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M2 Mini Review
August 2008

Physiology/Pathophysiology Of Coronary Blood Flow

Louis G. D' Alecy, Professor of Physiology

Coronary Blood Flow Outline

1) Myocardial Ischemia
   - Supply
   - Demand
2) Coronary Flow Reserve
3) Determinants of Coronary Blood Flow
4) Neural (autonomic) Mechanisms
5) Endothelial Factors (Mechanisms)
6) NOS, NO and ADMA

Myocardial Ischemia (MI)

- blood flow to a tissue or organ (heart) that is

inadequate to maintain function.

Heart statistics

300g / 70,000g = 0.0043 or < 0.5% Body Weight.

Heart consumes more energy than any other organ.

Coronary flow = 4% of cardiac output.

"Resting " flow 30X flow/g tissue of skeletal muscle.

Highest oxygen consumption per g of tissue in body.

(arterial oxygen 20 Vol % to coronary sinus 8 Vol %)

(typical mixed venous oxygen higher at 17 Vol %)

***SEE SLIDE 37 & 38 FOR SUMMARY OF OTHER TISSUES

**Must increase coronary blood flow to increase oxygen delivery.

Vol % = mL O_2 / 100mL blood

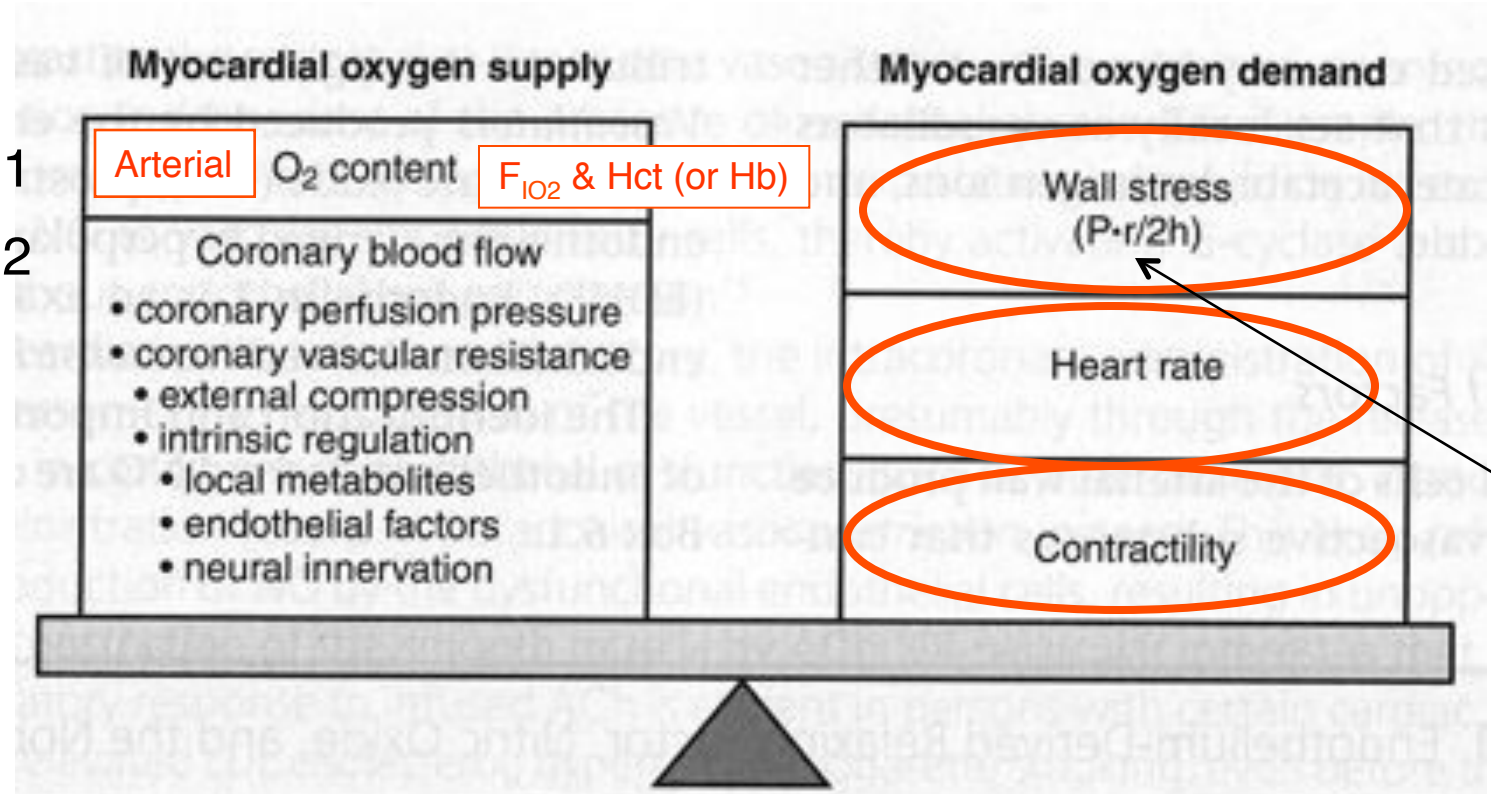


Figure 6.1. Major determinants of myocardial oxygen supply and demand.
h, ventricular wall thickness; P, ventricular pressure; r, ventricular radius.

Thus an enlarged heart has greater demand.

r = radius

Pressure X Rate Product

How can coronary flow remain relatively constant with an 80% "lesion"??

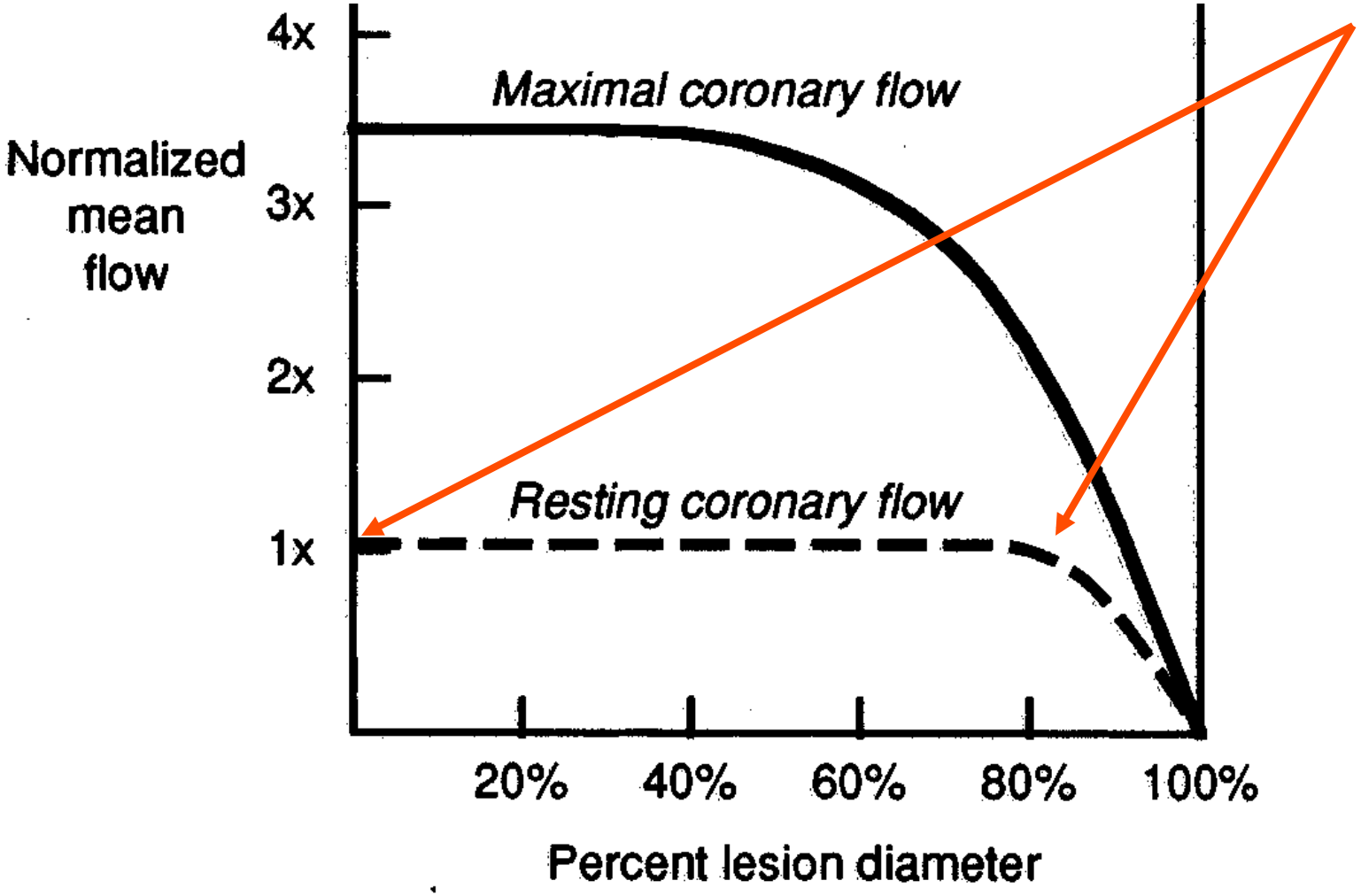


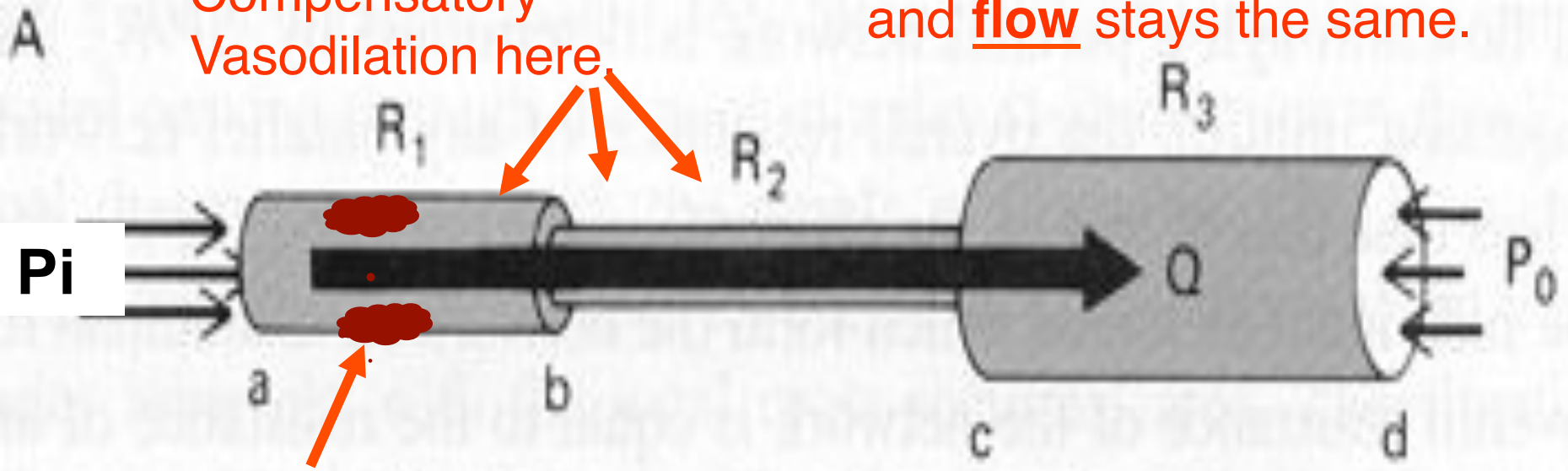
Fig. 6.3

Occlusion

"…proximal arterial stenosis…"

