *P*<0.0001; Tables 1 and 3), and this finding was consistent after adjustment for potential confounders (odds ratio, 1.85 [1.07–3.21]; *P*=0.018). A significantly higher percentage of the youngest patients had excessive dietary Na$^+$ intake, defined as 24-hour U-Na$^+$ excretion ≥200 mEq, compared with elderly patients (43.8% versus 22.5%; *P*<0.0001; Table 1), suggesting that increased dietary Na$^+$ and its effect on the cardiorenal axis[38] may play a greater role in the development of treatment resistance in young patients with RHTN than in the elderly.

We further analyzed how phenotypes are associated with age groups. The conditional inference trees revealed that obesity was significantly associated with age groups (*P*<0.001), followed by race in obese and nonobese patients. Obese white men with U-Na$^+$ excretion ≤200 were least likely to be ≤40 years (youngest); however, when U-Na$^+$ excretion was >200, 41 to 55 group had the highest proportion in this subgroup. In white nonobese patients, PRA (*P*<0.001) was strongly associated with the age group, with both elevated and normal PRA seen the least in patients aged ≤40 years. The result demonstrates

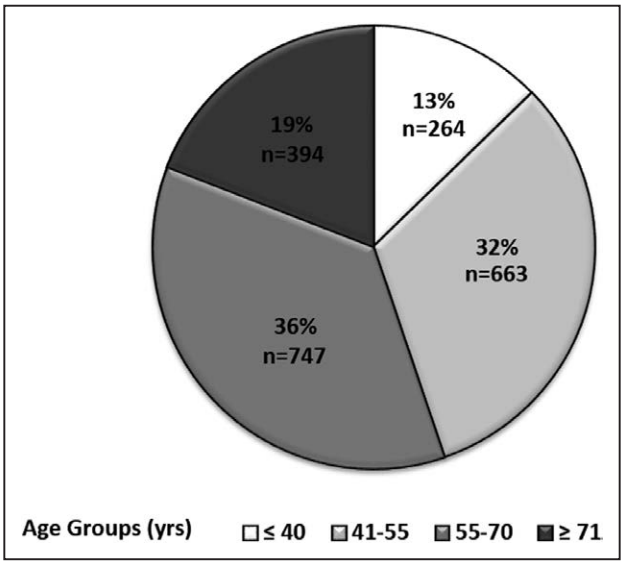

Figure 2. Prevalence of patients with resistant hypertension according to age groups in a cohort of 2068 patients.

Table 3. Comparison of Patient Characteristics Between Age Groups

Characteristics	≤40 vs 41–55 y	≤40 vs 56–70 y	≤40 vs ≥71 y	41–55 vs 56–70 y	41–55 vs ≥71 y	56–70 vs ≥71 y
Demographics						
Women	1	1	0.0004	0.97	<0.0001	0.0002
Black race	<0.0001	0.0002	<0.0001	<0.0001	<0.0001	0.0001
Other characteristics						
BMI, kg/m^2	0.008	0.94	<0.0001	<0.0001	<0.0001	<0.0001
HTN age onset	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
No. of antihypertensive agents	0.17	0.05	0.06	1	1	1
Systolic BP, mm Hg	0.72	0.003	<0.0001	0.08	<0.0001	0.028
Diastolic BP, mm Hg	1	0.0002	<0.0001	<0.0001	<0.0001	<0.0001
Comorbidities						
Obesity, %	0.65	1	<0.0001	0.65	0.0005	<0.0001
Dyslipidemia, %	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.035
OSA, %	0.007	0.05	0.31	1	<0.0001	<0.0001
CKD, %	1	0.0006	<0.0001	<0.0001	<0.0001	0.008
Diabetes mellitus, %	<0.0001	<0.0001	<0.0001	0.01	0.39	1
CAD, %	0.014	<0.0001	<0.0001	0.005	<0.0001	0.12
Stroke, %	0.05	<0.0001	<0.0001	0.04	0.01	1
Primary aldosteronism, %	0.29	1	0.27	0.07	<0.0001	0.02
Laboratory measures						
Creatinine, mg/dL	1	0.06	0.004	0.12	0.006	1
K^+, mEq/dL	1	0.5	<0.0001	0.03	<0.0001	<0.0001
eGFR, mL/min per 1.73 m2	0.005	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PAC, ng/dL	1	1	0.005	1	0.0004	0.008
PRA, ng/mL per hour	0.11	0.087	0.001	1	0.32	0.34
ARR	0.2	0.04	<0.0001	1	0.004	0.02
U-Aldo, μg/24 h	1	0.33	<0.0001	0.91	<0.0001	<0.0001
U-Na^+, mEq/24 h	1	0.01	<0.0001	0.0001	<0.0001	0.0008
U-Na^+>200 mEq/24 h, %	0.99	0.14	0.003	0.03	<0.0001	0.01
U-Vol, mL/24 h	0.04	<0.0001	0.001	0.11	0.58	1
24-h U-Cr, mg/24 h	0.32	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

