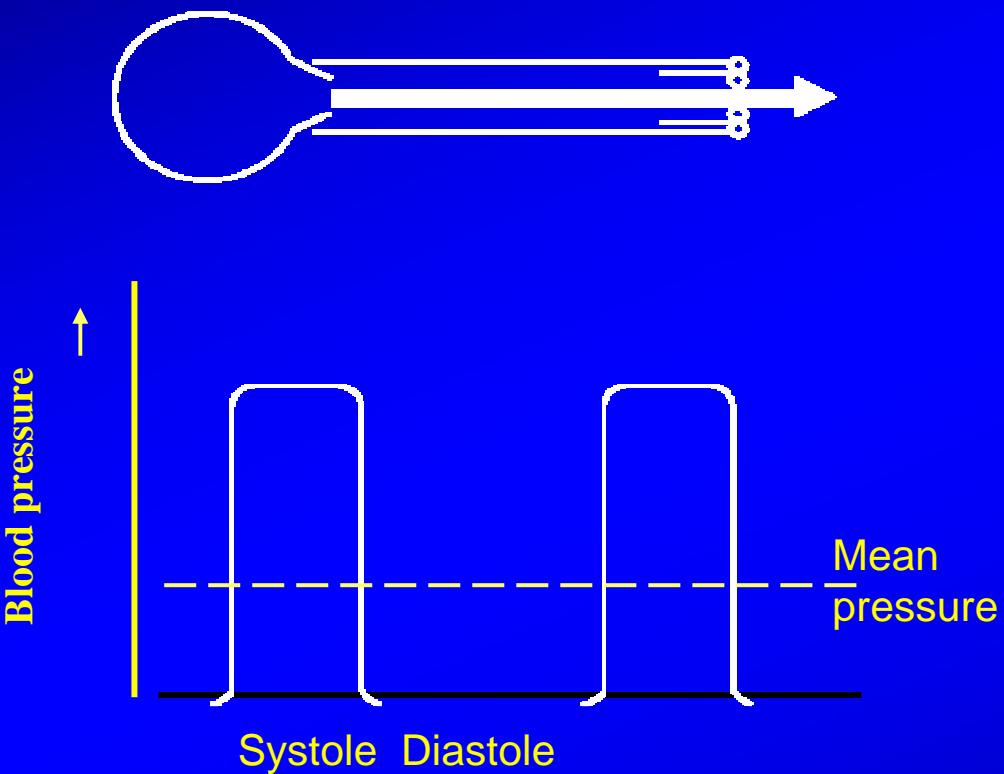


Les gros vaisseaux chez l'hypertendu

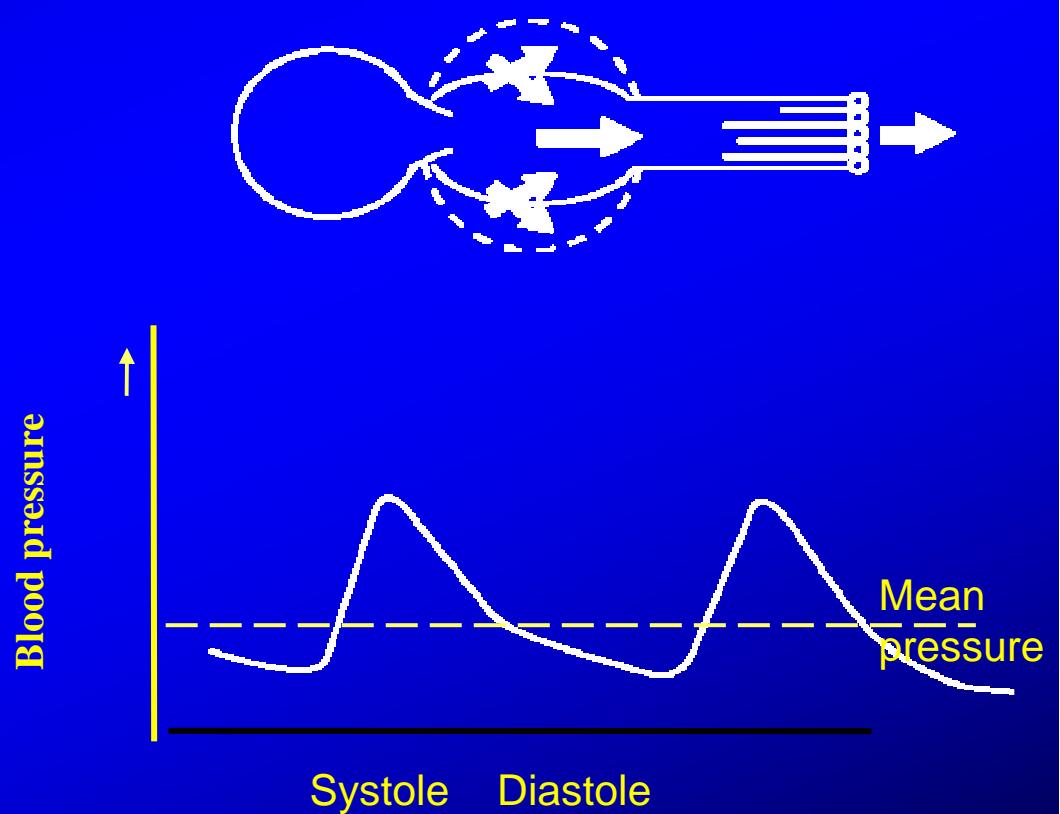
B Pannier
Hopital Manhes, Fleury-Merogis

Arterial function and blood pressure

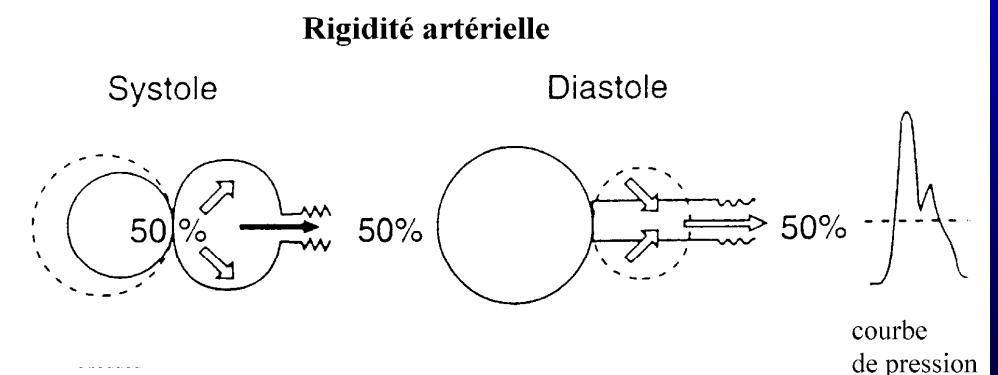
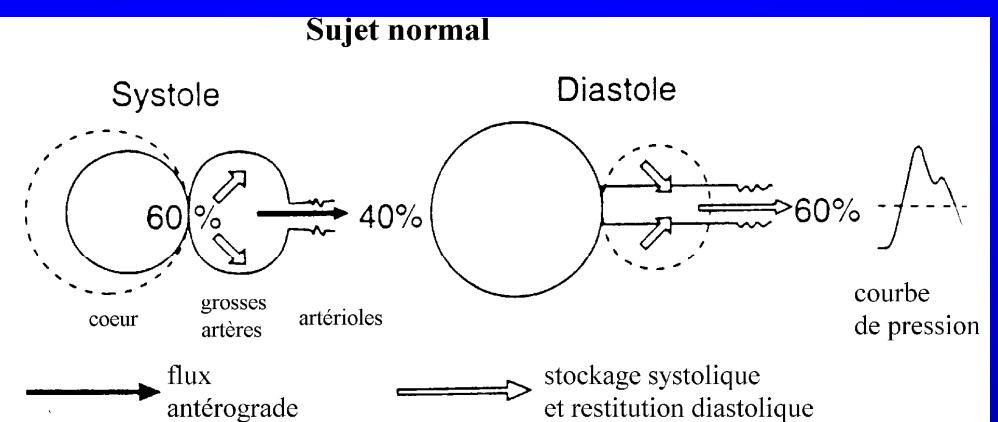
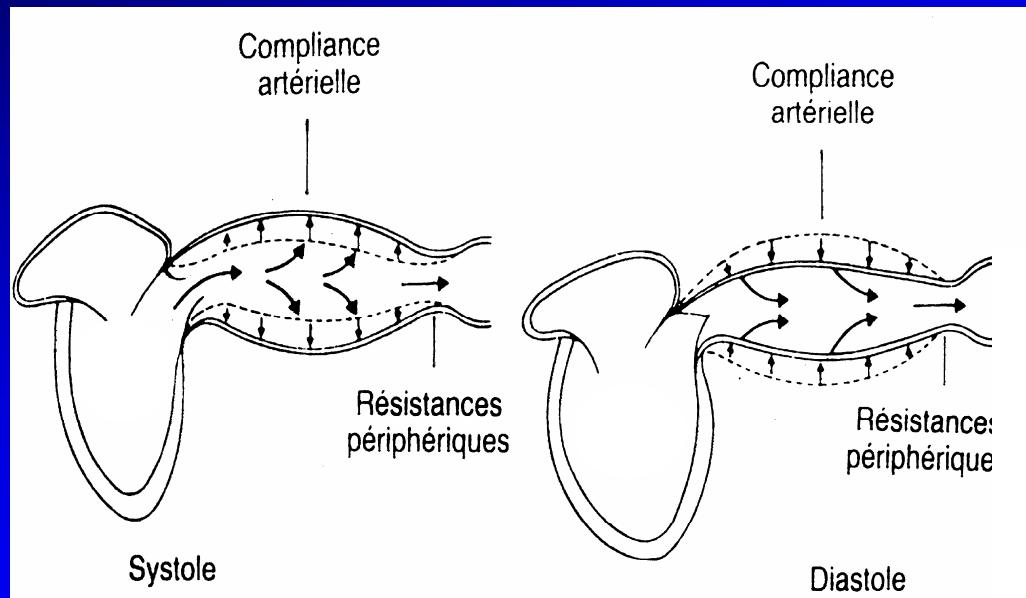
Pure Conduit Function



Conduit and Cushioning Function



RIGIDITE ou COMPLIANCE ARTERIELLE

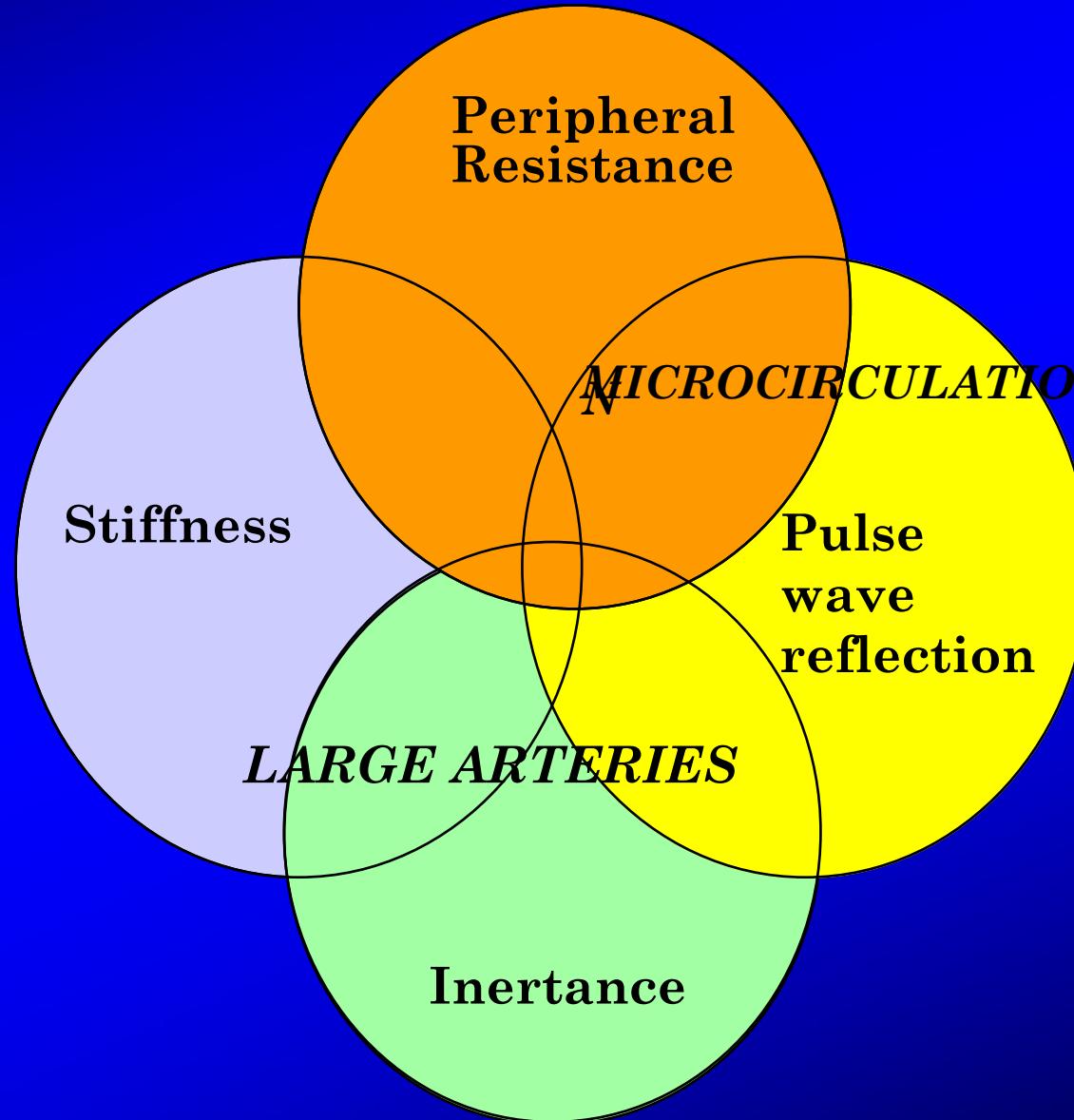


d'après G London,
J Hypertens, 1999

Structure des grosses artères

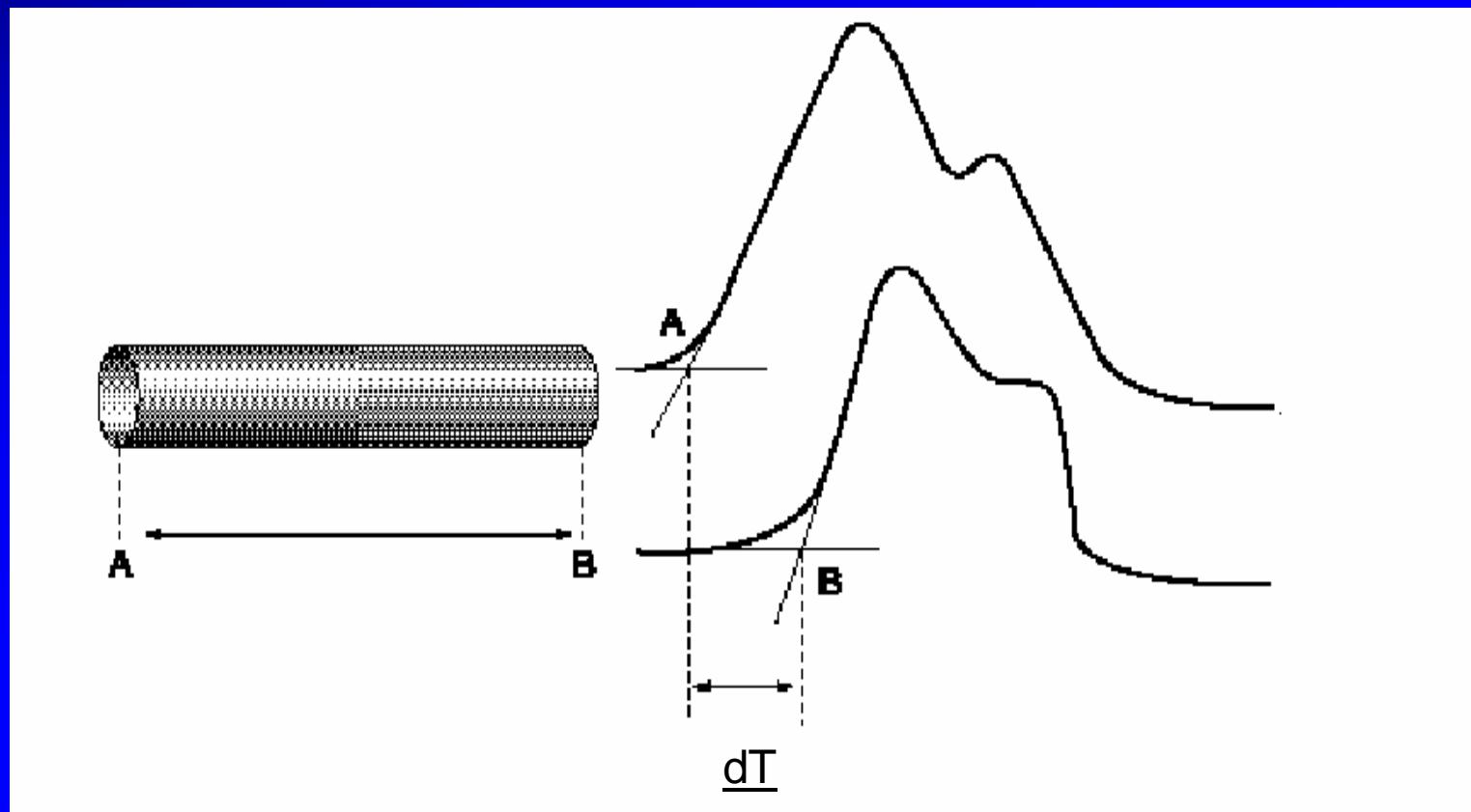
- Artères élastiques
 - Riches en élastine et collagène
 - Cellules musculaires lisses
 - Aorte ascendante>thoracique>>abdominale
- Artères musculaires
 - Pauvres en élastine
 - Riches en cellules musculaires
 - Toutes les autres « grosses » artères:
 - Coronaires,
 - Humérale
 - Fémorale..
- Attachements cellules musculaires-fibres par récepteurs membranaires musculaires (fibronectine ..): architecture pariétale
- Géométrie: réduction du calibre du centre à la périphérie et embranchements

Determinants of vascular overload (afterload) on the heart



Rigidité segmentaire (de chambre)

Apport de la vitesse de l'onde du pouls

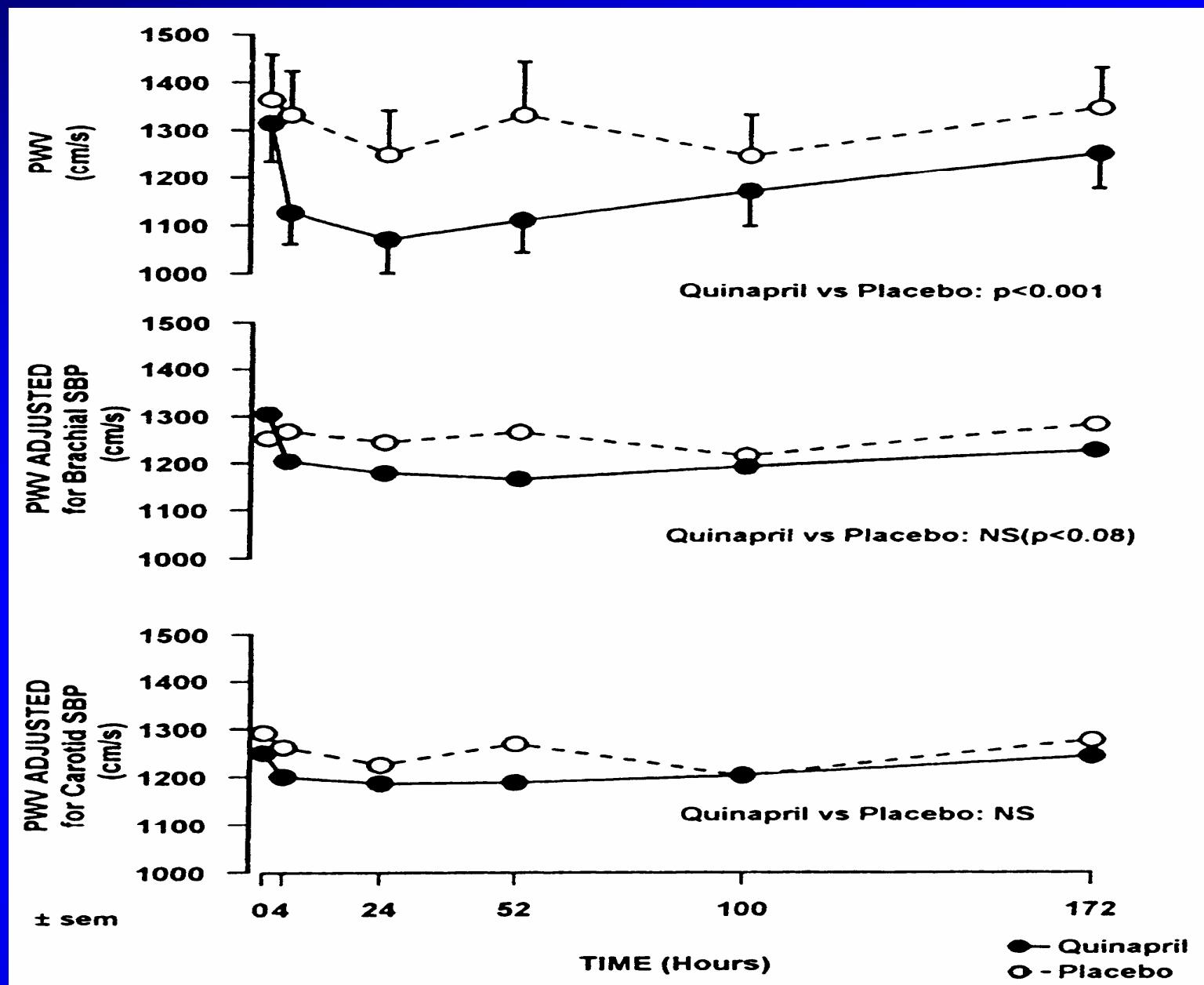


$$VOP = AB / dT \text{ (m/sec).}$$

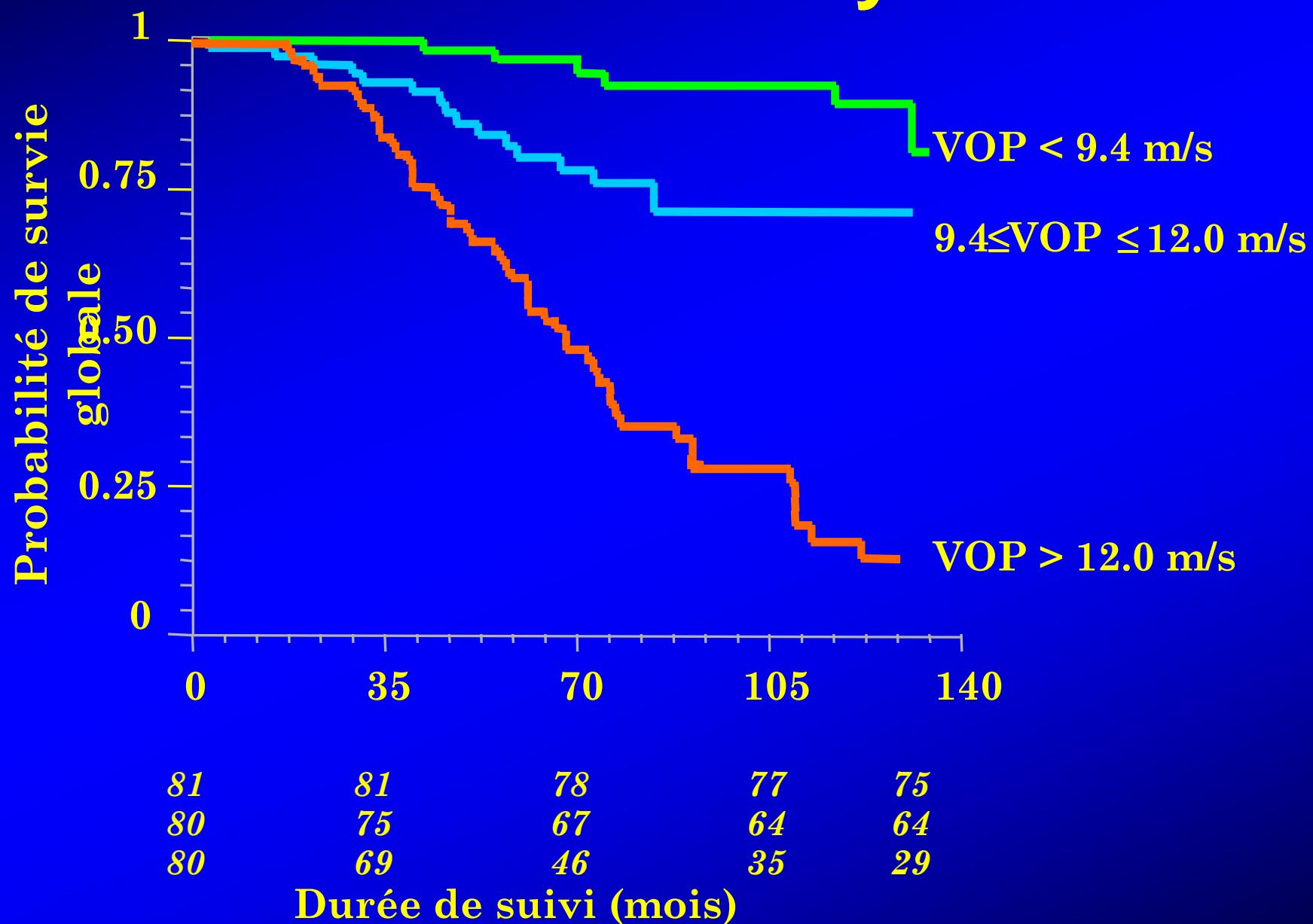
Determinants of PWV

Parameters (dependent variable)	Parameter estimate	Standard error	Single r^2	P value
Aortic PWV (m/second), nonuremic population ($N = 469$), $r^2 = 0.65$				NON UREMIC
Intercept	2.934	0.625		<0.001
Age years	0.0793	0.0038	0.53	<0.001
Mean arterial pressure mm Hg	0.0427	0.0039	0.31	<0.001
Gender (1 male; 2 female)	-0.415	0.121	0.01	<0.001
Heart period m/second	-0.0014	0.0004	0.02	<0.001
Aortic PWV (m/second), ESRD population ($N = 242$), $r^2 = 0.57$				ESRD
Intercept	2.773	1.350		0.04
Age years	0.1189	0.0075	0.39	<0.001
Mean arterial pressure mm Hg	0.0616	0.0074	0.08	<0.001
Gender (1 male; 2 female)	-0.842	0.261	0.01	0.001
Heart period m/second	-0.0039	0.0009	0.02	<0.001
Aortic PWV (m/second), entire population ($N = 711$), $r^2 = 0.62$				Global population
Intercept	1.832	0.662		0.006
Age years	0.0917	0.0036	0.44	<0.001
Mean arterial pressure mm Hg	0.0449	0.0037	0.18	<0.001
Gender (1 male; 2 female)	-0.543	0.122	0.01	<0.001
Heart period m/second	-0.0021	0.0004	0.03	<0.001
Code (nonuremic, 1; ESRD, 2)	1.092	0.124	0.06	<0.001

