CARDIOVASCULAR PHYSIOLOGY

LECTURE 1

Organization of the cardiovascular system.
Cardiac electrophysiology - Properties of the myocardium: Excitability, Automatism and Conductivity

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The need for a competitive circulatory system

- Isolated/single cells vs. multicellular organisms

- Connection between external - internal milieu: from simple diffusion to complex, highly regulated, circulatory systems
Cardiovascular System:  
- an interplay of fast and complex mechanisms to maintain body homeostasis and adaptive capacity

1) The **heart**, a dual pump, that circulates a liquid

2) the **blood**

3) through the **vessels of systemic and pulmonary circulations**

4) **Integrated regulatory system** to adapt to the changing circumstances
1. Primary roles of the circulatory system - transport system function

- Nutrition, growth and repair
  transport between all parts of the body of nutrients, metabolic products, respiratory gases (O₂, CO₂):
  relation CO₂ ↔ pH ↔ homeostasis

- Maintenance of circulatory parameters:
  **cardiac output** - 5 L/min at rest, for an adult;
  capacity to increase 5 fold during exercise

  **blood pressure**
  **blood volume,**
  **blood fluidity/viscosity**
2. Secondary roles of the circulatory system:

(1) **fast chemical signaling** to cells by means of:
circulating hormones, neurotransmitters, signaling molecules, including the ones secreted by itself

(2) **dissipation of heat** by delivery of heat from the core to the surface of the body

(3) **mediation of inflammatory and host defense responses** against invading microorganisms:
‘Channel’ for the immune response/defense mechanisms:
immune cells, antibodies, clotting proteins
2. Secondary roles of the circulatory system:

(4) Secretory function of the circulatory system:

- **Atrial Natriuretic Peptide (ANP):**
  released by atrial fibers as a response to heart overload
  powerful vasodilator, reduce water & sodium on the circulatory system, thereby reducing blood pressure

- **Nitric oxide - NO (Endothelial Derived Relaxing Factor):**
  vasodilator, inhibits platelets adherence & aggregation

- **Endothelial Derived Hyperpolarizing Factor**

- **Endothelin (ET):** vasoconstrictor on ET$_A$, ET$_B$ receptors

- **Prostaglandins (PGs) - PGE2, PGI2 (prostacyclin):** increase Na$^+$ excretion by the kidneys, vasodilators
Components of the cardiovascular system and their function:

1. **the heart** consists in two pumps, operating in series, requiring equalization of their outputs (5 L/min)
   - Left heart (LH) – main pump
   - Right heart (RH) – boost pump

2. **the blood**

3. **a vascular system** (two serial circuits):
   - systemic / pulmonary circulation
   - high-pressure / low-pressure
   - vessels (arteries, veins, capillaries) respond with changes in blood flow to changing metabolic demands
   - angiogenesis: self-repairing/self-expanding capacity of endothelial cells
Components of the Cardiovascular System and their function:

4. an integrated regulation system to adapt to variable demands:
   - intrinsic: automatism
   - systemic: nervous system
     endocrine system
   - local/metabolic regulation

Coupling of blood tissue perfusion with the level of activity/metabolic rate

E.g., increase in muscular metabolic rate during physical activity

muscular blood perfusion - resting conditions – 4 ml/100g/min
- physical activity - 80 ml/100g/min
Example of adaptation to variable demands during heavy exercise
Life-threatening human diseases are caused by failure of:
- the **heart** as a pump (e.g., congestive heart failure),
- the **blood** as an effective liquid organ (e.g., thrombosis and embolism),
- the **vasculature** either as a competent container (e.g., hemorrhage) or as an efficient distribution system (e.g., atherosclerosis),
- the **interactions among all these components** can by itself elicit or aggravate many human pathological processes.

All components of the cardiovascular system cooperate for serving its functions and maintain body homeostasis.
Heart – morphological data

- Weight ~ 300 g
- Longitudinal diam. = 100-120 mm
- Transversal diam. = 80-100 mm

- Measurement methods:
  - clinical: aria of cardiac dullness
  - echocardiography
  - radiology

The ventricles occupy the bulk of the heart. The arteries and veins all attach to the base of the heart.
Morphological components of the heart

- **Pericardium:** thin-walled membranous cavity surrounding the heart; small volume of *pericardial fluid* in the space between its two surfaces.

- **Myocardium:** working myocardium, peacemaker cells, cardiac conduction system

- **Fibrous skeleton**
  - 4 intracardiac valves:
    - AV valves: Right (tricuspid)
    - Left (mitral)
    - Semilunar valves: Aortic & Pulm.
  - chordae tendineae

- **Endocardium**

- **Coronary circulation**
One-way flow through the heart is ensured by two sets of valves.
The cardiac muscle: myocardium

- **Peacemaker cells**
- **Conductive system**
- **Working myocardium**
  - involuntary contraction
  - striated in appearance (sarcomeres and myofilaments similar to skeletal muscle ones);
  - small cells, electrical and mechanical cell-to-cell communication (**syncytium**)
  - mechanical performance complex and subtle.
Myocardial cell (MC) structure