P<0.05 denotes statistical significance. 24-h U-Cr indicates 24-h urinary creatinine; ARR, aldosterone:renin ratio; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; K^+, serum potassium; U-Na^+>200 mEq/24 h, upper normal limit; OSA, obstructive sleep apnea; PAC, plasma aldosterone concentration; PRA, plasma renin activity; U-Aldo, 24-hour urinary aldosterone; U-Na^+, 24-hour urinary sodium; and U-Vol, urinary volume.

that both obesity and race contributed significantly to the distribution of the age group, and sex, PRA, sodium excretion, and OSA affected varying subgroups of patients.

Discussion

This cross-sectional study of a large, diverse cohort of patients with RHTN has several novel findings: (1) half of the patients were <55 years and reported an onset of hypertension, in their mid-20s, whereas elderly patients were first diagnosed at an average age of 55 years; in comparisons to the elderly patients, (2) younger patients had a higher prevalence of obesity and OSA, (3) younger patients had significantly higher PAC, PRA, and 24-hour U-Aldo levels with a higher prevalence of PA, (4) younger patients had significantly higher 24-hour U-Na^+ excretion and the latter remained true after multivariable logistic regression analysis, and (5) obesity and race affect the distribution of RHTN by different age groups. This study, to our knowledge, is the first to describe these characteristics as a phenotype with distinct risk factor profile of younger patients with RHTN.

Recent evidence has shown the emergence of unfavorable age and sex-specific trends in CHD and related mortality in younger individuals.[8–11,18] These unfavorable trends in CHD may be attributable to an emerging cardiovascular phenotype in times of increasing obesity, diabetes mellitus, and sodium consumption rates among the young, which may affect cardiovascular remodeling including increased arterial stiffness in younger individuals.[11–13]

In our study, we found a distinctive phenotype of younger patients with RHTN, characterized by higher rates of obesity, OSA, high aldosterone levels, and high dietary sodium ingestion, all factors that were observed to a lesser extent in elderly patients.

These age-related findings are consistent with observations in a prospective study of 19- to 65-year-old Polish patients (n=204)

Table 4. Result of Multivariable Logistic Regressions

Outcome	U-Na+, mEq/24 h (>200)			Obesity (Yes)			OSA (Yes)		
Variable	Adj. OR	95% CI	*P* Value	Adj. OR	95% CI	*P* Value	Adj. OR	95% CI	*P* Value
Age, y			0.018			0.002			0.037
≤40	1.85	1.07–3.21		2.33	1.37–3.95		0.94	0.54–1.65	
41–55	1.94	1.23–3.08		2.22	1.46–3.38		1.56	0.99–2.44	
56–70	1.41	0.89–2.21		1.78	1.19–2.66		1.52	0.99–2.34	
≥71	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Sex (F vs M)	0.36	0.27–0.47	<0.0001	1.37	1.03–1.82	0.03	0.49	0.37–0.64	<0.0001
Race (black vs white)	NA	NA	NA	0.49	0.37–0.64	<0.0001	1.35	1.02–1.79	0.039
U-Na+, mEq/24 h	NA	NA	NA	2.41	1.8–3.23	<0.0001	1.03	0.77–1.37	0.85
Obesity (yes)	2.33	1.75–3.1	<0.0001	NA	NA	NA	2.28	1.71–3.03	<0.0001
OSA	1.04	0.79–1.38	0.77	2.3	1.73–3.06	<0.0001	NA	NA	NA
PAC	NA	NA	NA	0.57	0.36–0.9	0.017	1.04	0.66–1.64	0.86
PRA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PA	1.17	0.77–1.81	0.48	1.12	0.71–1.76	0.63	1.07	0.69–1.64	0.77
U-Aldo, µg/24 h	1.03	0.69–1.53	<0.0001	1.32	0.88–1.98	0.17	1.58	1.07–2.34	0.02

CI indicates confidence interval; F, female; M, male; OR, odds ratio; OSA, obstructive sleep apnea; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; U-Aldo, 24-hour urinary aldosterone; and U-Na+, 24-hour urinary sodium.

with confirmed RHTN.[5] In that analysis of 204 consecutively enrolled patients with true RHTN, mean age was 48.4±10.4 years, patients were more men (60.3%), and had a history of hypertension for 11.0±8.5 years. Similar to our patients in that age group, more than half of study participants were obese and had a high prevalence of OSA, PA, and metabolic syndrome, which were frequently overlapping. Excessive sodium ingestion in the study conducted by Florczak et al[5] was evident in 33.3% of patients while we observed and even higher prevalence.