Series Resistance Network

Therefore series resistance and **flow** stays the same.



$$R_s = R_1 + R_2 + R_3$$

$$\Delta P = P_i - P_0$$

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

6.3 MH

With the same perfusion pressure, the same measured flow means the overall (series) resistance is the same regardless of a focal lesion!
BUT * You have used up vasodilator reserve !!!!!!**

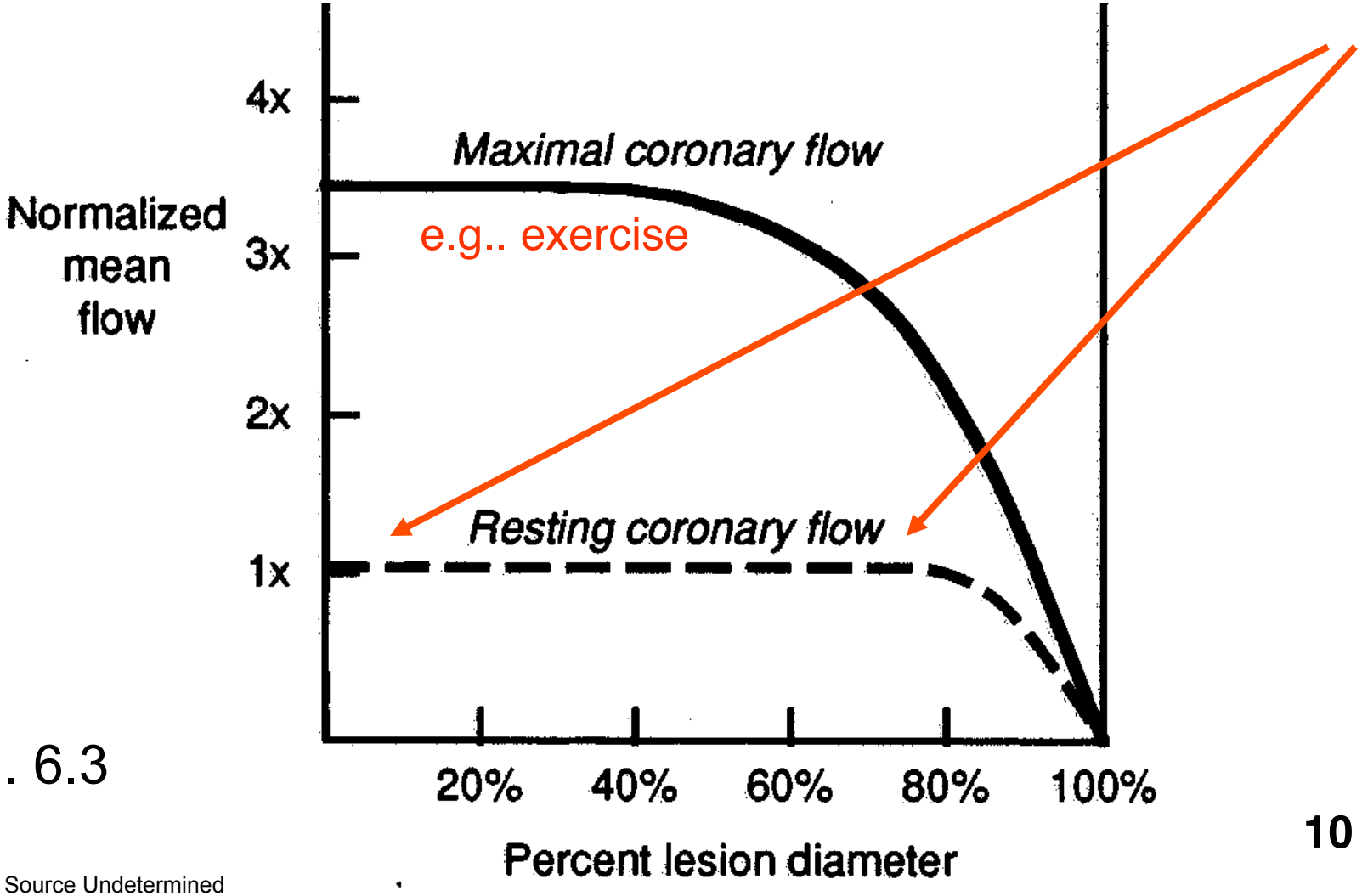
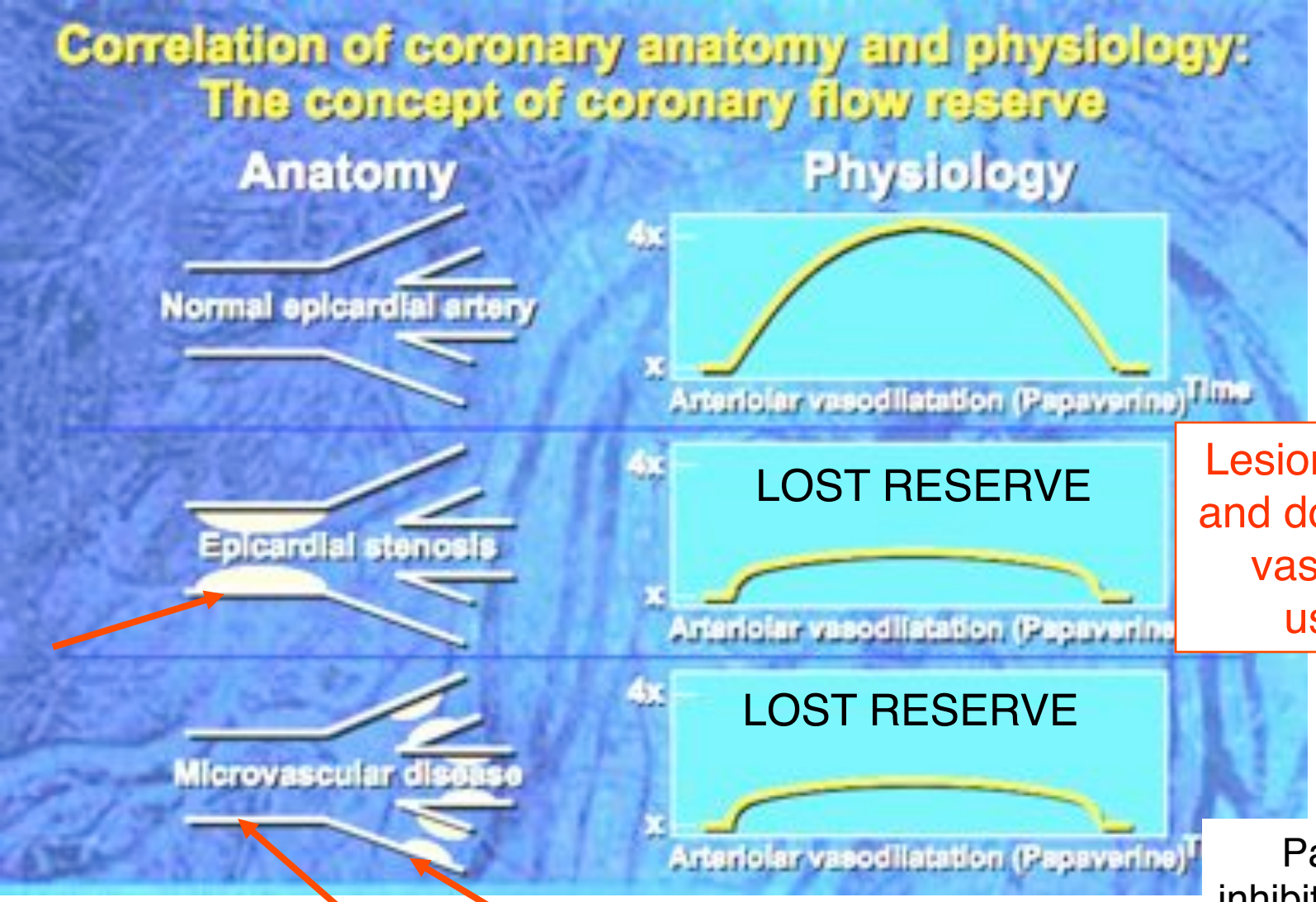


Fig. 6.3



Lesion upstream and down stream vasodilation used up.

Lesion down stream and large vessel vasodilation used up even with no upstream lesion.

Papaverine inhibits breakdown of cGMP & cAMP by PDE

DETERMINANTS OF CORONARY BLOOD FLOW (PERFUSION)

1 DIASTOLIC PERFUSION PRESSURE ΔP

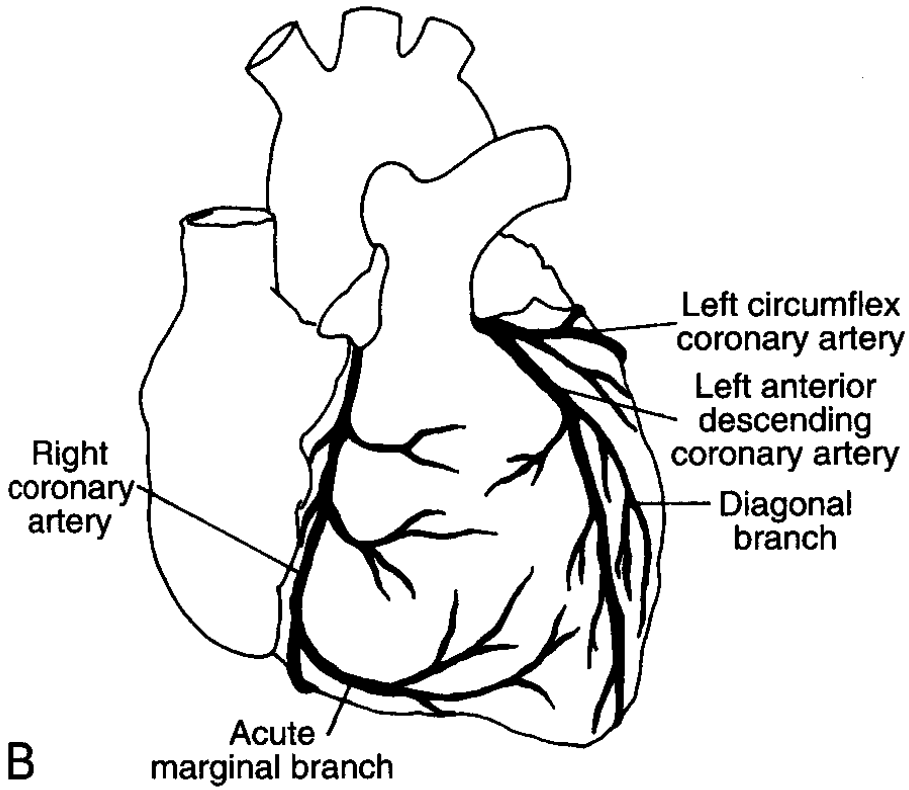
2 SYSTOLIC COMPRESSION ("Resistance")

