MOUNT SINAI SCHOOL OF MEDICINE

Pharmacology

DRUGS USED IN CONGESTIVE HEART FAILURE I & II

Original Syllabus by Dr. Joseph Goldfarb  October 29, 2012: 11:00am - 11:50am
Modified by Dr. Tonia Kim  12:00pm 12:50pm

GOALS: Drugs used in congestive heart failure (CHF) include vasoactive peptides, diuretics, inotropes, vasodilators, and β agonists. This lecture will review the actions of some selected endogenous peptides, and discuss pharmacological agents that modify either peptide synthesis and degradation, or act as agonists or antagonists at peptide receptors. Major emphasis will be on the renin-angiotensin system.

OBJECTIVES:
1. Describe the components of the renin-angiotensin system, how the system is regulated, and the physiological effects of angiotensin II.
2. Compare and contrast the effects of renin inhibitors, ACE inhibitors and angiotensin receptor antagonists on the components of the renin-angiotensin system
3. List the therapeutic uses and adverse effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (AT1 receptor), and indicate how they differ in their overall effects
4. Describe the sources of, and triggers for release of, natriuretic peptides (ANP and BNP) and endothelins, and these peptides' physiological effects. Describe the clinically available drugs relevant to these two peptides.
5. List 4 classes of inotropic agents and give an example of each.
6. Describe the cellular mechanism of action of digoxin, explain how this can lead to a positive inotropic effect.
7. List some of the common signs and symptoms of digoxin toxicity and how it can be treated.
8. Explain why phosphodiesterase 3 inhibitors act as inotropic agents, their therapeutic uses and adverse effects.

KEY DRUGS(and endogenous substances):
renin, angiotensinogen, angiotensin I, angiotensin II, aliskiren, captopril, enalapril, enalaprilat, losartan, bradykinin, endothelin (ET-1), bosentan, atrial natriuretic peptide(ANP), natriuretic peptide B(BNP), nesiritide
digoxin, milrinone, dopamine, dobutamine, digoxin immune fab

KEY WORDS AND PHRASES:
renin-angiotensin system, juxtaglomerular cells, angiotensin converting enzyme (ACE), AT1 receptors, angiotensin receptor antagonists, kallikrein, kinins, endothelins, natriuretic peptides.

TEXTBOOK READING:
KATZUNG 11TH ED. Chapter 17, Vasoactive Peptides, pp 293-311
Chapter 13, Drugs Used in Heart Failure pp 209-224
KATZUNG 12TH ED. http://eresources.library.mssm.edu:2059/content.aspx?aid=55823193
http://eresources.library.mssm.edu:2059/content.aspx?aid=55822108
LECTURE OUTLINE

VASOACTIVE PEPTIDES

I. The renin-angiotensin system

FIGURE 1 Enzymatic cascade of the RAS: classic and alternative pathways. CAGE, chymostatin-sensitive angiotensin II-generated enzyme; t-PA, tissue plasminogen activator. From Brenner and Rector’s *The Kidney, 8th Edition.*

Figure from *New England Journal of Medicine* 2008: 358;23, p. 2504. Aliskiren and Dual Therapy in Type 2 Diabetes Mellitus, Julie R. Ingelfinger, M.D.

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Figure 1. The Renin–Angiotensin–Aldosterone System and Drugs That Inhibit It.

In the renin–angiotensin–aldosterone system, renin, an aspartic protease, cleaves a leucine–valine bond in the angiotensinogen molecule, its substrate, to release the decapeptide angiotensin I, which, in turn, is cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II binds to the angiotensin type 1 receptor (AT₁) and type 2 receptor (AT₂), as well as to several less well characterized receptors (AT₃). The AT₁ receptor mediates many of the pressor effects of angiotensin II. Angiotensinogen and angiotensin peptides are also cleaved by angiotensin-converting enzyme 2 (ACE2) and other nonrenin enzymes. In addition, ACE is responsible for the breakdown of bradykinin into inactive peptides. There are now many ACE inhibitors, multiple AT₁ inhibitors, two aldosterone-receptor antagonists, and one approved renin inhibitor.
A. Prorenin
1. It can be converted to renin in the juxtaglomerular cells of the kidney, but can be secreted as prorenin into the circulation both from the kidney and from extrarenal tissues. It normally circulates at much higher levels than does renin.
2. It can bind to and activate a single transmembrane spanning receptor that is phosphorylated upon binding and can activate kinases and transcription factors associated with fibrosis. Because this receptor can be activated by both prorenin and renin it is termed the (pro)renin receptor (P)RR.
3. Unbound prorenin has essentially no enzymatic activity, but binding to the (P)RR permits it to convert angiotensinogen to angiotensin I

B. Renin
1. An enzyme that is released by exocytosis from juxtaglomerular (JG) cells in the renal afferent arterioles and circulates in blood, (another form is expressed in brain). It converts angiotensinogen to angiotensin I. Note that binding of renin to the (P)RR both increases its enzymatic activity and mediates the same signaling as prorenin
2. Control of release:
   a. Macula densa pathway:
      i. increased uptake of NaCl into macula densa inhibits renin release via increased adenosine acting at A1 receptors on JG cells
      ii. decreases in NaCl flux into macula densa stimulate renin release via increased prostaglandin production.
   b. Intrarenal baroreceptor pathway:
      i. increased preglomerular pressure decreases renin release
      ii. decreased preglomerular pressure increases renin release
   c. β-adrenergic receptor pathway:
      i. via β1 receptors on juxtaglomerular cells (sympathetic activation in response to low blood pressure)
   d. Short loop feedback -- AT II acting on AT1 receptors on the JG cell inhibits renin release
   e. Long loop feedback
      i. AT II on AT1 receptors in vasculature increases BP
         a. the increased BP causes a pressure natriuresis which decreases proximal tubule Na reabsorption leading to more NaCl flux into the macula densa inhibiting renin release.
         b. the increased BP causes a reflex decrease in renal sympathetic tone which decreases the β1 receptor mediated increase in renin release

C. Angiotensinogen
1. The precursor of angiotensin I whose major source is the liver. It is continuously synthesized and circulates at about 1µM, roughly the Km of renin for it.
D. Angiotensin I (AT I)
1. A decapeptide
2. The product of renin action on angiotensinogen, it is rapidly converted to angiotensin II.
3. Angiotensin I is approximately 100 times less potent than angiotensin II as a vasoconstrictor and releaser of aldosterone.

E. Angiotensin Converting Enzyme (ACE)(dipeptidyl carboxypeptidase)
1. The major enzyme converting AT I to AT II. Not selective for AT I, but cleaves many kinins including bradykinin. -- primary location of ACE acting on circulating AT I is on luminal surface of vascular endothelium

F. Angiotensin II (AT II)
1. An octapeptide
2. The primary active angiotensin in the periphery. It acts via two G-protein coupled receptors, AT₁ and AT₂.

G. Primary Angiotensin Receptors
1. AT₁ receptors-- G protein coupled (Gq, Gi, G12/13), This receptor is responsible for most of the observed actions of AT II (see Figure 4 below).
2. AT₂ receptors-- G protein coupled (Gi prominent) The physiological function of this receptor is not known-- it might act to counter the growth effects mediated by AT₁ receptors. Consequences of AT2 activation include activation of phosphatases, potassium channels, and bradykinin and NO production and inhibition of calcium channels. The A2 receptor may dimerize with and antagonize the AT1 receptor.

Figure 4 Primary actions of Angiotensin II mediated via AT1 receptors. Goodman and Gilman 11th Edition.
III. Renin Inhibitor
   A. Aliskiren (Tekturna)
      1. A competitive renin inhibitor that can be administered orally
      2. It can lower BP without tachycardia.
      3. Secondary to loss of negative feedback from ATII, renin levels increase, but
         because of inhibition, plasma renin activity does not.
      4. Because production of ATI is blocked, all subsequent pathways for formation of
         ATII (except for possible direct production from angiotensinogen by cathepsin G)
         are affected,
      5. Approved for use in hypertension either as sole drug or in combination.
      6. Pharmacokinetics
         a. Oral administration (F: 0.02-0.03)
         b. Minimal metabolism
         b. T1/2 about 40 hrs,
      7. Adverse effects
         a. pregnancy—teratogenic (discontinue as soon as possible)
         b. angioedema
         c. hyperkalemia
         d. cough (less than ACEIs)
         e. diarrhea
         f. dizziness

IV. Angiotensin Converting Enzyme (ACE) Inhibitors
   A. Mechanism
      1. Competitive inhibition of ACE. The primary consequence is to reduce the
         conversion of AT I to AT II, but metabolism of other substrates of ACE is
         also inhibited.
         a. Bradykinin levels increase--doesn't seem to contribute to BP effect but may
            be involved in adverse effect--cough in certain individuals.
         b. Ac-SDKP (N-acetylseryl-aspartyl-lysyl-proline), a stem cell regulator
            increases.
      2. Both short and long-loop feedback is reduced so renin increases, AT I
         increases, and it is preferentially metabolized along alternative routes to
         increase AT(1-7)--consequences unknown.
      3. The reduction in AT II reduces activation at both AT₁ (desired) and AT₂
         receptors (consequences unknown)

B. Prototype drugs:
   1. Captopril was the first marketed ACE inhibitor and prototype. It is an
      analog of prolyl cysteine. Shorter t½ (3 hours) than other ACEi.
      Advantage: Can titrate in CHF patients with low BP
      Disadvantage: Must be dosed every 6 – 8 hrs
Captopril also contains a sulfhydryl group and this may contribute to one side effect--alteration of taste sensation. All other orally available inhibitors can be effective in single daily doses in many patients.

2. **Enalapril** (Vasotec) is a pro drug designed to enhance oral bioavailability, that is converted by hepatic esterases to the active drug **enalaprilat** (Vasotec IV).

3. There are many other ACE inhibitors (e.g. benazepril, fosinopril, lisinopril, ramipril(Altace)) (16 or so used worldwide). They differ in pharmacokinetics, but there is no overwhelming evidence that any one is superior for treating hypertension or heart failure. There have been variable results in studies of therapeutic effects of ACE inhibitors in patients with CAD. (E.g. ramipril and perindopril significantly increased survival whereas trandolapril and quinapril did not.) To what extent these reflect differences in effects of individual ACE inhibitors, doses used, or the patient populations studied is not clear.

4. All ACEI available in the US (except fosinopril) are predominantly cleared renally, so doses must be reduced in patients with renal impairment.

C. **Therapeutic Utility** (Different ACEI have different FDA approved uses)

1. **Hypertension**
   a. Although initial BP decline is greatest in patients with high plasma renin activity (PRA) and high **AT II** levels, after several weeks efficacy no longer correlates with pretreatment PRA or **AT II**.
      i. Normal PRA unexpected in hypertension
      ii. Tissue rather than circulating **AT II** may contribute
   
   b. The only causes of hypertension not amenable to ACEI treatment are primary aldosteronism and bilateral renal artery stenosis.

   c. There are still sympathetic responses to postural change and exercise, but the chronic lowering of BP is not accompanied by an increase in HR or in circulating NE (? adaptation of baroreceptor reflex, increased compliance of large arteries, loss of **AT II** enhancement of NE release?).

   d. There is a reduction in aldosterone levels in most patients, but because the ACTH and K mediated regulation of aldosterone are still intact, the primary danger of hyperkalemia is in patients who take K supplements, take drugs that impair K excretion, or who have kidney damage that impairs their K regulating ability.

   e. ACEI can be used as monotherapy in many patients, or can be combined with Ca blockers, beta blockers, or diuretics.

   f. ACEIs used as antihypertensives, can induce regression of hypertension-induced left ventricular hypertrophy, and decrease cardiac remodeling.
g. They have also been first choice in diabetics with and without evidence of nephropathy and in other patients with proteinuria with hypertension because of studies showing that they have a beneficial effect in reducing risk for nephropathy in diabetics and in slowing progression of nephropathy. The mechanisms postulated for this effect are a decrease in glomerular pressure, an increase in the permeability selectivity of the filtering mechanism thus reducing the exposure of the mesangium to proteins that may stimulate mesangial cell proliferation and matrix production, and a reduction in AT II promotion of mesangial growth. (Note that some recent meta analyses have suggested that the primary renal effects of ACEIs (and angiotensin receptor blockers) are via BP reduction, not independent from it. This is still not a settled area and there are conflicting data. Study size, duration, drug dosage, and specific endpoints selected all influence reported outcomes outcomes).

h. It is also possible that they may decrease the incidence of new-onset diabetes.

2. Heart Failure
   a. Prevents or delays progression of heart failure and decreases incidence of sudden death and MI
      i. Decreased afterload and systolic wall stress--increasing CO
      ii. Decreased HR
      iii. Decreased renovascular resistance and decreased aldosterone and thus improved natriuresis and reduced extracellular fluid volume
      iv. Venodilation (with chronic administration)
      v. Reverse ventricular remodeling

3. Acute MI
   a. Reduced mortality when treatment started in the immediate peri-infarction period--can be given along with beta blockers, aspirin, thrombolytics

4. CAD--controversy
   a. HOPE (Heart Outcomes Protection Study): in patients with CAD and preserved LV function, addition of ramipril (10 mg/day) decreased MI, stroke, overall mortality.
   b. EUROPA (European trial on Reduction of Cardiac Events with Perindoprol in Stable Coronary Artery Disease)—addition of perindopril (8 mg/day) decreased cardiovascular death, MI, cardiac arrest
   c. PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibitors)—addition of trandolapril (4 mg/day) had no effect on cardiovascular death, MI

D. Adverse Effects/CI
   1. Hypotension--first dose effect especially in patients with high plasma renin activity(PRA)
2. Cough—5% -20%, dry cough generally develops in less than 6 mos.—possibly bradykinin, prostaglandin or substance P mediated
3. Hyperkalemia—in patients with renal insufficiency, on K sparing diuretics, beta blockers, K supplements, or NSAIDS
4. Angioedema—0.1-0.5% incidence—rapid swelling in nose, throat, mouth, glottis, larynx, lips, and/or tongue. Mechanism may involve bradykinin, tissue-specific autoantibodies, or inhibition of complement 1-esterase inactivator. (often occurs after 1st dose or within 1 week)
5. Alteration in taste (most common with captopril)
6. Decreased GFR
7. CI in pregnancy—teratogenic, fetopathic
8. CI in patients with bilateral renal artery stenosis or unilateral stenosis in patients with 1 kidney (AT II is necessary to maintain filtration fraction)—caution in patients with severe congestive heart failure and acute decline in renal function

V. AT II Receptor Antagonists (ARB):
A. Mechanism and prototype.
   1. Prototype drug is losartan (Cozaar), (others include candesartan(Atacand), valsartan(Diovan), irbesartan(Avapro)). Losartan itself is active, but it also has an active metabolite with higher affinity than the parent drug.

