

Diastolic Heart Failure: What, So What and Now What?

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What Is It?

The Elephant in the Room

Until two decades ago, the notion that heart failure (HF) could occur in the presence of normal ejection fraction (EF) was met with great skepticism. While most physicians could recall encounters with hypertensive elderly ladies in acute pulmonary oedema despite a normal EF, it was not until large epidemiologic studies provided evidence for the existence of this syndrome that clinicians began to acknowledge “the elephant in the room”. These epidemiologic studies have confirmed that half of patients with HF indeed have preserved EF¹⁻⁶ and that this half of the HF population are predominantly women aged over 65 years with a history of hypertension. Obesity occurs in 30% to 50% of patients, diabetes in 30% to 50% and atrial fibrillation in 20% to 40% of cases. The prevalence of renal disease is high, while the reported prevalence of coronary artery disease varies widely.⁷

The Blind Men and the Elephant

With the acknowledgement of the elephant in the room came attempts to name and describe it, which sparked much controversy (Fig. 1).

The Blind Men and the Elephant (John Godfrey Saxe)

*It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
Though all of them were blind,
That each by observation
Might satisfy his mind.*

*The First approach'd the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"*

*The Second, feeling of the tusk,
Cried, - "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"*

*The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"*

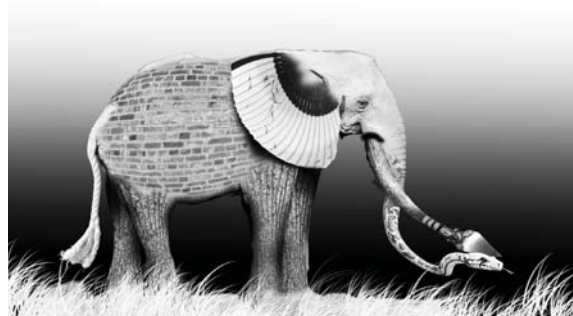


Fig. 1. The blind men and the elephant.

The term “diastolic HF” was the first to be popularly accepted. This term was proposed to underscore the fundamental difference in pathophysiologic mechanisms believed to cause HF in these patients, as opposed to patients with reduced EF, that is, systolic HF. The diastolic/systolic HF distinction is easy to use, neatly divides the HF world into two halves and is supported by seminal data showing a major role of diastolic dysfunction in most, if not all, patients.^{8,9} However the distinction is flawed, because in practice there is often no confirmation of diastolic dysfunction, while occult systolic dysfunction can co-exist with so-called diastolic HF in a given patient. Further, many patients with systolic HF clearly demonstrate diastolic dysfunction.

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To overcome the difficulties in demonstrating diastolic dysfunction, the term “HF with normal systolic function” was suggested. This term is also suboptimal as it is still uncertain whether systolic function is truly normal in these patients. Importantly, a normal EF does not necessarily mean that systolic contractility of the myocardium is normal. Indeed, recent reports have shown that systolic chamber contractility is increased or preserved, while myocardial contractility is reduced in these patients.¹⁰

The term “HF with normal EF” has been adopted in most recent guidelines^{11,12} as the broadest, most clinically useful term to describe this syndrome without assumptions regarding the underlying mechanisms. The term accommodates pathophysiologic processes beyond diastolic dysfunction (including systolic, arterial, atrial and right heart dysfunction) – all of which have been shown to importantly contribute to the syndrome and therefore represent potential therapeutic targets. However, EF is a continuous variable with a normal distribution within the population, and the threshold value to define “normal” versus “reduced” EF is arbitrary. Indeed, distinct physiological differences have been described among Chinese with HF and EF >55%, compared with those with HF and EF 40% to 55%.¹³ Consensus seems to be building towards the use of an EF >50% to designate the syndrome. However, the question of how to approach patients with “borderline (40% to 50%) EF” adds to the complexity of the classification and has given rise to the term **“HF with preserved EF”**.

*And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!*

The Blind Men and the Elephant by John Godfrey Saxe

Ideally the HF population should be divided according to pathophysiology, which in turn will form the basis of specific therapeutic strategies. A greater understanding of the syndrome should ultimately lead to a widely accepted terminology, which reflects the underlying pathophysiologic mechanisms and which aids in investigating and developing treatment modalities.

So what?

Regardless of the nomenclature, it is now clear that diastolic heart failure cannot be ignored. Not only is it as common as systolic HF, but as a syndrome affecting mainly the elderly, its prevalence is expected to increase in ageing populations to epidemic proportions.¹⁴ Furthermore, recent studies have shown that diastolic HF carries similarly dismal outcomes compared to systolic HF, with minimal differences in readmission rates for HF and the overall

survival of patients.^{1,3,4}

Notably, while survival has improved over the last decade for patients with systolic HF, it has not changed for patients with diastolic HF.² This failure to improve outcomes reflects the lack of proven effective treatments for diastolic HF, in sharp contrast to the wealth of evidence-based treatments in systolic HF. Indeed, the treatment for diastolic HF has largely been based on expert opinion and extrapolation from the information obtained for systolic HF. To date, the results from randomised placebo-controlled multi-centre drug trials in diastolic HF have been disappointing (Table 1), and suggest that the treatment hypotheses that apply in patients with systolic HF cannot provide the same clinical benefits for patients with diastolic HF.

Now What?

The failure of recent clinical trials (Table 1) raises yet more questions regarding the appropriateness of diagnostic or inclusion criteria for diastolic HF, and how best to treat such patients.

Diagnostic Criteria for Diastolic HF

Two sets of criteria by which clinicians may diagnose diastolic HF have been proposed.^{19,20} Both have limitations and neither has been formally validated.

