Renal Denervation for Resistant Hypertension

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Disclosures
- Advisory Board
  • Abbott Vascular, Access Closure
- Speakers Bureau
  • Abbott Vascular, Eli Lilly, Astra-Zeneca
- Clinical Research Trials
  • Medtronic, Abbott Vascular

Suicide Note found...

Dear Jerry Jones...
I've been a Cowboy fan all my life
I can't take it anymore!
BIG TEX
Agenda

- Define Resistant Hypertension
- Role of Sympathetic Nervous System in HTN
- Renal Denervation as therapy
- Summary of prior investigations
- Symplicity HTN-3 clinical study design
- Future Applications

Resistant Hypertension & Overview of the Sympathetic Nervous System in Hypertension

Definition of Resistant Hypertension

**Uncontrolled Hypertension**
- Includes all patients who lack BP control on treatment, including those on inadequate treatment regimens, those with poor adherence, those with undetected secondary hypertension, as well as those with true treatment resistance


**Resistant Hypertension**
- BP that remains above goal in spite of compliance with full doses of ≥3 antihypertensive medications of different classes; ideally, 1 of the 3 agents should be a diuretic
- The treatment plan must include attention to lifestyle measures
- Includes those patients who achieve BP control but require ≥4 antihypertensive agents to do so

What is the prevalence of resistant HTN in your practice?

- A) 5%
- B) 10%
- C) 20%
- D) 30%
- E) > 50%

Prevalence of Resistant Hypertension

- Exact prevalence of resistant hypertension is unknown
- Small studies estimate the prevalence at approximately:
  - 5% in general practice
  - >50% in nephrology clinics
- NHANES estimated prevalence of resistant hypertension (15,968 pts):
  - 8.9% of all adults with hypertension
  - 12.8% of all drug-treated hypertensive adults in the US

Cardiovascular Mortality Risk Doubles With Each 20/10 mm Hg Increase in BP*
Consequences of Hypertension

- Pre-hypertension
- Established hypertension
- Left-ventricular hypertrophy
- Retinopathy
- Binswanger lesions
- Hypertensive encephalopathy
- Proteinuria
- Nephrosclerosis
- Chronic renal failure
- Congestive heart failure
- Tachycardia/tachyarrhythmias
- Ventricular fibrillation
- Atrial fibrillation
- Systolic/diastolic
- DEATH


Even Small Reductions in BP Reduce Risk of CV Mortality

- Meta-analysis of 61 prospective, observational studies
- 1 million adults (40-89 years; 70% Europe, 20% North America or Australia, 10% Japan or China)
- 12.7 million person-years
- 2 mm Hg decrease in mean office SBP
- 10% reduction in risk of stroke mortality
- 7% reduction in risk of ischemic heart disease mortality


Drivers of Arterial Blood Pressure

- Peripheral resistance
- Cardiac output
- Arterial pressure
- Extracellular fluid volume
- Blood volume
- Arteriovenous compliance
- Structure and function of heart and blood vessels
- Neuroendocrine factors
- Structure and function of kidney

The Sympathetic Nervous System

- The SNS supplies catabolic signals to the body, acting whenever rapid response to the environment is needed.
- Functions include:
  - Accelerating the heart
  - Dilating coronary vessels
  - Increasing arterial BP
  - Emptying blood reservoirs
  - Dilating bronchi
  - Releasing glucose
  - Inhibiting GI activity

Afferent (not Efferent) Renal Sympathetics send signals from the Kidneys to the CNS?

- A) True
- B) False

Renal Nerves and the SNS

- Effect of Efferent Renal Nerves on Sympathetic Activity
  - Sympathetic signals from the CNS modulate the physiology of the kidneys
- Effect of Afferent Renal Nerves on Sympathetic Activity
  - The kidney is a source of central sympathetic activity, sending signals to the CNS

Sympathetic Imbalance

Acute Adrenergic Stimulation is critical for survival

Chronic Adrenergic Stimulation is maladaptive

Central Sympathetic Drive in Hypertension

Sympathetic drive is elevated in multiple types of hypertension

- Renovascular
- White coat
- Normal pressure
- High-normal pressure
- Essential hypertension–stage 1
- Essential hypertension–stage 2/3

Surgical Sympathectomy in Essential Hypertension: Provided Beneficial Effect on Survival

- **Group 1:** Patients with persistently elevated BP, minimal/no eye changes or abnormalities in cerebral, cardiac, or renal nerves.
- **Groups 2-4:** Patients with increasing amounts of cardiovascular disease.

However, surgical sympathectomy was associated with significant morbidity: postural hypotension, orthostatic tachycardia, intestinal disturbances, ED, palpitations.

