Heart failure with a preserved ejection fraction

Heart failure is a progressive clinical syndrome generally associated with poor prognosis and characterized by a triad of dyspnoea, fatigue and oedema. Heart failure affects ~900 000 people in the UK and has a 5-year survival of only 58% (Yip et al, 1999; Al-Mohammad et al, 2010). Half of all patients with heart failure have reduced left ventricular ejection fraction, known as heart failure with left ventricular systolic dysfunction or heart failure with reduced ejection fraction. This group has been the focus for the majority of heart failure research and pharmacological innovation. However, the remaining 50% of heart failure patients have preserved left ventricular ejection fraction.

Technically, many conditions (e.g. valvular disease, anaemia, thyrotoxicosis, pulmonary hypertension, and arrhythmia) may result in heart failure with preserved left ventricular ejection fraction and so these must be excluded. In the absence of a secondary cause, and when there is evidence of impaired diastolic function, the terms heart failure with a preserved ejection fraction and diastolic heart failure become synonymous.

For the purposes of this review, heart failure with preserved left ventricular ejection fraction will refer to heart failure with preserved ejection fraction secondary to diastolic impairment (Al-Mohammad et al, 2010; McMurray et al, 2012). Among non-experts, awareness of heart failure with preserved left ventricular ejection fraction (and those at risk) remains low and is diagnosed with some difficulty. This article reviews the epidemiology, pathophysiology, diagnosis and management of heart failure with preserved left ventricular ejection fraction.

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Definition

Heart failure with preserved left ventricular ejection fraction is a clinical syndrome characterized by symptoms and signs of heart failure, a preserved ejection fraction and abnormal diastolic function (McMurray et al, 2012).

Epidemiology

Heart failure affects 2–3% of the adult population in developed countries (McKee et al, 1971; Mosterd and Hoes, 2007). Relative to the number of patients with left ventricular systolic dysfunction, the number with heart failure with preserved left ventricular ejection fraction is increasing year on year (Tschope and Westermann, 2009) but this could relate to increasing awareness and ability to make the diagnosis.

Patients with heart failure with preserved left ventricular ejection fraction are typically older than those with left ventricular systolic dysfunction (Vasan et al, 1999), possibly as a result of age-associated rise in arterial hypertension, ischaemic heart disease and diabetes, all of which increase the risk of heart failure with preserved left ventricular ejection fraction (Mandinov et al, 2000). Such conditions must be identified and treated optimally in the context of heart failure with preserved left ventricular ejection fraction since targeting the cause remains the primary aim when managing heart failure with preserved left ventricular ejection fraction.

Yip et al (1999) reported a high prevalence of diabetes among patients with heart failure with preserved left ventricular ejection fraction and that female gender is over-represented in this group. This is may be because left ventricular systolic dysfunction is most commonly the result of ischaemic heart disease which affects twice as many men as women. Heart failure with preserved left ventricular ejection fraction is becoming increasingly common in non-western countries, a fact attributed to the increasing prevalence of poorly controlled systemic hypertension and diabetes in these populations (Yip et al, 1999).

The Framingham Heart Study reported a 6-year mortality rate of 8.1% in the heart failure with preserved left ventricular ejection fraction group, compared with 3% in controls and 18.9% in the left ventricular systolic dysfunction group. Among UK patients with heart failure with preserved left ventricular ejection fraction, those who have been hospitalized have a 1-year mortality rate comparable to those with left ventricular systolic dysfunction (Cleland et al, 2006). The morbidity impact of heart failure with preserved left ventricular ejection fraction and its related health-care resource consumption are large: the 1-year hospital readmission rate is as high as 50% (Zile and Brutsaert, 2002).

Pathophysiology

For the heart to pump efficiently, it has to have adequate filling and efficient emptying during diastole and systole respectively. Both phases are active, energy-dependent processes since, according to the sliding filament mechanism of muscle contraction, actin and myosin filaments require ATP to engage and disengage. Diastolic dysfunction results when this is prolonged, delayed or incomplete. The result is insufficient filling of the ventricles, reduced stroke volume and elevation of the left ventricular end diastolic pressure.

