RENAL SYMPATHETIC DENERVATION FOR RESISTANT HYPERTENSION

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The kidney as origin of sympathetic drive carried centrally via renal afferent sympathetic nerves generating central sympathetic drive

- Vasoconstriction
- Atherosclerosis
- Insulin Resistance
- Sleep Disturbances
- Hypertrophy
- Arrhythmia
- Oxygen Consumption
- Heart failure

Renal Afferent Nerves

- Decreased renal blood flow
- Renin release
- RAAS activation
- Sodium retention
Surgical thoracolumbar sympathectomy lowered blood pressure, improved life expectancy but had important side effects (orthostatic hypotension, bowel and bladder dysfunction)
Early data show that Renal Denervation

- Reduces systemic sympathetic activation
- Improves hypertension
- Reduces fluid overload
- Induces LVH regression & ventricular remodeling
- May improve renal function
- Reduces some arrhythmias
- Improves sleep apnoea
- Improves diabetic control
95% of Renal Sympathetic Nerves are within 2.5mm of the arterial lumen

Renal sympathetic nerves are distributed around the circumference of the renal artery in the adventitia.

The proximity of the nerves to the renal artery renders them susceptible to catheter treatments.

Equal in number proximally and distally.

Increased in number in hypertensive patients (one report only).
A number of different energy sources can cause ablation of renal nerves. Renal nerves are more susceptible to damage and have limited recovery potential.

- **Radiofrequency**
  Thermally induced tissue damage

- **Cooling**
  Profound cooling can produce cell death.
  May have higher recurrence rate.

- **Ultrasound**
  Can cause thermally mediated tissue damage.

- **Injection of neurotoxic drugs**
A Common Question

How will the kidney function without sympathetic control?

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

**Physiologic Responses of the Transplanted Human Kidney***

Sodium Regulation and Renin Secretion

M. Donald Blaufox, 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.

Medtronic Symplicity RF Ablation System

- 6F compatible catheter
- Articulating tip
Symplicity (Medtronic) 2mm point-by-point ablation
Symplicity HTN-1

Lancet. 2009;373:1275

- First-in-man, non-randomized
- 45 patients with resistant HTN (SBP ≥160 mmHg ≥3 anti-HTN drugs, including a diuretic)
  Expanded cohort of patients (n=153)
- 36-month follow-up
Symplicity I Trial
Sustained office BP reduction at 36 months

P < .001 for systolic and diastolic BP changes from baseline

Krum ACC abs 2012
Responder rate increased over time in Symplicity I

Responder rate was defined as a systolic BP reduction $\geq 10$ mm Hg

Krum ACC abstract 2012
**Randomized trial** Renal sympathetic denervation and ongoing medical treatment vs medical treatment alone

**Inclusion Criteria** Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus) Stable drug regimen of 3+ more anti-HTN medications

**Patients:** 106 patients randomized 1:1 to renal denervation vs. control

*Symplicity HTN-2 Investigators. Lancet. 2010;376:1903*
Primary Endpoint Symplicity HT-2: 6-Month Office BP

84% of RDN patients had ≥ 10 mmHg reduction in SBP
10% of RDN patients had no reduction in SBP

Lancet Conclusions

• Renal denervation in a randomised trial caused significant reductions in office SBP in patients with resistant HT

• The BP reduction is predicted to affect hypertension-related diseases and mortality

• No major complications

RD Reduces Fasting Glucose
(50 diabetic pts Symplicity HT 2 37RDN, 13 control)

![Graph showing change in fasting glucose levels]

- **1 month**
  - Renal denervation: -8.9 mg/dl, p=0.043
  - Control: +3.9 mg/dl, p=0.402

- **3 months**
  - Renal denervation: -9.4 mg/dl, p=0.039
  - Control: +0.9 mg/dl, p=0.847

Mahfoud F et al., Circulation 2011; 123:1940-46
RD Improves Glucose Tolerance compared with baseline

Mahfoud F et al., Circulation 2011; 123:1940-46
Limitations

• Not a prespecified endpoint
• Small numbers
• Not proof but hypothesis generating
New Technologies
130 μm-diameter needle
Spiral unipolar electrode
Pores in balloon seep fluid to cool and limit tissue damage
Focused ultrasound energy delivered from outside (Kona Medical)

Far less energy is needed for necrosis of renal nerves requires far less heat energy than for surrounding tissues.

Focused therapeutic ultrasound produces a thin plane of heat that encompass a cross-section of the renal artery, plus a margin of surrounding perivascular tissue.

Figure 1. Kona Medical noninvasive treatment system based on Doppler signals from the renal artery.

Figure 2. The concept of “outside-in” energy delivery to the renal nerves without instrumentation of the vessel.
Trans-ureteric route for RF energy delivery

Sympathetic nerves surround the renal pelvis and can be ablated via a retrograde ureteric approach

Monopolar delivery of electrical energy

Not limited by renal arterial anatomy

No arterial puncture

Potential office procedure
Summary

Catheter based renal sympathetic ablation
With Medtronic Symplicity system (and others)

• Lowers BP in 85% of patients with HT resistant to 3 drugs or more

• Effect is -30mmHg at 6 months with most technologies

• Sustained at 3 yrs in Symplicity

• % responders increased with time in Symplicity I

• Favourable effect on glycaemic control

• Minimal complication rate

• Linking of procedural success with long term clinical data is absent to date
The future

Expanded indications
• Diabetes?
• Heart failure?
• Renal failure?
• Sleep apnoea?
• Less severe hypertension eg 140 systolic
• Those with good control but unacceptable side effects

Technology
• Technological improvements eg shorter more predictable delivery
• Non-invasive renal denervation?
Renal Denervation: Questions to be Answered

- Will ‘next gen’ catheter designs address therapy’s anatomical limitations?
- How do we explain the ‘non-responders’?
Patient GMD for renal denervation

Mrs GMD is a 52yr old woman
Referred by Dr Fleischel and Dr Hulett

Problems
1. Poorly controlled hypertension despite medication
2. No blood transfusions

Current medications
1. Clonidine TTS patch daily
2. Frusemide 40mg/d
3. Spironolactone 25mg/d
Intolerant of calcium channel blockers, ACE inhibitors, angiotensin receptor blockers

Investigated for secondary causes of hypertension

Increased LV wall thickness on Echo (2011)
Renal function: Creat 76mmol/L eGFR 70ml/min/1.73m2

Office BPs  179/99, 185/101, 205/112, 191/101
Hospital admission May 2012 BP 233/100

How did she feel?
**CT angiography**

Renal artery anatomy
Number
Diameter
Takeoff
Distance to branching
Stenosis?

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<thead>
<tr>
<th>Number</th>
<th>Diameter</th>
<th>Takeoff</th>
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![3D images of renal arteries](image-url)
Mrs GD renal artery ablation 3/10/12
No complications
How do you feel now 8 months later?

Only drug therapy is Clonidine patch 0.2mg/d
Baseline office BPs (on 3 meds)
Office BPs 205/112, 179/99, 185/101,, 191/101

Follow-up BPs (on 1 medication- clonidine patch 0.2mg every 7 days)
Office BPs 163/107, 165/104, 164/107

24hr Ambulatory
Mean daytime 149/99
Mean night time 146/95