Patient Safety: Drug Induced Cardiovascular Disease

C. Michael White, Pharm.D., FCP, FCCP
Distinguished Professor and Chair, Pharmacy Practice
UConn School of Pharmacy

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Disclosures:

- Dr White has received no funding from any company that makes any of the drugs covered in this presentation and is not an individual stock owner for any of the companies either. He does not have any financial or nonfinancial conflicts of interest germane to this presentation. In addition, he will be discussing drug adverse events which are aligned with those already denoted in the drugs package inserts, albeit in much greter depth. He will not be talking about investigational drugs or the off-label use of drugs.

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Objectives

At the conclusion of this lecture the successful learner will be able to:

- Identify heart block
- Differentiate between 1st, type-1 2nd, type-2 2nd, and 3rd degree AV block
- Describe the drugs and dietary supplements that can cause heart block and what to do if drug induced heart block occurs acutely and chronically
- Identify QTc interval prolongation and describe how much of an elevation dramatically enhances the risk of Torsade de Pointes
- Describe drugs and dietary supplements that may prolong QTc interval and interventions for acute Torsade de Pointes or chronic QTc interval prolongation
- Apply knowledge to a patient relevant case

This entire lecture is based on the following book chapter:
White CM, **Kalus J. Cardiac Arrhythmias, Chapter 20.** In: Alldredge BK, Corelli RL, Ernst ME (Eds). Applied Therapeutics: The Clinical Use of Drugs. 11th Edition. Lippincott Williams & Wilkins, NY, NY. 2021 pg. 20.1-20.35.

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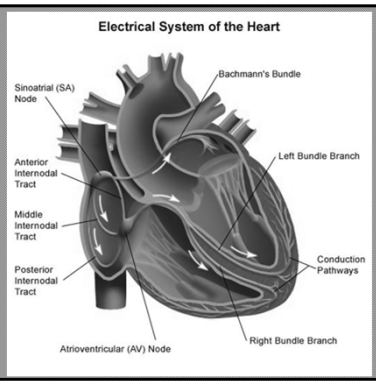

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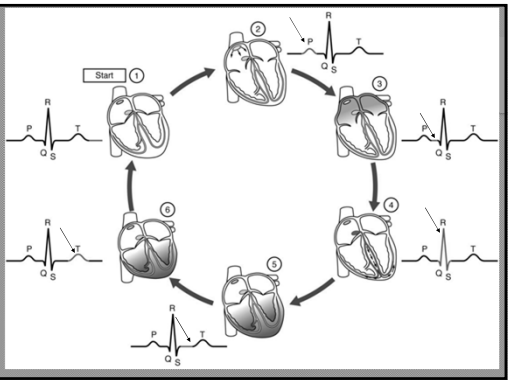
ECG to Contraction



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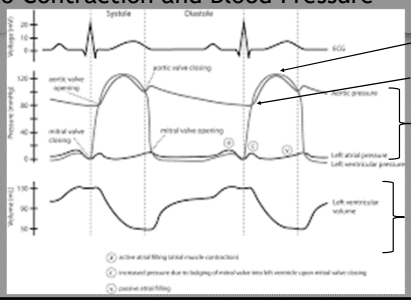
ECG to Contraction and Blood Pressure

ECG Findings



Systolic Blood Pressure

Diastolic Blood Pressure

Green Hump Shows Pressure Building in Ventricles During Systole

Brown Hump Shows Volume of Blood Going Down During Systole and Up During Diastole

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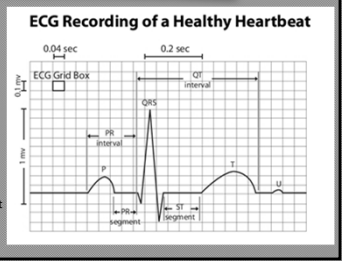
Normal Durations: Each Small Block = 40ms

- PR Interval = 8 blocks:
  - 8 blocks X 0.04 sec/block = 0.36sec
  - 0.36 sec = 360 ms
- Normal PR interval <200ms
- First degree AV block PR>200ms
  - Severe PR prolongation >240ms



White CM, Song J, Kalus J. Cardiac Arrhythmias, Chapter 20. In: Alldredge BK, Corelli RL, Ernst ME (Eds). Applied Therapeutics: The Clinical Use of Drugs. 11th Edition. Lippincott Williams & Wilkins, NY, NY. 2018 pg. 20.1-20.35.