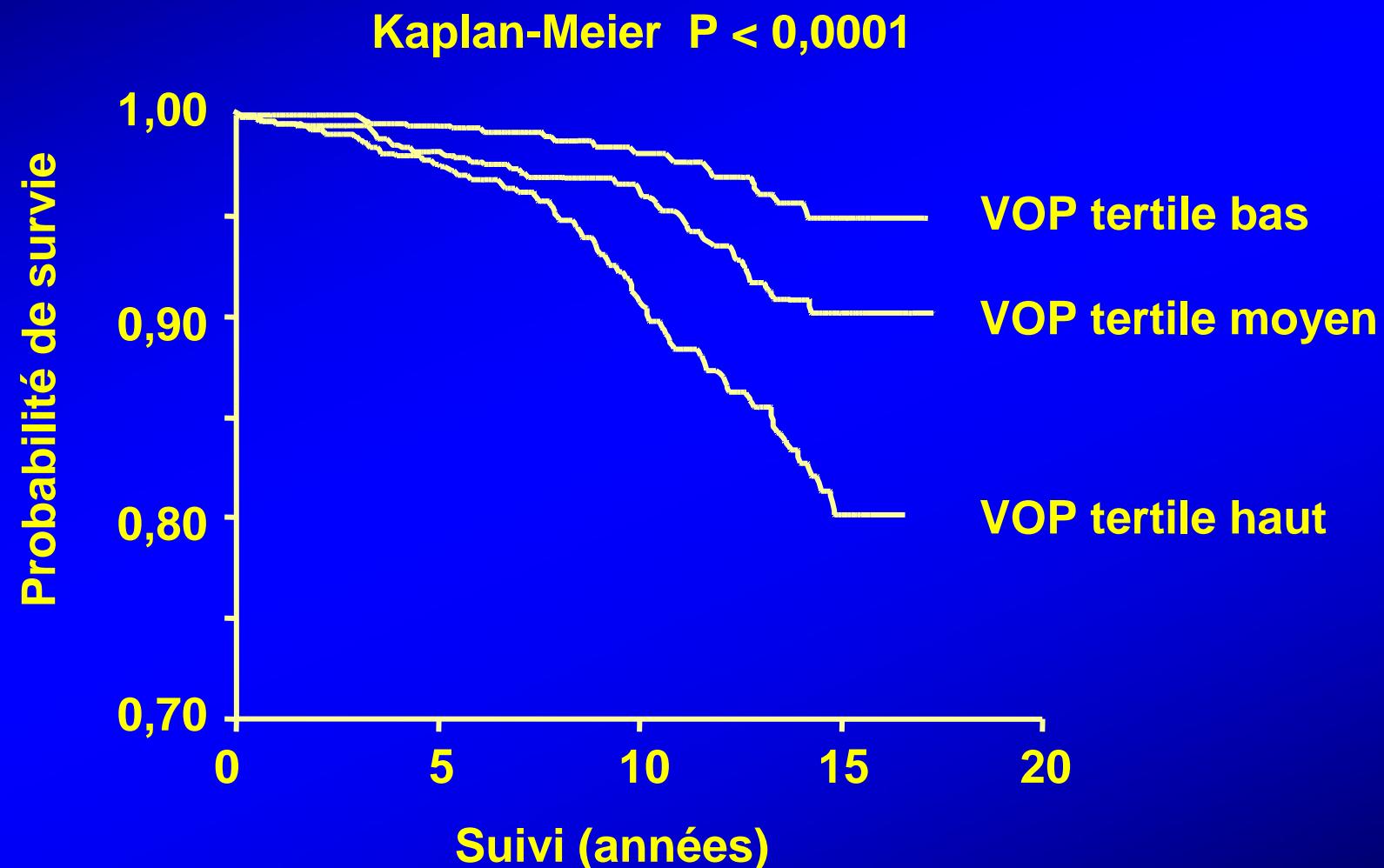
La VOP est dépendante de la pression



VOP et mortalité: Insuffisant rénal Hémodialysé



VOP et mortalité: hypertension



VOP et mortalité: Diabète type II

TABLE 3. Final Cox Model of Factors Predicting Mortality in a Cohort of Population-Based Control and Type 2 Diabetes Participants

	Hazard Ratio	95% CI	P
Age (per 1 year older)	1.07	1.04–1.09	<0.0001
Sex (female)	0.66	0.48–0.89	0.007
BP treated	1.10	0.82–1.48	0.54
Systolic BP (per 5 mm Hg)	1.02	0.98–1.06	0.34
GTT status (normoglycemia)	1		
Glucose intolerant*	2.12	1.11–4.01	0.021
Known diabetes	2.34	1.50–3.74	<0.0001
PWV (per 1 m/s)	1.08	1.03–1.14	0.001
Smoking status (never)	1		
Current	1.57	1.10–2.23	0.012
Exsmoker	1.16	0.81–1.66	0.42
Ethnicity (European)	1		
Gujerati	0.68	0.49–0.94	0.02
African-Caribbean	0.41	0.25–0.69	0.001
Other	1.34	0.80–2.33	0.25

follow-up =10.7 years
(survivors =12.7 [12.6 to 12.8] years
those who died=6.9 [6.4 to 7.3] years)

n=565. Six people without smoking data were omitted.

*Baseline fasting glucose ≥ 6.1 mmol/L or 2-hour glucose ≥ 11.1 mmol/L.

Cruickshank K, et al,
Circulation 2002

CONSENSUS EUROPEEN SUR LA RIGIDITE ARTERIELLE

Table 4 Longitudinal studies reporting the independent predictive value of arterial stiffness, according to the site of measurement (adapted from Ref. 1)

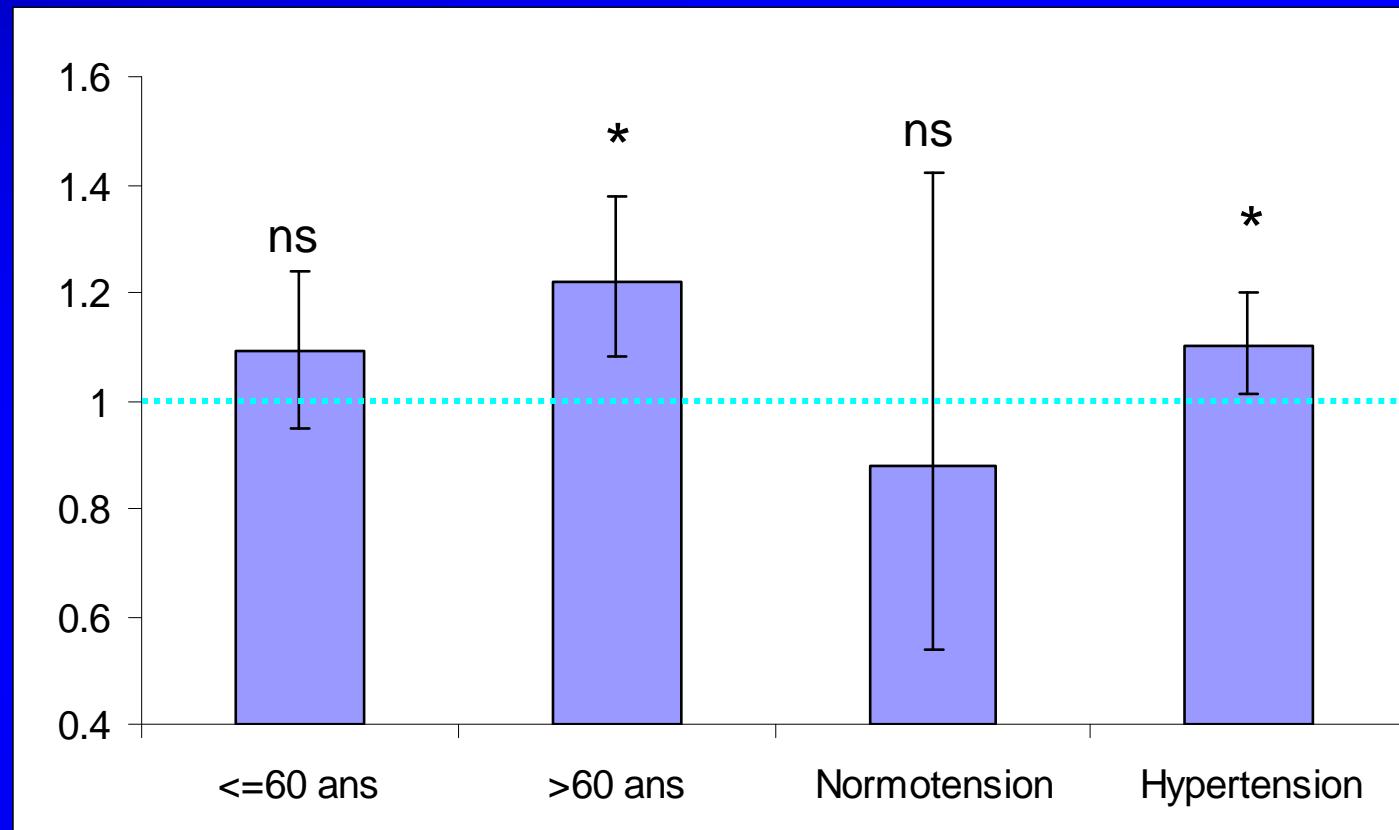
Measurement site	First author (year, country)	Events	Follow-up (years)	Type of patient (number)	Mean age at entry (years)	Ref.
Aortic PWV	Blacher (1999, Fr)	CV mortality	6.0	ESRD (241)	51	3
	Laurent (2001, Fr)	CV mortality	9.3	Hypertension (1980)	50	4
	Meaume (2001, Fr)	CV mortality	2.5	Elderly (>70) (141)	87	5
	Shoji (2001, Jp)	CV mortality	5.2	ESRD (265)	55	6
	Boutouyrie (2002, Fr)	CHD events	5.7	Hypertension (1045)	51	7
	Cruickshank (2002, GB)	All cause mortality	10.7	IGT (571)	51	8
	Laurent (2003, Fr)	Fatal strokes	7.9	Hypertension (1715)	51	9
	Sutton-Tyrrell (2005, USA)	CV mortality and events	4.6	Elderly (2488)	74	10
	Shokawa (2005, Jp)	CV mortality	10	General pop. (492)	64	11
	Hansen (2006, Dk)	CV mortality	9.4	General pop. (1678)	55	12
	Mattace-Raso (2006, Neth.)	CV mortality, CHD	4.1	Elderly (2835)	72	13
Carotid stiffness	Blacher (1998, Fr)	All cause mortality	2.1	ESRD (79)	58	19
	Barenbrock (2001, Ge)	CV events	7.9	ESRD (68)	43	20

ESRD: end-stage renal disease; IGT: impaired glucose tolerance; CHD: coronary heart disease and pop.: population.

Countries: Dk: Denmark; Fr: France; GB: Great Britain; Ge: Germany; Gr: Greece; Jp: Japan; and Ne: Netherlands.

Population IPC VOP et Mortalité toutes causes

HR, IC 95%



*: p<0.05

n= 1952 (H/F= 1319/633), suivi = 13.4 ± 1.2 ans, ajusté,
décès: 61 H (4.6%); 18 F (2.8%)

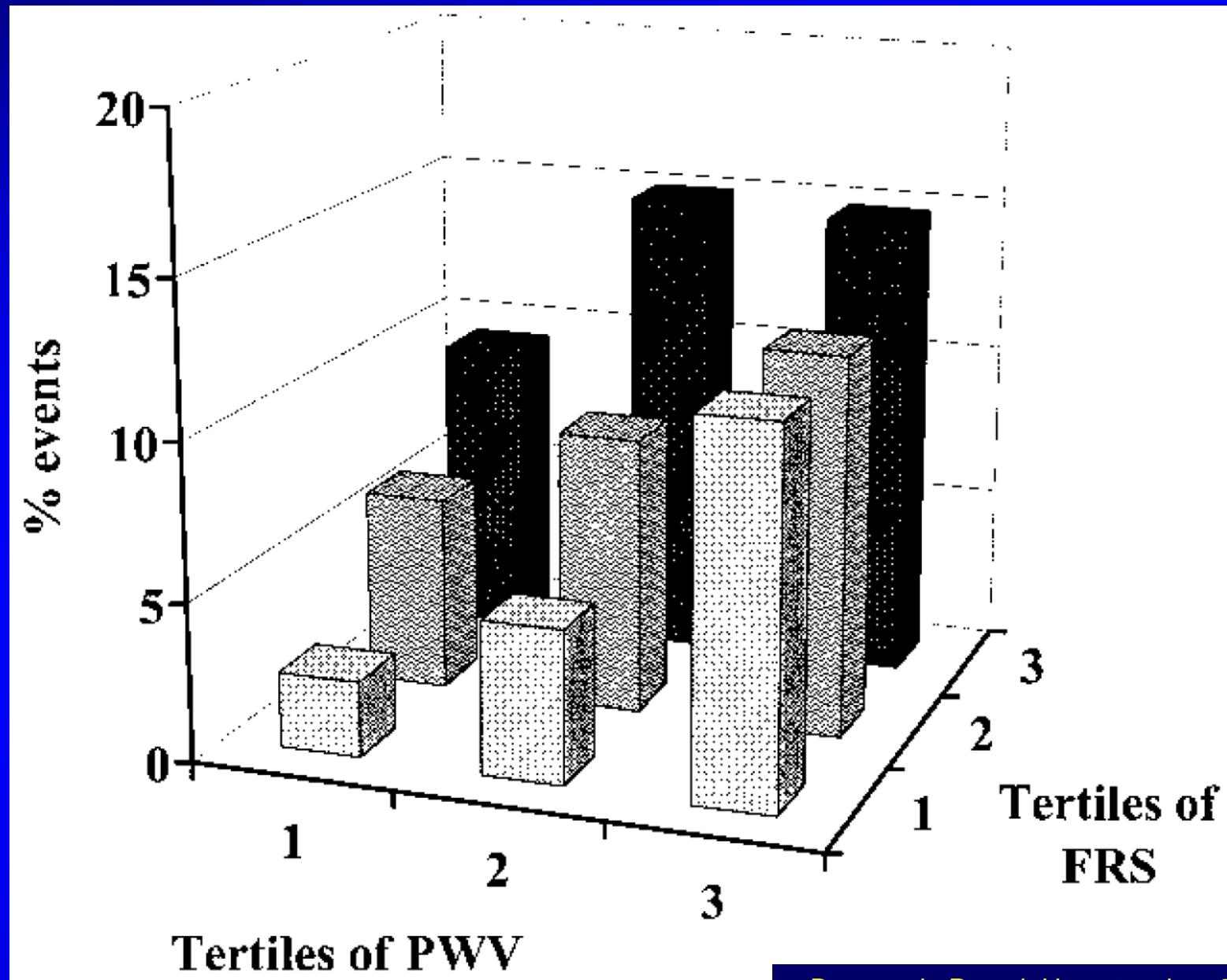
BPannier et al.

VOP et mortalité par AVC: hypertension essentielle

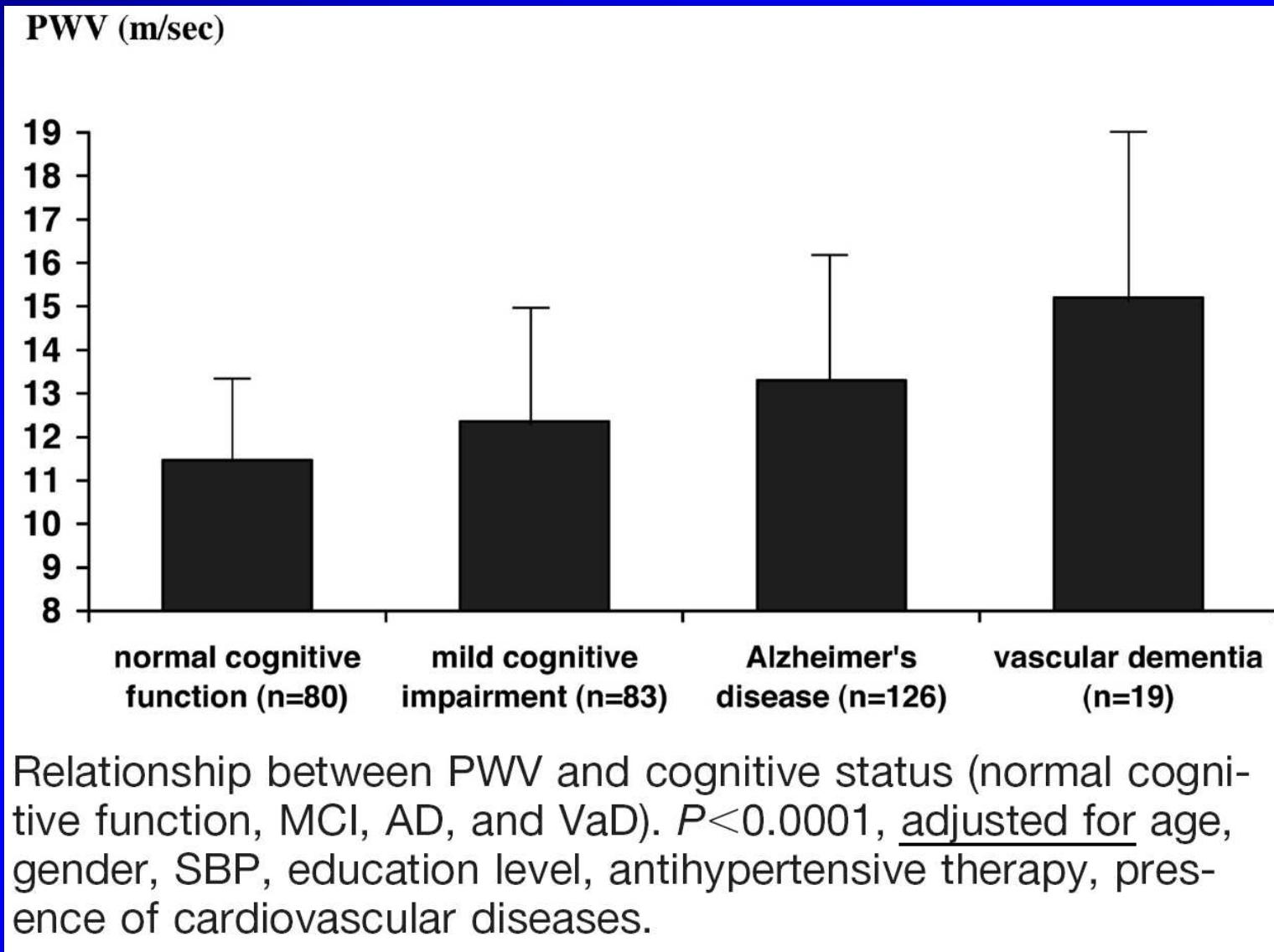
TABLE 3. Relative Risk of Stroke Death According to PWV or Pulse Pressure, and Other CV Risk Factors: Multivariate Models

Parameters	Relative Risk	95% CI	P
Model including PWV			
$\chi^2=39.0$			
PWV (4 m/s)	1.39	1.08–1.72	0.022
Age (10 y)	1.80	1.37–2.35	<0.001
Smoking (yes/no)	3.34	1.06–10.50	0.03
Model including pulse pressure			
$\chi^2=30.3$			
PP (10 mm Hg)	1.19	0.96–1.47	0.10
Age (10 y)	2.39	1.54–3.71	<0.001

VOP et évènements coronaires: hypertension essentielle

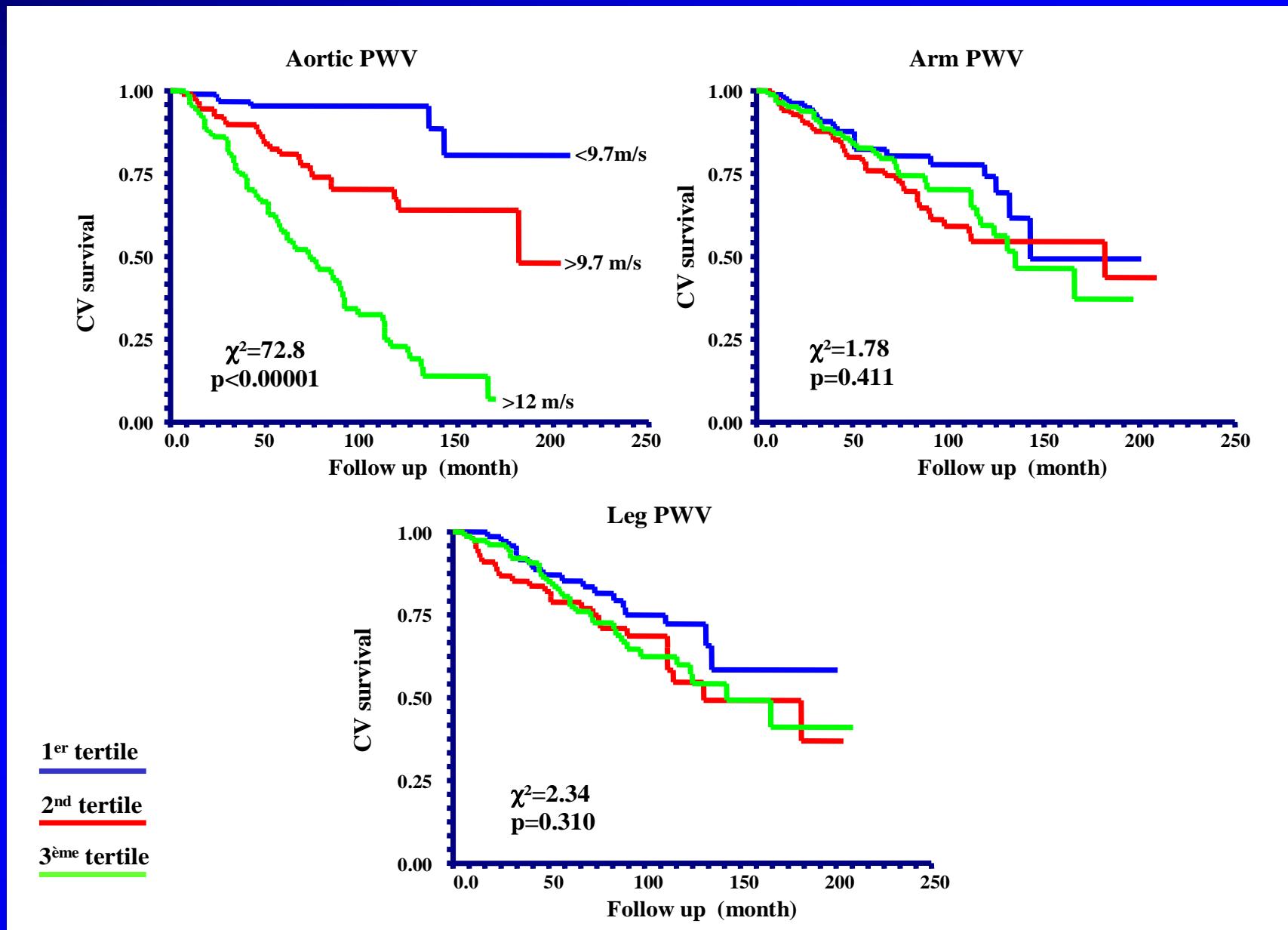


VOP et fonction cognitive

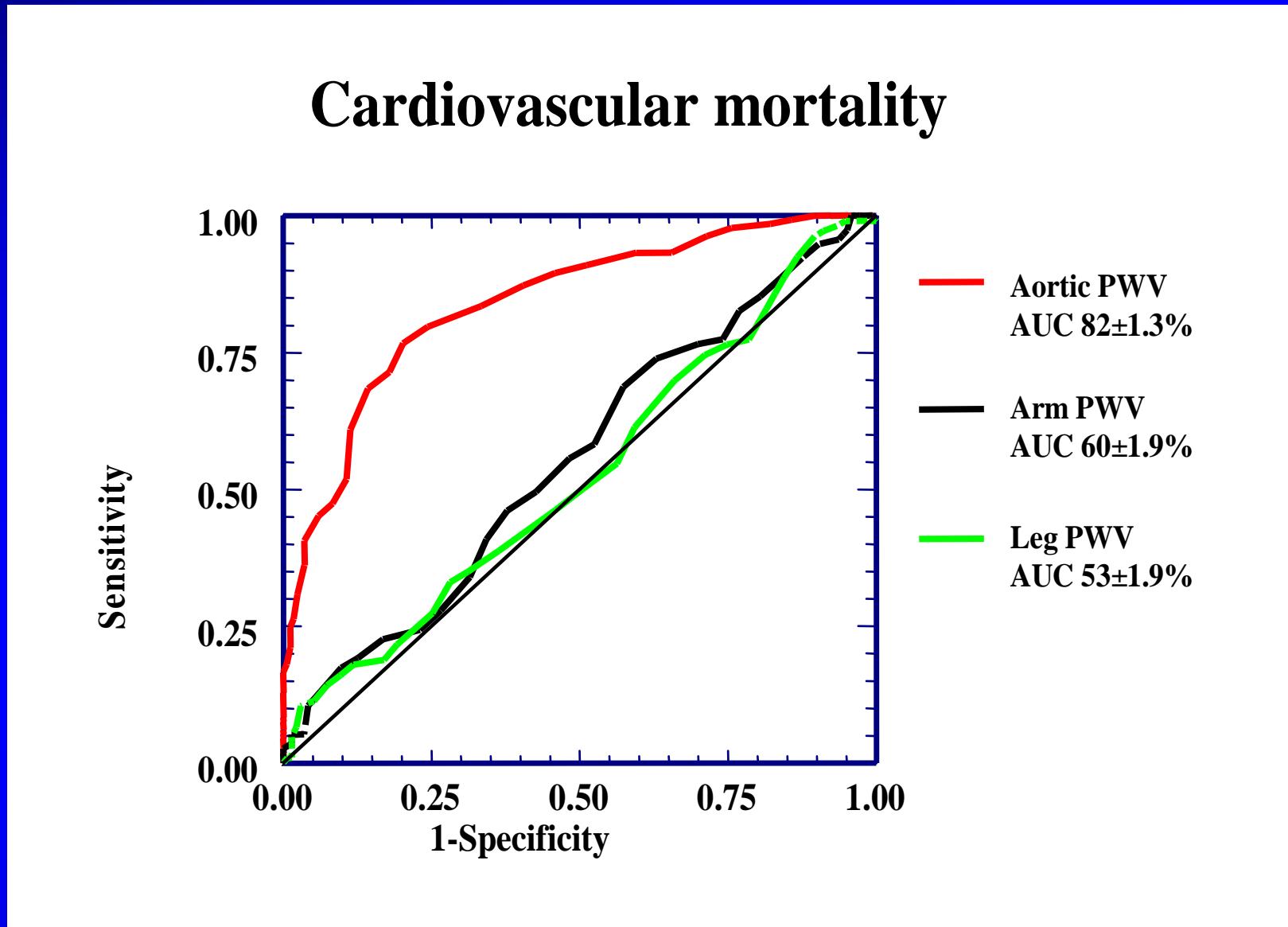


N=308, 78 ± 8 years, 64% F, 26% had normal cognitive function, 27% had MCI, 41% experienced AD, and 6% experienced VaD. Hanon O, et al, Stroke, 2005