Sarcolema - T tubules & terminal cisterns
Sarcoplasmic reticulum (SR)
Sarcomere
Intercalated disks
Mitochondria
Myocardial cell (MC) structure

**Sarcolemma - T tubules & terminal cisterns:** continuous with the cell membrane, carry the AP; more developed in the ventricles

**Sarcoplasmic reticulum (SR):**
- in close proximity to the contractile elements
- site of storage and release of Calcium

**Sarcomere:** contractile unit of the MC
- between 2 Z lines
- contains: thin filaments - actin, troponin, tropomyosin
  - thick filaments – myosin

**Intercalated disks:** paracellular connections
- hold the cells (desmosomes)
- connect them electrically (gap junctions),
  → heart behaves as an electrical syncytium
    (sync, synch: informal for synchronization)

**Mitochondria** (> than in skeletal muscle)
Myocardial properties

1. Excitability (bathmotropia)
2. Rhythmic activity/automaticity (chronotropia)
3. Conductibility (dromotropia)
4. Contractility (inotropia)
5. Relaxation (lusitropia)

Different cardiac cells serve different and very specialized functions, but all are electrically active.

The heart’s electrical signal normally originates in a group of cells high in the right atrium that depolarize spontaneously; it then spreads throughout the heart from cell to cell.
Myocardial Excitability

- **Excitability** is the capacity to respond to a stimulus that has a minimum threshold intensity and depends on ionic gradients across the cell membrane (polarized membrane), through the action of the membrane ionic transport system: ionic channels, pumps, exchangers.

- Heart is an excitable tissue capable of generating and responding to electrical signals.

- The response generated as an **action potential (AP)** propagates through the heart, through specialized conducting pathways or cell-to-cell within the working myocardium that generate the force of contraction.

- AP displays different appearances within the different cardiac cells. Based on the speed of the upstroke, AP are either **slow** (sinoatrial and atrioventricular nodes) or **fast** (atrial myocytes, Purkinje fibers, and ventricular myocytes).
Cardiac action potentials (APs) have distinctive shapes at different sites.

- Heart contains cells that generate spontaneously APs = Pacemaker Cells (exhibits automaticity)
  - slow response AP → induce a pace…

- Working myocardium – respond to electrical stimuli
  - fast response AP → contraction…

Cardiac action potentials (APs) have distinctive shapes at different sites.
Electrophysiology of Cardiac Cells

The cardiac AP starts in specialized muscle cells with intrinsic \textit{pacemaker} activity, or \textit{automaticity}, located in the \textit{sinoatrial node (SAN)}, within the right atrium (RA). APs then propagates in an orderly fashion throughout the heart.

SAN’ cells depolarize spontaneously and fire APs at a regular, \textit{intrinsic rate} ranging from 60 - 100 \textit{times/minute} for an adult individual at rest. This rate can be modulated by parasympathetic and sympathetic neural inputs.

Cardiac cells are electrically coupled through \textit{gap junctions}, thus spontaneous AP originating in the SAN propagates from cell-to-cell throughout the right atrial muscle and spread to the left atrium.

About 0.1 sec after its origination in SAN, AP arrives at the \textit{atrioventricular node (AVN)}, then, because of the presence of a fibrous atrioventricular ring, spreads directly through the only available pathway towards the ventricles – the \textit{His-Purkinje fiber system}, a network of specialized conducting cells that carries the signal to the muscle of both ventricles.
Conduction in the heart

- Interatrial tract (Bachman’s bundle) to left atrium
- Superior vena cava
- Aorta
- AV node
- Bundle of His
- Mainstem, left bundle branch
- Anterosuperior left bundle branch
- Posteroinferior left bundle branch
- Internodal pathways
- Atrial muscle
- Right bundle branch
- Purkinje fibers
- Ventricular muscle
The cardiac AP conducts from cell to cell via gap junctions

The electrical influence of one cardiac cell on another depends on the voltage difference between the cells and on the resistance of the gap junction connecting them and permits electrical current to flow - Ohm’s law.

An AP conducting from left to right causes intracellular current to flow from fully depolarized cells on the left, through **gap junctions**, and into cell A. Depolarization of cell A causes current to flow from cell A to cell B ($I_{AB}$). Part of $I_{AB}$ discharges the capacitance of cell B (depolarizing cell B), and part flows downstream to cell C.
Conduction in the heart – gap junctions and currents flow

Depolarization with Na+ and Ca2+ inflow (cell A) produces a flow of positive charge = **intracellular current** that discharges the membrane capacitance of the next cell connected through gap junctions (cell B), thereby depolarizing it and **releasing extracellular positive charges that had been associated with the membrane (capacitative current)**. The movement of this extracellular positive charge (from cell B to cell A) constitutes the **extracellular current**.

The intracellular and extracellular currents are **equal and opposite**. The flow of this **extracellular current** in the heart gives rise to an **instantaneous electrical vector**, which changes with time. Each point on an **electrocardiogram** is the sum of the many such electrical vectors, generated by the cells of the heart.
Underlying APs are four major time-dependent and voltage-gated membrane currents:

The myocytes in each region of the heart have a characteristic set of channels:

1. The **Na+ current** ($I_{Na}$) is responsible for the rapid **depolarizing** phase of the action potential in atrial and ventricular muscle and in Purkinje fibers.

