Renal Denervation

Henry Krum MBBS PhD FRACP

Centre of Cardiovascular Research & Education in Therapeutics, Monash University/Alfred Hospital;

Alfred Heart Centre, The Alfred Hospital, Melbourne Australia
Background

- Hypertension, heart failure & chronic kidney disease represent a significant, growing & interdependent global health issue

- A characteristic common to these three disease states is chronic activation of the sympathetic nervous system, especially the renal sympathetic nervous system (SNS)

- Chronic activation of the SNS is a maladaptive response that drives the progression of these disease states

- Reducing over-activity of the SNS, and/or its sequelae, has long been a primary target of pharmaceutical therapy
Interrelationship of Heart & Kidney Disease

- Hypertension
- Chronic Kidney Diseases
- Heart Failure Syndromes
- Chronic Sympathetic Activation
Sympathetic Nervous System

Afferent

Efferent
Patients cannot develop and/or maintain elevated BP without renal involvement.
Chronic Effect of ↑ SNA

↑ Neurohormones
↑ Wall Thickness
↓ Compliance
Atherosclerosis

↑ Blood Pressure
Hypertrophy
Ischemia
Arrhythmia
Heart Failure
Worsening HF

↓ GFR
Ischemia
Kidney Failure
Worsening Kidney Failure
↑ Renal Afferent Nerve Activity

↑ Neurohormones

↑ Blood Pressure

↑ Vasoconstriction

Amplifies central, or systemic, sympathetic outflow

Kidney impairment, or dysfunction, ↑ afferent activity

↓ RBF/GFR

↑ Renin

↑ Na⁺/Volume

↓ Ang II

Aldo
Renal Denervation

↑ Neurohormones

↑ Blood Pressure

Disrupt the renal nerves, break the cycle

Simultaneously reduce both efferent & afferent effects
Established Physiology of Renal Sympathetics

- Renal sympathetic efferent & afferent activity elevated in:
  - Essential hypertension
  - Chronic kidney disease
  - Heart failure
- Efferent sympathetic activation mediates:
  - RAAS activation
  - Fluid retention
  - Reduced renal blood flow
- Afferent sympathetic activation mediates:
  - LVH
  - Arrhythmogenesis
  - Systemic hypertension
Renal Denervation in Animal Models of Hypertension

• Reduced blood pressure in:
  ▪ Salt sensitive swine
  ▪ SHR genetically hypertensive rats
  ▪ Two-kidney one-clip Goldblatt hypertension
  ▪ One-kidney renal hypertension

• Prevented or abolished hypertension in:
  ▪ Canine obesity model hypertension
  ▪ Low-birth weight rats
Renal Denervation in Animal Models of Heart Failure

- Reduced or abolished sodium retention in:
  - Rats with cirrhosis
  - Rats with heart failure
  - Dogs with AV fistula
  - Dogs with compensated high output heart failure

- Improved ventricular function in:
  - Rats with myocardial infarction
Effect of Renal Denervation in SHR Rats
Effect of Renal Denervation in SHR Rats

SYSTOLIC ARTERIAL PRESSURE

F-RATIO 9.547 (1, 12)

P < 0.01

mmHg (±SEM)

SHAM-OPERATED SHR (n=7)

RENALE-DENERVATED SHR (n=7)

AGE IN WEEKS

7 8 9 10 11 12 13 14
Sympathectomy in Hypertension: Effects on Survival

Smithwick, R JAMA 1953
Renal Denervation in Obesity Hypertension

![Bar charts showing body weight, arterial pressure, and heart rate over weeks on a high-fat diet.](chart.png)
Renal Denervation in Obesity Hypertension

**Graph: UNaV (mmol/day)**

**Bar Chart:**
- UNaV (mmol/day) for different groups over weeks.

**Line Graph:**
- CUMULATIVE SODIUM RETENTION (mmol) over weeks.

**Legend:**
- HIGH FAT DIET
### Sympathectomy & Cardiac Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Sympathectomy</th>
<th>Beta-blockade</th>
<th>Alpha blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td><img src="image1" alt="Sham" /></td>
<td><img src="image2" alt="Sham" /></td>
<td><img src="image3" alt="Sham" /></td>
<td><img src="image4" alt="Sham" /></td>
</tr>
<tr>
<td>Aortic banding</td>
<td><img src="image5" alt="Aortic banding" /></td>
<td><img src="image6" alt="Aortic banding" /></td>
<td><img src="image7" alt="Aortic banding" /></td>
<td><img src="image8" alt="Aortic banding" /></td>
</tr>
</tbody>
</table>

*Perlini S Hypertension 2005*
Renal Sympathetics as Denervation Target

- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
Anatomy of Renal Artery

- Nerves
- Lumen
- Endothelium
- Media
- Adventitia
- Fat
Therapeutic Renal Denervation

- Ardian, Inc. has developed a catheter-based procedure to therapeutically denervate the kidneys
- Procedure accesses and disrupts the renal nerves via the renal arteries
- A 40-minute outpatient procedure performed in the cardiac cath lab by an interventional cardiologist
- Both the procedure and the effect of therapeutic renal denervation are under evaluation for the treatment of hypertension, heart failure & CKD
Preclinical Experience

- **Safety**
  - Swine model with angiography, gross pathology, histopathology & clinical pathology at 7, 30, 60 & 180 days
  - Intact endothelium by 7 days
  - Vascular architecture & integrity preserved at all follow-up points
  - Vascular healing observed at 30 days, complete in some by 60 days
  - No renal artery stenosis out to 180 days
Preclinical Experience

Effectiveness

- Renal norepinephrine levels were assayed in swine in the following groups:
  - Untreated control (N=24)
  - Catheter-based denervation (N=33)
  - Open surgical denervation (N=4)

![Graph showing norepinephrine levels in different groups with p-values ]
Human Feasibility Trials

- Feasibility trials underway in Australia & Europe in patients with refractory hypertension

  - Objectives:
    - Safety – confirm preclinical experience
    - Evidence of denervation (direct renal NE spillover, muscle sympathetic nerve activity)
    - Evidence of a physiologic effect (BP reduction, LVH regression, HOMA, HRV)

  - Follow-up visits at 3 days, 30 days, 3 months, 6 months, 9 months, and 1 year post-procedure
Preliminary Feasibility Results: Safety

- No adverse renal events
  - No change in sCr or eGFR at any point in follow-up
- No electrolyte disturbances at any point in follow-up
- No vascular abnormalities at 1, 3, 6, or 9 months post-procedure
- No adverse acute or chronic hemodynamic events
Preliminary Feasibility Results: Denervation

- Success in renal denervation demonstrated by:
  - Direct measures of renal NE spillover
  - Muscle sympathetic nerve activity pre-procedure and 5 months post-procedure
Clinical results are to be reported soon, however, a single patient is presented as illustration of the potential impact of this therapeutic strategy....
Renal Denervation Case Study

- 63 year old male
- History of hypercholesterolemia, cigarette smoking
- Chronic hypertension uncontrolled by numerous drugs & drug combinations
- No renovascular disease found on imaging
Representative Therapeutic Renal Denervation Patient

Minoxidil dose reduced after 1 Month visit

SBP

DBP

Minoxidil dose reduced after 1 Month visit
Therapeutic Renal Denervation

Conclusions

- We have successfully denervated the human kidney with an intravascular procedure.
- Renal denervation has a substantial physiological effect, consistent with the substantial animal preclinical literature, and human surgical precedent literature.
- A novel catheter-based strategy, without permanent implantation is being explored for applications in:
  - Hypertension
  - Heart failure
  - Chronic kidney disease