CEREBRAL BLOOD FLOW AND METABOLISM

Part 3-2018

Cerebral Circulation

- Blood flow to CNS
  - delivers O_2, glucose, nutrients
  - removes CO_2, lactic acid, metabolites
- Cerebral vasculature
  - unique anatomy & physiology
  - safety mechanisms
- Brain highly vulnerable to disrupted blood flow

Vascular Endothelium

It has many important roles to maintain vascular homeostasis:

- Vascular tone regulation
- Vascular smooth muscle cell proliferation
- Inflammatory responses
- Haemostasis

It produces and releases vasoactive, thromboregulatory and growth factor substances

What is Endothelial Function?

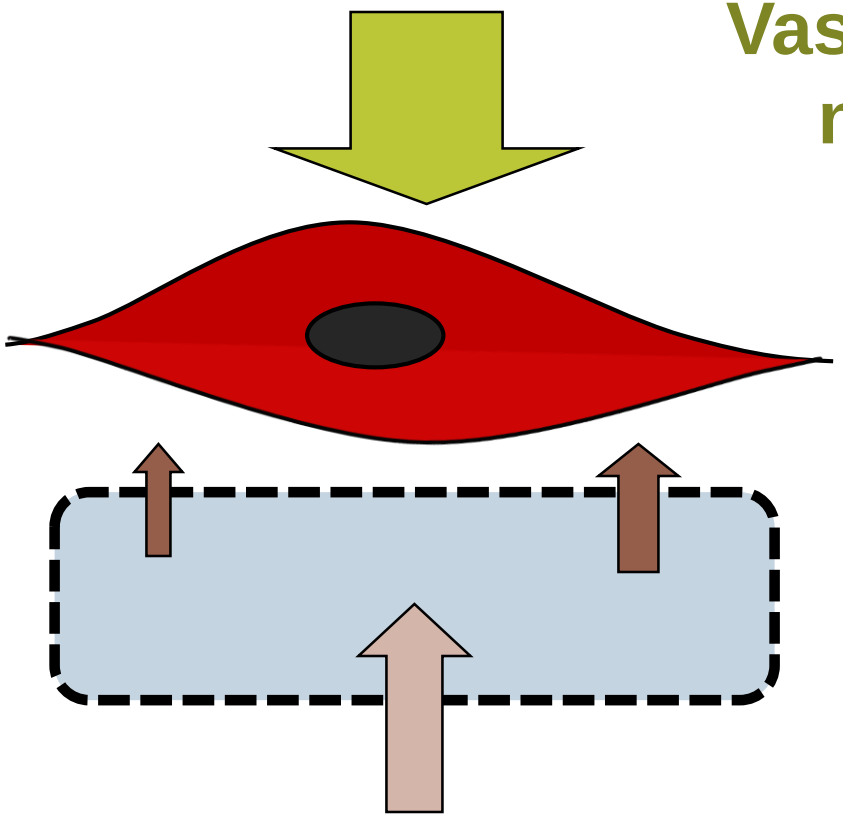
The vascular endothelium serves multiple functions:

1) Regulates fluid and molecule traffic between blood and tissues
2) Serves as an anti-coagulant (anti-clotting) surface
3) Contributes to vascular homeostasis and repair
4) Plays a central role in angiogenesis and tissue wound healing
5) Plays a vital role in vascular tone and blood flow regulation

Assessing this last function is the most practical way of measuring endothelial function.

Vascular Regulation

PARENCHYMA



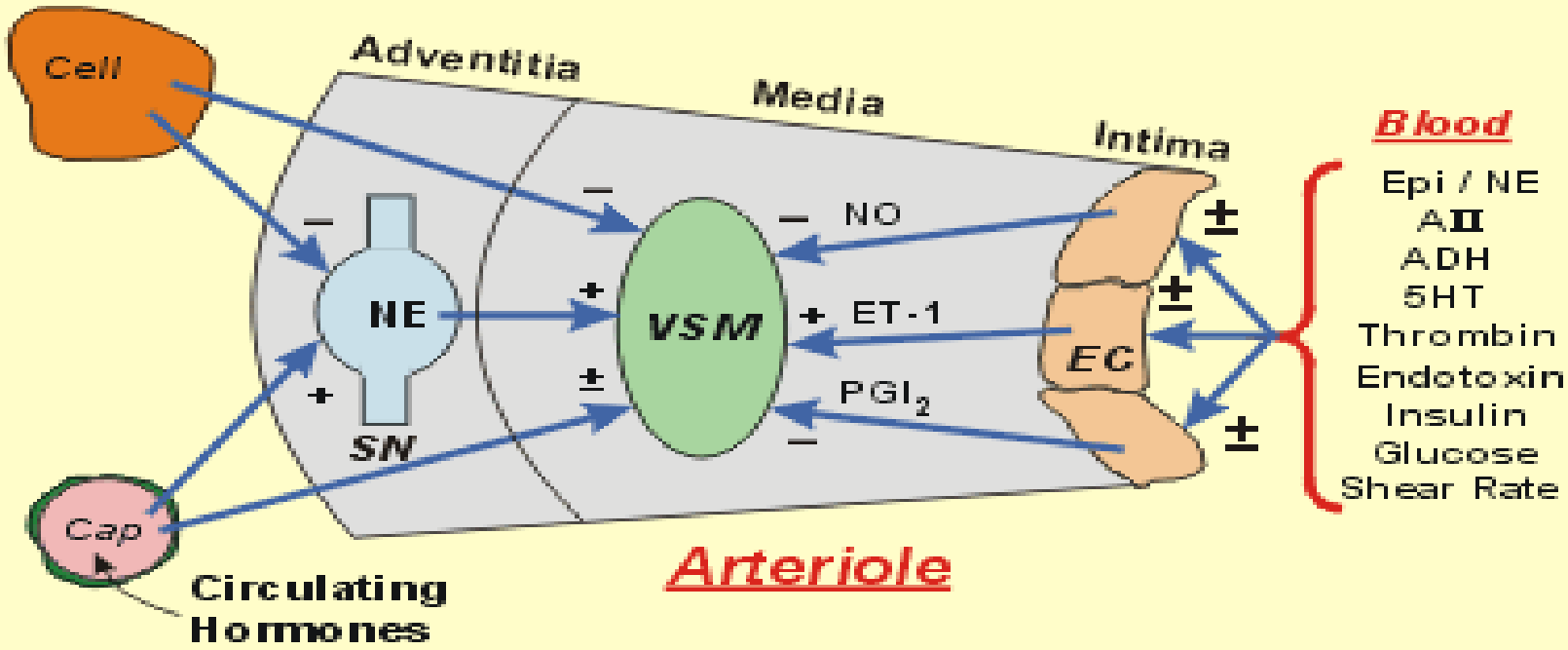
Vasoactive metabolites neurotransmitters

Vascular smooth muscle

ENDOTHELIUM

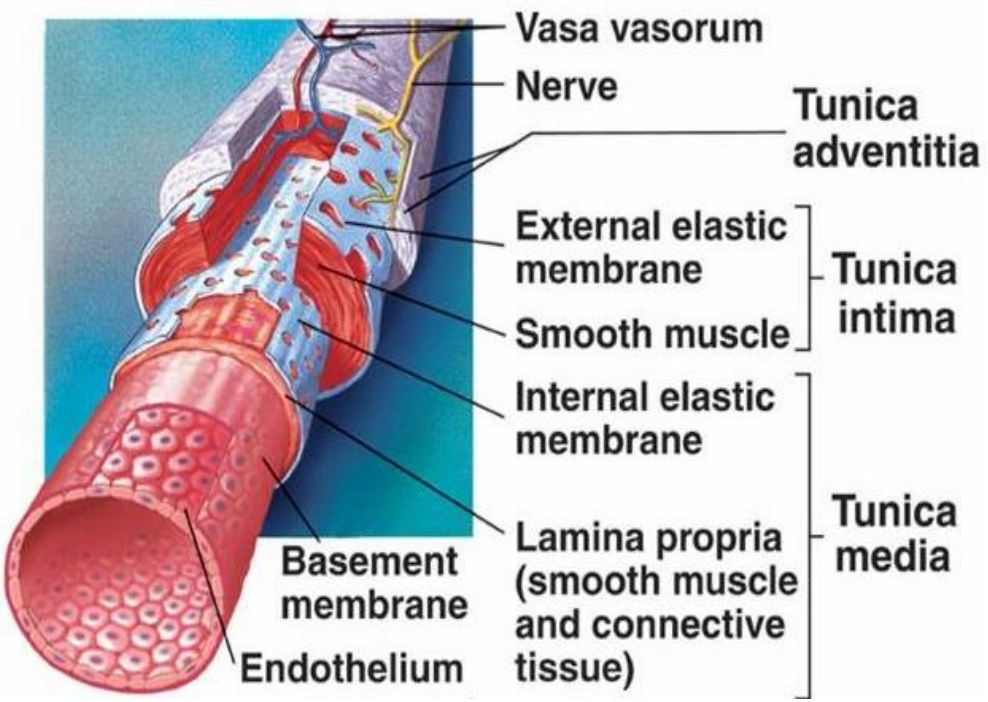
LUMEN

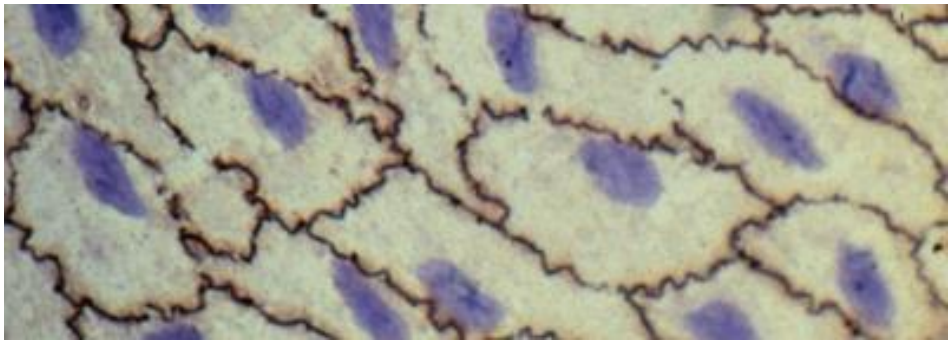
Vascular Regulation



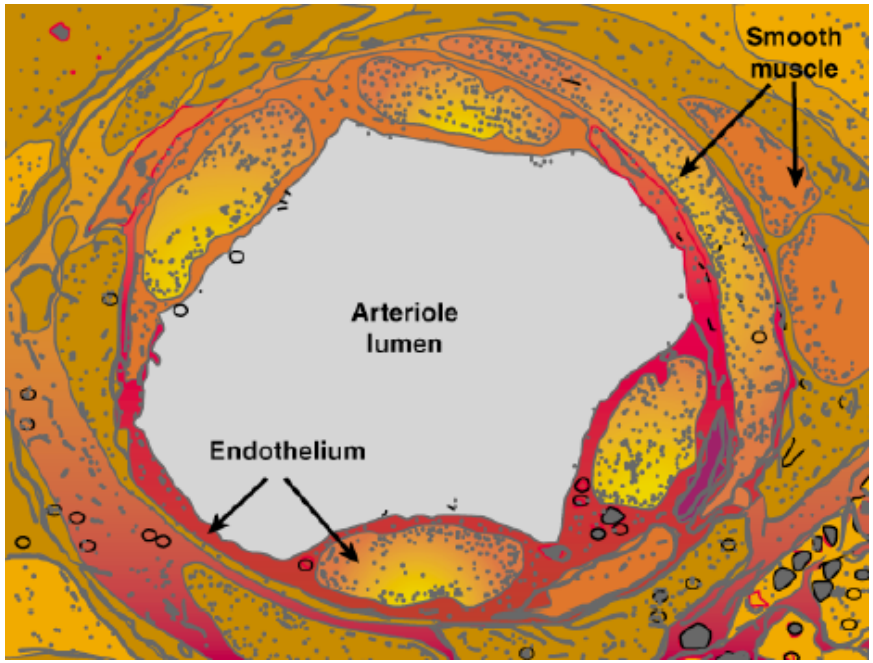
Endothelial and non-endothelial factors acting upon vascular smooth muscle in arterioles. *Abbreviations:* Cap, capillary; SN, sympathetic nerve; NE, norepinephrine; VSM, vascular smooth muscle; NO, nitric oxide; ET-1, endothelin-1; PGI_2, prostacyclin; EC, endothelial cell; Epi, epinephrine; AII, angiotensin II, ADH, antidiuretic hormone; 5HT, serotonin; + and -, contraction and dilation, respectively.

