“LEARNING BY BURNING”

RENAL SYMPATHETIC DENERVATION
THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM
PAST, PRESENT AND FUTURE

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SATURDAY 02/08/2014
PHENOMENON

OR

NOUmenon

NOUmenon
Systemic HPT is a major global public health burden and represents a major cardiovascular (CV) epidemic in the developed and developing world.

It is the leading attributable cause of mortality worldwide, causing 7.5 million deaths annually.

Projections by 2025 suggest that up to 50% of the adult populations of Western countries will meet standard guideline definitions of HPT.
- Every 20/10 mm Hg increase in blood pressure is associated with the doubling of 10 year CV mortality

- A recent meta-analysis by Law et al (BMJ 2009) showed that irrespective of the type of medication used, the incidence of coronary heart disease events was reduced by 22%, after a systolic BP reduction of 10 mm Hg or diastolic BP reduction of 5 mm Hg. Even more, the incidence of stroke was reduced by 41%

- Despite the plethora of anti-HPT drugs, HPT remains resistant in a considerable no. of patients (5-30%), thus creating the need for an alternative strategy including interventional approaches.

- Treated hypertensive patients – 12.8%
Cardiovascular mortality risk and BP

CV = cardiovascular.
SBP = systolic blood pressure.
DBP = diastolic blood pressure.

*In individuals aged 40 to 69 years (10-year study period), starting at BP 115/75 mm Hg.
## Timeline of Renal Sympatholysis for Hypertension

<table>
<thead>
<tr>
<th>Period</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930-1940s</td>
<td>- Thoraco-lumbar splanchnicectomy</td>
</tr>
<tr>
<td>1950-1960s</td>
<td>- Medical treatments improved</td>
</tr>
<tr>
<td></td>
<td>- Early physiology sympathetic tone</td>
</tr>
<tr>
<td>1970-1980s</td>
<td>- Refined animal models of RDN</td>
</tr>
<tr>
<td>1990-2000s</td>
<td>- Sophisticated measurement of sympathetic tone</td>
</tr>
<tr>
<td></td>
<td>- Clinical studies of HTN treatment (HTN 1 &amp; HTN 2)</td>
</tr>
<tr>
<td>2013-beyond</td>
<td>- Many new RDN technologies</td>
</tr>
<tr>
<td></td>
<td>- New applications beyond HTN</td>
</tr>
</tbody>
</table>
There is ample evidence that sympathetic nervous system (SNS) hyperactivity contributes to the initiation, maintenance and progression of HPT, with the renal SNS playing a crucial role.

It is customary to acknowledge that amongst the earliest insights into the influence of the renal nerves on renal function was that of Claude Bernard in 1859. He observed cutting the greater splanchnic nerve (i.e. renal denervation) produced diuresis, whereas electrical stimulation of its peripheral cut end produced antidiuresis.

Before the advent of pharmacological therapy, radical sympathectomy (or variations thereof e.g. splanchnicectomy) were performed for malignant HPT (100% 5 yr mortality) – pioneering work done by Smithwick et al in the 1940’s.
Figure 5: Schematic representation of sympathetic innervations of the kidney.
- Nerves arise from T10 - L2
- The nerves arborize around the artery and primarily lie within the adventitia
Nerve Bundles

Nonmyelinated Efferent Nerve Bundle

- N = schwann cells associated with multiple axons
- F = endoneurial fibroblasts, S = Schwann cells, P = pericyte

Longitudinal

Cross-section

100 µm

100 µm
Neural Recognition Markers
Sympathetic nerves around the renal artery

<table>
<thead>
<tr>
<th>Efferent nerve fibers</th>
<th>Afferent nerve fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>UnMyelinated 96%</td>
<td>Myelinated 4%</td>
</tr>
<tr>
<td>Sensory Aδ</td>
<td>Sensory C</td>
</tr>
<tr>
<td>Adrenergic</td>
<td></td>
</tr>
<tr>
<td>pain fibers</td>
<td></td>
</tr>
</tbody>
</table>

NEURAL MARKERS

- Protein Gene Product 9.5 [PGP9.5]
- Neurofilament protein [NFP]
- Nerve growth Factor [NGF]
- NGF receptor p75 [NGFRp75]
- Tyrosine kinase receptor-A [Trk-A]
- Substance P [SP]
- Calcitonin gene-related peptide [CGRP]
- Neuropeptide Y [NFY]
- Dopamine β-hydroxylase (DBH)
- Tyrosine Hydroxylase [TH]

