Nitric oxide: a basic science hero, but what about safety and therapies?

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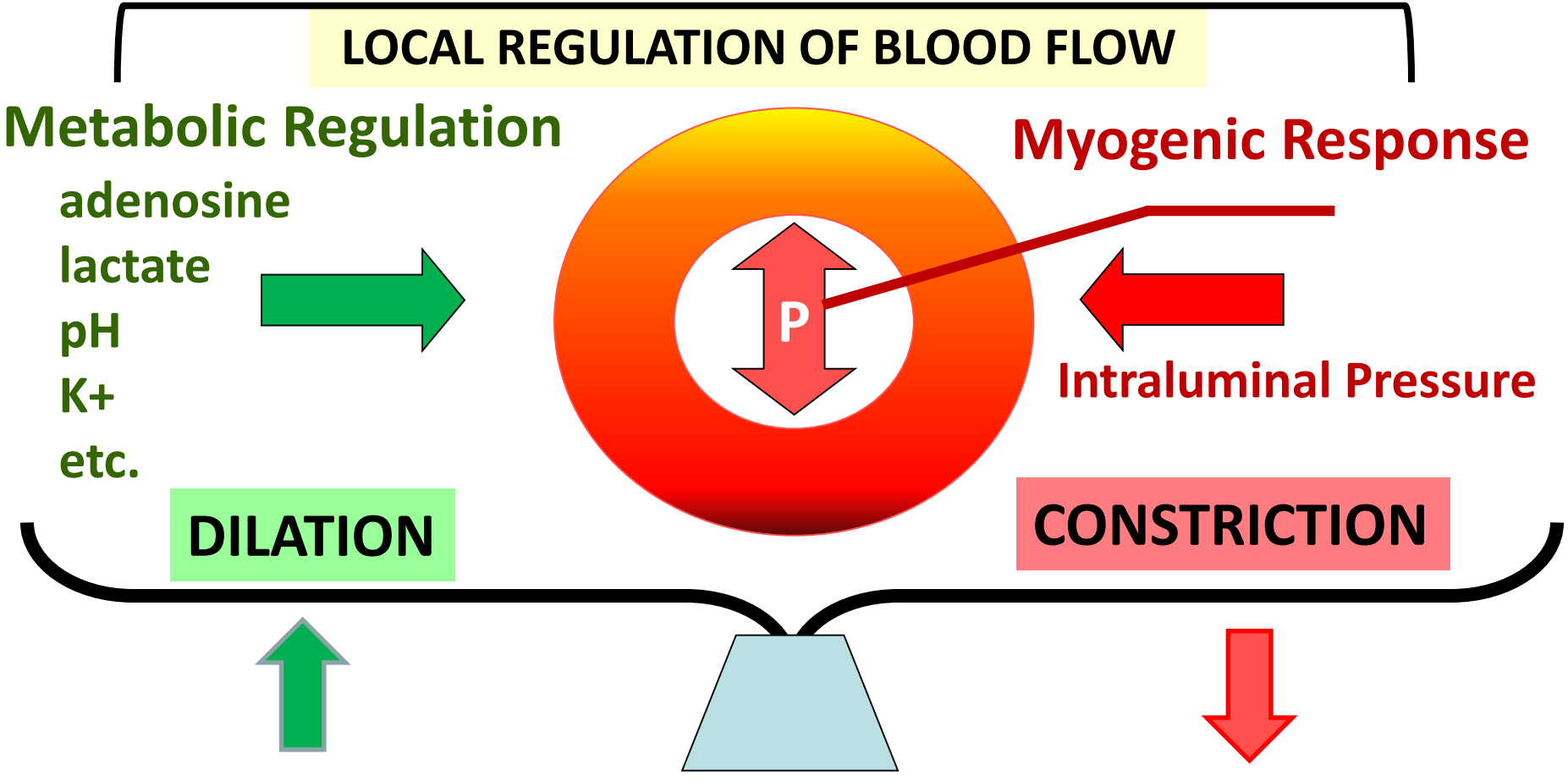
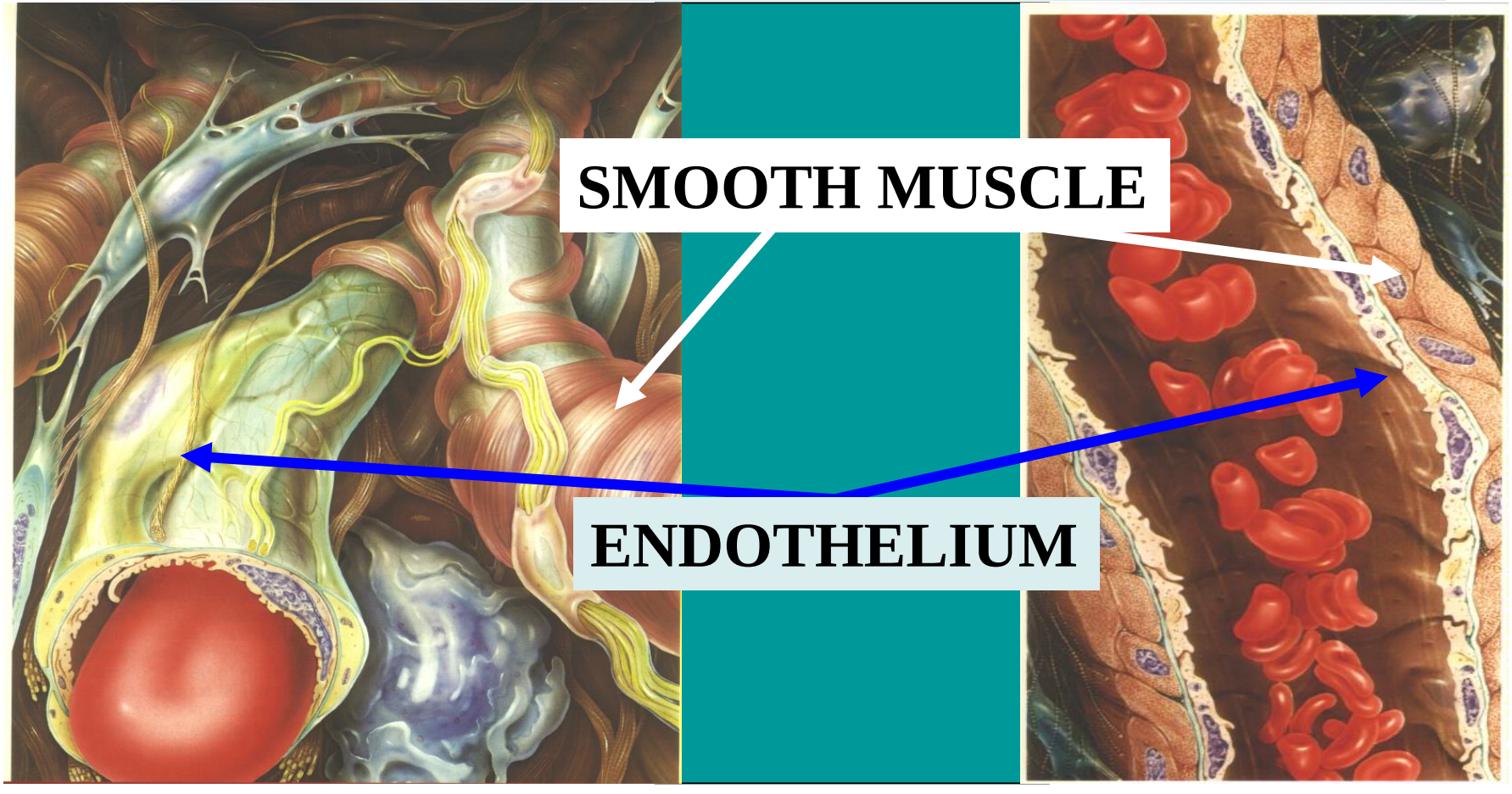
Biological therapies and vaccines: safety issues, physiological and immunological mechanisms
Summer School for PhD students and young researchers
15-16. 06. 2021.

Before 1980s: blood vessels were considered:
"a smooth muscle tube"

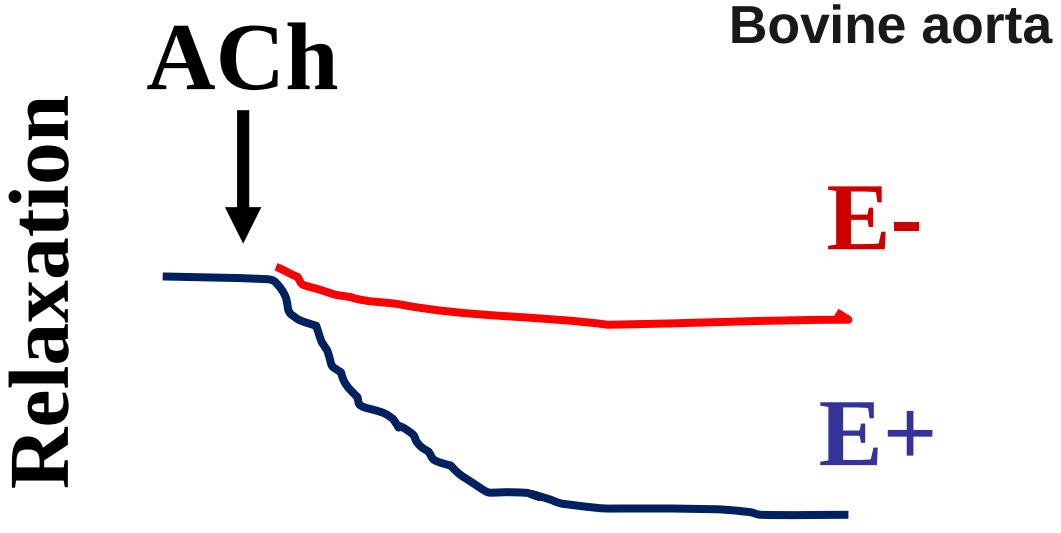


For many years endothelium was viewed….



Provides a smooth surface preventing the development of blood clots

Endothelium mediates ACh-induced relaxation of isolated large arteries



Endothelium derived relaxing factor: EDRF

1980: Nature, Furchgott and Zawadsky

AORTA

EDRF

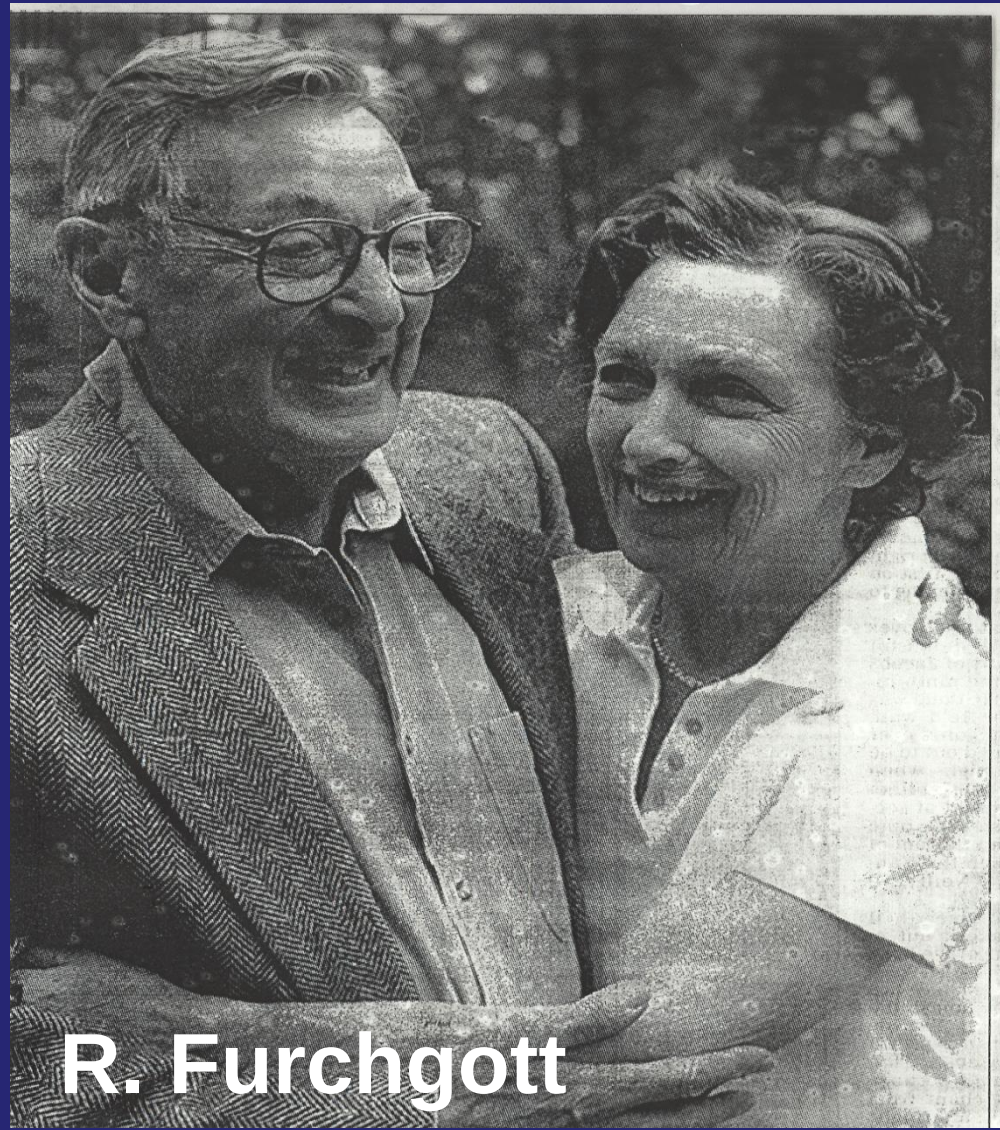
ACh → **Dilation**

EDRF: NO, EDHF, ROS, PGs

After 15 years of research,
the chemical identity of EDRF was established
Nitric Oxide (NO)

Furchgott: endothelium, EDRF, NO
Ignarro: nitrate compounds, nitroglycerin, NO
Murad: NO vs. Role of cGMP in vasodilation

Nobel Price 1998



R. Furchgott

It's Nobel cause in Brooklyn

Prof wins prize in medicine

By ROBERT GEARTY and VIRGINIA BREEN
Daily News Staff Writers

An 82-year-old Brooklyn professor had planned a dental checkup and a few rounds of golf yesterday. Instead, he won the Nobel Prize for Medicine.

"I was pleased to hear the news, but I also was disappointed that it woke me on a holiday. I was going to sleep late," Robert Furchgott quipped, hours after a reporter roused him at 5:30 a.m.

The pharmacologist at the State University of New York Health Science Center at Brooklyn will share the honor with two other Americans for discovering new properties of nitric oxide, an odorless gas that acts as a messenger between cells.

The other winners were Louis Ignarro of UCLA and Ferid Murad of the University of Texas Medical School in Houston.

Their findings laid the groundwork for understanding high blood pressure, and for developing the anti-impotence drug Viagra.

"The prizes are good to have, but the fun of it is doing the re-

"I'm happy for him. He works very hard from morning to night," she said.

She reported that her husband ate a home-packed lunch at his desk every day. He never turns down students' requests to read their research papers, she said.

The professor wasn't sure what he'd do with his share of the $978,000 prize money. But, noting that he still drives to work in Brooklyn just about every weekday, he joked, "Maybe I should use part of the money to get a driver."

At the SUNY center that has been his academic home for the last 42 years, the news prompted cheers among colleagues and students. The Nobel Prize is a first for the modest East Flatbush campus in the shadows of Kings County Hospital.

Growing up in Charleston S.C., Furchgott's love affair with science began early. "I would go on field trips for birds and shells," he said.

