

TENNER PHARM REVIEW: PART I

Note: Dr. Tenner used slides from his regular lecture powerpoint presentation. He said that everything he's covering in this review should basically be the same material on last year's review.

I. COAGULATION

A. HEMOSTASIS

1. Thrombogenesis—platelets get down and dirty, interact with each other and form platelet plug
2. Coagulation—fibrinogen is a profactor; turned into fibrin by thrombin; clot is very unstable without fibrin setting a mesh work over it; leading to accumulation of more platelets and, in the case of venous thrombosis, red blood cells; stabilize clot so it doesn't move
 - a. Turning on Thrombin via intrinsic and extrinsic pathway (measured by two different lab assays)
 1. **Intrinsic pathway measured by aPTT (minutes)**
 - a. Prothromboplastin time has no prothrombin in it; all kaolin and phospholipids
 2. Extrinsic pathway measured by PT (seconds) and International Normalizing Ratio (INR)
 - a. actually uses thromboplastin
 - b. rabbit vs. human thromboplastin; differences in US and European measurements led to the development of INR which standardizes everything
 - b. **MUST MEMORIZE: Factors II, VII, IX, X requires calcium for activation;** require gamma—carboxylation of glutamate residues (chelator—in Greek means “crab”) which are vitamin K dependent
3. Fibrinolysis—plasminogen comes along like PAC-MAN and chews up the fibrin monomer, mesh breaks apart, and clot goes away and the vessel is recanalated

B. THROMBOLYTIC AGENTS: streptokinase, urokinase, tPa (tissue plasminogen activator)

1. **Streptokinase**—not an enzyme
 - a. binds to plasminogen to enables activation
 - b. pulmonary thrombosis
 - c. deep vein thrombosis
 - d. Acute myocardial infarction
 - e. Anaphylactic reaction
2. **Urokinase**—from human fetus
 - a. true activator
 - b. half-life=16 minutes
 - c. very costly
 - d. tainted
3. **tPa**
 - a. half-life= 5-8 minutes
 - b. chews up plasminogen and looks for plasmin bound to a clot
 - c. for MI costs a bundle
 - d. no clear evidence for decrease in mortality

C. ANTI-THROMBOTIC INHIBITORS

1. **COX Inhibitors: Aspirin**
 - a. Cox stands for **cyclo-oxygenase** found in platelets and in endothelial lining of vessel wall
 - b. Endothelial cells are the only substance in the whole world that doesn't make blood clot, because endothelium squirts all kinds of anti-thrombotic juices such as **prostacyclin and nitric oxide**
 - c. Platelet does the reverse of endothelial cells
 - d. Potent pro-aggregatory is **Thromboxane** and anti-aggregatory is **Prostacyclin**
 - e. **Aspirin eliminates cyclo-oxygenase from blood stream;** since endothelial cells are nucleated they can produce more cyclo-oxygenase

- f. **Platelets** are non-nucleated so **can't make cyclo-oxygenase** on their own; platelets live 7-10 days
 - g. When hit with aspirin (acetosalicylic acid), the aceto part irreversibly binds to cyclo-oxygenase, preventing the platelets from "playing but just float around being warm and fuzzy (dead!)"
 - h. Serum thromboxane level at 80mg of aspirin is almost zero, further decrease at 325mg
 - i. Serum prostacyclin level in both arteries and veins at 80mg of aspirin is not as inhibited
 - j. However, at high dose (2 aspirins/day) both thromboxane and prostacyclin serum level is nearly zero; thus, lose the beneficial effect of aspirin at high dose
 - k. Just take a baby aspirin or just one aspirin every other day
 - l. **ADVERSE EFFECTS :**
 - 1. Bleeding
 - 2. Hemorrhagic stroke
 - 3. GI distress
 - 4. Ulcers
 - m. **PHARMACOLOGY:**
 - 1. > 80% of myocardial infarctions result from thrombus formation: Unstable Angina
 - 2. Use in secondary prevention of vascular events is well documented.
 - 3. Effectiveness in primary prevention less well defined.
 - 4. Thrombo-embolic stroke—not that clear, Clopidogrel may be better
 - 5. FDA approves 325mg/d for primary but urges caution.
2. **ADP inhibitors:** ADP is one of the pro-aggregate substances secreted by platelets
- a. **Ticlopidine** (ticlid®)
 - 1. *Thienopyridine*; prodrug
 - 2. **Inhibits ADP pathway** (inhibits formation of ADP)
 - 3. Effective in prevention of second thrombotic stroke and MI (anyone with TIA should be put on these compound)
 - 4. **No effect on cAMP or cyclo-oxygenase**
 - 5. 1% agranulocytosis, usually reversible; aplastic anemia
 - 6. Discontinuation rates (↑) than aspirin
 - 7. **Cimetidine** (over the counter) (↓) clearance; antacids (↓) absorption.
 - b. **Clopidogrel** (plavix®)
 - 1. Analog of ticlid, prodrug (remember digoxin and digitoxin differ by one hydroxyl group?—same applies here)
 - 2. Approved by FDA as effective in prevention of secondary thrombotic stroke or MI (recent studies show slight advantage over aspirin)
 - 3. **MOA : irreversibly inhibits platelet aggregation by ADP inhibition**
 - 4. **Intracranial and gastrointestinal hemorrhage** are prominent side effects
 - 5. No significant agranulocytosis (as in Ticlid)
 - 6. Very expensive for an 8% advantage over aspirin
3. **Gp IIb/IIIa inhibitors: "Super Aspirin"**
- a. **Characteristic and MOA**
 - 1. Platelets have 2 proteins linked together called GpIIb/IIIa; when turned on, the protein link "pop out" to the cell surface and binds to fibrinogen, linking other platelets together
 - 2. "Platelet anesthesia": **CABG** (Coronary Artery Bypass Graft), **PTA** (Percutaneous Transluminal Angioplasty)
 - b. **ABCIXIMAB** : antibody fragment (study called "epic" showed that it worked and effective in CABG surgery; must give IV]
 - c. **EPTIFIBATE** (integrilin®) : synthetic peptide; administer IV; study called Impact II demonstrated effectiveness
 - d. **TIROFIBAN** (aggrastat®) non-peptide; administer IV; based on study called "restore"
 - e. All intravenous, short duration,
 - f. All cause bleeding as adverse effect

