ABC of heart failure

History and epidemiology

R C Davis, F D R Hobbs, G Y H Lip

Heart failure is the end stage of all diseases of the heart and is a major cause of morbidity and mortality. It is estimated to account for about 5% of admissions to hospital medical wards, with over 100 000 annual admissions in the United Kingdom.

The overall prevalence of heart failure is 3-20 per 1000 population, although this exceeds 100 per 1000 in those aged 65 years and over. The annual incidence of heart failure is 1-5 per 1000, and the relative incidence doubles for each decade of life after the age of 45 years. The overall incidence is likely to increase in the future, because of both an ageing population and therapeutic advances in the management of acute myocardial infarction leading to improved survival in patients with impaired cardiac function.

Unfortunately, heart failure can be difficult to diagnose clinically, as many features of the condition are not organ specific, and there may be few clinical features in the early stages of the disease. Recent advances have made the early recognition of heart failure increasingly important as modern drug treatment has the potential to improve symptoms and quality of life, reduce hospital admission rates, slow the rate of disease progression, and improve survival. In addition, coronary revascularisation and heart valve surgery are now regularly performed, even in elderly patients.

"The very essence of cardiovascular practice is the early detection of heart failure"
Sir Thomas Lewis, 1933

Some definitions of heart failure

"A condition in which the heart fails to discharge its contents adequately" (Thomas Lewis, 1933)

"A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure" (Paul Wood, 1950)

"A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues" (E Braunwald, 1980)

"Heart failure is the state of any heart disease in which, despite adequate ventricular filling, the heart's output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits" (H Denolin, H Kuhn, H P Krayenbuehl, F Loogen, A Reale, 1983)

"A clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses" (Philip Poole-Wilson, 1985)

"[A] syndrome … which arises when the heart is chronically unable to maintain an appropriate blood pressure without support" (Peter Harris, 1987)

"A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy" (Jay Cohn, 1988)

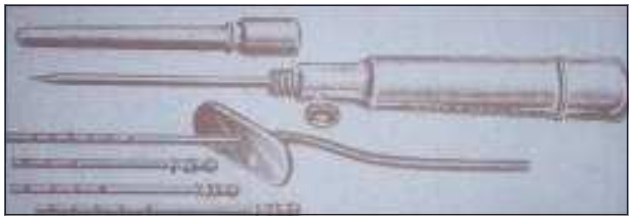
"Abnormal function of the heart causing a limitation of exercise capacity" or "ventricular dysfunction with symptoms" (anonymous and pragmatic)

"Symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure" (Task Force of the European Society of Cardiology, 1995)

A brief history

Descriptions of heart failure exist from ancient Egypt, Greece, and India, and the Romans were known to use the foxglove as medicine. Little understanding of the nature of the condition can have existed until William Harvey described the circulation in 1628. Röntgen's discovery of *x* rays and Einthoven's development of electrocardiography in the 1890s led to improvements in the investigation of heart failure. The advent of echocardiography, cardiac catheterisation, and nuclear medicine have since improved the diagnosis and investigation of patients with heart failure.

Blood letting and leeches were used for centuries, and William Withering published his account of the benefits of digitalis in 1785. In the 19th and early 20th centuries, heart failure associated with fluid retention was treated with Southey's tubes, which were inserted into oedematous peripheries, allowing some drainage of fluid.



Southey's tubes were at one time used for removing fluid from oedematous peripheries in patients with heart failure

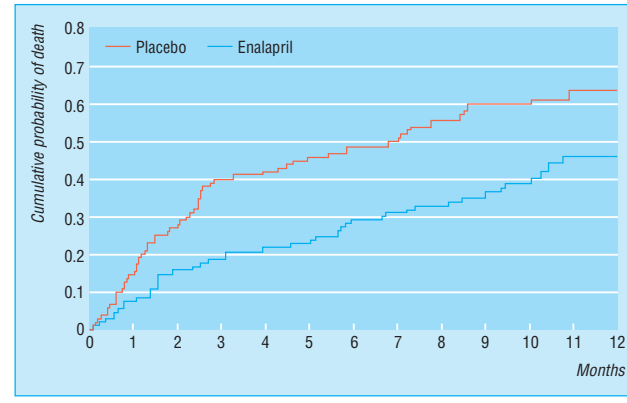
The foxglove was used as a medicine in heart disease as long ago as Roman times

In 1785 William Withering of Birmingham published an account of medicinal use of digitalis

A brief history of heart failure

1628	William Harvey describes the circulation
1785	William Withering publishes an account of medical use of digitalis
1819	René Laennec invents the stethoscope
1895	Wilhelm Röntgen discovers *x* rays
1920	Organomercurial diuretics are first used
1954	Inge Edler and Hellmuth Hertz use ultrasound to image cardiac structures
1958	Thiazide diuretics are introduced
1967	Christiaan Barnard performs first human heart transplant
1987	CONSENSUS-I study shows unequivocal survival benefit of angiotensin converting enzyme inhibitors in severe heart failure
1995	European Society of Cardiology publishes guidelines for diagnosing heart failure

It was not until the 20th century that diuretics were developed. The early, mercurial agents, however, were associated with substantial toxicity, unlike the thiazide diuretics, which were introduced in the 1950s. Vasodilators were not widely used until the development of angiotensin converting enzyme inhibitors in the 1970s. The landmark CONSENSUS-I study (first cooperative north Scandinavian enalapril survival study), published in 1987, showed the unequivocal survival benefits of enalapril in patients with severe heart failure.



Mortality curves from the CONSENSUS-I study

Epidemiology

Studies of the epidemiology of heart failure have been complicated by the lack of universal agreement on a definition of heart failure, which is primarily a clinical diagnosis. National and international comparisons have therefore been difficult, and mortality data, postmortem studies, and hospital admission rates are not easily translated into incidence and prevalence. Several different systems have been used in large population studies, with the use of scores for clinical features determined from history and examination, and in most cases chest radiography, to define heart failure.

The Task Force on Heart Failure of the European Society of Cardiology has recently published guidelines on the diagnosis of heart failure, which require the presence of symptoms and objective evidence of cardiac dysfunction. Reversibility of symptoms on appropriate treatment is also desirable. Echocardiography is recommended as the most practicable way of assessing cardiac function, and this investigation has been used in more recent studies.

In the Framingham heart study a cohort of 5209 subjects has been assessed biennially since 1948, with a further cohort (their offspring) added in 1971. This uniquely large dataset has been used to determine the incidence and prevalence of heart failure, defined with consistent clinical and radiographic criteria.

Several recent British studies of the epidemiology of heart failure and left ventricular dysfunction have been conducted, including a study of the incidence of heart failure in one west London district (Hillingdon heart failure study) and large prevalence studies in Glasgow (north Glasgow MONICA study) and the West Midlands ECHOES (echocardiographic heart of England screening) study. It is important to note that

The Framingham heart study has been the most important longitudinal source of data on the epidemiology of heart failure

Contemporary studies of the epidemiology of heart failure in United Kingdom

Study	Diagnostic criteria
Hillingdon heart failure study (west London)	Clinical (for example, shortness of breath, effort intolerance, fluid retention), radiographic, and echocardiographic
ECHOES study (West Midlands)	Clinical and echocardiographic (ejection fraction $<40\%$)
MONICA population (north Glasgow)	Clinical and echocardiographic (ejection fraction $\leq 30\%$)

epidemiological studies of heart failure have used different levels of ejection fraction to define systolic dysfunction. The Glasgow study, for example, used an ejection fraction of 30% as their criteria, whereas most other epidemiological surveys have used levels of 40-45%. Indeed, prevalence of heart failure seems similar in many different surveys, despite variation in the levels of ejection fraction, and this observation is not entirely explained.

Prevalence of heart failure (per 1000 population), Framingham heart study

Age (years)	Men	Women
50-59	8	8
80-89	66	79
All ages	7.4	7.7

Prevalence of heart failure

During the 1980s the Framingham study reported the age adjusted overall prevalence of heart failure, with similar rates for men and women. Prevalence increased dramatically with increasing age, with an approximate doubling in the prevalence of heart failure with each decade of ageing.

In Nottinghamshire, the prevalence of heart failure in 1994 was estimated from prescription data for loop diuretics and examination of the general practice notes of a sample of these patients, to determine the number who fulfilled predetermined criteria for heart failure. The overall prevalence of heart failure was estimated as 1.0% to 1.6%, rising from 0.1% in the 30-39 age range to 4.2% at 70-79 years. This method, however, may exclude individuals with mild heart failure and include patients treated with diuretics who do not have heart failure.

Methods of assessing prevalence of heart failure in published studies

- Clinical and radiographic assessment
- Echocardiography
- General practice monitoring
- Drug prescription data

Incidence of heart failure

The Framingham data show an age adjusted annual incidence of heart failure of 0.14% in women and 0.23% in men. Survival in the women is generally better than in the men, leading to the same point prevalence. There is an approximate doubling in the incidence of heart failure with each decade of ageing, reaching 3% in those aged 85-94 years.

The recent Hillingdon study examined the incidence of heart failure, defined on the basis of clinical and radiographic findings, with echocardiography, in a population in west London. The overall annual incidence was 0.08%, rising from 0.02% at age 45-55 years to 1.2% at age 86 years or over. About 80% of these cases were first diagnosed after acute hospital admission, with only 20% being identified in general practice and referred to a dedicated clinic.

The Glasgow group of the MONICA study and the ECHOES Group have found that coronary artery disease is the most powerful risk factor for impaired left ventricular function, either alone or in combination with hypertension. In these studies hypertension alone did not appear to contribute substantially to impairment of left ventricular systolic contraction, although the Framingham study did report a more substantial contribution from hypertension. This apparent difference between the studies may reflect improvements in the treatment of hypertension and the fact that some patients with hypertension, but without coronary artery disease, may develop heart failure as a result of diastolic dysfunction.

Annual incidence of heart failure (per 1000 population), Framingham heart study

Age (years)	Men	Women
50-59	3	2
80-89	27	22
All ages	2.3	1.4

The MONICA study is an international study conducted under the auspices of the World Health Organisation to monitor trends in and determinants of mortality from cardiovascular disease

Prevalence of left ventricular dysfunction

Large surveys have been carried out in Britain in the 1990s, in Glasgow and the West Midlands, using echocardiography.

In Glasgow the prevalence of significantly impaired left ventricular contraction in subjects aged 25-74 years was 2.9%; in the West Midlands, the prevalence was 1.8% in subjects aged 45 and older.

The higher rates in the Scottish study may reflect the high prevalence of ischaemic heart disease, the main precursor of impaired left ventricular function in both studies. The numbers of symptomatic and asymptomatic cases, in both studies, were about the same.

Prevalence (%) of left ventricular dysfunction, north Glasgow (MONICA survey)

Age group (years)	Asymptomatic		Symptomatic	
	Men	Women	Men	Women
45-54	4.4	1.2	1.4	1.2
55-64	3.2	0.0	2.5	2.0
65-74	3.2	1.3	3.2	3.6

Ethnic differences

Ethnic differences in the incidence of and mortality from heart failure have also been reported. In the United States, African-American men have been reported as having a 33% greater risk of being admitted to hospital for heart failure than white men; the risk for black women was 50%.

A similar picture emerged in a survey of heart failure among acute medical admissions to a city centre teaching hospital in Birmingham. The commonest underlying aetiological factors were coronary heart disease in white patients, hypertension in black Afro-Caribbean patients, and coronary heart disease and diabetes in Indo-Asians. Some of these racial differences may be related to the higher prevalence of hypertension and diabetes in black people and coronary artery disease and diabetes mellitus in Indo-Asians.

