RENAL DENERVATION: WHAT WENT WRONG?

A more careful look at the data

Vasilios Papademetriou, MD
Professor of Medicine
Georgetown University
Mean Change in Blood Pressure (mmHg)
Presented with 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>-14</td>
<td>-10</td>
</tr>
<tr>
<td>3 months</td>
<td>-21</td>
<td>-10</td>
</tr>
<tr>
<td>6 months</td>
<td>-22</td>
<td>-11</td>
</tr>
<tr>
<td>9 months</td>
<td>-24</td>
<td>-11</td>
</tr>
<tr>
<td>12 months</td>
<td>-27</td>
<td>-17</td>
</tr>
</tbody>
</table>

Lancet 2009
92% of patients have BP ↓

THE SIMPLICITY HTN-2 TRIAL: OFFICE BLOOD PRESSURE RESPONSE

![Graph showing changes in blood pressure measurements from baseline to 6 months for renal denervation group and control group.](image)

**Figure 2:** Paired changes in office-based measurements of systolic and diastolic blood pressures at 1 month, 3 months, and 6 months for renal denervation and control groups.

Two-way repeated measures ANOVA, p<0.001

Lancet November 17 2010
ENLIGHTN I: 12 MONTH DATA

Worthley S, Tsioufis C……Papademetriou V; EHJ 2013
Papademetriou V, Tsioufis C,,,,,,,,,Hypertension 2014
Several other studies single arm, uncontrolled reported similar results.

A couple of small studies were negative.

But then.............
A CONTROLLED TRIAL OF RENAL DENERVATION FOR RESISTANT HYPERTENSION: SYMPHPLICITY HTN-3

Change in Office SBP

Change from baseline, $-14.13\pm23.93$ mm Hg
P<0.001

Change from baseline, $-11.74\pm25.94$ mm Hg
P<0.001

Difference in change, $-2.39$ mm Hg (95% CI, $-6.89$ to $2.12$)
P=0.26

(N=364) (N=353)

(N=171) (N=171)

Change in ABPM SBP

Change from baseline, $-6.75\pm15.11$ mm Hg
P<0.001

Change from baseline, $-4.79\pm17.25$ mm Hg
P<0.001

Difference in change, $-1.96$ mm Hg (95% CI, $-4.97$ to $1.06$)
P=0.98

(N=360) (N=329)

(N=167) (N=162)

Bhatt DL,…Bakris G. N EJM 2014;370:1393-401
Despair !!!!!

Shock !!!!!

Anger !!!!!
Put Renal Denervation

Medtronic  Boston Scientific  Suspended programs
Covedian  St Jude Medical

Into Permanent

Preclinical work revived

Hibernation
The study was well designed.
Patient Disposition: 6 Months to 1 Year

Crossover subjects were denervated after unblinding at 6 months if blood pressure criteria for treatment were met and subjects elected to proceed.

- Sham Control Group
  - 171 subjects

- Denervation Group
  - 361 Subjects
  - 4 died
  - 3 withdrew
  - 354 eligible for 12M follow-up
  - 322 Subjects (91%)
    - 12M post-RDN follow-up

- Crossover Group
  - 101 Subjects
  - 2 died
  - 3 withdrew
  - 96 eligible for 6M post-RDN follow-up
  - 93 Subjects (96.9%)
    - 6M post-RDN follow-up

- Non-Crossover Group
  - 70 Subjects
  - 2 died
  - 6 withdrew
  - 62 eligible for 12M follow-up
  - 48 Subjects (77%)
    - 12M follow-up
Change in Office Blood Pressure through 12 Months Post-Procedure

<table>
<thead>
<tr>
<th></th>
<th>Denervation 6 Months</th>
<th>Denervation 12 Months</th>
<th>Crossover* 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>180</td>
<td>179</td>
<td>184*</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td>96</td>
<td>95</td>
<td>102*</td>
</tr>
</tbody>
</table>

Note: BP changes are vs. patient baseline, not RDN vs Control. Error Bars = 1.96SE

P<0.001 for change from baseline at all time points
Change in 24-h Ambulatory Blood Pressure at 6 and 12 Months for Denervation Subjects

Denervation 6 Months

- SBP: -6.4
- DBP: -3.8

Denervation 12 Months

- SBP: -7.6
- DBP: -4.7

Crossover 6 Months

- SBP: -9.2
- DBP: -4.9

P = 0.229 for SBP difference

Note: BP changes are vs. patient baseline, not RDN vs Control. Error Bars = 1.96SE

