Cardiovascular Pharmacology and Myocardial Performance

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The Quality of a Person’s Life is Directly Proportional to Their Commitment to Excellence

Vince Lombardi
Class Focus:

Using Pharmacology to Optimize Myocardial Performance

A Critical Thinking Approach

Case Study

• 78 year old female is admitted to the hospital with shortness of breath.
• She has become increasingly short of breath with routine activity over the past 2 days. Today she is short of breath at rest.
• Her weight has increased 6 pounds in the past 3 days.
• She has not taken her medications for 4 days because her prescriptions ran out and she was waiting on her son to get back in town to get them filled.
Home Meds and History

• Furosemide 20 mg daily
• Lisinopril 20 mg daily
• Metoprolol 25 mg BID
• Aldactone 25 mg daily
• Warfarin 5 mg daily
• Synthroid
• OTC NSAIDs
• History of ischemic cardiomyopathy
• CABG @ age 70
• History of atrial fibrillation (? Remote)
• History TIA
• Last known ejection fraction 26%
• Osteoarthritis
• Hypothyroidism

Physical Assessment / Diagnostics

BP: 88/72
HR: 110’s to 130’s
Rhythm: Atrial fib with RBBB and PVCs
RR 28-32
Pale and cool to touch
Somewhat lethargic
Heart Sounds with audible S3, systolic murmur 3/6 loudest at apex
Lungs with crackles ½ up bilaterally
JVD
Right Upper quadrant tenderness
2+ peripheral edema to mid calf

Urine output is 10cc in first hour
SaO2 88% on 4L nasal cannula
Mild right sided weakness
K+ 4.9
H & H 9.2 / 30.1
BUN 42 / Creatinine 2.0
Determinants of Myocardial Performance

- Stroke Volume
  - Preload
  - Afterload
  - Contractility
- Heart Rate
- Synergy
- Synchrony

Myocardial Oxygen Demand

- Myocardial oxygen demand affected by:
  - Heart Rate
  - Preload
  - Afterload
  - Contractility

Same Parameters as Cardiac Output
Drugs Used to Manipulate Preload

Pharmacological Options for Increasing Preload

| Volume expanders | Isotonic crystalloids such as 0.9% saline or lactated ringers  
|                  | Colloids such as albumin, dextran, or hetastarch  
|                  | Blood and/or blood products |

| Decrease dose or stop drugs that cause venous vasodilatation | Decrease or stop medications such as: intravenous nitroglycerin, neseritide, and morphine sulfate (venous vasodilatation pools blood away from the heart and decreases preload – direct impact on right sided preload) |

Exercise also increases venous return to the heart.
Pharmacological Options for Decreasing Preload

<table>
<thead>
<tr>
<th>Stop or decrease fluid</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td>▪ A loop diuretic such as furosemide eliminates circulating volume</td>
</tr>
<tr>
<td><strong>Venous Vasodilators</strong></td>
<td>▪ Intravenous nitroglycerin, neseritide, or morphine sulfate (Venous vasodilation pools blood away from the heart and decreases preload)</td>
</tr>
<tr>
<td><strong>ACE Inhibitors or Angiotensin II Receptor Blockers (ARBs)</strong></td>
<td>▪ Interrupt renin-Angiotensin-aldosterone system (RAAS). Aldosterone secretion is decreased and there is less sodium and water retention. ▪ ACE inhibitors end in “pril” / ARBs end in “sartan”</td>
</tr>
<tr>
<td><strong>Aldosterone antagonists</strong></td>
<td>▪ Spironolactone or epleranone ▪ Directly block aldosterone and there is decreased sodium and water retention.</td>
</tr>
</tbody>
</table>

Drugs Used to Manipulate Afterload
# Pharmacological Options for Increasing Afterload

Vasopressor is the term given to medications used to increase afterload.

