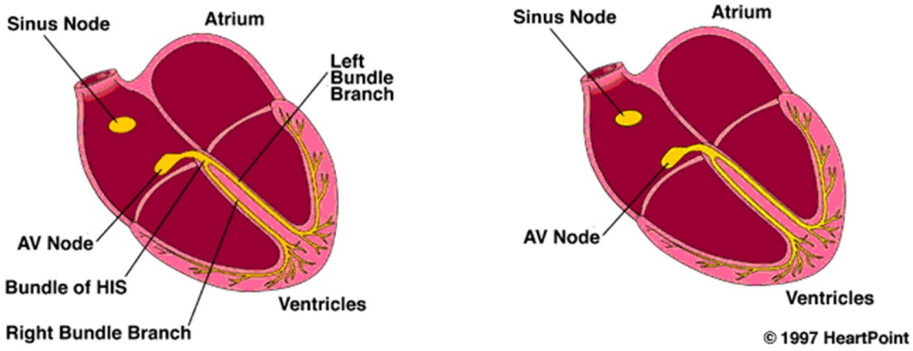
ADVANCED PHARMACOTHERAPUETICS
GUIDED LECTURE NOTES
CARDIAC: ARRHYTHMIAS

1. Arrhythmias Pharmacotherapy
   a. Core Concepts
      i. to function efficiently, heart needs to contract sequentially (atria, then ventricles) and in synchronicity
      ii. Relaxation must occur between contractions (not true for other types of muscle (exhibit tetany → contract and hold contraction for certain length of time)
      iii. Coordination of heartbeat is a result of a complex, coordinated sequence of changes in membrane potentials and electrical discharges in various heart tissues
   b. Arrhythmia is a heart condition where disturbances in
      i. Pacemaker impulse formation
      ii. Contraction impulse conduction
      iii. Combination of the two
         1) Results in rate and/or timing of contraction of heart muscle that is insufficient to maintain normal cardiac output (CO)

2. To understand how antiarrhythmic drugs work, need to understand electrophysiology of normal contraction of heart

   a. Normal heartbeat and atrial arrhythmia



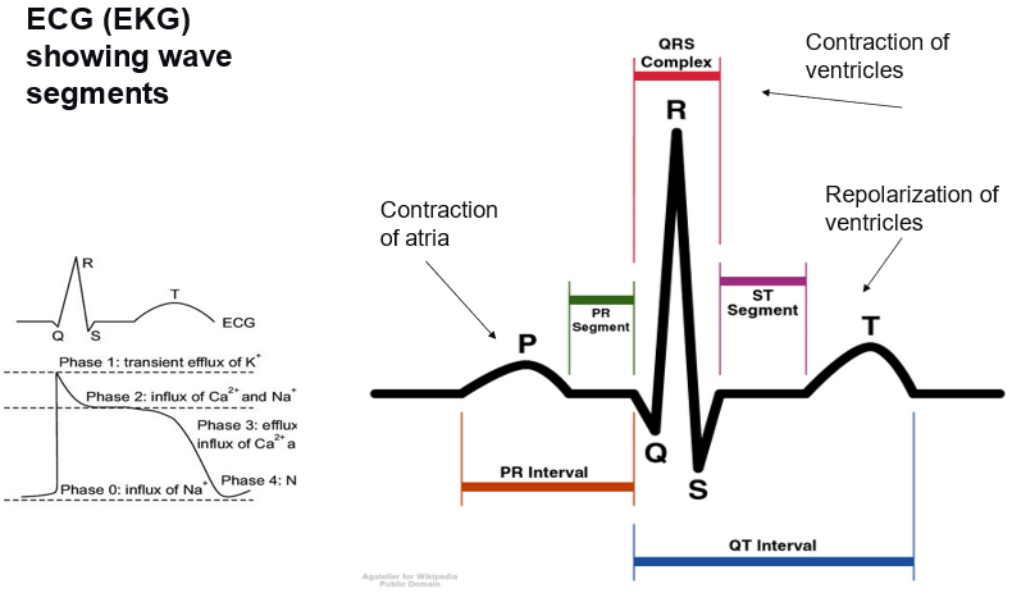
   b. Ventricular Arrhythmia
      i. Ventricular arrhythmias are common in most people and are usually not a problem but…

