The Cardiovascular System

- Integrates three functional parts:
  - The heart, a dual pump that circulates
  - a liquid, the Blood,
  - in two serial circuits of Vessels: the Systemic and the Pulmonary Circulations
The Cardiovascular System

- Provides a steep concentration gradient from **blood** to the **tissues** for **nutrients** and in the **opposite direction** for **waste products**

- The gradient can be maintained by a rapidly circulating fluid between regions that equilibrate with the external milieu (lungs, guts, kidneys, skin)
Other Functions of the CV System

- Transports also:
  - hormones, signaling molecules \(\rightarrow\) involvement in fast signaling processes
  - immune cells, antibodies, clotting proteins \(\rightarrow\) roles in the immune response/defense mechanisms
  - heat - dissipation from the body core to the surface \(\rightarrow\) thermoregulation
Other Functions of the CV System

- Secrets a number of hormones and vasoactive compounds:

  - **Atrial natriuretic peptide (ANP)**, produced by the atrial fibers – is a powerful vasodilator, and enhances renal excretion of water and sodium as well, thereby reducing blood pressure

  - **Factors derived from endothelium**: NO (endothelial derived relaxing factor, EDRF), endothelial derived hyperpolarizing factor (EDHF), endothelin, prostaglandins PGE2, PGI2 (prostacyclin) etc.
• Heart Physiology
• Hemodynamics
• Blood Physiology
The Heart

- Superior vena cava
- Right atrium
- Tricuspid valve
- Inferior vena cava
- Pulmonary semilunar valve
- Right ventricle
- Mitral valve
- Left atrium
- Left pulmonary arteries
- Left pulmonary veins
- Left ventricle
- Chordae tendineae

Myocardium

Endocardium

Pericardium
Myocardium

- Excito-conductory system
- Contractile myocardium
Myocardial Properties

- EXCITABILITY/ bathmotropia
- AUTOMATICITY/ chronotropia
- CONDUCTIBILITY/ dromotropia
- CONTRACTILITY/ inotropia
- RELAXATION/ lusitropia
Electrical Properties of the Heart

Excitability
- Automaticity
- Conductibility

bathmotropia
chronotropia
dromotropia
Excitability (Bathmotropia)

- Of the myocardial fiber: the ability to produce a new action potential in response to a stimulus that has a minimum threshold intensity

- Of the whole heart: the property of the myocardium to produce a specific answer to a threshold stimulus
Electrophysiology of the Myocardial Fiber

- Myocardial fibers have polarized membranes

- There are voltage differences between the intra- and extracellular medium

- Electrical phenomena of the cell are the consequence of the unequal distribution of ions across membranes due to the activity of specific membrane transport systems: ion channels, pumps, exchangers
Ion Channels in the Myocardium

Each subunit in a voltage-gated channel consists of six helical segments.

Channels are usually oligomeric complexes that are composed of multiple subunits.

Voltage-gated Na⁺, Ca²⁺, and K⁺ channels; Ca-release channel

Nicotinic ACh receptor channel

A half gap-junction channel, or connexon, made up of six connexins

TETRAMER

PENTAMER

HEXAMER
Potassium Channels

- **Inward rectifier potassium channels**, active during the resting phase:
  - $K_{ir}(K_1)$
    - responsible for maintaining the resting potential at about -90 mV;
    - their activation is not voltage dependent, but the conductance decreases while the membrane depolarizes
- **Mediator dependent K channels** (acetylcholine-, adenosine-dependent channel, $K_{ACH}$, $K_{ado}$), determine membrane hyperpolarization and decreases heart rate in nodal cells
- **ATP-dependent K channels**, $K_{ATP}$, are directly regulated by adenine nucleotides: low levels of intracellular ATP stimulates it, hyperpolarizes the membrane, protecting the heart during ischemia
Potassium Channels

