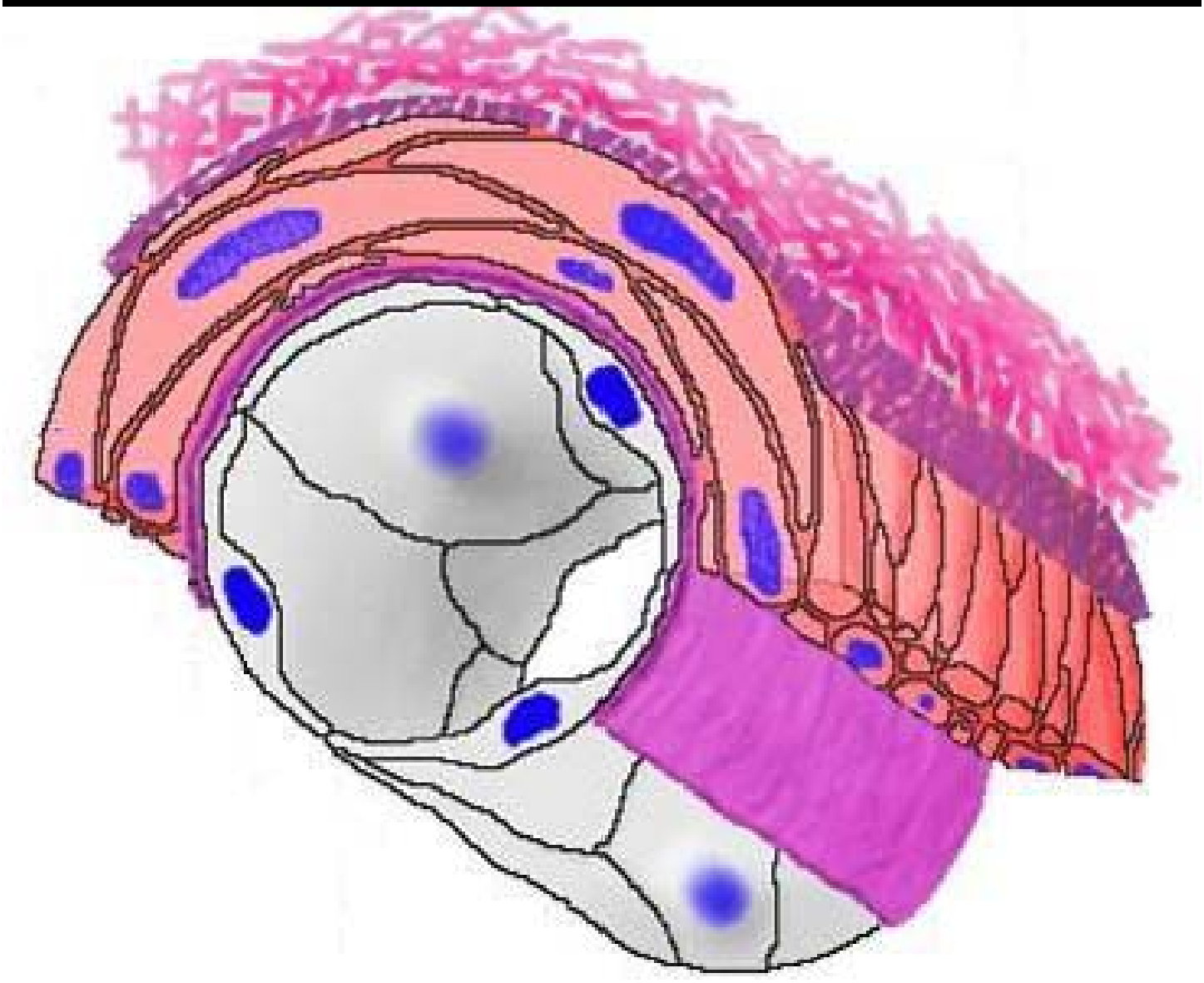
Annual Spring Scientific Conference of the Korean Society of Lipidology and Atherosclerosis

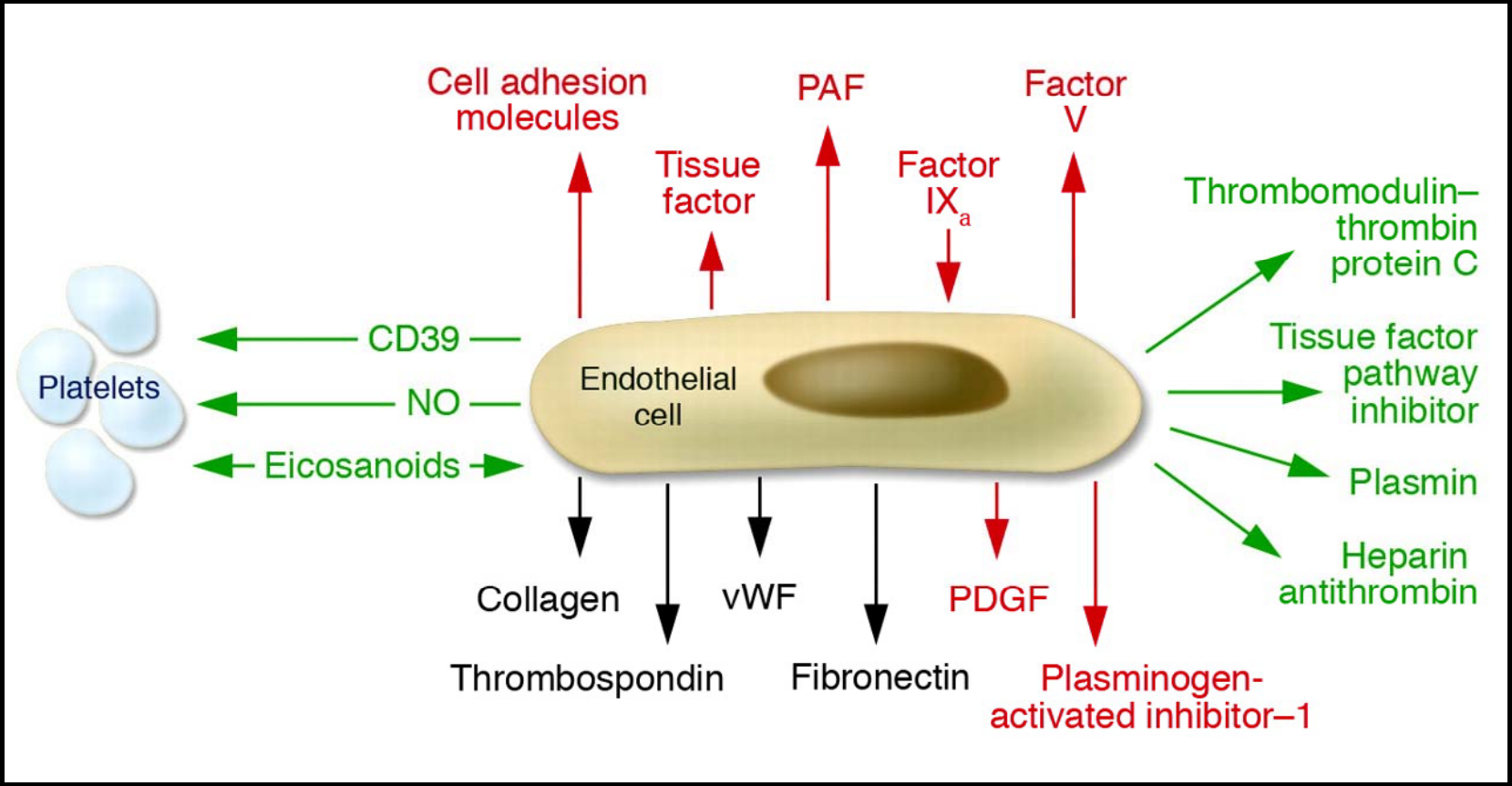
Red Blood Cell Aggregation and Endothelial Function

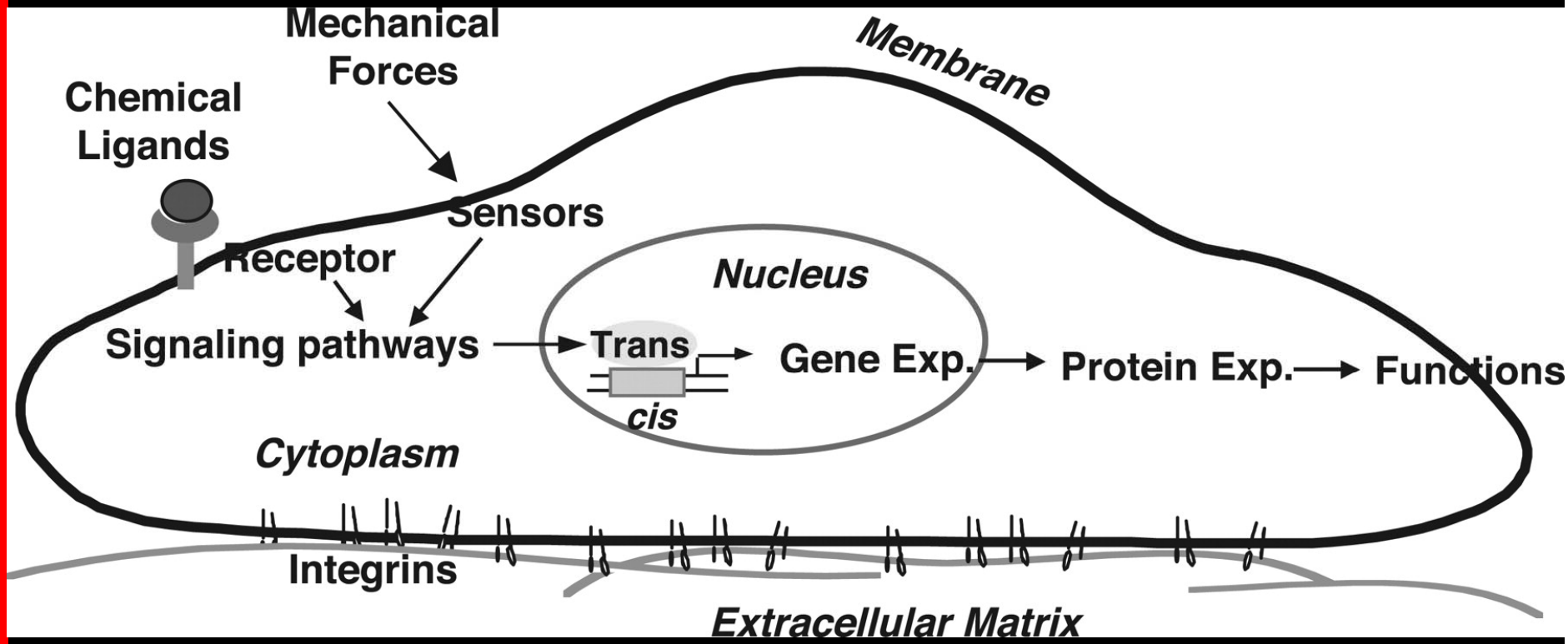
Oguz K. Baskurt, Ozlem Yalcın, and
Herbert J. Meiselman



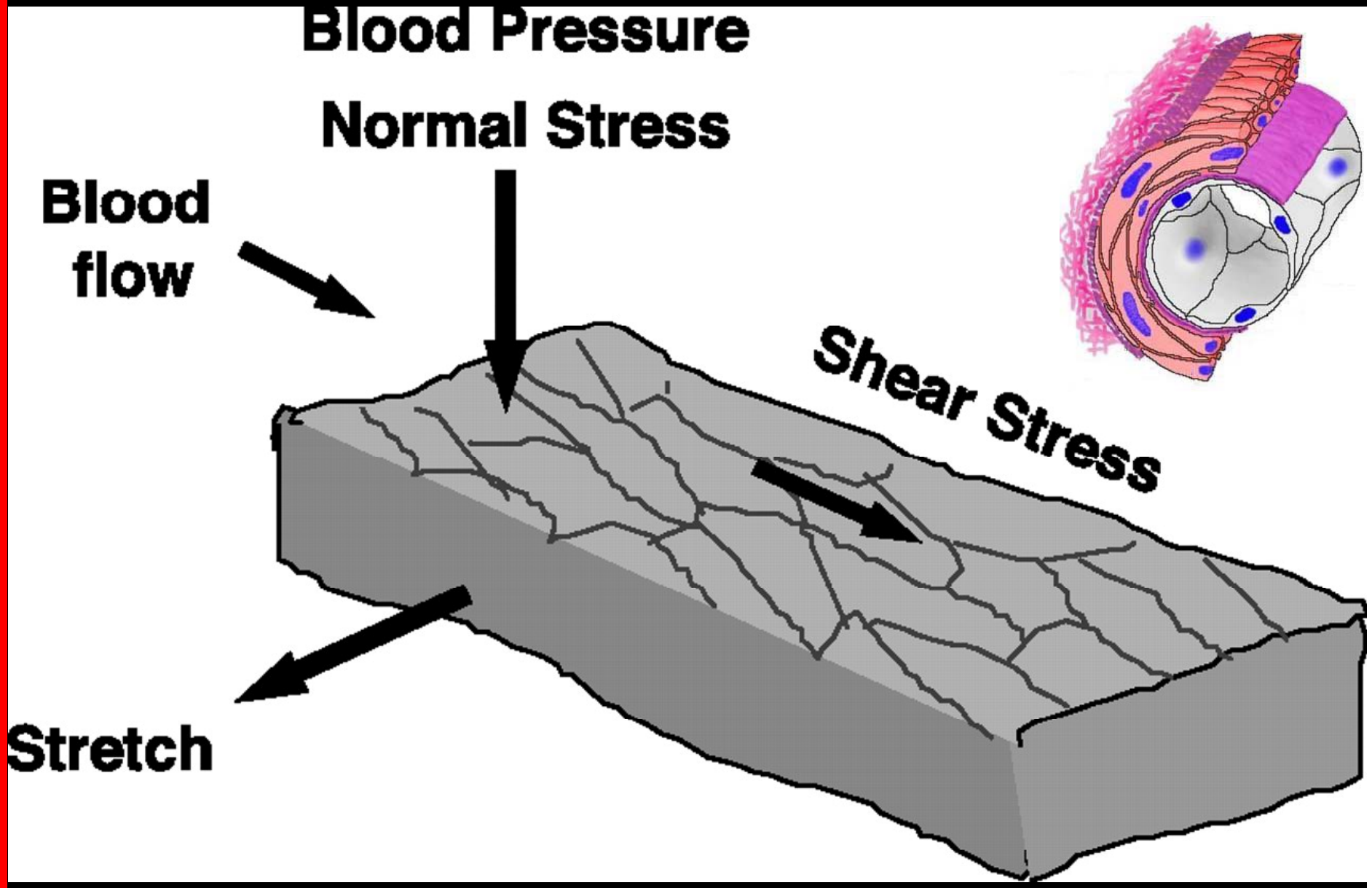
Endothelial function

- Permeability barrier
- Production, secretion and metabolization of biochemical substances
- Migration, remodeling, proliferation, apoptosis
- Regulation of vascular smooth muscle tonus


Cell adhesion molecules
PAF
Factor V
Tissue factor
Factor IX$_a$
Thrombomodulin–thrombin protein C
Tissue factor pathway inhibitor
Plasmin
Heparin antithrombin
CD39
NO
Eicosanoids
Platelets
Endothelial cell
Collagen
vWF
PDGF
Thrombospondin
Fibronectin
Plasminogen-activated inhibitor–1



Chien, S. Am J Physiol Heart Circ Physiol 292: H1209-H1224 2007.

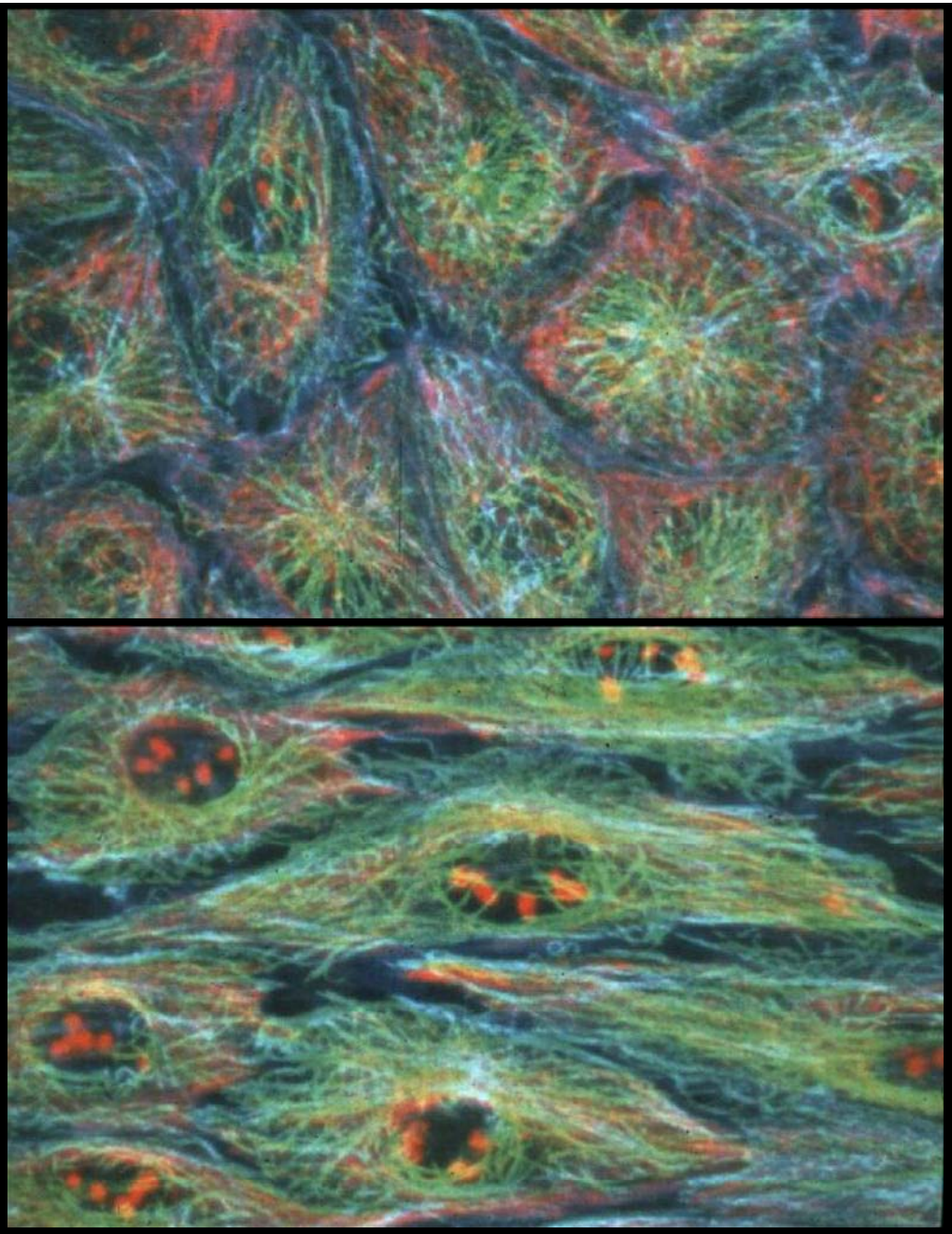

Blood Pressure
Normal Stress
Blood
flow
Shear Stress
Stretch

Endothelial function

- Permeability barrier
- Production, secretion and metabolization of biochemical substances
- Migration, remodeling, proliferation, apoptosis
- Regulation of vascular smooth muscle tonus

