

63. Effect of Diuretic on Ventricular Function Curve (see web page)

1. venous return, stroke volume, and cardiac output decrease
 - you're sliding back to the left on the curve ("sliding down" Frank Starling curve)
2. how is this beneficial?
 - by decreasing blood volume, you decrease VEDS (which means less stretch on the myocardium)
 - greater efficiency via the better alignment of contractile proteins
 - you're putting the heart in a better working environment and you don't lose much cardiac function
 - you reduce the amount of O₂ the heart requires
3. A diuretic is bad to use when you're not congested
 - you're on the steep part of the curve
 - at this point, you need the preload to stretch the heart and the diuretic takes away that preload
4. you don't shift off of the curve when you're congested
 - all you do is drop blood volume and change the end diastolic volume you're working with.

64. Vasodilators Effecting Preload

1. Venodilators :
 - (↑) venous capacity (↓ venous resistance)
 - (↓) LVEDV
 - (↓) wall stress
 - drugs that act only on resistance of the veins will also "slide down" the Frank Starling curve like a diuretic
 - ex. low dose nitroglycerin
2. Effective in systolic & diastolic dysfunction
 - only if you are congested
3. Ineffective in poorly compliant hypertrophied ventricles (e.g. aortic stenosis)

"decreasing preload in aorta is like kissing your sister. It ain't doing anything, you're just taking away preload. The problem is the stenotic valve."

65. Effect of Nitrates on Ventricular Function Curve (see web site)

1. The far right curve is the same as Slide #63, except the vasodilator is a nitrate.
2. The curve in the middle is similar conditions to far right curve, *except the dose of nitroglycerin is increased.*
 - this causes a drop in not only venous resistance, but also arterial resistance.
 - the afterload is reduced by this and CO now increases.
 - you still slide down the Frank Starling curve, but the decreased afterload allows you to shift onto a new curve (anytime you increase the amount of blood ejected for the same amount of work, you jump onto a new curve)

66. Vasodilators Effecting Afterload

1. Arteriodilators :
 - (↓) afterload (resistance to outflow from heart)
 - (↓) wall stress
 - (↑) SV & CO
 - anytime that you increase SV and CO you shift to a new Frank Starling curve

67. ACE Inhibitors

1. (↓) VR (by decreasing volume) and TPR;
 - via inactivation of renin-angiotensin-aldosterone system
2. (↓) TPR
 - via lack of angiotensin II
3. (↔) HR; (↑) SV, CO
 - sounds strange that decreased VR increases SV, but we're in the "magic forest of CHF"
 - less volume allows better alignment of the myofilaments and more efficient contraction.

4. (↓) Sympathetic tone (Indirect & Direct)
 - “because CO went up and the brain’s chilling and pulling it back”
5. (↓) AT-II-induced aldosterone release
6. Heart - (↓) A-II adaptation:
 - inhibits hypertrophy & remodeling (AII receptors in the heart “turn on a bunch of DNA machinery and rocket-science type stuff to cause hypertrophy”)
 - this is why you have greater survivability with ACE inhibitors in CHF
7. (↓) Formation of A-II and (↓) breakdown of bradykinin
 - ACE (not ACE inhibitors) forms angiotensin II and destroys bradykinin.
 - inhibition of this mechanism is why you get angioedema and cough in some people.

68-69. ACE Inhibitors

1. Synergistic with diuretics (beneficial effect)
2. (↓) diuretic K⁺ wasting (beneficial effect)
 - now aldosterone is blocked, which blocks renal Na/K exchange
 - get more diuretic effect
 - spare potassium
3. (↓) renal autoregulation of glomerular perfusion pressure (adverse effect)
 - pt. with CHF and a stenotic renal artery will do poorly on an ACE inhibitor
 - will lose the effect of constricting the efferent artery to maintain GFR
4. Cough (adverse effect)
5. Angioedema (adverse effect)
6. ACE Inhibitors
 - i. Captopril (Capoten ®)
 - ii. Enalapril (Vasotec ®), et al.

