

**M2 Mini Review**  
**August 2008**

**Physiology/Pathophysiology**  
**Of**  
**Coronary Blood Flow**

Louis G. D'Alecy, Professor of Physiology

**Author(s):** Louis D'Alecy, D.M.D., Ph.D., 2009

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# 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.**

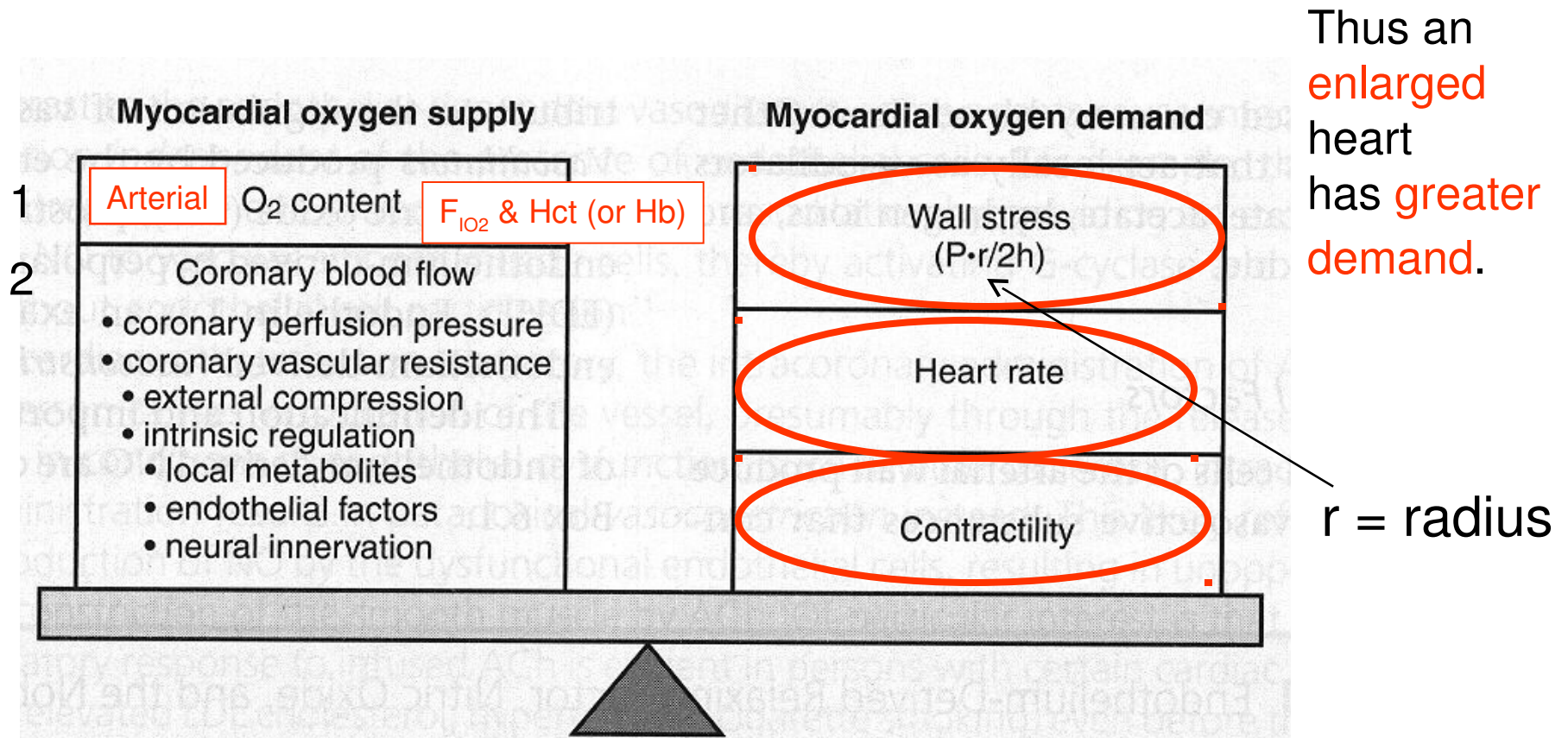
(arterial oxygen 20 Vol % to coronary sinus 8 Vol %)

(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<sub>2</sub> / 100mL blood



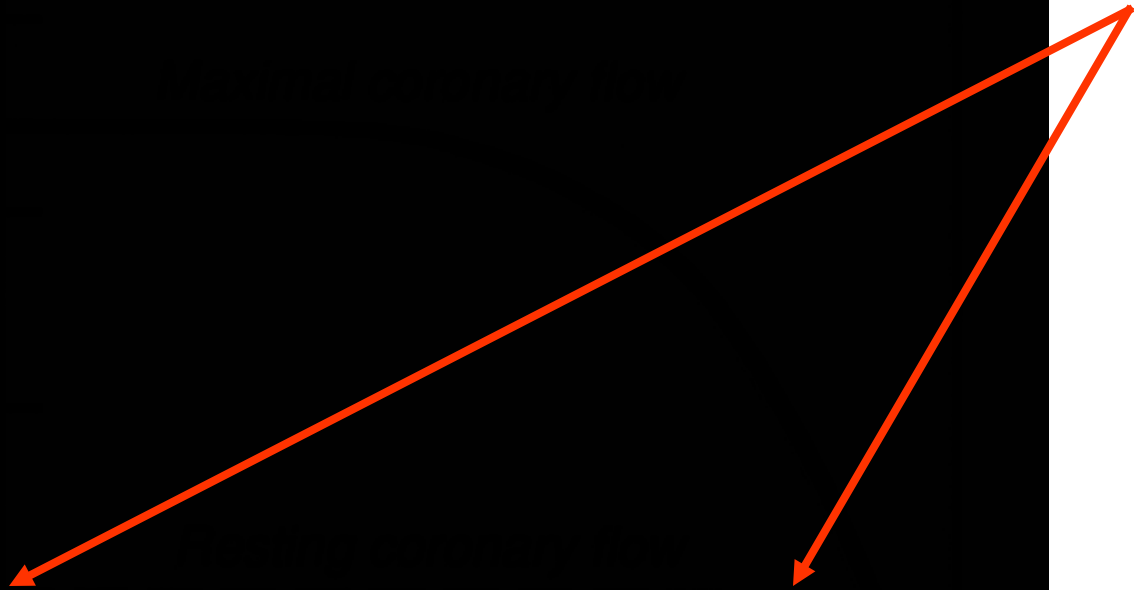
**Figure 6.1. Major determinants of myocardial oxygen supply and demand.**  
 h, ventricular wall thickness; P, ventricular pressure; r, ventricular radius.

