CENTRAL BLOOD PRESSURE: A New Vital Sign?

Mary J. Roman, M.D.
Professor of Medicine
Weill Cornell Medical College
New York, New York, USA

The Korean Society of Cardiology
55th Annual Scientific Meeting
December 2, 2011

BLOOD PRESSURE = $\frac{\text{Systolic Pressure}}{\text{Diastolic Pressure}}$

in the **BRACHIAL ARTERY**

Palpation of the Pulse

Ancient Chinese Drawing

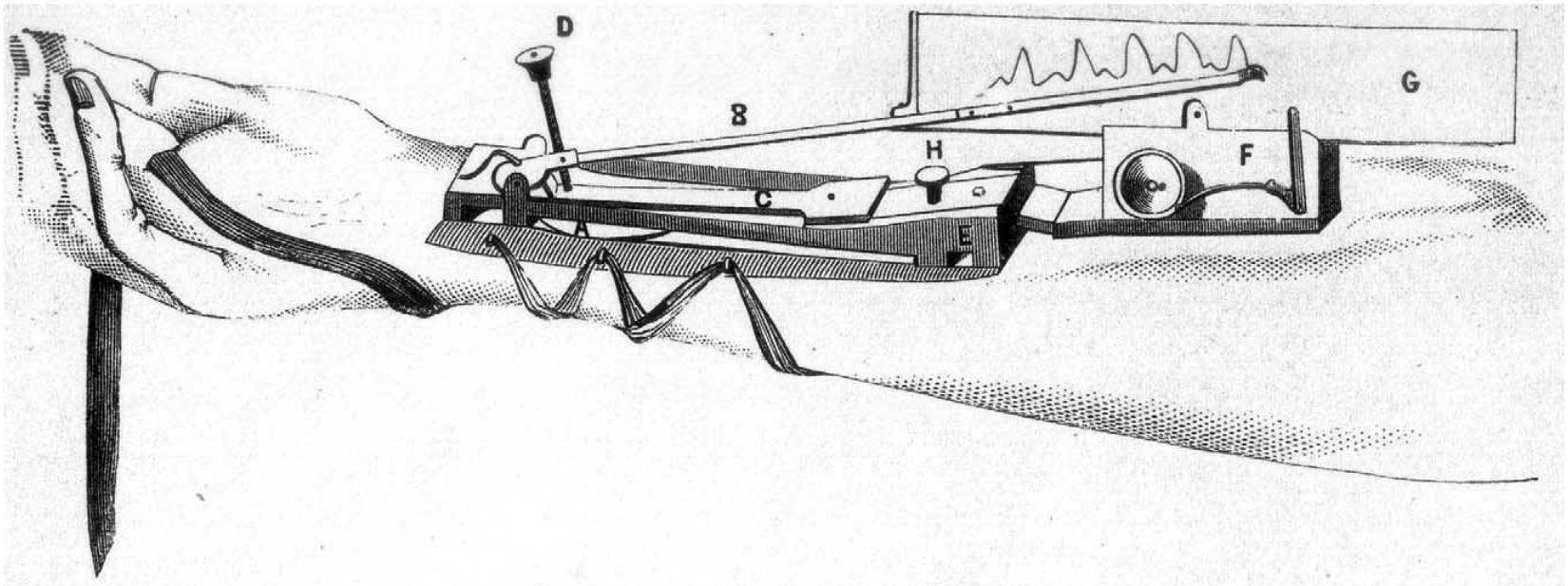
Jan Steen, *The Lovesick Woman*, 1660

Palpation of the Pulse

Physician Taking Pulse, Delhi painter, c. 1830

A-C Guillemot, *Erasistratus Discovering the Cause of Antiochus' Disease,* 1808

Pulse Wave Recording



PROF. MAREY'S SPHYGMOGRAPH.

A, the pulse spring; **B,** the tracer, or writing lever; **C,** the lever for transmitting motion from the former to the latter (A to B); **D,** the pressure screw; **E,** the body of the instrument; **F,** the box containing clock-work; **G,** the traveller; **H,** the screw for adjusting pulse spring at a proper obliquity.

Etienne Jules Marey (1830-1904)

Pressure Waveform in Health and Disease

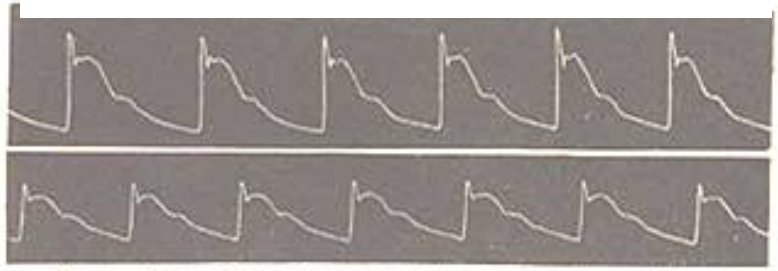
"Soft and frequent pulse of mild pyrexia"

"Normal soft pulse"

"Pulse of the same person after exercise and residence in the country"

"Wiry pulse of rheumatic carditis"

"Hard and long pulse of hypertrophy of the left ventricle with dilatation"



"Hard pulse of chronic Bright's disease"

J. Burdon Sanderson, *Handbook of the Sphygmograph: Being a Guide to its Use in Clinical Research*, 1867.

Mercury Sphygmomanometry

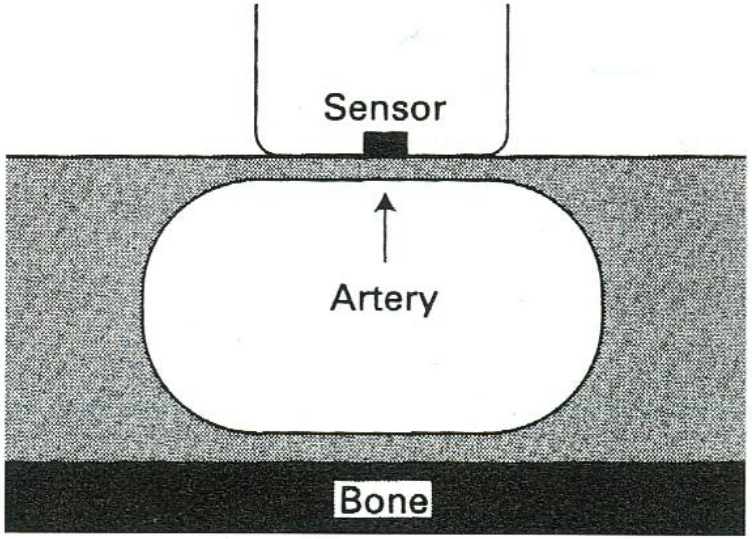
Riva-Rocci (1896)

Nikolai Korotkoff (1905)

