Drug Therapy of Heart Failure

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Drug Therapy of Heart Failure

Definition of Heart Failure

Causes

Classifications
<table>
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<tr>
<th>Chronic heart failure</th>
<th>Acute heart failure</th>
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<tr>
<td>Diuretics</td>
<td>Diuretics</td>
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<tr>
<td>Aldosterone receptor antagonists</td>
<td>Vasodilators</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Beta agonists</td>
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<tr>
<td>Angiotensin receptor blockers</td>
<td>Bipyridines</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Natriuretic peptide</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
</tr>
</tbody>
</table>
Definition of Heart Failure

- Heart is unable to provide adequate perfusion of peripheral organs to meet their metabolic requirements
- Characterized by:
  1. Decreased CO
  2. Increased TPR
- Progression to congestive heart failure (CHF) is accompanied by peripheral and pulmonary edema.

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CAUSES OF CONGESTIVE HEART FAILURE

A. Mechanical Causes
   1. Pressure Overload
      a. Hypertension
      b. Aortic Valve Stenosis
      c. Pulmonary Hypertension
   2. Volume Overload
      a. Valvular Regurgitation
      b. Shunts
      c. Increased Blood Volume

B. Impaired Cardiac Filling
   1. Pericardial Disease (constriction or tamponade)
   2. Restrictive Heart Disease (endo- or myocardial)
   3. Ventricular Hypertrophy
   4. Ventricular Aneurysm

C. Myocardial Failure
   1. Primary
      a. Loss of functioning muscle (myocardial infarction)
      b. Cardiomyopathy
      c. Myocarditis
   2. Secondary
      a. Dysdynamic heart failure (response to chronic overload)
      b. Drug-induced
      c. Involvement in systemic disease (hypothyroidism)
CARDIAC OUTPUT

PRELOAD
End diastolic volume

CONTRACTILITY

AFTERLOAD
Ejection tension

HEART RATE
Mechanisms of H. F.

Reduction in the intrinsic myocardial contractility

1. Depletion of NE in heart muscle.
3. ATP and other high energy phosphate compounds.
4. $\beta$ receptor density (due to down regulation after chronic exposure to high circulating catecholaminas).
5. Abnormal Ca$^{++}$ binding:
   1. Less stored in SR
   2. More stored in Mitochondria
   3. Less released
   4. Lesser reuptake into SR.
   5. Slow reuptake into mitochondria leading to slow relaxation.
Compensatory Mechanisms in Heart Failure

- **Frank Starling Mechanism**

- **Increased Activity of SNS:**
  - a- Tachycardia and increased CO.
  - b- Increased myocardial contractility
  - c- Vasoconstriction leading to redistribution of blood to important viscera.
  - d- Renin release leading to increased plasma volume.

- **Myocardial Hypertrophy** leading to increased wall tension.
Compensatory SNS Mechanisms in HF

- In a failing heart, the loss of contractile function leads to a decline in CO and a decrease in BP.

- Baroreceptors sense the hemodynamic changes and initiate countermeasures to maintain support of the circulatory system. This is achieved by activation of the SNS.

- This helps maintain adequate cardiac output by:
  1. Increasing myocardial contractility and heart rate ($\beta_1$-adrenergic receptors)
  2. Increasing vasomotor tone ($\alpha_1$-adrenergic receptors) to maintain systemic blood pressure
Consequences of hyperadrenergic state

• Enhancement of RAAS.

• Irreversible myocyte damage, cell death, and fibrosis.

• Increased peripheral vasomotor tone increases LV afterload.

• This places an added stress upon the left ventricle and an increase in myocardial O$_2$ demand (ventricular remodeling).

