Blood pressure control
Mean arterial blood pressure is determined by:

- **Blood volume**: determined by fluid intake and fluid loss
- **Cardiac output**: determined by heart rate and stroke volume
- **Peripheral resistance**: determined by diameter of arterioles and number of capillaries
- **Blood capacitance**: determined by diameter of veins and storage of blood volume

Also, the site where most of the blood volume is found and where regional blood volume is regulated.
The cardiac output is determined by stroke volume or heart rate or both.

Cardiac output = Stroke Volume X number of heart beats

The maximum percentage that the cardiac output can increase above normal is called the cardiac reserve.

In the normal young adult the cardiac reserve is 300 to 400 percent (trained athletes >600%, weak elderly ~200%)

For example, running to catch a tramway would cause an increase in oxygen demand which must be balanced by increased blood circulation and blood pressure.
Mean arterial blood pressure

- **Blood volume**
  - determined by
    - Fluid intake
    - Fluid loss

- **Cardiac output**
  - determined by
    - Heart rate
    - Stroke vol.

- **Peripheral resistance**
  - determined by
    - Diameter of arterioles
    - Number of capillaries

- **Blood capacitance**
  - determined by
    - Diameter of veins

  Also site where most of the blood volume is found and where regional blood volume is regulated.
Peripheral resistance

rule of laminar flow by Hagen-Poiseuille:

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

- \( R \): resistance
- \( \eta \): viscosity
- \( l \): length of vessel
- \( r_i \): lumen diameter
Peripheral resistance

- **Resistance**: \[ R \sim \frac{1}{\text{radius}^4} \]
  - Tube A: \[ R \sim \frac{1}{1^4} \]
  - Tube B: \[ R \sim \frac{1}{2^4} \]
  - Tube A: \[ R \sim 1 \]
  - Tube B: \[ R \sim \frac{1}{16} \]

- **Flow**: \[ \text{Flow} \sim \frac{1}{\text{resistance}} \]
  - Tube A: \[ \text{Flow} \sim \frac{1}{1} \]
  - Tube B: \[ \text{Flow} \sim \frac{1}{16} \]
  - Tube A: \[ \text{Flow} \sim 1 \]
  - Tube B: \[ \text{Flow} \sim 16 \]
Peripheral resistance

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

<table>
<thead>
<tr>
<th>Occlusion*</th>
<th>healthy artery</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>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>41 cm³/min</td>
<td>293 mmHg</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>6.3 cm³/min</td>
<td>1920 mmHg</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>0.16 cm³/min</td>
<td>75,000 mmHg</td>
<td></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!
Peripheral resistance

Resistance to blood flow/pressure is significant only in arterial vessels with a lumen diameter of <300 µm. Thus, any change in lumen diameter of these resistance vessels or complete loss off will affect blood pressure.
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
Mean arterial blood pressure is determined by:

- **Blood volume**
  - Determined by:
    - Fluid intake
    - Fluid loss

- **Cardiac output**
  - Effectiveness of the heart as a pump
  - Determined by:
    - Heart rate
    - Stroke vol.

- **Peripheral resistance**
  - Resistance of the system to blood flow
  - Determined by:
    - Diameter of arterioles
    - Number of capillaries

- **Blood capacitance**
  - Storage of blood volume
  - Determined by:
    - Diameter of veins
      - Also site where most of the blood volume is found and where regional blood volume is regulated

**Baroreceptor reflex**
The Baroreceptor reflex is a rapidly acting feedback loop. Elevated blood pressure reflexively causes blood pressure to decrease; Decreased blood pressure depresses the baroreflex, causing blood pressure to rise. Baroreceptors in various organs can detect changes in blood pressure, and adjust the mean arterial pressure by altering the force and speed of the heart's contractions (cardiac output) and the total peripheral resistance.
Baroreceptors are present in the **aortic arch**, and the **carotid sinuses** of the left and right internal carotid arteries.
Baroreceptors are stretch-induced mechanoreceptors. Mechanoreceptors are primary neurons that respond to mechanical stimuli by firing action potentials. Active baroreceptors fire action potentials ("spikes") more frequently than inactive baroreceptors. The greater the stretch, the more rapidly baroreceptors fire action potentials. The frequency of afferent impulses increases when the pressure is rising during systole and decreases when the pressure is falling during diastole.
Autonomic nervous system (Sympathicus/Parasympathicus)

- Baroreceptor afferent
  - Low pressure
  - High pressure
- Vagal center
- Parasympathicus
- Heart
- Arterial pressure
- Sympathicus
- Arterioles
- Vasomotor center
- Brain

Transduction and sensing occur at the baroreceptors.
Parasympathicus: cholinergic fibers from the ganglion to the effector organ
Neurotransmitter = **Acetylcholine**

Sympathicus: noradrenergic fibers from the ganglion to the effector organ
Neurotransmitter = (Nor-)**Epinephrine**

![Chemical structures](image)

**Heart**
- decreased cardiac output

**Arterioles**
- vasoconstriction
Epinephrine stimulates β1-adrenergic receptors of the heart and increases cardiac rhythm and force of contraction, and α1 smooth muscle cell receptors on arterioles to vasoconstrict (fight-or-flight response).