Mercury Sphygmomanometry

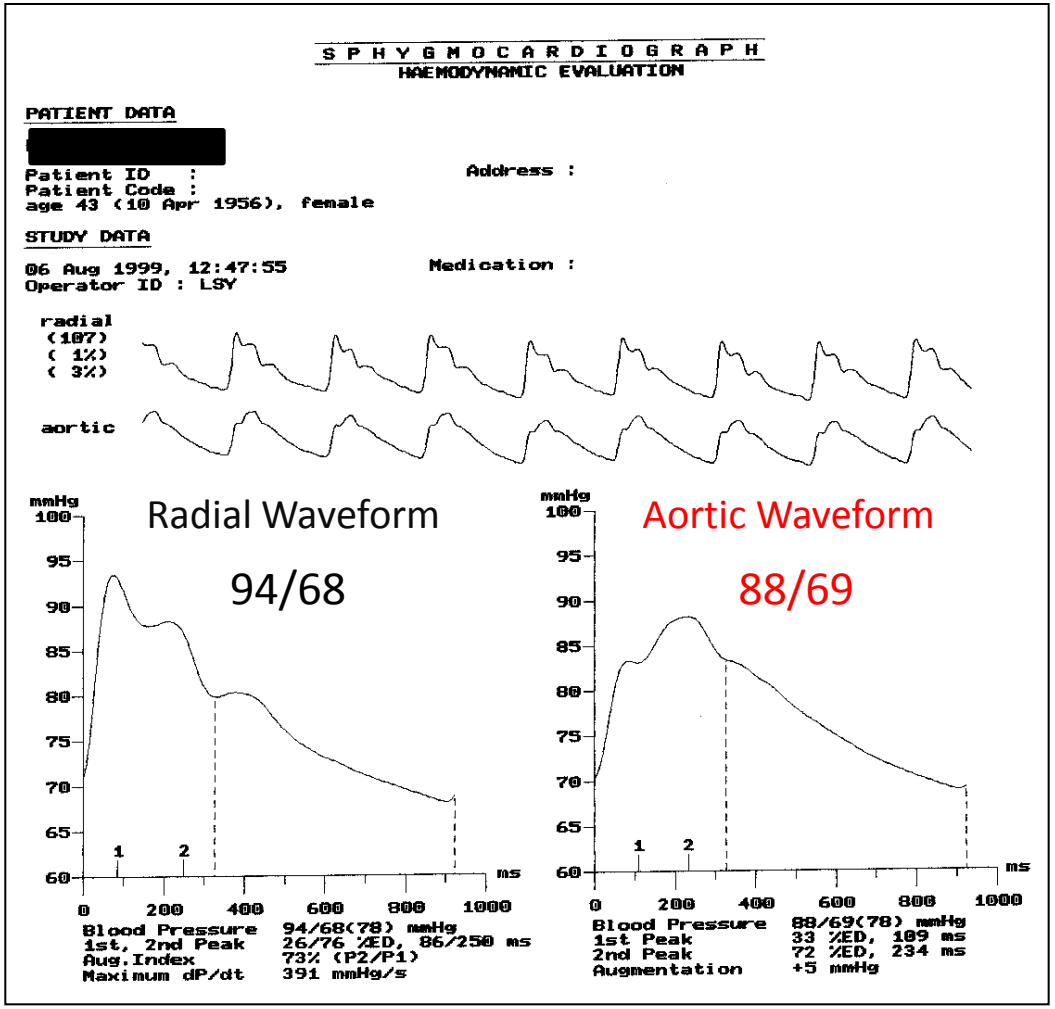
Modern-Day Sphygmography

Applanation Tonometry



SphygmoCor

Pulse Wave Analysis
Noninvasive Central BP Measurement



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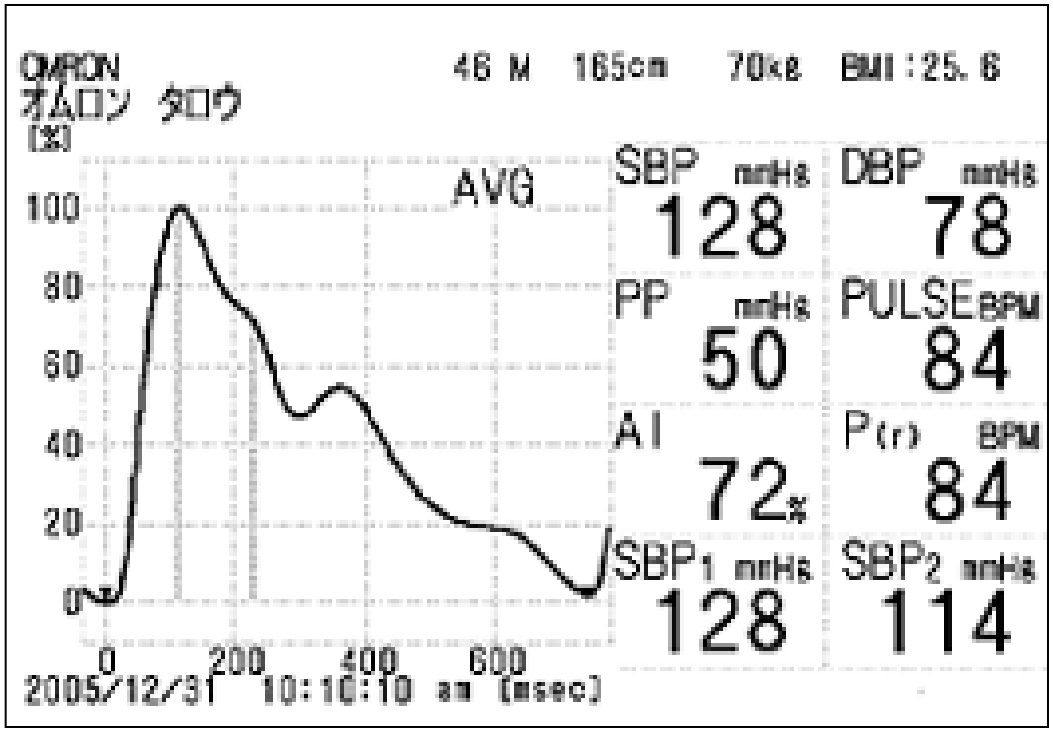
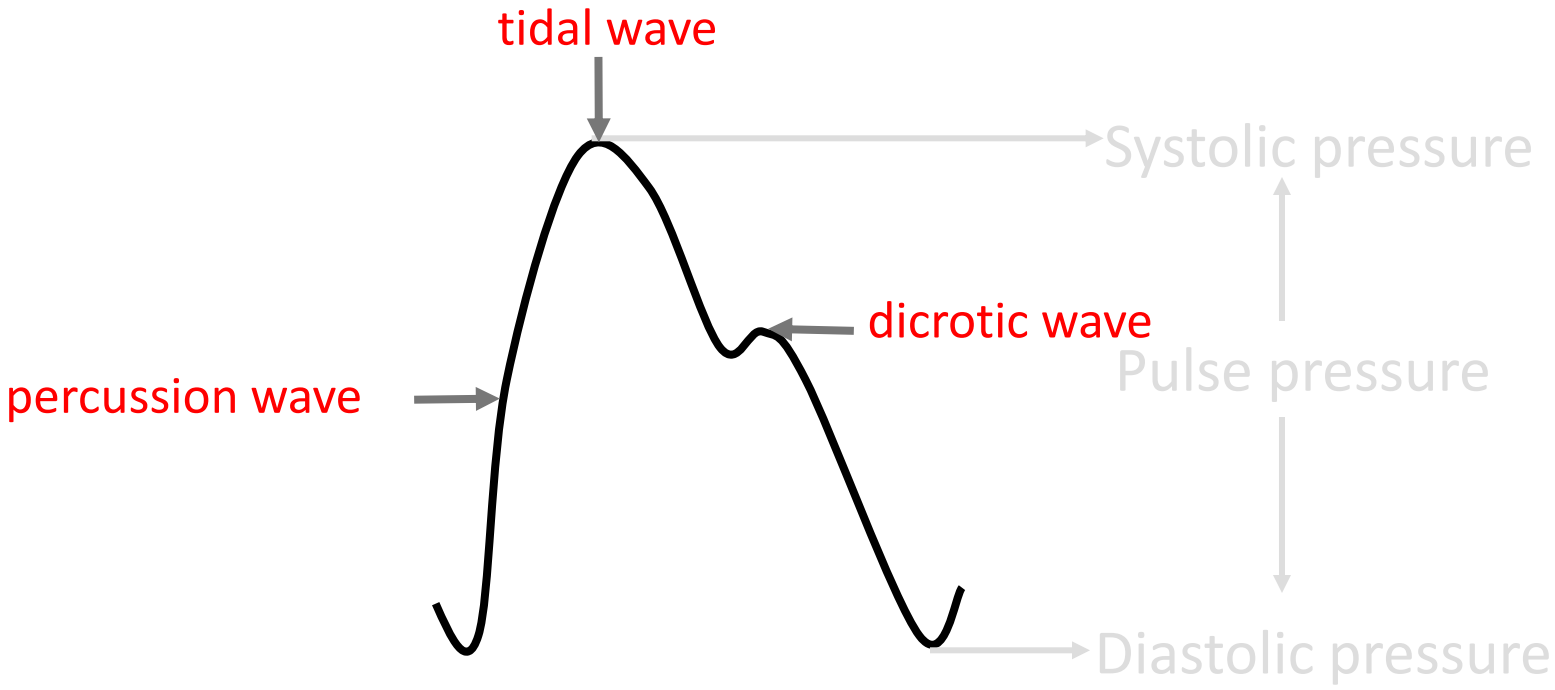


Omron

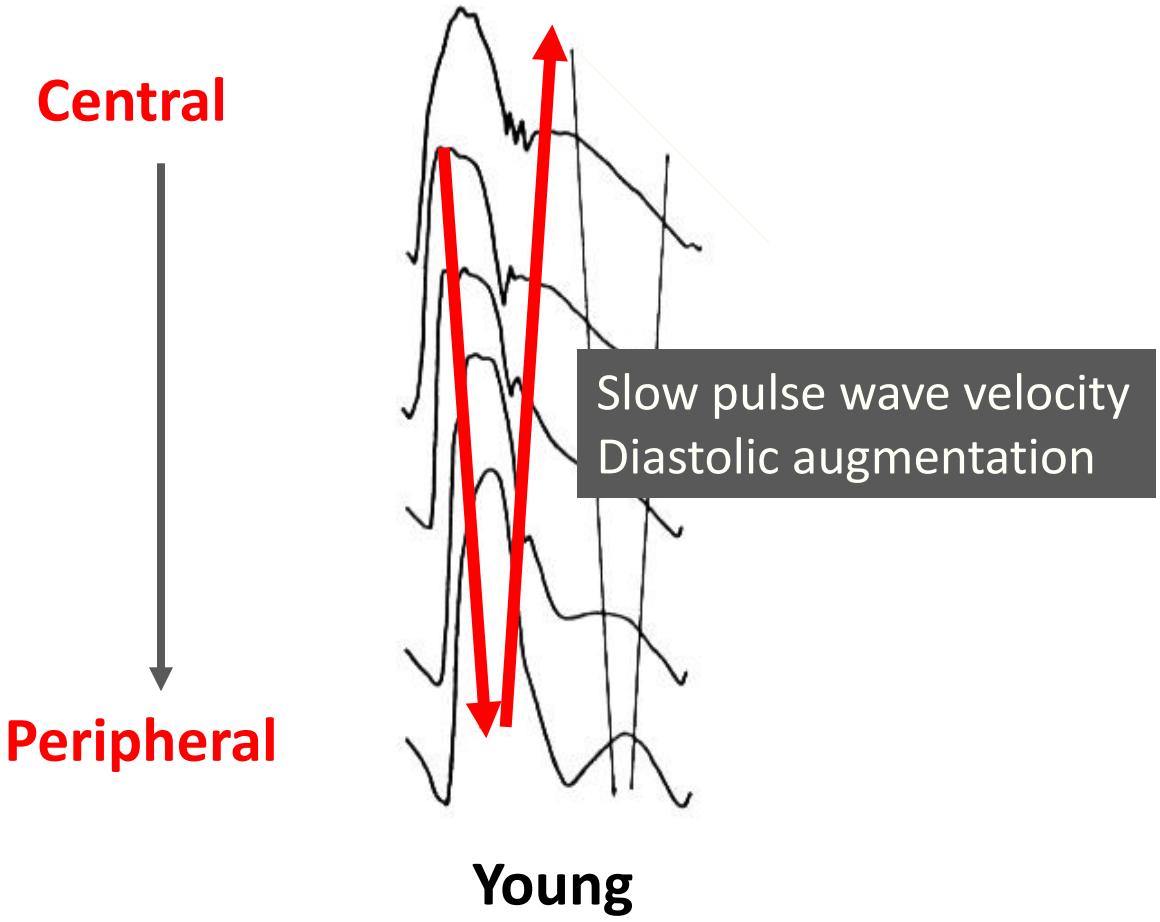
Why do central and peripheral blood pressures differ?

CENTRAL PRESSURE WAVEFORM



CENTRAL PRESSURE WAVEFORM

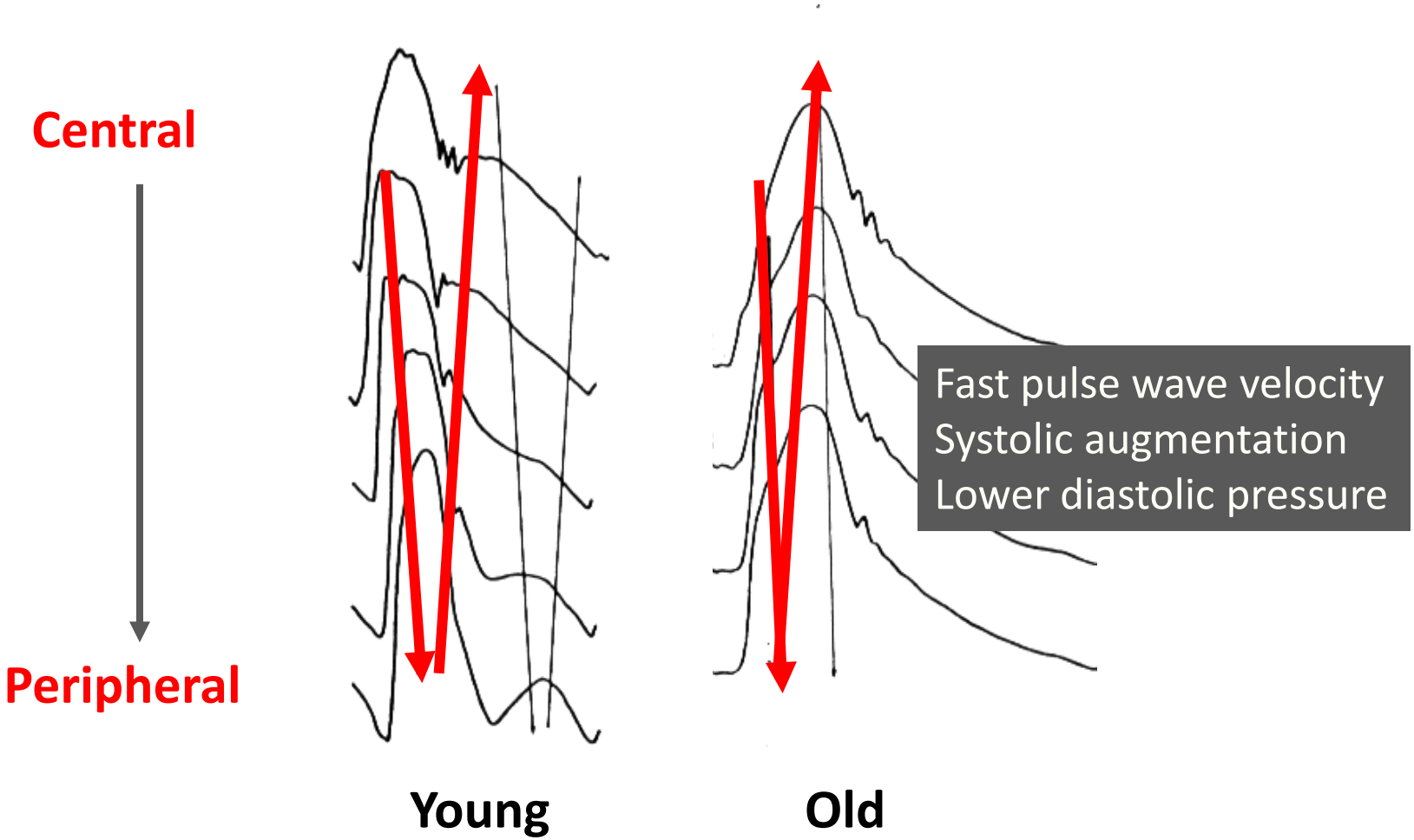
Aging Changes



O'Rourke MF. *Arterial Function in Health and Disease*, 1982.