Static condition

Laminar flow



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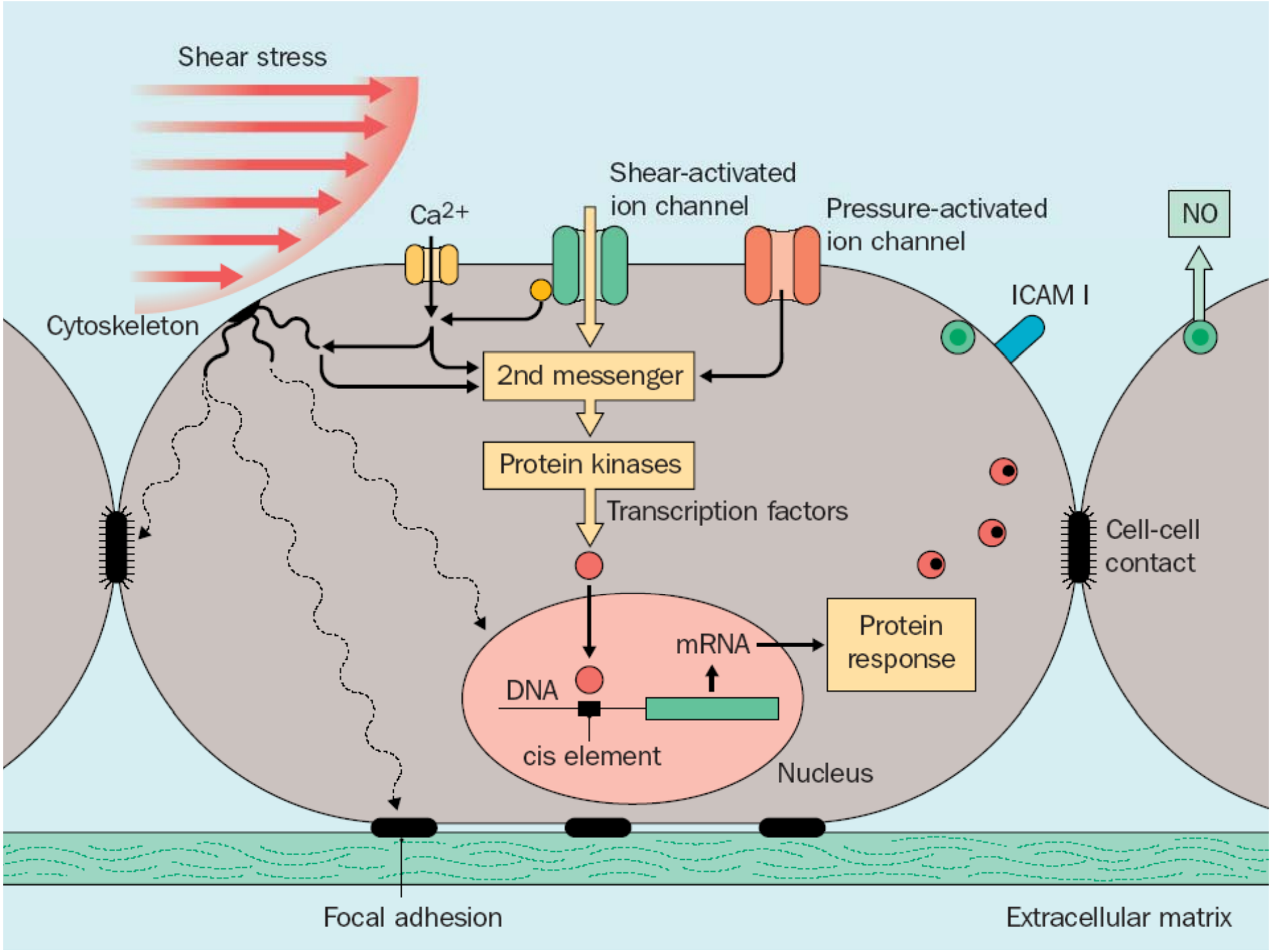
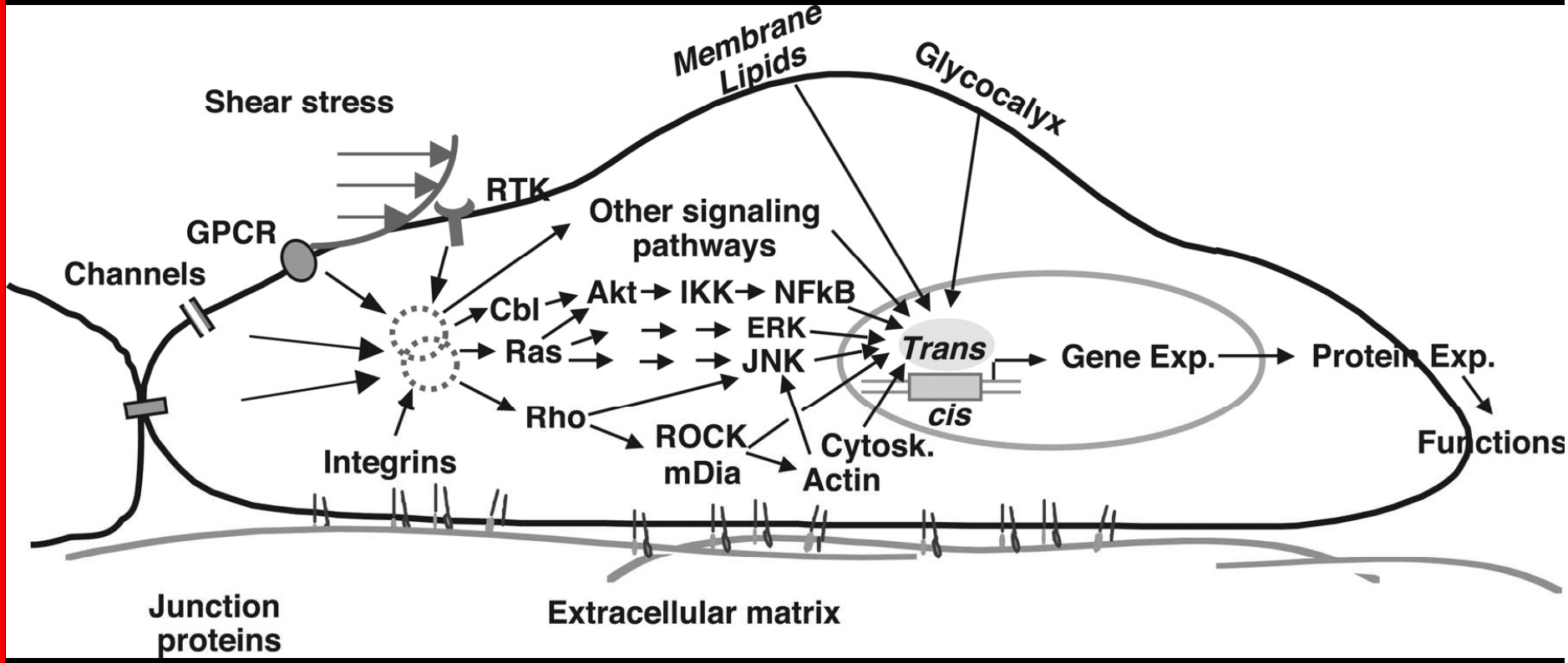
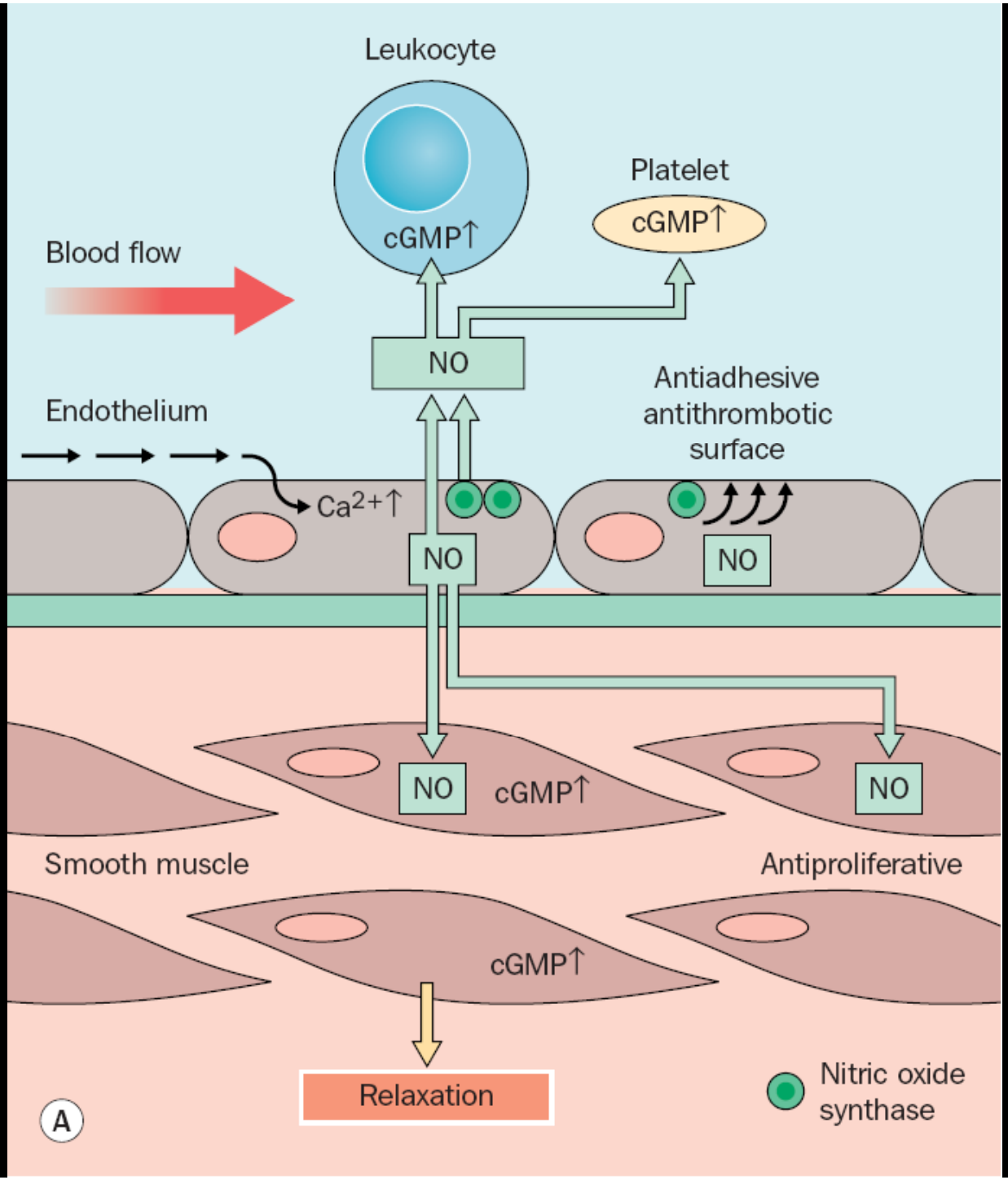
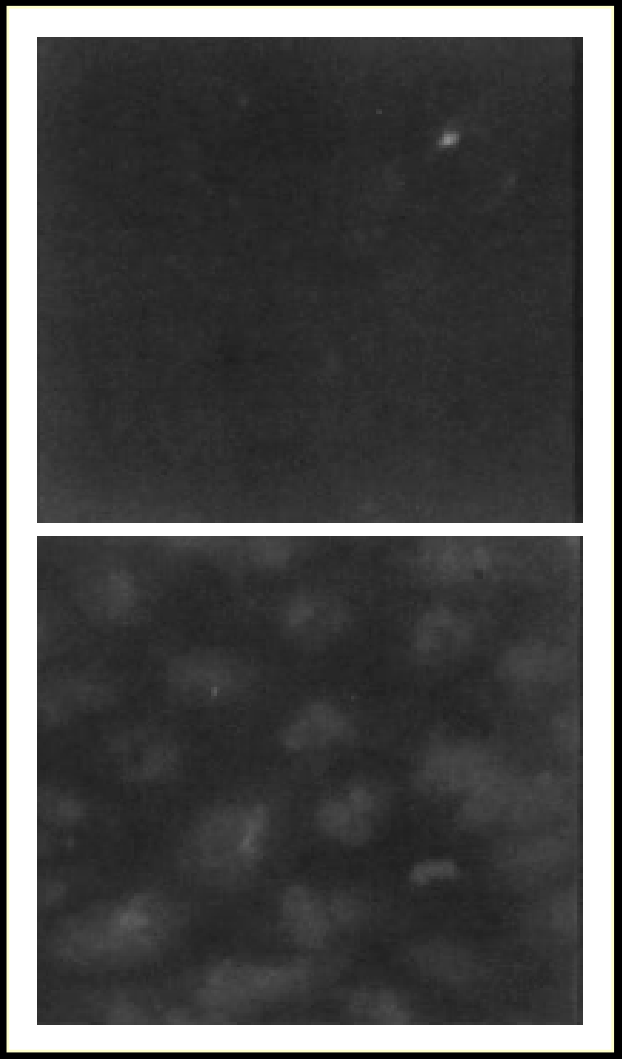

Shear stress
Ca2+
Shear-activated ion channel
Pressure-activated ion channel
NO
ICAM I
Cytoskeleton
2nd messenger
Protein kinases
Transcription factors
Cell-cell contact
mRNA
Protein response
DNA
cis element
Nucleus
Focal adhesion
Extracellular matrix

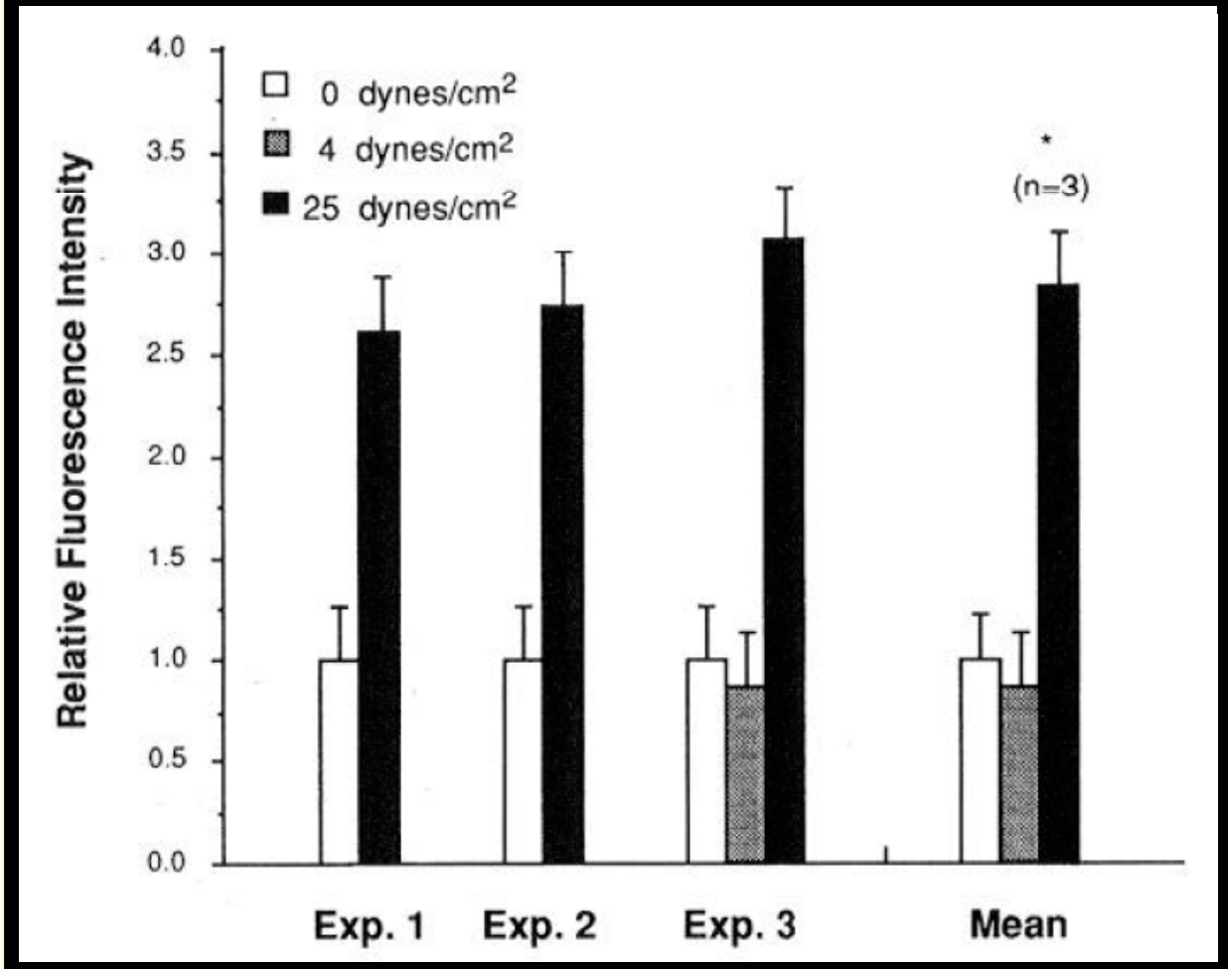


Chien, S. Am J Physiol Heart Circ Physiol 292: H1209-H1224 2007.


Leukocyte
cGMP↑
Platelet
cGMP↑
Blood flow
NO
Endothelium
Antiadhesive
antithrombotic
surface
Ca2+↑
NO
NO
NO
cGMP↑
NO
Smooth muscle
Antiproliferative
cGMP↑
Relaxation
A
Nitric oxide
synthase

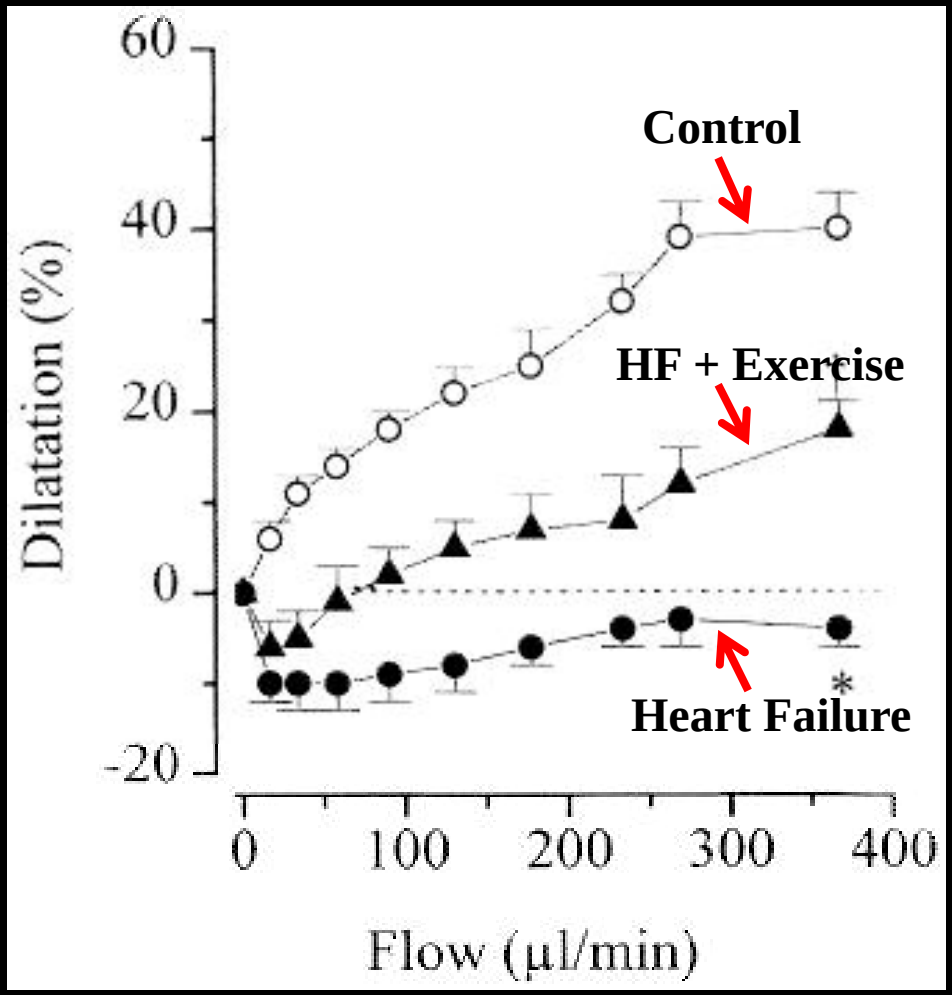
Effect of Blood Flow on NO synthesis mechanisms





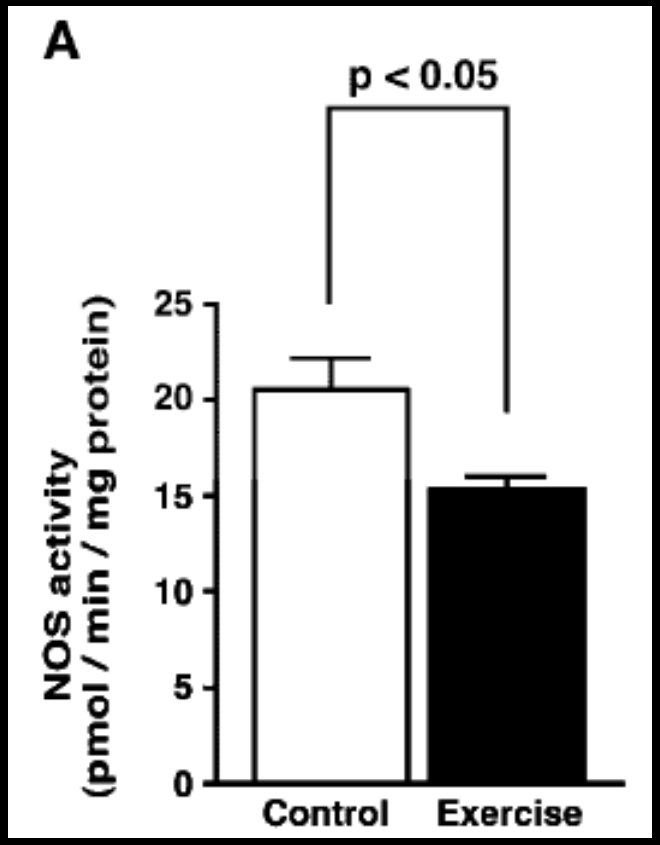
Ranjan V et al., Am. J. Physiol. 269: H550, 1995.

Effect of Blood Flow on NO synthesis mechanisms

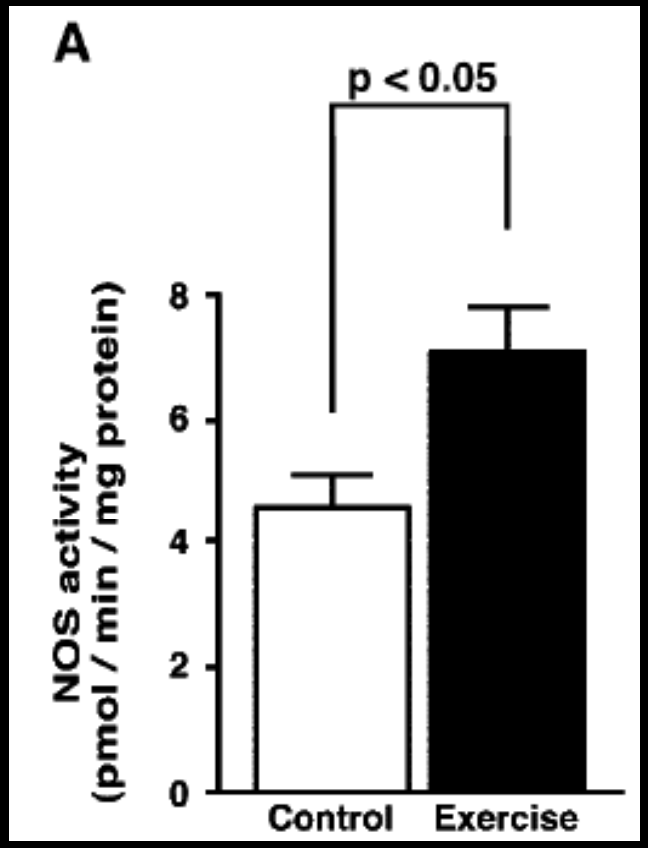


Varin R et al., Circulation 99: 2951, 1999.

