

Endothelial dysfunction **in hypertension:** from bench to bedside

Stefano Taddei

*Department of Clinical and Experimental Medicine
University of Pisa, Italy*





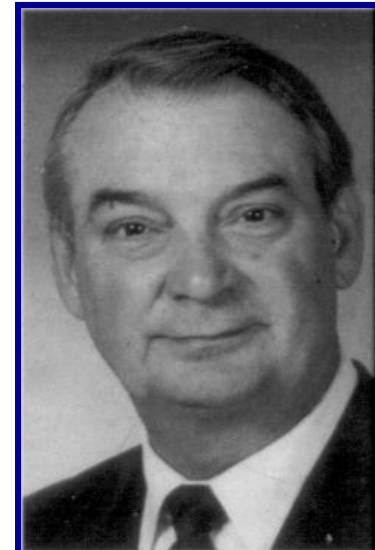
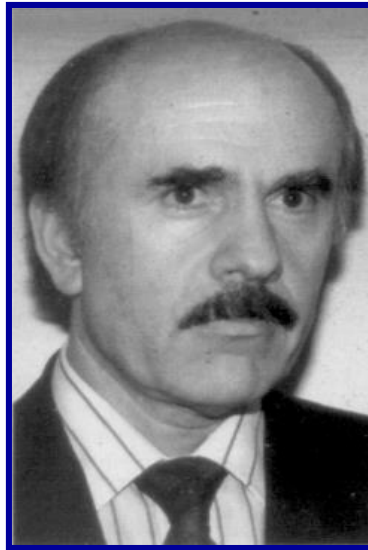
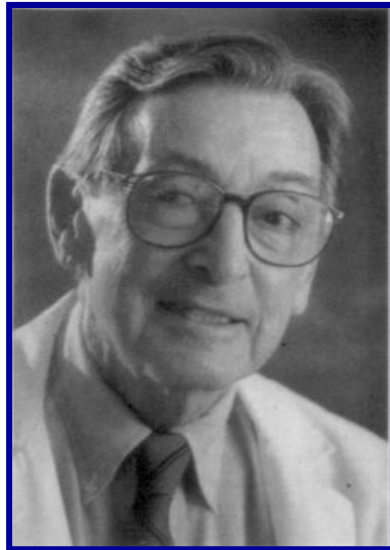
Press Release: The 1998 Nobel Prize in Physiology or Medicine
NOBELFÖRSAMLINGEN KAROLINSKA INSTITUTET
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

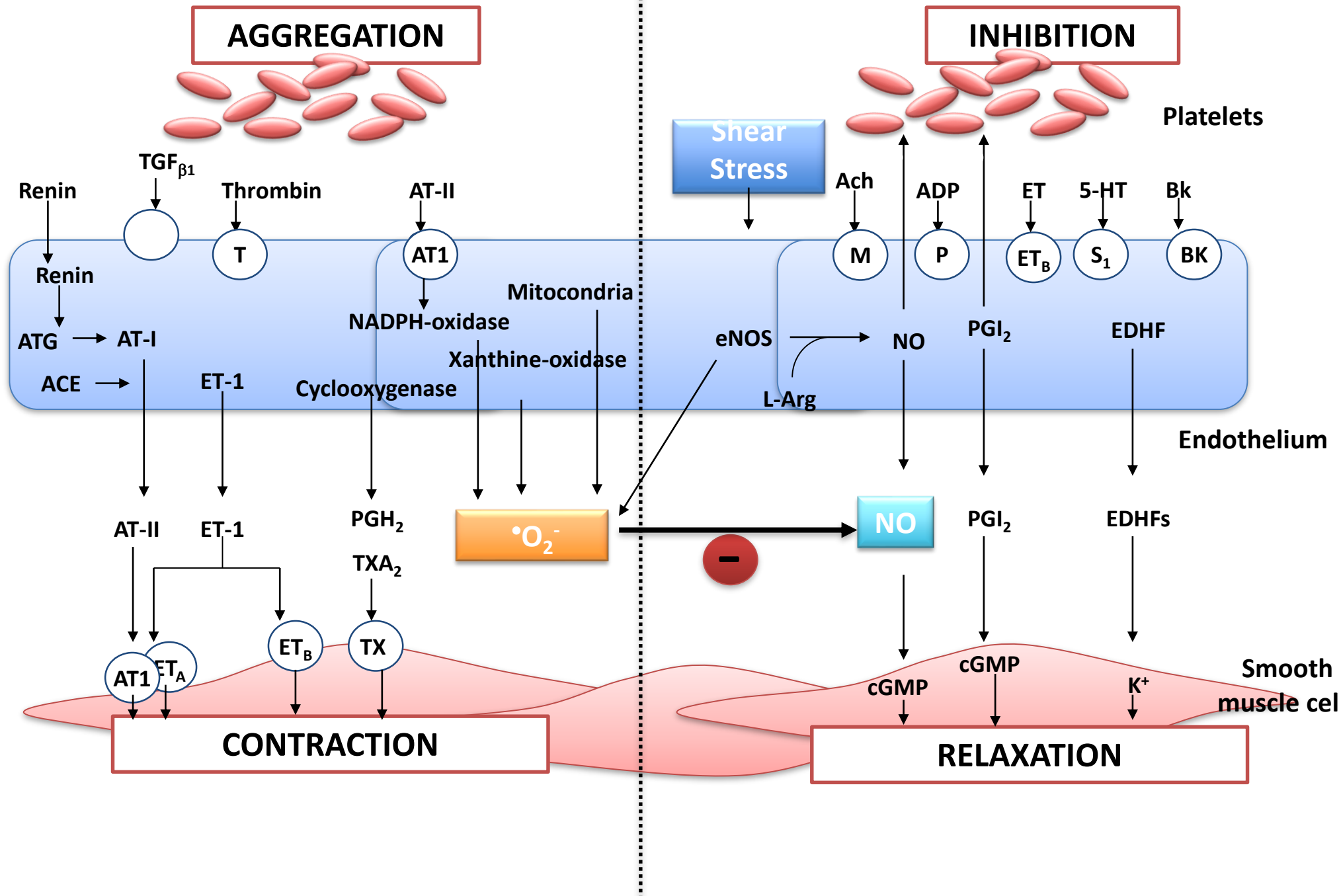
October 12, 1998

[The Nobel Assembly at Karolinska Institutet](#) has today decided to award
the Nobel Prize in Physiology or Medicine for 1998 jointly to

Robert F. Furchgott, Louis J. Ignarro and Ferid Murad

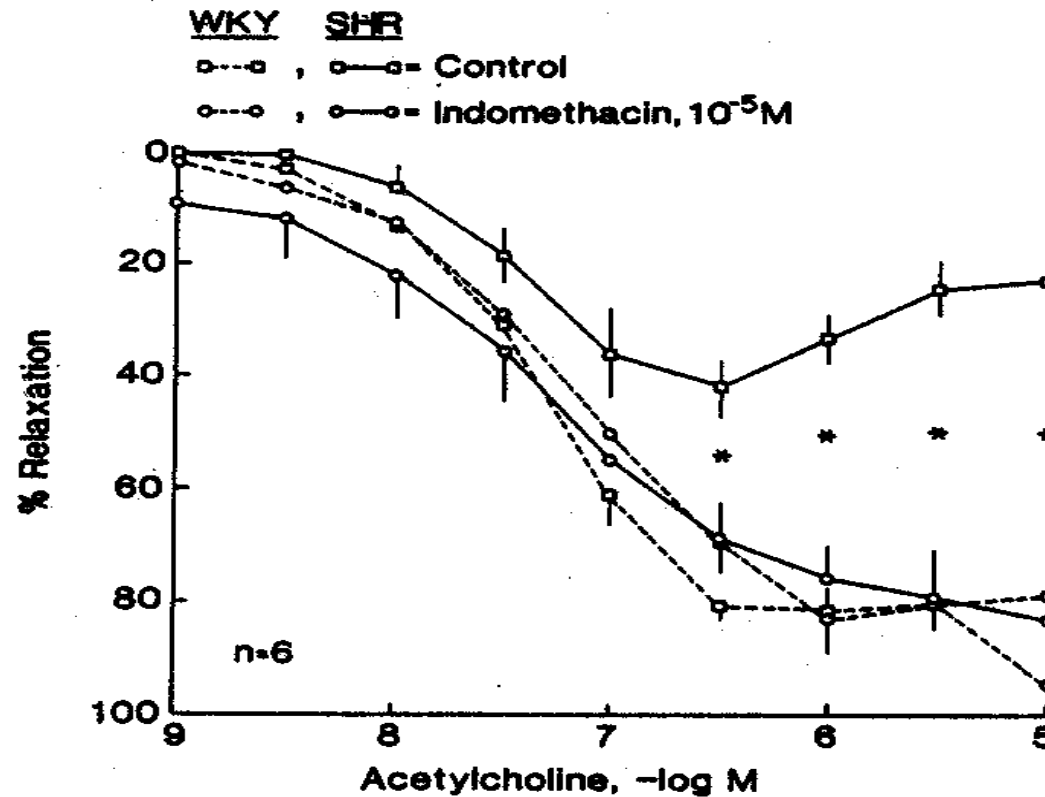
for their discoveries concerning "nitric oxide as a signalling molecule in the cardiovascular system"



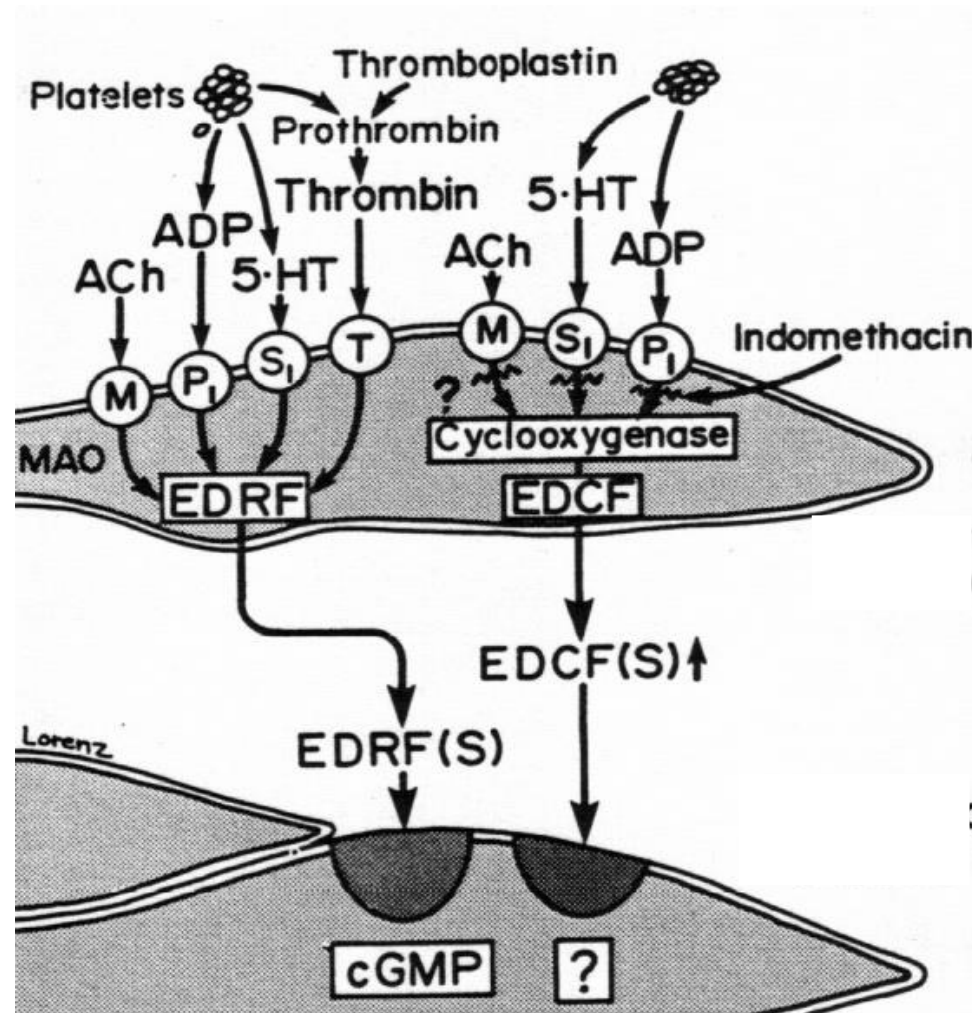


Endothelial dysfunction in human hypertension

Endothelium-dependent relaxation in WKY and SHR

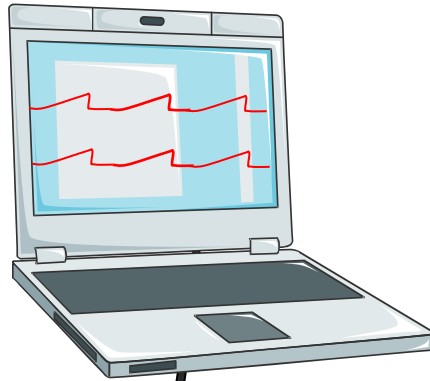


Genetic Hypertension



Forearm blood flow (plethysmography)

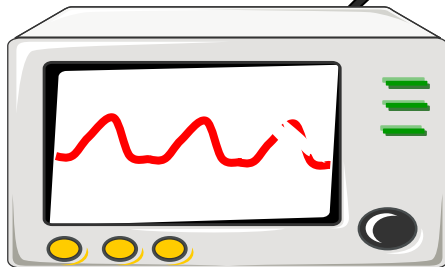
Data acquisition and analysis



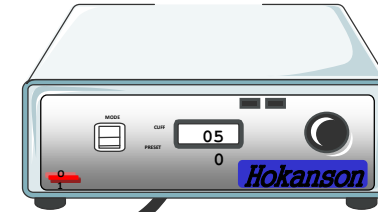
Plethysmograph



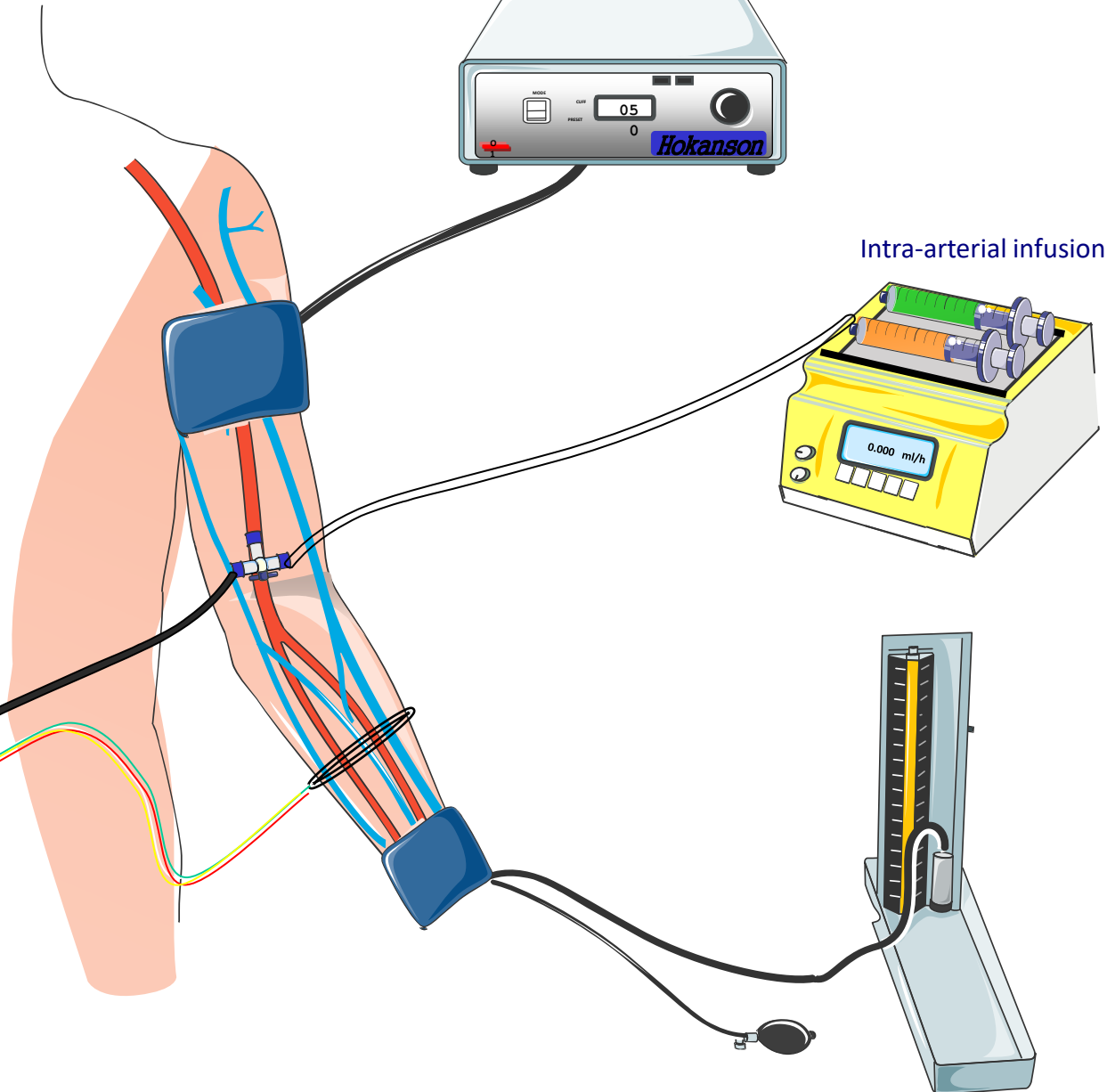
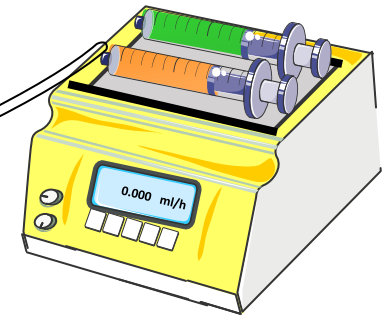
BP and HR monitoring



