Lecture 7. CONGESTIVE HEART FAILURE

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DEFINITION

“The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return.”

E. Braunwald
Incidence and prevalence

Heart failure is an epidemic affecting 1-2 million Ukrainians and nearly 15 million people worldwide.

Heart failure carries worse prognosis, as 50% of patients with heart failure will die within 5 year, and in patient with sever heart failure more than 50% will die within 2 year.
DETERMINANTS OF VENTRICULAR FUNCTION

- Synergistic LV contraction
- LV wall integrity
- Valvular competence
Pathophysiology of heart failure
DIAGNOSIS

- HISTORY.
- PHYSICAL EXAMINATION.
- APPROPRIATE INVESTIGATION.

1. SYMPTOMS OF HEART FAILURE (AT REST OR DURING EXERCISE).
2. Objective evidence of cardiac dysfunction.
3. Response to treatment directed towards heart failure.
CRITERIA FOR CONGESTIVE HEART FAILURE

- **MAJOR CRITERIA**
  1. Paroxysmal nocturnal dyspnea or orthopnea.
  2. Rales.
  3. Cardiomegaly.
  4. Acute pulmonary edema.
  5. S₃ Gallop.
  6. Increased venous pressure > 16 cm of water.
  8. Hepatogenous reflux.

- **MINOR CRITERIA**
  1. Ankle edema.
  2. Night cough.
  3. Dyspnea on exertion.
  4. Pleural effusion.
  5. Vital capacity decreased 1/3 from maximum.
  6. Tachycardia (rate > 120/min).

- **MAJOR OR MINOR**
  Weight loss > 4.5 Kg in 5 days in response to treatment.
Symptomatic classification of exercise tolerance
New York Heart Association (NYHA)

NYHA Class I: No complaints under heavy physical load.

NYHA Class II: Complaints under heavy physical load.

NYHA Class III: Complaints under light physical load.

NYHA Class IV: Complaints at rest.
Descriptive terms in heart failure

Acute vs Chronic heart failure.

Systolic vs Diastolic.

Right vs Left heart failure.
Types of Heart Failure

- include left, right or both sides
- **left ventricular heart failure**
  - most common
  - systolic failure: unable to contract
  - diastolic failure: unable to relax
- **right ventricular heart failure**
  - usually occurs after left failure
  - less blood received causes right damage
  - less pumping by right side
  - venous pooling of blood in legs
Causes of Chronic Heart Failure

*Systolic dysfunction:*

- Coronary artery disease.
- Hypertension.
- Dilated Cardiomyopathy.
- Myocarditis.
Causes of Chronic Heart Failure cont.

**Diastolic Dysfunction:**
- Coronary artery disease.
- Systemic Hypertension.
- Diabetis Mellitus.
- Aortic stenosis.
- Hypertrophic cardiomyopathy.
- Infiltrative cardiomyopathy
- Endocardial fibrosis.
- Normal aging process.
Causes of worsening Heart Failure cont.

Cardiac:

- Atrial fibrillation.
- Other supraventricular or ventricular arrhythmias.
- Bradycardia.
- Appearance or worsening mitral or tricuspid regurgitation.
- Myocardial ischaemia.
- Excessive preload reduction (diuretics, ACE inhibitors).
Causes of worsening Heart Failure
Non-cardiac:

- Non compliance to the prescribed regimen (salt, liquid, medication).
- Recently co-prescribed drugs (antiarrhythmic, beta-blockers, non steroidal anti-inflammatory drugs, verapamil, diltiazem).
- Renal dysfunction.
- Infection.
- Pulmonary embolism.
- Thyroid dysfunction.
- Anemia.
- Alcohol abuse.
The Heart Failure Milieu

Clinical Presentation

- Disease Process
- Ventricular Dysfunction
- Haemodynamic Abnormalities
- Compensatory Mechanism
- Metabolic Changes

Symptoms And Physical Finding
Metabolic Changes

- Azotemia.
- Hyponatraemia.
- Hypokalemia.
- Hypomagnesemia.
- Hyperuricemia.
- Acidosis/Alkalosis.
- Hypoxia/O2 desaturation.
- Decreased MVO2.
Symptomes

