Blood Pressure-lowering Interventions Beside Renal Denervation
What is on the Horizon?

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Frankfurt, Germany
Blood Pressure-lowering Interventions Beside Renal Denervation

• Deep brain stimulation
• Carotid sinus stimulation
  - electrical
  - mechanical
• Carotid body ablation
• Bladder trigone stimulation
• Vagal nerve stimulation
• Central arteriovenous fistula
Deep brain stimulation

- Minimal invasive neurosurgical intervention
- Used since 50 years, nowadays well established in the treatment of Parkinson disease and other neurological disorders
- Also used for treatment of refractory pain syndromes since 20 years
- Known to decrease BP
- Potentially a very selective stimulation could have a selective effect on BP
Periaqueductal gray stimulation

Ventral PAG
30Hz  2v

Dorsal PAG

Jonathan Hyam, TRENDS 2013
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Baroreflex Activation Therapy (BAT)

The CVRx Implantable Carotid Sinus Modulation System

Kidneys
↓
HR
↑
Vasodilation
↓
Stiffness
↑
Natriuresis
↓
Renin secretion

Carotid Baroreceptor Stimulation

Brain

Autonomic Nervous System
Inhibited Sympathetic Activity
Enhanced Parasympathetic Activity

Heart
↓ HR

Vessels
↑ Vasodilation
↓ Stiffness

Kidneys
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First Generation Lead (Bilateral)

New Generation Lead (Unilateral)

Electrode, implanted at the carotid bulb
BP and Acute Muscle Sympathetic Nerve Activity After 3 Months of Therapy

Heusser et al., J Hypertens 2009;27(suppl):S288
Barostim has entered the ESH/ESC guidelines as an option to treat resistant hypertension.

### 2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

**Authors/Task Force Members:** Giuseppe Mancia (Chairperson) (Italy)*, Robert Fagard (Chairperson) (Belgium)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redon (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis MiguelRuiloa (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viligimaa (Estonia), Bernard Waebber (Switzerland), Faiez Zannad (France)

### Therapeutic strategies in patients with resistant hypertension

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In resistant hypertensive patients it is recommended that physicians check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists.</td>
<td>IIa</td>
<td>B</td>
<td>604, 606, 607, 608</td>
</tr>
<tr>
<td>In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.</td>
<td>IIb</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>It is recommended that the invasive approaches are considered only for truly resistant hypertensive patients with clinic values ≥160 mmHg SBP or ≥110 mmHg DBP and with BP elevation confirmed by ABPM.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

*ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

*aClass of recommendation.

*bLevel of evidence.

*cReference(s) supporting levels of evidence.
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MobiusHD concept

- Implant placed in the carotid sinus
- It passively amplifies the signal generated by the baroreceptors surrounding the carotid sinus
  - thereby signaling the Central Nervous System to lower blood pressure.
Mechanism of Action

- MoebiusHD reshapes the artery to a non-circular cross section
- This increases the rate of change and amplitude of the vessel movement
- This leads to higher and more frequent afferent signaling to the central nervous system

- Fadali 1969
- Bagshaw 1987
- McKevitt 2003
Case Example

- Female 53 years
- L 168 cm W 84 kg  BMI 29.7
- CRF: AHT, nicotine

- Blood pressure range (official office cuff readings):
  - Inclusion BP: 183/126 mmHg
  - ABPM 178/118 mmHg
  - Medication: labetalol, valsartan, HCTZ, amlodipine, furosemide, spironolacton 2dd 50 mg

- 2010 Renal Denervation with no effect
Device Implantation

PRE

POST

Jan van der Heyden, TRENDS 2014, Frankfurt
Case Example

Daily blood pressure monitoring prior to implantation

Daily blood pressure monitoring after implantation

Jan van der Heyden, TRENDS 2014, Frankfurt
Results Summary:
Mean Office 24hr Blood Pressure Reduction

24 Hr Ambulatory Blood Pressure Reduction - All Patients -

Day 90 (n=6)

Day 180 (n=3)

4 out of 10 patients Required Reduction In Medications

Blood Pressure (mmHg)

-25

-15

-10

-5

0

SBP - ABPM  DBP - ABPM
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What is the Carotid Body?