• The frequency and severity of cardiac arrhythmias are enhanced in the failing heart.
Angiotensin II facilitates NE release.
Cardiac performance

1. ↓CO
   - ↑NE, AII
   - ↑ET
   - ↑Afterload

2. ↓CO
   - ↑NE, AII
   - ↑ET
   - ↑Afterload
   - ↓EF

B. ↓EF
   - ↑NE, AII
   - ↑ET
   - ↑Afterload

Time

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Signs and Symptoms of HF

- Tachycardia, sweating
- Decreased exercise tolerance & SOB
- Peripheral and pulmonary edema
- Cardiomegaly (Cardiomegaly and Hypertrophy)
Normal heart

Dilated (congestive) heart

Hypertrophic heart
Factors that May Precipitate Acute Decompensation in Patients with Chronic Heart Failure

- Dietary indiscretion
- Myocardial ischemia/infarction
- Arrhythmias (tachycardia or bradycardia)
- Discontinuation of HF therapy
- Infection
- Anemia

Initiation of medications that worsen HF:
- Calcium antagonists (verapamil, diltiazem)
- Beta blockers
- Nonsteroidal anti-inflammatory drugs
- Antiarrhythmic agents [all class I agents, sotalol (class III)]
- Anti-TNF antibodies

- Alcohol consumption
- Pregnancy
- Worsening hypertension
- Acute valvular insufficiency
Objectives of Long Term Management of Chronic Cardiac Failure

- Improve cardiac performance (hemodynamics) at rest and during exercise.
- Relieve symptoms.
- Improve myocardial efficiency.
- Improve quality of life (particularly symptom-free and effort tolerance).
- Improve patient survival.
Cardiac vs Noncardiac Therapeutic Targets

• Conventional belief that the primary defect in HF is in the heart.
• Reality is that HF involves many other processes and organs.
• Research has shown that therapy directed at noncardiac targets is more valuable than cardiac targets.

CHF should be viewed as a complex, interrelated sequence of events involving hemodynamic, and neurohormonal events.
Therapeutic Overview

The Problems

- Reduced force of contraction
- Decreased cardiac output
- Increased total peripheral resistance
- Inadequate organ perfusion
- Edema
- Decreased exercise tolerance
- Ischemic heart disease
- Sudden death
- Ventricular remodeling and decreased function
Nonpharmacologic Treatment:

- Salt Restriction
- Treat the Cause
- Moderate Exercise
- Heart Transplantation
Drug Groups Commonly Used in Heart Failure.

Diuretics
Aldosterone receptor antagonists
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Beta blockers
Cardiac glycosides
Vasodilators
Beta agonists
Bipyridines
Natriuretic peptide
**TABLE 13-3** Classification and treatment of chronic heart failure.

<table>
<thead>
<tr>
<th>ACC/AHA Stage(^1)</th>
<th>NYHA Class(^2)</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Prefailure</td>
<td></td>
<td>No symptoms but risk factors present(^3)</td>
<td>Treat obesity, hypertension, diabetes, hyperlipidemia, etc</td>
</tr>
<tr>
<td>B I</td>
<td></td>
<td>Symptoms with severe exercise</td>
<td>ACEI/ARB, β blocker, diuretic</td>
</tr>
<tr>
<td>C II/III</td>
<td></td>
<td>Symptoms with marked (class II) or mild (class III) exercise</td>
<td>Add aldosterone antagonist, digoxin; CRT, hydralazine/nitrate(^4)</td>
</tr>
<tr>
<td>D IV</td>
<td></td>
<td>Severe symptoms at rest</td>
<td>Transplant, LVAD</td>
</tr>
</tbody>
</table>

\(^1\)American College of Cardiology/American Heart Association classification.

\(^2\)New York Heart Association classification.

\(^3\)Risk factors include hypertension, myocardial infarct, diabetes.

\(^4\)For selected populations, eg, African American.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device.
Diuretics

Only for congestive symptoms:

Do not C.O....... may Co

Can be used alone initially ...........IV

May be used in combination with digitalis or others.

Cause K+ Loss, BP,........etc.

