Endovascular Renal Artery Denervation for Treatment of Therapy-Refractory Hypertension

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Renal Sympathetic Efferent Nerve Activity: 
Kidney as Recipient of Sympathetic Signals

Patients early in the course of hypertension often have been shown to have increased efferent sympathetic activity to the kidney. 

Katholi et al., *Curr Hypertens Rep* 2010
Patients with essential hypertension in the later course (with chronic renal disease) have been found to have increased centrally mediated sympathetic activity.

Katholi et al., *Curr Hypertens Rep* 2010
Renal Nerve Anatomy Allows a Catheter-Based Approach

Sympathetic nerves lie within and immediately adjacent to the renal artery wall.

• Standard interventional technique
• 4-6 two-minute treatments per artery
• Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms
Male patient (56 yr)
Poorly controlled BP - 7 antihypertensive drugs
Symplicity HTN-1

- N=153 Patients; SBP ≥160 mmHg on ≥3 anti-HTN drugs; eGFR ≥ 45 mL/min
- 81 patients with 6-month renal CTA/MRA/Duplex - no vascular abnormalities at any site of RF delivery

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>-20 -10</td>
<td>-24 -11</td>
</tr>
<tr>
<td>3 M</td>
<td>-25 -11</td>
<td>-26 -14</td>
</tr>
<tr>
<td>6 M</td>
<td>-32 -14</td>
<td>-32 -14</td>
</tr>
<tr>
<td>12 M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 M</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Simplicity HTN-1 Investigators  Hypertension 2011
Symplicity HTN-2

THE LANCET

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial


- **Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial

- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control

- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)
Symplicity HTN-2 Trial

Inclusion Criteria:
- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:
- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m² (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

Symplicity HTN-2 Study Centers
Europe & Australia/NZ

PI: Prof. Murray Esler

Universitätsklinikum des Saarlandes, Homburg, Germany
CardioVascular Center Frankfurt, Frankfurt, Germany
Universitätsklinikum Düsseldorf, Düsseldorf, Germany
Universität Erlangen-Nürnberg, Erlangen, Germany
William Harvey Research Institute, Queen Mary University of London and Barts, London, UK
Pauls Stradins Clinical University Hospital, Riga, Latvia
Assistance Publique des Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France
John Hunter Hospital, Newcastle, Australia
Cliniques Universitaires Saint-Luc, Brussels, Belgium
Universitätsklinikum Schleswig-Holstein, Lübeck, Germany
Universität zu Köln, Köln, Germany
The Alfred Hospital, Melbourne, Australia
Universität Leipzig – Herzzentrum, Leipzig, Germany
Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria
Samodzielna Pracownia Hemodynamiczna, Warsaw, Poland
Hospital 12 de Octubre, Madrid, Spain
St. Vincent’s Hospital, Melbourne, Australia
Universitätsklinikum Essen, Essen, Germany
Kent and Canterbury Hospital, Canterbury, UK
University Hospital Zurich, Zurich, Switzerland
University of Glasgow, Glasgow, UK
Auckland City Hospital, Auckland, New Zealand
Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany
The John Paul II Hospital, Krakow, Poland

Patient Disposition

Assessed for Eligibility (n=190)

Excluded Prior to Randomization (n=84)
- BP < 160 after 2-weeks of compliance confirmation (n=36; 19%)
- Ineligible anatomy (n=30; 16%)
- Declined participation (n=10; 5%)
- Other exclusion criteria discovered after consent (n=8; 4%)

Randomized (n=106)

Allocated to RDN (n=52)

Allocated to Control (n = 54)

No Six-Month Primary Endpoint Visit (n = 3)
Reasons:
- Withdrew consent (n=1)
- Missed visit (n=2)

No Six-Month Primary Endpoint Visit (n = 3)
Reasons:
- Withdrew consent (n=2)
- Lost to follow-up (n=1)

Follow-up

Analysis

Analysed (n = 49)

Analysed (n = 51)

# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=52)</th>
<th>Control (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Systolic BP (mmHg)</strong></td>
<td>178 ± 18</td>
<td>178 ± 16</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Baseline Diastolic BP (mmHg)</strong></td>
<td>97 ± 16</td>
<td>98 ± 17</td>
<td>0.80</td>
</tr>
<tr>
<td>Age</td>
<td>58 ± 12</td>
<td>58 ± 12</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>35%</td>
<td>50%</td>
<td>0.12</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>98%</td>
<td>96%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31 ± 5</td>
<td>31 ± 5</td>
<td>0.77</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>40%</td>
<td>28%</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>19%</td>
<td>7%</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>52%</td>
<td>52%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>eGFR (MDRD, ml/min/1.73m²)</td>
<td>77 ± 19</td>
<td>86 ± 20</td>
<td>0.013</td>
</tr>
<tr>
<td>eGFR 45-60 (% patients)</td>
<td>21%</td>
<td>11%</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Urine Alb/Creat Ratio (mg/g)†</td>
<td>128 ± 363</td>
<td>109 ± 254</td>
<td>0.64</td>
</tr>
<tr>
<td>Cystatin C (mg/L)††</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 15</td>
<td>71 ± 15</td>
<td>0.23</td>
</tr>
</tbody>
</table>