The earlier diagnostic criteria proposed by Vasan and Levy¹⁹ provided different levels of diagnostic certainty, giving a classification into definite, probable, or possible cases of diastolic HF. A diagnosis of definite “diastolic HF” requires the triad of: (1) Definitive evidence of congestive HF; (2) Objective evidence of normal left ventricular systolic function (EF ≥50%) in proximity to the HF event (within 72 hours of presentation); and (3) Objective evidence of diastolic dysfunction as established on cardiac catheterisation.

These criteria may lack sufficient sensitivity, because the definitive diagnosis mandates invasive demonstration of diastolic abnormalities. Furthermore, diastolic abnormalities are often present in patients without HF. Finally, the stipulation that patients must have EF measured within 72 hours of presentation is likely unnecessary.²¹ The more recent criteria proposed by the European Society of Cardiology (ESC)²⁰ propose 3 obligatory conditions for the diagnosis: (a) the presence of signs or symptoms of congestive heart failure, (b) the presence of normal or mildly abnormal left ventricular systolic function, and (c) evidence of diastolic left ventricular dysfunction. The strength of the current ESC guideline is the practical recommendation on how to evaluate diastolic dysfunction using 3 principal approaches, viz cardiac catheterisation, Doppler echocardiography, and the measurement of plasma levels of natriuretic peptides. However, these criteria do not take into account mechanisms,

Table 1. Completed Randomised Placebo Controlled Drug Trials in Diastolic HF

Name	Drug	Subjects	Follow-up	Results for primary endpoint
DIG-PEF ¹⁵	Digoxin	n = 988 EF >45%, sinus rhythm, current or past clinical symptoms, signs or radiological evidence of HF	37 months	No effect on hospitalisation or mortality; trend towards decreased HF hospitalisations ($P = 0.094$) negated by trend towards increased hospitalisations for unstable angina ($P = 0.061$).
CHARM-Preserved ¹⁶	Candesartan	n = 3023 EF >40%, NYHA II-IV, prior cardiac hospitalisation	36.6 months	No effect on cardiovascular mortality; trend towards decreased HF hospitalisations with candesartan (RRR 15%; $P = 0.072$) which only reached statistical significance after adjusting for baseline characteristics (RRR 16%; $P = 0.047$).
PEP-CHF ¹⁷	Perindopril	n = 846 EF ≥40%, age ≥70 years, diuretics, specific clinical and echo criteria, cardiovascular hospitalisation in prior 6 months	26.2 months	No effect on mortality or HF re-hospitalisation over the entire duration of the study; at one year a reduction in HF re-hospitalisation with perindopril was observed (RRR 37%; $P = 0.033$).
I-PRESERVE ¹⁸	Irbesartan	n = 4128 EF ≥45%, age >60 years, NYHA II-IV	49.5 months	No effect on all-cause mortality or cardiovascular hospitalisation.

other than diastolic dysfunction, which also cause heart failure in the presence of a normal EF. A particular problem not addressed by the ESC criteria is the lack of sensitivity in patients who have increased filling pressures only during exercise, but not at rest.

Treatment of Diastolic HF

In general, the management of diastolic HF has 2 objectives: (1) To treat the presenting syndrome of HF (relieve venous congestion using diuretics and eliminate precipitating factors such as rapid atrial fibrillation); (2) To reverse the factors responsible for diastolic dysfunction or other perturbations which lead to diastolic HF (i.e. control hypertension). Therapeutic recommendations are available to achieve these aims.^{11,12} However, until more clinical trials have been made in patients with diastolic HF, the empirical nature of recommendations for specific treatments and their uncertain benefits must be recognised.

Future Directions

Ongoing clinical trials in diastolic HF aim to test the efficacy of aldosterone antagonists [Trial of aldosterone antagonist therapy in adults with preserved ejection fraction and congestive heart failure (TOPCAT) study], nesiritide (Use of nesiritide in the management of acute diastolic heart failure trial), beta-blockers [Japanese diastolic heart failure (J-DHF) trial] and sildenafil [Phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure (RELAX) trial].

Whereas great progress has been made in defining the importance of diastolic HF as a public health problem, more information is urgently needed on regional and ethnic variation in the characteristics and outcomes of patients with diastolic HF. A better understanding of the pathophysiology of diastolic HF will aid in the identification of novel therapeutic targets, and the development of new treatment approaches.

REFERENCES

- Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis* 2005;47:320-32.
- Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251-9.
- Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317-27.
- Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260-9.
- Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006;47:76-84.
- Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiadu M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007;50:768-77.

7. Choudhury L, Gheorghiade M, Bonow RO. Coronary artery disease in patients with heart failure and preserved systolic function. *Am J Cardiol* 2002;89:719-22.
8. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation* 2007;115:1982-90.
9. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;350:1953-9.
10. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and Ventricular Systolic Stiffening in Hypertensive Heart Disease: Insights into the Pathogenesis of Heart Failure with Preserved Ejection Fraction. *J Am Coll Cardiol* 2009;54:410-8.
11. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388-442.
12. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:e391-479.
13. He KL, Burkhoff D, Leng WX, Liang ZR, Fan L, Wang J, et al. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus <40%. *Am J Cardiol* 2009;103:845-51.
14. Redfield MM. Heart failure—an epidemic of uncertain proportions. *N Engl J Med* 2002;347:1442-4.
15. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006;114:397-403.
16. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, 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.
17. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;27:2338-45.
18. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;359:2456-67.
19. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000;101:2118-21.
20. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. 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* 2007;28:2539-50.
21. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;344:17-22.