LOCAL AND HUMORAL BLOOD FLOW CONTROL

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Learning Objectives

• By the end of lecture student should be able to
  • Outline the purpose of blood flow
  • Mention the amount of blood flow to various organs
  • Explain the mechanisms of blood flow control
  • Summarize the acute blood flow control
  • Explain the mechanism of action of vasodilator substances
  • Explain active and reactive hyperemia with examples
  • Summarize the chronic blood flow control
  • Enlist the hormones and local agents causing vasoconstriction
Specific Needs Of Tissues For Blood Flow

1. Delivery of $O_2$ to tissues.
3. Removal of $CO_2$ from tissues
4. Removal of $H^+$ from tissues
5. Maintenance of proper conc. of ions
6. Transport of hormones & specific substances
Local Blood Flow Control

- Blood flow to different organs is not constant but varies in accordance with the demands of tissue (metabolism).
- Maintained at the minimal level so that the blood supply is just sufficient to meet the tissue requirements—no more, no less.
- Each tissue has the ability to control its own local blood flow in proportion to its metabolic needs.
- Metabolic needs keep changing.
- Increase in metabolism—-increase in blood flow.
Local Blood Flow Control

• Greater is the metabolism in an organ, the greater is the blood flow.

• **Skin** = *(Cool Weather)* 300 ml/min
  • Blood flow to skin determines heat loss *(controls body temperature)*

• **Kidneys** = 1100ml/min.
  • Adequate blood flow for excretion of waste products

• **Liver**
  • Portal: 1050 ml/min 1350 ml/min
  • Arterial: 300 ml/min

• **Muscles**
  • Inactive (Rest): 750 ml/min or 4 ml/min/100gm (30-40% Body mass)
  • Severe Exercise: ↑ 20 fold or 80 ml/min/100 gm (↑BMR 60 fold)
### Blood Flow to different organs (basal conditions)

<table>
<thead>
<tr>
<th></th>
<th>Per cent</th>
<th>ml/min</th>
<th>ml/min/100</th>
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<tbody>
<tr>
<td>Brain</td>
<td>14</td>
<td>700</td>
<td>50</td>
</tr>
<tr>
<td>Heart</td>
<td>4</td>
<td>200</td>
<td>70</td>
</tr>
<tr>
<td>Bronchi</td>
<td>2</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td><strong>Kidneys</strong></td>
<td>22</td>
<td>1100</td>
<td>360</td>
</tr>
<tr>
<td>Liver</td>
<td>27</td>
<td>1350</td>
<td>95</td>
</tr>
<tr>
<td>Portal</td>
<td>(21)</td>
<td>1050</td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>(6)</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle (inactive state)</strong></td>
<td>15</td>
<td>750</td>
<td>4</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>250</td>
<td>3</td>
</tr>
<tr>
<td>Skin (cool weather)</td>
<td>6</td>
<td>300</td>
<td>3</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>1</td>
<td>50</td>
<td>160</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>0.5</td>
<td>25</td>
<td>300</td>
</tr>
<tr>
<td>Other tissues</td>
<td>3.5</td>
<td>175</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100.0</td>
<td>5000</td>
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</table>
Local Blood Flow Control

- Microvessels (arterioles, metarterioles and capillaries)
  - Present within the terminal organs
  - Supply blood to the respective organ

\[
\text{Flow} = \frac{\Delta P}{R}
\]

- At constant pressure, blood flow to a tissue is altered by changing arteriolar resistance

\[
\text{Flow} \propto \frac{1}{R}
\]
Capillary Beds

- Precapillary sphincters
- Metarteriole
- Vascular shunt
- Thoroughfare channel
- True capillaries
- Terminal arteriole
- Postcapillary venule

(a) Sphincters open
Local Blood Flow Control

• Arterioles, metarterioles and precapillary sphincters
  • Act as control valves
  • Alter blood flow to tissues by varying resistance (diameter)
(b) Sphincters closed
Local Blood Flow Control