      ii. VA's are most common cause of sudden death

3. Majority of sudden death occurs in people with neither a previously known heart disease nor history of VA's

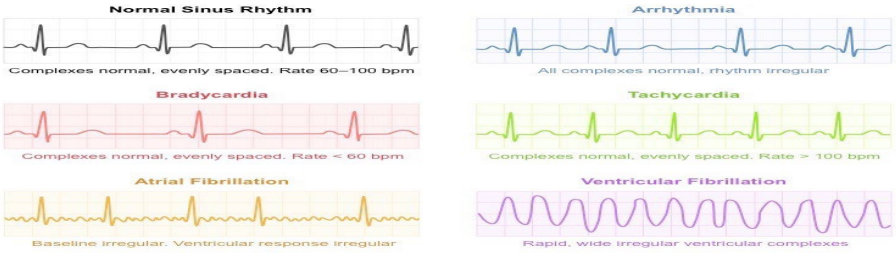
4. Medications which decrease incidence of VA's do not decrease (and may increase) the risk of sudden death >>> treatment may be worse than the disease!

5. Electrophysiology - resting potential
   a. A transmembrane electrical gradient (potential) is maintained, with the interior of the cell negative with respect to outside the cell



   b. Caused by unequal distribution of ions inside vs. outside cell
   c. Na+ higher outside than inside cell
   d. Ca+ much higher " " " "

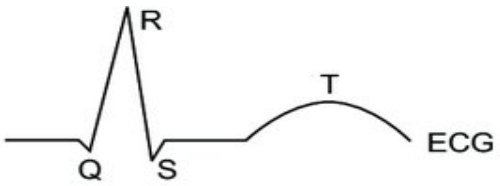
Types of arrhythmias	
PAC's	Bradyarrhythmias
PVC's	Tachyarrhythmias
Afib/flutter	Sinus node dysfunction
PSVT	Long QT syndrome
VFIb/Vtach	AV nodal re-entry tachycardia



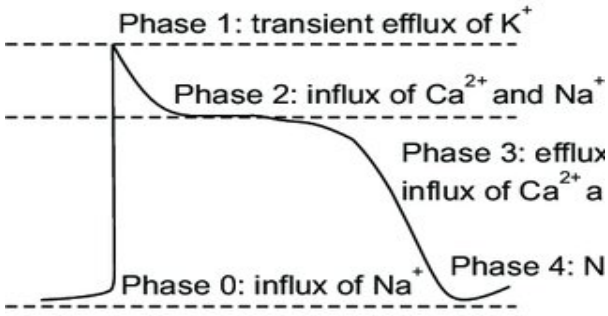
e. K+ higher inside cell than outside

6. Maintenance by ion selective channels, active pumps and exchangers

7. Differences between non- pacemaker and pacemaker cell action potentials
   a. Pacemaker Cells - Slow, continuous depolarization during rest
   b. Continuously moves potential towards threshold for a new action potential (called a phase 4 depolarization)



8. Cardiac Action Potential Divided into five phases (0,1,2,3,4)



   a. Phase 4 - resting phase (resting membrane potential)
      i. Phase cardiac cells remain in until stimulated
      ii. Associated with diastole portion of heart cycle
      iii. Addition of current into cardiac muscle (stimulation) causes:

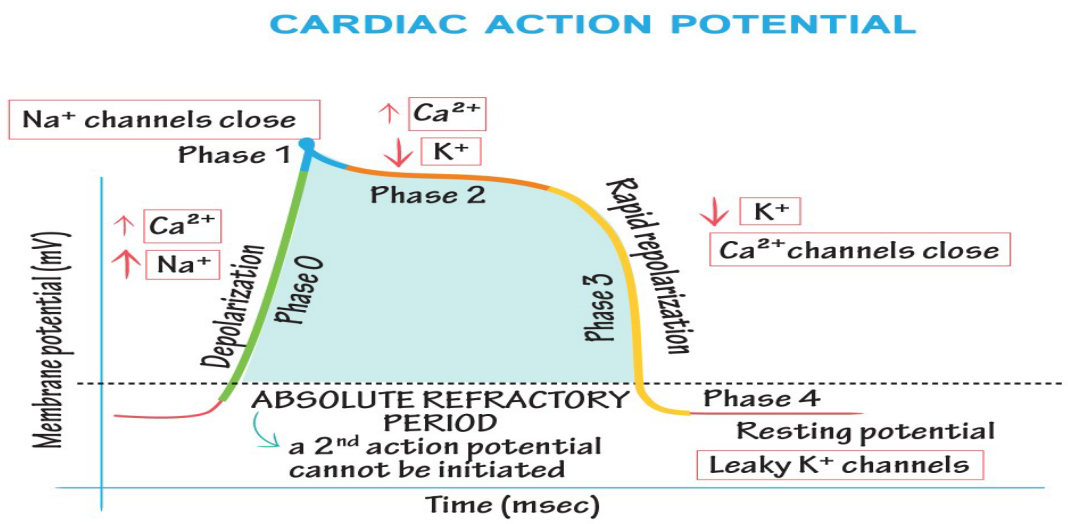
   b. Phase 0 – opening of fast Na channels and rapid depolarization
      i. Drives Na+ into cell (inward current), changing membrane potential
      ii. Transient outward current due to movement of Cl- and K+

