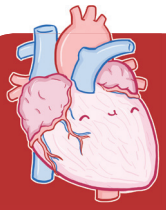

NOTES
CARDIAC ELECTROPHYSIOLOGY

ACTION POTENTIALS IN PACEMAKER CELLS

osms.it/pacemaker-cell-action-potentials

Pacemaker cells
- Groups of cardiac muscle cells with ability to spontaneously create action potential (automaticity) and comprise intrinsic conduction system
- Directly influenced by sympathetic and parasympathetic nervous systems
- Comprise about 1% of heart cells
- Differ in speed of spontaneous depolarization
- Cells with fastest rate of depolarization at any given time determine heart rhythm
  - Remaining/slower cells called latent pacemakers

SA node
- Primary pacemaker cells located in wall of right atrium
- *Rate:* 60–100bpm
  - Usually determines normal heart rhythm

Latent pacemaker cells
- AV node
  - Located at base of right atrium, near septum
  - *Rate:* 40–60bpm
- Bundle of His
  - Divides into right and left bundle branches, travels through septum between ventricles
  - *Rate:* 20–40bpm
- Purkinje fibers
  - Spread throughout ventricles
  - *Rate:* 20–40bpm

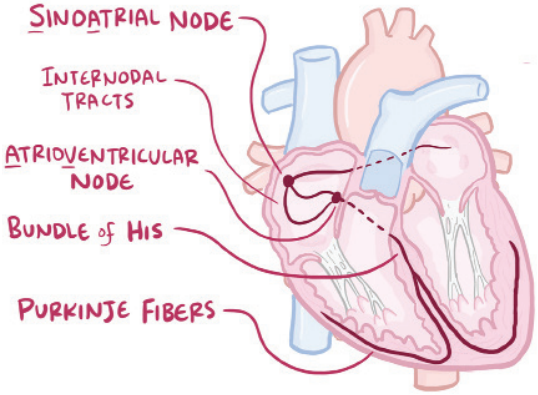

Figure 17.1 Locations of pacemaker cells within the heart.

Action potentials in pacemaker cells
- Rapid electrical changes across membrane of pacemaker cells
- Conducted to rest of heart

Action potential phases
- *Phase 4:* sodium moves into cell through funny channels (open in response to hyperpolarization); slowly depolarizes cell until threshold potential met
  - Responsible for instability of resting membrane potential
- *Phase 0:* strong inward calcium current; responsible for rapid depolarization
- *Phase 3:* strong potassium current moves out of cell; responsible for repolarization
  - Phases 1, 2 absent in pacemaker cells → no plateau

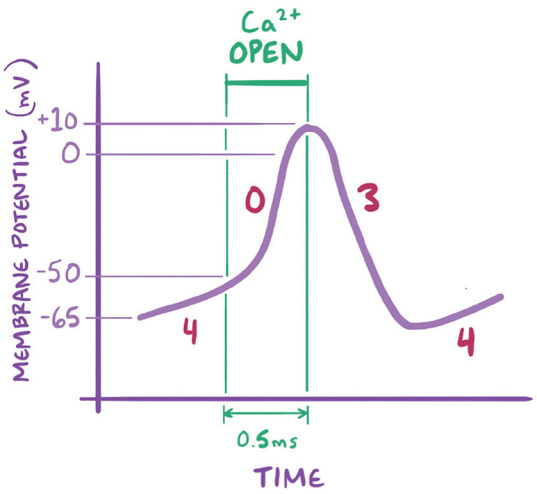

Figure 17.2 Graph depicting the action potential of a pacemaker cell.

