Regulation of Arterial Pressure and Cardiac Output

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By controlling the **systemic mean arterial pressure**, the circulatory system provides a great **flexibility** for distributing blood flow:

- All organs receive approximately the same mean arterial pressure
- Each organ controls local blood flow by adjusting local arteriolar resistance
- As long as the heart **maintains** the mean arterial pressure, a change in blood flow in one vascular bed does not affect blood flow in other beds

**Arterial pressure** is kept fairly **constant** over time, whereas **cardiac output** and **peripheral resistance** are quite **variable**
\[ P = F \times R \rightarrow \text{in the circulation } P = CO \times TPR \]
Regulation of Arterial Pressure

- Arterial pressure is regulated by:

- **Short-term mechanisms** (seconds to minutes):
  - neural reflexes
  - targets:
    - heart
    - vessels
    - adrenal medulla

- **Long-term mechanisms** (hours, days):
  - humoral control
  - targets:
    - blood vessels
    - kidneys in their control of extracellular fluid volume
Regulation of Cardiac Output

- **Cardiac output** – influences to a large degree the arterial pressure
  - its regulation is important for maintaining arterial pressure within the normal range

- Cardiac output is regulated by mechanisms
  - **intrinsic** to the heart: preload, afterload, contractility etc.
  - **extrinsic** to the heart: neural and hormonal pathways

*The cardiac output is controlled mainly by the sum of all the local tissue flows (venous return)*
Short-Term Regulation of Arterial Pressure

Baroreceptor Control
Chemoreceptor Control
Low-pressure Receptor Control
Short-Term Regulation of Arterial Pressure

- Mediated by **neural reflexes** that operate as **negative feedback loops**
- Each loop is composed of:
  - **Receptors**
    - **Baroreceptors** (high-pressure receptors) - stretch receptors
    - **Chemoreceptors** – sense changes in blood O$_2$, CO$_2$ and pH
    - **Low-pressure receptors** – stretch receptors (volume sensors)
  - **Afferent neural pathways**
  - **CNS center**
    - Processes the information and generates a response
    - Located in **medulla, hypothalamus, cerebral cortex**
  - **Efferent neural pathways**
  - **Effectors**
    - **Heart**: pacemaker and muscle cells
    - **Arteries and veins**: VSCMs
    - **Adrenal medulla**
Baroreceptor Control of Arterial Pressure
Is the main mechanism for maintaining arterial pressure (AP) within normal ranges

Causes **vasodilation** and **bradycardia** in response to **increased AP**
Baroreceptors

- **Type:** mechanoreceptors
- **Location:** at strategic high-pressure sites, the **carotid sinus** and **aortic arch**
- **Stimulus:** distension of the vascular wall; baroreceptors are not pressure sensitive, but stretch sensitive
- **Response:** the overall baroreceptor response to a pressure increase includes
  - an increased firing rate
  - recruitment of more units

Compared to the carotid sinus receptor, the **aortic arch receptor** has a higher threshold and a higher saturation level = set for a higher pressure regimen
Response of Baroreceptors to Pressure

- In the normal operating range of arterial pressure (around 100 mm Hg) the baroreceptor feedback mechanism functions **most effectively**: even a slight change in pressure causes a strong change in the baroreceptor signal for maintaining the AP at the most needed level.

- The firing rate of baroreceptors is higher at **sudden increases** in AP (i.e. from 100 to 150 mm Hg) than to a constant high value (i.e. 150 mm Hg).

\[ \Delta I, \text{change in carotid sinus nerve impulses per second;} \]
\[ \Delta P, \text{change in arterial blood pressure in mm Hg.} \]
Afferent Pathways

Afferent pathway for the carotid sinus reflex:
- sinus nerve
- glossopharyngeal trunk
- petrosal ggl

Afferent pathway for the aortic arch reflex:
- depressor branch of the vagus nerve
- superior laryngeal nerves
- nodose ggl of the vagus
Medullary Cardiovascular Center

