HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

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DEPT OF MEDICINE

AGA KHAN UNIVERSITY HOSPITAL
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

• What are we treating
• Why do we need to treat
• With what can we treat
• Which treatment do we give
# Hypertension – Physiologic Basis for Treatment

## International Classification

<table>
<thead>
<tr>
<th></th>
<th>JNC 7</th>
<th>ESH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>SBP &lt;120 and DBP &lt;80</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Pre-HTN</strong></td>
<td>SBP 120–139 DBP 80–89</td>
<td>High normal</td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td>SBP 140–159 DBP 90–99</td>
<td>Grade 1</td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td>SBP 160 DBP 100</td>
<td>Grade 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td><strong>Grade 3</strong></td>
<td>SBP 180 or DBP 110</td>
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</tbody>
</table>
### Classification of blood pressure levels by the British Hypertension Society

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
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<tr>
<td>Normal</td>
<td>&lt;130</td>
<td>&lt;85</td>
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<tr>
<td>High normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>&gt;180</td>
<td>&gt;110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>140-159</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Grade 2</td>
<td>&gt;160</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

This classification equates with those of the European Society of Hypertension, the World Health Organization and the International Society of Hypertension.
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

• What are we treating
• Why do we need to treat
• With what can we treat
• Which treatment do we give
Cardiovascular Disease Risk Doubles With Each 20/10 mm Hg BP Increment*

*Individuals aged 40 to 70 years, over the BP range 115/75 mm Hg to 185/115 mm Hg.
## Recent Trials Supporting EARLY BP Lowering to Reduce CV Events

<table>
<thead>
<tr>
<th>Trial Acronym (initial drugs)</th>
<th>Δ SBP 0-6 Months (mm Hg)</th>
<th>Reduction in CV Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT (diuretic vs ACEI)</td>
<td>5-8</td>
<td>9</td>
</tr>
<tr>
<td>ALLHAT (diuretic vs CCB)</td>
<td>2-5</td>
<td>4</td>
</tr>
<tr>
<td>ASCOT (CCB vs β-blocker)</td>
<td>2-6</td>
<td>16</td>
</tr>
<tr>
<td>LIFE (ARB vs β-blocker)</td>
<td>2-4</td>
<td>13</td>
</tr>
<tr>
<td>VALUE (ARB vs CCB)</td>
<td>2-5</td>
<td>25*</td>
</tr>
</tbody>
</table>

*post-hoc comparison of nonrandomized groups.*
Target-organ damage precedes clinical events

Risk factors: diabetes, obesity, smoking, age

Vasoconstriction
• vascular hypertrophy
• endothelial dysfunction
• atherosclerosis

Hypertension

Pro-thrombotic state

Decreased GFR
• Proteinuria/albuminuria
• Glomerulosclerosis

Apoptosis
• LVH
• Fibrosis

Cerebro-Vascular disease

MI
• Heart failure
• Arrhythmia

Stroke
• Cognitive dysfunction

Death

Renal failure
CKD

Risk factors:
- diabetes
- obesity
- smoking
- age
Reducing target-organ damage

Reduced blood pressure slows the rate of GFR decline

Mean arterial pressure (mmHg)

Decline in GFR (mL/min/year)

Untreated hypertension

$r = 0.69; P < 0.05$
Importance of achieving target BP

Felodipine Event Reduction (FEVER) study

▲ Felodipine vs placebo added to ongoing HCTZ with additional antihypertensives as required

Placebo group
142.5/85.0 mmHg
(did not reach goal)

Felodipine group
137.3/82.5 mmHg
(reached goal)

Decrease in events with Felodipine

- All cardiovascular events: -27%
- Fatal and non-fatal stroke: -27%
- Cardiac events: -35%
- Heart failure: -30%
- Certain Cancers: -36%
Summary

- Endothelial dysfunction is an early and key feature of vascular disease that predicts future events
- The endothelium is in a constant state of injury and repair, the dynamics determined by function
- It is an attractive target for diagnosis, as it is the “gateway” to vascular disease
- In addition to inhibition of the RAS when treating our hypertensive and CVD patients, we should also be aware of the benefits of stimulation of NOS and the modern agents that enable us to achieve this
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENTS

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20th Century: Key Discoveries That Revolutionized CV Medicine

