Vascular Remodeling & Hypertension

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Structural changes in

Large arteries

Small arteries /arterioles

1.

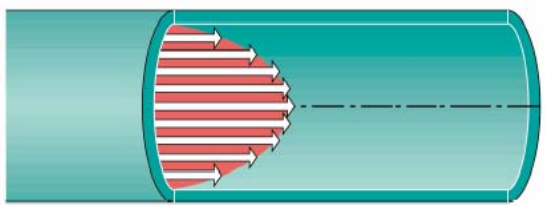
Capillaries

2.

Resistance vessels in blood pressure control

Resistance to blood flow/pressure is significant only in arterial vessels with a lumen diameter of <300 µm.

Any ***change in lumen diameter*** of these resistance vessels or ***complete loss off*** will ***affect blood pressure.***



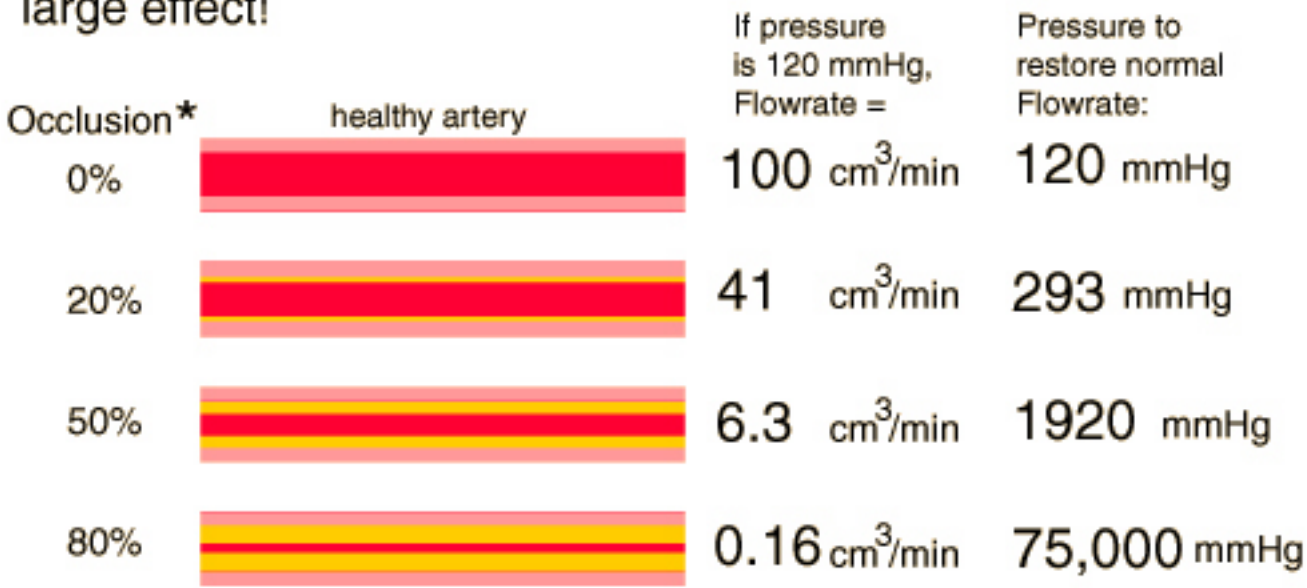
rule of laminar flow by Hagen-Poiseuille:

$$R = \frac{8\eta l}{r_i^4 \pi}$$

R: resistance
h: viscosity
l: length of vessel
r: lumen diameter

Resistance vessels in blood pressure control

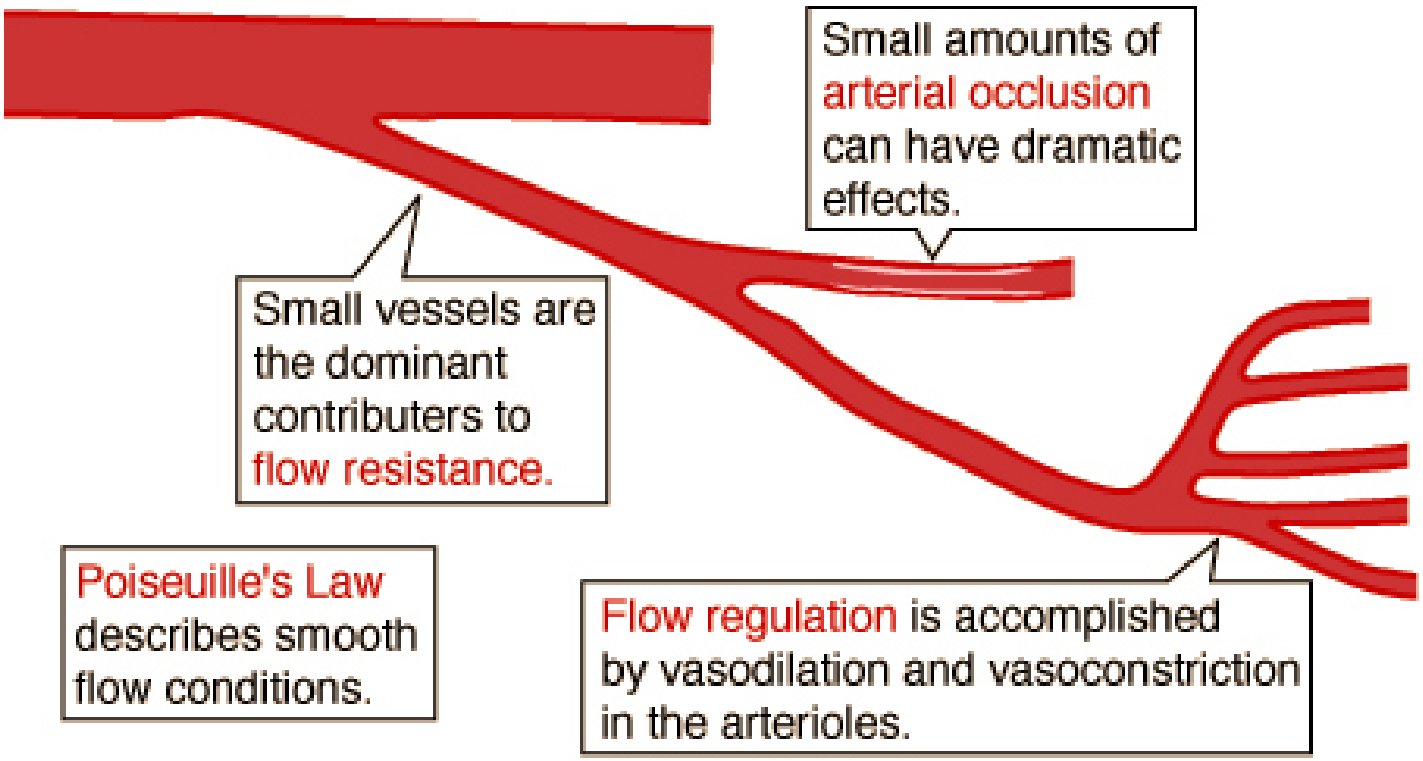
A small amount of arterial occlusion can have a surprisingly large effect!



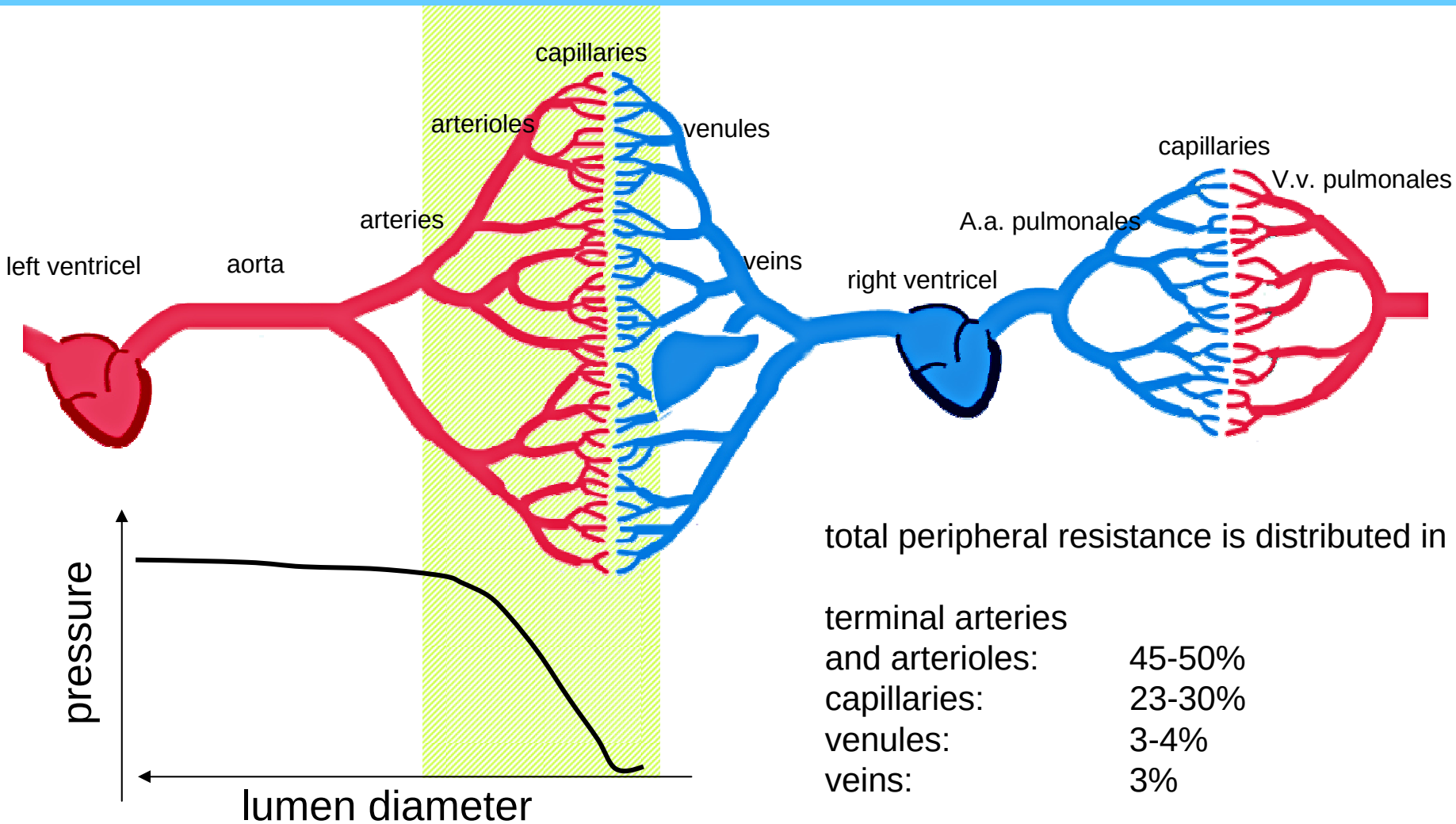
*20% occlusion here is taken to mean a reduction of the inside radius by 20%, to 80% of its original radius.

