Pathophysiology of Vascular Function in CKD

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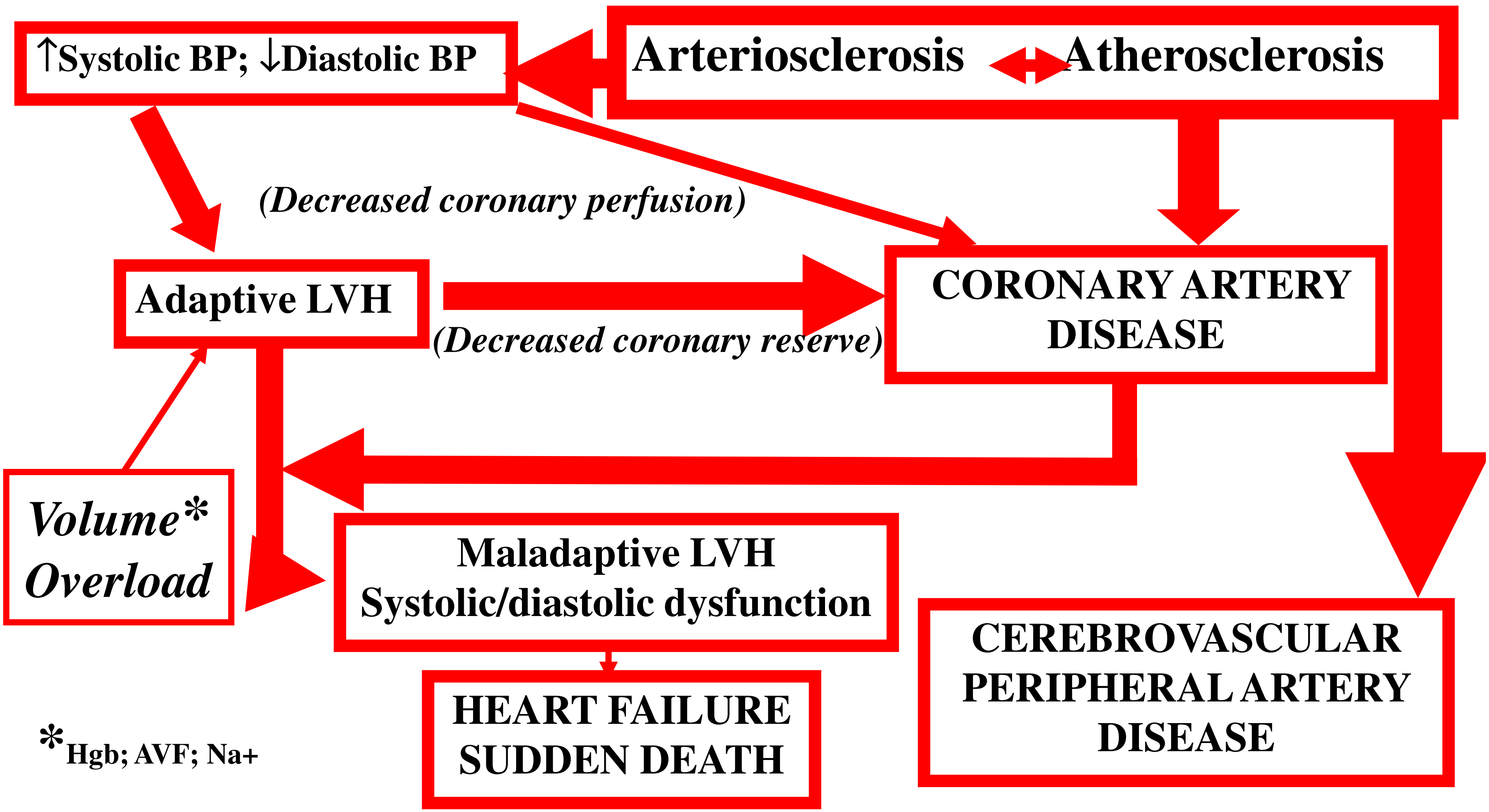
Paris

Arterial Pathophysiology and Cardiovascular Diseases in CKD

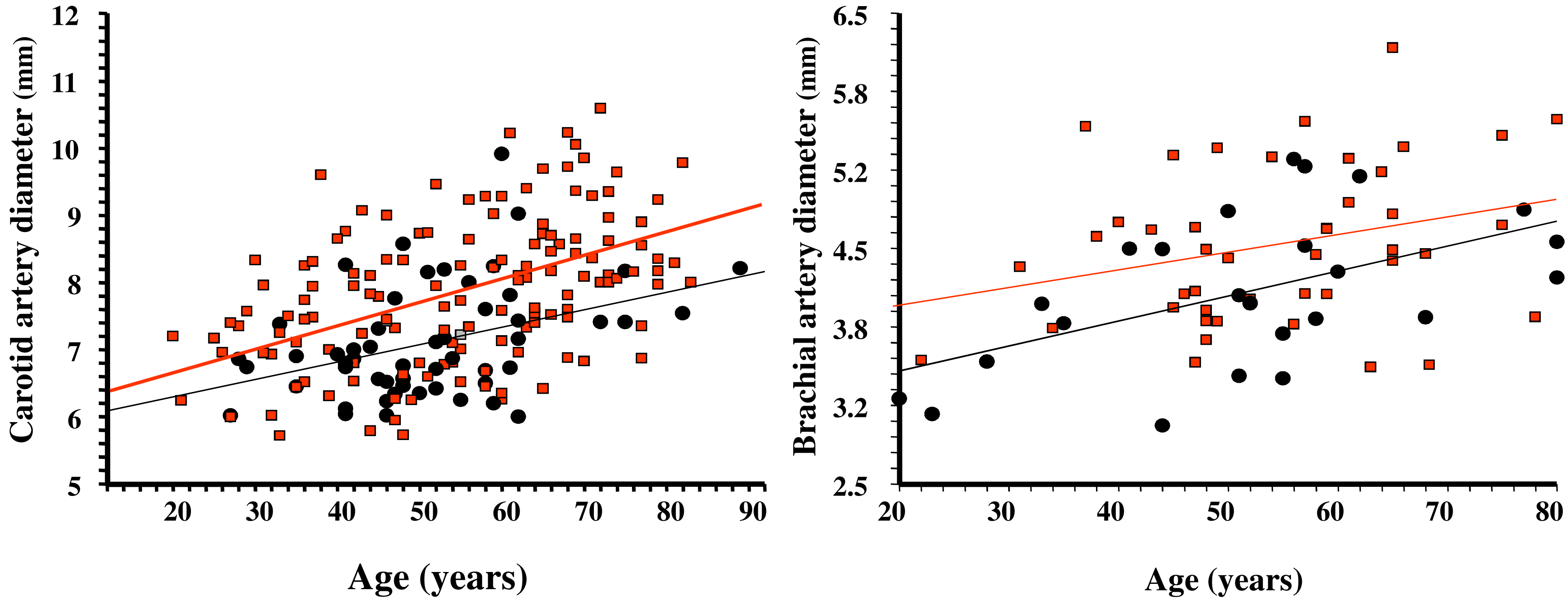


Prevalence of discrete plaques on common carotid artery in control subjects and ESRD patients

	Controls	ESRD	
Age (years)	48.5 ± 16	51 ± 16	NS
Plaques (%)	17.8%	56.3%	< 0.01
Type of plaques			
• Calcified	23.1%	91.5%	<0.01
• Soft/mixed	77%	9%	<0.01

London et al Sem Dial 1999

Age related changes in arterial internal diameters



Controls (r = 0.400; P < 0.01)

ESRD (r = 0.438; P < 0.0001)

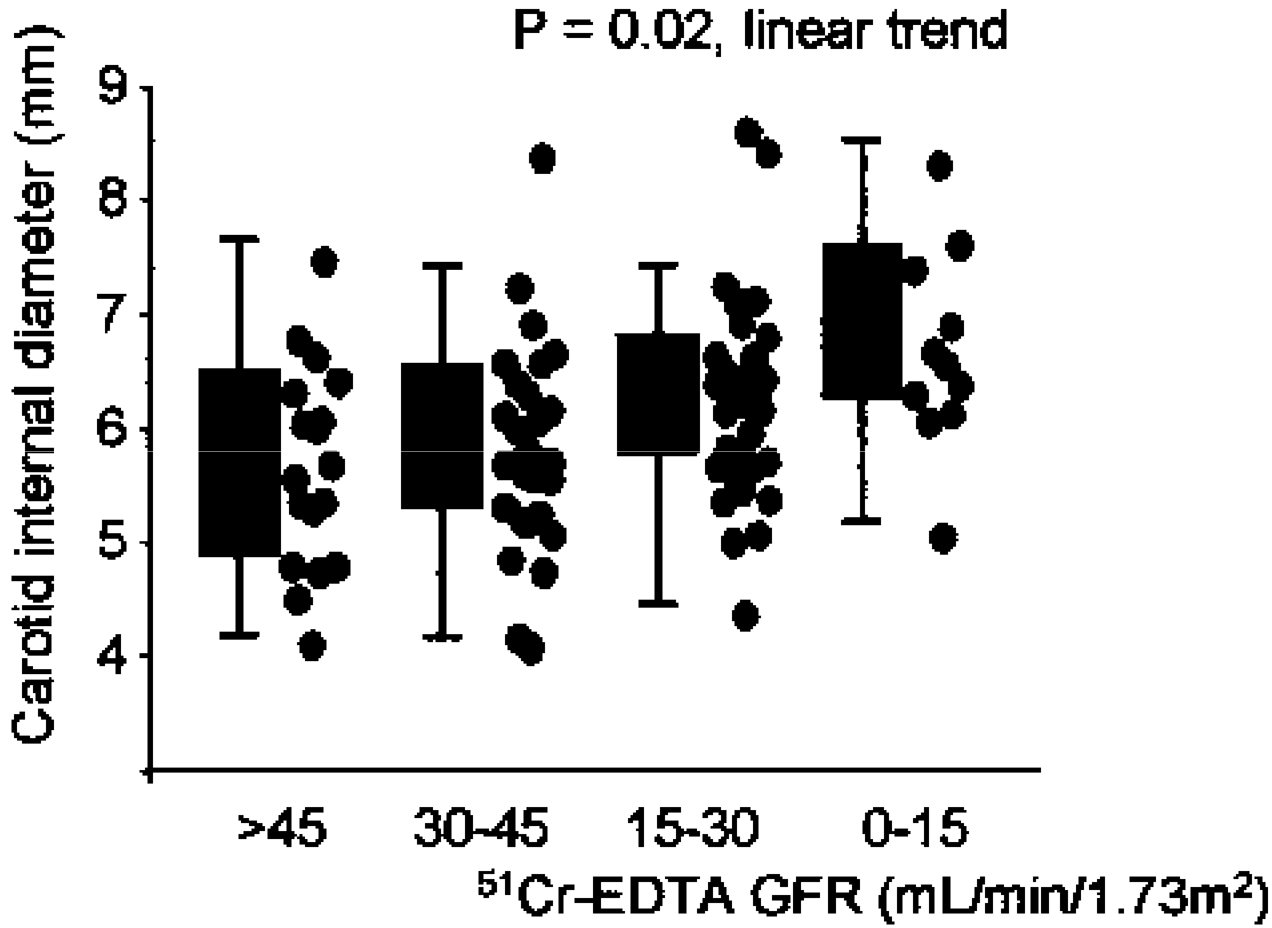
Controls (r = 0.525;P < 0.01)

ESRD (r = 0.277;P = 0.065)

Controls

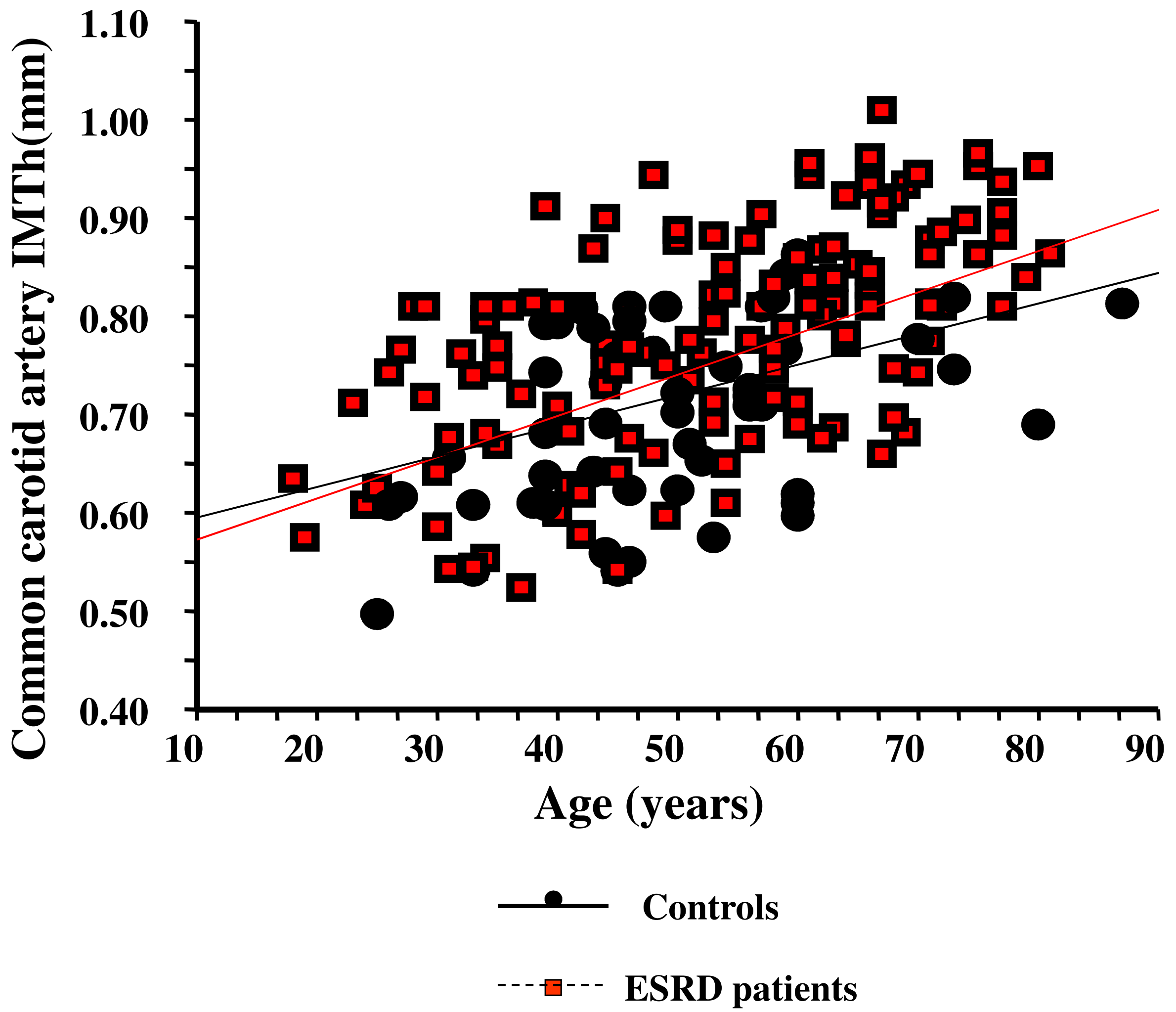
ESRD patients

Evolution of Carotid diameter with progression of CKD stages

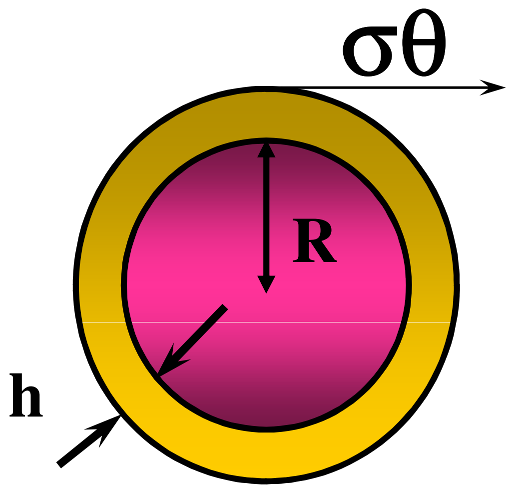


Briet M. et al Kidney Int 2006

Age related changes in Carotid IMTh

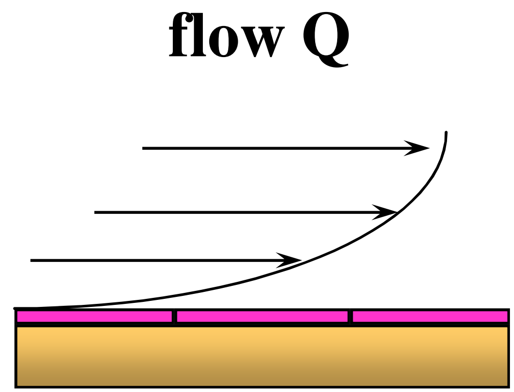


Mechanical stresses in the blood vessel



circumferential wall stress

$$sq = \frac{P\ x\ R}{h}$$



fluid shear stress

$$t = \frac{4\ \mu\ Q}{p\ R\ 3}$$

Brachial artery characteristics

	Controls	ESRD	
Baseline BA diameter (mm)	4.12 ± 0.13	4.56 ± 0.11	< 0.01
BA compliance ($m^2.kPa^{-1}.10^{-7}$)	0.45 ± 0.02	0.37 ± 0.02	< 0.01
BA distensibility ($kPa^{-1}.10^{-3}$)	3.5 ± 0.22	2.6 ± 0.19	< 0.001
BA incremental elastic modulus ($kPa.10^3$)	3.0 ± 0.22	5.0 ± 0.42	< 0.001
Baseline mean flow velocity (cm/s)	4.6 ± 0.40	3.4 ± 0.30	< 0.01
Baseline mean flow (ml/min)	39 ± 4.6	33 ± 3.6	NS
Baseline mean SR (s^{-1})	53 ± 2.9	39 ± 3.5	< 0.01
Baseline peak SR (s^{-1})	365 ± 23	324 ± 26	< 0.05
Whole blood viscosity (cPoise)	3.57 ± 0.07	2.79 ±0.06	<0.001
Baseline mean SS ($dynes/cm^2$)	19 ± 1.15	10.7 ± 1.0	<0.001
Baseline peak SS ($dynes/cm^2$)	129 ± 9	83 ± 5	<0.001

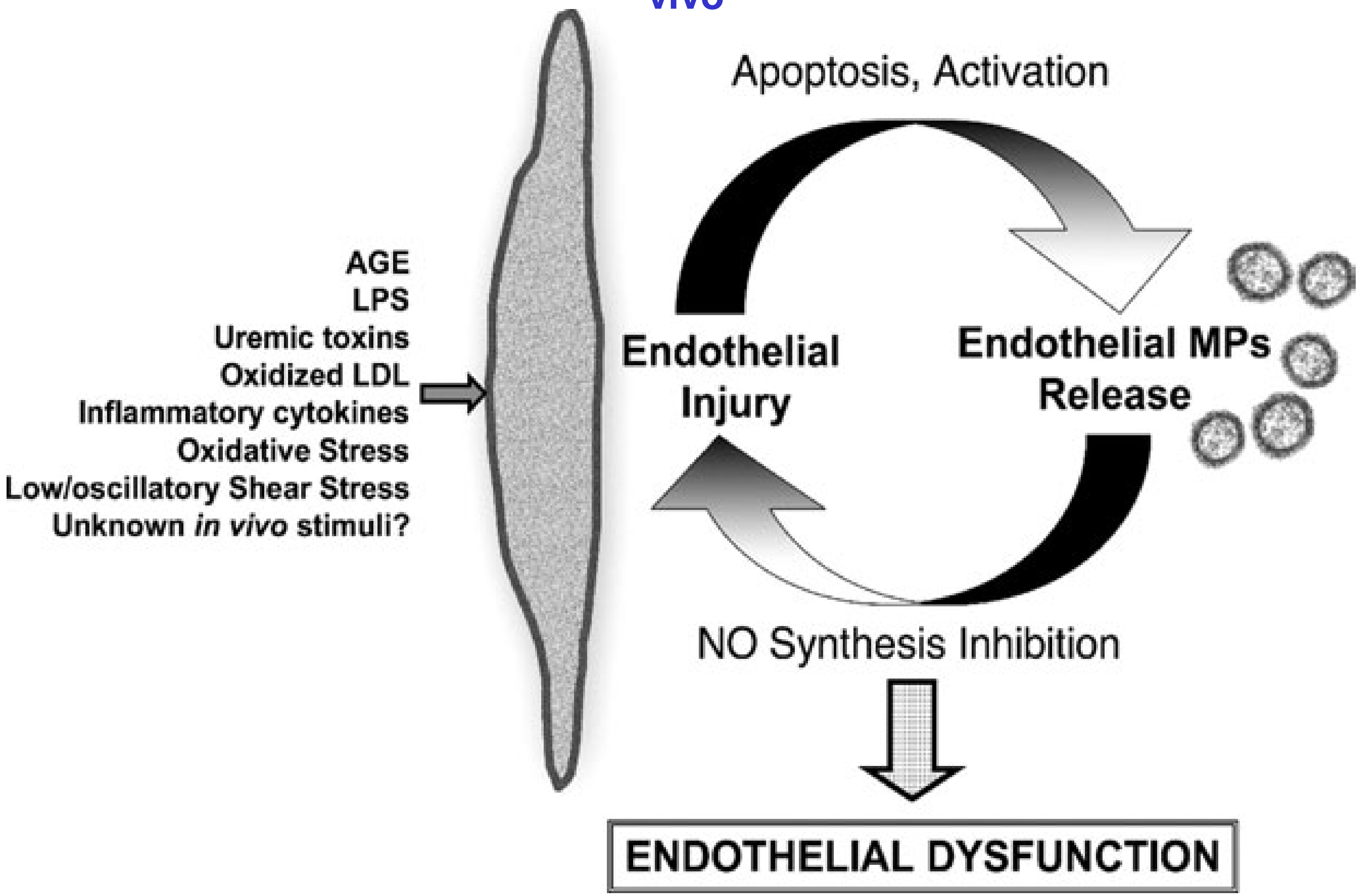
flow Q

3

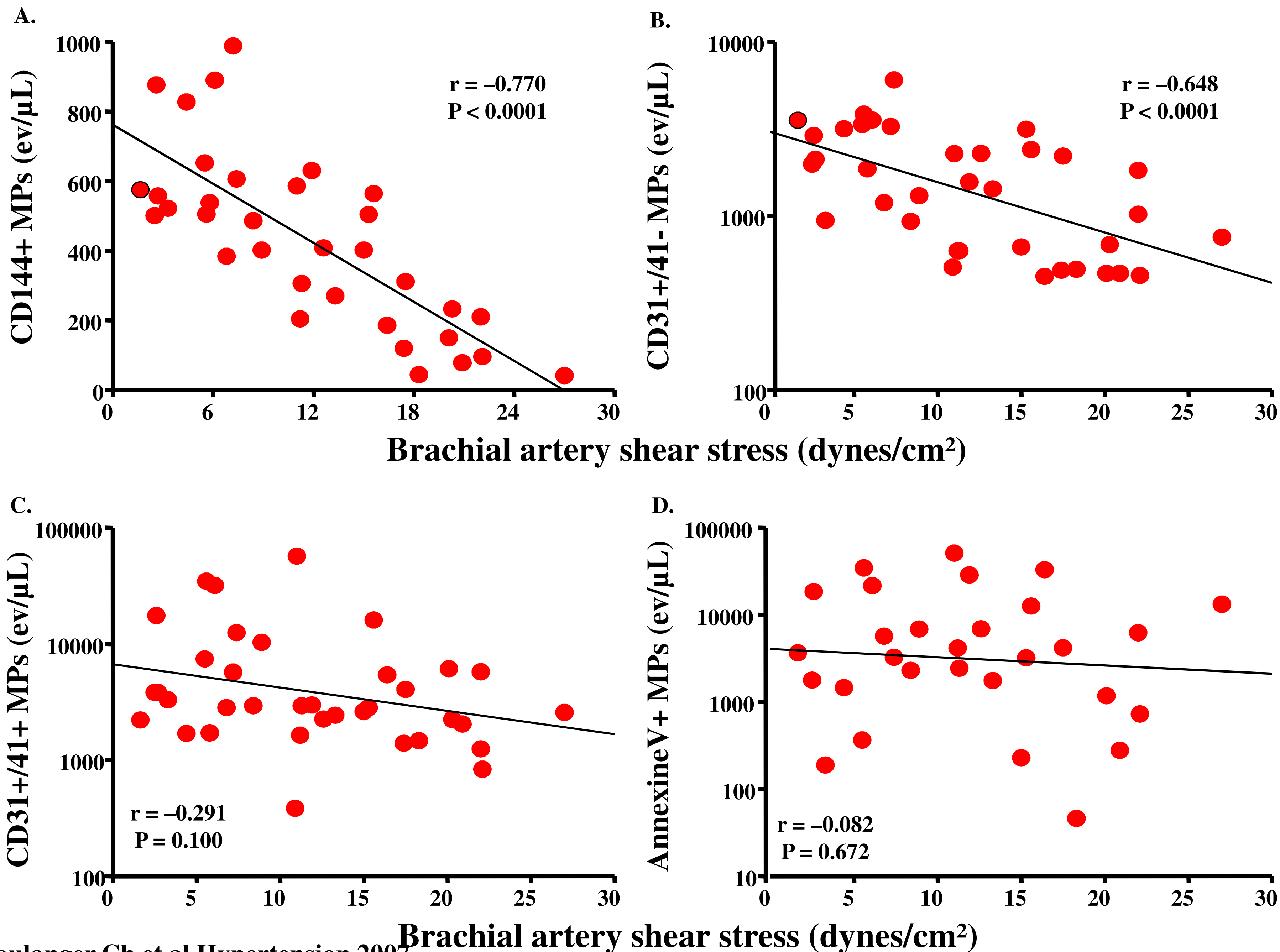
$t = \frac{4\,\mu\,Q}{p\,R}$

Verbeke et al JASN 2007

Paracrine effect(s) of endothelial MPs predisposing to endothelial dysfunction in vivo



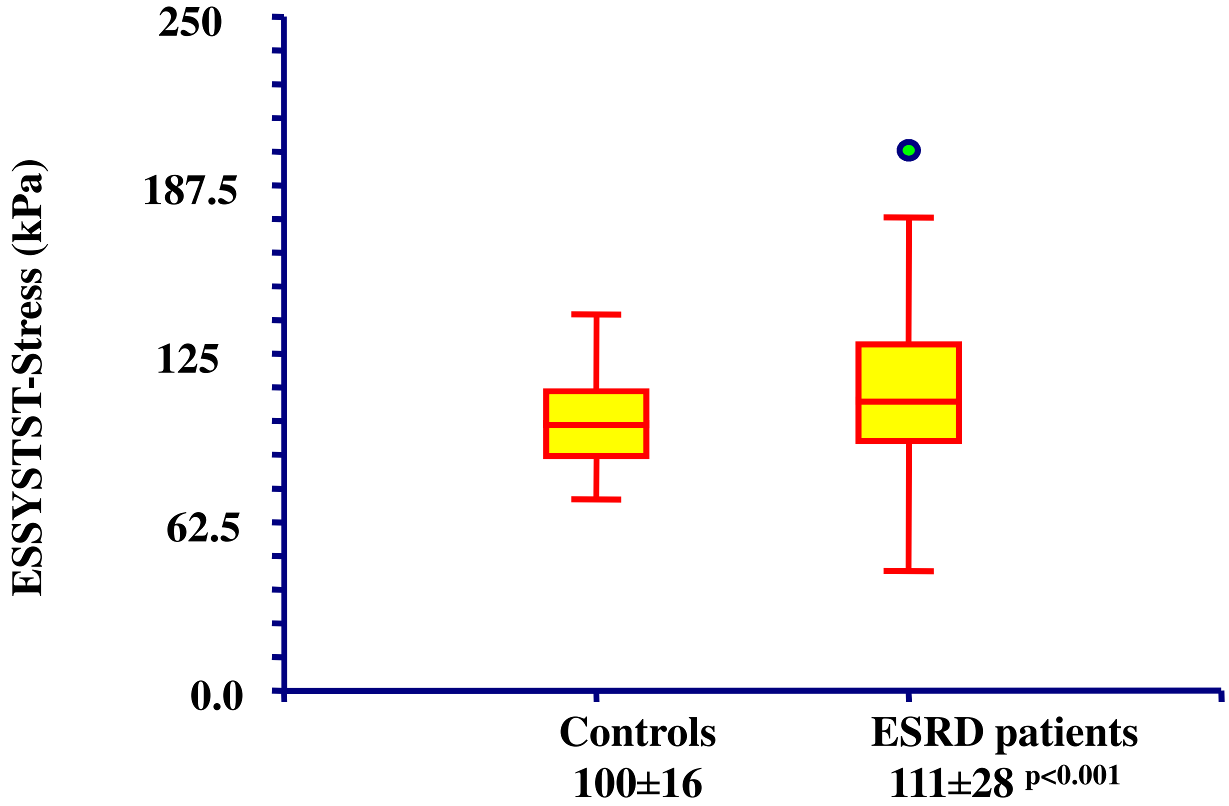
Boulanger, C. M. et al. Hypertension 2006;48:180-186