1785: William Withering discovered digitalis

1960: Rosalyn Yalow discovered that patients with T2D were insulin resistant

1929: Werner Forssman undertook the first cardiac catheterization

1971: Sir John Vane discovered that aspirin inhibited prostaglandin synthesis

1974: Michael Brown and Joseph Goldstein discovered the LDL receptor

1958: The first thiazide diuretic launched for the treatment of HTN

1964: Propranolol discovered by Sir James Black

1976: The first statin with pioneering work by Akira Endo

1975: David Cushman and Miguel Ondetti developed first ACE inhibitor
Numerous factors contribute to the pathophysiology of hypertension:

- Systemic and local renin-angiotensin system
- Kallikrein-kinin system
- Sympathetic nervous system
- Prostaglandins
- Vasoactive substances, such as nitric oxide, endothelin
- Natriuretic peptides
- Insulin resistance
- Obesity
- Arterial stiffness
- Endothelial function
Renin-angiotensin-aldosterone system

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Angiotensin II is central to atherosclerotic mechanisms.

**Oxidative Stress**
- NAD(P)H oxidase activity ^
- Reactive oxygen species ^
- LDL peroxidation ^
- LDL peroxidation ˘
- Nitric oxide ˘

**Inflammation**
- Vascular permeability ^
- Leucocyte infiltration ^
- Activation of signalling pathways
- Production of inflammatory mediators
- Proliferation of Vascular Smooth Muscle Cells
- Matrix deposition

**Endothelial dysfunction**
- Vasoconstriction
- PAI-1 activation
- Platelet aggregation
- Activation of Matrix Metalloproteinases

**Tissue remodelling**
- LDL peroxidation ˘
- Reactive oxygen species ^
- Nitric oxide ˘
Improving outcomes in hypertensives

Rationale for selective angiotensin II type 1 receptor blockade

Bradykinin/NO

\[ \text{ACE inhibitor} \]

Inactive fragments

\[ \text{ANGIOTENSIN I} \]

\[ \text{ANGIOTENSIN II} \]

\[ \text{Chymase, tPA, Cathepsin ‘Angiotensin II escape’} \]

\[ \text{AT}_1 \text{ RECEPTOR} \]

\[ \text{Vasoconstriction} \]

\[ \text{Sodium retention} \]

\[ \text{SNS activation} \]

\[ \text{Inflammation} \]

\[ \text{Growth-promoting effects} \]

\[ \text{AT}_2 \text{ RECEPTOR} \]

\[ \text{Vasodilation} \]

\[ \text{Natriuresis} \]

\[ \text{Tissue regeneration} \]

\[ \text{Inhibition of inappropriate cell growth} \]

\[ \text{ARBs} \]
THE KKS AND RAAS SYSTEMS

**KKS**

- Kininogen
- HK
- Bradykinin

**RAAS**

- Prorenin
- Angiotensinogen
- Angiotensin 1
- Angiotensin 1 - 7

**Circulation**

- Bradykinin 1-5
- Angiotensin II
- Angiotensin 1 - 7R

**Markers**

- tPA
- PAI-1
- ATP4
- ATR
- Ang 1 - 7R

**Actions**

- Vasodilation
- Vasoconstriction

**Endothelial Factors**

- BK
- NO2
- PGI2
PROSTAGLANDINS AND HTN
Obesity and Cardiovascular Risk

Visceral Obesity

- Sodium Retention Volume Expansion
- Heart Rate $\uparrow$
- Endothelial Dysfunction
- Diabetes Mellitus Dyslipidemia

Hypertension

- Cardiac Output $\uparrow$
- Atherosclerosis Arterial Resistance $\uparrow$
- Eccentric Hypertrophy
- Concentric Hypertrophy

Congestive Heart Failure, CAD, Sudden Death

(Sharma AM. Pathophysiology and Pharmacological Management of Obesity Hypertension. 2000)
ARTHEROSCLEROSIS & PLAQUE FORMATION

Vessel narrowing and vessel stiffness
Potential Effects of NSAIDs on Renal Physiology

Arachidonic acid

NSAIDs

COX-1

COX-2

PGE$_2$

- ↑ Blood pressure
- Sodium retention
- Peripheral edema
- ↑ Weight
- CHF (rarely)

PGI$_2$

Hyperkalemia

Acute renal failure

CHF = congestive heart failure.
How Do NSAIDs Increase BP*?