2. All are selective AT\(_1\) receptor antagonists (>10,000 fold selectivity vs AT\(_2\)). All of the antagonists have some degree of insurmountable antagonism (losartan is fully surmountable, but its active metabolite is not). The mechanism for this lack of surmountability is not clear

3. Efficacy in treating hypertension is similar to that of ACEIs, but note that the effects of ARBs and ACEIs differ on various components of the renin-angiotensin system. The clinical consequences of many of these differences as yet unknown.
   a. Inhibition of AT\(_1\) effects are better with antagonists because receptor is blocked, whereas with ACEIs alternative paths to ATII synthesis, and other peptides with AT\(_1\) agonist activity still exist.
   b. Antagonists indirectly activate AT\(_2\) receptors because they block feedback and increase PRA and AT II production
   c. ARBs do not increase levels of other ACE substrates such as bradykinin—presumably the reason why cough is much less of a problem

B. Therapeutic Utility:
   1. Current FDA approvals (differs for different drugs) are similar to those for ACEIs: hypertension, heart failure, myocardial infarction. ARBs are also approved for diabetic nephropathy.

   2. Numerous trials have reported beneficial effects of combining ARBs with ACEIs in patients with heart failure. This is not a generalizable conclusion for all uses of ATII related drugs. Large randomized trials such as
ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) in patients with vascular disease without heart failure, or diabetes with end-organ damage, with primary outcome as a composite of cardiovascular mortality, non-fatal stroke, acute MI and CHF requiring hospitalization showed equivalent effects of the ACEI and the ARB, no additional benefit of the combination, and a slightly increased discontinuation of therapy due to adverse effects.

C. Adverse effects/ CI
   1. Much lower incidence of cough and of angioedema. Otherwise similar to ACE inhibitors.

VI. Summary comparison of effects of drugs on components of the circulating renin-angiotensin system

(adapted by Dr. J. Goldfarb from Staesssen JA, Li Y, Richart T Lancet 368:1449-56, 2006)

<table>
<thead>
<tr>
<th></th>
<th>PRA</th>
<th>PRC</th>
<th>Angiotensinogen</th>
<th>AT I</th>
<th>AT II</th>
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<tbody>
<tr>
<td>Beta blockers</td>
<td>↓</td>
<td>↓</td>
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<td>NA</td>
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<tr>
<td>Renin inhibitors</td>
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<td>NA</td>
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<td>↓</td>
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<td>ACE inhibitors</td>
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</tr>
<tr>
<td>ARBs</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

PRA = plasma renin activity; PRC = plasma renin concentration
ACE = angiotensin converting enzyme; ARB = angiotensin II type 1 receptor antagonis
VII. Bradykinin

A. Synthesis
1. Kallikreins (in plasma and tissues) convert kininogens (HMW and LMW) to kinins (bradykinin and kallidin (lysylbradykin), respectively):
2. Kallikreins exist in many tissues, pancreas, kidney, GI, salivary glands, sweat glands--

B. Metabolism
1. rapidly metabolized ($t_{1/2} = 15$ seconds) by Kininases I (carboxypeptidase) and II (identical to ACE)

C. Receptors and Actions
1. Both receptors can couple via Gq/11 and PLC, or via Gi to activate PLA2 and release arachidonic acid
2. B1-- synthesis induced by inflammatory mediators, activation produces--redness, heat, swelling, pain, release of cytokines from macrophages
3. B2--mediates most non-inflammatory effects
   a. arterial vasodilation (via endothelial NO or via PGE2 or PGI2),
   b. venoconstriction (direct or via PGF2alpha)
   c. contraction of most visceral smooth muscle

D. Antagonists
1. Icatibant--synthetic decapeptide, competitive B2 antagonist--approved in Europe for treatment of acute attacks of hereditary angioedema (HAE) (Phase III trials in US for HAE, Phase I trial for tx ACEI-induced angioedema)

Fig 5. Bradykinin-Kallidin system. Note that ACE inactivates kinins, and that actions of kinins are opposite to that of AT II. Adapted from Goodman and Gillman 11th Ed, McGraw-Hill, 2006
VIII. Natriuretic Peptides:
A. Source and Actions
1. First discovered in the 1980s, in atrial myocytes, atrial natriuretic peptide (ANP)
2. Subsequently other similar peptides, BNP (first isolated from brain) and CNP

<table>
<thead>
<tr>
<th>Peptide</th>
<th>ANP</th>
<th>BNP</th>
<th>CNP</th>
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<tbody>
<tr>
<td>Size</td>
<td>28 AA</td>
<td>32 AA</td>
<td>22 AA</td>
</tr>
<tr>
<td>Activity</td>
<td>Endocrine/paracrine</td>
<td>Endocrine/paracrine</td>
<td>Paracrine</td>
</tr>
<tr>
<td>Clearance</td>
<td>Neut endopeptidase NPR-C</td>
<td>Neut. endopeptidase NPR-C</td>
<td>Neut. endopeptidase NPR-C</td>
</tr>
<tr>
<td>Tissue distribution</td>
<td>Cardiac atria &amp; ventricles</td>
<td>Cardiac ventricles &amp; brain</td>
<td>Brain, ovaries, uterus, testes</td>
</tr>
<tr>
<td>Principal phenotype, KO mice</td>
<td>Salt sensitive hypertension</td>
<td>Myocardial fibrosis</td>
<td>Dwarfism Early death</td>
</tr>
</tbody>
</table>

Table adapted from M. Vanderheyden et al. European J. Heart Failure 6:261-268, 2004

3. Natriuretic peptide receptors are membrane bound homodimeric receptors with guanylyl cyclase activity in the cytoplasmic domain. NPR-A is the most prominent receptor mediating actions of ANP and BNP, another subtype, NPR-B is preferentially activated by CNP. A third receptor NPR-C appears to mainly serve as a clearance receptor binding all three natriuretic peptides, effecting their intracellular internalization with subsequent enzymatic destruction

4. Natriuretic peptides can also be inactivated by neutral endopeptidase on the luminal surface of endothelial cells

5. ANP is released by atrial stretch--e.g. volume expansion, increased venous return (going from standing to supine), and release is modulated by alpha1A activation, endothelins, and vasopressin. Circulating levels of ANP are increased in CHF, SIADH, primary aldosteronism, and chronic renal failure. BNP is secreted by left ventricular myocardium in response to stretch, wall tension, e.g. in CHF

6. ANP and BNP increase Na excretion and urine flow (increased GFR with little or no change in RBF, decreased proximal tubular reabsorption of Na), reduces secretion of renin, aldosterone and ADH

7. ANP and BNP decrease blood pressure directly via increased production of cGMP in vascular smooth muscle, indirectly via a reduction in sympathetic tone and they may counteract cardiac growth and remodeling. There is arterial, venous and coronary vasodilation.

8. In general you can think of ANP/BNP actions as opposite those of AT II.
B. Therapeutic applications related to natriuretic peptides
   1. BNP levels diagnostic for heart failure presence (high negative predictive value) and prognosis.

   2. Nesiritide (Natrecor)(synthetic recombinant human BNP) is approved for short-term (48 hour) treatment of acute congestive heart failure. Although nesiritide can vasodilate and lower pulmonary capillary wedge pressure, improve cardiac output and relieve dyspnea, there is currently much controversy over the safety and value of this treatment, (and even more over its off-label outpatient use) with some analyses indicating significant increases in 30 day mortality and kidney damage, and others neither of these 2, and lower mortality than dobutamine or milrinone. The most common acute adverse reaction was hypotension.

IX. Endothelins:
   A. Source and Actions
      1. A family of potent vasoconstrictor peptides. The most widely distributed is ET-1, the predominant endothelin secreted by the vascular endothelium. (Other sites of endothelin production include kidney and intestine( ET-2) and CNS (ET-3), but distribution is more widespread for all.

      2. Pharmacologic actions of ET-1.
         a. ET_A receptors are G_{q/11} and G_s coupled, and ET_B receptors are G_{q/11} and G_i coupled
         b. IV injection of ET-1 induces a transient fall in BP (via release of PGI and NO from vascular endothelium—ET_B) followed by a prolonged increase in BP via direct constriction of vascular smooth muscle (ET_A).
         c. ET-1 induces proliferation of pulmonary vascular cells and may play a role in pathogenesis of pulmonary arterial hypertension. Endothelins are also positive inotropes and chronotropes, coronary vasoconstrictors, and renal vasoconstrictors that decrease GFR and Na and water excretion. They increase the secretion of renin, aldosterone, vasopressin and ANP.

   B. Bosentan (Tracleer)
      1. A non-selective, orally active ET receptor antagonist, it is approved for treatment of pulmonary arterial hypertension. (in investigational use it also lowered blood pressure in patients with essential hypertension, and vasodilated patients with CHF)

      2. Major cautions/toxicities:
         a. hepatic injury --must check liver enzymes (AST/ALT) initially and monitor monthly
         b. Anemia--appears reversible
         c. Teratogenic, pregnancy is a CI
         d. It is metabolized by CYP3A4 and CYP2C9--caution with other drugs that are competitive substrates or inhibitors—CI with cyclosporine and glyburide
         e. Because of liver injury and teratogenic effects, bosentan can be prescribed only through a special monitored program.
INOTROPIC AGENTS

X. Digitalis Glycosides
A. Chemistry and source
A family of drugs with a steroid nucleus, a lactone ring at C17 and one or more glycosidic residues at C3. They are plant alkaloids, most prominently found in several species of floxglove, as well as in many other plants. Digoxin is the prototype.

Although ouabain is used experimentally, only digoxin is in clinical use in the US today.

B. Molecular Mechanism of Action
1. Inhibition of Na,K ATPase.
   a. Digoxin binds, reversibly, to an extracellular site on the alpha subunit.
   b. Extracellular potassium decreases the affinity of the enzyme for digoxin.
   c. There are multiple isoforms of the subunits of the Na/K-ATPase with differing tissue distribution, and differing affinity for digoxin. It is likely that inhibition of the transporter in non-cardiac tissues underlies many of the adverse effects of digoxin.

C. Cellular Actions
1. Positive Inotropic Action
   a. The positive inotropic effect induced by digoxin is secondary to the increase in intracellular Na, which, in turn, either decreases the extrusion of Ca by the Na/Ca exchanger (in cells near resting potential) or increases the entry of Ca through the exchanger (in depolarized cells).
   b. The increased Ca is stored in the sarcoplasmic reticulum leading to a larger intracellular store to be released as triggering cytoplasmic Ca rises with each action potential.
   c. Digoxin has also been observed to increase transient cytoplasmic Ca levels in the absence of an active Na/Ca exchanger, perhaps through direct interactions of the Na/K ATPase and the Na channel to permit Ca entry. (The Na/K ATPase has been shown to participate in numerous intracellular signaling pathways, independent of its ion pumping role, and these actions can be activated by binding of cardiac glycosides)

2. Baroreceptor action
   a. Digoxin increases the baroreceptor response to BP (which had desensitized with chronic heart failure and resulted in high baseline sympathetic activity)
   b. This action decreases sympathetic outflow and increases vagal outflow.
Effects of a **cardiac glycoside**, ouabain, on isolated cardiac tissue. The top tracing shows action potentials evoked during the control period, early in the "therapeutic" phase, and later, when toxicity is present. The middle tracing shows the light (L) emitted by the calcium-detecting protein aequorin (relative to the maximum possible, $L_{max}$) and is roughly proportional to the free intracellular calcium concentration. The bottom tracing records the tension elicited by the action potentials. The early phase of ouabain action (A) shows a slight shortening of action potential and a marked increase in free intracellular calcium concentration and contractile tension. The toxic phase (B) is associated with depolarization of the resting potential, a marked shortening of the action potential, and the appearance of an oscillatory depolarization, calcium increment, and contraction (arrows).

(Unpublished data kindly provided by P Hess and H Gil Wier.)  Katzung 11th ed, Fig 13-5

**D. Electrical Effects**

1. Direct actions on heart’s electrical properties
   a. Early, brief prolongation of action potential
   b. Then, shortening of action potential (particularly plateau phase)
      i. Probably due to increased conductance of calcium, caused by higher intracellular calcium
   c. Higher dig concentrations: Reduced resting membrane potential (less negative)
      i. Caused by inhibition of Na+/K+ ATPase, which causes decreased intracellular potassium.
   d. Higher toxic levels: oscillatory depolarizing afterpotentials (called delayed after depolarizations [DADs]) occur after normally evoked action potentials. Afterpotentials reach threshold, eliciting action potentials→ premature depolarizations, ectopic beats coupled to preceding normal action potential. Seen as bigeminy on EKG.
e. Even higher toxic levels: each afterpotential-evoked action potential will elicit its own afterpotential → self-sustaining tachycardia. May become ventricular fibrillation.