Renal Denervation

Disrupt the renal nerves, break the cycle
Simultaneously reduce both efferent & afferent effects


Renal Sympathetic-Nerve Ablation for Uncontrolled Hypertension

New Engl J Med Case Study

59-year-old patient, resistant hypertension on 7 BP meds, had renal sympathetic-nerve activity modulated by catheter-based radiofrequency (RF) ablation


Reduced Sympathetic-Nerve Activity After Catheter-Based RDN*

New Engl J Med Case Study

<table>
<thead>
<tr>
<th>Time</th>
<th>MSNA (burst/min)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>56</td>
<td>161/107</td>
</tr>
<tr>
<td>1 Month</td>
<td>41</td>
<td>141/90 (-20/-17)</td>
</tr>
<tr>
<td>12 Months</td>
<td>19</td>
<td>127/81 (-34/-26)</td>
</tr>
</tbody>
</table>

*Improvement in cardiac baroreflex sensitivity after RDN (7.8 → 11.7 msec/mm Hg)

59-year-old male on antihypertensive medications.

Targeting Renal Nerves

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia

Renal Nerve Anatomy Allows a Catheter-Based Approach

- Access achieved using standard interventional technique
- 4-6 120-second treatments per artery

Investigational Symplicity™ Renal Denervation System

- Generator will automatically control RF energy delivery:
  - Power automatically ramped and maintained (5-8W)
  - Continuously monitors temperature and impedance
  - Automatically shuts off after 120 seconds or when either impedance or temperature exceed program limits
Six Month Post-Procedure Histology (Porcine Model)

Movat’s Pentachrome Stain

- An area of medial injury (yellow) is located between the arrows on the left. An enlargement of the boxed region is shown on the right.
- Findings: minimal intimal thickening and minimal internal elastic lamina injury overlying areas of mild full thickness medial fibrosis (yellow [fibrosis]) with green [proteoglycan deposition] and adventitial fibrosis (yellow).


Six Month Post-Procedure Nerve Histology (Porcine Model)

H&E

- Nerve from untreated vessel: Periarterial nerve bundle surrounded by a thin fibrous connective tissue sheath (perineurium).
- Nerve from treated vessel: Periarterial nerve bundle has a hypercellular appearance and the perineurium has a thickened and fibrotic appearance.


The Symplicity HTN Trials
Symplicity Staged Evaluation in Hypertension and Beyond

Symplicity HTN-1
- First-in-Man
- Series of Pilot Studies

Symplicity HTN-2
- EU/AU Randomized Clinical Trial

Symplicity HTN-3
- US Randomized Clinical Trial (enrolling)

Approved Geographies
- EU/AU
- USA
- Other Areas of Research
- Global SYMPLICITY Registry

References:
2. Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917

Symplicity HTN-2 Design

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

- Patients: 106 patients with drug-resistant hypertension randomized 1:1 to treatment with RDN vs. control
- Clinical Sites: 24 centers in Europe, Australia, & New Zealand
  - 67% were designated hypertension centers of excellence
- Primary Endpoint: Office systolic BP change from baseline at 6 months

Patient Population

**Inclusion Criteria:**
- Office SBP ≥160 mm Hg (≥150 mm Hg 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
- 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 Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Symplicity RDN Group (n=52)</th>
<th>Control Group (n=54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD (years)</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>98</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (%)</td>
<td>40</td>
<td>29</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>Mean eGFR ± SD (mL/min/1.73m²)</td>
<td>77 ± 19</td>
<td>86 ± 20</td>
<td>0.013</td>
</tr>
<tr>
<td>eGFR 45-60 mL/min/1.73m² (%)</td>
<td>21</td>
<td>11</td>
<td>0.19</td>
</tr>
</tbody>
</table>

2. Data on file, Medtronic.

### Symplicity HTN-2 Trial: Baseline Characteristics (cont)

<table>
<thead>
<tr>
<th></th>
<th>Symplicity RDN Group (n=52)</th>
<th>Control Group (n=54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline SBP ± SD (mm Hg)</td>
<td>178 ± 18</td>
<td>178 ± 18</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean baseline DBP ± SD (mm Hg)</td>
<td>97 ± 16</td>
<td>98 ± 17</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean number of antihypertensive medications ± SD</td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>89</td>
<td>91</td>
<td>0.07</td>
</tr>
<tr>
<td>Aldosterone blocker (%)</td>
<td>17</td>
<td>17</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>ARB/ACEI (%)</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>0.90</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>83</td>
<td>89</td>
<td>0.12</td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>18</td>
<td>83</td>
<td>0.62</td>
</tr>
<tr>
<td>Centrally acting sympatholytic (%)</td>
<td>52</td>
<td>52</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Vasoconstrictor (%)</td>
<td>15</td>
<td>17</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Alpha blocker (%)</td>
<td>35</td>
<td>19</td>
<td>0.13</td>
</tr>
</tbody>
</table>

