Blood Vessel Dysfunction & Osteoporosis

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Neurovascular Instability

Blood Vessel Anatomy & Function

Large Vessel Dysfunction

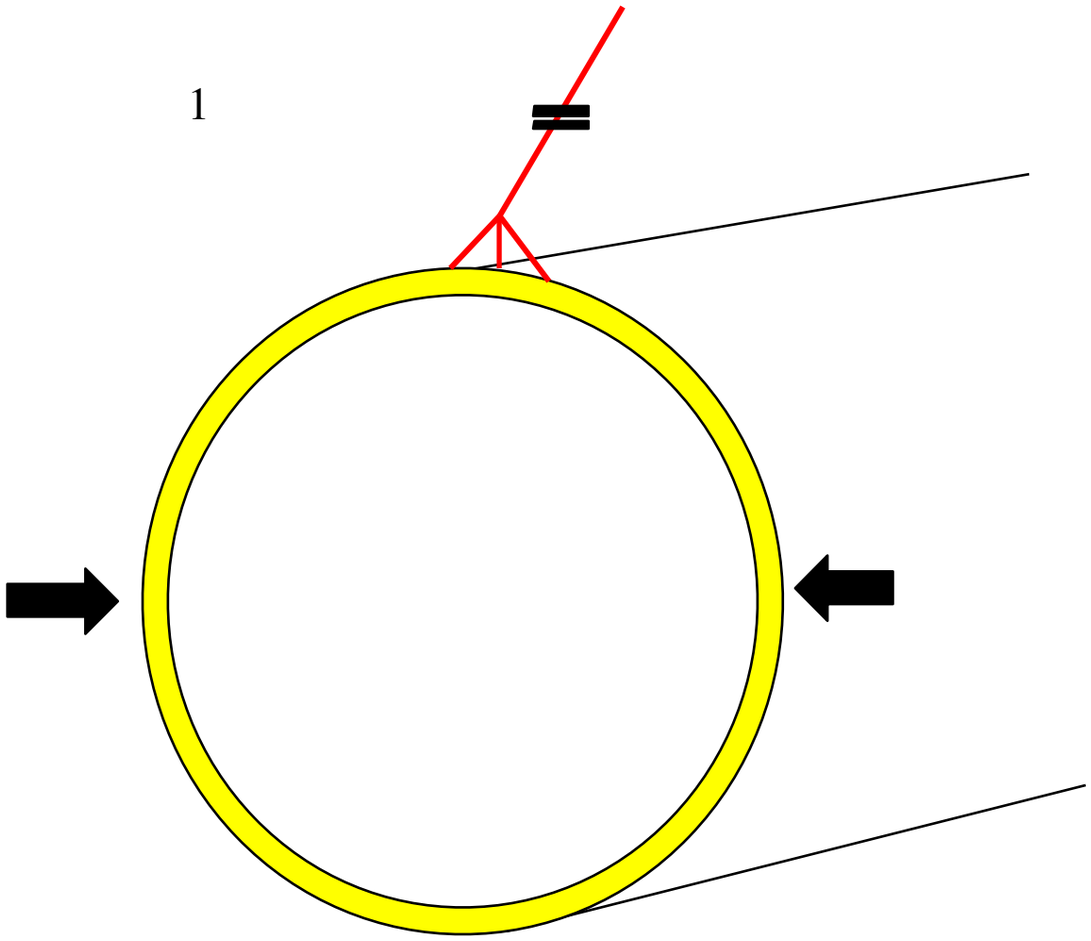
Resistance Vessel Dysfunction

Capillary – Endothelial Dysfunction

Osteovascular Instability

Kyphosis induced VBI

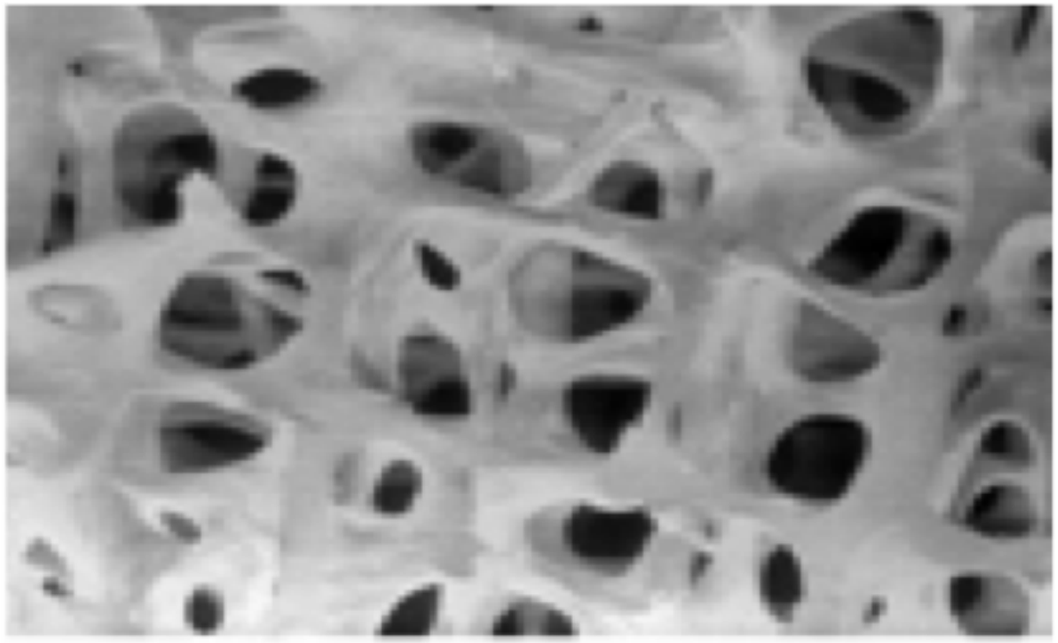
1

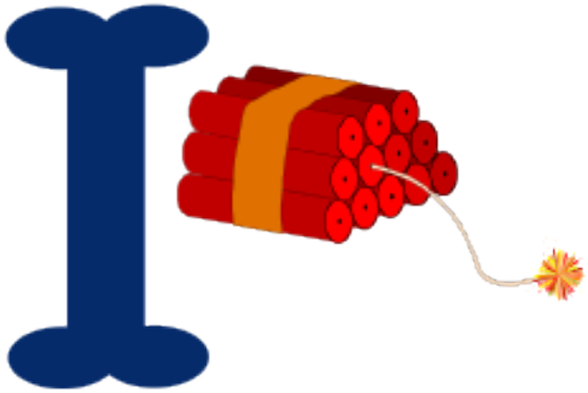


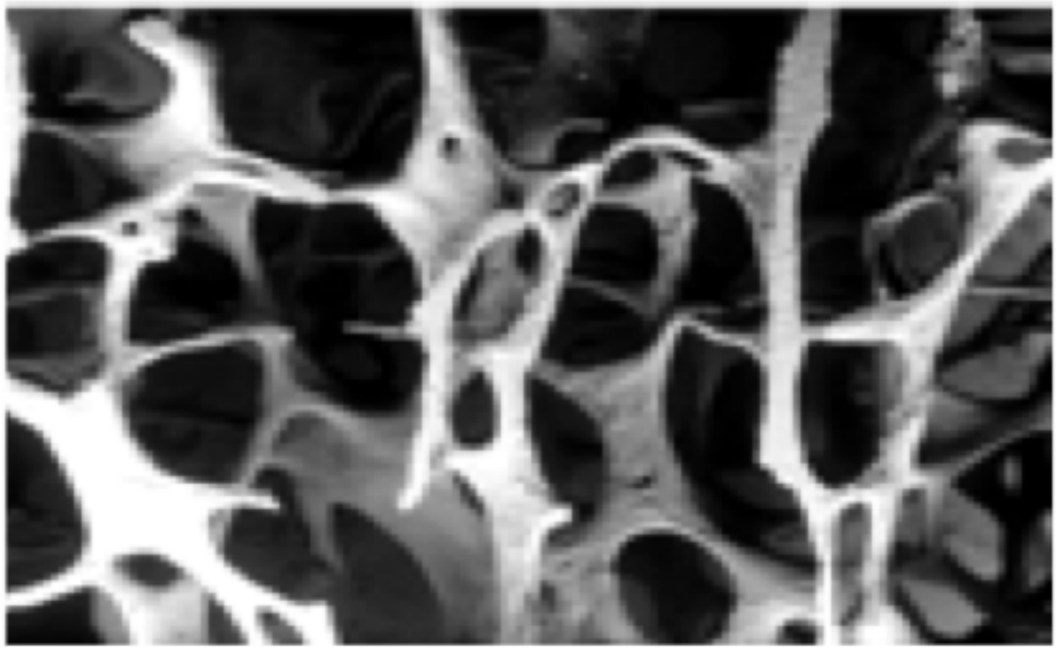
2 **Brain**
Muscle
Skin

3 **Postural Tone & Falls**
Fatigue

Architectural Integrity V Applied Force

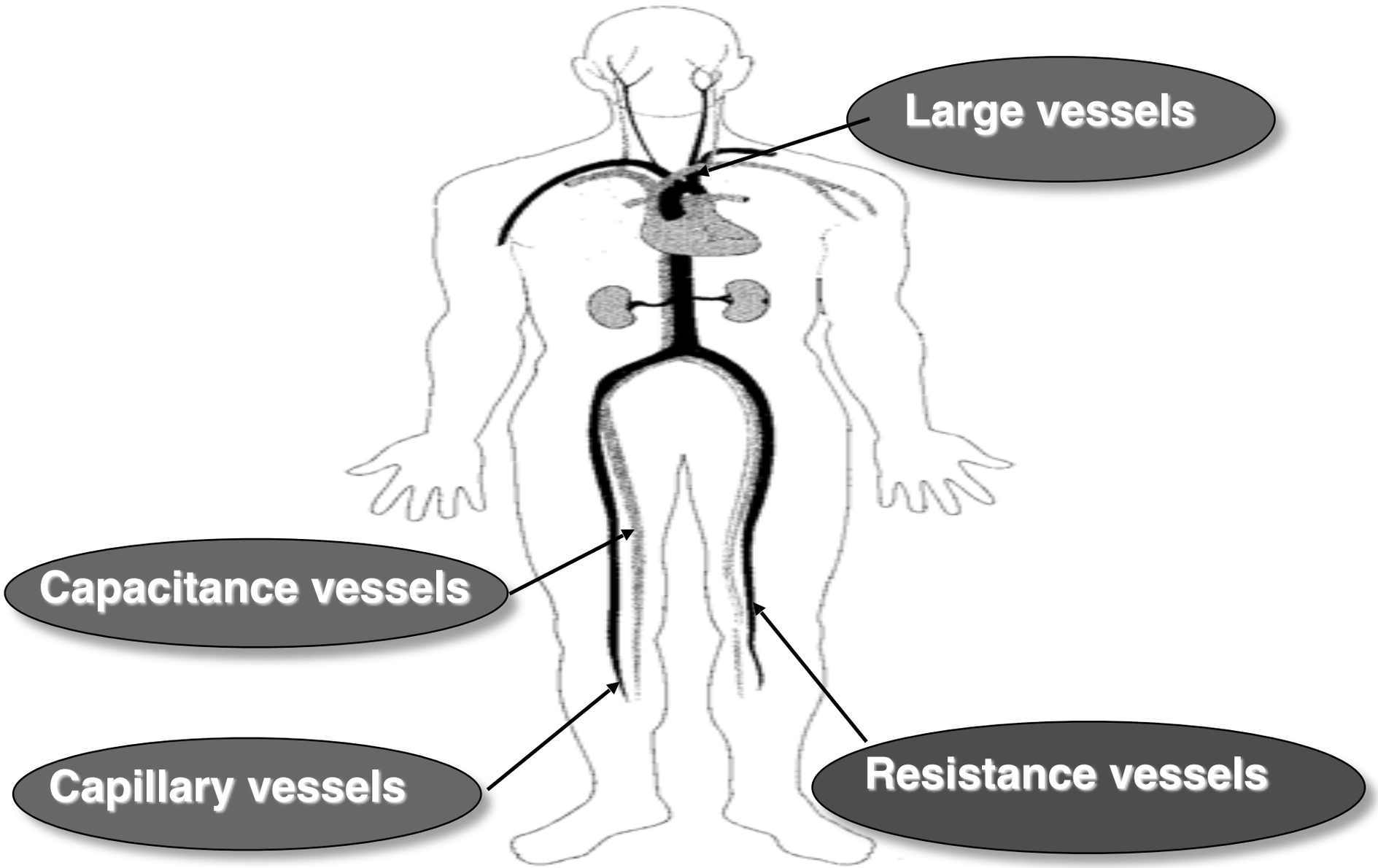




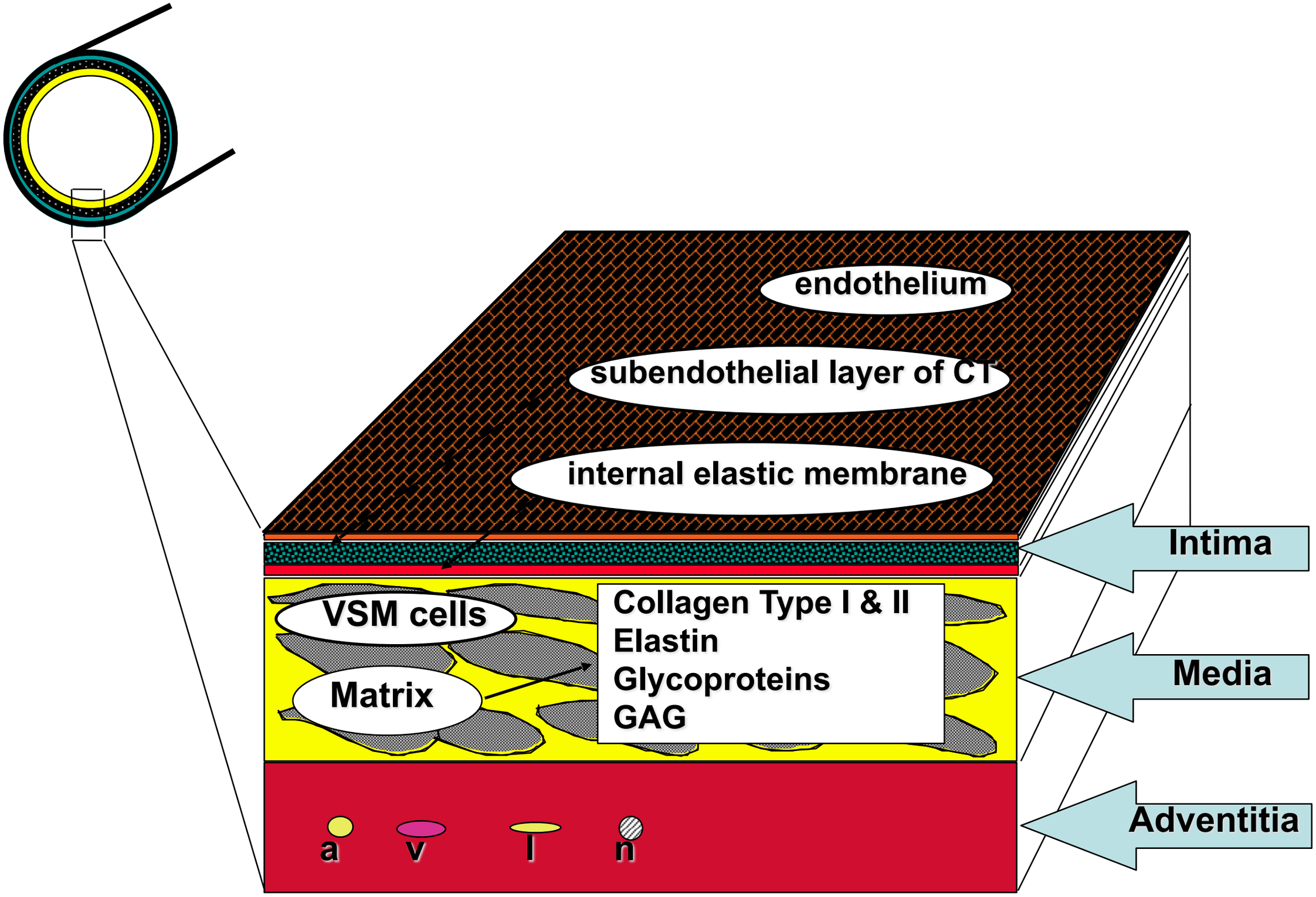


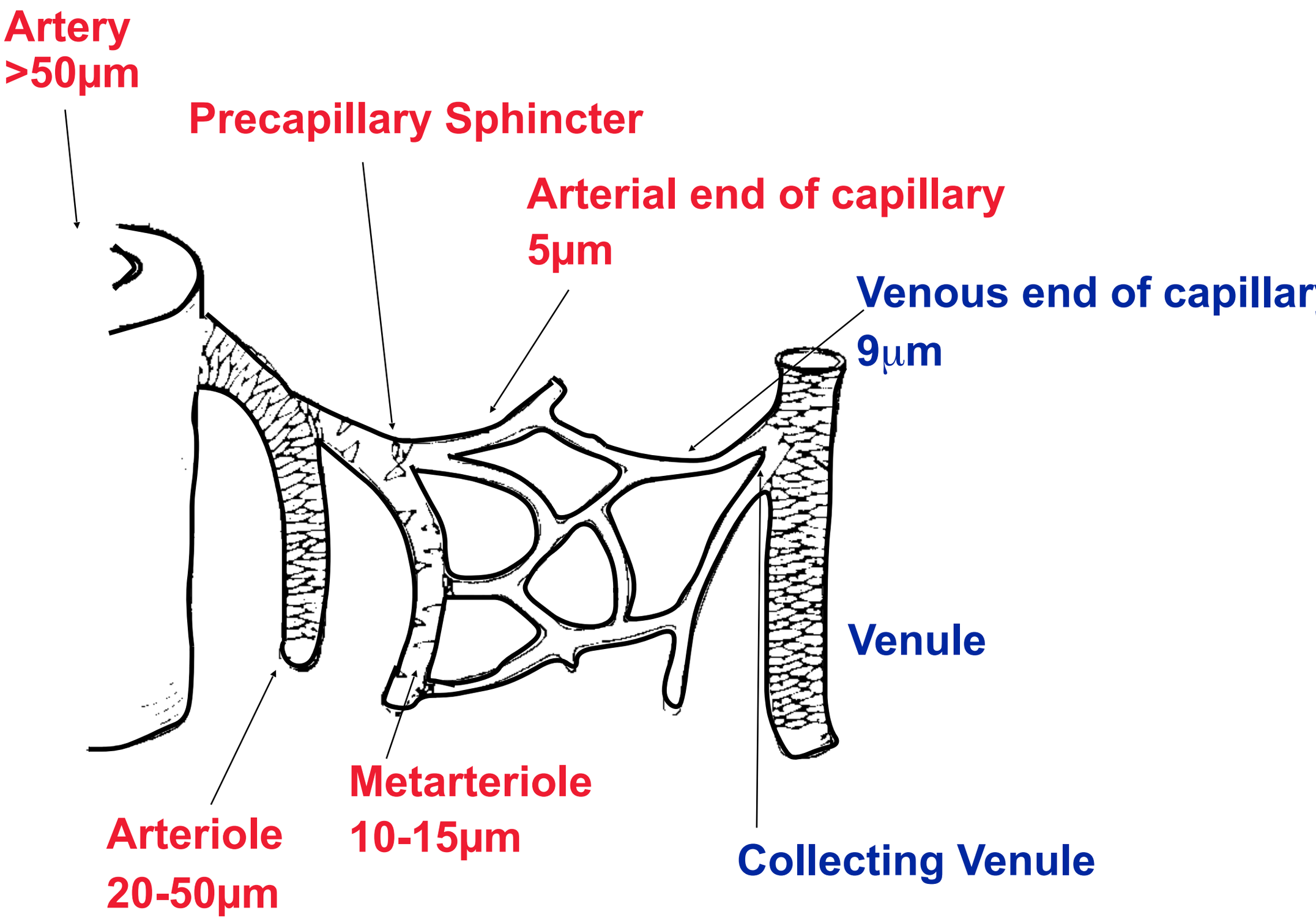
diag	Total	Pcnt	Avg LOS	Inpat Bed	Daycases	Avg Age
Z5188 Other specified medical	1630	16.40	2.6000	13	1625	56.9454
R074 Chest pain, unspecified	401	4.04	4.1144	1510	34	54.0549
R51 Headache	315	3.17	3.5361	587	149	41.0476
E831 Disorders of iron metabo	304	3.06	1.5000	3	302	54.9737
J22 Unspecified acute lower	274	2.76	7.2780	1885	15	61.1131
R55 Syncope and collapse	200	2.01	4.6512	400	114	54.0550
L0311 Cellulitis of lower limb	186	1.87	9.8696	227	163	65.8656
J441 Chronic obstructive pulm	168	1.69	8.3750	1407	0	70.7679
R42 Dizziness and giddiness	157	1.58	4.2745	218	106	56.7070
K529 Noninfective gastroenter	151	1.52	6.1944	446	79	50.1391
I500 Congestive heart failure	148	1.49	9.9931	1439	4	75.6149
R101 Pain localised to upper	139	1.40	5.0938	163	107	45.3165
