Arterial Stiffness in Geriatric Hypertension: Mechanisms and Management

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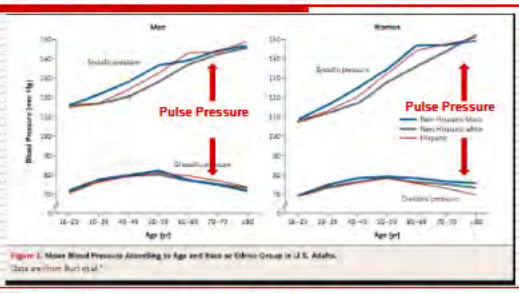
OUTLINE

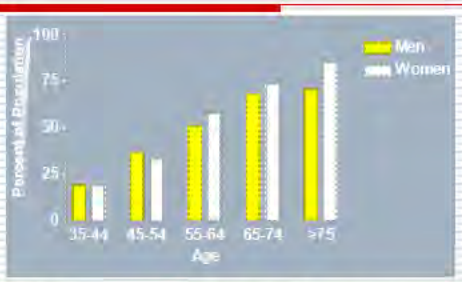
- Epidemiology
- Physiological Characteristics / Mechanisms
- Vascular stiffness as CV risk factor
- SPRINT – Pulse Wave Velocity Ancillary Study

Blood Pressure by Age and Sex



Chobanian, NEJM 357, 2007

Hypertension Prevalence by Age and Sex



NHANES III; 1999-2002; CDC NCHS Data

Will you live long enough to develop hypertension?

Residual lifetime risk for developing hypertension

Time (years)	Women age 55 % (95% confidence interval)	Women age 65 % (95% confidence interval)
10	52 (46-58)	64 (60-69)
15	72 (68-76)	81 (77-84)
20	83 (80-86)	89 (86-92)
25	91 (89-93)	–

Vasan et al.; JAMA 287:1003, 2002

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

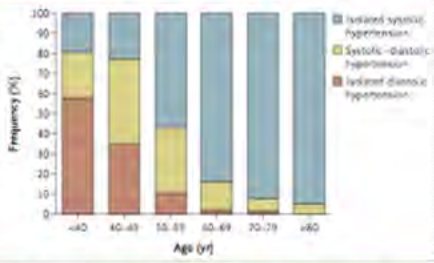
Physiological Characteristics - 1

Characteristic	Clinical Implication
Decreased vascular compliance.	Increased systolic BP and pulse pressure.
Decreased baroreceptor sensitivity.	Greater BP variability.
	Postural hypotension.
Heightened SNS activity.	Increased peripheral vascular resistance.
Increased α-adrenergic receptor responsiveness.	

Physiological Characteristics - 2

Characteristic	Clinical Implication
Increased total and central adiposity.	Effectiveness of weight loss.
Salt-sensitivity of blood pressure.	Effectiveness of salt restricted diet.
Metabolic insulin resistance.	Screen for diabetes.
Increased RAAS activity?	

Hypertension Pattern by Age



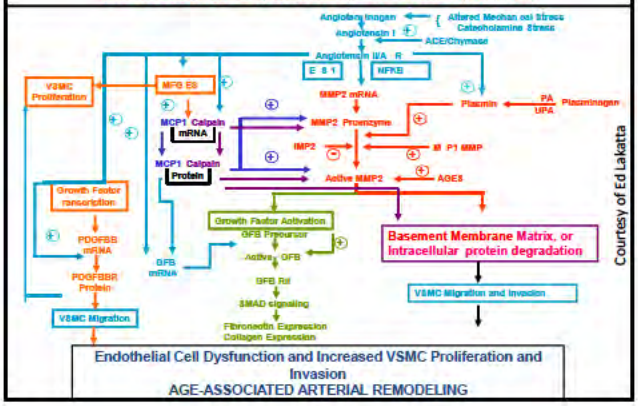
Chobanian, NEJM 357, 2007

Age-related Vascular Changes

- 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



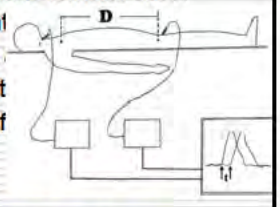
Clinical correlates of vascular aging

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

Pulse Wave Velocity: Applanation Tonometry

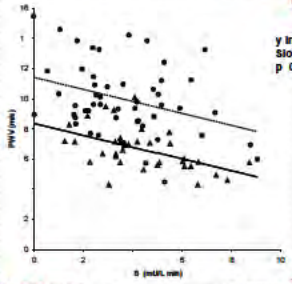
Pulse Wave Velocity (PWV): Methodology

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 dif
6. PWV= D/t (m/sec)



Stiffer arteries propagate pulse waves faster.

