The Cardiovascular System Part II: Heart

Outline of class lecture

After studying part I of this chapter you should be able to:

1. Describe the characteristics of the two types of cardiac muscle cells (contractile and autorhythmic).
2. Describe the autorhythmic cells and the conduction system of the heart. Include the reason for why the SA node is the pacemaker of the heart.
3. Explain the details of how action potentials in autorhythmic cells are produced and how the parasympathetic and sympathetic nervous system can modify these potentials.
4. Explain the details of how myocardial action potentials are produced. Describe Excitation-Contraction Coupling in Heart Muscle and how digitalis works in the treatment of congestive heart failure and how calcium channel blockers work in the treatment of hypertension and angina.
5. Explain what an ECG is, what it measures, and correlate the waves of an ECG with the sounds of the heart.
6. Describe the following: Cardiac flutter, fibrillation and what an ectopic pacemaker.
7. Discuss the Clinical Applications from the study guide and be able to describe the disorders from the Applications to Health located at the end of this chapter.

Cardiovascular System: Heart, Part II

- Contractile vs. Autorhythmic cells
- Cardiac conduction system
- Production of pacemaker potentials
- Production of Myocardial Action Potentials
- ECG and electrical activity
- Flutter vs. Fibrillation:

Cardiac Muscle Cells

- The bulk of the myocardium consists of cardiac muscle cells. There are 2 types of cardiac muscle cells:
  1. **Contractile cells** – 99%: Generate the force involved in pumping
  2. **Autorhythmic cells** – Ability to spontaneously depolarize to

- Provide the mechanical force/pressure that pumps blood
- Involuntary, striated, most cells are

- Cells are linked by **intercalated discs**, which consist of 2 structures:
  1. **Desmosomes** – physically connect adjacent cardiac muscle cells and prevent cells from separating during a contraction
  2. **Gap junctions**: Electrical synapses - electrically connect adjacent cardiac muscle cells.

  - Provide a channel between cell membranes that

  - **Important**: Junctions allow the depolarization wave (action potential) initiated
by autorhythmic cells to spread through the cardiac musculature and allow the heart to function as a single coordinated unit (a functional syncytium). What’s the advantage of this?

Autorythmic Cells and the Conduction System of the Heart
- Autorhythmic cells spontaneously and rhythmically depolarize. Groups of autorhythmic cells are found at the:
  1. **Sinoatrial (SA) node** – Located near the opening of the
  2. **Atrioventricular (AV) node** – Located in the inferior interatrial septum near the tricuspid orifice.
  3. **Atrioventricular (AV) bundle or Bundle of His** – Found in the superior
  4. **Right and left bundle branches** – Travel thru the interventricular septum to the apex of the heart.
  5. **Purkinje fibers** – Extend throughout the

- The above list also gives the path of electrical conduction system within the heart

Conduction System of the Heart: Steps in the Process
- Steps in the process:
  1. Action potentials (wave of depolarization) originate in the SA node and spread over the Rt and Lt atria, causing them to contract
    - Without any input (neural or hormonal), the rate of SA node depolarization determines
  2. Action potentials travel to the AV node and the depolarization wave is briefly delayed – this allows the atria to complete contraction before the ventricles begin.
  3. Action potentials travel down the
  4. Action potentials travel throughout the ventricles via the Purkinje fibers and the ventricular cells depolarize.
    - Ventricular depolarization and thus contraction begins at the
  5. Ventricular contractile cells contract.

- The fibrous skeleton of the heart helps to electrically isolate the atria and the ventricles. The AV bundle is the only electrical connection between them.
Conduction System of the Heart

Electrocardiogram

- **Electrocardiogram (ECG or EKG)** is a record of the electrical activity conducted through the heart during a cardiac cycle.
  - The waves of the ECG are produced by the combined effects of action potentials generated by myocardial cells.
  - Each cardiac cycle produces three distinct waves:
    1. **P wave**: Period during which the atria are depolarizing.
       - The spread of an action potential from SA node cells depolarize.
    2. **QRS wave (complex)**: The period during which the ventricles are depolarizing, which precedes their contraction.
    3. **T wave**: Period during which the ventricles are repolarizing.
       - Indicates

