Transcatheter Renal Denervation for Refractory Hypertension: Current Understanding and Future Projections

Horst Sievert, Ann-Kathrin Ziegler, Benjamin Kaltenbach, Ilona Hofmann, Undine Pittl
CardioVascular Center Frankfurt, Frankfurt, Germany
The Renin-Angiotensin-System

Renal Sympathetic Efferent Nerves

Kidney as the recipient of central sympathetic signals

Renal efferent nerves

Renin release ↑
NaCl-retention ↑
Renal blood flow ↓
Renal Afferent Nerves

Kidney as the origin of central sympathetic drive

Vasoconstriction
Arteriosclerosis

Hypertrophy
Arrhythmia
O₂ consumption
Heart failure

Renal afferent nerves

Insulin Resistance ↑

Renin- release ↑
NaCl-retention ↑
Renal blood flow ↓
The central sympathetic drive is directly influenced by the kidneys via afferent renal nerves. The interruption of these nerves lowers blood pressure and may have other beneficial effects.
Surgical Precedent of Renal Denervation: Thoracolumbar Sympathectomy
Sympathectomy in Hypertension: Effects on survival, but side effects and complications

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

Smithwick RH, J Am Med Assoc. 1953;152:1501-1504
How to do this minimal invasively by catheter technique?
The Renal Nerves

- Follow the renal artery to the kidney
- Primarily lie within the adventitia
Generator

- Energy maximum 8 Watt
- It automatically switches off if
  - temperature increases too fast or too slowly
  - temperature is higher than 75 °C
  - Impedance does not decrease sufficiently
Simplicity™ Catheter

- Radiofrequency electrode tip
- Handle allows bending of the tip and rotation
- Compatible with a 6 F guiding catheter
Procedural details

• Premedication
  - Aspirin 100 mg/day (to be continued for 1 week)
  - 10-20 mg morphin + sedatives
  - 5,000 U heparin
  - Nitro i.a.
• 6 F femoral sheath
• 6 F renal guiding catheter
• Angiography of all renal arteries
• Introduce radiofrequency catheter
• 4-8 ablations, 2 min each
Treatment Strategy

- Focal ablations
  spaced along vessel

- Multiple focal ablations
  ↑ circumferential coverage
TREND 2012 ASIA-PACIFIC
SEPTEMBER 29, 2012 | HONG KONG

Neuro-Humoral Interventions
Catheter and Device Based Treatment of Hypertension and Heart Failure
Transcatheter Renal Denervation

www.csi-trend.org

TREND Frankfurt, Germany, Frankfurt, March 1-2. 2013
Where is the evidence?
Symplicity HTN-1 Trial
single arm
with extended cohort

Symplicity HTN-2 Trial
randomized

Symplicity HTN-3 Trial
randomized, sham control
ongoing
Symplicity HTN-2

THE LANCET

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


• **Study design:** randomized, controlled, clinical trial
• **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
• **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand
Symplicity HTN-2 Trial

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

Exclusion Criteria:
- 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

Safety

- No serious device or procedure related adverse events (n=52)
- No change in renal function
- No severe hypotension or orthostasis
- Minor adverse events (all unrelated to RF)
  - 1 femoral artery pseudoaneurysm → manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 6-month renal imaging (n=43)
  - No vascular abnormality at any RF treatment site
  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy)

Primary Endpoint: 6-Month Office BP

- **RDN (n=49)**
  - Systolic: -32 mmHg
  - Diastolic: -12 mmHg

- **Control (n=51)**
  - Systolic: 1 mmHg
  - Diastolic: 0 mmHg

**difference between RDN and Control highly significant (p<0.0001)**

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

How does this compare to medical treatment?
Randomized Trials in Resistant Hypertension

Mean Reduction in Systolic BP

- Darusentan\(^2\)
  - 12mmHg

- Spironolactone\(^3\)
  - 16mmHg

- ISMN + Sildenafil\(^4\)
  - 22mmHg

- Renal Denervation\(^1\)
  - 32mmHg

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\(^1\) Lancet. 2010
\(^3\) Hypertension. 2010 Jan;55(1):147-52
Symplicity HTN-2 Trial – Distribution of Office SBP Post-RDN

