Circulatory System and Disorders

Lesson 1

Physiological Properties of Cardiac Muscle

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Overview

1. Cellular Structure of Cardiac Muscle
2. Cardiac Action Potential
    a. Fast response action potentials
    b. Slow response action potentials
3. Action potential and extracellular ion changes
4. Excitation-Contraction Coupling in Cardiac Muscle

Introduction

Cardiac muscle combines features of **skeletal** and **smooth** muscles.

Like skeletal muscle;	Like smooth muscle;
• Striated structure • Myofibrils with repeating sarcomeres • Troponin in its thin filaments, • T-tubules that conduct action potentials • Sarcoplasmic reticulum (SR) terminal cisternae that store Ca^{2+}.	• Involuntary controlled • Small and single nucleated • Layers around hollow cavities • Gap junctions. Functional syncytium. • No motor unit. • Both excitatory and inhibitory nerve stimulation. • Innervated by autonomous nervous system.

Cellular Structure

- Cardiac myocytes are mononuclear.
- Smaller than skeletal muscle cells.
- Their SR is less dense and more primitive.
- Have more connective tissue.
  - Low rupture risk
  - Hard to stretch
- Have much more mitochodria (30% by volume)
  - Dependent to oxidative metabolism.

Cellular Structure

- Adjacent cells are joined end to end at structures called «**intercalated disks**»
  - Desmosomes: holds the cells together, and to which myofibrils are attached.
  - Gap junctions: specialized intercellular connections which conducts ions and electrical impulses.
- «Electrical» and «mechanical» syncytium also known as **functional syncytium.**

Intercalated Disk Structure

- It consists of two different type of connection
  1. Desmosomes: Mechanical
  2. Gap junctions: Electrical

- It creates funtional syncytium.

Cellular Structure

- The heart actually is composed of two syncytiums:
  - the ***atrial syncytium,*** which constitutes the walls of the two atria,
  - the ***ventricular syncytium,*** which constitutes the walls of the two ventricles.

- The atria are separated from the ventricles by fibrous tissue (The ***cardiac skeleton***, also known as the ***fibrous skeleton of the heart***).
  - Potentials are not conducted directly through this fibrous tissue.
  - Atrial and ventricular muscle fibers are seperated from each other.

- Atrial potentials are conducted to ventricle only by way of a specialized conductive system called the ***«bundle of His or A-V bundle».***

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The Action Potential

- Typical action potential curve in nerve and skeletal muscle fibers.
- Consists of three phases:
  - Depolarization
  - Repolarization
  - Hyperpolarization
  - Resting membrane potential

Cardiac Action Potential

- Two main types of action potentials ocur in the heart:
  - Fast response
  - Slow response

Fast vs. Slow

Fast Response	Slow Response
Occurs in atrial and ventricular myocytes and in the specialized conducting fibers (Purkinje)	Occurs in sinoatrial (SA) and atrioventricular (AV) nodes
Have Phase I (Early Repolarization)	Lacks Phase I (Early Repolarization)
Resting Membrane Potential (RMP) is more negative.	RMP is less negative.
Slope of the upstroke (Phase 0) is more steep.	Slope of the upstroke is less steep.
Amplitude of the action potential is bigger.	Amplitude of the action potential is smaller.
Propagation velocity (slope&amplitude) is fast	Propagation velocity (slope&amplitude) is slow

Fast Response Action Potential

- Occurs in atrial and ventricular myocytes, and in the specialized conducting fibers (Purkinje fibers).

- Consists of five phases:
  - **Phase 0:** Depolarization
  - **Phase 1:** Early repolarization
  - **Phase 2:** Plateau
  - **Phase 3:** Final repolarization
  - **Phase 4:** Resting membrane potential

Resting Membrane Potential (Phase 4)

- The resting membrane is much more permeable to K^+ so RMP is much closer to the K^+ equilibrium potential.

1. K^+ efflux (outward K^+ current) is the primary responsible
2. Na^+ - K^+ ATPase also contributes the of RMP continuum.