Can be reduced or withdrawn
Causes of Diuretic Resistance in Heart Failure

*Noncompliance with medical regimen; excess dietary Na\(^+\) intake

*Decreased renal perfusion and glomerular filtration rate

*Selective reduction in glomerular perfusion pressure following initiation (or dose increase) of ACE inhibitor therapy

*Nonsteroidal anti-inflammatory drugs

*Primary renal pathology

*Reduced or impaired diuretic absorption due to gut wall edema and reduced splanchnic blood flow
• The Relationship between the Renin-Angiotensin-Aldosterone System and Heart Failure
Effects of AT-II

Decreased cardiac function
  Decreased renal perfusion
  Vasoconstriction
  Sodium depletion (diuretics)

Plasma Angiotensinogen
  Renin
  Plasma Angiotensin I
  ACE
  Plasma Angiotensin II

Sympathetic activation
Aldosterone release
Myocyte hypertrophy
Myocardial fibrosis
Myocyte apoptosis
Endothelial dysfunction
Altered gene expression
  Vasoconstriction
  Sodium retention
  Myocardial and vascular fibrosis
  Endothelin synthesis
  Cytokine release

AT1 Receptor

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### Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>PATHOPHYSIOLOGICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Na(^+) and water retention</td>
<td>Edema, elevated cardiac filling pressures</td>
</tr>
<tr>
<td>K(^+) and Mg(^{2+}) loss</td>
<td>Arrhythmogenesis and risk of sudden cardiac death</td>
</tr>
<tr>
<td>Reduced myocardial norepinephrine uptake</td>
<td>Potentiation of norepinephrine effects: myocardial remodeling and arrhythmogenesis</td>
</tr>
<tr>
<td>Reduced baroreceptor sensitivity</td>
<td>Reduced parasympathetic activity and risk of sudden cardiac death</td>
</tr>
<tr>
<td>Myocardial fibrosis, fibroblast proliferation</td>
<td>Remodeling and ventricular dysfunction</td>
</tr>
<tr>
<td>Alterations in Na(^+) channel expression</td>
<td>Increased excitability and contractility of cardiac myocytes</td>
</tr>
</tbody>
</table>

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Angiotensin Converting Enzyme Inhibitors
"ACEI"

**Pharmacological Actions:**

- Blockade of ACE
- Reduce angiotensin II levels.
- Increase bradykinin.
- Inhibit SNS, leading to decreased NE release and upregulation of $\beta_1$ receptors.
- Balanced vasodilators causing reduction of both afterload and preload
- Reduce myocyte & fibroblast growth factors causing reduced cardiac remodeling.
- Decrease aldosterone causing decreased fluid retention, decreased K+ loss, and consequently reduced arrhythmias.
Sympathetic stimulation → J-g cells of kidney

Bradykinin → β₁ receptor antagonists → Bradykinin receptors → NO, PG₁₂

Angiotensinogen → Renin → Angiotensin I

ACE inhibitors → Angiotensin I → Angiotensin II

ACE (Kininase II) → Inactive Peptides

AT₁ receptor antagonists → AT₁ receptors → Aldosterone

AT₂ receptors → Vasoconstriction, Sympathetic stimulation, Cellular hypertrophy, Renovascular effects

ACE-independent pathways, (e.g., chymase)
Therapeutic Values of ACEI

• Nowadays drugs of choice.
• No tolerance.
• Retard progression of HF.
• Decrease arrhythmias.
• Proved to decrease mortality, but only when the highest tolerated doses are used.
Preparations of ACEI

- Captopril
- Enalapril
- Lisinopril
- Quinapril
- Fosinopril

*All are similarly effective*

*Might differ in toxicity*
Toxicity of ACEI

• Hypotension .......... First dose phenomenon
• Renal Impairment .......... Proteinurea
• K+ retention
• Cough
Angiotensin (AT1) Receptor Blockers

ARBs

- Losartan.
- Candesartan.
- Valsartan.
- Irbesartan(Approvel).
- Telmisartan(Micardis).

