Physiologic Control Systems

- Goal: overall effect of the system
- Process steps: pathways, basic mechanisms
- Points of regulation: where can we alter the process?
  - uni/bi-directional?
  - time to action?
- Sensors
  - local or remote?
  - direct or indirect?
- Feedback mechanisms: control
  - pathways, gain, time to action
  - set point determination
Control of the Circulation Overview

• Goal: adjust circulation so that adequate blood flow is provided to all tissues; secondary goal is to provide proper pressure in capillaries for fluid balance.

• Process steps and regulation points:
  – Cardiac output (rate and stroke volume)
  – Peripheral circulation
    • arteriole diameter, resistance changes
    • hormonal influence on vessels (pharmacomechanical coupling)
    • ANS modulation: mostly sympathetic
  – Blood pressure
    • depends on cardiac output and peripheral resistance
    • fluid balance, adjust blood volume

• Sensors: Local and remote; pressure, chemo
• Feedback: Local and remote, fast and slow

Response to Exercise

<table>
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<th>Organ</th>
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Distribution of Blood Flow [l/min]
Local Regulation = Autoregulation

- **Regulation Mechanisms**
  - Change in resistance of the vessels
    - myogenic or metabolic reflexes
  - Vascularization: angiogenesis, collaterals
    - long term response (and more powerful)

- **Sensors**
  - stretch, metabolites, ions

![Graph showing immediate and delayed responses to changes in flow and pressure](image)

**At Constant Metabolic Rate**

- Immediate response
- Response after several minutes

**Control of Circulation**

---

**Autoregulation: Feedback Mechanisms**

### Myogenic Mechanism

- Arterial Pressure $\uparrow$
- Flow $\uparrow$
- Arterial Distension $\uparrow$
- Smooth Muscle Tone $\uparrow$
- Arterial Resistance $\downarrow$
- Arterial Diameter $\uparrow$

Set point???

### Metabolic Mechanism

- Arterial Pressure $\uparrow$
- Flow $\uparrow$
- Nutrients $\uparrow$
- Vasodilator $\uparrow$
- Arterial Diameter $\downarrow$
- Arterial Resistance $\uparrow$

- Actual mechanism not clear
**Metabolic Feedback Mechanism**

**Reactive Hyperemia**

**Vasodilator Theory**

For:
- vasodilatory substances exist (e.g., CO$_2$, lactic acid, K-ions, adenosine)

Against:
- none acts strongly enough by itself to explain the data

**Nutrient Theory**

Sensitive to O$_2$ or other nutrient

For:
- vasomotion occurs in some capillary beds

Against:
- most smooth muscle does not need much O$_2$ to contract
- but arterial smooth muscle may...

- Vasodilator versus Nutrient
- Or a combination of both?

**Long Term Local Regulation**

**Vascularization**

- Factors
  - Time: hours to days in infants; weeks to never in aged
  - Angiogenesis factor: attracts buds that break from vessels walls
  - Collateral circulation: metabolically driven, leads to bypass

- Examples
  - Coarction of the aorta (congenital: large differences in pressure even though flow is normal)
  - Retrolental fibroplasia: sudden drop in oxygen concentration in premature babies leads to vessel growth

Note: long term regulation more powerful than short!!
Central Regulation of Blood Flow/Pressure

- Process Steps
  - Hormonal
    - Most important mechanism, especially long term
    - Many substances involved
  - Central (ANS)
    - Sympathetics influence venous more than arterial vessels
    - Parasympathetic only minor role
    - Dual effects:
      - constricting (α fibers)
      - relaxing (β fibers)
- Sensors
  - Pressure, stretch, chemo, psychological

Autonomic Innervation of the Circulation

- Sympathetics carry both constricting (α) and relaxing (β) fibers.
- Parasympathetics have no direct influence
Central Control Overview

- Distributed sensors
- Pressure set point
- Integrator (CNS)
- Actuation via ANS

Vasoconstrictive Substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>adrenal medulla</td>
<td>vasoconstrictive in almost all cases (α-receptors).</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>adrenal medulla</td>
<td>vasoconstrictive except in skeletal and cardiac muscle where vasodilative (β-receptors)</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>kidneys/plasma</td>
<td>powerful constrictor in response to drop in $P_a$</td>
</tr>
<tr>
<td>Vasopressin (Antidiuretic Hormone)</td>
<td>Hypothalamus/pituitary</td>
<td>even more powerful vasoconstrictor; important in case of major hemmorhage and regulating water retension in the kidney</td>
</tr>
</tbody>
</table>
### Vasodilator Substances