- V_m (membrane potential) ≈ -90,8 mV in resting.

Potassium Current in RMP

- There are several types of ion channels exist in the cardiac cell membrane:
  1. Channels regulated by V_m (voltage-gated channel)
  2. Channels regulated by a chemical signal (e.g. ACh) (ligand-gated channel)

- The channel which is responsible of the K^+ current in **phase 4** is a voltage-regulated channel called «$\mathbf{i_{k1}}$».

Rapid Depolarization (Phase 0)

- **Voltage-gated** Na^+ channels (i_{Na+}).
- Na^+ entry depolarizes the cell and sustains the opening of more Na^+ channels in positive feedback fashion.
- Treshold ($V_m \approx 65$ mV)
- Opens rapidly (≈0,1 mSec), become inactive rapidly (≈1-2 mSec).
- The sodium channels remain in inactivated state until membrane begins to repolarize (phase 3).

  Open → Inactive → Closed (excitable)

Rapid Depolarization (Phase 0)

- Sodium channels cannot be opened in inactive state.
  - That causes **effective (absolute) refractory period.**
- As the cell repolarizes the inactivated channels begin to transition to **closed** state.
  - This period is called **relative refractory period.**
- When V_m returns to RMP (phase 4) all Na^+ channels returns to **closed** state.

The puffer fish (aka. Fugu)

- **Tetradotoxin**, blocks these type of sodium channels.
- It is 20 time more poisonous than cyanide.

Early Repolarization (Phase 1)

- Phase 1 is represented as a notch between upstroke and plateau.
- Activation of **transient outward current** ($\mathbf{i_{to}}$).
- Density of i_{to} channels defines the <u>height</u> of notch. Prominent in epicardium and Purkinje, negligible in endocardium.
- **4-Aminopyridine** blocks these channels.

- The action potential pattern in different locations of heart
  - Epi = Epicardial
  - Mid = Midmyocardial
  - Endo = Endocardial

- Please discuss the density of i_{to} channels in given locations of the heart.

Plateau (Phase 2)

- Voltage-gated Ca^{2+} channels
  - **L-Type Ca^{2+} channels:** (L=long-lasting)
    - Predominant type.
    - Activated at ≈ +20 mV.
    - Once opened, inactivates slowly and enable a long-lasting Ca^{2+} influx.
    - Blocked by verapamil, amlodipine and diltiazem.
  - **T-Type Ca^{2+} channels:** (T=transient)
    - Much less abundant.
    - Activates at ≈ -70 mV.
    - Rapidly becomes inactive.

Plateau (Phase 2)

- Ca^{2+} influx is counterbalanced by K^{+} efflux during plateau phase.

- i_{to}, i_K, and i_{K1}.
  - i_{to} is not completely inactivated.
  - i_K which is in closed state at phase 4, are activated slowly. Minor effect on phase II
    - $i_{Kr:}$ rapid
    - $i_{Ks:}$ slow
  - i_{K1} and **inward rectification**.

All ionic currents during cardiac action potential

- Inward rectification.
- Is it possible to observe similar changes in other channels with V_m change?

Duration of the Plateau

- Duration of plateu determines the duration of action potential also effects the contraction because of the Ca^{2+} influx.
- Duration of plateau is deterimined by the balance between Ca^{2+} influx and K^{+} efflux.
- i_K current is the main K^{+} current that ends the plateau so distrubition of i_K subtypes is crucial (i_{Kr} and i_{Ks}).
- Ca^{2+} channel antagonists shortens the plateau.

- Effect of diltiazem which is a L-Type Ca^{2+} channel antagonist on action potential (phase 2 duration) and contractile force.
- Different diltiazem concentrations 3, 10 and 30 µmol/L

Final Repolarization (Phase 3)

- K^+ efflux is responsible for final repolarization
- i_K and i_{k1} channels contributes, i_{to} current is inactive
- i_{K1} does not effect the initiation of final repolarization but increases the rate of repolarization.