**Note**: There is no wave to show atrial relaxation because the stronger QRS wave masks this event.
Correlation of ECG with Heart Sounds
• The first heart sound (lub) is produced immediately after the QRS wave starts as this is the beginning of ventricular systole.
  – The rise in intraventricular pressure causes
• The second heart sound (dub) is produced immediately after the T wave begins as this is during ventricular diastole.
  – The fall in intraventricular pressure causes the aortic and pulmonary semilunar valves to close as

Analysis of ECG can determine:
• Cardiac arrhythmias –
• Heart size - measurement of the size of the voltage changes:
  – Excessively large QRS complex: May indicate of an enlarged heart.
  – Smaller QRS complex: May indicate decreased heart muscle mass
• Conduction disturbances which can be determined by the measurement of time between segments and intervals:
  – Segments: Sections between two waves.
    • P-R segment: Time between the end of the P wave and the beginning of the QRS complex.
      • Time for depolarization to travel through the AV node to the bundle of His to the bundle branches.
      • Referred to as the P-R segment instead of the P-Q segment because the Q wave is often absent.
    • S-T segment: Time between the end of the QRS complex and the beginning of the T wave.
      • The period when the ventricles are depolarized – roughly corresponds to the plateau phase of ventricular action potential.
      • Important in the diagnosis of ventricular ischemia - depression of the
– **Intervals**: Combinations of
  - **P-R Interval**: Extends from the start of the P wave to the start of the QRS complex.
    - Interval represents the time between the start of atrial depolarization and the start of ventricular depolarization.
    - Referred to as the P-R interval instead of the P-Q interval because the Q wave is often absent.
    - Can be lengthened by conduction problems especially
  - **Q-T Interval**: Extends from the start of the Q wave to the end of the T wave.
    - Time for both ventricular depolarization and repolarization to occur, and therefore roughly estimates the duration of an average ventricular action potential.

**Clinical Considerations**
- **Ectopic Pacemaker**: The SA node is the pacemaker of the heart, but other cells of the conduction system are capable of producing action potentials spontaneously.
  - When action potentials originate in an area other than that SA node it is referred to as an ectopic beat or pacemaker. The resulting heart rate is much slower than normal.
- **Artificial Pacemaker**: Placed under the skin, pacemaker electrodes are fixed to the wall of the atria or ventricle and deliver impulses to

- **Flutter**: Rapid contractions (200 to 300/min) but are coordinated.

- **Fibrillation**: Uncoordinated contractions of myocardial cells.
  - Continuous recycling of electrical waves, known as circus rhythms resulting in a quivering heart.
  - Normal refractory period of cardiac cells is interrupted by:
    - Enlarged heart
    - Damage to the myocardium which
  - **A defibrillator** administers a powerful electrical shock that
    - Hopefully, after repolarization, the SA node will be the first area send an action potential and a normal beat will follow
  - **Ventricular fibrillation**, also known as **cardiac arrest**, is much worse than atrial fibrillation, because the heart quivers and stops pumping blood.
SA Node: Autorhythmic Cells

- Why is the sinoatrial (SA) node considered to be the pacemaker of the heart?
  - All of the autorhythmic cells found in the above locations have the ability to rhythmically and spontaneously depolarize.
  - The **SA node** cells have the fastest rate of depolarization and therefore set the pace for autorhythmic cells and the rest of the heart.
    - Thus, the SA node is known as the **pacemaker**.
  - The action of cardiac muscle tissue contracting on its own in the absence of neural stimulation is called **automaticity**.

### Normal Rate of Action Potential Discharge in Autorhythmic Tissues of the Heart

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Action Potentials per Minute*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA node (normal pacemaker)</td>
<td>70–80</td>
</tr>
<tr>
<td>AV node</td>
<td>40–60</td>
</tr>
<tr>
<td>Bundle of His and Purkinje fibers</td>
<td>20–40</td>
</tr>
</tbody>
</table>

### Production of Action Potentials in Autorhythmic Cells

- **Action potentials of autorhythmic** cells can be divided into **three phases**. Note, the numbering of these phases may seem odd, but they correspond to similar phases of cardiac myocyte action potentials.