3 METABOLIC CONTROL (Resistance)

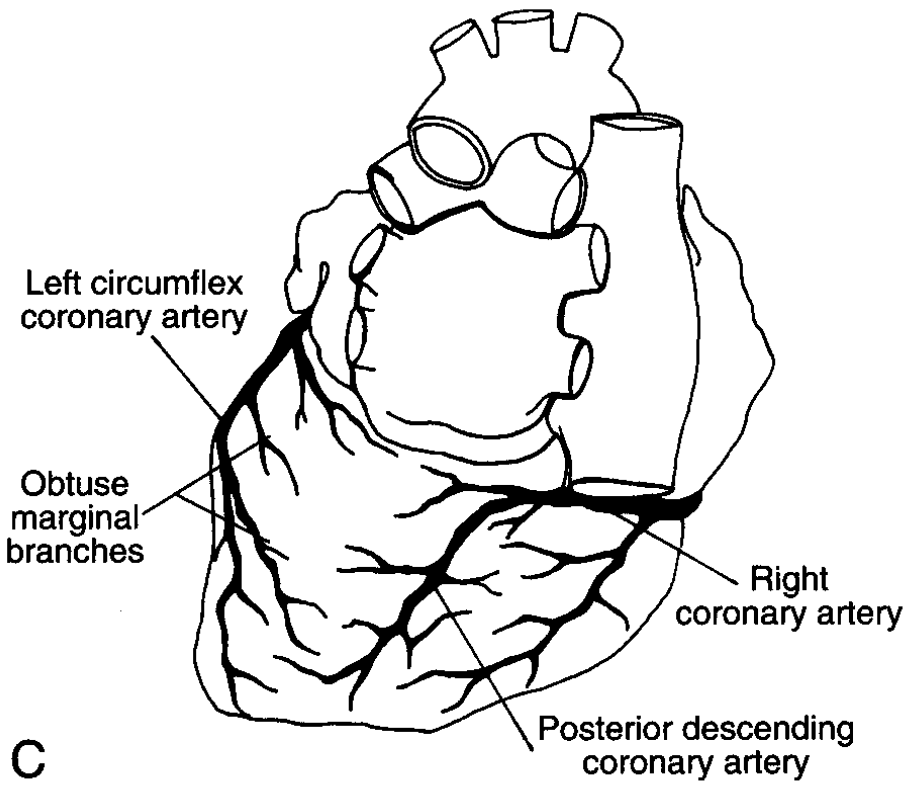
O_2 & adenosine

4 NEURAL CONTROL (Resistance)

Sympathetic & Parasysmpathetic

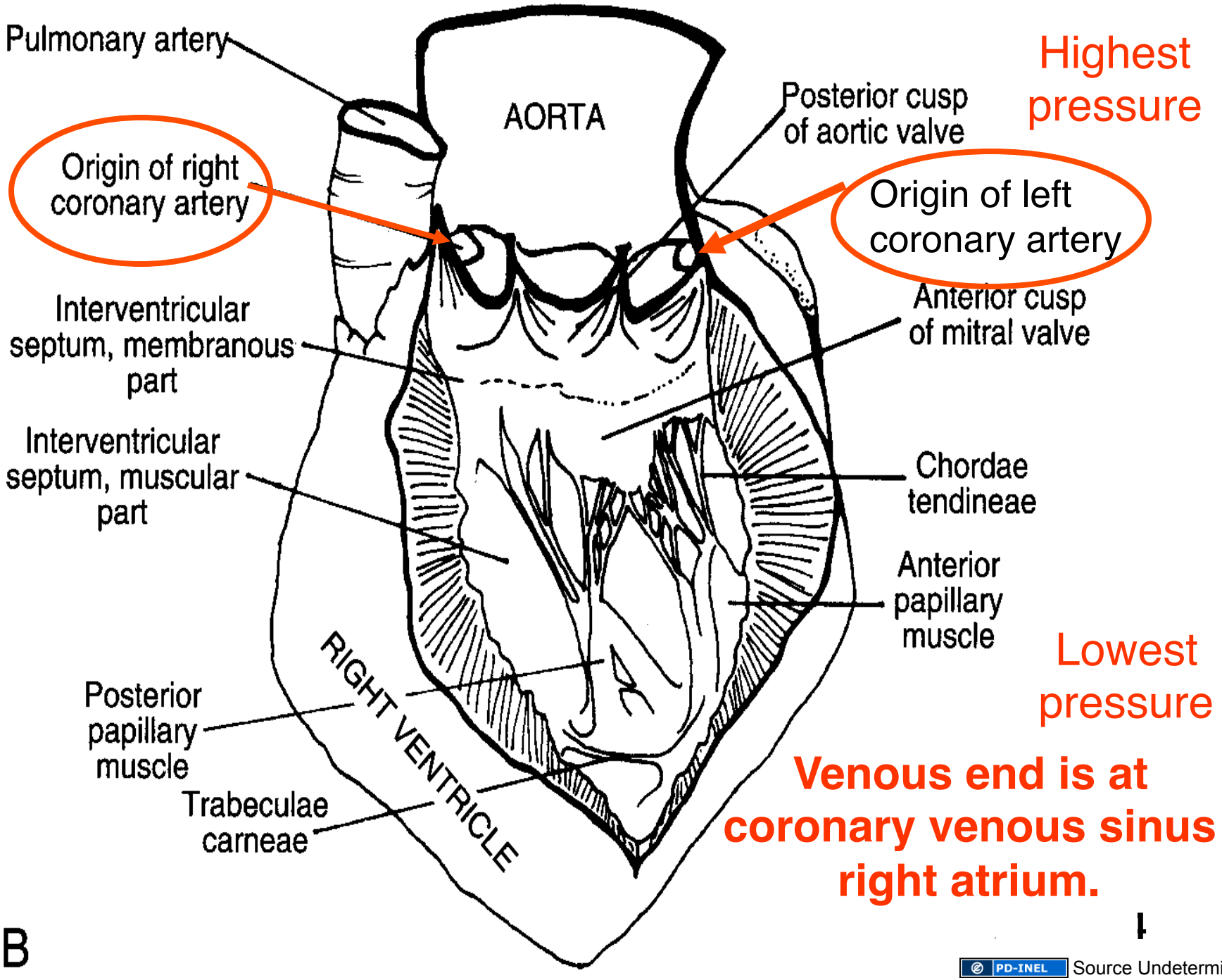


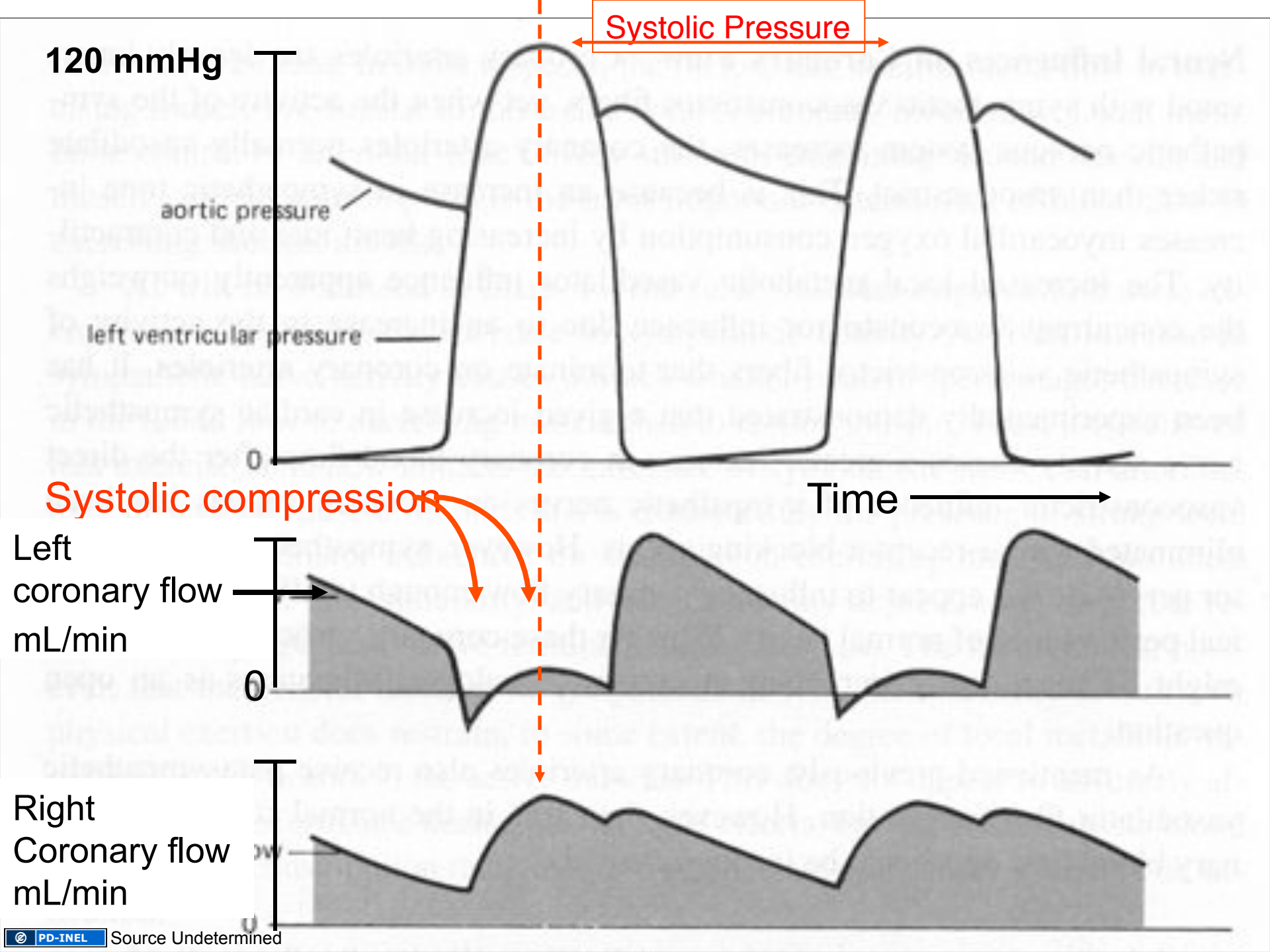
Anterior view



Posterior view

But where is the origin of perfusion pressure?





DETERMINANTS OF CORONARY BLOOD FLOW

1 PERFUSION PRESSURE

2 SYSTOLIC COMPRESSION

3 METABOLIC CONTROL

4 NEURAL CONTROL

TISSUE VASCULAR RESISTANCE

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

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

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

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

“Flow” vs. “Perfusion”

- Angiography
- Large surface
- “Focal”
- “Fixed” diameter
- Bypass
- Stent

- Nuc. Imaging
- Arteriolar
- Vasodilator reserve
- Functional flow
- Distributed resistance
- Collateral channels

Intrinsic Regulation of Coronary Blood Flow

"Thus any additional **oxygen** requirement must be met by an increase in blood flow."

P 143 Lilly

You must use vasodilator reserve --- assuming you have any left!