Resting Membrane Potential (Phase 4)

- Restoration of Ionic Concentrations,
  - Na^+ - K^+ ATPase
  - $3Na^+$ - Ca^{2+} antiporter (NCX)
  - ATP driven Ca^{2+} pumps

Summary

Slow Response Action Potential

- Cells in the SA and AV nodes, exhibit slow-response action potentials.
- Depolarization is achieved by influx of Ca^{++} through **L-type calcium channels** instead of influx of Na^{+} through fast sodium channels.
- Repolarization is accomplished by inactivation of the calcium channels and by the increased K^{+} conductance through the i_{K1} and i_{K} channels.

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Hypo/Hyperkalemia

- Normal Range: 3,5 - 5 mEq/L
- Hypokalemia (Low Potassium)
  - hyperpolarizes cardiac myocytes.
  - may lead to cardiac arrythmias and heart can stop contracting = **asystole**.
- Hyperkalemia (High Potassium)
  - Increases RMP. Gradually inactivates Na^+ channels
  - may lead to cardiac arrythmias and may be fatal
  - Lethal injection

Solid line: Normal; Dashed line: Hyperkalemic

1. RMP is increased.
2. Slope of Phase 0 is less steep. Treshold V_m is increased.
3. The notch of Phase 1 is blunted.
4. Plateu is shortened.
5. Slope of Phase 3 is more steep.

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Excitation-Contraction Coupling

- Cardiac muscle has two different Ca^{++} sources.
  - Extracellular (secondary but trigger) (≈ 30%)
  - Sarcoplasmic (primary) (≈ 70%)
- Cardiac muscle can not contract in the absance of extracellular Ca^{++}(skeletal?).
- Extracellular Ca^{++} serves as a **trigger** for release of Ca^{++} from the SR. **«Ca^{++}-induced Ca^{++} release»**
  - Without it action potential can still be initiated but it is unable to initiate a contraction.

Excitation-Contraction Coupling

- The α_1 subunit of the L-type calcium channel is also called the **dihydropyridine receptor (DHPR).** Isoform of skeletal muscle DHPR.
- Ryanodine receptors (RYRs) in cardiac muscle is **Ca^{++}-gated calcium channels**.
- Excitation-contraction coupling in;
  - cardiac muscle is termed **electrochemical coupling** (Ca^{++}-induced release of Ca^{++}),
  - skeletal muscle is termed **electromechanical coupling** (voltage induced release of Ca^{++}).

Contraction Mechanism

- As in skeletal muscle;
  - Contraction of cardiac muscle is regulated by thin filaments.
  - Elevation in intracellular [Ca^{++}] is necessary to promote actin-myosin interaction.
    - At low (<50 nmol/L) intracellular [Ca^{++}], binding of myosin to actin is blocked by tropomyosin.
    - Troponin, serves as calcium sensor.
    - As long as cytosolic [Ca^{++}] remains elevated, and hence myosin binding sites are exposed, myosin will bind to actin, undergo a ratchet action, and contract the cardiac muscle cell.
  - Cross-bridge cycle is also identical to skeletal muscle.

Contraction Mechanism

- All the cardiac muscle cells are activated during contraction (recall **functional syncytium**).
  - Recruiting more cells is not an option for increasing contractile force.
  - The rise in intracellular [Ca^{++}] can be regulated which affords the heart an important means of modulating the force of contraction.
  - Sympathetic stimulation increases [Ca^{++}] entry, increases contractility. **=(+) inotropy**.
- Cardiac muscle cannot undergo tetanic contraction. Tetany of cardiac muscle cells would prevent any pumping action and thus be fatal.

Tetanic Contraction and Heart

- Action potentials in cardiac muscle are prolonged, lasting 150 to 300 msec,
  - Skeletal muscle (≈5 msec).
- Cardiac muscle cannot undergo tetanic contraction.

Relaxation Mechanism

- For relaxation intracellular [Ca^{++}] should be lowered.
  - In skeletal muscle, **sarcoplasmic endoplasmic reticulum calcium-ATPase (SERCA),** also known as the **SR Ca^{++}pump** simply reaccumulates Ca^{++} inside SR.

