Renal Denervation Therapy: Anxiolytic for nervous kidneys

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OBJECTIVES
• Outline problem of hypertension and treatment resistance
• Introduce renal denervation therapy (RDN) and evidence for its use
• Potential future indications for RDN (other disorders with ‘nervous’ kidneys)
• Intersperse with clinical scenarios
Patient

- 73 y.o. male
- Referred for HTN management
- Multiple CV risk factors
  - Type II DM
  - Dyslipidemia
  - Sedentary
  - 20+ year history of HTN
  - CKD - creatinine 160 - 200umol/L
Initial Assessment

- Adherent with 8 medications: Acebutolol 400mg bid, Doxazosin 16mg qhs, Verapamil MR 240mg od, Clonidine 0.2mg tid, Enalapril 20mg bid, HCTZ 25mg od, Losartan 100mg od, Aliskiren 300mg od.

- BP 180/110 - repeated testing

- Rest of examination normal
What would you do?

A. Refer for further investigation to R/O secondary causes
B. Refer for RDN
C. Add spironolactone
D. All of the above
Hypertension

• Major healthcare burden
• Causative risk factor:
  • stroke, ischemic heart disease, CHF, CKD
• Increased mortality rates
  • Cardiovascular and all cause
• Affects 25% of global population
• Responsible for 7,000,000 p.a. (13% of global mortality)

WHO. Global health risks: Mortality and burden of disease attributable to selected major risks. 2009:1-62
Hypertension

- Increasingly recognised problem
- Recent Canadian study
  - 26 million Canadians over nine-year period
  - ↑ prevalence from 12.5% to 19.6%
  - Higher all-cause mortality in patients with HTN (HR 1.9-4.2)

Resistant Hypertension

- Recognised for some time
  - Gifford & Tarazi (1978): “the failure to control blood pressure adequately (arbitrarily <150/100 mmHg) with a good regimen, provided that medications are taken as prescribed”
- Recent tightening of definition
  - Above-target BP despite compliance with three different anti-hypertensive agents - at adequate dosage and including a diuretic
Resistant Hypertension

- Increasingly recognised as a problem
- Incidence 1.9% in newly diagnosed hypertensives after 1.5 years treatment
- Prevalence up to 15% hypertensive patients
- Poor prognosticator
  - After 3.8 years, presence of RH associated with increased risk of adverse events (HR 1.47, 95% CI, 1.33-1.62,

Secondary Hypertension
Causes to be excluded

- Renovascular disease
- Hyperaldosteronism
- Glucocorticoid excess
- Phaeochromocytoma
- Hyperthyroid/parathyroid
- Obstructive sleep apnea
- Medications (illicit/prescribed
- Aortic coarctation
- Renal parenchymal disease

Calhoun et al. Hypertension. 2008;51:1403-1419
Renovascular Disease

- 43y.o. male
- Dyslipidemic, smoker, +ve FHx CAD
- Approx 3 year history ↑BP
- Persisting despite increasing numbers/doses anti-hypertensives
- 3x admissions with hypertensive crises and symptoms CHF
- Duplex USS of renal arteries
  - Inconclusive due to body habitus
- Referred for consideration of RDN
Anatomic suitability
Further Evaluation

Captopril MAG3 Scan

Right Kidney - 82% uptake
Left - 18% uptake
Hyperaldosteronism

• 5-12% of patients with presumed essential hypertension, 23-26% of patients with resistant hypertension
• Patients tend to be normokalemic
• Spironolactone is useful adjunct in patients with resistant hypertension
Sympathetic Activity in HTN

Esler et al, Clin Exp Hypertens 1989
Renal Sympathetic Innervation

- Ipsilateral paravertebral sympathetic ganglia T11 - L3
- Enter the kidneys with the renal arteries and spread through the parenchyma following the blood vessels
Renal Sympathetic Innervation

Cutting of the greater splanchnic nerve resulted in the ureter becoming distended with urine....

Stimulation of the ends of the greater splanchnic nerve and urine flow ceases”

Claude Bernard 1859
SYMPATHECTOMY IN THE TREATMENT OF HYPERTENSION
REVIEW OF 122 CASES

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Renal Arteries as Therapeutic Target

- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Less invasive
  - Built-in safety algorithm
**Initial Cohort – Reported in the Lancet, 2009:**
First-in-man, non-randomized
Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- 12-month data