*Not superior to ACEIs, but may be useful for patients who cannot tolerate ACEIs because of cough.*
Beta Blockers

- Traditionally, they have negative inotropic effects.
- However, nowadays there is overwhelming evidence to support the use of β-blockers in CHF.
- Not useful in refractory HF.
- Mechanism involved remains unclear.
- Part of their beneficial effects may derive from slowing of heart rate, decreased cardiac work and consequently decreased myocardial O₂ consumption and enhanced efficiency.
- This would lessen the frequency of ischemic events and arrhythmias.

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Beta blockers

- Suggested mechanisms also include reduced remodeling of the heart muscle.
- $\beta$-Blockers may be beneficial through resensitization of the down-regulated receptor, thus improving myocardial contractility.
- Should be started with low doses and gradually increased.
- Recent studies with metoprolol, carvedilol, bicindolol, and bisiprolol showed a reduction in mortality in patients treated with these drugs.
- This does not mean that other older agents are not effective.
- Contraindicated in severe, refractory, unstable cases.
*p < 0.005 vs. placebo
**p < 0.0001 vs. placebo

Δ LVEF (EF units)

Placebo  6.25 mg bid  12.5 mg bid  25 mg bid

Carvedilol


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Positive Inotropic Agents

- Logically will improve cardiac function.
- These drugs increase force of contraction by increasing intracellular cardiac Ca^{++} concentration.

- **Cyclic AMP Independent Agents:**
  - Digitalis
  - Pimobendan

- **Cyclic AMP Dependant Agents:**
  - β-adrenergic Agonists
  - Phosphodiesterase Inhibitors
Role of Calcium and Sodium in Myocardial contraction

1. Calcium entry from outside the cell triggers the release of a much larger quantity of calcium from the sarcoplasmic reticulum.

2. Increased calcium concentration initiates the contractile process.

3. Calcium is removed by re-uptake into the sarcoplasmic reticulum and by extrusion from the cell by a calcium/sodium exchange.

4. Sodium balance is restored by sodium/potassium ATPase.
Portion of cardiac myocyte

Action potential (AP) depolarises plasma membrane

NA acts on β₁-adrenoceptors, resulting in phosphorylation of Ca²⁺ channel, which increases channel open times

Mechanisms involved in the increase in [Ca²⁺]:

(i) Depolarisation allows Ca²⁺ influx through voltage-gated Ca²⁺ channels

(ii) Ca²⁺-activated Ca²⁺ release from sarcoplasmic reticulum (SR) increases [Ca²⁺] still further

Mechanisms involved in the decrease in [Ca²⁺]:

(i) Ca²⁺ is extruded in exchange for Na⁺ by Ca²⁺ exchanger (CE)

(ii) Na⁺ is exchanged with K⁺ by the Na⁺/K⁺ ATPase (sodium pump; SP)

Calcium interacts with troponin C, causing contraction

Cardiac glycosides inhibit the sodium pump, leading to:
• ↑[Na⁺], which decreases transmembrane Na⁺ gradient and slows extrusion of Ca²⁺ by CE; this leads to:
  • ↑[Ca²⁺], which leads to:
  • ↑force of contraction

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Positive Inotropic Agents

Cyclic AMP Independent Agents:

- **Digitalis**: inhibits Na/KATPase.
- **Pimobendan**: sensitizes myocytes to Ca^{++}, also inhibits PDE.
Digitalis Glycosides

History:

- Egyptians ------- Squill
- Chinese ------- Toad skin
- William Withering ----- Foxglove 1785

- Digitalis purpura
- Digitalis lanata
- Strophanthus
lactone ring

steroid nucleus

sugar residues

Source: Brunton LL, Lazo JS, Parker KL; Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 11th Edition: http://www.accessmedicine.com

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Digitalis Glycosides

Mechanism:
• Inhibition of Na+/K+ ATPase
Digitalis inhibits Na⁺-K⁺ exchange by Na⁺/K⁺-ATPase.  