- **Voltage gated K channels**, activate slowly during the AP and play an important role in membrane repolarization and AP duration.
- **Transient outward current**: is activated early after depolarization, produces the $I_{to}$ current responsible for phase 1 of AP. Has a role during phase 3 as well, and can be activated by sympathetic stimulation with the shortening of the AP duration.
- **$K_s$**, slow, activated early after the depolarization with a progressive increase that reaches the peak at the end of phase 2; is stimulated by sympathetic, producing the shortening of AP.
- **$K_r$**, rapid, has a rapid but partial activation at the beginning of phase 2, and a complete activation in the end of the plateau of the AP.
- **$K_{ur}$ – ultrarapid current**, present in the atrial fibers, responsible for a shorter AP in these cells.
Repolarizing Potassium Currents

Diagram showing various potassium currents, including $I_{Kr}$, $I_{Ks}$, and $I_{Ca_L}$, with annotations for chloride and sodium ions.
Voltage Gated Sodium Channel

- Active during upstroke
- Inactivated by tetrodotoxine and lidocaine
Calcium Channels

- **L-type** (long lasting)
  - voltage-gated
  - with an activation threshold at about -40 mV
  - stimulated by catecholamines and Bay K 8644
  - inhibited by Ach and specific blockers (nifedipine, verapamil, diltiazem)

- **T-type** (transient)
  - voltage-gated
  - activated at a less negative threshold (< -40 mV)
  - produces a low current, important for the last part of diastolic depolarization in nodal cells
<table>
<thead>
<tr>
<th>Property</th>
<th>L</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetics:</td>
<td>Long duration</td>
<td>Transient</td>
</tr>
<tr>
<td>Voltage activation:</td>
<td>High threshold (&gt;-40 mV)</td>
<td>Low threshold (&lt;-40 mV)</td>
</tr>
<tr>
<td>Pharmacology:</td>
<td>Blocked by DHPs</td>
<td>Less sensitive to DHPs</td>
</tr>
<tr>
<td>Location:</td>
<td>Heart, skeletal muscle, neurons, vascular smooth muscle, uterus, neuroendocrine cells</td>
<td>Sinoatrial node of heart, brain neurons</td>
</tr>
<tr>
<td>Function:</td>
<td>Phase 2 of the AP in working fibers, upstroke of AP in nodal cells, EC coupling in skeletal muscle</td>
<td>Repetitive firing of action potentials in heart and many neurons</td>
</tr>
</tbody>
</table>
Nonselective Ion Channels

- Nonselective channel that mediate the **pacemaker current, If** (the funny current), responsible for spontaneous diastolic depolarization in pacemaker cells;
  - allows an influx of Na+, but also the transfer of K+ in certain circumstances;
  - is activated by hyperpolarization, with a threshold below \(-40\) mV;
  - changes of its conductance adjusts the heart rate;
  - is stimulated by catecholamines, and inhibited by Ach and ivabradine

- Stretch-activated channels, responsible for the mechano-electric feedback (AP can be influenced by myocardial stretch)
Ion Pumps

- Enzymes that pump ions against gradients with energy obtained by cleaving ATP (ATP-ases); maintain the chemical gradient between extra- and intracellular milieu

- **Na+/K+ ATP-ase**
  - pushes 2 K+ inside and 3 Na+ outside the cell → is electogenic (creates a small outward current)
  - provides a chemical gradient for Na+ that feeds the secondary active exchangers (Na+/Ca++, Na+/H+)
  - Is inhibited by digitalis

- **Ca++ ATP-ase**, involved in Ca++ extrusion from the cytoplasm
  - Sarcolemma – lower efficiency than the Na+/Ca++ exchanger
  - Endoplasmic reticulum – important in myocardial relaxation
Exchangers

- Secondary active transport mechanisms, depend on the activity of Na+/K+ ATP-ase