N390 Urinary tract infection,	126	1.27	7.3577	905	3	58.8571
J189 Pneumonia, unspecified	126	1.27	12.3162	1441	9	64.1349
R11 Nausea and vomiting	108	1.09	4.8261	222	62	53.4074
I802 Phlebitis and thrombophl	104	1.05	3.7333	56	89	58.9904
R002 Palpitations	99	1.00	3.6250	145	59	49.5758
I48 Atrial fibrillation and	98	0.99	5.8554	486	15	67.4082
K20 Oesophagitis	91	0.92	3.8000	19	86	54.3297
K30 Dyspepsia	90	0.91	2.0000	4	88	48.0778
Selected	4915	49.46	6.4097	11576	3109	56.5583
Total	9937	100.00	7.6367	34961	5359	55.5208

Key Pathophysiological Sites – Blood Vessel Dysfunction

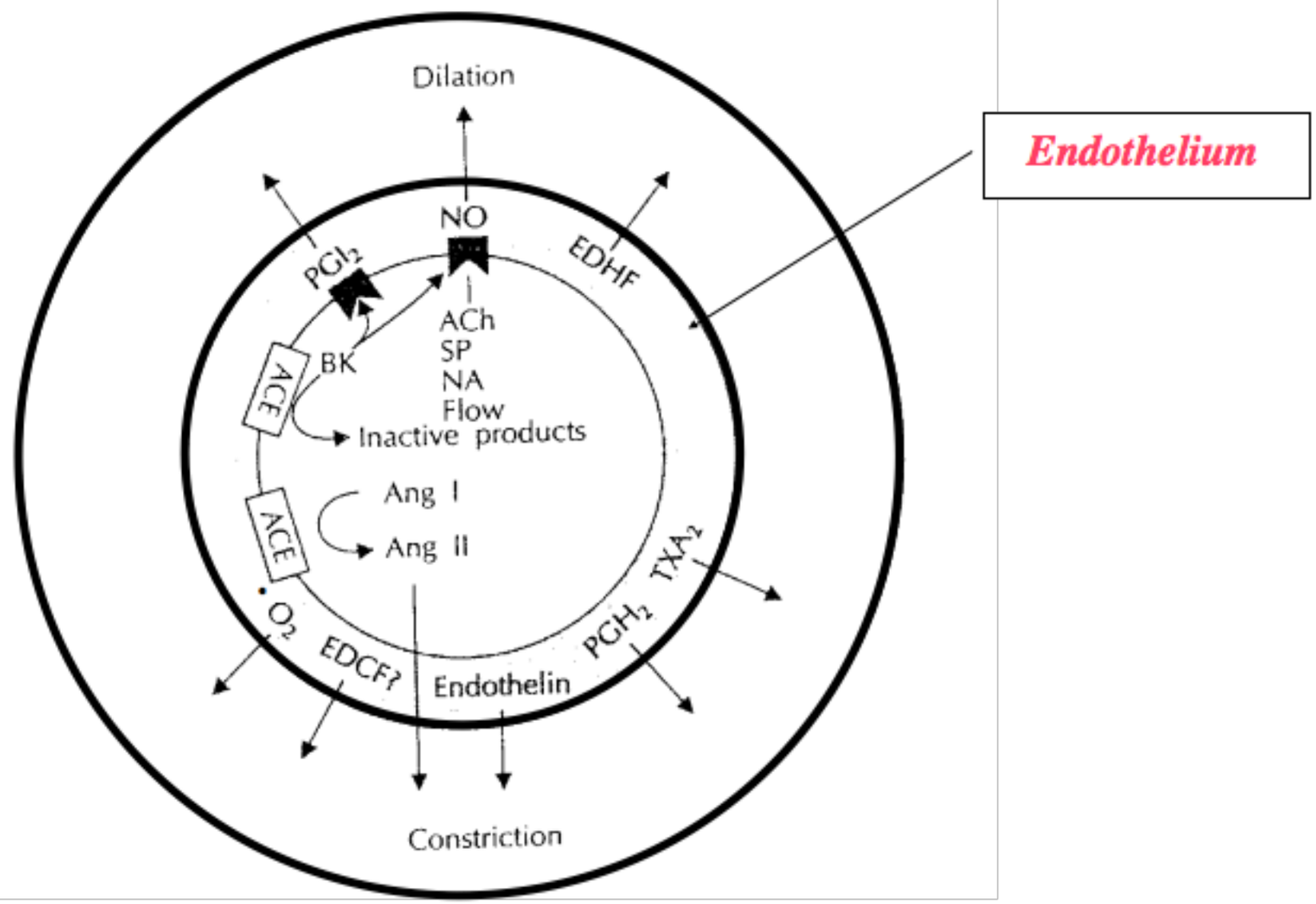


Blood Vessel Anatomy & Function


endothelium
subendothelial layer of CT
internal elastic membrane
Intima
VSM cells
Matrix
Collagen Type I & II
Elastin
Glycoproteins
GAG
Media
a
v
l
n
Adventitia

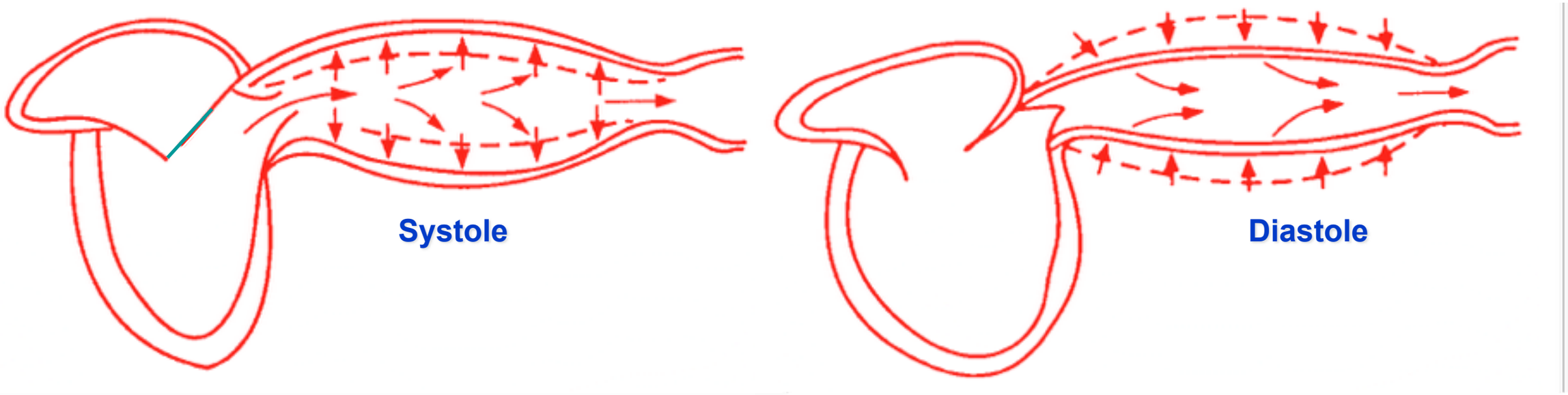


25 mm (1 inch) in the aorta - 8 µm in the capillaries. This is a 3000-fold range. ≤ 0.2mm – resistance vessel


Endothelium
Dilation
NO
PGI2
EDHF
ACh
SP
NA
Flow
BK
ACE
Inactive products
Ang I
Ang II
ACE
TXA2
O2
EDCF?
Endothelin
PGH2
Constriction

Large Vessel Dysfunction

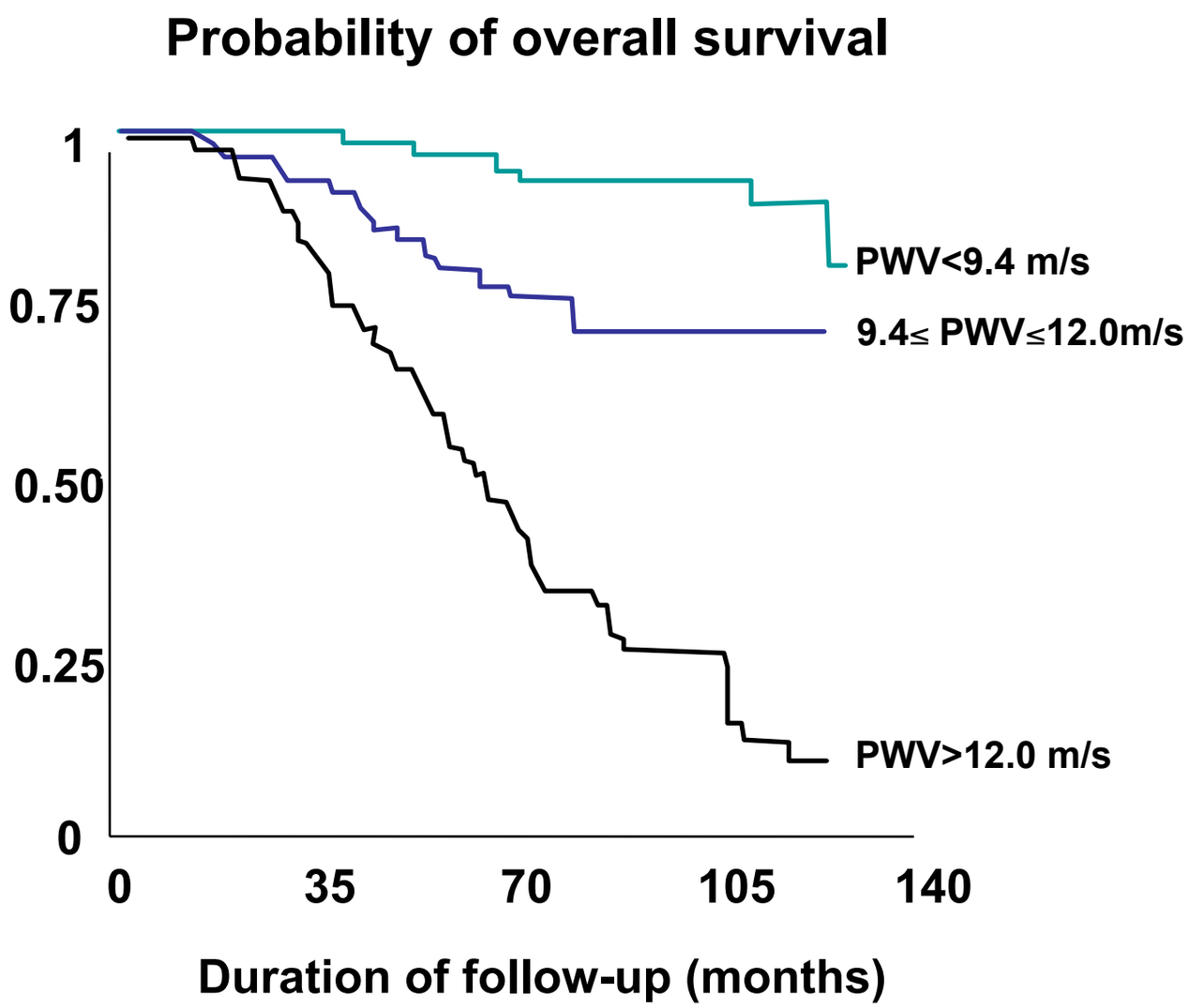
Arterial distensibility

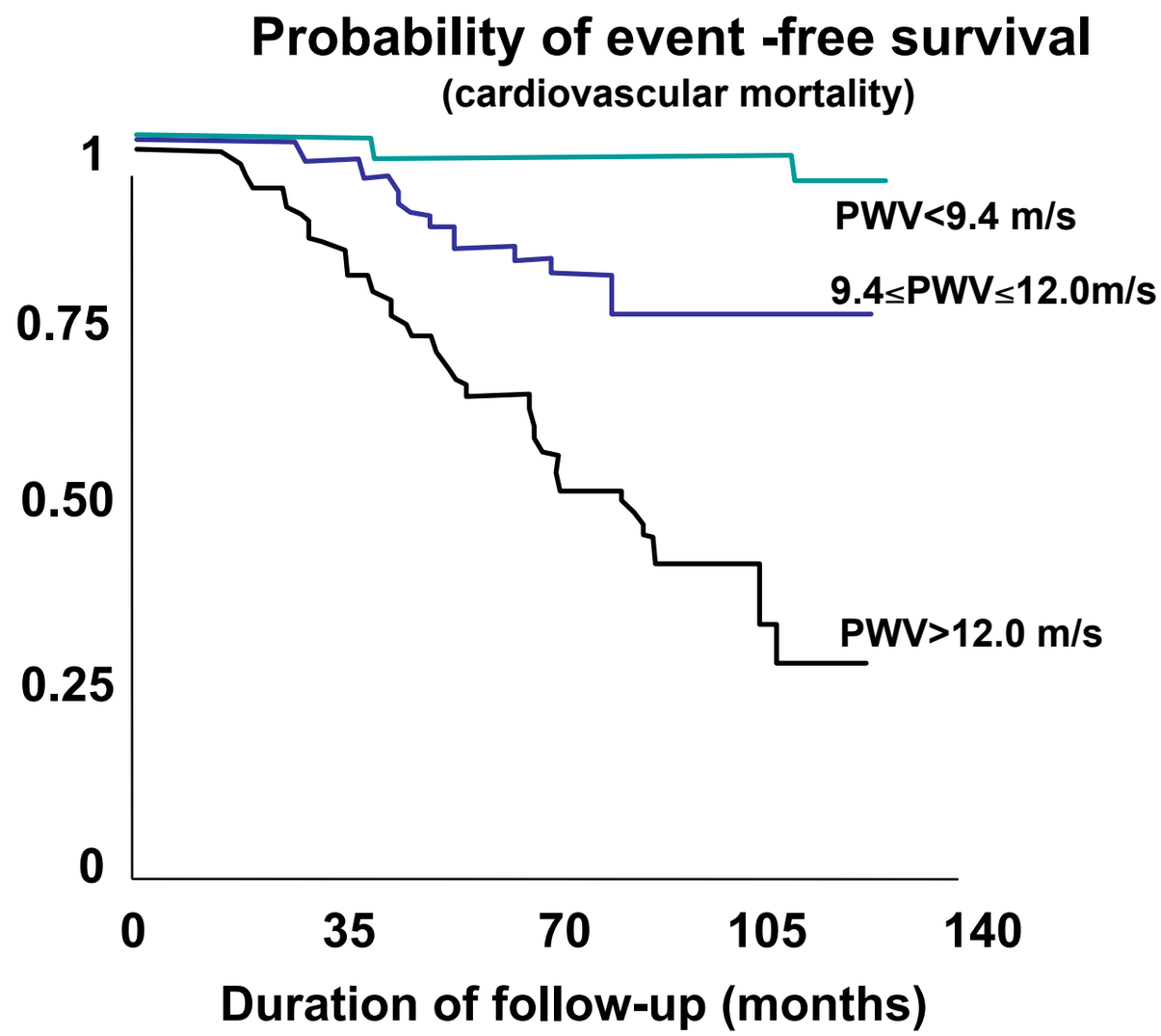


Intermittent cardiac output → Continuous peripheral flow

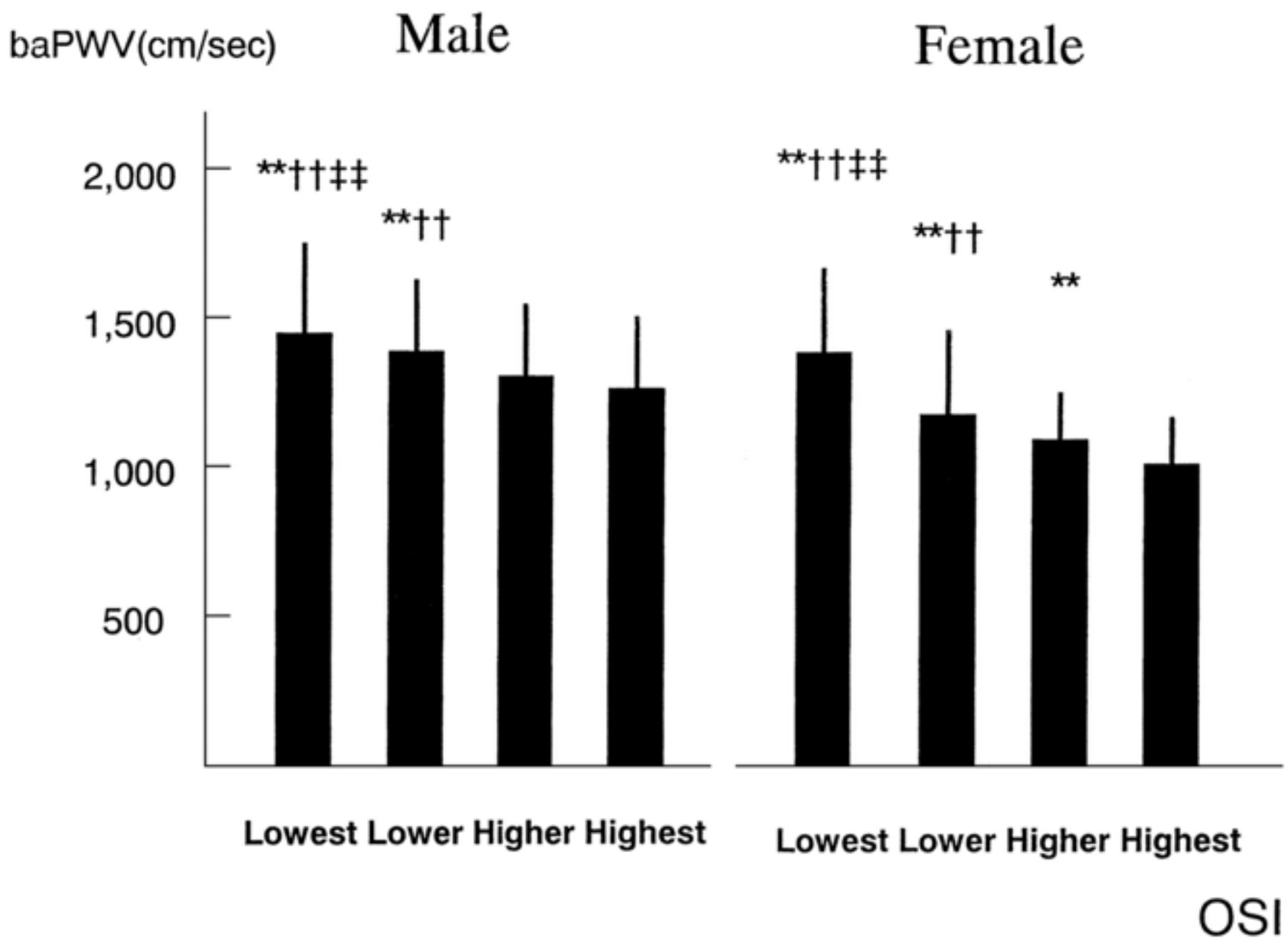
Mean Blood Velocity	**11cm/sec**
Pulse Pressure Wave Velocity	**9m/sec**