Boulanger Ch et al Hypertension 2007

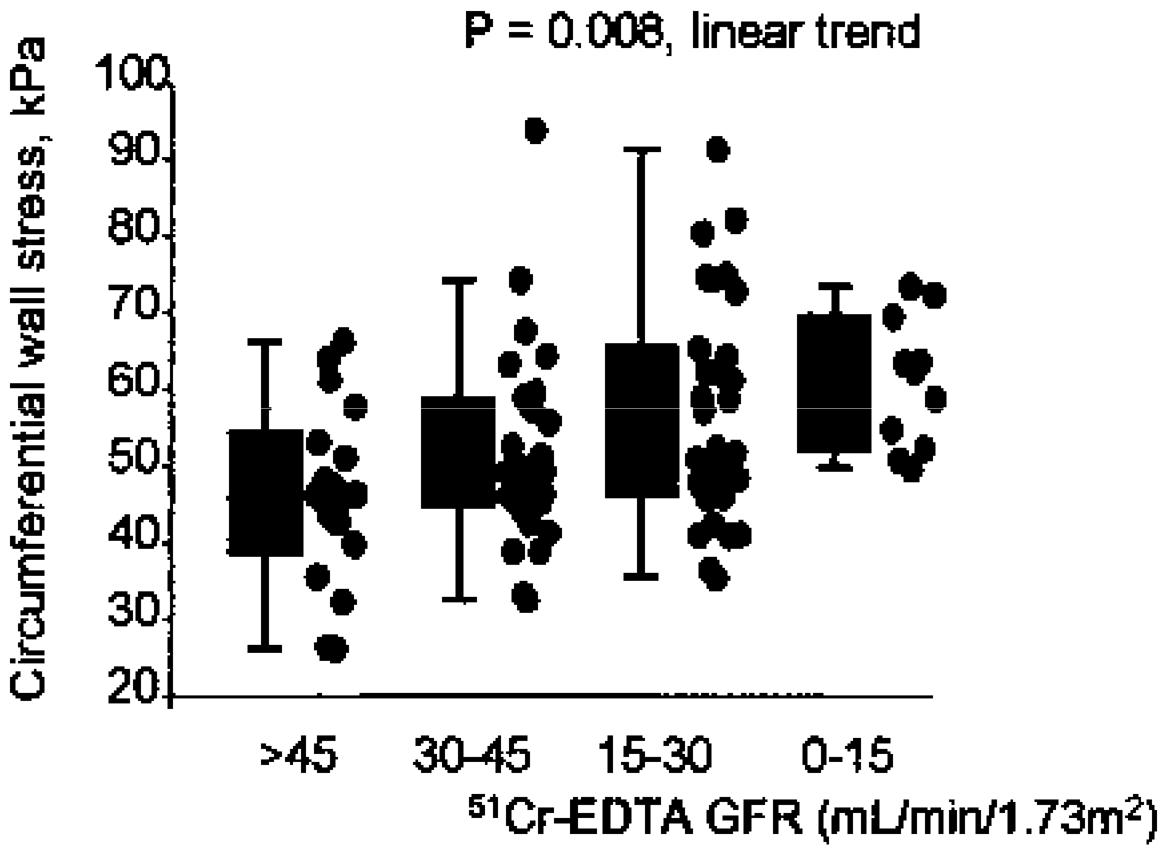
circumferential wall stress

$$sq = \frac{P \times R}{h}$$

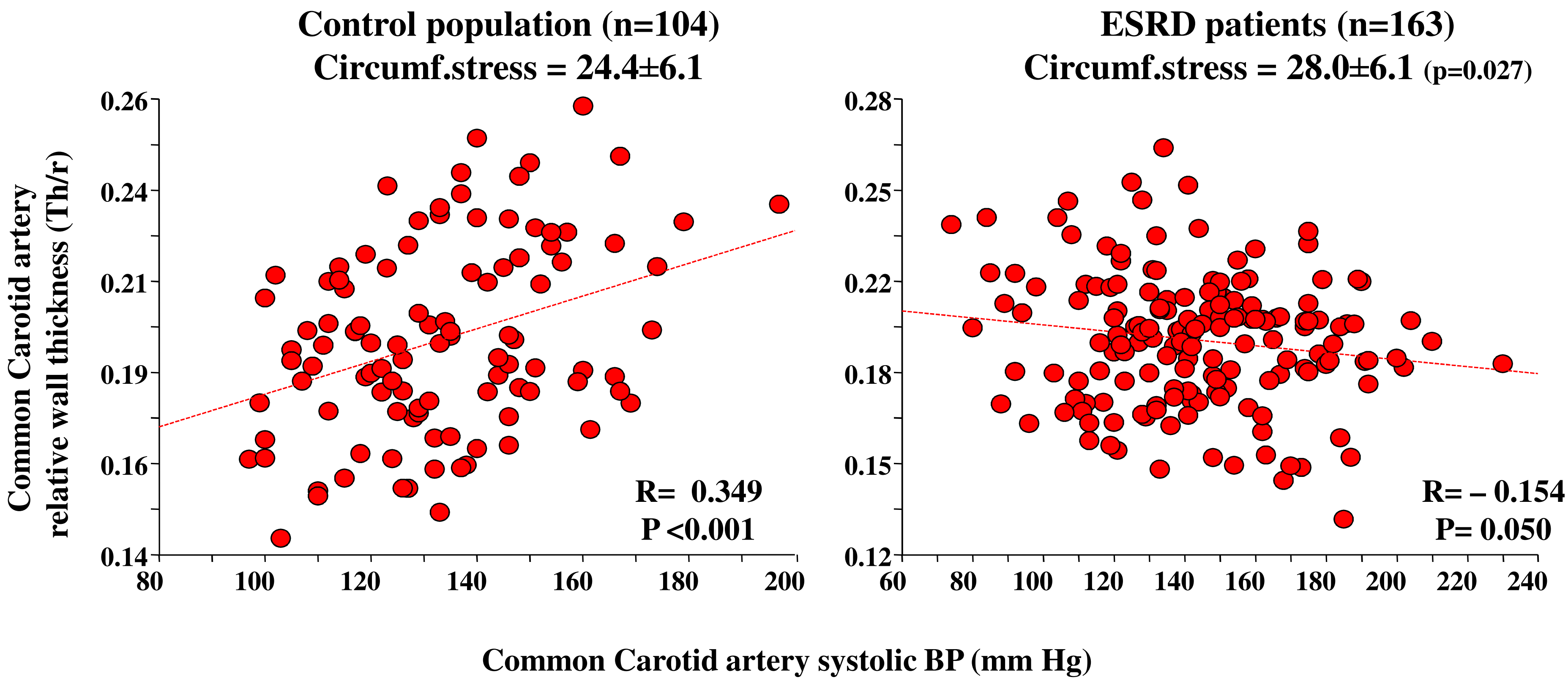


London GM (submitted)

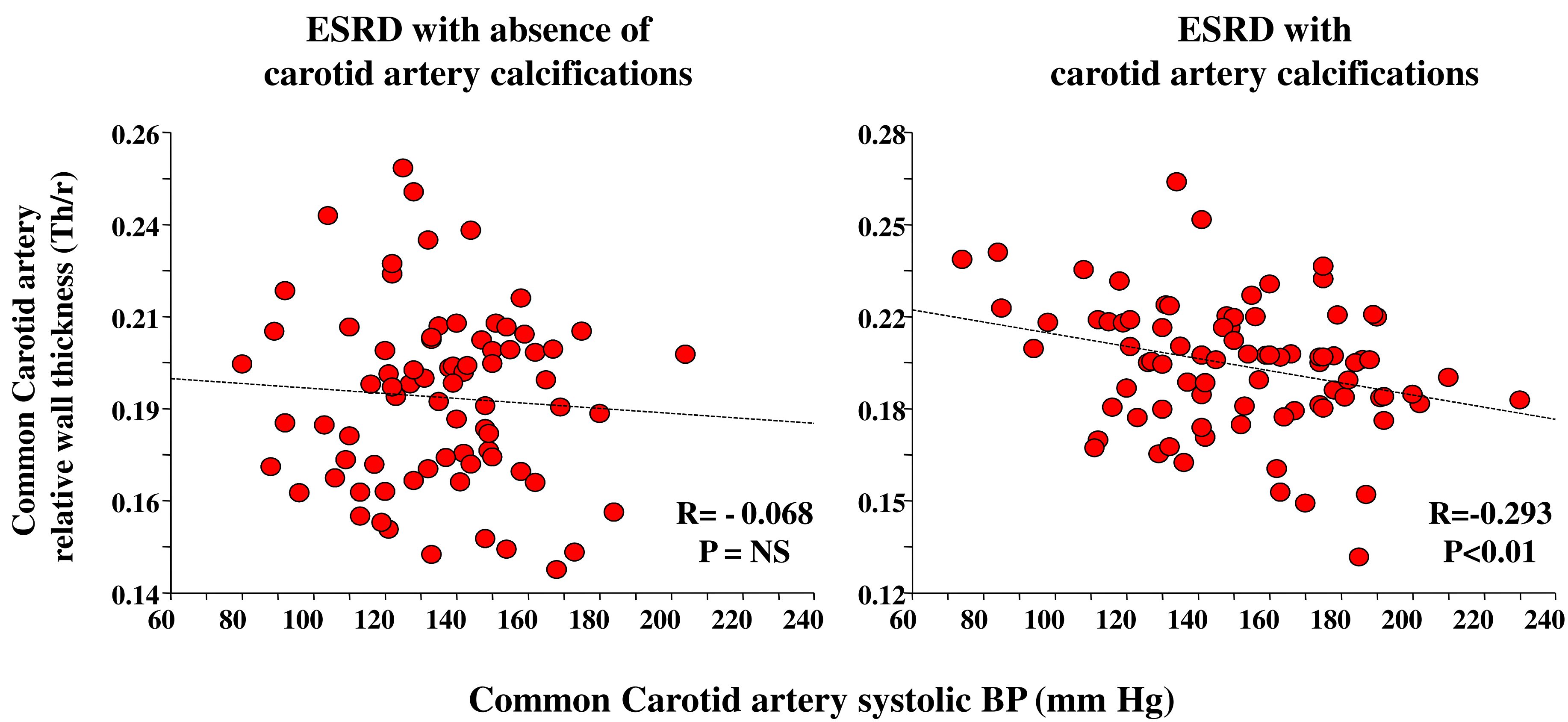
Evolution of Carotid Circumferential wall stress with progression of CKD stages



Briet M. et al Kidney Int 2006

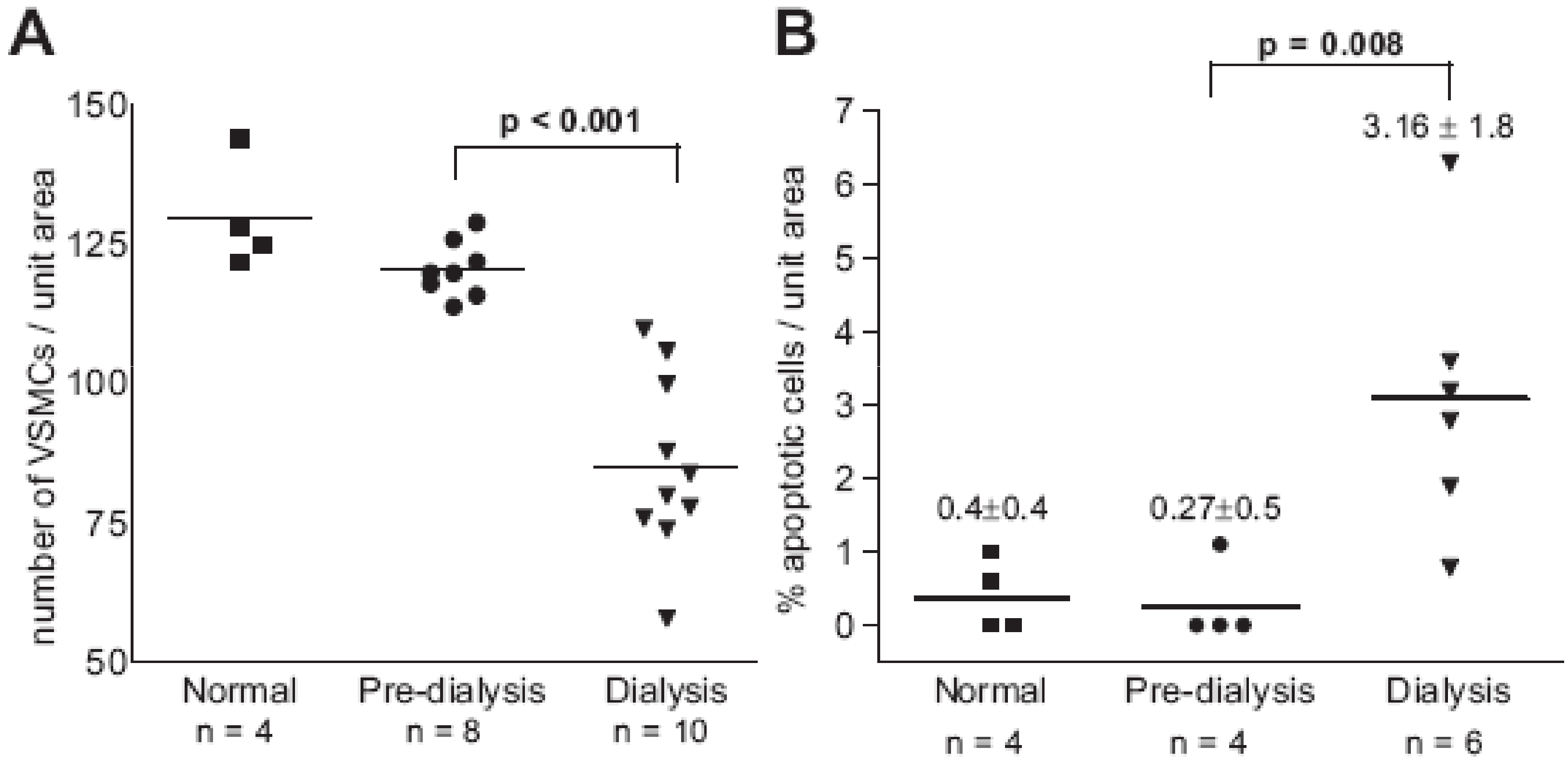


London GM et al (submitted)

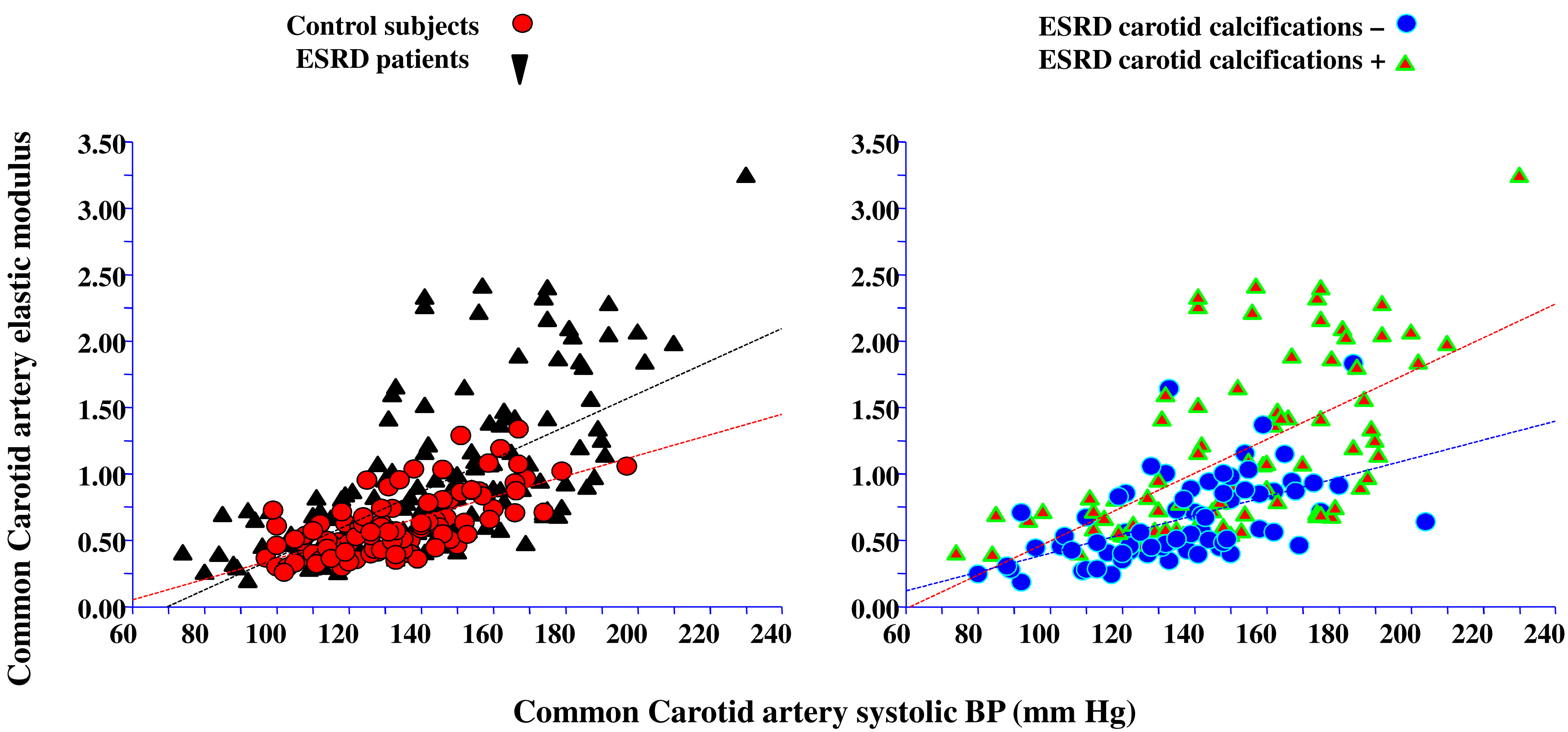


London GM et al (submitted)

Dialysis Accelerates Medial Vascular Calcification in Part by Triggering Smooth Muscle Cell Apoptosis



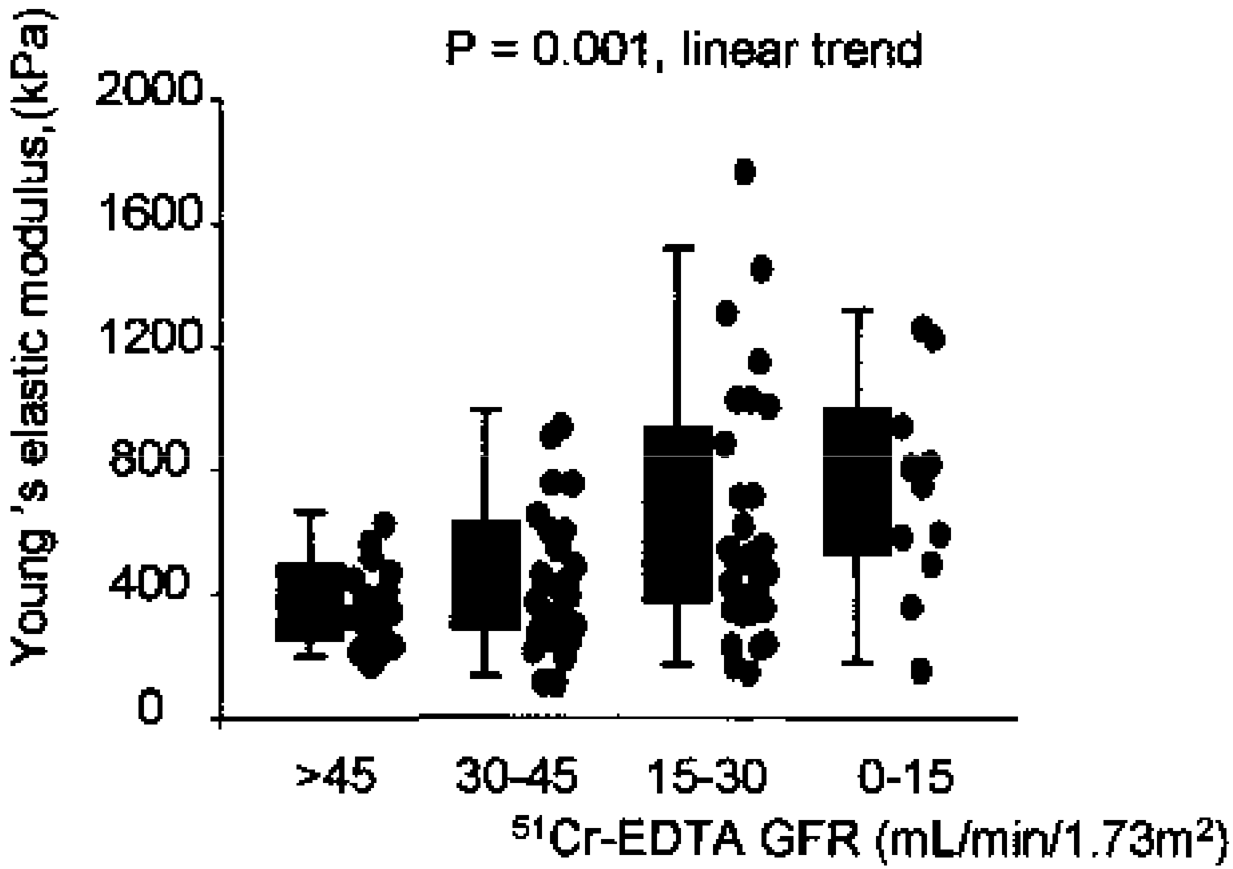
Shroff et al Circulation 2008;118:1748-57



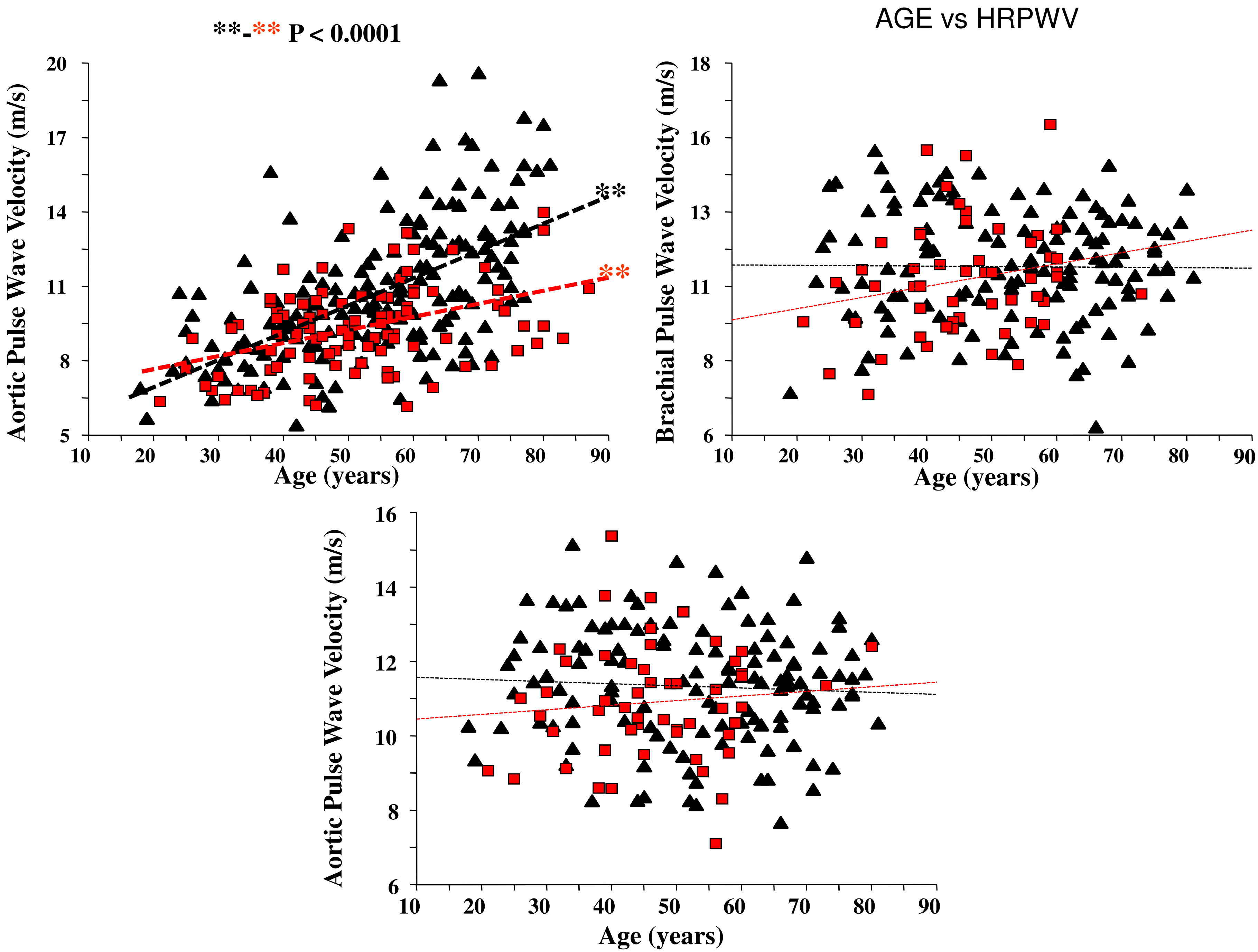
All categories P<0.00001

London GM et al (submitted)

Evolution of Carotid elastic modulus with progression of CKD stages

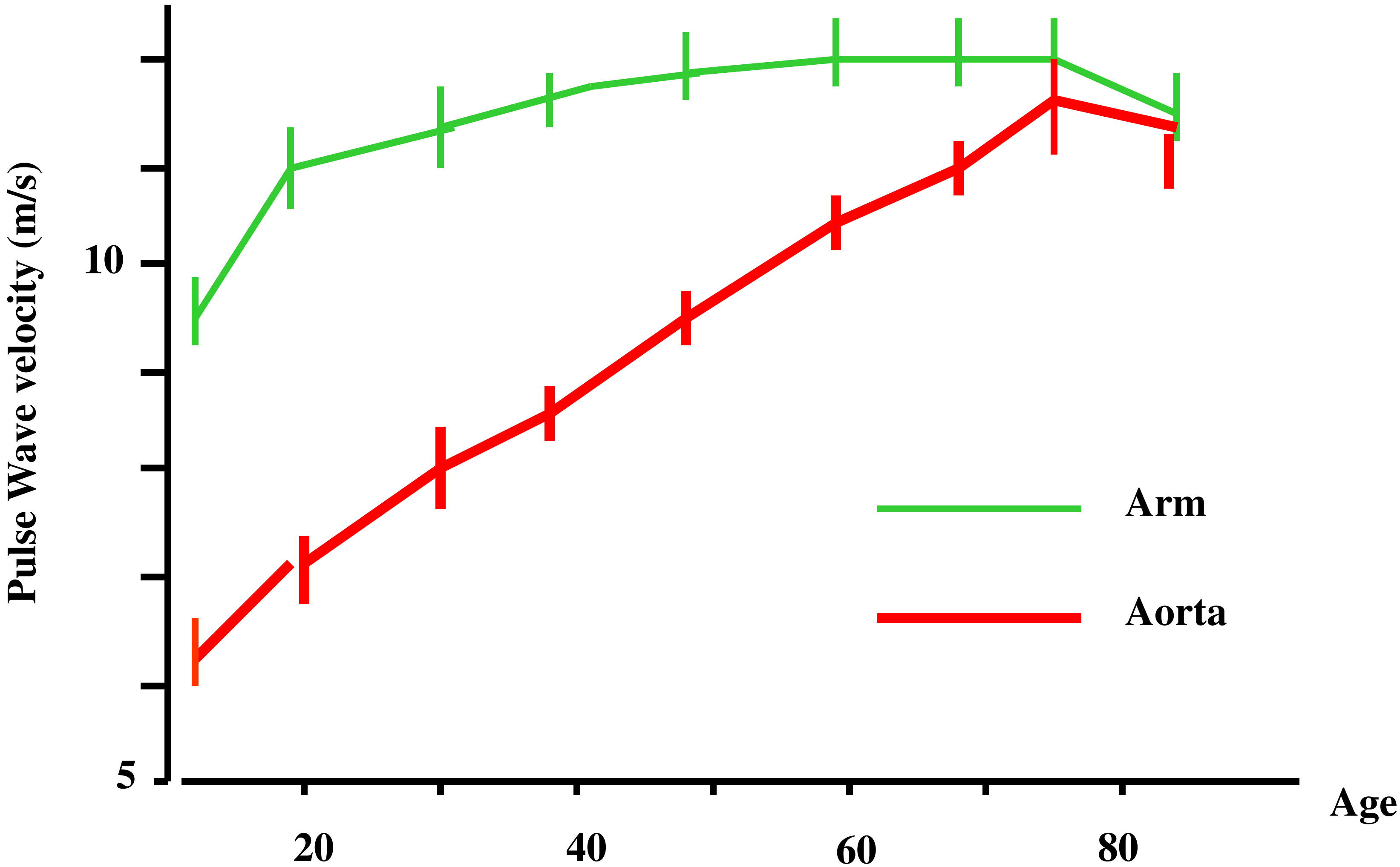


Briet M. et al Kidney Int 2006



- P < 0.0001
AGE vs HRPWV
Aortic Pulse Wave Velocity (m/s)
Brachial Pulse Wave Velocity (m/s)
Age (years)
Aortic Pulse Wave Velocity (m/s)
Age (years)
Age (years)

