Update on Resistant Hypertension

George Mangos
St George Hospital
UNSW Kogarah Sydney
• Failure to reach office BP < 140/90 mmHg
• Three or more agents including a diuretic
• Patients adherent with regimen
• Maximal tolerated doses

*Calhoun, AHA Statement, Circulation, 2008*
Evolving Definition of TRHT

• Controlled resistant hypertension
  – Patients fulfilling criteria for TRHT BUT controlled with 4 or more agents

• Refractory hypertension
  – Patients who remain HT despite maximal doses of 4 or more antihypertensive agents

Calhoun, AHA Statement, Circulation, 2008
Pseudoresistant Hypertension

- Not allowing 3-5 min to rest before measuring blood pressure
- Not taking 2-3 readings
- Incorrect cuff size
- Permitting smoking
- Permitting caffeine!
PREVALENCE
• General population v referred populations
• National Health And Nutrition Examination Survey (NHANES)
• N=13 154
• 12.8% of hypertensives had TRHT by AHA criteria
  – 86 % on diuretic, of those 64.4% HCTZ

Persell, Hypertens, 2011
Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring

Alejandro de la Sierra, Julián Segura, José R. Banegas, Manuel Gorostidi, Juan J. de la Cruz, Pedro Armario, Anna Oliveras, Luis M. Ruilope

- Spanish HT/ABPM registry
- 68,045 patients
- 12.2% of this population of HT patients had resistant HT
  - Office BP > 140/90 mmHg on at least 3 drugs including a diuretic

De la Sierra et al, HT, 2011
Apparent v True resistance

- 2 studies
- Australian and Spanish data
- Assessed resistant HT by using 24 hour ABPM
- Determine rate of true BP resistance
Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring

Alejandro de la Sierra, Julián Segura, José R. Banegas, Manuel Gorostidi, Juan J. de la Cruz, Pedro Armario, Anna Oliveras, Luis M. Ruilope

• Spanish HT/ABPM registry
• 68 045 patients
• 12.2% of this population of HT patients had resistant HT
  – Office BP > 140/90 mmHg on at least 3 drugs including a diuretic
  – Evaluated using Spacelabs ABPM

De la Sierra et al, HT, 2011
24 hour ABPM evaluation

- True resistance n=5182 = 62.5 %
- Controlled HT = 3113 = 37.5 %
- True RHT – male, duration, smokers, diabetics, AER, CVD, > 4 drugs

Table 1. Clinical Features in Resistant Hypertensives With Normal or Elevated 24-Hour Blood Pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>True RH (N=5182)</th>
<th>White-Coat RH (N=3113)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.0±11.7</td>
<td>65.0±10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>54.6</td>
<td>46.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.4±4.7</td>
<td>30.5±5.0</td>
<td>0.228</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>11.4±8.7</td>
<td>10.5±8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>14.8</td>
<td>10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetics, %</td>
<td>35.1</td>
<td>27.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>75 (62 to 89)</td>
<td>72 (61 to 84)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.23±1.06</td>
<td>5.21±1.06</td>
<td>0.495</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.33±0.37</td>
<td>1.36±0.37</td>
<td>0.022</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.64±0.93</td>
<td>1.54±0.72</td>
<td>0.005</td>
</tr>
<tr>
<td>UAE, mg/g</td>
<td>11.0 (3.4 to 44.5)</td>
<td>7.0 (2.7 to 20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UAE &gt;30 mg/g, %</td>
<td>30.1</td>
<td>19.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH by ECG, %</td>
<td>18.5</td>
<td>14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous CV disease, %</td>
<td>19.1</td>
<td>18.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment with ≥4 AH drugs, %</td>
<td>38.3</td>
<td>34.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients taking part of their medication in the evening, %</td>
<td>24.9</td>
<td>25.8</td>
<td>0.319</td>
</tr>
</tbody>
</table>

De la Sierra et al, HT, 2011
Is Resistant Hypertension Really Resistant?

Mark A. Brown, Megan L. Buddle, and Allison Martin

- 72% treated hypertensives truly resistant
- 28% treated hypertensives actually controlled using ABPM
- 32% of those on no medication had normal BP using ABPM (WCH)

ABPM useful in evaluation and diagnosis of RHT

Brown et al, AJH, 2001
• n=304 patients referred to tertiary HT clinic (University of Alabama) over 8 years
• Retrospective analysis
• WC effect excluded in those suspected of WCE
Treatment

- Usual ACEI/ARB+CCB+diuretic combination
- Chlorthalidone or frusemide if CKD
- Lifestyle changes
- MR antagonist added generally 4th line
- Therapies for PAL and RAS allowed.
- Refractory HT defined as not achieving goal (140/90 mmHg) over 6 months

Acelajado et al, J Clin Hyperten , 2012
Controlled Resistant v Refractory HT

• After 6 months
  – 9.5% remained refractory

• Refractory HT phenotype
  – Higher baseline BP
  – Faster HR
  – Same BMI

### TABLE I. Baseline Demographic Characteristics of Patients With Refractory and Controlled Resistant Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Refractory Hypertension (n=29)</th>
<th>Controlled RHTN (n=275)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.4±14.9</td>
<td>55.4±10.3</td>
<td>.16</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.2±6.2</td>
<td>32.8±6.6</td>
<td>.75</td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>174.6±22.9</td>
<td>157.9±24.6</td>
<td>.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>97.0±15.0</td>
<td>88.5±15.2</td>
<td>.005</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>76.1±10.6</td>
<td>71.5±10.8</td>
<td>.03</td>
</tr>
<tr>
<td>African Americans</td>
<td>16 (55)</td>
<td>120 (44)</td>
<td>.23</td>
</tr>
<tr>
<td>Women</td>
<td>16 (55)</td>
<td>132 (48)</td>
<td>.46</td>
</tr>
<tr>
<td>Antihypertensive drugs, No.</td>
<td>4.9±1.4</td>
<td>4.1±1.1</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; BP, blood pressure; RHTN, resistant hypertension. Values are expressed as means or number (percentage). P values denote refractory hypertension group compared with the controlled RHTN group.