Effect of Blood Flow on NO synthesis mechanisms

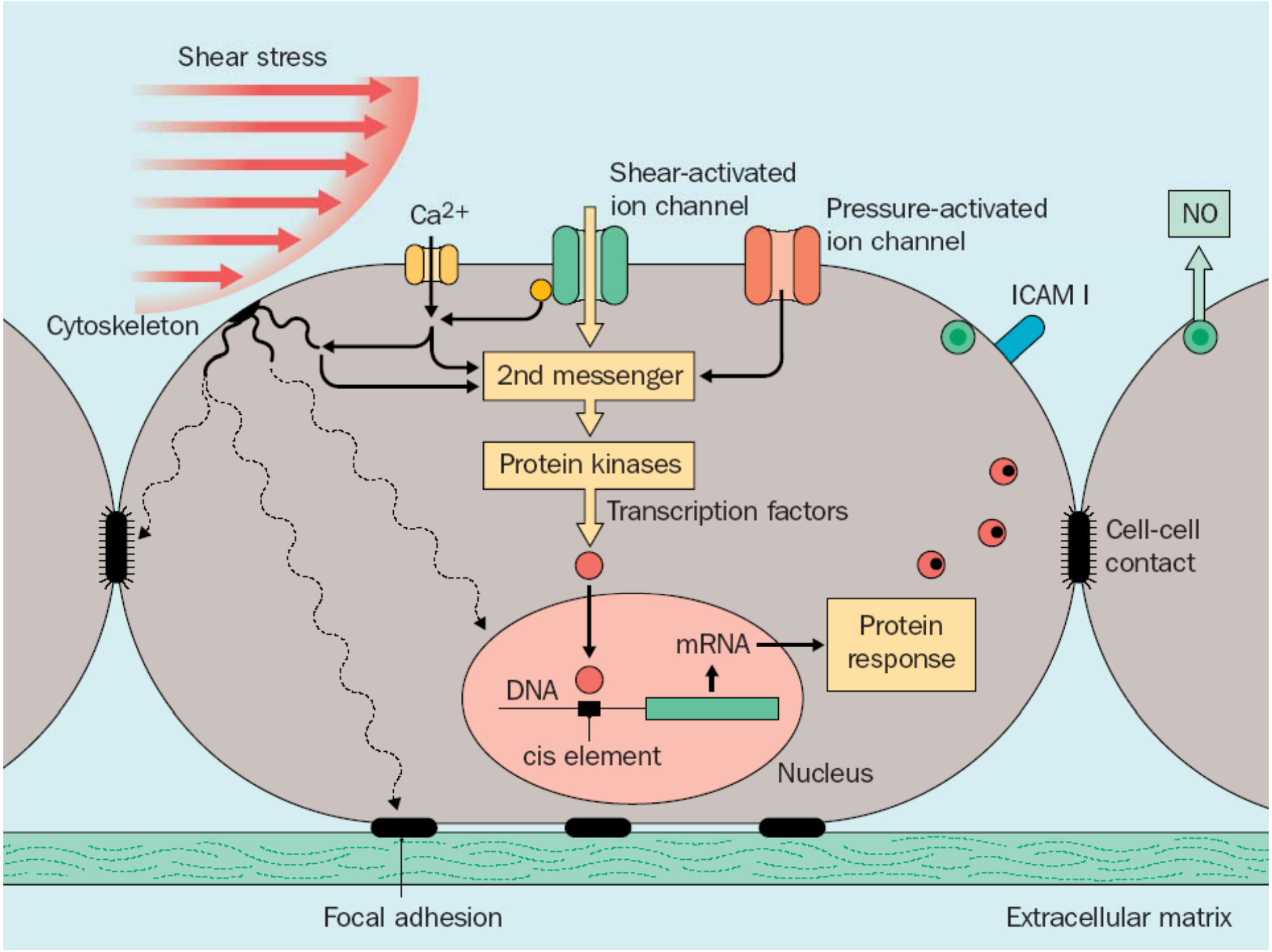


KIDNEY

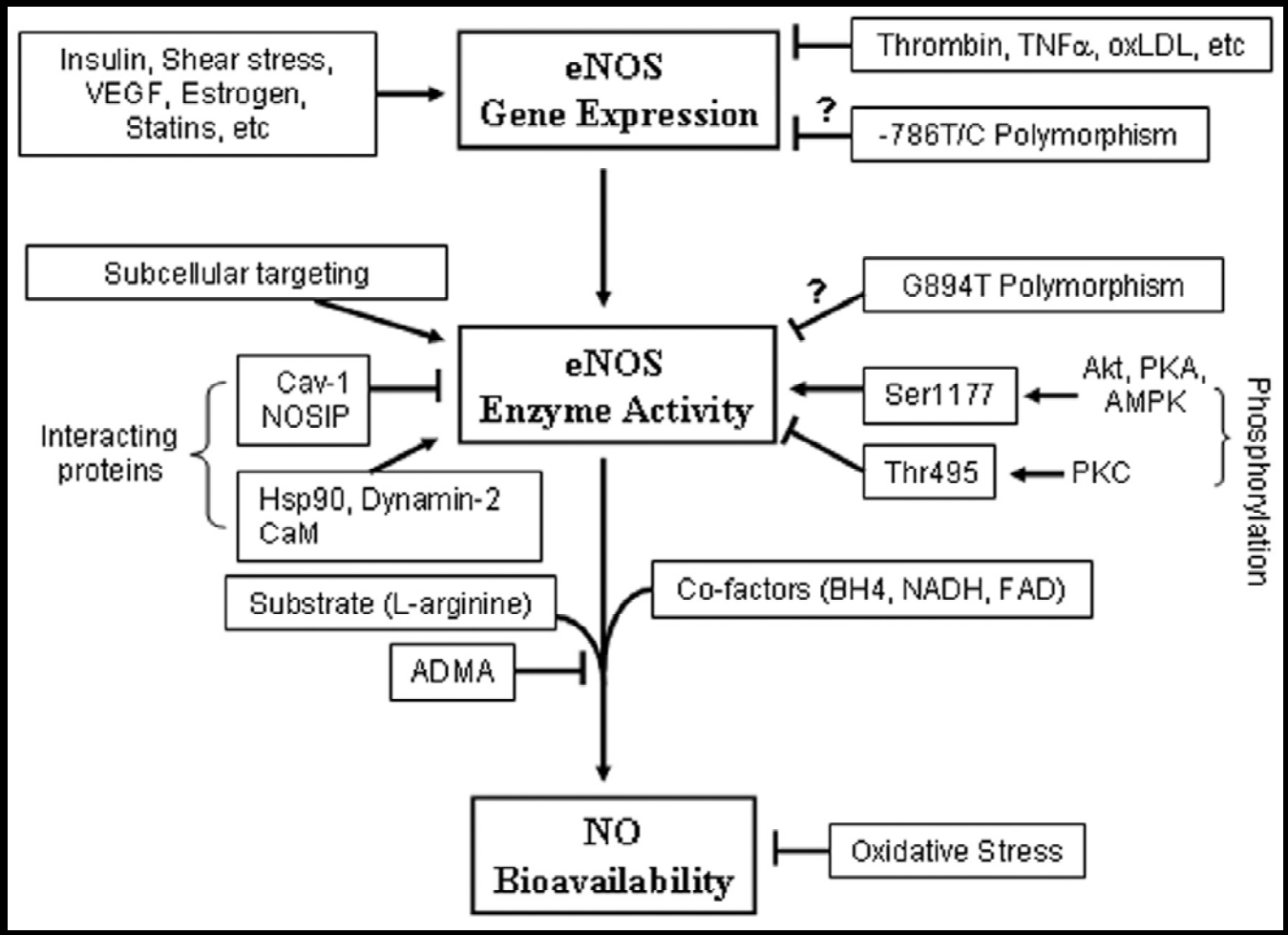


LUNG

Miyauchi T et al., J. Appl. Physiol. 94: 60, 2003.


Shear stress
Ca2+
Shear-activated ion channel
Pressure-activated ion channel
NO
ICAM I
Cytoskeleton
2nd messenger
Protein kinases
Transcription factors
Cell-cell contact
mRNA
Protein response
DNA
cis element
Nucleus
Focal adhesion
Extracellular matrix

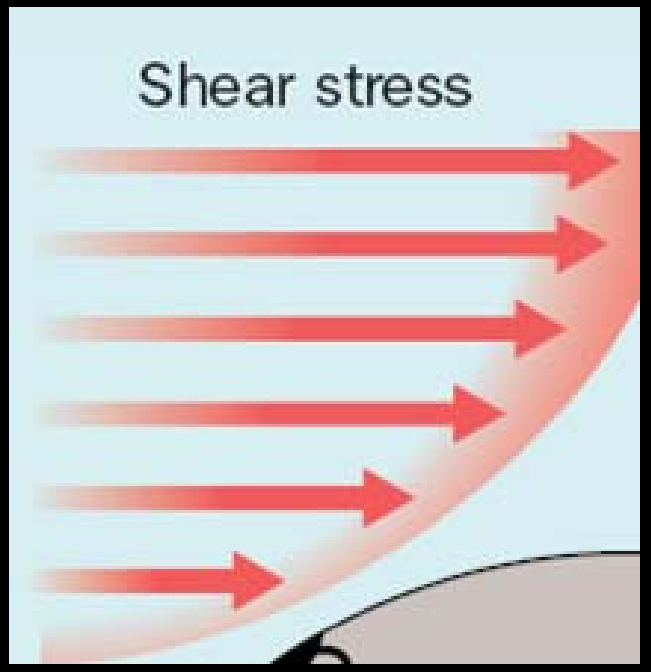
eNOS activation



Yang Z and Ming XF, Clin. Med. Res. 4: 53, 2008.

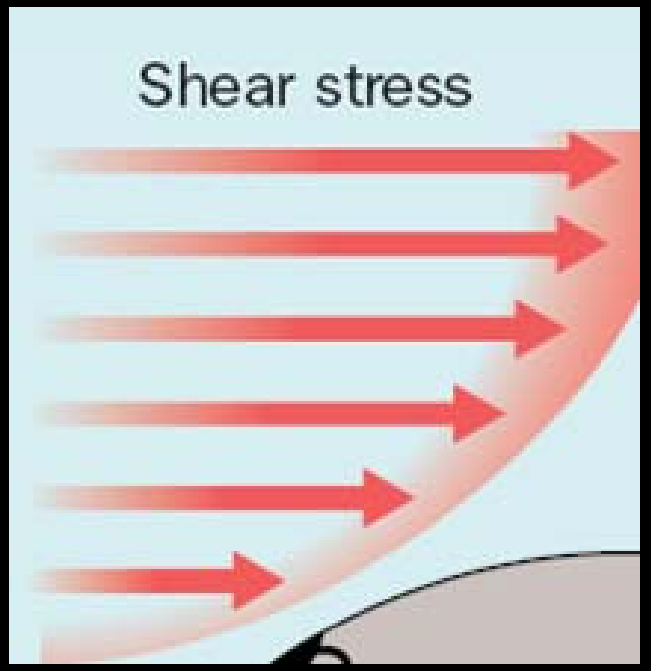
Wall shear stress

WSS= viscosity x velocity/diameter



Wall shear stress

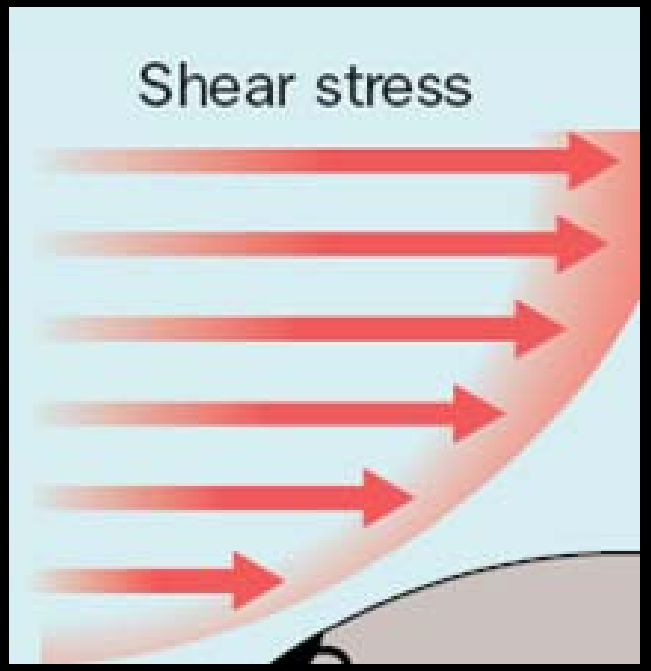
WSS= viscosity x velocity/diameter

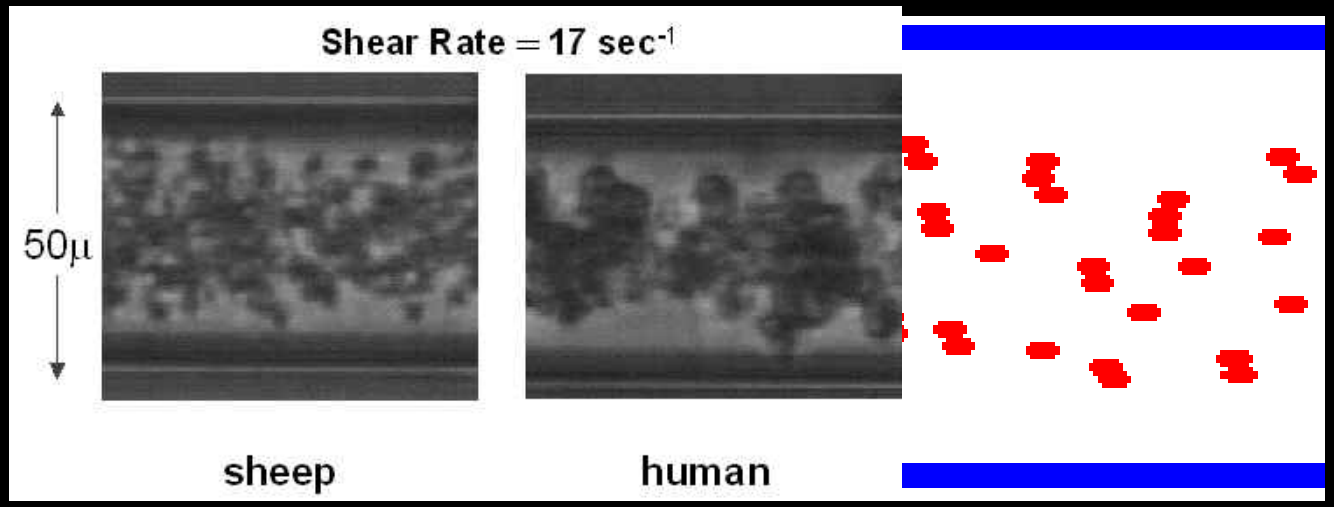


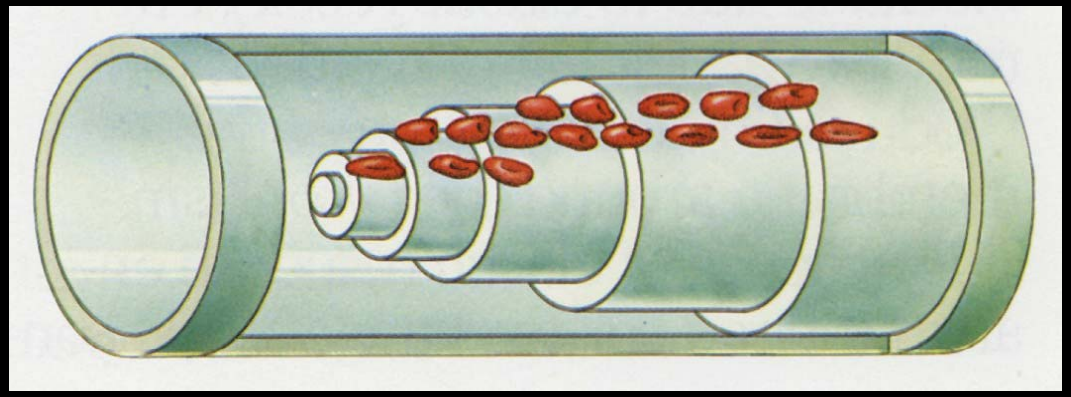
Wall shear stress

WSS= viscosity x velocity/diameter

- Plasma viscosity
- Hematocrit value (local)




Shear Rate = 17 sec-1
50μ
sheep
human

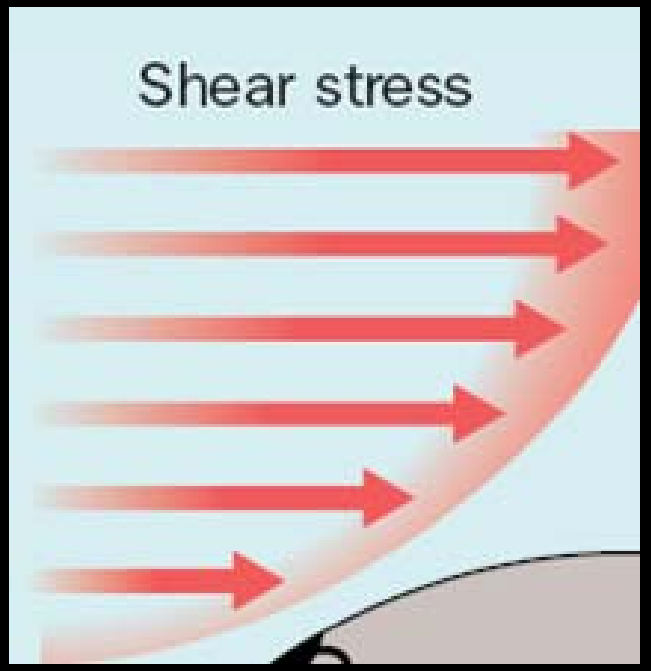


Wall shear stress

WSS= viscosity x velocity/diameter

- Plasma viscosity
- Hematocrit value (local)

RBC Aggregation

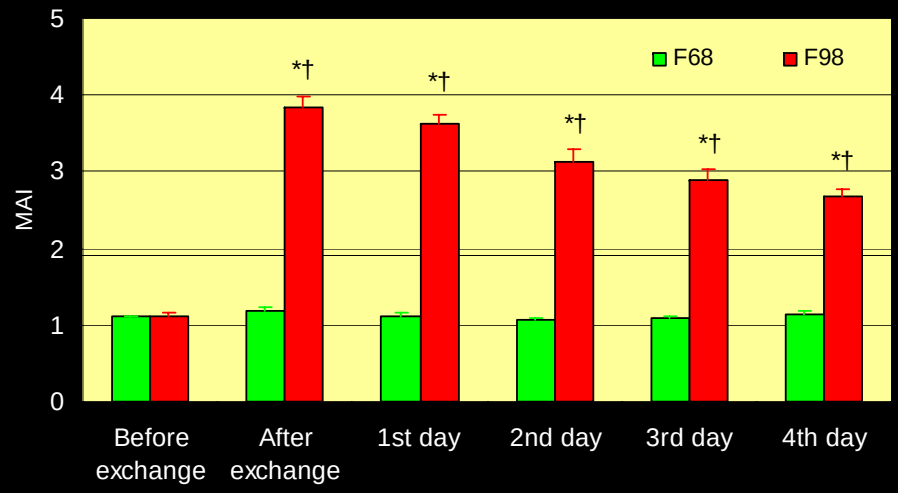


Aggregation vs vasomotor control

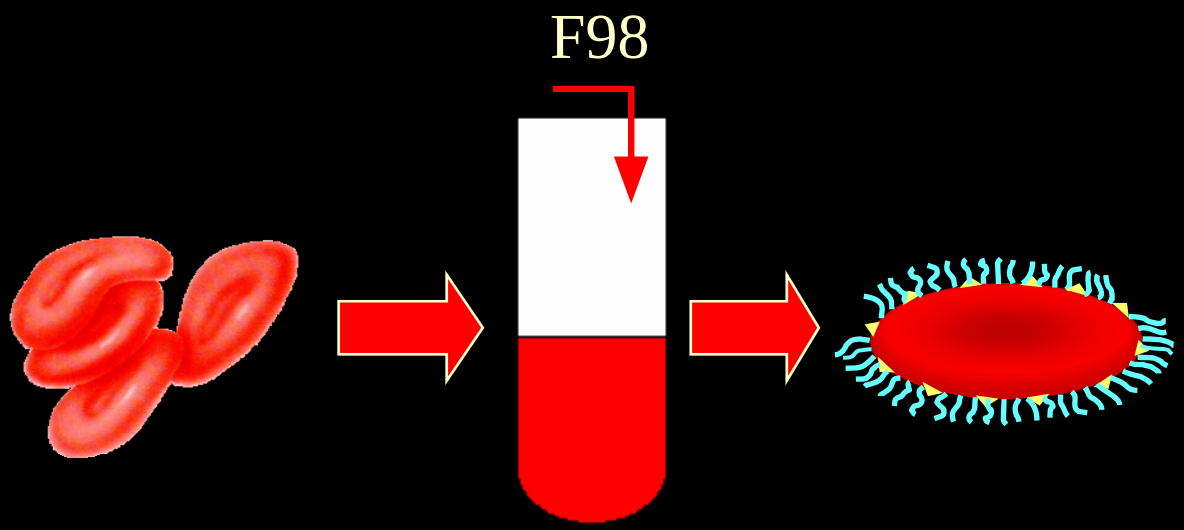
- Effect on vascular control mechanisms

  Baskurt et al., Am. J. Physiol. 286: H222, 2004.