2. The **Ca2+ current** ($I_{Ca}$) is responsible for the rapid **depolarizing** phase of the action potential in the SA node and AV node; it also triggers contraction in all cardiomyocytes.

3. The **K+ current** ($I_K$) is responsible for the **repolarizing** phase of the action potential in all cardiomyocytes.

4. The **pacemaker current** ($I_f$) is responsible, in part, for pacemaker activity in SA nodal cells and AV nodal cells.
Diversity of the cardiac ion channels

While the cellular and organ-level function correlates with the classical channels described, important subtleties in the detailed function can depend on the additional channel subtypes that may be expressed at varying levels and that can change under stress or during disease.

- Along with the Nav1.5 “cardiac” Na+ channel, Nav1.4, normally found in skeletal, muscle can be expressed in the heart.

- In addition to the L-type Ca2+ channel, cardiac myocytes may also express the T-type Ca2+ channel, mainly in heart diseases.

- Ventricular and atrial myocytes may express K+ channels in a diversity much greater than classically described. Moreover, the subtypes of K+ channels often changes in disease processes.
Two *electrogenic* transporters carry current across plasma membranes:

**NCX1 - type 1 Na-Ca exchanger** - normally moves 3 Na+ into the cell in order to *extrude* 1 Ca2+, using the electrochemical gradient for Na+ as an energy source for transport → *produces an inward or depolarizing current*. This electrochemical gradient reverses *transiently* early during the cardiac AP (due to the positive Vm), when the Na-Ca exchanger may be able to reverse and mediate entry of Ca2+ and a net outward current. Later during the AP, the Na-Ca exchanger returns to its original direction of operation (i.e., Ca2+ extrusion and inward current). During the plateau phase of the action potential, the inward current mediated by the Na-Ca exchanger tends to prolong the action potential.

**Na-K pump** - normally moves 2 K+ into the cell for 3 Na+ transported out of the cell, using ATP → produces an outward or hyperpolarizing current.

*Cardiotonic drugs* *(digoxin, ouabain)* inhibit the Na-K pump and thereby cause an increase in [Na+]i, reduces the outward current carried by the pump and therefore depolarizes the cell.
The changes in membrane potential ($V_m$) during the cardiac AP are divided into separate phases, with particularities in the SA node and ventricular muscle.

**Phase 0** - the **upstroke** of the AP.
- Slow upstroke due only to $I_{CA}$ (pacemaker cells),
- Fast upstroke due to both $I_{CA}$ and $I_{Na}$

**Phase 1** - the **rapid repolarization component** of the AP
- due to almost total inactivation of $I_{Na}$ or $I_{Ca}$ and may also depend on the activation of a minor K+ current, called $I_{to}$ (for transient outward current).

**Phase 2** - the **plateau phase** of the AP, prominent in ventricular muscle.
- depends on the continued entry of Ca$^{2+}$ or Na$^{+}$ ions through their major channels and on a minor membrane current due to the Na-Ca exchanger NCX1.

**Phase 3** - the **repolarization phase** of the AP.
- depends on $I_k$

**Phase 4** - the **electrical diastolic phase** of the AP.
- $V_m$ during phase 4 is termed the *diastolic potential*;
- in **SA and AV nodal cells**, changes in $I_k$, $I_{Ca}$, and $I_f$ produce **pacemaker activity** during phase 4.
- **Purkinje fibers** also exhibit pacemaker activity but use only $I_f$.
- Atrial and ventricular muscle have no time-dependent currents during phase 4.
Figure 21-4  Phases of cardiac action potentials. The records in this figure are idealized. $I_K$, $I_{Na}$, $I_{Ca}$, and $I_I$ are currents through $K^+$, $Na^+$, $Ca^{2+}$, and nonselective cation channels, respectively.
Fast Action Potentials

- Resting potential
- Membrane potential (mV)
- Threshold
- Overshoot
- Depolarization
- Repolarization
- Stimulus
- Posthyperpolarization
- Repolarization

Diagram showing the various phases of a fast action potential in response to a stimulus.
AP Phases:
0- depolarization/upstroke of the AP; 1-initial repolarization; 2-plateau; 3-repolarization; 4- resting membrane potential
The Na+ current is the largest current in the heart

Abundant (200 Na+ channels / µm² of membrane) in ventricular and atrial muscle, Purkinje fibers, and specialized conduction pathways of the atria. Current through Na+ channels (I₊Na) is not present in SA or AV nodal cells.

Voltage-gated Na+ channel has both α and β₁ subunits. The α subunit (Nav1.5) - specific for the cardiac Na+ channel, has several phosphorylation sites that make it sensitive to cAMP-dependent protein kinase (PKA) which stimulates the cardiac Na+ channel

The Na+ channels:
- closed at the negative resting potentials of the ventricular muscle cells,
- rapidly activate (in 0.1-0.2 ms) in response to local depolarization produced by conducted APs → massive inward current → rapid upstroke of the cardiac AP (phase 0).
- close if Vm remains at a positive level, a time-dependent process known as inactivation (slower than activation, but still rapid, half-time, ~1 ms), partly responsible for the rapid repolarization of the AP (phase 1).
- at the potentials maintained during the plateau of the cardiac AP, slightly + to 0 mV during phase 2, a very small but important component of this current remains (I₊Na,late), and contribute to prolong phase 2; also can contribute to myocytes’ proarrhythmic behavior.
The Na+ current

The regenerative spread of the conducted AP depends in large part on the magnitude of Na+ current ($I_{Na}$).