Two-thirds of the diastolic filling time occurs passively driven by the greater left atrial pressure compared to the left ventricle diastolic pressure (corresponding to the E wave on echocardiography). The remaining one-third of filling time is aided by atrial contraction (corresponding to the A wave). Complete left ventricle filling is essential since, according to the Frank–Starling law, pre-load stretches the myocardium resulting in increased contractility. Chronically impaired diastolic function raises left ventricular end diastolic pressure which causes raised left atrial pressure and pulmonary arterial pressure. This results in dyspnoea and symptoms of heart failure.

The precise pathophysiology of heart failure with preserved left ventricular ejection fraction remains the subject of considerable debate. Zile et al (2004) reported that impaired left ventricle relaxation and increased passive left ventricle diastolic stiffness (decreased compliance) are the major mechanisms. This explains why many of the risk factors for developing heart failure with preserved left ventricular ejection fraction are similar to those that cause left ventricular hypertrophy. Left ventricle stiffening results from a combination of derangements in:

- Calcium homeostasis
- Myofilament arrangement
- Cellular energetics (mitochondrial and electron transport mechanisms)
- Cellular cytoskeletal structure
- Composition of the extracellular matrix
- Endothelial function
- Renin–angiotensin–aldosterone axis (Mann, 2004).

It is important to note that heart failure with left ventricular systolic dysfunction will be associated with diastolic dysfunction.

Aetiology

Some of the common clinical conditions associated with heart failure with preserved left ventricular ejection fraction are summarized in *Table 1*.

Pressure overload (systemic hypertension and aortic stenosis)

Any condition that causes chronic left ventricle pressure overload may result in diastolic dysfunction; the commonest cause of heart failure with preserved left ventricular ejection fraction is systemic arterial hypertension (Cohn and Johnson, 1990; Mandinov et al, 2000; Borlaug et al, 2009). Left ventricle pressure overload stimulates concentric left ventricular hypertrophy. Left ventricular hypertrophy involves myocyte enlargement and intracellular collagen deposition which result in stiffening of the myocardium, reduced compliance, impaired diastolic filling, elevated left ventricular end diastolic pressure and raised left atrial pressures (Mandinov et al, 2000). Chronically elevated left atrial pressure causes left atrial enlargement, which is a well-recognized cause of atrial fibrillation. Patients with heart failure with preserved left ventricular ejection fraction are more dependent on atrial augmentation of left ventricle filling than healthy individuals with more compliant ventricular walls. Atrial fibrillation is therefore poorly tolerated in the presence of heart failure with preserved left ventricular ejection fraction and often results in significant clinical deterioration and poorer outcomes (Olsson et al, 2006).

Table 1. Causes of heart failure with preserved left ventricular ejection fraction

Common	Systemic hypertension
	Diabetes
	Coronary artery disease
	Obesity
Less common	Hypertrophic cardiomyopathy
	Restrictive cardiomyopathy

Diabetes

Iribarren et al (2001) reported abnormal left ventricle filling patterns in type 2 diabetics, independent of age, blood pressure, left ventricle mass and left ventricle systolic function. A study by Van Heerebeek et al (2008) demonstrated increased myocardial fibrosis, advanced glycation end-products and myocardial stiffness in diabetics and demonstrated a close correlation between haemoglobin A_{1c} level and the severity of the diastolic impairment. Patients with diabetes and hypertension developed more severe impairment of left ventricle relaxation than those with only one condition, suggesting a synergistic effect (Iribarren et al, 2001).

How does hyperglycaemia lead to left ventricle diastolic dysfunction? Several mechanisms have been postulated (Magri et al, 2012):

1. Impaired glucose metabolism places a greater dependence on fatty acid metabolism. This consumes more oxygen, causing a relative hypoxia and a lower ATP yield
2. Chronic hyperglycaemia results in increased collagen deposition and fibrosis within the myocardium. This increases ventricular stiffness and restricts diastolic filling
3. Left ventricular hypertrophy is more common in diabetics, independent of blood pressure and other factors.

