Refractory Hypertension
Evidence of Heightened Sympathetic Activity as a Cause of Antihypertensive Treatment Failure

Tanja Dudenbostel, Maria C. Acelajado, Roberto Pisoni, Peng Li, Suzanne Oparil, David A. Calhoun

Abstract—Refractory hypertension is an extreme phenotype of treatment failure defined as uncontrolled blood pressure in spite of ≥5 classes of antihypertensive agents, including chlorothalidone and a mineralocorticoid receptor antagonist. A prospective evaluation of possible mechanisms of refractory hypertension has not been done. The goal of this study was to test for evidence of heightened sympathetic tone as indicated by 24-hour urinary normetanephrine levels, clinic and ambulatory heart rate (HR), HR variability, arterial stiffness as indexed by pulse wave velocity, and systemic vascular resistance compared with patients with controlled resistant hypertension. Forty-four consecutive patients, 15 with refractory and 29 with controlled resistant hypertension, were evaluated prospectively. Refractory hypertensive patients were younger (48±13.3 versus 56.5±14.1 years; P=0.038) and more likely women (80.0 versus 51.9%; P=0.047) compared with patients with controlled resistant hypertension. They also had higher urinary normetanephrine levels (464.4±250.2 versus 309.8±147.6 µg per 24 hours; P=0.03), higher clinic HR (77.8±7.7 versus 68.8±7.6 bpm; P=0.001) and 24-hour ambulatory HR (77.8±7.7 versus 68.8±7.6; P=0.0018), higher pulse wave velocity (11.8±2.2 versus 9.4±1.5 m/s; P=0.009), reduced HR variability (4.48 versus 6.11; P=0.03), and higher systemic vascular resistance (3795±1753 versus 2382±349 dyne·s·cm⁻²·m⁻²; P=0.008). These findings are consistent with heightened sympathetic tone being a major contributor to antihypertensive treatment failure and highlight the need for effective sympatholytic therapies in patients with refractory hypertension. (Hypertension. 2015;66:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05449.)

Key Words: aldosterone ■ arterial stiffness ■ blood pressure monitoring, ambulatory ■ catecholamines ■ sympathetic activity

Refractory hypertension has been proposed as a clinical phenotype of antihypertensive treatment failure.¹ The initial description of this phenotype was based on a retrospective analysis of patients referred to a hypertension specialty clinic for resistant hypertension (RHTN).¹ Of 304 consecutive patients with confirmed RHTN, 29 patients, or ≈10%, were identified as having refractory hypertension defined as failure to control systolic and diastolic blood pressure (BP) to <140/90 mm Hg after a minimum of 6 months of treatment by a clinical hypertension specialist. In that analysis, patients with refractory hypertension were receiving an average of 6 classes of antihypertensive agents, including the thiazide-like diuretic chlorothalidone and a mineralocorticoid receptor antagonist (MRA), most often spironolactone. Patients with refractory hypertension manifested a consistently higher resting clinic heart rate (HR) compared with patients with controlled RHTN. This elevation in HR was interpreted as evidence of heightened sympathetic tone, suggesting that increased sympathetic nervous system activity may play a potentially important role in the pathogenesis of antihypertensive treatment failure.

In a recent cross-sectional analysis of 14,809 hypertensive adults participating in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, refractory hypertension, defined as uncontrolled hypertension (>140/90 mm Hg) with use of ≥5 antihypertensive classes of agents, had a prevalence of 0.5% of all hypertensive participants and 3.6% of participants with RHTN.² Black race, male sex, obesity, chronic kidney disease (CKD), diabetes mellitus, and history of stroke and coronary heart disease were associated with refractory hypertension in the REGARDS population. In this analysis, clinic HR was not higher in participants with refractory hypertension compared with all hypertensive participants or with participants with controlled RHTN.

This study was conducted to prospectively test for evidence of heightened sympathetic tone as indicated by 24-hour urinary normetanephrine levels, clinic and ambulatory HR, arterial stiffness, and peripheral vascular resistance in patients...
with refractory hypertension. In addition, brain natriuretic peptide (BNP) and thoracic fluid content (TFC) were measured as indices of intravascular fluid volume. Contemporary patients also referred for RHTN but whose BP was controlled with treatment, that is, controlled RHTN, served as a comparator group. The study design also allowed for prospective determination of the prevalence of refractory hypertension among patients referred to a hypertension specialty clinic for RHTN.

Methods

Patient Identification

Consecutive patients referred to the University of Alabama at Birmingham Hypertension Clinic for RHTN (BP >140/90 mm Hg with use of ≥3 antihypertensive medications, including a diuretic) and who were subsequently diagnosed with refractory hypertension or controlled RHTN were prospectively enrolled into the study protocol.

All referred patients underwent determination of aldosterone and cortisol status by measurement of plasma aldosterone concentration, plasma renin activity, and 24-hour urinary excretion of aldosterone, cortisol, sodium, potassium, and creatinine as part of their routine clinical care for RHTN. Other secondary causes of hypertension were excluded as clinically indicated.

Routine Treatment Approach

Patients were identified as having refractory or controlled RHTN based on the BP in response to routine treatment provided by hypertension specialists. All patients referred for RHTN were seen by 2 clinical hypertension specialists at every clinic visit. The patient’s antihypertensive medication regimen was revised according to routine clinical care if the clinic BP remained above goal. All patients were counseled to ingest a low-salt/high-fiber diet according to guidelines. Other secondary causes of hypertension were excluded as clinically indicated.

Patient Survey

All patients were surveyed, and medical records were reviewed for estimated duration of hypertension and history of diabetes mellitus, dyslipidemia, coronary artery disease (CAD), stroke, and HF. During clinic visits, patients were routinely asked whether they have taken their antihypertensive medications regularly. Medication adherence was routinely assessed by the Morisky 8-Item Medication Adherence Questionnaire. Adherence was considered inadequate if patients scored ≥2 points.

Biochemical Testing

Biochemical evaluation per study protocol included measurement of 24-hour urinary normetanephrine levels, serum creatinine, estimated glomerular filtration rate, serum potassium, BNP, and high-sensitivity C-reactive protein. Blood samples were obtained in the morning between 7 to 9 AM at the study visit after overnight fasting and before taking the morning medication after being seated for 5 minutes.

The 24-hour urine collections were done while patients were consuming their usual diet and without change in their level of physical activity. Adequacy of the 24-hour urine collection was assessed by measuring 24-hour creatinine excretion rates.

Clinic BP Measurements

Clinic BP was measured by a hypertension specialist after at least 5 minutes of quiet rest in the sitting position with the back supported using the auscultatory method while supporting the arm at the heart level during BP measurement. An appropriate sized cuff was used with a cuff bladder encircling at least 80% of the arm. Three BP readings were taken at intervals of 2 minutes by the physician, and the second and third readings were used to average BP. The BP was measured in both arms, and the arm with the higher BP was used for further BP measurements. All BP measurements were performed according to guidelines.