- Fatigue, weakness and decreased exercise tolerance.
- Dyspnea and fluid retention symptoms.
- Nocturia.
- Gastrointestinal symptoms.
- Diminished mentation.
Physical Findings

- Peripheral edema.
- Ascites.
- Jugular venous distension.
- Rales.
- Tachycardia.
- Hypotension.
- Cachexia.
- Disease specific findings.
**Systemic organ failure**

- Renal failure.
- Hepatic failure.
- Respiratory failure.
- Multi-organ failure.
- Pulmonary embolism.
- Peripheral & cerebral embolism.
Evaluation of heart failure patient

- Physical Examination
- Laboratory tests
- History
- Diagnostic studies
Investigation
Laboratory

- Complete Blood Count.
- Serum electrolytes, blood urea nitrogen, serum creatinine.
- Liver function test.
- Prothrombin time.
- Lipid profile.
- Thyroid function test.
- Anaemia evaluation.
- Arterial blood gases.
- Serum drug levels (digoxin, phenytoin).
- Atrial natriuretic peptides.
- Urin analysis.
Chest X-ray

Chest roentgenogram of patient with heart failure. This roentgenogram demonstrates cardiomegaly (cardiothoracic ratio 0.77), pulmonary congestion, and bilateral pleural effusions (note blunted costophrenic angles).
12-Leads ECG
Other investigation

- Transthoracic Echocardiography.
- Stress Echo.
- Exercise stress testing.
- 24-hour Holter monitoring.
- Nuclear imaging, thallium perfusion scan, cardiac MRI.
- Coronary angiography
Chronic Congestive Heart Failure

EVOLUTION OF CLINICAL STAGES

NORMAL
No symptoms
Normal exercise
Normal LV fxn

Asymptomatic LV Dysfunction
No symptoms
Normal exercise
Abnormal LV fxn

Compensated CHF
No symptoms
Exercise
Abnormal LV fxn

Decompensated CHF
Symptoms
Exercise
Abnormal LV fxn

Refractory CHF
Symptoms not controlled with treatment

Chronic Congestive Heart Failure
Treatment Options

- **Non-pharmacological.**

- **Pharmacological therapy.**
  - Angiotensin-converting enzyme inhibitors (ACE).  
  - Beta-adrenoreceptor antagonists.  
  - Cardiac glycosides.  
  - Diuretics.  
  - Vasodilators (nitrates, hydralazine).  
  - Antiarrhythmic agent.  
  - Anticoagulant.  
  - Oxygen.

- **Devices and surgery.**
  - Revascularization.  
  - Pacemaker.  
  - Implantable cardioverter defibrillator (ICD).  
  - Cardiac transplantation.  
  - Ultrafiltration, haemodialysis.
TREATMENT

Correction of aggravating factors

MEDICATIONS

- Endocarditis
- Obesity
- Hypertension
- Physical activity
- Dietary excess

Pregnancy
- Arrhythmias (AF)
- Infections
- Hyperthyroidism
- Thromboembolism

MEDICATIONS
TREATMENT
PHARMACOLOGIC THERAPY

- DIURETICS
- INOTROPES
- VASODILATORS
- NEUROHORMONAL ANTAGONISTS
- OTHERS (Anticoagulants, antiarrhythmics, etc)
TREATMENT

Normal

Asymptomatic LV dysfunction
EF <40%

Symptomatic CHF
NYHA II

Symptomatic CHF
NYHA - III

ACEI

Diuretics mild
Neurohormonal inhibitors
Digoxin?

Symptomatic CHF
NYHA - IV

Inotropes
Specialized therapy
Transplant

Secondary prevention
Modification of physical activity
Thiazides
Inhibit active exchange of Cl-Na in the cortical diluting segment of the ascending loop of Henle

K-sparing
Inhibit reabsorption of Na in the distal convoluted and collecting tubule