70. Angiotensin II Receptor Antagonist : Losartan (Cozaar®)

1. AII Receptor Antagonist :
 - blocks angiotensin II receptors at the arteries → dilation
 - block at the adrenal cortex to reduce aldosterone release
 - allows for spilling of Na⁺ and water

(↓) VR and TPR ; (↔) HR; (↑) SV, CO

(↓) Sympathetic tone (Indirect & Direct)

(↓) A-II- induced aldosterone release
2. For ACE- Inhibitor Intolerance :
 - doesn’t build up bradykinin, so ...
 - i. No Cough
 - ii. No angioedema

71. Effect of ACE - Inhibitors on Ventricular Function Curve (see web site)

- note the decrease in TPR caused by ACE inhibitors allows you to shift into a new Frank Starling curve (same explanation as in slide #65)
- brain sees an increased CO and “chills out” by withdrawing sympathetic tone (and RAAS, which isn’t working anyway because of the ACE inhibitor)
 - this causes a decrease in TPR → cycle
 - you slide down the curve and get to a more beneficial level.

72. Direct Vasodilators:

I. Hydralazine

1. MOA : (↓)TPR

- Arterial dilator
- Renal vasodilator

2. Adverse effects - common:

- Headache and dizziness
 - Hepatic dysfunction (↑) bioavailability
- * **Lupus** * - a must know for the test.

73. Effect of Hydralazine on Ventricular Function Curve

- like before, a shift up in the curve and then you slide down.
- again, you're sliding down because the brain is withdrawing sympathetic tone and the kidney is withdrawing renin-angiotensin-aldosterone.

74. Effect of Nitroprusside on Ventricular Function Curve

- same thing, but is also a venous dilator
- get decreased venous return as well as decreased TPR → increased CO

75. Effect of Hydralazine + ISDN on Ventricular Function Curve

- ISDN = isosorbide dinitrate
- hydralazine decreases TPR → jump to a new curve
- ISDN relaxes the veins so you slide down the curve

76. β-Blockers :

I. Carvedilol (Coreg ®)

1. FDA approval for NYHA II & III ('97)
2. α_1 & β -blockers : (↓) effects of SAS
3. Initial (↓) TPR, VR
4. Subsequent (↓) HR, (↑) SV
5. Antiarrhythmic Action
6. Slows Progression of CHF;
7. (↓) Mortality ???

Dr. Tenner skipped this slide.

78. Problems with Potassium #4:

1. Problem with Digoxin Toxicity :
 - Too much potassium makes Ventricles MORE Excitable
 - Too much potassium makes AV Node LESS Excitable
- Therefore:
- AV-Block and Ventricular Escape

Dr. Tenner skipped this slide.

78. CLASSIFICATION OF ANTIARRHYTHMIC AGENTS

- | | |
|------------------|----------------------------|
| CLASS I : | Na Channel Blockers |
| CLASS II: | Beta Blockers |
| CLASSIII: | K Channel Blockers |
| CLASS IV: | Ca Channel Blockers |
| CLASS V: | Miscellaneous |

“This is EASY!” – Dr. Tenner, obviously said after being blinded by and put in a stupor by Amar’s yellow pullover shirt.

79. MOA OF CLASS I ANTIARRHYTHMIC AGENTS

CLASS Ia:

1. decreased upstroke
 - long tau (2-9 seconds)
 - whenever one of the sodium channels “uncloaks”, quinidine and procainamide will sit on it (2-9 seconds.)
 - slope of action potential decreases
 - widen QRS because the Na channels don’t open in synch.
 - action potentials, then are also not in synch.
2. prolonged action potential duration because activation of K⁺ channels is delayed
 - this prolonged AP duration due to delayed K⁺ channel activation can cause *Torsades de pointes*.
 - due to a dispersion of refractoriness
 - not everybody is prolonged the same – weird circuitry can happen because of this.