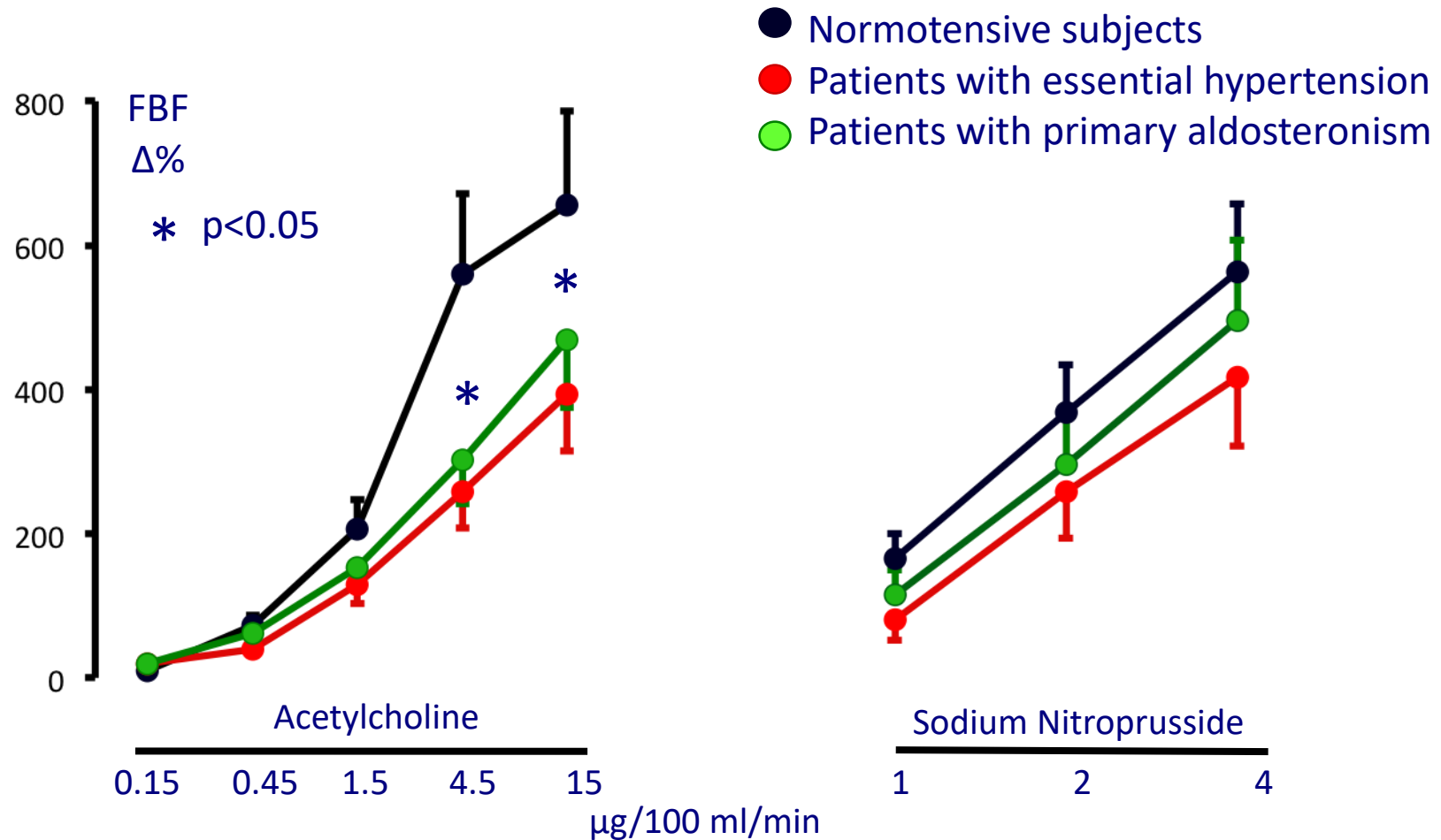
Cuff inflator



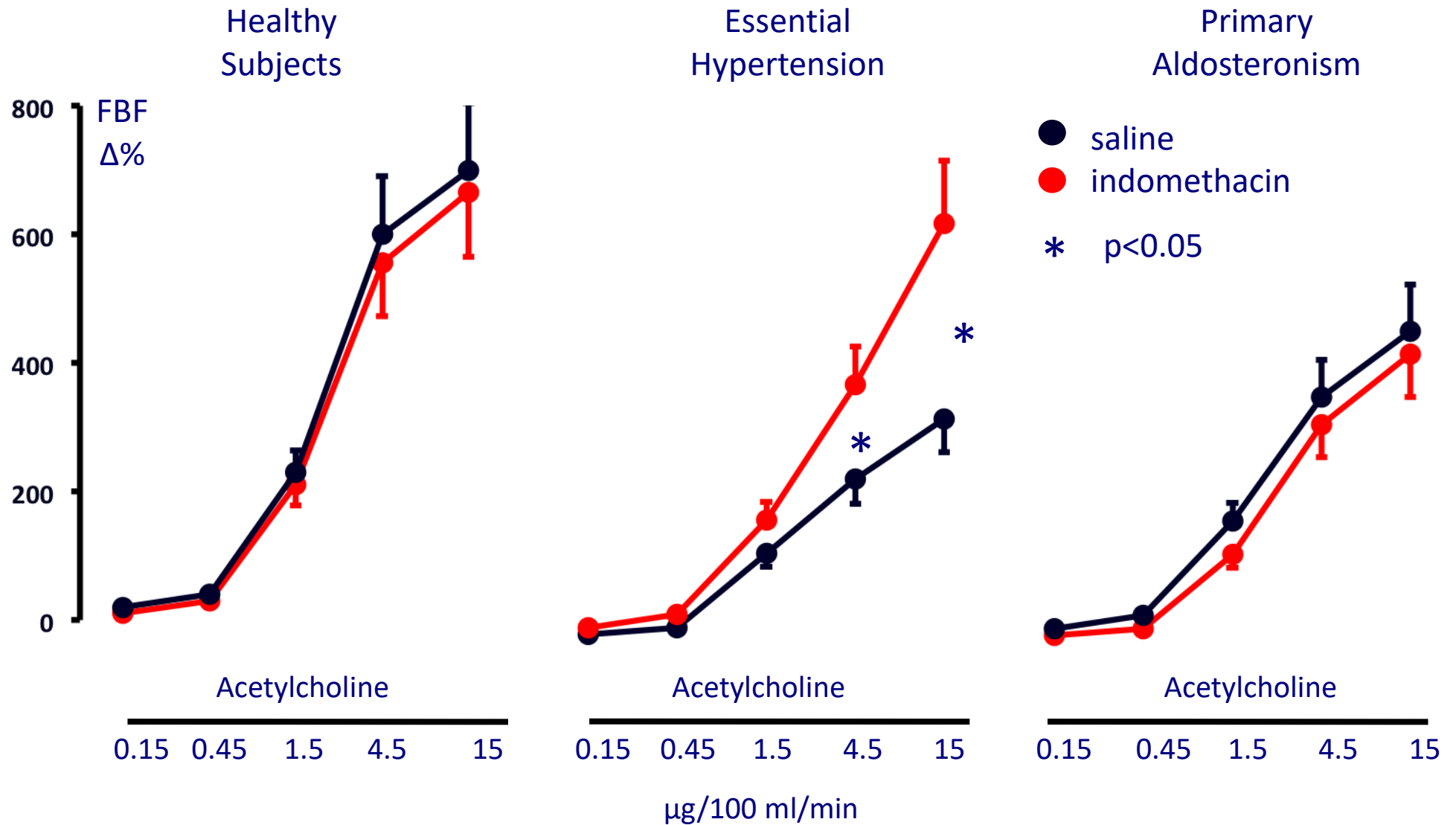
Intra-arterial infusion



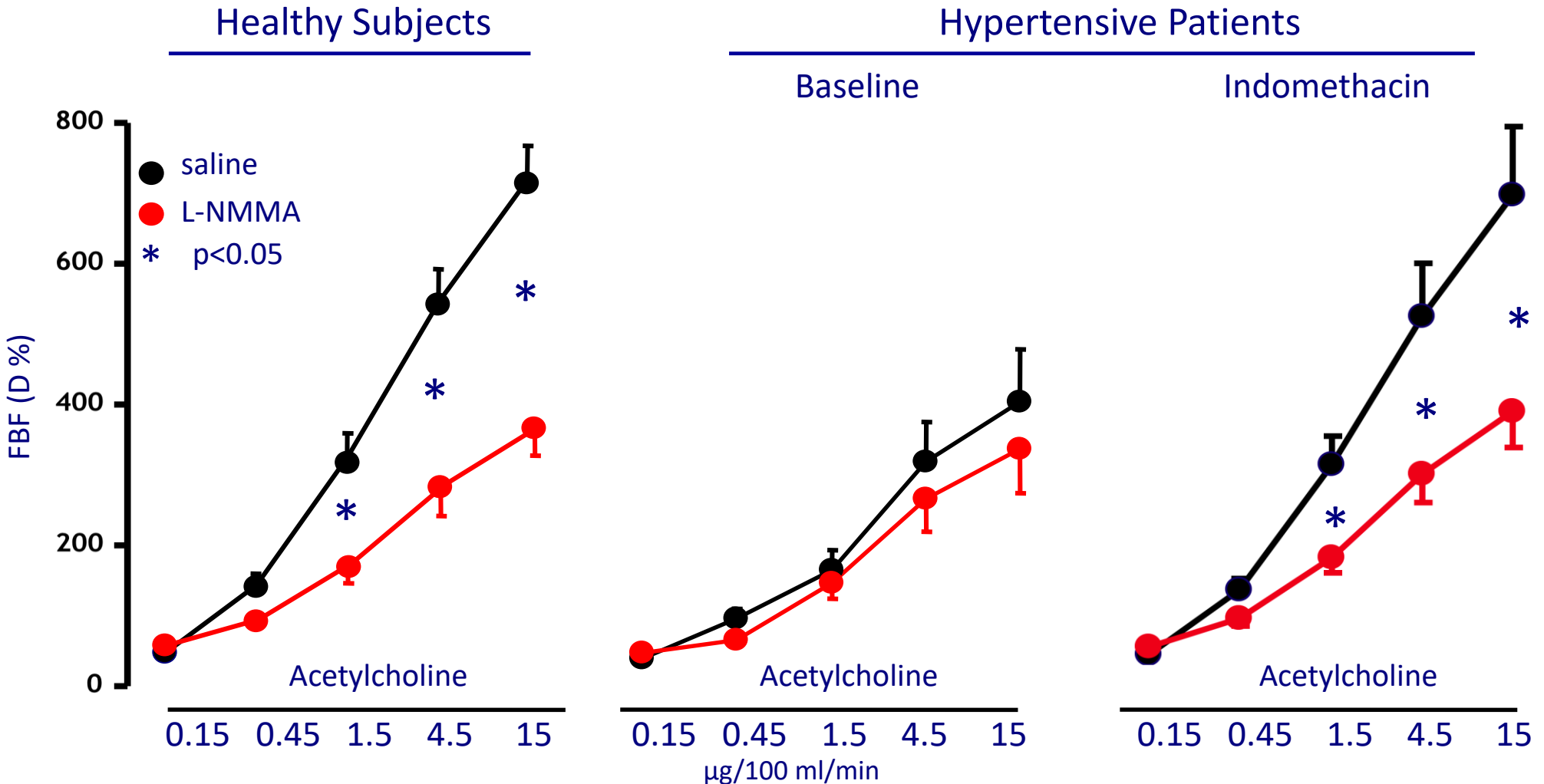
Endothelium-dependent vasodilation in patients with essential hypertension or primary aldosteronism



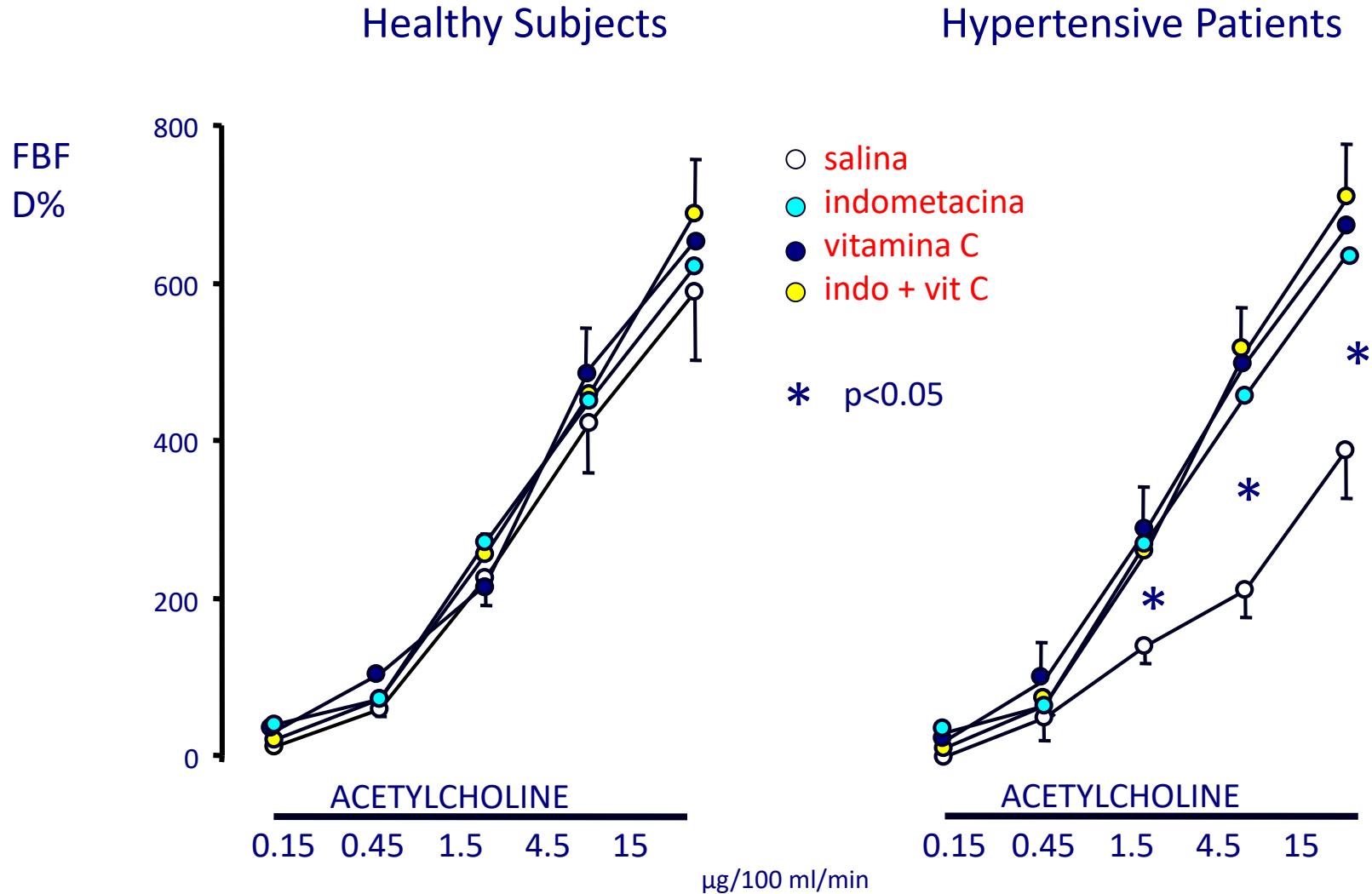
COX is responsible for endothelial dysfunction in patients with essential hypertensive but not in patients with primary aldosteronism

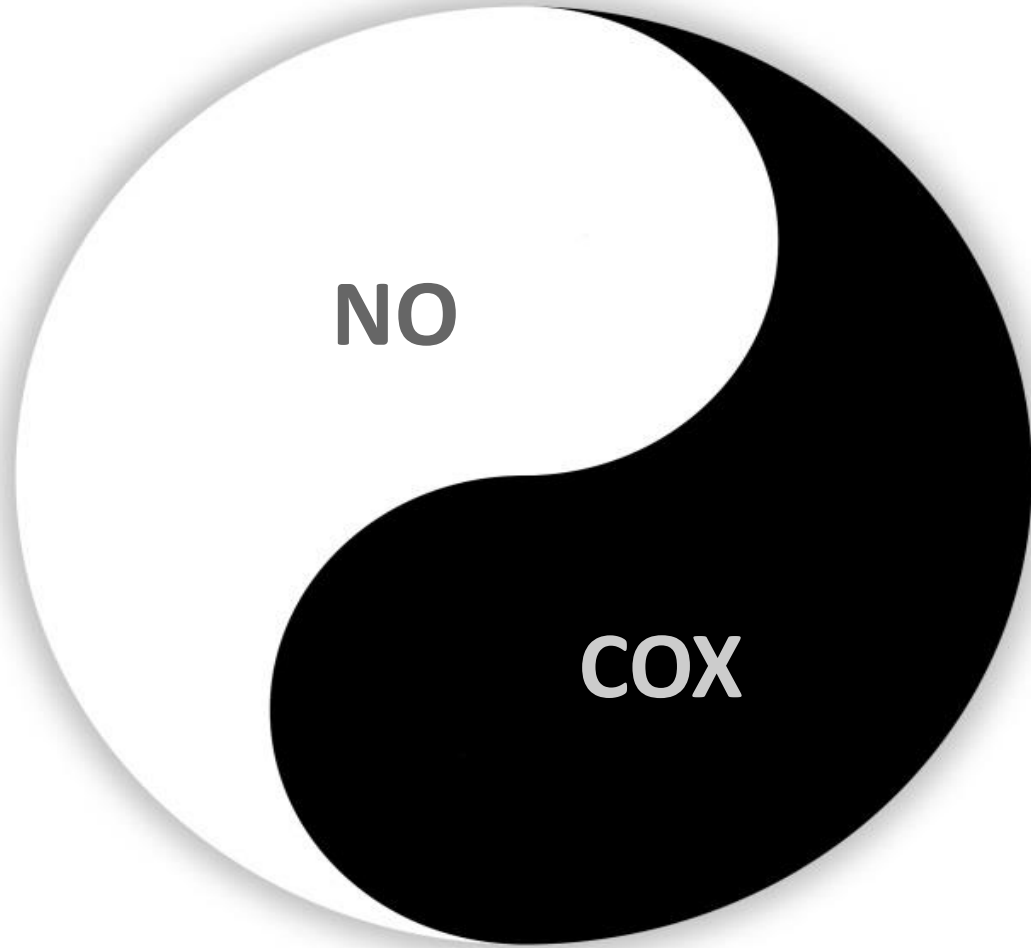


Cyclooxygenase inhibition restores NO activity in essential hypertension



Cyclooxygenase is a major source of oxidative stress in essential hypertension





COX and endothelial dysfunction in essential hypertensive patients: *unsolved questions*

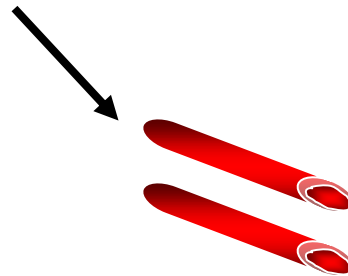
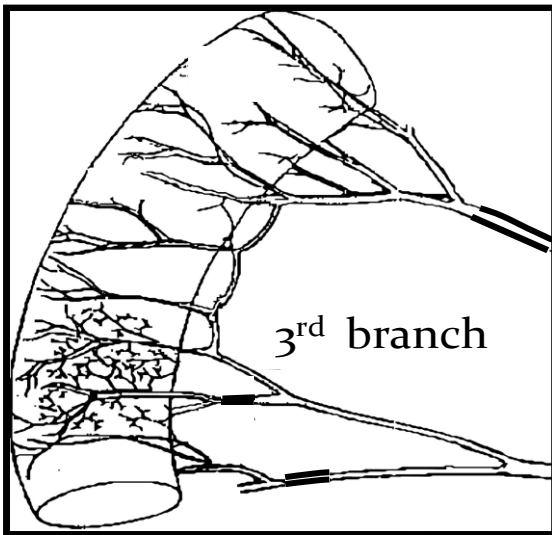
- Which COX isoenzyme is the predominant isoform contributing to ROS generation in essential hypertension?
- Is COX the only recognized ROS source, in small resistance arteries from essential hypertensive patients?



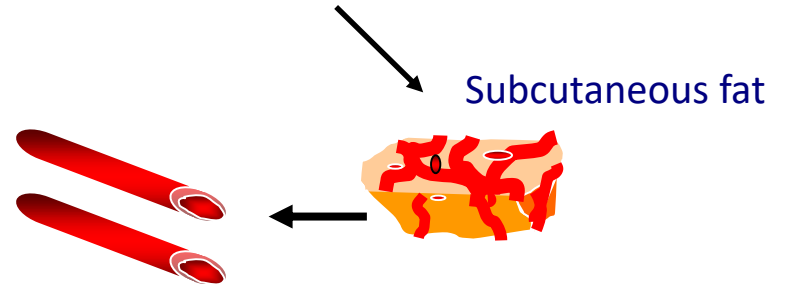
Micromiography



Gluteal subcutaneous or intrasurgery biopsy



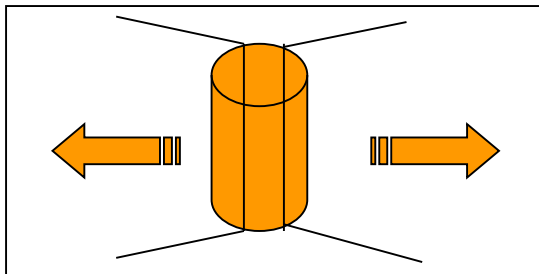
Mesenteric artery (150 ~ 350 μm)



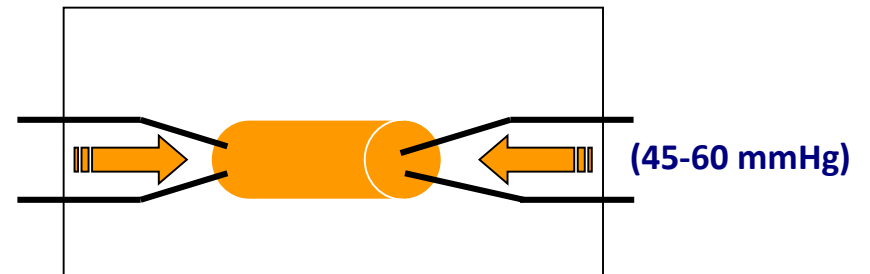
Subcutaneous fat

Peripheral resistance artery (150 ~ 350 μm)

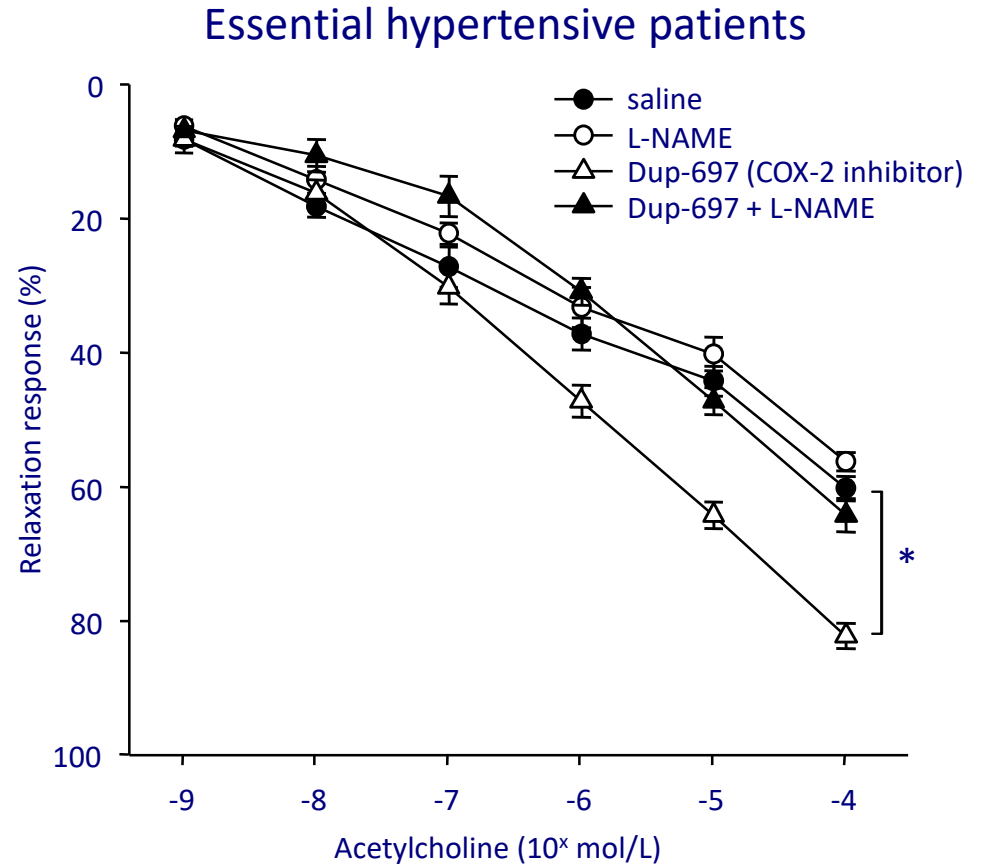
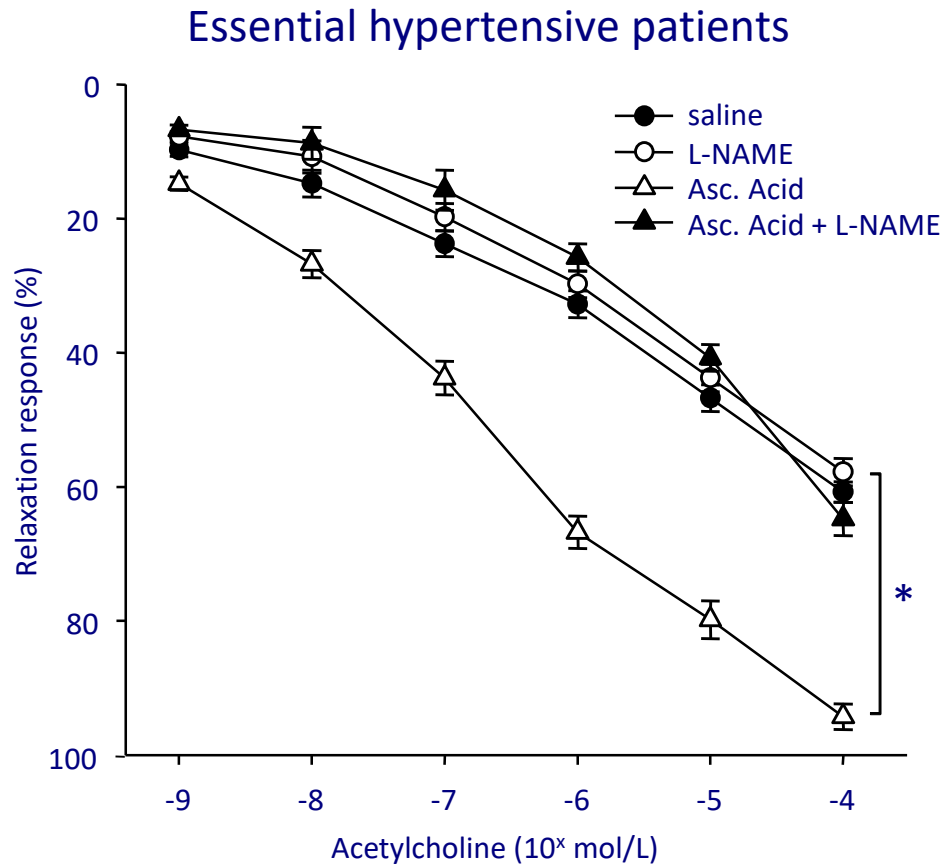
Isometric (wire myograph)