CV Survival curves ESRD

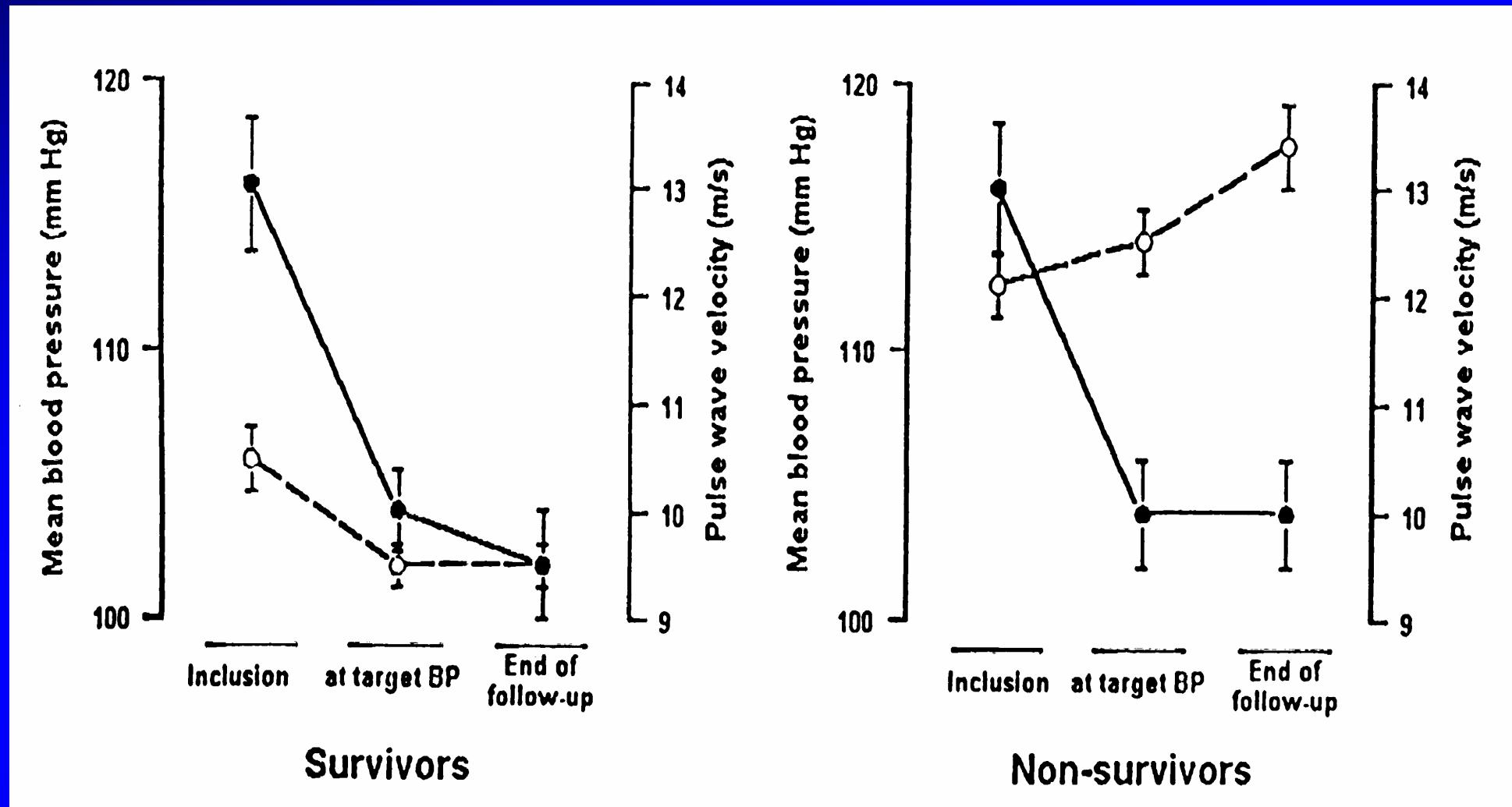


ROC curves for Cardiovascular mortality ESRD

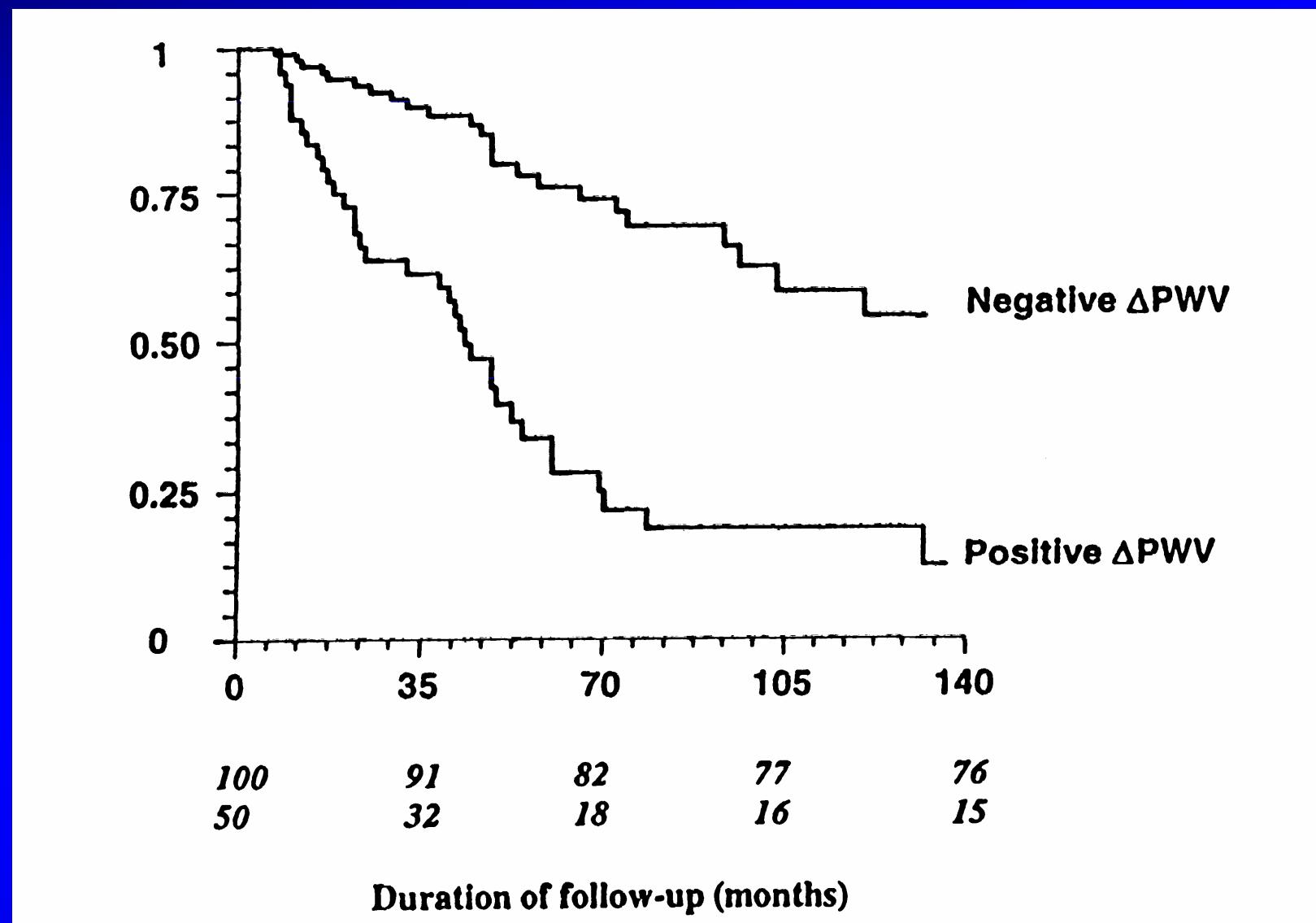


Role des traitements

HEMODIALYSE: Survie et évolution de la VOP aortique



HEMODIALYSE: Survie et évolution de la VOP aortique

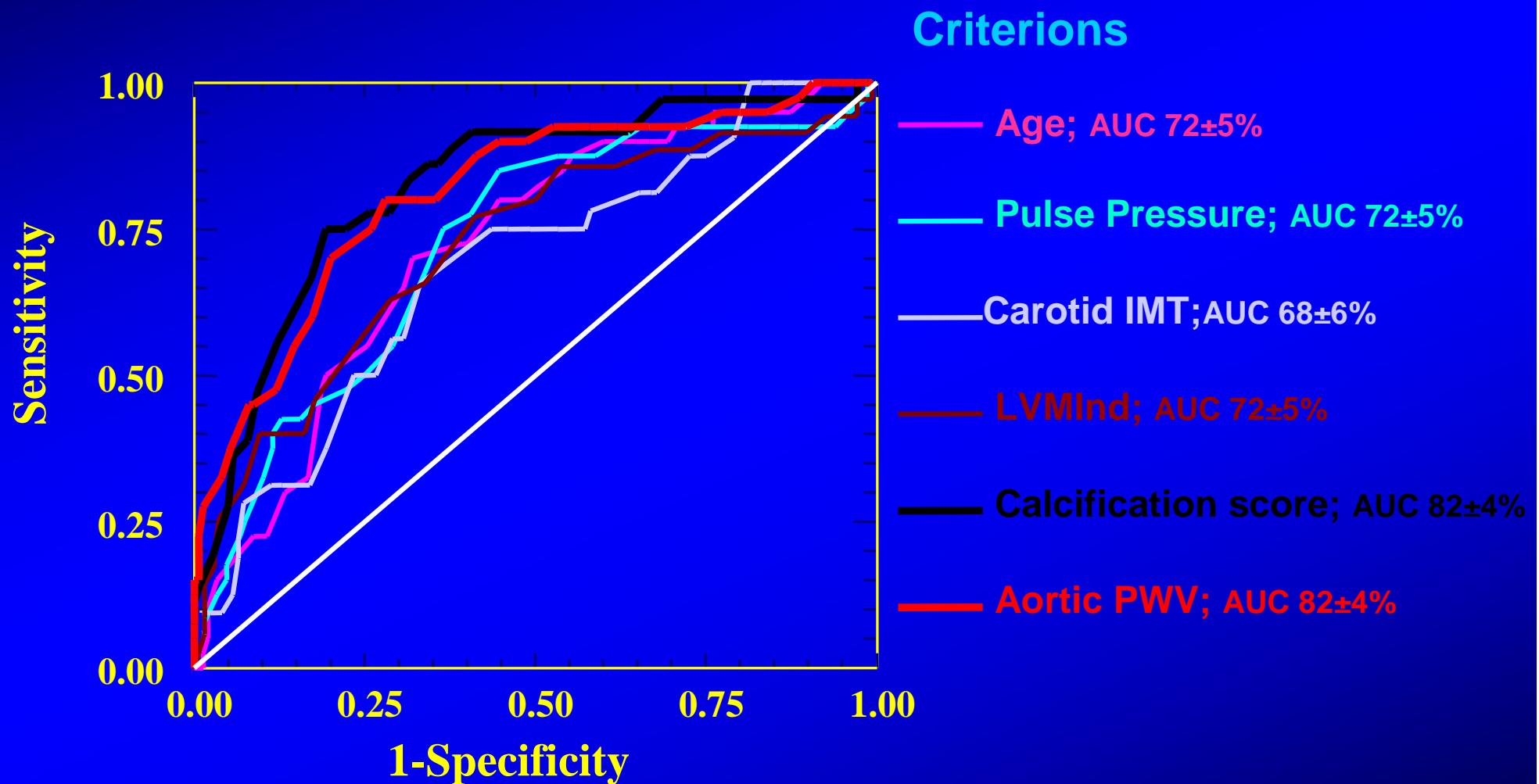


Études à end-point fonctionnels:

- Médicaments vasodilatateurs (anti HTA)
- ICE
- ARA2
- Anticalciques
- BB avec propriétés vasculaires
- Certains diurétiques avec propriétés vasculaires (indapamide)
- Anti TNF α (dans maladies inflammatoires)
- Essai avec AGE breakers...

**Pas d'étude d'intervention
disponible pour un end-point
robuste de morbi-mortalité...**

ESRD: ROC Curve for CV mortality



Calcification score: cut-off 390;sensitivity 83%;specificity69%; PPV41%;NPV94%

Aortic PWV: cut-off 10.75 m/s;sensitivity 84%;specificity 73%;PPV72%; NPV93%

Appareils de mesure

Complior®, (Artech medical)

Sphygmocor ®(Atcor)

Pulse pen® (DiaTecne)

FCP-4731® (Fukuda Denshi)

bPWV (Colin)

...

Appareils de mesure: reproductibilité

Table 4. Reproducibility of devices and methods based on measurement of pulse transit time

Device	Bland & Altman Repeatability Coefficient (SD of diff.)	Mean Value of Population Sample (measure1/measure2)	Number of Subjects
Complior system (aortic)	0.89 m/sec*	10.8 ± 2.39 m/sec 10.96 ± 2.69 m/sec	56
Sphygmocor (aortic)	1.25 m/sec* 1.17 m/sec†	8.15 ± 3.01 m/sec	24
Automated ultrasound pulse wave velocity			
QKd system			

* Interobserver reproducibility; † Intraobserver reproducibility.

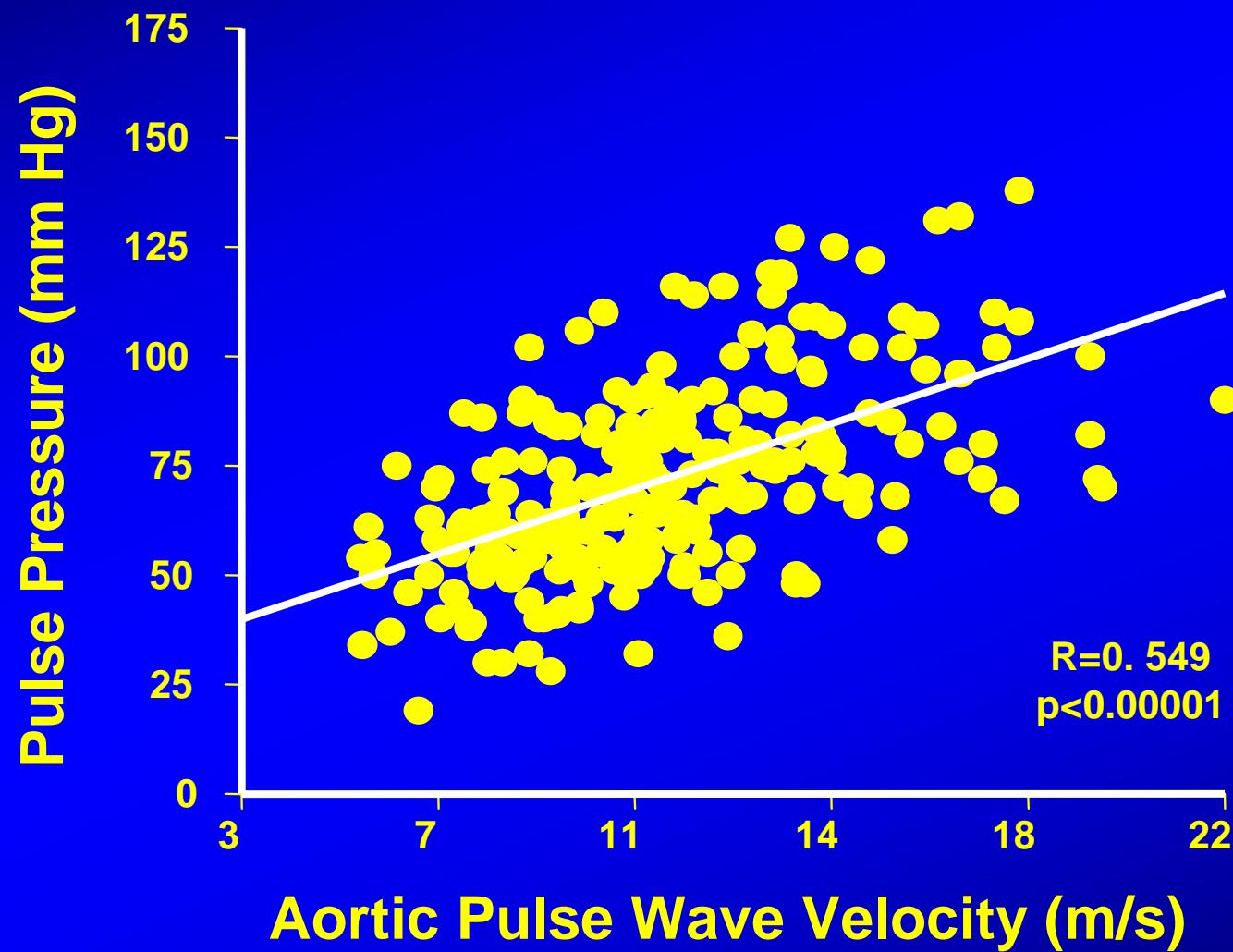
Vitesse de l'onde du pouls Aortique

- Le meilleur index de rigidité artérielle
- Mesure aisée et automatisée
- Période d'entraînement usuellement brève

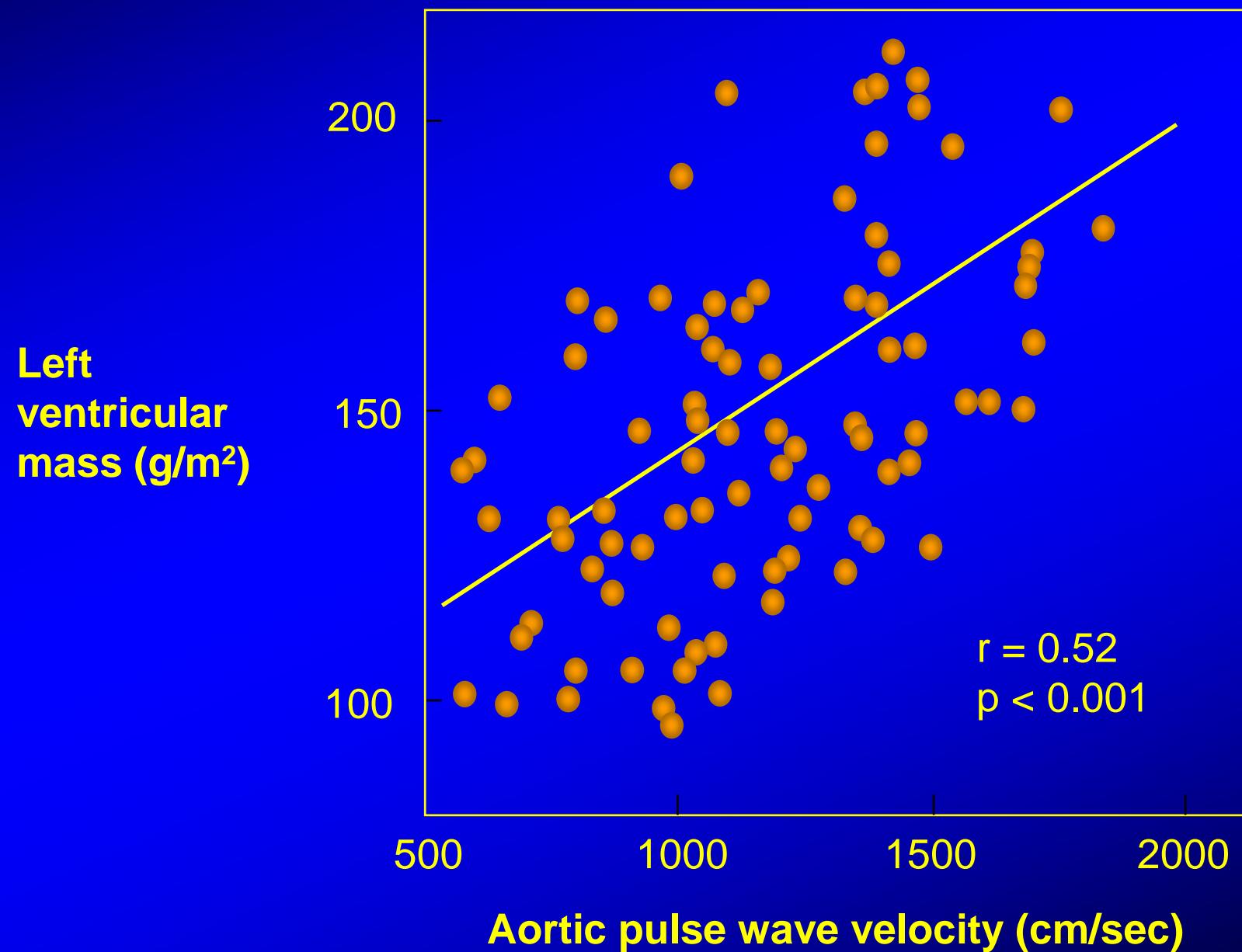
- Une homogénéisation de mesure nécessaire
- Un nomogramme indispensable...

- Dépendance à la pression de distension (PAS, PAM)
à prendre en compte dans l'analyse pharmacologique
- Une seule étude en faveur d'un bénéfice pronostique
en cas de variation
- De futures études pharmacologiques...(?).

Correlation between Aortic Pulse Wave velocity and Pulse Pressure in ESRD patients



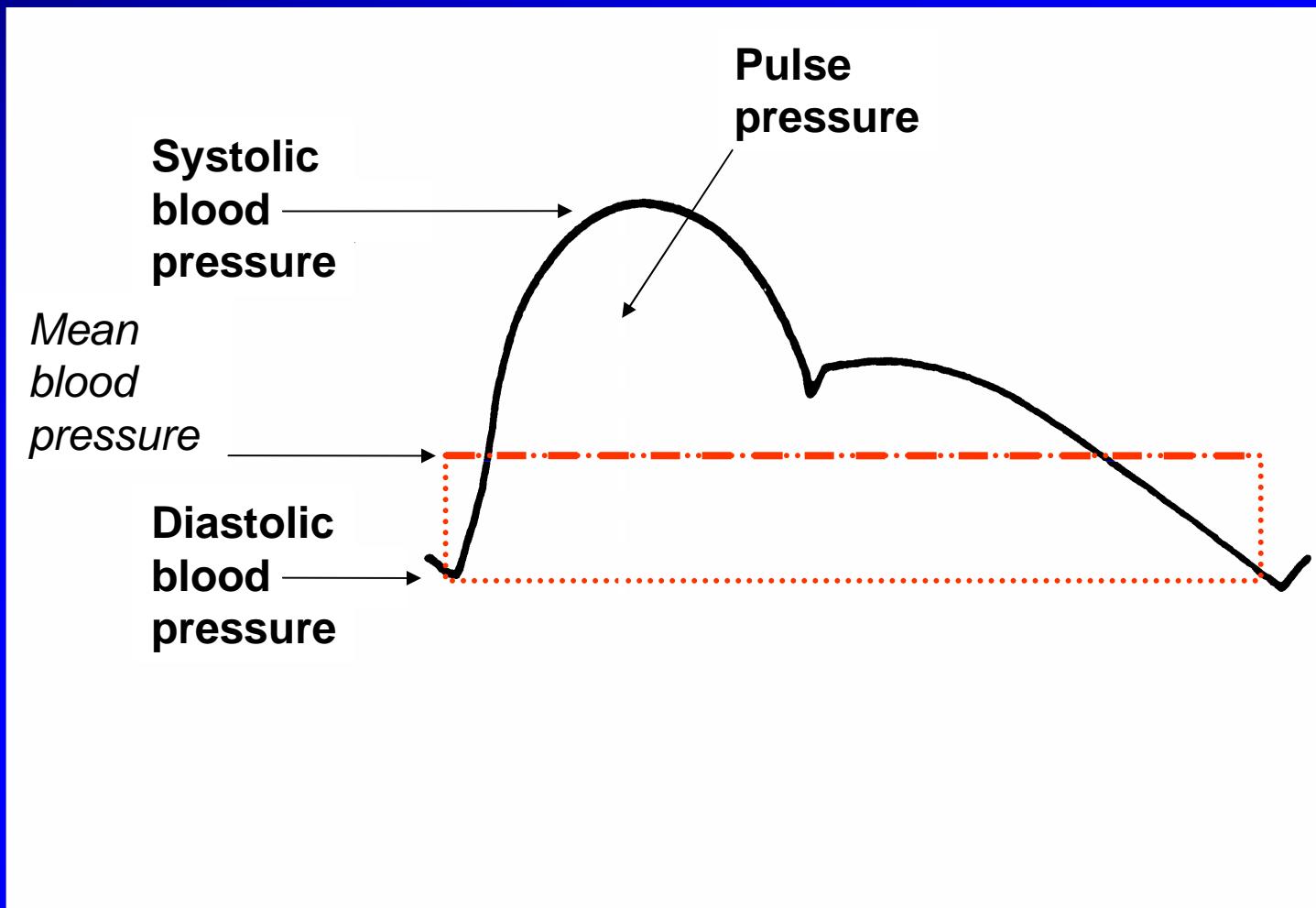
Correlation between morphologic and functional cardiovascular parameters in HD patients

