



## Management of Diastolic Heart Failure

Dr. Godwin TC Leung

FHKCP, FHKAM  
Specialist in Cardiology



Dr. Godwin TC Leung

### Case Presentation

A 70 year-old lady with known history of uncontrolled hypertension for years, presented with bilateral ankle swelling and impaired exercise tolerance. Her serum N-terminal pro B-type natriuretic peptide (BNP) was increased. Echocardiogram showed normal left ventricular systolic function but there was presence of left ventricular hypertrophy with diastolic dysfunction. Her symptoms were controlled with diuretics and angiotensin receptor blocker. However, she stopped the treatment by herself after her symptoms had improved. She was finally admitted to the hospital because of acute pulmonary oedema.

### Epidemiology

Patients with diastolic heart failure (DFH) are not uncommonly encountered by primary care physician. About 30% to 55% of patients with heart failure have preserved systolic function, often defined as left ventricular ejection fraction (LVEF) greater than 40 to 50%<sup>1-3</sup>. In Asia, due to the high prevalence of hypertension, 50% of patients with heart failure have normal systolic function<sup>4, 5</sup> and the incidence of DHF will further increase due to the aging population. The mortality of DHF is about 5-8% per year<sup>6, 7</sup>, which is about half of that of systolic heart failure. In a recent community-based prospective cohort of patients with heart failure, more than half (55%) had preserved systolic function and the mortality of DFH (16% at 6 months) was shown to be comparable to that of systolic heart failure<sup>8</sup>. The morbidity in terms of reduction in quality of life and exercise tolerance, hospitalisation rates and health-care costs per person for both systolic and DHF are similar<sup>6, 9</sup>.

### Pathophysiology

The clinical manifestations and haemodynamic consequences of systolic and DFH are similar, although the primary pathophysiology mechanisms are different. DFH is caused by left ventricular diastolic dysfunction, leading to increased resistance to left ventricular filling and eventually resulting in heart failure syndrome. Hypertension, diabetes mellitus, and coronary artery disease are common conditions that predispose to the development of DFH. Impaired ventricular relaxation and increased ventricular stiffness are the underlying mechanisms causing diastolic dysfunction. Activation of

the renin-angiotensin-aldosterone system plays an important role in the development of myocardial fibrosis and stiffness<sup>10, 11</sup>. Inhibition of renin-angiotensin-aldosterone system has been demonstrated to reduce myocardial stiffness and leads to regression of myocardial fibrosis<sup>12</sup>.

### Diagnosis of DHF

According to ACC/AHA guidelines, the diagnosis of DFH is based on the clinical findings of heart failure with the findings of preserved LVEF and the absence of valvular abnormalities<sup>13</sup>. The European guidelines require the finding of evidence of diastolic dysfunction<sup>14</sup>. Echo-Doppler assessment is a convenient and effective way of assessing diastolic function. Echocardiogram can also exclude other specific conditions, such as hypertrophic cardiomyopathy, aortic stenosis, infiltrative cardiomyopathies and pericardial disease. BNP, a cardiac neurohormone released by the ventricles in response to volume expansion and pressure overload, has recently emerged as a marker for heart failure<sup>15</sup>. BNP is elevated in systolic and DHF, though more markedly elevated in systolic heart failure<sup>8</sup>. The level of BNP correlates with severity of diastolic dysfunction and is highest among those with a restrictive filling pattern<sup>15</sup>. Study in Hong Kong has shown that N-terminal pro BNP can help in the diagnosis of DHF<sup>16</sup>. Several studies report the use of BNP in the diagnosis of systolic and DHF in the primary care, urgent care, and emergency department settings<sup>17, 18</sup>. It can be used as a screening test to rule out heart failure due to its high negative predictive value.

### Principles of Treatment

The current strategy for the management of DHF focuses on symptom relief and modification of underlying causes of DHF. Diuretic therapy is required in symptomatic patients but should be used cautiously, as excessive diuretics may decrease cardiac output and cause hypotension and renal failure. Compared with systolic heart failure, DHF patients require lower doses of diuretics and may tolerate their withdrawal without increasing heart failure symptoms<sup>19</sup>. Tachycardia is very poorly tolerated in DHF, and in the presence of atrial fibrillation, adequate control of heart rate by beta-blockers or calcium channel blockers and maintenance of sinus rhythm are beneficial. Reduction in heart rate



may be associated with improved ventricular filling and haemodynamics. Non-pharmacological measures such as salt restriction, weight control and exercise have been shown to reduce symptoms in patients with DHF<sup>20</sup>. For primary care physicians, hypertension is the most common underlying cause of diastolic dysfunction; therefore, aggressive management of hypertension is essential in the prevention and management DHF. In patients with coronary artery disease, therapies to relieve myocardial ischaemia are also likely to be beneficial.