CLASS Ib: (lidocaine)

1. little effect on upstroke
2. shortened action potential duration
 - done by increasing potassium conductance
3. doesn’t have much of an effect on normal ventricular cells
 - tau of recovery is 0.1-0.4 seconds
 - on and off very quickly
 - binds preferentially to the inactive state of Na⁺ channel; this means that it seeks out ischemic tissue and “takes it out of the game”
 - channel opens, goes to inactive phase and lidocaine jumps on and off.
4. lidocaine does not cause Torsades

CLASS Ic: (Flecainide, Propafenone and Moricizine)

1. decrease upstroke of action potential
2. no effect on action potential duration
3. Will flecainide cause Torsades?
 - No. it doesn’t prolong the action potential

80. Class II ; β -Blockers :

1. ↓ Automaticity related to SAS
2. ↓SAS - related Responsiveness of Ischemic tissue
3. ↓AV Nodal Conduction

Dr. Tenner skipped this slide.

81. Class III; K⁺ Blockers:

- if you block potassium channels, the action potential duration is prolonged
- can get Torsades de pointes like class Ia.
- mortality is lower than in pts. using class I antiarrhythmics
 - both cause Torsades de pointes, so something else has to be going on.

I. Amiodarone:

- unique drug (turns you blue). Also acts as:
 1. Na⁺ blocker, Inactive State; $\tau = 1.6$ sec
 - decreases upstroke of action potential
 2. B-blocker (noncompetitive, irreversible)
 3. Ca channel blocker
- amiodarone is the only drug that can be classified as a class I, II, III and IV antiarrhythmic.
- 4. ↓ CV in all cardiac tissue

II. Sotalol:

- is only a B-blocker and K⁺ blocker

- K⁺ block effects prolong the action potential
- can cause Torsades de pointes

82. Class IV: Ca⁺⁺ Antagonists:

I. Verapamil and Diltiazem:

1. SA & AV node
 - good for treating supraventricular tachycardia
 - Ca channel blockers are good for treating any arrhythmia in the AV node
 2. ↓SA Automaticity
 3. ↓AV Nodal CV
- NOTE : Nifedipine is not an anti-arrhythmic!!**
- with atrial fibrillation and flutter, these are Na channel dependent arrhythmias (action potential)
- same thing with ventricular arrhythmias
- Ca channel blockers don't help with these at all.
4. Ca channel blocker action is primarily at the AV node.
 5. So on the test, if he has a lady in atrial fibrillation that is given verapamil:
 - it does nothing for the atrial fib, but does protect the ventricles
 - the only thing we care about is CO, and this protects it.

83. Class V; Cardiac Glycosides:

- Class V antiarrhythmics are the vagomimetics
- digoxin stimulates the vagus to release Ach at the AV node
- adenosine through adenosine receptors stimulates the same signal transduction pathway that Ach does.

1. Automaticity :

- i. Na/K ATPase blockade
 - this causes slow depolarization
 - this puts you closer to threshold potential
 - “don't need as much juice” to get an action potential

Dr. Tenner scenario: You're in your residency and in an experimental mood. You have a patient on digoxin and you decide to hit him with NE. NE raises TPR and you'll get a reflex bradycardia. When NE hits the ventricles the His-Purkinje system starts firing and you increase the rate of diastolic depolarization. With digoxin on board, you're closer to threshold potential, so you get ventricular arrhythmias. (“That experiment has already been done; don't do it”)

ii. Delayed After Depolarization (DAD)

- sarcoplasmic reticular incontinence
 - sarcoplasmic reticulum is stuffed with Ca²⁺
 - spills out, adding another positive charge to the inside of the cell
 - this depolarizes the cell slightly
 - if the cell is already close to threshold potential, you can get extra action potentials/arrhythmias.

iii. Why does digoxin decrease responsiveness?