Loop diuretics
Inhibit exchange of Cl-Na-K in the thick segment of the ascending loop of Henle
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Relative potency</th>
<th>Site of Action</th>
<th>Onset of Action</th>
<th>Advantages</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>Moderate</td>
<td>Excreted into proximal tubule, inhibition of Na and Cl, absorption in distal segment</td>
<td>1-2 h</td>
<td>Mild, relatively nontoxic, oral administration, antihypertensive</td>
<td>K loss. hyperglycemia, decreases platelets. ineffective when GFR &lt; 20 mL/min. hyperuricemia</td>
</tr>
<tr>
<td>Oral: 50-200 mg/day</td>
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<tr>
<td>Loop diuretics</td>
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</tr>
<tr>
<td>Furosemide 40-200 mg</td>
<td>High</td>
<td>Inhibition of Cl transport in ascending limb of loop of Henle</td>
<td>Oral: 1 h IV: 10-20 min</td>
<td>Rapid onset, potency, independent of acid-base balance, effective even when GFR is reduced</td>
<td>Excessive diuresis; hypovolemia; K loss and hypokalemia; hyperuricemia; transient or irreversible deafness with IV administration, especially when used with aminoglycoside antibiotic</td>
</tr>
<tr>
<td>1, 2. or 3 times/day; IV: 40 mg initially; may increase to 200-400 mg, depending on response</td>
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<td>Torosimide 5-10 mg/d</td>
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<td>Ethacrynic acid IV: 50 mg initially; may increase, depending on response</td>
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</tbody>
</table>
DIURETICS
ADVERSE REACTIONS
Thiazide and Loop Diuretics

- Changes in electrolytes:
  - \( \downarrow \) Volume
  - \( \downarrow \) Na\(^+\), K\(^+\), Ca\(^{++}\), Mg\(^{++}\)
  - metabolic alkalosis

- Metabolic changes:
  - \( \uparrow \) glycemia, uremia, gout
  - \( \uparrow \) LDL-C and TG

- Cutaneous allergic reactions
POSITIVE INOTROPES

- CARDIAC GLYCOSIDES
- SYMPATHOMIMETICS
  - Catecholamines
  - β-adrenergic agonists
- PHOSPHODIESTERASE INHIBITORS
  - Amrinone
  - Milrinone
  - Enoximone
  - Piroximone
- Others
# DOPAMINE AND DOBUTAMINE EFFECTS

<table>
<thead>
<tr>
<th></th>
<th>DA (µg / Kg / min)</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2</td>
<td>2 - 5</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>DA₁ / DA₂</td>
<td>β₁</td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td><strong>Heart Rate</strong></td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td><strong>Arterial Press.</strong></td>
<td>±</td>
<td>+</td>
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<tr>
<td><strong>Renal perfusion</strong></td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Arrhythmia</strong></td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Agent</td>
<td>Dose and Route</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>ADRENERGIC AGONISTS</strong></td>
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<tr>
<td>Epinephrine</td>
<td>300-500µg SC or IM (0.3-0.5 mL of 1/1000 solution of hydrochloride salt); 25-50 µg IV (slowly) every 5-15 min; titrate as needed</td>
<td>Nonselective alpha and beta agonist; increases BP, heart rate Bronchodilation</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2-4 µg of NE base/min IV; titrate as needed</td>
<td>Alpha and beta₁ agonist Vasoconstriction predominates Extravasation causes tissue necrosis; infuse through IV cannula</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2.5-25 (µg/kg)/min IV</td>
<td>Selective beta₁ agonist with greater effect on contractility than heart rate; a congener of dopamine but not a dopaminergic agonist</td>
</tr>
<tr>
<td><strong>DOPAMINERGIC AGONISTS</strong></td>
<td></td>
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</tr>
<tr>
<td>Dopamine</td>
<td>2-5 (µg/kg)/min IV (dopaminergic range) 5-10 (µg/kg)/min IV (dopaminergic and beta range) 10-20 (µg/kg/min) IV (beta range) 20-50 (µg/kg)/min IV (alpha range)</td>
<td>Pharmacologic effects are dose dependent: renal and mesenteric vasodilation predominate at lower doses; cardiac stimulation and vasoconstriction develop as the dose is increased</td>
</tr>
</tbody>
</table>
POSITIVE INOTROPES

CONCLUSIONS

- May increase mortality
- Safer in lower doses
- Use only in refractory CHF
- NOT for use as chronic therapy
VENOUS
Nitrates
Molsidomine

MIXED
Calcium antagonists
α-adrenergic Blockers
ACEI
Angiotensin II inhibitors
K+ channel activators
Nitroprusside

