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>
<thead>
<tr>
<th>Organ</th>
<th>Max Exercise</th>
<th>At Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles</td>
<td>1</td>
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</tr>
<tr>
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<td>0.75</td>
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</tr>
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<td></td>
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<tr>
<td>Remainder</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

*Distribution of Blood Flow [l/min]*
Another View of Exercise

Control of Circulation

Local Control
Local Regulation: the Data

- **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

### At Constant Metabolic Rate

**Immediate response**

**Response after several minutes**

**Control value**

---

Control of Vascular Flow

**↑ Myocardial contractile activity** → **↑ Metabolism**

**↓ Myocardial P02**

Autonomic control

- Sympathetic nerves: α-Receptors, β-Receptors
- Vagus nerves:
  - Myogenic mechanism
  - Systolic compression

Other metabolic factors: PO2, PCO2, H+, K+
Local Control

Autoregulation: Feedback Mechanisms

Myogenic Mechanism

- Arterial Pressure
- Flow
- Arterial Distension
- Smooth Muscle Tone
- Arterial Resistance
- Arterial Diameter

Metabolic Mechanism

- Arterial Pressure
- Flow
- Oxygen
- Vasodilator
- Arterial Diameter
- Arterial Resistance

• Details of mechanisms not clear
**Metabolic Feedback Mechanism**

**Reactive Hyperemia**

- **Metabolism** → **Oxygen**
- **Metabolism** → **Vasodilator**

**Long Term Local Regulation**

- **Arterial pressure** → **Vascularization** → **Oxygen** → **Metabolism**
- **Angiogenesis factor** → **Vascularization** → **Metabolism**

**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**
- Coarctation 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 Control

Central Regulation of Blood Flow/Pressure

• Process Steps
  – Hormonal
    • Most important mechanism, especially long term
    • Many substances involved but norepinephrine is major player
    • Main effect is vasodilation via β receptors in vascular smooth muscle
  – Central (ANS)
    • Sympathetics influence venous more than arterial vessels
    • Parasympathetic only minor role
    • Main effect is vasoconstriction via α receptors in vascular smooth muscle

• Sensors
  – Pressure, stretch, chemo, psychological
Autonomic Nervous System

See Eckert Figure 8-18, page 296

Autonomic Innervation of the Circulation

- Sympathetics release norepinephrine to both constricting ($\alpha$) and relaxing ($\beta$) receptors in the vascular smooth muscle.
- Parasympathetics have little 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 ((\alpha)-receptors).</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>adrenal medulla</td>
<td>vasoconstrictive except in skeletal and cardiac muscle where vasodilative ((\beta)-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>
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### Vasodilator Substances

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<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>Prostoglandins</td>
<td>all tissues</td>
<td>usually dilator, but can cause constriction; effect usually local but role unclear; subject of extensive research.</td>
</tr>
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</table>

### Effects of Ions

<table>
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<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>
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Regulation of Arterial Pressure

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

Baroreceptors

• Found in carotid sinus, aortic arch and subclavian, common carotid, pulmonary arteries
• Respond differently to pulsatile vs. constant response
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: Examples

I-VI: increasing duration of hemorrhage

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

In progressive shock, heart eventually suffers!
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: 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

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Distribution of Blood Flow [l/min]
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