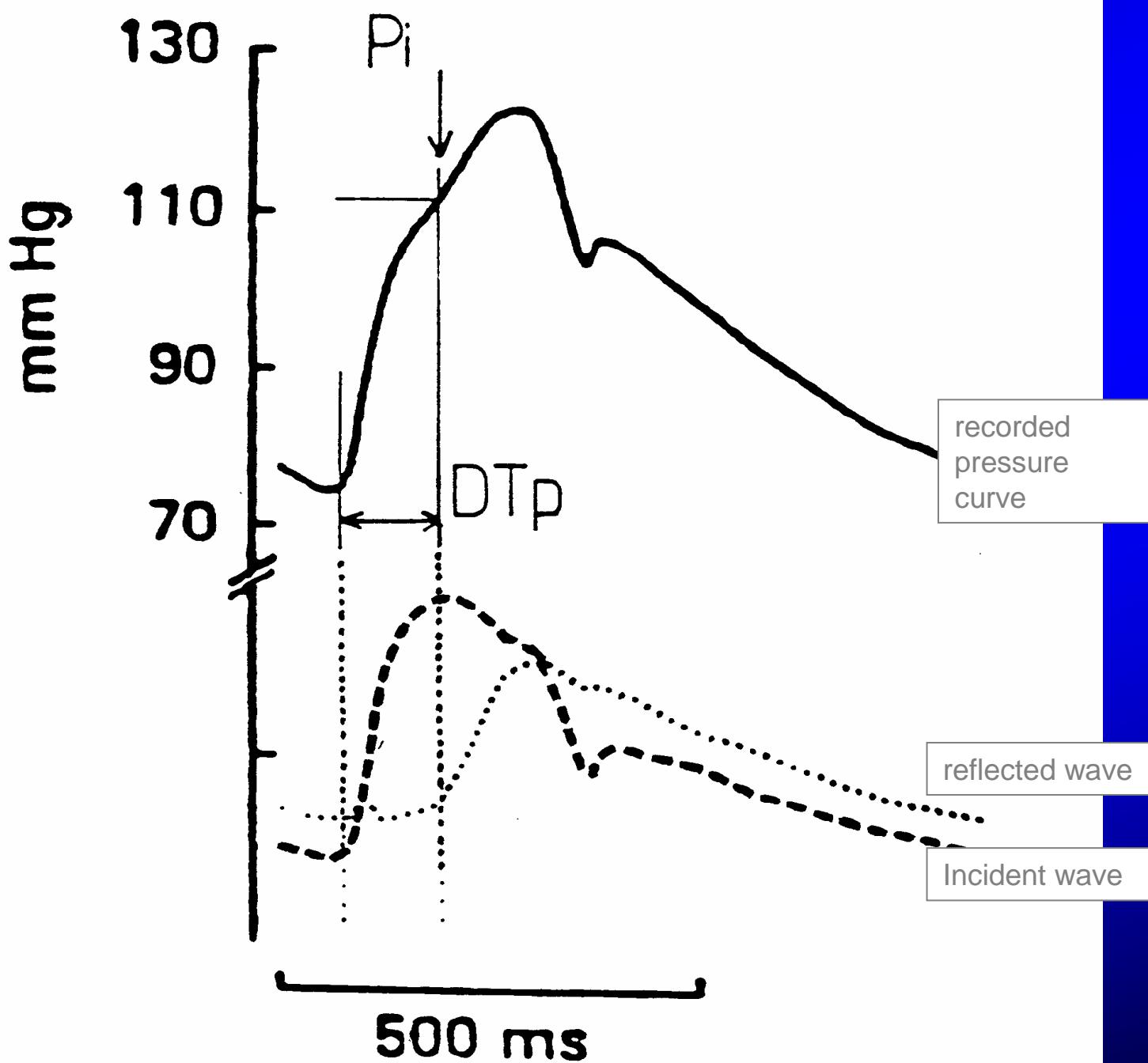


Couplage cœur vaisseaux: les ondes de réflexion

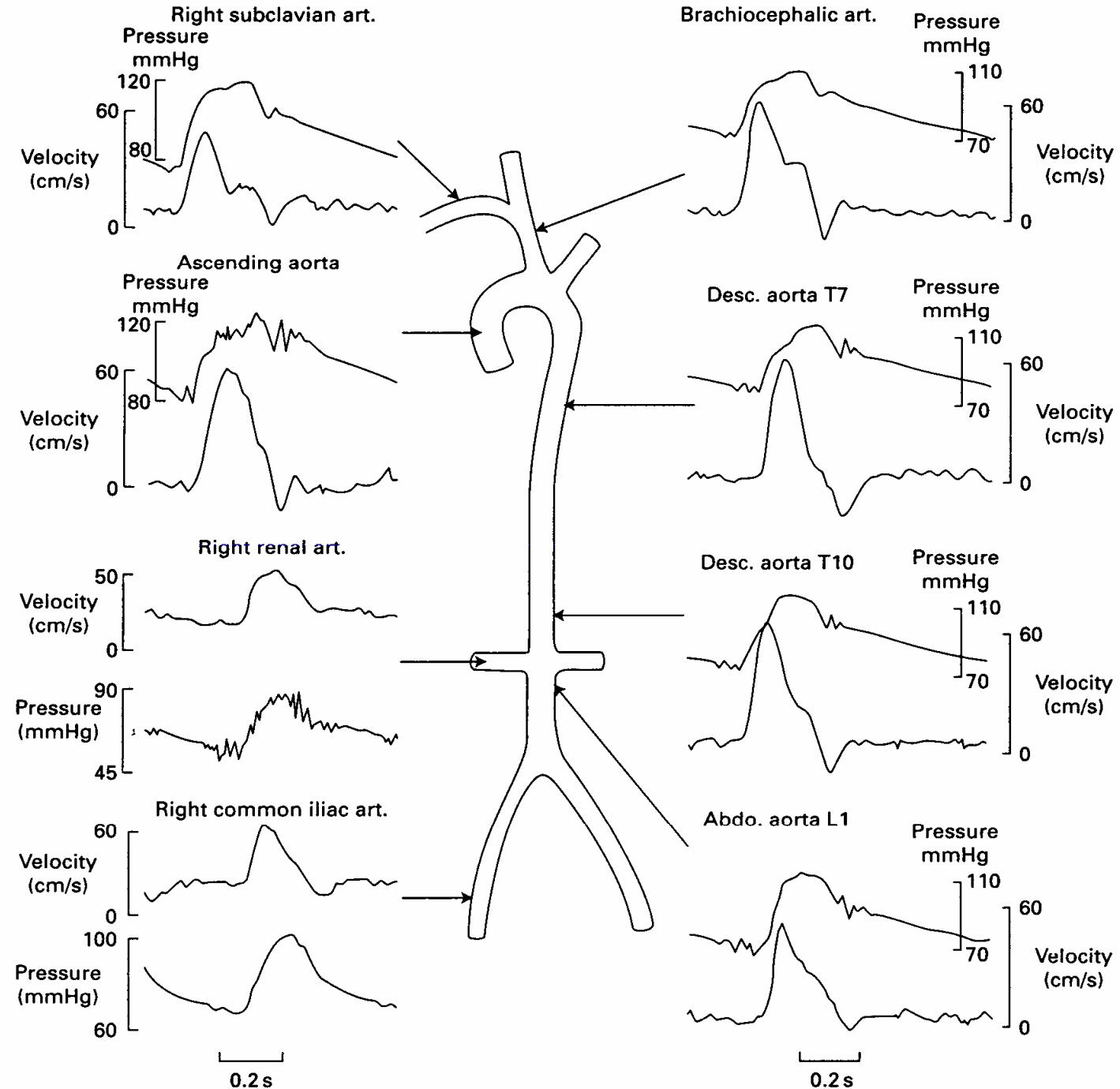
Apport de la tonométrie

Pressure wave





From M O'Rourke



Impact of SBP, DBP and PP on coronary disease

	β Coefficient	SD	RELATIVE RISK (95% CI)
Age<50 years			
SBP	0.13	0.04	1.14 (1.06-1.24)**
DBP	0.29	0.06	1.34 (1.18-1.51)***
PP	0.02	0.07	1.02 (0.89-1.17)
Age : 50-59 ys			
SBP	0.08	0.03	1.08 (1.02-1.15)*
DBP	0.10	0.06	1.11 (0.99-1.24)
PP	0.11	0.05	1.11 (1.02-1.22)*
Age \geq 50 ys			
SBP	0.16	0.03	1.17 (1.11-1.24)***
DBP	0.11	0.06	1.12 (0.99-1.27)
PP	0.21	0.04	1.24 (1.16-1.33)***

Adjusted on age, gender, BMI, tabagisme, diabetes, HDLchol/Total chol., heart rate

Clinical Impact of high Pulse Pressure

Table 2 Prediction of cardiovascular disease from high pulse pressure and low diastolic blood pressure

Surrogate endpoints	
Cardiac hypertrophy	Pannier <i>et al.</i> [16], Gardin <i>et al.</i> [17]
Carotid artery stenosis	Salonen and Salomen [18], Psaty <i>et al.</i> [19], Bots <i>et al.</i> [20], Sutton-Tyrrell <i>et al.</i> [21], Franklin <i>et al.</i> [22]
Aortic calcifications	Whitteman <i>et al.</i> [23]
Hard endpoints	
CHD events	Darne <i>et al.</i> [24], Benetos <i>et al.</i> [25], Franklin <i>et al.</i> [11]
Acute myocardial infarction	Madhavan <i>et al.</i> [26], Fang <i>et al.</i> [27]
Myocardial dysfunction	Mitchell <i>et al.</i> [28], Domanski <i>et al.</i> [29]
Heart failure	Chae <i>et al.</i> [30], Haider <i>et al.</i> [31]
Total cardiovascular risk (ABPM)	Verdecchia <i>et al.</i> [32]
Cardiovascular death	Lee <i>et al.</i> [33]
Thrombotic stroke	Scuteri <i>et al.</i> [34]
Hemorrhagic stroke	Selker <i>et al.</i> [35]
End-stage renal disease	Perry <i>et al.</i> [36]

EUROPEAN CONSENSUS on ARTERIAL STIFFNESS

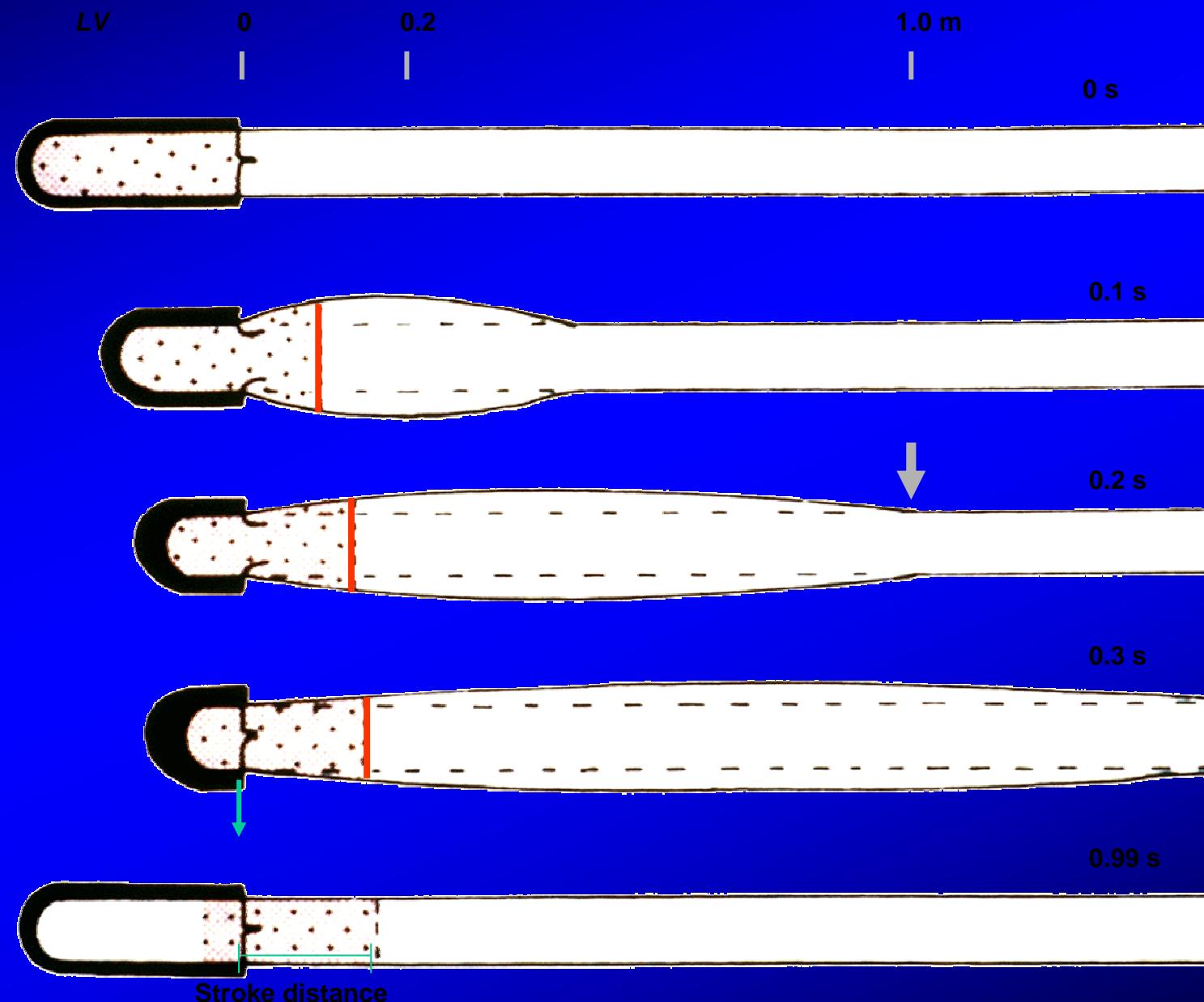
Table 5 Longitudinal studies reporting the independent predictive value of central pulse pressure and augmentation index (adapted from Ref. 1)

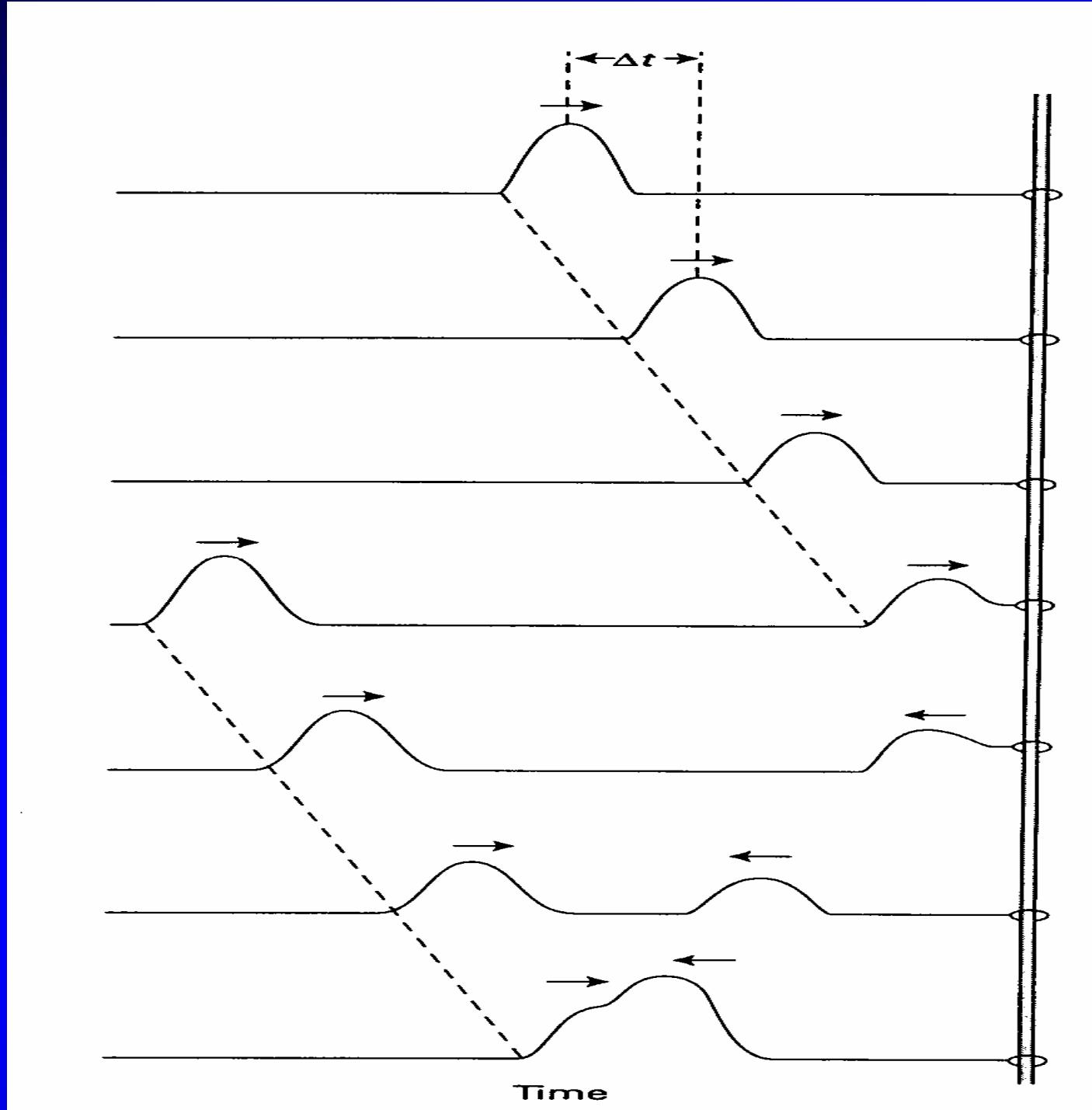
Parameter	First author (year, country)	Events	Follow-up (years)	Type of patient (number)	Mean age at entry (years)	Ref.
Central pulse pressure	Safar (2002, Fr)	All cause mortality	4.3	ESRD (180)	54	23
	Williams (2006, UK)	CV events	3.4	HT, ASCOT study (2073)	63	26
Carotid augmentation index	London (2001, Fr)	All cause and CV mortal.	4.3	ESRD (180)	54	22
	Weber (2005, Austria)	Severe CV events	2	Undergoing PCI (262)	66	24
	Chirinos (2005, USA)	Severe CV events	3.2	Undergoing PCI (297)	64	25
	Williams (2006, UK)	CV events	3.4	HT, ASCOT study (2073)	63	26

Legends as in Table 4; PCI: percutaneous coronary intervention.

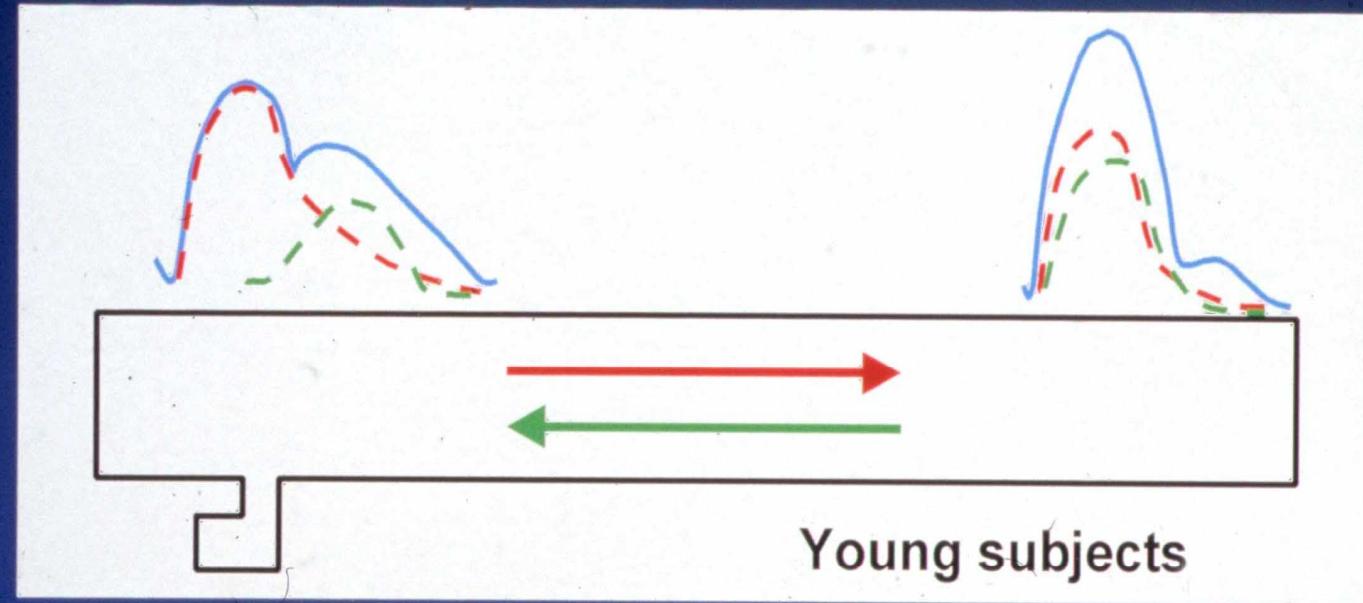
WAVE REFLECTION

Sketch to illustrate transmission of the pressure pulse at 5 m/s along the arterial system



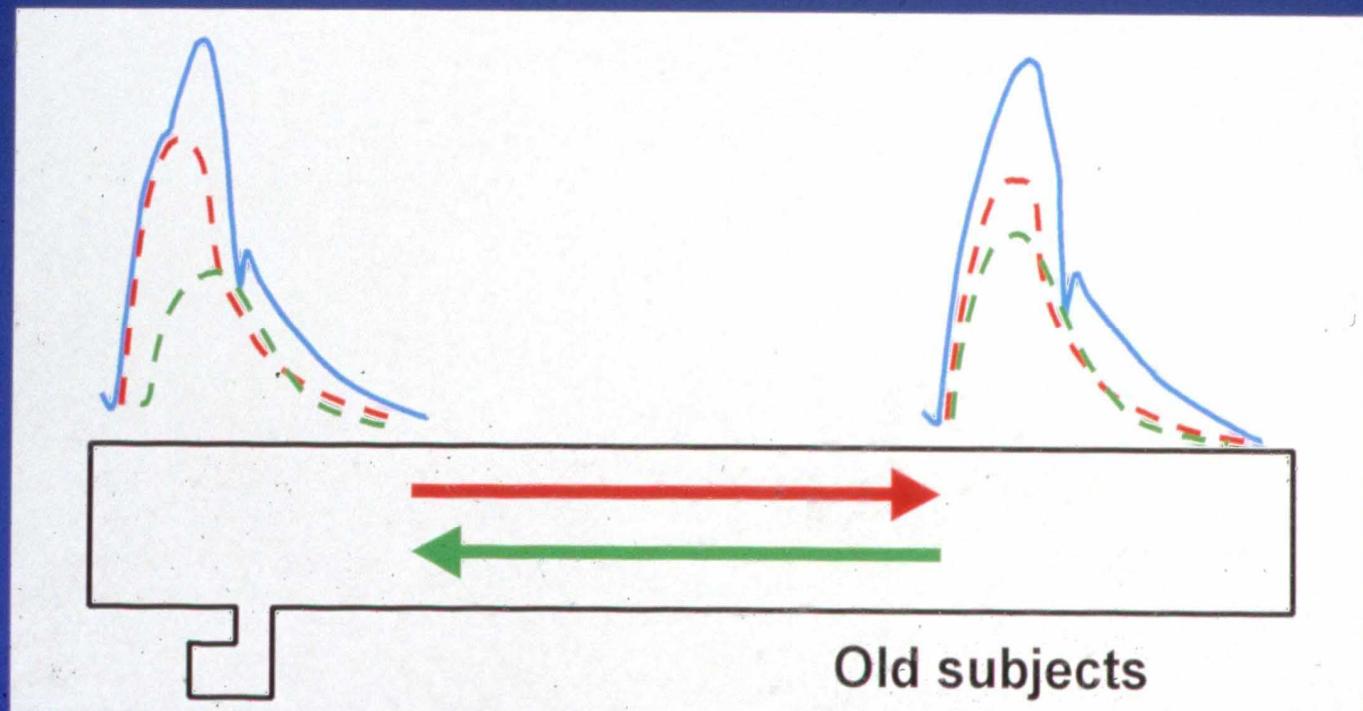


SCHEMATIC REPRESENTATION OF PRESSURE WAVES AMPLIFICATION, REFLECTION AND TIMING BETWEEN AORTIC ARCH AND PERIPHERAL ARTERIES



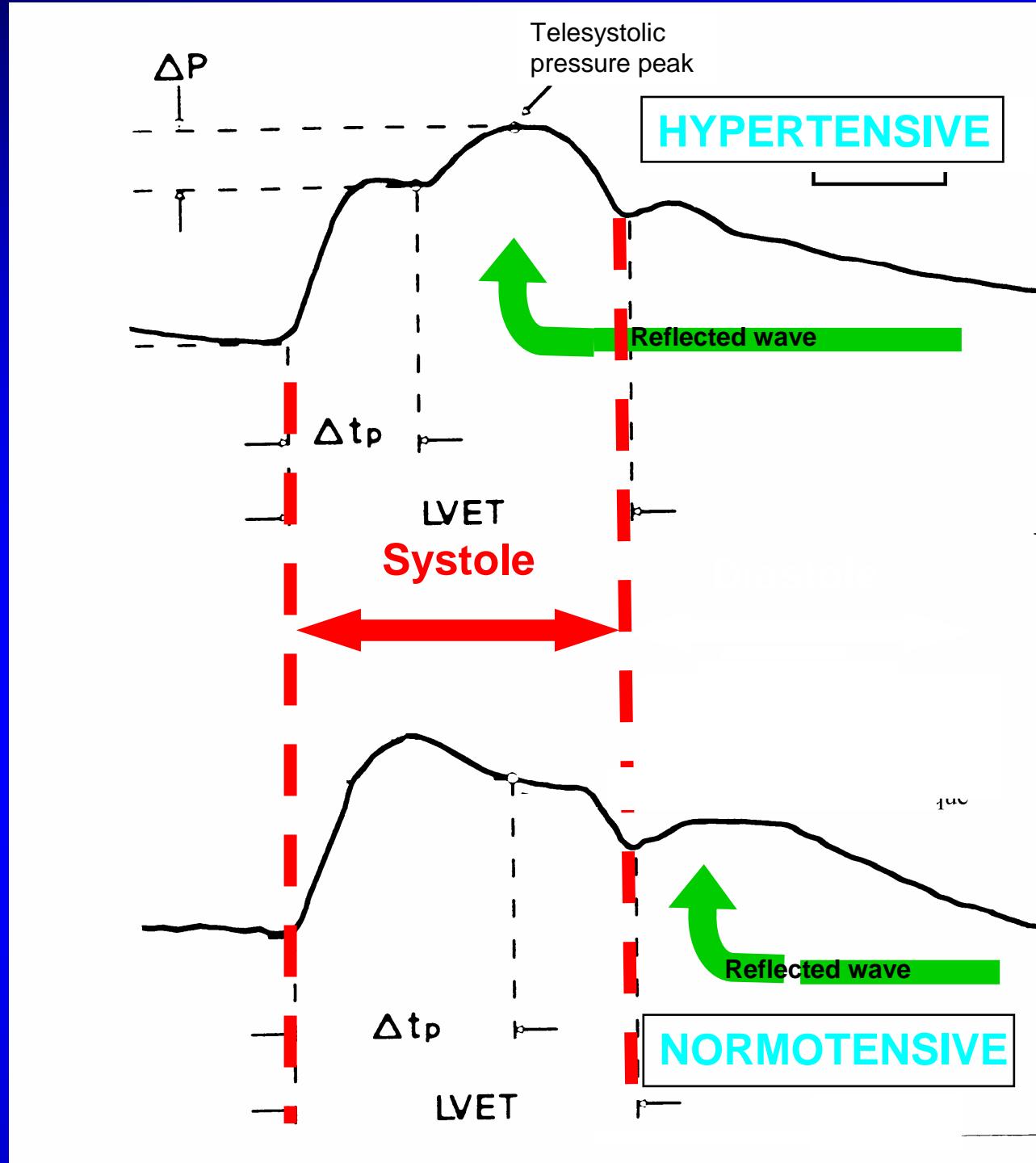
Young subjects

- (—) measured pressure wave
- (....) forward/incident pressure wave,
- (....) reflected pressure wave
- pulse wave velocity
- ← pulse wave velocity