PD-INEL Source Undetermined

Pressure X Rate Product



**How can coronary flow remain relatively constant with an 80% “lesion”??**



Fig

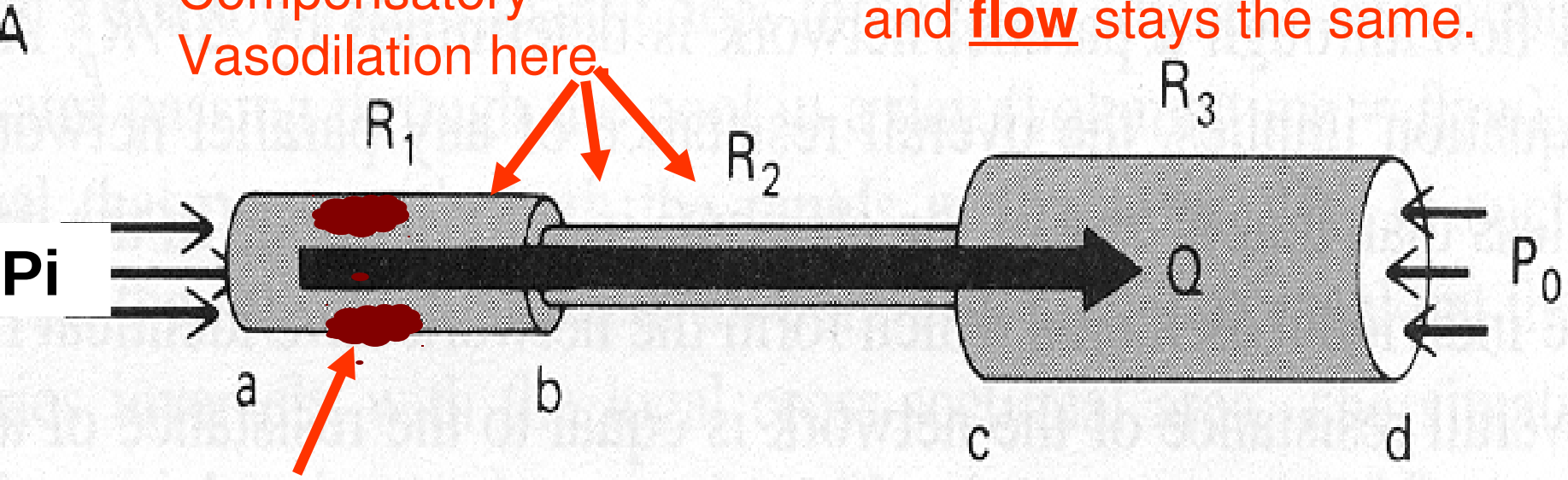
**Occlusion**

**“...proximal arterial stenosis...”**

# Series Resistance Network

Therefore series resistance and flow stays the same.

Compensatory Vasodilation here



Lesion here

$$R_s = R_1 + R_2 + R_3$$

$$\Delta P = P_i - P_o$$

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

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 !!!!!**



e.g., exercise

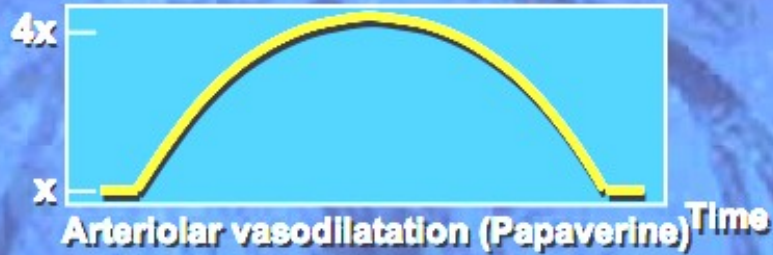
F

# Correlation of coronary anatomy and physiology: The concept of coronary flow reserve

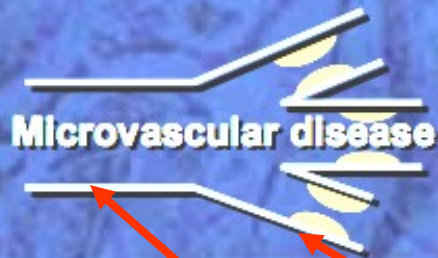
## Anatomy



## Physiology



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  $\Delta P$**
- 2      **SYSTOLIC COMPRESSION (“Resistance”)**
- 3      **METABOLIC CONTROL (Resistance)**  
         **O<sub>2</sub> & adenosine**
- 4      **NEURAL CONTROL (Resistance)**  
         **Sympathetic & Parasympathetic**

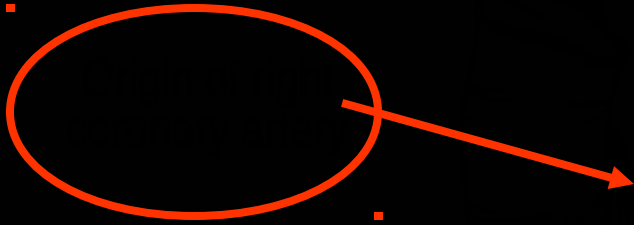
Anterior view

Posterior view

 PD-INEL Source Undetermined

But where is the origin of perfusion pressure?