- Is the major coordinating center for cardiovascular homeostasis
- Broad subdivisions can be distinguished, such as:
  - **Vasomotor area** in the ventrolateral medulla, includes
    - A1 and C1 areas in the rostral ventrolateral medulla
    - Inferior olivary complex and other nuclei
    - C1 area produces a spontaneous tonic output that promotes vasoconstriction
  - **Cardioinhibitory area** includes
    - nucleus ambiguus
    - dorsal motor nucleus of the vagus – the cardiac component of the baroreceptor reflex (promotes bradycardia)
  - **Cardioacceleratory area** in the dorsal medulla (increased heart rate and contractility)
Baroreceptor Signals Coordinated by the Medulla

- Impulses from baroreceptors project to the nucleus tractus solitarius (NTS) in the brain stem.
- From NTS project:
  - **Inhibitory interneurons** onto the vasomotor area:
    increased mean arterial pressure $\rightarrow$ baroreceptors $\rightarrow$ NTS neurons inhibit C1 neurons $\rightarrow$ vasodilation
  - **Excitatory interneurons** onto the cardioinhibitory area:
    increased mean arterial pressure $\rightarrow$ baroreceptors $\rightarrow$ NTS neurons stimulate the cardioinhibitory area $\rightarrow$ bradycardia
  - **Inhibitory interneurons** onto the cardioacceleratory area:
    increased mean arterial pressure $\rightarrow$ baroreceptors $\rightarrow$ NTS neurons inhibit the cardioacceleratory area $\rightarrow$ decreased heart rate and contractility
Efferent Pathways

Sympathetic Efferents

- Neurons from vasoconstrictor C1 and cardioacceleratory areas send axons down the spinal cord
  - → preganglionic sympathetic neurons located in the intermediolateral gray matter, T1 – L3 → postganglionic sympathetic neurons located within ganglia of the paravertebral sympathetic chain
  - postganglionic fibers innervate arteries, arterioles and veins or, through the cardiac nerves, the heart;
  - some preganglionic fibers innervate the adrenal gland through the splanchnic nerves

- Increased sympathetic activity produces vasoconstriction; the baroreceptor reflex produces vasodilation because it inhibits the output of C1 neurons
Parasympathetic Efferents

- The **cardioinhibitory** area activated by baroreceptor impulses stimulates **preganglionic** parasympathetic fibers of the **vagus nerve** (dashed line in the figure)

  → **postganglionic neurons** in the walls of the atria and the vessels

  → short **postganglionic fibers** to the SAN, the atria, the AVN or the vicinity of VSMCs
Effectors in the Neural Control of AP

HEART

- **Sympathetic input** (cardiac nerves)
  - **norepinephrine**, to SA node, atria, ventricles → increased heart rate and contractility;
  - at rest their firing rate is lower than that of the vagus nerve → low tonic cardioacceleratory effect on the heart

- **Parasympathetic input** (vagus nerve)
  - **acetylcholine**, to SA node (right branch), AV node (left branch), atria;
  - exerts an intense activity: decreases heart rate, conduction through AV node and to a lesser extent, contractility
BLOOD VESSELS

• **Sympathetic input**
  
  • *Vasoconstrictor response* (norepinephrine, binds on vascular $\alpha_1$ receptors); postganglionic fibers are most abundant in the **skin** and the **kidney**, sparse in the **coronary** and the **cerebral** vessels, absent in the placenta;
  
  • *Vasodilator response* in the skeletal muscle (*acetylcholine*, binds on vascular $M_2$ receptors); sympathetic vasodilator fibers receive impulse from **cerebral cortex** – **hypothalamus** – spinal cord – preganglionic sympathetic neurons – sympathetic ganglia – postganglionic fibers – VSMCs of the blood vessels of the **skeletal muscle** → vasodilation in “fight or flight” response

• **Parasympathetic input**
  
  • *Vasodilator response* (*acetylcholine* – indirectly, NO; acts on $M_2$ and $M_3$ vascular receptors); the fibers are far less compared to the sympathetic ones; they supply the salivary and some gastrointestinal glands; they are crucial for vasodilating erectile tissue in the external genitalia
Vasoconstrictor Tone

- The continual firing of the C1 area is called **sympathetic vasoconstrictor tone** and maintains a partial state of contraction in the blood vessels, called **vasomotor tone**; a total spinal anesthesia induces a fall in mean AP from 100 mm Hg to 50 mm Hg, proving the importance of the vasomotor tone in keeping AP at normal levels.
Sympathetic Effects on Vascular Tone

Arteriole diameter is controlled by tonic release of norepinephrine.