A 19% decrease in radius will halve the volume flowrate!

Resistance vessels in blood pressure control



Resistance vessels in blood pressure control



total peripheral resistance is distributed in

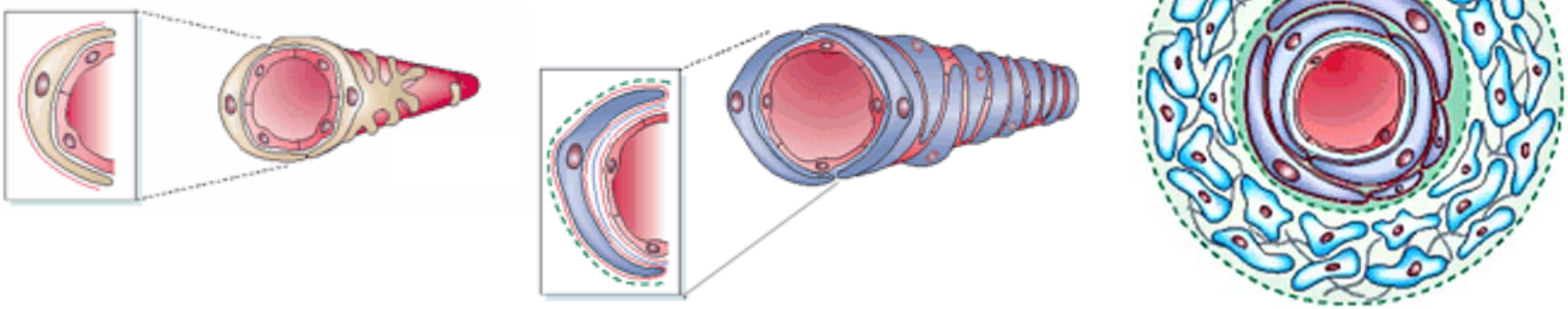
terminal arteries and arterioles:	45-50%
capillaries:	23-30%
venules:	3-4%
veins:	3%

resistance vessels

: arteries <300 µm in diameter

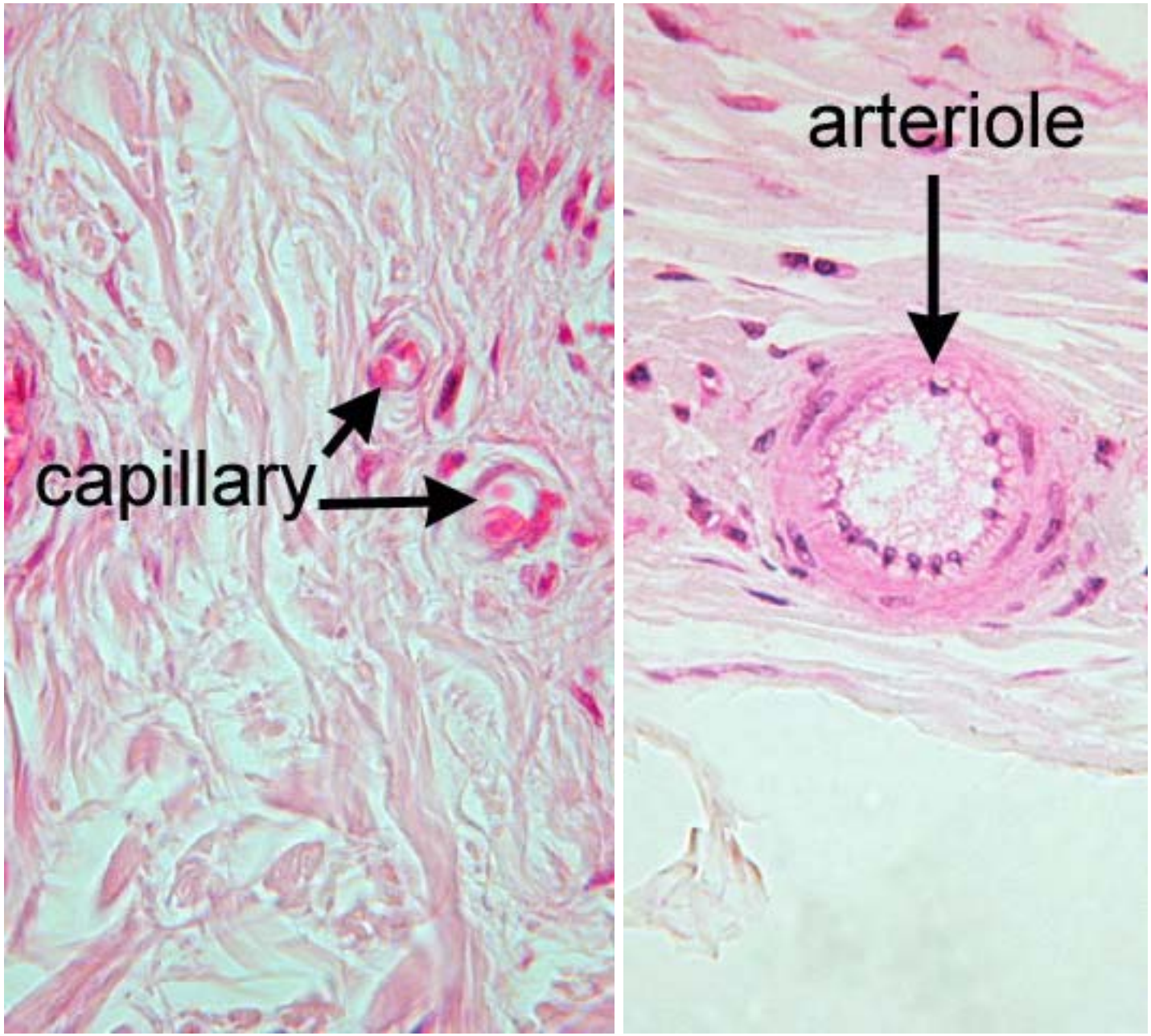
: capillaries <100µm in diameter

Vessel structure: capillary to artery



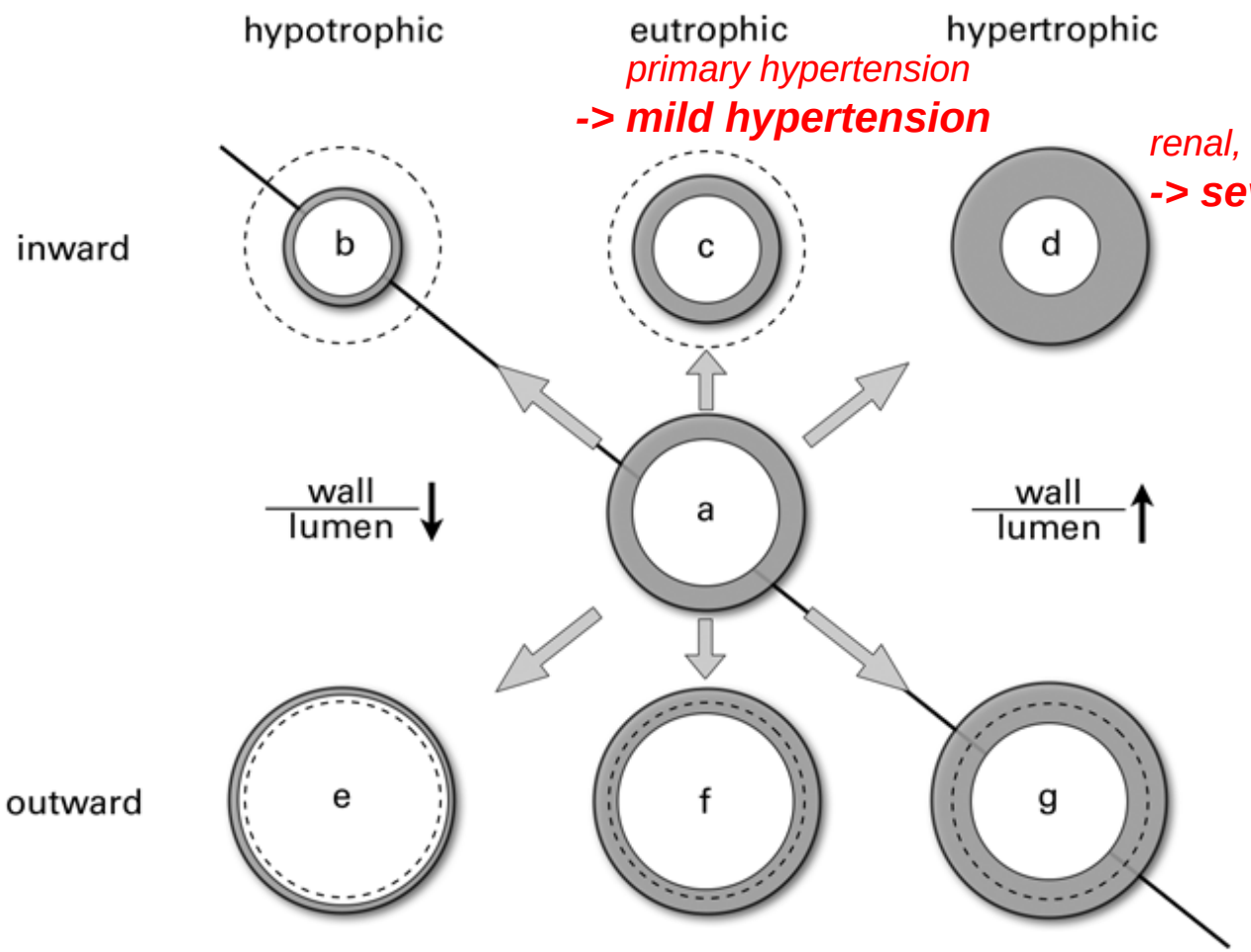
Capillary	***Arteriole***	***Artery***	
Endothelial cell tube	Endothelial cell tube	Endothelial cell tube	-> intima
	Internal elastica lamina	Internal elastica lamina	
Pericytes	Smooth muscle cells	Smooth muscle cells	-> media
Basal lamina	Basal lamina	Basal lamina	
	External elastic lamina	Fibroblasts	->adventita
		Extracellular matrix	
		External elastica lamina	