- **Extrinsic control**
  - Nervous
  - Humoral

- **Local (intrinsic) control**
  - Intrinsic ability of tissues to control their blood flow in response to locally produced agents
  - Achieved by adjusting the tone of arterioles, metarterioles & precapillary sphincters
Reduced Oxygen Availability Increases Tissue Blood Flow

- At a high altitude at the top of a high mountain
- In pneumonia
- In carbon monoxide poisoning (oxygen delivery is affected)
- In cyanide poisoning (oxygen utilization is affected)
Local Blood Flow Control

• Arterioles, metarterioles and precapillary sphincters
  • act as control valves
  • Alter blood flow to tissues by varying resistance (diameter)

VASOMOTION

• Cyclical opening of the pre capillary sphincters---several times per minute
• Duration of opening phase is directly proportional to metabolic needs
Vasomotion

• Number of open precapillary sphincters at any given time is roughly proportional to the requirements of the tissue for nutrition

• Precapillary sphincters and metarterioles open and close cyclically

• The cyclical opening and closing is called *vasomotion*. 
Local Blood Flow Control

• Acute control
  • Occurs within sec—min
  • Less effective control (not perfect)
  • Vasodilation or vasoconstriction of precapillary sphincters, metarterioles & arterioles

• Long-term control
  • Occurs within days, weeks or months
  • More effective control (almost perfect)
  • Change in size and numbers of vessels
Short Term/Acute Control of Blood Flow
(b) Normal arteriolar tone

Caused by:
- Myogenic activity
- Oxygen ($O_2$)
- Carbon dioxide ($CO_2$) and other metabolites
- Endothelin
- Sympathetic stimulation
- Vasopressin; angiotensin II
- Cold

(c) Vasoconstriction (increased contraction of circular smooth muscle in the arteriolar wall, which leads to increased resistance and decreased flow through the vessel)

Caused by:
- Myogenic activity
- $O_2$
- $CO_2$ and other metabolites
- Nitric oxide
- Sympathetic stimulation
- Histamine release
- Heat

(d) Vasodilation (decreased contraction of circular smooth muscle in the arteriolar wall, which leads to decreased resistance and increased flow through the vessel)
Local Blood Flow Control

- Acute control of local blood flow
- Regulation depends on
  - Rate of tissue metabolism
  - Availability of oxygen
Local Blood Flow Control

- Acute control
  - Metabolic mechanism
    - Vasodilator theory
    - Oxygen (nutrient) lack theory
  - Myogenic mechanism
Metabolic mechanism

• Metabolic mechanism
  • Intrinsic ability of tissues to control their blood flow in response to change in metabolism and/or supply of oxygen
  • Greater is the rate of metabolism or less availability of $O_2$ (or some other nutrient) $\rightarrow$ Greater is the rate of formation of vasodilator substances
Metabolic mechanism

• Vasodilator theory
  • Vasodilator substances
  • Released by tissue cells (mainly in response to O$_2$ deficiency)
  • Diffuse through the tissues to precapillary sphincters, metarterioles and arterioles
  • Vasodilation
Metabolic mechanism

• Vasodilator substances
  • Adenosine
  • CO$_2$
  • Adenosine phosphate compounds
  • Hydrogen ions
  • Potassium ions
  • Prostaglandins
  • Histamine
Metabolic mechanism

- *Increased CO2*—by-product during increased oxidative phosphorylation as a result of increased activity.

- *Increased acid.*
  - More carbonic acid is generated from the increased CO2 produced as the metabolic activity of a cell increases.
  - Lactate (lactic acid) accumulates if the glycolytic pathway is used for ATP production.

- *Increased K*—Repeated action potentials that outpace the ability of the Na–K pump to restore the resting concentration gradients result in an increase in K in the tissue fluid of an actively working organ.
Metabolic mechanism

- *Increased osmolarity*—during elevated cellular metabolism because of increased formation of osmotically active particles.

- *Adenosine release*. Especially in cardiac muscle, adenosine is released in response to increased metabolic activity.