4. **Heparin**—random pentapeptide sequence occurs randomly in nature
 - a. Glycosaminoglycan
 - b. Hog gastric or beef lung
 - c. Strongly acidic
 - d. **USES:**
 1. Venous thrombosis: goal is to get **PTT** prolonged 2 to 2 1/2 times control.
 2. Acute myocardial infarction: goal is to get PTT prolonged 1.5 to 2 times (Dr. Tenner said he's not too worried about this)
 - e. **MOA**
 1. Heparin binds to antithrombin III (protease inhibitor)
 2. Antithrombin III binds to thrombin irreversibly and both are inactivated.
 3. Binding of Thrombin to Antithrombin III inactivates Factor IIa (uses high molecular weight heparin)
 4. Antithrombin III also binds Factor Xa (uses low molecular weight heparin)
 5. Must be given SubQ or IV; can't give orally
 6. Does NOT cross BBB; no cranial hemorrhaging
 7. Does not cross placenta—good for pregnancy
 - f. **ADVERSE EFFECTS**
 1. DO NOT give IM—causes bleeding;
 2. Spontaneous hemorrhage; antidote is **PROTAMINE SULFATE** which binds and eliminates heparin
 3. Alopecia—patient on heparin therapy longer than 6 months loses their hair
 4. Hypersensitivity
 5. Skin necrosis
 6. Osteoporosis and spontaneous fractures
5. **Enoxaparin** (lovenox):
 - a. low molecular weight than heparin
 - b. advantages in surgery
 - c. decrease probability of pentasaccharide bonds, but probably more targeted at Factor X
6. **Hirudin** (refludan®)—probably the most potent anti-coagulant discovered in nature; Derived originally from leech saliva
 - a. Independent of antithrombin III
 - b. Given parenterally
 - c. Prolongs PTT like heparin
7. **Warfarin**: Wisconsin Agricultural Research Foundation
 - a. Discovery of warfarin
 1. Cows would bleed to death from scratching against barbed wire fences
 2. Turns out cows were eating substance that prevent blood clotting
 - b. Orally active: 100% bioavailability
 - c. It's almost malpractice to have old, women in atrial fib. and not have them on warfarin
 - d. Highly protein bound (95-99%); small volume of distribution; therapeutic effect is small; toxicity is problem;
 - e. **DRUG CHARACTERISTICS**
 1. Long half-life = 36h
 2. Metabolized by liver
 3. **Gamma-Carboxyglutamate**—have two carboxy groups to hold on to calcium, which is essential for function
 4. Gamma carboxylation is dependent on Vit. K; Warfarin looks exactly like Vit. K; thus, preventing the reduction of Vit. K
 - f. **ADVERSE EFFECTS:**
 1. **Cross BBB and placenta; Contraindicated in pregnancy**
 2. Hemorrhage: bowel & brain
 3. Hypersensitivity with coumarins
 4. Skin necrosis : decrease protein c
 5. Placenta- fetal death birth defects

- g. DRUG INTERACTIONS:**
- 1. Cimetidine** : (↓) metabolism; increase blood level; small therapeutic index
 - 2. Cholestyramine**: (↓) absorption
 - 3. Phenobarbital** : (↑) metabolism
 - 4. Phenytoin** : (↑) metabolism
- h. THERAPEUTIC EFFECTS**
1. Requires about a day to start seeing effect, but can then use warfarin to prevent stroke secondary to atrial fibrillation
 2. Acute MI—can decrease as much as 50%
 3. Pulmonary embolism
 4. In severe bleeding , administer Vit. K

II. CARDIOVASCULAR

A. $BP = CO \times TPR$

1. TPR is maintained by sympatholytic system
2. Renin—Angiotensin—Aldosterone system—AII binds to AII receptors on the arteries and causes constriction and increases TPR. AII also goes to adrenal cortex where it releases Aldosterone which goes to the kidneys where sodium is reabsorbed, and water following sodium, causes an increase in blood volume

B. Effect of NE (IV) on Afterload

1. (↑) TPR (α)
2. (↓) HR
3. (↑) LVESV
4. (↑) VR (α)
5. (↑) LVEDV
6. = Frank-Starlings
7. ± Ejection Fraction, because although you increase TPR you also give the heart the ability to overcome that increase.
8. ± CO

C. Effect of EPI (IV) on Afterload

1. (±) TPR (β_2 α)—not the same algebraic increase
2. (↑) HR (β_1)—stimulation in SA node
3. (±) LVESV
4. (↑) VR (α)
5. (↑) LVEDV—by increased venous return
6. (↑) Frank-Starlings
7. (↑) Ejection Fraction
8. (↑) CO
9. **Isoproterenol** will do better because it will cause a drop in TPR, making it easier for the ventricle to eject blood. Also able to eject more blood by increasing the heart rate.

D. 1998 Exam Question

1. Which of the following statement about NE is FALSE?
 - a. Drug of choice for increasing CO.**
 - b. Shortens the AP duration in AV node and AV muscle. Why?—from increase in potassium conductance. Is that good?—yes, remember NE is being leached out of the nerve terminals. Its job is to increase HR, increase pump function, increase CO. By shrinking down the contraction you can stick in more effective contractions into a unit of time.*
 - c. Preferentially activates β_1 to β_2
 - d. Increase rate of diastolic repolarization in AV node and His Purkinje cells.
 - e. IV injection causes bradycardia.

E. RENIN: ANGIOTENSIN: ALDOSTERONE SYSTEM (RAAS)

1. Increase TPR from direct effect of AII

2. Increase in Na/H₂O retention causes increased in blood volume.
3. AII also hits pre-junctional sympathetic terminals and causes increase release of NE.