† n=42 for RDN and n=43 for Control, Wilcoxon rank-sum test for two independent samples used for between-group comparisons of UACR
†† n=39 for RDN and n=42 for Control

## Baseline Medications

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=52)</th>
<th>Control (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number Anti-HTN medications</strong></td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>% patients on HTN meds &gt;5 years</td>
<td>71%</td>
<td>78%</td>
<td>0.51</td>
</tr>
<tr>
<td>% percent patients on ≥5 medications</td>
<td>67%</td>
<td>57%</td>
<td>0.32</td>
</tr>
<tr>
<td>% patients on drug class:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>96%</td>
<td>94%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Direct renin inhibitor</td>
<td>15%</td>
<td>19%</td>
<td>0.80</td>
</tr>
<tr>
<td>Beta-adrenergic blocker</td>
<td>83%</td>
<td>69%</td>
<td>0.12</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>79%</td>
<td>83%</td>
<td>0.62</td>
</tr>
<tr>
<td>Diuretic</td>
<td>89%</td>
<td>91%</td>
<td>0.76</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>17%</td>
<td>17%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>15%</td>
<td>17%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Alpha-1 adrenergic blocker</td>
<td>33%</td>
<td>19%</td>
<td>0.12</td>
</tr>
<tr>
<td>Centrally acting sympatholytic</td>
<td>52%</td>
<td>52%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Primary Endpoint: 6-Month Office BP

\[ \Delta \text{ from Baseline to 6 Months (mmHg)} \]

- **Systolic**
  - **RDN (n=49)**: -32 mmHg
  - **Control (n=51)**: 1 mmHg

- **Diastolic**
  - **RDN (n=49)**: -12 mmHg
  - **Control (n=51)**: 0 mmHg

33/11 mmHg difference between RDN and Control (p<0.0001)

- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Medication Changes

Despite protocol guidance to maintain medications, some medication changes were required:

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<th>Control (n=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Med Dose Decrease (%)</td>
<td>10 (20%)</td>
<td>3 (6%)</td>
<td>0.04</td>
</tr>
<tr>
<td># Med Dose Increase (%)</td>
<td>4 (8%)</td>
<td>6 (12%)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Censoring BP after medication increases:

- Renal Denervation → Reduction of 31/12 ± 22/11 mmHg (p<0.0001 for SBP & DBP)
- Control → Change of 0/-1 ± 20/10 mmHg (p=0.90 & p=0.61 for SBP & DBP, respectively)

**Home & 24 Hour Ambulatory BP**

24-h ABPM:
- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/-1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Time Course of Office BP Change

RDN
\[ \Delta \text{ from Baseline (mmHg)} \]

- Systolic
- Diastolic

1M
-20 \( ^\dagger \)
-7 \( ^{\ddagger} \)

3M
-24 \( ^\dagger \)
-8 \( ^{\ddagger\ddagger} \)

6M
-32 \( ^\dagger \)

\( ^\dagger \) p<0.0001 for between-group comparisons
\( ^{\ddagger} \) p=0.002 for between-group comparisons
\( ^{\ddagger\ddagger} \) p=0.005 for between-group comparisons
Two-way repeated measures ANOVA, p=0.001

Control
\[ \Delta \text{ from Baseline (mmHg)} \]

- Systolic
- Diastolic

0 0

-4 \(-2 \)

1 0

Procedural Safety

- No serious device or procedure related adverse events (n=52)
- Minor adverse events
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 6-month renal imaging (n=43)
  - No vascular abnormality at any RF treatment site
  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

## Renal Function

<table>
<thead>
<tr>
<th>Δ Renal Function (baseline - 6M)</th>
<th>RDN Mean ± SD (n)</th>
<th>Control Mean ± SD (n)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (MDRD) (mL/min/1.73m²)</td>
<td>0 ± 11 (49)</td>
<td>1 ± 12 (51)</td>
<td>-1 (-5, 4)</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.0 ± 0.2 (49)</td>
<td>0.0 ± 0.1 (51)</td>
<td>0.0 (-0.1, 0.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Cystatin-C (mg/L)</td>
<td>0.1 ± 0.2 (37)</td>
<td>0.0 ± 0.1 (40)</td>
<td>0.0 (-0.0, 0.1)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Possible Areas for Future Research…

Key Topics of Future Research:
1) Insulin Resistance / Diabetes
2) HF / Cardiorenal Syndrome
3) Arrhythmia
4) Sleep Apnea

Vasoconstriction
Atherosclerosis
Insulin Resistance
Sleep Disturbances

Renal Afferent Nerves

Hypertrophy
Arrhythmia
Oxygen Consumption

Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
Conclusions

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.

- The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality.

- The technique can be applied without major complications.

- This new option for treatment-resistant hypertension may also play a role in other co-morbid diseases driven by elevated central sympathetic drive.