CENTRAL PRESSURE WAVEFORM

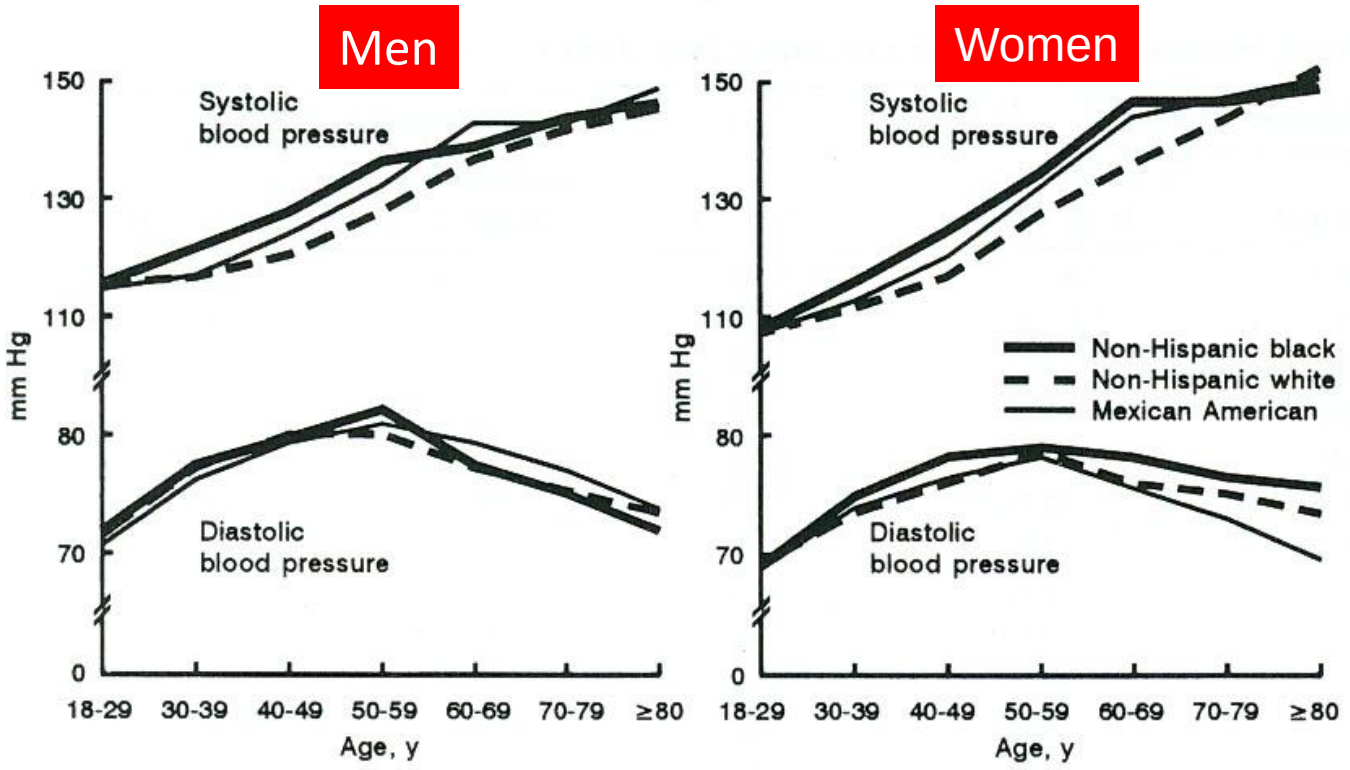
Aging Changes



O'Rourke MF. *Arterial Function in Health and Disease*, 1982.

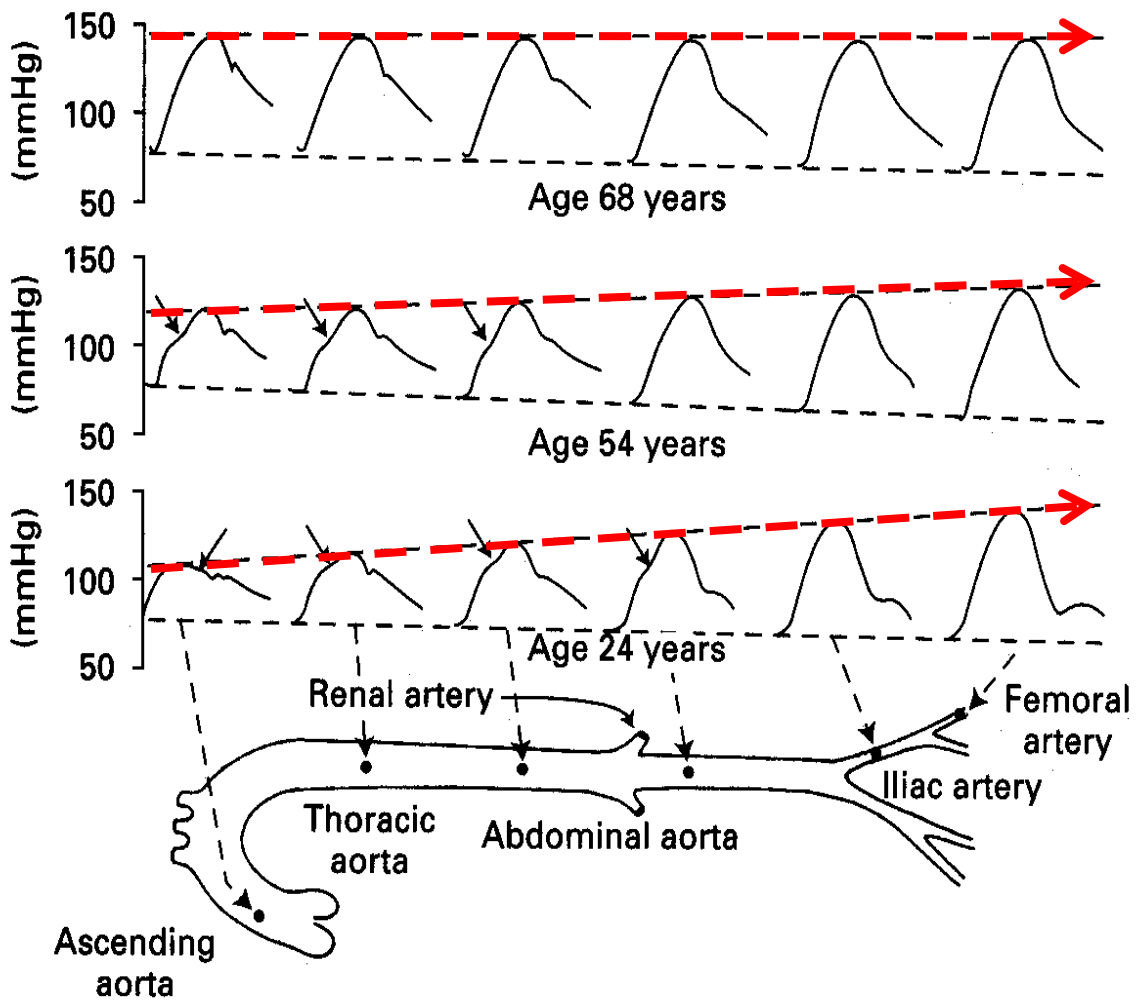
BLOOD PRESSURE

Aging Changes



NHANES 3. *Hypertension* 1995;25:305-313 (9901 adults).

Pressure Wave (PP) Amplification



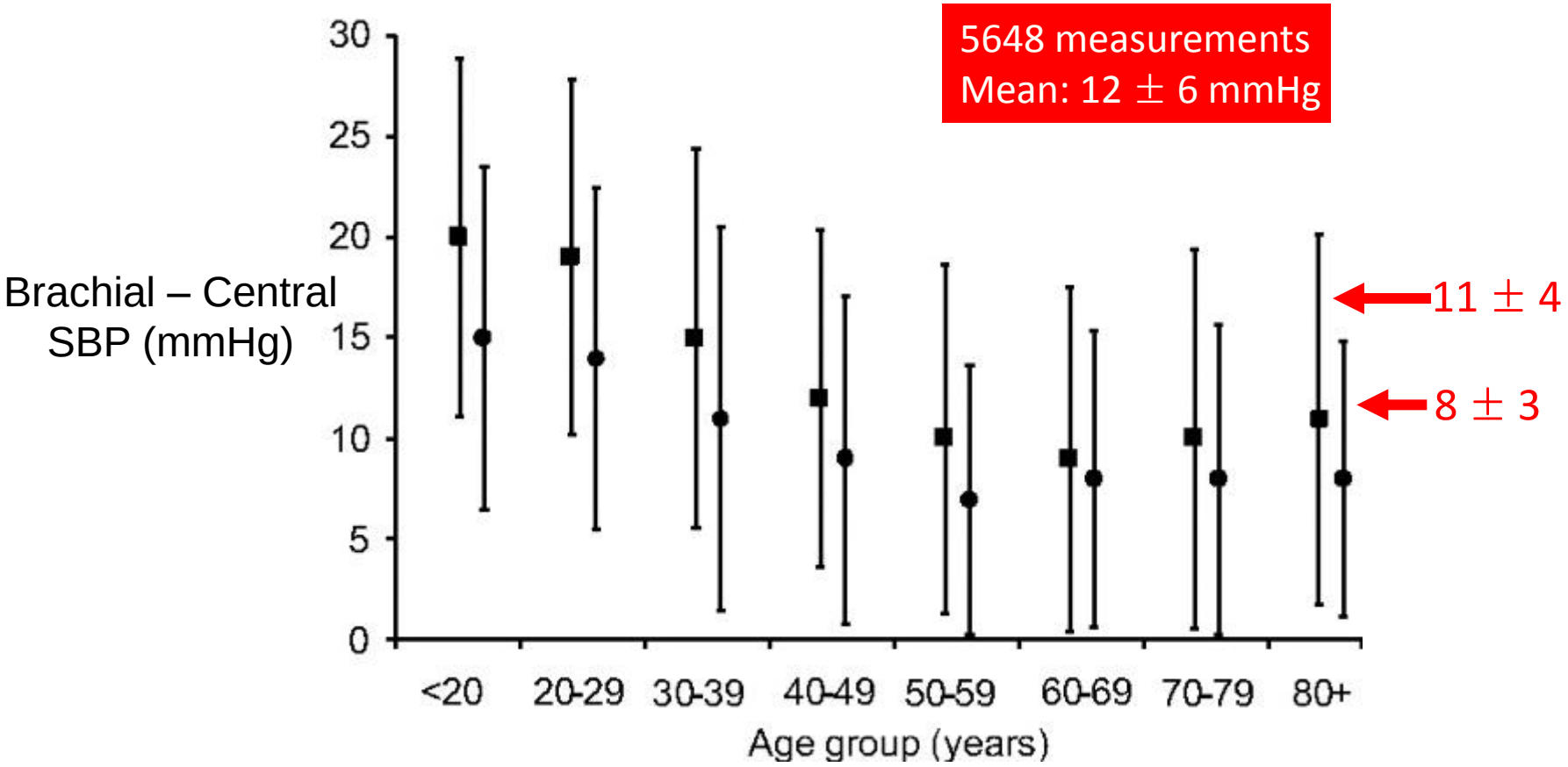
Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries* (5th Ed.); 2005:88.