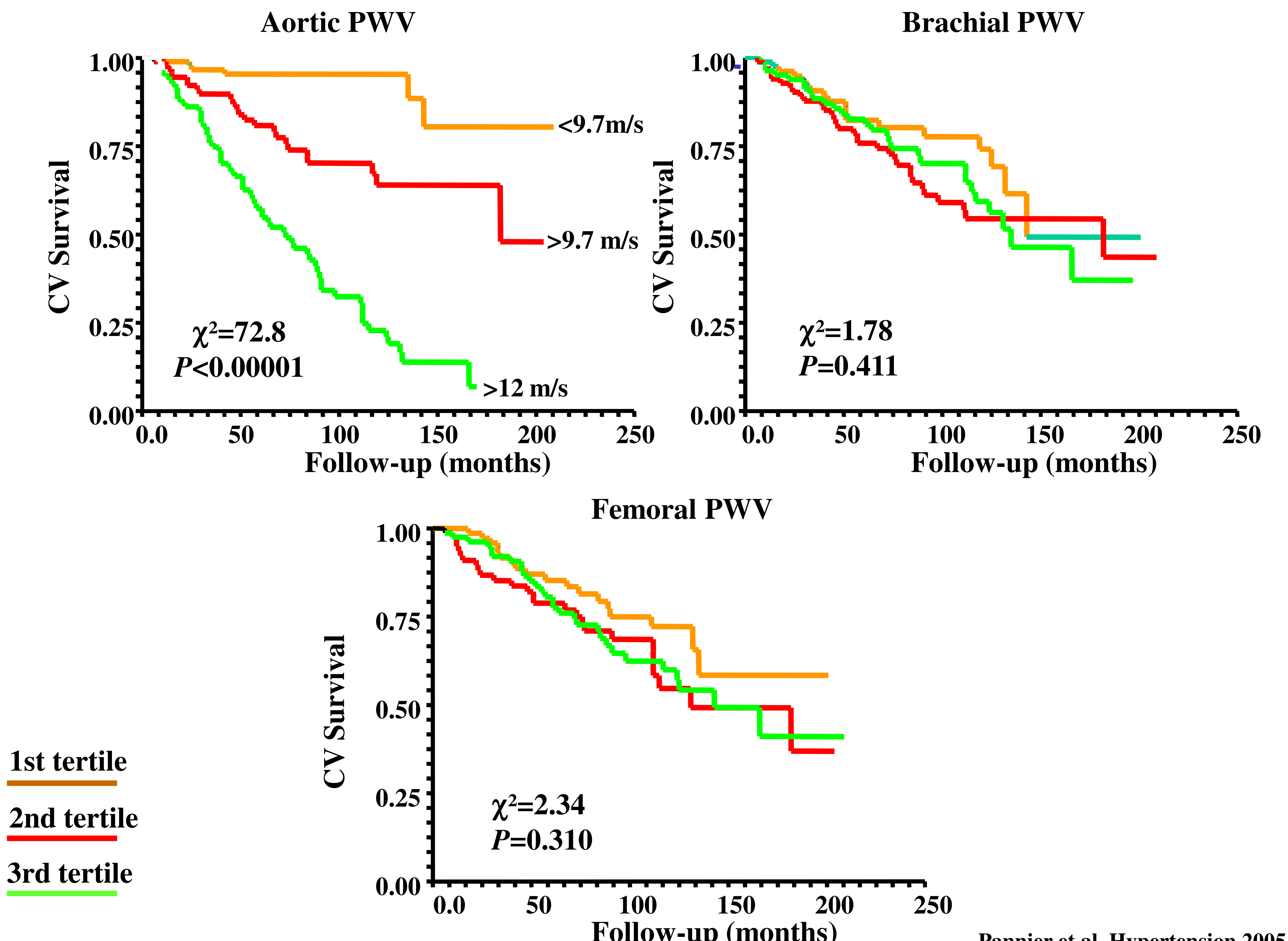
Aortic and arm pulse wave velocities as as function of age



Avolio et al Circulation 1983

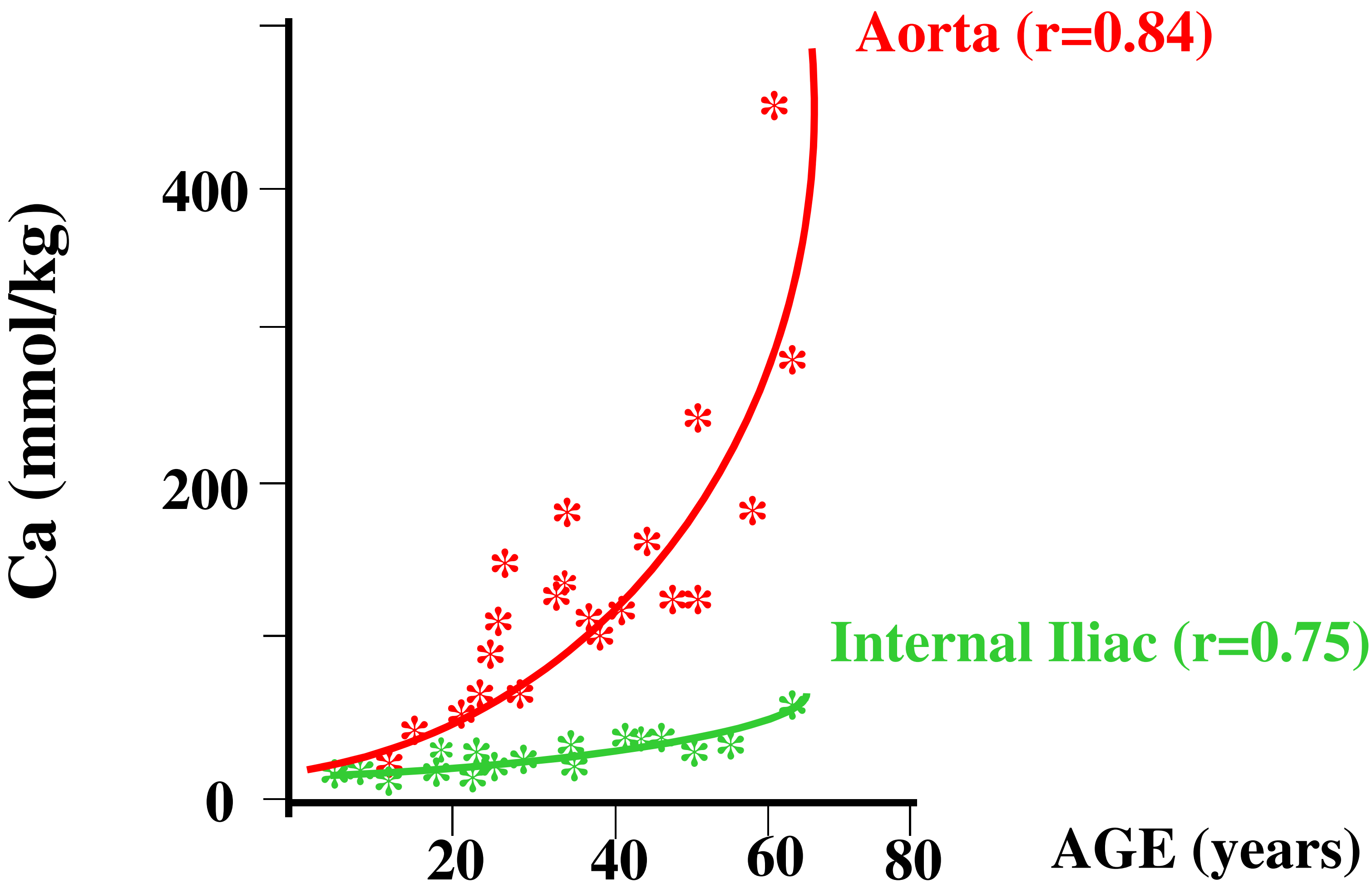
Characteristics of arterial system in controls and ESRD patients

	Controls	ESRD
•Peripheral/femoral PWV (m/s)	11.0 ±1.75	11.20 ±1.80
Age (years)	48.5 ± 16	51 ± 16
•Aortic PWV (m/s)	9.70 ±1.80	10.60 ±2.5**



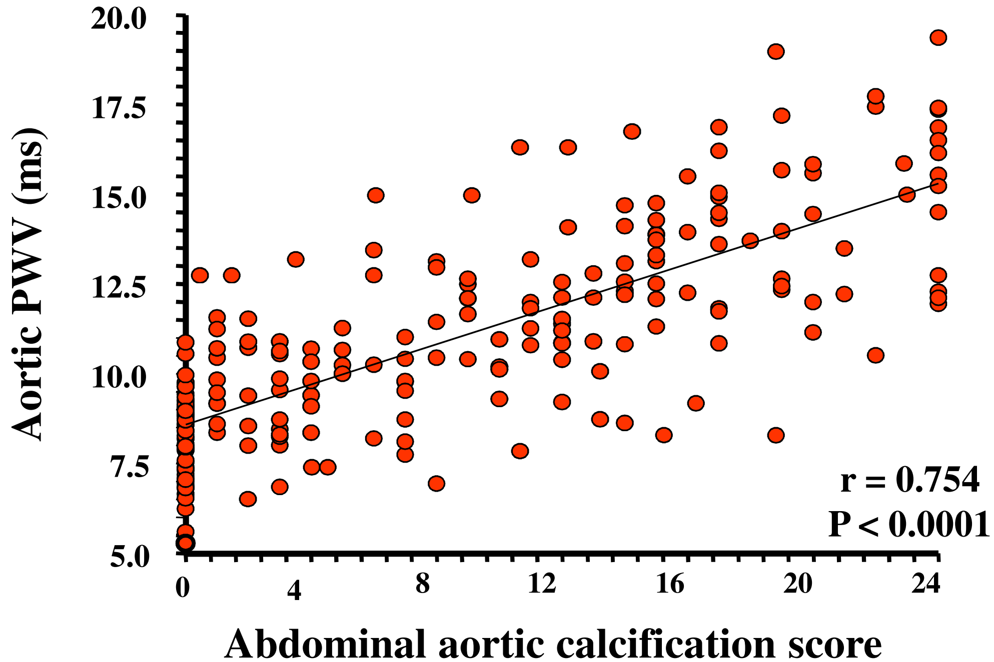
Pannier et al Hypertension 2005

Correlation between age and arterial calcium (Ca) concentration in the aorta and internal iliac artery in nonuremic control subjects

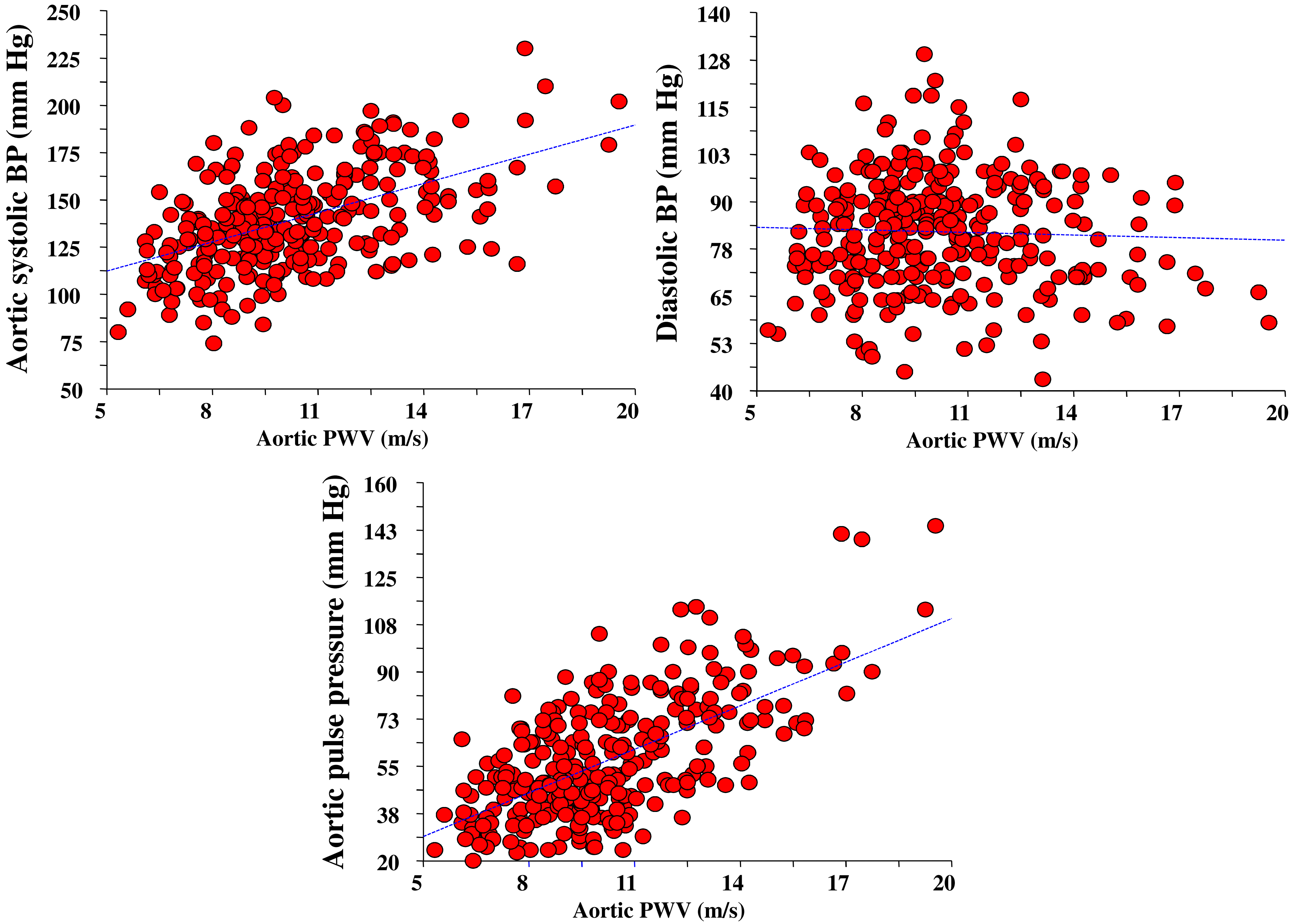


Ibels et al. Am J Med 1979

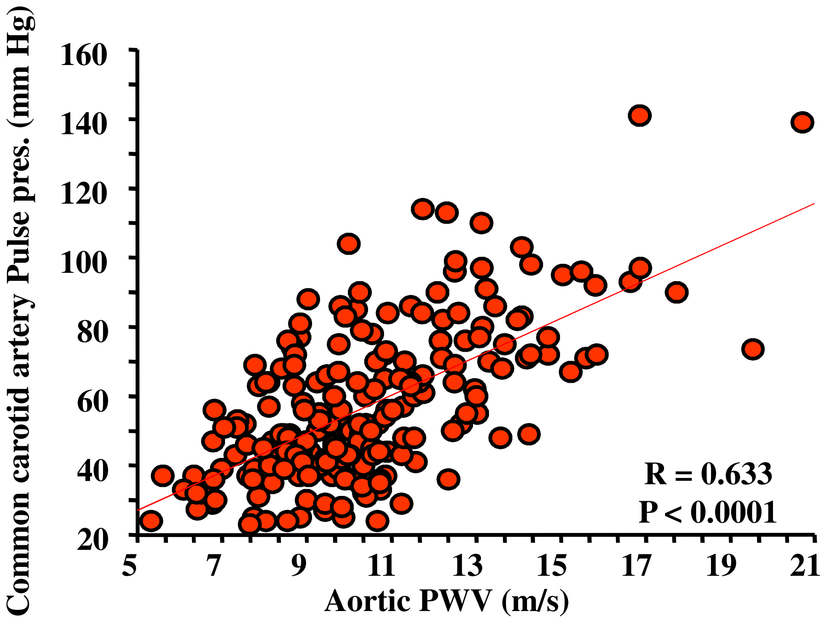
Correlation between aortic calcification score and aortic PWV in ESRD patients

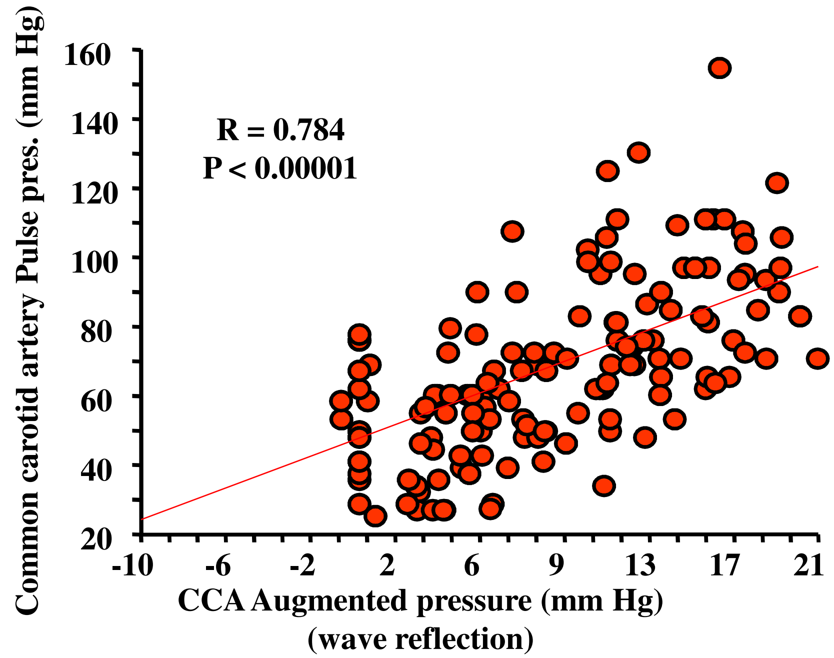


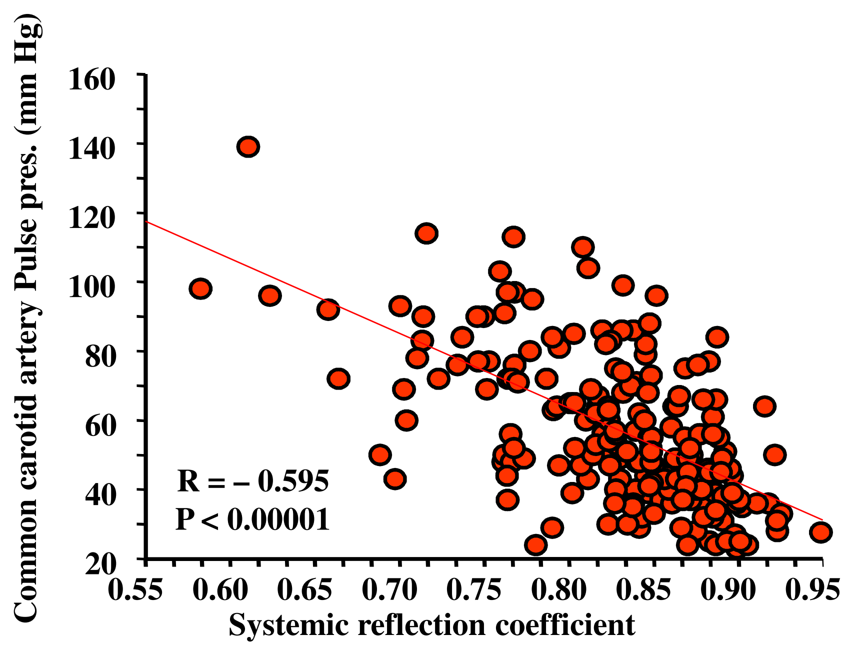
Pannier et al. Artery 2007



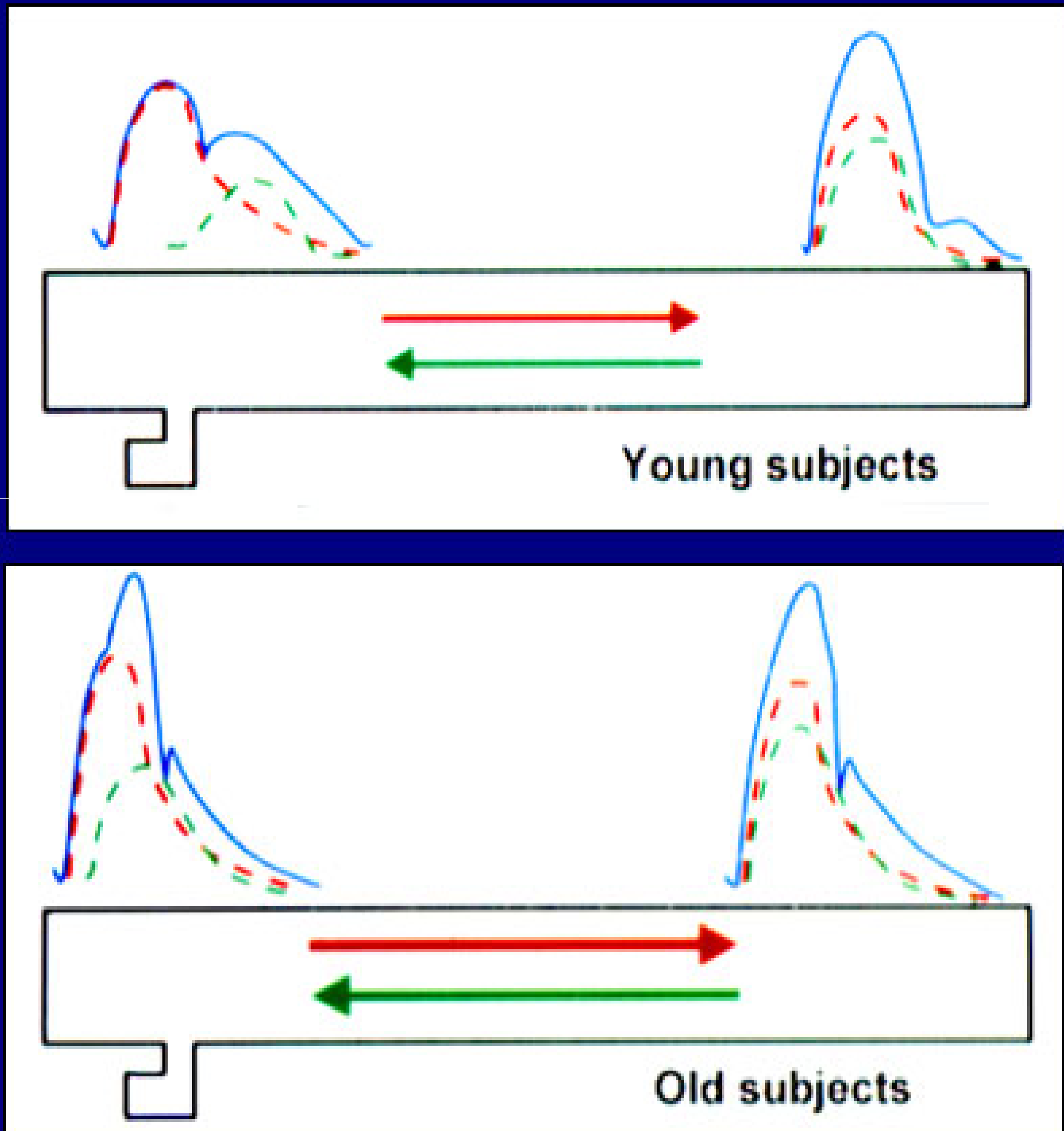
Aortic systolic BP (mm Hg)
250
225
200
175
150
125
100
75
50
5
8
11
14
17
20
Aortic PWV (m/s)
Diastolic BP (mm Hg)
140
128
115
103
90
78
65
53
40
5
8
11
14
17
20
Aortic PWV (m/s)
Aortic pulse pressure (mm Hg)
160
143
125
108
90
73
55
38
20
5
8
11
14
17
20
Aortic PWV (m/s)


Common carotid artery Pulse pres. (mm Hg)
160
140
120
100
80
60
40
20
5
7
9
11
13
15
17
19
21
Aortic PWV (m/s)
R = 0.633
P < 0.0001


Common carotid artery Pulse pres. (mm Hg)
160
140
120
100
80
60
40
20
-10
-6
-2
2
6
9
13
17
21
CCA Augmented pressure (mm Hg)
(wave reflection)
R = 0.784
P < 0.00001


Common carotid artery Pulse pres. (mm Hg)
160
140
120
100
80
60
40
20
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
Systemic reflection coefficient
R = – 0.595
P < 0.00001