  - **Na+/Ca++ exchanger**
    - Is distributed mainly at the level of the T tubules
    - Principal mechanism for removing Ca from the cell
    - Is electrogenic (exchanges 1 Ca++ for 3 Na+)
    - Is voltage-sensitive: at membrane potentials < - 40 mV pushes Ca outside the cell, whereas at > - 40 mV works in the opposite direction

  - **Na+/H+ exchanger**
    - Protects the heart against intracellular acidosis during myocardial ischemia
Cardiac Action Potentials

- Based on the speed of the upstroke, we can differentiate two types of action potentials in the myocardium:
  
  - Fast action potentials – in atrial myocytes, Purkinje fibers and ventricular myocytes; they have 5 distinct phases
  
  - Slow action potentials – in SAN, AVN, with only 3 phases
Phases of Fast Action Potential

0. Fast Na⁺ channel
1. K⁺ channel (i₁₀)
2. Ca⁺⁺ channel
3. K⁺ channels (iₖ, i_K₁, i₁₀)
4. K⁺ channels (iₖ, i_K₁)

Phases of Fast AP

- **Phase 4**: the resting phase
  - with a membrane voltage maintained at about –90 mV due to
    - the unequal ion distribution inside and outside the cell, and
    - a low membrane conductance for Na\(^+\) and Ca\(^{++}\), and
    - a high conductance for K\(^+\)
  - the resting potential approaches the equilibrium potential for potassium, as predicted by the Nernst equation

- **Phase 0**: the rapid upstroke, due to a sudden increase of membrane conductance for Na\(^+\), that makes the inside of the cell more positive than the outside, with a change in membrane electric polarity
Phases of Fast AP

- **Phase 1:** the early partial repolarization - the chemical and electrostatic forces both favor the efflux of $K^+$ through $I_{to}$ channels, and an influx of $Cl^-$

- **Phase 2:** during the plateau phase, the net influx of $Ca^{++}$ through L-type $Ca^{++}$ channels is balanced by the efflux of $K^+$ through $I_K$, $I_{Kir}$, and $I_{to}$ currents.

- **Phase 3:** the final repolarization, when the membrane becomes again more negative inside, due to the efflux of $K^+$ through $i_K$, $i_{K1}$, and $i_{to}$ channels
Repolarizing Potassium Currents
Heterogeneity of Membrane K+ Currents in the Myocardium
Refractoriness
Refractory Period

- Once a ventricular muscle cell is activated electrically, it is refractory to additional activation.

- The **effective refractory period** (ERP) arises because the inward currents ($I_{Na}$ and $I_{Ca}$) that are responsible for activation are largely inactivated by the membrane depolarization. During the ERP, an additional electrical stimulus has no effect on the action potential.

- At the end of the plateau, the cell begins to repolarize as $I_{K}$ increases in magnitude. $I_{Ca}$ and $I_{Na}$ begin to recover from inactivation, producing the **relative refractory period** (RRP), when an additional electrical stimulus can produce an action potential, but a smaller one than usual.
Action potential amplitude and slope of the upstroke change as premature action potentials are initiated at different stages of the relative refractory period of the preceding excitation in a fast-response fiber (bar = 100 msec)
Refractoriness And the Na+ Channel
• 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, a feature observed in skeletal muscle. Tetanus of the heart would mean perpetual systole, and no further contractions
Response to Stimulus

Cardiac muscle

Skeletal muscle
Skeletal muscle fast-twitch fiber

- Membrane potential (mV)
- Peak
- Muscle contraction
- Muscle relaxation
- Refractory period

Tetanus in a skeletal muscle. Action potentials not shown.