Nerve development and survival

adapted from Tokushige, 2007
Dual Staining: Efferent and Afferent Sensory Neurons

RED: Tyrosine Hydroxylase
Green: Substance P [SP]

RED: Tyrosine Hydroxylase
Green: Calcitonin Gene Related Peptide [CGRP]

Hematoxylin & Eosin

PGP 9.5
NFP

Tyrosine Hydroxylase

PGP9.5 = Protein Gene Product
NFP = Neuro Fibrillary Protein

Immuno-Localization of Select Neuronal Markers in Human Renal Arteries
A Common Question

How will the kidney function without sympathetic control?

PHYSIOLOGIC RESPONSES OF THE TRANSPLANTED HUMAN KIDNEY*
Sodium Regulation and Renin Secretion
M. Donald Blafox, M.D., Edmund J. Lewis, M.D., Paul Jagger, M.D.,
David Lauler, M.D., Roger Hickler, M.D. and John P. Merrill, M.D.

Transplanted kidneys:
- Lack innervation
- Effectively maintain fluid and electrolyte balance

Supports that sympathetic component of control represents “overdrive” system, rather than foundation of basic renal function
SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston
Redrawn From Smithwick and Thompson; JAMA.1953;152:1501-5.
Although the important factor to be considered in evaluation of any form of treatment for hypertension is its influence on the mortality and the survival rate, the effect of treatment on the actual level of blood pressure is of considerable interest. In fact, it appears that blood pressure lowering in hypertension is desirable if it can be accomplished. It is fairly well established that in most cases the lowering of blood pressure in hypertensive patients is not harmful, providing such lowering is not excessive. The prognosis for patients whose blood pressure is lowered after splanchnicectomy is significantly better than for those whose blood pressure is not lowered by operation. Both of these groups, however, exhibit an improved prognosis when compared with the medical control series.²b
It appears, therefore, that the outlook for

**Table 3.—Mortality for Medically and Surgically Treated Hypertensive Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Medical Series</th>
<th></th>
<th>Surgical Series</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Mortality at 5 Yr.</td>
<td>No. of Cases</td>
<td>Mortality at 5 Yr.</td>
</tr>
<tr>
<td>1</td>
<td>62</td>
<td>19%</td>
<td>158</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>38%</td>
<td>735</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>108</td>
<td>71%</td>
<td>244</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>97</td>
<td>99%</td>
<td>129</td>
<td>59%</td>
</tr>
<tr>
<td>Total</td>
<td>467</td>
<td>54%</td>
<td>1,266</td>
<td>19%</td>
</tr>
</tbody>
</table>

Statistical analysis of the comparative five year mortalities between the medical and surgical groups is as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>Chi²</th>
<th>p</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.92</td>
<td>0.03</td>
<td>Significant</td>
</tr>
<tr>
<td>2</td>
<td>60.6</td>
<td>&lt; 0.001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>3</td>
<td>83.2</td>
<td>&lt; 0.001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>4</td>
<td>24.6</td>
<td>&lt; 0.001</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

*Yates correction used throughout.

hypertensive patients can be improved by splanchnicectomy even if the basal blood pressure levels are not significantly lowered postoperatively. Our data show that 45% of living operated patients have a significant lowering of basal blood pressure levels in the early years (1 to 5) after splanchnicectomy, and 55% have no change or show an increase in blood pressure.
CASE 1.—A 31-year-old man had an abnormal electrocardiogram, an enlarged heart, and congestive failure when examined prior to operation. His resting horizontal blood pressure was 160/122 mm. Hg. At examination 10 years after operation, his electrocardiogram was the same, his heart was normal in size, and there was no evidence of congestive failure. His eyegrounds showed minimal arteriovenous compression. The blood pressure (ambulatory) was 132/80 mm. Hg. This patient is an example of improvement in blood pressure and in cardiovascular status 10 years after splanchnicectomy (fig. 2).