The Normal Vascular Endothelium

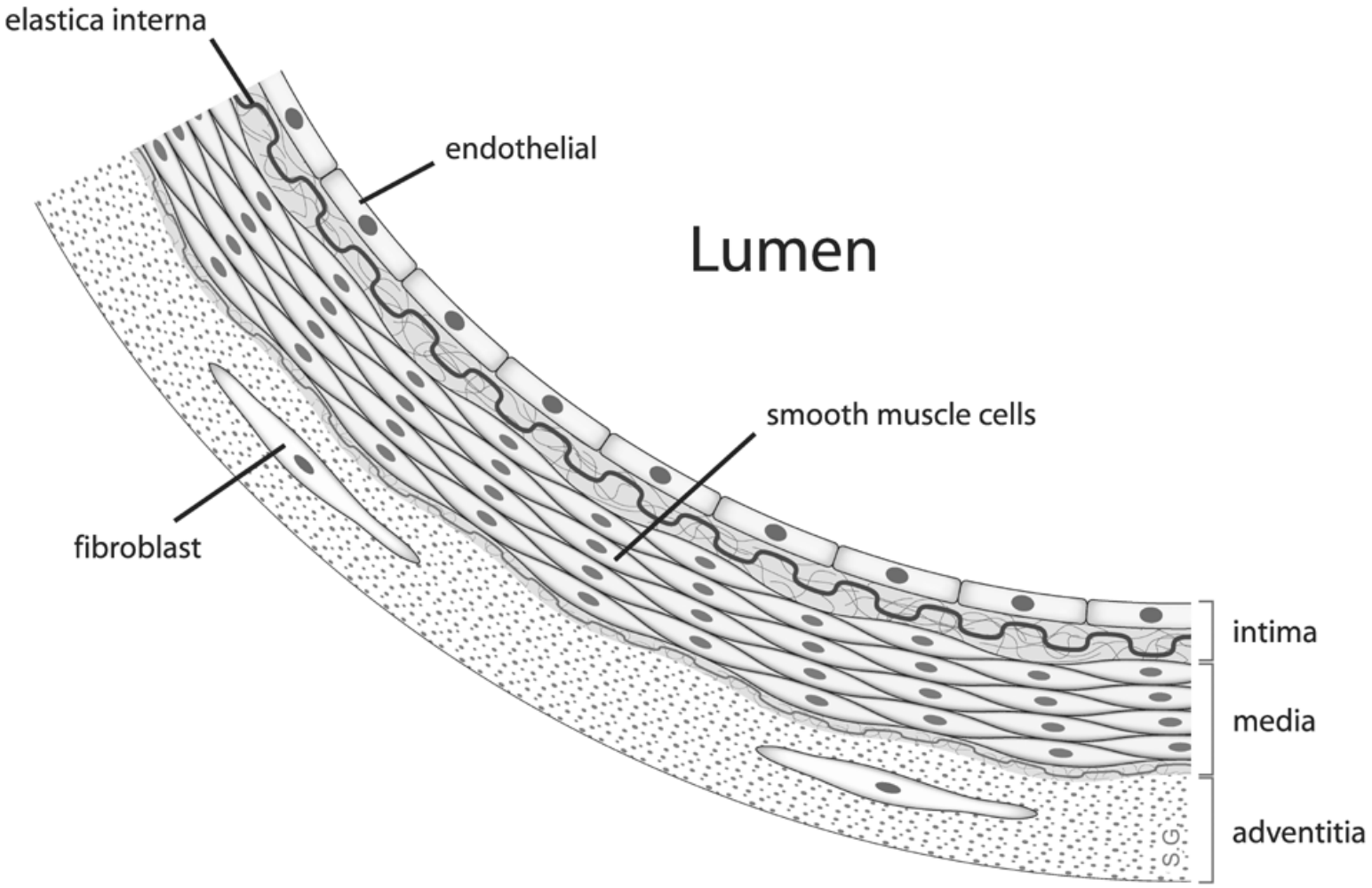




Historically viewed as a passive vascular lining



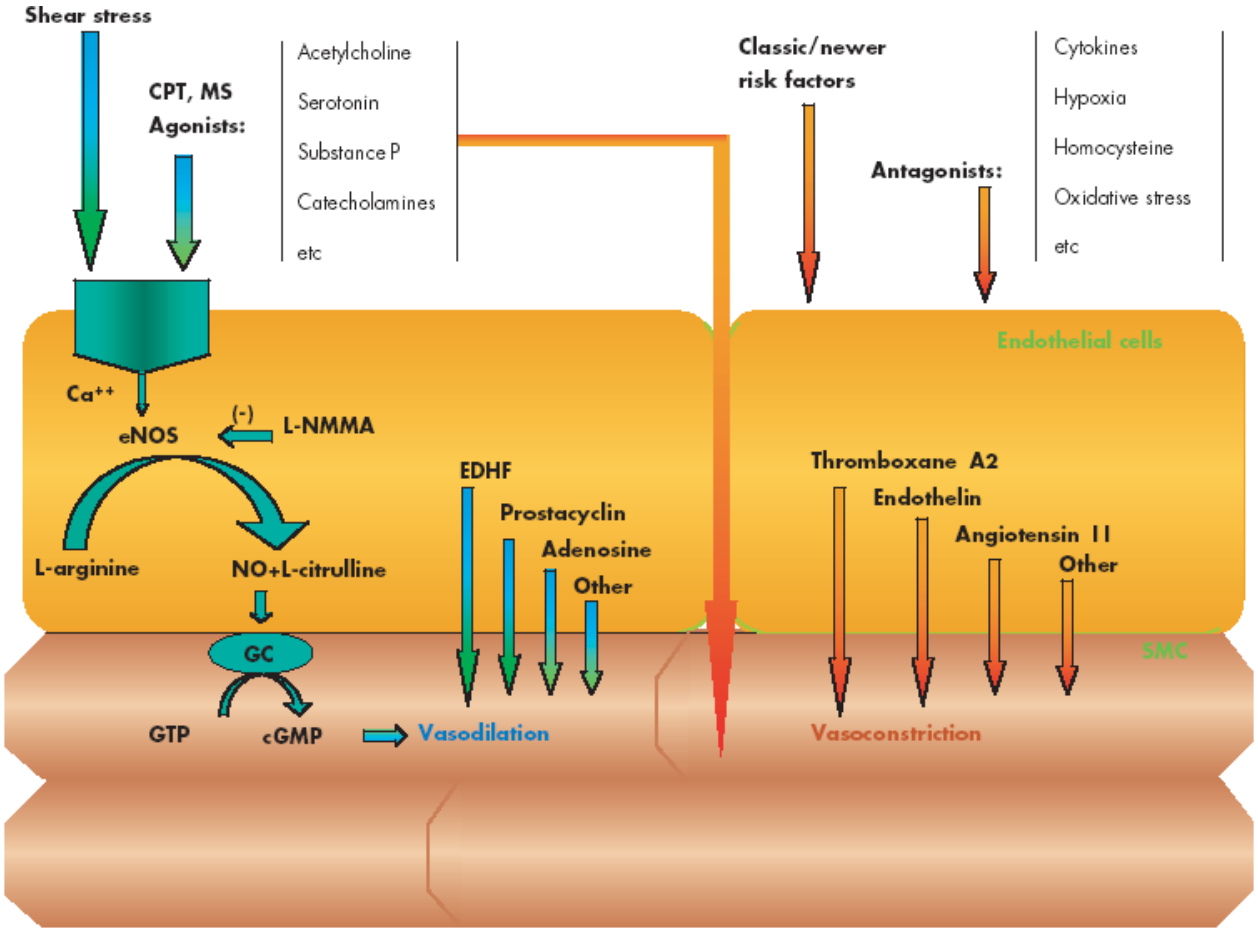
Structure of Vessels



Endothelial Cell Function

- Maintaining the vascular tone:

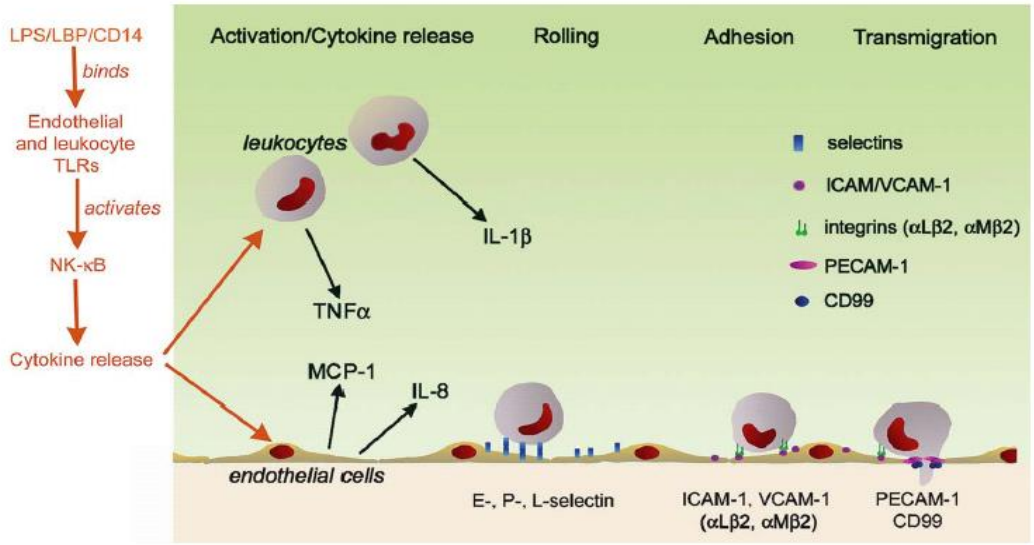
Vasodilation and Vasoconstriction



Tousoulis et al., Heart 2005; 91: 353-358.

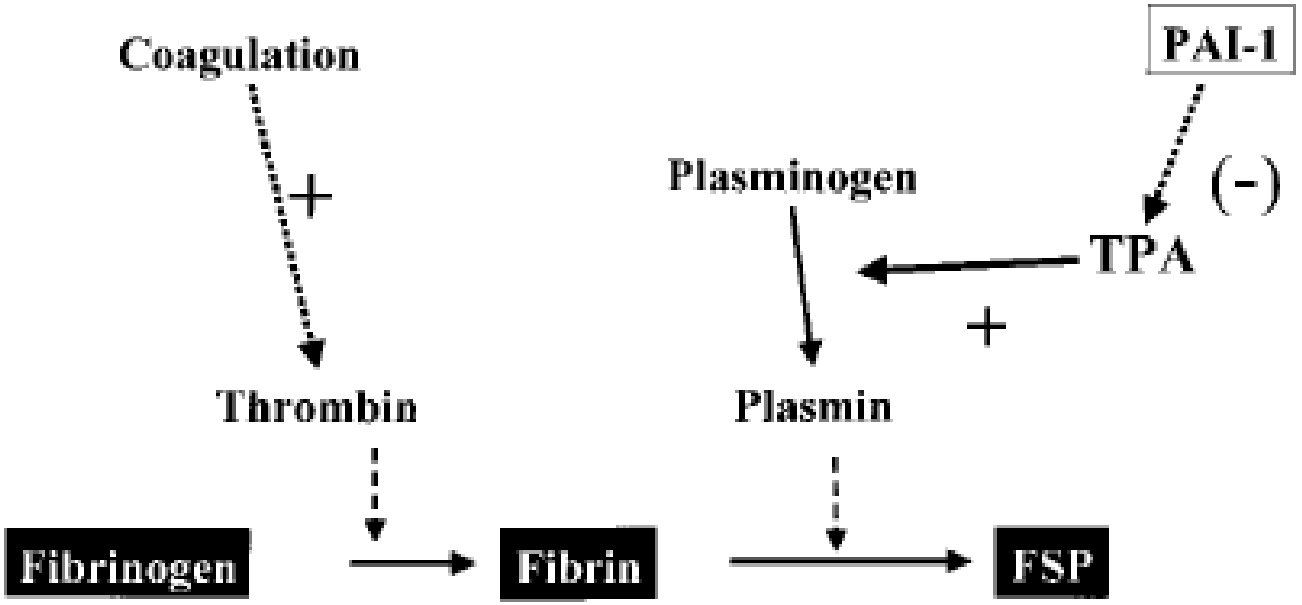
Endothelial Cell Functions

Functional targets	Physiological action/Mediators	
Growth	Stimulation	Inhibition
	PDGF, FGF, IGF-1, ET, AII	NO, PGI_2, TGF
Inflammation	Proinflammatory	Antiinflammatory
	Adhesion molecules Selectin-E, VCAM-1, ICAM-1, PECAM-1	



