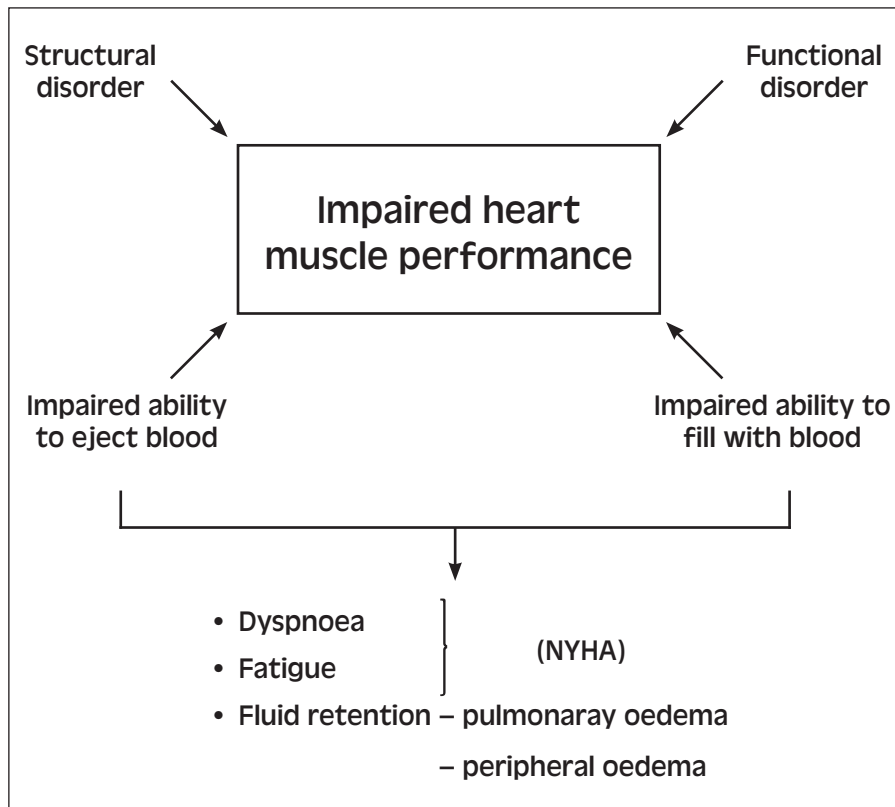# 2 Heart failure – an overview

Heart failure is a clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with blood or eject blood (Fig. 1).

Therefore: heart failure as a clinical syndrome can result from disorders of the pericardium, myocardium, endocardium and large blood vessels. However, the majority of patients with the clinical syndrome of heart failure have impairment of left ventricular myocardial function.

Figure 1. Schematic representation of heart failure.

Epidemiology

Between one and two per cent of the adult population have heart failure but the prevalence increases with age so that six to ten per cent of people over the age of 65 years have the disorder. It is estimated that a person living to the age of 40 years has a one-in-five risk of developing heart failure and once the disorder is apparent, a one-in-three chance of dying within the first year of diagnosis.

Epidemiological information suggests that roughly half of patients with symptomatic heart failure in the community have reduced systolic function and the other half have preserved systolic function. About half of the cases of left ventricular systolic dysfunction are asymptomatic. Community-based surveys show that 30 to 40% of patients die within a year of diagnosis and 60 to 70% die within five years.