PWV - a determinant of mortality ESRD



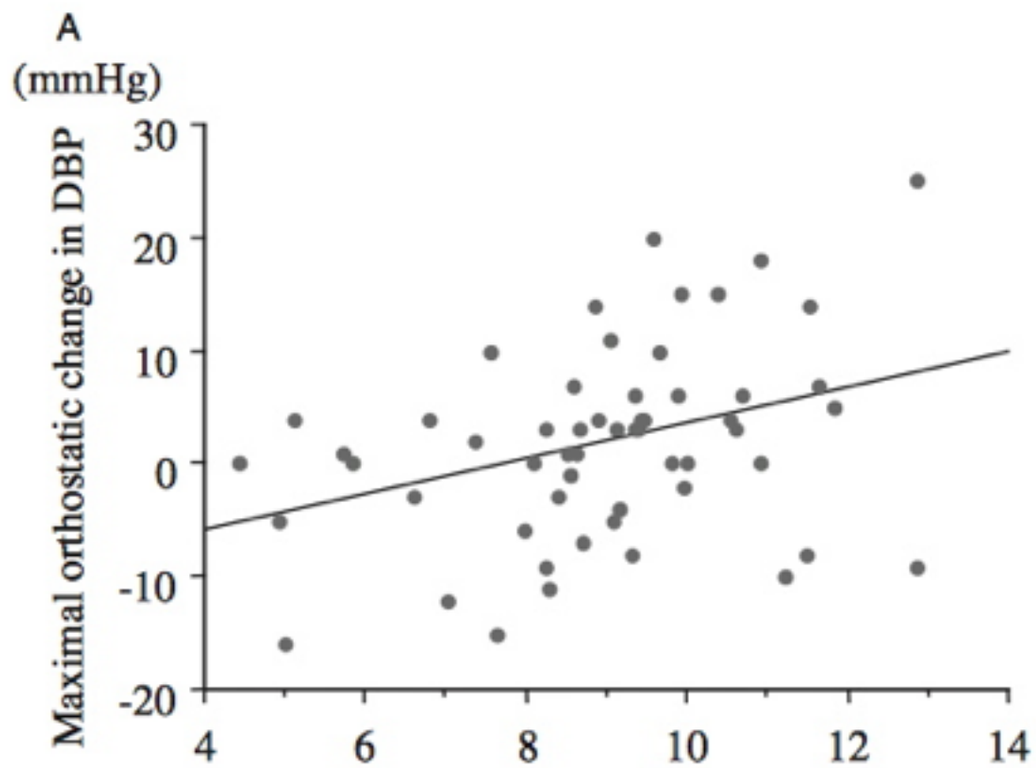


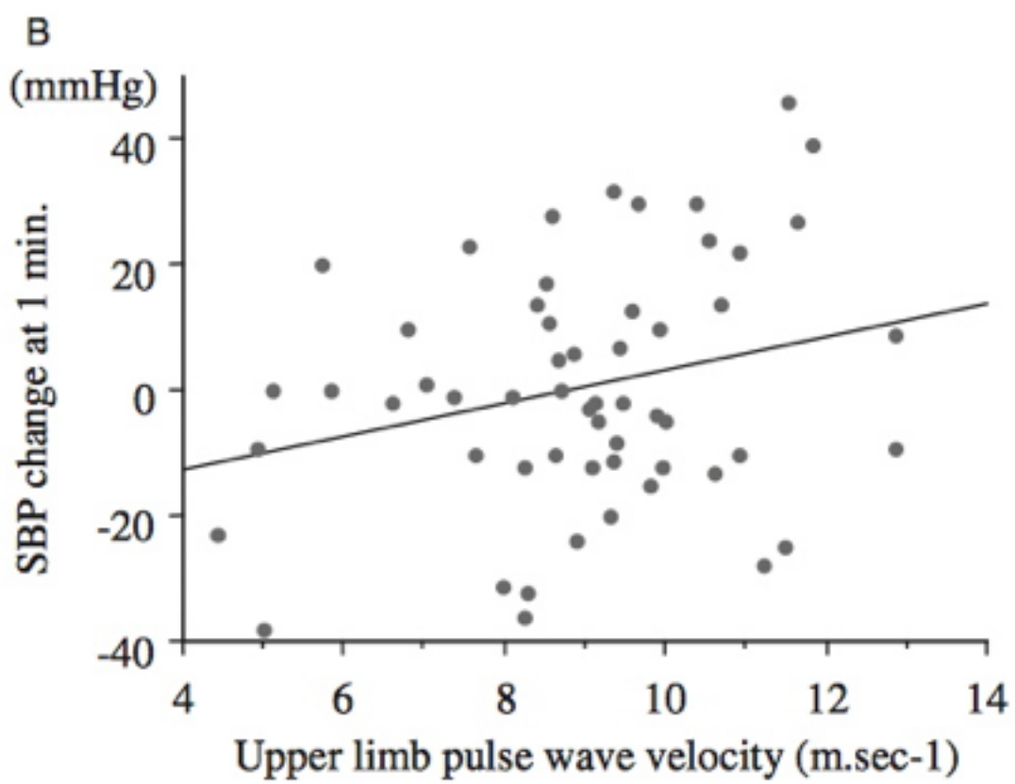
Blacher J, Guérin A, Pannier B, Marchais S, Safar M, London G. *Circulation* 1999; 99: 2434-2439



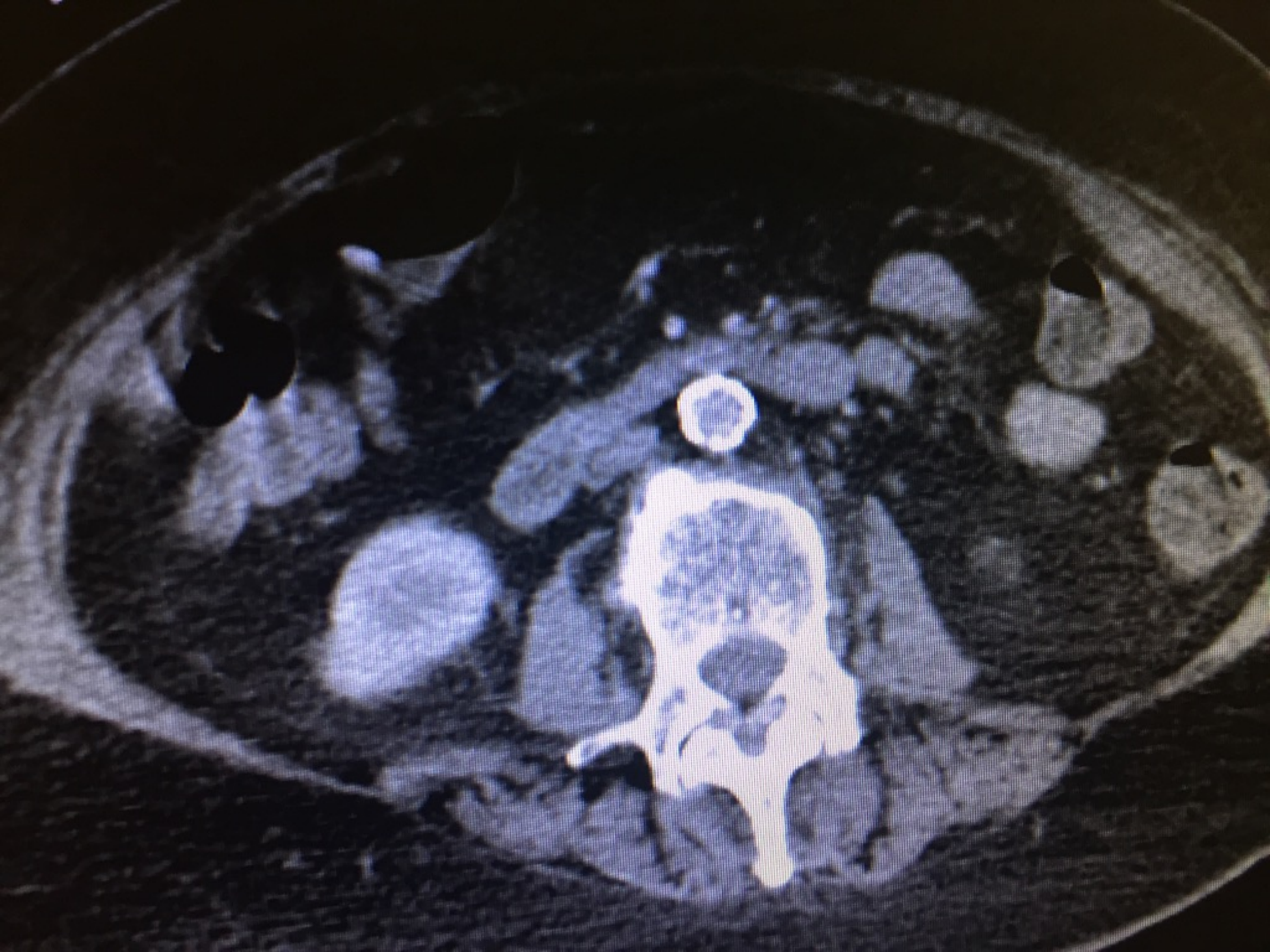
From: Increased Pulse Wave Velocity Associated with Reduced Calcaneal Quantitative Osteo-sono Index: Possible Relationship Between Atherosclerosis and Osteopenia

J Clin Endocrinol Metab. 2003;88(6):2573-2578. doi:10.1210/jc.2002-021511





Jacques Boddaert et al



	Properties	Knockout Mice
Osteoprotegrin (OPG)	TNF super family	Osteopaenia vasc medial calcification
Matrix Gla Protein (MGP)	Circulating extrahepatic **vitamin K**-dependent protein. Medial VSMCs	Medial calcification Neonatal death by aortic rupture
Osteopontin (OPN)	Cytokine and cell attachment protein produced by osteoblasts	Normal
Fetuin-A	potent inhibitor of apatite crystal formation found in VSMC vesicles	Extensive tissue calcification sim to Renal osteodystrophy
Madh6	Intracellular protein mediators	Hypoplastic valves and stiff vessel walls no bone phenotype
Klotho Y	age-suppressor gene	Ageing osteoporosis & medial calcification & atheroma

Large Vessel Dysfunction

↑ PWV

↑ SBP

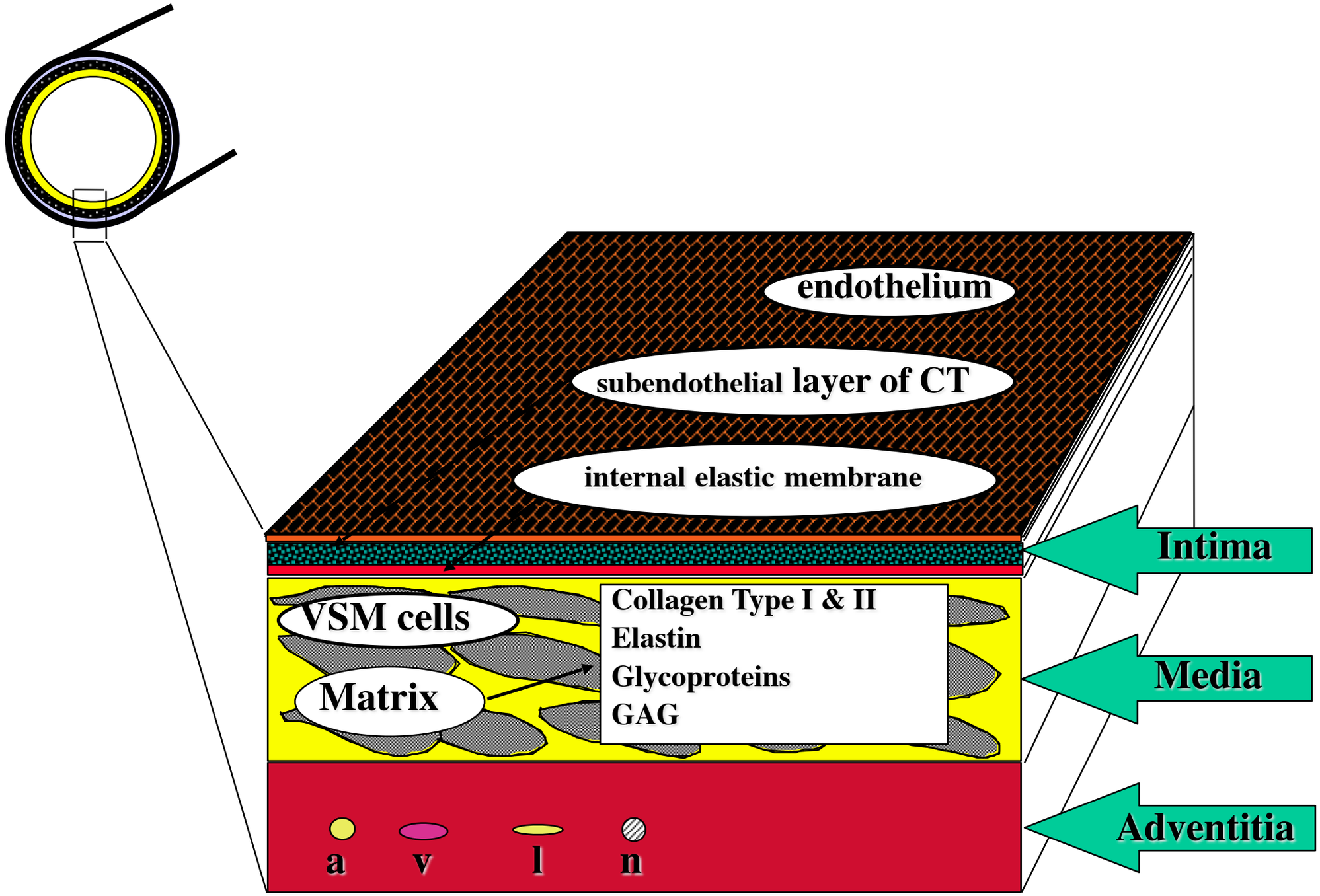
↓DBP

↑ OH

↓BMD

May share a common pathogenic mechanism for OP

Resistance Vessel Dysfunction


endothelium
subendothelial layer of CT
internal elastic membrane
Intima
VSM cells
Matrix
Collagen Type I & II
Elastin
Glycoproteins
GAG
Media
a
v
l
n
Adventitia