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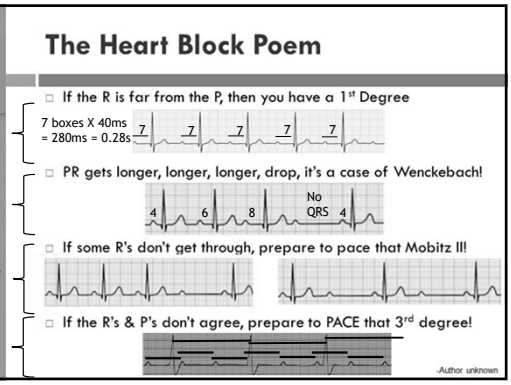
Notes:

PR is fixed duration but >200m, no lost QRS complexes

PR progressively lengthens until a QRS complex is dropped, then pattern repeats

No progressive lengthening in PR but still missing a QRS in a pattern

Green is consistent distance, blue is consistent distance but no relationship between the P and QRS complexes



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Drugs That Induce Heart Block: (Red Box = Gotta Know)

Anti-Hypertensive/Anti-Anginal	Anti-Arrhythmic	Psychoactive	Other
Beta-Blockers: Metoprolol, Propranolol, Atenolol, etc	Class Ia AAs: Quinidine, Procainamide	Opioids	Propofol
Non-DHP-CCBs: Verapamil, Diltiazem	Class Ib AAs: Lidocaine, Mexelitine	Donepazil	Succinylcholine
Clonidine	Class Ic AAs: Flecainide & Propafenone	Phenothiazines: Chlorpromazine, etc	Cannabis
Methyldopa	Class III AAs: Amiodarone, Dronedarone, Sotalol	Phenytoin	
Ivabridine	Digoxin, Natural Cardiac Glycosides	SSRIs: fluoxetine, sertraline, etc	
	Adenosine	Tricyclics: amitriptyline, etc	

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Acutely Managing Heart Block

- Hold offending agent(s)
- If symptoms mild (slight dizziness) and PR>200ms, or no symptoms but PR >240ms
  - Watchful waiting
- If symptom moderate/severe
  - Atropine 0.5 to 2mg IV
  - Isoproterenol infusion
  - Transvenous temporary pacing
- If major overdose – activated charcoal, consider dialysis
  - Measures for moderate/severe as above
  - Glucagon 3-10mg IV

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What Do You Do After Heart Block?

- Once heart block resolves (PR < 200ms, symptoms resolved):
  - Is drug really needed, are their equally good alternatives?
    - Yes – use alternative

  [IF THE ANSWER IS NO]…
  - If due to gross overdose – is risk of new overdose low?
    - Yes – restart; No - Stop
  - If due to inappropriate dose for age, renal function, hepatic function
    - Can a lower dose or drug in same class with different clearance pathway be used?
    - Yes – restart; No - Stop
  - If due to drug interaction – can interaction be avoided?
    - Yes - restart one of the offending agents; No – use lower doses and monitor more closely

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Pharmacokinetic/Dynamic Drug Interactions

Drugs	Elimination Pathway	Some Inhibitors	Pharmacodynamic Interactions
Metoprolol, Propranolol, Carvedilol	CYP2D6	Quinidine, ritonavir, SSRIs (fluoxetine, paroxetine, sertraline), duloxetine, buproprion, CBD, cinacalcet, amiodarone, dronedarone	All other PR interval prolonging drugs
Atenolol, Nadolol	Renal	Renal Dysfunction	
Verapamil	CYP3A4	Ketoconazole, itraconazole, HIV protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone, amiodarone, dronedarone	[For digoxin, drugs that lower potassium (loop diuretics, thiazide diuretics) increase risk of digoxin toxicity including heart block]
Diltiazem	Multiple CYP's	Quinidine (due to kinetic and dynamic)	
Digoxin	P-Glycoprotein	Quinidine, amiodarone, flecainide, propafenone, verapamil	