   c. Phase 1 – initial rapid repolarization
      i. Closure of the fast Na+ channels
      ii. Phase 0 and 1 together correspond to the R and S waves of the ECG
      iii. Cardiac Na+ channels

   d. Phase 2 - plateau phase
      i. sustained by the balance between the inward movement of Ca+ and outward movement of K +
      ii. Has a long duration compared to other nerve and muscle tissue
      iii. Normally blocks any premature stimulator signals (other muscle tissue can accept additional stimulation and increase contractility in a summation effect)
      iv. Corresponds to ST segment of the ECG.

   e. Phase 3 – repolarization
      i. K+ channels remain open,
      ii. Allows K+ to build up outside the cell, causing the cell to repolarize

iii. K + channels finally close when membrane potential reaches certain level
iv. Corresponds to T wave on the ECG



9. Mechanisms of Cardiac Arrhythmias

    a. Result from disorders of impulse formation, conduction, or both

    b. Causes of arrhythmias

        i. Cardiac ischemia

        ii. Excessive discharge or sensitivity to autonomic transmitters

        iii. Exposure to toxic substances

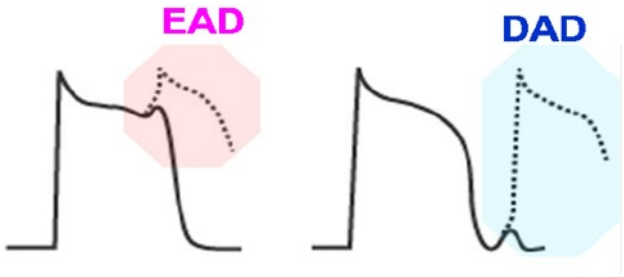
        iv. Unknown etiology

10. Disorders of impulse formation
    a. No signal from the pacemaker site

11. Development of an ectopic pacemaker
    a. May arise from conduction cells (most are capable of spontaneous activity)
    b. Usually under control of SA node if it slows down too much conduction cells could become dominant
    c. Often a result of other injury (ischemia, hypoxia)

12. Development of oscillatory afterdepolarizations
    a. Can initiate spontaneous activity in nonpacemaker tissue
    b. May be result of drugs (digitalis, norepinephrine) used to treat other cardio pathologieS

13. After depolarizations



14. Disorders of impulse conduction
    a. May result in
        i. Bradycardia (if have AV block)
        ii. Tachycardia (if reentrant circuit occurs)

15. Antiarrhythmic drugs
    a. Biggest problem – antiarrhythmics can cause arrhythmia!

    b. Example: Treatment of a non-life-threatening tachycardia may cause fatal ventricular arrhythmia

    c. Must be vigilant in determining dosing, blood levels, and in follow-up when prescribing antiarrhythmics

16. Atrial Fibrillation
    a. Chaotic and irregular atrial arrhythmia, the prevalence of which increases progressively with age

17. Treatment strategy
    a. depends on the severity of symptoms
    b. duration of AF
    c. presence of comorbid conditions
    d. Treatment involves correction of the abnormal rate, or rate plus rhythm, along with anticoagulation in high-risk patients.

18. RATE CONTROL VS. RHYTHM CONTROL

    a. Pharmacotherapeutics
    b. utilizing beta-blockers, calcium blockers, digoxin, anti-arrhythmic agents

c. ablation therapy (catheter-based or surgical)
d. pulmonary vein isolation and left atrial substrate modification, pacemakers, and ablation of the atrioventricular node need to be weighed

e. based on multiple clinical factors to optimize patient outcome

19. Acute Afib management
    a. 3 areas of management of new-onset AF are:
        1) Ventricular rate control
        2) Restoration and maintenance of sinus rhythm
        3) Prevention of thromboembolic events

20. Management of new-onset AF depends on:
    a. Nature of its presentation
    b. Most cases revert within 24 hours
    c. Will still need antiarrhythmic drugs
    d. **urgency of the treatment required should be assessed on case by case