**Expanded Cohort* – This Report (Symplicity HTN-1):**
Expanded cohort of patients (n=153)
36-month follow-up
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age (years)</th>
<th>57 ± 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Race (% non-Caucasian)</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus II (%)</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>CAD (%)</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>83 ± 20</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BP (mmHg)</td>
<td>176/98 ± 17/15</td>
<td></td>
</tr>
<tr>
<td>Number of anti-HTN meds (mean)</td>
<td>5.1 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Aldosterone blocker (%)</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Direct Renin Inhibitor</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Centrally acting sympatholytic (%)</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Vasodilator (%)</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Alpha-1 blocker</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>
Symplicity HTN1 - Results to 3 years

BP change (mmHg)

P<0.01 for ∆ from BL for all time points

Systolic BP
Diastolic BP
Responder was defined as an office SBP reduction ≥ 10 mmHg

<table>
<thead>
<tr>
<th>Time (Mo)</th>
<th>1 Mo</th>
<th>2 Mo</th>
<th>3 Mo</th>
<th>4 Mo</th>
<th>5 Mo</th>
<th>6 Mo</th>
<th>7 Mo</th>
<th>8 Mo</th>
<th>9 Mo</th>
<th>10 Mo</th>
<th>11 Mo</th>
<th>12 Mo</th>
<th>13 Mo</th>
<th>14 Mo</th>
<th>15 Mo</th>
<th>16 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>69%</td>
<td>74%</td>
<td>71%</td>
<td>79%</td>
<td>81%</td>
<td>90%</td>
<td>92%</td>
<td>100%</td>
<td>100%</td>
<td>92%</td>
<td>90%</td>
<td>81%</td>
<td>79%</td>
<td>71%</td>
<td>74%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Symplicity HTN-2

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2

Inclusion Criteria:
- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:
- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m² (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

• Treatment-resistant HTN population
• BL OBP 178/97 mmHg
• 49 RDN, 51 Control
• Age 58 years
• BMI 31 kg/m²
• 40% with Diabetes
• eGFR 77*
• Avg # meds 5.2
• RDN and Control groups generally well-matched
### Baseline Medications

<table>
<thead>
<tr>
<th></th>
<th>RDN (n=52)</th>
<th>Control (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Anti-HTN medications</td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>% patients on HTN meds &gt;5 years</td>
<td>71%</td>
<td>78%</td>
<td>0.51</td>
</tr>
<tr>
<td>% percent patients on ≥5 medications</td>
<td>67%</td>
<td>57%</td>
<td>0.32</td>
</tr>
<tr>
<td>% patients on drug class:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>90%</td>
<td>94%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Direct renin inhibitor</td>
<td>15%</td>
<td>19%</td>
<td>0.60</td>
</tr>
<tr>
<td>Beta-adrenergic blocker</td>
<td>83%</td>
<td>69%</td>
<td>0.12</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>79%</td>
<td>83%</td>
<td>0.62</td>
</tr>
<tr>
<td>Diuretic</td>
<td>89%</td>
<td>91%</td>
<td>0.76</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>17%</td>
<td>17%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>15%</td>
<td>17%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Alpha-1 adrenergic blocker</td>
<td>33%</td>
<td>19%</td>
<td>0.12</td>
</tr>
<tr>
<td>Centrally acting sympatholytic</td>
<td>52%</td>
<td>52%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>
Symplicity HTN2 - extended follow up

Primary Endpoint (6M post Randomisation)

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

Latest Follow-up (12M post Randomisation)

- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥160 mmHg at 6 M)
- p<0.01 for Δ from baseline
- p<0.01 for difference between RDN and Control
‘Nervous’ Kidney Disorders

- Hyperglycemia
- Obstructive sleep apnea
- Congestive heart failure
- CKD - hemodialysis
Sympathetic Activity in Human Heart Failure

Nasking et al. Circulation 1985
St. Michael’s Experience

- Resistant hypertension clinic established
- Input from cardiology/nephrology
- Patients undergo thorough evaluation
  - 24hr ABPM
  - Imaging - renal/cardiac MRI
- Approximately 20-25% of those referred go forward to RDN
St. Michael’s Experience

- Province-wide study
- Efficacy, economic evaluation
- Early versus delayed RDN
- Co-ordinated through Applied Health Research Centre
- Imminently enrolling patients
Recent assessment

Now on 5 medications - stopped aliskiren, doxazosin, enalapril

Recent office BP - 134/80 (lowest recorded BP in >10 years)
Summary

- Hypertension is becoming commoner and is a major healthcare burden
- Resistant hypertension is increasingly recognised and is associated with worse outcomes
- Renal sympathetic overactivity is implicated in HTN (and other common conditions)
- Percutaneous attenuation of renal sympathetic activity is possible and offers an effective treatment option for patients with resistant hypertension
Thank you

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  - Tel: 416-864-5846/5399
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