Dr. Sedjelmaci Nesrine
Lecturer in Toxicology

HEART FAILURE (INSUFFISANCE CARDIAQUE)

Definition

Inability of the heart to maintain adequate work. It is a failure of the cardiac pump with pulmonary edema and/or venous stasis:

- ↓ blood ejection ⇒ ↓ cardiac output
- ↓ filling capacity (left) ⇒ pulmonary congestion
- ↓ filling capacity (right) ⇒ venous stasis

Symptoms

1. Due to decreased cardiac output:

- ↓ cardiac output → ↓ blood pressure → ↓ CNS perfusion → syncope
- ↓ renal flow → ↑ aldosterone → ↑ sodium and water retention

2. Due to pulmonary congestion:

- Dyspnea on exertion, paroxysmal nocturnal dyspnea, cardiac asthma, and pulmonary edema
  → severe dyspnea = emergency
- Cough, infection, cyanosis

3. Due to venous stasis:

- Engorged veins, congested and painful liver, ↓ protein synthesis → edema
- Gastric congestion and dyspepsia, ↓ digestion → ↓ proteins → edema
- Renal congestion → proteinuria and edema

Edema locations: ascites, sacrum, ankles

4. Compensatory tachycardia: 100 beats/min

5. Cardiac dilation and hypertrophy

Etiologies of Heart Failure

- Ischemia
- Myocardial infarction
- Congenital heart disease
- Anemia
- Thyrotoxicosis
- Hypertension
- Vitamin B1 deficiency (thiamine) = Beriberi disease

- **Treatment of Heart Failure**

1. Diuretics
2. Diet: ↓ salt (not complete elimination)
3. Absolute rest
4. Digitalis drugs (cardiac glycosides): positive inotropic effect without increasing O_2 consumption, ↓ heart rate, ↓ conduction, ↓ excitability
5. Vasodilators
6. Inotropic agents: dopamine, dobutamine, aminophylline

DIGITALIS DRUGS

Definition

Steroidal glycosides used in the treatment of chronic heart failure, extracted from plants:

- Digitalis (leaves)
- Strophanthus (seeds)
- Squill

Precursors are inactive → become active by enzymatic or alkaline hydrolysis

Composition (2 parts):

- Sugar: physicochemical properties
- Aglycone (genin): steroid nucleus = active part

Main drugs:

- Digitoxin
- Digoxin
- Ouabain

- **Pharmacokinetics and Metabolism**

Parameter	Digitoxin	Digoxin	Ouabain
GI absorption	95%	Partial	-
Route	Oral	Oral, IV	IV
Liposolubility	++	+	-
Plasma protein binding	+++	+ (25%)	Low
Metabolism	+++ (not in hepatic insufficiency)	+/-	-
Renal elimination	Metabolites	Not given in renal failure	Unchanged, not given in renal failure
Onset	2 h	30 min	5 min
Half-life	6–7 days	1.5–2 days	6–8 h
Duration	18–21 days	6–7 days	1–1.5 days

Factors Influencing Pharmacokinetics

Absorption:

- Malabsorption
- Antidiarrheals (pectin, kaolin): adsorption
- Antacids (Al, Mg)
- Metoclopramide: ↑ motility
- Atropine: ↑ absorption
- Cholestyramine

Distribution:

- Quinidine, verapamil: displacement from plasma proteins

Metabolism:

- Enzyme inducers (phenobarbital, phenylbutazone…)

Elimination:

- Quinidine

- **Actions of Digitalis**

A) On the Heart

Cardiotonic action summarized by the "3R rule":
Slow (Ralentir), Strengthen (Renforcer), Regulate (Régulariser)

1. ↑ Contraction (positive inotropic effect)

- Strong and short systole (good ejection)
- Long diastole (good filling)
- ↑ myocardial elasticity → ↑ contraction → ↑ cardiac output → ↓ venous pressure

Mechanism:

At therapeutic dose:

- Partial inhibition of Na^+/K^+ ATPase
- ↑ intracellular Na^+ → ↑ Ca^{2+} (via Na^+/Ca^{2+} exchanger inhibition)
- Ca^{2+} binds troponin → contraction

At high dose:

- Complete ATPase inhibition
- ↑↑ Na^+, ↑↑ Ca^{2+}, ↓↓ K^+ → arrhythmia + hyperkalemia

2. ↓ Heart rate (negative chronotropic effect)

