Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (USC 17 § 105)

Public Domain – Expired: Works that are no longer protected due to an expired copyright term.

Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.

Creative Commons – Zero Waiver

Creative Commons – Attribution License

Creative Commons – Attribution Share Alike License

Creative Commons – Attribution Noncommercial License

Creative Commons – Attribution Noncommercial Share Alike License

GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (USC 17 § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (USC 17 § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

Hemodynamics

M1 – Cardiovascular/Respiratory Sequence

Louis D'Alecy, Ph.D.

Fall 2008

Monday 11/03/08, 9:00
Hemodynamics

26 slides, 50 min

1. Pressure & pressure pulses
2. Pressure gradient (perfusion pressure)
3. Determinants of Blood Flow
4. Resistance in series and in parallel

Hemodynamics

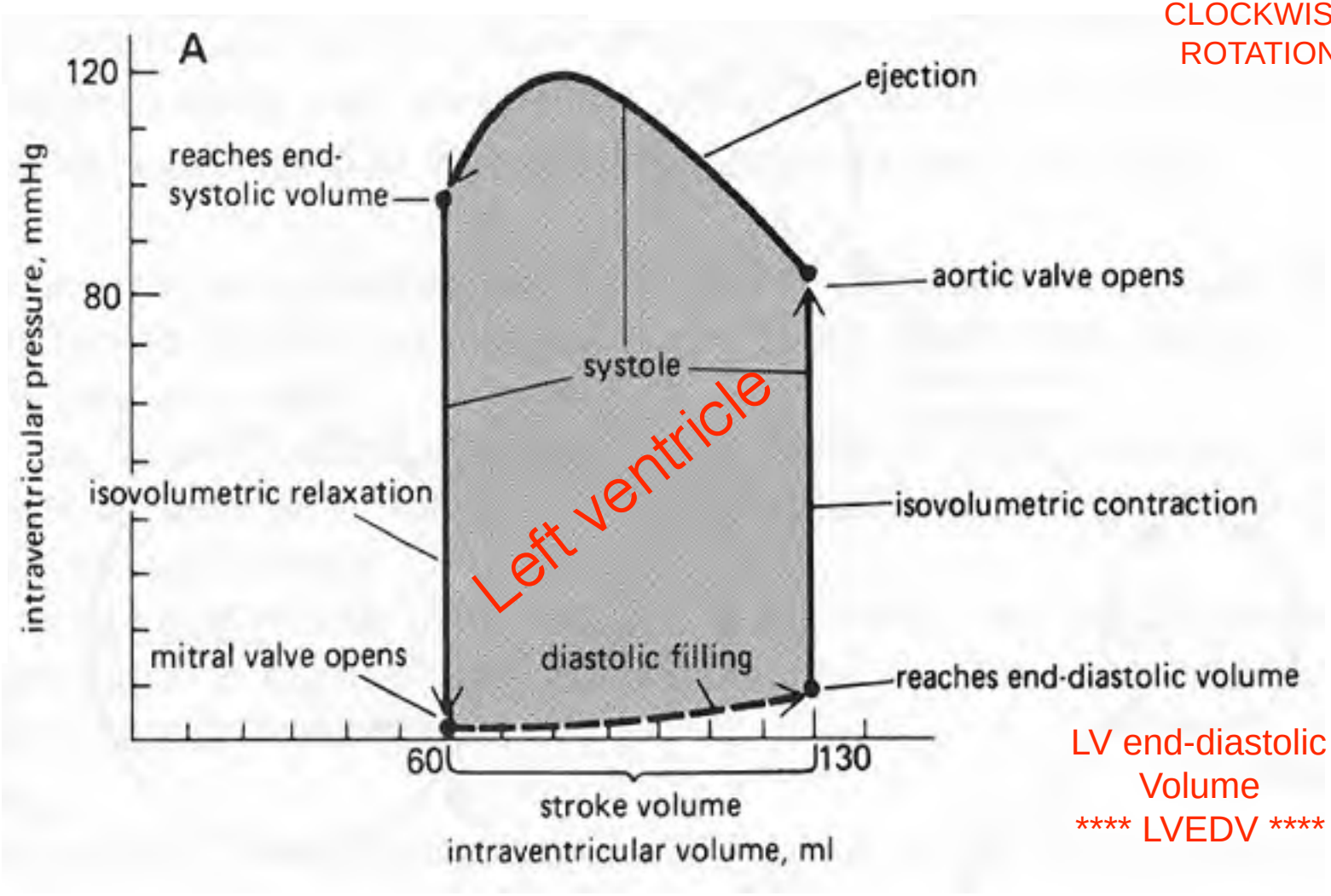
"Hemodynamics is concerned with the forces generated by the heart and the motion of blood through the cardiovascular system."

from ucdavis.edu

Blood Pressures and Blood Flow

Flow out

COUNTER CLOCKWISE ROTATION



Pressure down

Pressure up

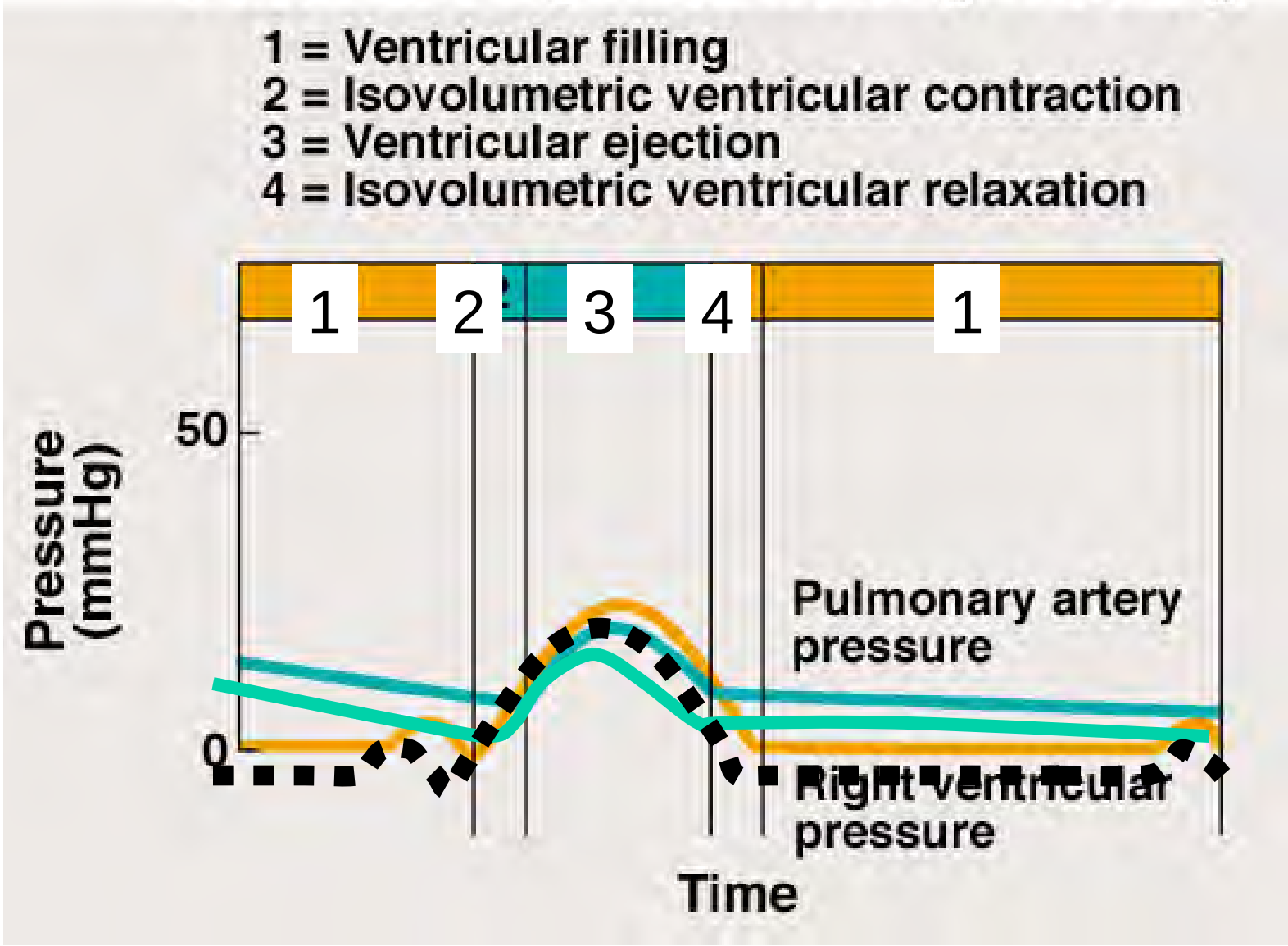
LV end-diastolic Volume
**** LVEDV ****

Flow in

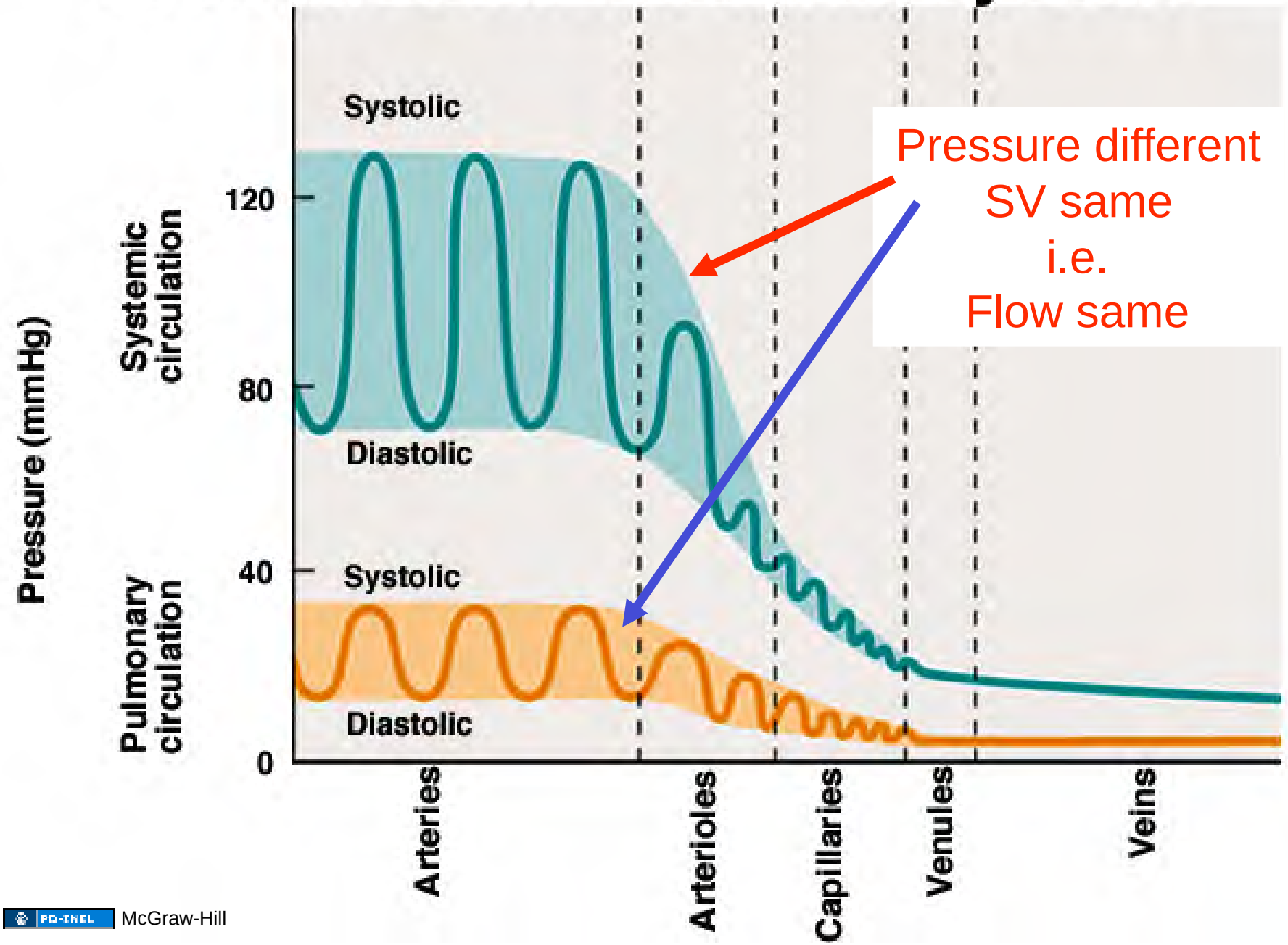
Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

3.3 MH

Pressures in right ventricle/pulmonary artery



Pressures in vascular system



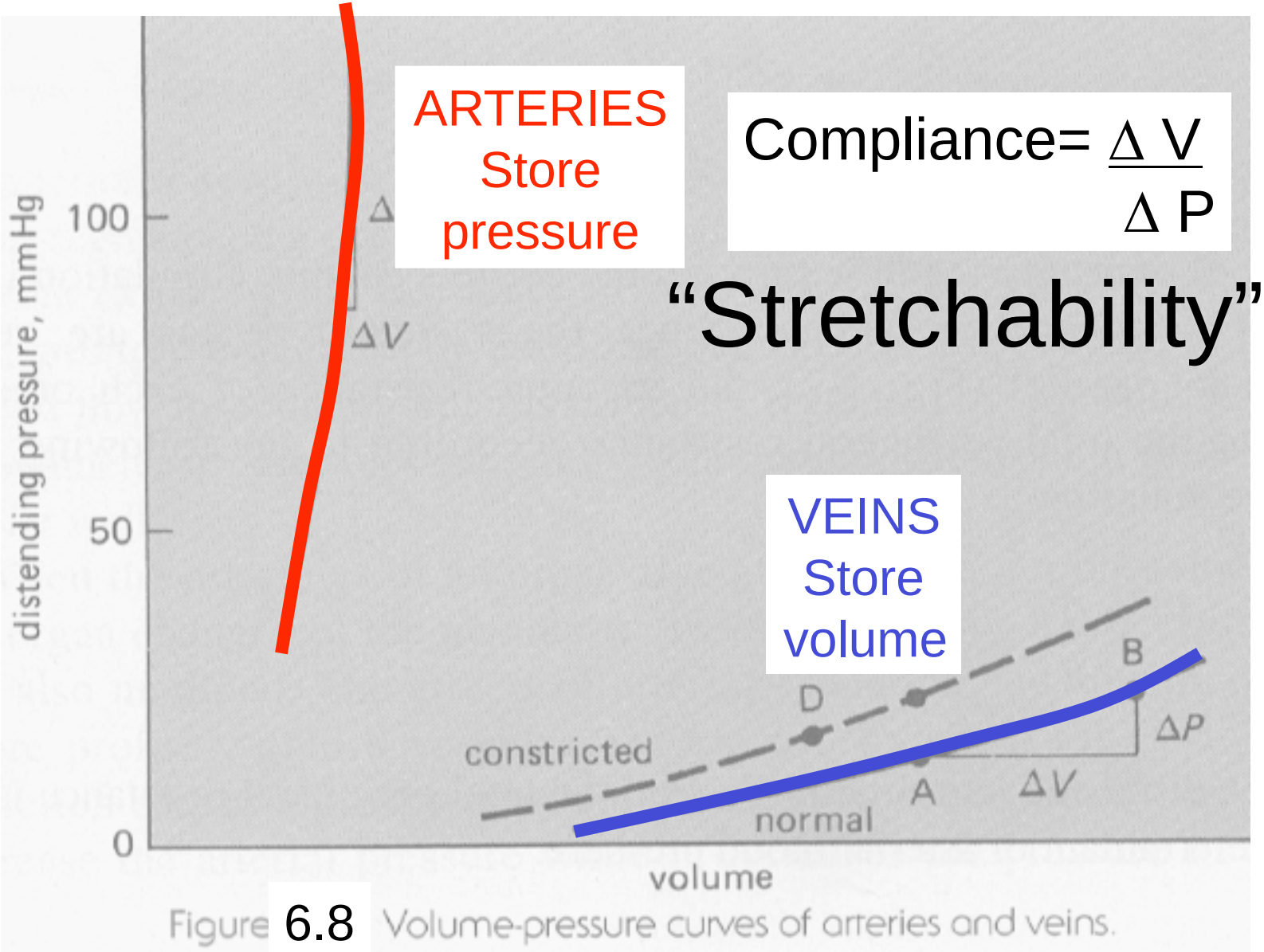
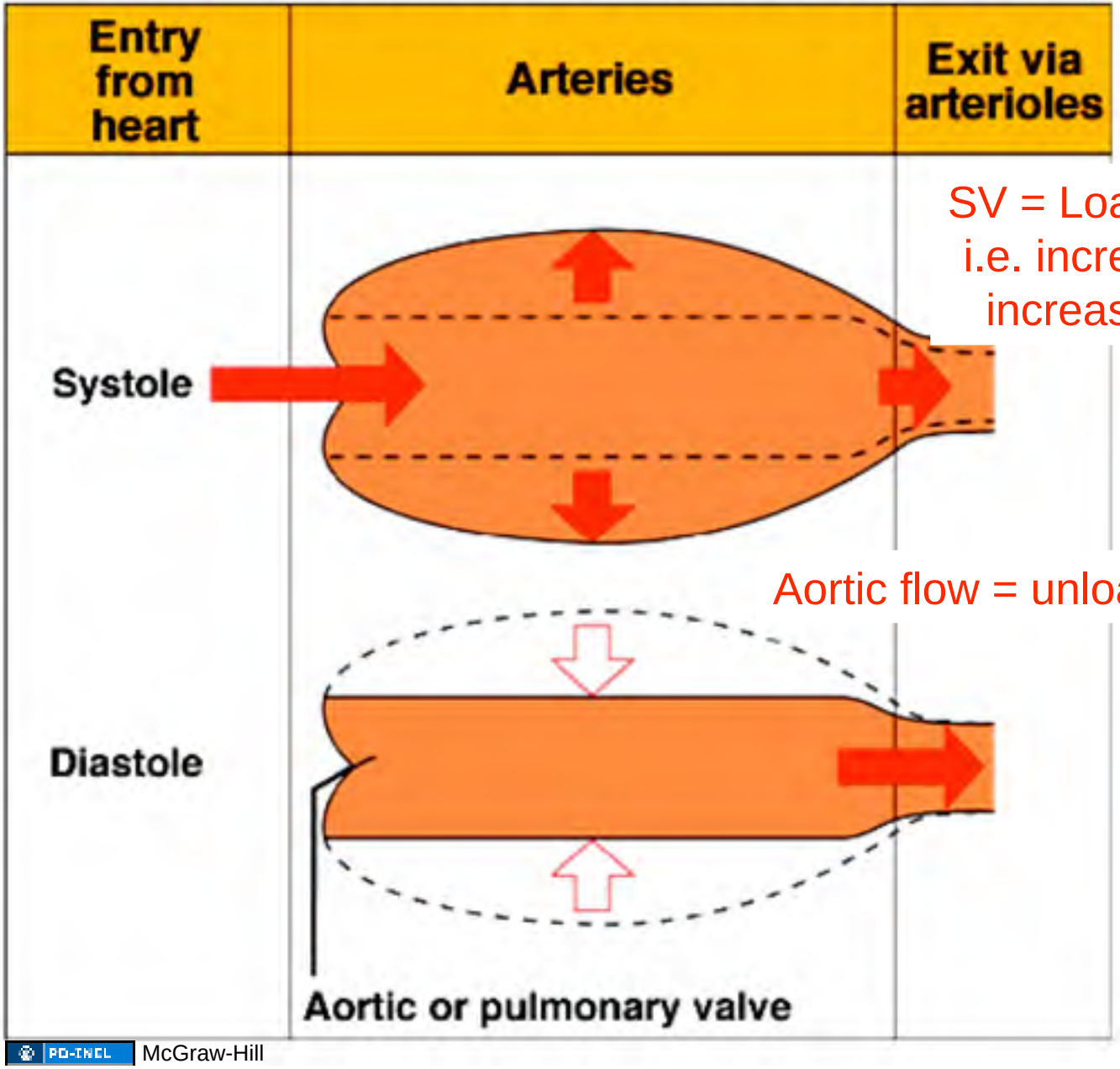


Figure 6.8 Volume-pressure curves of arteries and veins.