Jain et al, *Nature Medicine* **9**, 685 - 693 (2003)


capillary
arteriole

Types of resistance artery remodeling

according Michael J. Mulvany



antihypertensive treatment (ACE inhibition)

Exercise induced vascular remodeling of small and larger arteries in humans

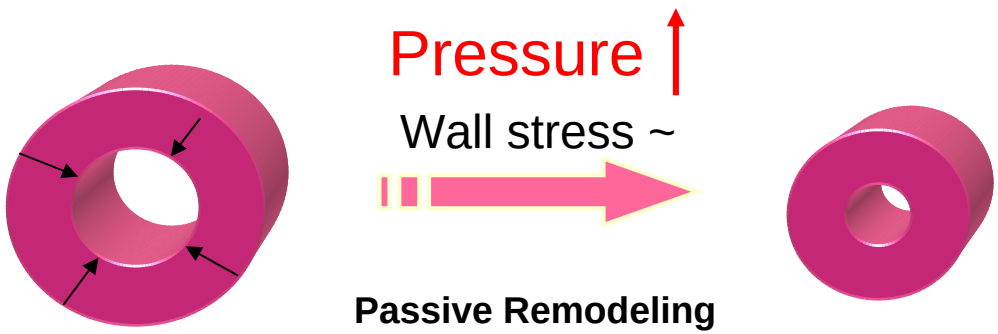
ACE-inhibitor treatment of SHRs

Determinants of resistance artery remodeling

according Michael J. Mulvany

Eutrophic inward Remodeling

Vasoconstrictors (Ang II Endothelin)



Essential hypertension is associated with eutrophic remodeling of the small arteries.

Increased neurohumoral activity leads to vasoconstriction and increased blood pressure.

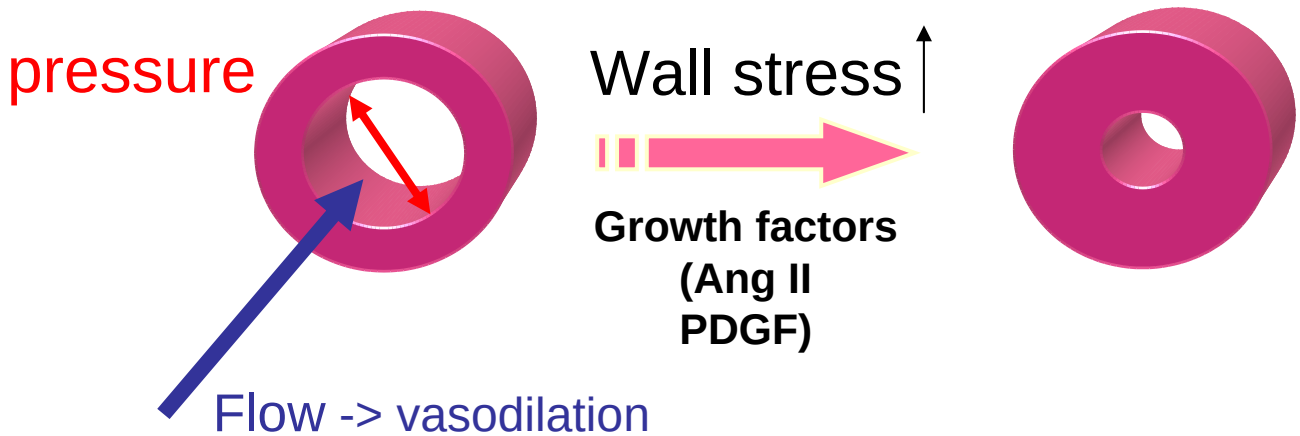
Decrease in diameter (and resulting increase in wall thickness) ensures that the wall stress remains normal, thus eliminating a hypertrophic response.

Active vasoconstriction (during essential hypertension) changes to a passive remodeling.

Determinants of resistance artery remodeling

according Michael J. Mulvany

Hypertrophic inward Remodeling



Intravascular **pressure** causes an increase in the wall stress, which then stimulates a hypertrophic process leading to an increase in wall thickness

Increases in **flow** lead to increases in diameter and in wall thickness

Hypertrophic processes are also thought to be initiated through **growth factors**, including angiotensin II (AII), or PDGF

Laplace relation: wall tension = pressure x radius

Mechanism of remodeling

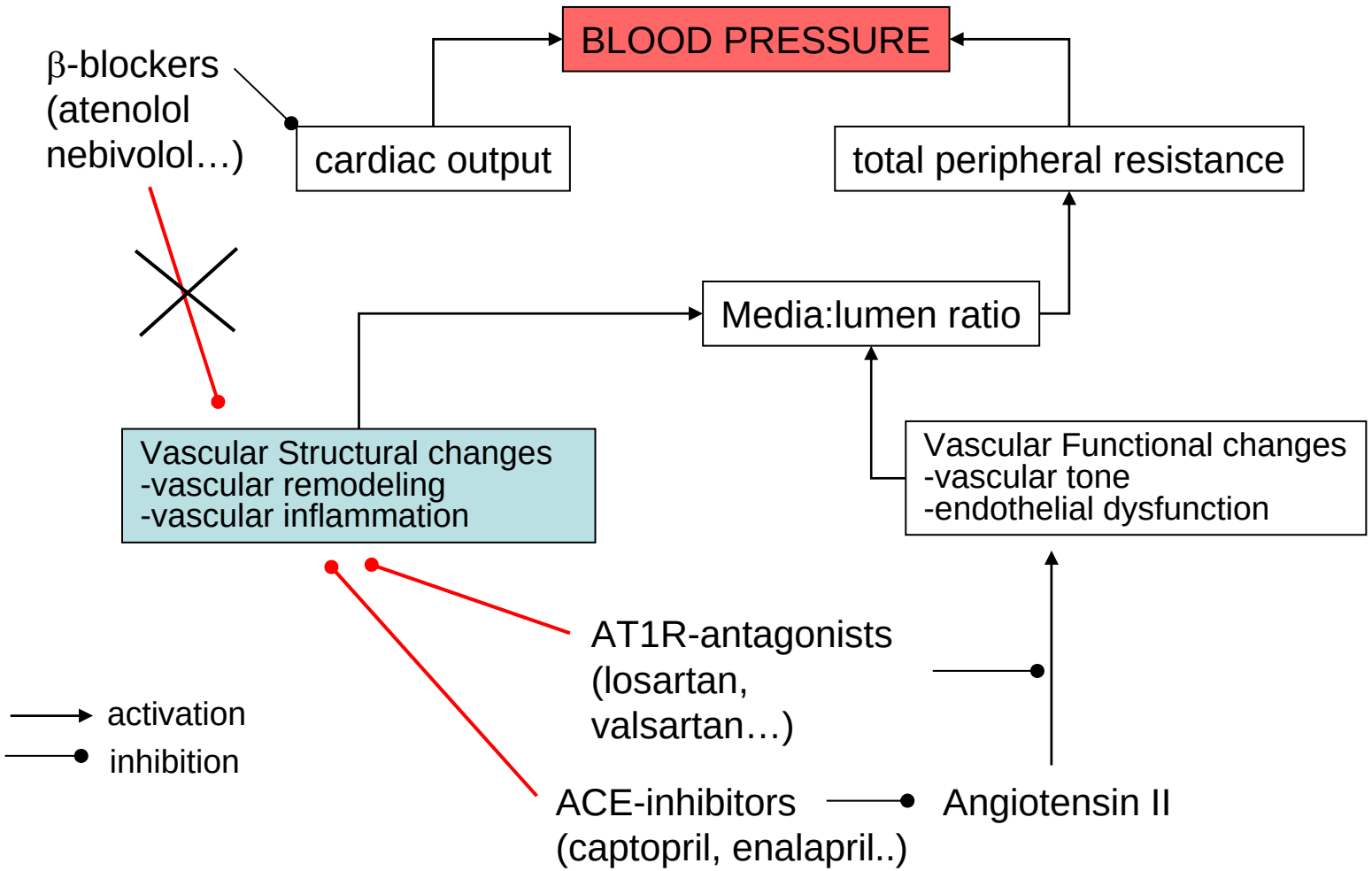
Haemodynamic stimuli → **Increased blood pressure**
Shear stress / Flow

Humoral factors → **Angiotensin II, PDGF, TGFβ**

Transduction events within cell
or to adjacent cell → G-protein coupled signaling
Ras/MAPK signaling
PI3K signaling

Reorganization of cells
Matrix modulation
Hypertrophy → **SMC phenotype modulation**
Proliferation
Cell elongation
Cell migration
Apoptosis (Anoikis)

Antihypertensive treatment -> reversal of resistance vessel remodeling



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Effectors of Remodeling

Smooth Muscle Cell Phenotype

Expression of extracellular matrix proteins and their cellular receptors is closely related to smooth muscle cell phenotype.