Baseline SBP (mm Hg)

- 158

Baseline DBP (mm Hg)

- 86

*Baseline = time of RDN procedure
OFFICE BP CHANGE IN NON-CROSSOVER PATIENTS

Change in Office Blood Pressure through 12-Months Post-Procedure for Non-Crossover Subjects

Subjects unblinded

- 6 Months: SBP change from baseline = -32.9 mm Hg
- 12 Months: SBP change from baseline = -21.4 mm Hg

\[ \Delta 6 \text{ to } 12 \text{ months} = +11.5/+5 \text{ mm Hg} \]

P=0.010 for SBP difference

P<0.001 for change from baseline at all time points

Baseline SBP (mm Hg) | 176 | 176
Baseline DBP (mm Hg) | 94  | 94

Note: BP changes are vs. patient baseline, not RDN vs Control. Error Bars = 1.96 SE
Conclusions

- The 12-month results of SYMPLICITY HTN-3 are consistent with the 6-month findings previously reported. The safety of the procedure is maintained but blood pressure reductions are similar to a sham procedure.

- The positive correlation of the total number of ablations and the circumferential pattern of ablations on systolic BP drop is maintained and enhanced when the 6-month data from the crossover subjects are added.

- These *post hoc* observations suggest hypotheses concerning optimization of the denervation procedure that may inform the design of future renal denervation trials.
VARIABILITY OF THE PROCEDURE

Procedural Variability

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

Cross-section of artery

Inferior
Anterior
Superior
Posterior

4-quadrant ablation pattern

Symplicity

Vessix

EnligHTN
Number of ablations remains significant after adjustment for baseline blood pressure
Systolic Blood Pressure Change at 6 Months According to Ablation Pattern

**RDN Only**

- Office: n=253, -14.2, n=68, -17.2, n=19, -24.3
- ABPM: n=236, -6.3, n=62, -7.7, n=17, -10.3

**RDN + Crossover**

- Office: n=314, -14.6, n=83, -16.7, n=27, -27.3
- ABPM: n=289, -6.4, n=76, -8.2, n=24, -12.1
- Home: n=308, -7.5, n=82, -8.2, n=27, -10.6

Four quadrants = 1 superior, 1 inferior, and 2 posterior

Legend:
- 0 Four-quadrant ablations
- 1 Four-quadrant ablation (Right or Left)
- 2 Four-quadrant ablations (Right and Left)
Very SIMPLE.. The single tip catheter did no cause effective RENAL DENERVATION

I’ll Explain: It is all technical
- Too few lesions placed (4-5)
- Placement was random, not all quadrants addressed
- No circumferential ablation achieved
- Target temperature too low
- Depth not taken into consideration
- Fibers were not interrupted
- Possible that fiber repair took place

Bottom line: Incomplete, partial or ineffective fiber injury

SO!!! WHY DID SIMPLICITY HTN-3 FAILED???
HOW DO WE EXPLAIN RESULTS FROM PREVIOUS TRIALS

- Single arm, no controls, no shams
- Study design, mostly first in human
  - Open label, not blinded
  - Could introduce observer bias
  - Allow regression to the mean
- Selection bias
  - Pick patients on high BP day (Big day bias)
  - Hawthorne effect
- Baseline BP not adequately stabilized
  - Main problem
Renal Nerve Ablation for Resistant Hypertension: How Did We Get Here, Present Status, and Future Directions
Vasilios Papademetriou, Amir Adel Rashidi, Costas Tsioufis and Michael Doumas

Circulation. 2014;129:1440-1451
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There is little doubt that RNA is effective in most patients with renal-mediated sympathetic hyperactivity and resistant hypertension. The overall magnitude of BP response, however, still needs to be determined. BP is a dynamic measure and has considerable variability, particularly among patients with resistant hypertension. Until well-done, blinded, placebo-controlled, sham-masked studies are completed, we will not be certain about the true effect of RNA in this population. Sham-controlled studies are underway in the United States (Symplicity III and EnligHTN IV).* These
RENAL NERVE ABLATION FOR RESISTANT HYPERTENSION
HOW DID WE GET HERE, PRESENT STATUS, AND FUTURE DIRECTIONS

