Arterial Stiffness in Geriatric Hypertension: Mechanisms and Management

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OUTLINE
- Epidemiology
- Physiological Characteristics / Mechanisms
- Vascular stiffness as CV risk factor
- SPRINT – Pulse Wave Velocity Ancillary Study

Blood Pressure by Age and Sex
Hypertension Prevalence by Age and Sex

Will you live long enough to develop hypertension?
Residual lifetime risk for developing hypertension

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Women age 55 % (95% confidence interval)</th>
<th>Women age 65 % (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>52 (48-58)</td>
<td>64 (60-69)</td>
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<tr>
<td>15</td>
<td>72 (68-76)</td>
<td>81 (77-84)</td>
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<tr>
<td>20</td>
<td>83 (80-86)</td>
<td>89 (86-92)</td>
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<tr>
<td>25</td>
<td>91 (88-93)</td>
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</tbody>
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Epidemiology Summary

Hypertension eventually develops in 90% of people who have normal blood pressure at age 55.
**OUTLINE**

- Epidemiology
- Physiological Characteristics / Mechanisms
  - Biomarkers of vascular aging
  - Metabolic syndrome and insulin resistance
  - Renin-angiotensin aldosterone system
  - Chronic kidney disease

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**Physiological Characteristics - 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased vascular compliance</td>
<td>Increased systolic BP and pulse pressure.</td>
</tr>
<tr>
<td>Decreased baroreceptor sensitivity</td>
<td>Greater BP variability.</td>
</tr>
<tr>
<td>Heightened SNS activity</td>
<td>Postural hypotension.</td>
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<tr>
<td>Increased α-adrenergic receptor</td>
<td>Increased peripheral vascular resistance.</td>
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</tbody>
</table>

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**Physiological Characteristics - 2**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clinical Implication</th>
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</thead>
<tbody>
<tr>
<td>Increased total and central adiposity</td>
<td>Effectiveness of weight loss.</td>
</tr>
<tr>
<td>Salt sensitivity of blood</td>
<td>Effectiveness of salt restricted diet.</td>
</tr>
<tr>
<td>Metabolic insulin resistance</td>
<td>Screen for diabetes.</td>
</tr>
<tr>
<td>Increased RAAS activity?</td>
<td></td>
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</tbody>
</table>
Hypertension Pattern by Age

Age-related Vascular Changes
The Internal Wall
- Increased thickness of intima and media.
- Matrix
  - collagen deposition
  - increased fibronectin
  - crosslinking (Advanced Glycosylation Endproducts)
  - inflammation

Net result is increased vascular stiffness.

Age-Associated Remodeling of Large Arteries

Endothelial Cell Dysfunction and Increased VSMC Proliferation and Apoptosis
AGE-ASSOCIATED ARTERIAL REMODELING
Clinical correlates of vascular aging

- Metabolic syndrome and insulin resistance
  - Advanced glycosylated end-products (AGEs)
- Renin-angiotensin aldosterone system (RAAS)
- Chronic kidney disease

Pulse Wave Velocity: Aplanation Tonometry

Pulse Wave Velocity (PWV): Methodology

1. Distance (D) cm from carotid to femoral sites.
2. Carotid artery pressure cont
3. Pressure contours timed to
4. Femoral artery contours obt
5. Time (t)= femoral-carotid diff
6. PWV= D/t (m/sec)

Stiffer arteries propagate pulse waves faster.
Vascular Stiffness and Insulin Sensitivity

Advanced glycosylated end-products (AGEs)
- In non-diabetics, HgbA1c predicts future hypertension.

Glycated hemoglobin associated with PWV
- GHb predicted higher PWV (OR 1.79, 95% CI 1.09–2.93)
Breaking up AGE: ALT-711 - Alagebrium

Cross-Link Breaker Therapy

- 21 yr old rhesus monkeys
- 3 weeks ALT-711

Renin-Angiotensin Aldosterone System
Aldosterone Effects

Well Known  Less well known
- Sodium reabsorption  - Decreased vascular compliance
- Water retention  - Myocardial fibrosis
- K+ and Mg++ loss  - Decreased baroreceptor function
- Hypertension  - Endothelial dysfunction
- Thrombosis

- Aldosterone is produced by vascular smooth muscle cells.
- Aldosterone promotes vascular remodeling:
  - Perivascular fibrosis
  - Vascular stiffness
  - Organ (cardiac, renal) fibrosis