ACTION POTENTIALS IN MYOCYTES

osms.it/myocyte-action-potentials

Myocytes

- Receive signal from from pacemaker cells causing them to contract
- Able to depolarize, spread action potentials
- Action potential phases:
  - *Phase 0 (depolarization phase):* rapid influx of sodium into cell (inward current); responsible for rapid depolarization
  - *Phase 1:* sodium current stops, potassium slowly flows out of cell; depolarization stops, re-polarization starts
  - *Phase 2:* calcium current moves into cell, balances potassium current moving out of cell; charge balance between inside, outside of cell creates plateau
  - *Phase 3:* calcium current moving into cell stops; potassium current moving out of cell continues; repolarization continues
  - *Phase 4:* potassium current moving out of cell approaches equilibrium between inside, outside of cell; sodium, calcium current moving into cell balance outward potassium current; resting membrane potential achieved

ELECTRICAL CONDUCTION IN THE HEART

osms.it/heart-electrical-conduction

- Transmission of electrical signals across heart cells leads to rhythmic myocardial contraction
- Intercalated discs connect cells and allow myocardium to act as syncytium
  - Contain desmosomes (holds cells together) and gap junctions (areas of low resistance to electrical flow)
- *Cardiac action potential:* sequential flow of electrons across ion channels in cardiac cell membranes, resulting in electrical activation of myocardial cells
  - *Depolarization:* cation movement into cell, producing positive cell charge relative to outside
  - *Polarization:* anion movement into cell, producing negative cell charge relative to outside
- Pathway of electrical conduction
  - Sinoatrial node (SA node) → atrial internodal fibers → atrioventricular node (AV node) → bundle of His → Purkinje fibers → ventricular myocytes
  - These structures responsible for electrical conduction, spontaneous depolarization; do not generate contractile force

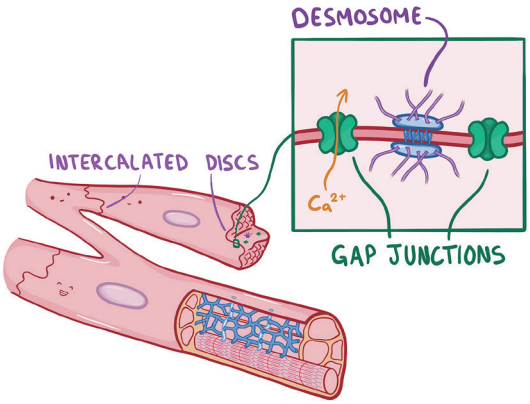

Figure 17.3 Desmosomes and gap junctions present at intercalated discs allow the myocardium to act as a syncytium.

CARDIAC CONDUCTION VELOCITY

osms.it/cardiac-conduction-velocity

- Speed at which depolarization wave spreads among myocardial cells
  - Measured in meters per second (m/s)
- Each myocardial structure has a different conduction speed related to its purpose
  - *Slowest:* AV node
  - *Fastest:* Purkinje fibers
- *AV delay:* slow conduction through AV node ensures adequate ventricular filling
  - *Speed:* 0.01–0.05m/s
  - Blood flows from atria to ventricles
- Rapid conduction through Purkinje fibers ensures adequate blood ejection
  - *Speed:* 2–4m/s

Velocity depends on two factors

- Amount of ions going into cell during action potential
  - More ions → faster depolarization → faster spread
  - Fewer ions → slower depolarization → slower spread

- Interconnectedness of myocardial conduction cells
  - More gap junctions → more interconnected cells → less resistance to ion flow between cells
  - Fewer gap junctions → fewer interconnected cells → increased resistance to ion flow between cells