Old subjects

Aortic wave reflection: Contribution to central Pulse Pressure



Augmentation index: $\Delta p/ PP$, ($\Delta p/ Pi$)

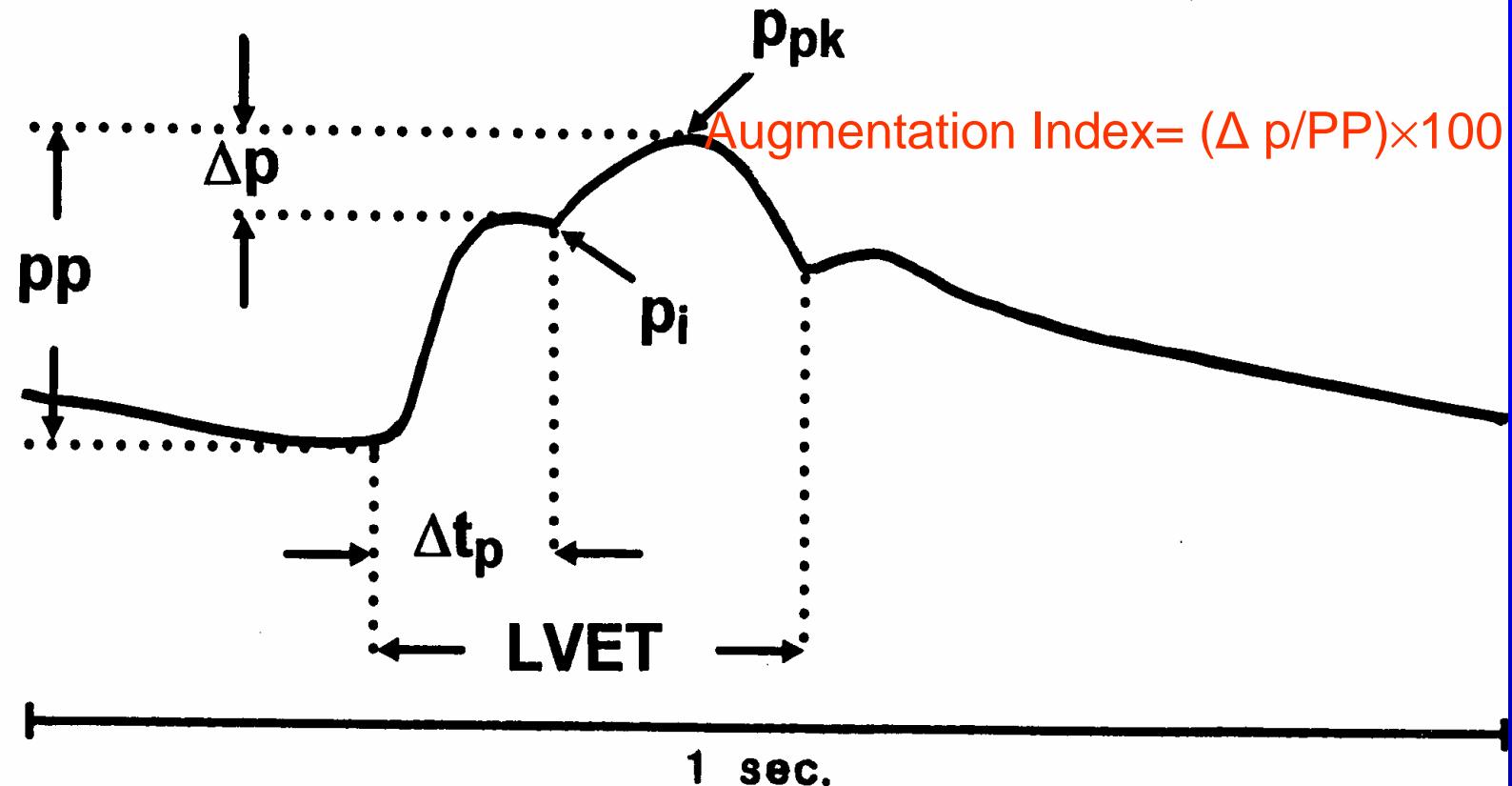
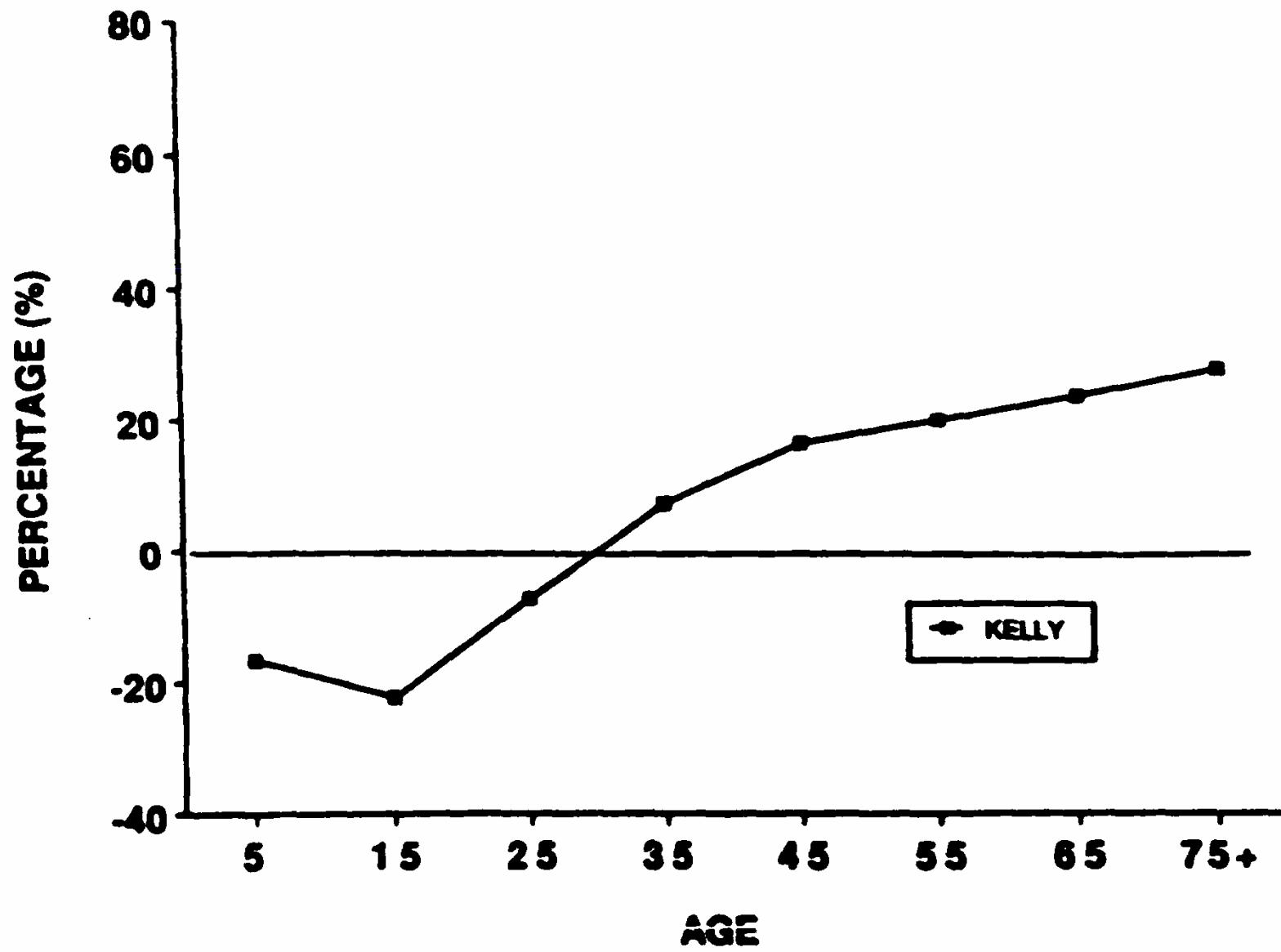
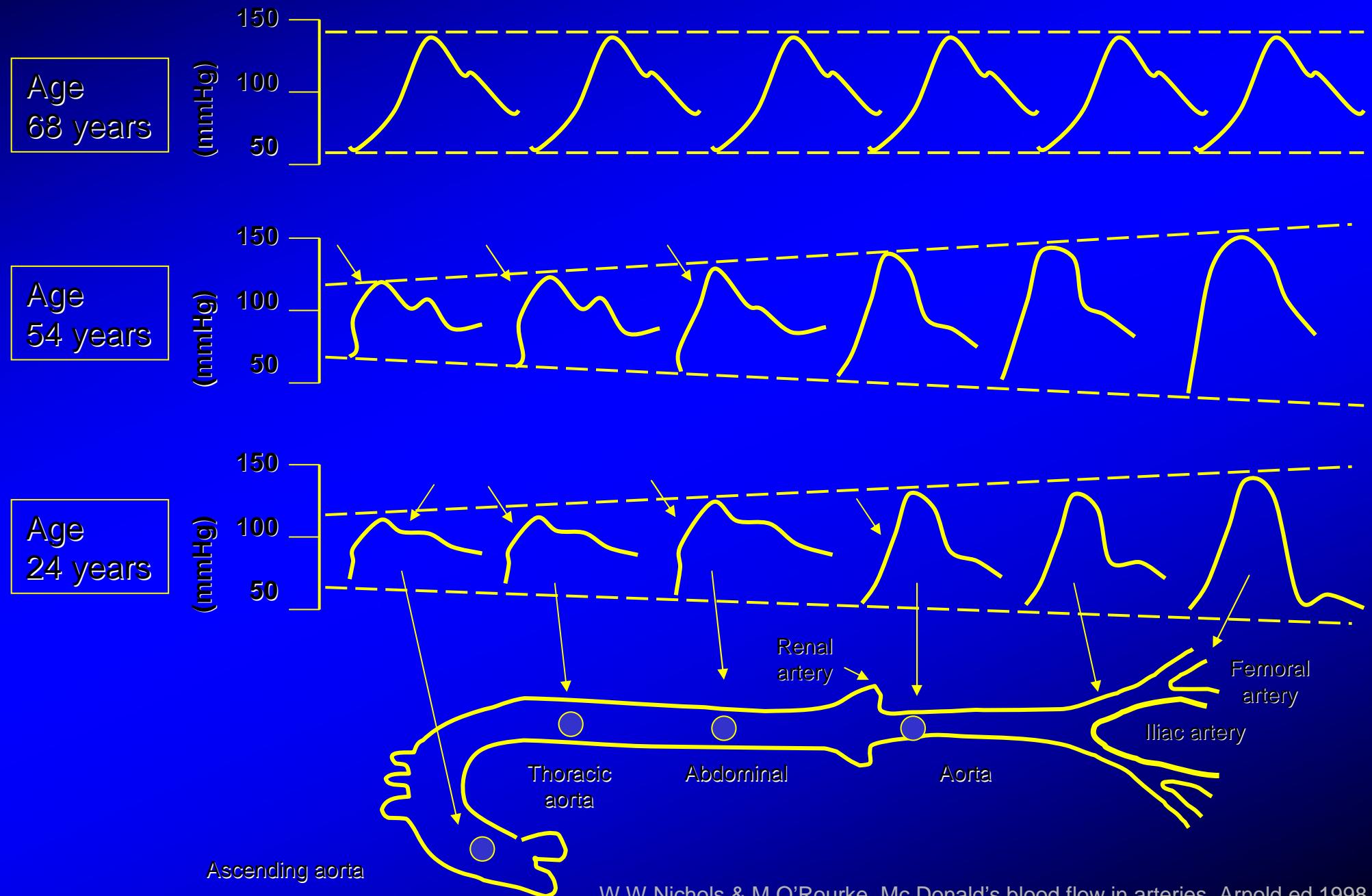


Figure 1 Carotid pressure wave contour. PP = pulse pressure; ΔP = late systolic peak amplitude; P_i = early systolic shoulder; LVET = left ventricular ejection time; Δt_p = travel time of the reflected wave, sec. = second.

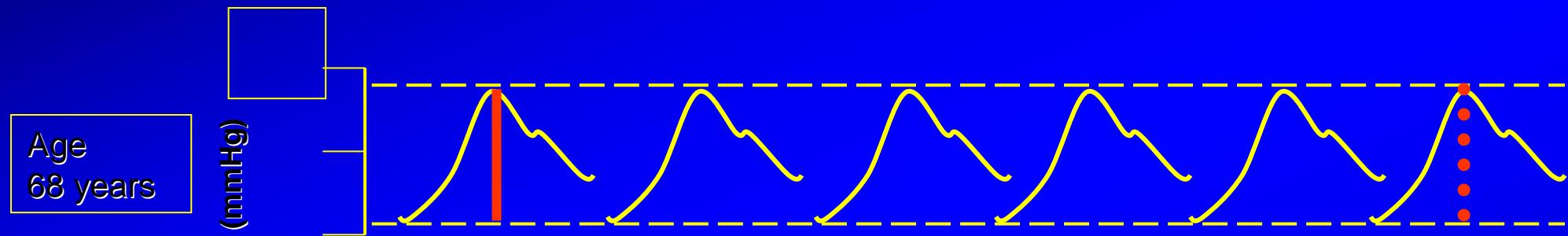
AUGMENTATION INDEX - CAROTID ARTERY



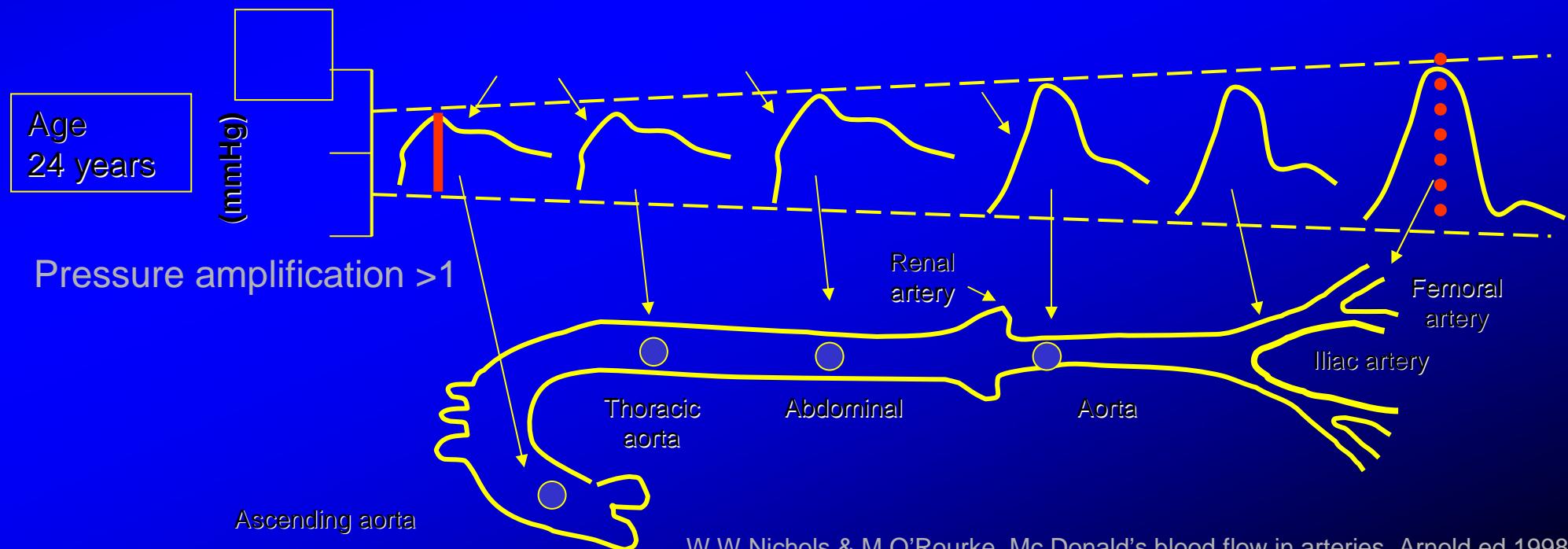
Aorta characteristics



Pressure Amplification : peripheral P / central P



Pressure amplification = 1



DETERMINANTS OF WAVE REFLECTION AND CENTRAL PULSE PRESSURE

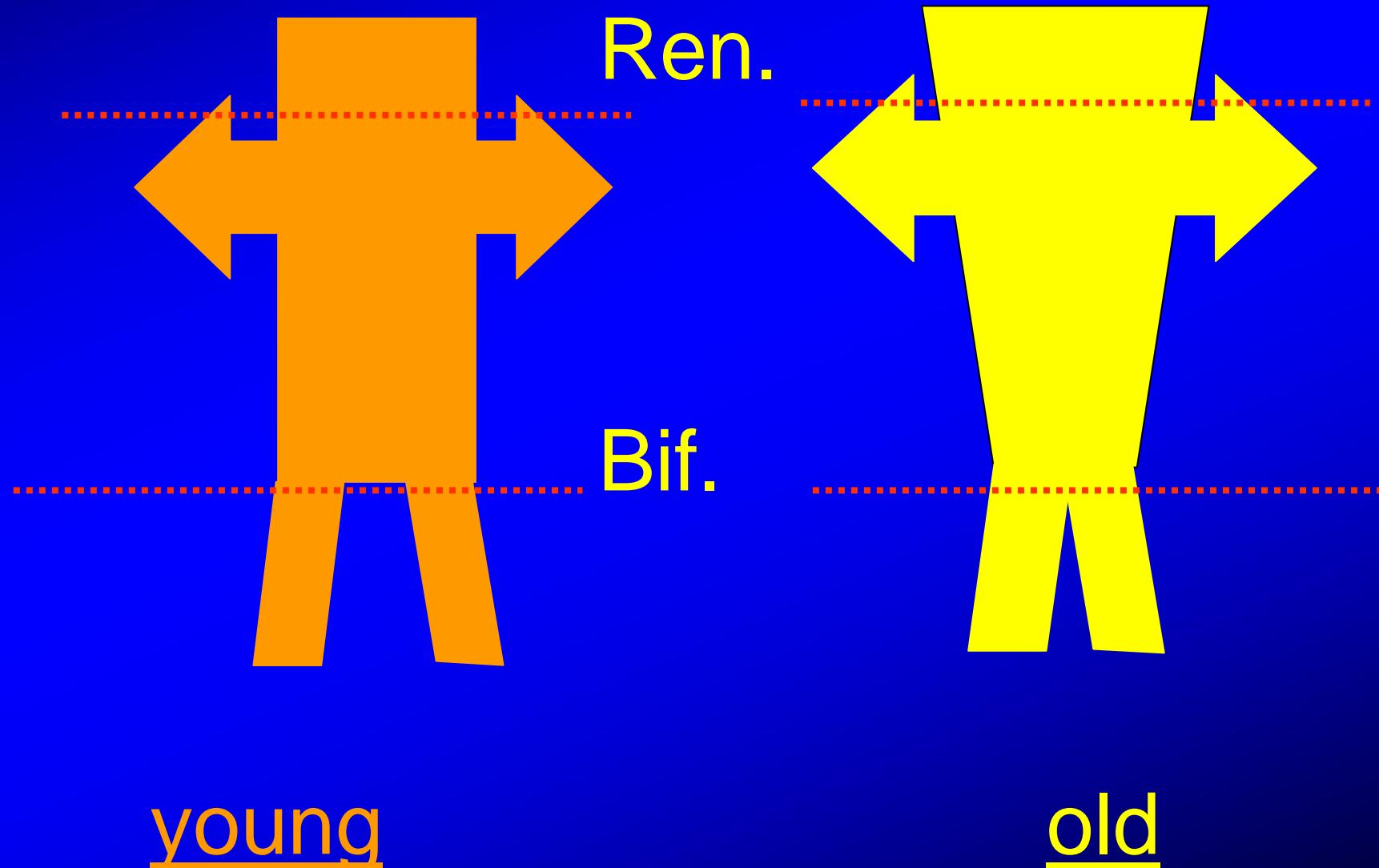
- Left ventricular work (ejection strength and velocity)
- Functional and structural properties of aorta:
 - Stiffness
 - Length and geometry (change in diameter)
 - Visco elastic properties of aortic wall: absorption coefficient of wave energy
- Arteriolar resistance
 - Site
 - Degree of vasoconstriction

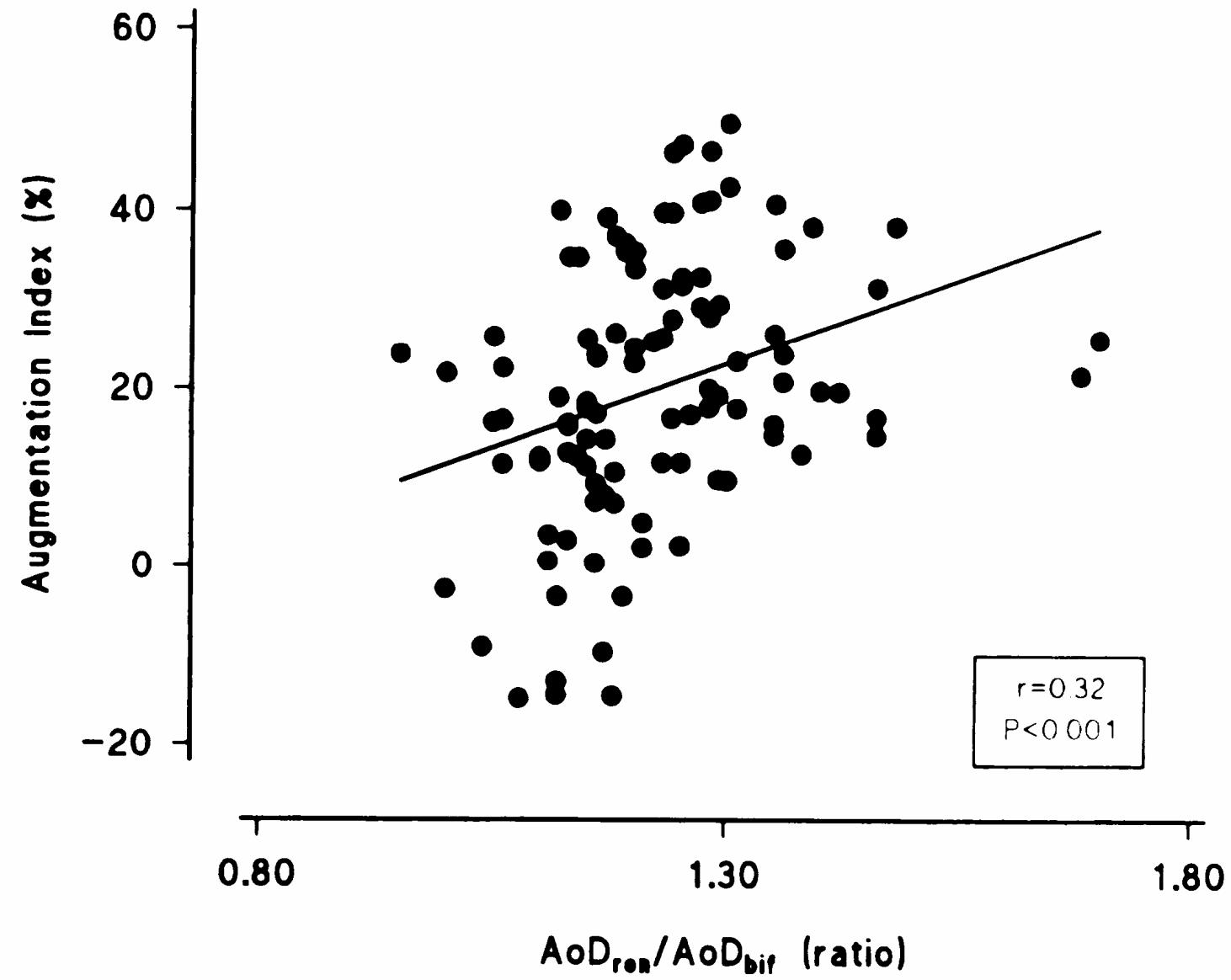
Determinants of augmentation index

variables	t value	Probability	%RMSE
Height (cm)	-7.7	<0.00001	18.4
Aortic PWV (cm/sec)	6.8	<0.00001	14.7
LVET (msec)	5.2	<0.00001	8.8
ESRD (1, no; 2, yes)	3.1	0.0023	3.0
Age (yr)	0.7	0.4617	0.2
$R^2 = 0.5830$ ($p < 0.0001$)			
F ratio = 39.7 ($p < 0.0001$)			
RMSE = 10.6			