Cardinal manifestations of heart failure

Dyspnoea, fatigue, limited effort tolerance and fluid retention (pulmonary congestion, peripheral oedema) are the cardinal manifestations of heart failure, but they may not necessarily dominate the clinical picture at the same time. It is important to remember that there is no single diagnostic test for heart failure and it remains largely a clinical diagnosis based on symptoms and signs (history and physical examination).
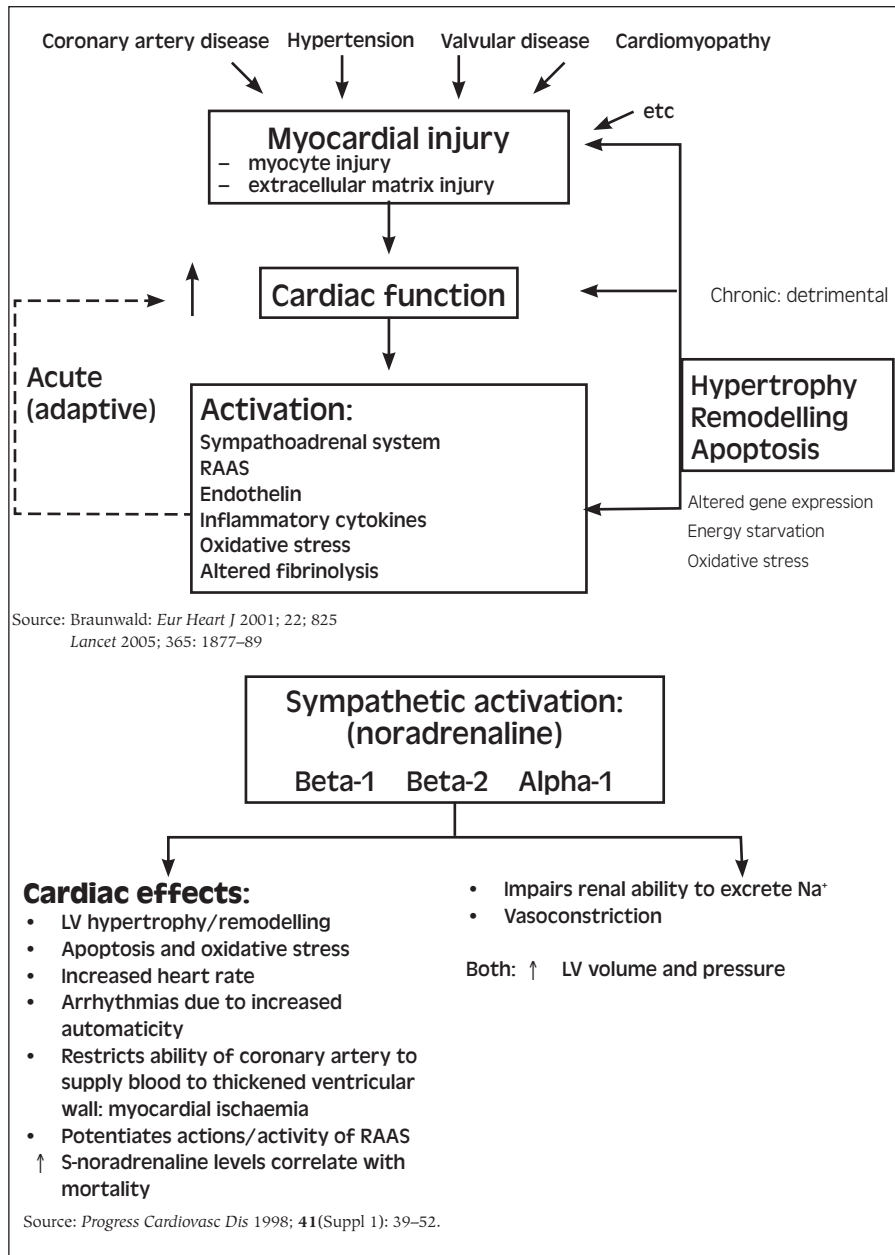
The New York Heart Association (NYHA) scale of I to IV is used to quantify the functional impairment of patients with heart failure, but this system does not indicate the nature or extent of the underlying abnormality of the myocardium.

Progressive nature of heart failure

Left ventricular dysfunction begins with some injury to the myocardium. The myocardium then changes size (dilates) becomes hypertrophied and more spherical – this is the process of ventricular remodelling. Cardiac remodelling generally precedes the development of heart failure symptoms.