After earning a doctorate in biochemistry at Northwestern University in Illinois, he headed to New York's Cornell Med-

Dr. L. Ignarro, Dr. R. Furchgott:

- **Does the endothelium has a role in the regulation of microvascular diameter?**

PRESSURE DISTRIBUTION IN THE VASCULAR SYSTEM

Cardiac output:
~ 5 L/min

~ 15 mmHg

~ 0 mmHg

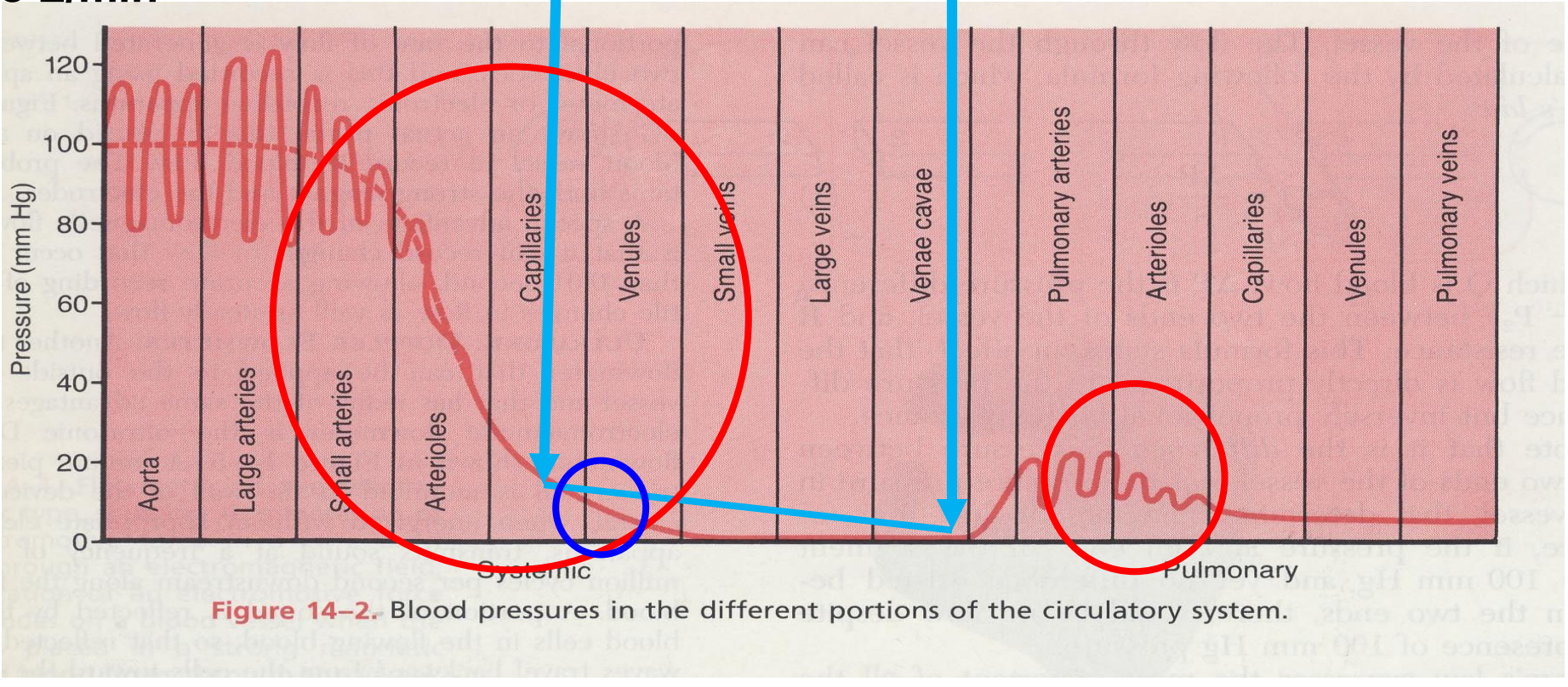


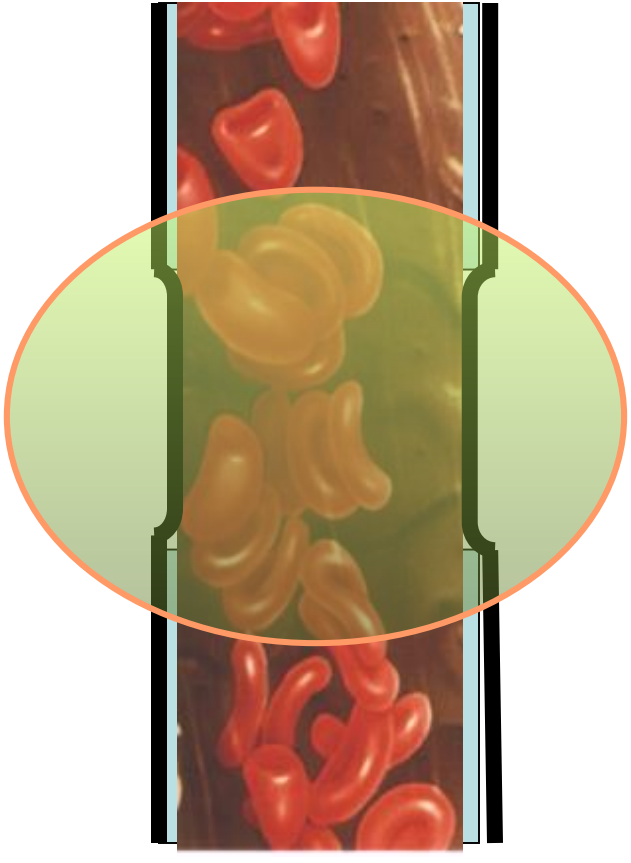
Figure 14–2. Blood pressures in the different portions of the circulatory system.

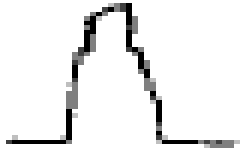
MICROCIRCULATION

Impairment of the endothelium of a small arteriole by Light/Dye method

20 micron

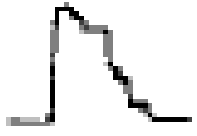
Changes in diameter to ACh, an endothelium dependent dilator



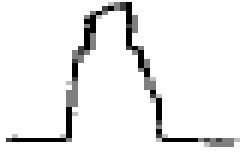


Intact segment

Impaired segment



ACh **Adenosine**



Intact segment

Loss of dilation of arterioles to ACh after impairment of endothelium

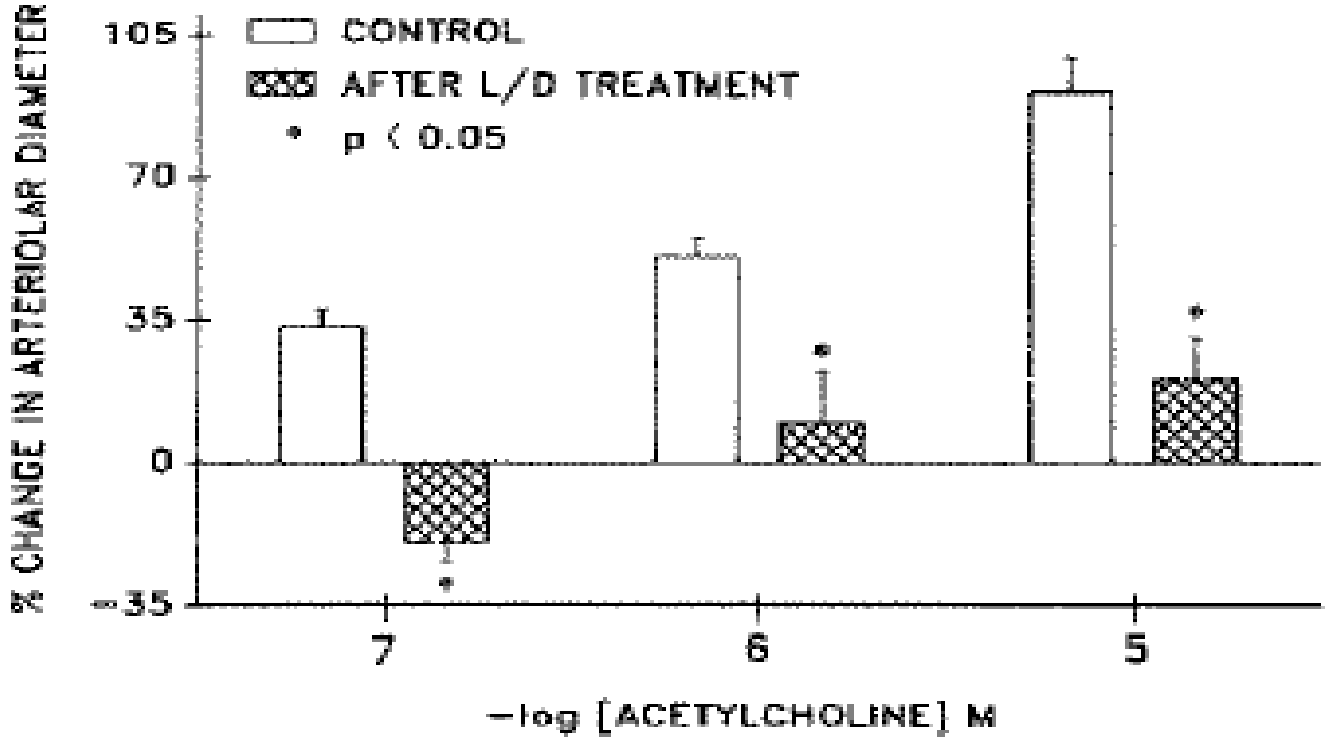


FIG. 2. Summary data of effects of light-dye treatment on arteriolar responses to various doses of acetylcholine (n = 10–14). * Significant changes in response from control.

In microcirculation, the vascular endothelium releases prostaglandins and EDRF dilating microvessels

Koller, A., E.J. Messina, M.S. Wolin and G. Kaley. Effects of endothelial impairment on arteriolar dilator responses in vivo. Am. J. Physiol. 257 (Heart Circ. Physiol. 26):H1485-H1489, 1989.

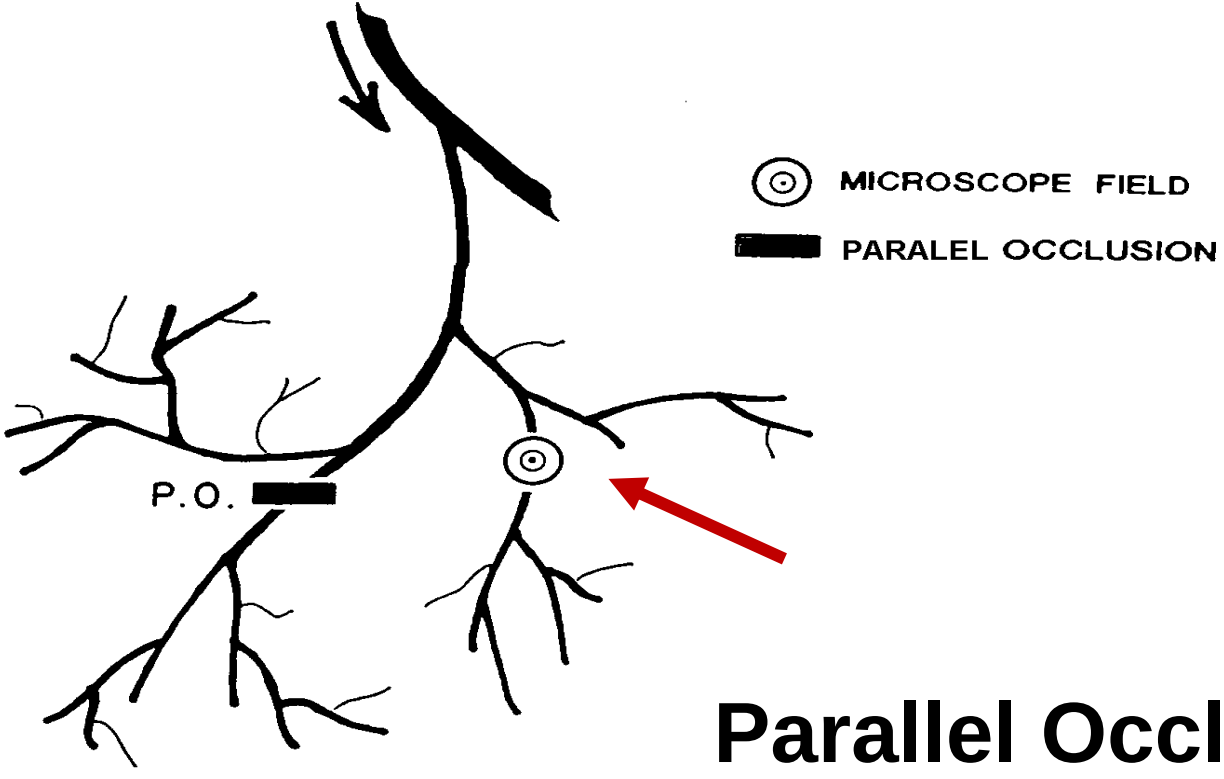
Koller, A., E.J. Messina, M.S. Wolin and G. Kaley. Endothelial impairment inhibits prostaglandin and EDRF-mediated arteriolar dilation in vivo. Am. J. Physiol. 257 (Heart Circ. Physiol. 26):H1966-H1970, 1989.

However! **ACh does not play role in regulation of basal diameter, exercise-, metabolic-, or reactive hyperemia.**

If so,

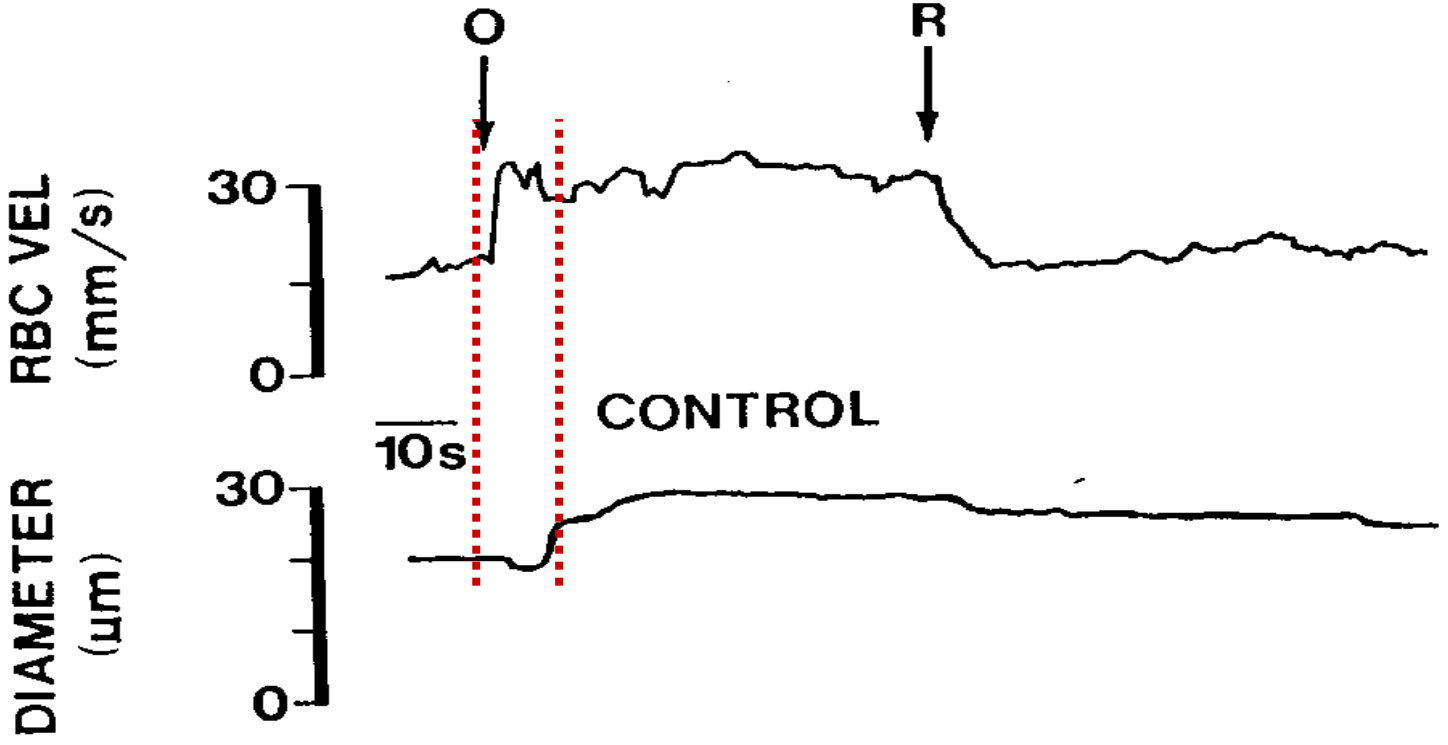
What is the physiological stimulus for release of NO and PGs?