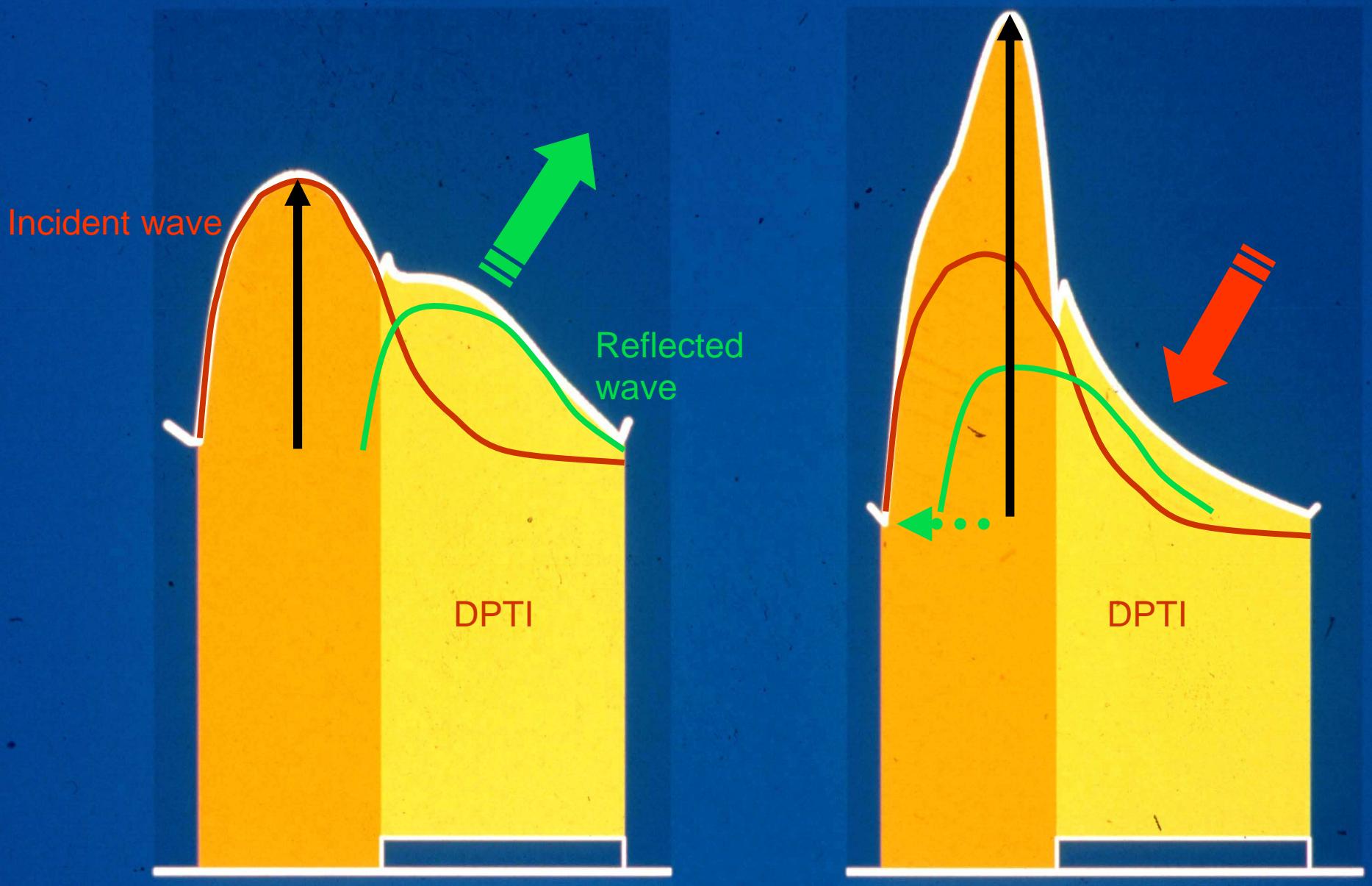
Dependent variable, $\Delta P/PP (\%)$. $\Delta P/PP (\%) = P_{\text{peak}} - P_i/PP$, augmentation index

Conicity of aorta with aging





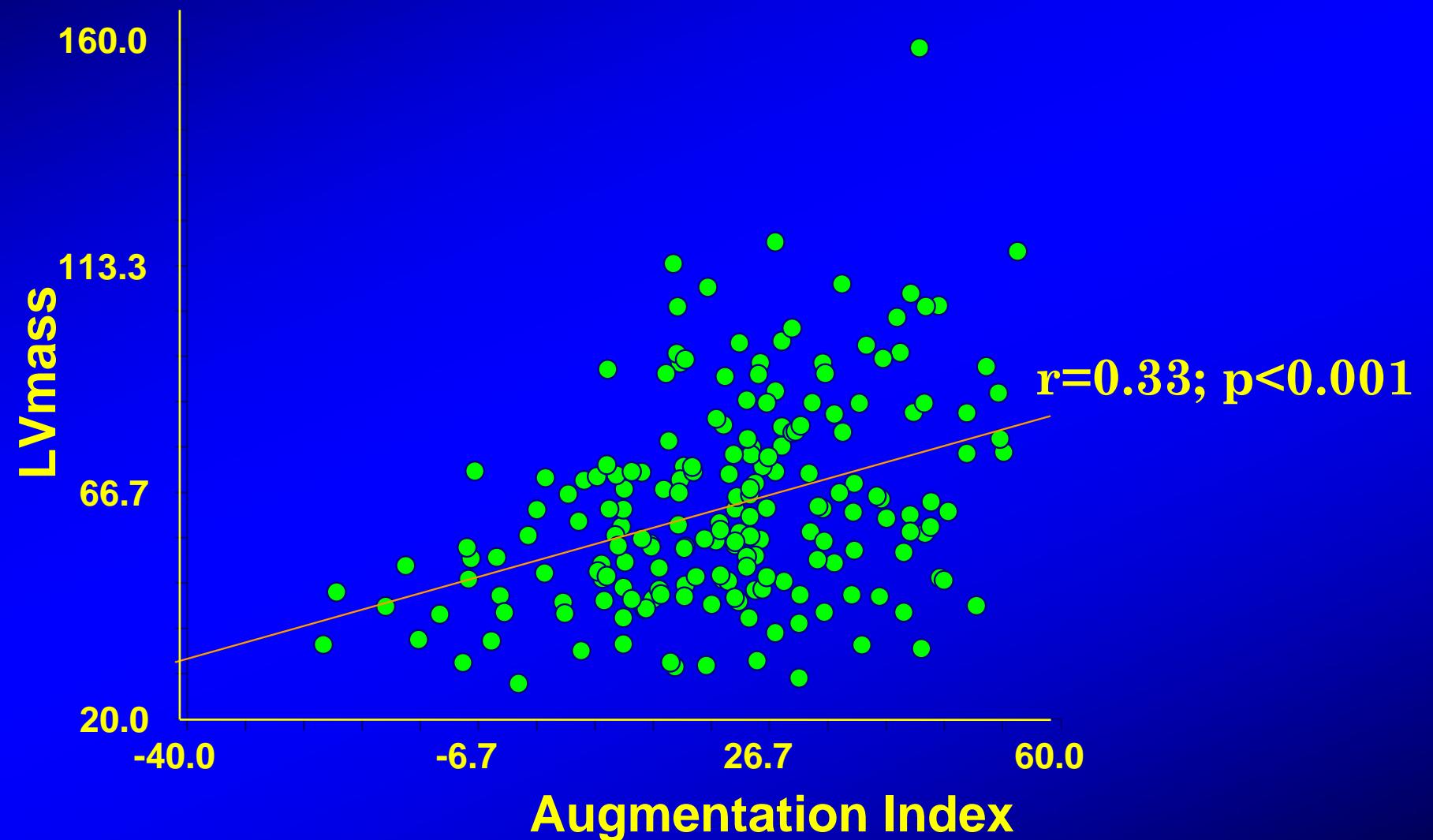
CLINICAL IMPACT OF WAVE REFLECTION



Diagrammatic representation of the effects of arterial degeneration (right) on aortic systolic pressure time index (orange area) and aortic diastolic pressure time index (yellow area)

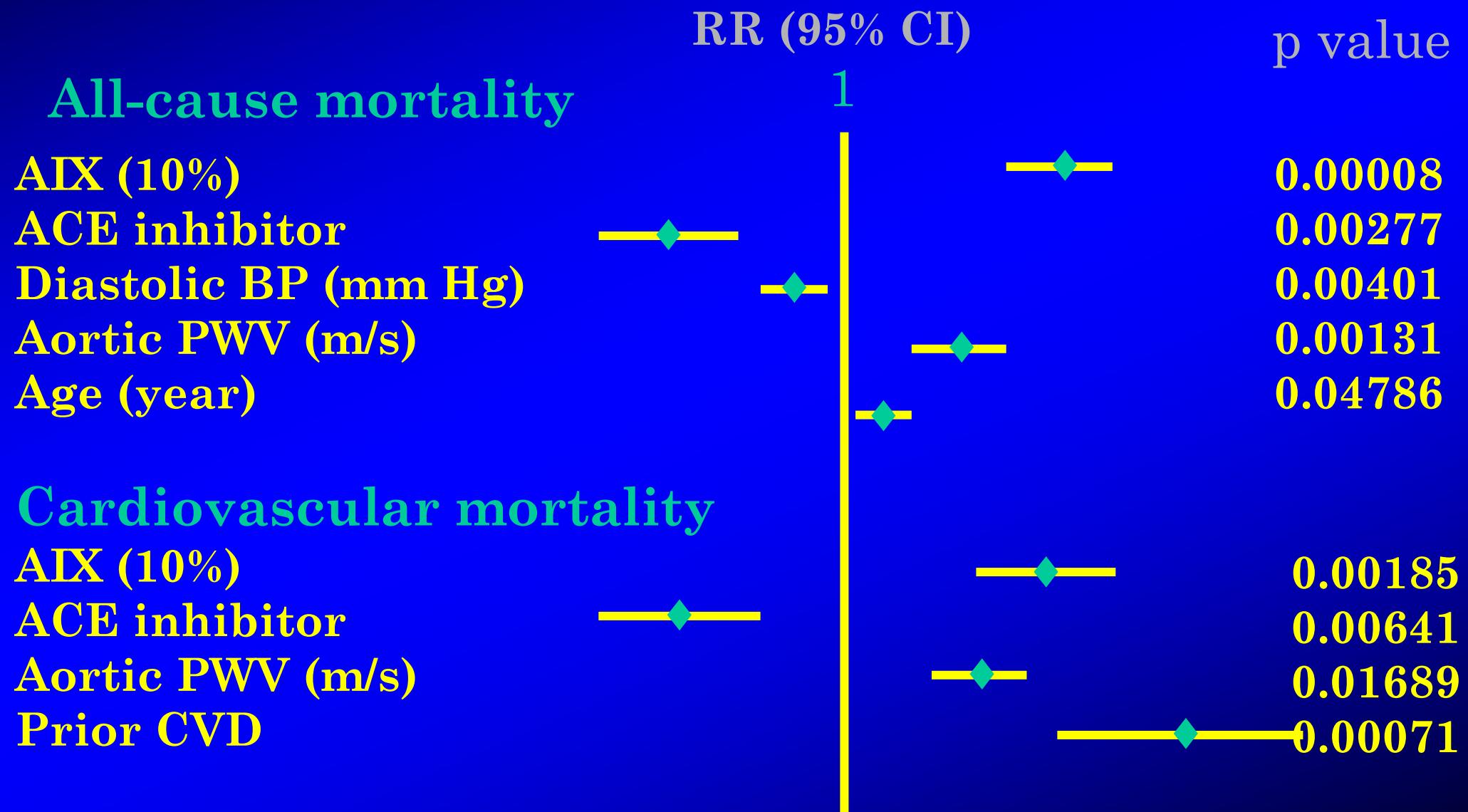
DPTI: diastolic pressure-time index

Augmentation Index vs LV mass (echo)

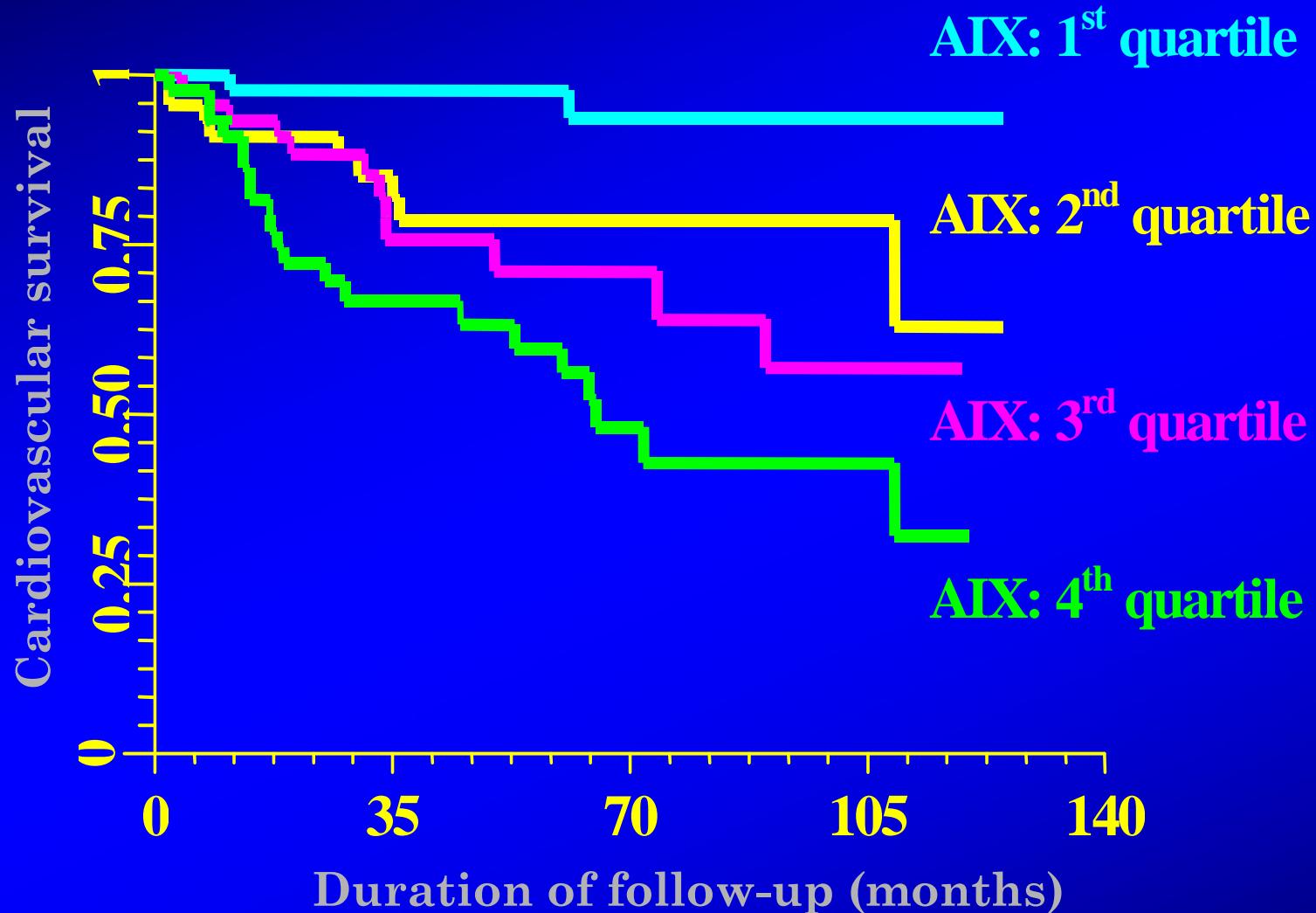


LV mass: Left Ventricular Mass ($\text{g}/\text{m}^{2.7}$)

Adjusted proportional hazards RR analyses in Hemodialyzed patients



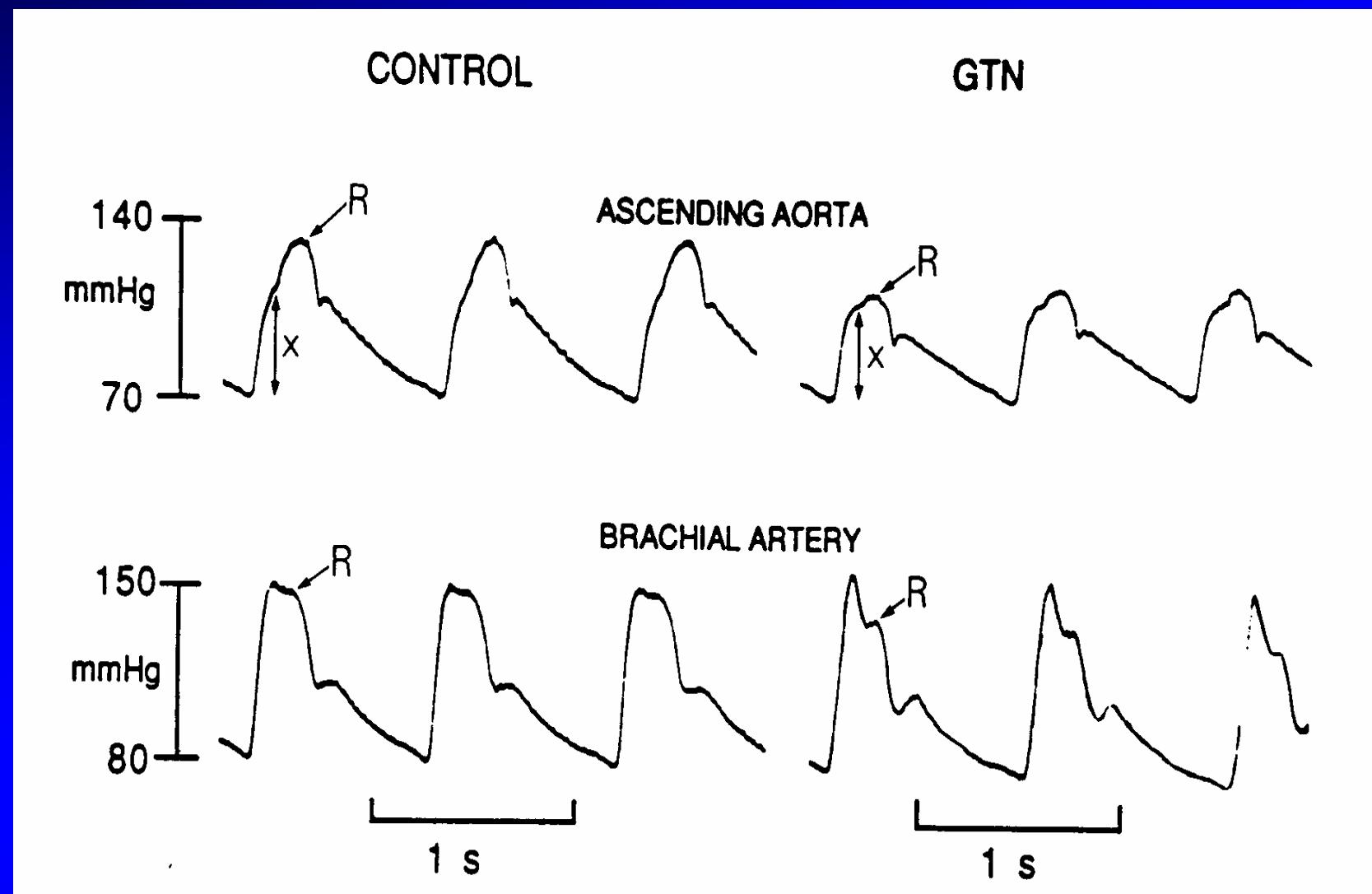
Augmentation Index (AIX) and cardiovascular survival

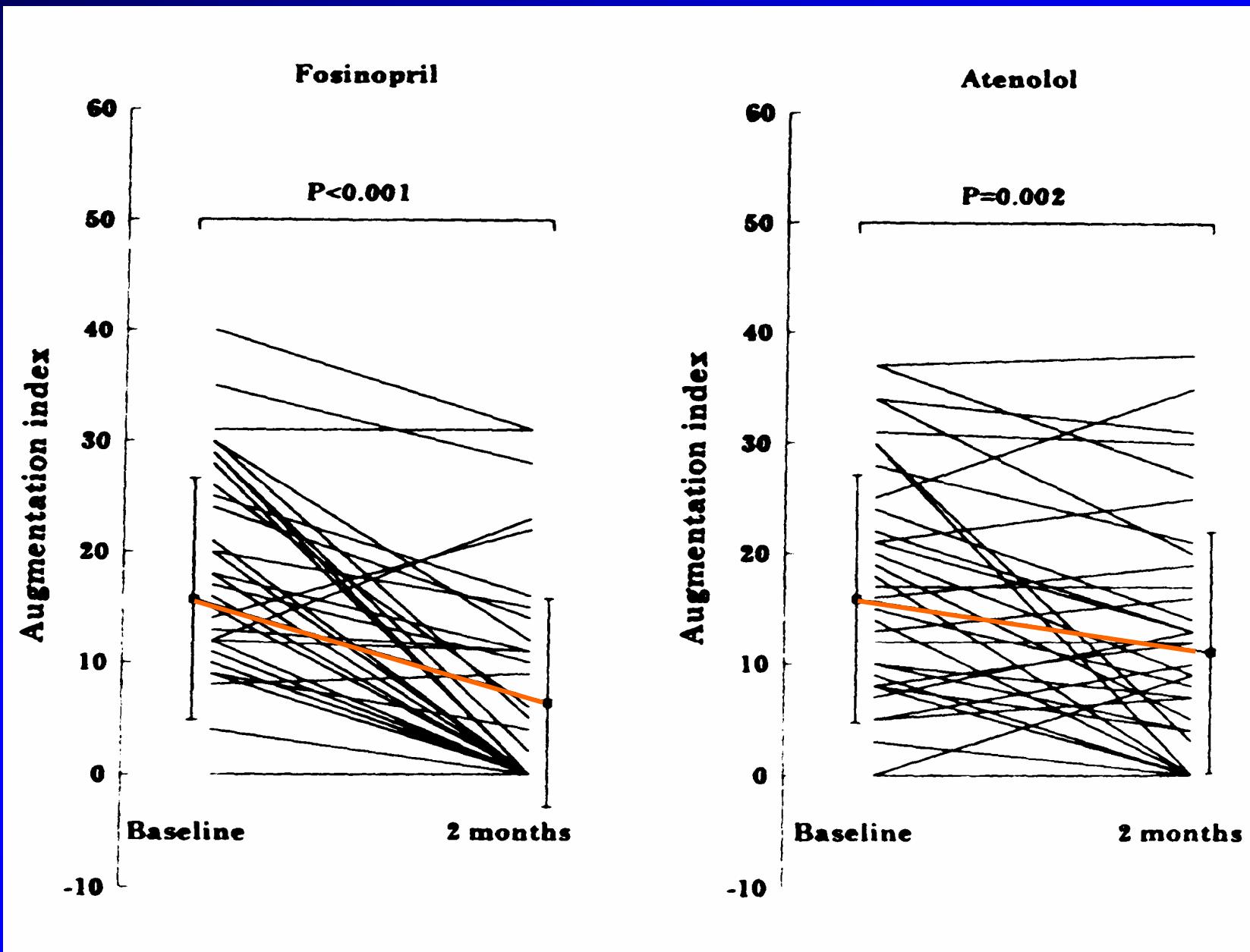


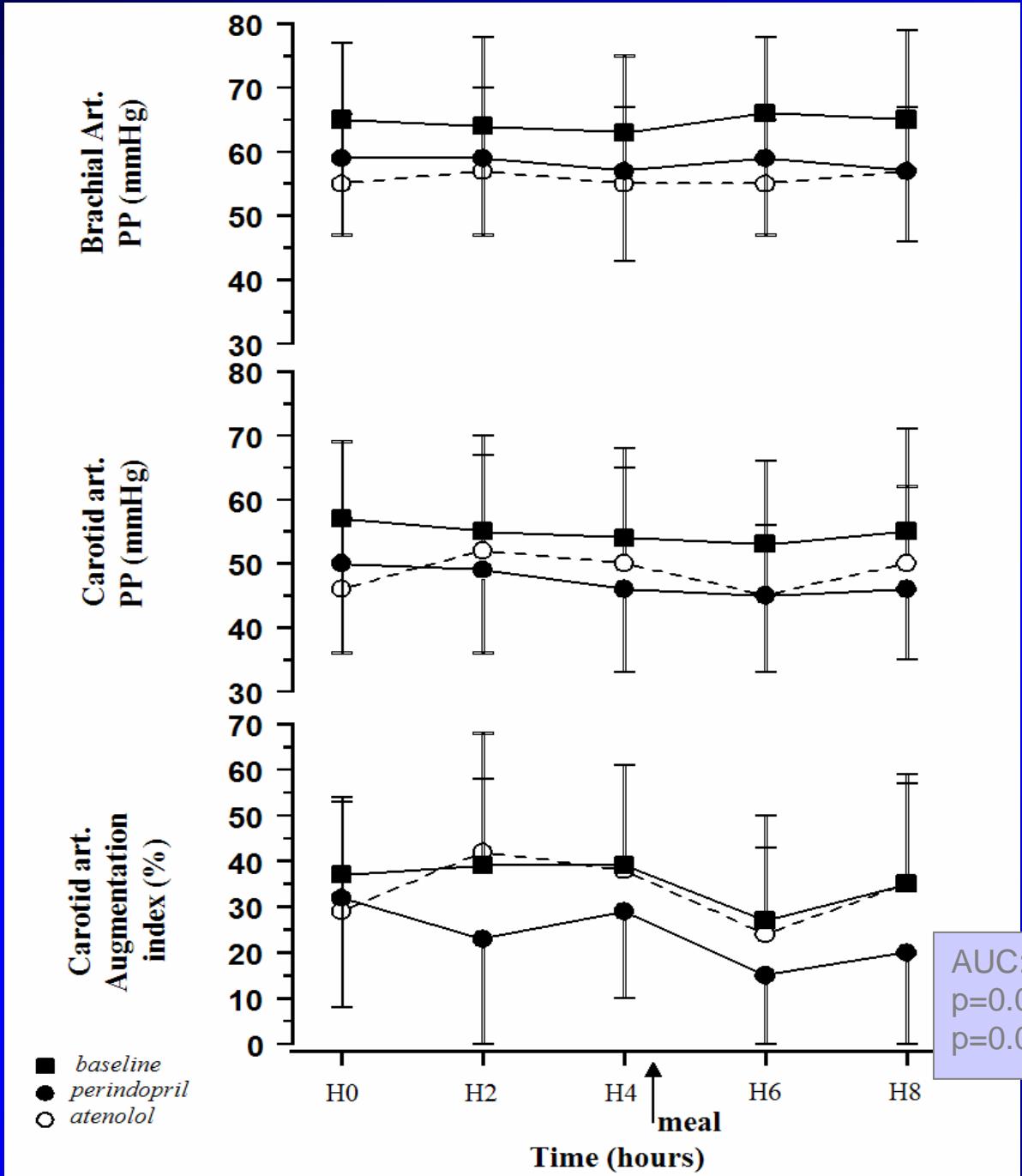
Log rank test for cardiovascular mortality: Chi square=23.11, p<0.0001

G London et al. Hypertension, 2001.