The activation of the endogenous neurohormonal system plays an important role in cardiac remodelling. The activated neurohormonal system includes an activated sympathetic system, elevated levels of norepinephrine, angiotensin II, aldosterone, endothelin, vasopressin and various cytokines. These neurohormonal factors increase the haemodynamic stress on the ventricles by causing sodium retention and peripheral vasoconstriction, but they also exert a direct toxic effect on the myocardium, stimulating myocardial fibrosis and altering the phenotype of the myocardial cells (Fig. 2).
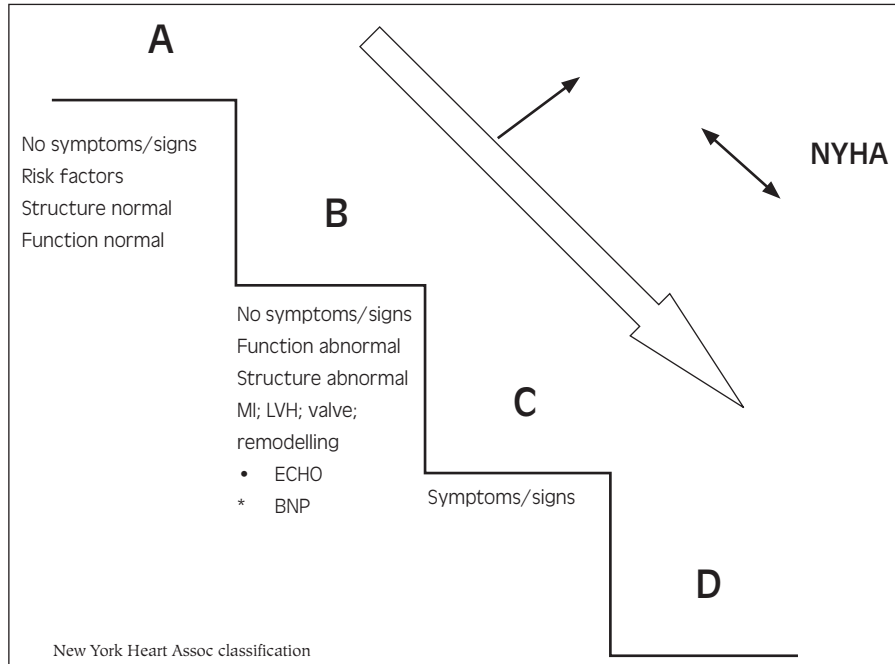
Figure 2.   Pathogenesis of heart failure.

Coronary artery disease   Hypertension   Valvular disease   Cardiomyopathy

Myocardial injury
- – myocyte injury
- – extracellular matrix injury

etc

Cardiac function

Chronic: detrimental

Acute (adaptive)

Activation:
Sympathoadrenal system
RAAS
Endothelin
Inflammatory cytokines
Oxidative stress
Altered fibrinolysis

Hypertrophy Remodelling Apoptosis

Altered gene expression
Energy starvation
Oxidative stress

Source: Braunwald: *Eur Heart J* 2001; 22; 825
          Lancet 2005; 365: 1877–89

Sympathetic activation: (noradrenaline)

Beta-1   Beta-2   Alpha-1

Cardiac effects:
- • LV hypertrophy/remodelling
- • Apoptosis and oxidative stress
- • Increased heart rate
- • Arrhythmias due to increased automaticity
- • Restricts ability of coronary artery to supply blood to thickened ventricular wall: myocardial ischaemia
- • Potentiates actions/activity of RAAS
- ↑ S-noradrenaline levels correlate with mortality

- • Impairs renal ability to excrete Na^+
- • Vasoconstriction

Both: ↑   LV volume and pressure

Source: *Progress Cardiovasc Dis* 1998; **41**(Suppl 1): 39–52.