E. Pharmacokinetics:

1. **Digoxin** is primarily eliminated renally as the unchanged drug, with a half life of 1.5 to 2 days in patients with normal renal function.
2. Because of its large Vd (4-7 L/kg), it is not amenable to peritoneal- or hemodialysis in the event of overdose.
3. Most of the drug resides in muscle, rather than fat, so dosing regimens are based on lean body mass, not total body weight.
4. Because of its narrow therapeutic window, (target levels are commonly 0.5 to 1 ng/ml) serum levels are commonly determined at the onset of dosing and in the event of a decline in renal function or the introduction of drugs known to interact with **digoxin**
F. Therapeutic Utility:
1. Heart failure.
   Digitalis glycosides have been used for centuries (originally as plant preparations) to treat heart failure. Digoxin use has declined markedly both because of its narrow therapeutic window and because in the Digitalis Investigation Group (DIG) trial it but reduced symptoms and hospitalizations, but did not decrease mortality. A post hoc analysis of the DIG data, however, suggests that the latter finding may have been due to non-optimal dosing. In that analysis, patients with digoxin serum concentrations between 0.5 and 0.9 ng/ml did show a reduction in 1-year mortality.

2. Atrial flutter and fibrillation
   Digoxin can be used for rate control.

G. Adverse effects/toxicity
1. Visual: blurred or yellow vision, halos
2. GI: anorexia, nausea, vomiting, abdominal pain
3. Cardiac: a sagging ST segment is common—not necessarily reflecting toxic levels.
   dose related AV block, sinus bradycardia, sinoatrial arrest
   AV junctional or ventricular ectopic beats, virtually any arrhythmia
4. Psychiatric: delirium, fatigue, confusion

H. Treatment of overdose
1. If stopping or reducing dose is not sufficient, an effective antidote is a digoxin immune fab (Digibind)

I. Drug Interactions
1. Because of digoxin's narrow therapeutic window, drug interactions are of particular concern. A few classic interactions include (will learn more about following drugs in future lectures):
   a. pharmacokinetic
      i. cholestyramine decreases digoxin absorption
      ii. propafenone, quinidine, quinine, amiodarone—decrease renal Cl, decrease Vd
   b. pharmacodynamic
      i. non-K sparing diuretics—increase digoxin inhibition of Na/K ATPase
      ii. beta blockers—enhanced probability of SA or AV block

XI. Phosphodiesterase Inhibitor Inotropic Agents
A. Mechanism of action
1. Selective inhibition of PDE type 3 Milrinone is the prototype.
2. Net effect is increase in cAMP in cardiac tissue leading to increased contractility and acceleration of myocardial relaxation (equivalent to beta receptor stimulation) in addition to balanced arterial and venous dilation with a concomitant fall in both preload and afterload.
3. Cardiac output increases and pulmonary arterial wedge pressure decreases. The net effect on vascular resistance and contractility is in between that of a beta agonist positive inotrope and a pure nonselective vasodilator.

B. Therapeutic Utility
1. Used intravenously for short-term management of acute severe heart failure.
   Development of an oral form for chronic use in heart failure was discontinued because of evidence of increased mortality.
C. Adverse effects
1. Atrial fibrillation and other arrhythmias,
2. Hypotension

XII. Myofilament Calcium Sensitizers
A. Levosimendan
1. Enhances cardiac contractility without increasing intracellular Ca
2. Currently in Phase III trials in the US (but approved for clinical use in about 30 other countries), it binds to troponin C stabilizing the Ca bound configuration thus prolonging actin-myosin cross bridging without increasing oxygen utilization.
3. Levosimendan, at concentrations in the upper therapeutic range and higher also inhibits PDE 3. An active metabolite of levosimendan has greater selectivity for troponin C vs PDE 3.
4. In addition to its positive inotropic action it is also a vasodilator. This may involve, in addition to PDE 3 inhibition, opening of KATP channels.
5. Its adverse effect profile is better than that for milrinone.
XIII. Myosin ATPase activators
1. CK-1827452–increases cardiac myosin ATPase activity and speeds Pi release associated with myosin-actin bridging (This drug is in very early clinical trials).

XIV. Catecholamines (Reviewed in Autonomic Nervous System Drugs in Cardiovascular and Neuromuscular Physiology Lecture)
A. Dopamine
B. Dobutamine
GOALS: To discuss the role of endogenous nitric oxide and the pharmacology of drugs that mimic or enhance its action. To discuss the pharmacology of L-calcium channel blockers. To introduce other, less commonly used drugs that act as direct vasodilators, but use mechanisms different from mimicking NO or blocking Ca channels.

OBJECTIVES
1. Describe the synthesis and mechanism of action of endogenous nitric oxide(NO).
2. Discuss the mechanism of action of organic nitrates, using nitroglycerin as prototype, and indicate how the action of nitroprusside differs from that of the organic nitrates.
3. Indicate the rationale for sub-lingual nitroglycerin.
4. Describe the adverse effects of, and the contraindications to nitrates, the conditions under which tolerance to their effects develops, and possible mechanisms underlying tolerance.
5. Discuss the mechanism of action of sildenafil and its potential drug interactions and adverse effects.
6. List a prototype member for each of the three chemical classes of Ca channel blockers and describe how their pharmacodynamic effects differ. Explain how this influences the therapeutic utility of the various classes and their adverse effects.
7. Indicate how hydralazine and minoxidil differ from other vasodilators discussed in this lecture. List prominent side effects of these two drugs.
8. List the therapeutic uses for each of the key drugs and indicate the mechanistic rationale for the use.

KEY DRUGS
nitric oxide (NO), nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, nitroprusside, sildenafil, amlodipine, nifedipine, diltiazem, verapamil, hydralazine, minoxidil.

KEY WORDS AND PHRASES
nitric oxide synthase (nos), preload, afterload, L calcium channel, guanylyl cyclase, cGMP, phosphodiesterase, ATP-dependent K channel

TEXTBOOK READING
Katzung, 12th Ed. Chapter 19, Nitric Oxide
Chapter 12, Vasodilators and the Treatment of Angina Pectoris
Chapter 11 Antihypertensive Agents--sections on Vasodilators and Ca channel blockers
I. Nitric Oxide (NO)

A. Normal Physiology

1. The primary source of tissue NO is the enzymatic conversion of arginine to citrulline. The enzymes responsible are known as NOS, nitric oxide synthases. Some are constitutive such as neuronal NOS (nNOS or NOS1) and endothelial NOS (eNOS or NOS3). These are activated by increases in intracellular calcium. There is also an inducible NOS (iNOS or NOS2) in macrophages and other cells whose transcription is induced by inflammatory mediators (e.g. TNF-α, interferon-γ). There are antagonists of the synthase such as L-NMMA an arginine analog. With NOS blocked, drugs that normally release NO from endothelium lose their dilating effect, as they would if the endothelium were damaged.

The figure shows contraction of a strip of rat aorta in a tissue bath upon exposure to phenylephrine. In panels A, C, and D, the endothelium is intact. In panel B the endothelium has been removed. Panel A shows the normal relaxant effect of ACh in an intact preparation. Panel B, the fact that in the absence of endothelium, the ACh loses its vasodilator property. Panel C shows that by blocking NOS, the ACh dilator response is diminished, and panel D that inclusion of hemoglobin in the bath blocks the dilator response to ACh. (From Katzung, 8th Edition)

2. NO acts in the vasculature by interacting with the iron in the heme moiety of soluble (cytoplasmic) guanylyl cyclase and increasing the production of cGMP.

3. The cGMP via activation of a kinase(PKG) can reduce vascular tone by multiple mechanisms including decreasing cytosolic free calcium, opening Ca-activated K channels, and activation of myosin light-chain phosphatase which dephosphorylates the myosin light chain and the muscle relaxes.
4. In vasculature, NO from endothelial cells is a primary determinant of resting vascular tone (it diffuses into the smooth muscle and induces relaxation) and an inhibitor of platelet adhesion and aggregation. Endothelial NO synthesis is enhanced by hormone mediated calcium entry or by shear stress to the vessel wall.

5. Targets of NO aside from guanylyl cyclase include other metal containing enzymes including CYP450 and cytochrome oxidase which are inhibited, thiols including glutathione which can be nitrosylated. Interactions with superoxide can convert NO to peroxynitrite which can nitrate tyrosines in proteins (consequences not clear) and cause oxidative damage to nucleic acids.

6. Other actions of NO: In immune system cells, NO mediates macrophage-induced cytotoxicity and it is a mediator of inflammatory states. In the CNS it serves as a neuromodulator. In cardiac tissue it can decrease remodeling.

7. NO can be inactivated by oxyhemoglobin and by superoxides.

B. Therapeutic Use
1. The only FDA approved use is inhalation in term and near-term infants with respiratory failure associated with pulmonary hypertension, but there is no clearly established long-term outcome improvement in mortality or brain injury. There is some support for off-label use in adults with acute respiratory distress syndrome, pulmonary hypertension, and other conditions but again long-term outcome improvement is not established. In general, minimal systemic effects occur because NO strongly binds to oxyhemoglobin which inactivates it by sequestration and by oxidation to nitrate. (Note effect of hemoglobin included in the tissue bath in the figure above)

C. Modulation of endogenous NO effects—PDE5 inhibitors
1. Sildenafil (Viagra, Revatio), tadalafil (Cialis, Adcirca), vardenafil (Levitra)—are selective inhibitors of phosphodiesterase 5, the main phosphodiesterase in corpus cavernosum. This increases the half-life of cGMP formed in response to NO, thus enhancing NO’s vasodilating effects.

2. Sildenafil—metabolized by CYP3A4

3. Side effects:
   a. headache, disturbance in color vision (sildenafil has only 10 fold selectivity for PDE5 vs. PDE6, both exist in the retina)
   b. abrupt loss of vision and abrupt loss of hearing have been reported (uncertainty as to whether these cases represent actual effects of these drugs)

4. Drug interactions—
   a. if taken with nitrate vasodilators profound hypotension can result. **Cl in patients using nitrates.**
   b. if taken with alpha blockers, hypotension (especially orthostasis) may be enhanced, caution with all drugs that have alpha blockade as part of their action.

5. Approved uses:
   a. erectile dysfunction—PDE5 in corpus cavernosum
   b. pulmonary hypertension (sildenafil, tadalafil)—in patients with pulmonary hypertension, PDE5 is induced in small pulmonary arterioles and in right
ventricular myocytes (in myocytes the increased cyclic G inhibits PDE3, thus increasing contractility)
c. benign prostatic hyperplasia (tadalafil)

6. Potential uses
   a. pulmonary effects may be beneficial in heart failure
   b. PDE5 blockade in cardiac myocytes may limit hypertrophic response to pressure
      and beta agonism.

II. Organic nitrate vasodilators:

\[
\begin{align*}
\text{Nitroglycerin} & \quad \text{Isosorbide dinitrate} & \quad \text{Isosorbide mononitrate} \\
\text{(Glyceryl trinitrate)} & \quad & \\
\text{CH}_2\text{–ONO}_2 & \quad \text{O}_2\text{NO} & \quad \text{O}_2\text{NO} \\
\mid & \quad \text{OH} & \quad \text{OH} \\
\text{CH–ONO}_2 & \quad \text{H} & \quad \text{H} \\
\mid & \quad \text{ONO}_2 & \quad \text{ONO}_2 \\
\text{CH}_2\text{–ONO}_2 & & \\
\end{align*}
\]

A. Mechanism of action.
   1. These drugs release NO or an NO-like substance which in turn activates a cytoplasmic guanylyl cyclase thus increasing intracellular cGMP and leading to smooth muscle relaxation
   2. The precise mechanism of the denitrification of these compounds is controversial. All interact with some tissue component (a "nitrate receptor") that mediates the NO or NO-like substance production.
   3. Nitroglycerin is activated by the mitochondrial aldehyde dehydrogenase (ALDH2) to form NO itself (nitrite (NO\(^2\)-), which is reduced to NO in the mitochondria) or some other NO-like substance. While this appears to be a therapeutically relevant pathway, it is not the only mechanism for formation of NO from nitroglycerin
   4. Other organic nitrates such as isosorbide dinitrate and mononitrate do not appear to be ALDH2 substrates, and may be metabolized by cytoplasmic aldehyde dehydrogenase (ALDH1a1) CYP450s, or other enzymes to release NO.
   5. Note that all of these agents themselves provide NO or an NO equivalent. They are not dependent on endogenous NO and NOS. They can vasodilate even in the absence of intact vascular endothelium.
mtALDH mediates GTN-induced vasodilation in vitro and in vivo.

(A) Aortic relaxation in vitro.

(Upper) Polygraph tracings of strain gauge output illustrate typical dose–response relations in vitro for GTN- and SNP-induced vasorelaxation of aortic ring segments from wild-type (wt) and mtALDH /− mice. Initial tension was induced with prostaglandin F2 (PGF). Dosages of GTN and of SNP are given as log molar concentrations.

(Lower) Graphical summaries of dose–response curves illustrate that GTN-induced relaxation (Left) is essentially eliminated in mtALDH /− aorta at GTN concentrations less than 0.5 M and that the attenuation of responsiveness of mtALDH /− vs. wild-type aorta decreases with increasing GTN concentration (n = 12; * P < 0.05). (Note that the dose–response curve for wild-type aorta is biphasic, with a distinct region of reduced slope.) (Right) In contrast, vasorelaxation induced by the NO donor SNP (n = 6) or by the nitrovasodilator ISDN (n =2–4) is indistinguishable between wild-type and mtALDH / aorta.

(B) Blood pressure in vivo. The decrease in mean arterial blood pressure induced by i.v. administration of GTNs is significantly attenuated in mtALDH /− vs. wild-type mice, whereas the response to SNP is unaltered(n = 12–13; *, P < 0.05). (Chen, Z et al., PNAS 102:12159-12164, 2005) GTN=nitroglycerin, SNP = nitroprusside, ISDN = isosorbide dinitrate.
B. Effects:

1. Systemic vessels:
   a. Venous vasodilation > arterial (presumably due to differential distribution of the enzyme(s) mediating conversion. At low doses, the result is decreased RVEDP, LVEDP, and ventricle size with much smaller change in TPR (although face and neck arterioles may dilate producing flush). BP may fall slightly and HR may increase slightly; pulmonary vascular resistance and cardiac output (CO) are slightly reduced. Decreased preload can decrease O₂ demand, and relieve congestive symptoms in patients with CHF.
   b. As dose is increased, frank venous pooling may occur as well as arterial dilation, and there is a decrease in systolic and diastolic BP with reduced CO which may lead to dizziness, pallor, and compensatory sympathetic reflexes which can shore up BP and CO. (If patients have autonomic failure and can't compensate, angina may worsen as CO and coronary flow decrease, and hypotension my become severe.)