- Electrical signals from neuron
- Time
- Tonic activity
- Change in signal rate
- ↑ Norepinephrine release onto α receptors → Blood vessel constricts
- ↓ Norepinephrine release onto α receptors → Blood vessel dilates
ADRENAL MEDULLA

- Preganglionic sympathetic fibers release Ach on cromaffin cells of the adrenal medulla (= modified postganglionic neurons)
  - release into the blood of epinephrine and some norepinephrine → generalized effects on the circulation (heart and blood vessels)

- Epinephrine binds mostly on
  - Vascular $\beta_2$ receptors (skeletal muscle, coronary vessels) inducing vasodilation
  - Cardiac $\beta_1$ receptors increasing the cardiac output
## Effects of Sympathetic and Parasympathetic Pathways on the Cardiovascular System

<table>
<thead>
<tr>
<th>Effector Response</th>
<th>Anatomic Pathway</th>
<th>Neurotransmitter</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Sympathetic</td>
<td>Norepinephrine</td>
<td>(\beta_1) on cardiac pacemaker</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Parasympathetic</td>
<td>Acetylcholine</td>
<td>(M_2) on cardiac pacemaker</td>
</tr>
<tr>
<td>Increase cardiac contractility</td>
<td>Sympathetic</td>
<td>Norepinephrine</td>
<td>(\beta_1) on cardiac myocyte</td>
</tr>
<tr>
<td>Decrease cardiac contractility</td>
<td>Parasympathetic</td>
<td>Acetylcholine</td>
<td>(M_2) on cardiac myocyte</td>
</tr>
<tr>
<td>Vasoconstriction in most blood vessels (skin, kidney)</td>
<td>Sympathetic</td>
<td>Norepinephrine</td>
<td>(\alpha_1) on VSMCs</td>
</tr>
<tr>
<td>Vasodilation in most blood vessels (muscle, myocardium)</td>
<td>Adrenal medulla</td>
<td>Epinephrine</td>
<td>(\beta_2) on VSMCs</td>
</tr>
<tr>
<td>Vasodilation in “fight or flight” response</td>
<td>Sympathetic</td>
<td>Acetylcholine</td>
<td>(M_2) receptor</td>
</tr>
<tr>
<td>Vasodilation in blood vessels of salivary gland and erectile blood vessels</td>
<td>Parasympathetic</td>
<td>Acetylcholine</td>
<td>(M_2) and (M_3) receptor</td>
</tr>
</tbody>
</table>
Baroreceptor Control of High AP

Blood pressure → Firing of baroreceptors in carotid arteries and aorta → Sensory neurons → Cardiovascular control center in medulla oblongata → Sympathetic output: less NE released → Arteriolar smooth muscle: Vasodilation → Peripheral resistance: ↓ Blood pressure

Parasympathetic output: more ACh on muscarinic receptor → Ventricular myocardium: ↓ Force of contraction → Cardiac output: ↓ Heart rate → Blood pressure: ↓

KEY: Stimulus, Receptor, Afferent pathway, Integrating center, Efferent pathway, Effector, Tissue response, Systemic response
Baroreceptor Control of Low AP

- Mean arterial blood pressure upon standing
- Firing of carotid and aortic baroreceptors
- Cardiovascular control center in medulla
  - ↓ Sympathetic output
    - Arterioles and veins
      - Vasoconstriction
      - ↓ Peripheral resistance
    - ↓ Blood pressure to normal
  - ↓ Parasympathetic output
    - Ventricles
      - Force of contraction
      - ↓ Heart rate
    - SA node
      - ↓ Cardiac output
**Arterial pressure** (mmHg)

- Normal:
  - Basal frequency: Action potentials (APs)
  - Increased frequency: Action potentials (APs)
  - Decreased frequency: Action potentials (APs)

**Baroreceptor membrane potential** (mV)

- Basal frequency: Action potentials (APs)
- Increased frequency: Action potentials (APs)
- Decreased frequency: Action potentials (APs)
Because the baroreceptor system opposes either increases or decreases in arterial pressure, it is called a **pressure buffer system**.

A denervated dog presents an extreme variability of pressure caused by simple events of the day, such as lying down, standing, excitement, eating, defecation, and noises.