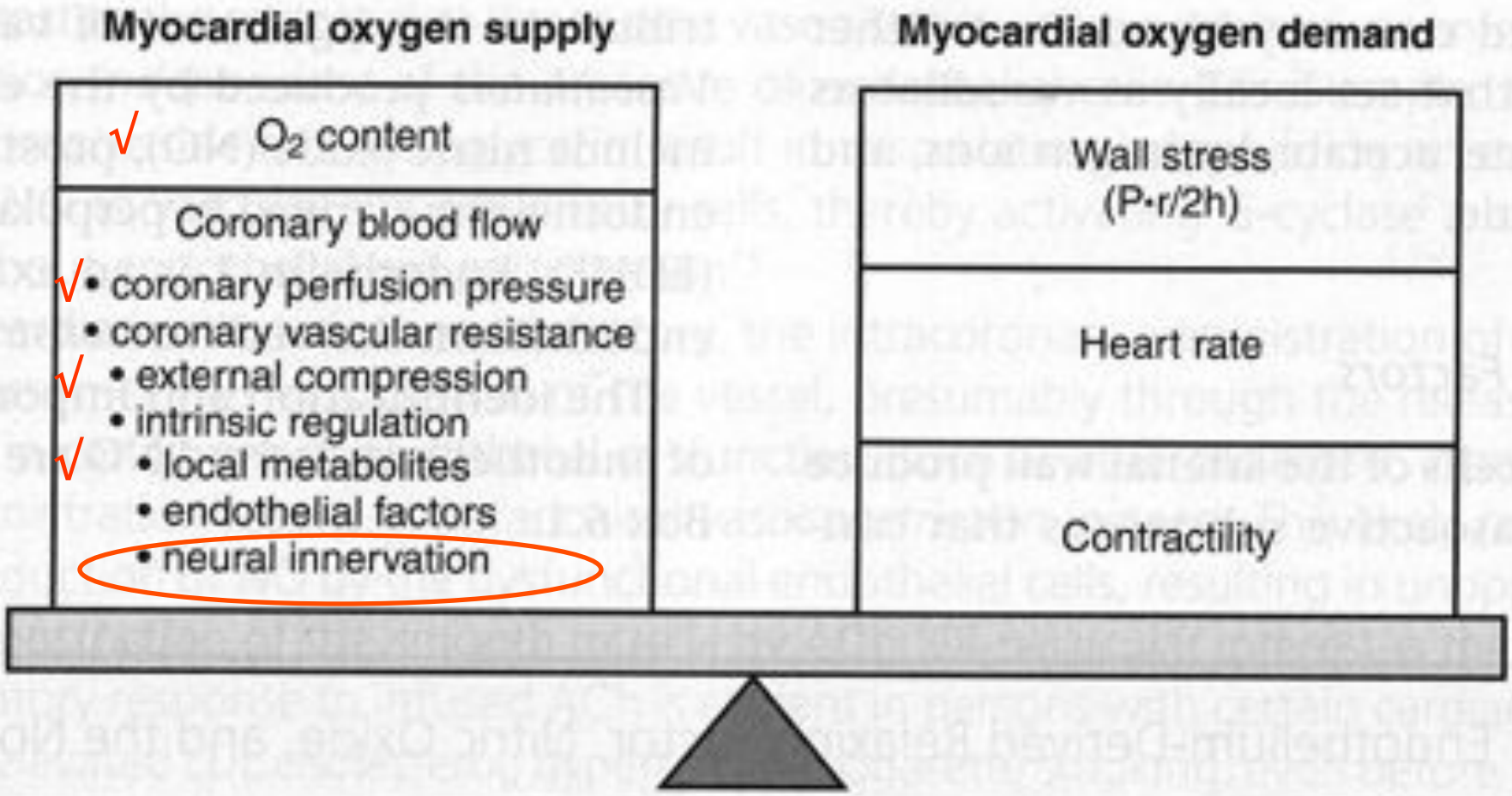


Figure 6.1. Major determinants of myocardial oxygen supply and demand. h, ventricular wall thickness; P, ventricular pressure; r, ventricular radius.

Isolated Vascular Effects

(vessel strips or rings in bath)

- Sympathetic alpha adrenergic
  - α_1 vasoconstriction
- Sympathetic beta adrenergic vasodilation
  - β_1 (evidence for innervated VSM)
  - β_2 non-innervated VSM
- Parasympathetic cholinergic vasodilation

BUT HOW DOES IT WORK IN VIVO ????

Parasympathetic Activation

Stimulate parasympathetic to heart >> Ach >>SA node
>> ↓↓ HR >>↓↓ metabolism >> ↓↓ Coronary Blood flow

BUT

PACE heart (i.e. fixed heart rate) >> no change in HR >>
no change metabolism ---------- Therefore
Stimulate parasympathetic to paced heart >> >>
Ach vasodilation >> ↑↑ coronary blood flow !!

BUT HOW DOES IT WORK IN VIVO ????

Sympathetic Activation

Stimulate sympathetic nerves to heart >> ↑↑ Norepi >> >> ↑↑ HR + ↑↑ inotropism >> ↑↑ metabolism >> >> ↑↑ ↑↑ Coronary Blood flow

BUT

Block $\beta_{1\&2}$ receptors and Stimulate sympathetics to heart >> ↑↑ Norepi (stress) >> no change in HR >> >> no change inotropism >> >> no change in metabolism >> potential for >> ↓↓ Coronary Blood flow

by "unmasked" α_1 adrenergic vasoconstriction

Can Metabolic control still dominate??

