Hypertension, Aging, and Arterial Stiffness

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Arterial Stiffness

- Now an established cardiovascular risk factor and single best prognostic index for future events in hypertensive population

- Cardiovascular conditions and risk factors:
  - Aging
  - Hypertension
  - Coronary artery disease
  - Diabetes
  - Smoking (acute and chronic)
  - End-stage renal disease
  - Hypercholesterolemia

Structure of the Artery

Intima
- endothelium
- connective tissue

Media
- smooth muscle
- protein matrix of elastin/collagen
- internal elastic lamina

Adventitia
- strong, fibrous tissue to maintain vessel shape

Lumen
Heterogeneity of changes

- Not all arteries become stiff with age
  - thoracic aorta and its branches: increased stiffness
  - more peripheral muscular branch (such as brachial artery)
    - retain their normal increased elasticity in hypertension.

Loss of elastin

- arterial elasticity dependent on matrix protein elastin.
- fatigue of elastin fiber and lamella occur in aging process.
- hypertension accelerates development of conduit artery stiffness
Aorta of Young Healthy Adult
Aorta of Old Hypertensive Patient
Arterial Stiffness: Augmentation Pressure (AP)

Old subject
PWV = 12 m/s

Young subject
PWV = 8 m/s

Augmentation pressure

Systole  Diastole

Measured wave  Backward wave  Forward wave
Arterial Stiffness: Augmentation Index (AI)

- Height of a reflected wave relative to the incident wave
- AP expressed as a percentage of the PP
- Quantify the stiffness of the artery
- Strong independent markers for premature CAD
- Low compliance → high AI

Balcher et al. Hypertension 1999
Weber T et al. Circulation 2004
Pulse wave velocity (PWV): the speed of blood pressure wave to travel a given distance between 2 sites of the artery.

- correlates well with arterial distensibility and stiffness
- strongly associated with the presence and extent of atherosclerosis and a forceful marker and predictor of CV risk in HT patients
- correlates with the severity of DM complications

Ankle-Brachial Index (ABI)
Arterial Stiffness: PWV
Arterial Stiffness and Aging: ACCT Trial

McEniery et al. ACCT trial. J Am Coll Cardiol 2005
Arterial Stiffness and Aging: ACCT trial

McEniery et al. ACCT trial. J Am Coll Cardiol 2005
Peripheral and central pulse pressure, AP, AI, and aortic and brachial PWV all increased significantly with age.

Age-related changes in AI and aortic PWV were non-linear:
- AI increasing more in younger individuals
- Changes in PWV were more prominent in older individuals

AI: more sensitive marker of risk in younger individuals
Aortic PWV: more sensitive marker of risk in older individuals

McEniery et al. ACCT trial. J Am Coll Cardiol 2005
Arterial Stiffness and Hypertension

- High BP
  - Transient increase in arterial stiffness without any structural changes of the arterial wall initially
  - Sustained elevations in arterial stiffness with structural changes

- Changes in arterial structure
  - SMC hyperplasia and hypertrophy
  - Elastin degradation
  - Collagen deposition

Factors Contributing to Increase Arterial Stiffness

- Dyslipidemia
- Hyperinsulinemia
- Hyperglycemia
- Hypertension

Endothelial Dysfunction

- Oxidative Stress
- Aging
- Elastin fracture
- ↑ Arterial Stiffness
- ↑ Pulse pressure/Hypertension
- ↑ Collagen deposition
- Myocardial ischemia/↑ Metabolic demand

- Aging
- Left ventricular Dysfunction/Hypertrophy
- ↑ Arterial Stiffness
Which Drugs Are Ideal?
Endothelial Dysfunction

Traditional Risk Factors

- Non-traditional Risk Factors
- Local Factors

Endothelial Dysfunction: “The Risk of the Risk Factors”

- Vascular Lesion and Remodeling
- Inflammation
- Vasoconstriction
- Thrombosis
- Plaque Rupture/Erosion

Genetic Predisposition
Unknown Factors
ACE inhibition is very important to prevent or regress atherosclerosis.