F. ANTI-HYPERTENSIVE AGENTS

1. KIDNEYS

a. Diuretics

1. Mechanism of Action

- a. (↓) in plasma volume (PV) and ECFV—because losing sodium
- b. (↓) VR
- c. (↓) CO
- d. (↑) TPR (Reflex)
- e. (↓) MAP
- f. (↑) PRA (plasma renin activity)
- g. (↑) CO
- h. $I^o = (\downarrow)$ intravascular volume
- i. $\Pi^o = (\downarrow)$ vascular responsiveness because of $(\downarrow) [Na^+]$, $(\downarrow) [Ca^{++}]$
- j. Maintained lowered TPR—you lose plasma because you're losing sodium; RAAS tries to save some sodium through aldosterone; by decreasing intracellular sodium, intracellular calcium will also decrease causing a decrease in vascular activity maintaining the lower blood pressure

2. Adverse Effects Of Diuretics

- a. SEXUAL DYSFUNCTION (Most Common)
- b. HYPOVOLEMIA: Caution in Elderly WITH 20% volume depletion
- c. HYPOKALEMIA: predispose to arrhythmias
- d. HYPOMAGNESEMIA: predispose to arrhythmias
- e. HYPOCALCEMIA: occurs with thiazides; loops decreases
- f. HYPERURICEMIA: don't worry about it
- g. HYPERLIPIDEMIA: don't know if anyone worries about it
- h. ALLERGIC RXN: problem
- i. HYPERGLYCEMIA: problem with diabetics

b. ACE INHIBITORS

1. **Captopril** : sulfhydryl may be responsible for rash, blood dyscrasias. Oral twice a day (bid) or three times a day (tid); 1- 2hr before meal, $t_{1/2} = 2-3hr$
2. **Enalapril** : PRODRUGS activated in liver or small intestines. Oral once or bid; $t_{1/2} = 11hr$
3. **Lisinopril** : lysine derivative of enalapril; Once daily; $t_{1/2} = 12hr$
4. African-Americans don't do well on ACE inhibitors; if ACE inhibitor therapy is required then you need to give combination of both diuretics and ACE inhibitor
 - a. with only diuretics, they start to lose sodium
 - b. Kidney compensates by elevating renin
 - c. Adding ACE inhibitor, you take out the increase in renin
 - d. Decreases mortality
 - e. ADVANTAGE: LITTLE EFFECT ON LIPIDS OR SEXUAL FUNCTION

d. SYMPATHOLYTICS

e. **VASODILATORS**—potassium channel activators

f. **CALCIUM CHANNEL BLOCKERS**—just on arteries

Cardiac Pharmacology Review

Note: If you have seen last year's scribe of this, you know that it was 25 pages long due to the fact that it included all of the information on Dr. Tenner's power points. I will only include what he said in the review. If he didn't say it, you won't have to read it. Hopefully this shorter length will be good for overall class morale. I will, though, let you know where you can find relevant figures. I didn't see a specific power point presentation for the review. I am planning to use abbreviations that we have all been exposed to multiple times by now without spelling them out. I hope no one has a problem with this ☺- D.S.

I. Adverse Effects of Ace Inhibitors

- A. **Hypotension**- especially in the elderly (they will "fall down on these")
- B. **Cough**
- C. **Hyperkalemia**- you're going to knock out the aldosterone and keep the Na⁺, thus increasing Na⁺/K⁺ exchange
- D. **Angioedema**-probably related to the kinins: if you want to put someone on a RAAS inhibitor but did not want to have them on an ACE inhibitor you could put them on **Losartan**
- E. Renal failure can also be a problem with **renal artery stenosis** patients

Question from Travis: How big a role does B1 activation in the kidney play in the RAAS system?

Answer: Quite a bit. This is why you don't need to put people on a B-blocker on a diuretic. It's a tonic thing- you think of all sympathetic tone as tonic. There is always a basal symp tone on the kidney to give a certain amount of renin release. If you block that (at the B receptor) you lower RAAS, but if you knock someone with a diuretic and you block the B receptor, you're still going to see an increase (in RAAS, I guess) because the juxtaglomerular cells can work by themselves. It's a tonic modulation, not an on/ off thing.

Question from Martin H.: What's angioedema?

Answer: Angioedema is an inflammation or allergic reaction involving the mouth/ esophagus in which they swell up, you get edema, and you can suffocate.

Another question from Travis: I thought you gave digitalis and diuretics before you gave B-blockers...

Answer: In terms of CHF, true. This is because you want to support their contractility before you knock out the B- receptors in the heart.

II. Sympatholytic Agents- anti-hypertensives

- A. **CNS a-agonist**: clonidine and methyl-dopa
- B. **Ganglionic blockers**- are used in the hospital and nowhere else because they knock out all sympathetic and parasympathetic
- C. **Depletors of NT**
 1. **Reserpine**- gets into the brain, causes suicidal depression
 2. **Guanethidine**- does not get into the brain
- D. **A- blockers**- increase TPR- good (this is what he said, but I think he meant "decrease"), decrease VR- could care less in terms of HTN
- E. **B-blockers**- effective in hyperkinetic hearts by decreasing contractility and heart rate
 1. **Non-selective**- propranolol
 2. **Cardioselective**- metoprolol and atenolol
 3. ISA- "don't worry about it"
 4. Remember the **difference** between nadolol and atenolol and propranolol:
 - a. **propranolol, metoprolol, timolol**- metabolized by the **liver**, if you have a cirrhotic liver, these will build up
 - b. **natolol and atenolol** are excreted by the **kidneys**, so if you have bad kidneys, these will build up

III. B-blockers mechanism of action

- A. Decrease CO by heart rate and contractile force
- B. Will **increase TPR** by reflex
- C. **Adverse effects**:
 1. **bronchospasm**- people with emphysema, COPD or asthma do poorly on these
 2. **heart failure**- if their CO is dependent on high symp tone and you give a B-blocker, the patient will do poorly/ decompensate
 3. **bradycardia/ AV node**- the AV node is innervated with symp and parasymp, it's a tonic interaction. If you take away the symp, the parasymp predominates, conduction velocity will drop and you may actually get a blockade. Impulses invading from the atria can't get into the ventricle