Fig. 2.—Blood pressure levels 10 years after splanchnicectomy in patient in case 1.
Case 2.—A 48-year-old man had hemorrhages, exudates, and papilledema in his eyegrounds, an abnormal electrocardiogram, markedly enlarged heart, and severe congestive failure when examined prior to operation. His resting horizontal blood pressure was 204/104 mm. Hg. When examined seven and a half years postoperatively, his eyegrounds showed only arteriovenous compression and his heart was normal in all respects. His renal function showed slight evidence of impairment. His blood pressure (ambulatory) was 188/114 mm. Hg. This patient is an example of the marked improvement that may follow splanchnicectomy even though the basal blood pressure level was apparently not changed.
Although improvement in BP and survival benefit, issues arose:

→ skilled surgeon with specialised expertise required
→ prolonged hospital stay (2 – 4 weeks)
→ long recovery period (1 – 2 months)
→ only few centres in the U.S and Europe

As procedure was non-selective (affected abdominal, pelvic, lower extremity innervation), systemic side effects experienced:

→ orthostatic hypotension and tachycardia
→ bowel and bladder dysfunction
→ sexual dysfunction
→ thoracic duct injury
Advent of effective pharmacological therapy made surgical sympathectomy unattractive and undesirable in most patients which drove surgical sympathectomy into obscurity.

Building on the concept of surgical sympathectomy to control HPT, a novel catheter based endovascular renal artery sympathetic denervation (RASD) has been developed which offers more selective sympathetic denervation with:

- no systemic side effects (as selective and specific)
- localised procedure, minimally invasive
- short procedure and recovery times
- can be assumed to be widely adaptable
Management of hypertension

Lifestyle

Medication

Devices
# Lifestyle

## Influence on blood pressure

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Recommendation</th>
<th>Blood Pressure Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight</strong></td>
<td>BMI 18–25 kg/m²</td>
<td>5–20 mmHg/10kg</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td>Fruit, vegetable</td>
<td>6–14 mmHg</td>
</tr>
<tr>
<td><strong>Salt</strong></td>
<td>Salt intake &lt; 2400 mg/day</td>
<td>3–8 mmHg</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>30 min/day, min 5 days/week</td>
<td>4–9 mmHg</td>
</tr>
</tbody>
</table>
| **Alcohol** | Men: ≤2E alcohol/day  
Women: ≤1E alcohol/day | 2–4 mmHg |
| **Total** | | **20 mmHg!** |
After a 2 year loan to the United States, David returns to Italy...
...Proud Sponsors
Calcium-channel blockers

Centrally acting antihypertensives

Baroreceptor discharge

Vascular smooth muscle
Calcium-channel blockers

$\alpha_1$-blockers

$\beta$-blockers reset peripheral resistance

$\beta$-blockers

Vasodilation

Angiotensinogen

Renin

Angiotensin I

Thiazide diuretics

Angiotensin II

ACEIs

Aldosterone

Peripheral resistance

Na$^+$

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, white coat hypertension 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

Sympathetic Set Point
Nucleus tractus solitarius (NTS)
Hypothalamic paraventricular nucleus (PVN)
Rostral ventrolateral medulla (RVLM)
Pariaqueductal gray (PAG)

CNS-MAP “set point”
Baroreceptors (-)
Peripheral chemoreceptors (+)
Differential patterning

MAP
Perfusion Pressure – Organ Blood Flow

Heart Rate
Contractility
Resistance
Immune

Capacitance
RAAS
Na⁺ Reabsorpt’n

Resistance
Re-modelling
Bone marrow

Sobotka, Osborn, Paton. Euro Intervention 2013
DiBona GF et al, Am J Physiol Regul Integr Comp Physiol 298:R246, 2010
Renal sympathetic efferent nerves
- Promote renin release (β1 - AR)
- Increase tubular sodium reabsorption (α1b - AR)
- Reduce renal blood flow via renal arterial constriction (α1a - AR)

Renal sympathetic afferent nerves
- Modulate CNS outflow
- Mechanoreceptors & chemoreceptors signal renal injury
- Feedback to hypothalamus and contralateral kidney
Flexible Tip
(self-orienting)
5 mm
Deflectable Shaft
12 mm

The catheter: new and 'old'
Renal Nerve Anatomy Allows a Catheter-Based Approach

- Renal artery access via standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF generator
  - Automated
  - Low power
  - Built-in safety algorithms
## (Some) RF Based RDN Technologies