Veins are more compliant than arteries.

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

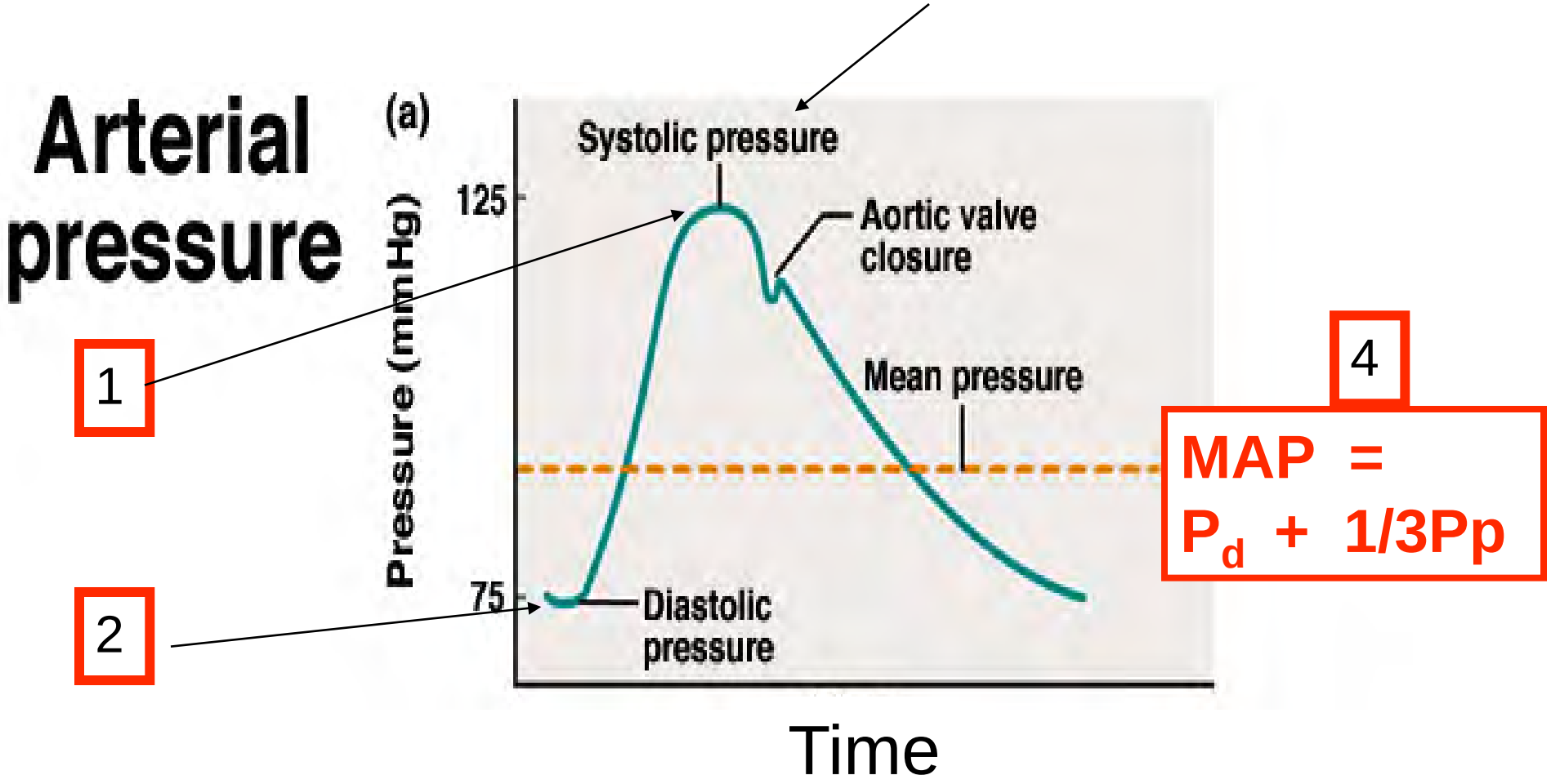
Movement of blood/cardiac cycle

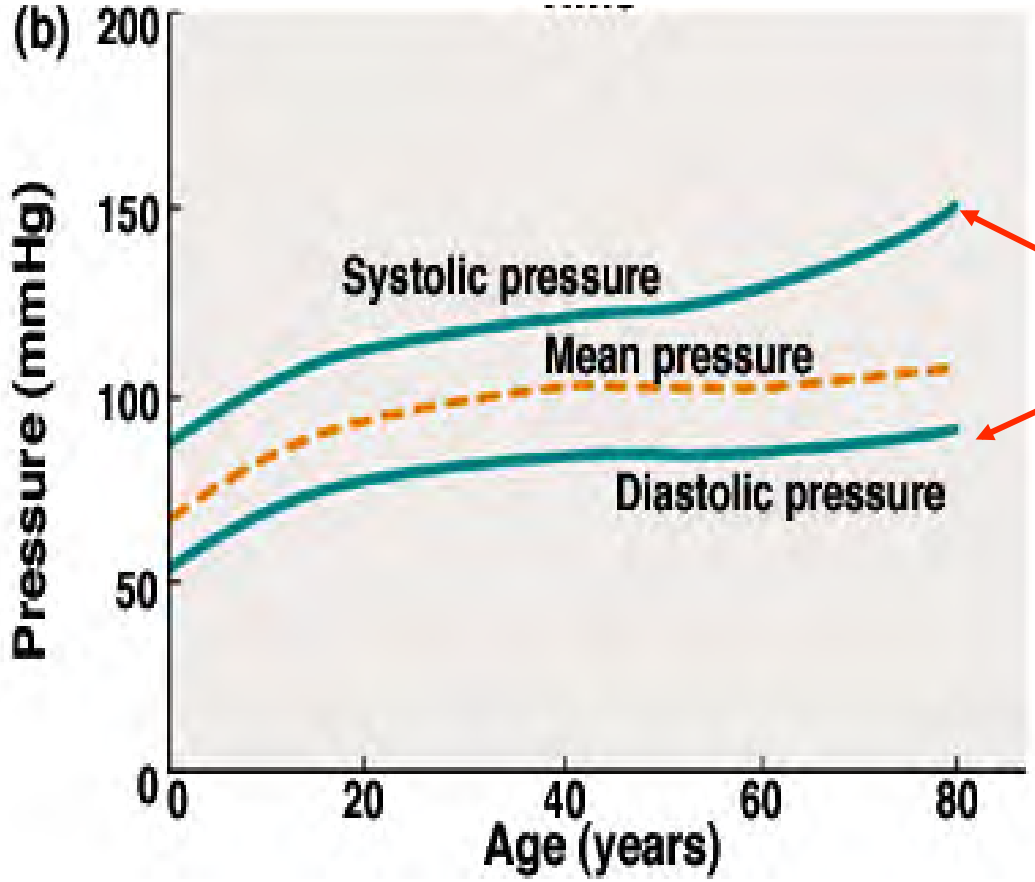


SV = Loads the spring, i.e. increased volume increases pressure

Aortic flow = unloads the spring

.0





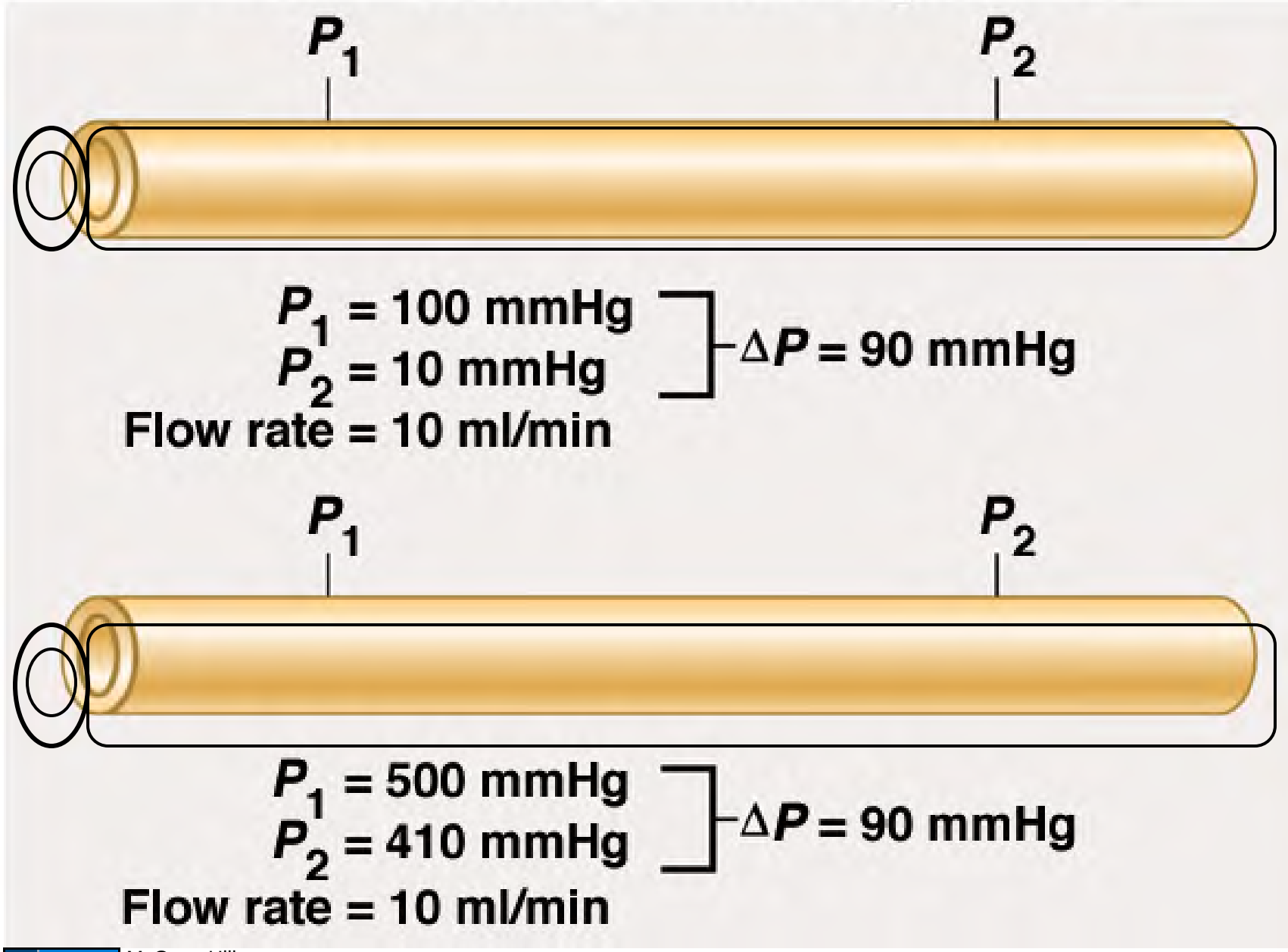
Pulse Pressure Increases with age

$$\text{Flow} = \frac{P_{artery} - P_{vein}}{R}$$

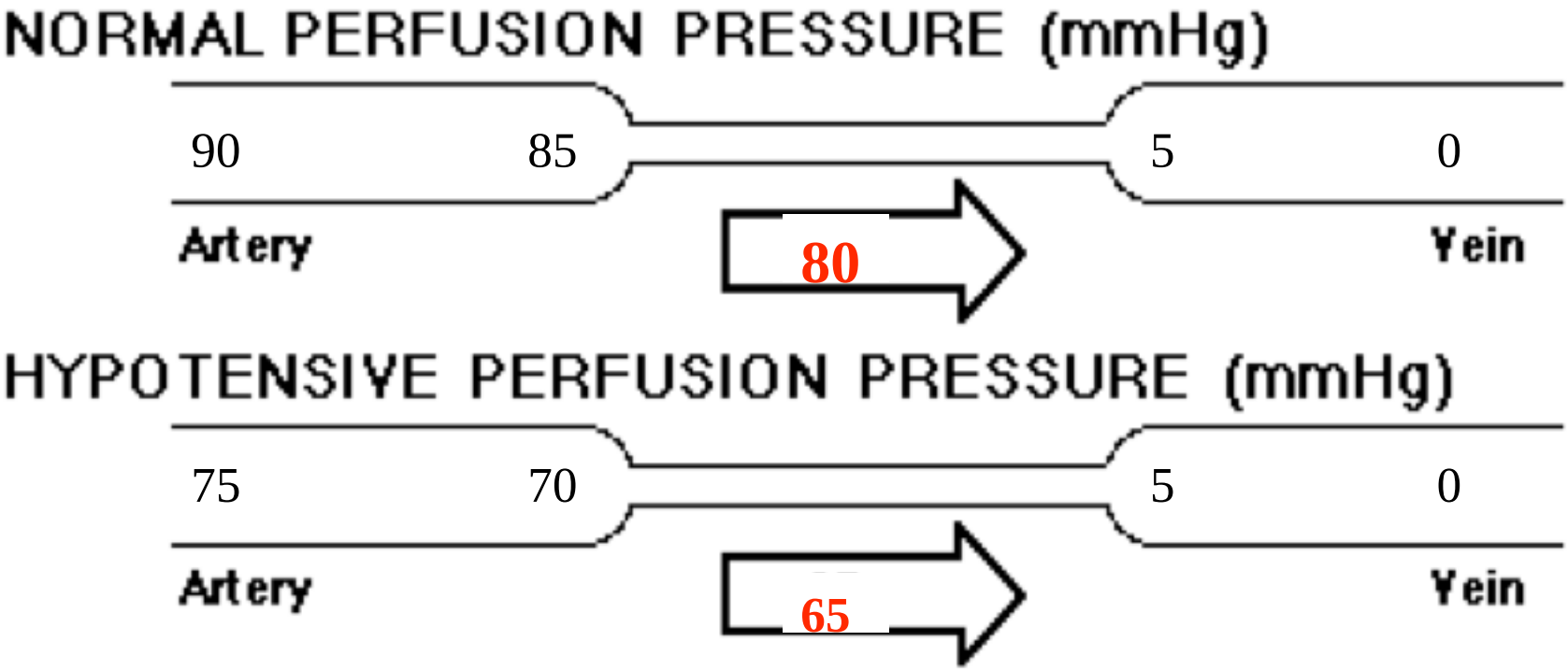
Flow is directly proportional to the pressure difference.