21. CHADsVas Risk

22. Preferred treatments
    a. Beta-blockers
        i. new-onset AF is associated with an acute myocardial infarction or angina
        ii. new-onset AF is precipitated after exercise
        iii. Esmolol
        iv. use in patients with beta blockade complications:
        v. reactive airway disease
        vi. left ventricular dysfunction
        vii. peripheral vascular disease

23. CCBs are preferred
    a. chronic lung disease where bronchospasm may occur with beta-blockers

24. Preferred treatments
    a. Beta-blockers and calcium-channel blockers (CCBs)
    b. slow AV nodal conduction of cardiac impulses=subsequently reduce ventricular rate

    c. Both groups of medications may cause hypotension, severe bradycardia, heart failure or heart block, asystole

    d. If rate control is inadequate with monotherapy, a combination of a beta-blocker and CCB may be used.

25. CHA2DS2-VASc score 0-1
    a. observation
    b. rate control with beta-blocker and/or calcium-channel blocker
        i. electrical or pharmacologic cardioversion

26. CHA2DS2-VASc score ≥2
    a. anticoagulation
    b. observation
    c. rate control with beta-blocker and/or calcium-channel blocker
    d. electrical or pharmacologic cardioversion

27. Chronic Afib

    a. 3 core areas in the management of chronic AF are:
        i. Ventricular rate control
        ii. Restoration and maintenance of sinus rhythm
        iii. Prevention of thromboembolic events

    b. GOT: alleviate symptoms, prevent tachycardia-induced cardiomyopathy and thromboembolic events and improve quality of life

28. Anticoagulation in Afib
    a. Should the patient be anticoagulated?
    b. If yes, which anticoagulant will be used?
    c. How should the oral anticoagulants be initiated?

29. Moderate to high risk =anticoagulation
    a. CHA2Ds2VAsc level >2

30. Low to minimal risk = case by case, may anti-coagulate some patients
    a. RISK/BENEFIT analysis

    b. ***annual risk of ischemic stroke in untreated patients was 0.2, 0.6, and 2.2 percent for those with CHA2DS2-VASc scores of 0, 1, and 2

31. Therapeutic overview Antiarrhythmic Agents

    a. Na+ channel blockade
    b. β-adrenergic receptor blockade

c. Prolong repolarization
d. Ca2+ channel blockade
e. Adenosine
f. Digitalis glycosides

Antiarrhythmic Agents

I. Membranes stabilizing agents (sodium channel blockers)	A. Quinidine, procainimide, disopyramide B. Lidocaine, phenytoin C. Encainide, lorcainide, flecainide
II. Beta blockers	Propranolol, metoprolol, sotalolol, and others
III. Agents which prolong duration of the action potential (potassium channel blockers)	Amiodarone, bretylium
IV. Calcium channel blockers	Verapamil, diltiazem, bepridil

32. Drugs for Arrhythmias (your role in Primary Care)
    a. Ideally in primary care setting consult with cardiology team
    b. Pharmacological management of arrhythmias requires an office that is prepared, ready, and able to handle emergencies.
    c. You will see these patients for infections, depression, anemia, fatigue, etc.

    d. Be aware of action and adverse drug potentials.

33. For All Antiarrhythmics
    a. Monitoring
    b. Potassium, blood urea nitrogen (BUN), creatinine, therapeutic drug levels
    c. Electrocardiogram

    d. Patient education
    e. Take exactly as prescribed, do not double doses.
    f. Be aware of food and drug interactions.
    g. Monitor HR for regularity of rate and rhythm.
    h. Monitor BP at home.

34. Classification of antiarrhythmics (based on mechanisms of action)

35. Class I – blockers of fast Na+ channels
36. Subclass IA
    a. Cause moderate Phase 0 depression
    b. Prolong repolarization
    c. Increased duration of action potential
37. Includes
    a. Quinidine – 1st antiarrhythmic used, treat both atrial and ventricular arrhythmias, increases refractory period
    b. Procainamide - increases refractory period but side effects
    c. Disopyramide – extended duration of action, used only for treating ventricular arrhythmias

38. Classification of antiarrhythmics (based on mechanisms of action)
    a. Subclass IB
        i. Weak Phase 0 depression
        ii. Shortened depolarization
        iii. Decreased action potential duration
    b. Includes
        i. Lidocaine (also acts as local anesthetic) – blocks Na+ channels mostly in ventricular cells, also good for digitalis-associated arrhythmias
        ii. Mexiletine - oral lidocaine derivative, similar activity
        iii. Phenytoin – anticonvulsant that also works as antiarrhythmic similar to lidocaine