<table>
<thead>
<tr>
<th></th>
<th>BSC Vessix</th>
<th>MDT Symplicity</th>
<th>MDT Spyral</th>
<th>STJ EnliGHTN</th>
<th>COV OneShot</th>
<th>JNJ ThermoCool</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheter Design</strong></td>
<td>Balloon catheter 4-8 electrodes</td>
<td>Catheter with single electrode</td>
<td>Pigtail catheter 4 electrodes</td>
<td>Basket with 4 electrodes</td>
<td>Balloon catheter helical electrode and cooling</td>
<td>Pigtail catheter with 5 electrodes and cooling</td>
</tr>
<tr>
<td><strong>Balloon</strong></td>
<td>✓</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td><strong>Guidewire</strong></td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>Bipolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
<td>Monopolar RF</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>~1W</td>
<td>8W</td>
<td>Unknown</td>
<td>6W</td>
<td>25W</td>
<td>15W</td>
</tr>
<tr>
<td><strong>Energy Delivery Time</strong></td>
<td>30 sec</td>
<td>2 min</td>
<td>1 min</td>
<td>90 sec</td>
<td>2 min</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Total Treatment Time</strong></td>
<td>2 min</td>
<td>16-24 min</td>
<td>2 min</td>
<td>24 min</td>
<td>4 min</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Comprehensive SYMPLICITY Clinical Trial Program will follow over 5000 patients across multiple indications.
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

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

### Baseline Patient Characteristics (n=153)

#### Demographics
- **Age (years)**: 57 ± 11
- **Gender (% female)**: 39%
- **Race (% non-Caucasian)**: 5%

#### Co-morbidities
- **Diabetes Mellitus II (%)**: 31%
- **CAD (%)**: 22%
- **Hyperlipidemia (%)**: 68%
- **eGFR (mL/min/1.73m²)**: 83 ± 20

#### Blood Pressure
- **Baseline BP (mmHg)**: 176/98 ± 17/15
- **Number of anti-HTN meds (mean)**: 5.1 ± 1.4

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic (%)</td>
<td>95%</td>
</tr>
<tr>
<td>Aldosterone blocker (%)</td>
<td>22%</td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>91%</td>
</tr>
<tr>
<td>Direct Renin Inhibitor</td>
<td>14%</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>82%</td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>75%</td>
</tr>
<tr>
<td>Centrally acting sympatholytic (%)</td>
<td>33%</td>
</tr>
<tr>
<td>Vasodilator (%)</td>
<td>19%</td>
</tr>
<tr>
<td>Alpha-1 blocker</td>
<td>19%</td>
</tr>
</tbody>
</table>
38 minute median procedure time
   - Average of 4 ablations per artery
Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
No catheter or generator malfunctions
No major complications
Minor complications 4/153:
   - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
   - 3 access site complications, treated without further sequelae

81 patients with 6-month renal CTA, MRA, or Duplex
  - No vascular abnormalities at any site of RF delivery
  - One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)

- Two deaths within the follow-up period; both unrelated to the device or therapy
- No orthostatic or electrolyte disturbances
- No change in renal function at one year (Δ eGFR)
  - 12 Months: -2.9 mL/min/1.73m² (n.s.) (n=64)

Simplicity HTN-1: Significant, Sustained BP Reduction to 3 Years

- 6 Months (n = 144)
- 1 Year (n = 132)
- 2 Years (n = 105)
- 3 Years (n = 58)

Change in Blood Pressure (mmHg)

- Systolic
- Diastolic

p < 0.01 for Δ from baseline for all time points. Data is reported only on the patients available at each time point.
Symplicity HTN-1: SBP Distribution Improved After RDN - Lowering Risk of CV Events*

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: Renal Function Was Maintained Following RDN Therapy at 36 Months

![Graph showing eGFR levels over time](graph.png)

Not all patients consented to collection of lab values
• **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)

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

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

Allocated to Control (n = 54)
- No Six-Month Primary Endpoint Visit (n = 3)
  Reasons:
  - Withdrew consent (n=2)
  - Lost to follow-up (n=1)

Analysis
- Analyzed (n = 51)
- Analyzed (n = 49)

Screening

Allocation

Follow-up

Analysis

### 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>Baseline Systolic BP (mmHg)</td>
<td>178 ± 18</td>
<td>178 ± 16</td>
<td>0.97</td>
</tr>
<tr>
<td>Baseline Diastolic BP (mmHg)</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>Number Anti-HTN medications</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

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

- RDN (n=49)
  - Systolic: -32 mmHg
  - Diastolic: -12 mmHg

- Control (n=51)
  - Systolic: 1 mmHg
  - Diastolic: 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

Office Systolic BP Distribution

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)

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)

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 was applied without major complications.