- seems counterintuitive, but ...
- as you start to depolarize the membrane, you start to inactivate Na⁺ channels
- even though you're increasing excitability by getting the membrane potential closer to threshold, you're decreasing the number of Na⁺ channels that can open, therefore the decreased responsiveness → slower action potential and a decrease in the phase 0 slope.

84. Class V; Adenosine:

1. Remember that adenosine acts like acetylcholine
 - in asthma, Ach constricts the bronchioles
 - adenosine does the same thing, so don't use on an asthmatic or smoker.
2. If you have a patient with SVT and you need to break it and have verapamil, propranolol and adenosine, which do you use?

- Answer is adenosine is the drug of choice for SVT because it gets rid of SVT (by slowing conduction through the AV node) and has a short half-life (10 seconds)
- propranolol and adenosine can both cause vasospasm.
- verapamil doesn't, but since adenosine only lasts 10 seconds it's not a problem.

BOTTOM LINE: remember that adenosine (like B blockers) will impair respiration in a patient with COPD.

85. TREATMENT OPTIONS FOR ATRIAL TACHYARRHYTHMIAS

1. Verapamil, propranolol and digoxin all hit the AV node
 - don't do a thing in the ventricle (digoxin might even worsen the situation by shortening APD)
 2. for prevention of atrial fibrillation and flutter, quinidine is still used.
 3. Ibutilide is also used for termination
 - ibutilide is a class III antiarrhythmic
 - breaks a-fib/flutter by prolonging the action potential in the atria (remember the line he drew across the wall in blue chalk)
 - eliminates many of the aberrant impulses
 - the impulses "slam into cells" that are refractory and are stopped.
- arrhythmias are "asynchronously synchronous"
- this means that although there is an alteration in the rhythm, the pattern of this change is cyclic and it doesn't hit cells when they are refractory
 - ibutilide makes the arrhythmia "asynchronously asynchronous"
 - alteration in rhythm hits cells that are refractory and it dies out.
 - works in 60% of atrial tachyarrhythmias

86. TREATMENT OF SUPRAVENTRICULAR TACHYCARDIA

- supraventricular tachycardia is an arrhythmia in the AV node, whereas supraventricular tachyarrhythmia are all arrhythmias above the AV node.

1. VAGAL MANEUVERS
 2. EDROPHONIUM
 3. DIGOXIN
 4. PHENYLEPHRINE
 - 1-4 all work through Ach.
 - an alpha agonist works through Ach due to reflex.
 - pull back of sympathetic tone
- increase in vagal tone, which breaks the arrhythmia.
5. β -BLOCKERS; SAS; ESMOLOL, IV
 - better options than 1-4.
 - esmolol only lasts 10 minutes.
 6. VERAPAMIL, IV (80-100% SUCCESS)
 7. ADENOSINE = DRUG OF CHOICE
 - again, lasts 10 seconds
 - 100% chance of success.

87. TREATMENT OF PRE-EXCITATION SYNDROME: ACCESSORY PATHWAY W PW (cont.)

1. WPW = Wolff-Parkinson-White
 - pathway of the tachyarrhythmia through the AV node is a slow (Ca²⁺) path
 - however, an accessory fast Na⁺ pathway (Kent bundle) which directly connects atria and ventricles is also present in the case of WPW
 - if they have atrial fibrillation/flutter and you slow conduction at the AV node, you allow the impulses to come through the fast accessory pathway and get a 1:1 ratio (atrial:ventricular beats), which is uglier than Haden if your atrial rate is 300 beats per minute.
 - this doesn't happen normally because the atrial fibrillation (asynchronous synchrony) is keeping the fast pathway refractory, protecting the ventricles
 - if you break the afib, you can conduct through the fast Na⁺ channel in the AV node.

- in this case, you don't want to slow the AV node
- good options are flecainide, amiodarone, ibutilide
 - things that make the Na⁺ channel run slower
- bad option = lidocaine
 - doesn't do squat to the Na⁺ channels of the Kent bundle because they are not ischemic – just an accessory pathway
 - it shortens the action potential duration, which increases the number of beats that can be carried on.

