Renal Artery Denervation

New Concepts in Hypertension Treatment

Istanbul Course of Interventional Cardiology

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Medizinische Klinik II – Kardiologie, Angiologie und internistische Intensivmedizin

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Conflict of Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship          Company
Honoraria for lectures                  Medtronic, Astra
Honoraria for advisory board activities  Medtronic, Actelion
Concepts in Hypertension Treatment

„The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it“

Hay J., Brit Med J 1931
Prevalence of Hypertension

In 2000, 972 million (26%), of the adult population had hypertension.

By year 2025, 1.56 billion (29%) are projected to have hypertension.

Source: High Blood Pressure and Health Policy, 2005
Renal Nerves and the SNS

**Efferent Nerves**

Sympathetic signals from the CNS modulate the physiology of the kidneys

**Afferent Renal Nerves**

The kidney is a source of central sympathetic activity, sending signals to the CNS

Renal Sympathetic System
Surgical treatment of hypertension

- Onset of hypertension 3 years previously with toxemia of pregnancy, severe headaches, nausea and vomiting, blurred vision, complete incapacitation, confined to bed
- Systolic blood pressure:
  - 280 mmHg
  - 135 mmHg
  - 144 mmHg
  - 140 mmHg
  - 140 mmHg

- Diastolic blood pressure:
  - 110 mmHg
  - 110 mmHg
  - 106 mmHg
  - 96 mmHg
  - 90 mmHg

- Maximum concentration:
  - 1.034
  - 1.029
  - 1.027
  - 1.028
  - 1.026

- Urea clearance (%):
  - 87%
  - 85%
  - 73%
  - 77%
  - 75%

- Time (years):
  - OPR. 1 2 3 4 5 6 7 8 9 10 11 12 13
  - 85%
  - 85%
  - 10.5%
  - 94%

Peet et al., Am J Surg 1948
Renal Denervation – The Therapeutic Principle

Energy is transmitted through the artery wall, disabling the renal nerves.
Renal Angiogram – Eligible Anatomy

1. Absence of flow-limiting obstructions and significant disease
2. Vessel diameter ≥ 4 mm in targeted area
3. Absence of renal stents, or aortic grafts

Aug-13/9
Delivering the Symplicity Catheter

Use the catheter shaft (not handle) to position catheter within vessel

Position electrode ≥5 mm proximal to bifurcation
Symplicity Catheter: Handle Features

- Deflect tip by pulling lever towards back of handle
- Straighten tip by pushing lever towards front of handle
- Handle rotator has tactile “click” every 45 degrees
Optimizing Wall Contact

Sufficient Wall Contact

Excessive Wall Contact
(avoid distending vessel wall with electrode)
Repeat for Additional Treatment Sites

Initial treatment location

≥5 mm (approximately 3 electrode lengths)

Secondary shaft marker

New treatment location
- Areas to Avoid

- Avoid small branch arteries, such as those perfusing the adrenal glands
- Avoid treating areas of visible disease
- There is no clinical experience treating in vessels with renal artery aneurysms
→ Symplicity: Staged Evaluation in Hypertension and Beyond

Symplicity HTN-1²

First-in-Man¹ ✓

Series of Pilot Studies ✓

Symplicity HTN-2³ ✓
EU/AU Randomized Clinical Trial

USA
Symplicity HTN-3: US Randomized Clinical Trial (upcoming)

EU/AU
Other Areas of Research: Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

Symplicity HTN-2  Key Inclusion/Exclusion Criteria

- **Inclusion Criteria**
  - >18 years of age
  - Elevated office systolic blood pressure (SBP) ≥160 mm Hg
  - ≥3 antihypertensive medications (including 1 diuretic)

- **Exclusion Criteria**
  - Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m²
  - Type 1 diabetes mellitus
  - Known secondary cause of hypertension other than sleep apnea or chronic kidney disease
  - Significant renovascular abnormalities
### Symplicity HTN-2 Patient Disposition

#### Assessed for Eligibility (n=190)
- Excluded prior to randomization (n=84)
  - SBP <160 mm Hg after 2 weeks of compliance confirmation (n=36)
  - Ineligible anatomy (n=30)
  - Declined participation (n=10)
  - Other exclusion criteria discovered after consent (n=8)

#### Randomized (n=106)
- Allocated to RDN (n=52)
  - No 6-month primary endpoint visit (n=3)
    - Withdrew consent (n=1)
    - Missed visit (n=2)
- Allocated to Control (n=54)
  - No 6-month primary endpoint visit (n=3)
    - Withdrew consent (n=2)
    - Missed visit (n=1)