Arachidonic acid

NSAIDs /\[\text{COX}^\dagger\]

PGs\(\ddagger\) (PGE\(_2\) and PGI\(_2\))

Increased antidiuretic hormone

Decreased renal blood flow

Decreased glomerular filtration rate

Increased proximal tubular reabsorption

Increased sodium and chloride reabsorption

Increased salt and water retention

Increased BP

*BP = blood pressure
†COX = cyclooxygenase
‡PG = prostaglandin

Generation of NO from L-arginine Occurs Intracellularly Through the NOS Enzymes

- Three nitric oxide synthase (NOS) isoforms discovered to date
  - 2 constitutives (neuronal and endothelial, nNOS or NOS I and eNOS or NOS III)
  - 1 inducible (NOS II)

Pharmacologic Approaches to Endothelial Dysfunction

- RAS-Inhibitors/Certain CCBs
- Statins
- Endothelial Function
- New Generation β-Blockers
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

• Management of Hypertension
  – Physical Methods
    • Exercises, Control weight, Dietary Management (salt, sugar, fat control)
  – Pharmacologic Methods
    • Monotherapy – Diuretics, vasodilators, CCBs, ACEI ARBs, betablockers
    • Dual & Multiple Therapy – Rational Combination
      – β blockers with diuretics,
      – β blockers with vasodilators
      – β blockers with CCBs
      – CCBs with ARBs
      – CCB. with ACE inhibitors
      – CCB and Beta-blocker
      – ARBs with ACEI;
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HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

Choice of Drugs: depends on:

• Patient's previous experience with particular drug class(es)
• The effects of particular drugs on the specific details of a given patient's cardiovascular, renovascular, neurovascular risk profile
• Presence of sub-clinical organ damage, cardiovascular disease, chronic kidney disease, or diabetes
• Presence of other disorders that may limit use of particular antihypertensive drug classes
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

Choice of Drugs: depends on:

- Possible drug interactions
- Cost of drugs - a strong consideration (but never over efficacy, tolerability, or protection of the patient)
- Preference for drugs that have a 24-hour effect with once-daily administration covering the early morning surge
- Continued attention to side effects
ESH recommendations

Initial drug combination

- Thiazide diuretic and ACE inhibitor;
- Thiazide diuretic and ARB;
- Thiazide diuretic and CCB
- CCB and ACE inhibitor;
- CCB and ARB;
- CCB. and Beta-blocker
ESH Guidelines:
The stated primary goal of treatment is:
“To achieve maximum reduction in the long-term total risk of cardiovascular cerebro and renal disease.”

Target blood pressures are set as
< 140/90 mm Hg in all hypertensive patients
< 130/80 mm Hg in diabetic and high/very high-risk patients
The early morning blood pressure surge

<table>
<thead>
<tr>
<th>Time of day</th>
<th>18:00</th>
<th>22:00</th>
<th>02:00</th>
<th>06:00</th>
<th>10:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24-h blood pressure profile

- **Sleep**
- **Time of awakening**

![Graph showing the early morning blood pressure surge with data points for different times of the day, highlighting the surge occurring around 06:00.]
Circadian variation of blood pressure


• Continuous intra-arterial blood-pressure and electrocardiogram recordings were obtained in hypertensive and normotensive ambulant patients.

• Blood-pressure was highest mid-morning and then fell progressively throughout the remainder of the day.
Circadian variation of blood pressure

• Blood-pressure was lowest at 3 A.M. and began to rise again during the early hours of the morning before waking.

• These findings may have important consequences with regard to the therapeutic management of hypertension.
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

Meta-analyses indicate that between 0400 hr and 1000 hr (compared with the rest of the day) there is a:

- 40% higher relative risk of acute myocardial infarction
- 29% increased risk of sudden cardiac death
- 49% higher relative risk of stroke
The early morning BP surge
Increased cardiovascular and cerebrovascular risk

Time of day

Cerebrovascular events (per 2 h)

Myocardial infarction (n=2,999)

Stroke (n=1,167)

Early morning blood pressure surge
Renin Angiotensin Aldosterone System Blockade: AVENUES