Heart failure – an overview   5

Stages of heart failure

The development of heart failure can be described in four stages (Fig. 3). This system recognises that heart failure has risk factors, certain structural changes, an asymptomatic and then a symptomatic stage, and that specific treatments at each stage can reduce morbidity and mortality.

Figure 3. Stages of heart failure: natural history.

Stage A

Patients in this stage have no structural abnormalities of the heart and no symptoms or signs of heart failure but they have risk factors that put them at risk to develop heart failure. These risk factors are: hypertension, atherosclerotic heart disease, diabetes, obesity, the metabolic syndrome, using cardiotoxins (alcohol, chemotherapy drugs, etc.), and having a family history of cardiomyopathy. This stage is clearly not heart failure, but is intended to help identify those patients who are at risk of developing heart failure.

The treatment of this group of patients includes treating the risk factors and considering the use of ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs) where appropriate (e.g. in proven coronary atherosclerosis).

Stage B

Patients in this stage also do not have any signs or symptoms of heart failure but there is structural and/or functional heart disease present, e.g. left ventricular hypertrophy, previous myocardial infarction, asymptomatic valvular disease, left ventricular remodelling on X-ray (cardiomegaly) or echocardiography, low ejection fraction or elevated NT-proBNP. These patients clearly are not in heart failure, but are at great risk of developing heart failure and should be treated with ACEI or ARBs and/or appropriate beta-blockers. They are at high risk to progress further into clinical heart failure or die.

Stage C

These patients all have structural heart disease and prior or current signs and symptoms of heart failure. They should be managed according to current evidence-based guidelines. At this stage, patients have a high mortality and a high tendency to progress to the next stage.

Stage D

These patients have refractory heart failure and require specialised interventions, e.g. heart transplantation, mechanical support or experimental drugs.
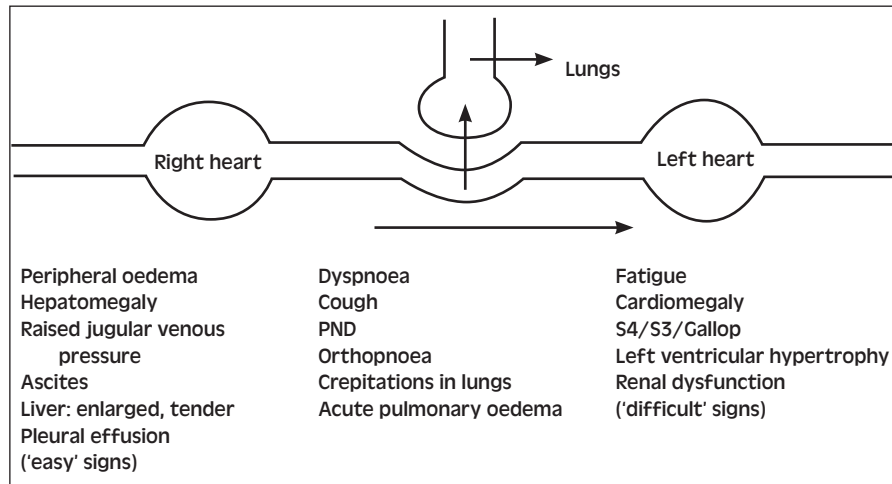
Prognosis of patients with heart failure

Prognosis is poor, with five-year mortality ranging from 26 to 75%. Sudden death, mainly caused by ventricular arrhythmias, is responsible for up to half of the deaths. The annual mortality of people with preserved ejection function is lower than those with reduced ejection fractions. Patients with asymptomatic left ventricular dysfunction are at increased risk of a cardiovascular event (e.g. myocardial infarction).

Clinical aspects of heart failure (Fig. 4)

The symptoms of heart failure are mainly those of dyspnoea, reduced exercise tolerance and fluid retention (peripheral oedema).