Na+ current activates $I_{Na}$ in neighboring cells and also activates other membrane currents in the same cell, including $I_{Ca}$ and $I_{K}$.

In cardiac myocytes the depolarization, initiated by Nav1.5, activates the L-type cardiac Ca$^{2+}$ channel (Cav1.2), which greatly prolongs the depolarizing phase of the cardiac AP due to its long-duration opening events.

Local anesthetic antiarrhythmic drugs, such as lidocaine, work by partially blocking $I_{Na}$.

Note that during AP $[Na^+]_i$ increases by only 0.02%
The Ca2+ current in the heart passes primarily through L-type Ca2+ channels

The Ca2+ current (Ica) is present in all cardiac myocytes:
- L-type Ca2+ channel (Cav1.2) is the dominant one in the heart.
  - activation ~ 1 ms; inactivation ~ 10-20 ms
  - are dihydropyridine receptors
  - blocked by nifedipin, verapamil, diltiazem

- T-type Ca2+ channels is present but in smaller amounts.

In the SA node, the role of Ica is to contribute to pacemaker activity.

In both the SA and AV nodes, Ica is the inward current source that is responsible for the upstrokes (phase 0) of the SA & AV nodal slower APs → the speed of the conducted APs is much slower than that of any other cardiac tissue → electrical delay between atrial contraction and ventricular contraction that permits more time for the atria to empty blood into the ventricles.
The Ca2+ current

$I_{\text{Ca}}$ sums with $I_{\text{Na}}$ during the upstroke of the APs of the ventricular and atrial muscle and the Purkinje fibers \(\rightarrow\) it increases the velocity of the conducted AP

$I_{\text{Ca}}$ participate in **Phase 2 (plateau phase)** of AP in atrial and ventricular muscle \(\rightarrow\) **long refractory period of the AP**

In atrial and ventricular muscle cells, the Ca2+ entering via L-type Ca2+ channels activates the release of Ca2+ from the sarcoplasmic reticulum (SR) by calcium-induced Ca2+ release
Sarcoplasmic Reticulum

T (transverse) tubule

L-type Ca\(^{2+}\) channel
(Cav1.2. dihydropirididine receptors)

Ca\(^{2+}\) dependent Ca\(^{2+}\) releasing channel
(ryanodine receptor)

Sarcoplasmic Reticulum (SR)

Ca\(^{2+}\)
K+ Currents

$I_K$
- repolarization currents present in all cardiac myocytes
- very small at negative potentials
- with depolarization **slowly activates** (20-200 ms), but does not inactivate
- responsible for repolarizing the membrane at the end of AP, during **Phase 3 of the AP**
- deactivating at the diastolic membrane voltage

$I_{to}$
- early transient outward K current (A-type)
- activated by depolarization; rapidly inactivates
- contributes to **Phase 1 of the AP**

$I_{K1}$ inward rectifying K channel
- responsible for the **resting membrane potential** (Phase 4)
K+ Currents

G-protein activated K+ current
-vagal nerv stim. of SAN & AVN → Ach → muscarinic receptor M2 → G-protein (βγ subunit) → GIRK K channels: outward K current → hyperpolarization → slows pacemaker rate & slows AP conduction through AVN

KATP current:
-ATP-sensitive channels, present in abundance, activated by low intracellular [ATP]; low probability to open at normal [ATP]~ 5 mM
-K currents dependent on ATP/ADP ratio; high activity/hypoxia → ↓ATP & ↑ADP → K channels activation & K outflow
-possible role in electrical regulation of contractile behavior by coupling cellular metabolism & membrane excitability; cardioprotection

Note that the [K+]i changes just by 0.001% during AP.
Pacemaker Current \( I_f \)

- found in SAN & AVN cells and in Purkinje fibers

- slow activation (100 ms) by hyperpolarization at the end of Phase 3 ("f" from funny); they do not conduct at positive potentials

- Produces an inward, depolarizing current of Na+

- \( I_f \) through a nonspecific cation channel (permeable for Na & K) called HCN (hyperpolarization-activated cyclic nucleotide (AMPc, GMPc)-gated channels)

- \( I_f \) current is not the only current that contributes to pacemaker activity; in SA and AV nodal cells, \( I_{Ca} \) and \( I_K \) also contribute significantly to the phase 4 depolarization.
Cardiac ion channels and their modulation

The membrane currents involved in the membrane potential and AP phases:

- are under the control of local and circulating agents: acetylcholine, epinephrine, and norepinephrine

- are targets for therapeutic agents designed to modulate the heart’s rhythm: Ca2+ channel blockers β-adrenergic blockers. 
  Local anesthetic antiarrhythmic drugs (lidocaine)
Different cardiac tissues uniquely combine ionic currents to produce distinctive action potentials

- cell specific combination of various currents, both voltage-gated/time-dependent currents and “background” currents, present in each cell type.