Ambulatory BP, HR, and HR Variability

All patients underwent 24-hour ambulatory BP monitoring (ABPM) to confirm uncontrolled BP in patients with refractory hypertension and to confirm controlled BP in patients with clinically controlled RHTN. An automated, noninvasive, oscillometric device (Oscar 2; SunTech Medical, Inc, Morrisville, NC) was used to perform ABPM. An appropriate sized cuff was used with a cuff bladder encircling at least 80% of the arm, according to guidelines. The first measurement was obtained in the clinic to ensure a proper function. Recordings were made every 20 minutes for the daytime (awake) and every 30 minutes for the nighttime (asleep) for a 24-hour period. Awake and asleep periods were defined individually according to the patient’s self-reported data. All patients took prescribed medications normally during ABPM, which were performed on working days, whereas usual activities were maintained. Standard calculations for ABPM were recorded. Valid 24-hour ABPM had to have recorded >80% of successful measurements. Controlled ambulatory BP was defined as mean 24-hour BP <130/80 mm Hg with a daytime (awake) BP of <135/80 mm Hg and a nighttime (asleep) BP of <120/70 mm Hg by ambulatory monitoring according to guidelines.

HR variability (HRV) was estimated by calculating the SD of daytime and nighttime HR values obtained with ABPM.

Pulse Wave Analysis and Pulse Wave Velocity

All patients underwent applanation tonometry for measurement of carotid-femoral pulse wave velocity (PWV) and central pulse wave analysis computed from the radial artery waveform using a transfer function (SphygmoCor; AtCor Medical, Sydney, Australia) according to guidelines. Pulse wave assessments were done during the same early morning session (7:00–9:00 AM) after overnight fasting and before morning medication under standardized conditions. Both tests were performed with the patient in a supine position after resting for at least 10 minutes. Three measurements were acquired, and the median was calculated.

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Impedance Cardiography
Transthoracic impedance cardiography (Bio-Z ICG; Sonosite Inc, Bothell, WA, USA), was performed in the same session to assess TFC during systole (synchronized ECG monitoring) and systemic vascular resistance (SVR) by using bilateral neck and thoracic electrodes and a low-voltage high-amplitude alternating current to derive stroke volume.17–19

Statistical Analysis
Descriptive data are expressed as mean±SD. Categorical variables are expressed as percentages. Baseline variables for patients with refractory and RHTN were analyzed by 2-tailed Student t test. Statistical significant level was set at a P value of ≤0.05. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

Results
Prevalence
During the study period (January 2010 to December 2012), 709 patients were referred to the University of Alabama at Birmingham Hypertension Clinic for RHTN. Of these, 150 patients were controlled on <3 antihypertensive medication classes and therefore identified as having controlled hypertension. The remaining 559 patients were confirmed to have RHTN based on elevated clinic BP measurements although prescribed ≥3 different classes of antihypertensive agents, that is, uncontrolled RHTN (Figure). During follow-up, 276 patients were excluded from the analysis because of suspected medication nonadherence, control of BP on <5 medications, not receiving spironolactone or eplerenone, control of ambulatory BP, that is, white coat RHTN, presence of CKD stage 4 or 5, or inadequate follow-up (≤ 2 visits). Thus, >90% of patients initially suspected of having refractory hypertension were controlled with medication changes, were pseudorefractory (nonadherent, white coat refractory), were lost to follow-up, or had uncontrolled hypertension in the setting of advanced CKD. Of the 559 patients confirmed to have RHTN, 15 never achieved BP control in the office or by 24-hour ABPM despite treatment with maximum tolerated doses of at least 5 antihypertensive agents, including chlorthalidone and an MRA. These 15 patients were identified as having refractory hypertension, resulting in an overall prevalence 2.7% among patients originally referred for RHTN.

Patient Characteristics and Comorbidities
Compared with patients with controlled RHTN (n=29), patients with refractory hypertension were younger, more often women, had higher clinic BP, higher clinic HR, and were treated with more antihypertensive medications (Tables 1 and 2; Table S1 in the online-only Data Supplement), including greater use of treated combined α–β-antagonists, calcium channel blockers, MRAs, α2-adrenergic agonists, vasodilators, and centrally acting agents. There was no difference in the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers and thiazide or thiazide-like diuretics (Table 2; Table S1). Other characteristics, including race, ethnicity, body weight, smoking status, and family history of hypertension, were also analyzed (Table S1). However, none of these variables were significantly associated with the development of refractory hypertension. The overall prevalence of diabetes mellitus (DM) was 53.4% in the overall cohort and 51.9% (n=15) in the refractory hypertension group. The prevalence of DM was significantly greater in the refractory hypertension group compared with the controlled hypertension group (P<0.05). The mean HbA1c level was 6.8% (range, 5.6% to 9.6%) in the overall cohort and 6.3% (range, 4.6% to 9.6%) in the refractory hypertension group. The prevalence of DM was significantly lower in the refractory hypertension group compared with the controlled hypertension group (P<0.05).

Figure. Prevalence of refractory hypertension. CBP indicates clinic blood pressure; CHT, chlorthalidone; CKD, chronic kidney disease; HBP, home blood pressure; RHTN, resistant hypertension; and SPL, spironolactone.
Table 1. Baseline Characteristics of Patients With Refractory and Controlled Resistant Hypertension

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Refractory Hypertension, n=15</th>
<th>Controlled RHTN, n=29</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.0±13.3</td>
<td>56.5±14.1</td>
<td>0.038</td>
</tr>
<tr>
<td>Women, %</td>
<td>80.0</td>
<td>51.9</td>
<td>0.047</td>
</tr>
<tr>
<td>Black race, %</td>
<td>60.0</td>
<td>55.2</td>
<td>0.765</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.4±7.1</td>
<td>32.6±7.0</td>
<td>0.942</td>
</tr>
<tr>
<td>No. of antihypertensive medication drug classes at maximum dose</td>
<td>6±1</td>
<td>4.1±1.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Clinic systolic BP, mmHg</td>
<td>178.0±27.9</td>
<td>134.3±13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic diastolic BP, mmHg</td>
<td>103.3±17.4</td>
<td>79.3±9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic heart rate, bpm</td>
<td>75.1±11.2</td>
<td>63.1±10.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>12.4±7.8</td>
<td>16.9±9.1</td>
<td>0.122</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>13.3</td>
<td>10.3</td>
<td>0.784</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>35.7</td>
<td>21.7</td>
<td>0.360</td>
</tr>
<tr>
<td>CKD stage 3, %</td>
<td>35.7</td>
<td>28.6</td>
<td>0.652</td>
</tr>
<tr>
<td>CAD, %</td>
<td>14.3</td>
<td>7.4</td>
<td>0.521</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>6.6</td>
<td>17.2</td>
<td>0.276</td>
</tr>
<tr>
<td>OSA, %</td>
<td>41.6</td>
<td>63.6</td>
<td>0.180</td>
</tr>
<tr>
<td>HF/hospitalization, %</td>
<td>40.0</td>
<td>0.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Morisky score</td>
<td>0.6</td>
<td>1.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%). BMI indicates body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; OSA, obstructive sleep apnea; and RHTN, resistant hypertension.

Table 2. Type of Antihypertensive Medications Among Adults With Refractory and Resistant Hypertension

<table>
<thead>
<tr>
<th>Antihypertensive Class</th>
<th>Refractory Hypertension, n=15</th>
<th>Controlled RHTN, n=29</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARBs</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>BBs</td>
<td>100</td>
<td>51.7</td>
<td>0.038</td>
</tr>
<tr>
<td>CCBs</td>
<td>100</td>
<td>75.9</td>
<td>0.038</td>
</tr>
<tr>
<td>Thiazides/loop</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>MRAs</td>
<td>100</td>
<td>58.6</td>
<td>0.004</td>
</tr>
<tr>
<td>α2-agonists</td>
<td>93.3</td>
<td>6.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>60</td>
<td>13.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are n (%). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; NS, not significant; and RHTN, resistant hypertension.