We found higher dietary sodium intake in younger patients, similarly obesity was more prevalent in the youngest patients (53.4%) and less in the elderly (26.9%). This is consistent with current reports of increasing rates of obesity among adults and youth nationwide, with highest rates reported in the Southeastern United States..[14,39–41] Although BMI decreases with age because of sarcopenia, but studies show that the reported weight loss because of aging alone is small 0.1 to 0.2 kg/yr, thus the observed trend in our younger

Table 5. Result of Multivariable Logistic Regressions

Outcome	PAC (>21)			PRA (≥1)			PA (yes)		
Variable	Adj. OR	95% CI	*P* Value	Adj. OR	95% CI	*P* Value	Adj. OR	95% CI	*P* Value
Age, y			0.56			<0.0001			NA
≤40	1.2	0.51–2.81		3.22	2–5.19		NA	NA	
41–55	1.35	0.66–2.76		1.73	1.19–2.52		NA	NA	
56–70	0.97	0.47–1.97		1.41	0.98–2.02		NA	NA	
≥71	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Sex (F vs M)	NA	NA	NA	NA	NA	NA	0.46	0.34–0.62	<0.0001
Race (black vs white)	0.79	0.52–1.2	0.27	1.55	1.21–1.99	0.0006	0.55	0.41–0.74	<0.0001
U-Na+, mEq/24 h	NA	NA	NA	NA	NA	NA	NA	NA	NA
Obesity (yes)	0.61	0.4–0.94	0.03	NA	NA	NA	1.47	1.08–2	0.015
OSA	0.97	0.63–1.5	0.9	NA	NA	NA	1.59	1.18–2.16	0.003
PAC	NA	NA	NA	NA	NA	NA	3.13	2.06–4.78	<0.0001
PRA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PA	NA	NA	NA	NA	NA	NA	NA	NA	NA
U-Aldo, µg/24 h	5.18	3.32–8.08	<0.0001	0.58	0.45–0.74	<0.0001	NA	NA	NA

CI indicates confidence interval; F, female; M, male; OR, odds ratio; OSA, obstructive sleep apnea; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; U-Aldo, 24-hour urinary aldosterone; and U-Na+, 24-hour urinary sodium.

Table 6. Result of Multivariable Logistic Regressions

Outcome	U-Aldo, µg/24 h (≥12)		
Variable	Adj. OR	95% CI	*P* Value
Age, y			0.0001
≤40	3.01	1.73–5.26	
41–55	2.83	1.76–4.53	
56–70	2.33	1.46–3.7	
≥71	Ref	Ref	Ref
Sex (F vs M)	0.44	0.34–0.58	<0.0001
Race (black vs white)	NA	NA	NA
U-Na^+, mEq/24 h	NA	NA	NA
Obesity (yes)	1.43	1.09–1.89	0.011
OSA	1.61	1.22–2.13	0.0008
PAC	5.31	3.37–8.37	<0.0001
PRA	0.57	0.43–0.74	<0.0001
PA	NA	NA	NA
U-Aldo, µg/24 h	NA	NA	NA

CI indicates confidence interval; F, female; M, male; OR, odds ratio; OSA, obstructive sleep apnea; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; U-Aldo, 24-hour urinary aldosterone; and U-Na^+, 24-hour urinary sodium.

patients being more obese is significant, specifically with obesity being associated with age groups (Figure S1 in the online-only Data Supplement).[42] Obesity has been shown to be highly predictive of development of hypertension[16,39] via mechanisms that include increased activity of the sympathetic nervous system and the renin–angiotensin–aldosterone system.[43] Increased aldosterone levels have been associated with BMI in patients with HTN,[44] and we have previously shown that BMI predicts aldosterone levels in patients with RHTN and that adiposity stimulates aldosterone release independent of renin.[45] Importantly, our data demonstrated a negative relation between BMI and PRA consistent with an adipose-related secretagogue stimulating aldosterone release.[45]

Relating the high aldosterone levels in our patients with RHTN to obesity suggests a possible causative relation between indices of obesity and aldosterone release. Observational studies show a correlation between obesity and aldosterone levels, whereas experimental studies implicate adipocyte-related factors as possible stimuli of aldosterone release.[46] Early clinical studies have shown that aldosterone levels correlate with indices of obesity,[44,47,48] and weight loss studies have demonstrated an association between successful weight loss and significant decreases in plasma aldosterone levels.[47–49]

Aldosterone excess has deleterious effects on the cardiovascular system in the setting of inappropriately high sodium levels.[50] A high dietary sodium intake indexed by 24-hour U-Na^+ excretion was found in the current study in younger patients suggesting not only an increased dietary sodium intake in those individuals but also an associated increase in cardiovascular risk. In the current study, biochemical analysis revealed that 24-hour U-Na^+ was highest in youngest patients with 43.8% having levels above the upper normal limit per our laboratory (>200 mEq/24 h) and age stayed significant in the multivariable logistic regression, whereas the majority of elderly patients had a low-to-normal sodium excretion. These findings suggest that excessive sodium intake is especially common in younger patients with RHTN and plays an important role that is yet to be clearly defined.

