Hypertension and Antihypertensive Agents - Introduction

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Agents used in the treatment of HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>CHF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td><em>/</em></td>
<td>*</td>
<td>*/</td>
<td>*</td>
<td>Caution: CHF (unstable CHF, bronchospasm, significant bradycardia); or in diabetes, asthenia (use β1-selective), depression</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td><em>/</em></td>
<td>*</td>
<td>*/</td>
<td><em>/</em></td>
<td>CHF, Gastrointestinal, reflex tachycardia, constipation</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td>**</td>
<td>*</td>
<td>*/</td>
<td>*</td>
<td>Low GFR, renal steatosis, glomerulosclerosis, hyperkalemia, cough (ACEI), taste, tremor, rash, angioedema</td>
</tr>
<tr>
<td>Diuretics</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>/</td>
<td>Low GFR, hyperkalemia -- CO; glucose intolerance -- diabetes</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>**</td>
<td>*</td>
<td>*/</td>
<td>/</td>
<td>Many Rx interactions, low T, [K+]↑, important, low [K+]↑毒性</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>/</td>
<td>Flushing, dizziness, headache, reflex tachycardia, combo Rx</td>
</tr>
<tr>
<td>Non-Channel blockers</td>
<td><em>/</em></td>
<td>*</td>
<td>*/</td>
<td><em>/</em></td>
<td>Effects enhanced in degranulated tissue, damaged tissue; Phase 0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>**</td>
<td>*</td>
<td>*/</td>
<td>/</td>
<td>Tolerance, flushing, dizziness, headache, reflex tachycardia</td>
</tr>
</tbody>
</table>

Introduction
Blood Pressure Regulation: Frank’s Formula
BP = Cardiac output (CO) X Total peripheral resistance (TPR)
CO = Stroke volume (SV) X Heart rate (HR)

120/80 mmHg
70 bpm

Fast acting

Long acting

Baroreceptor Reflex Arc
- oppose direct change in BP
- bidirectional, responds to ↑ or ↓ in BP
- not concerned with HR
- not concerned with pulse pressure

Systolic – Diastolic Blood Pressure

Leading Causes of Death in the U.S

Data NIH 2000
Definition of Hypertension (HT)

Sustained elevation of systolic and/or diastolic BP above an arbitrarily defined level
• systolic >139 mmHg and/or diastolic >89 mmHg

General population (15-20%) hypertensive
45 – 60 million in USA

Secondary HT (10%): can be cured by surgical procedures (early diagnosis of cause, ie renal stenosis, pheochromocytoma)

Primary (essential) HT (90%): is a lifelong disease, long-term control & treatment, cause unknown

Classification of Hypertension

(Prior 2003)

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;130</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td>Stage 1 (mild)</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>180-209</td>
<td>110-119</td>
</tr>
<tr>
<td>Stage 4 (very severe)</td>
<td>&gt;209</td>
<td>&gt;119</td>
</tr>
</tbody>
</table>

*Require three measurements (repeat visits)
BP lowest in the morning → ↑ during the day

Blood Pressure Classification – JNC VII (Post 2003)

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>or &gt;100</td>
</tr>
</tbody>
</table>

Hypertension (HT)

Secondary HTs (10%)
- neurogenic HT caused by brain damage
- cortisol overproduction: hypophysis or adrenal gland tumor
- aldosterone overproduction: adrenal gland tumor hyperplasia
- renal artery stenosis or occlusion
- adrenal medulla tumor: pheochromocytoma

Primary (essential) HTs (90%)
- primary cause(s) unknown, possibly multi-factorial defects
  - genetics
  - smoking
  - stress
  - salt intake
  - obesity
  - age
  - alcohol
  - caffeine
  - others

Renal Stenosis
Primary cause of 2o HT

Decreased renal blood flow
- ↓ renal BP
- ↑ renin release
- ↑ aldosterone
- ↑ Na+, water retention
- ↑ systemic BP

Pheochromocytoma

Tumor: ↑ synthesis, ↑ release of NE & EPI into the circulation.
Result: ↑ TBP, ↑ HR → hypertensive crisis
Treatment: - surgical removal for solid tumor
- α- / β-blocker ie. Labetolol
- α-blocker ie, phenoxybenzamine or phentolamine
- inhibit tyrosine hydroxylase ie. α-methyl-p-tyrosine
- β-blocker only after α-blockade

Rule of Ten
10% Pheochromocytomas are:
- Malignant
- Bilateral
- Extra-adrenal
- In children
- Familial
- Recur within 5 to 10 years
- Present after stroke
Exam Stress

Normal BP: 120 / 80 mmHg  HR: 72 bpm
Before exam: 140 / 99 mmHg  HR: 97 bpm
During exam: 179 / 149 mmHg  HR: 110 bpm
End of exam: 111 / 74 mmHg  HR: 76 bpm

Consequences of Sustained Hypertension

- failure in blood supply, renal failure (fibrinoid necrosis)
- loss of microcirculation
- aneurysms (rupture of blood vessels)
- myocardial and/or cerebral infarction
- increased risk of stroke
- increased risk of congestive heart failure

Health Consequences - Age

USA
45-60 million HT
↓Na⁺ → ↓rise rate

Health Consequences – Cardiovascular Diseases

Health Consequences – Effective Treatment

Better understanding, better treatments, better results
Health Consequences – Risk Factors

↓ Risk factors → ↑ life expectancy

<table>
<thead>
<tr>
<th>Gain in Life Expectancy in Years for 35-Year-Old Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gain in Life Expectancy</strong></td>
</tr>
<tr>
<td>Reduce cholesterol level:</td>
</tr>
<tr>
<td>T&lt;200 mg/dl if 200-239 mg/dl</td>
</tr>
<tr>
<td>T&gt;200 mg/dl if 240-299 mg/dl</td>
</tr>
<tr>
<td>T&gt;200 mg/dl if ≥300 mg/dl</td>
</tr>
<tr>
<td>Reduce number of cigarettes smoked:</td>
</tr>
<tr>
<td>By 50%</td>
</tr>
<tr>
<td>Eliminate smoking</td>
</tr>
<tr>
<td>Reduce diastolic blood pressure:</td>
</tr>
<tr>
<td>TO BP mm Hg if ≥90-94 mm Hg</td>
</tr>
<tr>
<td>TO BP mm Hg if ≥95-99 mm Hg</td>
</tr>
<tr>
<td>TO BP mm Hg if ≥100 mm Hg</td>
</tr>
<tr>
<td>Reduce weight:</td>
</tr>
<tr>
<td>TO ideal &lt;30% over ideal</td>
</tr>
<tr>
<td>TO ideal ≥30% over ideal</td>
</tr>
</tbody>
</table>

Benefits of Lowering BP

<table>
<thead>
<tr>
<th>Average Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke incidence</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
</tbody>
</table>

In stage 1 HTN and additional CVD risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated.

Non Drug Treatment – Life Style Modification

For mild – moderate hypertension
Less side effects, cheap, improved lifestyle

- ↓ salt intake (Japan, ↑ intake → ↑ BP)
  2.5gm/day (250meq) → 1gm/day (100meq)
- ↓ calorie intake, weight loss
- ↓ alcohol consumption (low dose ↓ BP)
- ↑ physical activity
- ↓ stress factors
- ↓ smoking
- ↓ caffeine intake