Ambulatory BP, HR, and HRV

Daytime and nighttime periods were defined according to participants’ self-report. The average nighttime period based on patient diary was from 10 pm to 6 am. Mean daytime and nighttime systolic and diastolic BP levels were all significantly greater in the refractory patients compared with the patients with controlled RHTN (Table 4). Likewise, mean daytime and nighttime HR was significantly higher in the refractory patients compared with controls. The largest difference in HR was during the daytime (82.1±11.5 versus 71.1±12.3 bpm, refractory versus controlled resistant, P=0.012). Patients with refractory hypertension had significantly reduced HRV compared with controlled resistant hypertensive patients (4.48 versus 6.11; P=0.036).

Pulsatile Hemodynamic Parameters

PWV was significantly greater in the patients with refractory hypertension compared with those with controlled RHTN (Table 5) indicative of greater arterial stiffness.15,16 Central systolic and diastolic pressures were significantly greater in refractory patients, as was the augmentation index (Table 5).

Impedance Cardiography

TFC was similar in both groups. SVR index normalized for body surface area was 1.6-fold greater in patients with refractory hypertension compared with control patients (3795±1753 versus 2382±349 dyne·s/cm²·m²; P=0.008; Table 5) in spite of greater use of vasodilators (Table 2 and Table S1).

Discussion

This study is the first prospective assessment of patients diagnosed with refractory hypertension, an extreme phenotype...
of antihypertensive treatment failure. Novel findings demonstrate that patients with refractory hypertension compared with patients with controlled RHTN have (1) greater 24-hour urinary normetanephrine levels, (2) increased arterial stiffness, (3) higher HR, (4) lower HRV, and (5) higher SVR. Collectively, these findings imply heightened sympathetic nervous system increases progressively and in parallel with hypertension severity. In patients with RHTN, catheter-based radiofrequency ablation of the renal nerves lowers BP concomitant with reductions in muscle SNA as measured by microneurography. The current findings add to this body of literature in suggesting that persistent sympathetic hyperactivity also contributes importantly to antihypertensive failure.

There is growing evidence that SNA may be associated with arterial stiffness and that the degree of sympathetic activation may influence arterial compliance. In an Italian study carried out in people with unilateral lesions of the upper or lower extremity that required surgical intervention, reduction of adrenergic tone by ipsilateral brachial plexus anesthesia or ipsilateral removal of the lumbar sympathetic ganglia resulted in markedly increased distensibility of the radial and femoral arteries, respectively.

Furthermore, recent studies in normotensive and hypertensive humans have shown that SNA is an independent determinant of PWV. Finally, there is growing evidence that increased HR, a reliable marker of SNA and cardiovascular tone as an important cause of antihypertensive treatment failure. The prevalence of true refractory hypertension was only 2.7% of patients referred to a hypertension specialty clinic for RHTN, considerably less than observed in a previous retrospective analysis. Combined, these findings indicate that true antihypertensive treatment failure is uncommon but is characterized by biochemical and hemodynamic parameters consistent with excessive sympathetic output.

Table 4. Clinic and Ambulatory Blood Pressure Monitoring in Patients With Refractory and Controlled Resistant Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertension, n=15</th>
<th>Controlled RHTN, n=29</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h systolic BP, mmHg</td>
<td>174.0±20.2</td>
<td>139.8±16.3</td>
<td>0.0017</td>
</tr>
<tr>
<td>Daytime</td>
<td>178.1±97.4</td>
<td>141.0±15.7</td>
<td>0.0046</td>
</tr>
<tr>
<td>Nighttime</td>
<td>165.2±19.2</td>
<td>133.5±19.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>24-h diastolic BP, mmHg</td>
<td>94.7±19.8</td>
<td>75.7±11.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Daytime</td>
<td>97.4±19.8</td>
<td>77.2±11.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Nighttime</td>
<td>87.7±16.5</td>
<td>70.2±15.1</td>
<td>0.007</td>
</tr>
<tr>
<td>24-h PP, mmHg</td>
<td>74.7±29.4</td>
<td>64.0±12.7</td>
<td>0.022</td>
</tr>
<tr>
<td>Daytime</td>
<td>80.0±21</td>
<td>64.0±12.6</td>
<td>0.022</td>
</tr>
<tr>
<td>Nighttime</td>
<td>77.5±18.5</td>
<td>63.6±14.7</td>
<td>0.03</td>
</tr>
<tr>
<td>24-h heart rate, bpm</td>
<td>77.8±7.7</td>
<td>68.8±7.6</td>
<td>0.0018</td>
</tr>
<tr>
<td>Daytime</td>
<td>82.1±11.5</td>
<td>71.1±12.3</td>
<td>0.0118</td>
</tr>
<tr>
<td>Nighttime</td>
<td>72.7±9</td>
<td>65.6±9</td>
<td>0.038</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>4.48</td>
<td>6.11</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Values are mean±SD. BP indicates blood pressure; PP, pulse pressure; and RHTN, resistant hypertension.

Table 5. Results of Pulsatile and Impedance Hemodynamics in Patients With Refractory and Controlled Resistant Hypertension

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertension, n=15</th>
<th>Controlled RHTN, n=29</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75.0±11.7</td>
<td>63.0±10.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>177.2±28.9</td>
<td>133.6±13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>101.4±16.5</td>
<td>79.3±6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>130.3±16.8</td>
<td>97.6±10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>75.8±28.1</td>
<td>54.4±14.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Central aortic measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>163.7±26.1</td>
<td>121.9±14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>103.3±16.7</td>
<td>80.1±9.8</td>
<td>&lt;0.001</td>
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<tr>
<td>PP, mmHg</td>
<td>60.4±26.9</td>
<td>41.8±14.0</td>
<td>0.034</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>18.9±12.7</td>
<td>10.7±10.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Aix, %</td>
<td>29.6±10.7</td>
<td>22.4±14.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Aix75, %</td>
<td>30.9±6.7</td>
<td>16.8±12.0</td>
<td>0.004</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>11.8±2.2</td>
<td>9.4±1.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Impedance measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVRI, dyne·s·cm−5·m−2</td>
<td>3795±1753</td>
<td>2382±349</td>
<td>0.008</td>
</tr>
<tr>
<td>TFC, k ohm/m²</td>
<td>32.3±5.4</td>
<td>31.8±7.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. Aix indicates augmentation index; Aix75, augmentation index standardized to a heart rate of 75 bpm; AP, aortic pressure; BP, blood pressure; MAP, mean arterial pressure; NS, not significant; PP, pulse pressure; PWV, pulse wave velocity; RHTN, resistant hypertension; SVRI, systemic vascular resistance normalized for body surface area; and TFC, thoracic fluid content.
RHTN who were receiving β-blockers. Higher 24-hour urinary normetanephrine levels were still observed in the refractory group in spite of use of β-blockers by both groups of patients suggesting a β-blocker independent increase.