CHANGE IN OFFICE, AMBULATORY AND HOME BP MEASUREMENTS

**Change in Systolic Blood Pressure**

- **Office-S**
- **24h ABPM-S**
- **Day ABPM-S**
- **Home BP-S**

**Change in Diastolic Blood Pressure**

- **Office-D**
- **24h ABPM-D**
- **Day ABPM-D**
- **Home BP-D**

AMBULATORY BLOOD PRESSURE CHANGES AFTER RENAL SYMPATHETIC DENERVATION IN PATIENTS WITH RESISTANT HYPERTENSION (N=303)

BLOOD PRESSURE CHANGES AFTER RENAL DENERVATION AT 10 EUROPEAN EXPERT CENTERS (N=109)

Office BP (Basel. 174.5/98)

ABP (Basel. 156.7/91.5)

For now, RDN should remain the last resort in patients in whom all other ways to control BP failed.

EFFECT OF CATHETER-BASED RENAL SYMPATHETIC DENERVATION ON 24-H AMBULATORY BLOOD PRESSURE IN PATIENTS WITH RESISTANT HYPERTENSION (N=22)

RENAL DENERVATION IS NOT A SIMPLE MATTER

Simplicity

Complexity

Felix Mahfoud
The industry and Academia responded
Went back to drawing board
Examined pre-clinical Evidence
Engaged in successful preclinical studies
  ▪ To understand the impact of RF ablation
  ▪ Correlate RF ablation with surgical renal denervation
Studied new pre-clinical experimental models
Data presented in Recent meetings
Here is what they found:
  ▪ historical perspective
# Evidence That Renal Denervation Works

- In SHR Rats with increased RSNA, hypertension onset is delayed and the severity attenuated by prior bilateral renal sympathetic denervation.

EXPERIMENTAL MODELS OF RENAL DENERVATION

Renal Denervation in DOCA-Hypertensive Yucatan Miniature swine (YMS)

Renal Denervation in Insulin-Infused Rats

**Figure 1.** Changes in systolic blood pressure in control rats and insulin-infused rats with and without bilateral renal denervation. Control rats (CON) received vehicle alone. Insulin was administered via subcutaneous osmotic minipump (3 mU/kg per minute). □ indicates control rats, n=8; ■, insulin infusion alone (IN), n=8; ○, concurrent insulin administration and bilateral renal denervation (INRDa), n=8; and ◊, insulin administration and bilateral renal denervation performed 4 weeks later (INRDb), n=8. RD indicates bilateral renal denervation. ★ and † denote P<0.05 vs preinsulin period and vs control rats, respectively.

**FIGURE 1.** Mean arterial pressure (MAP, mm Hg; top graph) and sodium (Na) balance (mEq/kg/day; bottom graph) in four DOCA-YMS for one week prior to RDX and for three weeks after RDX.
Trans vascular Vagal Nerve Ablation Through a catheter placed in the Inferior Vena Cava or the right pulmonary artery

Shouarte et al; Circulation 2000
Renal Nerve Ablation Systems with CE-Mark approval in Europe

Papademetriou, Tsioufis, Doumas…… Circulation (In Press)
CATHeter-based renal denervation reduces total body and renal noradrenaline spillover and blood pressure in resistant hypertensive patients.
What is the microanatomy of renal nerves?
Is there a threshold of denervation for NEPI reduction?
Does NEPI change correlate for BP reduction?
Can we explain variable responses?
Can we optimize therapy?
Here is what we learned
DISTRIBUTION OF RENAL SYMPATHETIC NERVES

Variable Distribution and Density of Renal Sympathetic Nerves

Nerves from 20 human autopsy specimens

- Greater number of nerves prox/mid vs. distal as well as ventral (anterior) vs. dorsal (posterior)
- Greater distance from lumen to nerves from prox to distal
RENAL NERVE DISTRIBUTION

Renal nerves may have a positional bias: distal nerves are closer to the arterial lumen.

- Histological analysis by Sakakura\(^1\) and others\(^{2,3}\) suggest that a more distal approach could increase the frequency of successful ablations.
- Distal ablation strategies can be executed with the existing catheters.

1Sakakura K et al. J Am Coll Cardiol. 2014 Aug 19;64(7):635-43.
2Tzafriri ARJ Am Coll Cardiol. 2014 Sep 16;64(11):1079-87.
IS THERE A DENERVATION THRESHOLD FOR EFFICACY?

Efficacy biomarker (NEPI)

Control NEPI (ng/g)

Control NEPI (ng/g)

Titration to neural ablation

Threshold to -50% NEPI

Mean % affected nerves/artery (multiple ablation zones)

N = 70 arteries
Mean = 649
SD = 161

N = 125 arteries
Range of RF power & duration

Tzafriri et al
IS THERE A THRESHOLD DOSE NEEDED IN ORDER FOR RDN TO WORK?