- $V_m$ is described in terms of the conductances for the different ions ($G_{Na}$, $G_{K}$, $G_{Ca}$, $G_{Cl}$) relative to the total membrane conductance ($G_m$) and the equilibrium potentials ($E_{Na}$, $E_{K}$, $E_{Ca}$, $E_{Cl}$):

$$V_m = \frac{G_K}{G_m} E_K + \frac{G_{Na}}{G_m} E_{Na} + \frac{G_{Ca}}{G_m} E_{Ca} + \frac{G_{Cl}}{G_m} E_{Cl} \ldots$$

As the relative contribution of a particular membrane current becomes dominant, $V_m$ approaches the equilibrium potential for that membrane current. How fast $V_m$ changes during AP depends on the magnitude of each of the currents. Each current independently affect the shape of AP, but the voltage- and time dependent currents interact with one another because they affect, and are affected by $V_m$.

<table>
<thead>
<tr>
<th>ION</th>
<th>INTRACELLULAR CONCENTRATION (mM)</th>
<th>EXTRACELLULAR CONCENTRATION (mM)</th>
<th>EQUILIBRIUM POTENTIAL (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$</td>
<td>10</td>
<td>145</td>
<td>+72</td>
</tr>
<tr>
<td>K$^+$</td>
<td>120</td>
<td>4.5</td>
<td>−88</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>35</td>
<td>116</td>
<td>−32</td>
</tr>
<tr>
<td>H$^+$</td>
<td>pH = 7.1</td>
<td>pH = 7.4</td>
<td>−19</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>0.0001</td>
<td>1.0</td>
<td>+123</td>
</tr>
<tr>
<td>Name</td>
<td>Voltage (V)-Gated or Ligand (L)-Gated</td>
<td>Functional Role</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Voltage-gated Na(^+) channel (fast, (I_{Na}))</td>
<td>V</td>
<td><strong>Phase 0</strong> of action potential (permits influx of Na(^+))</td>
<td></td>
</tr>
<tr>
<td>Voltage-gated Ca(^{2+}) channel (slow, (I_{Ca}))</td>
<td>V</td>
<td>Contributes to <strong>phase 2</strong> of action potential (permits influx of Ca(^{2+}) when membrane is depolarized); (\beta)-adrenergic agents increase the probability of channel opening and raise Ca(^{2+}) influx; <em>Acetylcholine (ACh)</em> lowers the probability of channel opening</td>
<td></td>
</tr>
<tr>
<td>Inward rectifying K(^+) channel ((I_{K1}))</td>
<td>V</td>
<td>Maintains resting membrane potential (<strong>phase 4</strong>) by permitting outflux of K(^+) at highly negative membrane potentials</td>
<td></td>
</tr>
<tr>
<td>Outward (transient) rectifying K(^+) channel ((I_{to}))</td>
<td>V</td>
<td>Contributes briefly to <strong>phase 1</strong> by transiently permitting outflow of K(^+) at positive membrane potentials</td>
<td></td>
</tr>
<tr>
<td>Outward (delayed) rectifying K(^+) channels ((I_{Kr}, I_{Ks}))</td>
<td>V</td>
<td>Cause <strong>phase 3</strong> of action potential by permitting outflow of K(^+) after a delay when membrane depolarizes; (I_{Kr}) channel is also called HERG channel (‘r’ for rapid, ‘s’ for slow).</td>
<td></td>
</tr>
<tr>
<td>G protein–activated K(^+) channel ((i_{K1.G}, i_{K.ACh}, i_{K.ado}))</td>
<td>L</td>
<td>G protein–operated channel, opened by ACh and adenosine (ado); this channel hyperpolarizes membrane during <strong>phase 4</strong> and <strong>shortens phase 2</strong></td>
<td></td>
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</tbody>
</table>
Events associated with the ventricular action potential

- **Phase 0**: 
  - Membrane potential approaches Na⁺ equilibrium potential
  - Ca²⁺ channels open and i_{to1} channels close
  - Membrane potential stays near zero

- **Phase 1**: 
  - Na⁺ channels inactivated and i_{to1} channels open
  - Membrane potential nears zero

- **Phase 2**: 
  - Ca²⁺ channels close and i_K1 channels close
  - Membrane potential stays near zero

- **Phase 3**: 
  - Membrane potential approaches K⁺ equilibrium potential
  - i_Kr and i_Ks channels open

- **Phase 4**: 
  - Na⁺ channels activate
  - Resting membrane potential

**Depolarization**
- Positive charges displaced into adjacent areas

**ERP** (Effective refractory period)

**RRP** (Relative refractory period)

**VENTRICULAR MUSCLE**

- **V_m (mV)**
  - Outward: I_K
  - Inward: I_{Na}, I_Ca
The SA node is the primary pacemaker of the heart

**Pacemaker activity** = spontaneous time-dependent depolarization of the cell membrane that leads to an AP in an otherwise quiescent cell.

The normal heart has three intrinsic pacemaking tissues: the **SA node**, the **AV node**, and the **Purkinje fibers**. Any cardiac cell with pacemaker activity can initiate the heartbeat. The pacemaker with the highest frequency will be the one to trigger an AP that will propagate through the heart.