This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of BP in patients with hypertension.

Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Figure 1. Patient disposition. At 12 months, follow-up data from 47 patients allocated to immediate renal denervation and 35 crossover patients meeting the same preprocedure eligibility criteria are available for analysis. BP indicates blood pressure; PI, principal investigator; and SBP, systolic blood pressure.
Figure 2. Change in office-based blood pressure. Both the initial renal denervation (RDN) group and the crossover group denervated at 6 months after randomization experienced significant drops in systolic (SBP) and diastolic blood pressure (DBP). *P < 0.001 for SBP and DBP change after renal denervation; †P = 0.026 for SBP change from baseline and P = 0.066 for DBP change from baseline for the crossover group before denervation at 6 months.
Symplicity HTN-2: BP Reductions Sustained to 30 Months

Sustained Reductions in the Pooled (RDN and Crossover Combined) Group

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>6M</td>
<td>-28</td>
<td>-10</td>
</tr>
<tr>
<td>12M</td>
<td>-26</td>
<td>-10</td>
</tr>
<tr>
<td>12M</td>
<td>-31</td>
<td>-12</td>
</tr>
<tr>
<td>24M</td>
<td>-31</td>
<td>-11</td>
</tr>
<tr>
<td>30M</td>
<td>-34</td>
<td>-13</td>
</tr>
</tbody>
</table>

\( \Delta \) from Baseline to 30 Months (mmHg)

\( P < .01 \) at all time points

*Expanded results presented at the American Society of Hypertension annual meeting 2013*
Symplicity HTN-2: Control Group Showed BP Reduction from RDN After Crossover

*Expanded results presented at the American Society of Hypertension annual meeting 2013*
Symplicity HTN-2: Renal Function Was Maintained Following RDN Therapy at 12 Months

![Chart showing eGFR values at different stages and time points after RDN therapy.](chart.png)

- **Stage I**
  - Baseline: 76.9, n = 49
  - 6 Mo Post-RDN: 77.1, n = 49
  - 12 Mo Post-RDN: 78.2, n = 49
  - Crossover: 81.2, n = 31

- **Stage II**
  - Baseline: 88.8, n = 35
  - 6 Mo Post-RDN: 85.2, n = 35

- **Stage III**

- **Stage IV**

- **Stage V**

- **ESRD**

- **Stage VI**

- **eGFR was monitored until 12M post-RDN**

*Expanded results presented at the American Society of Hypertension annual meeting 2013*
RF Energy Clinical Data

EnligHTN

OneShot

Vessix

Symplicity

Symplicity

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 60 sites
  - Randomization (2:1)
  - All patients maintained on baseline meds for 6 months
SYMPPLICITY HTN-3: Severe drug-resistant HTN

- 2:1 randomization
- Sham procedure in control patients that included renal angiogram
- 535 subjects randomized
- Rigorous screening process

**Primary Efficacy Endpoint:**
Change in Office Systolic Blood Pressure

**Primary Safety Endpoint:** MAE through 1 month, including Renal Artery Stenosis within 6m
1441 subjects assessed for eligibility

Excluded:
- 880 not eligible for randomization
- 26 eligible but not randomized because randomization cap was reached

535 subjects randomized

364 subjects randomly allocated to renal denervation
- 2 subjects died
- 1 subject withdrew
- 11 missed 6-month visit

171 subjects randomly allocated to sham control
- 1 subject died
- 1 missed 6-month visit

350 (96.2%) subjects with 6 month follow-up

169 (98.8%) subjects with 6 month follow-up
Safety analysis

• Composite endpoint of death, renal injury, vascular complications, and embolic tissue injury to 1 month and renal artery stenosis to 6 months. <7% MAE rate required to meet the primary safety endpoint.