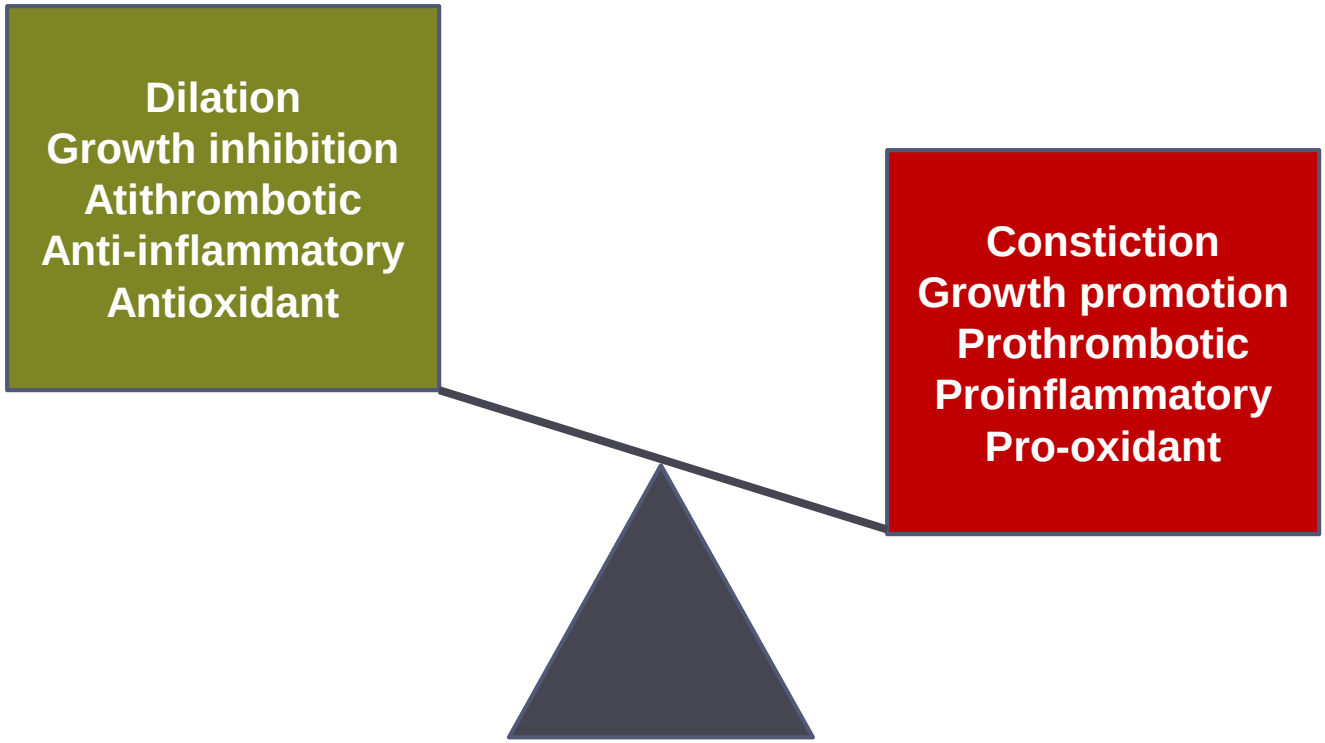
dothelial cell functions

Functional targets	Physiological action/Mediators	
Hemostasis	Prothrombotic	Antithrombotic
	PAI-1	PGI_2, TPA



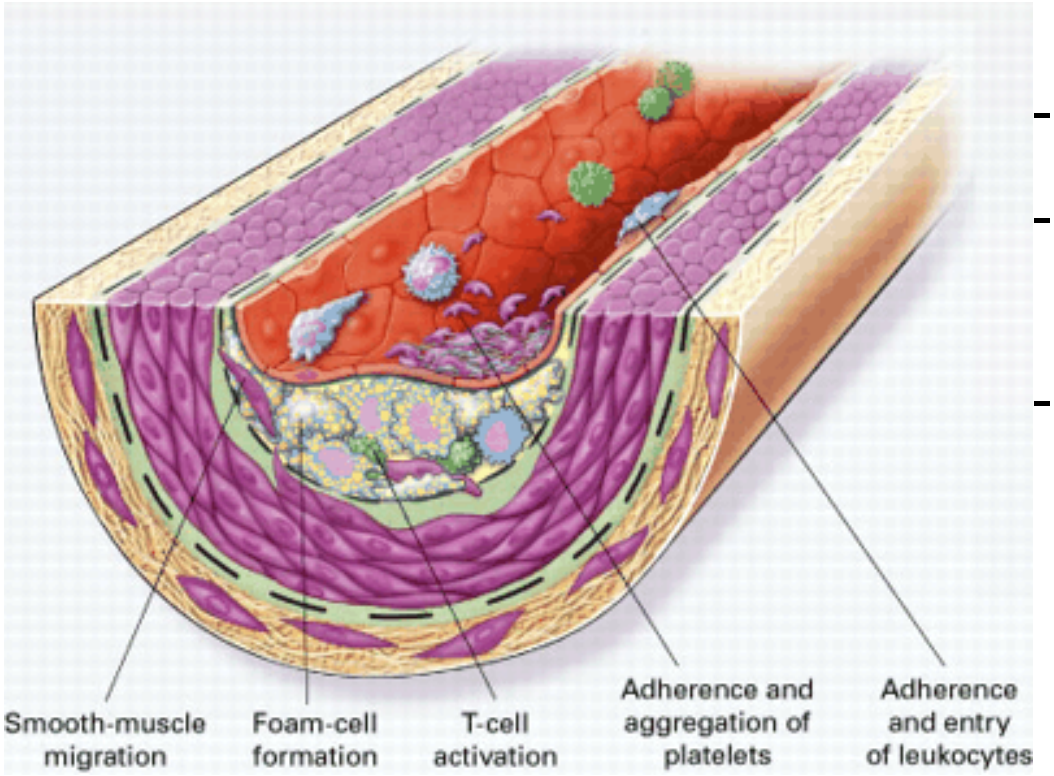
Calles-Escandon and Cipolla, Endocrine Rev 2001; 22: 36-52.

Factors Affecting Vascular Tone and Structure



Endothelium maintains vascular health

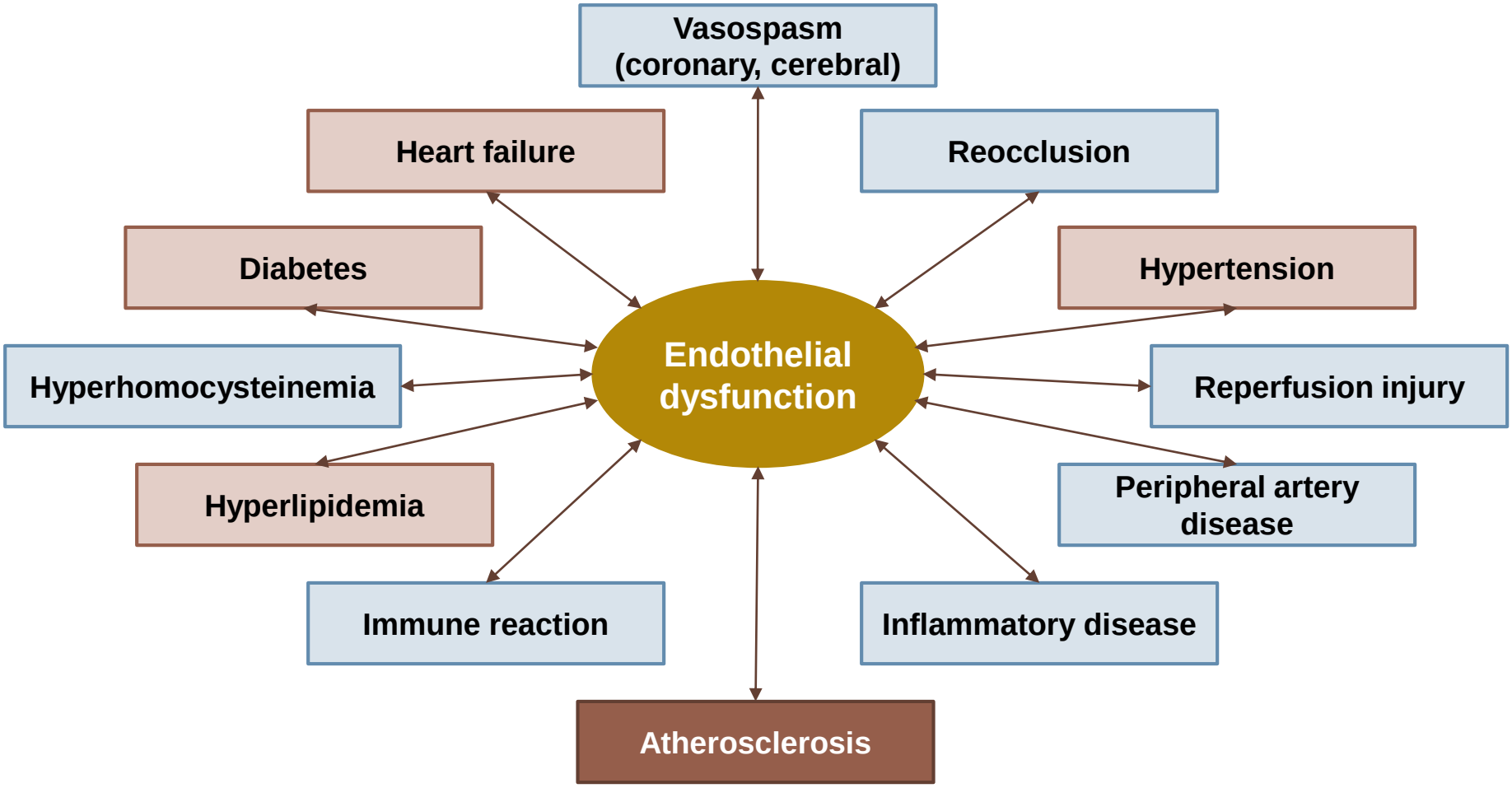
Endothelial Dysfunction



- pathological conditions
- altered anticoagulant & anti-inflammatory properties
- impaired modulation of vascular growth & dysregulation of vascular remodeling

An impairment of endothelium-dependent vasorelaxation caused by a loss of NO bioactivity in the vessel wall

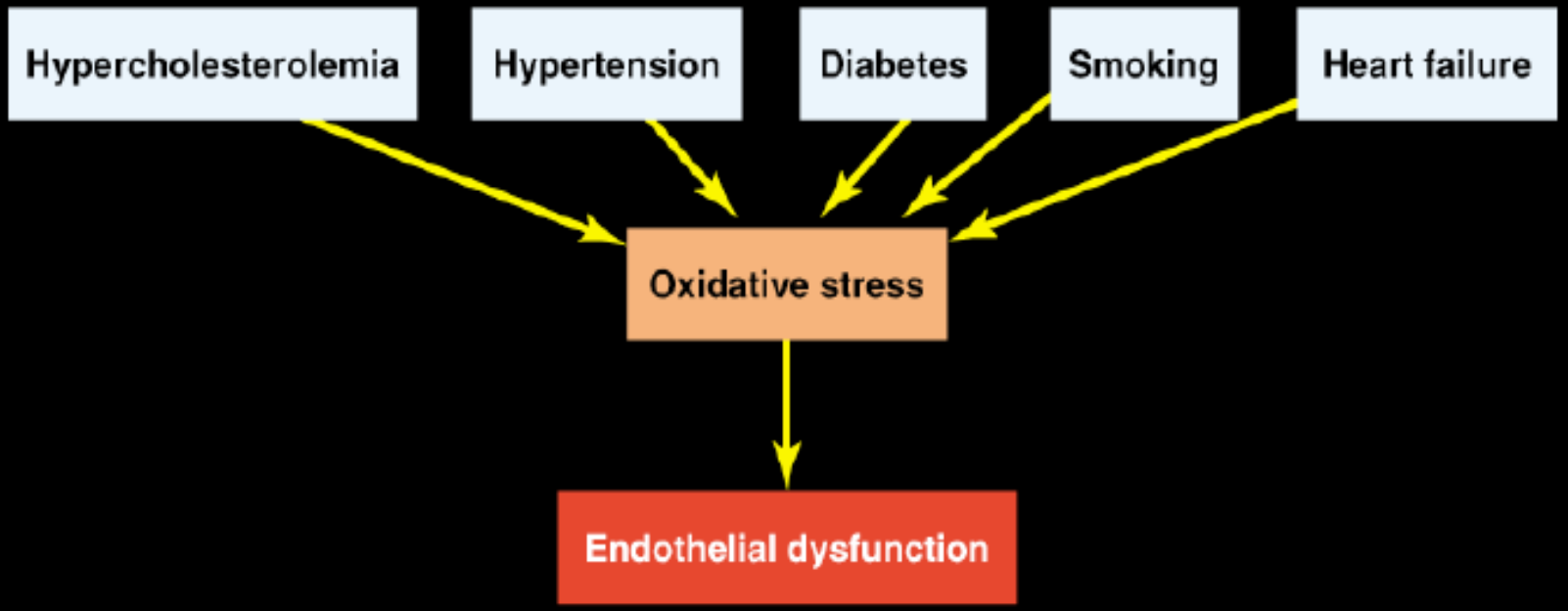
Causes and Consequences of Endothelial Dysfunction