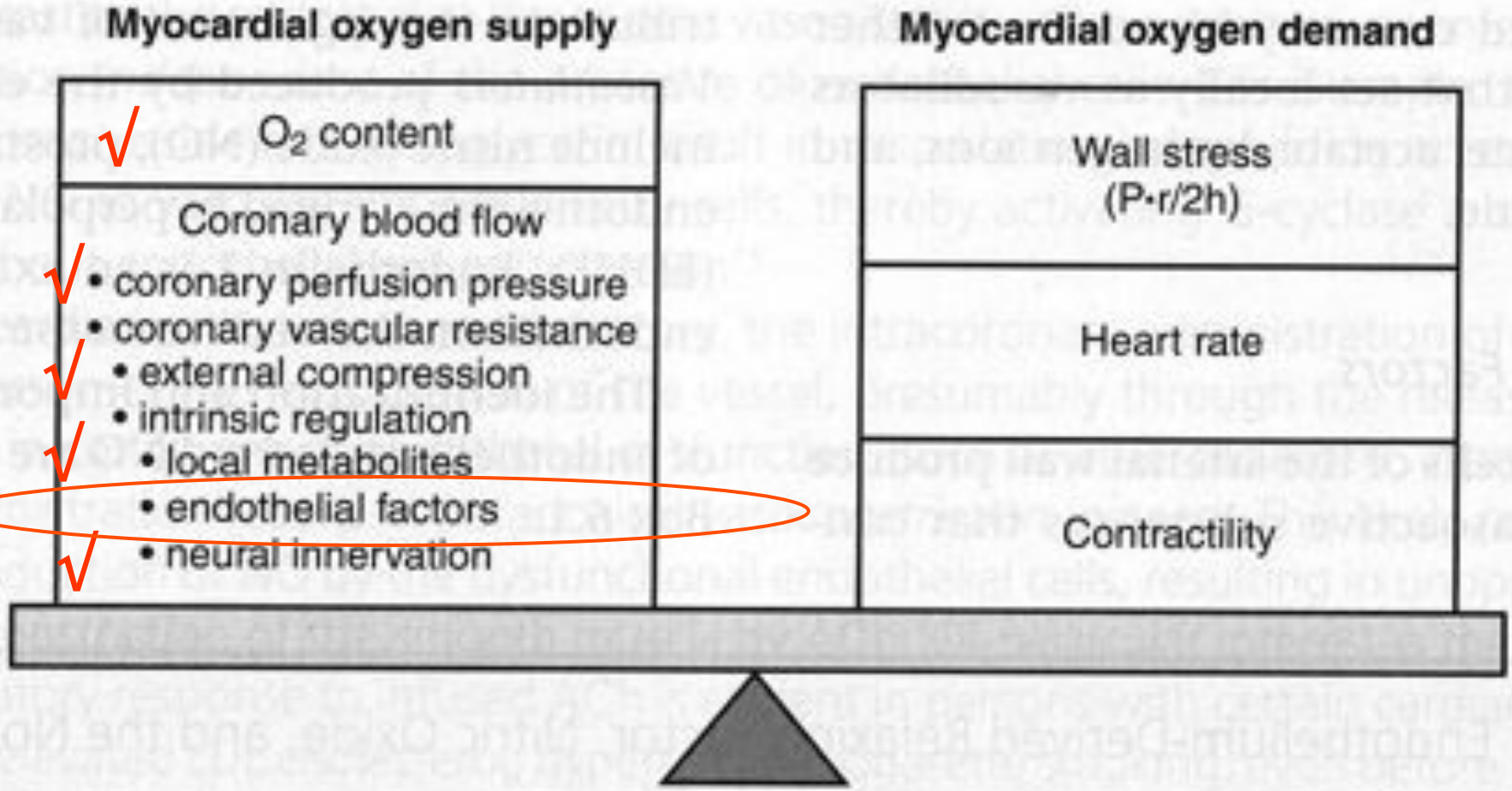


Figure 6.1. Major determinants of myocardial oxygen supply and demand.
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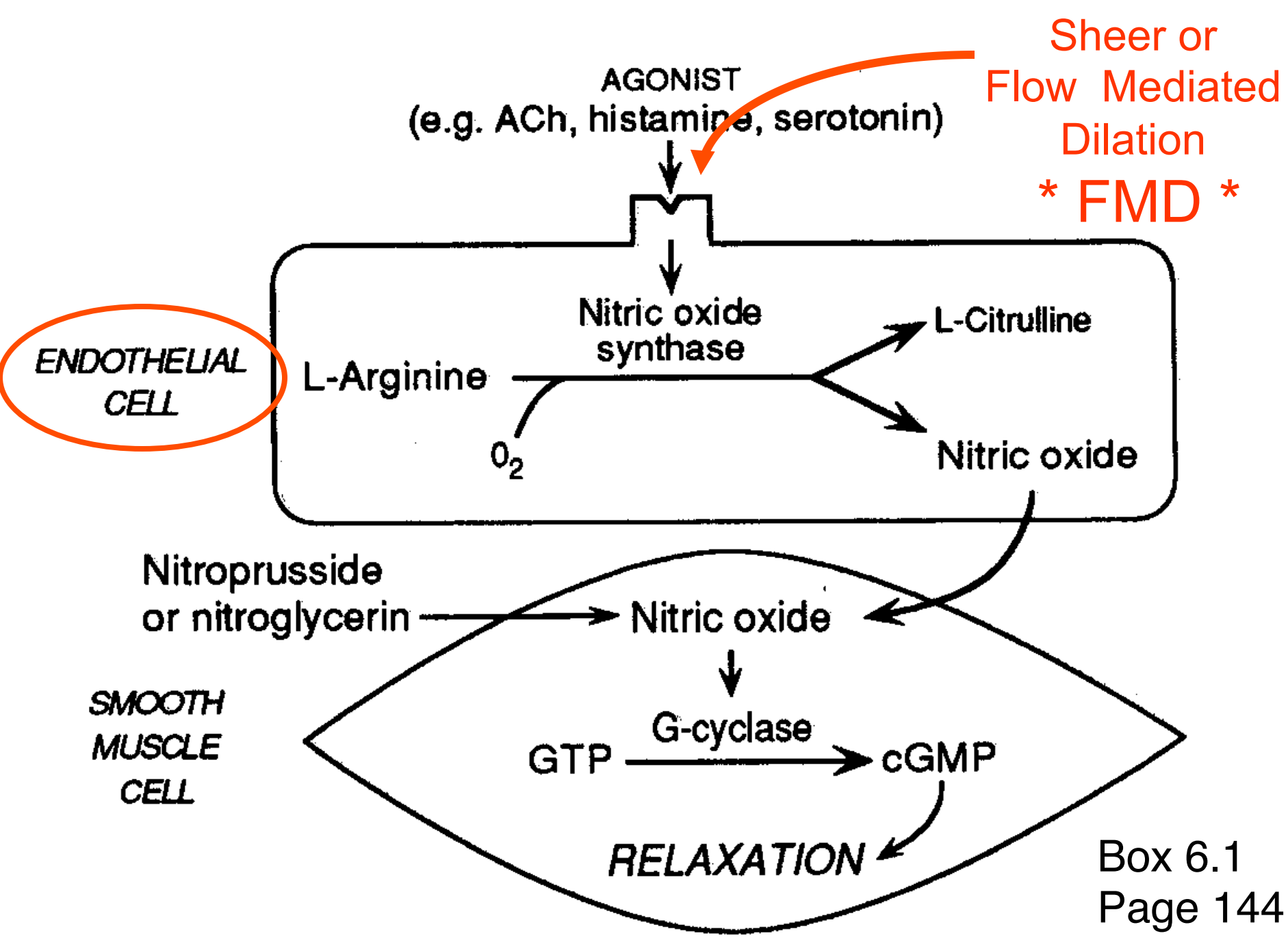
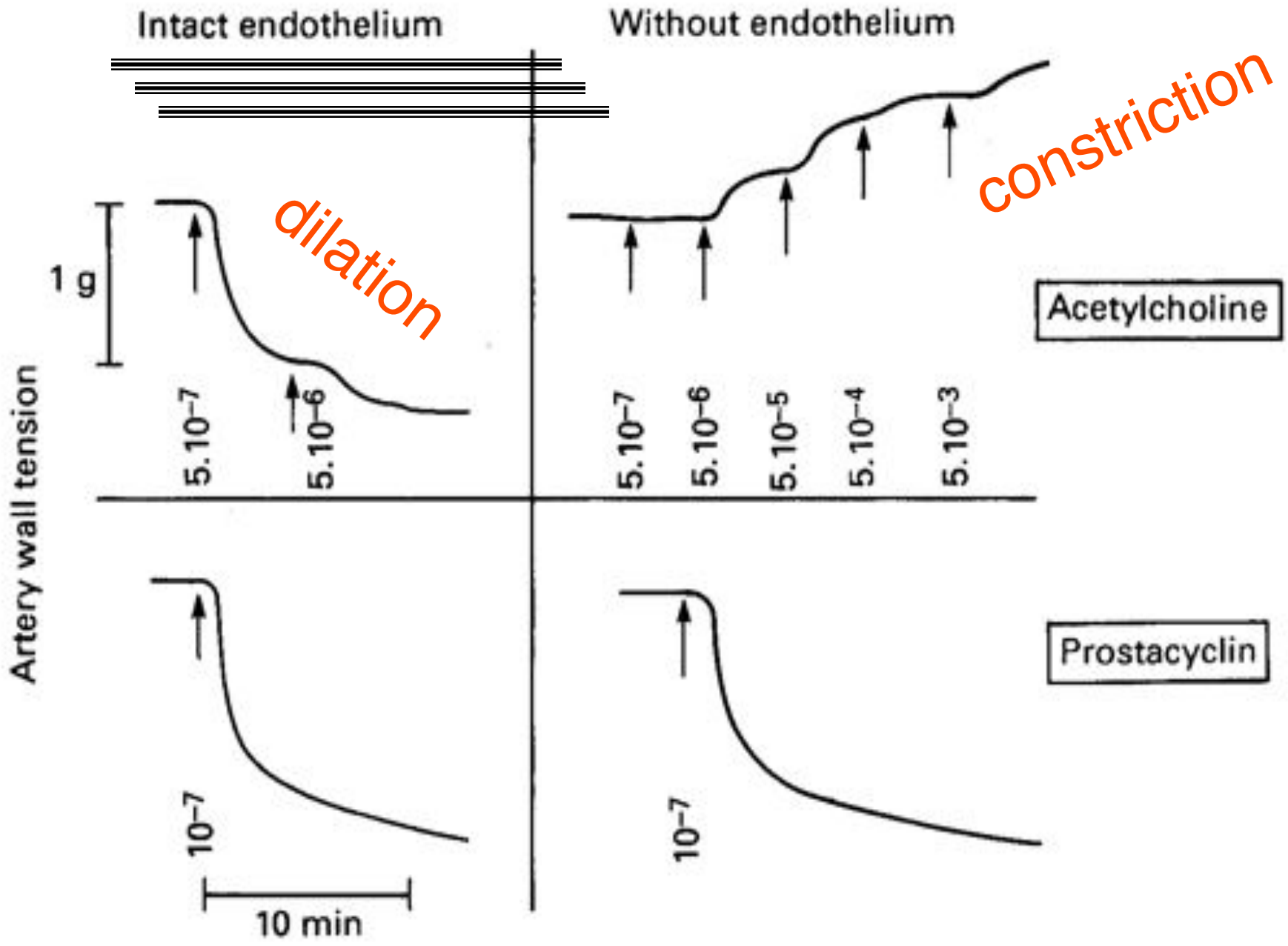


Box 6.1
Page 144



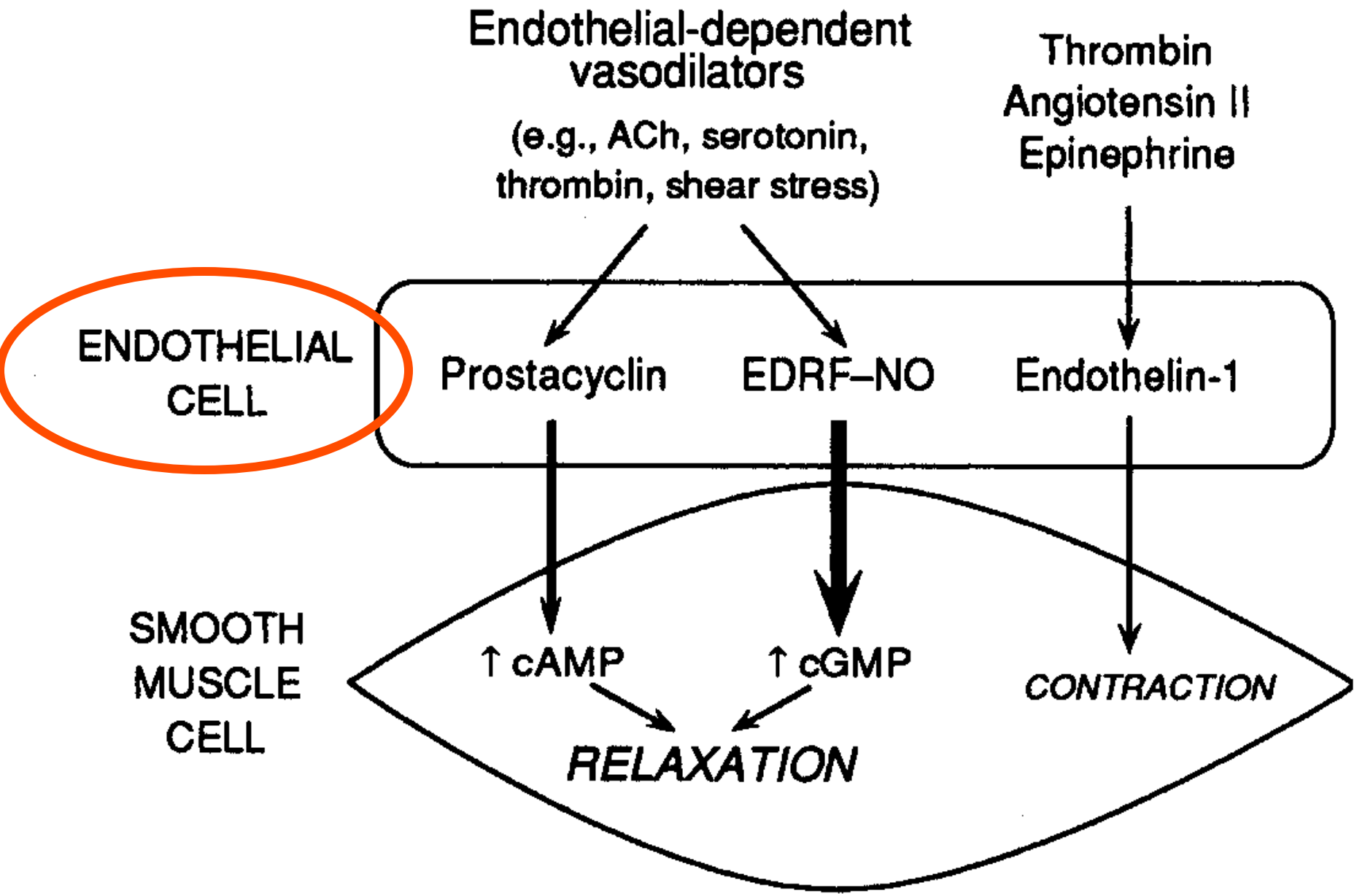
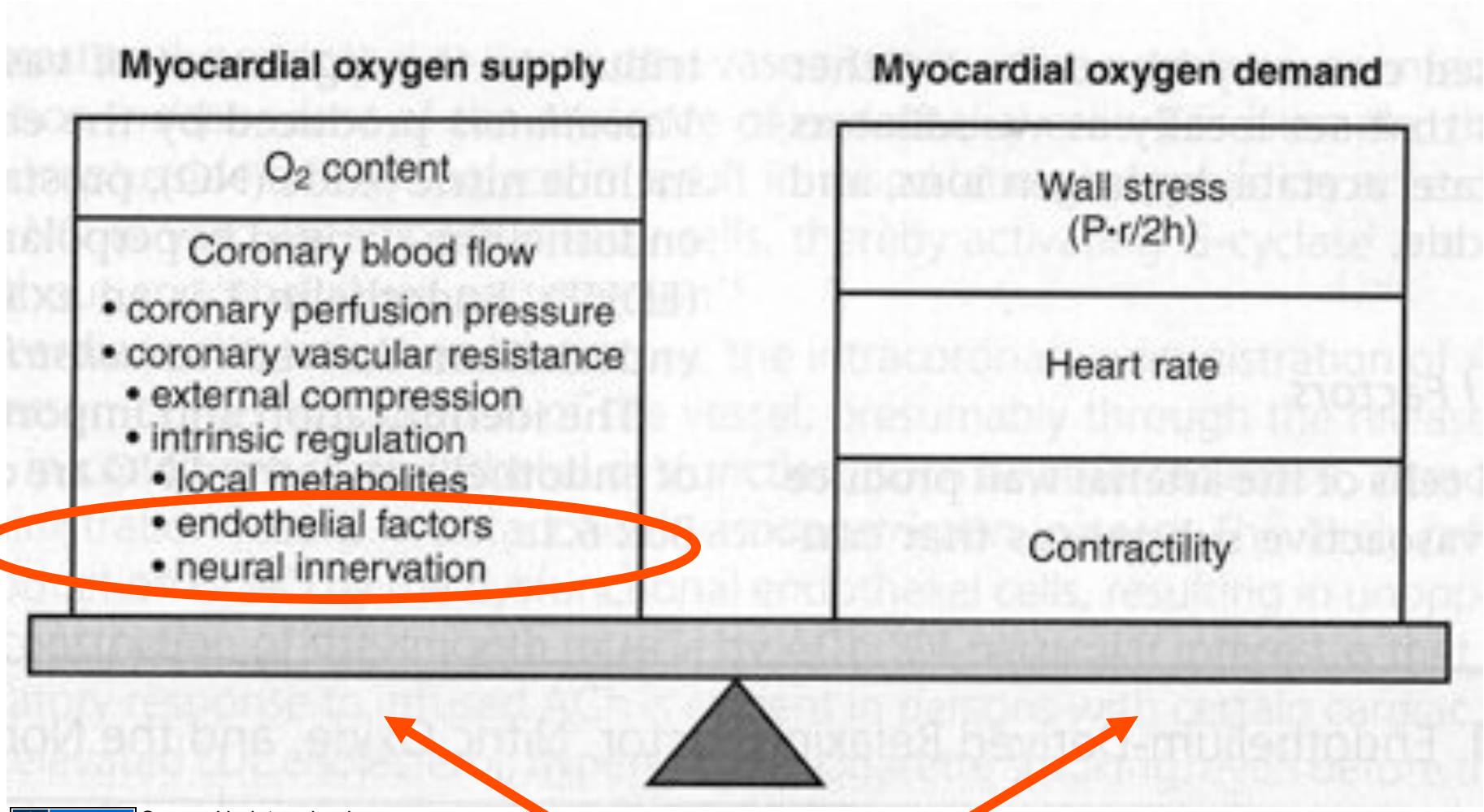