Normal

contractile phenotype
differentiated phenotype

Tissue injury -

synthetic
enhanced expression of extracellular matrix
High motility and prolifertion, hypertrophy

Induction of the IGF/PI 3-K keeps SMC in a differentiated state

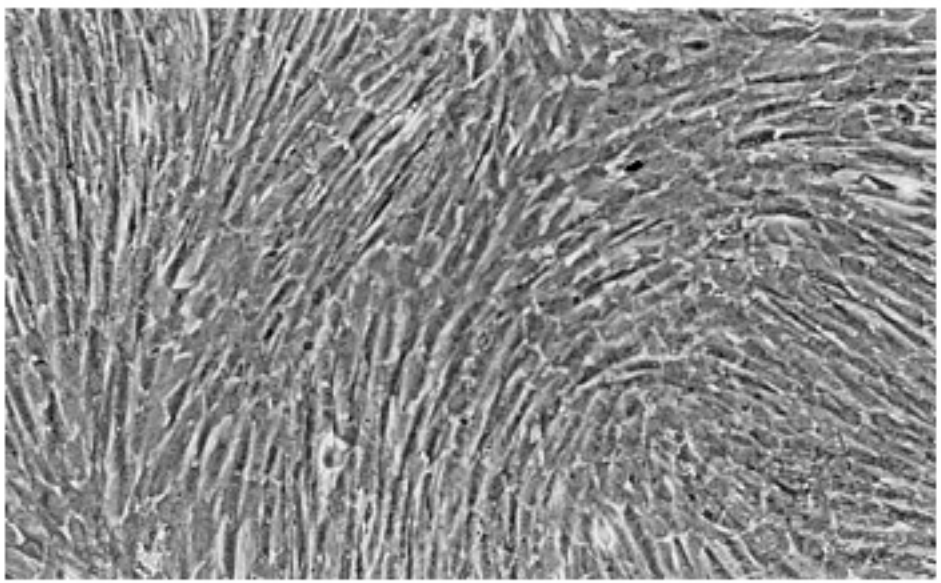
EC-cell layer (producing IGF) important to keep SMC in differentiated state
endothelial denudation

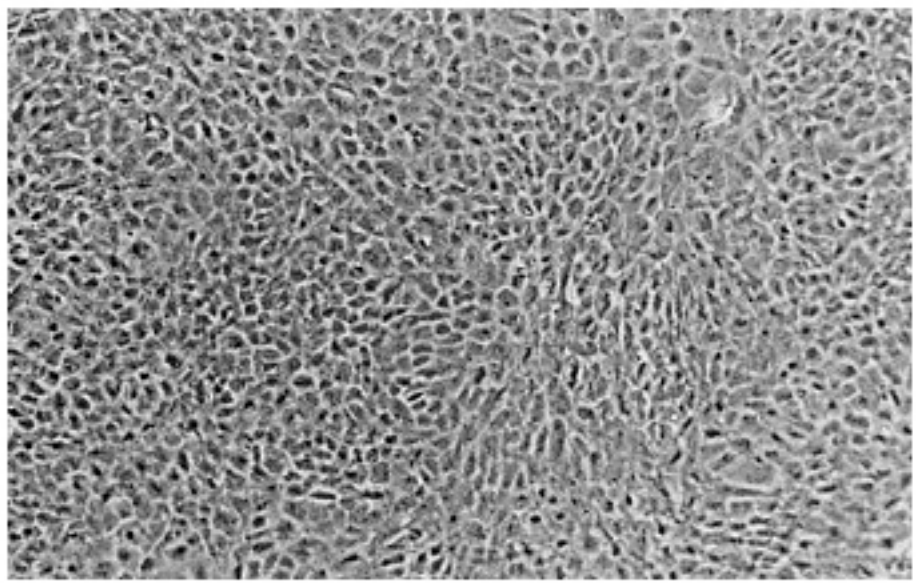
Rho proteins and SMC phenotype

Phenotypic modulation of smooth muscle cells (SMC) involves dramatic changes in **expression and organization of contractile and cytoskeletal proteins**

Changes in **RhoA and Rho kinase** gene expression are required for a transition of vSMC from a stable to a dynamic, remodeling-prone state.

contractile, differentiated ⟷ ***synthetic, proliferative***

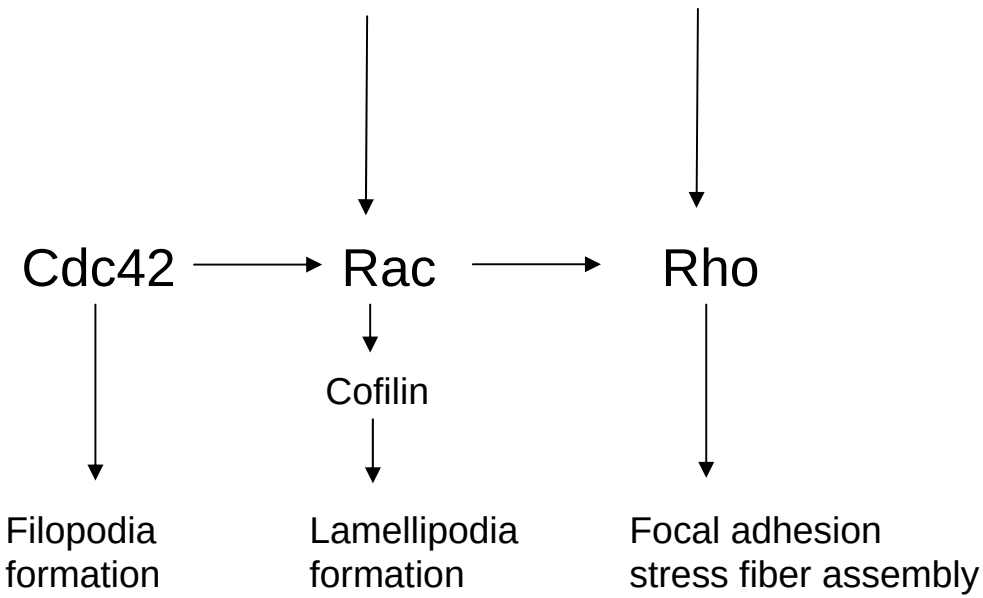




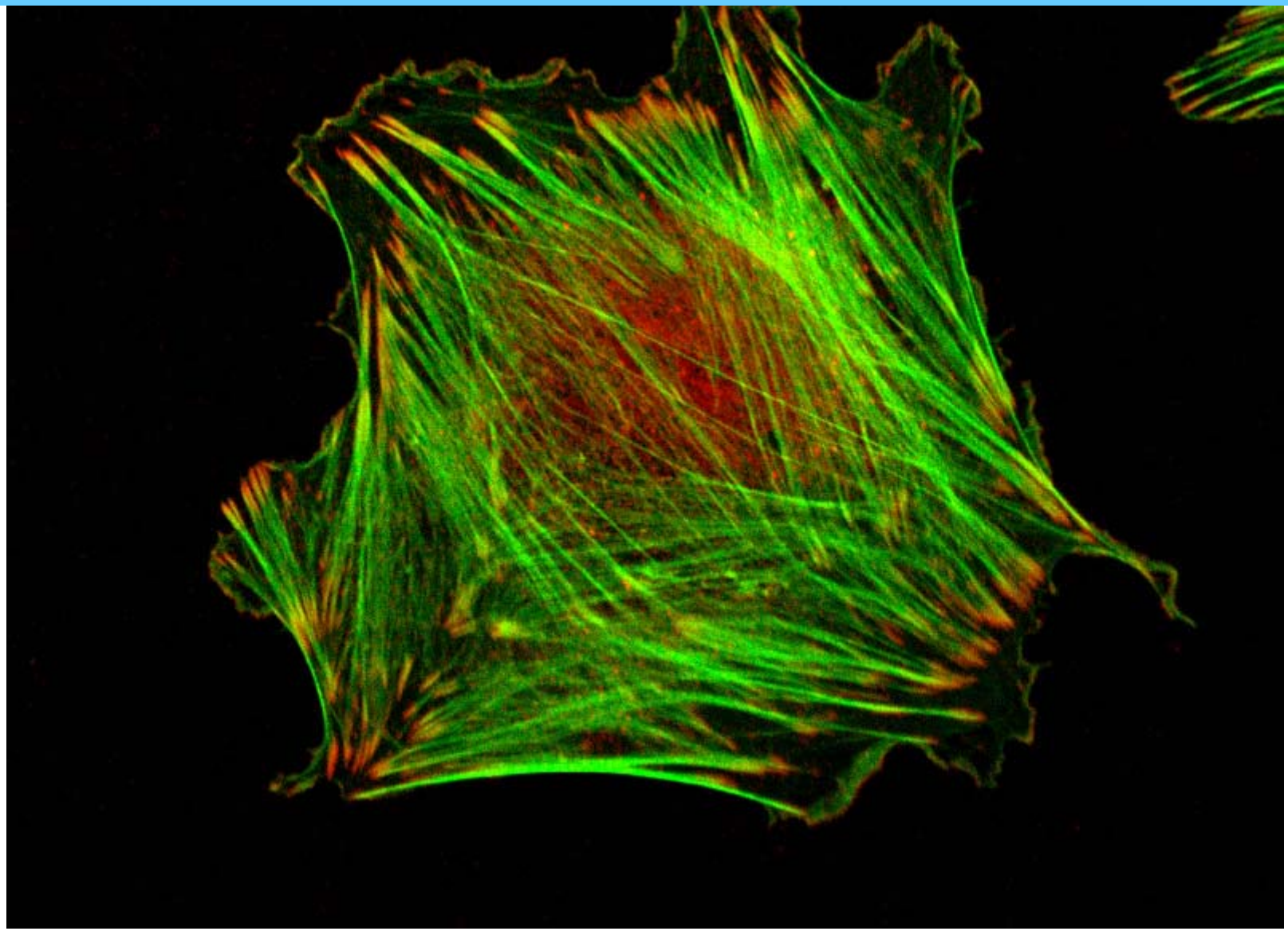
Rho proteins and resistance artery remodeling

Rho protein signaling is involvled in excessive
vSMC migration and proliferation
in arterial diseases such as hypertension or atherosclerosis

Upstream signals: G-protein coupled agonists (**Ang II**, PDGF, stretch)