Determinants of Amplification

- Arterial stiffness
- Wave reflections
- Heart rate
- LV contractility

How much do central and brachial blood pressures differ?

Central *vs*. Brachial Systolic Pressure



McEniery CM *et al*. *Hypertension* 2008;51:1476-82.

Importance of Central Blood Pressure

- More accurate representation of load imposed on the left ventricle and coronary and cerebral vasculature
- Higher central systolic pressure increases left ventricular afterload
- Lower central diastolic pressure decreases coronary perfusion

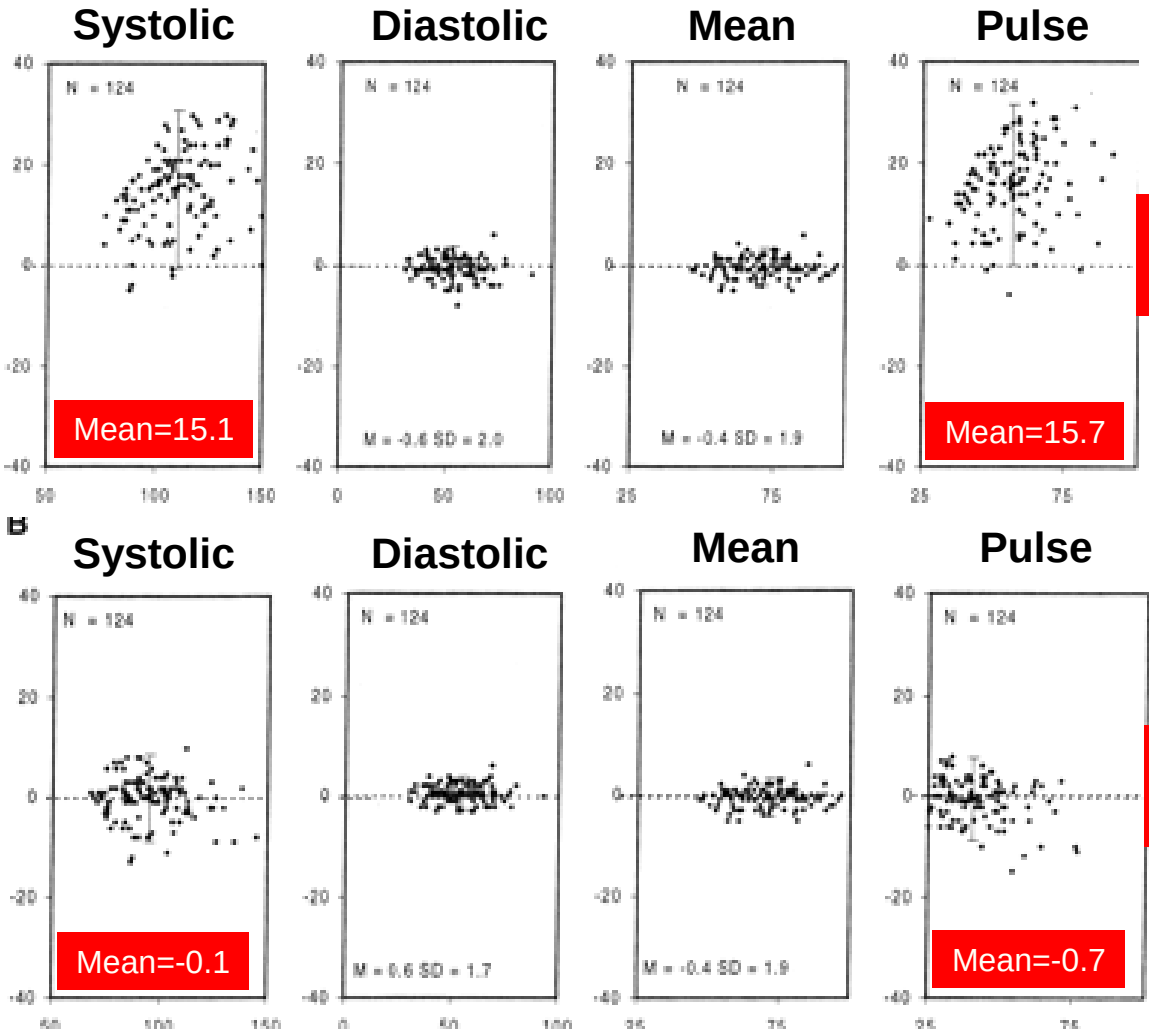
Should we supplement brachial BP measurement with central BP measurement?

Is central BP measurement an effective biomarker that can be used to stratify risk and guide therapy?

Requirements for a New Biomarker

- Safe, accurate, reproducible

ACCURACY



Invasively measured radial and aortic pressures

Noninvasively estimated and invasively measured aortic

Bland-Altman plots for measured radial and aortic pressures (top) and estimated (by generalized transfer function) and measured aortic pressures (bottom).

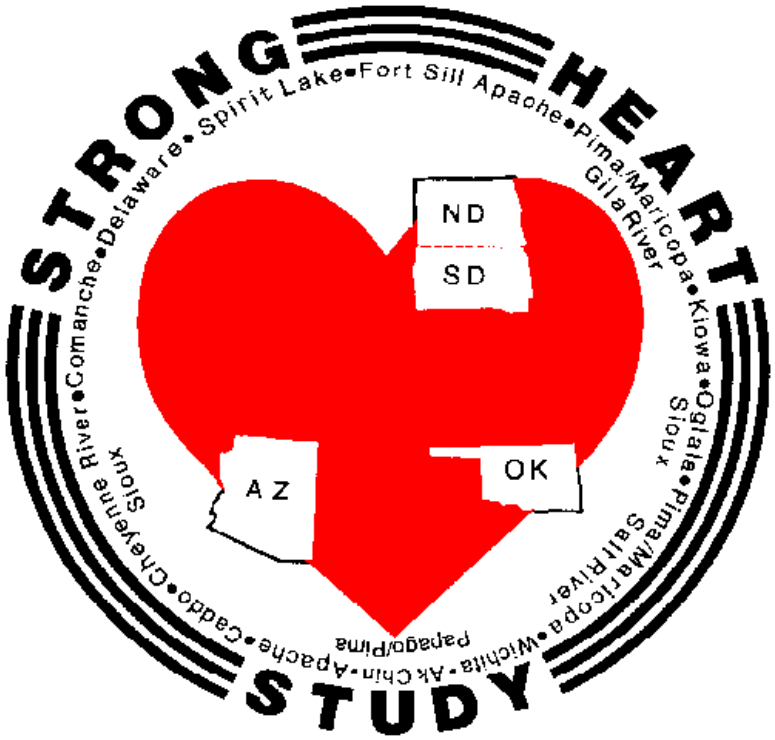
Pauca AL *et al*. *Hypertension* 2001;38:932-937 (62 subjects with aortic and radial artery catheters ± NTG).

Requirements for a New Biomarker

- Safe, accurate, reproducible
- Correlate with disease

STRONG HEART STUDY

STRONG HEART STUDY



- NHLBI-funded study of prevalent and incident cardiovascular disease
- Initiated in 1988
- 4,549 people (age 45-74)
- 13 American Indian tribes
- High rates of obesity and diabetes

SHS STUDY POPULATION

3,520 American Indians who underwent radial applanation tonometry and carotid ultrasound at Exam 3 of The Strong Heart Study

- Age: 63±8 years (51-84 years)
- Female: 65%
- Diabetes: 47%
- Hypertension: 52%

Blood Pressure Measurement

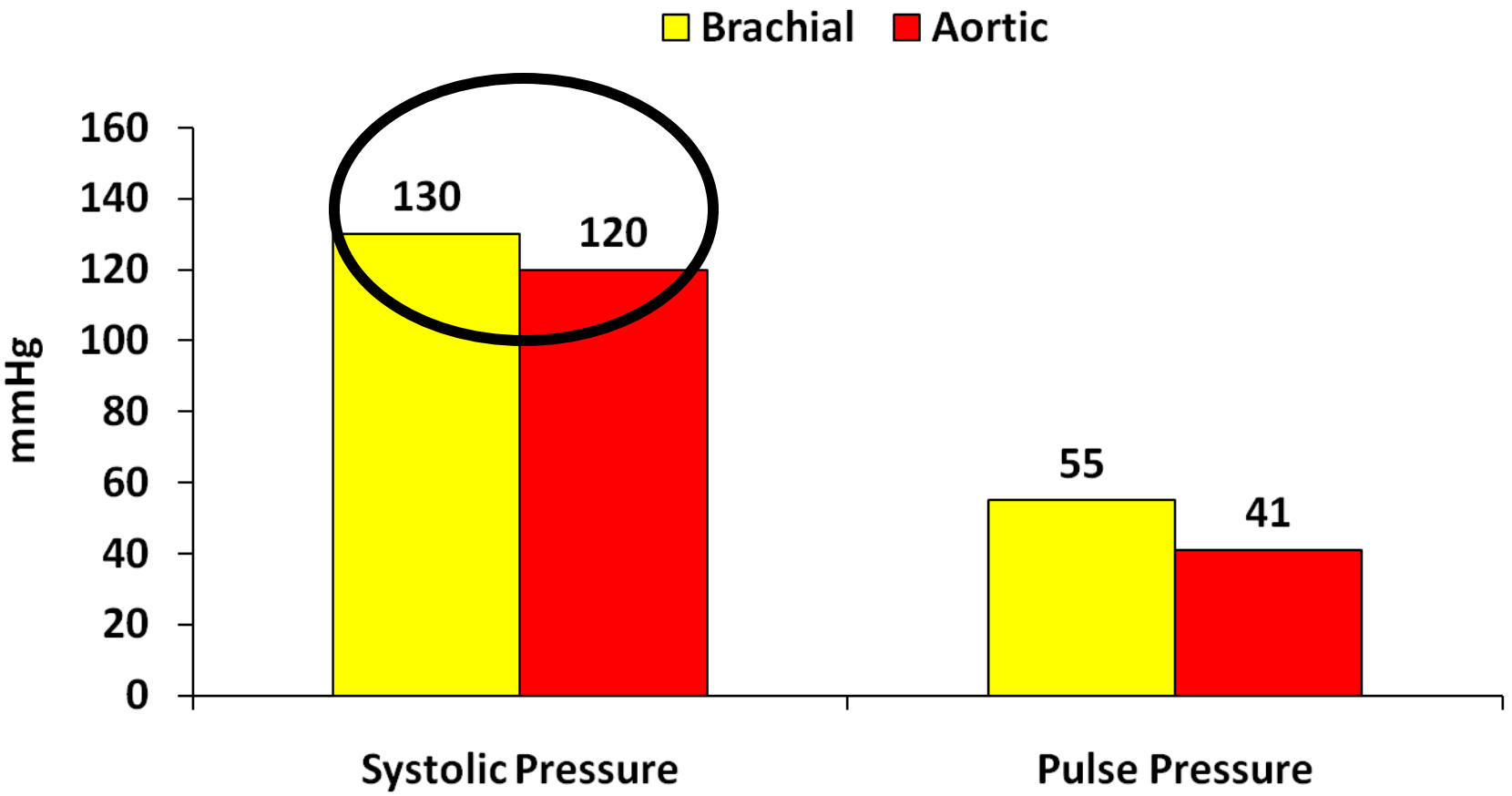
Brachial Blood Pressure

- Seated and resting for 5 minutes
- Measured with cuff and mercury sphygmomanometry
- Last 2 of 3 measurements averaged