<table>
<thead>
<tr>
<th>Sympathomimetics stimulating the alpha receptors of the sympathetic nervous system</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Norepinephrine</td>
</tr>
<tr>
<td></td>
<td>Phenylephrine</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arginine Vasopressin</th>
<th>Vasoconstrictive and antidiuretic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restores catecholamine sensitivity</td>
</tr>
</tbody>
</table>

# Pharmacological Options for Decreasing Afterload

All therapies involve arterial vasodilatation

<table>
<thead>
<tr>
<th>Smooth muscle relaxants</th>
<th>Nipride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydralazine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcium channel blockers</th>
<th>Dihydropyridines (ending in &quot;ine&quot;) calcium channel blockers such as amlodipine</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Alpha₁ receptor blockers</th>
<th>Labetolol (combination alpha and beta blocker)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prazoxin, Terazosin</td>
</tr>
</tbody>
</table>

| Central anti-adrenergics | Clonidine, Methyldopa |
| Peripheral anti-adrenergics | Resperine, Guanethidine |

<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>Interrupt the RAAS and limit production of angiotensin II a potent arterial vasoconstrictor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medications ending in “pril”</td>
</tr>
<tr>
<td></td>
<td>Directly block the effects angiotensin II</td>
</tr>
<tr>
<td></td>
<td>Medications ending in “sartan” such as valsartan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiotensin II Receptor Blockers (ARBs)</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Is used as an intravenous inotrope but also has arterial vasodilator properties</td>
</tr>
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</table>

<table>
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<tr>
<th>Phosodiesterase Inhibitors (PDE Inhibitors)</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Is used as an intravenous inotrope but also has arterial vasodilator properties</td>
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</tbody>
</table>
Drugs Used to Decrease Right Sided Afterload

- Oxygen
- Pulmonary vasodilators
  - IV
    - NTG
    - Sodium Nitroprusside
    - Prostaglandins (PGE₁, PGI₂)
    - PDE₁ (phosphodiesterase enzyme)
  - Inhaled
    - Any of the above
    - Nitric Oxide
    - Prostacyclin (PGI₂, Epoprostenol, Flolan) or derivative Iloprost
Drugs Used to Manipulate Contractility

Pharmacological Options for Increasing Contractility

| Inotrope is the term used for medications used to increase contractility |
|-----------------------------|--------------------------------------------------------------------------------|
| Sympathomimetics stimulating the β1 receptors of the sympathetic nervous system | • Dobutamine: most commonly used because it is a predominant beta one stimulator  
• Other sympathomimetics may have inotropic properties even if not used primarily for an inotropic purpose |
| Phosodiesterase Inhibitors (PDE Inhibitors) | • Milrinone  
• Is used as an intravenous inotrope but also has arterial vasodilator properties |
| Cardiac Glycoside | • Digoxin  
• Weak inotrope and is never used intravenously to support left ventricular dysfunction. Exerts weak inotropic properties when given orally. |
### Pharmacological Options for Decreasing Contractility

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Beta Blockers blocking the β₁ receptors of the sympathetic nervous system | • Metoprolol  
• Carvedilol  
• "olol" medications |
| Calcium Channel Blockers     | • Diltiazem  
• Verapamil                  |

### Drugs Used to Manipulate Heart Rate
### Pharmacological Options for Increasing Heart Rate

<table>
<thead>
<tr>
<th>Parasympatholytic (lyses the parasympathetic nervous system)</th>
<th>• Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetics stimulating the β1 receptors of the sympathetic nervous system</td>
<td>• Epinephrine • Dopamine</td>
</tr>
</tbody>
</table>

Note: The non-pharmacological intervention of pacing the heart with either an external, temporary or permanent pacemaker is often the preferred method of increasing the heart rate to a set and controlled rate.

### Pharmacological Options for Decreasing Heart Rate

1. Beta Blockers blocking the β1 receptors of the sympathetic nervous system
   - Metoprolol / Cardvedilol
   - "olol" medications
   - Class II antiarrhythmic

2. Calcium Channel Blockers
   - Diltiazem / Verapamil
   - Class IV antiarrhythmic

3. Cardiac Glycoside
   - Digoxin

4. Unclassified antiarrhythmics
   - Adenosine: Slows conduction through the AV node

5. Other antiarrhythmics
   - Class I and Class III antiarrhythmics
   - Used to establish and / or maintain a normal rhythm and therefore control heart rate
A Closer Look at Pharmacological Agents

Let’s Clear Up Some Terminology

• Vasopressors
  – Term given to any medication in any class that is used to increase left ventricular afterload (systemic vascular resistance)

• Inotropes
  – Term given to any medication in any class that is used to increase myocardial contractility
Sympathomimetics

These drugs are used to:
✓ Increase afterload
✓ Increase contractility
✓ Increase HR

✓ We often refer to these drugs as inotropes or vasopressors depending on why we are giving them.