Two fundamental principles underlie pacemaker activity:
1 - inward or depolarizing membrane currents interact with outward or hyperpolarizing membrane currents to establish regular cycles of spontaneous depolarization and repolarization.
2 - in a particular cell, these currents interact during phase 4 within a narrow range of diastolic potentials: between −70 and −50 mV in SA and AV nodal cells, and between −90 and −65 mV in Purkinje fibers.
Cardiac muscle cells contract without nervous stimulation

- 1% from the myocardium: pacemaker/autorhythmic cells (99% contractile cells)

- **Pacemaker cells:**
  - organized in a specialized excitatory & conductive system
  - anatomically distinct
  - smaller, contain few contractile fibers

- electrogenic system: EXCITABILITY, CHRONOTROPISM
  generate AP **spontaneously, rhythmically**

- set the rate of the heart beat: CONDUCTIVITY
  rapidly **conduct APs** throughout the heart
  generate rhythmical contraction
Specialized excitatory & conductive system

1. **S-A Node (SAN):**
   - primary, fastest pacemaker of the heart in normal conditions; generate AP at a rate of 60 beats/min, higher than the one in AV node and His-Purkinje system
   - located in the superior posterolat. wall of the RA; ellipsoid shape: 15/3/1 mm
   - **P cells of the SAN:**
     - are stable oscillators whose currents are always varying with time, and they do not have a constant resting potential;
     - membrane permeability to Na and Ca during diastole; inward Ca current during upstroke (phase 0) of AP.
Membrane currents in the SA node cells

The interactions among three time-dependent and voltage-gated membrane currents (ICa, IK, and If) control the intrinsic rhythmicity of the SA node.

The sum of a decreasing outward current (IK) and two increasing inward currents (ICa and If) produces the slow pacemaker depolarization (phase 4) associated with the SA node.

The maximum diastolic potential (i.e., the most negative Vm) of the SA nodal cells, which occurs during phase 4 of the AP ∼ −60 ÷ −70 mV.

As Vm rises toward the threshold of about −55 mV, ICa becomes increasingly activated and eventually becomes regenerative, producing the upstroke of AP. This depolarization rapidly turns off/deactivates If, and the whole process begins again.

Contribution of the Na-Ca exchanger NCX (the Ca2+ clock):
- the time-dependent subcellular Ca2+ release (Ca2+ sparks) from the SR in SA and AV nodal cells → subcellular Ca2+ sparks activate an inward (depolarizing) INCX.
Phases of SAN action potential.
The records in this figure are idealized. $I_K$, $I_{Na}$, $I_{Ca}$, and $I_f$ are currents through $K^+$, $Na^+$, $Ca^{2+}$, and nonselective cation channels, respectively.
2. **Internodal & interatrial pathways**

3. **A–V Node:**
   - located just above the AV ring,
   - is the secondary site of origin of the electrical signal in the heart
   - intrinsic rate ~ 40 beats / min or faster
   - its intrinsic depends on the interaction of IK, ICa, and If.
   - inward Ca current during upstroke of AP;
   - here, impulse conduction delay of 0.1 sec

4. **AV bundle (His-Purkinje)**
   - intercalated disks, gap junctions
   - left & right branches of the AV bundle
   - accessory AV pathways - **reentry loops**

5. **Purkinje fibres:**
   - slowest intrinsic pacemaker rate (20 beats/min or less)
   - **I**Na is large → conduct APs rapidly (rapid upstroke)
   - distribute to the endocardium, causes ventricles to contract, from bottom up, pushing blood out top of heart
Atrioventricular and ventricular conduction system. Purkinje network distribution.
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<tr>
<th>TISSUE NAME</th>
<th>FUNCTION</th>
<th>PRINCIPAL TIME-DEPENDENT AND VOLTAGE-DEPENDENT CURRENTS</th>
<th>β-ADRENERGIC EFFECT (e.g., EPINEPHRINE)</th>
<th>CHOLINERGIC EFFECT (e.g., ACh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA node</td>
<td>Primary pacemaker</td>
<td>$I_{Ca}, I_k, I_l$</td>
<td>$\uparrow$ Conduction velocity</td>
<td>$\downarrow$ Pacemaker rate</td>
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<td>$\downarrow$ Conduction velocity</td>
</tr>
<tr>
<td>Atrial muscle</td>
<td>Expel blood from atria</td>
<td>$I_{Na}, I_{Ca}, I_k$</td>
<td>$\uparrow$ Strength of contraction</td>
<td>Little effect</td>
</tr>
<tr>
<td>AV node</td>
<td>Secondary pacemaker</td>
<td>$I_{Ca}, I_k, I_l$</td>
<td>$\uparrow$ Conduction velocity</td>
<td>$\downarrow$ Pacemaker rate</td>
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<td>$\uparrow$ Pacemaker rate</td>
<td>$\downarrow$ Conduction velocity</td>
</tr>
<tr>
<td>Purkinje fibers</td>
<td>Rapid conduction of action potential</td>
<td>$I_{Na}, I_{Ca}, I_k, I_l$</td>
<td>$\uparrow$ Pacemaker rate</td>
<td>$\downarrow$ Pacemaker rate</td>
</tr>
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<td></td>
<td>Tertiary pacemaker</td>
<td></td>
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<tr>
<td>Ventricular muscle</td>
<td>Expel blood from ventricles</td>
<td>$I_{Na}, I_{Ca}, I_k$</td>
<td>$\uparrow$ Contraction</td>
<td>Little effect</td>
</tr>
</tbody>
</table>
Myocardial conductivity (dromotropia)