  - Rat, chronically enhanced RBC aggregation
  - Exchange transfusions with Pluronic-coated RBC
  - Flow-mediated dilation and eNOS expression

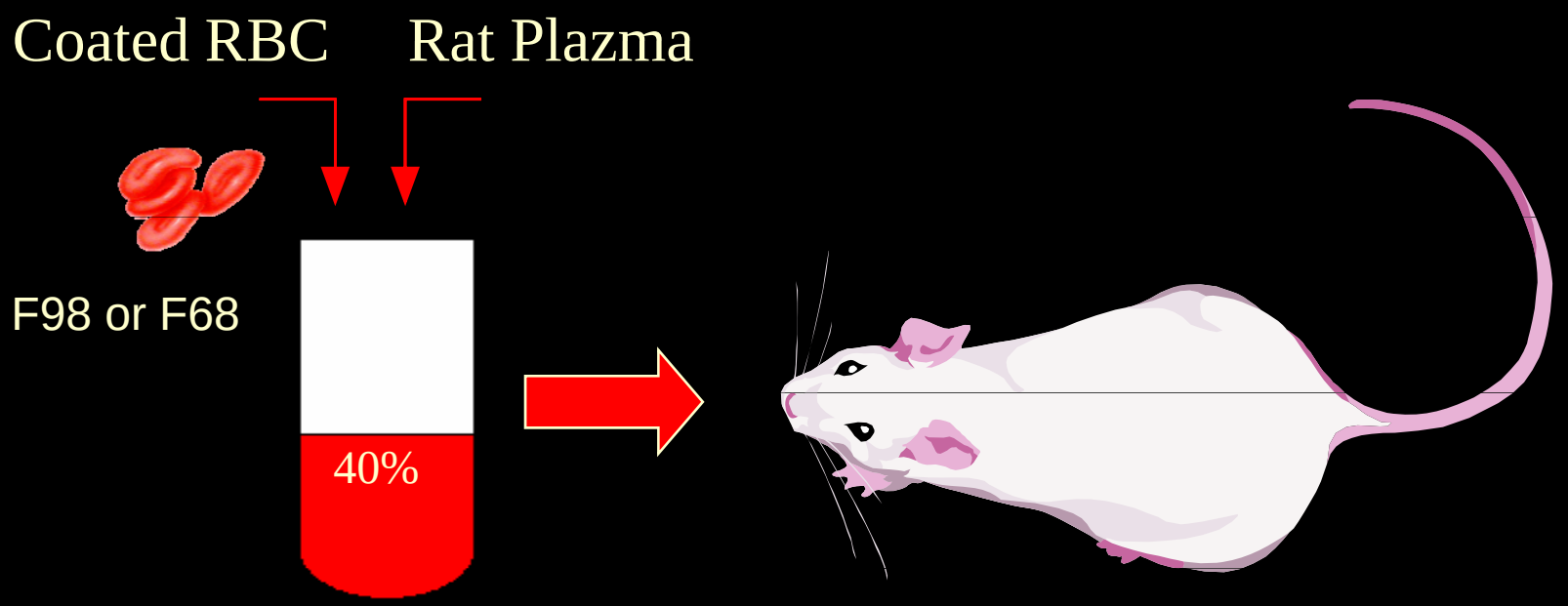


Chronically enhanced red cell aggregation



Armstrong J et al., Biorheology 38: 239, 2001.

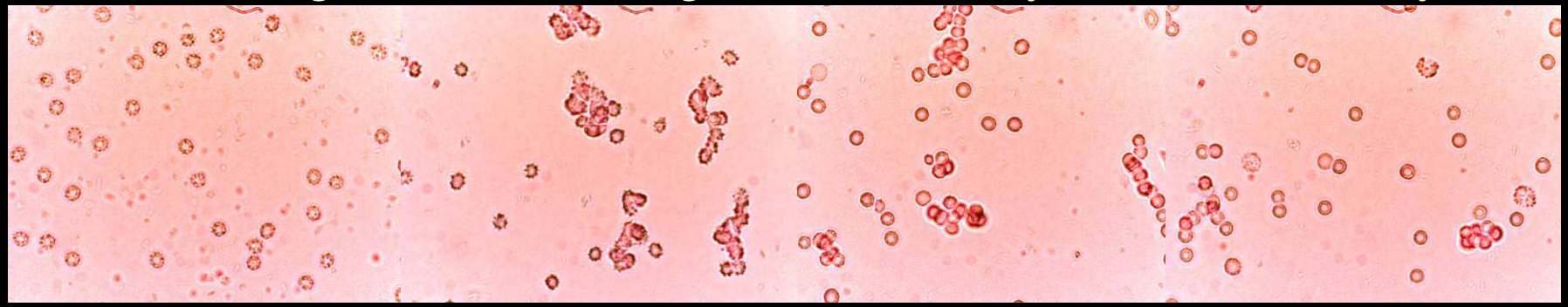
Chronically enhanced red cell aggregation



Chronically enhanced red cell aggregation

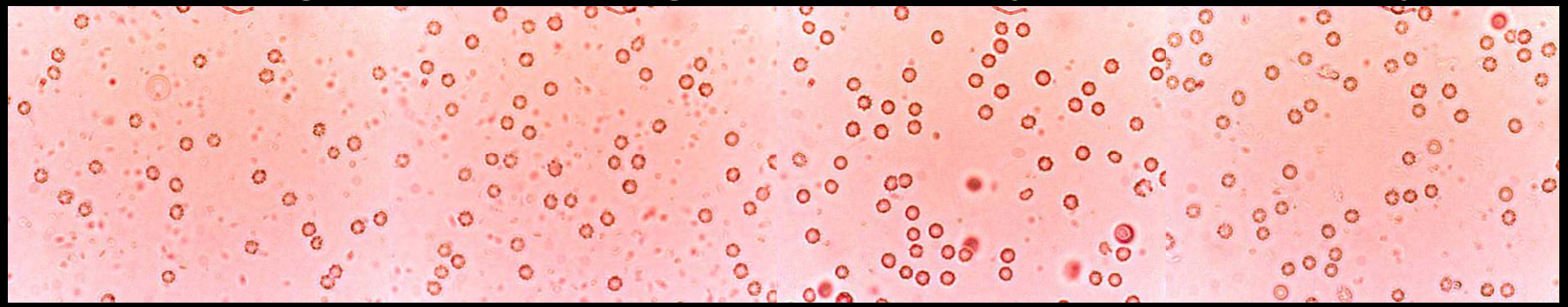
F98

Before exchange | After exchange | 1st day | 3rd day



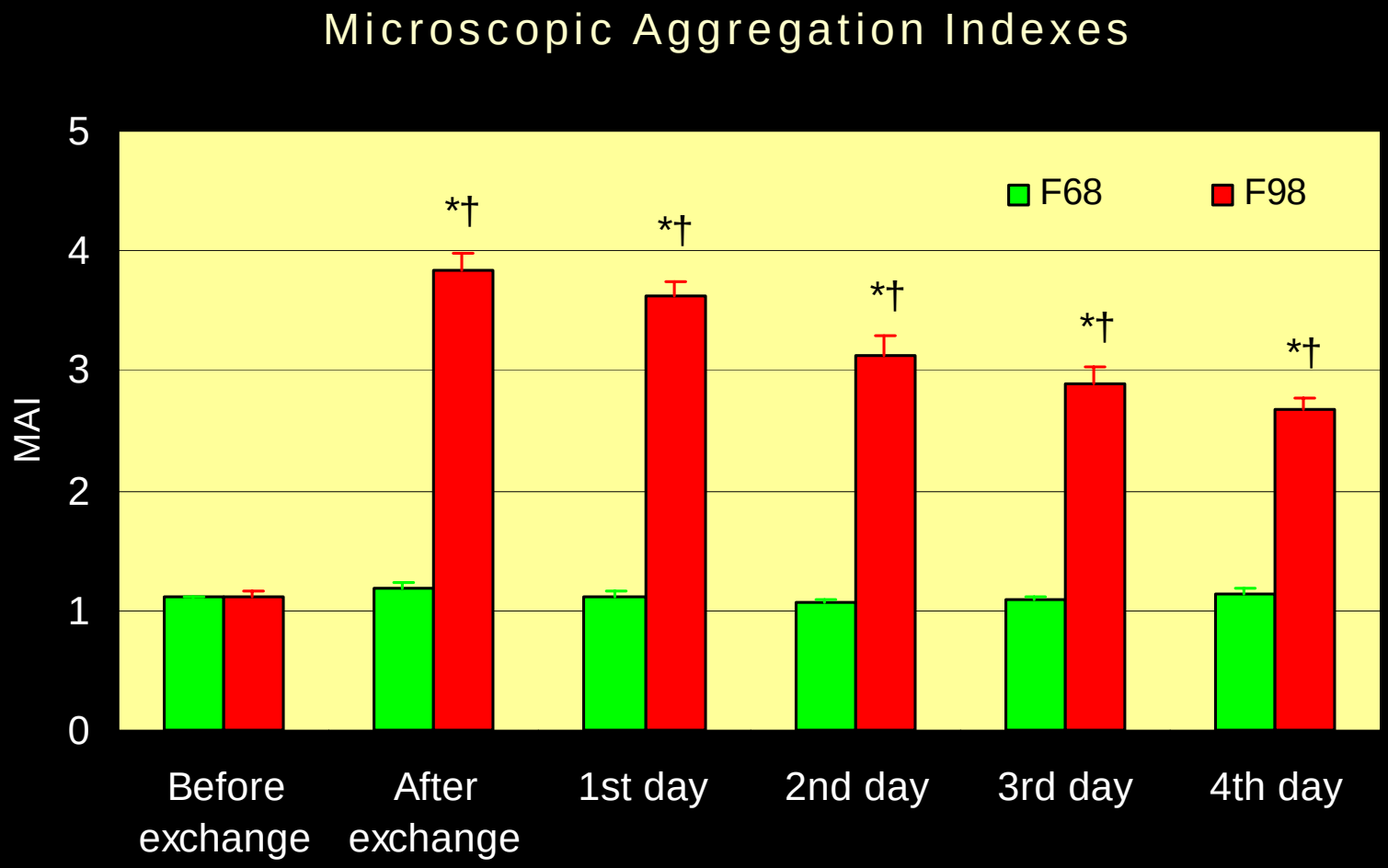
F68

Before exchange | After exchange | 1st day | 3rd day



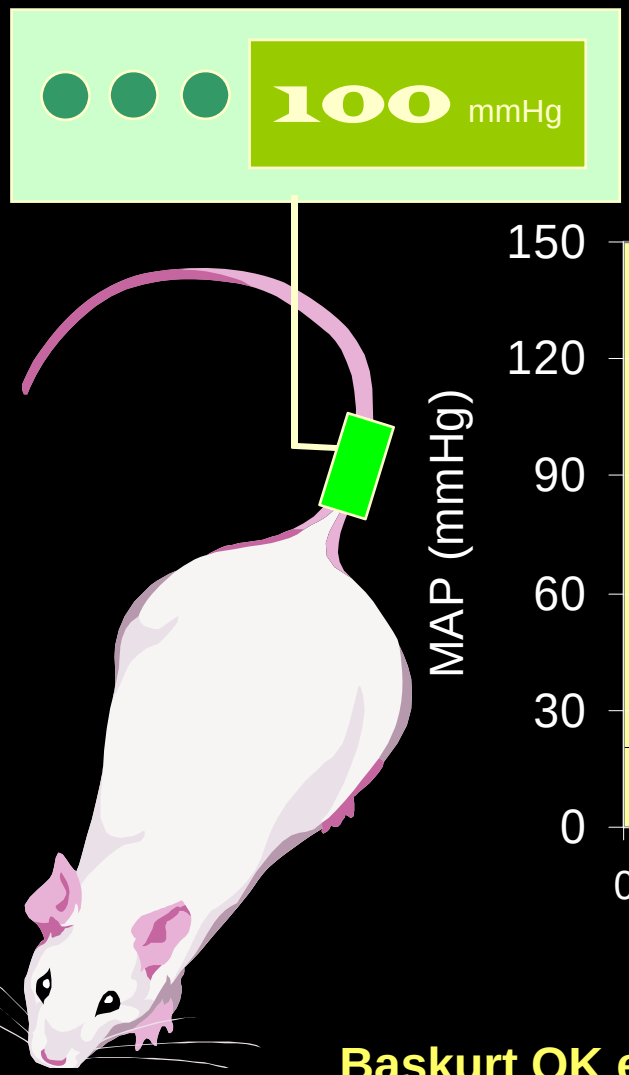
Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

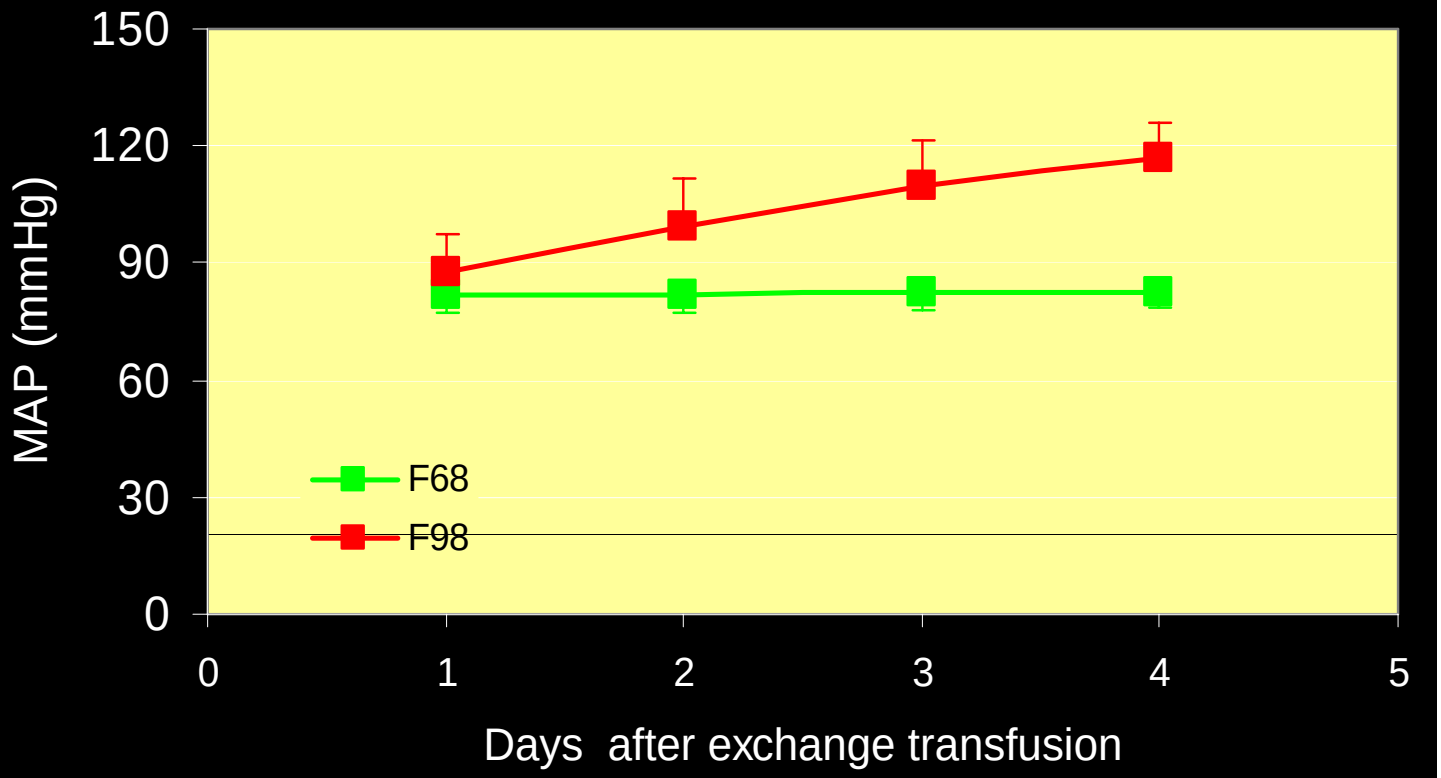
Chronically enhanced red cell aggregation



Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

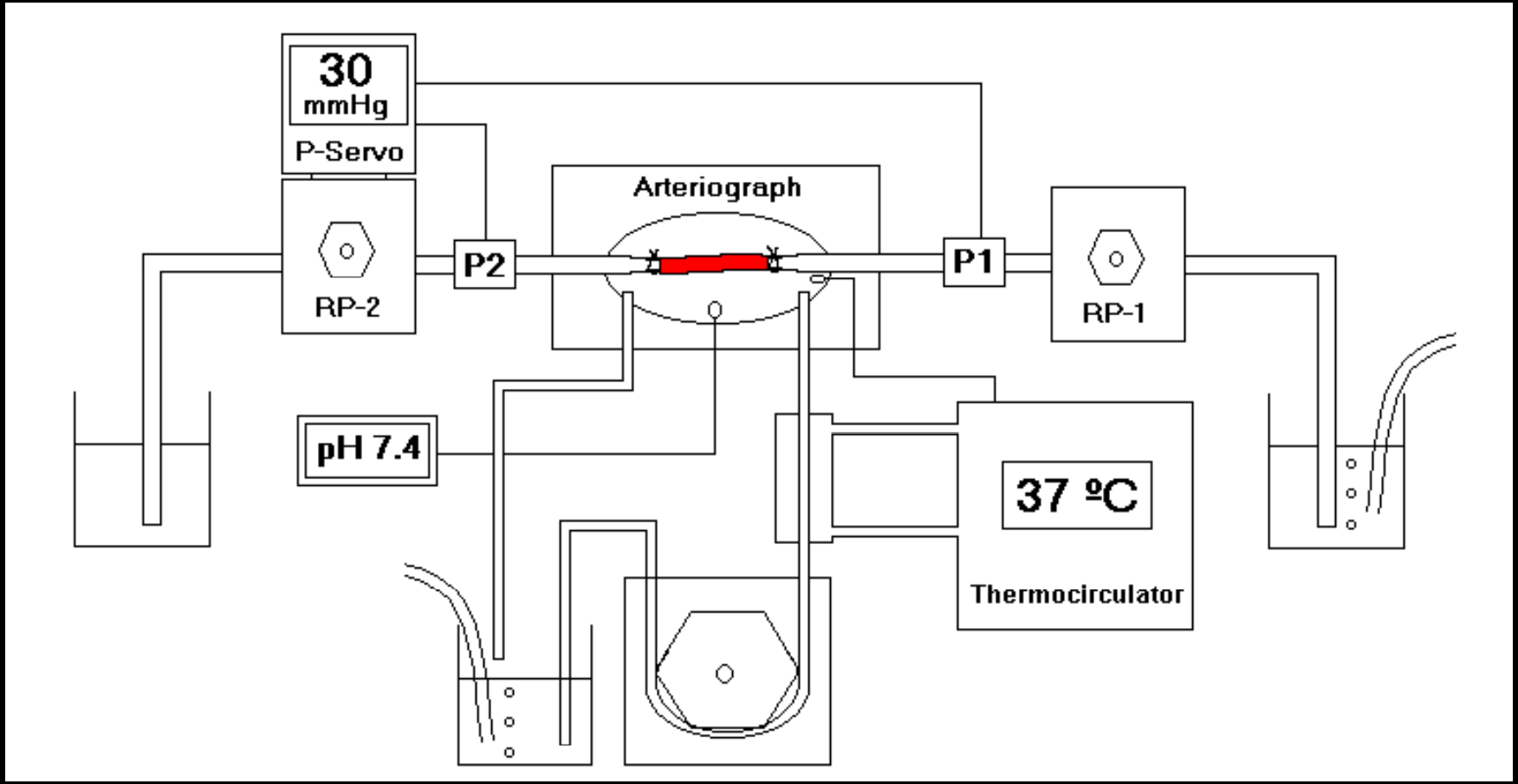
Mean arterial pressure



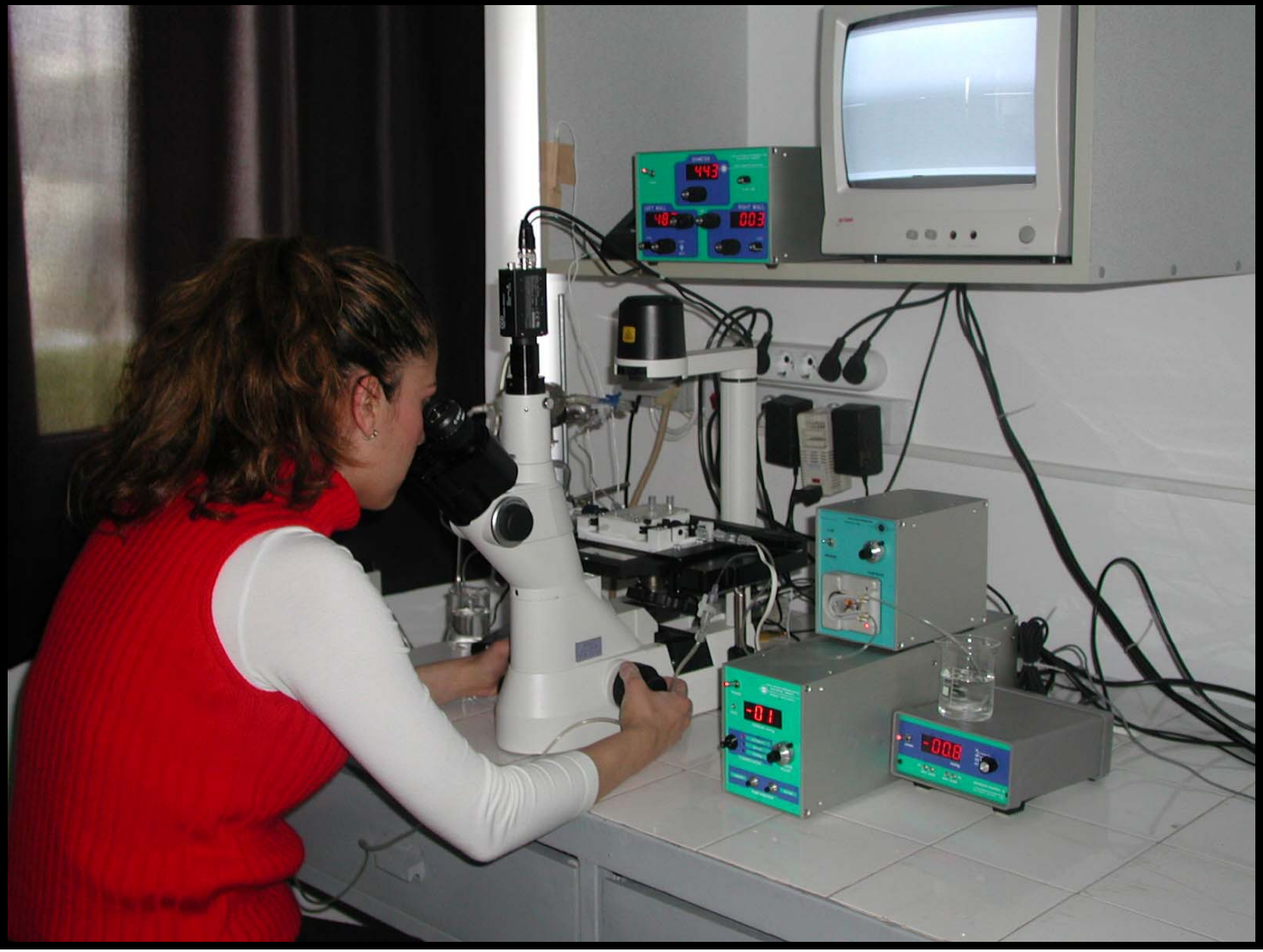


Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

Vascular studies



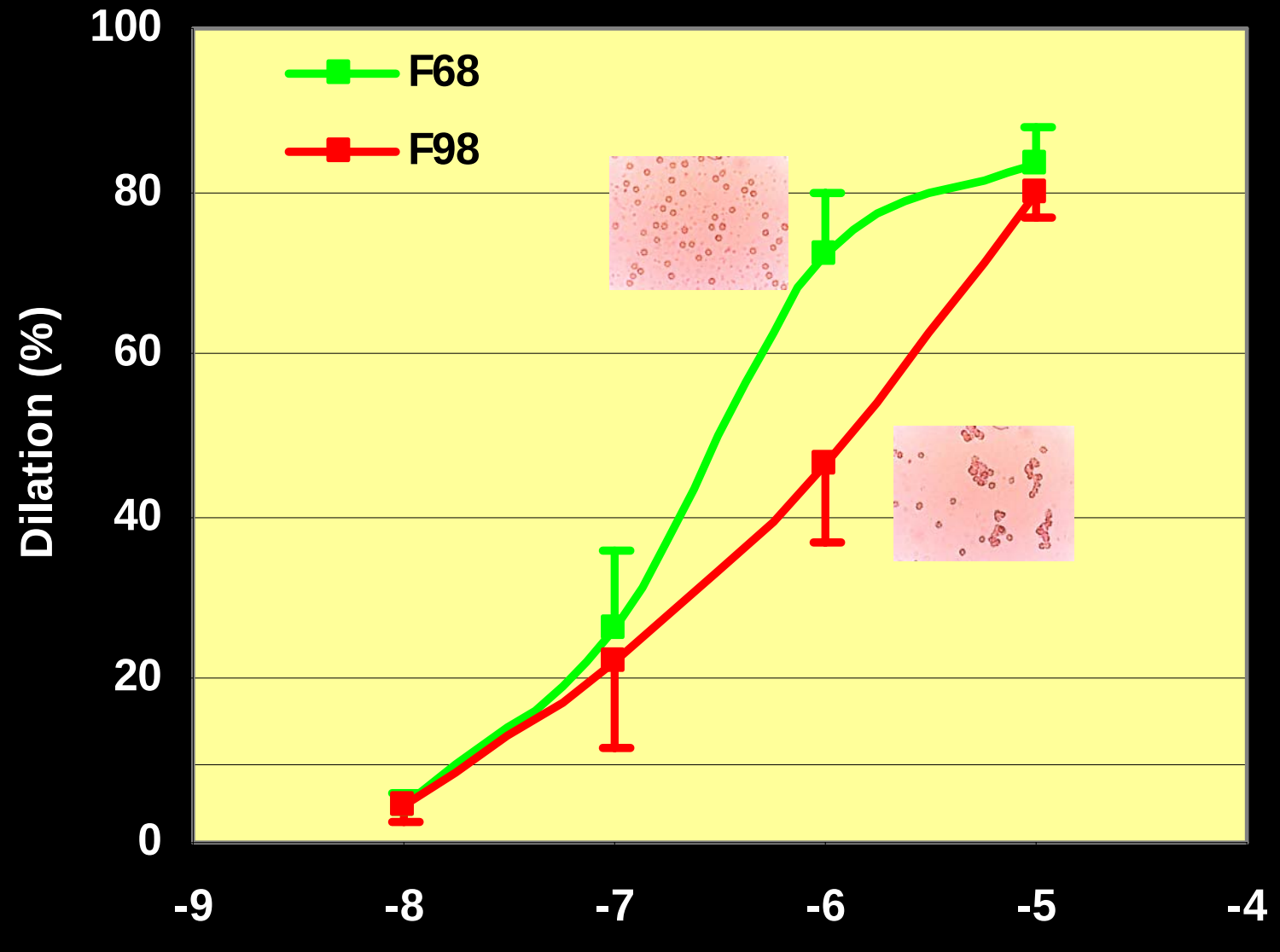
Vascular studies



Acetylcholine-induced dilation

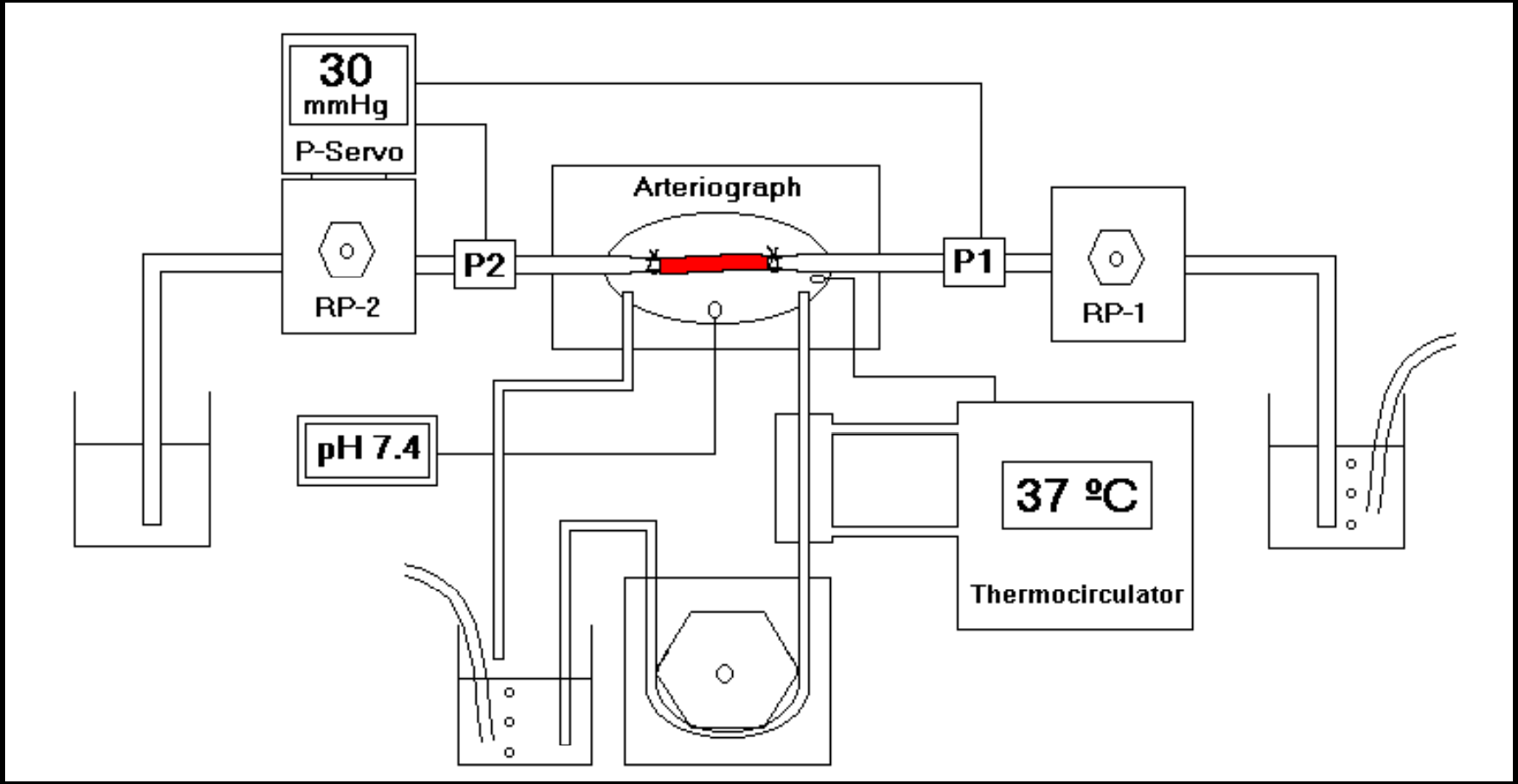
Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

Acetylcholine-induced dilation

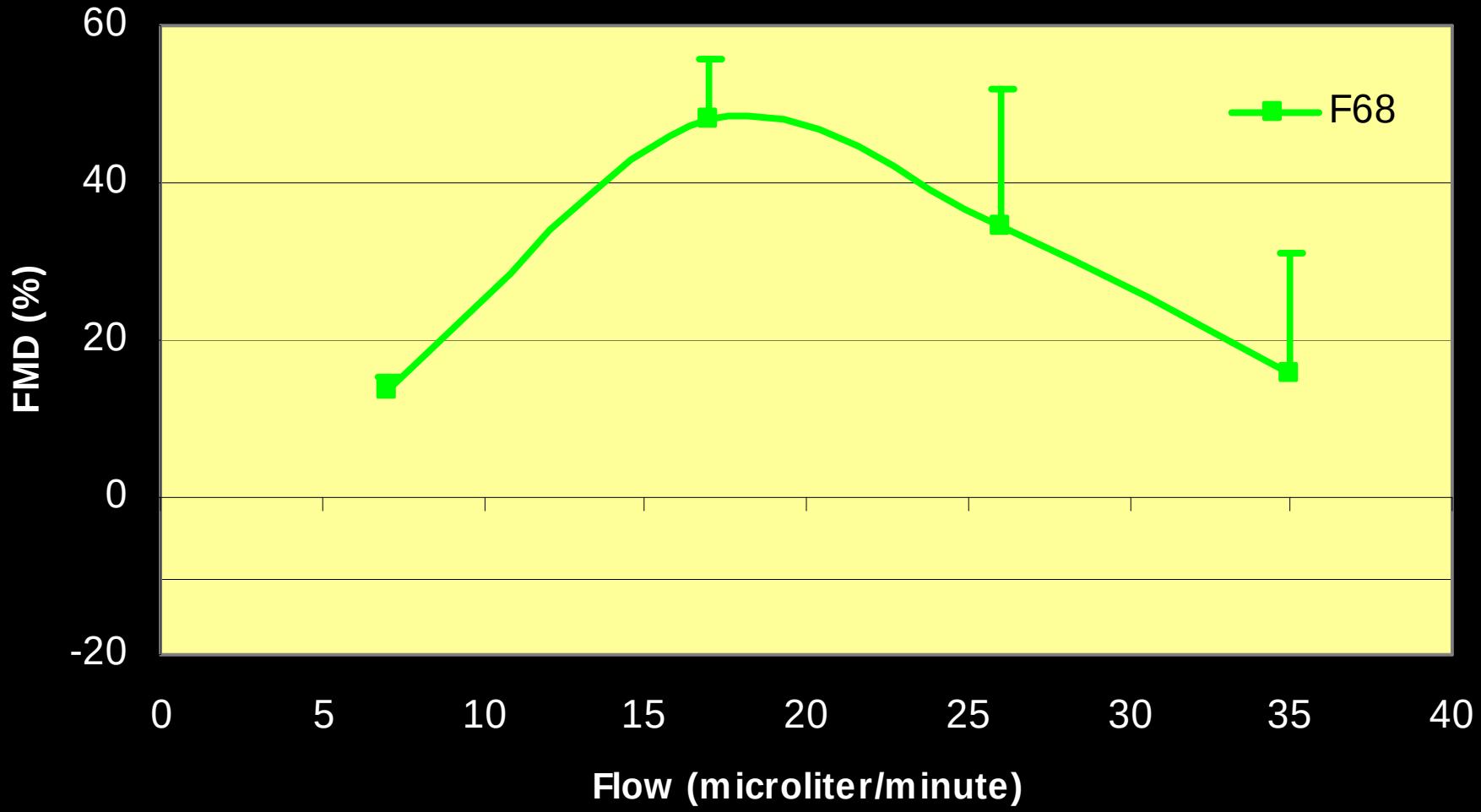


Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

Vascular studies



Flow-mediated dilation



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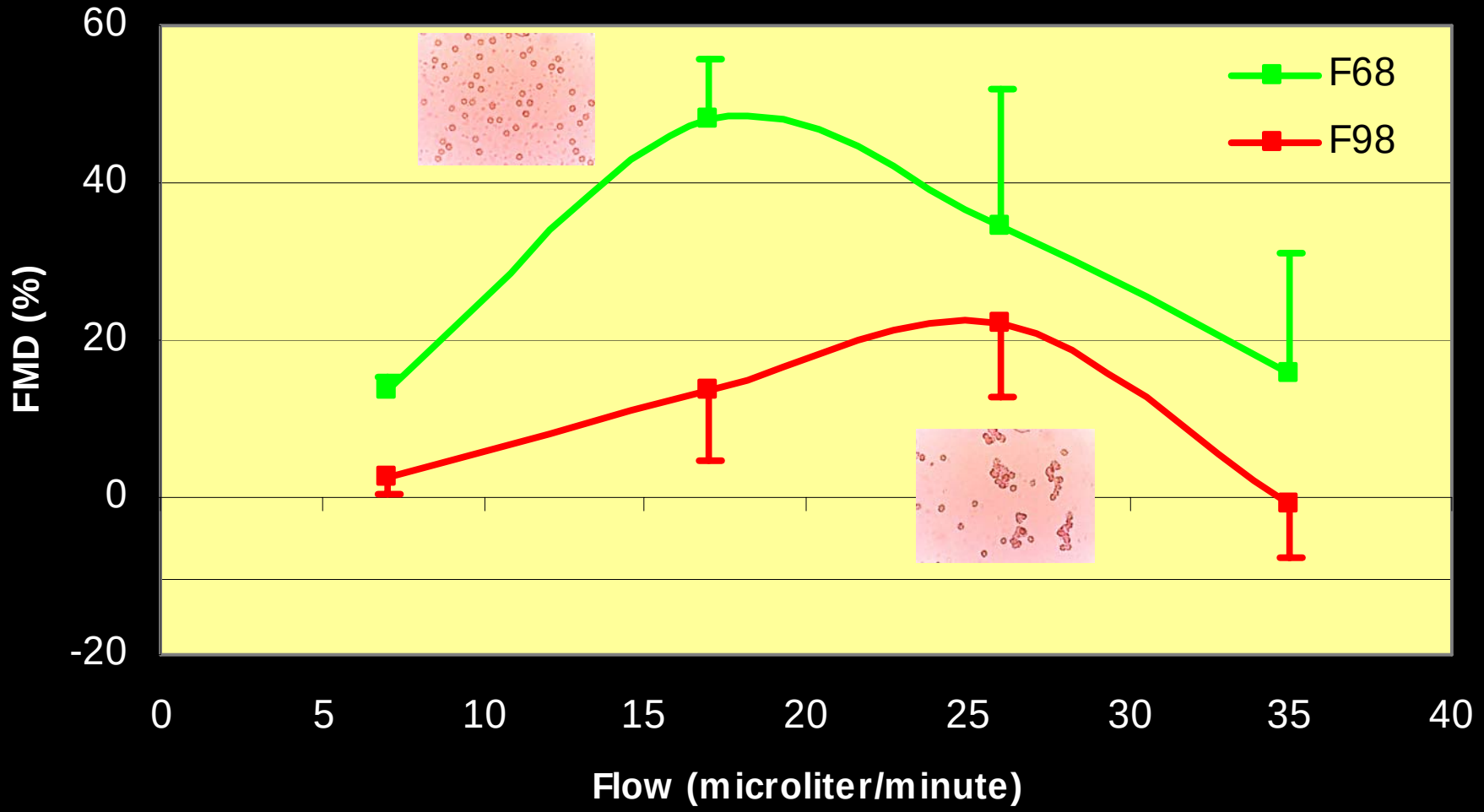
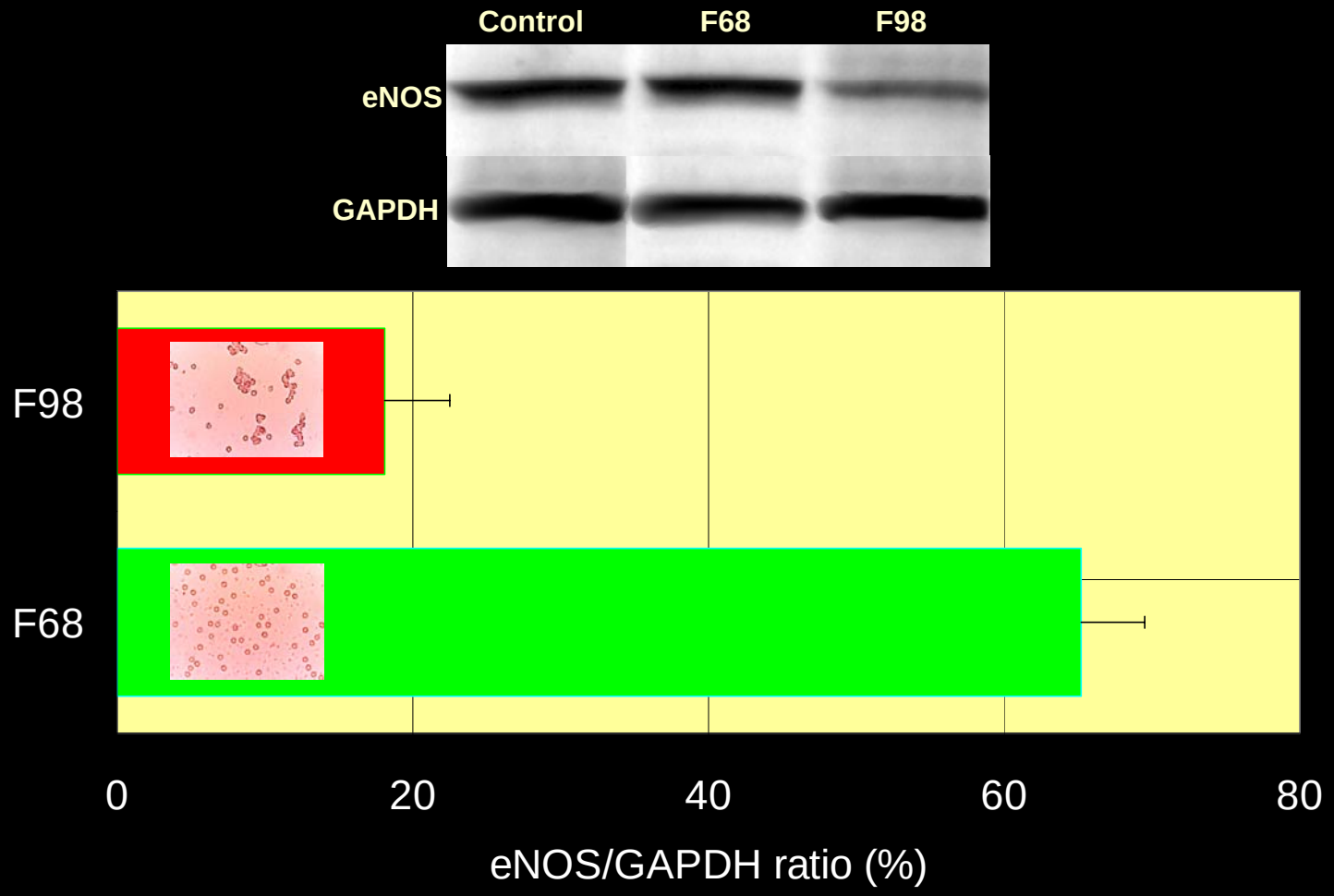
Flow-mediated dilation



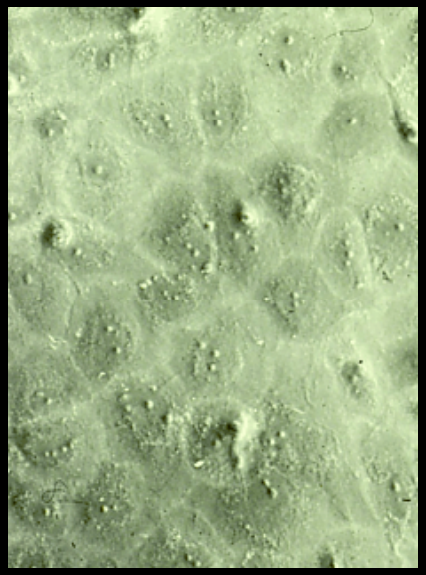
Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

eNOS expression

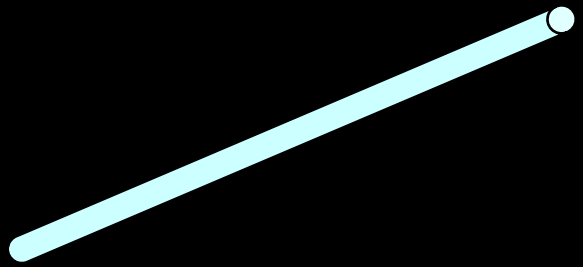


Baskurt OK et al., Am. J. Physiol. 286: H222, 2004.