Acelajado et al, J Clin Hyperten, 2012
All Hypertensives Controlled HT 88% (NHANES, Spanish)

Apparent Resistant HT 12%

Resistant HT 12%

ABPM Controlled HT 30% (white coat effect)

ABPM true Resistant HT 70%

(Spanish, Australian)

Controlled Resistant HT 90%

(Calhoun)

Refractory HT 10%

Refactory HT
  • Similar age & wt
  • Higher baseline BP
  • More antiHT agents
  • Higher HR
  • Less effect MR blockade
  • No diff PRA/aldo
  • ? SNS overactivity

HOW MANY PATIENTS REALLY HAVE RESISTANT HT ??
Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study

- n=8575 ABPM studies, 11 centres, Australia
- Least product regression to compare with Clinic BP measured by Doctors and trained staff

*Head G et al for ABPWGHBPRA, BMJ, 2010*
Daytime ABPM results

- Drs measure 9/7 mmHg > trained staff
- Trained staff 6/3 mmHg > daytime ABPM average

| Table 1 | Characteristics of patients by method of clinic blood pressure measurement |
|-----------------|-----------------|-----------------|-----------------|
|                | Staff measured blood pressure (n=8529) | Doctor measured blood pressure (n=1593) | P for differences between groups |
| Age in years   | 56.4 (15.4)     | 53.8 (15.9)     | <0.001          |
| Age range      | 18-98           | 18-94           | –               |
| Body mass index| 28.9 (5.5)      | 28.9 (5.5)      | 0.719           |
| Female sex (%) | 4626 (54%)      | 886 (56%)       | –               |
| Treated hypertensives (%) | 5866 (69%) | 1138 (71%) | – |
| White (%)      | 7026 (82%)      | 1313 (82%)      | –               |
| Asian (%)      | 1290 (15%)      | 264 (17%)       | –               |

Office blood pressure (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Staff measured blood pressure (n=8529)</th>
<th>Doctor measured blood pressure (n=1593)</th>
<th>P for differences between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seated measurements</td>
<td>5327</td>
<td>1490</td>
<td>–</td>
</tr>
<tr>
<td>Systolic seated</td>
<td>141.6 (19.0)</td>
<td>150.2 (23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic seated</td>
<td>81.7 (12.1)</td>
<td>88.8 (12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reclining measurements</td>
<td>3399</td>
<td>1165</td>
<td>–</td>
</tr>
<tr>
<td>Systolic reclining</td>
<td>142.3 (21.0)</td>
<td>151.8 (22.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic reclining</td>
<td>83.8 (12.1)</td>
<td>88.7 (11.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ambulatory blood pressure (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Staff measured blood pressure (n=8529)</th>
<th>Doctor measured blood pressure (n=1593)</th>
<th>P for differences between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour systolic</td>
<td>132.0 (14.6)</td>
<td>132.1 (14.8)</td>
<td>0.867</td>
</tr>
<tr>
<td>24 hour diastolic</td>
<td>76.6 (10.2)</td>
<td>77.3 (10.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Day systolic</td>
<td>135.5 (14.8)</td>
<td>135.5 (15.0)</td>
<td>0.938</td>
</tr>
<tr>
<td>Day diastolic</td>
<td>79.2 (10.6)</td>
<td>80.0 (10.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Night systolic</td>
<td>120.5 (17.0)</td>
<td>120.8 (17.4)</td>
<td>0.509</td>
</tr>
<tr>
<td>Night diastolic</td>
<td>67.8 (10.3)</td>
<td>68.3 (10.9)</td>
<td>0.075</td>
</tr>
</tbody>
</table>

Values presented as total, percentage of total, or mean (SD).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinic seated blood pressure</th>
<th>24-hour</th>
<th>Night</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 hypertension</td>
<td>&gt;180/110</td>
<td>163/101</td>
<td>157/93</td>
<td>168/105</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>&gt;160/100</td>
<td>148/93</td>
<td>139/84</td>
<td>152/96</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>&gt;140/90</td>
<td>133/84</td>
<td>121/76</td>
<td>136/87</td>
</tr>
<tr>
<td>Target blood pressure plus one condition</td>
<td>&lt;130/80</td>
<td>125/76</td>
<td>112/67</td>
<td>128/78</td>
</tr>
<tr>
<td>Target blood pressure with proteinuria</td>
<td>&lt;125/75</td>
<td>121/71</td>
<td>107/63</td>
<td>124/74</td>
</tr>
<tr>
<td>Normal blood pressure</td>
<td>&lt;120/80</td>
<td>117/76</td>
<td>102/67</td>
<td>120/78</td>
</tr>
</tbody>
</table>
Causes of resistance to treatment