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<th>Action</th>
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</thead>
<tbody>
<tr>
<td>Bradykinin</td>
<td>plasma and tissue fluids</td>
<td>dilation, increases permeability; role unclear but may be activated by tissue injury</td>
</tr>
<tr>
<td>Seratonin</td>
<td>chromaffin tissue, intestines</td>
<td>can be both dilator and vasoconstrictor, depending on tissue; role even less clear</td>
</tr>
<tr>
<td>Histamine</td>
<td>all tissues</td>
<td>not important in normal circulation but does cause dilation and increased capillary permeability in damaged areas, leading to edema.</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>all tissues</td>
<td>usually dilator, but can cause constriction; effect usually local but role unclear; subject of extensive research.</td>
</tr>
</tbody>
</table>

### Effects of Ions

<table>
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<th>Action</th>
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</thead>
<tbody>
<tr>
<td>Ca$^{+2}$</td>
<td>vasoconstriction via direct influence on smooth muscle cells</td>
</tr>
<tr>
<td>K$^+$</td>
<td>dilation via inhibition of smooth muscle (raise resting potential)</td>
</tr>
<tr>
<td>Mg$^{+2}$</td>
<td>dilation through inhibition of smooth muscle (blocks Ca channels by ion replacement mechanism?)</td>
</tr>
<tr>
<td>H$^+$</td>
<td>drop in pH causes dilation in most tissues; rise in pH causes first constriction, then dilation</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>mild vasodilation in most tissues, marked in brain, but its main action is via other central control mechanisms</td>
</tr>
</tbody>
</table>
**Regulation of Arterial Pressure**

- Critical for homeostasis
- Both fast and slow components
- Fast do not last, slow are most powerful

**Baroreceptors**

- Pulsatile vs. constant response
- Found in carotid sinus, aortic arch and subclavian, common carotid, pulmonary arteries
### Baroreceptor System

#### Arterial Baroreceptor Reflex

- Most important in the short term
- Response varies across vessels
- Gain is variable (time, hypertension, NE)
Venous Response to Posture

- Vasoconstriction to maintain venous return
  - Inadequate over time
  - Blood pooling, fainting
- Long necked animals require more active regulation
  - Aortic pressures: 160–200 mm Hg
  - Rapid regulation of vasodilation
  - Kidney especially critical
- Blood pooling in fish tails
  - Large, central return veins
  - Accessory caudal heart

Hemorrhage and Shock: Basics

- Blood loss leads to drop in venous return and blood pressure
- Resulting shock can be progressive or nonprogressive
- Response represents balance of compensatory and decompensatory mechanisms
- End result?
  - a dynamic battle between negative and positive feedback
  - can reach a point of no return (damage is too extensive for recovery)
  - rapid treatment (replacement) is imperative!
Hemorrhage and Shock: Examples

I–VI: increasing duration of hemorrhage

Function curves for different times after hemorrhage
- animal bled until $P_A = 30$ mm Hg
- animal maintained at this pressure for indicated time
- measured cardiac function curves at indicated time points

In progressive shock, heart eventually suffers!

Hemorrhage and Shock: Compensatory Mechanisms

- Baroreceptor reflex: increased HR, vasoconstriction, recruitment of blood reservoirs (cold skin)
- Cerebral ischemia: massive central response!!
- Chemoreceptor responses: adds to vasoconstriction and increase respiration (good for increasing venous return)
- Reabsorption of fluid from the tissues, due to atrial hypotension upsetting normal fluid balance
- Humoral (catecholamine) response: up to 50x normal levels in the blood
- Vasopressin/Renin/Angiotensin: all potent vasoconstrictors and increase kidney water retention
Hemorrhage and Shock: Decompensatory Mechanisms

- Cardiac failure: coronary hypotension leads to failure and reduction in CO (see lower panel of Figure two slides before)
- Acidosis: reduced flow leads to drop in pH, which further compromises contraction and response to vasoconstrictors
- CNS Depression: hypoxia compromises central control
- Blood clotting: increases at first, which can block vessels and affect both heart and brain; decreases later and promotes internal bleeding

Response to Exercise

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<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.75</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Remainder</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td></td>
<td>24</td>
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Response to Exercise I

• Heart rate
  – Release of parasympathetic tone
  – Increase in sympathetic stimulation
  – 4-5 fold increase possible, function of exercise level

• Stroke volume
  – Increases, can even double
  – Frank-Starling plays small role at moderate exercise, larger role at high intensity exercise

• Venous return
  – Increases due to venous constriction and respiration

What happens to TPR?

Key Messages

• Vascular control is essential, multifaceted, and complex (we have only touched the surface)

• Local mechanisms
  – Myogenic
  – Metabolic

• Central mechanisms
  – Baroreceptor system
  – Venous response

• Exercise as example