Vascular Stiffness and Insulin Sensitivity



	Normotensives	Hypertensives	p value
y intercept	8.34±0.53 m/s	11.40±0.64 m/s	p<0.0001
Slope	0.33±0.11	0.40±0.15	
p	0.97		

Sengstock DM. J Clin Endocrinol Metab 2005;90:2823

Advanced glycosylated end-products (AGEs)

- In non-diabetics, HgbA1c predicts future hypertension.

Table 1. Selected Characteristics of the Study Participants, According to the Glycated Hemoglobin Value at Baseline.*

Value	Glycated Hemoglobin Category					
	Any (N=11,092)	<5.0% (N=949)	5.0 to <5.5% (N=4950)	5.5 to <6.0% (N=3683)	6.0 to <6.5% (N=1031)	≥6.5% (N=479)
Glycated hemoglobin (%)	5.5±0.6	4.8±0.2	5.2±0.1	5.7±0.1	6.1±0.1	7.4±1.4
Hypertension (%)	32.0	26.9	26.7	33.8	49.4	56.8

Selvin, N Engl J Med 2010;362:800

Glycated hemoglobin associated with PWV

- GHb predicted higher PWV (OR 1.79; 95% CI (1.09–2.93)

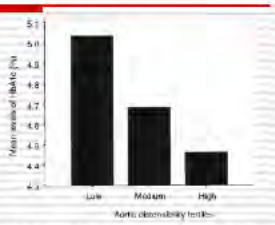
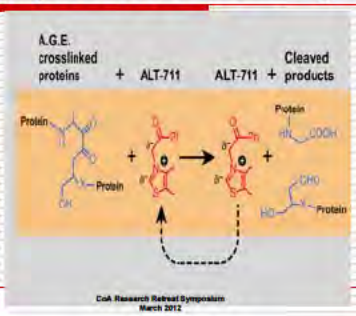


Figure 1 HbA1c levels (modelled continuously) were inversely correlated with overall aortic distensibility tertiles (Kendall's τ-b; τ = −0.205, P = 0.001). Model adjusted for age, gender, BSA, smoking status, lipid profile, and systolic blood pressure.

Stakos. Euro J of Endo (2007) 157 63–68

Breaking up AGE: ALT-711 - Alagebrium



Cross-Link Breaker Therapy

Fig. 1. ALT-711 significantly decreases the AGE of the carotid artery and PWV. Baseline measures before drug are indicated as B1, B2, and B3. Values postdrug are depicted as percent of average baseline value ± SE. The overall drug effect, assessed by one-way ANOVA for repeated measures was $P = 0.007$ for the changes from the average baseline value in PWV and $P = 0.046$ for AGE. *, significant difference from control by Bonferroni–Dunn post hoc analysis.

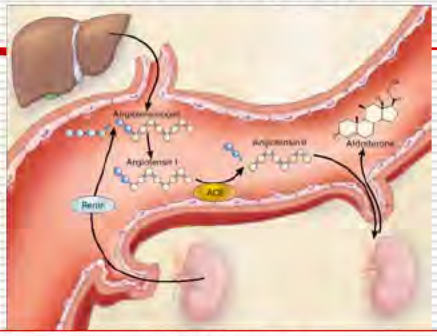
beginning with the first set of measurements at 4 weeks after the end of exposure to drug. PWV and AGE progressively decreased, both reaching a nadir at 6 weeks [PWV to 74.2 ± 4.4% of baseline (B), $P = 0.007$; AGE to 41 ± 7.3% of B, $P = 0.046$]. Thereafter, both parameters gradually increased and had returned to baseline values at 39 weeks. There were no significant differences among the three baseline serial determinations of PWV or AGE, demonstrating the reproducibility of these measurement techniques (Fig. 1). The magnitude of the drug-induced reduction of the PWV and AGE was proportional to the baseline measurement (PWV, $r = 0.80$, $P < 0.05$; AGE, $r = 0.75$, $P = 0.07$).