- *Prostaglandin release*—local chemical messengers derived from fatty acid chains within the plasma membrane
Metabolic mechanism

• Adenosine --- Most important vasodilator
  • Coronary insufficiency
    • Released from heart muscle cells
    • Vasodilation of coronary blood vessels
  • Increased cardiac activity
    • Increased metabolism, increased utilization of oxygen
    • Decreased $O_2$ conc----ATP degradation----increase release of adenosine
  • Controller of blood flow in skeletal muscle
Coronary Insufficiency

↓ Coronary Blood Flow → Release of Adenosine → Coronary Vasodilation

↑Coronary Blood Flow

When heart is very active

↑Rate of Metabolism & ↑O2 utilization

↑ Coronary blood flow

↑ Supply of nutrients

↓ O2 Concentration → ↑ Adenosine Release

↑ Degradation of ATP
Metabolic mechanism

• Vasodilator theory—Difficult to prove
  • Sufficient quantities of single vasodilator substance
  • Combination of several different vasodilator
Metabolic mechanism

• Nutrient lack theory/Oxygen lack theory
  • $O_2$ ----potent vasoconstrictor
  • During vascular muscle contraction—Absence of adequate $O_2$ ----
    blood vessels relax (anemia)
  • Increased utilization of $O_2$ (increased metabolism)
  • Lack of glucose----vasodilation
  • Amino Acids, Fatty acids
  • Vitamin B deficiency—beriberi—vasodilation—blood flow
    increases two to three fold
Myogenic Mechanism

• Intrinsic ability of arteriolar smooth muscle to change its tone (diameter) in response to stretch (pressure)
• Not related to tissue metabolism
• Inherent response
• Can occur in the absence of neural or hormonal influences
• Most pronounced in arterioles
Myogenic Mechanism

• Contraction of vascular smooth muscle when stretched by ↑ pressure
  • High arterial pressure— increased blood flow—reactive vascular constriction----decreased blood flow-- arterial pressure back to normal

• Role of stretch sensitive Ca^{++} channels
  • Stretch induced vascular depolarization
  • Ca^{++} entry from ECF into cells
  • Reduction in local blood flow

• Relaxation when stretch decreases due to ↓ arterial blood pressure leading to rise in local blood flow—Protective role
Metabolic mechanism override Myogenic mechanism
Acute Blood Flow Control-examples

• Metabolic mechanisms
  • Reactive hyperemia
  • Active hyperemia
• Metabolic and Myogenic
  • Autoregulation
Special mechanisms

- **Kidney**
  - Tubuloglomerular feedback - role of juxtaglomerular apparatus

- **Brain**
  - Prominent role of $\text{H}^+$ and $\text{CO}_2$ (vasodilation in $\text{H}^+$ and/or $\text{CO}_2$ excess to washout)

- **Skin**
  - Linked to regulation of body temperature
Reactive hyperemia

- Increased blood flow when a pre-occluded artery to a tissue is released
  - Blood supply blocked for sec-hrs
  - Unblocked
  - Blood flow increases---4-7 fold
  - Repays almost exactly the tissue $O_2$ deficit
- Metabolic mechanism
  - Vasodilator theory
  - $O_2$ lack theory
Active hyperemia

• Tissue becomes highly active----rate of blood flow increases
• Increased blood flow in response to rise in tissue metabolism
  • Lack of nutrients, Oxygen lack theory
  • Release of vasodilator substances, Vasodilator theory
• Increased blood flow to muscles during exercise
  • Blood flow increased 20 fold
Autoregulation

- Intrinsic ability of tissues to control blood flow in response to changes in arterial blood pressure (constant metabolism)
Autoregulation

• Blood flow is related to the arterial pressure
• Acute increase in arterial pressure causes immediate rise in blood flow
• Within min the blood flow in most tissues return almost to the normal level although the arterial pressure is elevated
• This return of flow to normal is called autoregulation of blood flow
Endothelial derived constricting and relaxing substances