Coronary artery disease

Ischaemia causes functional stiffening of the ventricular myocardium. Thus, left ventricle diastolic dysfunction is one of the earliest consequences of ischaemia. This is seen in angina pectoris where diastolic dysfunction is reversible. Poulsen et al (1999) observed diastolic dysfunction in 60% of patients presenting with acute myocardial infarction, and this was symptomatic in 70% of these. Patients with acute myocardial infarction and normal left ventricle filling pattern rarely have signs and symptoms of heart failure. In the weeks following acute myocardial infarction, myocardial remodelling continues. Collagen deposition, fibrosis and hypertrophy all result in reduced ventricular compliance. If systolic function becomes impaired, heart failure with preserved left ventricular ejection fraction may be followed by, and further confounded by heart failure with reduced ejection fraction (Poulsen et al, 1999).

Controversy

Despite the term heart failure with preserved left ventricular ejection fraction, systolic function is not entirely normal in patients with diastolic dysfunction. More subtle indices of systolic function are impaired or abnormal, even when the left ventricular ejection fraction appears to be preserved.

Nikitin et al (2002) and Yip et al (2002) demonstrated depressed ventricular long axis function in patients with heart failure with preserved left ventricular ejection fraction yet left ventricular ejection fraction remains normal as radial contraction compensates for longitudinal dysfunction. There is potentially a continuum from heart failure with preserved left ventricular ejection fraction to heart failure with reduced ejection fraction. There is probably some overlap between those with heart failure with preserved left ventricular ejection fraction and those with subtle systolic impairment.

Clinical features and diagnosis

As previously mentioned, the presenting features of heart failure with preserved left ventricular ejection fraction are identical to those of heart failure with left ventricular systolic dysfunction. Typically, symptoms occur periodically and are often precipitat-

ed by factors such as ischaemia or atrial fibrillation. Features typically associated with heart failure with preserved left ventricular ejection fraction include:

- Advanced age
- Female gender
- Chronic systemic hypertension
- Diabetes mellitus.

In 2012, the European Society of Cardiology updated its guidelines for the diagnosis of heart failure with preserved left ventricular ejection fraction (McMurray et al, 2012). Three criteria must be satisfied (*Table 2* and *Figure 1*).

The first criterion is easily assessed with a good history and clinical examination. The second can be elucidated by a routine echocardiographic study, but the third causes uncertainty, especially among non-specialists. Evidence of diastolic dysfunction can be gained by cardiac catheterization or transthoracic echocardiography, and can be supported by elevated natriuretic peptides (Paulus et al, 2007).

Invasive parameters

Elevated left ventricular end diastolic pressure (>16 mmHg) or pulmonary capillary wedge pressure (>12 mmHg) are required for a diagnosis of heart failure with preserved left ventricular ejection fraction to be made as long as criteria one and two are also satisfied (Paulus et al, 2007; Tschope and Westermann, 2009).

Transthoracic echocardiography

Transthoracic echocardiography is commonly used to demonstrate evidence of impaired diastolic function. Unless specifically requested, routine echocardiographic studies will not assess diastolic function. A combination of measures are typically used, including:

1. Mitral valve inflow patterns with Doppler
2. Mitral annular velocity during diastole with tissue Doppler
3. Pulmonary vein inflow patterns.

Doppler echocardiography can be used to assess the pattern of blood flow at the mitral valve (*Figures 2* and *3*). In sinus rhythm Doppler echocardiography identifies an E wave (passive ventricular filling) followed by an A wave (atrial systole). During ventricular filling (ventricular diastole), the left ventricle cavity volume expands, so the left ventricle walls move in an outward direction. Tissue Doppler can be used to assess the velocity of these myocardial movements. If the left ventricle is stiff, filling is slow and thus the velocity at which the left ventricle displaces will be reduced. Tissue Doppler analysis of the mitral valve annulus during ventricular diastole identifies two waves: E' (corresponding to displacement during passive filling of the ventricle) and A' (corresponding to active filling of the ventricle). Both A and A' are lost in atrial fibrillation.

