Regulation of Cardiac Output

- Cardiac Output = Heart Rate x Stroke Volume
- Cardiac output is regulated by changing HR and SV
- SV is regulated both by changes in cardiac pumping performance (e.g. $E_{\text{max}}$, afterload (e.g. TPR) and preload (e.g. blood volume))
- Major control of HR is via autonomic regulation of the SA node:
  - Sympathetic Nervous System (SNS) increases automaticity (exercise, emotional stress)
  - Parasympathetic Nervous System (PSNS) decreases automaticity (sleep)
- HR control is typically achieved by reciprocal action of both SNS and PSNS

Effects of Autonomic Antagonists on Heart Rate

Parasympathetic tone (blocked by muscarinic receptor agonist, atropine) normally dominates sympathetic tone (blocked by β-adrenergic receptor blocker, propranolol) at rest.

Cardiac Parasympathetic Nerve Pathways

- Cardiac parasympathetic fibers originate in the medulla oblongata at the dorsal motor nucleus of the vagus
- Efferent vagal fibers pass via neck to synapse with postganglionic cells on epicardium near the SAN and AVN
- Right vagus nerve → SAN mostly, inhibits SAN firing
- Left vagus nerve → AVN mostly, delay AV conduction or even cause complete heart block
- Neurotransmitter is Ach, but the SAN and AVN are rich in acetylcholinesterase

- Ach directly activates $K_{\text{AC}}$ current so effects are rapid (<100 ms) because no second messenger is needed but transient (due to Ach-esterase activity)
- Thus vagal activity can regulate HR on a beat to beat basis
- PSNS is faster than SNS because no second messenger is needed
Vagal Effects on HR

- When vagus nerves are stimulated for just a few seconds HR decreases rapidly and reaches steady state within two beats.
- Vagal stimulation has a much greater effect than SNS stimulation because ACh suppresses release of norepinephrine from sympathetic nerve terminals.

Cardiac Sympathetic Nerve Pathways

- Cardiac sympathetic fibers originate in lower cervical and upper thoracic segments of the spinal cord.
- Pre- and post-ganglionic neurons synapse in the stellate and middle cervical ganglia.
- SNS and PSNS nerves join to form a mixed efferent cardiac plexus.
- SNS nerves approach along the vessels and spread out over epicardium of atria and ventricles, penetrating the myocardium along the intramural coronaries, which they also innervate.

SNS Effects on Heart

- Myocardial adrenergic receptors are primarily β1, β2, and β3 agonized by isoproterenol and blocked by propranolol.
- Left and right SNS nerves distribute differently: Left have more effect on contractility, right more on HR.
- SNS stimulation effects take 15 seconds to activate and 2 minutes to deactivate.
- This is because of signaling and the fact that norepi is not released as rapidly or inactivated as quickly.
- PDEs take time to degrade cAMP the main second messenger.
SNS and PSNS Cellular Mediators

Higher Centers Affect Cardiac Function

• Frontal lobe, motor and pre-motor cortex,...... (excitement and exercise)
• Thalamus (tachycardia)
• Hypothalamus (temperature responses → HR and TPR)
• Stimulation of parahypoglossal region of medulla activates cardiac SNS and inhibits PSNS pathways
• Dorsal medulla has distinct tachycardia and bradycardia sites (ipsilateral)

Baroreflex also Affects HR

• The relationship between HR and MAP is mediated by reciprocal changes in SNS and vagal firing
• Below 100 mmHg high HR is dominated by SNS fibers
• Above 100 mmHg vagal dominates
Bainbridge Reflex (1915)

- At low HR right atrial filling increases HR (blocked by cutting vagi)
- At high HR RA filling decreases HR due to baroreflex
- ANP is released with atrial stretch having strong diuretic and natriuretic effects on the kidneys
- Atrial stretch sensing cells primarily in venoatrial junctions. They also activate a neurally mediated reduction in vasopressin (ADH) from posterior pituitary acting to increase urine volume

Heart Failure

- Activation of renin-angiotensin-aldosterone (RAAS) system
  - Salt and water retention due to aldosterone release from the adrenal cortex
  - Ventricular expression of ANP and increased ANP secretion act to attenuate fluid and salt retention
- Sympathetic activation
  - Chronic activation of beta adrenergic receptors downregulates them and blunts adrenergic responsiveness

Respiratory Effects on HR

- Respiratory Sinus Arrhythmia
  - HR increases during inspiration (partial SNS effect)
  - HR decreases during expiration (increased vagal activity)
- Vagal effects dominate
- Thoracic pressure influences venous return and atrial filling pressure
- Lung stretch receptors also activate cardiac vagal center in the medulla
- Respiratory activity affects HR via peripheral arterial chemoreceptors
  - Decreased oxygen saturation at carotid chemoreceptors affects HR
Control of Contractility

- Frank Starling Mechanism and Anrep Effect are mediated by stretch
- Extrinsic factors: circulating catecholamines, SNS
- Lusitropy and inotropy
- Force-frequency relation
- Adrenomedullary hormones
  - Epinephrine
  - Thyroid hormones increase Ca uptake and BAR sensitivity
  - Insulin-positive inotropic and chronotropic effects
- Oxygen and CO2
  - Decreased pO2 and increased pCO2 decrease contractility

Autonomic Nervous System

<table>
<thead>
<tr>
<th>Target</th>
<th>Sympathetic (adrenergic)</th>
<th>Parasympathetic (muscarnic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>β1, (β2): increases</td>
<td>M2: decreases</td>
</tr>
<tr>
<td>SA node: heart rate</td>
<td>β1, (β2): increases</td>
<td>M2: decreases</td>
</tr>
<tr>
<td>Atrial contractility</td>
<td>β1, (β2): increases</td>
<td>M2: decreases</td>
</tr>
<tr>
<td>Ventricular contractility</td>
<td>β1, (β2): increases</td>
<td>—</td>
</tr>
<tr>
<td>AV node</td>
<td>β1: increases conduction</td>
<td>M2: decreases conduction</td>
</tr>
<tr>
<td></td>
<td>increases automaticity</td>
<td>Atrioventricular block</td>
</tr>
</tbody>
</table>

β-adrenergic signaling and cardiovascular disease (CVD)

- Mediator of sympathetic autonomic responses of the heart
- Fight or flight “response” to stress
- Adaptive response to impaired function in CVD
- Beta blockers used by 10’s of millions of Americans (5th most widely prescribed class of medicines)
- Prescribed for high blood pressure, heart failure, cardiac arrhythmia, coronary heart disease
- Congestive heart failure affects 4.9 million Americans
- Coronary heart disease affects 13 million Americans

(American Heart Association, Heart Disease and Stroke Statistics — 2005 Update)
Ginsburg KS, Bers DM

Sanguinetti MC, et al.

Base model: Puglis JL, Bers DM.
AJP 281:C2049 (2001)
Modulation of Calcium Transients

Increased inotropy and lusitropy with PKA phosphorylation of LCC, PLB, RyR, and TnI.


In silico KO’s reveal functional roles of PKA targets

Single target phosphorylation

• Big contractility increase from PLB, LCC phosphorylation
• No increase in systolic Ca for RyR phosphorylation
• Apparent increased relaxation w/ LCC phosphorylation

Single target phosphodisruption

• PLB disruption does not restore t80
• PLB and LCC anti-cooperative for t80
• No sig. role for TnI in Ca dynamics


Congestive Heart Failure

β1-AR: -75%

Sham 8 wk 16 wk

SERCA: -30%

NCX: +55%

Congestive Heart Failure

Holt, ET et al. (1998) J Mol Cel Cardiol 30(8): 1581-93