A Closer Look at Sympathomimetics

• Sympathetic Nervous System Adrenergic Receptors
  – Alpha₁ Receptors
  – β₁ Receptors
  – β₂ Receptors
  – Dopaminergic Receptors
Sympathetic Nervous System Adrenergic Receptors and Effects

Alpha Receptors (Alpha₁)
Located in Vessels
Vasoconstriction of most vessels especially the arterioles

Β₁ Receptors
- Located in the heart
- Increases heart rate (chronotropic)
- Increases conductivity (dromotropic)
- Increase contractility (inotropic)
- Increase automaticity
- Increase conduction velocity

β₂ Receptors
- Located in bronchial and vascular smooth muscle
- Causes bronchial dilatation
- Causes arterial vasodilatation to skeletal muscle
- Causes renin release and therefore activation of the RAAS

Dopaminergic Receptors (D₁)
- Located in renal and mesenteric artery bed
- Dilation of renal and mesenteric arteries
A Closer Look at Sympathomimetics

- Sympathomimetics that increase heart rate ($\beta_1$ receptors)
  - Dopamine
  - Epinephrine
  - Isuprel (no longer used except with cardiac transplants)

- Sympathomimetics that increase afterload (vasopressors) ($\alpha_1$ receptors)
  - Dopamine
  - Norepinephrine (Levophed)
  - Phenylephrine (Neo-Synephrine)
  - Epinephrine
A Closer Look at Sympathomimetics

- Sympathomimetics that increase contractility (inotropes) ($\beta_1$ receptors)
  - Epinephrine
  - Dobutamine
  - Dopamine
  - Norepinephrine

Epinephrine

| What receptors are stimulated: | $\beta_1$ and $\beta_2$
| Alpha receptors |
|-------------------------------|-----------------------------|
| What are the resultant actions: | Increase contractility (+inotrope) $\beta_1$
|                               | (+chronotrope) $\beta_1$
|                               | Bronchodilation $\beta_2$
|                               | Selective vasoconstriction (alpha) |
| When and why do we use: | ACLS first line drug for cardiac standstill; V-fib;
pulseless electrical activity
| Hypotension or profound bradycardia
| Anaphylactic Shock |
| What are special nursing considerations: | Onset instant
| Peak 20 minutes
| 1mg every 3-5 minutes during cardiac standstill |

Endogenous catecholamine
### Dobutamine

| What receptors are stimulated: | Primarily $\beta_1$
| | Some alpha $\alpha_1$ receptor stimulation
| | Some $\beta_2$ stimulation
| | Modest $\beta_2$ (more $\beta_2$ than alpha $\alpha_1$)
| What are the resultant actions: | Increase contractility (+ inotrope) ($\beta_1$)
| | Increase AV node conduction
| | Modest vasodilatation
| When and why do we use: | Used as an inotrope (resultant preload reduction) with modest afterload reduction (ACC / AHA Guidelines for Heart Failure*)
| What are special nursing considerations: | Onset 1 to 2 minutes; Peak 10 minutes
| | Half-life 2 minutes
| | Note: Blood pressure response is variable; $\beta_2$ causes vasodilatation; $\beta_1$ increases cardiac output and may increase BP

### Dopamine

| What receptors are stimulated: | Dopaminergic at low doses (0.5-2.0 mcg/kg/min)
| | $\beta_1$ also at moderate doses (2.0-10.0 mcg/kg/min)
| | Pure alpha stimulation at high doses > 10mcg/kg/min
| What are the resultant actions: | Increase GFR at low doses
| | Increase contractility at moderate doses (greater effects on contractility than heart rate)
| | Vasoconstriction (alpha) at high doses
| When and why do we use: | Refractory hypotension / shock
| | * Not indicated for routine treatment or prevention of acute renal failure
| What are special nursing considerations: | Onset 1-2 minutes; Peak 10 minutes
| | Maximal effects @20/mcg/kg/min
| | Large IV line or central line; Regitine (alpha blocker) for infiltrate

*Not indicated for routine treatment or prevention of acute renal failure.*
### Norepinephrine

| What receptors are stimulated: | Primarily alpha stimulation  
|                               | Some β<sub>1</sub>  
|                               | (In lower doses β<sub>1</sub> can be more dominant)  

| What are the resultant actions: | Potent vasoconstrictor (increased afterload)  
|                                | Some increased contractility (+inotrope)  

| When and why do we use: | Refractory hypotension / shock  
|                        | (used as a vasopressor but will have inotropic properties)  

| What are special nursing considerations: | Onset: rapid; very short half-life  
|                                          | Duration 1-2 minutes (BP checks q2 minutes while titrating)  
|                                          | Large IV line or central line  
|                                          | Regitine (alpha blocker) for infiltrate  