Primary safety analysis

• A performance goal established from renal artery stenting required the major adverse event rate for safety be <9.8%. This requires the observed MAE rate to be <7%, given the expected confidence interval for this endpoint.
Efficacy analysis

• Comparison of SBP change from baseline to 6 mo in RDN arm compared with change from baseline to 6 mo in control arm
  • Endpoint = (SBP_{RDN \, 6 \, mo} - SBP_{RDN \, baseline}) - (SBP_{CTL \, 6 \, mo} - SBP_{CTL \, baseline})

Primary efficacy (OBP) endpoint assumptions

• Superiority analysis
  • Superiority margin of 5 mm Hg, per FDA recommendation

• Assuming a standard deviation of 25 mm Hg for both arms, 10 mm Hg is the minimum treatment difference required to meet the efficacy endpoint (95% CI)

Secondary efficacy (ABPM) endpoint assumptions

• Superiority analysis
  • Superiority margin of 2 mm Hg, per FDA recommendation

• Assuming a standard deviation of 18 for both arms, 5.5 mm Hg is the minimum difference required to meet the efficacy endpoint (95% CI)
Illustrative examples of endpoint scenarios, either meeting or not meeting the set assumptions for the primary endpoint.
January 9th, 2014

Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint

MINNEAPOLIS - January 9, 2014 - Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPlicity HTN-3, failed to meet its primary efficacy endpoint. The trial met its primary safety endpoint, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.

- Primary efficacy endpoint was not met
- Primary safety endpoint was met
**HTN-3 Results: Primary Safety Endpoint**

- **Performance Goal**: 9.8%
- **MAE Rate**:
  - Renal Denervation (N = 364): 1.4% (5/361)
  - Sham Procedure (N = 171): 0.6% (1/171)
  - Difference (95% CI): 0.8% (-0.9%, 2.5%)  
    - **P-value**: 0.67
Primary Efficacy Endpoint
Office Systolic Blood Pressure at 6 Months, 5 mm Superiority Margin

-2.39 (-6.89, 2.12), \( P = 0.255 \) (Primary analysis with 5 mm Hg superiority margin)

- Did not meet primary efficacy endpoint
Patient behavior

- Due to being enrolled and closely monitored in a clinical trial, as well as blinded to treatment, the patients in SYMPLICITY HTN-3 may have improved or modified their lifestyle and drug adherence.

Study population

- The population studied and the requirement for maximum tolerated medication dosage were different from other SYMPLICITY studies.

Procedural experience and variability

- SYMPLICITY HTN-3 included a greater number of trial sites and proceduralists compared to SYMPLICITY HTN-1 and HTN-2, which may have led to greater procedural variability.
- Case proctoring was different and not comparable.
Procedural Variability

Correlation with # of ablations
Correlation with 4-quadrant ablation pattern

Cross-section of artery

Lesion

Inferior  Anterior  Superior  Posterio

4 quadrant ablation pattern
Impact of Number of Ablations on Change in Office SBP: Matched Cohort Analysis

$P$ value for trend = 0.01

<table>
<thead>
<tr>
<th>Denervation</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP</td>
<td>178.2 180.1 178.6 180.3 178.2 180.5 179.0 179.4 179.1 179.7 178.3 181.3 181.9 182.3 183.2 182.8 185.4 189.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.7(-7.1, 3.7) -3.1(-8.6, 2.4) -5.4(-11.3, 0.5) -7.1(-13.9, -0.3) -8.4(-14.0, 0.7) -11.5(-19.8, -1.2) -14.1(-26.0, 7.7) -12.0(-30.0, 5.9) -12.4(-44.6, 19.8)</td>
</tr>
<tr>
<td>$P^*$</td>
<td>0.54 0.27 0.07 0.04 0.07 0.03 0.06 0.18 0.43</td>
</tr>
</tbody>
</table>

Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients

*P value change in SBP for RDN compared with sham

Data presented are mean (SD)
Impact of Number of Ablations on Change in Ambulatory SBP: Matched Cohort Analysis

P value for trend= 0.16

Non-denervation vs. Denervation:

Baseline SBP

- Non-denervation: 156.0, 158.0, 158.3, 158.1, 158.0, 159.0, 158.6, 157.1, 158.4, 158.2, 159.3, 159.8, 160.8, 160.2
- Denervation: 159.4, 159.9, 159.5, 159.1, 159.0, 158.6, 157.2, 157.1, 158.4, 158.2, 159.3, 159.8, 160.2