Physiological Consequences of Arteriolar Changes in Hypertension

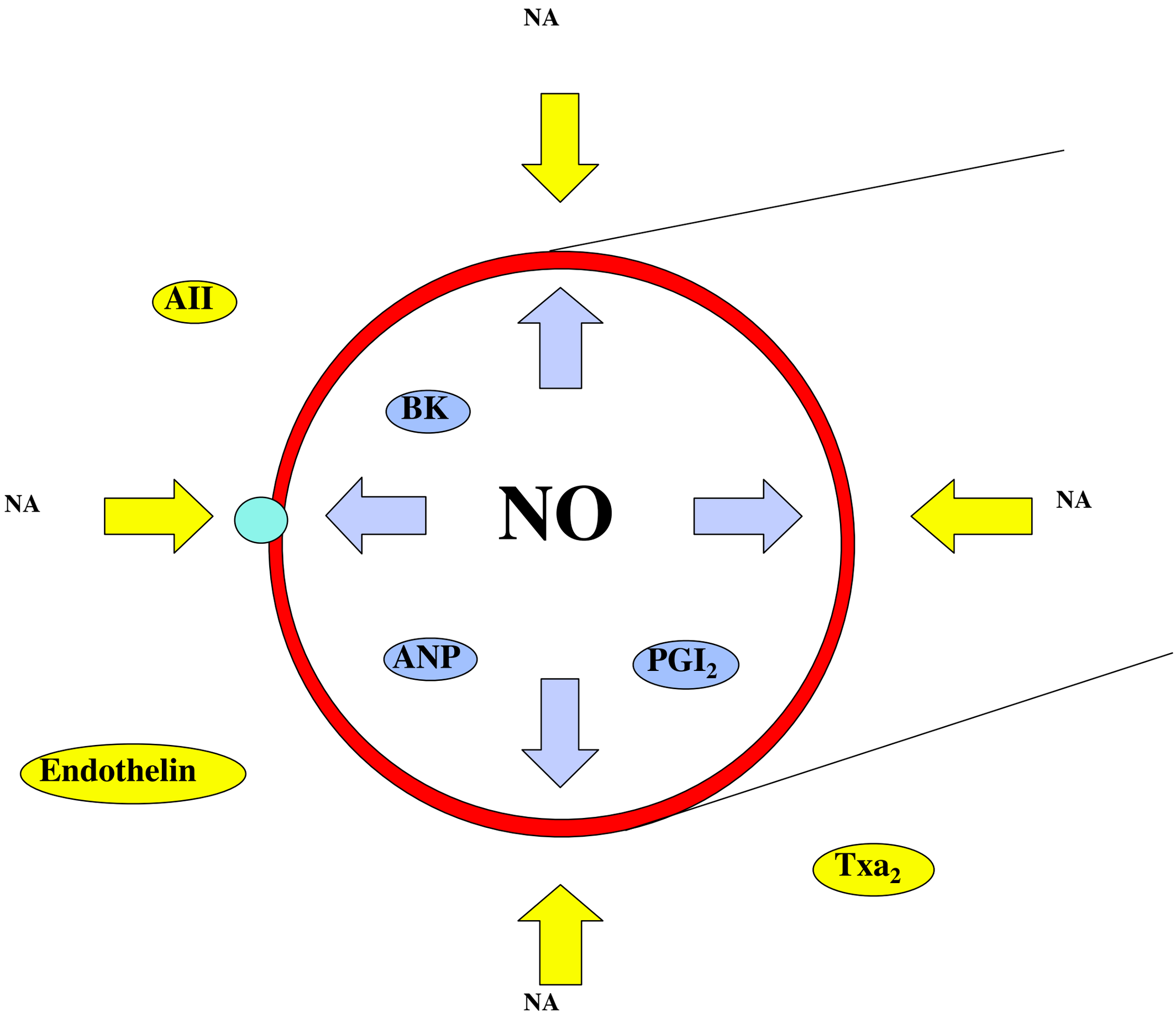
$$R = P / Q$$

$$R = 8\eta L / r^4$$

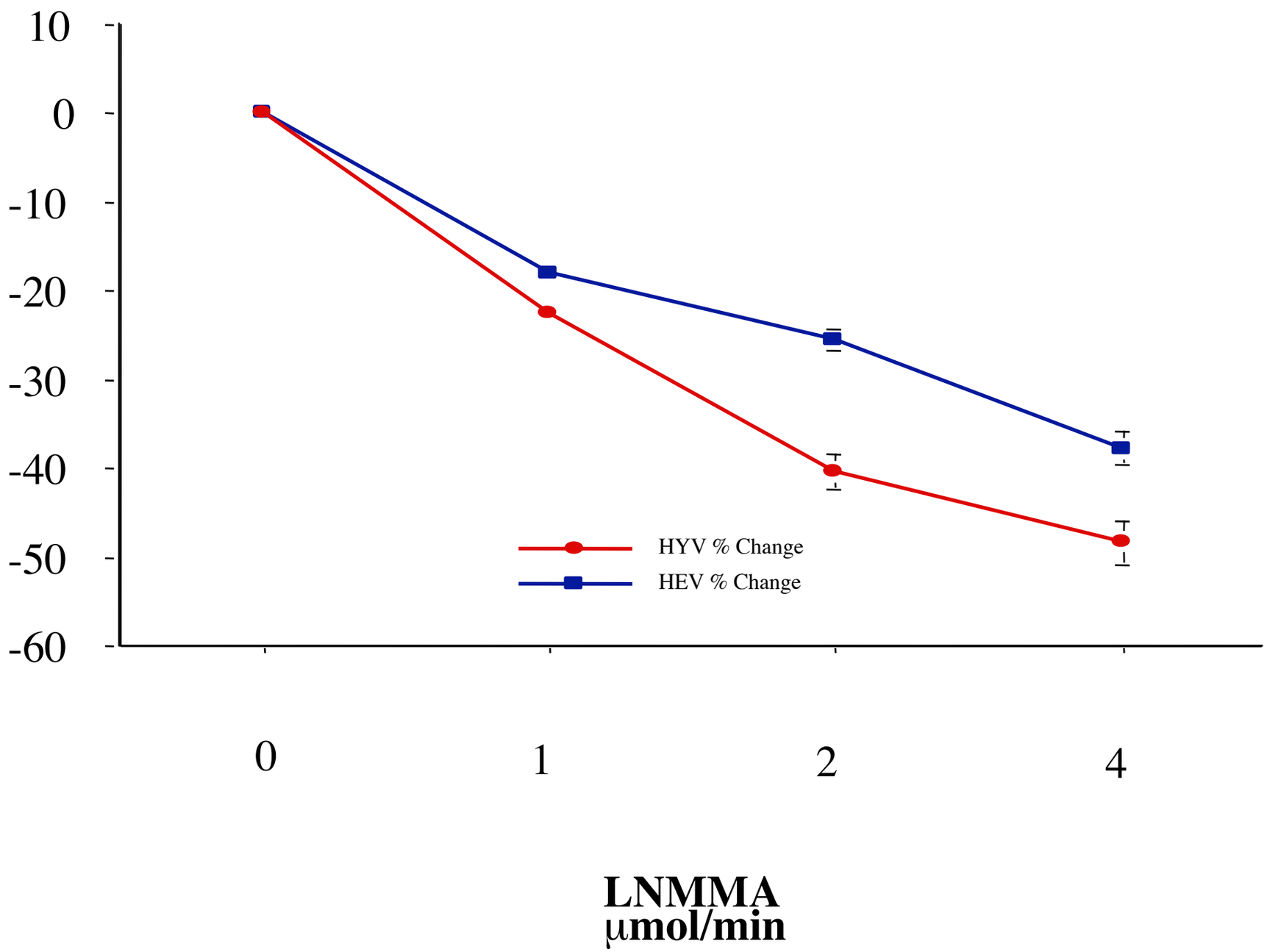
examples

1/2 radius — ↓ to 6% of original

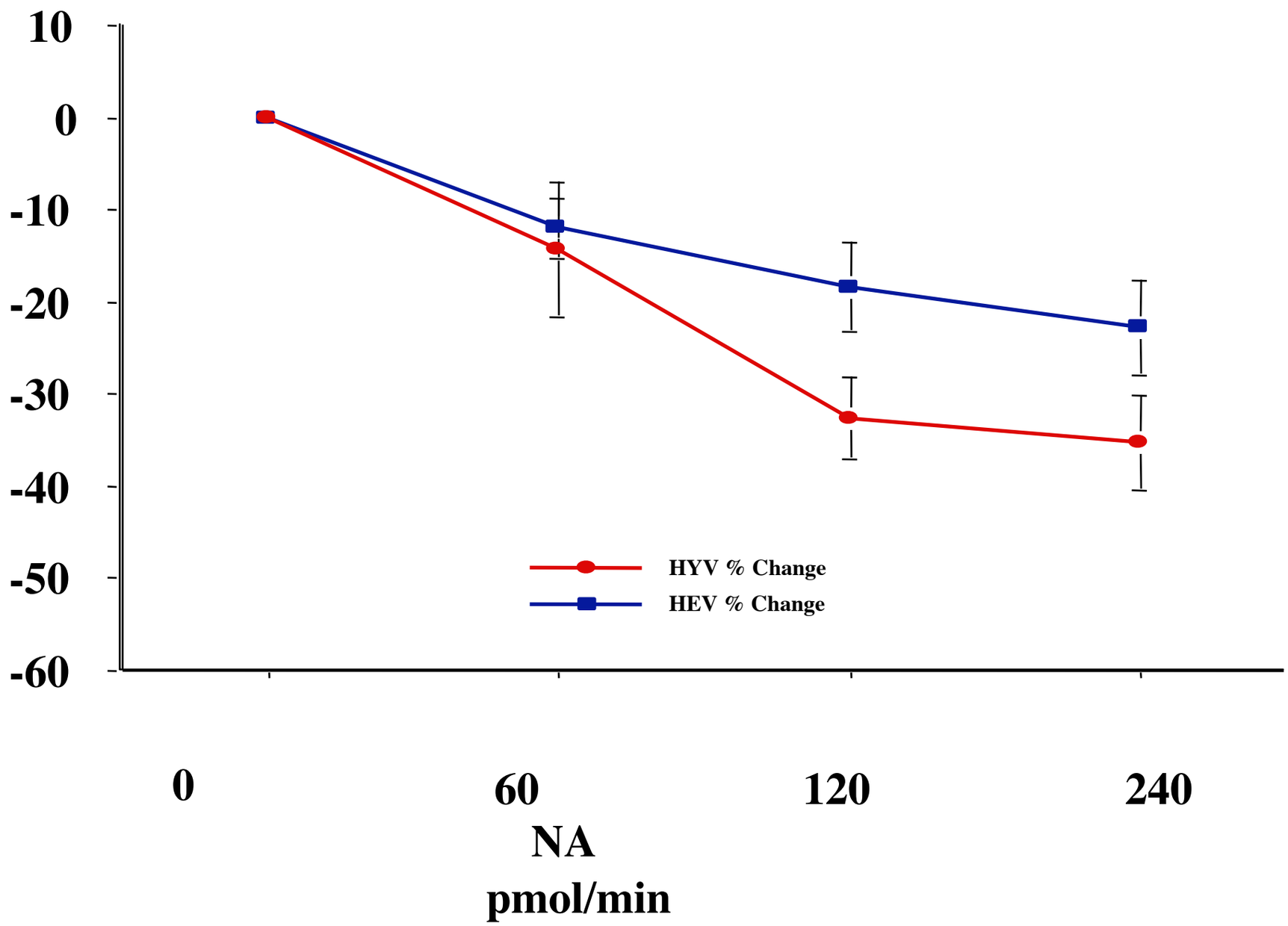
flow is doubled — ↑ 19% in radius

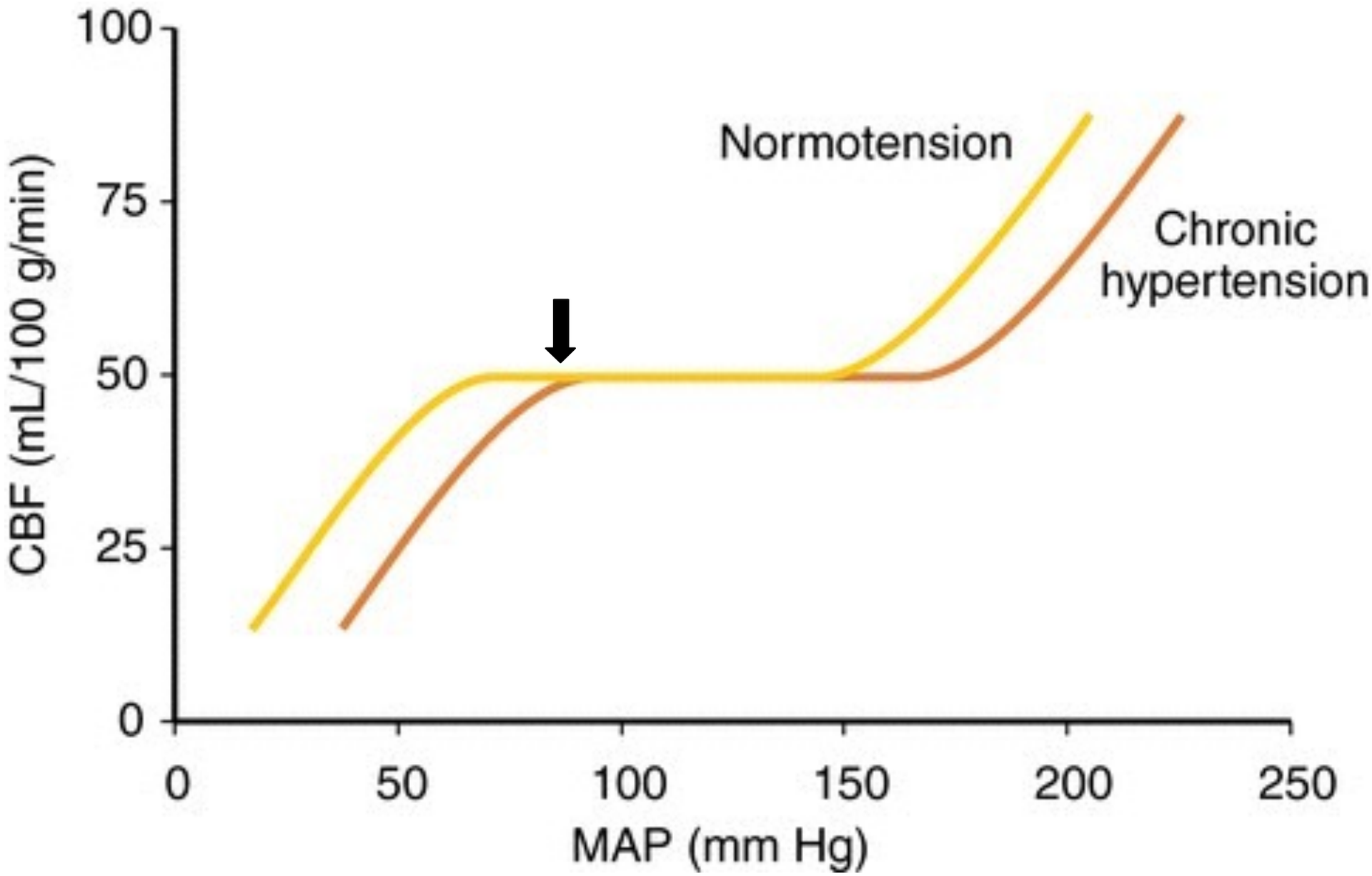

NA
AII
BK
NA
NO
NA
ANP
PGI2
Endothelin
Txa2
NA

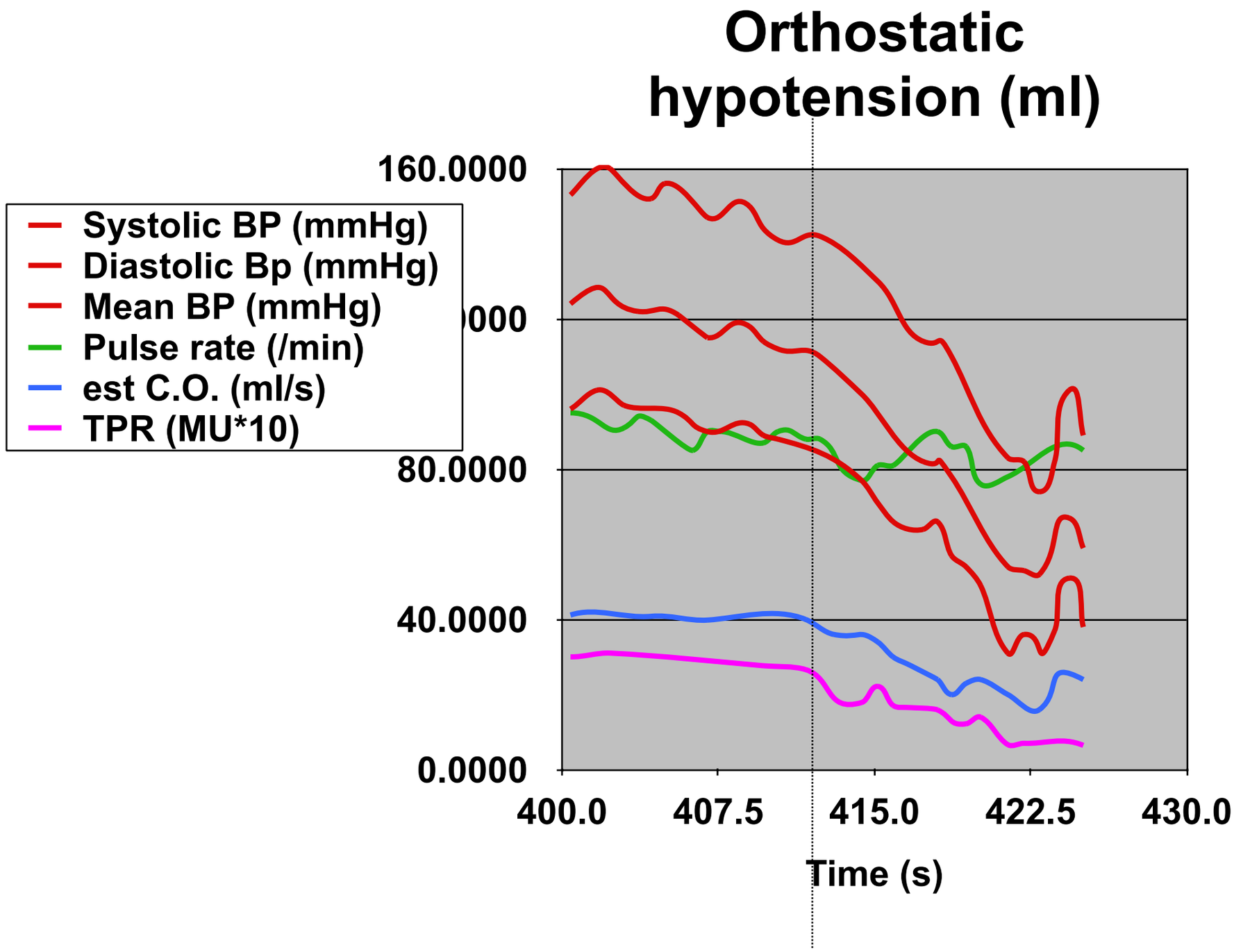
Forearm bloodflow response to LNMMA



Forearm bloodflow response to Noradrenaline




100
75
50
25
0
CBF (mL/100 g/min)
Normotension
Chronic
hypertension
0
50
100
150
200
250
MAP (mm Hg)


Orthostatic hypotension (ml)
Systolic BP (mmHg)
Diastolic Bp (mmHg)
Mean BP (mmHg)
Pulse rate (/min)
est C.O. (ml/s)
TPR (MU*10)
160.0000
80.0000
40.0000
0.0000
400.0
407.5
415.0
422.5
430.0
Time (s)

Blood Pressure & Osteoporosis

Yearly Change in Femoral Neck BMD for SBP Quartiles

1st	4th
2.26 mg/cm2 (95% CI 1.48-3.04)	3.79 mg/cm2 (95% CI 3.13-4.45)
0.34% (0.20-0.46)	0.59% (0.49-0.69)

*age, initial BMD, wt & wt change, smoking, use of HRT,

"High blood pressure in elderly white women is associated with increased bone loss at the femoral neck."