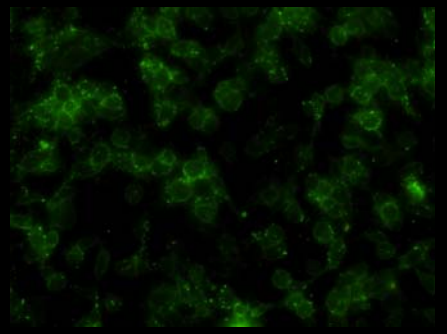
Collagenase

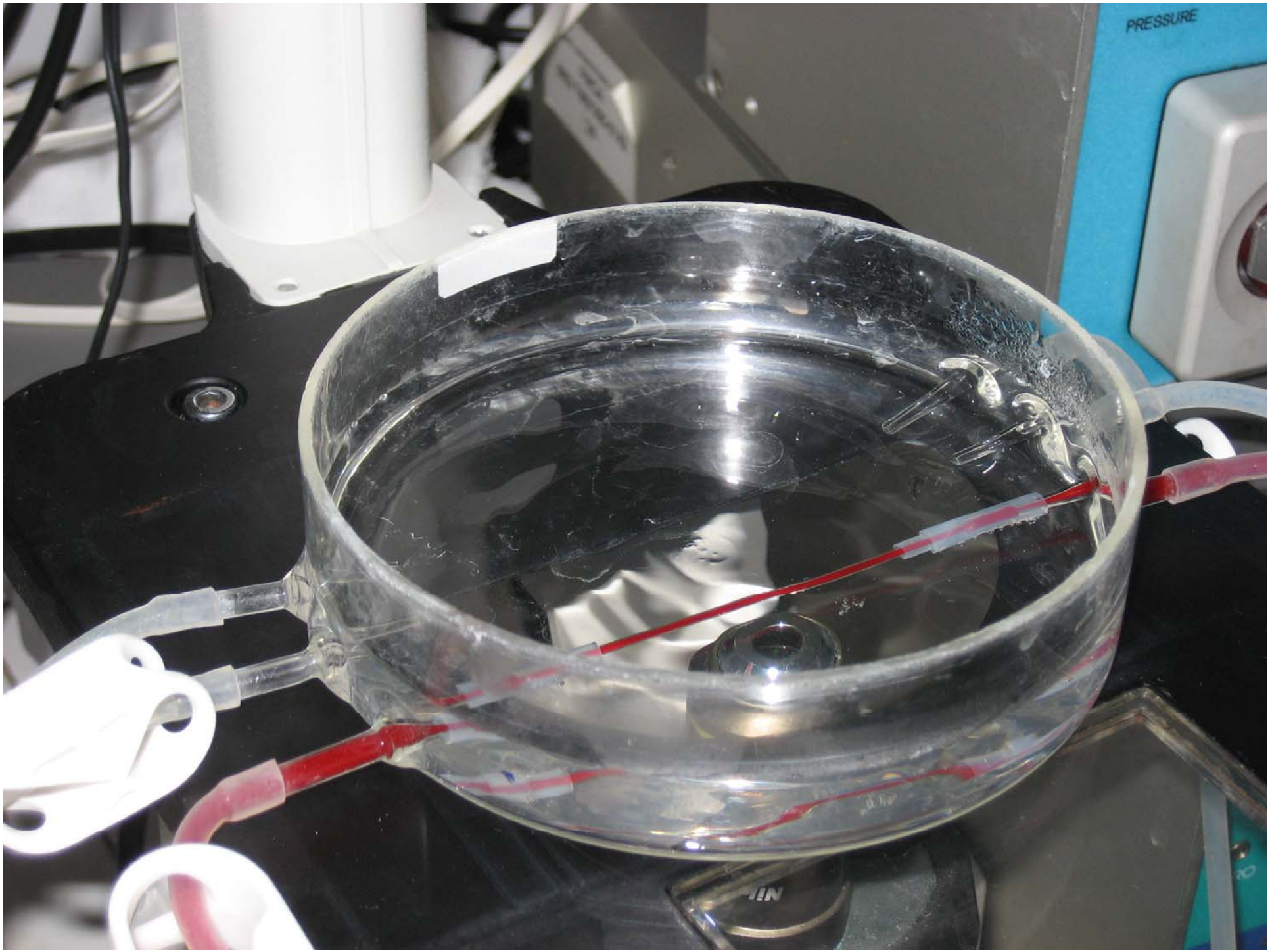


HUVEC Culture



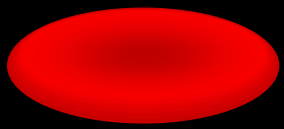
d: 0.1 cm; L: 7.5 cm

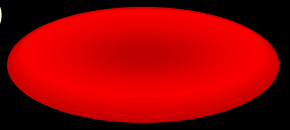



PRESSURE

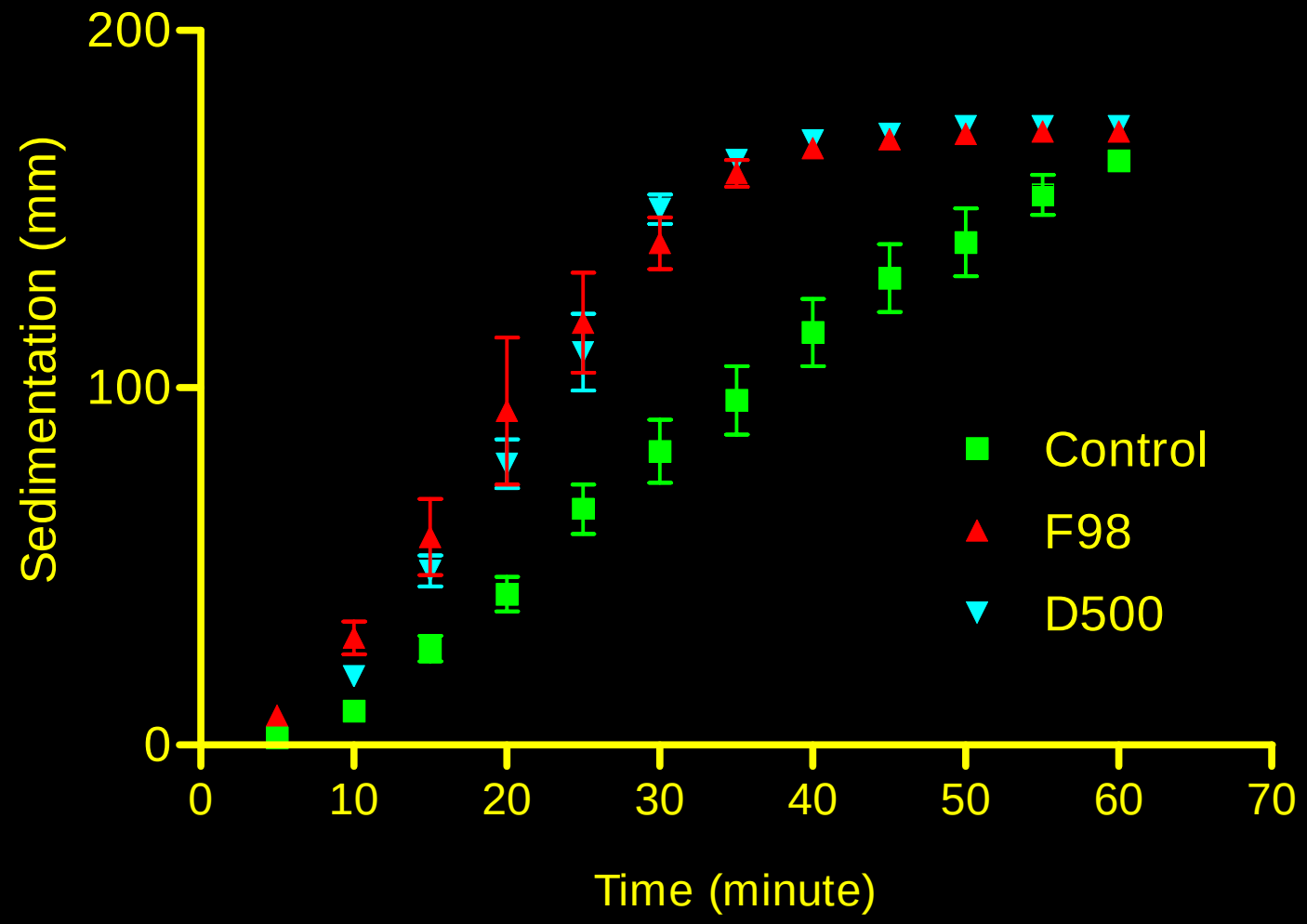
RBC Suspensions (Hematocrit: 30%)

- Normal RBC + Normal plasma
  (Control)
- F98 coated RBC + Normal plasma
  (F98 group)
- Normal RBC + Plasma containing 0.5% Dextran 500
  (D500)