#### Analysis
- Analyzed (n=49)
- Analyzed (n=51)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>BP</th>
<th>RDN Group (n=52)</th>
<th>Ctr Group (n=54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline SBP ± SD (mm Hg)</td>
<td>178 ± 18</td>
<td>178 ± 16</td>
<td>0.97</td>
</tr>
<tr>
<td>Mean baseline DBP ± SD (mm Hg)</td>
<td>97 ± 16</td>
<td>98 ± 17</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean number of antihypertensive medications ± SD</td>
<td>5.2 ± 1.5</td>
<td>5.3 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>89</td>
<td>91</td>
<td>0.76</td>
</tr>
<tr>
<td>Aldosterone blocker (%)</td>
<td>17</td>
<td>17</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>96</td>
<td>94</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Direct renin inhibitor (%)</td>
<td>15</td>
<td>19</td>
<td>0.80</td>
</tr>
<tr>
<td>Beta-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>Centrally acting sympatholytic (%)</td>
<td>52</td>
<td>52</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 blocker (%)</td>
<td>33</td>
<td>19</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Symplicity HTN-2 Primary Endpoint

- 84% of patients in the RDN group had ≥10 mm Hg reduction in SBP
- 10% of patients in the RDN group had no reduction in SBP

*P<0.0001 for SBP and DBP vs. Ctr.
Summary and Conclusion

- Renal sympathetic nerves are a major contributor to the pathophysiology of hypertension.
- RDN represents a novel and effective approach to the management of hypertension in pts. refractory to conventional pharmacological therapy.
- So far no serious complications have been described.
- Long term results are warranted.
- Future trials need to address the effectiveness of RDN in milder forms of essential hypertension.
The Symplicity Catheter
Guide Catheter Selection

Typical: RDNC1 or RDC-1

Alternate: IMA or LIMA
Symplicity Catheter Tip Features

Flexible Tip (self-orienting)

Deflectable Shaft

5 mm

12 mm
Histology (HE staining)
Ultraschalltechnologie – *Paradise Catheter*®
Ballon-basiertes Mulitelektroden System - Vessix®
Mikroinjektionskatheter - *Bullfrog®*
The Effective Dose Calculated from DAP Measurements\(^1\)

<table>
<thead>
<tr>
<th>Group</th>
<th>DAP (Gycm(^2))</th>
<th>Effective Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (coronary angiography)</td>
<td>35.14 ± 0.99</td>
<td>9.13 ± 0.26</td>
</tr>
<tr>
<td>Group 2 (elective PCI)</td>
<td>74.57 ± 4.21(^*)</td>
<td>19.40 ± 1.10(^*)</td>
</tr>
<tr>
<td>Group 3 (emergency PCI)</td>
<td>90.46 ± 4.82(^{**+})</td>
<td>23.5 ± 1.25(^{**+})</td>
</tr>
<tr>
<td>Group 4 (RDN)</td>
<td>48.78 ± 4.56(^*)</td>
<td>12.68 ± 1.18(^*)</td>
</tr>
</tbody>
</table>

\(^*\) p<0.05 vs. Group 1, \(^+\) p<0.05 vs. Group 2 (ANOVA)

\(^1\) conversion coefficients (DCC=Dose conversion coefficient): 0.26

fluoroscopy time (FT); radiation exposure (dose area-product; DAP)
Effective Dose Estimates in Comparison

- RDN: 12 mSv
- PCI: 19 mSv
- Coronary angiogram: 9 mSv
- Thallium stress test: 25 mSv
- CT chest: 7 mSv
- Coronary CT: 1 mSv
- Radon at home: 3.20 mSv
- Round-trip-flight: 0.03 mSv
- Chest X-ray: 0.02 mSv

Kaufmann and Knuuti E Heart J 2011;32:269-71
Pathophysiology of Therapy-Resistant Hypertension

- Inappropriately high sympathetic outflow
- Variable patterns of cardiac output
- Vasoconstriction due to multiple mediators
- Abnormal renal salt/water handling
- Inappropriately high aldosterone and/or plasma renin activity
- Variable patterns of vasoconstriction and venous return
→ Sympathetic Effects at the Kidney

JGGC = juxtaglomerular cells

\[ \text{RSR} \quad \beta_1 - \text{AR} \]

\[ \text{U}_{\text{Na}} \quad \alpha_{1B} - \text{AR} \]

\[ \text{RBF} \quad \alpha_{1A} - \text{AR} \]

T = tubular epithelial cells

V = renal vessels

Management of Hypertension

- Lifestyle
- Medications