Highest pressure



Lowest pressure

**Venous end is at  
coronary venous sinus  
right atrium.**



120 mmHg

Systolic Pressure

aortic pressure

left ventricular pressure

0

Systolic compression

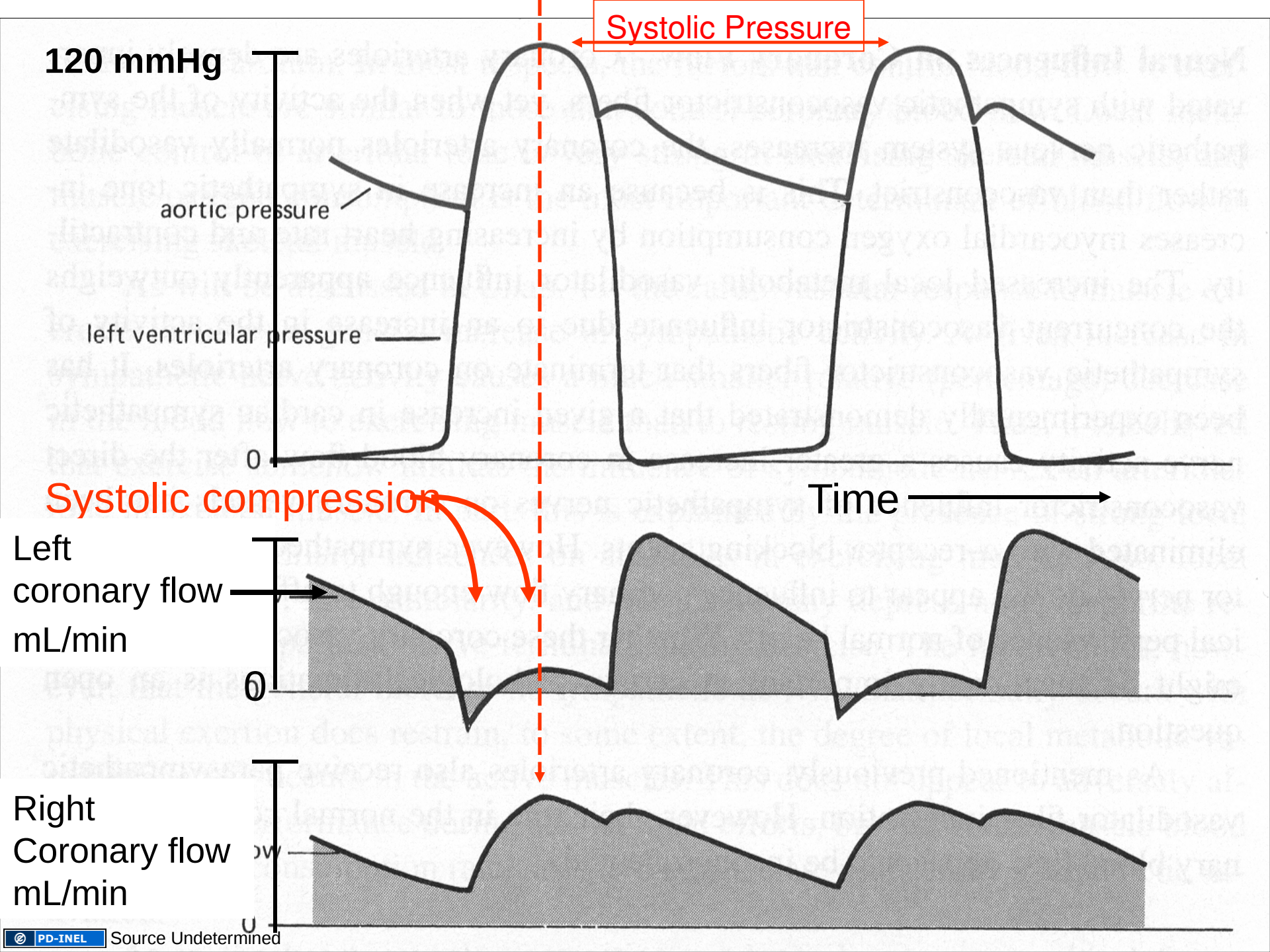
Time

Left  
coronary flow  
mL/min

0

Right  
Coronary flow  
mL/min

0





# 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  $\Rightarrow$   $\square$  **F**<sub>tissue</sub>

• **Vasodilation**

$\Rightarrow$   $\square$  **r**  $\Rightarrow$   $\square$  **R**<sub>tissue</sub>  $\Rightarrow$   $\square$  **F**<sub>tissue</sub>

**F**<sub>tissue</sub> = Perfusion Pressure = **Coronary flow**

**R**<sub>tissue</sub>

# “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

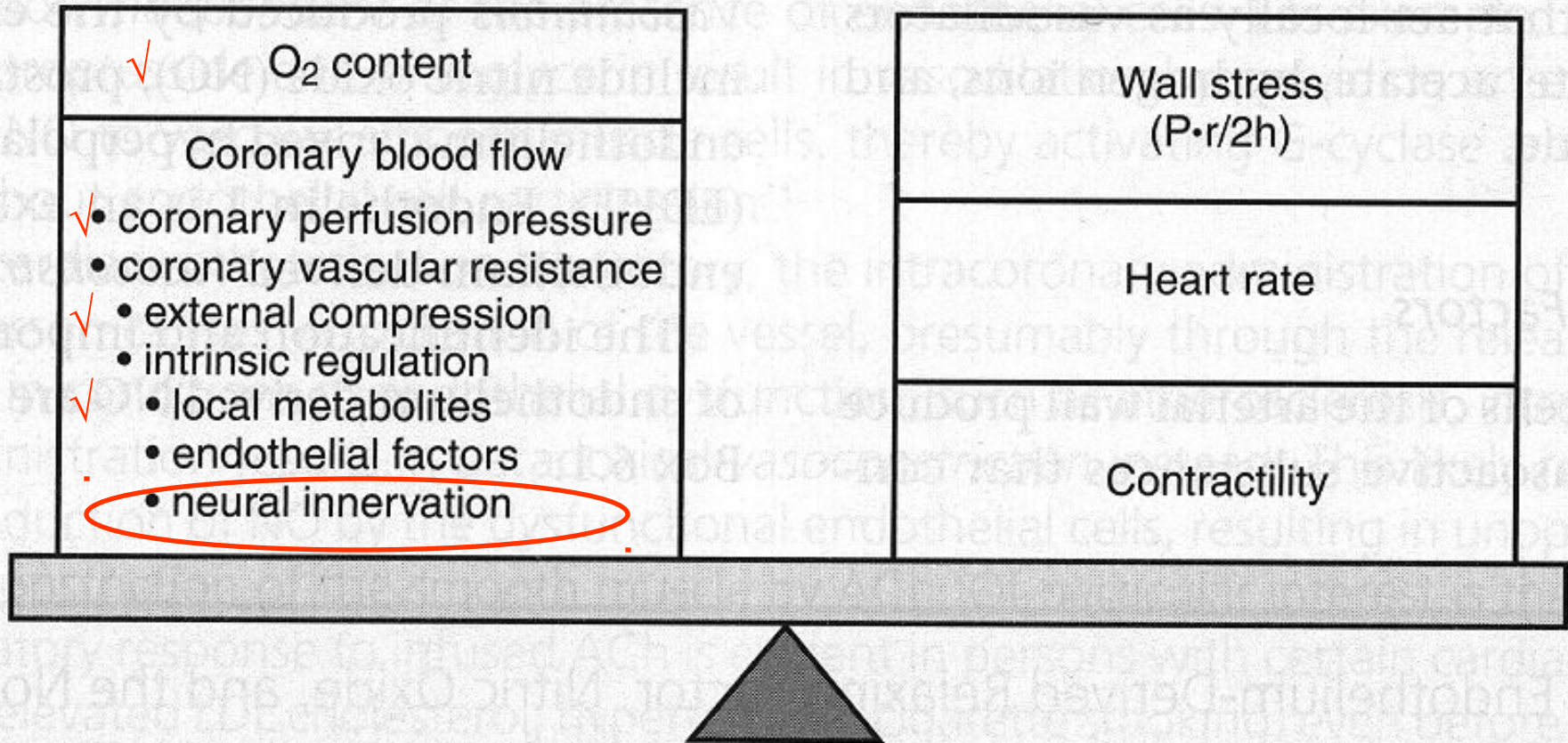
“Thus any additional **oxygen** requirement must be met by an increase in blood flow.”