- Maximum tension
- Refractory period
- ▲ = Stimulus for action potential

Cardiac muscle fiber

- Membrane potential (mV)
- Peak
- Muscle contraction
- Muscle relaxation
- Refractory period

Long refractory period in a cardiac muscle prevents tetanus.
The Law of Periodic Unexcitability

- The heart is unexcitable during systole
Automaticity (Chronotropia)
Automaticity (Chronotropia)

- The property of the myocardium to produce spontaneous action potentials in a rhythmic fashion

- Is based on the activity of specialized myocardial cells, able to fire AP independently of any external stimulation; these are the so-called pacemaker cells that form three pacemaking structures:
  - the sino-atrial node: 70 – 80 AP/min
  - the atrio-ventricular node: 40 - 50 AP/ min
  - the bundle of His and its branches and the Purkinje network: 20 - 30 AP/min

Pacemaker cells produce slow response AP; however, Purkinje cells discharge fast AP but are able to depolarize spontaneously at a low rate.
Slow AP Myocardial Cells

- Less negative maximal diastolic potential ($I_{Kr}$ is absent)
- Spontaneous diastolic depolarization (If mediated)
- Slow upstroke ($I_{Ca-L}$ dependent)
- Low amplitude
Phases of Slow Action Potential

-65

$0$

$0$

-65

$0$

$0$

100 ms

exterior

interior

$I_K$

$I_f$

$I_{Ca-L}$

$I_{Ca-T}$
Phases of Slow Action Potential

- **Phase 0:** slow upstroke, due to the regenerative activation of L-type and T-type Ca++ channels

- **Phase 3:** membrane repolarization/ hyperpolarization, due to gradual activation of Kr and Ks following depolarization; IK is active until the potential becomes low enough to activate If (the pacemaker current)

- **Phase 4:** spontaneous diastolic depolarization, due to
  - activation of If by membrane hyperpolarization
  - decrease of K currents
  - recovery from inactivation of Ca channels that allows a low inward current

Thus, the sum of a decreasing *outward* current ($I_K$) and two *increasing* *inward* currents ($I_{Ca}$ and $I_f$) produce the slow pacemaker depolarization associated with the SA node.
SAN Is the Primary Pacemaker of the Heart

- Cardiac myocytes contract due to AP fired by the SAN and transmitted along well established conduction pathways

- SAN discharges AP at the highest rate, inhibiting the subsidiary centers (AVN, Purkinje fibers)

- AVN can become dominant when SAN node does not produce AP or when the electrical communication between SAN and AVN is blocked

- Purkinje cells become dominant when SAN and AVN do not fire AP or the electrical communication between the Purkinje fibers and the superior pacemaker centers is interrupted
Overdrive Suppression

Overdrive → Na accumulation → Na/K ATP-ase is stimulated = 3:2 → hyperpolarization

Recovery time of the SAN
Modulation of Pacemaker Activity

A DECREASED RATE OF DEPOLARIZATION

- Membrane potential (mV)
- Time (msec)

Control

Threshold

Slower depolarization requires more time to reach threshold.

Modulation of Pacemaker Activity

B NEGATIVE SHIFT IN MAXIMUM DIASTOLIC POTENTIAL

Starting from a more negative value, $V_m$ requires more time to reach threshold.
Modulation of Pacemaker Activity

**C** POSITIVE SHIFT IN THRESHOLD

- **Membrane potential (mV)**
- **Threshold**

Reaching a more positive threshold requires more time.

SP and PSP Innervation of the Heart

Cardiac sympathetic and parasympathetic nerves. (The vagus nerves to the heart are parasympathetic nerves.)
Effects of ANS on HR

Parasympathetic stimulation

Sympathetic stimulation
Pharmacologic Modulation of HR
Cardiac stimulator

Biotechnology: pacemaker engineering
Changes of Normal Automatism

- Produces cardiac arrhythmias

- Can be the result of
  - Enhanced automaticity
  - Triggered activity
Enhanced Automaticity

- Enhancement of normal automaticity in latent pacemaker fibers
- Development of automaticity in plain atrial or ventricular cells

- Can arise when the maximum diastolic potential becomes reduced
  - to -50 mV and $I_{Ca}$ and $I_K$ may be operative
  - at membrane potentials more negative than -70 mV, due to $I_f$