In the United States mortality from heart failure at age <65 years has been reported as being up to 2.5-fold higher in black patients than in white patients

Impact on health services

Heart failure accounts for at least 5% of admissions to general medical and geriatric wards in British hospitals, and admission rates for heart failure in various European countries (Sweden, Netherlands, and Scotland) and in the United States have doubled in the past 10-15 years. Furthermore, heart failure accounts for over 1% of the total healthcare expenditure in the United Kingdom, and most of these costs are related to hospital admissions. The cost of heart failure is increasing, with an estimated UK expenditure in 1996 of £465m (£556m when the costs of community health services and nursing homes are included).

Hospital readmissions and general practice consultations often occur soon after the diagnosis of heart failure. In elderly patients with heart failure, readmission rates range from 29-47% within 3 to 6 months of the initial hospital discharge. Treating patients with heart failure with angiotensin converting enzyme inhibitors can reduce the overall cost of treatment (because of reduced hospital admissions) despite increased drug expenditure and improved long term survival.

Cost of heart failure

Country	Cost	% Healthcare costs	% Of costs due to admissions
UK, 1990-1	£360m	1.2	60
US, 1989	$9bn	1.5	71
France, 1990	FF11.4bn	1.9	64
New Zealand, 1990	$NZ73m	1.5	68
Sweden, 1996	Kr2.6m	2.0	75

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The pictures of William Withering and of the foxglove are reproduced with permission from the Fine Art Photographic Library. The box of definitions of heart failure is adapted from Poole-Wilson PA et al, eds (*Heart failure*. New York: Churchill Livingstone, 1997:270). The table showing the prevalence of left ventricular dysfunction in north Glasgow is reproduced with permission from McDonagh TA et al (see key references box). The table showing costs of heart failure is adapted from McMurray J et al (*Br J Med Econ* 1993;6:99-110).

The ABC of heart failure is edited by C R Gibbs, M K Davies, and G Y H Lip. CRG is research fellow and GYHL is consultant cardiologist and reader in medicine in the university department of medicine and the department of cardiology, City Hospital, Birmingham; MKD is consultant cardiologist in the department of cardiology, Selly Oak Hospital, Birmingham. The series will be published as a book in the spring.

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One hundred years ago

The Bogey of Medical Etiquette.

There is a widespread opinion amongst the public that a rule of conduct obtains in the medical profession the object of which is to protect the profession and individual members thereof against the consequences of their ignorance or mistakes. Probably opinions differ as to the extent to which we are prepared to go in this direction, and perhaps few believe that we would go so far as to commit perjury or sacrifice human life, but we certainly are supposed to be capable of suppressing the truth in order to avoid exposing the mistakes of a colleague. We admit that there are members of the medical profession who regard their patients as their property, and we believe that the petty tyranny sometimes exercised is responsible for the opinions upon medical etiquette which are undoubtedly entertained by the laity. But these extreme views are not endorsed by any representative body in the medical profession, and we are quite certain that we are expressing the general view when we say that the profession recognises no other rules of medical etiquette than are consistent with the best interests of our patients and with courtesy and consideration for our colleagues. (*BMJ* 1900;i:156)

Aetiology

G Y H Lip, C R Gibbs, D G Beevers

The relative importance of aetiological factors in heart failure is dependent on the nature of the population being studied, as coronary artery disease and hypertension are common causes of heart failure in Western countries, whereas valvar heart disease and nutritional cardiac disease are more common in the developing world. Epidemiological studies are also dependent on the clinical criteria and relevant investigations used for diagnosis, as it remains difficult, for example, to distinguish whether hypertension is the primary cause of heart failure or whether there is also underlying coronary artery disease.

Coronary artery disease and its risk factors

Coronary heart disease is the commonest cause of heart failure in Western countries. In the studies of left ventricular dysfunction (SOLVD) coronary artery disease accounted for almost 75% of the cases of chronic heart failure in male white patients, although in the Framingham heart study, coronary heart disease accounted for only 46% of cases of heart failure in men and 27% of chronic heart failure cases in women. Coronary artery disease and hypertension (either alone or in combination) were implicated as the cause in over 90% of cases of heart failure in the Framingham study.

Recent studies that have allocated aetiology on the basis of non-invasive investigations—such as the Hillingdon heart failure study—have identified coronary artery disease as the primary aetiology in 36% of cases of heart failure. In the Hillingdon study, however, researchers were not able to identify the primary aetiology in 34% of cases; this methodological failing has been addressed in the current Bromley heart failure study, which uses coronary angiography as well as historical and non-invasive findings.

Coronary risk factors, such as smoking and diabetes mellitus, are also risk markers of the development of heart failure. Smoking is an independent and strong risk factor for the development of heart failure in men, although the findings in women are less consistent.

In the prevention arm of SOLVD diabetes was an independent risk factor (about twofold) for mortality, the

Causes of heart failure

Coronary artery disease
- Myocardial infarction
- Ischaemia

Hypertension

Cardiomyopathy
- Dilated (congestive)
- Hypertrophic/obstructive
- Restrictive—for example, amyloidosis, sarcoidosis, haemochromatosis
- Obliterative

Valvar and congenital heart disease
- Mitral valve disease
- Aortic valve disease
- Atrial septal defect, ventricular septal defect

Arrhythmias
- Tachycardia
- Bradycardia (complete heart block, the sick sinus syndrome)
- Loss of atrial transport—for example, atrial fibrillation

Alcohol and drugs
- Alcohol
- Cardiac depressant drugs (β blockers, calcium antagonists)

"High output" failure
- Anaemia, thyrotoxicosis, arteriovenous fistulae, Paget's disease

Pericardial disease
- Constrictive pericarditis
- Pericardial effusion

Primary right heart failure
- Pulmonary hypertension—for example, pulmonary embolism, cor pulmonale
- Tricuspid incompetence

Epidemiological studies of aetiology of heart failure. Values are percentages

Aetiology	Teerlink et al (31 studies 1989-90)	Framingham heart study*		Hillingdon study
		Men	Women	
Ischaemic	50	59	48	36
Non-ischaemic:	50	41	52	64
Hypertension	4	70	78	14
Idiopathic	18	0	0	0
Valvar	4	22	31	7
Other	10	7	7	10
"Unknown"	13	0	0	34

Because of rounding, totals may not equal 100%.
*Total exceeds 100% as coronary artery disease and hypertension were not considered as mutually exclusive causes.

Relative risks for development of heart failure: 36 year follow up in Framingham heart study

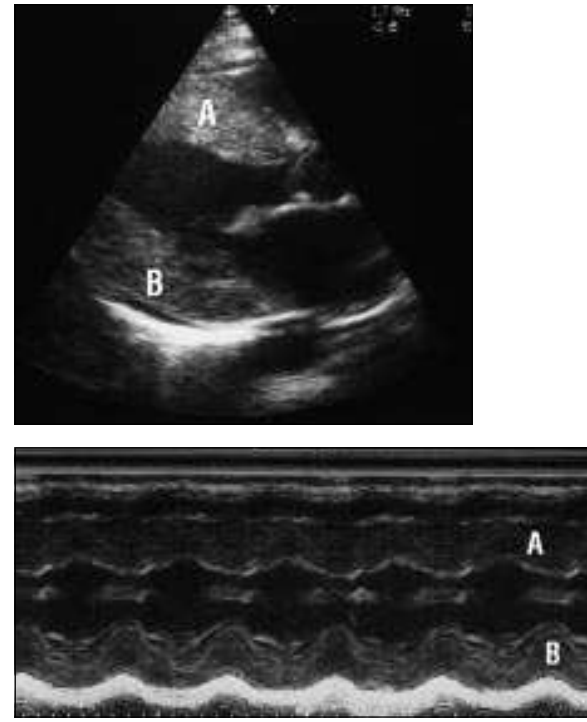
Variable	Age (years)			
	Men		Women	
	35-64	65-94	35-64	65-94
Serum cholesterol (>6.3 mmol/l)	1.2	0.9	0.7	0.8
Hypertension (>160/95 mm Hg or receiving treatment)	4.0	1.9	3.0	1.9
Glucose intolerance	4.4	2.0	7.7	3.6
Electrocardiographic left ventricular hypertrophy	15.0	4.9	12.8	5.4

development of heart failure, and admission to hospital for heart failure, whereas in the Framingham study diabetes and left ventricular hypertrophy were the most significant risk markers of the development of heart failure. Body weight and a high ratio of total cholesterol concentration to high density lipoprotein cholesterol concentration are also independent risk factors for heart failure. Clearly, these risk factors may increase the risks of heart failure through their effects on coronary artery disease, although diabetes alone may induce important structural and functional changes in the myocardium, which further increase the risk of heart failure.

Hypertension

Hypertension has been associated with an increased risk of heart failure in several epidemiological studies. In the Framingham heart study, hypertension was reported as the cause of heart failure—either alone or in association with other factors—in over 70% of cases, on the basis of non-invasive assessment. Other community and hospital based studies, however, have reported hypertension to be a less common cause of heart failure, and, indeed, the importance of hypertension as a cause of heart failure has been declining in the Framingham cohort since the 1950s. Recent community based studies that have assessed aetiology using clinical criteria and relevant non-invasive investigations have reported hypertension to be the cause of heart failure in 10-20%. However, hypertension is probably a more common cause of heart failure in selected patient groups, including females and black populations (up to a third of cases).

Hypertension predisposes to the development of heart failure via a number of pathological mechanisms, including left ventricular hypertrophy. Left ventricular hypertrophy is associated with left ventricular systolic and diastolic dysfunction and an increased risk of myocardial infarction, and it predisposes to both atrial and ventricular arrhythmias. Electrocardiographic left ventricular hypertrophy is strongly correlated with the development of heart failure, as it is associated with a 14-fold increase in the risk of heart failure in those aged 65 years or under.



Two dimensional echocardiogram (top) and M mode echocardiogram (bottom) showing left ventricular hypertrophy. A=interventricular septum; B=posterior left ventricular wall

Effective blood pressure lowering in patients with hypertension reduces the risk of heart failure; an overview of trials has estimated that effective antihypertensive treatment reduces the age standardised incidence of heart failure by up to 50%

Cardiomyopathies

Cardiomyopathies are defined as the diseases of heart muscle that are not secondary to coronary disease, hypertension, or congenital, valvar, or pericardial disease. As primary diseases of heart muscle, cardiomyopathies are less common causes of heart failure, but awareness of their existence is necessary to make a diagnosis. Cardiomyopathies are separated into four functional categories: dilated (congestive), hypertrophic, restrictive, and obliterative. These groups can include rare, specific heart muscle diseases (such as haemochromatosis (iron overload) and metabolic and endocrine disease), in which cardiac involvement occurs as part of a systemic disorder. Dilated cardiomyopathy is a more common cause of heart failure than hypertrophic and restrictive cardiomyopathies; obliterative cardiomyopathy is essentially limited to developing countries.

Dilated cardiomyopathy

Dilated cardiomyopathy describes heart muscle disease in which the predominant abnormality is dilatation of the left ventricle, with or without right ventricular dilatation. Myocardial cells are also hypertrophied, with increased variation in size and increased extracellular fibrosis. Family studies have reported

Causes of dilated cardiomyopathy

Familial

Infectious
- Viral (coxsackie B, cytomegalovirus, HIV)
- Rickettsia
- Bacteria (diphtheria)
- Mycobacteria
- Fungus
- Parasites (Chagas' disease, toxoplasmosis)
- Alcohol
- Cardiotoxic drugs (adriamycin, doxorubicin, zidovudine)
- Cocaine
- Metals (cobalt, mercury, lead)
- Nutritional disease (beriberi, kwashiorkor, pellagra)
- Endocrine disease (myxoedema, thyrotoxicosis, acromegaly, phaeochromocytoma)

Pregnancy

Collagen disease
- Connective tissue diseases (systemic lupus erythematosus, scleroderma, polyarteritis nodosa)

Neuromuscular
- Duchenne muscular dystrophy, myotonic dystrophy

Idiopathic

that up to a quarter of cases of dilated cardiomyopathy have a familial basis. Viral myocarditis is a recognised cause; connective tissue diseases such as systemic lupus erythematosus, the Churg-Strauss syndrome, and polyarteritis nodosa are rarer causes. Idiopathic dilated cardiomyopathy is a diagnosis of exclusion. Coronary angiography will exclude coronary disease, and an endomyocardial biopsy is required to exclude underlying myocarditis or an infiltrative disease.