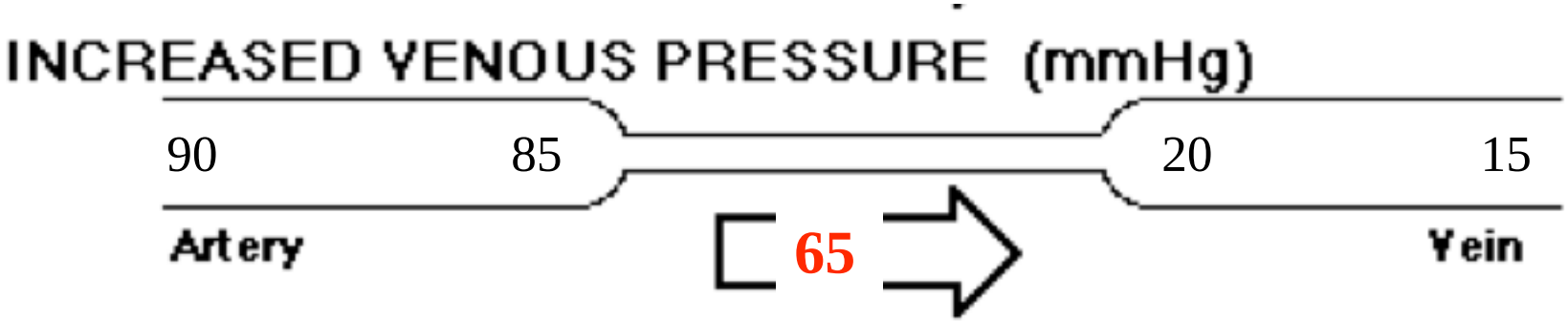
“pressure gradient” or ΔP

Flow between two points



Arterial
Determinants of Perfusion Pressure





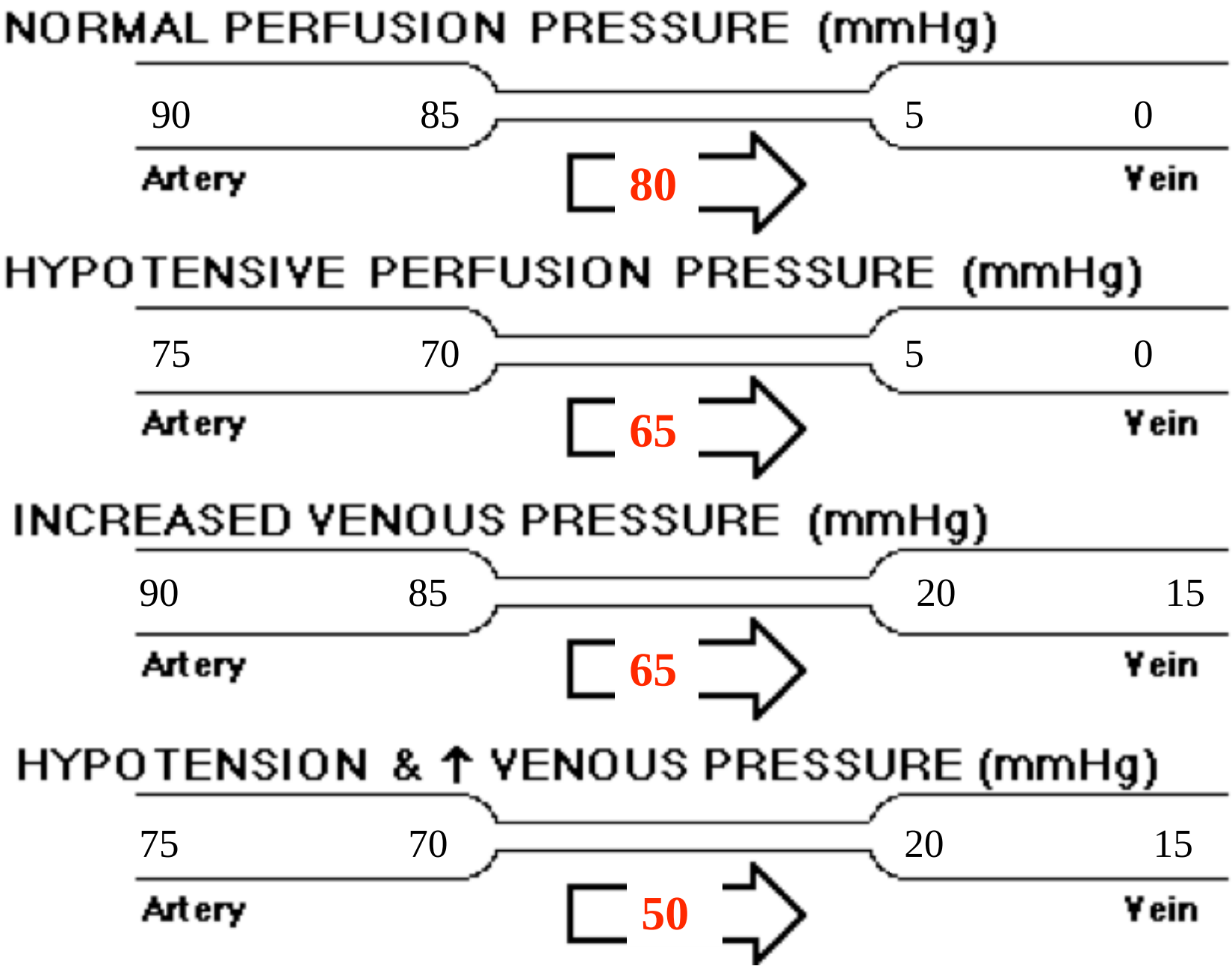
e.g. due to excessive hydration

Or Laparoscopic Surgery ?

Abdominal Compartment Syndrome

Both can compress great veins and reduce visceral perfusion pressure.

DETERMINANTS OF PERFUSION PRESSURE



$$\text{Flow} = \frac{P_{artery} - P_{vein}}{R}$$

Flow is

directly proportional to ΔP

and

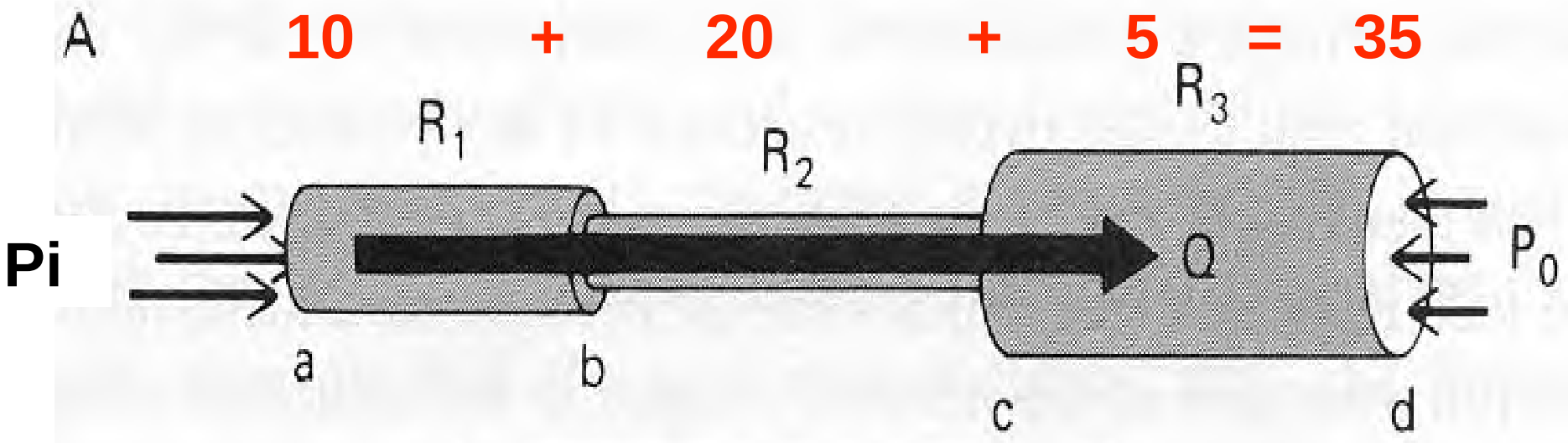
inversely proportional to R

R = resistance

Resistance ~ hindrance to flow

Series Resistance Add

A 10 + 20 + 5 = 35



$$R_s = R_1 + R_2 + R_3$$

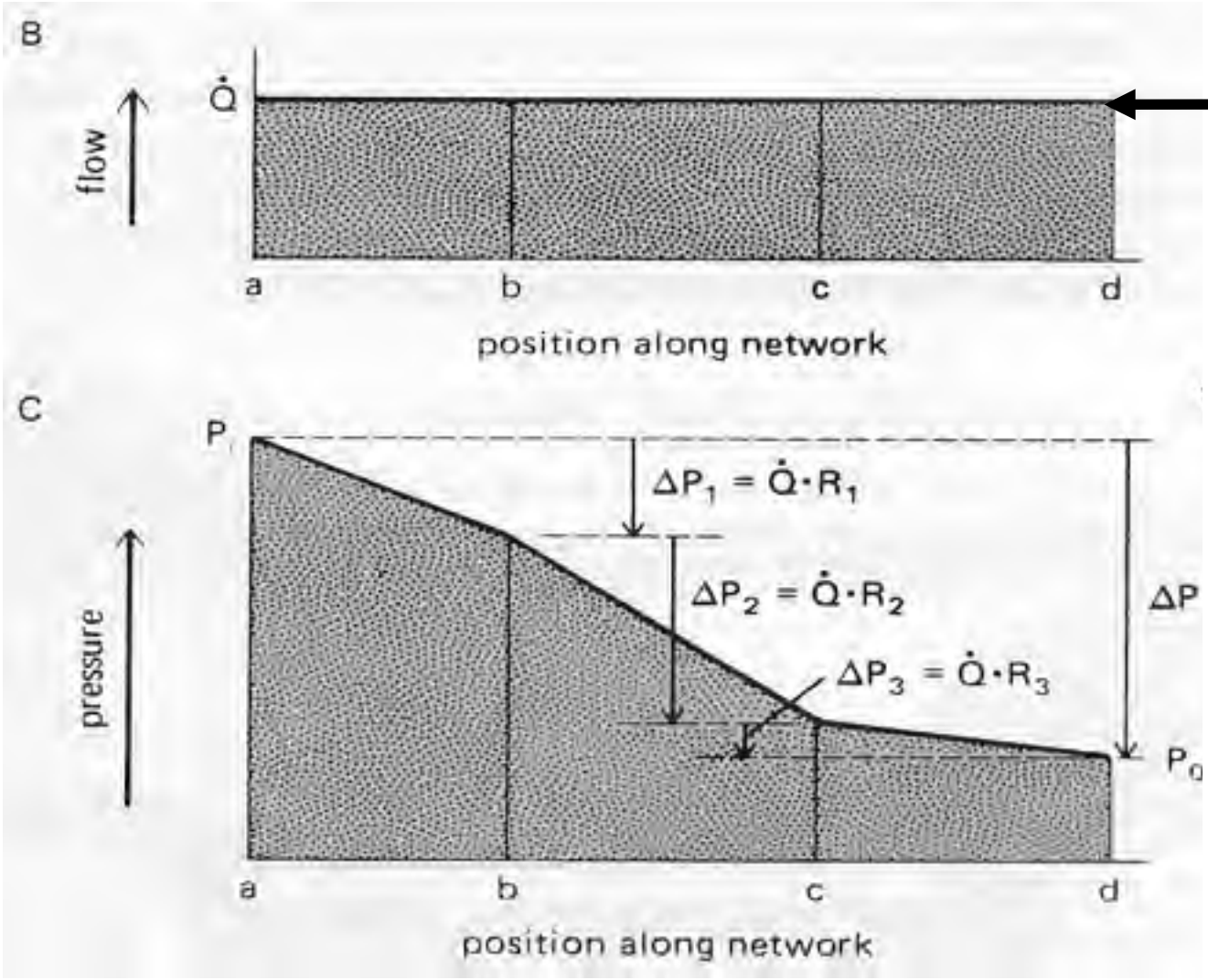
$$\Delta P = P_i - P_0$$

$$\dot{Q} = \Delta P / R_s$$

Q = flow

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

F = Δ P/R 10 = 100/10 10 = 200/20 10 = 50/5



10 = 350/35
Flow is same

**Measure flow and pressure drop and calculate resistance.

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

R = Resistance r = radius

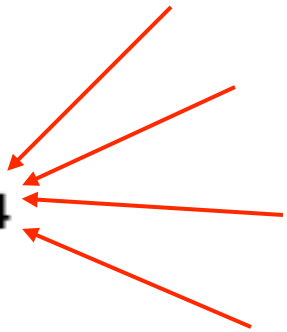
$$R = \frac{8 \eta L}{\pi r^4}$$

L = length
eta = viscosity
r = radius

$$R = \frac{8 \eta L}{\pi r^4} \approx \frac{1}{r^4}$$

Flow = Perfusion Pressure / Resistance

$$\approx PP \times r^4$$



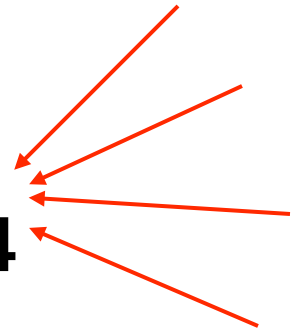
Thus 2X r produces 16X flow!!

Flow is

directly proportional to ΔP

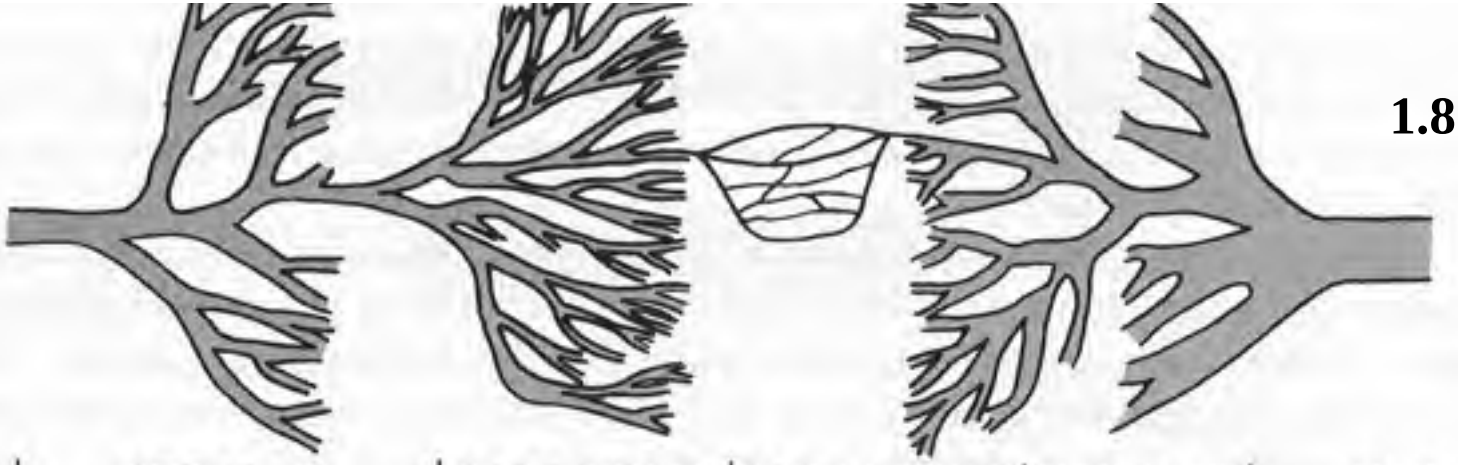
and

directly proportional to r^4



i.e. the 4th power of the radius

1.8 MH



	ARTERIES		ARTERIOLES	CAPILLARIES	VENULES		VEINS
	Aorta						Venae cavae
internal diameter	2.5 cm	0.4 cm	30 μm	5μm	70 μm	0.5 cm	3 cm
wall thickness	2 mm	1 mm	20 μm	1 μm	2 μm	0.5 mm	1.5 mm
number	1	160	5×10^7	10^{10}	10^8	200	2
total cross-sectional area	4.5 cm^2	20 cm^2	400 cm^2	4500 cm^2	4000 cm^2	40 cm^2	18 cm^2