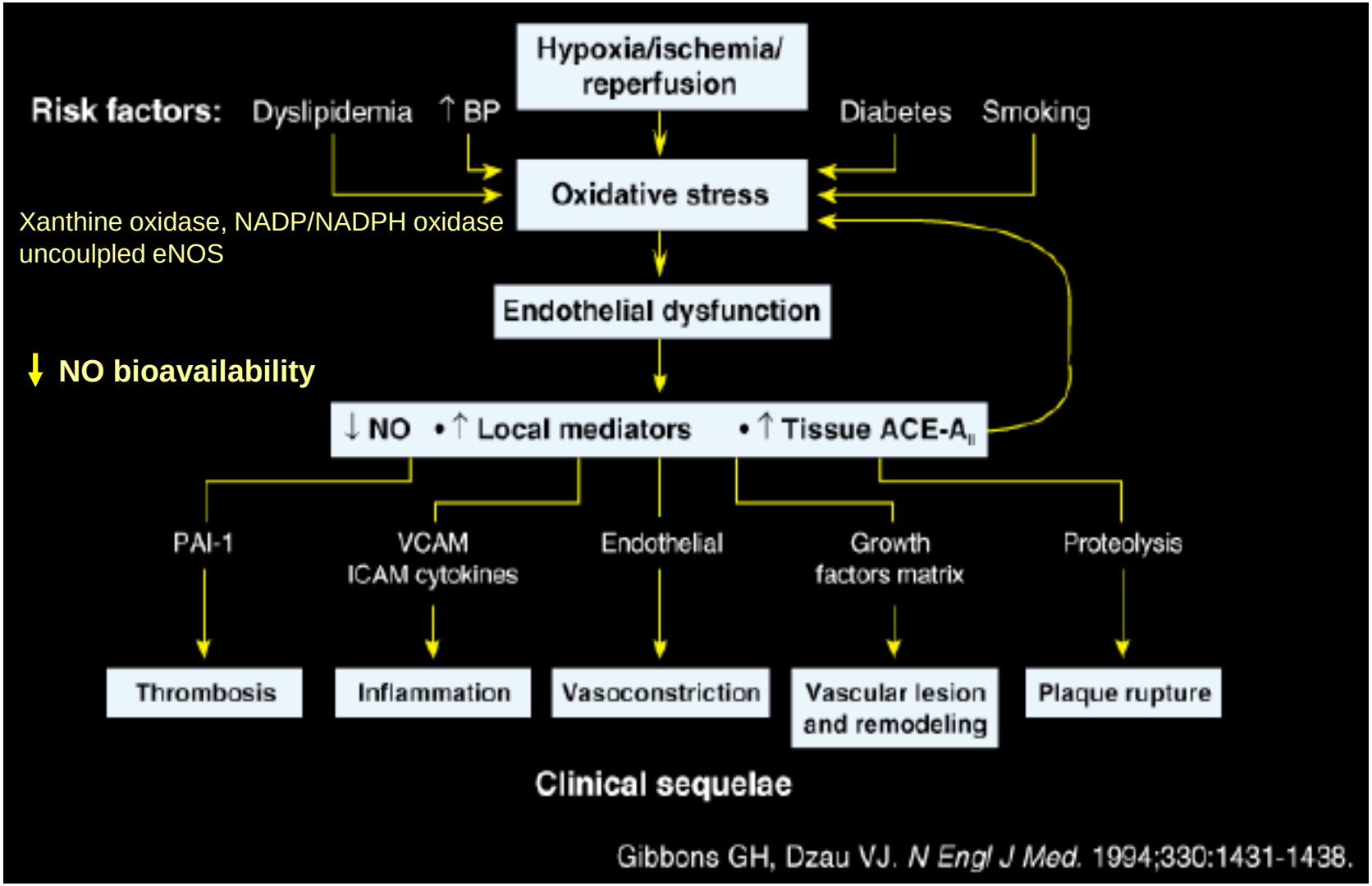
Rubanyi GM. J Cardiovasc Pharmacol. 1993;22(suppl 4):S1-S4.

VBWG

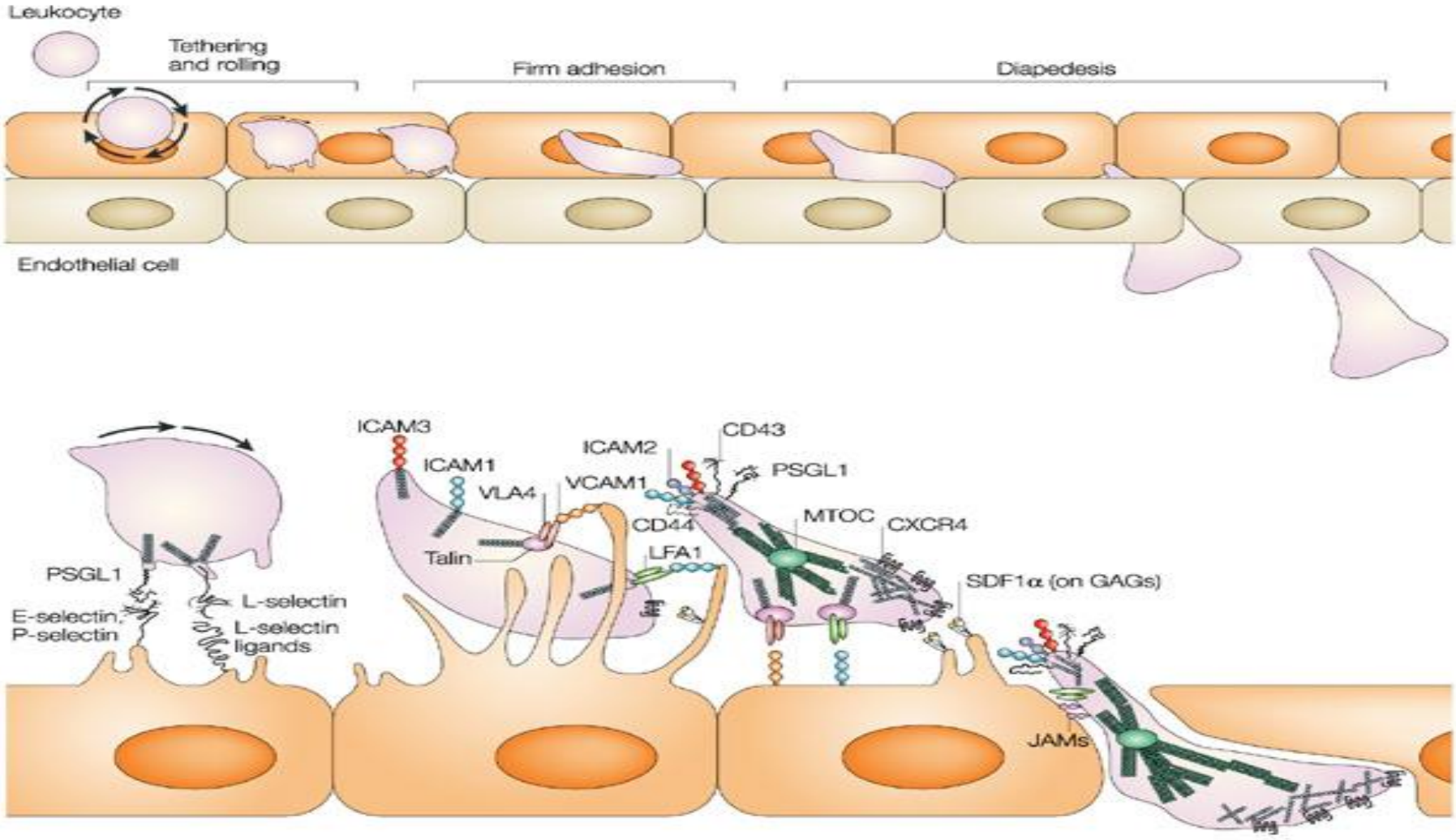
Risk factors and endothelial dysfunction: Mediator role of oxidative stress



Unifying Model: Endothelial Dysfunction to Cardiovascular Disorder



The Role of Endothelium in Leukocyte Function



therefore...

Impaired Vascular Reactivity

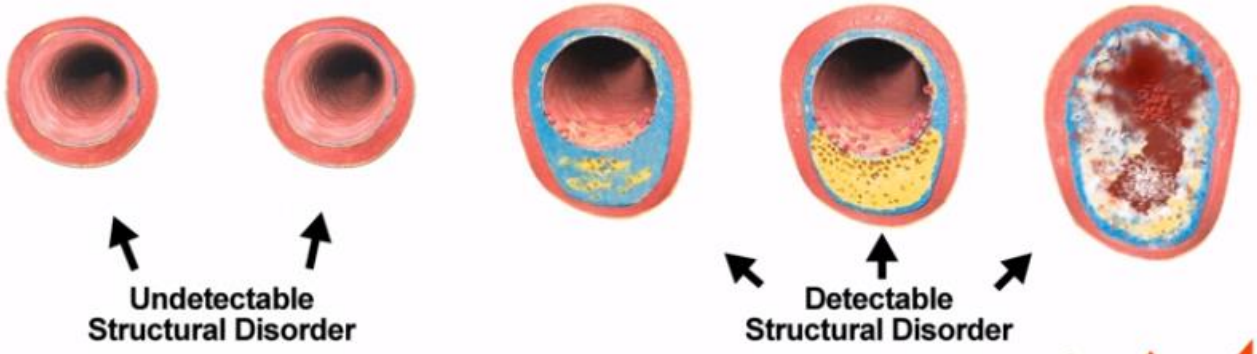
Vascular Dysfunction

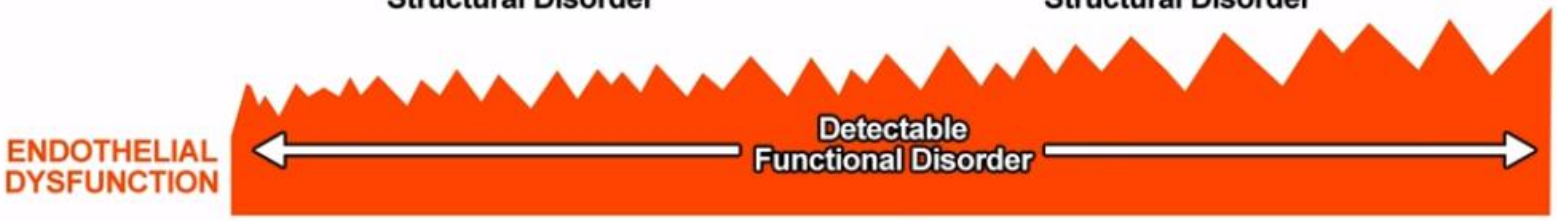
Endothelial Dysfunction

are used here interchangeably.

Natural Course of Atherosclerotic CVD (heart attack, stroke, PAD,....)

Unlike endothelial dysfunction, structural disorders in arteries occur slowly, appear later in life, and do not respond quickly to treatments.





Endothelial dysfunction precedes structural disorders, plaque build up, and clinical events.

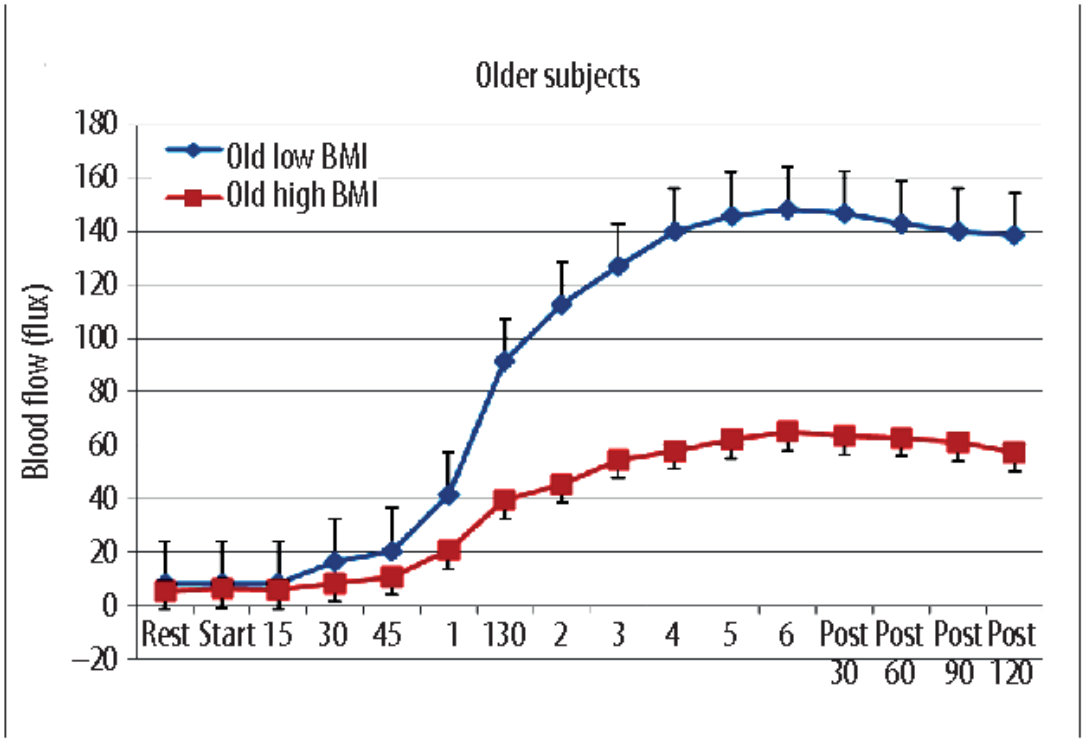


Figure 2. The average blood flow in the skin above the quadriceps muscle in 10 older subjects with low BMI and 10 with high BMI at rest, during 6 minutes of exposure to heat and for 2 minutes after heat

