Heart failure: classification and pathophysiology

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Abstract

Heart failure (HF) is a clinical syndrome in which there are characteristic signs and symptoms (e.g. oedema, breathlessness, fatigue) resulting from an underlying abnormality of cardiac function. Understanding the cause of the cardiac dysfunction and the body's response to it is essential in effective management. HF can present acutely, for example as a consequence of an acute myocardial infarction, or in a chronic form in which acute decompensation can then occur. HF results in a plethora of changes in the heart, at the cellular, microscopic and macroscopic levels, with the heart remodelling in response to the abnormal conditions. The underlying cardiac dysfunction also triggers the activation of an array of neuro-hormonal compensatory mechanisms that can ultimately become deleterious to cardiac and other organ function; they include sodium and fluid retention, increased sympathetic tone, altered breathing patterns, arrhythmia and, in more advanced stages, an inflammatory state with immune activation.

Keywords Heart failure; pathophysiology; renin–angiotensin–aldosterone system; sympathetic nervous system

Key points

- Heart failure (HF) is a multisystem syndrome in which the underlying cardiac abnormality must be determined and the systemic response understood to achieve effective treatment
- Coronary artery disease (often associated with hypertension) is the single most common cause of HF in Europe and North America
- HF can result from systolic or diastolic dysfunction of the left (and/or right) ventricular myocardium, valve disease, arrhythmia, congenital heart disease, pericardial disease or a combination of these problems
- HF can be associated with ventricular dyssynchrony and cardiac arrhythmia
- HF is often associated with renal dysfunction, anaemia, skeletal muscle abnormalities, cachexia and sleep-disordered breathing – these are markers of a poor prognosis
- Modern therapy of HF is based on addressing many of these pathophysiological abnormalities.

Definition

Heart failure (HF) is a clinical diagnosis in which there are symptoms (breathlessness, fatigue, oedema and/or orthopnoea) and signs (elevated venous pressure, pulmonary crackles, displaced apex beat), with evidence of abnormal cardiac function on investigation.[1] It should be stressed that HF is a clinical syndrome rather than merely an abnormality found on cardiac imaging.

HF can be categorized in several ways: by the time course of development of symptoms (acute or chronic), by the systolic function of the left ventricle (usually expressed as the ejection fraction), by the aetiology of the underlying cardiac dysfunction, and by the symptomatic severity.

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Acute HF refers to the relatively sudden onset of symptoms, which are usually severe and require hospitalization for stabilization. This state is usually precipitated by an event such as the onset of arrhythmia (e.g. atrial fibrillation, ventricular tachycardia) or acute myocardial infarction. Chronic HF describes a longer term syndrome, although acute deterioration can occur, which is often described as 'acute decompensated HF'.

Historically, cardiac dysfunction has been quantified with reference to left ventricular ejection fraction (LVEF), usually derived from echocardiography, with values of $\geq$50% accepted as normal. In the UK and other European countries, most people admitted to hospital have HF with a reduced ejection fraction (HFrEF), but the HF syndrome can present where LVEF appears normal, a condition termed HF with preserved ejection fraction (HFpEF). This type of HF is more common in the USA than in Europe, and is more common in older patients and those with a history of poorly controlled hypertension.

Currently recommended diagnostic criteria for HFpEF require confirmation of a cardiac cause of symptoms and signs, and elevated plasma natriuretic peptides (brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-proBNP)) and/or structural abnormalities such as left atrial enlargement or left ventricular hypertrophy.[1]

The subgroup of patients for which there is most evidence on which to base treatment (and improve outcome) is those with HFrEF. In the current guidelines from the European Society of Cardiology, a further subdivision is labelled as 'HF with mid-range EF', with an ejection fraction of around 40–49%. Whether this third subdivision is useful in clinical practice remains to be seen.

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In addition to left ventricular dysfunction, abnormalities of cardiac rhythm, valve function, congenital structural or functional abnormalities, and pericardial disease can lead to HF syndrome either on their own or acting together.

The functional severity of the HF syndrome is usually classified using the New York Heart Association classification, ranging from class I (no limitations, no symptoms on usual activity), through class II (mild symptoms, or symptoms only on moderate exertion) and III (moderate symptoms, or symptoms on even mild exertion), to class IV (symptoms at rest). Other methods of assessing severity include cardiopulmonary exercise testing with estimation of peak oxygen consumption, or distance walked in 6 minutes. Several patient-reported outcome measures have been developed, such as the Minnesota Living with Heart Failure questionnaire, which can provide a more detailed assessment of the impact of symptoms of HF syndrome.