Patients in this study with refractory hypertension were characterized by increased vascular stiffness, as indexed by PWV, and central aortic BP, compared with patients with controlled RHTN. Although this is being described for the first time in association with refractory hypertension, the finding is consistent with previous evaluations of patients with uncontrolled RHTN. For example, in the prospective community-based Maine Syracuse Longitudinal Study, a subgroup of 46 patients met the criteria for uncontrolled RHTN that is, elevated BP with use of ≥3 antihypertensive drug classes, including a diuretic.36,37 PWV was significantly higher in this group compared with a control group of 48 patients without RHTN, that is, BP controlled with ≤2 antihypertensive drug classes. Similarly, in a prospective evaluation of 90 Brazilian patients with RHTN by Martins et al,38 47 patients were classified as having uncontrolled RHTN. PWV was significantly higher in this uncontrolled group compared with patients whose BP was treatment resistant but controlled.

In a previous retrospective analysis, we reported that patients with refractory hypertension had a consistently higher resting BP compared with patients whose BP was treatment resistant but controlled.

The current evaluation includes an estimate of SVR as measured by transthoracic impedance cardiography. Despite being on more vasodilators, a 1.6-fold higher SVR was observed in patients with refractory hypertension (Table 6). This elevation in HR was interpreted as evidence of heightened sympathetic tone, suggesting that increased sympathetic nervous system activity may play a potentially important role in the pathogenesis of antihypertensive treatment failure. This prospective study confirms those previous findings in demonstrating that cardiac HR was again significantly higher in patients with refractory versus controlled RHTN. We further show that HR as measured during ambulatory monitoring is also significantly higher in refractory patients, particularly at night.

The current evaluation includes an estimate of SVR as measured by transthoracic impedance cardiography. Despite being on more vasodilators, a 1.6-fold higher SVR was observed in patients with refractory hypertension (Table 5). However, greater use of centrally acting agents in refractory hypertensive patients may have affected these results by increasing SVR.

The validity of the calculation of cardiac output by impedance cardiography has limitations, including (1) the difficulty of acquiring the signal because of spontaneous movements of the patient, disorders of heart rhythm, and interference from electric devices in the environment and (2) invalidation of the physical modeling of the system because of the presence of conditions, such as pregnancy, obesity, pleural effusion, chronic congestive HF with pulmonary edema, or severe aortic valve disease that can change baseline thoracic impedance.18 In our study, participants were evaluated when clinically stable in normal sinus rhythm and without HF or clinical signs of volume overload at the time of the study.18

An alternative hypothesis to refractory hypertension being neurogenic in pathogenesis is it being secondary to inappropriate fluid retention. Such an effect is consistent with what has been described of RHTN in general, that is, being volume dependent. For example, Taler et al39 used impedance cardiography to demonstrate that intensification of diuretic therapy based on high TFC values improved BP control rates in patients with RHTN. To test this possibility, we measured BNP levels and TFC in patients with refractory and controlled RHTN as indices of intravascular volume. We have previously reported that BNP levels do correlate with intravascular volume expansion in patients with RHTN.40 BNP levels and TFC values were the same in the refractory patients and patients with resistant but well-controlled hypertension. This argues against persistent fluid retention as being a major cause of refractory hypertension. The absence of a critical role of fluid retention in causing refractory hypertension has important clinical implications as it suggests that continued intensification of diuretic therapy, as is often suggested for lack of BP control, may not be appropriate or effective.

This study confirms important negatives in terms of potential mechanisms of antihypertensive treatment failure, foremost being hyperaldosteronism. Aldosterone excess has been demonstrated in multiple studies to be an important contributor to RHTN.3,4 However, aldosterone levels, both serum and 24-hour urinary levels, as well as the aldosterone:renin ratio were not different in patients with refractory versus controlled RHTN. Furthermore, as previously shown, patients with refractory hypertension were unresponsive to use of an MRA,1 along with all other classes of antihypertensive agents. Although aldosterone and renin activities are ideally assessed after the withdrawal of antihypertensive agents, this was not possible for safety reasons in these high-risk patients. Although β-blockers predictably suppress diuretics, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers increase plasma renin activity, effects on aldosterone release are minimal or absent.42 These observations suggest that although hyperaldosteronism may commonly contribute to antihypertensive treatment resistance, aldosterone excess is not likely a mediator of antihypertensive treatment failure in patients with refractory hypertension.

Likewise, lower levels of 24-hour urinary sodium excretion in patients with refractory hypertension argue against extreme dietary sodium excess as being the primary cause of refractory hypertension.

Indicators of mineralocorticoid excess other than aldosterone excess were not observed in patients with refractory hypertension. For example, biochemical abnormalities suggestive of apparent mineralocorticoid excess (ie, low plasma aldosterone concentration and low plasma renin activity) were absent. Similarly, comparable 24-hour urinary cortisol levels did not suggest glucocorticoid excess (Table 3).

In the current prospective analysis, the overall prevalence of refractory hypertension was 2.7% of patients referred to a hypertension specialty clinic for RHTN. Patients remained refractory to treatment despite being adherent to treatment regimens that included on average, 6 different classes of agents, including in all patients, use of a diuretic, and a MRA. In our previous retrospective analysis, the prevalence of refractory hypertension was estimated at ≈10% of patients referred to our hypertension specialty clinic with RHTN.41 The lower prevalence observed in the current prospective analysis is likely attributable to a more systematic use of the combination of chlorothalidone and spironolactone. We and others have found this combination to be particularly effective for treatment of RHTN.15 In the current analysis, all participants diagnosed with refractory hypertension were receiving diuretic...
and an MRA, whereas, during the time period of the retrospective analysis, the combination was used in only 1 of 3 of the patients designated as being refractory to treatment.

In this study, patients with refractory hypertension were more likely black and women compared with subjects with controlled RHTN, the latter difference being statistically significant. Similar observations were reported in the previous retrospective study of refractory hypertension. In the cross-sectional analysis of the REGARDS cohort, black race and male sex were associated with higher risk of having refractory hypertension. Together, the findings of the 3 studies suggest that blacks are more likely to have refractory hypertension, as is true of RHTN, whereas the association with sex, if any, needs clarification with additional studies.

This study has some limitations, including (1) the reliance on patient report and an 8-item questionnaire for assessing medication adherence, both known to be of inconsistent reliability, (2) use of greater number of classes and, in some cases, higher doses of antihypertensive agents in patients with refractory hypertension, which may have contributed to the higher urinary normetanephrine levels, and (3) the lack of a direct measure of sympathetic activity as with microneurography or norepinephrine secretion from sympathetic nerve terminals, such as plasma norepinephrine with or without the spillover approach.

This study is strengthened by its prospective design, rigorous comparison with patients with controlled RHTN, and exclusion of common causes of pseudoresistance, including white coat effect, inadequate treatment, and poor medication adherence.

Perspectives

In summary, refractory hypertension is being used to identify an extreme clinical phenotype of antihypertensive treatment failure, which in this study was defined as BP that remains elevated in spite of use of at least 5 different classes of antihypertensive agents, including chlorothalidone and an MRA. The current results suggest that the former is more likely neurogenic in pathogenesis. If true, such patients may preferentially benefit from treatment strategies that effectively reduce sympathetic output, if and when such strategies are available.

Sources of Funding

Research reported was supported by the National Institutes of Health (NIH 1R01 HL113004), National Center for Advancing Translational Sciences of the National Institutes of Health (NIH UL1TR001865), NIH T32 HL007457, and NIH T32HL079888.