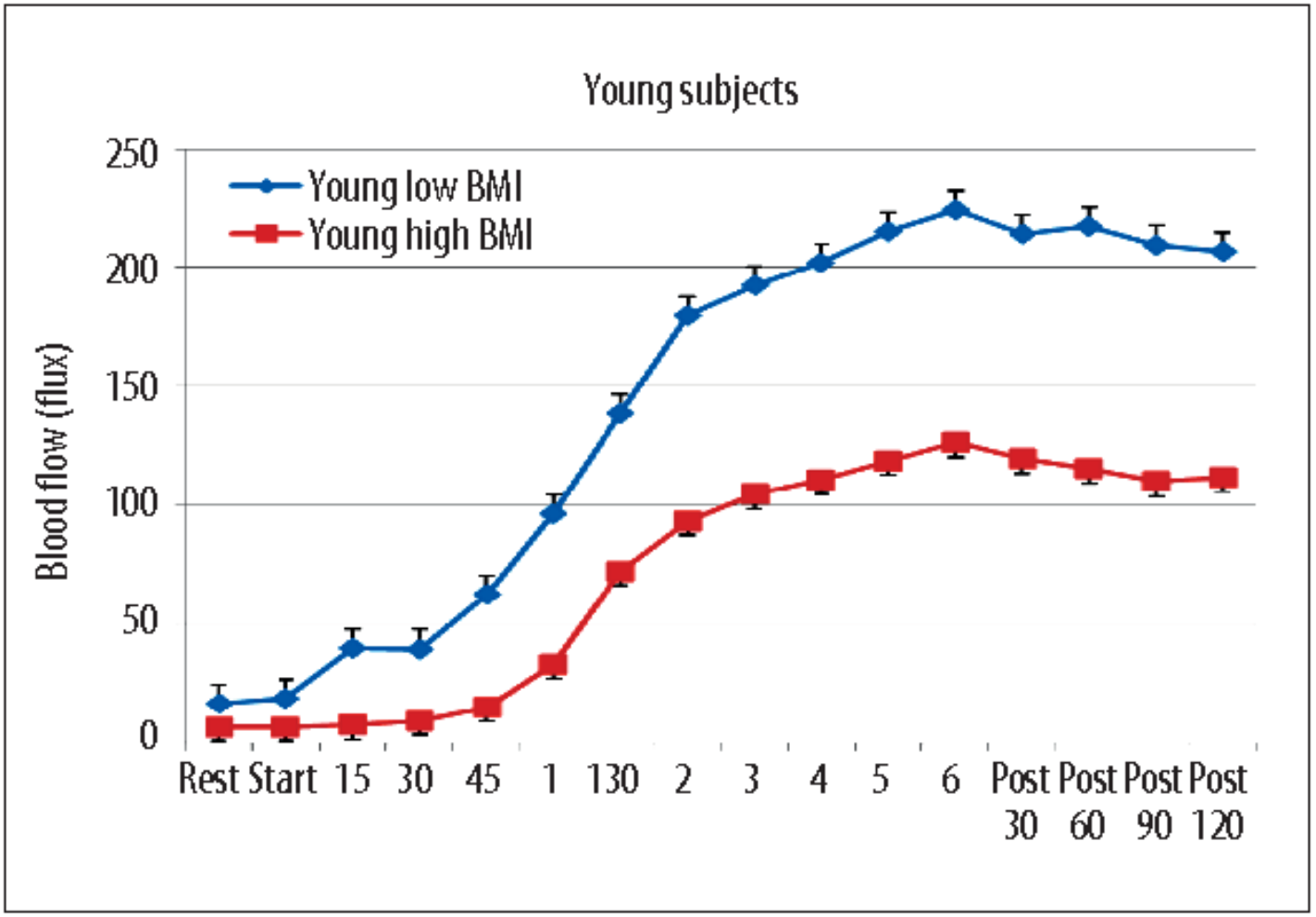
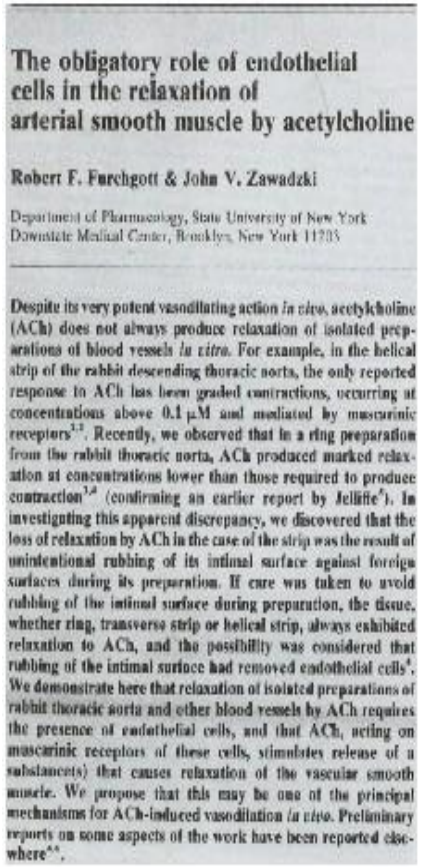


Figure 1. The average blood flow in the skin above the

How Can We Assess the Endothelial Function?

The Nobel Prize in Physiology or Medicine 1998
Robert F. Furchgott, Louis J. Ignarro, Ferid Murad

Furchgott, R., Zawadzki, J., “The Obligatory Role of Endothelial Cells in the Relaxation of Arterial Smooth Muscle by Acetylcholine,” Nature, vol. 288, Nov. 27, 1980, pp. 373-376;



The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine

Robert F. Furchgott & John V. Zawadzki

Department of Pharmacology, State University of New York Downstate Medical Center, Brooklyn, New York 11203

Despite its very potent vasodilating action *in vivo*, acetylcholine (ACh) does not always produce relaxation of isolated preparations of blood vessels *in vitro*. For example, in the helical strip of the rabbit descending thoracic aorta, the only reported response to ACh has been graded contractions, occurring at concentrations above 0.1 μM and mediated by muscarinic receptors[1,2]. Recently, we observed that in a ring preparation from the rabbit thoracic aorta, ACh produced marked relaxation at concentrations lower than those required to produce contraction[3,4] (confirming an earlier report by Jelliffe[5]). In investigating this apparent discrepancy, we discovered that the loss of relaxation by ACh in the case of the strip was the result of unintentional rubbing of its intimal surface against foreign surfaces during its preparation. If care was taken to avoid rubbing of the intimal surface during preparation, the tissue, whether ring, transverse strip or helical strip, always exhibited relaxation to ACh, and the possibility was considered that rubbing of the intimal surface had removed endothelial cells[4]. We demonstrate here that relaxation of isolated preparations of rabbit thoracic aorta and other blood vessels by ACh requires the presence of endothelial cells, and that ACh, acting on muscarinic receptors of these cells, stimulates release of a substance(s) that causes relaxation of the vascular smooth muscle. We propose that this may be one of the principal mechanisms for ACh-induced vasodilation *in vivo*. Preliminary reports on some aspects of the work have been reported elsewhere[4,6].

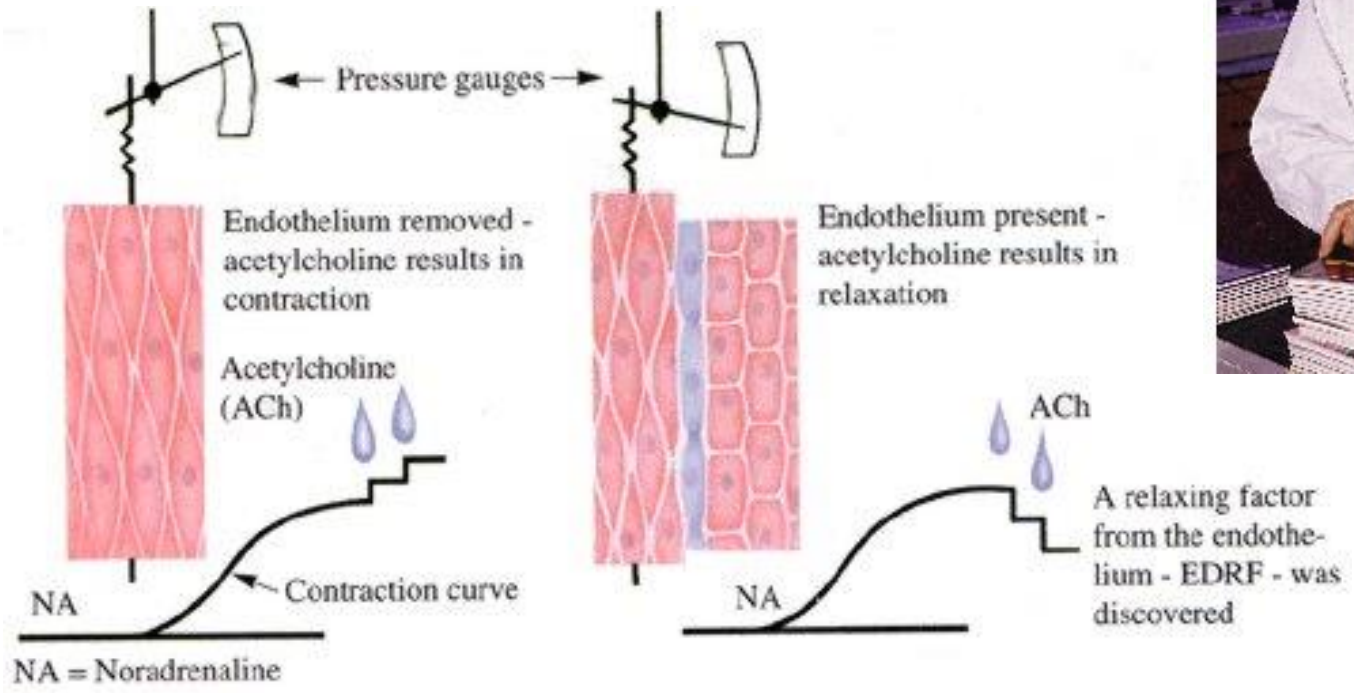
Furchgott's Sandwich

Circulation Research NOVEMBER 1983
VOL. 53 NO. 5
An Official Journal of the American Heart Association

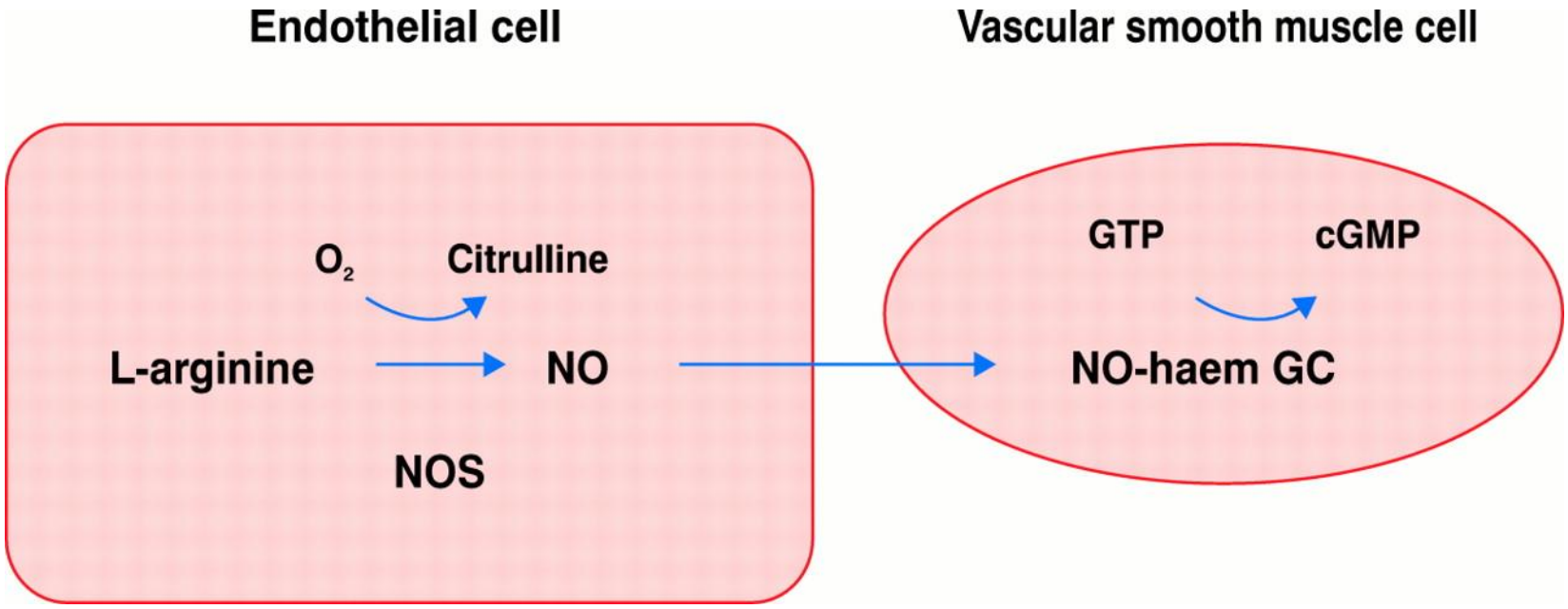
BRIEF REVIEWS

Role of Endothelium in Responses of Vascular Smooth Muscle

Robert F. Furchgott
From the Department of Pharmacology, State University of New York, Downstate Medical Center Brooklyn, New York



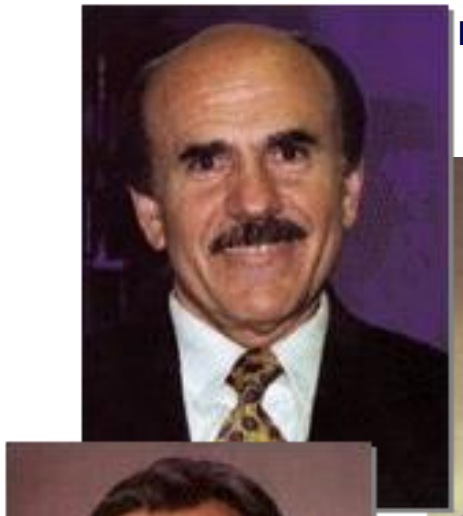
The L-arginine: Nitroc Oxide Pathway



Vallance P , Chan N Heart 2001;85:342-350

What is Nitric Oxide (NO)?

