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!

<table>
<thead>
<tr>
<th>Occlusion</th>
<th>Flowrate</th>
<th>Pressure to restore normal Flowrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100 cm³/min</td>
<td>120 mmHg</td>
</tr>
<tr>
<td>20%</td>
<td>41 cm³/min</td>
<td>293 mmHg</td>
</tr>
<tr>
<td>50%</td>
<td>6.3 cm³/min</td>
<td>1920 mmHg</td>
</tr>
<tr>
<td>80%</td>
<td>0.16 cm³/min</td>
<td>75,000 mmHg</td>
</tr>
</tbody>
</table>

*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

Small vessels are the dominant contributors to flow resistance.

Small amounts of arterial occlusion can have dramatic effects.

Poiseuille's Law describes smooth flow conditions.

Flow regulation is accomplished by vasodilation and vasoconstriction in the arterioles.
Resistance vessels in blood pressure control

- Resistance vessels: arteries <300 µm in diameter, capillaries <100 µm in diameter

Total peripheral resistance is distributed in:

- Terminal arteries and arterioles: 45-50%
- Capillaries: 23-30%
- Venules: 3-4%
- Veins: 3%
Vessel structure: capillary to artery

<table>
<thead>
<tr>
<th>Capillary</th>
<th>Arteriole</th>
<th>Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cell tube</td>
<td>Endothelial cell tube</td>
<td>Endothelial cell tube</td>
</tr>
<tr>
<td>Pericytes</td>
<td>Internal elastica lamina</td>
<td>Internal elastica lamina</td>
</tr>
<tr>
<td>Basal lamina</td>
<td>Smooth muscle cells</td>
<td>Smooth muscle cells</td>
</tr>
<tr>
<td></td>
<td>Basal lamina</td>
<td>Media</td>
</tr>
<tr>
<td></td>
<td>External elastic lamina</td>
<td>Adventitia</td>
</tr>
</tbody>
</table>

Types of resistance artery remodeling

According Michael J. Mulvany

- Hypotrophic
- Eutrophic (primary hypertension) -> mild hypertension
- Hypertrophic (renal, secondary hypertension) -> severe hypertension

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)

Pressure  
Wall stress ~  
Passive Remodeling

*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.*
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 (Ang II) or PDGF.

Laplace relation: wall tension = pressure x radius.
Mechanism of remodeling

Haemodynamic stimuli $\rightarrow$ Increased blood pressure
Shear stress / Flow

Humoral factors $\rightarrow$ Angiotensin II, PDGF, TGFβ

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

Reorganization of cells
Matrix modulation
Hypertrophy
Proliferation
Cell elongation
Cell migration
Apoptosis (Anoikis) $\rightarrow$ SMC phenotype modulation
Antihypertensive treatment -> reversal of resistance vessel remodeling

- **BLOOD PRESSURE**
  - cardiac output
  - total peripheral resistance
  - Media:lumen ratio

**Vascular Structural changes**
- vascular remodeling
- vascular inflammation

**Vascular Functional changes**
- vascular tone
- endothelial dysfunction

- AT1R-antagonists (losartan, valsartan...)
- ACE-inhibitors (captopril, enalapril..)
- Angiotensin II

- β-blockers (atenolol, nebivolol...)

activation

inhibition
Mechanism of remodeling

Haemodynamic stimuli → Increased blood pressure
   \[\text{Shear stress / Flow}\]
Humoral factors → Angiotensin II, PDGF, TGF\(\beta\)
Transduction events within cell or to adjacent cell → G-protein coupled signaling
   \[\text{Ras/MAPK signaling}\]
   \[\text{PI3K signaling}\]
Reorganization of cells
Matrix modulation
Hypertrophy
Proliferation
Cell elongation
Cell migration
Apoptosis (Anoikis) → SMC phenotype modulation
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 proliferation, 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 protein signaling is involved in excessive \textit{vSMC migration and proliferation} in arterial diseases such as hypertension or atherosclerosis.

Upstream signals: G-protein coupled agonists (\textit{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 phosphorylation promoting myosin/actin interaction
- Myosin light chain phosphatase
- 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

![Control](image1.png) ![Angiotensin II](image2.png) ![Ang II + Fasudil (30 mg/kg/day)](image3.png) ![Ang II + Fasudil (100 mg/kg/day)](image4.png)

[Graph showing the effect of Fasudil on wall-to-lumen ratio.](image5.png)

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
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.

New microvessel formation in Left Ventricular Hypertrophy

- 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.

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 against 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 be **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 recruitment 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
Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension
Antonios et al., Heart, 2003 Feb;89(2):175-8.
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 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 hormones and elements of the RAAS.
Antihypertensive treatment -> improvement of angiogenesis

- Vascular Structural changes: angiogenesis
- Vascular Functional changes: vascular tone, endothelial dysfunction

BLOOD PRESSURE

Cardiac output

Total peripheral resistance

Media:lumen ratio

VEGF, bFGF, nitric oxide

Bradykinin

BK2R

BK1R (?)

ACE-inhibitors (perindopril, captopril...)

Angiotensin II

not studied:
- β-blockers
- Ca2+ antagonists
- diuretics
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.
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.