#### Pacemaker potential phase

- **Pacemaker potential phase**: Pacemaker potentials are slow spontaneous depolarization's to **threshold** that triggers an action potential. They **involve the movement of Na⁺, K⁺, and Ca²⁺ ions**.
  - During **diastole** the cell starts out as being **hyperpolarized** (-60 mV) as a result of the preceding action potential.
  - This **hyperpolarization** opens special **voltage-gated Na⁺ channels** which are also known as **HCN channels** or **funny channels**. These channels function to depolarize the cell by allowing a net movement of Na⁺ ions into the cell.
**Basis for the different names of these channels:**

(A) **Voltage gated Na⁺ channels:** Channels are activated by a change in voltage (hyperpolarization) but are permeable to both Na⁺ and K⁺ ions. However, the channel is more permeable to Na⁺ so it is the net movement of Na⁺ into the cell that causes the slow depolarization.

(B) **HCN channels:** The channels have dual activation — are activated by both a change in voltage and by cyclic nucleotides. Thus, the channels have also been named HCN channels - Hyperpolarization-activated Cyclic Nucleotide gated channels. Cyclic adenosine monophosphate (cAMP) molecules bind directly to HCN channels and cause them to open. The importance of cAMP activation will be discussed in relation to sympathetic stimulation of heart rate.

(C) **Funny (Iᵢf) channels:** The unusual behavior of these channels led to them being called funny, or Iᵢf, channels. “Funny” because typically, voltage-gated channels open when the membrane becomes less negative (depolarizes), but these unique channels open when the potential becomes more negative (hyperpolarizes) at the end of repolarization from the previous action potential. The dual activation and permeability to both Na⁺ and K⁺ ions also contribute to their “funny” properties.

- **Increased inward Ca²⁺ current:** During the second half of the pacemaker potential, transient Ca²⁺ channels (T-type Ca²⁺ channels) open, further depolarizing the membrane to threshold, at which time the Funny and T-type Ca²⁺ channels close.
  - “T” stands for transient
  - Occurs as the membrane potential reaches about -50 mV.

- **Decreased outward movement of K⁺:** The voltage gated K⁺ channels that were opened during repolarization from the preceding action potential close slowly and gradually reduce the outflow of K⁺ ions as Na⁺ flow inward through the funny channels.
0. **Depolarization Phase**: At threshold (-40 mV), voltage-gated L-Type Ca^{2+} channels open along the plasma membrane.
   - **“L” stands for long-lasting**
   - The inward diffusion of Ca^{2+} produces the steep upward phase of the action potential.

3. **Repolarization Phase**: Repolarization is produced by the closing of the voltage-gated L-type Ca^{2+} channels and the opening of voltage-gated K+ channels allowing the outward diffusion of K+.

Effect of the parasympathetic and sympathetic nervous system on heart rate?
   - **Slowing Heart Rate**: ACh from parasympathetic axons (via the vagus nerve) bind to muscarinic receptors (G-protein coupled receptors) and cause the opening of K+ channels and the closing of T-type calcium channels.
     - The opening of K+ channels hyperpolarizes the SA node cells because more positive K+ ions leave making the inside even more negative.
     - The closing of T-type Ca^{2+} channels slows the pacemaker depolarization to threshold.
     - Acts to slow heart rate by slowing depolarization to threshold.
• Increasing Heart Rate: Norepinephrine from sympathetic axons (via cardiac nerve) and epinephrine stimulate β1 receptors.
  - β1 receptors are G-protein coupled receptors that when activated, stimulate the production of the cAMP.
  - Cyclic adenosine monophosphate (cAMP) molecules bind directly to HCN (funny channels) and increase the number of channels that are open and their permeability to Na+, allowing more Na+ to enter.
  - This speeds the depolarization to threshold and increases heart rate.

Myocardial Action Potentials

Production of Myocardial Action Potentials
• Myocardial cells have a resting membrane potential of ~ -90mV
  0. Action potentials from pacemaker cells and other myocardial cells stimulate myocardial cells to go from their resting membrane potential of ~ -90 mV, to depolarize to threshold (~ -85mV).
  • At threshold, fast Voltage-gated Na+ channels open causing a rapid depolarization as

1. At ~ +20 mV, fast voltage-gated Na+ channels close and the outward movement of K+ by potassium leak channels brings a brief, small repolarization as the membrane becomes
slightly less positive. There is some indication that voltage-gated potassium channels briefly open then close and contribute to the depolarization spike.