4. **Peripheral vascular disease**- B2 blockade: think of the cardiologist in New Orleans who put patients on B-blockers, they were fine there but when they went skiing in Colorado they had trouble
5. **Depression**
6. **Weird dreams**- Dr. Tenner understands that these are pretty good though he has never had them himself
7. **Sexual dysfunction**- main reason for non-compliance (B-blockers have a 20-30% non-compliance)

IV. Labetalol- "the best and worst of both worlds"

- A. B and A- antagonist
- B. Decreases TPR and VR by A-blockade
- C. Decrease HR and SV by B1-blockade
- D. **No reflex tachycardia**
- E. **Adverse effects:**
 1. Alpha effects: orthostatic hypotension
 2. Beta effects- bradycardia, heart block, asthma

V. Vasodilators

- A. **Pure arterial dilators: hydralazine, minoxidil, diazoxide** (this one can only be given IV- used to be the drug of choice for HTN-sive emergencies but is no longer used)
- B. Hydralazine and minoxidil are both given orally, but again, they will drop TPR, and thus the brain will kick in, increasing HR and CF (contractile force) to get stroke volume up, and increase VR by squeezing the veins. The CNS will try to squeeze the arteries but there will be a functional antagonism due to the drug which it will be unable to overcome, so the brain will offset this effect by raising CO. The kidney will release renin and A-II to try to squeeze the arteries. Again, it will be in competition with the hydralazine and you will increase blood volume to the heart.
- C. Therefore the brain and kidney will be trying to decrease the effectiveness of these drugs. So, with these drugs you will need **triple therapy**. At least a diuretic to take the edge off the volume increase, and probably a B-blocker for contractile force and heart rate.
- D. **Nitroprusside**: is a "card-carrying nitrate" which releases NO and thus it is not only an arterial dilator but works on veins as well to decrease VR. The effect we are talking about here is, though, a decrease in TPR
- E. **Adverse effects:**
 1. **Hydralazine**- **SLE-like** disorder in **slow acetylators** as you increase the dose (doesn't happen as much these days)
 2. **Minoxidil**- hair growth (Dr. T thinks this is a benefit), tachycardia as a reflex, angina (for both drugs)- if someone has stable angina, the reflex tach and the lowered perfusion pressure will cause pain. Diastolic pressure drops and as blood flows to the periphery it bypasses the coronary arteries.

Class question: Is this the same as "coronary steal?"

Answer: This refers to the fact that vessels distal to an occlusion are already dilated and the other arteries in the heart are not. If you hit the vessels with hydralazine or nitroglycerin, you will dilate the guys that don't need dilating and blood will shunt around the occlusion.

VI. Calcium Channel Blockers

- A. The three "biggies": **verapamil, diltiazem, nifedipine**
- B. **Verapamil and diltiazem** are mainly effective in the **heart**
- C. **Nifedipine** mainly hits the **arteries**
- D. They can **all decrease TPR**, but nifedipine is the best at this
- E. Decreased HR- verapamil and diltiazem
- F. Decreased contractile force- mainly verapamil
- G. Remember **constipation** with **verapamil**
- H. **Mortality**: people die with short-acting **nifedipine** when docs double up the dose so the patient wouldn't have to take it as often- causes a big hit to TPR with a reflex back to the heart- if it's already damaged, they'll go into failure

Propranolol treatment of HTN is associated with an initial increase in TPR. Which of the following anti-hypertensives also increase TPR?

- a. Nifedipine- works on arteries
- b. Reserpine- depletor of NE- when it's gone, it's gone- can't increase TPR
- c. **Hydrochlorothiazide**-will decrease blood volume, VR does down, SV goes down, CO goes down, MAP goes down and the brain causes reflex
- d. Prazosin- increased TPR
- e. Minoxidil- vasodilator

Scribe note: Prazosin and nifedipine also cause reflexes(according to last year's scribe). I guess that the difference is in how much more quickly this occurs with diuretics.

Class question: Doesn't the decreased blood volume also increase Ca⁺⁺ conc in the blood?

Answer: That's a kidney effect, and blood Ca⁺⁺ is irrelevant. The amount of Ca⁺⁺ in your blood is plenty.

Captopril prevents A-II formation. Which of the following anti-hypertensive drugs inhibits the A-II receptor?

- a. hydralazine
- b. enalapril
- c. labetalol
- d. losartan**
- e. spironolactone

Dr. T said he was trying to be tricky by putting the two "L's" together. Whatever. He says we hate him anyway right now, but apparently this feeling of loathing for him disappears around Christmas time. (Amy doubts it. We'll see ☺)

An 83-year old woman is placed on antihypertensive therapy and quickly develops orthostatic hypotension. Which medication might induce this?

- a. Hydrochlorothiazide- already volume depleted as she's old
- b. Captopril- not in normal people, but in the volume-depleted it will
- c. Clonidine- it can
- d. Guanethidine- no explanation (but anything that removes symp tone can cause this)
- e. all of the above**

A forty-year old white male with asthma is newly diagnosed with essential HTN and is placed on a fairly high dose of anti-HTN medications. While taking the medication, his heart rate is low, (56/min). He complains of tightness in his chest and difficulty breathing. He later complains of depression and decreased sexual drive. (Everything up to this point says "B-blocker")Of particular interest is that he is sensitive to the orthostatic hypotensive(this says "alpha") effects of this medication, but is not sensitive to cold.(Why?-because of the alpha blocking) What medication is he taking?

- a. enalapril
- b. propranolol
- c. prazosin
- d. hydralazine
- e. labetalol-** only choice with both alpha and beta activity

Using the above vignette, what would be the appropriate monotherapy?