- NO is one of the most powerful, endogeneous vasodilators
- Vasodilators improve circulation throughout the body
- In 1998 The Nobel Prize in Physiology or Medicine was awarded to 3 Americans for their discoveries concerning the Nitric Oxide molecule in the cardiovascular system



Louis J. Ignarro

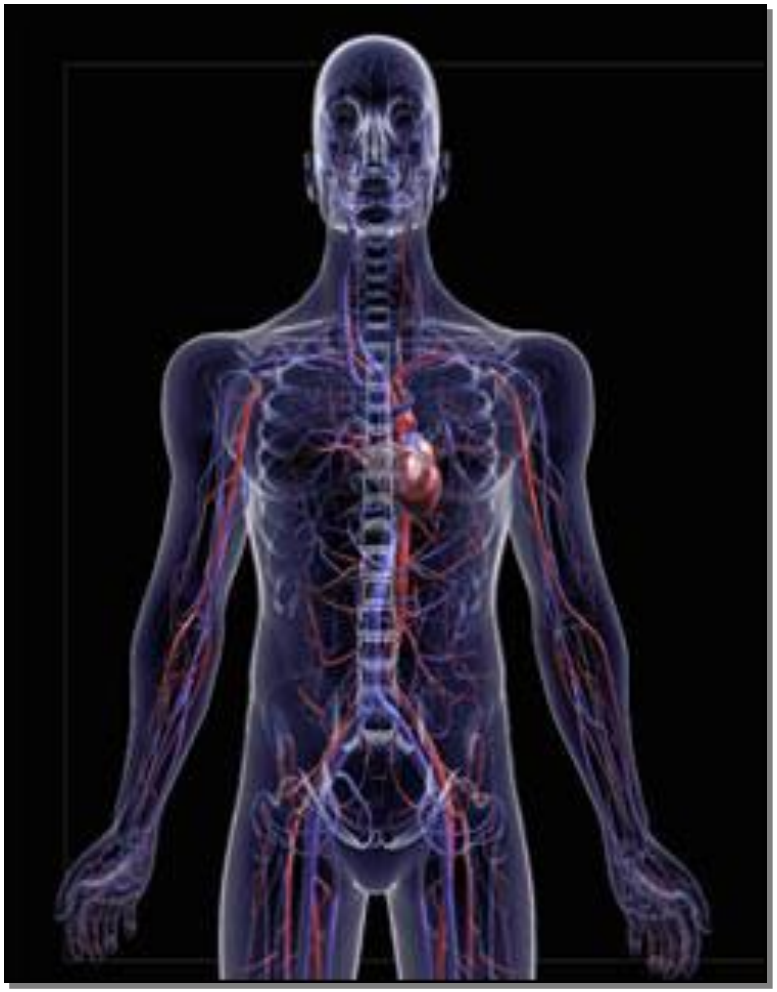
Ferid Murad

Robert F. Furchgott

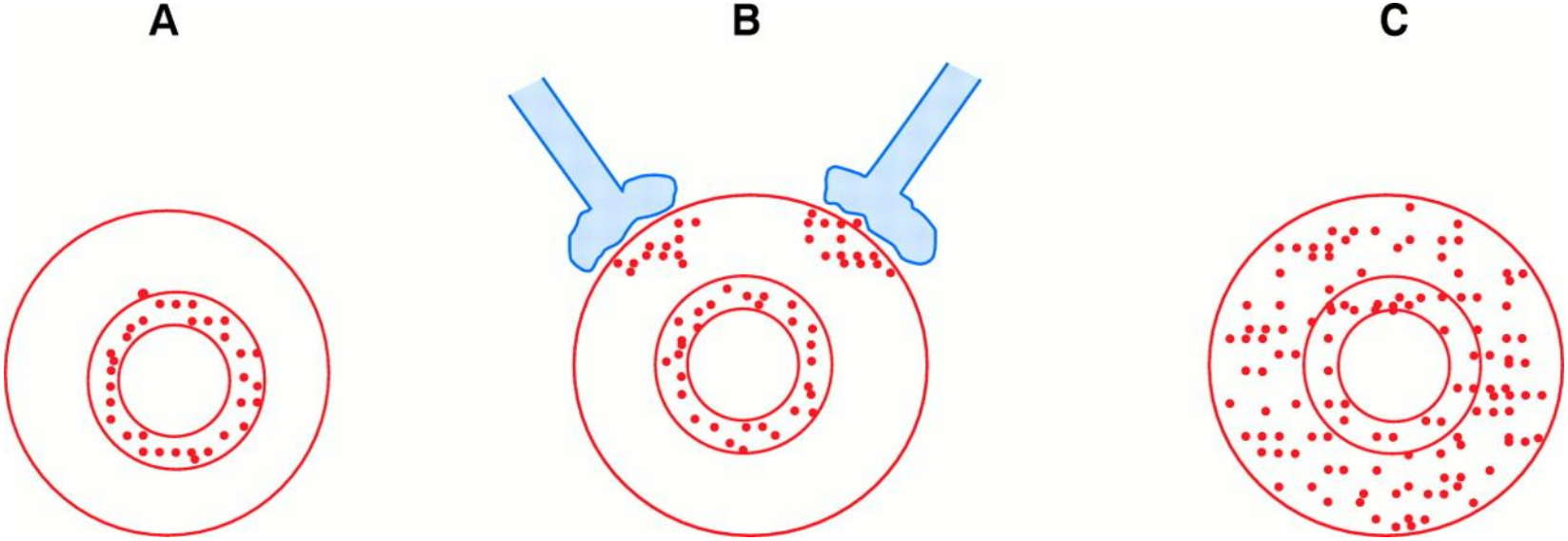
Why Does the Body Need NO?

The Answer: Better Circulation

- Dilates existing vessels; arterioles, venules and lymphatics
- Angiogenesis - the growth of new blood and lymph vessels
- Decreases edema and swelling
- Increases nutritional flow to cells
- Increases antibiotic delivery and action
- Restores blood flow to nerves

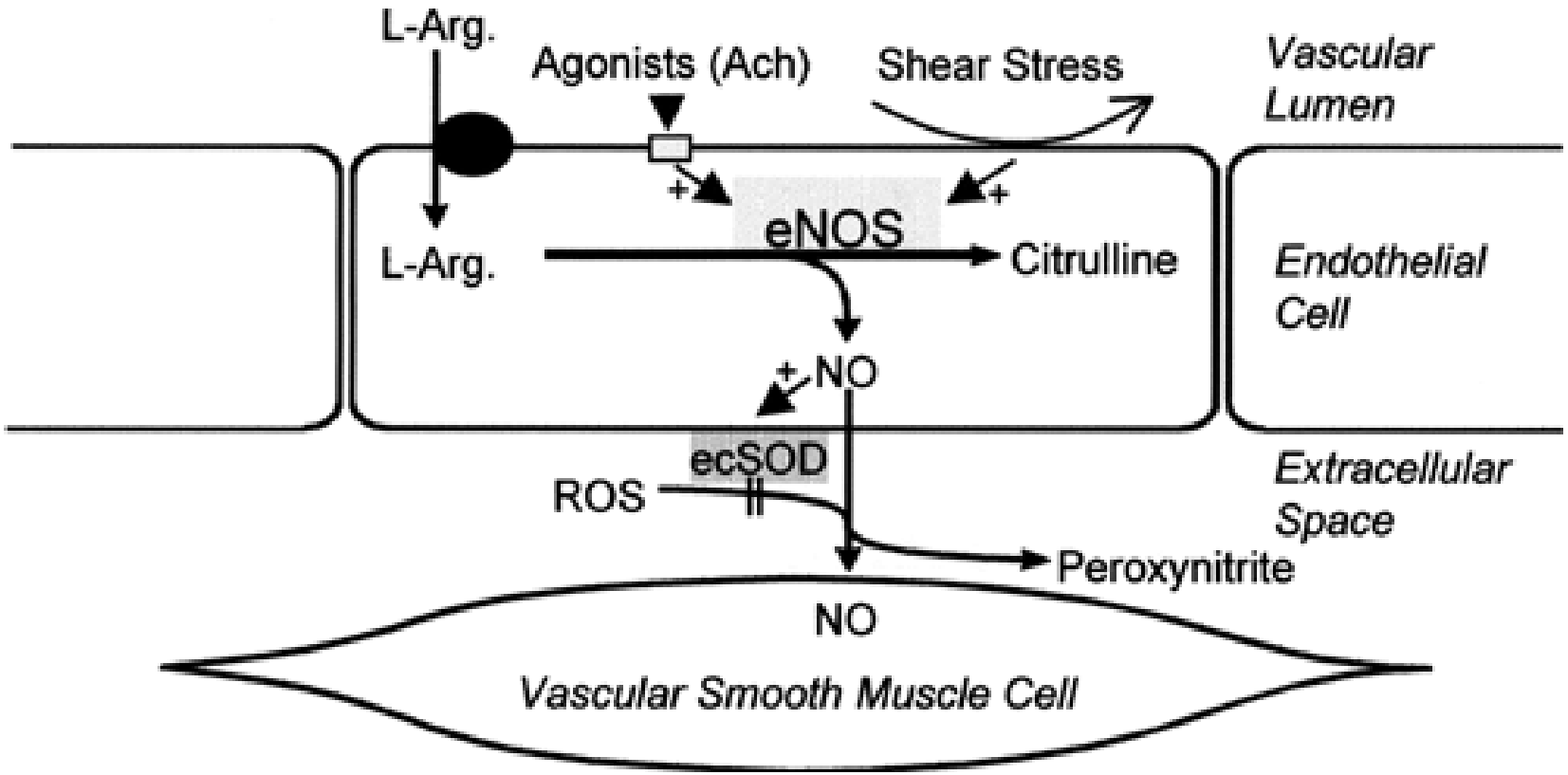


(A) In most, if not all, vessels nitric oxide is synthesised within the endothelium.