## Specific drugs

It is likely that most of the proven drugs used in treating systolic heart failure (ACEI, angiotensin receptor blockers, beta-blockers, aldosterone antagonists) may also be beneficial in the treatment of DHF<sup>21</sup>. However, evidence-based treatment strategies for DHF are limited. Two large-scale randomized controlled trials have recently provided some evidence for the treatment of DHF. The Candesartan in Heart Failure - Assessment of Reduction in Mortality (CHARM) - Preserved study is a randomized placebo-controlled trial of candesartan (with a target dose of 32 mg daily) in 3023 patients with DHF, NYHA II-IV and an LVEF of >40%<sup>22</sup>. After a median follow-up of 3 years, candesartan group had significantly fewer hospitalisations (HR 0.84; CL 0.70-1.00; p=0.047), and there was a trend towards reduction in the primary composite end point of heart-failure hospitalisation and death from cardiac cause (HR 0.86; CI 0.74-1.00; p=0.051).

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study randomised 850 DHF patients who were over 70 years of age with an LVEF of  $\geq$ 45% and echocardiographic features suggesting possible diastolic dysfunction to receive perindopril at 4 mg per day or placebo<sup>23</sup>. The primary endpoint was a composite of all-cause mortality and unplanned heart failure related hospitalisation. No significant improvement in the primary outcome was shown, but by 1 year, reduction in hospitalisation for heart failure was observed (HR 0.628, CI 0.408-0.966; p=0.033) and functional class and 6-min corridor walk distance had improved in those assigned to perindopril. This study suggested that perindopril may be of benefit in this patient population.

## Conclusion

HF is common and may account for more than 50% of heart failure cases among the elderly. The principles of treatment include symptom relief by judicious use of diuretics, rate control of atrial fibrillation, and aggressive control of hypertension. Limited evidence from randomised control trials suggested that angiotensin receptor blockers and ACEI are beneficial. More evidence-based treatment strategies to enhance the care of this condition will be available when some of the on-going clinical trials are completed.

## References

- Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998; 98: 2282-9.
- Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients  $\geq$ 65 years of age. *Am J Cardiol* 2001; 87: 413-9.
- MacCarthy PA, Kearney MT, Nolan J, et al. Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study. *BMJ* 2003; 327: 78-9.
- Sanderson JE, Chan S, Chan WWM et al. The aetiology of heart failure in the Chinese population of Hong Kong - a prospective study of 730 consecutive patients. *Int J Cardiol* 1995; 51: 29-35.
- Yip GWK, Ho PPY, Woo KS et al. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. *Am J Cardiol* 1999; 84: 563-7.
- O'Conner CM, Gattis WA, Shaw L, Cuffe MS, Califf RM. Clinical characteristics and long-term outcomes of patients with heart failure and preserved systolic function. *Am J Cardiol* 2000; 86: 863-7.
- Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. *J Am Coll Cardiol* 1991; 18: 377-82.
- Bursi F, Weston S, Redfield M, et al. Systolic and diastolic heart failure in the community. *JAMA*. 2006;296:2209-16.
- Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002; 288: 2144-50.
- Zannad F, Dousset B, Alla F. Treatment of congestive heart failure: interfering the aldosterone-cardiac extracellular matrix relationship. *Hypertension* 2001; 38: 1227-32.
- Zile M, Brutsaert D. New concepts in diastolic dysfunction and diastolic heart failure: part II: causal mechanism and treatment. *Circulation* 2002; 105: 1503-8.
- Brilla CG, Funck CR, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000; 102: 1388-93.
- Hunt SA, Baker DW, Chin MH et al. Guidelines for the evaluation and management of chronic heart failure in adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the evaluation and management of heart failure). *J Am Coll Cardiol* 2001; 38: 2101-13.
- European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eu Heart J* 1998; 19: 990-1003.
- Dickstein K. Natriuretic peptides in detection of heart failure. *Lancet* 1998; 351: 4
- Ko WC, Leung TC, Choi MC, Chan CK, Tse TS, Tsui KL, Chan KK, Li SK. Brain natriuretic peptide- An emerged tool in assessment of congestive heart failure. *J HK Coll Cardiac* 2006; 14 (Suppl 1), A89.
- Cowie M, Struthers A, Wood D, Coats A, Thompson S, Poole-Wilson P. Value of natriuretic peptides in assessment of patients with possible heart failure in primary care. *Lancet* 1997; 350: 1347-51.
- Dao Q, Krishnaswamy P, Kazanerga R, Harrison A, Amirnovin R, Lenert L. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001; 37: 379-85.
- Van Kraaij DJ, Jansen RW, Bouwels LH, Gribnau FW, Hoefnagels WH. Furosemide withdrawal in elderly heart failure patients with preserved left ventricular systolic function. *Am J Cardiol* 2000; 85: 1461-6.
- Kitzman DW, Brudbaker PH, Anderson RA, et al. Exercise training improves aerobic capacity in elderly patients with diastolic heart failure: a randomized, controlled trial [abstract]. *Circulation* 1999; 100: 296
- Wu EB, Yu CM. Management of diastolic heart failure: a practical review of pathophysiology and treatment trial data. *Int J Clin Pract*. 2005; 59(10):1239-1246.
- Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; 362: 777-81.
- Cleland JG, Tendera M, Adamus J, Freemantle N, Polonske L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006; 27(19):2238-45.