- a. Enalapril-** will remove all of the above effects (in young people this will not cause orthostatic hypotension, generally)
- b. propranolol
- c. prazosin
- d. hydralazine
- e. labetalol

African-Americans with HTN respond best to monotherapy with:

- a. diuretics-** hope you know this by now
- b. ACE inhibitors
- c. B-blockers
- d. Ca⁺⁺ blockers
- e. Direct vasodilators

A smoker with emphysema placed on prophylactic therapy following MI for secondary prevention develops angioedema. What is she taking?

- a. propranolol
- b. labetaolol
- c. hydralazine
- d. enalapril-** ACE- inhibitors are the class we dicussed which cause this

VII. Effort angina

- A. Double product- how we measure this
- B. Occurs at the **same level** of cardiac work each time- same double product each time
- C. Rest relieves the pain

VIII Nitrates in Angina

- A. Decrease cardiac work and O₂ demand by lowering VR and SV-> decreases CO, decreases O₂ demand (think of CO as equivalent to O₂ demand by the heart)
- B. **Decrease preload in effort** angina, you **dilate coronary arteries in vasospastic/variant** angina. In mixed, you get a little bit of both.
- C. **With MI**, many times nitroglycerin will clear it up due to an anti-thrombotic effect- destabilizes the clot.
- D. **Adverse effects:** blushing of the face, headache, postural hypotension (again, the veins are dilated), methemoglobinemia ("irrelevant"), and bad breath (though he didn't discuss it really, you might remember that tolerance develops to nitrates and patients often need a short period off the drug to maintain efficacy)

IX. B-blockers in Angina

- A. In acute MI, they are **protecting the heart** from massive sympathetic stimulation- in any cardiovascular problem, the brain's answer is to slam the heart with sympathetic tone
- B. More than any ionic effect, B-blockers block B-receptors and protect the heart
- C. **Not used for variant angina**- all they would do is knock B₂'s and make things worse- because in variant angina you don't care what the heart rate and contractile force are, you've got the spastic artery that's giving you the problem
- D. MOA- again, decreased heart rate and contractile force

X. Ca⁺⁺ Channel Blockers

- A. They work the same- decrease heart rate and contractile force
- B. **Verapamil** is the **most effective** at this and is most often used in **effort angina**.
- C. However, in variant, with the **vasospastic** component, you can use **all three**, including nifedipine.
- D. These do nothing to blood clots. With an MI with a clot, if you give these (or a B-blocker) you will decrease HR and CF, you may decrease TPR, but you won't touch the clot.
- E. Use them with effort angina which is refractory to nitrates and/or B-blockers. Usually the nitrates are given as needed (PRN). If these don't work, you go to B-blockers, and if there's a problem with these, you go to Ca⁺⁺ channel blockers.
- F. Remember that there is **no indication that survivability is enhanced with these**. They relieve symptoms, don't save lives
- G. All are **orally active** and well-absorbed. Verapamil has a significant first-pass effect- cleared by the liver. With cimetidine, blood levels of verapamil increase because you're blocking metabolism. Verapamil also has the ability to decrease its own metabolism- through its effects on the heart, blood flow to the liver decreases, so you get less metabolism, and more of the drug for a longer period of time.

XI. Effort Angina and Cardiac Work (I know that there's a slide for this, but I'm sorry I couldn't find it- I expect it's in the angina stuff, though)

- A. Heart increases its activity (B₁ effect) and you perform more work to meet the demand until, at a certain level of activity, the amount of O₂ getting to the heart cannot increase any more. (this is the pink dotted line on the figure)- the heart can't deliver enough blood to meet the O₂ demand and you have angina.
- B. This is the patient's limit of exercise, You want to extend this.
- C. In treatment with anti-anginal agents, (**Ca⁺⁺ channel blockers or nitrates**) you **increase the amount of physical work** the patient can do at the **same level of cardiac work**. (Cardiac work is decreased for any level of physical work). He can surpass the old tolerance level and continue working without chest pain until he gets to the same level of cardiac work, at which point he will experience chest pain.
- D. This tells us that **these drugs do not increase coronary blood flow to the ischemic area** because if they did you could keep going to a higher level of cardiac work without pain. You get increased exercise time without chest pain. You hope the patient gets pooped out at a level below the pink line where he experiences pain.
- E. **B-blockers** also decrease cardiac work at the same level of physical work. The **difference** is that by removing symp tone, they increase the duration of systole when the ventricle is squeezing the coronary arteries allowing for less blood flow. There is also a swelling of the heart that actually worsens the ability to perfuse the heart for high levels of work. You don't care, because most patients don't get to this high level before they get tired.

Which of the following drugs would be least effective for treatment of variant angina?

- a. isosorbide dinitrate
- b. nifedipine
- c. verapamil
- d. nitroglycerine
- e. **propranolol**- "B-blocker, right?"

A 52-yr-old caucasian male with chronic stable angina reports that the nitroglycerin he has been taking prophylactically for the past year no longer provides relief during anginal attacks. Likewise, it no longer burns under his tongue or gives him the slight headache that he used to experience. The cause of this is:

- a shift from stable to unstable angina
- the nitroglycerin tablets have gone bad**- the key is the burning sensation, if he had developed tolerance, this sensation would still be present
- the patient has developed tolerance to the nitroglycerin
- his angina now has a vasospastic component
- a daily baby aspirin is required for nitro to be effective in treating effort angina

The B-blockers (propranolol) and Ca⁺⁺ blockers (verapamil) are effective in treatment of stable angina because they both:

- decrease HR and contractility**- if you read this far, I hope you got this
- decrease the size of the heart- no, propranolol increases
- decrease LVEDV- goes up due to loss of contractility
- decrease TPR- Ca²⁺ do this, but not B's
- dilate spastic coronary arteries- not the problem in effort angina

All of the following antianginal agents undergo extensive first pass metabolism except:

- verapamil
- propranolol
- metoprolol
- atenolol**- is water soluble and excreted by the kidneys
- nitroglycerin**- if taken sublingually, this would also be true, it depends on the method of administration- Dr. T admits his error here (though he takes this time to let us know that he will accept challenges on something like this, but not on what he calls a "BS point")