Pressure wave analysis

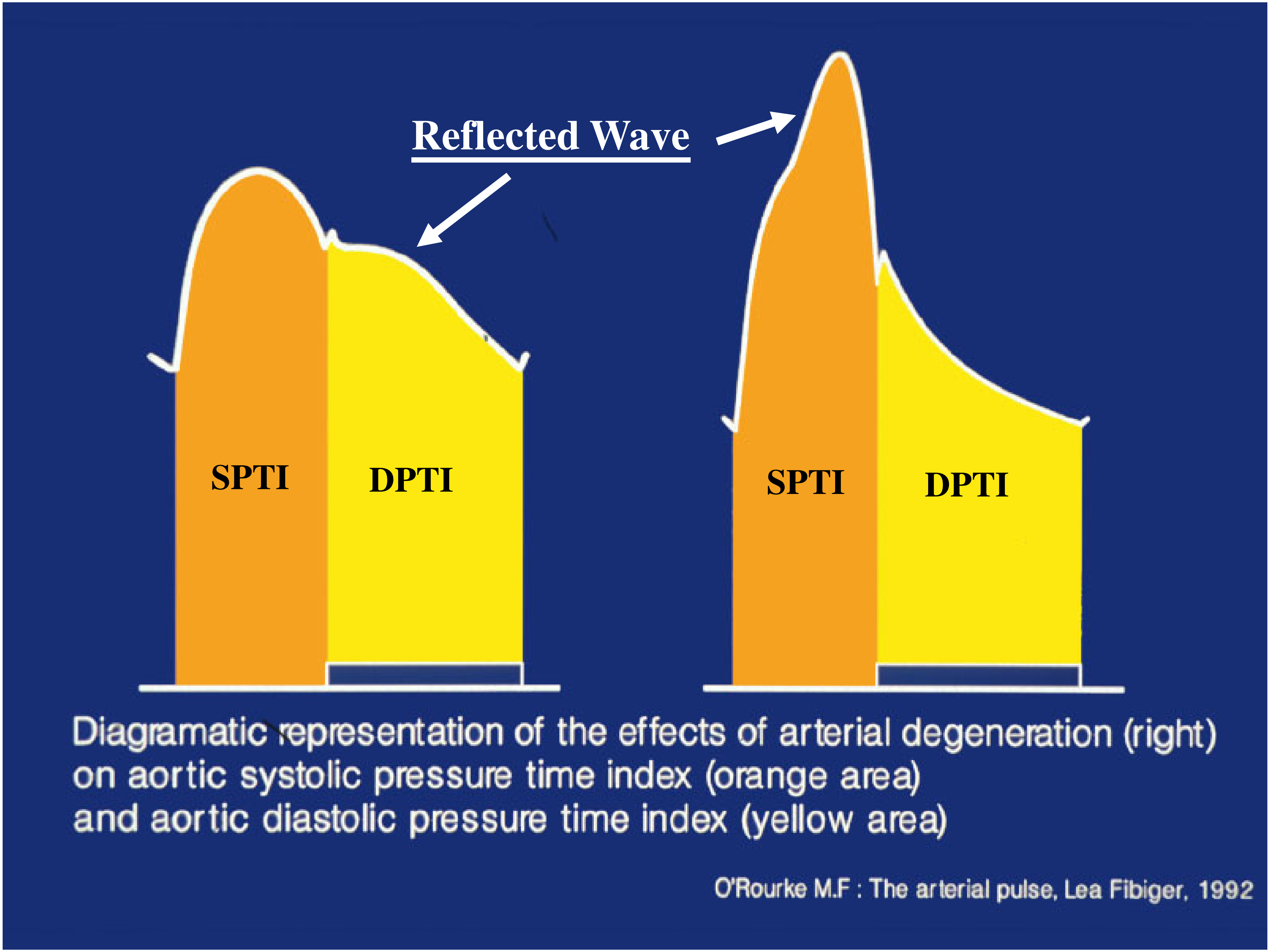


measured pressure wave

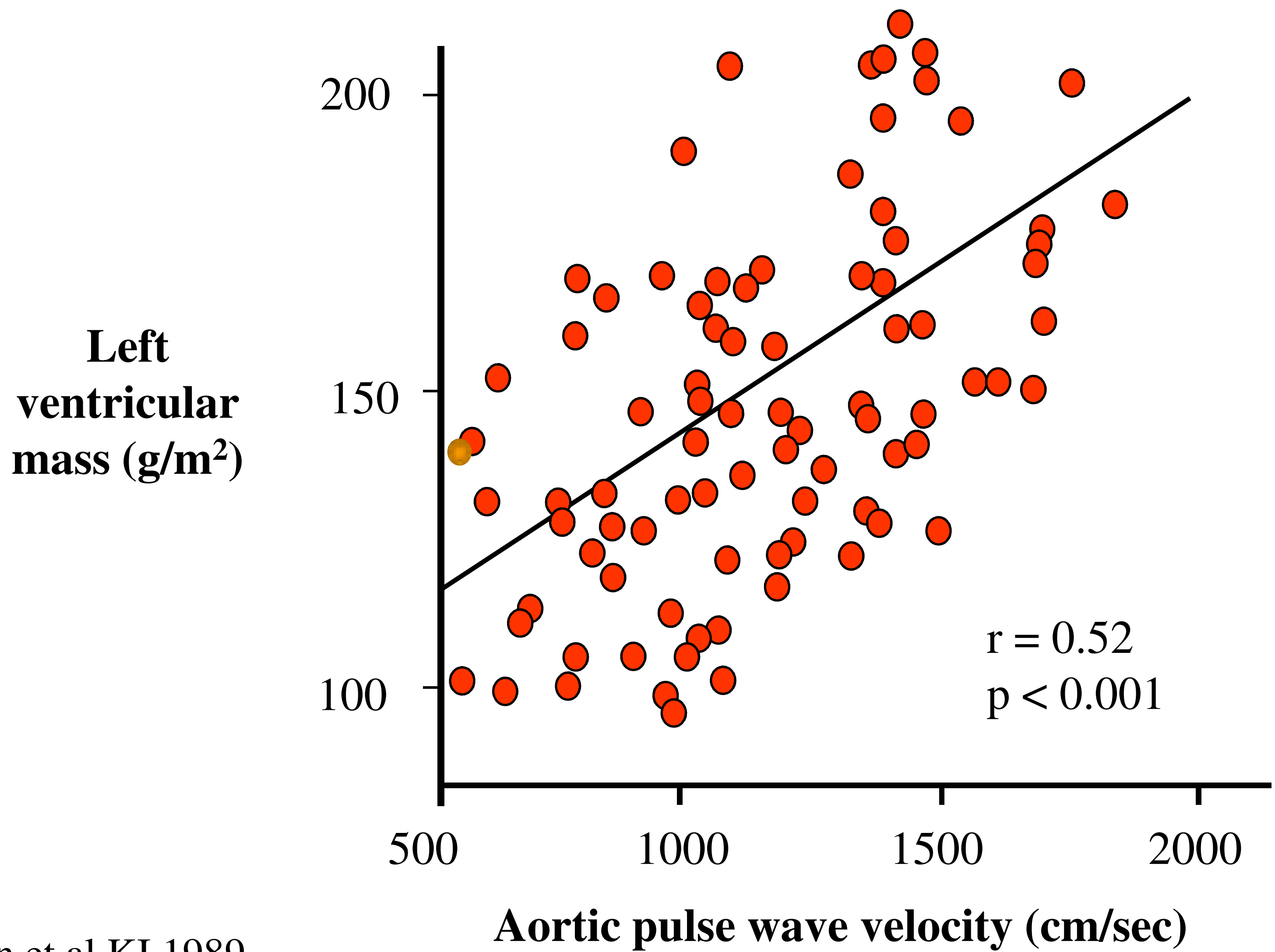
forward/incident pressure wave

reflected pressure wave

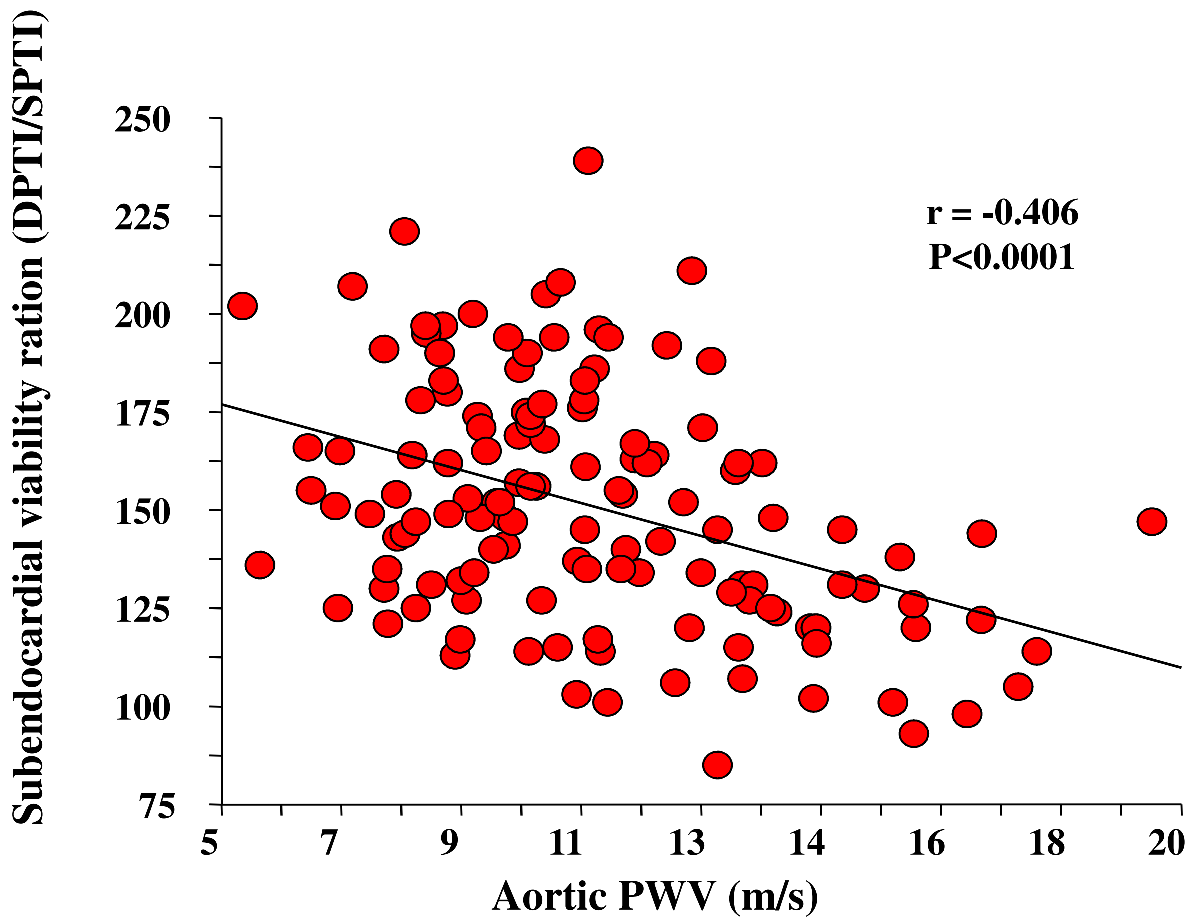
pulse wave velocity


Reflected Wave
SPTI
DPTI
SPTI
DPTI
Diagramatic representation of the effects of arterial degeneration (right) on aortic systolic pressure time index (orange area) and aortic diastolic pressure time index (yellow area)
O'Rourke M.F : The arterial pulse, Lea Fibiger, 1992

Correlation between left ventricular mass and aortic pulse wave velocity

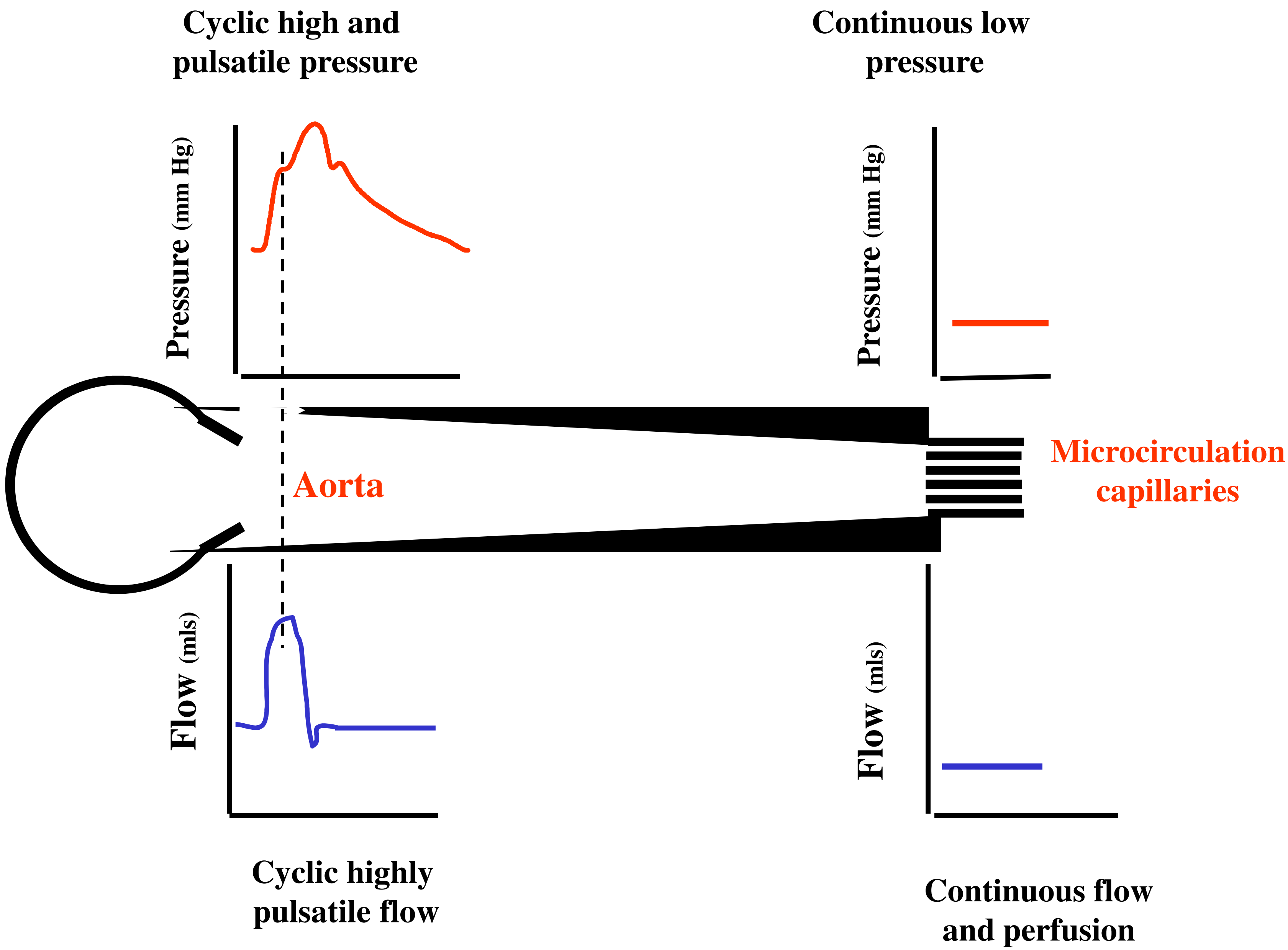


London et al KI 1989



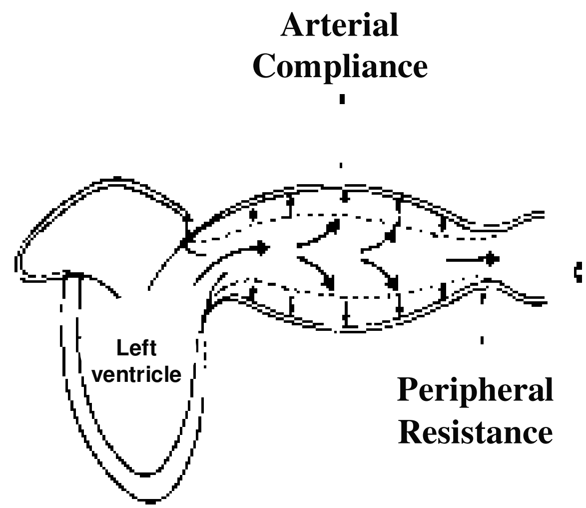
Subendocardial viability ration (DPTI/SPTI)
250
225
200
175
150
125
100
75
r = -0.406
P<0.0001
5
7
9
11
13
14
16
18
20
Aortic PWV (m/s)

Arterial system as « hydraulic filter »



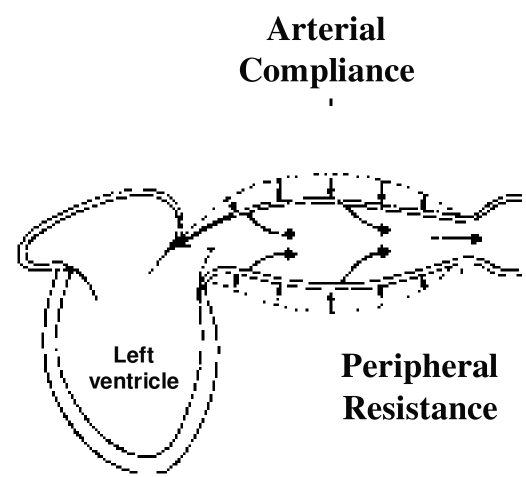
A. Systole

In normally compliant arterial system important part of the stroke volume is stored in the arteries during ventricular systole stretching the arterial walls

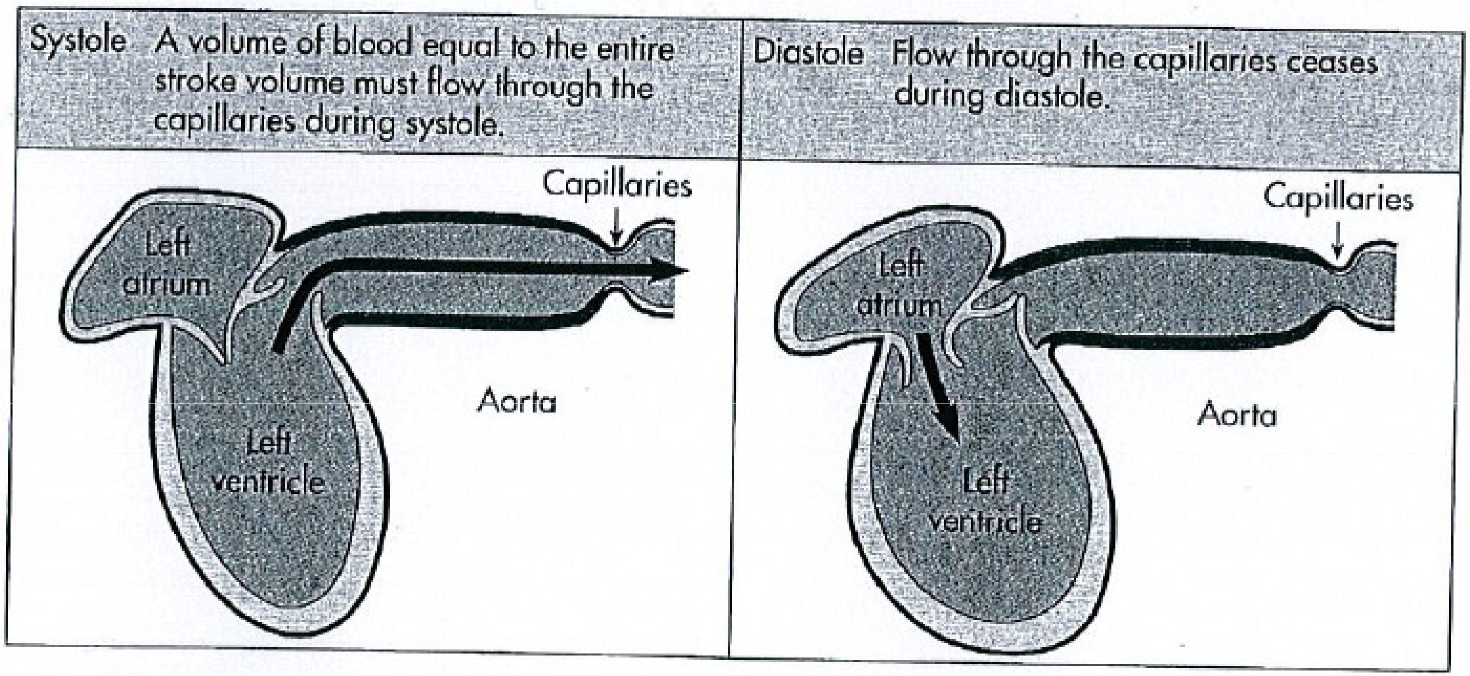


B. Diastole

During ventricular diastole the previously stretched arterial walls recoils with the stored volume insuring continuous perfusion of tissues and organs



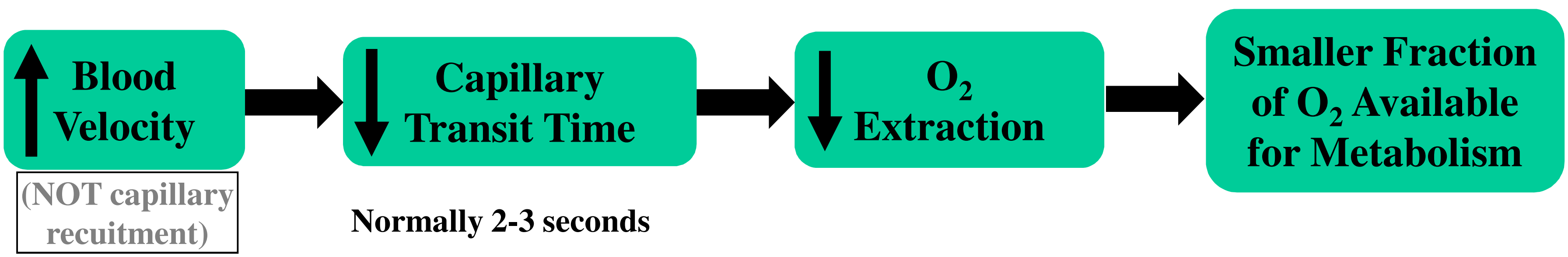
Rigid arteries

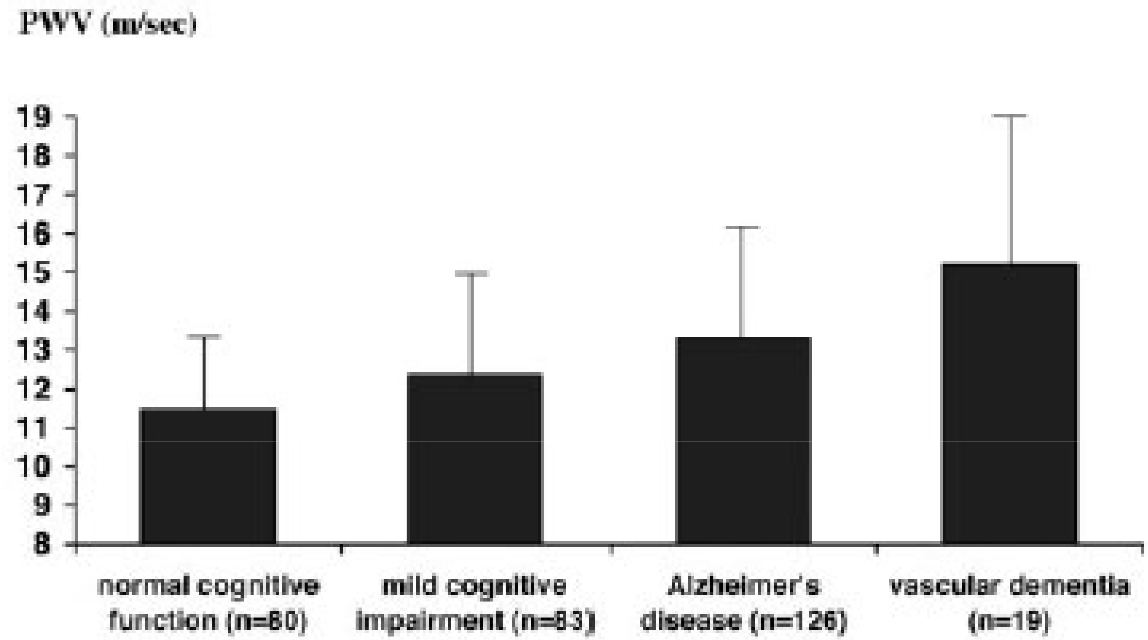


C, When the arteries are rigid, virtually none of the stroke volume can be stored in the arteries.

D, Rigid arteries cannot recoil appreciably during diastole.

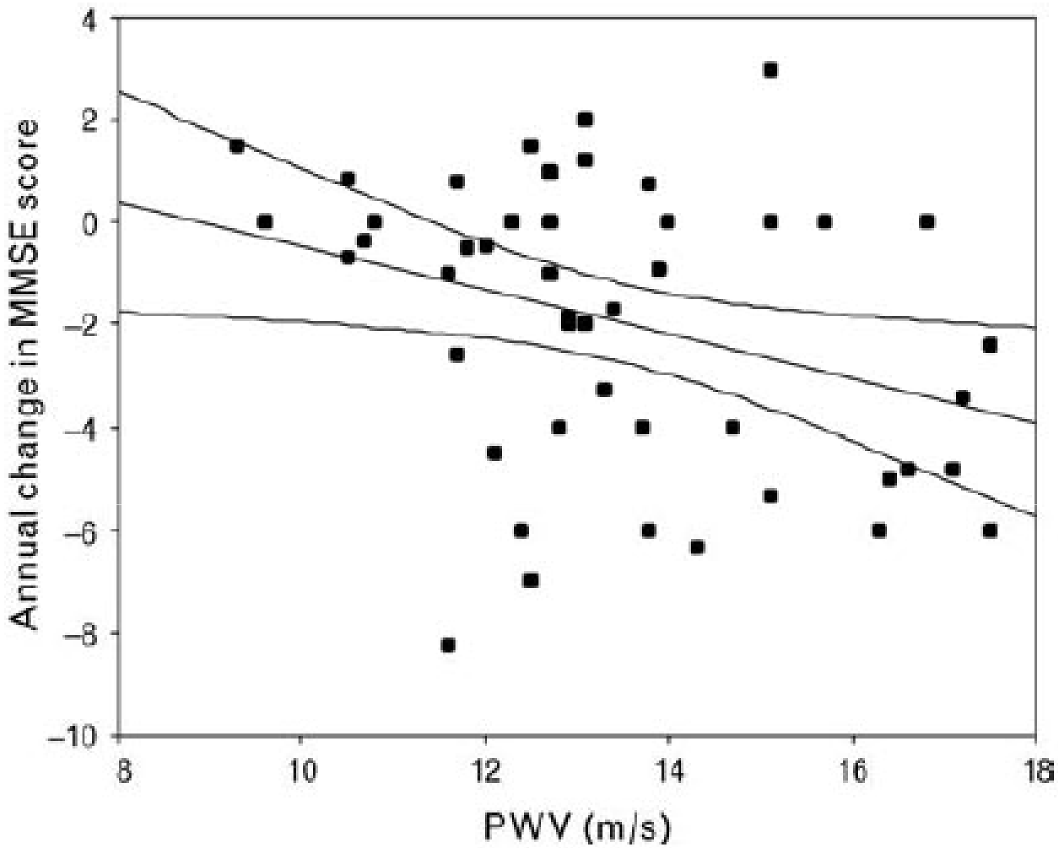
Oxygen Limitation Model





Relationship between PWV and cognitive status (normal cognitive function, MCI, AD, and VaD). $P<0.0001$, adjusted for age, gender, SBP, education level, antihypertensive therapy, presence of cardiovascular diseases.

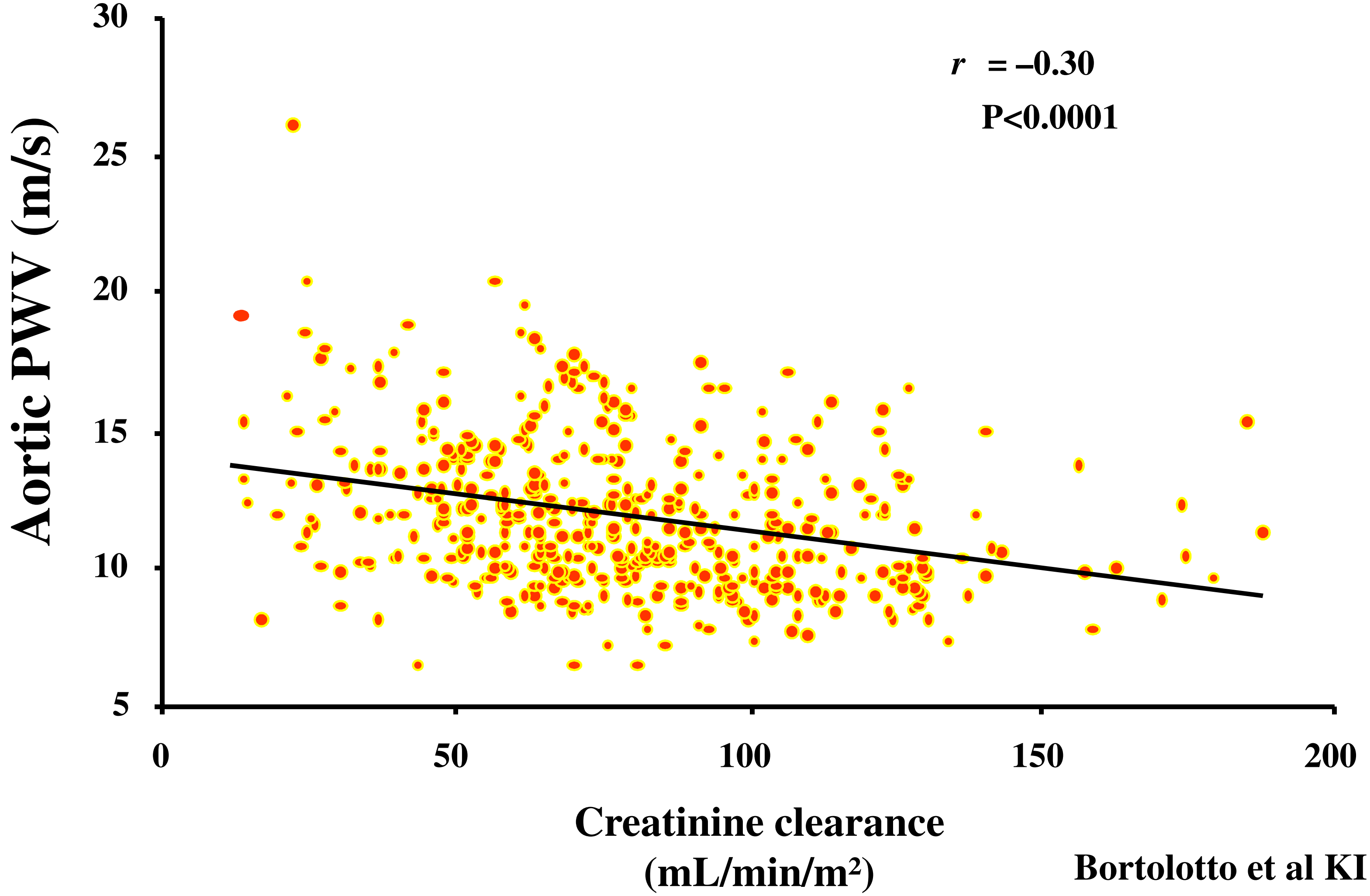
Hanon O et al. Stroke 2005;36:2193



Univariate association and confidence intervals between the pulse wave velocity (PWV) and the annual change in Mini-Mental Examination State (MMSE) score ($r = -0.333$, $P < 0.001$).