Disclosures

None.

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Refractory hypertension is an extreme clinical phenotype of antihypertensive treatment failure defined as elevated blood pressure in spite of use of at least 5 different classes of antihypertensive agents, including chlorthalidone and a mineralocorticoid receptor antagonist. The phenotype seems distinct from resistant hypertension in general, which has been broadly attributed to inappropriate fluid retention, in that, the current study findings suggest that refractory hypertension is more likely caused by excess sympathetic output. Additional prospective studies are needed to further elucidate mechanisms of antihypertensive treatment failure. Patients with refractory hypertension may preferentially benefit from treatment strategies that effectively reduce sympathetic output, rather than intensified diuretic treatment. Clinically, successful pharmacological treatments that reduce sympathetic output, at least at doses that are well tolerated, are currently not available. Device-based procedures, such as renal denervation, although promising, have failed to date to show convincing blood pressure-lowering effects in large, sham-controlled clinical trials. The current findings highlight the potential clinical need for effective sympatholytic therapies for patients with refractory hypertension.

Novelty and Significance

What Is New?

• This is the first prospective study that characterizes patients with refractory hypertension, a proposed novel phenotype of antihypertensive treatment failure.

What Is Relevant?

• This study demonstrates that heightened sympathetic tone as indicated by clinic and ambulatory heart rate, arterial stiffness, and 24-hour urinary metanephrine and normetanephrine levels may contribute importantly to antihypertensive treatment failure.

Summary

Refractory hypertension refers to an extreme clinical phenotype of antihypertensive treatment failure defined as elevated blood pressure in spite of use of at least 5 different classes of antihypertensive agents, including chlorthalidone and a mineralocorticoid receptor antagonist. The phenotype seems distinct from resistant hypertension in general, which has been broadly attributed to inappropriate fluid retention, in that, the current study findings suggest that refractory hypertension is more likely caused by excess sympathetic output. Additional prospective studies are needed to further elucidate mechanisms of antihypertensive treatment failure. Patients with refractory hypertension may preferentially benefit from treatment strategies that effectively reduce sympathetic output, rather than intensified diuretic treatment. Clinically, successful pharmacological treatments that reduce sympathetic output, at least at doses that are well tolerated, are currently not available. Device-based procedures, such as renal denervation, although promising, have failed to date to show convincing blood pressure-lowering effects in large, sham-controlled clinical trials. The current findings highlight the potential clinical need for effective sympatholytic therapies for patients with refractory hypertension.
Refractory Hypertension: Evidence of Heightened Sympathetic Activity as a Cause of Antihypertensive Treatment Failure
Tanja Dudenbostel, Maria C. Acelajado, Roberto Pisoni, Peng Li, Suzanne Oparil and David A. Calhoun

Hypertension. published online May 18, 2015;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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REFRACTORY HYPERTENSION: EVIDENCE OF HEIGHTENED SYMPATHETIC ACTIVITY AS A CAUSE OF ANTIHYPERTENSIVE TREATMENT FAILURE

Short title: Dudenbostel et al.; Refractory hypertension

Tanja Dudenbostel, MD¹; Maria C. Acelajado, MD²; Roberto Pisoni, MD³; Peng Li, PhD⁴; Suzanne Oparil, MD,¹; David A. Calhoun, MD¹

¹Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama, Birmingham, Alabama; ²Department of Medicine, University of South Alabama, Mobile, Alabama; ³Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and the ⁴Department of Biostatistics, University of Alabama, Birmingham, Alabama

Address for Correspondence:

Tanja Dudenbostel, MD
University of Alabama at Birmingham
933 19th Street South, CHSB Suite 115
Birmingham, AL, 35294
Phone: 1-205-934-9281
Fax: 1-205-934-1302
E-Mail: tduden@uab.edu
S1. Antihypertensive Medications among Adults with Refractory and Controlled Resistant Hypertension

<table>
<thead>
<tr>
<th>Antihypertensive class</th>
<th>Subclass, generic</th>
<th>Refractory hypertension (n=15)*</th>
<th>Controlled RHTN (n=29)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>Lisinopril</td>
<td>40±0 (7)</td>
<td>40±0 (13)</td>
</tr>
<tr>
<td></td>
<td>Benazepril</td>
<td>40±0 (4)</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>Olmesartan</td>
<td>40±0 (4)</td>
<td>40±0 (10)</td>
</tr>
<tr>
<td></td>
<td>Valsartan</td>
<td>0±0</td>
<td>320±0 (4)</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>0±0</td>
<td>50±0 (1)</td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>0±0</td>
<td>300±0 (1)</td>
</tr>
<tr>
<td>Non-selective BB</td>
<td>Labetalol</td>
<td>725±150 (4)</td>
<td>489±23 (9)</td>
</tr>
<tr>
<td></td>
<td>Carvedilol</td>
<td>45±11 (5)</td>
<td>46±19 (6)</td>
</tr>
<tr>
<td>Selective BB</td>
<td>Nebivolol</td>
<td>10±0 (3)</td>
<td>10±9 (3)</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>175±50 (3)</td>
<td>150±71 (2)</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>0±0</td>
<td>50±0 (1)</td>
</tr>
<tr>
<td>CCB DHP</td>
<td>Amlodipine</td>
<td>12±4 (13)</td>
<td>9±2 (22)</td>
</tr>
<tr>
<td>CCB Non-DHP</td>
<td>Diltiazem</td>
<td>320±139 (2)</td>
<td>0±0</td>
</tr>
<tr>
<td>Thiazide-like diuretics</td>
<td>Chlorthalidone</td>
<td>27±7 (13)</td>
<td>24±4 (22)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>HCTZ</td>
<td>50±0 (2)</td>
<td>21±7 (4)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Furosemide</td>
<td>53±23 (4)</td>
<td>35±10 (4)</td>
</tr>
<tr>
<td>MRAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α2 adrenergic agonists</td>
<td>Clonidine</td>
<td>0.9±0 (11)</td>
<td>0.2±0 (1)</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Guanfacine</td>
<td>2±0</td>
<td>(3)</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>150±0</td>
<td>(4)</td>
<td>100±41</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>9±7</td>
<td>(5)</td>
<td>0±0</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Dose per day in mg (n)

ACEi indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DHP, Dihydropyridine; HCTZ, hydrochlorothiazide; MRA, mineralocorticoid receptor antagonist; RHTN, resistant hypertension.
Refractory Hypertension
Evidence of Heightened Sympathetic Activity as a Cause of Antihypertensive Treatment Failure
Tanja Dudenbostel, Maria C. Acelajado, Roberto Pisoni, Peng Li, Suzanne Oparil, David A. Calhoun