- Non-adherence to treatment
- The office or white coat effect
- Other contributing conditions
  - Obesity
  - Drugs, alcohol, liquorice, salt
  - Sedentary lifestyle
  - Obstructive sleep apnoea
- “Hidden sodium and water”
  - “normal” or high sodium intake
  - failure to use a diuretic in such a patient
- SNS overactivity
- Secondary causes of HT
  - Primary and obesity aldosteronism
  - Renal parenchymal disease
  - Renal artery stenosis
  - Phaeochromocytoma
# Lifestyle modifications to manage hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>SBP Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>BMI 18.5-24.9</td>
<td>5-20 mmHg/10kg</td>
</tr>
<tr>
<td>DASH plan</td>
<td></td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Na reduction</td>
<td>&lt; 100 mmol or 6g salt</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>30 min/day, most days</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>Max 2/day men 1/day women</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

Sodium Restriction

Reduced Dietary Salt for the Prevention of Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials (Cochrane Review)

Rod S. Taylor¹, Kate E. Ashton², Tiffany Moxham³, Lee Hooper⁴ and Shah Ebrahim⁵

- RCTs, > 6 m
- CVD morbidity or mortality
- 7 studies
- 3 HT, 3 normotension, 1 CCF

Taylor et al, AJH, 2011
Cochrane – SBP at end of trials

Taylor et al, AJH, 2011

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favors-reduced salt</th>
<th>Favors control</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.6.1 Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPT 1989 [36 mo]</td>
<td>-2.8</td>
<td>6.6</td>
<td>174</td>
<td>-3</td>
</tr>
<tr>
<td>TOHP I 1992 [18 mo]</td>
<td>-5.1</td>
<td>7.9</td>
<td>304</td>
<td>-3</td>
</tr>
<tr>
<td>TOHP II 1997 [36 mo]</td>
<td>-0.7</td>
<td>9</td>
<td>515</td>
<td>0.5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>993</td>
<td>1,068</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.78; \chi^2 = 8.06, df = 2 (P = 0.05); \hat{I}^2 = 67%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.79 (P = 0.07)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.6.2 Hypertensive

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favors-reduced salt</th>
<th>Favors control</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Morgan 1978 [24 mo]</td>
<td>-5.5</td>
<td>22.3</td>
<td>31</td>
<td>-4</td>
</tr>
<tr>
<td>TONE 1998 [30 mo]</td>
<td>-4.6</td>
<td>11.3</td>
<td>317</td>
<td>-0.4</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>348</td>
<td>327</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.00; \chi^2 = 0.22, df = 1 (P = 0.64); \hat{I}^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 4.75 (P &lt; 0.00001)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.6.3 Heart failure

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favors-reduced salt</th>
<th>Favors control</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Paterna 2008 [6.4 mo]</td>
<td>107</td>
<td>13</td>
<td>99</td>
<td>111</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>112</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.40 (P = 0.02)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cochrane – All cause mortality

Taylor et al, AJH, 2011
Sodium restriction in management of resistant hypertension

- Insufficient dataset to conclude no effect
- Effective but overall effect is small
- Use 24 hour urinary sodium excretion as “reality check”
OSA - sleep disordered breathing and hypertension

- Autonomic activity
- Altered intrathoracic mechanics
- RAAS activation
- Endothelial dysfunction
- Inflammation
- Metabolic factors
- Genetic aspects

Parati et al, ERS/ESH taskforce, Eur Resp J, 2013
The Impact of Continuous Positive Airway Pressure on Blood Pressure in Patients With Obstructive Sleep Apnea Syndrome

Evidence From a Meta-analysis of Placebo-Controlled Randomized Trials

Patrick Haentjens, MD, PhD; Alain Van Meerhaeghe, MD; Antonio Moscariello, MD; Sonia De Weerdt, MD; Kris Poppe, MD, PhD; Alain Dupont, MD, PhD; Brigitte Velkeniers, MD, PhD

• RCTs CPAP v placebo
• N=572 from 12 trials reporting 24hr ABPM
• Random effects model

Haentjens et al, Arch Int Med, 2007
CPAP v placebo on 24 hr MBP

- Net difference
  MBP 1.69 mmHg

Haentjens et al, Arch Int Med, 2007
Current antihypertensive therapy

• Vasodilator therapy
  – ACEI & ARB (don’t use together! *Makani et al BMJ 2013*)
  – CCB
• Diuretic therapy
  – 3rd line (Accomplish Study)
• SNS blockade
  – Beta blockade
  – Central and peripheral alpha blockade
  – Imidazoline agonists
• Mineralocorticoid blockade
• Direct smooth muscle dilators
• Retrospective analysis of MRFIT data
• MRFIT multifaceted RCT to lower CVEs
• Both drugs lowered CVEs c/w neither
• N=12 866 ages 35 to 57
• Thiazide 50-100 mg daily

_Dorsch et al, Hypertens, 2011_
MRFIT

- Chlorthalidone superior
  - SBP
  - LDL
  - BSL
  - Lower K
  - Chol
MRFIT - CLD v HCTZ - survival

Dorsch et al, Hypertens, 2011
Case Study - Anastasia

- 32yo, severe HT confirmed by 24 hr ABPM
- Presentations to ED with migraine > 6/year
- Admissions to STGH with accelerated HT
- Mild-mod LVH
- ARB, HCTZ, moxonidine, CCB
- Normal ARR, renal angiogram, metanephrines
- Pregnancy
Pregnancy 2006

