Catheter- Based Renal sympathetic Denervation

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Bnai Zion Medical Center
Technion
THE NEED
In 2000, 972 million (26%), of the adult population had hypertension.

By year 2025, 1.56 billion (29%) will have hypertension.
APPROXIMATELY 70% OF PATIENTS* IN EUROPE DO NOT REACH BP GOAL

*Treated for hypertension
BP goal is <140/90 mmHg

REAL LIFE HYPERTENSION CONTROL

Hypertension Control in Treated Hypertensive Patients

BNAI ZION ADMISSIONS TO CARDIOLOGY

- Hypertensive 88%
- Of the hypertensive group
  + Uncontrolled by Meds 38%
  + 2 classes of Meds 26%
  + 3 classes of Meds 15%
2.7 BP MEDS/PATIENT TO ACHIEVE TARGET BP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVEST</td>
<td>(136 mm Hg)</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>(137 mm Hg)</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>(138 mm Hg)</td>
</tr>
<tr>
<td>IDNT</td>
<td>(138 mm Hg)</td>
</tr>
<tr>
<td>RENAAL</td>
<td>(141 mm Hg)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>(144 mm Hg)</td>
</tr>
<tr>
<td>ABCD</td>
<td>(132 mm Hg)</td>
</tr>
<tr>
<td>MDRD</td>
<td>(132 mm Hg)</td>
</tr>
<tr>
<td>HOT</td>
<td>(138 mm Hg)</td>
</tr>
<tr>
<td>AASK</td>
<td>(128 mm Hg)</td>
</tr>
</tbody>
</table>

# Adherence to Common CV Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Self-Reported Adherence, %</th>
<th>Consistent Adherence, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>83</td>
<td>71</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>63</td>
<td>46</td>
</tr>
<tr>
<td>β-blockers</td>
<td>61</td>
<td>44</td>
</tr>
<tr>
<td>Aspirin + β-blocker</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Aspirin + β-blocker + lipid-lowering agent</td>
<td>39</td>
<td>21</td>
</tr>
</tbody>
</table>

*More than 2 consecutive follow-up surveys over 6±12 months.

Baroleti et al Circ 2010:121;1455
## Impact of a 5 mmHg SBP Reduction

<table>
<thead>
<tr>
<th>Overall Reduction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>14%</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>9%</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>7%</td>
</tr>
</tbody>
</table>
MAJOR INFLUENCERS IN HYPERTENSION

In human and animal models there are 2 basic, well-defined contributors to the pathophysiology of HBP

Other influencers include:
- Na & Water retention
- Co morbidities
- Genetic Factors

INCREASED CENTRAL SYMPATHETIC DRIVE IN HYPERTENSION

- Sympathetic drive is elevated in multiple types of hypertension

s-MSNA=single-unit efferent sympathetic nerve activity.
LVH=left ventricular hypertrophy.
*P<0.05 Compared with borderline hypertension.
†P<0.05 Compared with white coat hypertension.
‡P<0.05 Compared with normal pressure.
§P<0.05 Compared with high-normal pressure.
¶P<0.05 Compared with essential hypertension – stage 1.
#P<0.05 Compared with essential hypertension – stage 2/3.

CLASSICAL NEURO-HORMONAL AXIS:
KIDNEY AS A PASSIVE RECIPIENT OF SYMPATHETIC SIGNALS

Renal Efferent Nerves

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
CROSSTALK BETWEEN KIDNEY AND CNS

↑ Neurohormones

↑ Blood Pressure

↑ Vasoconstriction

↑ Contractility/Rate

↑ Renin

↓ RBF/GFR

↑ Na⁺/Volume

↑ NE

↓ NE

Patients cannot develop and/or maintain elevated BP without renal involvement
THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON
From the Laboratories of Physiology in the Harvard Medical School
Received for publication March 24, 1931

THE BRITISH JOURNAL OF SURGERY
1952
SYMPATHECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT HYPERTENSION
A REVIEW OF 76 PATIENTS
By C. J. LONGLAND AND W. E. GIBB

THE JOURNAL
of the American Medical Association
Published Under the Auspices of the Board of Trustees

SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION
RESULTS IN 1,246 CASES
Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