Lancet 1999 Sep 18;354(9183):971-975 Cappuccio FP et al

Stroke & Osteoporosis

BMD at the femoral neck (F)

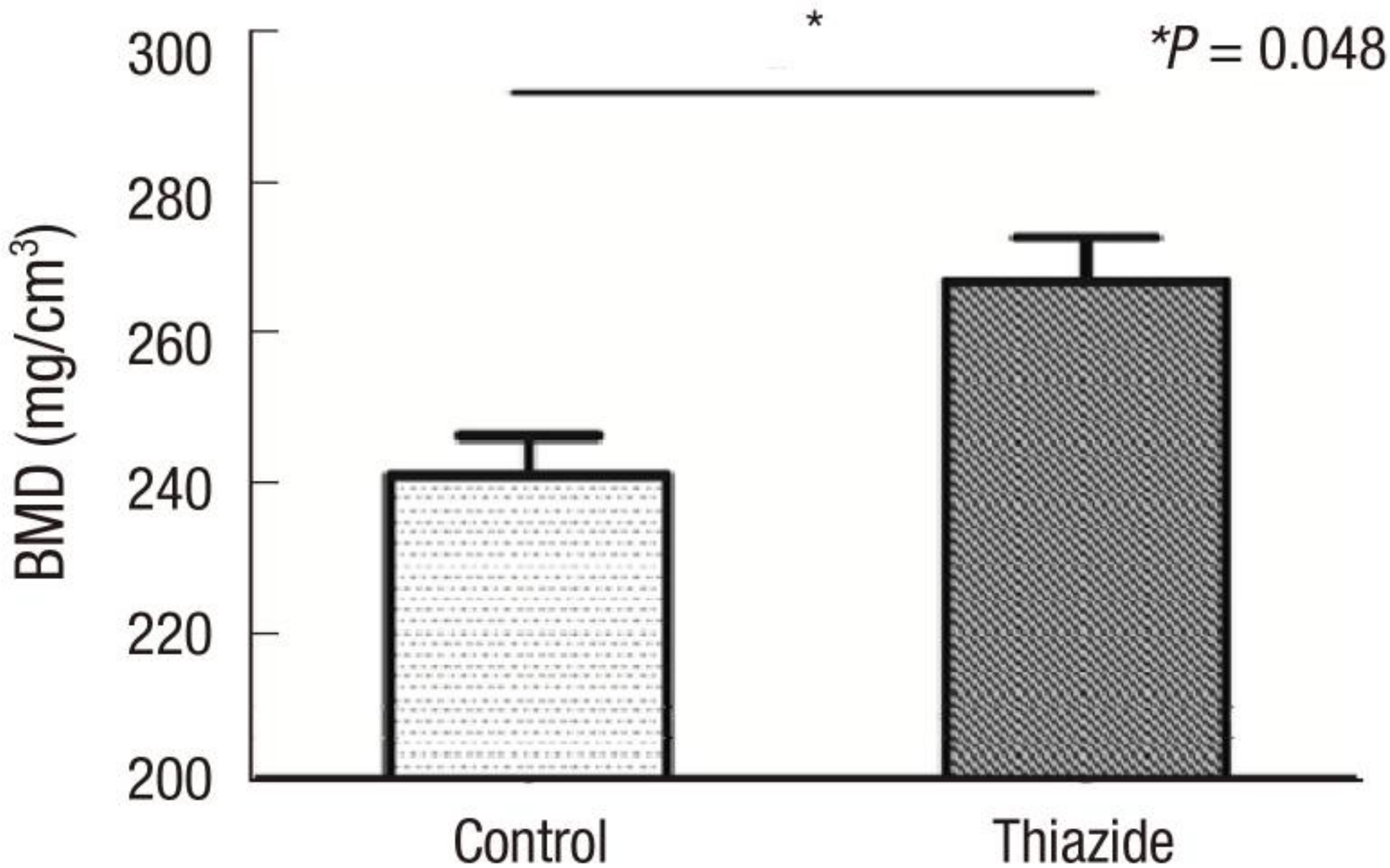
- Stroke patients : control **8% lower (*P*=0.007)**
- Stroke risk: BMD lowest quartile > BMD highest quartile (OR 4.8),
- OR for stroke increased 1.9 per SD (0.13 g/cm2) reduction in BMD

BMD at the femoral neck M

- stroke patients : control **NS**

Jørgensen *Stroke*. 2001;32:47.

Comparison of BMD in thiazide-treated OVX mice vs. control mice



Young Kang et al J Korean Med 2013

Resistance Vessel Dysfunction

↑ BP

→Cerebral Autoregulatory Curve

↑ OH

↓Endothelial Function

↑ Stroke

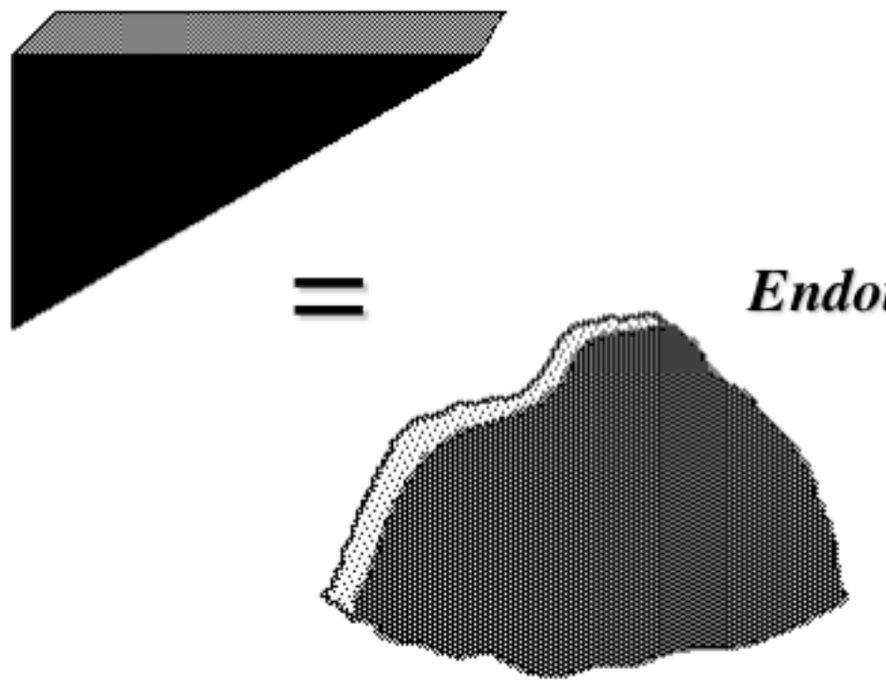
↓BMD

May share a common pathogenic mechanism for OP

Capillary – Endothelial Dysfunction

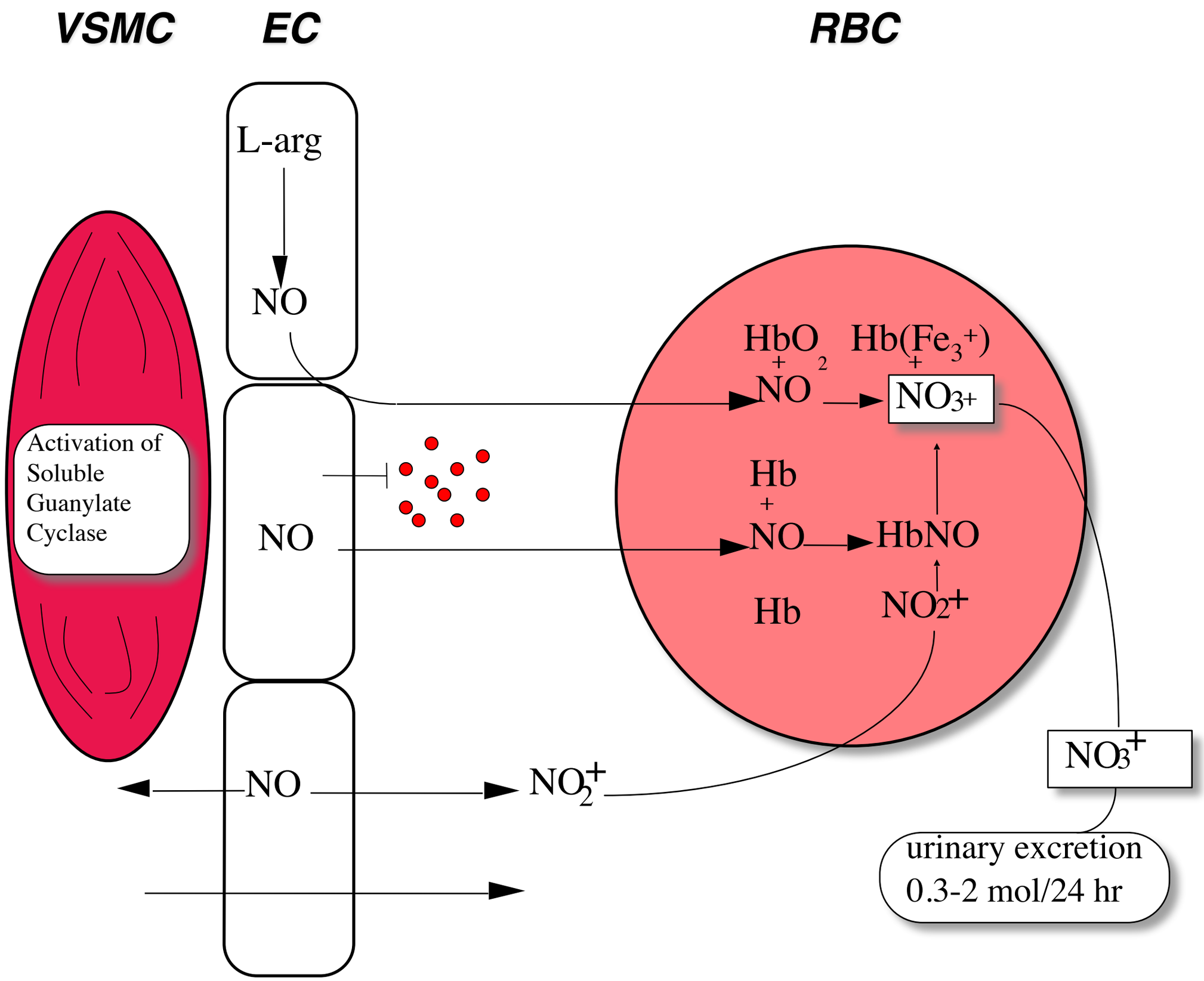
ENDOTHELIUM

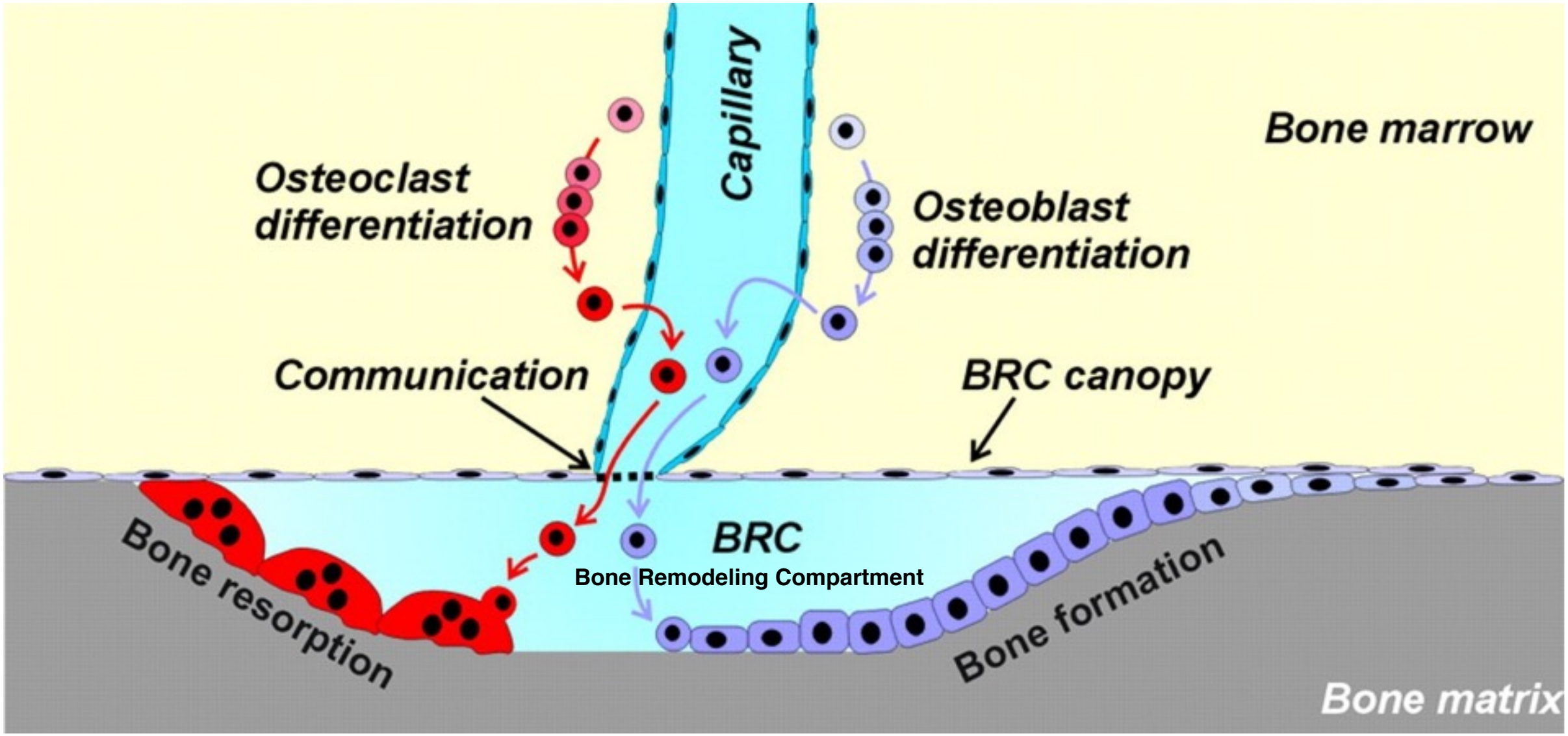
Liver 1.5 Kg



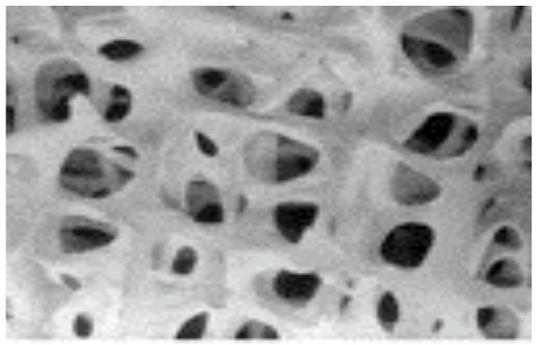
Endothelium 1.5 Kg

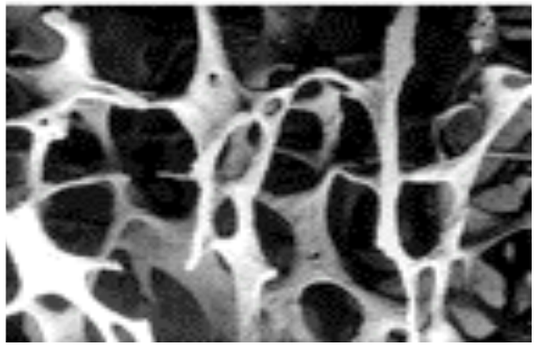
METABOLISM OF NITRIC OXIDE

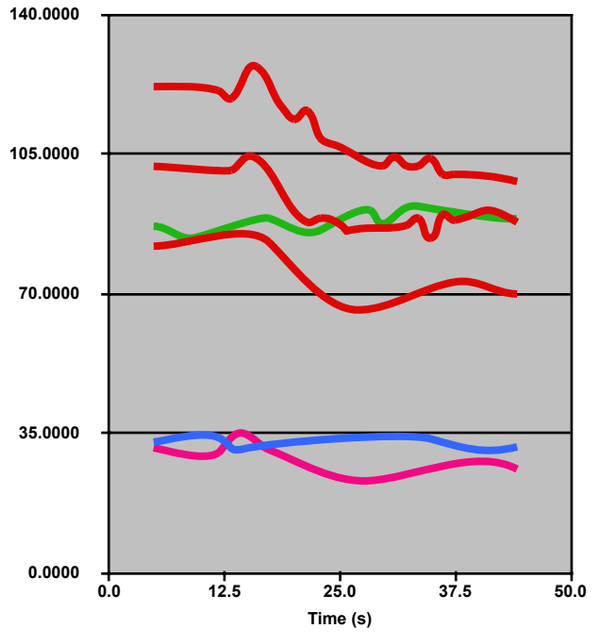


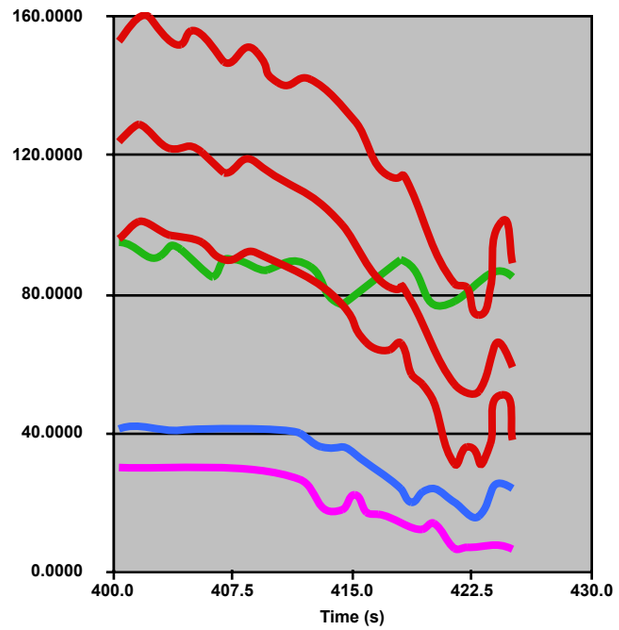

Capillary
Bone marrow
Osteoclast differentiation
Osteoblast differentiation
Communication
BRC canopy
BRC
Bone Remodeling Compartment
Bone resorption
Bone formation
Bone matrix