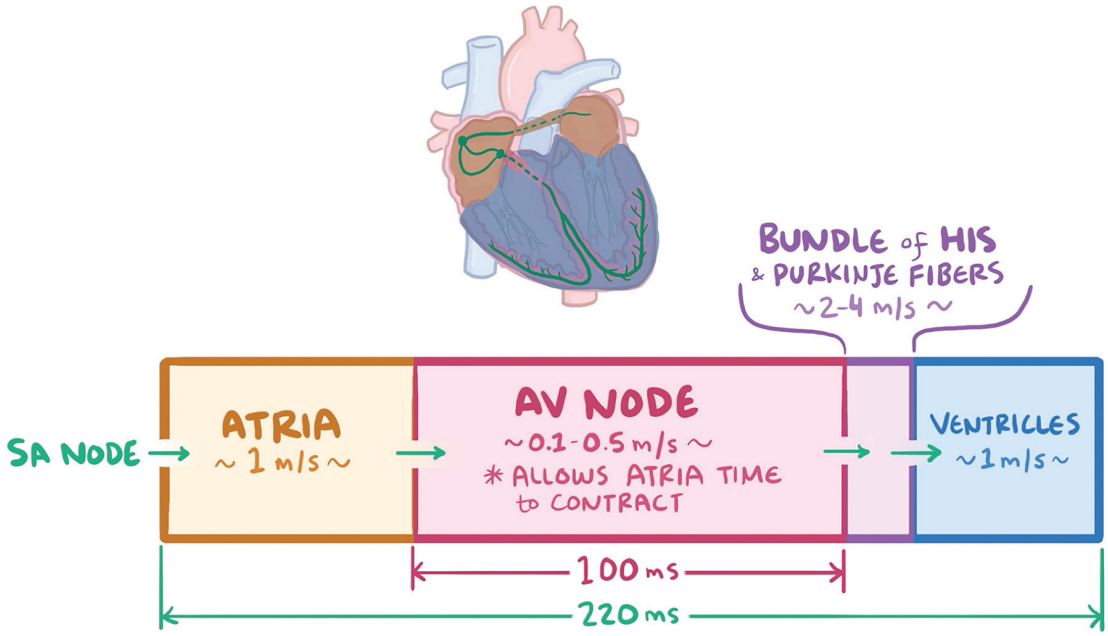

Figure 17.4 Conduction speeds of different myocardial structures.

EXCITABILITY & REFRACTORY PERIODS

osms.it/excitability-refractory-periods

Refractory period

- Time in which myocardial cell cannot be depolarized
- *Absolute refractory period:* no stimulus, no matter its size, can depolarize cell
  - Phases 0, 1; part of phase 2
- *Effective refractory period:* large stimulus can generate action potential
  - However, too weak to be conducted
- *Relative refractory period:* large stimulus can generate action potential
  - Big enough to be conducted

Excitability

- Ability of myocardial cells to depolarize in response to incoming depolarizing current
- *Supranormal period:* < normal stimulus may produce action potential large enough to be conducted
  - Resting membrane potential has not yet been achieved
  - Membrane potential closer to threshold than normal, refractory periods over

CARDIAC EXCITATION-CONTRACTION COUPLING

osms.it/cardiac_excitation-contraction_coupling

- Plateau in action potential of myocyte membrane allows influx of calcium, stimulating muscle contraction
  - Calcium enters cell via L-type voltage gated channels
  - Higher intracellular Ca^{2+} triggers release of more Ca^{2+} from sarcoplasmic reticulum through ryanodine receptors (AKA calcium-induced release)
  - Released Ca^{2+} attaches to troponin C → tropomyosin moves → actin-myosin cross bridges → contraction
- Cross bridges last as long as Ca^{2+} occupies troponin
  - Tension is proportional to intracellular Ca^{2+} concentration
- Intracellular Ca^{2+} removed by two mechanisms that induce relaxation, keep Ca^{2+} from damaging cell contents
  - Ca^{2+} ATPase uses ATP energy, Na^+/Ca^{2+} ATP exchanger uses Na^+ inward current to remove Ca^{2+} from cell through sarcolemmal membrane, remove Na^+ through Na^+/K^+ ATPase
  - Ca^{2+} ATPase removes Ca^{2+} into sarcoplasmic reticulum; calsequestrin 2 inside sarcoplasmic reticulum binds Ca^{2+}, keeping it inside

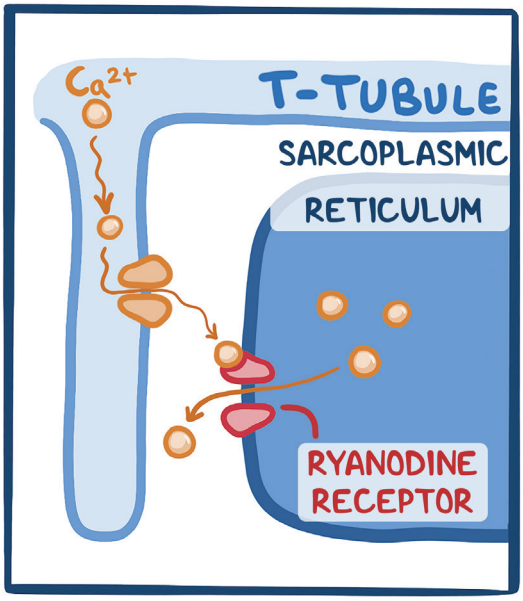

Figure 17.5 Depolarization of a cardiomyocyte by calcium-induced calcium release.