Dr. Reginald H. Smithwick
Denervating lower half of the body produced:
- Mortality benefit
- Inconsistent BP results
- Significant morbidity including orthostatic hypotension, bowel & bladder dysfunction

THE SYMPATHETIC RENAL NERVES

- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- ≈ 70% within 15mm of the ostium
- ≈ 95% are within 2.5mm of the vessel lumen
# Human Renal Artery:

Total number (%) of nerves per ring (0-0.5 to 2.0-2.5 mm) and per segment (proximal to distal) in non-perfusion fixed arteries

<table>
<thead>
<tr>
<th>Ring</th>
<th>Proximal</th>
<th>Middle</th>
<th>Distal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 0.5</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td>6 (0.6%)</td>
<td>10</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>87 (9.1%)</td>
<td>152 (15.9%)</td>
<td>223 (23.3%)</td>
<td>462</td>
</tr>
<tr>
<td>1.0 – 1.5</td>
<td>65 (6.8%)</td>
<td>86 (6.0%)</td>
<td>94 (9.8%)</td>
<td>245</td>
</tr>
<tr>
<td>1.5 – 2.0</td>
<td>43 (4.5%)</td>
<td>47 (4.9%)</td>
<td>58 (6.1%)</td>
<td>148</td>
</tr>
<tr>
<td>2.0 – 2.5</td>
<td>19 (2.0%)</td>
<td>36 (3.8%)</td>
<td>36 (3.8%)</td>
<td>91</td>
</tr>
<tr>
<td>Total</td>
<td>216 (22.6%)</td>
<td>323 (33.8%)</td>
<td>417 (43.6%)</td>
<td>956</td>
</tr>
</tbody>
</table>

NUMBER OF NERVES IN PERIADVENTITIAL FAT
(Nerves x mm²)

Sangiorgi et al TCT 2012
Renal Artery Sympathetic Nerves
Hypertensive vs. Normotensive Pts

Normotensive

Hypertensive

Sangiorgi et al TCT 2012
3D Reconstruction
Hypertensive vs. Normotensive
Hypertensive patients
3D Reconstruction

Sangiorgi et al TCT 201
BASIC PRINCIPLES OF RDN

Reduction in afferent/efferent Sympathetic flow

Sympathetic renal nerve disruption

Transluminal application of energy to renal intima

Reduction MSNA, total NE “spillover” —→ reduction in SBP

No intermediate/long-term renal artery injury, No renal dysfunction
CATHETER-BASED RENAL DENERVATION

- Semi-standard interventional technique
- Dedicated ablation catheter
- RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms
TREATMENT STRATEGY

Multiple focal ablations spaced along vessel

↑ circumferential coverage
SELECTIVE DENERVATION OF THE RENAL SYMPATHETIC NERVES BY RF ABLATION
RF ABLATION AT 6 MONTHS

No pathologic change in arterial wall

Extensive perineural fibrosis

Digestion chamber
NEOINTIMAL THICKENING IS UNCOMMONLY OBSERVED IN ANIMALS EVEN IN THE PRESENCE OF SEVERE INJURY TO MEDIA
**NE “spillover”**
measures amount of transmitter from sympathetic nerves that escapes neuronal uptake and local metabolism and “spills over” into circulation

Muscle Sympathetic Nerve Activity (MSNA)
records postganglionic nerve traffic

**Uncontrolled Hypertension**
- N dB.P 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 above goal
- Compliance with full doses of ≥3 antihypertensive medications of different classes; ideally, 1 of the 3 agents should be a diuretic
- Includes those patients who achieve BP control but require ≥4 antihypertensive agents to do so

---

59-year-old patient

- Resistant hypertension

- Renal sympathetic nerve activity modulated by catheter-based radiofrequency (RF) ablation

↓ of Renal Contribution to Central Sympathetic Drive: MSNA in Resistant Hypertension Patient

<table>
<thead>
<tr>
<th></th>
<th>MSNA (burst/min)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>56 → 161/107</td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>41 (-27%) → 141/90 (-20/-17)</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>19 (-66%) → 127/81 (-34/-26)</td>
<td></td>
</tr>
</tbody>
</table>

* 59 year old male on 7 HTN meds

* Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 → 11.7 msec/mmHg)