ARTERIAL
Minoxidil
Hydralazine
1- VENOUS VASODILATATION

- Preload

2- Coronary vasodilatation

- Myocardial perfusion

3- Arterial vasodilatation

- Afterload

4- Others

NITRATES
HEMODYNAMIC EFFECTS

- Pulmonary congestion
- Ventricular size
- Vent. Wall stress
- MVO₂

Cardiac output
Blood pressure
<table>
<thead>
<tr>
<th>Classification</th>
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<th>Advantages</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>Nitroglycerin</td>
<td>Nitrate receptor</td>
<td>Immediate</td>
<td>Rapid onset; various routes of administration; good for emergencies</td>
<td>Headache; hypotension; methemoglobinemia; tolerance if not given intermittently</td>
</tr>
<tr>
<td></td>
<td>Sublingual: 0.4 mg pm</td>
<td></td>
<td>Immediate 30-60 min</td>
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<tr>
<td></td>
<td>Oral: 20-60 mg q 4-6 h</td>
<td></td>
<td>2-5 min</td>
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<td></td>
<td>IV: 10-100 μg/min</td>
<td></td>
<td>20-40 min</td>
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<td></td>
<td>Isosorbide dinitrate</td>
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<tr>
<td></td>
<td>Sublingual: 2.5-10mg q 2-4 h</td>
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<tr>
<td></td>
<td>Oral: 20-60 mg q 4-6 h</td>
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<tr>
<td>Arterial vasodilators</td>
<td>Hydralazine</td>
<td>Smooth muscle</td>
<td>30-45 min</td>
<td>Specific arteriolar vasodilator</td>
<td>Tachycardia; lupus phenomenon; long-term benefit requires nitrates</td>
</tr>
<tr>
<td></td>
<td>Oral: 25-100 mg q 6 h</td>
<td></td>
<td></td>
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<td>Hypotension; thiocyanate accumulation</td>
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<tr>
<td></td>
<td>Minoxidil</td>
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<td></td>
<td>Tachycardia; aggravates angine; marked fluid retension; hair growth on face and body, coarsening of facial features</td>
</tr>
<tr>
<td></td>
<td>Oral: 25-40 mg twice daily</td>
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<td>Hyperglycemia, hyperuricemia, sodium retention</td>
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<tr>
<td></td>
<td>Diazoxid IV: 1-3 mg/kg up to 150 mg rapidly</td>
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<td>Cianide toxicity</td>
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<tr>
<td></td>
<td>Nitroprusside</td>
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</tbody>
</table>
PROBABILITY OF DEATH

NITRATES SURVIVAL

Placebo (273) —
Prazosin (183) —
Hz + ISDN (186) —

VHefT-1

N Engl J Med 1986;314:1547
NITRATES TOLERANCE

"Decrease in the effect of a drug when administered in a long-acting form"

- Develops with all nitrates
- Is dose-dependent
- Disappears in 24 h. after stopping the drug
- Tolerance can be avoided
  - Using the least effective dose
  - Creating discontinuous plasma levels
NITRATES
CONTRAINDICATIONS

- Previous hypersensitivity
- Hypotension (< 80 mmHg)
- AMI with low ventricular filling pressure
- 1st trimester of pregnancy

WITH CAUTION:
- Constrictive pericarditis
- Intracranial hypertension
- Hypertrophic cardiomyopathy
ACE-Inhibitors
MECHANISM OF ACTION

VASOCONSTRICTION
ALDOSTERONE
VASOPRESSIN
SYMPATHETIC
Angiotensinogen
Angiotensin I
RENIN
Angiotensin II

VASODILATATION
PROSTAGLANDINS
Kininogen
Kallikrein
tPA

BRADYKININ
Kininishase II
Inactive Fragments

A.C.E. - Inhibitor -
ACEI
HEMODYNAMIC EFFECTS

- Arteriovenous Vasodilatation
  - ↓ PAD, PCWP and LVEDP
  - ↓ SVR and BP
  - ↑ CO and exercise tolerance
- No change in HR / contractility
- ↓ MVO$_2$
- ↑ Renal, coronary and cerebral flow
- Diuresis and natriuresis
No Additional Treatment Necessary (%)

Quinapril Heart Failure Trial
*JACC 1993;22:1557*
ACEI

INDICATIONS

- Clinical cardiac insufficiency
  - All patients

- Asymptomatic ventricular dysfunction
  - LVEF < 35 %
ACEI
UNDESIRABLE EFFECTS

• Inherent in their mechanism of action
  - Hypotension
  - Hyperkalemia
  - Angioneurotic edema
  - Dry cough
  - Renal Insuff.