Do flow increases effect the diameters of vessels?

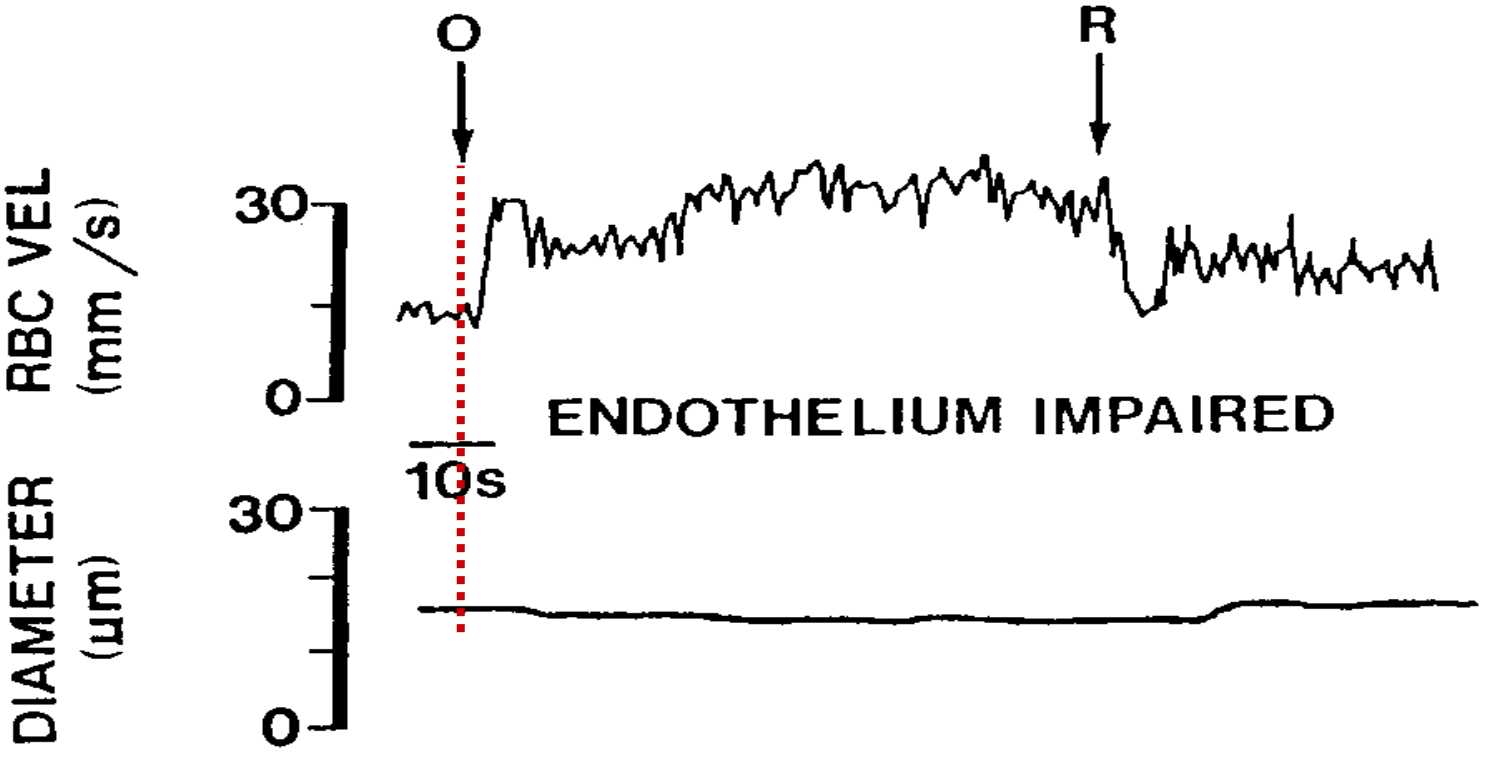


Parallel Occlusion

Flow-dependent dilation in vivo (E+)



Flow-dependent dilation in vivo (E-)



Microvascular endothelium can sense the „flow” (shear stress) and releases dilator factor(s)

Microcirc Endothelium Lymphatics. 1989 Dec;5(6):519-29.

Flow velocity-dependent regulation of microvascular resistance in vivo.

Koller A, Kaley G.

Source

Department of Physiology, New York Medical College, Valhalla 10595.

In vivo

Abstract

In skeletal (cremaster) muscle of pentobarbital anesthetized rats we tested the hypothesis that blood flow-dependent regulation of vascular resistance exists in the microcirculation. During occlusion of an arteriole we found that the consequent increase in red blood cell (RBC) velocity in a proximal parallel arteriole was followed by a mean increase in diameter of 32 percent (mean control diameter: 21.5 +/- 0.5 microns) of the arteriole under study. The increase in arteriolar diameter always appeared with a delay (mean: 8.4 +/- 0.5 s) following the onset of changes in RBC velocity. Upon release of the occlusion RBC velocity decreased followed by a decline in diameter of the arteriole under study. Since the changes in arteriolar diameter during this experimental intervention cannot be explained on the basis of previously described blood flow-regulatory mechanisms in the microcirculation we conclude that changes in blood flow velocity **(wall shear stress) per se** induced the changes in arteriolar diameter. The existence of this phenomenon suggests a new, flow velocity-sensitive mechanism which can regulate - via changes in diameter - the supply and distribution of blood flow in the microcirculation in vivo.

An isolated arteriole

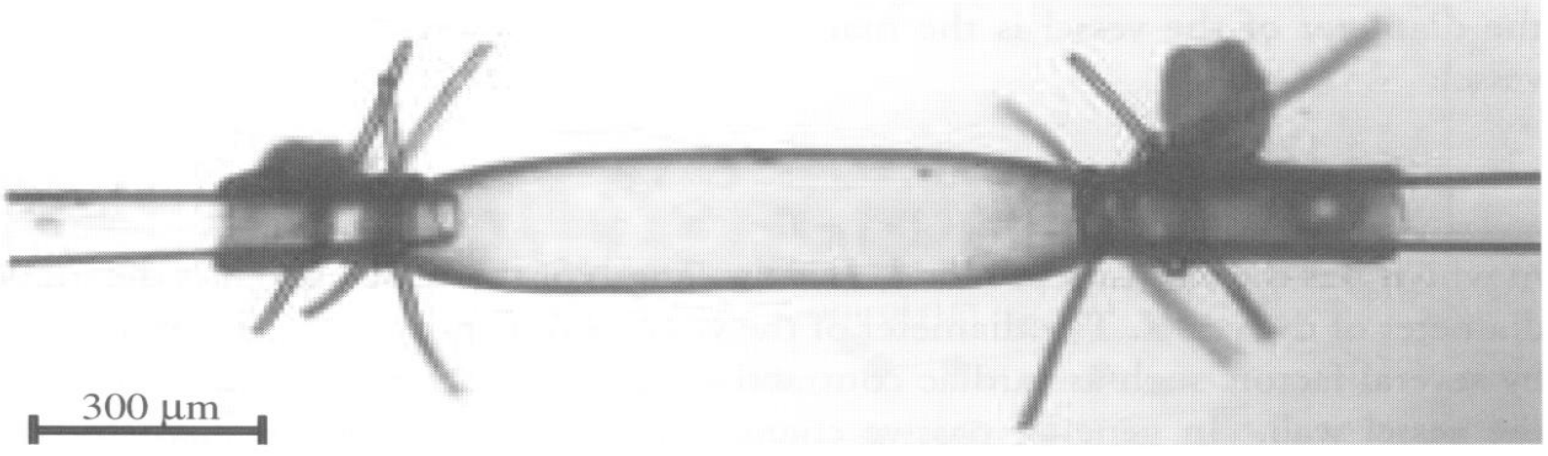


Figure 1.3: *The pressure myograph technique developed to investigate control mechanisms in isolated vessels. Shown is a cannulated rat mesenteric small artery with a diameter of ~250 µm attached to two glass cannulas, by means of very thin nylon sutures.* Kuo et al.

An isolated arteriole

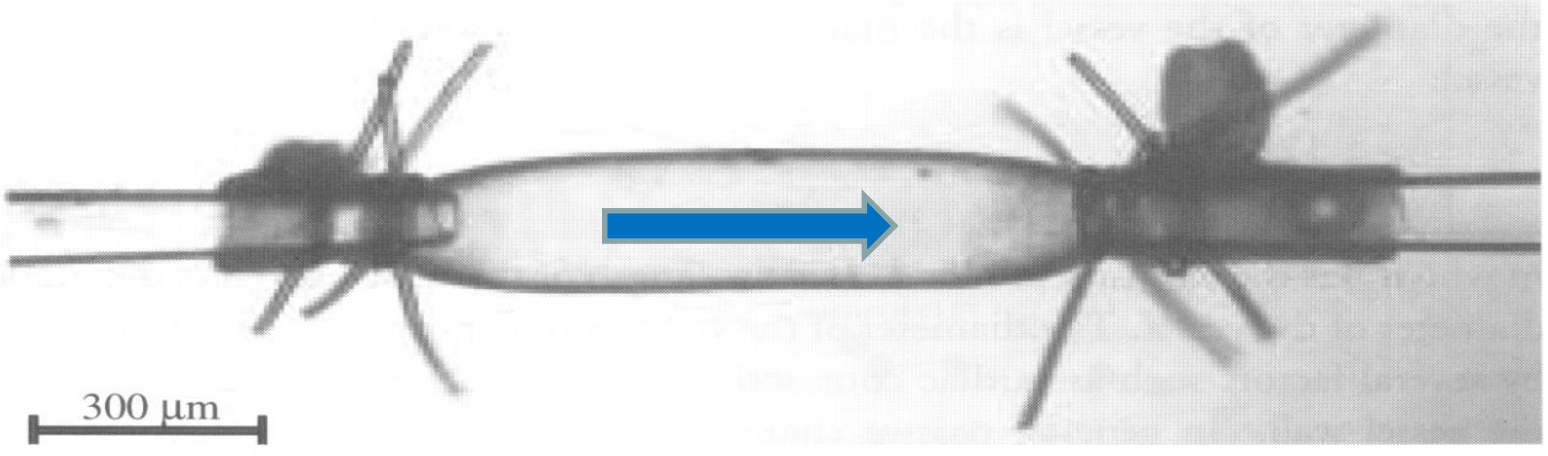
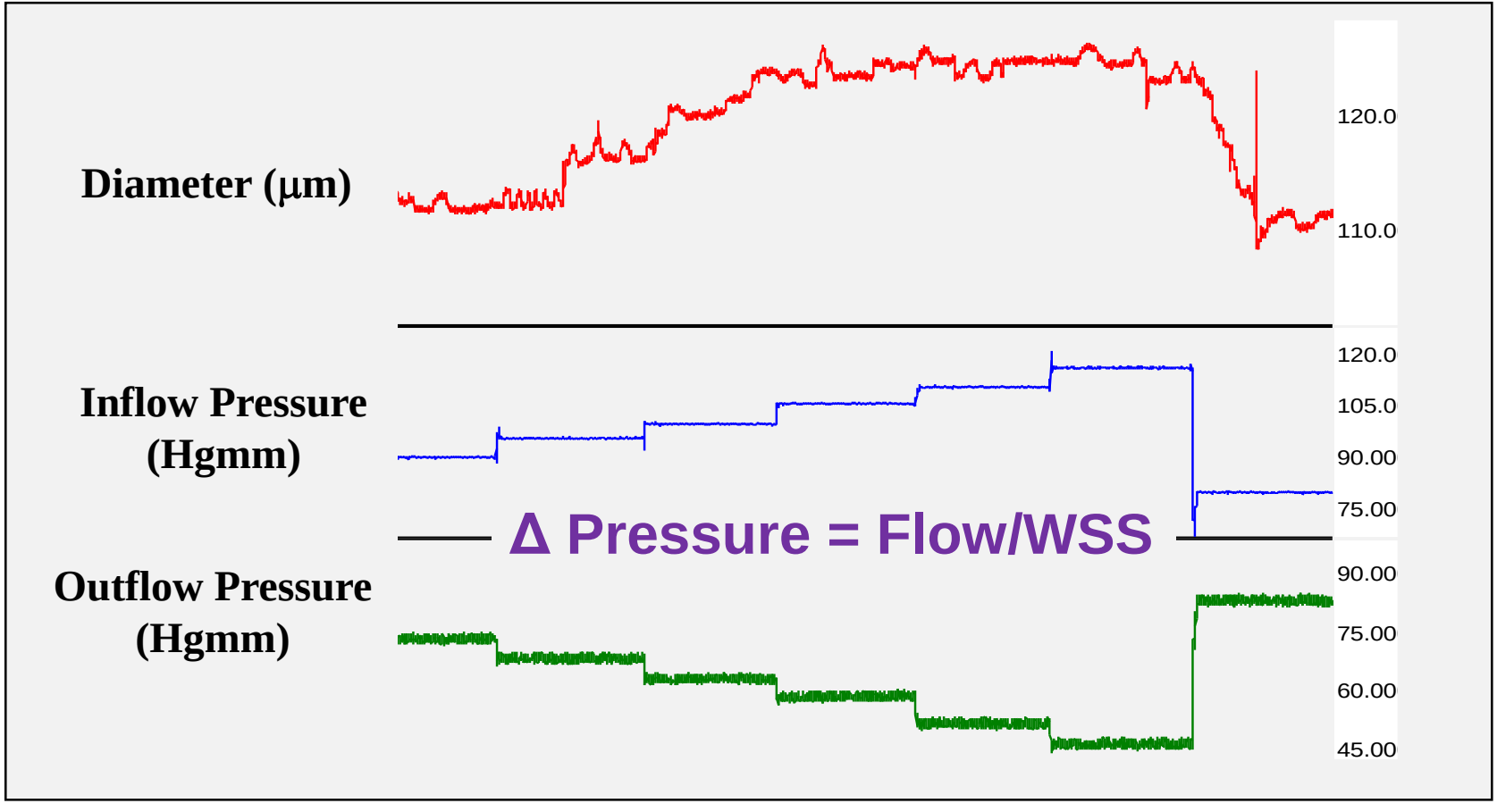


Figure 1.3: *The pressure myograph technique developed to investigate control mechanisms in isolated vessels. Shown is a cannulated rat mesenteric small artery with a diameter of ~250 µm attached to two glass cannulas, by means of very thin nylon sutures.* Kuo et al.