2. **Slow Voltage-gated (L-type) Ca^{2+} channels** open allowing Ca^{2+} to slowly enter the cell.
   i. This depolarization is maintained for 200 to 300 msec before Ca^{2+} channels close and complete repolarization occurs.
   ii. The **plateau phase** results from a slow inward diffusion of Ca^{2+} through **slow voltage gated (L-type) Ca^{2+} channels** balanced by a slow

3. **Rapid repolarization** at the end of the plateau phase is achieved by the closing of the **slow voltage-gated Ca^{2+} channels** and the opening of **voltage-gated K+ channels** which causes a rapid outward diffusion of K+.

4. **Phase 4 (resting potential):** Voltage gated K+ channels close and the permeability’s for sodium, potassium and calcium return to their resting levels by ion pumps that actively pump Ca^{2+} into the SR and out of the cell and Na+ K+ pumps.

**Significance of Plateau Phase**
- The prolonged plateau phase functions to:
  1. Increase cardiac contractile time to ensure adequate time and strength to eject the blood.
  2. Provide a **long refractory period** that acts as a protective mechanism in the heart by preventing multiple action potentials from occurring (i.e., it limits the frequency of depolarization and therefore heart rate). This is important because at very high heart rates, the heart would be unable to adequately fill with blood and therefore ventricular ejection would be reduced.
Excitation-Contraction Coupling in Heart Muscle

- **Cardiac muscle cells** contract in response to increased sarcoplasmic Ca\(^{2+}\) concentrations.
- The process of increased Ca\(^{2+}\) occurs in two steps:
  1. Calcium ions entering the cell membrane during the **plateau phase** of the action potential.
  2. Arrival of extracellular calcium triggers the release of additional Ca\(^{2+}\) from the **sarcoplasmic reticulum**. This process is known as **Ca\(^{2+}\)-induced Ca\(^{2+}\) release**.
- Ca\(^{2+}\) then binds to troponin and stimulates a contraction as previously discussed.
- During cardiac cell **repolarization** (relaxation) the intracellular concentration of Ca\(^{2+}\) is decreased by:
  1. Active transport of Ca\(^{2+}\) into the sarcoplasmic reticulum.
  2. Extrusion through the plasma membrane by
- Cardiac cells relax and prepare for the next action potential.
Congestive Heart Failure and Digitalis

- Congestive heart failure can be treated with Digitalis.
- Digitalis indirectly interferes with the Na+-Ca2+ exchanger which produces a rise in the intracellular Ca2+ concentrations.
  - Specifically, digitalis inhibits Na+-K+ ATP pumps. This results in an increased intracellular concentration of Na+ and decreased concentration gradient across the cell membrane. The diffusion of sodium into the cells is decreased. The decreased diffusion of sodium into the cells then reduces the ability of the Na/Ca exchangers to extrude calcium.
  - This leads to an increase in cytoplasmic calcium concentration, which improves cardiac contractility.
- Increased Ca2+ concentrations allows more to be taken up by the sarcoplasmic reticulum.
- The sarcoplasmic reticulum can then release more Ca2+ for a stronger contraction.

Ca2+ Channel Blockers: Hypertension and Angina Pectoris

- Calcium channel blockers work by blocking voltage-gated calcium channels in cardiac muscle and smooth muscle cells within the walls of blood vessels.
  - Vascular Effects:
    - Heart Effects: Decrease in calcium available for each beat results in a decrease in cardiac contractility.
  - Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops.
  - With a relatively low blood pressure, the afterload on the heart decreases; this decreases how hard the heart must work to eject blood into the aorta, and so the amount of oxygen required by the heart decreases accordingly. This can help treat symptoms of ischaemic heart disease such as angina pectoris.
  - However, because calcium channel blockers result in a decrease in blood pressure, the baroreceptor reflex often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility. A beta blocker may be combined with a calcium channel blocker to minimize these effects.
Detailed Mechanical Events of the Cardiac Cycle

The mechanical events of the cardiac cycle – contraction, relaxation, and the resultant changes in blood flow through the heart – are brought about by the rhythmic changes in cardiac electrical activity.