If the left ventricle is stiff, passive ventricular filling is reduced and A wave becomes greater than E (E:A reversal is a marker of mildly impaired diastolic function). With time, the left ventricular end diastolic pressure and atrial pressures rise. Thus E wave becomes greater than A wave (pseudo-normalized pattern). To differentiate normal from pseudo-normal pattern, E' wave can be used. An elevated E:E' ratio (>10–15) is a reliable marker for diastolic dysfunction (McMurray et al, 2012).

Combination of elevated natriuretic peptides and echocardiographic findings

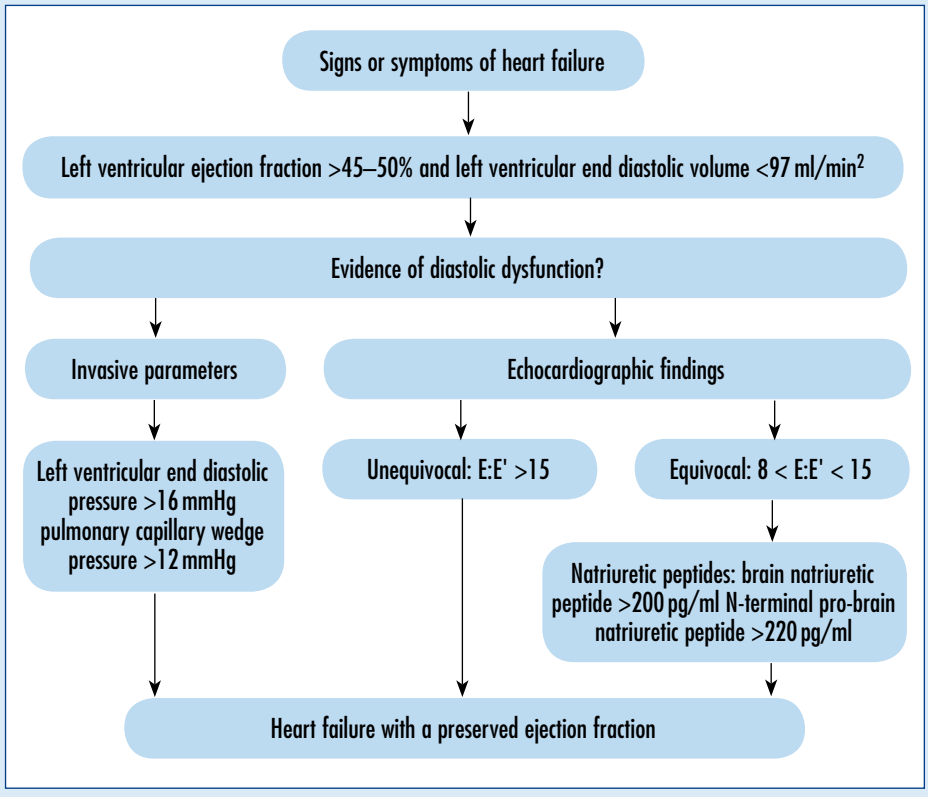
B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are increasingly used when diagnosing heart failure. Natriuretic peptides can be used to confirm the diagnosis of heart failure with preserved left ventricular ejection fraction in patients with abnormal, but equivocal Doppler findings. The European Society

Table 2. European Society of Cardiology guidelines for the diagnosis of heart failure with a preserved ejection fraction

Presence of signs and/or symptoms of chronic heart failure (dyspnoea, oedema and fatigue)
Presence of normal or only mildly abnormal left ventricular systolic function (left ventricular ejection fraction ≥45–50%) in a non-dilated heart (left ventricular end diastolic volume <97 ml/m^2)
Evidence of diastolic dysfunction (abnormal left ventricular relaxation or diastolic stiffness)

From McMurray et al (2012)

Figure 1. Diagnostic algorithm for heart failure with a preserved ejection fraction according to European Society of Cardiology guidelines (McMurray et al, 2012).



of Cardiology guidelines consider BNP >200 pg/ml or NT pro-BNP >220 pg/ml as elevated. As natriuretic peptides are more sensitive than specific, they are more accurate when ruling out heart failure than when making a positive diagnosis (McDonagh et al, 2004; Al-Mohammad et al, 2010).