Fig 6.2

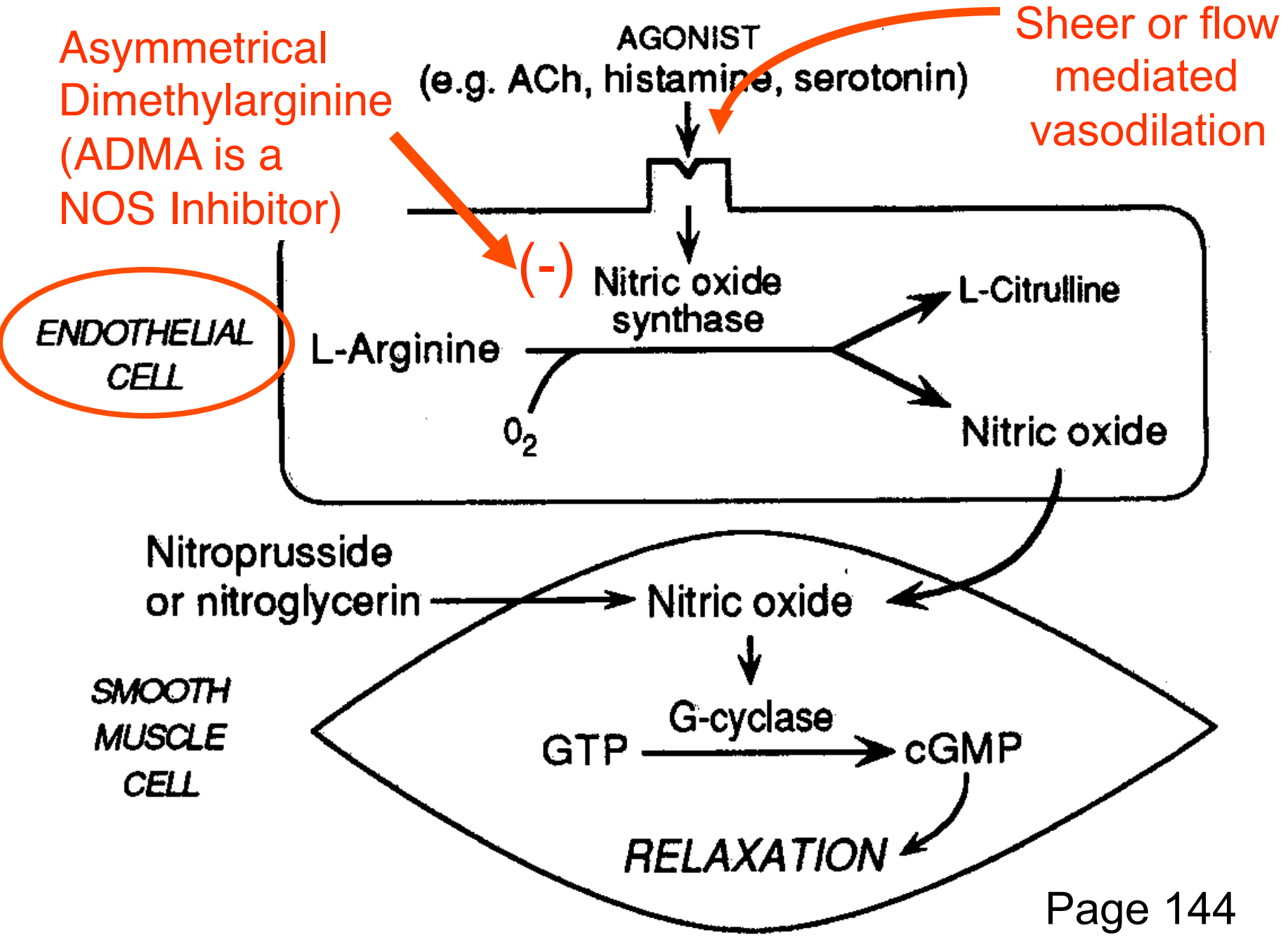
Page 148-149, Inappropriate Vasoconstriction. Lilly

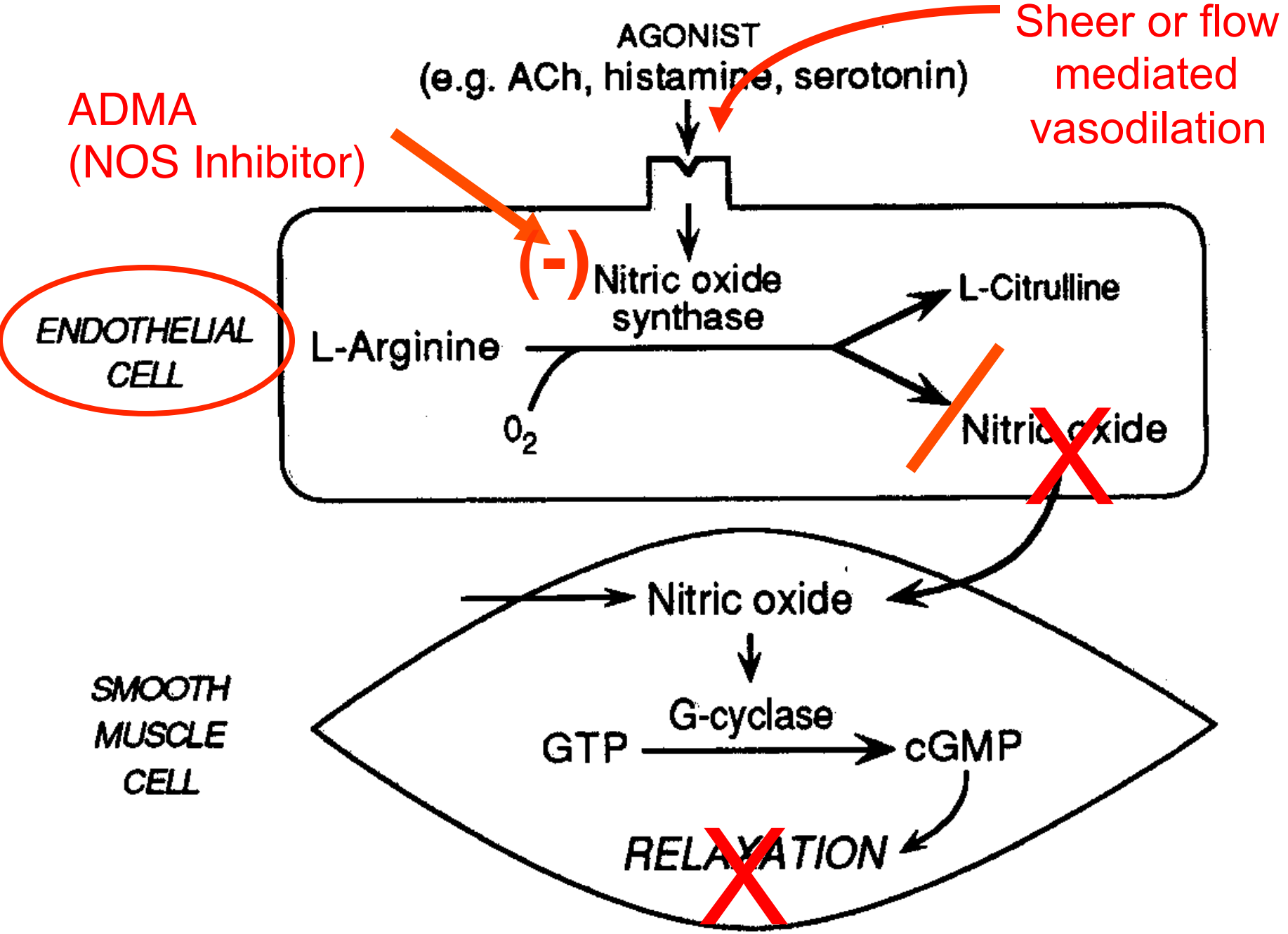
lated that in normal individuals, the relaxation effect of EDRF-NO outweighs the direct α-adrenergic constrictor effect of catecholamines on arterial smooth muscle, such that vasodilatation results. However, in patients with dysfunctional endothelium (e.g., atherosclerosis), an *impaired release of endothelial vasodilators* leaves the direct catecholamine effect unopposed, such that relative *vasoconstriction* occurs instead. The resultant decrease in coronary blood flow and myocardial oxygen supply contributes to ischemia. Of note, in patients with risk factors

"unmasked" α_1



++ Drug effects ++ Endothelial Dysfunction





Does ADMA Cause Endothelial Dysfunction?

John P. Cooke

(Arterioscler Thromb Vasc Biol. **2000**;20:2032-2037.)

THEN

LATER

Special Review

Asymmetrical Dimethylarginine

The Über Marker?

2004

ADMA: A Major Cause of Endothelial Dysfunction

ADMA Regulates Vascular Resistance

(*Circulation* 2004;109:1813-1819.)

 Circulation 2004; 109:1813-1819

Asymmetrical Dimethylarginine Predicts Progression to Dialysis and Death in Patients with Chronic Kidney Disease: The Mild to Moderate Kidney Disease Study.
Danilo Fliser, et al.

J Am Soc Nephrol 16:2449-2445, **2005**

"ADMA…independent risk marker for progression...mortality"

Elevation of asymmetric dimethylarginine in patients with Unstable angina and recurrent cardiovascular events.
Tanja K. Krempl et al.

