INTRODUCTION TO HEART FAILURE
Contents

Heart failure definition

Etiology

Pathophysiology

Clinical manifestations
Heart failure definition

- **ESC 2012**: Heart failure (HF) is an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues\(^1\)

- **ACCF/AHA 2013**: HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood\(^2\)

ESC: European Society of Cardiology; AHA: American Heart Association; ACCF: American College of Cardiology Foundation
The pathophysiology of chronic HF

Damage to cardiac myocytes and extracellular matrix leads to changes in the size, shape and function of the heart (remodeling) and cardiac wall stress.

These changes lead to systemic neurohormonal imbalance.

This may lead to fibrosis, apoptosis, hypertension, hypertrophy, cellular and molecular alterations, myotoxicity.

Remodeling and progressive worsening of LV function

Hemodynamic alterations, salt and water retention

Morbidity and mortality arrhythmias, pump failure

HF symptoms dyspnea, edema, fatigue

LV=left ventricular
Terminology related to left ventricular ejection fraction

Heart failure definition

**Systole**
ventricles contracting

**Diastole**
ventricles relaxing

Amount of blood pumped out of the ventricle

Total amount of blood in the ventricle

= Ejection fraction (%)
HFrEF and HFpEF
Heart failure definition

Systolic dysfunction

HFrEF
EF≤35–40%

Diastolic dysfunction

HFpEF
EF>40–50%

Echocardiography is a useful method for evaluating left ventricular ejection fraction

HFrEF: heart failure with reduced ejection fraction
HFpEF: heart failure with preserved ejection fraction
Heart failure definition

An abnormality of cardiac structure or function

From myocardial infarction (MI) to HF: Ventricular Remodeling after MI

Contents

- Heart failure definition
- Etiology
- Pathophysiology
- Clinical manifestations
Most common causes of Heart Failure

Etiology

- Coronary heart disease
- Hypertension
- Valvular disease
- Cardiomyopathy
  - Idiopathic cardiomyopathy
  - Alcoholic cardiomyopathy
  - Toxin-related cardiomyopathy e.g. adriamycin
  - Post-partum cardiomyopathy
  - Hypertrophic obstructive cardiomyopathy
  - Tachyarrhythmia-induced cardiomyopathy
- Infiltrative disorders (e.g. amyloidosis)
- Congenital heart disease
- Pericardial disease
- Hyperkinetic states
  - Anemia
  - Arterio-venous fistula
  - Beriberi
- Others: Including hypertension, diabetes, exposure to cardiotoxic agents, peripartum cardiomyopathy, etc.

*Others: Including hypertension, diabetes, exposure to cardiotoxic agents, peripartum cardiomyopathy, etc.
<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure definition</td>
</tr>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
</tr>
<tr>
<td>Clinical manifestations</td>
</tr>
</tbody>
</table>
Different co-morbidities and pathophysiological processes can lead to different types of heart failure

A range of risk factors and co-morbidities contribute to the development of HF

<table>
<thead>
<tr>
<th>Age</th>
<th>Smoking</th>
<th>Obesity</th>
<th>Hypertension</th>
<th>Coronary artery disease</th>
<th>Diabetes</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Systolic dysfunction</td>
<td>HFpEF</td>
<td>HFrEF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LV hypertrophy

Normal LV structure and function

LV remodeling

Subclinical LV dysfunction

Clinical HF

‡ Patients with an LV ejection fraction of 35–50% represent a ‘gray area’ and may have primarily mild systolic dysfunction

HF=heart failure; LV=left ventricular; LVEF=left ventricular ejection fraction; MI=myocardial infarction

Figure reproduced with permission from Krum, Gilbert. Lancet 2003;362:147–58 Copyright © 2003 Elsevier
Patterns of ventricular remodeling are different for HFrEF and HFpEF

**HFrEF** – a condition of volume overload
- characterized by eccentric hypertrophy
- results in thinning of the LV walls, decreased systolic function and enlarged LV volume