THERAPEUTIC IMPLICATIONS



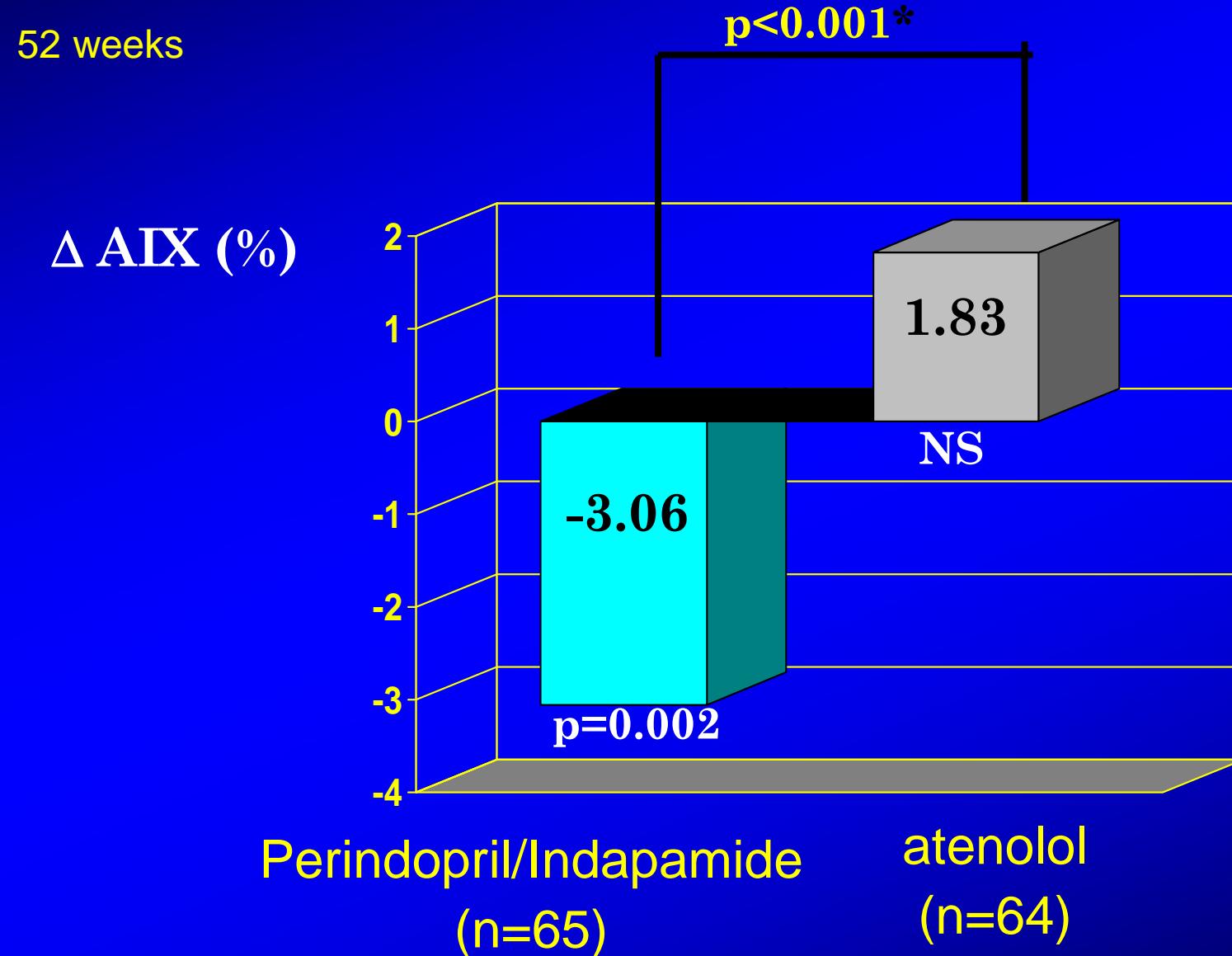




Cross-over: 3x 4 weeks

B Pannier et al., Clin Exp Pharmacol Physiol, 2001

Reason Study : Augmentation Index (Aorta)

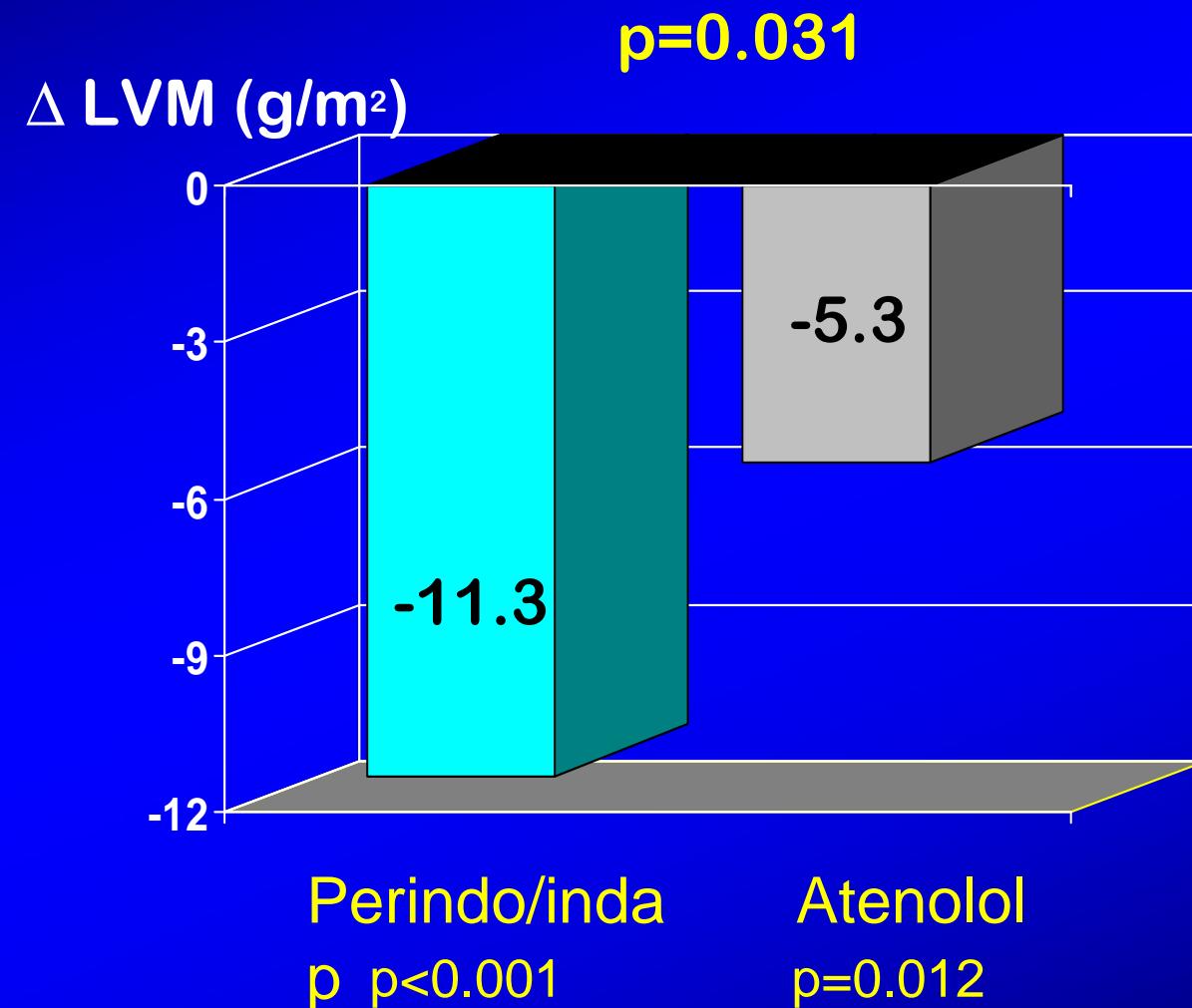


R Asmar et al., Hypertension, 2001

*p value: Fischer test of the ANCOVA, adjusted for age, sex and baseline

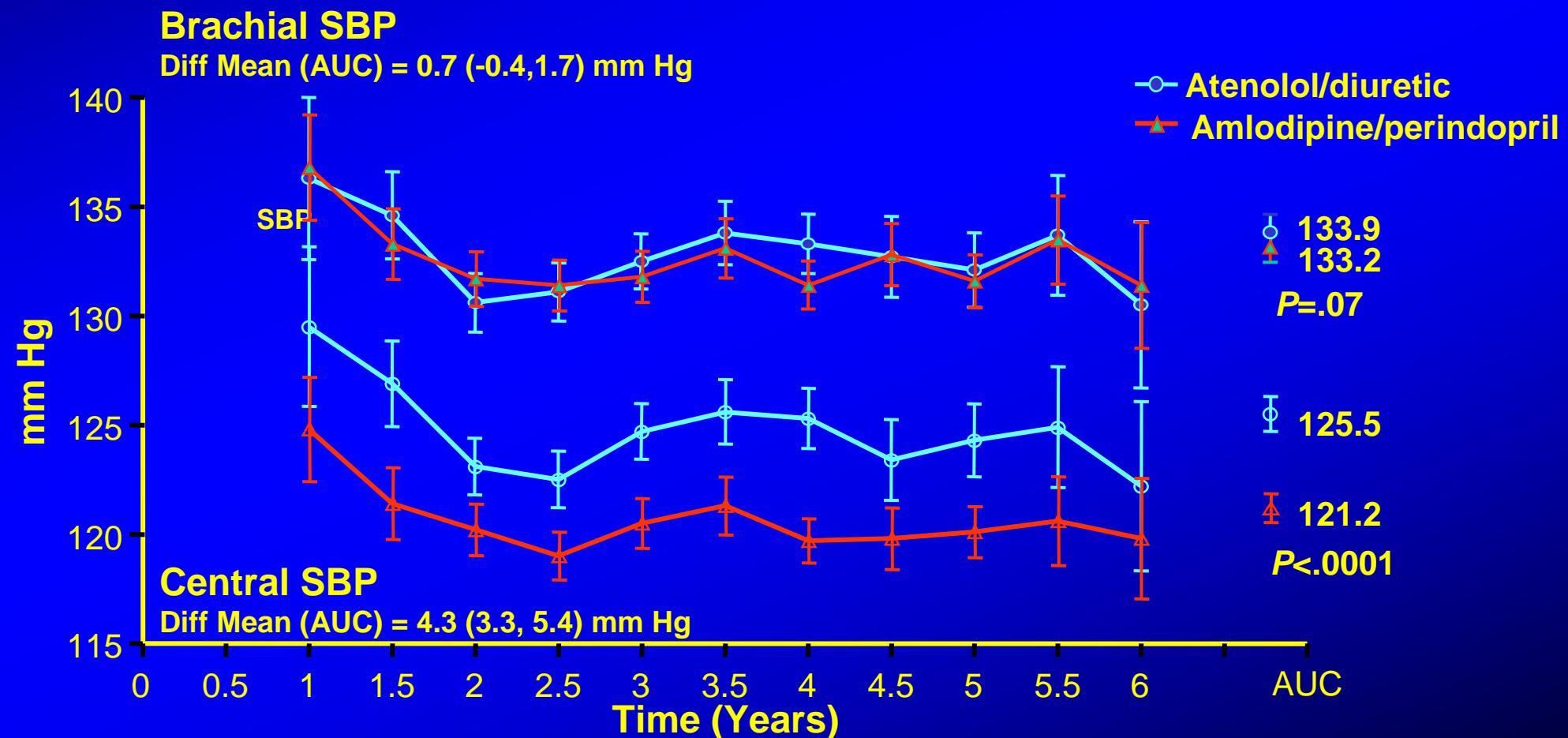
Reason Study: Left ventricular mass

52 weeks



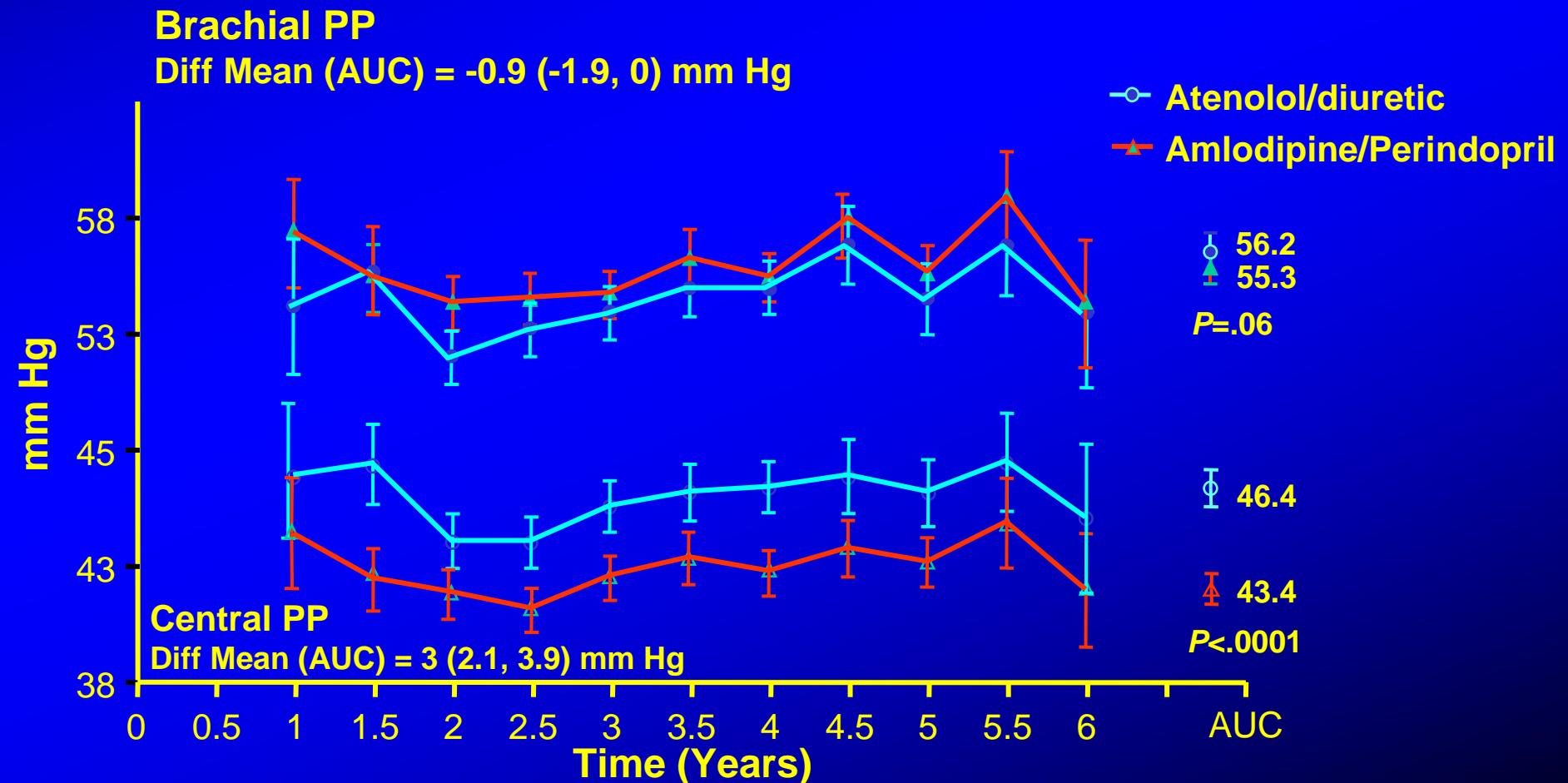
The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT: SBP

N=2073



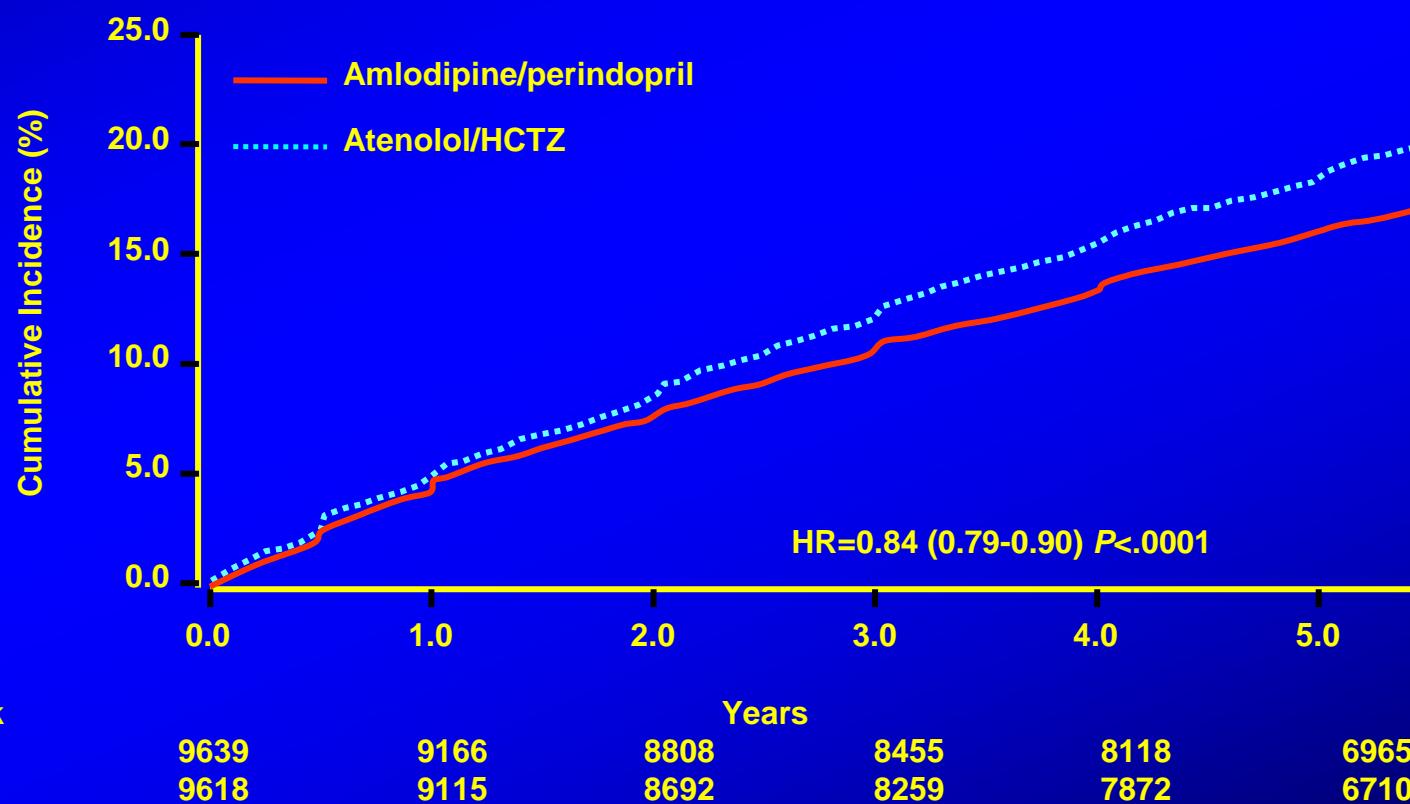
The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT: PP

N=2073



The Conduit Artery Functional Evaluation (CAFE) Study in ASCOT

Total CV Events and Procedures + Development of Renal Impairment



Clinical Outcomes in the CAFE Study

Multiple regression (Hazard/10 mm Hg)

Updated Cox proportional hazard model for the composite endpoint,
adjusted for baseline variables (305 events)

Factor	X ²	P	HR	CI
Peripheral PP	3.83	.050	1.10	1.00-1.22
Central PP	3.91	.048	1.11	1.00-1.23

Take Home messages

1-Pulse pressure is associated to heart work and arterial stiffness together with aortic wave reflection. In hypertensives and elderly, main determinants are stiffness and wave reflections

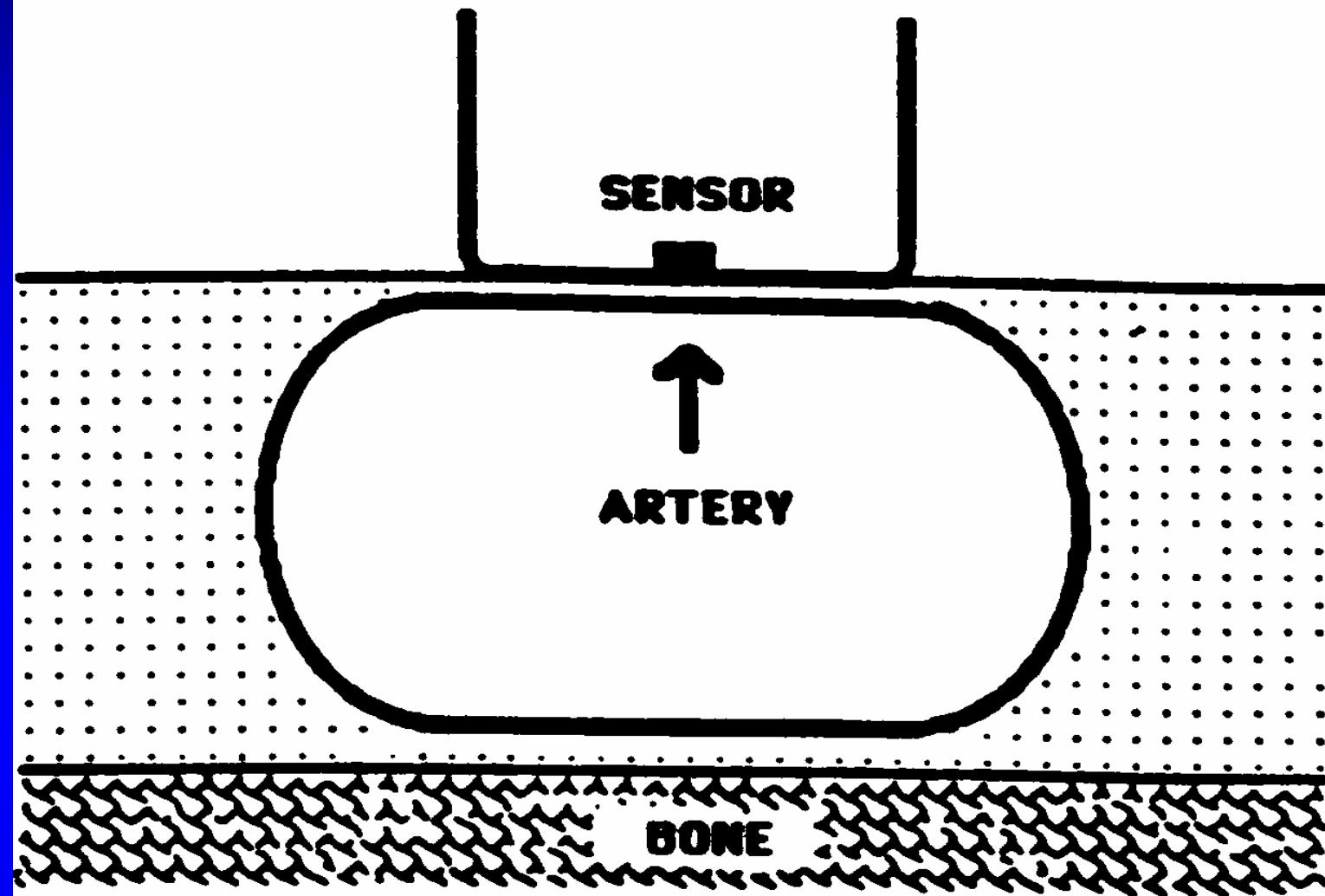
2-Pulse pressure exposes the left ventricle to a double constraint: Increased systolic pressure (particularly in late period of contraction) and decrease in coronary flow (during diastole) with an unbalance between oxygen supply and consumption by myocardium

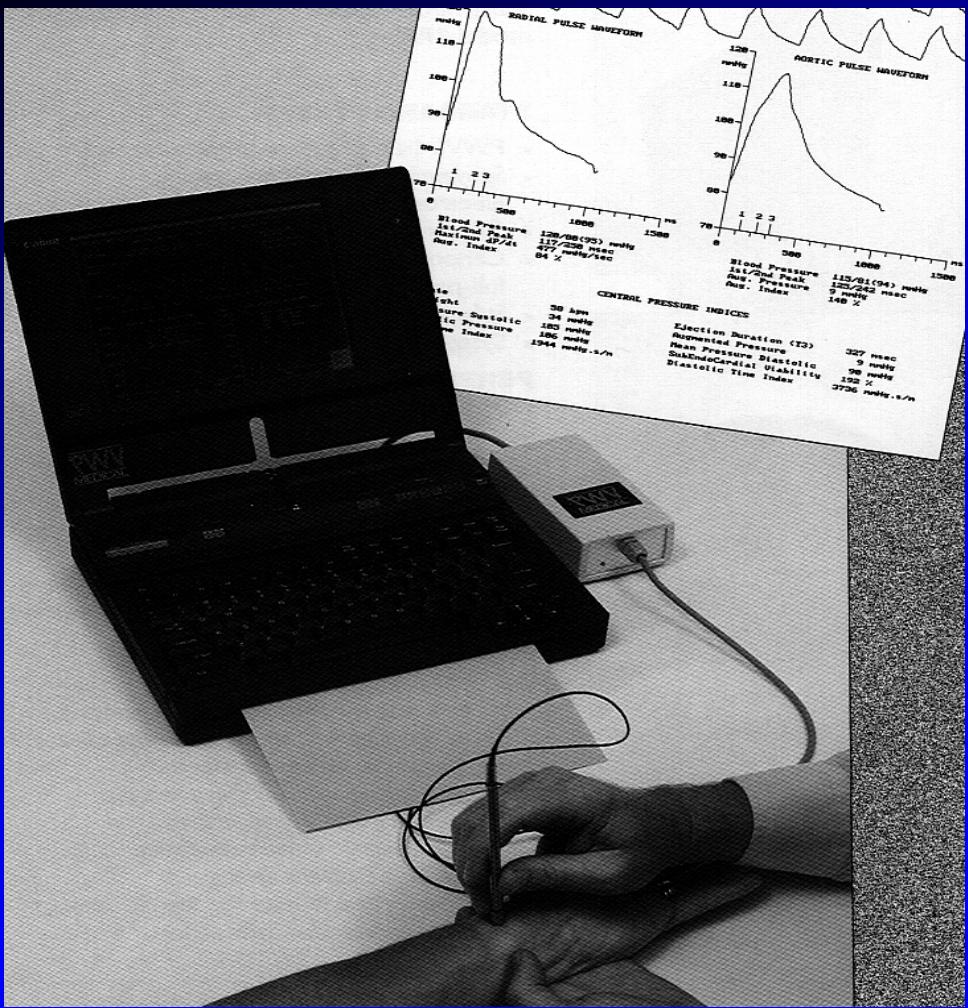
3- The consequences of this double impact are left ventricular hypertrophy and decrease in coronary reserve: with clinical consequences of coronary disease and heart failure

4- Central pressure is not reflected by brachial blood pressure, and all the pharmacological anti hypertensives families are not equivalent on central pressure.

