Pressures in the Circulation

Stephen Hales and Assistant Measure BP

Time to Pay for Life Insurance

<table>
<thead>
<tr>
<th>MEN</th>
<th>Life Expectancy (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Age 35</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Reduction</td>
</tr>
<tr>
<td>130/90</td>
<td>37 1/2</td>
</tr>
<tr>
<td>140/95</td>
<td>32 1/2</td>
</tr>
<tr>
<td>150/100</td>
<td>25</td>
</tr>
</tbody>
</table>

Death Rate vs Blood Pressure

Blood Pressure Distribution in 35 year-olds

Incidence of “Hypertension”
Mechanisms of Hypertension

- **Vasoconstrictors:**
  - norepinephrine
  - angiotensin II
  - antidiuretic hormone
  - others

- **Vasodilators:**
  - nitric oxide (NO)
  - atrial natriuretic peptide
  - CGRP
  - adenosine
  - others

**BP ~ CO x vascular resistance**

**HPT due to Excessive Vasoconstriction**

**Pheochromocytoma**

**Renin-Angiotensin System**

- angiotensinogen
- renin
- angiotensin I
- converting enzyme
- angiotensin II
- vasoconstriction

**HPT due to Excessive Vasoconstriction**

**Renin-Angiotensin System**

**Renal Artery Stenosis**

**HPT Due to Renal Artery Stenosis**

- Control
- ACE inhibition

**Renin-Angiotensin System and Salt Retention**

- angiotensinogen
- renin
- angiotensin I
- converting enzyme
- angiotensin II
- aldosterone
- CDTR
- efferent constriction;
- FF and PTR
HPT due to Chronic Renal Artery Stenosis: High ECFV

- Excess Aldosterone due to Adrenal Tumor
- Excess Aldosterone due to Genetic Mutation
- Kidney with Hyperactive Na\(^+\) Channel

Hyperactive Na\(^+\) Channel: Lyddle’s Syndrome

Liddle’s Syndrome: Lack of ENaC Internalization
Hyperactive Na\(^+\) Channel: Lydde’s Syndrome

Clinical features:

<table>
<thead>
<tr>
<th>Case</th>
<th>Blood pressure (mmHg)</th>
<th>Serum potassium (mEq/l)</th>
<th>Urinary potassium (mmol/24h)</th>
<th>PRA (ng/ml/hr)</th>
<th>PAC (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>160/100</td>
<td>3.3</td>
<td>40</td>
<td>0.3</td>
<td>30</td>
</tr>
<tr>
<td>Case 2</td>
<td>160/110</td>
<td>3.7</td>
<td>40</td>
<td>&lt;0.1</td>
<td>30</td>
</tr>
<tr>
<td>Case 3</td>
<td>240/150</td>
<td>3.1</td>
<td>46</td>
<td>0.2</td>
<td>30</td>
</tr>
</tbody>
</table>

PRA, plasma renin activity (normal range 0.9-2.4 ng/ml/hr); PAC, plasma aldosterone concentration (normal range 30-160 pg/dl); ND, not determined.

Uehara 1998

Extracellular Fluid Volume and BP in Renal Failure

Blumberg et al 1967

HPT Due to High ECFV

- Kidney with Hyperactive Na\(^+\) Channel
- Loss of Kidney Excretory Function: Renal failure

HPT Due to High ECFV

- Chronic Renal Artery Stenosis
- Excess Aldosterone due to Adrenal Tumor
- Excess Aldosterone due to Genetic Mutation
- Kidney with Hyperactive Na\(^+\) Channel
- Loss of Kidney Excretory Function (Renal Failure)
- High Na\(^+\) intake with no clear abnormality

Frequency of “HPT” in Societies with Different Na\(^+\) Diets

Denton et al, 1965

BP Effect of Addition of NaCl to Diet

Denton et al, 1965

rats

 chimpanzees
Why High ECFV Causes HPT?
BP ≈ CO x vascular resistance
CO ≈ myocardial work x cardiac return
ΔECFV = Δ blood volume - Δ cardiac return
Problem: no detectable CO
Probable cause: increased vasoconstriction

Endogenous “Ouabain” is Secreted During ECFV Expansion and Causes Vasoconstriction
Inhibitors of Na-Ca Exchanger Lower BP

Vascular Smooth Muscle Membrane Potential

K⁺ Channels and Vascular Smooth Muscle
Tone

K⁺ Channels and Vascular Smooth Muscle
- ATP-gated: links cell metabolism with tone
- $K_{Ca}$: calcium-activated; blunts vasoconstrictor action
- $K_{IR}$: inner-rectifying; activated by extracellular K⁺
- $K_{v}$: voltage-activated

ATP-gated K Channel ($K_{ATP}$)
Elevated Blood Pressure in Sur2−/− mice

K⁺ Channels and Vascular Smooth Muscle
- $K_{ATP}$: ATP-gated; links cell metabolism with tone
- $K_{Ca}^{+}$: calcium-activated; blunts vasoconstrictor action
- $K_{IR}$: inner-rectifying; activated by extracellular K⁺
- $K_{V}$: voltage-activated

Effect of K⁺ in Diet in Rat with High ECFV Hypertension

Cardiovascular Consequences of HPT

PDGF-induced Growth of VSM by Increased Strain

Causes of Death in the USA
HPT, a History

- 1920-30’s; insurance industry recognition that HBP is bad for business
- 1940’s; discovery of the first mechanism of secondary hypertension: renal artery stenosis
- 1960-70’s; demonstration that lowering BP saves lives
- 1970-90’s; introduction of modern anti-hypertensive medications and demonstration of the epidemiological impact of HPT treatment
- 2000’s elucidation of the mechanism for “essential” hypertension (~ 99% of hypertensives)