Catheter-Based Renal Denervation Reduces Total Body and Renal Noradrenaline Spillover and Blood Pressure in Resistant Hypertension

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Update from Lancet 11 April 2009
Renal Sympathetic Denervation First in Man Study

*Study Sites*

- Melbourne, AU (x2)
- Newcastle, AU
- Warsaw, Poland
- Frankfurt, Germany
Increased Noradrenaline Spillover into the Renal Vein in Essential Hypertension

Renal Denervation Delays or Prevents Development of Many Experimental Forms of Hypertension

- SHR (rat)
- Stroke Prone SHR (rat)
- New Zealand SHR (rat)
- BHR (rat)
- Goldblatt 1K, 1C (rat)
- Goldblatt 2K, 2C (rat)
- Aortic coarctation (dog)
- Aortic nerve transection (rat)
- DOCA-NaCl (rat, pig)
- Angiotensin II (rat, rabbit)
- Fat feeding - Obesity (dog)
- Renal wrap (rat)

G. DiBona  Physiol Rev 77:75-197, 1997
The Sympathetic Nervous System

The dominant pathophysiology, but the “Forgotten Pathway” in hypertension control

A novel, targeted anti-adrenergic therapy - - -
RF Ablation Approach to Renal Sympathetic Denervation

Electrode

Insulated arch wire

Symplicity® Catheter System, Ardian, Inc., Palo Alto, CA, USA
“Neurogenic Essential Hypertension”

Historical origins of the concept

* anatomical description of sympathetic nerves and ganglia
* their identification as “pressor” nerves
* **surgical sympatheticectomy for hypertension**
* identification of noradrenaline as sympathetic transmitter
* development of anti-adrenergic antihypertensive drugs
* techniques developed for measuring human sympathetic activity and SNS activation demonstrated in hypertension
Anatomical Location of Renal Sympathetic Nerves

- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

Vessel

Lumen

Media

Adventitia

Renal Nerves

1000 μm
**Procedure Characteristics**

- **Procedure time:** Median 38 minutes

- **Ablation accompanied by pain:**
  - Managed by intravenous narcotics and/or sedatives
  - Pain did not persist beyond the RF energy application
Study Aims

To perform a first-in-man evaluation of the safety and blood pressure lowering efficacy of endovascular renal sympathetic denervation in patients demonstrated to be resistant to intensive medical anti-hypertensive therapy:

– Vascular safety
– Renal safety
– Evidence of renal denervation
– Blood pressure reduction
Key Inclusion Criterion

- Office SBP ≥160 mmHg despite 3+ anti-hypertensive medications (including diuretic)

Key Exclusion Criteria

- Currently taking clonidine, moxonidinide, or rilmenidinide
- Renovascular abnormalities: significant renal artery stenosis, prior renal stenting or angioplasty, dual renal arteries
50 patients enrolled

Treatment eligibility determined by angiographic evaluation of renal artery anatomy

45 patients treated

5 patients not treated
### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients Undergoing Procedure (N=45)</th>
<th>Patients Anatomically Ineligible for Procedure (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 9</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>Number of anti-HTN meds (mean)</td>
<td>4.7 ± 1.5</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>96</td>
<td>80</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>96</td>
<td>60</td>
</tr>
<tr>
<td>Race (% non-Caucasian)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes Mellitus II (%)</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>72 ± 11</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>81 ± 23</td>
<td>95 ± 15</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>177/101 ± 20/15</td>
<td>173/98 ± 8/9</td>
</tr>
</tbody>
</table>
Was the Sympathetic Denervation Successful?

Renal Noradrenaline Spillover as an Index

Renal NA SO (ng/min) (Lander)

Baseline

Left: 75% reduction

Right: 85% reduction
Results

*Office BP: All Treated Patients*

Change in Blood Pressure (mmHg)

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month (n=41)</td>
<td>-14</td>
<td>-10</td>
</tr>
<tr>
<td>3 months (n=39)</td>
<td>-21</td>
<td>-10</td>
</tr>
<tr>
<td>6 months (n=26)</td>
<td>-22</td>
<td>-11</td>
</tr>
<tr>
<td>9 months (n=20)</td>
<td>-24</td>
<td>-11</td>
</tr>
<tr>
<td>12 months (n=9)</td>
<td>-27</td>
<td>-17</td>
</tr>
</tbody>
</table>

n=45
Current data as of May 13, 2009

### All Treated

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>-16</td>
<td>-10</td>
</tr>
<tr>
<td>3 months</td>
<td>-23</td>
<td>-11</td>
</tr>
<tr>
<td>6 months</td>
<td>-23</td>
<td>-11</td>
</tr>
<tr>
<td>9 months</td>
<td>-23</td>
<td>-11</td>
</tr>
<tr>
<td>12 months</td>
<td>-32</td>
<td>-17</td>
</tr>
</tbody>
</table>

**Legend:**
- □ Systolic
- ■ Diastolic

**Notes:**
- Data is presented as the change in systolic and diastolic blood pressure (mmHg) from baseline.
- The number in parentheses (n) represents the sample size for each time point.
Central Sympathetic Nervous System Inhibition?

Fall in total body noradrenaline spillover of 28% (p = 0.043)

(- - - of this approx. one third is attributable to the renal sympathetic denervation)
Effects of renal denervation on muscle sympathetic nerve activity

Baseline | 30 days FU | 12 M FU
---|---|---
**ECG** | | |
**BP** | | |
**MSNA** | 56 bursts/min | 41 bursts/min | 19 bursts/min

10 sec
**Procedure Safety**

- Treatment delivered without complication in 43/45:
  - 1 renal artery dissection during catheter delivery (before RF energy application), stented without further sequelae
  - 1 femoral pseudoaneurysm, manually reduced without further sequelae

- No long-term vascular complications observed:
  - 18 patients with angiograms at 14-30 day post-procedure
  - 14 patients with MRA 6-months post-procedure

- Renal function is preserved
Summary & Conclusions

• Therapeutic renal sympathetic denervation involves a brief, simple percutaneous procedure

• Substantial, sustained reductions in blood pressure were achieved in patients with resistant hypertension

• Despite the non-randomized nature of this first in man study, the procedure is apparently beneficial in the management of hypertension in patients refractory to pharmacological therapy

• Prospective randomized controlled trials are required to definitively determine the role of this therapy in essential hypertension, and in allied disorders (renal hypertension, heart failure, resistant hepatic ascites)
A cure for hypertension?
Cold Fusion ???