APPLANATION TONOMETRY

APPLANATION TONOMETRY





PWV Medical, Sydney, Aus



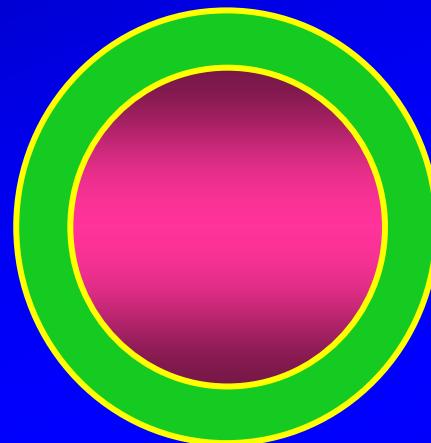
Rigidité intrinsèque (de paroi)

Compliance cross-sectionnelle: $\Delta D / \Delta P$

Distensibilité cross-sectionnelle: $\Delta D / (\Delta P \cdot D)$

Module élastique: E_{inc} : $D \cdot \text{Distensib} / \text{IMT}$

Normal



Atherosclerosis

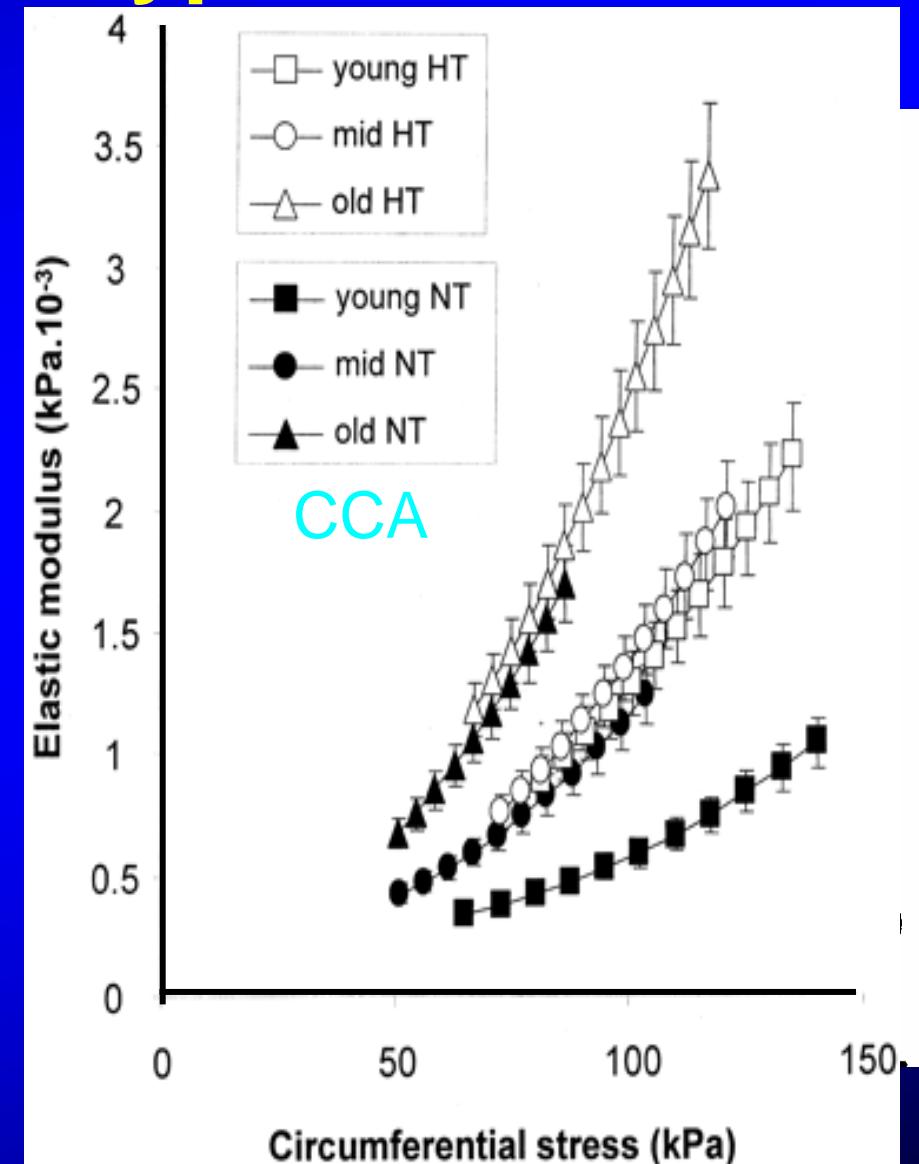
Hypertension

Functional properties of the arterial tissue in essential hypertension

- increased distensibility (at the same level of BP)
- Identical E_{inc} (at the same level of wall stress)

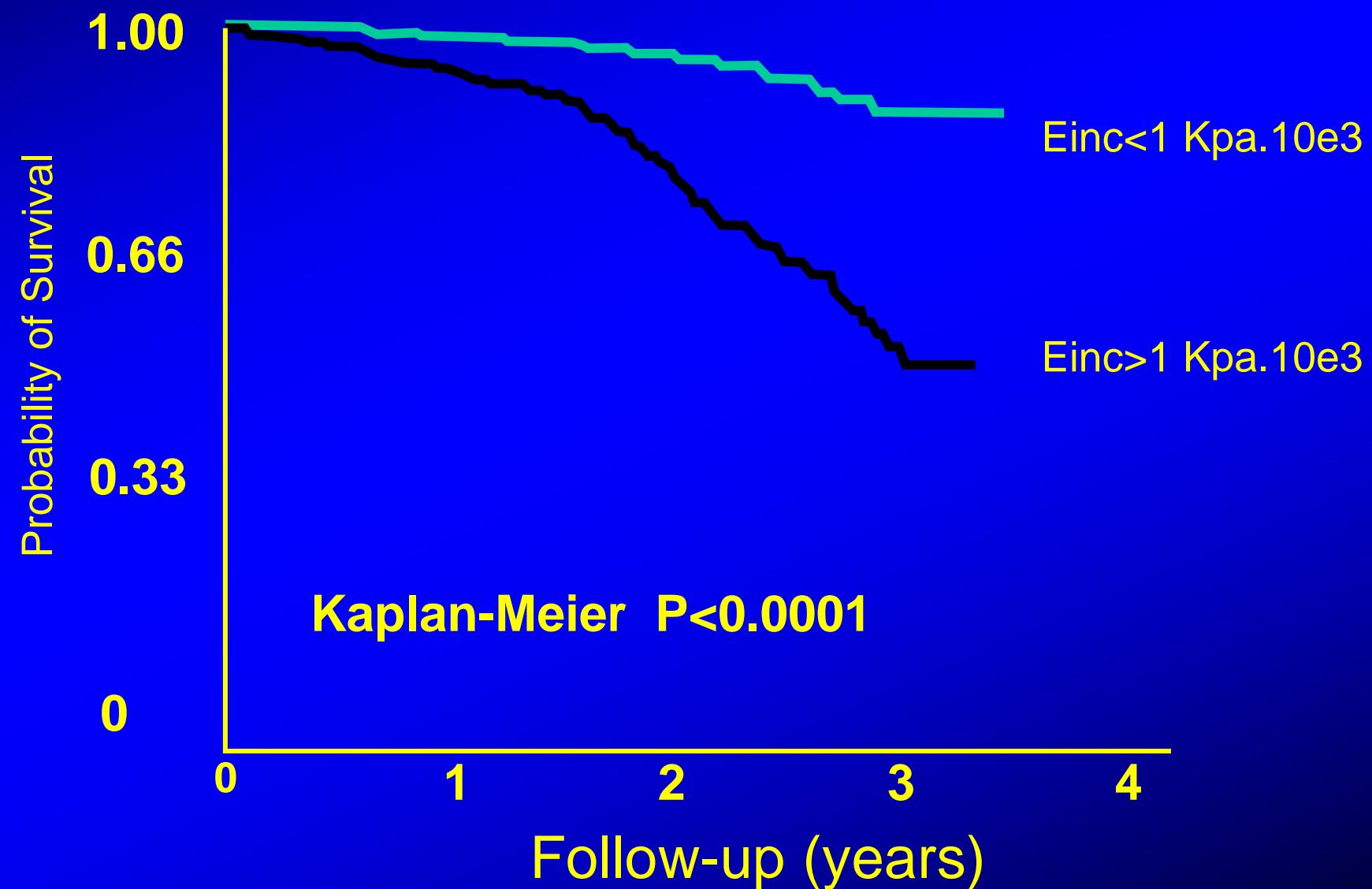


Adaptation of mechanical properties at elevated wall stress

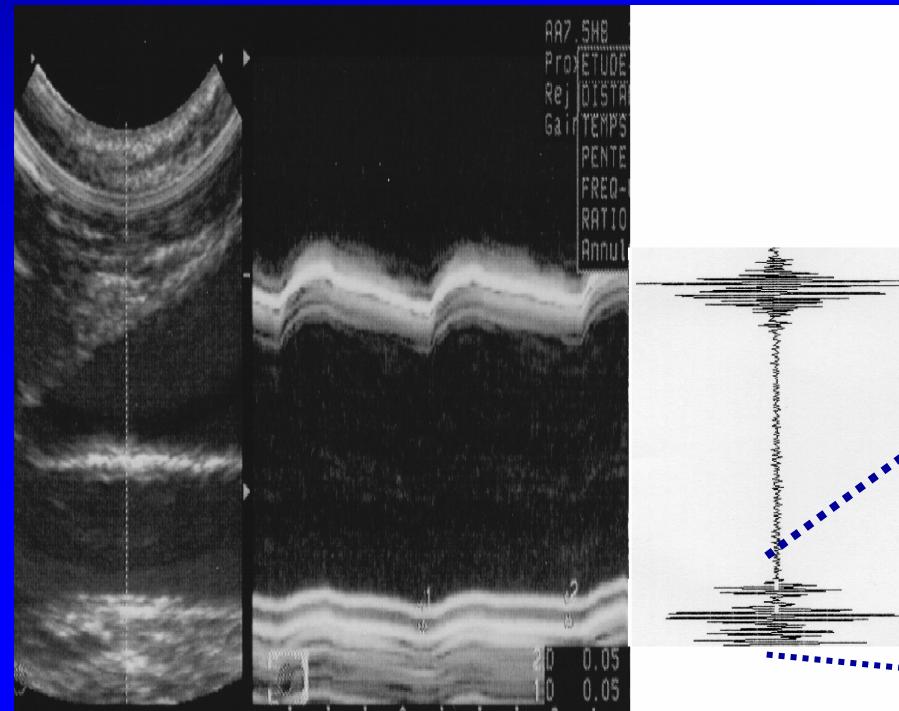


Bussy et al, hypertension 2000

Carotid artery local stiffness and all-cause mortality in patients with ESRD



Echotracking is 3 to 10 x more precise than image based techniques



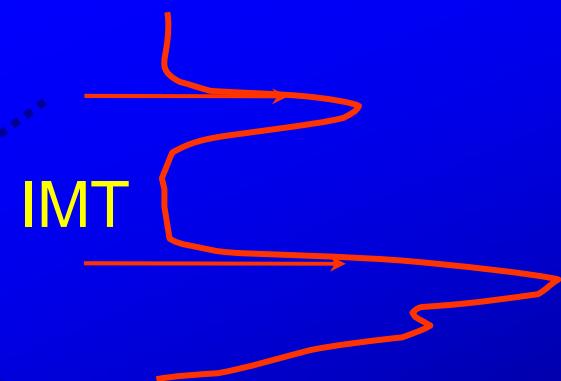
2 D

TM

Spatial
resolution

200-400 μm

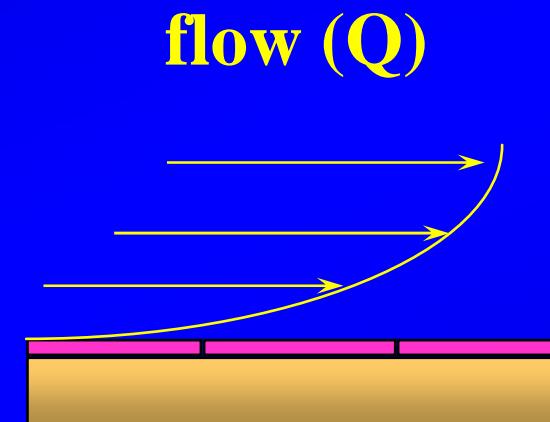
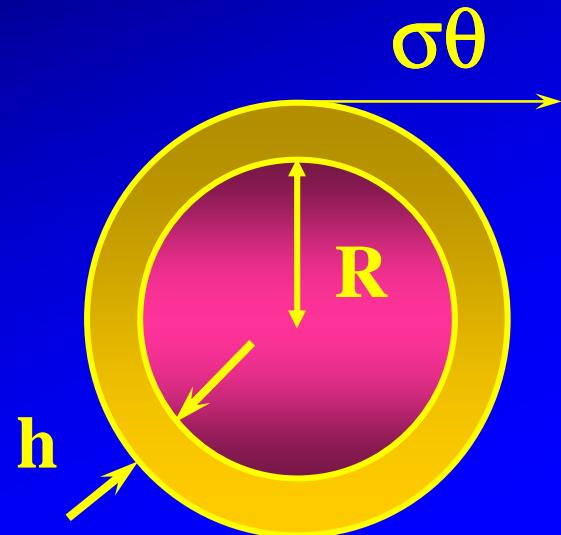
Signal averaging
10-10 000 RF lines



RF
Signal
20-40 μm

Shear stress et vasodilatation endothelium dependante

Mechanical characteristics of the vessels



circumferential wall stress:

$$\sigma\theta = \frac{P \times R}{h}$$

fluid shear stress:

$$\tau = \frac{4 \mu Q}{\pi R^3}$$

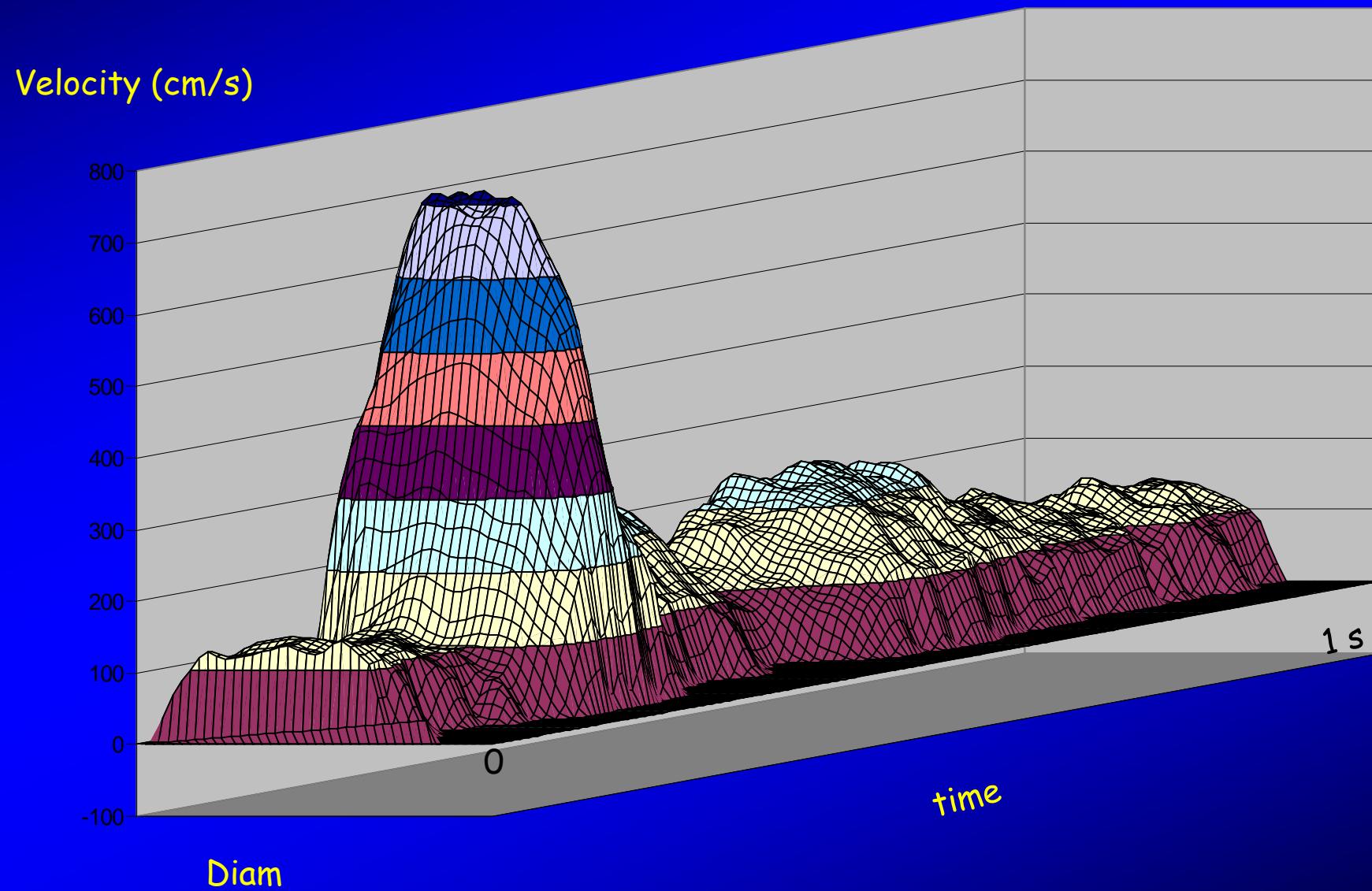
Cross sectional compliance, distensibility coefficient:
(Δ Diameter/ Δ Pressure)

From P Boutouyrie

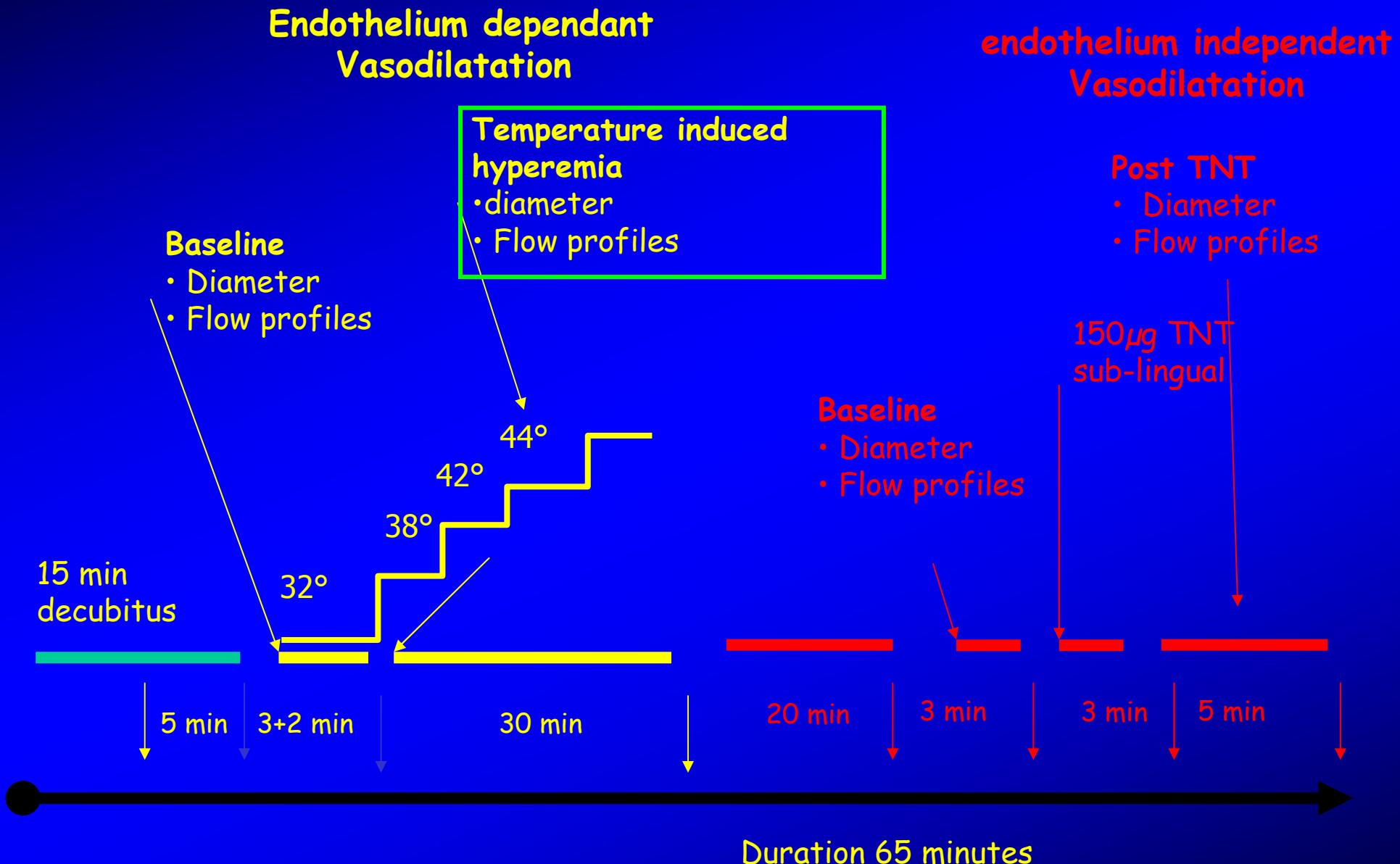
Clinical relevance of endothelial dysfunction

- Coronary heart disease; Acetyl Choline :
 - Coronary artery:
 - Al Suwaidi et al: Circulation, 2000;101:948 :associated with cardiovascular events.
 - Schächinger et al: Circulation, 2000 ; 101:899 : associated with coronary events.
 - Forearm:
 - Heitzer et al: Circulation, 2000;104:2673 : predictor of cardiovascular events..
- Chest pain; Forearm Flow mediated vasodilation:
 - Neunteufl et al: Am J Cardiol,2000; 86:207 : Prognostic value
- Essential hypertension; Acetyl Choline:
 - Perticone et al: Circulation, 2001;104:191 : predictor of cardiovascular complications.
- ESRD: Forearm Flow mediated vasodilation:
 - London GM, et al, Kidney Int, 2004. 65. 700-4: independent predictor of all-cause and CV mortality

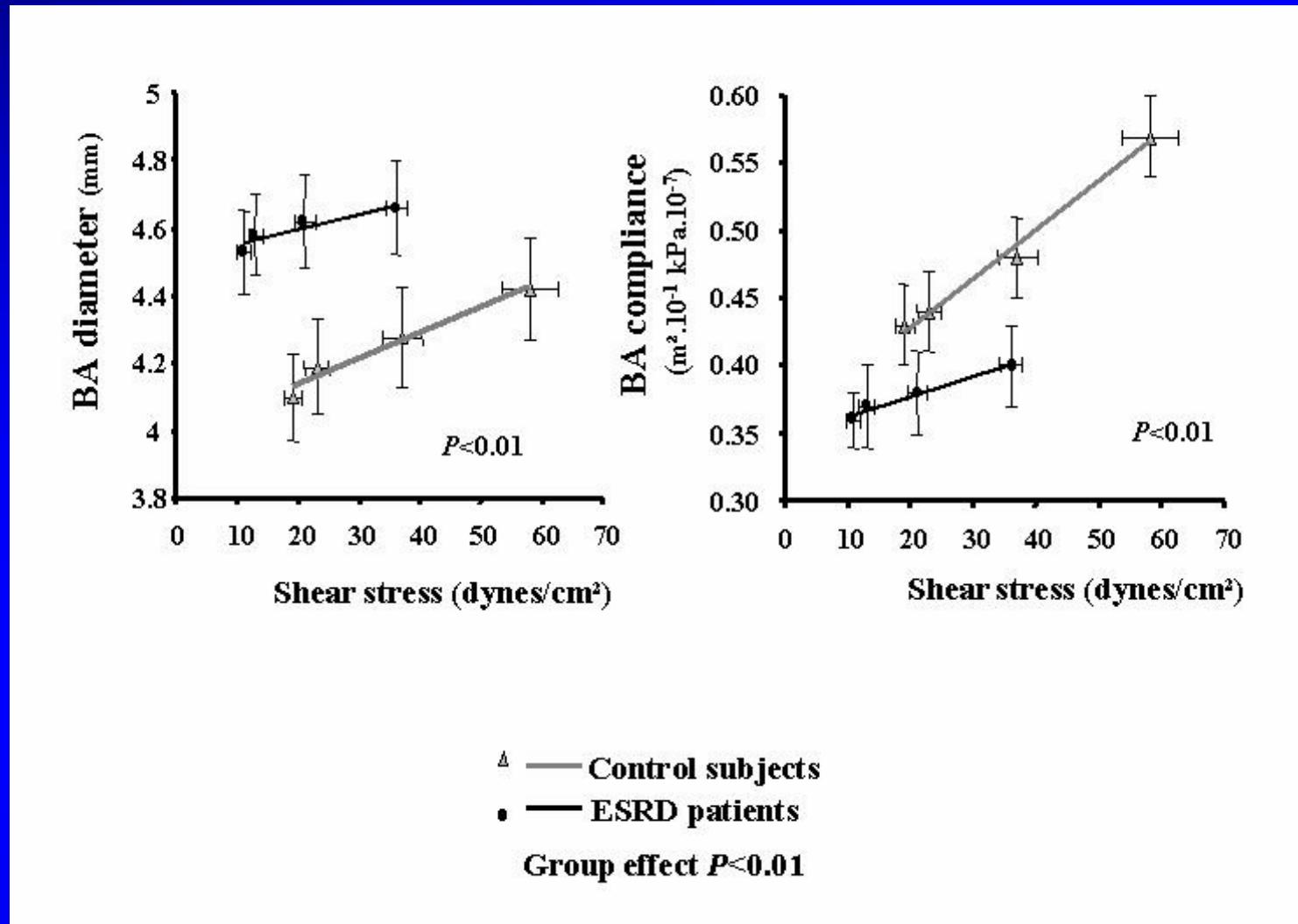
Wall track system® : measurement of flow profiles



Temperature induced hyperemia



Endothelium dependent vasodilation



Conclusions: les gros vaisseaux

- Totalement impliqués dans l'hémodynamique cardiovasculaire (physiologie et physiopathologie)
- Fonction conduit et amortissement mettant en jeu rigidité segmentaire et locale, et ondes de reflexion
- Un impact pour la thérapeutique encore sous estimé