→ **A primary purpose** of the arterial baroreceptor system is to **reduce the minute by minute variation in arterial pressure**.
Reseting of Baroreceptors

- Baroreceptors tend to reset in 1 to 2 days to the pressure level to which they are exposed.
  - This “resetting” of the baroreceptors may **attenuate their potency as a control system for correcting AP for longer than a few days** at a time.

- However, baroreceptors have a role in **long-term regulation** of AP: during prolonged increases in AP, the baroreceptor reflexes mediate **decreases in renal sympathetic nerve activity** → **vasodilation** → **increased excretion of sodium and water by the kidneys** → gradual decrease in blood volume, which helps to restore arterial pressure toward normal.
Higher Brain Centers

- Neurons located throughout the reticular substance of the pons, mesencephalon, and diencephalon can either excite or inhibit the vasomotor center:
  - lateral and superior portions of the reticular substance cause excitation
  - medial and inferior portions cause inhibition

- Hypothalamus – exerts powerful excitatory (posterolateral areas) or inhibitory (anterior nuclei) cardiovascular effects; integrates many cardiovascular responses (e.g. during exercise)

- Forebrain areas – influence the hypothalamic integration areas along inhibitory and excitatory pathways (e.g. emotions → fainting); conditioned reflexes → cardiovascular responses such as change heart rate
Response to Exercise

- **Hypothalamus**, under the general control of the **cerebral cortex**, coordinate the *early response to exercise* = an increased alertness that anticipates exercise by producing:
  - Increased cardiac output
  - Vasoconstriction in inactive muscle regions, and renal, splanchnic and cutaneous circulations
  - Early vasodilation in active muscle mediated by **Ach**
Delayed cardiovascular response to exercise is generated by muscular contraction, whereas the early response precedes contraction.
Response to Acute Emotional Stress

- **Vasovagal syncope** (fainting)
  - Is induced by specific activation of areas in the anterior cingulate gyrus
  - Occurs through a massive stimulation of the **parasympathetic system** and the removal of the sympathetic tone
The fight or flight response originates entirely within the CNS, without involvement of peripheral sensors or reflexes; it is a defense reaction that causes a generalized increase in skeletal muscle tone and increased sensory attention.

Under the control of the cortex, the hypothalamus acts through:
- the medullary cardiovascular center
- the postganglionic sympathetic cholinergic neurons
Chemoreceptor Control of Arterial Pressure
Chemoreceptor Control of AP

- A secondary neural regulation of arterial blood pressure that operates like the baroreceptor reflex except it is initiated by chemoreceptors

- **Chemoreceptors**
  - Are cells sensitive to oxygen lack (low $P_{O_2}$), carbon dioxide excess (high $P_{CO_2}$), and hydrogen ion excess (low $pH$)
  - Their primary role is to regulate ventilation
  - According to their location, there are
    - **Peripheral chemoreceptors**
    - **Central chemoreceptors**
Peripheral Chemoreceptors

- Primarily sense a low $\text{Po}_2$
- Are located in several small chemoreceptor organs:
  - Two **carotid bodies** (glomus caroticum) in the bifurcation of common carotid arteries; glomus cells synapses with fibers of the glossopharyngeal nerve
  - One to three **aortic bodies** adjacent to the aorta, that synapse with fibers of the vagus nerve
Afferent fibers from glomus caroticus and aortic bodies project to the NTS in the medulla → dis-inhibition of vasomotor center from NTS influences → vasoconstriction; the final effect on the heart is tachycardia.

The fluctuation in $P_{O_2}$ that normally occur in humans cannot induce changes in arterial pressure or heart rate → peripheral chemoreceptor play a role only during severe hypoxia (hemorrhagic hypotension).
Central Chemoreceptors

- Located in the ventrolateral medulla, sense mainly a high brain $\text{PCO}_2$ and a low pH
- Once stimulated, these areas dis-inhibit the vasomotor area from NTS influences induced by baroreceptor signals (if the case) $\rightarrow$ vasoconstriction
Low-Pressure Baroreceptor Control of Arterial Pressure
Low-Pressure Baroreceptors