XII Pathophysiological Sequence of CHF

- Inadequate CO-> the brain and kidney want their share, they kick out symp tone
- This increases RAAS
- Frank Starling's curve gets shifted. ("again, that's the normal curve"-I think at this point he just showed a figure of the normal Starling's curve- power pt #5 on angina)

XIII Drug therapy of CHF

- Cardiac glycosides**
- B- Agonists**- mainly **dobutamine**
- Phosphodiesterase inhibitors**- mainly **milrinone** (kills more people than it saves with long term use- given for a day or so in the hospital, then cut off)
- Diuretics- loops** are more effective than thiazides, the K⁺ sparing are an afterthought, though now we know that **spironolactone increases survivability** (and it's cheap)
- Vasodilators**
 - ACE inhibitors** (captopril, et al)- are vasodilators only indirectly in that they remove the vasoconstriction of All
 - Angiotensin II antagonists- **Losartan**- are very good, no angioedema, but no study has demonstrated that they improve survivability, though everyone assumes they will
- Direct vasodilators**- hydralazine, again, are K⁺ channel activators
- Sodium nitroprusside**- hits both the arterial and venous side
- Nitroglycerin and ISDN**- only hit the venous side
- Remember that both **ACE inhibitors** and the combo of **hydralazine and ISDN** have been shown to **decrease mortality**, but the combo is iffy because one study has contradicted this
- Cardiac glycosides and diuretics **improve symptoms** but **not survivability**
- Spironolactone**- "**big winner**"
- A- agonists, Ca⁺⁺ channel blockers, and phosphodiesterase inhibitors may kill people to a greater extent on them than off them

XIV Pharmacokinetics of Digoxin and Digitoxin

- Digoxin** has less lipid solubility, shorter half-life, and larger VD (volume of distribution)
- Digitoxin** is metabolized by the **liver**, **digoxin** by the **kidney**

XV Mechanism of Action of Dig. (See power pt #5 in the glycosides stuff)

- Inhibitor of Na⁺/K⁺ ATP-ase** (in case he hadn't emphasized this enough already)

- B. Reversible- binds to the phosphorylated form, K^+ is also a competitive inhibitor (increase K^+ , decrease the effectiveness of digoxin)
- C. What dig. does- you have an MI, knock out CF, you're down onto a new curve, this isn't good enough for the brain and kidney which kick in all of their reflexes, and basically you get an increase in blood volume at the heart and you'll climb back up to a CO which satisfies the brain and kidney
- D. At this point, the brain and kidney pull away, and you'll sit there. Problem- too much blood gives you edema and the congestion part of CHF (two pillow a night, etc.) Can't do this very long. Remember LaPlace's law- the bigger the ventricles, the more they have to work to get the same ejection fraction
- E. Give digoxin, you get an **inotropic effect**. Na^+ goes up, Ca^{++} goes up. CF goes up, Sv goes up, CO goes up without a change in VR, so you just shift up on the curve (C->B)
- F. The brain senses this new CO and doesn't want to overdo it, so it pulls back symp tone and the kidney pulls back RAAS and you start to "pee off" blood volume, and you start to slide back down the curve out of the congestion and into a more reasonable LVEDP and "that's where you hang"
- G. **Improved symptoms but no increased survival**
- H. If you give dig with CHF, you increase SV, CO, the brain pulls back symp tone and TPR decreases. If you give dig. to a normal person you'll have very little effect on CO. However, what you'll see is an increase in symp tone which will increase TPR when Na^+ increases in the cell. The decrease in TPR with CHF is much larger than the increase in a normal person. You basically end up at the same level of TPR in both cases.
- I. **Narrow TI**- easy to get into trouble
- J. **Drug interactions:**
 1. **Quinidine and verapamil**- increase the levels of dig., thus increasing the potential for toxicity
 2. **Cholestyramine, Kaolin-pectin and neomycin** bind to dig. in the gut and **decrease** its levels
- K. **Pharmacodynamics:**
 1. **B-agonists and dig** are a **bad** combination- increased excitability and symp tone- can throw the patient into arrhythmias
 2. **B-antagonists/ Ca^{++} channel blockers and dig.** - sum with the parasympathomimetic effect of dig. to decrease AV nodal conduction velocity and throw you into **AV block**
 3. **Loop and thiazides**- you waste K^+ - **increase toxicity** of dig,
- L. **Adverse effects**- nausea and vomiting, yellow halos, cardiac arrhythmias
- M. **Counterindications** to use:
 1. Cardiac glycoside toxicity
 2. **Idiopathic hypertrophic subaortic stenosis**- because it's an obstruction and increased contractility actually increases the obstruction. The stronger the heart is, the more it pulls the obstruction into the outflow tract, decreasing SV. These patients should receive something that decreases contractility (B-blockers, Ca^{++} channel blockers). Do not want to decrease VR because the problem is with SV and decreasing VR would give an increase in SV
 3. AV block
 4. MI's
- N. **Treatment of dig. Toxicity**- atropine (blocks parasympathomimetic effect), K^+ (if it's low, but not if it's normal), lidocaine and Fab fragments

XVI. CHF and Various Agents (see slide #48 in glycosides)

- A. With **glycosides**- Slide down the Frank Starling's law- all you are doing is decreasing blood volume thereby decreasing LEDV
- B. Same with **nitrates**- just slide down the curve (#61).
- C. **ACE inhibitors** (#56) also decrease blood volume to some extent
- D. **Losartan**- same as ACE inhibitors, because you are lowering TPR, you allow the damaged heart to develop enough pressure in its bloated condition to increase SV and thus, CO, the kidneys back off, and you slide back down. The arrow is "tilted" because you have both increased CO and decreased blood volume. The flatter the arrow, the greater the effect on blood volume. The more vertical arrow indicates a greater change in TPR and the inotropic state of the heart. Here you have a little of both.
- E. **Vasodilators** (#58)-affect afterload. Important because you decrease afterload and increase CO and SV. So the arrow goes straight up. Once you get up there, the brain and kidney pull back and you begin to lose blood volume because you lose this stimulus. But overall, the effect is just to unload the heart.
- F. **Nitroprusside** (#61)- the arrow is bent because these decrease afterload and preload
- G. **Hydralazine and ISDN** (#63)- again you hit both TPR and veins
- H. **Carvedilol**- both alpha and beta- what you're doing is pulling away congestion by dilating the veins and pulling away afterload by dilating the arteries. This gives you inotropic support. And protection from catecholamines.