2. Myocardial oxygen supply--Coronary vessels
   a. There may or may not be an increase in total coronary flow, but there is clearly a redistribution of flow in the presence of partial coronary occlusion such that flow increases primarily in ischemic regions. For endocardial vessels, flow increases because of the reduction in end diastolic ventricular pressure. Large epicardial vessels dilate (nitroglycerin preferentially dilates vessels > 200µm in diameter) without dilation of the smaller resistance vessels that would produce coronary steal. Collateral flow to ischemic regions increases.
   b. In patients with angina secondary to coronary vasospasm (Prinzmetal's variant, vasospastic angina) coronary dilation may be the major mechanism of organic nitrates.

3. Myocardial oxygen demand:
   a. Oxygen demand is related to cardiac work, which is in turn a function of ventricular wall tension (determined by preload and to a lesser extent, afterload), heart rate, and myocardial contractility. The net effect of nitroglycerin is to reduce oxygen demand.

4. Other smooth muscles:
   a. Can relax almost all smooth muscle including bronchial, biliary tract, esophagus

5. Tolerance:
   a. Frequently repeated or continuous exposure to organic nitrates leads to a diminution of effect. There are multiple hypotheses about the cause of the tolerance (and data are conflicting).
      i. Diminished ability for enzymatic conversion of the parent drug to NO or NO-like substances (Aldehyde dehydrogenase has sulphydryls adjacent to the enzymatic site and these are postulated to be involved in the denitration of nitroglycerin. Prolonged administration of nitroglycerin in vitro decreases the activity of this enzyme, and historically administration of large quantities of reducing agents could prevent or reverse nitrate tolerance).
      ii. Alteration in soluble guanylyl cyclase or subsequent step in the vasorelaxant pathway
      iii. Physiological compensatory reactions that counter the nitrate effect.
iv. Endothelium superoxide generation contributes to nitrate tolerance by inactivating NO.
b. Significant tolerance can be prevented by interrupting therapy for 8-12 hrs a day.

C. Kinetics:
1. Hepatic glutathione organic nitrate reductase converts nitrates into denitrated metabolites and inorganic nitrite.
2. Sublingual nitroglycerin is available as tablets or as a metered dose spray. It has peak plasma level in 4-7 min and a t$_{1/2}$ of about 1-3 min. (The dinitrate metabolite is about 1/10 the potency and has a t$_{1/2}$ of about 40 min). This route of administration avoids first pass metabolism and offers rapid absorption from the mucosa.
   - Isosorbide dinitrate is also available as a sublingual preparation (as well as oral).
3. Nitroglycerin, in addition to the sublingual preparations is also available in an IV preparation, an ointment, a transdermal disc, and a sustained release oral preparation (which has poor bioavailability)
4. Isosorbide 5-mononitrate (t$_{1/2}$ = 3-6 hrs)(which is also a metabolite of isosorbide dinitrate) has little first pass metabolism and thus has excellent bioavailability p.o. It is also available in an extended release preparation

D. Therapeutic utility: FDA approved indications for nitroglycerin (for others FDA approval is for angina):
1. Effort angina: prophylactic and to terminate attack
   a. Relieves symptoms but does not increase survival.
2. Variant (vasospastic) angina
3. Congestive heart failure associated with an MI
4. Unstable angina, myocardial infarction
   a. May be beneficial in reducing pain, no clear evidence for survival benefit
5. Control of intraoperative blood pressure
6. As ointment: moderate to severe pain associated with chronic anal fissure

E. Adverse effects/CI and Drug interactions:
1. Headache, flushing, tachycardia, dizziness (postural hypotension), fainting.
2. Relative contraindication in hypertrophic cardiomyopathy (the decrease in LVEDP contributes to block of access to aortic valve).
3. Interaction with sildenafil and other PDE5 inhibitors : see above

F. Future possibilities
1. Nitrates of other drugs have been synthesized that can donate NO, and thus serve as dual action cardiovascular drugs (e.g. valsartan dinitrate; valsartan mononitrate). Whether this will lead to enhanced clinical efficacy is unknown.
III. Sodium nitroprusside

A. Mechanism
1. A nitrovasodilator, that releases NO rapidly, via poorly understood enzymatic and non-enzymatic mechanisms. Once released the NO mechanism of action is identical to that described above.

B. Effects
1. **Nitroprusside** dilates both arterioles and venules and thus both lowers TPR and venous return (so the hypotensive effect is greater when the patient is upright) and CO generally falls in patients with normal left ventricular function. If left ventricular function is impaired, then afterload reduction predominates and CO rises.
2. Tolerance is not reported with continued use of this drug, and patients tolerant to organic nitrates may show no cross tolerance to nitroprusside.

C. Kinetics
1. **Nitroprusside** must be given by continuous IV infusion because the effects of a single injection last only about 5 minutes.
2. Metabolism releases not only NO but CN as well.

D. Therapeutic utility:
1. Hypertensive emergencies
2. Acute exacerbation of CHF
3. For controlled hypotension in surgery
4. Post MI to decrease oxygen consumption (off label)

E. Adverse effects:
1. Excessive vasodilation—need close monitoring of BP and a variable infusion pump.
2. Although the CN produced by metabolism of the nitroprusside is, in turn, metabolized by hepatic rhodanese to thiocyanate which is eliminated in the urine, CN poisoning can occur with high infusion rates and it may be necessary to also give thiosulfate to prevent accumulation of CN. Thiocyanate is also toxic and with long-term administration, especially with renal impairment, you may get toxicity including anorexia, nausea, fatigue, disorientation and psychosis. (Thiocyanate is dialysable)
IV. Calcium Channel Blockers:

A. Overview of Ca channels, Ca channel blockers, and molecular mechanism of action

1. Voltage gated calcium channels consist of a large pore forming $\alpha_1$ subunit with 4 domains each with 6 membrane spanning units (similar to Na channel) and modulatory subunits ($\alpha_2$–$\delta$, $\beta$, $\gamma$). There are many subtypes of alpha subunits, they differ among the various classes of Ca channels (L,N,P/Q, R,T) and even within classes.

2. Classes of calcium channel blockers approved in the U.S and prototype drugs.
   a. phenylalkylamines--verapamil
   b. benzothiazepine--diltiazem
   c. dihydropyridine--nifedipine is prototype, amlodipine, felodipine, isradipine, nicardipine, nisoldipine,

3. All act by binding to the $\alpha_1$ subunit (the pore forming subunit) of the channel and are selective for L channels, but the different classes have different binding sites on the channel, different selectivities for L calcium channels relative to other cation channels, and, in vivo, different relative potencies for cardiac vs. vascular actions.
   a. for cardiac vs. vascular effects in vivo: verapamil, diltiazem> dihydropyridines (e.g. nifedipine, amlodipine) (which have "selective" vascular actions)
   b. for Ca channel vs. Na channel blocking potency:
      dihydropyridines, diltiazem
      >>verapamil

4. The action of the drugs is to decrease the probability that a channel will open at any given level of depolarization. In the heart, modulation of L channels by $\beta_1$agonists shifts the curve in the opposite direction.
B. Pharmacological actions:

1. Vasculature
   a. Ca blockers are most potent in blocking voltage activated Ca channels (L); at higher concentrations they can also block receptor activated Ca channels and Ca release from sarcoplasmic reticulum.
   b. By reducing cytoplasmic Ca, there is a reduction in Ca-calmodulin activation of myosin light chain kinase, and thus reduced phosphorylation of myosin light chain and blockade of muscle contraction.
   c. The effects are predominantly arterial (including coronary arteries), not venous so afterload is significantly reduced but not preload.

2. Heart
   a. Ca is involved in both action potential formation and conduction (SA and AV nodes) in maintenance of the plateau in atrial and ventricular action potentials, and in excitation-contraction coupling (via binding to troponin and thus releasing the inhibitory troponin from blocking actin-myosin interaction).
   b. All Ca blockers can thus potentially produce a negative inotropic and dromotropic effect. The dihydropyridines are somewhat more potent on vasculature than they are on heart. At concentrations that directly affect cardiac channels, the profound arterial dilation results in compensatory sympathetic drive on the heart that virtually obliterates the direct action of the drug. In nodal tissue, in addition to the reflex response is the fact that nifedipine does not show use-dependent block and does not increase the recovery time for inactivated Ca channels as do verapamil and diltiazem. Thus dihydropyridines, at clinically used doses, are essentially devoid of effects on nodal conduction, or on cardiac contractility.
   c. Verapamil both increases recovery time of cardiac L channels (by selective affinity for inactivated channels --similar to mechanisms of action of local anesthetics at the sodium channel which we discussed earlier in the course) and has rate dependent blocking effects. Because verapamil is more potent than dihydropyridines at cardiac L channels relative to vascular channels, verapamil will slow AV conduction (increases the PR interval) and can have negative inotropic effects. At high concentrations, verapamil also can block sodium channels.
   d. Diltiazem also has higher cardiac L channel potency relative to vascular potency than dihydropyridines.

3. Net hemodynamic effects of the dihydropyridines vs. verapamil:
   a. Nifedipine acutely decreases BP with little venous pooling, cardiac output and HR increase. Other drugs in the class are similar. Amlodipine produces less reflex tachycardia, perhaps because with its plasma half-life of 1-2 days and slow absorption, there is little peak to trough variation with chronic once a day dosing.
   b. Verapamil, at doses producing arterial vasodilation, also often has some negative inotropic, dromotropic, and chronotropic effects. Because of activation of sympathetic reflexes, in patients without decreased left ventricular function CO may actually improve, but in patients with CHF, who are already generally under high sympathetic tone, CO may decrease.
c. Net effects of drugs are dependent on dose, cardiac status, and reflex responsiveness

<table>
<thead>
<tr>
<th>Effect</th>
<th>Nifedipine</th>
<th>Diltiazem</th>
<th>Verapamil</th>
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<tbody>
<tr>
<td>Coronary vasodilation</td>
<td>↑↑↑</td>
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<tr>
<td>Peripheral vasodilation</td>
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<td>Myocardial contractility</td>
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<td>Cardiac output</td>
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<td>Resting Heart Rate</td>
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<tr>
<td>AV conduction</td>
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C. Kinetics
1. All can be given orally, bioavailability varies (e.g. verapamil 0.2-0.3, diltiazem 0.4, nifedipine 0.3-0.6, amlodipine 0.6-0.9) primarily because of first pass metabolism. Elimination is primarily metabolic. Thus, in patients with hepatic disease, doses should be decreased.
2. Half-lives vary considerably, but short-acting drugs are available in sustained release preparations. Both diltiazem and verapamil have active metabolites, but they are less potent than the parent compounds.
3. Parenteral preparations are available for verapamil, diltiazem, and nicardipine.

D. Therapeutic utility:
1. FDA approved:
   a. Angina --amlodipine nifedipine, diltiazem, verapamil
   b. Arrhythmias--verapamil, diltiazem
   c. Hypertension--amlodipine, nifedipine, diltiazem, verapamil
   d. Prophylaxis--pts with angiographically documented CAD without heart failure--amlodipine
2. Some Off label uses:
   a. Hypertrophic cardiomyopathy--verapamil
   b. Migraine--verapamil
   c. Raynaud's syndrome--nifedipine, diltiazem, amlodipine
   d. Diabetic nephropathy--amlodipine, verapamil, diltiazem
3. Note that some calcium channel blockers are extensively marketed as combination drugs. E.g. amlodipine is marketed with aliskiren, aliskiren+hydrochlorothiazide, olmesartan, olmesartan + hydrochlorothiazide, benazepril, valsartan, valsartan +hydrochlorothiazide, and telmisartan.--all indicated for hypertension, and in combination with atorvastatin for hypertension with hyperlipidemia.

E. Adverse effects, Toxicity, CIs:
1. Excessive arteriolar dilation: dizziness, hypotension, headache, flushing, edema
2. Dihydropyridines (short acting) may increase anginal discomfort if given without a beta blocker, due to sympathetic reflex increasing cardiac oxygen demand. Thus long-acting preparations are preferred.
3. Interference with other calcium dependent processes: constipation, GI reflux (relaxation of lower esophageal sphincter)

4. Add for **verapamil** and **diltiazem**: bradycardia, exacerbation of CHF, AV block—especially if given with a beta blocker. Relative CIs for verapamil and diltiazem are SA or AV nodal disturbances or ventricular dysfunction. Both are also CYP3A4 inhibitors, **Verapamil**, in addition blocks the P-glycoprotein transporter.

V. K-channel openers:

A. Minoxidil:

1. Mechanism
   a. A pro-drug that is metabolized by hepatic sulfotransferase to minoxidil N-O sulfate (a minor metabolite) which activates the ATP-modulated K channel (increased ATP closes the channel) thus moving the resting potential of smooth muscle towards the K equilibrium potential (hyperpolarization) which in turn decreases voltage dependent Ca entry and thus induces relaxation.

2. Effects
   a. Its action is essentially that of an arterial vasodilator which induces sympathetic baroreceptor reflexes that increase cardiac rate and contractility. There is marked increase in cardiac output secondary to increased venous return (due to distribution of blood to regional vascular beds with fast time constant for return).