CARDIAC LENGTH TENSION

osms.it/cardiac-length-tension

- Degree filament overlap correlates to tension
  - L_{max} = 2.2 μm is maximal tension
  - In shorter/longer cells, tension will be decreased
- ↑ L → ↑ Ca^{2+} sensitivity of troponin C → ↑ Ca^{2+} release from sarcoplasmic reticulum
- Can extend to ventricle length/tension relationship curve
  - Cardiac muscle < elastic than skeletal; only ascending curve demonstrates its contraction
- ↑ *resting tension:* small changes produce ↑ tension
- Frank–Starling basis; ↑ fiber length → stronger contraction
  - Preload = LV end-diastolic volume (L), if ↑ means ventricular fiber length ↑
  - Afterload = aortic pressure; if preload ↑ → afterload tension and pressure ↑

CARDIAC CONTRACTILITY

osms.it/cardiac-contractility

- *Positive inotropes:* ↑ force of myocardial contraction
- *Negative inotropes:* ↓ force of myocardial contraction
- Proportional to Ca^{2+} concentration
  - Proportional to Ca^{2+} released
  - Depends on storage, current size

WHAT AFFECTS INOTROPISM? – AUTONOMIC NERVOUS SYSTEM

Sympathetic

- *Positive inotropic effects:* ↑ contractility
- Causes faster relaxation, faster refill, increased heart rate (HR)
- Increased tension development rate
  - β1 receptor is G_s coupled, activates adenylyl cyclase → cAMP produced
  - pKA activated → phosphorylation → ↑ sarcolemmal Ca^{2+} channel activity → ↑ contraction
  - Phospholamban phosphorylation; stops sarcoplasmic Ca^{2+} ATPase inhibition, decreasing time of IC Ca^{2+}, making HR faster, systole shorter; Frank–Starling effective
  - Na^+/K^+ ATPase phosphorylation; increases relaxation due to secondary channel activations
  - Troponin I phosphorylation; Ca^{2+} binds less troponin C → effect on excitation contraction coupling, prolongs filling, higher ejection fraction

Parasympathetic

- *Negative inotropic effects:* ↓ contractility on atria via muscarinic receptors
- Acidosis also has negative inotropic effect → ↓ contractility
- G_k (type of G_i), adenylyl cyclase couple, resulting in
  - Decreased Ca^{2+} plateau current
  - ACh increases I_{kACh}
  - → ↓ action potential duration → ↓ Ca^{2+} current → ↓ AP width
- Phosphodiesterase metabolises cAMP, inhibit phosphodiesterase, increase contractility IP3 stimulates Ca release in SR, increases force of contraction

Heart rate (HR)

- HR increases contractility
- Diastole affected more than systole
- Ca can't be removed as quickly as it accumulates → new equilibrium
  - ↑ *action potentials/time:* increased total trigger Ca^{2+}, increased inward current
  - ↑ Ca^{2+} influx → ↑ stores; phospholamban phosphorylated, thus inhibited
- Positive staircase effect/Bowditch staircase/Treppe phenomenon
  - On first, beat still no extra Ca^{2+}
  - Afterward, Ca^{2+} accumulates until max Ca^{2+} storage achieved
- Postextrasystolic potentiation
  - Same effect as positive staircase
  - Extrasystole < powerful, but creates one more chance for calcium entry
  - Because the voltage channels are open more, postextrasystolic beat has higher tension than extrasystolic

WHAT AFFECTS INOTROPISM? – DRUGS

Cardiac glycosides

- Digoxin, digitoxin, ouabain; congestive heart failure treatment
  - Inhibit Na^+/K^+ ATPase; + inotropic, ↑ intracellular Na^+ changes Na/Ca → decreases exchange → intracellular calcium increases → increases tension
  - Nifedipine also acts on Ca^{2+} by blocking ryanodine receptors

Beta adrenergics

- Isoproterenol, norepinephrine, epinephrine, dopamine, dobutamine
  - ↑ cAMP → ↑ contractility