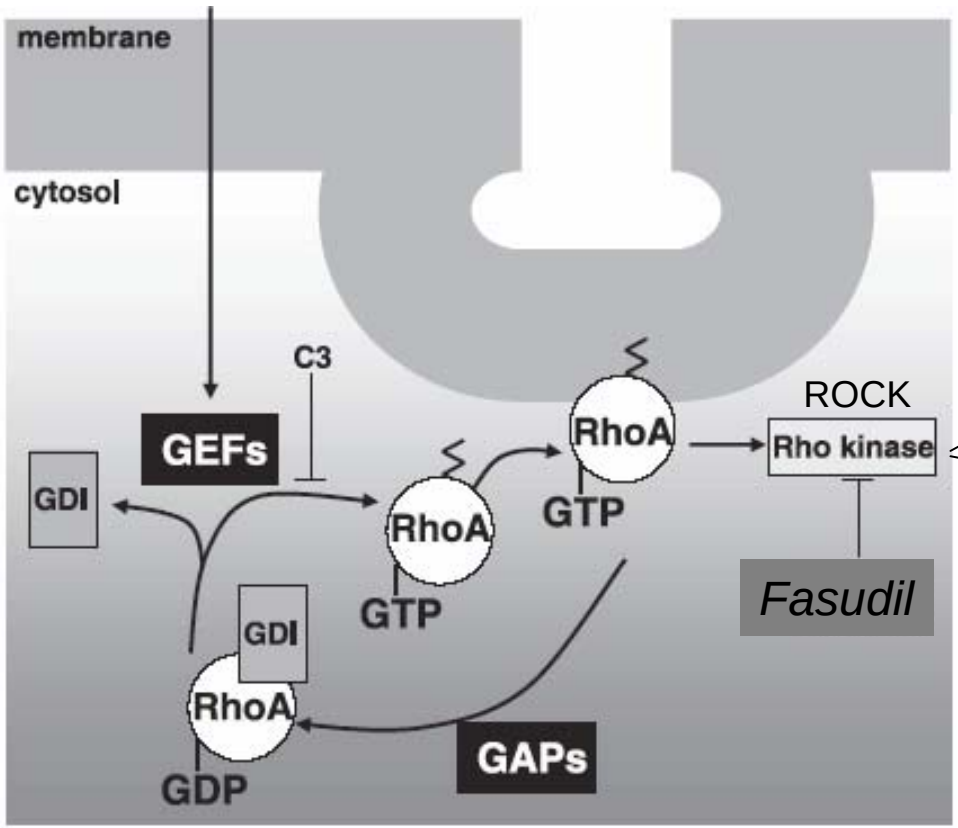
SMC phenotype; contractile



α-SM actin (green); vinculin (red)

Rho proteins and resistance artery remodeling

Angiotensin II / Flow



Myosin light chain phosphatase

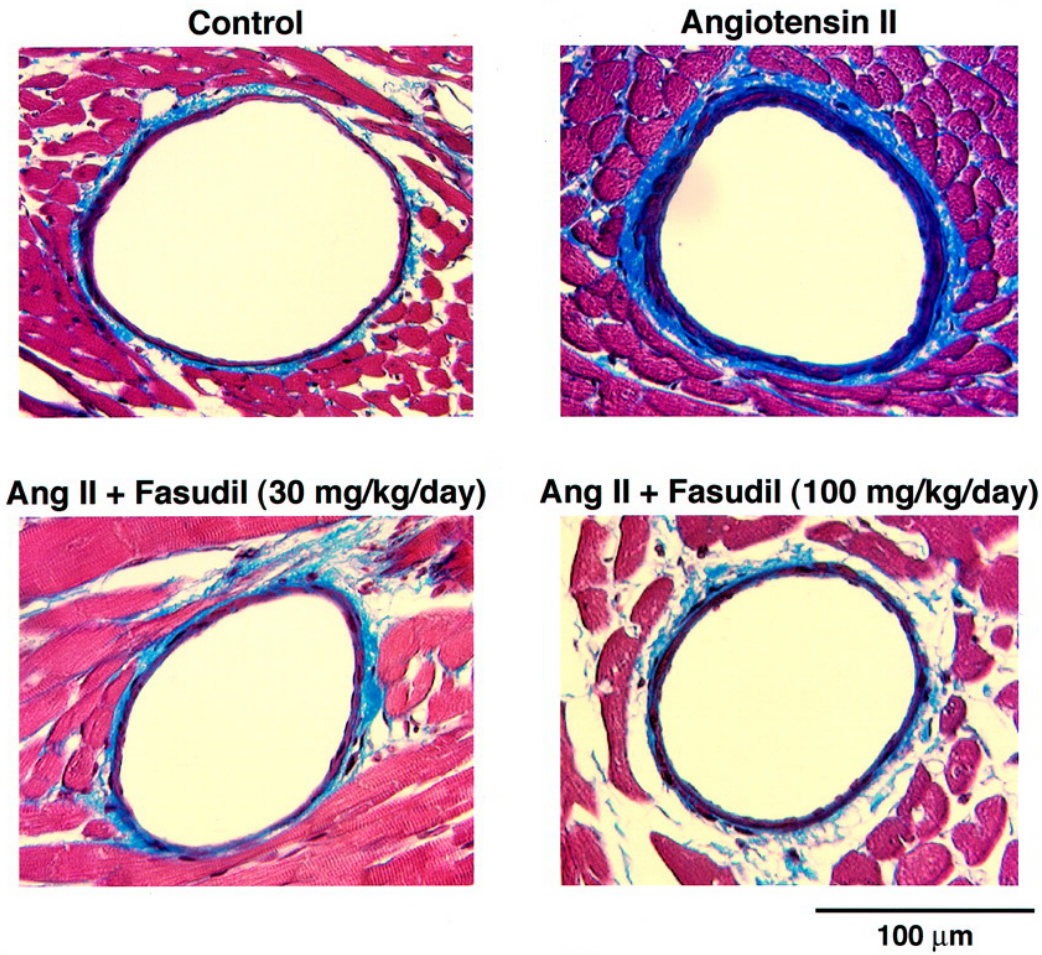
Myosin light chain phosphorylation promoting myosin/actin interaction

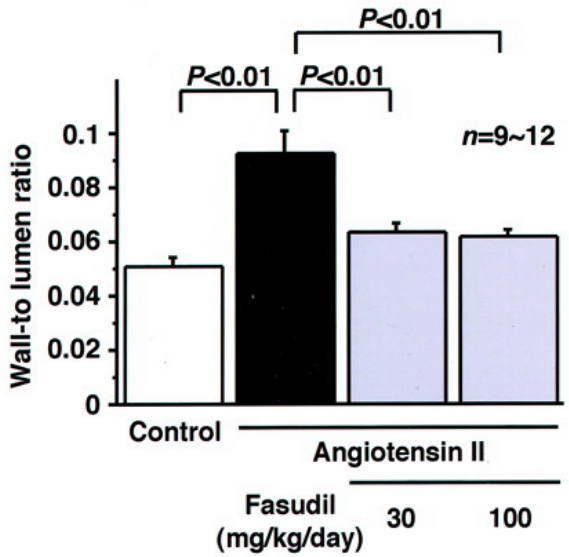
stress fiber development and contraction