3. Adverse effects:
   a. Retention of salt and water secondary to increased renin production Diuretics can control the fluid retention.
   b. The sympathetic reflex can increase cardiac oxygen consumption and thus in patients with coronary artery disease myocardial ischemia can be induced. Beta blockers can be used to control this.
   c. Increased venous return coupled with the retention of salt and water can cause pulmonary hypertension in patients with left ventricular hypertrophy and diastolic dysfunction (loss of ventricular compliance)
   d. Flattened and inverted T waves secondary to the activation of cardiac K channels that shorten APD.
   e. Hypertrichosis—see therapeutic utility

4. Therapeutic utility:
   a. Primary current use is as a topical preparation for hair growth (Rogaine)
   b. Severe chronic hypertension refractory to other agents and combinations: Never use it alone, always with a diuretic and beta blocker (see above)
VI. Hydralazine

A. Mechanism
1. A direct vasodilator whose mechanism of action is not definitively established.

B. Effects
1. It selectively dilates arterioles (coronary, cerebral and renal vessels more than skin and muscle, but not epicardial coronary arteries) and is associated with a powerful sympathetic baroreceptor reflex resulting in increased HR and contractility, increased renin and increased salt and water retention. (can give with beta blocker to modulate cardiac stimulation).
2. Hydralazine appears, in addition, to have some direct positive inotropic action.
3. Hydralazine inhibits vascular superoxide production

C. Kinetics
1. Hydralazine is metabolized by N acetylation (recall pharmacogenetics of acetylation) but because there are other pathways of metabolism and hepatic clearance is high extraction, hepatic blood flow, not pharmacogenetic variation in acetylator status is the main determinant of half-life.

D. Therapeutic utility:
1. Not generally used as sole drug for treatment of chronic hypertension because of cardiovascular reflex effects and fluid retention. Most common use is in hypertension developing in mid to late pregnancy, and for hypertensive emergencies in pregnancy
2. Hydralazine (37.5 mg) plus isosorbide dinitrate (20 mg) (BiDil) when added to standard therapy in black patients with congestive heart failure (NYHA Stage III/IV) significantly reduced mortality. (The African-American Heart Failure Trial, A-HeFT (This may be in part due to hydralazine’s antioxidant actions decreasing the destruction of NO). FDA approval for the combination (BiDil) is as adjunct in black patients with heart failure.

E. Adverse effects
1. Similar to minoxidil without the consequences of shortened APD. The probability of coronary steal is so high that it is CI in patients with coronary artery disease.
2. Immune reactions--drug-induced lupus erythematosis is most common (generally after at least 6 months of use of higher than minimally effective doses)--ANA conversion is faster in slow acetylators, not all ANA positive patients actually develop lupus. (may also induce hemolytic anemia, glomerulonephritis, vasculitis)
GOALS: To present the basic mechanisms of action, and effects of drugs that can alter impulse generation and conduction in cardiac tissue, and to discuss how these actions contribute to antiarrhythmic activity as well as arrhythmogenesis.

OBJECTIVES
1. Review the ion currents that underlie cardiac action potentials, and the relationship between the normal sequence of cardiac conduction and the electrocardiogram. Compare and contrast the shape of, and the currents underlying action potentials and diastolic potentials in SA node, atrial muscle, AV node, Purkinje system, and ventricular muscle.
2. List the major channel types and receptors that are the targets of the various classes of antiarrhythmic drugs and indicate the primary mechanisms of action underlying the Vaughan Williams classification of antiarrhythmics. List drugs altering cardiac electrophysiology that do not fall into this classification and their mechanisms of action.
3. Describe how the cellular actions of the various drugs affect action potential conduction, and refractoriness and how these changes can terminate a re-entrant arrhythmia.
4. Explain how the cellular mechanism of action of the various classes of antiarrhythmics is reflected in the changes they would produce in a normal EKG, and describe the EKG changes produced by a prototypical antiarrhythmic in each of the classes.
5. Indicate in general terms the differential utility of various antiarrhythmics for supraventricular versus ventricular arrhythmias.
6. Describe the two pharmacological approaches to the treatment of atrial fibrillation, and the antiarrhythmics that might be used for each. List antiarrhythmics useful in PSVT and VT.
7. Describe the impact of CAST (Cardiac Arrhythmia Suppression Trial) on the use of antiarrhythmics and the implications for choosing appropriate end-points in designing efficacy studies.

KEY DRUGS
quinidine, procainamide, lidocaine, flecainide, propafenone(just class identification) propranolol, esmolol, sotalol, carvedilol, amiodarone, dronedarone, dofetilide, verapamil, adenosine, digoxin

KEY WORDS AND PHRASES
arrhythmia, ion channel, re-entry, automaticity, refractoriness, action potential, atrial fibrillation, PSVT (paroxysmal supraventricular tachycardia), VT (ventricular tachycardia), CAST

TEXTBOOK READING
Katzung, 12th Ed. Chapter 14 Agents Used in Cardiac Arrhythmias
I. Review of cardiac electrophysiology

A. Normal Cardiac Action Potentials,
   1. Their sequence, and relationship to the electrocardiogram.

Schematic representation of the heart and normal cardiac electrical activity (intracellular recordings from areas indicated and ECG). Sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje cells display pacemaker activity (phase 4 depolarization). The ECG is the body surface manifestation of the depolarization and repolarization waves of the heart. The P wave is generated by atrial depolarization, the QRS by ventricular muscle depolarization, and the T wave by ventricular repolarization. Thus, the PR interval is a measure of conduction time from atrium to ventricle, and the QRS duration indicates the time required for all of the ventricular cells to be activated (i.e., the intraventricular conduction time). The QT interval reflects the duration of the ventricular action potential.

Katzung, Masters, Trevor Basic & Clinical Pharmacology 12th Ed
2. Normal EKG nomenclature: (D. Vorchheimer, Cardiovascular Pathophys.)

3. The ionic currents involved
   a. The figure shows ionic currents in a generalized non-nodal cell. Although there are many channels with different gating properties, the basic pattern is:

   **Phase 0** is mediated by Na
   **Phase 1** by transient K
   **Phase 2** by Ca, (Na) and K
   **Phase 3** by the increasing predominance of K vs. Ca
   **Phase 4** by K (if automaticity present, an inward cationic "pacemaker" (Na/K) current (Iₙ)

   b. In AV and SA node, the major ion carriers are:
   **Phase 0** is Ca current (T and L) with a minor contribution from Na,
   **Phase 1 and 2** are absent
   **Phase 3** is again the increasing predominance of K vs. Ca
   **Phase 4** by declining K, and the inward pacemaker Iₙ.

   c. Subtypes of channels may differ in different cardiac regions. For example in

   4. refractoriness
a. Refractoriness occurs because voltage-gated Na and Ca channels inactivate after opening and must recover before they can conduct again. The Na recovery time-course is voltage-dependent (figure B). It is faster in hyperpolarized than in depolarized tissue.

b. Note that whereas return to resting potential permits rapid recovery of Na activation, (figure A) recovery of Ca activation is delayed so refractoriness of nodal cells far outlasts the duration of their action potentials (figure C).

![Diagram A](https://via.placeholder.com/150)

![Diagram B](https://via.placeholder.com/150)

![Diagram C](https://via.placeholder.com/150)

**Goodman and Gilman 10th edition**

**B. Arrhythmias--disturbances in impulse formation and conduction**

1. Changes in automaticity—
   a. Enhanced SA nodal automaticity leading to sinus tachycardia
   b. Depression of SA nodal automaticity so that secondary pacemakers take over
   c. Enhancement in non SA nodal pacemakers so that extra beats are triggered. This can occur with depolarization of the tissue such as occurs with ischemia, or with excess sympathetic stimulation that enhances $I_f$
2. Triggered automaticity--
   a. Delayed after-depolarizations--secondary to an increase in 
cytoplasmic calcium. The 
Na-Ca antiporter exchanges 
3Na for 1 Ca and so is 
electrogenic. They are more 
likely to be larger and reach 
threshold for an ectopic beat 
at faster heart rates.
   b. Early after-depolarizations -- 
due to instability of 
membrane during repolar-
ization involving both Na and L Ca channels. 
They are more likely to occur when AP durations are prolonged such as when 
heart rate is slow, during hypokalemia, or (see below) when antiarrhythmics block 
K channels

3. Failure of impulse conduction--e.g. dropped beats with AV block

4. Reentry.

Conditions Required for Reentry

- **Loop Circuit**
- **Unidirectional Block**
- **Decremental Conduction**

D. Vorchheimer, Cardiovascular Pathophysiology

a. A pattern of excitation in a loop of excitable tissue that, because of unequal 
refractoriness in two pathways permits one-way block of action potentials and 
retrograde reentry into the blocked path.
b. This can occur because of structural abnormalities like an accessory atrio-
ventricular bundle (Wolff-Parkinson-White syndrome), slow and fast branches of 
the AV node (AV reentrant tachycardias, Paroxysmal supraventricular 
tachycardia-PSVT), or with conduction decrement in a region secondary to 
ischemia.
c. The figure above shows anterograde block in the lower path. Depending on circumstances this circuit could produce an extra reentrant action potential following each normal (that is SA nodal triggered) anterograde potential, or, if the timing is right, repeated excitation around the loop and a sustained tachycardia.

d. Such excitable loops can also form because of inhomogeneities in cellular properties leading to a functional rather than anatomic core that forms in multiple locations and moves over the myocardium (fibrillation)

5. Channelopathies

a. Arrhythmias can be the result of insults to the heart such as ischemia, actions of drugs that alter channel function, inherited mutations in channel proteins that can involve either loss of function or gain of function, and interactions among these. Some examples of channelopathies include:

i. A loss of function mutation in HERG that alters the delayed rectifier current IKr resulting in long QT syndrome and increased risk of torsade de pointes (note that known gene mutations associated with long QT syndromes involve at least 8 genes which include both K, Na and Ca channels as well as ankyrin-B),

ii. Gain of function mutations in hRYR2 the ryanodine “receptor” (the channel that controls Ca release from the sarcoplasmic reticulum) that causes ventricular arrhythmias triggered during adrenergic stimulation of the heart

iii. Loss of function mutation in HCN4, a component of If that causes sick sinus syndrome

b. The identification of particular channels as causal for arrhythmias holds out the hope for development of selective antiarrhythmic drugs with better adverse effect profiles than those currently available.
II. Classification and basic mechanisms of antiarrhythmic agents (Vaughan Williams classification)

Note that the Vaughan Williams classification is really a combination of description of drug actions (e.g. Na channel block (class I), potassium channel block (class III)) and classification of drugs based on predominant actions or combinations of actions (e.g. quinidine as Class IA—Na and K block, amiodarone as class III even though it has actions representative of all four Vaughan Williams classes)

A. Class I drugs: Na channel blockers

1. Mechanisms by which Na channel block can be antiarrhythmic
   a. decrease conduction velocity in fast Na action potential tissues
   b. increase refractoriness in fast Na action potential tissues (by shifting the relationship between membrane potential and recovery from inactivation)
   c. decrease aberrant impulse generation by increasing threshold, decreasing automaticity by blocking other Na currents--e.g. If (pacemaker current), primarily in ectopic pacemakers

Left: The fraction of sodium channels available for opening in response to a stimulus is determined by the membrane potential immediately preceding the stimulus. The decrease in the fraction available when the resting potential is depolarized in the absence of a drug (control curve) results from the voltage-dependent closure of $h$ gates in the channels. The curve labeled Drug illustrates the effect of a typical local anesthetic antiarrhythmic drug. Most sodium channels are inactivated during the plateau of the action potential. Right: The time constant for recovery from inactivation after repolarization also depends on the resting potential. In the absence of drug, recovery occurs in less than 10 ms at normal resting potentials (~85 mV). Depolarized cells recover more slowly (note logarithmic scale). In the presence of a sodium channel-blocking drug, the time constant of recovery is increased, but the increase is far greater at depolarized potentials than at more negative ones.
2 Subclassification of Class I drugs.
   IA: Na channel blockade with intermediate dissociation time (1-3 sec) from resting
   channel plus increase in action potential duration (APD) (Also has K+ channel
   block--Class III activity). (quinidine, procainamide, disopyramide.)
   IB: Na channel blockade with rapid dissociation time (0.1-0.4 sec)
   APD shortening (block of window Na current)
   (lidocaine, mexiletine)
   IC: Na channel blockade with long dissociation time (10 sec)
   "no change in APD" (but this varies with region and action potential
   frequency)
   (flecainide, propafenone)

B. Class II drugs: Beta Blockers
   1. Mechanisms by which beta blockers can be antiarrhythmic
      Decrease sympathetic tone to heart, thus decreasing automaticity and increasing
      refractoriness at the AV node and decreasing sympathetic-induced DADs.
      (propranolol, acebutalol, esmolol, sotalol(also has class III activity), carvedilol
      (also blocks ryanodine (RyR2) receptor decreasing intracellular Ca release)

C. Class III drugs: Action potential lengtheners—most are K channel blockers
   1. Mechanisms by which K channel blockers can be antiarrhythmic
      Increase refractoriness by increasing the action potential duration.
      (dofetilide, sotalol, amiodarone and dronedarone (both also class I, II
      and IV actions))
   2. Another mechanism for increasing APD is to enhance the “window” (or persistent) Na
      current--ibutilide does this (as well as some K blocking action)

D. Class IV drugs: Calcium channel blockers (nondihydropyridine)
   1. Mechanisms by which Ca channel block can be antiarrhythmic
      Decreases conduction velocity and increases threshold and refractoriness in nodal
      cells and decreases the terminal portion of phase 4 depolarizations via block of Ca
      component which also decreases excitability.
      (verapamil, diltiazem)

E. Other drugs that alter cardiac impulse initiation and conduction
   1. Adenosine
      Activation of A1 receptors (Gi/o coupled) increases K permeability, and inhibits
      adenyl cyclase, and decreases Ca conductance at the AV node (and in atrial
      tissue) (action similar to activation of M2 receptors by acetylcholine). The clinical
      use of adenosine is based on its ability to slow conduction and increase
      refractoriness at the AV node. AV actions are greater than SA actions.
   2. Digoxin
      Inhibits cardiac Na/K ATPase and enhances vagal effects on the heart. Slows heart
      rate and AV conduction and increases AV refractoriness.
3. Vernakalant
   Currently approved in Europe for treatment of atrial fibrillation— in phase III trials in the US. Considered "atrial selective" it blocks K channels underlying $I_{Kr}$ and $I_{KAc}$ which are much more prominent in human atria compared to ventricles. In addition it has rapid offset Na channel block that appears to be more prominent in atria.