Isobaric (pressure myograph)

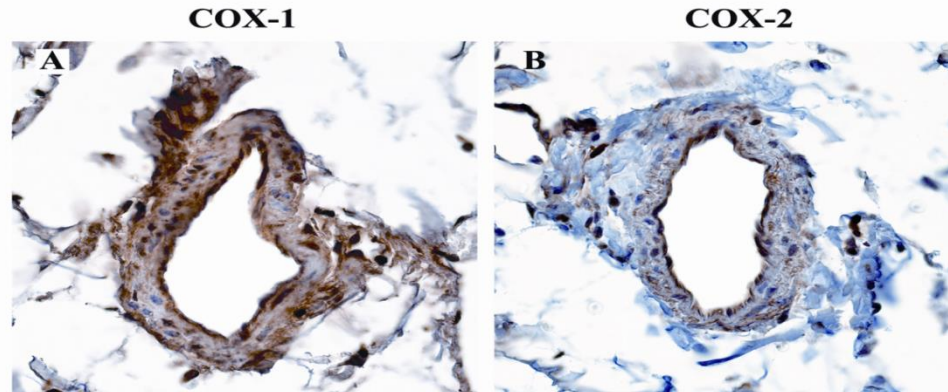


Identification of sources of oxidative stress in small arteries of essential hypertensive patients

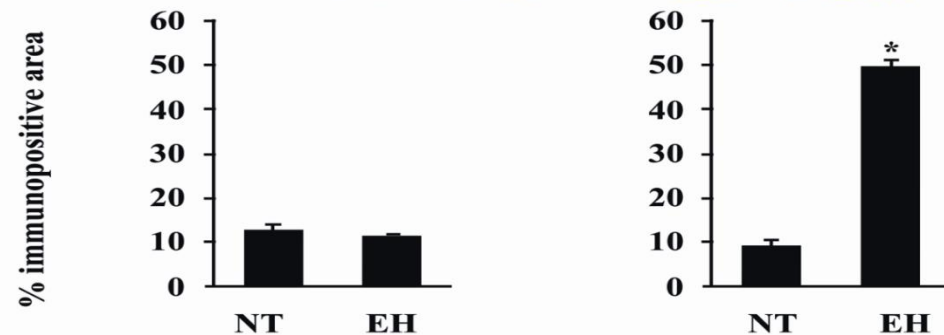
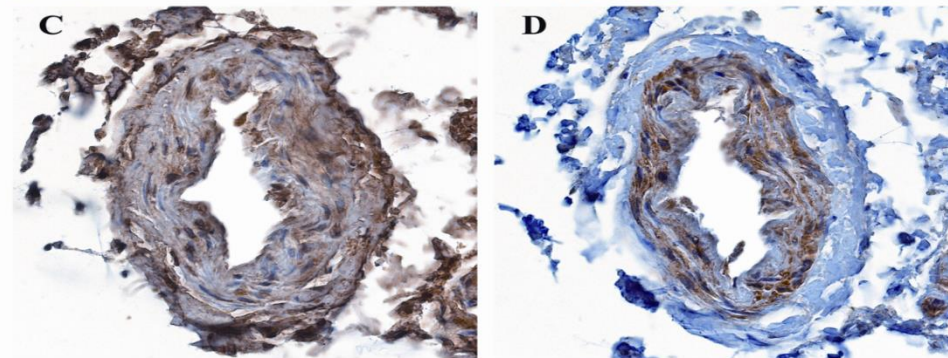


Immunostaining of COX-1 and COX-2 in controls and hypertensive patients

NORMOTENSIVE
CONTROLS

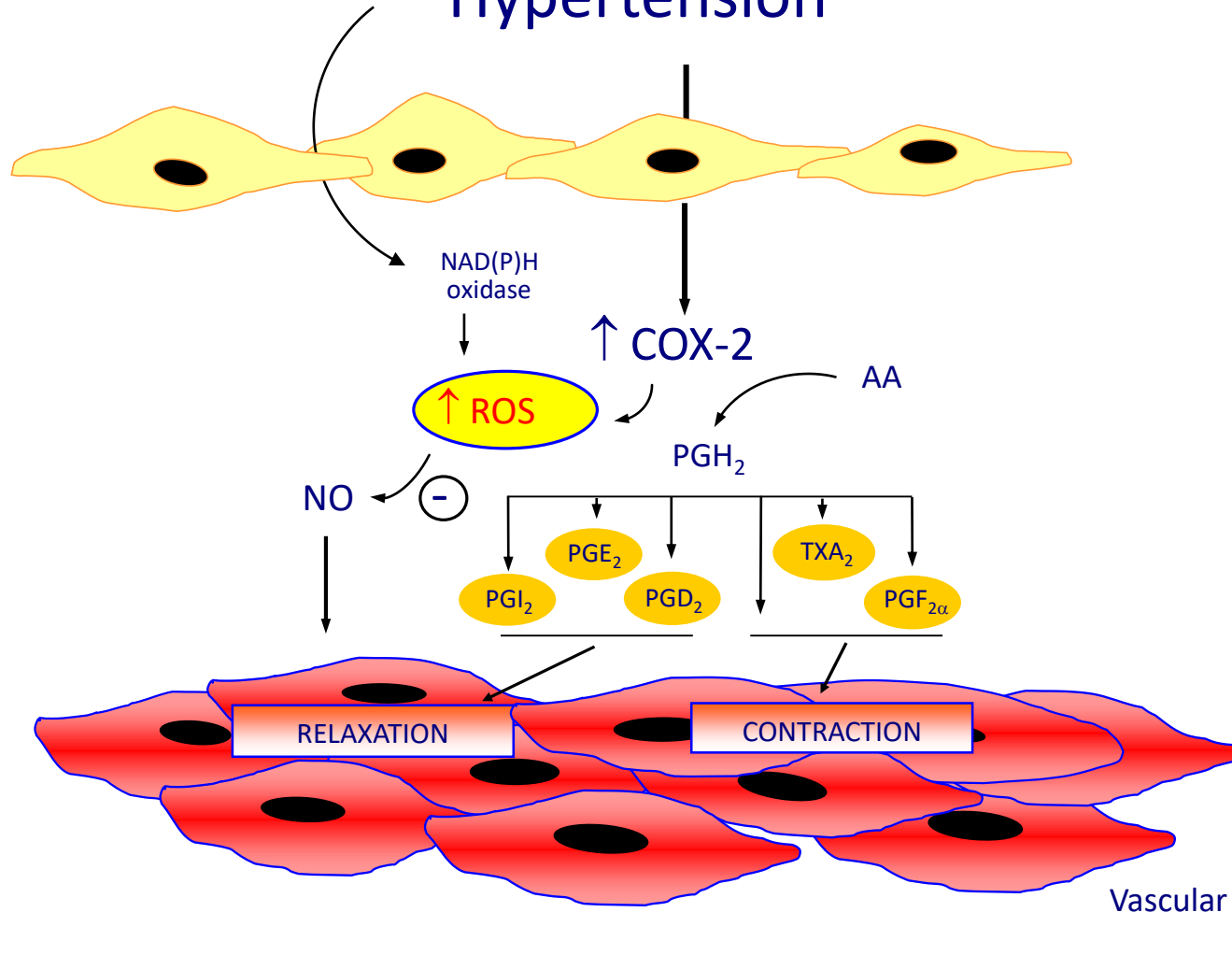


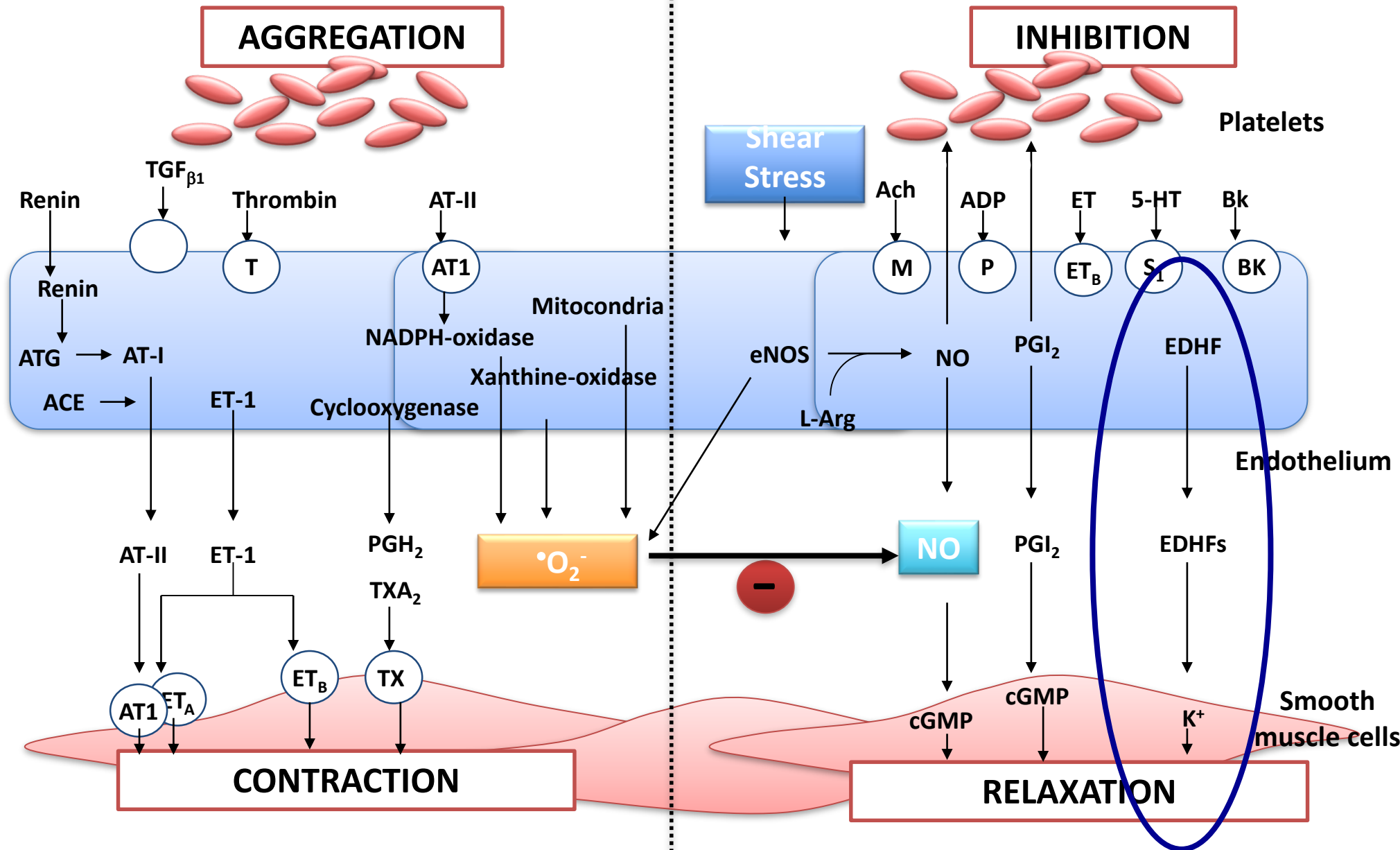
HYPERTENSIVE
PATIENTS



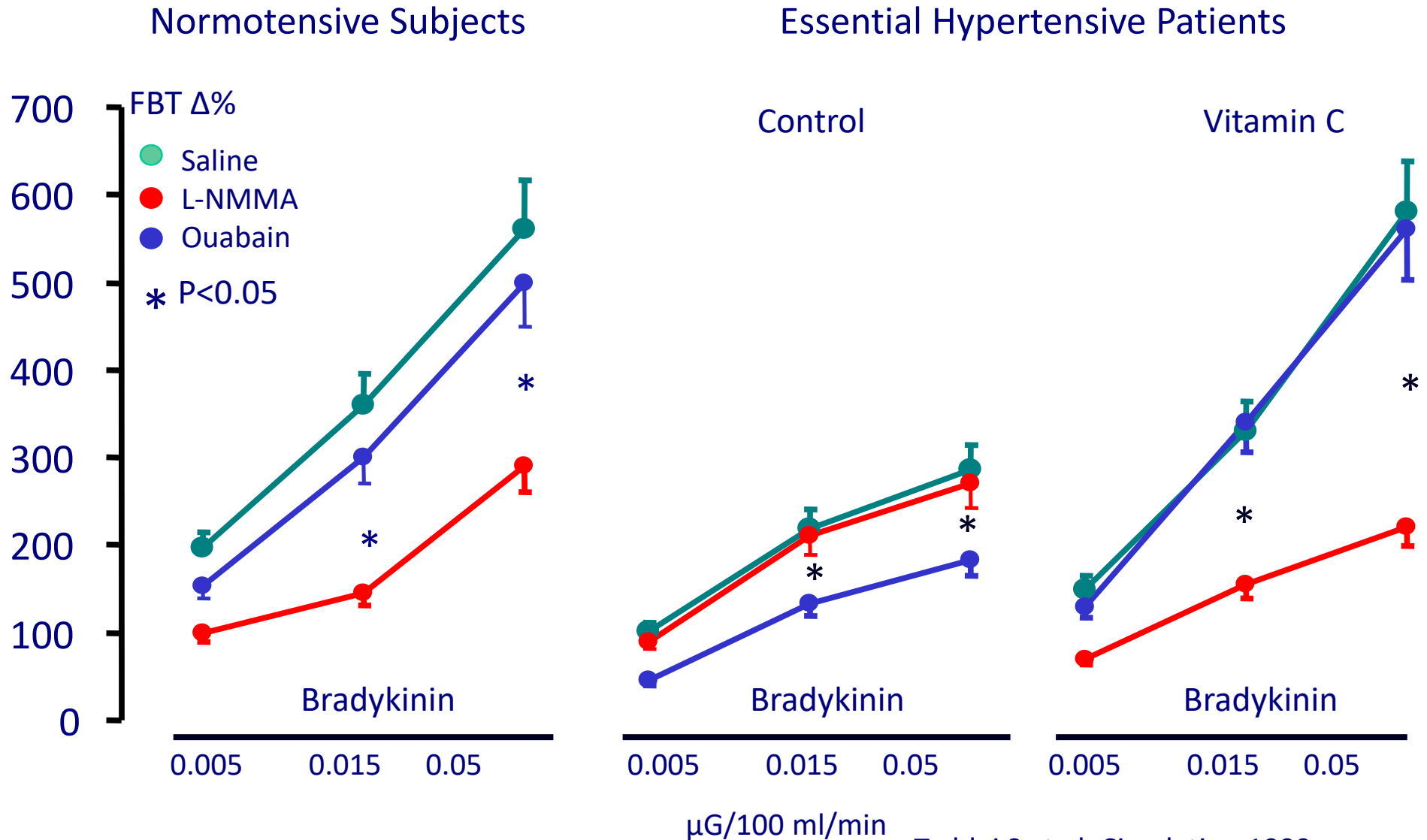
Essential Hypertension

Endothelial cells

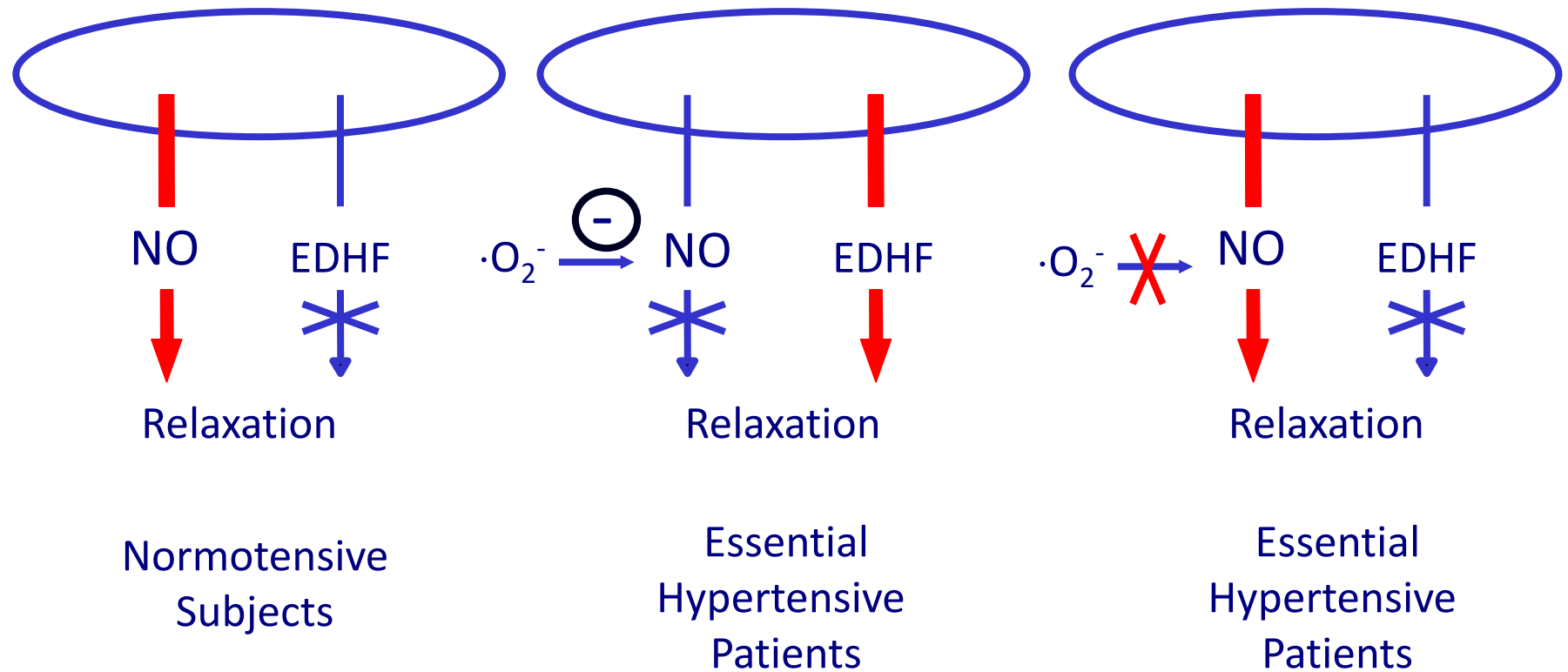




Effect of L-NMMA (to block NO-synthase) and ouabain (to block hyperpolarization) on response to bradykinin

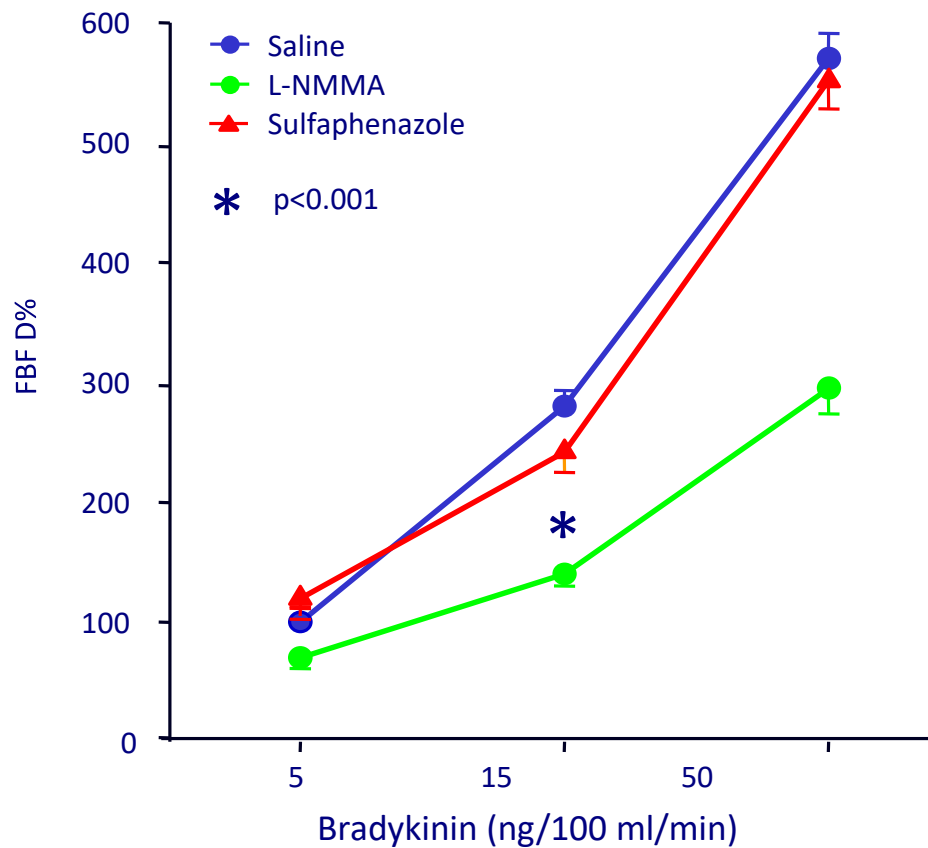


Mechanisms responsible for endothelium-dependent vasodilation in human hypertension