• Due to their chemical structure
  - Cutaneous eruptions
  - Neutropenia, thrombocytopenia
  - Dysgeusia
  - Proteinuria
  - Digestive upset
ACEI
CONTRAINDICATIONS

- Renal artery stenosis
- Renal insufficiency
- Hyperkalemia
- Arterial hypotension
- Intolerance (due to side effects)
ANGIOTENSIN II INHIBITORS
MECHANISM OF ACTION

<table>
<thead>
<tr>
<th>Renin</th>
<th>Angiotensinogen</th>
<th>Angiotensin I</th>
<th>ACE</th>
<th>Angiotensin II</th>
<th>AT1</th>
<th>AT2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angiotensinogen</td>
<td>Angiotensin I</td>
<td>ACE</td>
<td>Angiotensin II</td>
<td>AT1 Receptor Blockers</td>
<td>AT2</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Vasoconstriction</td>
<td>Proliferative Action</td>
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<td></td>
<td></td>
<td></td>
<td>Vasodilatation</td>
<td>Antiproliferative Action</td>
</tr>
</tbody>
</table>
AT1 RECEPTOR BLOCKERS
DRUGS

- Losartan
- Valsartan
- Irbesartan
- Candesartan

Competitive and selective blocking of AT1 receptors
ALDOSTERONE INHIBITORS

Spironolactone

Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)

- Retention $\text{Na}^+$
- Retention $\text{H}_2\text{O}$
- Excretion $\text{K}^+$
- Excretion $\text{Mg}^{2+}$

Edema

Arrhythmias

Collagen deposition
- myocardium
- vessels

Fibrosis
## CLINICAL AND PHARMACOLOGIC PROPERTIES OF VASODILATORS

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drugs</th>
<th>Site of Action</th>
<th>Onset of Action</th>
<th>Advantages</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitors of Angiotensin converting enzyme (ACE)</td>
<td>Captopril 6.25 mg bid. up to 200 mg/d Enalapril 2.5-40 mg/d Lisinopril 5-40 mg/d Quinapril 10-80 mg/d Ramipril 2.5-20 mg/d Quinapril 10-30 mg bid; Fosinopril 5-30 mg qd;</td>
<td>Angiotensin converting enzyme (ACE) [inhibition of]</td>
<td>60-90 min 60 min 60 min 60-90 min 60-90 min</td>
<td>Proven symptomatic relief and improved survival</td>
<td>Impaired renal function; proteinuria; dysgeusia; glomerulonephritis; leukopenia; cough Contraindications: pregnancy, bilateral renal artery stenosis</td>
</tr>
<tr>
<td>Angiotensin e receptor antagonists</td>
<td>Losartan 25-50 mg once or twice daily Irbesartan 5-10 mg once or twice daily</td>
<td>2-4 h 60-90 min</td>
<td>Proven symptomatic relief and improved survival</td>
<td>Hypotension, acute renal failure in bilateral renal artery stenosis, hyperkalemia Contraindications: pregnancy, bilateral renal artery stenosis</td>
<td></td>
</tr>
</tbody>
</table>
ALDOSTERONE INHIBITORS

INDICATIONS

FOR DIURETIC EFFECT
• Pulmonary congestion (dyspnea)
• Systemic congestion (edema)

FOR ELECTROLYTE EFFECTS
• Hypo K⁺, Hypo Mg⁺
• Arrhythmias
• Better than K⁺ supplements