39. Classification of antiarrhythmics (based on mechanisms of action)
    a. Subclass IC
        i. Strong Phase 0 depression
        ii. No effect of depolarization
        iii. No effect on action potential duration

    b. Includes
        i. Flecainide (initially developed as a local anesthetic)
            1) Slows conduction in all parts of heart
            2) Also inhibits abnormal automaticity
        ii. Propafenone
            1) Also slows conduction
            2) Weak β – blocker
            3) Also some Ca2+ channel blockade

40. Classification of antiarrhythmics (based on mechanisms of action)

a. Class II – β–adrenergic blockers
    i. Based on two major actions
        1) blockade of myocardial β–adrenergic receptors
        2) Direct membrane-stabilizing effects related to Na+ channel blockade

b. Includes
    i. Propranolol
    ii. causes both myocardial β–adrenergic blockade and membrane-stabilizing effects
    iii. Slows SA node and ectopic pacemaking
    iv. Can block arrhythmias induced by exercise or apprehension
    v. Other β–adrenergic blockers have similar therapeutic effect

c. Metoprolol/Nadolol/Atenolol/Acebutolol/Pindolol/Stadalol/Timolol/Esmolol

41. Classification of antiarrhythmics (based on mechanisms of action)
    a. Class III – K+ channel blockers
        i. Developed because some patients negatively sensitive to Na channel blockers (they died!)
        ii. Cause delay in repolarization and prolonged refractory period
    b. Includes
        i. Amiodarone – prolongs action potential by delaying K+ efflux but many other effects characteristic of other classes
        ii. Ibutilide – slows inward movement of Na+ in addition to delaying K + influx.
        iii. Bretylium – first developed to treat hypertension but found to also suppress ventricular fibrillation associated with myocardial infarction
        iv. Dofetilide - prolongs action potential by delaying K+ efflux with no other effects

42. Classification of antiarrhythmics (based on mechanisms of action)
    a. Class IV – Ca2+ channel blockers
    b. slow rate of AV-conduction in patients with atrial fibrillation

    c. Includes
        i. Verapamil – blocks Na+ channels in addition to Ca2+; also slows SA node in tachycardia
        ii. Diltiazem

43. Amiodarone/CODORONE
    i. Mechanism of Action
    prolongs action potential phase 3 (class III antiarrhythmic)

ii. Metabolism: liver extensively; CYP450: 2C8, 3A4 substrate; Info: active metabolite
iii. Excretion: bile primarily
iv. Half-life: 58 days (22-100 days)
v. Note: variable, slow elimination from plasma/tissues

vi. Baseline Parameters
1) LFTs
2) TFTs at baseline, then periodically
3) chest x-ray- PFTs incl. diffusion capacity at baseline, then q3-6mo;
4) BP; ECG;
5) Electrolytes
6) funduscopy, slit-lamp

44. BLACK BOX WARNING
i. Appropriate Use: restrict use to indicated life-threatening arrhythmias due to drug-assoc. toxicity
ii. Pulmonary Toxicity: Hypersensitivity pneumonitis or interstitial/alveolar pneumonitis
iii. Hepatotoxicity: common but usually mild w/ only elev. LFTs; overt hepatic failure can occur w/ few fatal cases
iv. Proarrhythmic Effects: arrhythmias worsened, significant heart block, or sinus bradycardia

b. Common ADR's
i. nausea, vomiting, constipation
ii. numbness or tingling; tremors
iii. loss of coordination, feeling weak or tired
iv. dizziness, vision problems, optic neuritis

c. Severe reactions:
i. Severe bradycardia; AV block
ii. QT prolongation; torsade's de pointes
iii. ventricular arrhythmia exacerbation or new onset
iv. CHF
v. May cause issues with
vi. abnormal liver function tests
vii. TFTs resulting in hypo or hyperthyroidism

Resources

Various sources are paraphrased and combined to provide most up to date information

Arcangelo. (2020). Pharmacotherapeutics for Advanced Practice – 4th ed.
Dipiro, T., & Talbert, R. (2019). Pharmacotherapy-A pathophysiological Approach 10th ed.
Epocrates (various topics)
FamilyPracticeNotebook.com (various topics)
Up to date (various topics)
Woo, T., & Wynne, A. (2021). Pharmacotherapeutics for Nurse practitioner Prescribers -5th ed.