Osteovascular Instability

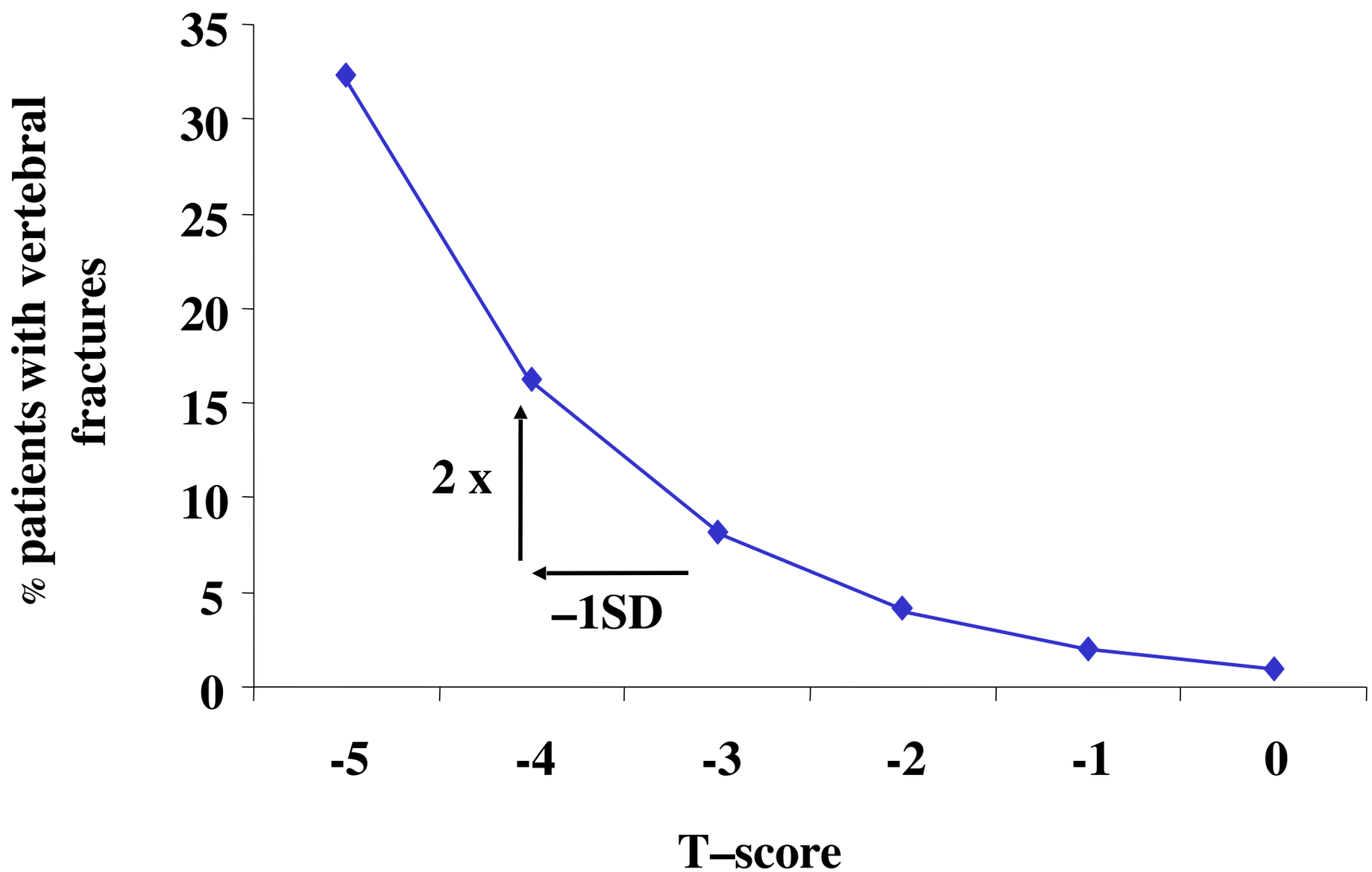





140.0000
105.0000
70.0000
35.0000
0.0000
0.0
12.5
25.0
37.5
50.0
Time (s)

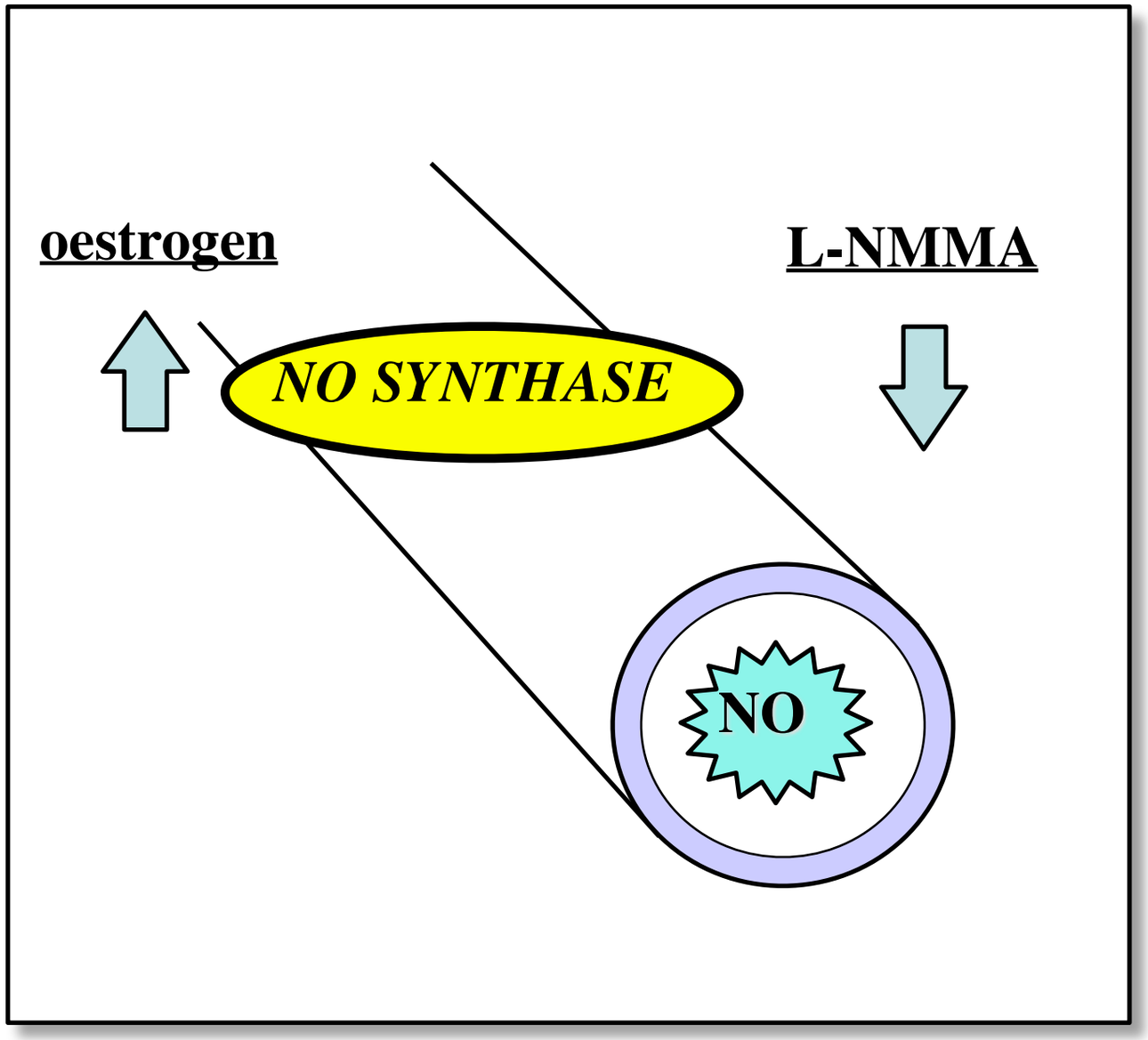

160.0000
120.0000
80.0000
40.0000
0.0000
400.0
407.5
415.0
422.5
430.0
Time (s)

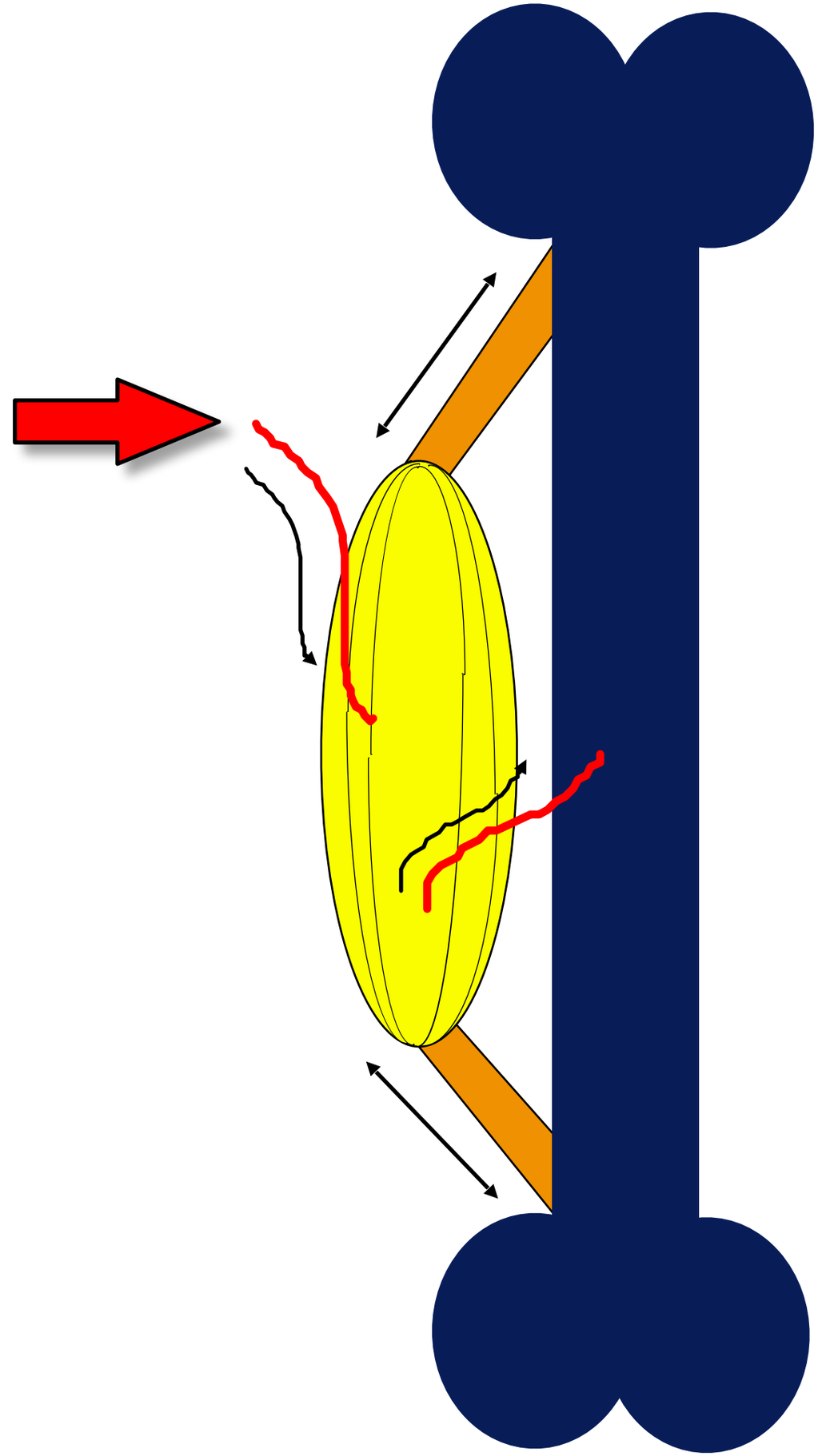
Relationship Between BMD and Fracture Risk