Central Blood Pressure

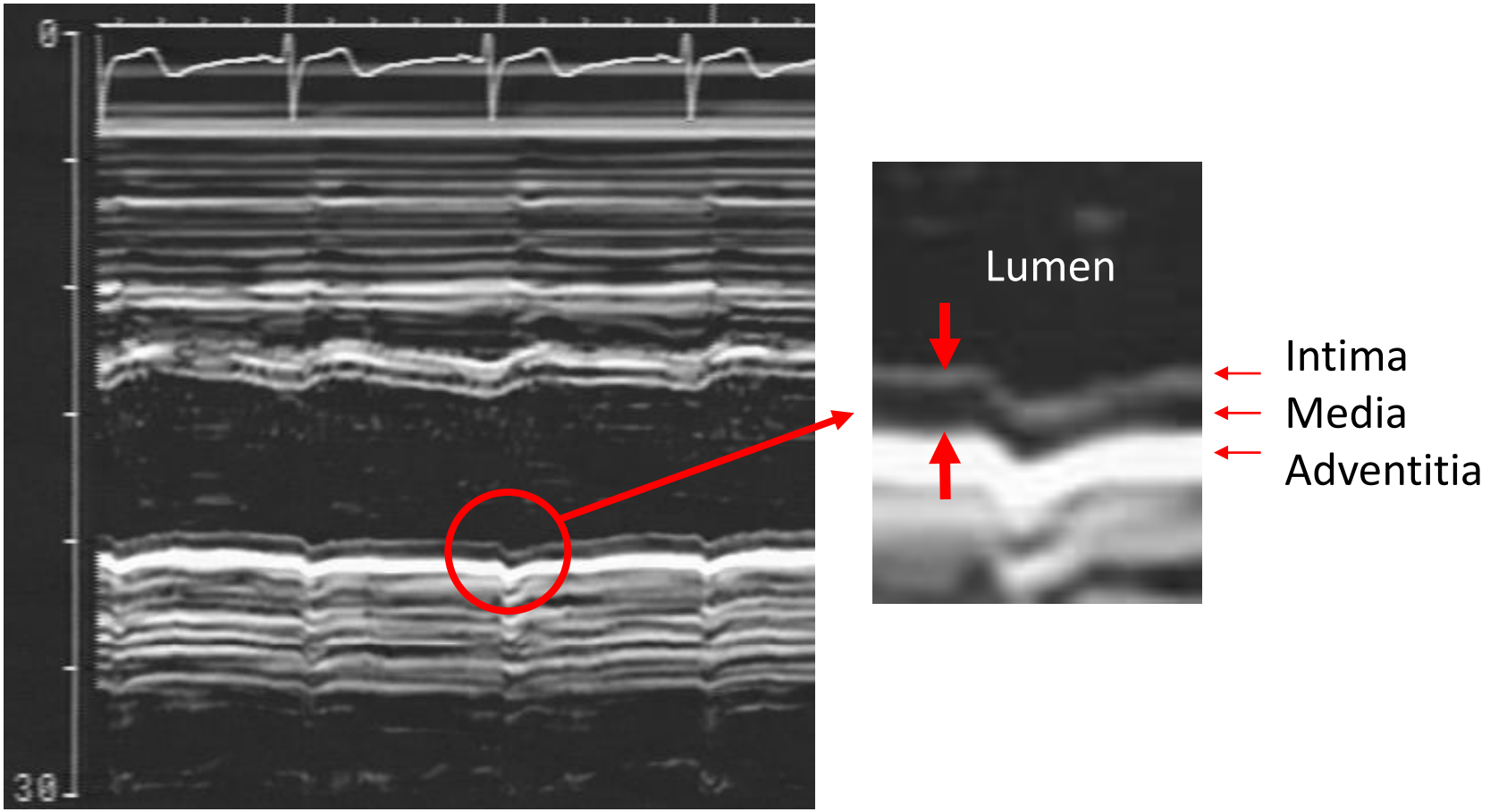
- Radial applanation tonometry (SphygmoCor)

Brachial & Aortic Blood Pressures*



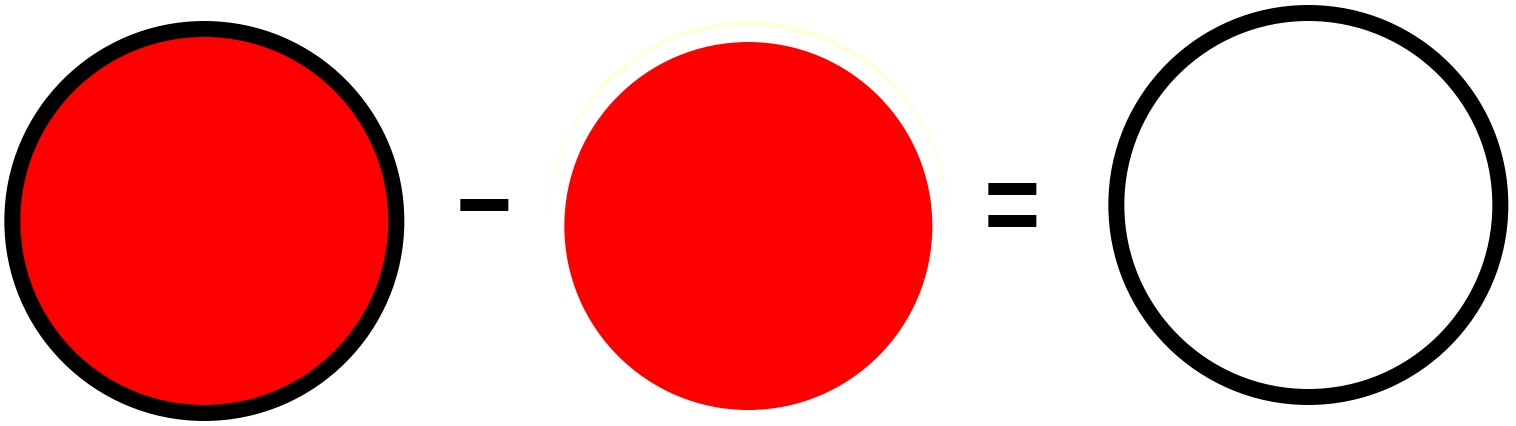
*p<0.001 for both comparisons

Carotid Intimal-Medial Thickness (IMT)



VASCULAR MASS

Arterial Hypertrophy



π (IMT + Diameter/2)^2 − π (Diameter/2)^2 = Wall Cross-Sectional Area

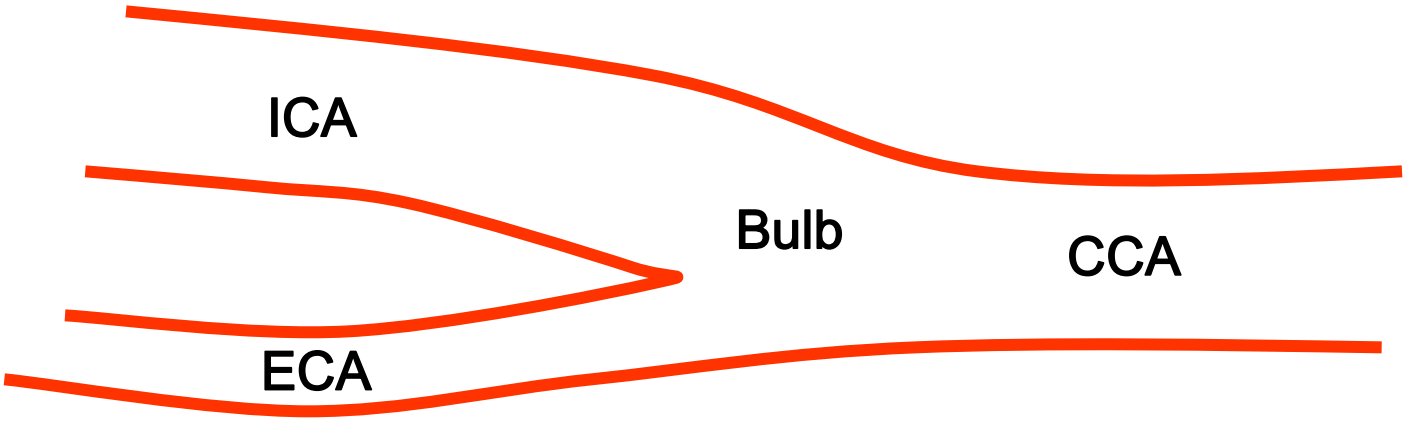
SUBCLINICAL ATHEROSCLEROSIS

Carotid Plaque

Focal thickening >50% of surrounding wall

PLAQUE SCORE

Extent of Atherosclerosis



Presence of plaque assessed in each of the 4 segments of the right and left vessels

Possible score: 0-8

Relations of BP to Arterial Hypertrophy and Extent of Atherosclerosis

	IMT	Vascular Mass	Plaque Score
Brachial SBP	0.196	0.264	0.221
Central SBP	0.257	0.317	0.288
Brachial PP	0.249	0.289	0.309
Central PP	0.293	0.320	0.364

$p<0.001$ for all correlations

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P, Brachial **PP** *vs*. SBP	**<0.001**	**<0.02**	**<0.001**
P, Central **PP** *vs*. SBP	**<0.001**	ns	**<0.001**