- Vasodilator----Nitric oxide
- Activates soluble guanylate cyclase activates cGMP
- Inhibits cGMP specific phosphodiesterase that decomposes cGMP
- Clinical implications
  - Treatment of angina pectoris
  - Treatment of erectile dysfunction
    - Development and clinical use of drugs (e.g., sildenafil) that inhibit $cGMP$-specific phosphodiesterase-5 ($PDE-5$), an enzyme—degrades cGMP.
    - Parasympathetic innervation
    - By preventing the degradation of NO, the PDE-5 inhibitors enhance the dilation of the blood vessels in the penis and aid in erection,
6 seconds in blood

Blood

Shear stress

Receptor-dependent activation

eNOS

O₂ + L-Arginine → NO + L-Citrulline

Endothelial cells

Soluble guanylate cyclase

cGTP → cGMP

Vascular smooth muscle

Relaxation
Long Term/Chronic Control of Blood Flow
Long-term Control of Blood Flow

- Almost complete control of local blood flow
- Important when there are long term metabolic needs of tissues change
- Increase in vascularity
  - Vascularity proportional to metabolism
  - Dependent on metabolism
  - Arterioles and capillaries usually increase in number and size
  - Occurs within days to weeks
  - Dependent on the age (neonate or old)
  - Adjustment is more accurate in younger tissue
Long-term Control of Blood Flow

Low oxygen as stimulus for vascularization
- Animals living at high altitudes
- Fetal chicks hatched in low oxygen
- Premature babies

Retrolental fibroplasia
- Occurs in premature babies who are put in O₂ tents
- High O₂ leads to cessation of new vessel growth in retina
- Excessive overgrowth of vessels in retina after removal from O₂ tent
- Vascular growth in vitreous humor
- Leads to total blindness
Angiogenic factors

Factors enhancing vascularization
- VEGF
- Fibroblast Growth Factor
- Angiogenin
Formation of new blood vessels

- New vessel sprout from old vessel
  - Dissolution of basement membrane of endothelial cells
    - Reproduction of endothelial cells in cord like fashion
      - Toward angiogenic factor
        - Rapidly divide and fold over
          - Connects to another donor vessel via capillary loop
            - Blood flow begins
Long Term Control Of Blood Flow

Chronic O$_2$ lack

Release of angiogenic factors

Increased tissue vascularity
Long Term Control of Blood Flow

• Applied Physiology
  • Cancerous tissue & angiogenesis
    • Release of angiogenic factors by cancerous cells
    • Suppression of angiogenesis as anticancer therapy
Collateral circulation

• A new vascular channel develops around the blockage
  • Principle of Acute control
  • Dilation of vascular loop
  • Opening of collateral vessels
    • Rapid neurogenic and metabolic dilation

• Principle of Long-term control
  • Growth and enlargement of new vessels
Extrinsic Control of Blood Flow

• Autonomic nervous system (primarily geared to regulate arterial blood pressure not blood flow)
  • Sympathetic nervous system
    • Stimulation - vasoconstriction
    • Inhibition - vasodilation
Extrinsic Control of Blood Flow

- Humoral control
  - Blood flow control exerted by hormones, paracrine and autocrine agents
    - Vasoconstrictor agents
    - Vasodilator agents
### Humoral Control of Blood Flow

**Vasoconstrictor agents**
- Norepinephrine and epinephrine
- Angiotensin II
- Vasopressin (ADH)
- Endothelin-A

**Vasodilator agents**
- Nitric oxide (Endothelium derived relaxing factor)
- Bradykinin
- Histamine
- Atrial natriuretic peptide (ANP)
- Vasoactive intestinal peptide (VIP)
# Control of Blood Flow by Ions

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<thead>
<tr>
<th>Vasodilator ions</th>
<th>Vasoconstrictor ions</th>
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<tbody>
<tr>
<td>K+</td>
<td>Ca++</td>
</tr>
<tr>
<td>Mg++</td>
<td></td>
</tr>
<tr>
<td>H+</td>
<td></td>
</tr>
<tr>
<td>Acetate</td>
<td></td>
</tr>
<tr>
<td>Citrate</td>
<td></td>
</tr>
<tr>
<td>CO$_2$</td>
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THANK YOU