Treated with RDN

Crossover group Treated after 6 M follow up

- Baseline RDN
- 6 M RDN
- 12 M RDN

- Baseline
- Pre-RDN
- 6 M post-RDN

- ≥180 mmHg
- 160-179 mmHg
- 140-159 mmHg
- <140 mmHg
Subgroup analyses

- Age
- Gender
- Diabetes

→ no differences
Any late complications?
HTN-1: Chronic Safety Out to 3 Years

- One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- One new moderate stenosis which was not hemodynamically relevant and no treatment
- 3 deaths within the follow-up period; all unrelated to the device or therapy
- No hypotensive events that required hospitalization
- There were no observed changes in mean electrolytes or eGFR

What is the time course of the effect?
Symplicity HTN-2
Time Course of Office BP Change

RDN
△ from Baseline (mmHg)

Control
△ from Baseline (mmHg)

1M 3M 6M 12M
-20 -7 ††† -8 ††† -12 † -10
-24 † -32 † -28

† p<0.0001 for between-group comparisons
†† p=0.002 for between-group comparisons
††† p=0.005 for between-group comparisons
Two-way repeated measures ANOVA, p=0.001

Symplicity HTN-1
Significant, Sustained BP Reduction through 3 yrs

BP change (mmHg)

P<0.01 for ∆ from BL for all time points

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Symplicity HTN-1
Change in Office Blood Pressure for 24 Pts with 3 yrs Follow-up

BP change (mmHg)

-19
-23
-31
-31
-33
-33
-33

1 M (n=18)
3 M (n=24)
6 M (n=24)
12 M (n=22)
18 M (n=23)
24 M (n=22)
30 M (n=12)
36 M (n=24)

Systolic BP
Diastolic BP

P<0.01 for Δ from BL for all time points

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Distribution of SBP Change at BL, 1, 12, 24, and 36 Months

- Baseline (N=150)
- 1 Month (N=143)
- 12 Months (N=130)
- 24 Months (N=59)
- 36 Months (N=24)

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Percentage Responders Over Time

Responder was defined as an office SBP reduction ≥10 mmHg
.... and the future?
Does it work in less severe resistant hypertension?
Renal Denervation in Borderline Hypertension - Mean Office BP

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<th>20</th>
<th>40</th>
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<td>83.0</td>
<td>82.4</td>
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- Systolic (mmHg)
- Diastolic (mmHg)
Other potential indications

- Sleep apnea syndrome
- Heart failure
- Ventricular arrhythmias
- Diabetes
Impact of Type 2 Diabetes Mellitus on Sympathetic Neural Mechanisms in Hypertension

Robert J. Huggett, MD, DS; Eleanor M. Scott, DM, DS, MD; Stephen G. Gilbey, DA, MD; John B. Stoker, BSc, MB, ChB; Alan F. Mackintosh, MA, MD; David A.S.G. Mary, MB, ChB, PhD

F. Mahfoud et al, Trend Asia Pacific, 2011

RD improves insulin sensitivity

F. Mahfoud et al, Trend Asia Pacific, 2011
RD improves glucose tolerance

Glucose tolerance test, 75 g glucose per os

Renal denervation

3 months

-9
-27*

60-min glucose level
120-min glucose level

*significant reduction (p<0.05)
compared to baseline

F. Mahfoud et al, Trend Asia Pacific, 2011
New Devices for Renal Denervation
Balloons with radiofrequency

Maya Medical

Vessix Vascular
Other radiofrequency techniques

- St. Jude Medical
- Cordis
- ....
Balloon with needle

Bullfrog® Micro-Infusion Catheter

- Low pressure balloon (2 atm)
- Deploys micro-needle into the adventitia
- Allows drug delivery to renal sympathetic nerve sheath
  - Guanethidline
- Catheters available for >2 mm arteries

Mercator Medsystems
Ultrasound

- Recor Medical
- CardioSonic
- Sound Interventions
- Kona
Radiation

- Best Medical International
Take Home Messages

• Trans-catheter Renal Denervation results in significant reductions in BP
• With the Ardian-Medtronic system, no major complications occurred
• TRenD is beneficial for patients with treatment-resistant essential hypertension
• The effect is sustained up to 3 years
• It may also be beneficial in patients with diabetes, heart failure and other diseases
• New devices are on the horizon