Treatment of 8 renal arteries from 4 pigs undergoing bilateral multipolar denervation near ostium

Efficacy (1/8) requirements:
- 4 quadrant ablation
- Significant depth (9.1 mm)
- >50% of nerves affected

%DENERVATION IS INVERSELY RELATED TO ARTERIAL DIAMETER
EnligHTN Renal Denervation System

- Multi-electrode ablation catheter
  - Non-occluding, Nitinol basket design
  - 8F 4 electrode deflectable atraumatic tip
  - Predictable 4 lesion ablation pattern
  - Simultaneous 60 second ablation
- Touch-screen pole-mounted RF generator

### Default Settings

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>60 seconds simultaneous</td>
</tr>
<tr>
<td><strong>Impedance</strong></td>
<td>100-400 Ω</td>
</tr>
<tr>
<td><strong>Maximum Power</strong></td>
<td>8 Watts</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>70 degrees C</td>
</tr>
</tbody>
</table>
ENLIGHTN RENAL DENERVATION

LESION PROGRESSION

Theoretical lesion pattern

Adventitial Surface: Acute Transmural lesions

Luminal Surface: Acute TTC Stained Renal Artery

Luminal Surface 5 Days Healing Progression

Luminal Surface 30 Days Healing Progression

Luminal Surface 90 Days Healing Progression

Papademetriou V, Euro PCR 2014
EnligHTN™ Multi-electrode basket design provides:
- consistent lesion pattern

Lesion Width

P-Value = 0.665

Lesion Length

P-Value = 0.604

Papademetriou V, Euro PCR 2014
Norepinephrine Reduction

8 lesions /side
54% reduction in NEPI
Two RF ablation sites (red arrows)

- Nerve runs parallel to the artery outside of the treatment area (circle) stained strongly positive for TH.
- Nerve parallel to the artery (rectangle) stains negative for TH in the treatment zone (solid black arrow) but positive for TH outside of the RF treatment zone (broken arrow).

Papademetriou V, Euro PCR 2014
Injury to the renal nerves and artery caused by catheter-based renal denervation. (a) Injured nerve with perineural fibrosis and axon loss (hematoxylin and eosin staining). (b) Injured nerve with inflammation (hematoxylin and eosin staining). (c) Nerve from non-renal denervation animal.

Henegar JR…..Hall JE; American Journal of Hypertension 2013
Approximately 85% of renal nerves are within 3.5 mm of the renal artery lumen-intima interface

Henegar JR.....Hall JE; American Journal of Hypertension 2013
CATHETER-BASED RADIOREFREQUENCY RENAL DENERVATION LOWERS BLOOD PRESSURE IN OBESE HYPERTENSIVE DOGS

Average systolic blood pressure during control (CON) and for 8 weeks after renal denervation

47% of fibers affected

Correlation between SBP and mean renal tissue norepinephrine (NE) levels

NEPI change: -42%

Each bar represents the average of 7 days of blood pressure measurements, 18 hours a day
- 36 y/o female
- Resistant hypertension since the age of 9 years
- Ruptured of the ascending aorta due to dissection
- Underwent bilateral RDN using Symplicity Flex 12 days before

Felix Mahfoud TCT 2014
VESSIX BIPOLAR RF ABLATION
PRE-CLINICAL RESULTS

Norepinephrine Reduction

- Untreated
- Single Treatment (N=5) 79% reduction
- Full-length Treatment (N=5) 89% reduction

Percent reduction in NEPI

- Vessix™ Treatment, 68°C, 30 sec (n=19) 74% NEPI Reduction
- Surgical Denervation (n=3) 77% NEPI Reduction

- Efficacy comparable to surgical denervation

Vivek Y. Reddy, MD TCT 2014
SUBSTANTIAL VARIABILITY IN NEPI CONTENT: REVIEW OF 66 TREATED AND 64 NAÏVE SWINE

Robert J. Melder, ScD, TCT 2014

<table>
<thead>
<tr>
<th>Group</th>
<th>% Non-functional Area</th>
<th>Cortical Axon Area per mm²</th>
<th>Mean NE (pg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve 7 day N=64</td>
<td>14.6 ± 8.0</td>
<td>207.2 ± 134.6</td>
<td>264.8 ± 82.9</td>
</tr>
<tr>
<td>Symplicity 7 Day N=54</td>
<td>56.9 ± 28.3</td>
<td>66.8 ± 84.6 (68% Decrease)</td>
<td>92.7 ± 92.7 (65% Decrease)</td>
</tr>
<tr>
<td>Spyral 7 Day N=12</td>
<td>47.3 ± 26.5</td>
<td>97.4 ± 73.1 (54% Decrease)</td>
<td>88 ± 75 (68% Decrease)</td>
</tr>
</tbody>
</table>