- Stretch receptors located at low-pressure sites: pulmonary artery, the junction of the atria with their veins, the atria themselves
- Their distension depends on the venous return to the heart → detect fullness of the circulation = volume sensors
- Their stimulation generate reflexes that
  - Help control the volume of blood
  - Help regulating cardiac output
→ Indirectly regulate AP
Atrial Receptors

- Most studied low-pressure receptors, they are A or B fibers that join the **vagus** nerve
  - **A fibers** – fire in synchrony with atrial systole → monitor HR
  - **B fibers** – increase their firing as the atria fill → monitor the atrial volume and the central venous pressure (CVP)
- Afferent, efferent pathways and the effectors are similar to the baroreceptor reflex
Effects of B-Fibers Stimulation

- **Heart**
  
  Increased atrial filling *raises the heart rate* = Bainbridge reflex
  
  → increased **cardiac output** in response to an increased venous return
  
  → helps prevent damming of blood in the veins, atria, and pulmonary circulation

- **Vessels**
  
  Increased stretch of B-fibers decreases sympathetic vasoconstrictor output *only to the kidney* → renal vasodilation → increased diuresis = *low-pressure receptors attempt to eliminate fluid*
  
  when venous return increases → ↓*AP*

- **Hormone release**
  
  Afferent fibers of the atrial receptors project also on the hypothalamus → **inhibits** arginine vasopressin (**AVP**) release in response to increased venous return → **increased diuresis** → ↓*AP*
Atrial stretch has **non-neural effects** as well: induces **release** of atrial natriuretic peptide (ANP) from stretched atrial myocytes, followed by **increased diuresis** → lowering of AP

**In summary:**

**Increased atrial filling** → stretch of atria mechanoreceptors → **increased diuresis** (decrease of extracellular fluid and eventually blood volume) by three efferent mechanisms:

- **2 neurally mediated:**
  - Tachycardia combined with renal vasodilation, producing *increased renal blood flow*
  - *Inhibition of AVP release*

- **1 non-neural:** *ANP release*
Regulation of Cardiac Output
Regulation of Cardiac Output

- Heart is an important effector organ in the feedback loops that regulate AP

- \( \text{CO} = \text{SV} \times \text{HR} \)

- Both SV and HR are under the control of regulatory mechanisms \text{intrinsic} and \text{extrinsic} to the heart
Intrinsic Control of Heart Rate

- The firing rate of SA node depends on
  - The maximum diastolic potential
  - The slope of the diastolic depolarization (phase 4)
  - The threshold potential

- \([\text{K}^+]_o\) and \([\text{Ca}^{++}]_o\) are intrinsic modifiers that influence the SA node activity without being part of a cardiovascular feedback loop
Intrinsic Control of Stroke Volume

- $SV = EDV - ESV$
- **EDV** depends on
  - **Filling pressure** – increased *venous return* increases atrial filling pressure $\rightarrow$ EDV rises
  - **Filling time** – increased **HR** may decrease EDV
  - **Ventricular compliance** – high compliance $\rightarrow$ for a given filling pressure, produces an increase in ventricular volume rising EDV
- **ESV** depends on
  - **Preload** – Starling principle: a high pre-load increases SV
  - **Afterload** – increased after-load increases ESV
  - **HR** – increased HR increases contractility, may reduce ESV
  - **Contractility** – positive inotropic agents enhance the force of contraction and decrease ESV
Extrinsic Control of HR and SV

- **Baroreceptor response** – adjusts cardiac output only as a response to an alteration of AP:
  
  - Baroreceptors do not respond to an increase in cardiac output that matches a decrease in peripheral resistance, leaving AP unchanged.
  
  - If peripheral resistance alters AP, the baroreceptor reflex adjusts cardiac output and arterial tonus in order to maintain AP at a proper level.
• **Chemoreceptor response** – adjusts cardiac output only as a response to an *alteration in pH, Po2, PCO2*:
  low cardiac output $\rightarrow$ low AP $\rightarrow$ decreased perfusion $\rightarrow$ low PO2, high PCO2, low pH $\rightarrow$ peripheral and central chemoreceptor are stimulated $\rightarrow$ tachycardia $\rightarrow$ increase in CO

• **Low-pressure receptor response** – monitors heart rate, effective circulating volume and venous return
  Venous return influences cardiac output by adjusting both SV (Frank-Starling mechanism) and HR (Bainbridge reflex, baroreceptor reflex)
Cardiac Output is Proportional to Venous Return