Vallance P , Chan N Heart 2001;85:342-350

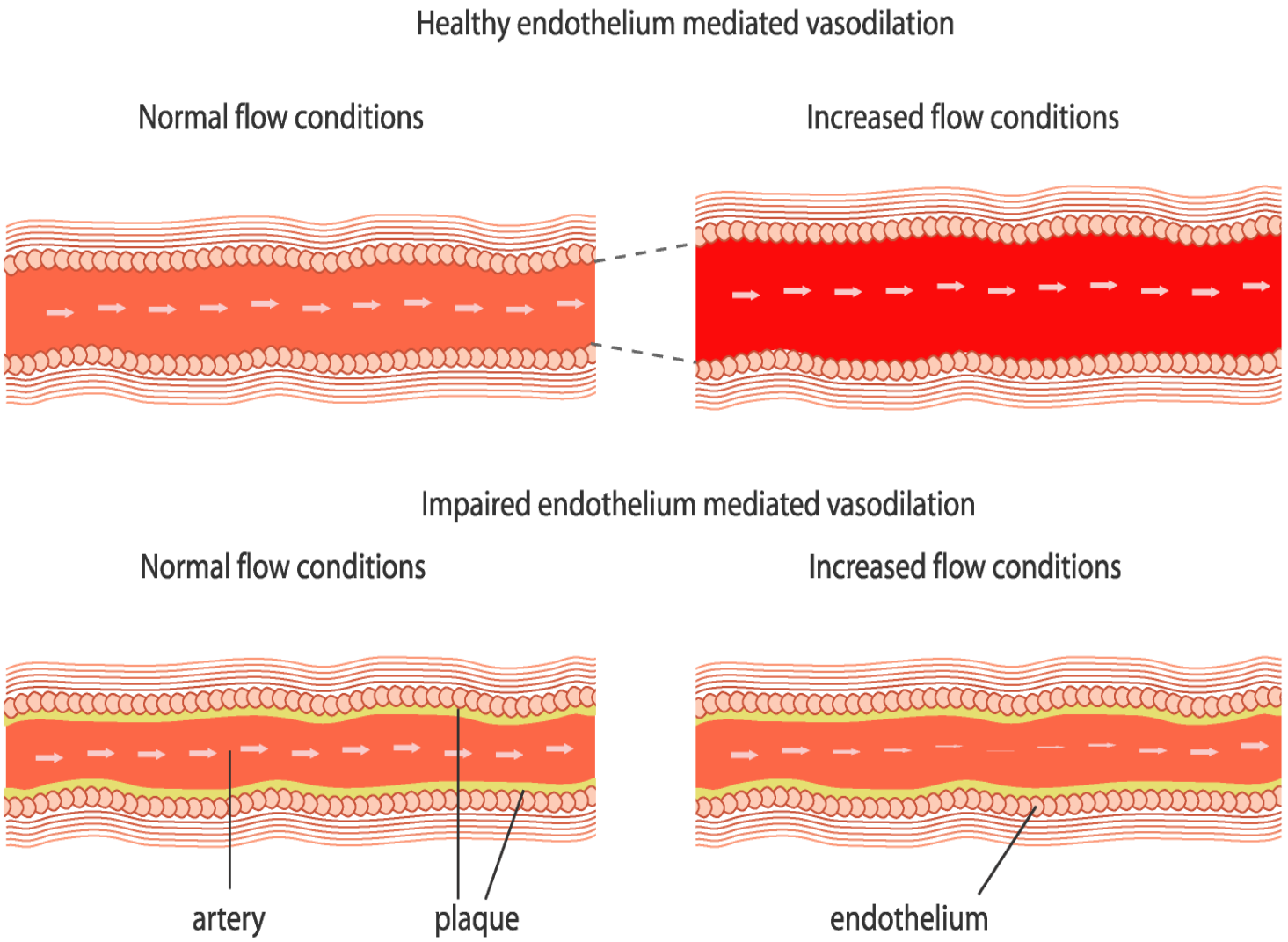
Regulation of NO Synthesis



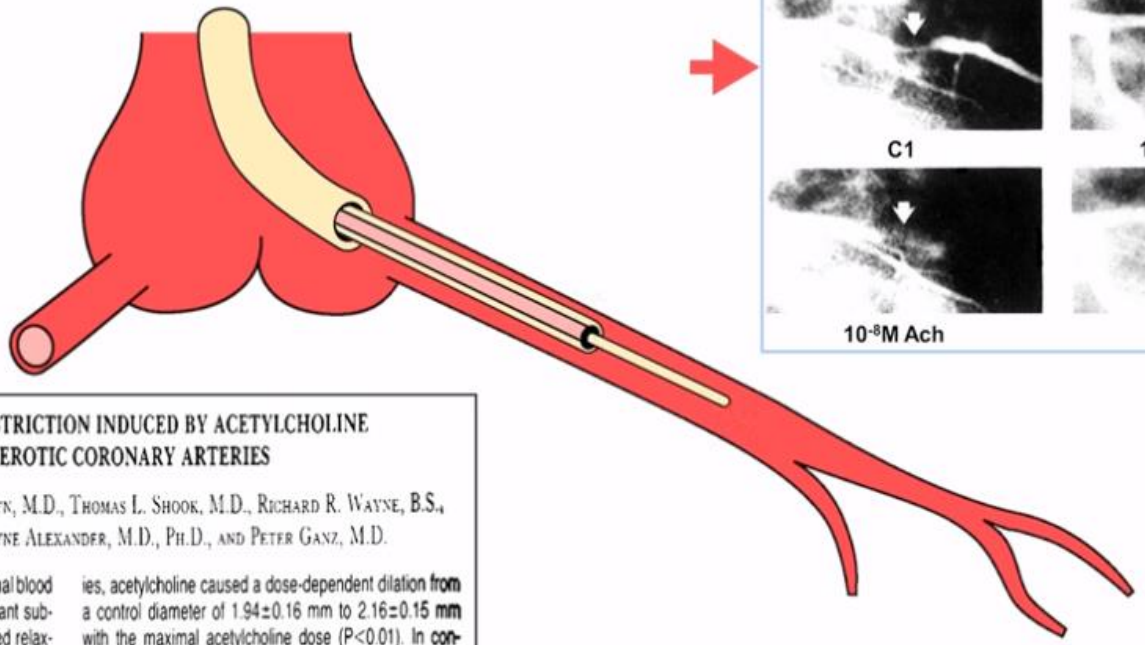
Methods for exploring endothelial function.
(Guerci *et al*., Diabetes Metab 2001; 27: 425-434.)

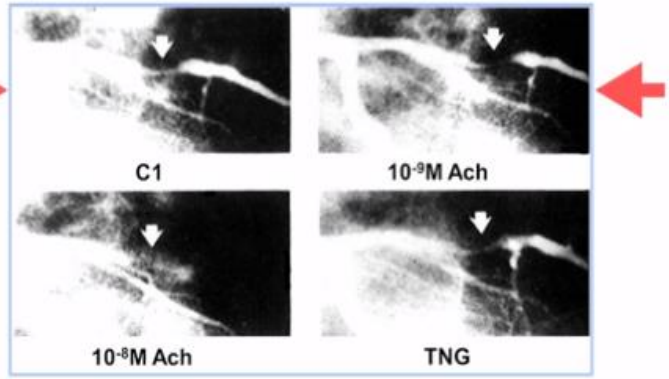
Type	Stimulus	Parameters measured	Evaluation techniques
In vitro direct methods	Pharmacological (L-NAME, phenylephrine, noradrenaline, inhibitors of NOS and COX)	Flow	Cell culture
	Physiological (shear stress)	Shear rate	Isolated artery
Biochemical *in vivo* indirect methods	Pharmacological (L-arginine)	Plasma NO and PGI_2	Biochemical assays
	Physiological (ADP, 5-HT, histamine)	Urinary nitrate, nitrites	
		Adhesion molecules	
		Coagulation factors	
Invasive *in vivo* direct methods	L-NMMA (intra arterial)	Arterial diameter	Ultrasonography
	Acetylcholine, serotonin, bradykinin, substance P (intra arterial)	Arterial flow	Plethysmography
Non-invasive *in vivo* direct methods	Shear stress (post-ischemic dilation)	Arterial diameter	Ultrasonography
		Arterial flow	Plethysmography
			Echotracking
	Dipyridamole (intra venous)	Arterial flow	Positron emission tomography

Flow-mediated Vasodilation



How is Endothelial Function Measured?





PARADOXICAL VASOCONSTRICTION INDUCED BY ACETYLCHOLINE IN ATHEROSCLEROTIC CORONARY ARTERIES

PAUL L. LUDMER, M.D., ANDREW P. SELWYN, M.D., THOMAS L. SHOOK, M.D., RICHARD R. WAYNE, B.S., GILBERT H. MUDGE, M.D., R. WAYNE ALEXANDER, M.D., PH.D., AND PETER GANZ, M.D.

Abstract Acetylcholine is believed to dilate normal blood vessels by promoting the release of a vasorelaxant substance from the endothelium (endothelium-derived relaxing factor). By contrast, if the endothelium is removed experimentally, acetylcholine constricts blood vessels. We tested the hypothesis that muscarinic cholinergic vasodilaies, acetylcholine caused a dose-dependent dilation from a control diameter of 1.94±0.16 mm to 2.16±0.15 mm with the maximal acetylcholine dose ($P<0.01$). In contrast, all eight of the arteries with advanced stenoses showed dose-dependent constriction, from 1.05±0.05 to 0.32±0.16 mm at the highest concentration of acetylcho-

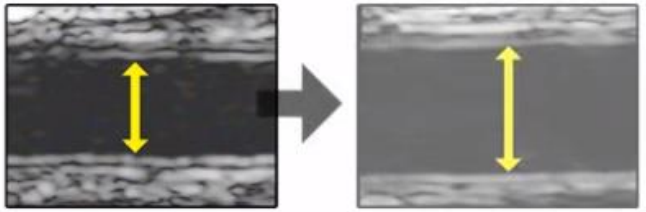
The Problem With This Method...

Invasive

Hospitalization Required

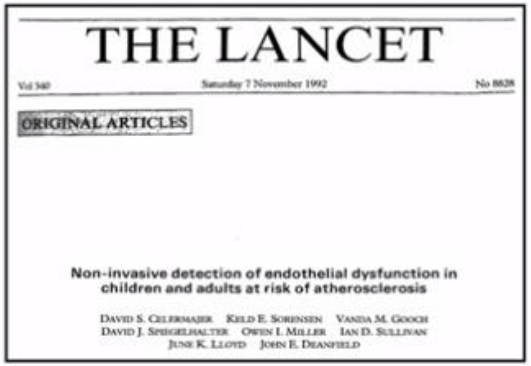
Expensive

Research Method Uses Ultrasound Imaging



BASELINE

POST OCCLUSION



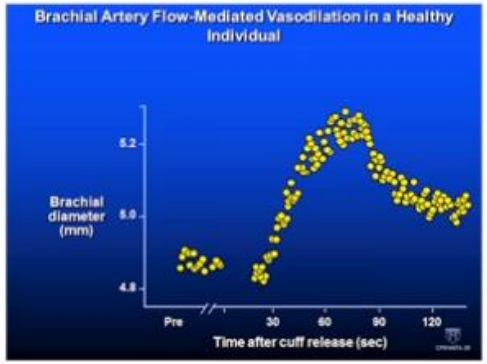
THE LANCET

Vol 340 Saturday 7 November 1992 No 8828

ORIGINAL ARTICLES

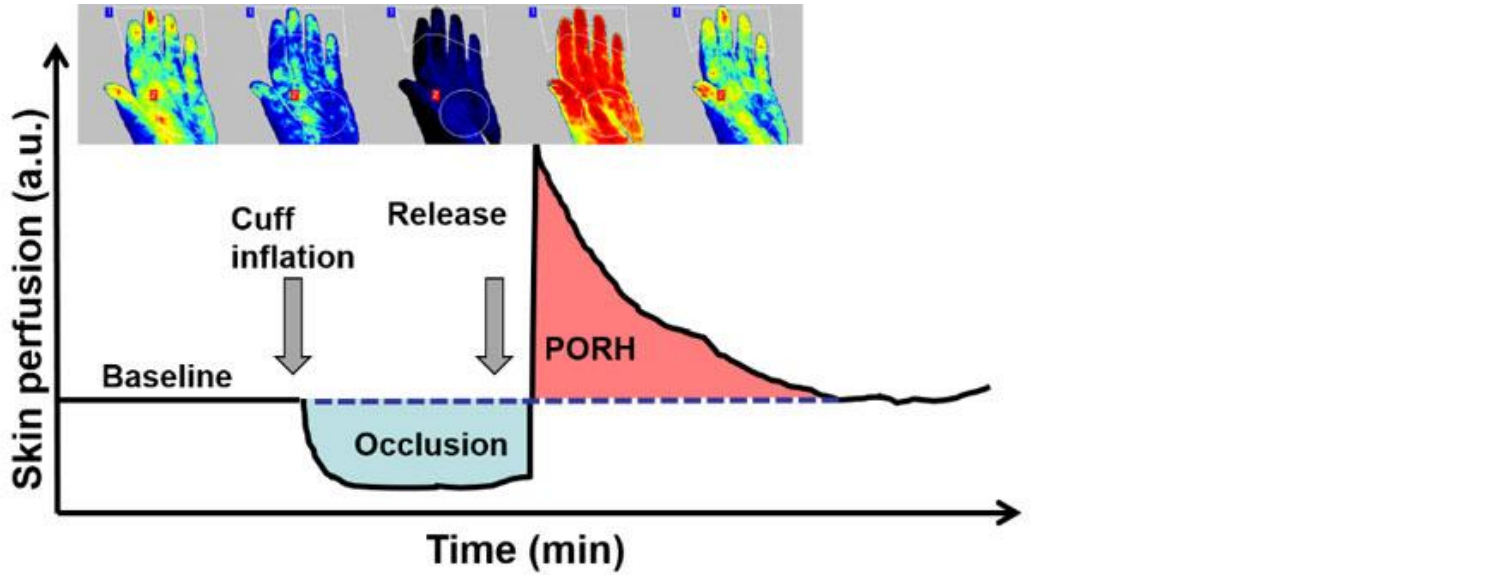
Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis

David S. Celermajer Keld E. Sorensen Vanda M. Gooch
David J. Spiegelhalter Owen I. Miller Ian D. Sullivan
June K. Lloyd John E. Deanfield

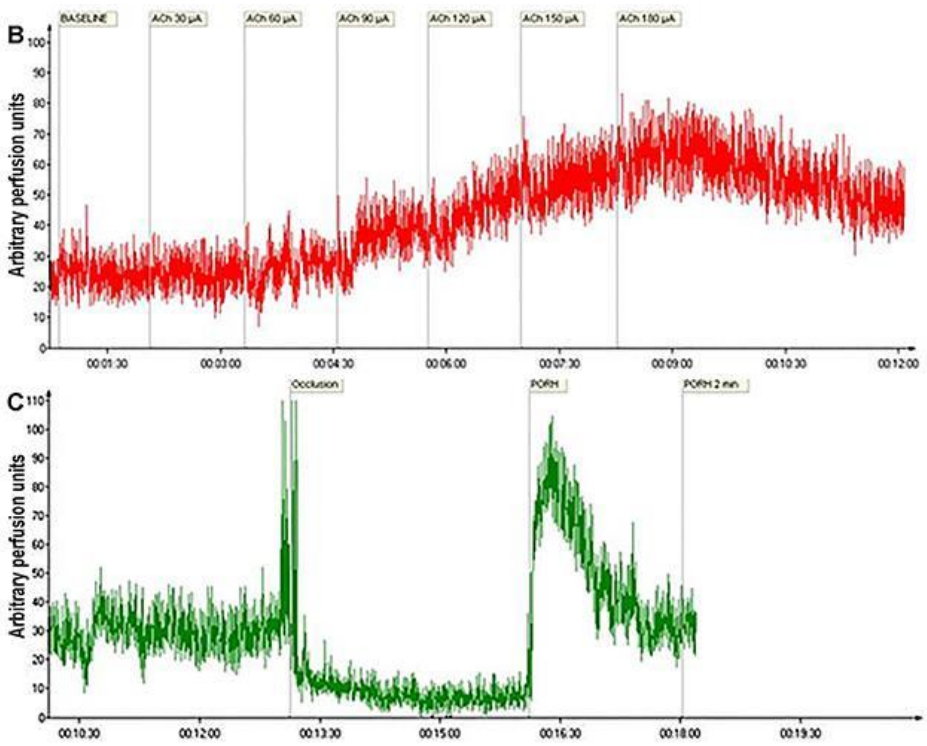


The Problem With This Method...