Scuteri A et al. J Hypertens 2007;25:1035

Correlation Between CCr (C-G formula) and Aortic PWV

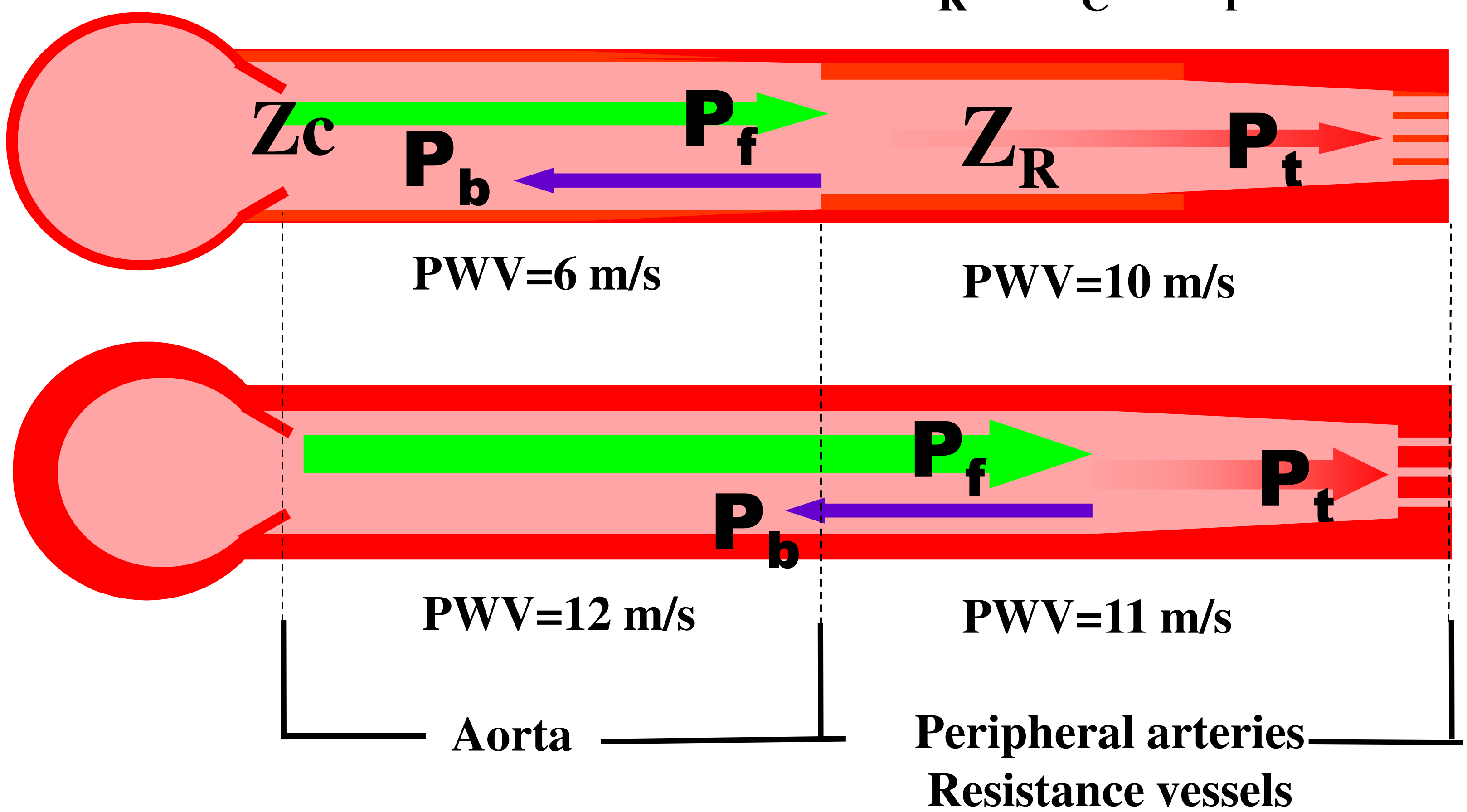


Bortolotto et al KI 2001

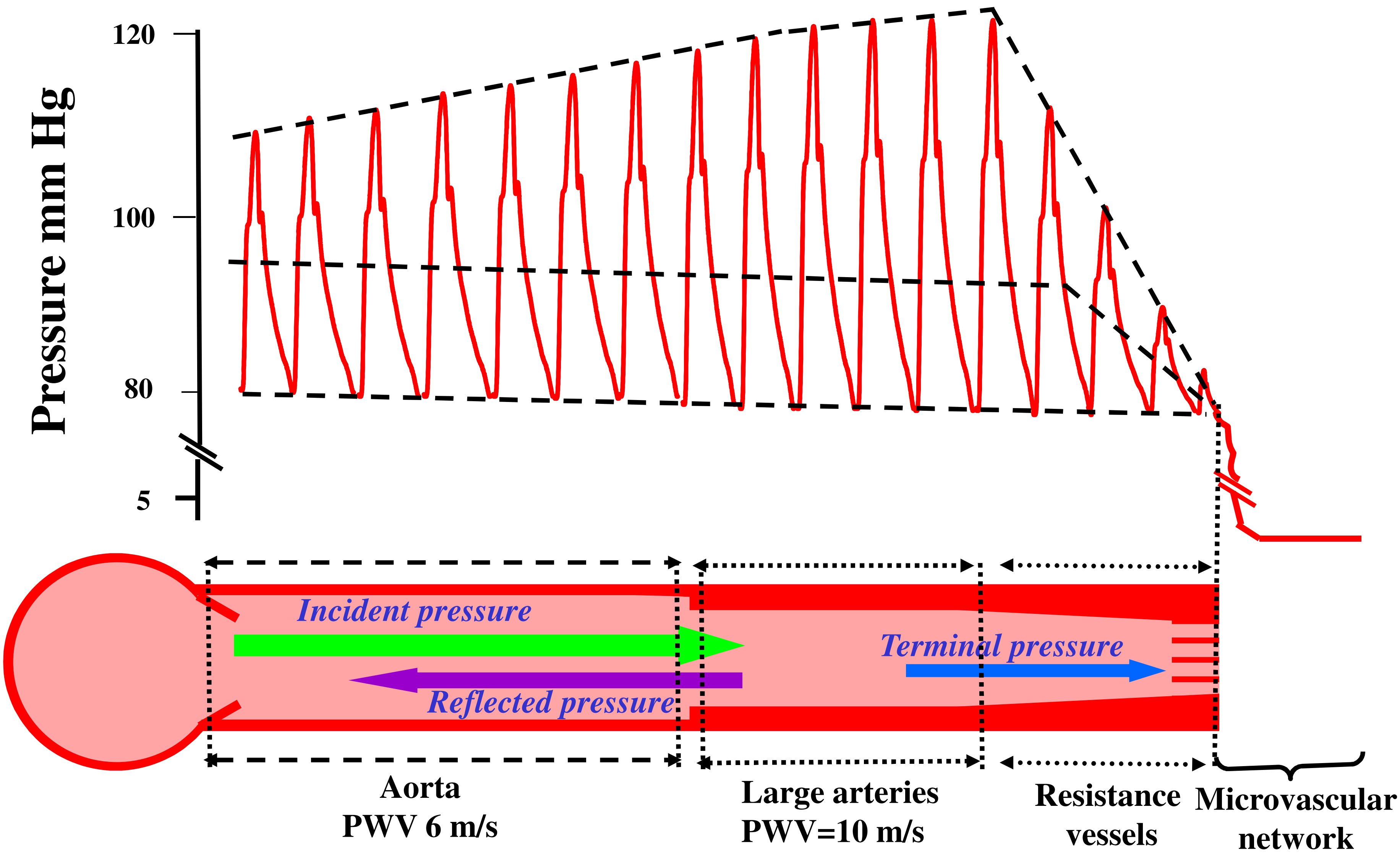
Arterial Impedance Gradients

Zc-characteristic impedance; Zr-peripheral resistance

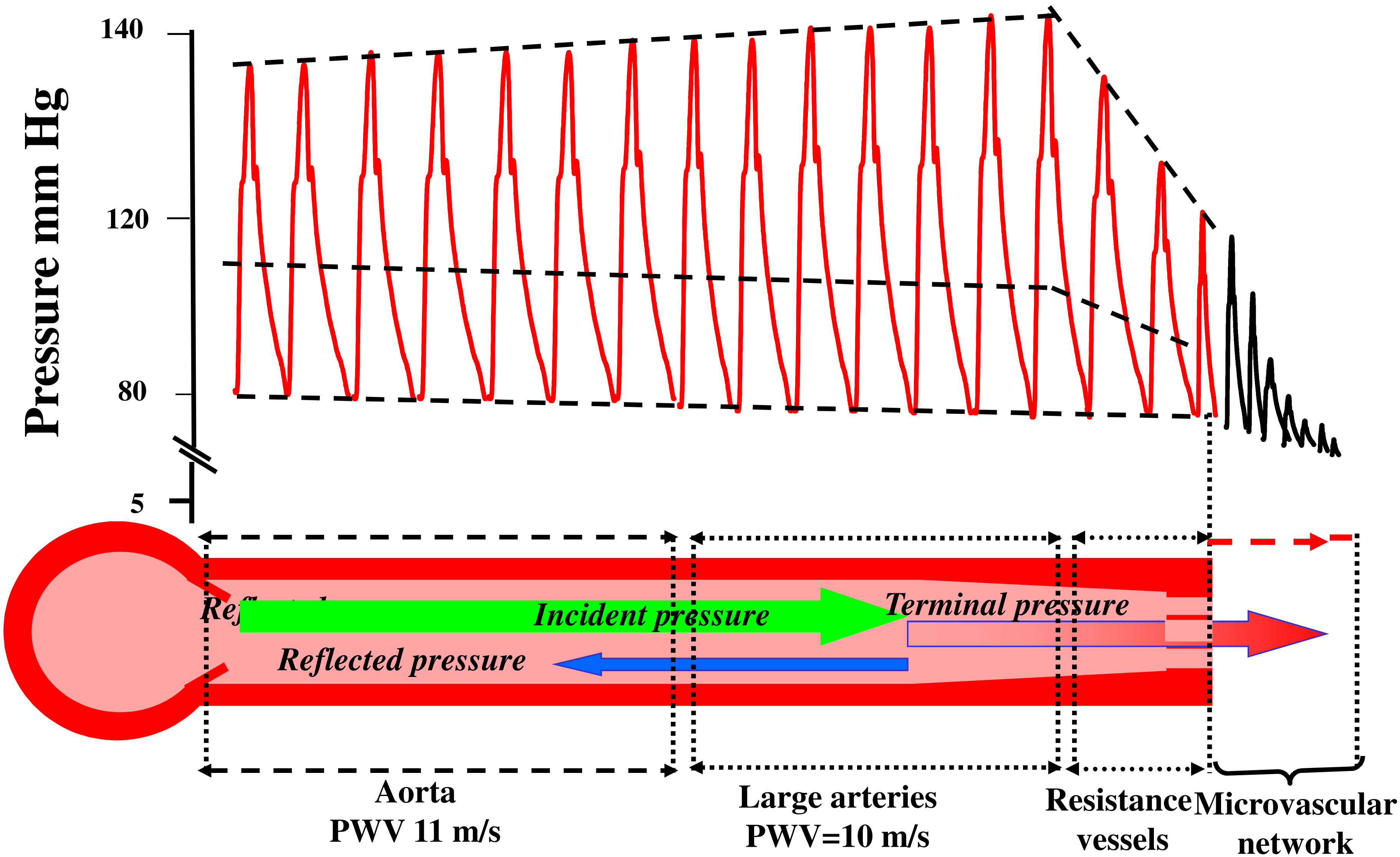
$$\text{Reflection Coefficient}(\Gamma) = \frac{Z_R - Z_C}{Z_R + Z_C} = \frac{P_b}{P_f}$$

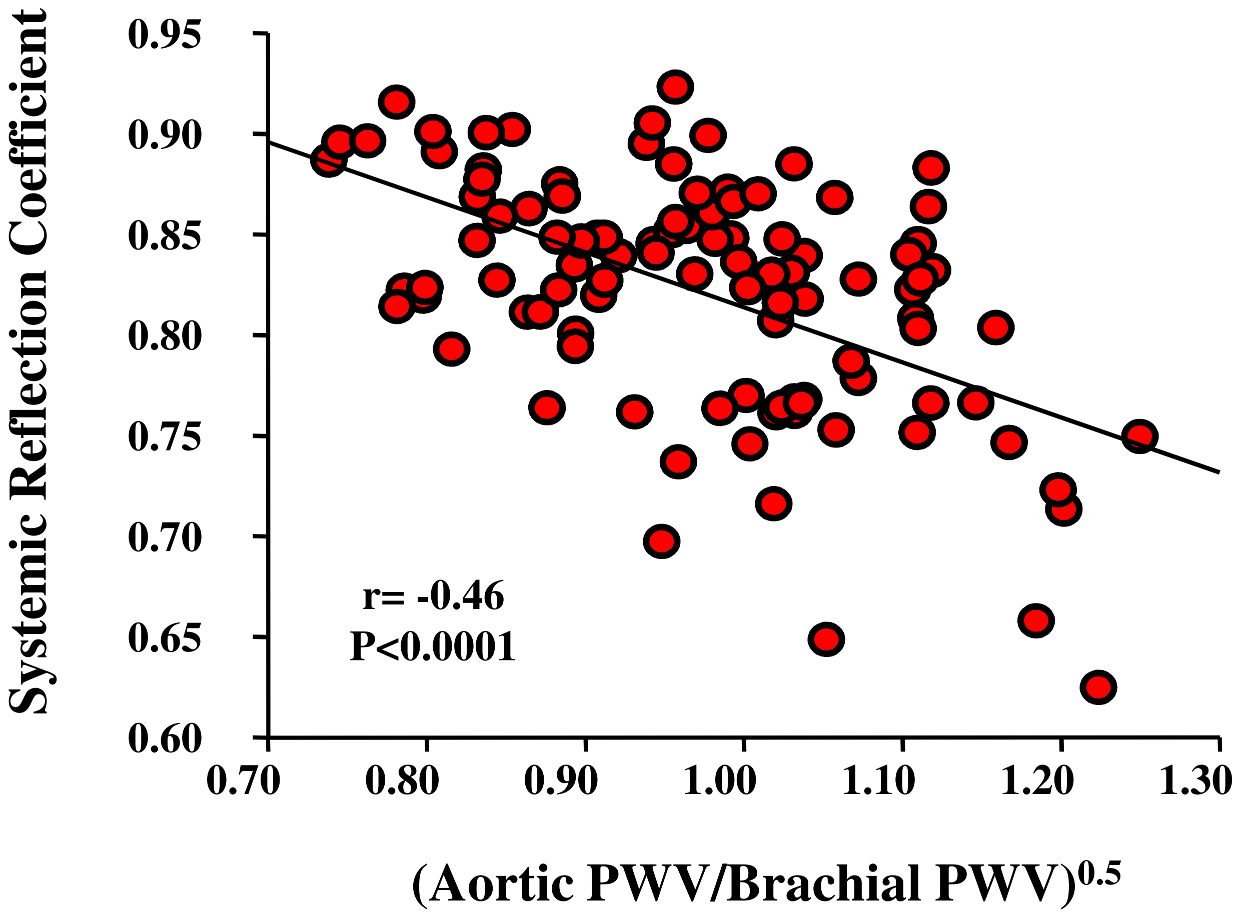


Pressure transmission in the presence of arterial stiffness gradients

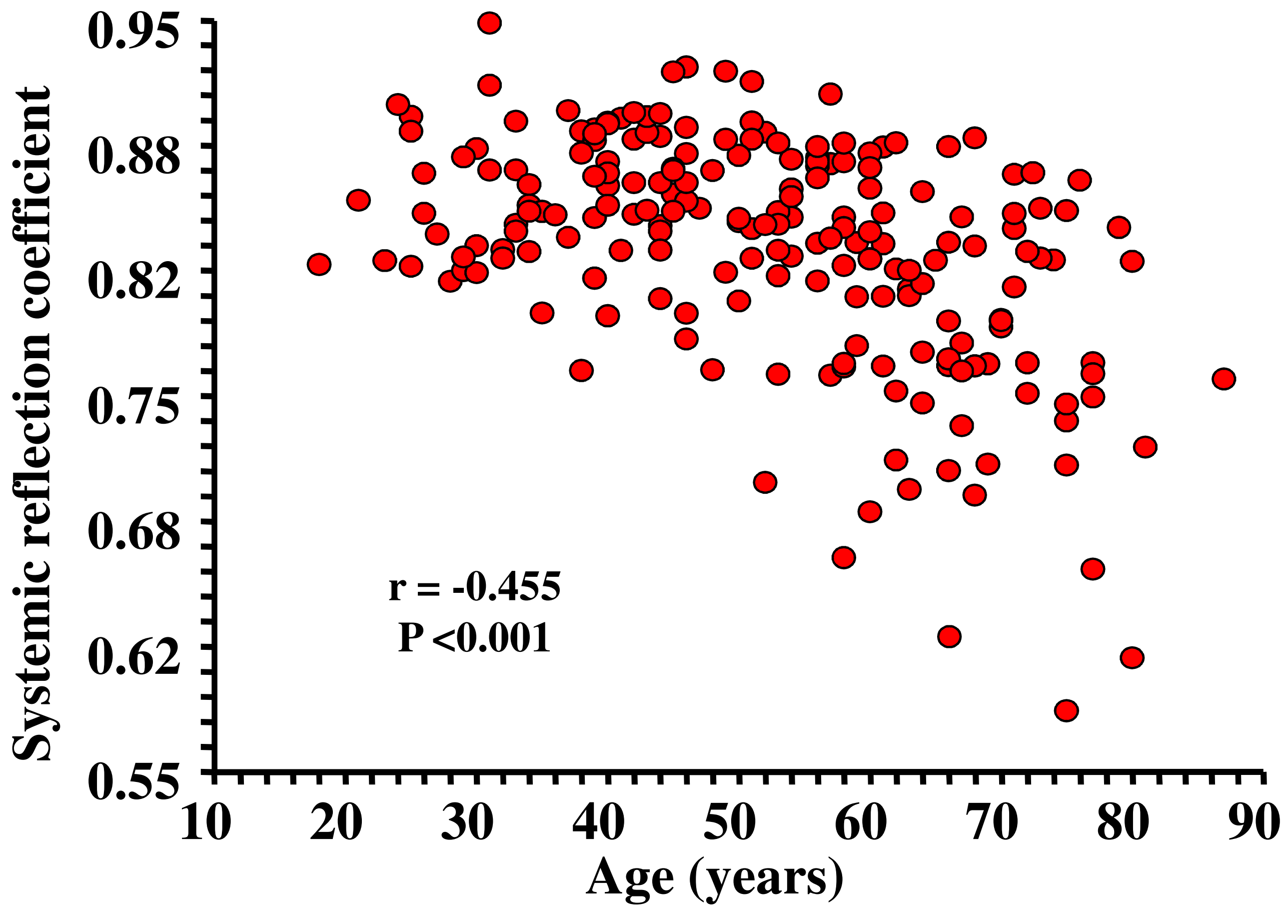


Pressure transmission in "low peripheral resistance" organs (kidney; brain) when arterial stiffness gradient is decreased or abolished

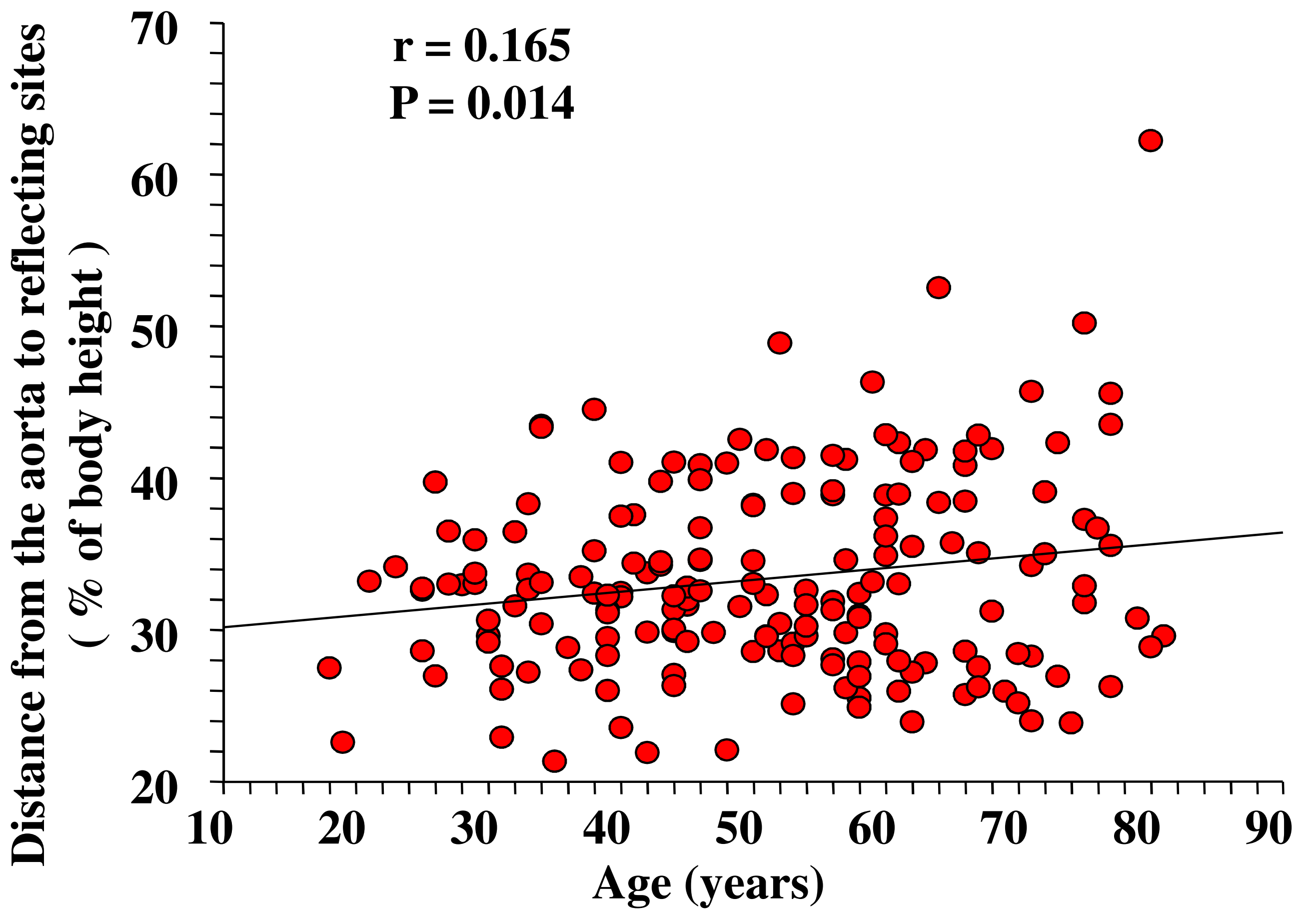




London GM (submitted)



London GM (submitted)

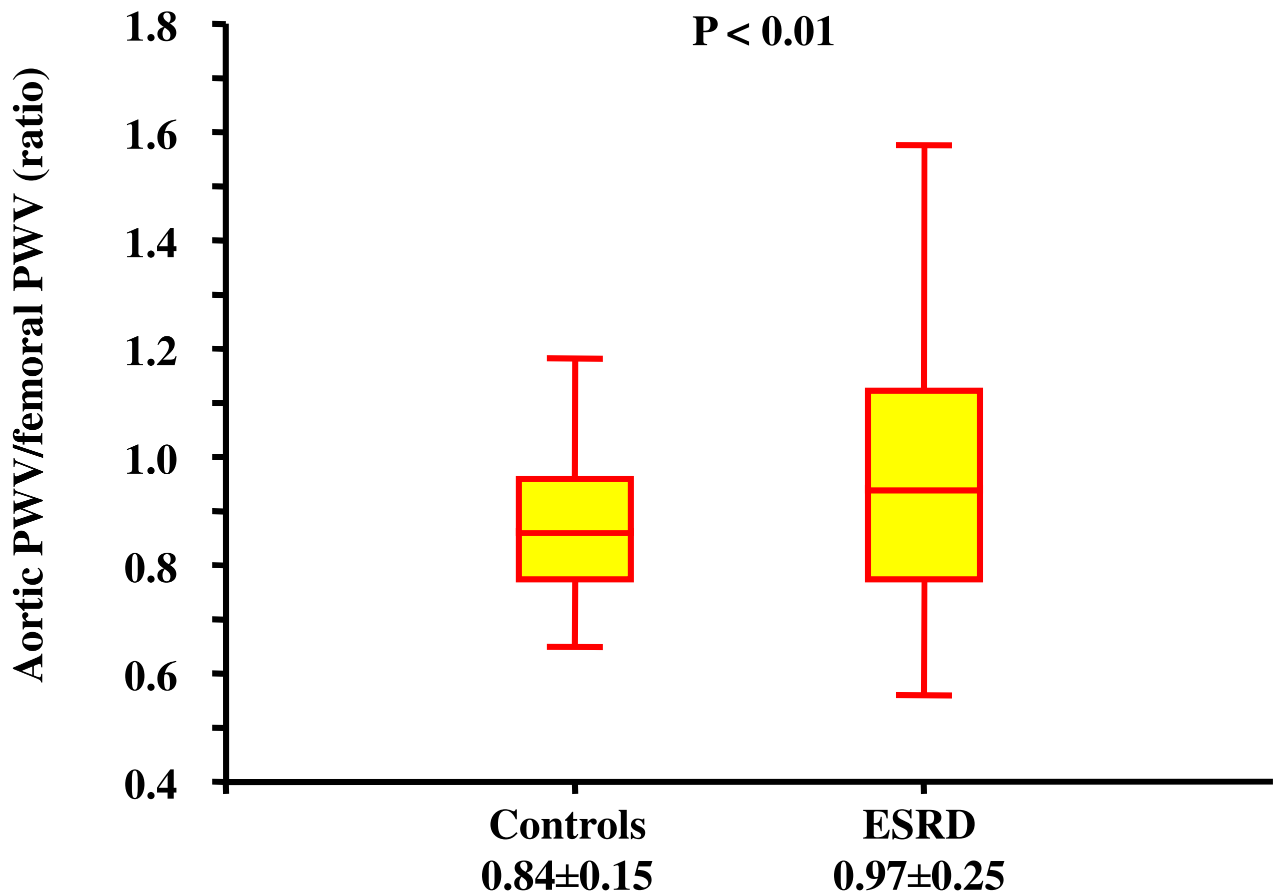


London GM (submitted)

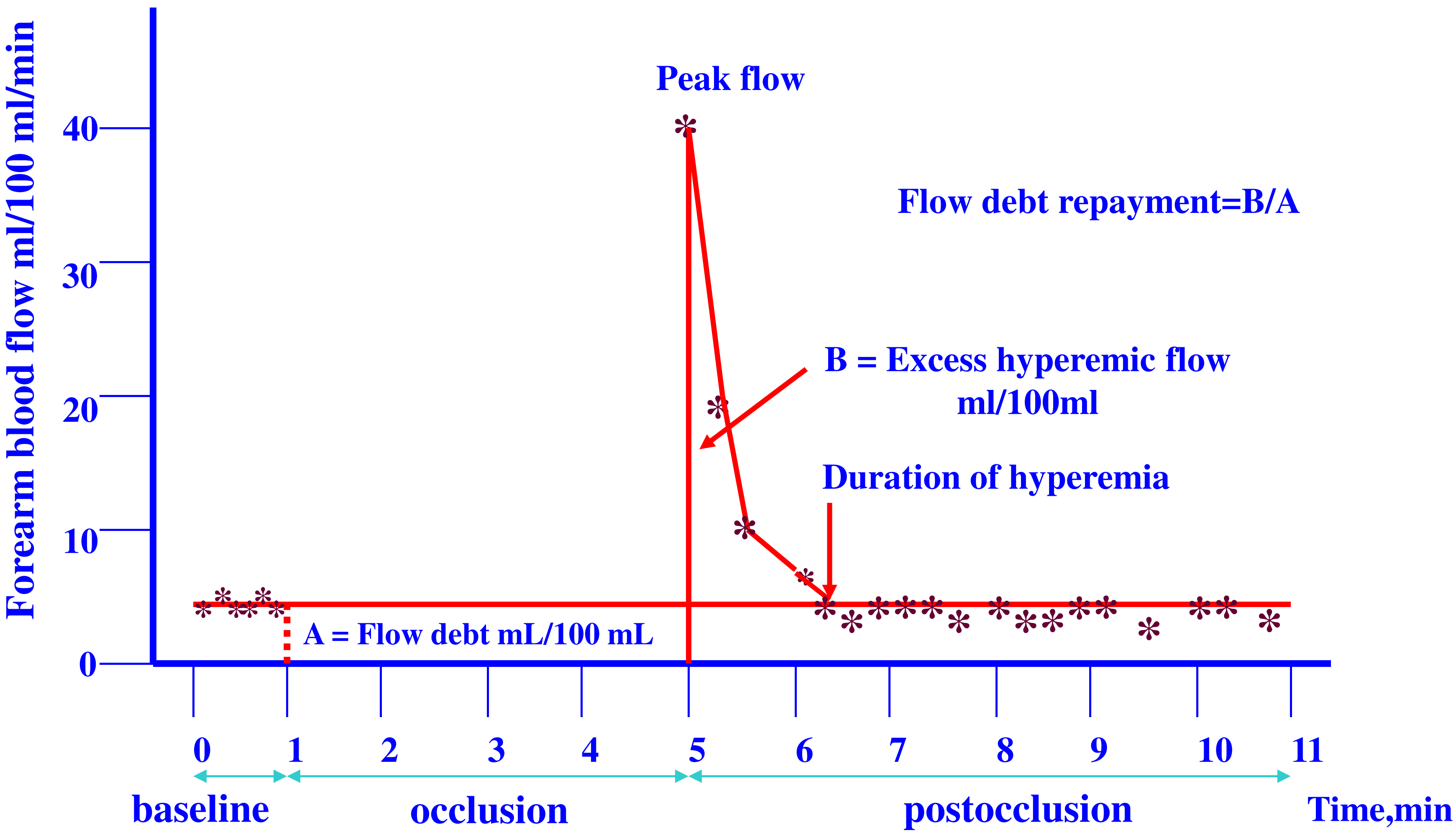
Characteristics of arterial system in controls and ESRD patients

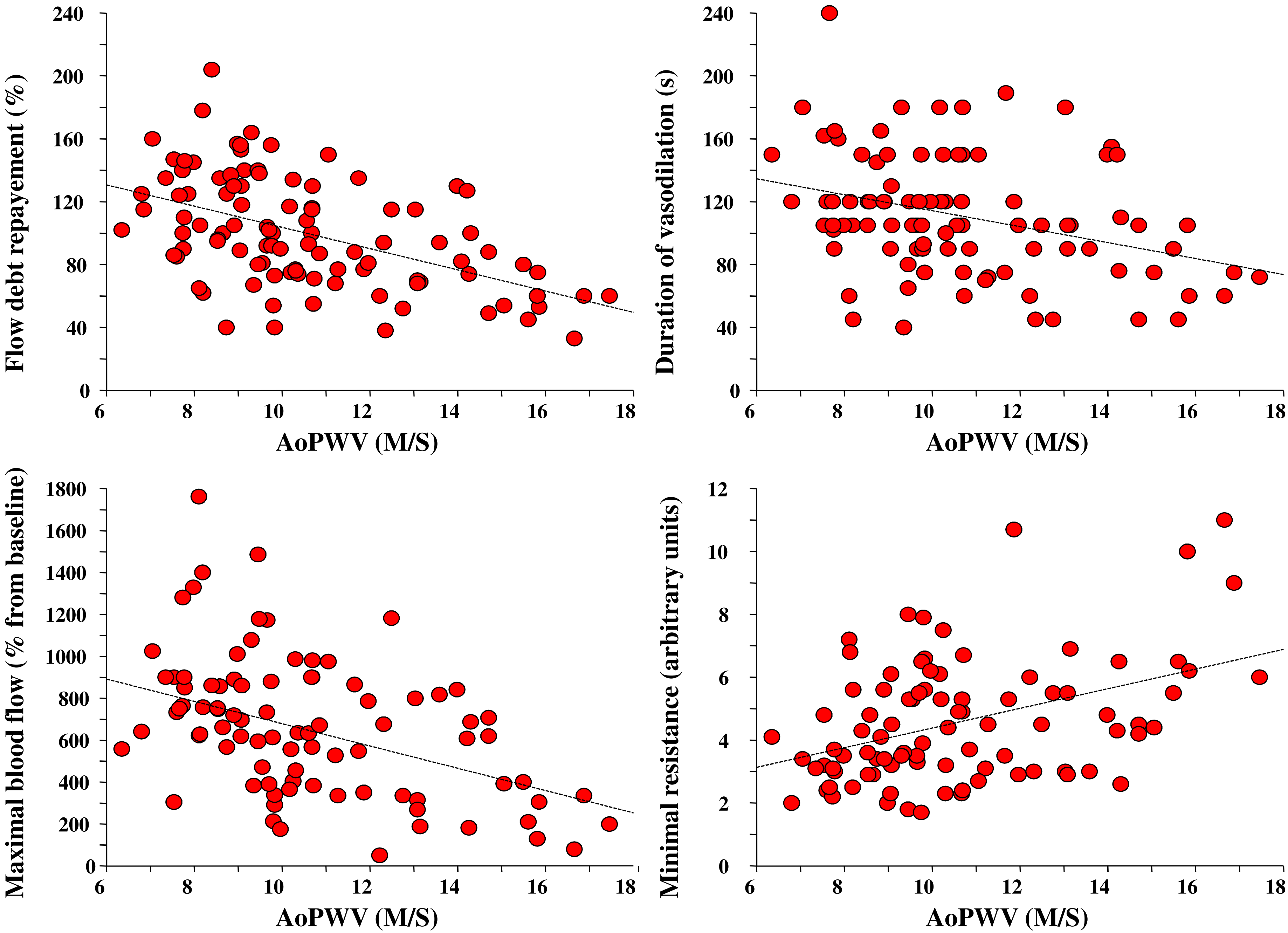
	Controls	ESRD
•Forward pressure (mm Hg)	38 ± 11	44 ± 16**
•Wave reflection (% of PP)	17 ±17	25 ±15***
•Reflected pressure (mm Hg)	11 ± 6	14 ± 8*
•Reflected wave arrival time (ms)	128 ±15	108 ± 16**
•Zr (dynes.s.cm-5)	2309 ±530	2260 ±1175
•Zc (dynes.s.cm-5)	179 ± 52	214 ±103**
•Γ (reflection coefficient)	0.85 ± 0.04	0.81 ±0.06**
•Aortic PWV (m/s)	9.70 ±1.80	10.60 ±2.5**
•Peripheral/femoral PWV (m/s)	11.0 ±1.75	11.20 ±1.80