### Phenylephrine

| What receptors are stimulated: | Direct effect: Dominant alpha stimulation  
|                               | No substantial β<sub>1</sub> effect at therapeutic doses  
|                               | Indirect effect: Releases norepinephrine  

| What are the resultant actions: | Vasoconstriction (increased afterload)  

| When and why do we use: | As a vasopressor for Unresponsive hypotension  

| What are special nursing considerations: | Pressor effect occurs almost immediately  
|                                          | Persists for 10 to 15 minutes  

Remember!!

• Titrate up based on onset of action

• Wean based on duration of action

Other Dopaminergic Stimulators

• Fenoldopam (Corlopam)
  – Selective dopamine receptor agonist
  – Rapid acting vasodilator
  – Produces vasodilatation in coronary, renal, mesenteric and peripheral arteries

Not proven effective in preventing contrast induced nephropathy.
Non Sympathomimetic Vasopressor

Arginine Vasopressin

- Vasoconstrictive effects
  - Allowing for regional vasodilation
- Antidiuretic effects
- Restoration of catecholamine sensitivity

- Use in refractory shock
  - Also consider methylene blue
  - Also consider adrenal insufficiency as cause
- Low dose exogenous
  - 0.04 units / min
Non Sympathomimetic Inotropes

Phosphodiesterase Inhibitors

Used as an Inotrope

BUT

Preload Reduction

Also has......

Afterload Reduction
Phosphodiesterase Inhibitors

- New generation: Milrinone (Primacor)
- Creates + inotropic effect by increasing availability of calcium
  - Inhibits the degradation of cyclic AMP which is indirectly responsible for increasing the influx of calcium through the calcium channel
- Smooth muscle relaxant (venous and arterial vasodilator)
- Indications:
  - Refractory heart failure (in combination with dobutamine)
  - Left ventricular failure in MI
  - Patients waiting transplant
- Side Effects:
  - Ventricular arrhythmias, thrombocytopenia (new generation less)
- Nursing Considerations:
  - Onset IV: Immediate
  - Peak: 10 minutes

Venous and Arterial Vasodilators
A Closer Look at Venous Versus Arterial Vasodilators

Venous Vasodilators
 Decrease Preload

Arterial Vasodilators
 Decrease Afterload

Preload reduction:
- Decreased pulmonary venous congestion
- Decreased ventricular wall stress
- Increased diastolic coronary blood flow
- Improved myocardial oxygen delivery

Afterload reduction:
- Reduction in ventricular wall stress
- Increased coronary blood flow
- Enhanced oxygen delivery and utilization
- Improved systolic contractile function
- Reduction in mitral regurgitation
A Closer Look at Venous Versus Arterial Vasodilators

- Some medications do both
- Some depend on dose
  - Nesiritide
  - NTG
  - Nipride
  - CA Channel blockers
  - PDE Inhibitors
  - ACE Inhibitors
  - Other Vasodilators

Nesiritide (Natrecor)

- Recombinant form of human B type natriuretic peptide (BNP)
- BNP is a naturally occurring cardiac neurohormone secreted by the heart in the body’s response to heart failure
- BNP allows the heart to participate in the regulation of vascular tone and extracellular volume status
- The BNP system and the renin-angiotensin system counteract each other in heart failure
- BNP levels are elevated in heart failure
Nesiritide (Natrecor)

- Balanced arterial and venous vasodilatation
  - Causes rapid reduction in right and left sided ventricular filling pressures (preload reduction)
  - Reduces afterload

- Indicated for acutely decompensated heart failure patients who have dyspnea at rest

- Patient must have systolic BP > 90 mmHg
- PAOP should be estimated to be > 20 mmHg

- Given by IV bolus and maintenance infusion (bolus to be taken from reconstituted IV bag and not from vial)
- Infusion is usually 24-48 hours

Monitor BP closely during administration.
Nitroglycerin

- Mixed venous and arterial vasodilator
  - Dosage < 1mcg/kg/min = venous vasodilator
  - Dosage > 1mcg/kg/min = arterial and venous vasodilator
  - Sublingual tablets provide high enough dosage to dilate arteries and veins
  - Nitrate tolerance can be avoided by providing nitrate free interval preferably during night time hours
  - Decreases activity of Heparin