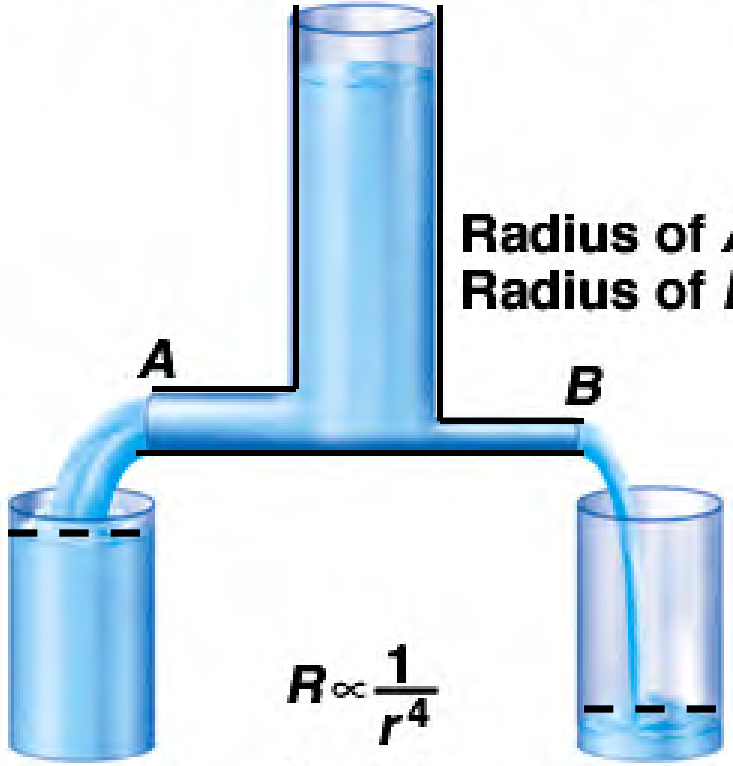
25,000 μm range **X 5,000**

one-way valves

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

Effect of tube radius

Same ΔP



Radius of A $(r_A) = 2$
Radius of B $(r_B) = 1$

$$R \propto \frac{1}{r^4}$$

$$R_A \propto \frac{1}{(r_A)^4} = \frac{1}{2^4} = \frac{1}{16} = 0.0625$$

$$R_B \propto \frac{1}{(r_B)^4} = \frac{1}{1^4} = \frac{1}{1} = 1.0$$

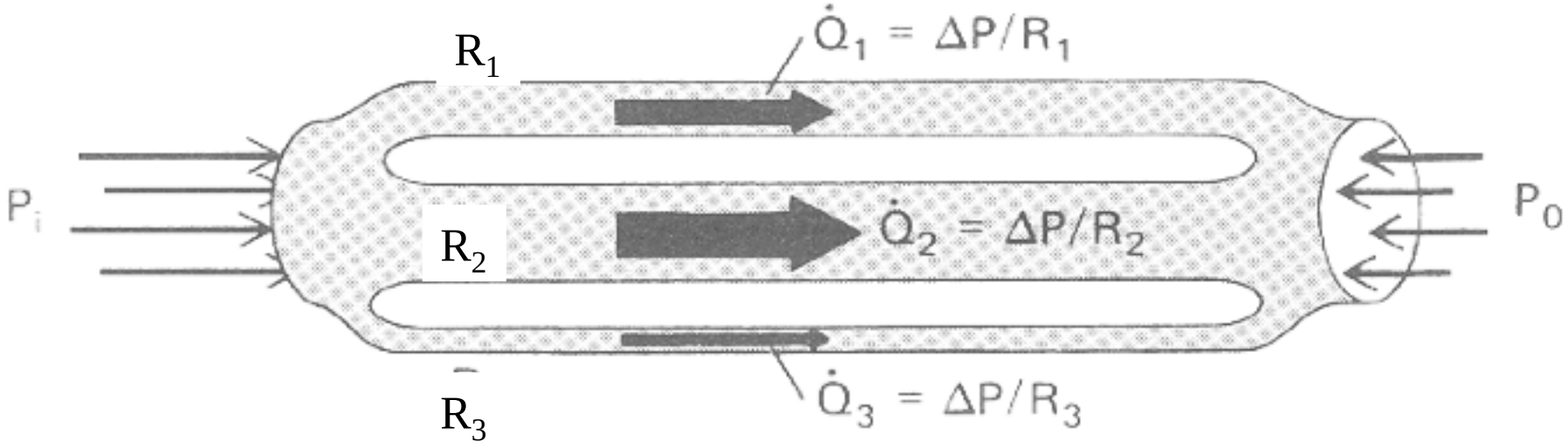
Therefore $R_B = 16\ R_A$

$$\text{Flow} = \frac{\Delta P}{R}$$

Therefore flow in $B = \frac{1}{16}$ th of flow in A

Parallel Resistance Network

With different individual resistances



$$\frac{1}{R_p} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$$

$$\Delta P = P_i - P_0$$

$$\dot{Q}_{total} = \dot{Q}_1 + \dot{Q}_2 + \dot{Q}_3$$

Flow adds

$$\dot{Q}_{total} = \Delta P / R_p$$

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

Another example:

Parallel Resistance Network

With identical individual resistances

Assume you have four vessel paths in parallel and each has the same individual resistance of 4.

What is the overall resistance of this parallel network?

$$\frac{1}{R_t} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4}$$

$$\frac{1}{R_t} = \frac{1}{4} + \frac{1}{4} + \frac{1}{4} + \frac{1}{4}$$

$$\frac{1}{R_t} = \frac{4}{4}$$

$$R_t = 1$$

COMBINED (Total)

The parallel resistance network has less resistance than any individual component.

Parallel Resistance Network

More checkout lines means that there is less resistance to “flowing” out of the store.

Parallel resistances add as reciprocals.

Tissue Blood Flow and Tissue Vascular Resistance

(*Assume Perfusion Pressure is Constant ***)**

- **Vasoconstriction**
- $\Rightarrow \Downarrow r \Rightarrow \Uparrow R_{tissue} \Rightarrow \Downarrow F_{tissue}$

- **Vasodilation**

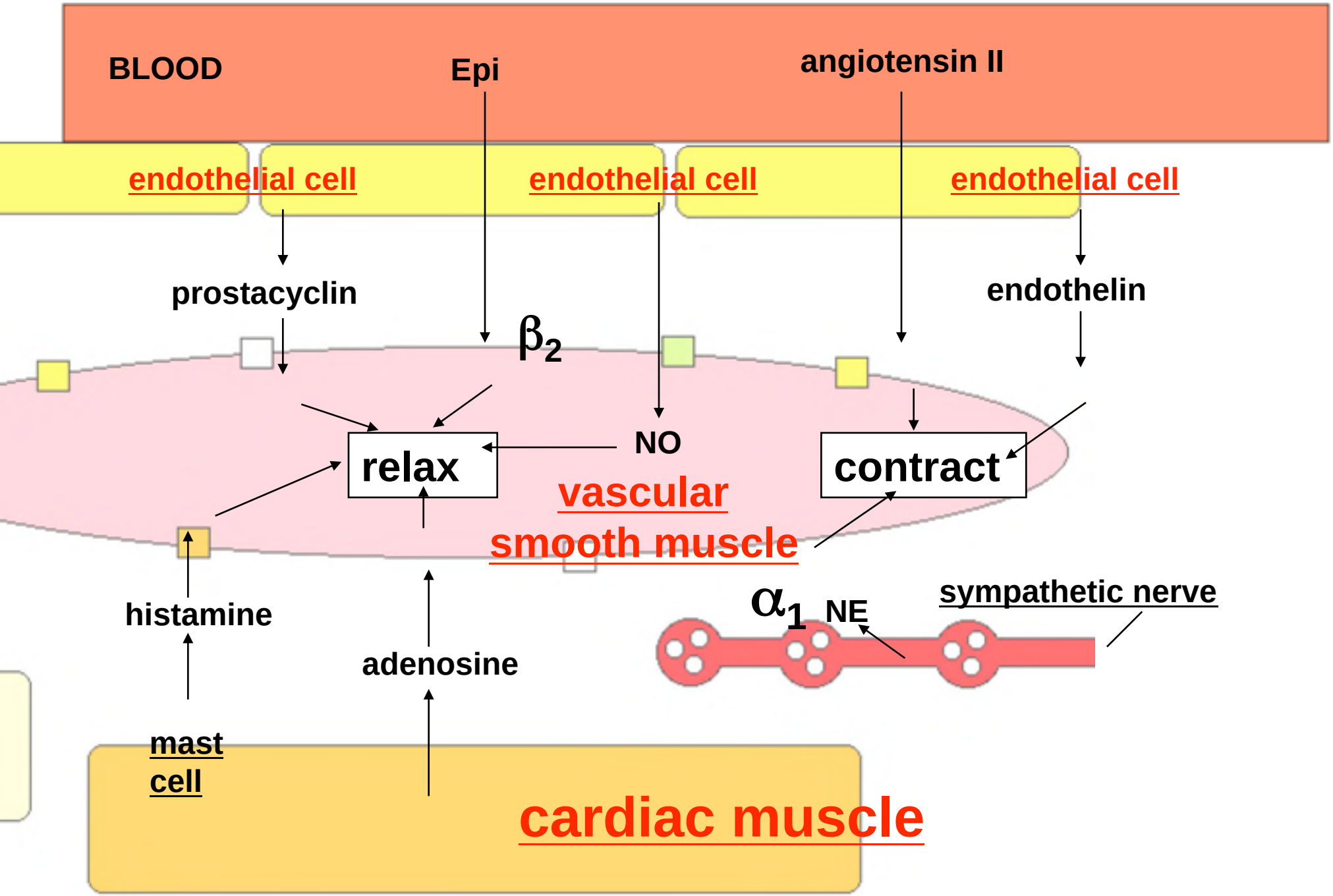
$\Rightarrow \Uparrow r \Rightarrow \Downarrow R_{tissue} \Rightarrow \Uparrow F_{tissue}$

$$F_{tissue} = \frac{\text{Perfusion Pressure}}{R_{tissue}}$$

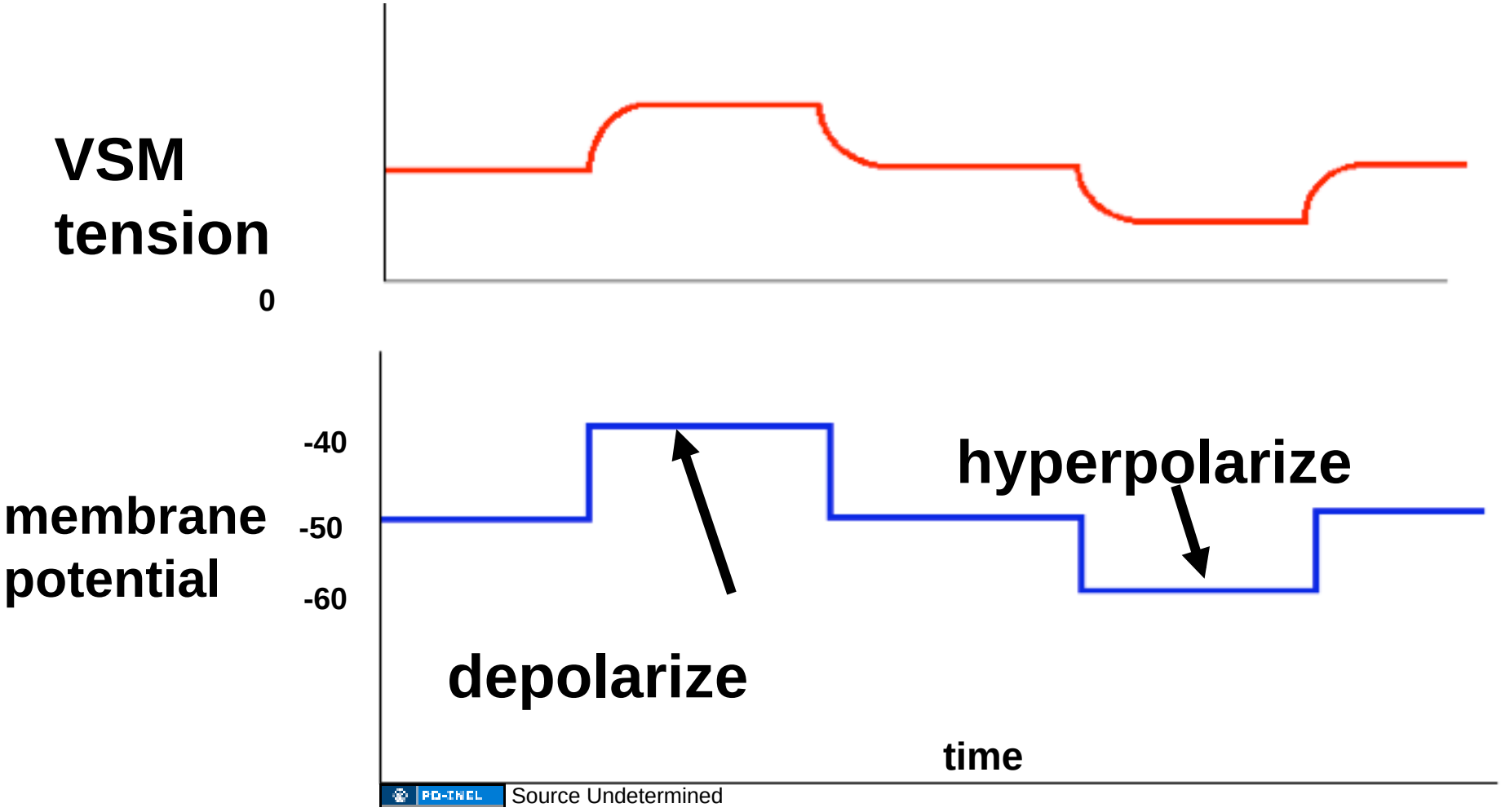
Monday 11/03/08, 10:00
Vascular Smooth Muscle

33 slides, 50 min.

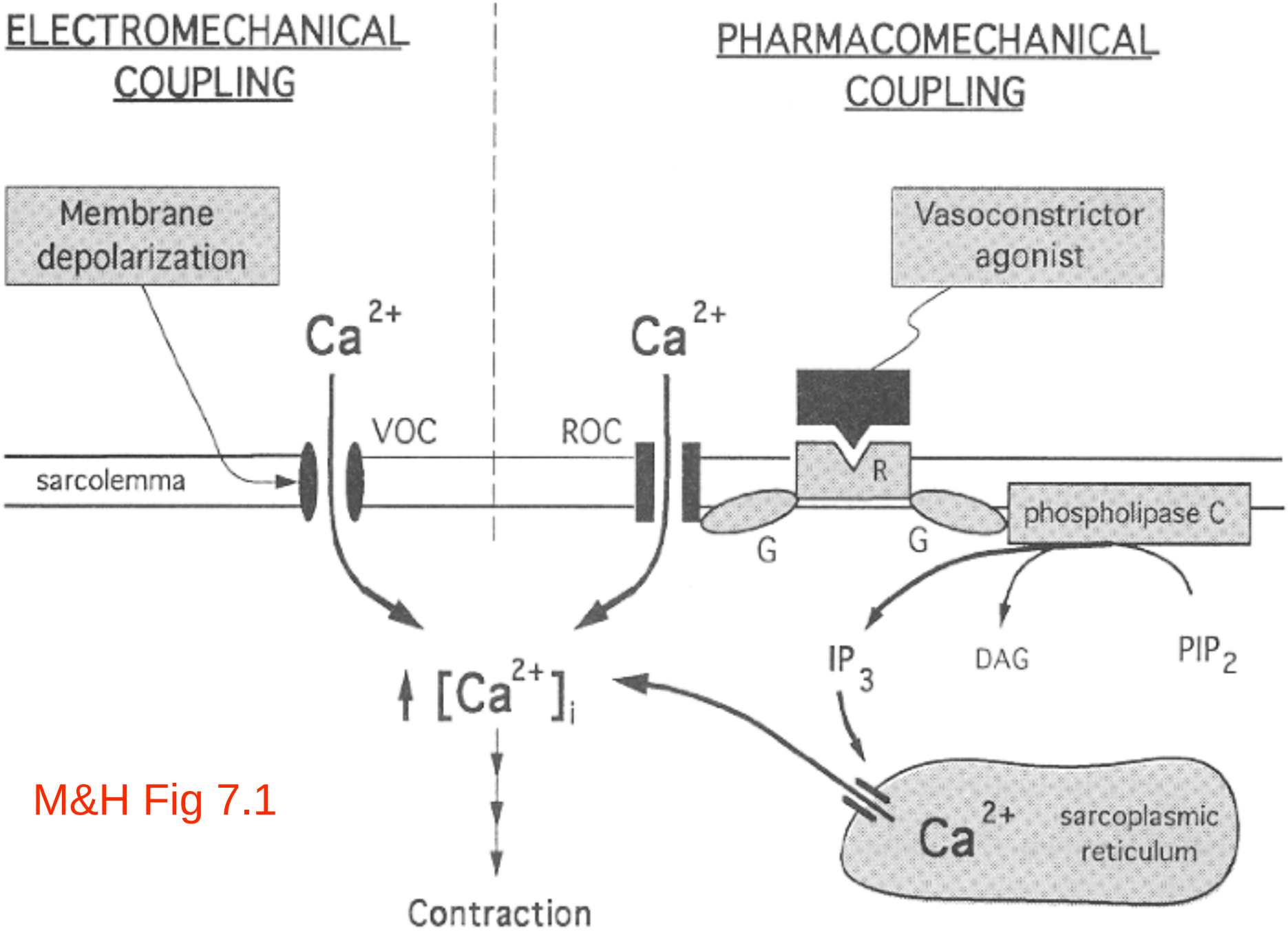
1. Vasoconstrictors and Vasodilators
2. Neural control of resistance
3. Humoral control of resistance
4. Local control of resistance
5. Nitric oxide, Nitric oxide synthase (NOS)
6. Asymmetrical dimethylarginine


BLOOD
Epi
angiotensin II
endothelial cell
endothelial cell
endothelial cell
prostacyclin
endothelin
β2
relax
NO
contract
vascular
smooth muscle
histamine
adenosine
α1 NE
sympathetic nerve
mast
cell
cardiac muscle