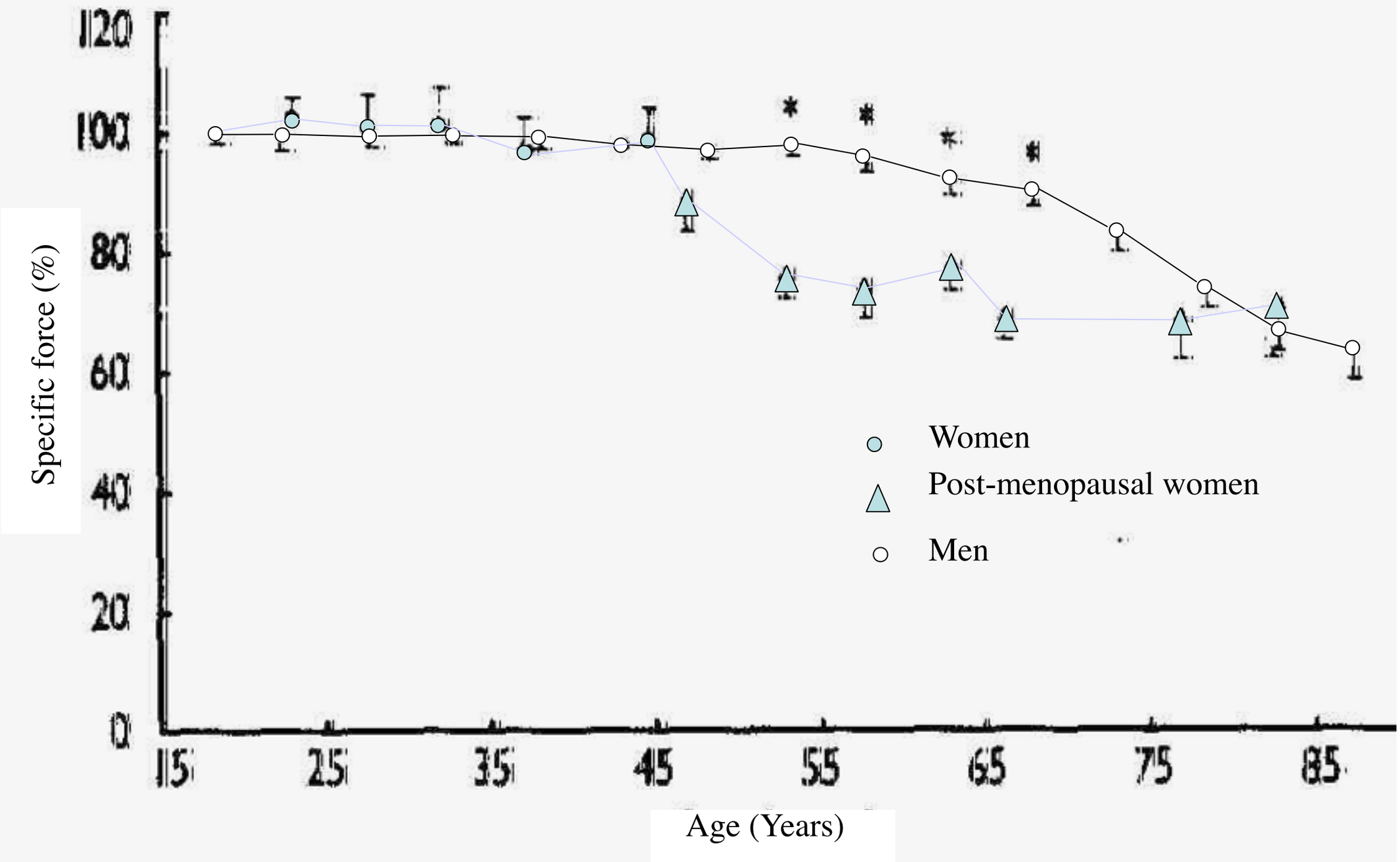
SD – Standard deviation

1. Watts NB. Oral Presentation at ASBMR 2001. (Reproduced with permission)


oestrogen
L-NMMA
NO SYNTHASE
NO

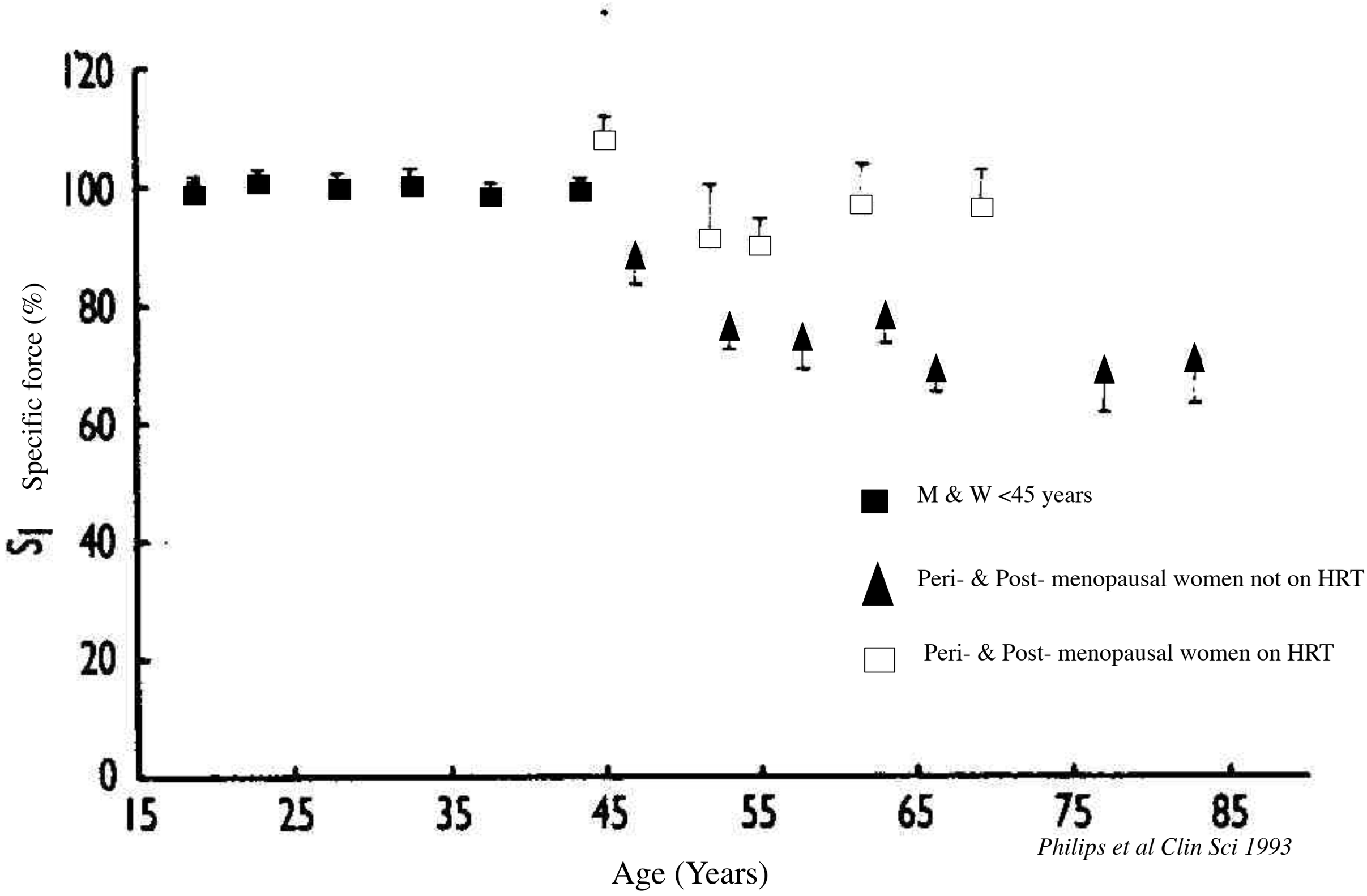


Relationship between Specific Force & Age



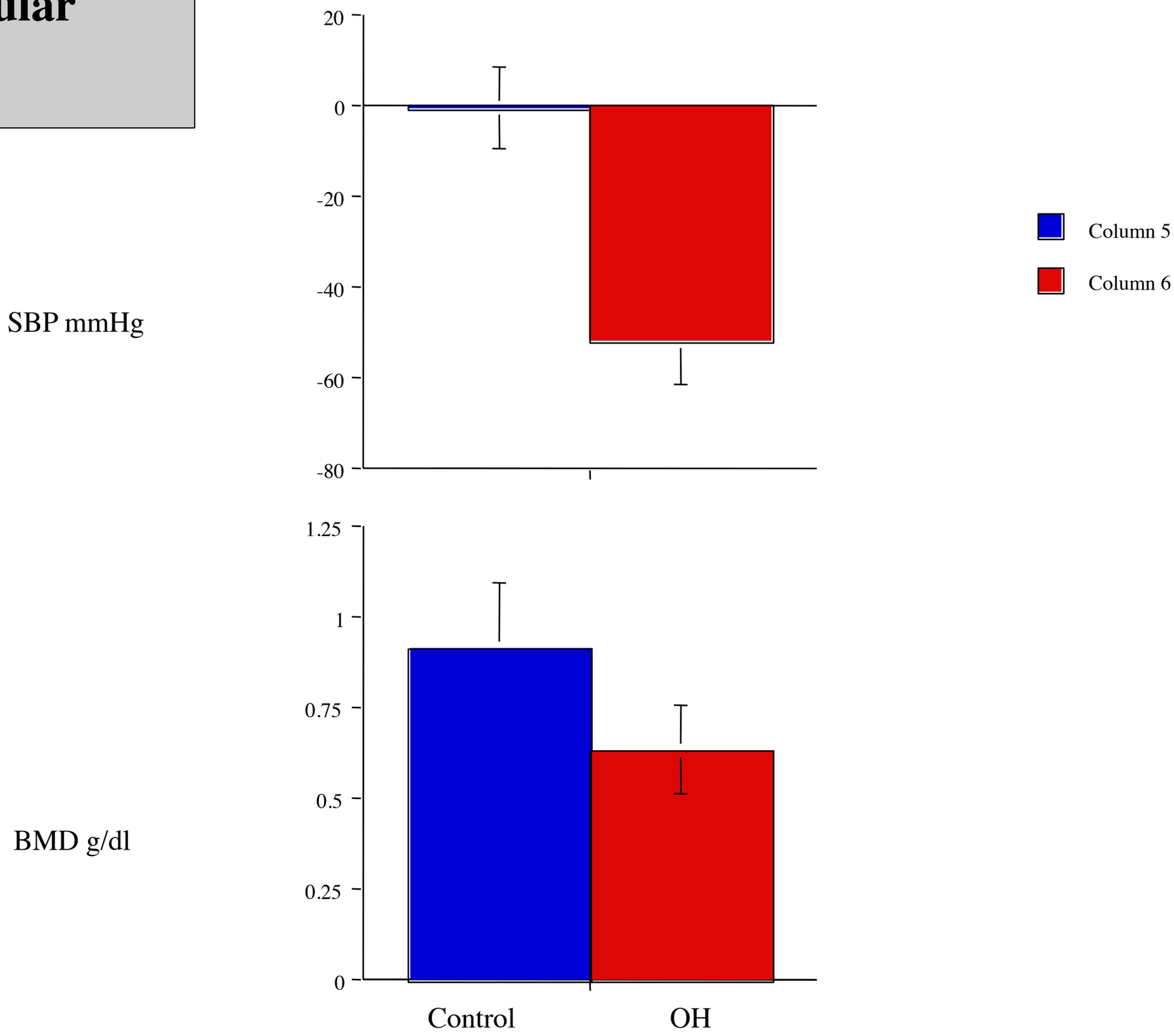
Philips et al Clin Sci 1993

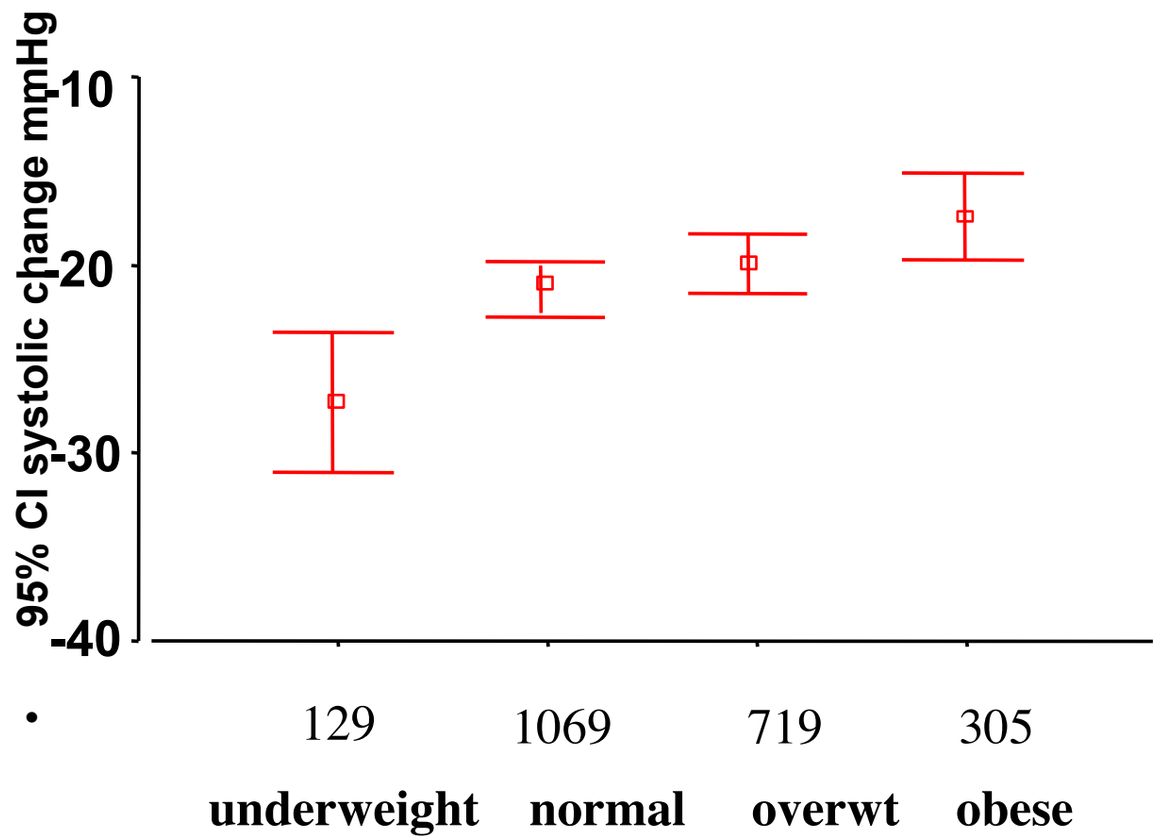
Relationship between specific force and age in both men & pre-menopausal women aged 45 years & under

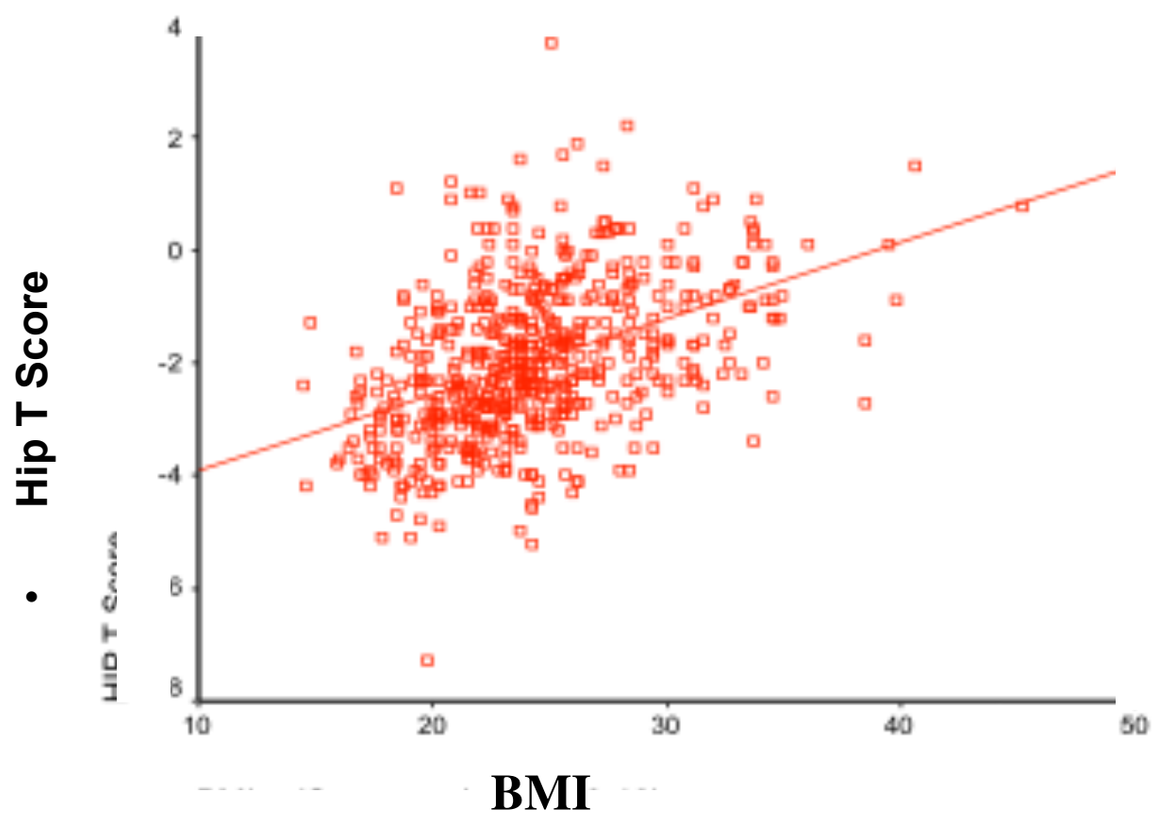


Philips et al Clin Sci 1993

Osteovascular Instability




95% CI systolic change mmHg
-10
-20
-30
-40
129
1069
719
305
underweight
normal
overwt
obese


Hip T Score
4
2
0
-2
-4
-6
-8
10
20
30
40
50
BMI

BMI predicts OH

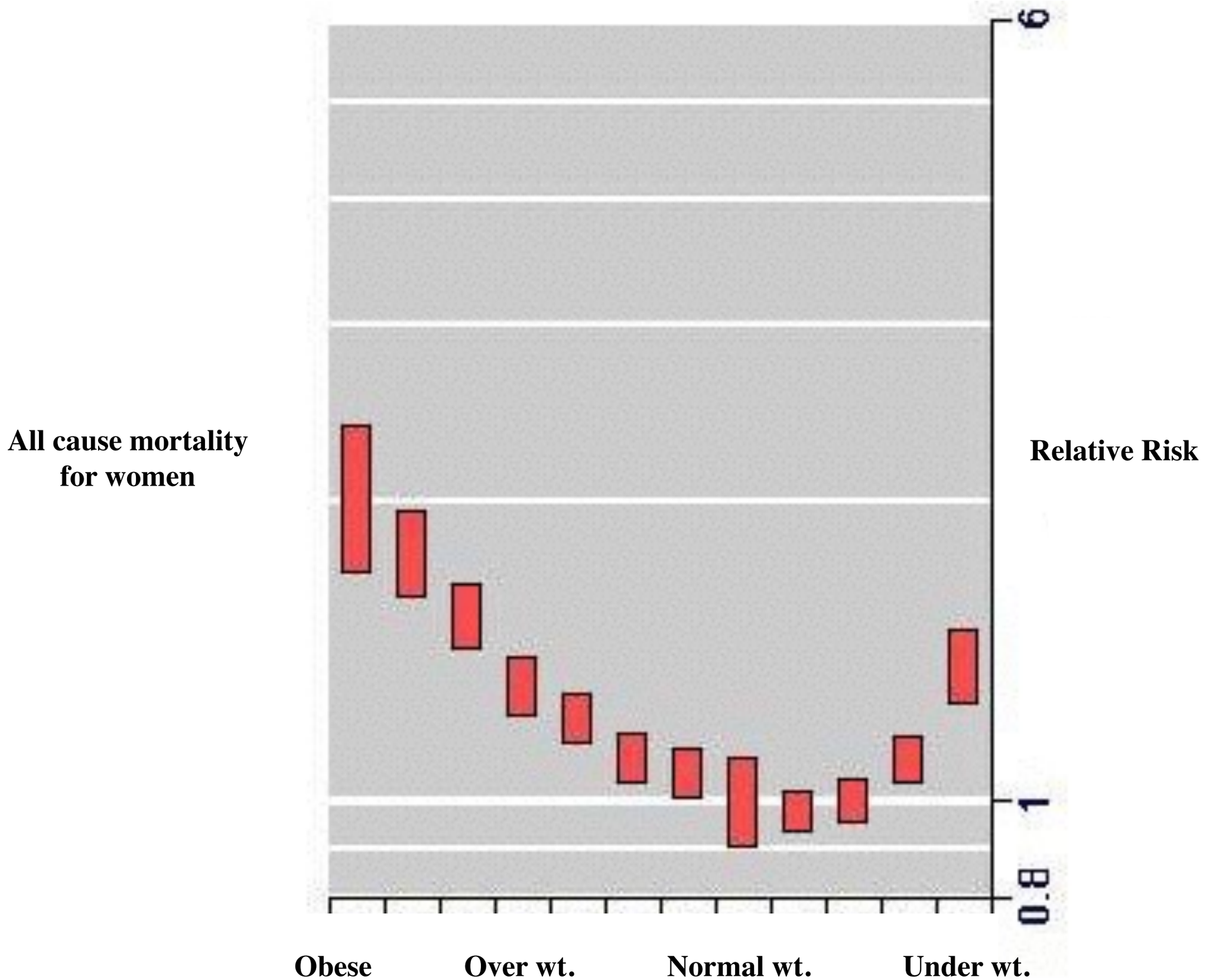
Each unit ↑ BMI ↓ likelihood of OH by 4%.

odds ratio was 0.96 (95% CI, 0.95, 0.98).

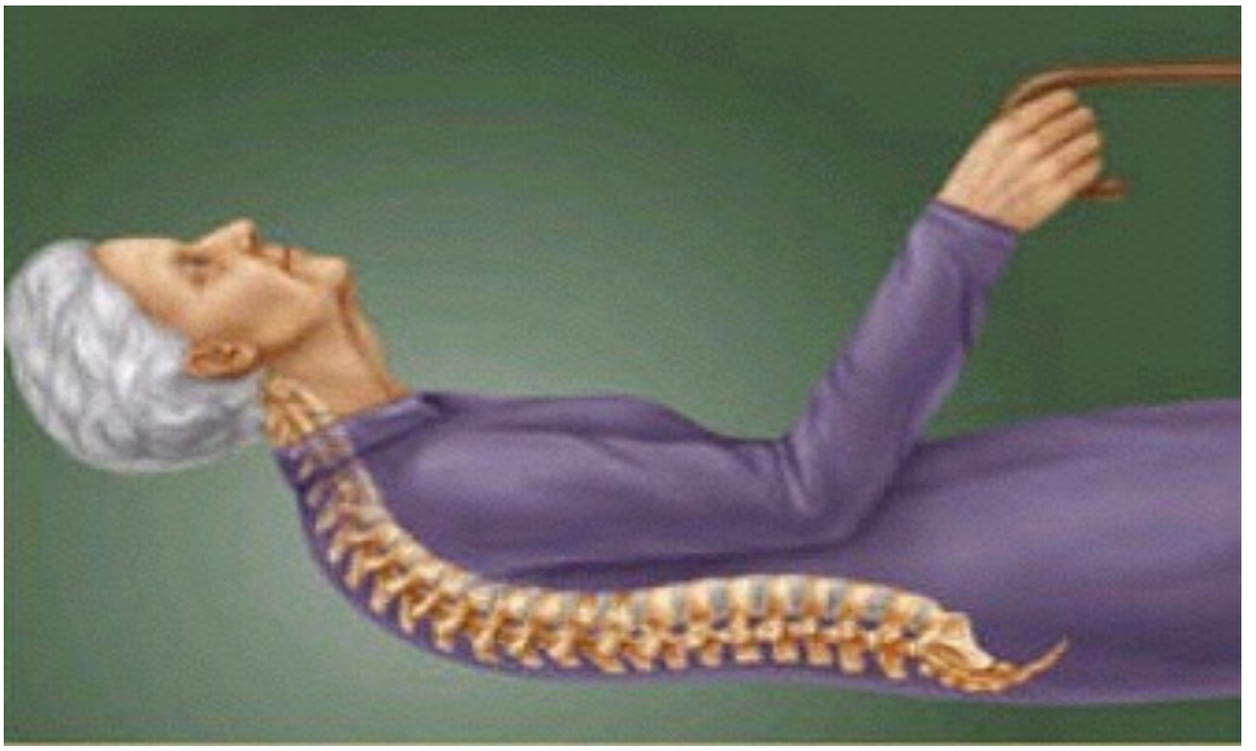
BMI predict osteoporosis

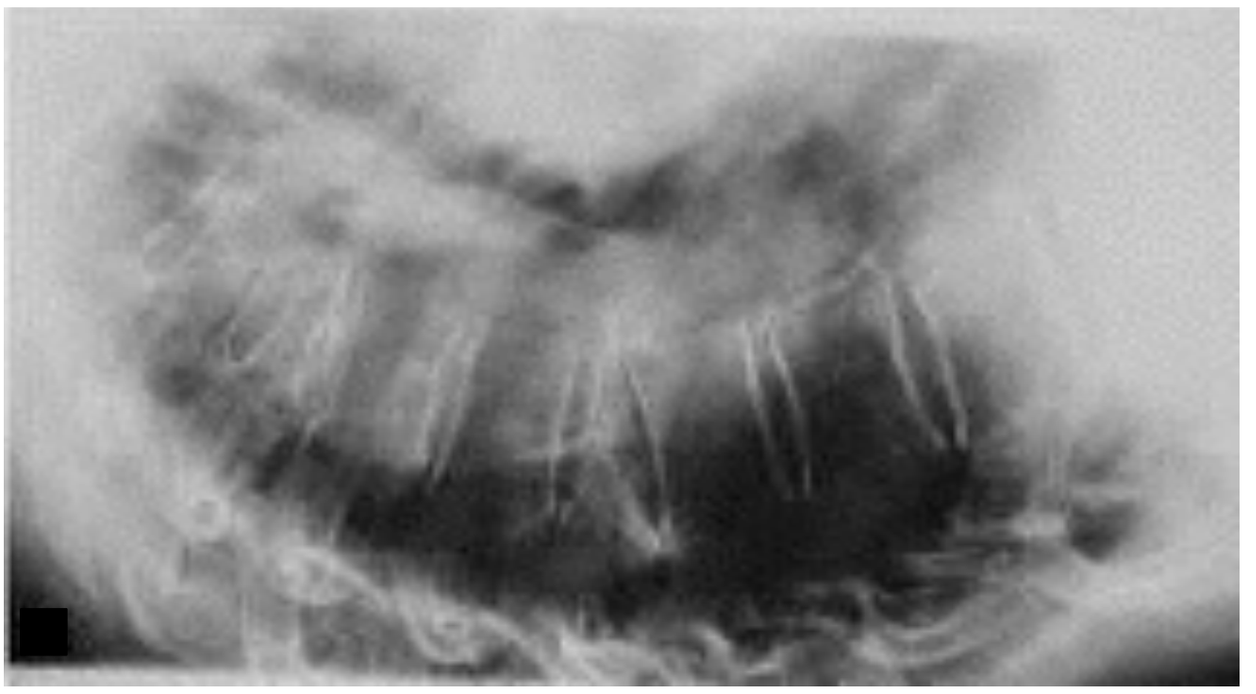
Each unit ↑ BMI ↓ likelihood of OP 20%.