Schlaich et al. NEJM. 2009; 36(9): 932-934.
Study Aims:
First-in-man 12-month safety and BP-lowering efficacy of percutaneous renal sympathetic denervation in patients with resistant hypertension
CHANGE IN OFFICE BLOOD PRESSURE THROUGH 36 MONTHS

P<0.01 for ∆ from BL for all time points

Sobotca et al. ACC 2012
DISTRIBUTION OF SBP CHANGE AT BL, 1, 12, 24, AND 36 MONTHS

Sobotca et al ACC 2012
Responder was defined as an office SBP reduction ≥10 mm Hg
# Change in Office BP in Diabetic and Non-Diabetic Patients

<table>
<thead>
<tr>
<th></th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (N=44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DM (N=86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM (N=17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DM (N=42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM (N=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DM (N=16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagram:**
- Δ SBP
- Δ DBP
RENAL FUNCTION OVER TIME

eGFR (mL/min/1.73m²)

- BL (N=143)
- 3 M (N=131)
- 6 M (N=141)
- 12 M (N=128)
- 18 M (N=53)
- 24 M (N=35)
- 30 M (N=11)
- 36 M (N=3)
• **Purpose:** Prospective CRT, Effectiveness of catheter-based renal denervation for reducing BP in patients with uncontrolled hypertension

• **Patients:** 106 patients, 1:1 randomization, RDN vs. control
PRIMARY ENDPOINT: 6-MONTH OFFICE BP

- 33/12 mmHg difference between RDN and Control
- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

OFFICE SYSTOLIC BP DISTRIBUTION @ 6 MONTHS

DISTRIBUTION OF OFFICE SBP FOR CROSSOVER GROUP

% Patients

Crossover Baseline | Crossover Pre-RDN | Crossover 6-month

- ≥180 mm Hg
- 160-179 mm Hg
- 140-159 mm Hg
- <140 mm Hg
AIM

To describe our initial experience with Renal Denervation (RDN) on Blood Pressure in patients with resistant Hypertension
METHODS

1. Team approach
2. Screening by Nephrologist (SS)
3. Procedure by Interventional Cardiologist
4. Follow-up by Nephrologist
5. F/U
   1. Office/ABP measurements of BP
   2. Clinical F/U
<table>
<thead>
<tr>
<th>Method</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-office</td>
<td>Two readings, 5 minutes apart. Sitting in chair, not on exam table. Confirm elevated reading in contralateral arm.</td>
</tr>
<tr>
<td>Ambulatory BP monitoring</td>
<td>Indicated for evaluation of “white-coat” HTN. Can be used to confirm self-measurement when inconsistent with in-office measurement. Reimbursable.</td>
</tr>
</tbody>
</table>
Inclusion Criteria: (Based on HTN-1, HTN-2 studies)

1. Office SBP $\geq 160$ mmHg ($\geq 150$ mmHg with Type II Diabetes Mellitus)
2. Drug regimen: $\geq 3+$ anti-HTN medications,
4. Renal artery: diameter $\geq 4$ mm,
   length $\geq 20$ mm
5. eGFR of $\geq 45$
6. Age $>18$ years
METHODS

Exclusion Criteria: (Based on HTN-1, HTN-2 studies)

1. Significant renal artery abnormalities
2. Type 1 Diabetes Mellitus
3. Valvular heart disease
4. AMI, unstable angina, or CVA in the prior 6 months
5. ICD or pacemaker
6. Pregnant, nursing or planning to be pregnant
## RESULTS

Demographics (n=19)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>57%</td>
</tr>
<tr>
<td>Age</td>
<td>60 +/- 7.1 yrs</td>
</tr>
<tr>
<td>DM</td>
<td>63%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>73%</td>
</tr>
<tr>
<td>Smokers</td>
<td>63%</td>
</tr>
<tr>
<td>CAD</td>
<td>57%</td>
</tr>
<tr>
<td>PVD</td>
<td>9%</td>
</tr>
<tr>
<td>eGFR</td>
<td>89 +/- 25</td>
</tr>
</tbody>
</table>
## RESULTS