P 143 Lilly

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

## Myocardial oxygen supply

## Myocardial oxygen demand



**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
  - $\alpha_1$  vasoconstriction
- Sympathetic beta adrenergic vasodilation
  - $\beta_1$  (evidence for innervated VSM)
  - $\beta_2$  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

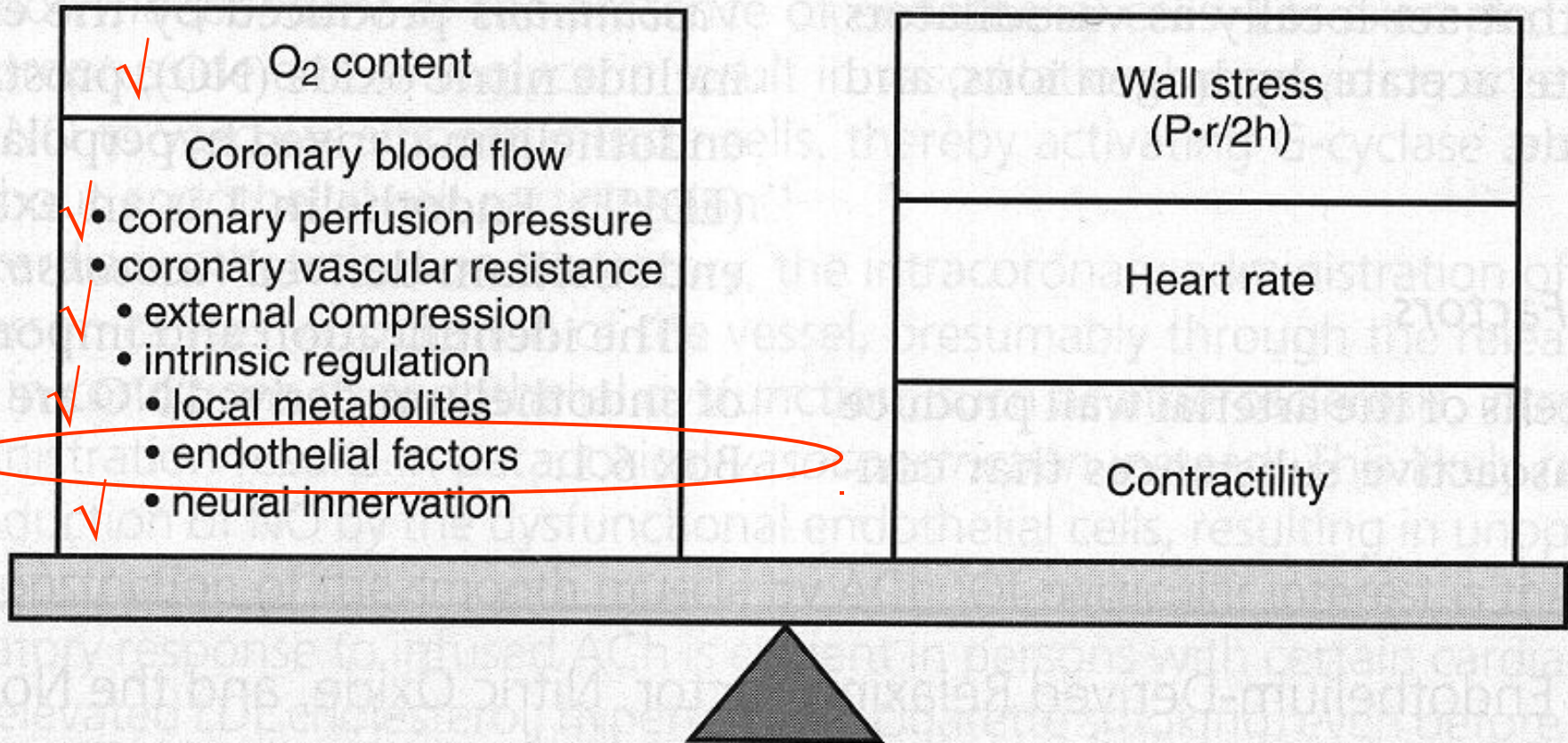
by “unmasked”  $\alpha_1$  adrenergic vasoconstriction

Can Metabolic control still dominate???