The signs of right heart failure are quite easy to diagnose: peripheral oedema, ascitis, tender enlarged liver, which may be pulsating (due to tricuspid insufficiency), elevated jugular venous pressure (JVP), etc. The signs of left heart failure, however, may be much more subtle to detect. Finding a summation gallop or a displaced apex beat or a third heart sound is diagnostic but not always present and more difficult to detect.

Figure 4. Clinical aspects of heart failure.

Peripheral oedema	Dyspnoea	Fatigue
Hepatomegaly	Cough	Cardiomegaly
Raised jugular venous pressure	PND	S4/S3/Gallop
	Orthopnoea	Left ventricular hypertrophy
Ascites	Crepitations in lungs	Renal dysfunction
Liver: enlarged, tender	Acute pulmonary oedema	('difficult' signs)
Pleural effusion		
('easy' signs)		

Measurement of the blood levels of natriuretic peptides (e.g. NT-proBNP) can help in the diagnosis of heart failure, especially in the acute setting.

Diagnosis of heart failure should ideally be confirmed by:
• echocardiography: 'gold standard'
• measuring left ventricular ejection fraction (LVEF):
  reduced LVEF (systolic dysfunction)
  normal LVEF (diastolic dysfunction)
• radioactive ventriculography (MUGA)
• ventriculogram: only with heart catheterisation.

Aetiology of heart failure

Coronary artery disease is the most common cause of heart failure, but hypertension is also prevalent. Other causes include cardiomyopathy and valvular heart disease, as well as other rarer conditions.

Pathophysiology

The most common insult is an injury to the myocardium, which causes a reduction in cardiac output. The body responds by stimulating the endogenous neurohormonal system to compensate and keep the cardiac output normal. In the short term, this works well but in the long term, these compensatory mechanisms increase the load on the already injured heart (pe-

ripheral vasoconstriction) and it becomes directly toxic to the myocardium – a process that is also aided by the increased levels of cytokines.

'Generic' complications of heart failure

- Dysrhythmias
  - atrial fibrillation: increases severity of failure
                      causes embolism
  - ventricular fibrillation: causes sudden death
- Mural thrombi
  - embolism
- Low perfusion of organs
  - renal dysfunction
  - tiredness
  - liver congestion
  - cold extremities.
- Heart murmurs = mitral insufficiency/tricuspid insufficiency
  - dilatation of heart
  - ventricular dyssyncrony (QRS prolonged > 120 ms).

Management of heart failure

Reduction of symptoms of heart failure

- The use of diuretics – initially loop diuretics (e.g. furosemide), and a thiazide diuretic on its own or in severe cases combined with loop diuretics, remains the mainstay of reducing the symptoms and signs of fluid retention, but this does not contribute to altering the natural history of the disease.
- Trinitroglycerine (e.g. Isordil)
- Digoxin: reduces symptoms, reduces hospitalisations, does not reduce deaths.
  problem: high incidence of toxicity.
  (Digoxin should only be given to patients who continue to have symptoms while receiving optimal medical treatment, including ACE inhibitors and beta-blockers.)
  Consider graded exercise programme.

Reduction of mortality

This has been one of the major advances in the management of heart failure and should be one of the aims of treatment.

- *ACE inhibitors*: all patients should be put on ACE inhibitors, starting with a low dose and increasing the dose over the weeks to reach maxi-

mum doses. ACE inhibitors were found to significantly reduce ischaemic events, mortality and hospitalisations for acute exacerbations of heart failure in multiple, randomised, controlled trials. ACE inhibitors can reduce the total mortality in heart failure by 23% (95% CI: 12–34%, $p <$ 0.001); it also reduces hospitalisations for heart failure by 33%. Despite their proven efficacy, ACE inhibitors are often under-prescribed or used in too-low doses.