1st generation β-blockers block β1 and β2.

2nd generation β-blockers mainly block β1.

3rd generation β-blockers block β1 and α1.

1st generation
- Nadolol
- Pindolol

2nd generation
- Acebutolol
- Atenolol (Atenil®, Cardaxen®, Selobloc®)
- Bisoprolol
- Nebivolol (Nebilet®)

3rd generation
- Carvedilol (Dilatrend®)
- Labetalol
Mean arterial blood pressure

- **Blood volume**
  - Determined by:
    - Fluid intake
    - Fluid loss

- **Cardiac output**
  - Effectiveness of the heart as a pump
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  - Storage of blood volume
  - Determined by:
    - Diameter of veins

- **Aldosterone**

- **Renin-angiotensin system (RAS)** or renin-angiotensin-aldosterone system (RAAS)
The Renin-Angiotensin-Aldosterone System (RAAS) is a hormone system that helps regulate long-term blood pressure and extracellular volume in the body.

The RAAS begins with the release of renin from specialized kidney tissue, the juxtaglomerular apparatus, when:

- Blood flow through glomeruli is decreased
- Blood pressure as measured by baroreceptors (Vas afferens) is decreased
- Drop in blood volume, that is filtered by glomeruli
- Activation of sympatheticus
Angiotensin Converting Enzyme

Liver

Angiotensinogen

Angiotensin I

Renin

Kidney

BP↓

Angiotensin Converting Enzyme

Angiotensin I

Angiotensin II

Bradykinin

BK degradation

BKR2

SMC

AT2

SMC

AT1

SMC arterioles

AT1

SMC Venules

AT1

CNS

Adrenal cortex

Pituitary Gland
The Renin-Angiotensin-Aldosteron System (RAAS)

Liver

Angiotensinogen → Angiotensin I

Renin → Angiotensin II

Kidney

Bradykinin → BK degradation

Angiotensin Converting Enzyme

Angiotensin II → AT1

AT1 → Adrenal cortex

AT1 → Pituitary Gland

AT1 → SMC arterioles

AT1 → SMC Venules

AT2 → SMC

BKR2 → SMC

Vasodilation

Vasoconstriction

Remodeling Vascular Growth

Vasodilation

NO production

Sympathicus (Norepinephrine)

BP ↓

BP ↑

Hirnanhangdrüse, Hypophyse
The Renin-Angiotensin-Aldosteron System (RAAS)

- Angiotensinogen
- Angiotensin I
- Angiotensin II
- Bradykinin
- BK degradation
- AT1
- AT1
- AT1
- AT2
- BKR2
- SMC
- Liver
- Kidney
- Adrenal cortex
- Pituitary Gland
- CNS
- Sympathicus
- BP↓
- BP↑
- BV↑
- Transport of Cl⁻ and H₂O from urine to blood
- NaCl in blood and blood volume (BV) increase
- ADH
- Anti Diuretic Hormone/Vasopressin
- Retention of H₂O and NaCl
- Vasoconstriction
  - decrease in vessel lumen diameter
  - increase in peripheral resistance
  - BP ↑
- Vasodilation
  - NO production
- Remodeling
  - Vascular Growth
- Cerebral Cortex, Hypophyse
- Sympathicus
Inhibition of the Renin-Angiotensin-Aldosteron System (RAAS)

**Liver**
Angiotensinogen → Angiotensin I

**Renin**
Kidney → Angiotensinogen

**Angiotensin Converting Enzyme (ACE)**
Angiotensinogen → Angiotensin I

**Angiotensin II**
- **AT1**
  - SMC arterioles
- **AT2**
  - SMC Venules

**BK degradation**
Bradykinin → BKR2

**Vasodilation**
- NO production
- Remodeling
- Vascular Growth

**Vasoconstriction**
- Decrease in vessel lumen diameter
- Increase in peripheral resistance

**BP**
- Increase
- Decrease

**Adrenal cortex**

**Pituitary Gland**

**Sympathicus**

**Transport of Cl− and H2O from urine to blood**

**NaCl in blood and blood volume (BV) increase**

**Sulphydryl-containing ACE inhibitors**
- Captopril (Lopirin®), the first ACE inhibitor
- Enalapril (Reniten®)
- Ramipril (Triatec®/Vesdil®)
- Quinapril (Accupro®)
- Perindopril (Coversum®)
- Lisinopril (Prinil®/Zestril®)
- Benazepril (Cibacen®)

**Dicarboxylate-containing ACE inhibitors**
- Dicarboxylate-containing ACE inhibitors
  - Enalapril (Reniten®)
  - Ramipril (Triatec®/Vesdil®)
  - Quinapril (Accupro®)
  - Perindopril (Coversum®)
  - Lisinopril (Prinil®/Zestril®)
  - Benazepril (Cibacen®)