- Although SERCA plays a key role in the decrease in cytosolic [Ca^{++}] in cardiac muscle
  - A mechanism must exist to extrude «trigger Ca^{++}»; otherwise, the amount of Ca^{++} in the SR would continuously increase.
  - Some Ca^{++} is extruded from the cardiac muscle cell though the sarcolemmal **$3Na^{+}$-Ca^{++} antiporter (NCX)** and a **sarcolemmal Ca^{++} pump.**

Relaxation Mechanism

- $3Na^{+}$-Ca^{++} antiporter contributes significantly to Ca^{++} extrusion during relaxation.

- The sarcolemmal Ca^{++} pump,
  - is in lower abundance than the $3Na^{+}$-Ca^{++} antiporter
  - has a higher affinity for Ca^{++} (=may bind Ca^{++} in lower Ca^{++} levels)
  - thus may contribute more to the regulation of resting intracellular [Ca^{++}].

Digitalis

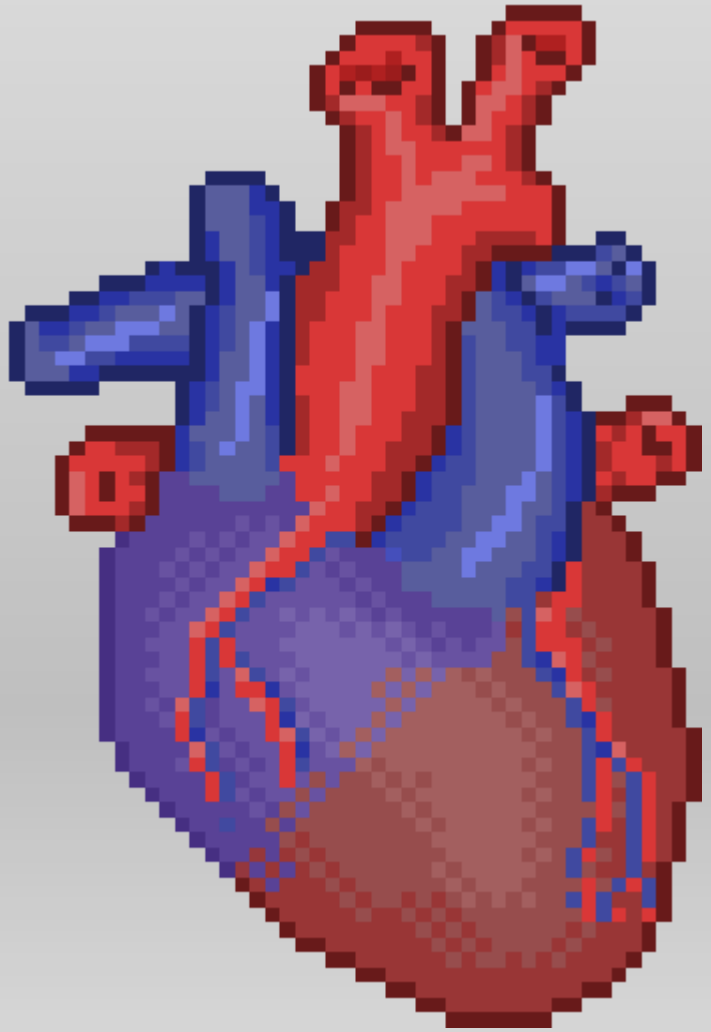
Digitalis purpurea
(Common foxglove)

Portrait of Dr. Gachet, 1890

Action Mechanism of Digitalis

- **Cardiotonic drugs**, such as digitalis, on increases the contractile strength of the cardiac muscle.
- Inhibition of the Na^{+}-K^{+} ATPase increases intracellular sodium concentration and slows the Na^{+}- Ca^{++}- exchange pump.
- Lowered Ca^{++} extrusion would increase contractility.

Hypothesis: Van Gogh had suffered from digitalis-induced xanthopsia (‘Xanthopsia’ is, an overriding yellow bias in vision)



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Thank you for your patience!