ACE inhibition leads to:
- Plaque regression
- Plaque stabilization
- Vasodilation
- Antithrombotic state
- Noninflammatory state
- ↓ Lipid peroxidation
- ↓ Smooth muscle
- ↓ Ang II
- ↓ Nitric oxide
- ↓ Superoxide anion
- ↓ Oxidative stress
- ↓ Inflammation
- ↓ Prothrombotic state
- ↓ Vasoconstriction

Endothelial dysfunction

ACE inhibition
Effects of AEC Inhibition: TREND Study

- randomized, double-blind, placebo-controlled study
- followed up 105 patients with CAD for 6 months

Improvement of endothelial function with ACE inhibition

Effects of AEC Inhibition: BANFF Study

- compared the effectiveness of 4 anti-hypertensive drugs
- improves FMD of the brachial artery by ACE inhibition

Anderson TJ et al. JACC 1998
Lacidipine restores endothelium dependent FMD of brachial artery in patients with HT

: Taddei et al. Hypertension 1997

Combination of nifedipine and cerivastatin improves coronary endothelial function measured by QCA change of coronary diameter after intracoronary infusion of acetylcholine

Benidifine improves endothelium dependent FMD of brachial artery in patients with HT


Calcium channel blocker not only protect the endothelium through their blood pressure lowering action but also improve endothelial function through the stimulation of NO production

## Effects of Anti-hypertensive Drug on Arterial Stiffness

<table>
<thead>
<tr>
<th></th>
<th>PWV</th>
<th>Wave reflexion</th>
<th>Carotid dist.</th>
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</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
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<tr>
<td>Hydrochlorthiazide</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>Indapamide</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>Bendrofluazide</td>
<td>NC</td>
<td>NC</td>
<td></td>
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<tr>
<td><strong>β-blockers</strong></td>
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<tr>
<td>Propranolol</td>
<td>↓</td>
<td>NC</td>
<td></td>
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<tr>
<td>Bisoprolol</td>
<td>↓</td>
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<tr>
<td>Dilevalol</td>
<td>↓</td>
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<tr>
<td>Atenolol</td>
<td>↓</td>
<td>NC/↓</td>
<td></td>
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<tr>
<td>Metoprolol</td>
<td>NC</td>
<td>NC</td>
<td></td>
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<tr>
<td>Nebivolol</td>
<td>↓</td>
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<tr>
<td>Dihydropyridine</td>
<td></td>
<td></td>
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<tr>
<td>Nitrendipine, isradapine</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacidipine, nifedipine, felodipine</td>
<td>↓</td>
<td></td>
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<tr>
<td>Verapamil</td>
<td></td>
<td></td>
<td>↓</td>
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<tr>
<td><strong>Aldosterone antagonists</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Canreonate</td>
<td></td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>NC/↓</td>
<td>↓</td>
<td></td>
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<tr>
<td>Eplerenone</td>
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<td><strong>ACE inhibitors</strong></td>
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<tr>
<td>Captopril</td>
<td>↓</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Ramipril, lisinopril, cilazapril</td>
<td>↓</td>
<td></td>
<td></td>
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<tr>
<td>Trandolopril</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>Quinapril</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Fosinapril</td>
<td>↓</td>
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<tr>
<td><strong>Angiotensin II receptor antagonists</strong></td>
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<tr>
<td>Losartan</td>
<td>↓</td>
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<tr>
<td>Telmisartan</td>
<td>↓</td>
<td></td>
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<tr>
<td>Valsartan</td>
<td>↓</td>
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</tbody>
</table>
Arterial Stiffness - Case (78/M)

Essential HT (Stage 1)
: diagnosis at 2004. 01. 30
: Cilnidipine 10mg
  plus
Dichlozid 12.5mg

Baseline PWV was measured
PWV results
: 2004. 08. 05 (7 months later)
: Cilnidipine 10mg
plus
Dichlozid 12.5mg
Arterial Stiffness - Case (78/M): 17 Months Later

**How is your artery?**

Let's check your atherosclerosis level from vascular "stiffness" and "occlusion."

- **Age:** 77
- **Height:** 154 cm
- **BMI:** 19.4
- **Weight:** 46.0 kg
- **Diagnosis:**

**Blood Pressure Value**

- **R-arm:** 106/65  
  (Pre-value: 134/83)
- **L-arm:** 114/64
  (Pre-value: 156/83)

**HR:** 75 sec

**How is your arterial stiffness (baPWV)?**

- **R:** 1695  
  **L:** 1799  
  (Pre-value: R: 2061 L: 2389)

Compared to the healthy male of the age 77, it is within normal range.