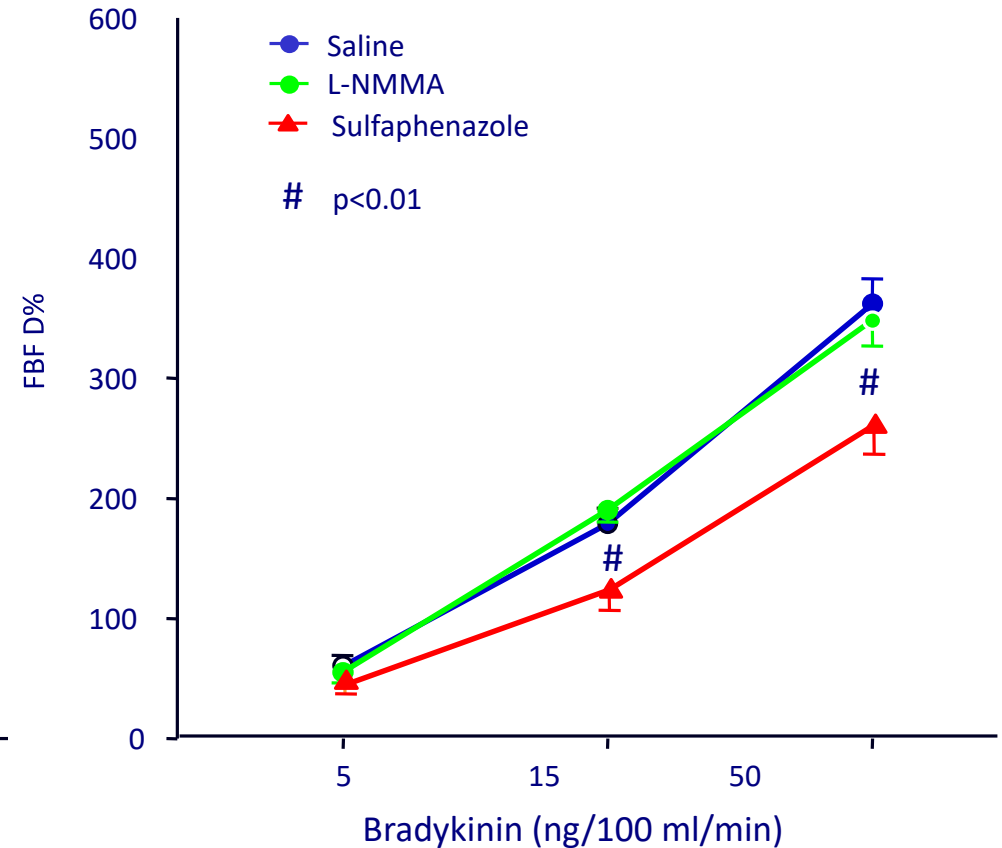


Effects of L-NMMA and sulfaphenazole on vasodilation to bradykinin

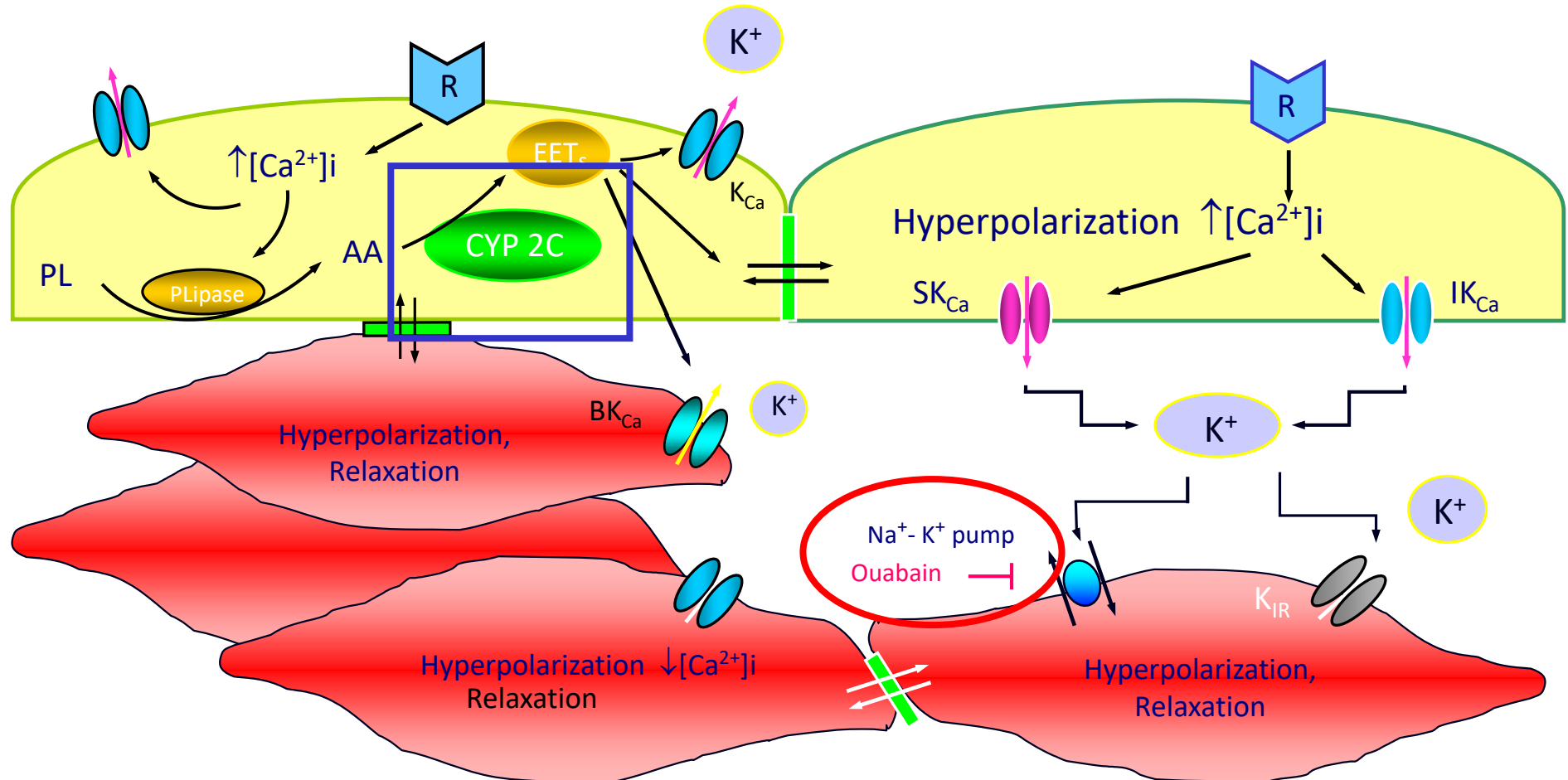
Normotensive subjects

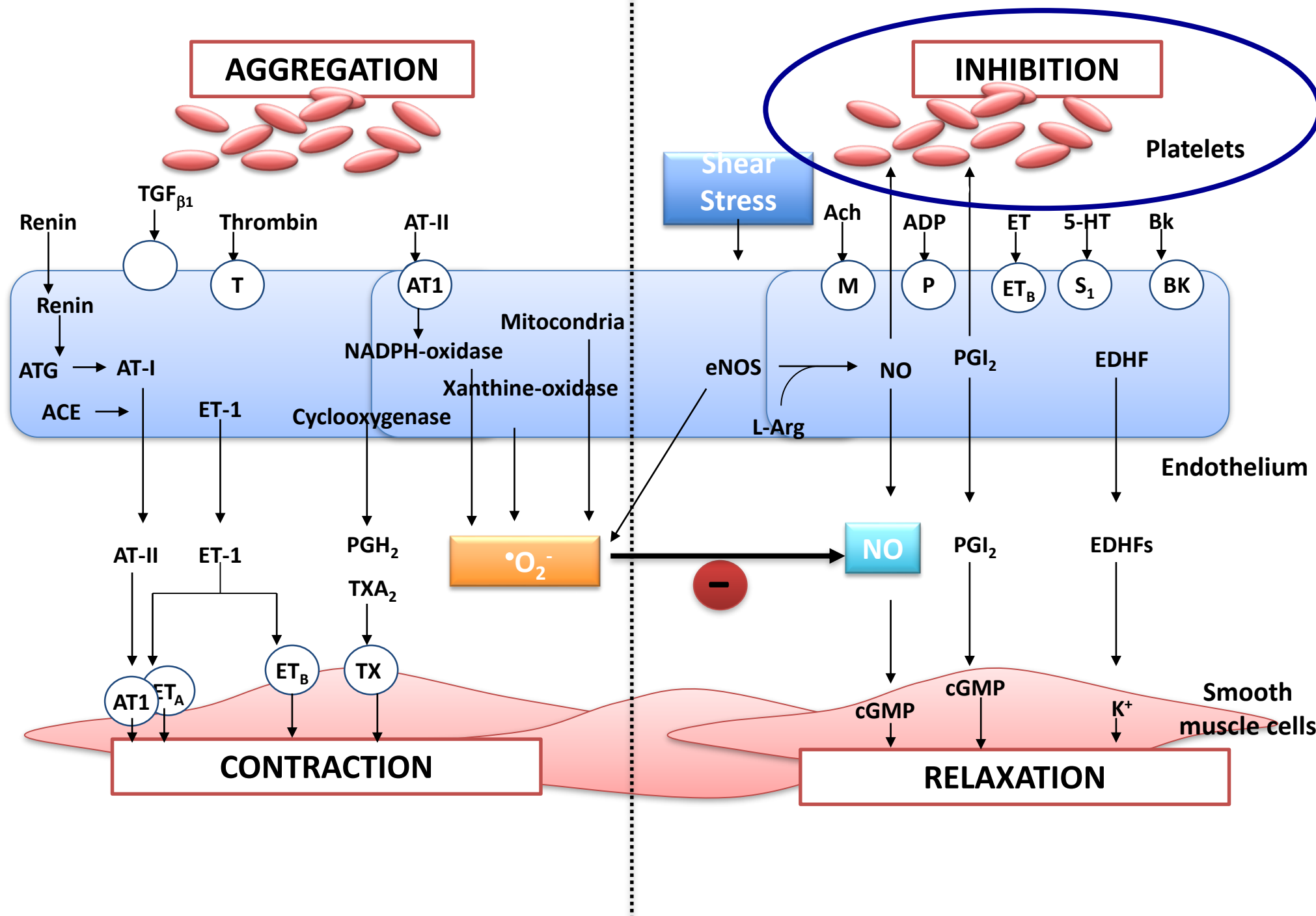


Hypertensive patients

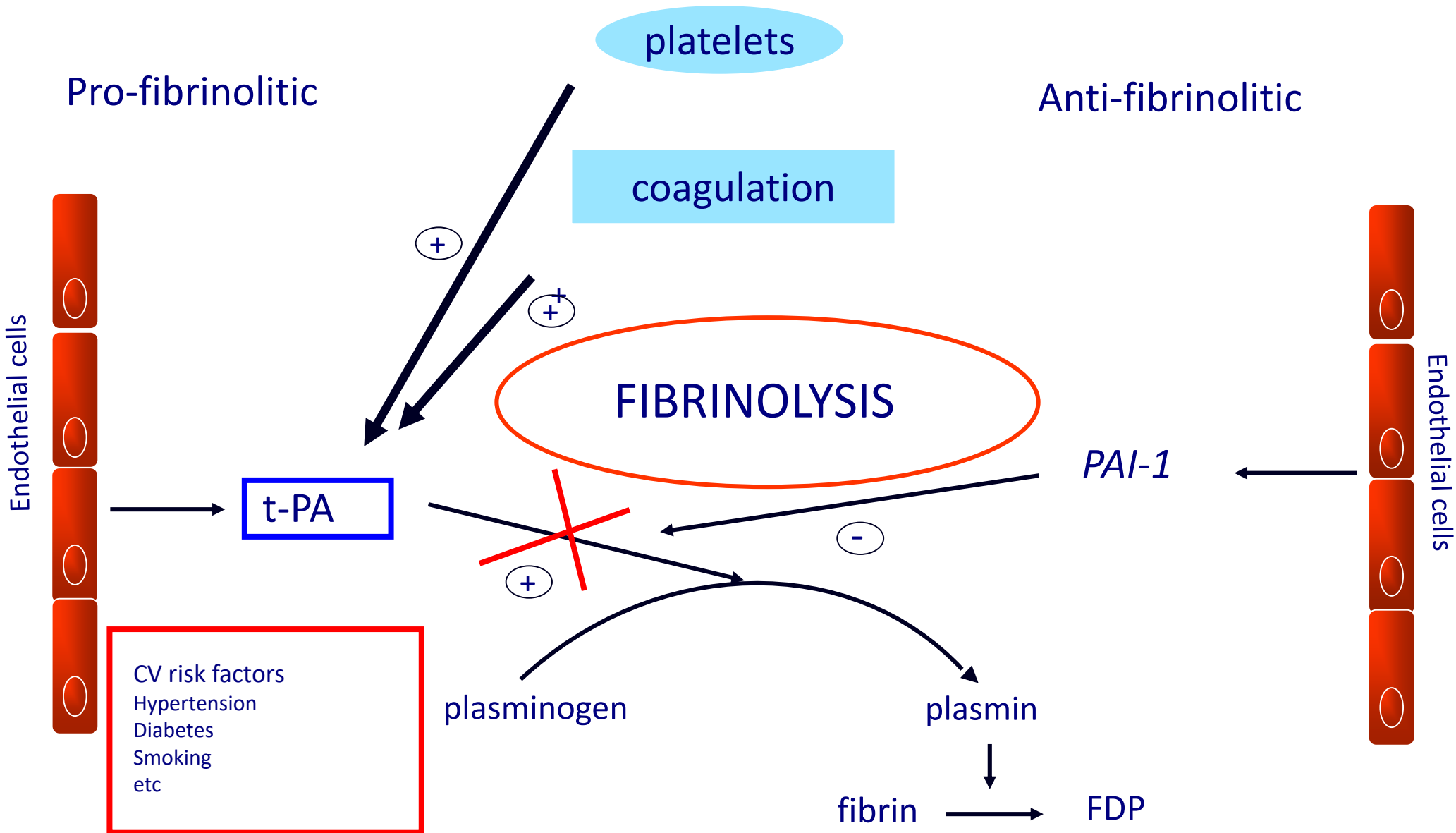


The isoenzyme 2C of the cytochrome P450 epoxidegenase (named CYP 2C) is a major source of EDHF





Fibrinolytic properties of endothelial cells



Simultaneous blood sampling for the determination of venous-arterial differences



Venous value greater than arterial value



RELEASE

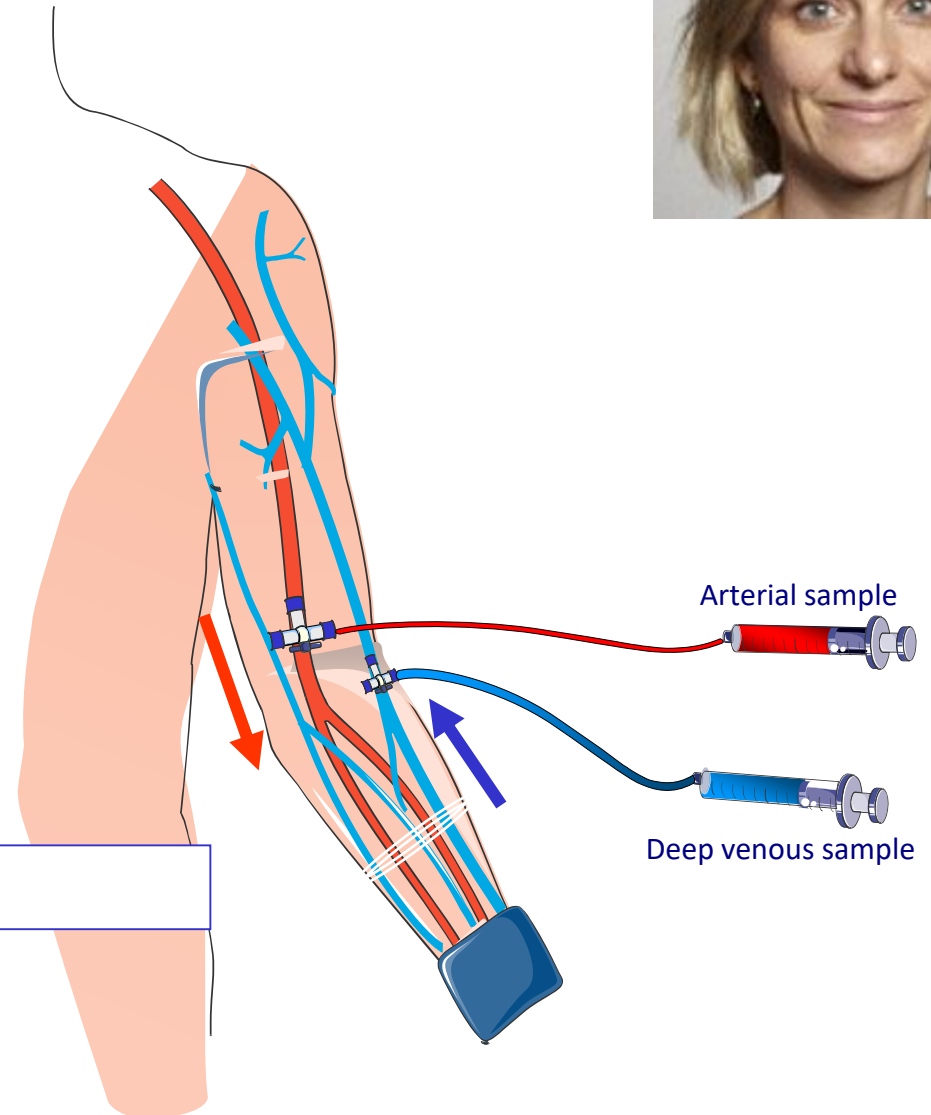
Venous value lower than arterial value



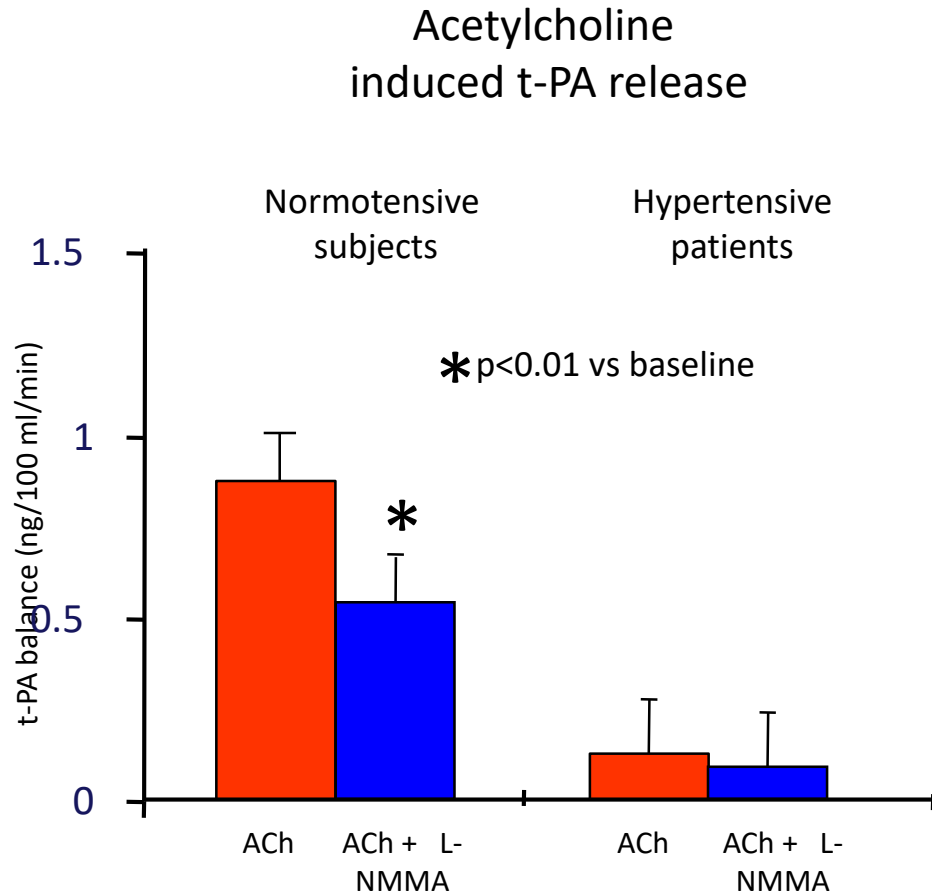
UPTAKE

$$\text{Net balance} = (C_v - C_a) \times [\text{FBF} \times (1 - \text{Ht})]$$

C_v = venous concentration
 C_a = arterial concentration
FBF = forearm blood flow
Ht = hematocrit

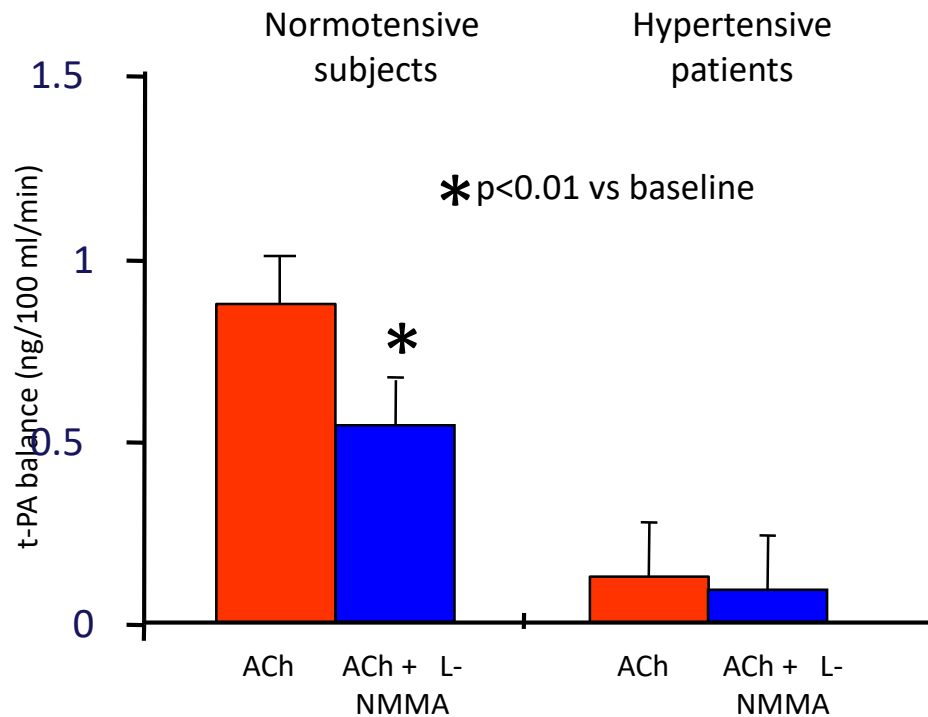


Bradykinin, but not acetylcholine, can release t-PA in hypertensive patients with impaired NO availability by a mechanism involving a sulfaphenazol (SULFA)-sensitive pathway (EDHF?)



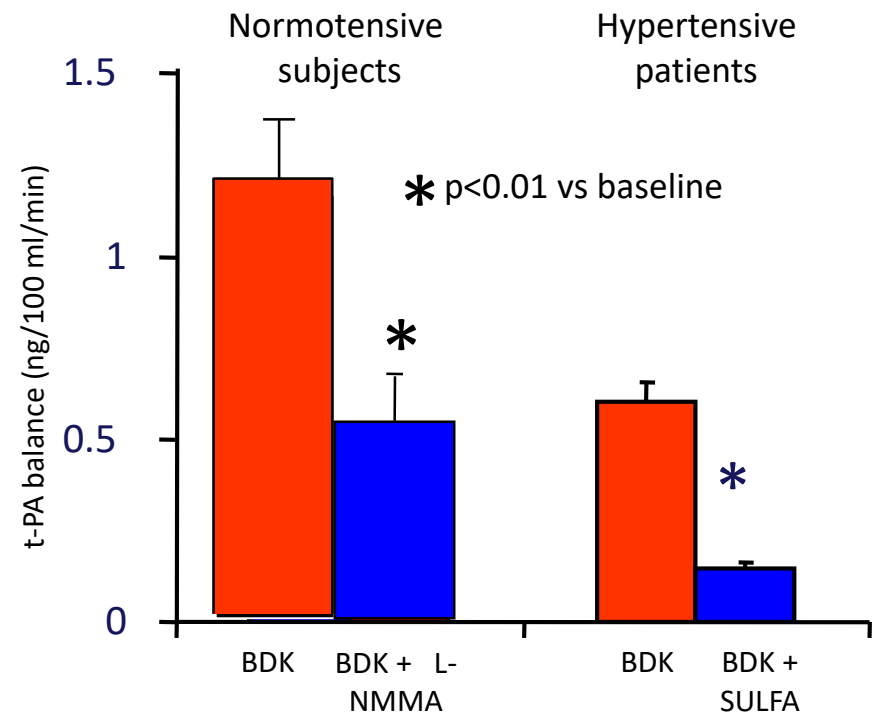
Bradykinin, but not acetylcholine, can release t-PA in hypertensive patients with impaired NO availability by a mechanism involving a sulfaphenazol (SULFA)-sensitive pathway (EDHF?)