Dilatation can be associated with the development of atrial and ventricular arrhythmias, and dilatation of the ventricles leads to "functional" mitral and tricuspid valve regurgitation.

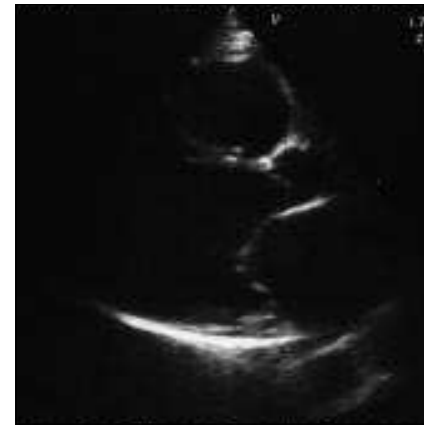
Hypertrophic cardiomyopathy

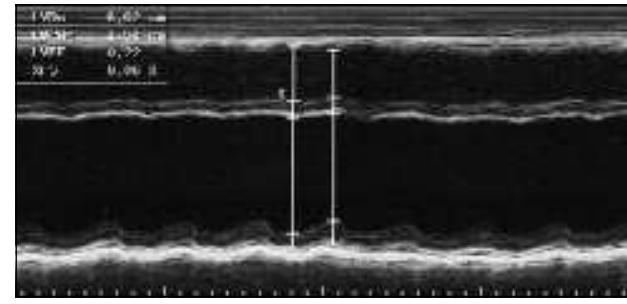
Hypertrophic cardiomyopathy has a familial inheritance (autosomal dominant), although sporadic cases may occur. It is characterised by abnormalities of the myocardial fibres, and in its classic form involves asymmetrical septal hypertrophy, which may be associated with aortic outflow obstruction (hypertrophic obstructive cardiomyopathy).

Nevertheless, other forms of hypertrophic cardiomyopathy exist—apical hypertrophy (especially in Japan) and symmetrical left ventricular hypertrophy (where the echocardiographic distinction between this and hypertensive heart disease may be unclear). These abnormalities lead to poor left ventricular compliance, with high end diastolic pressures, and there is a common association with atrial and ventricular arrhythmias, the latter leading to sudden cardiac death. Mitral regurgitation may contribute to the heart failure in these patients.

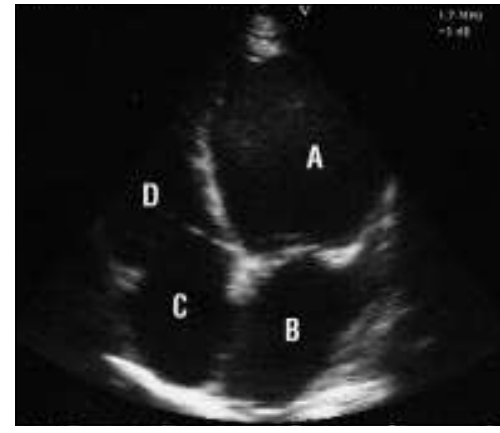
Restrictive and obliterative cardiomyopathies

Restrictive cardiomyopathy is characterised by a stiff and poorly compliant ventricle, which is not substantially enlarged, and this is associated with abnormalities of diastolic function (relaxation) that limit ventricular filling. Amyloidosis and other infiltrative diseases, including sarcoidosis and haemochromatosis, can cause a restrictive syndrome. Endomyocardial fibrosis is also a cause of restrictive cardiomyopathy, although it is a rare cause of heart failure in Western countries. Endocardial fibrosis of the inflow tract of one or both ventricles, including the subvalvar regions, results in restriction of diastolic filling and cavity obliteration.





Two dimensional (long axis parasternal view) echocardiogram (top) and M mode echocardiogram (bottom) showing severely impaired left ventricular function in dilated cardiomyopathy

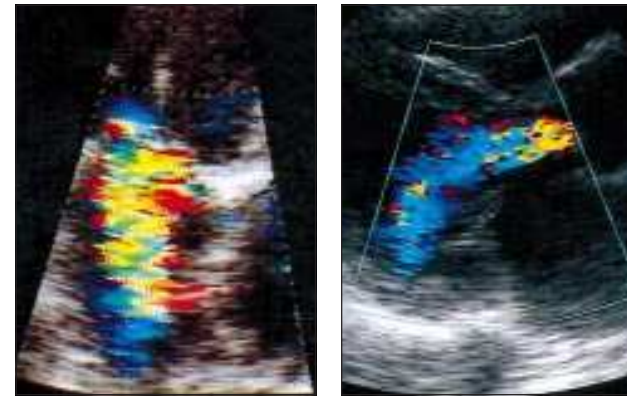


Two dimensional, apical, four chamber echocardiogram showing dilated cardiomyopathy. A=left ventricle; B=left atrium; C=right atrium; D=right ventricle

Valvar disease

Rheumatic heart disease may have declined in certain parts of the world, but it still represents an important cause of heart failure in India and other developing nations. In the Framingham study rheumatic heart disease accounted for heart failure in 2% of men and 3% of women, although the overall incidence of valvar disease has been steadily decreasing in the Framingham cohort over the past 30 years.

Mitral regurgitation and aortic stenosis are the most common causes of heart failure, secondary to valvar disease. Mitral regurgitation (and aortic regurgitation) leads to volume overload (increased preload), in contrast with aortic stenosis, which leads to pressure overload (increased afterload). The progression of heart failure in patients with valvar disease is dependent on the nature and extent of the valvar disease. In aortic stenosis heart failure develops at a relatively late stage and, without valve replacement, it is associated with a poor prognosis. In contrast, patients with chronic mitral (or aortic) regurgitation generally decline in a slower and more progressive manner.



Colour Doppler echocardiograms showing mitral regurgitation (left) and aortic regurgitation (right)

Arrhythmias

Cardiac arrhythmias are more common in patients with heart failure and associated structural heart disease, including hypertensive patients with left ventricular hypertrophy. Atrial fibrillation and heart failure often coexist, and this has been confirmed in large scale trials and smaller hospital based studies. In the Hillingdon heart failure study 30% of patients presenting for the first time with heart failure had atrial fibrillation, and over 60% of patients admitted urgently with atrial fibrillation to a Glasgow hospital had echocardiographic evidence of impaired left ventricular function.

Atrial fibrillation in patients with heart failure has been associated with increased mortality in some studies, although the vasodilator heart failure trial (V-HeFT) failed to show an increase in major morbidity or mortality for patients with atrial fibrillation. In the stroke prevention in atrial fibrillation (SPAF) study, the presence of concomitant heart failure or left ventricular dysfunction increased the risk of stroke and thromboembolism in patients with atrial fibrillation. Ventricular arrhythmias are also more common in heart failure, leading to a sudden deterioration in some patients; such arrhythmias are a major cause of sudden death in patients with heart failure.

Alcohol and drugs

Alcohol has a direct toxic effect on the heart, which may lead to acute heart failure or heart failure as a result of arrhythmias, commonly atrial fibrillation. Excessive chronic alcohol consumption also leads to dilated cardiomyopathy (alcoholic heart muscle disease). Alcohol is the identifiable cause of chronic heart failure in 2-3% of cases. Rarely, alcohol misuse may be associated with general nutritional deficiency and thiamine deficiency (beriberi).

Chemotherapeutic agents (for example, doxorubicin) and antiviral drugs (for example, zidovudine) have been implicated in heart failure, through direct toxic effects on the myocardium.

Other causes

Infections may precipitate heart failure as a result of the toxic metabolic effects (relative hypoxia, acid base disturbance) in combination with peripheral vasodilation and tachycardia, leading to increased myocardial oxygen demand. Patients with chronic heart failure, like patients with most chronic illnesses, are particularly susceptible to viral and bacterial respiratory infections. "High output" heart failure is most often seen in patients with severe anaemia, although thyrotoxicosis may also be a precipitating cause in these patients. Myxoedema may present with heart failure as a result of myocardial involvement or secondary to a pericardial effusion.

The table of epidemiological studies of the aetiology of heart failure is adapted and reproduced with permission from Cowie MR et al (*Eur Heart J* 1997;18:208-25). The table showing relative risks for development of heart failure (36 year follow up) is adapted and reproduced with permission from Kannel WB et al (*Br Heart J* 1994;72:S3-9).

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The ABC of heart failure is edited by C R Gibbs, M K Davies, and G Y H Lip. CRG is research fellow and GYHL is consultant cardiologist and reader in medicine in the university department of medicine and the department of cardiology, City Hospital, Birmingham; MKD is consultant cardiologist in the department of cardiology, Selly Oak Hospital, Birmingham. The series will be published as a book in the spring.

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Arrhythmias and heart failure: mechanisms

Tachycardias

- Reduce diastolic ventricular filling time
- Increase myocardial workload and myocardial oxygen demand, precipitating ischaemia
- If they are chronic, with poor rate control, they may lead to ventricular dilatation and impaired ventricular function ("tachycardia induced cardiomyopathy")

Bradycardias

- Compensatory increase in stroke volume is limited in the presence of structural heart disease, and cardiac output is reduced

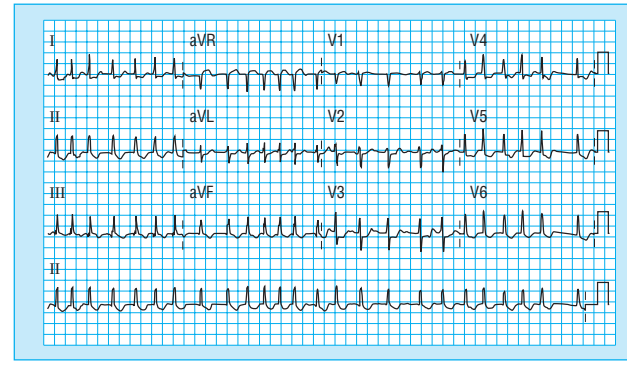
Abnormal atrial and ventricular contraction

- Loss of atrial systole leads to the absence of active ventricular filling, which in turn lowers cardiac output and raises atrial pressure—for example, atrial fibrillation
- Dissociation of atrial and ventricular activity impairs diastolic ventricular filling, particularly in the presence of a tachycardia—for example, ventricular tachycardia

Prevalence (%) of atrial fibrillation in major heart failure trials

Trial	NYHA class*	Prevalence of atrial fibrillation
SOLVD	I–III	6
V-HeFT I	II–III	15
V-HeFT II	II–III	15
CONSENSUS	III–IV	50

CONSENSUS = cooperative north Scandinavian enalapril survival study.
*Classification of the New York Heart Association.



Electrocardiogram showing atrial fibrillation with a rapid ventricular response

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Pathophysiology

G Jackson, C R Gibbs, M K Davies, G Y H Lip

Heart failure is a multisystem disorder which is characterised by abnormalities of cardiac, skeletal muscle, and renal function; stimulation of the sympathetic nervous system; and a complex pattern of neurohormonal changes.