- **Heart Rate** and Venous Return

  - Decreasing the circulating blood volume (= *volume depletion*, decreased venous return, lowering of AP) *increases heart rate* due to decreased firing of *high-pressure baroreceptors*

  - Increasing the circulating blood volume (= *volume loading*, increased venous return) *increases heart rate* through *low-pressure baroreceptor reflex* (Bainbridge reflex)

  - Heart rate is at its minimum when circulating blood volume is normal
- Stroke Volume and Venous Return

- **SV increases gradually** with venous return while correcting a **volume depletion** - because of Starling’s law effect and decreased firing from high-pressure baroreceptors that induces sympathetic stimulation.

- **SV stays constant** during **volume overload** - because Starling’s law effect is less steep and the baroreceptor reflex is reducing contractility.

- Therefore, the cardiac output \((CO = HR \times SV)\) rises monotonically with the circulating blood volume.
Cardiac output dependence on venous return is the result of the interplay among:

1. Bainbridge reflex
2. Baroreceptor reflex
3. Starling’s law
Intermediate and Long-Term Control of the Arterial Pressure

- Vasoactive Compounds
- Renal Control
Operating within **hours** or **days**, contribute to circulatory homeostasis by means of two classes of **humoral control**:

1) **Vasoactive substances**
   - Released in the blood or in the proximity of VSMCs
   - *Modulate the vascular tone* → affect blood pressure and the distribution of blood flow

2) **Nonvasoactive substances**
   - Act on targets other than the cardiovascular system (*kidneys*)
   - *Modulate extracellular fluid volume* → control the circulating blood volume → modulate the arterial pressure and cardiac output by determining the filling of the blood vessels
1. Vasoactive Compounds

- Biogenic amines
- Peptides
- Prostaglandins
- Gases
- Ions
Biogenic Amines

1. **Epinephrine** – produced by the adrenal medulla
   - binds to $\beta_2$ receptors of VSMCs (skeletal muscle, heart, liver, adrenal medulla itself) causing **vasodilation**
   - binds to $\alpha_1$ receptors of VSMCs (skin) causing **vasoconstriction**
   - binds to $\beta_1$ receptors in the heart *increasing heart rate* and *contractility*

   The effects of epinephrine are **minor** compared with those of norepinephrine released by the sympathetic nerves

2. **Serotonin** - present in nerve terminals, platelets, mast cells
   - local **vasoconstrictor**, important with vessel damage

3. **Histamine** – present in nerve terminals, mast cells
   - local **vasodilator**, released in response to tissue injury and inflammation; increases capillary permeability $\rightarrow$ edema (allergic reactions)
Peptides

1. Angiotensin II (ANG II)
   - **Genesis:** angiotensinogen (liver) $\rightarrow$ cleaved to angiotensin I by renin (kidney) $\rightarrow$ cleaved to ANG II by angiotensin-converting enzyme (ACE, released by the endothelial cells, particularly those of the lung) $\rightarrow$ cleaved by aminopeptidases to angiotensin III, less vasoactive than ANG II

   - Important during **blood loss**, exercise and other circumstances that reduce renal blood flow $\rightarrow$ renin release $\rightarrow$ ANG II synthesis, that:
     - Acts a powerful *vasoconstrictor* in the renal and splanchnic territories; keeps the glomerular filtration rate at functional levels during falls of renal artery blood pressure
Indirectly increases AP by a number of other than direct vasoactive effects:

- Increases cardiac contractility
- Reduces renal plasma flow, increases renal Na+ absorption
- ANG II and ANG III stimulate the release of aldosterone
- In CNS stimulates thirst and release of arginine vasopressin
- Facilitates the release of norepinephrine
- Acts as a cardiac growth-factor (cardiac hypertrophy)
2. **Arginine vasopressin (AVP) or antidiuretic hormone (ADH)**
   - Released by the posterior pituitary
   - *Vasoconstrictor* at high concentration (hemorrhagic shock)

3. **Endothelins (ETs)**
   - Produced by endothelial cells
   - Local *vasoconstrictors*, the most powerful