## Myocardial oxygen supply

## Myocardial oxygen demand



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

Sheer or  
Flow Mediated  
Dilation  
\* FMD \*



Intact endothelium

Without endothelium

Artery wall tension

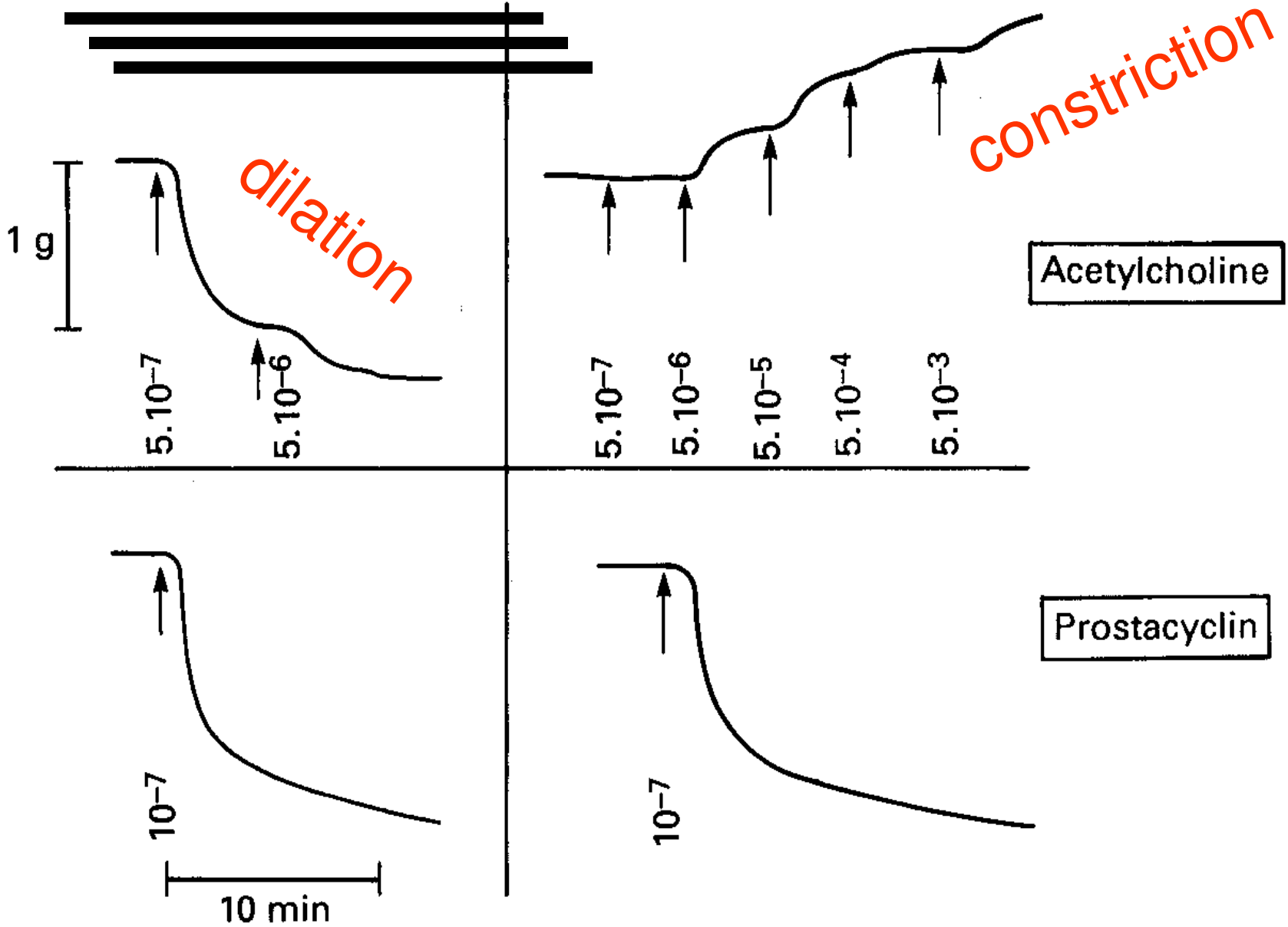
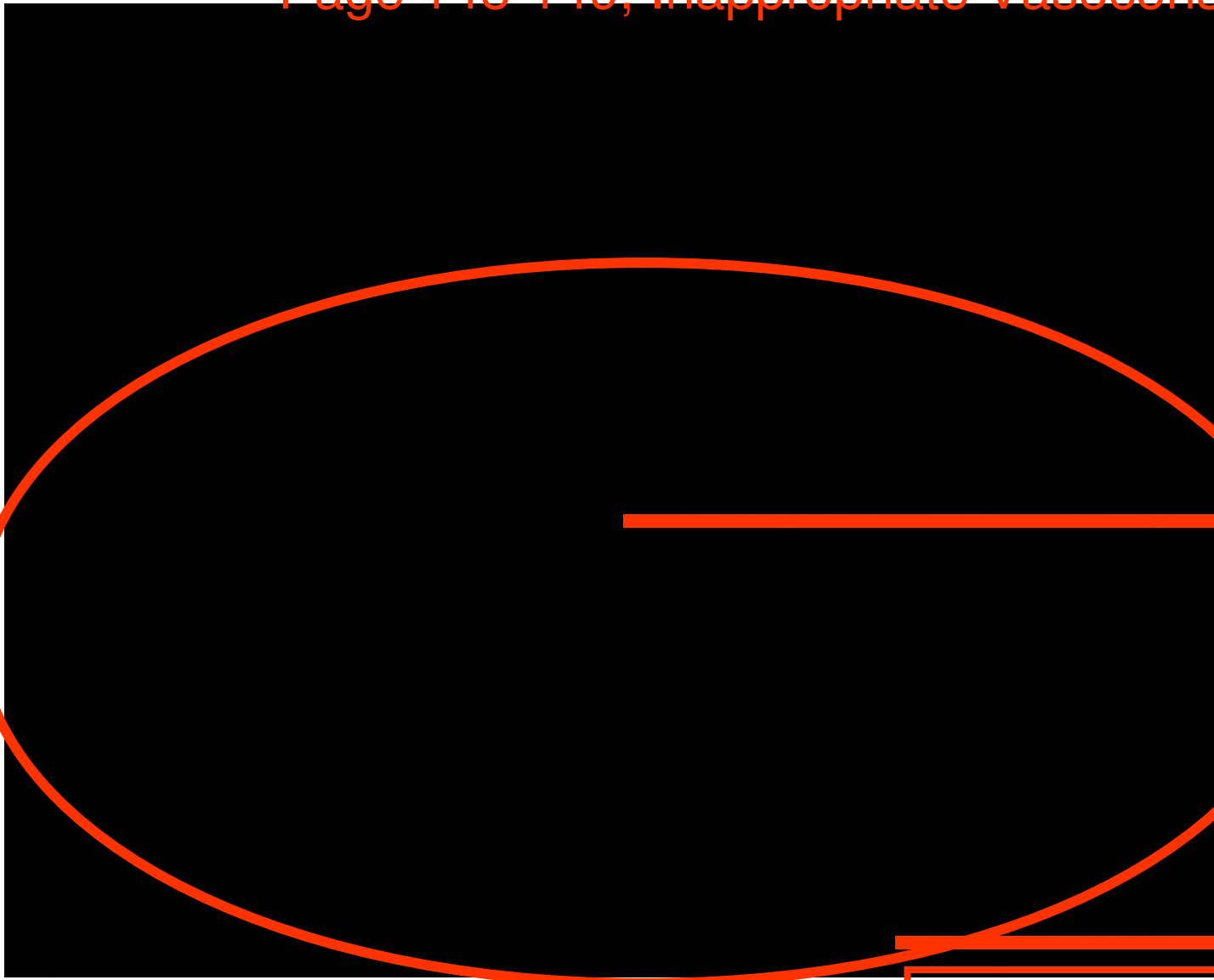