Developments in our understanding of the pathophysiology of heart failure have been essential for recent therapeutic advances in this area

Myocardial systolic dysfunction

The primary abnormality in non-valvar heart failure is an impairment in left ventricular function, leading to a fall in cardiac output. The fall in cardiac output leads to activation of several neurohormonal compensatory mechanisms aimed at improving the mechanical environment of the heart. Activation of the sympathetic system, for example, tries to maintain cardiac output with an increase in heart rate, increased myocardial contractility, and peripheral vasoconstriction (increased catecholamines). Activation of the renin-angiotensin-aldosterone system (RAAS) also results in vasoconstriction (angiotensin) and an increase in blood volume, with retention of salt and water (aldosterone). Concentrations of vasopressin and natriuretic peptides increase. Furthermore, there may be progressive cardiac dilatation or alterations in cardiac structure (remodelling), or both.

Neurohormonal activation

Chronic heart failure is associated with neurohormonal activation and alterations in autonomic control. Although these compensatory neurohormonal mechanisms provide valuable support for the heart in normal physiological circumstances, they also have a fundamental role in the development and subsequent progression of chronic heart failure.

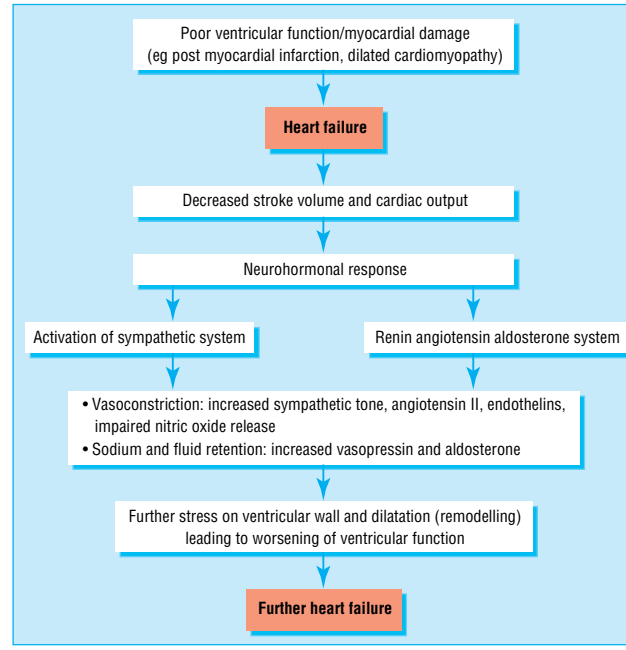
Renin-angiotensin-aldosterone system

Stimulation of the renin-angiotensin-aldosterone system leads to increased concentrations of renin, plasma angiotensin II, and aldosterone. Angiotensin II is a potent vasoconstrictor of the renal (efferent arterioles) and systemic circulation, where it stimulates release of noradrenaline from sympathetic nerve terminals, inhibits vagal tone, and promotes the release of aldosterone. This leads to the retention of sodium and water and the increased excretion of potassium. In addition, angiotensin II has important effects on cardiac myocytes and may contribute to the endothelial dysfunction that is observed in chronic heart failure.

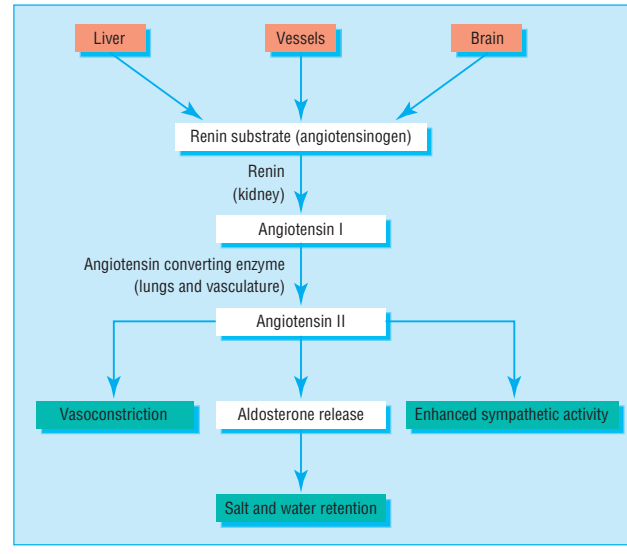
Sympathetic nervous system

The sympathetic nervous system is activated in heart failure, via low and high pressure baroreceptors, as an early compensatory mechanism which provides inotropic support and maintains cardiac output. Chronic sympathetic activation, however, has deleterious effects, causing a further deterioration in cardiac function.

The earliest increase in sympathetic activity is detected in the heart, and this seems to precede the increase in sympathetic outflow to skeletal muscle and the kidneys that is present in advanced heart failure. Sustained sympathetic stimulation activates the renin-angiotensin-aldosterone system and other neurohormones, leading to increased venous and arterial tone



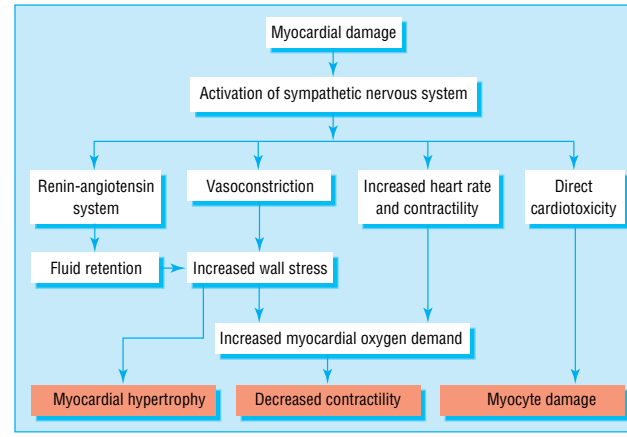
Neurohormonal mechanisms and compensatory mechanisms in heart failure



Renin-angiotensin-aldosterone axis in heart failure

(and greater preload and afterload respectively), increased plasma noradrenaline concentrations, progressive retention of salt and water, and oedema. Excessive sympathetic activity is also associated with cardiac myocyte apoptosis, hypertrophy, and focal myocardial necrosis.

In the long term, the ability of the myocardium to respond to chronic high concentrations of catecholamines is attenuated by a down regulation in β receptors, although this may be associated with baroreceptor dysfunction and a further increase in sympathetic activity. Indeed, abnormalities of baroreceptor function are well documented in chronic heart failure, along with reduced parasympathetic tone, leading to abnormal autonomic modulation of the sinus node. Moreover, a reduction in heart rate variability has consistently been observed in chronic heart failure, as a result of predominantly sympathetic and reduced vagal modulation of the sinus node, which may be a prognostic marker in patients with chronic heart failure.



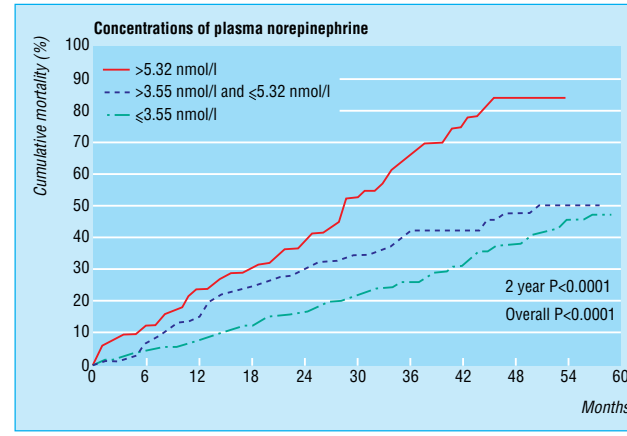
Sympathetic activation in chronic heart failure

Natriuretic peptides

There are three natriuretic peptides, of similar structure, and these exert a wide range of effects on the heart, kidneys, and central nervous system.

Atrial natriuretic peptide (ANP) is released from the atria in response to stretch, leading to natriuresis and vasodilatation. In humans, brain natriuretic peptide (BNP) is also released from the heart, predominantly from the ventricles, and its actions are similar to those of atrial natriuretic peptide. C-type natriuretic peptide is limited to the vascular endothelium and central nervous system and has only limited effects on natriuresis and vasodilatation.

The atrial and brain natriuretic peptides increase in response to volume expansion and pressure overload of the heart and act as physiological antagonists to the effects of angiotensin II on vascular tone, aldosterone secretion, and renal-tubule sodium reabsorption. As the natriuretic peptides are important mediators, with increased circulating concentrations in patients with heart failure, interest has developed in both the diagnostic and prognostic potential of these peptides. Substantial interest has been expressed about the therapeutic potential of natriuretic peptides, particularly with the development of agents that inhibit the enzyme that metabolises atrial natriuretic peptide (neutral endopeptidase), and non-peptide agonists for the A and B receptors.



Norepinephrine concentrations and prognosis in chronic heart failure

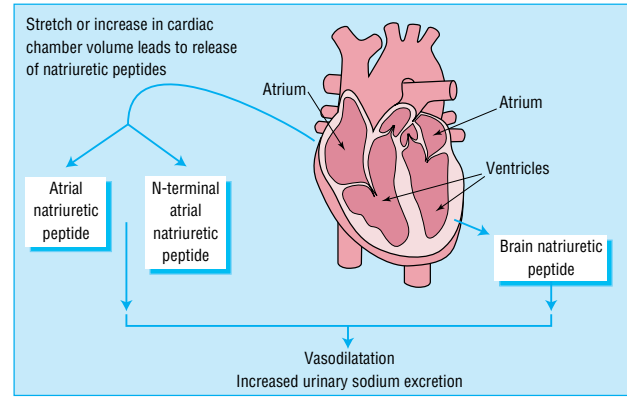
Antidiuretic hormone (vasopressin)

Antidiuretic hormone concentrations are also increased in severe chronic heart failure. High concentrations of the hormone are particularly common in patients receiving diuretic treatment, and this may contribute to the development of hyponatraemia.

Endothelins

Endothelin is secreted by vascular endothelial cells and is a potent vasoconstrictor peptide that has pronounced vasoconstrictor effects on the renal vasculature, promoting the retention of sodium. Importantly, the plasma concentration of endothelin-1 is of prognostic significance and is increased in proportion to the symptomatic and haemodynamic severity of heart failure. Endothelin concentration is also correlated with indices of severity such as the pulmonary artery capillary wedge pressure, need for admission to hospital, and death.

In view of the vasoconstrictor properties of endothelin, interest has developed in endothelin receptor antagonists as cardioprotective agents which inhibit endothelin mediated vascular and myocardial remodelling.



Effects of natriuretic peptides

Other hormonal mechanisms in chronic heart failure

- The arachidonic acid cascade leads to increased concentrations of prostaglandins (prostaglandin E_2 and prostaglandin I_2), which protect the glomerular microcirculation during renal vasoconstriction and maintain glomerular filtration by dilating afferent glomerular arterioles
- The kallikrein kinin system forms bradykinin, resulting in both natriuresis and vasodilatation, and stimulates the production of prostaglandins
- Circulating concentrations of the cytokine tumour necrosis factor (αTNF) are increased in cachectic patients with chronic heart failure. αTNF has also been implicated in the development of endothelial abnormalities in patients with chronic heart failure

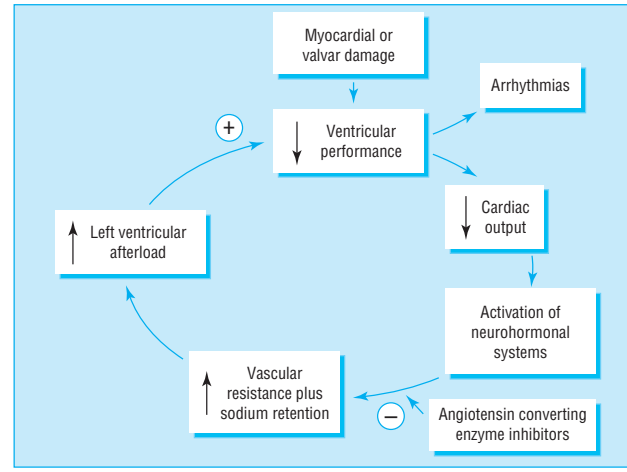
Patterns of neurohormonal activation and prognosis

Asymptomatic left ventricular dysfunction
Plasma norepinephrine concentrations increase early in the development of left ventricular dysfunction, and plasma renin activity usually increases in patients receiving diuretic treatment. Norepinephrine concentration in asymptomatic left ventricular dysfunction is a strong and independent predictor of the development of symptomatic chronic heart failure and long term mortality. Plasma concentrations of N-terminal proatrial natriuretic peptide and brain natriuretic peptide also seem to be good indicators of asymptomatic left ventricular dysfunction and may be useful in the future as an objective blood test in these patients.