*P<0.05; **P<0.01; ***P<0.001 ESRD: fmin=4.62Hz ; Control: fmin=3.90Hz

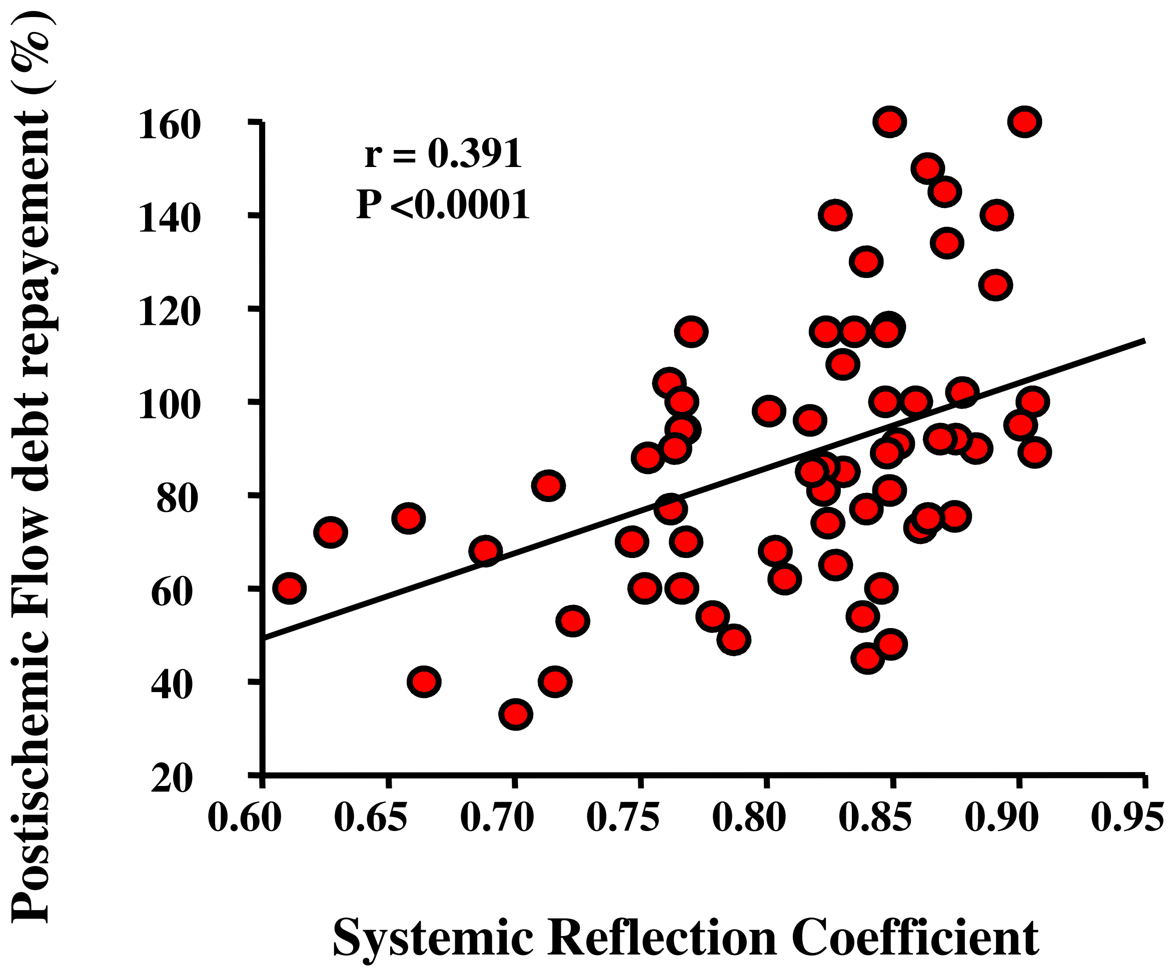

P < 0.01
Aortic PWV/femoral PWV (ratio)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
Controls
0.84±0.15
ESRD
0.97±0.25

Schematic representation of reactive hyperemic response in the human forearm after five minutes of ischemia





Flow debt repayement (%)
Duration of vasodilation (s)
Maximal blood flow (% from baseline)
Minimal resistance (arbitrary units)
AoPWV (M/S)
AoPWV (M/S)
AoPWV (M/S)
AoPWV (M/S)



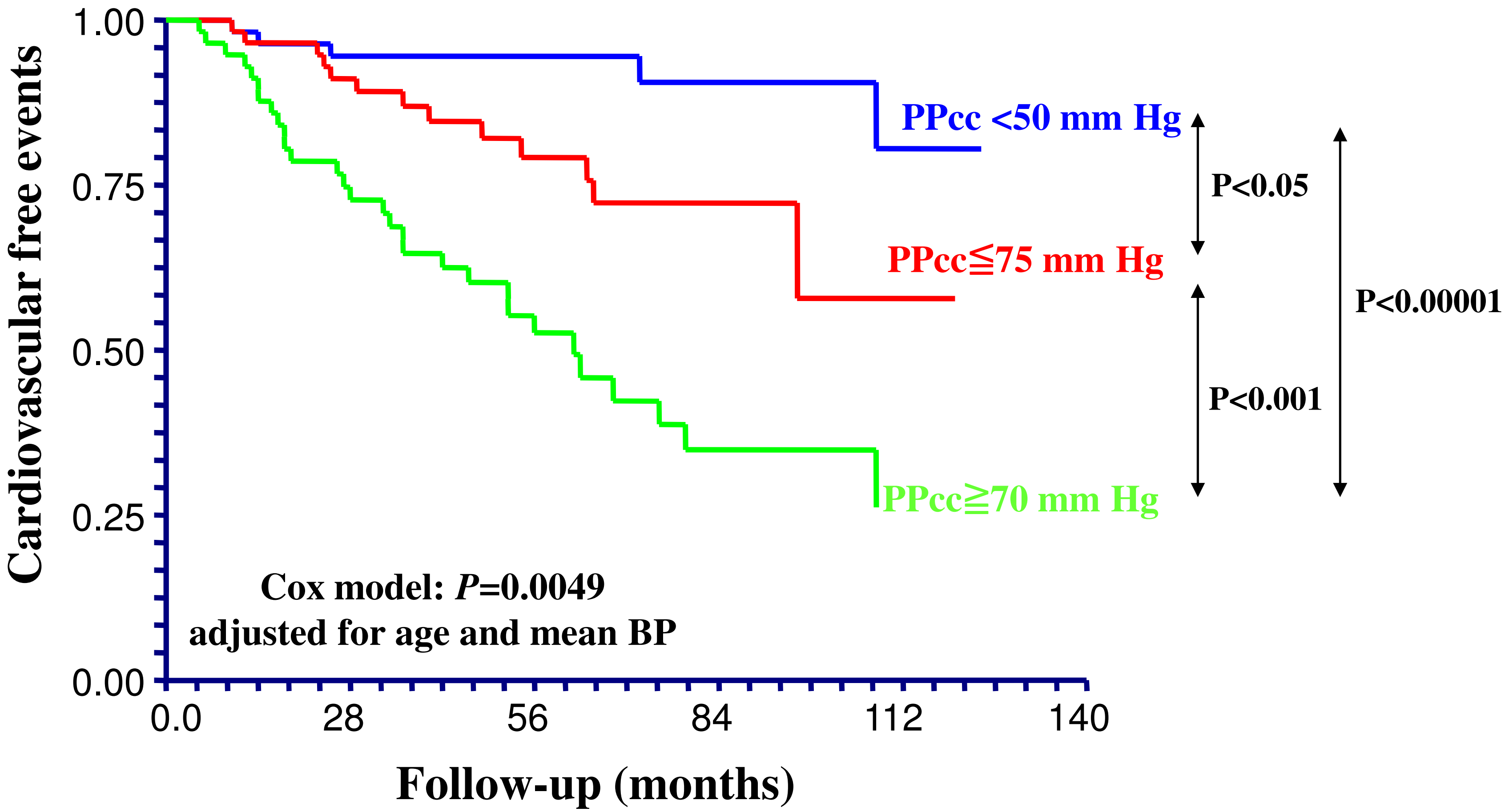
London GM (submitted)

Arterial changes in CKD

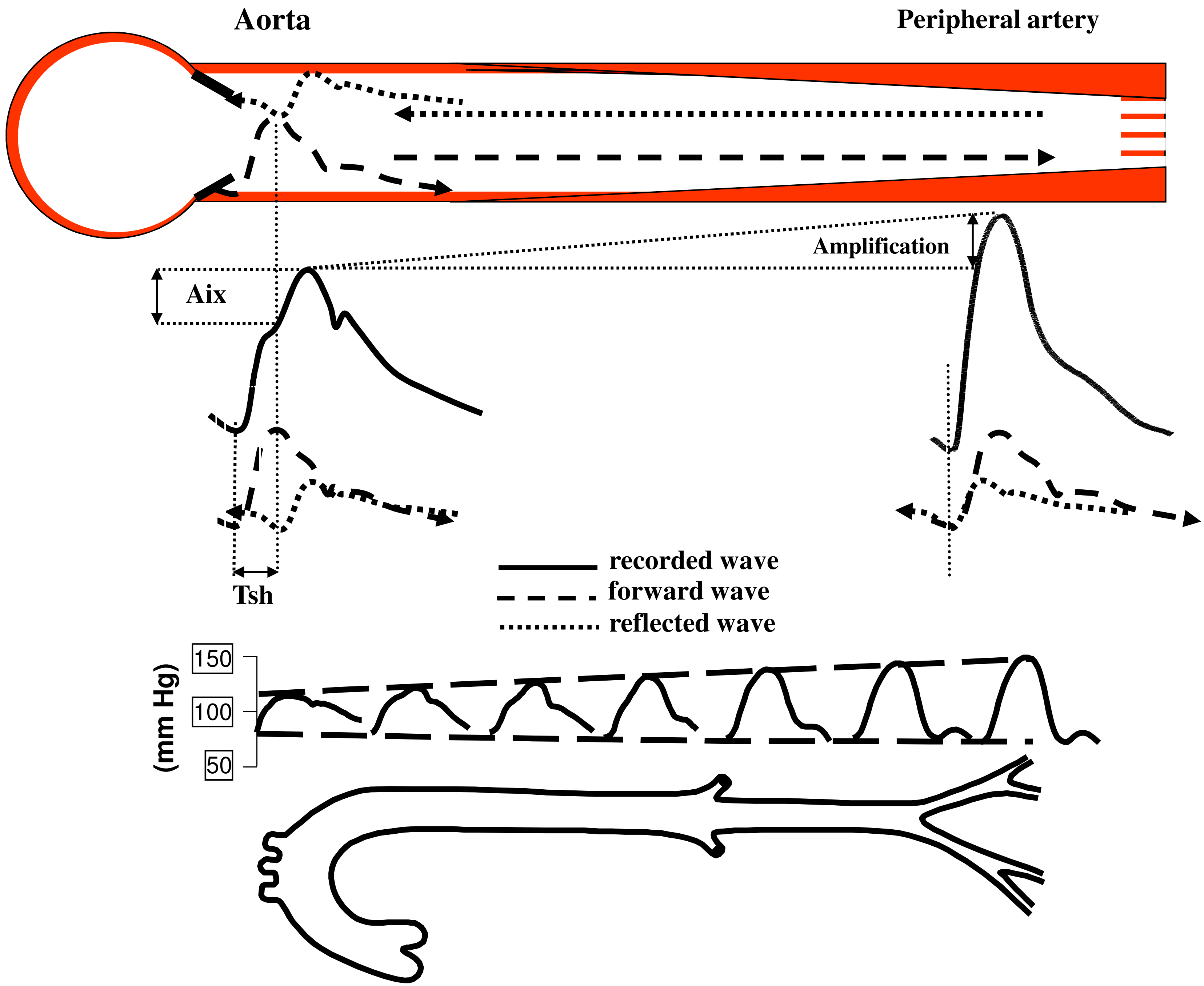
- **Premature Aortic Aging: increased diameter and stiffness.**
- **Accelerated in the presence of calcifications**
- **Lost or Impairement of Hydraulic Filter : high Systolic and Pulse pressure in Aorta and Central arteries (LVH poor Coronary perfusions), and abnormal pressure transmission to microcirculation (impaired vasodilation)**

Common Carotid Pulse Pressure and Cardiovascular mortality in ESRD patients

(log rank p<0.0001)

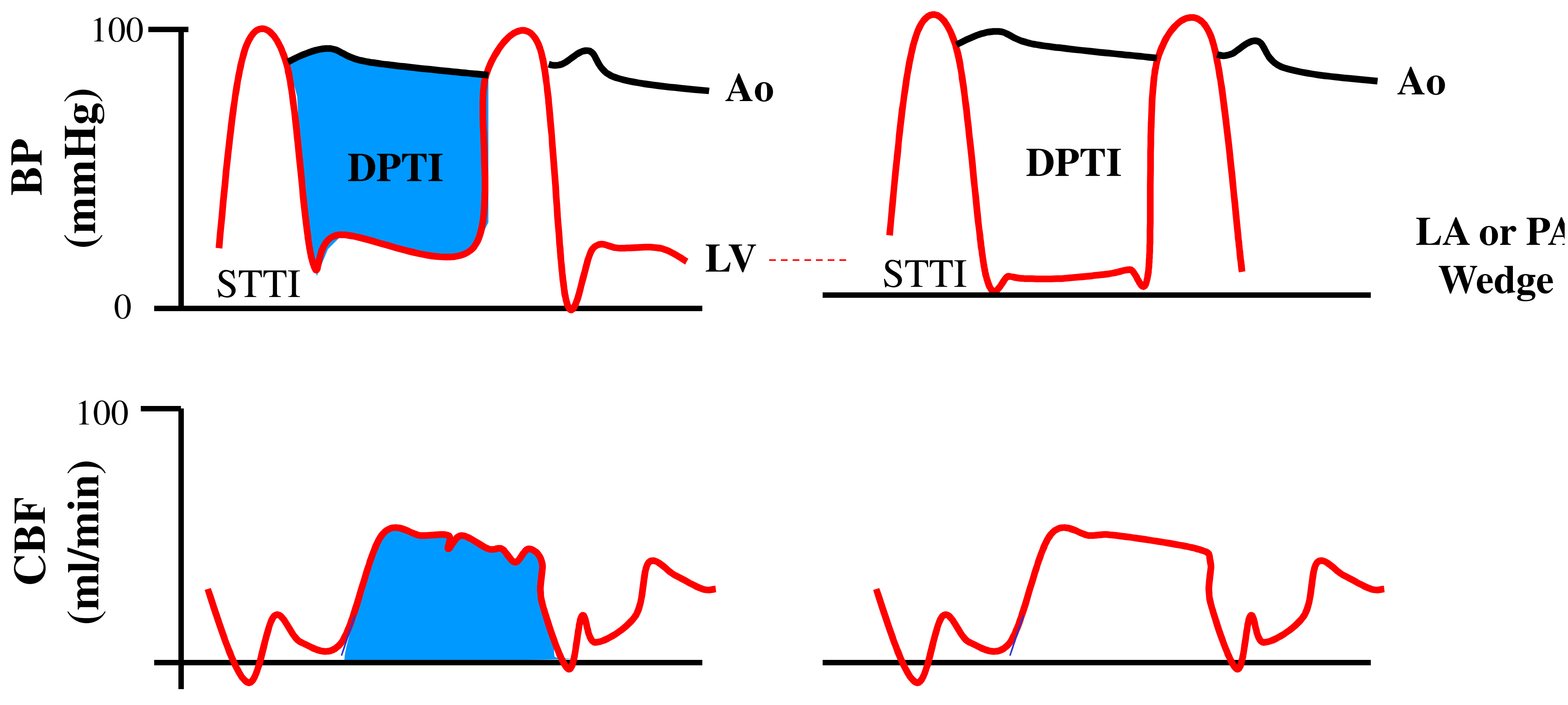


Safar et al Hypertension 2002



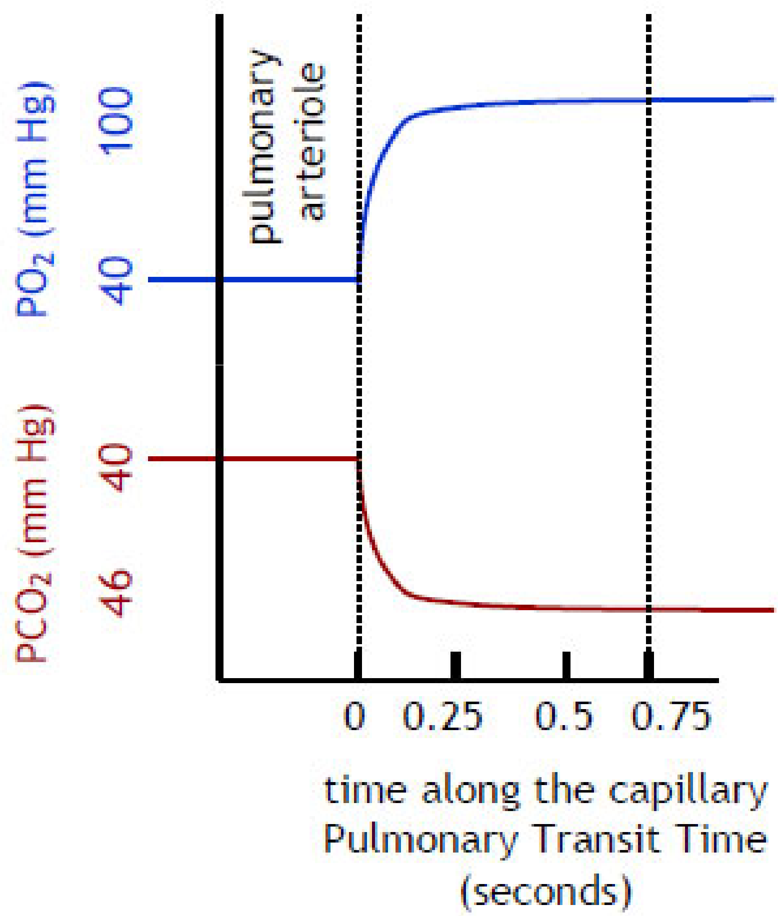
Aorta
Peripheral artery
Amplification
Aix
Tsh
recorded wave
forward wave
reflected wave
150
100
50
(mm Hg)

Superimposed simultaneous phasic recording of aortic (Ao), left ventricular (LV) pressures and coronary blood flow (CBF) (Buckeberg et al. Circ Res. 1972)



GAS EXCHANGE ACROSS THE PULMONARY CAPILLARY

Is Complete Within ¼ Second



- at rest pulmonary transit time [¾ second] is more than that required to complete gas exchange [¼ second].
- during exercise, despite increased cardiac output, pulmonary transit time remains > ¼ second & gas exchange is complete.
- in pulmonary fibrosis, reduced gas exchange is often seen in patients during exercise. At rest, the additional time spent in the capillary is sufficient to compensate for the thickened barrier .
- elite athletes with very high cardiac outputs have pulmonary transit times below ¼ second during intense exercise→ inadequate oxygen exchange at the lungs ⟶ low oxygen levels in the blood [arterial hypoxemia]

Effects of age on arterial stiffness and wave reflections
For males (circle and solid lines) and females (squares and dashed line)

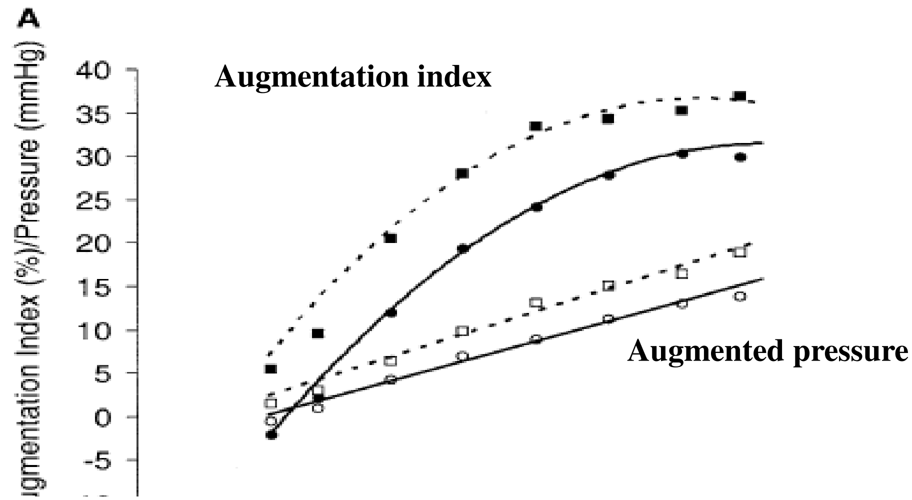
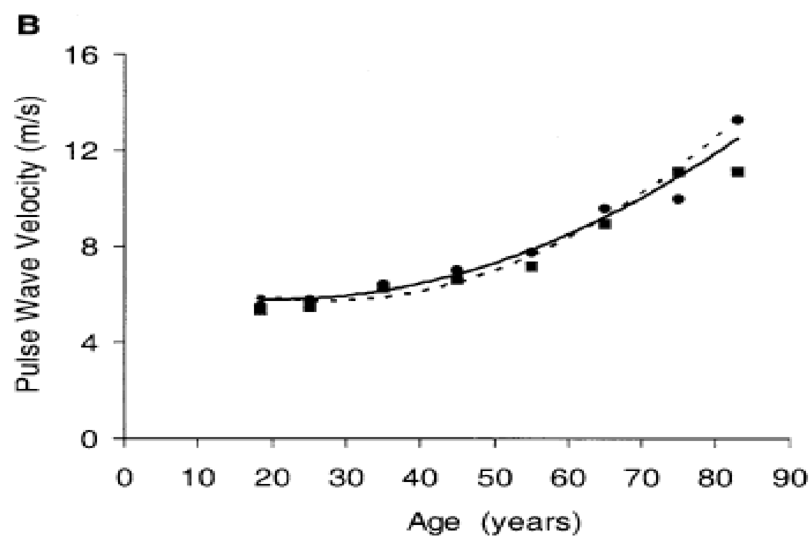
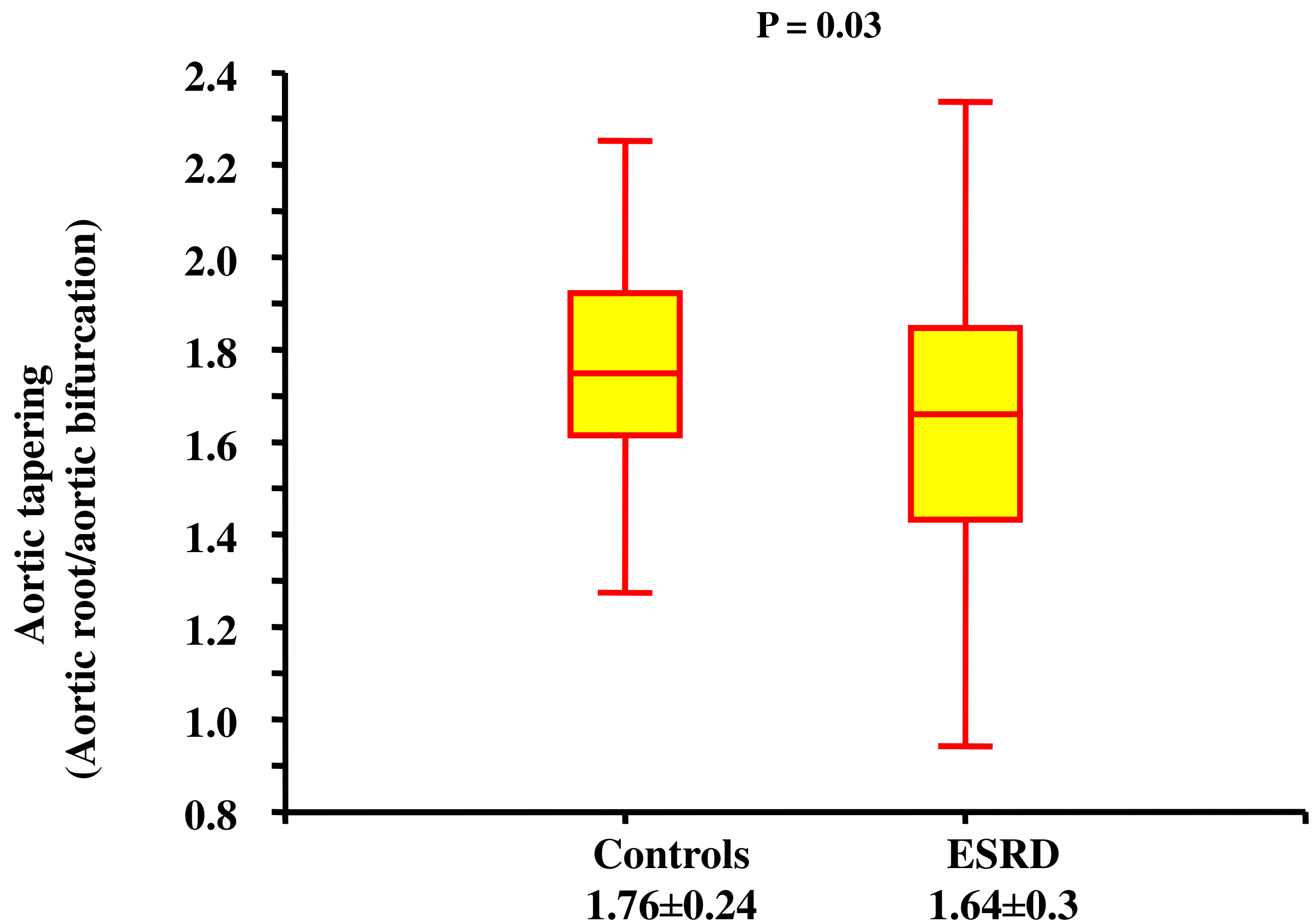
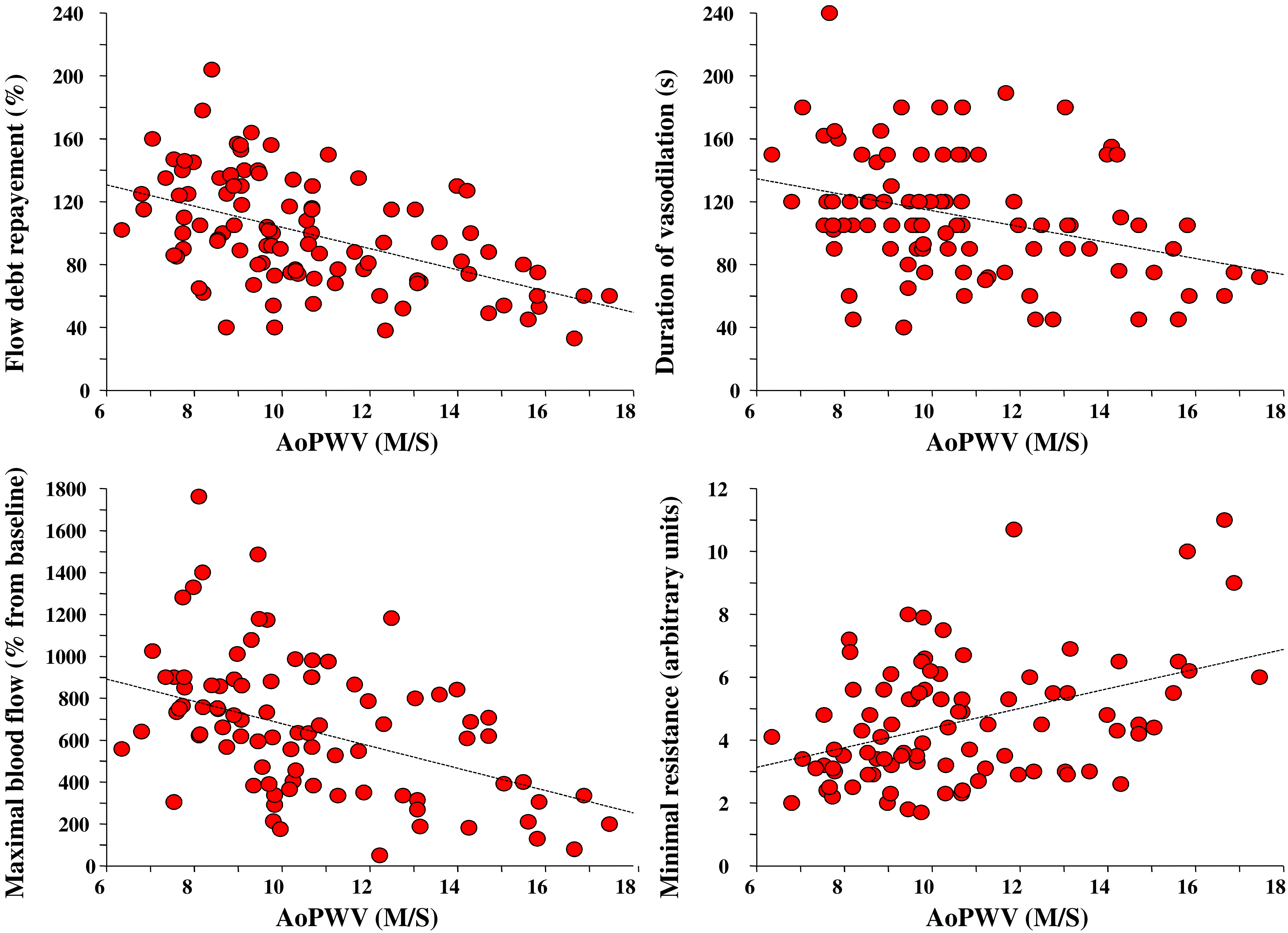