Increases in intraluminal flow (shear stress) elicit substantial dilations of an isolated arteriole



Stimuli of NO production

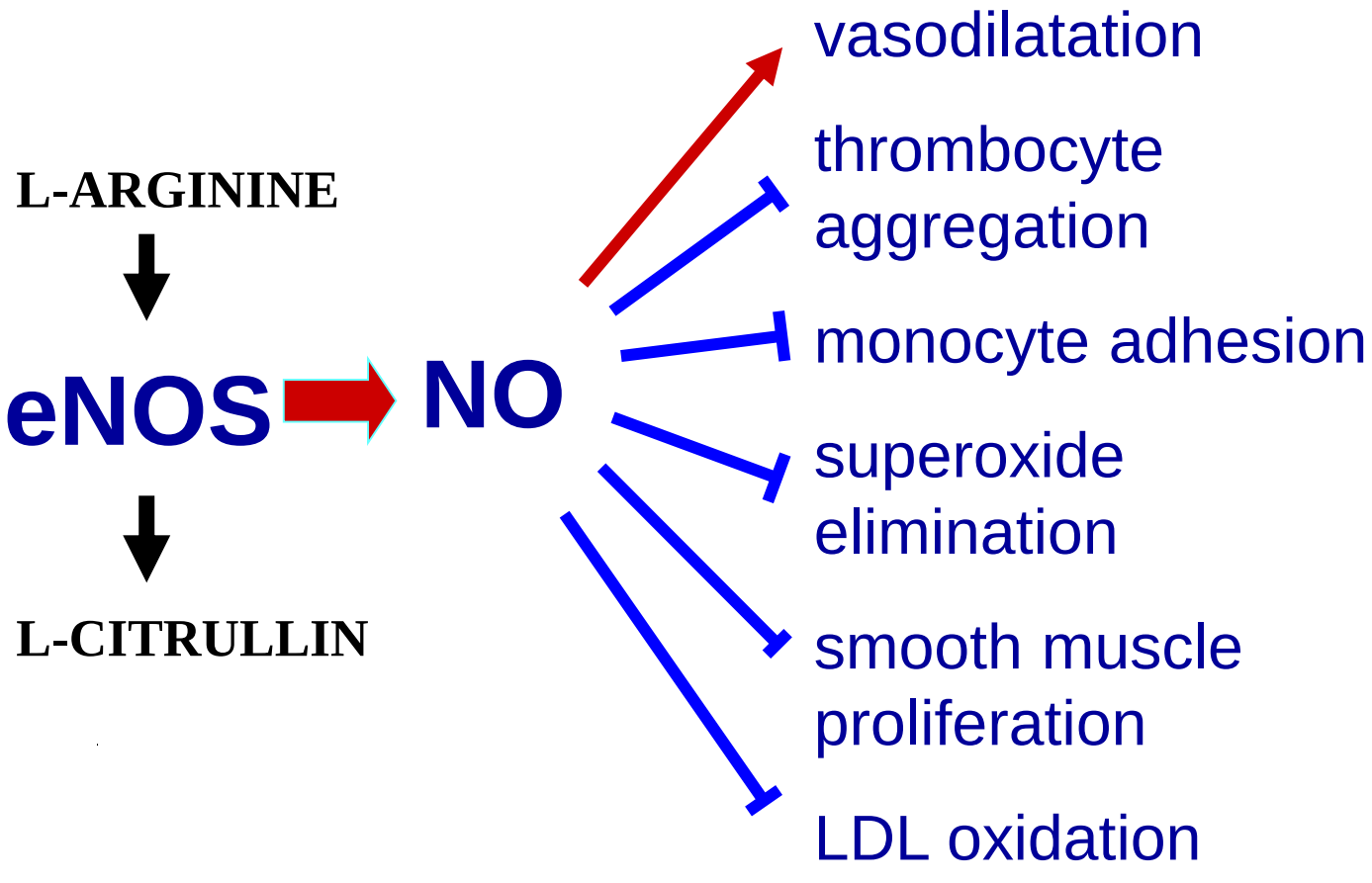
1. Humoral agonists of eNOS increase $[Ca^{2+}]_i$:
acetylcholine (M_3-receptor), bradykinin, thrombin, substance P, vasoactive intestinal polypeptide (VIP), insulin, histamine)

2. Mechanical agonist (wall shear stress)
- flow induced vasodilatation
- Mechano-sensitive ion channels, tyrosine kinase, PECAM

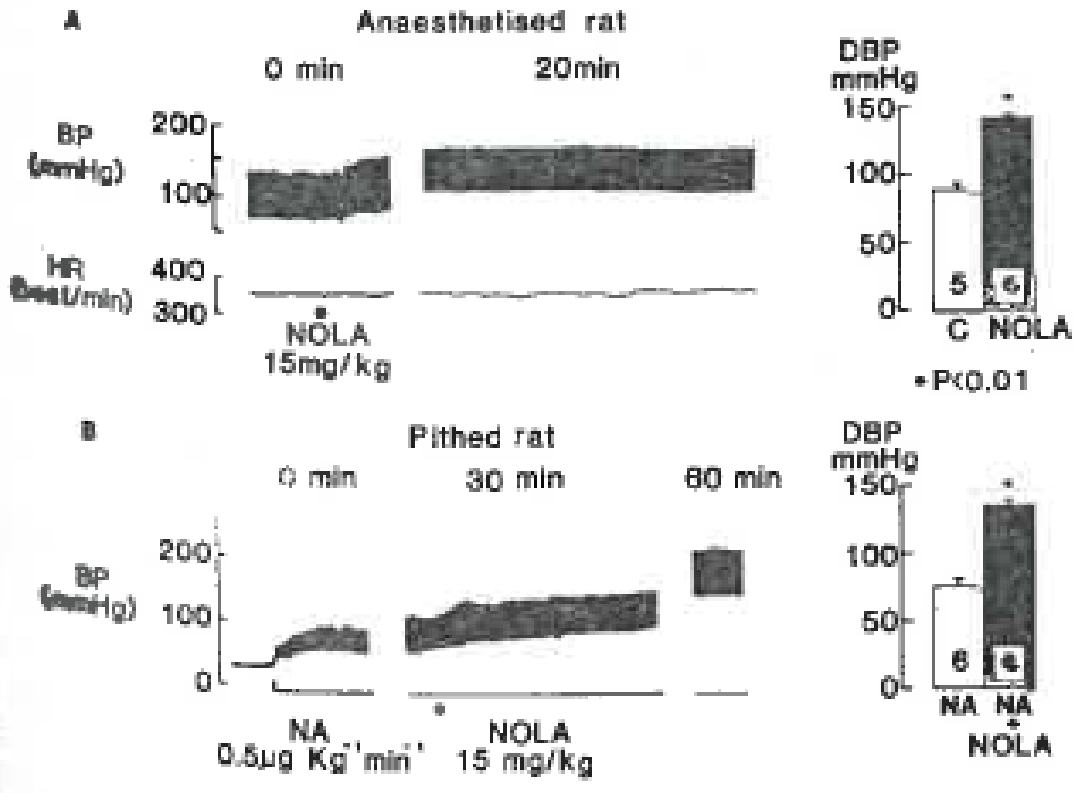
3. Endotoxin shock and inflammation (via iNOS)
***in shock:* -lipopolysacharide induced shock**
-direct reaction to TNF-α from monocytes
-results too much NO ->generalized vasodilatation
in inflammation:
-in reaction to interleukins (e.g. IL-1) and TNF
-contributes to reddening (rubor), and local heat (calor) in inflammation

4. Nitrites- sodium nitroprusside etc.

EFFECTS OF NO



Nitric oxide determines peripheral resistance



Blood pressure

Methylated L-arginine

FIG. 5. Experimental records showing the effect of NOLA (15 mg/kg) on the blood pressure (BP) of urethane-anesthetized rats and pithed rats (columns and symbols as in Fig. 1). **(A)** In anesthetized rats, NOLA caused a significant rise in BP, maximal after 20 min. **(B)** In pithed rats, infusion of norepinephrine (NA, indicated by the horizontal bar) raised the resting BP to a stable level approximating that in anesthetized rats. Subsequent administration of NOLA caused a further increase in BP to a maximum after a further 30 min. The columns represent the stable, mean diastolic BP (DBP) during NA infusion (NA), and 20 min after NOLA (NA + NOLA).

J Cardiovasc Pharmacol, Vol. 17 (Suppl. 3), 1991

Nitric Oxide and the Regulation of Blood Pressure in the Hypertension-Prone and Hypertension-Resistant Sabra Rat

Daryl Rees, Drori Ben-Ishay, Salvador Moncada

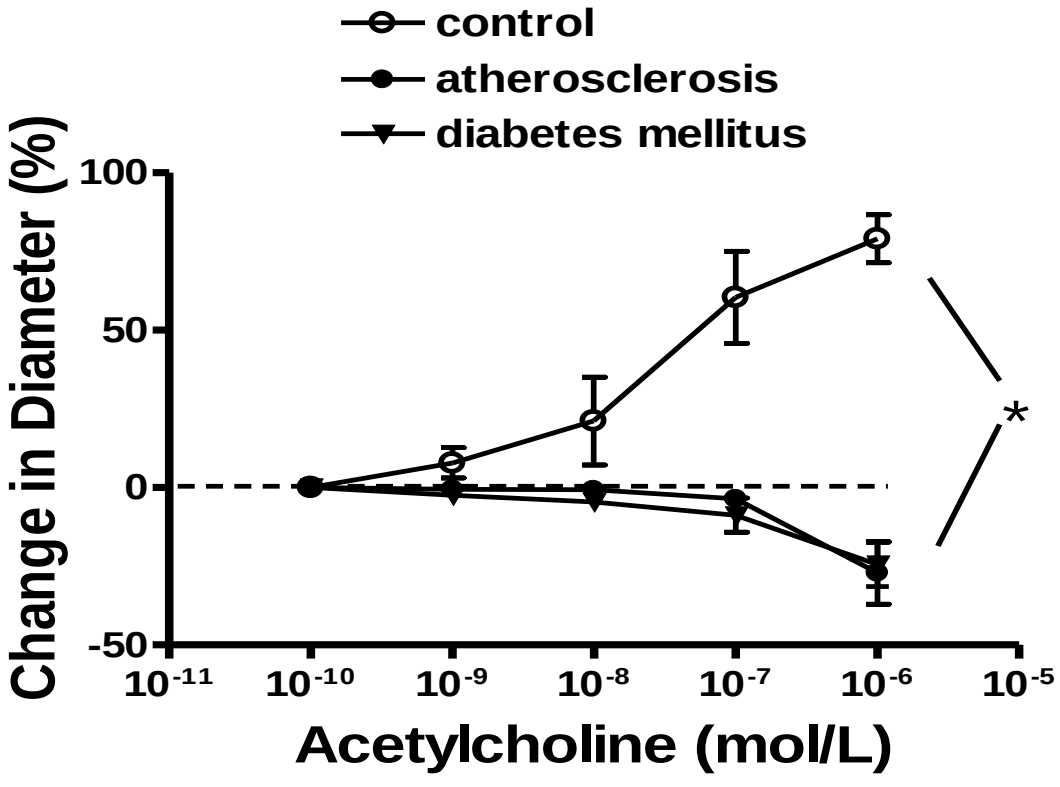
https://doi.org/10.1161/01.HYP.28.3.367

Hypertension. 1996;28:367-371

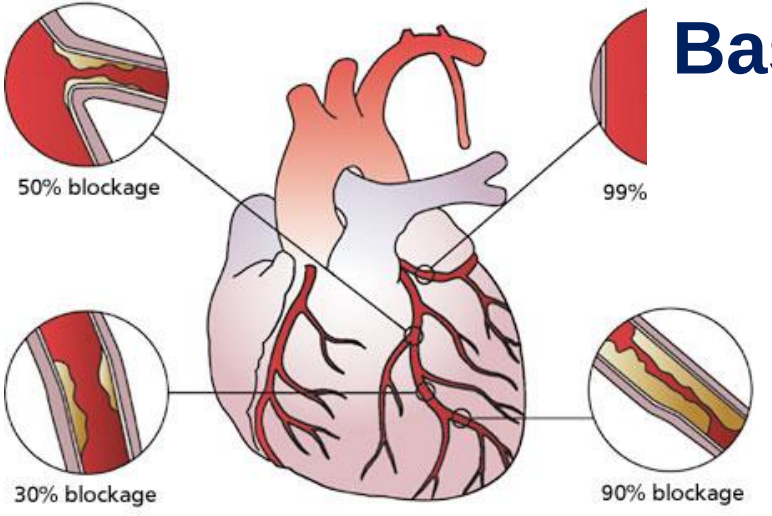
Vascular release of NO is important in the regulation of peripheral vascular resistance

Studies in human vessels:

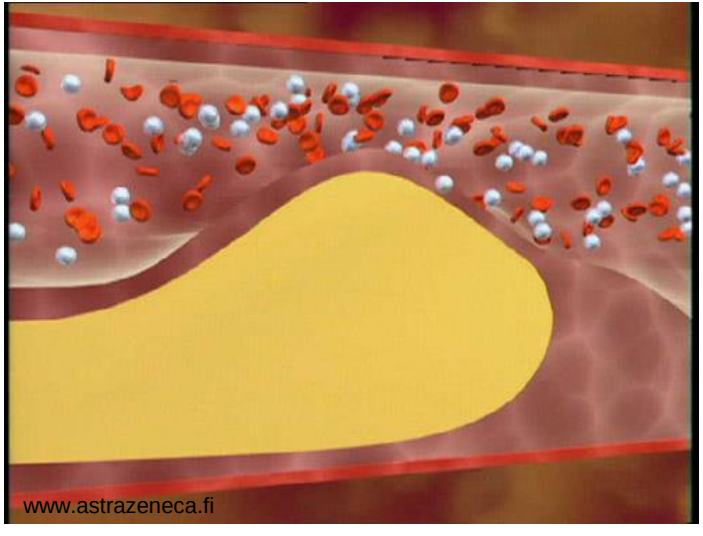
ACh elicited dilations in coronary arterioles of control patients, but induced constrictions in patients with atherosclerosis and diabetes.

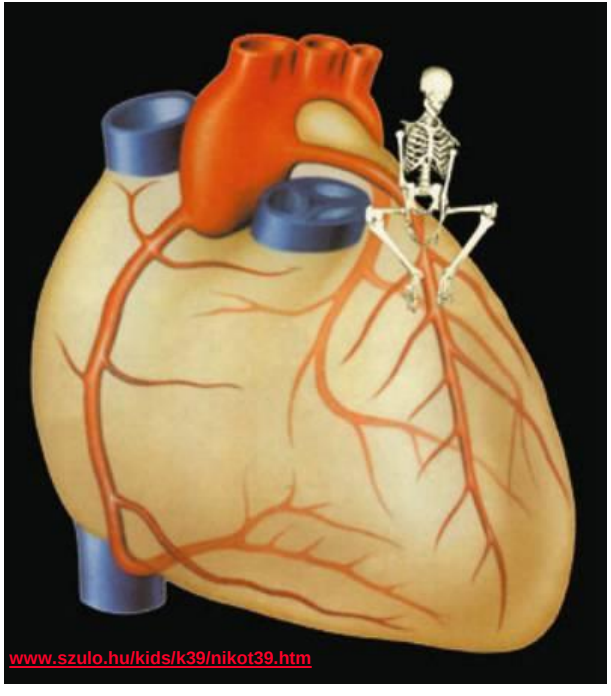


Basic science conclusion: NO prevents vascular diseases!