1. S-A Node area

2. Internodal & interatrial pathways

3. A–V Node:
   inward Ca current during upstroke of AP; AP delay 0.1 s

4. AV bundle (His-Purkinje)
   - intercalated disks, gap junctions
   - split into left & right branches

5. Purkinje fibres: causes ventricles to contract, from bottom up, pushing blood out top of heart
The myocardial conductivity is needed for an efficient pumping.

Atria contraction precedes ventricles contraction, because of AV nodal delay:
- the impulse travels rather slowly through AV node (0.09 sec) & penetrating part of the AV bundle (0.04 sec) (cause of the delay: less gap junctions…)

Both atria and ventricles should contract as a unit
- the impulse spreads so rapidly through the conducting system that all myocardial cells in the atria and ventricles, respectively, contract at about the same time.
Conduction velocity

- Reflects the time required for excitation to spread from SAN to the entire cardiac tissue
- Fastest in the Purkinje system, slowest in AVN (important for ventricular filling...)
  - 0.02 to 0.1 m/sec in SA & AV nodes; AV delay: ~ 0.1 sec
  - 1 m/sec. in internodal & interatrial anterior pathways
  - 0.3-0.5 m/sec in A & V muscle (Endocardium → Epicardium)
  - 1.5 - 4 m/sec in Purkinje fibers

  longer fibers, distributed in 1/3 of ventricular volume
  gap junctions (no., permeability...), direct connection with myocytes
  fast Na currents, “regenerative spread of conducted AP” → rapid conduction
  of cardiac impulse

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>CONDUCTION VELOCITY (m/s)</th>
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</thead>
<tbody>
<tr>
<td>SA node</td>
<td>0.05</td>
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<tr>
<td>Atrial pathways</td>
<td>1</td>
</tr>
<tr>
<td>AV node</td>
<td>0.05</td>
</tr>
<tr>
<td>Bundle of His</td>
<td>1</td>
</tr>
<tr>
<td>Purkinje system</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular muscle</td>
<td>1</td>
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</table>
Atrial activation

*Step 1:* AP generated in the SAN is propagated and depolarize the atria, following a general axis from right to left and downward.

Ventricular activation completes in ~100 ms:

*Step 2:* The septum depolarizes from left to right.

*Step 3:* The anteroseptal region depolarizes.

*Step 4:* The myocardium always depolarizes from the endocardium (the cells lining the ventricles) toward the epicardium (cells on the outer surface of the heart). The left ventricle depolarizes at the apex while the Purkinje fibers are still in the process of conducting the action potential toward the base of the left ventricle.

*Step 5:* Depolarization spreads from the apex toward the base, carried by the Purkinje fibers. This spread to the base begins even as the signal in the apex is still spreading from the endocardium to the epicardium. The last region to depolarize is the posterobasal region of the left ventricle.

*Step 6:* The ventricles are fully depolarized.
**Ventricular muscle** has three major time- and voltage gated membrane currents: INa, ICa, and IK, and has no If (normally does not show no pacemaker activity).

**Ventricular AP:**
- starts from a resting potential of −80 mV,
- rapid upstroke results from the activation of INa by an external stimulus
- Ca2+ current is of particular importance to ventricular muscle because it provides the Ca2+ influx that activates the release of Ca2+ from the SR.

The rapid repolarization (phase 1), the plateau (phase 2), and the repolarization (phase 3) all appear to be governed by mechanisms similar to those found in the Purkinje fibers. However, the plateau phase is prolonged in ventricular muscle because the inward and outward currents are rather stable during that time.
Cardiac PA - Refractory periods

Once a ventricular muscle cell is activated electrically, it is refractory to additional activation because the inward currents (INa and ICa) that are responsible for activation are largely inactivated by the membrane depolarization → effective/absolute refractory period. During the effective refractory period, an additional electrical stimulus has no effect on the AP.

The relative refractory period begins at the end of the plateau, when the cell begins to repolarize as IK increases in magnitude and ICa and INa begin to recover from inactivation. During this period, an additional electrical stimulus can produce an AP, but a smaller one than usual.