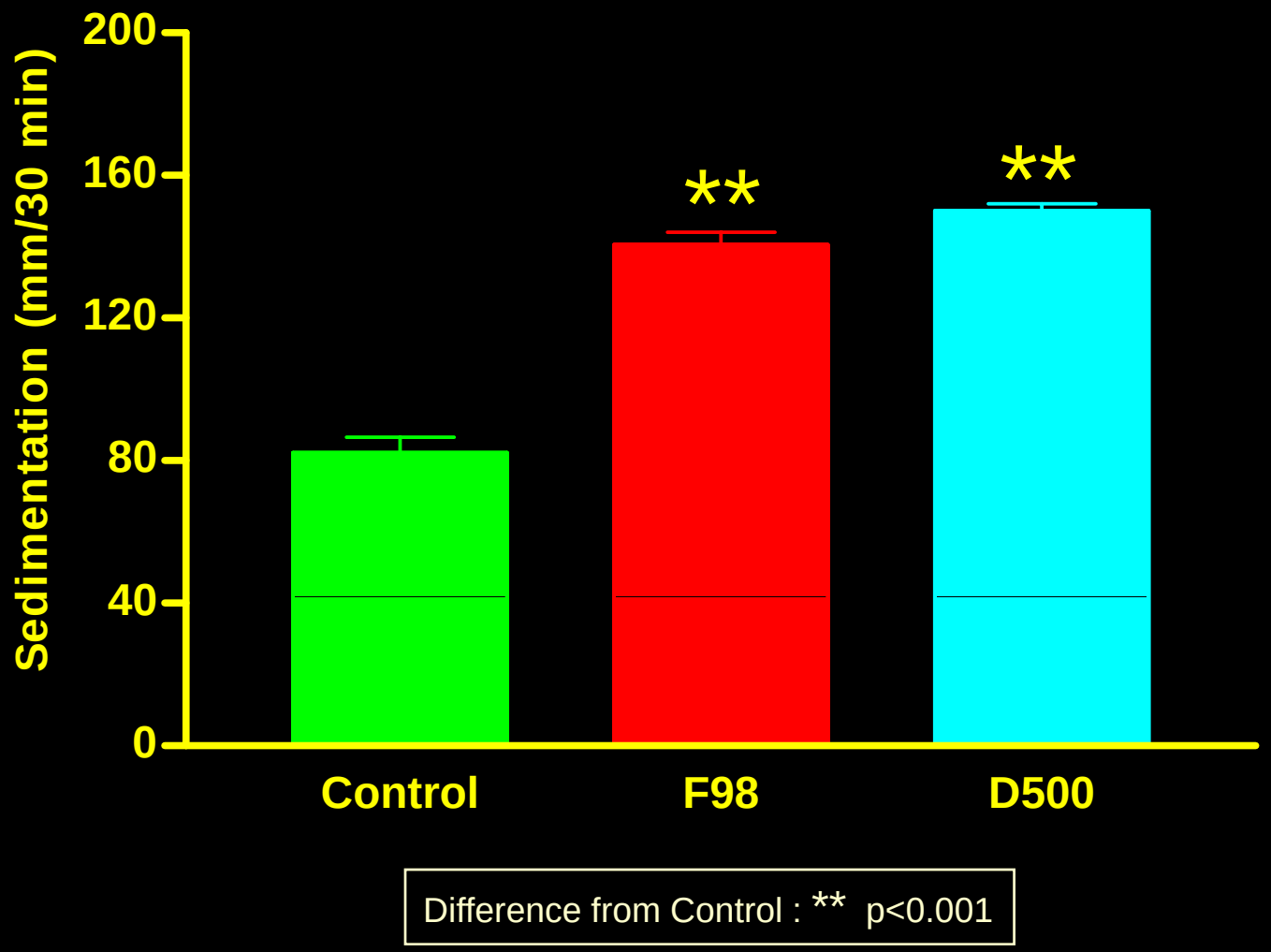




Erythrocyte sedimentation rate

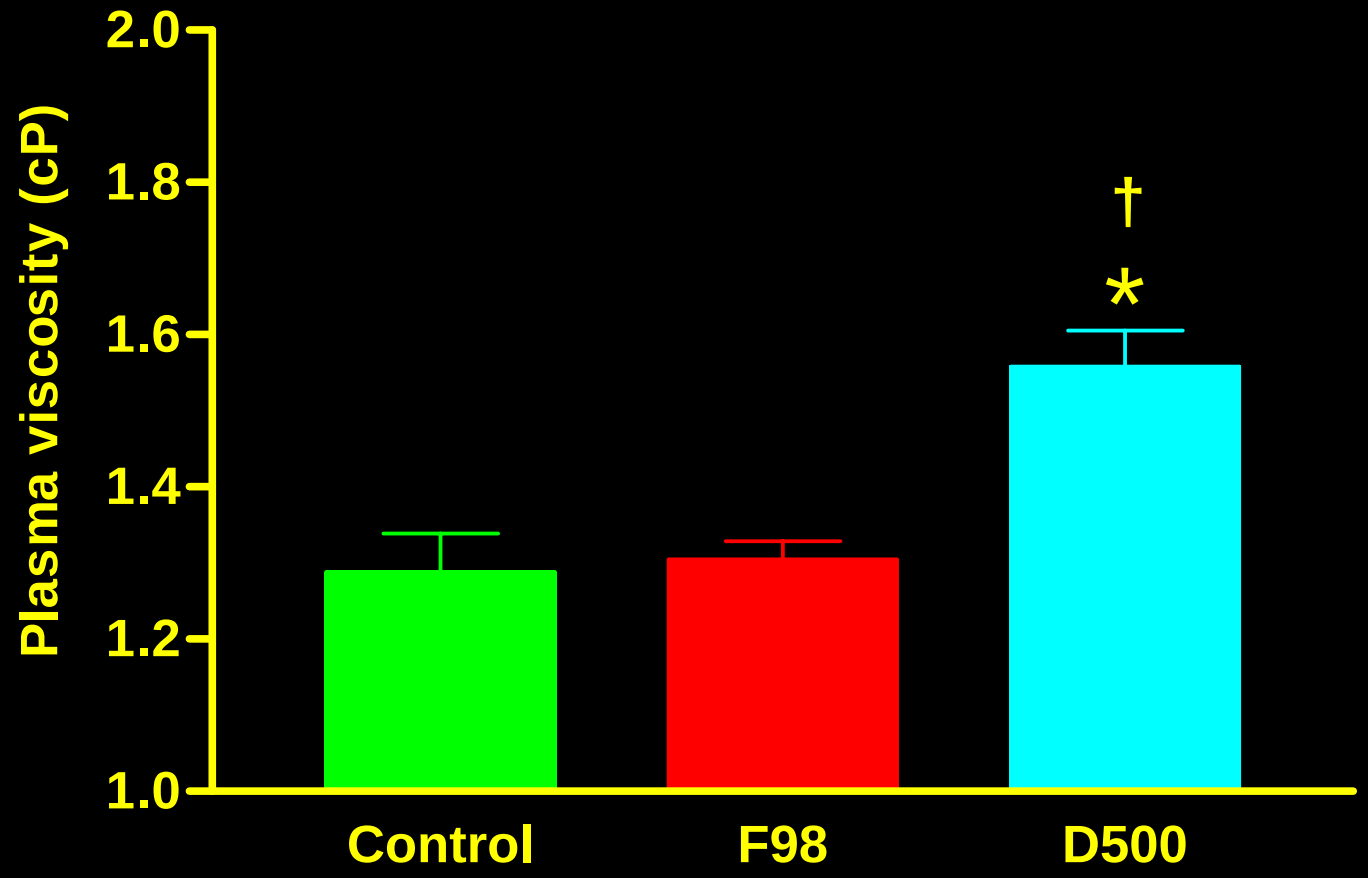


Erythrocyte sedimentation rate



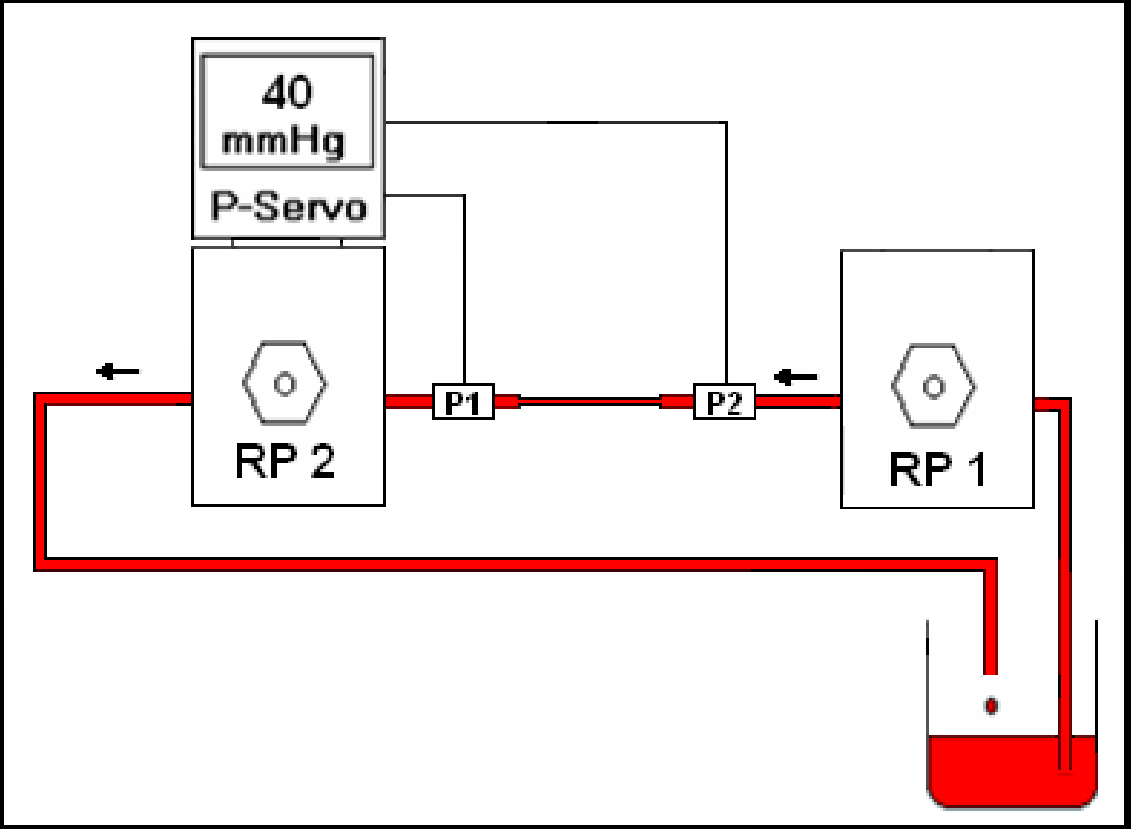
Difference from Control : ** p<0.001

Plasma viscosity

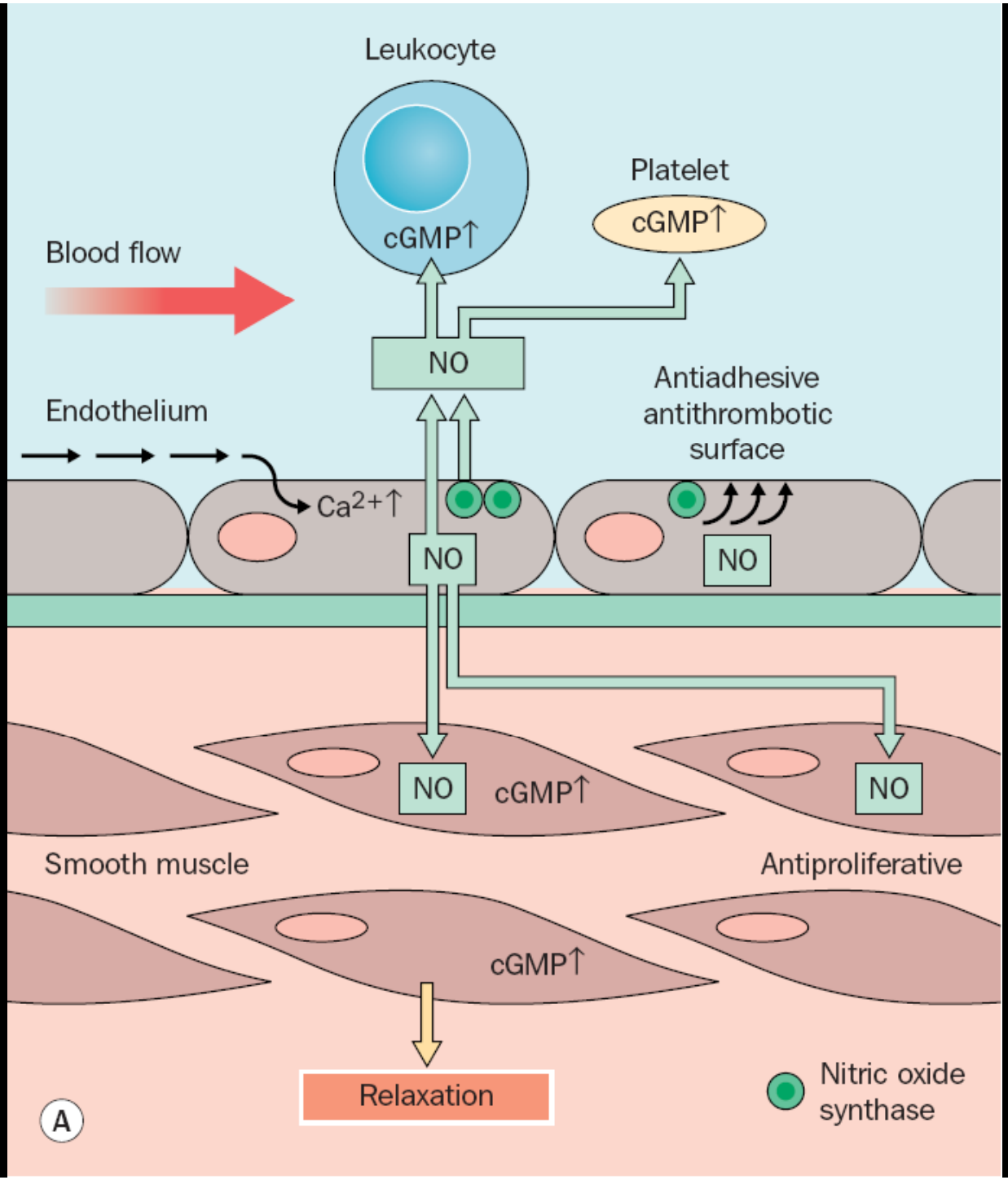


Difference from Control: * p<0.01;
Difference from F98 : † p<0.01

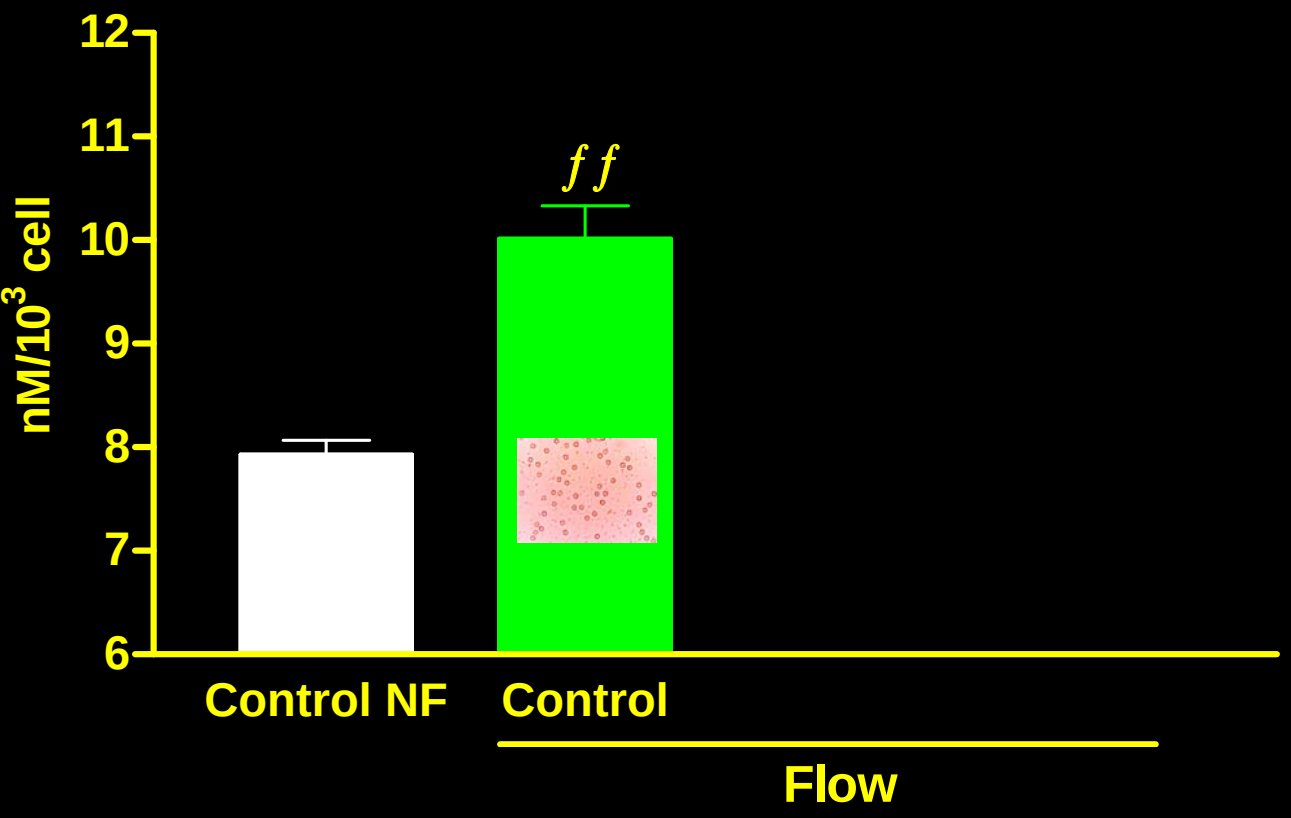
Perfusion



- Wall shear stress (nominal): 15 dyn/cm^2
- Mean pressure: 40 mmHg
- 37 ˚C; 30 minutes

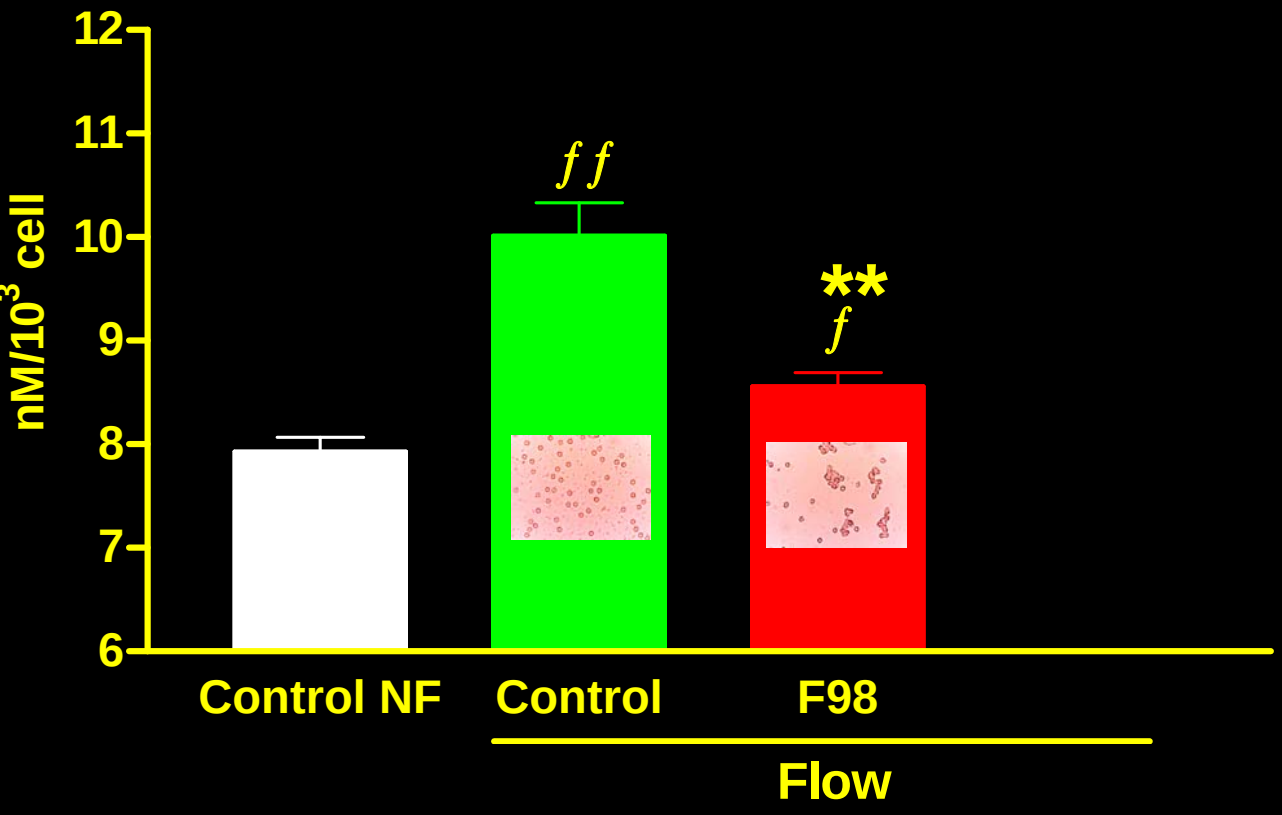

Leukocyte
cGMP↑
Platelet
cGMP↑
Blood flow
NO
Endothelium
Antiadhesive
antithrombotic
surface
Ca2+↑
NO
NO
NO
cGMP↑
NO
Smooth muscle
Antiproliferative
cGMP↑
Relaxation
A
Nitric oxide
synthase

Nitrite/nitrate



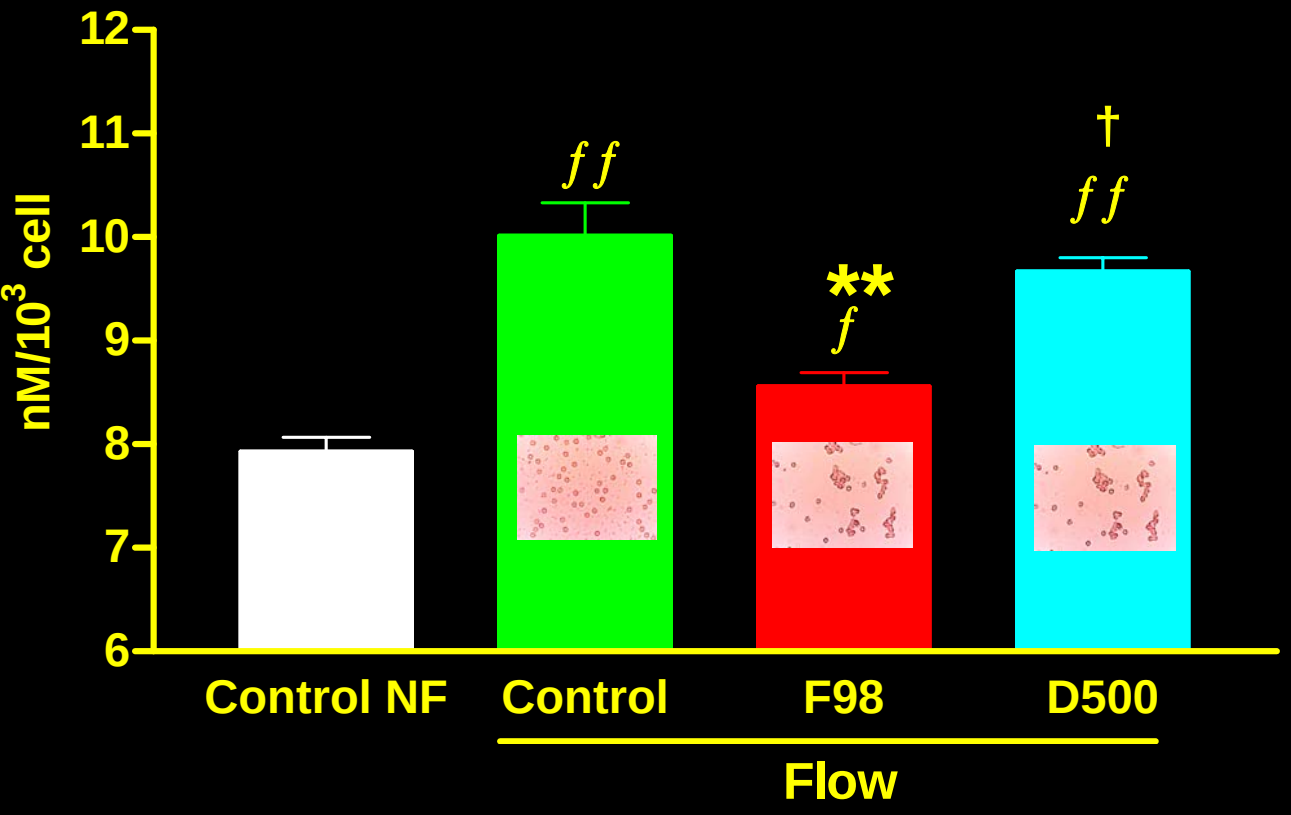
Difference from Control NF: ƒ p<0.05; ƒ ƒ p<0.001
Difference from Control : **p<0.001
Difference from F98 : † p<0.01

Nitrite/nitrate



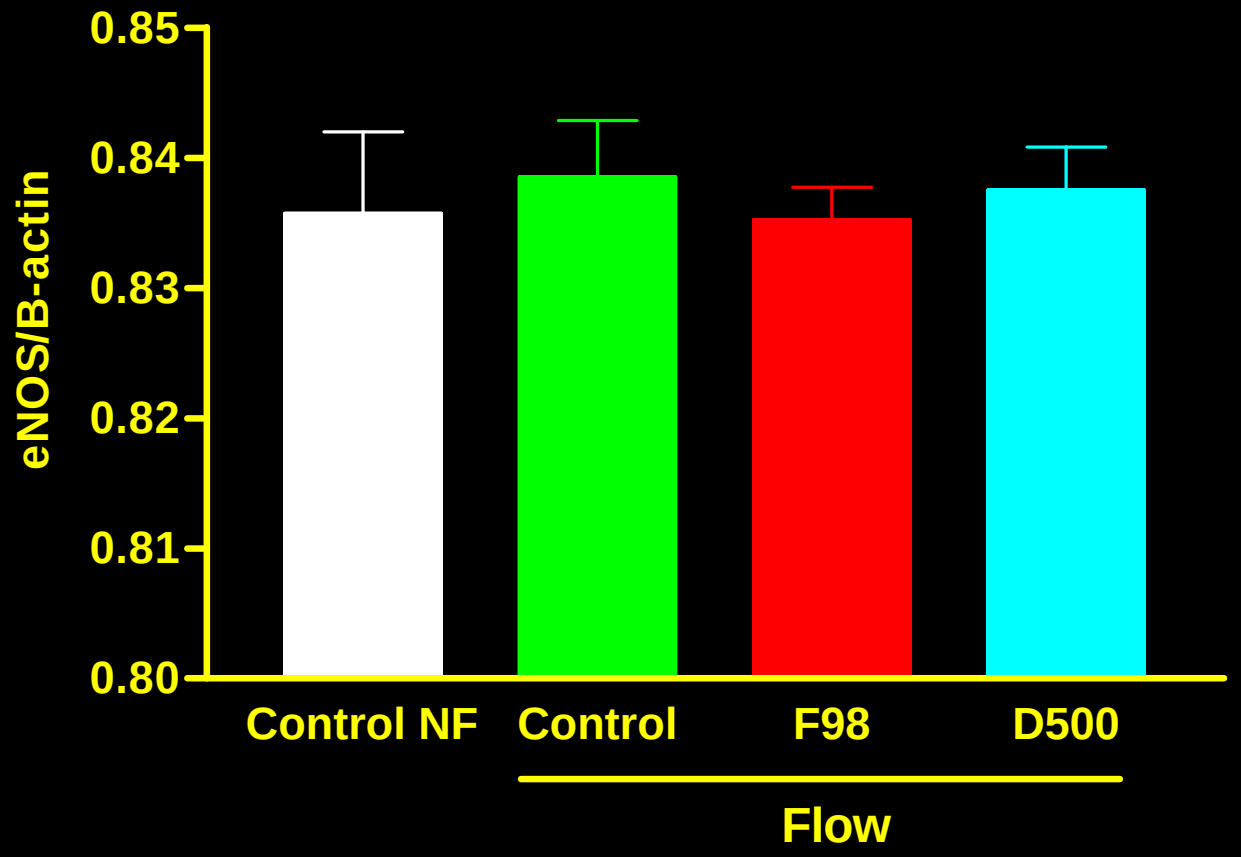
Difference from Control NF: ƒ p<0.05; ƒ ƒ p<0.001
Difference from Control : **p<0.001
Difference from F98 : † p<0.01

Nitrite/nitrate

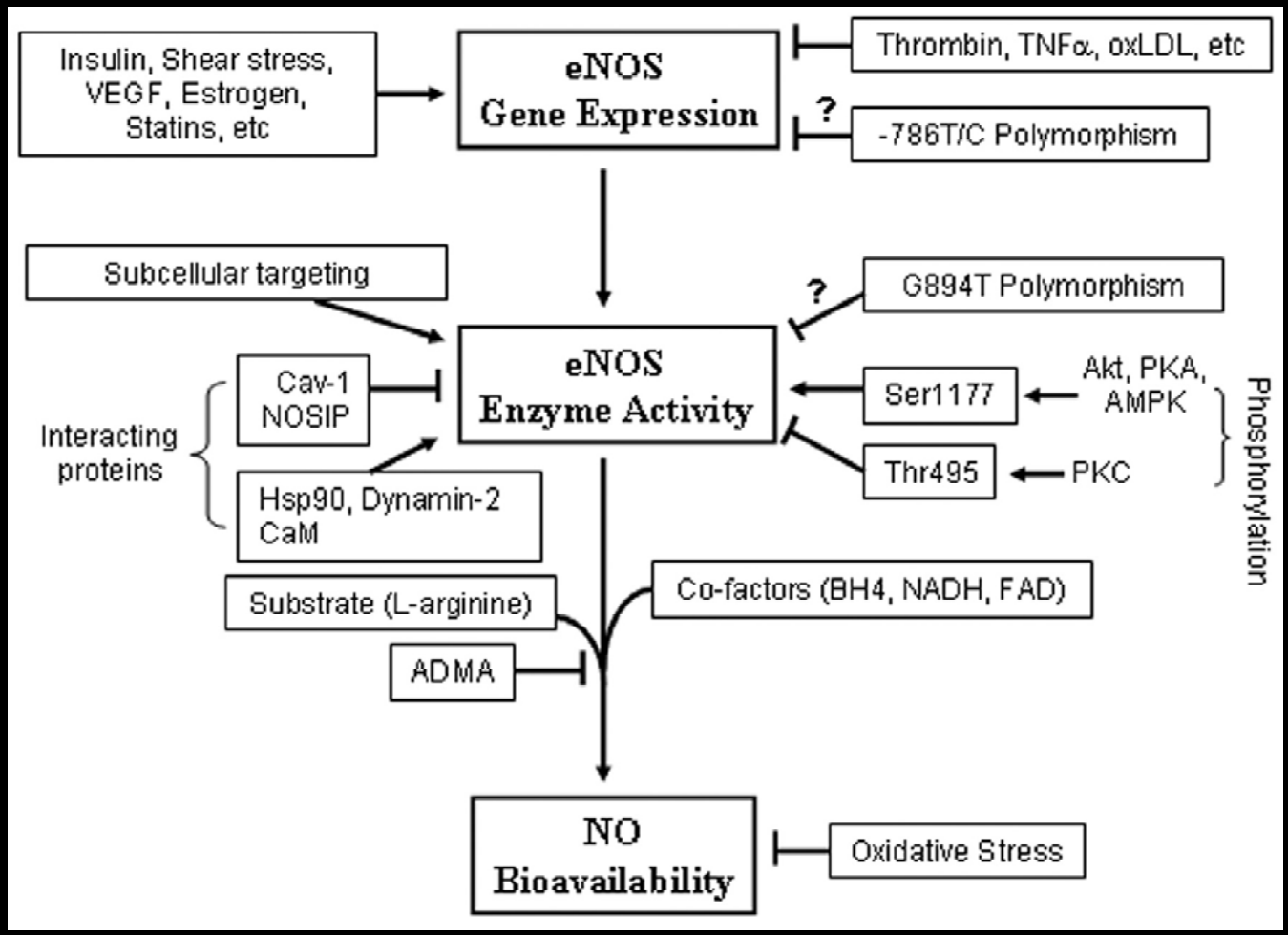


Difference from Control NF: ƒ p<0.05; ƒ ƒ p<0.001
Difference from Control : **p<0.001
Difference from F98 : † p<0.01

