Renal Denervation Is the Answer to Drug-Resistant Hypertension: HOPE or HYPE?

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Burns & Allen Chair in Cardiology Research
Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Hypertension Center
Associate Director, The Heart Institute
Disclosure of Relationships

Over the past 12 months

Ronald Victor, MD

- Northwind: SAB
- Medtronic: Steering committee
Renal denervation: hope or hype?

- Premise
- Promise
- Problems
Observational Data

Fatal Stroke

Fatal MI

Hypertension

- 78 million Americans
- #1 cause for an office visit
- 400,000 deaths per year
- 50% of MIs, 70% of strokes
- Cost to US healthcare $70+ billion/year
- 1 in 2 controlled to BP <140/90
- Racial disparities

Go AS et al. Circulation. 2013
Egan BM et al. JAMA 2010
Definition of Drug-Resistant HTN

- BP > 140/90 despite 3 drugs
- 4 or more drugs regardless of BP
Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008
Brent M. Egan, Yumin Zhao, R. Neal Axon, Walter A. Brzezinski and Keith C. Ferdinand

8 million Americans with apparent drug-resistant HTN (4+ drugs) in 2008

Greater odds if:
- NH Black
- Obese
- Chronic kidney disease
- 10-year risk of CV disease $\geq 20\%$
**Apparent Drug-Resistant HTN**

**Pseudo-Resistant**
- White coat HTN
- Inadequate regimen
- Non-compliance
- Interfering medication (NSAIDs)

**Truly Resistant**
- Secondary HTN
- Difficult primary HTN

**Renal denervation?**
Medtronic’s Ardian Purchase is a Bet on New Anti-Hypertension Tech

By Katherine Hobson

Yesterday medical-device giant Medtronic said it would buy Ardian, which makes an anti-hypertension device not yet approved by the FDA, for $800 million plus milestone payments. You might not have thought of hypertension as a market for device-makers. But Medtronic called treating uncontrolled high blood pressure via devices one of the most “exciting growth markets” for the industry. Boston Scientific has said the market could someday be as big as $5 billion.
Renal denervation (RDN)

Sympathetic nerves

Symplicity catheter
Renal sympathetic (efferent) nerves

- Stimulates renin release
- Enhances renal sodium and water resorption
- Causes renal vasoconstriction

**RDN**

- Efferent nerves

**Vasoconstriction**

**Renin release**

**Na + H₂O resorption**

Renal denervation: hope or hype?

- Premise
- Promise
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Medtronic Symplicity-HTN Clinical Trials

- Phase 1 *HTN-1*
- Phase 2 *HTN-2*
- Phase 3 *HTN-3*
Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study

Henry Krum, Markus P Schlaich, Michael Böhm, Felix Mahfoud, Krishna Rocha-Singh, Richard Katholi, Murray D Esler

www.thelancet.com Published online November 7, 2013

http://dx.doi.org/10.1016/S0140-6736(13)62192-3
Design:
- Open label
- No controls

Inclusion Criteria:
- SBP ≥ 160
- ≥ 3 drugs or intolerance
- eGFR ≥ 45
## Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Enrolled patients (n=150)*</th>
<th>Patients followed up to 36 months (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1 (11.1)</td>
<td>57.0 (11.4)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>56 (38%)</td>
<td>37 (42%)</td>
</tr>
<tr>
<td>Non-white ethnic origin (%)</td>
<td>7 (5%)</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Enrolled patients (n=150)*</th>
<th>Patients followed up to 36 months (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes mellitus (%)</td>
<td>47 (31%)</td>
<td>25 (28%)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>33 (22%)</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>92 (61%)</td>
<td>62 (71%)</td>
</tr>
<tr>
<td>Estimated GFR (mL/min per 1.73m²)</td>
<td>83.4 (19.7)</td>
<td>84.6 (18.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Enrolled patients (n=150)*</th>
<th>Patients followed up to 36 months (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline systolic (mm Hg)</td>
<td>175.1 (15.9)</td>
<td>174.6 (12.5)</td>
</tr>
<tr>
<td>Number of antihypertensive medications</td>
<td>5.0 (1.7)</td>
<td>5.2 (1.7)</td>
</tr>
</tbody>
</table>
BP change (mm Hg)

