CATHETER-BASED RENAL DENERVATION INCREASES INSULIN SENSITIVITY AND IMPROVES GLUCOSE METABOLISM IN PATIENTS WITH RESISTANT HYPERTENSION

F. Mahfoud, Ch. Ukena, B. Cremers, I. Kindermann, M. Kindermann, P. A. Sobotka, M. Schlaich, M. Böhm

Klinik für Innere Medizin III
Kardiologie, Angiologie und Internistische Intensivmedizin
Universitätsklinikum des Saarlandes
Direktor: Prof. Dr. med. M. Böhm
Disclosures

• The presenter declares that his institution has received scientific grants from ARDIAN Inc.
Background

• Sympathetic hyperactivity links resistant hypertension to insulin resistance
  – Sympathetic hyperactivity directly mediates vascular resistance
  – Increases of vascular resistance shifts blood flow from striated muscle to visceral tissue
  – Visceral tissue is less insulin sensitive than striated muscle

• Catheter-based renal denervation has been shown to reduce central sympathetic drive
Hypothesis

• Reduction of central sympathetic drive by renal denervation should improve insulin sensitivity and glucose metabolism
Methods

• 36 sequential patients with resistant hypertension referred for consideration of therapeutic renal denervation
  – 25 patients → renal denervation
  – 11 patients → control

• Measurements at baseline and 1, 3 and 6 months
  – fasting glucose, insulin, C-peptide, oral glucose tolerance test
  – Calculation of HOMA-IR
Inclusion and exclusion criteria

• **Key inclusion criteria**
  – Office blood pressure $\geq 160$ mmHg despite $\geq 3$ anti-hypertensive medications
  – eGFR (MDRD formula) $\geq 45$ mL/min/1.73m$^2$

• **Key exclusion criteria**
  – known secondary cause of hypertension
  – Type I diabetes mellitus
  – renovascular abnormalities: significant renal artery stenosis, prior renal stenting or angioplasty, dual renal arteries
Patients characteristics

- n=36 (11 control), age 56.9 ± 10 years
- BMI 31.4 ± 5.5 kg/m²
- Type 2 diabetes on oral medication, n=15
  - None of the patients was on insulin treatment
- HR 71 ± 14 bpm
Patients characteristics

- RR 178/94 ± 16/13 mmHg
- 5.6 ± 1.4 antihypertensive medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Denervation (n=25)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I/ARB</td>
<td>96%</td>
<td>91%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>76%</td>
<td>73%</td>
</tr>
<tr>
<td>CCB</td>
<td>64%</td>
<td>55%</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td>64%</td>
<td>55%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
  - Aldosterone AT      | 36%                | 36%            |

- Patients were instructed not to change any medication
Radio frequency ablation

- Renal arteriography via femoral access
Radio frequency ablation

- Diameter >4 mm
- Length >20 mm
- 5 F LIMA or RDC guiding catheter
Ablations are separated both longitudinally and rotationally (spacing >5 mm)
Sympathetic nerves in adventitia of renal artery in rat

Renal artery, Sprague Dawley rat, tyrosin hydroxylase antibody staining

red: tyrosine hydroxylase, green: α-smooth muscle actin, blue: DAPI
Procedure characteristics

- Procedure time: median 46 min

- \( \leq 6 \) RF ablations up to 2 min (low dose) per artery

- Ablation was accompanied by diffuse visceral abdominal pain limited to the electrical ablation
  - managed by IV morphine and midazolam
  - did not persist beyond the RF energy application
Procedure safety

• No detectable vascular complications at 3 and 6 months
  – Renal duplex ultrasound or MRI

• One access site complication, treated with manual compression without further sequelae

• No changes in renal function
Blood pressure reduction after renal denervation

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (25)</td>
<td>180 ± 14</td>
<td>97 ± 5</td>
</tr>
<tr>
<td>1 month (25)</td>
<td>157 ± 14*</td>
<td>87 ± 11*</td>
</tr>
<tr>
<td>3 months (25)</td>
<td>155 ± 20*</td>
<td>86 ± 11*</td>
</tr>
</tbody>
</table>

*significant reduction (p<0.05) compared to baseline
Blood pressure reduction after renal denervation

92% of patients have BP ↓

<table>
<thead>
<tr>
<th>Time (M)</th>
<th>BP Change (mmHg)</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>-20</td>
<td>-10</td>
<td></td>
</tr>
<tr>
<td>3 M</td>
<td>-24</td>
<td>-11</td>
<td></td>
</tr>
<tr>
<td>6 M</td>
<td>-25</td>
<td>-11</td>
<td></td>
</tr>
<tr>
<td>12 M</td>
<td>-24</td>
<td>-11</td>
<td></td>
</tr>
<tr>
<td>18 M</td>
<td>-25</td>
<td>-15</td>
<td></td>
</tr>
<tr>
<td>24 M</td>
<td>-33</td>
<td>-15</td>
<td></td>
</tr>
</tbody>
</table>

Schlaich M, ESH Oslo 2010
Renal denervation reduces fasting glucose

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting glucose (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Baseline (25/11)</td>
<td>118 ± 20</td>
<td>120 ± 22</td>
</tr>
<tr>
<td>1 month (25/11)</td>
<td>110 ± 14*</td>
<td>132 ± 43</td>
</tr>
<tr>
<td>3 months (25/11)</td>
<td>106 ± 12*</td>
<td>121 ± 21</td>
</tr>
<tr>
<td>6 months (25/11)</td>
<td>105 ± 18*</td>
<td>119 ± 25</td>
</tr>
</tbody>
</table>