Fig 0.2

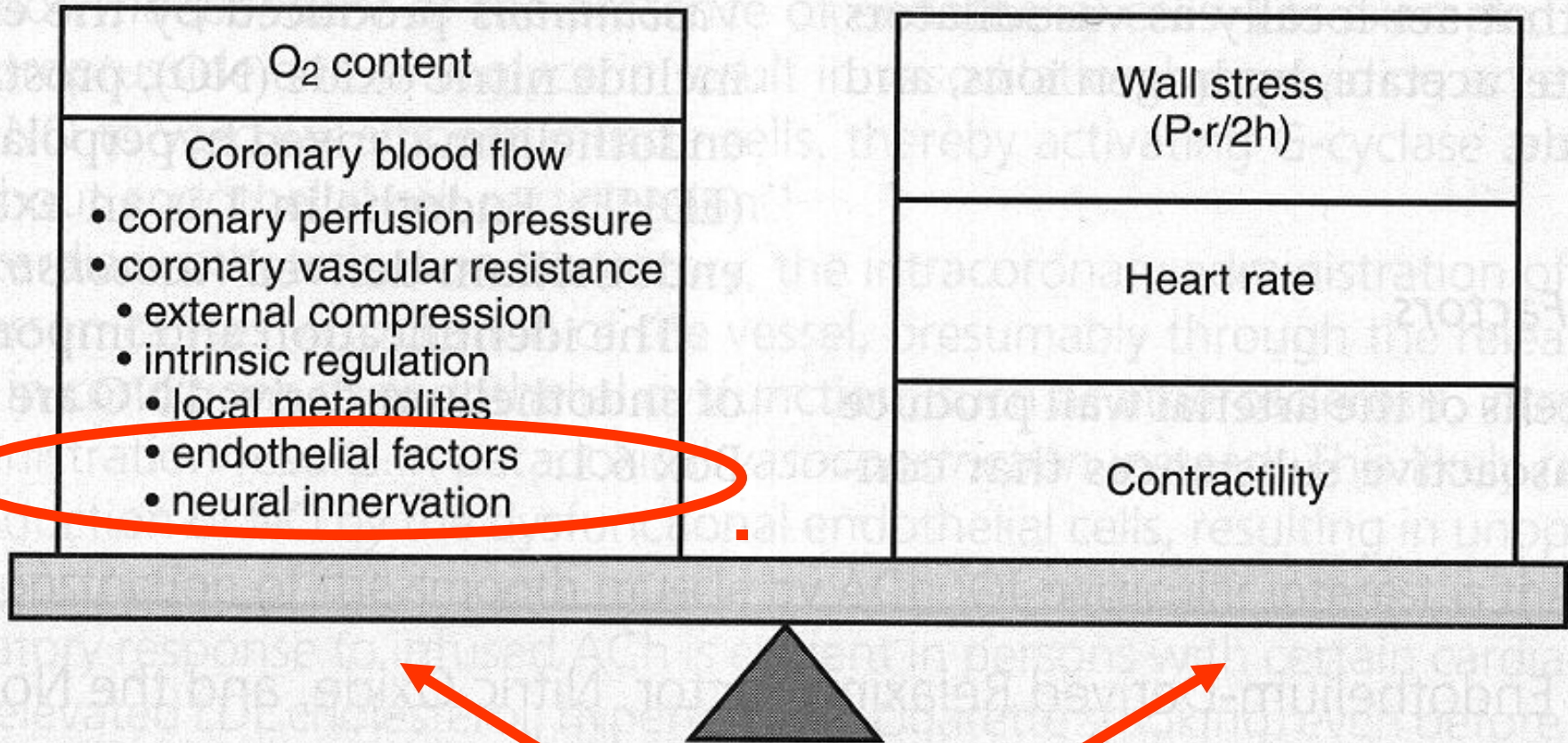


“unmasked”

$\alpha_1$

## Myocardial oxygen supply

## Myocardial oxygen demand



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**++ Drug effects ++ Endothelial Dysfunction**

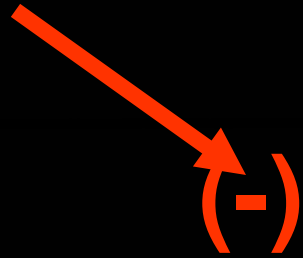
Asymmetrical  
Dimethylarginine  
(ADMA is a  
NOS Inhibitor)

(-)

Sheer or flow  
mediated  
vasodilation



ADMA  
(NOS Inhibitor)



Sheer or flow  
mediated  
vasodilation





# Does ADMA Cause Endothelial Dysfunction?

John P. Cooke

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

THEN

## Special Review

LATER

# Asymmetrical Dimethylarginine The Über Marker?

**2004**

**ADMA: A Major Cause of  
Endothelial Dysfunction**

**ADMA Regulates Vascular Resistance**

(*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.

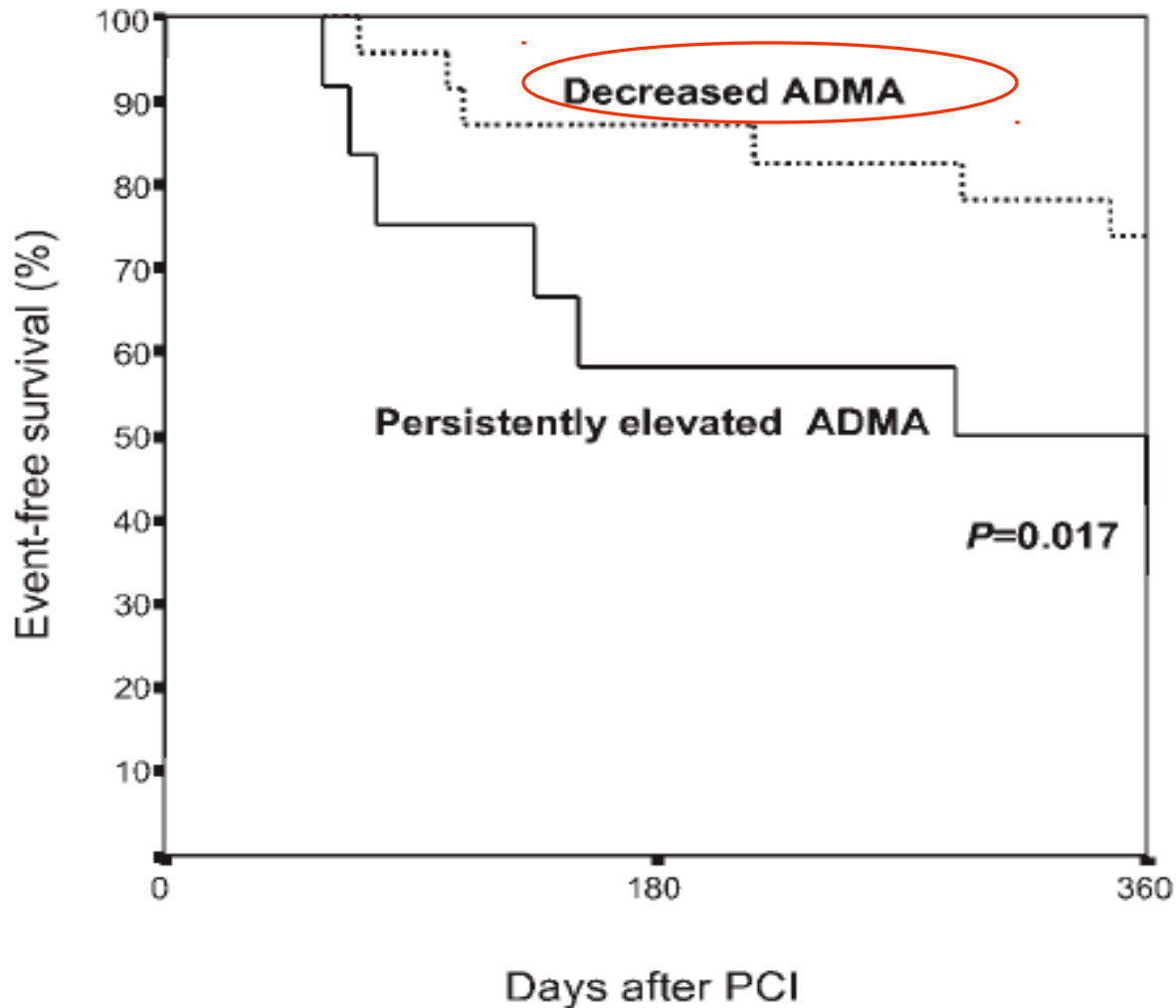
Tanja K. Krempl et al.