- A small cluster of cells with chemoreceptors
- located near the carotid bifurcation
- It detects changes in
  - the partial pressure of oxygen and carbon dioxide,
  - pH,
  - Temperature
- Activation of the carotid body increases ventilation and blood pressure
Preclinical data: Additive effect of CSDN and RDN irrespective of the sequence

FD McBryde, AP Abdala, EB Hendy, W Pijacka, P Marvar, DJA Moraes, PA Sobotka, JFR Paton
Nature Communications 2013
Human Carotid Body Denervation

- Surgical proof of principle trial is underway
  - NCT01745172
- Non surgical device development by Cibiem, Inc.
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Bladder Trigone Stimulation

- Stimulation of the bladder
- Reduces sympathetic activity
Bladder Trigone Stimulation Effect on Renal Blood Flow (RBF) and Mean Arterial Pressure (MAP)

Nephera Ltd., Caesarea, Israel
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Vagal nerve stimulation

• Baroreceptors located in the aortic arch send their information to the brainstem via the vagal nerve
• Access to the vagal nerve may be easier and less risky than approaches to the carotid sinus or to the aortic arch directly
• However, stimulation of the vagal nerve may cause side effects like bradycardia and bradypnea
• Techniques for selective stimulation of baroreceptive fibers of the vagal nerve are needed and currently developed
MAP and heart rate during vagal nerve stimulation
The bars indicate the stimulus time

Baroreceptive electrode
The respiration rate of the rat is represented by the oscillation of the BP

Non-baroreceptive electrode
Heart rate decreases and respiration stops during stimulation

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Can arteriovenous fistula decrease blood pressure?

- Arteriovenous fistula are used since decades as access for hemodialysis
- Prof. G. Schäfer, chief of nephrology and my first boss to our vascular surgeon:
  "Please make the fistula big enough to decrease blood pressure"
  "But not so big that it causes heart failure"
Effects of arteriovenous fistula formation on arterial stiffness and cardiovascular performance and function

Shvan Korsheed¹, Mohamed. T. Eldehni¹, Stephen G. John¹, Richard J. Fluck¹ and Christopher W. McIntyre¹,²

Table 4. Effect of AVF creation on arterial stiffness, systemic haemodynamics, BPs and EF in 21 patients with successful AVF formation who completed all three study sessions using repeated measures one-way ANOVA design

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 Weeks</th>
<th>3 Months</th>
<th>Overall significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF-PWV (m/s)</td>
<td>12.6 ± 3.5</td>
<td>11 ± 3</td>
<td>11 ± 2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>AIx%</td>
<td>22 ± 9</td>
<td>19 ± 9</td>
<td>20 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.5 ± 1.5</td>
<td>7.6 ± 2</td>
<td>7.3 ± 1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>TPR (mmHg-s/mL)</td>
<td>1.0 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>113 ± 33</td>
<td>124 ± 41</td>
<td>126 ± 37</td>
<td>0.18</td>
</tr>
<tr>
<td>HR (b.p.m.)</td>
<td>60 ± 11</td>
<td>64 ± 10</td>
<td>62 ± 10</td>
<td>0.05</td>
</tr>
<tr>
<td>Central SBP (mmHg)</td>
<td>133 ± 26</td>
<td>121 ± 19</td>
<td>120 ± 21</td>
<td>0.01</td>
</tr>
<tr>
<td>Central DBP (mmHg)</td>
<td>73 ± 13</td>
<td>67 ± 11</td>
<td>64 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>BP%</td>
<td>43 ± 13</td>
<td>32 ± 12</td>
<td>33 ± 11</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure.
• So the answer is yes, arteriovenous fistula can decrease blood pressure
• The vascular surgeons always said "I know what you want – but you never tell me how big the fistula should be"
• Prof. Schäfer always: "Just do it right!"
Thank you!
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