However, be aware the artery is getting older with age.

*baPWV mainly measures the large arterial stiffness and it does not indicate or cardiovascular stiffness.

**How is your arterial occlusion (ABI)?**

- **R-leg:** 1.09  
  **L-leg:** 1.08  
  (Pre-value: R-leg: 1.09 L-leg: 1.08)

This examination result is within the normal range.

**Progress of atherosclerosis and its target value**

Check up the atherosclerosis periodically.

**Date/Time**

- **R-Bra.**
  - Jan/30/2004: 15:18
  - Aug/5/2004: 8:00
  - Jun/10/2005: 15:58
- **L-Bra.**
  - Jan/30/2004: 15:18
  - Aug/5/2004: 8:00
  - Jun/10/2005: 15:58
- **R-Ank.**
  - Jan/30/2004: 15:18
  - Aug/5/2004: 8:00
  - Jun/10/2005: 15:58
- **L-Ank.**
  - Jan/30/2004: 15:18
  - Aug/5/2004: 8:00
  - Jun/10/2005: 15:58
- **Weight:** 46.0 kg
To evaluate the ability of an antihypertensive therapy to improve arterial stiffness as assessed by aortic pulse wave velocity (PWV) in a large population of hypertensive patients.

Table 1: Treatment effects on blood pressure and pulse wave velocity; mean values and changes from baseline (M0) during (M2) and at the end of the study (M6).

<table>
<thead>
<tr>
<th>Variables</th>
<th>M0</th>
<th>M2</th>
<th>M6</th>
<th>Δ(M2−M0)</th>
<th>P</th>
<th>Δ(M6−M0)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>158 ± 15</td>
<td>139 ± 16</td>
<td>134 ± 13</td>
<td>−20 ± 17</td>
<td>&lt; 0.001</td>
<td>−24 ± 17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>98 ± 7</td>
<td>86 ± 9</td>
<td>84 ± 8</td>
<td>−12 ± 10.1</td>
<td>&lt; 0.001</td>
<td>−14 ± 10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>118 ± 8</td>
<td>103 ± 10</td>
<td>100 ± 9</td>
<td>−15 ± 11</td>
<td>&lt; 0.001</td>
<td>−18 ± 11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>59 ± 15</td>
<td>52 ± 12</td>
<td>50 ± 10</td>
<td>−7 ± 14</td>
<td>&lt; 0.001</td>
<td>−9 ± 15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>75 ± 10</td>
<td>75 ± 9</td>
<td>75 ± 10</td>
<td>−0.4 ± 10</td>
<td>NS</td>
<td>−0.3 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>11.6 ± 2.6</td>
<td>10.7 ± 2.2</td>
<td>10.5 ± 2.1</td>
<td>−0.9 ± 1.4</td>
<td>&lt; 0.001</td>
<td>−1.1 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP: mean arterial pressure; PP, pulse pressure; HR, heart rate; PWV, pulse wave velocity.

Asmar R et al. J of Hypertens 2001
Combination therapy of ACE inhibitor and calcium channel blocker achieves superior blood pressure control compared with calcium channel blocker monotherapy in patients with stage 2 HT

: Kenneth et al. AJH 2004

Combination therapy of ACE inhibitor and calcium channel blocker achieves greater improvement of arterial compliance than ACE inhibitor monotherapy

: Winer N et al. Prev Cardiol 2005
Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension Trial

ongoing clinical study (from 2003 to 2008)

compare two different types of drug combination

(ACEI + CCB versus ACEI + diuretics)

expect 15% relative reduction of CV events

Kenneth AJ et al. AJH 2004
Not all antihypertensive agents restore endothelial function and reduce arterial stiffness.

ACE inhibitors and calcium channel blockers could restore endothelial function.

The strongest evidence is for ACE inhibitors, ARBs, and CCBs which have shown to reduce arterial stiffness.

**Summary of Clinical Study**

Combination of ACE inhibitor and CCB: can be an ideal therapeutic strategy for reducing atherosclerotic complications of HT.