4. Ranolazine
   Blocks the window (persistent) sodium current. (FDA approved in 2006 for angina), and IKr and appears atrial selective for block of initial phase 0 Na current.

5. Ivabradine
   A selective blocker of the pacemaker current $I_f$, ivabradine has been used to slow the heart rate in patients with angina. This drug is currently in phase III clinical trials in the U.S.

III. Some pharmacology of individual antiarrhythmic drugs.
   A. Quinidine

   ![Quinidine molecule]

   1. The prototype IA antiarrhythmic, but use as an antiarrhythmic is now much curtailed. (Some recent evidence for possible revival— in A fib with verapamil, and for particular ventricular arrhythmias—Brugada syndrome and Short QT syndrome)
      It is an isomer of quinine and is used IV to treat malaria.

   2. Has vagolytic properties (common to all IA antiarrhythmics but to varying degrees) in addition to IA, so effects on SA and AV node are a combination of direct actions (Na block in AV transitional cells) and vagal block. If given alone with atrial flutter or fibrillation can produce "paradoxical" ventricular tachycardia

   3. Arrhythmogenic—torsades de pointes (classic "quinidine syncope")—secondary to prolongation of ventricular action potentials (QT). The incidence of torsades with quinidine is reduced if verapamil is also given,

   4. Negative inotropic effects.

   5. Most common non-cardiac effects are GI—diarrhea, nausea/vomiting; and cinchonism (headache, dizziness, tinnitus)

   6. Inhibitor of CYP2D6 (It is marketed with dextromethorphan for treatment of pseudobulbar affect, to increase the bioavailability and decrease the clearance of dextromethorphan. Quinidine levels are well below those necessary for antiarrhythmic action.)

   7. Inhibitor of P-glycoprotein, reduces renal clearance of digoxin.
B. Procainamide
1. Similar to quinidine, but much less vagolytic action, less toxicity
2. Only available for IV administration—approved for treatment of monomorphic ventricular tachycardia
3. Classic non-cardiac effect (when drug was used chronically) is drug-induced lupus erythematosis-like syndrome. (Like many other drugs that can causes ANA and lupus, procainamide is metabolized by N-acetyltransferase)

C. Lidocaine

\[
\begin{align*}
\text{Lidocaine} & \quad \text{CH}_3 \\
& \quad \text{CH}_3 \\
& \quad \text{O} \\
& \quad \text{N} - \text{C} - \text{CH}_2 - \text{N} - \text{C}_2\text{H}_5 \quad \text{C}_2\text{H}_5
\end{align*}
\]

1. The prototype IB antiarrhythmic, lidocaine primarily blocks inactivated channels, but has rapid dissociation so that with normal diastolic intervals most channels become unblocked and the normal EKG is unaffected.
2. Lidocaine is particularly effective in depolarized tissue and except for digoxin toxicity, use is restricted to ventricular arrhythmias.
3. Lidocaine can only be given parenterally because there is extensive first pass metabolism and the metabolites contribute to toxicity, but not to the therapeutic effect.
4. Most important non-cardiac effects are neurological—dizziness—lightheadedness to seizures (see local anesthetic syllabus)

D. Mexiletine
1. Mexiletine can be considered to be like an oral lidocaine.

E. Flecainide

\[
\begin{align*}
\text{Flecainide} & \quad \text{O} - \text{CH}_2 - \text{CF}_3 \\
& \quad \text{O} - \text{CH}_2 - \text{CH}_2 - \text{CF}_3 \\
& \quad \text{C} - \text{NH} - \text{CH}_2 - \text{N}
\end{align*}
\]

1. The prototype IC antiarrhythmic, flecainide has a very slow off-rate from the sodium channel so that conduction is depressed even at slow rates. It was originally described as a sodium blocker that did not change the APD. However, it can block K channels, but unlike quinidine which has optimal K blocking activity at low heart rates, flecainide has significant K blocking activity only at faster rates.
2. Eliminated both by metabolism (some via CYP2D6), and unchanged in urine (<50%)
3. Arrhythmogenic—
   CAST (The Cardiac Arrhythmia Suppression Trial)
   Asymptomatic premature ventricular contractions are a risk factor for sudden death after myocardial infarction. A trial of the use of a Class IC antiarrhythmic
(including **flecainide**) selected based on its efficacy in reducing PVCs in an initial open phase of the trial, and then in a randomized blind trial with patients receiving either drug or placebo, was terminated early for all drugs used, because the treated patients had significantly greater mortality from arrhythmia than the placebo arm. This and other trials highlighted the arrhythmogenic potential of these drugs. They also stress that evaluation of clinical utility requires that the appropriate endpoint be chosen for evaluation.

**F. Propranolol** (see autonomies syllabus for general pharmacology)
1. Primary action is to block sympathetic tone, thus decreasing conduction and increasing AV refractoriness. This can be used for "rate control" in patients with atrial fibrillation and to block AV re-entrant tachycardias (PSVT). Beta blockade will also reduce DADs evoked by high sympathetic tone in patients with no myocardial damage who have ventricular tachycardia triggered by the DADs

**G. Esmolol**
1. A beta blocker with a half-life of about 10 minutes due to metabolism by blood esterases. It is well suited for rapid titration of appropriate plasma levels by IV infusion.

**H. Carvedilol**
1. A beta blocker with alpha blocking activity and antioxidant properties is very effective in reducing ventricular arrhythmias and sudden death in patients with heart failure.
2. Recent work (Zhou et.al, Nature Medicine 17: 1003-1009, 2011) has shown that this superior efficacy may be due to direct blockade of calcium release from overloaded sarcoplasmic reticulum (SOICR) which can cause DADs and subsequent ventricular tachycardias.
3. The block of release is via open channel block of the cardiac ryanodine receptor (the RYR2 Ca channel in the sarcoplasmic reticulum). None of the other beta blockers share this property. Because beta agonism induces Ca overload, carvedilol exerts two favorable actions.

**I. Amiodarone**

![Chemical structure of Amiodarone]
1. A drug that has been variously classified in class III and in Class I, it has activity across all four antiarrhythmic classes, it has Na blocking activity, beta blocking activity, K channel blocking activity and Ca channel blocking activity. Its class III action is sustained at rapid heart rates so the incidence of Torsade de pointes is very low compared to other class IA and III drugs. These other drugs have what is called “reverse” use-dependence—that is they have their greatest K channel blocking effects at slow heart rates.

2. The drug is structurally related to thyroid hormone and interactions with thyroid hormone receptors may contribute to its therapeutic effect.

3. Pharmacokinetics. **Amiodarone** has an extremely long half-life (weeks to months) because the drug has a very large Vd (66L/kg) (high lipid solubility). For chronic oral use, it takes a long time to build concentration to therapeutic levels so an extended period of higher than maintenance doses is generally used for oral administration.

4. Metabolized by CYP3A4 and 2C8 to N,desethylamiodarone (active, -Na>Ca block, t1/2=2 months).

5. There are some differences in the relative magnitude of the various class effects of amiodarone given intravenously vs. those that are seen with chronic oral administration. A reasonable generalization is that the ratio of the class III effects relative to the AV nodal effects are greater with chronic oral administration.

6. FDA approved for ventricular arrhythmias, it also has shown significant efficacy in preventing recurrent atrial fibrillation, and is used off-label.

7. Adverse effects:
   a. acute--with IV administration: -hypotension—most likely in patients with left ventricular dysfunction
   b. chronic--related to maintenance dose and cumulative dose--so may involve tissue accumulation
      i. pulmonary fibrosis
      ii corneal microdeposits
      iii. hepatic dysfunction
      iv--thyroid abnormalities--hypo and hyperthyroidism
      v. peripheral neuropathy and myopathy
      vi. photosensitivity

8. Drug interactions--**Amiodarone** is an inhibitor of CYP3A4 , 2C9, 1A2, 2D6 as well as the P-glycoprotein drug transporter. Reduced doses of warfarin, **digoxin**, **flecainide**, procainamide, **quinidine**, theophylline are often required.

**J. Dronedarone**

1. An iodine free analog of amiodarone, with similar actions across the spectrum of antiarrhythmic mechanisms. As with amiodarone there are active metabolites, and caution is warranted with concomitant inhibitors of CYP3A4, as well as substrates for P-gP, CYP2D6 and CYP3A4 all of which can be inhibited by dronedarone.
2. Lacks the thyroid and pulmonary toxicity associated with amiodarone, but has recently been associated with rare but severe liver toxicity including 2 cases where transplant was necessary.
3. Contraindicated in class IV heart failure or class II or III, if recent decompensation
4. Has half-life of only about 1 day.

K. Sotalol

1. A non selective beta blocker with prominent K blocking activity (d isomer).
2. Torsade de pointes
3. Primarily excreted unchanged in urine.

L. Dofetilide

1. A prototype Class III agent, **dofetilide** blocks the rapidly activating component of the delayed rectifier ($I_{Kr}$). It exhibits reverse use dependence. It is used in atrial fibrillation and flutter to convert patients (better success with flutter) and to prevent reoccurrence. It is available for oral use.
2. Torsade de pointes—Because of danger of torsades, it is only available to those with special training and treatment initiation must be done in hospital.
3. Virtually no important extracardiac effects.

M. Verapamil (see Vasodilators and Ca channel blockers for general pharmacology)

1. Prototype Class IV antiarrhythmic it can be used for rate control in atrial fibrillation or to control AV nodal reentrant tachycardias (PSVT). There may be some role in ventricular tachycardias that are sympathetically-evoked, but caution, it can be dangerous in patients with ventricular tachycardia secondary to myocardial damage (hypotension and ventricular fibrillation may result), so diagnosis must be accurate.
2. Cardiac side effects include complete AV block, sinus arrest in patients with diseased sinus node, and negative inotropic activity.

N. Adenosine.

1. **Adenosine**'s plasma half-life is on the order of seconds, Thus, its major therapeutic use is for termination of PSVT. It is rapidly taken up into tissues and metabolized by adenosine deaminase. A rapid bolus intravenous dose is needed. Slow IV administration results in elimination of drug from plasma before it reaches the heart.
2. Adverse effects are transient flushing, asystole, chest fullness and dyspnea, hypotension.
3. Drug interactions:
   - dipyridamole—an **adenosine** uptake blocker potentiates caffeine (and other methyl xanthines) are A1, A2 receptor antagonists.
O. Digoxin
1. Primary use is as an inotropic agent,
2. Electrophysiological effects mediated both directly and via an increase in parasympathetic tone to the heart. Net result is decrease in heart rate and AV conduction velocity, and an increase in refractoriness at the AV node. ST depression is not uncommon, and T wave inversion may occur.
3. Can be used for rate control in patients with atrial fibrillation, but less effective than beta blockers and Ca blockers in countering the effects of exercise.
4. Arrhythmia can be an adverse effect of higher plasma levels of digoxin, block of the Na/K ATPase results in depolarization during phase 4, and shortening of myocardial APD.

P. Magnesium sulfate
1. can be used IV to prevent recurrence of torsades; effective in some arrhythmias caused by digoxin toxicity.

IV. Summary of Effects of Drug Classes on the Normal EKG

Note that the Table below deals in generalities based on major mechanisms of the various classes. Different drugs within these classes may have somewhat different effects because the relative balance of different mechanisms of action are not the same from drug to drug in a class. These differences are, generally speaking, beyond the scope of knowledge appropriate to a second year student in pharmacology. Table 14-3 in Katzung provides similar summary information for individual drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heart Rate</th>
<th>AV refractoriness</th>
<th>PR Interval</th>
<th>QRS Duration</th>
<th>QTc interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>↑ (anticholinergic) ↓ (direct)</td>
<td>↓ (anticholinergic) ↑ (direct)</td>
<td>↑↓</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>IB</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>IC</td>
<td>none</td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑ (via QRS)</td>
</tr>
<tr>
<td>II</td>
<td>↓ ↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>III (pure)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>IV</td>
<td>↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Amiodarone p.o.</td>
<td>↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Amiodarone i.v.</td>
<td>↓↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>adenosine</td>
<td>slight ↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Digoxin</td>
<td>↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
V. Some ridiculously oversimplified treatment paradigms for some common arrhythmias.

A. Atrial fibrillation

- Rate? 100 bpm
- Regularity? irregular
- P waves? none
- PR interval? none
- QRS duration? 0.06 s

Interpretation? Atrial Fibrillation

D. Vorchheimer, Cardiovascular Pathophysiology

1. The most common arrhythmia encountered in general practice, prevalence is about 0.4–1% in the general population, increasing with age to over 8% in those over 80. Most patients have concomitant CV conditions including hypertension, mitral valve disease, ateriosclerosis, heart failure.

2. Annual risk of ischemic stroke is 5% per year. Risk of stroke also increases with age.

3. For prevention of thromboembolism, aspirin only in those with no other risk factors, otherwise warfarin (INR target 2.5)

4. Rate control--leave the arrhythmia, but decrease the number of impulses that reach the ventricles (to maintain cardiac output)--beta blockers, non-dihydropyridine calcium channel blockers, digoxin (2nd line agent--not as effective during exercise)

5. Rhythm control: conversion to sinus rhythm
   a. Pharmacologic in hospital
      i. first line: flecainide, dofetilide, propafenone, ibutilide
      ii. second line: amiodarone, dronedarone
      iii. third line: quinidine, procainamide
      iv. do not attempt digoxin or sotalol
   b. “Pill-in-the-pocket” single oral dose of propafenone or flecainide to terminate persistent AF outside hospital in patients without other cardiac problems
   c. Electrical cardioversion
   d. Pharmacologic enhancement of electrical conversion
      i. pretreatment with amiodarone, flecainide, ibutilide, propafenone, sotalol

5. maintenance of sinus rhythm
   a. in patients with recurrent symptomatic paroxysmal AF choice of drug varies with comorbidities: e.g. heart failure: amiodarone and dofetilide(restricted distribution) are preferred. avoid flecainide and propafenone,

   b. catheter ablation of trigger zone
6. Some preliminary evidence that ACE inhibitors or angiotensin receptor blockers may reduce recurrence, perhaps by inhibition of myocardial fibrosis and other structural changes that may form a substrate for AF.