Figure 2. Regression curves representing the effect of age on parameters of arterial stiffness and wave reflection for males **(circles, solid lines)** and females **(squares, dashed lines). Panel A** represents augmentation pressure

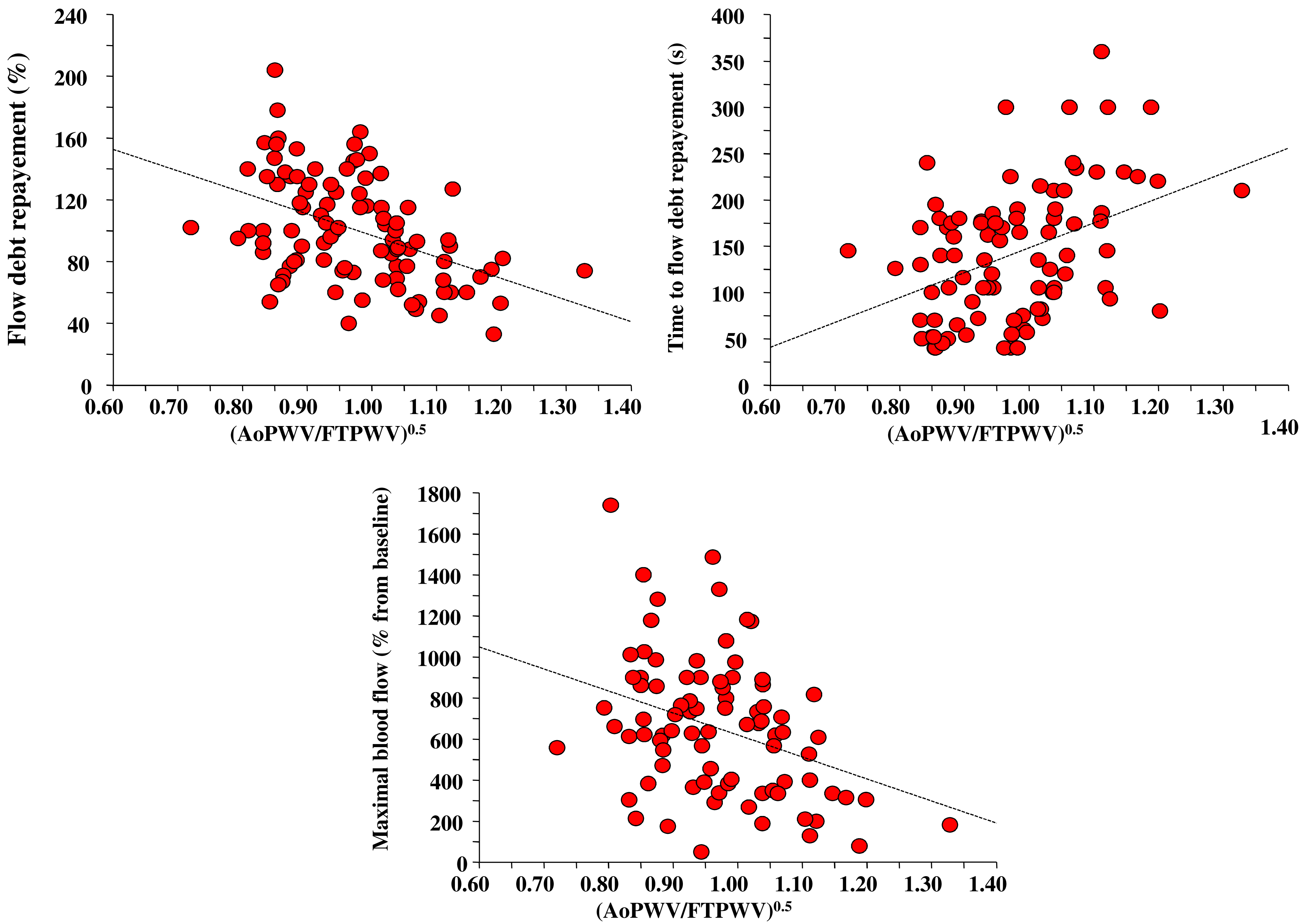


Carmel M. McEniery et al .JACC 2005;46:1753


P = 0.03
Aortic tapering
(Aortic root/aortic bifurcation)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
Controls
1.76±0.24
ESRD
1.64±0.3



Flow debt repayement (%)
AoPWV (M/S)
Duration of vasodilation (s)
AoPWV (M/S)
Maximal blood flow (% from baseline)
AoPWV (M/S)
Minimal resistance (arbitrary units)
AoPWV (M/S)



Flow debt repayement (%)
240
200
160
120
80
40
0
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
1.40
(AoPWV/FTPWV)^0.5
Time to flow debt repayement (s)
400
350
300
250
200
150
100
50
0
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
1.40
(AoPWV/FTPWV)^0.5
Maximal blood flow (% from baseline)
1800
1600
1400
1200
1000
800
600
400
200
0
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
1.40
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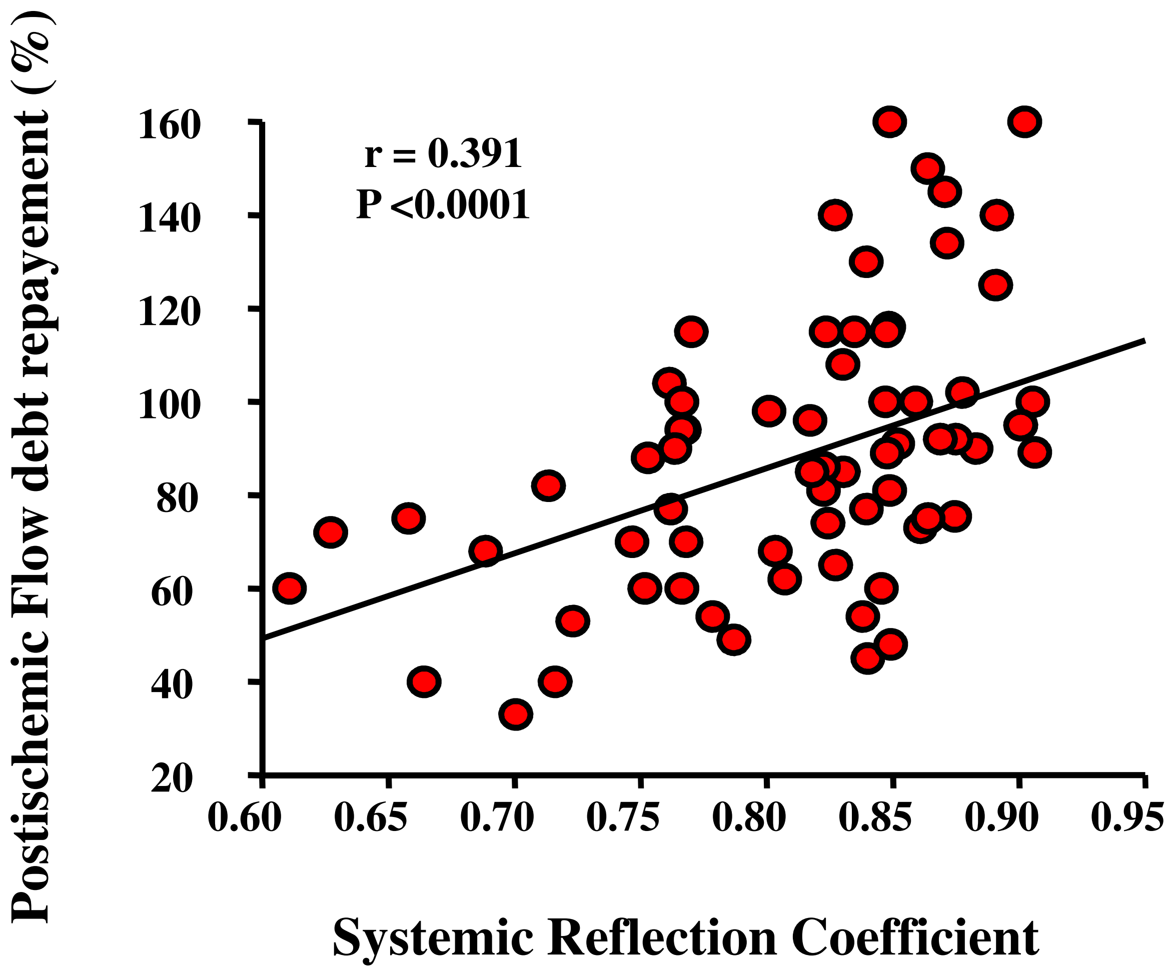
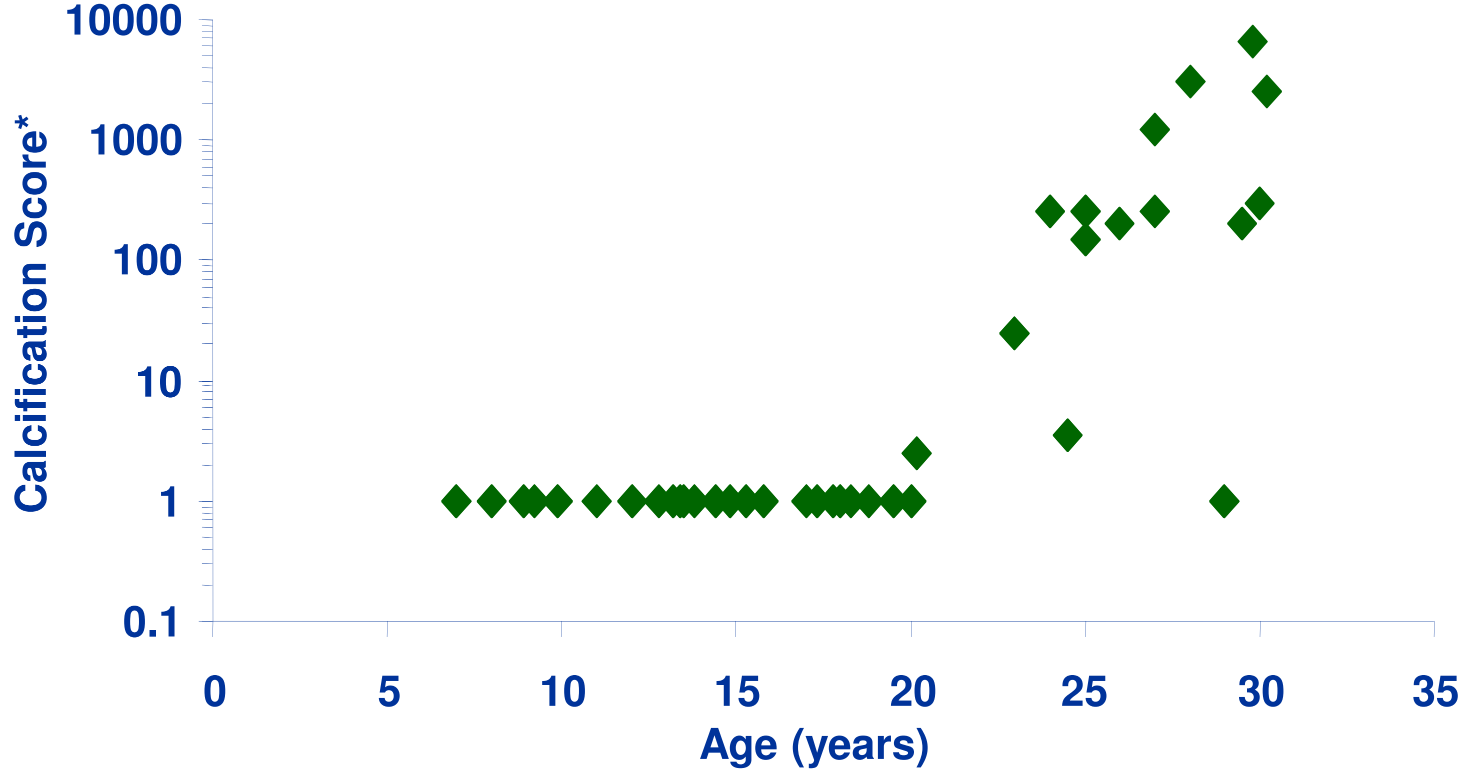


London GM (submitted)

Clinical Characteristics

	Controls (n=59)	ESRD (n=121)	P-value
Age (yrs)	48±13	51±15	NS
Weight (kg)	76±15	64±13	<0.0001
Height (m)	1.70±0.11	1.64±0.11	<0.001
Systolic BP (mmHg)	144±21	152±30	0.020
Diastolic BP (mm Hg)	86±14	83±15	NS
Mean BP (mm Hg)	105±15	106±18	NS
Pulse Pressure (mm Hg)	58±15	68±24	<0.0001

Coronary Artery Calcification in Young Dialysis Patients



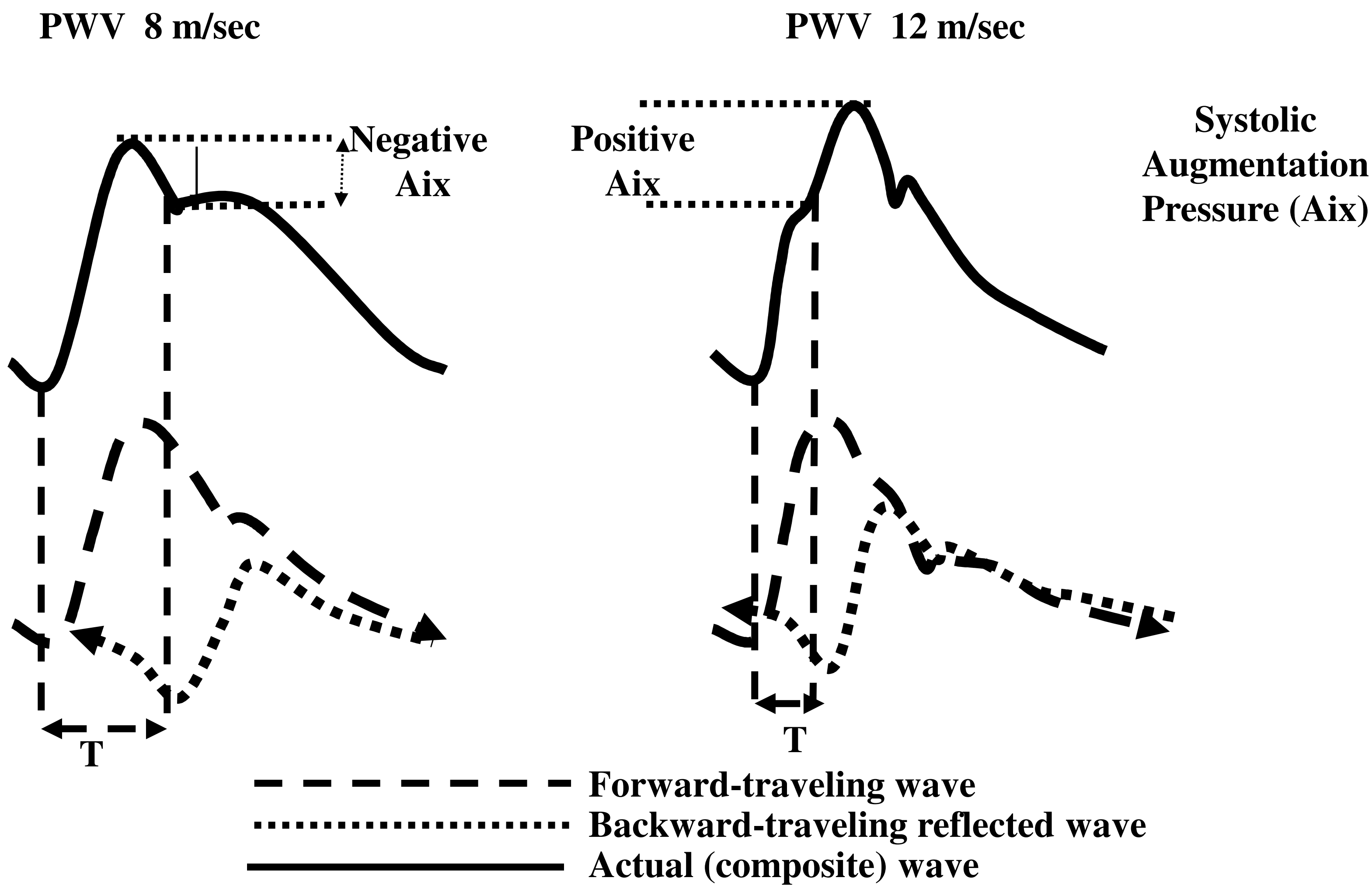
N=39

*Determined by EBT.

Goodman WG et al. *N Engl J Med*. 2000;342:1478-1483.

Calcification scores nearly doubled in a majority of patients with positive initial scan when rescanned at 20 months

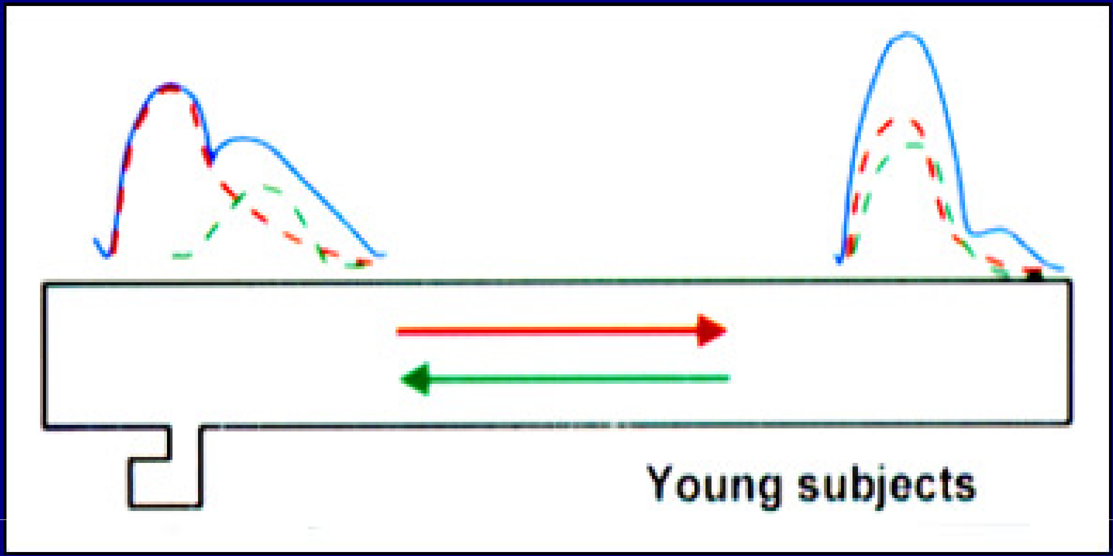
Effect of arterial stiffness on timing of forward and reflected Waves

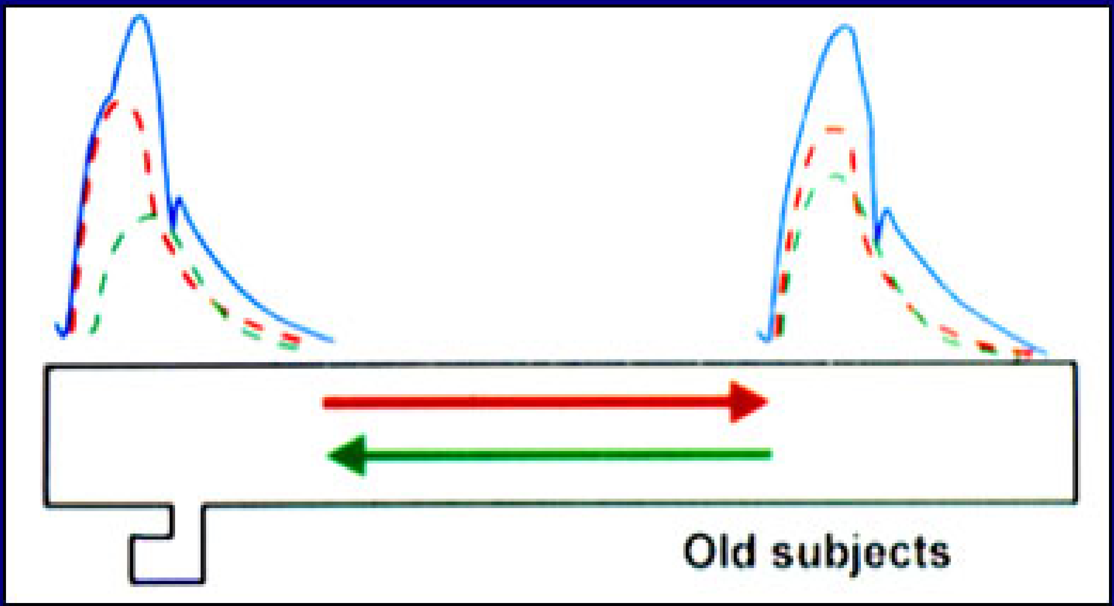


T - traveling time of pressure wave to reflecting sites and back

.

Pressure wave analysis





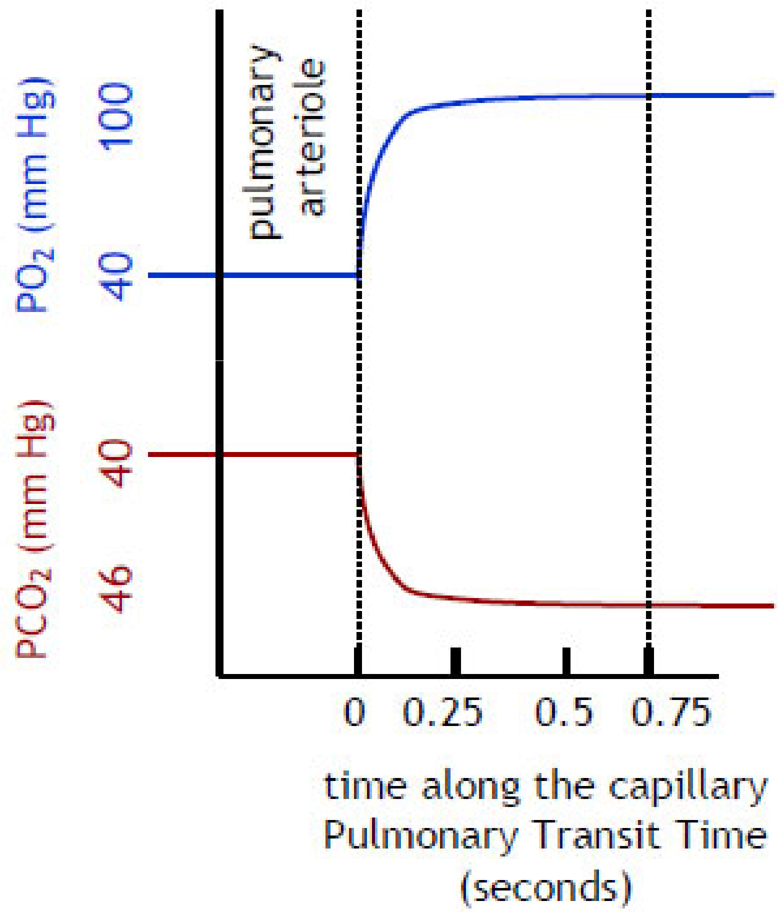
measured pressure wave

forward/incident pressure wave

reflected pressure wave

pulse wave velocity

GAS EXCHANGE ACROSS THE PULMONARY CAPILLARY
Is Complete Within ¼ Second



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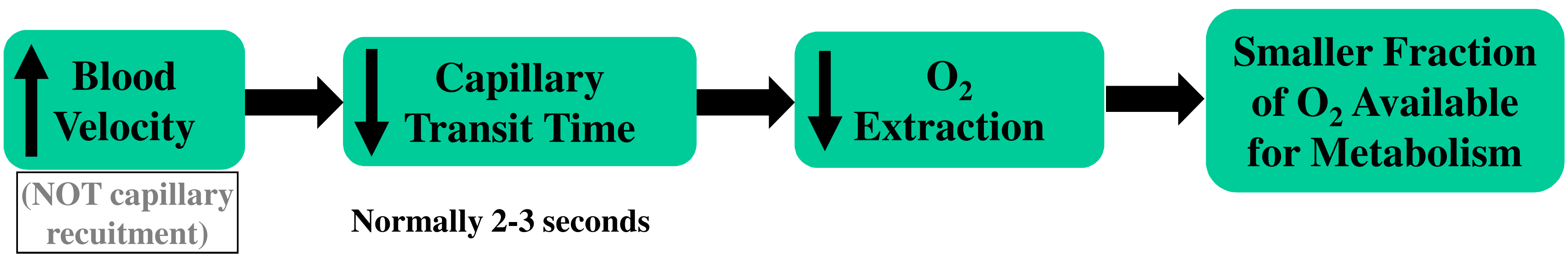
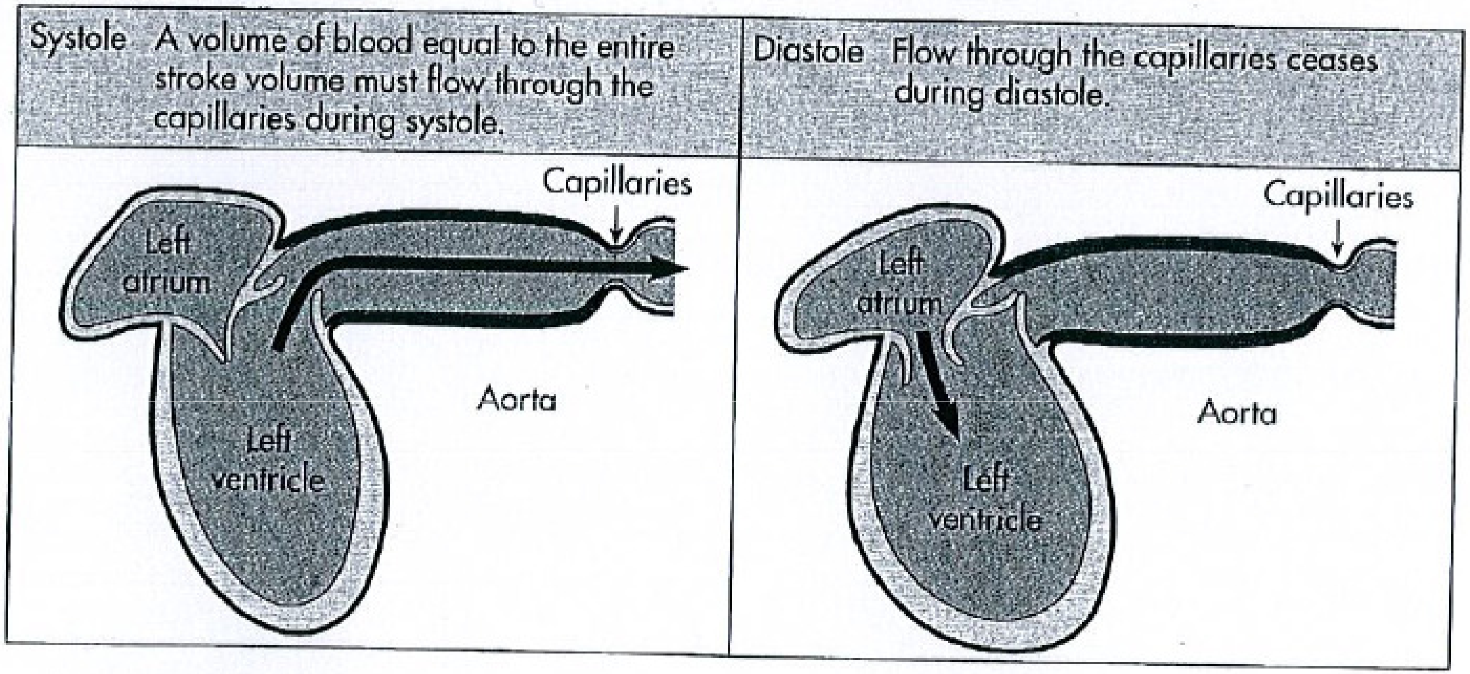
Oxygen Limitation Model