Congestive heart failure
In severe untreated chronic heart failure, concentrations of renin, angiotensin II, aldosterone, noradrenaline, and atrial natriuretic peptide are all increased. Plasma concentrations of various neuroendocrine markers correlate with both the severity of heart failure and the long term prognosis. For example, raised plasma concentrations of N-terminal and C-terminal atrial natriuretic peptide and of brain natriuretic peptide are independent predictors of mortality in patients with chronic heart failure. Patients with congestive heart failure and raised plasma noradrenaline concentrations also have a worse prognosis.

After myocardial infarction

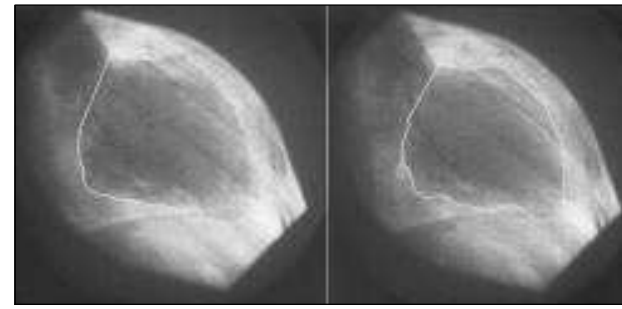
- Plasma noradrenaline is of prognostic value in patients early after myocardial infarction, predicting subsequent changes in left ventricular volume
- Natriuretic peptides have also been shown to predict outcome after myocardial infarction, although it is not clear whether the predictive value is additive to measurements of ventricular function



Effect of angiotensin converting enzyme inhibitors in heart failure

Other non-cardiac abnormalities in chronic heart failure

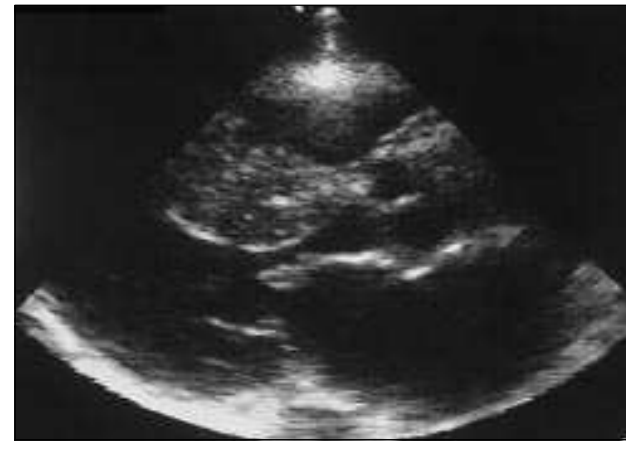
Vasculature
The vascular endothelium has an important role in the regulation of vascular tone, releasing relaxing and contracting factors under basal conditions or during exercise. The increased peripheral resistance in patients with chronic heart failure is related to the alterations in autonomic control, including heightened sympathetic tone, activation of the renin-angiotensin-aldosterone system, increased endothelin concentrations, and impaired release of endothelium derived relaxing factor (or nitric oxide). There is emerging evidence that impaired endothelial function in chronic heart failure may be improved with exercise training and drug treatment, such as angiotensin converting enzyme inhibitors.


Contrast left ventriculogram in patient with poor systolic function (diastolic (left) and systolic (right) views)

Skeletal muscle changes
Considerable peripheral changes occur in the skeletal muscle of patients with chronic heart failure. These include a reduction in muscle mass and abnormalities in muscle structure, metabolism, and function. There is also reduced blood flow to active skeletal muscle, which is related to vasoconstriction and the loss in muscle mass. All these abnormalities in skeletal muscles, including respiratory muscles, contribute to the symptoms of fatigue, lethargy, and exercise intolerance that occur in chronic heart failure.

Diastolic dysfunction

Diastolic dysfunction results from impaired myocardial relaxation, with increased stiffness in the ventricular wall and reduced left ventricular compliance, leading to impairment of diastolic ventricular filling. Infiltrations, such as amyloid heart disease, are the best examples, although coronary artery


Two dimensional echocardiogram in patient with hypertrophic cardiomyopathy showing asymmetrical septal hypertrophy

disease, hypertension (with left ventricular hypertrophy), and hypertrophic cardiomyopathy are more common causes.

The incidence and contribution of diastolic dysfunction remains controversial, although it has been estimated that 30-40% of patients with heart failure have normal ventricular systolic contraction. Indices of diastolic dysfunction can be obtained non-invasively with Doppler echocardiography or invasively with cardiac catheterisation and measurement of left ventricular pressure changes. There is no agreement as to the most accurate index of left ventricular diastolic dysfunction, but the Doppler mitral inflow velocity profile is probably the most widely used.

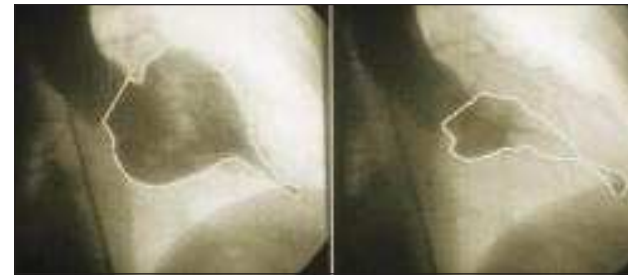
Although pure forms exist, in most patients with heart failure both systolic and diastolic dysfunction can be present. Knowing about diastolic dysfunction, however, has little effect on management of most patients with chronic heart failure, as there are still many uncertainties over its measurement and optimal management strategies.

Myocardial remodelling, hibernation, and stunning

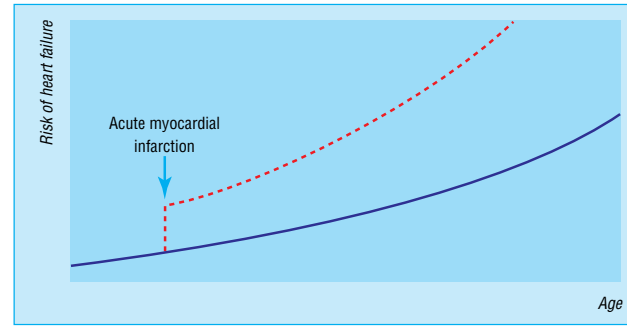
After extensive myocardial infarction, cardiac contractility is frequently impaired and neurohormonal activation leads to regional eccentric and concentric hypertrophy of the non-infarcted segment, with expansion (regional thinning and dilatation) of the infarct zone. This is known as remodelling. Particular risk factors for this development of progressive ventricular dilatation after a myocardial infarction include a large infarct, anterior infarctions, occlusion (or non-reperfusion) of the artery related to the infarct, and hypertension.

Myocardial dysfunction may also occur in response to "stunning" (postischaemic dysfunction), which describes delayed recovery of myocardial function despite restoration of coronary blood flow, in the absence of irreversible damage. This is in contrast to "hibernating" myocardium, which describes persistent myocardial dysfunction at rest, secondary to reduced myocardial perfusion, although cardiac myocytes remain viable and myocardial contraction may improve with revascularisation.

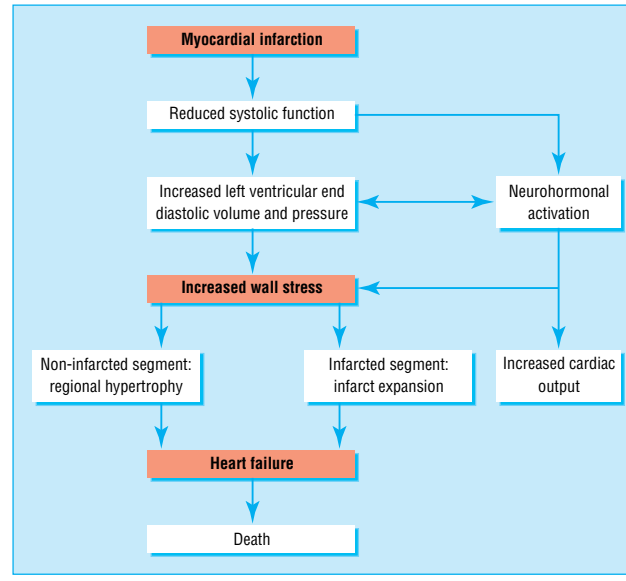
When stunning or hibernation occurs, viable myocardium retains responsiveness to inotropic stimulation, which can then be identified by resting and stress echocardiography, thallium scintigraphy and positron emission tomography. Revascularisation may improve the overall left ventricular function with potential beneficial effects on symptoms and prognosis.



Contrast left ventriculogram in patient with hypertrophic cardiomyopathy (diastolic (left) and systolic (right) views)



Risk of heart failure and relation with age and history of myocardial infarction



Process of ventricular remodelling

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The graph showing mortality curves is adapted from Cohn et al (*N Engl J Med* 1984;311:819-23); the diagram of the process of ventricular remodelling is adapted from McKay et al (*Circulation* 1986;74:693-702).

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The ABC of heart failure is edited by C R Gibbs, M K Davies, and G Y H Lip. CRG is research fellow and GYHL is consultant cardiologist and reader in medicine in the university department of medicine and the department of cardiology, City Hospital, Birmingham; MKD is consultant cardiologist in the department of cardiology, Selly Oak Hospital, Birmingham. The series will be published as a book in the spring.

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Clinical features and complications

R D S Watson, C R Gibbs, G Y H Lip

Clinical features

Patients with heart failure present with a variety of symptoms, most of which are non-specific. The common symptoms of congestive heart failure include fatigue, dyspnoea, swollen ankles, and exercise intolerance, or symptoms that relate to the underlying cause. The accuracy of diagnosis by presenting clinical features alone, however, is often inadequate, particularly in women and elderly or obese patients.

Symptoms

Dyspnoea

Exertional breathlessness is a frequent presenting symptom in heart failure, although it is a common symptom in the general population, particularly in patients with pulmonary disease. Dyspnoea is therefore moderately sensitive, but poorly specific, for the presence of heart failure. Orthopnoea is a more specific symptom, although it has a low sensitivity and therefore has little predictive value. Paroxysmal nocturnal dyspnoea results from increased left ventricular filling pressures (due to nocturnal fluid redistribution and enhanced renal reabsorption) and therefore has a greater sensitivity and predictive value. Nocturnal ischaemic chest pain may also be a manifestation of heart failure, so left ventricular systolic dysfunction should be excluded in patients with recurrent nocturnal angina.

Fatigue and lethargy

Fatigue and lethargy in chronic heart failure are, in part, related to abnormalities in skeletal muscle, with premature muscle lactate release, impaired muscle blood flow, deficient endothelial function, and abnormalities in skeletal muscle structure and function. Reduced cerebral blood flow, when accompanied by abnormal sleep patterns, may occasionally lead to somnolence and confusion in severe chronic heart failure.

Oedema

Swelling of ankles and feet is another common presenting feature, although there are numerous non-cardiac causes of this symptom. Right heart failure may manifest as oedema, right hypochondrial pain (liver distension), abdominal swelling (ascites), loss of appetite, and, rarely, malabsorption (bowel oedema). An increase in weight may be associated with fluid retention, although cardiac cachexia and weight loss are important markers of disease severity in some patients.

Physical signs

Physical examination has serious limitations as many patients, particularly those with less severe heart failure, have few abnormal signs. In addition, some physical signs are difficult to interpret and, if present, may occasionally be related to causes other than heart failure.