顽固性高血压一直被视为抗高血压治疗失败的一种临床表型[1]。这一表型最初描述是基于一项回顾性分析，即难治性高血压(resistant hypertension, RHTN)患者[1]。在304例连续入组的确诊RHTN的患者中，29例患者()被确定为顽固性高血压，即由一位临床高血压专科医师经过至少6个月的治疗，但仍然未能将收缩压和舒张压控制在140/90 mmHg以下。在该项分析中，顽固性高血压患者接受平均6类抗高血压药物，包括噻嗪样利尿剂氯噻酮，一种盐皮质激素受体拮抗剂(mineralocorticoid receptor antagonist, MRA)，最常用的螺内酯。与血压已控制的RHTN患者相比，顽固性高血压患者表现出持续的静息诊室心率(heart rate, HR)增快。这种HR增快可以作作为交感神经张力增高的证据，这提示，交感神经激活在抗高血压治疗
一项名为卒中地理和种族差异原因（Reasons for Geographic and Racial Differences in Stroke，REGARDS）的研究，近期对其中14809例高血压成人进行横截面分析，其中顽固性高血压定义为采用≥3类抗高血压药物治疗，但仍然无法控制的高血压（>140/90 mmHg），顽固性高血压的患病率在所有高血压受试者中为0.5%，在RHTN受试者中为3.6%[2]。黑人、男性、肥胖、慢性肾病（CKD）、糖尿病、有卒中和冠心病病史与REGARDS人群中的顽固性高血压密切相关。在该项分析中，与所有高血压受试者或血压已控制的RHTN受试者相比，顽固性高血压受试者的诊室HR并未增快。

本研究的目的是在顽固性高血压患者中前瞻性地检验交感神经张力增高的证据，后者以24小时尿异丙肾上腺素水平、血浆肌酐、估算肾小球滤过率[10]、血清钾、BNP、高敏C反应蛋白。在研究随访的早上7点至9点之间采集血样，患者需经过一晚上禁食，并且在早上服药之前、静坐休息5分钟之后才开始采血[11]。在患者保持平常膳食、不改变体力活动水平的情况下，收集24小时尿样。通过测定24小时肌酐清除率来评估24小时尿样是否充足。

### 方法

#### 确定患者

因RHTN（采用≥3种抗高血压药物治疗，包括一种利尿剂，但血压>140/90 mmHg）至阿拉巴马大学Birmingham高血压诊所就诊，随后被诊断为顽固性高血压或血压已控制的RHTN患者，连续入组，前瞻性地进入研究流程。

所有就诊患者进行醛固酮和皮质醇状况测定，测量指标有血浆醛固酮浓度、血浆肾素活性、24小时尿中醛固酮、皮质醇、钠、钾和肌酐排泄量，将其作为RHTN常规临床治疗的一部分[3-5]。根据临床表现，排除高血压的其他继发性原因[5]。

### 常规治疗方法

根据患者血压对高血压专科医师常规治疗措施的反应，确定患者有顽固性高血压或血压已控制的RHTN。在每次临床随访中，因RHTN就诊的所有患者由两位临床高血压专科医师诊疗。依据常规临床诊疗流程，如果诊室血压仍然高于目标值，将调整患者的抗高血压药物治疗方案[5]。依据指南，建议所有患者摄入低盐/高纤维膳食[5]。为达到血压控制，标准化的治疗方案包括起始并将血管紧张素转换酶抑制剂或血管紧张素受体阻滞剂的剂量调至最大；使用钙通道阻滞剂（最常用氨氯地平）；优先使用利尿剂氯噻酮；加用螺内酯（或依普利酮，若螺内酯不能耐受）；优先使用α-受体阻滞剂（最常用拉贝洛尔）；加用交感神经系统阻滞剂（最常用可乐定）；最后，加用β受体阻滞剂（最常用比索洛尔）。对于有液体潴留临床表现的患者，可以使用利尿剂。

在≥6个月内经过≥3次的常规临床随访后，确定顽固性高血压患者。顽固性高血压的定义为，尽管采用超过5类抗高血压药物治疗，包括每天25 mg氯噻酮和MRA（每天25 mg螺内酯，或50 mg依普利酮，两天4次），并且依从方案，同时没有潜在的继发性高血压的病因，但血压仍然未得到控制（>140/90 mmHg）。血压已控制的RHTN患者，根据美国心脏协会的技术参数，定义为采用≥4种抗高血压药物治疗诊室血压已得到控制的患者，被确定为对照组受试者[5]。

血压已控制的难治性高血压和顽固性高血压患者以2:1的比例前瞻性地进入试验方案，即每1例受试者纳入顽固性高血压组，就有2例受试者进入对照组。在进入1例顽固性高血压受试者后，就从诊所患者中招募对照受试者。研究中排除了以下患者：有心力衰竭（heart failure, HF）的体征或症状，且在30天内因HF急性发作[6,7]或房颤而入院，担心患者不依从处方的抗高血压方案，患者有4期或5期CKD[8]。

本研究得到阿拉巴马大学Birmingham伦理审查委员会的批准，在进入研究前获得所有患者的书面知情同意书。研究依据机构指南开展。

### 患者调查

#### 调查所有患者，评估患者病历，了解高血病症程，以及糖尿病、血脂异常、冠状动脉疾病（coronary artery disease, CAD）卒中和HF病史情况。在门诊随访中，常规询问患者是否规律服用抗高血压药物。采用8项Morisky服药依从性问卷[9]，常规评估服药依从性。如果患者评分>2分，则认为依从性不佳。

### 生化测定

按照研究方案，生物评估包括测定24小时尿量和尿中肾素水平，血清肌酐，估算肾小球滤过率[10]，血清钾，BNP，高敏C反应蛋白。在研究随访的早上7点至9点之间采集血样，患者需经过一晚上禁食，并且在早上服药之前、静坐休息5分钟之后才开始采血[11]。在患者保持平常膳食、不改变体力活动水平的情况下，收集24小时尿样。通过测定24小时肌酐清除率来评估24小时尿样是否充足。

### 诊室血压测量

在患者至少安静休息5分钟之后，由一位高血压专科
医师测量诊室血压，测量血压时，患者坐位，后背挺直，采用听诊法，而且手臂与心脏保持在一个平面。采用合适大小的袖带。袖带气囊至少环绕手臂的80%。医师测量3个血压读数，每次间隔2分钟，第2个和第3个读数用于计算平均血压。测量双臂血压，血压较高的一侧手臂用于进一步测量血压。所有血压测量均依据指南而行[5]。

动态血压、HR、HR变异性
所有患者进行24小时动态血压监测（ABPM），以证实顽固性高血压患者的血压未控制，证实临床已控制RHTN患者的血压得到控制。采用一种自动化、无创的示波装置（Oscar 2; SunTech Medical, Inc, Morrisville, NC）来进行ABPM[12,13]。依据指南[9]，采用合适大小的袖带，袖带气囊至少环绕手臂的80%。在诊室进行第一次测量，以确保功能正常。24小时内，日间（觉醒时）每20分钟记录一次，夜间（熟睡时）每30分钟记录一次。根据患者自我报告的数据，分别确定日间和夜间。ABPM在工作日进行，在ABPM期间，所有患者正常服用处方的药物，并且保持平时的活动。记录ABPM的标准算法。有效的24小时ABPM需要记录到成功测量的80%以上。依据指南[12,13]，通过动态监测，已控制的动态血压定义为，24小时平均血压<130/80 mmHg，日间（觉醒时）血压<135/80 mmHg，夜间（熟睡时）血压<120/70 mmHg。

通过计算ABPM获得的日间和夜间HR数值的SD，来评估HR变异性（HR variability, HRV）[14]。

脉搏波分析和脉搏波传导速度
依据指南[15,16]，所有患者通过平面压力测量法来测定颈-股动脉脉搏波传导速度（pulse wave velocity, PWV），采用一个转换函数，通过挠动脉波形进行中心脉搏波分析（SphygmoCor; AtCor Medical, Sydney, Australia）。在标准化条件下，经过一晚上禁食，早上服药之前，在同一个早上（7点至9点）进行脉搏波分析。至少休息10分钟之后，患者仰卧位进行这两项测量。需要测量3