95% CI

- Non-denervation: -1.4(-5.1, 2.3), -1.9(-5.7, 1.9), -3.9(-8.0, 0.2), -4.8(-9.6, -0.04), -8.4(-13.7, -3.1), -8.1(-14.6, -1.5), -6.8(-16.4, 2.7), -7.8(-20.6, 5.1), -15.1(-37.1, 7.0)
- Denervation: 0.47, 0.33, 0.06, <0.05, 0.002, 0.02, 0.16, 0.23, 0.17

*P value change in SBP for RDN compared with sham

Data presented are mean (SD)
HTN-3: Continuing Areas of Investigation

- Heterogeneity of US Operator Experience
- Patient Demographics
- Catheter Design
- Medication Changes or Adherence
- Trial Conduct
- Hawthorne Effect
- Placebo Effect
- Regression to Mean

Trademarks may be registered and are the property of their respective owners. A reminder that this is a discussion of SYMPLECTICITY trial results and their implications for the future of RDN. Today’s discussion may regard information or indications not evaluated by regulatory authorities in your geography. Always refer to the Instructions for Use prior to using the Symplicity renal denervation system. Investigational use only in the USA © 2014 Medtronic, Inc. All rights reserved.UC2014006134IE 3/14
SYMPLICITY HTN-3 did not reach the primary or powered secondary efficacy endpoints in this trial. There may be many factors that contributed to the outcome, which we continue to investigate.

SYMPLICITY HTN-3 did meet its safety endpoint, which is consistent with all other Symplicity trials, including the Global SYMPLICITY Registry.

Based upon our detailed analysis of HTN-3, we believe further clinical investigation is warranted and Medtronic will, in consultation with FDA, pursue a new IDE trial.

An unmet need in this uncontrolled hypertension population still exists. Medtronic will continue to provide access to the Symplicity system in countries where it has regulatory approval and will continue to support a global hypertension clinical program.
PLEIOTROPIC EFFECTS
ADVERSE CONSEQUENCES OF SYMPATHETIC ACTIVATION

- Aggravation of hypertension
- Progression of renal disease
- Trophic effects (LVH)
- Heart failure
- Cardiac arrhythmias (SCD)
- Adverse metabolic effects

HIGH CARDIOVASCULAR MORTALITY
Renal Sympathetic Denervation Reduces Left Ventricular Hypertrophy and Improves Cardiac Function in Patients With Resistant Hypertension

Conclusions

Besides the known effect on blood pressure, our study showed for the first time that RD significantly reduces LV mass and improves diastolic function, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk. (J Am Coll Cardiol 2012;59:901–9) © 2012 by the American College of Cardiology Foundation
Conclusions: Renal denervation improves glucose metabolism and insulin sensitivity in addition to a significantly reducing blood pressure. However, this improvement appeared to be unrelated to changes in drug treatment. This novel procedure may therefore provide protection in patients with resistant hypertension and metabolic disorders at high cardiovascular risk.

SNS activity in multiple diseases

Cost-Effectiveness and Clinical Effectiveness of Catheter-Based Renal Denervation for Resistant Hypertension

Benjamin P. Geisler, MD, MPH,* Brent M. Egan, MD,† Joshua T. Cohen, PHD,‡
Abigail M. Garner, MS,* Ronald L. Akehurst, MFPHM,§ Murray D. Esler, MBBS, PHD,||
Jan B. Pietzsch, PHD*

Menlo Park, California; Charleston, South Carolina; Boston, Massachusetts; Sheffield, United Kingdom; and Central Melbourne, Victoria, Australia

JACC Vol. 60, No. 14, 2012
October 2, 2012:1271–7
What is Success?

- Is BP a sensitive marker of RDN technical success?
  - Are there patient subtypes where BP response is unlikely?
  - Are there patient subtypes where BP response is delayed (e.g. is the time course of some benefit different amongst patient types)?