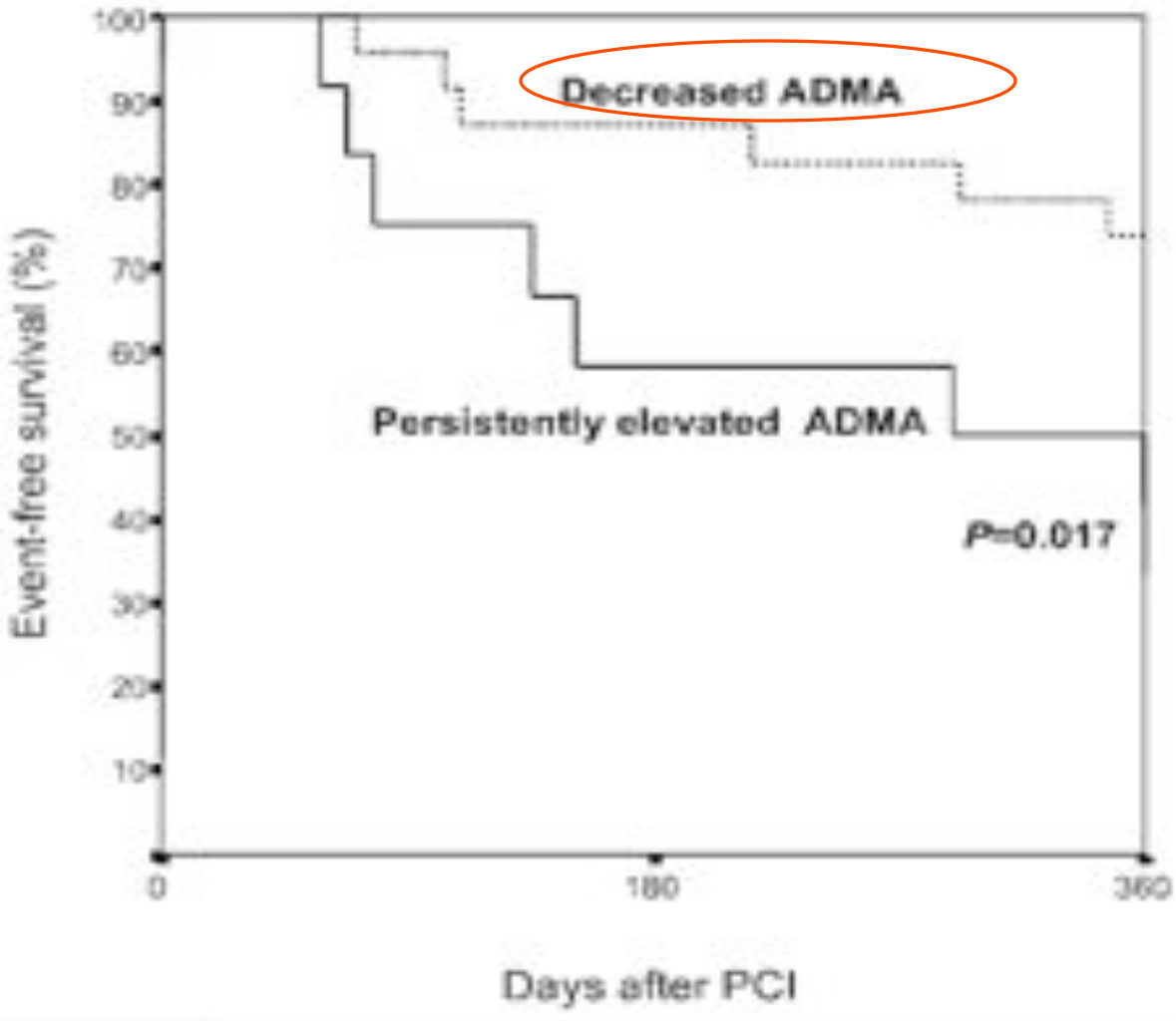
European Heart Journal (**2005**) 26, 1846-1851

"ADMA … significantly elevate…

reduction may indicate decreased risk."

Tanja K. Krempl et al. European Heart Journal (2005) 26, 1846-1851

Percutaneous Coronary Intervention (previously called Angioplasty)



After PCI
Pts with decreased ADMA had greater survival!

 Tanja K. Krempl et al. European Heart Journal (2005) 26, 1846-1851

Asymmetric Dimethylarginine Independently Predicts Fatal and Nonfatal Myocardial Infarction and Stroke in Women

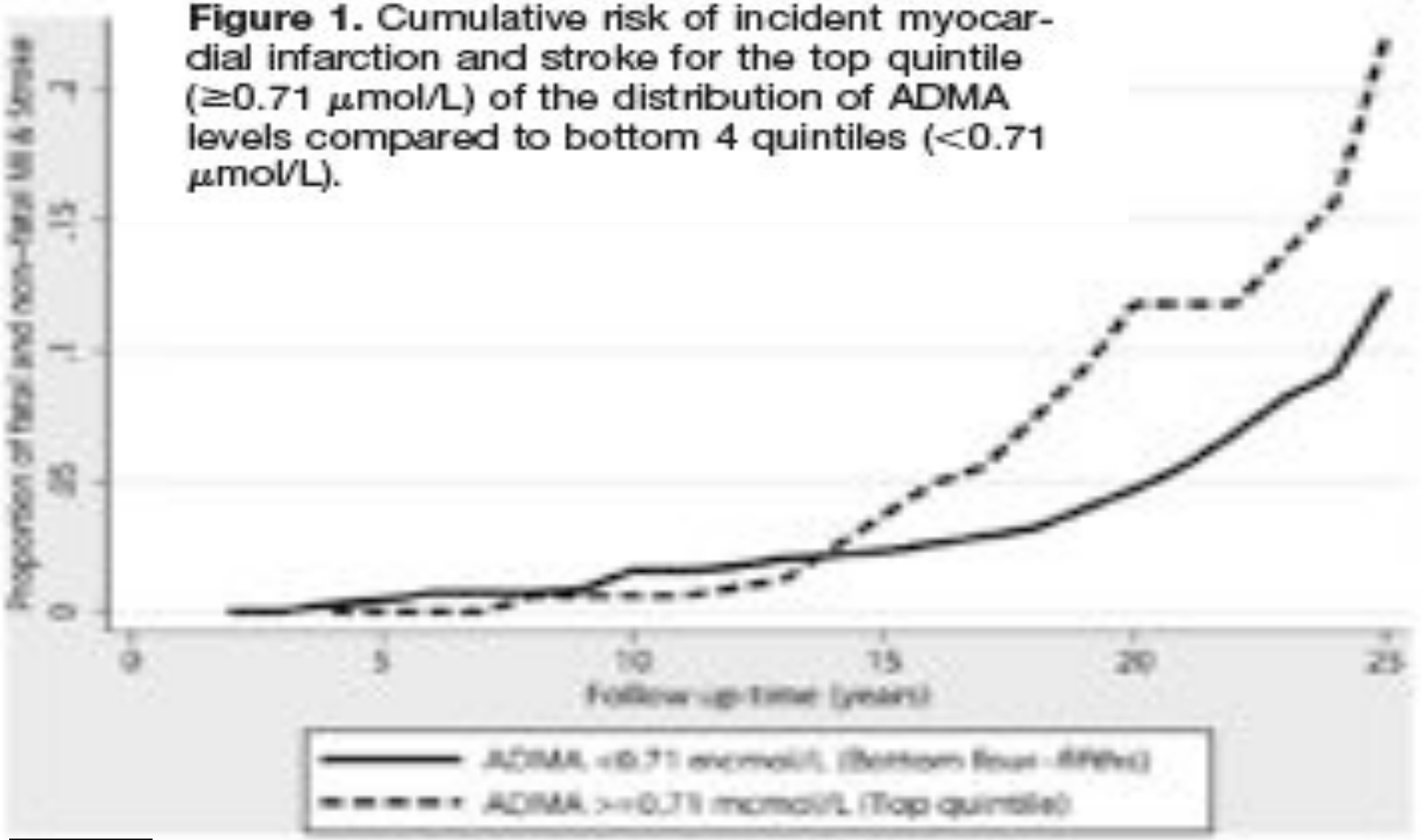
24-Year Follow-Up of the Population Study of Women in Gothenburg

Tora Leong, Dimitri Zylberstein, Ian Graham, Lauren Lissner, Deirdre Ward, Jane Fogarty, Calle Bengtsson, Cecilia Björkelund, Dag Thelle; for The Swedish-Irish-Norwegian (SIN) Collaboration

in women. (*Arterioscler Thromb Vasc Biol* 2008;28:961-967)

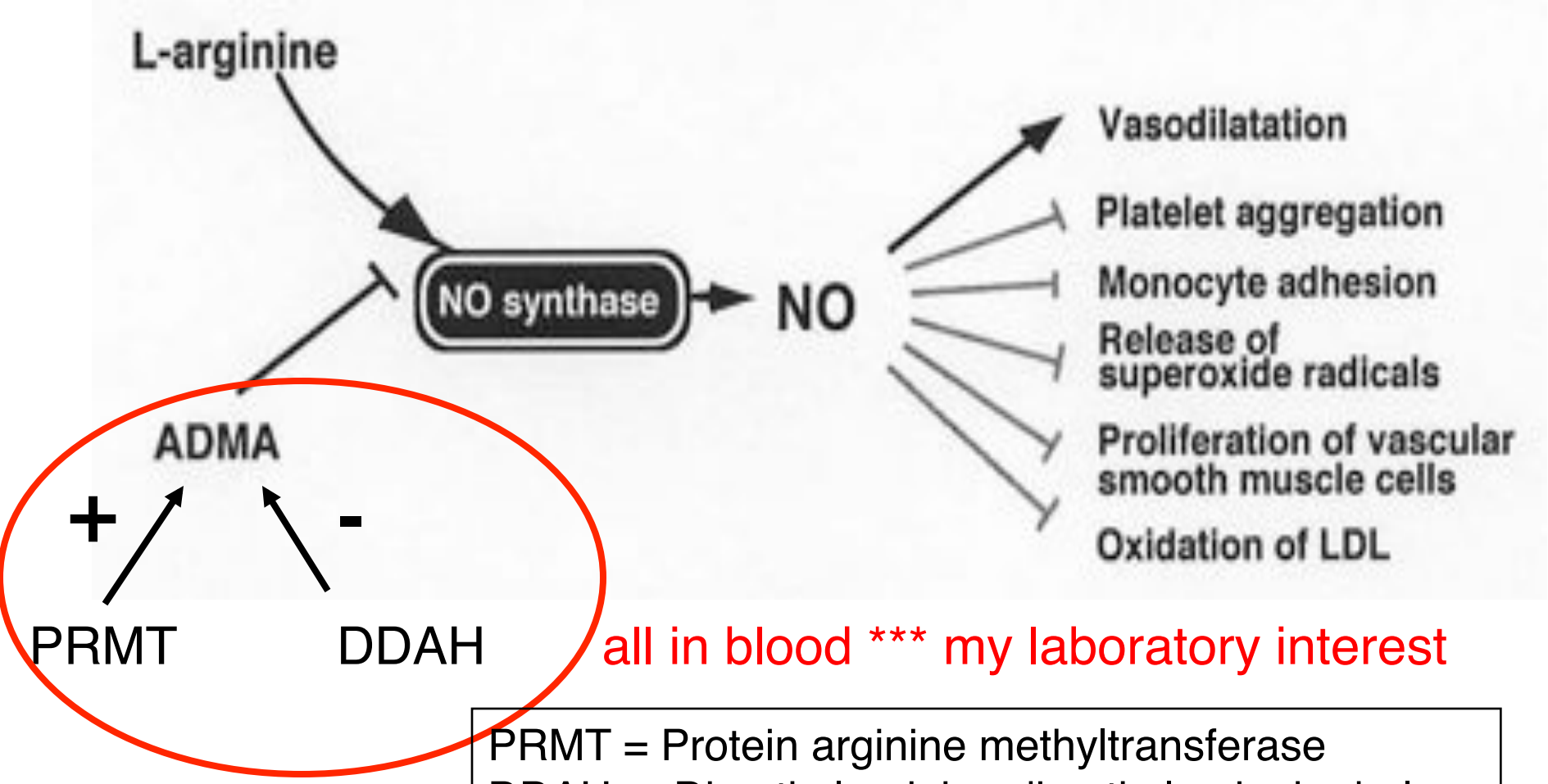
2008

Figure 1. Cumulative risk of incident myocardial infarction and stroke for the top quintile (≥0.71 μmol/L) of the distribution of ADMA levels compared to bottom 4 quintiles (<0.71 μmol/L).