eNOS protein

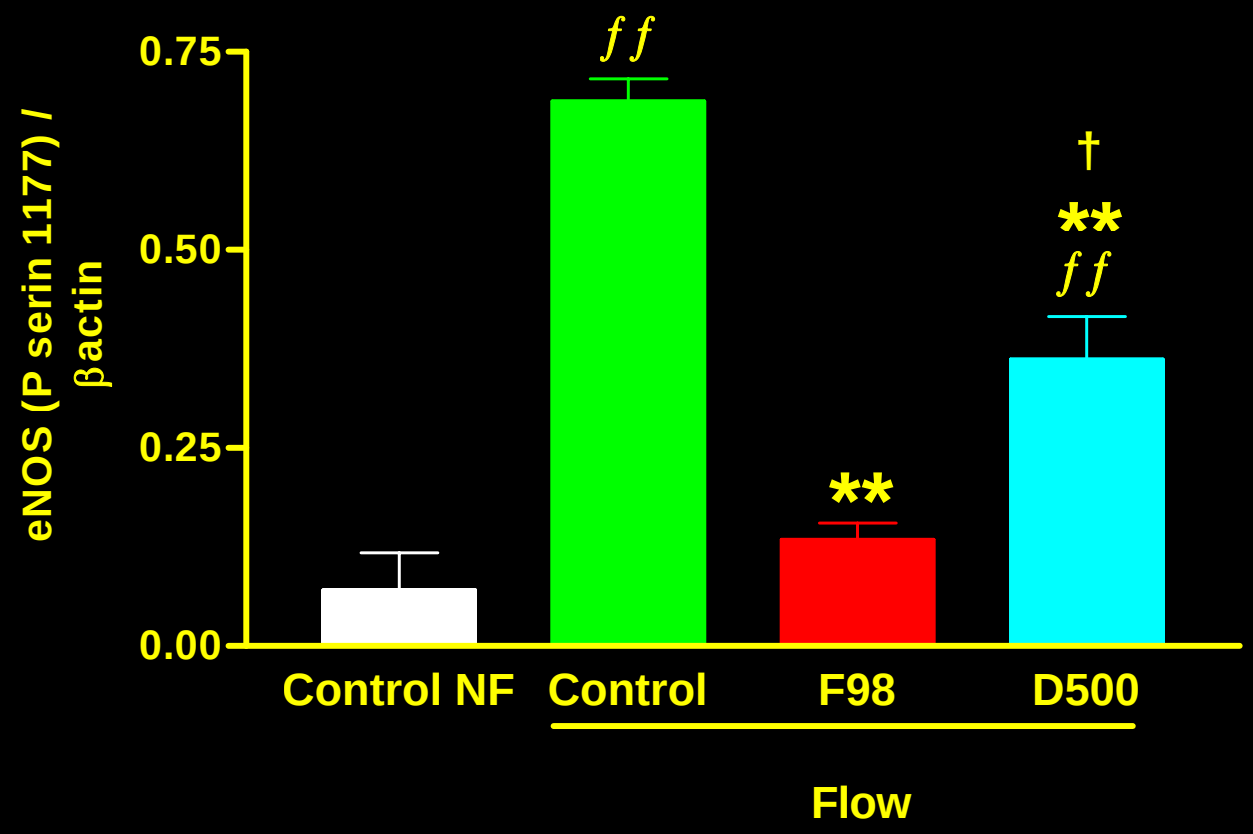


eNOS activation

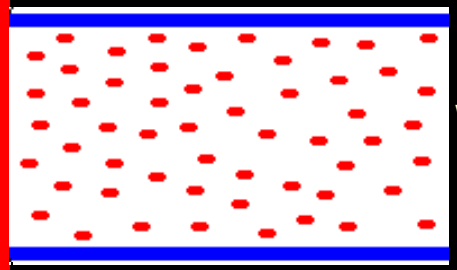


Yang Z and Ming XF, Clin. Med. Res. 4: 53, 2008.

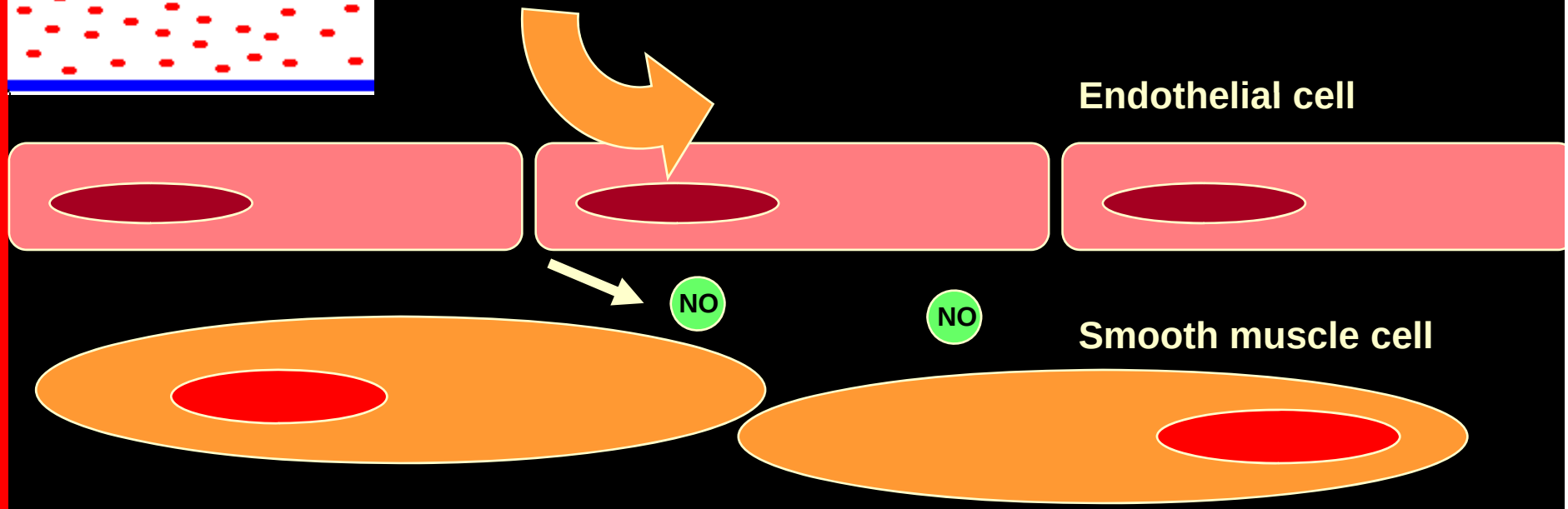
Serine 1177 phosphorylated eNOS

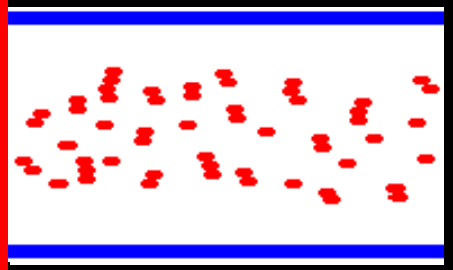


Difference from Control NF:	ƒ ƒ p<0.001
Difference from Control	: ** p<0.001
Difference from F98	: † p<0.01

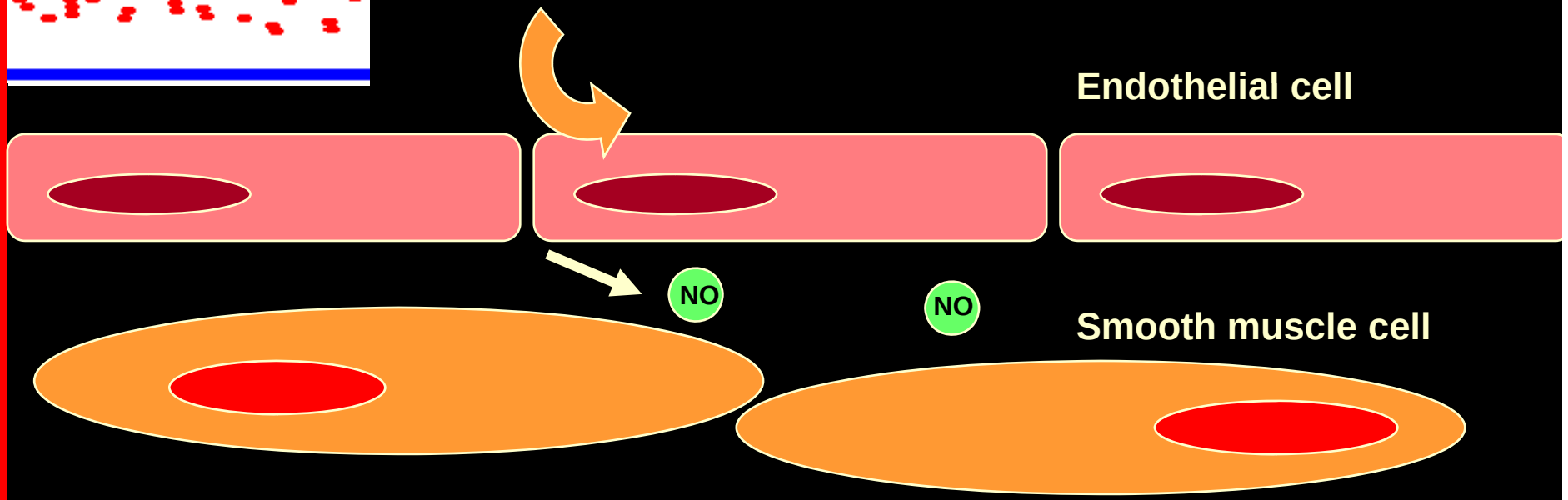


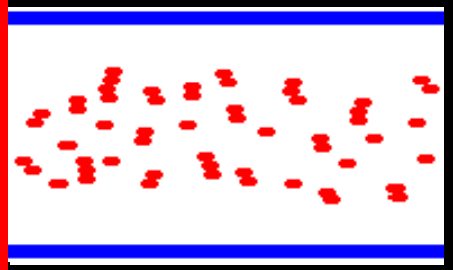
Wall shear stress = Fluid velocity x Fluid viscosity





Wall shear stress = Fluid velocity x **Fluid viscosity**

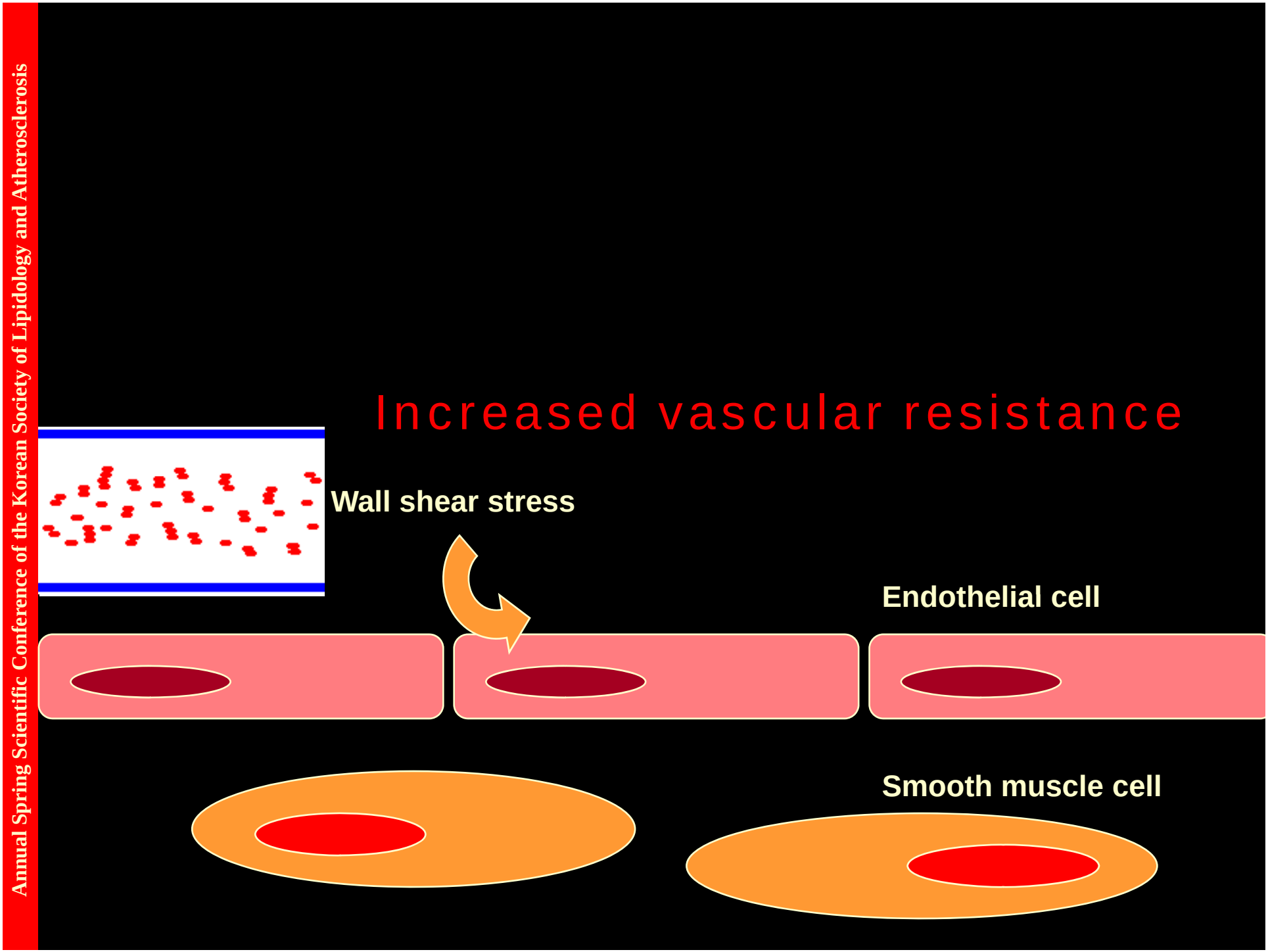




Wall shear stress = Fluid velocity x **Fluid viscosity**

Endothelial cell

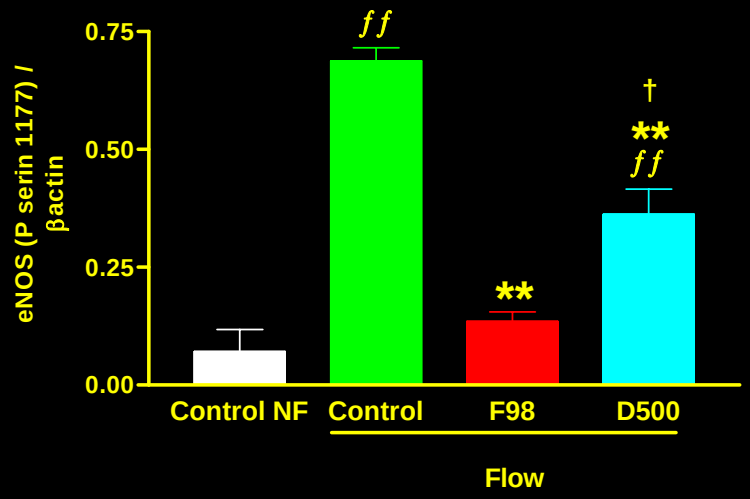
Smooth muscle cell

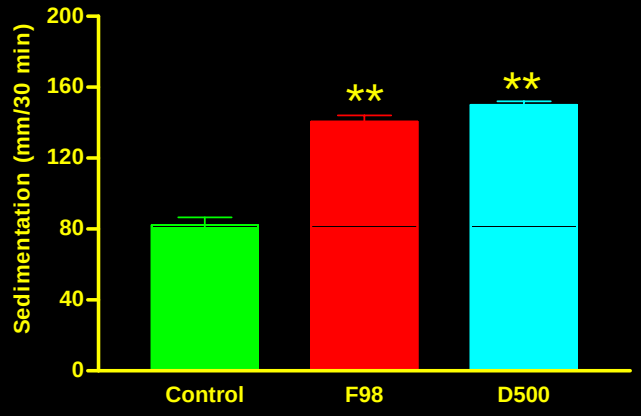

Increased vascular resistance
Wall shear stress
Endothelial cell
Smooth muscle cell

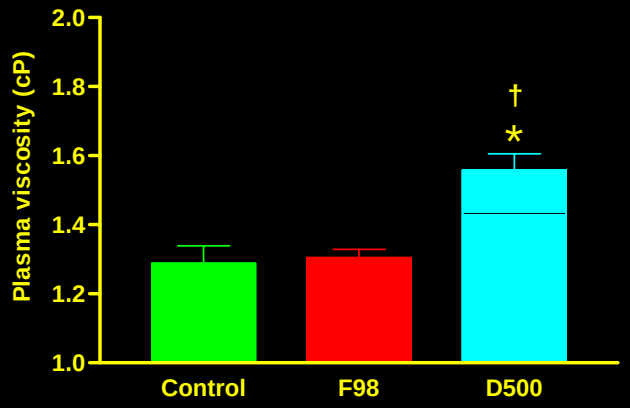
	Hemodynamic Shear Stress	
	Physiologic Arterial Magnitude (τ_S>15 dyne/cm^2)	Low Arterial Magnitude (τ_S~ ± 0-4 dyne/cm^2)
Endothelial cell morphology	Fusiform aligned	Polygonal unaligned
Endothelial cell function		
Vasoactive agents		
Vasoconstrictors		
ET-1[102]/ECE[86]	Low	High
ACE[60]	Low	High
Vasodilators		
NO/NO syntase[67-69,81-83]	High	Low
PGI_2/PGI_2 synthase[66-84]	High	Low
CNP[86]	High	Low
Adrenomedullin[87]	High	Low
Antioxidant enzymes		
COX-1, 2[85]	High	Low
Mn SOD[85]	High	Low
Cu/Zn SOD[93]	High	Low
Growth regulators		
Growth factor		
PDGF-B[78,97]	Low	High
PDGF-A[59]	Low	High
Growth inhibitor		
TGF-β[88]	High	Low
Inflammatory mediators		
MCP-1[101]	Low	High
Adhesion molecules		
VCAM-1[100,101,103]	Low	High
Thrombosis/fibrinolysis		
tPA[89,90]	High	Low
TM[89]	Low	High
Endothelial proliferation[78]	Low	High
Endothelial apoptosis[79]	Low	High

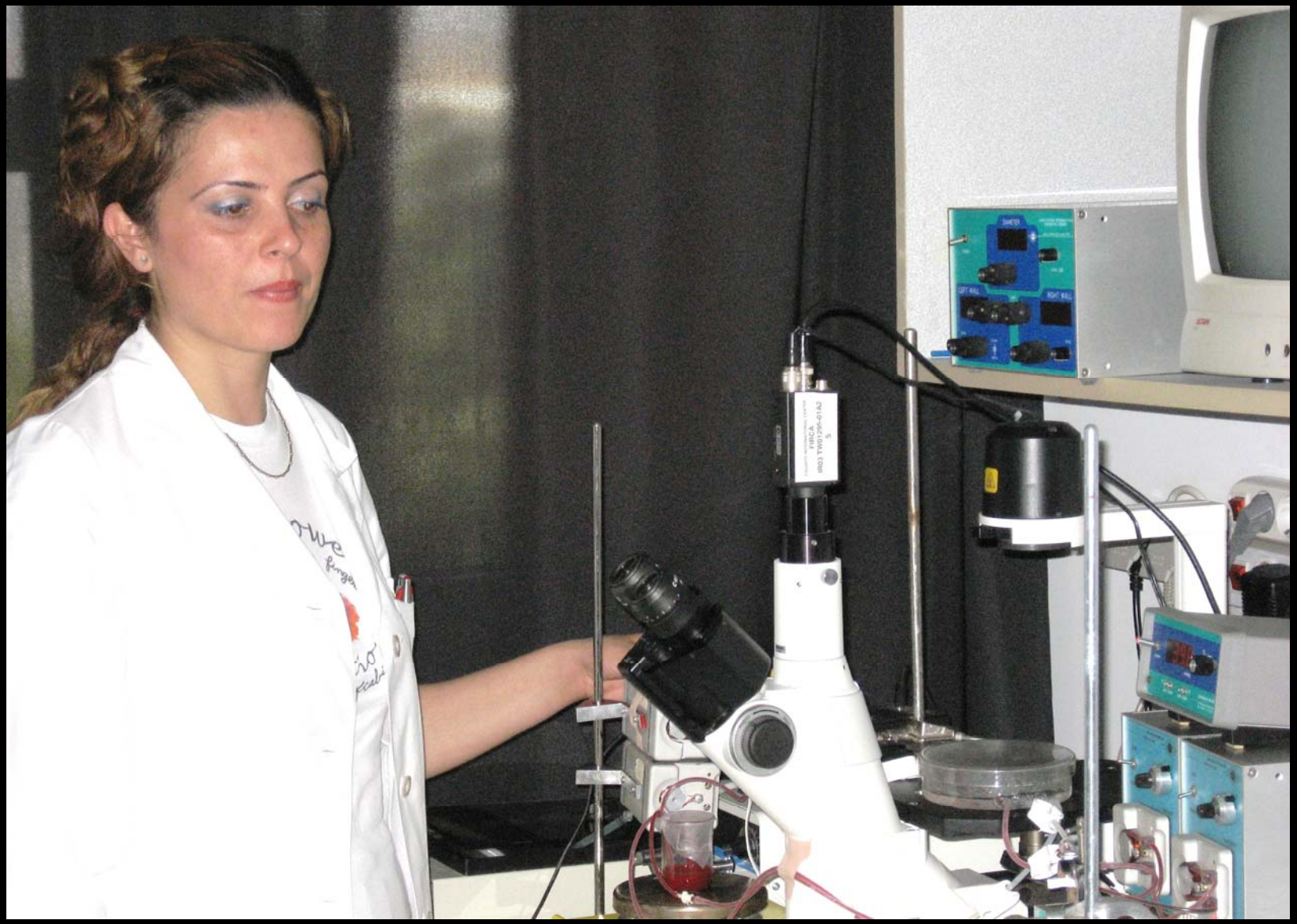
Malek AM et al., JAMA 282: 2035, 1999.

Serine 1177 phosphorylated eNOS









Dr. Ozlem Yalcin

Thank you.