VSM can change tension without action potentials

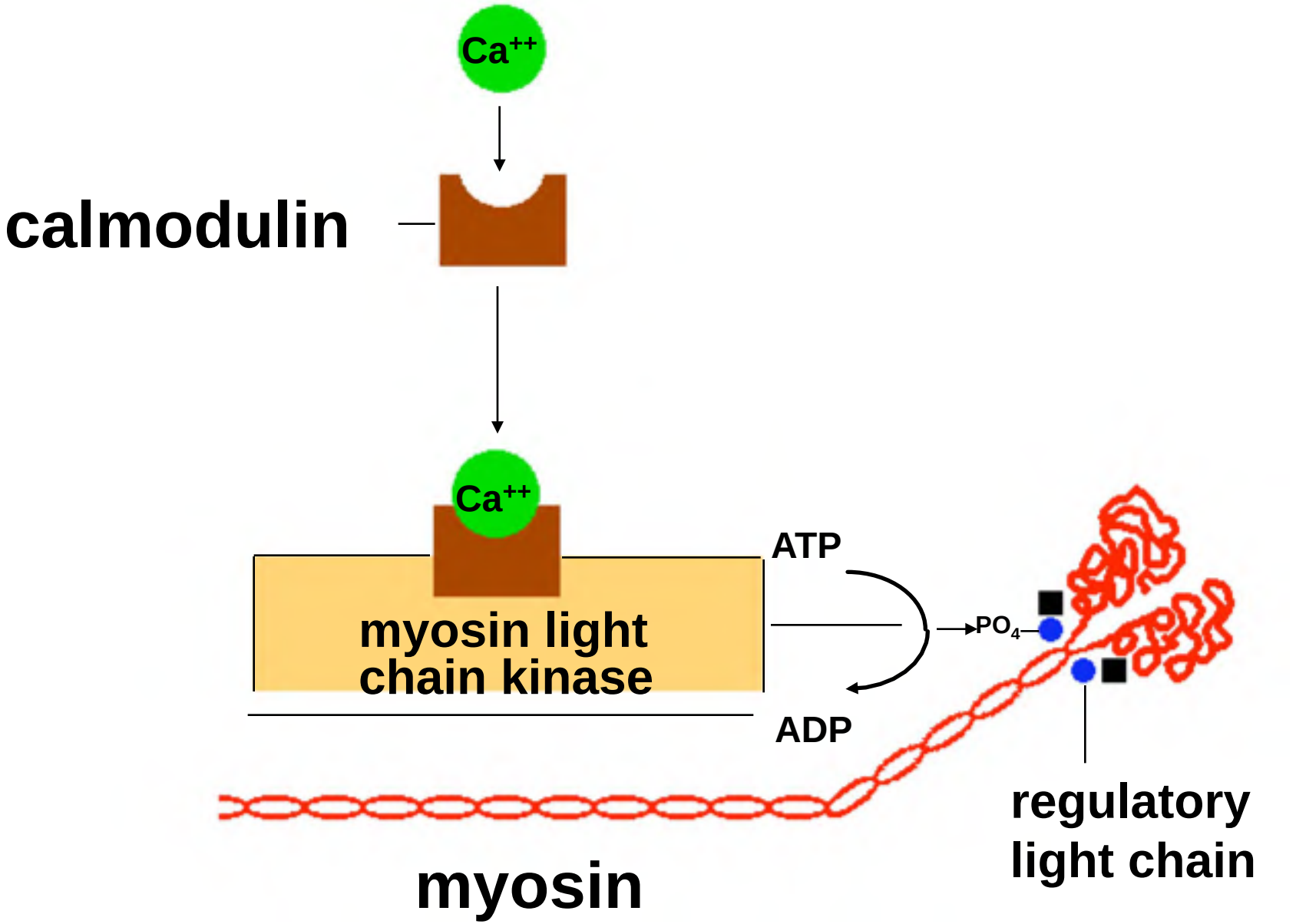


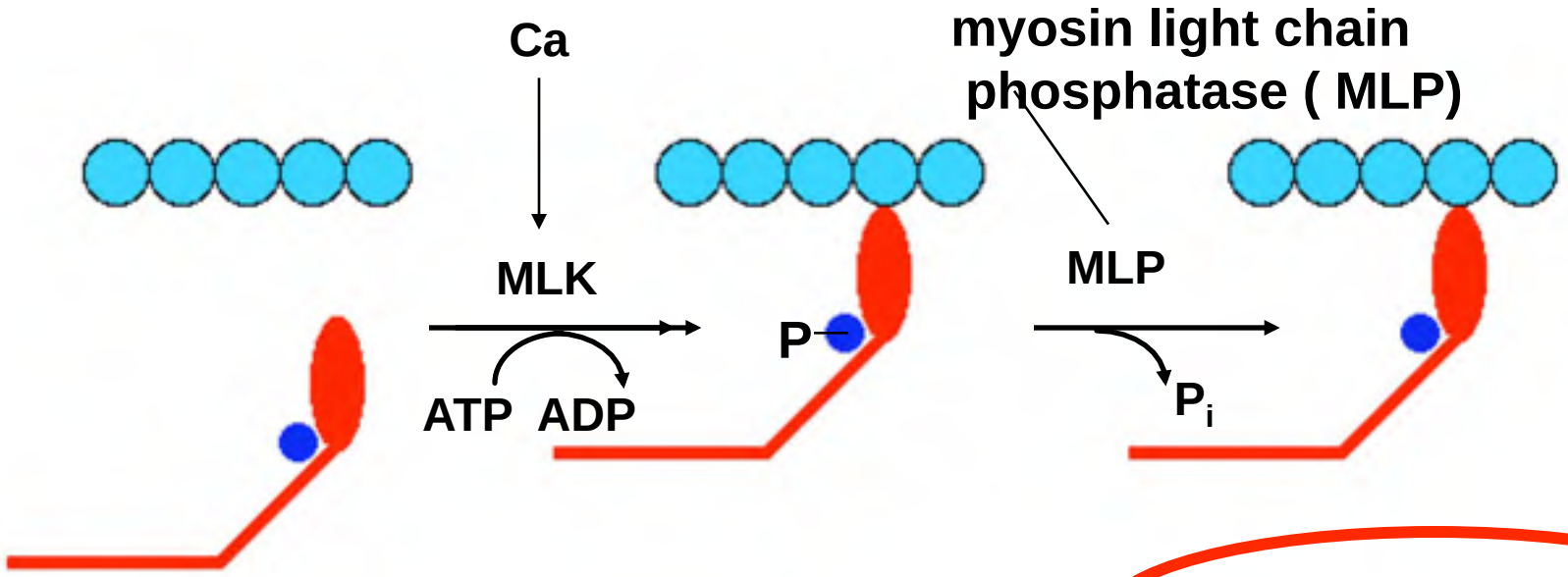
A change in VSM tension causes vasodilation or vasoconstriction



M&H Fig 7.1

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.


Ca++
calmodulin
Ca++
ATP
myosin light
chain kinase
PO4
ADP
regulatory
light chain
myosin



At rest

myosin can not bind to actin in absence of light chain phosphorylation

Cycling bridges

myosin rapidly dissociates from actin upon binding ATP during each cycle

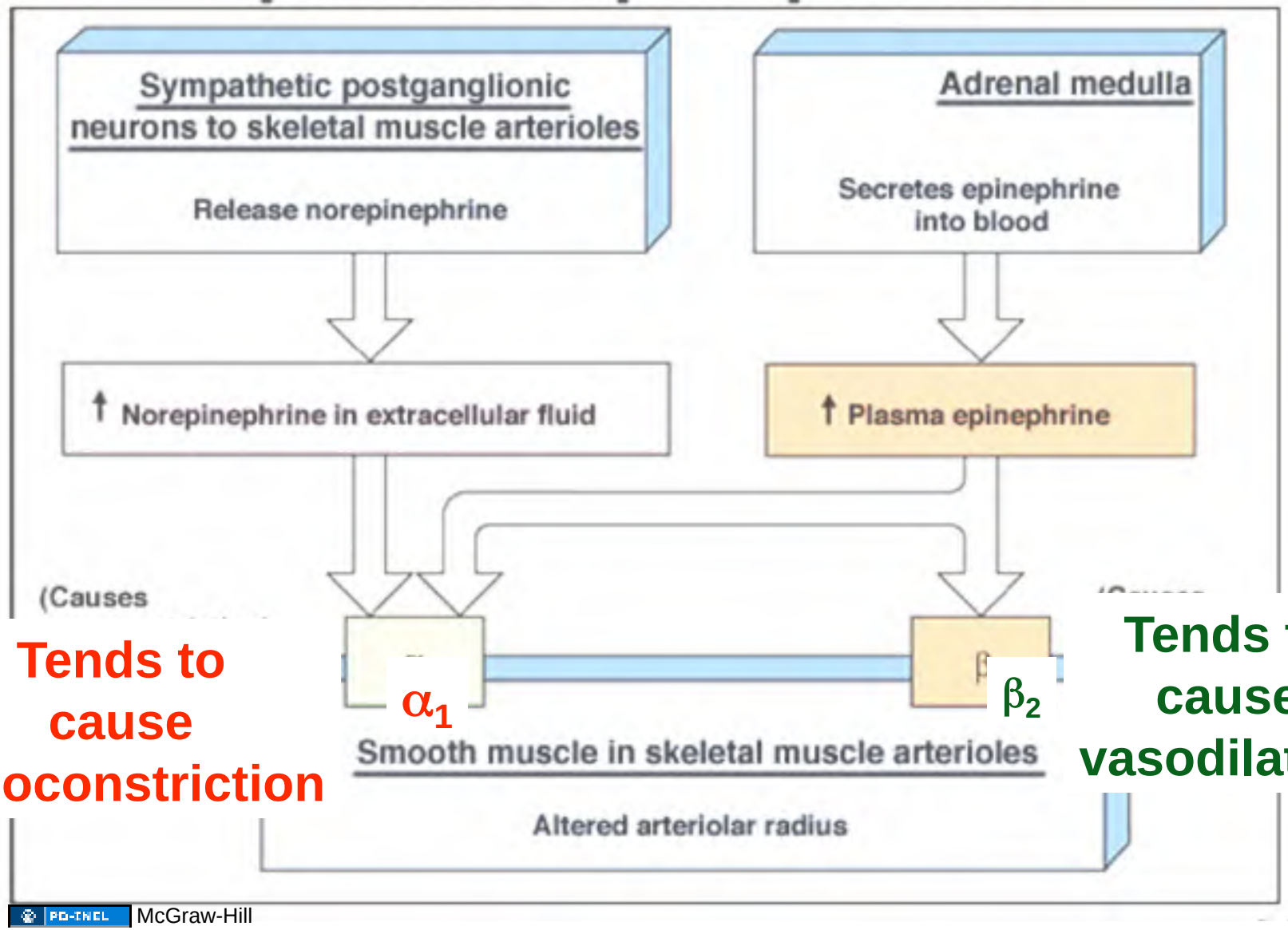
initial rise in muscle tension

Latch bridges

dephosphorylated myosin dissociates from actin very slowly producing slow bridge cycling

maintained tension tonic contraction

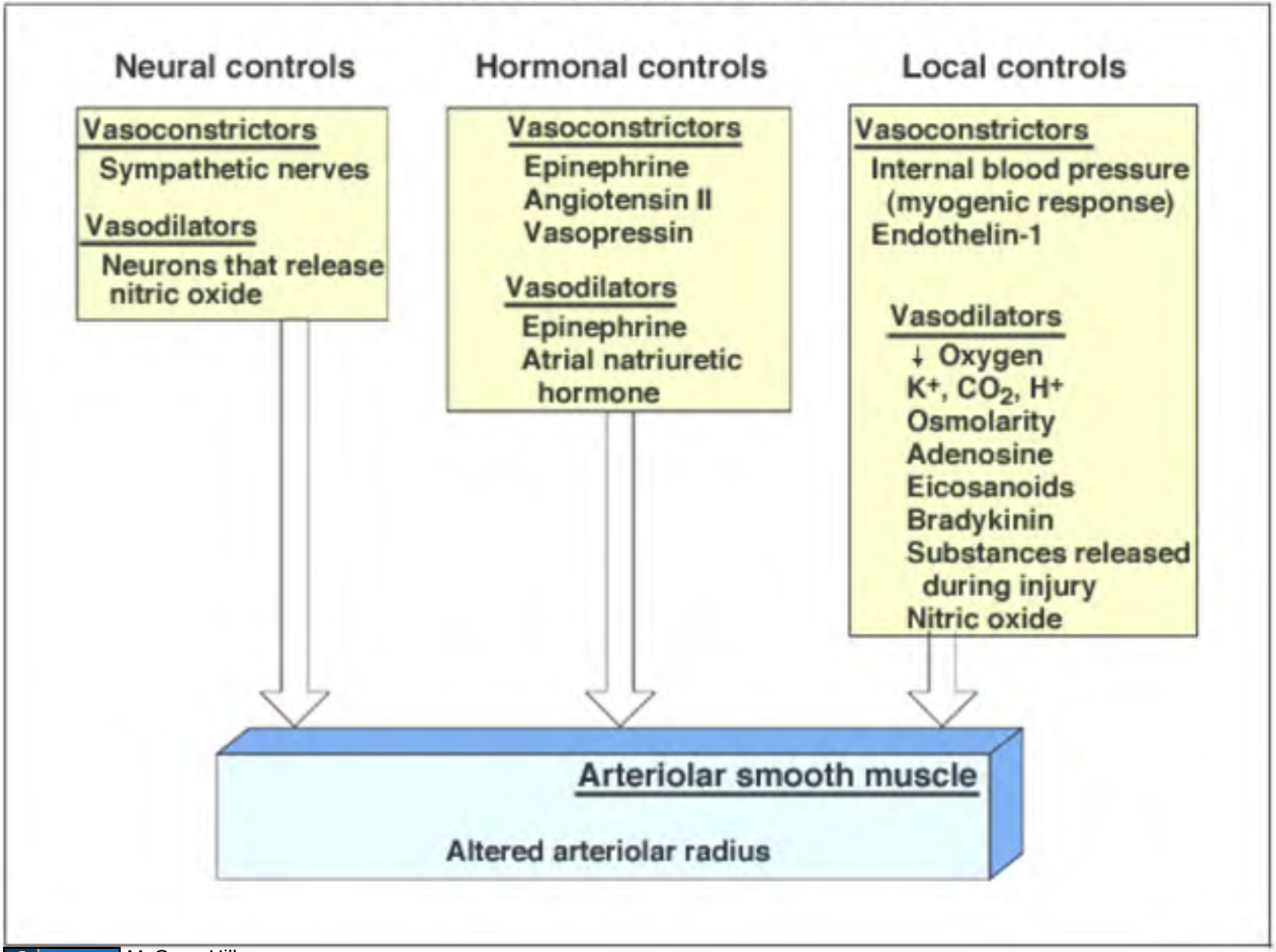
Sympathetic nerves/ plasma epinephrine



Tends to cause vasoconstriction

Tends to cause vasodilation

Arteriolar radius



Local Influences on Arterioles

(Local = no neural or humoral control)

Active Hyperemia

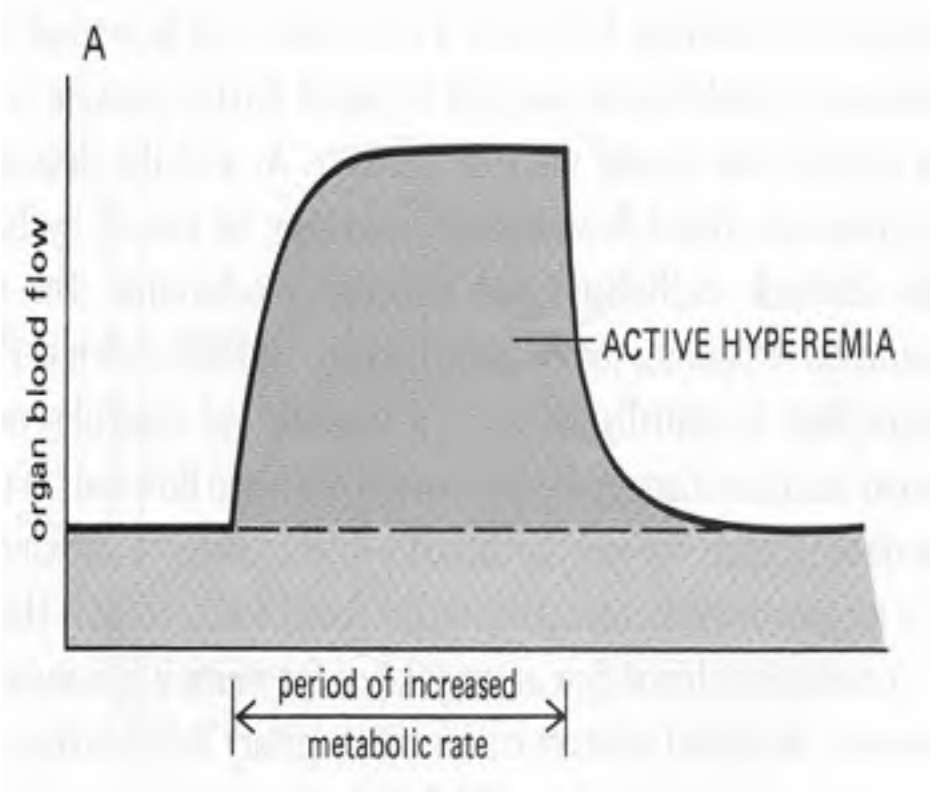
Reactive Hyperemia

Autoregulation

Think of accumulation of vasodilator metabolites.