 Arterioscler Thromb Vasc Biol 2008; 28:961-967

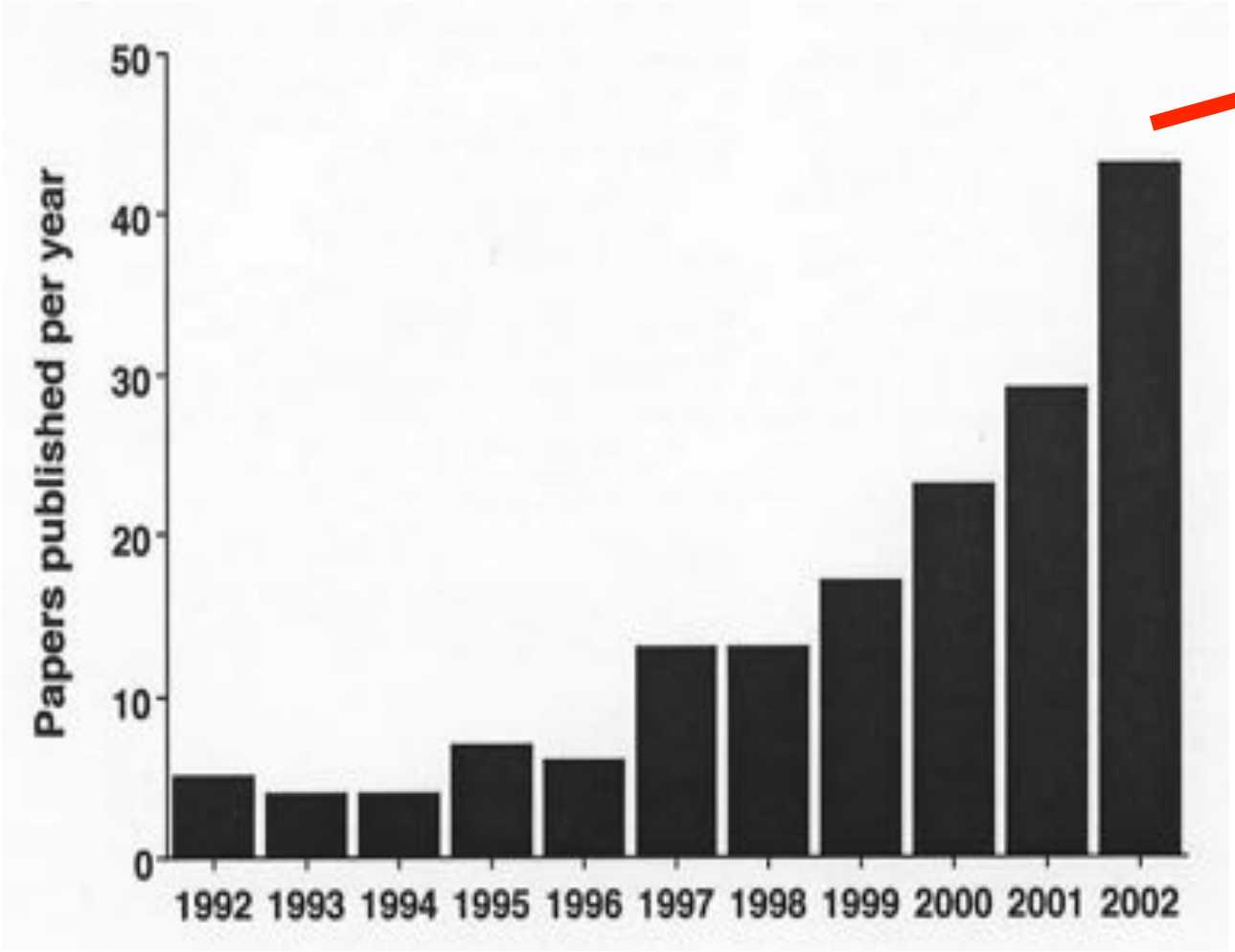
ADMA-NOS-NO Pathway
the newest drug target?



all in blood *** my laboratory interest

PRMT = Protein arginine methyltransferase
DDAH = Dimethylarginine dimethylaminohydrolase

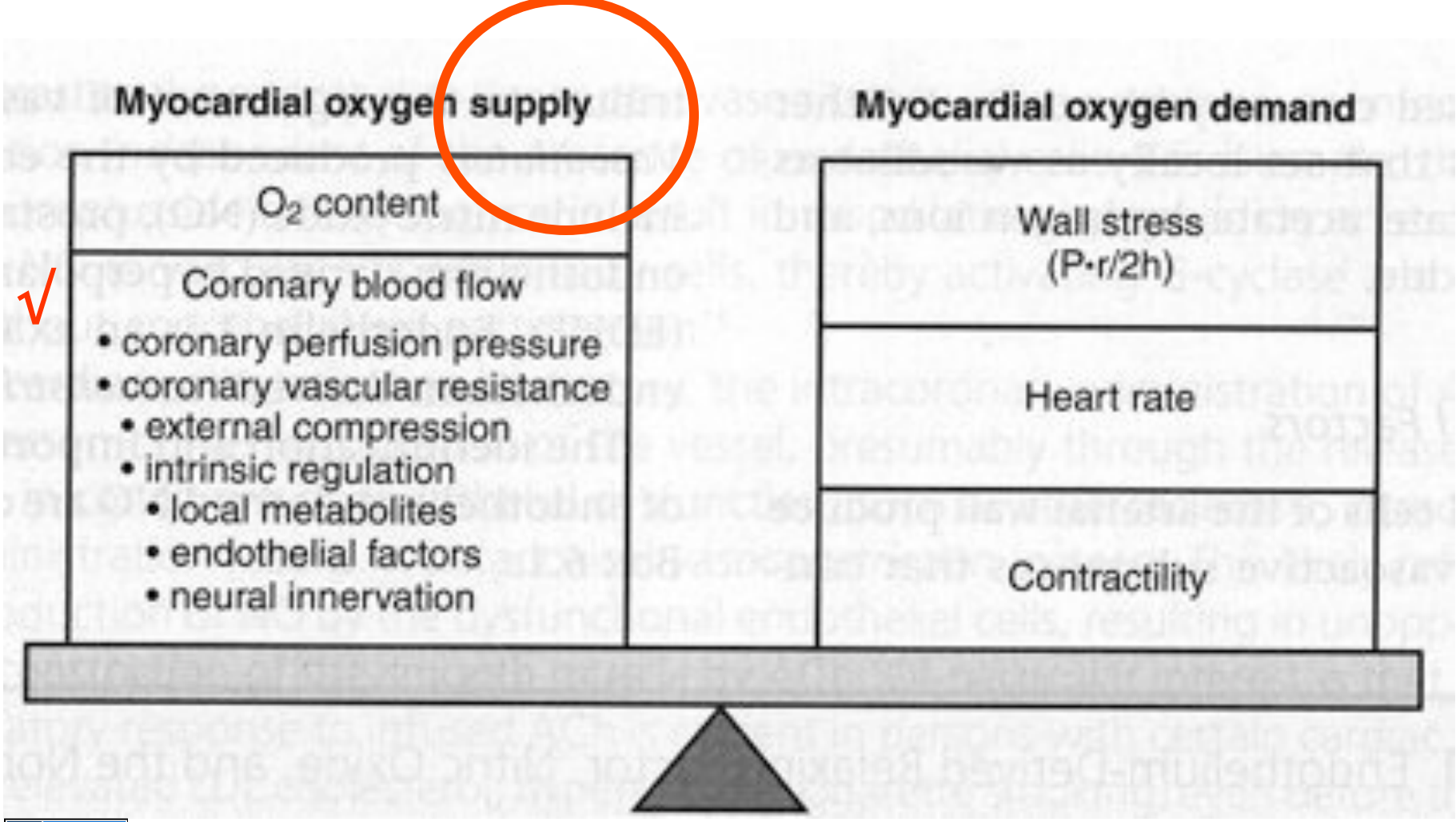
Published interest in ADMA



84 Publications In 2003

111 Publications In 6 MONTHS of 2008 !!!

Atherosclerosis Supplements 4 (2003)1–3



√

Look out for Limits to Compensatory VD and EC Dysfunction

Table 32–1. Resting Blood Flow and O_2 Consumption of Various Organs in a 63-Kg Adult Man with a Mean Arterial Blood Pressure of 90 mm Hg and an O_2 Consumption of 250 mL/min.

		Blood Flow			Oxygen Consumption		Resistance (R units)*		Percentage of Total	
Region	Mass (kg)	mL/min	mL/100 g/min	Arteriovenous Oxygen Difference(mL/L)	mL/min	mL/100 g/min	Absolute	per kg	Cardiac Output	Oxygen Consumption
Liver	2.6	1500	57.7	34	51	2.0	3.6	9.4	27.8	20.4
Kidneys	0.3	1260	420.0	14	18	6.0	4.3	1.3	23.3	7.2
Brain	1.4	750	54.0	62	46	3.3	7.2	10.1	13.9	18.4
Skin	3.6	462	12.8	25	12	0.3	11.7	42.1	8.6	4.8
Skeletal muscle	31.0	840	2.7	60	50	0.2	6.4	198.4	15.6	20.0
Heart muscle	0.3	250	84.0	114	29	9.7	21.4	6.4	4.7	11.6
Rest of body	23.8	336	1.4	129	44	0.2	16.1	383.2	6.2	17.6
Whole body	63.0	5400	8.6	46	250	0.4	1.0	63.0	100.0	100.0

*R units are pressure [mm Hg] divided by blood flow (mL/s).

Reproduced, with permission, from Barrett P (editor): *Medical Physiology*, 11th ed. Mosby, 1963.

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Asymmetric Dimethylarginine Independently Predicts Fatal and Nonfatal Myocardial Infarction and Stroke in Women

24-Year Follow-Up of the Population Study of Women in Gothenburg

Tora Leong, Dimitri Zylberstein, Ian Graham, Lauren Lissner, Deirdre Ward, Jane Fogarty, Calle Bengtsson, Cecilia Björkelund, Dag Thelle; for The Swedish-Irish-Norwegian (SIN) Collaboration

Objective—Asymmetrical dimethylarginine (ADMA) reduces nitric oxide by inhibiting nitric oxide synthase is associated with cardiovascular disease (CVD). Our study examined the association of ADMA with CVD prospectively in a healthy population-based cohort of women.

Methods and Results—We measured baseline ADMA of 880 women in the Population Study of Women in Gothenburg using high-performance liquid chromatography. After adjustment for traditional risk factors, creatinine clearance, and homocysteine using Cox models, the HR (95% CI in parentheses) of CVD end points at 24 years for a 0.15 μmol/L (1 SD) increase in ADMA were: all-cause mortality 1.12 (0.96, 1.32), fatal CVD 1.30 (1.04, 1.62), total CVD events 1.29 (1.09, 1.53). The top quintile (ADMA ≥0.71 μmol/L) compared with the bottom four-fifths, conferred a cumulative risk 22 versus 14%, relative risk 1.75 (95% CI 1.18, 2.59) and population attributable risk 12.7% of total CVD events, and further identified individuals who are at higher than expected risk based on the SCORE and Framingham systems.

Conclusions—A 0.15 μmol/L increase in baseline ADMA levels is associated with approximately 30% increase in incident cardiovascular risk at 24 years in women after adjustment. ADMA levels ≥0.71 μmol/L enhances CVD risk assessment in women. (*Arterioscler Thromb Vasc Biol* 2008;28:961-967)

 Arterioscler Thromb Vasc Biol 2008; 28:961-967

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