Acetylcholine
induced t-PA release



Giannarelli C et al. *Hypertension* 2007

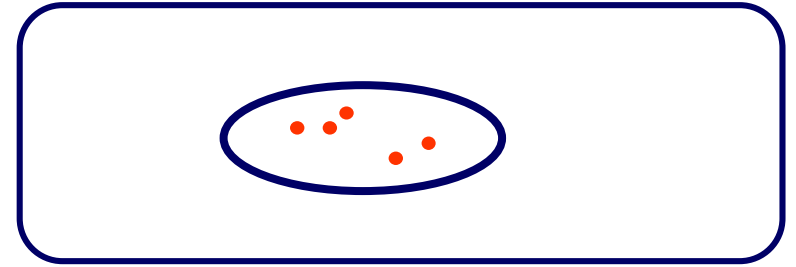
Bradykinin
induced t-PA release



Giannarelli C et al. *Circulation* 2009

Relaxation

t-PA release



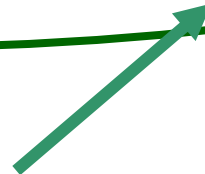
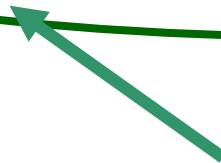
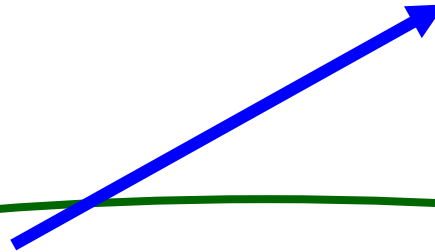
Healthy Conditions

NO

CYP 2C9-derived EDHF

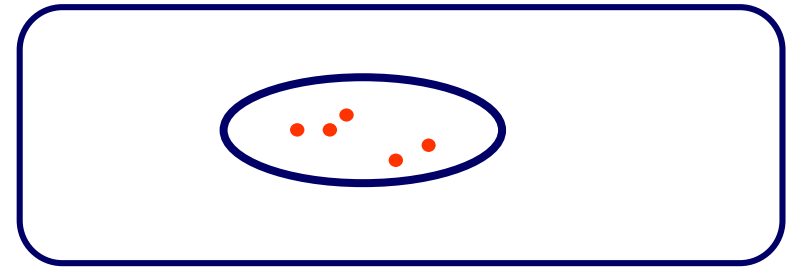
Bradykinin

Endothelial cells



Relaxation

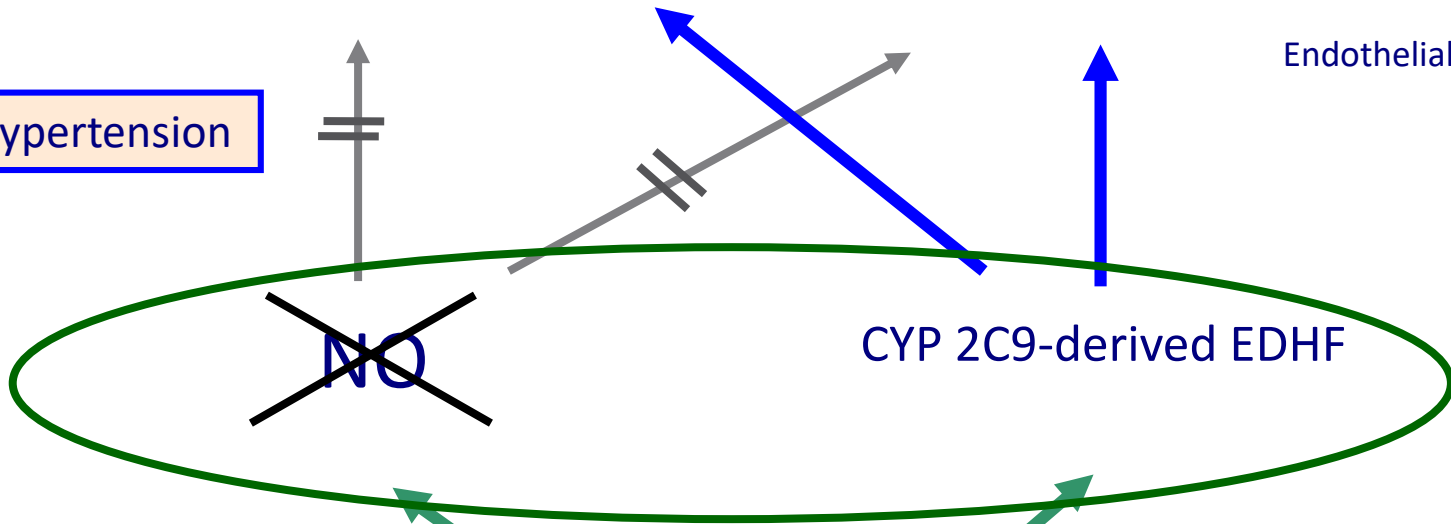
t-PA release



Smooth muscle cells

Endothelial cells

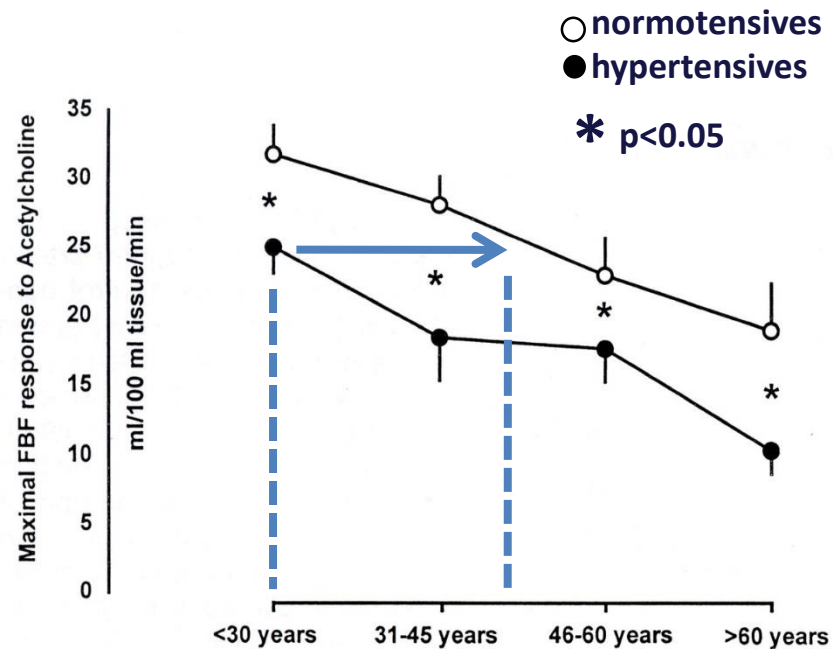
Essential Hypertension



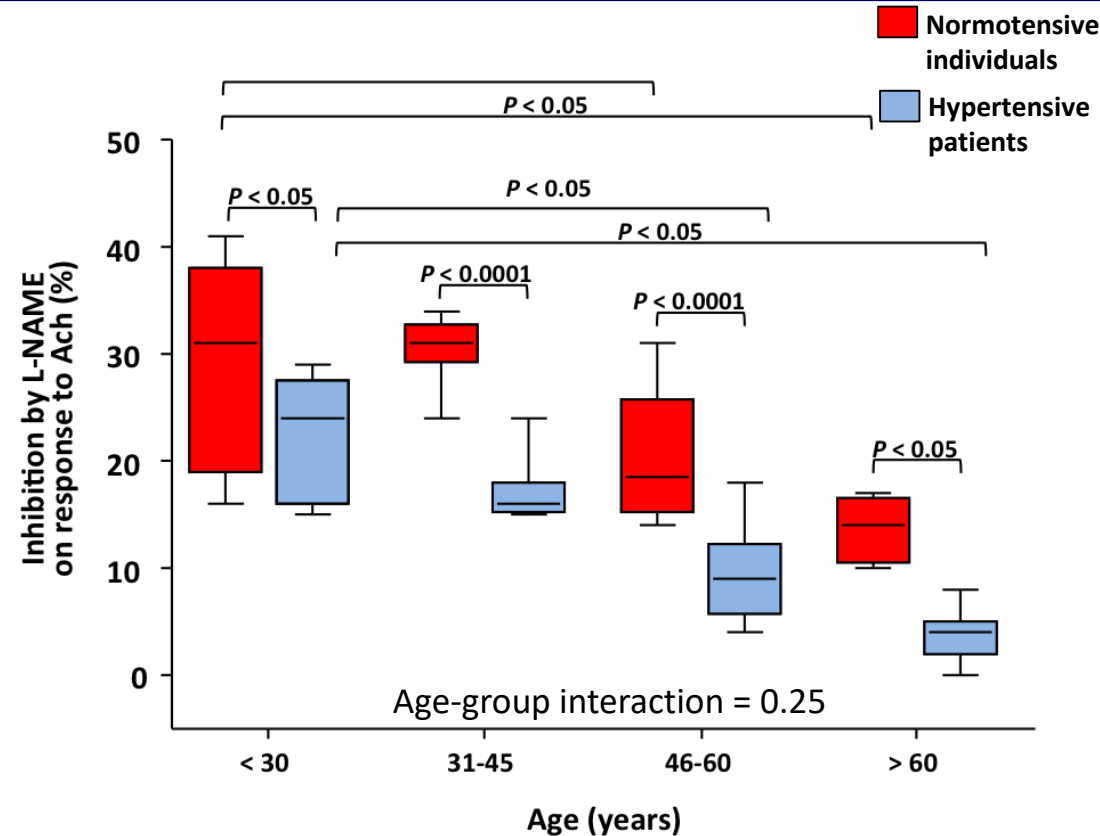
CYP 2C9-derived EDHF

Bradykinin

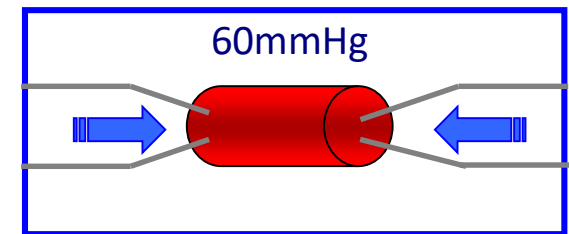
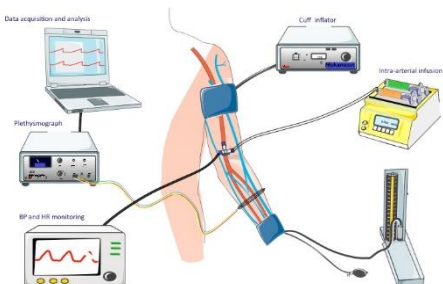
Hypertension causes premature aging of endothelial function in humans



Taddei S et al, Circulation 1996



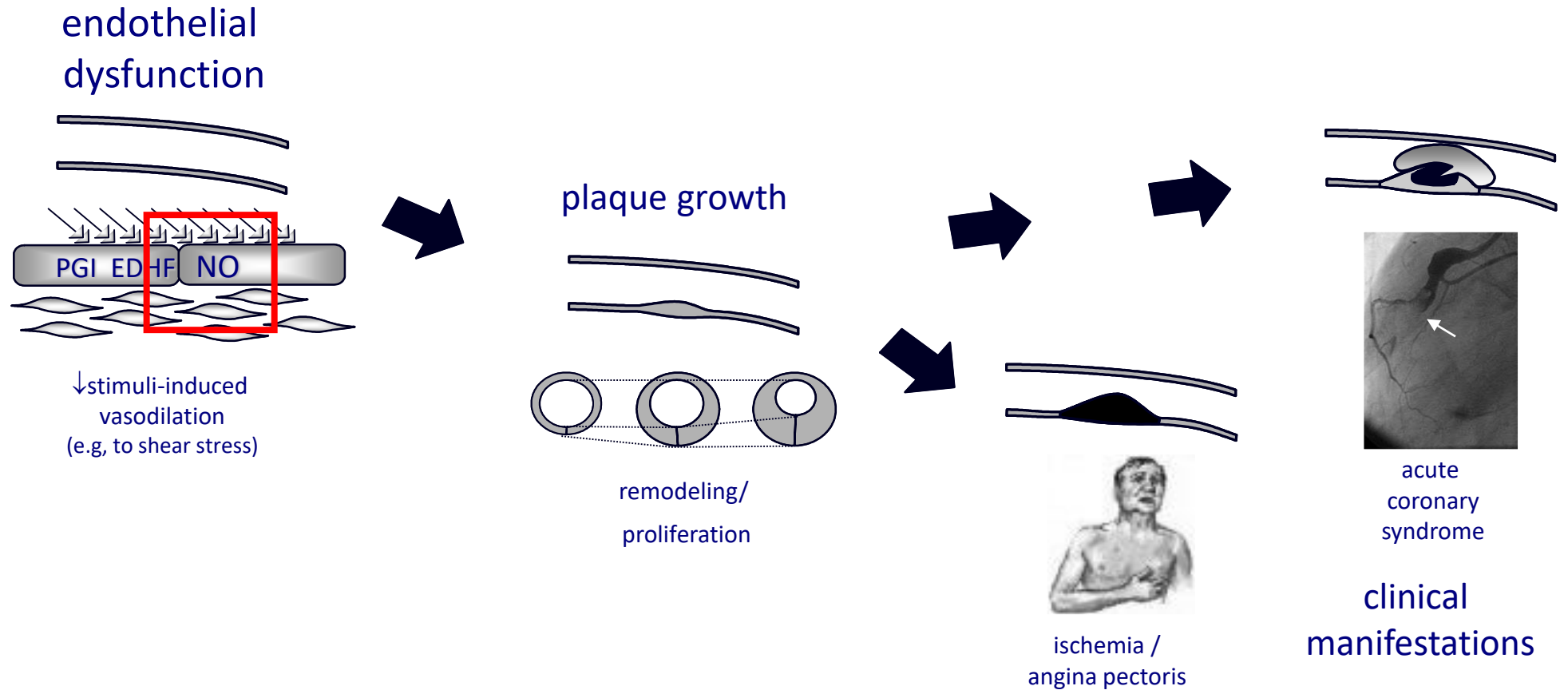
Bruno RM et al, Hypertension 2017



Clinical significance of endothelial dysfunction
in hypertension: moving to non-invasive tests

Pathogenesis of atherosclerosis

from endothelial dysfunction to clinical disease

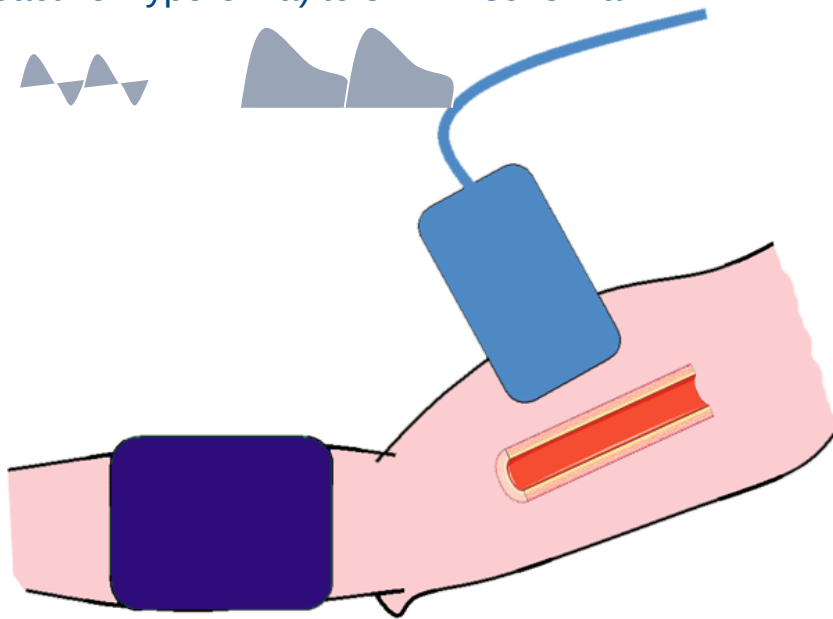




Brachial Artery Flow Mediated Dilation (FMD)

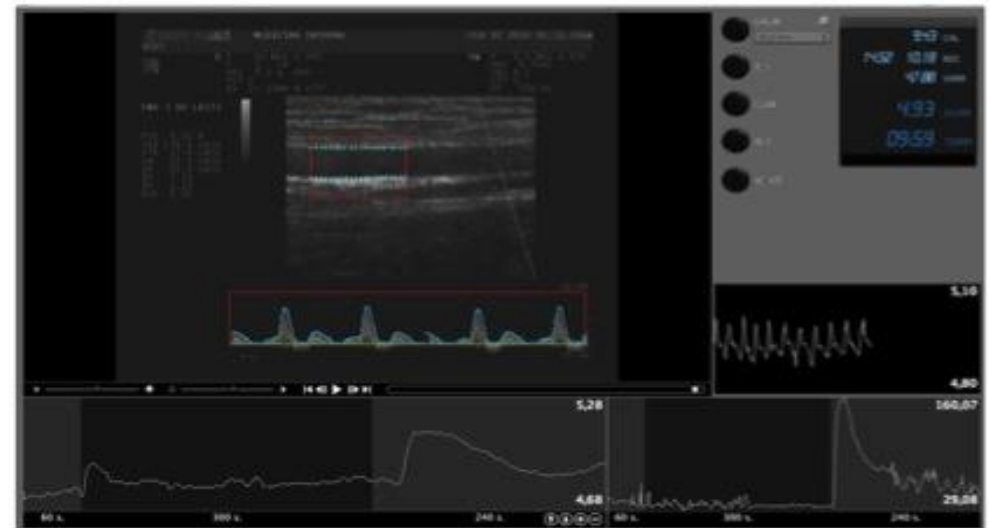
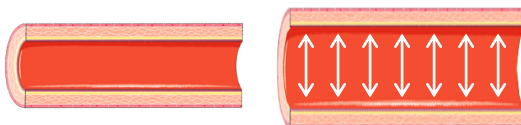
Endothelium-dependent stimulus

↑ shear stress = post-ischemic flow
(Reactive Hyperemia) to 5 min. ischemia



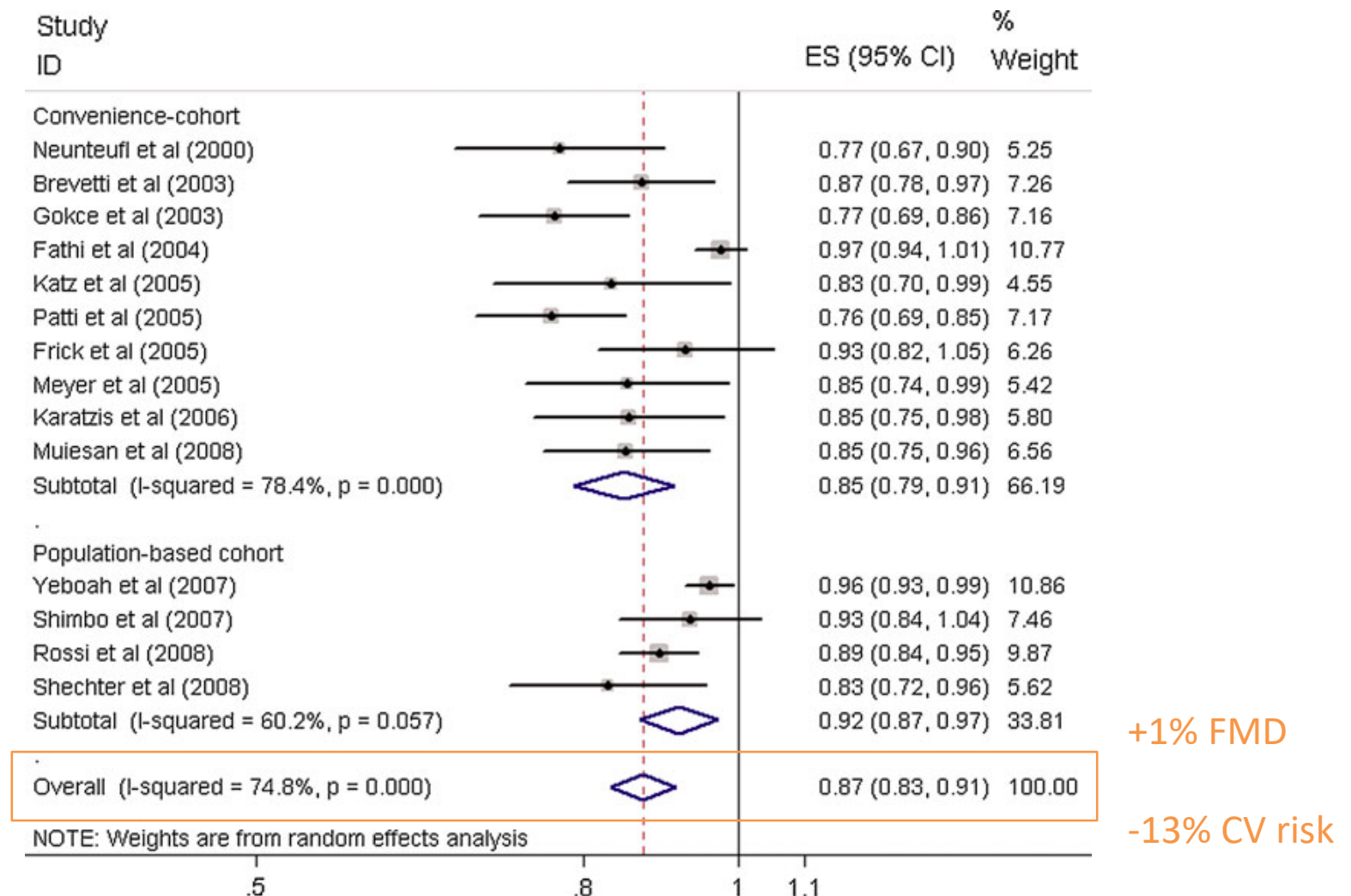
Endothelium-dependent response

↑ Diameter following Reactive Hyperemia



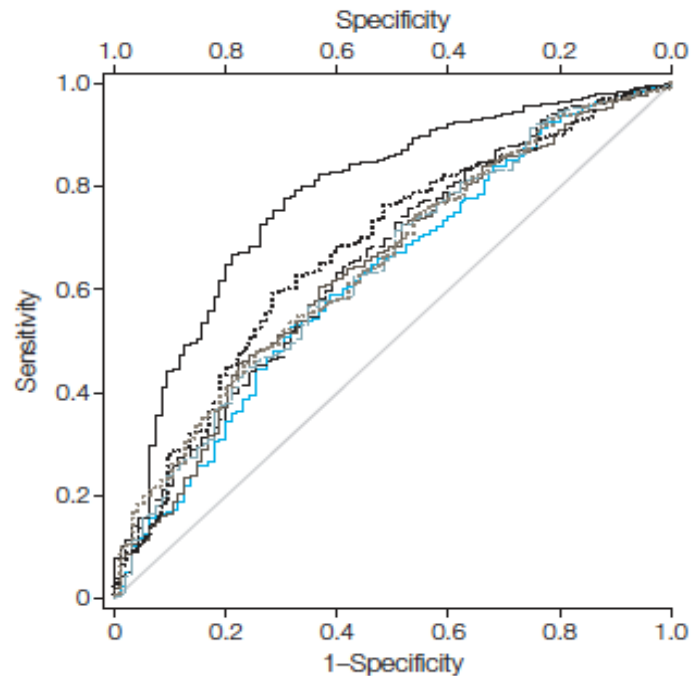
FMD Studio (www.quipu.eu)