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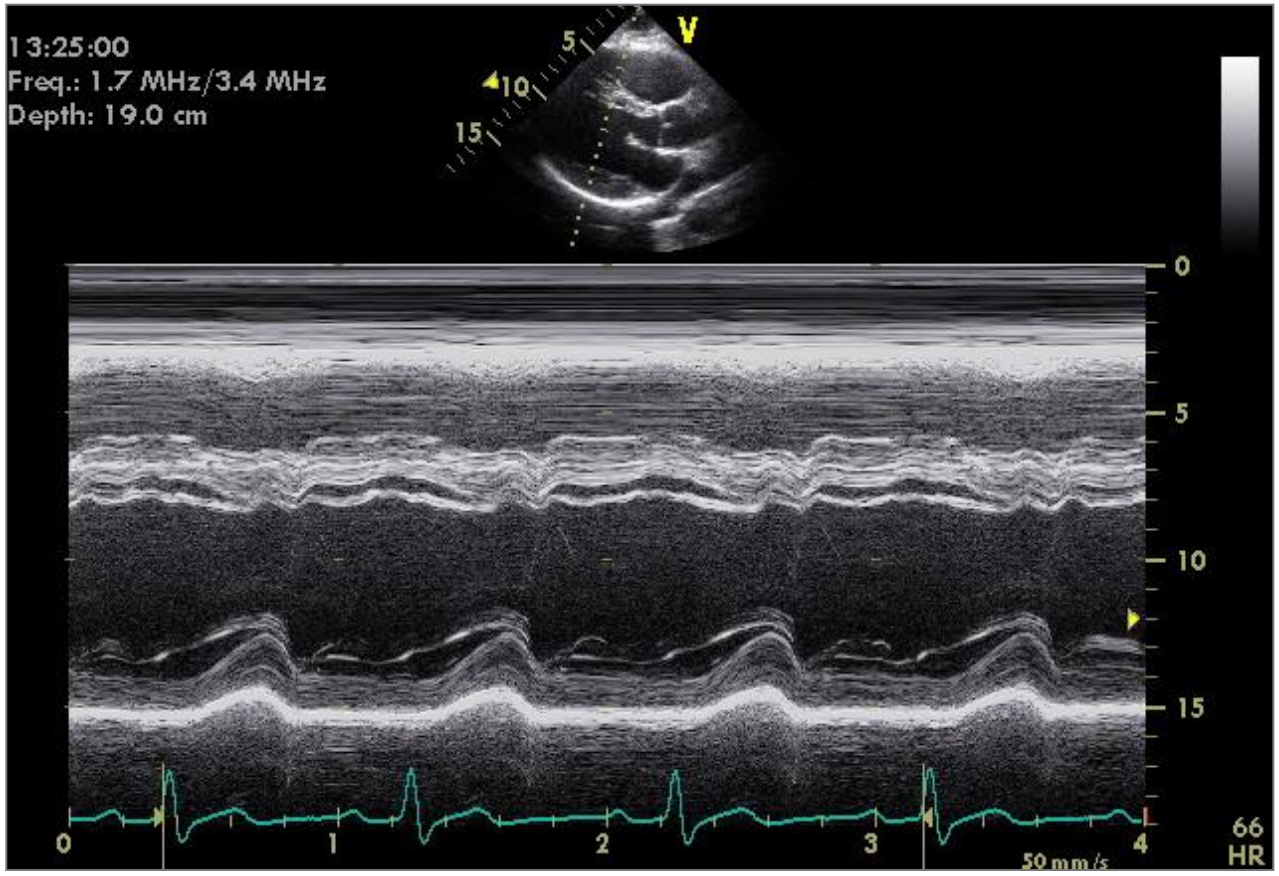
P, Central PP *vs*. SBP	<0.001	ns	<0.001
P, **Central** *vs*. Brachial SBP	**<0.001**	**<0.001**	**<0.001**
P, **Central** *vs*. Brachial PP	**<0.002**	**<0.05**	**<0.001**

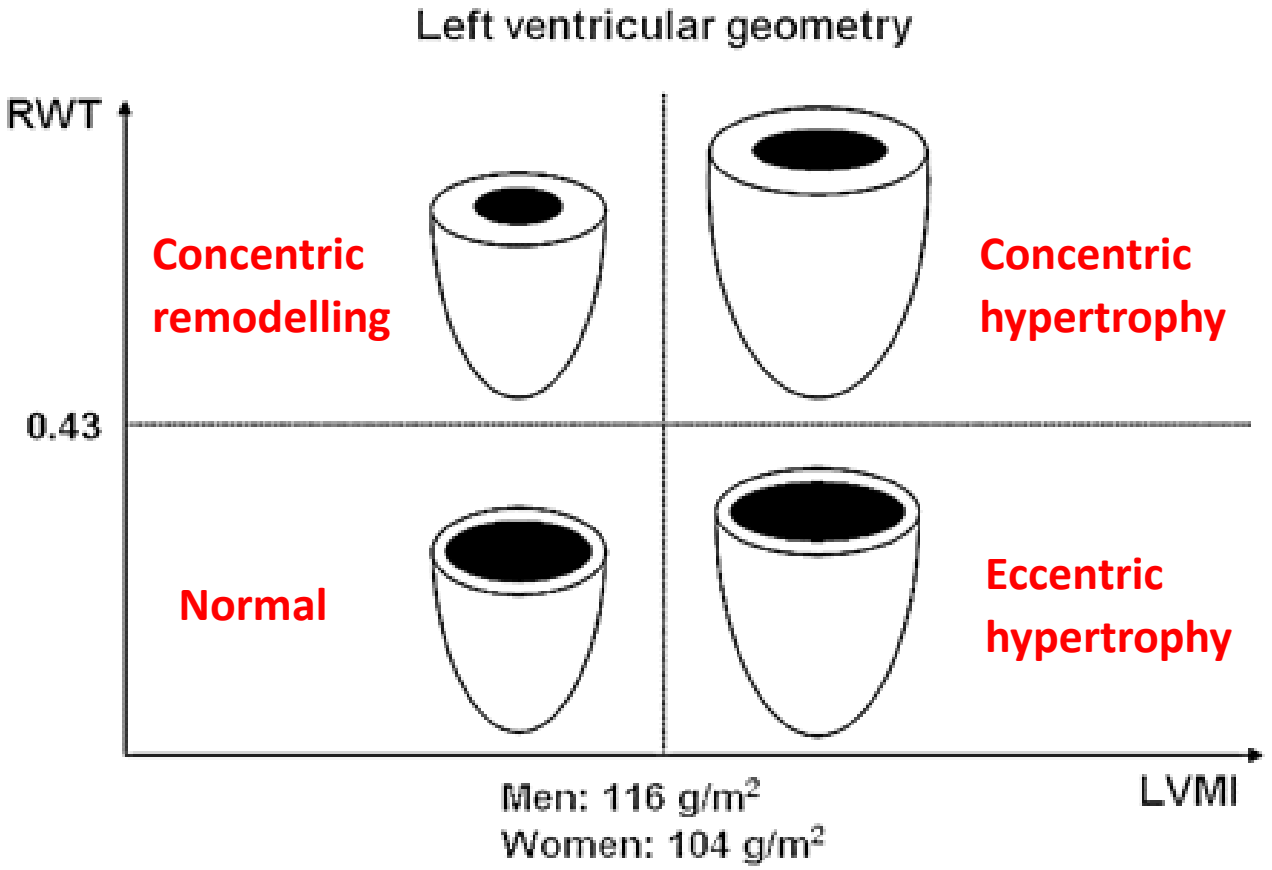
Roman MJ *et al*. *Hypertension* 2007;50:197-203.

MEASUREMENT OF LV MASS



LVM = 0.8 (1.04[($LVID_d$ + PWT_d + SWT_d)^3 - $LVID_d^3$]) + 0.6 gm

LV GEOMETRY
Relative Wall Thickness



Ganau *et al*. *JACC* 1992; 19:1550-1558

Relations of BP to LV Mass and Geometry

	Relative Wall Thickness	Left Ventricular Mass Index
Brachial SBP	0.250	0.374
Brachial PP	0.130	0.290
Central SBP	0.286	0.396
Central PP	0.167	0.335

$p<0.001$ for all correlations

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P, Brachial **SBP** vs. PP	**<0.001**	**<0.001**
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Roman MJ *et al*. *J Hypertens* 2010;28:384-388.

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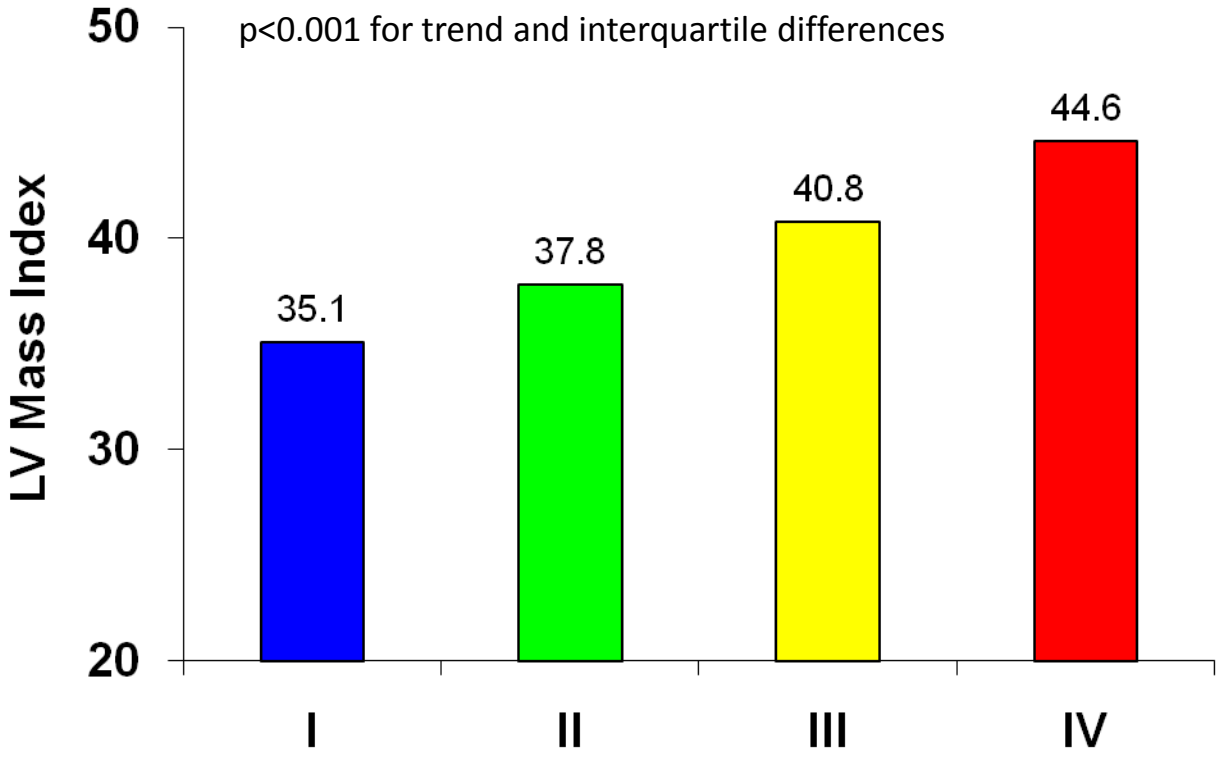
Central SBP	0.286	0.396
Central PP	0.167	0.335
P, **Central** vs. Brachial SBP	**<0.005**	NS
P, **Central** vs. Brachial PP	**<0.02**	**<0.005**

Roman MJ *et al*. *J Hypertens* 2010;28:384-388.

LV Mass Index *vs*. Quartiles of Central Systolic Pressure



Roman MJ *et al*. *J Hypertens* 2010;28:384-388.

Central BP better correlates with cardiovascular target organ damage than does brachial BP.

HYPOTHESIS

Absolute (systolic) pressure is a more important stimulus to LV hypertrophy and remodeling, whereas pulsatile stress (PP) is a more important stimulus to vascular hypertrophy and atherosclerosis.

Taiwan Study

Rank Order of Correlation Coefficients

IMT	LV Mass
Central PP >	**Central SBP** >
Central SBP >	Brachial SBP >
Brachial SBP >	Central PP >
Brachial PP	Brachial PP

Wang *et al*. *J Hypertens* 2009;27:461-7 (1272 healthy normotensive or untreated hypertensive).