Which of the following statements about digoxin is false?

- proven to decrease mortality in CHF**
- increases excitability of His-Purkinje cells- increases Na^+ , maximum diastolic potential is floating toward the threshold potential
- produces vagomimetic effect at therapeutic doses- true
- has a half-life of 40 hours- true
- can result in T-wave inversion and ST segment depression- Dr. T says he is "teaching" with this one- don't be fooled by this one just because it's "technical"

Question from Field: What's the principle behind the vagomimetic effect?

Answer: The principle is that dig. is increasing Na^+ in the brain cells and what you'll see is that low doses cause parasymp stimulation and with increased doses the sympathetics kick in. All you are doing is raising excitability in nerve cells and the vagus fires faster. The antiarrhythmic effect is dependent on the parasympathetic effect. In CHF, this effect is unimportant.

In the individual with normal cardiac function glycosides can:

- shorten the PR interval-this would increase AV conduction velocity (this is not true)
- cause nausea and vomiting by stimulating the CTZ- true
- increase TPR- true
- cause arrhythmia associated with hypokalemia- true
- all of the above- obviously Dr. T messed up with this one- they would shorten the QT interval, though.

You have a patient with CHF, AV block, premature contraction, elevated serum K^+ levels. He has been taking several medications but can't recall what he's taking. Which of the following drugs would be responsible for triggering the arrhythmias?

- dobutamine- would not increase serum K^+
- milrinone- no
- diuretic- no
- ACE inhibitor**

What would be responsible for increasing K^+ ?

Enalapril (sorry, he didn't say what the other choices were this time)

XVII. Anti-arrhythmic agents

- Class I-** Na^+ channel blockers
- Class II-** B- blockers- all these do is take away sympathetic tone (which is bad for arrhythmias)
- Class III-** K^+ channel blockers
- Class IV-** Ca^{++} channel blockers
- Class V-** Miscellaneous- can almost think of these as parasympathomimetics (digoxin, adenosine)
- Basically, we have three ions to work with- Na^+ , Ca^{++} , and K^+ - if you hit their channels, you're going to have an effect
- If we have an **arrhythmia in atrial muscle, ventricular muscle or in His-Purkinje:**
 - Class I- ineffective** because Na^+ is the driving force for fast channels (which these are)- except in **atrial flutter, Ib** (lidocaine) is **ineffective** because it shortens the AP duration in normal cells
 - Class II- would be effective** to the extent that they remove sympathetic tone
 - Class III-** they prolong the AP and slam the aberrant impulses into refractory tissue (so effective)
 - Class IV- no
 - Class V- no
- In an **arrhythmic SA or AV nodal cell:** (where the Ca^{++} channels predominate)
 - Class I- no
 - Class II- yes**
 - Class III- maybe, probably not
 - Class IV- these are the biggies**
 - Class V-** yes, because the vagal input will slow them down

Question from Kory (paraphrased by Dr. T): When we talked about atria and digoxin, we said the parasympathomimetic effect decreases the AP duration with no effect on the ERP. When we talked about the AV node we said that it shortened the AP duration and increased the ERP. Why?

Answer: Atrial muscle: give Ach (dig.) which kicks on the K^+ current and forces repolarization. This is Na^+ -driven and is mainly dependent on voltage. At the AV node, you increase the K^+ current, you increase efflux, you shorten the AP duration but this is not only voltage-dependent but also time dependent associated with the ERP. Now Ach, in addition to shortening the AP duration, prolongs the ERP. With NE, though, will increase K^+ , shorten the AP and the ERP. In the AV node, increases Ca^{++} , increases K^+ efflux, shortens the AP duration and the ERP. This is why you can shorten the ERP in the atria and lengthen it in the AV node. So, you increase conduction velocity in the

atrial muscle and decrease it in the AV node. If you have someone with atrial flutter (350 beats) what you could do is give the guy dig. And the main effect is the parasympathomimetic effect- shorten the AP duration in the atria and shorten the ERP. This means that globally in the atria, the refractive period is decreasing, so aberrant impulses have "more people to play with" so the rate in the atria may increase to 450 /min. Counterproductive in terms of atrial function. But in the AV node, the parasympathomimetic effect is going to be to shorten the APD but increase the ERP and the global refractive period in the AV node is lengthened and the aberrant impulses hit refractive tissue and die. So there are fewer impulses getting across the the ventricles.

Let's say this guy is in atrial fibrillation (600/min) and his ventricular rate is 200. You have nothing but some old quinidine which is parasympatholytic in the AV node. So with AP duration you have more NE, and the ERP shortens. So the global refractoriness of the AV node is shortened and promiscuous beats into the AV node are increased. So the number of impulses getting into the ventricles increase. This could cause an increase in the ventricular rate. Quinidine would be bad, bad, bad for this guy. At this point, Dr. T said, I'm sorry, I didn't really need to take you through that, (you're telling me!) but they're really on opposite sides of the fence- quinidine and digoxin.