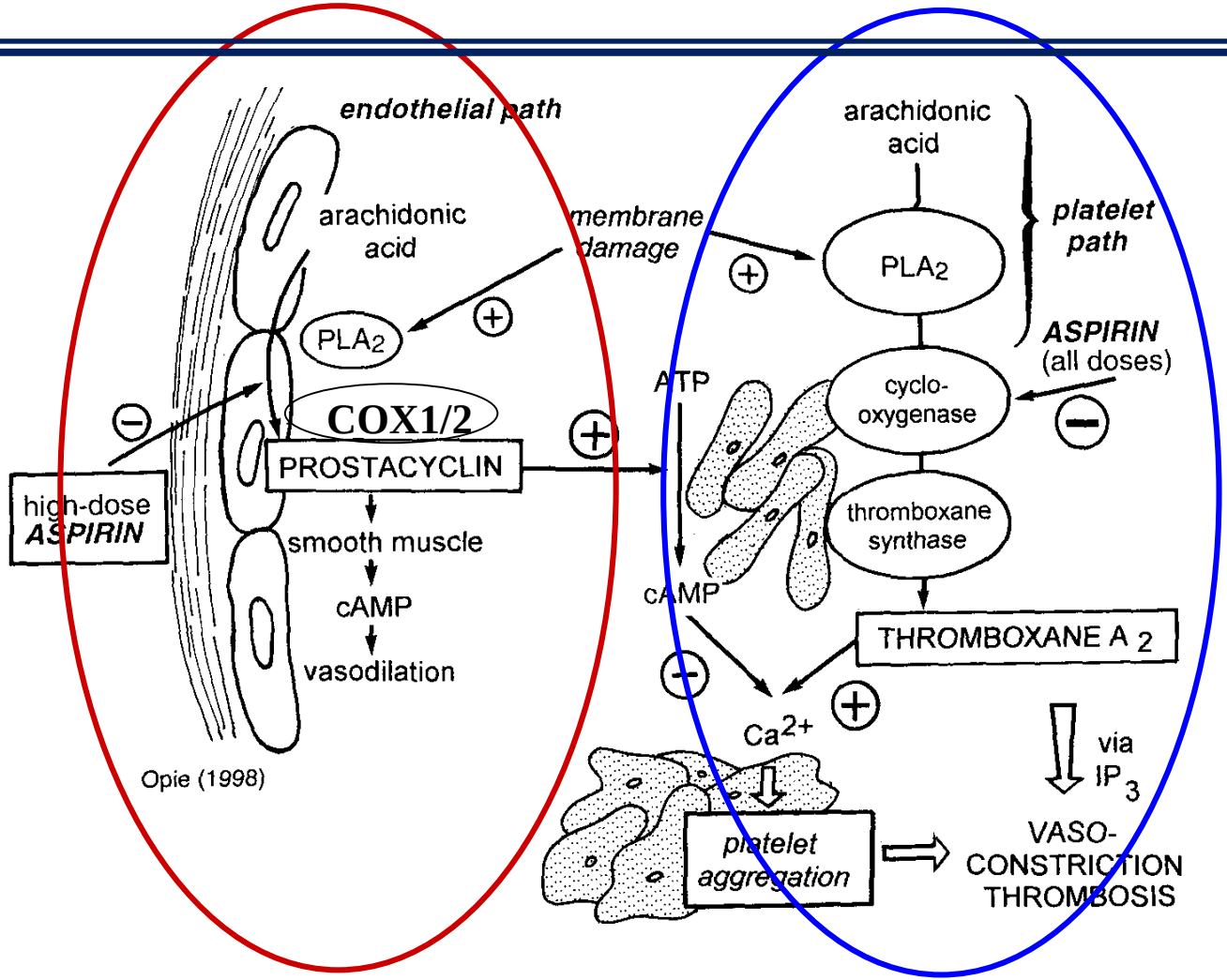


www.surgery.usc.edu

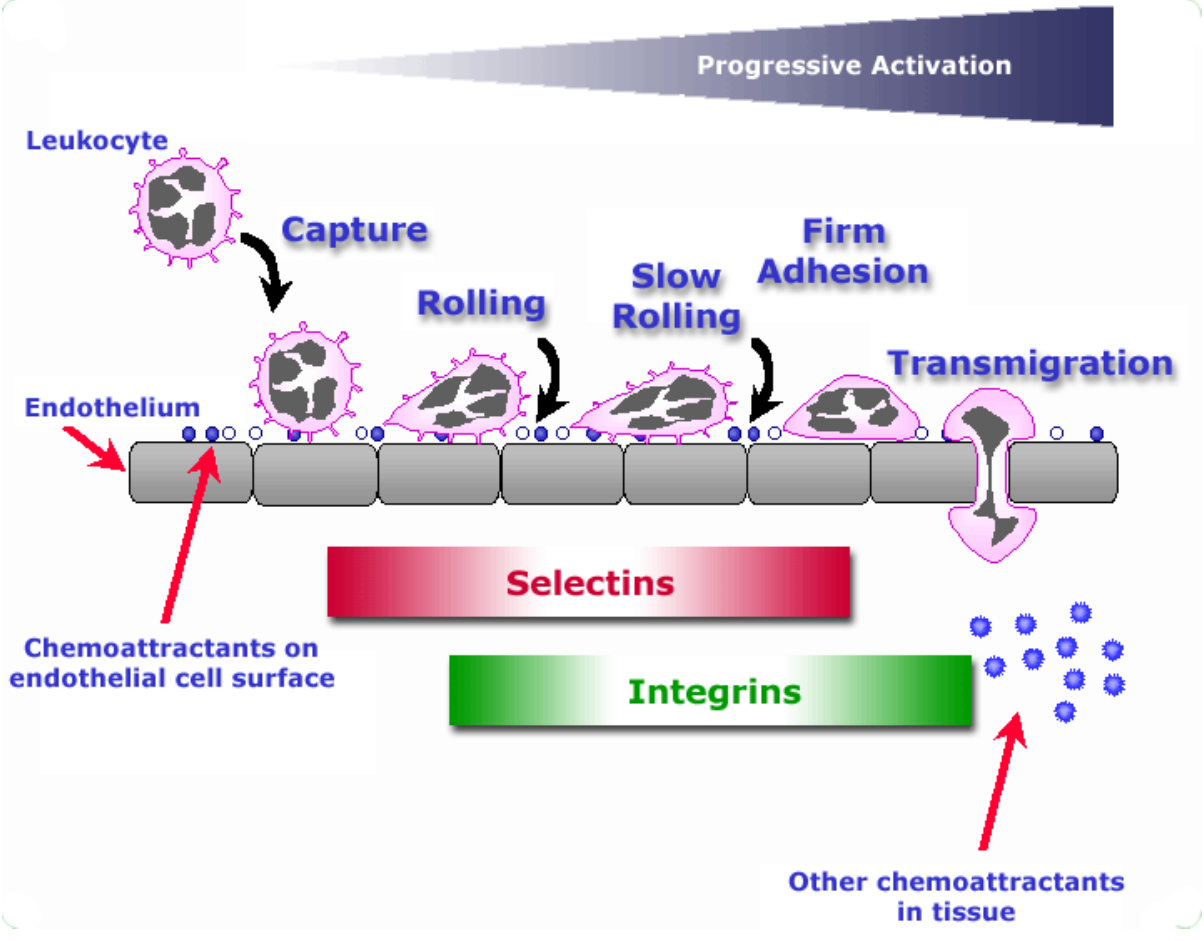




Endothelium-derived prostaglandins



Inflammation: The Leukocyte Adhesion Cascade



FUNCTIONS OF VASCULAR ENDOTHELIUM I

Release of vasodilator agents

Nitric oxide

Prostacyclin (PGI_2)

Bradykinin

EDHF (endothelium-derived hyperpolarizing factor)

Release of vasoconstrictor agents

Thromboxane

Endothelin

Angiotensin I (angiotensin II)

Protection of vascular smooth muscle

vasoconstrictor → to vasodilator stimuli

(acetylcholine and serotonin)

FUNCTIONS OF VASCULAR ENDOTHELIUM II

Antiaggregatory effect

Acts via NO (nitric oxide) and PGI_2 (prostaglandins)

Prevention of coagulation

Thromboresistant surface

Immune function

Supply of antigens to immunocompetent cells

Secretion of interleukin I

Enzymatic activity

Angiotensin-converting enzyme (ACE)

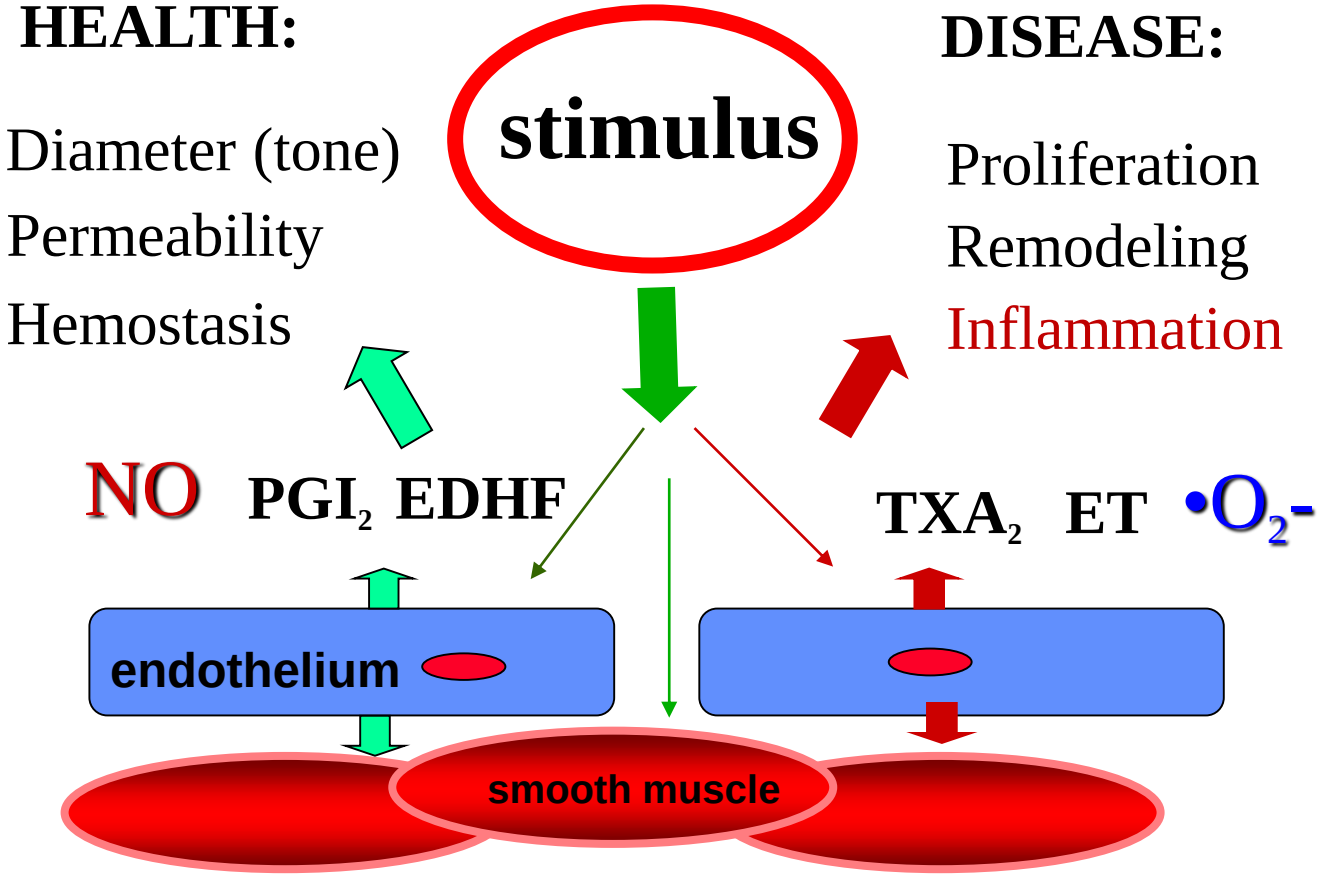
Carbonic anhydrase (large amounts in lung endothelium)

Growth signal to vascular smooth muscle

VEGF (vascular endothelial growth factor)

Heparin-like inhibitors of growth

Role of the endothelium in regulation of microcirculation



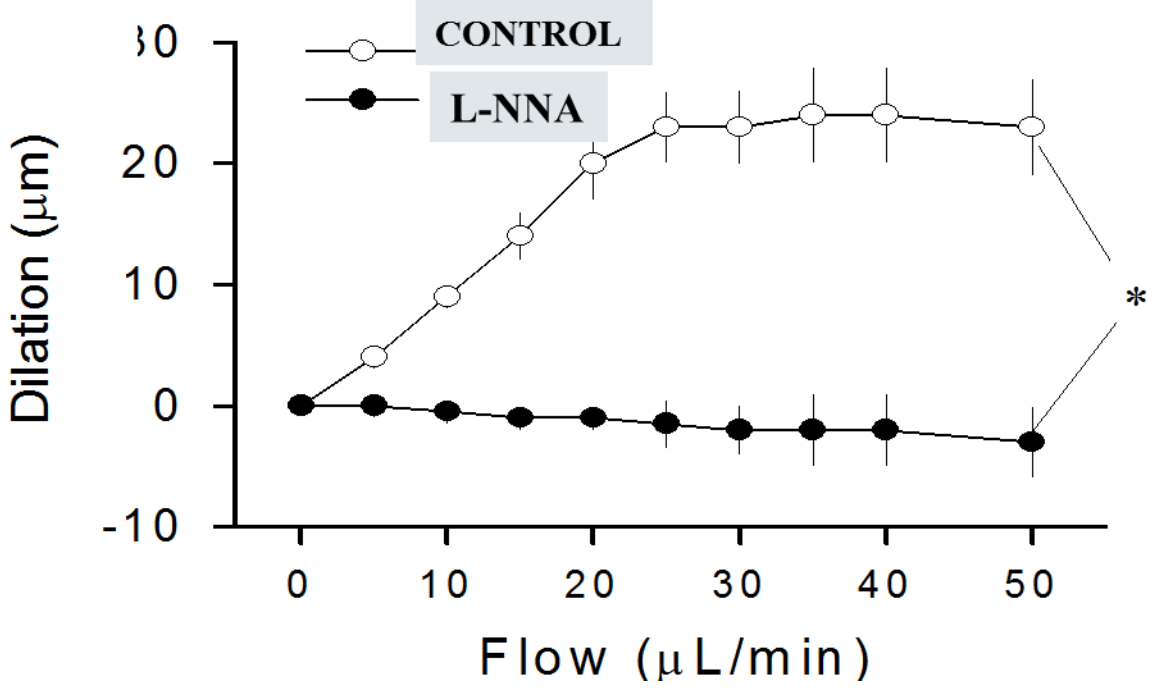
PATHOPHYSIOLOGICAL IMPORTANCE OF ENDOTHELIUM IMPAIREMENTS

- **Hypertension**
- **Diabetes Mellitus**
- **Aging**
- **Atherosclerosis**
- **Hyperhomocysteinemia**
- **Hemodynamic shock**
- **Etc.**

Signal Transduction of NO

- Methylated L-arginines (L-NNA)
- Ca2+
- cGMP
- Phosphodiesterase (PDE) inhibitors