Figure 2. The Doppler cursor is positioned at the tips of the mitral valve leaflets. The Doppler signal represents the velocity of blood during passive left ventricular filling (E wave). The blood is moving towards the probe and so results in a positive signal. The second signal represents the velocity of blood during active left ventricular filling, i.e. atrial contraction (A wave).

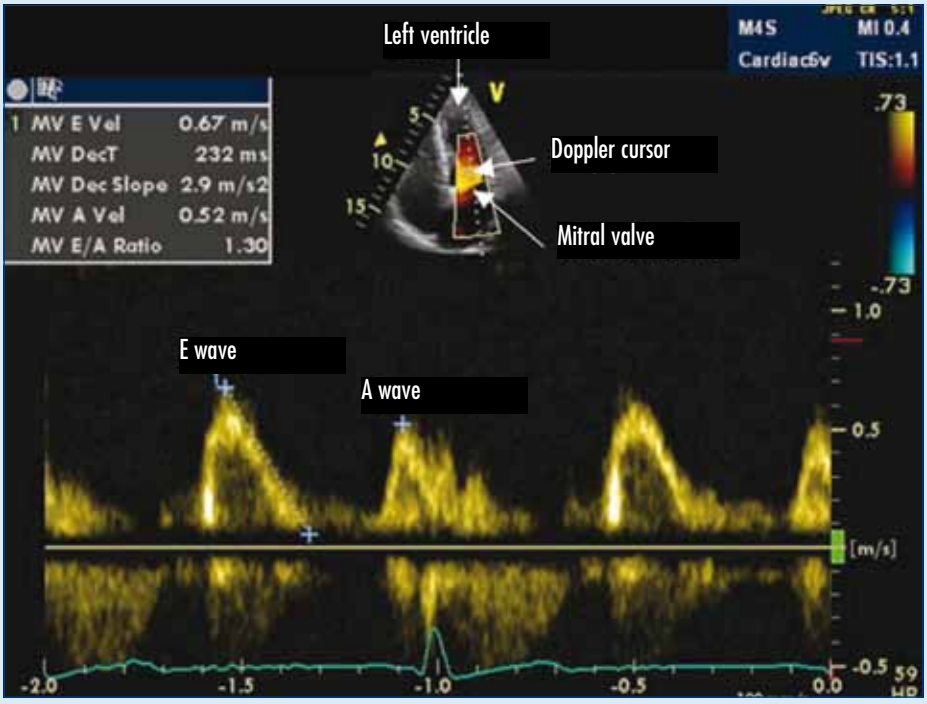
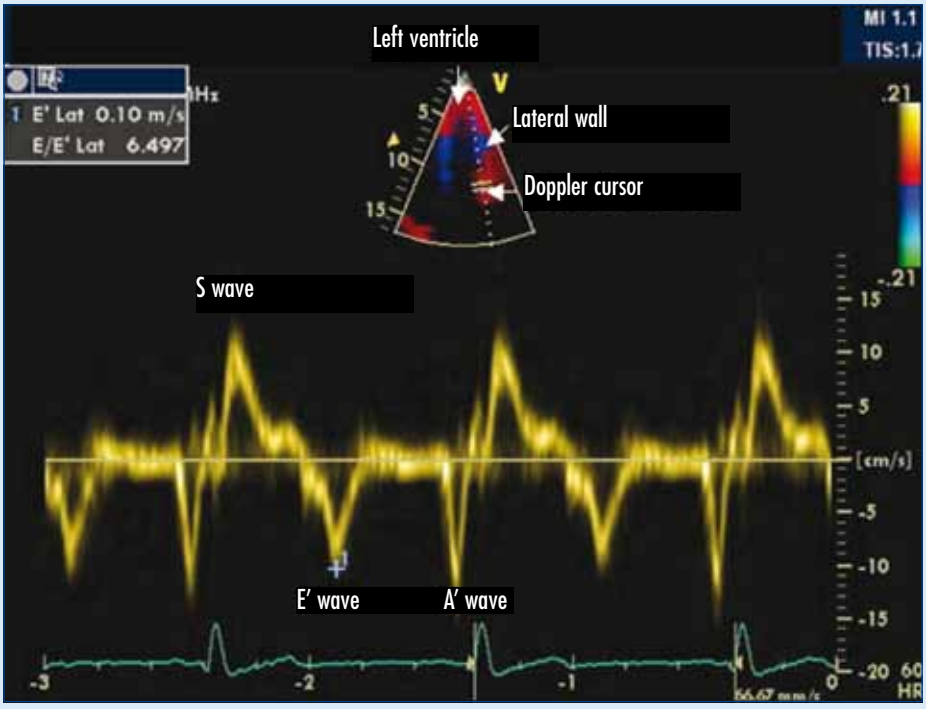