-21
-26
-27
-30
-32

Systolic BP
Diastolic BP

p<0.01 for all timepoints

1 (n=80) 6 (n=88) 12 (n=85) 24 (n=82) 36 (n=88)
Overactivity of the sympathetic nervous system plays an important role in the development of hypertension. RDN is a straightforward, minimally invasive percutaneous method of denervation (panel). We found that this procedure was associated with substantial lowering of blood pressure in patients with treatment-resistant hypertension, could be performed without any major safety issues, and that the effects persisted up to 36 months. The blood-pressure-lowering effects were not altered by age, baseline renal function, or diabetes status.
We suggest that durable responses after RDN will eventually be possible in most if not all patients with treatment-resistant hypertension.
Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators*  
*Lancet 2010; 376: 1903-09

Design features:

- 2nd screening visit (Hawthorne effect)
- Stable BP medication (variability)
- HTN Centers of Excellence (data quality)
- But not blinded
190 assessed for eligibility

84 excluded
- 36 blood pressure < 160 mm Hg at baseline visit (after 2 weeks of medication compliance confirmation)
- 30 ineligible anatomy
- 10 declined to participate
- 8 other

106 randomly allocated to treatment or control group

52 allocated to renal denervation group
- 3 did not attend 6-month follow-up
  - 1 withdrew consent
  - 2 missed visit

49 analysed

54 allocated to control group
- 3 did not attend 6-month follow-up
  - 2 withdrew consent
  - 1 missed visit

51 analysed
Symplicity HTN-2 Trial: Primary outcome

Change from baseline, mm Hg

5 BP Meds
- + RND
-32
- RND

Office BP
178/96 to 146/84
178/98 to 177/98

No change in BP in the control group!
<table>
<thead>
<tr>
<th></th>
<th><strong>HTN-1</strong></th>
<th><strong>HTN-2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>153</strong></td>
<td><strong>106</strong></td>
</tr>
<tr>
<td><strong>Trial design</strong></td>
<td>Multicenter, prospective, open-label (pooled analysis of first-in-man and phase I studies)</td>
<td>Multicenter, open-label, randomized trial; ( n = 52 ) randomized to immediate RDN, ( n = 54 ) controls</td>
</tr>
<tr>
<td><strong>Patient age (mean ± SD), y</strong></td>
<td>57 ± 11</td>
<td>58 ± 12</td>
</tr>
<tr>
<td><strong>No. antihypertensive medications</strong></td>
<td>5.1 ± 1.5</td>
<td>5.2 ± 1.5 (RDN), 5.3 ± 1.8 (control)</td>
</tr>
<tr>
<td><strong>Antihypertensive use by class at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td>β-blocker</td>
<td>82%</td>
<td>75%</td>
</tr>
<tr>
<td>CCB</td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>95%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Mean baseline blood pressure (mean ± SD), mm Hg</strong></td>
<td>176/98 ± 17/14</td>
<td>178/96 ± 18/16 (RDN), 178/97 ± 17/16 (control)</td>
</tr>
<tr>
<td><strong>Reduction in blood pressure</strong></td>
<td>(-25/−11 \text{ (at 6 months; } n = 86)), (-32/−14 \text{ (at 24 months; } n = 18))</td>
<td>(-32/−12 \text{ (RDN group at 6 months; } n = 49)), +1/0 (control group at 6 months; ( n = 51 ))</td>
</tr>
</tbody>
</table>
Only 17% of patients in Symplicity HTN-2 were on spironolactone or eplerenone.

Laragh’s Lessons

Clinical Pearl #1: The “Miracle” of Low-Dose Spironolactone

1972
<table>
<thead>
<tr>
<th>Office BP</th>
<th>Ambulatory BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>-32/-12</td>
<td>-11/-7</td>
</tr>
<tr>
<td>(n=49)</td>
<td>(n=20)</td>
</tr>
</tbody>
</table>

*RDN for white coat syndrome?*

*Lancet 2010; 376: 1903–09*
Masked Hypertension

BP is normal ONLY in the physician’s office, masking the diagnosis of hypertension

Masked HTN
- CKD 40%
- Diabetics 29%

(Franklin SS et al. *Hypertension.* 2013;61:964-71
Superiority of ambulatory BP for predicting CV death