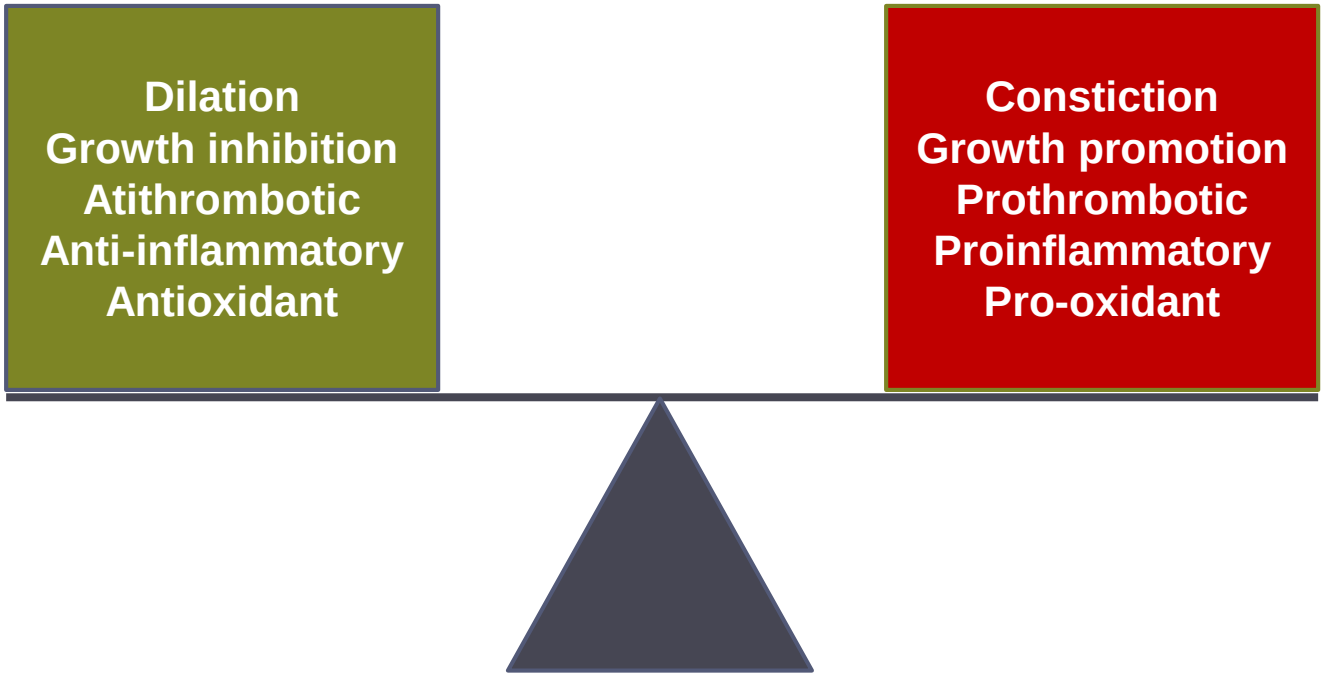
- Lacks feasibility for doctors' offices
- Requires experienced sonographer
- Operator-dependent
- Sensitive to position of the arm


Skin perfusion (a.u.)
Cuff inflation
Release
Baseline
PORH
Occlusion
Time (min)


A
1
2
3

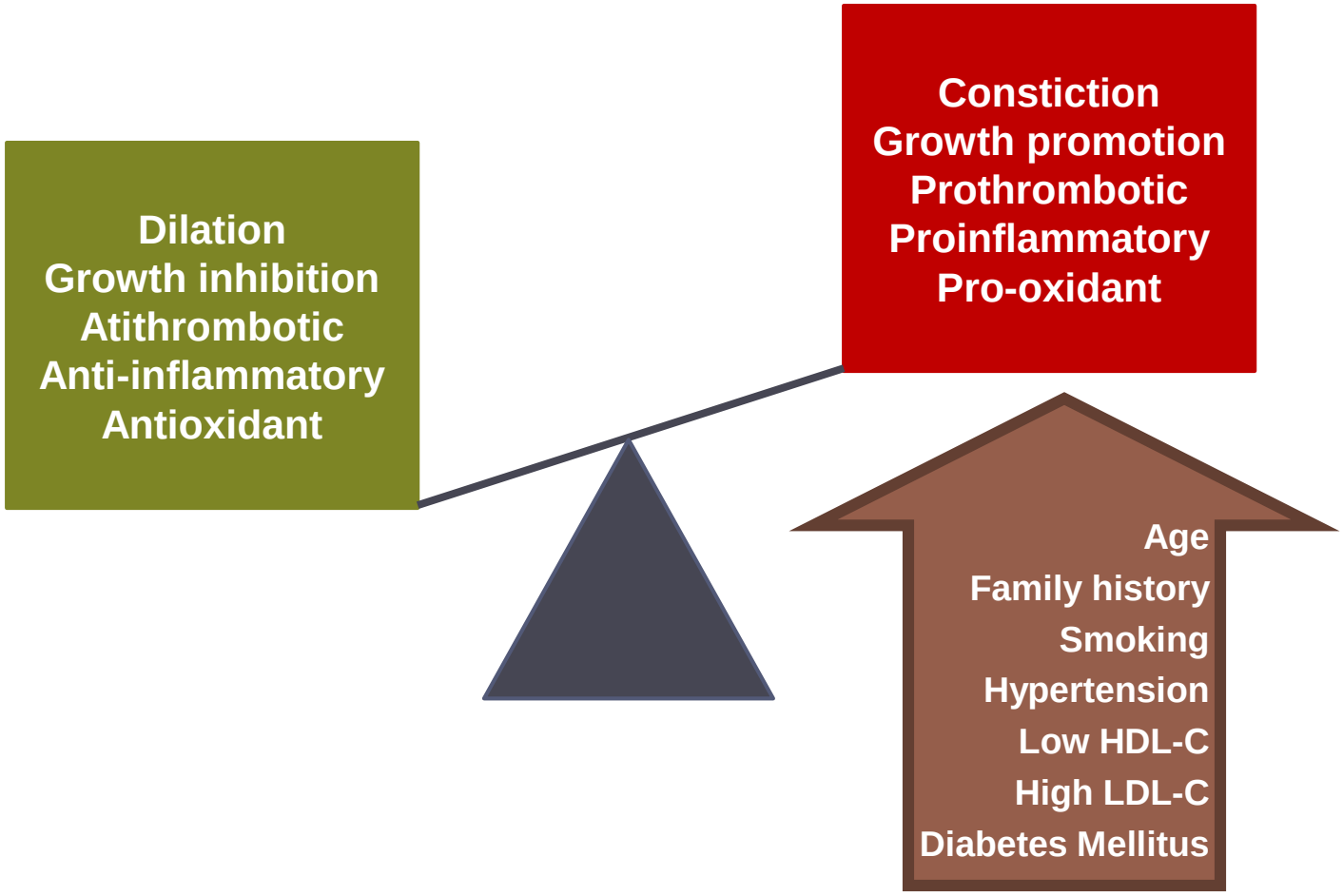

B
BASELINE
ACh 30 µA
ACh 60 µA
ACh 90 µA
ACh 120 µA
ACh 150 µA
ACh 180 µA
Arbitrary perfusion units
C
Occlusion
PORH
PORH 2 min
Arbitrary perfusion units

Endothelial Function

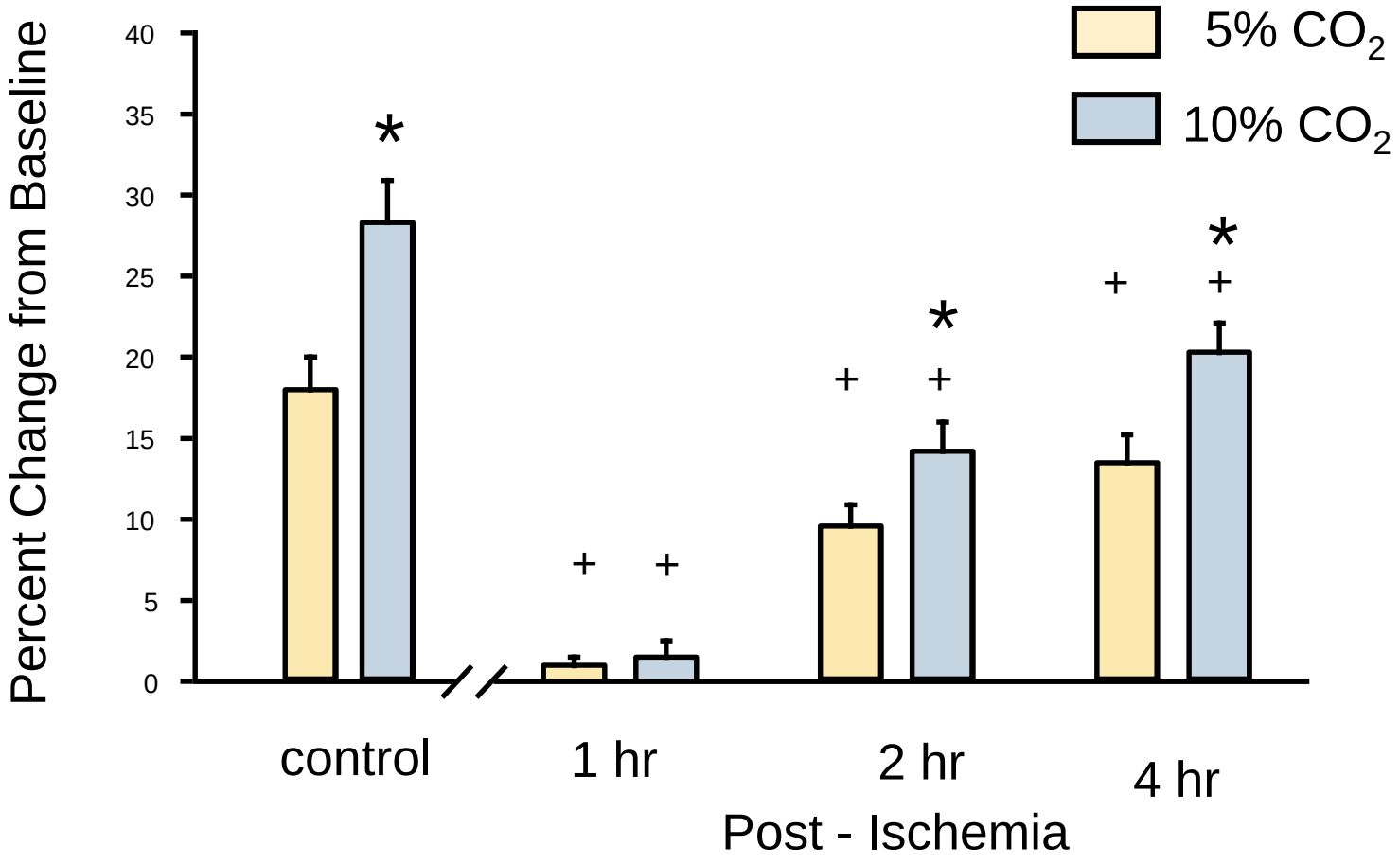


Endothelial Dysfunction

the *sine qua non* of the atherogenic process



Hypercapnia-induced Vasodilation is Endothelium-dependent and Sensitive to Ischemia



Bari et al, Brain Res, (1998)