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)



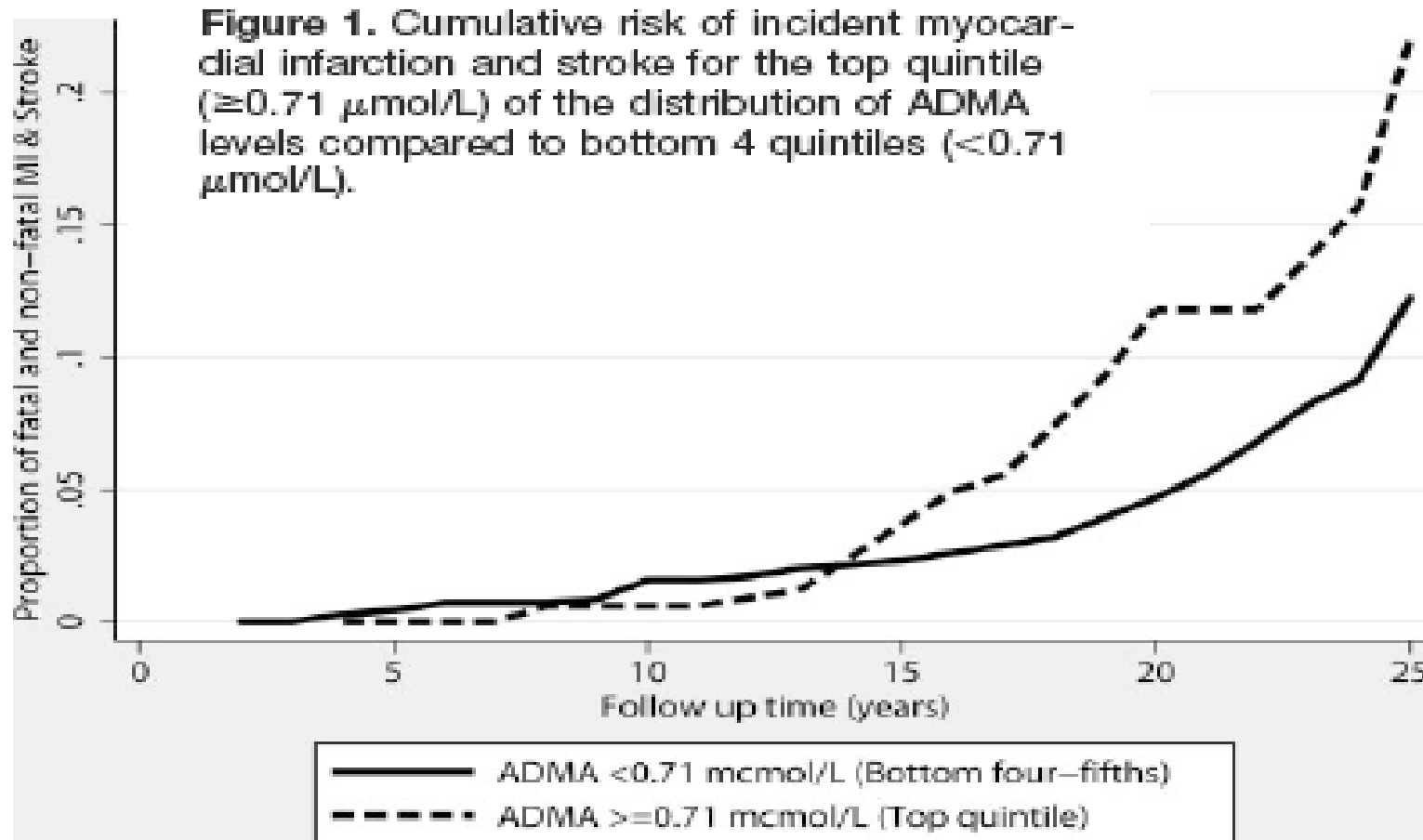
**After PCI  
Pts with decreased  
ADMA had  
greater survival!**

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

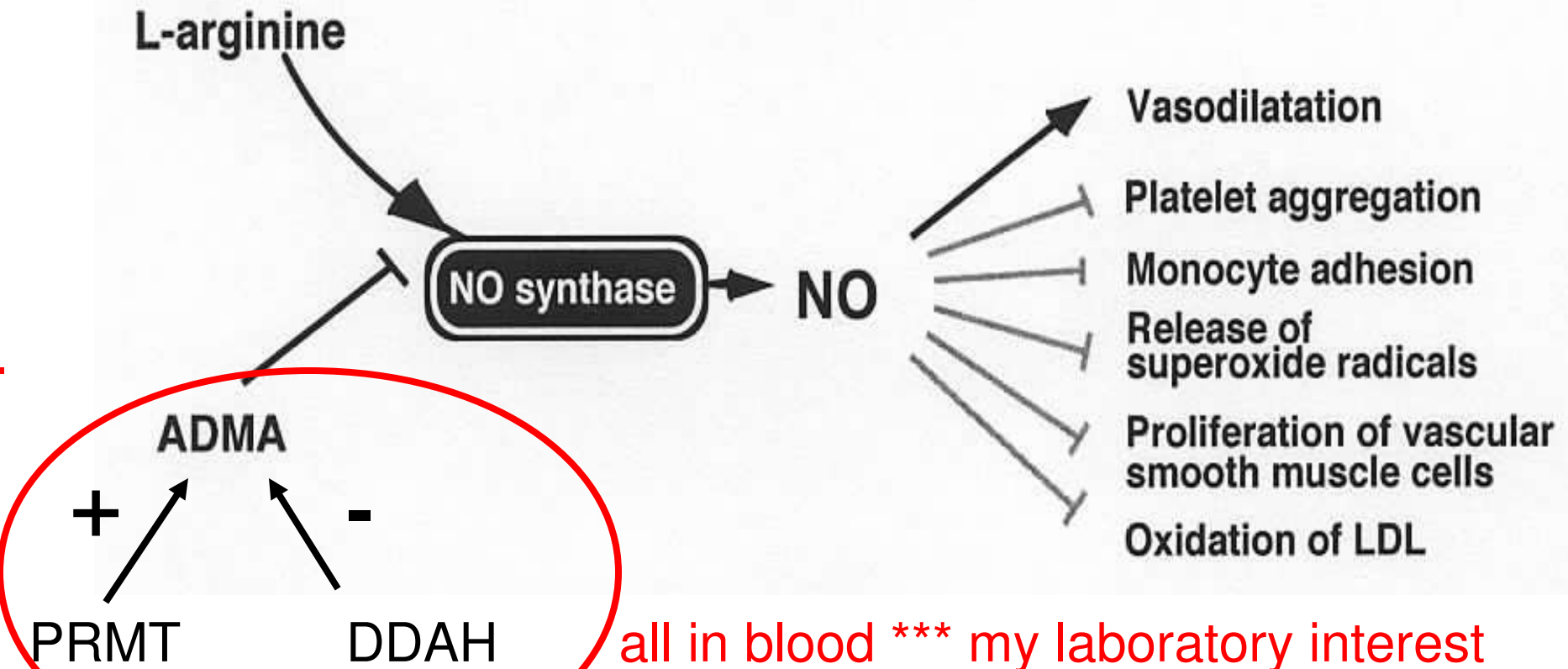
## 24-Year Follow-Up of the Population Study of Women in Gothenburg