Prediction of future cardiovascular outcomes by brachial artery FMD: a meta-analysis

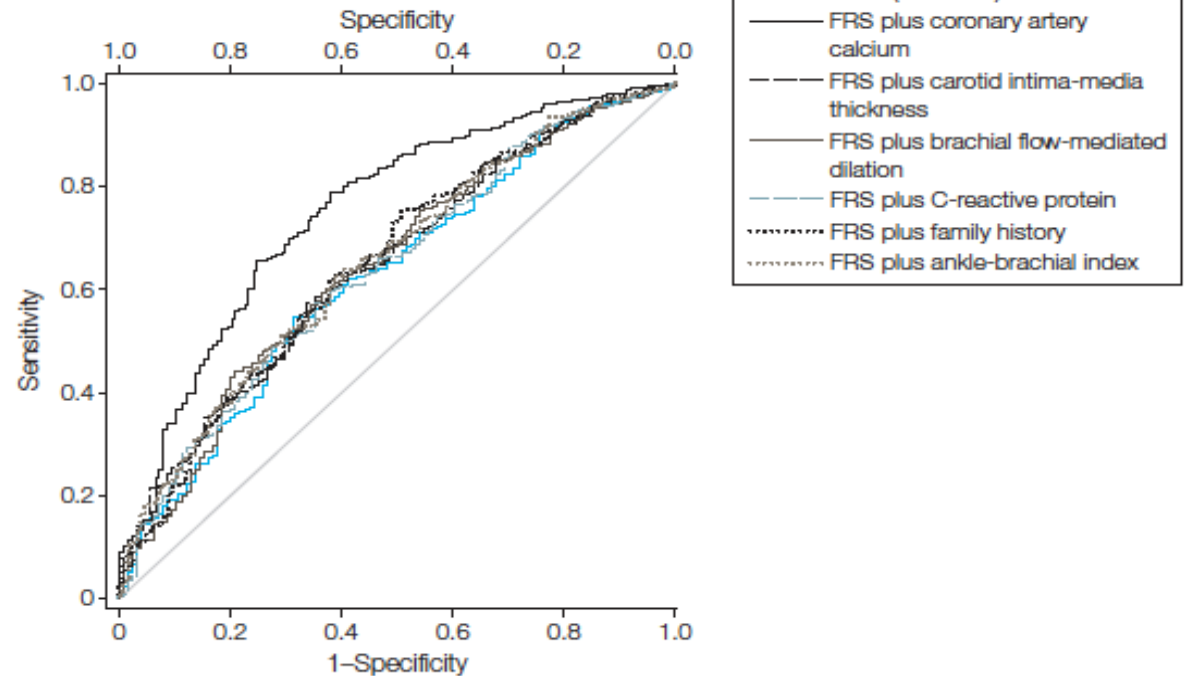


In the MESA study FMD did not improve cardiovascular risk assessment in intermediate-risk individuals

A Incident coronary heart disease



B Incident cardiovascular disease



A, Receiver operator characteristic curves showing area under the curve for FRS alone, 0.623; FRS plus coronary artery calcium, 0.784 ($P<.001$); FRS plus intima-media thickness, 0.652 ($P=.01$); FRS plus flow-mediated dilation, 0.639 ($P=.06$); FRS plus high-sensitivity C-reactive protein, 0.640 ($P=.03$); FRS plus family history, 0.675 ($P=.001$); and FRS plus ankle-brachial index, 0.650 ($P=.01$). B, Receiver operator characteristic curves showing area under the curve for FRS alone, 0.623; FRS plus coronary artery calcium, 0.784 ($P<.001$); FRS plus intima-media thickness, 0.652 ($P=.01$); FRS plus flow-mediated dilation, 0.639 ($P=.06$); FRS plus high-sensitivity C-reactive protein, 0.640 ($P=.03$); FRS plus family history, 0.675 ($P=.001$); and FRS plus ankle-brachial index, 0.650 ($P=.01$). MESA indicates Multi-Ethnic Study of Atherosclerosis.

FMD reproducibility in the MESA study: was it enough?

Reproducibility in the MESA study:

- CAC: intraobserver and interobserver agreement $k=0.90$ and 0.93
- IMT: coefficient of variation 7.07%
- FMD: intraclass coefficient 0.54

Jeboah J et al. JAMA. 2012;308(8):788-795

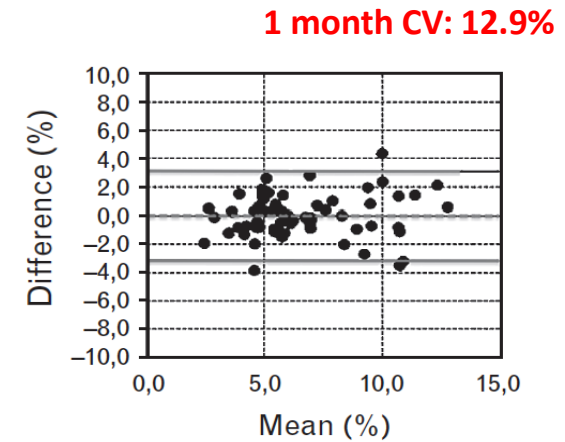
FMD standardization improves reproducibility



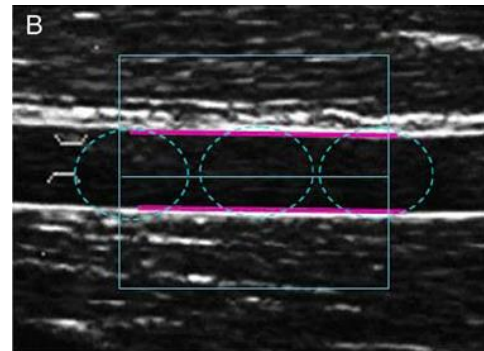
Ghiadoni L et al. Curr Pharm Des 2008



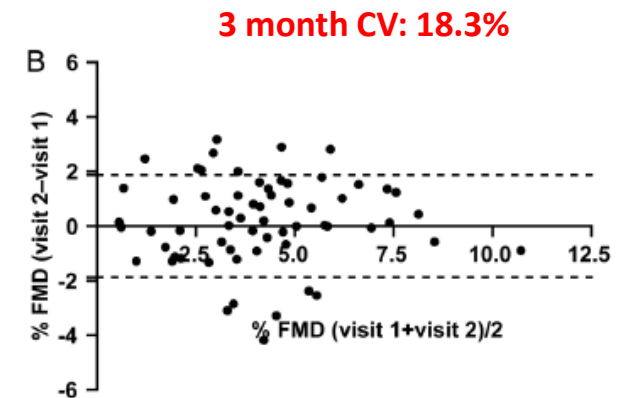
Gemignani V et al. UM&B 2007



Ghiadoni et al. J Hypertens 2012



Charakida M et al. Eur Heart J 2010



Charakida M et al. Eur Heart J 2013

FMD as a surrogate endpoint in clinical trials



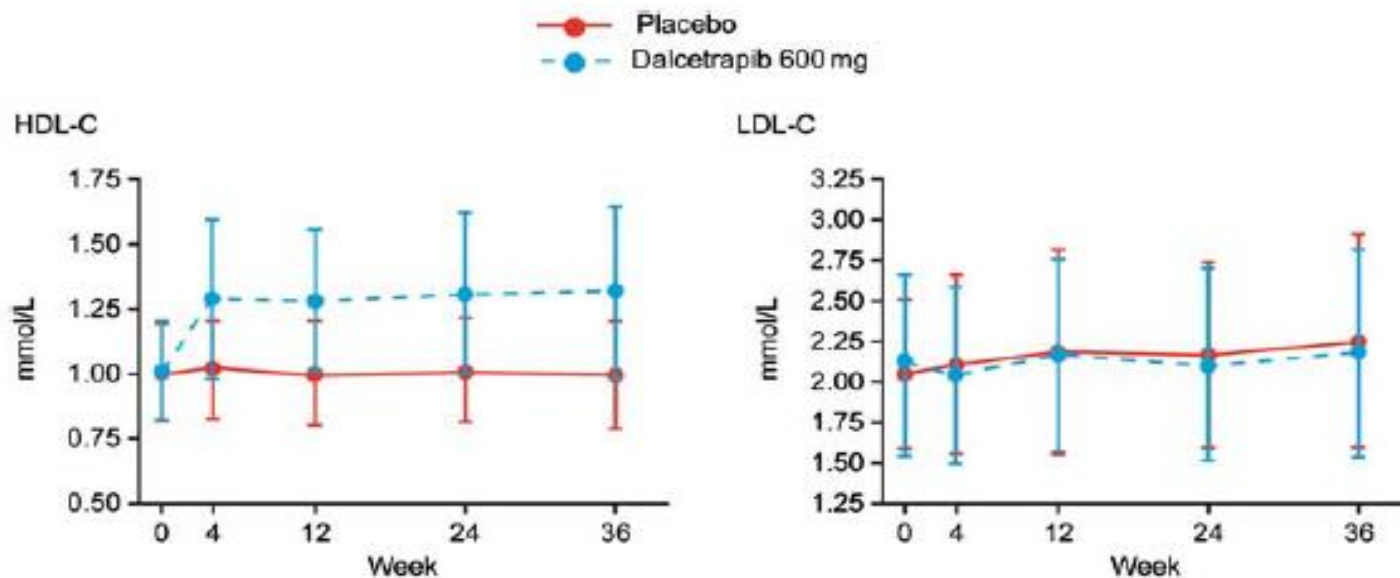
European Heart Journal (2012) 33, 857–865
doi:10.1093/eurheartj/ehs019

FASTTRACK CLINICAL

Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial

Thomas F. Lüscher^{1*}, Stefano Taddei², Juan-Carlos Kaski³, J. Wouter Jukema⁴, David Kallend⁵, Thomas Münzel⁶, John J.P. Kastelein⁷, and John E. Deanfield⁸, on behalf of the dal-VESSEL Investigators

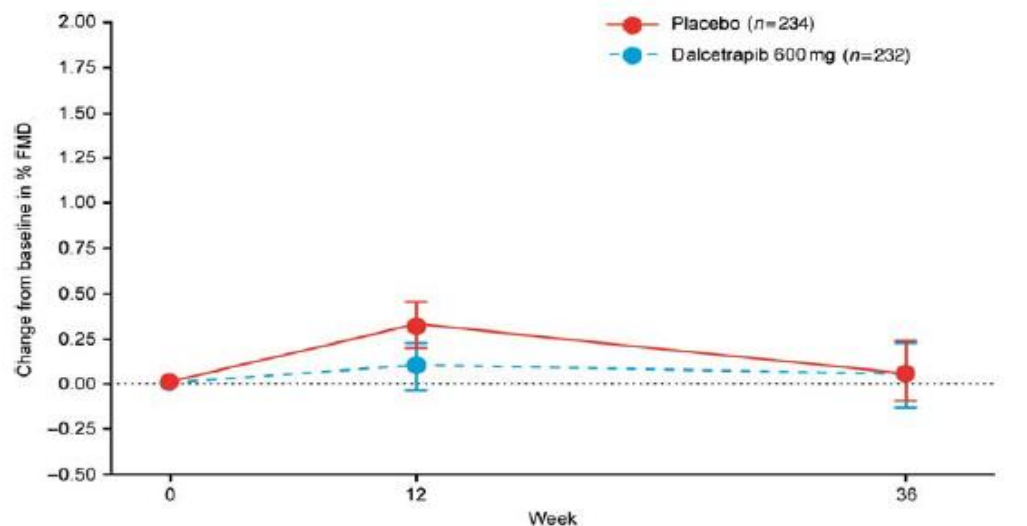
- 466 patients with target LDL-C levels received dalcetrapib (a CETP-inhibitor) 600 mg/day or placebo for 36 weeks on top of standard therapy (including statins).
- The primary outcome measures were the change from baseline of flow-mediated dilatation (%FMD) of the right brachial artery



No change in FMD, despite increased HDL levels

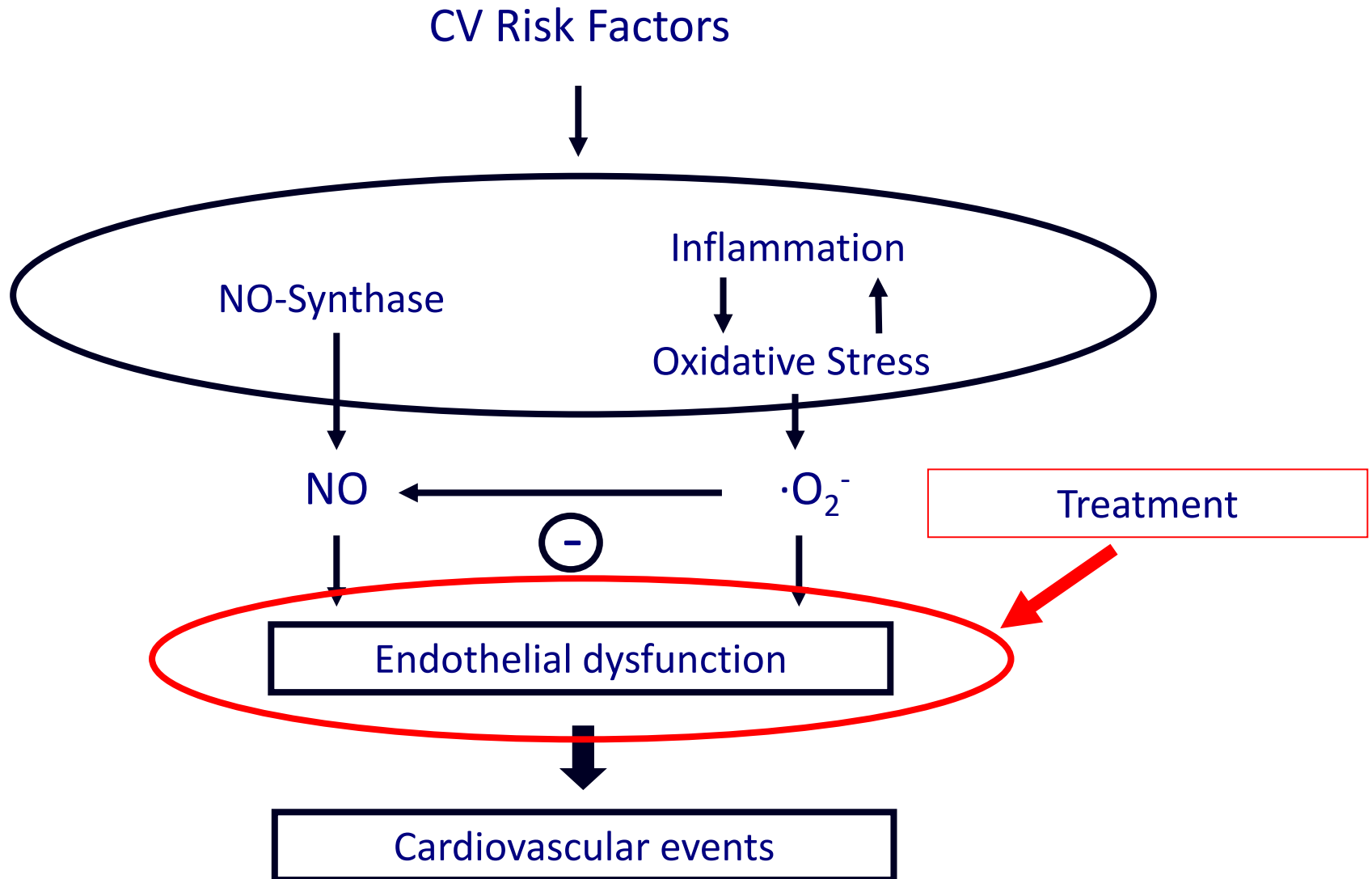


No benefit on CV events in the DAL-outcome study

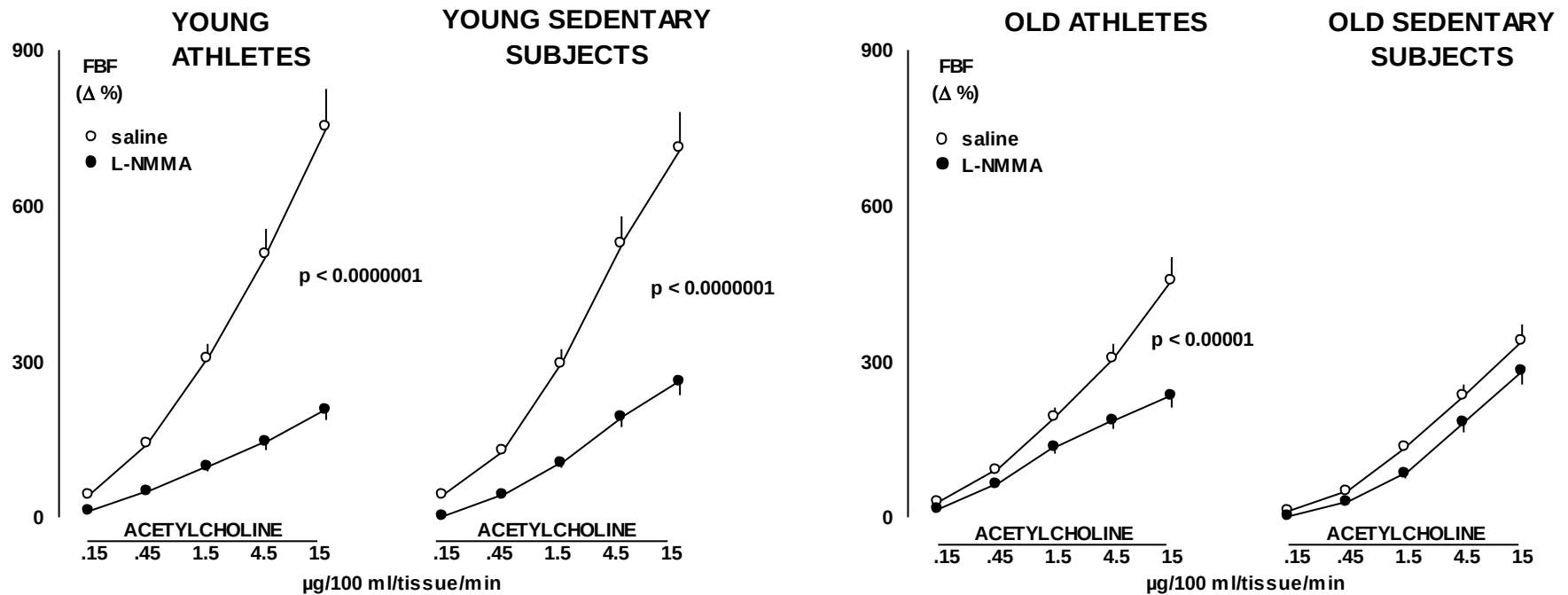


Data presented as least squares mean (SE) absolute change from baseline in %FMD at weeks 12 and 36

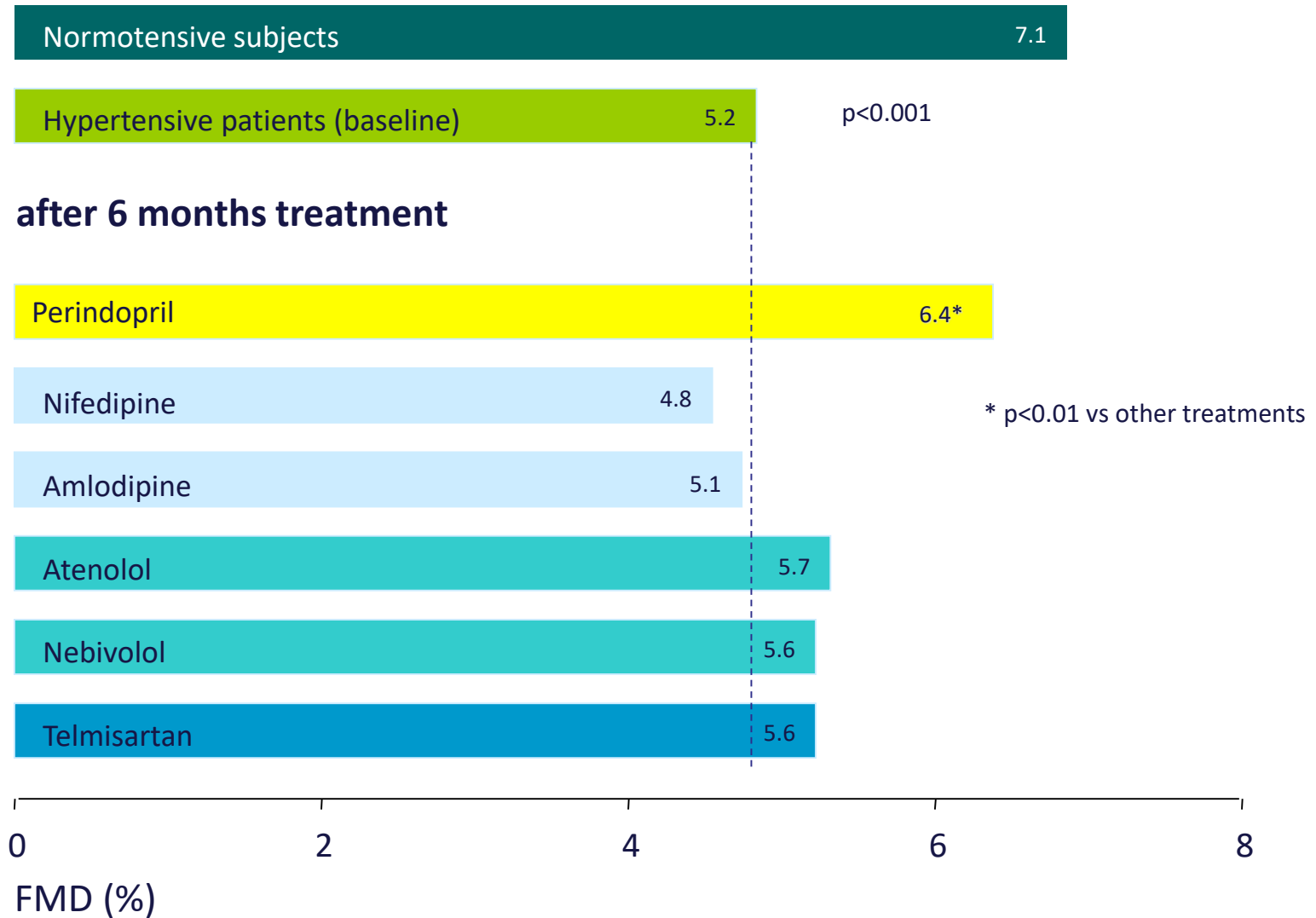
Figure 2 Flow-mediated dilatation (FMD) of the brachial artery in percent change from baseline as assessed by high resolution ultrasound of the brachial artery in patients on placebo (—; $n = 234$) or dalcetrapib (---; $n = 232$). Data are mean $\pm$ SD.