- Average of four RF ablations in each artery
- Significant (P<0.05) increase in non-functional axonal area along artery
- Significant drop (P<0.05) in sympathetic axonal density measured by immuno-histochemistry in the renal cortex
- Significant drop (P<0.05) in tissue norepinephrine (NE) values measured in the renal cortex

Catheter-based Renal Denervation has a significant impact on sympathetic nerve function and viability but with substantial variability

Mean 291 ± 88
N = 238
OPTIMIZATION OF THE TREATMENT METHODOLOGY: A COMBINED TARGET APPROACH TO RENAL DENERVATION

RF treatment of the Main Artery

RF treatment of each Branch

RF treatment of the Main Artery and Branches

Robert J. Melder, ScD, TCT 2014
RENAL TISSUE NOREPINEPHRINE ANALYSIS

Robert J. Melder, ScD, TCT 2014

- All treatments significantly reduced tissue NE
- No meaningful dose response to multi-cycle Spyral treatment could be observed in the Main Renal Artery
- Branch and Distal Main treatments showed decreased variability
A CLOSER LOOK AT RESPONSE: GREATER LEVELS OF NE REDUCTION WITH INCREASED UNIFORMITY OF RESPONSE

Renal NE Concentration:
Treatment Arms with Matching Controls

- Control
- 1 Cycle
- Branch
- Distal Main

Unpaired t-test with Welch’s correction to matched control:
* P = 0.0017
& P = 0.0001
$ P = 0.0001

- Branch treatment reduced mean tissue NE by 84% with 2 outliers
- Distal Main treatment with reduced Mean tissue NE by 84%, also with 2 outliers but most values near zero
**RENAL TISSUE ANALYSIS – CORTICAL AXON DENSITY**

**Cortical Axon Area:**

**Treatment Arms with Matching Controls**

- **N**: 12, 12, 12, 12, 12, 12, 15, 15, 8, 8
- **4 lesions**, **8 lesions**, **12 lesions**
- **Control**, **1 Cycle**, **2 Cycle**, **Control**, **3 Cycle**, **Control**, **Branch**, **Control**, **Distal Main**

**Unpaired t-test with Welch’s correction to matched control**

- $P=0.0096$
- $P=0.0634$
- $P=0.0015$
- $P=0.0001$
- $P=0.0001$

- **Treatments closely paralleled renal NE response**
- **No meaningful dose response to multi-cycle Spyral treatment could be observed in the Main Renal Artery**
- **Branch and Distal Main treatments showed decreased variability**
A CLOSER LOOK AT RESPONSE: GREATER LEVELS AXON REDUCTION WITH INCREASED UNIFORMITY OF RESPONSE

Cortical Axon Area:
Treatment Arms with Matching Controls

- **Branch treatment** reduced mean axon area by 82%
- **Distal Main treatment** reduced mean axon area by 88%

Unpaired t-test with Welch's correction to matched control

* P = 0.0096
& P = 0.0001
$ P = 0.0001
BRANCH & MAIN ARTERY TREATMENT HIGHLY EFFECTIVE IN REDUCING RENAL NE

- Untreated or undertreated branches can give rise to outliers (red circle) in response
- Combination treatment of renal artery branches and main artery seem to be optimal in reducing outlier impact 2-cycles of treatment in the main artery do not improve response more than 1 cycle of treatment
CONCLUSIONS

- New data indicate that nerve distribution varies
- There are more nerve fibers proximally, but at more distance from the lumen
- Fewer fibers distally and closer to the lumen
- There is a threshold of fiber interruption that can affect NEPI reduction in the kidney parenchyma
- Relationship of NEPI reduction and target effect (BP) needs to be determined
- Ablation in the distal segment of RA and branches may be more effective
- Renal denervation technique needs to be modified before we move forward with more large sham control studies in humans with drug resistant hypertension
- Studies in HF and AF should await modification and perfection of technique