Rho kinase blockers -> in clinical trials phase I/II

Rho proteins and resistance artery remodeling

1. Inhibition of Rho-kinase suppresses angiotensin II-induced cardiovascular hypertrophy in rats in vivo

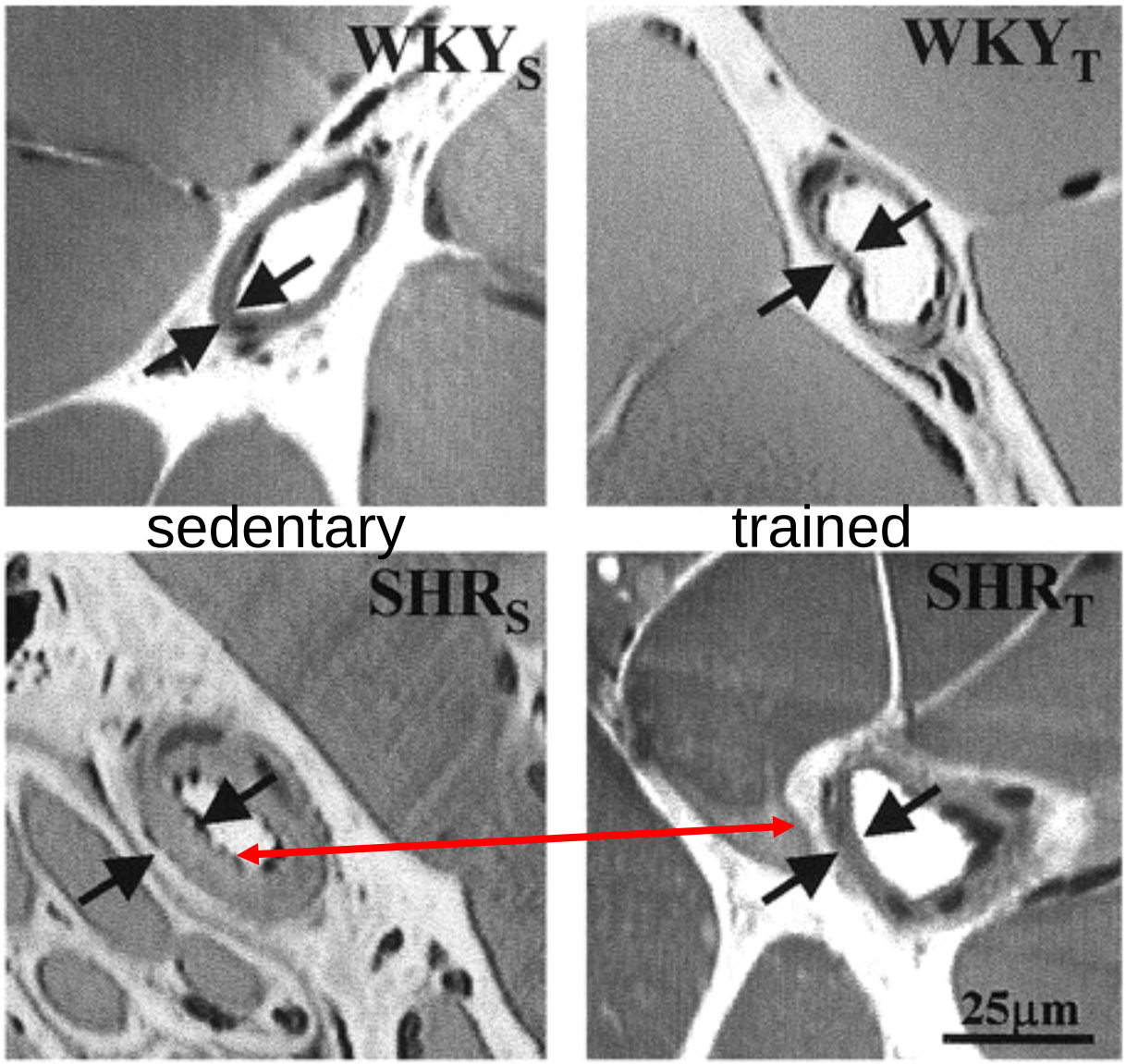




2. Rho inhibition increases regional myocardial blood flow in ischemic hearts

Higashi et al, Circ Res. 2003 Oct 17;93(8):767-75

Reversal of hypertension by exercise



Training-induced, pressure-lowering effect in hypertensive rats

Melo et al., Hypertension. 2003 Oct; 42(4): 851-7

Remodeling in the heart

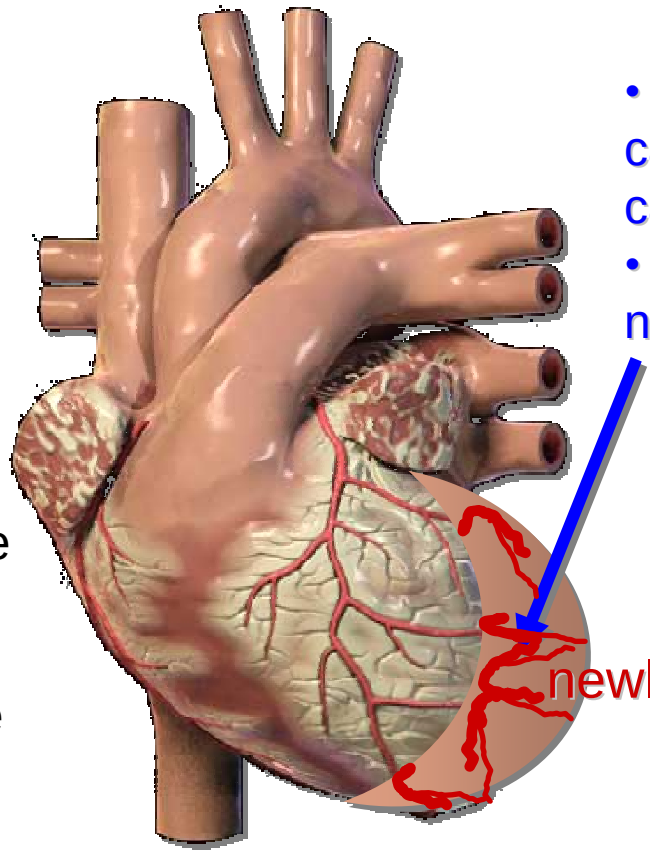
Mechanical stress on the heart can lead to crucially different outcomes:

Exercise is beneficial because it causes heart muscle cells to enlarge (hypertrophy).
Recent research shows that stimulation of physiological (beneficial) hypertrophy involves several signaling pathways, including those mediated by protein kinase B (also known as Akt) and the extracellular-signal-regulated kinases 1 and 2 (ERK1/2).

Chronic hypertension also causes hypertrophy, but in addition it causes an excessive increase in fibroblasts and extracellular matrix (fibrosis), death of cardiomyocytes and ultimately heart failure.
Hypertension, β-adrenergic stimulation and agonists such as angiotensin II (Ang II) activate not only ERK1/2 but also p38 and the Jun N-terminal kinase (JNK), leading to pathological heart remodeling.

Wakatsuki T. et al.,Trends Biochem Sci. 2004 Nov;29(11):609-17.

New microvessel formation in Left Ventricular Hypertrophy



- Mismatch of number of capillaries and cardiomyocytes:
- Limited supply of nutrients and oxygen

newly forming microvessels

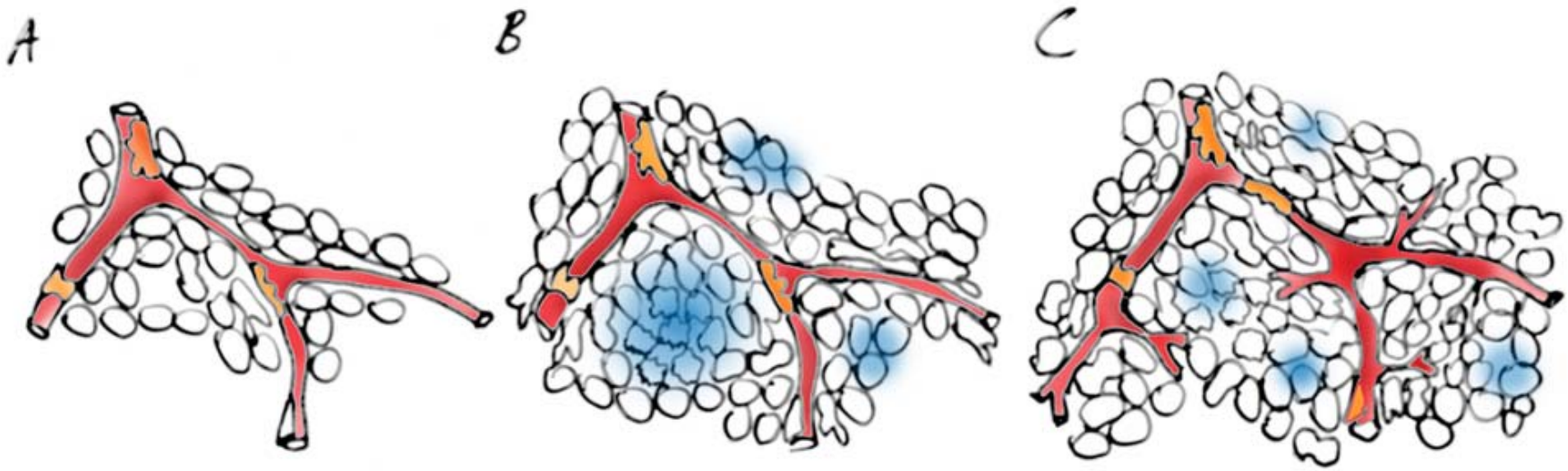
- Left ventricular hypertrophy occurs in 62% of hypertensive patients;

- first condition of heart failure

VEGF is required to maintain myocardial capillary density and reductions in the vascular bed are associated with the transition from compensatory hypertrophy to failure.

Friehs I., Ann Thorac Surg. 2004; 77(6):2004-2001

New microvessel formation in response to hypoxia



A tissue is fed and grows
Along **blood vessels**

Increased growth leads
to **hypoxia** and necrosis

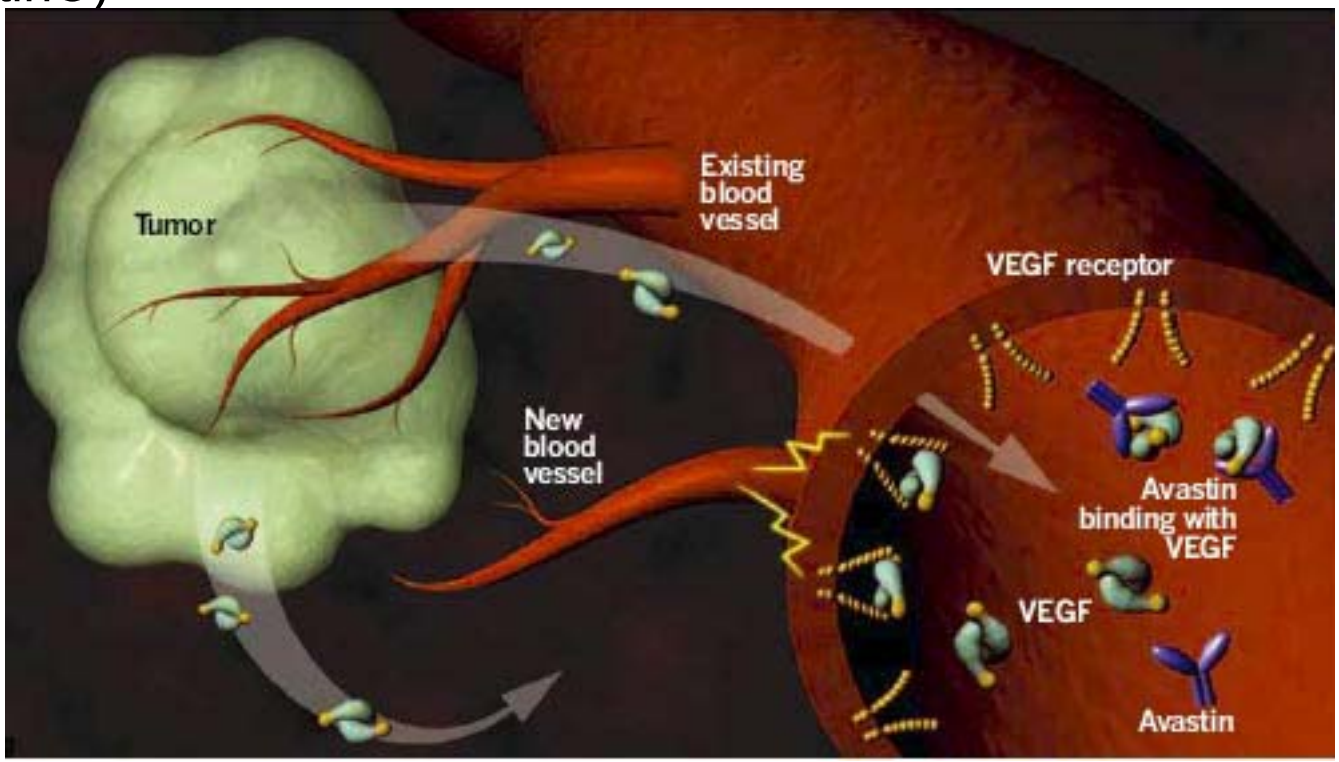
Hypoxia induces **HIF-1α**
-> upregulation of **VEGF**