Requirements for a New Biomarker

- Safe, accurate, reproducible
- Correlate with disease presence
- Predict clinical outcome

CLINICAL OUTCOMES

2,403 American Indians free of prevalent CVD (MI, CVA, CHF, atrial fibrillation) at Exam 3

- Mean follow-up = 4.8±1.3 years
- 319 (13%) cardiovascular events occurred during follow-up (67 fatal and 252 non-fatal MI or CVA, CHF or definite CHD diagnosis)

STATISTICAL MODELS

Cox Regression Models

- Age
- Gender
- Body mass index
- Current smoking
- Cholesterol:HDL
- Diabetes
- Creatinine
- Fibrinogen
- Heart rate
- + Blood pressure parameter

HRs for Incident CVD

Age ($p<0.001$), diabetes ($p<0.001$), heart rate ($p<0.05$) and creatinine ($p<0.05$ to <0.001) $\pm$ fibrinogen ($p=0.06$ to 0.008) entered all models.

PARAMETER	HR	95% CI	p value
Aortic pulse pressure*	**1.15**	**(1.07-1.24)**	**<0.001**
Aortic systolic pressure*	1.07	(1.01-1.14)	<0.05
Brachial pulse pressure*	1.10	(1.03-1.18)	<0.01
Brachial systolic pressure*	1.08	(1.02-1.14)	<0.05

*per 10 mmHg

Remained significant after addition of carotid atherosclerosis and brachial pulse pressure

Roman MJ *et al*. *Hypertension* 2007;50:197-203.

Is there a partition value of central PP that might be of clinical utility in predicting adverse CVD outcomes and provide a target for intervention strategies?

HRs for Incident CVD

Age ($p<0.001$), smoking ($p<0.05$), diabetes ($p<0.001$), heart rate ($p<0.005$), creatinine ($p<0.005$) and fibrinogen ($p<0.05$) entered all models.

PARAMETER	HR	95% CI	p value
Brachial PP quartiles	1.115	(0.999-1.248)	0.052

Roman MJ *et al*. *J Am Coll Cardiol* 2009;54:1730-1734.

HRs for Incident CVD

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Brachial PP quartiles	1.115	(0.999-1.248)	0.052
Aortic PP quartiles	**1.229**	**(1.098-1.376)**	**<0.001**

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HRs for Incident CVD

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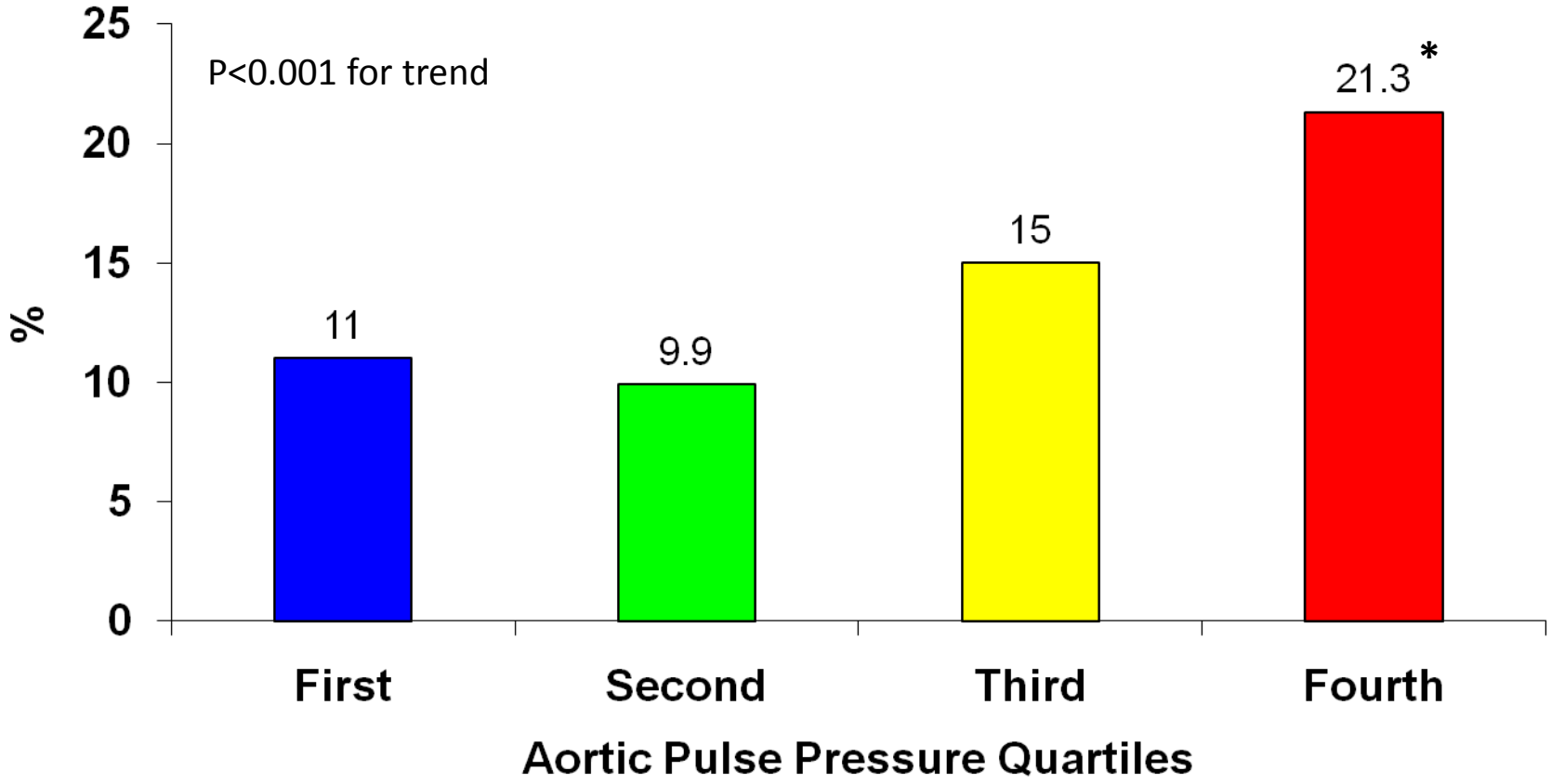
PARAMETER	HR	95% CI	p value
Brachial PP quartiles	1.115	(0.999-1.248)	0.052
Aortic PP quartiles	**1.229**	**(1.098-1.376)**	**<0.001**
2nd (32-39 mmHg)	0.89	(0.62-1.29)	0.538
3rd (40-49 mmHg)	1.28	(0.91-1.82)	0.160
4th (≥50 mmHg)	**1.696**	**(1.20-2.39)**	**0.003**

Incident CVD per Aortic PP Quartile



*P=0.003 *vs*. first quartile

Use of Aortic Pulse Pressure ≥50 mmHg in Subgroups

	n	HR	95% CI	P value
Men	838	2.06	(1.39-3.04)	<0.001
Women	1567	2.03	(1.55-2.65)	<0.001

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Men	838	2.06	(1.39-3.04)	<0.001
Women	1567	2.03	(1.55-2.65)	<0.001
Diabetes absent	1259	1.91	(1.29-2.83)	0.001
Diabetes present	1122	1.84	(1.41-2.39)	<0.001

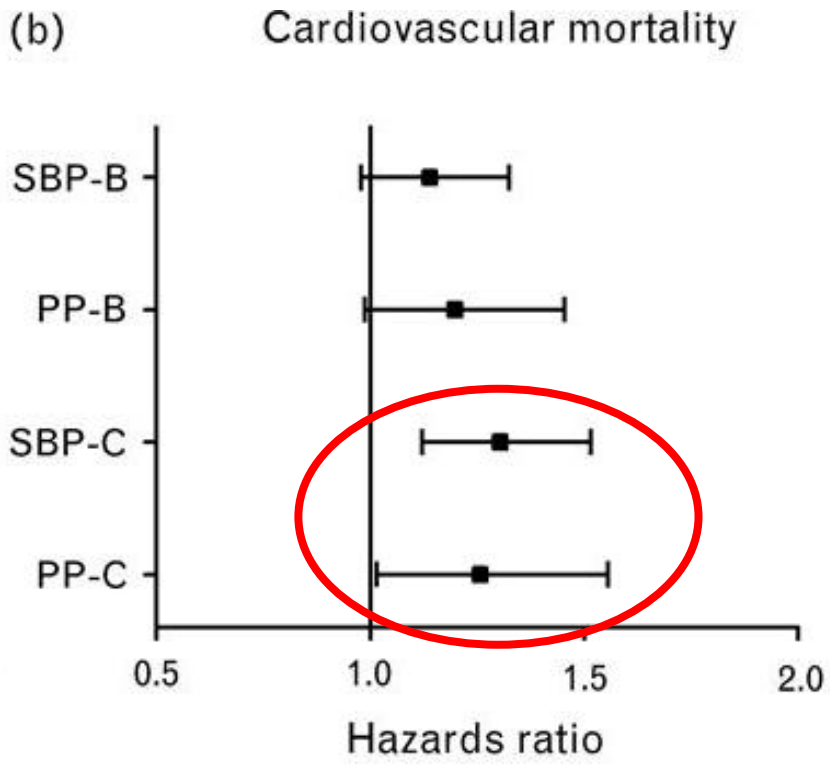
Use of Aortic Pulse Pressure ≥50 mmHg in Subgroups

	n	HR	95% CI	P value
Men	838	2.06	(1.39-3.04)	<0.001
Women	1567	2.03	(1.55-2.65)	<0.001
Diabetes absent	1259	1.91	(1.29-2.83)	0.001
Diabetes present	1122	1.84	(1.41-2.39)	<0.001
Age <60 years	994	2.51	(1.59-3.95)	<0.001
Age ≥60 years	1411	1.53	(1.19-1.97)	0.001

Roman MJ *et al*. *J Am Coll Cardiol* 2009;54:1730-1734.

Taiwan Study

1272 healthy normotensive or untreated hypertensive Taiwanese aged 30-79, followed for 10 years; 130 all-cause deaths and 37 (3%) cardiovascular deaths

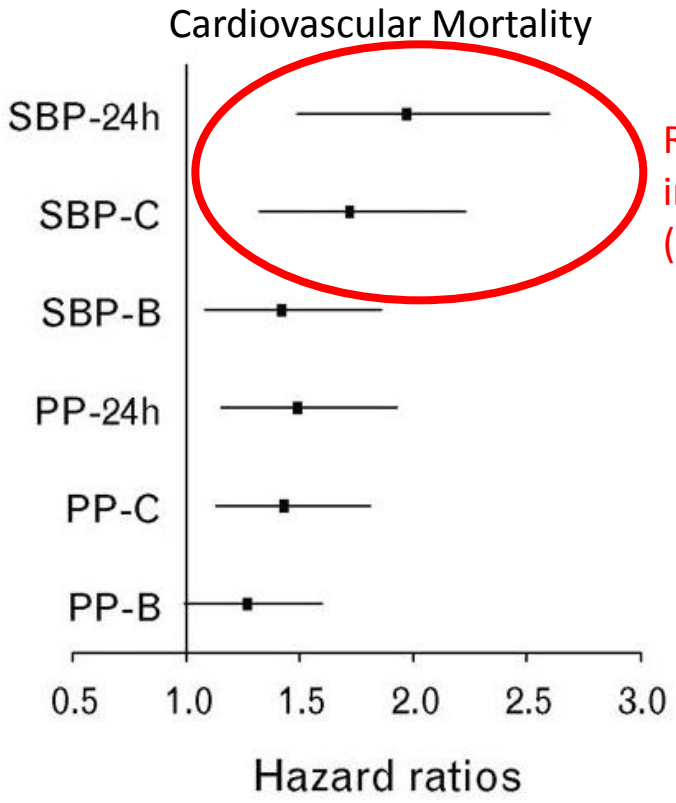


Wang *et al*. *J Hypertens* 2009;27:461-7.