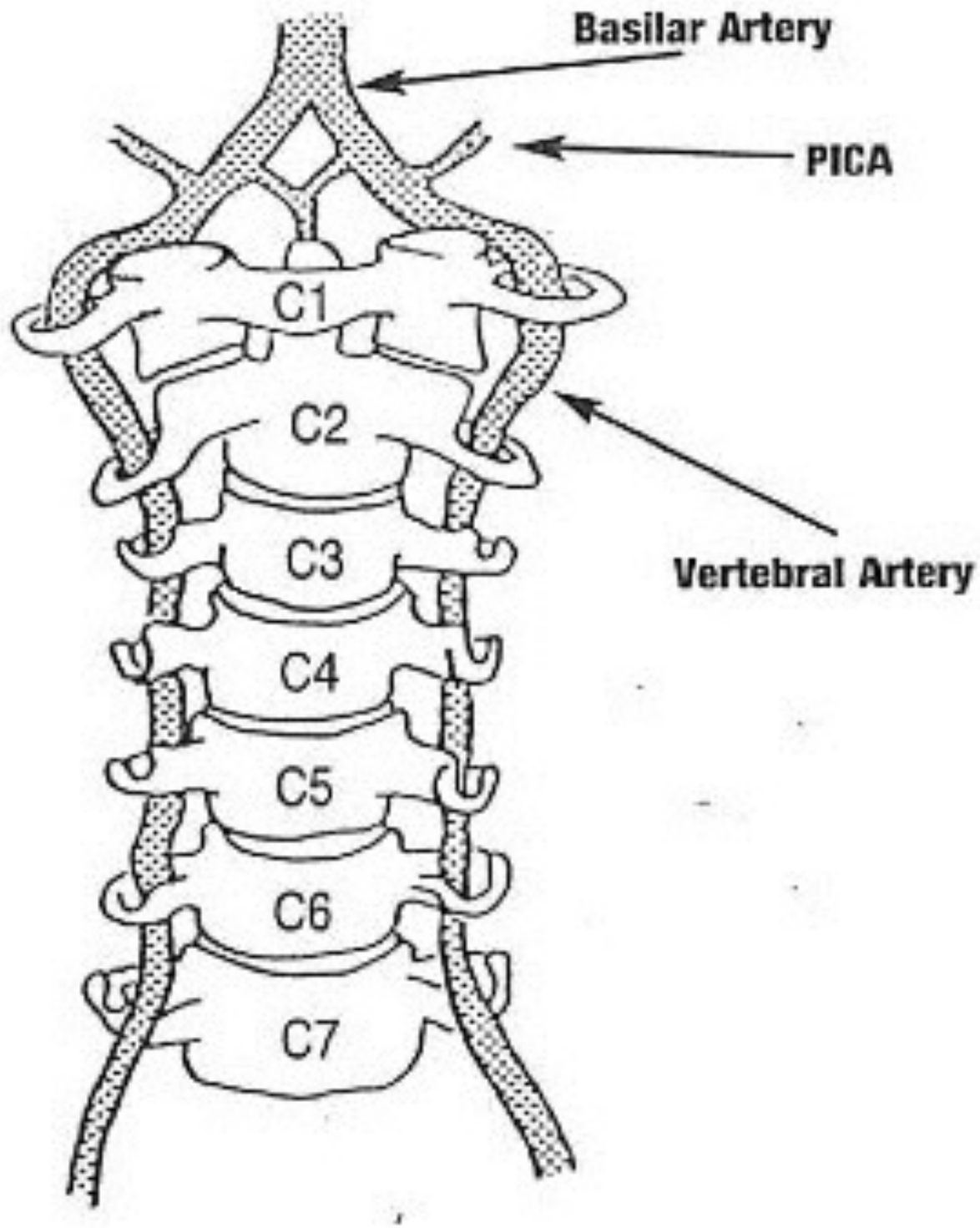
odds ratio was 0.80 (95% CI, 0.76, 0.84).

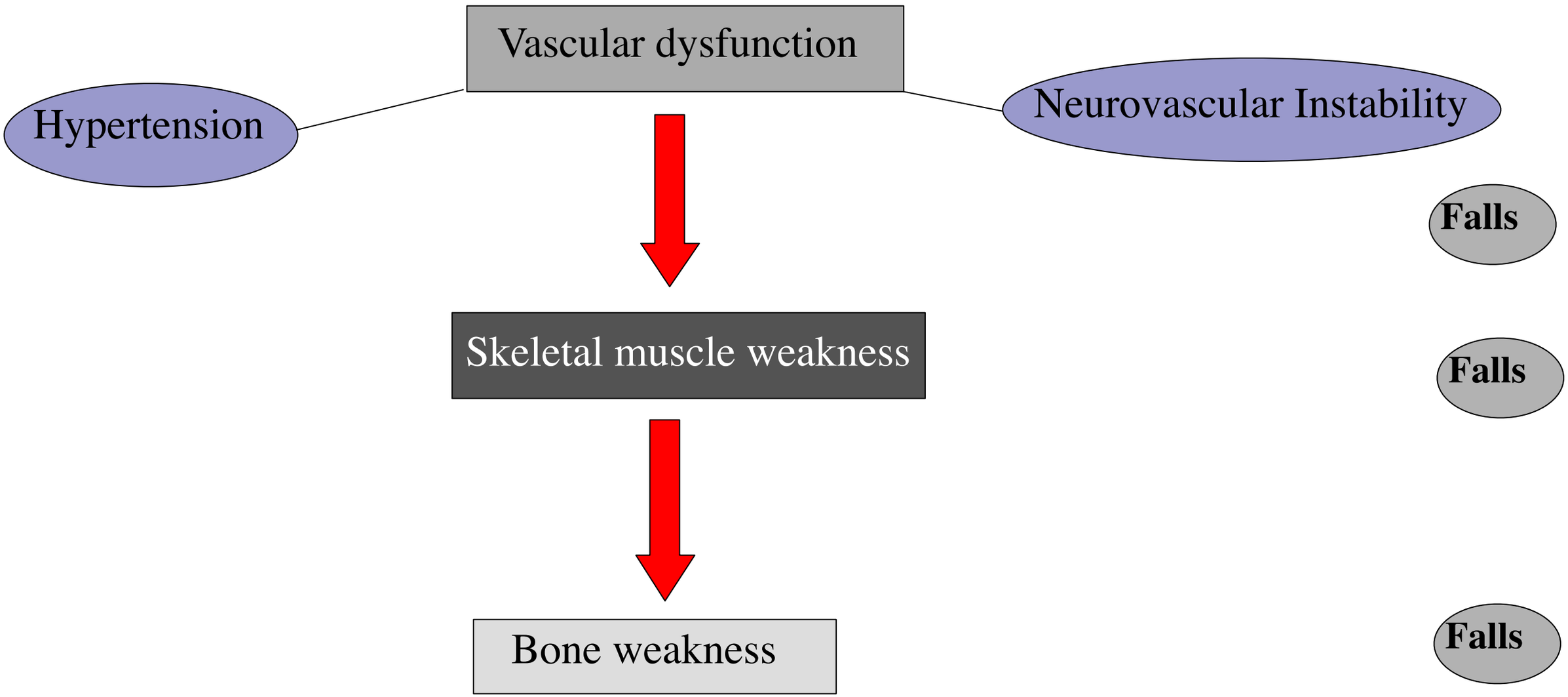

All cause mortality
for women
Relative Risk
6
1
0.8
Obese
Over wt.
Normal wt.
Under wt.

Kyphosis induced VBI (KVBI)






Basilar Artery
PICA
C1
C2
C3
C4
C5
C6
C7
Vertebral Artery

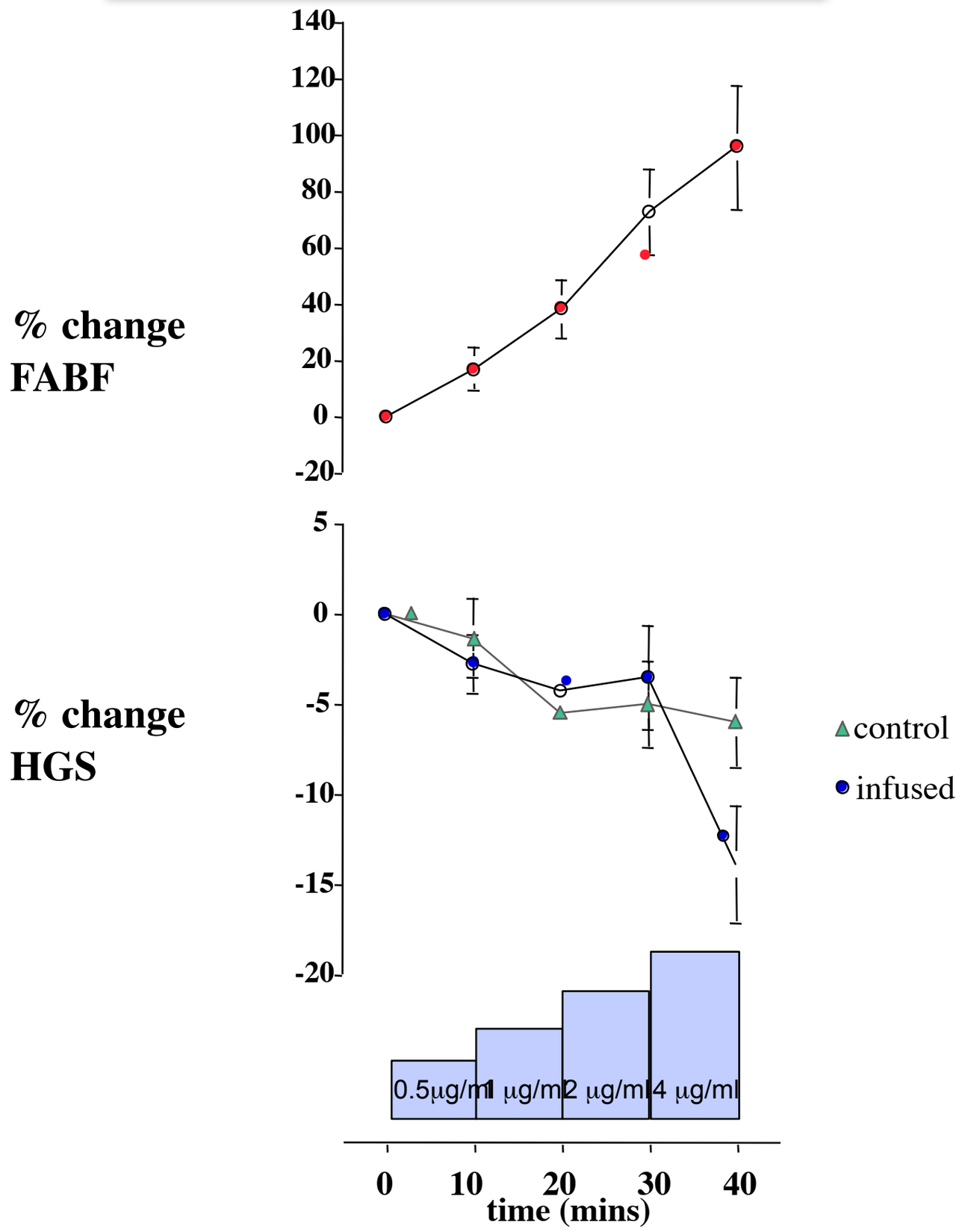


Vasculo-musculo-skeletal syndrome

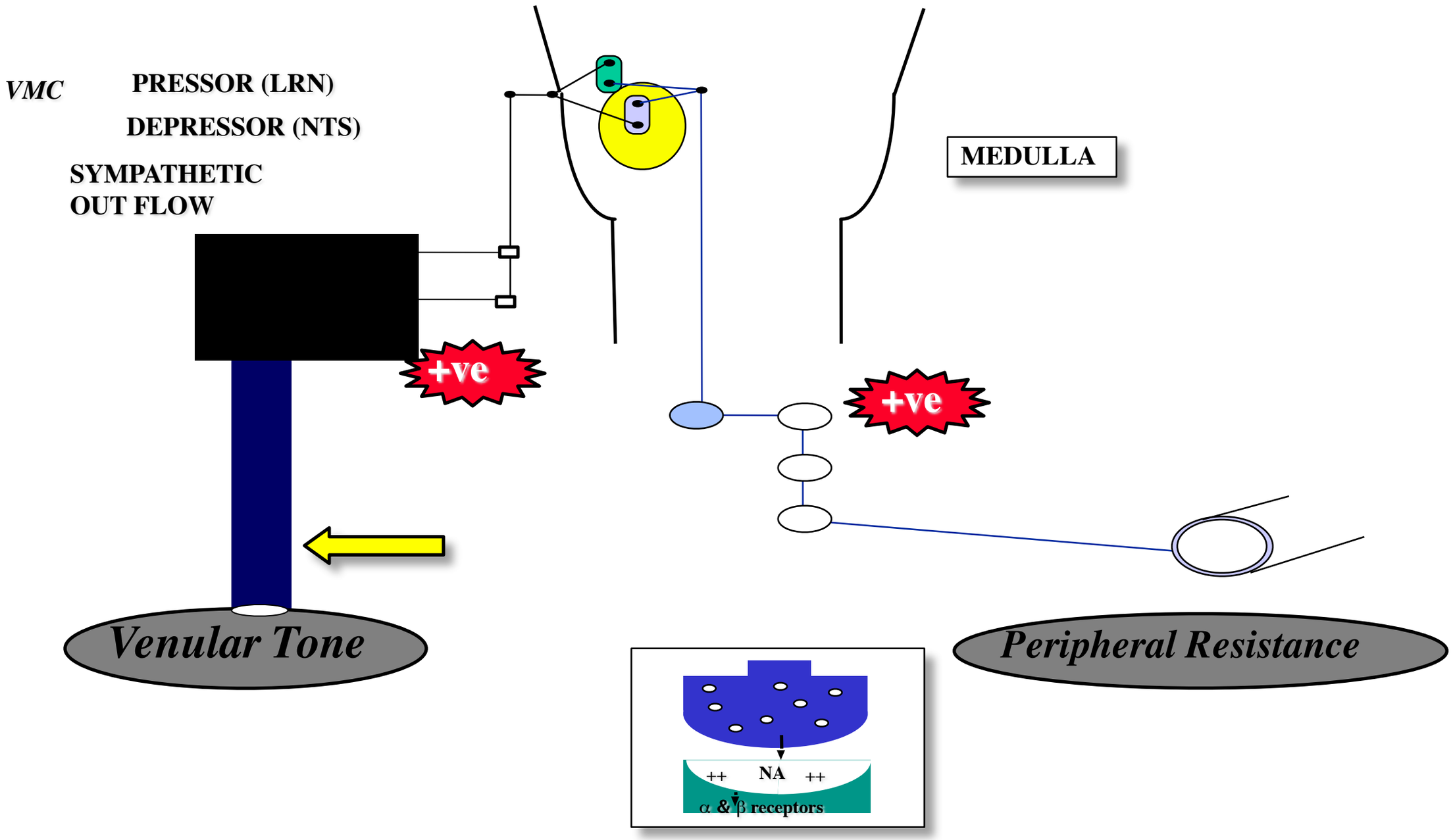
Blood Vessel Pathology

Thank You

SNP: % Change in FABF & HGS

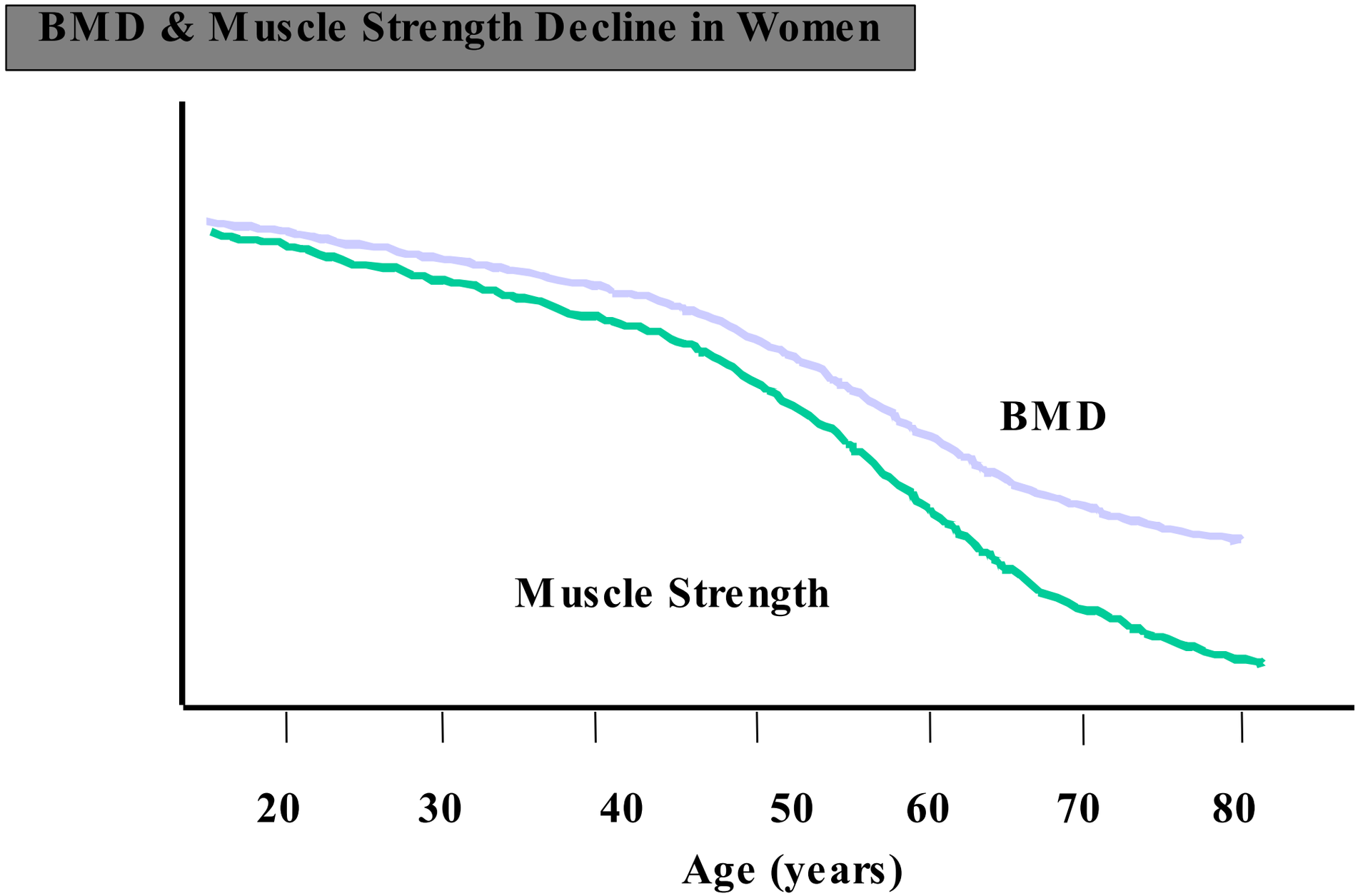


Venulo Cardio Resistance Vessel Arc




C1
C2

Oestrogen and Muscle



Osteoprotegerin: a link between osteoporosis and arterial calcification?

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