B. PSVT

1. Most commonly an AV nodal reentry tachycardia (usually narrow complex, with regular rate and no discernible P wave) due to block of anterograde conduction of a premature atrial impulse through the fast path of the AV node. Anterograde transmission through the slow path and then retrograde transmission through the fast path is responsible for the arrhythmia. Also possible is an accessory pathway between atria and ventricle (Wolff-Parkinson-White) where the accessory path has the properties of atrial muscle. (Here tachycardia may be wide complex if orthograde through the bypass tract)

2. Short term treatment
   a. Vagal maneuvers
   b. Pharmacological—drugs depressing AV node or, if present, accessory pathway
      i. Adenosine i.v.
      ii. Verapamil i.v.
      iii. Diltiazem or beta blocker i.v.
      iii. If above fails, or if preexcitation, can try procainamide, ibutilide, propafenone, flecainide

3. Long term treatment of recurrent PSVT without preexcitation
   a. Ablation
   b. Verapamil, diltiazem, beta blocker, digoxin
   c. Class IC or III: flecainide, propafenone, amiodarone, sotalol
   d. “Pill-in-pocket” for patients with infrequent (3-4 per year) but prolonged episodes (>1-2 hrs) Ca blockers, beta blockers, flecainide, propafenone

4. SVT with Wolff-Parkinson-White syndrome
   a. Ablation
   b. Flecainide, propafenone
   c. Ca blockers and digoxin contraindicated

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C. Ventricular tachycardia

- Rate? 160 bpm
- Regularity? regular
- P waves? none
- PR interval? none
- QRS duration? wide (> 0.12 sec)
- Interpretation? Ventricular Tachycardia

D. Vorchheimer, Cardiovascular Pathophysiology

1. Originates from a ventricular ectopic focus at > 100 beats per minute; wide complex, no associated P waves.
3. Acute treatment of sustained monomorphic VT
   a. cardioversion
   b. pharmacotherapy is IV amiodarone, procainamide, lidocaine,
4. Combination of antiarrhythmic drugs and implantable defibrillators. Drugs are used to reduce other supraventricular arrhythmias that may trigger unnecessary shocks from the defibrillator and to lower the defibrillation threshold (Class III agents with the exception of amiodarone)
5. Verapamil and diltiazem should be avoided in wide-complex ventricular tachycardia (must clearly differentiate from PSVT) because there is an increased probability that VT can convert to fibrillation. (Verapamil and diltiazem can be used in certain ventricular arrhythmias that are based on triggered activity but generally have no beneficial effects on ventricular re-entrant arrhythmias)
GOALS:
To discuss differences in federal regulation of alternative/complementary medicines vs. approved drugs, and some of the consequences of these differences.
To identify some common remedies and discuss evidence for efficacy. To alert you to possible problems with alternative medicines including batch to batch variation, adulteration, adverse effects and drug interactions.

OBJECTIVES:
1. Describe the differences in the federal government’s regulation of prescription and OTC drugs, and herbal/alternative medicines (aka dietary supplements).
2. Discuss the purity, and consistency of herbal preparations, and indicate why this may cause problems.
3. List the common uses for ginseng, kava, echinacea, saw palmetto, ginkgo biloba, St. John's wort., potential drug interactions and adverse effects with these herbas.
4. Define the basic principle underlying homeopathy, describe homeopathic preparations, and indicate any concerns that may arise if a patient uses these in addition to prescribed drugs.

KEY DRUGS:
ginseng, ginkgo biloba, echinacea, St. John's wort, saw palmetto, kava

KEY WORDS AND PHRASES
Complementary and Alternative Medicine (CAM), Dietary Supplement and Health Education Act, health claims, structure-function claims, nutrient content claims, adulterants, quality control, homeopathy

TEXTBOOK READING:
Katzung 12th Ed. Chapter 64 Dietary Supplements and Herbal Medications

LECTURE OUTLINE:
I. Prevalence of use of Complementary and Alternative Medicine (CAM)
   A. (2007 National Health Interview Survey by the CDC)
      1. 18% of adults and 4% of children used some form of natural product CAM therapy (vitamins and minerals excluded) during the 12 months preceding the survey
      2. The most commonly used substances by adults were fish oil or omega-3 fatty acids, glucosamine, Echinacea, flaxseed oil or pills, ginseng, gingko biloba, chondroitin, garlic, co-enzyme Q10.
   B. In a recent survey, the most common reasons patients gave for not informing their physician of CAM use were “[He/she] didn’t ask,” “It’s not important for the physician to know,” “They’re not drugs.”
II. Regulation

A. Herbals and other alternative medicines are sold over the counter and are not required to meet the same standards as drugs (either prescription or over the counter).

B. The relevant legislation is the 1994 Dietary Supplement and Health Education Act (DSHEA)

1. A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites.

2. The FDA issued Current Good Manufacturing Practices in 2007 that requires a manufacturer to ensure that ingredients used met standards, that facilities and processes prevent contamination and adulteration of products, and that ingredients are accurately listed on the label.

3. Most of these remedies can be marketed without prior FDA approval for efficacy and safety. The only requirement for pre approval for safety is if a manufacturer wants to market a substance that was not marketed before October 15, 1994 and is not present in the food supply.

4. In December 2007 the FDA began requiring that manufacturers report all "serious" adverse events. This produced approximately a 3-fold increase in reporting the first year, but still fewer than 1,000 reports. Under DSHEA, if problems arise post-marketing, the FDA can request withdrawal of the product, but the burden of proof for required removal from the market rests with the FDA (e.g. the removal of herbal supplements containing ephedra).

5. These products may not be labeled or marketed as a treatment or cure for a specific disease. If they are so labeled or marketed they would be considered unapproved illegal drugs. There are three types of claims that manufacturers (distributors) can make about these products:

   a. **Health claims** describe a relationship between a food, food component, or dietary supplement ingredient, and reducing risk of a disease or health-related condition.

   b. **Structure/function claims** describe the role of a nutrient or dietary ingredient intended to affect normal structure or function in humans, for example, "calcium builds strong bones." In addition, they may characterize the means by which a nutrient or dietary ingredient acts to maintain such structure or function, for example, "fiber maintains bowel regularity," or "antioxidants maintain cell integrity." Manufacturers who make structure/function claims must include on the label and in advertising "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."

   c. **Nutrient content claims**: the amount of a particular substance or characterization of the amount of that substance (high, low etc)
III. General Safety Issues
A. NATURAL DOES NOT EQUAL SAFE—poisons abound in nature. Herbals, like other medicines may produce adverse effects. Some may be lethal.

<table>
<thead>
<tr>
<th>Cardiototoxicity</th>
<th>Neurotoxicity or convulsions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconite root tuber</td>
<td>Aconite root tuber</td>
</tr>
<tr>
<td>Herbs rich in cardioactive glycosides</td>
<td>Arctostaphylos uva-ursi root tuber</td>
</tr>
<tr>
<td>Herbs rich in colchicine</td>
<td>Artemisia species rich in santonin</td>
</tr>
<tr>
<td>Leiongrongong</td>
<td>Essential oils rich in ascorbidole</td>
</tr>
<tr>
<td>Lycoris root</td>
<td>Essential oils rich in thujone</td>
</tr>
<tr>
<td>Mahuang</td>
<td>Ginkgo seed or leaf</td>
</tr>
<tr>
<td>Pokeweed leaf or root</td>
<td>Herbs rich in colchicine</td>
</tr>
<tr>
<td>Scotch broom‡</td>
<td>Herbs rich in podophyllotoxin</td>
</tr>
<tr>
<td>Squirtting cucumber‡</td>
<td>Indian tobacco herb</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Kava rhizome‡</td>
</tr>
<tr>
<td>Certain herbs rich in anthranoids</td>
<td>Mahuang</td>
</tr>
<tr>
<td>Certain herbs rich in protoberberine alkaloids</td>
<td>Nux vomica</td>
</tr>
<tr>
<td>Chaparral leaf or stem</td>
<td>Pennyroyal oil</td>
</tr>
<tr>
<td>Germander species</td>
<td>Star fruit</td>
</tr>
<tr>
<td>Green tea leaf†</td>
<td>Yellow jessamine rhizome</td>
</tr>
<tr>
<td>Herbs rich in coumarin</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td>Herbs rich in podophyllotoxin</td>
<td>β-Aescin (saponin mixture from horse-chestnut seed)</td>
</tr>
<tr>
<td>Herbs rich in toxic pyrrolizidine alkaloids</td>
<td>Cape aloe‡</td>
</tr>
<tr>
<td>Impilia root</td>
<td>Cat’s claw‡</td>
</tr>
<tr>
<td>Kava rhizome</td>
<td>Certain essential oils</td>
</tr>
<tr>
<td>Kombucha</td>
<td>Chaparral leaf or stem‡</td>
</tr>
<tr>
<td>Mahuang</td>
<td>Chinese yew</td>
</tr>
<tr>
<td>Pennyroyal oil</td>
<td>Herbs rich in aristolochic acids</td>
</tr>
<tr>
<td>Skullcap</td>
<td>Impila root</td>
</tr>
<tr>
<td>Soy phytoestrogens‡</td>
<td>Jering fruit</td>
</tr>
<tr>
<td></td>
<td>Pennsilvestre oil</td>
</tr>
<tr>
<td></td>
<td>Squirtting cucumber‡</td>
</tr>
<tr>
<td></td>
<td>Star fruit</td>
</tr>
</tbody>
</table>

*The full version of this table is available from the National Auxiliary Publications Service (NAPS). (See NAPS document no. 05609 for 33 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.) Adverse effects of multiple-herb therapies are not included. Case reports do not always provide adequate evidence that the remedy in question was labeled correctly. As a result, it is possible that some of the adverse events reported for a specific herb were actually due to a different, unidentified botanical or another adulterant or contaminant.

†A single case was reported without reference to previous cases.

‡Convulsions have been observed after large doses of yingguo (gingko seed), a traditional Asian food and medicine, which contains the convulsive agent 4′-O-methylpyridoxine (MPN).12,13 Recently, anecdotal reports have associated ginkgo-containing preparations available on the Western market with seizures,14 and these adverse events have also been reported in patients with seizure disorders stabilized by valproate.18 How Western ginkgo preparations might induce seizures is still unclear. MPN has been detected in ginkgo leaf and preparations that contain it, but usually at subtoxic levels.18

B. Two additional safety issues are the possible presence of adulterants or contaminants, and the possibility of drug interactions or just additive effects with prescription or OTC medications also being used by the patient. (Approximately 1 in 6 adults taking prescription drugs report concomitant use of at least one herbal or other product (not including vitamin or mineral supplements) during the preceding week.

IV. What is actually in the CAM preparation and quality control

A. Some CAM are single compounds (e.g., CoQ10, glucosamine) so content of active constituent is as easy to control as for standard prescription and OTC drugs.

B. For herbal and other “natural” remedies which contain plants or plant extracts the nature of the contents and quantitative quality control are much more difficult.

1. Herbs with the same common name may be different species and their biologically active constituents may be qualitatively or quantitatively different.
      i. Ginseng is a key component of traditional Chinese medicine and one of the more common herbs used in the west. Among reports on its effects are that it promotes wound healing by increasing angiogenesis, and that it inhibits tumor growth by decreasing angiogenesis. How to rationalize opposing action of the same herb?
      ii. There are multiple species of ginseng: Chinese and Korean ginseng (Panax ginseng), American ginseng (Panax quinguefolium) and Sanqui ginseng (Panax notoginseng). The plants contain multiple substances with biological activity commonly known as “ginsenosides”. Two of the more prominent have been labeled as Rg1 and Rb1.
      iii. Mass spectroscopic analysis of the various species found that the two ginsenosides were present in all species but the amounts and the ratio of Rg1:Rb1 differed in different species.
      iv. When tested in vitro, Rb1 inhibited the migration of human umbilical vein endothelial cells in response to a chemoattractant, whereas Rg1 potentiated the migration. Both ginsenosides promoted proliferation after injury to a cell monolayer.
      v. When tested in vivo in a mouse implant model, varying ratios of the two ginsenosides produced very different vascularization results (see figure on the next page)
Figure 5. Effects of extracts, reconstituted with defined ratio of Rg1 and Rb1, on angiogenesis in a murine Matrigel implant. Growth factor–reduced Matrigel was injected subcutaneously into C57/BL6 mice and allowed to gel. On day 9, the animals were euthanized, and the implants were excised, cryosectioned, and immunostained for vWF, which was detected with the use of a species-specific secondary antibody coupled with FITC. Propidium iodide was added to counterstain the nuclei. Photomicrographs show angiogenesis in control (A), Rg1 (50 μg) plus Rb1 (20 μg) (B), and Rg1 (20 μg) plus Rb1 (50 μg) (C) per implant. The images were captured with a Zeiss LSM510 confocal microscope at a resolution of 512×512 pixels. Controls undertaken by omitting the primary antibody were imaged with the same settings for laser power and gain and showed no specific fluorescence. D, Vessel density in the different treatment groups. Veh indicates vehicle. Data are expressed as mean±SEM; n=3. ***P<0.001 vs vehicle control; *P<0.01 vs HGF/SF treatment.
2. Even with the same herbal species, there may be qualitative and quantitative differences in biologically active constituents depending on the location in which the herb is grown, the season in which it is collected, the part of the plant that is used, and the manufacturing method for the herbal extract or preparation. It is virtually impossible with herbal preparations to standardize the strength of the product across all possible active components.

3. The preparations may contain adulterants/contaminants that may contribute to efficacy (e.g. NSAIDs, sildenafil or its analogs) and/or to toxicity (e.g. heavy metals). A recent study of Ayurvedic medicines obtained from internet suppliers found 20% of samples contained toxic levels of lead, mercury or arsenic. (and there was no difference in products manufactured in the US or in India).