**Phosphonate-containing ACE inhibitors**
- Fosinopril (Fositen®),
The Renin-Angiotensin-Aldosteron System (RAAS)

- **Liver**
  - Angiotensinogen
  - Renin
  - Kidney
    - BP ↓
    - BP ↑
    - Aldosterone
      - Transport of Cl⁻ and H₂O from urine to blood
      - NaCl in blood and blood volume (BV) increase

- **Renin**
  - Angiotensin I
    - Angiotensin Converting Enzyme
      - Angiotensin II
        - AR1B
        - AT1
          - Adrenal cortex
          - Pituitary Gland
          - CNS
          - AT2
            - SMC arterioles
            - Vasodilation
              - NO production
            - Remodeling
              - Vascular Growth
            - Vasoconstriction
              - decrease in vessel lumen diameter
              - increase in peripheral resistance
              - BP ↑
            - AT1
              - SMC Venules
              - BV ↑
            - AT1
              - SMC
              - BP ↑
            - Candesartan (Atacand®, Blopess®)
            - Eprosartan (Teveten®)
            - Irbesartan (Aprovel®)
            - Losartan (Cosaar®)
            - Olmesartan (Votum®, Olmetec®)
            - Telmisartan (Micardis®, Kinzal®)
            - Valsartan (Diovan®)

- **BP**
  - Increase in peripheral resistance
The Renin-Angiotensin-Aldosteron System (RAAS)

Liver

Angiotensinogen → Angiotensin I → Angiotensin Converting Enzyme → Angiotensin II

Kidney

Renin

β-blocker

Renin-I.

BP ↓

At1

Adrenal cortex

Aldosterone

BP ↑

At1

Pituitary Gland

ADH

Transport of Cl\(^{-}\) and H\(_2\)O from urine to blood
NaCl in blood and blood volume (BV) increase

BP ↑

AVP

At1

CNS

Sympathicus

Vasodilation

NO production

Remodeling

Vascular Growth

Vasoconstriction

decrease in vessel lumen diameter
increase in peripheral resistance

BP ↑

AT1

SMC arterioles

AT2

SMC

BKR2

SMC

First in class renin inhibitor:
Aliskiren (Tekturna®)

Approved by FDA in Feb 2007 for
Novartis/Speedel
Mean arterial blood pressure is determined by:

- **Blood volume**
  - determined by: Fluid intake, Fluid loss

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  - Effectiveness of the heart as a pump
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- **Blood capacitance**
  - Storage of blood volume
  - determined by: Diameter of veins

  Also site where most of the blood volume is found and where regional blood volume is regulated

Vascular remodeling
Vascular Remodeling

**Capillary**
- Endothelial cell tube
- Pericytes
- Basal lamina

**Arteriole**
- Endothelial cell tube
- Internal elastica lamina
- Smooth muscle cells
- Basal lamina
- External elastic lamina
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.
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.
Inhibition of Rho-kinase suppresses angiotensin II-induced cardiovascular hypertrophy in rats in vivo

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

Bevacizumab (Avastin®) mAB aginst VEGF

side effect grade 3 (severe) hypertension = 180/110
control group -> 0.5%
Avastin group -> 17.5%

Miller et al., Journal of Clinical Oncology, 23 (4) 2005: pp. 792-799
Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension

Capillary rarefaction may be hereditary and predispose to hypertension

Antonios et al., Heart, 2003 Feb; 89(2): 175-8
Long term antihypertensive treatment & reversal of remodeling

Kidney → Renin → Angiotensinogen → Angiotensin I → Angiotensin Converting Enzyme (ACEI) → Angiotensin II → AT1 → Adrenal cortex (Aldosterone) → BP ↓

Liver → Angiotensinogen

AT1 → Pituitary Gland (ADH) → Anti Diuretic Hormone/Vasopressin (ADH) → BV ↑

AT2 → SMC arterioles → Vasoconstriction

AT1 → Vascular Growth

Angiotensin Converting Enzyme (ACEI) → BK degradation

Bradykinin → BKR2 → SMC → Vasodilation

NO production

Vasodilation

Adrenal cortex

Brain (CNS)

Sympathicus

Vasoconstriction

decrease in vessel lumen diameter
=increase in peripheral resistance

BP ↑
Longterm antihypertensive treatment & capillary rarefaction

Angiogenic Molecules
- VEGF; bFGF

Vasodilation
- NO production

Angiogenesis
- reversal of capillary rarefaction
- decrease in peripheral resistance and BP
Summary

Blood volume

Cardiac output
- Effectiveness of the heart as a pump
  - determined by: Heart rate, Stroke vol.

Peripheral resistance
- Resistance of the system to blood flow
  - determined by: Diameter of arterioles, Number of capillaries

Blood capacitance
- Storage of blood volume
  - determined by: Diameter of veins

Also site where most of the blood volume is found and where regional blood volume is regulated

Renin-Angiotensin Aldosterone system (RAAS)

Baroreceptor reflex

Determined by:
- Fluid intake
- Fluid loss

Vascular remodeling