FOR NEUROHORMONAL EFFECTS
• ? Pending the RALES results
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Relative Potency</th>
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</thead>
<tbody>
<tr>
<td>Potassium-sparing diuretics</td>
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<tr>
<td>Spironolactone</td>
<td>Moderate to low</td>
<td>Aldosterone homolog, competitive inhibition for receptor site in distal tubule. Secondary: inhibition of aldosterone biosynthesis</td>
<td>2-3 days for maximum effect</td>
<td>Useful in combination with more proximal-acting diuretic to spare K</td>
<td>Hyperkalemia when K salts are given concomitantly or renal function is reduced markedly</td>
</tr>
<tr>
<td>Oral: 25-50 mg bid to qid</td>
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</tbody>
</table>
ALDOSTERONE INHIBITORS
CONTRAINDICATIONS

- Hyperkalemia
- Severe renal insufficiency
- Metabolic acidosis
ß-ADRENERGIC BLOCKERS
POSSIBLE BENEFICIAL EFFECTS

- Density of β₁ receptors
- Inhibit cardiotoxicity of catecholamines
- Neurohormonal activation
- HR
- Antihypertensive and antianginal
- Antiarrhythmic
- Antioxidant
- Antiproliferative
# BETA-ADRENERGIC RECEPTOR BLOCKERS

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Site of Action</th>
<th>Precautions and special considerations</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol 3.125 mg bid; titrate to target dose 25 mg bid.</td>
<td>Noncardioselective β- and α1-adrenergic receptor block, without ISA</td>
<td>Should not be used in patients with asthma, chronic obstructive pulmonary disease (COPD) with bronchospasm, congestive heart failure, heart failure, heart failure, may mask symptoms of hypoglycemia; hyperglycemia; hypertriglyceridemia, decreased high-density lipoprotein (HDL) cholesterol (except for drugs with ISA and labetalol)</td>
<td>Bronchospasm, peripheral arterial insufficiency, fatigue, insomnia, sexual dysfunction, exacerbation of congestive heart failure, may mask symptoms of hypoglycemia; hyperglycemia; hypertriglyceridemia, decreased high-density lipoprotein (HDL) cholesterol (except for drugs with ISA and labetalol)</td>
</tr>
<tr>
<td>Bisoprolol 1.25 mg bid; titrate to target dose 10 mg bid.</td>
<td>Noncardioselective, without ISA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol tartrate 6.25 mg bid; titrate to target dose 50 mg bid.</td>
<td>Cardioselective, without ISA</td>
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</tr>
<tr>
<td>Metoprolol succinate (extended release) 12.5- 25 mg bid; titrate to target dose 200 mg bid.</td>
<td>Cardioselective, without ISA</td>
<td>Should not be discontinued abruptly in patients with ischemic heart disease. ISA = intrinsic sympathomimetic activity.</td>
<td></td>
</tr>
</tbody>
</table>
ß-ADRENERGIC BLOCKERS
IDEAL CANDIDATE?

- Suspected adrenergic activation
- Arrhythmias
- Hypertension
- Angina
β-ADRENERGIC BLOCKERS
CONTRAINDICATIONS

- Hypotension: BP < 100 mmHg
- Bradycardia: HR < 50 bpm
- Clinical instability
- Chronic bronchitis, ASTHMA
- Severe chronic renal insufficiency
CALCIUM ANTAGONISTS
POTENTIAL EFFECTS

- Antiischemic
- Peripheral Vasodilatation
- ↓ Inotropy
CALCIUM ANTAGONISTS POSSIBLE UTILITY

- Diltiazem contraindicated
- Verapamil and Nifedipine not recommended
- Vasoselective (amlodipine, nisoldipine), may be useful in ischemia + CHF
- Amlodipine may be useful in nonischemic CHF
### DIGOXIN PHARMACOKINETIC PROPERTIES

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption (%)</td>
<td>60 - 75</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>25</td>
</tr>
<tr>
<td>Volume of distribution (l/Kg)</td>
<td>6 (3-9)</td>
</tr>
<tr>
<td>Half life</td>
<td>36 (26-46) h</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
</tr>
<tr>
<td>Onset (min)</td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>5 - 30</td>
</tr>
<tr>
<td>oral</td>
<td>30 - 90</td>
</tr>
<tr>
<td>Maximal effect (h)</td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>2 - 4</td>
</tr>
<tr>
<td>oral</td>
<td>3 - 6</td>
</tr>
<tr>
<td>Duration</td>
<td>2 - 6 days</td>
</tr>
<tr>
<td>Therapeutic level (ng/ml)</td>
<td>0.5 - 2</td>
</tr>
</tbody>
</table>
### DIGOXIN DIGITALIZATION STRATEGIES