Angiogenic sprouting is initiated

Nutrient and oxygen supply is
reestablished

Microvessel regression & Hypertension

Bevacizumab (Avastin®)
mAB aginst VEGF

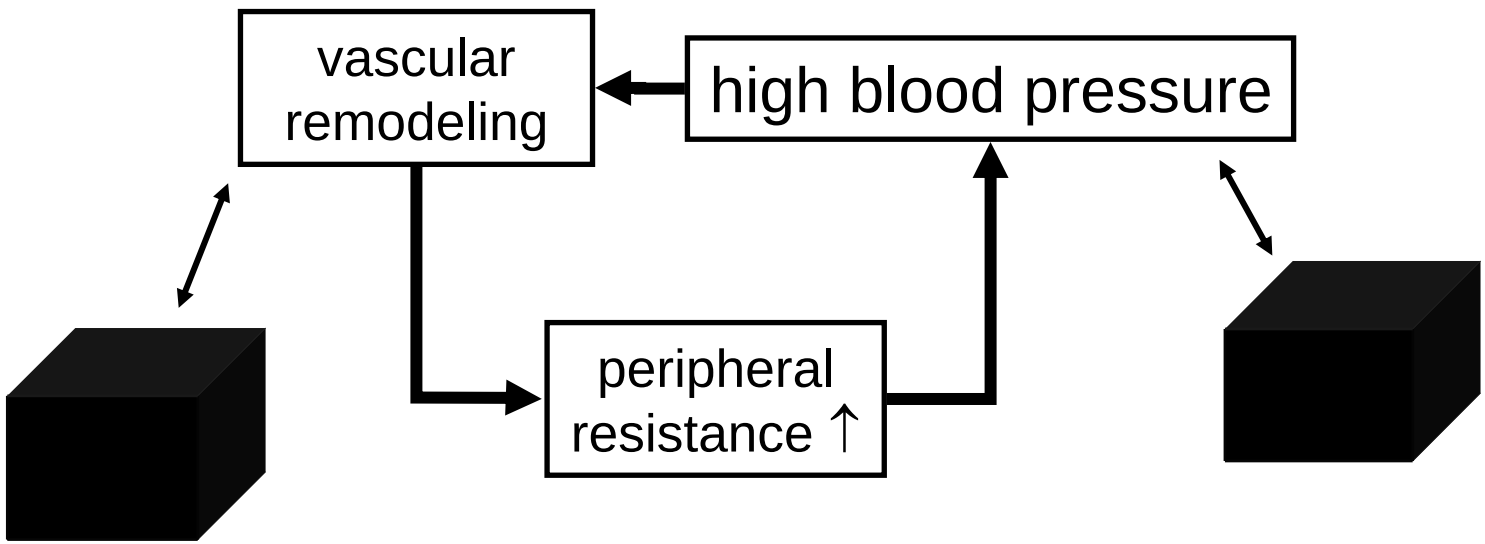


only side effect **grade 3 hypertension**:
control group -> 0.5%
Avastin group -> **17.5**%

Miller et al., Journal of Clinical Oncology, 23 (4) 2005: pp. 792-799

What comes first?

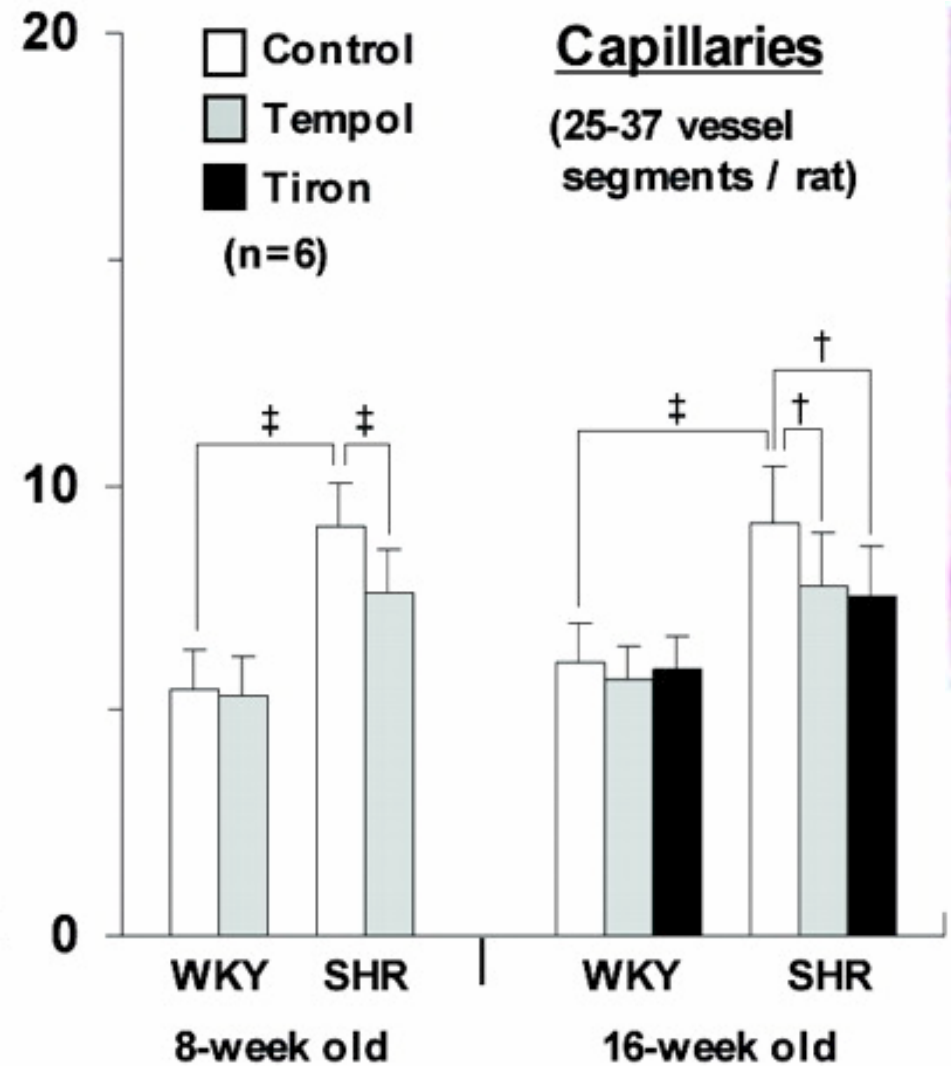
Rarefaction may by
primary (antedated the onset of hypetension) and a result of impaired angiogenesis
or
secondary (occurs as a consequence of prolonged elevation of blood pressure) associated with impaired recruitement of non-perfused capillaries or destruction of capillaries

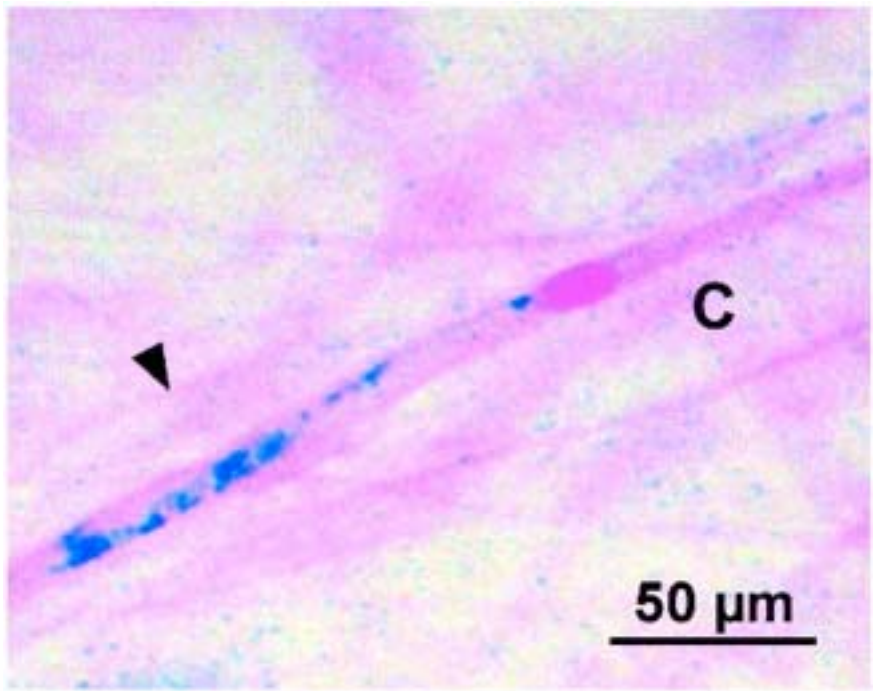


Are these processes primary **causative** events or secondary **adaptive** phenomena?