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight</th>
<th>Urea</th>
<th>B.P.</th>
<th>Oxytetracycline</th>
<th>Gestation</th>
<th>FHR</th>
<th>Presentation &amp; Position</th>
<th>Section</th>
<th>Manual</th>
<th>Uterine Aspiration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.12.05</td>
<td>NAD</td>
<td>100</td>
<td>10</td>
<td>N/D</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6.18.05</td>
<td>NAD</td>
<td>100</td>
<td>10</td>
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<td></td>
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<tr>
<td>11.06.05</td>
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<td>10</td>
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<tr>
<td>21.06.05</td>
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<td>10</td>
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<td>19.06.06</td>
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<td>N/D</td>
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<td>11:30</td>
<td>N/D</td>
<td>10</td>
<td></td>
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</tr>
</tbody>
</table>

**PROBLEM LIST:**

- LSCS 1/7/06

**Cord Blood Donated:** Yes

**INSTRUCTIONS OF ADMISSION:**

- Post Natal
- $70 10/30
- $10/10/9

**Paternity:**

- $250 10/10/9
## Progress

<table>
<thead>
<tr>
<th></th>
<th>Morning (2 readings, 2 min apart)</th>
<th>Evening (2 readings, 2 min apart)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY 1</strong></td>
<td>169/117  170/116</td>
<td>163/105  154/103</td>
</tr>
<tr>
<td>Wednesday,</td>
<td>2nd April 2008</td>
<td>7:10am  7:02am</td>
</tr>
<tr>
<td><strong>DAY 2</strong></td>
<td>160/115  177/111</td>
<td>161/120  176/121</td>
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<tr>
<td>Thursday,</td>
<td>3rd April 2008</td>
<td>7:02am  7:02am</td>
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<tr>
<td><strong>DAY 3</strong></td>
<td>159/117  159/115</td>
<td>179/119  169/121</td>
</tr>
<tr>
<td>Friday,</td>
<td>4th April 2008</td>
<td>7:09am  7:02am</td>
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<tr>
<td><strong>DAY 4</strong></td>
<td>159/117  159/116</td>
<td>173/113  174/119</td>
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<tr>
<td>Saturday, 5th</td>
<td>5th April 2008</td>
<td>6:00pm  6:02pm</td>
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<tr>
<td><strong>DAY 5</strong></td>
<td>169/119  151/110</td>
<td>188/118  189/122</td>
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<tr>
<td>Sunday,</td>
<td>6th April 2008</td>
<td>6:00pm  6:02pm</td>
</tr>
<tr>
<td><strong>DAY 6</strong></td>
<td>169/123  169/122</td>
<td>169/123  169/121</td>
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<tr>
<td>Monday,</td>
<td>7th April 2008</td>
<td>7:50pm  7:50pm</td>
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<tr>
<td><strong>DAY 7</strong></td>
<td>163/121  172/125</td>
<td>178/123  178/122</td>
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<tr>
<td>Tuesday,</td>
<td>8th April 2008</td>
<td>7:30pm  7:30pm</td>
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<tr>
<td><strong>AVERAGE</strong></td>
<td></td>
<td></td>
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</table>
Spironolactone

- Rapid resolution of chronic “migraine”
- No further presentations
- Normal HBP and 24hr ABP
- Spironolactone & amlodipine
- Progesterone effect
Mineralocorticoid Blockade

**Efficacy of Low-Dose Spironolactone in Subjects With Resistant Hypertension**

Mari Konishi Nishizaka, Mohammad Amin Zaman, and David A. Calhoun

- $n = 74$ with resistant hypertension
  - 34 PAL
- Regimen included ACE/ARB and diuretic

*Nishizaka et al, AJH 2003*
Spironolactone - overall

**FIG. 1.** Spironolactone-induced reduction in systolic blood pressure (BP) (filled bars) and diastolic BP (open bars) at 6 weeks, 3 months, and 6 months follow-up in subjects with resistant hypertension (*n* = 76). BP reduction was significant at all time points compared to baseline.

*Nishizaka et al, AJH 2003*
Spironolactone – PAL v no PAL

**FIG. 2.** Spironolactone-induced reduction in systolic blood pressure (SBP) and diastolic BP (DBP) at 6 weeks, 3 months, and 6 months follow-up in subjects with primary aldosteronism (filled bars, *n = 34*) and without primary aldosteronism (open bars, *n = 42*). BP reduction was not significantly different between primary aldosteronism and non-primary aldosteronism subjects at any time point.

*Nishizaka et al, AJH 2003*
Nishizaka Study

• Mean BP reduction 25±20/12±12 mmHg
• No correlation with baseline ARR
• Breast tenderness
  – 10% men
  – 4% overall
• 5 had AKI, 4 due to large BP drop, 3 restarted
• Hyperkalaemia in 2 with CKD

Nishizaka et al, AJH 2003
ASCOT Trial

Effect of Spironolactone on Blood Pressure in Subjects With Resistant Hypertension

Neil Chapman, Joanna Dobson, Sarah Wilson, Björn Dahlöf, Peter S. Sever, Hans Wedel, Neil R. Poulter, on behalf of the Anglo-Scandinavian Cardiac Outcomes Trial Investigators

• ASCOT compared CCB/ACE v BB/Thiazide
• N=20000
• Cardiac endpoint
• Spironolactone 4th line add-on
  – CCB then ACE then α-blocker then discretion

Chapman et al, HT, 2007
ASCOT Study – spironolactone arm

- N=1411
- Mean duration 1.3 years
- N=2.9 other drugs
- $\Delta$ BP -21.9/9.5 mmHg
- 6% breast discomfort
- 2% hyperkalaemia

Chapman et al, HT, 2007
Spironolactone

Glycyrrhetinic acid

Aldosterone

Cortisol
Spironolactone for resistant hypertension

- 6% breast tenderness, 10% males
  - Breast lumps
- 2% hyperkalaemia
- Erectile dysfunction, menstrual irregularities.
- Eplerenone not reimbursed for hypertension
- Amiloride - 5 -10 mg bd
When to add SNS Blockade?