Figure 3. The Doppler cursor is positioned within the lateral left ventricular wall. The Doppler signal now represents the velocity the myocardium, termed tissue Doppler. As the left ventricle expands during diastole, the left ventricle walls will move away from the cursor, resulting in a negative signal. The E′ and A′ waves are therefore seen below the baseline. The positive signals, e.g. S wave, reflect systolic left ventricular movement. In this case, the E:E′ ratio is 6.5 indicating normal diastolic left ventricular relaxation and function.



Treatment

There is scant evidence for treatment of heart failure with preserved left ventricular ejection fraction. However, several large multicentre trials have looked at heart failure with preserved left ventricular ejection fraction treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Targeting symptoms

Cleland et al (2006) observed a 4% reduction in hospitalization as a result of decompensated heart failure with preserved left ventricular ejection fraction in patients treated with perindopril. There was also an improvement in the 6-minute walk distance (mean 38 m). However, over the full 3 years of follow up, these effects lost significance and overall there was no difference in morbidity or mortality between the placebo and perindopril-treated groups.

Yusuf et al (2003) demonstrated a 3% reduction in hospital admissions in patients with heart failure with preserved left ventricular ejection fraction taking candesartan, but no mortality benefit compared with placebo. A larger, more recent study treated heart failure with preserved left ventricular ejection fraction patients with irbesartan (I-Preserve) and was entirely negative. The National Institute for Health and Clinical Excellence and European Society of Cardiology guidelines therefore recommend that treatment of heart failure with preserved left ventricular ejection fraction should include symptomatic therapy with diuretics and optimal treatment of any aetiological conditions (Al-Mohammad et al, 2010; McMurray et al, 2012).

Targeting underlying causes

Therapy should target aetiological conditions such as ischaemic heart disease, hypertension and diabetes. Overstimulation of the renin–angiotensin–aldosterone system increases left ventricular hypertrophy and adverse remodelling. It has therefore been proposed that renin–angiotensin–aldosterone

system antagonists (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) might be the preferred agents when treating hypertension in the context of heart failure with preserved left ventricular ejection fraction in an effort to reduce adverse left ventricle remodelling (McMurray et al, 2012).

However, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) cast some doubt on this hypothesis. ALLHAT investigated 33 000 patients with hypertension over 5 years: 36% were diabetic and the mean age was 67 years. Patients taking diuretics were 38% less likely to develop heart failure than those taking angiotensin-converting enzyme inhibitors and 19% less likely than those taking calcium-channel antagonists. As a result of these findings, Flack and Nasser (2003) suggested a potential role of diuretics in the treatment of heart failure with preserved left ventricular ejection fraction, or for prevention in those at high risk.

Targeting mechanisms

There are currently no therapies which target the pathophysiological mechanisms responsible for heart failure with a preserved ejection fraction. Novel agents such as the cardiac-specific myosin activator omecamtiv mecarbil and device-based therapies have been developed but, as yet, there is no evidence of their clinical utility (Chung, 2010; Cleland et al, 2011).

