Heart failure
Failure?

- blood supply insufficient for body needs

CHF = **congestive** heart failure

- increased blood volume, interstitial fluid
Underlying causes/risk factors

- **Ischemic heart disease (CAD)**
- hypertension
- myocardial infarction (MI)
- valvular heart disease
- congenital heart disease
- dilated cardiomyopathy

70%
Drugs which might exacerbate HF

- NSAIDs (fluid retention, HTN)
- metformin (lactic acidosis)
- thiazolidinediones (fluid retention)
- PDE-5 inhibitors (vasodilation)
- anti-arrhythmic drugs (negative inotropic effect)
- tricyclic antidepressants (negative inotropic effect)
- CCBs (negative inotropic effect)
Heart failure

Underlying causes

chronic activation of sympathetic nerve system and of renin-angiotensin-aldosteron axis

additional neuro-humoral activation promoted

pumping function disrupted

heart tissue remodeling (hypertrophy)

vicious cycle
Compensatory mechanisms (1)

↓ blood pressure

additional sympathetic activation

β-adrenergic stimulation

α₁-adrenergic stimulation

↑ venous return

increased heart rate, stronger contraction
Compensatory mechanisms (2)

- ↓ cardiac output
- decreased renal blood flow
  - ↑ renin, angiotensin, aldosterone
  - ↑ total peripheral resistance
  - water and sodium retention
- increased blood volume
  - peripheral edema
  - pulmonary edema
Compensatory mechanisms (3)

- failing heart
  - myocardial infrastructure disrupted
    - myocardial hypertrophy
      - impaired contractility
        - systolic heart failure
      - impaired relaxation
        - diastolic heart failure

- ejection fraction <40%
Heart failure

Compensated HF
- Compensatory mechanisms preserve CO

Decompensated HF
- Compensatory mechanisms fail to preserve CO
Clinical presentation

- dyspnea on exertion
- orthopnea
- paroxysmal nocturnal dyspnea
- fatigue
- peripheral edema
- weight gain
- jugular vein distention
Functional classification

**NYHA (1996)**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>no limitation of physical activity</td>
</tr>
<tr>
<td>II</td>
<td>slight limitation of physical activity: symptomatic at ordinary physical activity, asymptomatic at rest</td>
</tr>
<tr>
<td>III</td>
<td>marked limitation of physical activity: symptomatic at minimal physical activity, asymptomatic at rest</td>
</tr>
<tr>
<td>IV</td>
<td>any physical activity symptomatic, might be symptomatic at rest</td>
</tr>
</tbody>
</table>
# Functional classification

**ACC/AHA (2001)**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>a high risk HF in the future but no structural heart disorder</td>
</tr>
<tr>
<td>B</td>
<td>a structural heart disorder but no symptoms at any stage</td>
</tr>
<tr>
<td>C</td>
<td>previous/current symptoms of HF in the context of an underlying structural heart problem, managed with Tx</td>
</tr>
<tr>
<td>D</td>
<td>advanced disease requiring hospital-based support, a heart transplant or palliative care</td>
</tr>
</tbody>
</table>

**other classifications:**

left/right-sided, systolic/diastolic, low CO/high TPR
Non-pharmacological management of HF

• reduced physical activity
• dietary measures: restricted sodium, alcohol intake
• restricted fluid intake
• weight control and monitoring
Pharmacological management of HF (1)

- Adjunct measures:
  - co-morbidities
  - contra-indicated drugs (CCBs, NSAIDs)
Pharmacological management of HF (2)

- Diuretics
- RAAS modifiers
- β-blockers
- Direct vasodilators
- Inotropic drugs

 symptom relief
disease-course modifiers
1. Diuretics

Heart failure

K⁺-sparing

thiazides

Loop diuretics

Why all these colors?
Segment name in violet
Diuretic name in pink
Reabsorption in red
Secretion in green
Percentage in blue
Hormone in orange
1. Diuretics

Mechanisms of action:

- **Loop diuretics** *(furosemide = Fusid®)*
  reduce Na\(^+\), H\(_2\)O reabsorption at ↑ limb of loop of Henle

- **Thiazides** *(hydrochlorothiazide = Disothiazide®)*
  reduce Na\(^+\), H\(_2\)O reabsorption at distal tube