<table>
<thead>
<tr>
<th>Category</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Antihypertensive Rx</td>
<td>3.75</td>
</tr>
<tr>
<td>Diuretics</td>
<td>11</td>
</tr>
<tr>
<td>ACEI and/or ARB</td>
<td>11</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>8</td>
</tr>
<tr>
<td>Ca Channel Blockers</td>
<td>7</td>
</tr>
<tr>
<td>Central Activity (Clonidine)</td>
<td>2</td>
</tr>
</tbody>
</table>
LEARNING CURVE

- **Procedure Time**
  - First 3 pts: 101 min
  - Last 3 pts: 70 min (-Δ44%)

- **Fluoroscopy Time**
  - First 3 pts: 17 min
  - Last 3 pts: 11 min (-Δ35%)

- **Contrast (1:2 diluted)**
  - First 3 pts: 155 ml
  - Last 3 pts: 70 ml (-Δ55%)
RESULTS

Procedure Details:
Ablations/Artery  5-7
IV Pain Management
  Midazolam 2mg
  Fentanyl 0.25mg
RESULTS

Procedure Success:
Device introduction and energy application without complications - 95%

1 severe spasm
SBP decreased significantly in 18 of 19 patients
Baseline SBP was 184 ±14
Post RDN- 154 ±22, 146 ±15, 141 ±13 @ 1, 3, 6 mths, p<0.0001
Baseline SBP = 184 ±14 mmHg
Decreased to 154 ±20, 146 ±15 & 141 ±13 @ 1, 3 & 6 mont, respectively
p<0.0001
RESULTS

Procedure Safety
No early major/minor complication
One severe spasm after RF delivery
No change in renal function or electrolyte disturbances
מציאת מקום

ג.ס. בן 66 נשים + 4 רוח ב_tensors

• ת חוק משקל - 36

• הער הפילות גודל הדרור

• סוכרתי - 25 שנות’, תלוי אינסולין - 8 שנות’

• COPD - 45 שנות’ קופה

• יזור לוחם דם - 21 שנות’
וְזָהַבְּמִימָה

רשימה הוראות ללהק דם:
EXFORAGE 160/5 MG X1
CARDILOC 10 MG X1
CADEX 2 MG X2
FUSID 40 MG X1
DIOVAN 160 MG X1
הצגת מקרה

- תרשת עורקים
- CAD-CABG 2004
- CVA-2004
- RT CAROTID PTA 2004
- דום נשימה בשינה - מונו ב- CPAP
ḥesem mashe

הצגה מרחב

לא ולהשנקה הזו. DOE- 5.2011

מיירי לב: פגז מילי חולה חזה בודד

צנטרור כרני: מздрав פתרון

עורקים כרניים חסומים

צמרת דם בגובהיםISIBLE אצלופ

ליניו דמגבודים במדליاء אשפוז
Average day = 168/92 HR = 75 night = 135/71 HR = 70
הצגת מקרה

10.2011 קוצר נשימה עם גודש ריאתי
לוזן דם סיסטולי >200مم"כ
RENAL DENERVATION
(6 אובליציות熥 מאל 5 מימי).
הולר לחצי דם אחרי 6 חודשים

Average day = 132/75 HR = 66 night = 122/73 HR = 59
רשימה חורפית חוות לאמור Rene:

- LOTAN 100 MG X1
- NORVASC 10 MG X1
- CARDILOC 10 MG X1
LIMITATIONS OF CURRENT TECHNOLOGY

- Technology is limited
  - Not guide wire based
  - Wide variance in ablation geometry
  - Variance in energy delivered

- Ablation
  - No obvious target during procedure
  - No way to measure effect (e.g. change in sympathetic activity on line)
No guidewire
Choice of Guide Catheter critical
“Deep throat”, “Mother & child”
UNFAVORABLE ANATOMY
LIMITATIONS OF CURRENT TECHNOLOGY

- Technology is limited
  - Not guide wire based
  - Wide variance in ablation geometry
  - Variance in energy delivered

- Ablation
  - No obvious target during procedure
  - No way to measure effect (e.g. change in sympathetic activity on line)
TIVUS™ Core Technology

- High-intensity, ultrasonic catheter (0.014” OTW)
- Selective thermal modulation
- No contact with the vessel intima
- Short, total treatment: 5-10 min/artery
TIVUS™ CORE TECHNOLOGY: NON-FOCUSED HIGH INTENSITY ULTRASONIC CATHETER