**HFpEF** – a condition of pressure overload
- characterized by concentric hypertrophic growth
- results in normal sized LV cavity with thickened walls and preserved systolic function

- **HFrEF**
  - Volume overload
  - Increased diastolic pressure
  - Increased diastolic wall stress
  - Series addition of new sarcomeres
  - Chamber enlargement
  - Eccentric hypertrophy

- **HFpEF**
  - Pressure overload
  - Increased systolic pressure
  - Increased systolic wall stress
  - Parallel addition of new myofibrils
  - Wall thickening
  - Concentric hypertrophy

LV=left ventricular; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction
Adapted from Colucci (Ed.). Atlas of Heart Failure, 5th ed. Springer 2008;
Cardiac dysfunction triggers the activation of three compensatory neurohormonal systems

Cardiac structure/function abnormality

↓

Activation of compensatory mechanisms to maintain cardiac output and organ perfusion

- **SNS**
  - Activated in response to reduced cardiac output
  - Short-term effects are beneficial in early HF
  - Long-term activation exerts unfavourable effects

- **RAAS**
  - Release of NPs in response to cardiac stress
  - Opposes the actions of the RAAS and SNS

- **NP system**

NP=natriuretic peptide; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system
The SNS and RAAS are overactivated in heart failure and are responsible for many of the pathophysiological responses that contribute to disease progression.

**SNS**
- Epinephrine
- Norepinephrine
- $\alpha_1, \beta_1, \beta_2$ receptors

**Vasoconstriction**
- RAAS activity $\uparrow$
- Vasopressin $\uparrow$
- Heart rate $\uparrow$
- Contractility $\uparrow$

**RAAS**
- Ang II $\rightarrow$ AT$_1$R

**Vasoconstriction**
- Blood pressure $\uparrow$
- Sympathetic tone $\uparrow$
- Aldosterone $\uparrow$
- Hypertrophy $\uparrow$
- Fibrosis $\uparrow$
- Sodium and water retention $\uparrow$

AN=angiotensin; AT1R=angiotensin type 1 receptor; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

Secretion of natriuretic peptides results in a number of responses that act to reduce the symptoms and progression of heart failure.

NP system

NPRs ↔ NPs
Vasodilation
↓ Blood pressure
↓ Sympathetic tone
↑ Natriuresis/diuresis
↓ Vasopressin
↓ Aldosterone
↓ Fibrosis
↓ Hypertrophy

HF SYMPTOMS & PROGRESSION

Inactive fragments

NP=natriuretic peptide; NPRs=natriuretic peptide receptors
As heart failure advances, the RAAS and SNS become the predominantly activated neurohormonal systems.

**NP system**
- NPRs ↔ NPs
- Vasodilation: ↓ Blood pressure, ↓ Sympathetic tone, ↑ Natriuresis/diuresis, ↓ Vasopressin
- ↓ Aldosterone
- ↓ Fibrosis
- ↓ Hypertrophy

**RAAS**
- Ang II ➔ AT₁R
- Vasoconstriction: ↑ Blood pressure, ↑ Sympathetic tone, ↑ Aldosterone, ↑ Hypertrophy, ↑ Fibrosis, ↑ Sodium and water retention

**SNS**
- Epinephrine Norepinephrine ➔ α₁, β₁, β₂ receptors
- Vasoconstriction: RAAS activity ↑, Vasopressin ↑, Heart rate ↑, Contractility ↑

ANG=angiotensin; AT1R=angiotensin type 1 receptor; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system.

Natriuretic peptides have potential for protection of the heart, vessels and kidneys

NPs are released in response to cardiac wall stress and act in the brain, adrenal gland, kidney, vasculature and heart.