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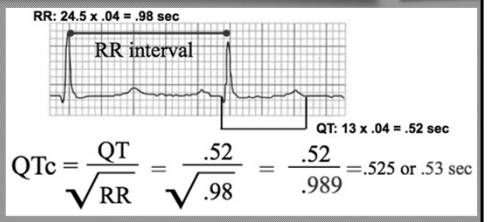
Calculating QTc Interval on Resting ECG: Everything MUST BE in Seconds not MS

- Calculate QT interval in sec
- Calculate RR interval in sec
- Apply formula:
- QTc interval = $QT/(RR)^{1/2}$



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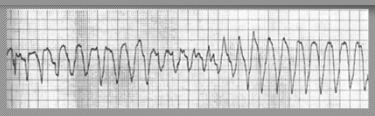
Torsade de Pointes (TdP)



- A polymorphic ventricular tachycardia
- Can be caused by R-on-T phenomenon (depolarization in vulnerable repolarization state)

White CM. *Pharmacotherapy.* 1999;19:635-640.

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Torsade de Pointes

- Polymorphic Ventricular Tachycardia
  - Caused by QTc interval prolongation >500ms (0.5 sec)
    - Or increased >60 ms from baseline
  - Caution with Class Ia or III agents if baseline QTc interval is >440ms
  - Caution with non-AA agents that prolong QTc interval (antipsychotics, flouroquinolones, macrolides, select opioids [methadone, kratom, oliceridine, loperamide]) if baseline QTc interval >470ms
  - Female gender has higher QTc interval than men (13 msec higher)
  - Hypokalemia, hypomagnesemia increases QTc interval
  - Class Ia and III agents except amiodarone have greater QTc interval prolongation when heart rate slower (reverse use dependence)

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Acute Treatment of TdP

- Hemodynamically stable:
  - IV magnesium is drug of choice (2g bolus then 1g/hour for 18 hours)
  - Lidocaine is second line therapy (see lidocaine)
- Hemodynamically unstable (unconscious, can't mentate, causing myocardial ischemia)
  - Electrically shock right away

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What Do You Do After TdP or Severe QTc Interval Prolongation?

- Once QTc interval resolves (< 440ms or less than 30ms increase from baseline, symptoms resolved):
  - Is drug really needed, are their equally good alternatives?
    - Yes – use alternative

  [IF THE ANSWER IS NO]…
  - If due to gross overdose – is risk of new overdose low?
    - Yes – restart; No - Stop
  - If due to inappropriate dose for age, renal function, hepatic function
    - Can a lower dose or drug in same class with different clearance pathway be used?
    - Yes – restart; No - Stop
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Quinidine	CYP3A4	Ketoconazole, itraconazole, HIV protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone	All other QTc Prolonging drugs in column A + macrolides, antipsychotics, tricyclic antidepressants, flouroquinolones, methadone, kratom, loperamide (mega-dose),
Procainamide	Cation tubular secretion inhibitors	Ketoconazole, megestrol, cimetidine, hydrochlorothiazide, prochlorperazine, trimethoprim	
Sotalol	Renal	Renal dysfunction	
Dofetilide	Cation tubular secretion inhibitors	Ketoconazole, megestrol, cimetidine, hydrochlorothiazide, prochlorperazine, trimethoprim	
Amiodarone	CYP3A4 (minor) biliary excretion	Ketoconazole, itraconazole, hiv protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone	
Dronedarone	CYP3A4 (minor) biliary excretion	Ketoconazole, itraconazole, HIV protease inhibitors, cyclosporin, grapefruit juice, erythromycin, clarithromycin, nefazodone	

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Conclusions

- Pharmacists need to use proper dosing and avoid drug interactions that can increase the risk of drug-induced disease
- Pharmacists need to look specifically for evidence of drug induced disease
  - Catch them early before severe toxicity results
- Pharmacists need to identify potential acute treatments and suggest whether and how to restart the drugs after the acute issues have passed

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