- **K\(^+\)-sparing** *(spironolactone = Aldospirone®)*
  aldosterone antagonism at late distal tube and collecting tube
1. Diuretics

Reduction of volume overload

- ↓ plasma volume
  - ↓ afterload
    - ↓ peripheral edema
  - ↓ preload
    - ↓ pulmonary congestion
- ↓ HF symptoms
1. Diuretics

Which diuretic for HF?

furosemide:

- potent
- hypovolemia
- hypomagnesemia
- hypokalemia
- ototoxicity?

use lowest dose achieving an edema-free state
1. Diuretics

Which diuretic for HF?

thiazide:

- less potent
- ↑ lipids?
- hypokalemia
1. Diuretics – aldosterone antagonist

Which diuretic for HF?

$K^+$-sparing (spironolactone):

- even less potent as a diuretic
- correction of hypokalemia
- useful as an additive in non-responding patients
- hyperkalemia
1. Diuretics – aldosterone antagonist

Which diuretic for HF?

*spironolactone reduces mortality in advanced HF*

![Graph showing survival probability over time for spironolactone and placebo groups. The graph indicates that spironolactone significantly improves survival compared to placebo.](image)

*other diuretics not shown to affect survival*
1. Diuretics - combined

Which diuretic for HF?

**severe edema: sequential nephron blockade:**

2. Renin-angiotensin system (RAS) inhibitors

2.1 Angiotensin-converting enzyme inhibitors (ACEIs)

mortality reduction:

- asymptomatic HF
- moderate HF
- severe HF

![Graphs showing mortality reduction in different stages of HF with placebo and enalapril](image-url)
2. Renin-angiotensin system (RAS) inhibitors

2.1 Angiotensin-converting enzyme inhibitors (ACEIs)

CO increased:

- ↓ water and sodium retention
- ↓ BP
- ↓ vascular resistance
- ↓ ejection fraction

2.2 Angiotensin-receptor blockers (ARBs)

- alternative/addition to ACEIs
3. β-blockers

• past common practice: **contra-indicated in HF**

• **PARADOX:** negative inotropic effect in HF ??

• possible explanation:
3. β-blockers

• improved systolic function
• reversal of cardiac remodeling
3. β-blockers

Approved in HF:

• metoprolol (*Lopressor*®, *Neobloc*®)
  (selective β₁-adrenoreceptor antagonist)

• bisoprolol (*Concor*®, *Cardiloc*®)
  (selective β₁-adrenoreceptor antagonist)

• carvedilol (*Dimitone*®)
  (nonselective β-adrenoreceptor antagonist
   and α₁-adrenoreceptor antagonist)
3. β-blockers

Which β-blocker?

carvedilol: \(\alpha_1\)-blocker properties

vasodilation

benefit in hyperTN  ↓ BP  risk in hypoTN

prefer carvedilol  consider metoprolol
3. β-blockers

Risks:

- fluid retention (asymptomatic: weigh daily)
- fatigue
- bradycardia
- hypotension

NOT to be used in:

- severe HF
- acute HF

adjust medications dosing

diuretic

avoid
4. Direct vasodilators

Isosorbide-dinitrate (ISDN) + hydralazine combination

- Conversion to NO
  - ↓ vascular tone
    - ↑ venous filling
      - ↓ arterial resistance
    - ↓ arterial tone
      - ↓ cardiac load

- ↓ arterial resistance
4. Direct vasodilators

**Isosorbide-dinitrate (ISDN)** + **Hydralazine** combination

**ADEs:**
- **headache**
- dizziness
- weakness
- hypotension
- rash

**ADEs:**
- **hypotension**
- reflex tachycardia
- dizziness
- weakness
- headache
- diarrhea
4. Direct vasodilators

Isosorbide-dinitrate (ISDN) + hydralazine combination

for use in:

- African Americans
- alternative to non-respondent pts.
- alternative in ACEIs/ARBs non-tolerant pts.
Heart failure

4. Direct vasodilators

Isosorbide-dinitrate (ISDN) + hydralazine combination

ACE inhibitor more effective than hydralazine and nitrates in CHF

Nitrate plus hydralazine beneficial in blacks with HF

![Graph showing cumulative mortality percent over years for Enalapril and Hydral-IDN.](chart1)