4. In a Dec 10, 2010 news release the FDA indicated that in recent years it had alerted consumers to nearly 300 tainted products marketed as dietary supplements and received numerous complaints of injury associated with these products. The three most common classes of products that are sold illegally because they include unlabeled drugs are those for weight loss, body building, and male sexual enhancement.

### Table 1. Potential Adulterants and Contaminants That Can Affect the Quality of Herbal Remedies.*

<table>
<thead>
<tr>
<th>Type of Adulterant or Contaminant</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botanicals</td>
<td>Aristolochia, digitalis, colchicum, rauwolfia, plants containing belladonna or pyrrolizidine alkaloids†</td>
</tr>
<tr>
<td>Microorganisms</td>
<td>Staphylococcus aureus, Escherichia coli (certain strains), salmonella, shigella, Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Microbial toxins</td>
<td>Aflatoxins, bacterial endotoxins</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Chlorinated pesticides, organic phosphates, carbamate insecticides and herbicides, dithiocarbamate fungicide, triazin herbicides</td>
</tr>
<tr>
<td>Fumigation agents</td>
<td>Ethylene oxide, methyl bromide, phosphine</td>
</tr>
<tr>
<td>Toxic metals</td>
<td>Lead, cadmium, mercury, arsenic</td>
</tr>
<tr>
<td>Drugs</td>
<td>Analgesic and antiinflammatory drugs (e.g., aminophenazone, phenylbutazone, indomethacin), corticosteroids, benzodiazepines; warfarin, fenfluramine, sildenafil*</td>
</tr>
</tbody>
</table>

"For Immediate Release: October 8, 2010

FDA: Potentially harmful stimulant found in Slimming Beauty capsules

‘All natural’ products contain controlled substance sibutramine

The U.S. Food and Drug Administration today advised consumers who have Slimming Beauty Bitter Orange Slimming Capsules not to use the product. FDA warns that Slimming Beauty Bitter Orange Slimming Capsules contain the active pharmaceutical ingredient sibutramine, a prescription-only drug which is a stimulant. Sibutramine is not listed on the product label and could harm consumers, especially those with cardiovascular conditions.

Sibutramine is a powerful stimulant that should not be used without a prescription due to the safety risks associated with it.

Slimming Beauty is being sold over the Internet by Beautiful Health Inc., formerly LL Health and Beauty. Slimming Beauty sample packets also have been distributed by individuals at community events. The product and the sample packets are falsely labeled as “100% Herbal.” The sample packet label is misleading because it indicates that it is a natural vitamin and calcium capsule for use in children as young as 2 years old.

The FDA has determined that Slimming Beauty sample packets were distributed at the 40th Annual Mexican Independence Day Parade in Chicago, on Sept. 12, 2010. The agency is aware of several reports of serious side effects from the use of this product including elevated blood pressure, headaches, vomiting, and insomnia.

Consumers and health care professionals are encouraged to report adverse events related to the use of Slimming Beauty capsules to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program at www.fda.gov/MedWatch/report.htm or by phone at 800-FDA-1088 (800-332-1088)."
"For Immediate Release: Nov. 19, 2010

**FDA warns consumers not to use Vigor-25**

*Marketed as a 'male sexual stimulant,’ product contains hidden drug ingredient*

The U.S. Food and Drug Administration says Vigor-25, a product marketed as a natural dietary supplement to enhance male sexual performance, should not be purchased or used because it contains sildenafil, the active ingredient in the prescription drug Viagra.

Sildenafil may interact with prescription drugs known as nitrates, including nitroglycerin, and can dangerously lower blood pressure. The FDA is investigating the reported death of a 26-year old man, possibly associated with the use of Vigor-25.

Vigor-25, distributed by Piston Corp., is sold on Internet sites and possibly in some retail outlets.

“This product is dangerous to consumers because it claims to contain only natural ingredients when it actually contains a prescription drug ingredient,” said Deborah M. Autor, director of the Office of Compliance in the FDA’s Center for Drug Evaluation and Research. “Tainted products place consumers at risk of injury and death, especially those consumers with underlying health conditions.”

The FDA has found many products marketed as dietary supplements for sexual enhancement during the past several years that can be harmful because they contain active ingredients in FDA-approved drugs or variations of these ingredients. Sexual enhancement products promising rapid effects (e.g., claim to work in minutes to hours) or long-lasting effects (e.g., claim to last 24-72 hours) are likely to contain a contaminant.

The FDA advises consumers who have experienced any negative side effects from sexual enhancement products to stop using such products and consult a health care professional and to safely discard the product. The FDA urges health care professionals and consumers to report adverse events or side effects from use of Vigor-25 to the FDA’s MedWatch Adverse Event Reporting program either online, by regular mail or by fax:

- Complete and submit the report online: [www.fda.gov/MedWatch/report.htm](http://www.fda.gov/MedWatch/report.htm)
- Download form or call 800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 800-FDA-0178"
V Selected popular herbal drugs

A. Pharmacologic Profile

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Latin Name</th>
<th>Main Active Compounds</th>
<th>Principal purported pharmacologic actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingko</td>
<td>Ginkgo biloba</td>
<td>glinkolides bilobide flavone glycosides</td>
<td>Antihypoxic, antiplatelet, free radical scavenging</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Hypericum perforatum L.</td>
<td>hypericin hyperforin</td>
<td>Antidepressant (SSRI)</td>
</tr>
<tr>
<td>Ginseng (Asian)</td>
<td>Panax ginseng</td>
<td>ginsenosides panaxans</td>
<td>CNS stimulation, antifatigue, anti-inflammatory, antineoplastic, antiplatelet</td>
</tr>
<tr>
<td>Echinacea</td>
<td>E. angustifolia, E. pallida, E. purpura</td>
<td>polysaccharides glycoproteins alkamides caffeic acid</td>
<td>Immune stimulant, antifungal, antiinflammatory</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Serena repens</td>
<td>fatty acids sterols</td>
<td>Inhibits testosterone metabolism</td>
</tr>
<tr>
<td>Kava</td>
<td>Piper methysticum</td>
<td>kavalactones</td>
<td>Anxiolytic, muscle relaxant, analgesic, sedative</td>
</tr>
</tbody>
</table>

Adapted from Ernst E  Ann Intern Med 136:42-53, 2002

B. Reviews of Efficacy, Adverse Effects, Drug Interactions

1. Ginkgo biloba
   a. Efficacy
      i. dementia— inconsistent—some hint of efficacy but better trials needed--two recent trials:
         a. ineffective in reducing rate of dementia or Alzheimers in elderly (3,072 participants >75 y o) with normal cognition or mild impairment (JAMA 300:2253-2261, 2008)
         b. not effective overall, significant if take adherence into account (122 participants >85 y o) Neurology 70: 1809-1817, 2008
      ii. tinnitus—no effect
      iii. altitude sickness—no effect
   b. Adverse Effects
      i. GI, nausea, vomiting
      ii. headache
      iii. bleeding
      iv. seizures—contamination of prep with ginkgo seeds
   c. Drug Interactions
      i. may increase bleeding with anticoagulants/antiplatelet drugs
2. St. John's wort
   a. Efficacy
      i. depression—a recent Cochrane review indicates that controlled trials suggest
         superiority to placebo similar to that for standard antidepressants for use in
         mild to moderate depression (with fewer side effects than TCAs or SSRIs)
         but evidence for severe depression insufficient
   b. Adverse Effects
      i. nausea
      ii. hypersensitivity
   c. Drug Interactions
      i. CYP450 induction—reduced concentrations of amitriptyline,
         cyclosporine, indinavir, oxycodone, decrease in INR with warfarin
         a. This is a good example of how different preparations of an herb can alter
            adverse effects. The extent of enzyme induction of CYP3A4 and P-
            glycoprotein varies with the content of hyperforin in St. John’s wort, and
            this content is different in different preparations.
      ii. serotonin syndrome when combined with SSRIs

3. Ginseng
   a. Efficacy
      i. physical performance—conflicting 4/7 studies show no effect
      ii. cognitive performance—small trials show small effect; a Cochrane review
         (2010) concludes "lack of convincing evidence to show a cognitive enhancing
         effect of Panax ginseng in healthy participants and no high quality evidence…
         in patients with dementia."
   b. Adverse Effects
      i. GI-diarrhea, nausea
      ii. hypertension, hypotension
      iii headache
      iv CNS euphoria, insomnia
      v. “ginseng abuse syndrome”
   c. Drug Interactions
      i. warfarin—decrease INR, but also antiplatelet
      ii. phenelzine—tremulousness, mania

4. Echinacea
   a. Efficacy
      i. prevention and treatment of common cold—both positive and negative
         reports, but data are confounded by the large number of preparations
         available (different species, different parts of the plant, different extraction
         procedures). Meta analyses have indicated decrease in duration of symptoms
         and decreased incidence (the lancet 7: 473-480, 2007). A 2009 Cochrane
         review of 16 controlled trials concluded that there is some evidence for a
         positive treatment effect of aerial parts of E. purpurea, but evidence for
         prevention has not been rigorously demonstrated.
   b. Adverse Effects
      i. rare--rashes in children (one trial)
   c. Drug Interactions?
5. Saw palmetto
   a. Efficacy
      i. benign prostatic hyperplasia—Early randomized controlled trials suggested
         improvement in urinary symptoms and flow with short term treatment. A
         2006 report in men with moderate to severe BPH showed that compared to
         placebo, 1 year of treatment had no significant effect on either objective
         measures (e.g. prostate size, urinary flow rate, residual volume after voiding),
         quality of life symptoms, or side effects. (NEJM 354: 557-566, 2006). A
         Cochrane review (2010) based on 30 trials involving a total of 5,222 subjects
         reached a similar conclusion.
   b. Adverse effects
      i. GI—constipation, diarrhea, nausea
      ii. decreased libido
      iii. False negative on PSA
   c. Drug Interactions

6. Kava
   a. Efficacy
      i. anxiety—Trials suggest superiority to placebo, but also association with
         serious hepatotoxicity which has led to liver transplant. (FDA warning
         in 2002, sales banned in some countries.)
   b. Adverse effects
      i. hepatic failure? (improper preparation of herbal?)—incidence rare—whether kava
         is causal agent has been questioned.
      ii. yellow discoloration of skin, nails (with chronic use)
      iii. dizziness, stupor, ataxia, visual disturbances
   c. Drug Interactions
      i. At least additive effects and possible synergy with anxiolytics and
         alcohol
V. Homeopathy

A. Founded by Samuel Hahnemann (1755-1834) in the early 19th century, homeopathy is a treatment paradigm formulated around the principle that like treats like. Substances that produce signs and symptoms in healthy volunteers are used to treat diseases that present with the same sign/symptom set. This is based on the belief that low concentrations of a substance will produce effects opposite to those of high concentrations.

B. When used in treatment, the substances are given in extremely dilute solutions prepared by rhythmic shaking (succession). Dilutions (called potencies) are labeled 6X, 12X, 24X etc.—with each X representing a 10 fold dilution.
   - 1X—1 part substance to 9 parts water.
   - 2X—1 part 1x to 9 parts water
   - 3X—1 part 2X to 9 parts water.
   The more dilute the solution the higher the homeopathic potency.

C. Some potencies (24X and higher) are so dilute that one Liter of solution has a high probability of containing not even one molecule of the original substance (that is, the concentration is less than \(10^{-24}\) M) (Avogadro’s number is \(6.02 \times 10^{23}\) molecules / gram MW)

D. Efficacy—there have been small clinical trials reported with positive results, but the designs have been frequently criticized, and the replicability has been poor. There is no reasonable scientific rationale to explain effects other than placebo effect.

E. Safety
   1. nominally safe (except if necessary life-saving or morbidity decreasing treatments are avoided)
   2. adverse effects (higher reported incidence in children) and a few deaths associated with homeopathic remedies
      i. adulteration?
      ii. heavy metal toxicity with “low potency” arsenicum album (arsenic oxide)
      iii. belladonna

"For Immediate Release: Oct. 23, 2010

FDA Issues Consumer Safety Alert

Hyland’s Teething Tablets may pose a risk to children

The U.S. Food and Drug Administration today is warning consumers that Hyland’s Teething Tablets may pose a risk to children. The FDA recommends that consumers not use this product and dispose of any in their possession. The manufacturer is issuing a recall of this product.

Hyland’s Teething Tablets are manufactured to contain a small amount of belladonna, a substance that can cause serious harm at larger doses. For such a product, it is important that the amount of belladonna be carefully controlled. FDA laboratory analysis, however, has found that Hyland’s Teething Tablets contain inconsistent amounts of belladonna. In addition, the FDA has received reports of serious adverse events in children taking this product that are consistent with belladonna toxicity. The FDA has also received reports of children who consumed more tablets than recommended, because the containers do not have child resistant caps.

The FDA advises consumers to consult their health care professional if their child experiences symptoms such as seizures, difficulty breathing, lethargy, excessive sleepiness, muscle weakness, skin flushing, constipation, difficulty urinating, or agitation after using Hyland’s Teething Tablets.

20-12
Hyland’s Teething Tablets is a homeopathic product intended to provide temporary relief of teething symptoms in children that is sold over-the-counter (OTC) in retail outlets. The FDA has not evaluated Hyland’s Teething Tablets for safety or efficacy, and is not aware of any proven clinical benefit offered by the product.

An ongoing inspection at the manufacturer also indicates substandard control of the manufacturing operation. After consultation with the FDA today, the manufacturer of the product, Standard Homeopathic Company agreed to voluntarily recall Hyland’s Teething Tablets from the market.

FDA urges both health care professionals and consumers to report side effects from use of Hyland’s Teething Tablets to the FDA’s MedWatch Adverse Event Reporting program either:

- Complete and submit the report online: [www.fda.gov/MedWatch/report.htm](http://www.fda.gov/MedWatch/report.htm)
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178