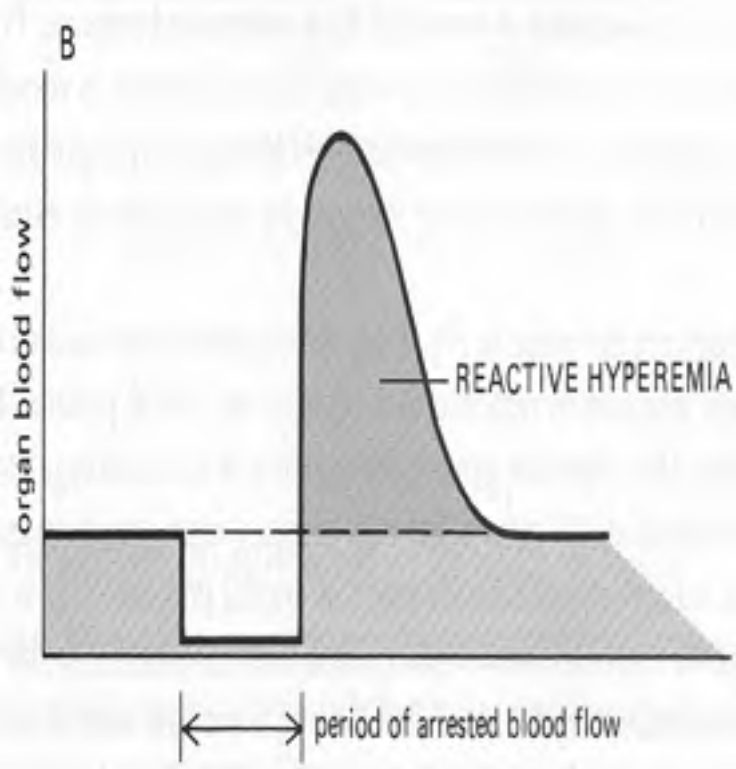
Active hyperemia

= increased blood flow in response to increased metabolic demand



Reactive Hyperemia

= increased blood flow following a period of no flow



M&H 7.3

 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

Reactive Hyperemia

Vascular Biology

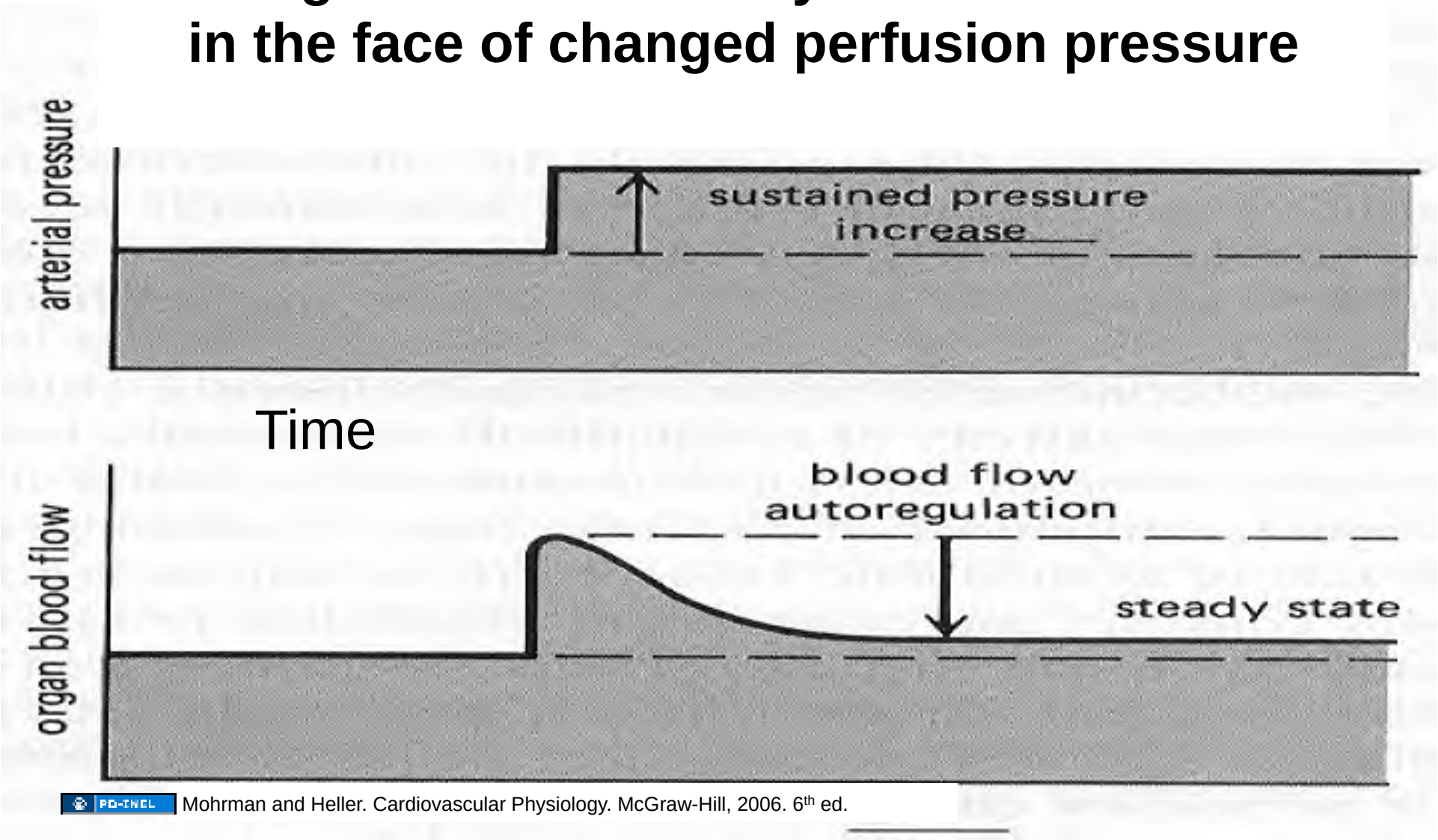
Predictive Value of Reactive Hyperemia for Cardiovascular Events in Patients With Peripheral Arterial Disease Undergoing Vascular Surgery

(*Arterioscler Thromb Vasc Biol.* 2007;27:2113-2119.)

Conclusions—Thus, lower reactive hyperemia is associated with increased cardiovascular risk in patients with peripheral arterial disease. Furthermore, flow-mediated dilation and reactive hyperemia incrementally relate to cardiovascular risk, although impaired flow-mediated dilation was the stronger predictor in this population. These findings further support

Arteriosclerosis Thrombosis Vascular Biology

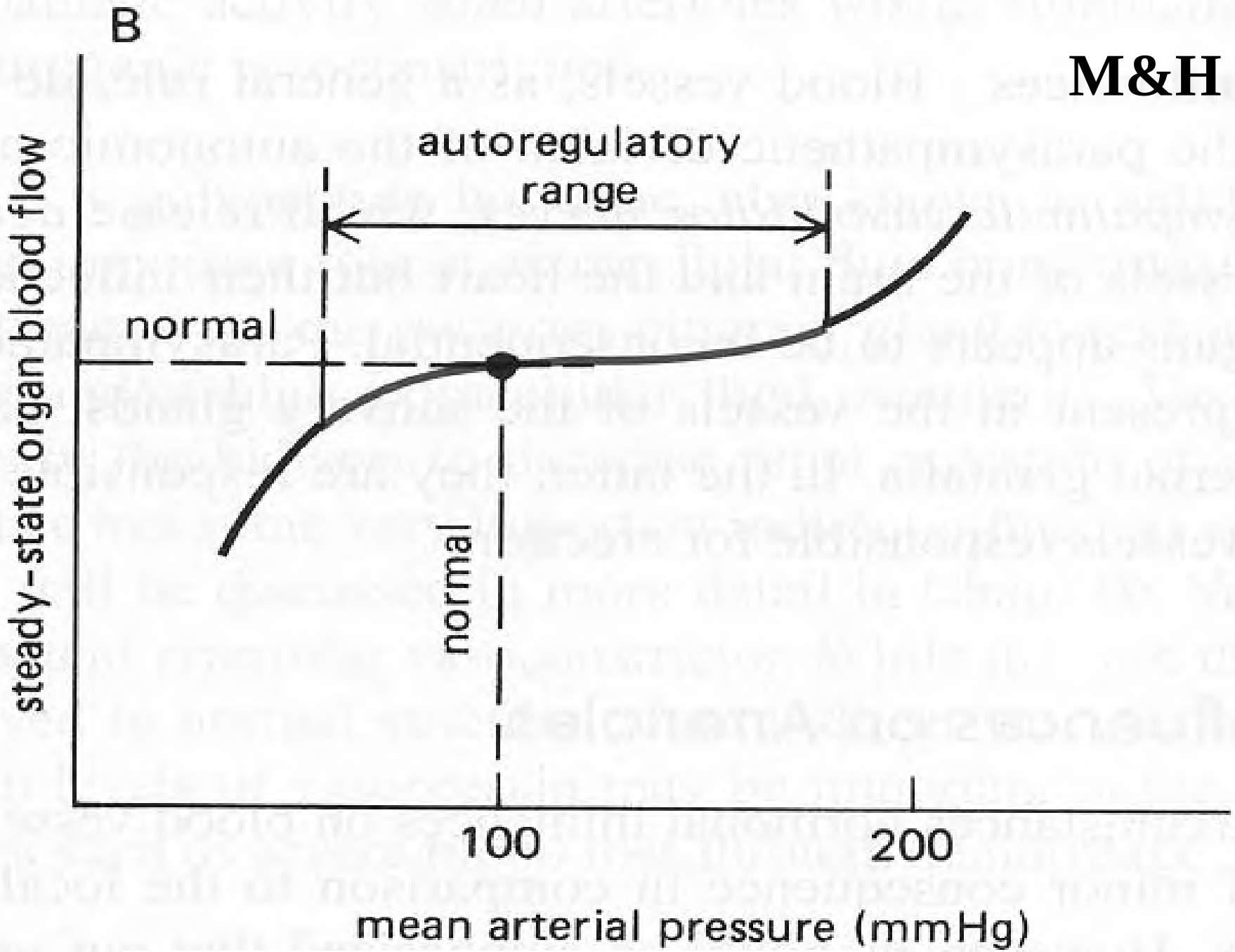
Autoregulation = relatively constant blood flow in the face of changed perfusion pressure



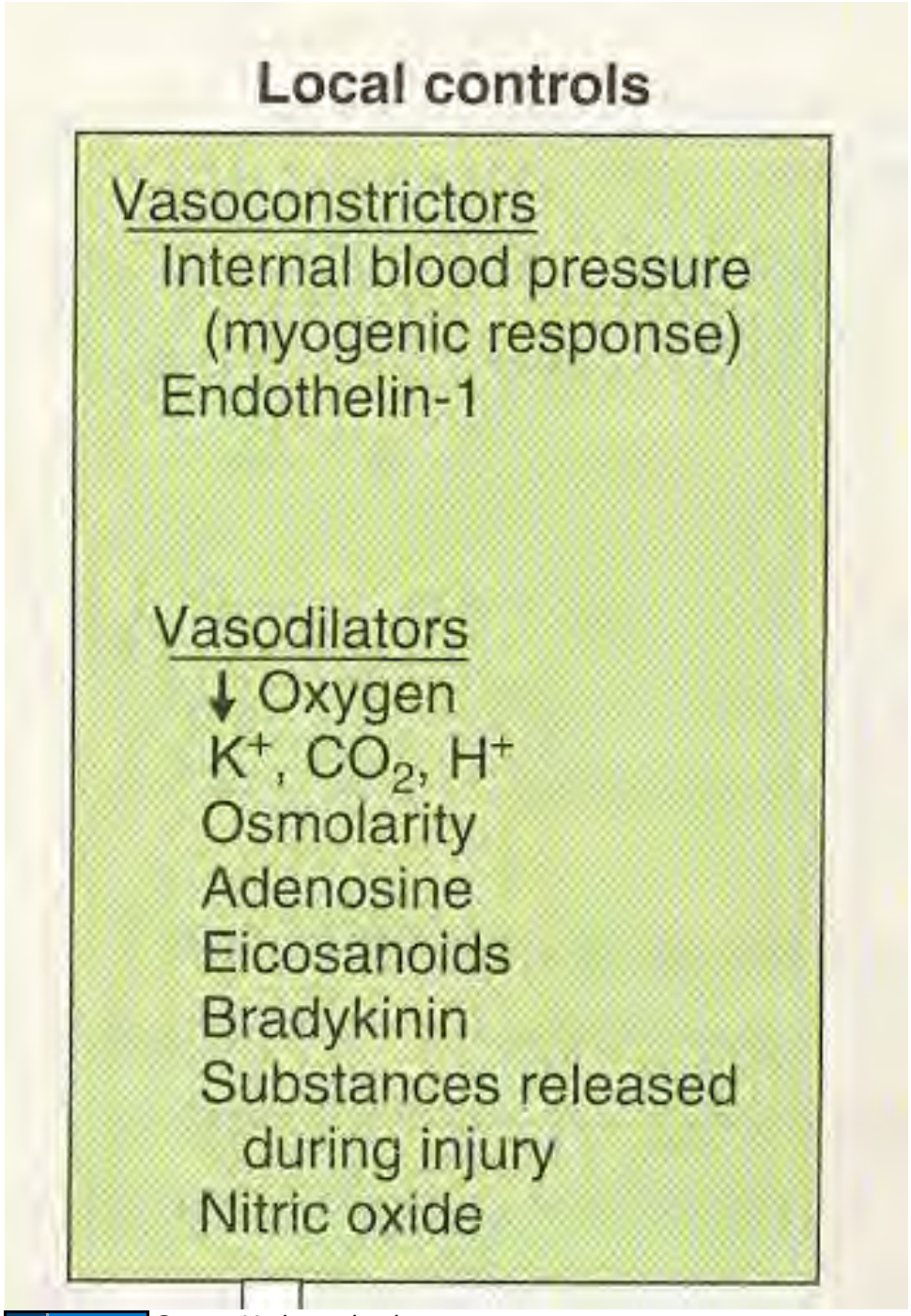
PD-INEL Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.

Think of vasodilator metabolite washout.

M&H 7.4



 Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.



Other Smooth Muscles

Vascular

- arteries, arterioles, venuoles, veins, lymphatic

Gastrointestinal

- longitudinal vs circular, esophageal, gastric, intestinal
- sphincter smooth muscles, gallbladder
- bile and pancreatic ducts

Pulmonary

- tracheal, bronchial, bronchiolar

Urinary System

- bladder, ureters, urethra

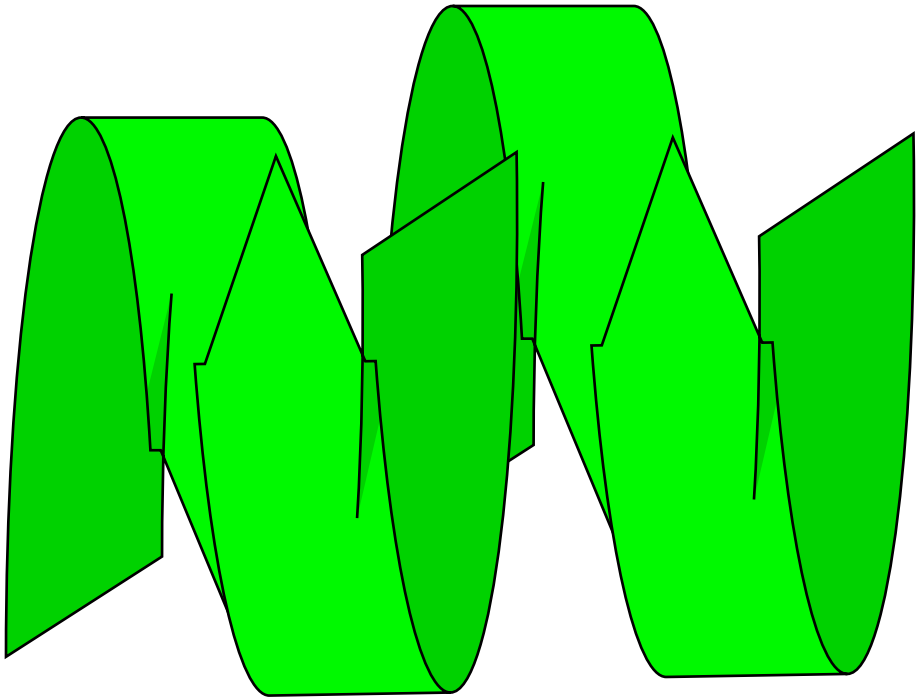
Reproductive System

- uterus, vagina, oviducts, vas deferens, prostate capsule

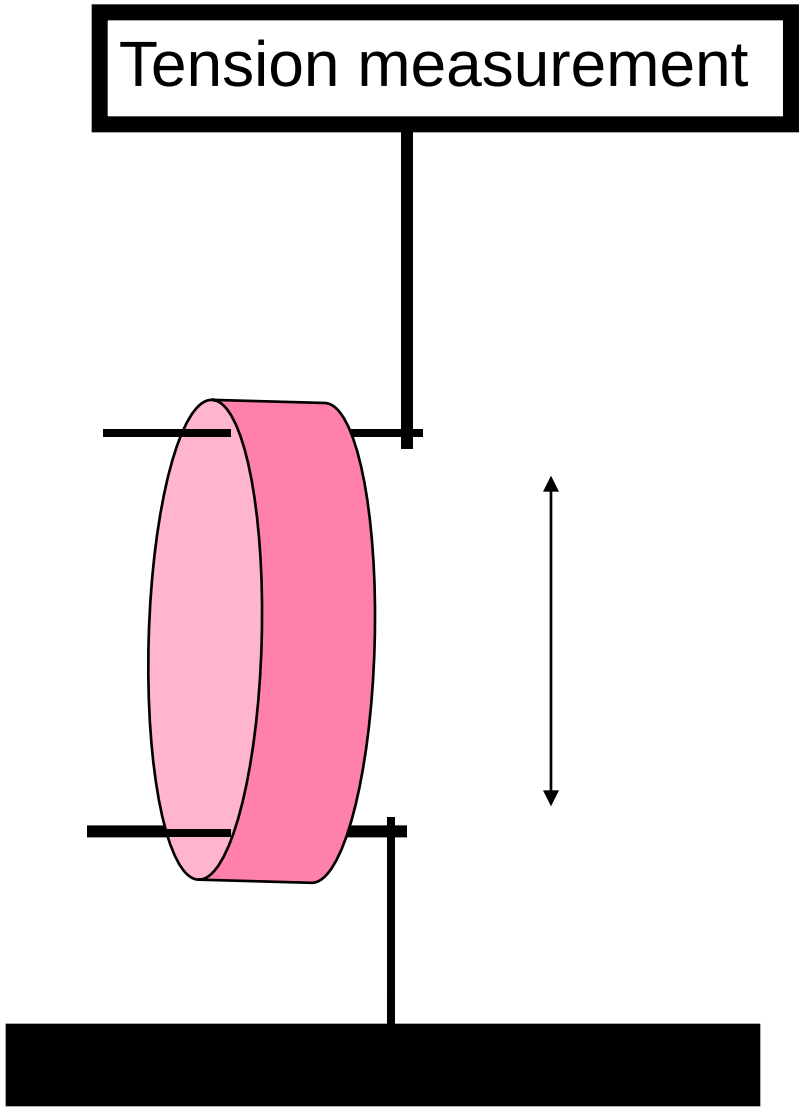
Miscellaneous

- iris of eye
- capsule of spleen
- piloerector muscles of skin hairs
- myoepithelial cells of glands