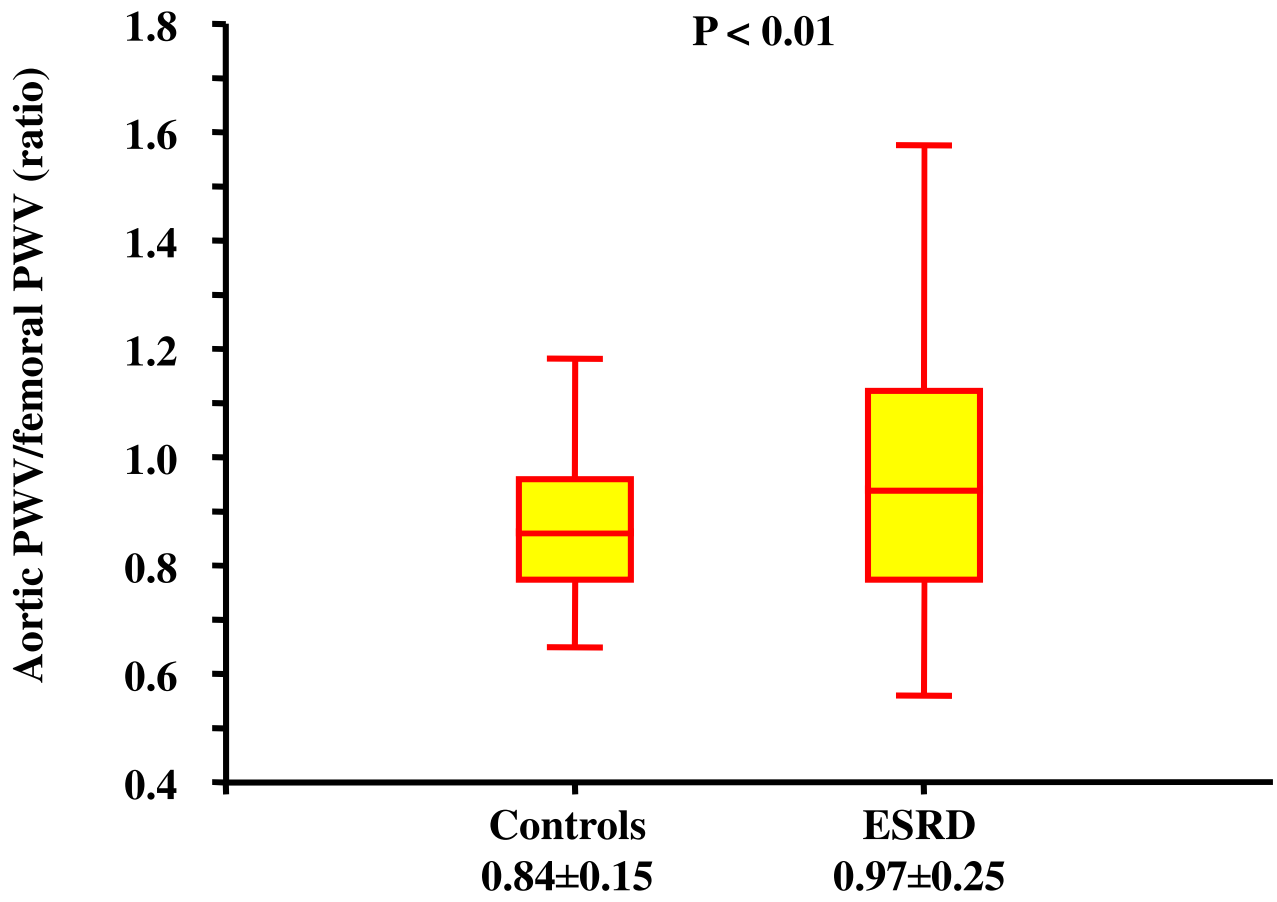


Rigid arteries

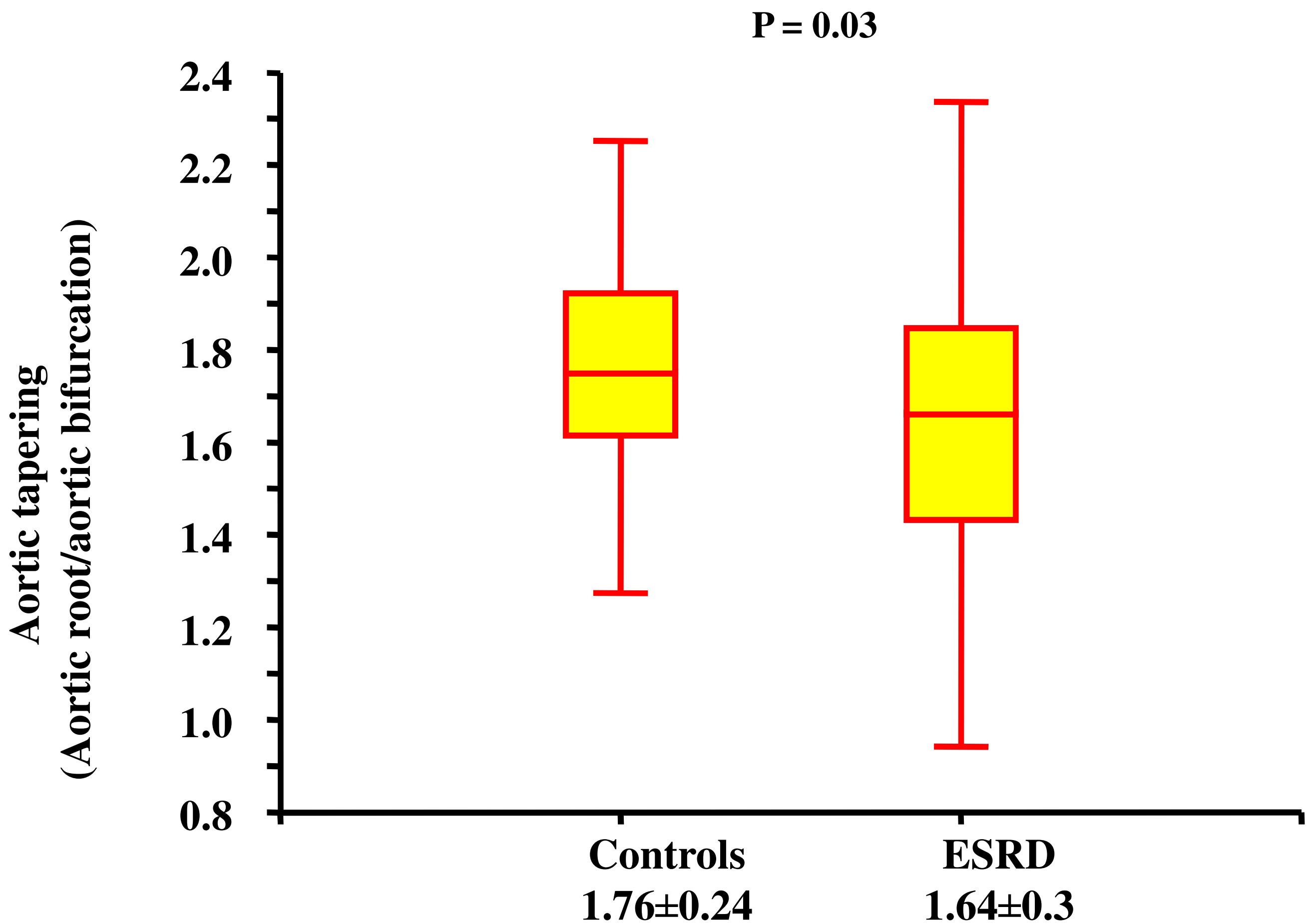


C, When the arteries are rigid, virtually none of the stroke volume can be stored in the arteries.

D, Rigid arteries cannot recoil appreciably during diastole.



P < 0.01
Aortic PWV/femoral PWV (ratio)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
Controls
0.84±0.15
ESRD
0.97±0.25



P = 0.03
Aortic tapering
(Aortic root/aortic bifurcation)
2.4
2.2
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ESRD
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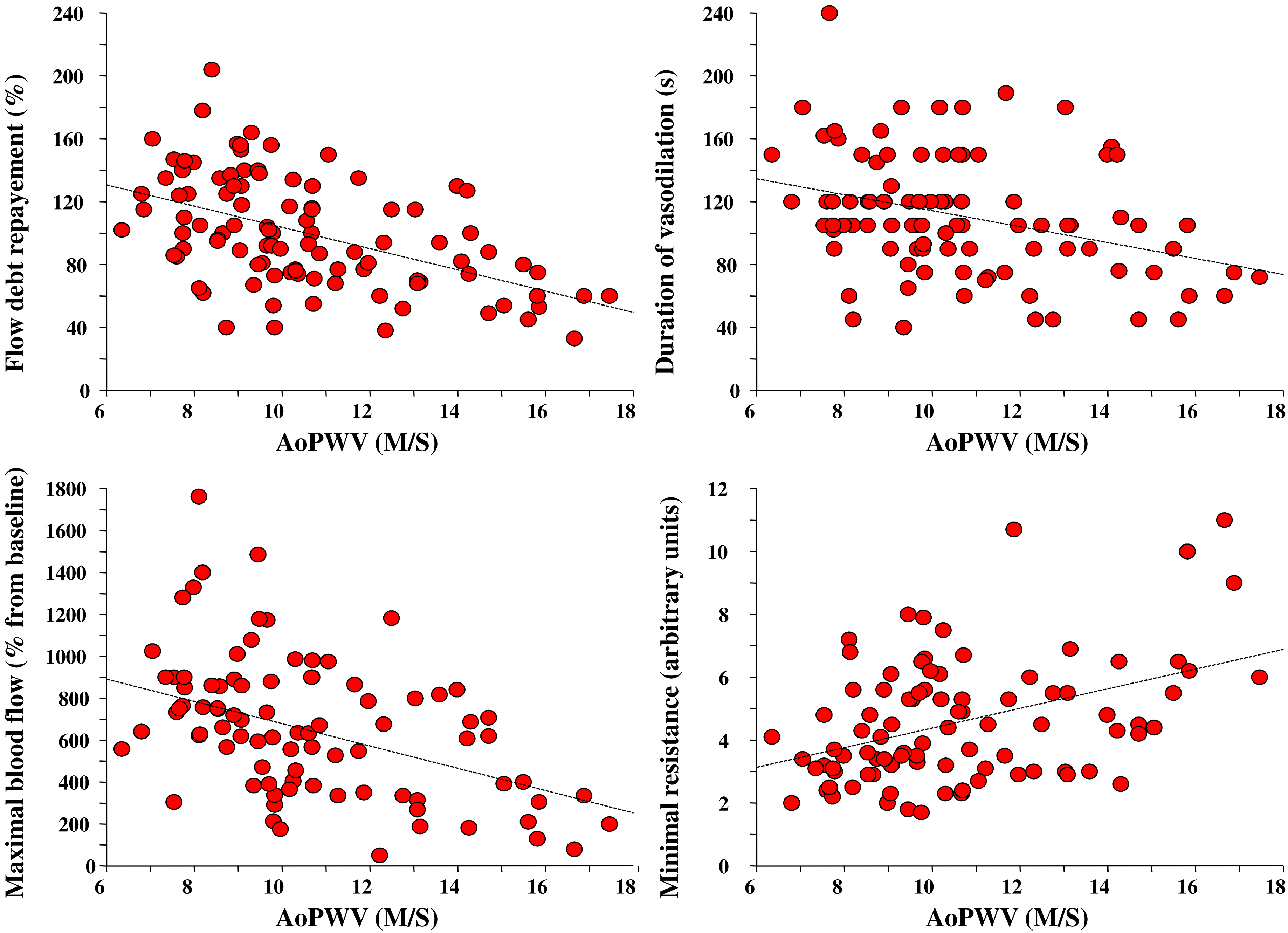
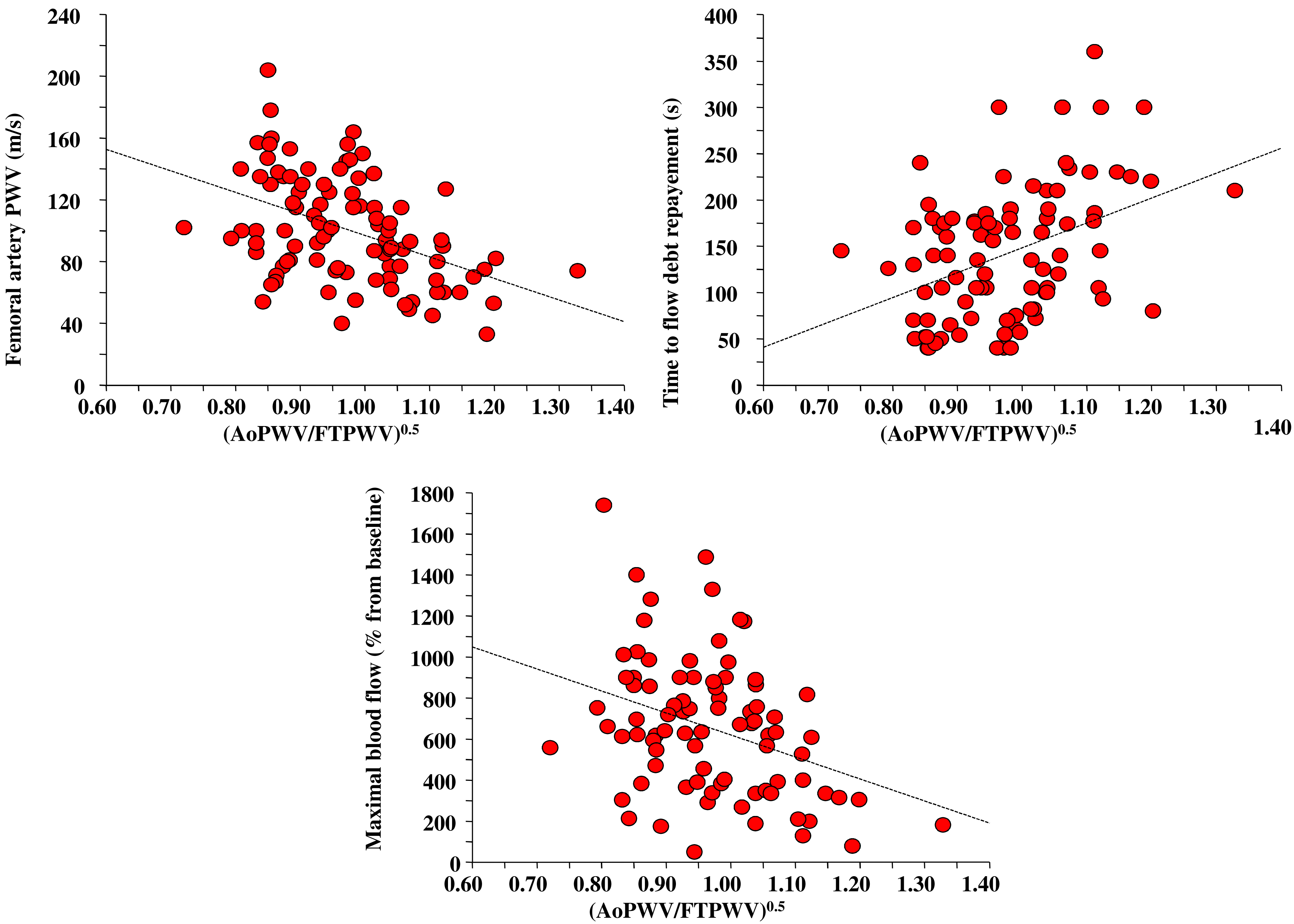
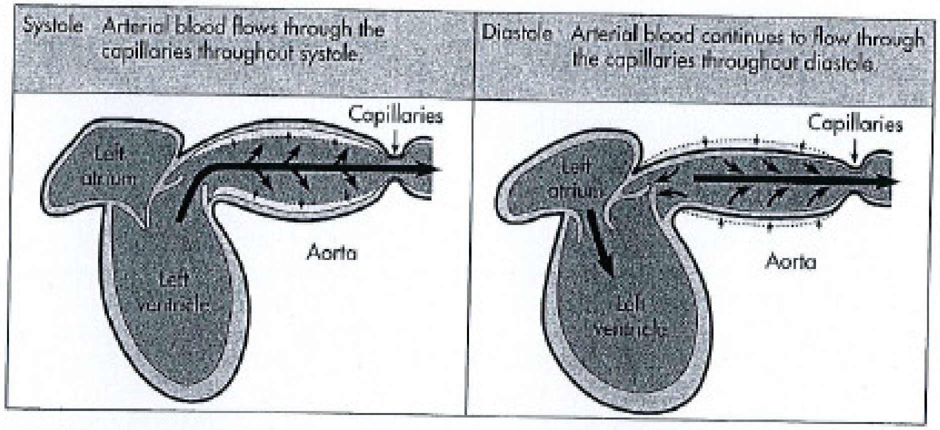


240
200
160
120
80
40
0
Flow debt repayement (%)
6
8
10
12
14
16
18
AoPWV (M/S)
240
200
160
120
80
40
0
Duration of vasodilation (s)
6
8
10
12
14
16
18
AoPWV (M/S)
1800
1600
1400
1200
1000
800
600
400
200
0
Maximal blood flow (% from baseline)
6
8
10
12
14
16
18
AoPWV (M/S)
12
10
8
6
4
2
0
Minimal resistance (arbitrary units)
6
8
10
12
14
16
18
AoPWV (M/S)



Femoral artery PWV (m/s)
240
200
160
120
80
40
0
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
1.40
(AoPWV/FTPWV)0.5
Time to flow debt repayement (s)
400
350
300
250
200
150
100
50
0
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
1.40
(AoPWV/FTPWV)0.5
Maximal blood flow (% from baseline)
1800
1600
1400
1200
1000
800
600
400
200
0
0.60
0.70
0.80
0.90
1.00
1.10
1.20
1.30
1.40
(AoPWV/FTPWV)0.5

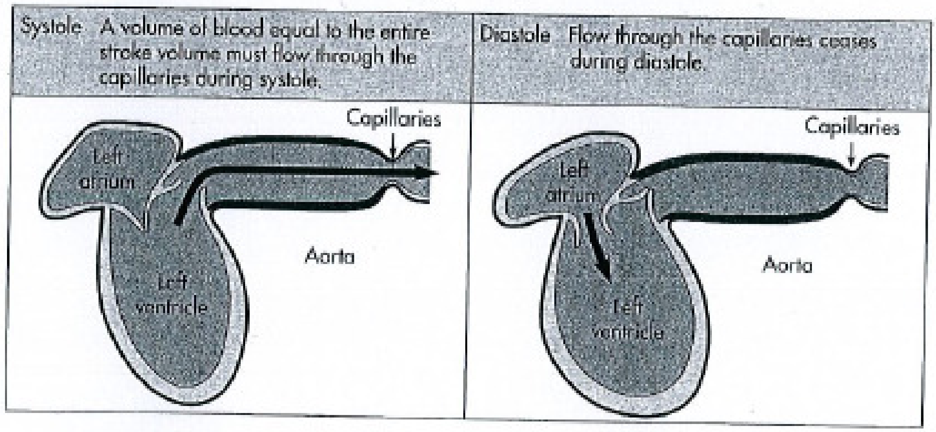
Compliant arteries



A, When the arteries are normally compliant, a substantial fraction of the stroke volume is stored in the arteries during ventricular systole. The arterial walls are stretched.

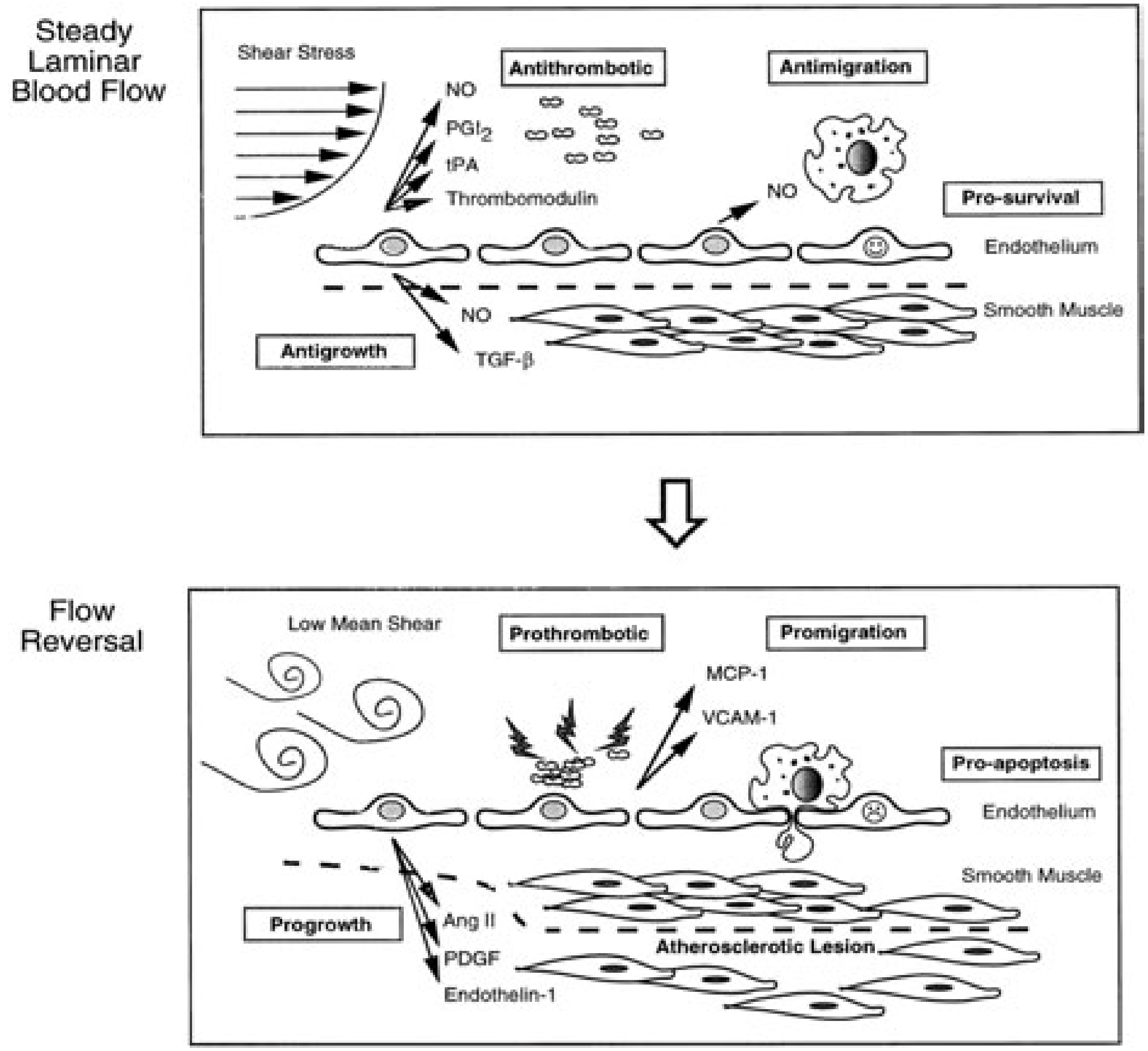
B, During ventricular diastole the previously stretched arteries recoil. The volume of blood that is displaced by the recoil furnishes continuous capillary flow throughout diastole.

Rigid arteries



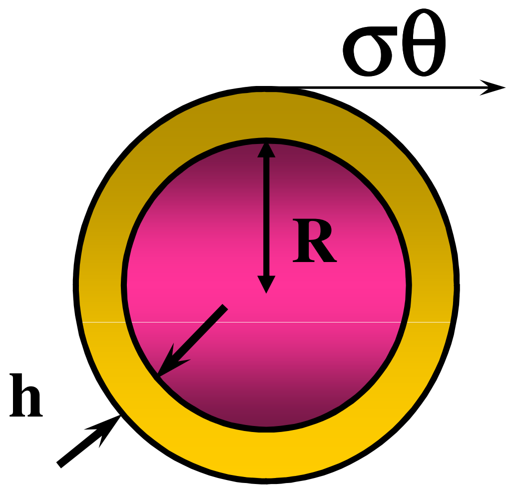
C, When the arteries are rigid, virtually none of the stroke volume can be stored in the arteries.

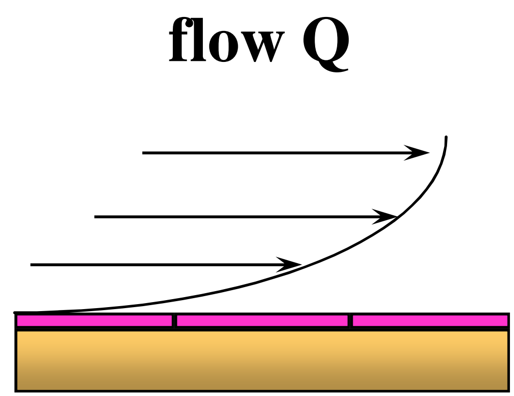
D, Rigid arteries cannot recoil appreciably during diastole.



Traub, O. et al. Arterioscler Thromb Vasc Biol 1998;18:677-685

Mechanical stresses in the blood vessel



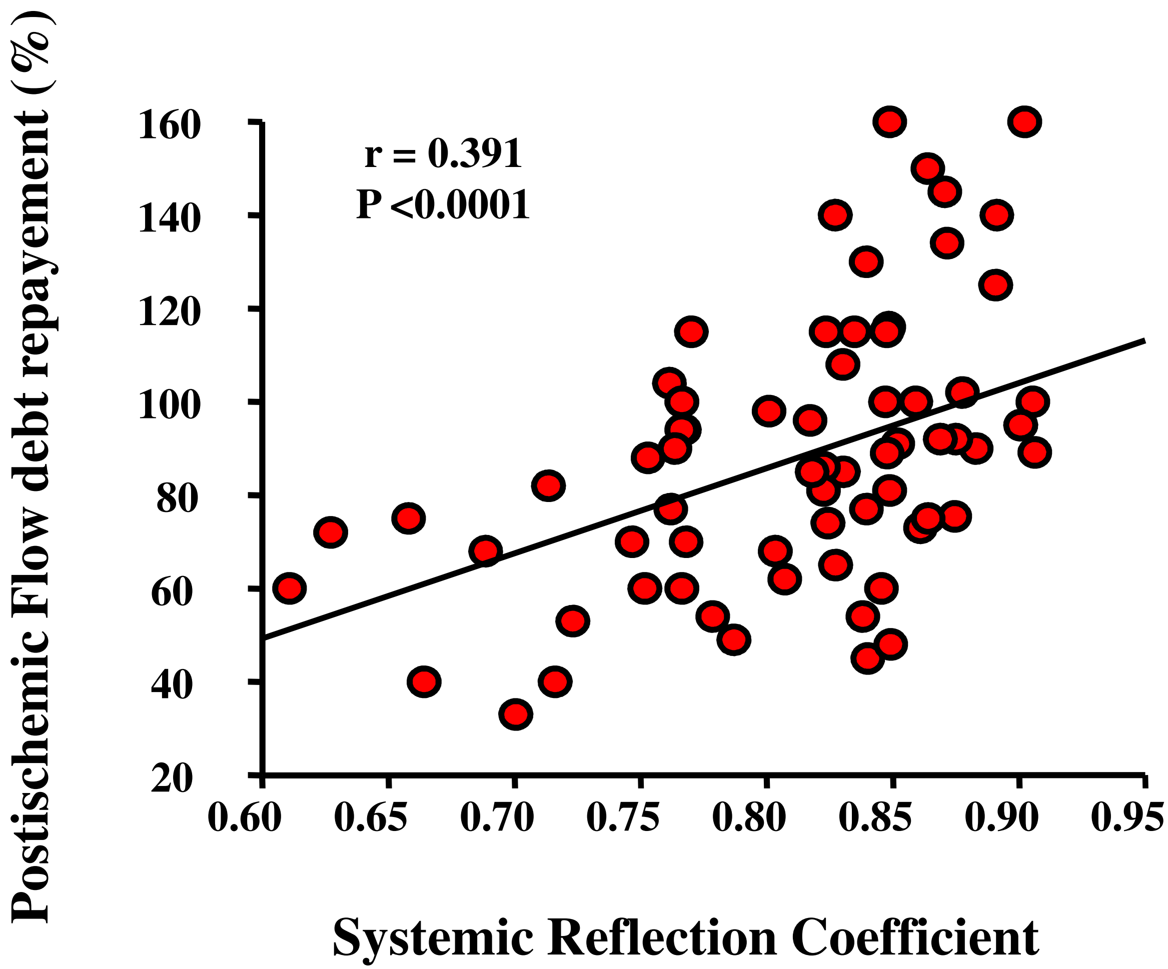


circumferential wall stress

$$sq = \frac{P \text{ x } R}{h}$$

fluid shear stress

$$t = \frac{4 \mu Q}{p R \; 3}$$



London GM (submitted)