Nitroglycerin

- Uses: Acute MI, unstable angina, CHF
- Side Effects: H/A, Hypotension, flushing
- Nursing Considerations:
  - Contraindicated with Sildenafil like drugs
  - Caution (all venous vasodilators) with:
    - Hypertrophic cardiomyopathy, aortic stenosis, right ventricular MI
  - Treat H/A with pain meds and decrease dose
  - Onset IV: 1-2 minutes
  - Duration: 3-5 minutes
Nipride

- Mixed venous and arterial dilator (primarily arterial)
- Decreases SVR, BP, PVR, PAOP, RAP
- Uses:
  - Hypertensive crisis
  - CHF
  - Acute Mitral Regurgitation
  - Other Indications for Afterload Reduction
- Side Effects:
  - Hypotension
  - Thiocyanate toxicity: tinnitus, blurred vision, delirium, seizures, muscle twitching, absent reflexes, dilated pupils
  - Several days – high doses
- Nursing Considerations:
  - Onset: 1-2 minutes
  - Duration: 1-10 minutes
  - Monitor BP carefully- arterial line encouraged

Non ACE Inhibitor Arterial Vasodilators

- All non ACE Inhibitor vasodilators are potent stimulators of the renin angiotensin system
  - Thus side effects include increased intravascular volume and progressive edema
- Direct Smooth Muscle Relaxants
  - Examples: Hydralazine, Minoxidil
- Alpha_1_ Adrenergic Blockers
  - Examples: Prazosin, Terazosin, Doxazosin
- Central anti-adrenergics
  - Examples: Clonidine, Methyldopa
- Peripheral anti-adrenergics
  - Examples: Resperine, Guanethidine
- “INE” Calcium Channel Blockers
  - Nifedipine, isradipine, amlodipine, felodipine, mimodipine
Nursing Implications for Some Arterial Vasodilators

- Terazosin (Hytrin) and Prazosin (Minipress) have the potential for a significant first dose hypotension and syncope, particularly in the elderly
  - Hyponatremia worsens hypotensive episodes
  - First dose should be taken at bedtime and patient warned to use extreme caution if getting out of bed
  - These are not first choice medications and are reserved for refractory hypertension

Acute Conditions Requiring Vasodilator Therapy

- Vasodilators can be life saving in conditions which require immediate afterload reduction or reduction of systemic blood pressure
  - Severe acute mitral regurgitation (papillary muscle rupture) (inferior / posterior MI)
  - Ventricular septal rupture (anterior MI)
  - Severe acute aortic insufficiency
  - Hypertensive emergency
  - Aortic dissection
Shifting Gears!

Common Oral Medications to Optimize Cardiac Performance in Chronic Disease Management

Digoxin

- Inhibits the NA+ and K+ membrane pump
- Increase in intracellular Na+
- Enhances the Na+ and Ca++ exchange
- Leads to ▲ in intracellular Ca++
- ▲ inotropic activity
**Digoxin**

- Increases vagal activity
- Digoxin decreases conduction velocity through the AV node (sympathetic stimulation easily overrides the inhibitory effects of digoxin on AV node conduction)
- The conduction velocity increases in the atria, but decreases in the AV node.
- Automaticity is also increased, in the atria, AV node, Purkinje fibers and ventricles.
  - Calcium channel blockers are replacing digoxin as agent for rate control in atrial arrhythmias
  - Digoxin no better than placebo in converting atrial fibrillation to sinus rhythm
- **Digoxin decreases sympathetic outflow and decreases renin production**
  - Beneficial in heart failure

**Indications**
- HF
- Atrial arrhythmias (older indication)
  - Still an option when BP is a concern

**Contraindication / cautions**
- Acute MI
- Ventricular arrhythmias, HB, Sick Sinus Syndrome
- Obstructive Hypertrophic Cardiomyopathy
- Electrolyte abnormalities (decreased K+, Ca++, and Mg++)
Digoxin

- Has a narrow therapeutic range
- Toxicity may occur at therapeutic levels
- Lower doses now routinely used 0.125 mg daily
- Amiodorone increases serum digoxin concentration (digoxin doses must be reduced if starting amiodarone)
- Multiple other medication interactions
- Dialysis is not effective with digoxin toxicity because of high tissue binding of digoxin