Cardiac Parameters. The cardiac parameters LV EDD and ESD,

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

Vaitkevicius PNAS 98:1171, 2001

Renin-Angiotensin Aldosterone System



Weber. NEJM 345: 1689, 2001

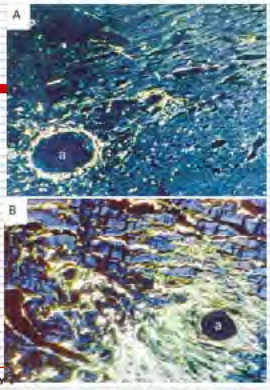
Aldosterone Effects

Well Known

- Sodium reabsorption
- Water retention
- K^+ and Mg^{++} loss
- Hypertension

Less well known

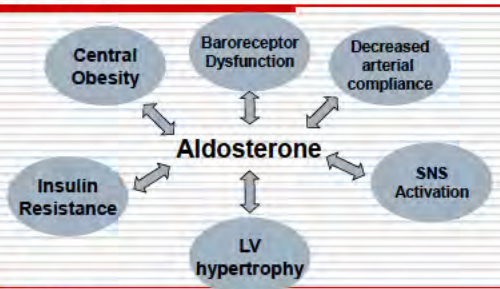
- Decreased vascular compliance
- Myocardial fibrosis
- Decreased baroreceptor function
- Endothelial dysfunction
- Thrombosis



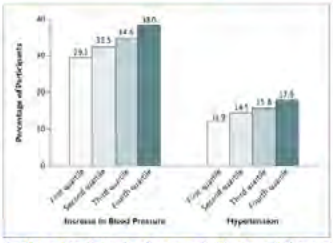
- Aldosterone is produced by vascular smooth muscle cells.
- Aldosterone promotes vascular remodeling.
  - Perivascular fibrosis
  - Vascular stiffness
  - Organ (cardiac, renal) fibrosis

Websr. NEJM 345: 1689, 2001

Aldosterone and the Hypertension Syndrome



Age- and Sex-Adjusted Rates of Blood-Pressure Outcomes at Four Years According to Quartile of Serum Aldosterone Level



Aldosterone levels in the physiological range influence future risk of hypertension.

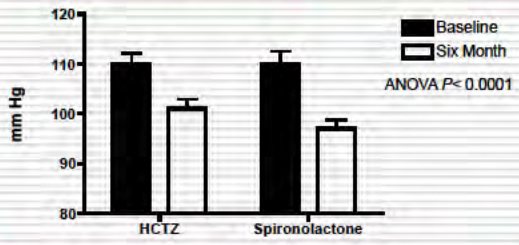
Vasan, R. S. et al. N Engl J Med 2004;351:33

Hypothesis

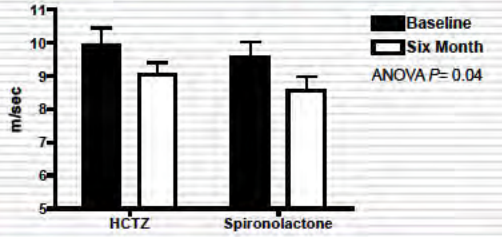
Compared to older hypertensive subjects randomized to therapy with a thiazide diuretic, those treated with spironolactone will demonstrate greater improvements in vascular and neurohumoral outcome measures.

- **Decreased SNS activity**
- **Improved metabolic insulin sensitivity**
- **Decreased arterial stiffness**

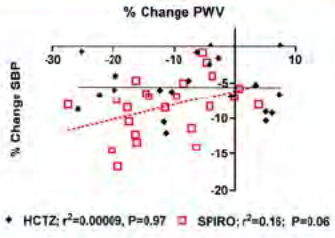
Mean Arterial Blood Pressure



Pulse Wave Velocity



Is change in PWV solely due to BP reduction?

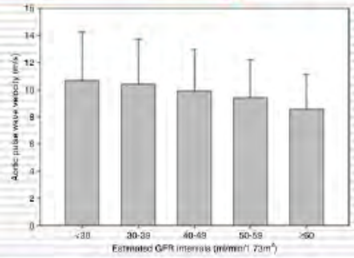


Conclusions

- 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.