- *Beta-adrenergic receptor blockers* reduce all-cause mortality by at least 30% when added to ACE inhibitors. In addition, they also reduce symptoms of heart failure and the rate of hospital admissions for heart failure. Beta-blockers probably work by protecting the heart from the harmful effects of norepinephrine and epinephrine. The addition of a beta-blocker to an ACE inhibitor, initiated at a low dose and slowly titrated upwards, should be considered as the cornerstone of heart failure treatment.
- *Angiotensin receptor blockers* are broadly similar in terms of outcome to ACE inhibitors. In certain circumstances, ACE inhibitors and angiotensin receptor blockers can be combined but the patient then needs careful monitoring for side effects.
- *Aldosterone antagonists* have been studied in selective, severe heart failure and shown to be of value, but with side effects of hyperkalaemia, renal intolerance and gynaecomastia in men.
- *The combination of hydralazine and isosorbide dinitrate* was shown to reduce mortality in African-Americans by 34%.
- *Devices that reduce mortality*: An implantable cardioverter defibrillator may reduce mortality by 23% in those patients already on optimal medical therapy. About 25% of patients with heart failure develop an abnormally prolonged QRS duration with subsequent dyssynchronous contraction of the ventricles, resulting in an increased severity of heart failure. The use of atriobiventricular or multisite pacing resynchronises cardiac contraction and reduces mortality and hospitalisations for heart failure.

Drugs with proven ability to reduce mortality

Anti-neurohormonal drugs:
- ACEI: reduce mortality ± 30%
- β-blockers: reduce mortality ± 34%
- α-/β-blockers: reduce mortality ± 35%
- Spirinolactone: reduces mortality (eplerenone)
- ARBs: valsartan; CHARM programme (candesartan) reduced mortality by 15% when added to ACEI, β-blockers
- Hydralazine + nitrate [black (Americans)] reduced mortality by 34%.

Captopril: (ACEI) starting dose 6.25–12.5 mg three times daily: target dose 50 mg three times daily

Enalapril: (ACEI) starting dose 2.5–5 mg bd: target dose 10–20 mg bd

Ramipril: (ACEI) starting dose 2.5 mg bd: target dose 5 mg bd

Trandolapril: (ACEI) starting dose 1 mg daily: target dose 4 mg daily

Bisoprolol: (beta-1 selective blocker) starting dose 1.25 mg daily: target dose 10 mg daily

Metoprolol: (beta-1 selective blocker) starting dose 12.5–25 mg: target dose 200 mg daily

Carvedilol: (alpha-1, non-selective beta-blocker) starting dose 3.125 mg bd: target dose 25 mg bd (50 mg bd for patients > 85 kg)

Nebivolol: (cardio-selective beta-blocker) starting dose 1.25 mg; target dose 10 mg daily.

Treatment of comorbidity

Heart failure does not occur in isolation, and in many patients, other diseases or the underlying cause of the heart failure are still present and need attention. Angina, uncontrolled hypertension, diabetes, smoking-related lung disease, osteoarthritis and gout (often due to diuretics) are common. Some conditions, for example, anaemia, depression, cachexia and disorders of breathing are not fully explained. Renal dysfunction, due to various causes, is so prominent that the phrase cardiorenal syndrome has been developed. Sometimes a precipitating factor, such as an infection, electrolyte disturbance, or anaemia, needs management.

• Treat dysrhythmia: prevent fatal (ventricular) dysrhythmias
                      prevent atrial fibrillation
• Reduce left ventricular wall stress: dual chamber pacing (resynchronisation) reduces mortality by 20% (companion)
                      left ventricular assist devices
                      intra-cardiac defibrillator (Sudden Cardiac Death Heart Failure trial) reduces mortality by 23%

Prevention of heart failure

By treating people in stage A (those with risk factors) adequately, the risk of developing heart failure can be significantly reduced. For example, by treating hypertension properly, the risk to develop heart failure can be reduced by almost 50%.

People in stage B, those with structural abnormality of the myocardium, need to be started on an ACE inhibitor to reduce the risk of remodelling and subsequent heart failure.

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3. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. *J Am Coll of Cardiol* 2005; **46**: 1116–1143.