More About Digoxin Toxicity

- EKG Changes with Toxicity
  - Increased automaticity with impaired conduction is common (example: PAT with AV Block)
- Other Signs and Symptoms of Toxicity
  - N & V, HA, Confusion
  - Visual disturbances: halos, change in color perception
Diuretics

Thiazide Diuretics

– Inhibit reabsorption of Na+ and Cl-
  • In the distal tubule.
– Delayed onset but longer duration of action than loop diuretics
– Low ceiling diuretics
– Less potent diuretic than loop diuretics
– Diminished effectiveness in presence of renal failure
**Thiazide Diuretics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>General side effects of thiazide diuretics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendrofluazide (Naturetin)</td>
<td>Blood Chemistry changes:</td>
</tr>
<tr>
<td>Benthiazide (Aquatag, Exna)</td>
<td>Hypokalemia (↓ K⁺)</td>
</tr>
<tr>
<td>Chlorothiazide (Diuril)</td>
<td>Hyperglycemia (↑ blood sugar)</td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton)</td>
<td>Hyperuricemia (↑ uric acid)</td>
</tr>
<tr>
<td>Cyclothiazide (Anhydron)</td>
<td>Hypercalcermia (↑ Ca²⁺)</td>
</tr>
<tr>
<td>Hydrochlorothiazide (HCTZ)</td>
<td>Decreased glomerular filtration in</td>
</tr>
<tr>
<td>Hydroflumethazide (Saluron, Dincardin)</td>
<td>kidneys (↑ BUN, creatinine)</td>
</tr>
<tr>
<td>Indapamide (Lozol)</td>
<td>↑ cholesterol</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>↑ triglycerides</td>
</tr>
<tr>
<td>Polythiazide (Renese)</td>
<td>↓ HDL cholesterol</td>
</tr>
<tr>
<td>Trichlormethazide (Metahydrin, Naqua)</td>
<td>Other side effects:</td>
</tr>
</tbody>
</table>

Other side effects:
- Impaired glucose tolerance
- Gout
- Impotence
- Ventricular arrhythmias (↓ K⁺)
- Nausea, dizziness, headache

**Loop Diuretics**

- Work in ascending loop of Henle
- Loss of H₂O, K⁺, Na⁺, Cl⁻, H⁺
- More loss of H₂O and less K⁺ and Na⁺ than thiazides
- Promotes venous vasodilatation
- Rapid onset and short duration
- Can be effective in presence of renal failure
- High ceiling diuretic
# Loop Diuretics

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<thead>
<tr>
<th>Drug</th>
<th>General side effects of loop diuretics:</th>
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<tbody>
<tr>
<td>Bumetanide (Bumex)</td>
<td>Blood Chemistry changes (less severe than with thiazides):</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia (↓ K⁺)</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia (↑ blood sugar)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia (↑ uric acid)</td>
</tr>
<tr>
<td></td>
<td>↑ cholesterol</td>
</tr>
<tr>
<td></td>
<td>↑ triglycerides</td>
</tr>
<tr>
<td></td>
<td>↓ HDL cholesterol</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>Other side effects:</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Ototoxicity (deafness, reversible)</td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
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## Beta Blockers

"lol" medications
A Closer Look at Beta Blockers

- Decrease HR
- Decrease Contractility

\[ \text{Blood pressure} = \text{CO} \times \text{SVR} \]

Cardiovascular Indications for Beta Blockers

- Hypertension
- Angina
- AMI
- Post Infarction
- Supraventricular arrhythmias
- Ventricular arrhythmias
- Aortic Dissection
- Hypertrophic cardiomyopathy (actually increase C.O.)
- Mitral valve prolapse
- Prolonged QT syndrome
- Heart failure
- Digitalis induced ventricular arrhythmias
A Closer Look at Beta Blockers

**Common Cardiac Indications**

- **Angina**: Used with angina to decrease myocardial oxygen demand and increases diastolic filling time
- **ACS**: Decreases ventricular fibrillation short term and ventricular remodeling long term
  - Mortality benefit
- **HF**: Decrease contractility, however, now indicated in HF because they block the neurohormonal response of the SNS
  - Decrease ventricular remodeling
  - Mortality benefit
  - Avoid in acute decompensated HF