- Enhanced endothelial function
- Endothelin inhibition
- Vasodilation
- Antiproliferative effect: reverse vascular remodeling (arterial stiffness)
- Inhibition of RAAS
- Lusitropic
- Attenuation of cardiac remodeling (LVH) and fibrosis
- Renin inhibition
- Improved renal hemodynamics
- Increased natriuresis and diuresis
- Attenuation of renal fibrosis

ANP=atrial natriuretic peptide; BNP=brain natriuretic peptide; LVH=left ventricular hypertrophy; NPs=natriuretic peptides; RAAS=renin-angiotensin-aldosterone system

Natriuretic peptides inhibit the activity of the RAAS and counterbalance the sympathetic nervous system

ANP and BNP inhibit the RAAS via actions in the kidneys and the adrenal glands$^1$

- ANP/BNP
  - Inhibition of renin secretion
  - Inhibition of aldosterone secretion
  - Decrease in BP

ANP interacts with baroreflex control of the circulation to inhibit the activity of the SNS$^2$

- ANP
  - Modulation of arterial and cardiopulmonary baroreceptors
  - Decrease in SNS outflow
  - Decrease in BP

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; BP=blood pressure; NPs=natriuretic peptides; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

Summary

• Hypertension and myocardial infarction are major contributors to the development of heart failure

• The RAAS and SNS are activated in response to reduced cardiac output and are responsible for many of the pathophysiological responses that contribute to disease progression in HF

• Secretion of NPs results in a number of physiological responses that act to reduce the symptoms and progression of HF via inhibition of the RAAS and counterbalance SNS activation

• As HF advances, excessive activation of the SNS and the RAAS occurs leading to cardiac stress and overcomes any benefits of NPs, leading to a neurohormonal imbalance

NPs=natriuretic peptides; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system
Symptoms and Signs
Clinical manifestations

- **Main symptoms**
  - Breathlessness
  - Orthopnea
  - Paroxysmal Nocturnal Dypsnea
  - Reduced exercise tolerance
  - Fatigue
  - Ankle swelling

- **Main signs**
  - Elevated jugular venous pressure
  - Hepato-jugular reflux
  - Third heart sound
  - Laterally displaced apical impulse
  - Cardiac murmur

McMurray et al. Eur Heart J 2012;33:1787–847
Frequency of signs and symptoms
Clinical manifestations

Signs and symptoms in 4,537 residents of Worcester, Massachusetts, USA, hospitalized for acute HF between 1995 and 2000

- Dyspnea
- Edema
- Cough
- Orthopnea
- Anginal/chest pain
- Weakness
- Nocturnal paroxysms
- Nausea/vomiting
- Fatigue
- Ascites
- Mental obtundation
- Weight gain
- Palpitations
- Abdominal pain

Patients (%)

## Symptomatic severity of heart failure

### Clinical manifestations

<table>
<thead>
<tr>
<th>New York Heart Association functional classification based on severity of symptoms and physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
</tr>
<tr>
<td><strong>Class II</strong></td>
</tr>
<tr>
<td><strong>Class III</strong></td>
</tr>
<tr>
<td><strong>Class IV</strong></td>
</tr>
</tbody>
</table>

- Clear relationship between severity of symptoms and survival
- Poor relationship between severity of symptoms and ventricular function
- Patients with mild symptoms may still have a relatively high absolute risk of hospitalization and death

McMurray et al. Eur Heart J 2012;33:1787–847
NYHA class is related to prognosis in chronic HF

Clinical manifestations

Among 411 outpatients with NYHA class II, III or IV HF, total mortality was 7.1%, 15.0% and 28.0%, respectively during a mean follow-up period of 1.4 years.
A progressive condition with high mortality
Clinical manifestations

- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality
- With each acute event, myocardial injury may contribute to progressive LV dysfunction

LV: left ventricular
Summary

• Heart Failure is an abnormality of cardiac structure or function leading to failure of the heart to deliver sufficient oxygen to metabolizing tissues

• The most common cause of HF is coronary artery disease

• The most frequently reported signs and symptoms of HF are dyspnea, edema and cough

• HF has a complex pathophysiology involving activation of two key neurohormonal systems:
  • Renin–angiotensin–aldosterone system
  • Sympathetic nervous system

• Natriuretic peptides counteract the detrimental effects of RAAS and SNS activation

RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system