Aldosterone and the Hypertension Syndrome

Central Obesity  Baroreceptor Dysfunction  Decreased arterial compliance

Aldosterone  SNS Activation

Insulin Resistance  LV hypertrophy
Hypothesis

- Compared to older hypertensive subjects randomized to therapy with a thiazide diuretic, those treated with spironolactone will demonstrate greater improvements in vascular and neurohumoral outcome measures.
  - Decreased SNS activity
  - Improved metabolic insulin sensitivity
  - Decreased arterial stiffness

Mean Arterial Blood Pressure

- Baseline
- Six Month
- ANOVA P<0.0001
Pulse Wave Velocity

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<th>Baseline</th>
<th>Six Month</th>
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<tr>
<td>HCTZ</td>
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<tr>
<td>Spironolactone</td>
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ANOVA p = 0.04

Is change in PWV solely due to BP reduction?

% Change PWV

% Change BP

HCTZ: r²=0.0000, p=0.97
SPR: r²=0.11, p=0.06

Conclusions

- Aldosterone shares many effects in common with the neurohumoral features observed among older hypertensives.
- Aldosterone antagonist therapy is an effective antihypertensive.
- Changes in neurohumoral and vascular characteristics are similar following six months of HCTZ and spironolactone treatment.

Kotfas and Supiano, JACC 56: 1322; 2010
Vascular stiffness contributes to age-related increase in BP

PWV predicts incident hypertension – 1

Vascular stiffness association with CV Risk – independent of BP – 1

**Vascular stiffness association with CV Risk – Independent of BP – 2**

**SPRINT**

- Will lower blood pressure reduce the risk of heart and kidney diseases, stroke, or age-related declines in memory and thinking?
- More than 9,000 participants will be enrolled into the study at over 90 clinics.
- At the end of the trial, the results of SPRINT will tell us if a lower recommended blood pressure might help to decrease stroke, heart disease, progression of chronic kidney disease, and age-related losses of memory and thinking.

**SPRINT – Pulse Wave Velocity – 1**

- Hypothesis: measures of vascular stiffness will be predictive of the main SPRINT outcomes independent of the achieved peripheral SBP.
- Specific Aim 1: To determine if aPWV (and sub-aim 1, measures of central BP) in SPRINT study subjects randomized to the intensive treatment group at year three post-randomization will be lower compared to the usual care treatment group.
SPRINT – Pulse Wave Velocity – 2

Specific Aim 2: To determine if the aPWV (and sub-aim 2, measures of central BP) achieved (adjusted for baseline value) in SPRINT study subjects will be an independent predictor of the primary SPRINT outcomes (CV disease events) as well as all cause mortality, decline in renal function, rate of incident dementia and age-related cognitive decline.

SPRINT – Pulse Wave Velocity – 3

Specific Aim 3: To determine the associations at baseline between aPWV and central BP and relevant biomarkers of vascular aging and stiffness (fasting glucose, insulin, insulin sensitivity, hemoglobin A1C, and renin and aldosterone) and markers associated with chronic kidney disease (CKD – serum calcium, phosphorous, parathyroid hormone levels, hemoglobin, uric acid and urinary albumin).

Timeline

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Unanswered Questions

- Treatment goals in very old.
- How to further improve blood pressure control rates.
- How to prevent the age-related increase in blood pressure.

Strategies to delay arterial aging

- Lifestyle
  - Exercise
  - Reduced NaCl intake
  - Dietary caloric restriction
  - Resveratrol

- Currently Available Drugs
  - ACEi, ARBs
  - Aldosterone antagonists
  - Statins, SNP, L-arginine
  - Hormonal Rx in Post Menopause

- Novel Drugs
  - Cross-Link Breakers
  - Elastase inhibitors
  - MMP inhibitors

Modified from Lakatta

Acknowledgements

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  - Utah
    - Phil Kilham, MD, PhD
    - Walter Wray, PhD
    - Russ Richardson, PhD
  - Alfred Cheung, MD and the Utah SPRINT CCN sites
  - Jeff Chids
Questions...

About our logo...

The bristlecone pine tree (Pinus longaeva) – the earth's oldest inhabitant with a life span of 4,000 years – is found only in Utah and five other western states. Its extraordinary longevity and ability to adapt and survive in extremely harsh environmental conditions above 10,000 feet embodies the investigative spirit and mission of the Utah Center on Aging.