• Generally 4th line agents
  – Beta-blockers
    • Tachycardia, caution in DM, COPD & PVD
  – Methyl-dopa, prazosin (ALLHAT)
    • AMD 250 mg tds max 500 mg tds
    • Prazosin 1-5 mg tds start ½ mg nocte
  – Physiotens
    • 0.2-0.4 mcg bd, generally not potent
Fifth line therapies for TRHT

- **Hydralazine** 25 mg tds
  - Side effects – nasal stuffiness
- **Minoxidil** – 5-10 mg tds
  - Hairy & swollen
  - Avid sodium retention – use loop diuretic
New therapies for hypertension

• New drugs
  – Aldosterone synthase inhibitors
  – LCZ 696 -combined AT1R/NEP blocker
    • (ACE/NEP agents angioedema)
  – PS433540 – AT1RA/endothelin A blocker
    • (ET-A RA cause oedema)
  – ECE/NEP inhibitor
  – PL 3994 – natriuretic peptide receptor A agonist
  – AR 9281 – epoxide hydrolase inhibitor
    • Inhibition lowers BP in rats

• Electrical Baroreflex stimulation

• Renal Sympathetic Nerve Ablation
Other new agents for hypertension

• Endothelin antagonists
  – Showed promise but not effective
  – Bosentan - Pulmonary HT

• Renin Inhibitors
  – Aliskirin
  – No significant benefit over existing RAS agents
Blood pressure breakthrough: neck surgery could drastically reduce hypertension

September 4, 2013

Lucy Carroll
Reporter

View more articles from Lucy Carroll

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Tweet 26  Recommend 101  Share 1  Share  Pin it  submit

Email article  Print  Reprints & permissions

Top 10 Credit Cards (AUS)  www.CreditCardFinder.com.au
Upcapped Frequent Flyer Rewards. $0 Annual Fee & 0% Balance Transfer

Jaymes Diaz laughs off campaign gaffe
Failed Liberal candidate Jaymes Diaz appears on the ABC's Hamster Decides program after virtually disappearing from public view after a disastrous election campaign.
Carotid baroreceptor stimulation

- Autonomic nervous system
  - ↓ Sympathetic activity
  - ↑ Parasympathetic activity

- Vasodilation
- Stiffness
- Renin release
- Diuresis
- Sodium reabsorption
- ↓ Heart rate
- ↓ O₂ consumption
- ↓ LV hypertrophy
Baroreceptor stimulators

• Sends afferent information via CN9 to medulla (NTS) then parasympathetic afferents
• 25-40/15 mmHg improvement in BP
• Suggests role of carotid baroreceptors in long term regulation
• 35% of patients had nerve injury
• Available in Europe
• Technical improvements over next few years
RENAL SYMPATHETIC NERVE ABLATION
# Symplicity RDN Global Clinical Program

## Enrollment Complete / In Follow Up

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Region(s)</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Symplicity HTN-1</td>
<td>Series of Non-randomised Pilot Studies n = 153</td>
<td>EU, AU</td>
<td>3 yr</td>
</tr>
<tr>
<td>Symplicity HTN-2</td>
<td>Randomised Controlled Trial (1:1) n = 106</td>
<td>EU, AU</td>
<td>2 yr</td>
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</table>

## Enrolling / Planning

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Region(s)</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>SYMPPLICITY HTN-3</td>
<td>Randomised Controlled Trial (2:1), n=530</td>
<td>USA</td>
<td>Enrollment Completed</td>
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<tr>
<td>SYMPPLICITY HF</td>
<td>Feasibility Study n=40</td>
<td>EU, AU</td>
<td>Enroll</td>
</tr>
<tr>
<td>Global SYMPLICITY Registry</td>
<td>Prospective Registry n=5,000</td>
<td>Global</td>
<td>Enroll</td>
</tr>
<tr>
<td>Symplicity HTN-Japan</td>
<td>Randomised Controlled Trial (1:1) n=100</td>
<td>Japan</td>
<td>Enroll</td>
</tr>
<tr>
<td>Symplicity HTN-4</td>
<td>Randomised Controlled Trial (2:1) n= 530+</td>
<td>USA</td>
<td>Plan</td>
</tr>
<tr>
<td>Symplicity HTN-India</td>
<td>Single-arm Trial n= 40</td>
<td>India</td>
<td>Plan</td>
</tr>
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</table>
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Lancet. 2009;373:1275-1281

The Initial Cohort – Reported in the Lancet, 2009:
- First-in-man, non-randomized
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- 12-month data

The Expanded Cohort – This Report (Symplicity HTN-1):
- Expanded cohort of patients (n=153)
- 24 and 36-month follow-up

Schlaich M – TCT 2012
Symplicity HTN-1: Significant, Sustained BP Reduction to 3 Years

$p < 0.01$ for $\Delta$ from baseline for all time points.

Data is reported only on the patients available at each time point.