Oedema and a tachycardia, for example, are too insensitive to have any useful predictive value, and although pulmonary crepitations may have a high diagnostic specificity they have a low sensitivity and predictive value. Indeed, the commonest cause of lower limb oedema in elderly people is immobility, and pulmonary crepitations may reflect poor ventilation with infection, or pulmonary fibrosis, rather than heart failure. Jugular venous distension has a high specificity in diagnosing

Symptoms and signs in heart failure

Symptoms
Dyspnoea
Orthopnoea
Paroxysmal nocturnal dyspnoea
Reduced exercise tolerance, lethargy, fatigue
Nocturnal cough
Wheeze
Ankle swelling
Anorexia

Signs
Cachexia and muscle wasting
Tachycardia
Pulsus alternans
Elevated jugular venous pressure
Displaced apex beat
Right ventricular heave
Crepitations or wheeze
Third heart sound
Oedema
Hepatomegaly (tender)
Ascites

Common causes of lower limb oedema

- Gravitational disorder—for example, immobility
- Congestive heart failure
- Venous thrombosis or obstruction, varicose veins
- Hypoproteinaemia—for example, nephrotic syndrome, liver disease
- Lymphatic obstruction

Sensitivity, specificity, and predictive value of symptoms, signs, and chest *x* ray findings for presence of heart failure (ejection fraction <40%) in 1306 patients with coronary artery disease undergoing cardiac catheterisation

Clinical features	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
History:			
Shortness of breath	66	52	23
Orthopnoea	21	81	2
Paroxysmal nocturnal dyspnoea	33	76	26
History of oedema	23	80	22
Examination:			
Tachycardia (>100 beats/min)	7	99	6
Crepitations	13	91	27
Oedema (on examination)	10	93	3
Gallop (S3)	31	95	61
Neck vein distension	10	97	2
Chest *x* ray examination:			
Cardiomegaly	62	67	32

heart failure in patients who are known to have cardiac disease, although some patients, even with documented heart failure, do not have an elevated venous pressure. The presence of a displaced apex beat in a patient with a history of myocardial infarction has a high positive predictive value. A third heart sound has a relatively high specificity, although its universal value is limited by a high interobserver variability, with interobserver agreement of less than 50% in non-specialists.

In patients with pre-existing chronic heart failure, other clinical features may be evident that point towards precipitating causes of acute heart failure or deteriorating heart failure. Common factors that may be obvious on clinical assessment and are associated with relapses in congestive heart failure include infections, arrhythmias, continued or recurrent myocardial ischaemia, and anaemia.

Clinical diagnosis and clinical scoring systems

Several epidemiological studies, including the Framingham heart study, have used clinical scoring systems to define heart failure, although the use of these systems is not recommended for routine clinical practice.

In a patient with appropriate symptoms and a number of physical signs, including a displaced apex beat, elevated venous pressure, oedema, and a third heart sound, the clinical diagnosis of heart failure may be made with some confidence. However, the clinical suspicion of heart failure should also be confirmed with objective investigations and the demonstration of cardiac dysfunction at rest. It is important to note that, in some patients, exercise-induced myocardial ischaemia may lead to a rise in ventricular filling pressures and a fall in cardiac output, leading to symptoms of heart failure during exertion.

Classification

Symptoms and exercise capacity are used to classify the severity of heart failure and monitor the response to treatment. The classification of the New York Heart Association (NYHA) is used widely, although outcome in heart failure is best determined not only by symptoms (NYHA class) but also by echocardiographic criteria. As the disease is progressive, the importance of early treatment, in an attempt to prevent progression to more severe disease, cannot be overemphasised.

Complications

Arrhythmias

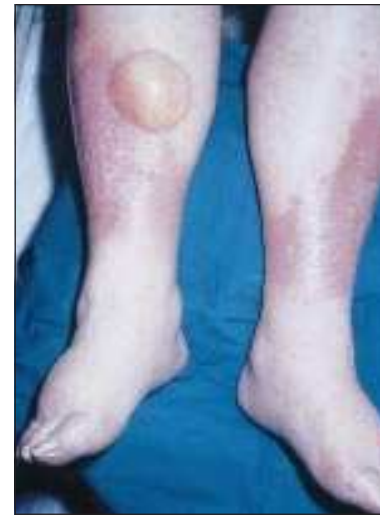
Atrial fibrillation

Atrial fibrillation is present in about a third (range 10-50%) of patients with chronic heart failure and may represent either a cause or a consequence of heart failure. The onset of atrial fibrillation with a rapid ventricular response may precipitate overt heart failure, particularly in patients with pre-existing ventricular dysfunction. Predisposing causes should be considered, including mitral valve disease, thyrotoxicosis, and sinus node disease. Importantly, sinus node disease may be associated with bradycardias, which might be exacerbated by antiarrhythmic treatment.

Atrial fibrillation that occurs with severe left ventricular dysfunction following myocardial infarction is associated with a poor prognosis. In addition, patients with heart failure and atrial fibrillation are at particularly high risk of stroke and other thromboembolic complications.

Ventricular arrhythmias

Malignant ventricular arrhythmias are common in end stage heart failure. For example, sustained monomorphic ventricular



Gross oedema of ankles, including bullae with serous exudate

Precipitating causes of heart failure

- Arrhythmias, especially atrial fibrillation
- Infections (especially pneumonia)
- Acute myocardial infarction
- Angina pectoris or recurrent myocardial ischaemia
- Anaemia
- Alcohol excess
- Iatrogenic cause—for example, postoperative fluid replacement or administration of steroids or non-steroidal anti-inflammatory drugs
- Poor drug compliance, especially in antihypertensive treatment
- Thyroid disorders—for example, thyrotoxicosis
- Pulmonary embolism
- Pregnancy

European Society of Cardiology's guidelines for diagnosis of heart failure

Essential features

Symptoms of heart failure (for example, breathlessness, fatigue, ankle swelling)

and

Objective evidence of cardiac dysfunction (at rest)

Non-essential features

Response to treatment directed towards heart failure (in cases where the diagnosis is in doubt)

NYHA classification of heart failure

Class I: asymptomatic

No limitation in physical activity despite presence of heart disease. This can be suspected only if there is a history of heart disease which is confirmed by investigations—for example, echocardiography

Class II: mild

Slight limitation in physical activity. More strenuous activity causes shortness of breath—for example, walking on steep inclines and several flights of steps. Patients in this group can continue to have an almost normal lifestyle and employment

Class III: moderate

More marked limitation of activity which interferes with work. Walking on the flat produces symptoms

Class IV: severe

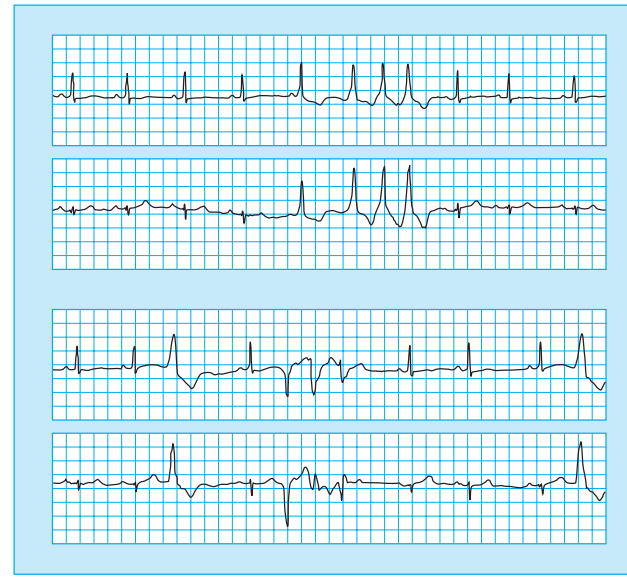
Unable to carry out any physical activity without symptoms. Patients are breathless at rest and mostly housebound

tachycardia occurs in up to 10% of patients with advanced heart failure who are referred for cardiac transplantation. In patients with ischaemic heart disease these arrhythmias often have re-entrant mechanisms in scarred myocardial tissue. An episode of sustained ventricular tachycardia indicates a high risk for recurrent ventricular arrhythmias and sudden cardiac death.

Sustained polymorphic ventricular tachycardia and torsades de pointes are more likely to occur in the presence of precipitating or aggravating factors, including electrolyte disturbance (for example, hypokalaemia or hyperkalaemia, hypomagnesaemia), prolonged QT interval, digoxin toxicity, drugs causing electrical instability (for example, antiarrhythmic drugs, antidepressants), and continued or recurrent myocardial ischaemia. β Blockers are useful for treating arrhythmias, and these agents (for example, bisoprolol, metoprolol, carvedilol) are likely to be increasingly used as a treatment option in patients with heart failure.

Predisposing factors for ventricular arrhythmias

- Recurrent or continued coronary ischaemia
- Recurrent myocardial infarction
- Hypokalaemia and hyperkalaemia
- Hypomagnesaemia
- Psychotropic drugs—for example, tricyclic antidepressants
- Digoxin (leading to toxicity)
- Antiarrhythmic drugs that may be cardiodepressant (negative inotropism) and proarrhythmic



24 Hour Holter tracing showing frequent ventricular extrasystoles

Stroke and thromboembolism

Congestive heart failure predisposes to stroke and thromboembolism, with an overall estimated annual incidence of approximately 2%. Factors contributing to the increased thromboembolic risk in patients with heart failure include low cardiac output (with relative stasis of blood in dilated cardiac chambers), regional wall motion abnormalities (including formation of a left ventricular aneurysm), and associated atrial fibrillation. Although the prevalence of atrial fibrillation in some of the earlier observational studies was between 12% and 36%—which may have accounted for some of the thromboembolic events—patients with chronic heart failure who remain in sinus rhythm are also at an increased risk of stroke and venous thromboembolism. Patients with heart failure and chronic venous insufficiency may also be immobile, and this contributes to their increased risk of thrombosis, including deep venous thrombosis and pulmonary embolism.

Recent observational data from the studies of left ventricular dysfunction (SOLVD) and vasodilator heart failure trials (V-HeFT) indicate that mild to moderate heart failure is associated with an annual risk of stroke of about 1.5% (compared with a risk of less than 0.5% in those without heart failure), rising to 4% in patients with severe heart failure. In addition, the survival and ventricular enlargement (SAVE) study recently reported an inverse relation between risk of stroke and left ventricular ejection fraction, with an 18% increase in risk for every 5% reduction in left ventricular ejection fraction; this clearly relates thromboembolism to severe cardiac impairment and the severity of heart failure. As thromboembolic risk seems to be related to left atrial and left ventricular dilatation, echocardiography may have some role in the risk stratification of thromboembolism in patients with chronic heart failure.

Complications of heart failure

Arrhythmias—Atrial fibrillation; ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation); bradyarrhythmias
Thromboembolism—Stroke; peripheral embolism; deep venous thrombosis; pulmonary embolism
Gastrointestinal—Hepatic congestion and hepatic dysfunction; malabsorption
Musculoskeletal—Muscle wasting
Respiratory—Pulmonary congestion; respiratory muscle weakness; pulmonary hypertension (rare)

Prognosis

Most long term (more than 10 years of follow up) longitudinal studies of heart failure, including the Framingham heart study (1971), were performed before the widespread use of angiotensin converting enzyme inhibitors. In the Framingham study the overall survival at eight years for all NYHA classes was 30%, compared with a one year mortality in classes III and IV of 34% and a one year mortality in class IV of over 60%. The prognosis in patients whose left ventricular dysfunction is asymptomatic is better than that in those whose left ventricular dysfunction is symptomatic. The prognosis in patients with congestive heart failure is dependent on severity, age, and sex, with a poorer prognosis in male patients. In addition, numerous prognostic indices are associated with an adverse prognosis,

Morbidity and mortality for all grades of symptomatic chronic heart failure are high, with a 20-30% one year mortality in mild to moderate heart failure and a greater than 50% one year mortality in severe heart failure. These prognostic data refer to patients with systolic heart failure, as the natural course of diastolic dysfunction is less well defined

including NYHA class, left ventricular ejection fraction, and neurohormonal status.