**proof note: just read page 4 of Antiarrhythmic Agents II & III*

88. TREATMENT OF VENTRICULAR TACHYCARDIA

1. not too many options here, mainly B blockers.
2. BRETYLIUM : ↑ ADP, ↑ ERP
3. Class I agents seem to kill more than they help
4. Class II and III work
5. Class IV don't kill more people, but don't seem to help much.

89. See web page

90. TREATMENT OF DIGOXIN TOXICITY:

1. DISCONTINUE
2. GIVE K, NOT TOO MUCH (WHY??)
3. LIDOCAINE: HYPERPOLERIZATION PHENYTOIN : ALSO (↑) A VCV DIGOXIN Fab FRAGMENTS
4. AVOID DC CARDIOVERSION, VERAPAMIL (IV), BRETYLIUM
 - with DC cardioversion, you depolarize the entire heart
 - SA node takes charge normally
 - with digitalis you are closer to the threshold potential because of the block of Na/K ATPase
 - His-Purkinje cell depolarizes more quickly
 - can go into ventricular fibrillation

91. ADVERSE EFFECTS OF QUINIDINE:

1. WIDENING OF QRS
 - “you've got to know this.”
2. PROLONGATION OF QT, (↑) ERP
3. DISPERSION OF REFRACTORINES: TORSADE DE POINTES
4. "QUINIDINE SYNCOPE": SUDDEN DEATH (0.5 - 4%)

92. ADVERSE EFFECTS OF PROCAINAMIDE:

- almost as bad as quinidine
 - ** *LUPUS-LIKE SYNDROME* **
 - happens with high dose and slow acetylators.
 -

93. ADVERSE EFFECTS OF LIDOCAINE:

- “not much here”
1. CNS
 2. CIRCUMORAL PARESTHESIAS
 - usually the first sign of lidocaine toxicity.
 3. TINNITUS

94. ADVERSE EFFECTS OF AMIODARONE:

1. *SEVERE PULMONARY FIBROSIS*
2. HEPATIC DYSFUNCTION :
 - may be irreversible.
3. TORSADES DE POINTES

95. SOTALOL:

1. Is **NOT an alpha blocker** “...even though the name belies that”
2. BETA- BLOCKER
3. K CHANNEL BLOCKER
4. TORSADES DE POINTES

96. SPECIFIC CAUTION WITH VERAPAMIL

1. AV block and AV dysfunction
2. STRONG NEGATIVE INOTROPIC EFFECT
 - because it does block Ca²⁺ channels, therefore ...
 - caution with propranolol, CHF (anything that lowers ejection fraction)
3. verapamil, like quinidine, increases digoxin levels.

97. ADVERSE EFFECTS OF ADENOSINE:

1. Shortness of breath, bronchospasm
2. CONTRAINDICATED :HEART TRANSPLANT

98. A 69-year-old woman with a history of hypertension for which she is taking medication presents with atrial fibrillation of recent onset. The resident administers quinidine gluconate (iv), which causes torsades de pointes, ventricular fibrillation, and ultimately death.

Factors associated with torsades de pointes include all of the following except:

- a. QT interval prolongation
- b. a prolonged action potential duration
- c. hypokalemia
- d. hypomagnesemia
- e. increased AV conduction velocity

Answer is E.

A: essentially defines torsades de pointes

B: “when you prolong the action potential duration of **all** of the cells you get a prolonged QT interval”

C and D: both make torsades worse

99. The rapid onset of torsades de pointes is a result of co-administration of which anti-hypertensive medication?

- a. verapamil
- b. losartan
- c. hydrochlorothiazide
- d. enalapril
- e. atenolol

Answer is C. Hydrochlorothiazide potentiates quinidine via hypokalemia, A is incorrect because verapamil won't effect dispersion.