The cardiac cycle consists of alternate periods of systole (contraction and emptying) and diastole (relaxation and filling). Contraction results from the spread of excitation across the heart, whereas relaxation follows the subsequent repolarization of the cardiac musculature. The atria and ventricles go through separate cycles of systole and diastole. Usually the terms systole and diastole refer to what is happening with the ventricles.

The following discussion and corresponding figure correlate various events that occur concurrently during the cardiac cycle, including ECG features, pressure changes, volume changes, valve activity, and heart sounds. Only the events on the left side of the heart are described, but keep in mind that identical events are occurring on the right side of the heart, except that the pressures are lower. To complete one full cardiac cycle, our discussion will begin and end with ventricular diastole.

**Mid Ventricular Diastole:**
During most of ventricular diastole, the atrium is still also in diastole. This stage corresponds to the TP interval on the ECG – the interval after ventricular repolarization and before another atrial depolarization. Because of the continuous inflow of blood from the venous system into the atrium, atrial pressure slightly exceeds ventricular pressure even though both chambers are relaxed (Point 1 in figure). Because of this pressure differential, the AV valve is open, and blood flows directly from the atrium into the ventricle throughout ventricular diastole (heart a in figure). As a result of this passive filling, the ventricular volume slowly continues to rise even before atrial contraction takes place (Point 2).

**Late Ventricular Diastole:**
Late in ventricular diastole, the SA node reaches threshold and
fires. The impulse spreads throughout the atria, which appears on the ECG as the P wave (point 3). Atrial depolarization brings about atrial contraction, raising the atrial pressure curve (point 4) and squeezing more blood into the ventricle. The excitation-contraction coupling process takes place during the short delay between the P wave and the rise in atrial pressure. The corresponding rise in ventricular pressure (point 5) that occurs simultaneously with the rise in atrial pressure results from the additional volume of blood added to the ventricle by atrial contraction (point 6 heart b). Throughout atrial contraction, atrial pressure still slightly exceeds ventricular pressure, so the AV valve remains open.

End of Ventricular Diastole: Ventricular diastole ends at the onset of ventricular contraction. By this time, atrial contraction and ventricular filling are completed. The volume of blood in the ventricle at the end of diastole (point 7) is known as the end-diastolic volume (EDV), which averages about 135 ml. No more blood will be added to the ventricle during this cycle. Therefore, the end-diastolic volume is the maximum amount of blood that the ventricle will contain during this cycle.

Ventricular Excitation and Onset of Ventricular Systole: After atrial excitation, the impulse travels through the AV node and specialized conduction system to excite the ventricles. Simultaneously, the atria are contracting. By the time ventricular activation is complete, atrial contraction is already over. The QRS complex represents this ventricular excitation (point 8), which induces ventricular contraction. The ventricular pressure curve sharply increases shortly after the QRS complex, signaling the onset of ventricular systole (point 9). The slight delay between the QRS complex and the actual onset of ventricular systole is the time required for the excitation-contraction coupling process to occur. As ventricular contraction begins, ventricular pressure immediately exceeds atrial pressure. This backward pressure differential forces the AV Valve closed (point 9).

Isovolumetric Contraction: After ventricular pressure exceeds atrial pressure and the AV valve has closed, to open the aortic valve, the ventricular pressure must continue to increase until it exceeds aortic pressure. Therefore, after closing of the AV valve and before opening of the aortic valve is a brief period of time when the ventricle remains a closed chamber (point 10). Because all valves are closed, no blood can enter or leave the ventricle during this time. This interval is termed the period of isovolumetric ventricular contraction (isovolumetric means “constant volume and length”) (heart c). Because no blood enters or leaves the ventricle, the ventricular chamber stays at constant volume. During isovolumetric ventricular contraction, ventricular pressure continues to increase as the volume remains constant (point 11).