Aetiology

HF is a syndrome rather than a complete diagnosis, and the underlying cause of the cardiac dysfunction should always be determined. The major disease aetiologies are detailed in Table 1. In high-income countries, ischaemic heart disease and hypertension remain the leading causes of HF. Rates of hypertensive HF are declining with improved management of blood pressure in primary care. The prevalence of HF caused by degenerative valve disease (commonly aortic stenosis) is likely to increase as the population ages.

Rheumatic heart disease continues to be a major health problem in low-income countries in Africa and Asia, and Chagas' disease remains an important cause of HF in South America. In African and African-American populations, hypertension is the main aetiology of HF in almost half of all cases. In the past decade, the epidemiology of HF in middle-income countries has become similar to that in high-income countries, presumably because of a 'Westernization' of diet and environment, and increased life expectancy.

Pathophysiology

Whatever the aetiology of the cardiac damage, the body's response to this tends to be similar (Figure 1).

In **HFrEF**, the disease process affects contraction of the heart muscle. This can be regional (e.g. after myocardial infarction) or global (as in dilated cardiomyopathy or chronic mitral regurgitation). The result is that although the heart may fill well during diastole, the failing myocardium is unable to eject sufficient blood during systole. This leads to dilatation of the heart and stretching of the muscle fibres. According to Starling's law, there is an initial increase in the force of contraction that helps to restore cardiac output. Eventually, however, this compensatory mechanism starts to fail and cardiac output falls, with progressive dilatation of the ventricle.

A similar process is seen in valvular disease. Regurgitant lesions cause volume overload of the ventricles, whereas valve stenosis causes pressure loading. In addition, mitral stenosis causes high pulmonary pressures, leading to right ventricular failure while impairing diastolic filling of the left ventricle. The plasticity of the cardiac chambers in response to an abnormal pressure or volume load, with a change in shape, size and function, accompanied by changes at the cellular level, is termed 'remodelling'. Some of the changes observed within the heart as it remodels are shown in Table 2.

In **HFpEF**, systolic function of the left ventricle is preserved but there is impairment of cardiac filling during diastole. This can be visualized using Doppler echocardiography by assessing flow through the mitral valve and the movement of the ventricular wall during diastole.

It is unclear whether HFpEF is a single entity or a collection of syndromes sharing certain characteristics.[3] It is, however, not merely the effect of an 'ageing' heart as those in whom HF syndrome develops despite a preserved ejection fraction have a worse outcome than age-, gender- and co-morbidity-matched controls. It is vital that a full diagnostic work-up is performed, as other conditions leading to breathlessness or fluid retention in the presence of normal left ventricular systolic function can be missed if the HFpEF label is used without due consideration. This is why guidelines suggest there should be confirmatory evidence with elevation of natriuretic peptides (markers of cardiac wall stretch) and/or structural abnormalities of the heart (e.g. left atrial enlargement as a marker of raised intracardiac pressure, left ventricular hypertrophy).

The result of either HFrEF or HFpEF can be a fall in cardiac output at rest or, more often, an inadequate increase on exercise or an increase accompanied by a rise in intracardiac pressures. This can lead to an underperfusion of organs and activation of baroreceptors, triggering a complex neuro-hormonal response. This response leads to increased heart rate and blood pressure, accompanied by salt and water retention — which is perhaps appropriate in the short term to maintain organ perfusion, but in the longer term causes further cardiac and other organ damage.

Typically, as the HF syndrome progresses, left ventricular end-diastolic pressure increases, and the ventricle and atrium both enlarge. Back-pressure into the pulmonary veins increases, leading to extravasation of fluid into the alveoli — pulmonary oedema. Ultimately, pulmonary artery pressure rises and the right ventricle may dilate and fail; this is often accompanied by increasing tricuspid regurgitation and increased vena caval pressure, which can be associated with increasing liver, gut and kidney congestion.

It is increasingly recognized that many patients with hypertrophic or dilated cardiomyopathy have an underlying genetic defect in cell proteins (sarcolemma, nuclear membrane, connecting proteins). Although single-gene defects have been identified in many families, the situation is complex as there appears to be modification by other genes, epigenetic processes and the environment. Specific therapies targeted at these gene defects are not yet available.

Sympathetic nervous system

Falling pressure at the baroreceptors in the carotid bodies and aortic arch leads to increased sympathetic and decreased parasympathetic nervous system activity. High concentrations of plasma noradrenaline (norepinephrine) are found in patients with HF, particularly in more advanced stages. The increase in sympathetic tone results in an increased heart rate and stroke volume (the volume of blood ejected from the left ventricle with each beat), and this acts to maintain cardiac output. Sympathetic activity also causes peripheral vasoconstriction, renin release

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