Survival can be prolonged in chronic heart failure that results from systolic dysfunction if angiotensin converting enzyme inhibitors are given. Longitudinal data from the Framingham study and the Mayo Clinic suggest, however, that there is still only a limited improvement in the one year survival rate of patients with newly diagnosed symptomatic chronic heart failure, which remains at 60-70%. In these studies only a minority of patients with congestive heart failure were appropriately treated, with less than 25% of them receiving angiotensin converting enzyme inhibitors, and even among treated patients the dose used was much lower than doses used in the clinical trials.

Some predictors of poor outcome in chronic heart failure

- High NYHA functional class
- Reduced left ventricular ejection fraction
- Low peak oxygen consumption with maximal exercise (% predicted value)
- Third heart sound
- Increased pulmonary artery capillary wedge pressure
- Reduced cardiac index
- Diabetes mellitus
- Reduced sodium concentration
- Raised plasma catecholamine and natriuretic peptide concentrations

Cardiac mortality in placebo controlled heart failure trials

Trial	Patients' characteristics	Ischaemic heart disease (%)	Treatment	Cardiovascular mortality		Follow up (years)
				Treatment (%)	Placebo (%)	
CONSENSUS	NYHA IV (cardiomegaly)	73	Enalapril	38	54	1
SOLVD-P	Asymptomatic (EF <35%)	83	Enalapril	13	14	4
SOLVD-T	Symptomatic (EF <35%)	71	Enalapril	31	36	4
SAVE	Postmyocardial infarction (EF <40%)	100	Captopril	17	21	4
V-HeFT I	NYHA II-III (EF <45%)	44	H-ISDN	37	41	5
V-HeFT II	NYHA II-III (EF <45%)	52	Enalapril	28	34*	5
PRAISE	NYHA III-IV (EF <30%)	63	Amlodipine	28	33	1.2

EF ejection fraction. SOLVD-P, SOLVD-T = studies of left ventricular dysfunction prevention arm (P) and treatment arm (T).
H-ISDN = hydralazine and isosorbide dinitrate.
*Treatment with H-ISDN.

Treatment with angiotensin converting enzyme inhibitors prevents or delays the onset of symptomatic heart failure in patients with asymptomatic, or minimally symptomatic, left ventricular systolic dysfunction. The increase in mortality with the development of symptoms suggests that the optimal time for intervention with these agents is well before the onset of substantial left ventricular dysfunction, even in the absence of overt clinical symptoms of heart failure. This benefit has been confirmed in several large, well conducted, postmyocardial infarction studies.

Sudden death

The mode of death in heart failure has been extensively investigated, and progressive heart failure and sudden death seem to occur with equal frequency. Some outstanding questions still remain, however. Although arrhythmias are common in patients with heart failure and are indicators of disease severity, they are not powerful independent predictors of prognosis. Sudden death may be related to ventricular arrhythmias, although asystole is a common terminal event in severe heart failure. It has not been firmly established whether these arrhythmias are primary arrhythmias or whether some are secondary to acute coronary ischaemia or indicate in situ coronary thrombosis. The cause of death is often uncertain, especially as the patient may die of a cardiac arrest outside hospital or while asleep.

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The table on the sensitivity, specificity, and predictive value of symptoms, signs, and chest *x* ray findings is adapted with permission from Harlan et al (*Ann Intern Med* 1977;86:133-8).

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Investigation

M K Davies, C R Gibbs, G Y H Lip

Clinical assessment is mandatory before detailed investigations are conducted in patients with suspected heart failure, although specific clinical features are often absent and the condition can be diagnosed accurately only in conjunction with more objective investigation, particularly echocardiography. Although open access echocardiography is now increasingly available, appropriate pre-referral investigations include chest radiography, 12 lead electrocardiography, and renal chemistry.

Investigations if heart failure is suspected

Initial investigations
- Chest radiography
- Electrocardiography
- Echocardiography, including Doppler studies
- Haematology tests
- Serum biochemistry, including renal function and glucose concentrations, liver function tests, and thyroid function tests
- Cardiac enzymes (if recent infarction is suspected)

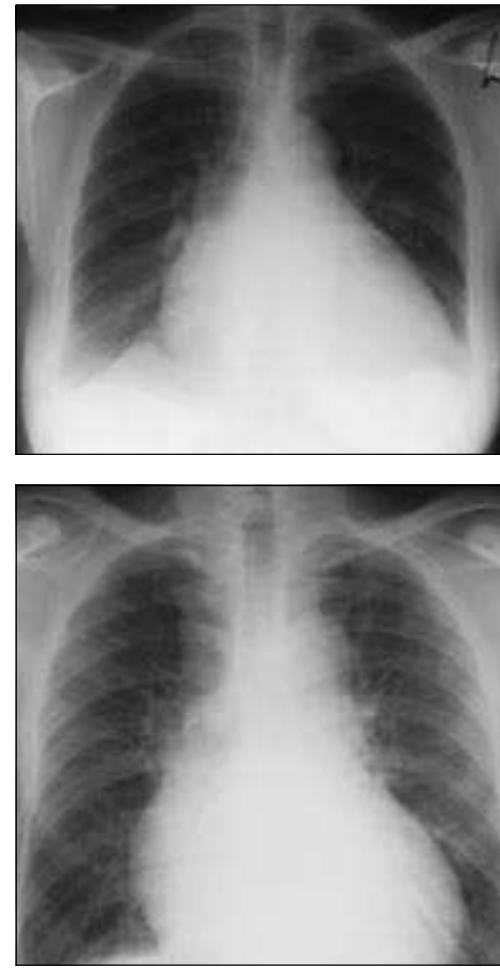
Other investigations
- Radionuclide imaging
- Cardiopulmonary exercise testing
- Cardiac catheterisation
- Myocardial biopsy—for example, in suspected myocarditis

Chest *x* ray examination

The chest *x* ray examination has an important role in the routine investigation of patients with suspected heart failure, and it may also be useful in monitoring the response to treatment. Cardiac enlargement (cardiothoracic ratio >50%) may be present, but there is a poor correlation between the cardiothoracic ratio and left ventricular function. The presence of cardiomegaly is dependent on both the severity of haemodynamic disturbance and its duration: cardiomegaly is frequently absent, for example, in acute left ventricular failure secondary to acute myocardial infarction, acute valvar regurgitation, or an acquired ventricular septal defect. An increased cardiothoracic ratio may be related to left or right ventricular dilatation, left ventricular hypertrophy, and occasionally a pericardial effusion, particularly if the cardiac silhouette has a globular appearance. Echocardiography is required to distinguish reliably between these different causes, although in decompensated heart failure other radiographic features may be present, such as pulmonary congestion or pulmonary oedema.

In left sided failure, pulmonary venous congestion occurs, initially in the upper zones (referred to as upper lobe diversion or congestion). When the pulmonary venous pressure increases further, usually above 20 mm Hg, fluid may be present in the horizontal fissure and Kerley B lines in the costophrenic angles. In the presence of pulmonary venous pressures above 25 mm Hg, frank pulmonary oedema occurs, with a "bats wing" appearance in the lungs, although this is also dependent on the rate at which the pulmonary oedema has developed. In addition, pleural effusions occur, normally bilaterally, but if they are unilateral the right side is more commonly affected. Nevertheless, it is not possible to distinguish, when viewed in isolation, whether pulmonary congestion is related to cardiac or non-cardiac causes (for example, renal disease, drugs, the respiratory distress syndrome).

Rarely, chest radiography may also show valvar calcification, a left ventricular aneurysm, and the typical pericardial calcification of constrictive pericarditis. Chest radiography may also provide valuable information about non-cardiac causes of dyspnoea.



Chest radiographs showing gross cardiomegaly in patient with dilated cardiomyopathy (top); cardiomegaly and pulmonary congestion with fluid in horizontal fissure (bottom)

12 lead electrocardiography

The 12 lead electrocardiographic tracing is abnormal in most patients with heart failure, although it can be normal in up to 10% of cases. Common abnormalities include Q waves, abnormalities in the T wave and ST segment, left ventricular hypertrophy, bundle branch block, and atrial fibrillation. It is a

useful screening test as a normal electrocardiographic tracing makes it unlikely that the patient has heart failure secondary to left ventricular systolic dysfunction, since this test has high sensitivity and a negative predictive value. The combination of a normal chest *x* ray finding and a normal electrocardiographic tracing makes a cardiac cause of dyspnoea very unlikely.

In patients with symptoms (palpitations or dizziness), 24 hour electrocardiographic (Holter) monitoring or a Cardiomemo device will detect paroxysmal arrhythmias or other abnormalities, such as ventricular extrasystoles, sustained or non-sustained ventricular tachycardia, and abnormal atrial rhythms (extrasystoles, supraventricular tachycardia, and paroxysmal atrial fibrillation). Many patients with heart failure, however, show complex ventricular extrasystoles on 24 hour monitoring.

Echocardiography

Echocardiography is the single most useful non-invasive test in the assessment of left ventricular function; ideally it should be conducted in all patients with suspected heart failure. Although clinical assessment, when combined with a chest *x* ray examination and electrocardiography, allows a preliminary diagnosis of heart failure, echocardiography provides an objective assessment of cardiac structure and function. Left ventricular dilatation and impairment of contraction is observed in patients with systolic dysfunction related to ischaemic heart disease (where a regional wall motion abnormality may be detected) or in dilated cardiomyopathy (with global impairment of systolic contraction).

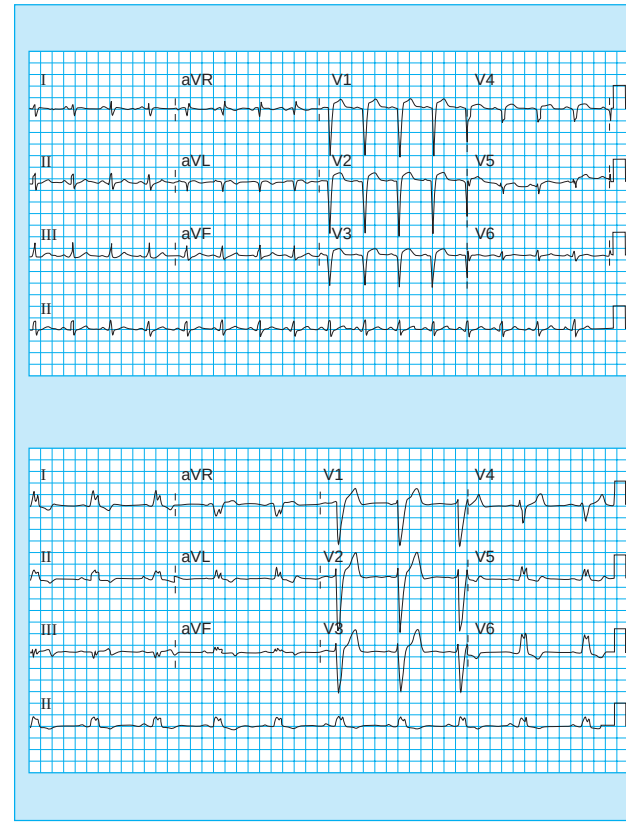
A quantitative measurement can be obtained from calculation of the left ventricular ejection fraction. This is the stroke volume (the difference between the end diastolic and end systolic volumes) expressed as a percentage of the left ventricular end diastolic volume. Measurements, and the assessment of left ventricular function, are less reliable in the presence of atrial fibrillation. The left ventricular ejection fraction has been correlated with outcome and survival in patients with heart failure, although the assessment may be unreliable in patients with regional abnormalities in wall motion. Regional abnormalities can also be quantified into a wall motion index, although in practice the assessment of systolic function is often based on visual assessment and the observer's experience of normal and abnormal contractile function. These abnormalities are described as hypokinetic (reduced systolic contraction), akinetic (no systolic contraction) and dyskinetic (abnormalities of direction or timing of contraction, or both), and refer to universally recognised segments of the left ventricle. Echocardiography may also show other abnormalities, including valvar disease, left ventricular aneurysm, intracardiac thrombus, and pericardial disease.