![Graph showing overall survival percent over days since baseline visit for Placebo, Isosorbide dinitrate plus hydralazine.](chart2)
5. Inotropics

5.1. cardiac glycosides - digoxin

binding to myocyte Na⁺/K⁺ ATPase pump

↑ intracellular Na⁺

activation of Na⁺/Ca²⁺ channels

↑ intracellular Ca²⁺

↑ myocyte contraction force

continued…
5. Inotropics

5.1. cardiac glycosides - digoxin

↑ myocyte contraction force

↑ ejection faction

↑ cardiac output (CO)

↓ sympathetic activity

↓ peripheral resistance

↓ HF symptoms
5. Inotropics

5.1. cardiac glycosides - digoxin

PK:

- once-daily administration
- rapid onset (oral – 1-2 hr)
- renal excretion (adjust dose in renal dysfunction)
5. Inotropics

5.1. cardiac glycosides - digoxin

narrow therapeutic index:

- TDM - therapeutic drug monitoring
- timing of peak serum drug concentrations: >6hr post-oral dose
- timing of trough serum drug concentrations: just prior to next oral dose
- therapeutic range (peak): 0.8-2mg/L
5. Inotropics

5.1. cardiac glycosides - digoxin

ADEs/toxicity (20%):

• arrhythmias
• nausea, vomiting
• headache, dizziness
• vision impairment: color, halo, blur

• Tx of toxicity: D/C, gastric-lavage, charcoal, atropine, anti-arrhythmics, pacemaker, antibody
5. Inotropics

5.1. cardiac glycosides - digoxin
5. Inotropics

5.1. cardiac glycosides - digoxin

DDIs:

- hyperkalemic drugs (K\(^+\)-sparing diuretics): ↓ effect
- hypokalemic drugs (loop diuretics, insulin, steroids): ↑ effect
- IV calcium salts: ↑ effect
- verapamil, nifedipine, quinidine, amiodarone: ↑ levels
5. Inotropics

5.1. cardiac glycosides - digoxin

• no longer 1\textsuperscript{st}-line
• indicated for systolic HF, ejection fraction $< 40\%$
• for persistent HF despite ACEI/ARB + BB + diuretic
• proven ineffective in decreasing morbidity/mortality
5. Inotropics

5.2. β-adrenergic agonists: dobutamine

β₁-receptor activation

activation of protein-kinase

phosphorylation of slow Ca++ channels

↑ intracellular Ca++

↑ myocyte contraction force
5. Inotropics

5.2. β-adrenergic agonists: dobutamine (dopamine)

- 2nd most-used inotropic
- IV administration
- for acute HF
5. Inotropics

5.3. Phosphodiesterase inhibitors: amrinone, milrinone

- prolonged action of protein-kinase
- phosphorylation of slow Ca^{++} channels
- ↑ intracellular Ca^{++}
- ↑ myocyte contraction force
5. Inotropics

5.3. Phosphodiesterase inhibitors: amrinone, milrinone

• ↑ mortality in long term use
• effective for short-term
• IV administration
5. Inotropics

summary
### Selection of therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptom Improvement</th>
<th>Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ARBs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>β-blockers</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diuretics</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Digoxin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Hydralazine+nitrates</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Selection of therapy

- lifestyle and dietary modifications, pt. education
- initial Tx: loop diuretic (fluid control)
- 1st line: ACEIs
  alternative: ARBs
- 2nd line: addition of beta blocker (initial worsening symptoms)
- 3rd line: add ARB, hydralazine+nitrate, digoxin
- start low, go slow, achieve target dose
Heart failure

Diuretic + ACE inhibitor (or ARB) Adjust to achieve clinical stability

Beta-blocker

Persisting signs and symptoms?

Yes

Add aldosterone antagonist or ARB, in blacks, consider combination hydralazine-isosorbide dinitrate therapy as well

Persisting symptoms?

Yes

QRS ≥120 msec?

Yes

Consider CRT-P or CRT-D

No

Consider digoxin, LVAD, transplantation

No

Consider ICD

LV EF ≤35%

Yes

No further treatment required

No
DRUGS FOR EXAM

- furosemide
- isosorbide dinitrate
- digoxin
- dobutamine
- carvedilol