- **6 Months** ($n = 144$)
- **1 Year** ($n = 132$)
- **2 Years** ($n = 105$)
- **3 Years** ($n = 88$)

Expanded results presented at the European Society of Cardiology Annual Meeting 2013.
Symplicity HTN-1: Responder Rate Did Not Decrease Over Time

- RDN responder rate sustained up to three years

Respensor was defined as an office SBP reduction ≥10 mmHg
Number of patients represents data available at time of data-lock

Expanded results presented at the European Society of Cardiology Annual Meeting 2013.
Symplicity HTN-1: SBP Distribution Improved After RDN - Lowering Risk of CV Events*

Symplicity HTN-1: Renal Function Was Maintained Following RDN Therapy at 36 Months

Not all patients consented to collection of lab values
Chronic Safety Out to 36 months

- 1 patient with Hypotension and Renal Failure (18 m)
  - Due to sepsis
  - Successfully treated
  - Renal failure resolved
- 1 patient with Hypotension and Renal Failure (24 m)
  - Post-operative hypovolemia with continuation of antihypertensive medications leading to acute tubular necrosis (ATN)
  - Responded to treatment and ATN resolved

- Hypotension Episode
  - Associated with severe diarrhoea and dehydration
  - Resolve without further incident
- Two episodes Orthostatic Hypotension in 1 patient (Both resolved)
- 13 subjects with hypertensive episodes requiring hospitalization
- 3 deaths previously reported, deemed unrelated to procedure
  - Myocardial Infarction - After 3-day visit
  - Sudden death (cardiac) - After 6 months
  - Cardio-respiratory arrest - After 18 months
Conclusions

• The magnitude of clinical response is significant and sustained through 36 months
  • Average number of medications were similar at each time point
• Increasing responder rates indicate:
  • Some subjects respond late to RDN
  • No loss of treatment effect out to 36 months
• The treatment effect was consistent across subgroups (age, diabetes status, and baseline renal function)

Analysis includes data on patients available through 36 months
GTN 300 mcg per artery
Heparin 100 U/kg
Aspirin +/- clopidogrel
Assessed for Eligibility N=190

Total of 84 patients excluded:
36 - BP < 160 at baseline visit (after 2-week compliance period)
30 - ineligible anatomy
10 - declined participation
8 - other (exclusion criteria discovered after consent)

Randomized N=106

Allocated to renal denervation group N=52
- 2 missed 6-month visit
- 1 withdrew consent

6 Month follow-up N=49
- 1 withdrew consent
- 1 lost to follow-up

12-month follow-up N=47

Allocated to control group N=54
- 1 lost to follow-up
- 2 withdrew consent

6 Month follow-up N=51

Crossover group N=46
- 5 did not crossover:
  1 - withdrawn by PI
  1 - no femoral access
  1 - unsuitable anatomy
  2 - SBP < 140 mm Hg

12 month follow-up Crossover group N=35
- 2 lost to follow-up
- 9 no longer eligible (SBP < 160 mm Hg)
Symplicity 2 - baseline data

- Office BP

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Demographics at Time of Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Denervation Group</td>
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<tr>
<td>Group (n=49)</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex, % female</td>
</tr>
<tr>
<td>Race, % white</td>
</tr>
<tr>
<td>Body mass index</td>
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<tr>
<td>Type 2 diabetes mellitus, %</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
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<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²†</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
</tr>
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</table>
Symplicity 2 – 12 month outcomes
## Table 6. Renal Function at Baseline and 6 and 12 Months

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation Group</th>
<th>Crossover Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR, mL/min per 1.73 m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76.9±19.3 (n=49)</td>
<td>88.8±20.7 (n=35)</td>
</tr>
<tr>
<td>6 mo</td>
<td>77.1±18.8 (n=49)</td>
<td>89.3±19.5 (n=35)</td>
</tr>
<tr>
<td>12 mo</td>
<td>78.2±17.4 (n=45)</td>
<td>85.2±18.3 (n=35)</td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.03±0.29 (n=49)</td>
<td>0.84±0.21 (n=35)</td>
</tr>
<tr>
<td>6 mo</td>
<td>1.04±0.32 (n=49)</td>
<td>0.83±0.18 (n=35)</td>
</tr>
<tr>
<td>12 mo</td>
<td>1.01±0.28 (n=45)</td>
<td>0.86±0.20 (n=35)</td>
</tr>
<tr>
<td><strong>Cystatin C, mg/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.91±0.25 (n=38)</td>
<td>0.78±0.17 (n=27)</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.98±0.36 (n=40)</td>
<td>0.82±0.16 (n=26)</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.98±0.30 (n=38)</td>
<td>0.89±0.20 (n=26)</td>
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</tbody>
</table>

Values are mean±SD. eGFR indicates estimated glomerular filtration rate.
Mean changes in systolic and diastolic blood pressures (A) and estimated glomerular filtration rate (B) after renal sympathetic denervation over 24 months of follow-up.