*significant reduction (p<0.05) compared to baseline
Renal denervation improves glucose metabolism

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (mU/l)</th>
<th>C-peptide (µg/l)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (25)</td>
<td>118 ± 20</td>
<td>20.7 ± 11.8</td>
<td>6.1 ± 3.6</td>
<td>6.1 ± 4.3</td>
</tr>
<tr>
<td>1 month (25)</td>
<td>110 ± 14*</td>
<td>12.9 ± 7.3*</td>
<td>3.3 ± 1.5*</td>
<td>3.5 ± 1.8*</td>
</tr>
<tr>
<td>3 months (25)</td>
<td>106 ± 12*</td>
<td>11.1 ± 4.8*</td>
<td>3.1 ± 1.1*</td>
<td>2.9 ± 1.3*</td>
</tr>
<tr>
<td>6 months (25)</td>
<td>105 ± 18*</td>
<td>10.5 ± 4.6*</td>
<td>3.2 ± 1.1*</td>
<td>2.7 ± 1.4*</td>
</tr>
</tbody>
</table>

*significant reduction (p<0.05) compared to baseline

HOmeostasisModelAssessment-InsulinResistance (HOMA-IR) = (FPI x FPG)/405
Renal denervation improves glucose metabolism

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (mU/l)</th>
<th>C-peptide (µg/l)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (25)</td>
<td>118 ± 20</td>
<td>20.7 ± 11.8</td>
<td>6.1 ± 3.6</td>
<td>6.1 ± 4.3</td>
</tr>
<tr>
<td>1 month (25)</td>
<td>110 ± 14*</td>
<td>12.9 ± 7.3*</td>
<td>3.3 ± 1.5*</td>
<td>3.5 ± 1.8*</td>
</tr>
<tr>
<td>3 months (25)</td>
<td>106 ± 12*</td>
<td>11.1 ± 4.8*</td>
<td>3.1 ± 1.1*</td>
<td>2.9 ± 1.3*</td>
</tr>
<tr>
<td>6 months (25)</td>
<td>105 ± 18*</td>
<td>10.5 ± 4.6*</td>
<td>3.2 ± 1.1*</td>
<td>2.7 ± 1.4*</td>
</tr>
</tbody>
</table>

*significant reduction (p<0.05) compared to baseline

HOmeostasisModelAssessment-InsulinResistance (HOMA-IR) = (FPI x FPG)/405
Renal denervation improves glucose metabolism

HOmeostasisModelAssessment-InsulinResistance (HOMA-IR) = (FPI x FPG)/405

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (mU/l)</th>
<th>C-peptide (µg/l)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (25)</td>
<td>118 ± 20</td>
<td>20.7 ± 11.8</td>
<td>6.1 ± 3.6</td>
<td>6.1 ± 4.3*</td>
</tr>
<tr>
<td>1 month (25)</td>
<td>110 ± 14*</td>
<td>12.9 ± 7.3*</td>
<td>3.3 ± 1.5*</td>
<td>3.5 ± 1.8*</td>
</tr>
<tr>
<td>3 months (25)</td>
<td>106 ± 12*</td>
<td>11.1 ± 4.8*</td>
<td>3.1 ± 1.1*</td>
<td>2.9 ± 1.3*</td>
</tr>
<tr>
<td>6 months (25)</td>
<td>105 ± 18*</td>
<td>10.5 ± 4.6*</td>
<td>3.2 ± 1.1*</td>
<td>2.7 ± 1.4*</td>
</tr>
</tbody>
</table>

*significant reduction (p<0.05) compared to baseline
Renal denervation improves glucose tolerance

Glucose tolerance test, 75 g glucose per os

Renal denervation

3 months 6 months

-21 -37* -25* -39*

Reduction in glucose level (mg/dl)

*significant reduction (p<0.05) compared to baseline

60-min glucose level
120-min glucose level
Progression of diabetic status

- Progression of diabetic status (GIT $\rightarrow$ DM, new GIT)
  - Renal denervation: 0/25
  - Control: 2/11 (18%)

- Reversal of diabetic status (GIT $\rightarrow$ normal, DM $\rightarrow$ GIT)
  - Renal denervation: 4/25 (16%)
  - Control: 0/11

Glucose intolerance (GIT):
- impaired fasting glycaemia
- impaired glucose tolerance or both
Renal denervation improves glucose metabolism

• Renal denervation significantly reduces insulin, c-peptide, and fasting glucose in resistant hypertensive patients
• Renal denervation improves insulin sensitivity measured by HOMA-IR
• Hypertension treatment with renal denervation reduces the rate of progression to diabetes or to glucose intolerance
Limitations

• The durability of these observations remains to be documented.
• Prospective trials on cardiovascular, renal and retinal consequences of these findings in hypertensives are required:
  – The potential value of insulin reduction as a therapeutic goal of hypertension care.
  – The potential role of renal denervation in the treatment of type two diabetes requires consideration.
Thank you for your attention!

Dr. Felix Mahfoud

Klinik für Innere Medizin III
Universitätsklinikum des Saarlandes
Homburg/Saar, Germany
Tel. +49 6841-16-23000
Fax. +49 6841-16-21415
felix.mahfoud@uks.eu