图 顽固性高血压的患病率。CBP：诊室血压；CHT：氯噻酮；CKD：慢性肾病；HBP：家庭自测血压；RHTN：难治性高血压；SPL：螺内酯。
患者的基线变量。统计学检验水准设定在P值<0.05。所有分析采用SAS 9.3软件进行（SAS Institute, Cary, NC）。

结果

患病率

在研究期间（2010年1月至2012年12月），709例患者因RHTN至阿拉巴马大学Birmingham高血压诊所就诊。在这些患者中，150例采用不到3类抗高血压药物治疗而使血压得到控制，因此确认为已控制的高血压患者。尽管处方了≥3种不同类别的抗高血压药物，但基于诊室血压升高，其他559例患者被确诊为RHTN，即血压未控制的RHTN（图）。在随访期间，因为怀疑对药物治疗不依从、采用不足5种药物控制血压，未接受螺内酯或依普利酮，控制动态血压，即白色大衣RHTN，存在4期或5期CKD，随访不够（≤2次），276例患者被排除在分析之外。因此，超过90%的最初怀疑为顽固性高血压的患者通过改变药物治疗而使血压得到控制，属于假性顽固性高血压（不仅从白色大衣顽固性高血压），失去随访，或有晚期CKD的情况下未控制的高血压。在被确诊RHTN的559例患者中，尽管采用至少5种抗高血压药物的最大可耐受剂浓度治疗，包括氨氯地平或一种MRA，但15例患者的诊室血压或24小时ABPM血压从来没有得到控制。这15例患者被确定为顽固性高血压，因此在最初因RHTN而就诊的患者中，其总患病率为2.7%。

患者特征与合并症

与血压已控制的RHTN患者（n=29）相比，顽固性高血压患者更年轻，女性更多，诊室血压更高，诊室HR更快，使用的抗高血压药物更多（表1，表2；表1见于在线补充数据），包括更多使用α-β受体阻滞剂、钙通道阻滞剂、血管扩张剂和β阻滞剂。
表4. 顽固性高血压和血压已控制的难治性高血压患者的诊室血压及动态监测血压

<table>
<thead>
<tr>
<th>参数</th>
<th>顽固性高血压，n=15</th>
<th>血压已控制的RHTN，n=29</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h收缩压，mm Hg</td>
<td>174.0±20.2</td>
<td>139.8±16.3</td>
<td>0.0017</td>
</tr>
<tr>
<td>日间</td>
<td>178.1±97.4</td>
<td>141.0±15.7</td>
<td>0.0046</td>
</tr>
<tr>
<td>夜间</td>
<td>165.2±19.2</td>
<td>133.5±19.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>24-h舒张压，mm Hg</td>
<td>94.7±19.8</td>
<td>75.7±11.8</td>
<td>0.006</td>
</tr>
<tr>
<td>日间</td>
<td>97.4±19.8</td>
<td>77.2±11.4</td>
<td>0.007</td>
</tr>
<tr>
<td>夜间</td>
<td>87.7±16.5</td>
<td>70.2±15.1</td>
<td>0.007</td>
</tr>
<tr>
<td>24-h PP，mm Hg</td>
<td>74.7±29.4</td>
<td>64.0±12.7</td>
<td>0.022</td>
</tr>
<tr>
<td>日间</td>
<td>80.0±21</td>
<td>64.0±12.6</td>
<td>0.022</td>
</tr>
<tr>
<td>夜间</td>
<td>77.5±18.5</td>
<td>63.6±14.7</td>
<td>0.03</td>
</tr>
<tr>
<td>24-h心率，bpm</td>
<td>77.8±7.7</td>
<td>68.8±7.6</td>
<td>0.0018</td>
</tr>
<tr>
<td>日间</td>
<td>82.1±11.5</td>
<td>71.1±12.3</td>
<td>0.0018</td>
</tr>
<tr>
<td>夜间</td>
<td>72.7±9</td>
<td>65.6±9</td>
<td>0.038</td>
</tr>
<tr>
<td>HR变异系数</td>
<td>4.48</td>
<td>6.11</td>
<td>0.036</td>
</tr>
</tbody>
</table>

数值表示为均值±SD，BP：血压，PP：脉压，RHTN：难治性高血压。

MRAs, α-2受体激动剂、血管扩张剂和中枢作用药物。
在血管紧张素转换酶抑制剂/血管紧张素受体阻滞剂、噻嗪类或噻嗪样利尿剂的使用方面无差异（表2；表S1）。其他特征，包括种族、体重指数（body mass index, BMI）和高血压病程，两组之间相似。对于合并症，包括糖尿病、CKD、CAD或卒中，两组之间无统计学意义的差异。

然而，顽固性高血压患者之前因HF而入院的发生率较高（P=0.002）。

动态血压、HR和HRV

两组的TFC相似。尽管已使用较多的血管扩张剂（表2，表S1），但与对照组患者相比，顽固性高血压患者的心率和舒张压也明显较高，增强指数同样如此（表5）。

心阻抗图

两组的TFC相似。尽管已使用较多的血管扩张剂（表2，表S1），但与对照组患者相比，顽固性高血压患者的心率和舒张压也明显较高，增强指数同样如此（表5）。

讨论

本研究第一次前瞻性地评估了顽固性高血压患者，后者是抗高血压治疗失败的一种极端表型。新的发现显示，与血压已控制的RHTN患者相比，顽固性高血压患者有以下特点：(1) 24小时尿素氮水平较高，(2) 动脉僵硬度更大，(3) HR较快，(4) HRV较低，(5) SVR较大。总之，这些发现提示，交感神经张力增高可以作为抗高血压治疗失败的一个重要原因。[20-24]。真正的顽固性高血压的患病率已占因RHTN至高血压专科门诊就诊患者的2.7%，明显少于之前回顾性分析观察到的数据。同
样，这些发现提示，真正的抗高血压治疗失败并不常见，但具有与交感神经张力过高相一致的生化及血流动力学参数特征。

之前的研究已经明确，交感神经活性（sympathetic nerve activity, SNA）增高与动脉高血压的发生发展及维持密切相关[25]。交感神经系统活性进行性增高，与高血压严重程度同步发展[26-30]。对于RHTN患者，肾神经导管射频消融治疗可以降低血压，同时伴随着肌肉SNA下降，后者由显微神经检查法测定[31-33]。本研究的发现为这些文献增加新的证据，提示持续性交感神经高活性对抗高血压治疗失败也非常重要。

有越来越多的证据显示，SNA可能与动脉僵硬度密切相关，而且交感神经活性的增高可能影响动脉顺应性[24-26]。在一项意大利研究中，对于需要外科干预的上肢或下肢动脉病变患者而言，通过麻醉同侧臂丛神经，或者去除同侧的腰交感神经节，降低肾上腺素能神经的紧张力，可以明显提高桡动脉和股动脉的可扩张性[24-25]。