1. Angiotensin converting enzyme inhibition
2. Angiotensin I (AT1) receptor blockade
3. Aldosterone receptor blockade
4. Addition of aldosterone blockade to ACE inhibition
5. Addition of Angiotensin receptor blocker blockade (ARB) to Angiotensin converting enzyme inhibition (ACEI)
Superior BP reduction in morning hours when using ARBs

Meta-analysis of ABPM data in the morning period (06:00–12:00)

<table>
<thead>
<tr>
<th>Change from baseline (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan 50 mg</td>
</tr>
<tr>
<td>Valsartan 80 mg</td>
</tr>
<tr>
<td>Amlodipine 5 mg</td>
</tr>
<tr>
<td>Telmisartan 80 mg</td>
</tr>
</tbody>
</table>

P<0.0125 vs Losartan and Valsartan

Pathophysiologic Effects of Angiotensin II

Abnormal vasoconstriction

↑PAI-1/thrombosis

↑Contractility

Platelet aggregation

Activate SNS

↑Aldosterone

Superoxide production

↑Vasopressin

Vascular smooth muscle growth

↑Endothelin

Myocyte growth

↑Collagen

ANGIOTENSIN (AT\textsubscript{2}) ADVANTAGES

Telmisartan:

- Has unique evidence of efficacy in the early morning hours based on the largest set of ABPM trials in the medical literature
- Provides superior reductions in blood pressure in the last hours of the dosing interval compared with valsartan, losartan, ramipril, perindopril and amlodipine
- Reduces the EMBPs compared with ramipril in patients with high EMBPs
- Is effective and well-tolerated in patients with kidney disease, including those on dialysis
Angiotensin II is central to atherosclerotic mechanisms:

- Oxidative Stress
- Inflammation
- Endothelial dysfunction
- Tissue remodelling
- Vascular permeability
- Leucocyte infiltration
- Activation of signalling pathways
- Production of inflammatory mediators
- Proliferation of VSMCs
- Matrix deposition
- MMP activation
- Platelet aggregation
- PAI-1 activation
- Vasoconstriction
- Nitric oxide
- LDL peroxidation
- Reactive oxygen species
- NAD(P)H oxidase activity
- Angiotensin II

The Many Roles of Nitric Oxide in Both Health and Disease

- **Inhibits**
  - SMC Proliferation
  - Endothelial Apoptosis
  - Thrombosis • Platelets • Tissue Factor

- **Promotes**
  - Vasodilation
  - Arterial Compliance
  - Positive Remodeling
  - Inflammation • Cytokines • Chemokines • CAMs
Improving outcomes in hypertensives

Rationale for selective angiotensin type 1 receptor blockade

- Bradykinin/NO
- Inactive fragments

**ANGIOTENSIN I**

**ANGIOTENSIN II**

- **ARBs**
  - AT1 receptor
  - Vasoconstriction
  - Sodium retention
  - SNS activation
  - Inflammation
  - Growth - promoting effects

- **AT2 receptor**
  - Vasodilation
  - Natriuresis
  - Tissue regeneration
  - Inhibition of inappropriate cell growth

**Chymase, tPA, Cathepsin**

**Angiotensin II escape**

**ACE inhibitor**

---

**The Evolution in Beta-Blockade**

<table>
<thead>
<tr>
<th>Decade</th>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>Nonselective</td>
<td>Propranolol</td>
</tr>
<tr>
<td>1970s</td>
<td>Selective</td>
<td>Atenolol, Metoprolol</td>
</tr>
<tr>
<td>1980s-1990s</td>
<td>Nonselective</td>
<td>Carvedilol, Labetalol</td>
</tr>
<tr>
<td>2007</td>
<td>Selective</td>
<td>Nebivolol</td>
</tr>
</tbody>
</table>

**Vasodilating**
- (α-blockade)
- (nitric oxide-mediated)
Effects of Nebivolol on Nitric Oxide in White and African-American Endothelium

Change in ACh-stimulated NO release (nM)

- Whites
- African Americans

<table>
<thead>
<tr>
<th>Condition</th>
<th>1 μM</th>
<th>50 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebivolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td></td>
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</tr>
</tbody>
</table>

HUVECs

IAECs
Major actions of ACE inhibitors and ARBs

Kininogens
- Bradykinin

ACE inhibitors
- Angiotensinogen
  - Renin
  - Ang I
  - Ang II

ACE
- B<sub>2</sub> receptor
  - Vasodilation:
    - ↑ NO
    - ↑ Prostaglandins
    - ↑ EDHF
    - ↑ tPA
  - Inactive peptides

AT<sub>1</sub> receptor
- Vasoconstriction
- Proliferation
- Matrix formation
- Aldosterone secretion

ARBs
Limitations of ACE inhibitors – Ang II formation by Non-ACE dependent pathways

- ACE
- Angiotensin I
- Angiotensin II
- AT₁ receptor
- CAGE = chymostatin-sensitive angiotensin II-generating enzyme.