FLOW-INDUCED DILATION OF CORONARY ARTERIOLES IS MEDIATED BY NITRIC OXIDE



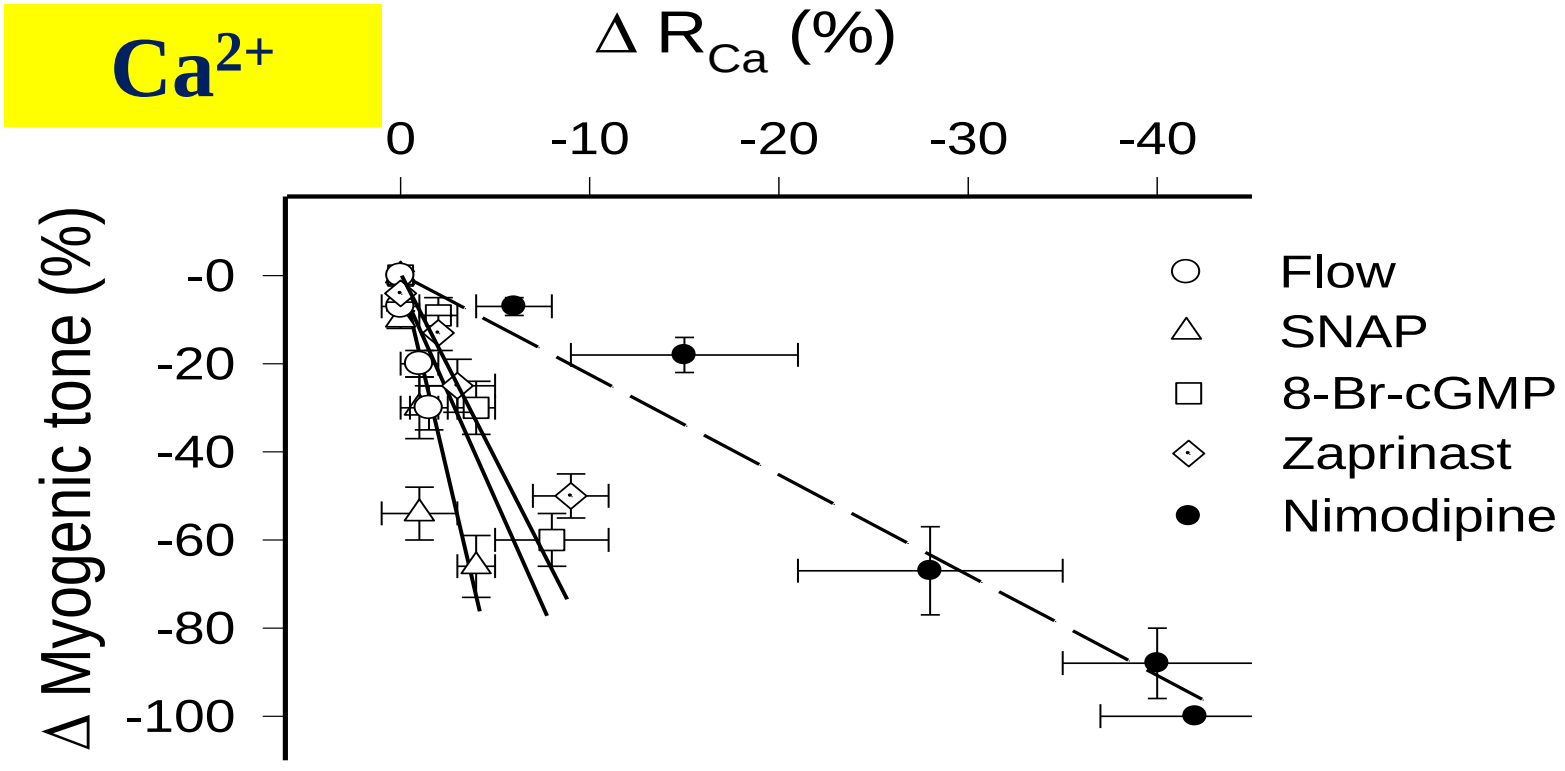
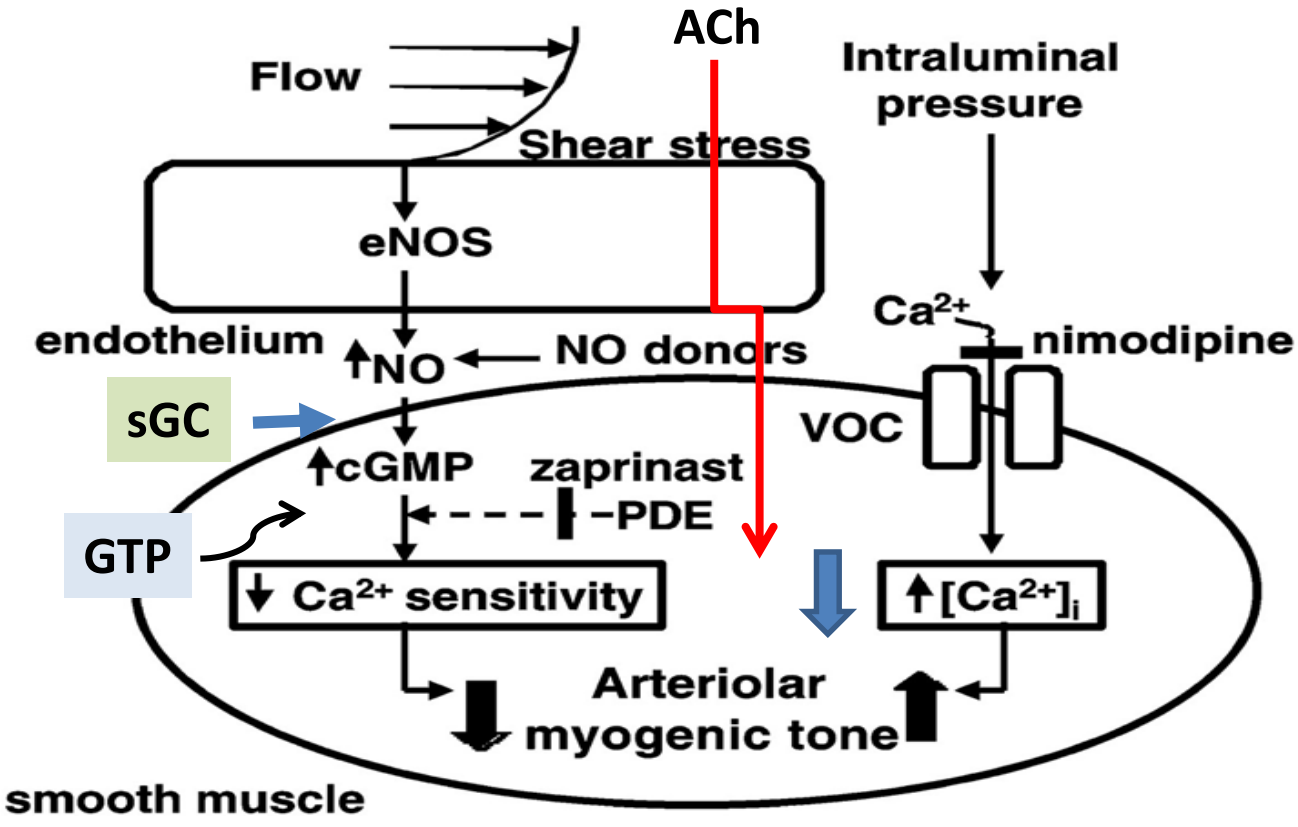


Fig 5. **Relationship between decreases in smooth muscle $[Ca^{2+}]_i$ and arteriolar tone. The steeper regression lines for flow, SNAP, cGMP and zaprinast (as compared to the Ca^{2+} channel antagonist nimodipine) indicate that reduction of the myogenic tone by endogenous and exogenous NO/cGMP depends on a decrease in smooth muscle calcium sensitivity, rather than changes in smooth muscle $[Ca^{2+}]_i$.**



Flow-induced endothelial release of NO modulates arteriolar myogenic tone by decreasing calcium sensitivity of the contractile apparatus in the smooth muscle. (PDE: type V phosphodiesterase, VOC: voltage-operated Ca2+ channel) sGC: soluble guanylate cyclase

Basic science success of NO

NO has been assigned to many physiological function and impairment of NO related to dysfunction

- **Could be inhibited by NOS inhibitors (isoforms?)**
- **Methylated L-arginines (specificity?)**
- **Antioxidants reversed NO impairments**
  (SOD, CAT, allopurinol, apocynin, resveratrol, etc.)
- **Peroxynitrite (proof)**

Clinical success of NO???

Not much…..

Antioxidants, vitamins, resveratrol (red vine), TCM, etc., do not restore NO related dysfunction:

hypertension, atherosclerosis, remodeling, platelet aggregations...

What can be there reasons?

- Difficult to measure NO
- LNNA = NO? NO!!
- High concentrations of inhibitors and agonists (non- specific effects)
- Anesthesia
- Wrong animal model
- Young and healthy animals vs. old and diseased humans
- Adaptive mechanisms (eNOS-KO)
- Multiple mechanisms
- HUMAN FACTORS (you have to publish! whatever….)

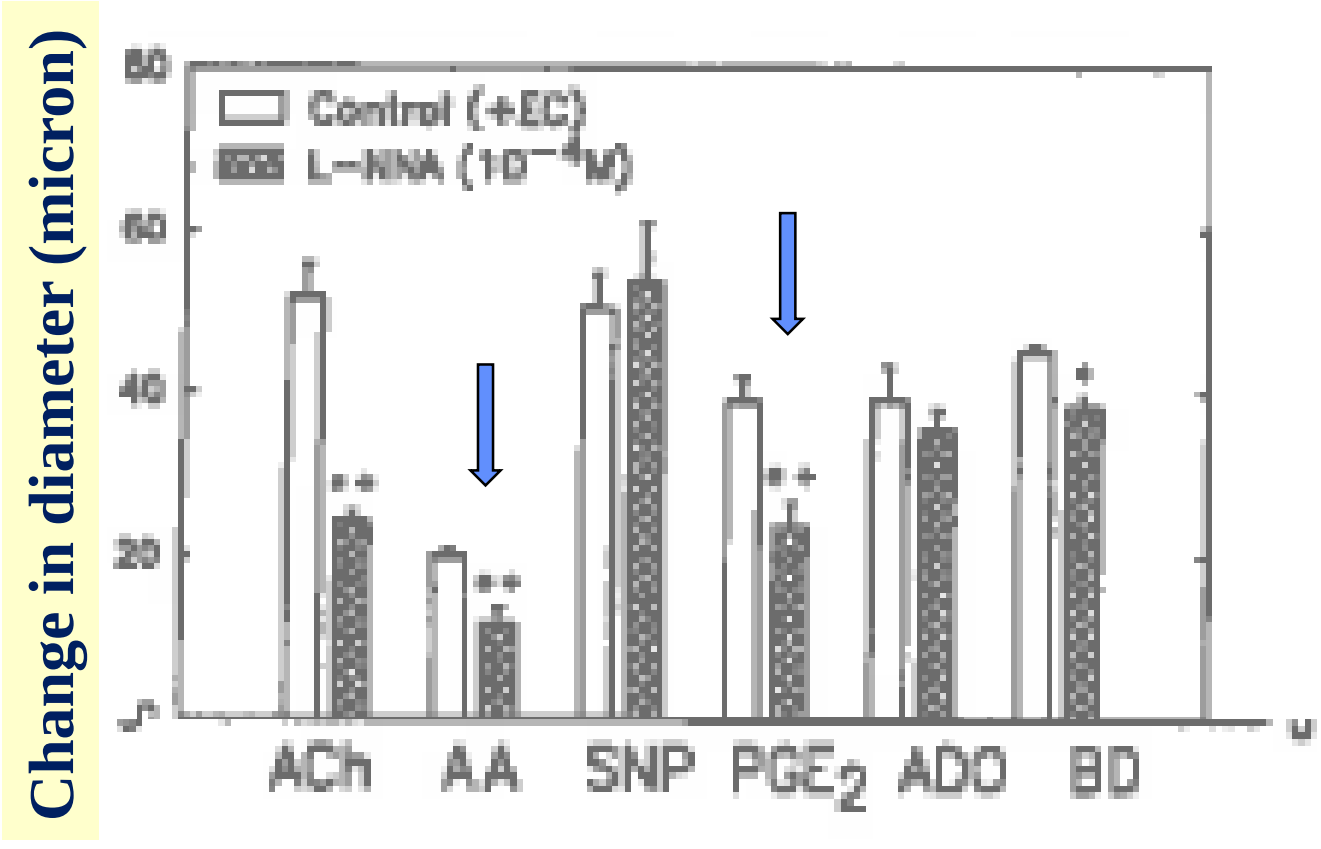
An example…

Am J Physiol. 1993 Apr;264(4 Pt 2):H1194-9.

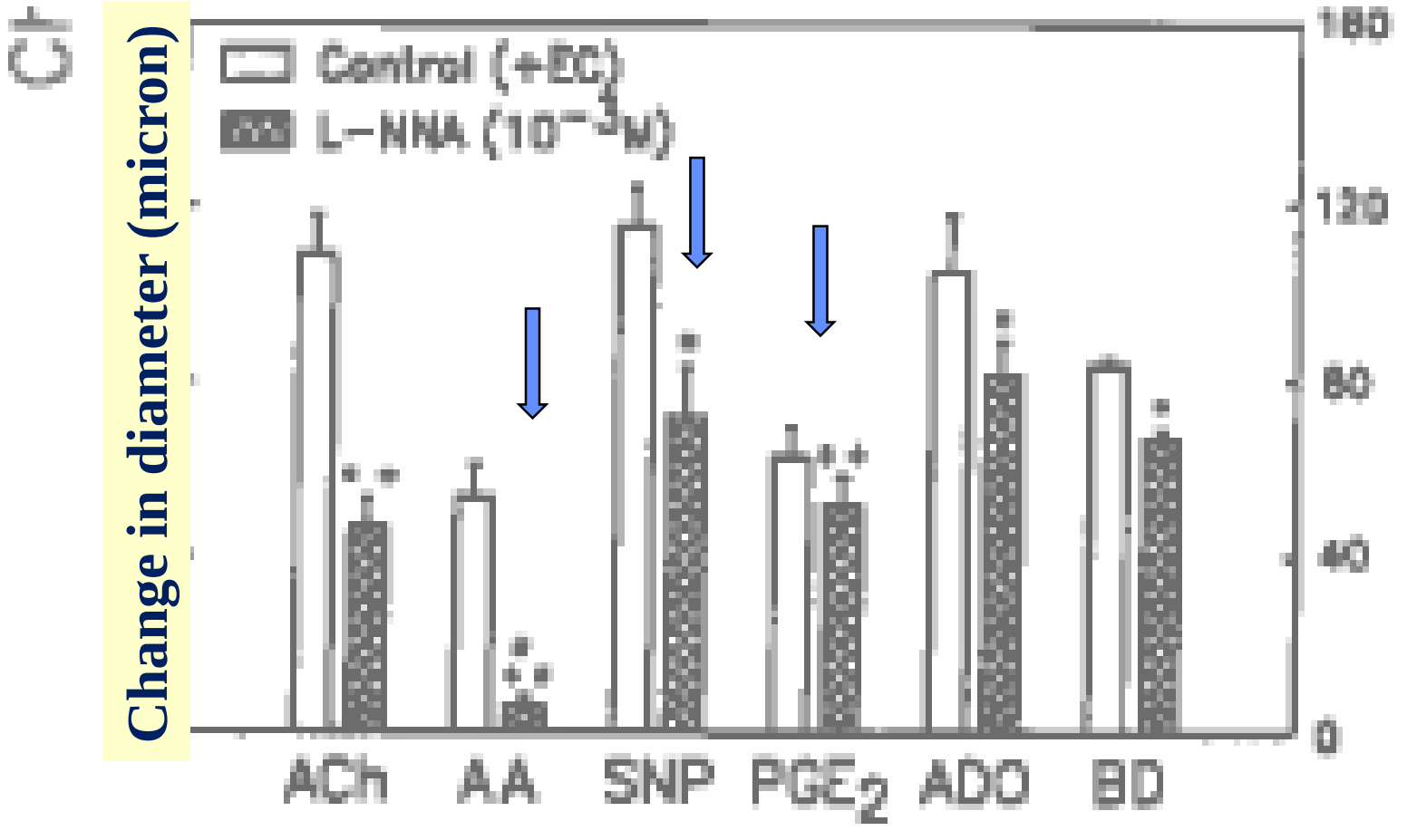
L-arginine analogues blunt prostaglandin-related dilation of arterioles.

Koller A, Sun D, Messina EJ, Kaley G.

L-NNA 10^{-4} M


Change in diameter (micron)
80
60
40
20
Control (+EC)
L-NNA (10^{-4}M)
**
**
**
*
ACh
AA
SNP
PGE_2
ADO
BD

L-NNA 10^{-3} M


Control (+EC)
L-NNA (10^{-3}M)
Change in diameter (micron)
180
120
80
40
0
ACh
AA
SNP
PGE_2
ADO
BD

Am J Physiol. 1993 Apr;264(4 Pt 2):H1194-9.

L-arginine analogues blunt prostaglandin-related dilation of arterioles.

Koller A, Sun D, Messina EJ, Kaley G.

The highest concentration of L-NNA (10^{-3} M), significantly reduced the dilations to AA, SNP, PGE2 and ADO.

Clinical success of NO???

Back to NO donors?:

NO gas, sodium nitroprusside, and sodium trioxodinitrate (Angeli's salt), Nitromint, Nitropenton Nitrodur, Nitroglycerin, etc

Tao Hongjing (456-536)

Bencao jing jizhu (Collected Commentaries to the Canonical Pharmacopoeia), a commentary on the earliest known **Chinese pharmacopoeia**, the Shennong bencao (Canonical Pharmacopoeia of the Divine Husbandman). The original text contained notes on 365 drugs. To these Tao added 365 more, taken from a corpus of writings that he refers to as "Separate Records of Eminent Physicians."

Among other was KNO_3, saltpetre (an NO donor) to treat cardiovascular diseases

Circ Res 2017 and http://www.goldenelixir.com/taoism/tao_hongjing.html

Clinical success of NO?

- **Tolerance** limits the clinical use of organic nitrite and nitrate esters; it is associated with increased angiotensin II–dependent vascular production of **superoxide anion** from NAD(P)H oxidase and endothelial NO synthase (eNOS)
- **Mutagenic effects**

Nitric Oxide Donors and Cardiovascular Agents Modulating the Bioactivity of Nitric Oxide An Overview
Louis J. Ignarro, Claudio Napoli, Joseph Loscalzo
https://doi.org/10.1161/hh0102.102330Circulation Research. 2002;90:21-28
Originally published January 11, 2002

Clinical success of NO?

Nitroaspirins - Ignarro

?

NO donors do not have long term beneficial effects…

Safety and history

The nitric-oxide, for which

Alfred Nobel could have receive the

***Nobel Prize*!**

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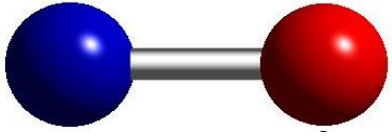
nitric-oxide:

NO



A new/old wonder drug.
R. Furchgott, F. Murad and L. Ignarro
Nobel Prize in 1998

Alfred Nobel's work

- **A. Nobel was exceptionally talented, he had more than 300 patents**

- **His most important invention was the dynamite, which was based on an observation in 1866**

- **Nitroglycerin, a highly explosive liquid was invented by his Italian chemist teacher, Ascanio Sobrero, in 1843, which drew Alfred's attention**

Alfred Nobel's work

- **Usage of nitroglycerin was held up by its danger. It could explode by a minimal mechanical action and caused many accidents.**
- **Sadly, Alfred' experiments resulted in accidents that killed several people, including his younger brother, Emil.**
- **Nobel found that when nitroglycerin was mixed with an absorbent inert substance, like kieselguhr (diatomaceous sand) it became safer and more convenient to handle, but could be ignited by a lighting fuse.**

Barge on Lake Mälaren

The Lab…

A painting of Immanuel Nobel demonstrating his naval or sea mines to the Tsar of Russia

The foundations of the Prize

- **The dynamite was made extensive use of industrial blasts (tunnels, roads, mines, etc), but also for military purpose**

- **So, Nobel's thought to promote the world peace, not lead by his remorse, but philanthropy**

Establishing the prize

Nobel did not get married, and in his will, which was dated 27. November 1895, he left all his possessions to a foundation.