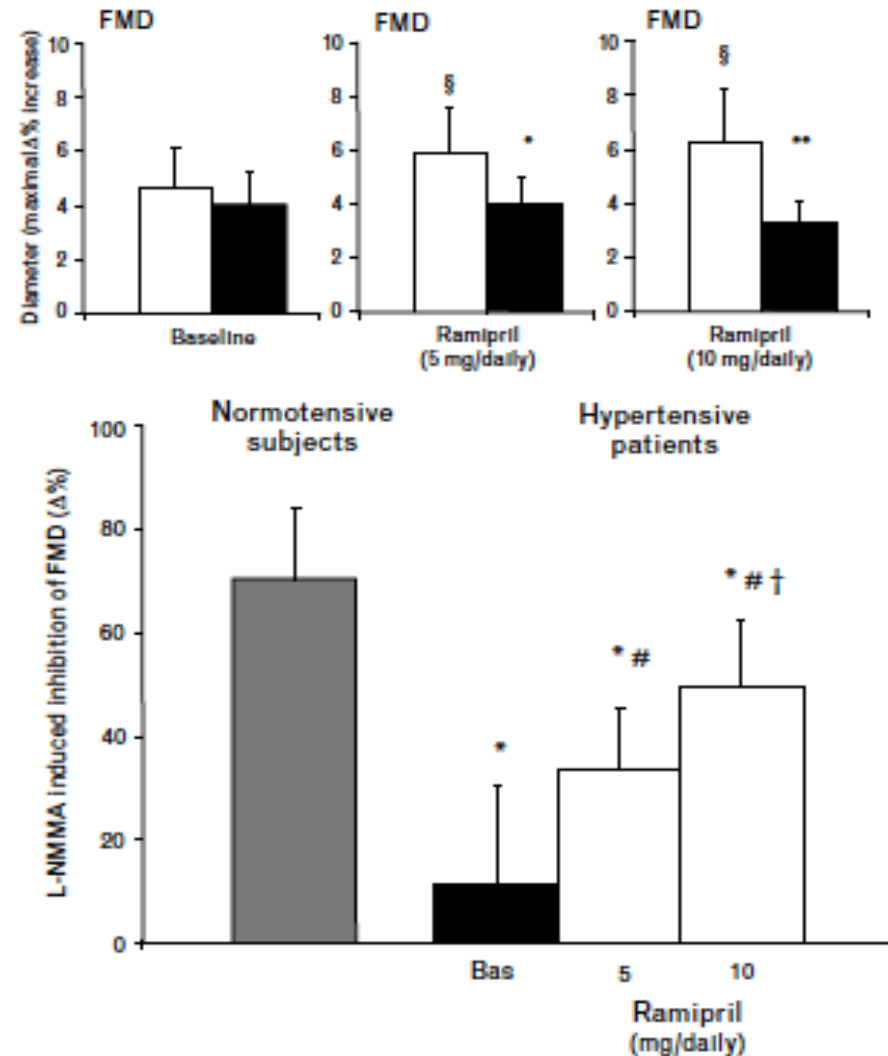
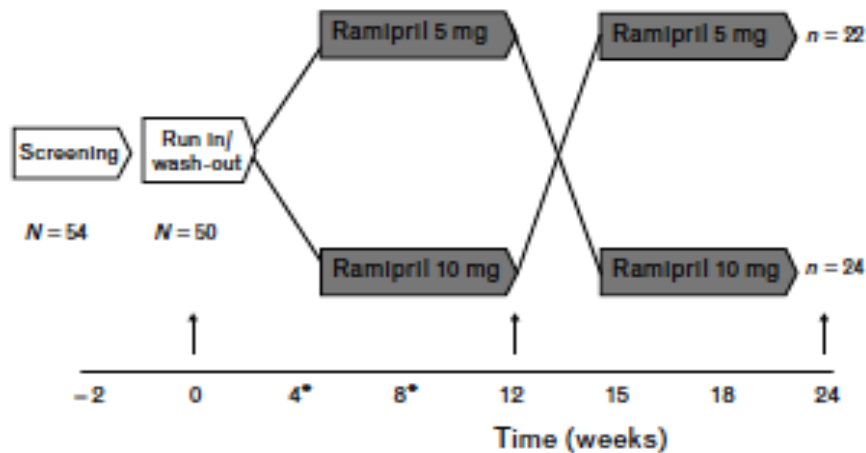
Aging, endothelial dysfunction and aerobic physical exercise



Different Effect of Antihypertensive Drugs on Conduit Artery Endothelial Function



Ramipril dose-dependently increases nitric oxide availability in the radial artery of essential hypertension patients

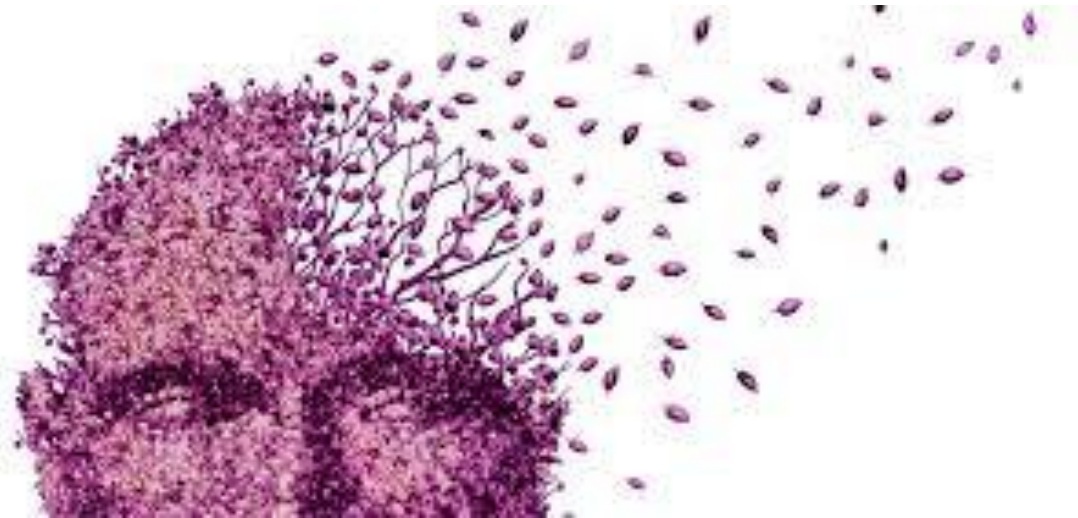


Effect of pharmacological treatment on endothelial dysfunction

	ACE-I	AT ₁ -Ant	Ca-Ant
Conduit arteries			
coronary	+	+	+
peripheral	+	-	-
Subcutaneous microcirculation	+	+	+
Muscle microcirculation			
acetylcholine, metacholine	-	-	+
bradikynin	+	no data	+

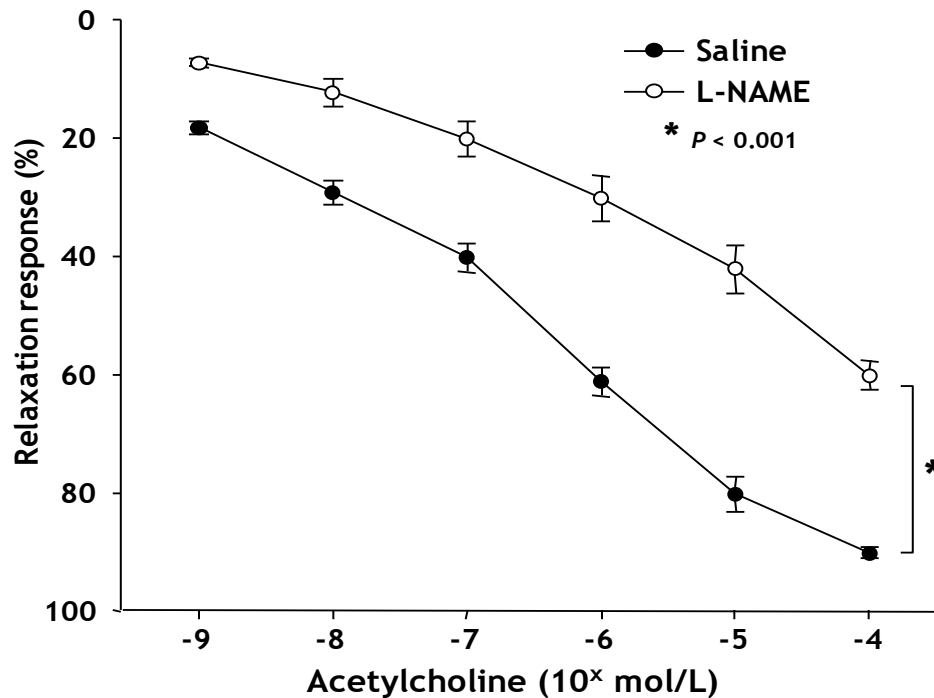
Beyond hypertension: endothelial dysfunction
is a key player in the greatest epidemics of XXI century:

- Obesity
- Dementia

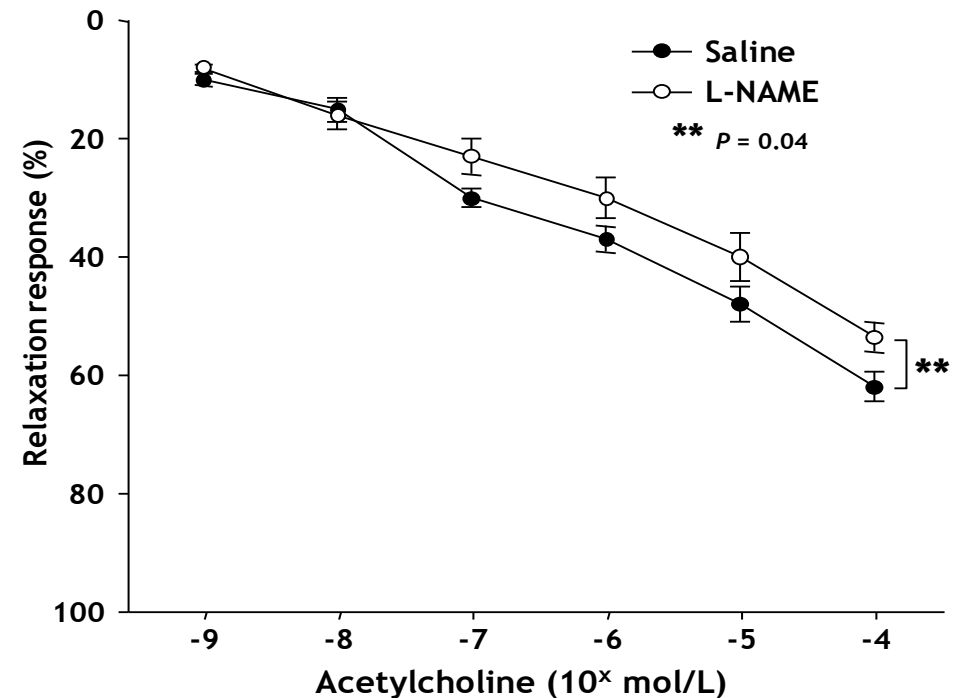


Nitric oxide availability in obese patients and control subjects

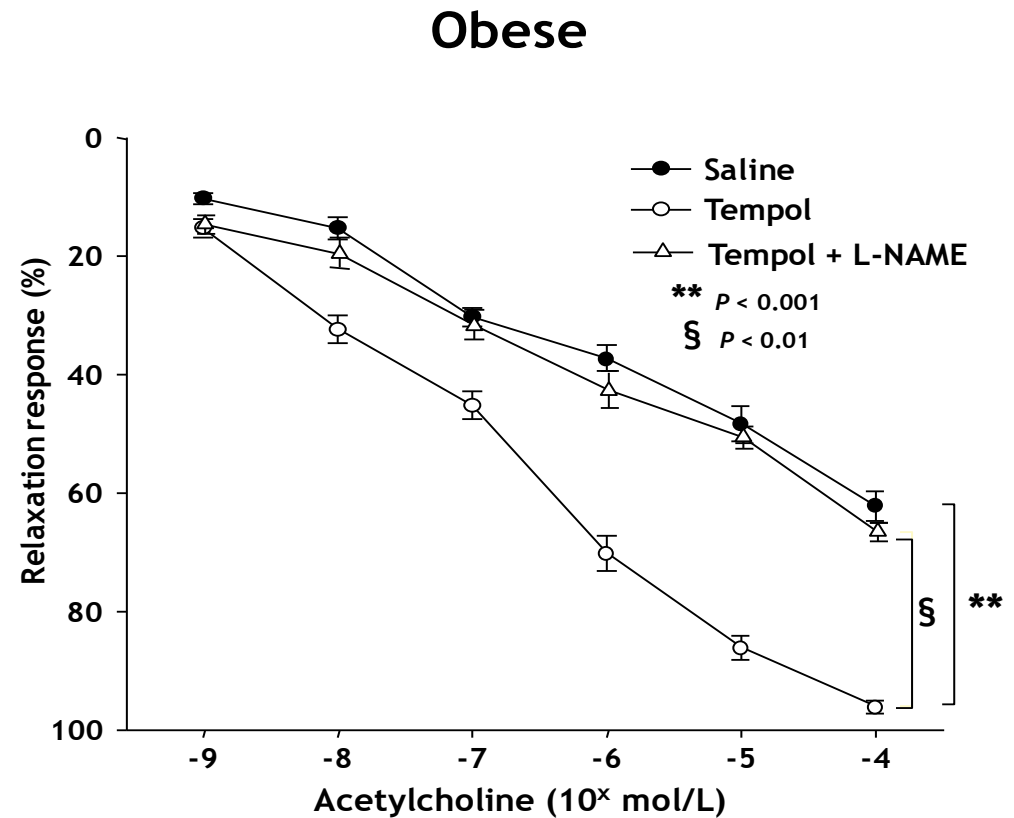
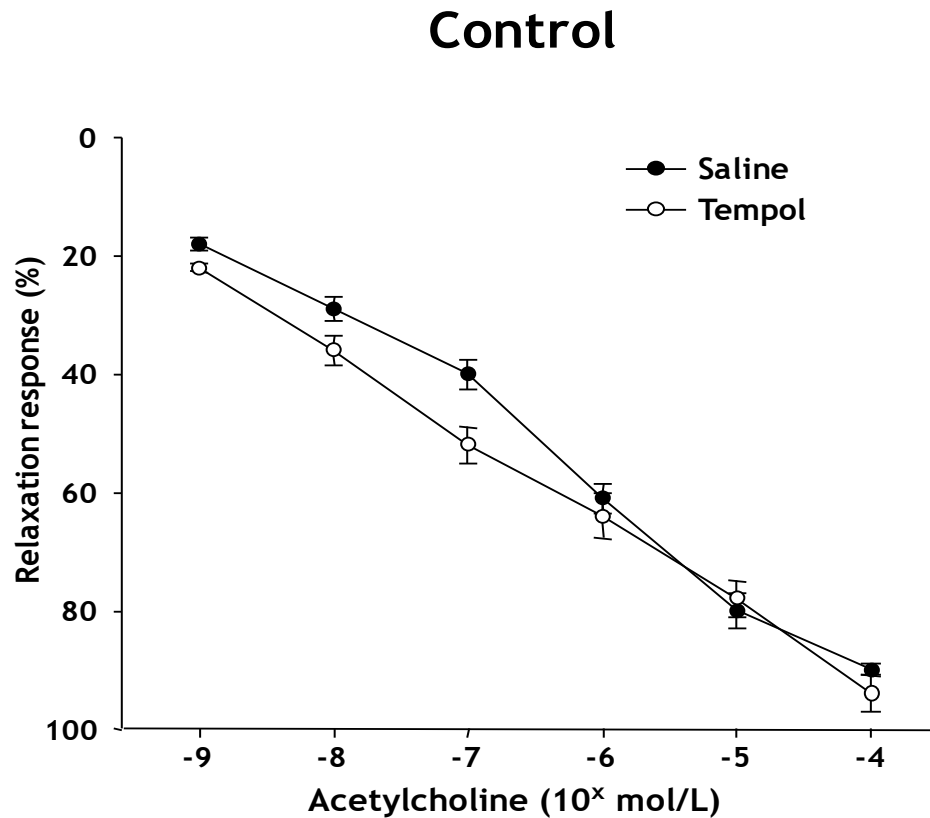
Control



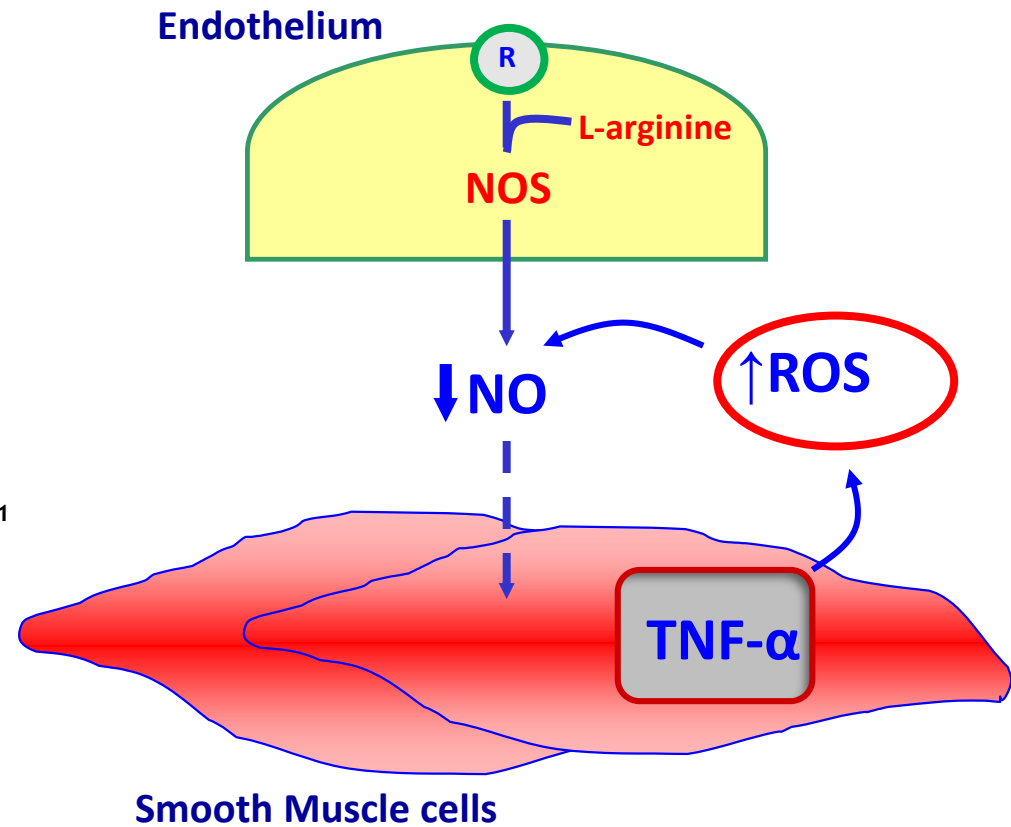
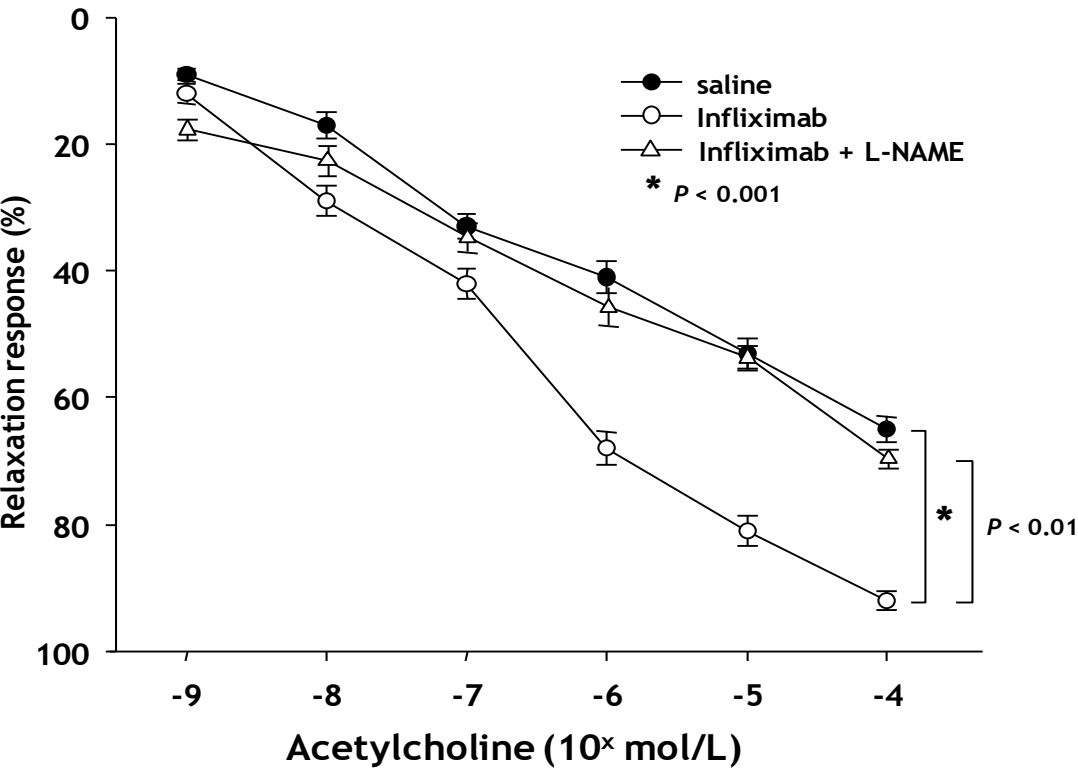
Obese