Conclusions

Heart failure with preserved left ventricular ejection fraction accounts for half of all heart failure cases. Although this proportion is increasing, little is known about how to effectively treat the condition, beyond treating the comorbidities that may have an aetiological role such as systemic hypertension, diabetes and ischaemic heart disease. While the prognosis for heart failure with left ventricular systolic dysfunction has improved, the prognosis associated with heart failure with preserved left ventricular ejection fraction has not. There is a need for novel therapies to combat this increasingly prevalent condition. **BJHM**

Conflict of interest: none.

Al-Mohammad A, Mant J, Laramee P et al (2010) Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. National Institute for Health and Clinical Excellence, London

Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM (2009) Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. *J Am Coll Cardiol* **54**: 410–18

Chung ES (2010) Cardiac resynchronisation therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail* **12**: 581–7

Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* **27**: 2338–45

Cleland JG, Teerlink JR, Senior R et al (2011) The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. *Lancet* **378**: 676–83

Cohn JN, Johnson G (1990) Heart failure with normal ejection fraction. The V-HeFT Study. Veterans Administration Cooperative Study Group. *Circulation* **81**(III): 48–53

Flack JM, Nasser SA (2003) The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *Curr Hypertens Rep* **5**: 189–91

Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV (2001) Glycemic control and heart failure among adult patients with diabetes. *Circulation* **103**: 2668–73

Magri CJ, Cassar A, Fava S, Felice H (2012) Heart failure with preserved ejection fraction and diabetes mellitus. *Journal of Diabetes Research and Clinical Metabolism* (doi: http://dx.doi.org/10.7243/2050-0866-1-2)

Mandinov L, Eberli FR, Seiler C, Hess OM (2000) Diastolic heart failure. *Cardiovasc Res* **45**: 813–25

Mann DL (2004) *Heart Failure*. Philadelphia, Saunders

McDonagh TA, Holmer S, Raymond I, Luchner A, Hildebrant P, Dargie HJ (2004) NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. *Eur J Heart Fail* **6**: 269–73

McKee PA, Castelli WP, McNamara PM, Kannel WB (1971) The natural history of congestive heart failure: the Framingham study. *N Engl J Med* **285**: 1441–6

McMurray JJ, Adamopoulos S, Anker SD et al (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* **33**(14): 1787–847

Mosterd A, Hoes AW (2007) Clinical epidemiology of heart failure. *Heart* **93**: 1137–46

Nikitin NP, Witte KK, Clark AL, Cleland JG (2002) Color tissue Doppler-derived long-axis left ventricular function in heart failure with preserved global systolic function. *Am J Cardiol* **90**: 1174–7

Olsson LG, Swedberg K, Ducharme A et al (2006) Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* **47**: 1997–2004

Paulus WJ, Tschope C, Sanderson JE et al (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* **28**: 2539–50

Poulsen SH, Jensen SE, Egstrup K (1999) Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. *Am Heart J* **137**: 910–18

Tschope C, Westermann D (2009) Heart failure with normal ejection fraction. Pathophysiology, diagnosis, and treatment. *Herz* **34**: 89–96

Van Heerebeek L, Hamdani N, Handoko ML et al (2008) Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* **117**: 43–51

Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D (1999) Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* **33**: 1948–55

Yip GW, Ho PP, Woo KS, Sanderson JE (1999) Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. *Am J Cardiol* **84**: 563–7

Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE (2002) Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? *Heart* **87**: 121–5

Yusuf S, Pfeffer MA, Swedberg K et al (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* **362**: 777–81

Zile MR, Brutsaert DL (2002) New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation* **105**: 1387–93

Zile MR, Baicu CF, Gaasch WH (2004) Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* **350**: 1953–9

KEY POINTS

- Heart failure with a preserved ejection fraction is thought to account for 50% of cases of chronic heart failure.
- The diagnosis is known by multiple descriptive names and terms.
- There are no treatments currently proven to improve prognosis.
- Treatments are focused on underlying causes and alleviating symptoms.