Beta Blockers

**Nonselective**: Block both Beta ₁ and Beta ₂
- Propranolol (Inderal)
- Timolol (Blocadren)
- Nadolol (Corgard)
- Sotalol (Betapace)
- Carvedilol (Coreg)
  (also alpha blockade)

**Cardio Selective**: Block Beta ₁
- Acebutolol (Sectral)
- Metoprolol (Lopressor)
- Atenolol (Tenormin)
- Esmolol (Brevibloc)
- Bisoprolol (Z Beta)
- Nebivolol (Bystol)
  (also nitric oxide vasodilatory properties)
Beta Blockers Recommended by Disease State

• Post MI
  – Atenolol
  – Carvedilol
  – Metoprolol
  – Propanolol
  – Timololol

• Heart Failure
  – Bisoprolol
  – Carvedilol
  – Metoprolol

Calcium Channel Blockers
**A Closer Look at Calcium Channel Blockers**

- **Decrease HR**
- **Decrease Contractility**
- **Decrease Afterload**

*Note:* Not all calcium channel blockers are created equal; therefore not all calcium channel blockers have the same actions.

**Three potential effects of Calcium Channel Blockers**

- **Cardiac Muscle Contractility**
  - Blocks inward flow of calcium in Phase II of action potential and decreases force of contraction
- **Cardiac Conduction**
  - Depresses automaticity and velocity and decreases HR
- **Vascular Smooth Muscle Relaxant**
  - Coronary artery dilatation and increases blood flow to coronary arteries (except nifedipine)
A Closer Look at Calcium Channel Blockers

<table>
<thead>
<tr>
<th></th>
<th>Verapamil</th>
<th>Dihydropyridines</th>
<th>Diltiazem</th>
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<tbody>
<tr>
<td>Heart Rate</td>
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<tr>
<td>AV Nodal Conduction</td>
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<tr>
<td>Contractility</td>
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<td>Arterial Vasodilation</td>
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Calcium Channel Blockers: Indications

- Atrial Fibrillation / Flutter and PSV
  - Diltiazem and Verapamil
- Treatment of angina in combination with beta blockers and nitrates
  - Diltiazem and Verapamil with Nitrates
  - “Ines” with Beta Blockers
- Hypertension (decreases SVR)
  - “Ines”
- Adjunct treatment for diastolic not systolic heart failure
- Hypertrophic cardiomyopathy (verapamil)
- Prevention of coronary spasm for patients undergoing PCI
A Closer Look at “Ine” Calcium Channel Blockers

• Newer Dihydropyridines Calcium Channel Blockers
  – Amlodipine (Norvasc)
  – Effects vascular smooth muscle with minimal to no effect on heart rate or conductivity
  – Good decrease in total peripheral vascular resistance
  – Directly dilates coronary arteries (nitric oxide release)

ACE Inhibitors and Angiotensin II Receptor Blockers
A Closer Look at ACE Inhibitors and Angiotensin II Receptor Blockers

Afterload and preload reduction

Renin-Angiotensin System

↓ Renal Flood Flow

Renin release

β blockers

Angiotensinogen → Angiotensin I (converting enzyme)

(ACE inhibitors)

Angiotensin II

Angiotensin Receptor Blockers

Vasoconstriction

Aldosterone release

Aldosterone Blockers

Na+ & H2O retention

↑ BP
A Closer Look at ACE Inhibitors

- ACE Inhibitors impact afterload and preload because they block the vasoconstrictive effects of angiotensin II
  - Very important in reducing workload of left ventricle in systolic dysfunction

- ACE Inhibitors additionally assist with preload reduction by blocking the effects of aldosterone release

A Closer Look at ACE Inhibitors and Angiotensin II Receptor Blockers

- Angiotensin-converting enzyme inhibitors ("pril" medications)
  - Captopril, Enalapril, Lisinopril, Quinapril, Ramipril, Benazepril, Fosinopril

- Angiotensin II Receptor Blockers ("sartan" medications)
  - Losartan, Irbesartan, Candesartan, Telmisartan, Valsartan, Eprosartan
A Closer Look at ACE Inhibitors

• The effects of blocking the Renin Angiotensin Aldosterone system are complex:
  – Overall cardioprotective and vasculoprotective effect
  – Improved balance of myocardial oxygen supply and demand by decreasing left ventricular preload and afterload
  – Reduction of left ventricular mass in LV hypertrophy
  – Can decrease the progression rate of kidney failure especially in insulin dependent diabetics
  – Kinins and Prostaglandins