Increased dietary sodium intake contributes importantly to RHTN and cardiovascular organ damage and cardiovascular remodeling including early vascular aging that can be accelerated by high sodium intake.[38,51] We have previously shown in a group of well-characterized patients with RHTN that lowering sodium intake from 250 to 50 mmol/24 h reduced systolic BP and diastolic BP by 22.7 and 9.1 mm Hg, respectively.[38] These results demonstrate the important contribution of increased dietary sodium to RHTN. Future strategies targeting reduction of excess dietary sodium intake may provide benefit especially for younger patients with RHTN, as this group tends to consume significantly more sodium than elderly individuals consume.

The high prevalence of OSA along with other comorbidities such as obesity, PA, and high sodium intake in younger patient with RHTN supports the presence of a distinct phenotype among young patients. A higher prevalence of OSA was seen in the youngest compared with the elderly although not significant; our results are in line with previous reports that indicate that OSA increases from young adulthood and seems to be less prevalent in the elderly.[52–56] We and others have reported that the prevalence of OSA is increased in obese patients with RHTN and that high aldosterone levels are associated with the severity of OSA compared with patients without hyperaldosteronism.[57] The role of aldosterone in OSA was confirmed in a small interventional study, where we further demonstrated that treatment with an aldosterone antagonist reduces the severity of OSA in patients with RHTN.[58] One pathophysiological mechanism that has been suggested is that obesity is associated with an increase in aldosterone release contributing to an overnight rostral increase in salt and water retention promoting pharyngeal fluid accumulation and increases in the upper airway obstruction.[59] The high sodium intake in young patients might further suggest sodium and water retention as potential mechanism contributing to OSA in RHTN.

Strengths of our study include (1) examination of a large diverse cohort of >2000 patients with RHTN, (2) thorough evaluation for secondary causes of hypertension including PA by 24-hour urinary collection. Potential limitations are the cross-sectional design in a single Hypertension Clinic, office BP measurement using auscultatory technique, lack of confirmation of true RHTN by 24-hour ambulatory BP monitoring, and adherence to BP medications only assessed by medical records and clinical and biochemical observations.

We conclude that in our cohort, young patients with RHTN develop hypertension at an early age and have a very high prevalence of obesity, PA, high dietary sodium ingestion, and OSA compared with elderly patients; these factors interplay in several known and unknown mechanisms, suggesting a specific phenotype that characterizes this group and may affect cardiovascular outcomes.

Perspectives

In this large cohort of patients with RHTN, younger individuals had an earlier onset of hypertension in their mid-20s, were

more likely to be obese, had higher rates of OSA, had higher aldosterone levels, and had 24-hour urinary sodium excretion compared with elderly patients. These results demonstrate age-dependent differences in biochemical factors and comorbidities that may be important in better understanding the mechanisms and complications of RHTN.

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All authors contributed to each of the following aspects of the study: (1) substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, (2) drafting the work or revising it critically for important intellectual content, (3) final approval of the version to be published, (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Drs Ghazi and Lin take responsibility for the accuracy and integrity of the data analysis.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We examined the prevalence of resistant hypertension according to age groups in a large diverse cohort.
- We also evaluated clinical and biochemical characteristics of patients with resistant hypertension according to age groups.

What Is Relevant?

- It has been shown that there is an increase in cardiovascular disease death among younger individuals in mortality data from the United States and United Kingdom.
- Population studies on patients with resistant hypertension, a known risk factor for cardiovascular disease mortality, have examined the characteristics of patients according to age groups including individuals as young as 16 years of age.

Summary

Among a large population-based cohort of patients with resistant hypertension, younger patients with resistant hypertension have an earlier onset of hypertension in their mid-20s, are more likely to be obese, have higher rates of obstructive sleep apnea, and have significantly higher aldosterone levels and 24-hour urinary sodium excretion compared with elderly patients.

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Distinctive Risk Factors and Phenotype of Younger Patients With Resistant Hypertension: Age Is Relevant

Lama Ghazi, Suzanne Oparil, David A. Calhoun, Chee Paul Lin and Tanja Dudenbostel

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AGE IS RELEVANT: DISTINCTIVE RISK FACTORS AND PHENOTYPE OF YOUNGER PATIENTS WITH RESISTANT HYPERTENSION

Short Title: Younger resistant hypertensive patients phenotype

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Figure S1. Conditional inference trees of age group.

p < 0.05 denotes statistical significance