1. Concentration of intracellular Na⁺ increases.  
2. Increased Na⁺ leads to a greater Ca⁺⁺ influx, causing stronger systolic contraction.  
3. Ca⁺⁺ stores (Sarcoplasmic reticulum) free Ca⁺⁺.
Digitalis Glycosides

Actions:

- Positive Inotropic Effect
- Vascular Muscle Contraction
- Vagal Stimulation
- Effects on Electrical Properties of Cardiac Tissues.
Digitalis

Contractility
(Heart and Vascular Muscle)

Normal

Failure

C.O

PVR

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# Effects of Digoxin on the Electrical Properties of Cardiac Tissues

<table>
<thead>
<tr>
<th>Tissue or Variable</th>
<th>Effects at Therapeutic Doses (vagal Stimulation)</th>
<th>Effects at Toxic Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus node</td>
<td>↓ Rate</td>
<td>↓ Rate</td>
</tr>
<tr>
<td>Atrial muscle</td>
<td>↓ Refractory period</td>
<td>↓ Refractory period, arrhythmias</td>
</tr>
<tr>
<td>Atrioventricular node</td>
<td>↓ Conduction velocity, ↑ refractory period</td>
<td>↓ Refractory period, arrhythmias</td>
</tr>
<tr>
<td>Purkinje system, ventricular muscle</td>
<td>Slight ↓ refractory period</td>
<td>Extrasystoles, tachycardia, fibrillation</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>↑ PR interval, QT interval</td>
<td>Tachycardia, fibrillation, arrest at extremely high dosage</td>
</tr>
</tbody>
</table>

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Digitalis Toxicity

- **G.I.T.** (Anorexia, nausea, intestinal cramping, diarrhea)
- **Visual** (Xanthopsia, abnormalities in color vision)
- **Neurologic** (Malaise, confusion, depression, vertigo)
- **Cardiac** (bradycardia, Palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia).

**Interactions.**

- Pharmacological and toxic effects are greater in hypokalemic patients.
- $K^+$-depleting diuretics are a major contributing factor to digoxin toxicity.
ST
Digitalis Toxicity

Treatment of Toxicity:

Reduce or stop the drug.

Cardiac pacemaker for heart block.

Digitalis antibodies (Digoxin Immune Fab).

Arrhythmias may be converted to normal sinus rhythm by $K^+$ when the plasma $K^+$ conc. is low or within the normal range.

When the plasma $K^+$ conc is high, antiarrhythmic drugs, such as lidocaine, phenytoin, procainamide, or propranolol, can be used.
Digitalis Glycosides

Therapeutic Benefits:

- Nowadays, only useful in CCHF with supraventricular arrhythmia
  - Might decrease morbidity
  - ?? Withdrawal
  - ?? Mortality
### Basic Data of Three Cardiac Glycosides

<table>
<thead>
<tr>
<th></th>
<th>Digitoxin</th>
<th><strong>Digoxin</strong></th>
<th>Ouabain</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI absorption</td>
<td>100%</td>
<td>70 – 85%</td>
<td>0</td>
</tr>
<tr>
<td>Polarity</td>
<td>Least</td>
<td>Somewhat</td>
<td>Highest</td>
</tr>
<tr>
<td>Protein binding</td>
<td>97%</td>
<td>&lt; 30%</td>
<td>5 – 10%</td>
</tr>
<tr>
<td>Half-life</td>
<td>4 – 7 days</td>
<td>1.5-1.6 days</td>
<td>21 hr</td>
</tr>
<tr>
<td>Excretion route</td>
<td>Stool and kidneys; as hepatic metabolites*</td>
<td>Kidneys; largely unchanged</td>
<td>Kidneys; largely unchanged</td>
</tr>
<tr>
<td>Enterohepatic recycling</td>
<td>27%</td>
<td>6.8%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Optimum serum levels</td>
<td>20-35 ng/ml</td>
<td>0.5-2.5 ng/ml</td>
<td>Unknown</td>
</tr>
<tr>
<td>$V_d$</td>
<td>0.6 L/kg</td>
<td>5-10 L/kg</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* About 8% of digitoxin is metabolized and excreted as digoxin in the urine. Digitoxin seems to be largely recycled to complete its metabolic degradation.
Positive Inotropic Agents