- In heart failure: compensatory tachycardia
- Digitalis normalizes heart rate via vagal effect → ↓ AV conduction

At high dose:

- Severe AV block → bradycardia

⚠ If HR < 60 + nausea/vomiting → toxicity warning

Toxicity progression:

- Bradycardia → tachycardia → fibrillation

Atropine can reverse cardiac toxicity

3. ↓ AV conduction

- Direct and vagal effect

4. ↑ Refractory period

- Heart unresponsive to stimulation
- Due to ↓ AV conduction

5. ↑ Automaticity (at high dose – harmful)

6. ECG Changes (toxic dose)

- ↑ PR interval
- ↓ QT interval
- Flattened or inverted T wave
- ↓ ST segment
- Tachycardia, fibrillation, extrasystoles

7. Blood Pressure

- Normalizes BP in patients
- Increases BP in hypertensive patients
- Stimulates vagal and vasomotor centers

8. Blood Volume

Digitalis are diuretics:

- ↑ renal flow → ↑ GFR → ↑ diuresis
- ↓ renin → ↓ aldosterone → ↑ diuresis
- Competition with aldosterone at distal tubule
- Action on renal Na^+/K^+ ATPase

B) On the Kidney

- Diuretic effect → reduces edema

C) Gastrointestinal

- Nausea, vomiting (toxicity signs)
- CTZ stimulation
- GI irritation

D) CNS

- Stimulates vagal center, CTZ, vasomotor center

E) Eye

- Blurred vision
- Yellow-green vision
- Scotoma
- Black moving spots
- Micropsia

- **Therapeutic and Toxic Levels (Digoxin)**
- Therapeutic: 0.5–2 ng/mL
- Toxic: > 2 ng/mL

DIGITALIS INTOXICATION

1. Digestive Disorders

- Nausea, vomiting (early signs in >80%)
- Gastric irritation, abdominal pain
- Diarrhea (5–7 stools/day)
- Severe cases: intestinal ischemia, hemorrhagic necrosis

2. Neuro-sensory Disorders

- Drowsiness or agitation
- Acute psychosis (delirium, hallucinations)
- Headache, myalgia, fatigue
- Rare seizures

Visual disorders:

- Colored halos
- Scotomas
- Blurred vision
- Micropsia

3. Functional Renal Failure

- Due to hemodynamic changes or dehydration

4. Respiratory Disorders

- Dyspnea
- Cyanosis
- Increased ventilation

5. Cardiac Disorders (most serious)

- Conduction disorders: bradycardia
- Rhythm disorders:
    - Ventricular extrasystoles (early sign)
    - Ventricular tachycardia and fibrillation

ECG:

- Flattened T wave
- Short QT interval

6. Electrolyte Disorders

- Hyperkalemia

Causes of Death

- Ventricular fibrillation
- Prolonged asystole
- Cardiogenic shock

- **Factors Increasing Toxicity**
- Hypokalemia
- ↓ Mg^{2+}
- ↑ Ca^{2+}
- Acidosis
- Renal failure (digoxin), hepatic failure (digitoxin)
- Thyrotoxicosis
- Hypothyroidism
- Age
- Myocardial infarction

Treatment of Intoxication

A. Decontamination

- Gastric lavage (within 2 hours)
- Activated charcoal or cholestyramine

B. Symptomatic Treatment

- Correct electrolytes

Cardiac treatment:

- Atropine (bradycardia)
- External pacing (severe cases)
- Lidocaine (ventricular arrhythmias)
- Diphenylhydantoin (second-line)

C. Specific Treatment

- Fab fragments (DIGIDOT®)

Mechanism:

- Bind digitalis → inactive complex
- Release from receptors
- Restore ATPase activity
- ↑ renal elimination
- ↓ half-life

D. Elimination Treatment

- Hemodialysis: no clinical benefit

TOXICOLOGICAL ANALYSIS

A. Extraction

- From plasma/serum using solvents (DCM, chloroform)

B. Qualitative Tests

- Antimony pentachloride test → color change
- Thin-layer chromatography (TLC):
    - Chromatin T reagent: brown ring (visible), blue-green (UV)
    - Perchloric reagent: gray/blue-green (digoxin), red (digitoxin)

C. Quantification

- Radioimmunoassay
- Immunoenzymatic (EMIT)
- Fluoroimmunoassay
- Chromatography (HPLC, GC)