Nobel worded his will himself, without the contribution of lawyers, whom he did not particularly respect.

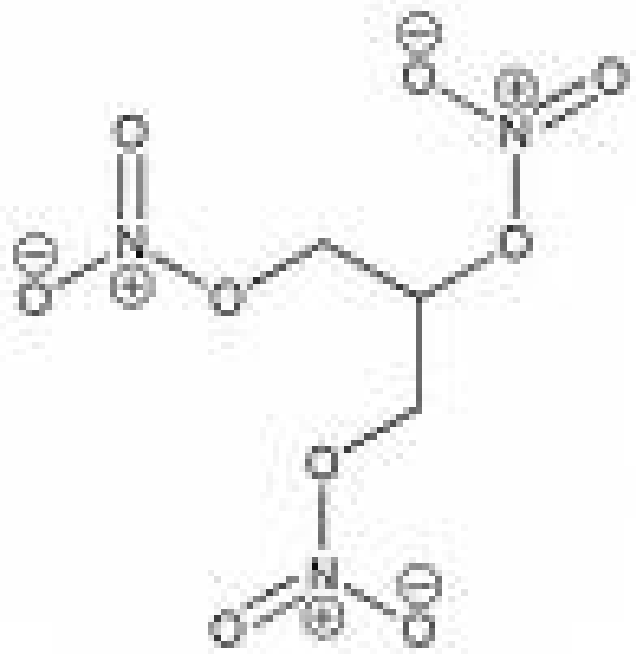
Later the legal inaccuracies gave opportunity to many debates. The charter of the Nobel Foundation was presented in the Royal Palace, in Stockholm on 29. June 1900.

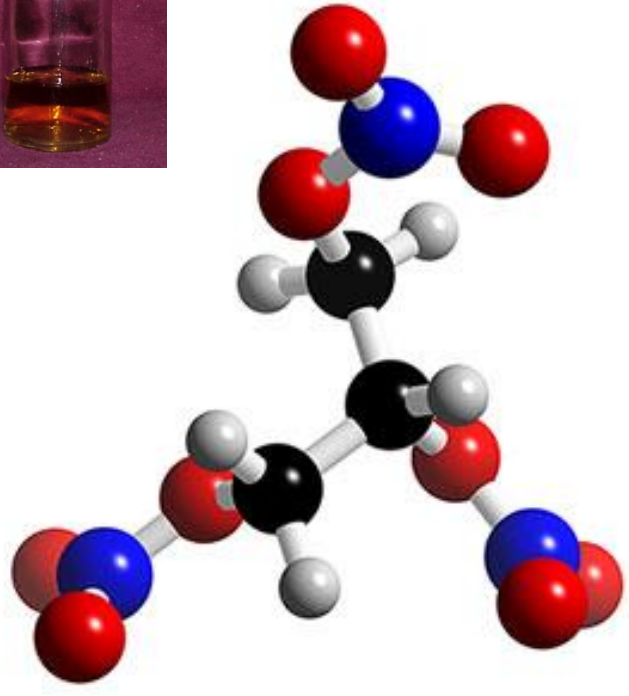
In his factory Nobel observed that workers,
who had heart disease,
felt better on weekdays

???

we had to wait 100 years to explain this

NITROGLYCERINE





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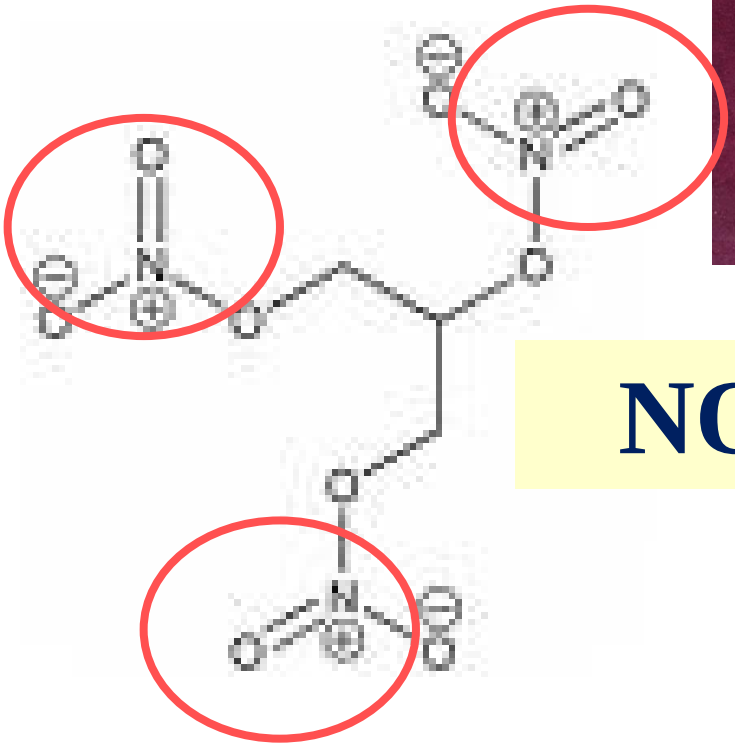
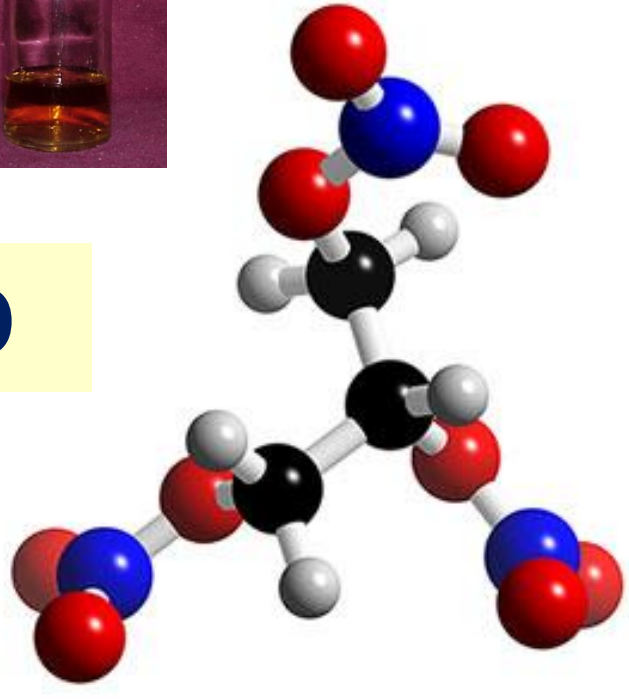


NO

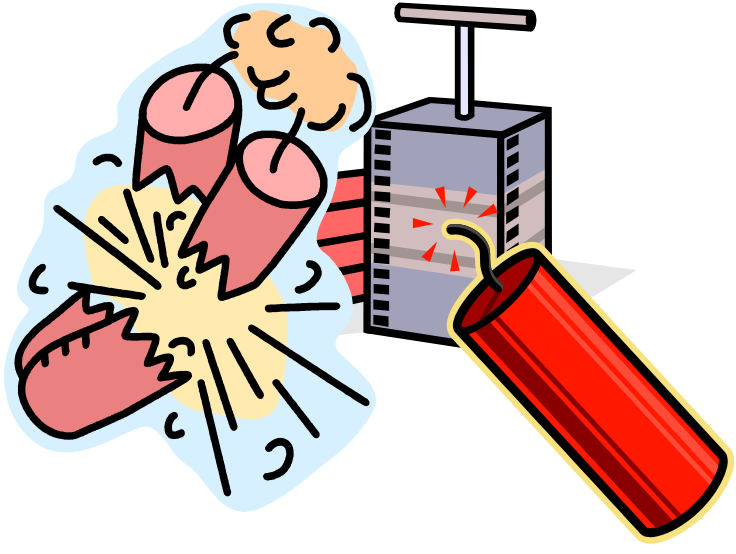


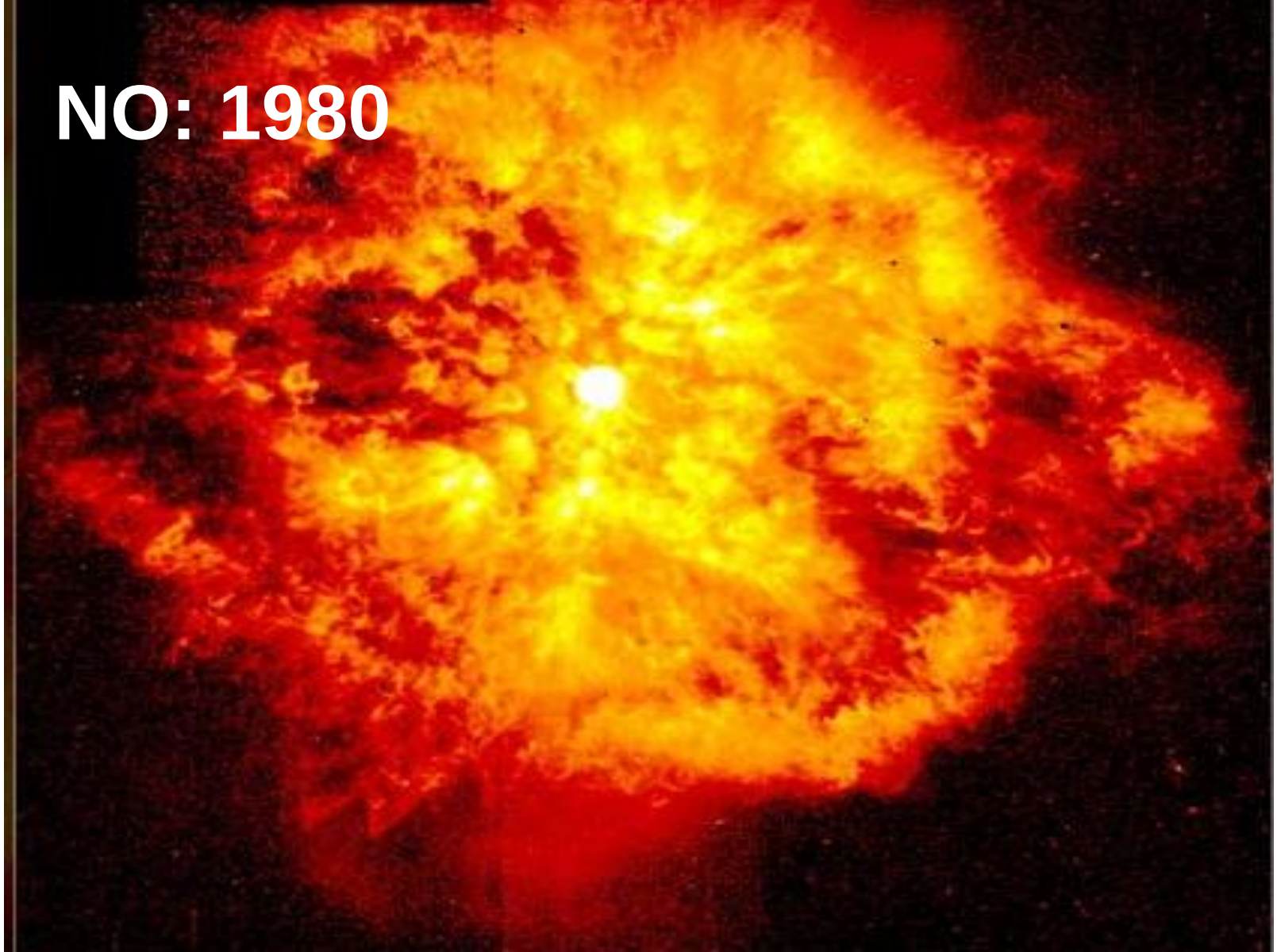
NITROGLICERIN

NO

Heart medicine

Dynamite

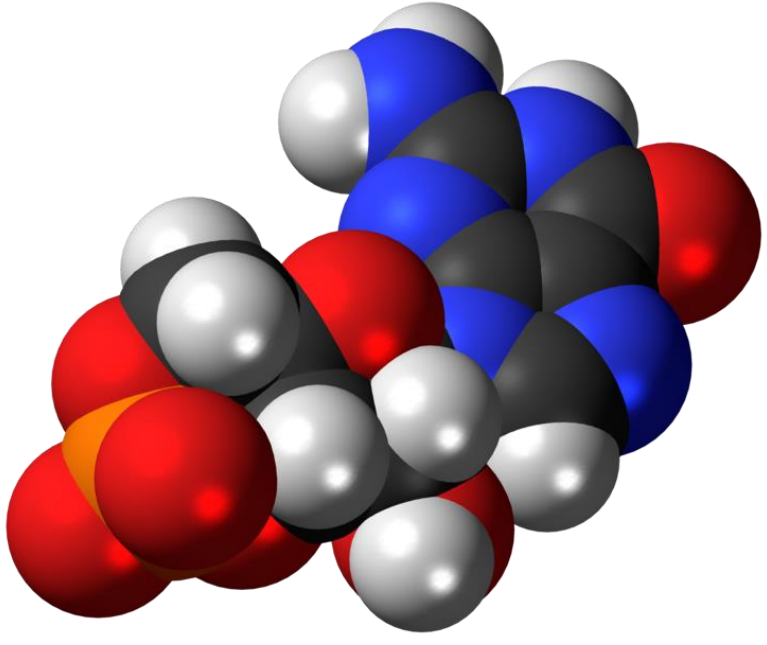


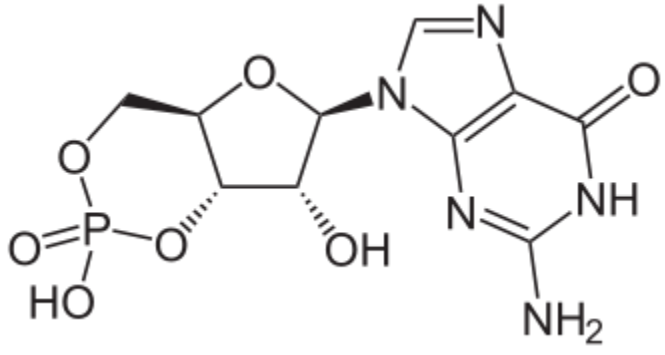

NO: 1980

Clinical success of NO?

IF NOT NO, THEN WHAT?