Cyclic AMP Dependent Agents:

\[ \beta \text{-adrenergic Agonists:} \]

- NE
- Dopamine
- Dobutamine

**Phosphodiesterase Inhibitors:**

- Amrinone
- Inamrinone
- Milrinone
- Vesanirone
- Sildenafil
Positive Inotropic Agents

Cyclic AMP Dependent Agents:

β-adrenergic Agonists:

All increase myocardial oxygen consumption, so not helpful for chronic use, may be used (IV) for short term or in acute heart failure.

NE:

Was used in cardiogenic shock, but caused severe vasospasm and gangrene.

Ep:

Still used in cardiac arrest, by intracardiac injection.

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Positive Inotropic Agents

**Dopamine:**
Widely used in cardiogenic shock.

- **Low doses:** stimulate DA$_1$ receptors leading to renal vasodilation and improved renal function.
- **Intermediate doses:** work on β$_1$ receptors leading to positive inotropic actions.
- **High doses:** stimulate α receptors leading to vasoconstriction and elevation of blood pressure. Can cause arrhythmias and ischemic changes.

**Dobutamine:**
Selective β$_1$ agonist, used intermittently (IV) in CCHF. Produces mild vasodilation.

Has more inotropic than chronotropic actions.
Voltage sensitive slow Ca++ channel

1. Binding of β-adrenergic agonist (such as, dopamine, dobutamine) activates adenylyl cyclase, which produces cAMP

2. cAMP activates protein kinase, which in turn phosphorylates a calcium channel.

3. Phosphorylation of calcium channel increases calcium flow into cell causing increased force of contraction of heart muscle.

4. Phosphodiesterase inhibitors prevent hydrolysis of cAMP and thus prolong action of protein kinase.

Myofibrils

Increased force of contraction

Protein kinase (active)

Protein kinase (inactive)

cAMP

ATP

AMP

Phosphodiesterase inhibitors (for example, amrinone)

Figure 16.11

Sites of action of β-adrenergic agonists on heart muscle.
Positive Inotropic Agents

Phosphodiesterase Inhibitors:
PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation.

Toxic: arrhythmias, and thrombocytopenia.

Short acting, so reserved for parenteral therapy of acute heart failure.

- Inamrinone (PDE-3)
- Milrinone (PDE-3)
- Vesanirone (PDE-3)
- Sildenafil (PDE-5)
Vasodilators

- Affect preload and/or afterload without directly affecting contractility.
- Consequently can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO2.
- Can be used in acute heart failure and for short periods in CCHF.
- Hydralazine-Isosorbide dinitrate combination was found to decrease mortality, maybe by reducing remodeling of the heart.
- Can be combined with ACEI, diuretics and digitalis.
<table>
<thead>
<tr>
<th>Venous Dilators</th>
<th>Mixed Action</th>
<th>Arterial Dilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Nitroprusside</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Captopril</td>
<td>Minoxidil</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydralazine + Nitrate</td>
<td></td>
</tr>
</tbody>
</table>

- **LV**EDV: **↓** LVEDV, **↓** MVO2, **↓** CO
- **LV**EDV: **↓** LVEDV, **↓** MVO2, **↑** CO
- **LV**EDV: **↓** LVEDV, **↓** MVO2, **↑** CO

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## Vasodilator Drugs Used to Treat Heart Failure