Blood vessel wall

Lumen + Blood Flow

Ultrasonic Catheter

Blood Flow Cooling

Non-Focused Ultrasonic Ray

Transducer

Thermal modulation

T [°C]

Tissue Damage Threshold

Depth [mm]
Histological Analysis

Renal Artery Cross-Section

- Large nerve fibers bundles with fat cover
- Nerve fibers
- Adventitia
- Media
- Endothelium

Ultrasonic transducer X3

Damaged nerves
STUDY OVERVIEW

- Prospective, single arm study
- RDN in pts with resistant hypertension
- 50-75 patients at up to 15 sites:
  + Europe, Australia & Israel
- Follow-up through 12 months
- Eligibility:
  + Systolic OBP $\geq 160$
  + Systolic 24h ABP $\geq 135$
  + Stable drug regimen, >3 drug classes, one diuretic
Device-Based Approaches to Autonomic Modulation

Baroreflex Sensitisation

Renal Sympathetic Denervation
CONCLUSIONS

1. Encouraging initial experience
2. Exciting new treatment strategy targeting the renal artery adventitial autonomic nervous system
3. New exciting technologies on the horizon
ניירון חרש!!
Quantification of human sympathetic activity

Muscle sympathetic nerve activity (MSNA) (Peroneal nerve activity)

Measuring transmitter release from sympathetic nerves to plasma (noradrenaline “spillover”)

Sympathetic Nerve Traffic

Noradrenaline

Sympathetic Nerve Traffic

Muscle sympathetic nerve activity (MSNA) (Peroneal nerve activity)
Treatment by Micro-Infusion Catheter
NEW TECHNOLOGIES ARE UNDERWAY
LOCALIZED GUANETHIDINE SYMPATHECTOMY

Drugs can be targeted directly to adventitial nerves with the Bullfrog Catheter

TCT 2010
**CONTROL OF CENTRAL SYMPATHETIC DRIVE**

- **Chemosensors**
  - Carotid body

- **Mechanosensors**
  - Baroreceptor

**Afferent Pathways**

- HTN & Insulin Resistance
- Dyspnea, Exercise Intolerance, Central Sleep Apnea

**Efferent Pathways**

- Congestion
- Acute HF
- Obstructive Sleep Apnea

- Hypertrophy
- Arrhythmia

- CKD progression
DIABETES MELLITUS

RDN GROUP SHOWED IMPROVEMENTS IN SEVERAL KEY INSULIN RESISTANCE MARKERS

Fasting Glucose

-8.9 (p=0.043)  -9.4 (p=0.039)

1 month 3 months

p for interaction (ANOVA)=0.043

Fasting C-peptide

-2.0 (p=0.006)  -2.3 (p=0.002)

1 month 3 months

p for interaction (ANOVA)=0.031

Fasting Insulin

-8.7 (p=0.036)  -11.6 (p=0.006)

1 month 3 months

p for interaction (ANOVA)=0.016

HOMA-IR

-3.1 (p=0.008)  -3.7 (p=0.001)

1 month 3 months

p for interaction (ANOVA)=0.003

Renal denervation (n=37)
Control (n=13)

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

Mathias C. Brandt, MD,*† Felix Mahfoud, MD,§ Sara Reda, MD,*† Stephan H. Schirmer, MD, PhD,§ Erland Erdmann, MD,† Michael Böhm, MD,§ Uta C. Hoppe, MD*‡
Salzburg, Austria; and Cologne and Homburg/Saar, Germany
Effects of Renal Sympathetic Denervation on Blood Pressure, Sleep Apnea Course, and Glycemic Control in Patients With Resistant Hypertension and Sleep Apnea

Adam Witkowski, Aleksander Prejbisz, Elżbieta Florzak, Jacek K dziela, Paweł Zliwiński, Przemysław BieleD, Ilona Michałowska, Marek Kabat, Ewa Warchoł, Maria Hałas, Mirosław Kusiak, Agnieszka Glinka, Ewa Czosny, Robert Słodko

Figure 2. Changes of apnea/hypopnea index (AHI) at 3 and 6 months after denervation. Data of individual cases.