- Pathophysiologic states: increased catecholamines, electrolyte disturbances (e.g. hypokalemia), hypoxia or ischemia, mechanical stretch, drugs (e.g. digitalis)
Triggered Activity

- Requires the presence of an action potential
- Initiated by *afterdepolarizations* = depolarizing oscillations in membrane voltage induced by preceding AP
  - Early afterdepolarizations (EAD) – arise during phases 2 and 3 of AP
  - Delayed afterdepolarizations (DAD) – arise during phase 4 of AP
- When the after-depolarization reaches threshold, triggers a sequence of pacemaker-like action potentials that generate extrasystoles
EAD

- During a **prolonged AP** (bradycardia, hypokalemia, drugs that block outward K currents etc.) Ca++ channels recover from inactivation and can lead to a spontaneous depolarization.
DAD

- Spontaneous release of Ca++ from SR during Ca++ overload (digitalis intoxication, injury-related cellular depolarization, hyperkalemia etc.) produces a transient inward current, $I_{ti}$
- $I_{ti}$ is a composite current, resulting from
  - Na+/Ca++ exchange current
  - non-specific cation current
that are activated by increased intracellular Ca++ concentration
- When large enough, $I_{ti}$ can produce a spontaneous AP
Conductibility (Dromotropia)

Is the ability to transmit the AP generated by the pacemaker cells in the entire myocardial territory

Follows a well established temporal and spatial pattern, that predetermines the pattern of myocardial contraction
Intracellular Conduction

- The speed of AP propagation along the membrane depends on how fast the membrane gets depolarized → faster propagation in fibers with fast AP
Intercellular Conduction

Branched structure of cardiac muscle

A. GAP-JUNCTION CHANNELS IN APPOISING MEMBRANES
- There are six connexin monomers per gap junction in each membrane.
- A gap junction consists of two connexons, stacked end to end.

B. OPEN AND CLOSED CONFIGURATIONS OF A CONNEXON
- OPEN
- CLOSED

Myosin, Actin, Microfibril, Intercalated disk

Desmosome, Mitochondrion, Gap junction, Z-line

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Intercellular Conduction

- The heart behaves like a sincitium

- Myocardial fibers communicate through gap junctions, provided with a number of hydrophilic membrane channels, named connexons; they allow the passage of ions and of some metabolites with low MW

- The conduction velocity and the direction of propagation of AP in the myocardium depends on the density, the distribution and the activity of gap junctions
- **AV node** – gap junctions are rare, with an unsystematic distribution → low speed of conduction, dispersion of currents

- **Atrial and ventricular myocytes** – dense distribution of gap junctions at the extremities, rare on the sides → higher velocity in the longitudinal direction of the fibers than in the transversal axis = anisotropy

- **Purkinje fibers** – very dense distribution of gap junctions, in all parts of the membrane → very high conduction velocity; nonetheless, the communication with ventricular myocytes occurs only longitudinally
(a) The conducting system of the heart

(b) SA node depolarizes.

(c) Electrical activity goes rapidly to AV node via internodal pathways.

(d) Depolarization spreads more slowly across atria. Conduction slows through AV node.

(e) Depolarization moves rapidly through ventricular conducting system to the apex of the heart.

(f) Depolarization wave spreads upward from the apex.
Conduction Through Various Types of Myocardial Cells

- SAN: < 0.05 m/sec
- AVN: 0.01 - 0.1 m/sec
- Internodal and interatrial anterior pathways: 1 m/sec.
- His bundle, Purkinje fibers: 2 - 4 m/sec
- Atrial and ventricular myocytes 0.3-0.5 m/sec

Transmission of the cardiac impulse through the heart, showing the time of appearance (in fractions of a second after initial appearance at the sinoatrial node) in different parts of the heart.
Organization of the A-V Node

Has three functional regions:

- **Atrio-nodal** (AN), a transitional zone
- **Nodal** (N) - the middle part of the AV node
- **Node-hissian** (NH) region, the nodal fibers gradually merge with the bundle of His

AP characteristics:

- **Long refractory periods** – provides protection against high frequency discharges from A to V during atrial tachyarrhythmia
- **Low conduction velocity** → physiologic delay of about 0.1 - 0.2 s, allows atrial systole to occur before the beginning of ventricular contraction
SP and PSP Influences on Dromotropia

- Parasympathetic stimulation
  - Negative dromotropic effect: ↓ inward Ca current $\rightarrow$ ↓ conduction velocity through AVN

- Sympathetic stimulation
  - Positive dromotropic effect: ↑ inward Ca current $\rightarrow$ ↑ conduction velocity through AVN
Disturbances in AP Conduction through the Heart

- Preexcitation syndrome
- Reentrant arrhythmia
- Blocks
Accessory Conduction Pathways

- Normally, AVN is the only access pathway for the AP towards the ventricle

- When an accessory (aberrant) pathway conducts potential directly from A to V, providing a short circuit around the delay in the AV node → preexcitation syndrome

  - Antegrade conduction occurs over both the accessory pathway and the normal conducting system

  - The accessory pathway, being faster, depolarizes some of the V earlier
Accessory conduction pathways in cases with Wolff–Parkinson–White syndrome.

K, bundle of Kent; J, bundle of James; M, Mahaim fibres; the hatched area represents the atrioventricular border.
When the accessory pathway conducts in a retrograde direction, it can participate in *reentrant tachycardia* (PSVT).
Re-entry

- A re-entrant pathway (re-entrant excitation or circus movement)
  - Is a wave of depolarization that travels in an endless circle
  - Occurs when an action potential loops and results in **self-perpetuating** impulse formation
Re – entrant Excitation

- Re-entry has three requirements:

  1. a *closed* conduction loop,
  2. with *unidirectional conduction*, provided by a region of unidirectional block,
  3. a *sufficiently slow conduction* of action potentials around the loop (relative to the path length and the action potential duration)
• **Unidirectional block**

• Partial conduction block in which impulses travel in one direction, but not in the opposite one.

• May arise as a result of a local depolarization or may be due to pathologic changes in functional anatomy.
NORMAL CONDUCTION THROUGH A BIFURCATION

Impulse arriving

Refractory

Action potentials collide, but cannot pass each other because of refractory period.

Wave of excitation can travel in reverse direction.

RE-ENTRANT EXCITATION

Unidirectional conduction block prevents further transmission.

Unidirectional conduction block allows retrograde transmission.

The system now behaves as an independent (ectopic) pacemaker, with a rate much higher than that of the "originating impulse" (i.e., sinus rhythm).

This is the originating impulse that will set up the re-entrant excitation.
When the pathway isn’t long enough, the head of the re-entrant impulse “bites” its own refractory tail, resulting in extinction of the excitation.

**Pathway Length ≤ APD x Conduction Velocity**

APD – action potential duration
The impulse can continue to travel around a closed loop, causing re-entrant excitation if:

- the **pathway** around the circle is long (dilated hearts)
- the **velocity** of conduction decreases (blockage of the Purkinje system, ischemia, hiperpotasemia etc.)
- the refractory period of the muscle is shortened (short APD) (drugs, such as epinephrine, or after repetitive electrical stimulation)

**Pathway Length > APD x Conduction Velocity**

APD – action potential duration
Blocks

- AV block $\Rightarrow$ delay of conduction between A and V

- Bundle branch blocks
  - Right or left BBB
Synchronization of the Left and Right Ventricular Contraction is important for the efficiency of the ventricular pump.

Normal synchronous activation of the heart
Mechanical Consequences of the Left Bundle Branch Block

1. Initial contraction of VD
   Low pressure

2. LV free wall contraction
   High pressure

RV – LV activation asynchronism
Resynchronization Therapy