另外，近期在正常血压和高血压人群中进行的研究显示，SNA是PWV的独立决定因素[24,26]。最后，也越来越多的证据说明，HR增快，作为SNA和心血管风险的一个可靠指标，是交感神经活性增高的证据，这提示，交感神经系统活性增高可能在抗高血压治疗失败的原因中发挥重要的潜在作用。这项前瞻性研究证实了之前的发现，即与血压已控制的RHTN患者相比，顽固性高血压患者的诊室HR同样明显增快。我们进一步显示，在顽固性高血压患者中，在动态监测中测得的HR也明显增快，尤其是在夜间。

在之前的一项回顾性分析中，我们曾经报道，与血压已控制的RHTN患者相比，顽固性高血压患者的静息诊室HR—性地增快[1]。这一HR增快可做为交感神经张力增高的证据，这提示，交感神经活性增高的证据在抗高血压治疗失败的原因中发挥重要的潜在作用。这项前瞻性研究证实了之前的发现，即与血压已控制的RHTN患者相比，顽固性高血压患者的诊室HR同样明显增快。我们进一步显示，在顽固性高血压患者中，在动态监测中测得的HR也明显增快，尤其是在夜间。

本项研究还包含了对SVR的评估，以经胸心阻抗图测得。尽管使用了多种血管扩张剂，但仍然观察到顽固性高血压患者的SVR升高了1.6倍（表5）。然而，顽固性高血压患者使用较多中枢作用药物，通过增加SVR，而影响了这些结果[18]。通过心阻抗图计算心输出量有局限性，局限性包括：(1) 由于患者自主运动、心率异常、来自环境中电力装置的干扰，故很难获得信号；(2) 由于存在一些疾病，如妊娠、肥胖、胸腔积液、慢性充血性HF合并肺水肿，或严重的主动脉瓣膜疾病，可以改变基线经胸阻抗，导致系统的物理模型失效[18]。在我们的研究中，在患者临床病情稳定，有正常的窦性节律，无HF或容量超负荷的临床体征时，评估受试者[18]。

有关顽固性高血压神经源性机制的一个假说是，顽固性高血压继发于不恰当的液体潴留。这样的效应与之前对RHTN的描述相基本一致，即是容量依赖性。例如，Taler等人[39]采用心阻抗图显示出，基于TFC值较高，采用强化利尿剂治疗，可以提高RHTN患者的血压控制率。
了检验这一可能性，我们测定了顽固性高血压和血压已控制RHTN患者的BNP水平和TFC值，作为血管内容量的指标。我们之前报告称，在RHTN患者中，BNP水平与血管内容量扩大之间相关[40]。在顽固性高血压和血压已良好控制的RHTN患者中，BNP水平和TFC值相似。这反驳了持续性液体潴留作为顽固性高血压的一个重要原因。在引起顽固性高血压的因素中，液体潴留没有发挥关键作用有重要的临床意义，这提示，继续强化利尿剂治疗，如同没有控制血压所提示的，可能并不合适或有效。

本研究证实了重要的方面，即抗高血压治疗失败的潜在机制，其中最重要的机制是高醛固酮血症。多项研究显示，醛固酮过多是RHTN的一个重要原因[5,41]。然而，醛固酮水平，无论是血浆还是24小时尿醛固酮值，以及醛固酮/肾素比值，在顽固性高血压和血压已控制的RHTN患者中并没有差异。另外，之前已有研究显示，顽固性高血压患者使用MRA[1]，以及所有其他类型的抗高血压药物治疗无效。尽管在停用抗高血压药物之后，醛固酮和肾素活性已得到理想评估，但基于这些高危患者的特殊性原因，也是不可能的。尽管可以预测，β受体阻滞剂抑制血浆肾素活性，而利尿剂、血管紧张素转换酶抑制剂、血管紧张素受体阻滞剂提高血浆肾素活性，但它们对醛固酮释放的影响很小，甚至没有影响[42]。这些观察提示，尽管高醛固酮血症可能是抗高血压治疗抵抗的常见原因，但醛固酮过多不太可能是顽固性高血压患者抗高血压治疗失败的中间因素。

同样，顽固性高血压患者中24小时尿钠排泄量较低，反驳了膳食中钠摄入量极度增多是顽固性高血压的主要原因。

除了醛固酮过多外，在顽固性高血压患者中没有观察到，盐皮质激素过多的指标。例如，缺乏提示盐皮质激素明显过多的生化指标异常（如血浆醛固酮浓度低、血浆肾素活性低），同样，可比较的24小时尿皮质醇水平没有提示糖皮质激素过多（表3）。在本项前瞻性分析中，在因RHTN至高血压专科诊所就诊的患者中，顽固性高血压的总体患病率是2.7%。尽管患者依从治疗方案，方案包括平均6种不同类别的药物，所有患者使用一种利尿剂和一种MRA，但患者的血压仍然没有得到控制。在我们之前的回顾性分析中，在因RHTN至我们高血压专科诊所就诊的患者中，估计顽固性高血压的患病率约在10%[1]。本项前瞻性分析中观察到的患病率较低，可能是因为更多患者同时使用了氯噻酮和螺内酯。我们及其他研究人员发现，这种联合用药对于RHTN的治疗特别有效[15]。在本项分析中，确诊为顽固性高血压的所有受试者正在接受利尿剂和一种MRA；然而，在回顾性分析时期，这种联合用药仅用于1/3的认为属于顽固性高血压的患者。

在本项研究中，与血压已控制的RHTN受试者相比，顽固性高血压患者中黑人和女性更多，两组间后者的差异具有统计学意义。在之前开展的顽固性高血压研究中，也报告过相似的观察结果[1]。在对REGARDS队列的横断面研究中，黑人种族和男性性别与顽固性高血压的风险较高密切相关[2]。综上，这三项研究的结果提示，黑人更可能出现顽固性高血压，对RHTN同样如此[8]；不过，与性别的相关性，需要其他研究进一步阐明。

本项研究具有某些方面的局限性，包括（1）患者报告和8项评估服药依从性问卷的可靠性，已知二者的可靠性并不一致；（2）使用更多类别的药物，在某些情况下，顽固性高血压患者服用抗高血压药物的剂量较高，这可能引起患者尿中异丙肾上腺素水平升高；（3）没有直接测量交感神经活性，而是采用显微神经检查法，或交感神经末梢分泌的异丙肾上腺素，如血浆异丙肾上腺素水平，用或没用溢出方法。

本项研究的优势之处在于前瞻性设计，与血压已控制的RHTN患者的严格比较，排除了假性难治性的常见病因，包括白大衣效应、治疗不充分和服药依从性差。总的来说，顽固性高血压被用以确定抗高血压治疗失败的一种极端表型，其在本项研究中的定义是，尽管使用至少5种类别的抗高血压药物治疗，包括氯噻酮和一种MRA，但患者的血压仍然较高。本项研究的结果显示，在最初因RHTN至高血压专科医师处就诊的患者中，真正的顽固性高血压并不常见。顽固性高血压的机制似乎更为独特，相对于RHTN更为常见的表型，后者可更广泛地归因于不恰当的液体潴留，然而，本项研究的结果提示，前者更可能有神经系统病因参与其中。如果确实如此，这些患者更有可能从有效降低交感神经张力的治疗策略中获益，当然前提是确实有这些策略。

**资金来源**

本项研究得到美国国立卫生研究院（NIH 1R01 HL113004）、国立卫生研究院全国高级转化医学中心（NIH UL1TR00165、NIH T32HL007457、NIH T32HL079888）的支持。

**利益声明**

无。
Hypertension  
July 2015

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