Superiority of Home BP as a Determinant of LVH

Adjusted probability of LVH by MRI

Rader R et al., Unpublished data from Dallas Heart Study

Systolic BP, mm Hg

NH Black  
NH White

p<0.01  
p<0.35
Reviews

Catheter-Based Renal Denervation for Resistant Hypertension: Rationale and Design of the SYMPLICITY HTN-3 Trial

David E. Kandzari, MD; Deepak L. Bhatt, MD, MPH; Paul A. Sobotka, MD; William W. O’Neill, MD; Murray Esler, MBBS, PhD; John M. Flack, MD, MPH; Barry T. Katzen, MD; Martin B. Leon, MD; Joseph M. Massaro, PhD; Manuela Negoita, MD; Suzanne Oparil, MD; Krishna Rocha-Singh, MD; Craig Straley; Raymond R. Townsend, MD; George Bakris, MD

Screening

Initial Screening
- Office SBP ≥160 mm Hg
- Full doses of ≥3 meds
- No HTN med changes in past 2 weeks
- No plan to change meds for 6 M

2 weeks

Home BP & Med Confirmation

Confirmatory Screening
- Office SBP ≥160 mm Hg
- 24-h ABPM SBP ≥135
- Documented compliance on meds
Randomization and Blinding

Conscious sedation
(retrograde amnesia)

- Patient and research staff assessing BP are blinded to treatment status
- No changes in medications for 6 M
Inclusion criteria

• Age 18-80
• Stable medication on ≥ 3 BP drugs
• Office SBP ≥ 160
Exclusion criteria

- Renal artery stenosis or anomalies
- eGFR < 45 ml/min/1.73 m²
- > 1 HTV crisis/hospitalization
- 24 hour ABPM systolic BP < 135 mmHg
- Orthostatic hypotension
- Pregnancy
- Multiple chronic illnesses
Primary Endpoint
reduction in office-based systolic BP after 6 months

Assuming a true difference between treatment means of 15 mm Hg and with a 25 mmHg SD of the change score per group, 316 RDN and 158 sham subjects provides > 95% power to show a > 5 mmHg treatment effect at a 1-sided alpha level of 0.025.
Priority Secondary Endpoint

reduction in 24 hour systolic BP by ABPM after 6 months
Renal denervation: hope or hype?

- Premise
- Promise
- Problems
Medtronic's Renal Denervation System Fails

Published: Jan 9, 2014 | Updated: Jan 9, 2014

By Todd Neale, Senior Staff Writer, MedPage Today

The pivotal SYMPLICITY HTN-3 trial evaluating the use of Medtronic's renal denervation system in patients with treatment-resistant hypertension failed to meet its primary efficacy endpoint, the company announced Thursday.

No specific numbers were provided, but the announcement confirms rumors that renal denervation was no better than a sham intervention for lowering office systolic blood pressure through 6 months among patients who continued taking their anti-hypertensives.
MINNEAPOLIS, MN — Catheter-based renal denervation for the treatment of resistant hypertension has featured prominently at recent hypertension and cardiology congresses in the past few years, with numerous experts believing the procedure was one of the hottest fields in medicine.

The American Heart Association highlighted renal denervation as one of the top advances in cardiology in 2012, and the American College of Cardiology rightly predicted that the results of the SYMPLICITY HTN-3 trial would be one of the top news stories in 2014.

Well, the top-line results of SYMPLICITY HTN-3 trial were released yesterday, and while 2014 is only 10 days old, they are definitely a big deal. As reported by heartwire, the phase 3 study testing catheter-based renal denervation for the treatment of resistant hypertension failed to achieve its primary efficacy end point, which was a sustained reduction in systolic blood pressure at six months[1].
European approval based solely on unblinded data (Symplicity HTN-1,2)
Blood pressure changes after renal denervation at 10 European expert centers

N=88 patients
Patient-Specific Data:
Systolic BP

Office

24-Hour
Diastolic BP

Office

24-Hour

\[ \Delta \text{Office DBP (mm Hg)} \]

\[ \Delta 24-\text{H DBP (mm Hg)} \]

Baseline  6 Months
Does RDN block effects of renal SNA?

No evidence!