Cyclic guanosine monophosphate (cGMP)

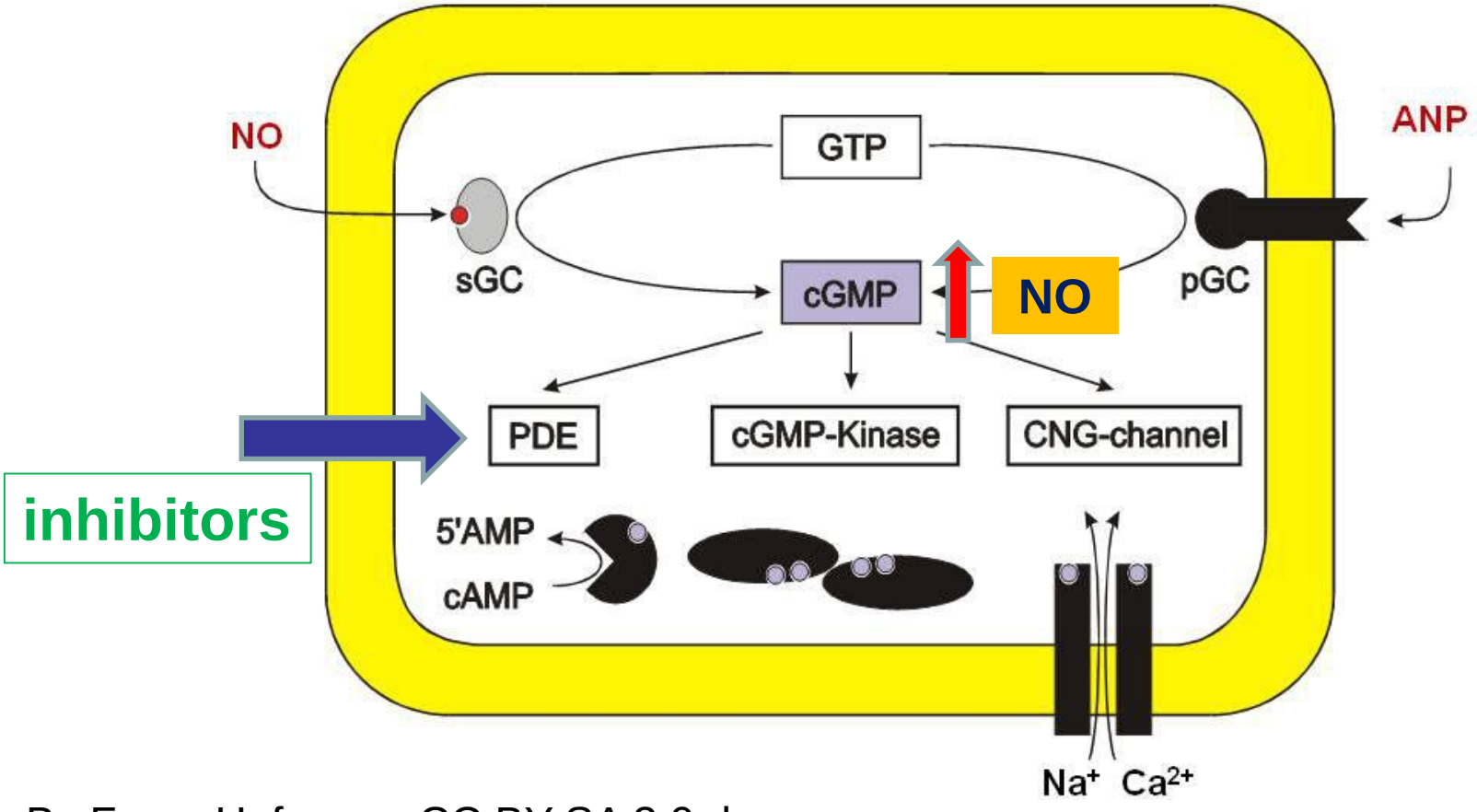




PDE

NON-VASOMOTOR METABOLITES

Increase the physiological effects of cGMP



Can PDE inhibitors reduce systemic blood pressure?

PDE5 inhibitors vs. Hypertension

Unexpected findings with PDE inhibitors

Burnett AL. Nitric oxide regulation of penile erection: biology and therapeutic implications. J Androl 2002; 23: S20–S26.

Francis SH, Corbin JD. Molecular mechanisms and pharmacokinetics of phosphodiesterase-5 antagonists. Curr Urol Rep 2003; 4: 457–465.

- Stief CG, U¨ ckert S, Becker AJ, Harringer W, Truss MC, Forssmann WG, Jonas U. Effects of sildenafil on cAMP and cGMP levels in isolated human cavernous and cardiac tissue. Urology. 2000;55:146–150.

- Burnett AL. The role of nitric oxide in erectile dysfunction: implications for medical therapy. J Clin Hypertens 2006; 8:53–62

Who cares about hypertension?

Adverse effects of sildenafil!

The occurrence of adverse drug reactions (ADRs) with PDE5 inhibitors appears to be dose related. Headache is a very common ADR, occurring in >10% of patients. Other common ADRs include: dizziness, flushing, dyspepsia, nasal congestion or rhinitis.
In 2007, the FDA) announced that a warning about possible sudden hearing loss would be added to drug labels of PDE5 inhibitors.
Since 2007 there is evidence that PDE5 inhibitors can cause an anterior optic neuropathy.

Stockman, A; Sharpe, LT; Tufail, A; Kell, PD; Ripamonti, C; Jeffery, G (June 2007). "The effect of sildenafil citrate (Viagra) on visual sensitivity" (Free full text). J Vis. 7 (8): 4. doi:10.1167/7.8.4. PMID 17685811.

https://en.wikipedia.org/wiki/PDE5_inhibitor

Basic scientists do not give up!

Dundore RL, Clas DM, Wheeler LT, Habeeb PG, Bode DC, Buchholz RA, Silver PJ, and Pagani ED. Zaprinast increases cyclic GMP levels in plasma and in aortic tissue of rats. Eur J Pharmacol 249: 293–297, 1993

Sildenafil Inhibits Hypoxia-Induced Pulmonary Hypertension. L. Zhao, N.A. Mason, N.W. Morrell, B. Kojonazarov, A. Sadykov, A. Maripov, M.M. Mirrakhimov, A. Aldashev and M.R. Wilkinsion. 2001;104:424-428. http://dx.doi.org/10.1161/hc2901.093117).

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- Zaccolo M, Movsesian MA. cAMP and cGMP signaling cross-talk: role of phosphodiesterases and implications for cardiac pathophysiology. Circ Res. 2007;100:1569-78.

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RESEARCH ARTICLE | *Renal Hemodynamics*

Phosphodiesterase 5 inhibition ameliorates angiotensin II-dependent hypertension and renal vascular dysfunction

Manuel Thieme,[1]* Sema H. Sivritas,[1]* Evanthia Mergia,[2] Sebastian A. Potthoff,[1] Guang Yang,[1] Lydia Hering,[1] Katharina Grave,[1] Henning Hoch,[1] Lars C. Rump,[1] and Johannes Stegbauer[1]

[1]*Department of Nephrology, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; and* [2]*Department of Pharmacology and Toxicology, Ruhr-University Bochum, Bochum, Germany*

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Journal of Andrology, Vol. 22, No. 4, July/August 2001

Intracavernosal Sildenafil Facilitates Penile Erection Independent of the Nitric Oxide Pathway

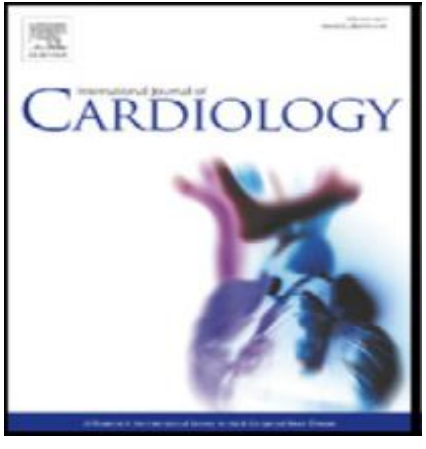
IAIN W. MCAULEY,* NOEL N. KIM,* KWEONSIK MIN,* IRWIN GOLDSTEIN,* AND ABDULMAGED M. TRAISH*†

*From the Departments of *Urology and †Biochemistry, Boston University School of Medicine, Boston, Massachusetts.*

A sudden cardiac death induced by sildenafil and sexual activity in an HIV patient with drug interaction, cardiac early repolarization, and arrhythmogenic right ventricular cardiomyopathy

Masamune Kobayashi, Yoshifumi Takata , Yoshinari Goseki, Hajime Mizukami , Shu-ichi Hara , Fumi Kuriiwa , Katshuyuki Fukutake, Ken-ichi Yoshida,

International Journal of Cardiology 179 (**2015**) 421–423.



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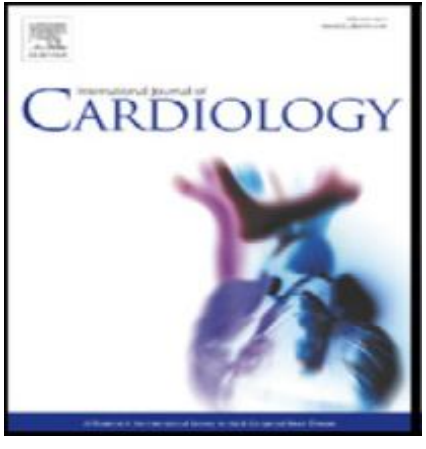
International Journal of Cardiology 179 (**2015**) 421–423.

SAFETY IS IMPORTANT!



What else can be done to „save” NO signaling for clinical use?

Nat Rev Drug Discov. 2006 Sep; 5(9): 755–768.

NO-independent stimulators and activators of soluble guanylate cyclase: discovery and therapeutic potential

Oleg V. Evgenov,[*‡] Pál Pacher,[§] Peter M. Schmidt,[‖¶] György Haskó,[#] Harald H. H. W. Schmidt,[‖¶] and Johannes-Peter Stasch[**]

doi: 10.1038/nrd2038
PMCID: PMC2225477
NIHMSID: NIHMS38124

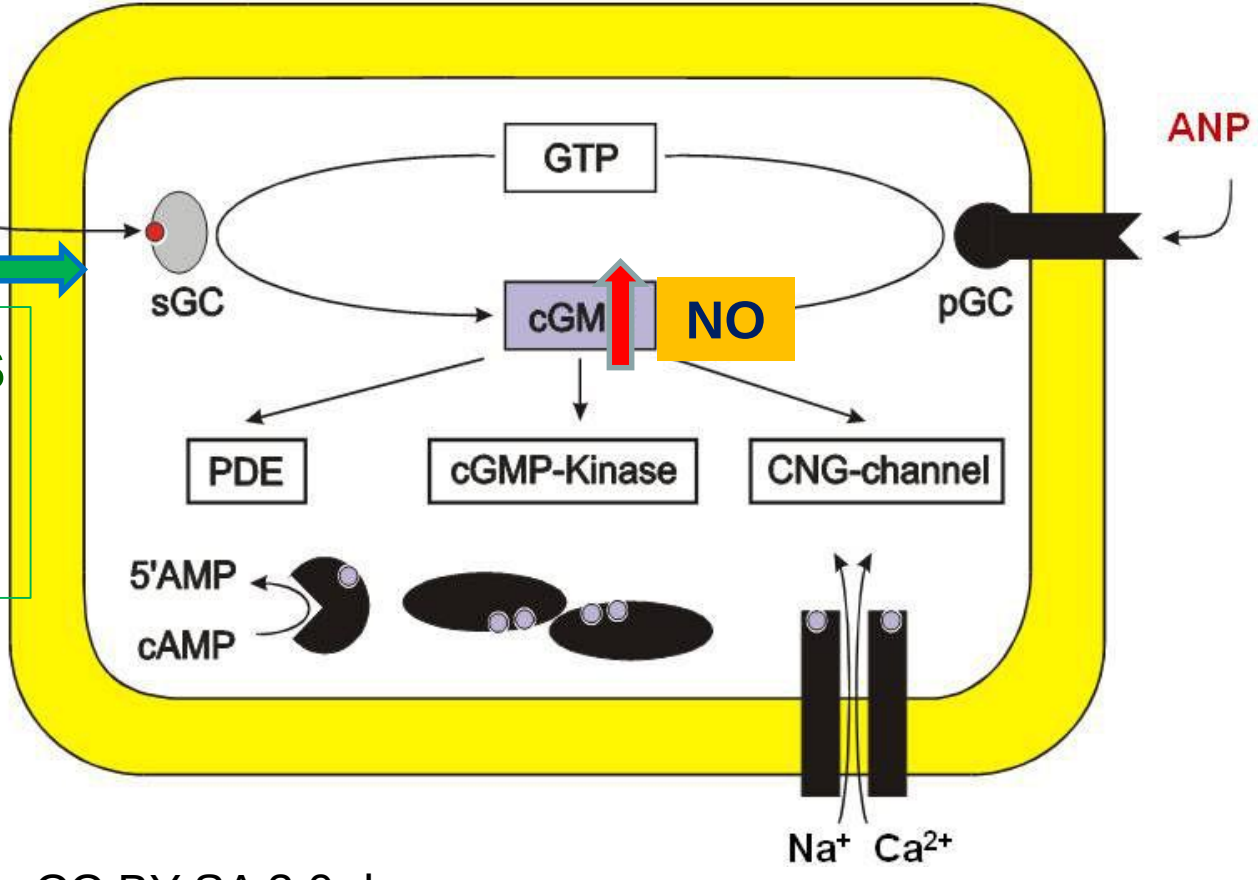
Two novel drug classes seem to be able to overcome these obstacles:

- **sGC stimulators stimulate sGC directly and enhance sensitivity of the reduced enzyme to low levels of bioavailable NO**
- **sGC activators activate the NO-unresponsive, haem-oxidized or haem-free enzyme**

Nat Rev Drug Discov. 2006 Sep; 5(9): 755–768.

Increase the physiological effects of cGMP

stimulators and activators



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Will see….

doi: 10.1038/nrd2038
PMCID: PMC2225477
NIHMSID: NIHMS38124

Prostaglandins and Safety

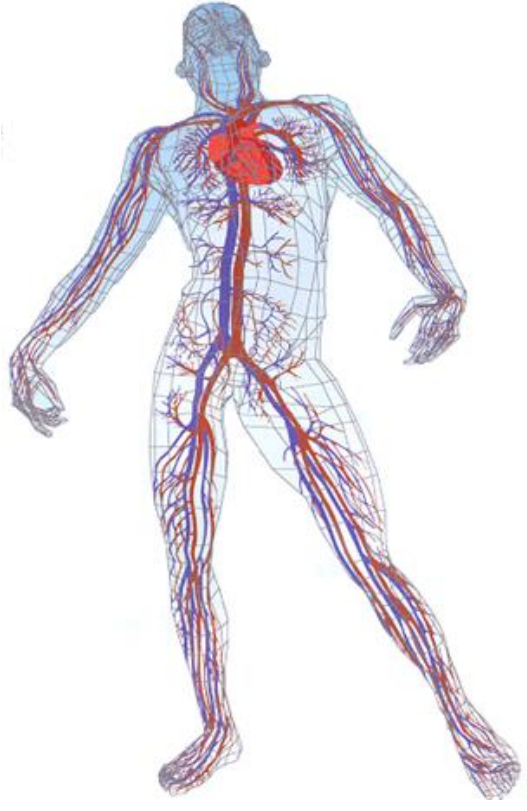
Remember VIOXX…

- **Aspirin / Cox / Prostaglandins: Nobel Price 1982**
- **JR Vane, S Bergström and B Samuelsson**
- **Cox-1: „good" needed for normal function**
- **Cox-2: „bad" expressed (only) in inflammation**
- **Selective Cox-2 inhibitors: caused unexpected cardiovascular morbidity and mortality.**
- **Rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the market in 2004/2005, because they excessively increased the risk of heart attacks and strokes with long term use.**

- **Systemic use of these, or any drugs or intervention can effect multiple organs and cells, thus their combined effects can only be assed by long-term studies in patients with different age, gender and comorbidity.**

- **Thus the most important is the safety of any medical intervention.**

„Primum nil nocere”



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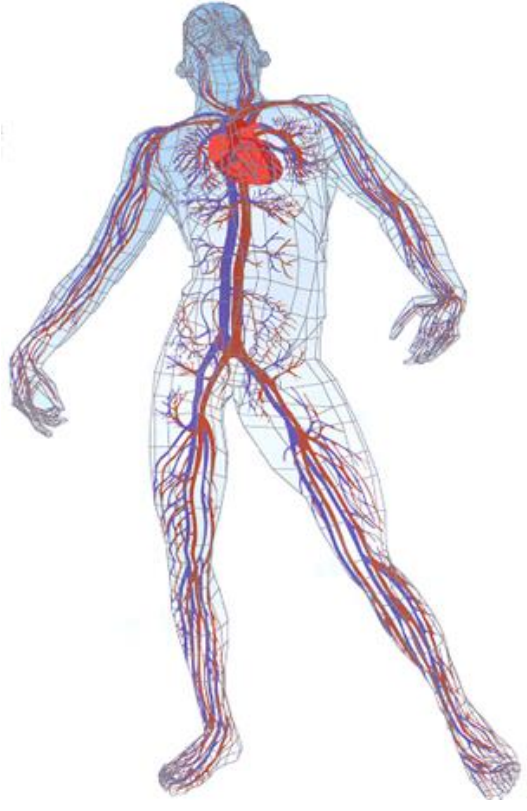

„Primum nil nocere”

Thank you for your attention!