Taiwan Study

Ambulatory Brachial BP *vs.* Central BP

1014 healthy normotensive or untreated hypertensive Taiwanese aged 30-79, followed for 15 years; 201 all-cause deaths and 55 (5.4%) cardiovascular deaths



Remained predictive independent of brachial SBP (HRs 1.7-2.0)

Huang *et al*. *J Hypertens* 2011;29:454-9.

Central pressure better predicts adverse CVD outcomes than does brachial pressure.

Requirements for New Biomarkers

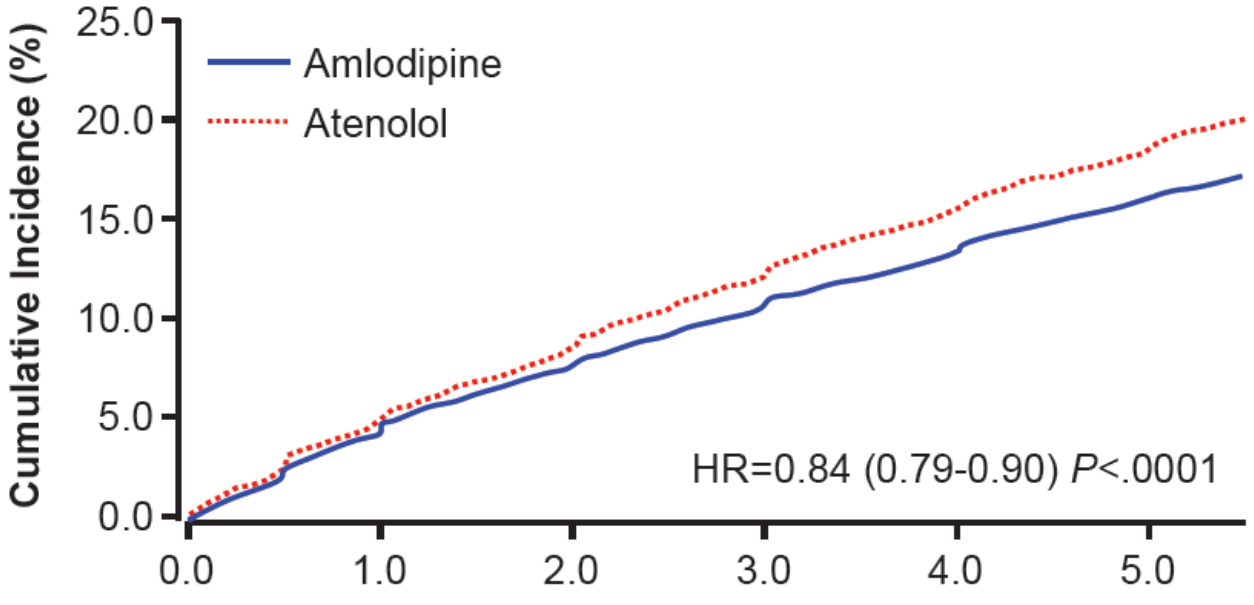
- Safe, accurate, reproducible
- Correlate with disease presence
- Predict clinical outcome
- Change in biomarker should influence clinical outcome

ASCOT* Study

- Hypertensives aged 40-79 plus 3 other risk factors
- Randomized to amlodipine±perindopril (n=9639) vs. atenolol±diuretic (n=9618)
- Study stopped prematurely (5.5 year median follow-up)
- Amlodipine-based therapy:
  - ↓ all-cause mortality (p=0.025)
  - ↓ CV events and procedures (p<0.0001)
  - ↓ incidence of diabetes (p<0.0001)

*Anglo-Scandinavian Cardiac OutcomesTrial
Dahlof *et al*. *Lancet* 2005;366:895-906.

ASCOT Study



Number at risk						
Amlodipine	9639	9166	8808	8455	8118	6965
Atenolol	9618	9115	8692	8259	7872	6710

ASCOT Study

FINAL BLOOD PRESSURES*		
	Systolic	Diastolic
Atenolol	137.7	79.2
Amlodipine	136.1	77.4

HRs for AMLODIPINE			
	Unadjusted	Adjusted for SBP	P for Adjusted
Primary outcome	0.86	0.87	0.018
Stroke	0.77	0.83	0.015

*P<0.0001

Better outcome is independent of lower brachial BP.

Poulter *et al*. *Lancet* 2005;366:907-913.

CAFE* Study

2073 Hypertensives + 3 CVD Risk Factors

Atenolol±Diuretic

Amlodipine±Perindopril

1 YEAR

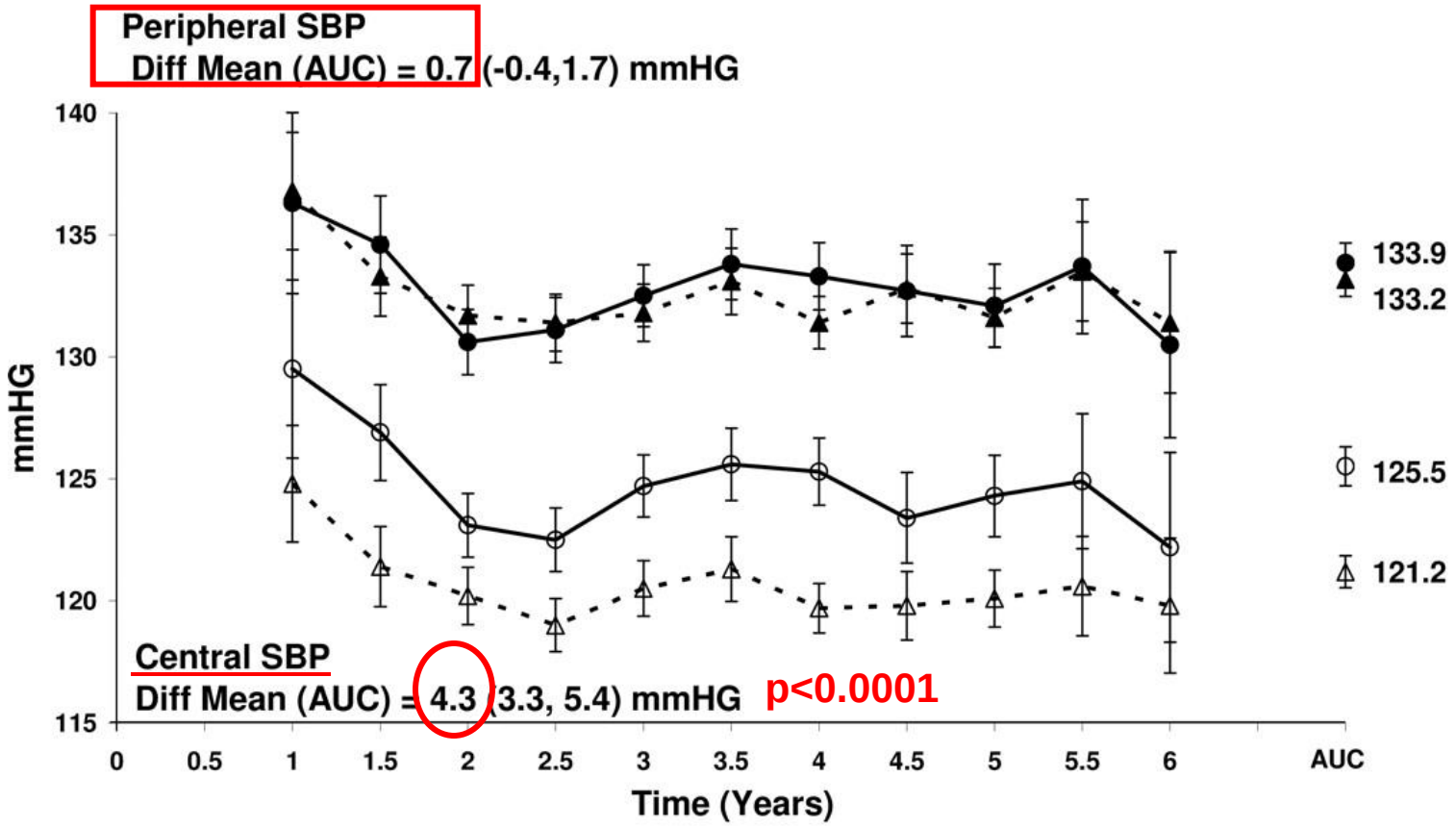
Radial Applanation Tonometry

4-Year Follow-Up

*Conduit Artery Function Evaluation (substudy of ASCOT)

Williams *et al*. *Circulation* 2006;113:1213-1225.

CAFE Study



Williams *et al*. *Circulation* 2006;113:1213-1225.

The lower central pressure associated with amlodipine-based therapy *may* explain the better clinical results in this treatment arm in the overall ASCOT Study.

Lowering central pressure *may* improve clinical outcome and *may* be a more important target than brachial pressure.

Comparative Effects of Anti-Hypertensive Agents on Central SBP

CLASS	Central Systolic Pressure
ACE Inhibitors	↓
Angiotensin Receptor Blockers	↓↔
Beta-Blockers	↑↑
Calcium Channel Blockers	↓↔
Diuretics	↔
Nitrates	↓↓

SUMMARY

1. Central SBP and PP may be substantially lower than their brachial counterparts.
2. Central PP is more strongly related to cerebrovascular damage than is brachial PP.
3. Central SBP is more strongly related to left ventricular hypertrophy than is brachial SBP.
4. Central SBP and PP are more strongly associated with clinical CVD events than are brachial pressures based on several large diverse population-based and patient-based studies.

SUMMARY

5. Pharmacologic interventions differ in their ability to lower central BP for a given brachial BP.
6. Central BP lowering may be a more important target than brachial BP lowering.
7. Treatment based on achieved central BP has not yet been proven to be effective in altering subclinical and clinical outcomes.

FUTURE NEEDS

1. Establish normative values for central blood pressure from large samples of healthy individuals over a broad age range and of varying ethnicities.

Central BP Reference Values*

*n~50,000

FUTURE NEEDS

1. Establish normative values for central blood pressure from large samples of healthy individuals over a broad age range and of varying ethnicities.

2. Establish thresholds predictive of outcome, e.g., from longitudinal observational studies and individual-subject meta-analyses.

Central BP Outcomes Meta-Analysis

Individual Data

Study	Year	n	Age	% Male
Strong Heart Study	2007	2405	63	35
Dicomano Study	2008	398	73	45
Taiwan Study	2009	1272	52	53
CaPS (Caerphilly)	unpubl.	864	72	100
Jankowski (invasive)	2008	971	57	73
Ilyas (CAD)	2009	285	62	74
Weber (CAD)	2010	520	63	100
CAFE	2006	2073	63	81
ANBP2	2006	484	72	100
Total		**9272**	**62**	**66**

FUTURE NEEDS

3. Design intervention studies targeting lowering of central pressure rather than brachial blood pressure since drugs may have differential impacts on central hemodynamics.

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3. Design intervention studies targeting lowering of central pressure rather than brachial blood pressure since drugs may have differential impacts on central hemodynamics.

4. Document that lowering of central pressure improves clinical outcomes better than lowering brachial pressure.

ACKNOWLEDGMENTS

Richard B. Devereux, MD
Jorge R. Kizer, MD, MSc
Barbara V. Howard, PhD
Other Strong Heart Study Investigators