Renal Denervation for Resistant Hypertension

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Objectives

- Current understanding of SNS contribution to HTN
- Novel invasive treatments:
  - BRS modulation
  - Renal Sympathetic modulation
- The Sheba experience
SNS & Hemodynamic control

- Hypothalamic centers
- Cortex
- NTS
- RVLN
- Postrema
- BP
Peripheral SNS

\begin{align*}
\text{N} &= \text{Normotenstion} \\
\text{B} &= \text{Borderline} \\
\text{H} &= \text{Hypertension}
\end{align*}

G Grassi, Curr pharm des, 2004
Pathogenesis - nerve endings

The Tracer Dilution Principle
Pathogenesis - nerve endings

- Systemic and particularly Cardiac and Renal NE spillover are higher in hypertensives

M. Esler, Hypertension 2004
Essential hypertension is **neurogenic** and is **initiated** and **sustained** by sympathetic nervous system over-activity.
Those with high SNS tone will develop hypertension: lessons from stress studies
Job Strain

• CARDIA study: 3200 young adults, 13 y FU
  – High job demands
  – Decision makers
  – Time pressure
  – Hostile / competitive environment

• **Double the risk for HTN**

  » Yan, *JAMA*, 2003
Mental stress: Probability of remaining normotensive according to reactivity to video game
Prognostic implication of exaggerated BP response to exercise

Sharabi et al, J Hum HTN, 2001
Therapeutic implications
Beta blockers

• Excellent drugs for certain subjects
  – Young
  – Tachycardia
  – IHD
  – CHF
HOWEVER...

SNS-directed treatment must do better, particularly due to its importance

Perhaps – invasive strategies?
Resistant Hypertension
Direct Baroreceptor Stimulation?
Implanted Components
DEBuT-HT Clinical Trial First Implant (March 2004)

2 Months Post Implant
Response repeatability: systolic, mean, and diastolic arterial blood pressure (ABP) and relative total MSNA over time in patient 12

Renal Sympathetic Nerve Activity:
Kidney as Origin & Recipient of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis

Efferent Nerves

- ↑ Contractility
- ↑ Heart rate

Blood Pressure

- ↑ Renin Release → RAAS activation
- ↑ Sodium Retention
- ↓ Renal Blood Flow

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Fig. 4. Arterial pressure vs. steady-state daily urinary sodium excretion in groups of dorsal rhizotomized (DRX) rats and sham DRX rats

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- Atherosclerosis

Efferent Nerves

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
↓ Kidney function

Afferent Nerves

↑ Contractility
↑ Heart rate
Hypertrophy
Arrhythmia
Heart Failure


Blood Pressure

+ Increase co-morbidities
Renal Sympathetic Nerve Activity:
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• Vasoconstriction
• Atherosclerosis

Brain

• ↑ Contractility
• ↑ Heart rate
• Hypertrophy
• Arrhythmia
• Heart Failure

Kidney

• ↑ Renin Release → RAAS activation
• ↑ Sodium Retention
• ↓ Renal Blood Flow
• ↓ Kidney function

RDN

Blood Pressure

+ Increase co-morbidities

Catheter-based Renal Denervation
Renal Anatomy Allows a Catheter-Based Approach

- Arise from T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
Symplicity Catheter System

• Low profile, electrode-tipped catheter
• Delivers RF energy to treatment site
• Proprietary RF generator
  - Low power
  - Automated
  - Built-in safety control algorithms
• Standard interventional technique
• 40-minute procedure time
Multiple Discrete Treatments
Maximize Nerve Coverage Without Applying Circumferential Energy in a Single Segment
Carefully Staged Clinical Evidence Generation

Symplicity HTN-1

- First-in-man ✓
- Series of pilot studies ✓

Symplicity HTN-2 ✓
EU/AU randomised clinical trial

USA

Symplicity HTN-3
US randomised clinical trial (enrolling)

EU/AU

Other areas of research
Insulin resistance, HF/cardiorenal, sleep apnea, more

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Insulin resistance, HF/cardiorenal, sleep apnea, more
Results Recognized for Their Importance

The Lancet. Published electronically on Nov 17, 2010.
Primary Endpoint: 6-Month Office BP

Δ from Baseline to 6 Months (mmHg)

-32 Systolic
-12 Diastolic

RDN (n = 49)

Control (n = 51)

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

Chronic Procedural Safety

- No chronic vascular complications
- No chronic renal (Δ eGFR) complications
- No orthostatic or electrolyte disturbances
Renal Denervation Improves Glucose Tolerance

Oral Glucose Tolerance Test (75 g)

- **Baseline (n=25)**
- **3 months (n=15)**
- **6 months (n=7)**

*significant reduction (p<0.05) compared to baseline

The Sheba Experience

• Started July, 2011

• Collaboration
  – Hypertension Unit
  – Heart Institute
  – Invasive Radiology Unit

• 10 RDN procedures so far
Eligible Anatomy
Example Treatment Sites
Six examples of patients with FU

- 5 ♂, 1 ♀
- All with resistant hypertension
- 5 or more antihypertensive medications
- All underwent hypertension specialist evaluation
- All underwent workup for secondary HTN
- All had ABPM
• G. A.
• 56 y/o ♂
• Background: HOCM
• M. K.
• 77 y/o ♂
• Background: Past smoker, IHD
• A. S.
• 60y/o ♂
• Background: Obesity
• B. I.
• 66y/o ♂
• Background: IHD, OSA, DM, Nephrotic synd, Cr- 1.4-1.6
• R. Z,
• 57 y/o ♂
• Background: DM, CVA
• N. M.
• 66y/o ♀
• Background: DM
Results

- Femoral approach
- Procedure time: ~ 1.5 hours
- No immediate or up to 22 month follow up complications
A.G.

No of medications: 6 → 5
Dose of medications: ↓
М. К.

No of medications: 5 → 4
Dose of medications: ↓
No of medications: 7 → 5
Dose of medications: ↓
A. S.

No of medications: 6 → 5
Dose of medications: ↓
R. Z.

No of medications: 6 → 6
Dose of medications: Same
No of medications: 6 → 5
Dose of medications: ↓
RDN = 12.7.2012

RDN = 2.10.2012
Summary and conclusions

• Pathological SNS-Kidney crosstalk induce and maintain high blood pressure
• Novel invasive procedures target this interaction in resistant hypertension
• Worldwide experience – showed safety and primarily Office BP efficacy, up to 3Y
• Long term effect – not known yet
The Sheba experience – more conservative:

• Sheba management of resistant HTN
  – Rigid definition only based on ABPM
  – Patient education
  – Careful medication selection
  – R/O secondary hypertension
• Skilled team of interventional cardiology and invasive radiology
• Close follow-up
• Similar non-response rate
  – Even more careful selection in the future?
  – Redo?
  – New technologies?
Thank you!