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

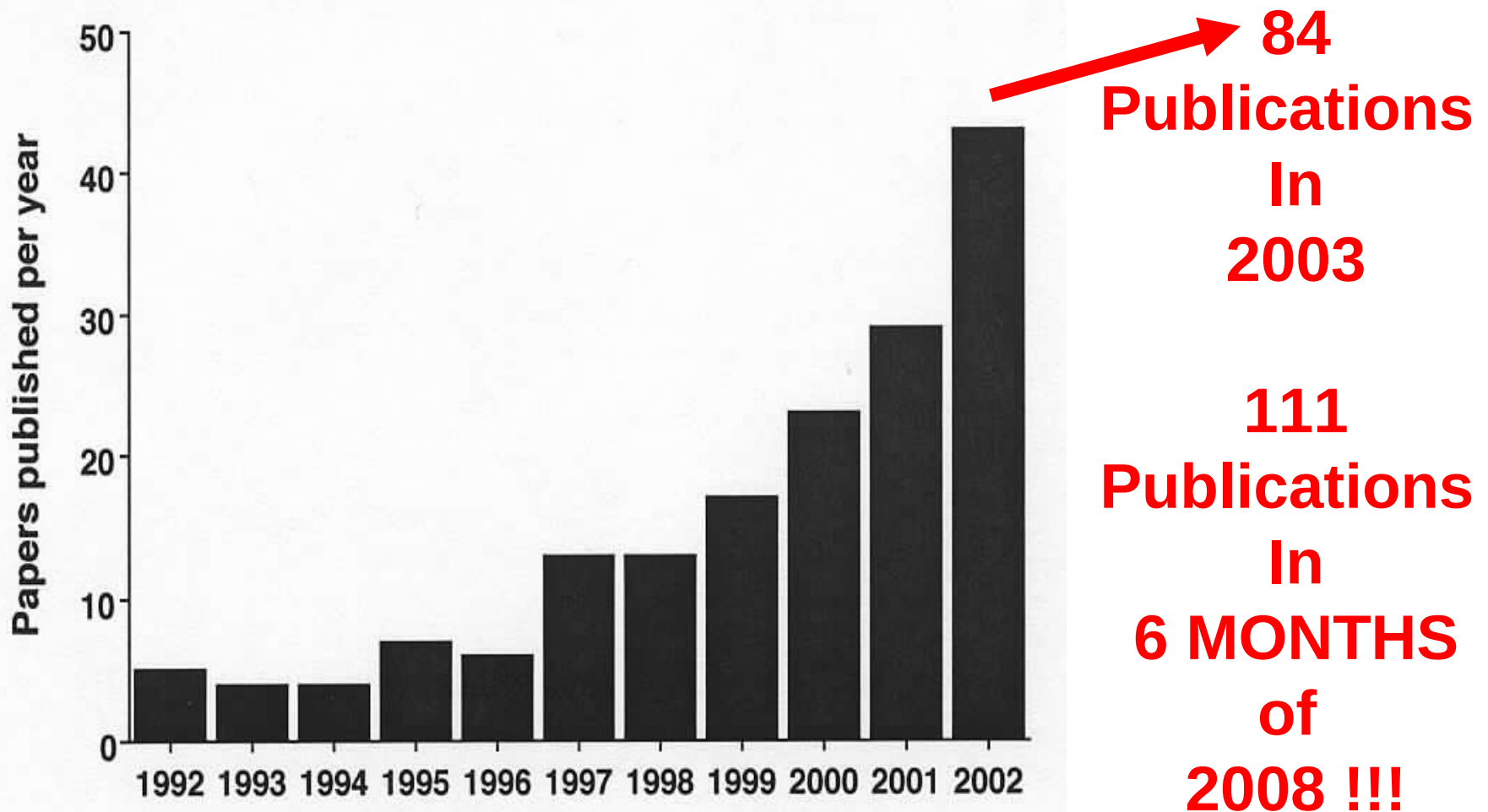


# ADMA-NOS-NO Pathway the newest drug target?



PRMT = Protein arginine methyltransferase  
DDAH = Dimethylarginine dimethylaminohydrolase

# Published interest in ADMA



Atherosclerosis Supplements 4 (2003)1-3

38

## Myocardial oxygen supply

O<sub>2</sub> content

Coronary blood flow

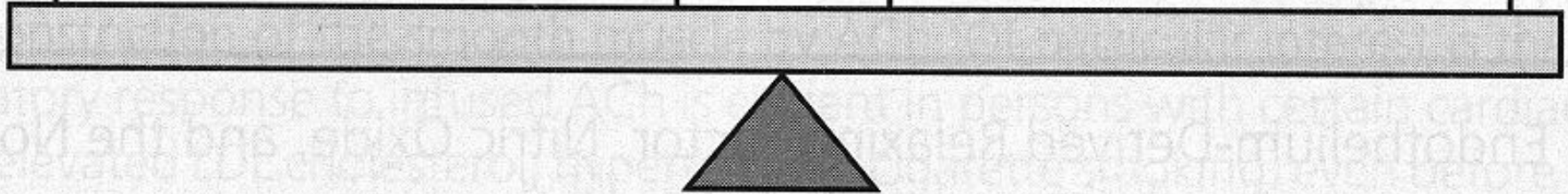
- coronary perfusion pressure
- coronary vascular resistance
- external compression
- intrinsic regulation
  - local metabolites
  - endothelial factors
  - neural innervation

## Myocardial oxygen demand

Wall stress  
( $P \cdot r / 2h$ )

Heart rate

Contractility



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**Look out for Limits to Compensatory VD  
and  
EC Dysfunction**



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Lange Physiology > Section VI. Circulation > Chapter 32. Circulation Through Special Regions > Introduction: Circulation Through Special Regions >

**Table 32–1. Resting Blood Flow and O<sub>2</sub> Consumption of Various Organs in a 63-Kg Adult Man with a Mean Arterial Blood Pressure of 90 mm Hg and an O<sub>2</sub> Consumption of 250 mL/min.**

Region	Mass (kg)	Blood Flow			Oxygen Consumption		Resistance (R units) <sup>a</sup>		Percentage of Total	
		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

<sup>a</sup>R units are pressure (mm Hg) divided by blood flow (mL/s).

Reproduced, with permission, from Bard P (editor): *Medical Physiology*, 11th ed. Mosby, 1961.



**Table 32–1. Resting Blood Flow and O<sub>2</sub> Consumption of Various Organs in a 63-Kg Adult Man with a Mean Arterial Blood Pressure of 90 mm Hg and an O<sub>2</sub> Consumption of 250 mL/min.**

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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  $\mu\text{mol/L}$  (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  $\geq 0.71 \mu\text{mol/L}$ ) 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  $\mu\text{mol/L}$  increase in baseline ADMA levels is associated with approximately 30% increase in incident cardiovascular risk at 24 years in women after adjustment. ADMA levels  $\geq 0.71 \mu\text{mol/L}$  enhances CVD risk assessment in women. (*Arterioscler Thromb Vasc Biol* 2008;28:961-967)

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Slide 30: Source Undetermined

Slide 31: Source Undetermined

Slide 32: Circulation 2004; 109:1813-1819

Slide 34: Source Undetermined

Slide 35: Arterioscler Thromb Vasc Biol 2008; 28:961-967

Slide 36: Source Undetermined

Slide 37: Source Undetermined

Slide 38: Source Undetermined

Slide 39: McGraw-Hill

Slide 40: McGraw-Hill

Slide 41: Arterioscler Thromb Vasc Biol 2008; 28:961-967