<table>
<thead>
<tr>
<th>Loading dose (mg)</th>
<th>Maintenance Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v 0.5 + 0.25 / 4 h</td>
<td>oral 12-24 h 0.75 + 0.25 / 6 h</td>
</tr>
<tr>
<td>ILD: 0.75-1</td>
<td>1.25-1.5</td>
</tr>
</tbody>
</table>

**ILD = average INITIAL dose required for digoxin loading**
# DIGITALIZATION SCHEDULE

<table>
<thead>
<tr>
<th></th>
<th><strong>Digoxin</strong></th>
<th><strong>Digitoxin</strong></th>
<th><strong>Ouabain</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral. 24 h</strong></td>
<td>0 h: 0.5 mg</td>
<td>0 h: 0.6 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 h: 0.25 mg</td>
<td>8 h: 0.3 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 h: 0.25 mg</td>
<td>16 h: 0.2 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h: 0.25 mg</td>
<td>24 h: 0.1 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Thereafter, daily maintenance dose</strong>++</td>
<td><strong>Thereafter, daily maintenance dose</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Oral. 48 h</strong></td>
<td>0.25 mg q 8 h x 6</td>
<td>0.2 mg q 8 h x 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Thereafter, daily maintenance dose</strong>++</td>
<td><strong>Thereafter, daily maintenance dose</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Oral, gradual</strong></td>
<td>0.25 mg/day</td>
<td>0.1 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(digitalization achieved in 5-7 days)++</td>
<td>(digitalization achieved in 10-14 days)</td>
<td></td>
</tr>
<tr>
<td><strong>IV. 24 h</strong></td>
<td>0 h: 0.5 mg</td>
<td>0 h: 0.6 mg</td>
<td>0 h: 0.3 mg</td>
</tr>
<tr>
<td></td>
<td>6 h: 0.25 mg</td>
<td>8 h: 0.3 mg</td>
<td>4 h: 0.2 mg</td>
</tr>
<tr>
<td></td>
<td>12 h: 0.125 mg</td>
<td>16 h: 0.2 mg</td>
<td>8 h: 0.1 mg</td>
</tr>
<tr>
<td></td>
<td>18 h: 0.125 mg</td>
<td>24 h: 0.1 mg</td>
<td>12 h: 0.1 mg++</td>
</tr>
<tr>
<td></td>
<td><strong>Thereafter, daily maintenance dose</strong>++</td>
<td><strong>Thereafter, daily maintenance dose</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Daily maintenance dose, oral</strong></td>
<td>0.25-0.375 mg/day</td>
<td>0.1 mg 5 times/wk to 1.5 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

* Doses are designed to produce effective but prudent plasma and tissue concentrations (see text for details).

** Abnormal renal function prolongs plasma half-life, necessitating reduction in suggested dosage. *DigoxinDigitoxinOuabainPreferred route*Oral. IV
DIGOXIN
HEMODYNAMIC EFFECTS

- Cardiac output
- LV ejection fraction
- LVEDP
- Exercise tolerance
- Natriuresis
- Neurohormonal activation
OVERALL MORTALITY

Placebo
n=3403

DIGOXIN
n=3397

p = 0.8

%

N Engl J Med 1997;336:525
DIGOXIN
LONG TERM EFFECTS

- Survival similar to placebo
- Fewer hospital admissions
- More serious arrhythmias
- More myocardial infarctions
DIGOXIN
CLINICAL USES

• AF with rapid ventricular response
• CHF refractory to other drugs
• Other indications?
• Can be combined with other drugs
DIGOXIN
CONTRAINDICATIONS

• ABSOLUTE:
  - Digoxin toxicity

• RELATIVE
  - Advanced A-V block without pacemaker
  - Bradycardia or sick sinus without PM
  - PVC’s and TV
  - Marked hypokalemia
  - W-P-W with atrial fibrillation
DIGOXIN TOXICITY
CARDIAC MANIFESTATIONS

- ARRHYTHMIAS:
  - Ventricular (PVCs, TV, VF)
  - Supraventricular (PACs, SVT)