4. **Atrial natriuretic peptide (ANP)**
   - Released from atrial myocytes in response to stretch
   - Potent *vasodilator*
   - Powerful diuretic and natriuretic → lowers plasma volume and the arterial pressure
5. **Kinins (bradikinin)**
   - Breakdown products of kininogens, catalysed by kallikreins (enzymes present in plasma, digestive glands and kidney); produced during inflammation and other tissue reactions; inactivated after only a few minutes from their formation by kininases (kininase II is ACE that generates ANG II)
   - **Vasodilators**
   - Like histamine, increase capillary permeability $\rightarrow$ edema (allergic reactions)
Prostaglandins
- Derivatives of arachidonic acid synthesized by many tissues
- $\text{PGI}_2$ and $\text{PGE}_2$ are strong local *vasodilators*

Gases
- **Nitric oxide (NO)**
  - Produced from arginine in endothelial cells by nitric oxide synthase (NOS)
  - Strong local *vasodilator*
- **Carbon dioxide** causes
  - *Moderate vasodilation* in most tissues
  - *Marked vasodilation* in the brain
  - Acting on the brain vasomotor center, has an extremely powerful indirect effect, transmitted through the sympathetic nervous vasoconstrictor system, to cause widespread vasoconstriction throughout the body
• Ions
  • Calcium – *vasoconstriction*, by stimulating VSMCs contraction
  • Magnesium – *vasodilation*, inhibits VSMCs contraction
  • Potassium – *vasodilation*, inhibits VSMCs contraction
  • Hydrogen ions – acidosis causes *dilation* of the arterioles, whereas a *discrete alkalosis* produces arteriolar *constriction*
2. Renal Control of ECF

- Plasma volume, and therefore blood pressure, is determined by extracellular fluid (ECF = plasma plus the interstitial fluid) and the Starling forces across the capillary wall.
- The **effective circulating volume**, which is the functional blood volume as sensed by the fullness or pressure in the vessels, is defended by:
  - **High-pressure receptors**, in the short term they regulate blood pressure via direct cardiovascular effects, and in the longer term they regulate effective circulating volume.
  - **Low-pressure receptors**, regulate effective circulating volume.
  - **Other sensors**: baroreceptors in the renal artery, stretch receptors in the liver, the atrial myocytes, osmoreceptors in the CNS.

These **sensors** send signals to the **dominant effector organ: the kidney**
The signals to the kidney follow four *efferent pathways*:
1. The renin - ANG II - aldosterone axis
2. The autonomic nervous system
3. The posterior pituitary that release AVP
4. Atrial myocytes that release ANP

*The kidney* determines ECF volume by regulating **total-body Na+ content** → ultimately governs the blood volume → *the kidney is the principal agent in the long-term control of mean arterial pressure*

(A detailed presentation of the long-term renal regulation of blood pressure will be provided in the lectures on renal physiology)
Summary
MEAN ARTERIAL BLOOD PRESSURE

is determined by

Blood volume
  determined by
    Fluid intake
    Fluid loss

Effectiveness of the heart as a pump (cardiac output)
  determined by
    Heart rate
    Stroke volume

Resistance of the system to blood flow
  determined by
    Diameter of the arterioles

Relative distribution of blood between arterial and venous blood vessels
  determined by
    Diameter of the veins

Fluid intake may be
  Passive
  Regulated at kidneys
Basic Principles Governing the Circulation of Blood

- The rate of **blood flow to each tissue** of the body is controlled in relation to the tissue need.

- The **cardiac output** is controlled mainly by the sum of all the local tissue flows (venous return).

- In general the **arterial pressure** is controlled independently of either local blood flow control or cardiac output control by nervous- and kidney-regulated mechanisms.

→ Arterial pressure is kept fairly constant over time, whereas blood flow (cardiac output) and peripheral resistance are quite variable.
Cardiovascular Control Systems

Venous return
- Filling pressure
  - Filling time
  - Ventricular compliance
- Heart rate
- Pre-load
  - After-load
  - Contractility
- End-diastolic volume
- End-systolic volume
- Intrinsic regulation
- Stroke volume
- Heart rate
- Cardiac output
- Mean arterial pressure
- Systemic vasomotor control
- Extrinsic regulation
- Local vasomotor control
- Total peripheral resistance
- Baroreceptor
- ANS
- Humoral factors