Mitral incompetence is commonly identified on echocardiography in patients with heart failure, as a result of ventricular and annular dilatation ("functional" mitral incompetence), and this must be distinguished from mitral incompetence related to primary valve disease. Two dimensional echocardiography allows the assessment of valve structure and identifies thickening of cusps, leaflet prolapse, cusp fusion, and calcification. Doppler echocardiography allows the quantitative assessment of flow across valves and the identification of valve stenosis, in addition to the assessment of right ventricular systolic pressures and allowing the indirect diagnosis of pulmonary hypertension. Doppler studies have been used in the assessment of diastolic function, although there is no single reliable echocardiographic measure of diastolic dysfunction. Colour flow Doppler techniques are

Value of electrocardiography* in identifying heart failure resulting from left ventricular systolic dysfunction

Sensitivity	94%
Specificity	61%
Positive predictive value	35%
Negative predictive value	98%

*Electrocardiographic abnormalities are defined as atrial fibrillation, evidence of previous myocardial infarction, left ventricular hypertrophy, bundle branch block, and left axis deviation.



Electrocardiograms showing previous anterior myocardial infarction with Q waves in anteroseptal leads (top) and left bundle branch block (bottom)

Who should have an echocardiogram?

- Almost all patients with symptoms or signs of heart failure
- Symptoms of breathlessness in association with signs of a murmur
- Dyspnoea associated with atrial fibrillation
- Patients at "high risk" for left ventricular dysfunction—for example, those with anterior myocardial infarction, poorly controlled hypertension, or arrhythmias

Echocardiography as a guide to management

- Identification of impaired systolic function for decision on treatment with angiotensin converting enzyme inhibitors
- Identification of diastolic dysfunction or predominantly right ventricular dysfunction
- Identification and assessment of valvar disease
- Assessment of embolic risk (severe left ventricular impairment with mural thrombus)

particularly sensitive in detecting the direction of blood flow and the presence of valve incompetence.

Advances in echocardiography include the use of contrast agents for visualisation of the walls of the left ventricle in more detail, especially as in about 10% of patients satisfactory images cannot be obtained with standard transthoracic echocardiography. Transoesophageal echocardiography allows the detailed assessment of the atria, valves, pulmonary veins, and any cardiac masses, including thrombi.

The logistic and health economic aspects of large scale screening with echocardiography have been debated, but the development of open access echocardiography heart failure services for general practitioners and the availability of proved treatments for heart failure that improve prognosis, such as angiotensin converting enzyme inhibitors, highlight the importance of an agreed strategy for the echocardiographic assessment of these patients.

Haematology and biochemistry

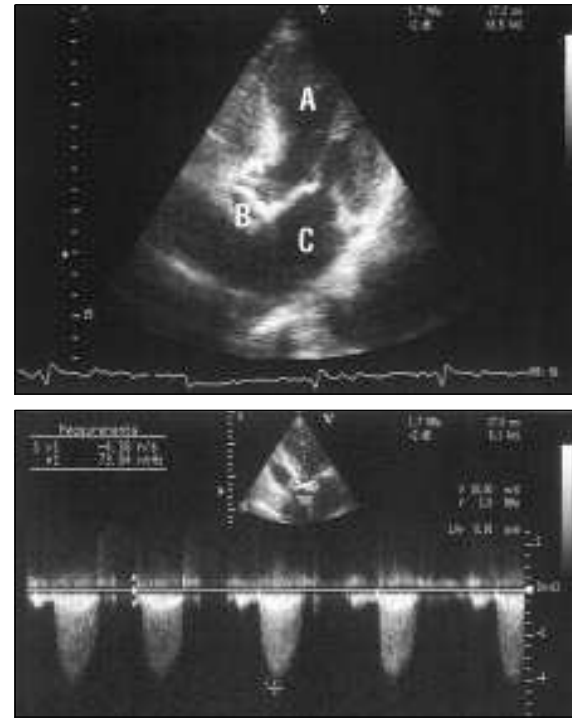
Routine haematology and biochemistry investigations are recommended to exclude anaemia as a cause of breathlessness and high output heart failure and to exclude important pre-existing metabolic abnormalities. In mild and moderate heart failure, renal function and electrolytes are usually normal. In severe (New York Heart Association, class IV) heart failure, however, as a result of reduced renal perfusion, high dose diuretics, sodium restriction, and activation of the neurohormonal mechanisms (including vasopressin), there is an inability to excrete water, and dilutional hyponatraemia may be present. Hyponatraemia is, therefore, a marker of the severity of chronic heart failure.

A baseline assessment of renal function is important before starting treatment, as the renal blood flow and the glomerular filtration rate fall in severe congestive heart failure. Baseline serum creatinine concentrations are important: increasing creatinine concentrations may occur after the start of treatment, particularly in patients who are receiving angiotensin converting enzyme inhibitors and high doses of diuretics and in patients with renal artery stenosis. Proteinuria is a common finding in severe congestive heart failure.

Hypokalaemia occurs when high dose diuretics are used without potassium supplementation or potassium sparing agents. Hyperkalaemia can also occur in severe congestive heart failure with a low glomerular filtration rate, particularly with the concurrent use of angiotensin converting enzyme inhibitors and potassium sparing diuretics. Both hypokalaemia and hyperkalaemia increase the risk of cardiac arrhythmias; hypomagnesaemia, which is associated with long term diuretic treatment, increases the risk of ventricular arrhythmias. Liver function tests (serum bilirubin, aspartate aminotransferase, and lactate dehydrogenase) are often abnormal in advanced congestive heart failure, as a result of hepatic congestion. Thyroid function tests are also recommended in all patients, in view of the association between thyroid disease and the heart.

Radionuclide methods

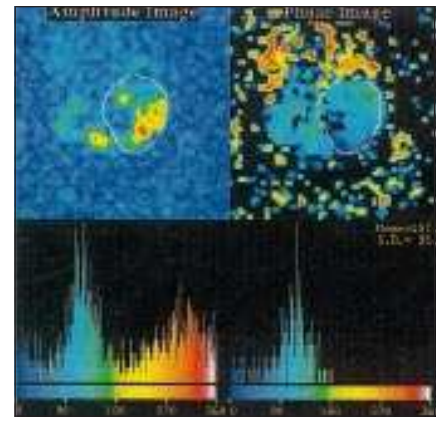
Radionuclide imaging—or multigated ventriculography—allows the assessment of the global left and right ventricular function. Images may be obtained in patients where echocardiography is not possible. The most common method labels red cells with technetium-99m and acquires 16 or 32 frames per heart beat by synchronising ("gating") imaging with electrocardiography. This allows the assessment of ejection fraction, systolic filling rate, diastolic emptying rate, and wall motion abnormalities. These



Transthoracic echocardiograms: two dimensional apical view (top) and Doppler studies (bottom) showing severe calcific stenosis, with an estimated aortic gradient of over 70 mm Hg (A=left ventricle, B=aortic valve, and C=left atrium)

Natriuretic peptides

- Biochemical markers are being sought for the diagnosis of congestive heart failure
- Brain natriuretic peptide concentrations correlate with the severity of heart failure and prognosis
- These could, in the future, be used to distinguish between patients in whom heart failure is extremely unlikely and those in whom the probability of heart failure is high
- At present, however, the evidence that blood natriuretic peptide concentrations are valuable in identifying important left ventricular systolic dysfunction is conflicting, and their use in routine practice is still limited
- Further studies are necessary to determine the most convenient and cost effective methods of identifying patients with heart failure and asymptomatic left ventricular dysfunction



Multigated ventriculography scan in patient with history of extensive myocardial infarction and coronary bypass grafting (left ventricular ejection fraction of 30%)

variables can be assessed, if necessary, during rest and exercise; this method is ideal for the serial reassessment of ejection fraction, but these methods do expose the patient to radiation.

Radionuclide studies are also valuable for assessing myocardial perfusion and the presence or extent of coronary ischaemia, including myocardial stunning and hibernating myocardium.

Stress studies use graded physical exercise or pharmacological stress with agents such as adenosine, dipyridamole, and dobutamine. Stress echocardiography is emerging as a useful technique for assessing myocardial reversibility in patients with coronary artery disease

Angiography, cardiac catheterisation, and myocardial biopsy

Coronary angiography is essential for accurate assessment of the coronary arteries

Angiography should be considered in patients with recurrent ischaemic chest pain associated with heart failure and in those with evidence of severe reversible ischaemia or hibernating myocardium. Cardiac catheterisation with myocardial biopsy can be valuable in more difficult cases where there is diagnostic doubt—for example, in restrictive and infiltrating cardiomyopathies (amyloid heart disease, sarcoidosis), myocarditis, and pericardial disease. Left ventricular angiography can show global or segmental impairment of function and assess end diastolic pressures, and right heart catheterisation allows an assessment of the right sided pressures (right atrium, right ventricle, and pulmonary arteries) and pulmonary artery capillary wedge pressure, in addition to oxygen saturations.

Pulmonary function tests

Objective measurement of lung function is useful in excluding respiratory causes of breathlessness, although respiratory and cardiac disease commonly coexist. Peak expiratory flow rate and forced expiratory volume in one second are reduced in heart failure, although not as much as in severe chronic obstructive pulmonary disease. In patients with severe breathlessness and wheeze, a peak expiratory flow rate of <200 l/min suggests reversible airways disease, not acute left ventricular failure.

Cardiopulmonary exercise testing

- Exercise tolerance is reduced in patients with heart failure, regardless of method of assessment
- Assessment methods include a treadmill test, cycle ergometry, a 6 minute walking test, or pedometry measurements
- Exercise testing is not routinely performed for all patients with congestive heart failure, but it may be valuable in identifying substantial residual ischaemia, thus leading to more detailed investigation
- Respiratory physiological measurements may be made during exercise, and most cardiac transplant centres use data obtained at cardiopulmonary exercise testing to aid the selection of patients for transplantation
- The maximum oxygen consumption is the value at which consumption remains stable despite increasing exercise, and it represents the upper limit of aerobic exercise tolerance
- The maximum oxygen consumption and the carbon dioxide production correlate well with the severity of heart failure
- The maximum oxygen consumption has also been independently related to long term prognosis, especially in patients with severe left ventricular dysfunction

Assessments for the investigation and diagnosis of heart failure

Assessments	Diagnosis of heart failure: Necessary	Supports	Opposes	Suggests alternative or additional disease
Symptoms of heart failure	++		++ (if absent)	
Signs of heart failure		++	+ (if absent)	
Response to treatment		++	++ (if absent)	
Electrocardiography			++ (if normal)	
Chest radiography (cardiomegaly or congestion)		++	+ (if normal)	Pulmonary
Echocardiography (cardiac dysfunction)	++		++ (if absent)	
Haematology				Anaemia
Biochemistry (renal, liver function, and thyroid function tests)				Renal, liver, thyroid
Urine analysis				Renal
Pulmonary function tests				Pulmonary

++ = Great importance; + = some importance.

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The table showing the value of electrocardiography is adapted from Davie et al (*BMJ* 1996;312:222). The table of assessments for the investigation and diagnosis of heart failure is adapted with permission from the Task Force on Heart Failure of the European Society of Cardiology (*Eur Heart J* 1995;16:741-51).

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