100. What is the therapy of choice for torsades de pointes?

- a. magnesium sulfate
- b. amiodarone
- c. lidocaine
- d. verapamil
- e. nifedipine

Answer is A, “even though we didn't talk about it and I'm not going to ask it.”

101. Other antiarrhythmic drugs known to cause torsades de pointes include all of the following except:

- a. amiodarone
- b. flecainide

- c. procainamide
- d. sotalol
- e. ibutilide

Answer is B, flecainide (lidocaine does the same)

- anything that prolongs the action potential duration will cause torsades.
- answers a, d, and e are all class III (Ca blockers) antiarrhythmics, which prolong the action potential duration
- answer c, procainamide is a class Ia, which also increases APD.

102. Answer questions 1-3 using the following choices:

- A. quinidine sulfate
- B. lidocaine
- C. flecainide

1. shortens the action potential duration of normal ventricular cells

Answer is B.

2. prolongs both the QRS and QT interval

Answer is A.

Why not flecainide? It won't prolong the APD, therefore it won't prolong QT.

3. decreases the upstroke of phase 0 as well as prolongs the action potential duration

Answer is A.

4. decreases phase 0 with little or no effect on action potential duration.

Answer is C.

He now moved to anticoagulants. He did a few slides and said that we knew what was relevant after that. You may want to look at the slides of the review that he says he'll post on the web.

105. ANTITHROMBOTIC AGENTS:

1. COX INHIBITORS: ASPIRIN

- COX = cyclooxygenase
- inhibit the formation of prostacyclin
- aspirin is a classic example and costs next to nothing.

2. ADP INHIBITORS:

- i. TICLOPIDINE (TICLID®)
- ii. CLOPIDOGREL (PLAVIX®)

3. GP IIb/IIIa INHIBITORS:

i. ABCIXIMAB

- an antibody to the IIb/IIIa protein.
- the antibody gets on it and fibrinogen can't bind to the platelet.
- "IIb/IIIa proteins are like landing gear on the platelet"
- platelet looks for fibrinogen, not fibrin
- MAIN POINT: you don't need coagulation (fibrinogen instead of fibrin) to get platelet aggregation. If you block the landing gear, you prevent aggregation of platelets.

ii. EPTIFIBATE (INTEGRILIN®)

- peptide fragment that resembles the active part of the antibody

iii. TIROFOBAN (AGGRASTAT®)

106. ANTICOAGULANTS:

BOTTOM LINE: heparin and hirudin can only be given IV, while coumarins (warfarin and coumadin) are oral.

- heparin and hirudin act instantaneously
- both take out thrombin

1. HEPARIN

- act by taking out thrombin
- 2. HIRUDIN
 - act instantaneously
 - binds antithrombin 3, which takes out thrombin.
- 3. COUMARINS (Indandiones)
 - work in the liver and inhibit the formation of active clotting factors
 - factors II, VII, IX and X need Ca²⁺ to work
 - glutamates are gamma-carboxylated and bind to Ca²⁺.
 - these function and can continue the clotting cascade
 - if they are not gamma carboxylated, they can't bind Ca²⁺ and don't work
 - "impotent clotting factors"
 - takes 12-16 hours before they work
 - patients are often put on heparin at first and then coumadin because of this.

107. THROMBOLYTIC AGENTS:

1. STREPTOKINASE
2. UROKINASE
3. TISSUE PLASMINOGEN ACTIVATOR (tPa)

- all he wants you to know about these is that they all are used for MI
- you have 6 hours after the MI to administer streptokinase
- tPa is the only one effective in embolic stroke (don't know why)

Dr. Tenner encourages you to see him during day hours (office or lab) if you have questions. You can also call or email him. We hope you enjoyed reading all 26 pages as much as we enjoyed scribing them. Hopefully it helped. And we did learn a valuable life lesson ... prostitution doesn't pay.

- jason and jason