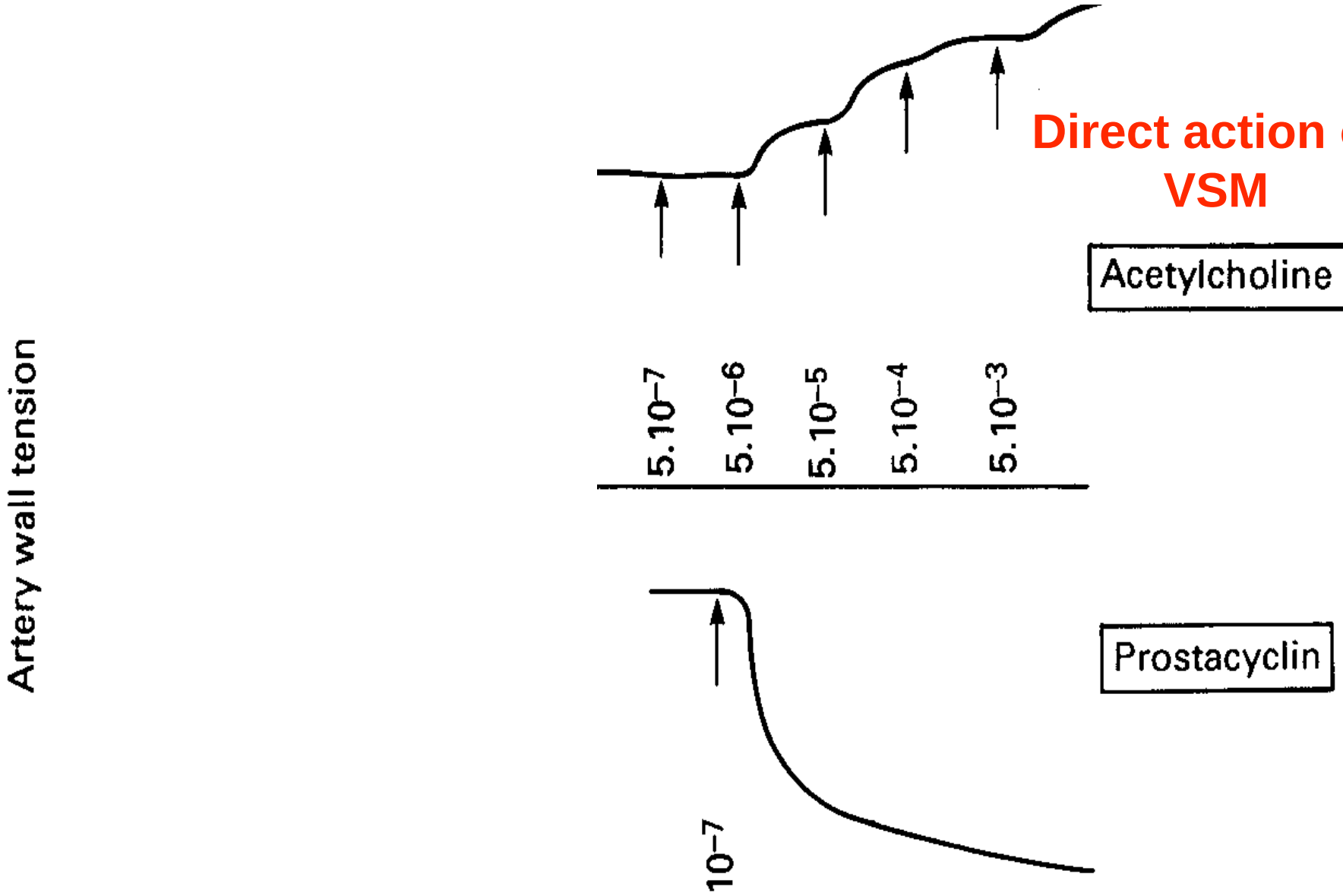
Spiral cut vessel strip



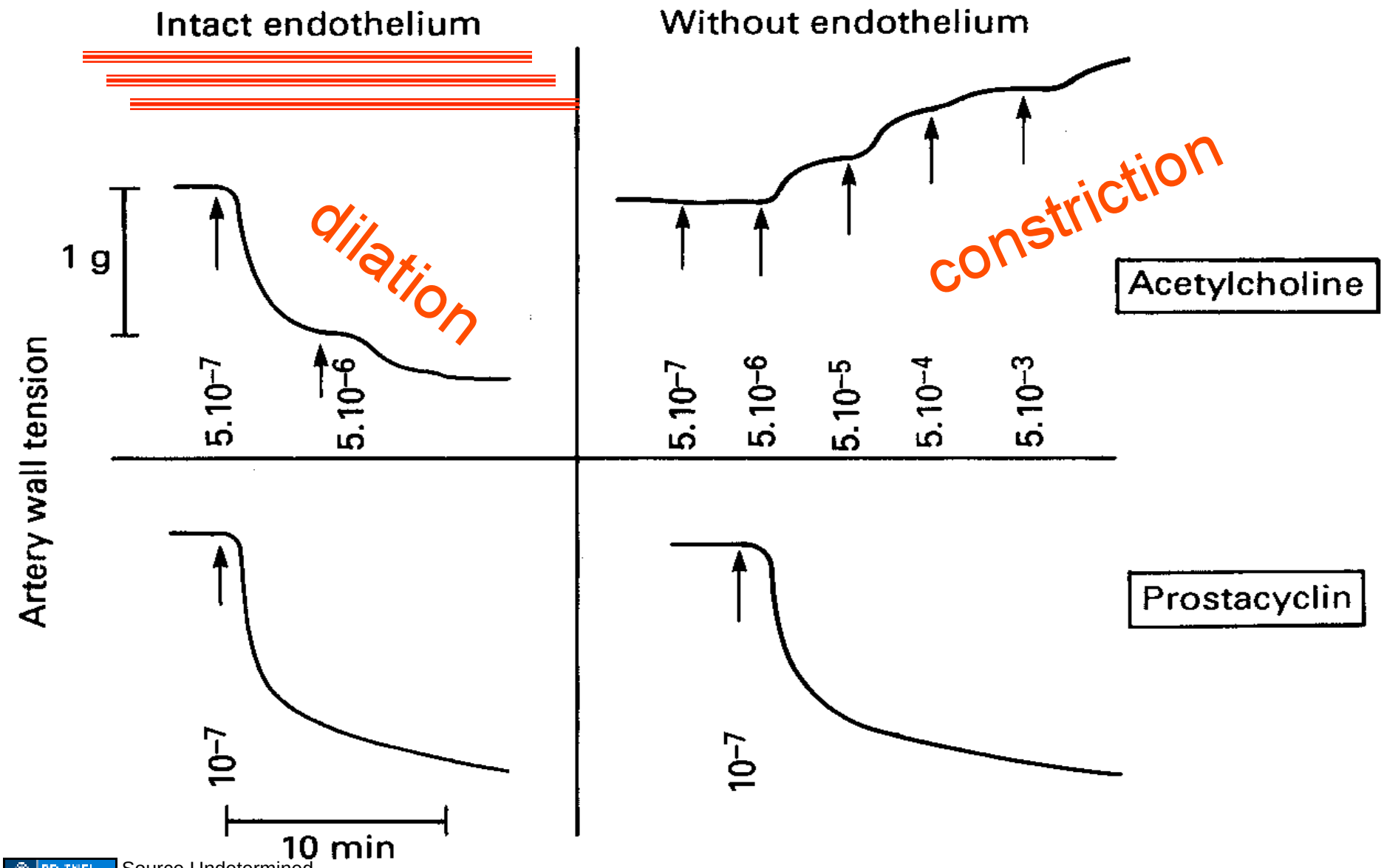
Vessel Ring



Historical Response to Ach = contraction !!



Vessel with intact endothelium relaxes to Ach !!!!!!
Via NO release from EC



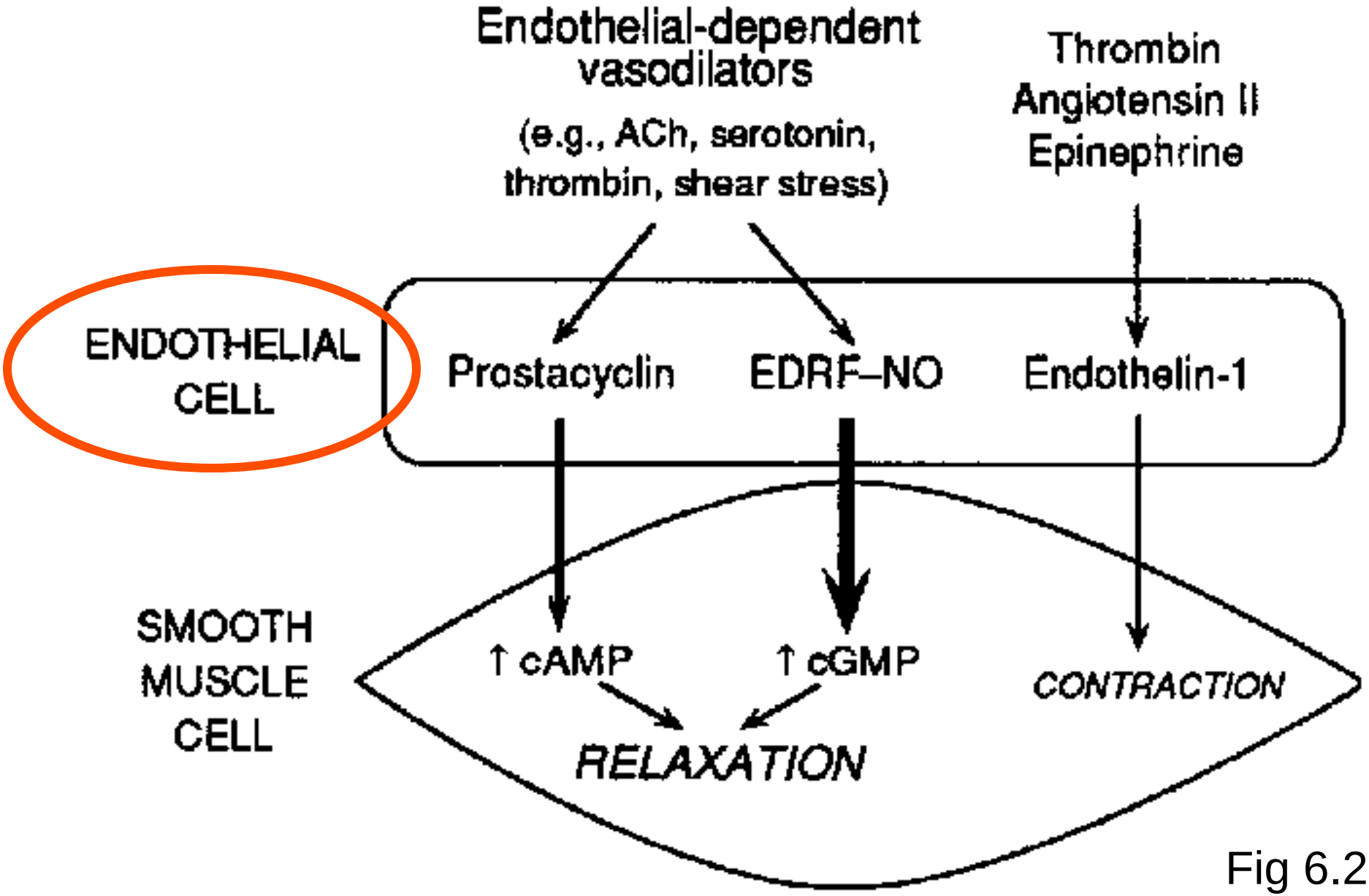
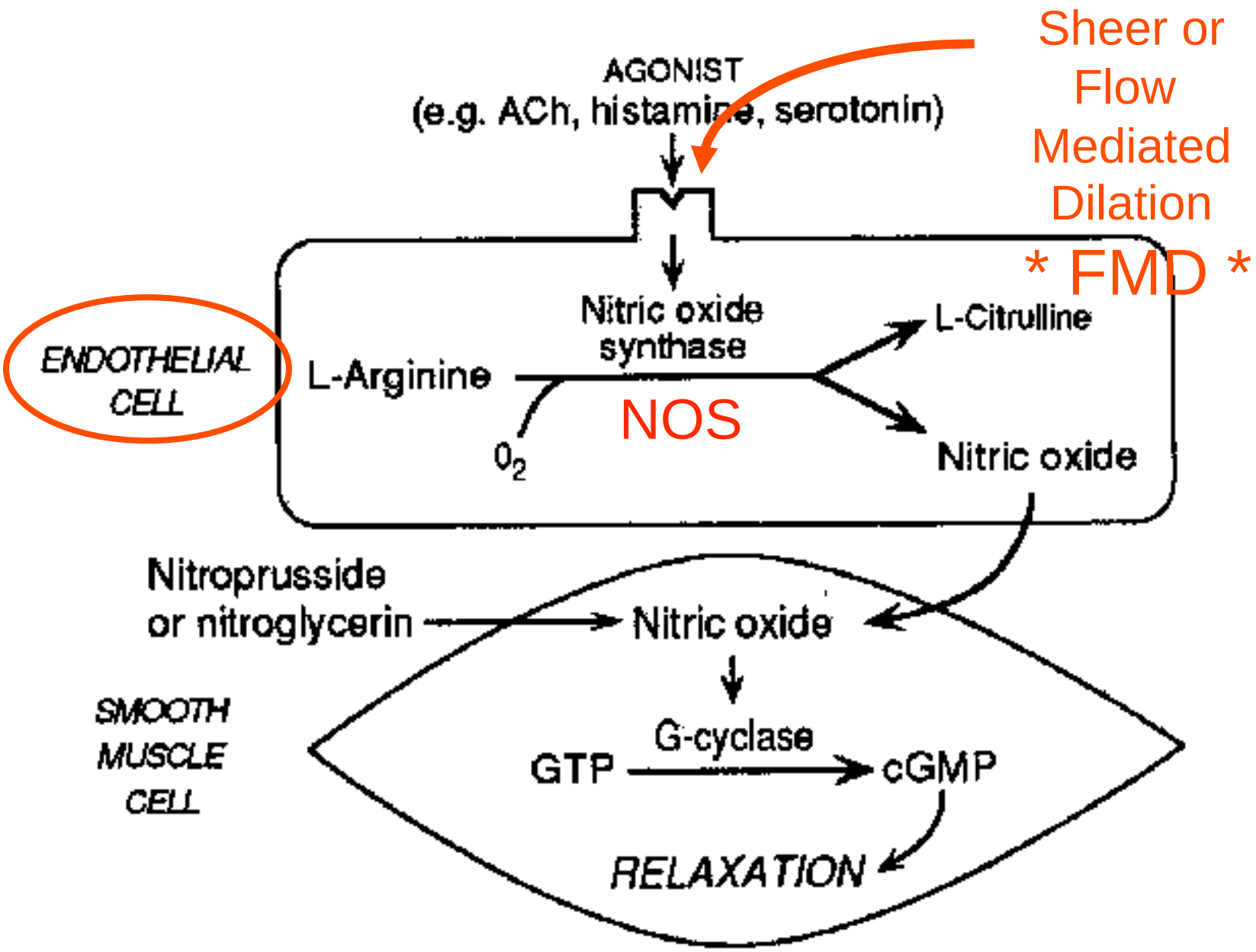


Fig 6.2

 Lilly, L. Pathophysiology of Heart Disease. Lippincott, 2007. 4th ed.

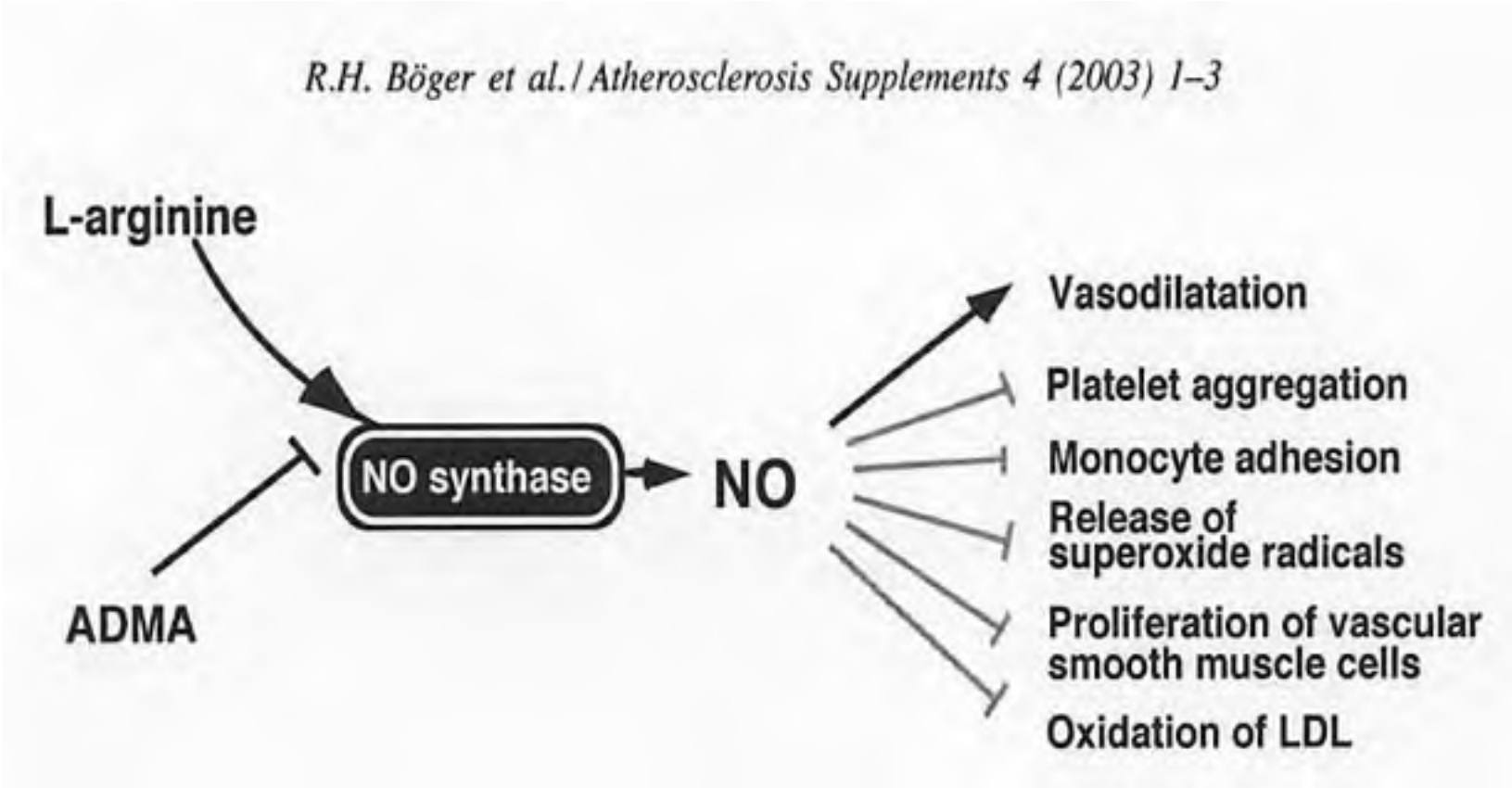


Lilly, L. Pathophysiology of Heart Disease. Lippincott, 2007. 4th ed.