- Is the only benefit of reduction of renal neurologic signaling BP reduction
  - If there are other exploitable clinical benefits, then using BP as the sole identifier of technical success is inappropriate
Efferent Denervation
- Renal Specific Metrics
  - Activity of the RAA system
  - Renal Salt
  - Renal Vascular Resistance
- Markers of Renal Neuro Activity
  - Renal NA Spillover

Afferent Denervation
- Systemic Sympathetic State
  - Total Body NA Spillover
- Change of Sympathetic state of down stream organs
  - Peripheral Microneurography
  - HRV
  - HR (?)
  - Euglycemic insulin Clamp; HOMA index
- Renal Afferent Nerve or systemic response to infusion of renal chemosensitive agents
Surrogate Measures of Mortality and Morbidity in Hypertension

- ECG Repolarization Improvements
- ECG Voltage Regression
- LV Mass Regression
  - MRI
  - LVH
- Renal Metrics
  - Improvement of eGFR
  - Reduction of population progressing to ESRD
- Vascular Metrics
  - Analogous to the lipid intervention trials
Limitations

- Relatively small numbers of patients in trials
  - Small trials tend to overestimate treatment effects
  - Small trials tend to underestimate side effects
  - Rare side effects (renal artery stenosis) missed?
  - No systematic imaging for renal artery stenosis
  - Generalizeable to broader patient populations?
  - Applicable to African patients with HTN?
  - Generalizeable to other operators?

- Limited number of patients with long-term follow-up
  - Durability of effect
Methodological limitations

- Not all patients on a diuretic.
- Low utilization of aldosterone blockade
- No ABPM to screen out “white coat hypertension”
- No rigorous assurance of “compliance”
10 year old boy

Severe resistant hypertension despite numerous agents

Autosomal Recessive Polycystic Kidney Disease
  - Creat 130mcmol/L
  - Multiple renal arteries
  - Small caliber aorta / renal vessels
  - Risk of Contrast-induced Nephropathy

Paediatric case
  - Complex consent / ethical / legal issues
Felodipine 10mg mane    Nifedipine 10 mg BD
Atenolol 75mg mane, 50mg nocte Prazosin 5mg tds
Hydralazine 25 mg BD    Furosemide 40 mg daily
Aspirin 100 mg alternate days
Phenytoin 75 mg BD, 50mg midday
Zonisamide 100 mg bd    Neulactil 2.5 mg nocte
Lamotrigine 200 mg bd   Clobazam 10 mg bd
Modafinil 200 mg BD    Strattera 35 mg mane
Amitriptyline 50mg nocte
Ferro liquid 7 mls BD    Aranesp 40 ug twice weekly
NaHCO3 i BD            Ostelin 1 tablet midday
Vessix™ Renal Denervation System

Technology Overview

- Balloon-based technology (4 - 7 mm diameters)
- Helical pattern of bipolar radiofrequency electrodes for uniform treatment
- 30 second treatment time
- All electrodes activated simultaneously

- Bipolar energy delivery, ~1 Watt
- Temperature-controlled algorithm ensures energy delivery at 68°C
- One button operation
- CE-marked and TGA-approved

Vessix™ is an investigational device and not available for sale in the US.
RF=Radiofrequency; TGA=Therapeutic Goods Administration, AU Regulatory Authority
At Baseline:
- Home BP >200/100 mmHg not uncommon
- 24hr ABPM = average daytime BP 154/89 mmHg

At 3-months – no home SBP > 180 mmHg

At 6-months – no home SBP > 160 mmHg

At 12-months – no home SBP > 140 mmHg
- 24hr ABPM = average daytime BP 129/69 mmHg
- No seizures since 6-months
- Dramatic reduction in poly-pharmacy
- Markedly improved academic performance / behaviour
Transcatheter renal denervation offers a safe and effective therapeutic option in the treatment of resistant hypertension.

However, many questions remain to be answered:
- long-term safety data
- absolute benefits on cardiovascular mortality
- cost-effectiveness
- de-escalation of antihypertensive drugs
- efferent sympathetic regrowth
Although renal denervation might prove to be revolutionary in the treatment of hypertension, the complexity of its pathophysiology discourages the simplistic notion that inhibition of one factor will be effective in all patients, over-optimism should be avoided.

SIMPLICITY 3 TRIAL has resulted in a ‘reality check’ and shifted focus into identifying predictors that will determine which patients will respond to this therapy.

However, the exciting results of the recent renal denervation studies have generated great expectation, the investigators have paved the way for interventional management of patients with resistant HPT.
Thank you for your attention