2. Data on file, Medtronic.

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**At 6-month follow up what was average drop in BP in treatment arm?**

- A) none
- B) 10/5 mmHg
- C) 20/10 mmHg
- D) 30/10 mmHg
- E) 40/15 mmHg
Primary Endpoint: 6-Month Office BP

- 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

RDN Procedural Safety

- Adverse events (n = 52)
  - 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)

Office BP 18 months Post Procedure

- Patients randomized to control were offered RDN following the primary endpoint assessment.
  Only patients still meeting entry criteria (SBP ≥160 mmHg) were included in this analysis (n=37)

- Primary Endpoint reached*
BP Reduction: RDN, Crossover, and Pooled Groups

Renal Function Over Time

Other Safety: 0-6 Months Post Randomization
Symplicity HTN-2 Trial: Medication Changes

<table>
<thead>
<tr>
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<th>Symplicity RDN Group (n=49)</th>
<th>Control Group (n=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication dose decreases (%)</td>
<td>20 (n=10)</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>Medication dose increases (%)</td>
<td>8 (n=4)</td>
<td>12 (n=6)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

- Censoring BP data (after medication increases)
  - Among those who had no drug increases, the absolute difference between groups after 6 months was 31/11 mm Hg (P<0.0001)

Symplicity HTN-3: Overview

- Design
  - Multicenter (90 sites in the United States), prospective, randomized, blinded, controlled study
- Population
  - 530 patients with treatment-resistant hypertension
- Treatment
  - Treatment group (endovascular catheter-based RDN with the Symplicity renal denervation system plus baseline antihypertensive medications)
  - Control group (sham procedure plus baseline antihypertensive medications)
- Primary Outcome Measures
  - Change in office SBP from baseline to 6 months
  - Safety

The SYMPLECTHTN-3 Trial

SYMPLECTITY HTN-3 Trial: Inclusion Criteria

- Average SBP ≥160 mm Hg (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80 years


SYMPLECTITY HTN-3 Trial: Exclusion Criteria

- Hemodynamically or anatomically significant renal artery abnormalities or stenosis (>50%) or prior renal artery intervention
- eGFR <45 mL/min/1.73m² (MDRD formula)
- In-patient hospitalization for HTN Crisis in past year
- 24-hour average ABPM SBP <135 mm Hg
- Type 1 diabetes mellitus
- Symptomatic orthostatic hypotension in past year
- Severe valvular heart disease for which ↓BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months
- Planned surgery or CV intervention within the next 6 months
- Known primary pulmonary HTN
- Known pheochromocytoma, Cushing’s disease, coarctation of the aorta, hyperthyroidism or hyperparathyroidism
- Known alcohol or drug abuse

SYMPLECTITY HTN-3 Trial: Study Design

- Patient and Research staff assessing BP are blinded to treatment status
- No changes in medications for 6M
What is the inclusion criteria for Symplicity HTN-3?

- A) SBP>180, >=3 BP meds
- B) SBP>180, >=3 BP meds with one a Diuretic
- C) SBP>160, >=3 BP meds
- D) SBP>160, >=3 BP meds with one a Diuretic
- E) SBP>160, >=3 BP meds plus a Diuretic

SYMPLICITY HTN-3: Summary

- Office SBP ≥160 mm Hg
- ≥3 antihypertensive medications (one must be a diuretic)
- On stable, ≥3 full tolerated dose antihypertensive medication regimen for at least 2 weeks
- No significant renal insufficiency (eGFR <45 mL/min)
- Meets inclusion/exclusion criteria by general medical review
- No known renal artery anatomy exclusion (i.e. dual renal arteries, known RA stenosis >50%)
- Until 6-month primary endpoint:
  - Patients must remain blinded
  - No changes in medication unless medically necessary
- After 6-month endpoint, control patients can crossover if still meet all initial criteria

Baylor University Medical Center Experience

- First Patient Screened: March 2012
- First Patient Randomized: May 2012
- Prescreened: 182 pts
- Screened: 56 pts (1st out of 88 sites)
- Angiogram: 21 pts
  - 1 renal cell carcinoma
- Randomized: 19 pts (1st out of 88 sites)
Special Thanks

• Cara East
• BHVH Cath Lab Team
• Robert Stoler
• Andrew Fennes
• Venkata Ram
• Jeff Schussler
• George Feghali

Future Applications

• ESRD
• Systolic CHF
• Afib
• Ventricular Tachycardia
• Metabolic Syndrome/Insulin resistance
• Polycystic Ovarian Disease
• Obstructive Sleep Apnea

The RDN field is crowded and devices are not differentiated by either physiology or biologic effect.