How do arrhythmias occur?

- An arrhythmia is an abnormal heart rhythm (= dysrhythmia). Can be fast (tachy) or slow (brady). Brady arrhythmias are usually due to conduction block, while tachyarrhythmias are due to:
  1. Automaticity (= sinus node dysfunction - less than 10%)
  2. Delayed after-depolarization (DAD, phase 4), and EAD (during phases 2, 3) leads to abnormal pacemaker activity
  3. Re-entry
- Occur during late phase 3 or phase 4 when the action potential is nearly or fully repolarized.
- Associated with high intracellular Ca.
- Triggered impulse can lead to a series of rapid depolarizations.

- Occur during late phase 2 or phase 3.
- Can lead to several rapid action potentials or a prolonged series of action potentials.
- Often associated with an increase in action potential duration.
**DAD at the cellular level and on the ECG**

- A small depolarization during diastole caused by intracellular Ca release from stores, which activates inward membrane currents. Depolarization reaches threshold ➔ action potential.
- On the 12-lead ECG a single normal beat is followed by three extra beats, initiated late after the T-wave.
EADs can cause tachyarrhythmias

- A small depolarization during systole, a reactivation of Ca currents, again caused by leads to repetitive fast potential oscillations

On the 12-lead ECG a normal beat is followed by multiple fast rhythms, initiated on the T-wave.
Re-entry

NORMAL CONDUCTION THROUGH A BIFURCATION

Unidirectional conduction block prevents further transmission.

RE-ENTRANT EXCITATION

1. This is the originating impulse that will set up the re-entrant excitation.

2. Unidirectional conduction block allows retrograde transmission.

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

4. No longer refractory

5. Still refractory

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

Wave of excitation can travel in reverse direction.
Re-entry

• Caused by transient or unidirectional block (i.e. clot), usually in diseased tissues.
• Probably the cause of many arrhythmias.
• Can occur in atria, ventricles and nodal tissue.
• AP’s conducted only one-way, but conduction is slower.
• Causes a constant loop of AP’s re-exciting repeatedly (Circus Rhythm).
• The tissue begins to beat independently of input.
Ventricular tachycardia

Rate > 120 beats/min. Rapid, bizarre, wide QRS complexes

- Slowed conduction in margin of ischemic area permits circular course of impulse and reentry with rapid repetitive depolarization

Infarct
Types of tachyarrhythmias (not an exhaustive list!)

- **Supraventricular tachycardia** – no more than 200 beats per min. Trivial compared to the other types, but dangerous if spreads from atria to ventricles.
- **Atrial flutter** – atria beat rapidly and regularly at 250-350 beats per min. Ventricles at half the rate.
- **Atrial fibrillation** – up to 500 beats per min. Irregular, uncoordinated contractions, fragmentary, ventricles beat at 100-200 beats per min, but not regularly.
- **Ventricular tachycardia** – a series of rapid beats 120 to 200 beats per min. A series of contractions called ventricular extrasystoles.
- **Ventricular fibrillation** – immediate cause of death, disordered electrical activity, electrical uncoupling of cells. Ventricles fail to pump in a coordinated manner, so cardiac output stops.
Two ways to stop re-entrant arrhythmias

B. Short excitable gap. Vulnerable Parameter = refractoriness.

Mechanistic approach: $I_{\text{Na}}$ block (long excitable gap) to prevent conduction; $I_{\text{Kr}}$ block to prolong refractoriness (short excitable gap).

Drugs Controlling Myocyte Excitability and Conduction at the AV node

Singh and Vaughan-Williams Classification

Class I
Na Channel Blockers
Flecainide
Propafenone

Class II
Beta Blockers
Propranolol
Metoprolol

Class III
K channel Blockers
Dofetilide, Dronedarone, Amiodarone

Class IV
Other
Digoxin

Class VI
Ca Channel Blockers
Diltiazem
How is Afib, the arrhythmia, treated?

• Not treated
  – For benign and mild (asymptomatic) the therapeutic risk is greater than the disease burden

• Electric shock – Electrical cardioversion
  – Brief external shocks to synchronize heart beat
    • Effective and safe, but expensive: requires fasting, sedation, delay and unpleasant to patient

• Ablation and surgery – particularly for pts refractory to medication
  – Catheter with RF heater in tip to ablate hyper-excitable areas and abnormal conduction pathways especially near the insertion of the pulmonary veins
    • Pulmonary vein ablation may be a cure –highly effective
    • But: expensive, efficacy may not persist, side-effects, irreversible
    • Maze procedure, multiple cross cuts across the atrium
    • AV node ablation and pacemaker insertion as a last resort
Two Strategies for Drugs Directly Treating Afib after anticoagulation

• **Rate Control**
  – Do not convert to sinus rhythm but reduce morbidity and mortality from tachycardia.

• **Adenosine (i.v.)** – acts on $A_1$ receptor in AV node. Receptor linked to cardiac $K^+$ channel ($K_{ACh}$). Thus, adenosine causes hyperpolarisation and slows rate of rise of pacemaker potential.

• **Cardiac glycosides e.g. digoxin. vagomimetic**– also increase force of contraction.
  1. Digitalis prolongs AV refractory period by releasing ACh from vagus.
  2. Causes 2:1 AV block.
  3. Eventually AV dissociation leads to safer ventricular rate.
Rate Control (oral)

Beta Blockers (Beta adrenergic receptor)
- *Propranolol and Metoprolol*
- Blocks action of noradrenaline released from sympathetic NS

Ca Channel blockers…..(why?)
- *Verapamil, Diltiazem*
  - Ca channels…..

Cardiac Glycosides
- *Digitalis* (as prev slide)
Two Strategies for Drugs Directly Treating AFib

• **Rhythm Control**
  – True antiarrhythmic drugs – designed to restore sinus rhythm by affecting ion channels during the action potential
  – Na channel blockers
    • *Flecainide* and *propafenone*
    • Inhibits……
  – K channel blockers
    • *Dofetilide*,
    • Inhibits……
  – Multi ion channel blockers
    • *Amiodarone* and *dronedarone*
    • All-in-one Na, K, Ca and beta blockers (has rate control properties)
    • *Vernakalant*, Na and K channel blocker
# Antiarrhythmic Drugs

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