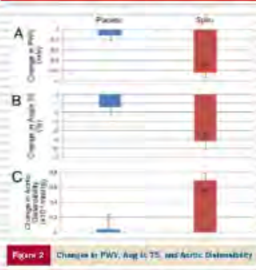
Kithas and Supiano; JAGS 58:1327; 2010

Chronic Kidney Disease: PWV in Chronic Renal Insufficiency Cohort (CRIC) Study



Townsend, Am J Hypertens 2010; 23:282

Aldosterone and PWV in CKD

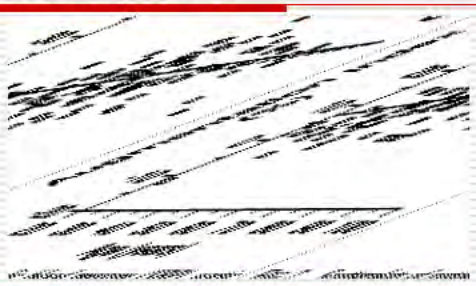


- CKD 2 or 3. 40 weeks Rx spironolactone 25 mg/d (with ACE or ARB)
- Edwards, J Am Coll Cardiol 2009;54:505

OUTLINE

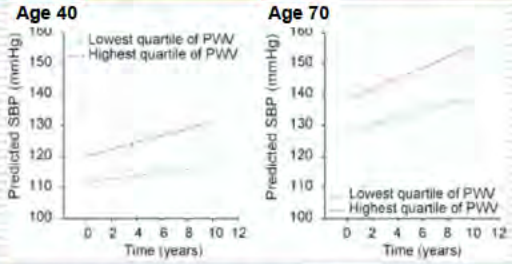
- Vascular stiffness as CV risk factor
- SPRINT – Pulse Wave Velocity Ancillary Study

Vascular stiffness contributes to age-related increase in BP



Vaitkevicius, *Circulation* 1993, 88:1456

PWV predicts incident hypertension – 1

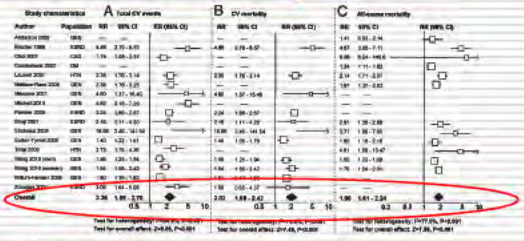


Najjar, J Am Coll Cardiol 2008;51:1377

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

- Inoue N, Maeda R, Kawakami H, et al. Aortic pulse wave velocity predicts cardiovascular mortality in middle-aged and elderly Japanese men. Circ J 2009;73 549-53.
- Matsuoka O, Otsuka K, Murakami S, et al. Arterial stiffness independently predicts cardiovascular events in an elderly community – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study. Biomed Pharmacother 2005;59 Suppl 1:S40-4.
- Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005;111 3384-90.
- Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004;43:1239-45.
- Hansen TW, Staessen JA, Torp-Pedersen C, et al. Ambulatory arterial stiffness index predicts stroke in a general population. J Hypertens 2006;24 2247-53.

Vascular stiffness association with CV Risk – independent of BP – 2



Vlachopoulos, Am Coll Cardiol 2010;55:1318

SPRINT

Systolic Blood Pressure Intervention Trial

- ***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 A_1C, 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

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018
SPRINT Parent Study									
• Recruitment		→							
• Annual Visits		X	X	X	X	X	X	X	
Proposed Ancillary Study									
• Recruitment		→							
• Annual Visits			X	X	X				
• Analyze and report baseline data				X	X				
• Program end-of-study analyses					X				

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
- Curren ly 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

- Research Support
  - NIA K07 AG028403
  - NHLBI R01 HL10741
  - VA R&D Merit Review
  - VA Salt Lake City GRECC
- Collaborators
- UMichigan
  - David Sengstock, MD
  - Peter Vaitkevicius, MD
- Utah
  - Phil Kithas, MD, PhD
  - Walter Wray, PhD
  - Russ Richardson, PhD
  - Alfred Cheung, MD and the Utah SPRINT CCN sites
  - Jeff Childs

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.