A Closer Look at ACE Inhibitors

• Influences bradykinin and can produce cough
• Cough is side effect in 10-20% of patients
• Need to assure cough is not sign of worsening heart failure
• Patient may need changed to ARB

Absolute Contraindication!
A Closer Look at ACE Inhibitors

• Can cause acute renal failure in patients with bilateral renal artery stenosis
  – Dilating efferent glomerular arterioles which result in decreased glomerular filtration

• Renal function
  – Evaluated prior to and 1-2 weeks after initiation of ACE inhibitors in high risk patients

• If acute kidney injury develops from ACE – I, then hydralazine in combination with isosorbide dinitrate should be used
  – Combination achieves venous and arterial vasodilation)

Aldosterone Antagonists
Clinical Effects of Aldosterone

- Promotes retention of sodium
- Promoted loss of potassium and magnesium
- Potentiates catecholamines
- Inhibits the parasympathetic nervous system
- Decreases arterial compliance
- Promotes direct remodeling
- Has prothrombotic properties
- Causes vascular inflammation and injury

Spironolactone (Aldactone)

- Non selective aldosterone blocker
  - Blocks aldosterone and androgen; stimulates progesterone

  Major side effect: gynecomastia, sexual dysfunction and menstrual problems due to non selectivity

- Side effect of hyperkalemia when used with ACE Inhibitor or ARB

- Mortality reduction
Eplerenone (Inspra)

• Selective aldosterone receptor antagonist

Eliminates most gynecomastia and sexual side effects associated with aldactone

• Side effect of hyperkalemia when used with ACE Inhibitor or ARB

• Indicated in MI with LV Dsyfunction
  – Prevent progression of heart failure
  – Prevent sudden cardiac death
  – Prevent recurrent MI

Newer / Future Agents

• Direct Renin Inhibitors
  – Aliskiren (Tekturna)
  – Currently used as antihypertensive

• Vasopressin 2 Antagonists
  – Vasopressin 1 (vascular)
  – Vasopressin 2 (renal collecting ducts)
  – Vasopressin 3 (pituitary)
  – Tolvaptan – in addition to standard IV therapy in acute decompensated HF

• Adenosine A1 Receptor Antagonists
  – Investigational
  – Enhances response to diuretics
Evidence Based Practice and Pharmacology

Making the Link

- Acute Coronary Syndrome / Angina / Coronary Artery Disease
- Heart Failure

Mortality Impacting Medications
Case Study Analysis

Case Study Evaluation

- Tissue oxygenation?
- Delivery of oxygen?
  - C.O. / Hgb / O₂ Sat
- Cardiac output?
  - Preload?
  - Afterload?
  - Contractility?
  - HR?
- Hemodynamic profile?
- Congestion and perfusion evaluation?

BP: 88/72  
HR: 110’s to 130’s  
RR 28-32  
Pale and cool to touch  
Somewhat lethargic  
S3, systolic murmur  
3/6 loudest at apex  
Lungs: Crackles ½ up  
JVD  
RUQ quadrant tenderness  
2+ edema  
Urine output is 10cc/hr  
SaO₂ 88% on 4L Mild right sided weakness  
K⁺ 4.9  
H & H 9.2 / 30.1  
BUN 42 / Creatinine 2.0
Warm and Dry:  
No Congestion  
Normal Perfusion
Warm and Wet:  
Congestion  
Normal Perfusion
Cold and Dry:  
No Congestion  
Low Perfusion
Cold and Wet:  
Congestion  
Low Perfusion

Pharmacology Evaluation

• Home meds?

• Medications for acute decompensated heart failure?
  – Understanding cause of hypotension
    • BP = CO x SVR

Furosemide 20 mg daily
Lisinopril 20 mg daily
Metoprolol 25 mg BID
Aldactone 25 mg daily
Coumadin 5 mg daily
Synthroid
OTC NSAIDs
Additional Discussion?

• Stage / NYHA Class?
  − Baseline functional status
• Cause of decompensation?
  − Additional diagnostics
• Oxygenation / ventilatory status?
• Murmur? Valve dysfunction?
• Atrial fib (recurrence or chronic?)
• Anemia – acute or chronic?
• Renal insufficiency – acute or chronic?
  − Pre or intrarenal
• Impact of BBB?
• Right sided weakness?
• Potassium?
• Patient education / Self-care?
• Advanced directives?