Autonomic Regulation of Cardiac Function
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OBJECTIVES:

1. Describe the autonomic innervation of the heart
2. Describe the ionic basis for chronotropic, dromotropic, and inotropic effects in various cardiac tissues
3. Describe the role of adrenergic receptors and G proteins in adrenergic (β₁) and muscarinic regulation of cardiac function

I. AUTONOMIC INNERVATION AND EFFECTS

A. Parasympathetic innervation by the vagus nerve (X cranial n.) is primarily supraventricular, that is, to the SAN, atria, and AVN. (A few parasympathetic fibers also innervate ventricular muscle and Purkinje fiber innervation.) Acetylcholine (ACh) released by postganglionic parasympathetic nerves terminals interacts with muscarinic (M₂) receptors in the heart. These receptors are blocked by atropine.

B. Sympathetic innervation via the superior cervical ganglion supplies all of the heart. Norepinephrine (NE) is released by post-ganglionic nerve terminals and interacts with β₁ receptors. β₁ receptors are blocked by non-selective β-blockers such as propranolol and cardioselective (i.e., β₁) blockers including metoprolol and practolol.

C. Sympathetic and parasympathetic nerves are usually antagonistic in their modulation of cardiac activity. For example, a decrease in parasympathetic tone usually has the same effect as an increase in sympathetic tone. In some cases, however, one branch dominates. At rest the heart is under parasympathetic control; blocking both autonomic inputs results in an increase in heart rate. Functionally, parasympathetic withdrawal (i.e., a decrease in parasympathetic tone) is a prompt and important regulator of cardiac function. The main autonomic effects are on:

1. Heart Rate – Chronotropic Effect
3. Muscle Contractility – Inotropic Effect

Positive effects imply increases (i.e., in heart rate), while negative effects imply decreases.
D. Action of autonamics largely can be explained by considering the effects of ACh and NE on three ionic currents (+, increase; –, decrease):

<table>
<thead>
<tr>
<th>Current</th>
<th>NE</th>
<th>ACh</th>
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<tbody>
<tr>
<td>$I_{K-ACh}$</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>$I_{Ca}$ (L-type)</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>$I_f$</td>
<td>+</td>
<td>–</td>
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</tbody>
</table>

$I_{K-ACh}$ is an $I_{K1}$-like current activated by ACh and adenosine.

II. CHRONOTROPIC EFFECTS

A. SA Node

1. **Sympathetic Stimulation (NE) increases HR = + Chronotropic effect:**
   a. Increased $I_f$ causes increased rate of phase 4 depolarization.
   b. Increased $I_{Ca}$ makes threshold potential more negative.

2. **Parasympathetic Stimulation (ACh) slows HR = – Chronotropic effect.**
   a. Decreased $I_f$ causes decreased rate of phase 4 depolarization.
   b. Increased $I_{K-ACh}$ causes hyperpolarization of MDP.
   c. Decreased $I_{Ca}$ makes threshold potential more positive
   d. *Parasympathetic withdrawal* strongly increases HR.
B. AV Node

The AV node normally does not exhibit automaticity when the heart beat originates from the SAN. Nevertheless, it is capable of initiating the heart beat, that is, it is a latent pacemaker. The effects of autonomics on SA and AV nodes are the same. Under pathophysiologic conditions, the intrinsic rate of the AV node can exceed that of the SA node and AV nodal automaticity can be expressed.

C. His-Purkinje System

NE enhances automaticity in the His-Purkinje system also. This automaticity usually remains latent, however. Block of the SA and AV nodes will result in ventricular escape, heart beats arising from Purkinje fibers due to their automaticity. The name 'ventricular' escape is a misnomer. Sympathetic tone modulates the frequency of ventricular escape beats.

III. DROMOTROPIC EFFECTS

A. AV Node

The AV node is the most important site of control of conduction velocity (CV) by the autonomic nervous system.

1. Sympathetic Stimulation (NE) Increases CV = + Dromotropic Effect
   a. Increased I_{Ca} causes increased inward current and gives rise to increased dV/dt of phase 0 and more rapid conduction. Decreases AV delay.
   b. Refractory Periods. An increase of I_{Ca} decreases the duration of the ARP and ERP and shifts the RRP earlier in the cardiac cycle.

      Mechanism: With more Ca^{2+} channels (i.e., increased I_{Ca}), a smaller fraction of the channels needs to recover from inactivation to support excitability.

      Implication: Decreased ERP means that the AVN can faithfully conduct action potentials at higher heart rates.

2. Parasympathetic Stimulation (ACh) Decreases CV = – Dromotropic Effect
   a. Increased I_{K-ACh} slows CV by opposing I_{Ca}.
   b. Decreased I_{Ca} reduces inward current, dV/dt, and slows CV.
   c. Increased I_{K-ACh} and decreased I_{Ca} prolong the ARP and ERP.
B. **Atrium**

1. **Parasympathetic Stimulation (ACh) Increases CV = + Dromotropic Effect**

   Increased $I_{K-ACh}$ causes hyperpolarization of atrial muscle. The responsiveness relationship predicts increased $dV/dt$ and increased CV because more Na$^+$ channels move from the inactivated to resting available state. This indirect effect on Na$^+$ channels is much more important in atria than the direct effect of increased $I_{K-ACh}$, which by itself would tend to slow conduction velocity.