ASN 2002 Satellite Symposium, Philadelphia, PA, November, 2002
Advantages of selective angiotensin receptor blockade

• Complete blockade of harmful AT$_1$-mediated angiotensin II effects, independent of ACE
  – Vasoconstriction, sodium retention, SNS activation, inflammation, growth-promoting effects, increase in aldosterone and apoptosis

• No kinin-induced catecholamine release
Advantages of selective angiotensin receptor blockade

• Retain AT$_2$ receptor-mediated beneficial effects
  – Vasodilation, natriuresis, tissue regeneration, inhibition of inappropriate cell growth, differentiation

• More complete blockade of ANG II pro-inflammatory and pro-coagulatory effects

• However, less beneficial effects of kinins, e.g. release of NO/ PGI2(??)
Do ARBs meet the criteria for a desirable antihypertensive?

• Effectively lower blood pressure
• High efficacy as monotherapy and demonstrated additional efficacy when used in combination
• Only some have sustained 24-hour blood pressure reduction, including the vulnerable early morning period when cardiovascular events are at their most frequent
Do ARBs meet the criteria for a desirable antihypertensive?

• Only some have ability to prevent or reduce target organ damage and incidence of poor cardiovascular outcomes
• Only some can be administered once daily
• Minimal side effects
• Offer benefits beyond blood pressure control and block deleterious effects of Angiotensin II
AT$_1$-receptor binding affinity
Longest dissociation half-life of clinically available ARBs

Valartan
Losartan$^\dagger$
Candesartan
Olmesartan
Telmisartan

Receptor dissociation half life (min)

$^\dagger$ Active metabolite EXP3174

Pharmacology summary

- **ARBs** bind very strongly (but reversibly) to the AT$_1$ receptor sites
- have long receptor-binding half-life
- have long plasma half-life and large volume of distribution compared to other anti HTN
- have PPARγ (peroxisome proliferator-activated receptor-gamma) activity at physiologically achievable concentrations
- have no requirement to adjust dose for age or gender
- is excreted by hepatic metabolism, and so no dose adjustment is required in renal disease
- do not have clinically-relevant interactions with other common co-medications
ARBS (Telmisartan) renoprotection in type 2 diabetic nephropathy

Reduced transition to overt nephropathy (INNOVATION)

Patients with and without hypertension

Placebo
Telmisartan 40mg
Telmisartan 80 mg

RRR: relative risk reduction
NNT: number needed to treat to prevent 1 transition

Makino et al. Diabetes Care 2007;
Telmisartan renoprotection in type 2 diabetic nephropathy

Reduced transition to overt nephropathy (INNOVATION)

Patients normotensive at baseline

Makino et al. Diabetes Care 2007; in press
Telmisartan Efficacy in Target-organ protection

• Vascular protection: Improves endothelial function and arterial stiffness
• Nephroprotection
  – Reduces microalbuminuria in hypertensives
  – Reduces microalbuminuria in type 2 diabetics
  – Reduction in proteinuria in non-diabetic nephropathies
  – Long term renal protection: Slows the decline of GFR in type 2 diabetics
• Cardiac protection: Superior reduction of LVH compared with HCTZ, Carvedilol and Ramipril
HYPERTENSION – PHYSIOLOGIC BASIS FOR TREATMENT

Improves glucose sensitivity
Improves cholesterol and lipids metabolism
Increases adiponectin levels
Hypertension summary

- Hypertension is common and is a major risk factor for cardio and renovascular disease.
- The early morning blood pressure surge is particularly associated with increased cardio/cerebral/renovascular risk.
- Lack of BP control, particularly in the risky, early morning hours, is still an unmet need.
- Hypertension causes target-organ damage, and regression of target-organ damage by antihypertensives improves prognosis.
- Modern antiHTNs have additional metabolic beneficial effects beyond BP control.
Thank You