Vasoconstriction
Renin release
Na + H₂O resorption
Renal norepinephrine not elevated in HTN after age 59

**QUESTION**
If renal SNA already is normal in older hypertensives, how does renal denervation work?


58yrs = mean age in Symplicity HTN-1, 2
“Those who cannot remember the past are condemned to repeat it”

-George Santayana-
RESULTS OF TREATMENT OF PATIENTS WITH HYPERTENSION BY TOTAL THORACIC AND PARTIAL TO TOTAL LUMBAR SYMPATHECTOMY, SPLANCHNICECTOMY AND CELIAC GANGLIONECTOMY*

Keith S. Grimson, M.D., Edward S. Orgain, M.D., Banks Anderson, M.D., Robert A. Broome, Jr., M.D.,† and Frank H. Longino, M.D.‡

Annals of Surgery
June, 1949

Annals of Surgery
October, 1941
BLOOD PRESSURE - SUPINE - READINGS IN OFFICE
31 PATIENTS HAVING REDUCTION TO NEAR NORMAL

Years

Pre-operative

Post-operative

Office, Supine BP

Sympathectomy

Systolic

Diastolic
BLOOD PRESSURE - SUPINE - READINGS IN OFFICE
43 PATIENTS HAVING REDUCTION BUT NOT TO NORMAL

[Graph showing blood pressure readings before and after sympathectomy over a period of 9 years.]
BLOOD PRESSURE - SUPINE - READINGS IN OFFICE

23 PATIENTS NOT HAVING SIGNIFICANT CHANGES

Pre-operative

Post-operative

Systolic

Diastolic

Years

Years

Sympathectomy

Office, Supine BP

Mm Hg
Renal afferent (sensory) nerves

Liu L and L Barajas, Anat Embryol 1993;188:345-361
Renal afferents reflexes?

Anxiety, Cognition
(Lenski 2013)
(Lambert 2012, 2013)

Cardiac SNA

Muscle SNA

Splenic SNA

LVH
(Brendt, 2012)

Arrhythmias
(Hoffmann, 2013)
(Hou 2013)
(Linz 2013)
(Scherlag 2013)

Insulin
Resistance
(Witkowski 2011)
(Mafoud 2011)

Vascular
Inflammation,
Atherosclerosis
(Ott 2013)

Salt-sensitive
Hypertension

Renal afferents
Microneurography

Sympathetic innervation of microvessels in skeletal muscle

Hagbarth, *Cervical Pain*, 1972
Microneurography

MSNA = muscle sympathetic nerve activity

Sympathetic vasoconstriction in skeletal muscle:
- hypertension
- insulin resistance

PG Guyenet Nature Reviews Neuroscience, 2006
### Case Report

**59 year old man on 7 BP meds**

<table>
<thead>
<tr>
<th></th>
<th>Muscle SNA (bursts/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</td>
</tr>
<tr>
<td>12 months</td>
<td>19</td>
<td>127/81</td>
</tr>
</tbody>
</table>

Schlaich et al. NEJM. 2009; 36(9): 932-934.
Substantial Reduction in Single Sympathetic Nerve Firing After Renal Denervation in Patients With Resistant Hypertension

Dagmara Hering, Elisabeth A. Lambert, Petra Marusic, Antony S. Walton, Henry Krum, Gavin W. Lambert, Murray D. Esler and Markus P. Schlaich

Catheter-Based Renal Nerve Ablation and Centrally Generated Sympathetic Activity in Difficult-to-Control Hypertensive Patients: Prospective Case Series

Julia Brinkmann, Karsten Heusser, Bernhard M. Schmidt, Jan Menne, Gunnar Klein, Johann Bauersachs, Hermann Haller, Fred C. Sweep, Andre Diedrich, Jens Jordan and Jens Tank
Non-responders:

- Wrong patients?
  - sympathetics not overactive
- Incomplete denervation?
  - no post-procedure verification
  - redundancy in afferent input
- Design issues?
  - medications, non-compliance, etc.
The mosaic theory 32 years later

Focal Points
1. Genetic
2. Environmental
3. Anatomical
4. Adaptive
5. Neural
6. Endocrine
7. Humoral
8. Hemodynamic

The nervous system may be ablated and yet, after a short period of adjustment, tissue perfusion and blood pressure remain unchanged. This does not signify that the nervous system is unimportant as a regulator: it merely indicates that it is replaceable.
The mosaic theory 65 years later

Please stay tuned…