   ![Graph showing atrial dV/dt impact](image)

IV. **INOTROPIC EFFECTS**

A. **Sympathetic Stimulation (NE) Increases Contractility = + Inotropic Effect**

1. Increased force is produced by both atrial and ventricular muscle at a given length. Several changes in the twitch are noted:
   a. increased peak tension
   b. increased rate of tension development ($dT/dt$)
   c. increased rate of relaxation.
   d. decreased twitch duration (not required for +inotropic effect)

   ![Graph showing effect of NE on tension](image)
2. In the intact heart, increased contractility implies more efficient pumping of blood and a shift of the systolic pressure-volume curve (Frank-Starling Curve) and greater cardiac output and decreased twitch duration maximizes time for ventricular refilling at high HR.

3. Increased $I_{Ca}$ results in a greater trigger for $Ca^{2+}$-induced $Ca^{2+}$ release and greater filling of the sarcoplasmic reticulum $Ca^{2+}$ stores. Thus, increased $I_{Ca}$ during the plateau results in a more rapid increase and higher levels of cytoplasmic $Ca^{2+}$ and, consequently, enhanced force production.

4. The basis for faster relaxation is:
   a. **Increased rate of $Ca^{2+}$ accumulation** by sarcoplasmic reticulum due NE-induced phosphorylation of phospholamban, an SR protein that regulates the SR $Ca^{2+}$ pump.
   b. **Decreased affinity of TnC for $Ca^{2+}$**. More rapid release of $Ca^{2+}$ from myofilaments makes it available for uptake by SR. By itself, this effect would decrease contractility.

B. **Vagal Stimulation (ACh) Decreases Contractility = − Inotropic Effect**

1. ACh has a strong negative inotropic effect on **atrial muscle**.

2. ACh decreases atrial contractility by increasing in $I_{K-ACh}$ and decreasing $I_{Ca}$.
   a. **Low doses**: Increase $I_{K-ACh}$ causing hyperpolarization and decreased action potential duration. Abbreviation of the action potential indirectly decreases $Ca^{2+}$ entry and contractility.
   b. **High doses**: ACh increases $I_{K-ACh}$ and directly decreases $I_{Ca}$. This gives rise to a profound negative inotropic effect.

3. ACh has a significant negative inotropic effect in **ventricle only** in the presence of high sympathetic tone. Thus parasympathetic stimulation counteracts sympathetic stimulation.
V. RECEPTOR MECHANISMS

A. G Proteins

1. $\beta_1$ and muscarinic receptors activate membrane bound target proteins (including channels and membrane bound enzymes) through a family of proteins referred to as G proteins. G proteins are *heterotrimers* with $\alpha$, $\beta$, and $\gamma$ subunits (i.e., 3 different subunits). The $\alpha$ subunits bind *guanosine triphosphate* (GTP) or *guanosine diphosphate* (GDP). The $\alpha$ subunits of various G proteins are distinct. A number of G proteins share common $\beta$ and $\gamma$ subunits, while others have distinct $\beta$ and $\gamma$ subunits.

2. Binding of a ligand to its receptor leads to activation of a G protein. Activation causes dissociation of the GTP-bound $\alpha$ subunit from $\beta\gamma$. Both $\alpha$ and $\beta\gamma$ remain within the membrane, and one or both act on target proteins. The messenger system deactivates in a reaction that reforms the heterotrimer while GTPase activating proteins assist the dephosphorylation of GTP to GDP. After dissociation of GDP and rebinding of another GTP to the $\alpha$ subunit, the G protein is once again capable of activation.

3. G proteins can stimulate or inhibit channels (e.g., $K^+$ and $Ca^{2+}$) and second messenger systems via, for example, adenylate cyclase. *Stimulatory G proteins* include $G_s$ and *inhibitory G proteins include $G_i$ and $G_K$*. $G_K$ is named for its stimulatory effect on $K^+$ channels. In some cases, effects of G proteins on channels are via cyclic AMP and protein kinase A. Direct effects on channels also have been noted. (Additional classes of G-proteins are known.)
B. $\beta_1$ Adrenergic Receptor Activation

$G_s$ couples the $\beta_1$ receptor to *adenylate cyclase*, a membrane bound enzyme that converts ATP to 3',5'-cyclic AMP (*cAMP*). Activation of the receptor increases the rate of cAMP formation and raises the cAMP level in the cell. cAMP in turn activates cytoplasmic *cAMP-dependent protein kinase (protein kinase A, PKA)*, which phosphorylates target proteins. Dephosphorylation of the target (or in some cases a second phosphorylation) terminates the effect.

![Diagram of cAMP signaling](chart.png)

Examples of targets include:

1. PKA targets
   a. $I_{Ca}$ channel – phosphorylation via PKA increases $I_{Ca}$ (stimulation)
   b. phospholamban – phosphorylation increases the rate of $Ca^{2+}$ uptake by the sarcoplasmic reticulum (stimulation)
   c. Troponin – phosphorylation decreases the $Ca^{2+}$ sensitivity of the myofilaments. (aids relaxation)

2. $G_s$ targets
   a. adenylate cyclase (stimulation)
   b. $Ca^{2+}$ channels (stimulation)

C. $M_2$ Muscarinic Receptor Activation

$G_K$ (a type of $G_i$) couples the muscarinic receptor to *adenylate cyclase*. $G_K$ *inhibits* adenylate cyclase and antagonizes the effects of $\beta_1$ receptor activation. $G_K$ appears to directly *activate* $K^+$ channels.
IV. REFERENCES