Refractoriness provides the heart with a measure of electrical safety because it prevents extraneous pacemakers (which may arise pathologically) from triggering ectopic beats. An extrasystolic contraction would make the heart a less efficient pump. Refractoriness also prevents tetanus (perpetual systole and no further contractions).
ERP/ARP - effective/absolute refractory period; 
RRP - relative refractory period
Changes in action potential amplitude and slope of the upstroke as premature (P) action potentials are initiated at different stages of the relative refractory period of the preceding excitation in a fast-response fiber (bar = 100 msec).
Premature contraction

- Early premature contraction
- Delayed premature contraction

P - premature contraction

- AP – electrical activity
- Contraction – mechanical activity

Compensatory pause
Modulation of the heart rate by the autonomic nervous system

Distribution of the nervous fibers
Autonomic effects on automatism and conduction velocity

**PS** vagal innervation

**Ach** mediated

**Muscarinic receptors** on SAN, atria, AVN

Negative chronotropic effect: ↓ $I_f$, delayed slow depolarization
  ↓ heart rate (sinus bradycardia)

Negative dromotropic effect: ↓ inward Ca current
  ↓ conduction velocity through AVN

**AP are conducted more slowly from A to V**

**S** innervation

norepinephrine mediated (also epinephrine - adrenal medulla)

**$\beta_1$ receptors**

Positive chronotropic effect: ↑ $I_f$, ↑ heart rate (sinus tachycardia)

Positive dromotropic effect: ↑ inward Ca current
  ↑ **conduction velocity through AVN**

↑ ventricular filling
Acetylcholine modulate pacemaker activity and conduction velocity

**Acetylcholine (ACh)**
- released from the vagus nerve (parasympathetic) onto the SA and AV nodes
- slows the intrinsic pacemaker activity by all three mechanisms:
  1. ACh decreases \( I_f \) in the SA node, reducing the steepness of the phase 4 depolarization.
  2. ACh opens GIRK channels, increasing relative K+ conductance and making the maximum diastolic potential of SA nodal cells more negative
  3. ACh reduces \( I_{Ca} \) in the SA node, thereby reducing the steepness of the phase 4 depolarization and also moving the threshold to more positive values.

All three effects cooperate to lengthen the time for the SA node to depolarize to threshold; the net effect is to lower the heart rate.

ACh has similar effects on currents in the AV and SA nodes. In AV node Ach slows conduction velocity by inhibition of \( I_{Ca} \) that also makes the threshold more positive for AV nodal cells. Because it is more difficult for one cell to depolarize its neighbors to threshold, conduction velocity falls.
Modulation of pacemaker activity to decrease the heart rate:

A. Prolonged slow depolarization, lengthening the time necessary for $V_m$ to reach threshold → diastole is longer and the heart rate falls

B. Hyperpolarization ($V_m$ starts phase 4 at a more negative potential and thus takes longer to reach threshold)

C. Threshold shift towards a more positive value ($V_m$ requires a longer time to reach a more positive Threshold).

A combination of these mechanisms could have either a negative or positive chronotropic effect.
Catecholamines modulate pacemaker activity, conduction velocity and contractility
- mostly norepinephrine, from sympathetic innervation; also, epinephrine released from the adrenal medulla
- act through β1-adrenergic receptors, to produce an increase in heart rate by
  1) increase If in the nodal cells, thereby increasing the steepness of the phase 4 depolarization
  2) Increase ICa in all myocardial cells.
     - in the SA and AV nodal cells steepens the phase 4 depolarization and also makes the threshold more negative
     - produce shorter APs as a result of the actions on specific currents.
- in atrial and ventricular muscle, cause an increase in the strength of contraction (positive inotropic effect) through:
  1) increased ICa (i.e., Ca2+ influx) leads to a greater local increase in [Ca2+]i and also a greater Ca2+-induced Ca2+ release from the SR.
  2) increase the sensitivity of the SR Ca2+-release channel to cytoplasmic Ca2+.
  3) enhance Ca pumping into the SR by stimulation of the SERCA Ca pump, thereby increasing Ca2+ stores for later release.
  4) the increased ICa presents more Ca2+ to SERCA, so that SR Ca2+ stores increase over time \(\rightarrow\) more Ca2+ available to troponin C, enabling a more forceful contraction
Digitalis compounds may be used to treat supraventricular tachycardias because these drugs may increase vagal tone and decrease sympathetic tone, thereby slowing the conduction of atrial impulses through the AV node. Patients with congestive heart failure may have a low baseline vagal tone and a high baseline sympathetic tone. In these patients, digitalis-like drugs increase myocardial contractility and cardiac output, causing a reflex increase in vagal tone.
In atrial tachycardia (atrial flutter, atrial fibrillation), electrical impulses from the AV node and above may drive the ventricles at a very high rate → the effectiveness of the ventricles’ pumping is hindered. Ach could be used to slow impulse conduction through the AV node can slow the ventricular rate. The vagal maneuvers, which increase parasympathetic activity and release Ach can decrease ventricular rate.

Valsalva maneuver is a vagal maneuver in which one makes a forced expiratory effort against a closed airway, raising intrathoracic pressure → opening of the airway allows intrathoracic pressure to fall, so that the now-increased transmural pressure stretches the aorta, stimulating the aortic baroreceptors and triggering a reflex activation of the vagus nerve.

Massage of the bifurcation of the carotid artery in the neck directly stretches the wall of the carotid sinus, thereby stimulating the baroreceptors.

By either above maneuver, the baroreceptor output signals brainstem centers to stimulate the vagus nerve, thereby slowing the heart.
Organization of the cardiovascular system (Boron, Ch. 17, p. 410-412)
Cardiac electrophysiology (Boron, Ch. 21, p. 483-493)