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>EXAMPLES</th>
<th>MECHANISM OF VASODILATING ACTION</th>
<th>PRELOAD REDUCTION</th>
<th>AFTERLOAD REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic nitrates</td>
<td>Nitroglycerin, isosorbide dinitrate</td>
<td>NO-mediated vasodilation</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nitric oxide donors</td>
<td>Nitroprusside</td>
<td>NO-mediated vasodilation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Captopril, enalapril, lisinopril</td>
<td>Inhibition of Ang II generation, decreased bradykinin degradation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Losartan, candesartan</td>
<td>Blockade of AT&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>Milrinone, inamrinone</td>
<td>Inhibition of cyclic AMP degradation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Direct-acting K&lt;sup&gt;+&lt;/sup&gt;-channel agonist</td>
<td>Hydralazine</td>
<td>Unknown</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Unknown</td>
<td>Minoxidil</td>
<td>Hyperpolarization of vascular smooth muscle cells</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>1 Adrenergic antagonists</td>
<td>Doxazosin, prazosin</td>
<td>Selective 1 adrenergic receptor blockade</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nonselective α adrenergic antagonists</td>
<td>Phentolamine</td>
<td>Nonselective adrenergic receptor blockade</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Vasodilating β&lt;sub&gt;1&lt;/sub&gt; adrenergic antagonists</td>
<td>Carvedilol, labetalol</td>
<td>Selective 1 adrenergic receptor blockade</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt; channel blockers</td>
<td>Amlodipine, nifedipine, felodipine</td>
<td>Inhibition of L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Adrenergic</td>
<td>Isoproterenol</td>
<td>Stimulation of vascular smooth muscle cells</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
(BNP)-Niseritide

- Brain (B-type) natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.

- BNP binds to receptors in the vasculature, kidney, and other organs, producing potent vasodilation with rapid onset and offset of action by increasing levels of cGMP.

- Niseritide is a recombinant human BNP approved for treatment of acute decompensated CHF.
BNP-Niseritide

- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis.

- Effective in HF because of reduction in preload and afterload.

- Hypotension is the main side effect.
Stage A: High risk with no symptoms

Stage B: Structural heart disease, no symptoms

Stage C: Structural disease, previous or current symptoms

Stage D: Refractory symptoms requiring special intervention

Hospice

Inotropes

Aldosterone antagonist, nesinotide

Consider multidisciplinary team

Revascularization, mitral-valve surgery

Cardiac resynchronization if bundle-branch block present

Dietary Na⁺ restriction, diuretics, and digoxin

ACE inhibitors and β blockers in all patients

ACE inhibitors or AT₁ blockers in all patients; β blockers in selected patients

Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or AT₁ blockers in some patients

Risk-factor reduction, patient and family education

Source: Brunton LL, Lazo JS, Parker KL: Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 11th Edition; http://www.accessmedicine.com

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### Steps in the Prevention and Treatment of Chronic Heart Failure.

<table>
<thead>
<tr>
<th>ACC/AHA Stage</th>
<th>Step</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, B</td>
<td>1</td>
<td>Control hypertension, hyperlipidemia, glucose metabolism (diabetes), obesity</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>Reduce workload of the heart (limit activity, put on temporary bed rest)</td>
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<td></td>
<td>3</td>
<td>Restrict sodium intake, give diuretics</td>
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<td></td>
<td>4</td>
<td>Restrict water (rarely required)</td>
</tr>
<tr>
<td>C, D</td>
<td>5</td>
<td>Give angiotensin-converting enzyme inhibitor or angiotensin receptor blocker</td>
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<td></td>
<td>6</td>
<td>Give digitalis if systolic dysfunction with third heart sound or atrial fibrillation is present</td>
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<tr>
<td></td>
<td>7</td>
<td>Give β blockers to patients with stable class II–IV heart failure</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Give aldosterone antagonist</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Give vasodilators</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>Cardiac resynchronization if wide QRS interval is present in normal sinus rhythm</td>
</tr>
</tbody>
</table>
Errors in Management of HF

- Missed diagnosis.
- Improper dosage of diuretics.
- Failure to assess quality of life.
- Failure to consider long term therapeutic goals.
- Underprescribing of ACEI.
- Use of potentially harmful drugs.
- Failure to use hydralazine-isosorbide combination which has proved evidence of benefit.
مفهوم لو اعيدلكم الدرس ....

Munir Gharibeh, MD, PhD, MHPE