- BLOCKS:
  - S-A and A-V blocks

- CHF EXACERBATION
TREATMENT OF DIGITALIS INTOXICATION

- Discontinue the drug
- ECG monitoring
- If serum K is low, 80 mEq of potassium chloride IV should be given in 1 L 5% D/W at a rate of 6 mL/min (0.5 mEq/min). *Potassium must not be employed in the presence of atrioventricular block or hyperkalemia*
- Administration of specific antibody fragments to digoxin (digoxin immune fab, Digibind®)
- Ventricular arrhythmias are treated with a 50- to 100-mg rapid IV injection of lidocaine, repeated in 3 to 5 min until a therapeutic effect is obtained, a total of 300 mg is given, or CNS toxicity occurs. When the arrhythmia is controlled, a continuous infusion of 2 to 4 mg/min should be started
- Alternatively, phenytoin 100 mg q 3 to 5 min can be given slowly up to a total of 1000 mg
- Heart block is best treated with a temporary perivenous pacemaker
- Electrical conversion may be lifesaving in digitalis-induced ventricular fibrillation
- Isoproterenol is *contra indicated* in digitalis intoxication because of the increased tendency to ventricular arrhythmia
Phosphodiesterase Inhibitors

- primarily used for management of acute heart failure
- positive inotropic effects
- increase rate of myocardial relaxation
- decrease total peripheral resistance and afterload
Mechanism of Action

- inhibitor of type III cAMP phosphodiesterase
- increased [cAMP]
- increased PKA
- phosphorylation of Ca2+ channels in cardiac muscle
- increased cardiac contraction
- relaxes vascular smooth muscle
Therapeutic Use

- Amrinone (Inocor) and Milrinone (Primacor)
- administered IV
- milrinone is ~10 fold more potent
- $T_{1/2} = 2.5\ h$ for amrinone and 30-60 min for milrinone
- effective in patients taking Beta-blockers
- does not stop disease progression or prolong life in CHF patients
- prescribed to patients non-responsive to other therapies
Side Effects

- sudden death secondary to ventricular arrhythmia
- hypotension
- thrombocytopenia
- long term clinical trials associated with increased adverse effects and increased mortality
- now only prescribed for acute cardiac decompensation in patients non-responsive to diuretics or digoxin
ANTICOAGULANTS

- PREVIOUS EMBOLIC EPISODE
- ATRIAL FIBRILLATION
- Identified thrombus
- LV Aneurysm (3-6 mo post MI)
- Class III-IV in the presence of:
  - EF < 30
  - Aneurysm or very dilated LV
- Phlebitis
- Prolonged bed rest
ANTIARRHYTHMICS

- Sustained VT, with/without symptoms
  - β Blockers
  - Amiodarone

- Sudden death from VF
  - Consider implantable defibrillator
Risk factors for increased mortality in heart failure include all of the following, except:

1. Anaemia (Hgb 8.0 g/dl).
2. Sleep apnea.
3. Chronic renal insufficiency.
4. Elevated BNP level.
5. Sustained VT.
Indications for anticoagulation with warfarin in heart failure patients include:

1. AF with controlled ventricular response.
2. LV thrombus.
3. Protein C or protein S deficiency.
4. Previous cardioembolic stroke.
5. All of the above.
EMERGENCY THERAPEUTIC MEASURES IN PATIENTS WITH PULMONARY EDEMA

- Morphine is administered intravenously repetitively, as needed, in doses from 2 to 5 mg
- 100% oxygen should be administered, preferably under positive pressure
- The patient should be maintained in the sitting position, with the legs dangling along the side of the bed
- Intravenous loop diuretics, such as furosemide or ethacrynic acid (40 to 100 mg), or bumetanide (1 mg)
- Intravenous sodium nitroprusside at 20 to 30 ug/min in patients whose systolic arterial pressures exceed 100 mmHg
- Inotropic support should be provided by dopamine or dobutamine
- Patients with systolic heart failure who are not receiving digitalis should receive 1.0 mg digoxin intravenously
- Aminophylline (theophylline ethylenediamine), 240 to 480 mg intravenously
- Rotating tourniquets should be applied to the extremities
THANK YOU