NOS Isoforms, Activity and Inhibition

- Three isoforms: endothelial, neuronal and inducible
- Catalyze formation of NO and citrulline from L-arg
- NO production in endothelium produces------
  – Vasodilation, inhibition of platelet aggregation & inhibition of pro-inflammatory response
- Inhibit NOS ⇒ ⇓NO ⇒ endothelial dysfunction ⇒
  –vasoconstriction
  –atherogenesis
  – cardiovascular disease

ADMA the newest “bad guy”; maybe?



R.H. Boger et. Al, Atherosclerosis Supplements 4 (2003) 1-3

Asymmetrical Dimethylarginine = ADMA

Asymmetrical Dimethylarginine (ADMA)

- What is it?
- What can it do?
- Where does it come from?
- Where does it go?
- What does it really do?
- Can we mimic or block it to therapeutic advantage?

The Cast of Players

ADMA = Asymmetrical dimethylarginine
(more abundant NOS inhibitor)

SDMA = Symmetrical dimethylarginine
(?? Inactive on NOS)

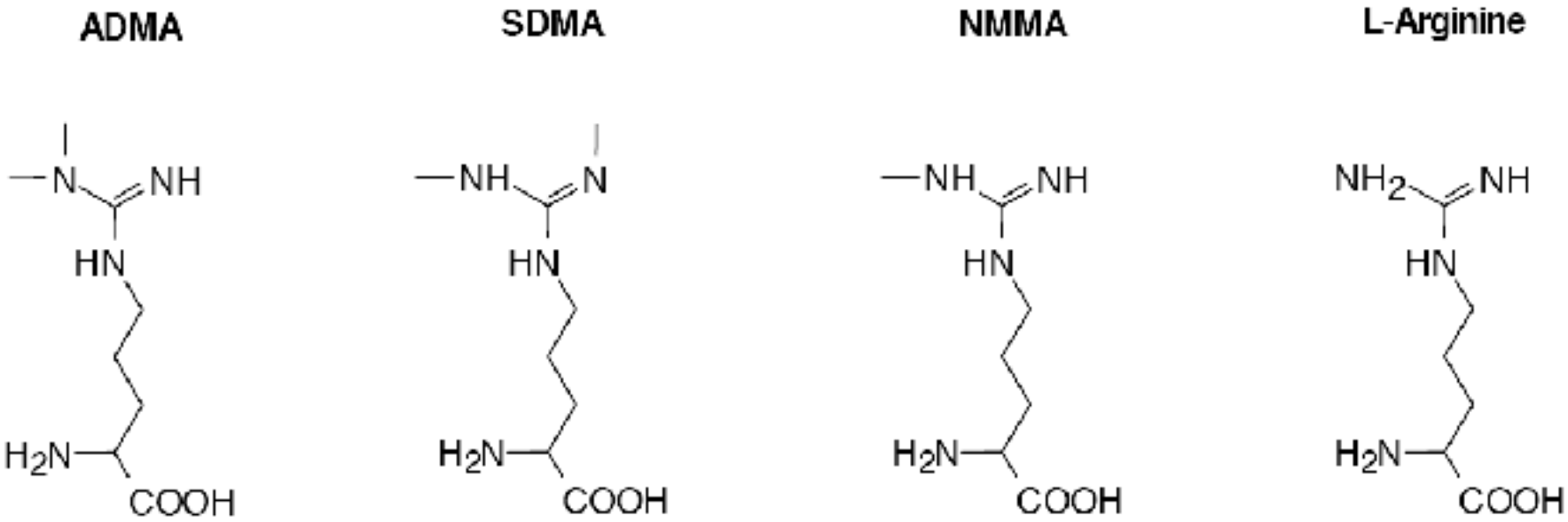
L-NMMA = Monomethylarginine
(less abundant NOS inhibitor)

DDAH = Dimethylarginine dimethylaminohydrolase
(hydrolyzes ADMA)

PRMT = Protein arginine methyltransferase
(makes ADMA and SDMA)

Arginine and endogenous derivatives

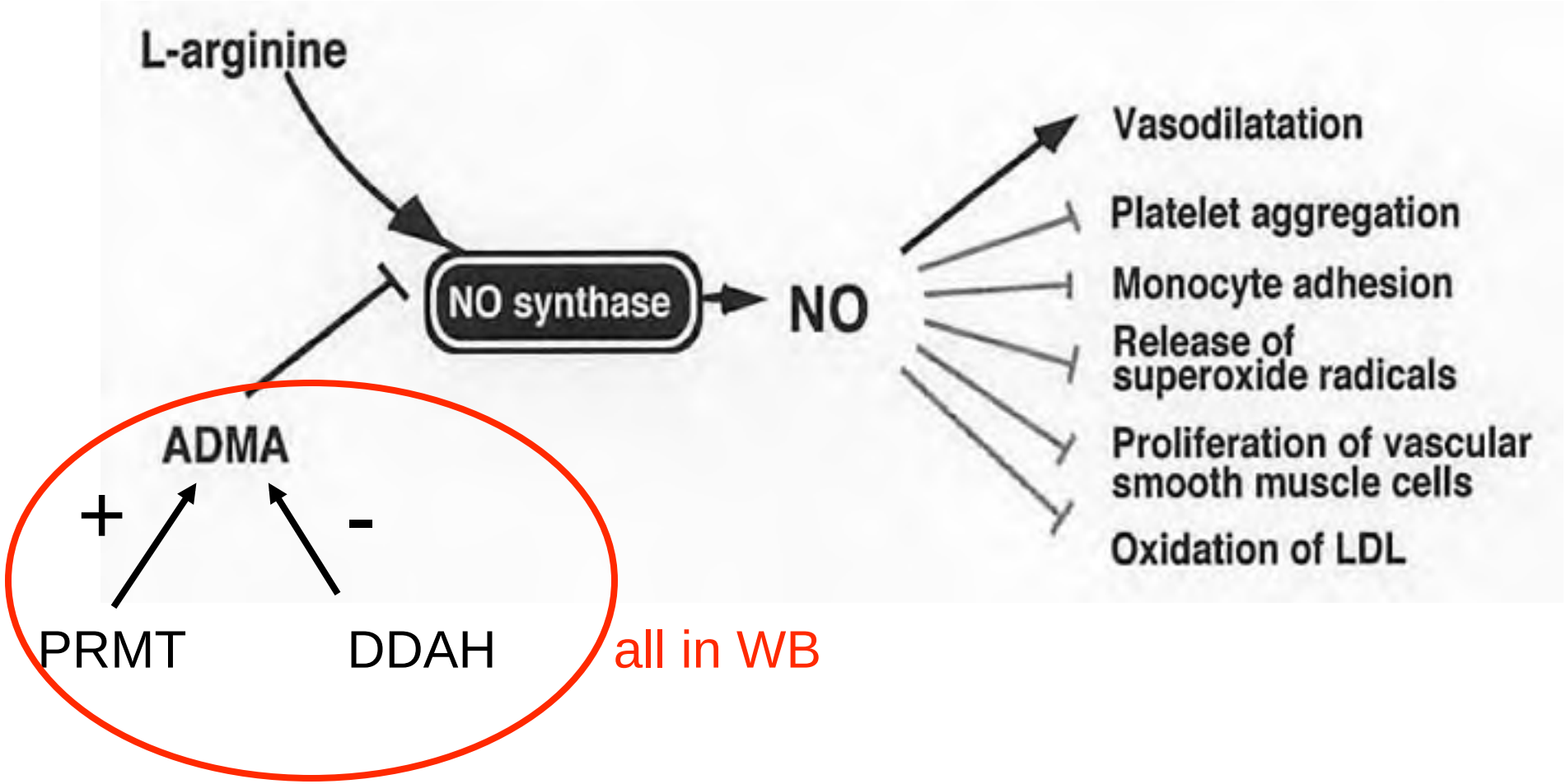
What is ADMA?



NOS Inhibitor DDAH Substrate	NOS-Inactive Regioisomer	NOS Inhibitor DDAH Substrate	NOS Substrate

PD-INCL Source Undetermined

Major control for NO??

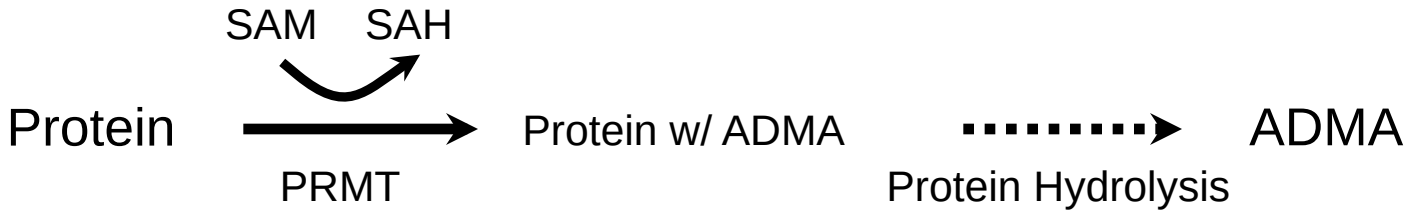


all in WB

R.H. Boger et. Al, Atherosclerosis Supplements 4 (2003) 1-3

ADMA: Formation/Release

- Protein-incorporated arginine residues are dimethylated by protein arginine methyltransferases (PRMTs)
  - No methylation of free arginine reported
- Free ADMA released via “normal protein turnover”



- Questions: Where does free plasma ADMA originate and how is it released in WB *ex vivo*?

Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study

Lancet 2001; 358: 2113–17

Zoccali C. et al tested the predictive power of ADMA for mortality and cardiovascular outcomes and concluded "ADMA is a stronger independent predictor of all-cause mortality and cardiovascular outcomes… in patients with CRF…"

"Predictor"

Where does ADMA come from?

- Elevated plasma ADMA in :
  - Hypercholesterolemia
  - Hypertension
  - Hyperhomocyct(e)inemia
  - Tobacco exposure ,
  - Peripheral arterial occlusive disease
  - Experimental hemorrhage (acute)
  - Pre-eclampsia
  - Hyperglycemia
  - Insulin resistance in patients --- and so on

Methods

- Incubation of rat whole blood (WB) and WB fractions
  - Sample placed in vial and incubated at 37˚C
- HPLC analysis of blood ADMA/SDMA
- Acid hydrolysis of blood components
  - Liberates free amino acids for their quantification

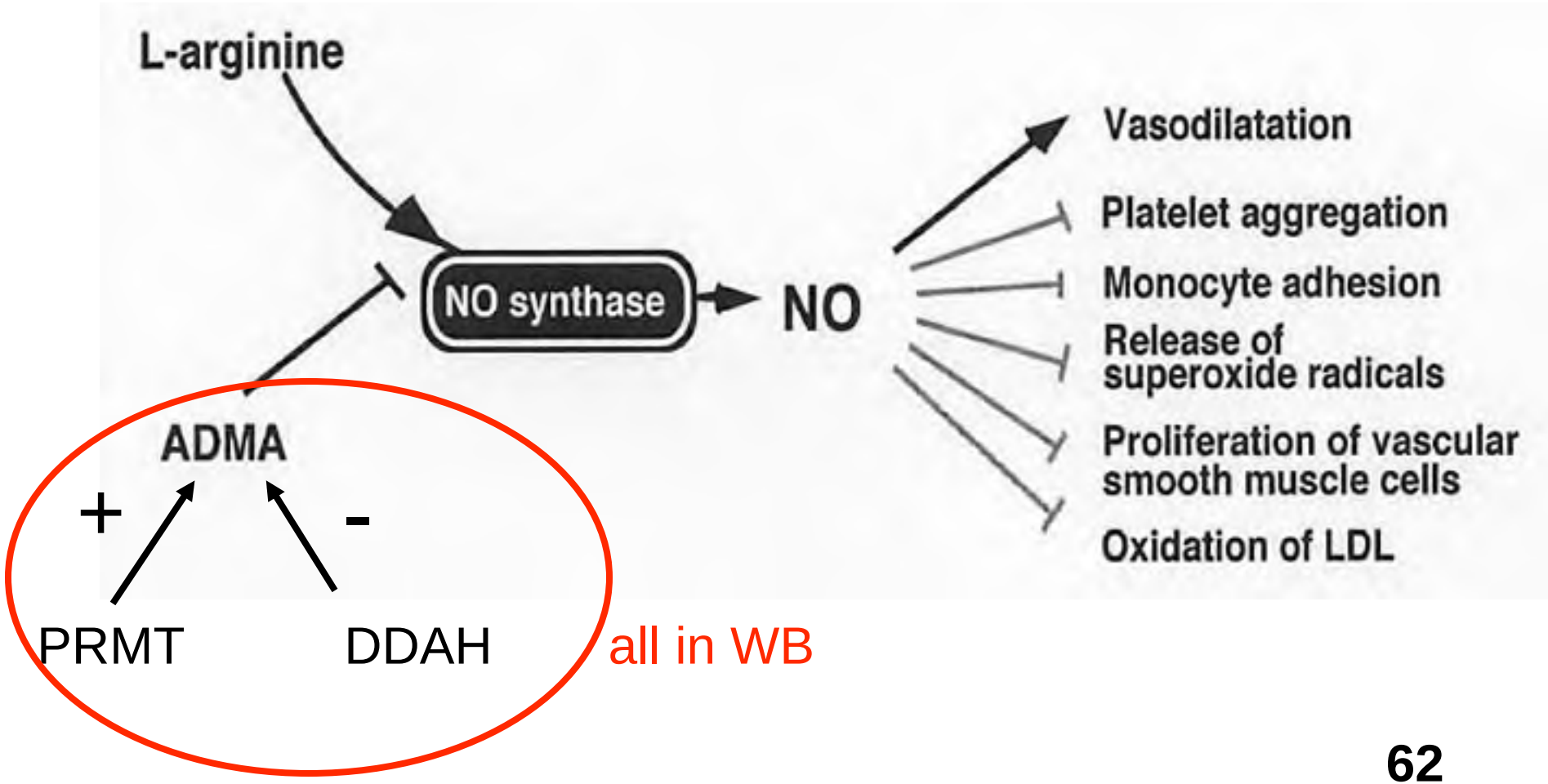
Summary

- WB plasma contains free ADMA at < 1 µM
- WB contains > 40 µM protein-incorporated ADMA with the majority (>95%) in RBCs
- WB possesses the proteolytic machinery necessary for ADMA release into the plasma
- Inhibition of protease activity attenuates ADMA release from blood *ex vivo*

Conclusion

- WB can be considered a 5 kg “liquid organ” in intimate contact with the vascular endothelium.
- WB has the capacity to release physiologically and pathophysiologically relevant amounts of ADMA *ex vivo.*
- WB is an independent source of ADMA and as such may play an etiological role in vascular disease.

ADMA-NOS-NO pathway the newest drug target?



all in WB

 R.H. Boger et. Al, Atherosclerosis Supplements 4 (2003) 1-3

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 6 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 7: McGraw-Hill
Slide 8: McGraw-Hill
Slide 9 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 10: McGraw-Hill
Slide 11: Source Undetermined
Slide 12: Source Undetermined
Slide 14: McGraw-Hill
Slide 19 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 20 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 23 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 24: McGraw-Hill
Slide 25 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 31: D'Alecy
Slide 32: Source Undetermined
Slide 33 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 34: D'Alecy
Slide 35: D'Alecy
Slide 36: McGraw-Hill
Slide 37: McGraw-Hill
Slide 39 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 40: Arteriosclerosis Thrombosis Vascular Biology
Slide 41 : Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 42: Mohrman and Heller. Cardiovascular Physiology. McGraw-Hill, 2006. 6th ed.
Slide 43: Source Undetermined
Slide 45: D'Alecy
Slide 46: Source Undetermined
Slide 47: Source Undetermined
Slide 48: Lilly, L. Pathophysiology of Heart Disease. Lippincott, 2007. 4th ed.
Slide 49: Lilly, L. Pathophysiology of Heart Disease. Lippincott, 2007. 4th ed.
Slide 51: R.H. Boger et. Al, Atherosclerosis Supplements 4 (2003) 1-3
Slide 54: Source Undetermined
Slide 55: R.H. Boger et. Al, Atherosclerosis Supplements 4 (2003) 1-3