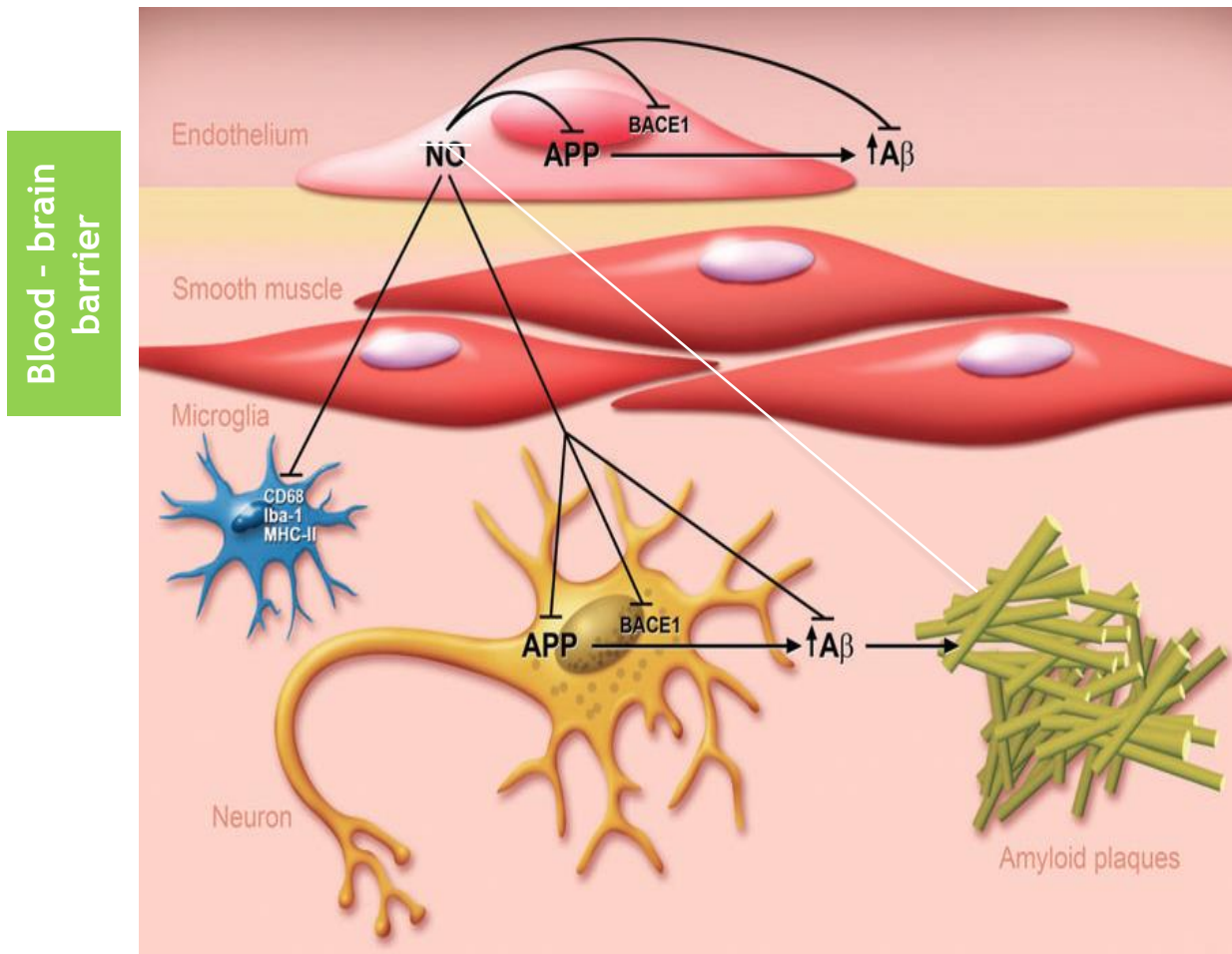
Role of ROS on endothelium-dependent relaxation in obese patients and control subjects



Role of TNF- α on endothelium-dependent relaxation and NO availability in obese patients



Endothelial nitric oxide: protector of an healthy mind



Katusic ZS and Austin SA. Eur Heart J. 2013

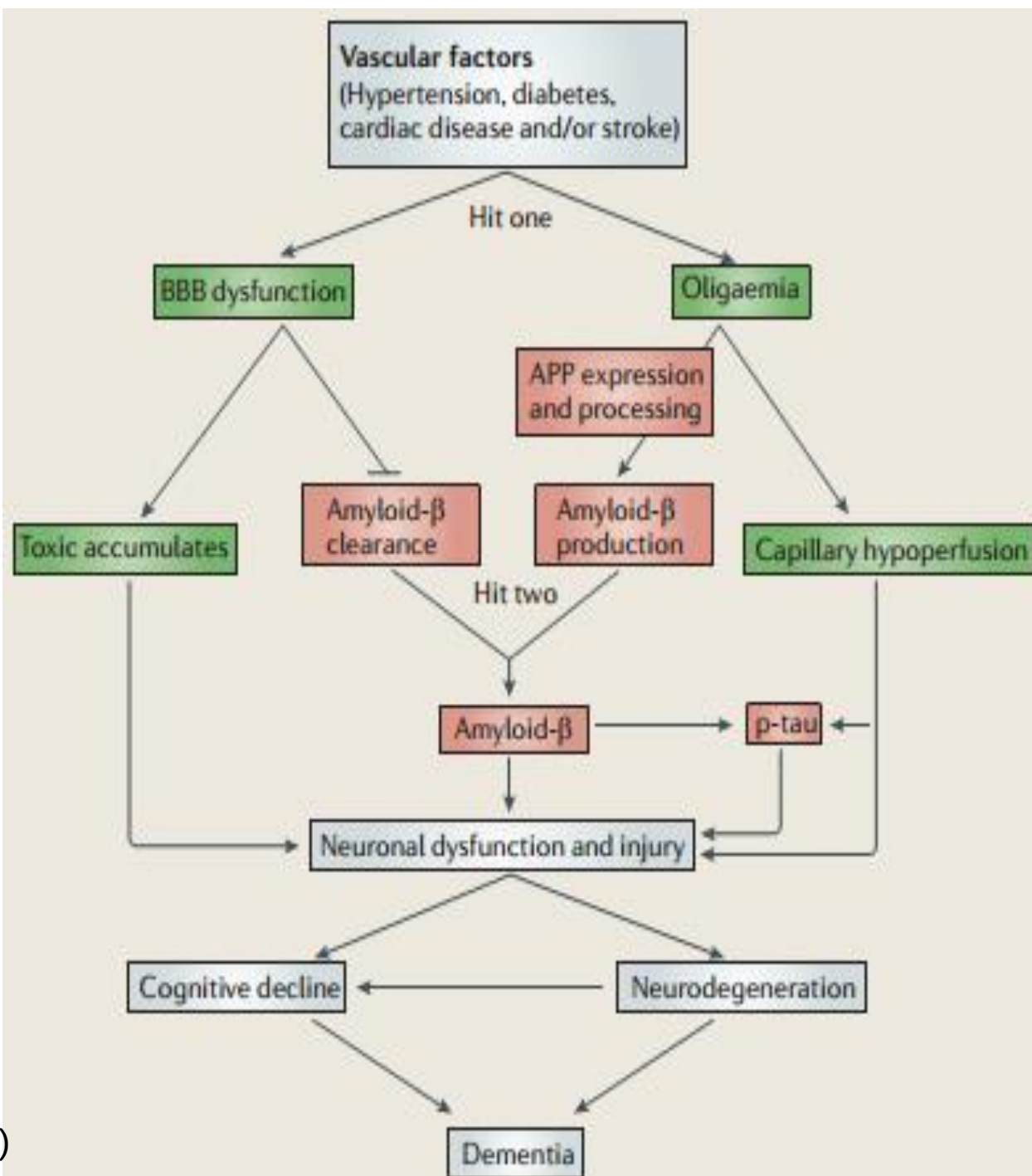
The vascular basis of dementia

Cardiovascular risk factors are involved in Amyloid-beta deposition and Alzheimer's dementia through two main mechanisms:

- Blood-brain barrier dysfunction
- Brain hypoperfusion



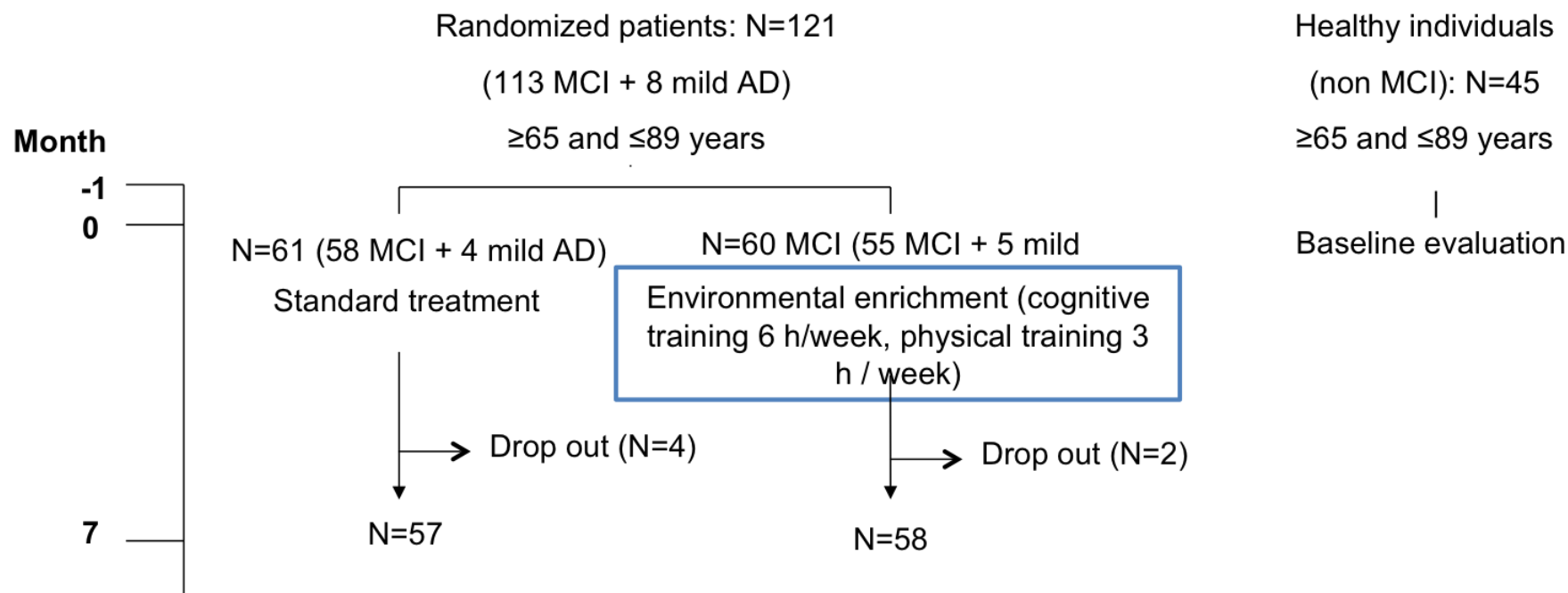
Endothelium-derived NO plays a role in both mechanisms





Cognitive-physical training in mild cognitive impairment: The Train the Brain – Mind the Vessel Study

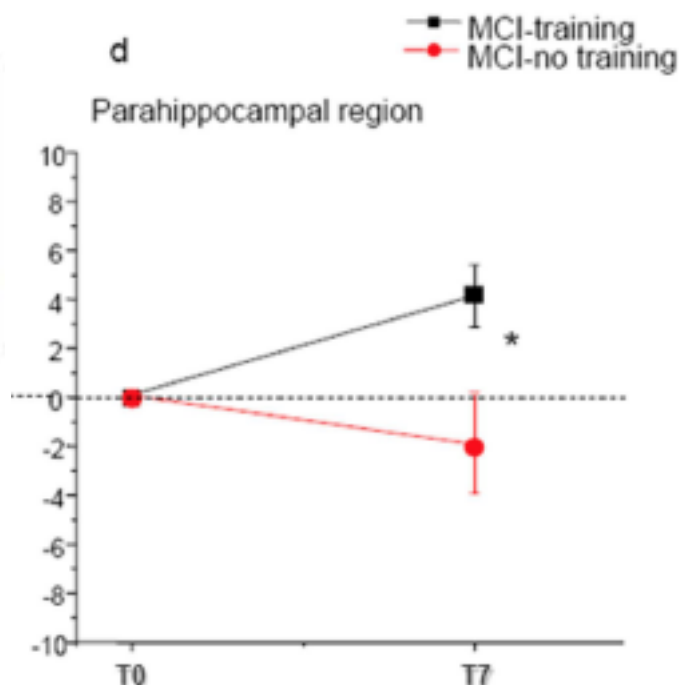
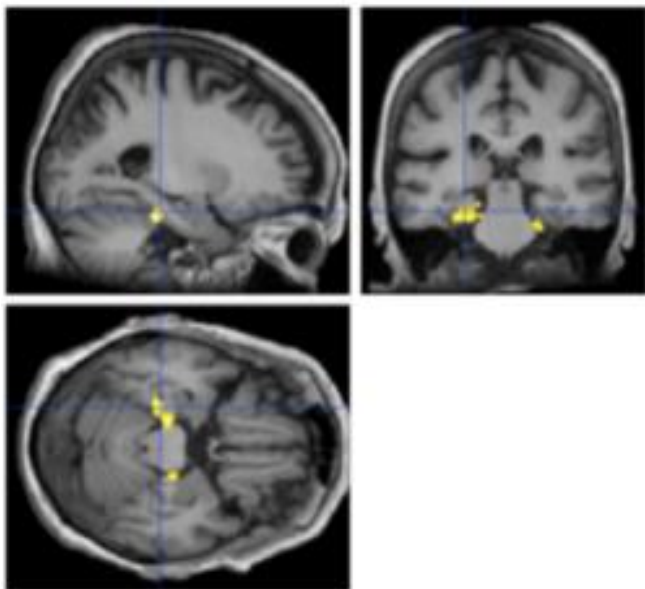
- cross-sectional study (MCI vs nonMCI) + single center, parallel group interventional study (MCI-EE vs MCI-noEE)
- clinicaltrials.gov. identifier NCT 01725178
- Funding source: Fondazione Pisa





Cognitive-physical training improves cognitive function, cerebral blood flow and endothelial function

MRI-cerebral blood flow

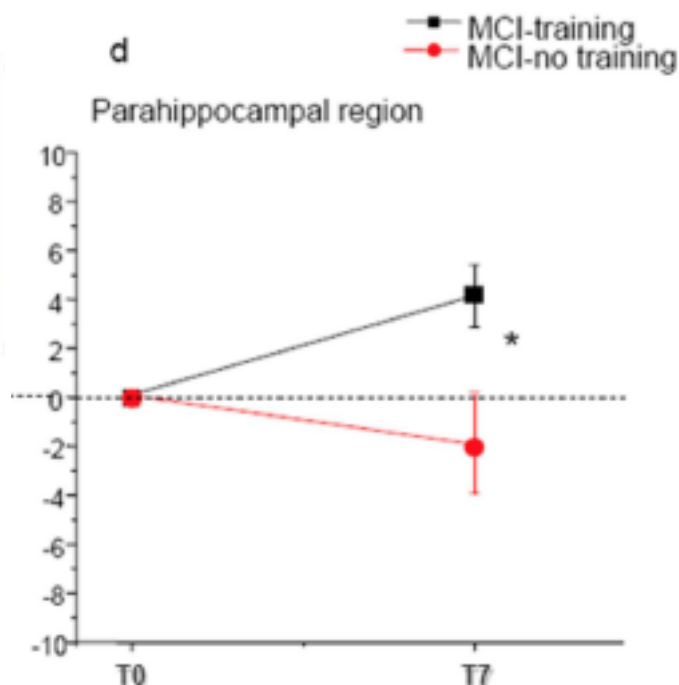
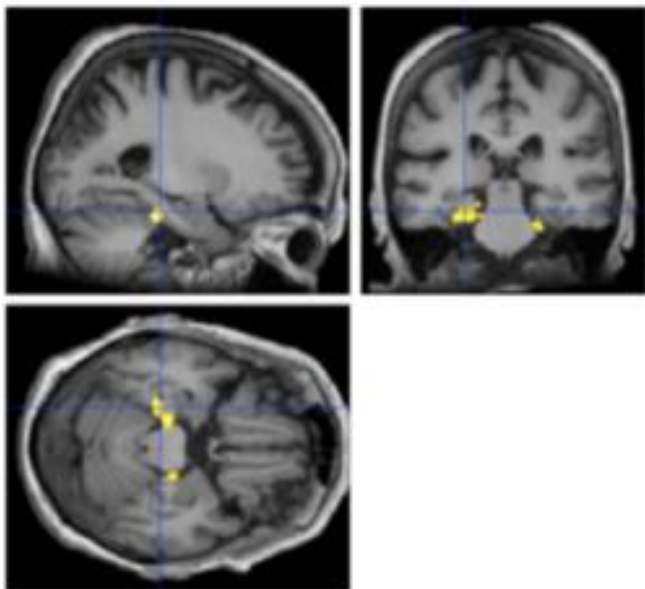


Hippocampal and parahippocampal regions are crucial for memory and processing of non-verbal / spatial information

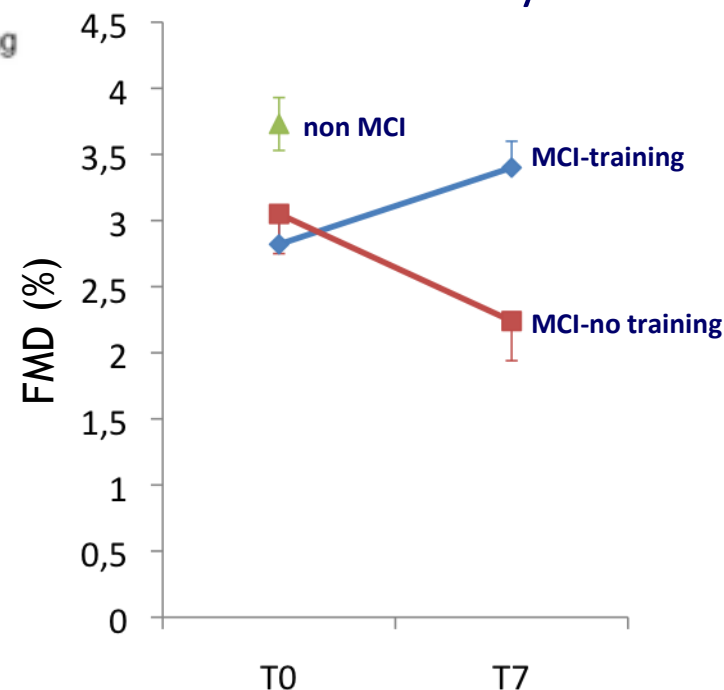


Cognitive-physical training improves cognitive function, cerebral blood flow and endothelial function

MRI-cerebral blood flow



Brachial artery FMD



Hippocampal and parahippocampal regions are crucial for memory and processing of non-verbal / spatial information

Bruno RM et al, Hypertension 2017 in press



Endothelial function is a determinant of parahippocampal blood flow in patients with mild cognitive impairment

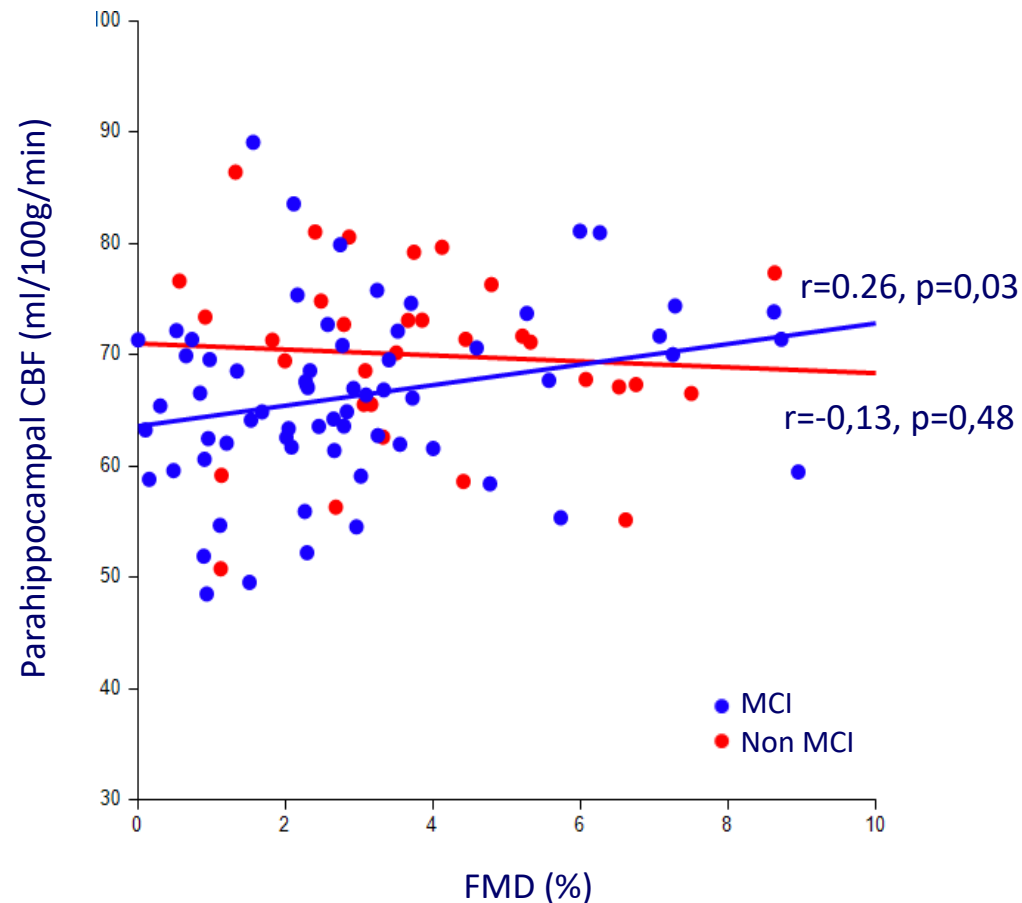
Clinical determinants: none

Vascular determinants:

- FMD ($r=0,26$, $p=0,03$)

Multiple regression model:

	beta	P value	r^2
Age	0,15	0,47	0,01
Male sex	-0,78	0,75	0,00
Mean BP	0,036	0,73	0,00
BMI	-0,39	0,17	0,03
BAD	1,44	0,36	0,01
FMD	0,93	0,04	0,06



I need to thank a lot of people!!!

My mentor Prof. Paul M. Vanhoutte



My group





My family