The scribe apologizes for the tedious paragraph form of the above. I hope you understand all that stuff OK. At one point, after he had been talking for a couple of minutes, he realized that he had been talking about lidocaine and not quinidine, so I hope I got the right things corrected

XVII "Back from that faraway place"- SVT's or when you want to protect the ventricle

- A. You may have atrial flutter and use **Class II, IV or V-** but they have no effect on atrial muscle. They are used to protect the ventricles
- B. Bottom line is always CO- if you aren't protecting CO, don't mess with it
- C. These aren't always life-threatening

XVIII Class I Antiarrhythmics

- A. **Class Ia-** (procainimide, quinidine)- go after the **open** channel- decrease the upstroke and prolong the Ap duration, blocks Na⁺ channels, blocks K⁺ channels
- B. **Class Ib-**(lidocaine)- go after **inactive** channels, no effect on upstroke, shorten the AP duration, block Na⁺ channels, no effect on K⁺
- C. **Class Ic-** **either** channel type, decrease upstroke, no effect on AP duration, block Na⁺ in ischemic cells, in normal fibers- increases K⁺ efflux
- D. In **normal cells** during arrhythmia, **lidocaine** is almost useless because it's just depolarizing. It jumps on the inactive channels, it comes off quickly and the membrane is allowed to depolarize. If anything, it increases conduction velocity- which may be beneficial in eliminating a unidirectional block. Basically, though, it has no effect.
- E. In **ischemic cells** where there are lots of inactive channels, it'll jump on and freeze the cell at a membrane potential where it cannot carry an AP. It takes the whole ischemic section out of the loop. Remember, for an arrhythmia, you have to have a fast and a slow loop. The slow loop is the ischemic tissue. You want to arrest that ischemic tissue if you can. In this situation it looks just like quinidine

XIX- **Class II-** all B-blockers do is protect the heart

XX **Class III-** K⁺ channel blockers

- A. By blocking K⁺ channels, you prolong the AP duration
- B. The idea is to surround an ischemic section with refractoriness so the bad impulses can't get out

XXI **Class IV-** Ca⁺⁺ channel blockers

- A. Work in SA node and AV node
- B. Are good in SVT's or to protect the ventricle
- C. **No nifedipine!**

XXII **Cardiac glycosides**

- A. The main thing to remember is that **they can cause any arrhythmia**
- B. And, **as anti-arrhythmics they are mainly vagomimetic**-like squirting Ach on the AV node
- C. Only used to treat an SVT

XXIII **Adenosine**

- A. Is "Ach in sheep's clothing"
- B. It goes to its own receptor but it works with the same cellular mechanism as Ach. It's **just like the vagus.**
- C. Conduction velocity is increased in the atria because the conduction velocity and overall refractoriness is shortened
- D. Decreases conduction velocity at the AV node and the AP in the AV node shortens
- E. The ERP will increase.
- F. Can cause bronchospasm because it's just like Ach
- G. **Very short duration**

XXIV Atrial Arrhythmias

- A. **Protect CO** (Ca⁺⁺ channel blocker, B-blocker, dig)
- B. **Break** the arrhythmia with **1a, 1c or III**
- C. Ibutilide will knock the AP duration so long that it breaks the arrhythmia

XXV. Ventricular Arrhythmias

- A. **Lidocaine** mainly due to its ability to knock out ischemic cells
- B. **Procainimide**- decreases upstroke of the AP, decreases conduction velocity, prolong AP duration- more refractive tissue
- C. Remember that with anything that **blocks K⁺ channels** you have to watch for **torsades**
- D. **Most anti-arrhythmics kill more than they save**
- E. Anything that decreases the upstroke of the AP is going to widen the QRS
- F. If we give **quinidine**, it will widen the QRS and prolong the QT in atrial and ventricular muscle, It will also increase the ERP in these areas because these are mainly voltage dependent.. It blocks K⁺ and when it pushes out the AP duration, it's going to push out the ERP.
- G. If we gave **lidocaine**- no widening of the QRS, not going to decrease upstroke globally (though if you blast hard enough you might see it), the QT interval is shortened
- H. With **flecainide**, the QT interval is unchanged and the QRS is widened.

XXVI Amiodarone-

- A. can cause severe **pulmonary fibrosis** in about 5% of patients- "they turn blue and get mad at you",
- B. can also cause **hyper- or hypothyroidism**, and **torsades** (because of K⁺ channel effect)

XXVII Sotalol

- A. **Type III** that has **B-blocker activity**
- B. Doesn't affect CA⁺⁺ or Na⁺

A 69-year old woman with a history of HTN for which she is taking medication presents with atrial fibrillation of recent onset. The resident administers quinidine, 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- yes, K⁺ blockers
- b. A prolongation of the AP duration- this is the same as "a"
- c. Hypokalemia-probably, will worsen the effect
- d. Hypomagnesemia- excitability increases in the absence of magnesium, which also happens to be the drug of choice for torsades
- e. **Increased AV conduction velocity**- is irrelevant

Answer the following questions using these choices:

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

- 1. **Shortens the AP duration of normal ventricular cells: B**
- 2. **Prolongs both the QRS and QT interval:A-** these two are the same thing
- 3. **Decreases the upstroke of phase 0 as well as prolongs the the AP duration: A**
- 4. **Decreases phase 0 with little or no effect on AP duration: C**

Believe it, or not, that's all! Good luck to everyone on the exam!

Here's some interesting factoids from the Harper's Index this month (Harper's Magazine- November 1999)

- 1. Change since 1987 in a US household's average annual spending on health insurance: +\$323.28
- 2. Change since then in a household's annual spending on medical services, supplies and drugs:-\$99.69
- 3. Percentage of American ER viewers who say they learn important health-care information from the program:53%
- 4. Percentage change since 1995 in the number of sugeons worldwide using maggots to cleanse wounds:+400%
- 5. Number of East Harlem ATM machines offereing free service for the neighborhood's 11,000 welfare recipients: 7
- 6. Number of Upper East Side ATM machines offering free service for the nieghborhood's 700 welfare recipients: 120
- 7. Chance that a Texan living below the poverty line receives welfare: 1 in 10
- 8. Federal anti-poverty funds granted to Texas since 1996 that have not been spent: \$149,000,000
- 9. Portion of the words in Webster's New World dictionary memorized by one nonEnglish-speaking Thai Scrabble champ: 2/3
- 10. Percentage of the tiles included in Scrabble games produced in the US this year that will be made in China: 100%
- 11. Number of films about Y2K disasters that Hollywood studios are planning to release in the next four months: 0
- 12. Number about battling Satan: 2