Persu A et al. Hypertension 2012;60:596-606
Renal Sympathetic Denervation Does Not Aggravate Functional or Structural Renal Damage

• 62 consecutive RSNA patients
• N-GAL, KIM-1, eGFR, Cr

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Blood Pressure and Laboratory Measurements</th>
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<tr>
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<td>Blood Pressure (mm Hg)</td>
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<tr>
<td>Systolic</td>
<td>161.0 ± 14.8</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.8 ± 16.5</td>
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</tbody>
</table>

Values are mean ± SD.
# Markers of AKI post-RSNA

## Table 3: Laboratory Measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 Hours</th>
<th>48 Hours</th>
<th>3 Months</th>
<th>1 Day</th>
<th>2 Days</th>
<th>3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.90 (IQR: 0.80–1.11)</td>
<td>0.90 (IQR: 0.74–1.10)</td>
<td>0.95 (IQR: 0.82–1.35)</td>
<td>0.85 (IQR: 0.80–1.10)</td>
<td>0.12</td>
<td>0.26</td>
<td>0.24</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>79.3 ± 27.3</td>
<td>81.2 ± 24.6</td>
<td>72.5 ± 24.4</td>
<td>79.5 ± 16.8</td>
<td>0.41</td>
<td>0.18</td>
<td>0.71</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>39.0 (IQR: 31.8–54.3)</td>
<td>36.0 (IQR: 30.0–48.0)</td>
<td>47.0 (IQR: 30.0–59.0)</td>
<td>39.0 (IQR: 30.5–51.0)</td>
<td>0.41</td>
<td>0.19</td>
<td>0.69</td>
</tr>
<tr>
<td>Urinary NGAL (ng/ml)</td>
<td>16.9 (IQR: 6.8–34.1)</td>
<td>14.0 (IQR: 6.2–39.8)</td>
<td>14.0 (IQR: 4.7–35.8)</td>
<td>13.3 (IQR: 4.8–27.9)</td>
<td>0.67</td>
<td>0.65</td>
<td>0.59</td>
</tr>
<tr>
<td>KIM-1 (ng/ml)</td>
<td>0.85 (IQR: 0.30–0.95)</td>
<td>0.53 (IQR: 0.37–0.82)</td>
<td>0.61 (IQR: 0.38–0.81)</td>
<td>0.61 (IQR: 0.38–0.81)</td>
<td>0.54</td>
<td>0.78</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**BUN** = blood urea nitrogen; **eGFR** = estimated glomerular filtration rate; **IQR** = interquartile range; **KIM-1** = kidney injury molecule-1; **NGAL** = neutrophil gelatinase-associated lipocalin; **RSD** = renal sympathetic denervation.
Objectives:

- Assess procedural and long term safety of renal denervation
- Evaluate effectiveness of renal denervation on clinical outcomes
- Establish procedural benchmarking & physician practice patterns
- Evaluate the effect of geographical variations in patients and procedural characteristics on clinical outcomes
- Perform Quality of Life analysis

Scope:

- Over 200 sites world wide; at least 5000 patients
- Prospective, single-arm, open-label, non-interventional registry
- In accordance with Instructions For Use
- Geographies with commercial availability of Medtronic Symplicity Renal Denervation System

First enrollment February 2\textsuperscript{nd}, 2012
SYMPPLICITY HTN-3

• Study Design
  – Multi-center, prospective, blinded, randomized controlled trial

• Study Objective
  – To demonstrate that catheter-based renal denervation is a safe and effective treatment for uncontrolled hypertension

• Study Population
  – Uncontrolled hypertension population
    • SBP ≥160 mmHg despite maximally tolerated doses of ≥3 antihypertensive medication classes
    • Without significant renal impairment (eGFR > 45mL/min)
  – 530 randomized subjects at 90 sites
    • Randomization (2:1)
    • All patients maintained on baseline meds for 6 months

• This study is actively enrolling patients
Chronic Safety Out to 36 months*

- Hypotension and Renal Failure (18 m)
  - Due to sepsis
  - Successfully treated
  - Renal failure resolved

- Hypotension and Renal Failure (24 m)
  - Post-operative hypovolemia with continuation of antihypertensive medications leading to acute tubular necrosis (ATN)
  - Responded to treatment and ATN resolved

- Hypotension Episode
  - Recently identified; not yet classified

- 3 deaths previously reported, deemed unrelated to procedure
  - Myocardial Infarction - After 3-day visit
  - Sudden death (cardiac) - After 6 months
  - Cardio-respiratory arrest - After 18 months

*Analysis includes data on all patients available through 36 months

Schlaich M – TCT 2012
Simplicity Spyral™ Multi-Electrode Renal Denervation Catheter

Design Goal
Reduce procedural time while maintaining similar clinical outcomes and reassurance of success compared to Simplicity Flex™ Catheter

✓ 1 minute ablation for 4 electrodes simultaneously
✓ 4 electrodes, independently selectable
✓ 6F guide catheter compatible
✓ Non-occlusive
✓ Natural conformability
✓ Rapid exchange

Simplicity Spyral Product Features
Spyral Multi-electrode RDN System
A Feasibility Study

**Purpose:** To assess performance of Symplicity Spyral™ multi-electrode RDN system

**Primary goal:** Acute procedural safety assessment

---

**Initial Screening**
- **n=57**
  - Office SBP ≥ 160 mm Hg (≥ 150 mm Hg diabetics)
  - ≥ 3 meds
  - eGFR ≥ 45mL/min

---

**Renal Angiogram**
- If eligible, procedure
  - ≥ 4mm diameter
  - No stenosis > 50%
  - No prior stent or angioplasty

---

**Excluded During Screening (n=17)**
- Ineligible anatomy (n=13; 23%)
- Additional I/E criteria not met (n=2; 38%)
- Withdrew consent (n=1; 2%)
- Unable to have ABPM (n=1; 2%)

---

**Participating Centers**
- St. Vincent’s Hospital, AU
- The Alfred Hospital, Melbourne, AU
- Wellington Regional Hospital, NZ
Denervation Procedure