Ventricular Ejection: When ventricular pressure exceeds aortic pressure (point 12), the aortic valve is forced open and ejection of blood begins (heart d). The amount of blood pumped out of each ventricle with each contraction is called the stroke volume (SV). The aortic pressure curve rises as blood is forced into the aorta from the ventricle faster than blood is draining off into the smaller vessels at the other end (point 13). The ventricular volume decreases substantially as blood is rapidly pumped out (point 14). Ventricular systole includes both the period of isovolumetric contraction and the ventricular ejection phase.

End of Ventricular Systole: The ventricle does not empty completely during ejection. Normally, only about half the blood within the ventricle at the end of diastole is pumped out during the subsequent systole. The amount of blood left in the ventricle at the end of systole when ejection is complete is the end-systolic volume (ESV), which averages about 70 ml (point 15). This is the least amount of blood that the ventricle will contain during this cycle.

The difference between the volume of blood in the ventricle before contraction and the volume of blood after contraction is the amount of blood ejected during the contraction: that is, \( EDV - ESV = \)
SV. In our example, the end diastolic volume is 135 ml, the end systolic volume is 65 ml, and the stroke volume is 70 ml.

**Ventricular Repolarization and Onset of Ventricular Diastole:** The T wave signifies ventricular repolarization at the end of ventricular systole (point 16). As the ventricle starts to relax, on repolarization, ventricular pressure falls below aortic pressure and the aortic valve closes (point 17). Closure of the aortic valve produces a disturbance or notch on the aortic pressure curve, the dicrotic notch (point 18). No more blood leaves the ventricular during this cycle, because the aortic valve has closed.

**Isovolumetric Ventricular Relaxation:** When the aortic valve closes, the AV valve is not yet open, because ventricular pressure still exceeds atrial pressure, so no blood can enter the ventricle from the atrium. Therefore, all valves are once again closed for a brief period of time known as isovolumetric ventricular relaxation (point 19 and heart e). The chamber volume (point 20) remains constant. No blood leaves or enters as the ventricle continues to relax and the pressure steadily falls.

**Ventricular Filling:** When ventricular pressure falls below atrial pressure, the AV valve opens (point 21), and ventricular filling occurs again. Ventricular diastole includes both the period of isovolumetric ventricular relaxation and the ventricular filling phase.

Atrial repolarization and ventricular depolarization occur simultaneously, so the atria are in diastole throughout ventricular systole. Blood continues to flow from the pulmonary veins into the left atrium. As this incoming blood pools in the atrium, atrial pressure rises continuously (point 22). When the AV valve opens at the end of ventricular systole, blood that accumulated in the atrium during ventricular systole pours rapidly into the ventricle (heart a again). Ventricular filling thus occurs rapidly at first (point 23) because of the increased atrial pressure resulting from the accumulation of blood in the atria. Then ventricular filling slows down (point 24) as the accumulated blood has already been delivered to the ventricle, and atrial pressure starts to fall. During this period of reduced filling, blood continues to flow from the pulmonary veins into the left atrium and through the open AV valve into the left ventricle. During late ventricular diastole, when the ventricle is filling slowly, the SA node fires again, and the cardiac cycle starts over (point 25).

**Special Note:** When the body is at rest, one complete cardiac cycle lasts 800 msec, with 300 msec devoted to ventricular systole and 500 msec taken up by ventricular diastole. Significantly, much of ventricular filling occurs early in diastole during the rapid filling phase. During times of rapid heart rate, diastole length is shortened much more than systole length is. For example, if the heart rate increased from 75 to 180 beats per minute, the duration of diastole decreases about 75%, from 500 msec to 125 msec. This greatly reduces the time available for ventricular relaxation and filling. However, because much ventricular filling is accomplished during early diastole, filling is not seriously impaired during periods of increase heart rate, such as during exercise. There is a limit, however, to how rapidly the heart can beat without decreasing the period of diastole to the point that ventricular filling is severely impaired. At heart rates greater than 200 beats per minute, diastolic time is too short to allow adequate ventricular filling. With inadequate filling, the resultant cardiac output is deficient. Normally ventricular rates do not exceed 200 beats per minute, because the relatively long refractory period of the AV nod will not allow impulses to be conducted to the ventricles more frequently than this.
Increasing Heart Rate: Sympathetic Control

Production of Myocardial Action Potentials