Hypertension increases Apoptosis in Endothelial Cells from Capillaries

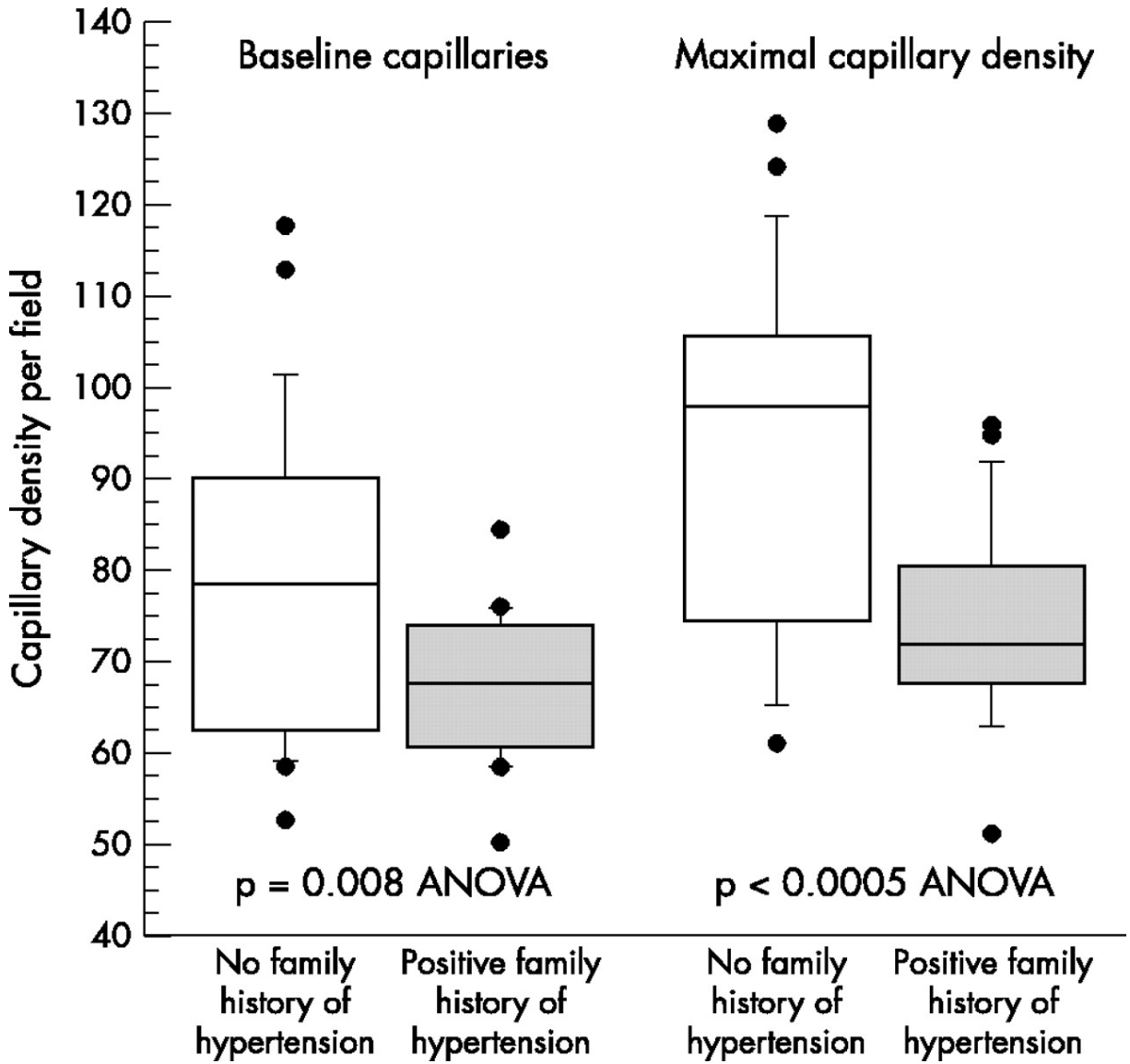
Kobayashi N. et al, Arterioscler Thromb Vasc Biol. 2005 Oct;25(10):2114-21.





Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension

Antonios et al., Heart, 2003 Feb;89(2):175-8.



Capillary rarefaction in hypertension

Likely, capillary rarefaction is **primary**
since
Capillary rarefaction is found before the onset of hypertension

- in experimental rat models
- in humans with mild intermittent hypertension

AND

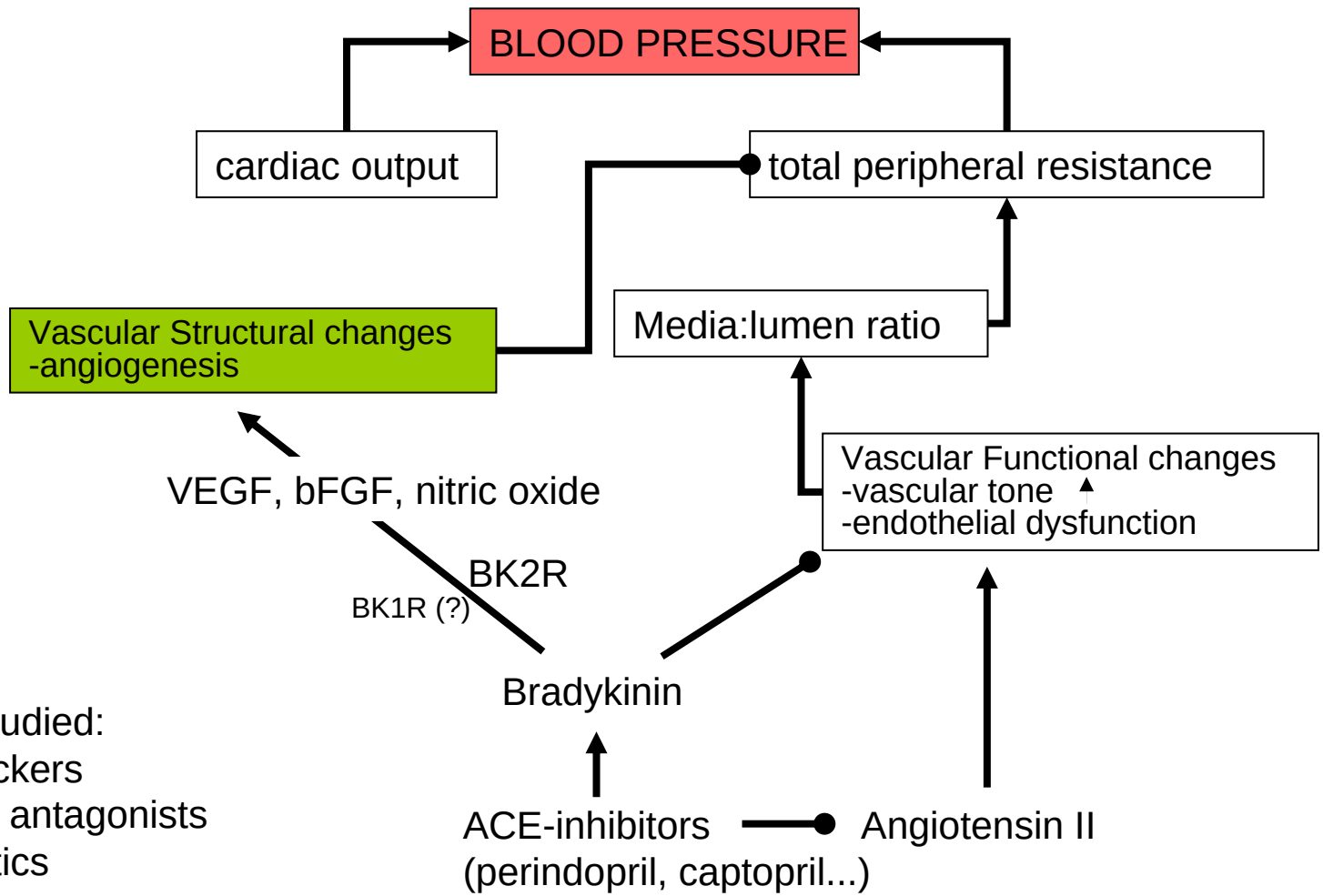
- Capillary rarefaction is associated with familial predisposition to essential hypertension: Offspring of parents with hypertension have fewer capillaries in the dorsum of their fingers before the onset of any significant hypertension

THUS:

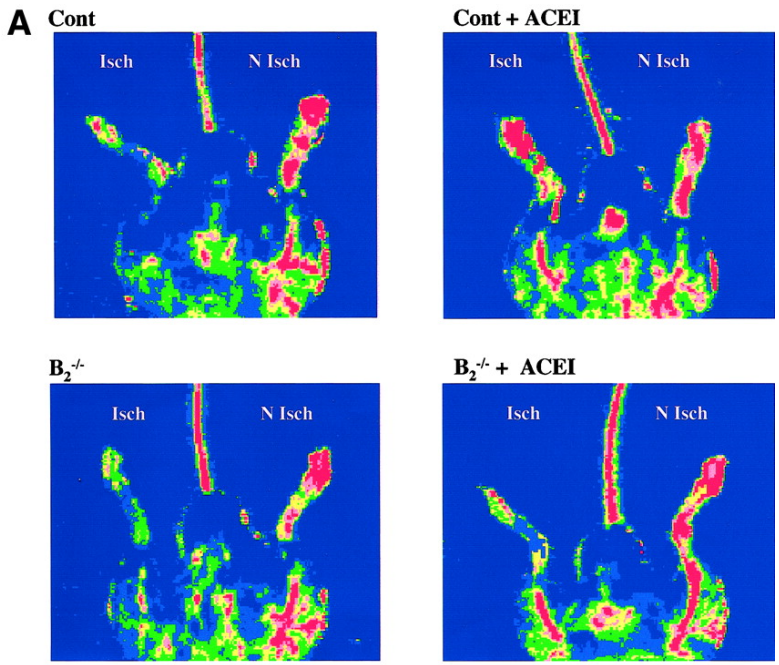
Capillary rarefaction may be genetically predetermined, and may be
- later on- one of the reasons for the onset of hypertension.

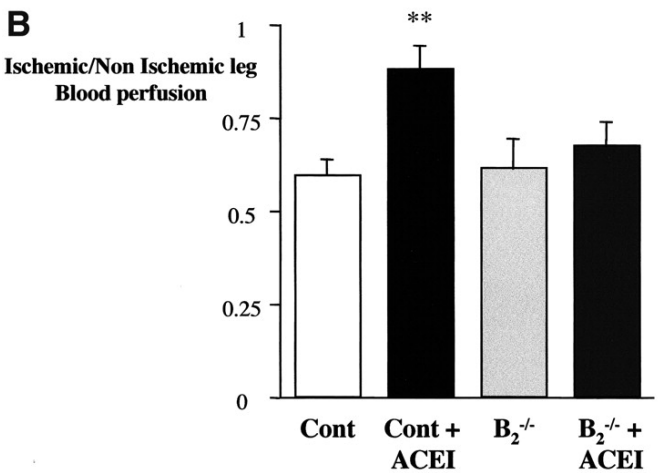
Genetic abnormalities of capillary growth in SHR have been mapped to a region also containing growth hormons and elements of the RAAS.

Antihypertensive treatment -> improvement of angiogenesis



ACE inhibition -> improvement of angiogenesis





Proangiogenic Effect of Angiotensin-Converting Enzyme Inhibition (by **perindopril**) Is Mediated by the Bradykinin B2 Receptor Pathway

Silvestre et al.
Circ Res. 2001 Oct 12;89(8):678-83.

Keypoints

- Blood vessels undergo structural changes i.e. microvascular rarefaction and vascular remodeling
- This is an adaptive process to changes in blood pressure

- Process can be malregulated and aggravates hypertension:
- **Small resistance vessel remodeling** contributes to hypertension by a decrease in luminal diameter through eutrophic or hypertrophic inward remodeling
- **Reduction of microvessel density by microvascular rarefaction** contributes to hypertension by decrease of total arteriolar and capillary cross-sectional area.