• Denervation video
STGH RSNA Enrolment criteria

- Treatment resistant hypertension
- Compliance with medication
- Exclusion of PAL, RAS, pheochromocytoma
- Preferably a trial of spironolactone
- ABPM proving BP > normal range (130/80 mmHg)
- Informed consent
Early Sympathetic Activation in the Initial Clinical Stages of Chronic Renal Failure

Guido Grassi, Fosca Quarti-Trevano, Gino Seravalle, Francesca Arenare, Marco Volpe, Silvia Furiani, Raffaella Dell’Oro, Giuseppe Mancia

See Editorial Commentary, pp XX-XX

Abstract—Direct and indirect indices of neuroadrenergic function have shown that end-stage renal disease is characterized by a marked sympathetic overdrive. It is unknown, however, whether this phenomenon represents a peculiar feature of end-stage renal disease or whether it is also detectable in the early clinical phases of the disease. The study has been performed in 73 hypertensive patients, of which there were 42 (age: 60.7±1.8 years, mean±SEM) with a stable moderate chronic renal failure (mean estimated glomerular filtration rate: 40.7 mL/min per 1.73 m², MDRD formula) and 31 age-matched controls with a preserved renal function. Measurements included anthropometric variables, sphygmomanometric and beat-to-beat blood pressure, heart rate (ECG), venous plasma norepinephrine (high-performance liquid chromatography), and efferent postganglionic muscle sympathetic nerve activity (microneurography, peroneal nerve). For similar anthropometric and hemodynamic values, renal failure patients displayed muscle sympathetic nerve activity values significantly and markedly greater than controls (60.0±2.1 versus 45.7±2.0 bursts per 100 heartbeats; P<0.001). Muscle sympathetic nerve activity showed a progressive and significant increase from the first to the fourth quartile of the estimated glomerular filtration rate values (first: 41.0±2.7; second: 51.9±1.7; third: 59.8±3.0; fourth: 61.9±3.3 bursts per 100 heartbeats), the statistical significance (P<0.05) between groups being maintained after adjustment for confounders. In the population as a whole, muscle sympathetic nerve activity was significantly and inversely correlated with the estimated glomerular filtration rate (r=−0.59; P<0.0001). Thus, adrenergic activation is a phenomenon not confined to advanced renal failure but already detectable in the initial phases of the disease. The sympathetic overdrive parallels the severity of the renal failure, state and, thus, it might participate, in conjunction with other factors, at the disease progression. (Hypertension. 2011;57:00-00.)

Key Words: chronic renal failure ■ microneurography ■ sympathetic nervous system
Renal Denervation in Moderate to Severe CKD.


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Abstract

Sympathetic activation contributes to the progression of CKD and is associated with adverse cardiovascular outcomes. Ablation of renal sympathetic nerves reduces sympathetic nerve activity and BP in patients with resistant hypertension and preserved renal function, but whether this approach is safe and effective in patients with an estimated GFR (eGFR) < 45 ml/min per 1.73 m(2) is unknown. We performed bilateral renal denervation in 15 patients with resistant hypertension and stage 3-4 CKD (mean eGFR, 31 ml/min per 1.73 m(2)). We used CO(2) angiography in six patients to minimize exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO(2) angiography. Mean baseline BP ± SD was 174±22/91±16 mmHg despite the use of 5.6±1.3 antihypertensive drugs. Mean changes in office systolic and diastolic BP at 1, 3, 6, and 12 months were -34/-14, -25/-11, -32/-15, and -33/-19 mmHg, respectively. Night-time ambulatory BP significantly decreased (P<0.05), restoring a more physiologic dipping pattern. In conclusion, this study suggests a favorable short-term safety profile and beneficial BP effects of catheter-based renal nerve ablation in patients with stage 3-4 CKD and resistant hypertension.
Significant Reductions in Ambulatory BP for Patients that Match Current Consensus Criteria*

* ≥ 150 mm Hg in Diabetes
† ≥ 100 mm Hg DBP

<table>
<thead>
<tr>
<th>Time</th>
<th>ABPM change (mmHg)</th>
<th>n</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>-14</td>
<td>288</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 months</td>
<td>-13</td>
<td>181</td>
<td>0.0001</td>
</tr>
<tr>
<td>12 months</td>
<td>-7</td>
<td>24</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

Renal Denervation

Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension After Witnessed Intake of Medication Before Qualifying Ambulatory Blood Pressure

Fadl Elmula Mohamed Fadl Elmula, Pavel Hoffmann, Eigil Fossum, Magne Brekke, Eyvind Gjønnaes, Ulla Hjørnholm, Vibeke N. Kjær, Morten Rostrup, Sverre E. Kjeldsen, Ingrid Os, Aud-E Stenehjem, Aud Høiegen

Table 1. Characteristics of Referred Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noneeligible for RDN (n=12)</th>
<th>Eligible for RDN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55 (39–68)</td>
<td>53 (45–67)</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.4 (21.3–34.0)</td>
<td>30.5 (28.4–35.3)</td>
</tr>
<tr>
<td>eGFR&lt;60 mL/min per 1.73 m²</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral arteriosclerosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>5 (3–7)</td>
<td>5 (3–8)</td>
</tr>
</tbody>
</table>

Values of age, body mass index, and No. of antihypertensive drugs represent mean (range); others represent total number of patients. eGFR indicates estimated glomerular filtration rate calculated by the MDRD equation; and RDN, renal denervation.

Figure 4. Daytime ambulatory mean systolic and diastolic blood pressures at baseline and 3 and 6 months after renal denervation (n=6).

Elmula, Hypertens. 2013;62:526-532